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Conjugate Addition Coupled with Enolate Oxidation in the Total Synthesis of Natural Polyphenols

Konjugované adice spřažené s oxidací enolátů v totální syntéze přírodních polyfenolů

Doctoral thesis

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DECLARATION

This work was carried out at the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences in years 2013-2023. I declare that I have worked on the Ph.D. thesis independently and that I have cited all used resources. I also declare that I did not use this work or its substantial part to obtain the same or another university degree.

Tato práce byla vypracována na Ústavu organické chemie a biochemie Akademie věd České republiky v letech 2013-2023. Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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ABSTRACT

This thesis describes the development of the concept of C-C bond forming conjugate addition/oxidative cyclisation reactions and their application in the total synthesis of natural polyphenols. The first part deals with the development of methodology for conjugate addition of main-group organometallic reagents to unsaturated carbonyl compounds coupled with *in situ* single electron transfer oxidation. The resulting radical undergoes stereoselective cyclisation, that can be followed by a second SET oxidation, leading to further cationic cyclisation. This methodology is ideally suited for the synthesis of furoindane stilbenolignans (FIS), a neglected and structurally distinct class of natural polyphenols. Using this process, racemic synthesis of a derivative of kompasinol A was achieved, confirming the relative configuration of FISs. In an effort to develop asymmetric route to FISs, an unprecedented direct conjugate addition of aryllithiums to ylidenemalonates mediated by diethers and diamines was discovered, leading to asymmetric synthesis of gnetifolin F and 11-deoxykompasinol A.

Based on X-ray evidence, a related annulation methodology consisting of direct conjugate addition/epoxide opening was shown to result in bridged lactones, instead of isomeric FISs. This finding led to an approach for the rapid assembly of the neopodophyllotoxin core. An asymmetric variant using organocatalytic Corey-Chaykovsky epoxidations was also explored. The nitrosative cleavage of ketone enolates, which was serendipitously discovered during the study of SET oxidation, was systematically explored in terms of scope and limitations. Through optimization it was developed into a useful method for anti-Beckmann cleavage of symmetrical as well as non-symmetrically substituted ketones.

SOUHRN

Tato práce popisuje vývoj reakcí složených z konjugované adice, vedoucí k tvorbě C-C vazby, spojené s oxidativní cyklizací a aplikaci této strategie v totální syntéze přírodních polyfenolů. První část se zabývá metodologií konjugované adice organokovových činidel první a druhé skupiny na nenasycené karbonylové sloučeniny spřažené *in situ* s jednoelektronovou oxidací. Stereoselektivní cyklizace takto vzniklého radikálu může být následována druhou jednoelektronovou oxidací vedoucí k následné další kationické cyklizaci. Tato metodologie je velmi vhodná pro syntézu furoindanových stilbenolignanů (FIS), strukturně unikátní a neprozkoumané skupiny přírodních polyfenolů. Za pomoci této metody bylo dosaženo racemické syntézy derivátu kompasinolu A, čímž byla potvrzena relativní konfigurace FIS. V rámci snahy o vývoj asymetrické syntézy FIS byla objevena dosud neznámá konjugovaná adice aryllithií na ylidenmalonáty, umožněná využitím bidentátních ligandů na bázi etherů či aminů, což vedlo k asymetrické totální syntéze gnetifolinu F a 11-deoxykompasinolu A.

Na základě krystalografických strukturních dat bylo prokázáno, že příbuzná anulační metoda, sestávající se z přímé konjugované adice a otevírání epoxidu, poskytuje přemostěné laktony namísto izomerických FIS. To vedlo k nové strategii rychlé výstavby základního skeletu neopodophyllotoxinu. Možnost asymetrické modifikace této metody adaptací organokatalytické Corey-Čajkovského reakce byla též prozkoumána. V rámci studia jednoelektronové oxidace byla pozorována nečekaná štěpná reakce enolátů, zprostředkovaná nitrosací. Tato reakce byla zoptimalizována a její použitelnost pro různé typy ketonů byla systematicky prostudována, včetně nalezení limitů aplikovatelnosti. To z ní dělá užitečnou metodu pro anti-Beckmannovské štěpení symetrických i nesymetrických ketonů.

LIST OF ABBREVIATIONS

Å	Ångström
APCI	atmospheric pressure chemical ionization
ATR	attenuated total reflection
BDE	bond dissociation energy
Bn	benzyl
BOM	benzyloxymethyl
BR	Beckmann rearrangement
br.	broad
BVO	Baeyer-Villiger oxidation
CI	chemical ionization
COSY	correlation spectroscopy
CSA	(*1S*)-(+)-10-camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIR	dirigent protein
DIBAL	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E1cB	elimination unimolecular conjugate base
EA	ethyl acetate
ee	enantiomeric excess
EPR	electron paramagnetic resonance
EI	electron ionization
ESI	electrospray ionization
equiv.	equivalent
EDTA	ethylenediaminetetraacetic acid disodium salt dihydrate
FCA	Friedel-Crafts alkylation or acylations
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IR	infrared (spectrum)
ITC	(–)-isothiocineole
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*meta*-chloroperoxybenzoic acid
MOM	methoxymethyl
mp	melting point

MS	mass spectrometry
NBS	N-bromosuccinimide
n.d.	not determined
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PE	petrol ether
PMB	*para*-methoxybenzyl
PRE	persistent radical effect
p-TsOH	para-toluensulfonic acid
RCM	ring-closing metathesis
Rf	retardation factor (in chromatography)
r.t.	room temperature
SET	single-electron transfer
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
THT	tetrahydrothiophene
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMOP	3,4,5-trimethoxyphenyl
TMP	2,2,6,6-tetramethylpiperidin-1-yl
TMS	trimethylsilyl
TS	transition state

COMMON LATIN ABBREVIATIONS

et al.	et alia - and others
e.g.	exempli gratia - for example
in situ	in its original place or position
in vitro	outside the living body, in an artificial environment

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Natural polyphenols

Natural (poly)phenols are a large and heterogenous group of natural products of plant, fungal and even animal origin, defined only by the presence of oxygenated aromatic rings bearing free or partially alkylated phenolic OH groups. These polar and dissociable phenolic groups are responsible for the characteristics physical and chemical properties of (poly)phenols, such as increased solubility in water or other protic solvents,[1] decreased solubility in nonpolar solvents, higher crystallinity, affinity to metal cations and easy oxidation or even sensitivity to air at high pH.

Polyphenols are highly pharmacologically significant, with a range of activities including antibiotic,[2,3] antiviral[4], antitumor [5,6,7], antidiabetic,[8] antifungal,[9,10,11] anthelmintic [7,10] and antioxidant, naturally mitigating oxidative stress. [12, 13] Better understanding of their chemistry and biology would also broadly benefit human health because polyphenols are naturally a part of human diet, being abundant in vegetables, fruits, cereals and legumes.[14] There is a growing body of evidence from prospective studies suggesting that dietary intake of some polyphenols is correlated with a decrease in cardiovascular as well as all-case mortality.[15] They are known to alter the absorption of essential nutrients, scavenge toxins and inhibit the growth of deleterious gut bacteria.[14] The study of polyphenols is further motivated by their potential as agrochemicals,[9] food preservatives and cosmetics ingredients.[12]

In their parent organisms, polyphenols fulfil a diverse range of functions including antioxidant,[12] signaling, deterrence against predation and defence against microbial and fungal pathogens,[11] suppression of competing plants (allelopathy),[16] melanization,[17] UV-B protection,[18] they may act as animal pigments,[19] or have a structural role such as increasing the stiffness of insect cuticles,[20] fungal tissues [21] or plant xylem.[17]

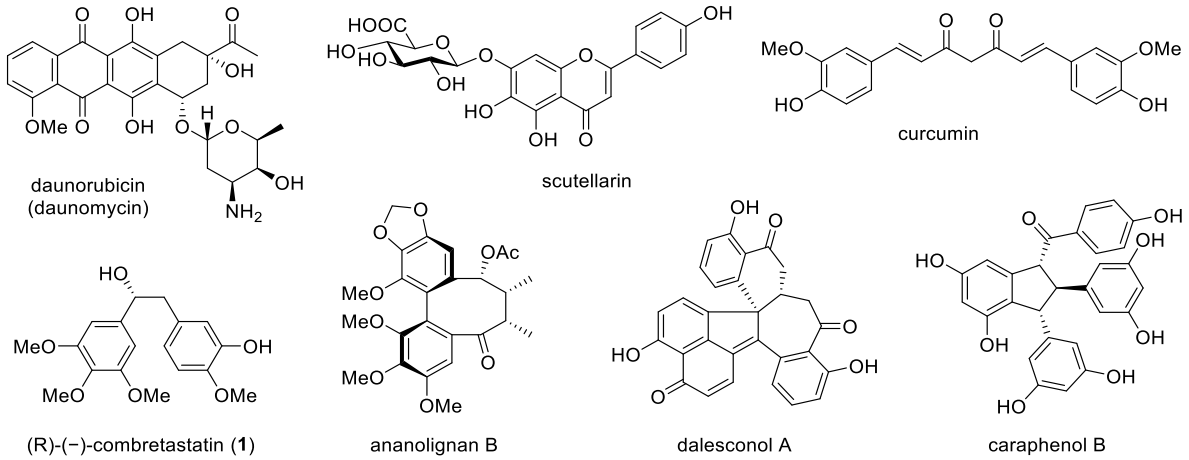


Figure 1. Examples of phenolic plant-produced secondary metabolites: daunorubicin (anthracycline),[22] scutellarin (flavone),[12,10] curcumin (curcuminoid), (*R*)-(−)-combretastatin (**1**, dihydrostilbenoid),[23] ananolignan B (dibenzocyclooctadiene lignan),[7] dalesconol A (1,8-dihydroxynaphthalene),[24] caraphenol B (stilbene dimer).[25]

As with most natural products, the most suitable organizing principle for systematic classification of polyphenols is their biosynthesis. The origin of the largest group of polyphenols can be traced back either to one of the intermediates of the shikimate pathway or to its end products phenylalanine and tyrosine. These are subsequently converted via oxidative deamination (and ring

oxidation in case of phenylalanine) to *p*-coumaric acid (**2a**). Activated as its thioester *p*-coumaroyl-CoA (**3**), it serves as the key biosynthetic crossroad *en route* to most groups of polyphenols of natural origin. Alone, **3** is the precursor of coumarins, combination of **3** with malonyl-CoA (**4**) gives rise to flavonoids,[10] curcuminoids and stilbenoids. Flavonoids are a large and pharmacologically important group of (poly)phenols that include flavones, flavanes, flavanols, their open-chain precursors chalcones, ionic anthocyanidins, rearranged isoflavonoids and other groups. Stilbenoids include simple stilbenes like **5-7** (figure 2), dihydrostilbenes like combretastain **1** (figure 1) and dimeric or oligomeric stilbenoids, which are formed in a large array of structural types by the coupling of free radicals formed from stilbenes by oxidation by laccases and other enzymes. Examples of such oligomers are caraphenol B (figure 1) and ampelopsin H (figure 2).[11, 9]

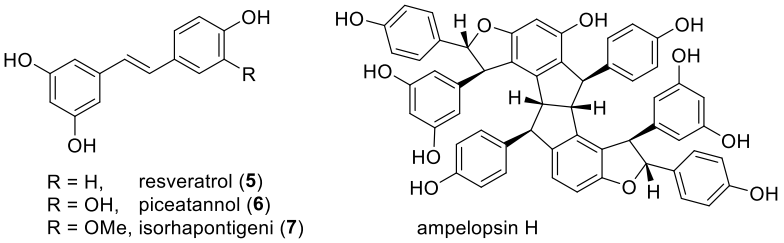
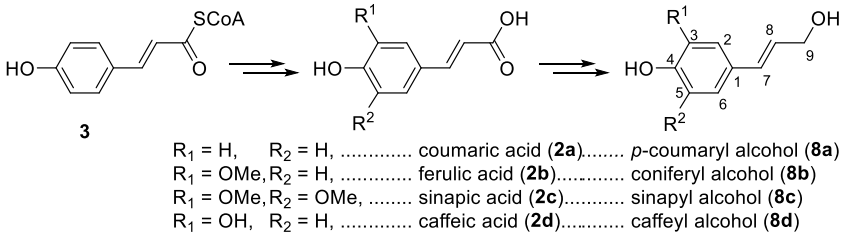


Figure 2. Examples of stilbenoids: simple stilbenes resveratrol (**5**), piceatannol (**6**) and isorhapontigenin (**7**) and stilbene tetramer ampelopsin H with indano-indane core.[9]

The other major biosynthetic pathway leading to polyphenols consists of decarboxylative condensation of several molecules of malonyl-CoA (**4**) followed by multiple dehydrative cyclisation. Products of this polyketide pathway include anthraquinones,[26] hydroxynaphthanenes and their dimers and trimers.[27] A relatively minor group of polyphenols that includes xanthonoids and their precursors hydroxybenzophenones arise from the union of **4** with benzoyl-CoA**.**

Oxidation of *p*-coumaric acid (**2a**) or **3** followed by O-methylation gives rise to an important series of substituted cinnamic acids **2b-d** (scheme 1). These are reduced via their thioesters with CoA to cinnamaldehydes and ultimately to substituted cinnamyl alcohols **8a-d**, termed monolignols. **8a-d** represent the basic building blocks of lignin, a phenolic polymer that constitutes about 20% of wood dry mass. More importantly for the purposes of the following chapters, monolignols very readily dimerize under oxidative conditions to form low molecular weight secondary plant metabolites called lignans.



Scheme 1. Structures of the most common substituted cinnamic acids **2a-d** and monolignols **8a-d** and standard numbering od phenylpropanoids.

1.2. Lignans

Lignans represent an enormous class of structurally diverse, pharmacologically active compounds.[28,29,4] The so-called true lignans are defined by the carbon-carbon bond linking the two

phenylpropanoid units between the C-8 atoms (figure 3). By convention, the carbon atoms belonging to the second phenylpropanoid fragment are numbered C-1' to C-9'.[30]

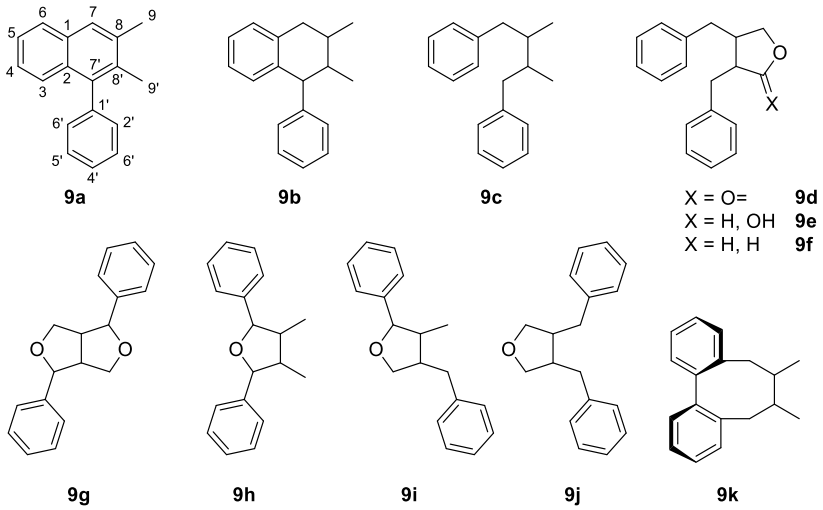


Figure 3. Lignan classification based on structural types **9a-k**, named in the same order as follows: arylnaphthanene, aryltetralin, dibenzylbutane, dibenzylbutyrolactone, dibenzylbutyrolactol, dibenzyltetrahydrofuran, furofuran, 2,5-diaryltetrahydrofuran, 2-aryl-4-benzyltetrahydrofuran, 3,4-dibenzytetrahydrofuran, dibenzocyclooctadiene.[7] Recommended numbering of 2,7'-cyclolignans according to IUPAC is shown on **9a**.[30]

Cyclolignans from the aryltetralin subgroup are characterized by the additional carbon-carbon bond between atoms C-2 and C-7'. Examples include (+)-galbulin from *Himantandra belgraveana* (Himantandraceae),[31,32] (–)-thuriferic acid (**10**) isolated from *Juniperus thurifera* (Cupressaceae),[33] (+)-linoxepin from *Linum perenne* (Linaceae) [34,32,31] and (+)-ovafolinin B from *Lyonia ovalifolia* (Ericaceae) and *Sinocalamus affinis* (Poaceae).[28,32,31]

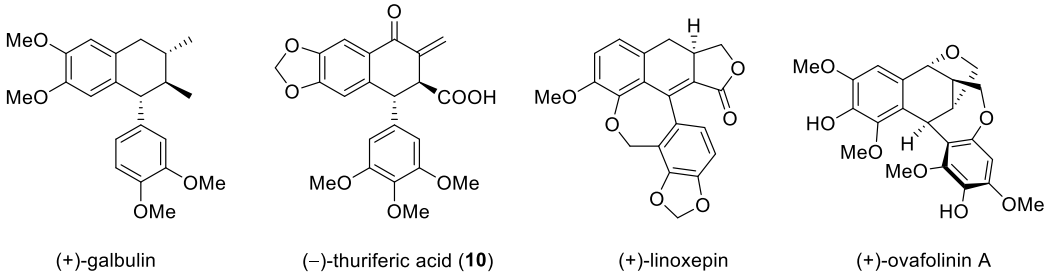


Figure 4. Structures of selected 2,7'-cyclolignans: (+)-galbulin, (–)-thuriferic acid (**10**), (+)-linoxepin, (+)-ovafolinin.

1.3. Podophyllotoxin

1.3.1. Isolation and biosynthesis of podophyllotoxin

The most extensively studied and most pharmacologically important C-2 and C-7' cyclolignan is (–)-podophyllotoxin (**11**) (figure 5). Isolated as early as 1880 from the roots and rhizomes of the North American mayapple or "American mandrake" (*Podophyllum peltatum*, Berberidaceae), it is also found in even higher concentrations in the Himalayan mayapple

(*Sinopodophyllum hexandrum*). At lower levels, it is also produced by several species of junipers (including *Juniperus sabina*) [35] and other plants from the genera *Diphylleia*,[36] *Linum*,[37] *Dysosma* [38] and *Hyptis*,[39] together with other related 2,7'-cyclolignans.

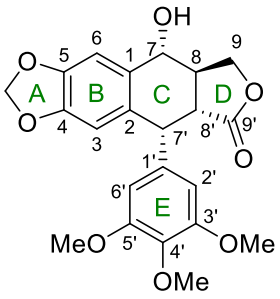
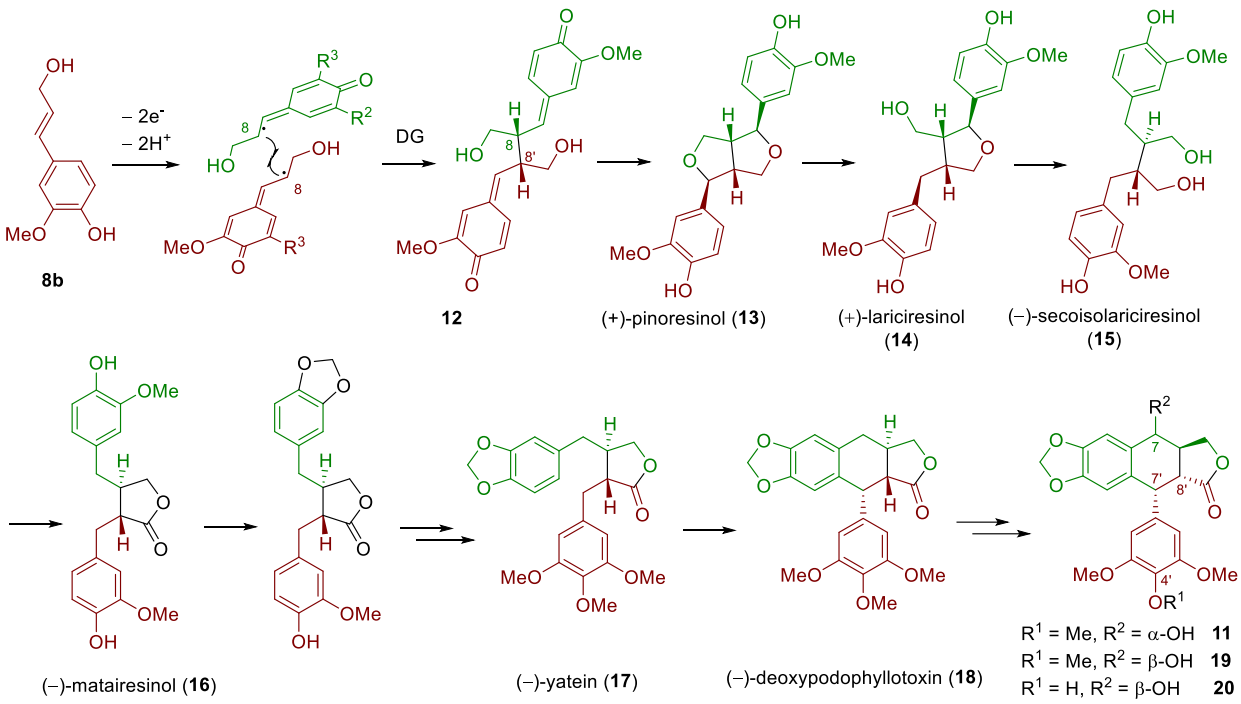


Figure 5. The structure of (–)-podophyllotoxin (**11**) including the recommended numbering [30] and ring designation A-E.

The structure, including absolute configuration was correctly assigned in a series of papers by L. Hartwell and A. W. Schrecker between 1951 and 1956.[40,41] It features a tetracyclic core of four fused rings designated A, B, C, D arranged in a linear array, to which a flanking 3,4,5-trimethoxyphenyl (TMOP) ring E is attached via C-7' (figure 5). All four stereocentres are contiguous and arranged around the C ring. The distinguishing feature of **11** is the *trans*-fusion of the C and D rings, which leads to high rigidity of the whole ABCD ring system, placing all of its atoms roughly into the same plane and forces the E ring into a pseudo-axial position below the ABCD plane.

As for all lignans, the biosynthesis of podophyllotoxin starts by oxidative dimerization of two molecules of a monolignol, in this case coniferyl alcohol (**8b**) (scheme 2). Single electron oxidation of **8b** accompanied by a loss of proton from phenolic group on C-4 results in a highly delocalized radical, which may undergo radical dimerisation via C-8 positions to produce bis-quinone methide adduct **12** as a single stereoisomer. The exceptional selectivity if the coupling is due to the involvement of so-called dirigent proteins (DIR), discussed in detail in chapter 1.4.2. The highly electrophilic nature of carbons C-7 and C-7' leads to a double intramolecular oxa-Michael addition yielding (+)-pinoresinol (**13**), which can be isolated from many vascular plants, notably from the genus *Forsythia*, which contains common garden shrubs like the weeping forsythia (*Forsythia suspensa*). In aryltetralin producing plants, both furan rings are reductively cleaved by a NADPH-dependent reductase to yield (+)-laricinresinol (**14**) and finally (–)-secoisolaricinresinol (**15**). This reduction demonstrates the weak nature of the benzylic ether bond with respect to heterolysis (chapter 4.2.10). Oxidation of one of the alcohol groups with concomitant lactonization yields (–)-matairesinol (**16**), which subsequently undergoes modification of the substitution pattern on both aryl rings. These involve the methylene-dioxy bridge formation, ring oxidation and *O*-methylation (not shown) and ultimately lead to (–)-yatein (**17**).[48]



Scheme 2. Structures and biosynthesis of (–)-podophyllotoxin (**11**), (–)-epipodophyllotoxin (**19**), (–)-4'-desmethyl-epipodophyllotoxin (**20**).

The key connection between C-2 and C-7'forming the C ring is created via oxidation of (–)-yatein by deoxypodophyllotoxin synthase, an iron(II)- and 2-oxoglutarate-dependent oxygenase. The structure of its complex with succinate and (–)-yatein (**17**) has recently been revealed, leading to better understanding of the oxidation mechanism.[42] The D and E rings of the substrate **17** are anchored tightly in the active site of the enzyme, exposing the pro*R* hydrogen atom at C-7' to hydrogen abstraction by the iron(iv)-oxo complex (figure 6, A, B-left).

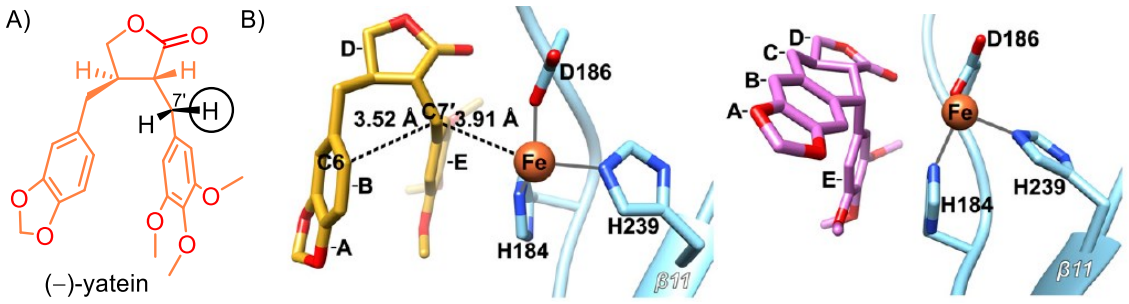
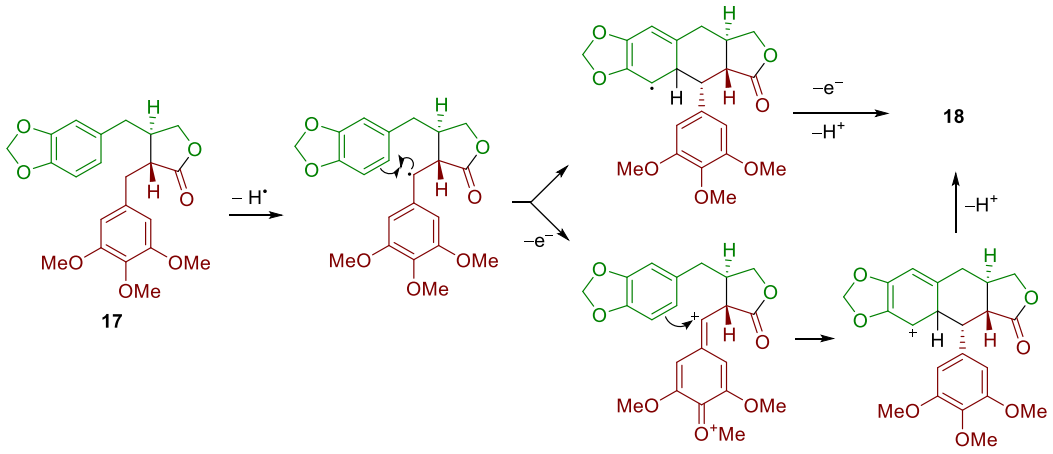


Figure 6. A) Structure of (–)-yatein (**17**) with pro*R* hydrogen on C-7' highlighted by black circle. B) Left: binding mode of **17** in the active site of deoxypodophyllotoxin synthase. Right: binding mode of the cyclic product **18**, where the position of rings D and E remain unchanged.[42]

After the hydrogen abstraction, the benzylic group containing the AB rings rotates, while the lactone ring D and the benzylic arm containing the free radical stabilised by the E ring remain in place (figure 7, B-right). This allows the stereospecific formation of the C-2 C-7' linkage to form the D ring, while still in the active site of the enzyme. Earlier understanding of this mechanism involved the formation of benzylic alcohol by the capture of a water molecule, now it is considered more likely that the benzylic carbocation (or radical) directly cyclises by attacking the A ring (scheme 3). It is yet unknown, whether C-C bond formation precedes the single electron oxidation or whether the

oxidation of the benzylic radical to the benzylic carbocation happens first, followed by Friedel-Crafts cyclisation of the carbenium ion (scheme 3). In either case, the cyclisation is accompanied by the overall loss of a proton and an electron to give **18**.[42] Interestingly, the oxidase is also able to process the other enantiomer (+)-**17**, which is stereospecifically, although less chemoselectively, converted to deoxypicropodophyllin derivatives that share the same configuration at C-7' as (–)-deoxypodophyllotoxin (**18**) (not shown).



Scheme 3. Suggested mechanism of the formation of podophyllotoxin C ring mediated by deoxypodophyllotoxin synthase.

The complex biosynthesis of podophyllotoxin remains the subject of intense ongoing research, however, as can be seen above, many of the key steps have been elucidated. The general reactivity patterns of lignols can be generalized to most other polyphenols and should also guide chemical synthesis. These patterns and how they can be reproduced *in vitro* are discussed in chapter 2.1.

1.3.2. Medicinal relevance of podophyllotoxin

The ethanolic extract of *Podophyllum peltatum* called podophyllin as well as formulations from other podophyllotoxin producing plants were historically used to treat warts and other diseases. In modern medicine, **11** is used topically for the treatment of skin diseases, for example genital warts caused by human papillomavirus (condyloma acuminata) and so called water warts affecting children, which are caused by a type of poxvirus (molluscum contagiosum virus).[43] Unfortunately, unmodified **11** cannot be used internally due to its unacceptable high toxicity. However, it possesses a broad spectrum of bioactivities, especially antiviral and antineoplastic, which can both be traced back to its ability to bind to tubulin via the colchicine binding site.[5,44,23] Tubulin is a dimeric protein that functions as a basic building block of microtubules, the major component of eucaryotic cytoskeleton. Tubulin disruption interferes with mitosis and is therefore one of the major targets for cancer therapy. The high gastrointestinal and general toxicity of **11** led early researchers to search for less toxic derivatives, especially glycosides.[45]

This effort eventually led to the discovery of important clinical antitumor drugs Etoposide (**21**) and Teniposide (**22**) [7,43] (figure 7, A), effective against several cancer types that were approved by FDA in 1983 and 1992 respectively. Etoposide is used as a part of therapy for testicular carcinoma,

glioblastoma, lymphoid and myeloid leukaemia, small and large cell lung cancers as well as stomach, ovarian, breast and pancreatic cancer. WHO included it on the list of essential medicines.[46]

Interestingly, these glycosides, which also differ from **11** by lacking the methyl group of C-4' oxygen, exhibit a new mode of action, different from the parent lead **11**. They were shown to cause strand breaks in DNA of dividing cells by targeting topoisomerase II, a key enzyme responsible for unwinding DNA during replication. Etoposide (**21**) was thought to irreversibly bind to the enzyme making the temporary DNA break permanent and causing premitotic block in late S or early G2 stage.[45] It was later shown that some of the general toxicity as well as the main activity against topoisomerase II comes from *o*-quinone **23** formed by degradation of **21** by cytochrome P450 and other oxidases. **23** acts as topoisomerase II poison and additionally causes depletion of glutathione in cancerous as well as healthy cell causing oxidative stress and eventually apoptosis.[47]

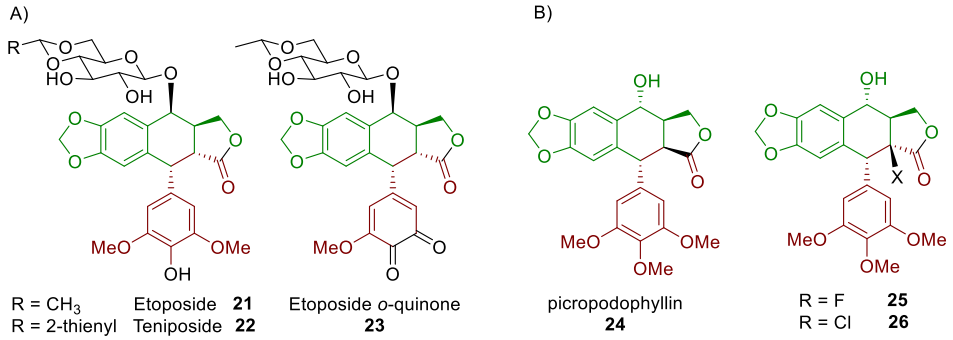


Figure 7. A) Structures of Etoposide (**21**), Teniposide (**22**) and the topoisomerase II poison Etoposide *o*-quinone (**23**). B) Podophyllotoxin derivatives picropodophyllin (**24**), 8'-fluoro- (**25**) and 8'-chloropodophyllotoxin (**26**)

Unfortunately, all podophyllotoxin derivatives, including the successful drugs **21** and **22** still suffer from serious limitations in clinical use due to drug resistance, low bioavailability and systemic toxicity. Undesired effects of the chemotherapeutic use of **11-13** include bone marrow suppression, hair loss, and neurotoxicity as they target fast-dividing cells.[43] This naturally drives the search for less toxic and even more active analogues and prodrugs, one such is etopophos, a water-soluble prodrug of etoposide that bears a phosphate group on the oxygen atom on C-4'. Hundreds of compounds were synthesized and shown to posses activities including cytotoxic, antiviral, anti-inflammatory, immunosuppressive, antirheumatic, antioxidative, antispasmogenic, hypolipidemic as well as insecticidal and antifungal.[35] The antiviral action of derivatives of **11** is believed to be mediated by similar mechanisms as the anticancer activity, that is to disrupt cytoskeleton by binding tubulin and thus interfere with viral replication. Some synthetic analogues also inhibit reverse transcriptase of RNA viruses (such as HIV).

Many structure activity studies aimed at improving antiproliferative effects were published that identify some conditions for maintaining cytotoxicity. Most important requirement is the conservation of the *trans* fusion of rings C and D. The *cis*-fused isomer picropodophyllin (**24**) (figure 7, B) lacks activity compared to **11**. Another requirement is the preservation of the dioxolane ring A, and free rotation of the ring E.[35] Substitution at C-7 is very common, configuration at this atom seems to switch the mode of action. The absence of the C-7 hydroxyl group in deoxypodophyllotoxin (**18**, scheme 2) leads to microtubule depolymerization, likely via binding to a different binding site.[48,43]

Derivatives possessing a halogen atom at C-8' are rather difficult to synthetize [49] but are of interest due to the blocked epimerization at C-8' and potentially slower biodegradation. The presence

of a chlorine atom at C-8' of **26** increases cytotoxicity.[43] **26** also has good insecticide activity against the northern armyworm (*Mythimna separata*), a major maize pest in Asia.[49-51] 8'-fluoropodophyllotoxin (**25**) has antiproliferative and antiviral activity. [52a,52b]

Due to the wide scope of bioactivities, the field of podophyllotoxin-based and podophyllotoxin-like drugs sees high levels of research activity, picking up pace especially after the year 2000 and remaining high to this day with 130-180 papers mentioning podophyllotoxin being published every year according to the SciFinder database (retrieved 19. Oct. 2022). Several reviews dedicated to medicinal properties and synthesis of podophyllotoxin derivatives have been published over the past 6 years [4,31,32,35,43,48,53] with the review journal Natural Product Reports dedicating 3 reviews to the topic just in the 2021-2022 period.

Clinical use of podophyllotoxin as well as broader interest from the medicinal chemistry community led to increasing demand for derivatives of **11**, which puts a significant strain on the existing sources. The development of sustainable production of **11** and its C-7 and C-4'-OH (**20**) derivatives is urgently needed to meet the demand and to relieve over-exploitation of natural plant sources, like the Himalayan mayapple (*Podophyllum hexandrum*), already an endangered species due to overharvesting and deforestation.[54-56]

Three general solutions to this problem were suggested. These are finding new renewable plant sources (*Podophyllum peltatum, Hyptis suaveolens*),[39] engineering a biotechnological process for the production of late intermediates or fully assembled **11** derivatives [56] or in developing shorter and economic routes for chemical synthesis. The large and still ongoing effort to fully elucidate biosynthesis of **11** [42] is partly driven by the desire to develop chemoenzymatic synthesis by manipulation of the biosynthetic pathway.[56-58]

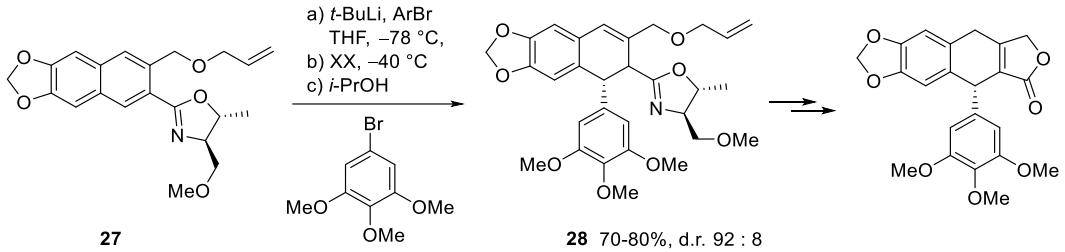
1.3.3. Selected total syntheses of podophyllotoxin

Over the years, many racemic as well as asymmetric total syntheses of **11** and its close derivatives appeared in the scientific literature. Several reviews were published on the topic, most recently by Gao *et al.*, Peng *et al.* and Sun *et. al.*,[31,32,48,53,59] showing the significance of **11** and the need for efficient synthetic route. Only selected examples will be treated in this section, due to their historic significance and/or relevance for the following chapters.

Before the first synthesis of **11** was reported by Gensler and Gatsonis in 1966, [60] synthetic routes to some of its derivatives had already been known, including the thermodynamically more stable *cis*-fused lactone **24** (figure 7). The first formal synthesis relied on irreversible (kinetic) protonation of enolate, generated from THP-protected **24** by thiphenylmethylsodium, that gave a roughly equimolar mixture of epimers, which could be separated and deprotected to yield **11**. For comparison, epimerization of THP-protected **24** by ethanolic NaOAc gives only about 3% of the less stable THP-protected **11**. The higher thermodynamic stability, combined with the relatively synthetically inefficient kinetic protonation of the enolate from the less thermodynamically favored side was called the "picropodophyllin thermodynamic trap" [61] and any newly designed total synthesis must take it into account.

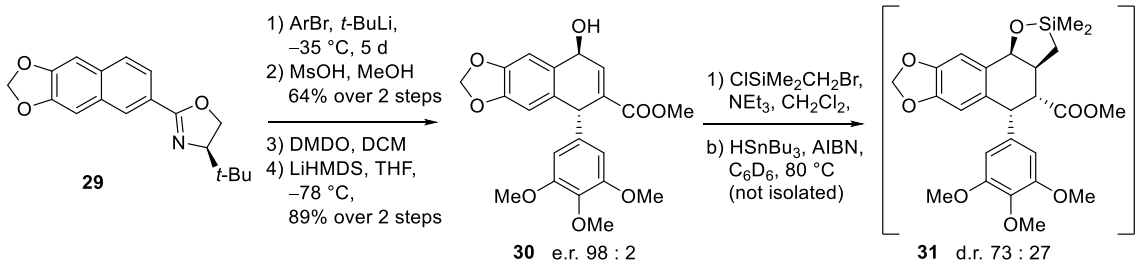
The first successful asymmetric approach to (–)-**11** was found by Meyers *et al.* in 1988,[62] using a chiral oxazoline auxiliary as a directing group for the dearomatization of naphthalene **27** by conjugate addition of aryllitium (scheme 4). The desired diastereomer of **28** is formed in high excess, however the authors do not comment on the stereochemistry at C-8' resulting from kinetic protonation.

The synthesis borrowed from previous racemic syntheses and required 24 steps, giving (–)-**11** in 5% overall yield and optical purity of 94% ee. Despite being very long, this synthesis represents a landmark achievement that set a benchmark for future asymmetric syntheses of **11** and directly inspired many approaches that rely on stereospecific conjugate addition (compare with Scheme 8).[63,64]



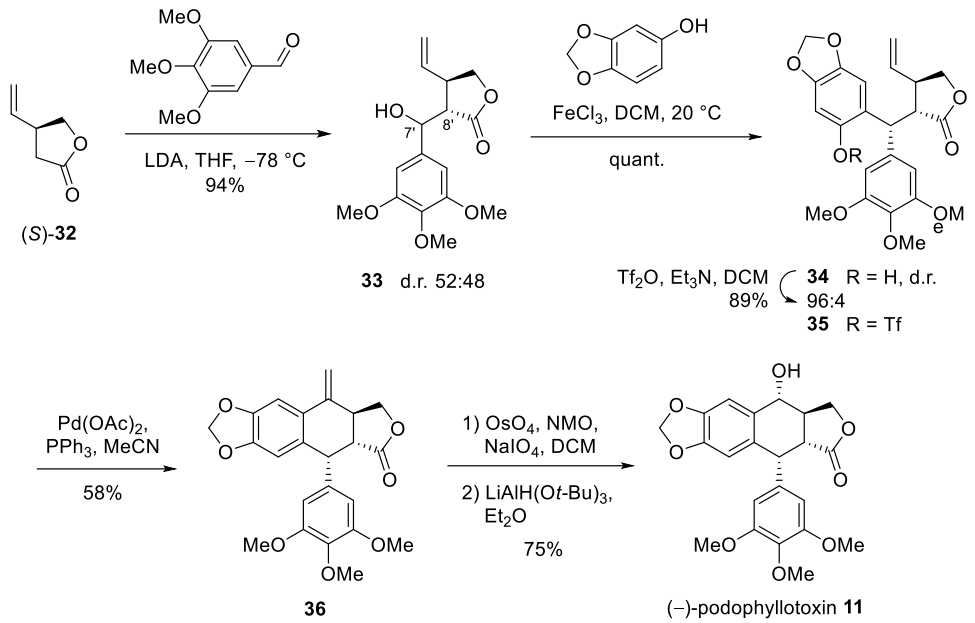
Scheme 4. Meyers' total synthesis of (–)-**11** via dearomatization of **27** using a chiral auxiliary approach.

One such approach, based on the use of *tert*-leucinol-derive oxazoline **29** was reported by Linker *et al.* in 2003 (scheme 4).[63] After dearomatization of **29** by diastereoselective addition of TMOP-lithium and removal of the auxiliary group, the reactive double bond of dihydronaphthalene is epoxidized by DMDO. LiHMDS is then used to trigger E1cB elimination resulting in allylic alcohol **30**. The remaining carbon atom (C-9) is then introduced by a two-step procedure relying on intramolecular reductive radical addition of bromomethylsilyl group to C-8. Reduction of the formed radical at C-8' then proceeds to give **31** which good 73:27 diastereoselectivity, placing the carboxylic ester group *cis* to the TMOP group.



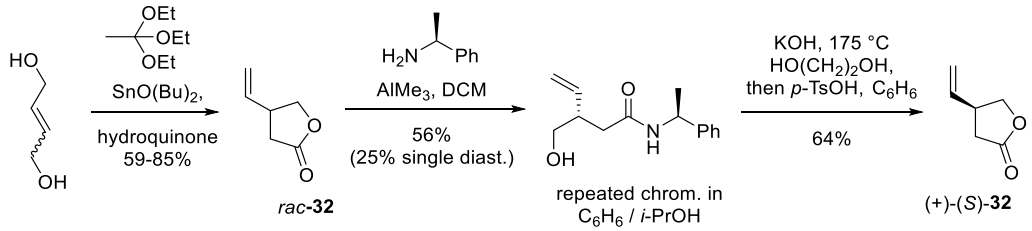
Scheme 5. Linker's total synthesis of (–)-**11** via dearomatization of **29** and intramolecular Giese addition. Intermediate was **31** not isolated.

The synthesis by Bach *et al.*, published in 2008 [65] remains one of the shortest and most inspired chemical synthesis, with a very logical and intuitive sequencing of the construction of stereocentres. It starts with an enolate of the optically pure β-branched γ-lactone **32** (scheme 6), which undergoes aldol addition to TMOP-carbaldehyde to yield **33** as a mixture of diastereomers at C-7'. The stereocentre at C-8' is formed with full selectivity, due to the natural face selectivity of β-substituted γ-lactone enolates. Diastereoselective Friedel-Crafts alkylation of sesamol by benzylic carbenium ion generated from **33** leads to a 96:4 mixture of diastereomers of **34**. The approach utilizes the natural reactivity of sesamol as well as the high stabilisation that the TMOP group provides to the benzylic carbenium ion at C7', themes already seen in lignan biosynthesis. The phenolic group on C-1, converted to a triflate (**35**) is ideally poised to trigger Pd-catalysed intramolecular Heck coupling to form ring C in **36**. Oxidative cleavage of the exocyclic double bond followed by known reduction at C-7 generates the remaining stereocentre and finishes the synthesis of **11** in 6 steps and 35% overall yield from lactone **32**.



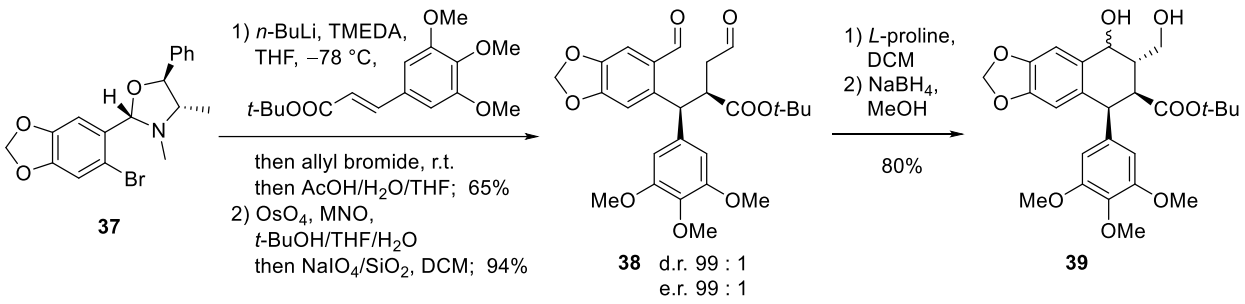
Scheme 6. Bach's total synthesis of (–)-**11** diastereoelective aldol/Friedel-Crafts sequence.

The picropodophyllin trap is avoided altogether by establishing the critical stereocentres at C-8, C-8' and C-7' before the C ring is closed. The major limitation of this approach it the availability of the starting material **32**, the Taniguchi lactone, which, as the authors admit, must be prepared from 2-butyne-1,4-diol in four steps that include a conventional resolution of diastereomeric pair of amides derived from (*R*)-(+)-1-phenylethylamine (scheme 7).[66]



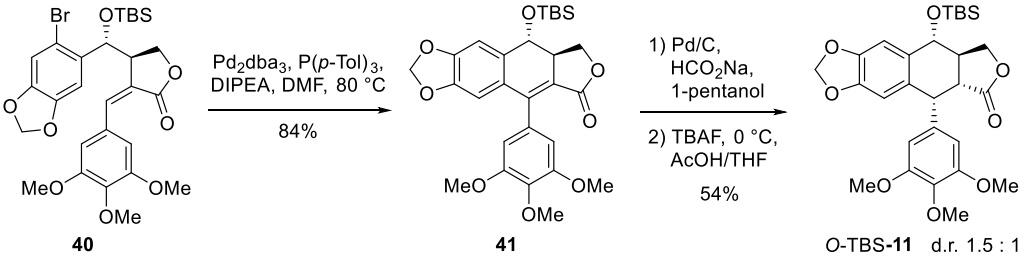
Scheme 7. Synthesis of Taniguchi lactone **32**.

Another chiral auxiliary-assisted approach to (+)-**11** was published in 2009 by Zhang *et al*.[64] The pseudoephedrine-based oxazolidine auxiliary in this approach is a part of the nucleophile **37**, as opposed to being connected to the electrophile in Meyers' and Linker's approaches. The synthesis started with addition of lithiated **37** to substituted cinnamic ester (Scheme 8; also see chapter 1.7.2, scheme 27), followed by *anti*-selective allylation of the enolate and subsequent oxidative cleavage of the allyl group resulting in **38** as essentially optically and diastereomerically pure compound. The key C ring is formed via *L*-proline-catalysed aldol addition, followed by stabilising the aldehyde by reduction with sodium borohydride to give **39**. The stereocentre at C-7 was formed unselectively, therefore the authors had to resort to oxidation of the C-7 hydroxyl to a (+)-podophyllone derivative (not shown) before establishing the stereocentre at C-7 by reduction with *L*-selectride. Overall, (+)-**11** was prepared in 8 steps and 29% yield.



Scheme 8. Zhang's synthesis of (+)-**11** using peudoephedrine-based auxiliary and organocatalytic cyclisation.

Another approach to the formation of the C ring was published in 2017 by Harja *et al.*[67] An intramolecular Heck reaction of bromide **40** is used to form the bond between C-2 and C-7' yielding unsaturated lactone **41** (scheme 9). Diastereoselective hydrogenation is used to establish the *cis* relationship between the groups at C7' and C-8'. Hydrogenation conditions were optimized to enable remote stereocontrol by the existing centre at C-8 in **41**. The authors of this study also addressed the syntheses of several diastereomers of **11** by a unified approach, with overall yields above 27%. Unfortunately, the early steps of the sequence (not shown) required rather expensive starting materials *D*-proline and methyl 4-oxobutanoate.



Scheme 9. Harja's synthesis of (–)-**11** by diastereoselective hydrogenation.

A conceptually unique approach was published by Peng *et al.* in 2018,[68] who used an Evans-type Auxiliary to direct the conjugate addition of aryl lithium, and a Ni-catalzed double reductive coupling to establish ring C. Many other approaches were published, most recent rewiews on on total synthesis of podophyllotoxin-like 2,7'-cyclolignans were published by Peng *et al.* [31] and Thomson *et al.*[32] Despite the immense effort invested, the problem of sourcing (–)-podophyllotoxin, epipodophyllotoxin and 4'-deoxypodophyllotoxin remains without a sustainable solution. In order to become widely accepted, such solutions must address all of the following requirements: be economic in terms of step count and the cost of inputs, lead to high optical purity of products and should avoid difficult chromatographic separations, especially of diastereomeric mixtures.

1.4. Stereoselective coupling of phenoxyl radicals

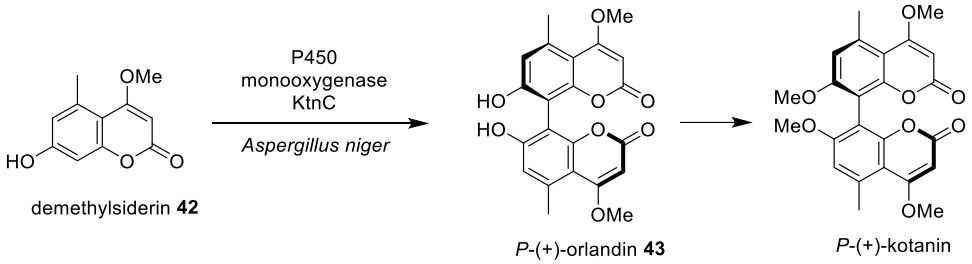
1.4.1. Stereoselective coupling by laccases and monooxygenases

The highly regio- and enantioselective oxidative dimerization of coniferyl alcohol (**8b**) during the biosynthesis of (+)-pinoresinol (**13**) (chapter 1.3.1) was believed to be a unique case among the otherwise nonselective reactions phenoxyl radicals, which were generally assumed to occur freely in solution, unassisted by biomolecules. Undirected radical dimerization is indeed behind the origin of

some racemic natural products.[69] Several classes of enzymes, such as peroxidases and laccases, are able to oxidize phenolic acids, monolignols and other phenols to form free radicals which then detach from the enzyme and undergo radical coupling in a non-stereospecific manner, a process especially important in the production of certain biopolymers like plant lignin and components of insect cuticules.[9,17,20,70] Both regio- and stereoselectivity of the coupling is usually believed to be dictated by the inherent reactivity of the monolignols and results in a mixture of stereo- and regioisomers, with varying point of connection between the monolignol units such as C-8/C-8', C-8/C-5', C-5/O-5' and C-8/O-4'.[70,71]

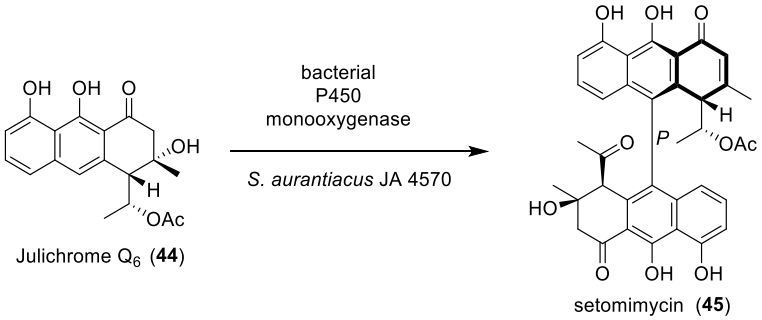
However, the universality of this paradigm has been gradually challenged over the last 25 years by new evidence coming from the discovery of optically enriched atropoisomeric biaryls from fungi, plants and bacteria. Two types of enzymes were shown to catalyse the formation of biaryls with some degree of regio- and stereocontrol during oxidative coupling, these are A) cytochrome P450 homologs and B) laccases.[72] In the following paragraphs, examples of optically active products arising from phenol oxidation by systems A) and B) will be given.

A) Cytochromes P450 are a huge family of heme-containing monoexygenases. Fungal monooxygenase KtnC from *Aspergillus niger* was found to catalyse regio- and stereoselective dimerization of the coumarin demethylsiderin (**42**) to give *P*-(+)-orlandin (**43**) (scheme 10),[73] which is then *O*-methylated to yield *P*-(+)-kotanin in >96% ee. The involvement of KtnC in the biosynthesis of **43** was proven by the knockout of the gene for KtnC, which led to shutdown of **43** production as well as to accumulation of **42**. Docking study of **43** with cytochrome P450 KtnC has also been disclosed.[74]



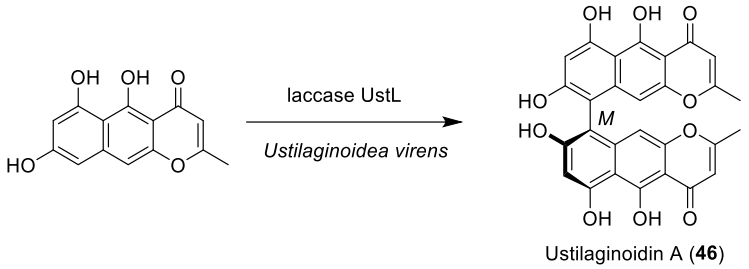
Scheme 10. Oxidative dimerization of demethylsiderin (**42**) catalysed by cytochrome P450 KtnC.

Biosynthetic gene clusters containing bacterial P450 monooxygenases were identified from *Streptomyces afghaniensis* NC 5228 and *S. aurantiacus* JA 4570 using genome analysis and deletion experiments.[75] The nonaketidic precursor is first cyclised to julichrome Q_6 (**44**), which subsequently serves as a precursor for dimeric julichromes as well as setomimycin (**45**). The configuration of **45** was assigned as *P* based on comparison of experimental and calculated VCD spectra. Unfortunately, the authors do not provide the enantiomeric excess of **45**.



Scheme 11. Oxidative dimerization of julichrome Q_6 (**44**) in *Streptomyces aurantiacus* JA 4570 leading to (*P*)-**45**.

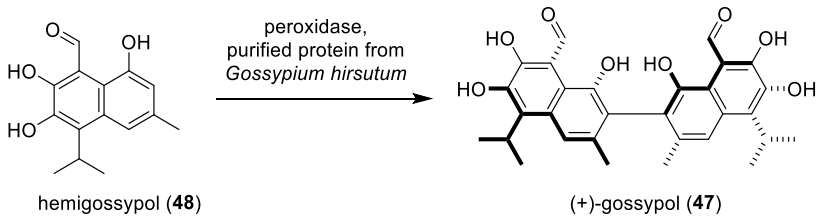
B) Laccases are a group of copper containing oxidases that mediate SET oxidation in bacteria, fungi and plants. A fungal laccase from *Daldinia eschscholzii* IFB-TL01, a fungus growing in the gut of a Chinese mantis *Tenodera aridifolia*, was shown to catalyse a regioselective and atroposelective radical coupling between naphthyl radicals in 67 % ee. The final products of the biosynthetic pathway are polycyclic naphthalene trimers with immunosuppressive activity (−)-dalesconols A-C (for dalesconol A, see figure 1).[76] Similarly, four fungal laccases from *Ustilaginoidea virens* and *Chaetomium arcuatum* catalyse site-selective dimerization of naphthopyrones to give axially chiral dimers. Three of these enzymes are *P*-selective, affording dimers in up to 99% ee, while the selectivity of the fourth enzyme UstL was found to be very sensitive to reaction conditions like concentration and temperature, giving either *P*- or *M*-enriched ustilaginoidin A (**46**) (scheme 12).[77]



Scheme 12. Laccase mediated atroposelective dimerization of naphthopyrone leading to *P*- or *M*-ustilaginoidin A (**46**).

These examples show that Nature is capable of taming the notoriously reactive free radicals to produce scalemic or even enantiopure natural products. In all these cases, the asymmetric induction stems from the chirality of the oxidase itself. However, the most paradigm-shifting discovery came with the description of the so-called dirigent proteins (DIRs). These are proteins that possess no oxidizing activity and instead serve as a template for regio-selective and stereoselective coupling of stabilised radicals generated by a separate enzyme like laccase.

One such enzyme complex was found to be responsible for the production of (+)-gossypol (**47**), found in cottonseeds of moco cotton (*Gossypium hirsutum* var. *marie-galante*). The structure of **47** contains a highly oxidized 2,2-binaphthyl moiety, which is formed by radical dimerization of symmetric hemigossypol (**48**), in turn biosynthetically derived from sesquiterpene (+)-δ-cadinene.[78] It was shown *in vitro*, that racemic **47** can be formed by oxidation of **48** by a peroxidase, laccase (with O_2 or H_2O_2) and even ammonium persulfate (scheme 13). However, when a partially purified protein from cotton flower petals is added, (+)-**47** if formed predominantly in 30% ee. When used alone, the protein doesn't show any activity. Interestingly, some plants of the tribe Gossypieae (Malvaceae), which includes the genus *Gossypium* (cotton), produce predominantly the (+) isomer of **47**, while other produce toxic (–)-**47** instead.[79]



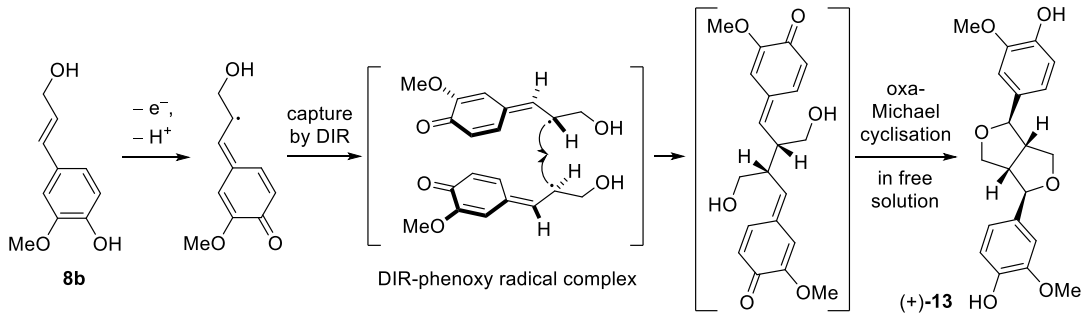
Scheme 13. Oxidative dimerization of **48** leading to **47** catalysed by either peroxidase or DIR/peroxidase complex.

The discovery of DIRs changed also the traditional view on lignin formation. A family of extracellular proteins (AtDIR family) containing so-called dirigent sites, that is monolignol radical binding sites, are now thought to be involved in initiation of lignification.[80,81] This helps explain the prevalence of 8-O-4' linkage in lignin as well as differential localization of monolignols **9a-d**, presumably via migration to their specific initiation sites. The expression of genes containing such dirigent-like sequences is linked to stress response in plants, possibly helping plants to react to stressors such as drought or infection. A fungal *α/β* hydrolase-like protein VdtD from *Paecilomyces variotii*, which lacks the catalytic centre, was shown to produce optically enriched (*P*)-viriditoxin.[82] Analysis of bacterial genomes also revealed dirigent-like domains,[83] which points to a broader role of DIRs or DIR-like proteins in both procaryotic as well as eucaryotic metabolism, which remains largely unexplored.

Despite these recent discoveries, the biosynthesis of pinoresinol (**13**), discussed in chapter 1.3.1, remains the of most well-explored biosynthetic process that involves DIRs. The following chapter describes the structure and activity of DIRs involved in the biosynthesis of **13**, key precursor for the biosynthesis of lignans.

1.4.2. Dirigent proteins and the stereoselective coupling of lignols

The unknown factor responsible for the remarkable selectivity during oxidative coupling of **8b** that leads to optically pure (+)-pinoresinol (**13**, scheme 2) was identified in 1997, when a protein complex responsible for the diastereo- and enantioselectivity of the coupling was isolated from a cell wall preparation from *Forsythia suspensa*, termed dirigent protein (DIR) FiDIR1.[84,85] It was shown not to have any oxidizing capacity on its own, but instead being able to capture two already formed phenoxyl radicals derived from **8b** into its cavity and bring them to react with each other in a highly stereospecific manner (scheme 14). The nature of the original oxidant, which could be different laccases or even inorganic oxidants, did not affect the stereochemical outcome of the coupling reaction, which gives essentially 100% ee.



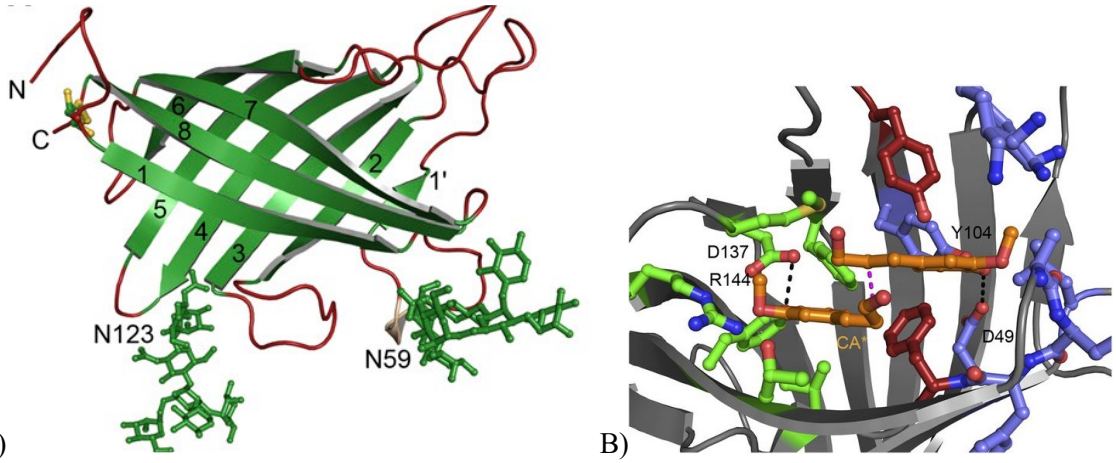
Scheme 14. Coupling of the stabilised phenoxyl radical in the presence of DIR.[84]

Since the initial discovery of FiDIR1, several DIRs were characterized coming for example from western red cedar (*Thuja plicata*),[86] Chinese medicinal plant *Schisandra chinensis* [87] and garden pea *Pisum sativum*.[88] Enantio-complementary lignan anabolism based on (–)-pinoresinol ((–)-**13**), instead of (+)-**13**, which is present in several plant genera, was explained with the discovery of (–)-**13** specific DIR AtDIR6 from the root tissue of *Arabidopsis thaliana*.[89,87] The wide spread of 8,8' lignans

among gymnosperms and angiosperms suggests that many more DIRs, both (+)-**13** and (–)-**13** selective, may be discovered in the future.[85]

All so far discovered DIRs display very high substrate specificity for coniferyl alcohol (**8b**), which corresponds to the known fact that **8b** is the universal precursor of almost all lignans.[85] Unlike oxidation of **8b**, oxidation of other monolignols *in vitro* in the presence of DIR only leads to regio-isomeric mixtures of dimers in racemic form. It was however suggested that similar DIR-like proteins might play a role in the biosynthesis of nonclassical (non 8-8') lignans [80] as well as lignin and other biopolymers.[85]

DIRs are heavily glycosylated extracellular glycoproteins. The X-ray structure of (+)-**13**-forming DIR (PsDRR206) from *Pisum sativum* was revealed in 2015.[90] The crystallographic trimer comprised of three eight-stranded β-barrels. A very similar β-barrel structure of AtDIR6 from *Arabidopsis thaliana* was published in 2016 (figure 8, A).[91] Interestingly, despite structural similarity to PsDRR206, AtDIR6 produces the opposite enantiomer (–)-**13**. The active site, including the aspartic acid residues, is conserved between (+) and (–)-**13**-forming DIRs. A model was proposed in which two radicals derived from **8b** bind to the DIR monomer (figure 8, B).



A) B)

Figure 8. The structure of dirigent protein (DIR) from *Arabidopsis thaliana*. A) Monomer based on eight-stranded β-barrel; B) Computational model of the active site with the two coordinated phenoxyl radicals derived from **8b**. [91]

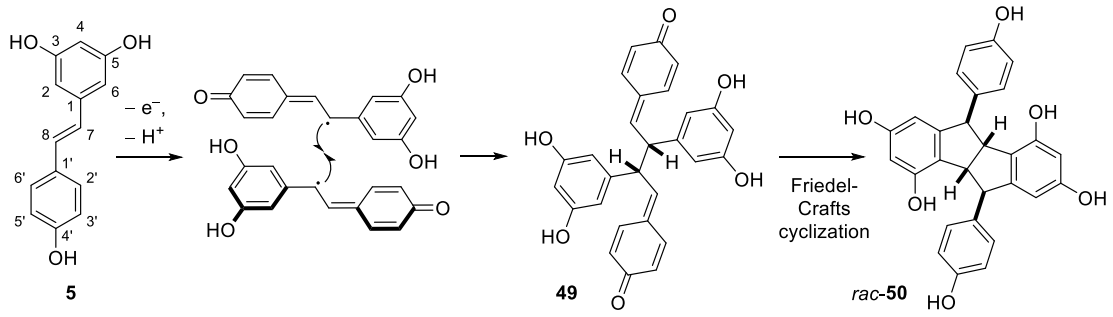
Even after isolation, structure elucidation and functional description of DIRs, details of the mechanism of **8b** dimerization are still being actively investigated. One of the key questions is connected to the stability of the radical and its transport to the DIR. A direct observation of the vinylphenoxyl radical using EPR was published recently.[92] The authors used white light inside the EPR cavity to generate radical from **8b**, which they proved by trapping experiment. In the absence of DIR, only signals of oligomeric side-product were observed. In the presence of AtDIR6 from *Arabidopsis thaliana* they observed the signal of DIR-bound **8b**-derived radical, proving that binding to the protein significantly increases lifetime of the radical, making selective dimerization possible from a kinetic perspective.

1.4.3. Diastereoselective coupling of persistent radicals in free solution

As discussed in the previous chapter, the remarkable regio- and stereoselectivity of pinoresinol (**13**) formation stems entirely from the involvement of DIR. However, there is some

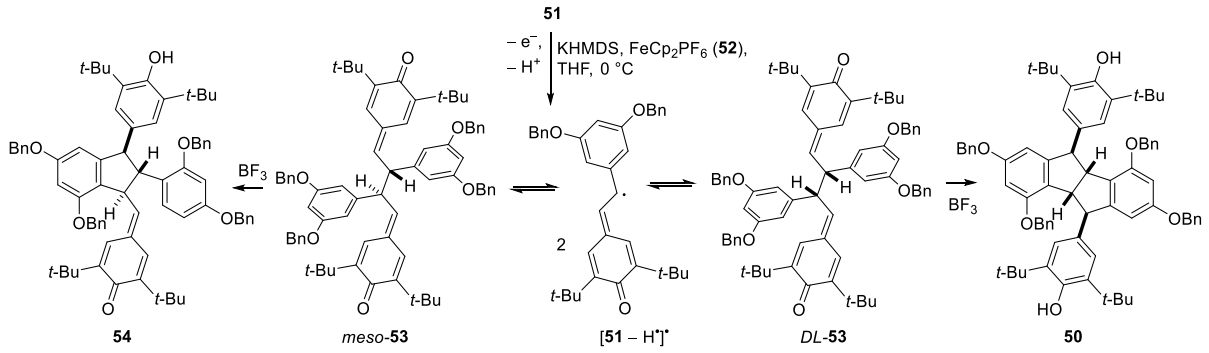
evidence that non-templated coupling of similar stabilised phenoxyl radicals can also sometimes occur in free solution with some degree of regio- and diastereoselectivity but giving racemic coupling products.

Such coupling is believed to play a role in the biosynthesis of stilbene oligomers like caraphenol B (figure 1 in chapter 1.1) and ampelopsin (figure 2). The dimerization of resveratrol (**5**) via 8-8' radical coupling (scheme 15) gives racemic intermediate **49** along with the other possible plane-symmetric diastereomer (not shown). Spontaneous double Friedel-Crafts cyclisation of the C_2-symmetric racemic quinone methide **49** forms the polycyclic dimer pallidol (**50**) via 8-8' coupling that resembles lignan biosynthesis (compare scheme 14, chapter 1.4.2).[9,93] Interestingly, also the relative configuration of **50** mirrors that of pinoresinol (**13**).



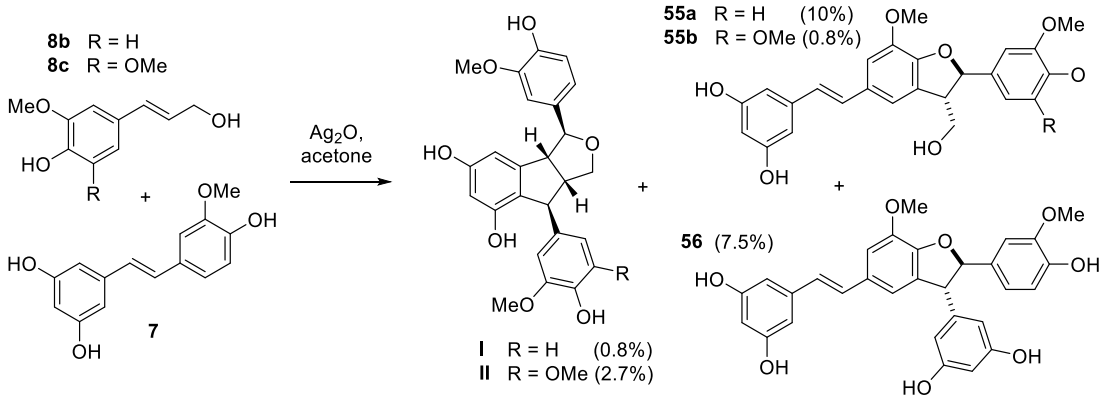
Scheme 15. Oxidative dimerization of resveratrol (**5**) leading to racemic pallidol (**50**).[9,93]

While the oxidative dimerization of **5** in free solution displayed little regioisomeric or stereochemical preference, its derivative containing blocking *tert*-butyl groups at C-3' and C-5' was shown to undergo a highly regioselective dimerization through the C-8 atom (not shown).[94] Based on this finding, the groups of Pratt and Stephenson developed an elegant total synthesis of **50** based on oxidation of protected resveratrol **51** (scheme 16).[95] Using KHMDS to deprotonate phenol **51** and ferrocenium hexafluorophosphate ($FeCp_2PF_6$, **52**) as a single electron transfer (SET) oxidant, a roughly equimolar mixture of diastereomeric intermediates **53** was formed. After addition of BF_3 etherate, *meso*-**53** cyclised to protected precursor of quadrangularin A (**54**) while *DL*-**53** underwent a double cyclisation to give pallidol (**50**).[96] Remarkably, the dimerization was later shown to be reversible, as the mixture of diastereomeric quinone methides *meso/DL*-**53** could be isomerized to **54** in 93% yield. The isomerization was shown to proceed through homolytic dissociation to give back the highly delocalized persistent radicals derived from **51**.



Scheme 16. Reversible regioselective coupling of persistent radical [**51**–H]$^{\cdot}$ giving protected quadrangularin A (**54**) and protected pallidol (**50**).[95,96]

Oxidative radical cross-coupling of isorhapontigenin (**7**) and two monolignols **8b** and **8c** mediated by Ag_2O was shown to proceed with little regioselectivity, giving mostly oxygen-bridged phenols **55a**, **55b** and **56** (scheme 17).[97] Minute quantities of polycyclic products gnetifolin F (**I**) and lehmbachol D (**II**) were also isolated. The authors had access to natural samples of **I** and **II** and could therefore verify their identity. Despite the low yields of **II** and **II** (0.8%, 2.7% resp.), it is interesting that the natural diastereomer was formed.



Scheme 17. Non-selective oxidative cross-coupling of stilbene- and monolignol-derived radicals.[97]

1.5. Non-classical lignans - furoindane stilbenolignans (FIS)

Furoindane stilbenolignans (FIS) are a little-known group of hybrid polyphenols produced by land plants, structurally related to furofuran lignans like **9g** (chapter 1.2, figure 3) and stilbene dimers like **50** (chapter 1.4.3). They are presumably formed by mixed oxidative coupling of two persistent phenoxyl radicals, one formed by oxidation a monolignol, the other by similar oxidation of a stilbene (see above, scheme **17**).[97] All known FISs therefore trace their origin to either coniferyl alcohol (**8b**) or sinapyl alcohol (**8c**) and to stilbenes resveratrol (**5**), isorhapontigenin (**7**) and piceatannol (**6**) (chapter 1.1, figure 2). The exact mechanism of their biosynthesis is unknown, but it is assumed to be similar to the biosynthesis of 8-8' lignans (*e.g.* furofuranes **9g**) and indanoindane stilbene dimers like **50**. At the time of writing, six members of this group have been isolated (figure 9).

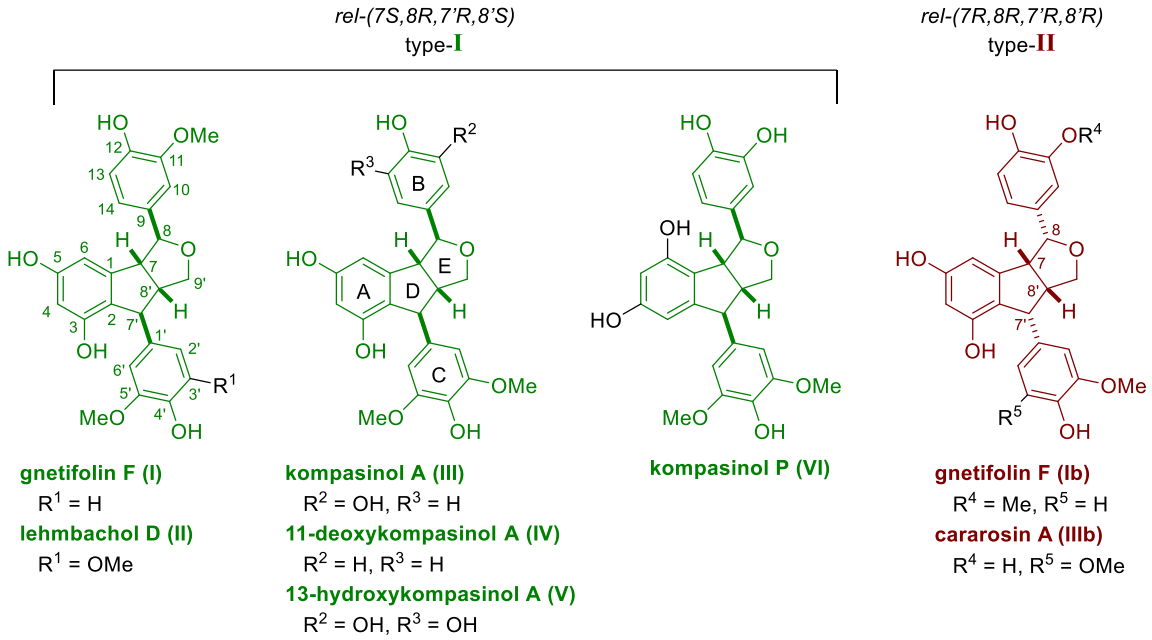


Figure 9. Structures of all known FISs as reported in the original isolation reports. Type-I: gnetifolin F (**I**), lehmbachol D (**II**), kompasinol A (**III**), 11-deoxykompasinol A (**IV**), 13-hydroxykompasinol A (**V**), kompasinol P (**VI**); Type-II: cararosin A (**IIIb**); the originally proposed structure of *rel*-(7*S*,8*R*,7'*R*,8'*S*)-gnetifolin F (**Ib**).

Gnetifolin F (**I**) was isolated in racemic form from four different species of the genus *Gnetum* and from *Pouzolzia sanguinea*,[97-101] Racemic lehmbachol D (**II**) was obtained from *Gnetum cleistostachyum*,[97] while optically active sample of (+)-**II** was obtained from *Salacia lehmbachii*.[102] First isolated from *Maackia amurensis* and therefore originally named maackoline,[103] kompasinol A (**III**) was subsequently isolated under the new name from the genera *Maackia*, *Kompassia*, *Caragana*, *Syagrus* and *Smilax*.[104-109] In all cases, **III** was obtained in racemic form. Optically active (–)-11-deoxykompasinol A (**IV**) was isolated from *Orychophragmus violaceus*.[110] Racemic 13-hydroxy kompasinol A (**V**) was found together with **III** in *Syagrus romanzoffiana*.[106] The last congener to be discovered so far is racemic kompasinol P (**VI**) from *Caragana stenophylla*.[109] All FISs mentioned so far, that is compounds **I-VI**, share the same relative configuration *rel*-(7*S*,8*R*,7'*R*,8'*S*), for the purposes of this discussion termed type-I.

In contrast to that, cararosin A (**IIIb**), isolated from two members of the genus *Caragana* [111,112] was assigned *rel*-(7*R*,8*R*,7'*R*,8'*R*), here referred to as type-II. However, comparison of its NMR spectra recorded in DMSO-*d6* [111] with the spectra of kompasinol A (**III**) taken in methanol-*d4* and acetone-*d6* [103,104,106,107] strongly suggest that **III3b** and **III** are an identical compound. Similarly, when first isolated, gnetifolin F (**I**) was assigned as *rel*-(7*R*,8*R*,7'*R*,8'*R*), type II (**Ib**),[98,100] based on NOE difference spectrum obtained from the more soluble pentaacetate of **Ib**. The characteristic interaction used were H-7/ H-8 and H-7'/H-8'. Authors of this study also obtained single crystal X-ray data on **Ib**, which contradict their conclusions about relative configuration, however for unknown reasons did not resolve the discrepancy. Later, based on the NOE study of the free phenol, the relative configuration was reassigned as *rel*-(7*S*,8*R*,7'*R*,8'*S*), type-I.[99] The identity of the original sample of **Ib**, studied as its pentaacetate, and later obtained samples of **I** from other plants have not been proven. It should be noted that in cyclopentanes, ^{1}H-^{1}H coupling constants as well as through-space interactions are sometimes difficult to predict and interpret. In structure type-I, NOE interaction between 7-H(α) and 8-H(β) and between 7'-H(β) and 8'-H(α) are seen even though the respective

hydrogens are *trans*-oriented, therefore interaction between 7-H and 6'-H should be used instead.[113] Based on these considerations it seems likely, that all natural FISs share type-I configuration. All isolation reports including available data regarding relative configuration and optical activity of FIS are summarized in table 1.

Table 1. Isolated natural furoindane stilbenolignans reported up to 2022, in chronological order.

Year	Compound [Ref.]	Isolated from	Family	[a]	$[\alpha]_D$ (solvent)
1991	**I** [98]	*Gnetum parvifolium*	Gnetaceae	II [b),c)]	0
1995	**III** [103]	*Maackia amurensis*	Fabaceae	I, [b)]	0
1996	**III** [113]	*Koompassia malaccensis*	Fabaceae	I [b)]	0 [d)]
1997	**II** [102]	*Salacia lehmbachii*	Celastraceae	n.d.	+25.1 (MeOH)
2003	**IIIb** [111]	*Caragana rosea*	Fabaceae	II [b)]	–3.7 (acetone)
2003	**I** [99]	*Gnetum klossi*	Gnetaceae	I [b)]	0 (MeOH)
2005	**III** [105]	*Caragana tibetica*	Fabaceae	I	n.d.
2006	**I** [97]	*Gnetum cleistostachyum*	Gnetaceae	I	n.d.
2006	**II** [97]	*Gnetum cleistostachyum*	Gnetaceae	I [b)]	n.d.
2008	**III** [106]	*Syagrus romanzoffiana*	Arecaceae	I [b)]	0
2008	**V** [106]	*Syagrus romanzoffiana*	Arecaceae	I [b)]	0 [e)]
2013	**III** [107]	*Smilax glabra*	Smilacaceae	I	n.d.
2017	**IIIb** [112]	*Caragana changduensis*	Fabaceae	n.d.	n.d.
2019	**I** [100]	*Gnetum latifolium*	Gnetaceae	II	n.d.
2020	**I** [101]	*Pouzolzia sanguinea*	Urticaceae	I	n.d.
2021	**III** [108]	*Caragana stenophylla*	Fabaceae	I	n.d.
2021	**III** [109]	*Caragana stenophylla*	Fabaceae	I	+4.0 (MeOH) [d)]
2021	**VI** [109]	*Caragana stenophylla*	Fabaceae	I [b)]	+5.0 (MeOH) [d)]
2022	**IV** [110]	*Orychophragmus violaceus*	Brassicaceae	I [b)]	–58.6 (MeOH) [e)]

[a)] Relative configuration (type-I: *rel*-(7*S*,8*R*,7'*R*,8'*S*), type-II: rel-(7*R*,8*R*,7'*R*,8'*R*)). [b)] Assigned by NOE. [c)] X-ray structure available. [d)] Assessed racemic by HPLC. [e)] Optical activity/inactivity confirmed by CD.

FISs are widely distributed, spanning 7 families of seed-bearing plants (spermatophytes) including both gymnosperms and angiosperms. These are Gnetaceae (tropical trees and lianas); Fabaceae (legumes); Celastraceae (tropical vines and shrubs); Arecaceae (commonly palms); Smilacaceae (tropical and subtropical herbs and wines); Urticaceae (nettles); and Brassicaceae (crucifers). This wide distribution, combined with their mostly racemic form, suggests that some FISs may be formed nonenzymatically by coupling of free radicals derived oxidatively from stilbenes and monolignols.[95,96] This may occur either in the living or dead cells of stilbene-producing plants, or as an artefact of extraction, purification and storage of plant materials.[114] Inorganic oxidants, potentially including molecular oxygen in the presence of transition metal ions (Fe, Cu), may be responsible for nonselective coupling of phenols (chapter 1.4.3, scheme 17).[97]

In contrast to that, lehmbachod D (**II**) [102] and 11-deoxykompasinol A (**IV**) [110] were found to be optically active, with values of $[\alpha]_D$ +25.1 (c 0.86, MeOH) and –58.6 (c 0.1, MeOH), respectively. This was further corroborated by comparison of their experimental and calculated ECD spectra. This strongly suggests that their biosynthesis involves yet undiscovered enzymes or dirigent proteins

(chapter, 1.4.2).[84] It remains however unclear whether the found specific rotation values for both natural products represent those of individual single enantiomers or those of an enriched mixture of both enantiomers. HPLC separation of the enantiomers from racemic natural kompasinol A (**III**) [109] provided samples with significantly higher values of $[\alpha]_D$ +103.6 and –135.5 (c 0.1, MeOH).

1.5.1. Biological activity of FIS

Due to the limited availability of natural FIS, only little bioactivity data have been reported (table 2). Besides antioxidant activity [105] that is common in natural and synthetic polyphenols, anti-inflammatory activity has been reported for **I** and **III** [97,100,108] and antidiabetic activity via inhibition of α-glucosidase type IV for **III** and **V**.[106]

Table 2. Reported biological activities of FIS.

Compound	Activity
I [97]	**Anti-inflammatory**: moderate inhibition of TNF-α production by murine peritoneal macrophages, IC_{50} = 9.2 µM.
I [100]	**Anti-inflammatory:** neuroinflammation reduction, suppresses the upregulation of NO release by $A\beta_{1\text{-}42}$ (amyloid $beta_{1\text{-}42}$) transfection in BV2- cells (microglial cells).
I [101]	**Cytotoxicity vs. CAL27**: 73.0 ± 1.0% viability at 30 µM, human oral adenosquamous carcinoma cells. Weak activity.
I [101]	**Cytotoxicity vs. MDA-MB-231**: 78.8 ± 0.9% viability at 30 µM, human breast cancer cells. Weak activity.
II [97]	**Anti-inflammatory**: moderate inhibition of TNF-α production by murine peritoneal macrophages, IC_{50} = 11.0 µM.
III [105]	**Antioxidant activity**: *in vitro* superoxide anion scavenging.
III [108]	**Anti-inflammatory:** rheumatoid arthritis, inhibition of NO production in lipopolysaccharide (LPS)-stimulated murine macrophage RAW 264.7 cells, IC_{50} = 68.54 ± 0.68 µM (N-nitro-*L*-arginine methyl ester hydrochloride pos. control 41.13±2.35 µM).
III [109]	**No cytotoxicity**: against RAW 264.7 cells.
III [106]	**Antidiabetic**: α-glucosidase type IV inhibition IC50 = 11.2 µM (acarbose control 40 nM), reduction of postprandial blood glucose level by 10.2% at 10 mg/kg in Wistar rats (sucrose challenge).
IIIb [111]	**No anti-HIV** activity *in vitro.*
IV [110]	**Cytotoxicity vs. Hela**: IC_{50} = 9.43±0.62 µM (Cisplatin pos. control 11.53±1.07 µM), human cervical cancer cell.
IV [110]	**Cytotoxicity vs. HepG2**: IC_{50} = 18.23±1.31 µM (Cisplatin pos. control 14.81±0.92 µM), human liver cancer cell.
V [106]	**Antidiabetic**: α-glucosidase type IV inhibition IC50 = 6.5 µM (acarbose control 40 nM).
VI [109]	**No anti-inflammatory**: activity: inhibition of NO production in LPS-stimulated RAW 264.7 cells. **No cytotoxicity** against RAW 264.7 cells.

Compounds **I** and **IV** were found to be cytotoxic.[101,110] This fact is not surprising, because FISs are derived from natural oxygenated stilbenes and resemble to some degree the highly cytotoxic alkaloid colchicine (**57**) and stilbenoid combretastatins (figuree 10).[5,115,116] The fixed dihedral angle between the B and C rings in on the FIS core mimics the three-dimensional structure of the antitumor *cis*-stilbene combretastatin A4 as well as many synthetic colchicine-binding site inhibitors.[117]

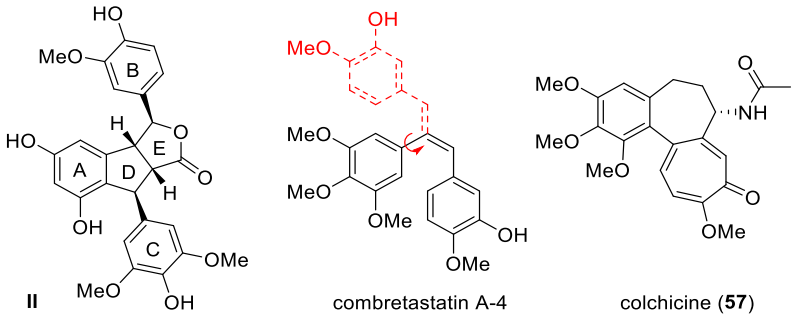


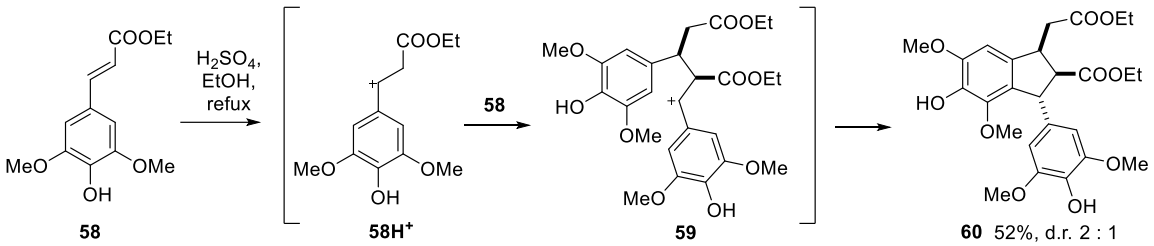
Figure 10. Comparison of the structure of lehmbachol D (II) with cytotoxic combretastatin A4 and colchicine (57).

1.6. Synthetic approaches to arylindanes

Unlike **11** and other aryltetralin cyclolignans, towards which substantial synthetic effort was directed (chapter 1.3.3),[118] very little has been published on the synthesis of FISs. No selective total synthesis has been achieved so far. The isolation of racemic **I** and **II** from mixtures resulting from unselective oxidation of monolignols **8b**, **8c** and stilbene **7** formally represents their first chemical synthesis (scheme 17, chapter 1.4.3).[97] However, the yields were very low, because in the absence of a directing factor like DIR, such oxidative cross-coupling is generally not regioselective.

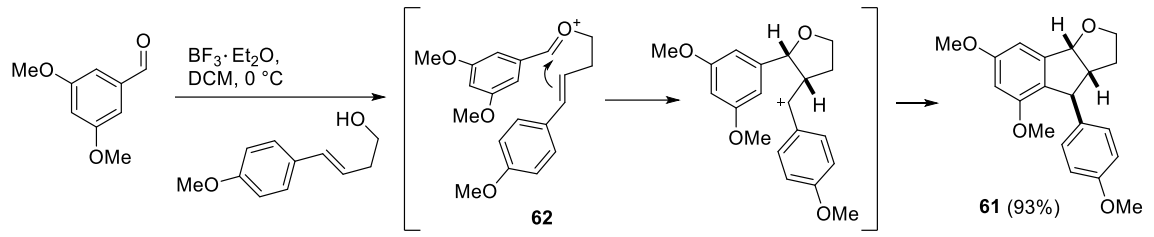
Many approaches were developed for the synthesis of medicinally relevant aryl-indanes and aryl-indane-based natural products, the topic has been recently reviewed.[119-121] Even though a many different reaction types have been utilized, including the Nazarov cyclisation, aryl C-H activation, radical and cationic rearrangements, organocatalytic Stetter reaction and even alkyne cyclotrimerization, the strategies most relevant to FIS can be categorized into four groups, **A**) Friedel-Crafts acylation, alkylations and related cationic cyclisations, **B**) Michael-like additions, **C**) transition metal-catalysed cyclisations and **D**) nucleophilic *5-exo-tet* opening of epoxides and halonium ions.

A) An illustrative example of the use of Friedel-Crafts alkylations, that relies solely on cationic processes, is the direct dimerization of ferulic and sinapic (**58**) esters in acidic ethanol (scheme 18).[122] Unlike the previously discussed 8-8'-selective radical dimerization, the attack of cation **58H**$^+$ on the neutral form of **58** leads to a rarer 8-7' connection. The intermediate **59** is then ideally poised for an intramolecular Friedel-Crafts *5-exo* cyclisation, creating a new 2-7' bond. The synthesis is only applicable to ferulic and sinapic esters, as it demands highly electron rich aromatic rings. Interestingly, the two stereocentres at C-8 and C-7' are formed in a 2:1 *anti/syn* orientation, therefore the configuration of the major product **60** resembles FIS.



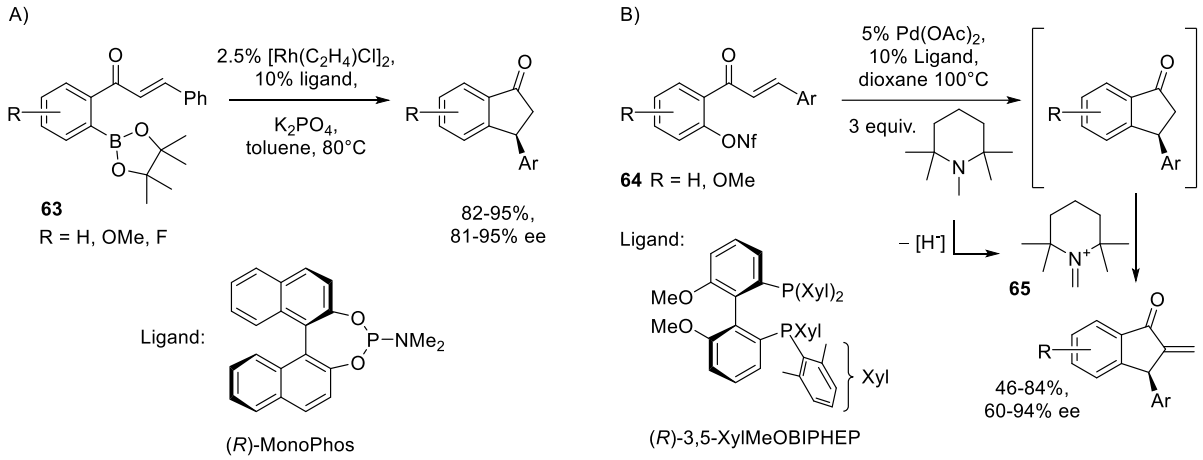
Scheme 18. Acid catalysed dimerization of ethyl sinapate (**58**).

The importance of benzylic stabilisation of carbocations in acid mediated annulations of lignol-like precursors is further demonstrated by the synthesis of arylfuroindanes **61**, isomeric to the natural FISs (scheme 19).[123] The high stabilisation of intermediate **62** switches cyclisation mode during the Prins-like cyclisation from the more common *6-endo* mode to *5-exo* mode, yielding indane X61X with a remarkable degree of stereoselectivity.



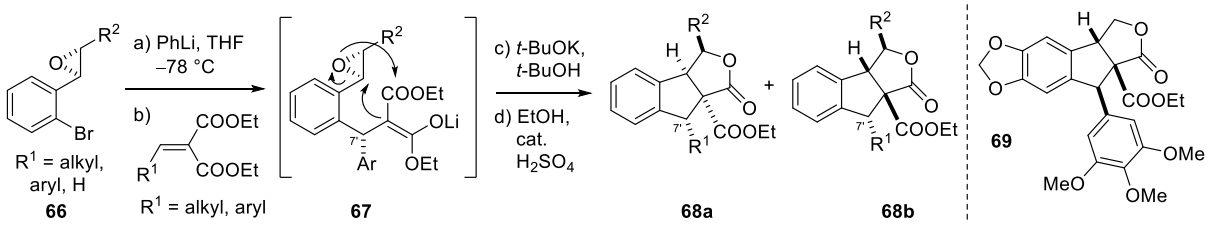
Scheme 19. Prins-like acid catalysed annulation of homocinnamyl alcohols.

B and **C)** While very straightforward and most ubiquitous, cationic cyclisation and annulation methods are rarely enantioselective. This is partly due to the very low kinetic barriers of cationic processes, which make little space for stereoinduction by catalysis. More stable anionic and organometallic intermediates employed in conjugate addition and organometallic coupling reactions are generally more suitable for asymmetric induction. Various variants of Michael addition have been used to form the indane cyclopentane ring stereoselectively, including phase transfer catalysis and the use of the Ellman auxiliary.[119] However, a particularly interesting example of rhodium-catalysed intramolecular conjugate addition of **63** reported by Xu *et al*. (scheme 20, A) [124] lends itself for comparison with an older Heck-like reductive cyclisation of **64** developed by the Buchwald group (scheme 20, B).[125] Both methods have a similar substrate scope and lead to the same type of product. However, the method of Xu using (*R*)-MonoPhos ligand is superior in terms of asymmetric induction to the method of Buchwald, which relies on (*R*)-3,5-XylMeOBIPHEP as ligand for palladium. The Pd-catalysed reductive coupling tolerates various sacrificial amines as formal hydride donors, which allows in situ methylenation of the resulting indanones by iminium salt **65**, derived from 1,2,2,6,6-pentamethylpiperidine (scheme 20, B).



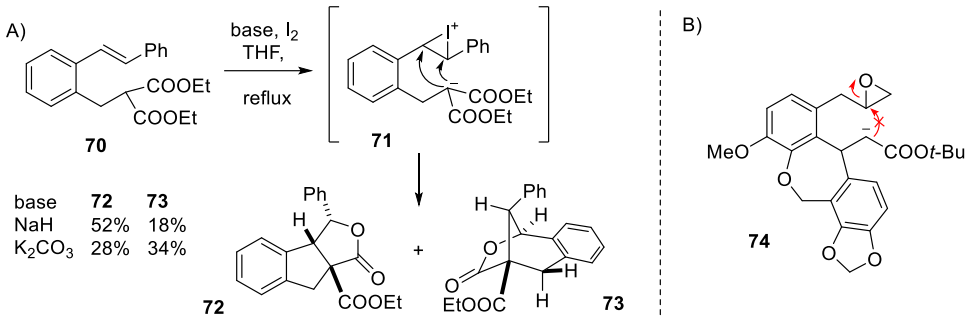
Scheme 20. A) Intamolecular Rh-catalysed conjugate addition by Xu *et al*.;[124] B) Reductive cyclisation of nonaflate by Buchwald *et al*.[125]

D) The most relevant strategy for the synthesis of arylindanes that leads directly to the partial FIS-skeleton is based on nucleophilic *5-exo-tet* opening of epoxides and halonium ions. In an attempt to access the aryltetralin core of podophyllotoxin (**11**), the Florio group developed lithiation of brominated epoxystyrenes and epoxystilbenes **66** (scheme 21).[126] The resulting chelated internally stabilised lithium nucleophile was then added to various ylidene malonates resulting in a double annulation via conjugate addition to give **67**, subsequent nucleophilic epoxide opening and lactonization. Two diastereomers of product **68a** and **68b**, epimeric at C-7', were reported. It should be noted that the structural assignment of **68** relied on analogy with other products in the series and was not independently confirmed by other data (see chapter 4.1.4).



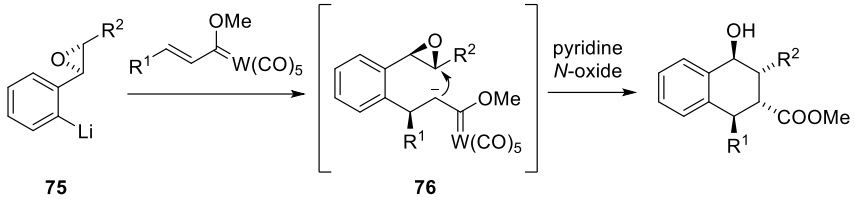
Scheme 21. Double annulation of stilbene oxides as reported by S. Florio *et al.*[126] Structure of indane **69,** obtained instead of podophyllotoxin-like aryltetralin.

Analogous opening of stilbene-derived halonium ion by malonate was reported by Wirth *et al*.[127] Treatment of stilbene **70** with a base and elemental iodine in refluxing THF triggered double cyclisation via iodonium ion **71** giving tricyclic products **72** and **73** (scheme 22, A). Interestingly, compared to the reported exclusive *5-exo-tet* cyclisation of epoxymalonate **67** (scheme 21), both products of *5-exo-tet* (**72**) and *6-exo-tet* (**73**) cyclisation were isolated, with the ratio dependent on the nature of the base used. The facility of *5-exo-tet* and *6-exo-tet* cyclisation contrasts the attempted unsuccessful cyclisation of epoxide **74** (scheme 22, B), explored during the synthesis of (+)-linoxepin (chapter 1.2, figure 4).[34] The cause of this failure may be either the much more basic nature of the less stabilised ester enolate, or geometric constraints imposed by the seven-membered ring.



Scheme 22. A) Cyclisation of iodonium ion leading indane and bridged tetralin.[127] B) Failed *6-exo-tet* cyclisation of epoxide **74**.[34]

The difficult predictability of the cyclisation mode during nucleophilic opening of epoxides is further demonstrated by the *6-exo*-selective cyclisation of Fischer carbene complex-stabilised anion **76** derived from lithiostilbene **75**, reported earlier by Florio *et al.* (scheme 23).[128]



Scheme 23. *6-exo*-selective cyclisation of Fischer carbene complex **76**.[128]

1.7. β-arylation of unsaturated esters

1.7.1. Transition metal catalysed asymmetric conjugate addition

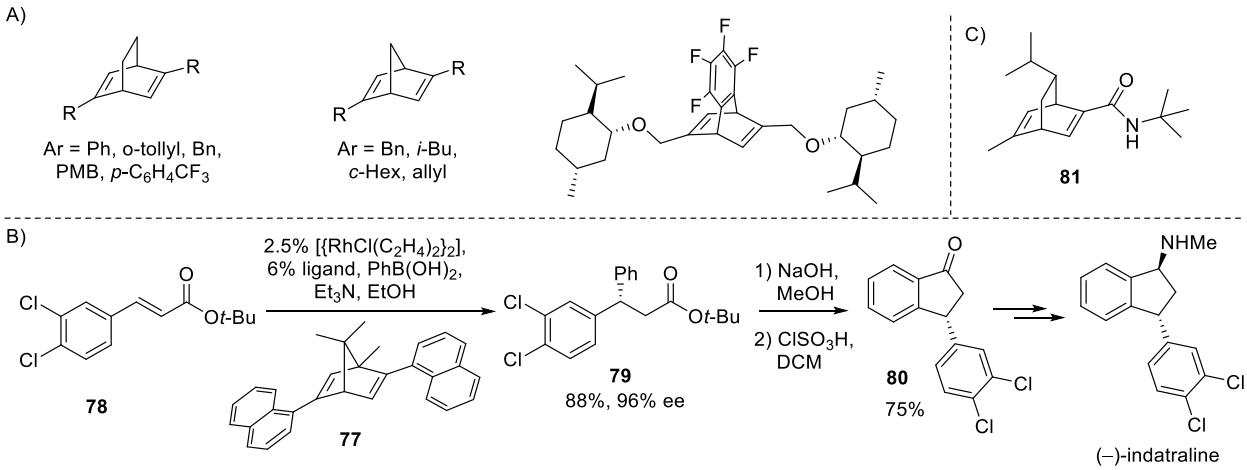
Together with the Michael addition of enolates, asymmetric conjugate addition of organometallic reagents to electron-poor double bonds in α,β-unsaturated ketones, esters, nitriles etc. is one of the most important strategies for the generation of all-carbon stereocentres in complex molecules. It has been used extensively in total synthesis of natural products and the topic has been reviewed several times.[129-132] More specifically, β-branched and especially β-diarylated esters are most commonly accessed by conjugate addition of arylmetals and arylborons to α,β-unsaturated esters, e.g. cinnamates, ylidenemalonates and 2-cyanoacetates. Aside from the more rarely used chiral auxiliary group approach, the two principal ways to enforce asymmetry are transition metal catalysis and addition of stoichiometric chiral directing agent.

Transition metal catalysed conjugate addition relies on the ability of reactive organometallic reagents like Grignard reagents, organolithium, organozinc and organoaluminium compounds to transmetalate transition metals. Less reactive nucleophiles like arylboronic acids and boronates must be activated prior transmetalation, for example by alkoxide bases. Most common among catalytic systems are complexes of low-valent soft metals like Cu, Rh and Pd with phosphine ligands, NHC ligands and chiral dienes.

Popular Cu-phosphine complexes developed by Feringa *et al.*,[132] Alexakis *et al.* [133] and other groups for addition to the more electrophilic unsaturated ketones and thioesters are less effective when used for unsaturated esters, even though they are occasionally used. Rhodium complexes of bidentate

phosphine and especially chiral diene ligands are generally much more versatile,[134,129,135] with norbornadiene and bicyclo[2.2.2]octa-2,5-diene ligands used most prominently (scheme 24, A).[136]

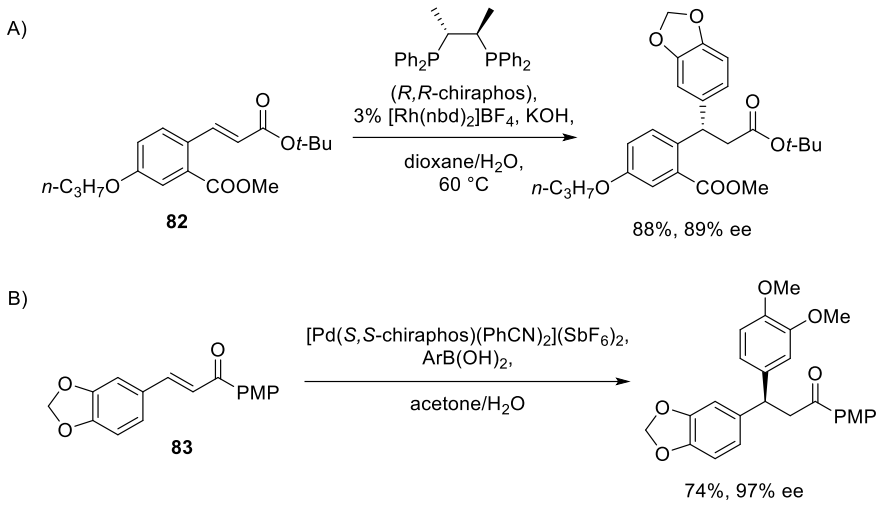
Due to the similar nature of the various methods developed, only selected examples of β-arylation of cinnamates will be discussed in the following section. Rhodium based catalytic system using norbornadiene ligand **77** (scheme 24, B) was developed by Wu *et al.* for arylation of *t*-Bu cinnamates as well as various unsaturated ketones.[137] The utility of the method was demonstrated by the formal synthesis of monoamine transporter inhibitor (–)-indatraline. The synthesis started with conjugate addition of $PhB(OH)_2$ to cinnamate **78**, giving adduct **79** in 88% yield and 96% ee. Saponification, followed by chlorosulfonic acid-mediated Friedel-Crafts cyclisation afforded in 75% yield arylindane **80**, which is a known precursor of (–)-indatraline.



Scheme 24. A) Examples of chiral diene ligands employed in Rh catalysed conjugate addition. B) Rh-catalysed conjugate addition of phenylboronic acid to cinnamate **78** applied in the synthesis of (–)-indatraline. C) Bifunctional bicyclo[2.2.2]hexadiene ligand for homogeneous and semi-heterogeneous catalysis using Rh/Ag nanoparticles.

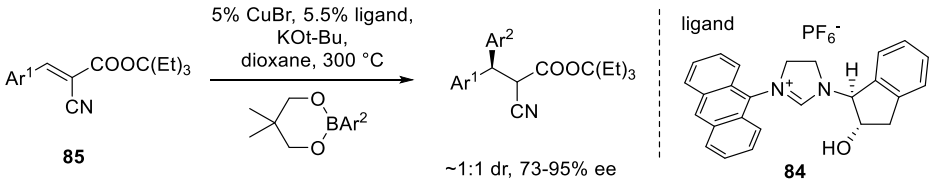
Kobayashi *et al.* reported similar Rh catalysed β-arylation of unsaturated esters and ketones (not shown), based on bifunctional bicyclo[2.2.2]hexadiene ligand **81** (scheme 24, C) in combination with either a soluble Rh complex $[Rh(C_2H_4)_2Cl]_2$ or under heterogeneous conditions using Rh/Ag nanoparticles, stabilised with polystyrene-based copolymer and carbon black.[138] Starting with two equivalents of arylboronic acids, both methods afforded β-arylated cinnamic and crotonic esters in good yields with high levels of asymmetric induction, 95-99% ee for most substrates.

Two catalytic systems for the conjugate addition to cinnamates were developed by the Miyaura group, both based on the bidentate phosphine ligand chiraphos. The first method used a rhodium chiraphos complex (scheme 25, A) and was successfully applied it the synthesis of 1,3-diarylindan-2-caraboxylic acid-derived endothelin A receptor antagonists.[139] The second method, based on palladium complex (scheme 25, B), was employed in the total synthesis of(*R*)-tolterodine, a muscarinic receptor antagonist.[139b,139c] Both methods are efficient at arylation of (masked) electron rich cinnamic esters like **82** and **83**, making them potentially well suited for the synthesis of natural phenolic compounds.



Scheme 25. Enantioselective conjugate addition to electron-rich cinnamate **82** and masked cinnamate **83** catalysed by A) Rh-chiraphos compex and B) Pd-chiraphos complex.

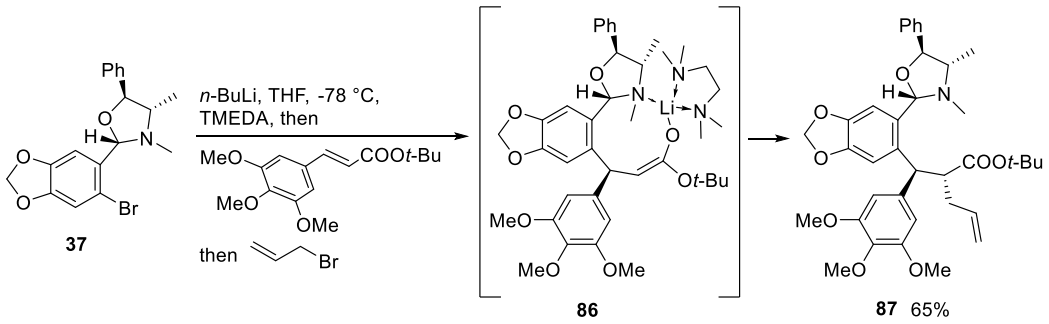
In a rare demonstration of catalytic enantioselective β-arylation of an ylidenemalonic acid derivative, Cu complex with NHC ligand **84** catalysed β-arylation of ylidene-2-cyanoacetates **85** (scheme 26).[140] Despite giving good yields and asymmetric induction, the method is limited to specific substrate type and the products were isolated as diastereomeric mixtures.



Scheme 26. β-arylation of ylidene-2-cyanoacetates **85**.

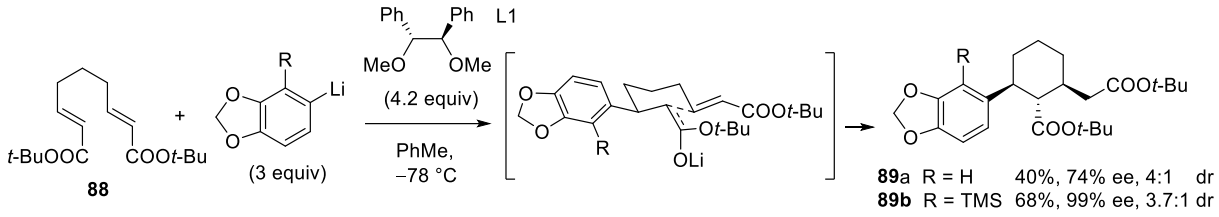
1.7.2. Direct asymmetric conjugate addition of organolithium compounds

The second major method for β-arylation of α,β-unsaturated esters is direct addition of the very reactive aryllithium species to sterically hindered cinnamates in the presence of a chiral Lewis base. The lithium coordinating Lewis-basic chiral element usually comprises of hard bases like oxygen and nitrogen atoms and can be incorporated in the substrate in the form of a chiral auxiliary or added as an external additive. Even though this method received much less attention than catalytic processes, it offers certain advantages, especially the possibility of direct utilization of the product enolate by reaction with electrophiles, instead of simple quenching by protonation. Such a strategy was employed in Zhang's synthesis of podophyllotoxin (scheme 8, chapter 1.3.3).[64] In the first key step, arylbromide **37**, equipped with pseudoephedrine-based chiral group, was lithiated in THF presumably leading to internally coordinated lithium species, which underwent direct conjugate addition to *tert*-butyl 3',4',5'-trimethoxy-cinnamate (scheme 27). The 1,4-selectivity of this addition should be attributed to the bulky *t*-Bu group of the ester. The presumably geometrically well-defined enolate **86** was then stereoselectively allylated with allylbromide to give **87** in 65% yield.



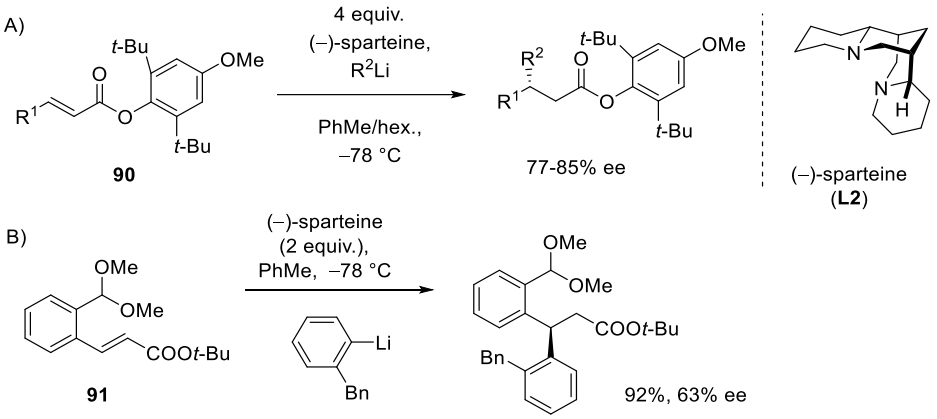
Scheme 27. One-pot conjugate addition/alkylation tactics used in the total synthesis of podophyllotoxin.[64]

Arguably the most versatile external Lewis base for coordination of aryllithiums was developed by the Tomioka group,[141] who used the C_2-symmetric (*S,S*)- or (*R,R*)-dimethylhydrobenzoin (**L1**) for conjugate addition of ArLi to unsaturated aliphatic *tert*-butyl esters. The remarkably simple method was used in the total synthesis of (+)-*trans*-dihydronarciclasine [142] and (+)-β-lycorane (scheme 28).[143,144] Only the noncoordinating solvent toluene and excess of ligand were needed to mediate the initial conjugate addition to **88**, the enolate subsequently underwent further diastereoselective Michael cyclisation to yield **89a** in 40% yield. The addition was not only compatible with *ortho*-substituted ArLi but the chemical yield as well as ee of the product **89b** increased with the addition of bulky substituent TMS to the *ortho* position of ArLi.



Scheme 28. The key step of Tomioka's (+)-β-lycorane synthesis.[143]

(–)-Sparteine-mediated conjugate addition of alkyllithium to severely hindered crotonates **90** has been reported by the Tomioka group (scheme 29, A).[145] Similarly to the Tomioka's diether-mediated addition, large excess of the ligand was needed to attain ee around 80%. In a very similar development, (–)-sparteine (**L2**) has been shown to mediate β-arylation of cinnamates like **91** (scheme 29, B). The yield and ee of β-arylated adducts however varied unpredictably with changing substitution of both nucleophile and electrophile.[146] Several other reports on the use of **L2** in carbolithiations exist.[147,148]



Scheme 29. (–)-Sparteine-mediated conjugate addition of RLi to A) hindered crotonates; B) *tert*-butyl cinnamate derivative.

2. HYPOTHESIS AND RETROSYNTHETIC ANALYSIS

2.1. Bioinspired approach to natural arylindanes and aryltetralins

The carbon atoms that make up the skeleton of stilbenoids, lignans and other polyphenols come from different biosynthetic pathways (chapter 1.1). However, starting with the key desymmetrizing oxidative coupling and further downstream, their chemistry follows common **reactivity patterns** that originate from the highly electron rich nature of the aromatic rings. We hypothesize, that some of these reactivity patterns can be reproduced *in vitro* by linking them to known synthetic transformations and thereby exploiting them in total synthesis of cyclolignans, FISs and other natural phenols.

Pattern 1) *SET oxidation of phenols to form highly delocalized phenoxyl radicals*, *followed by radical coupling to form 8-8' lignol dimers and other similar β-linked (hetero)dimers.* Coupling of free radicals, although possible to arrange in principle (see chapter 1.4.3), is an uncommon reaction type *in vitro* due to the high reactivity of free radicals. They can only form in low concentration which makes their collision in free solution a statistically unlikely event. However, radical addition to double bonds, especially intramolecular, doesn't suffer from this entropic limitation. Therefore, we propose radical cyclisation in *5-exo-trig*, *6-endo-trig* and *6-exo-trig* modes as a suitable substitute for the free radical coupling *in vitro*.

Pattern 2) *Nucleophilic capture of formal benzylic carbenium ions or quinone methides by intramolecular Friedel-Crafts (FCA) reaction and oxa-Michael addition*, *leading to indanes, tetrahydro- and dihydrofurans.* Friedel Crafts alkylation, despite being an important industrial process, is often unsuited for stereoselective synthesis, because of the high reactivity of carbenium ions and their tendency to rearrange. We propose to replace it with a reaction type more suited for exerting control - the conjugate addition to electron poor double bonds, which is often used for fragment union in the synthesis of complex molecules.[129,149] Conjugate addition occurs in a different kinetic regime than FCA (figure11),[150a-c] which combines weakly nucleophilic aromates with extremely electrophilic and short-lived carbenium ions. Instead, conjugate addition combines formally anionic stable reagents like organomagnesium and organolithium compounds with weakly or moderately electrophilic unsaturated esters. Figure 11 correlates nucleophile and electrophile strength in common reactions, FCA and the Michael addition are located in the opposing corners on the main diagonal, which represents the zone of controllable reaction rate.[150a-c]

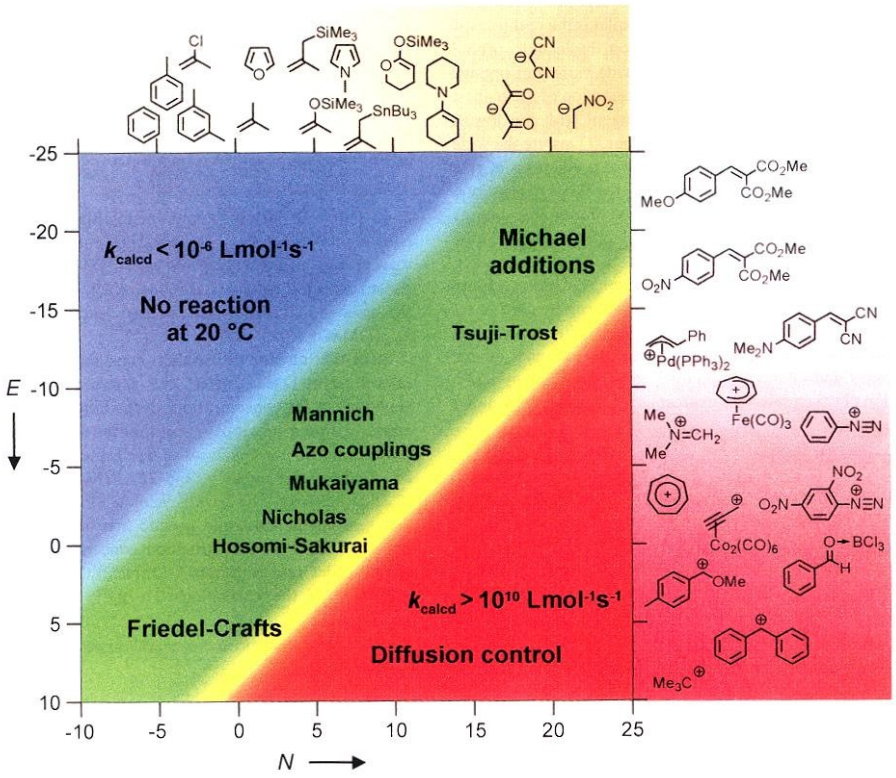
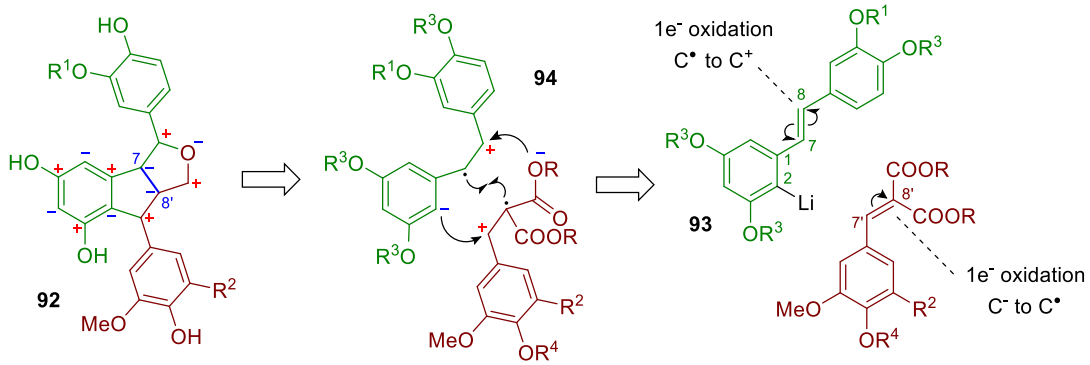


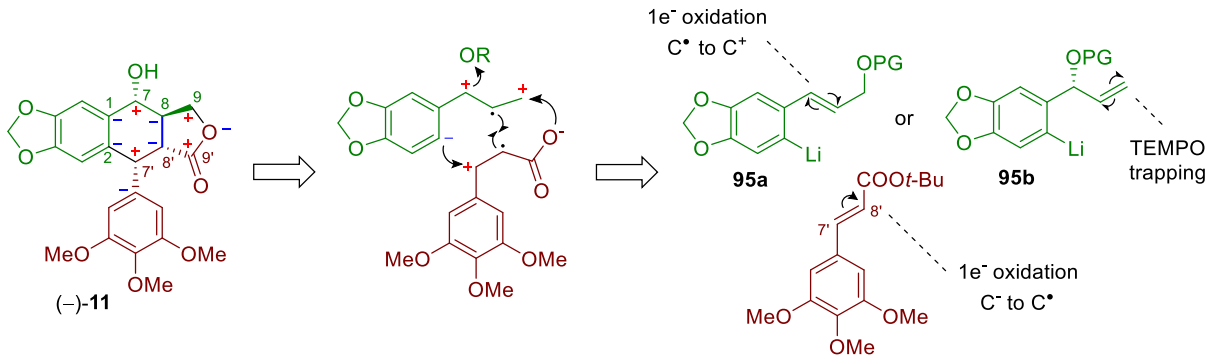
Figure 11. Nucleophilicity/electrophilicity correlation in common rection types.[151d]

Pattern 3) *Oxidation of aromatic rings and of the neighbouring benzylic positions*. Benzylic positions next to electron rich aromatic rings undergo easy oxidation, due to the increased stabilisation of benzylic carbocations. This should facilitate the formation of such cations by SET oxidation of stabilised benzylic radicals, formed by previous radical cyclisation (pattern 1). If such radicals are long-lived enough they could undergo a second SET oxidation leading to cationic lactonisation.

Pattern 4) *Heterolytic lability of benzylic C-O bonds*. The increased stability of benzylic carbocations next to electron-rich aromatic rings makes ether links at these positions sensitive to acid-catalysed opening.[152,153] While this may decrease the stability of the natural products or synthetic intermediates, it may also open an opportunity to correct the configuration on such benzylic centres, if the thermodynamic isomer is desired.

Based on these principles, we propose a general retrosynthesis, applicable to FISs (chapter 1.5) and 2,7′-cyclolignans like podophyllotoxin (**11**) (chapter 1.3). Although not included in this thesis, the strategy should also be applicable to the synthesis of arylindane stilbene dimers (chapter 1.4.3) and furofuran lignans like pinoresinol (**13**) (chapter 1.3.1).





Scheme 30. General retrosynthetic analysis for FISs (top) and (–)-podophyllotoxin (**11**) (bottom), based on inherent reactivity of natural lignols and stilbenes. Nucleophilic atoms marked by (–), electrophilic atoms marked by (+).

Using the so-called alternation rule, also known as the concept of consonant and dissonant rings,[154] each atom of the targets can be assigned natural polarity, annotated in scheme 30 by (+) and (–) signs. The inherent dissonance of five-membered rings in FISs (**92**) can be solved by two consecutive SET oxidation steps, that adjust the oxidation state of atoms C-7 and C-8' from formal anion in **93** to a radical in **94**. The bond between atoms C-2 and C-7' in **92** can be formed by conjugate addition, the second bond by addition of radical at C-8' to C-7 followed by SET oxidation and the third bond between C-8 and the oxygen atom on C-9' can be formed via lactonization of benzylic carbocation at C-8.

Similarly, in **11**, the dissonant relationship between nucleophilic atoms C-8 and C-8' can be solved by to consecutive SET oxidations with an "in-between" radical cyclisation. Therefore, the C-2/C-7' bond is formed by conjugate addition of **95** to *tert*-butyl cinnamate, followed by radical addition of C-8' to C-8. The C-O bonds at C-7 and C-9 can be either carried from the building blocks or formed by a formal oxidation of radical by TEMPO trapping (at C-9 of **95b**) or SET (at C-7 of **95a**). Such bioinspired disconnection respects the natural polarity and reactivity of each atom, and therefore leads to the most rapid decrease in molecular complexity. All starting synthons are derivatives of the natural polyphenol building blocks - stilbenes, cinnamic acids, and monolignols.

2.2. Dirigent protein hypothesis and optical purity of natural FIS

As discussed in chapter 1.5, at least two isolated natural FISs were optically active, namely lehmbachol D (**II**) [102] and 11-deoxykompasinol A (**IV**).[110] In all other cases, in which authors repot specific rotation, the natural products were either racemic, these were: gnetifolin F (**I**),[98,99] kompasinol A (**III**, maackoline) [103,106,113] and 13-hydroxykompasinol A (**IV**) [106] or the value of specific rotation was very low $[\alpha]_D < 5$, these were: kompasinol A,[109] kompasinol P [109] and Cararosin A.[111]

This naturally raises the question regarding the role of enzymes in their biosynthesis. The racemic compounds most likely result from oxidative radical coupling in free solution, either inside or outside of cells. Abiotic formation during drying of plant material or extraction cannot be ruled out,[114] as was demonstrated by the formation of racemic gnetifolin F (**I**) and lehmbachol D (**II**) by simple oxidation of precursor phenols using Ag_2O in acetone [97] (chapter 1.4.3). However, the optically active FISs must be formed by a separate pathway enzymatically, or other source of chirality must exist, for example they may be enantiomerically enriched post-synthetically through preferential degradation of one enantiomer.

Proving the enzymatic origin of some FISs would be of high interest in biology, because to our knowledge, there are no known enzymes capable of catalysing stereoselective cross-coupling of stilbenes with monolignols. The closest analogue of such process is the unique stereoselective dimerization of coniferyl alcohol assisted by dirigent proteins (DIR). Dirigent domains were found also in other extracellular proteins involved in lignification and plant stress response, therefore these proteins would be potential candidates in the search for the chiral factors behind the biosynthesis of optically active FISs.

However, in order to verify that there reported minute quantities of natural optically active FISs were indeed chemically and optically pure, their specific rotation values and ECD spectra should be compared with independently prepared samples of known composition. Total syntheses of selected members of FID family should give access to pure samples of either enantiomer, so that their physicochemical properties can be determined. This would provide additional evidence in favour or against their possible enzymatic origin.

3. AIMS OF THE WORK

Based on the points discussed in the previous chapter, the following aims of the work were formulated:

- To develop new methodology for one-pot annulation via Cu-catalysed conjugate addition/oxidative *5-exo-trig* cyclisation and to explore the potential of a second SET oxidation

- To establish the stereochemical outcome of the double cyclisation by crystallographic or spectroscopic methods or by independent synthesis of defined diastereomers

- To resolve the conflicting assignments of relative configuration of furoindanes by synthesis of a known derivative of kompasinol A (**III**)

- To develop the required methodology for β-arylation of cinnamate-like Michael acceptors by enantioselective conjugate addition of aryllithium compounds

- To implement the enantioselective conjugate addition in combination with oxidative cyclisation in the total synthesis of selected FISs (+)-gnetifolin F (**I**), (+)-11-deoxykompasinol A and (–)-11-deoxykompasinol A (**IV**)

- To establish the chiroptical characteristics of pure enantiomers of **IV** and compare the data to the otically active natural product to confirm its enzymatic origin

- To evaluate the feasibility of the conjugate addition/oxidative *6-exo-trig* cyclisation approach for total synthesis of podophyllotoxin (**11**)

- To explore the conjugate addition/polar cyclisation approach, based on reassignment of a published structure of furoindane retro-**68a**, in total synthesis of podophyllotoxin derivatives

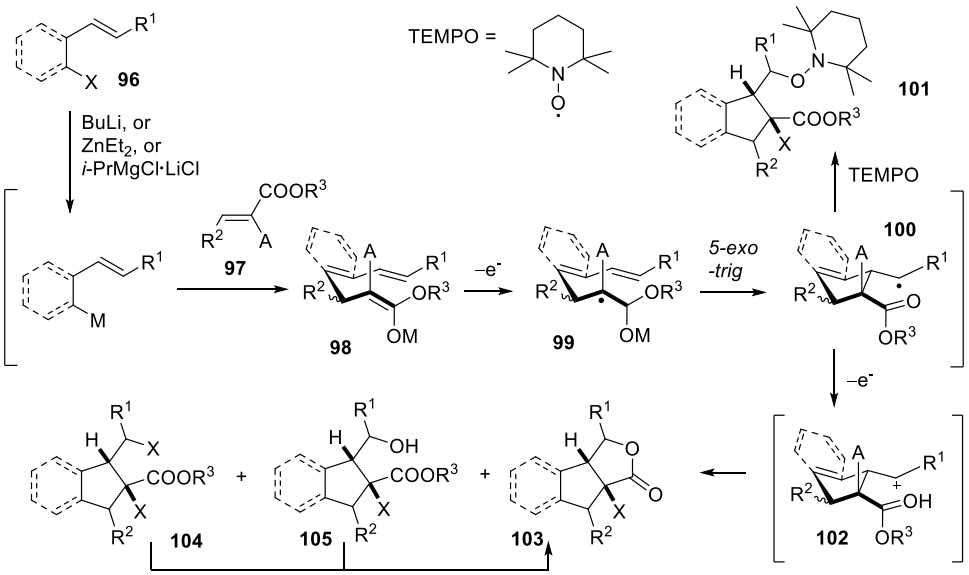
- To exploit the serendipitous discovery of oxidative C-C cleavage of ketone enolates by exploring its potential as a general synthetic method

4. RESULTS AND DISCUSSION

4.1. Part A. Cu-catalysed conjugate addition/oxidative cyclisation

4.1.1. Design of the key annulation combining conjugate addition/oxidation

The first aim of the work is merging of conjugate addition with oxidation of the resulting enolate followed by radical cyclisation into a one-pot operation. The general design of such process is outlined in scheme 31. It starts with metalation of homoallylic fragment **96** that undergoes conjugate addition to Michael acceptor **97**.



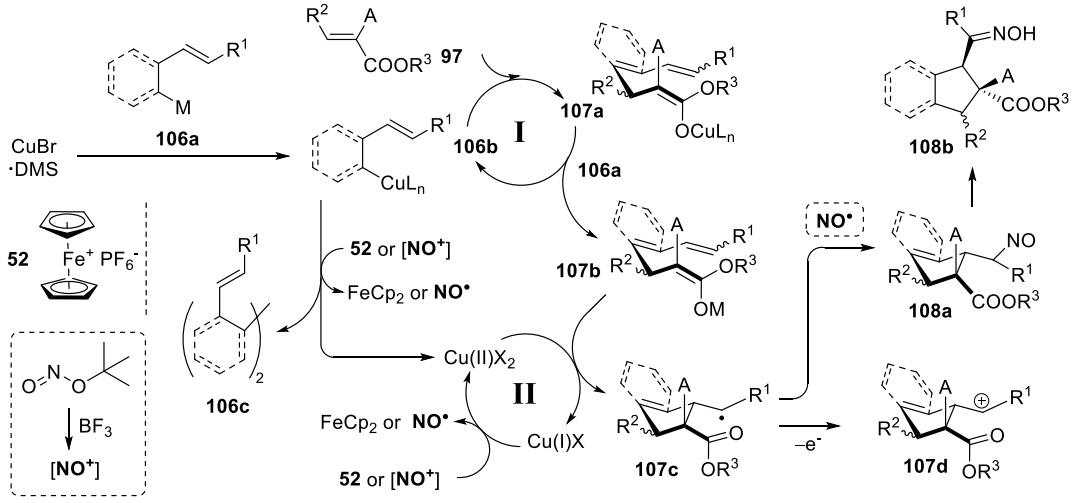
Scheme 31. Design of the key one-pot oxidative annulation to access lactones **103**.

The resulting enolate **98** should be stable under the conditions of the reaction and therefore accumulate. After addition of suitable single-electron oxidant, the enolate is transformed into the electrophilic α-carbonyl radical **99**, which rapidly attacks the pendant double bond in a *5-exo-trig* fashion, resulting in cyclic radical **100**. The fate of this radical should then be governed by the nature of the R^1 substituent and the presence or absence of fast radical traps like TEMPO. For non-stabilising R^1 substituents, TEMPO trapping is the method of choice to stabilise radical **100** [155-157] in the form of adduct **101**, so that hydrogen abstraction from the solvent, radical disproportionation and other undesired reactions can be avoided. For such R^1 substituents, that can sufficiently increase the lifetime of radical **100**, further oxidation to carbenium ion **102** can be envisaged that may lead directly to lactones **103** or to halogenated (**104**) or hydroxylated (**105**) products, which can be lactonized to **103** in a separate step.

The different reactivity of the reactive intermediates in their varying oxidation states imposes several constraints on the design of such one-pot reaction. The solvent needs to be tolerant of the strongly basic organometallic nucleophile, resistant to radical hydrogen abstraction and capable of dissolving oxidant salts. Furthermore, 1,4- over 1,2- selectivity must be enforced during the conjugate addition step, which should only involve catalysts and additives compatible with the follow-up oxidation. The oxidant system must be capable of single electron transfer (SET) oxidation of enolates to radicals, and at the same time it should either allow the coupling of nucleophilic radicals with persistent radicals, or alternatively it should be capable of another SET oxidation of these radicals to the stage of carbenium ion. Last but not least, the initial steps including metalation must proceed with

full conversion and as chemoselectively as possible, so that the following and more challenging cyclisation steps can be optimized without interference.

After reviewing the available literature (chapter 1.7.1), Cu catalysed conjugate addition of Grignard reagents and organolithiums was selected as the method of choice for the first step. In addition to being the most common method that gives metal enolates as products, it promised the possibility for future exploration of chiral ligands like phosphoramidites and Josiphos-type diprosphines. Copper(II) salts are also known to be strong oxidants, capable enolate oxidation.[158,159] This would potentially allow dual catalysis, in which a catalytic amount of Cu would be used for both conjugate addition and oxidation, as depicted in scheme 32.



Scheme 32. The concept of dual catalysis from the point of view of Cu catalyst: Cu catalysed conjugate addition (cycle I), Cu mediated oxidation of enolate **107b** (cycle II). Ferrocenium hexafluorophosphate (**52**) or *t*-BuONO can be envisaged as terminal oxidants.

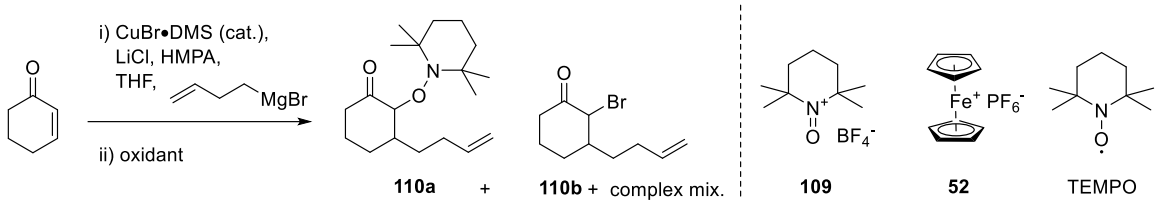
In this scenario, inorganic Cu source like CuBr.DMS is transmetalated with reactive organometal **106a**, which undergoes conjugate addition to **97** in the first catalytic cycle (I) yielding copper enolate **107a**. Exchange of Cu for Mg/Li to enolate **107b** releases Cu(I) catalyst back to the reaction. After addition of oxidant, remaining organocopper species **106a** is oxidized to **106c** and $Cu(II)X_2$ salts, which act as SET oxidant for enolate **107b** in the second cycle (II). Nucleophilic radical **107c** may follow different paths to stabilisation based on substituent R^1, either getting oxidized to carbenium ion **107d** of undergoing radical trapping with persistent radical. The terminal oxidant serves to reoxidize Cu(I) to Cu(II) species in cycle II. For this role ferrocenium hexafluorophosphate (**52**) and *t*-BuONO were selected, due to sufficient oxidation potential and known compatibility with radical reactions.[155-157,160-163] The use of alkyl nitrite in combination with a Lewis acid like BF_3 as the terminal oxidant system would have the additional advantage of generating persistent NO radical (scheme 32, right), which could couple to radical **107c** generating unstable nitroso compound **108a**, that would ultimately stabilise by tautomerization as oxime **108b**.

4.1.2. Initial exploration of in situ oxidative cyclisation

Initial attempts to put this design into practice using various Michael acceptors like cinnamates, crotonates and chalcones together with homoallylic Grignard reagents and alkyllithiums

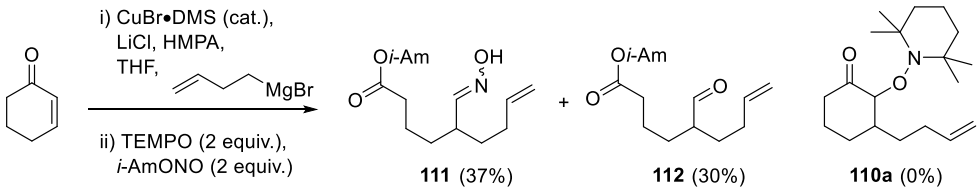
failed, either due to problems with enforcing complete conversion during the conjugate addition, or due to unselective oxidation.

Several oxidant systems, that were previously studies by the Jahn group,[155-157,160,161] were explored. These were 1) **52** in combination with TEMPO, 2) **109** (scheme 33), 3) **109** with catalytic amount of **52**. In most cases, after oxidation of the enolate, cyclisation was pre-empted either by rapid trapping of the α-carbonyl radical by TEMPO or by halogenation. The problem is illustrated on the example of Cu catalysed conjugate addition to cyclohex-2-en-1-one (scheme 33), followed by oxidation by methods 1)-3). The complex product mixtures contained predominantly TEMPO-adduct **110a** and halogenated **110b**, arising presumably from fast atom transfer halogenation of the α-carbonyl radical by Cu(II) bromide species.



Scheme 33. Conjugate addition to cyclohex-2-en-1-one followed attempted by *in situ* oxidative cyclisation.

This problem was ultimately solved by Kapras [157] during the total synthesis of *ent*-progesterone, who avoided the formation of **110b** by excluding Br atoms and found conditions for persistent-radical-effect-mediated thermal cyclisation of **110a**. This method however doesn't lend itself to the desired one-pot annulation. Attempts at using alkyl nitrites with or without BF_3 as the terminal oxidant were unsuccessful. Conjugate addition followed by oxidation with alkyl nitrite (scheme 34) resulted in no cyclisation. To our surprise, the product mixture largely consisted of acyclic aldoxime **111** and aldehyde **112**, likely originating from oxidant-assisted hydrolysis of **111**.[164]

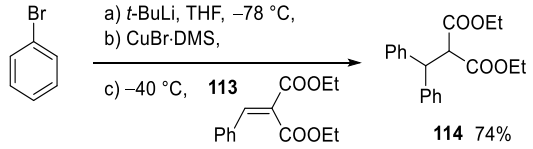


Scheme 34. Conjugate addition coupled with *in situ* enolate oxidation by *i*-AmONO leading to fragmentation.

This unexpected reactivity can be attributed to a direct 2-electron nitrosation of the enolate by the nitrite, followed by nucleophilic addition of alkoxide to the ketone triggering retro-aza-Claisen fragmentation. Further experiments showed that this is a general reaction pathway of nitrite-mediated oxidation of ketone enolates in THF and led to the discovery of synthetically useful C-C cleavage reaction, discussed in detail in chapter 4.5. On the other hand, it excluded the use of alkyl nitrites as terminal oxidants for the radical cyclisation.

Due to the undesired fast quenching of α-carbonyl radicals by TEMPO and the interference of $CuBr_n$ salts (scheme 33), we switched our focus to ylidenemalonates as Michael acceptors. Their increased electrophilicity was expected to improve the efficiency of the conjugate addition step. At the same time, oxidation of their enolates produces more stabilised and more electrophilic 2-malonyl radicals, which should be less easily quenched by TEMPO trapping or halogen transfer. Additionally, the products of such premature quenching may undergo homolysis, therefore group-transfer

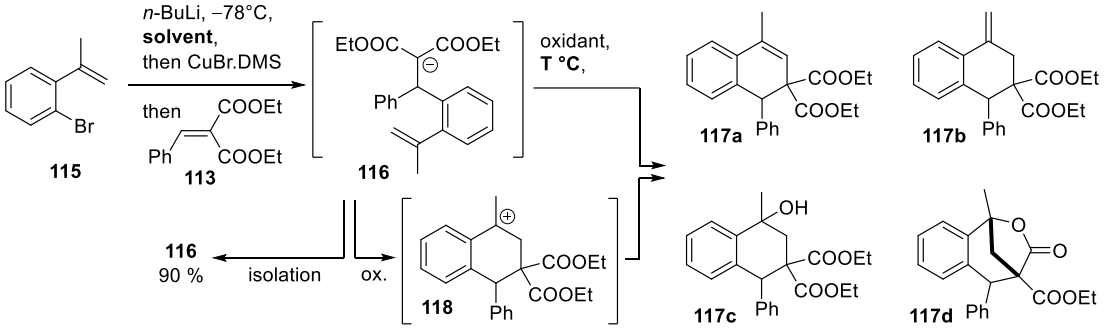
cyclisation may still occur from that stage. To find a suitable solvent and Cu source for the conjugate addition, model benzylidene malonate **113** was arylated using *in situ* generated PhLi in THF in the presence of 0.2 equiv. CuBr·DMS (scheme 35). Fast and fully regioselective addition proceeded at –40 °C, therefore these conditions were selected as the basis for the planned one-pot sequence.



Scheme 35. β-arylation of benzylidene malonate **113**.

The first system to successfully implement the conjugate addition/in-situ oxidation concept was addition of bromostyrene **115** to malonate **113**, followed by oxidation by excess **52** (table 3). First, smooth formation of the Michael adduct **116** was verified by quenching the enolate and isolating **116** in 90% yield. Oxidation of the enolate by **52** in the presence of TEMPO gave a mixture of cyclic products, including inseparable isomeric alkenes **117a** (24%) and **117b** (7%), tertiary alcohol **117c** (13%) and a trace of lactone **117d**. None of the products contained the TEMPO moiety, suggesting that a secondary oxidation of the cyclic benzylic radical took place. Alternatively, **117a** and **117b** may have been formed by TEMPOH elimination, due to the known instability of tertiary TMP-oxy ethers.[165] Oxidation by 2.2 equiv. of **52** (entries 2, 3) in the absence of TEMPO resulted in a very similar product distribution. Interestingly, introduction of O_2 to otherwise identical experiment (entry 4) still led to the formation of alkenes **117a**, **117b**, however, instead of alcohol **117c**, lactone **117d** was obtained in 22% yield.

Table 3. One-pot conjugate addition/*in-situ* oxidative cyclisation.



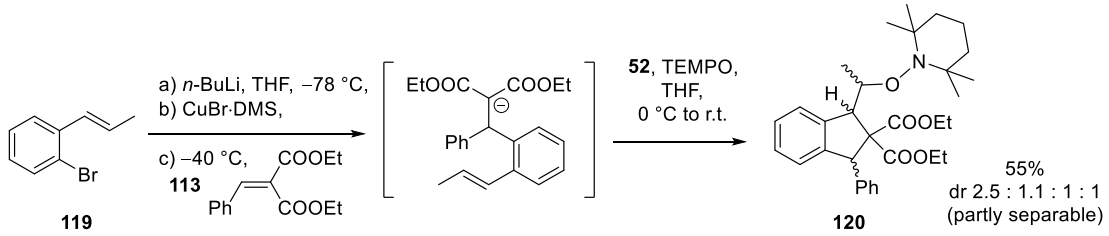
Entry	Solvent	Oxidant (equiv.)	T °C	**117a** (%)	**117b** (%)	**117c** (%)	**117d** (%)
1	THF	$FeCp_2^+$ PF_6^- (1.2), TEMPO (1.2)	–40	24	7	13	1
2 [a)]	THF	$FeCp_2^+$ PF_6^- (2.2)	0	30	8	15	2
3 [a)]	THF	$FeCp_2^+$ PF_6^- (2.2)	0	27	3	17	0
4	DME	$FeCp_2^+$ PF_6^- (2.2), O_2	0	30	12	0	22

[a)] Duplicate experiments.

Despite not being immediately useful for the synthesis of natural products, these results proved, that the concept of conjugate addition/*in-situ* oxidation is valid in principle. Compounds **117a-d** all result from a regioselective conjugate addition, followed by *6-endo*-selective cyclisation, and are all likely descended from cationic intermediate **118**. The benzylic stabilisation increases the lifetime of the radical and therefore allows the second SET oxidation. Similar double oxidation by **52** in the

context of 5-exo-trig cyclisation was in fact described earlier.[166] The exclusive *6-endo-trig* cyclisation mode is fully controlled by the position of the methyl group in α-styrene.

In order to reverse the cyclisation mode to *5-exo-trig*, lithiated β-methylstyrene **119** was subjected to Cu-catalysed conjugate addition to **113**, followed by oxidation of the enolate by the **52**/TEMPO system (scheme 36). As predicted, exclusive *5-exo-trig* cyclisation took place followed by TEMPO trapping of the cyclised radical, giving a partially separable mixture of all four possible diastereomers of **120** in 55% yield.



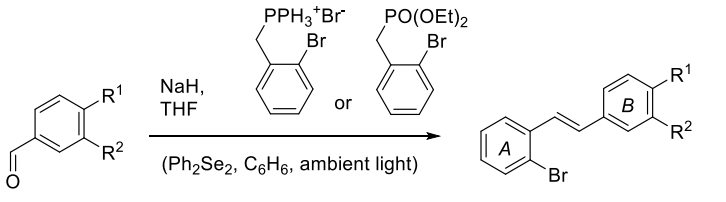
Scheme 36. One-pot conjugate addition/*in-situ* oxidative cyclisation of styrene **119**.

Unlike in the case of α-methylstyrene **115**, the non-stabilised nature of the proximate cyclisation product (the cyclic secondary radical intermediate) makes the use of persistent radical TEMPO mandatory in this cyclisation. Such radicals are not oxidized efficiently by FF due to short lifetime and the high energy of resulting secondary carbenium ion. Non-stabilised secondary alkyl radicals are however known to undergo very fast (near diffusion controlled) trapping by TEMPO.[165]

Considered together, the results of annulation of α- and β-styrene guided the next step on the way to the methodology required for the synthesis of FISs, that is annulation of stilbenes, which will be discussed in the following chapters. The fact that CuX_2 salts were tolerated during the oxidation and perhaps even aid in the SET process prompted us to invest more effort into the optimization of the Cu-catalysed conjugate addition using bromostilbenes.

4.1.3. Cu-catalysed conjugate addition of lithiated stilbenes to ylidene malonates

Three model stilbenes **121a-c** were prepared using standard approaches, that is by the Wittig olefination and the Horner-Wadsworth-Emmons reaction (scheme 37) from simple benzaldehydes. In addition to unsubstituted bromostilbene **121a**, one (**121b**) or two (**121c**) methoxy groups were added to the B ring to explore the compatibility of the lithiation/conjugate addition process with oxygenated substrates and, in the next stage, to study the influence of stilbene electron density on the second SET oxidation of the cyclic radical (chapter 4.1.4).

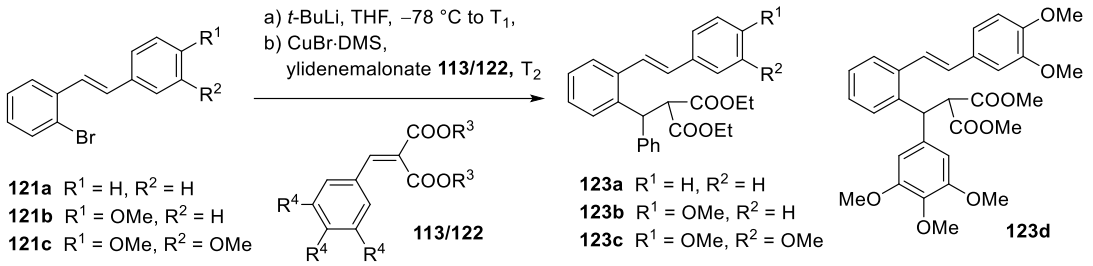


R^1 = H, R^2 = H	73%	**121a** R^1 = H, R^2 = H
R^1 = OMe, R^2 = H	84%	**121b** R^1 = OMe, R^2 = H
R^1 = OMe, R^2 = OMe	70%	**121c** R^1 = OMe, R^2 = OMe

Scheme 37. Preparation of stilbenes **S121a-c** by standard methods.

Table 4 shows the results of conjugate addition of lithiated **121a-c** to malonates **113** and **122**, prepared by the Knoevenagel reaction (see experimental part) of 3,4,5-trimethocybenzaldehyde and dimethyl malonate. Lithiation of **121a** by *n*-BuLi in THF at –78 °C, followed by Cu-catalysed addition to **113** at –40 °C, followed by warming to r.t. afforded only 30% of adduct **123a** (entry 1). Lithiation by *t*-BuLi was therefore tried (entry 2), using 2.2 equivalents of *t*-BuLi with respect to the stilbene, as it is known that *t*-BuBr, produced by the Li/halogen exchange, can interfere with reactions of organolithiums via dehydrohalogenation necessitating the use of a second equivalent of *t*-BuLi. However, no **123a** was formed, presumably due to the presence of unreacted *t*-BuLi. The half-life of *t*-BuLi in THF is 42 min at –20 °C [167] and therefore any excess should be consumed quickly by warming to r.t. Indeed, the yield of **123a** increased to 70% when the lithiation mixture was briefly warmed to r.t. and then cooled to –40 °C prior conjugate addition (entry 3). Under similar conditions, 56% yield of **123b** was obtained when stilbene **121b** was used.

Table 4. Optimization of Cu-catalysed conjugate addition.



Entry	**121** (equiv.)	R^1	R^2	Malonate	R^3	R^4	Base (equiv.)	T_1 °C	T_2 °C	**123** (%)
1	**a** (1.2)	H	H	**113**	Et	H	*n*-BuLi (1.2)	–78	–40 to 23	**a** (30)
2	**a** (1.6)	H	H	**113**	Et	H	*t*-BuLi (3.5)	–78	–78 to 0	**a** (0)
3	**a** (1.6)	H	H	**113**	Et	H	*t*-BuLi (3.5)	–78 to 23	–40 to 23	**a** (70)
4	**b** (1.3)	OMe	H	**113**	Et	H	*t*-BuLi (3.5)	–78 to 23	–40 to 23	**b** (56) [a]
5	**c** (1.3)	OMe	OMe	**113**	Et	H	*n*-BuLi (1.1)	–78	–78 to 0	**c** (0)
6	**c** (1.3)	OMe	OMe	**113**	Et	H	*t*-BuLi (1.1)	–78	–78 to 0	**c** (68)
7	**c** (1.3)	OMe	OMe	**113**	Et	H	*t*-BuLi (1.3)	–78	–78 to 0	**c** (98)
8	**c** (1.3)	OMe	OMe	**122**	Me	OMe	*t*-BuLi (1.3)	–78	–78 to 0	**d** (98)

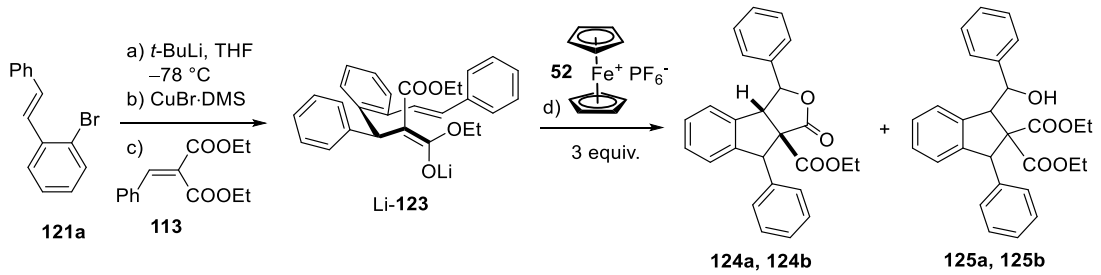
[a] Yield as established by ^{1}H NMR spectroscopy.

Despite obtaining acceptable yields of Michael adducts, the excess of *t*-BuLi was seen as a source of potential interference that could not be tolerated in the context of the envisioned one-pot sequence. Lithiation of **121c** by *n*-BuLi (entry 5) failed similarly to **121a**, however lithiation using sub-stoichiometric amount of *t*-BuLi with respect to **121c** at –78 °C gave 68% of **123c** (entry 6). Finally, it was found that using equimolar amount of *t*-BuLi at –78 °C, followed by addition of malonates **113, 122** at –78 °C afforded quantitative yields of **123c** and **123d** (entries 7, 8) with no risk of excess alkyllithium remaining in reaction mixture. The conjugate addition was compatible with ring oxygenation of on the part of stilbene as well as malonate and to tolerate Me as well as Et ester. With the optimized conditions for lithiation and conjugate addition established, we proceeded to the *in situ* oxidation of the enolate.

4.1.4. Radical v. polar annulation of model stilbenes

Using the optimized conditions from the previous chapter, conjugate addition of stilbene **121a** was reproduced, but instead of protonation, the Li enolate of **123a** was intercepted by oxidation with

excess **52** (scheme 38). When the solid salt **52** was added in a single portion, 46% of a diastereomeric mixture of lactones **124a/b** (dr 5:1) was obtained along with alcohols **125a** (20%) and **125b** (<13%). The relative configuration of **125a** and **125b** was not investigated, because a way to suppress their formation was soon discovered. Instead of adding **52** to **123a-Li**, the solution of **123a-Li** was cannulated into a suspension of **52** in THF, giving lactones **124Aa/b** in 60% yield, dr 7.5:1. The structure of all four products is consistent with the SET oxidation/cyclisation/second SET oxidation paradigm, similar to the cyclisation of styrene **115** (table 3). The second oxidation was efficient, as no products of hydrogen transfer to the secondary radical were observed. No significant amounts of brominated products were detected either, although their formation as intermediates cannot be ruled out.



Scheme 38. Model cyclisation of simple bromostilbene **121a**.

With the potential of this double cyclisation for the synthesis of FISs in mind, we were interested in finding the relative configuration of **124a** and **124b**. Due to the high geometric strain present in *trans*-bicyclo[3.3.0]octanes, these isomers were ruled out, leaving only four possible *cis*-bicyclo[3.3.0]octane based diastereomers **A-D** (figure 12) as possible candidates for **124a** and **124b**.

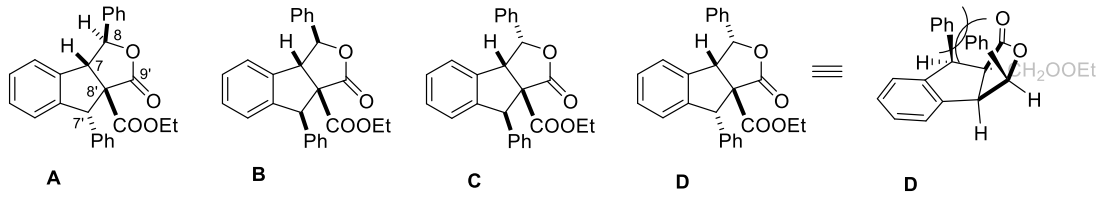


Figure 12. Four possible relative configurations of **124a** and **124b**.

Literature search revealed, that structures **A** and **C** had been reported previously by Florio *et al.* [126] (chapter 1.6, reported structures **68a**, **68b**). The published NMR data (figure 13, spectra 1, 2) however did not correspond to the data we obtained for compounds **124a** and **124b** (figure 13, spectrum 4). Additionally, the melting point we obtained for compound **124a,** 182-184 °C, also did not match the reported value of 157-158 °C for **68a**.

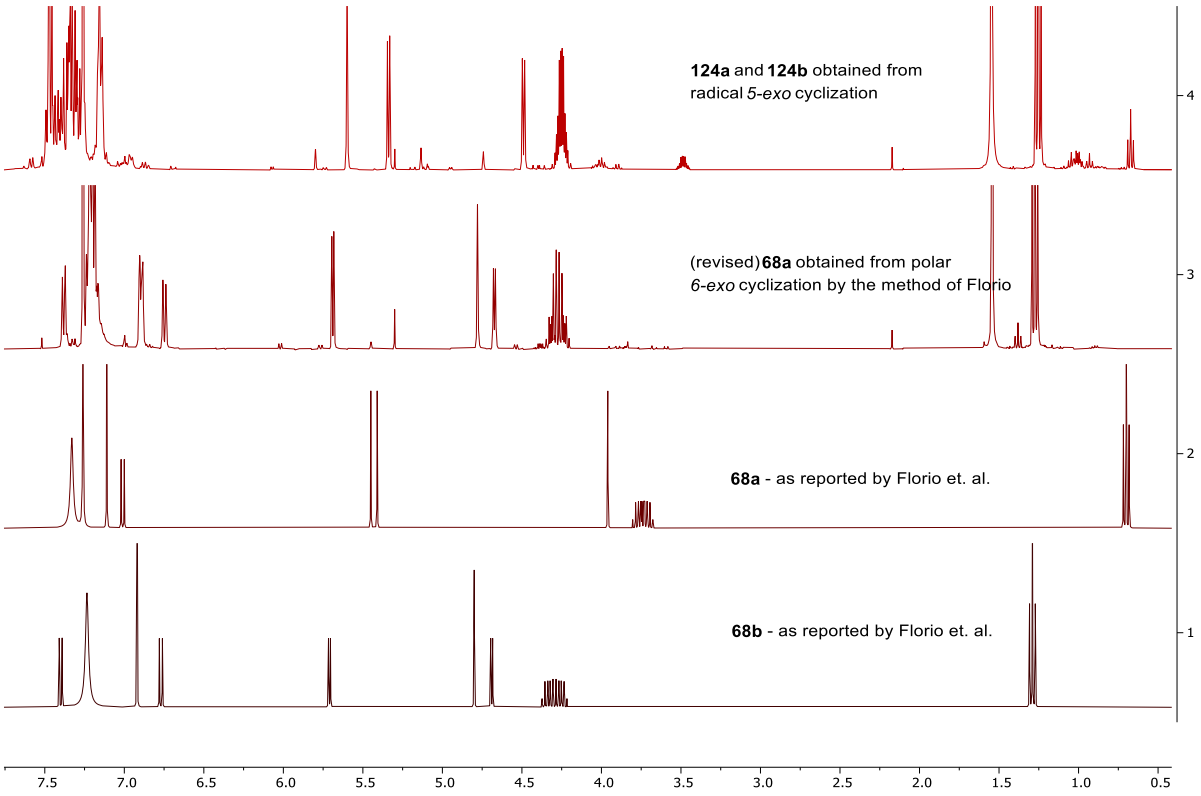


Figure 13. Comparison of ^{1}H NMR spectra in $CDCl_3$: 1), 2) computer-generated spectra of **68a** and **68b** based on reported data;[126] 3) experimental spectrum of **68a** obtained from polar cyclisation by the method of Florio; 4) experimental spectrum of **124a** (major diast.) and **124b** (minor d.) obtained from radical cyclisation of stilbene **123a**. Horizontal axis: chemical shift (ppm).

Heteronuclear multiple bond correlation (HMBC) NMR experiments confirmed our assignment of constitution of **124a,b**, we would therefore have to conclude that the relative configurations of **124a,b** correspond to the remaining isomers **B** and **D**. However, simple molecular modelling of diastereomer **D** suggested that the two flanking phenyl groups that occupy the concave side of the bent tricyclic furoindane system come into direct steric clash with each other, potentially destabilising isomer **D** (figure 12, right). We therefore sought crystallographic confirmation of relative configuration of **124a** or **124b**. Fortunately, the diastereomeric mixture produced good quality monocrystals with diffracted X-rays clearly. To our surprise, the single crystal X-ray analysis has unequivocally shown **124a** to have configuration **A** (figure 14, A). To exclude the possibility of accidentally measuring the minor constituent of the mixture or minor impurity, the crystal used for X-ray analysis was redissolved in $CDCl_3$ and ^{1}H NMR spectrum was recorded over several hours, confirming that the monocrystal indeed consisted of **124a.**

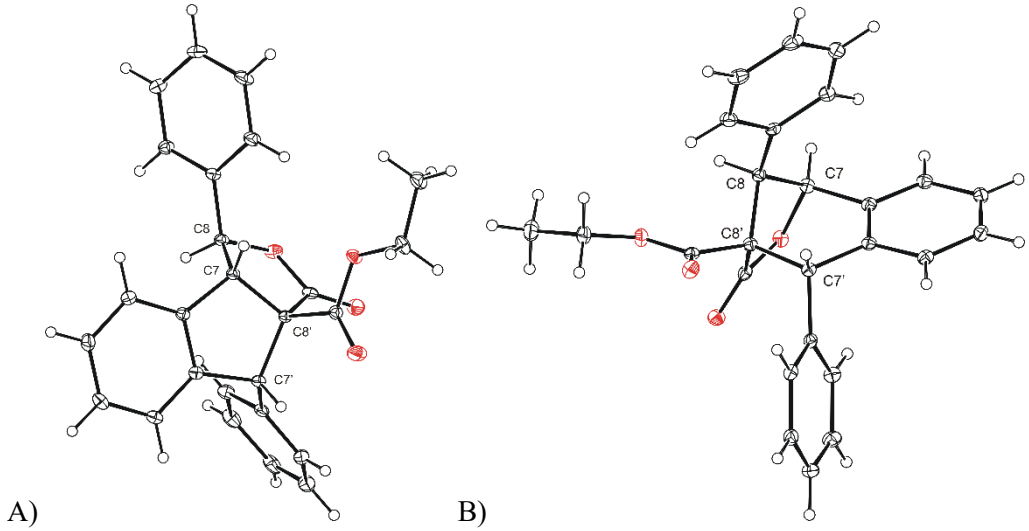
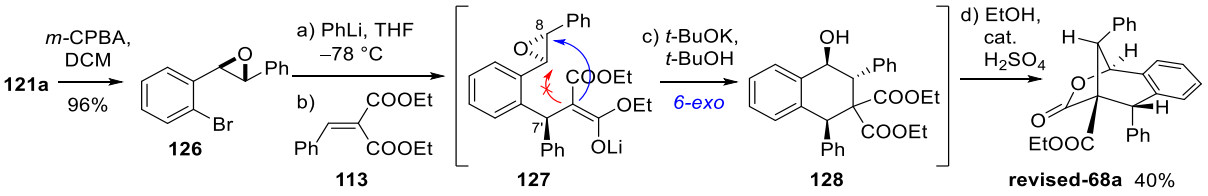


Figure 14. A) X-ray structure of **124a**; B) X-ray structure of **revised-68a**.

The assignment of **68a** of Florio *et al.* [126] therefore had to be re-evaluated. To gain more insight, we set off to reproduce the procedure of Florio *et al.* Stilbene oxide **126** was prepared from stilbene **121a** using *m*-CPBA in DCM, giving **126** in quantitative yield (scheme 39). Lithiation of **126** by PhLi in THF at –78 °C, followed by addition of malonate **113**, followed by addition of *t*-BuOK, warming to r.t. and finally followed by addition of H_2SO_4 and ethanol resulted in the formation of crystalline product **revised-68a** in 40% yield. Copound **revised-68a** had identical NMR spectra as described by Florio *et al.*, but had lower melting point of 148-149 °C, compared to the reported value of 157-158 °C. The product easily formed monocrystals suitable for X-ray analysis (figure 14, B), which revealed that **revised-4f** is actually a constitutional isomer of **124**, originating from an alternative *6-exo-tet* cyclisation of enolate **127**, followed by transannular lactonization of alcohol **128** (scheme 39). Based on analogy with congeners within a series, the authors of the original study assumed *5-exo-trig* cyclisation which would lead to the proposed furoindane structure.

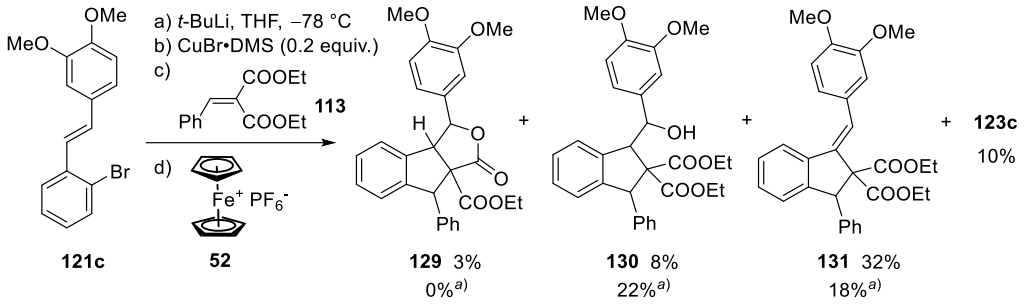


Scheme 39. Polar cyclisation of stilbene oxide **126** by the method of Florio *et al.*[126]

There is likely a delicate balance between the rates of *5-exo-tet* and *6-exo-tet* cyclisation in systems similar to **127**, as this cyclisation is a very close analogue of halonium opening reaction described by Wirth *et al.*,[127] who observed the simultaneous formation of the *5-exo* product **72** and the *6-exo* product **73** (chapter 1.6, scheme 22). This dichotomy between the formation of furoindanes and bridged lactones will be discussed further in chapter 4.4 in the context of neopodophyllotoxin synthesis.

The relative configuration of the minor diastereomer **124b**, formed along with **124a** during the radical cyclisation, remained unknown at this stage. The low value of ^{1}H-^{1}H coupling constants ($^3J < 2$ Hz) between atoms H-7 and H-8 suggested a *trans* relationship.[103] This observation, combined with the unlikeliness of the formation of **D**, led us to tentatively assign configuration **B** to **124b**.

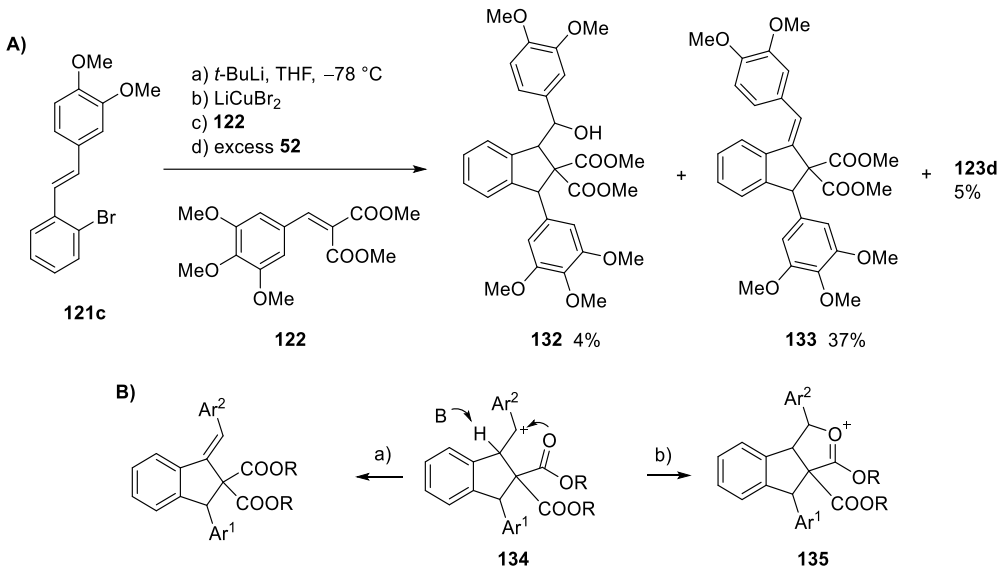
Successful implementation of the conjugate addition/oxidative bicyclisation design on model stilbene **121a** was very promising in the context of the envisioned total synthesis of furoindane stilbenolignans. Before moving on to the annulation of fully oxygenated systems, we decided to collect more data on a second model system, using stilbene **121c** (scheme 40). Addition of two methoxy groups to the B ring should in theory further facilitate the second SET oxidation, without having a significant influence on other steps in the sequence. Cu-catalysed conjugate addition of lithiated **123c** under optimized conditions developed earlier (table 4), followed by oxidation with excess **52** yielded a mixture of cyclic products **129**, **130** and **131** in 43% combined yield along with 10% of non-cyclised Michael adduct **123c**. However, the yield of the desired lactone **129** dropped to only 3 %. The major product of the reaction was alkene **131**, isolated in 32% yield.



Scheme 40. One-pot oxidative double annulation of partially oxygenated stilbene **123c**. [a)] $LiCuBr_2$ (0.2 equiv.) used instead of CuBr·DMS.

Alkene **131** was likely formed by deprotonation of cationic intermediate, that failed to undergo lactonization. This unexpected switch of reaction pathway was not well understood at that time. Attempts at optimizing the reaction conditions (not shown) did not significantly change the product distribution. However, rather surprisingly, changing the Cu source to soluble $LiCuBr_2$ increased yield of alcohol **130** to 22%, at the expense of **131**, which decreased in yield to 18%. We hypothesized, that the increased yield of alcohol **130** might be related to the increased concentration of LiBr in the reaction mixture. This hypothesis was later supported by complete disappearance of the alkene product, when excess LiBr was used during the cyclisation of fully oxygenated system (chapter 4.1.5).

One-pot conjugate addition of **121c** to dimethylmalonate **122** followed by oxidation resulted in even more alkene formation (**133**, 37%), despite using $LiCuBr_2$ as a catalyst (scheme 41, A). The key factor here is likely the changed Me group of malonate **122**, because cationic lactonization of esters occurs via dealkylation and is therefore sensitive to the nature of the ester alkyl group. The conjugate addition/double SET oxidation process takes a single reaction path up to the point of formation of cyclic benzylic cation **134** (scheme 41, B), which can then either be deprotonated to form an alkene (pathway a) or stabilise in the form of oxocarbenium ion **135** (pathway b). The ease of formation and stability of **135** should be increased by larger alkyl groups on the ester, which might be stable enough to survive until aqueous workup giving alcohols **133** (scheme 38) and **130** (scheme 40). The configuration of the double bond in alkene **133** was established by single crystal X-ray analysis (figure 15).



Scheme 41. A) One-pot oxidative annulation of stilbene **121c** with malonate **122**; B) Two possible pathways for stabilisation of cation **134**: a) deprotonation, b) capture of ester group.

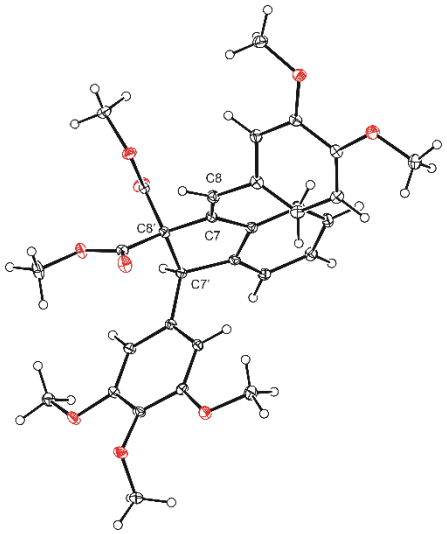
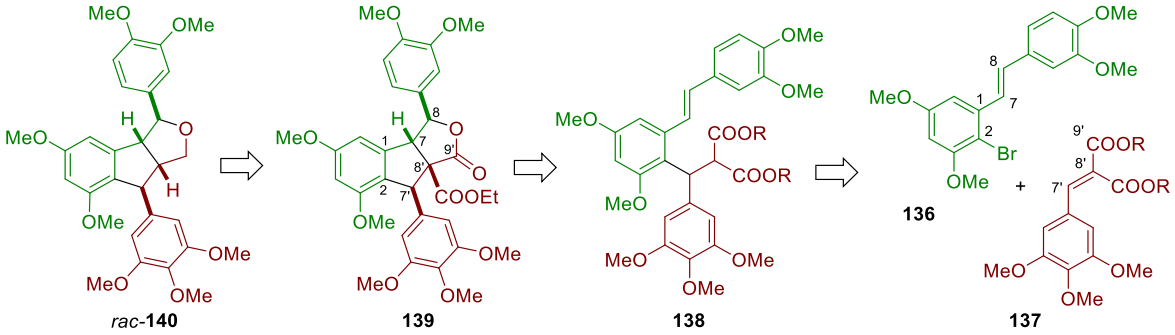


Figure 15. Crystal structure of alkene **133** showing the configuration of the double bond.

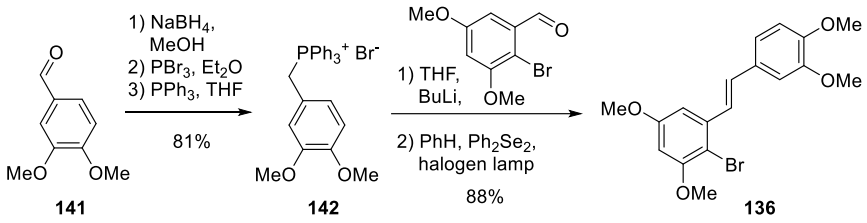
4.1.5. Racemic synthesis of kompasinol A pentamethyl ether

Even though the stereochemical outcome of our model cyclisation (chapter 4.1.4, scheme 38) was unfavourable for the prospects of total synthesis of FIS, giving predominantly lactone **124a** with unnatural relative configuration, we proceeded with the synthesis of the known pentamethyl derivative of kompasinol A **III** (scheme 42).[113] After scaling-up the conjugate addition of fully oxygenated stilbene **136** to malonate **137** leading to Michael adduct **138**, we planned to isolate the minor diastereomer of lactoester **139**, obtained by larger scale oxidation of **138**, and to use it in the downstream steps. To finish the synthesis of **140**, we planned to remove the ethoxycarbonyl group at C-8' by decarboxylation and to adjust the oxidation state of C-9'.



Scheme 42. Retrosynthetic analysis of pentamethyl derivative of kompasinol A *rac*-**140**.

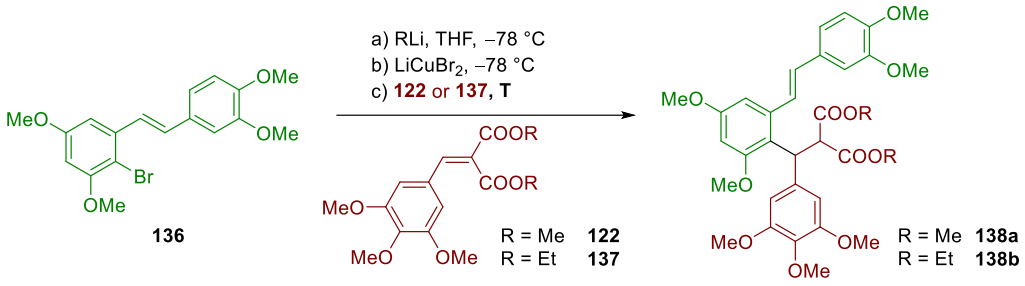
Stilbene **136** was prepared by a sequence of standard steps starting with 3,4-dimethoxybenzaldehyde **141** (scheme 43), which was reduced using $NaBH_4$ in MeOH to benzylic alcohol, followed by nucleophilic exchange to a somewhat unstable benzylic bromide which was stabilised as phosphonium salt **142** by reaction with PPh_3, giving 81% yield from **141**. Wittig reaction of the salt **142** with 2-bromo-3,5-dimethoxybenzaldehyde, followed by equilibration of the *E/Z* alkene mixture using Ph_2Se_2 and irradiation with white light in benzene afforded stilbene **(*E*)-136** in 88% yield.[168]



Scheme 43. Synthesis of stilbene **136**.

Conjugate addition of **136** to malonates **122** and **137** using the previously optimized conditions (chapter 4.1.3) was attempted, however the previously obtained high yields were not reproduced with **136**. Because successful one-pot oxidative annulation requires full conversion to the Michael adduct, re-optimization of the conjugate addition was necessary. The results of this optimization are summarized in table 5. As expected, using *n*-BuLi only afforded 16% of **138a** (entry 1). Using *t*-BuLi under standard conditions (entries 2,3), in a degassed solvent (entry 4) or in the presence of Li-coordinating additives TMEDA and HMPA (entries 5, 6) failed to deliver **138a** in a sufficient yield.

Table 5. Reoptimization of the Cu-catalayzed conjugate addition of **136**.

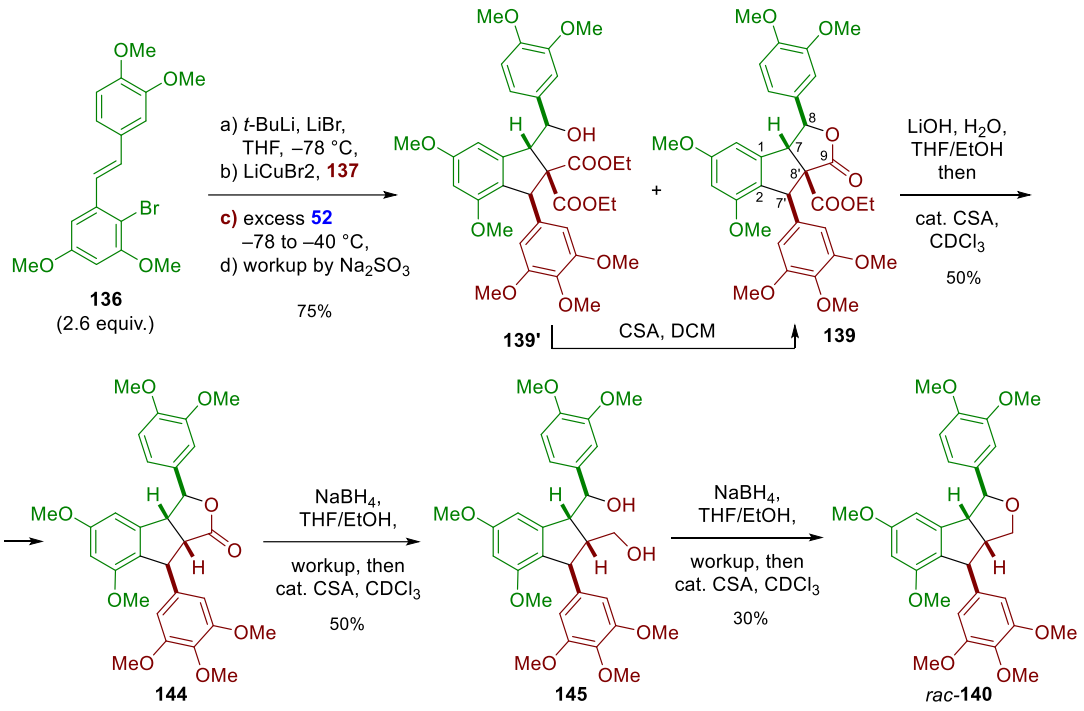


Entry	**136** equiv.	Base (equiv.)	T °C	Product (%)
1	1.3	*n*-BuLi (1.3)	–78 to 23	**138a** (16)
2	1.3	*t*-BuLi (1.3)	–78 to 23	**138a** (51)
3 [a)]	1.3	*t*-BuLi (1.3)	–78 to 23	**138a** (34)
4 [b)]	1.3	*t*-BuLi (1.3)	–78 to 40	**138a** (11)
5 [c)]	1.3	*t*-BuLi (1.3)	–78 to 23	**138a** (23)
6 [c), d)]	1.3	*t*-BuLi (1.3)	–78 to 0	**138a** (25)
7	1.5	*t*-BuLi (1.5)	–78 to –40	**138b** (30)
8	2.5	*t*-BuLi (2.5)	–78 to –40	**138b** (96)
9	2.0	*t*-BuLi (2.0)	–78 to –40	**138b** (98)

Conditions: lithiation for 5 min at –78 °C, then 0.2 equiv. $LiCuBr_2$, then **122**/**137** at T. [a)] Lithiation: 25 min at –78 °C. [b)] Solvent degassed. [c)] TMEDA (1 equiv.) added. [d)] HMPA (1.3 equiv.) added.

We speculated, that the high oxygenation of **138a** and the resulting Lewis basicity may interfere with the conjugate addition, presumably via the formation of mixed aggregates between lithiated **136** and the enolate of **138a**. In support of this hypothesis, it was observed that the reaction rate stalls at around the 30% conversion mark. To solve this problem, we switched to the potentially less coordinating diethyl malonate **138b**, however the yield did not improve and only 30% of **138b** was isolated (entry 7). The problem was finally solved by using a larger excess (2.0-2.5 equiv.) of the stilbene (entries 8, 9) which led to basically quantitative yields of **138b**, allowing us to proceed to *in situ* oxidation of its enolate.

Building on the experience with annulation of dimethoxystilbene **122c** (chapter 4.1.4, schemes 40 and 41), the key annulation step was repeated, but this time with excess LiBr added. Copper catalysed addition of **136** to **137**, followed by oxidation by excess **52** resulted in near-complete oxidation, giving lactone **139** (for discussion of rel. configuration, see below) in a mixture with a then-unidentified side-product, likely an open alcohol form of **139** (scheme 44). When a sample of crude cyclisation product was left standing in $CDCl_3$ at r.t. overnight, the compound united to **139**. In subsequent large-scale runs, the crude product was directly treated with CSA in DCM giving after purification 75% of **139** as a single diastereomer. The structure of the unknown side-product was elucidated, when the cyclisation was performed in the presence of cat. DIPA (not shown, see experimental part), giving 17% of **139**, 15% of alkene **143** and 54% of alcohol **139'**.



Scheme 44. Synthesis of kompasinol A pentamethyl ether (**140**).

Attempted Krapcho decarboxylation of **139** using various common halide salts in DMSO was unsuccessful, therefore we resorted to saponification of **139** by LiOH in THF/EtOH/water mixture. During acidic aqueous workup, the diacid intermediate decarboxylated spontaneously, however re-lactonization had to be enforced by addition of CSA to the $CDCl_3$ solution of the crude product. After purification, lactone **144** was obtained in 50% yield. The final reduction of **144** using $NaBH_4$ in THF/MeOH gave moderate yield of diol **145**, which was finally converted to tetrahydrofuran **140** in 30% yield by treatment of the $CDCl_3$ solution by catalytic CSA.

Several points regarding this synthetic sequence deserve to be discussed in more detail. The configuration and high yield of **139** and especially the absence of other diastereomers was surprising considering the previous results on model substrates. In the cyclisation of nonoxygenated model stilbene **121a** (chapter 4.1.4, scheme 38), the major cyclisation product **124a** had a *trans*-relationship between the Ph group at C7' and the hydrogen atom at C7 (figure 16, A). In contrast to that, the structure of **139**, proven unequivocally by single crystal X-ray crystallography (figure 16, B), corresponded to the minor diastereomer **134b** from the initial model cyclisation study. The chemical shifts of key atoms C7, C8, C7', C8', H7, H8 and H7' corresponded very closely to **124b** as well as the small value of the coupling constant between H7 and H8 (<1 Hz).

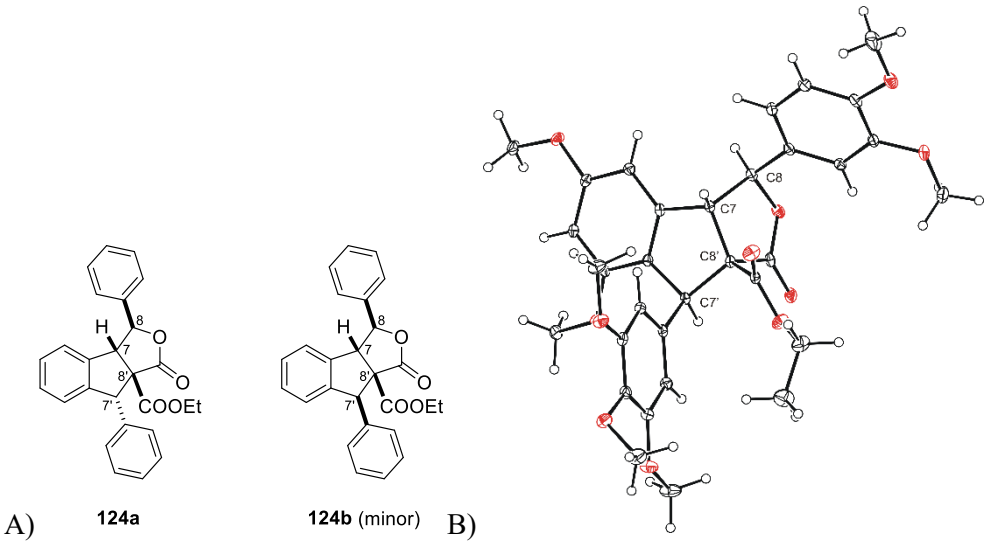


Figure 16. A) Structures of **124a** and **124b** (chapter 4.1.4). B) Crystal structure of **139**.

In order to explain the reversal of diastereoselectivity of the cyclisation step, we had to modify our previous understanding of transition state, which we originally presumed to have the common Beckwith-Houk chair-like geometry (figure 17, TS-I). The data may be better understood with an alternative boat-like transition state model (figure 17, TS-II), in which the steric clash between the MeO group at C-3 and the TMOP group is minimized compared to the TS-I or to the alternative boat-like TS-III. Although the classical Beckwith-Houk chair-like transition state TS-I would correctly predict the formation of **139** during the annulation of **136**, it does not explain the strong preference of **124a** over **124b**, observed during the annulation of non-oxygenated stilbene **121a** (lacking C3-OMe). Additionally, the boat-like model better represents the geometric requirements of trigonal carbon centres C1 and C2.

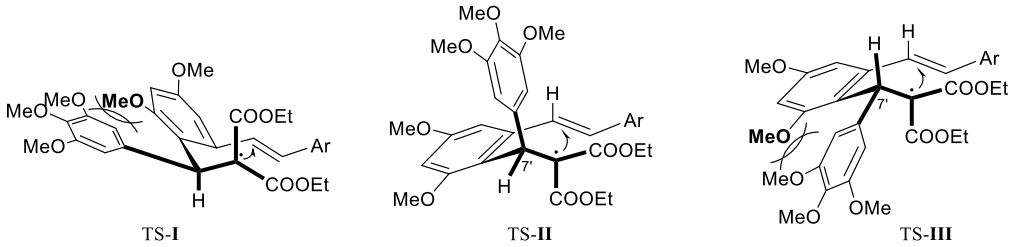


Figure 17. Presumed transition states of the radical cyclisation directed by C3-OMe group. The chair-like TS-I and boat-like TS-II lead to type-B configuration of **139** and **124b**, TS-III lead to type-A configuration as in **124a**.

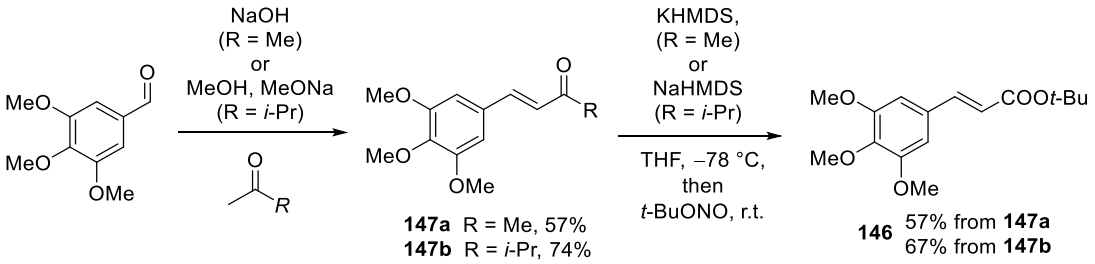
Another observation worth discussion is the stability of configuration at C8. This stereocentre is erased and recreated during the acid-catalysed etherification of diol **145** to cyclic ether **140**. The literature (chapters 1.5, 4.2.10) suggests that this transformation is thermodynamically controlled and should lead to a mixture of epimers that favours the more stable type-B isomer bearing the aryl group on the convex face of the bicyclo[3.3.0]octane core. Finally, the NMR spectra of **140** matched the data obtained previously from the methylated natural kompasinol A,[113] confirming the structure and relative configuration of **III** and other type-I FISs by synthesis.

4.2. Part B: Total synthesis of FIS via direct ArLi addition/oxidative cyclisation

4.2.1. Direct conjugate addition of ArLi to cinnamates – model study

The highly straightforward access to the racemic FIS discussed in the previous chapter could be in principle modified by using a chiral Cu-coordinating ligand to render the synthesis asymmetric. Despite there being a number of such diphosphine ligands available (see chapter 1.7.1), none of the methods seemed suitable for our addition/*in situ* oxidation of *ortho*-disubstituted stilbenyllithiums to malonates. The method developed by the Tomioka group for the enantioselective β-arylation of crotonates (chapter 1.7.2) [142-144] seemed more suitable due to its simplicity, lack of redox-active components and the fact, that reactive Li enolate is formed as opposed to silyl ethers or other neutral forms generated by other methods.

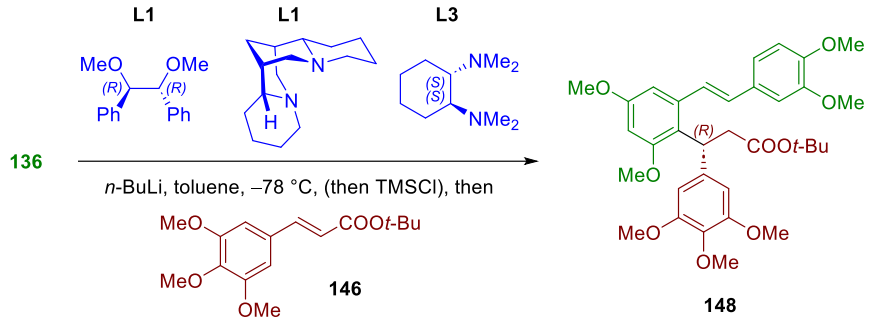
Preliminary experiments (not shown) indicated that Tomioka-type diether ligands indeed promote conjugate addition of aryllithiums to *tert*-butyl cinnamate as acceptor. Synthesis of *t*-Bu esters from acid by conventional methods usually requires the use of coupling reagents and may require difficult separation from side-products. We therefore decided to prepare cinnamate **146** utilizing our serendipitously discovered ketone cleavage reaction (chapter 4.5.2). Unsaturated ketones **147a** and **147b** were prepared by aldol condensation of 3,4,5-trimethoxybenzaldehyde with the respective ketone and purified by crystallisation (scheme 45). Oxidation of the potassium enolate of **147a** with *t*-BuONO yielded **146** in 57% yield. Similarly, oxidation of sodium enolate of **147b** yielded **146** in 67% yield (for full discussion of oxidative cleavage of ketones see chapter 4.5).



Scheme 45. Preparation of cinnamate **146** by oxidative scission of ketones **147a** and **147b**.

We next explored the conjugate addition of bromostilbene **136** to **147** under Tomioka's conditions using ligand (*R,R*)-**L1**. The ligand was premixed with **136** to facilitate lithiation, which proceeded rapidly (1-5 min.) at –78 °C in toluene using *n*-BuLi. The ligand likely aids lithiation by de-aggregating *n*-BuLi aggregates, which are known to form in hydrocarbon solvents.[169] Conjugate addition proceeded very slowly at –78 °C, therefore the mixture was slowly warmed to r.t. The crude product after workup still contained some unreacted cinnamate. Purification yielded 37% of **148**, which was analysed by chiral HPLC to show 70% ee (table 6, entry 1). To increase reactivity, in another experiment TMSCl was added to the lithiated **136** just before the addition of cinnamate **147** which led to increased yield of 66% (entry 2). Unfortunately, the enantiomeric excess dropped to 60%.

Table 6. Conjugate addition of **15** to **C0** by the method of Tomioka.

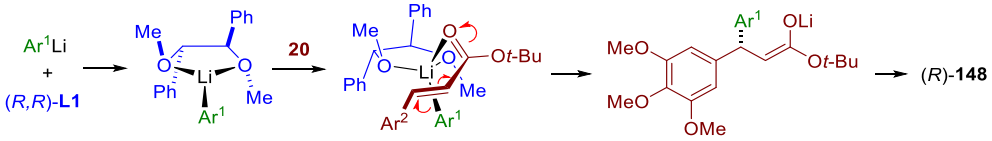


Entry	Ligand (equiv.)	TMSCl (equiv.)	**148** (%)	% ee
1	(*R,R*)-**L1** (1.5)	-	37	70 (*R*)
2	*(R,R)*-**L1** (1.5)	TMSCl (1.2)	66	60 (*R*)
3	*(S,S)*-**L3** (1.5)	-	39	20 (*R*)
4	(+)-**L2** (1.5)	-	29	19 (*S*)

Conditions: **136** (1.2 equiv.) lithiated at –78 °C in toluene in the presence of ligand, then TMSCl, then **146**, then slow warming to r.t. Quenched by KF solution in EtOH.

Diamine ligands (+)-sparteine ((+)-**L2**) and (*S,S*)-TMCDA (**L3**), which are also known to strongly bind organolithiums (chapter 1.7.2) [169-173] were tested under the same conditions (entries 3, 4). Overall, the reaction was less selective, with a substantial amount of unknown side-products formed along with **148**, which was obtained in 39% and 29% yield respectively. The enantiomeric excess in both cases was only around 19%.

Since **148** was not crystalline and no enantiopure HPLC standard was available, the transition state developed by Tomioka [144] for addition to *t*-Bu crotonates was considered (scheme 46) in order to determine the absolute configuration of **148**. The model is built around the 5-memnered ring that includes both oxygen atoms of the ligand and the lithium centre. *Trans*-orientation between the methyl groups and the neighbouring phenyl groups creates a strongly asymmetric environment for the coordinated cinnamate. The model predicts the formation of (*R*)-**148.**

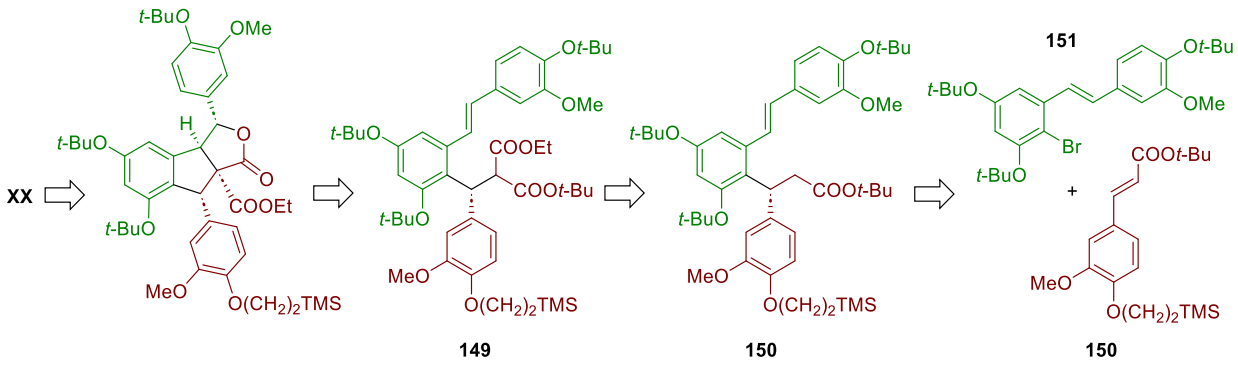


Scheme 46. Stereochemical model of conjugate addition of **136** to **146**. Using Tomioka's ligand (*R,R*)-**L1**.

4.2.2. Retrosynthetic analysis of gnetifolin F

The successful direct asymmetric addition of permethylated stilbene **136** to cinnamate **146** provided us with an opportunity to pursue asymmetric total synthesis of FISs by modifying our original proposal based on Cu-catalysed conjugate addition (scheme 47). Conjugate addition can be decoupled from the oxidative cyclisation, and instead trapping of the enolate of **150** by ethyl chloroformate would generate malonate **149** needed for cyclisation. The malonate can be isolated and

then in a second step re-deprotonated easily by LDA prior oxidation, or alternatively it can be deprotonated *in situ* to regenerate the enolate for oxidation.

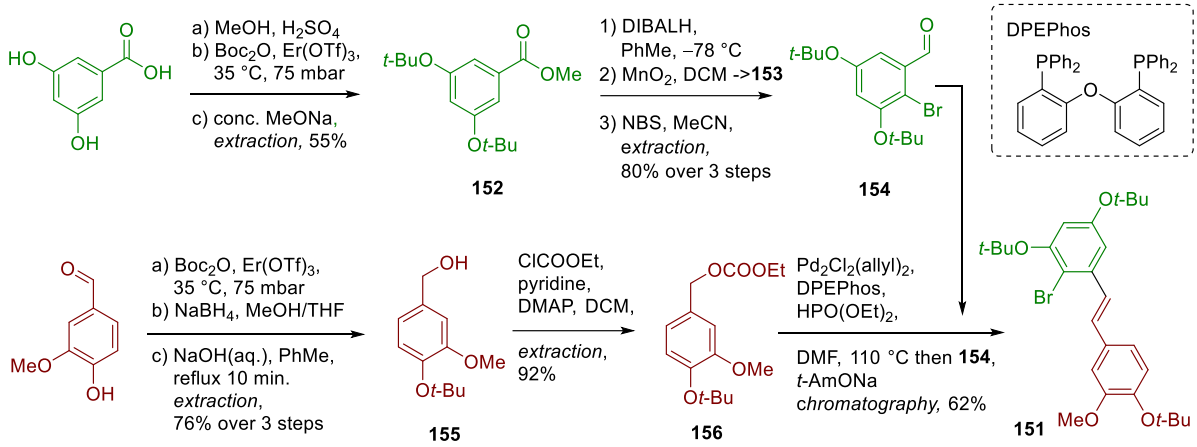


Scheme 47. Retrosynthetic analysis of gnetifolin F (**I**).

For the protection of phenolic groups of the isorhapontigenin part (in **151**) we decided to use the *t*-Bu ether group, because of its absolute stability towards strong bases as well as its steric bulk, which we speculated could help direct the conjugate addition to improve asymmetric induction. The *t*-Bu group can be deprotected by moderately strong acid, which is compatible with the envisioned synthetic steps. For the protection of C4'-OH on the Michael acceptor **150** we chose the base-stable 2-(trimethylsilyl)-ethyl group, which can be deprotected by acid or TBAF.

4.2.3. Synthesis of *tert*-butyl protected isorhapontigenin **151** and attempted conjugate addition to cinnamate **150**

The synthesis of **151** was planned in such a way as to reduce the number of chromatographic separations to a minimum and allow easy scale-up. Starting with 3,5-dihydroxybenzoic acid (α-resorcylic acid), it was converted to its methyl ester via Fischer esterification (scheme 48). Initial attempts at *O*-alkylation of the phenolic ester by isobutene/H_2SO_4 failed due to competing the Friedel-Crafts alkylation. The alternative alkylation with *O*-*t*-Bu-trichloroacetimidate was not practical on the required scale. The problem was solved by a modified protocol of Procopio [174,175] using Boc_2O and $Er(OTf)_3$. Using the original protocol, the reaction cannot be forced to completion by simple addition of larger excess of Boc_2O, because the mixture becomes diluted by its decomposition product *t*-BuOH. By running the reaction under regulated vacuum, the side-products can be continuously removed during addition of Boc_2O, which maintains high reactivity of the catalyst. The improved protocol allowed protection of both phenolic groups in 55% yield, based on 3,5-dihydroxybenzoic acid. Product **152** was purified by extraction of the methanolic solution containing NaOMe with petroleum ether (PE). Reduction of **152** by DIBAL, followed by reoxidation of co-formed benzylic alcohol by MnO_2 and bromination with NBS yielded aldehyde **154** in 80% yield after extraction.



Scheme 48. Synthesis of protected isorhapontigenin **151**.

In a parallel sequence, vanillin was alkylated by the same method as methyl resorcylate (scheme 48, bottom line). The resulting aldehyde was reduced by $NaBH_4$ in MeOH without purification. The resulting mixture was then extracted to toluene from hot 10% aqueous NaOH, giving pure **155** in 76% yield. Attempted activation of alcohol **155** as benzylic chloride or bromide resulted in decomposition via loss of the *t*-Bu group, presumably forming transient para-quinone methide intermediates. It was therefore acylated by ethyl chloroformate to yield the more stable carbonate **156** in 92% yield. To unite aldehyde **154** with carbonate **156**, a published one-pot protocol consisting of Tsuji-Trost benzylation of diethyl phosphite and subsequent *in situ* Horner-Wadsworth-Emmons reaction was used, [176] giving **151** on 62% yield after chromatography.

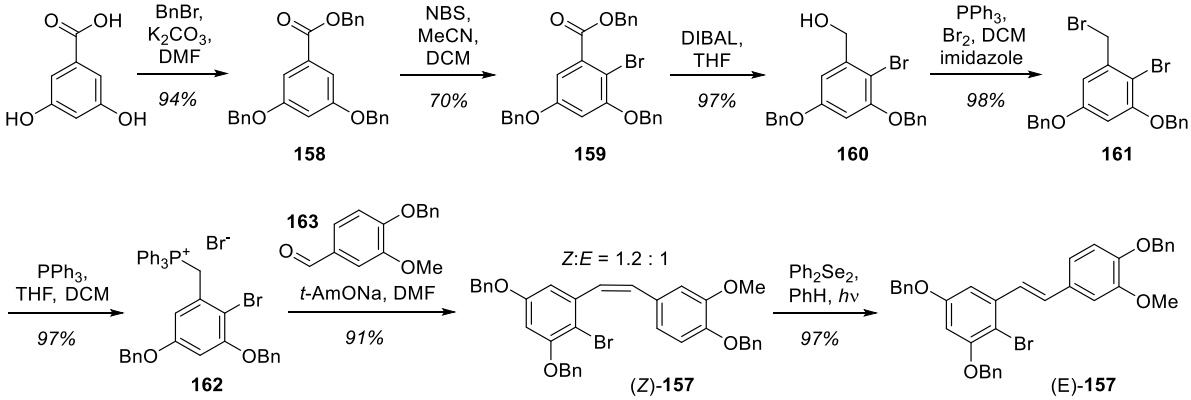
Unfortunately, addition of lithiated **151** to cinnamate **150** was unsuccessful under the modified Tomioka conditions developed for methylated isorhapontigenin **136**. Optimization of the reaction parameters did not lead to formation of any Michael adduct. Similarly, attempted Cu-catalysed addition to malonate **137** using the method developed earlier (chapter 4.1.3) did not lead to any detectable product of conjugate addition. We reasoned that the high steric demand of the *t*-Bu group next to the lithiated centre was likely not compatible with the conjugate addition.

4.2.4. Synthesis of benzyl-protected isorhapontigenin **157**

Based on the unsuccessful addition of **151**, the strategy for the protection of the isorhapontigenin part of gnetifolin F (**I**) was reconsidered. Because the conjugate addition was shown to be compatible with methyl group in **136** but fail completely with *t*-Bu group in **151**, the intermediate-sized benzyl group was chosen. The benzyl group is stable to very strong bases and easy to install.[177] On the other hand, its removal under standard hydrogenolysis conditions would likely not be possible on our system due to the expected lability of the benzylic C8-O bond in FISs. We were however encouraged by recent examples of successful removal of phenolic benzyl ether under mild conditions by BCl_3.[178,179]

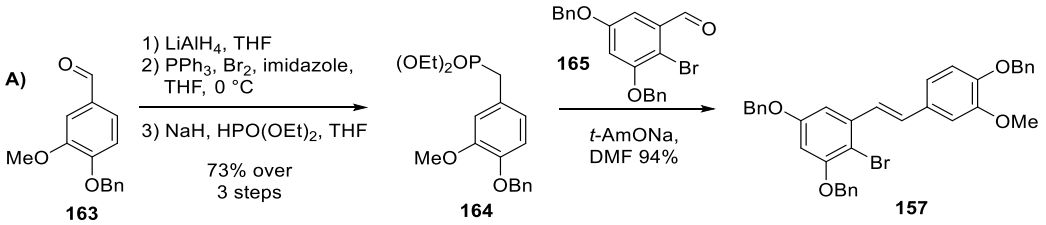
Two approaches to benzyl protected isorhapontigenin **157** were developed and compared with regard to overall yield and practicality. The first approach started with exhaustive benzylation of 3,5-dihydroxybenzoic acid by excess BnBr in DMF in the presence of K_2CO_3, yielding 94% of ester **158** (scheme 49). Bromination of **158** by NBS in MeCN proved difficult to stop at the stage of monobrominated product **159**. Optimization of solvent and temperature did not improve the result.

159 could be separated from the dibrominated side-product by chromatography, however the separation became the bottleneck of the whole sequence, limiting scale and throughput. Subsequent reduction of **159** by excess DIBAL in THF gave **160** in high yield. This reduction was later found to be selective for the monobrominated **159** as opposed to its dibrominated sideproduct, which does not undergo reduction under the conditions. Activation of **160** under Appel conditions afforded in quantitative yield benzyl bromide **161**, which was then stabilised as phosphonium salt **162** by reaction with PPh_3 in TFH/DCM mixture. The Wittig reaction between commercial aldehyde **163** and phosphonium salt **162** in DMF in the presence of sodium *tert*-pentoxide afforded 91% of stilbene **157** as roughly equimolar mixture of *E/Z* isomers. Irradiation of benzene solution of *E/Z*-**157** containing catalytic amount of Se_2Ph_2 with white light resulted in near-complete conversion to the more stable *E* isomer.[168] Purification of (*E*)-**157** did not require chromatography, as the *E* isomer is nearly completely insoluble in Et_2O and precipitates readily from supersaturated oils produced by concentration of (*E,Z*)-**157** from DCM or benzene. This method can also be used for the separation of (*Z*)-**157** and (*E*)-**157** directly after the Wittig reaction. The overall yield of (*E*)-**157** over the whole sequence was 53% based on 3,5-dihydroxybenzoic acid.



Scheme 49. The first approach to **157** based on the Wittig reaction.

The second approach relied on the Horner-Wadsworth-Emmons reaction between phosphonate **164** and aldehyde **165** (scheme 50). Phosphonate **164** was prepared from commercial O-benzylvanillin (**163**) in 73% overall yield by reduction with $LiAlH_4$ in THF, followed by the Appel bromination and nucleophilic displacement of Br with $NaPO(OEt)_2$. The 2-brominated benzaldehyde **165** was prepared by DIBAL reduction/MnO_2 reoxidation sequence from ester **158** (from previous approach). The Horner-Wadsworth-Emmons olefination proceeded well, combining **164** with a small excess of **165**. Sodium *tert*-pentoxide (*t*-AmONa) in DMF proved to be the optimal base, allowing the preparation of **157** on large scale in 94% yield. The overall yield of the sequence was 68% based on **163**.



Scheme 50. The second approach to **157** based on the Horner-Wadsworth-Emmons reaction.

The number of steps, overall yield as well as practicality clearly favoured the second approach over the first one. In both approaches, *t*-AmONa in DMF was used for the olefination step. The use

of this less-known base should be recommended. It is relatively inexpensive and is supplied as a concentraed 40%$_w$ solution in toluene, which allows much easier handling than hygroscopic solids like *t*-BuONa and *t*-BuOK, or the much less concentrated solutions of these less soluble bases (typically 1 M in THF). Unlike very strong bases like *n*-BuLi, *t*-AmONa is compatible with arylaldehydes, yet it is strong enough to deprotonate benzylic phosphonium salts and phosphonates in DMF. Therefore, the reagents for the Wittig or Horner-Wadsworth-Emmons reaction can be mixed at in any order at r.t., which facilitates scale-up.

4.2.5. Selection and synthesis of Li-specific ligands

Before turning to the conjugate addition of **157** to cinnamates, we sought to increase the chances of successful Michael addition by broadening the reaction parameter space with a small library Li-specific chiral ligands. Since no theoretical model was available to guide the selection of ligands, we turned to sampling the most common classes of diether and diamine ligands used for asymmetric deprotonation, carbolithiation and other reactions of organolithiums organolithiums.[141-145,169,170,172,173]

Only bidentate ligands were considered, because we reasoned that the simplified monomeric nature of their complexes with bulky ArLi should narrow down the number of potential reaction channels and therefore potentially lead to more predictable behaviour. Lastly, the ligands should be sufficiently soluble in aromatic hydrocarbons to be compatible with the cryogenic conditions of the conjugate addition. Three families of ligands were selected (figure 18), these are A) Tomioka-type diethers, B) dianhydrosugar-derived ethers and miscellaneous other diethers, C) diamines and O-methylcinchonine.

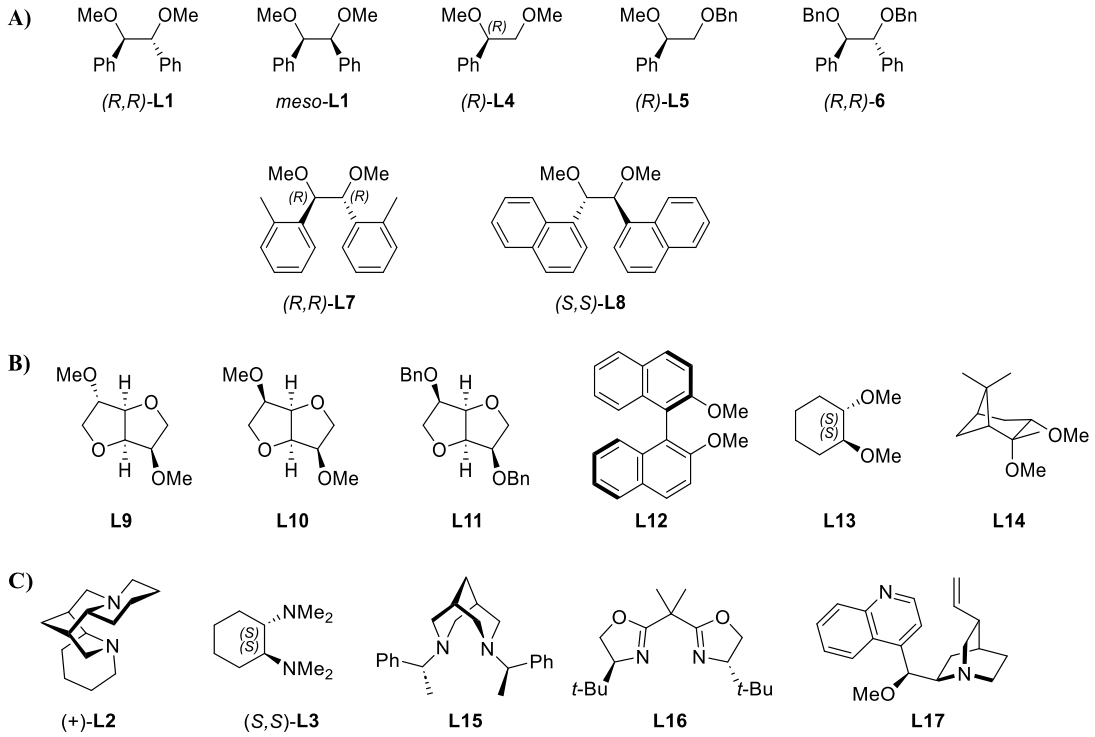
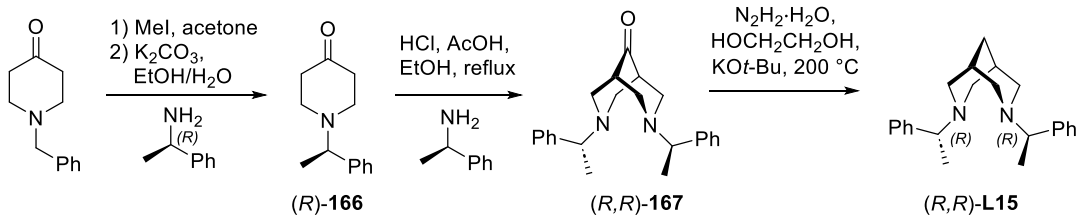


Figure 18. Library of selected lithium specific ligands: A) Tomioka-type diethers; B) dianhydrosugar-derived ethers and miscellaneous other diethers; C) diamines and O-methylcinchonine (**L17**).

The basis for the first group (A) was Tomioka's ligand **L1**, which had been previously used for conjugate addition of hindered aryllithiums to cinnamates (chapter 1.7.2).[143,144] In addition to preparing (*R,R*)-**L1**, (*S,S*)-**L1** and the symmetric *meso*-form **L1**, we sought to modify the steric demand of the substituents on oxygen atoms as well as on the backbone. Ligand **L4**, lacking one of the phenyl groups, is less rigid than the parent Tomioka ligand **L1**. Ligand **L5** can be seen as isomeric to **L1** with the Ph group migrated to the former OMe group. In ligand **L6**, the steric demand of the oxygen substituents is increased by using larger Bn group instead of Me group. In ligands **L7** and **L8** the rigidity of the backbone is reinforced by increasing the size of the backbone substituents while maintaining the strongly coordinating small OMe groups.

The second group (B) consists of other readily available chiral compounds with 1,2- or 1,3-relationship between oxygen atoms. Dimethylisosorbide **L9** is a commercial chiral solvent, two of its ether oxygen atoms form a cleft suitable for coordination of the Li atom. Ligands **L10** and **L11**, prepared by alkylation of D-isomannide, are C_2-symmetric analogues of **L9**. **L12** is a derivative of the axially chiral binol, known to provide strongly asymmetric environment for coordinated metals. The C_2-symmetric diether **L13** and non-symmetric **L14** were prepared from the commercially available diols *trans*-1,2-cyclohexanediol and (+)-pinanediol, respectively.

The third group (C) contains nitrogen-based ligands. Naturally occurring alkaloid (–)-sparteine ((–)-**L2**), and its more available optical antipode (+)-pachycarpine ((+)-**L2**), has a history of use as Li chelator (chapter 1.7.2). (*S,S*)-TMCDA (**L3**) has been shown in some cases to be a useful sparteine surrogate in asymmetric deprotonations.[133,171-173] Commercially available bisoxazoline ligand **L16** has also been used in conjunction with organolithiums thanks to its stability towards bases. Easilly accessible *O*-methylcinchonine (**L17**) possesses 1,3-aminoether arrangement that could potentially coordinate lithium. The design of bispidine-based diamine (*R,R*)-**L15** was inspired by the bispidine arrangement of the B and C rings of sparteine, with the chirality coming from the readily available (*R*)-1-phenylethylamine (scheme 51).



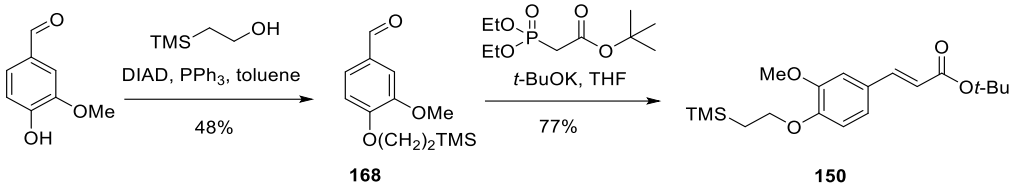
Scheme 51. Synthesis of ligand (*R,R*)-**L15**.

The synthesis of **L15** started with activation of *N*-benzyl-4-piperidone by MeI in acetone, followed by base-promoted displacement of the secondary amine with (*R*)-1-phenylethylamine to give **166**. Double Mannich reaction of **166** with formaldehyde and another equivalent of (*R*)-1-phenylethylamine gave bispidine **167**. The high polarity of **167** prevented chromatographic purification, therefore it was directly subjected to the Wolff-Kishner reduction.[266] Unoptimized, the reduction and subsequent repeated chromatographic purification yielded only 5% of diamie **L15** based on *N*-benzyl-4-piperidone.

4.2.6. Conjugate addition of stilbene **157** to cinnamate **150**

Suitably protected cinnamate **150**, required for the total synthesis of **I** was prepared starting from vanillin, which was alkylated by 2-(trimethylsilyl)ethanol using the Mitsunobu reaction (scheme

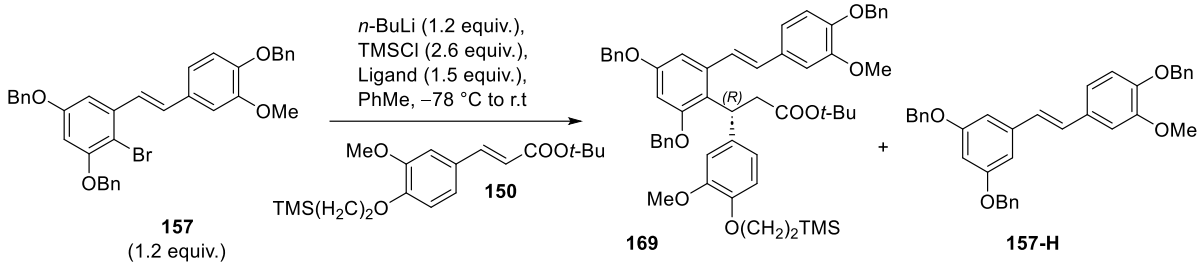
52). Standard reaction conditions using DCM as solvent only yielded 10-20% of **168**, however changing the solvent to toluene increased the yield to 48%.[180] Horner-Wadsworth-Emmons reaction of **168** with *tert*-butyl diethylphosphonoacetate using *t*-BuOK as base yielded 77% of **150**.



Scheme 52. Synthesis of cinnamate **150**.

To establish the baseline reactivity in TMSCl-assisted conjugate addition of lithiated **157** to **150**, a control experiment was performed in toluene without any added ligand, leading to **169** in only 39% yield (table 7, entry 1). Switching to THF led to almost complete breakdown of 1,4-selectivity, as only 9% of **169** was detected in the crude product which otherwise consisted of products of 1,2-addition and polymerization of **150** (entry 2). TMEDA and diphenyl-*tert*-butylhosphine oxide as ligands failed to promote conjugate addition in toluene (entries 3, 4). In order to obtain a pure sample of racemic **169** for use as a standard for chiral HPLC, needed in the following experiments, we tried using *meso*-**L1**, which indeed afforded 71% yield of racemic **169** (entry 5). Using (*R,R*)-**L1** in toluene afforded 60% yield of **169** with 61% ee on 50 μmol scale, reproducing the experiment on 150 μmol scale improved the yield to 70%, with essentially the same ee (entries 6, 7). Changing the solvent to a mixture of xylenes improved ee marginally, but the yield dropped to 57% (entry 8). The truncated analogue of Tomioka's ligand (*R*)-**L4** led to the formation of the same enantiomer of product (*R*)-**169**, however in inferior yield and asymmetric induction (entry 9). Using diamine ligand (+)-**L2** led to only 35% yield, with the opposite enantiomer (*S*)-**169** being predominantly formed in only 16% ee (entry 10). Both (*S,S*)-**L3** and (*R*)-**L12** were ineffective as ligands, as the yield of essentially racemic **169** dropped in their presence below the baseline yield obtained in pure toluene (entries 11, 12).

Table 7. Optimization of asymmetric conjugate addition of **157** to cinnamate **150**.



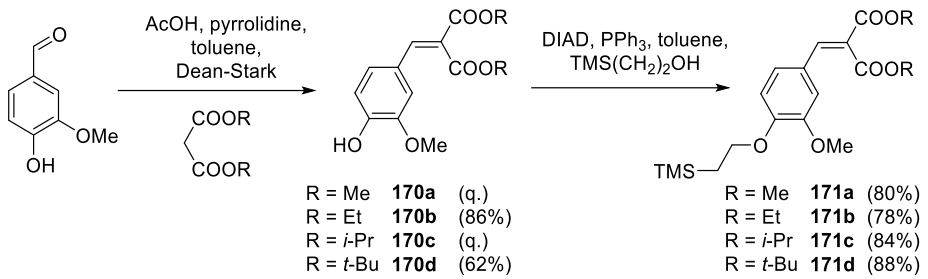
Entry	Ligand	Solvent	Yield (%)	ee (%)
1	-	Tol	39	-
2	-	THF	9 [a)]	-
3	TMEDA	Tol	0	-
4	Ph_2*t*-BuPO	Tol	0	-
5	*meso*-**L1**	Tol	71	0 [b)]
6	(*R,R*)-**L1**	Tol	60	61 (*R*)
7	(*R,R*)-**L1**	Tol	70 [c)]	60 (*R*)
8	(*R,R*)-**L1**	Xylenes	57	63 (*R*)
9	(*R*)- **L4**	Tol	43	37 (*R*)
10	(+)-**L2**	Tol	35	16 (*S*)
11	(*R*)-**L12**	Tol	25	1
12	(*S,S*)-**L3** [d)]	Tol	<5 [a)]	-

All reactions on 50 µmol scale. [a)] Yield by ^{1}H NMR spectroscopy. [b)] Used as racemic standard for HPLC. [c)] Triple scale (150 µmol). [d)] 3.0 equiv. of ligand used. Enantiomeric excess established by HPLC with chiral stationary phase.

Overall, the conjugate addition to **150** was slow at –78 °C and required gradual warming to r.t. in the presence of TMSCl. Before continuing with optimization using other ligands, we tested conjugate addition of **157** to diethyl benzylidenemalonate (not shown) under the same conditions using ligand *meso*-**Tomioka**. To our surprise, the reaction proceeded well with good 1,4-regioselectivity and, importantly, did not require TMSCl. This observation contrasts the common reactivity of unhindered unsaturated esters, which usually undergo 1,2-addition with organolithiums and requite a transition metal catalyst to switch to the 1,4-mode. Nevertheless, this opened a welcome window of opportunity for our synthesis of FISs, as the cyclisation of malonate was our original strategy anyway.

4.2.7. Asymmetric conjugate addition of **157** to malonates

A series of protected ylidenemalonates were prepared by the Knoevenagel condensation of vanillin with the respective malonic ester, followed by protection with the 2-(trimethylsilyl)ethyl group (scheme 53). The condensation leading to methyl ester **170a**, ethyl ester **170b** and ispopropyl ester **170c** afforded high (86-99%) yields of benzylidene malonates after simple precipitation. The subsequent Mitsunobu reaction with 2-(trimethylsilyl)ethanol in toluene afforded protected malonates **171a-d** in 78-88% yields.



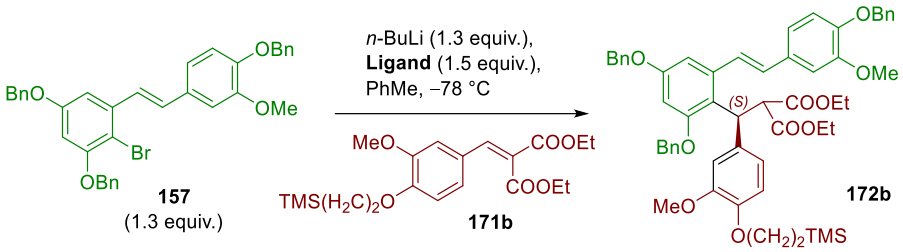
Scheme 53. Preparation of protected malonates **170a-d**.

The direct conjugate addition of stilbene **157** to malonates was optimized using malonate **171b** first (table 8). The baseline reactivity was again established in an experiment in the absence of any ligand (entry 1), which gave only 22% of the Michael adduct *rac*-**172b**. The original conditions using catalytic CuBr·DMS in THF similarly afforded 21% of **172b** (entry 2). The achiral form of Tomioka's ligand *meso*-**L1** this time failed to increase the yield significantly (entry 3). In contrast to that, the C_2-symmetric (*S,S*)-**L1** proved to be a very efficient promoter, affording 80% of (*S*)-**172b** in 51% ee. The configuration of the product was assigned based on Tomioka's model (chapter 4.2.1, scheme 46).

All modified Tomioka-type ligands were less effective both in terms of yield and ee, with **L4** and **L7** giving moderate yields of **172b** and rather low ee of 37-43% (entries 5, 9) and ligands **L5**, **L6** and **L8** failing to promote the reaction altogether (entries 6-8). Cyclohexane diol-derived **L13** performed almost equally well as (*S,S*)-**L1** giving 80% yield and 49% ee (entry 10). Pinane diol-derived **L14** was moderately competent in directing the 1,4-addition but failed to exert any asymmetric induction (entry 11). Binol-derived diether **L12** did not seem to affect the course of the reaction compared to the reaction in pure solvent at all (entry 12) giving 23% of racemic **172b**. Dianhydro-sugar derived ligands **L9**, **L10** and **L11** were all highly capable of promoting the 1,4-addition in very high yields, however the asymmetric induction was moderate, with **L11** giving the highest ee of 40% (entries 13-15).

Bisoxazoline ligand (*S,S*)-**L16** afforded 71% yield of close-to-racemic **172b** (entry 16). Cinchonine-derived aminoether **L17** on the other hand practically prevented conjugate addition, presumably due to its instability towards strong bases (entry 17). Diamine (*S,S*)-**L3** afforded a moderate yield of **172b**, but essentially no asymmetric induction, while reaction in the presence of bispidine (*R,R*)-**L15** was unchanged compared to the baseline reaction in pure toluene (entries 18, 19). In contrast to the other (di)amine ligands, pachycarpine (+)-**L2** proved very efficient, affording 76% yield of (*S*)-**172b** in 49% ee.

Table 8. Screening of ligands in direct conjugate addition of stilbene **157** to malonate **171b**.



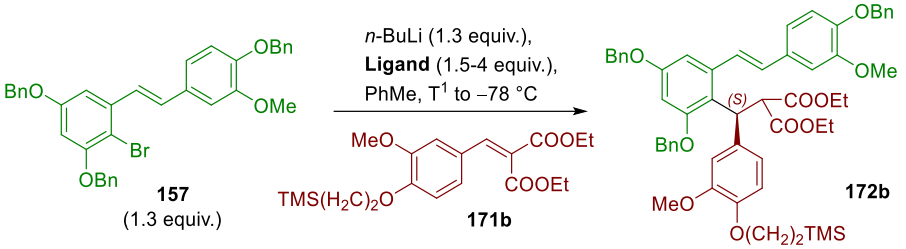
Entry	Ligand	**172b** (%)	ee (%)
1	-	22	-
2	-	21 [a)]	-
3	*meso*-**L1**	27	-
4	(*S,S*)-**L1**	80	51 (*S*)
5	(*R*)-**L4**	59	37 (*R*)
6	(*S*)-**L5**	10	-
7	(*R,R*)-**L6**	24	5 (*R*)
8	(*S,S*)-**L8**	32	3 (*S*)
9	(*R,R*)-**L7**	56	43 (*R*)
10	(*S,S*)-**L13**	80	49 (*S*)
11	(−)-**L14**	66	8 (*R*)
12	(*R*)-**L12**	23	-
13	D-**L9**	81	26 (*R*)
14	(+)-**L1**	95	36 (*R*)
15	(+)-**L11**	100	40 (*R*)
16	(*S,S*)-**L16**	71	19 (*S*)
17	(*9S*)-**L17**	10	-
18	(*S,S*)-**L3**	52	13 (*S*)
19	(*R,R*)-**L15**	21	0
20	(+)-**L2**	76	49 (*S*)

[a)] THF used as solvent instead of toluene, CuBr·DMS (0.2 equiv.) and LiBr (2.0 equiv.) used as additives.

Out of the three best-performing ligands, Tomioka's diether (**L1**) and sparteine (**L2**) were selected for further optimization due to their good availability. Increasing the loading of (*R,R*)-**L1** from 1.5 equiv. to 4 equiv. did not significantly increase the ee (table 9, entries 1-3). Previously, we observed that the **L2**-mediated conjugate addition was faster than the reaction mediated by other ligands, that is essentially instant at –78 °C. We therefore decided to test the lower temperature limit of the conjugate addition with (+)-**L2**. The melting point of toluene (–95 °C) and its increasing viscosity near the melting point necessitated the use of eutectic solvent mixture composed of toluene/ethylbenzene, to which *n*-pentane of isohexane can be added to further decrease viscosity. Addition at –90 °C using 4 equiv. of (+)-**L2** proceeded fast and afforded 68% of (*S*)-**172b** in increased 61% ee (entry 4). Decreasing the temperature further to –115 °C led to further improvement to 70% ee (entry 5). At –140 °C the ligand-organolithium complex precipitated, leading to a slight decrease

in ee to 65% (entry 6). In contrast to (+)-**L2**, decreasing the temperature when using diether ligand (*R,R*)-**L1** led to drop in both yield and ee (entry 7) due to issues with solubility of the lithium complex.

Table 9. Optimization of conjugate addition of **157** to **171b** focused on ligands (*R,R*)-**L1** and (+)-**L2**.



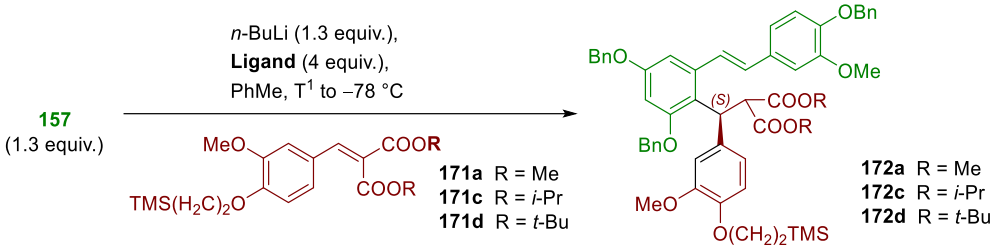
Entry	Ligand (equiv.)	Solvent	T^1 °C	Yield (%)	ee (%)
1	(*R,R*)-**L1** (1.5)	Tol	–78	78 [a]	53 (*R*)
2	(*R,R*)-**L1** (1.5)	Tol	–78	71	47 (*R*)
3	(*R,R*)-**L1** (4.0)	Tol	–78	73	53 (*R*)
4	(+)-**L2** (4.0)	Tol/PhEt (1:1)	−90	68	61 (*S*)
5	(+)-**L2** (4.0)	Tol/PhEt/*n*-pentane (1:1:1)	−115	79	70 (*S*)
6	(+)-**L2** (4.0)	Tol/PhEt/isopentane (1:2:2)	–140 [b]	77	65 (*S*)
7	(*R,R*)-**L1** (4.0)	Tol/PhEt/*n*-pentane (1:1:1)	−115 [c]	35	48 (*R*)

[a] TMSCl added prior addition of **171b**. [b] Lithiated **157**-sparteine complex precipitated prior addition of **171b**, the precipitate fully dissolved again at –90 °C. [c] Lithiated **157**-(*R,R*)-**L1** complex precipitated prior addition of **171b.**

To conclude the results presented in tables 8 and 9, ligands (*R,R*)-**L1** and (+)-**L2** performed roughly equally –78 °C both in terms of yield (70-80%) and ee (around 50%). Unlike the aromatic Tomioka's diether **L1**, the aliphatic diamine ligand (+)-**L2** performed better under the deep cryogenic conditions, presumably due to better solubility of its complexes, and/or stronger ligand- acceleration effect.

Next our attention turned to the last component of the direct conjugate addition, that is the Michael acceptor. Ylidenemalonates **171a,c,d**, differing in the size of the ester alkyl group were compared at –78 °C using ligands (*R,R*)-**L1** and (+)-**L2**. Dimethylmalonate **171a** behaved similarly to **171b**, affording very good yields of **172a** with similar ee (table 10, entries 1, 2). Assuming Tomioka's model, (*R,R*)-**L1** gave (*R*)-**171a**, therefore (+)-**L2** gave the opposite enantiomer. Diisopropyl malonate **171c** afforded 80% yield of (*S*)-**172c** in 52% ee using (+)-**L2**, but reactivity and selectivity was completely lost using (*R,R*)-**L1** (entries 3, 6). Decreasing the temperature in the reaction with (+)-**L1** to –93 °C led to improved asymmetric induction, the effect however levelled off at –115 °C giving (*S*)-**172c** in 85% yield and 65% ee (entries 4, 5). The most hindered di-(*tert*-butyl) malonate **171d** was significantly less reactive than the other acceptors and underwent addition with inferior asymmetric induction (entries 7-9). Based on these results, conjugate addition of **157** to ethyl ester **171b** or isopropyl ester **171c** using (+)-**SP** at –115 °C or lower was selected as the optimal method to carry into the one-pot *in situ* oxidative cyclisation protocol.

Table 10. Comparison of malonates **171a,c,d** as acceptors in asymmetric conjugate addition.

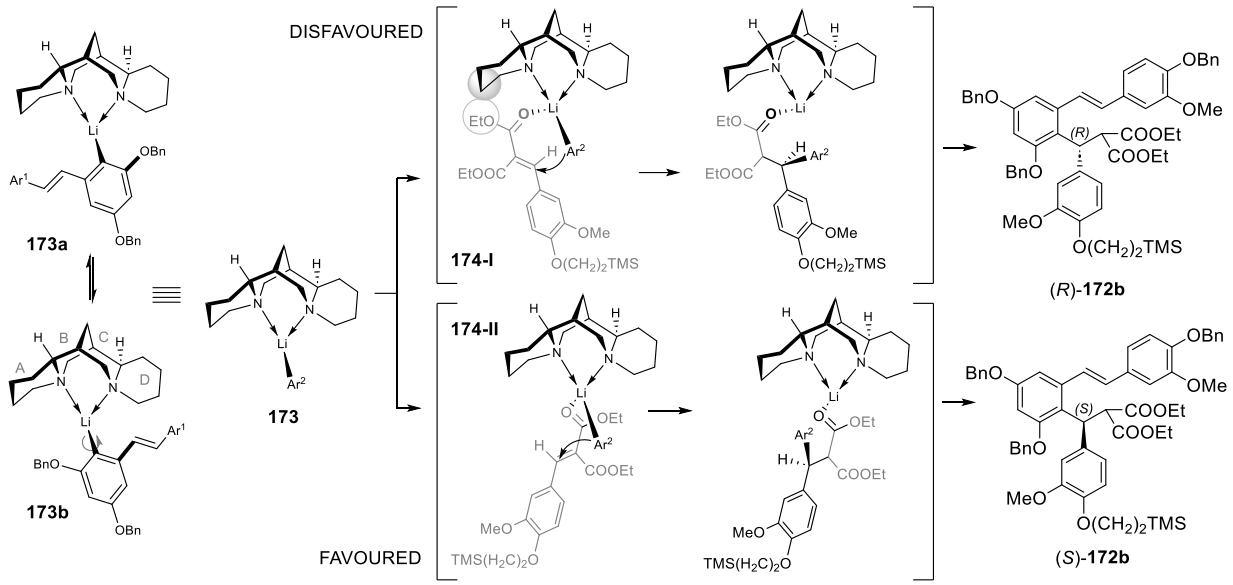


Entry	Malonate	Ligand	Solvent	T[1] °C	**172** (%)	ee (%)
1	**171a**	(+)-**L2**	Tol	–78	**172a** (82)	50 (*S*)
2	**171a**	(*R,R*)-**L1**	Tol	–78	**172a** (71)	54 (*R*)
3	**171c**	(+)-**L2**	Tol	–78	**172c** (80)	52 (*S*)
4	**171c**	(+)-**L2**	Tol/PhEt/pentane	–93	**172c** (72)	62 (*S*)
5	**171c**	(+)-**L2**	Tol/PhEt/cumene	–115	**172c** (85)	65 (*S*)
6	**171c**	(*R,R*)-**L1**	Tol	–78	**172c** (7)	29 (*R*)
7	**171d**	(+)-**L2**	Tol	–78	**172d** (61)	44 (*S*)
8	**171d**	(*R,R*)-**L1**	Tol	–78	**172d** (<12) [a]	-
9	**171d**	(*R,R*)-**L1**	Tol	–78 [b]	**172d** (30)	36 (*R*)

[a] Crude yield by ^{1}H NMR spectroscopy. [b] Warmed to –20 °C before quenching.

4.2.8. Enantioselectivity rationale – transition state

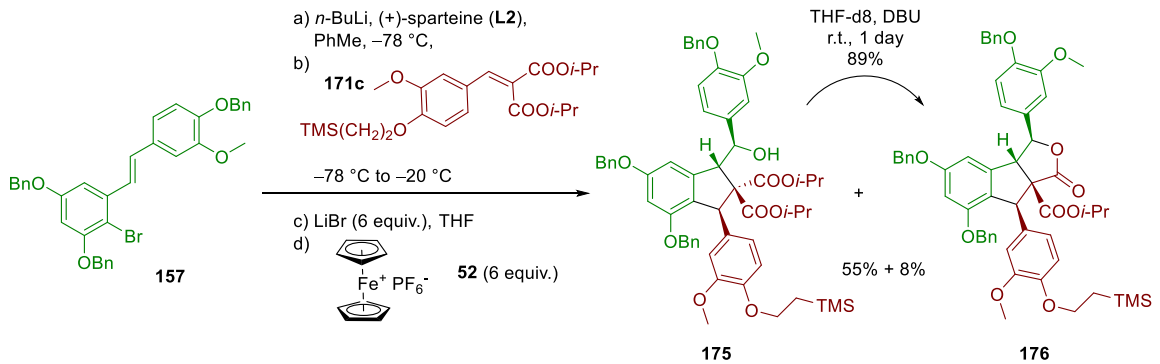
Sparteine (**L2**) is a well-known chiral director that strongly binds lithium in its bispidine-like pocket. Its organolithium complexes have been used successfully for asymmetric deprotonation of hindered carbamates [181a] and esters,[182] for asymmetric lithium-halogen exchange reactions [183] and carbolithiations of nonactivated [184] and activated [147,148] alkenes. Unfortunately, no model for the enantioselective conjugate addition of ArLi to ylidenemalonates mediated by **L2** exits to explain the absolute configuration of adducts **172a-d**. However, based on X-ray structures of organolithium-**L2** complexes 181b and the predictable stereochemical outcome of asymmetric deprotonation reactions,[181a-d] we assumed that the Lewis-basic *E*-positioned carbonyl group of the malonate approaches the monomeric sparteine complex **173** from the less hindered rear face (scheme 54), while the aryl group occupies the top face, leaning right towards the C, D rings of **L2** and away from the clash with the A, B ring system. In theory, the non-symmetrically substituted aryl ring of the stylbenyllithium gives rise to two rotameric forms **173a** and **173b**, which may give rise to distinct sets of transition states, however both rotamers predict the same optical isomer of the product and therefore are treated together as **173**. Coordination of the malonate may occur either from its *Re* face (scheme 54, top pathway) leading to transition state **174-I**, or from its *Si* face (bottom pathway) leading to TS **174-II**. The face selectivity is then governed by the clash between the ester group of the malonate and the AB ring system of **L2** present in **X174-I** but absent in **X174-II**., therefore the model predicts (*S*)-**172b** to be the major product.



Scheme 54. Model for enantioselective conjugate addition of **157** to malonate **171b** mediated by (+)-sparteine. Disfavoured pathway involving TS **174-I** leading to (*R*)-**172b** (top). Favoured pathway involving TS **174-II** leading to (*S*)-**172b** (bottom).

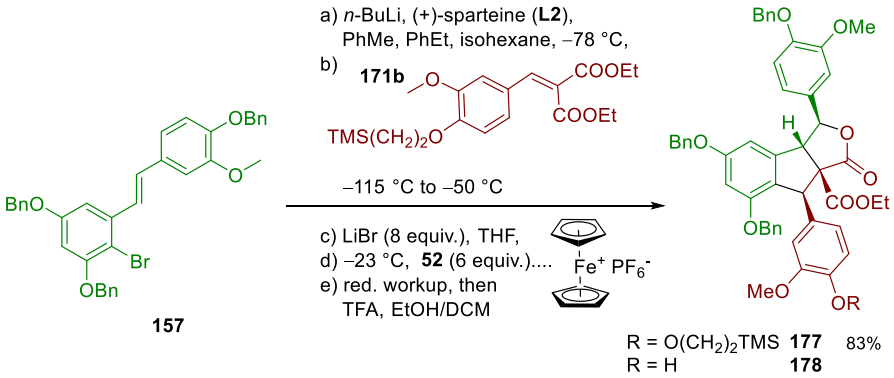
4.2.9. Total synthesis of (+)-gnetifolin F (**I**)

The next challenge on the way to total synthesis of **I** and other FISs was to merge the optimized conditions for conjugate addition with the oxidative cyclisation. The conditions developed earlier for the racemic approach (chapter 4.1.5) relied on using THF as a solvent and on adding excess LiBr, which is insoluble in toluene. Additionally, we did not know if the copper catalyst, absent in the asymmetric method, played any role during the oxidation step. To test the feasibility of *in situ* oxidation without modifying the protocol, enolate of **172c** was generated by conjugate addition of **157** to **171c** in toluene at –78 °C, followed by warming to –20 °C (scheme 55). THF was added so that the ration of THF/toluene was above 2:1, followed by LiBr (6 equiv.) and excess **52**. The radical *5-exo-trig* cyclisation proceeded well giving **175** as the main product in 55% yield together with 8% of the bicyclisation product **176**. The enantiomers of **176** could not be separated by chiral HPLC, therefore the optical yield of the sequence was established by analysing **176**, which showed 59% ee. This value is consistent with previously obtained values (table 10).



Scheme 55. One-pot conjugate addition/oxidation sequence using **157** and **171c**.

The structure of **176** was assigned based on similarity of its NMR spectra with the spectra of **139** (chapter 4.1.5). Hydroxymalonate **175** proved stable to acid (not shown), however treating the solution of **175** in THF-d8 with DBU resulted in slow conversion to **176**, proving the relative configuration of **175**. The increased formation of hydroxymalonate **175** and its stability towards acid and silica can be explained by a less facile dealkylation of the ester during acid catalysed lactonization. The one-pot sequence was therefore repeated with diethylmalonate **171b** (scheme 56) using the eutectic solvent conditions developed in chapter 4.2.7 (table 9). After reductive aqueous workup using Na_2SO_3, the crude product was treated with TFA in a mixture of DCM/EtOH, affording 83% of **177** after purification. When the treatment with TFA was replaced by extraction from 1 N HCl to EA, varying quantities of the dealkylated product **178** were obtained along with the desired product. The enantiomers of **177** were inseparable by chiral HPLC, analysis of **179** (see below) after saponification showed 69% ee.

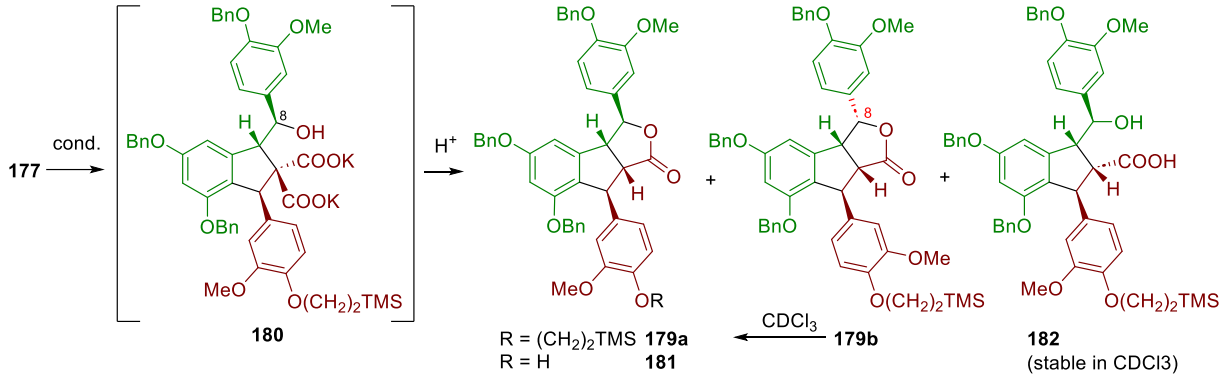


Scheme 56. One-pot conjugate addition/oxidation sequence using **157** and **171b**.

The yield of the double annulation based on conjugate addition using (+)-**L2** in toluene was even higher than during the racemic study. This proved that 1) copper salts did not play a key role in the oxidation mechanism and 2) that (+)-**L2** is fully compatible with the oxidation. In fact (+)-**L2** may even play a role in facilitating the oxidation by acting as a redox mediator.[166] Additionally, the LiBr·**L2** complex might act as a source of soluble bromide anion, which might facilitate ester dealkylation during lactonization.

The cyclic intermediate **177** contains the complete skeleton of **I**, with all four stereocentres set. The remaining steps of the synthesis deal with the removal of the carboxylic ester group at C-8', reduction of C-9' and removal of all protecting groups. As in the racemic approach, decarboxylation was achieved via saponification of **177**. Using KOH in water/EtOH/toluene mixture, followed by workup with aqueous HCl, low yields of **179a** were obtained (table 11, entries 1, 2). LiOH in aqueous dioxane only hydrolysed the lactone function, which recyclised back to **177** on workup (entry 3). Energetic conditions were required to fully saponify both the lactone and the ethoxycarbonyl groups to give di-salt **180**, which underwent re-lactonization followed by decarboxylation on treatment with 30% aqueous citric acid. The optimum 80% yield of lactone **179a** was obtained by resubmitting the crude product to the reaction conditions twice (entry 5). Aqueous citric acid proved to be the best protonation source for the decarboxylation, because it did not lead to significant loss of the 2-(trimethylsilyl)-ethyl protecting group on C4'-O, giving 181. Small amounts of unstable C-8 epimer **179b** were detected in samples of **179a**, it however converted spontaneously to **179a** in $CDCl_3$.

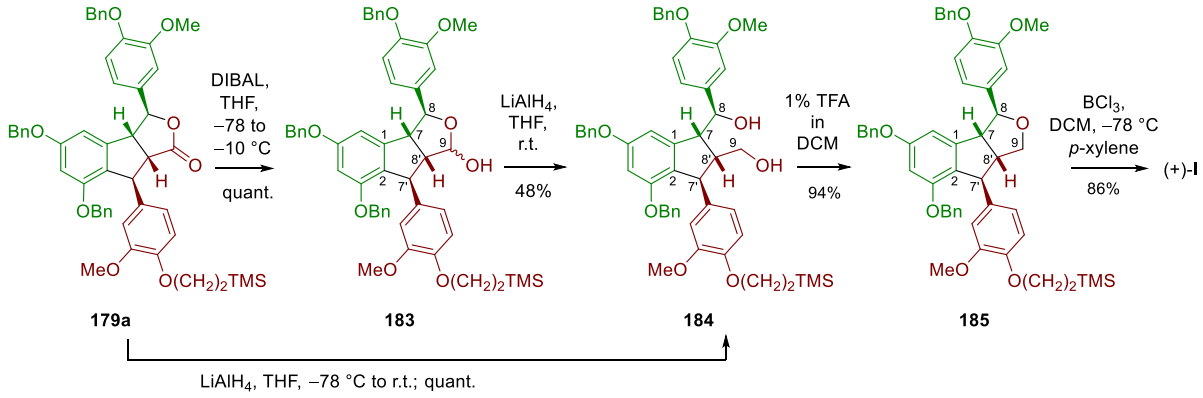
Table 11. Saponification of **177**.



Entry	Base (equiv.)	Solvent	Conditions	Workup	**179a** %	**181** (%)	**182** (%)
1	KOH (3.5)	EtOH/Tol/H_2O	4 h, 78 °C	0.5 N HCl	46%	0	2%
2	KOH (90)	EtOH/Tol/H_2O	4 h, 78 °C	1 N HCl	40%	22%	0
3	LiOH (40)	dioxane/H_2O	1 h, 100 °C	30% $_w$ citric a.	[a]	-	-
4	KOH (150)	dioxane/H_2O	16 h, 100 °C	30% $_w$ citric a.	42%	11%	0
5	KOH (165)	dioxane/H_2O	[b], 100 °C	30%$_w$ citric a.	80%	-	17%

[a] No conversion. [b] Three cycles of saponification/workup.

Reduction of lactone **179a** by DIBAL in THF at –78 °C to –10 °C afforded a mixture of anomeric lactols **183** that could be reduced to diol **184** by $LiAlH_4$ in moderate yield. Direct reduction of lactone **179a** by $LiAlH_4$ in THF gave diol **184** in essentially quantitative yield. Etherification by 1% TFA in DCM proceeded smoothly to give the fully protected gnetifolin F derivative **185**. Global deprotection at –78 °C by BCl_3 in DCM using *p*-xylene as a cation scavenger [178,179] afforded **I** in 86% yield, finishing the first asymmetric total synthesis of (+)-gnetifolin F (**I**) in 5 steps, 53% yield from malonate **171b**. The NMR spectra of the synthetic sample matched the reported spectra of the natural product (for comparison of NMR data, see chapter 6.2.11).[97,99]

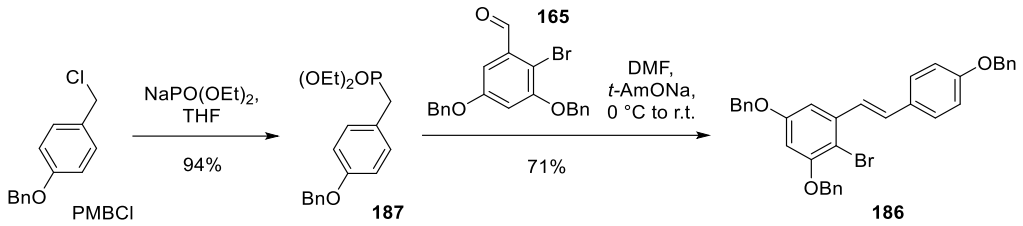


Scheme 57. Final reduction of **179a** and global deprotection leading to gnetifolin F (**I**).

4.2.10. Total synthesis of (+)-11-deoxykompasinol A (**IV**)

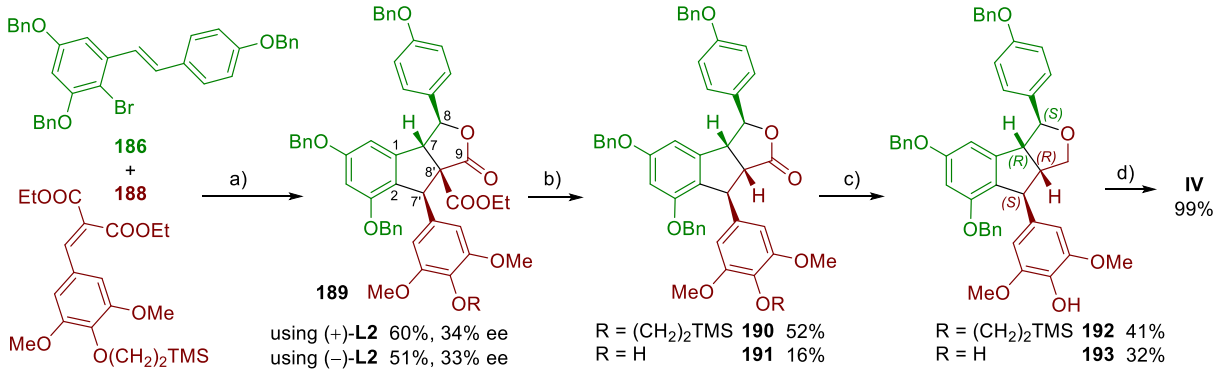
The total synthesis of **IV** started with the preparation of protected resveratrol **186**. Phosphonate **187** was prepared in 94% yield from commercial *para*-(benzyloxy)-benzyl chloride

(PMBCl). Horner-Wadsworth-Emmons olefination of **187** with aldehyde **165** using the standard conditions (chapter 4.2.4) afforded **186** in 71% yield after recrystallisation from Et_2O/MeOH mixture.



Scheme 58. Synthesis of stilbene **186**.

The required sinapic acid-derived ylidenemalonate **188** was prepared by analogous sequence as **171a-d** in 80% yield from syringaldehyde (see experimental part). Conjugate the addition of **186** to **188** using (+)-**L2** under the conditions previously used for **177** (previous chapter), followed by cyclisation afforded 60% yield of **189** as a single diastereomer (scheme 59). However, the asymmetric induction was only 33% ee, considerably lower than in the previous cyclisation. The reason behind this drop in induction is not clear, because structure of the nucleophile and electrophile differ from **157** and **171b** only by the position of one methoxy group (C-5' instead of C-11), which is far from the reacting centres.



Scheme 59. Synthesis of 11-deoxykompasinol A (**IV**). Conditions: a) **186**, *n*-BuLi, (+)-**L2**, toluene, EtPh, isohexane, –78 °C, then **188** at –125 °C, then LiBr, THF, excess **52**, –50 to 0 °C, then TFA, DCM; b) aq. KOH, EtOH/toluene, reflux, then 50% aq. citric acid; c) $LiAlH_4$, THF, –78 °C to r.t., then 1% TFA in DCM; d) BCl_3, *p*-xylene, DCM, –78°C.

Saponification-decarboxylation again required forcing conditions, affording 52% yield of **190** along with 17% yield of partially deprotected **191**. Reduction of **190** by $LiAlH_4$ proceeded well, however re-etherification of the resulting diol by TFA in DCM again caused partial loss of the $(CH_2)_2$TMS group giving 41% of protected **192** and 32% of dealkylated **193**. Global deprotection by BCl_3 in DCM/*p*-xylene mixture afforded **IV** in quantitative yield. This completed the total synthesis of optically enriched (+)-11-deoxykompasinol A (**I**) in 5 steps, 14% from malonate **188**. The NMR spectra of the synthetic sample matched the reported spectra of the natural product (for comparison of NMR data, see chapter 6.2.11).[110]

The synthetic sample of **IV**, obtained as a scalemic mixture (33% ee) had specific rotation of only α_D^{20} = +9.3 (c 1.330, MeOH). The reported rotation of natural (*7S,8R,7'R,8'S*)-**IV** was α_D^{20} = –58.6 (c 0.1, MeOH).[110] This was consistent with our assignment of (*7R,8S,7'S,8'R*)-**IV** for our synthetic (+)-**IV**, based on extension of Tomioka's model (chapter 4.2.1). Since the asymmetric induction during the conjugate addition to **188** was low, we decided not to prepare (–)-**IV** from (–)-

sparteine. Instead, we separated the enantiomers of **IV** using preparative chiral HPLC. The chemically and enantiomerically pure sample of (+)-(*7R,8S,7'S,8'R*)-**IV** had specific rotation of α_D^{20} = +30.3 (c 1.145, MeOH), while the minor synthetic enantiomer only α_D^{20} = –14.5 (c 1.117, MeOH). After the measurement of optical rotation and ECD spectra, the samples were collected and checked for purity by ^{1}H NMR. The (+) enantiomer showed no signs of decomposition, while the (–) enantiomer was contaminated by an impurity, likely the C-8 epimer. This explained the lower rotation value of this sample.

We observed this instability with respect to epimerisation at C-8 earlier in the synthesis of **I** (chapter 4.2.9, table 11). Similar acid-catalysed epimerisation equilibrium between furofuran lignans sesamin and asarinin,[152] and pinoresinol to epipinoresinol [153] has been observed before. This instability may also influence the measured values of optical rotation of isolated natural FISs, because due to minute quantities of isolated material, the presence of the C-8 epimer may go unnoticed. To confirm that natural (–)-**IV** [110] was indeed optically enriched, we compared the reported ECD spectrum of natural (–)-**IV** with ECD spectra of synthetic (+)-**IV** and (–)-**IV** (figure 18).

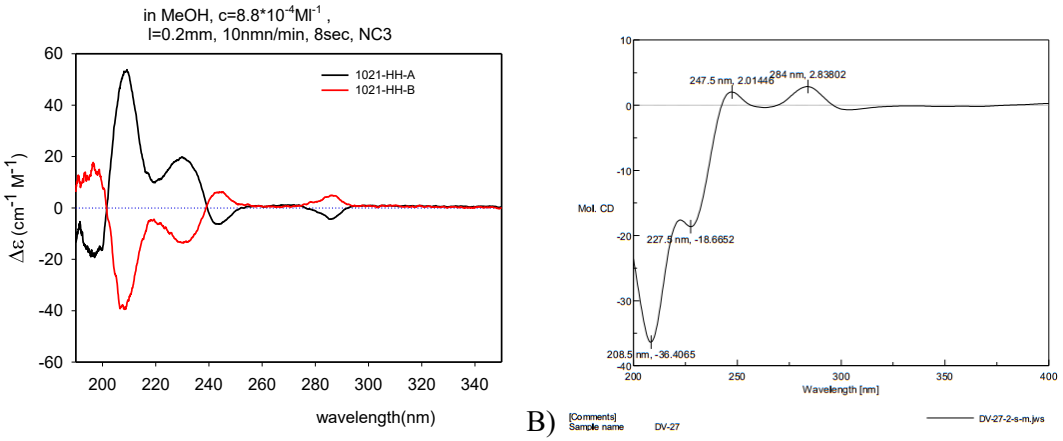
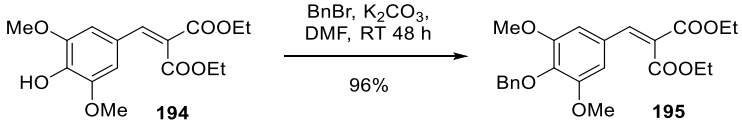


Figure 18. ECD spectra of **IV** in MeOH. A) Synthetic (+)-**IV** (black) and (–)-**IV** (red); B) Reported spectrum of natural (–)-**IV**.[110]

4.2.11. Towards kompasinol A (**III**)

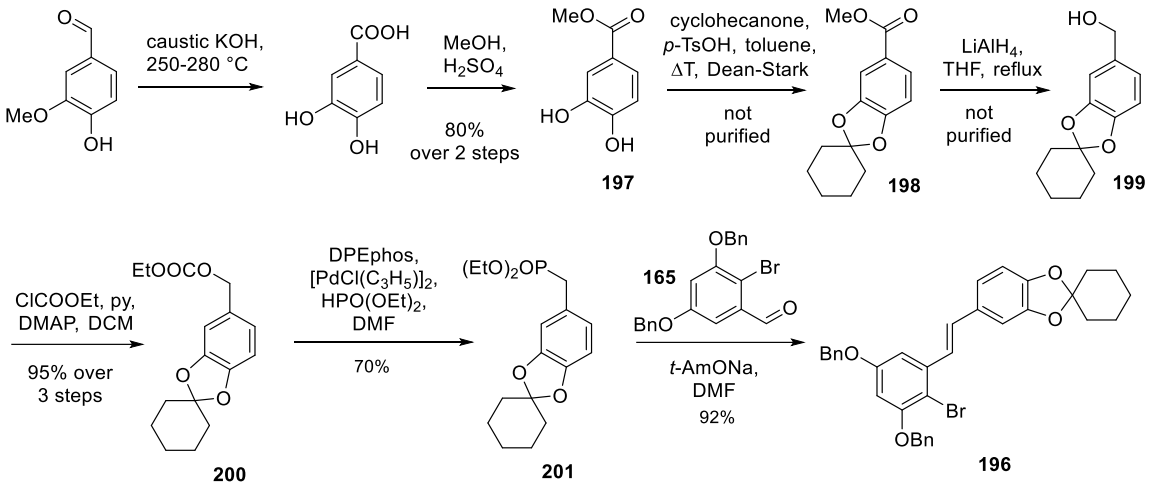
For the synthesis of kompasinol A (**III**) we decided to switch the protecting group at C4'-O due to the previous stability problems with 2-(trimethylsilyl)-ethyl group. Sinapic acid-derived phenol **194**, prepared from syringaldehyde (see experimental part), was protected by alkylation with BnBr in DMF giving malonate **195** in quantitative yield. The benzyl group proved ideal for the protection of stilbene part in the syntheses of **I** and **IV** and was reliably deprotected by BCl_3/*p*-xylene.



Scheme 60. Synthesis of malonate **195**.

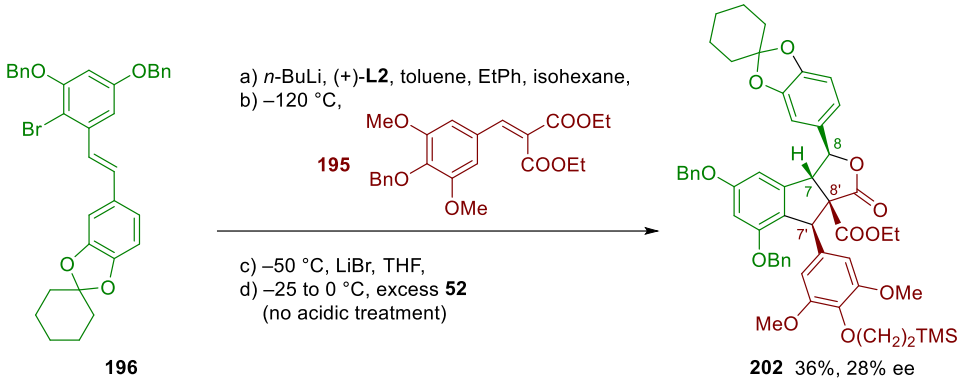
The synthesis of protected piceatannol **196** started with oxidation/demethylation of vanillin by hot caustic KOH,[185] followed by Fischer esterification to give methyl protocatechuate (**197**) in 80% yield over 2 steps. Ketalisation under the conditions of azeotropic water removal afforded spiroketal

198, which was directly without purification reduced to alcohol **199** and ethoxycarbonylated under standard conditions to yield carbonate **200** in essentially quantitative yield from **197**. Palladium-catalysed Tsuji-Trost reaction using the same conditions as for **151** (chapter 4.2.3) afforded in 70% yield phosphonate **201**, which was used for the Horner-Wadsworth-Emmons reaction with aldehyde **165** under standard conditions, affording **196** in 92 % yield.



Scheme 61. Synthesis of stilbene **196** from vanillin.

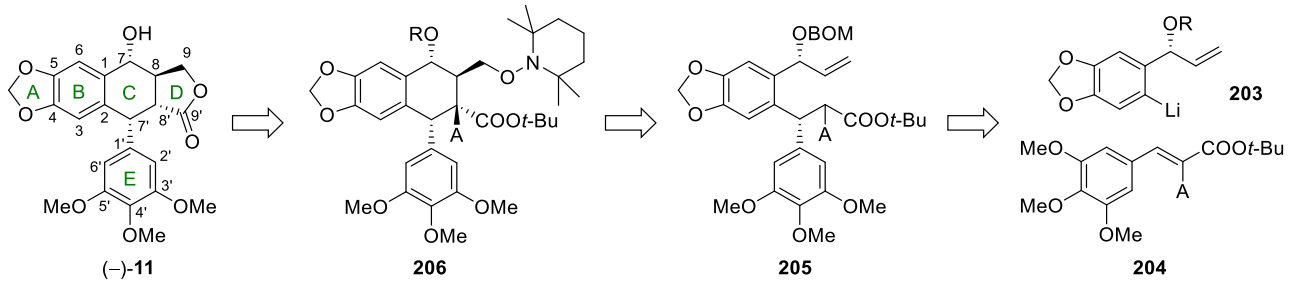
One-pot annulation was performed under standard conditions, except that acidic treatment (TFA) was omitted due to the unknown stability of the spiroketal protection group at C-11 and C-12. Cyclic lactoester **202** was obtained as a single diastereomer in 36% yield, but only 28% ee (scheme **62**). This low asymmetric induction confirmed, that sinapic acid-derived malonates (**188**, **195**) are not as good substrates for sparteine-mediated asymmetric conjugate addition as are the ferulic acid-derived malonates **171a-d**. The cyclic product **202** contains the full skeleton of **III** with all four sterocentres already in place. The synthesis of **III** was not continued due to time constrains. Future efforts towards (7*R*,8*S*,7'*S*,8'*R*)-**III** should swich focus on using Tomioka's diether ligand (*S,S*)-**L1** instead of (+)-**L2**.



Scheme 62. One-pot annulation of stilbene **196** with malonate **195**, leading to assembly of complete akeleton of kompasinol A (**III**).

4.3. Part C: Approaches to podophyllotoxin via direct conjugate addition to cinnamate

The direct conjugate addition of ArLi to ylidene malonates and *t*-Bu cinnamates, used to a great advantage for synthesis of FISs (chapter 4.1, 4.2), proved to be a suitable method for stereocontrolled union of planar synthons. Based on our experience and literature precedent (chapters 1.3.3, 1.7.2 [63,64]) we proposed a short total synthesis of podophyllotoxin (**11**) based on substrate-controlled conjugate addition of easy-to-access chiral synthon Li-**203** to a general Michael acceptor **203** (scheme 63).

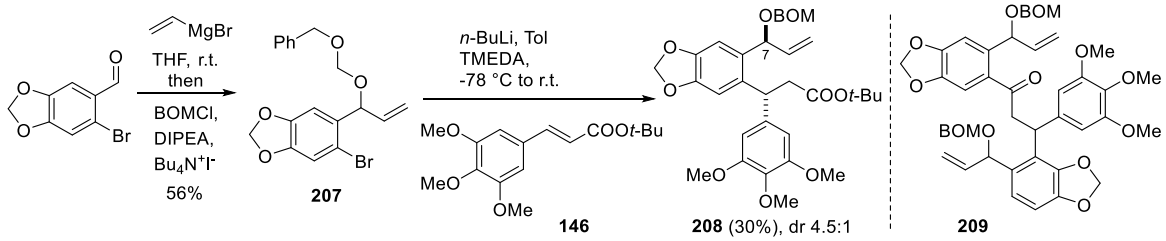


Scheme 63. Retrosynthetic analysis of (–)-**11** based on radical *6-exo-trig* cyclisation. A = H or COO*t*-Bu.

Oxidation of the enolized Michael adduct **205** should result in a radical *6-exo-trig* cyclisation, followed by trapping of the cyclic primary radical with TEMPO. Deprotection of the resulting adduct **206**, already oxygenated at C-9, followed by a known lactonization should lead to **11**. No model was available to predict the selectivity and the relative configuration of **205**, which results from a rather uncommon 1,4-transfer of chirality. However, assuming there is such a sufficient level of stereoinduction, the stereocentre at C-7 can be corrected through a known oxidation/reduction sequence via podophyllone (chapter 1.3.3),[64] Synthon **203**, which is the original source of chirality for all the subsequently created stereocentres, should be available in optically pure form via catalytic vinylation of piperonal, as well as in racemic form via Grignard addition to piperonal.

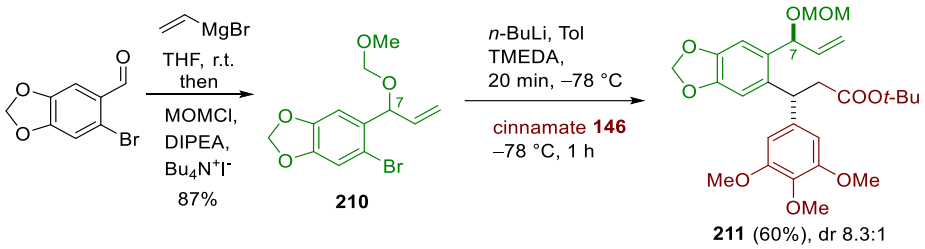
4.3.1. First generation radical *6-exo-tet* approach

The racemic synthesis started with addition of vinylmagnesium bromide to 6-bromopiperonal in THF (scheme 64). The resulting alkoxide was alkylated in situ using (benzyloxy)methyl chloride (BOMCl) to give rac-**207** (scheme. The (benzyloxy)methyl group was selected due to its high ability to coordinate lithium atoms, relative ease of deprotection and its larger steric demand in comparison with the more common (methoxy)methyl (MOM) group. However, purification of the BOM-protected **207** proved difficult, due to contamination with benzyloxymethyl benzyl ether, present in commercial BOMCl. After repeated chromatography, **207** was isolated in 56 % yield, still containing traces of the contaminant.



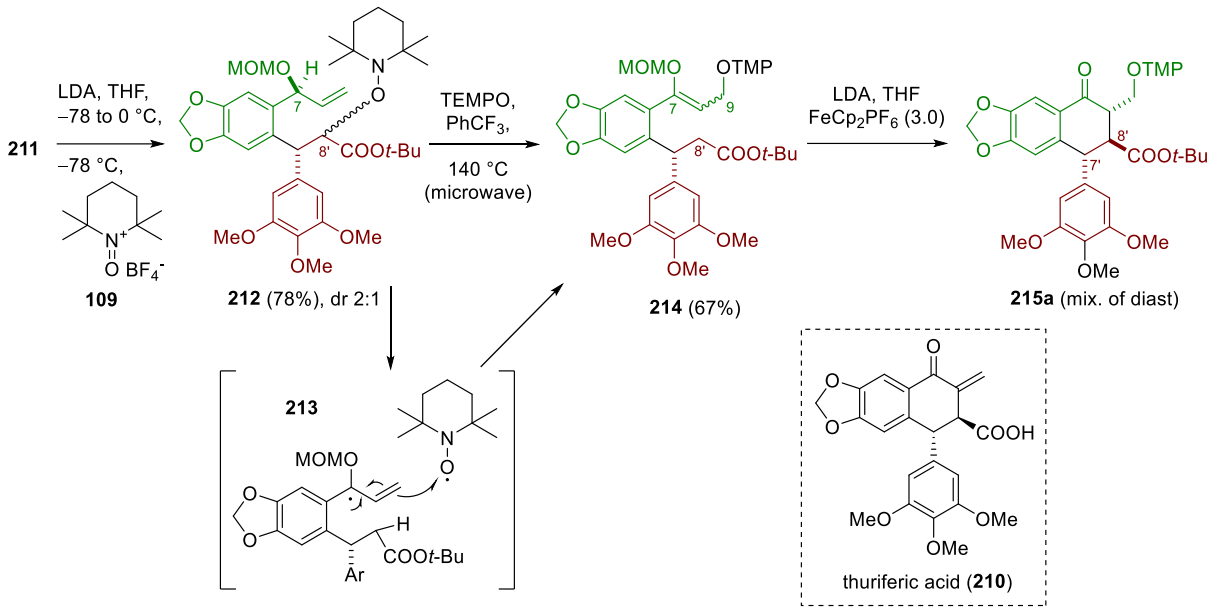
Scheme 64. Initial study of conjugate addition using (benzyloxy)methyl group (BOM).

Bromide **207** was then lithiated by *n*-BuLi in toluene in the presence of TMEDA, followed by addition of cinnamte **146**. Conjugate addition did indeed occur, giving **208** as a 4.5:1 mixture of diastereomers, however the yield was only 30% after purification. The relative configuration of **208** was not known at this time, later synthesis (see below, scheme 67) determined that the major isomer had anti configuration. Modifying the reaction conditions, including temperature and solvent did not improve the yield. Consistent with our previous observations, the reaction in THF or in the absence of TMEDA failed to deliver any **208**. Instead, polymers derived from cinnamate **146** and products of 1,2-addition like **209** were observed. We speculated, that the low yield of **208** resulted from the interference of oxygen containing impurities in **207**. We therefore decided to repeat the sequence using the MOM group to protect the alcohol function at C-7 instead of BOM. Due to the lower boiling point of the MOMCl and its contaminants, this should circumvent the above problem. Out hypothesis proved correct, as the yields of both Grignard addition/protection giving **210** and the conjugate addition steps improved dramatically to 87% and 60% respectively (scheme 65). The diastereomeric excess also improved to 5.5:1 in crude **211** and to 8.3:1 after purification.



Scheme 65. Conjugate addition of MOM-protected **210** to **146**.

In the next step, **211** was deprotonated by LDA reacted with the strongly oxidizing salt **109** to form TEMPO adduct **212** in 78% yield as a mixture of epimers at C8' (scheme 66). Such alkoxyamines like **212** derived from TEMPO are known to be homolytically unstable and can be activated by heat to undergo group transfer cyclisation utilizing the persistent radical effets (refs. in chapter 4.1.2.[157,165,178] Using a microwave reactor, a solution of **212** in trifluorotoluene was heated for 1 h to 140 °C. No cyclised products were formed, instead, an unexpected 1,5 hydrogen transfer from C-7 occurred, leading to a delocalized radical **213** that was captured by TEMPO at C-9 to give **214** in 67% yield as a mixture of *E/Z* isomers (dr 1:1).

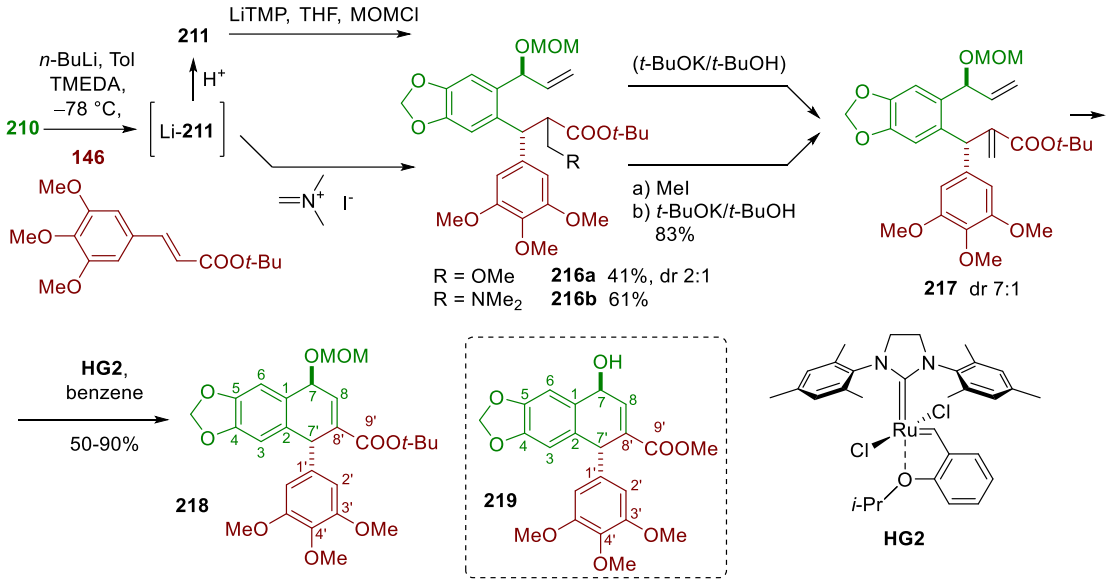


Scheme 66. Attempted radical cyclisation approach to **11**.

This isomerisation unfortunately destroyed the original stereocentre at C-7, but on the other hand led to a new placement of the double bond, so that an alternative *6-endo-trig* cyclisation could now be triggered. The resulting cyclic radical would now enjoy the same kind of benzylic stabilisation as during the *5-exo* cyclisations leading to the indane skeleton of FISs and be therefore amenable to secondary oxidation to carbenium ion. TEMPO adduct **214** was therefore deprotonated again using LDA in THF and oxidized by excess $FeCp_2PF_6$ (**52**). The expected cyclisation and secondary oxidation indeed occurred, followed by dealkylative stabilisation of the benzylic carbocation intermediate to give **215a**, together with another diastereomer and other unknown products. Unfortunately, the reaction was very unselective and **215a** was difficult to separate from sideproducts. The relative configuration of **215a**, assigned on the basis of ^{1}H-^{1}H coupling constants, did not match **11**. The *trans* relationship between the substituents at C7' and C8' is characteristic of another natural product, thuriferic acid (**10**).[33,186] At this stage, the radical cyclisation approach to **11** was abandoned, as there was no simple way how to override the unfavourable stereochemical outcome of the cyclisation.

4.3.2. Second generation approach based on RCM/conjugate addition

The stereoselective conjugate addition leading to **211,** from the ultimately unsuccessful radical *6-exo-trig/6-endo-trig* cyclisation-based approach to **11,** prompted us to explore an alternative strategy, based on ring-closing metathesis (RCM). In this revised approach, we decided to install one additional carbon atom at C-8' via one of the standard methylenation procedures. Deprotonation of **211** by LiTMP, followed by alkylation by MOMCl afforded **216a** in only 41% yield due to incomplete deprotonation of **211** (scheme 67). Optimization of the deprotonation conditions did not lead to improved conversion. Realizing that the enolate of **211** resulting from conjugate addition of **210** to **146** can be directly intercepted via alkylation, we used Eschenmoser's iodide salt as the electrophile leading to 61% yield of **216b** from the one-pot reaction. Methylation and base-induced elimination gave diene **217** in 83% yield from **216b**. The choice of solvent (*t*-BuOH) for the elimination step proved critical. When the elimination was attempted in THF, KO*t*-Bu caused fast decomposition of the diene **217** via migration of the double bond into conjugation with the adjacent aryl rings.



Scheme 67a. Ring-closing metathesis approach to **11**.

After purification, diene **217** was heated with the second generation Hoveyda-Grubbs catalyst in benzene. The expected DCM reaction proceeded smoothly, with diene **217** being cleanly and nearly quantitatively converted to **218**. However, unlike the diene, **218** was moderately sensitive to acid, including silica, therefore the yield of pure **218** ranged between 50-90%.

At this point, the relative configuration of **218**, and therefore of its precursors, could finally be determined. NMR spectra of **218** in $CDCl_3$ were compared with known methyl ester **219**.[63] Due to the high rigidity of the AB ring system, the chemical shifts of H3, H6, H7, H8, H2' and H7' in **218**, as well as of the respective C atoms, match well the values reported for **219** (table 12). The coupling constant pattern of the H7/H8/H7' spin system is conserved between **218** and **219** as well. The chemical shifts of the minor diastereomer **218'** on the other hand differed significantly from **219**.

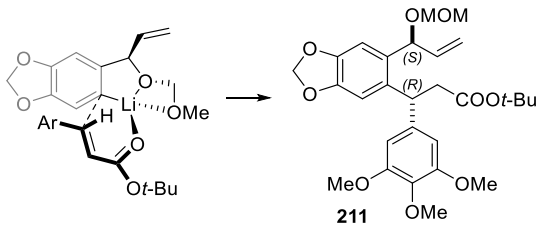
Table 12. Comparison of chemical shifts of selected atoms of **218** with reference compound **219**.[63]

Atom	^{1}H δ ppm (*J* Hz) [a]	^{13}C [a]	^{1}H δ ppm (*J* Hz) [b]	^{13}C δ ppm [b]	^{1}H δ ppm [c]	^{13}C δ ppm [c]
3	6.65	107.6	6.67	108.1	6.68	100.3
6	7.13	106.3	6.99	106.8	6.14	109.6
7	5.34 (ddd, 10.2, 3.7, 2.8)	65.6	5.35 (dd, 3.4, 2.8)	71.7	4.98	75.4
8	7.20 (d, 2.8)	139.4	7.17 (dd, 2.7, 1.1)	135.7	8.09	129.9
2'	6.30	104.8	6.30	105.3	6.63-6.45	- [d]
7'	4.93 (d, 3.7)	45.6	4.88 (d 3.5)	45.8	4.68	44.3
8'	-	136.3	-	135.2	-	~134 [e]
9'	-	166.3	-	165.4	-	~165 [e]

[a] NMR data of known methyl ester **219**.[63] [b] NMR data of major diastereomer of **218**. [c] NMR data of minor diastereomer **218'**. All data in $CDCl_3$. [d] Not detected. [e] Detected by HMBC.

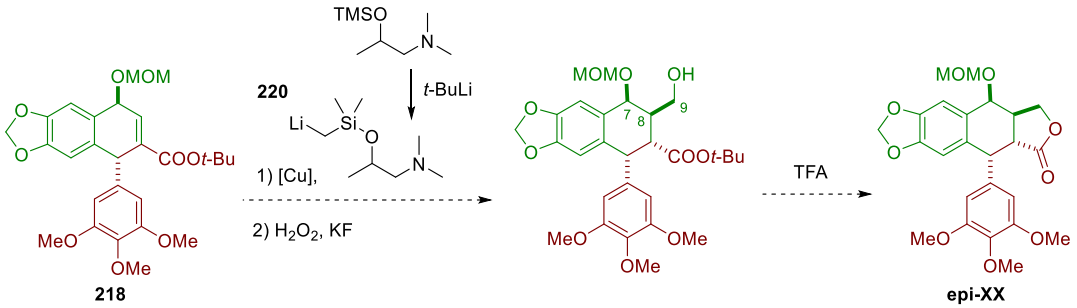
Having established the configuration of **218**, the transition state of conjugate addition was considered in order to explain the observed diastereoselectivity. Since toluene is a strictly non-coordinating solvent with respect to Li, the four coordination sites of the Li atom must be occupied by the substrates and/or TMEDA. The basis of the model is a 5-membered metallacycle, formed by chelation of the Li atom by the ether oxygen of the MOM group (scheme 68). Another site should be

occupied by the carbonyl group of the cinnamate, the last fourth site is occupied by the second oxygen atom of the MOM group, presumably blocking the opposite side of the 5-membered metallacycle with respect to the vinyl group. The acceptor therefore approaches from the same face as the vinyl group. The cinnamate orientation is chosen to minimize repulsion with the vinyl group, predicting the formation of *rel*-(7*S*,7'*R*)-**211**,



Scheme 68. Proposed model of the transition state for the formation of **211**.

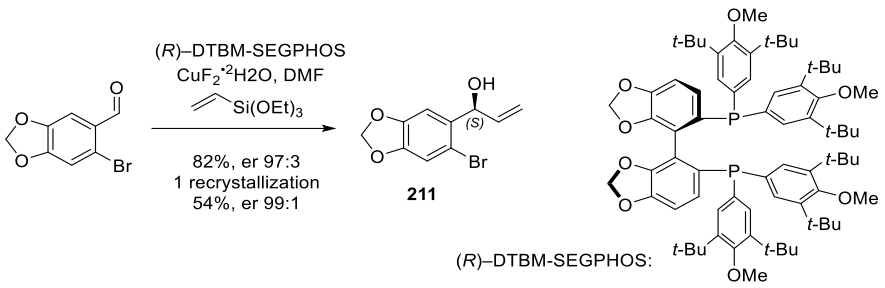
After establishing the short route to **218**, we planned to continue the synthesis by the addition of the remaining carbon C-9 by the means of another conjugate addition (scheme 69a). The strong coordinating ability of the MOM group at C-7 should favour *syn*-addition of hard metal-based organometallic nucleophiles like RLi and Grignard reagents, establishing the correct configuration at C-8. To this end, several silicon substituted one-carbon donor synthons were considered, envisioning a subsequent Fleming-Tamao oxidation to unmask the hydroxymethyl group. All attempts at reproducing a published directed lithiation of 2-trimethylsilylpyridine [187a-c] were unsuccessful, with the pyridine ring being attacked in preference to the desired lithiation of the TMS group. In contrast to that, directed lithiation of TMS-protected 3-(dimethylamino)-3-propanol [188] proceeded smoothly to give reagent **220**, which was proven by capture by model electrophiles (not shown).



Scheme 69a. Planned continuation of the synthesis of epipodophyllotoxin (**19**).

Due to time constraints, the conjugate addition hasn't been explored yet. If successful, the planned continuation of the synthesis of the medicinally relevant epipodophyllotoxin (**19**) (chapter 1.3) would include the cleavage of the Si-C bond by the Fleming-Tamao oxidation and a final deprotection by TFA with concomitant lactonization.

In order to render the synthesis asymmetric, enantioselective version of the initial vinylation of 6-bromopiperonal was explored. A method based on CuF_2·(*R*)-DTBM-SEGPHOS, developed for vinylation and phenylation of *para*-substituted benzaldehydes using tris(alkoxy)silanes was tested on 6-bromopiperonal (scheme 69b). Gratifyingly, alcohol **221** was obtained in 82% yied, er 97:3, using 4% catalyst loading. Essentially optically pure (*S*)-**221** was obtained by single crystallization from EA/hexane in 54% yield, er 99:1. The absolute configuration was proven by single crystal X-ray analysis (figure 19b).



Scheme 69b. Cu catalysed enantioselective vinylation of 6-bromopiperonal.[189]

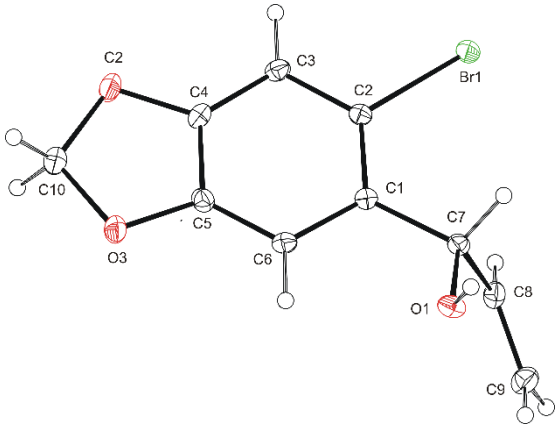
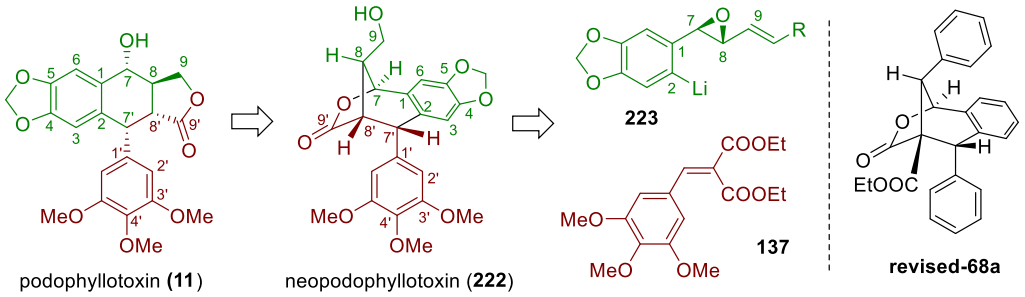


Figure 19. Crystal structure of alcohol (*S*)-**221**.

4.4. Part D: Approaches to neopodophyllotoxin polar bicyclisation of epoxystilbenes

In chapter 4.1.4 (scheme 39), the conjugate addition of lithiated stilbene oxide **126** to benzylidene malonate **113** was discussed. The following nucleophilic epoxide opening proceeded unexpectedly via *6-exo-tet* cyclisation mode giving bridged lactone **revised-68a**, as proven by X-ray crystallography. The bridged structure of **revised-68a**, including the relative configuration, resembles closely the structure of neopodophyllotoxin (**222**), a known isomer of podophyllotoxin (**11**) that easily undergoes translactonization to **11**.[190,191] Inspired by this analogy, we proposed an alternative synthetic strategy towards **11** via **222** that exploits the polar *6-exo-tet* cyclisation (scheme 70).

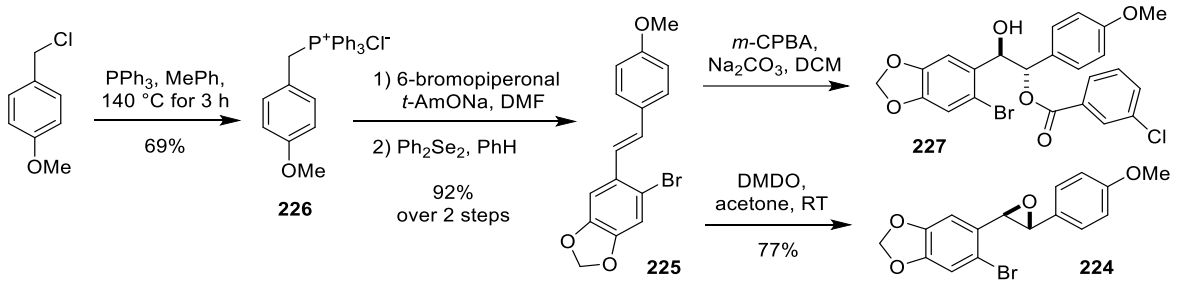


Scheme 70. Retrosynthesis of **222** based on conjugate addition/polar cyclisation of epoxide **223**.

This strategy conforms to our general conjugate addition/oxidative cyclisation paradigm, developed for biomimetic synthesis of lignans and related polyphenols. However, the oxidation step now precedes conjugate addition and even lithiation. This reversed sequencing of steps is enabled by the unusually high stability of lithiated oxiranes like **126** and **223**.[126]

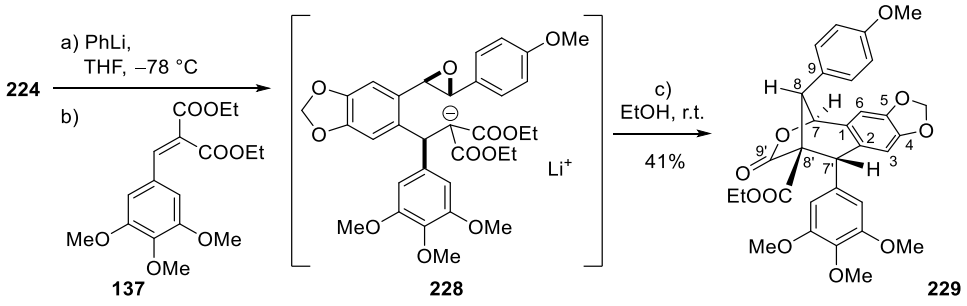
4.4.1. Synthesis of neopodophyllotoxin analog

A proof-of-concept study based on annulation of model stilbene oxide **224** was performed first to verify the reproducibility of the key *6-endo-trig* cyclisation. The required stilbene **225** was prepared using standard methods, starting from *para*-methoxybenzyl chloride, which was converted to phosphonium salt **226** in 69% yield (scheme 71). Witting reaction between **226** and 6-bromopiperonal using *t*-AmONa in DMF, followed by Ph_2Se_2 catalysed photoisomerization afforded (*E*)-**225** in 92% yield over 2 steps. Attempted epoxidation under standard conditions (chapter 4.1.4, scheme 39) using *m*-CPBA, either alone or buffered, led to significant decomposition with **227** being the only isolable product. Such behaviour of electron rich stilbenes has been described before [192] and stems from the instability of the product epoxide towards the acidic and/or nucleophilic reagent.



Scheme 71. Synthesis of epoxystilbene **224**.

Neutral dimethyldioxirane (DMDO) proved much better suited for the oxidation of stilbene **225**, giving epoxide **224** in 77% yield and sufficient purity, so that it could be immediately used in the next step without chromatographic purification. Following the previously discussed method (chapter 4.1.4),[126] **224** was lithiated at –78 °C in THF using PhLi (scheme 72), followed by addition of malonate **137**. After warming to r.t. and addition of protic solvent (EtOH), the enolate adduct cyclised as expected via enolate **228** giving trans lactone **229** in 41% yield. The crystalline nature of **229** allowed us to verify its structure and relative configuration by single crystal X-ray crystallography (figure 20).



Scheme 72. Synthesis of model neopodophyllotoxin analogue **229**.

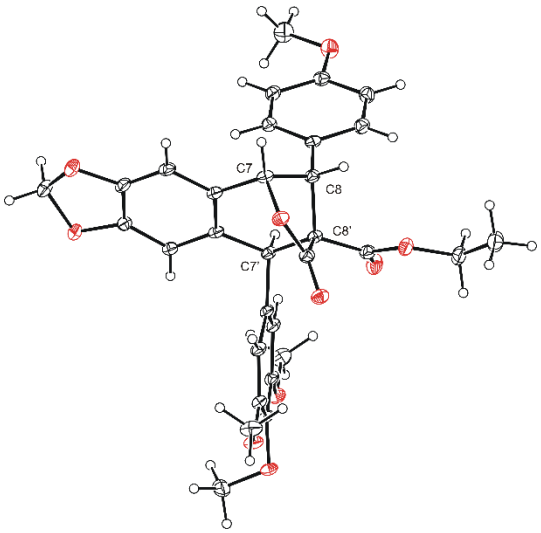
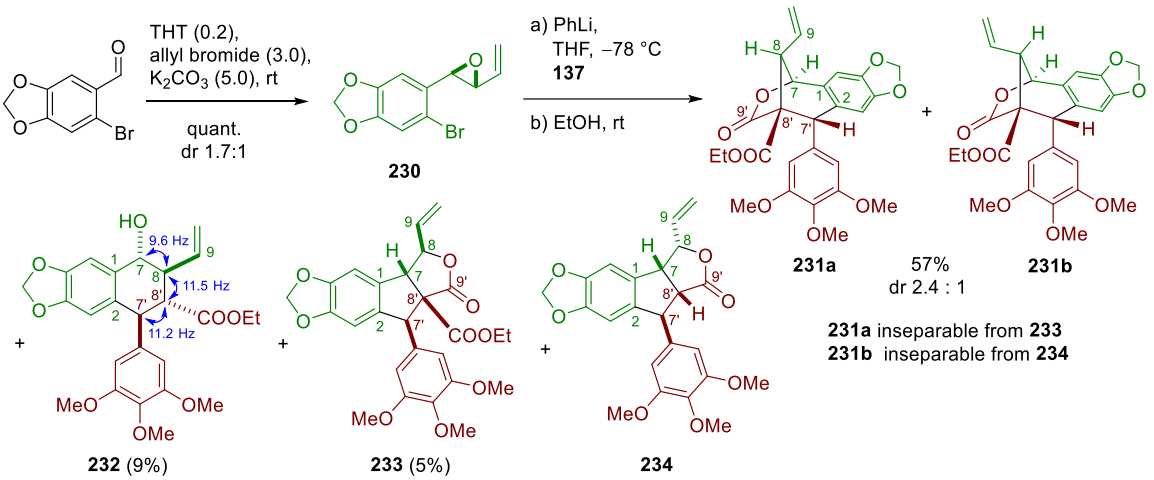


Figure 20. X-ray structure of **229**.

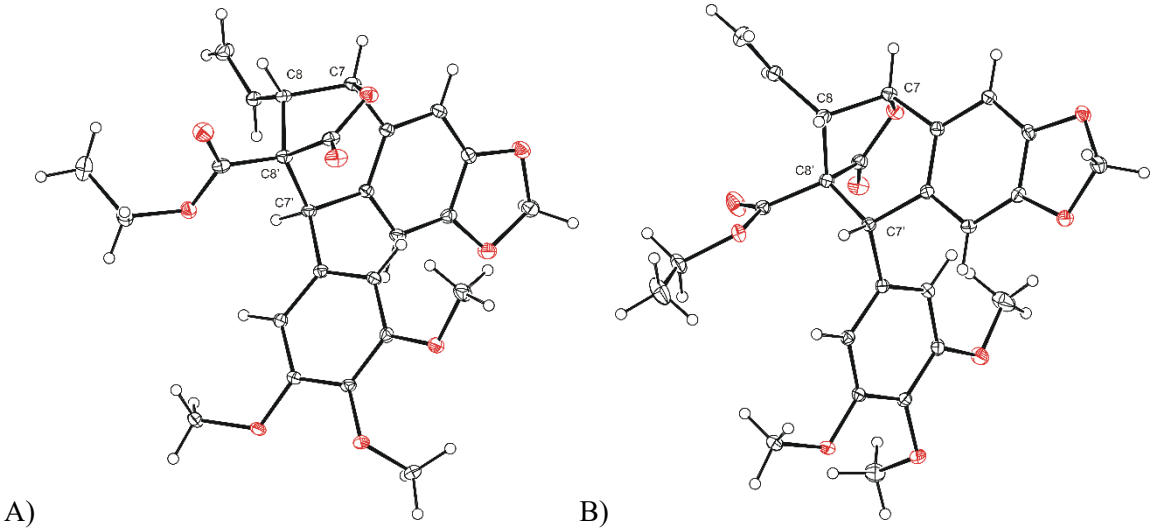
4.4.2. Rapid synthesis of neopodophyllotoxin core – racemic approach

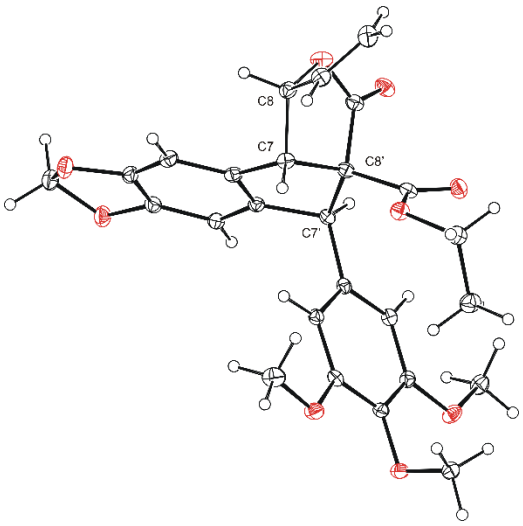
The reason, why the *6-endo-tet* cyclisation mode outcompeted the *5-exo-tet* mode during the cyclisation leading to **revised-68a** and **229** (chapters 4.1.4, 4.4.1) is likely due to the benzylic nature of atom C-8, as similar cyclisations of epoxides bearing a simple alkyl group on C-8 [126] usually prefer the *5-exo-tet* mode. It is reasonable to assume that the neighbouring aryl group, especially when bearing donor substituents, may stabilise the transition state of the S_N2 displacement of the epoxide oxygen atom. We hypothesize, that similar allylic stabilisation by a neighbouring vinyl group should lead to the same cyclisation outcome. Based on this idea, epoxide **230** was prepared from in one step by organocatalytic Corey-Chaykovsky epoxidation using cat. tetrahydrothiophene (THT) and K_2CO_3 in *t*-BuOH (scheme 73).[193] This remarkable transformation allowed the synthesis of the racemic cyclisation precursor **230** in a single step in essentially quantitative yield. Unfortunately, the reaction is not selective with respect to relative configuration of **230**, giving a 1.7:1 *trans*/*cis* mixture. The limited stability of **230** makes separation of its diastereomers unfeasible. Therefore, crude *trans*/*cis*-**230** was directly lithiated using PhLi in THF at –78 °C. Addition of malonate **137** was again followed by spontaneous double cyclisation, giving **231a/b** in 57 % yield as a 2.4:1 mixture of diastereomers. The formation of minor isomer **231b**, not observed during previous cyclisations, can be traced back to the minor *cis* isomer of epoxide **230**.



Scheme 73. Preparation and polar cyclisation of racemic epoxide **230**.

The cyclisation was run on multigram scale (approx. 10 g), which allowed the deetrmination of other minor cyclisation products **232**, **233** and **234**. Tetralin product **232** may be derived from **231b** via acid mediated inversion at C-7, partial hydrolysis and decarboxylation. Its relative configuration was assigned based on the large value of ^{1}H-^{1}H coupling constants between the C ring H atoms an C-7, C-8, C-8' and C-7' (scheme 73, left), which can be interpreted as near-antiperiplanar relationship between axial hydrogen atoms. Arylindane **233** resulted from a the less-favoured *5-exo-tet* cyclisation mode and therefore closely resembles FIS, including the relative configuration. Similarly, compound **234**, detected in trace amounts, was assigned arylindane structure related to diastereomer of **233** via decarboxylation. The structure of both diastereomers of **231a/b** as well as of indane **233** was assigned based on single crystal X-ray crystallography (figure 21).



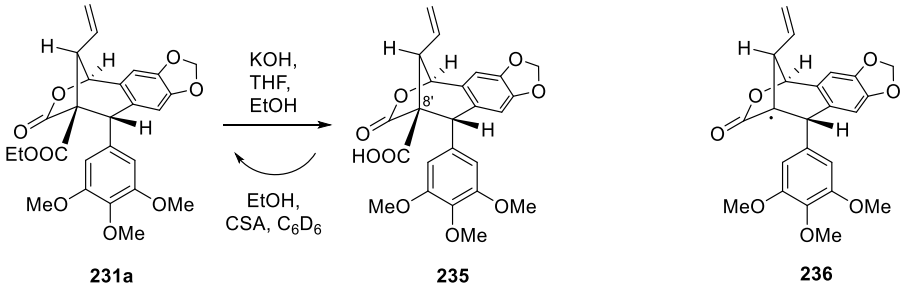


C)

Figure 21. Crystal structures of **231a** (A), **231b** (B) and **233** (C).

Unfortunately, diastereomers **231a/b** were only partially separable even after extensive chromatographic purification and resisted all attempts at fractional crystallization. Because extensive chromatography would make the synthesis of podophyllotoxin by such route impractical and expensive, a way to minimize the formation of **231b** was sought. Since **231b** is derived from the minor *cis* isomer of the epoxide **230**, the next round of effort was focused on optimizing the Corey-Chaykovsky epoxidation (chapter 4.4.3).

The major isomer **231a** accumulated by chromatography was used to briefly explore the reactivity of the bridged lactoester. When subjected to saponification by LiOH in THF/EtOH at r.t. (scheme 74), the material was converted to an unknown polar compound that spontaneously converted back to **231a** on contact with silica or aqueous workup. This observation can be explained by reversible hydrolysis of the lactone without saponification of the ester group. When saponification was carried out using KOH in THF/EtOH for 16 h, formation of a new, more stable compound was observed. Based on ^{1}H NMR spectra and HPLC-MS analysis, it was tentatively assigned the structure of free acid **235**. A sample of this acid in C_6D_6 was treated with CSA in the presence of EtOH, leading to full conversion of **235** back into the ethyl ester **231a**. No decarboxylation product was observed.



Scheme 74. Saponification of **231a** to stable lactoacid **235**. Structure proposed future intermediate **236** (right).

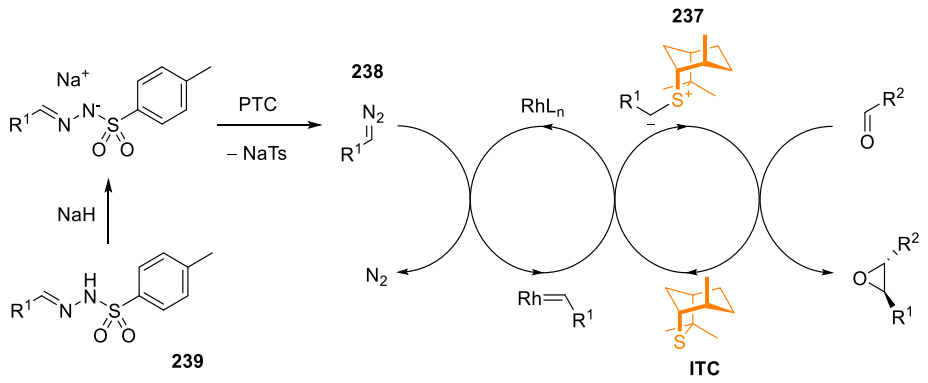
The stability of bridged acids like **235** is precedented in the literature and can be attributed to the inaccessibility of the anti-Bredt enol form, which is the proximate product of decarboxylation of β-oxoacids.[194,195] While the bridgehead atom C-8' cannot form enol due to its enforced tetrahedral geometry, it can bear a free radical as in proposed intermediate **236**. The future attempts at

decarboxylation via 236 should therefore focus on either a Barton-type reduction or oxidative decarboxylation using a variant of the Hunsdiecker reaction.[196,197]

4.4.3. Initial optimization of organocatalytic Corey-Chaykovsky epoxidation

A natural extension of the THT-catalysed Corey-Chaykovsky reaction, discussed in the previous chapter (scheme 73), would be to use a chiral thioether instead of THT in order to access optically enriched epoxides. A more sterically demanding catalyst might also exert some influence over the diastereoselectivity of the *3-exo-tet* ring closure, in which the oxygen atom displaces the sulfur atom forming the oxirane ring, and therefore may lead to the preferential formation of *trans* epoxide.

One such thioether was indeed extensively studied by the Aggarwal group, who used isothiocineole (**ITC**) as a chiral auxiliary for the synthesis of optically enriched epoxides [198a-c] and as a catalyst component in a dual catalyst syste.[198d-e] The key issue in the organocatalytic Corey-Chaykovsky epoxidation is the generation of the sulfur ylide **237** (scheme 75) which would require alkylation of sulfur and subsequent deprotonation, both potentially slow steps under the mild conditions required by the limited stability of the product. In the dual-catalyst design, this key issue is solved by the Rh carbenoid complex, which transfers the ylidene group to sulfur, directly forming the ylide and regenerating the Rh catalyst. The source of the formal carbene is the transiently formed diazocompound **238**, formed *in situ* from tosylhydrazone **239** by a phase transfer catalyst.

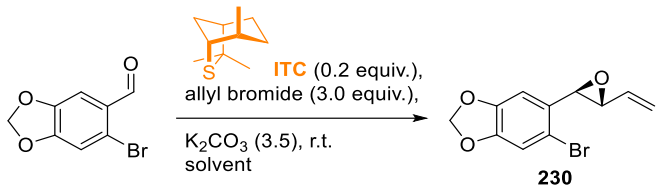


Scheme 75. Aggarwal's dual catalysis employing a Rh catalyst and **ITC** for the reaction of tosylhydrazones with aldehydes.

The scope of Aggarwal's method is unfortunately limited and does not directly allow adaptation of the dual catalysis to the podophyllotoxin synthesis. Despite this, we tested **ITC** as single catalyst replacing THT in the epoxidation of 6-bromopiperonal, because there is some precedent for direct organocatalytic epoxidation or cyclopropanation of very activated substrates like α-bromoacetophenone.[199,200]

Our first goal was to find the optimal solvent for the epoxidation. We opted for highly polar solvents as these should accelerate the S_N2 alkylation, deprotonation and ylide addition to aldehyde. Under the same condition as used previously with THT, we observed no reaction in DMSO, MeOH and DMF (table 13, entries 1-4). In aqueous MeCN (entry 5), traces of product oxirane **230** were detected, but it was accompanied by its decomposition products.

Table 13. Corey-Chaykovsky epoxidation of 6-bromopiperonal catalysed by **ITC** - initial solvent screening.



230

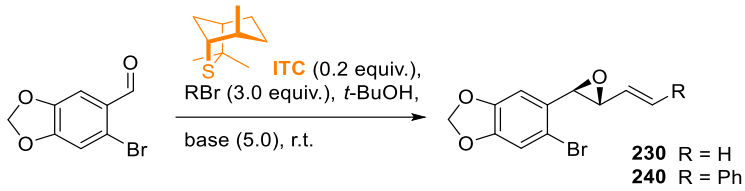
Entry	Solvent	Time	**230** by ^{1}H NMR [a)]	*trans* : *cis*
1	DMSO	30 h	0 %	-
2	MeOH	30 h	0 %	-
3	DMF	30 h	0 %	-
4	DMF	7 h [b)]	0 %	-
5	MeCN/H_2O 9:1	30 h	<1 %	-
6	*t*-BuOH	96 h	8 %	5.5:1
7	*t*-BuOH	144 h	13 %	6:1

[a)] Conversion relative to 6-bromopiperonal, no significant side-products detected. [b)] Heated to 60 °C.

Finally in *t*-BuOH (entries 6, 7), a very slow reaction occurred, giving 13% conversion to **230** after 144 h at r.t. Importantly, little decomposition of the product was observed. The diastereomeric ratio improved to 6:1 compared to the 1.7:1 obtained previously with THT. Although the reaction was impractically slow under these conditions, this result had proven that **ITS** can in principle be used as the sole catalyst for the Corey-Chaykovsky epoxidation.

The next reaction parameter we decided to optimize was the base. A set of parallel experiments was run with increased loading of the different bases (5 equiv.) to accelerate the reaction. The optical purity of the product was evaluated by chiral HPLC (table 14). Both K_2CO_3 and Cs_2CO_3 (entries 1, 2) promoted a slow reaction giving product **230** as a roughly 6:1 mixture of diastereomers, but only in 22% ee and 29% ee respectively. Addition of TBAI [199] seemed to moderately accelerate the reaction with Cs_2CO_3 (entry 3), giving a 9% yield after only 13 h instead of the 72 h previously required to attain equivalent yield. NaOH promoted faster reaction, leading to 47% conversion after 144 h (entries 4, 5), but the dr of **230** was lower at 4:1 as well as giving lower ee of 24%. DIPEA failed to promote the reaction with or without the addition of TBAI (entries 6-7). Based on these results, K_2CO_3 was selected for further study because it was roughly equivalent in performance to Cs_2CO_3 but is significantly cheaper.

Table 14. Corey-Chaykovsky epoxidation of 6-bromopiperonal catalysed by **ITC** - base screening.

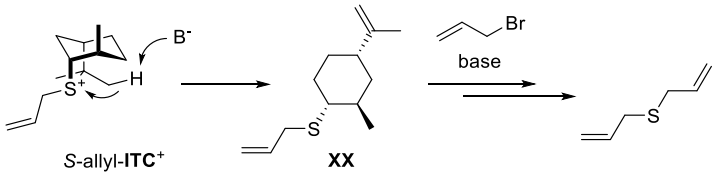


Entry	R	Base	Time (h)	Conv. (%) [a]	**230** (%)	*trans*:*cis*	% ee (*trans*) [b]
1	allyl	K_2CO_3	168	31	26	6:1	<22
2	allyl	Cs_2CO_2	72	10	10	6.5:1	<29
3	allyl	Cs_2CO_2 [c]	13	9	9	5.2	<30
4	allyl	NaOH [c]	72	33	-	4:1	-
5			114	47	37	4.6:1	<24
6	allyl	DIPEA	72	0	0	-	-
7	alllyl	DIPEA [c]	72	0	0	-	-
8	prenyl	K_2CO_3	72	0	0	-	-
9	cinn.	K_2CO_3	72	58	-	13:1	-
10			120	100	23	20:1	17

Yields refer to isolated **230**. Entries 4,5 and 9,10 each refer to the same experiment. [a] Conversion to **230**as measured by ^{1}H NMR. [b] Upper estimate of ee due to peak overlap with inseparable *cis*-**230** in chiral HPLC. [c] TBAI (1.0 equiv.) added. [d] Yield of **240**.

In an attempt to increase the diastereoselectivity and enantioselectivity, the more sterically demanding prenyl bromide was also tested (entry 8), but no reaction occurred after 72 h. Cinnamyl bromide (entries 9, 10) on the other hand reacted much faster than allyl bromide, giving 58% conversion after 72 h and reaching full conversion after 120 h. The diastereomeric ratio between *trans*- and *cis*-**240** was also much higher at 13:1 in the crude mixture and 20:1 in the isolated compound. The reason behind this observation is likely both the higher selectivity of the reaction itself and the faster decomposition rate of the *cis* isomer during purification as the yield after purification was only 23%. The increased reactivity of cinnamyl bromide likely stems from the faster rate of alkylation of **ITC** as well as higher stabilisation of the ylide form. Unfortunately, the enantiomeric excess was only 17%.

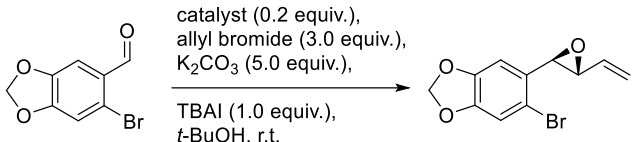
Increased diastereoselectivity of epoxidation using **ITC** bodes well for our synthetic strategy for the synthesis of neopodophyllotoxin, however the enantiomeric excess attained so far was too low. We hypothesized that the low selectivity might stem from catalyst decomposition, which instead of shutting the reaction down might lead to formation of more kinetically competent but unselective thioethers like diallyl ether etc. These may be formed by dealkylation of the sulfonium ion formed by alkylation of ITC via E2 elimination (scheme 76).



Scheme 76. Possible pathway of **ITC** decomposition via E2 elimination.

To test this hypothesis, we tested several simple off-the-shelf thioethers and sulfides for their ability to catalyse the epoxidation. Sodium methanethiolate, sodium sulfide, allyl phenyl thioether and dibutyl thioether (table 15, entries 1-4) failed to promote the reaction. This is strong evidence against the idea that diallyl sulfide or other simple thioethers kinetically overtake **ITC** during the organocatalytic epoxidation. In contrast to the previously mentioned sulfides, thioanisole (entry 5) did promote the reaction reaching 30% conversion after 168 h, although with poor diastereoselectivity (1.4:1). To help guide the future selection or design of potential future catalyst, several selenides were tested as well (table entries 6-8). Of those, only selenoanisole (entry 6) was found to be active, albeit less than thioanisole, reaching 9% conversion after 168 h.

Table 15. Screening of other organosulfur and organoselenium compounds for catalytic activity.



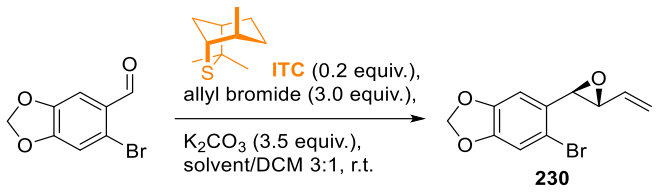
230

Entry	Catalyst	Time (h)	Conv. (%) [a)]	Yield (%)	*trans*:*cis*
1	MeSNa	168	0	-	-
2	Na_2S	168	0	-	-
3	PhS(allyl)	168	0	-	-
4	Bu_2S	168	0	-	-
5	thioanisole	24	2	-	1.8:1
		72	9	-	1.4:1
		168	30	29	1.4:1
6	selenoanisole	24	0	-	-
		72	6	-	1.3:1
		168	9	9	1.3:1
7	Ph_2Se_2	168	0	-	-
8	Ph_2Se	168	0	-	-

[a)] Conversion to **230** in crude as measured by ^{1}H NMR.

Since the initial solvent screening, all reaction ahd been done in *t*-BuOH. Even though it was found optimal for reactivity and product stabilisation, the starting 6-bromopiperonal has only limited solubility in *t*-BuOH. This puts a limit on maximum concentration, in turn limiting reaction rate. Addition of DCM (20-35%) was found to increase solubility while maintaining good reactivity. This prompted us to re-evaluate the base/solvent choice at higher concentration with added DCM (table 16). Parallel experiments in *t*-BuOH//DCM 3:1 using Na_2CO_3, K_2CO_3, Cs_2CO_3 and NaOH (entries 1-4) were run under otherwise identical conditions. Na_2CO_3 failed to promote the reaction completely, while NaOH caused excessive decomposition of the product even at low conversion. The reactions using K_2CO_3, Cs_2CO_3 were stopped after 23 days, when sufficient conversion for isolation of **230** was reached. Purification yielded 36% (dr 6:1) and 24% (dr 5.4:1) of **230** respectively. Importantly, the enantiomeric excess in both cases was around 41%, more than in the previous experiments (table 14).

Table 16. Re-optimization of the Corey-Chaykovsky epoxidation with added DCM.



230

Entry	Solvent	Base	1 day [a]	4 days [a]	9 days [a]	23 days [a]	*trans*:*cis*	% ee [b]
1	*t*-BuOH	Na_2CO_2	0	0	-	-	-	-
2	*t*-BuOH	K_2CO_3	4	12	21	36 [c]	6:1	<41
3	*t*-BuOH	Cs_2CO_3	6	12	21	24 [c]	5.4:1	<43
4	*t*-BuOH	NaOH	6	11	[d]	-	6:1	-
5	MeCN	Na_2CO_2	0	0	[d]	-	-	-
6	MeCN	K_2CO_3	8	21	41 [c]	-	4.3:1	<12
7	MeCN	Cs_2CO_2	12	24	[d]	-	6:1	-
8	MeCN	NaOH	5	4	[d]	-	20:1	-
9 [e]	*t*-BuOH	K_2CO_3	7	-	65 [c]	-	5:1	<28

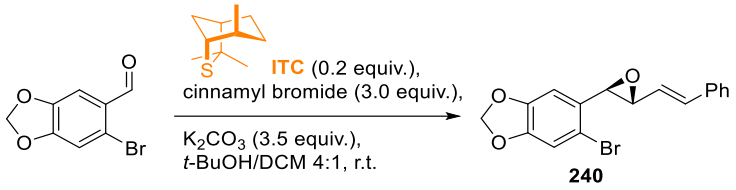
[a] Conversion to **230** in % by ^{1}H NMR (*p*-xylene as internal quant. standard). [b] Upper estimate of ee due to peak overlap with inseparable *cis*-**230** in chiral HPLC. [c] Isolated yield of **230**. [d] Decomposition. [e] Allyl iodide used instead of allyl bromide.

From a similar set of experiments in MeCN/DCM 3:1 (entries 5-8) under otherwise identical conditions, only the reaction using K_2CO_3 was chemoselective enough to allow isolation of **230** in 41% yield. The reaction rate was generally higher in MeCN, but product decomposition and lower stereoselectivity make acetonitrile an inferior solvent for the epoxidation. Additionally, the concentration of the catalyst decreased more significantly over time in MeCN compared to *t*-BuOH. To increase the reaction rate, allyl iodide was tested instead of allyl bromide using the optimal base K_2CO_3 in *t*-BuOH//DCM 3:1 (entry 9). Indeed, 65% yield of **230** (dr 5:1) was obtained only after 9 days. Together with the increased reactivity of cinnamyl bromide observed earlier (table 14, entry 10), this result suggested that more reactive allylic halides should be used for future optimisation.

4.4.4. Asymmetric Corey-Chaykovsky epoxidation with activated alkyl halides

Using the optimized conditions, the conversion of cinnamyl bromide to **240** was followed by ^{1}H NMR (table 17). The reaction reached 62% conversion after 18 h and was finished after 42 h. No decomposition products were detected.

Table 17. Organocatalytic epoxidation of 6-bromopiperonal using cinnamyl bromide - estimation of reaction rate.

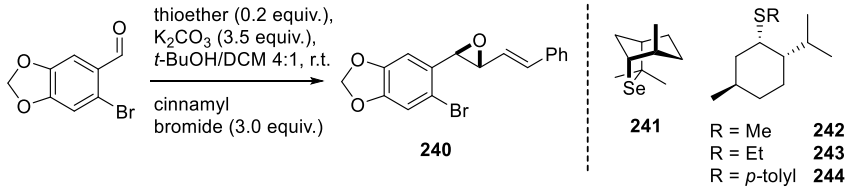


Entry	Time (h)	6-bromopiperonal (%) [a]	**240** (%) [a]	*trans*:*cis*
1	1	92	8	5.4:1
2	4	74	26	5.8:1
3	18	38	62	7.5:1
4	42	0	99	7.5:1

[a] Relative concentration by ^{1}H NMR based on internal quant. standard (*p*-xylene).

Repeated runs of this experiment in slightly different reaction setups showed moderate dependence on stirring rate and reaction vessel type. This is likely due to the heterogeneous nature of the base and high viscosity of the solvent. To ensure the validity of the following catalyst screening, all reactions were run in parallel in identical reaction vessels using a centrally controlled carousel. In addition to **ITC**, four previously described catalysts were prepared from chiral pool terpenes. Selenium analogue of ITC - catalyst **241**, previously shown to mediate stoichiometric Corey-Chaykovsky epoxidation [201] was prepared from (*R*)-(+)-limonene, γ-terpinene and elemental sulfur. Neomenthol derivatives **242**, **243** and **245** were prepared from (1*R*,2*S*,5*R*)-(–)-menthol via its tosylate (table 18).[202,203]

Table 18. Epoxidation of 6-bromopiperonal using cinnamyl bromide - catalyst screening.

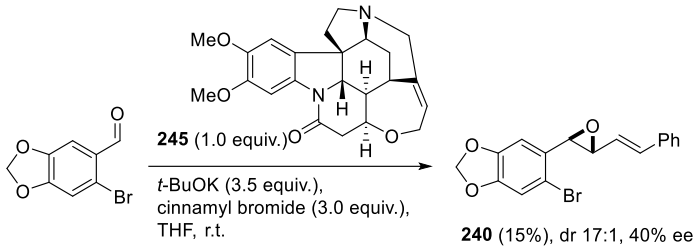


Entry	Thioether	Time (h)	6-bromopiperonal (%) [a]	**240** (%) [a]	*trans*:*cis*
1	**ITC**	5	80	14	7:1
		96	2	97	6.3:1
		336	3	90	7.5:1
2	**241**	5	88	2.5	1:1
		96	86	14	1.2:1
		336	70	14	1.1:1
3	**242**	5	85	5	4:1
		96	25	74	4.5:1
		336	3	90	3:1
4	**243**	5	75	1.5	-
		96	60	36	2.5:1
		336	15	86	2.4:1
5	**244**	5	94	0	-
		96	93	6	1:1
		336	90	9	1:1

[a] Relative concentration by ^{1}H NMR based on internal quant. standard (*p*-xylene).

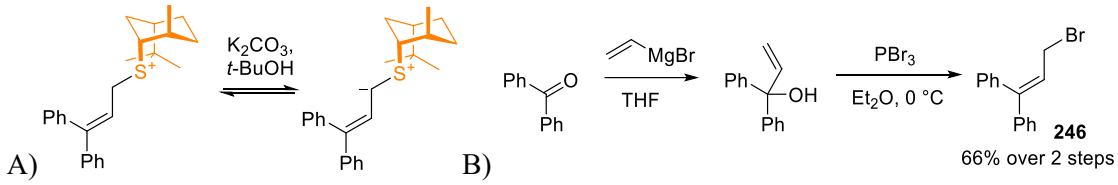
As the results in table 18 shows, none of the newly tested catalysts performed better than ITC, which gave 97% conversion to **240** after 96 h (entry 1). After purification, only 50% yield was obtained due to the instability of **240**. The *cis* isomer decomposed significantly faster on silica so that essentially pure *trans* isomer was obtained (dr 40:1). This allowed easier separation of enantiomers of *trans*-**240** by chiral HPLC as there was now no peak overlap with *cis*-**240**, giving 14% ee. Catalysts **241** (entry 2) and **244** (entry 5) were less active and more importantly, produced almost equimolar mixtures if *cis*-**240** and *trans*-**240**. Catalysts **242** (entry 3) and **243** (entry 4), bearing smaller Me and Et groups on sulfur, were reasonably competent at promoting the reaction, reaching almost full conversion after 336 h. The low final dr did not unfortunately allow separation of enantiomers by chiral HPLC even after attempted purification of *trans*-**240**. The absolute configuration of **247** was not assigned.

In search for a more selective catalyst, we were inspired by a report on tertiary amine-promoted epoxidation of benzaldehydes [204] Stoichiometric amount of alkaloid brucine (**245**) was tested under otherwise identical conditions as in previous experiments (scheme 77). The reaction proceeded to high conversion but afforded only 15% of *trans*-**240** (dr 17:1, 40% ee) after purification due to stability issues. Unfortunately, unlike the previous thioether-catalysed reactions, the crude product from this reaction cannot be directly used in the conjugate addition/cyclisation step, because **245** would interfere with lithiation.



Scheme 77. Asymmetric Darzens-type epoxidation using brucine (**250**).

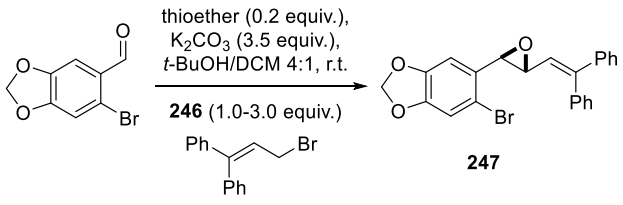
Even though the reactivity of cinnamyl bromide was much higher than allyl bromide, the reaction times were still impractically long, hampering optimization and screening of catalysts. The strategy was once again re-evaluated based on the following reasoning. 1) The choice of base and solvent are mostly dictated by the requirement for stabilisation of the epoxide, making K_2CO_3 in *t*-BuOH mandatory. 2) The rate limiting step of the organocatalytic epoxidation is likely either the initial alkylation of sulfur or more likely the ylide formation by deprotonation. 3) Changing the alkylating agent to be even stronger electrophile would accelerate the first step, while adding substituents that stabilise a negative charge would shift the unfavourable protonation equilibrium (scheme 78, A). Therefore, we proposed 3,3-diphenylallyl bromide (**246**) as an ideal reagent that would satisfy both requirements. **246** can be prepared easily from benzophenone by addition of vinylmagnesium bromide, followed by S_N2' bromination of the resulting diphenylvinylcarbinol. This peculiar reagent is a stable solid but must be protected from light as it photolyzes even under common laboratory lighting.



Scheme 78. A) Protonation equilibrium between sulfonium ion and ylide. B) Preparation of **246**.

Table 19 summarizes the screening of amine, thioether and selenoether catalysts in epoxidation of 6-bromopiperonal using **246**. Tertiary amines brucine (**245**) and **L17** were not catalytically active (entries 1, 2). Tetrahydrothiophene-catalysed reaction (entry 3) reached 42% conversion after 34 h, when **246** was depleted due to competing solvolysis. **242**-catalysed reaction reached nearly full conversion after 168 h giving 3.7:1 mixture of *trans*-**247** and *cis*-**247** (entry 4), while **243**-catalysed reaction was slower and les selective (entry 5). Finally, **ITC** proved very active, reaching nearly full conversion after 17 h using 3 equivalents of **246** (entry 6) or after 72 h using just 1 equiv. of **246** (entry 7). Reducing the loading of the catalyst **ITC** to just 5% still led to 83% conversion after 140 h. These results were very promising, because the short reaction time and the reduced loading of the alkylating reagent and catalyst, combined with good diastereoselectivity (~5.4:1) would make the product epoxide pure enough for direct lithiation and cyclisation.

Table 19. Asymmetric epoxidation of 6-bromopiperonal using **246** – catalyst screening.

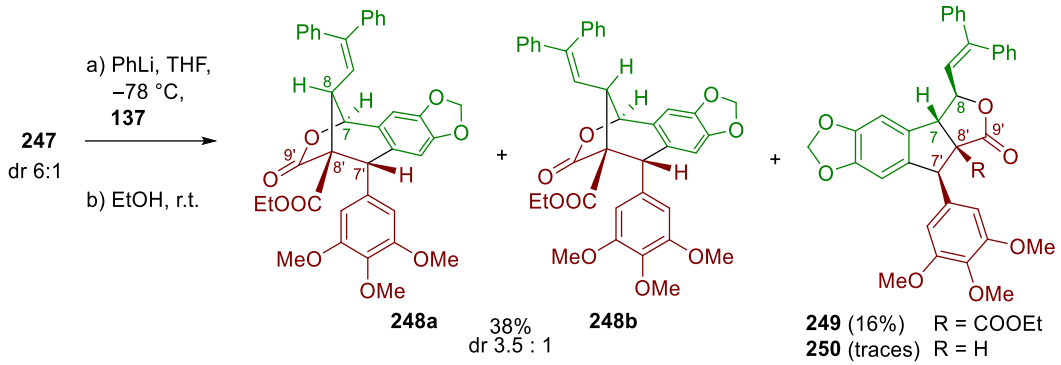


Entry	Catalyst	**246** (equiv.)	Time (h)	Conversion [a)]	*trans*:*cis*	Yield
1	**245**	2.0	15	0	-	-
2	**L17**	2.0	15	0	-	-
3	THT	2.0	34	42	3.0:1	28
4	**242**	1.4	168	95	3.7:1	-
5	**243**	1.4	192	45	2.6:1	-
6	**ITC**	3.0	17	95	5.4:1	10 [b)]
7	**ITC**	1.0	62	82	5.5:1	-
8	**ITC** [c)]	1.3	140	83	5.3:1	-

[a)] Conversion to **247** based on internal quant. standard (*p*-xylene). Reactions stopped when conversion asymptotically decayed due to depletion of RBr. [c)] Dr after purification 11:1. [b)] 5% of catalyst used.

As expected, **247** was even less stable to silica than previously studied epoxides, but isolation of reduced amounts was still possible (entries 3, 6). Unfortunately, the enantiomers could not be separated by chiral HPLC. Therefore, the only way to learn the enantiomeric excess was to carry the epoxide forward to the next step.

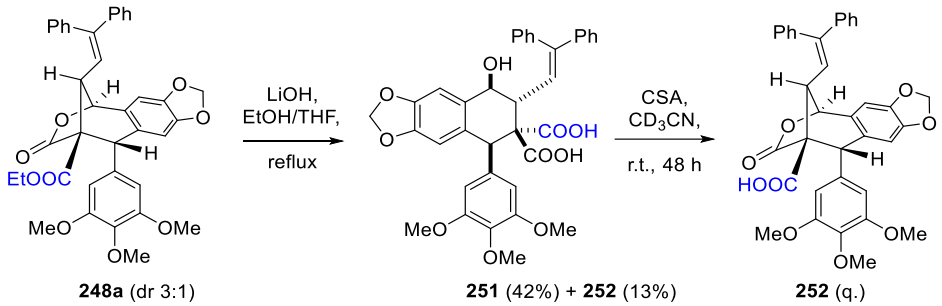
Further optimization for larger scale preparations led to reduction of the catalyst loading to 10% while using 1.4 equiv. of **246**. The reaction was monitored by ^{1}H NMR, until reaching full conversion while the concentration of **246** decreased below 5% due to a combination of epoxidation and solvolysis. The (near-) complete consumption of **246** is crucial, because if left in the mixture, it would interfere with the following step. Its solvolysis product is the inert 3,3-diphenylallyl *tert*-butyl ether, which is easily tolerated during the lithiation. In order to prevent decomposition, crude epoxide **247** (dr 6:1) was obtained from the reaction mixture by filtering off the base and removal of *t*-BuOH by co-evaporation with benzene. After drying, **247** was used directly in the next step (scheme 79).



Scheme 79. Conjugate addition/cyclisation of epoxide **247**.

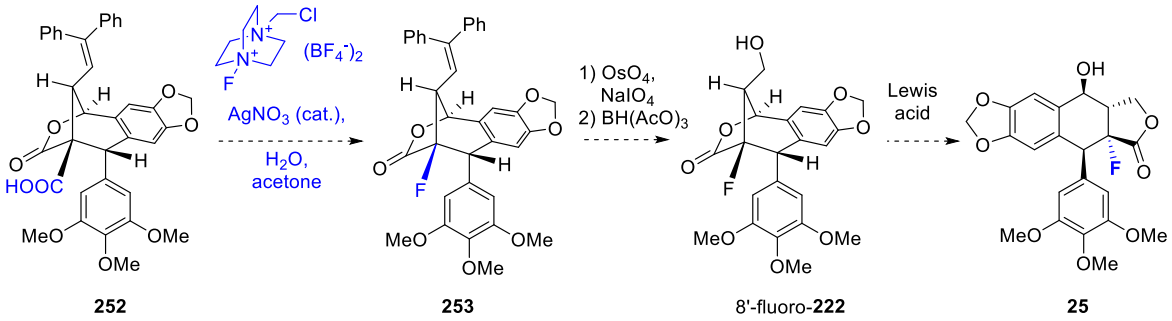
Conjugate addition/cyclisation of **247** under standard conditions of Florio resulted in the expected double cyclisation giving **248** in 38% yield (dr 3.5:1) over 2 steps from 6-bromopiperonal. Furoindane product **249** was formed in 16% yield and could be separated from **248** by chromatography. During attempted crystallization from benzene, it partially decarboxylated to **250**. The cyclisation selectivity (*6-exo*/*5-exo*) was approximately 2.3:1. Both **248a** and **248b** were formed from *trans*-**247**, while **248b** originates from *cis*-**247**. The ratio of cyclisation products derived from the respective diastereomers of the epoxide is 5.4:1, which roughly corresponds to the original *trans*/*cis* ratio 6:1 of **247**.

Most importantly, the enantiomeric purity of the cyclic products could be determined for the first time because **249** (and less reliably **248a**) could be separated by chiral HPLC giving enantiomeric excess of 49%, which can be also assumed for *trans*-**247** and its cyclisation product **248a**. This result was surprising, because none of the previously measured samples during optimization had similar or higher excess. The 3,3-diphenylallyl group therefore not only increases reactivity during the Corey-Chaykovsky olefination, but also increases asymmetric induction compared to allyl and cinnamyl groups. The absolute configuration of products **248-250** was not assigned. The synthesis was continued by decarboxylation of **248a** using LiOH in a refluxing mixture of EtOH and THF (scheme 80). After workup, insoluble **251** precipitated from benzene.



Scheme 80. Saponificaiton of **248a** followed by acid-induced decarboxylation.

Pure **252** proved surprisingly stable to both decarboxylation and lactonization, requiring treatment with CSA in deuterated acetonitrile to recyclise to **248a** without detectable decarboxylation. This result was consistent with the previously observed behaviour of **235** (chapter 4.4.2, scheme 72). The minor diastereomer **248b** resisted saponification by excess LiOH, presumably due to increased steric hindrance in the vicinity of the carbonyl group compared to **248a**. This allowed easy removal of this isomer and bodes well for the overall synthesis. Due to the lack of time, the synthetic effort was not continued. The planned final steps of the total synthesis of 8'-fluoropodophyllotoxin (**25**) via neopodophyllotoxin (**222**) are outlined in scheme 81.



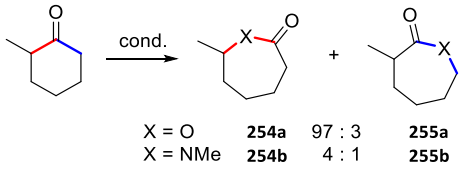
Scheme 81. Plan for the final oxidative decarboxylation and unmasking of the C-9 hydroxy group.

The stability of the free carboxylic acid at C-8' should allow oxidative generation of radical and may allow radical halogenation [197] instead of simple decarboxylation.[196] This would enable direct and elegant synthesis of the medicinally relevant 8'-fluoropodophyllotoxin (**25**) without the need for late-stage fluorination. After decarboxylation, the latent hydroxy group at C-9 should be unmasked by oxidative cleavage of alkene **253**, followed by reduction to 8'-fluoroneopodophyllotoxin (8'-fluoro-**222)**, which should easily undergo neopodophyllotoxin-like translactonization to **25**.

4.5. Part E: Regioselective C-C scission of ketone enolates mediated by nitrosation

Oxidative cleavage of the cyclohexanone derived enolate to open-chain ω-hydroxyimino ester **111** (chapter 4.1.2, scheme 34), observed during the initial exploration of oxidative cyclisation, was rather unexpected and led us to investigate this peculiar transformation in more detail. The C-C scission reaction seemed to have occurred regioselectively and the carbon termini of the resulting ω-hydroxyimino ester are differentiated in oxidation state as well as potential reactivity. Such oxidative cleavage of enolate could therefore represent a new and useful transformation.

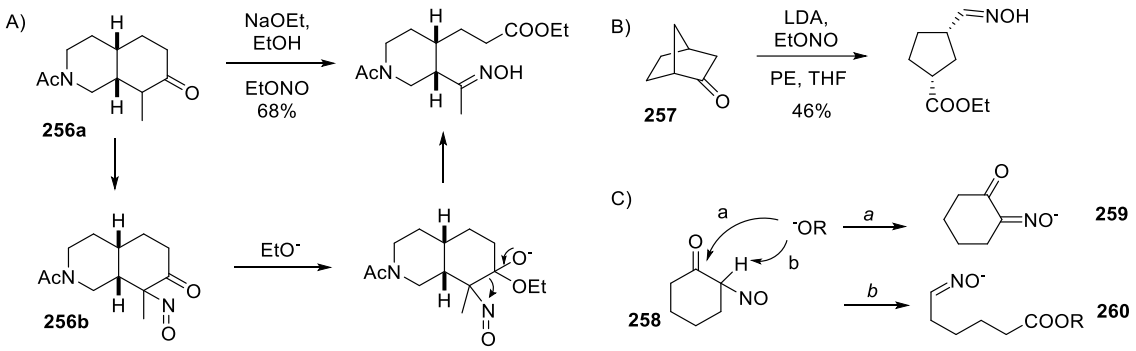
Cleavage of the α-C-C bond of ketones is an important synthetic tactics in the synthesis of complex molecules,[205,206] that can be executed using a variety of tools including insertion of transition metals,[207,208] ozonolysis of silyl enol ethers,[209] the Haller-Bauer reaction [210] and most importantly the Baeyer-Villiger oxidation (BVO) and the Beckmann rearrangement (BR).[205,211-215] The last two mentioned methods (BVO, BR) are particularly well known among synthetic chemists and new variants continually appear in the literature, like biocatalytic BVO [216] or organocatalytic BR.[217] Despite these modern modifications, the two principal methods of ketone degradation also suffer from the same key limitation – the site of cleavage cannot be freely chosen, as it is largely dictated by the structure of the substrate, *i.e.* relative group migratory aptitudes for BVO and configuration of the oxime C=N double bond for BR. This is illustrated on oxidative cleavage of 2-methylcyclohexanone (scheme 82), which can be selectively cleaved either by CF_3CO_3H or via its *O*-nosyl oxime giving derivatives **254a,b**, but not **255a,b**.[218,219]



Scheme 82. BV oxidation or Beckmann rearrangement of 2-methylcyclohexanone, conditions: CF_3CO_3H for X = O, NsONHMe for X = N.

Based on our initial observation of regioselective cleavage we speculated that nitrosative cleavage of enolates might be an attractive alternative to BVO and BR, that would circumvent the problem of fixed regiospecificity, as generation of isomeric enolates from unsymmetrical ketones by choosing the right enolization method is well established.[220,221]

However, most enols and enolates are known to undergo α-hydroxyimination without fragmentation when treated with alkyl nitrites or other nitrosating reagents in protic solvents. This reaction is in fact the standard method for the preparation of α-hydroxyiminoketones.[222,223] On the other hand, cleaved products have been detected after reaction with *n*-BuONO with enolates in the gas phase [224] or prepared by oxidation of enols by NOCl in SO_2 as solvent [225] and enolethers by $AgNO_2$.[226] The most important example of nistrosative cleavage is its use in the landmark 1945 total synthesis of quinine by Woodward and Doering,[227] who used ethyl nitrite in combination with EtONa in EtOH to cleave the ring in **256a** on the side of the more substituted carbon (scheme 83, A). These authors also suggested a plausible mechanism for this transformation that involves nucleophilic attack of ethoxide anion on nitroso ketone **256b**, followed by fragmentation. Finally, the Paquette group demonstrated cleavage of lithium enolates of norbornene derivatives like **257** by EtONO in aprotic mixture of THF/PE (scheme 83, B).[228] They noted that cleavage was not effective when the more available - but more hindered - nitrites like *i*-AmONO were used.



Scheme 83. A) Ring opening via nitrosation used in the Woodward-Doering total synthesis of quinine.[227] B) Cleavage of norbornanone via its enolate by ethyl nitrite by Paquette.[228] C) Pathway *a*: deprotonation of **258** by alkoxide leading to α-hydroxyiminoketone **259**; pathway *b*: 1,2-addition of alkoxide followed by fragmentation.

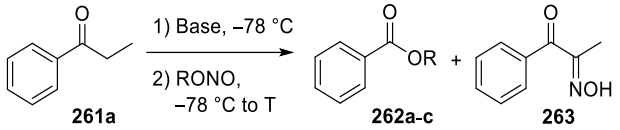
When considered all together, these reports reveal an interesting dichotomy in the reactivity of enolates toward nitrosating reagents, that can be explained by a simple model (scheme 83, C) in which the reaction paths diverge at the stage of the nitroso ketone **258**. In protic solvents, or when the nucleophilicity of the alcoholate is reduced for some other reason like steric hinderance, the deprotonation pathway *b* wins out resulting in the formation of α-hydroxyiminoketones like **259**. In aprotic solvents like THF and when a non-bulky nucleophile is available, the 1,2-addition pathway b takes over, resulting in retro-aza-Claisen fragmentation to ω-hydroxyiminoketones like **260**. In case no proton in available like in **256b**, the reaction may default to the fragmentation mode even in protic solvents like EtOH.

Building on this knowledge we hypothesized that using ethereal solvents in combination with more nucleophilic alkoxides, *in situ* nitrosative cleavage of ketone enolates could be developed into a generally applicable method for (regioselective) scission of symmetrical and asymmetrically substituted ketones.

4.5.1. Cleavage of phenones and symmetrical ketones

We started our systematic investigation by studying the oxidation of propiophenone **261a**, which undergoes unambiguous deprotonation on the side of the saturated chain. The lithium enolate generated at –78°C using LDA in Et_2O was oxidized by *t*-BuONO at –78 °C, followed by warming to r.t. (table 20, entry 1). *t*-Butyl benzoate (**262a**) was isolated in 47% yield along with a small amount of the non-cleaved hydroxyiminoketone **263**. This result alone demonstrated that the fragmentation pathway is preferred over simple tautomerization to hydroxyiminoketone even in the case of a hindered alkoxide like *t*-BuONO. Using THF instead of Et_2O only led to traces of **262a** along with significant amount of carcinogenic *N*-nitrosodiisopropylamine (entry 2). This led us to switch the base to LiHMDS (entry 3), which restored the reactivity giving 33% of **262a** and at the same time does not form stable nitrosamines.[229] To increase the nucleophilicity of the alkoxide generated during the initial nitrosation we switched to KHMDS. The yield of **262a** indeed dramatically increased to 82%. When *n*-BuONO and *i*-AmONO were used oxidants, essentially quantitative yields of **262b** and **262c** were obtained (entries 4-6).

Table 20. Cleavage of propiophenone (**261a**) using Li and K bases.



261a **262a-c** **263**

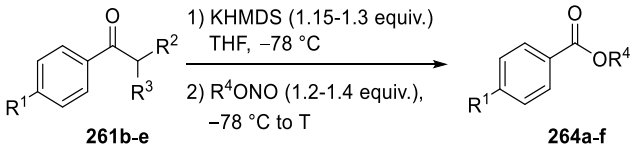
Entry	Solvent	Base	T (°C)	R	**260**	yield (%)
1	Et_2O	LDA	r.t	*t*-Bu	**a**	47 [a]
2	THF	LDA	r.t.	*t*-Bu	**a**	<5 [a),b)]
3	THF	LiHMDS	r.t.	*t*-Bu	**a**	33[c]
4	THF	KHMDS	r.t.[d]	*t*-Bu	**a**	82
5	THF	KHMDS	–20	*n*-Bu	**b**	99
6	THF	KHMDS	–20	*i*-Am	**c**	96

[a)] Oxime **263** detected in the crude mixture. [b)] Conversion to **262a** as determined by ^{1}H NMR spectroscopy. [c)] Oxime **263** isolated in 57% yield. [d)] *t*-BuONO added at −15 °C.

These results are in stark contrast to the observations of Paquette, who only observed cleavage using non-hindered EtONO, which has to be prepared prior reaction due to its very low boiling point. Moreover, K enolates reacted fast at temperatures below –30 °C to cleanly give fragmentation products, with no formation of **263** observed.

Having developed suitable conditions, we next compared the reactivity of a series of commercially available alkyl nitrites towards the potassium enolate of **261b** (table 21, entries 1-4). Esters **264a-d** have higher boiling points than volatile benzoates **262a-c**, leading to more reproducible yields which are less affected by the isolation procedure. The nature of the nitrite did not systematically affect the yield, as **264a-d** were obtained in high yields, while it did affect the reaction rate. Unhindered *n*-BuONO and *i*-AmONO reacted quickly at –78 °C, while *i*-BuONO required warming to –40 °C and *t*-BuONO to –20 °C as judged by GC monitoring. The more electron poor 4'-fluoropropiophenone (**261c**) was cleaved by *t*-BuONO and *n*-BuONO to give esters **264e** and **264f** in 83% and 95 yield respectively (entries 5-6). The more hindered isobutyrophenone (**261d**) was also cleaved in good yields (entries 7-8), while acetophenone (**261e**) only afforded moderate yield of 58% in reaction with *i*-AmONO (entry 9).

Table 21. Cleavage of alkyl aryl ketones.

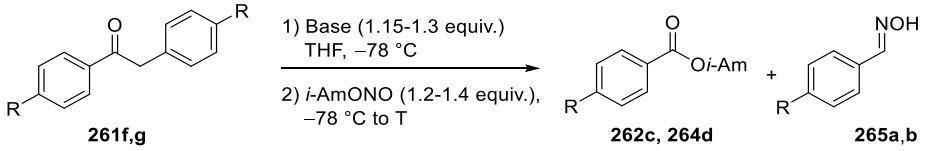


261b-e **264a-f** **262b,c**

Entry	**261**	R^1	R^2	R^3	T (°C)	R^4	Ester	(%)
1	**b**	OMe	Me	H	–78	*n*-Bu	**264a**	77
2	**b**	OMe	Me	H	–40	*i*-Bu	**264b**	97
3	**b**	OMe	Me	H	–20	*t*-Bu	**264c**	91
4	**b**	OMe	Me	H	–78	*i*-Am	**264d**	99
5	**c**	F	Me	H	–20	*t*-Bu	**264e**	83
6	**c**	F	Me	H	–20	*n*-Bu	**264f**	95
7	**d**	H	Me	Me	23	*n*-Bu	**262b**	66
8	**d**	H	Me	Me	0	*i*-Am	**262c**	98
9	**e**	H	H	H	10	*i*-Am	**262c**	58

To support our mechanistic understanding of the reaction, we sought to isolate the aldoxime product coming from the saturated sidechain. Since we could not detect acetaldoxime or other similar products in the reactions of simple phenones **261a-e**, we turned to oxidation of deoxybenzoin (**261f**) and deoxyanisoin (**261g**), which should produce isolable benzaldoximes **265a** and **265b** along with esters **262c** and **264d**. The reaction of **261f** with *i*-AmONO using KHMDS (table 22, entry 1) indeed resulted in the isolation of 64% of ester **262c** and 34% of aldoxime **265a**. The yield of both **262c** and **265a** improved significantly when we switched to NaHMDS (entry 2). Deoxyanisoin similarly underwent facile reaction giving 88% of ester **264d** and 84% of aldoxime **265b**.

Table 22. Cleavage of deoxybenzoins.

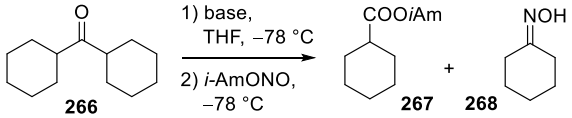


261f,g **262c, 264d** **265a,b**

Entry	**261**	Base	R^1	T (°C)	Ester	(%)	**265** (%)
1	**f**	KHMDS	H	0	**262c**	64	**a** 34 [a]
2	**f**	NaHMDS	H	0	**262c**	99	**a** 88 [b]
3	**g**	KHMDS	OMe	–5	**264d**	88	**b** 84

[a] NMR yield: <57%. [b] 4-Methoxybenzoic acid (12%) detected by ^{1}H NMR spectroscopy.

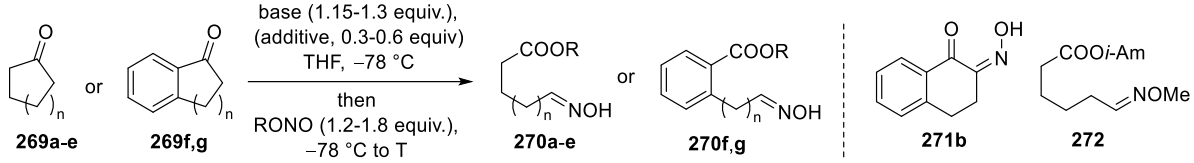
Aliphatic ketone **266** similarly produced two isolable fragments on scission with *i*-AmONO (scheme 84). Oxidation of the K enolate resulted in 76% yield of ester **267** and 92% yield of oxime **8**, while oxidation of Na enolate afforded slightly lower yield of **267** and only 58% of **268**.



Scheme 84. Cleavage of **266** to ester **267** and oxime **268**. Conditions: KHMDS or NaHMDS (1.2 equiv.), *i*-AmONO (1.4 equiv.).

In the next stage of our study, we focused on oxidation of cyclic ketones, which should be cleaved into a acyclic ω-hydroxyiminoesters. Despite being readily opened by other methods due to ring strain, cyclobutanone (**269a**) reproducibly afforded only 17% of hydroxyiminoester **270a** on oxidation with *i*-AmONO (table 23, entry 1). During purification, side-products resulting from self-aldol addition followed by nitrosation and cleavage were detected, suggesting the problem is already at the enolization stage rather than during the oxidation. Cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, cyclododecanone (**269b-e**) and 1-indanone (**269f**) underwent facile cleavage via their Li, Na and K enolates resulting in good yields of hydroxyiminoesters **270b-f** (entries 2-9). α-Tetralone (**269g**) was more resistant to cleavage providing only moderate 38% and 59% yields of ester **270g** using Li and Na bases (entries 10, 11). The reaction pathway switched completely when KHMDS was used in combination with *t*-BuONO, giving 2-hydroxyimino tetralone (**271b**) as the only product (entry 12). In an attempt to increase the concentration of active alkoxide nucleophile and therefore improve yield, we tried oxidation in the presence of additional *i*-AmOLi to the reaction mixture (entries 4, 5, 8, 10). This seemed to have limited beneficial effect (entry 8).

Table 23. Cleavage of simple cyclic ketones **269a-e**, 1-indanone (**269f**) and 1-tetralone (**269g**).[a)]



269a-e **269f,g** **270a-e** **270f,g** **271b** **272**

Entry	**269**	n	Base	Additive	T (°C)	R	Product	(%)	*E:Z* [a)]	*E:Z* [b)]
1	**a**	0	**Na**HMDS	-	–78	*i*-Am	**270a**	17	1.1:1	1.3:1
2	**b**	1	**Li**HMDS	-	–78	*i*-Am	**270b**	69	2.4:1	1.2:1
3	**b**	1	**Na**HMDS	-	–78	*i*-Am	**270b**	84	2.8:1	1.3:1
4	**c**	2	**Li**HMDS	*i*-AmOLi	–78	*i*-Am	**270c**	69	1.3:1	1.2:1
5	**d**	3	**Li**HMDS	*i*-AmOLi	–78	*i*-Am	**270d**	77	1.3:1	1.2:1
6	**e**	8	**K**HMDS	-	–78	*n*-Bu	**270e**	44 [c)]	1.2:1	0.7:1
7	**e**	8	**Li**HMDS	-	–78	*n*-Bu	**270e**	67	1:1	1.3:1
8	**e**	8	**Li**HMDS	*i*-AmOLi	–78	*n*-Bu	**270e**	82	1.1:1	1.3:1
9	**f**	1	**Na**HMDS		–78	*i*-Am	**270f**	71	1:1	0.9:1
10	**g**	2	**Li**HMDS	*i*-AmOLi	+23	*i*-Am	**270g**	39 [d)]	2.7:1	1.4:1
11	**g**	2	**Na**HMDS	-	–40	*i*-Am	**270g**	62 [f)]	n.d. [e)]	3.0:1
12	**g**	2	**K**HMDS	-	–5	*t*-Bu	**271b** [g)]	72	-	-
13	**c**	2	**Na**HMDS	MeI [h)]	–78	*i*-Am	**272**	51	1.9:1	1.4:1

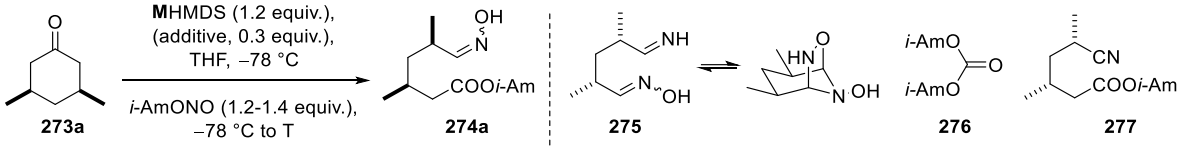
[a)] Oxime before purification. [b)] Oxime after purification. [c)] 2-(Hydroxyimino) cyclododecanone **271a** (16%) also isolated. [d)] **271b** (49%) also isolated. [e)] Not determined, immediately separated. [f)] **271b** (33%) also isolated. [g)] **270** not observed. [h)] Quenched after completed cleavage by MeI (30 equiv.) and K_2CO_3 (15 equiv.).

All of the oxime products were formed as *E/Z* mixtures, with the *E/Z* ratio generally close to equimolar and further decreased during purification. To better understand, whether this low *E/Z* ratio comes from the inherently low selectivity of the reaction of from the subsequent manipulation with the samples, the oxime anion of **270c** was alkylated *in situ* by MeI (table 23, entry 13) resultig in 51% yield of oxime ether **272**. However, the *E/Z* ratio was similar to the previous experiments.

The results of cleavage of cyclic ketones, presented in table 23 suggested that by fine tuning of the reaction conditions, namely the counter ion of the base, additives and precise reagent loading, could potentially further improve cleavage efficiency. Our hypothesis was, that the reaction is generally very fast and selective at low temperature, however once formed, the product slowly succumbs to degradation by excess reagents. We therefore decided to carefully reoptimize the reaction conditions using *cis*-3,5-dimethylcyclohexanone (**273a**) as substrate (table 24), tracking the formation of side products resulting from over-oxidation - dialdoxime **275** and diisoamyl carbonate (**276**), and from nitrite-induced Beckmann fragmentation - nitrile ester **277**. LiHMDS, NaHMDS and KHMDS were compared under the same conditions with or without added alkoxide (entries 1-6). The sodium enolate was cleaved in the highest yield of 91%, while the potassium enolate afforded 87% and lithium enolate only 74% of hydroxyminoester **274a**. In all cases, added alkoxide had a detrimental effect on yield and selectivity, leading to increased formation of side products **275** and **276**, which result from enolization and secondary cleavage of ester **274a**. Dioxime **275** exists as dynamic mixture of several acyclic and bicyclic isomers, such behaviour of 1,5-dioximes has been previously described.[230] Intentional overoxidation by excess base and nitrite led to the formation of **275** in 22-40% yield and **276** in 24-58% yield (entries 7-9), with the potassium base causing significantly more overoxidation. Finally, to see how stable the product was towards excess nitrite without additional base, K and Na

enolates of **273a** were treated with 2.5 equiv. of *i*-AmONO (entries 10, 11). At –78 °C, little difference to standard conditions was observed, but when the temperature was raised to 60 °C, complete degradation of **274a** occurred and 34-38% yield of nitrile **277** was obtained after isolation.

Table 24. Influence of reaction parameters on the cleavage of *cis*-3,5-dimethylcyclohexanone (**273a**).

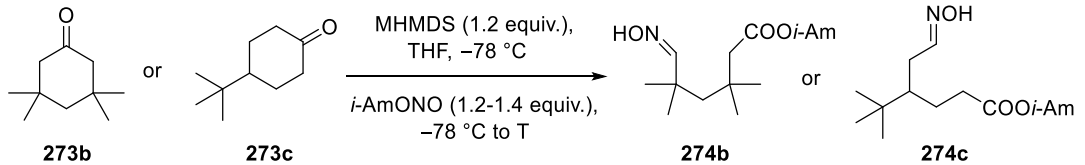


Entry	M	additive	T (°C)	**274a** (%)	*E*:*Z* [a]	*E*:*Z* [b]	**275** (%) [c]	**276** (%) [c]	**277** (%)
1	Li	-	–78	74	2:1	1.9:1	<1	<2	-
2	Li	LiO*i*-Am	–78	68	8:1	3.0:1	<1	4	-
3	Na	-	–78	91	3.7:1	3.5:1	-	-	-
4	Na	NaO*i*-Am	–78	81	6:1	2:1	<1	4	-
5	K	-	–78	87	2.3:1	1.9:1	<2	6	-
6	K	KO*i*-Am	–78	64	1.8:1	1.9:1	27 [d),e)]	24 [e)]	-
7	K [f),g)]	-	–78	20 [c)]	-	-	40	58	-
8	K [f),g)]	KO*i*-Am	–78	18 [c)]	-	-	34	38	-
9	Na [f),g)]	-	–78	70	7:1	3.7:1	22 [e)]	24 [e)]	-
10	K [g)]	-	+60	-	-	-	-	-	38
11	Na [g)]	-	+60	-	-	-	-	-	34

[a)] Oxime before purification. [b)] Oxime after purification. [c)] Determined by ^{1}H NMR spectroscopy, unless otherwise indicated. [d)] Isolated as dynamic *E*/*Z* mixture of cyclic and acyclic forms (See experimental part). [e)] Isolated yield. [f)] MHMDS (2.2 equiv.) used. [g)] *i*-AmONO (2.2-2.5 equiv.) used.

Sterically hindered 3,3,5,5-tetramethylcyclohexanone (**273b**) underwent cleavage by *i*-AmONO via its sodium enolate in moderate 44-50% yield (table 25, entries 1, 2). The reaction was slower than in the case of less hindered cyclohexanones **269c** or **273a** and did not reach full conversion even after warming to r.t. Full conversion could be achieved using the potassium enolate of **273b**, which led to improved yield of 64% (entry 3). The conformationally locked but relatively non-hindered 4-(*tert*-butyl)cyclohexanone (**273c**) underwent fast cleavage at –78 °C using KHMDS in 67% yield (entry 4).

Table 25. Cleavage of substituted cyclohexanones **273b,c**.



Entry	**273**	M	T (°C)	**274**	(%)	*E*:*Z* [a]	*E*:*Z* [b]	Recovered **273** (%) [c]
1	**b**	Na	–10	**b**	44	1:0	1:0	**b** (20)
2	**b**	Na	+23	**b**	50 [c)]	1:0	1:0	**b** (9)
3	**b**	K	+23	**b**	64	1:0	1:0	**b** (<1)
4	**c**	K	–78	**c**	67	1.1:1	0.7:1	-

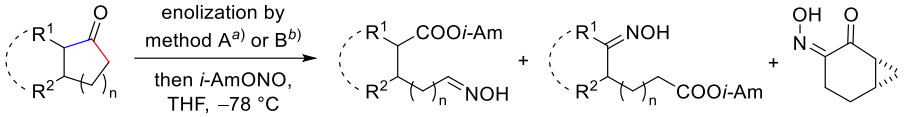
[a)] Oxime before purification. [b)] Oxime after purification. [c)] Determined by ^{1}H NMR spectroscopy.

4.5.2. Cleavage of unsymmetrically substituted and complex ketones

The stage was now set for the cleavage of unsymmetrical ketones for which two isomeric enolates potentially exist. The selective kinetic deprotonation of 2-methylcyclohexanone (**278a**) using lithium bases is well established.[221,231] However, these known conditions were not directly transferable. Successful regioselective cleavage can only be achieved if the following conditions are met: 1) the enolate can be generated in the absence of internal electrophile; 2) the rate of nitrosation is higher than the rate of equilibration of the two isomeric enolates; 3) the rate of nucleophilic attack of the alkoxide on the ketone must be faster than deprotonation of the nitroso intermediate.

A screening of base systems (table 26, entries 1-6) has shown, that sodium enolates best balance these kinetic limitations and are therefore superior both in terms of reactivity and selectivity providing 68% yield of isoamyl 2-methyl-6-hydroxyiminohexanoate (**279a**) (entry 6). The kinetic enolates of 2-methylcyclopentanone (**278b**) and trans 1-decalone (**278c**) also underwent efficient cleavage in 80% and 70% yield respectively (entries 7, 8). Bicyclo[4.1.0]heptan-2-one (**278d**), easily prepared by cyclopropanation of cyclohexenone, [232] was also subjected to kinetic deprotonation followed by cleavage, but only provided 28% yield of the desired ε-hydroxyimino ester **279d** along with a significant amount of the non-cleaved α-hydroxyiminoketone **281** (entry 9). These experiments confirmed the feasibility of anti-Beckmann cleavage of unsymmetrical ketones via their kinetic enolates.

Table 26. Directed cleavage of unsymmetrical ketones **278a-d**.



278a-d **279a-d** **280a-c** **281**

Entry	**278**	n	R^1	R^2	Method	Base	**279** (%)	**280** (%)
1	**a**	2	Me	H	A	LiHMDS	**a** (56)[c]	**a** (37)[c]
2	**a**	2	Me	H	A	LiHMDS, *i*-AmOLi	**a** (63)[c]	**a** (32)[c]
3	**a**	2	Me	H	A	KHMDS	**a** (23)	**a** (26)
4	**a**	2	Me	H	A	KHMDS [d]	**a** (49)	**a** (17)
5	**a**	2	Me	H	A	KHMDS, *i*-AmOK	**a** (62)[c]	**a** (12)[c]
6	**a**	2	Me	H	A	NaHMDS	**a** (68)	-
7	**b**	1	Me	H	A	NaHMDS	**b** (80)	**b** (8)
8	**c**	2		$-(CH_2)_4-$	A	NaHMDS	**c** (70)	-
9	**d**	2		$-(CH_2)-$	A	NaHMDS	**d** (28)[e]	-
10	**a**	2	Me	H	B	MeLi	-	**a** (82)
11	**b**	1	Me	H	B	MeLi	**b** (4)	**b** (81)
12	**c**	2		$-(CH_2)_4-$	B	MeLi	**c** (7)	**c** (58)

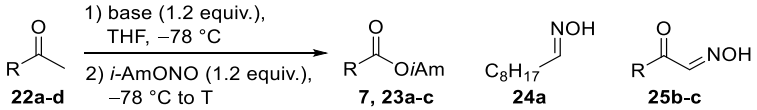
Conditions: [a] Method A: MHMDS (1.2 equiv.), THF, −78 °C, RONO (1.4 equiv.). [b] Method B: i) TMSCl, Et_3N, DMF; ii) MeLi (1.3 equiv.), THF, –78 to –20 °C, *i*-AmONO (1.5 equiv.), –78 °C. [c] Determined by ^1H NMR spectroscopy. [d] Ketone cannulated the solution of base. [e] 3-(Hydroxyimino)bicyclo[4.1.0]heptan-2-one (**281**, 49%) isolated.

Next, we aimed to demonstrate the possibility of directing the cleavage also to the more substituted side of unsymmetrical ketones. Enol ethers **278a'**, **278b'** and **278c'** were prepared by treating the respective ketones **278a**, **278b** and **278c** with TMSCl and Et_3N in DMF.[220] Predominantly thermodynamic (more substituted) lithium enolates were generated by treatment of these silyl enol

ethers with MeLi in THF. These enolates were then oxidized by addition of *i*-AmONO resulting in high yields of cleaved products **280a-280c** (table 26, entries 10-12).

Methyl ketones are another common class of ketones known to undergo regioselective enolization under kinetic conditions. A series of ketones **282a-d** were enolized by NaHMDS of KHMDS, followed by oxidation with *i*-AmONO (table 27). The yields of the respective esters **267**, **283a-c** were generally lower than for the previously studied ketones and decreased with the increasing steric demand of the bulkier chain from 64-66% obtained for cyclopropyl methyl ketone (**282a**) and 2-undecanone (**282b**) (entries 2, 4), 31% for **282c** to only 7-17% for pinacolone (**282d**, entries 6-8). The rest of the mass balance was composed of either aldoxime resulting from regioisomeric cleavage (entries 1, 2), unreacted starting material (entries 3, 5) or non-cleaved α-hydroxyiminoketone (entries 4, 7-9).

Table 27. Cleavage of methyl ketones.



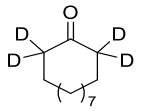
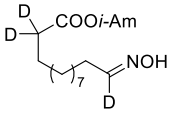
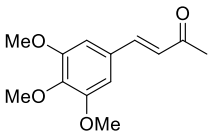
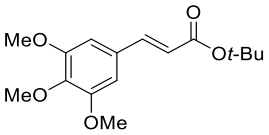
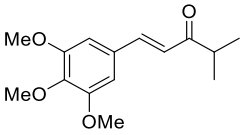
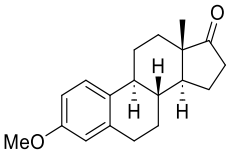
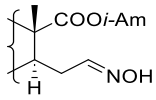
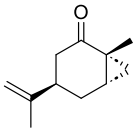
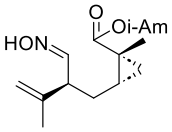
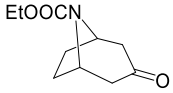
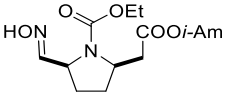
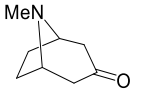
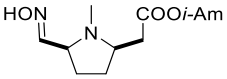
22a-d **7, 23a-c** **24a** **25b-c**

Entry	**282**	R	Base	T °C	Ester (%)	Other products (%)
1	**a**	Non	**Na**HMDS	−60	**283a** (67) [a]	**284a** (25)
2	**a**	Non	**K**HMDS	−78	**283a** (35)	**284a** (9)
3	**b**	*c*Pr	**Na**HMDS	−78	**283b** (32)	**282b** [b] (12 [c])
4	**b**	*c*Pr	**Na**HMDS	−35	**283b** (66)	**285b** (6)
5	**c**	Cy	**Na**HMDS	−78	**267** (31)	**282c** [b] (35)
6	**c**	Cy	**Na**HMDS	−35	**267** (49 [c])	**268** (19 [c])
7	**d**	*t*-Bu	**Na**HMDS	+23	**283c** (15)	**285c** (45)
8	**d**	*t*-Bu	**K**HMDS	+23	**283c** (6 [c])	**285c** (73)
9	**d**	*t*-Bu	**K**HMDS, *i*-AmOK [d]	−78	**283c** (17[c])	**285c** (56 [c])

[a] Inseparable from co-formed (*i*-AmO)$_2$CO (**276**). [b] Recovered ketone. [c] Determined by ^{1}H NMR spectroscopy. [d] *i*-AmOK (0.3 equiv.) added.

After finishing the systematic study of the cleavage reaction of all basic ketone structural types, we proceeded to demonstrate the applicability of the method to selected complex or naturally occurring ketones. Reaction of deuterated cyclododecanone **286a** using LiHMDS/*i*-AmONO proceeded smoothly to give 85% yield of deuterated aldoxime **287a** (table 7, entry 1). α,β-unsaturated ketones **147a** and **147b**, prepared by aldol condensation from 3,4,5-trimethoxybenzaldehyde (chapter 4.2, scheme 45),[233] were oxidized giving moderate to good yields of *t*-butyl cinnamate derivative **146** (entries 2, 3). Ready access to **146**, provided by this method, was important in the development of conjugate addition of aryllithiums to Michael acceptors (chapters 4.2.1 and 4.3).

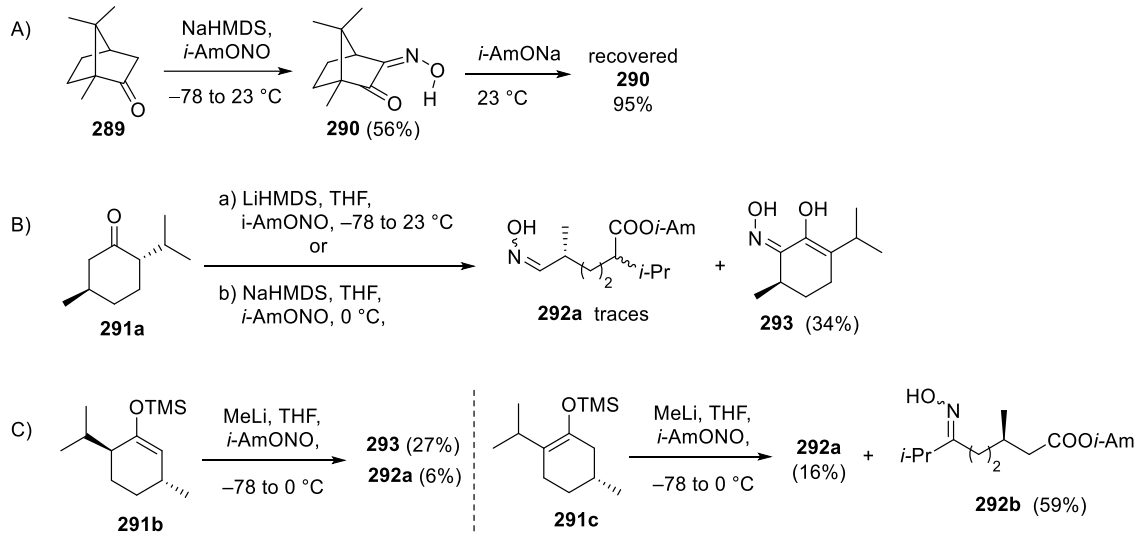
Table 28. Cleavage of complex ketones. [a)]

Entry	Starting ketone	Base	T (°C)	Product	(%)
1	**286a** 	LiHMDS LiO*i*-Am[b]	–78	**287a** 	84
2	**147a** 	KHMDS	+23	**146** 	67
3	**147b** 	NaHMDS	+23		57
4	**286b** 	NaHMDS	–78	**287b** 	78 [c)]
5		NaHMDS NaO*i*-Am [b)]	–78		89
6	**286c** 	NaHMDS	–20	**287c** 	24 [d)]
7	**286d** 	KHMDS	+23	**287d** 	39
8		NaHMDS	–20		62
9	**286e** 	LiHMDS	–5	**287e** 	31
10		NaHMDS	–30		37
11		NaHMDS[e]	–78		48

[a)] General conditions: Base (1.2 equiv.), THF, –78 °C, RONO (1.4 equiv.), –78 °C to T. [b)] NaO*i*-Am (0.3 equiv.) used. [c)] 16-Hydroxyimino-*O*-methylestrone (**288a**, 21%) isolated. [d)] (1*R*,4*S*,6*S*)-3-(Hydroxyimino)-1-methyl-4-(prop-1-en-2-yl)bicyclo[4.1.0]heptan-2-one (**288b**, 52%) isolated. [e] NaHMDS (1.4 equiv.), *i*-AmONO (1.3 equiv.), HMPA (1.4 equiv.), high dilution.

Nitrosation of the sodium enolate of O-methylestrone (**286b**) by *i*-AmONO resulted in opening of the D ring, giving 78-89% yield of hydroxyiminoester **287b** (entries 4, 5). Similar transformation has been previously accomplished by nitrosation of O-methylestrone (**286b**) by *i*-AmONO in butanol followed by reduction and $TiCl_4$ mediated Beckmann fragmentation.[234] The different outcome of nitrosation of **286b** in butanol and THF exemplifies the role of solvent proticity in deciding which reaction channel predominates. Carvone-derived **286c**, available via cyclopropanation from natural (–)-carvone, was subjected to the cleavage conditions but only 24% yield of the desired opened product **287c** was obtained along with 52% yield of the noncleaved hydroxyiminoketone **288b** (entry 6). This finding is consistent with the incomplete cleavage of the conformationally locked cyclopropanated cyclohexanone **278b** (table 28, entry 9). N-ethoxycarbonylnortropinone (**286d**) underwent cleavage via its potassium and sodium enolates in 39% and 62% yields, respectively (table 28, entries 7, 8). However, the tertiary amine-containing natural tropinone (**286e**) proved more resistant to cleavage (entries 9, 10). We reasoned that this might stem from low solubility of its enolates, as reactions of **286e** were often inhomogeneous. Using higher dilution conditions and HMPA as an additive increased the yield of **287e** to 48% (entry 11).

Severely sterically hindered and conformationally rigid camphor (**289**) was found to resist cleavage completely and only provided the known [235] hydroxyiminoketone **290** in 56% yield (scheme 85, A). Subjecting the isolated **290** to *i*-AmOK in THF did not lead to any reaction, the startimg material was recovered in near-quantitative yield. The last complex ketone to be studied was L-menthone (**291a**). Deprotonation of **291a** under kinetic conditions followed by oxidation by *i*-AmONO yielded predominantly hydroxyiminoketone **293** as a rapidly decomposing mixture of tautomers. An isolable amount of the opened product **292a** representing only 6% yield was obtained by nitrosation of the lithium enolate of **292a**, which was generated by first preparing and isolating TMS enol ether **291b**, followed by desilylation of **291b** using MeLi (scheme 85, B). However, even under these conditions the unopened product **293** predominated (27% yield). Hydroxyiminoester **292a** was isolated as an equimolar mixture of diastereomers, which can be explained by epimerization of the C-2 stereocentre of menthone, as has been observed earlier during other base-inducer reactions of **291a**.[236] In contrast with the inefficient cleavage of the kinetic enolate **291b**, the isomeric thermodynamic enolate generated by desilylation of silyl enol ether **291c** afforded 59% of opened oxime-ester **292b** on oxidation together with 16% of **292a**.



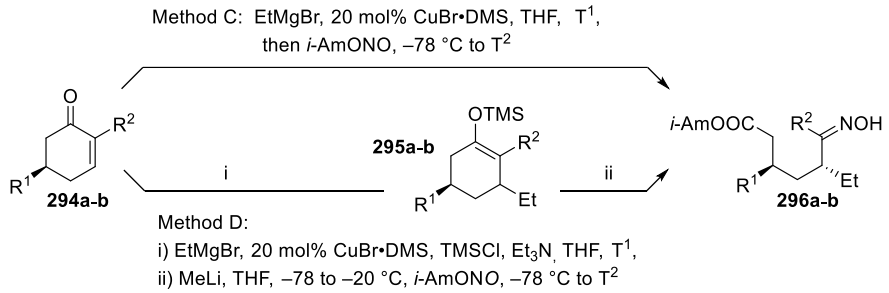
Scheme 85. Limitations of nitrosative cleavage. A) Unsuccessful cleavage of camphor (**289**). B) Direct cleavage of menthone (**291a**). C) Cleavage of **291a** via its enolates generated from enol ethers **291b** and **291c**.

Aside from direct deprotonation of ketones or desilylation of TMS enol ethers, non-isomeric enolates can be also generated by copper-catalysed conjugate addition of organometallic reagents to α,β-unsaturated ketones. This way, even enolates of ketones that would be otherwise difficult to selectively deprotonate at one defined position can be generated in racemic or optically enriched form.[130,149] Our initial attempts at one-pot nitrosative cleavage of such enolates in the presence of Cu salts had limited success, presumably due to redox processes triggered by oxidation of Cu(I) to Cu(II). For example, the magnesium enolate formed by CuBr·DMS catalysed addition of EtMgBr to cyclohex-2-enone (**294a**) afforded only 24% of the desired hydroxyiminoester **296a** (table 29, entry 1). To circumvent this problem, the magnesium enolates produced by conjugate addition were first trapped as TMS enol ethers [237] and regenerated as lithium enolates in a separate step prior oxidation with nitrite. Using this two-step protocol, the yield of hydroxyiminoester **296a** increased to 73% (entry 2).

Conjugate addition to *R*-(−)-carvone (**294b**) proceeds with a high degree of diastereoselectivity giving TMS enol ether **295b** after silylation of the magnesium enolate

intermediate.[237] Desilylation of **295b** by MeLi followed by oxidative cleavage afforded a very high 87% yield of hydroxyiminoester **296b** as a single diastereomer (table 29, entry 3). Direct one-step cleavage of **296b** in the presence of the Cu catalyst was also attempted, because the presence of the methyl group at C-2 in carvone prevents deprotonation of the α-nitrosoketone intermediate during oxidation, therefore tautomerization to α-hydroxyiminoketone cannot compete with the alkoxide addition that triggers fragmentation. During the course of optimization, we found that the initially low yield of **296b** (entry 4) is at least partially caused by interaction of copper salts with the oxime during quench or aqueous workup. Using metal-binding EDTA for workup, a synthetically useful yield of 42% was achieved after optimization (entries 5, 6), it however compared unfavourably with the two-step method.

Table 29. Conjugate addition to enones **294a,b** followed by nitrosative cleavage.



Entry	**294**	R^1	R^2	Method	T^1 (°C)	T^2 (°C)	**296**	(%)
1	**a**	H	H	C	–78	+23	**a**	24
2	**a**	H	H	D	–40	–78	**a**	73
3	**b**	propen-2-yl	Me	D	–40	–30	**b**	87
4	**b**	propen-2-yl	Me	C	0	+23	**b**	32
5	**b**	propen-2-yl	Me	C [a)]	0	+23	**b**	38
6	**b**	propen-2-yl	Me	C [a)]	–30	+23	**b**	42

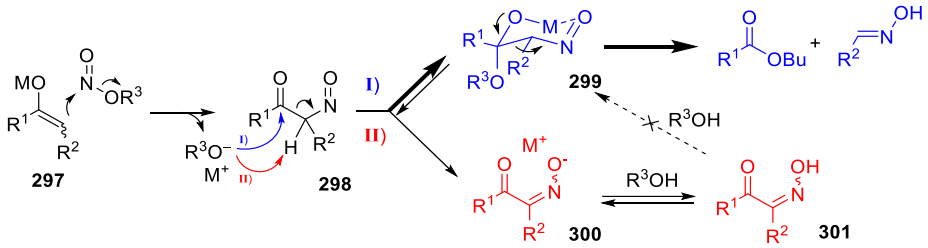
[a)] EDTA used for work-up.

To find out whether the poor yield of the one-pot protocol was due to the presence of Cu or due to the nature of enolate counterion, the magnesium enolate of 3,5-dimethylcyclohexanone (**273a**) was generated by direct deprotonation using *i*-Pr_2MgCl in THF or THF/HMPA mixture.[238] Oxidation by *i*-AmONO afforded only up to 31% (by ^1H NMR) of **274a**. It can be therefore concluded, that the lower yield of one-pot conjugate addition/cleavage protocol is likely due to lower reactivity of magnesium enolates, and only to a minor degree due to the presence of copper salts.

4.5.3. Mechanistic considerations and conclusions

Overall, the results presented in the previous chapters show that organic nitrites are very reactive towards metal enolates in ethereal solvents, resulting in fast nitrosation at temperatures as low as –78 °C. Contrary to some literature reports,[228] even the sterically hindered *t*-BuONO, which has been used previously to rather trigger single electron processes [239] reacts with such enolates. There is therefore no kinetic window for a redox catalyst like ferrocene of copper complexes to mediate SET oxidation that could result in radical cyclisation as was part of the original design (chapter 4.1.1, scheme 32).

Moreover, the expected α-hydroxyiminoketone is not the major product for most ketones. Instead, a very fast alkoxide attack on the carbonyl group results in a retro-aza-Claisen fragmentation cleaving the C-C bond between the carbonyl and the α-carbon atom. The results suggest that the products distribution is purely under kinetic control - decided at the stage of the first intermediate **298**, which can either undergo nucleophilic attack at the carbonyl group (pathway I) or be deprotonated by the alkoxide to give anion **300** (scheme 86, pathway II). The fragmentation (pathway I) presumably occurs via the cyclic Zimmerman-Traxler transition state **299** to give an ester and an oxime salt as products and is the dominant pathway for most unhindered ketones, especially when Na or K enolates are used. For ketones that are too sterically hindered to undergo nucleophilic attack on **298** or too conformationally rigid to adopt the transition state **299**, deprotonation to give the stable salt **300** predominates and the reaction defaults to the more common α-hydroxyimination. The formation of salt **300** is likely irreversible under the conditions, as attempts to cleave **300** or its neutral parent hydroxyiminoketone form **301** by alkoxide did not lead to cleavage. Which pathway dominates can be influenced by the choice of reaction conditions. In general, Na, K and Li enolates favour pathway I, Mg enolates favour pathway II. THF as solvent was found to promote the cleavage reaction as opposed to protic solvents, which favour α-hydroxyimination.

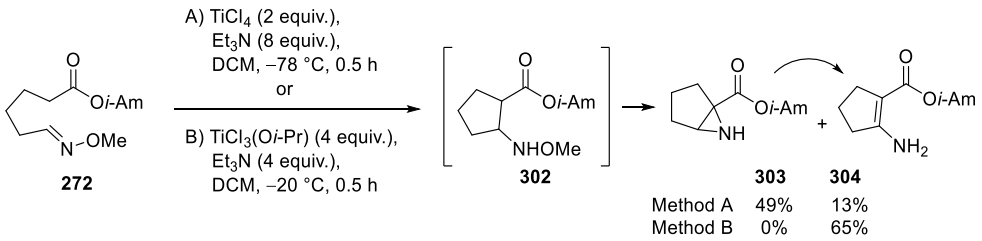


Scheme 86. Competing reaction channels during base mediated nitrosation of ketones. I) Nucleophilic addition of alkoxide, followed by retro-aza-Claisen fragmentation via Zimmerman-Traxler TS **299**. II) Deprotonation to give salt **300** as observed in hindered ketones.

We found that excess base (especially KHMDS) and oxidant can lead to secondary cleavage of esters and Beckmann fragmentation of aldoximines. By carefully controlling the loading of base and oxidant, the reaction can be stopped at the hydroxyamino ester product(s), making nitrosative cleavage a potentially useful method for the scission of the α-C-C bond in ketones. In particular, it allows anti-Beckmann cleavage of aryl ketones to benzoic esters, which is complementary to the standard methods like the BR and BVO. Simple and substituted cyclic ketones can be cleaved to ω-hydroxyiminoesters. Most importantly, regioisomeric enolates and TMS enol ethers can be cleaved with a high degree of regio-specificity. Methyl ketones are also amenable to the cleavage, although with lower efficiency (table 27). Unsaturated ketones can serve as substrates either directly via deprotonation (table 28, entries 2, 3) or the cleavage reaction can be coupled with prior conjugate addition (table 29). Both steric hindrance in the vicinity of the carbonyl group and conformational rigidity of certain cyclic substrates may hamper cleavage (scheme 85). However, some hindered substrates like O-methyl estrone (**286b**) and **273b** were cleaved very smoothly (table 28, entry 5; table 25), while the non-hindered bicyclo[4.1.0]heptan-2-one (**278d**) (table 26, entry 9) resisted cleavage, we should therefore conclude that conformational flexibility might be the key factor.

The products of the cleavage reaction may be of synthetic interest. The oxime functional group itself is a very versatile synthetic handle that can be converted to a primary amine, hydroxylamine, ketone or can undergo oxidative cycloadditions with alkynes and alkenes.[240,241] It contains the energy-loaded N-O bond that allows generation of high energy iminyl radicals or can be used to power transition metal catalysis.[242] Cyclic ketones may serve via oxidative cleavage as

precursors for ω-aminoacids. In this vein, we envisioned a potential use for this methodology in the preparation of valuable cyclic non-natural amino acids, used for the construction of foldamers.[243,244] Attempted Mannich-type cyclisation of oxime ether **272** (table 23, entry 13) under the conditions of soft enolization using $TiCl_4$ or $TiCl_3$(O*i*-Pr) and Et_3N indeed led to cyclic products, however the desired product **302** (scheme 87) proved too unstable under the conditions, undergoing a secondary enolization and aziridine formation to yield the isolable product **303**, along with varying amounts of rearranged vinylogous amide **304**. Extensive optimization of this reaction unfortunately did not lead to synthetically useful yields of **302**.



Scheme 87. Mannich cyclisation of **272** under the conditions of soft enolization.

5. CONCLUSIONS AND PERSPECTIVES

The concept of C-C bond forming conjugate addition coupled with oxidative cyclisation proved to be a feasible synthetic strategy for the total synthesis of indane-based natural polyphenols. The key step exploits the orthogonal reactivity of formally anionic organometallic intermediates, free radicals and carbenium ions by linking them in a sequence through SET oxidation. It involves conjugate addition of lithiated stilbenes to cinnamic ester derivatives, followed by SET oxidation of the enolate by $FeCp_2PF_6$ resulting in diastereoselective radical *5-exo-trig* cyclisation, followed by another SET oxidation that triggers the final cationic lactonization. Compared to aliphatic model substrates, annulation of aromatic natural product precursors proved easier to optimize, because the benzylic nature of the cyclic radicals allows efficient second SET oxidation directly resulting in lactonization. During the fully diastereoselective double annulation, four new stereocentres, two new C-C bonds and one C-O bond were formed in a single step from planar substrates.

The relative configuration of kompasinol A (**III**) was confirmed by a crystal structure of its derivative. The relative configuration of gnetifolin F (**I**) and 11-deoxykompasinol A (**IV**) was also confirmed to be *rel*-(7*S*,8*R*,7'*R*,8'*S*) by total synthesis. Based on the similarity of their NMR spectra, all other known furoindane stilbenolignans should also be regarded as *rel*-(7*S*,8*R*,7'*R*,8'*S*). Specific rotation of optically pure 11-deoxykompasinol A (**IV**) did not match the value of the natural sample, therefore the optical purity of the natural product could not be assessed. However, the ECD spectra of natural **IV** matched the synthetic sample. This can be counted as evidence in support of an enzymatic origin of at least those stilbenolignans with non-zero value of optical rotation. Heterolytic lability of the C-O bond in furoindanes can lead to epimerization at the C-8 centre, especially in non-basic solvents. Future isolation efforts should therefore take into account the potential interference of the epimer with measurement of specific rotation and independent assessment of optical purity by HPLC should be considered.

The modular approach to furoindanes should allow the synthesis of all remaining congeners lehmbachol D (**II**), 13-hydroxykompasinol A (**V**) as well as any other FIS isolated in the future, from a limited set of suitably protected stilbenes and ylidenemalonic esters. The racemic composition of some natural stibenolignans opens up the possibility of their statistical formation from available monolignols and phenolic stilbenes in the extracellular matrix of even in extracts during isolation. Optically pure synthetic samples obtained by synthesis can be used to guide isolation, identification as well as assessment of optical purity of future congeners.

While the key annulation methodology worked flawlessly in the *5-exo-trig* cyclisation mode, the similar *6-exo-trig* mode proved unfeasible due to the rapid competing hydrogen transfer. The strategy for the total synthesis of podophyllotoxin therefore had to be changed to instead construct the C ring via Ru-catalysed ring closing metathesis. A serendipitous discovery during the study of relative configuration of furoindanes opened up an opportunity for a conceptually new total synthesis of podophyllotoxin, based on conjugate addition steps coupled with polar *6-exo-tet* cyclisation reaction. Despite it not including SET oxidation, this strategy also relates closely to the overall conjugate addition/oxidative cyclisation concept. The difference is that the oxidation takes place before the conjugate addition and in the form of a stilbene epoxidation. This strategy proved feasible and led to the complete neopodophylltoxin skeleton in just two steps. Future efforts should aim at improving the asymmetric induction during the initial organocatalytic Corey-Chaykovsky reaction or optically enriching the product by crystallization. The free carboxylic acid group at C-8' is ideally posed to allow easy access to medicinally relevant 8'-substituted analogues of podophyllotoxin.

To facilitate the bioinspired total syntheses of natural polyphenols, some areas of methodology had to be advanced. Direct addition of aryllithiums to non-hindered ylidenemalonic esters was described for the first time. Like the much slower addition to hindered cinnamates, the reaction is mediated by lithium-binding diether or diamine ligands. In addition to existing ligands, some new ligands like the dianhydrosugar-derived diethers were found to be competent promoters of conjugate addition. In contrast to the good asymmetric induction afforded by (+)-sparteine during the conjugate addition of protected isorhapontigenin to ferulic acid derivative, similar sinapic acid derivatives afforded much lower ee using the same ligand. Future asymmetric syntheses lehmbachol D (**II**) and 13-hydroxykompasinol A (**V**) should therefore use Tomioka's hydrobenzoin diether ligand as the chiral promotor, which delivered a much more consistent asymmetric induction across a wider range of substrates. The organocatalytic Corey-Chaykovsky epoxidation, used in the approach to neopodophyllotoxin, was inspired by a previous dual-catalytic method. Finding a sufficiently active allylic electrophile and optimization increased the reactivity enough to allow isothiocineol to act as the sole catalyst, affording optically enriched epoxides in good dr.

The serendipitous discovery of nitrosative cleavage of ketone enolates via retro-aza-Claisen fragmentation turned out to be a general reactivity pattern of most simple and more complex ketones. The reaction is site-specific and allows anti-Beckmann cleavage of phenones and other non-symmetrically substituted ketones via their kinetic or thermodynamic enolates. Opening of cyclic ketones affords ω-hydroxyiminoesters, which can serve as precursor to ω-amino acids. Stereocomplex ω-hydroxyiminoesters can be accessed by Cu-catalysed conjugate addition followed by cleavage of the resulting enolates, potentially opening the way to optically pure complex unnatural ω-amino acids.

Dirigent and dirigent-like proteins may play a more important in the biosynthesis of fungal, bacterial and plant-produced secondary metabolites than previously believed. The search for DIRs and their functional characterisation can be facilitated by the total synthesis of the suspected DIR-related phenolic coupling products. In the future, the discovered or newly bioengineered DIRs may find important applications in the biotechnological production of pharmaceuticals like etoposide and teniposide.

6. EXPERIMENTAL PART

GENERAL INFORMATION

All reactions involving dry solvents, organometallic reagents and enolates were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Dry DCM and TMEDA were distilled from CaH_2 prior use. Dry toluene was distilled from sodium metal prior use. Dry THF and DME were distilled from potassium metal/benzophenone prior to use. Dry Et_2O and DIPA were distilled from CaH_2 and stored over activated 4 Å molecular sieves. Commercial technical grade *t*-BuONO and all other (reagent grade) alkyl nitrites were distilled prior to use. Commercial solutions of *n*-BuLi and MeLi were titrated using salicylaldehyde phenylhydrazone.[245] Deuterated chloroform was filtered through basic alumina and stored over activated 4 Å molecular sieves. Petroleum ether (PE) with bp range 40-65 °C was used for chromatography. All other commercially available solvents and reagents were purchased in p. a. (98%) quality or better and used as received. Reaction progress was monitored by TLC using POLYGRAM SIL G/UV_{254} plates or by GC using Agilent 6850 Series GC System with FID. Chromatographic separations were carried out manually on silica gel 60 (Fluka, 230-400 mesh) or automatically using a CombiFlash® NextGen 300+ instrument and RediSep Gold® silica gel disposable flash columns. Microwave-assisted reactions were performed using a CEM Discover® SP instrument. IR spectra of neat compounds were measured using a Bruker ALPHA FT-IR spectrometer using an ATR device. IR spectra in solution were measured using Thermo Scientific Nicolet 6700 FT-IR spectrometer. ^{1}H, ^{19}F, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker Avance III™ HD 400 MHz spectrometer equipped with a Prodigy cryo-probe working at 400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C, 161.8 MHz for ^{31}P and 376.3 MHz for ^{19}F respectively. ^{1}H-decoupled ^{19}F spectra were measured with α,α,α-trifluorotoluene as internal standard, δ = –63.7 ppm. ^{1}H-decoupled ^{31}P spectra were measured with 85% H_3PO_4 as internal standard, δ = 0 ppm. The connectivity was determined by ^{1}H-^{1}H COSY experiments and all signal assignments are based on ^{1}H-^{13}C HSQC or HMBC experiments. Nominal mass spectra were recorded on LCQ Fleet (Thermo Scientific), 5975B MSD/7890N GC/MS couple (Agilent) and GCT Premier (Waters) spectrometers. High resolution spectra were obtained using QTof Micro (Waters) and LTQ Orbitrap XL (Thermo Scientific) instruments. Combustion analyses were obtained from Perkin-Elmer 2400 Series II CHN analyzer, at the Microanalytical Laboratories of IOCB Prague. Optical rotation was measured using Autopol IV (Rudolph Research Analytical) polarimeter. Melting points were determined using a Stuart SMP 10 apparatus. Absolute contents of mixtures were determined by ^{1}H NMR spectroscopy using *p*-xylene as internal quantitative standard or by relating to a separately isolated component. All uncommented yields refer to isolated yields. All chiral separations were performed using Agilent 1200 Infinity Series HPLC system with UV detection (280 nm for stilbene-containing compounds, 254 nm for other compounds), YMC Amylose-SA S-5µm column (250×4.6 mm), isocratic elution in hexane/*i*-PrOH mobile phase, 1 mL/min flow.

6.1. Part A

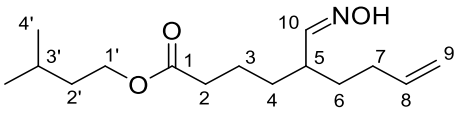
6.1.1. Initial exploration of in situ oxidative cyclisation

Conjugate addition/*in situ* enolate oxidation by *i*-AmONO leading to fragmentation

A flame dried Schlenk flask connected to dry nitrogen was charged with CuBr•DMS (20.6 mg, 0.1 mmol), calcinated LiCl (8.5 mg, 0.2 mmol), dry THF (1.5 mL) and HMPA (35 µL, 0.2 mmol). The resulting suspension was cooled to –35 °C, then a solution of homoallylmagnesium bromide (1.5 mL,

0.75 mmol, 0.49 M in Et_2O) was added dropwise resulting in yellow color, which dissipated after 5 min. to produce a grey suspension. A solution of 2-cyclohexanone (49 µL, 0.5 mmol) in THF (0.5 mL) was added dropwise at –35 °C. The reaction mixture was stirred at –35 °C for 5 min., followed by cooling to –50 °C. Solid TEMPO (156 mg, 1.0 mmol) was added, followed by quick addition of *i*-AmONO (201 µL, 1.5 mmol) in one portion. The mixture was stirred for 20 min at –50 °C before quenching with sat. NH4Cl (1.5 mL). The rection mixture was partitioned between water (1 mL) and pentane (25 mL). The aqueous layer was washed twice with DCM (25 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (PE/EA 10:1 to 2:1) to yield in order of elution 39 mg (30%) of **112** as a colourless oil and 50 mg (37%) of 3:1 *E/Z* mixture of **111** as a colourless oil.

Isopentyl 5-((hydroxyimino)methyl)non-8-enoate (**111**)



R_f 0.35 (hexanes/EA 5:1);

IR (film) ν[cm^{-1}]: 3500-3100 (br.), 3088 (w), 2966 (m), 2935 (m), 2880 (w), 1739 (s), 1646 (w), 1462 (m), 1392 (w), 1372 (w), 1170 (s), 1057 (w), 996 (m), 913 (s), 821 (w).

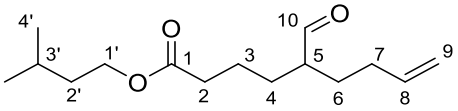
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.0 Hz, 1H, H-10^E), 6.47 (d, *J* = 8.1 Hz, 1H, H-10^Z), 5.85-5.72 (m, 2H, H-8^{EZ}), 5.05-4.94 (m, 4H, H-9^{EZ}), 4.10 (t, *J* = 6.9 Hz, 4H, H-1'^{EZ}), 3.18-3.10 (m, 1HB, H-5^Z), 2.36-2.24 (m, 3HA + 2HB, H-2^{EZ}, H-5^E), 2.14-1.96 (m, 4H, H-7^{EZ}), 1.78-1.60 (m, 2H, H-3'^{EZ}), 1.60-1.17 (m, 16H, H-2'^{EZ}, H-3^{EZ}, H-4^{EZ}, H-6^{EZ}), 0.92 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.6 (s, C-1^Z), 173.5 (s, C-1^E), 156.1 (br. d, C-10^Z), 155.1 (d, C-10^E), 138.0 (d, C-8^Z), 137.9 (d, C-8^E), 115.0 (t, C-9^E), 114.8 (t, C-9^Z), 63.01 (t, C-1'^{E}), 62.98 (t, C-1'^{Z}), 39.0 (d, C-5^E), 37.3 (t, C-2'^{EZ}), 34.1 (br. d, C-5^Z), 34.12 (t, C-2^Z), 31.10 (t, C-2^E), 32.18 (t, C-3^E), 32.08 (t, C-3^Z/6^Z), 32.04 (t, C-3^Z/6^Z), 31.99 (t, C-6^E), 31.4 (t, C-7^Z), 31.0 (t, C-7^E), 25.0 (d, C-3'^{EZ}), 22.6 (t, C-4^Z), 22.41 (q, C-4'^{EZ}), 22.39 (t, C-4^E);

MS (ESI+) *m/z*, (%): 292 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{27}O_3NNa$ 292.18831; found: 292.18836.

Isopentyl 5-formylnon-8-enoate (**112**)



R_f 0.55 (hexanes/EA 5:1);

IR (film); ν[cm^{-1}]: 2966 (m), 2936 (s), 2879 (m), 1737 (s), 1646 (w), 1469 (m), 1364 (m), 1249 (m), 1170 (s), 1135 (w), 1063 (w), 997 (w), 974 (m), 914 (m), 767 (w), 725 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.61 (d, *J* = 2.6 Hz, 1H, H-10); 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, H-8); 5.10-4.96 (m, 2H, H-9); 4.11 (t, *J* = 6.9 Hz, 2H, H-1'); 2.35-2.29 (m, 3H, H-2, H-5); 2.12-2.01 (m, 2H, H-7); 1.83-1.71 (m, 1H, H-6a); 1.71-1.19 (m, 9H, H-3, H-4, H-6b, H-2', H-3'); 0.93 (d, *J* = 6.6 Hz, 6H, H-4');

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 204.3 (s, C-10), 172.9 (d, C-1), 137.3 (d, C-8), 115.3 (t, C-9), 62.8 (t, C-1'), 50.6 (d, C-5), 37.1 (t, C-2'), 33.9 (t, C-2), 30.7 (t, C-7), 27.8 (t, C-3/6), 27.6 (t, C-3/6), 24.8 (d, C-3'), 22.2 (q, C-4'), 22.1 (t, C-4);

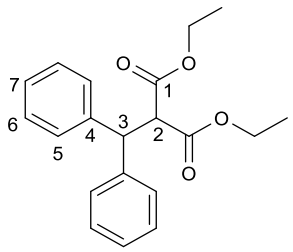
MS (ESI+) *m/z*, (%): 277 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{26}O_3Na$ 277.1774; found: 277.1775.

Model addition of PhLi to diethyl benzylidene malonate (113)

A solution of *t*-BuLi (0.78 mL, 1.33 mmol, 1.7 M in heptane) was added to a solution of PhBr (61 µL, 0.58 mmol) in dry THF (4 mL) at –78 °C. The mixture was stirred for 10 min at –78 °C, followed by warming to r.t. Solid CuBr·DMS (21 mg, 0.102 mmol) was added, followed by stirring at r.t. for 10 min. The reaction was cooled to –40 °C and a solution of diethyl benzylidenemalonate (115 µL, 0.51 mmol) in THF (3 mL) was added dropwise via cannula. The reaction was gradually warmed to 0 °C over 1 h, followed by addition of saturated NH_4Cl solution (20 mL) and DCM (100 mL). The aqueous phase was separated and extracted twice with DCM (2×100 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (hexane/EA 15:1 to pure EA) yielding 125 mg (74%) of **114** as a colourless amorphous solid.

Diethyl 2-benzhydrylmalonate (**114**)



R_f 0.29 (hexane/DCM/Et_2O 30:20:1);

IR (film); ν[cm^{-1}]: 3062 (w), 3029 (w), 2981 (w), 2937 (w), 1754 (m), 1727 (vs), 1630 (w), 1600 (w), 1495 (m), 1451 (m), 1368 (m), 1297 (m), 1259 (s), 1174 (s), 1153 (s), 1095 (m), 1060 (m), 1031 (s), 748 (m), 698 (vs), 605 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.32-7.24 (m, 8H, H-5, H-6), 7.17 (tt, *J* = 7.1, 1.5 Hz, 2H, H-7), 4.76 (d, *J* = 12.2 Hz, 1H, H-3), 4.33 (d, *J* = 12.2 Hz, 1H, H-2), 4.06-3.98 (m, 4H, OCH_2CH_3), 1.02 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 167.8 (s, C-1), 141.5 (s, C-4), 128.7 (d, C-6), 127.9 (d, C-5), 127.0 (d, C-7), 61.6 (t, OCH_2CH_3), 57.6 (d, C-2), 51.3 (d, C-3), 13.9 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 707 (6, $[2M + Na^+ + MeOH]^+$), 675 (16, $[2M + Na^+]^+$), 381 (20, $[M + Na^+ + MeOH]^+$), 365 (12, $[M + K^+]^+$), 349 (100, $[M + Na^+]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{20}H_{22}O_4Na$ 349.1410; found: 349.1411.

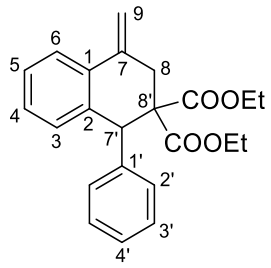
One-pot conjugate addition/in-situ oxidative cyclisation of α-methylstyrene

Styrene **115** was prepared using a known procedure from methyl 2-bromobenzoate via addition of MeMgBr, followed by dehydration by $KHSO_4$.[246]

A solution of *n*-BuLi (383 µL, 0.57 mmol, 1.5 M in heptane) was added to a solution of styrene **115** (91 µL, 0.6 mmol) in dry THF (2 mL) at –78 °C. The mixture was stirred for 30 min at –78 °C. CuBr·DMS (10 mg, 50 µmol) was added followed by addition of diethyl benzylidenemalonate (**113**) (112 µL, 0.50 mmol). The reaction mixture was gradually warmed to 0 °C over 1 h, followed by replacing of the inert atmosphere with O_2 from a balloon. Solid **52** (367 mg, 1.1 mmol) was then added in one portion. The mixture was stirred vigorously for 30 min, followed by addition of 5% aqueous ascorbic acid (5 mL). The mixture was partitioned between water (15 mL) and DCM (50 mL). The phases were separated, the aqueous phase was extracted twice with DCM (2×30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (hexane/EA 15:1 to 2:1) yielding 77 mg of an inseparable mixture of isomeric alkenes **117a**/**117b** (42%, dr 2.5:1) as a colourless oil and 37 mg of **117d** (22%) as colourless oil.

Oxidation under inert atmosphere instead of O_2 yielded 55 mg of **117a**/**117b** (30%, dr 9:1) as a colourless oil and 32 mg of **117c** (17%) as colourless oil.

Diethyl 4-methylene-1-phenyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**117a**)

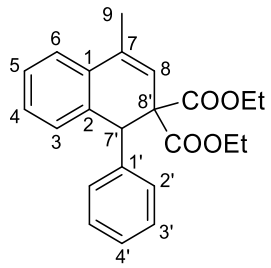


R_f 0.42 (hexane/EA 4:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.71-7.63 (m, 1H, H-6), 7.24-7.12 (m, 5H, H-4, H-5, H-3', H-4'), 7.05-6.98 (m, 3H, H-3, H-2'), 5.66 (dd, *J* = 2.3, 1.0 Hz, 1H, H-9a), 5.13 (dt, *J* = 2.4, 1.0 Hz, 1H, H-9b), 5.02 (t, *J* = 0.7 Hz, 1H, H-7'), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.04 (dq, *J* = 10.9, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.94 (dq, *J* = 10.8, 7.2 Hz, 1H, $OCH_aH_bCH_3$), 3.24 (dt, *J* = 14.9, 2.3 Hz, 1H, H-8a), 2.99 (ddd, *J* = 14.9, 1.4, 0.7 Hz, 1H, H-8b), 1.16 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.15 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.3 (s, *C*OOEt), 169.6 (s, *C*OOEt), 141.2 (s, C-1'), 138.8 (s, C-1), 137.7 (s, C-2), 133.1 (s, C-7), 130.7 (d, C-3), 130.1 (d, 2×C, C-2'), 128.8 (d, C-4/5/4'), 128.2 (d, 2×C, C-3'), 127.3 (d, C-4/5/4'), 126.7 (d, C-4/5/4'), 123.7 (d, C-6), 111.6 (t, C-9), 61.6 (t, OCH_2CH_3), 61.5 (t, OCH_2CH_3), 59.1 (s, C-8'), 49.2 (d, C-7'), 33.2 (t, C-8), 14.1 (q, OCH_2CH_3), 14.0 (q, OCH_2CH_3);

Diethyl 4-methyl-1-phenylnaphthalene-2,2(1H)-dicarboxylate (**117b**)

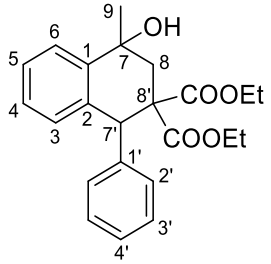


R_f 0.42 (hexane/EA 4:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.37-7.30 (m, 1H, H-6), 7.26-6.99 (m, 8H), 6.05 (qd, *J* = 1.5, 1.2 Hz, 1H, H-8), 4.89 (d, *J* = 1.2 Hz, 1H, H-7'), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 4.10-3.93 (m, 2H, OCH_2CH_3), 3.88 (dq, *J* = 10.8, 7.2 Hz, 1H, $OCH_aH_bCH_3$), 2.23 (d, *J* = 1.5 Hz, 3H, H-9), 1.17 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.08 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.6 (s, *C*OOEt), 169.3 (s, *C*OOEt), 139.8 (s, C-1'), 137.3 (s, C-2), 134.8 (s, C-1), 132.1 (s, C-7), 128.9 (d, C-3/4/5/4'), 128.8 (d, 2×C, C-2'/3'), 128.7 (d, C-3/4/5/4'), 128.3 (d, 2×C, C-2'/3'), 127.4 (d, C-3/4/5/4'), 127.1 (d, C-3/4/5/4'), 124.0 (d, C-6), 120.4 (d, C-8), 61.7 (t, OCH_2CH_3), 61.5 (t, OCH_2CH_3), 59.7 (s, C-8'), 48.8 (d, C-7'), 19.7 (q, C-9), 14.0 (q, OCH_2CH_3), 13.9 (q, OCH_2CH_3);

Diethyl 4-hydroxy-4-methyl-1-phenyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**117c**)



R_f 0.08 (hexane/EA 4:1);

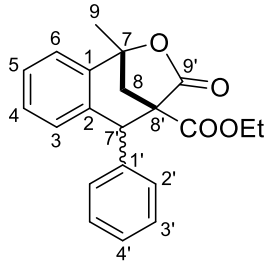
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 7.8, 1.4 Hz, 1H, H-6), 7.32-7.14 (m, 5H, H-4, H-5, H-2'/3', H-4'), 7.05 (dd, *J* = 7.8, 1.4 Hz, 1H, H-3), 6.91 (dd, *J* = 7.6, 1.9 Hz, 2H, H-2'/3'), 4.99 (s, 1H, H-7'), 4.22 (dq, *J* = 10.8, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 4.13-3.98 (m, 2H, OCH_2CH_3), 3.93 (dq, *J* = 10.8, 7.2 Hz, 1H, $OCH_aH_bCH_3$), 2.61 (d, *J* = 15.3 Hz, 1H, H-8a), 2.57 (d, *J* = 15.3 Hz, 1H, H-8b), 1.80 (s, 3H, H-9), 1.19 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.18 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.2 (s, *C*OOEt), 169.9 (s, *C*OOEt), 140.7 (s, C-1'), 139.4 (s, C-1/2), 137.0 (s, C-1/2), 130.6 (d, C-3), 130.0 (d, C-4/5/4'), 128.7 (d, 2×C, C-2'/3'), 128.3 (d, C-4/5/4'), 127.6 (d, 2×C, C-2'/3'), 127.3 (d, C-4/5/4'), 125.7 (d, C-6), 69.1 (s, C-7), 61.7 (t, OCH_2CH_3), 61.4 (t, OCH_2CH_3), 56.7 (s, C-8'), 49.1 (d, C-7'), 38.6 (t, C-8), 31.1 (q, C-9), 14.01 (q, OCH_2CH_3), 13.99 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 787 (41, $[2M + Na]^+$), 741 (25, $[2M + Na – EtOH]^+$), 695 (9, $[2M + Na – 2EtOH]^+$), 405 (100, $[M + Na]^+$), 365 (55, $[M + H – H_2O]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{23}H_{26}O_5Na$ 405.1673; found: 405.1673.

Ethyl (1S,4R,5S)-1-methyl-3-oxo-5-phenyl-1,5-dihydro-1,4-methanobenzo[c]oxepine-4(3H)-carboxylate (**117d**)



R_f 0.10 (hexane/EA 4:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.72-7.48 (m, 1H, H-6), 7.30-7.07 (m, 2H, H-4, H-5, H-2', H-3', H-4'), 6.97-6.91 (m, 1H, H-3), 4.90 (s, 1H, H-7'), 4.19-4.02 (m, 2H, OCH_2CH_3), 2.96 (d, J = 12.6 Hz, 1H, H-8a), 2.82 (d, J = 12.6 Hz, 1H, H-8b), 2.04 (s, 3H, H-9), 1.18 (t, J = 7.2 Hz, 3H, OCH_2CH_3);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 173.2 (s, C-9'), 167.4 (s, *C*OOEt), 140.8 (s, C-1'), 138.0 (s, C-1/2), 136.9 (s, C-1/2), 131.7 (d, C-3), 130.3 (d, 2×C, C-2'/3'), 129.9 (d, C-4/5/4'), 128.4 (d, 2×C, C-2'/3'), 127.9 (d, C-4/5/4'), 127.2 (d, C-4/5/4'), 123.4 (d, C-6), 81.9 (s, C-7), 61.9 (t, OCH_2CH_3), 59.4 (s, C-8'), 49.4 (d, C-7'), 39.3 (t, C-8), 21.3 (q, C-9), 14.0 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 695 (100, $[2M + Na]^+$), 396 (, $[M + H + H_2O + MeCN]^+$), 359 (, $[M + Na]^+$), 337 (, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{21}H_{20}O_4Na$ 359.1254; found: 359.1255, $[M + H]^+$ calcd. for $C_{21}H_{21}O_4$ 337.1434; found: 337.1436.

One-pot conjugate addition/in-situ oxidative cyclisation of β-methylstyrene

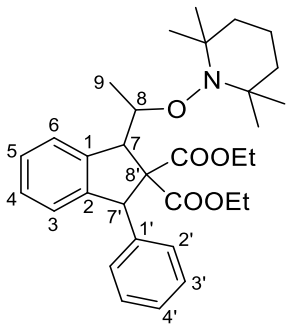
Styrene **119** (*E/Z* 17:1) was prepared by a known procedure from 2-bromobenzaldehyde by the Wittig reaction followed by Se_2Ph_2 catalysed isomerization. [247,168]

A solution of *n*-BuLi (383 µL, 0.57 mmol, 1.5 M in heptane) was added to a solution of styrene **119** (91 µL, 0.6 mmol) in dry THF (2 mL) at –78 °C. The mixture was stirred for 30 min at –78 °C. CuBr·DMS (10 mg, 50 µmol) was added followed by warming to –40 °C. Diethyl benzylidenemalonate (112 µL, 0.50 mmol) was added, followed by warming to 0 °C over 1 h. TEMPO (94 mg, 1.2 mmol) was added followed by **52** (367 mg, 1.1 mmol). The mixture was stirred vigorously for 30 min, followed by addition of 5% aqueous ascorbic acid (5 mL). The mixture was partitioned between water (15 mL) and DCM (50 mL). The phases were separated, the aqueous phase was extracted twice with DCM (2×30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (hexane/EA 15:1 to 2:1) yielding 144 mg of an inseparable mixture of isomeric cyclic products **120** (55%, dr 2.5 : 1.1 : 1 : 1) as colourless oil. The identity of products was assessed by MS data in combination with 2D NMR. HSQC correlations characteristic for secondary TEMPO-adducts were detected and assigned as C-8/H-8 correlations. The major isomer **120-A** could be partially separated.

δ (ppm)	Isomer A	Isomer B	Isomer C	Isomer D
H-7	3.83	4.02	4.42	4.51
C-7	56.7	57.3	56.0	54.5
H-8	4.57	4.75	4.63	4.24
C-8	77.8	80.9	79.2	78.7
H-7'	5.57	5.31	5.26	5.42
C-7'	56.8	59.2	57.7	56.4

Table 30. Characteristic ^{1}H and ^{13}C NMR signals of the diastereomers of **120**. All shifts in $CDCl_3$.

Diethyl 1-phenyl-3-{1-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]ethyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate (**120-A**)



^{1}H NMR (401 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 6.9 Hz, 1H, H-3/6), 7.35-7.10 (m, 7H, H-4, H-5, H-2', H-3', H-4'), 6.89 (d, *J* = 7.3 Hz, 1H, H-3/6), 5.75 (s, 1H, H-7'), 4.57 (qd, *J* = 6.8, 1.9 Hz, 1H, H-8), 4.36 (dq, *J* = 10.7, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.83 (d, *J* = 1.9 Hz, 1H, H-7), 3.76 (dq, *J* = 10.6, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.28 (dq, *J* = 10.6, 7.2 Hz, 1H, $OCH_aH_bCH_3$), 1.45 (d, *J* = 6.7 Hz, 3H, H-9), 1.43-1.17 (m, 6H, TMP-$CH_2CH_2CH_2$), 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.22 (s, 3H, TMP-CH_3), 1.08 (s, 3H, TMP-CH_3), 0.67 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 0.64 (s, 3H, TMP-CH_3), 0.17 (s, 3H, TMP-CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.8 (s, *C*OOEt), 169.8 (s, *C*OOEt), 144.5 (s, C-2), 142.4 (s, C-1), 140.7 (s, C-1'), 130.4 (d, 2×C, C-2'/3'), 127.7 (d, 2×C, C-2'/3'), 127.1 (d, 4/5/4'), 127.0 (d, 4/5/4'), 126.4 (d, 4/5/4'), 125.7 (d, 3/6), 125.3 (d, 3/6), 77.8 (d, C-8), 71.8 (s, C-8'), 61.1 (t, OCH_2CH_3), 61.0 (t, OCH_2CH_3), 60.8 (s, TMP-N*C*$(CH_3)_2$), 58.7 (s, TMP-N*C*$(CH_3)_2$), 56.8 (d, C-7'), 56.7 (d, C-7), 41.0 (t, TMP-*C*H_2), 40.6 (t, TMP-*C*H_2), 33.4 (q, TMP-*C*H_3), 32.5 (q, TMP-*C*H_3), 20.8 (q, 2×C, TMP-*C*H_3), 17.4 (t, TMP-*C*H_2), 16.9 (q, C-9), 14.0 (q, OCH_2CH_3), 13.3 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 522 (100, $[M + H]^+$);

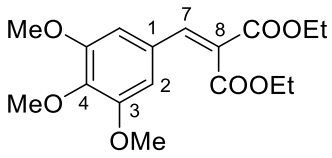
HRMS (ESI+) *m/z*: $[M + H]^+$ calcd. for $C_{32}H_{44}O_5N$ 522.3214; found: 522.3215.

6.1.2. Cu-catalysed conjugate addition of ArLi to ylidene malonates

Syhthesis of model ylidenemalonates

Diethyl 2-(3,4,5-trimethoxybenzylidene)malonate (**137**)

A mixture of 3,4,5-trimethoxybenzaldehyde (9.4 g, 48 mmol), diethyl malonate (7.6 mL g, 50 mmol), piperidine (0.8 mL, 8 mmol) and benzoic acid (0.64 g, 5.2 mmol) in benzene (50 ml) was heated to reflux using a Dean-Stark trap. Azeotropic distillation of water ceased after ~ 4 h. The mixture still contained unreacted starting materials (by TLC), therefore heating was continued overnight. After cooling to r.t., the solvent was removed under vacuum. The mixture was redissolved in EA (200 mL) and washed twice with saturated $NaHCO_3$ solution (2×50 mL) followed by deionized water (50 mL). The organic layer was dried over Na_2SO_4, concentrated, and dried under high vacuum. Recrystallization from heptane/EA yielded 12.1 g (74%) of large rhombic crystals in the first crop and 3.3 g (20%) in the second crop, mp 70-72 °C. NMR spectra matched those reported in the literature.[248]



R_f 0.35 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 2981 (w), 2940 (w), 2840 (w), 1721 (s), 1626 (m), 1580 (m), 1506 (m), 1455 (m), 1421 (m), 1378 (m), 1333 (m), 1239 (s), 1211 (s), 1154 (m), 1124 (vs), 1065 (m), 1003 (m), 861 (w), 839 (w), 641 (w), 622 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.64 (s, 1H, H-7), 6.74 (s, 2H, H-2), 4.36-4.28 (m, 4H, OCH_2CH$_3$), 3.88 (s, 3H, C4-OCH_3), 3.85 (s, 6H, C3-OCH_3), 1.35-1.30 (m, 6H, OCH$_2$CH_3);

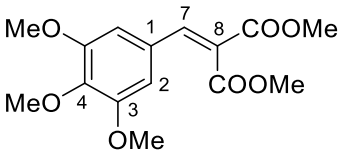
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.1 (s, *C*OOEt), 164.3 (s, *C*OOEt), 153.4 (s, C-3), 142.1 (d, C-7), 140.4 (s, C-4), 128.4 (s, C-1), 125.6 (s, C-8), 107.0 (d, C-2), 61.9 (t, O*C*H$_2$CH$_3$), 61.8 (t, O*C*H$_2$CH$_3$), 61.1 (q, C4-OCH_3), 56.2 (q, C3-OCH_3), 14.3 (q, OCH$_2$*C*H$_3$), 14.2 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 361 (100, [M + Na]$^+$), 289 (15, [M + Na − C_2H_4 − CO_2]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{17}H_{22}O_7Na$ 361.1258; found: 361.1258.

Dimethyl 2-(3,4,5-trimethoxybenzylidene)malonate (**122**)

Prepared following the procedure for **137** using 3,4,5-trimethoxybenzaldehyde (5.0 g, 25.5 mmol), dimethyl malonate (3.9 mL g, 34 mmol), piperidine (0.23 mL, 2.3 mmol), acetic acid (0.15 mL, 2.5 mmol) and toluene (25 mL). Purification by flash chromatography (11:1 hexane/EA to pure EA) yielded 4.95 g (62%) of **122** as colourless crystals, mp 71 °C.



R_f 0.22 (hexane/EA 3:1);

IR (film) ν[cm^{-1}]: 2951 (w), 2841 (w), 1724 (w), 1623 (s), 1580 (w), 1506 (m), 1434 (m), 1419 (m), 1374 (w), 1334 (w), 1245 (s), 1214 (s), 1153 (m), 1122 (vs), 1067 (s), 998 (m), 933 (w), 832 (w), 623 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.67 (s, 1H, H-7), 6.70 (s, 2H, H-2), 3.87 (s, 3H, C4-OCH_3), 3.85 (s, 3H, COOCH_3), 3.84 (s, 9H, C3-OCH_3, COOCH_3);

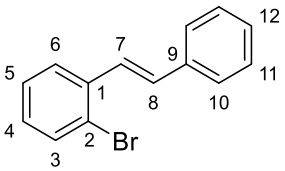
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.5 (s, *C*OOMe), 164.6 (s, *C*OOMe), 153.4 (s, 2×C, C-3), 142.8 (d, C-7), 140.5 (s, C-4), 128.1 (s, C-1), 124.7 (s, C-8), 106.9 (d, 2×C, C-2), 61.1 (q, C4-O*C*H$_3$), 56.2 (q, 2×C, C3-O*C*H$_3$), 52.83 (q, COO*C*H$_3$), 52.80 (q, COO*C*H$_3$);

MS (ESI+) *m/z*, (%): 643 (4, [2M + Na]$^+$), 333 (100, [M + Na]$^+$), 279 (7, [M + H – MeOH]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{15}H_{18}O_7Na$: 333.0945; found: 334.0945.

Synthesis of model bromostilbenes

(E)-1-Bromo-2-styrylbenzene (**121a**)



Prepared from following to a known procedure [249] using BnBr (3.24 mL, 27.3 mmol mmol), $PO(OEt)_3$ (4.95 mL, 28.4 mmol), NaH (1.42 g, 35.6 mmol, 60% in mineral oil) and 2-bromobenzaldehyde (4.39 g, 23.7 mmol) in THF (140 mL). Purified by flash chromatography in PE. Yield 4.50 g (73%) as a colourless oil. Spectroscopic data matched the lit.[249]

R_f 0.33 (hexane);

IR (film) ν [cm^{-1}]: 3023 (w), 1629 (w), 1598 (w), 1585 (w), 1559 (w), 1493 (m), 1464 (m), 1447 (m), 1434 (m), 1257 (w), 1216 (w), 1113 (w), 1023 (s), 957 (s), 753 (vs), 706 (s), 687 (s), 672 (s), 547 (m);

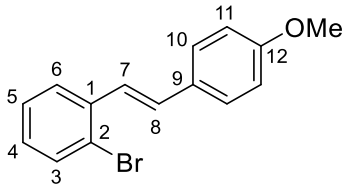
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 7.9, 1.6 Hz, 1H, H-3), 7.60 (d, *J* = 8.2 Hz, 1H, H-6), 7.57 (d, *J* = 7.6 Hz, 2H, H-10), 7.49 (d, *J* = 16.2 Hz, 1H, H-7), 7.40 (t, *J* = 7.5 Hz, 2H, H-11), 7.34-7.29 (m, 2H, CH-5, H-12), 7.13 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.06 (d, *J* = 16.2 Hz, 1H, H-8);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 137.3 (s, C-1/9), 137.1 (s, C-1/9), 133.2 (d, C-6), 131.6 (d, C-8), 128.92 (d, C-4), 128.87 (d, C-11), 128.2 (d, C-5/12), 127.7 (d, C-5/12), 127.6 (d, C-7), 127.0 (d, C-10), 126.8 (d, C-3), 124.3 (s, C-2);

MS (EI+) *m/z*, (%): 260/258 (63, $[M]^{\cdot+}$), 179 (97, $[M - Br]^+$), 178 (100, $[M - HBr]^{\cdot+}$);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{14}H_{11}{}^{79}Br$ 258.0044; found: 258.0043.

(E)-1-Bromo-2-(4-methoxystyryl)benzene (**121b**)



Prepared by the Horner-Wadsworth-Emmons olefination according to a published procedure [250] from 2-bromobenzaldehyde. Yield (84%) as a colourless hard solid, mp 66 °C (lit 65-67 °).[250]

R_f 0.39 (hexanes/EA 11:1);

IR (film); ν[cm^{-1}]: 3034 (w), 3001 (w), 2932 (w), 2834 (w), 1604 (m), 1509 (s), 1462 (m), 1436 (m), 1291 (m), 1245 (s), 1172 (s), 1113 (m), 1021 (s), 958 (s), 815 (s), 744 (s), 721 (m), 666 (m), 535 (s), 443 (m);

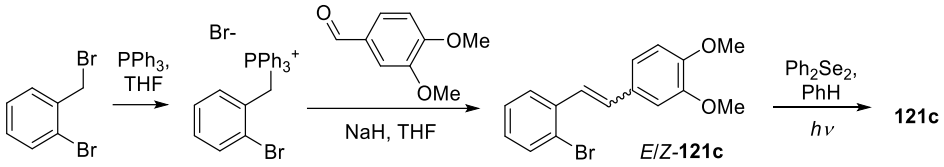
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 7.9, 1.7 Hz, 1H, H-2), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H, H-5), 7.51 (d, *J* = 8.7 Hz, 2H, H-10), 7.36 (d, *J* = 16.2 Hz, 1H, H-7), 7.31(t, *J* = 7.9 Hz, 1H, H-4), 7.10 (td, *J* = 8.0, 1.5 Hz, 1H, H-3), 7.01 (d, *J* = 16.2 Hz, 1H, H-8), 6.93 (d, *J* = 8.7 Hz, 2H, H-11), 3.85 (s, 3H, O*C*H_3);

^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$): δ 159.8 (s, C-12), 137.5 (s, C-6), 133.1 (d, C-5), 131.1 (d, C-8), 129.9 (s, C-9), 128.5 (d, C-3), 128.2 (d, 2×C, C-10), 127.6 (d, C-4), 126.6 (d, C-2), 125.4 (d, C-7), 124.1 (s, C-1), 114.3 (d, 2×C, 11), 55.4 (q, O*C*H_3);

MS (EI+) *m/z*, (%): 290/288 (100/98, $[M]^{\cdot+}$), 209 (6, $[M - Br]^+$), 194 (53, $[M - CH_3Br]^{\cdot+}$), 178 (22, $[M - Br - MeO]^{\cdot+}$), 177 (25, $[M - Br - MeOH]^+$), 166 (61), 165 (71);

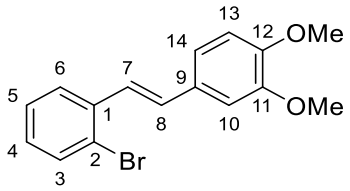
HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{15}H_{13}{}^{79}BrO$ 288.0150; found: 288.0153.

Preparation of stilbene 121c



2-Bromobenzyl bromide (2.98 g, 12.0 mmol) was added to a solution of PPh_3 (2.885 g, 11.0 mmol) in THF (20 mL) and stirred overnight at r.t. The solvent was removed in vacuum followed by addition of Et_2O (50 mL). The resulting suspension was sonicated and left to stand for 1 h. The precipitate was filtered to afford 5.97 g (93%) of a colourless powder, which was dissolved in THF (140 mL). NaH (0.555 g, 13.9 mmol, 60% dispersion in mineral oil) was added at 0 °C and the mixture was stirred for 30 min. A solution of 3,4-dimethoxybenzaldehyde (2.10 g, 12.6 mmol) in THF (15 mL) was added and the mixture was stirred at r.t. overnight. After quenching with saturated NH_4Cl solution (20 mL), n-hexane (100 mL) was added, and the phases were separated. The aqueous phase was extracted with additional n-hexane (100 mL) and the combined organic layers were dried over Na_2SO_4. The crude product was concentrated under vacuum, dissolved in benzene (60 mL) and Ph_2Se_2 (62 mg, 0.20 mmol) was added. The mixture was stirred at r.t. for 2 days under ambient light. Concentration followed by flash chromatography (hexane/EA 20:1 to pure EA) and crystallization (heptane/EA 10:1) yielded 2.49 g (70%) of **121c** as large colourless crystals, mp 101-103 °C.

(E)-4-(2-Bromostyryl)-1,2-dimethoxybenzene (**121c**)



R_f 0.58 (hexane/EA 3:1);

IR ν [cm^{-1}]: 3052 (w), 2998 (w), 2932 (w), 2833 (w), 1599 (w), 1582 (w), 1509 (vs), 1463 (m), 1437 (m), 1418 (m), 1305 (s), 1265 (s), 1246 (s), 1235 (m), 1156 (m), 1137 (vs), 1020 (vs), 956 (s), 799 (m), 743 (s), 667 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.65 (dd, J = 7.8, 1.6 Hz, 1H, H-6), 7.58 (dd, J = 8.1, 1.2 Hz, 1H, H-3), 7.32 (d, J = 16.3 Hz, 1H, H-7), 7.30 (td, J = 7.6, 0.8 Hz, 1H, H-4), 7.12-7.08 (m, 3H, H-5, H-10, H-14), 6.99 (d, J = 16.1 Hz, 1H, H-8), 6.88 (d, J = 8.8 Hz, 1H, H-13), 3.96 (s, 3H, C11-OCH_3), 3.91 (s, 3H, C12-OCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.4 (s, C-12), 149.3 (s, C-11), 137.4 (s, C-1), 133.2 (d, C-3), 131.4 (d, C-8), 130.3 (s, C-9), 128.6 (d, C-5), 127.7 (d, C-4), 126.7 (d, C-6), 125.7 (d, C-7), 124.1 (s, C-2), 120.4 (d, C-14), 111.4 (d, C-13), 109.3 (d, C-10), 56.11 (q, C12-OCH_3), 56.06 (q, C11-OCH_3);

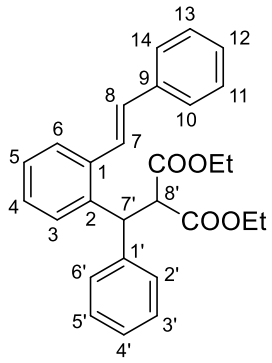
MS (EI+) *m/z,* (%): 320/318 (100, $[M]^{\cdot+}$), 305/303 (11, $[M - CH_3]^+$), 239 (55, $[M - Br]^+$), 224 (56, $[M - Br - CH_3]^{\cdot+}$), 208 (53, $[M - Br - CH_3O]^{\cdot+}$), 196 (30, $[M - Br - CH_3 - C_2H_4]^+$), 181 (35, $[M - Br - CH_3O - CO]^+$), 165 (38, $[M - Br - CH_3 - CO - CH_3O]^+$), 152 (45);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{16}H_{15}O_2{}^{79}Br$ 318.0255; found: 318.0254, calcd. for $C_{16}H_{15}O_2{}^{81}Br$: 320.0235, found: 320.0247.

Conjugate addition of model stilbenes 121a-c to benzylidene malonates 113 and 122

Diethyl (E)-2-[phenyl(2-styrylphenyl)methyl]malonate (**123a**)

A solution of *t*-BuLi (1.03 µL, 1.75 mmol, 1.7 M in heptane) was added to a solution of **121a** (207 mg, 0.80 mmol) in THF (5 mL) at –78 °C and the resulting mixture was stirred for 10 min, followed by warming to r.t. for 10 min. After cooling to –40 °C, solid CuBr·DMS (21 mg, 0.102 mmol) was added, followed by stirring for 5 min. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise, followed by warming to r.t. over 2 h. The reaction was quenched by saturated NH_4Cl solution (20 mL) and extracted with diethyl ether (3×100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by flash chromatography (hexane/EA 10:1 to pure EA) to yield 153 mg of **123a** (70%) as a colourless amorphous solid.



R_f 0.40 (hexane/EA 11:1);

IR (film) ν[cm^{-1}]: 3060 (w), 3027 (w), 2980 (w), 2934 (w), 1753 (s), 1727 (vs), 1598 (w), 1495 (m), 1449 (m), 1368 (m), 1301 (m), 1255 (s), 1174 (s), 1141 (s), 1096 (m), 1031 (s), 963 (m), 759 (s), 694 (s);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 7.63 (d, *J* = 16.0 Hz, 1H, C-7), 7.53-7.51 (m, 3H, C-2', C-6), 7.41-7.37 (m, 3H, C-3', C-3), 7.31-7.19 (m, 7H, C-4, C-5, C-10, C-11, C-12), 7.15 (tt, *J* = 7.1, 1.4 Hz, 1H, C-4'), 6.88 (d, *J* = 16.0 Hz, 1H, C-8), 5.20 (d, *J* = 12.0 Hz, 1H, C-7'), 4.39 (d, *J* = 12.1 Hz, 1H, C-8'), 4.04-3.99 (m, 4H, O*CH*$_2$CH$_3$), 1.02 (t, *J* = 7.1 Hz, 6H, OCH$_2$C*H*$_3$);

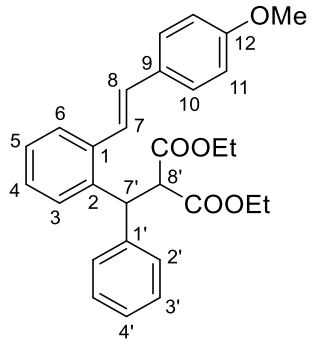
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.0 (s, C-9), 167.6 (s, C-9'), 140.8 (s, C-1'), 139.0 (s, C-2), 137.7 (s, C-9), 137.2 (s, C-1), 131.7 (d, C-7), 128.8 (d, C-10/11), 128.7 (d, C-10/11), 128.3 (d, C-3'), 127.84 (d, C-4/5/12), 127.81 (d, C-4/5/12), 127.3 (d, C-4/5/12), 127.2 (d, C-6), 127.0 (d, C-4'), 126.8 (d, C-2'), 126.6 (d, C-8), 126.4 (d, C-3), 61.7 (t, O*C*H$_2$CH$_3$), 57.9 (d, C-8'), 46.5 (d, C-7'), 13.92 (q, OCH$_2$*C*H$_3$), 13.89 (q, OCH$_2$*C*H$_3$');

MS (ESI+) *m/z*, (%): 879 (10, $[2M + Na]^+$), 488 (40, $[M + CH_3CN + H_2O + H]^+$), 451 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{28}H_{28}O_4Na$: 451.1880; found: 452.1880.

Diethyl (E)-2-{[2-(4-methoxystyryl)phenyl](phenyl)methyl}malonate (**123b**)

The same procedure including reagent loadings as for **121a** was used, except using stilbene **121b** (188 mg, 0.652 mmol). Yield 56% of **123b**, determined by ^1H NMR.



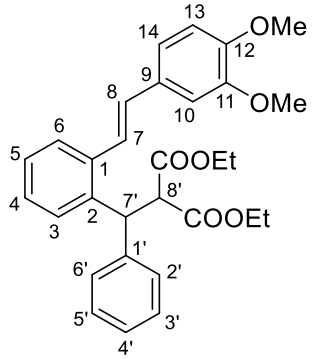
R_f 0.35 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47 (d, *J* = 16.0 Hz, 1H, H-8), 7.46 (d, *J* = 8.7 Hz, 2H, H-10), 7.51-7.12 (m, 9H, Ar), 6.93 (d, *J* = 8.7 Hz, 2H, H-11), 6.82 (d, *J* = 16.0 Hz, 1H, H-7), 5.19 (d, *J* = 12.0 Hz, 1H, H-7'), 4.38 (d, *J* = 11.9 Hz, 1H, H-8'), 4.01 (q, *J* = 7.1 Hz, 4H, OCH_2CH_3), 3.85 (s, 3H, C12-OCH_3), 1.02 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.01 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$): δ 168.1 (s, *C*OOEt), 167.7 (s, *C*OOEt), 159.4 (s, C-12), 140.8 (s, C-1), 138.7 (s, C-1'), 137.4 (s, C-2), 130.5 (s, C-9), 131.1 (d, C-8), 128.6 (d, C-10/2'/3'), 128.3 (d, C-10/2'/3'), 128.0 (d, C-10/2'/3'), 127.5 (d, C-5), 127.1 (d, C-4/4'), 127.0 (d, C-6), 126.9 (d, C-4/4'), 126.3 (d. C-3), 124.4 (d, C-7), 114.2 (d, 2×C, C-11), 61.7 (t, 2×C, OCH_2CH_3), 57.5 (d, C-8'), 55.5 (q, C12-OCH_3), 46.9 (d, C-7'), 13.92 (q, OCH_2CH_3), 13.88 (q, OCH_2CH_3).

Diethyl (E)-2-{[2-(3,4-dimethoxystyryl)phenyl](phenyl)methyl}malonate (**123c**)

A solution of *t*-BuLi (380 µL, 0.645 mmol, 1.7 M in heptane) was added to a solution of **121c** (208 mg, 0.652 mmol) in THF (8 mL) at –78 °C and the resulting mixture was stirred for 15 min. CuBr·DMS (21 mg, 0.102 mmol) was added, followed by stirring for 5 min. A solution of diethyl benzylidenemalonate (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise, followed by warming to 0 °C over 2 h. The reaction was quenched by saturated NH_4Cl solution (20 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under vacuum. Purification by flash chromatography (SiO_2, hexane/EA 10:1 to pure EA) afforded 247 mg (98%) of **123c** as a colourless amorphous solid.



R_f 0.28 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 2990 (w), 2846 (w), 1758 (m), 1734 (m), 1606 (w), 1588 (w), 1518 (s), 1469 (w), 1307 (w), 1264 (s), 1180 (m), 1160 (m), 1141 (s), 1028 (s), 910 (s), 805 (w), 728 (vs), 701 (s), 649 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.4 Hz, 1H, H-6), 7.41 (d, *J* = 16.0 Hz, 1H, H-7), 7.37 (d, *J* = 7.6 Hz, 1H, H-3), 7.28-7.20 (m, 6H, H-2', H-3', H-4, H-5), 7.18-7.13 (m, 1H, H-4'), 7.04 (d, *J* = 7.7 Hz, 1H, H-14), 7.03 (s, 1H, H-10), 6.87 (d, *J* = 7.9 Hz, 1H, H-13), 6.80 (d, *J* = 15.9 Hz, 1H, H-8), 5.17 (d, *J* = 13.3 Hz, 1H, H-7'), 4.36 (d, *J* = 13.5 Hz, 1H, H-8'), 4.04-3.97 (m, 4H, OCH_2CH_3), 3.96 (s, 3H, C11-OCH_3), 3.92 (s, 3H, C12-OCH_3), 1.01 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.00 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

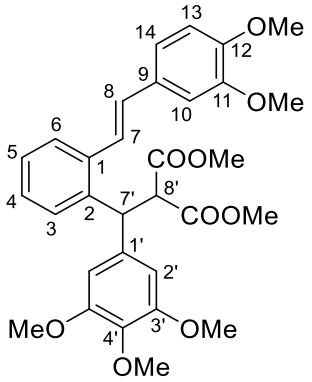
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.1 (s, *C*OOEt), 167.7 (s, *C*OOEt), 149.2 (s, C-11/12), 149.1 (s, C-11/12), 140.9 (s, C-1'), 138.7 (s, C-2), 137.4 (s, C-1), 131.2 (d, C-8), 130.9 (s, C-9), 128.6 (d, C-3'), 128.4 (d, C-2'), 127.5 (d, C-5), 127.2 (d, C-4/4'), 127.1 (d, C-6), 127.0 (d, C-4/4'), 126.3 (d, C-3), 124.8 (d, C-7), 120.1 (d, C-14), 111.3 (d, C-13), 109.1 (d, C-10), 61.7 (t, 2×C, OCH_2CH_3), 57.9 (d, C-8'), 56.1 (q, C12-OCH_3), 56.0 (q, C11-OCH_3), 46.7 (d, C-7'), 13.92 (q, OCH_2CH_3), 13.91 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 999 (30, $[2M + Na]^+$), 527 (35, $[M + K]^+$), 511 (100, $[M + Na]^+$), 329 (15, $[M + H - CH_2(COOEt)_2]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{30}H_{32}O_6Na$: 511.2091; found: 511.2089.

Dimethyl (E)-2-{[2-(3,4-dimethoxystyryl)phenyl](3,4,5-trimethoxyphenyl)methyl}malonate (**123d**)

Following the procedure for **123c**, except CuBr·DMS (13 mg, 0.063 mmol) was added as a solution in the form of mixed salt with LiBr (60 mg, 0.181 mg) in THF (3 mL). Starting with stilbene **121c** (208 mg, 0.652 mmol) and malonate **122** (93 mg, 0.30 mmol), 162 mg of **123d** (98%) was obtained as a colourless amorphous solid.



R_f 0.04 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 2999 (w), 2953 (w), 2836 (w), 1736 (m), 1588 (m), 1511 (m), 1456 (s), 1420 (m), 1248 (s), 1124 (vs), 1024 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 7.3, 1.8 Hz, 1H, H-6), 7.41 (d, *J* = 16.0 Hz, 1H, H-7), 7.31 (dd, *J* = 7.7, 1.6 Hz, 1H, H-3), 7.28-7.20 (m, 2H, H-4, H-5), 7.06 (dd, *J* = 8.4, 1.9 Hz, 1H, H-14), 7.01 (d, *J* = 2.0 Hz, 1H, H-10), 6.87 (d, *J* = 8.2 Hz, 1H, H-13), 6.79 (d, *J* = 16.0 Hz, 1H, H-8), 6.44 (s, 2H, H-2'), 5.11 (d, *J* = 12.0 Hz, 1H, H-7'), 4.39 (d, *J* = 12.0 Hz, 1H, H-8'), 3.94 (s, 3H, C11-OCH_3, C12-OCH_3), 3.92 (s, 3H, C11-OCH_3, C12-OCH_3), 3.76 (s, 3H, C4'-OCH_3), 3.71 (s, 6H, C3'-OCH_3), 3.59 (s, 3H, $COOCH_3$), 3.57 (s, 3H, $COOCH_3$');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.5 (s, *C*OOMe), 168.0 (s, *C*OOMe), 153.2 (s, 2×C, C-3'), 149.3 (s, C-11/12), 149.2 (s, C-11/12), 138.5 (s, C-2), 137.6 (s, C-1), 137.0 (s, C-4'), 136.4 (s, C-1'),

131.7 (d, C-8), 130.9 (s, C-9), 127.7 (d, C-4/5/6), 127.5 (d, C-4/5/6), 127.4 (d, C-4/5/6), 125.8 (d, C-3), 125.2 (d, C-7), 119.8 (d, C-14), 111.4 (d, C-13), 109.6 (d, C-10), 105.5 (d, C-2'), 60.9 (q, C4'-O*C*H$_3$), 57.4 (d, C-8'), 56.15-56.12 (q, 4×C, C3'-O*C*H$_3$, C11-O*C*H$_3$, C12-O*C*H$_3$), 52.9 (q, 2×C, COO*C*H$_3$), 46.8 (d, C-7');

MS (ESI+) *m/z*, (%): 610 (34, [M + CH$_3$CN + H$_2$O + H]$^+$), 573 (100, [M + Na]$^+$), 419 (5, [M + H – CH$_2$(COOCH$_3$)$_2$]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{31}H_{34}O_9Na$: 573.2095, found: 573.2091.

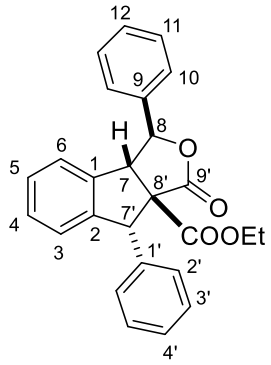
6.1.3. Annulation of model stilbenes

Oxidative radical-to-cationic annulation of stilbene 121a

Conditions I. To a solution of styrene **121a** (207 mg, 0.799 mmol) in THF (5 mL) at –78 °C was added *t*-BuLi (1.0 mL, 1.71 mmol, 1.7 M) and the mixture was stirred for 10 min, followed by quick warming to r.t. for 10 min. The reaction mixture was cooled to –40 °C and CuBr·DMS (21 mg, 0.10 mmol) was added. A solution of malonate **113** (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise by cannula, followed by warming to 0 °C over 2 h. Ferrocenium hexafluorophosphate (500 mg, 1.51 mmol) was added in a single portion. After 1 h, the reaction was quenched by saturated NH_4Cl solution (25 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic extract was washed by 10% $Na_2S_2O_3$ solution (50 mL) and brine (50 mL) and the organic layer was dried over anhydrous Na_2SO_4. Concentration under vacuum and purification by flash chromatography (hexane/EA 10:1 to pure EA) afforded in order of elution: 30 mg of **125b** (containing inseparable **113**), 89 mg of mixture of diastereomers **124a/b** (43%, dr 5:1) as a colourless crystalline solid, mp 182-184 °C and 46 mg of **125a** (20%), as a colourless amorphous solid.

Conditions II. The enolate, prepared by conjugate addition as above, transferred via cannula into a suspension of **52** in THF. Purification by flash chromatography yielded 123 mg of **124a/b** (60%), dr 7.5:1.

Ethyl (3S,3aS*,8R*,8aR*)-1-oxo-3,8-diphenyl-3a,8-dihydro-1H-indeno[1,2-c]furan-8a(3H)-carboxylate* (**124a**)



R_f 0.34 (hexane/EA 5:1);

IR ν [cm^{-1}]: 3029 (w), 2923 (m), 2851 (w), 1775 (s), 1735 (s), 1495 (w), 1454 (m), 1228 (s), 1147 (s), 1019 (s), 755 (m), 729 (m), 697 (vs);

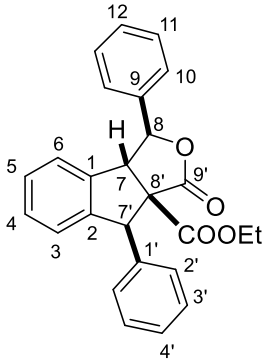
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.50-7.12 (m, 14H, H-3, H-4, H-5, H-6, H-10, H-11, H-12, H-2‘, H-3, H-4‘), 5.61 (s, 1H, CH-7‘), 5.35 (d, *J* = 5.8 Hz, 1H, H-8), 4.50 (d, *J* = 5.8 Hz, 1H, H-7), 4.31-4.20 (m, 2H, OCH_2CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.7 (s, C-9‘), 169.9 (s, *C*OOEt), 143.7 (s, C-2), 141.2 (s, C-1), 139.5 (s, C-9/1‘), 139.4 (s, C-9/1‘), 129.6 (d, C-2‘), 129.2 (d, C_{Ar}), 129.1 (d, C-11/3‘), 128.9 (d, C_{Ar}), 128.7 (d, C-11/3‘), 128.6 (d, C_{Ar}), 127.9 (d, C_{Ar}), 126.6 (d, C_{Ar}), 125.9 (d, C-10), 123.9 (d, C-6), 86.1 (d, C-8), 67.7 (s, C-8‘), 63.0 (t, O*C*H_2CH_3), 61.3 (d, C-7), 56.6 (d, C-7‘), 14.0 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 819 (5, $[2M + Na]^+$), 421 (100, $[M + Na]^+$), 399 (13, $[M + H]^+$);

HRMS (ESI+) *m/z*: [M + H^+] calcd. for $C_{26}H_{23}O_4$ 399.1591; found: 399.1593; [M + Na^+] calcd. for $C_{26}H_{22}O_4Na$ 421.1410; found: 421.1411.

Ethyl (3S,3aS*,8S*,8aR*)-1-oxo-3,8-diphenyl-3a,8-dihydro-1H-indeno[1,2-c]furan-8a(3H)-carboxylate* (**124b**)

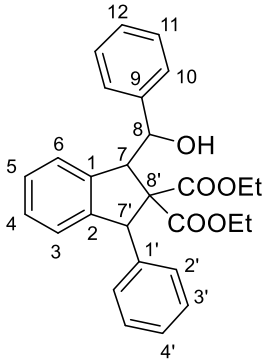


R_f 0.34 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.59-6.95 (m, 14H, H-3, H-4, H-5, H-6, H-10, H-11, H-12, H-2‘, H-3‘, H-4‘), 5.80 (s, 1H, H-8), 5.14 (s, 1H, H-7‘), 4.75 (s, 1H, H-7), 3.55-3.43 (m, 2H, O*C*H_2CH_3), 0.68 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.8 (s, C-9‘), 165.9 (s, *C*OOEt), 143.4 (s, C-2), 141.2 (s, C-1), 139.7 (s, C-9/1‘), 139.1 (s, C-9/1‘), 129.5 (d, C_{Ar}), 129.0 (d, C_{Ar}), 128.9 (d, C_{Ar}), 128.8 (d, C_{Ar}), 128.34 (d, C_{Ar}), 128.33 (d, C_{Ar}), 127.7 (d, C_{Ar}), 126.13 (d, C_{Ar}), 126.10 (d, C_{Ar}), 124.6 (d, C_{Ar}), 84.7 (d, C-8), 66.1 (s, C-8‘), 62.0 (t, O*C*H_2CH_3), 59.2 (d, C-7‘), 56.4 (d, C-7), 13.4 (q, OCH_2CH_3).

Diethyl 1-[hydroxy(phenyl)methyl]-3-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate (**125a**)



R_f 0.30 (hexane/EA 5:1);

IR (film) ν[cm^{-1}]: 3031 (w), 2981 (w), 2928 (w), 1780 (w), 1724 (m), 1701 (w), 1454 (w), 1368 (w), 1263 (s), 1198 (m), 1078 (m), 1031 (m), 734 (vs), 669 (vs), 588 (m);

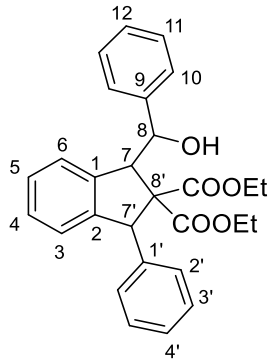
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 2H, H-10), 7.46 (t, *J* = 7.4 Hz, 2H, H-11), 7.44-7.29 (m, 6H, H-2‘, H-3‘, H-4‘, H-12), 7.12 (t, *J* = 7.5 Hz, 1H, H-4), 7.03 (t, *J* = 7.6 Hz, 1H, H-5), 6.89 (d, *J* = 7.6 Hz, 1H, H-3), 6.58 (d, *J* = 7.7 Hz, 1H, H-6), 5.20 (s, 1H, H-7‘), 5.09 (t, *J* = 9.7 Hz, 1H, H-8), 4.71 (d, *J* = 10.0 Hz, 1H, C8-O*H*), 4.51-4.39 (m, 2H, O*CH*$_2$CH$_3$‘), 4.42 (d, *J* = 9.7 Hz, 1H, H-7), 3.81-3.73 (m, 2H, O*CH*$_2$CH$_3$), 1.44 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$‘), 0.88 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.9 (s, *C*OOEt), 168.0 (s, *C*OOEt), 144.7 (s, C-9), 143.1 (s, C-2), 141.7 (s, C-1), 138.6 (s, C-1‘), 131.4 (d, 2×C, C-2‘), 129.1 (d, 2×C, C-11), 128.2 (d, C-12/4‘), 127.9 (d, 2×C, C-10), 127.72 (d, 2×C, C-3‘), 127.68 (d, C-12/4‘), 127.4 (d, C-5), 127.2 (d, C-4), 124.9 (d, C-3), 123.7 (d, C-6), 75.0 (d, C-8), 70.8 (s, C-8‘), 62.9 (t, O*CH*$_2$CH$_3$‘), 61.2 (t, O*CH*$_2$CH$_3$), 57.3 (d, C-7), 56.5 (d, C-7‘), 14.2 (q, OCH$_2$*C*H$_3$‘), 13.6 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 943 (3, [2M + Na + MeOH]$^+$), 911 (12, [2M + Na]$^+$), 499 (12, [M + Na + MeOH]$^+$), 467 (100, [M + Na]$^+$), 421 (13, [M + Na – EtOH]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{28}H_{28}O_5Na$ 467.1829; found: 467.1829.

Diethyl 1-[hydroxy(phenyl)methyl]-3-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate (**125b**)



R_f 0.42 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.9 Hz, 2H, H-10), 7.47-7.16 (m, 11H, H-2‘, H-3‘, H-4‘, H-3, H-4, H-5, H-11, H-12), 6.98-6.95 (m, 1H, H-6), 5.60 (s, 1H, H-8), 5.42 (s, 1H, H-7‘), 4.50-4.32 (m, 3H, C8-O*H*, O*CH*$_2$CH$_3$), 4.13 (s, 1H, H-7), 3.87-3.79 (m, 1H, O*CH*$_2$CH$_3$), 3.33-3.24 (m, 1H, O*CH*$_2$CH$_3$), 1.36 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.76 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$);

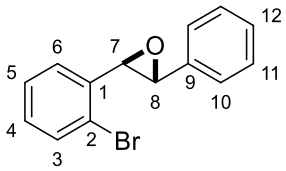
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.3 (s, *C*OOEt), 171.2 (s, *C*OOEt), 144.6 (s, C-9), 142.6 (s, C-2), 139.0 (s, C-1‘, C-1), 130.4 (d, 2×C, C-2‘), 128.5 (d, C-11/3‘), 128.1 (d, C-11/3‘), 127.7 (d, {C-3, C-4, C-5, C-12, C-4‘}*), 127.3 (d, *), 127.0 (d, *), 126.9 (d, *), 126.5 (d, *), 125.8 (d, C-10), 125.1 (d, C-6), 73.5 (s, C-8‘), 71.3 (d, C-8), 62.1 (t, O*C*H$_2$CH$_3$), 62.0 (t, O*C*H$_2$CH$_3$), 59.8 (d, C-7), 56.2 (d, C-7‘), 14.3 (q, OCH$_2$*C*H$_3$), 13.4 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 911 (17, [2M + Na]$^+$), 467 (100, [M + Na]$^+$), 427 (26, [M + H – H$_2$O]$^+$).

Preparation and anionic annulation of stilbene oxide 126 by the method of Florio *et al.*

trans-2-(2-Bromophenyl)-3-phenyloxirane (**126**)

m-CPBA (4.13 g, 17.5 mmol) was added at 0 °C to a stirred solution of 2-bromostilbene (1.30 g, 5 mmol) in DCM (50 mL). The solution was stirred at r.t. for 30 min, the solvent was stripped off. The solids were re-dissolved in fresh DCM followed again by evaporation. This cycle was repeated 6 times, then the solids were directly loaded onto a silica column. Flash chromatography (pure PE to 4% EA) yilelded 1.32 g (96%) of epoxide **126** as a colourless viscous oil (*trans/cis* > 96:4). Spectroscopic data matched lit.[251]



R_f 0.24 (hexane/EA, 22:1);

IR (film) ν [cm^{-1}]: 3064 (w), 3035 (w), 2983 (w), 1568 (m), 1473 (w), 1456 (w), 1440 (w), 1044 (w), 1024 (m), 893 (w), 855 (w), 797 (w), 744 (w), 714 (vs), 695 (vs), 672 (m), 611 (s);

^{1}H NMR (401 MHz, C_6D_6): δ 7.36 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6), 7.29-7.20 (m, 3H, H-3, H-10), 7.14-7.04 (m, 3H, H-11, H-12), 6.93 (td, *J* = 7.6, 1.2 Hz, 1H, H-5), 6.69 (td, *J* = 7.7, 1.8 Hz, 1H, H-4), 4.13 (d, *J* = 1.8 Hz, 1H, H-7), 3.45 (d, *J* = 1.9 Hz, 1H, H-8);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 137.7 (s, C-1/9), 137.4 (s, C-1/9), 132.4 (d, C-3), 129.4 (d, C-4), 128.8 (d, C-11), 128.6 (d, C-12), 127.8 (d, C-5), 126.6 (d, C-6), 126.0 (d, C-10), 122.9 (s, C-2), 62.5 (d, C-7), 62.3 (d, C-8);

MS (ESI+) *m/z*, (%): 299/297 (100/94, $[M + Na]^+$), 291/289 (68/73, $[M + H + MeOH - H_2O]^+$), 277/275 (26/26, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{11}O^{79}BrNa$ 296.9886; found: 296.9887.

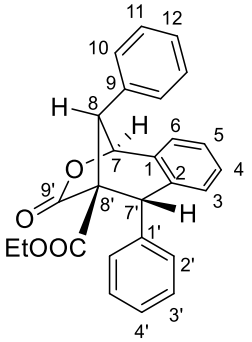
Ethyl (1S,4S*,5S*,10R*)-3-oxo-5,10-diphenyl-1,5-dihydro-1,4-methanobenzo[c]oxepine-4(3H)-carboxylate* (**revised-68a**)

Following the method of Florio *et. al.*, stilbene oxide **126** (275 mg, 1 mmol) was treated with PhLi (667 µL, 1.2 mmol, 1.8 M in Bu_2O) in THF (5 mL) at −78 °C for 45 min, followed by addition of **113** (269 µL, 1.2 mmol) in THF (2 mL). After 1 h at −78 °C the reaction was quenched with sat. NH_4Cl (20 mL). DCM (50 mL) was added, and the layers were separated. The aqueous was extracted twice with DCM (2×50 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and dried in high vacuum to yield 600 mg of a pale yellow oil.

This oil was dissolved in *t*-BuOH (5 mL) and KO*t*-Bu (2 mL, 2 mmol, 1 M in THF) was added, followed by stirring at r.t. for 4 h. The base was neutralized by sat. NH_4Cl (80 mL), DCM (50 mL) was added, and the layers separated. The aqueous was extracted twice with DCM (2×50 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and dried in high vacuum to yield 666 mg of yellow thick oil.

This oil was dissolved in EtOH (3 mL) and H_2SO_4 (40 µL, 2 mmol, 1 M in THF) was added followed by stirring at 60 °C for 12 h. After cooling, water (40 mL) and Et_2O (40 mL) were added, and the layers separated. The aqueous phase was extracted twice with Et_2O (2×40 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and separated using flash chromatography (silica, PE/EA 50:1 to 3:1) to yield 154 mg of **revised-68a** (41%) as colourless crystals, mp 148-149 °C.

Spectroscopic data correspond to the compound obtained by Florio *et al.*[126] The structure was reassigned based on single crystal X-ray data.



R_f 0.41 (hexane/EA 5:1);

IR ν [cm^{-1}]: 3062 (w), 3031 (w), 2982 (w), 2926 (w), 2854 (w), 1781 (vs), 1738 (s), 1602 (w), 1495 (w), 1453 (w), 1367 (w), 1278 (m), 1225 (s), 1109 (m), 1057 (m), 1008 (w), 973 (m), 769 (w), 745 (m), 700 (vs);

^{1}H (401 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.4, 1.5 Hz, 1H, H-3/6), 7.25-7.15 (m, 10H), 6.93-6.87 (m, 2H, H-10), 6.75 (dt, *J* = 7.7, 1.2 Hz, 1H, H-3/6), 5.69 (d, *J* = 5.0 Hz, 1H, H-7), 4.78 (s, 1H, H-7'), 4.68 (d, *J* = 5.0 Hz, 1H, H-8), 4.37-4.18 (m, 2H, OCH_2CH_3), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.2 (s, C-9'), 168.9 (s, *C*OOEt), 140.5 (s, C-1'), 138.4 (s, C-2), 133.4 (s, C-1), 133.0 (s, C-9), 131.9 (d, C-2'), 130.9 (d, C-3/6), 130.2 (d, C_{Ar}), 128.8 (d, C_{Ar}), 128.0 (d, C_{Ar}), 127.9 (d, C_{Ar}), 127.9 (d, C_{Ar}), 127.7 (d, C_{Ar}), 127.5 (d, C_{Ar}), 127.3 (d, C_{Ar}), 79.7 (d, C-7), 62.3 (t, OCH_2CH_3), 60.7 (s, C-8'), 53.7 (d, C-8), 44.9 (d, C-7'), 14.1 (q, OCH_2CH_3);

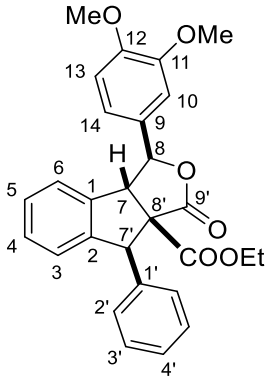
MS (ESI+) *m/z*, (%): 819 (29, $[2M + Na]^+$), 437 (7, $[M + K]^+$), 421 (100, $[M + Na]^+$), 399 (23, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{26}H_{22}O_4Na$ 421.1410; found: 421.1409.

Oxidative radical-to-cationic annulation of 121c with malonate 113

t-BuLi (0.38 mL, 0.65 mmol, 1.7 M) was added to a solution of stilbene **121c** (208 mg, 0.652 mmol) in THF (8 mL) at –78 °C and the mixture was stirred for 15 min. CuBr·DMS (21 mg, 0.10 mmol) was added and stirring was continued for 5 min. A solution of malonate **113** (115 µL, 0.513 mmol) in THF (8 mL) was added dropwise, followed by warming to 0 °C over 2 h. Salt **52** (300 mg, 0.91 mmol) was added in a single portion. After 1 h, the reaction was quenched by saturated NH_4Cl solution (25 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic extract was washed by 10% $Na_2S_2O_3$ solution (50 mL) and brine (50 mL) and the organic layer was dried over anhydrous Na_2SO_4. Concentration under vacuum and purification by flash chromatography (SiO_2, hexane/EA 10:1 to pure EA) afforded 7 mg (3%) of lactone **129**, 21 mg (8%) of alcohol **130,** 80 mg **(**32%) of alkene **131** and 25 mg (10%) of non-cyclised Michael adduct **123c**.

Ethyl (3S,3aS*,8S*,8aR*)-3-(3,4-dimethoxyphenyl)-1-oxo-8-phenyl-3a,8-dihydro-1H-indeno[1,2-c]furan-8a(3H)-carboxylate* (**129**)



R_f 0.32 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 2930 (w), 2853 (w), 1782 (m), 1730 (m), 1595 (w), 1516 (s), 1454 (m), 1256 (s), 1238 (s), 1141 (vs), 1025 (s), 803 (m), 734 (vs), 699 (s);

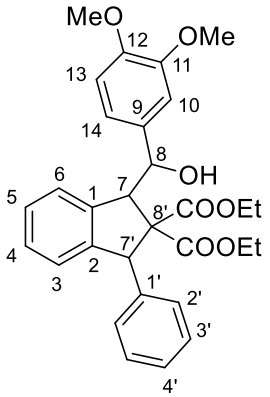
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.7 Hz, 1H, H-6), 7.42 (t, *J* = 7.2 Hz, 1H, H-5), 7.32 (t, *J* = 7.5 Hz, 1H, H-4), 7.21-7.17 (m, 3H, H-3', H-4'), 7.12 (d, *J* = 7.7 Hz, 1H, H-3), 6.99-6.94 (m, 3H, H-14, H-2'), 6.88-6.86 (m, 2H, H-10, H-13), 5.72 (s, 1H, H-8), 5.14 (s, 1H, H-7'), 4.75 (s, 1H, H-7), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.53 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 0.71 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.8 (s, C-9'), 166.3 (s, *C*OOEt), 149.4 (s, C-11/12), 149.1 (s, C-11/12), 143.3 (s, C-2), 141.3 (s, C-1), 139.8 (s, C-1'), 131.5 (s, C-9), 129.5 (d, C-4), 129.1 (d, C-2'), 128.9 (d, C-5), 128.4 (d, C-3'), 127.7 (d, C-4'), 126.1 (d, C-3), 124.0 (d, C-6), 117.5 (d, C-14), 111.3 (d, C-13), 108.1 (d, C-10), 85.1 (d, C-8), 66.3 (s, C-8'), 62.1 (t, O*C*H$_2$CH$_3$), 59.4 (d, C-7'), 56.1 (q, 2×C, C11-*C*H$_3$, C12-*C*H$_3$), 56.0 (d, C-7), 13.5 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 939 (7, $[2M + Na]^+$), 527 (11, $[M + Na + EtOH]^+$), 518 (26), 481 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{28}H_{26}O_6Na$ 481.1622; found: 481.1620.

Diethyl 1-[(3,4-dimethoxyphenyl)(hydroxy)methyl]-3-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate (**130**)



R_f 0.30 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 3061 (w), 3029 (w), 2981 (w), 2937 (w), 2836 (w), 1780 (m), 1734 (m), 1699 (m), 1515 (s), 1453 (m), 1262 (vs), 1238 (s), 1141 (s), 1026 (s), 751 (m), 702 (m);

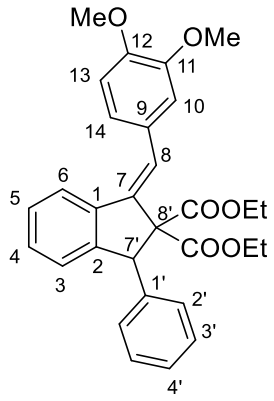
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H, H-2'), 7.32-7.29 (m, 3H, H-3', H-4'), 7.14-7.10 (m, 3H, H-4, H-10, H-14), 7.03 (t, *J* = 7.5 Hz, 1H, H-5), 6.94 (d, *J* = 8.6 Hz, 1H, H-13), 6.88 (d, *J* = 7.7 Hz, 1H, H-6), 6.56 (d, *J* = 7.6 Hz, 1H, H-3), 5.20 (s, 1H, H-7'), 5.03 (br t, *J* = 9.6 Hz, 1H, H-8), 4.59 (br d, *J* = 9.9 Hz, 1H, C8-O*H*), 4.48-4.38 (m, 3H, Et, H-7), 3.94 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.82-3.69 (m, 2H, OCH_2CH$_3$), 1.43 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 0.87 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.0 (s, *C*OOEt), 168.0 (s, *C*OOEt), 149.5 (s, C-11/12), 149.0 (s, C-11/12), 143.1 (s, C-2), 141.8 (s, C-1), 138.7 (s, C-1'), 137.3 (s, C-9), 131.4 (d, C-2'), 127.73 (d, C-3'), 127.70 (d, C-4'), 127.4 (d, C-4/5), 127.3 (d, C-4/5), 124.9 (d, C-6), 123.9 (d, C-3), 120.0 (d, C-14), 111.5 (d, C-13), 111.1 (d, C-10), 74.8 (d, C-8), 70.8 (s, C-8'), 62.9 (t, O*C*H$_2$CH$_3$), 61.2 (t, O*C*H$_2$CH$_3$), 57.2 (d, C-7), 56.6 (d, C-7'), 56.1 (q, 2×C, C11-*C*H$_3$, C12-*C*H$_3$), 14.2 (q, OCH$_2$*C*H$_3$), 13.6 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 1031 (14, $[2M + Na]^+$), 985 (4, $[2M + Na - EtOH]^+$), 564 (19), 527 (100, $[M + Na]^+$), 487 (31, $[M + H - H_2O]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{30}H_{32}O_7Na$ 527.2040; found: 527.2041.

Diethyl (E)-1-(3,4-dimethoxybenzylidene)-3-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate (**131**)



R_f 0.36 (hexane/EA 3:1), R_f 0.13 (hexanes/EA 5:1);

IR (film) ν [cm^{-1}]: 3062 (w), 2978 (w), 2934 (w), 2905 (w), 2836 (w), 1730 (vs), 1601 (w), 1513 (s), 1464 (m), 1263 (s), 1235 (vs), 1204 (m), 1138 (m), 1094 (m), 1027 (s), 762 (m), 701 (m);

^{1}H (401 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.9 Hz, 1H, H-6), 7.23 (d, *J* = 7.5 Hz, 2H, H-2'), 7.20 (tt, *J* = 6.7, 2.9 Hz, 1H, H-4'), 7.14-7.11 (m, 3H, H-3', H-4), 7.12 (s, 1H, H-8), 7.04 (d, *J* = 7.7 Hz, 1H, H-3), 7.03 (d, *J* = 8.1 Hz, 1H, H-14), 7.00 (s, 1H, H-10), 6.98 (t, *J* = 7.5 Hz, 1H, H-5), 6.90 (d, *J* = 8.1 Hz, 1H, H-13), 5.36 (s, 1H, H-7'), 4.32-4.23 (m, 2H, OCH_2CH_3), 3.94 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.75-3.48 (m, 2H, OCH_2CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 0.87 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.0 (s, *C*OOEt), 169.0 (s, *C*OOEt), 148.9 (s, C-11/12), 148.5 (s, C-11/12), 147.2 (s, C-1/2), 140.8 (s, C-1'), 137.8 (s, C-1/2/7), 137.5 (s, C-1/2/7), 130.2 (s, C-9), 129.8 (d, C-8), 129.6 (d, C-2'/3'), 129.1 (d, C-4), 128.2 (d, C-2'/3'), 127.3 (d, C-4'), 126.9 (d, C-5), 125.7 (d, C-3), 124.4 (d, C-6), 121.1 (d, C-14), 111.7 (d, C-13), 111.3 (d, C-10), 71.0 (s, C-8'), 62.1 (t, O*C*H$_2$CH$_3$), 61.1 (t, O*C*H$_2$CH$_3$), 56.1 (q, O*C*H$_3$), 56.03 (q, O*C*H$_3$), 55.97 (d, C-7'), 14.2 (q, OCH$_2$*C*H$_3$), 13.6 (q, OCH$_2$*C*H$_3$);

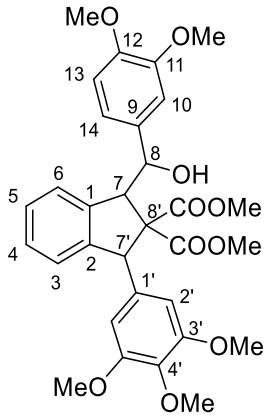
MS (ESI+) *m/z*, (%): 995 (17, $[2M + Na]^+$), 525 (12, $[M + K]^+$), 509 (100, $[M + Na]^+$), 487 (24, $[M + H]^+$), 469 (20, $[M + H - H_2O]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{30}H_{30}O_6Na$ 509.1935; found: 509.1935.

Oxidative radical-to-cationic annulation of stilbene 121c with malonate 122

t-BuLi (231 µL, 0.393 mmol, 1.7 M in pentane) was added to a solution of stilbene **121c** (125 mg, 0.393 mmol) in THF (8 mL) was cooled to –78 °C, followed by stirring for 15 min at –78 °C. A solution of CuBr·DMS (13 mg, 0.063 mmol) and LiBr (60 mg, 0.181 mmol) in THF (3 mL) was added and the mixture was stirred for 5 min. A solution of malonate **122** (95 mg, 0.306 mmol) in THF (3 mL) was added dropwise. The reaction mixture was warmed to 0 °C over 2 h, followed by addition of solid $FeCp_2PF_6$ (300 mg, 0.906 mmol). After 1 h at 0 °, saturated NH_4Cl solution (15 mL) was added. The phases were separated and the aqueous phase was extracted with diethyl ether (3×100 mL). The combine organic extracts were washed with 10% $Na_2S_2O_3$ solution (50 mL), dried over Na_2SO_4, concentrated and purified by column chromatography (hexane/EA 7:1 to pure EA) to yield 5% of Michael adduct **123d**, 4% of alcohol **132** and 37% of alkene **133**.

Dimethyl 1-[(3,4-dimethoxyphenyl)(hydroxy)methyl]-3-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate (**132**)



R*f* 0.11 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 2999 (w), 2932 (w), 2838 (w), 1736 (m), 1707 (m), 1591 (m), 1509 (m), 1460 (m), 1423 (m), 1332 (s), 1263 (s), 1239 (s), 1126 (vs), 1026 (m), 767 (w), 736 (w);

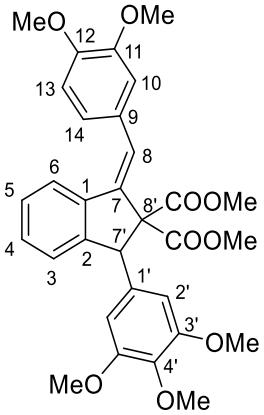
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.16-7.11 (m, 3H, H-4, H-10, H-13), 7.05 (t, *J* = 7.5 Hz, 1H, H-5), 6.96-6.91 (m, 2H, H-6, H-14), 6.63 (s, 2H, H-2'), 6.59 (d, *J* = 7.7 Hz, 1H, H-3), 5.08 (s, 1H, H-7'), 4.98 (br. t, *J* = 9.6 Hz, 1H, H-8), 4.41 (d, *J* = 9.6 Hz, 1H, H-7), 4.27 (br. d, *J* = 9.8 Hz, 1H, C8-O*H*), 3.97 (s, 3H, COOCH_3), 3.94 (s, 6H, C11-OCH_3, C12-OCH_3), 3.88 (s, 3H, C4'-OCH_3), 3.82 (s, 6H, C3'-OCH_3), 3.39 (s, 3H, COOCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.2 (s, *C*OOMe), 168.6 (s, *C*OOMe), 152.6 (s, 2×C, C-3'), 149.5 (s, C-11/12), 149.1 (s, C-11/12), 142.8 (s, C-2), 141.6 (s, C-1), 137.6 (s, C-4'), 137.0 (s, C-9), 134.0 (s, C-1'), 127.6 (d, C-5), 127.4 (d, C-4), 125.0 (d, C-6), 123.9 (d, C-3), 119.9 (d, C-14), 111.5 (d, C-13), 111.1 (d, C-10), 108.5 (d, 2×C, C-2'), 74.9 (d, C-8), 70.9 (s, C-8'), 61.0 (q, C4'-O*C*H_3), 57.1 (d, C-7), 57.0 (d, C-7'), 56.3 (q, 2×C, C3'-O*C*H_3), 56.11 (q, C11/12-O*C*H_3), 56.09 (q, C11/12-O*C*H_3), 53.6 (q, COO*C*H_3), 52.4 (q, COO*C*H_3);

MS (ESI+) *m/z*, (%): 1155 (68, $[2M + Na]^+$), 1123 (48, $[2M + Na – MeOH]^+$), 589 (100, $[M + Na]^+$), 557 (39, $[M + Na – MeOH]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{31}H_{34}O_{10}Na$ 589.2044; found: 589.2049.

Dimethyl (E)-1-(3,4-dimethoxybenzylidene)-3-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate (**133**)



mp 155-157 °C;

R_f 0.16 (hexane/EA 3:1);

IR (film) ν [cm^{-1}]: 2999 (w), 2950 (w), 2837 (w), 1731 (s), 1589 (m), 1509 (s), 1457 (m), 1422 (m), 1330 (m), 1231 (vs), 1123 (vs), 1096 (s), 1025 (s), 1007 (m), 919 (w), 780 (m), 761 (m), 732 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.9 Hz, 1H, H-6), 7.16 (t, *J* = 7.4 Hz, 1H, H-4), 7.10 (d, *J* = 7.9 Hz, 1H, H-3), 7.09 (s, 1H, H-8), 7.02-6.99 (m, 2H, H-5, H-14), 6.96 (d, *J* = 1.9 Hz, 1H, H-10), 6.89 (d, *J* = 8.2 Hz, H-13), 6.36 (s, 2H, H-2'), 5.33 (s, 1H, H-7'), 3.93 (s, 3H, C11/12-CH_3), 3.84 (s, 3H, C11/12-CH_3), 3.82 (s, 3H, COOCH_3), 3.81 (s, 3H, C4'-CH_3), 3.77 (s, 6H, C3'-CH_3), 3.27 (s, 3H, COOCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.5 (s, *C*OOMe), 169.5 (s, *C*OOMe), 152.9 (s, 2×C, C-3'), 149.0 (s, C-11/12), 148.6 (s, C-11/12), 146.6 (s, C-2), 137.8 (s, C-1), 137.4 (s, C-7/4'), 137.3 (s, C-7/4'), 136.0 (s, C-1'), 130.0 (s, C-9), 129.4 (d, C-8), 129.1 (d, C-4), 127.1 (d, C-5), 125.7 (d, C-3), 124.5 (d, C-6), 121.1 (d, C-14), 111.6 (d, C-13), 111.3 (d, C-10), 106.6 (d, 2×C, C-2'), 71.5 (s, C-8'), 61.0 (q, C4'-*C*H_3), 56.4 (q, C11/12-*C*H_3), 56.2 (q, 2×C, C3'-*C*H_3), 56.1 (q, C11/12-*C*H_3), 56.0 (d, C-7'), 53.5 (q, COO*C*H_3), 52.2 (q, COO*C*H_3);

MS (ESI+) *m/z*, (%): 1119 (5, $[2M + Na]^+$), 571 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{31}H_{32}O_9Na$ 571.1939; found: 571.1938.

6.1.4. Racemic synthesis of kompasinol A pentamethylether (**140**)

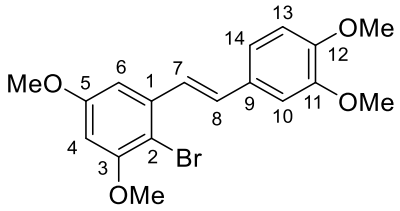
Synthesis of stilbene 136

At 0 °C, three equal portions of $NaBH_4$ (overall 1.14 g, 30.2 mmol) were added over 1 h to a solution of 3,4-dimehoxybenzaldehyde (5 g, 30.1 mmol) in MeOH (50 mL). The mixture was stirred at r.t. for 2 h, followed removal of the solvent under vacuum. The crude product was dissolved in Et_2O (50 mL) and cooled to 0 °C. PBr_3 (5.1 mL, 57 mmol) was added dropwise, followed by stirring at 0 °C for 5 h.

The reaction was quenched by pouring into water ice (50 mL) and extracted three times with DCM (3×150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was dissolved in dry THF (80 mL) and PPh_3 (8.5 g, 32.4 mmol) was added, followed by stirring at r.t. overnight. After removal of the solvent under vacuum, the solids were suspended in pentane (50 mL), sonicated, and filtered. The solid was washed with additional pentane and dried under high vacuum to yield 12.1 g (81%) of 3,4-dimethoxybenzyltriphenylphosphonium bromide (**142**) as a colourless solid.

The phosphonium salt **142** (9.09 g, 18.5 mmol) was dissolved in THF (150 mL), cooled to 0 °C and treated with *n*-BuLi (11.8 mL, 18.8 mmol, 1.6 M in hexanes). After 30 min, a solution of 2-bromo-3,5-dimethoxybenzaldehyde (4.29 g, 17.6 mmol) in THF (25 mL) was added by cannula. The mixture was stirred at r.t. for 2 h, cooled to 0 °C and quenched by saturated NH_4Cl solution (50 mL). The layers were separated and the aqueous phase was extracted with EA (2×100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was dissolved in benzene (50 mL), Ph_2Se_2 (0.30 g, 0.96 mmol) was added, and the solution was irradiated with a halogen lamp for 2 days while stirring. Concentration under vacuum followed by flash chromatography (hexane/EA 8:1 to pure EA) and crystallization from EA gave 5.8 g of **136** (88%) as large colourless crystals, mp 105-107 °C.

(E)-2-Bromo-1-(3,4-dimethoxystyryl)-3,5-dimethoxybenzene (**136**)



R_f 0.62 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3000 (w), 2936 (w), 2836 (w), 1582 (s), 1513 (s), 1451 (m), 1416 (m), 1331 (m), 1265 (s), 1232 (s), 1202 (m), 1160 (s), 1139 (m), 1081 (s), 1022 (s), 959 (w), 825 (w), 802 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.39 (d, *J* = 16.1 Hz, 1H, H-7), 7.11-7.08 (m, 2H, H-4, H-10, H-14), 6.96 (d, *J* = 16.1 Hz, 1H, H-8), 6.87 (d, *J* = 8.8 Hz, 1H, H-13), 6.80 (d, *J* = 2.7 Hz, 1H, H-6), 6.42 (d, *J* = 2.7 Hz, 1H, H-4), 3.95 (s, 3H, C11-OC*H*$_3$), 3.91 (s, 3H, C12-OC*H*$_3$), 3.88 (s, 3H, C3-OC*H*$_3$), 3.86 (s, 3H, C5-OC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.7 (s, C-5), 157.0 (s, C-3), 149.5 (s, C-12), 149.3 (s, C-11), 139.0 (s, C-1), 131.6 (d, C-8), 130.2 (s, C-9), 126.2 (d, C-7), 120.5 (d, C-14), 111.3 (d, C-13), 109.2 (d, C-10), 105.1 (s, C-2), 102.6 (d, C-6), 99.0 (d, C-4), 56.5 (q, C5-O*C*H$_3$), 56.11 (q, C3-O*C*H$_3$), 56.06 (q, C11/12-O*C*H$_3$), 55.7 (q, C11/12-O*C*H$_3$);

MS (ESI+) *m/z*, (%): 403/401 (100/93, $[M + Na]^+$), 381/379 (40/40, $[M + H]^+$), 300 (25, $[M + H - Br]^+$);

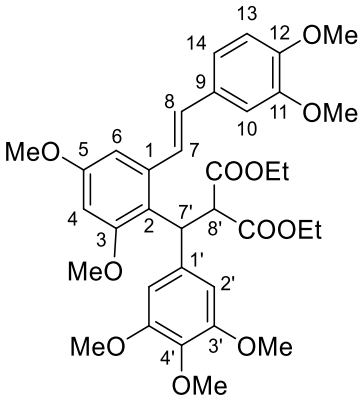
MS (EI+) *m/z*, (%): 380/378 (38/37, $[M]^{\cdot+}$), 299 (100, $[M - Br]^+$), 284 (50, $[M - Br - Me]^{\cdot+}$), 268 (50, $[M - Br - MeO]^{\cdot+}$), 253 (13, $[M - Br - MeO - Me]^+$), 241 (13);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{18}H_{19}{}^{79}BrNa\ O_4$ 401.0359; found: 403.0360.

Conjugate addition of 136 to 137 – isolation of Michael adduct 138b

Bromostilbene **136** (89 mg, 0.237 mmol) was dissolved in dry THF (7 mL) and cooled to –78 °C. A solution of *t*-BuLi (140 µl, 0.237 mmol, 1.7 M in pentane) was added followed by stirring for 15 min. An independently prepared solution of CuBr·DMS (8.5 mg, 0.041 mmol) and LiBr (41 mg, 0.47 mmol) in THF (3 mL) was added and the mixture was stirred for 5 min. A solution of malonate **137** (40 mg, 0.118 mmol) in THF (3 mL) was added dropwise. The reaction was slowly warmed to –40 °C over 2 h, and quenched by sat. NH_4Cl (15 ml). The layers were separated and the aqueous was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuum and purified by flash chromatography (hexane/EA 9:1 to pure EA) to yield 74 mg (98%) of **138b** as a colourless sticky solid.

Diethyl (E)-2-{[2-(3,4-dimethoxystyryl)-4,6-dimethoxyphenyl](3,4,5-trimethoxyphenyl)methyl}malonate (**138b**)



R_f 0.44 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2937 (w), 2836 (w), 1751 (m), 1731 (m), 1589 (m), 1511 (m), 1461 (m), 1420 (m), 1323 (m), 1258 (s), 1230 (s), 1200 (m), 1126 (vs), 1026 (m), 964 (w), 848 (w), 805 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.62 (br. d, *J* = 16.0 Hz, 1H, H-7), 7.13 (d, *J* = 8.2 Hz, 1H, H-14), 7.10 (s, 1H, H-10), 6.91 (d, *J* = 8.2 Hz, 1H, H-13), 6.83 (d, *J* = 15.9 Hz, 1H, H-8), 6.62 (d, *J* = 2.5 Hz, 1H, H-6), 6.60 (s, 2H, H-2'), 6.39 (d, *J* = 2.5 Hz, 1H, H-4), 5.20 (br. d, *J* = 10.7 Hz, 1H, H-7'), 4.96 (br. d, *J* = 11.1 Hz, 1H, H-8'), 4.11-3.97 (m, 4H, OC*H*$_2$CH$_3$), 3.97 (s, 3H, C11-OC*H*$_3$), 3.95 (s, 3H, C12-OC*H*$_3$), 3.83 (s, 3H, C5-OC*H*$_3$), 3.82 (s, 3H, C3-OC*H*$_3$), 3.77 (s, 3H, C4'-OC*H*$_3$), 3.72 (s, 6H, C3'-OC*H*$_3$), 1.16 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.04 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.9 (s, *C*OOEt), 168.3 (s, *C*OOEt), 159.5 (s, C-5), 159.0 (s, C-3), 152.7 (s, C-3'), 149.3 (s, C-12), 149.2 (s, C-11), 140.3 (s, C-1), 137.3 (s, C-1'), 136.4 (s, C-4'), 132.5 (d, C-8), 130.7 (s, C-9), 126.9 (d, C-7), 120.2 (s, C-2), 119.8 (d, C-14), 111.4 (d, C-13), 109.5 (d, C-10), 105.1 (d, C-2'), 104.2 (d, C-6), 98.8 (d, C-4), 61.6 (t, O*C*H$_2$CH$_3$), 61.4 (t, O*C*H$_2$CH$_3$), 60.9 (q, C4'-OC*H*$_3$), 56.14 (q, C3-OC*H*$_3$), 56.08 (q, C5-OC*H*$_3$), 56.0 (q, C3'-OC*H*$_3$), 55.5 (q, C12-OC*H*$_3$), 55.4 (q, C11-OC*H*$_3$), 54.9 (d, C-8'), 43.7 (d, C-7'), 14.1 (q, OCH$_2$*C*H$_3$), 14.0 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 661 (100, [M + Na]$^+$), 479 (34, [M + H – CH$_2$(COOCH$_2$CH$_3$)$_2$]$^+$), 339 (24);

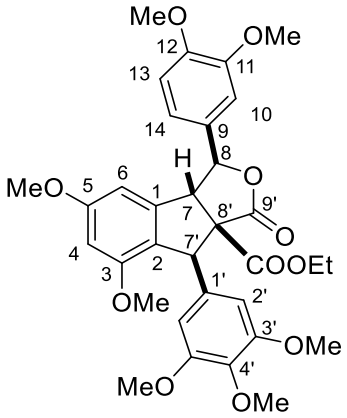
HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{35}H_{42}NaO_{11}$ 661.2619; found: 661.2619.

Conjugate addition of 136 to 138 – in situ oxidative cyclisation

In a Schlenk flask, bromostilbene **136** (112 mg, 0.296 mmol) was dissolved in dry THF (7 mL) and cooled to –78 °C. A solution of *tert*-BuLi (175 µl, 0.296 mmol, 1.7 M in pentane) was added followed by stirring for 5 min. An independently prepared solution of CuBr·DMS (5 mg, 0.024 mmol) and LiBr

(13 mg, 0.150 mmol) in THF (3 mL) was added and the mixture was stirred for 5 min. A solution of malonate **137** (40 mg, 0.118 mmol) in THF (3 mL) was added dropwise. The reaction was slowly warmed to –40 °C over 2 h. The Schlenk flask was opened and salt **52** (150 mg, 0.448 mmol) was quickly added, followed by flushing with dry N_2. The reaction was warmed to 0 °C over 2 h and quenched with sat. NH_4Cl (15 mL). The layers were separated and the aqueous was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with 10% $Na_2S_2O_3$ (20 mL), dried over Na_2SO_4, concentrated in vacuum and purified by flash chromatography (hexane/EA 8:1 to pure EA) to yield 54 mg of lactone **139** (75%) as a colourless solid, mp 163-165 °C.

Ethyl (3S,3aS*,8S*,8aR*)-3-(3,4-dimethoxyphenyl)-5,7-dimethoxy-1-oxo-8-(3,4,5-trimethoxyphenyl)-3a,8-dihydro-1H-indeno[1,2-c]furan-8a(3H)-carboxylate* (**139**)



R_f 0.23 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2938 (w), 2838 (w), 1780 (m), 1735 (w), 1593 (m), 1516 (m), 1461 (m), 1422 (m), 1329 (m), 1259 (m), 1234 (s), 1208 (m), 1151 (s), 1124 (vs), 1068 (m), 1025 (s), 857 (w), 810 (w), 734 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.93 (d, *J* = 8.3 Hz, 1H, H-14), 6.86 (d, *J* = 8.4 Hz, 1H, H-13), 6.83 (d, *J* = 2.0 Hz, 1H, H-10), 6.61 (d, *J* = 1.4 Hz, 1H, H-6), 6.38 (d, *J* = 1.7 Hz, 1H, H-4), 6.19 (br. s, 2H, H-2'), 5.70 (s, 1H, H-8), 5.04 (s, 1H, H-7'), 4.62 (s, 1H, H-7), 3.89 (s, 3H, C5-OCH_3), 3.88 (s, 3H, C11-OCH_3), 3.87 (s, 3H, C12-OCH_3), 3.75 (s, 3H, C4'-OCH_3), 3.72 (s, 6H, C3'-OCH_3), 3.66 (s, 3H, C3-OCH_3), 3.55 (q, *J* = 7.2 Hz, 2H, OCH_2CH$_3$), 0.71 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.8 (s, C-9'), 166.2 (s, *C*OOEt), 162.6 (s, C-5), 157.1 (s, C-3), 152.9 (s, C-3'), 149. 4 (s, C-11/12), 149.1 (s, C-11/12), 143.4 (s, C-1), 137.3 (s, C-4'), 134.9 (s, C-1'), 131.5 (s, C-9), 123.1 (s, C-2), 117.4 (d, C-14), 111.3 (d, C-13), 108.1 (d, C-10), 105.9 (d, C-2'), 99.5 (d, C-6), 99.0 (d, C-4), 84.4 (d, C-8), 66.6 (s, C-8'), 61.9 (t, O*C*H$_2$CH$_3$), 60.9 (q, C4'-OCH_3), 56.48 (d, C-7), 56.46 (d, C-7'), 56.3 (q, C3'-OCH_3), 56.2 (q, C5/11/12-OCH_3), 56.1 (q, C5/11/12-OCH_3), 55.9 (q, C5/11/12-OCH_3), 55.6 (q, C3-OCH_3), 13.6 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 1239 (6, [2M + Na]$^+$), 647 (14, [M + K]$^+$), 631 (100, [M + Na]$^+$);

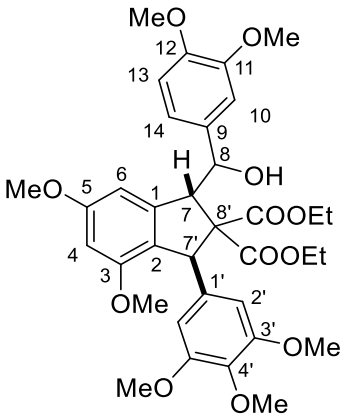
HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{33}H_{36}NaO_{11}$ 631.2150; found: 631.2154.

One pot conjugate addition-oxidative cyclisation of 136/137 with added diisopropylamine

Modifying of the procedure for one pot addition/cyclisation of stilbene **136** (see above), DIPA (10 µL, 0.071 mmol) was added immediately after oxidation by **52**, resulting in the following mixture of

products after chromatography: 17% of lactone **139**, 54% of alcohol **139'** and 15% of alkene **143**. Alcohol **139'** spontaneously lactonizes into **139** in $CDCl_3$ solution.

Diethyl (1S,3S*)-1-[(3,4-dimethoxyphenyl)(hydroxy)methyl]-4,6-dimethoxy-3-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate* (**139'**)



R_f 0.17 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2937 (w), 2837 (w), 1782 (m), 1727 (m), 1592 (m), 1514 (m), 1458 (m), 1421 (m), 1329 (m), 1258 (s), 1234 (s), 1200 (m), 1148 (s), 1123 (vs), 1069 (m), 1023 (s), 857 (m), 806 (m), 732 (m);

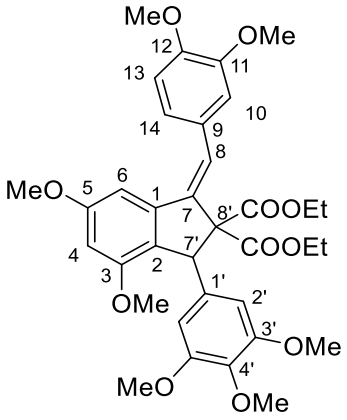
^{1}H NMR (401 MHz, $CDCl_3$): δ 6.95-6.85 (m, 3H, H-10, H-13, H-14), 6.25 (s, 2H, H-2'), 6.24 (d, *J* = 2.0 Hz, 1H, H-4), 5.78 (d, *J* = 1.7 Hz, 1H, H-6), 4.97 (s, 1H, H-7'), 4.75 (d, *J* = 8.8 Hz, 1H, H-8), 4.68 (d, *J* = 8.8 Hz, 1H, H-7), 4.34-4.15 (m, 2H, OC*H*$_2$CH$_3$), 3.83 (s, 6H, C11-OC*H*$_3$, C12-OC*H*$_3$), 3.79 (s, 3H, C4'-OC*H*$_3$), 3.73 (s, 6H, C3'-OC*H*$_3$), 3.72-3.58 (m, 2H, OC*H*$_2$CH$_3$), 3.57 (s, 3H, C5-OC*H*$_3$), 3.54 (s, 3H, C3-OC*H*$_3$), 2.04 (s, 1H, C8-O*H*), 1.27 (t, *J* = 6.7 Hz, 3H, OCH$_2$C*H*$_3$), 0.93 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.1 (s, *C*OOEt), 170.7 (s, *C*OOEt), 160.8 (s, C-3), 156.2 (s, C-5), 152.6 (s, C-3'), 149.2 (s, C-11/12), 149.1 (s, C-11/12), 142.7 (s, C-1), 136.8 (s, C-4'), 135.8 (s, C-1'), 135.3 (s, C-9), 124.1 (s, C-2), 120.4 (d, C-14), 111.0 (d, C-13), 110.8 (d, C-10), 106.0 (d, C-2'), 101.4 (d, C-6), 98.5 (d, C-4), 75.0 (d, C-8), 70.5 (s, C-8'), 62.0 (t, O*C*H$_2$CH$_3$), 61.6 (t, O*C*H$_2$CH$_3$), 60.9 (q, C4'-O*C*H$_3$), 57.1 (d, C-7), 56.2 (q, C3'-O*C*H$_3$), 55.93 (q, C11/12-O*C*H$_3$), 55.91 (q, C11/12-O*C*H$_3$), 55.5 (q, C3/5-O*C*H$_3$), 55.3 (q, C3/5-O*C*H$_3$), 54.1 (d, C-7'), 14.1 (q, OCH$_2$*C*H$_3$), 13.7 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 1285 (12, [2M + Na – EtOH]$^+$), 1239 (12, [2M + Na – 2EtOH]$^+$), 677 (47, [M + Na]$^+$), 637 (100, [M + H – H$_2$O]$^+$), 609 (19, [M + H – EtOH]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{35}H_{42}NaO_{12}$ 677.2569; found: 677.2559.

Diethyl (E)-1-(3,4-dimethoxybenzylidene)-4,6-dimethoxy-3-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate (**143**)



R_f 0.43 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2999 (w), 2935 (w), 2836 (w), 1733 (w), 1594 (m), 1512 (s), 1455 (m), 1420 (m), 1326 (m), 1262 (s), 1232 (s), 1200 (s), 1154 (s), 1138 (s), 1074 (m), 1025 (m), 964 (w), 829 (w), 807 (w), 734 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.14 (s, 1H, H-8), 7.03 (dd, *J* = 8.2, 1.8 Hz, 1H, H-14), 6.98 (d, *J* = 1.7 Hz, 1H, H-10), 6.89 (d, *J* = 8.2 Hz, 1H, H-13), 6.41 (s, 2H, H-2'), 6.39 (d, *J* = 2.1 Hz, 1H, H-4/6), 6.25 (d, *J* = 2.0 Hz, 1H, H-4/6), 5.10 (s, 1H, H-7'), 4.30-4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.92 (s, 3H, C11-OC*H*$_3$), 3.85 (s, 3H, C12-OC*H*$_3$), 3.78 (s, 3H, C4'-OC*H*$_3$), 3.77 (s, 6H, C3'-OC*H*$_3$), 3.75-3.69 (m, 2H, OC*H*$_2$CH$_3$), 3.65 (s, 3H, C3-OC*H*$_3$), 3.49 (s, 3H, C5-OC*H*$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.93 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

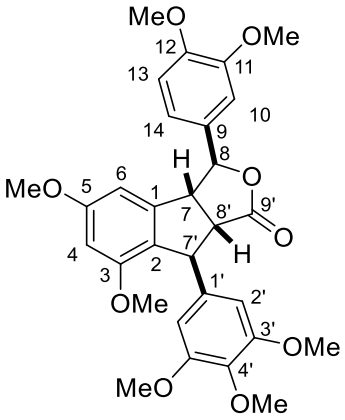
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.8 (s, *C*OOEt), 168.7 (s, *C*OOEt), 160.4 (s, C-5), 156.6 (s, C-3), 152.5 (s, C-3'), 148.9 (s, C-12), 148.6 (s, C-11), 139.2 (s, C-1), 137.3 (s, C-4'), 136.0 (s, C-1'), 130.6 (d, C-8), 130.2 (s, C-9), 128.4 (s, C-2), 121.4 (d, C-14), 113.3 (s, C-7), 111.9 (d, C-13), 111.2 (d, C-10), 106.4 (d, C-2'), 99.9 (d, C-4, C-6), 71.0 (s, C-8'), 62.1 (t, O*C*H$_2$CH$_3$), 61.1 (t, O*C*H$_2$CH$_3$), 61.0 (q, C4'-O*C*H$_3$), 56.13 (q, C11-O*C*H$_3$), 56.12 (q, C3'-O*C*H$_3$), 56.0 (q, C12-O*C*H$_3$), 55.6 (q, C3-O*C*H$_3$), 55.3 (q, C5-O*C*H$_3$), 53.1 (d, C-7'), 14.2 (q, OCH$_2$*C*H$_3$), 13.8 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 1295 (45, [2M + Na]$^+$), 659 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{35}H_{40}NaO_{11}$ 659.2463; found: 659.2457.

rac-9'-Oxokompasinol A pentamethylether (**144**)

A solution of LiOH (45 mg, 1.8 mmol) in demineralized water (0.4 mL) was added to a solution of **139** (14 mg, 0.023 mmol) in a mixture of THF (1.5 mL) and EtOH (1.5 mL). The reaction flask was flushed with N_2, sealed, and stirred at 75 °C for 27 h. After cooling, AcOH (1 mL) was added, the solution was stirred at r.t. for 30 min and filtered through a 2×4 cm silica column. The silica was washed with a mixture of PE and EA (1:1, 80 mL) and the combined filtrates were concentrated under vacuum to yield 24.6 mg of crude product, that was purified by column chromatography (PE/EA 4:1 to 1:1) to yield 7.8 mg of **144** (63%) as a colourless film.



R_f 0.32 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3001 (w), 2959 (w), 2937 (w), 2838 (w), 1763 (m), 1592 (m), 1592 (m), 1516 (m), 1463 (m), 1420 (w), 1330 (m), 1297 (w), 1264 (m), 1235 (m), 1202 (w), 1142 (s), 1125 (s), 1079 (w), 1025 (w), 907 (s), 832 (w), 725 (vs), 646 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.97-6.81 (m, 3H, H-10, H-13, H-14), 6.61 (dd, *J* = 2.0, 0.9 Hz, 1H H-6), 6.42 (d, *J* = 1.9 Hz, 1H, H-4), 6.24 (s, 2H, H-2'), 5.64 (s, 1H, H-8), 4.83 (s, 1H, H-7'), 4.08 (d, *J* = 7.5 Hz, 1H, H-7), 3.91 (s, 3H, C11/12-OC*H*$_3$), 3.89 (s, 3H, C5-OC*H*$_3$), 3.88 (s, 3H, C11/12-OC*H*$_3$), 3.79 (s, 3H, C4'-OC*H*$_3$), 3.74 (s, 6H, C3'-OC*H*$_3$), 3.71 (s, 3H, C3-OC*H*$_3$), 3.31 (dd, *J* = 7.4, 1.2 Hz, 1H, H-8');

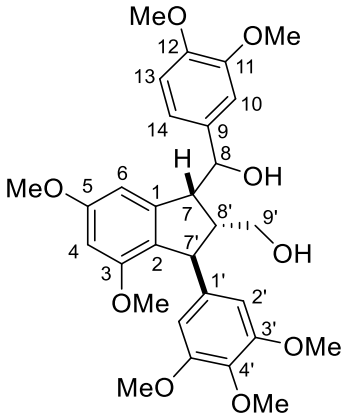
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 179.0 (s, C-9'), 162.4 (s, C-5), 157.4 (s, C-3), 153.4 (s, C-3'), 149.6 (s, C-11/12), 149.3 (s, C-11/12), 144.7 (s, C-1), 139.1 (s, C-1'), 136.8 (s, C-4'), 132.5 (s, C-9), 124.0 (s, C-2), 117.4 (d, C-14), 111.5 (d, C-13), 108.5 (d, C-10), 104.1 (d, C-2'), 99.9 (d, C-6), 98.6 (d, C-4), 85.3 (d, C-8), 60.9 (q, C4'-O*C*H$_3$), 56.27 (q, C3'-O*C*H$_3$), 56.26 (q, C3/5/11/12-O*C*H$_3$), 56.17 (q, C3/5/11/12-O*C*H$_3$), 55.8 (q, C3/5/11/12-O*C*H$_3$), 55.6 (q, C3/5/11/12-O*C*H$_3$), 53.7 (d, C-7), 53.0 (d, C-8'), 51.3 (d, C-7');

MS (ESI+) *m/z*, (%): 1095 (14, [2M + Na]$^+$), 559 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{30}H_{32}NaO_9$ 559.1939; found: 559.1942.

(3,4-Dimethoxyphenyl)[(1R,2R*,3S*)-2-(hydroxymethyl)-4,6-dimethoxy-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1H-inden-1-yl]methanol* (**145**)

144 (4.7 mg, 8.7 µmol) was suspended in EtOH (1 mL) but did not completely dissolve. THF (1 mL) was added leading to a clear solution. While maintaining vigorous stirring, $NaBH_4$ (25 mg, 0.66 mmol) was added in portions at r.t. After 20 min, the solvent was evaporated using a rotary evaporator. The solids were re-dissolved in THF (1 mL) and the evaporation repeated. TLC monitoring during the reaction indicated a fast reduction of less polar **144** (R_f 0.55, hexane/EA 1:1.5) initially leading to a moderately polar intermediate (R_f 0.45), followed more slowly by a second reduction to an even more polar diol **145** (R_f 0.18). The reaction was quenched by addition of water (15 mL), transferred into a separatory funnel, and extracted twice with a 1:1 mixture of THF and Et_2O (2×25 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under vacuum and dried in high vacuum to give 12 mg of crude diol **145** as a colourless amorphous solid.



R_f 0.18 (hexane/EA 1:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.93-6.71 (m, 3H, H-10, H-13, H-14), 6.29 (s, 2H, H-2'), 6.20 (d, *J* = 2.1 Hz, 1H, H-4), 5.31 (d, *J* = 2.1 Hz, 1H, H-6), 4.79 (d, *J* = 9.4 Hz, 2H, H-8), 4.16-4.02 (m, 2H, H-7', H-9'a), 3.88 (s, 3H, C11/12-OCH_3), 3.86-3.84 (m, 1H, H-9'b), 3.83 (s, 3H, C4'-OCH_3), 3.82 (s, 3H, C11/12-OCH_3), 3.76 (s, 6H, C3'-OCH_3), 3.69 (m, 1H, H-7), 3.50 (s, 3H, C3-OCH_3), 3.41 (s, 3H, C5-OCH_3), 2.79 (ddd, *J* = 7.8, 7.3, 3.8 Hz, 1H, H-8'), the OH resonances were not detected;

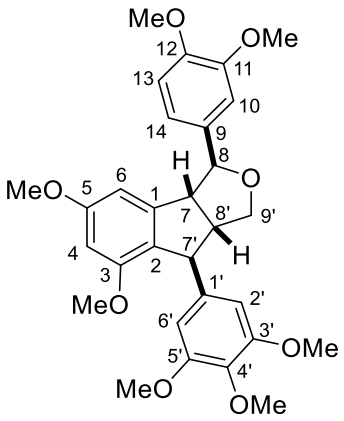
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.9 (s, C-5), 156.8 (s, C-3), 153.0 (s, C-3'), 149.1 (s, C-11/12), 149.0 (s, C-11/12), 145.0 (s, C-1), 140.0 (s, C-1'), 136.1 (s, C-4'), 135.7 (s, C-9), 125.1 (s, C-2), 119.9 (d, C-14), 110.9 (d, C-10/13), 110.5 (d, C-10/13), 104.6 (d, C-2'), 102.1 (d, C-6), 98.5 (d, C-4), 74.7 (d, C-8), 62.3 (t, C-9'), 61.0 (q, C4'-OCH$_3$), 56.7 (q, OCH$_3$), 56.3 (q, C3'-OCH$_3$), 56.1 (q, OCH$_3$), 55.4 (q, OCH$_3$), 55.2 (q, OCH$_3$), 53.8 (d, C-7), 49.8 (d, C-7');

MS (ESI+) *m/z*, (%): 563 (100, $[M + Na]^+$), 545 (14, $[M + Na - H_2O]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{30}H_{36}NaO_9$ 563.2252; found: 563.2243.

rac-Kompasinol A pentamethylether (**140**)

Upon standing for 2 days in $CDCl_3$, diol **145** developed a trace amount of **140** as indicated by ^{1}H NMR spectroscopy. The NMR sample in $CDCl_3$ (0.5 mL) was united with the rest of the crude diol **145** and camphor sulfonic acid (0.5 mg, 2 µmol) was added. After 2 h, the solution was diluted with DCM (10 mL), filtered through a 1 cm plug of K_2CO_3, concentrated and purified by flash chromatography (DCM/MeO*t*-Bu 50:1 to 9:1) to give 1.4 mg of **140** (30%) as a colourless film. The ^{1}H and ^{13}C NMR data matched the methylated natural compound.[113]



R_f 0.25 (hexane/EA 1:1), R_f 0.44 (DCM/MeO*t*-Bu 10:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.02-6.95 (m, 2H, H-10, H-14), 6.89 (d, *J* = 8.5 Hz, 1H, H-13), 6.41 (dd, *J* = 2.1, 0.8 Hz, 1H, H-6), 6.36 (d, *J* = 2.0 Hz, 1H, H-4), 6.24 (s, 2H, H-2', H-6'), 4.79 (d, *J* = 4.6 Hz, 1H, H-8), 4.53 (t, *J* = 8.4 Hz, 1H, H-9'a), 4.17 (d, *J* = 1.7 Hz, 1H, H-7'), 3.92 (s, 3H, C11/12-OCH_3), 3.90 (s, 3H, C11/12-OCH_3), 3.89 (m, 1H, H-7), 3.83 (s, 3H, C5-OCH_3), 3.81 (s, 3H, C4'-OCH_3), 3.76 (s, 6H, C3'-OCH_3), 3.68 (s, 3H, C3-OCH_3), 3.60 (t, *J* = 8.6 Hz, 1H, H-9'b), 3.14 (qd, *J* = 8.5, 1.8 Hz, 1H, H-8');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.9 (s, C-5), 157.7 (s, C-3), 153.2 (s, C-3', C-5'), 149.4 (s, C-11), 148.7 (s, C-12), 147.0 (s, C-1), 141.3 (s, C-1'), 136.2 (s, C-4'), 135.2 (s, C-9), 124.3 (s, C-2), 118.6 (d, C-14), 111.2 (d, C-13), 109.4 (d, C-10), 104.3 (d, C-2', C-6'), 100.4 (d, C-6), 97.9 (d, C-4), 87.6 (d, C-8), 74.2 (t, C-9'), 61.0 (q, C4'-OCH_3), 59.1 (d, C-7), 56.2 (q, C3'-OCH_3), 56.13 (q, OCH_3), 56.11 (q, OCH_3), 55.7 (q, OCH_3), 55.5 (q, OCH_3), 54.9 (d, C-8'), 51.3 (d, C-7');

MS (ESI+) *m/z*, (%): 1067 (13, $[2M + Na]^+$), 545 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{30}H_{34}NaO_8$ 545.2146; found: 545.2134.

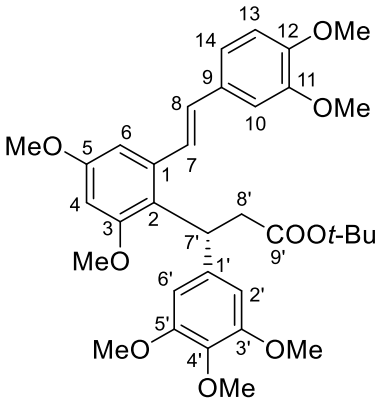
6.2. Part B

6.2.1. Direct conjugate addition of **136** to cinnamate **146**

Cinnamate **146** was prepared by cleavage of ketones **147a** and **147b**, see chapter 4.5.2 (table 28).

Under an inert atmosphere, dry toluene (2 mL) was added to a Schlenk flask containing stilbene **136** (45.4 mg, 0.15 mmol) and ligand (*R,R*)-**L1** (36.4 mg, 0.15 mmol). The stirred suspension was gently heated to fully dissolve the solids. The solution was cooled to –78 °C, followed by addition of *n*-BuLi (75 µL, 0.12 mmol, 1.6 M in hexanes). The mixture was stirred at –78 °C for 25 min. TMSCl (16 µL, 0.12 mmol) was added followed by a solution of cinnamate **146** (29.4 mg, 0.10 mmol) in toluene (0.5 mL). The reaction was stirred at –78 °C for 10 min, followed by warming to r.t. over 30 min. The reaction was quenched by saturated solution of KF in EtOH (0.2 mL), followed by filtration through a 4 cm silica plug (diameter 2.5 cm). The silica was washed with Et_2O (100 mL). The combined filtrates were concentrated and purified by flash chromatography (PE/EA 50: to 2:1) to yield 39.5 mg of **148** (66%) as a colourless film, 60% ee by chiral HPLC.

tert-Butyl (R,E)-3-[2-(3,4-dimethoxystyryl)-4,6-dimethoxyphenyl]-3-(3,4,5-trimethoxyphenyl)propanoate (**148**)



R_f 0.15 (hexane/EA 5:1);

^{1}H NMR (401 MHz, C_6D_6): δ 7.80 (d, *J* = 15.9 Hz, 1H, H-7), 7.05-7.00 (m, 3H, H-8, H-10, H-14), 6.91 (d, *J* = 2.5 Hz, 1H, H-4/6), 6.77 (d, *J* = 0.8 Hz, 2H, H-2', H-6'), 6.55 (d, *J* = 8.9 Hz, 1H, H-13), 6.46 (d, *J* = 2.5 Hz, 1H, H-4/6), 5.56 (t, *J* = 7.8 Hz, 1H, H-7'), 3.80 (s, 3H, C4'-OCH_3), 3.51 (s, 3H, C11/12-OCH_3), 3.44 (s, 3H, C3/5- OCH_3), 3.42 (s, 6H, C3'-OCH_3, C5'-OCH_3), 3.40-3.32 (m, 2H, H-8'), 3.39 (s, 3H, C11/12-OCH_3), 3.28 (s, 3H, C3/5-OCH_3), 1.30 (s, 9H, COOC(CH_3)$_3$);

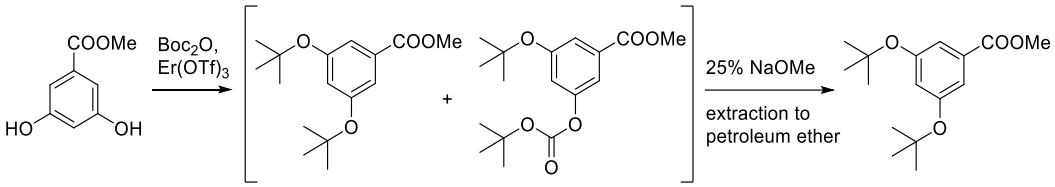
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 172.0 (s, C-9'), 160.0 (s, C-3/5), 159.8 (s, C-3/5), 154.0 (s, 2×C, C-3, C-5), 150.5 (s, C-11/12), 150.3 (s, C11/12), 140.4 (s, C-1/1'), 140.0 (s, C-1/1'), 137.9 (s, C-4'), 132.2 (d, C-8), 131.1 (s, C-9), 127.0 (d, C-7), 123.2 (s, C-1), 120.3 (d, C-14), 112.4 (d, C-13), 110.3 (d, C-10), 106.0 (d, 2×C, C-2', C-6'), 104.0 (d, C-4/6), 99.3 (d, C-4/6), 79.7 (s, O*C*(CH$_3$)$_3$), 60.5 (q, C4'-O*C*H$_3$), 55.9 (q, 2×C, C2'-O*C*H$_3$, C5'-O*C*H$_3$), 55.6 (q, 2×C, C11-O*C*H$_3$, C12-O*C*H$_3$), 55.2 (q, C3/5-O*C*H$_3$), 54.9 (q, C3/5-O*C*H$_3$), 40.6 (t, C-8'), 39.8 (d, C-7'), 28.1 (q, OC(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 1211 (100, [2M + Na]$^+$), 633 (100, [M + K]$^+$), 618 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{34}H_{42}O_9Na$ 617.2721; found: 617.2716.

6.2.2. Synthesis of *tert*-butyl protected isorhapontigenin **151**

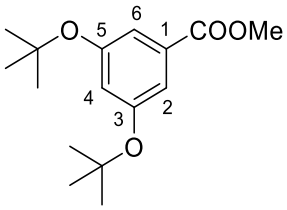
Etherification of methyl α-resorcylate



Step 1. Adapting a published method for etherification of alcohols by Boc_2O,[174,175] a 250 mL three-necked flask was charged with methyl α-resorcylate (8.07 g, 48 mmol) and Er(OTf)$_3$ (0.92 g, 1.5 mmol), equipped with a large stirring bar and a pressure equilibrating dropping funnel fitted to the central neck. Another neck was fitted with a 30 cm aspiring air condenser connected through a three-way tap to a vacuum pump and dry N_2 source. The remaining neck was closed with a stopper for access for TLC monitoring. The dropping funnel was charged with molten Boc_2O and sealed at the top. The reaction vessel was flushed with dry N_2 and heated to 35 °C and the first portion of Boc_2O (ca. 22 mL) was allowed to drip into the reaction. When the mixture became homogeneous, gas evolution started. The apparatus was evacuated, and the pressure was maintained at 75 mbar until bubbling ceased. Another portion of Boc_2O (22 mL) was added slowly, to avoid excessive foaming. Overall 6 portions of Boc_2O (135 mL, 588 mmol) were consumed. After bubbling ceased (~15 min), the pressure was raised to ambient pressure. The dark green glassy substance turned light pink on contact with air. TLC and NNR analysis showed this material consists mainly of the desired diether **152** (R_f 0.64, hexane/EA 5:1) together with intermediate mono-ether **152'** (R_f 0.21) and its tertbutyl carbonate (R_f 0.52).

Step 2. A solution of NaOMe (25%$_w$ in MeOH) was added to the crude material. The mixture was stirred for 10 min, transferred to a separatory funnel, and extracted with PE (350 mL). The PE layer was washed with MeOH (5 mL) and 2 portions of 5% aq. $NaHCO_3$ solution (2×50 mL), dried over Na_2SO_4, concentrated, and dried in high vacuum to yield 7.40 g (55%) of **152** as a viscous oil that solidified on standing. When seeded, the neat oil develops large (up to 15 mm) square prisms, mp 41 °C. Independent of scale, the reaction generally affords yields in the 47-61% range.

Methyl 3,5-di-tert-butoxybenzoate (**152**)



IR (film) $\tilde{\nu}$[cm^{-1}]: 2977 (m), 2934 (w), 2874 (w), 1724 (s), 1589 (m), 1473 (w), 1438 (m), 1391 (w), 1366 (m), 1318 (s), 1291 (m), 1258 (w), 1229 (s), 1170 (m), 1130 (vs), 1098 (w), 1035 (w), 1007 (s), 928 (w), 914 (w), 899 (w), 845 (w), 796 (m);

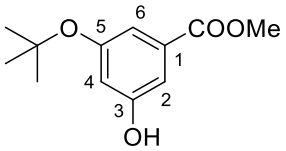
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.3 Hz, 2H, H-2, H-6), 6.84 (t, *J* = 2.2 Hz, 1H, H-4), 3.89 (s, 1H, OC*H*$_3$), 1.36 (s, 18H, OC(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.9 (s, *C*OOMe), 156.0 (s, C-3, C-5), 131.0 (s, C-1), 125.0 (d, C-4), 120.5 (d, C-2, C-6), 79.4 (s, O*C*(CH$_3$)$_3$), 52.3 (q, O*C*H$_3$), 29.0 (q, OC(*C*H$_3$)$_3$);

MS (EI+) *m/z*, (%): 280 (4, [M]$^{\bullet+}$), 249 (3, [M − MeO]$^{+}$), 224 (6, [M – isobutene]$^{\bullet+}$), 168 (100, [M – 2×isobutene]$^{\bullet+}$), 137 (26, [M – 2×isobutene – OMe]$^{+}$), 109 (4, [M – 2×isobutene – OMe – CO]$^{+}$);

HRMS (EI+) *m/z*: [M]$^{\bullet+}$ calcd. for $C_{16}H_{24}O_4$ 280.1675; found: 280.1676.

Methyl 3-(tert-butoxy)-5-hydroxybenzoate (**152'**)

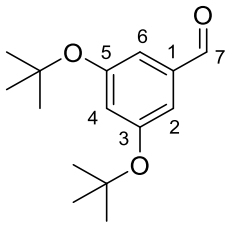


^{1}H NMR (401 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 2.4, 1.4 Hz, 1H, H-6), 7.24-7.22 (m, 1H, H-2), 6.73 (t, *J* = 2.3 Hz, 1H, H-4), 6.26 (m, 1H, OH), 3.89 (s, 3H, OC*H*$_3$), 1.35 (s, 9H, OC(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.4 (s, *C*OOMe), 156.7 (s, C-3/5), 156.6 (s, C-3/5), 131.4 (s, C-1), 117.5 (d, C-2), 116.3 (d, C-4), 111.9 (d, C-6), 79.7 (s, O*C*(CH$_3$)$_3$), 52.5 (q, O*C*H$_3$), 28.9 (q, OC(*C*H$_3$)$_3$).

3,5-Di-tert-butoxybenzaldehyde (**153**)

A solution of **152** (1.70 g, 6.06 mmol) in dry toluene (60 mL) was cooled to −78 °C under a dry N_2 atmosphere. Diisobutylaluminum hydride (8.5 mL, 8.5 mmol, 1 M in toluene) was added dropwise and the solution was stirred at −78 °C for 20 min. The reaction was stopped by addition of sat. solution of sodium potassium tartrate (50 mL) followed by stirring for 10 min. Water (20 mL) and PE (30 mL) were added, the layers were separated and the aqueous was extracted twice with a mixture of PE/Et_2O 10:1 (2×75 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to yield 1.47 g (95%) of a pale yellow crude oil. This oil was dissolved in DCM (100 mL) and passed through a 3×5 cm activated MnO_2 column. The collected solution was recycled on top of the column three times until there was only one spot on the TLC, indicating complete conversion of the benzyl alcohol side-product. Concentration provided 1.36 g (89%) of **153** as a colourless oil that solidified in the freezer. The soft solid melts over a wide temperature interval 23-43°C. The product contained 7% of the starting ester **152** and was used in the next step without purification.



R_f 0.25 (PE/Et_2O 20:1);

^1H NMR (401 MHz, $CDCl_3$): δ 9.90 (s, 1H, H-7), 7.23 (d, *J* = 2.3 Hz, 2H, H-2, H-6), 6.90 (t, *J* = 2.2 Hz, 1H, H-4), 1.37 (s, 18H, OC(CH_3)$_3$);

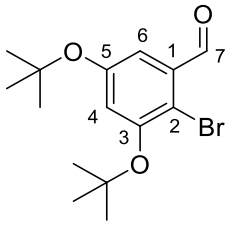
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.0 (d, C-7), 156.8 (s, C-3, C-5), 137.6 (s, C-1), 126.2 (d, C-4), 119.9 (d, C-2, C-6), 79.6 (s, 2×C, O*C*(CH_3)$_3$), 29.0 (q, 2×C, OC(*C*H_3)$_3$);

MS (EI+) *m/z*, (%): 250 (4, $[M]^{\bullet+}$), 235 (3, $[M - Me]^+$), 194 (20, $[M - isobutene]^+$), 179 (7, $[M - isobutene - Me]^+$), 138 (100, $[M - 2\times isobutene]^{\bullet+}$), 137 (37, $[M - isobutene - t\text{-}Bu]^+$), 109 (7, $[M - isobutene - t\text{-}Bu - CO]^+$), 57 (10, $[t\text{-}Bu]^+$);

HRMS (EI+) *m/z*: $[M]^{\bullet+}$ calcd. for $C_{15}H_{22}O_3$ 250.1569; found: 250.1570.

2-Bromo-3,5-di-tert-butoxybenzaldehyde (**154**)

A solution of *N*-bromosuccinimide (1.11 g, 6.23 mmol) in MeCN (25 mL) was added using a dropping funnel over 12 min to an ice-cooled stirred solution of aldehyde **153** (1.35 g, 5.41 mmol) in a mixture of MeCN (40 mL) and DCM (40 mL). After 30 min the cooling bath was removed, and the solution was stirred at r.t. overnight. The reaction mixture was partitioned between water (200 mL) and Et_2O (200 mL) and the aqueous layer was extracted with Et_2O (2×100 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by flash chromatography (5% Et_2O in PE) to yield 1.57 g of **154** (88%) as a colourless oil.



R_f 0.18 (PE/Et_2O 20:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2977 (m), 2934 (w), 2871 (w), 1691 (s), 1577 (m), 1459 (w), 1432 (w), 1391 (w), 1381 (w), 1366 (m), 1312 (s), 1258 (w), 1241 (w), 1168 (m), 1133 (vs), 1050 (w), 1017 (m), 900 (w), 837 (w), 766 (w), 705 (w);

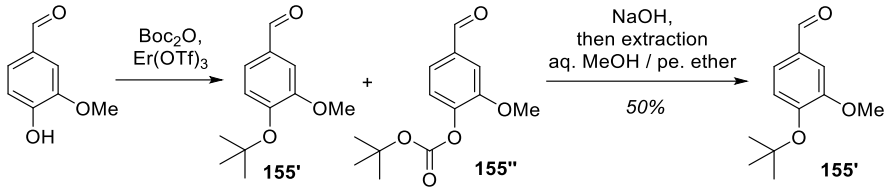
^1H NMR (401 MHz, $CDCl_3$): δ 10.39 (s, 1H, H-7), 7.28 (d, *J* = 2.8 Hz, 1H, H-6), 7.01 (d, *J* = 2.8 Hz, 1H, H-4), 1.47 (s, 9H, C3-OC(CH_3)$_3$), 1.37 (s, 9H, C5-OC(CH_3)$_3$);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.4 (d, C-7), 155.3 (s, C-5), 154.5 (s, C-3), 134.7 (s, C-1), 124.8 (d, C-6), 118.6 (d, C-4), 118.2 (s, C-2), 82.4 (s, C3-O*C*(CH_3)$_3$), 80.0 (s, C5-O*C*(CH_3)$_3$), 29.1 (q, OC(*C*H_3)$_3$), 28.9 (q, OC(*C*H_3)$_3$);

MS (ESI+) *m/z*, (%): 385/383 (50/53, $[M + Na + MeOH]^+$), 353/351 (100/97, $[M + Na]^+$);

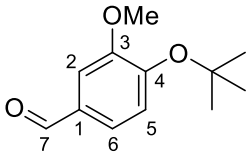
HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{21}{}^{79}BrNaO_3$ 351.0566; found: 351.0564.

Etherification of vanillin with basic workup



Following the method used for etherification of methyl α-resorcylate (preparation of **152**), vanilin (15.25 g, 100 mmol) was reacted with Boc_2O (137 mL, 0.6 mol) and erbium(III) triflate (2.1 g, 3.5 mmol). The reaction was stopped by addition of MeOH (140 ml) and water (20 ml). This methanolic solution was extracted with PE (6×120 ml) until no more product was detected by TLC in the MeOH phase. The combined PE extracts were dried over Na_2SO_4 and concentrated to yield 15.43 g of crude oil consisting of 2.6:1 mixture of the desired ether **155'** (10.5 g, 50%) and carbonate **155''** (4.9 g, 19%). Analytically pure samples of **155'** and **155'** were obtained by purification of a small portion of the material by flash chromatography (hexane/EA 9:1 to 4:1). The spectroscopic data matched those found in the lit.[252,253]

4-(tert-Butoxy)-3-methoxybenzaldehyde (**155'**)



R_f 0.52 (hexane/EA 5:1);

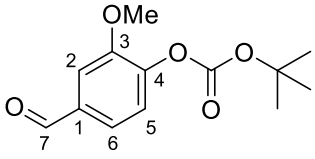
^{1}H NMR (401 MHz, $CDCl_3$): δ 9.88 (s, 1H, H-7), 7.41 (d, *J* = 1.9 Hz, 1H, H-2), 7.38 (dd, *J* = 8.0, 2.0 Hz, 1H, H-6), 7.14 (d, *J* = 8.1 Hz, 1H, H-5), 3.87 (s, 3H, OCH_3), 1.41 (s, 9H, OC(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 191.3 (d, C-7), 154.3 (s, C-3), 151.2 (s, C-4), 132.3 (s, C-1), 125.2 (d, C-6), 123.9 (d, C-5), 110.3 (d, C-2), 81.6 (s, O*C*(CH$_3$)$_3$), 55.9 (q, O*C*H$_3$), 28.8 (q, OC(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 439 (8, $[2M + Na]^+$), 231 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{16}NaO_3$ 231.0992; found: 231.0987.

tert-Butyl (4-formyl-2-methoxyphenyl) carbonate (**155''**)



R_f 0.43 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.95 (s, 1H, H-7), 7.50 (d, *J* = 1.8 Hz, 1H, H-2), 7.47 (dd, *J* = 8.0, 1.8 Hz, 1H, H-6), 7.30 (d, *J* = 8.0 Hz, 1H, H-5), 3.93 (s, 3H, OCH_3), 1.56 (s, 9H, OC(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 191.2 (d, C-7), 152.2 (s, C-3), 150.8 (s, O*C*OO*t*-Bu), 145.4 (s, C-4), 135.2 (s, C-1), 125.0 (d, C-6), 123.2 (d, C-5), 111.0 (d, C-2), 84.3 (s, O*C*(CH$_3$)$_3$), 56.3 (q, C3-O*C*H$_3$), 27.7 (q, OC(*C*H$_3$)$_3$);

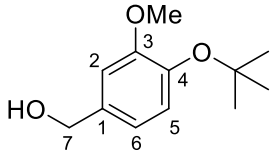
MS (ESI+) *m/z*, (%): 527 (58, $[2M + Na]^+$), 275 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{16}NaO_5$ 275.0889; found: 275.0886.

Etherification of vanillin with reductive workup

Following the method used for etherification of methyl α-resorcylate (preparation of **152**), vanillin (7.62 g, 50 mmol) was reacted with Boc_2O (92 mL, 0.4 mol) and erbium(III) triflate (0.9 g, 1.5 mmol). Instead of quenching with aqueous MeOH, the reaction mixture was dissolved in THF (40 mL). While maintaining good stirring, $NaBH_4$ (3.8 g, 0.1 mol) was added, followed by MeOH (40 mL) after 10 min. The mixture was stirred at r.t. until no starting material was detected by TLC. The solvents were stripped off under vacuum and sodium hydroxide solution ($10\%_w$, 150 mL) was added. The mixture was heated to reflux for 10 min, then toluene (150 mL) was added and the mixture was again heated to reflux for 2 min. After cooling, the layers were separated and the aqueous layer was extracted with fresh toluene (100 mL). The combined toluene extracts were dried over Na_2SO_4 and concentrated in vacuum to yield 8.03 g (76%) of **155** as a pale yellow oil, which was used in the next step without purification.

(4-(tert-Butoxy)-3-methoxyphenyl)methanol (**155**)



R_f 0.09 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3200 (br.), 2975 (m), 2934 (w), 2871 (w), 2839 (w), 1605 (w), 1584 (w), 1506 (m), 1464 (w), 1415 (w), 1389 (w), 1364 (m), 1262 (s), 1226 (w), 1170 (w), 1147 (vs), 1122 (s), 1035 (s), 881 (m), 855 (w), 826 (m), 733 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.0 Hz, 1H, H-5), 6.90 (d, *J* = 2.0 Hz, 1H, H-2), 6.79 (dd, *J* = 8.1, 2.0, Hz, 1H, H-6), 4.60 (s, 2H, H-7), 3.79 (s, 3H, O*CH*$_3$), 2.03 (br. s, 1H, OH), 1.33 (s, 9H, OC(*CH*$_3$)$_3$);

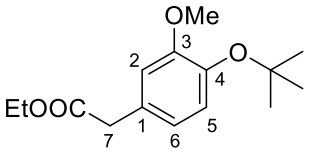
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.2 (s, C-3), 143.9 (s, C-4), 137.1 (s, C-1), 125.6 (d, C-5), 118.9 (d, C-6), 111.2 (d, C-2), 80.0 (s, O*C*(CH$_3$)$_3$), 65.3 (t, C-7), 55.7 (q, C3-O*C*H$_3$), 28.7 (q, OC(*C*H$_3$)$_3$);

MS (CI+) *m/z*, (%): 210 (15, $[M]^{\bullet+}$), 195 (13, $[M - Me]^+$), 154 (100, $[M - isobutene]^{\bullet+}$), 137 (38, $[M - isobutene - OH]^+$), 125 (17);

HRMS (CI+) *m/z*: $[M]^{\bullet+}$ calcd. for $C_{12}H_{18}O_3$ 210.1256; found: 210.1253.

Ethyl 2-(4-(tert-butoxy)-3-methoxyphenyl)acetate (**156**)

Following a modified published method, [254] benzyl alcohol **155** (8.0 g, 38 mmol), pyridine (9.2 mL, 114 mmol) and dimethylaminopyridine (232 mg, 1.9 mmol) were dissolved in a 1 L round-bottom flask in dry DCM (100 mL) and cooled to 0 °C. Ethyl chloroformate (4.6 mL, 48 mmol) was added dropwise. After at 20 min at 0 °C, sat. $NaHCO_3$ (200 mL), water (50 mL) and PE (350 mL) were added, the layers were separated and the aqueous was washed with PE (150 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and dried in high vacuum to yield 9.9 g (92%) of crude **156** as a colourless oil, that was used in the next step without further purification.



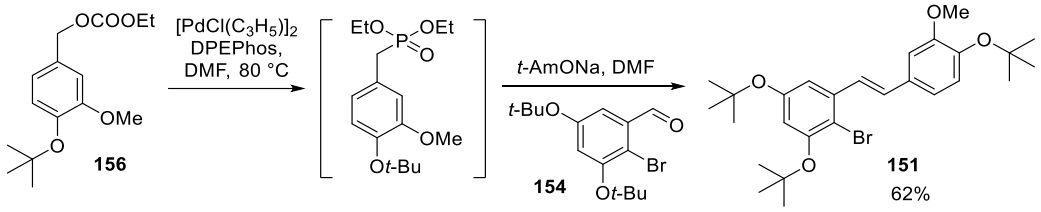
R_f 0.22 (hexane/EA 10:1), R_f 0.82 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.0 Hz, 1H, H-5), 6.90 (d, *J* = 2.1 Hz, 1H, H-2), 6.86 (dd, *J* = 8.0, 2.1 Hz, 1H, H-6), 5.08 (s, 2H, H-7), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.80 (s, 3H, C3-OCH_3), 1.33 (s, 9H, C4-$OC(CH_3)_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.2 (s, O*C*OOEt), 154.1 (s, C-3), 144.9 (s, C-4), 131.1 (s, C-1), 125.5 (d, C-5), 120.7 (d, C-6), 112.6 (d, C-2), 80.2 (s, C4-O*C*$(CH_3)_3$), 69.6 (t, C-7), 64.2 (t, O*C*H_2CH_3), 55.7 (q, C3-O*C*H_3), 28.7 (q, OC(*C*$H_3)_3$), 14.4 (q, OCH_2CH_3);

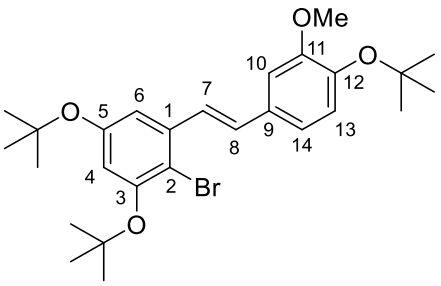
MS (ESI+) *m/z*, (%): 587 (23, $[2M + Na]^+$), 305 (100, $[M + Na]^+$).

Synthesis of stilbene 151 by one-pot Tsuji-Trost/HWE reaction



Following a modified published method,[176] allylpalladium(II) chloride dimer (7.3 mg, 0.02 mmol), DPEPhos (27 mg, 0.05 mmol) and diethyl phosphite (168 µL) were added to a solution of carbonate **156** (282 mg, 1 mmol) in dry DMF (1 mL). The reaction vessel was sealed and heated to 110 °C for 36 h. After cooling to r.t., a solution of aldehyde **154** (362 mg, 1.1 mmol) in DMF (0.5 mL) was added, followed by dropwise addition of *t*-AmONa (0.75 mL, 2.5 mmol, 40%$_w$ in toluene). The dark red reaction mixture was stirred overnight at r.t. under an inert atmosphere. The reaction mixture was partitioned between 5% Na_2CO_3 (100 mL) and PE (125 mL) and the aqueous layer was washed twice with PE (2×125 mL). The combined organic extracts were washed twice with water (2×20 mL), dried over Na_2SO_4 and concentrated in vacuum to give 508 mg of crude product, which was purified by flash chromatography (pure PE to 6:1 PE/EA) to yield 316 mg (62%) of **151** as a colourless amorphous solid. Increasing the scale to 4 mmol led to a drop in yield to 26%.

(E)-2-Bromo-1,5-di-tert-butoxy-3-[4-(tert-butoxy)-3-methoxystyryl]benzene (**151**)



R_f 0.15 (hexane/EA 10:1), R_f 0.75 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2975 (m), 2933 (w), 2872 (w), 2838 (w), 1571 (w), 1504 (w), 1462 (w), 1413 (w), 1389 (w), 1364 (m), 1334 (w), 1304 (w), 1259 (m), 1238 (w), 1136 (vs), 1124 (s), 1037 (w), 1014 (m), 959 (w), 887 (m), 833 (w), 822 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.40 (d, J = 16.1 Hz, 1H, H-7^E), 7.07 (dd, J = 2.0 Hz, 1H, H-10^E), 7.05 (dd, J = 8.1, 1.9 Hz, 1H, H-14^E), 7.01 (d, J = 2.8 Hz, 1H, H-6^E), 7.00 (d, J = 7.9 Hz, 1H, H-13^E), 6.89 (d, J = 16.1 Hz, 1H, H-8^E), 6.80 (d, J = 7.8, Hz, 1H, H-13^Z), 6.73 (d, J = 2.7 Hz, 1H, H-4^E), 6.67 (d, J = 2.7, 1H, H-6^Z), 6.65-6.62 (m, 2H, H-10^Z, H-14^Z), 6.59 (d, J = 2.7, 1H, H-4^Z), 6.58 (d, J = 11.8 Hz, 1H, H-7/8^Z), 6.54 (d, J = 12.0, 1H, H-7/8^Z), 3.87 (s, 3H, OCH_3^E), 3.57 (s, 3H, OCH_3^Z), 1.45 (s, 9H, OC(CH_3)$_3^E$), 1.45 (s, 9H, OC(CH_3)$_3^Z$), 1.38 (s, 9H, OC(CH_3)$_3^E$), 1.37 (s, 9H, OC(CH_3)$_3^E$), 1.30 (s, 9H, OC(CH_3)$_3^Z$), 1.17 (s, 9H, OC(CH_3)$_3^Z$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.63 (s, C-3/5^Z), 154.56 (s, C-3/5^E), 154.3 (s, C-11^E), 153.94 (s, C-3/5^Z), 153.88 (s, C-3/5^E), 153.6 (s, C-11^Z), 145.0 (s, C-12^E), 143.9 (s, C-12^Z), 139.7 (s, C-1^Z), 138.6 (s, C-1^E), 133.4 (s, C-9^E), 132.5 (s, C-1^Z), 131.3 (d, C-8^E), 130.8 (d, C-7/8^Z), 129.5 (d, C-7/8^Z), 127.5 (d, C-7^E), 125.7 (d, C-13^E), 125.2 (d, C-13^Z), 121.5 (d, C-14^Z), 120.8 (d, C-4^Z), 119.5 (d, C-14^E), 118.6 (d, C-4^E), 118.4 (d, C-6^Z), 117.2 (d, C-6^E), 115.6 (s, C-2^E), 113.9 (s, C-2^Z), 113.0 (d, C-10^Z), 110.5 (d, C-10^E), 81.7 (s, OC(CH$_3$)$_3^E$), 81.6 (s, OC(CH$_3$)$_3^Z$), 80.4 (s, OC(CH$_3$)$_3^E$), 80.1 (s, OC(CH$_3$)$_3^Z$), 79.3 (s, OC(CH$_3$)$_3^E$), 79.1 (s, OC(CH$_3$)$_3^Z$), 55.8 (q, OCH_3^E), 55.4 (q, OCH_3^Z), 29.2 (q, OC(CH$_3$)$_3^E$), 29.1 (q, OC(CH$_3$)$_3^Z$), 29.0 (q, OC(CH$_3$)$_3^E$), 28.9 (q, OC(CH$_3$)$_3^Z$), 28.8 (q, OC(CH$_3$)$_3^E$), 28.7 (q, OC(CH$_3$)$_3^Z$);

MS (EI+) *m/z*, (%): 506/504 (9, [M]$^{\bullet+}$), 450/448 (26, [M – isobutene]$^{\bullet+}$), 394/392 (23, [M–2×isobutene]$^{\bullet+}$), 338/336 (62, [M – 3×isobutene]$^{\bullet+}$), 313 (39, [M – 2×isobutene–Br]$^+$), 257 (100, [M – 3×isobutene – Br]$^+$), 225 (22), 197 (18), 57 (4, [*t*-Bu]$^+$);

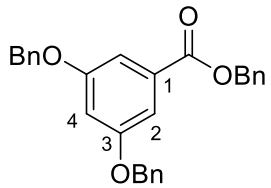
HRMS (EI+) *m/z*: [M]$^{\bullet+}$ calcd. for $C_{27}H_{37}{}^{79}BrO_4$ 504.1875; found: 504.1882.

6.2.3. Synthesis of **157**

Synthesis of 157 from α-resorcylic acid

Benzyl 3,5-bis(benzyloxy)benzoate (**158**)

BnBr (62.4 mL, 525 mmol) was added to a stirred suspension of 3,5-dihydroxybenzoic acid (15.4 g, 100 mmol) and K_2CO_3 (69.1 g, 500 mmol) in DMF (200 mL). The resulting mixture was vigorously stirred at r.t. overnight, followed by addition of DCM (200 mL) and filtration. The filtrate was concentrated and dried at 60 °C in high vacuum (nitrogen trap) for 5 h. Purification by flash chromatography (2.5% to 10% EA in PE) afforded 40.2 g of **158** (94%) as a colourless hard solid. Analytical data matched lit.[255]



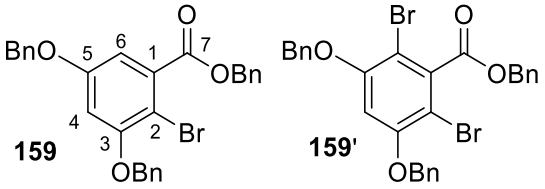
R_f 0.60 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.31 (m, 15H, Ph), 7.33 (d, J = 2.3 Hz, 2H, H-2), 6.81 (t, J = 2.3 Hz, 1H, H-4), 5.35 (s, 2H, COOCH_2Ph), 5.07 (s, 4H, C3-OCH_2Ph);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2 (s, *C*OOBn), 159.9 (s, C-3), 136.6 (s, Ph^{ipso}), 136.1 (s, Ph^{ipso}), 132.2 (s, C-1), 128.8 (d, Ph), 128.7 (d, Ph), 128.4 (d, Ph), 128.29 (d, Ph), 128.27 (d, Ph), 127.7 (d, Ph), 108.7 (d, C-2), 107.3 (d, C-4), 70.4 (t, C3-O*C*H_2Ph), 67.0 (t, COO*C*H_2Ph);

Benzyl 3,5-bis(benzyloxy)-2-bromobenzoate (**159**)

158 (40.2 g, 94.7 mmol) was dissolved in a mixture of MeCN (900 mL) and 250 ml DCM (250 mL). A solution of *N*-bromosuccinimide (19.4 g, 109 mmol) in MeCN (100 mL) was added dropwise with vigorous stirring using a dropping funnel over 20 min. After 1 h the solvent was removed under vacuum, the resulting solids were re-dissolved in DCM and the crude adsorbed on silica gel. Purification by two consecutive flash chromatography runs (3% to 10% EA in PE) afforded 44.3 g of a colourless hard solid, consisting of a 5:1 mixture of **159** and **159'**, corresponding to a yield of 33.6 g (70%) of **159** and 10.7 g (19%) of **159'**. The mixture was carried to the next step, in which only **159** undergoes reduction by DIBAL. Low selectivity during bromination of **158** leading to **159'** has been observed earlier.[256]



R_f 0.50 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49-7.31 (m, 15H, Ph), 6.95 (d, *J* = 2.8 Hz, 1H, H-6), 6.70 (d, *J* = 2.8 Hz, 1H, H-4), 5.39 (s, 2H, COOC*H*$_2$Ph), 5.12 (s, 2H, C3-OC*H*$_2$Ph), 5.02 (s, 2H, C5-OC*H*$_2$Ph);

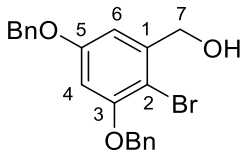
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 166.6 (s, *C*OOBn), 158.6 (s, C-5), 156.4 (s, C-3), 136.12 (s, Ph^{ipso}), 136.10 (s, Ph^{ipso}), 135.5 (s, Ph^{ipso}), 134.8 (s, C-1), 128.8 (d, 2×C, Ph), 128.74 (d, 2×C, Ph), 128.71 (d, Ph), 128.6 (d, Ph), 128.5 (d, Ph), 128.4 (d, Ph), 128.2 (d, Ph), 127.7 (d, 2×C, Ph), 127.1 (d, 2×C, Ph), 108.2 (d, C-6), 104.8 (d, C-4), 103.3 (s, C-2), 71.3 (t, C3-O*C*H_3), 70.6 (t, C5-O*C*H_3), 67.6 (t, COO*C*H_2Ph);

MS (ESI+) *m/z*, (%): 1031/1029/1027 (21, $[2M + Na]^+$), 543/541 (39, $[M + K]^+$), 527/525 (100, $[M + Na]^+$), 505/503 (19, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{28}H_{23}{}^{79}BrNaO_4$ 525.0672; found: 525.0671.

3,5-Bis(benzyloxy)-2-bromobenzyl alcohol (**160**)

A portion of the mixture of **159** and **159'** (12.4 g, corresponding to 20 mmol of **159**) was dissolved in dry THF (100 mL) and cooled to −78 °C. A solution of DIBAL (60 mL, 60 mmol, 1M in toluene) was added over 5 min. The mixture warmed to r.t over 30 min and stirred for additional 20 min. The reaction was quenched by slow addition of sat. sodium potassium tartrate solution followed by stirring for 15 min. Extraction into Et_2O (3×150 mL) followed by drying over Na_2SO_4, concentrated and purified by flash chromatography (pure PE to EA/PE 2:1) affording 9.57 g of colourless solid, mp = 84-85 °C, consisting of equimolar mixture of **160** and BnOH. Sonication in PE followed by filtration afforded 7.80 g of **160** (97%) as a colourless cottony solid, mp 111-112 °C.



R_f 0.25 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3150 (br.), 3088 (w), 3063 (w), 3031 (w), 2948 (w), 2919 (w), 2877 (w), 1590 (m), 1497 (w), 1452 (w), 1428 (m), 1373 (w), 1329 (w), 1281 (w), 1214 (w), 1165 (s), 1095 (w), 1058 (w), 1045 (w), 1010 (w), 967 (w), 905 (s), 824 (w), 813 (w), 753 (w), 731 (s), 695 (vs), 671 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.29 (m, 10H, Ph), 6.80 (d, J = 2.7 Hz, 1H, H-6), 6.56 (d, J = 2.7 Hz, 1H, H-4), 5.11 (s, 2H, OCH_2Ph), 5.04 (s, 2H, OCH_2Ph), 4.75 (s, 2H, H-7), 1.81 (br. s, 1H, OH);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.2 (s, C-5), 155.8 (s, C-3), 142.0 (s, C-1), 136.6 (s, Ph^{ipso}), 136.5 (s, Ph^{ipso}), 128.8 (d, Ph^{meta}), 128.7 (d, Ph^{meta}), 128.3 (d, Ph^{para}), 128.1 (d, Ph^{para}), 127.7 (d, Ph^{ortho}), 127.1 (d, Ph^{ortho}), 106.5 (d, C-6), 103.4 (s, C-2), 101.4 (d, C-4), 71.1 (t, OCH$_2$Ph), 70.5 (t, OCH$_2$Ph), 65.5 (t, C-7);

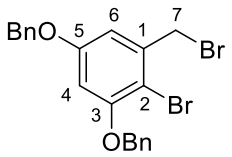
MS (ESI+) *m/z*, (%): 823/821/819 (12/41/12, [2M + Na]$^+$), 423/421 (100, [M + Na]$^+$), 401/399 (40, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{21}H_{19}BrO_3Na$ 421.0410; found: 421.0405; [M + H]$^+$ calcd. for $C_{21}H_{20}BrO_3$ 399.0590; found: 399.0589;

Anal. Calcd for $C_{21}H_{19}BrO_4$ (399.28): C, 63.17; H, 4.80; Br, 20.01. Found: C, 63.40; H, 4.73; Br, 19.91.

3,5-Bis(benzyloxy)-2-bromo-1-(bromomethyl)benzene (**161**)

Imidazole (2.72 g, 40 mmol) and PPh_3 (7.87 g, 30 mmol) were dissolved in dry DCM (100 mL) and the stirred solution was cooled to 0 °C. Bromine (1.5 mL, 30 mmol) was added dropwise, decoloration of each drop was observed (if the last few drops cause permanent coloration, a small amount of PPh_3 should be added until the color disappears). The solution was warmed to r.t. for 10 min, followed by cooling to 0 °C. A solution of benzyl alcohol **160** (7.98 g, 20 mmol) in dry DCM (100 mL) was added leading to the formation of copious precipitate. After 10 min, the reaction was warmed to r.t., followed by direct addition of silica gel to the mixture. The solvent was removed under vacuum and the solids were loaded on to a silica flash chromatography column. Elution with 2% EA in PE yielded 9.08 g (98%) of benzyl bromide **161** as a slowly crystallizing colourless solid, mp 84-85 °C.



R_f 0.45 (hexane/EA 11:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3064 (w), 3031 (w), 2868 (w), 1580 (m), 1497 (w), 1451 (w), 1428 (w), 1375 (w), 1326 (m), 1280 (w), 1239 (w), 1213 (w), 1163 (vs), 1082 (w), 1068 (m), 1020 (m), 954 (w), 907 (w), 830 (w), 733 (s), 694 (vs), 651 (w), 621 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.31 (m, 10H, Ph), 6.73 (d, J = 2.7 Hz, 1H, H-6), 6.56 (d, J = 2.7 Hz, 1H, H-4), 5.10 (s, 2H, OCH_2Ph), 5.02 (s, 2H, OCH_2Ph), 4.61 (s, 2H, H-7);

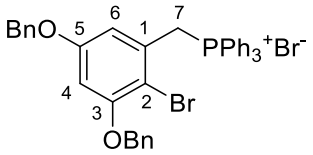
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 158.9 (s, C-5), 156.4 (s, C-3), 138.8 (s, C-1), 136.34 (s, Ph^{ipso}), 136.30 (s, Ph^{ipso}), 128.83 (d, Ph^{meta}), 128.76 (d, Ph^{meta}), 128.4 (d, Ph^{para}), 128.2 (d, Ph^{para}), 127.7 (d, Ph^{ortho}), 127.1 (d, Ph^{ortho}), 108.8 (d, C-6), 106.4 (s, C-2), 102.4 (d, C-4), 71.1 (t, O*C*H_2Ph), 70.6 (t, O*C*H_2Ph), 34.0 (t, C-7);

MS (ESI+) *m/z*, (%): 487/485/483 (37/100/42, $[M + Na]^+$), 465/463/461 (1/3/1, $[M + H]^+$), 393 (63); MS (APCI+) *m/z*, (%): 465/463/461 (37/100/42, $[M + H]^+$), 334/431 (17/17), 293/291 (59/61, [M + H – BnOH – Br]$^+$);

HRMS (ESI+) *m/z*: $[M + H]^+$ calcd. for $C_{21}H_{19}{}^{79}Br_2O_2$ 460.9746; found: 460.9746, *m/z*: $[M + Na]^+$ calcd. for $C_{21}H_{18}{}^{79}Br_2O_2Na$ 482.9566; found: 482.9562; HRMS (APCI+) *m/z*: $[M + H]^+$ calcd. for $C_{21}H_{19}{}^{79}Br_2O_2$ 460.9746; found: 460.9739.

[3,5-Bis(benzyloxy)-2-bromobenzyl]phosphonium bromide (**162**)

PPh_3 (10.3 g, 39.3 mmol) and **161** (9.08 g, 19.6 mmol) were dissolved in a mixture of dry THF (80 mL) and DCM (140 mL). The mixture was stirred under dry N_2 at ambient temperature overnight and heated to reflux for 1 h. The volume of the resulting slurry was reduced usinga rotary evaporator to ~1/4. PE (200 mL) and Et_2O (50 mL) were added, the solid was filtered off and washed with copious PE giving 13.9 g (97%) of **162** as a colourless powder, mp 218-220 °C.



IR (film) $\tilde{\nu}$[cm^{-1}]: 3036 (w), 2956 (w), 2838 (w), 2774 (w), 1587 (m), 1436 (m), 1391 (w), 1379 (w), 1336 (w), 1282 (w), 1265 (w), 1166 (m), 1110 (m), 1084 (w), 1068 (w), 1018 (w), 995 (w), 839 (w), 727 (vs), 689 (s), 618 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.77-7.56 (m, 15H), 7.36-7.21 (m, 10H), 6.86 (t, *J* = 2.6 Hz, 1H, H-6), 6.47 (t, *J* = 2.6 Hz, 1H, H-4), 5.55 (d, J_{CP} = 14.2 Hz, 2H, H-7), 4.99 (s, 2H, O*C*H_2Ph), 4.71 (s, 2H, O*C*H_2Ph);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 158.7 (s, $^{4}J_{CP}$ = 3.6 Hz, C-5), 155.9 (s, $^{4}J_{CP}$ = 3.3 Hz, C-3), 136.34 (s, Ph^{ipso}), 136.30 (s, Ph^{ipso}), 135.2 (d, $^{4}J_{CP}$ = 3.2 Hz, $PPh_3{}^{para}$), 134.4 (d, $^{2}J_{CP}$ = 10.0 Hz, $PPh_3{}^{ortho}$), 130.2 (d, $^{3}J_{CP}$ = 12.6 Hz, $PPh_3{}^{meta}$), 129.3 (s, $^{2}J_{CP}$ = 8.8 Hz, C-1), 128.6 (d, Bn^{meta}), 128.5 (d, Bn^{meta}), 128.10 (d, Bn^{para}), 128.09 (d, Bn^{ipso}), 127.9 (d, Bn^{ortho}), 126.9 (d, Bn^{ortho}), 117.5 (s, $^{1}J_{CP}$ = 85.8 Hz, $PPh_3{}^{ipso}$), 110.1 (d, $^{3}J_{CP}$ = 4.7 Hz, C-6), 108.9 (s, $^{3}J_{CP}$ = 6.8 Hz, C-2), 103.2 (d, $^{5}J_{CP}$ = 3.9 Hz, C-4), 70.8 (t, O*C*H_2Ph), 70.5 (t, O*C*H_2Ph), 31.3 (t, $^{1}J_{CP}$ = 48.3 Hz, C-7);

^{31}P NMR (162 MHz, $CDCl_3$) δ 23.17 (85 $\%_w$ H_3PO_4 standard);

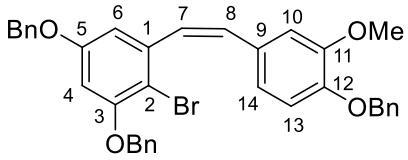
MS (ESI+) *m/z*, (%): 645/643 (100, $[M]^+$);

HRMS (ESI+) *m/z*: $[M]^+$ calcd. for $C_{39}H_{33}BrO_2P$ 643.1396; found: 643.1395.

(Z)-1,5-Bis(benzyloxy)-2-Bromo-3-(4-(benzyloxy)-3-methoxystyryl)benzene ((*Z*)-**157**)

Sodium *tert*-pentoxide solution (4.1 mL, 13.8 mmol, 40$\%_w$ in toluene) was added to a stirred suspension of phosphonium salt **162** (5.0 g, 6.9 mmol) and *O*-benzylvanilline (2.2 g, 8.9 mmol) in dry DMF (27 mL). The mixture spontaneously warmed to ~40 °C; intense red colour revealed the

formation of the ylide. The reaction vessel was sealed and stirred for 30 min, after which the red colour disappeared. DMF was stripped off under vacuum and the mixture was purified by flash chromatography (7% EA in cyclohexane) giving 3.82 g (91%) of (*Z*)-**157** as a colourless amorphous solid, as 1:1.2 *E*:*Z* mixture.



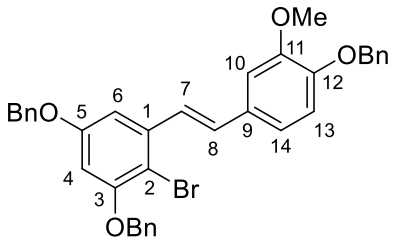
R_f 0.33 (hexane/EA 5:1);

Z isomer ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.50-7.22 (m, 15H, Ph), 6.73-6.68 (m, 3H, H-10, H-13, H-14), 6.58 (d, *J* = 12.1 Hz, 1H, H-7/8), 6.52 (d, *J* = 12.1 Hz, 1H, H-7/8), 6.51 (d, *J* = 2.7 Hz, H-4/6), 6.50 (d, *J* = 2.7 Hz, H-4/6), 5.13 (s, 2H, O*C*H_2Ph), 5.12 (s, 2H, O*C*H_2Ph), 4.76 (s, 2H, O*C*H_2Ph), 3.56 (s, 3H, OC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.5 (s, C-5), 156.1 (s, C-3), 149.0 (s, C-11), 147.7 (s, C-12), 140.3 (s, C-1), 137.2 (s, Bn^{ipso}), 136.54 (s, Bn^{ipso}), 136.53 (s, Bn^{ipso}), 131.0 (d, C-8), 139.7 (s, C-9), 127.73 (d, Bn^{meta}), 128.71 (d, Bn^{meta}), 128.67 (d, Bn^{meta}), 128.4 (d, C-7), 128.2 (d, Bn^{para}), 128.1 (d, Bn^{para}), 128.0 (d, Bn^{para}), 127.6 (d, Bn^{ortho}), 127.3 (d, Bn^{ortho}), 127.1 (d, Bn^{ortho}), 122.3 (d, C-14), 113.45 (d, C-10/13), 112.43 (d, C-10/13), 108.2 (d, C-6), 105.3 (s, C-2), 101.4 (d, C-4), 70.9 (t, 2×O*C*H_2Ph), 70.5 (t, O*C*H_2Ph), 55.7 (q, O*C*H_3).

(E)-1,5-Bis(benzyloxy)-2-Bromo-3-(4-(benzyloxy)-3-methoxystyryl)benzene ((*E*)-**157**)

Ph_2Se_2 (71 mg, 0.23 mmol) was added to a solution of (*E/Z*)-**157** (2.758 g, 4.54 mmol) in benzene (90 mL). The flask was evacuated until benzene started to boil gently, followed by flushing with dry N_2. The vacuum/N_2 cycle was repeated 7 times to remove dissolved molecular oxygen. The solution was irradiated by a high-power blue LED (450 nm) from a distance of 10 cm for 40 min. After removal of solvent in vacuum, the product was purified by flash chromatography (2% to 10% EA in cyclohexane) to yield 2.702 g (98%) of (*E*)-**157** as a colourless powder, mp 141-142 °C.



R_f 0.30 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3063 (w), 3031 (w), 2926 (m), 2869 (w), 1580 (s), 1510 (s), 1453 (m), 1423 (m), 1377 (m), 1348 (m), 1328 (m), 1289 (w), 1265 (s), 1224 (s), 1162 (vs), 1138 (s), 1082 (w), 1066 (m), 1020 (s), 956 (m), 911 (w), 845 (w), 825 (w), 799 (w), 734 (s), 695 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.51-7.28 (m, 16H, H-7, Ph), 7.11 (d, *J* = 2.0 Hz, 1H, H-10), 7.03 (dd, *J* = 8.4, 2.0 Hz, 1H, H-14), 6.91 (d, *J* = 15.8 Hz, 1H, H-8), 6.89 (d, *J* = 2.7 Hz, 1H, H-6), 6.88 (d, *J* = 8.3 Hz, 1H, H-13), 6.54 (d, *J* = 2.7 Hz, 1H, H-4), 5.19 (s, 2H, O*C*H_2Ph), 5.12 (s, 2H, O*C*H_2Ph), 5.07 (s, 2H, O*C*H_2Ph), 3.96 (s, 3H, OC*H*$_3$);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 158.7 (s, C-5), 156.1 (s, C-3), 149.9 (s, C-11), 148.6 (s, C-12), 139.1 (s, C-1), 137.1 (s, Bn^{ipso}), 136.7 (s, Bn^{ipso}), 136.6 (s, Bn^{ipso}), 131.6 (d, C-8), 130.7 (s, C-9), 128.8 (d, Bn^{meta}), 128.7 (d, 2×C, Bn^{meta}), 128.3 (d, Bn^{para}), 128.1 (d, Bn^{para}), 128.0 (d, Bn^{para}), 127.8 (d, Bn^{ortho}), 127.4 (d, Bn^{ortho}), 127.1 (d, Bn^{ortho}), 126.3 (d, C-7), 120.3 (d, C-14), 114.1 (d, C-13), 109.9 (d, C-10), 106.0 (s, C-2), 104.4 (d, C-6), 101.3 (d, C-4), 71.13 (t, O*C*H_2Ph), 71.08 (t, O*C*H_2Ph), 70.6 (t, O*C*H_2Ph), 56.2 (q, O*C*H_3);

MS (ESI+) *m/z*, (%): 1239/1237/1235 (11/8/6, $[2M + Na]^+$), 631/629 (100, $[M + Na]^+$), 609/607 (10, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{36}H_{31}{}^{79}BrNaO_4$ 629.1298; found: 629.1302;

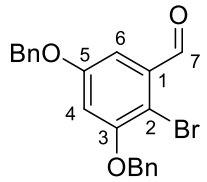
Anal. Calcd. for $C_{36}H_{31}BrO_4$ (607.54): C, 71.17; H, 5.14. Found: C, 71.15; H, 5.22.

Improved synthesis of (*E*)-157 by the Horner-Wadsworth-Emmons olefination

3,5-Bis(benzyloxy)-2-bromobenzaldehyde (**165**)

Following modified literature conditions,[257] 3,5-bis(benzyloxy)benzaldehyde (15.92 g, 50 mmol) was dissolved in MeCN (400 mL) and treated with NBS (13.35 g) at 0 °C. After the NBS dissolved, the bath was removed, and the solution was stirred a r.t. for 2 h leading to the formation of a significant amount of precipitate. A solution of ascorbic acid (50 g, 284 mmol) in water (200 mL) was added, the suspension was sonicated and let mature for 10 min. The solid was filtered, washed with water, and dried in vacuum to afford 20.15 g (quant.) of a colourless crystalline solid, mp 122 °C, containing 90% **165**, 4% of dibrominated product and 6% of unreacted starting material by ^{1}H NMR. This material was deemed sufficiently pure for use in the following step. Repeated runs on 1-50 mmol scale gave >90% yield of **165**, purity 90-98%.

Analytically pure material was obtained by recrystallization of a small sample from acetonitrile, mp 125-126 °C. The analytical data matched those found in the lit.[257]



R_f 0.40 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 10.43 (s, 1H, H-7), 7.50-7.31 (m, 10H, Ph), 7.16 (d, *J* = 2.8 Hz, 1H, H-6), 6.84 (d, *J* = 2.8 Hz, 1H, H-4), 5.15 (s, 2H, PhCH_2), 5.07 (s, 2H, PhCH_2);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 192.2 (s, C-7), 159.1 (s, C-3/5), 156.3 (s, C-3/5), 136.1 (s), 135.9 (s), 134.9 (s), 128.9 (d, Ph), 128.8 (d, Ph), 128.5 (d, Ph), 128.4 (d, Ph), 127.9 (d, Ph), 127.2 (d, Ph), 110.1 (a, C-2), 108.1 (d, C-4/6), 105.2 (d, C-4/6), 71.3 (t, PhCH_2), 70.7 (t, PhCH_2);

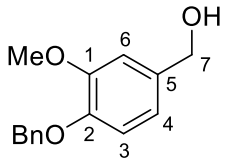
MS (ESI+) *m/z*, (%): 453/451 (81/85, $[M + MeOH + Na]^+$), 421/419 (25/31, $[M + Na]^+$), 413/411 (95/100, $[M + MeOH - OH]^+$), 399/397 (9/8, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{21}H_{17}O_3{}^{79}BrNa$ 419.0253; found: 419.0249, $[M + H]^+$ calcd. for $C_{21}H_{18}O_3{}^{79}Br$ 397.0434; found: 397.0433.

Synthesis of phosphonate 164 via Appel bromination/S_N2 substitution from 163

[4-(Benzyloxy)-3-methoxyphenyl]methanol (**163'**)

O-Benzylvanillin (24.2 g, 100 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. A solution of $LiAlH_4$ (20.8 mL, 50 mmol, 2.4 M in THF) was added at 0 °C over 3 min, followed by stirring for 20 min at 0 °C. The reaction was quenched by adding 10% NaOH (10 mL) dropwise at 0 °C. Additional 10% NaOH (140 mL) was added and the reaction mixture was stirred at r.t. for 30 min. Saturated sodium potassium tartrate (150 mL) and water (50 mL) were added and the product was extracted into a 1:1 toluene/Et_2O mixture (200 mL). The aqueous layer was extracted once again with 1:1 toluene/Et_2O mixture (200 mL). The combined organic layers were dried over Na_2SO_4, concentrated and dried under vacuum to afford 24.6 g (quant.) of **163'** as colourless crystals, mp 71-72 °C (lit. 66-74 °C).



R_f 0.37 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3200-3550 (broad), 3065 (w), 3033 (w), 3010 (w), 2931 (w), 2873 (w), 1608 (w), 1589 (w), 1511 (m), 1467 (m), 1456 (m), 1419 (m), 1383 (w), 1361 (w), 1329 (w), 1257 (m), 1233 (s), 1158 (s), 1133 (s), 1030 (s), 1002 (s), 915 (w), 854 (m), 800 (m), 790 (m), 735 (s), 715 (m), 694 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.41 (m, 2H, Ph), 7.39-7.34 (m, 2H, Ph), 7.33-7.27 (m, 1H, Ph-*para*), 6.95 (d, *J* = 1.9 Hz, 1H, H-6), 6.85 (d, *J* = 8.2 Hz, 1H, H-3), 6.83-6.79 (m, 1H, H-4), 5.16 (s, 2H, OC*H*$_2$Ph), 4.60 (s, 2H, H-7), 3.90 (s, 3H, OC*H*$_3$), 1.67 (s, 1H, OH);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.0 (s, C-1/2), 147.8 (s, C-1/2), 137.3 (s, C-5/Ph^{ipso}), 134.3 (s, C-5/Ph^{ipso}), 128.7 (d, Ph), 128.0 (d, Ph^{para}), 127.4 (d, Ph), 119.5 (d, C-4), 114.1 (d, C-3), 111.1 (d, C-6), 71.2 (t, OC*H*$_2$Ph), 65.4 (t, C-7), 56.1 (q, OC*H*$_3$);

MS (ESI+) *m/z*, (%): 267 (100, $[M + Na]^+$);

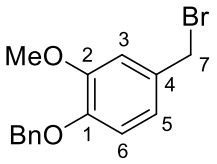
HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{16}O_3Na$ 267.0992; found: 267.099;

Anal. Calcd. for $C_{15}H_{16}O_3$ (244.29): C, 73.75; H, 6.60. Found: C, 73.68; H, 6.56.

1-(Benzyloxy)-4-(bromomethyl)-2-methoxybenzene (**163''**)

Imidazole (6.81 g, 100 mmol) and PPh_3 (19.7 g, 75 mmol) were dissolved in dry DCM (300 mL) and the stirred solution was cooled to 0 °C. Bromine (3.8 mL, 75 mmol) was added dropwise leading to a colourless solution. (If the last drops cause permanent brown coloration, a small amount of PPh_3 should be added until the color disappears). A solution of benzyl alcohol **163'** (12.2 g, 50 mmol) in dry DCM (200 mL) was added leading to the formation of a precipitate. After 10 min at 0 °C, the reaction was warmed to r.t. over 2 h. Saturated $NaHCO_3$ solution (50 mL) was added followed by water (200 mL). The layers were separated and the organic extract was dried over Na_2SO_4, concentrated and dried in high vacuum to afford 37.2 g of hard colourless solid containing a mixture of **163''** and triphenylphosphine oxide.

Purification of **163''** by chromatography on silica led to significant decomposition and yields below 60%. It was found that carrying the mixture of **163''** and TPPO forward into the next step affords significantly higher yield over two steps.



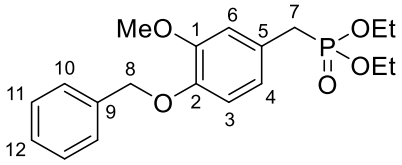
R_f 0.85 (hexane/EA 1:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.45-7.40 (m, 2H, Ph^{meta}), 7.38-7.35 (m, 2H, Ph^{ortho}), 7.34-7.26 (m, 1H, Ph^{para}), 6.93 (d, *J* = 2.1 Hz, 1H, H-3), 6.88 (dd, *J* = 8.2, 2.1 Hz, 1H, H-5), 6.81 (d, *J* = 8.2 Hz, 1H, H-6), 5.15 (s, 2H, OCH_2Ph), 4.48 (s, 2H, CH_2Br), 3.90 (s, 3H, OCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.8 (s, C-2), 148.5 (s, C-1), 137.0 (s, Ph^{ipso}), 130.8 (s, C-4), 128.7 (d, Ph^{meta}), 128.1 (d, Ph^{para}), 127.3 (d, Ph^{ortho}), 121.6 (d, C-5), 113.8 (d, C-6), 112.7 (d, C-3), 71.1 (t, OCH_2Ph), 56.2 (q, OCH_3), 34.5 (t, C-7).

Diethyl [4-(benzyloxy)-3-methoxybenzyl]phosphonate (**164**)

Diethyl phosphite (12.9 mL, 100 mmol) was added dropwise over 2 min to a suspension of sodium hydride 3.7 g (95 mmol, 60% in mineral oil) in THF (150 mL). The suspension was stirred overnight under inert atmosphere until the solids fully dissolved. In a separate flask, crude bromide **163''** (50 mmol) from the previous step was dissolved in dry THF (200 mL) and slowly added over 10 min via plastic cannula into a vigorously stirred solution of $NaPO(OEt)_2$. The mixture warmed to about 35-40 °C. After stirring for 5 h, saturated NH_4Cl solution (300 mL) was added followed by EA (500 mL). The layers were separated and the aqueous was extracted with additional EA (700 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and dried in vacuum. A mixture of cyclohexane (160 mL) and Et_2O (40 mL) was added, the resulting suspension was stirred for 30 min, allowed to stand for 4 h, and filtered. The solids were triturated with additional cyclohexane (160 mL) and Et_2O (40 mL) and filtered. The combined filtrates were concentrated and dried under vacuum to afford 17.2 g of crude phosphonate **164**, which was purified by flash chromatography (cyclohexane/EA 20:1 to pure EA) to yield 13.44 g of **164** (73% over 3 steps from **163**).



R_f 0.13 (Et_2O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3062 (w), 3033 (w), 2981 (w), 2934 (w), 2907 (w), 2873 (w), 2834 (w), 1591 (w), 1512 (m), 1454 (w), 1420 (w), 1389 (w), 1332 (w), 1241 (m), 1145 (w), 1052 (w), 1020 (vs), 959 (s), 938 (s), 857 (w), 798 (w), 736 (w), 721 (w), 696 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.46-7.40 (m, 2H, H-10), 7.49-7.35 (m, 2H, H-11), 7.34-7.29 (m, 1H, H-12), 6.91 (t, *J* = 2.3 Hz, 1H, H-6), 6.84 (d, *J* = 8.3 Hz, 1H, H-3), 6.77 (dt, *J* = 8.2, 2.4 Hz, 1H, H-2), 5.15 (s, 2H, H-8), 4.12-3.93 (m, 4H, OCH_2CH_3), 3.91 (s, 3H, OCH_3), 3.10 (d, $^2J_{HP}$ = 21.2 Hz, 2H, H-7), 1.26 (dd, *J* = 7.3, 6.9 Hz, 3H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.7 (s, $^4J_{CP}$ = 3.1 Hz, C-1), 147.3 (s, $^5J_{CP}$ = 3.7 Hz, C-2), 137.3 (s, C-9), 128.6 (d, C-11), 128.0 (d, C-12), 127.4 (d, C-10), 124.6 (s, $^2J_{CP}$ = 9.2 Hz, C-5), 122.0 (d, $^3J_{CP}$ = 7.6 Hz, C-4), 114.3 (d, $^4J_{CP}$ = 3.2 Hz, C-3), 113.56 (d, $^3J_{CP}$ = 5.9 Hz, C-6), 71.2 (t, C-8), 62.2 (t, $^2J_{CP}$

= 6.8 Hz, O*C*H$_2$CH$_3$), 56.1 (q, O*C*H$_3$), 32.7 (t, $^1J_{CP}$ = 139.0 Hz, C-7), 16.5 (q, $^3J_{CP}$ = 6.0 Hz, OCH$_2$*C*H$_3$);

^{31}P NMR (162 MHz, CDCl$_3$): δ 27.32 (85%$_w$ H$_3$PO$_4$ standard);

MS (ESI+) *m/z*, (%): 751 (3, [2M + Na]$^+$), 387 (47, [M + Na]$^+$), 365 (100, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{19}H_{26}O_5P$ 365.1512; found: 365.1512.

Preparation of (*E*)-157 by the Horner-Wadsworth-Emmons olefination

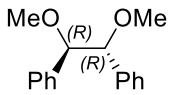
A round bottomed flask equipped with a large stirring bar was charged with phosphonate **164** (7.20 g, 19.8 mmol), aldehyde **165** (10.21 g, 25.7 mmol) and dry DMF (40 mL). A solution of sodium *tert*-pentoxide (11.9 mL, 40 mmol, 40% in toluene) was slowly added to the vigorously stirred suspension. During the addition all the solids dissolved leading to a brown solution. After 1 h, water (200 mL) was added, and the resulting heterogeneous mixture was stirred overnight followed by decantation. The liquid was discarded while the sticky solid was recrystallized from acetone (>50 mL) yielding 5.40 g of pure (*E*)-**157** (45%) as colourless crystalline solid in the first crop and 0.63 g (5%) in the second crop. The mother liquor was concentrated and purified by chromatography (silica, 0 to 20% EA in cyclohexane) to yield additional 4.87 g of (*E*)-**157** (42%). The spectroscopic data match (*E*)-**157** prepared by the Wittig olefination-photoisomerization route.

6.2.4. Synthesis of Li-specific ligands

Tomioka family of diethers

(1R,2R)-1,2-Dimethoxy-1,2-diphenylethane ((*R,R*)-**L01**)

A sealable pressure resistant flask was charged with (*1R,2R*)-1,2-diphenylethane-1,2-diol (4.74 g, 22.1 mmol), ground KOH (5.0 g, 89 mmol), DMSO (33 mL) and MeI (8.3 mL, 133 mmol). After sealing, the reaction mixture was heated to 60 °C overnight. During cooling a significant amount of precipitate formed from the dark brown solution. The mixture was partitioned between 5% Na_2SO_3 solution (200 mL) and Et_2O (200 mL) and the aqueous layer was extracted twice with Et_2O (2×100 mL). The combined extracts were dried over Na_2SO_4, concentrated in vacuum, and recrystallized from 1:1 Et_2O/PE. Three crops of crystals were harvested and combined to yield 4.16 g (77%) of (*R,R*)-**L01** as hard colourless needles, mp 98-99°C (lit. 99-100 °C). The spectroscopic data matched the lit.[258]



R_f 0.50 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3032 (w), 2984 (w), 2931 (w), 2862 (w), 2822 (w), 1492 (w), 1454 (w), 1265 (m), 1212 (w), 1182 (w), 1114 (m), 1091 (s), 1073 (w), 1027 (w), 985 (w), 963 (w), 833 (w), 765 (m), 734 (s), 699 (vs), 627 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 7.07-6.96 (m, 10H, Ph), 4.38 (s, 2H, PhC*H*), 3.16 (s, 6H, OC*H*$_3$);

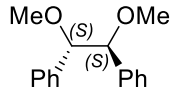
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 139.0 (s, *ipso*-Ph), 128.4 (d, *meta*-Ph), 127.9 (d, *ortho*-Ph), 127.7 (d, *para*-Ph), 87.9 (d, Ph*C*H), 57.2 (q, O*C*H$_3$);

MS (ESI+) *m/z*, (%): 507 (9, [2M + Na]$^+$), 265 (100, [M + Na]$^+$), 211 (40, [M + H – CH_3OH]$^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{16}H_{18}NaO_2$ 265.1199; found: 265.1201.

(1S,2S)-1,2-Dimethoxy-1,2-diphenylethane ((*1S,2S*)-**L01**)

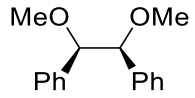
Prepared from (*1S*,*2S*)-1,2-diphenylethane-1,2-diol (536 mg, 2.5 mmol) using the same procedure as for its antipode (*R,R*-**L01**). Yield 426 mg (70%) after recrystallization form 1:1 Et_2O/PE mixture.



Colourless solid, crystal habit and spectroscopic data identical to (*R,R*-**L01**).

(1R,2S)-1,2-Dimethoxy-1,2-diphenylethane (*meso*-**L01**)

Prepared from (*1S*,*2R*)-1,2-diphenylethane-1,2-diol (536 mg, 2.5 mmol) using the same procedure as (*R,R*)-)**L01**. Purified by flash chromatography (pure cyclohexane to 30:1 cyclohexane/EA). Yield 498 mg (82%) as colourless crystals, mp 114 °C. Spectroscopic data matched lit.[259]



R_f 0.52 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3084 (w), 3060 (w), 3028 (w), 3000 (w), 2934 (m), 2886 (w), 2861 (m), 2821 (m), 1493 (w), 1465 (w), 1453 (w), 1434 (w), 1237 (w), 1198 (w), 1177 (m), 1103 (vs), 1070 (m), 1027 (w), 940 (s), 912 (w), 825 (w), 754 (s), 695 (vs), 615 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.32-7.26 (m, 6H, Ph^{ortho}, Ph^{para}), 7.19-7.16 (m, 4H, Ph^{meta}), 4.31 (s, 2H, PhC*H*), 3.16 (s, 6H, OCH_3);

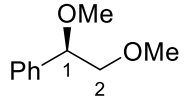
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.6 (s, Ph^{ipso}), 128.2 (d, Ph^{meta}), 128.0 (d, Ph^{ortho}), 127.8 (d, Ph^{para}), 87.1 (d, Ph*C*H), 57.3 (q, O*C*H_3);

MS (ESI+) *m/z*, (%): 265 (100, $[M + Na]^+$), 246 (9, $[M + H_2O + NH_3 – MeOH]$), 211 (26, $[M + H – MeOH]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{16}H_{18}NaO_2$ 265.1199; found: 265.1201.

(R)-[2-(Benzyloxy)-1-methoxyethyl]benzene ((*R*)-**L4**)

Prepared from (*R*)-1-phenylethane-1,2-diol (920 mg, 6.66 mmol) using the same procedure as for (*R,R*-**L1**). Purified by flash chromatography (pure cyclohexane to 20:1 cyclohexane/EA). Yield 994 mg (89%) as a light colourless oil with woody scent. The spectroscopic data matched the lit.[260]



R_f 0.25 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3063 (w), 3030 (w), 2981 (w), 2928 (m), 2883 (m), 2824 (m), 1493 (w), 1453 (m), 1355 (w), 1192 (m), 1131 (m), 1100 (vs), 1064 (m), 1029 (m), 974 (w), 937 (w), 868 (w), 827 (w), 758 (s), 700 (vs), 634 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 7.30-7.22 (m, 2H, *meta*-Ph), 7.19-7.13 (m, 2H, *ortho*-Ph), 7.09 (tt, *J* = 7.3, 1.4 Hz, 1H, *para*-Ph), 4.29 (dd, *J* = 7.4, 4.3 Hz, 1H, H-1), 3.56 (dd, *J* = 10.2, 7.3 Hz, 1H, H-2a), 3.35 (dd, *J* = 10.2, 4.3 Hz, 1H, H-2b), 3.12 (s, 3H, OCH_3), 3.11 (s, 3H, OCH_3);

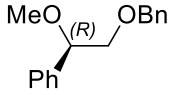
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 140.3 (s, *ipso*-Ph), 128.6 (d, *meta*-Ph), 128.0 (d, *para*-Ph), 127.4 (d, *ortho*-Ph), 83.7 (d, C-1), 77.8 (t, C-2), 58.9 (q, O*C*H$_3$), 56.9 (q, O*C*H$_3$);

MS (ESI+) *m/z*, (%): 189 (100, [M + Na]$^+$), 135 (56, [M − OMe]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{10}H_{14}NaO_2$ 189.0886; found: 189.0887.

(R)-[2-(Benzyloxy)-1-methoxyethyl]benzene ((*R*)-**L5**)

Pepared according to a known procedure [262] and generously donated by V. Chmela.

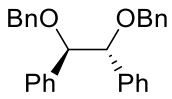


^{1}H NMR (401 MHz, $CDCl_3$): δ 7.12 (s, 1H, H-6),7.42-7.26 (m, 10H, Ph), 4.65 (d, *J* = 12.4 Hz, 1H, OCH_aH$_b$Ph), 4.53 (d, *J* = 12.4 Hz, 1H, OCH$_a$$H_b$Ph), 4.42 (dd, *J* = 8.0, 3.6 Hz, 1H, H-1), 3.67 (dd, *J* = 10.5, 8.0 Hz, 1H, H-2a), 3.51 (dd, *J* = 10.5, 3.6 Hz, 1H, H-2b), 3.31 (s, 3H, CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 139.2 (s, *ipso*-Ph), 138.3 (s, *ipso*-Ph), 129.2 (d), 128.9 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.1 (d), 83.3 (d, C-1), 74.8 (t, C-2), 73.6 (t, O*C*H$_2$Ph), 57.2 (q, O*C*H$_3$).

(1R,2R)-1,2-Bis(benzyloxy)-1,2-diphenylethane ((*R,R*)-**L6**)

Alkylation of (*1R*,*2R*)-1,2-diphenylethane-1,2-diol using BnBr and KOH in DMSO [258] gave a low yield as did the following conditions: BnBr, K_2CO_3 in DMF; BnBr, *t*-BuOK in DMSO. The best yield was obtained by treating (*1S*,*2S*)-1,2-diphenylethane-1,2-diol (214 mg, 1 mmol) with *t*-BuOK (730 mg, 6.5 mmol) and BnBr (7.1 mL, 6 mmol) in dry THF (5 mL) at 70 °C overnight in a sealed vessel. After cooling to r.t., brine (30 mL) and water (20 mL) were added, and the mixture was extracted with Et_2O (100 mL). Drying over Na_2SO_4, concentration under vacuum followed by flash chromatography (1.2% Et_2O in cyclohexane) afforded 281 mg (71%) of (*R,R*)-**L6** as a colourless soft solid, mp 43 °C. The spectroscopic data matched those found in the lit.[258]



IR (film) $\tilde{\nu}$[cm^{-1}]: 3086 (w), 3062 (w), 3029 (w), 2863 (w), 1495 (w), 1452 (m), 1390 (w), 1347 (w), 1310 (w), 1273 (w), 1202 (w), 1087 (m), 1066 (m), 1026 (m), 911 (w), 841 (w), 767 (w), 733 (s), 694 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.32-7.18 (m, 16H, Ph), 7.14-7.05 (m, 4H, *para*-Ph), 4.60 (s, 2H, PhC*H*OBn), 4.58 (d, *J* = 12.3 Hz, 2H, OCH_2Ph), 4.39 (d, *J* = 12.2 Hz, 2H, OCH_2Ph);

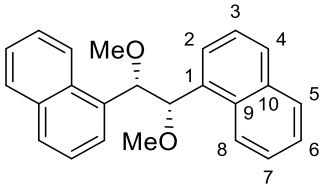
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.73 (s, *ipso*-Ph), 138.70 (s, *ipso*-Ph), 128.3 (d, Ph), 128.1 (d, Ph), 127.9 (d, Ph), 127.7 (d, *para*-Ph), 127.6 (d, Ph), 127.4 (d, *para*-Ph), 85.2 (d, PhC*H*OBn), 71.0 (t, OCH_2Ph);

MS (ESI+) *m/z*, (%): 417 (100, [M + Na]$^+$), 417 (100, [M − OBn]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{28}H_{26}NaO_2$ 417.1825; found: 417.1823.

(1S,2S)-1,2-Dimethoxy-1,2-di(naphthalen-1-yl)ethane ((*S,S*)-**L8**)

Prepared from *(1S,2S)*-1,2-di(naphthalen-1-yl)ethane-1,2-diol (250 mg, 0.8 mmol) using the same procedure as for (*R,R*-**L1**). Purified by flash chromatography (pure cyclohexane to 30:1 cyclohexane/EA). Yield 270 mg (>95%) as colourless microcrystalline solid, mp 114 °C. Spectroscopic data match lit.[261]



R_f 0.34 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3047 (w), 2980 (w), 2927 (w), 2820 (w), 1596 (w), 1509 (w), 1446 (w), 1393 (w), 1336 (w), 1228 (w), 1198 (w), 1165 (w), 1108 (m), 1090 (s), 1020 (w), 964 (m), 883 (w), 860 (w), 780 (m), 774 (vs), 733 (m), 625 (w);

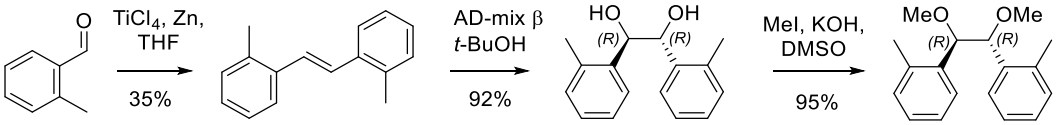
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 2H, H-8), 7.67 (d, *J* = 8.1 Hz, 2H, H-5), 7.54 (d, *J* = 8.1 Hz, 2H, H-4), 7.34 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 2H, 6), 7.27 (t, *J* = 6.2 Hz, 2H, H-7), 7.21-7.14 (m, 4H, H-2, H-3), 5.35 (s, 2H, C*H*OMe), 3.33 (s, 6H, OCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 134.1 (s, C-9/10), 133.7 (s, C-9/10), 131.7 (s, C-1), 128.6 (d, C-5), 128.4 (d, C-4), 126.7 (br. d, C-2), 125.6 (d, C-3), 125.2 (d, C-7), 124.8 (d, C-6), 123.9 (br. d, C-8), 85.8 (br. d, *C*HOMe), 57.3 (q, O*C*H$_3$);

MS (ESI+) *m/z*, (%): 707 (6, [2M + Na]$^+$), 365 (100, [M + Na]$^+$), 311 (11, [M − OMe]$^+$), 279 (10, [M − 2MeOH + H]$^+$);

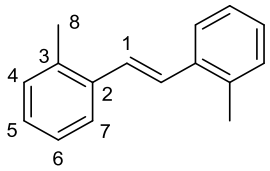
HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{24}H_{22}NaO_2$ 365.1512; found: 365.1510.

Preparation of (*R,R*)-**L7**



Step 1. Following a published procedure,[261] *o*-tolualdehdye (3.6 g, 30 mmol) was reduced using $TiCl_4$ (4.9 mL, 45 mmol) and zinc dust (5.9 g, 90 mmol) in THF (300 mL). Recrystallization from MeOH yielded 2.53 g (40%) of solid material, that was dissolved in benzene (50 mL) and treated with Ph_2Se_2 (75 mg, 0.24 mmol). The solution was degassed by 5 cycles of alternating vacuum (150 mbar) and N_2 purging and irradiated with a blue LED (450 nm) for 20 min. Concentration under vacuum followed by flash chromatography in cyclohexane and recrystallization from PE yielded 1.1 g (35%) of stilbene **L7'** as colourless solid, mp 81-82 °C (lit. 81-82 °C).

(E)-1,2-Di-o-tolylethene (**L7'**)



R_f 0.45 (PE);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3049 (w), 2974 (w), 2926 (w), 2862 (w), 1491 (w), 1461 (w), 1264 (m), 962 (m), 895 (), 757 (w), 734 (vs), 721 (s), 703 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.0 Hz, 2H, H-4/7), 7.25-7.18 (m, 6H), 7.21 (s, 2H, H-1), 2.43 (s, 6H, H-8);

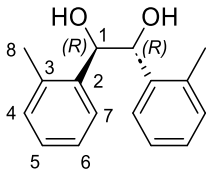
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 137.0 (s, C-2/3), 136.0 (s, C-2/3), 130.5 (d), 128.1 (d), 127.7 (d), 126.3 (d), 125.7 (d, C-4/7), 20.1 (q, C-8);

MS (ESI+) *m/z*, (%): 208 (100, $[M]^{\cdot+}$), 193 (67, $[M - Me]^+$);

HRMS (APCI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{16}H_{16}$ 208.1247; found: 208.1246.

Step 2. Following a published procedure,[261] **L7'** (520 mg, 2.5 mmol) was dihydroxylated using K_2CO_3 (1.73 g, 12.5 mmol), $K_3Fe(CN)_6$ (4.12 g, 12.5 mmol), $(DHQD)_2PHAL$ (88 mg, 0.11 mmol), $K_2OsO_4 \cdot (H_2O)_2$ (9 mg, 0.03 mmol) and methanesulfonamide (380 mg, 4 mmol) in water/*tert*-BuOH (30 mL, 1:1). Purification by flash chromatography (cyclohexane/EA 50:1 to 1:1) yielded 562 mg (92%) of **L7''** as colourless crystals, mp 111-112°C. The spectroscopic data matched the lit.[261]

(1R,2R)-1,2-Di-o-tolylethane-1,2-diol (**L7''**)



R_f 0.10 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3200 (broad), 3061 (w), 3024 (w), 2930 (w), 1490 (m), 1461 (m), 1378 (w), 1304 (w), 1261 (w), 1197 (m), 1181 (m), 1115 (w), 1041 (s), 1004 (m), 844 (w), 792 (w), 761 (s), 728 (m), 637 (w), 620 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 7.8, 1.5 Hz, 2H, H-4/7), 7.23 (td, *J* = 7.5, 1.4 Hz, 2H, H-5/6), 7.15 (td, *J* = 7.4, 1.5 Hz, 2H, H-5/6), 6.95 (dd, *J* = 7.5, 1.3, 2H, H-4/7), 5.02 (s, 2H, H-1), 2.89 (s, 2H, OH), 1.70 (s, 6H, H-8);

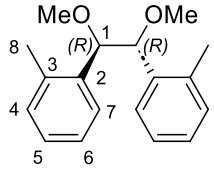
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.1 (s, C-2/3), 136.0 (s, C-2/3), 130.3 (d, C-4/7), 127.9 (d, C-5/6), 127.3 (d, C-4/7), 126.1 (d, C-5/6), 74.8 (d, C-1), 18.9 (q, C-8);

MS (ESI+) *m/z*, (%): 265 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{16}H_{18}NaO_2$ 265.1199; found: 265.1199.

Step 3. Diol (*R,R*)-**L7''** (1.45 mg, 6 mmol) was alkylated using the same procedure as for (*R,R*-**L1**). Purified by flash chromatography (pure cyclohexane to 20:1 cyclohexane/EA). Yield 1.55 mg of (*R,R*)-**L7** (95%) as colourless crystals, mp 92-93 °C.

(1R,2R)-1,2-Dimethoxy-1,2-di-o-tolylethane (**L7**)



R_f 0.41 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3051 (w), 2982 (w), 2930 (w), 2898 (w), 2822 (w), 1489 (w), 1461 (w), 1265 (m), 1209 (w), 1181 (w), 1114 (m), 1086 (m), 1051 (w), 988 (w), 962 (w), 840 (w), 761 (w), 728 (vs), 703 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.7, 1.6 Hz, 2H, H-4/7), 7.14 (td, *J* = 7.4, 1.3 Hz, 2H, H-5/6), 7.08 (td, *J* = 7.4, 1.6 Hz, 2H, H-5/6), 6.88 (ddt, *J* = 7.4, 1.4, 0.7 Hz, 2H, H-4/7), 4.67 (s, 2H, H-1), 3.23 (s, 6H, OC*H*$_3$), 1.79 (s, 6H, H-8);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 137.2 (s, C-2/3), 136.2 (s, C-2/3), 130.1 (d), 128.2 (d), 127.6 (d), 125.8 (d), 83.3 (d, C-1), 56.7 (d, O*C*H$_3$), 19.1 (q, C-8);

MS (ESI+) *m/z*, (%): 563 (35, [2M + Na]$^+$), 293 (100, [M + Na]$^+$), 239 (49, [M + H – MeOH]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{56}H_{62}NaO_{10}Si$ 293.1512; found: 293.15.1515;

α_D^{20} = −14.4 (c 0.662, MeOH).

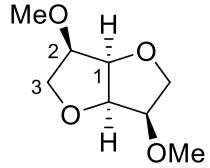
Dianhydrosugar-derived ethers and miscellaneous diethers

Dimethyl isosorbide (**L9**) was purchased from Merck KGaA (Sigma-Aldrich) in >99% purity, used as received.

(R)-(+)-2,2'-Dimethoxy-1,1'-binaphthalene (**L12**) was purchased from Merck KGaA (Sigma-Aldrich) in >97% purity, used as received.

Dimethyl isomannide (**L10**)

Prepared from 1,4:3,6-dianhydro-*D*-mannitol (isomannide, 2.0 g, 13.7 mmol) using the same procedure as for (*R,R*-**L1**). Purified by flash chromatography (5:1 cyclohexane/EA to pure EA) and recrystallization from Et_2O yielded 1.69 g (71%) of **L10** as large colourless sugar-like crystals, mp 75-76 °C (lit. 75-76 °C). The spectroscopic data matched the lit.[263]



R_f 0.25 (Et_2O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3056 (w), 2984 (w), 2945 (m), 2880 (m), 2833 (w), 1465 (w), 1448 (w), 1386 (w), 1310 (w), 1270 (w), 1219 (m), 1140 (m), 1106 (m), 1082 (s), 1027 (m), 998 (m), 969 (m), 858 (w), 821 (w), 730 (vs), 700 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 4.61-4.58 (m, 2H, H-1), 4.07 (dd, *J* = 8.5, 6.9 Hz, 2H, H-3a), 3.97-3.89 (m, 2H, H-2), 3.69 (t, *J* = 8.5 Hz, 2H, H-3b), 3.46 (s, 6H, OC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 82.0 (d, C-2), 80.3 (d, C-1), 71.0 (t, C-3), 58.4 (q, O*C*H$_3$);

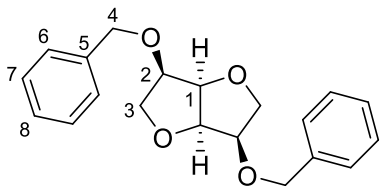
MS (ESI+) *m/z*, (%): 197 (100, $[M + Na]^+$), 175 (12, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_8H_{14}O_4Na$ 197.0784; found: 197.0783;

α_D^{20} = +176.1 (c 0.444, $CHCl_3$).

Dibenzyl isomannide (**L11**)

Prepared from 1,4:3,6-dianhydro-*D*-mannitol (2.92 g, 20 mmol) by heating with K_2CO_3 (13.8 g, 100 mmol), Cs_2CO_3 (1.3 g, 4 mmol), BnBr (12 mL, 100 mmol) and TBAI (0.74 g, 2 mmol) in DMF (20 mL) at 90 °C for 2 days. After cooling, the mixture was partitioned between 1 N NaOH (100 mL) and Et_2O (150 mL), the organic layer was dried over Na_2SO_4 and concentrated to yield 6.2 g of a crude mixture containing **L11** together with significant amount of BnOH and Bn_2O, which proved difficult to separate. Purification by column chromatography (cyclohexane/EA) yielded 459 mg (7%) of the title compound. Colourless solid, mp 66.0-66.5 °C.



R_f 0.58 (Et_2O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3067 (w), 3031 (w), 2988 (w), 2940 (w), 2919 (w), 2879 (m), 1498 (w), 1454 (w), 1402 (w), 1366 (w), 1339 (w), 1308 (w), 1215 (w), 1123 (s), 1085 (m), 1026 (m), 998 (w), 944 (w), 919 (w), 795 (w), 748 (s), 699 (s), 625 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.38-7.27 (m, 10H, Ph), 4.73 (d, *J* = 12.0 Hz, 2H, H-4a), 4.56 (d, *J* = 12.0 Hz, 2H, H-4b), 4.54-4.50 (m, 2H, H-1), 4.07 (tdd, *J* = 8.4, 3.4, 1.5 Hz, 2H, H-2), 4.00 (dd, *J* = 8.5, 7.0 Hz, 2H, H-3a), 3.75 (t, *J* = 8.4 Hz, 2H, H-3b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 137.9 (s, C-5), 128.6 (d, C-6/7), 128.1 (d, C-6/7), 128.0 (d, C-8), 80.6 (d, C-1), 79.5 (d, C-2), 72.6 (t, C-4), 71.3 (t, C-3);

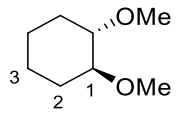
MS (ESI+) *m/z*, (%): 675 (11, $[2M + Na]^+$), 349 (100, $[M + Na]^+$), 327 (7, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{20}H_{22}NaO_4$ 349.1410; found: 349.1408;

α_D^{20} = +156.1 (c 0.451, $CHCl_3$).

(1S,2S)-1,2-Dimethoxycyclohexane (**L13**)

Prepared from (*1S,2S*)-*trans*-1,2-cyclohexanediol (1.0 g, 8.6 mmol, Sigma-Aldrich, >99% ee) using the same procedure as for (*R,R*-**L1**). Purified by flash chromatography (5:1 pentane/Et_2O). Yield 505 mg L (40%) of (*S,S*)-**L13** as a volatile colourless oil. The spectroscopic data matched those in the lit.[264]



R_f 0.42 (pentane/Et_2O 5:1);

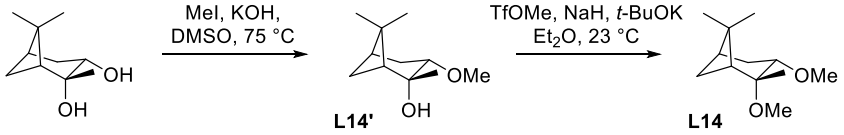
IR (film) $\tilde{\nu}$[cm^{-1}]: 2930 (m), 2861 (w), 2820 (w), 1452 (w), 1381 (w), 1192 (w), 1143 (m), 1097 (vs), 1027 (w), 961 (w), 907 (w), 891 (w), 843 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 3.42 (s, 6H, OCH_3), 3.15-3.03 (m, 2H, H-1), 2.08-1.95 (m, 2H, H-2a), 1.75-1.58 (m, 2H, H-3a), 1.34-1.08 (m, 4H, H-2b, H-3b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 82.5 (d, C-1), 57.2 (q, OCH$_3$), 29.3 (t, C-2), 23.6 (t, C-3);

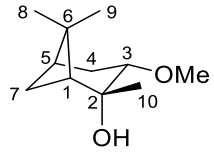
MS (ESI+) *m/z*, (%): 183 (14, $[M + K]^+$).

Preparation of L14



Step 1. (*1R,2R,3S,5R*)-(−)-pinanediol (1.33 g, 7.8 mmol) was heated with KOH (2.63 g, 46.9 mmol) and MeI (3.9 mL, 62.5 mmol) in DMSO (12 mL) to 75 °C for 16 h in a sealed pressure-resistant flask. After cooling, the mixture was partitioned between saturated Na_2SO_4 (40 mL) and Et_2O (50 mL), the organic layer was dried over Na_2SO_4 and concentrated to yield 1.42 g (98%) of **L14'** as a colourless oil.

(1R,2R,3S,5R)-3-Methoxy-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (**L14'**)



R_f 0.51 (pentane/Et_2O 2:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3400 (br.), 2982 (m), 2910 (s), 2826 (w), 1471 (w), 1448 (w), 1368 (w), 1338 (w), 1162 (w), 1124 (m), 1094 (s), 1018 (w), 984 (m), 949 (w), 937 (m), 901 (m), 865 (w), 813 (w), 747 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 3.67 (s, 1H, OH), 3.52 (dd, J = 9.2, 5.1 Hz, 1H, H-3), 3.46 (s, 3H, C3-OCH_3), 2.38 (dddd, J = 13.4, 9.2, 3.6, 2.4 Hz, 1H, H-4a), 2.17 (dtd, J = 10.4, 6.0, 2.4 Hz, 1H, H-7a), 1.96-1.88 (m, 2H, H-1, H-5), 1.65 (ddd, J = 13.8, 5.1, 2.5 Hz, 1H, H-4b), 1.39 (d, J = 10.4 Hz, 1H, H-7b), 1.30 (s, 3H, H-10), 1.26 (s, 3H, H-8/9), 0.97 (s, 3H, H-8/9);

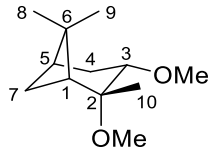
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 79.0 (d, C-3), 73.4 (s, C-2), 58.3 (q, C3-OCH$_3$), 54.0 (d, C-1), 40.4 (d, C-5), 38.5 (s, C-6), 35.1 (t, C-4), 31.1 (q, C-8/9), 28.3 (t, C-7), 28.0 (q, C-8/9), 24.4 (q, C-10);

MS (ESI+) *m/z*, (%): 207 (100, $[M + Na]^+$), 135 (5, $[M + H – H_2O – MeOH]^+$), 109 (4);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{20}NaO_2$ 207.1356; found: 207.1355.

Step 2. A solution of **L14'** (882 mg, 4.79 mmol) in Et_2O (10 mL) was added to a suspension of NaH (345 mg, 7.18 mmol, 50%$_w$ in oil) in Et_2O (10 mL). A catalytic amount of KO*t*-Bu was added, followed by heating to reflux for 20 min. After cooling to 0 °C, TfOMe (785 µL, 7.18 mmol) was added dropwise, followed by stirring at r.t. for 3 h. The mixture was partitioned between 0.5 M NaOH (50 mL) and Et_2O (120 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification by flash chromatography (pentane/Et_2O 10:1 to 2:1) yielded 480 mg of **L14** (50%) as a light colourless odourless oil.

(1R,2R,3S,5R)-2,3-Dimethoxy-2,6,6-trimethylbicyclo[3.1.1]heptane (**L14**)



R_f 0.30 (pentane/Et_2O 2:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2973 (m), 2907 (s), 2822 (w), 1466 (w), 1451 (w), 1387 (w), 1366 (m), 1333 (w), 1276 (w), 1240 (w), 1199 (w), 1160 (w), 1120 (s), 1087 (vs), 1062 (m), 987 (w), 930 (w), 875 (w), 858 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 3.70 (dd, *J* = 9.2, 6.8 Hz, 1H, H-3), 3.45 (s, 3H, C3-OC*H*$_3$), 3.14 (s, 3H, C2-OC*H*$_3$), 2.40 (dddd, *J* = 13.4, 9.2, 4.2, 2.2 Hz, 1H, H-4a), 2.15-2.07 (m, 2H, H-1, H-7a), 1.95 (tdd, *J* = 5.9, 4.0, 2.1 Hz, 1H, H-5), 1.74 (ddd, *J* = 13.5, 6.7, 2.1 Hz, 1H, H-4b), 1.47 (d, *J* = 9.4 Hz, 1H, H-7b), 1.31 (s, 3H, H-10), 1.28 (s, 3H, H-8/9), 0.97 (s, 3H, H-8/9);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 80.6 (d, C-3), 77.9 (s, C-2), 58.4 (q, C3-O*C*H$_3$), 51.2 (d, C-1), 49.1 (q, C2-O*C*H$_3$), 40.2 (d, C-5), 38.3 (s, C-6), 35.1 (t, C-4), 28.7 (q, C-8/9), 28.0 (t, C-7), 24.2 (q, C-8/9), 24.1 (q, C-10);

MS (ESI+) *m/z*, (%): 419 (24, $[2M + Na]^+$), 221 (100, $[M + Na]^+$), 167 (26, $[M - OMe]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{22}NaO_2$ 221.1512; found: 221.1512;

$\alpha_D^{20} = -5.6$ (c 0.514, $CHCl_3$).

Nitrogen-based ligands

(+)-Sparteine, (+)-pachycarpine ((+)-**L2**) was purchased from Fluorochem Limited (UK) in >98% purity, used as received.

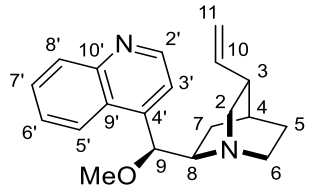
(–)-Sparteine, (−)-lupinidine ((–)-**L2**) was purchased from BDL Czech Republic s.r.o (TCI) in >98% purity, used as received.

(S,S)-N,N,N,N-Tetramethyl-trans-cyclohexane-1,2-diamine ((*S,S*)-**L3**) was prepared according to the known procedure by the Eschweiler–Clarke reaction from the diamine [171] and generously donated by V. Golubev.

2,*2'-Isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline]* (**L16**) was purchased from Merck KGaA (Sigma Aldrich) in >99% purity, used as received.

(+)-Cinchonine methyl ether (**L17**)

Prepared from cinchonine (3.24 g, 11.0 mmol) according to the published procedure.[265] Flash chromatography (DCM/MeOH 9:1) followed by recrystallization from acetonitrile afforded 1.61 g (47%) as large colourless crystals, mp 116-117 °C. The spectroscopic data matched the lit.[265]



R_f 0.40 (DCM/MeOH 9:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3048 (w), 2982 (m), 2933 (w), 2866 (w), 2814 (w), 1636 (w), 1591 (w), 1570 (w), 1508 (w), 1452 (w), 1422 (w), 1264 (m), 1105 (m), 1079 (w), 1066 (w), 913 (w), 844 (w), 827 (w), 761 (m), 733 (vs), 702 (m), 634 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.88 (d, *J* = 4.4 Hz, 1H, H-2'), 8.39 (dd, *J* = 8.5, 1.3 Hz, 1H, H-8'), 8.30 (d, *J* = 8.4 Hz, 1H, H-5'), 7.37 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, H-7'), 7.29 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H, H-6'), 7.17 (d, *J* = 4.5 Hz, 1H, H-3'), 6.10 (ddd, *J* = 17.1, 10.4, 7.7 Hz, 1H, H-10), 5.20-5.02 (m, 3H, H-9, H-11), 3.23 (ddd, *J* = 13.8, 7.6, 2.3 Hz, 1H, H-2a), 3.00-2.98 (m, 1H, H-8), 2.97 (s, 3H, OC*H*$_3$), 2.83 (ddd, *J* = 13.7, 9.9, 1.5 Hz, 1H, H-2b), 2.57 (ddt, *J* = 12.9, 9.9, 2.9 Hz, 1H, H-6a), 2.45 (ddd, *J* = 13.0, 9.6, 7.7 Hz, 1H, H-6b), 2.09-1.95 (m, 2H, H-3, H-7a), 1.53 (d quint, *J* = 4.2, 2.0 Hz, 1H, H-4), 1.17-1.00 (m, 3H, H-5, H-7b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.1 (d, C-2'), 149.4 (s, C-10'), 146.9 (s, C-4'), 140.8 (d, C-10), 131.1 (d, C-8'), 128.7 (d, C-7'), 126.8 (s, C-9'), 126.3 (d, C-6'), 123.5 (d, C-5'), 118.5 (d, C-3'), 114.2 (t, C-11), 82.9 (d, C-9), 60.5 (d, C-8), 56.5 (q, O*C*H$_3$), 49.7 (t, C-6), 49.3 (t, C-2), 40.2 (d, C-3), 28.2 (d, C-4), 26.2 (t, C-5), 22.0 (t, C-7);

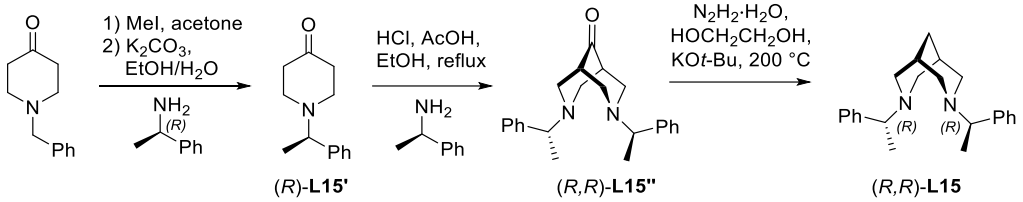
^{1}H NMR (401 MHz, CD_3CN): δ 8.84 (d, *J* = 4.4 Hz, 1H, H-2'), 8.30 (ddd, *J* = 8.6, 1.3, 0.6 Hz, 1H, H-8'), 8.06 (ddd, *J* = 8.4, 1.4, 0.7 Hz, 1H, H-5'), 7.72 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, H-7'), 7.58 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H, H-6'), 7.46 (d, *J* = 4.4 Hz, 1H, H-3'), 6.12 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1H, H-10), 5.10 (ddd, *J* = 17.2, 2.0, 1.3 Hz, 1H, H-11a), 5.07 (ddd, *J* = 10.2, 2.0, 1.2 Hz, 1H, H-11b), 4.92 (d, *J* = 8.1 Hz, 1H, H-9), 3.19 (s, 3H, OC*H*$_3$), 3.13 (dt, *J* = 9.6, 8.3 Hz, 1H, H-8), 2.92 (ddt, *J* = 13.7, 7.8, 1.5 Hz, 1H, H-2a), 2.67 (ddd, *J* = 13.9, 9.8, 1.5 Hz, 1H, H-2b), 2.50 (m, 2H, H-6), 2.22 (m, 1H, H-3), 1.84 (ddt, *J* = 13.4, 8.5, 2.0 Hz, 1H, H-7a), 1.71 (tt, *J* = 3.9, 2.0 Hz, 1H, H-4), 1.60 (dddd, *J* = 13.7, 9.3, 4.8, 1.8 Hz, 1H, H-7b), 1.55-1.40 (m, 2H, H-5);

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 151.1 (d, C-2'), 149.4 (s, C-10'), 148.6 (s, C-4'), 142.2 (d, C-10), 131.0 (d, C-5'), 129.9 (d, C-7'), 128.1 (s, C-9'), 127.2 (d, C-6'), 125.1 (d, C-8'), 120.8 (d, C-3'), 114.7 (t, C-11), 84.0 (d, C-9), 62.0 (d, C-8), 57.5 (q, O*C*H$_3$), 50.1 (t, C-6), 49.5 (t, C-2), 41.2 (d, C-3), 29.2 (d, C-4), 27.2 (t, C-5), 25.9 (t, C-7);

MS (ESI+) *m/z*, (%): 309 (100, $[M + Na]^+$), 277 (9, $[M - OMe]^+$);

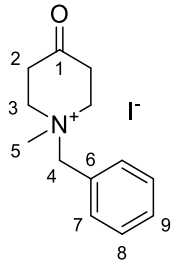
HRMS (ESI+) *m/z*: $[M + H]^+$ calcd. for $C_{20}H_{25}N_2O$ 309.1961; found: 309.1960.

Preparation of (*R,R*)-L15



Step 1. MeI (9.3 mL, 150 mmol) was added to a solution of 1-benzyl-4-piperidone (9.46 g, 50 mmol) in acetone (100 mL). The mixture was stirred at r.t. overnight. The resulting gummy semi-solid precipitate was triturated *in situ* to produce a suspension, which was further stirred under reflux for 1 h. The volume was reduced by distilling off ~1/2 of acetone. After cooling, the suspension was filtered, and the filtrate was washed with diethyl ether (200 mL) and dried to yield 16.9 g (quant.) of ammonium salt as a light pink solid.

1-Benzyl-1-methyl-4-oxopiperidin-1-ium iodide

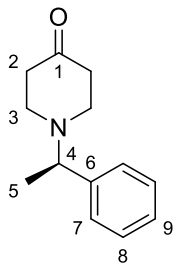


^{1}H (401 MHz, CD_3CN): δ 7.67-7.46 (m, 5H, H7-9), 4.78 (s, 1H, H-4), 3.89-3.82 (m, 2H, H-3a), 3.75-3.69 (m, 2H, H-3b), 3.19 (s, 3H, H-5), 2.88-2.80 (m, 2H, H-4a), 2.74-2.65 (m, 2H, H-4b);

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 201.0 (s, C-1), 134.2 (d, C-7/8), 131.8 (d, C-9), 130.1 (d, C-7/8), 127.9 (s, C-6), 68.8 (t, C-4), 59.4 (t, C-3), 47.4 (q, C-5), 36.0 (t, C-2).

Step 2. *N*-benzyl-*N*-methyl-4-oxopiperidinium iodide (16.6 g, 50 mmol) was dissolved in ethanol (100 mL) and water (50 mL). To this solution (*R*)-α-methylbenzylamine (7.1 mL, 55 mmol) was added followed by K_2CO_3 (24.2 g, 175 mmol). The resulting suspension was stirred under reflux (bath temp. 120 °C) for 4 hours, then stirred at 23 °C overnight. Aqueous NaOH (200 mL, 7%$_w$) was added and the mixture was extracted twice with DCM (2×150 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to give ~12.5 g of a crude oil. Further drying of this oil at 60 °C in high vacuum (0.02 mbar) yielded 10 g of crude **L15'** as a dark brown thick oil, which was carried forward without purification.

(R)-1-(1-Phenylethyl)piperidin-4-one (**L15'**)

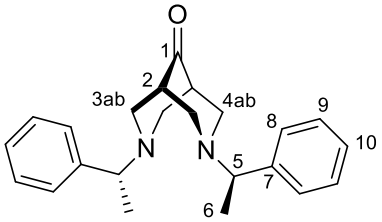


^{1}H (401 MHz, CD_3CN): δ 7.43-7.18 (m, 5H, Ph), 3.67 (q, J = 8.3, 5.9 Hz, 1H, H-4), 2.78-2.64 (m, 4H, H-3), 2.37-2.29 (m, 4H, H-2), 1.37 (d, J = 6.7 Hz, 3H, H-5);

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 209.7 (s, C-1), 144.9 (s, C-6), 129.2 (d, C-8/9), 128.3 (d, C-8/9), 127.9 (d, C-10), 63.6 (d, C-4), 50.7 (t, C-3), 42.1 (t, C-2), 19.7 (q, C-5).

Step 3. Crude **L15''** (10 g, <50 mmol) from the previous step was dissolved in dry EtOH (450 mL). Paraformaldehyde (6.0 g, 125 mmol) was added, followed by AcOH (3.0 mL, 50 mmol) and HCl (2.2 mL, 25 mmol, 35%$_w$ in H_2O). The mixture was stirred at r.t. for 2 min. A solution of (*R*)-1-phenylethylamine (6.4 mL, 50 mmol) and AcOH (3.0 mL, 50 mmol) in EtOH (50 mL) was added. The reaction was heated to reflux for 6 h, followed by distillation of EtOH to reduce the volume to ~1/2. After cooling, the mixture was partitioned between EA (300 mL) and 7%$_w$ NaOH (300 mL). The organic layer was washed with sat. $NaHCO_3$ solution (200 mL) and brine (2×100 mL), concentrated and dried under vacuum to yield 21 g of crude **L15''** as a brown glass, which was used without purification in the next step.

(1R,5R)-3,7-Bis[(R)-1-phenylethyl]-3,7-diazabicyclo[3.3.1]nonan-9-one (**L15''**)



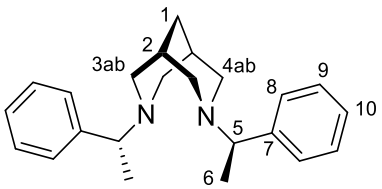
R_f 0.05 (DCM/MeOH 4:1);

^{1}H (401 MHz, CD_3CN): δ 7.37-7.10 (m, 10H, H-8-10), 3.59 (q, *J* = 6.7 Hz, 2H, H-5), 3.00-2.89 (m, 4H, 3a, 4a), 2.77-2.70 (m, 4H, 3b, 4b), 2.44-2.36 (m, 2H, H-2), 1.31 (d, *J* = 6.8 Hz, 6H, H-6);

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 215.2 (s, C-1), 144.3 (s, C-7), 129.1 (d, C-8/9), 128.5 (d, C-8/9), 127.9 (d, C-10), 63.3 (d, C-5), 56.6 (t, C-3/4), 54.7 (t, C-3/4), 47.9 (d, C-2), 18.6 (q, C-6).

Step 4. Attempted reduction of crude **L15** (21 g, <50 mmol) from the previous step using standard conditions for the Wolf-Kishner reduction (25.2 g KOH, 15.3 mL hydrazine hydrate in ethylene glycol) [266] led to a complex mixture containing undesired azine of **L15''**. The recovered starting material (5.0 g) was mixed with hydrazine hydrate (15 mL, 300 mol) in ethylene glycol (150 mL). KO*t*-Bu (10 g, 90 mmol) was added, followed by heating the mixture to 150 °C. A Dean-Stark apparatus was connected, followed by slow addition of benzene (15 mL). The bath temperature was slowly increased to 245 °C, while the azeotrope was collected. After 1 h at 245 °C, the temperature was set to 215 °C and maintained overnight. After cooling, the mixture was partitioned between 20%$_W$ NaOH (300 mL) and Et_2O (350 mL). The organic layer was washed twice with 20%$_W$ NaOH (2×50 mL), dried over Na_2SO_4, concentrated and purified by repeated flash chromatography (PE/Et_2O/Et_3N 100:100:1 to 10:10:1) to yield 870 mg of **L15** (5% based on 1-benzyl-4-piperidone) as a soft pale-yellow solid, mp 62-64 °C.

(1R,5R)-3,7-Bis[(R)-1-phenylethyl]-3,7-diazabicyclo[3.3.1]nonane (**L15**)



R_f 0.32 (PE/Et_2O/Et_3N 20:20:1), R_f 0.50 (DCM/MeOH 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3051 (w), 3019 (w), 2969 (w), 2896 (w), 2777 (w), 2745 (w), 2691 (w), 1599 (w), 1489 (w), 1448 (m), 1369 (w), 1336 (w), 1314 (w), 1300 (w), 1284 (w), 1251 (w), 1236 (w), 1145

(w), 1134 (w), 1119 (w), 1076 (w), 1058 (w), 1025 (w), 997 (w), 956 (w), 922 (w), 910 (w), 758 (s), 699 (vs);

^{1}H (401 MHz, C_6D_6): δ 7.58-7.53 (m, 4H, H-8/9), 7.34-7.25 (m, 4H, H-8/9), 7.20-7.11 (m, 2H, H-10), 3.21 (q, *J* = 6.6 Hz, 2H, H-5), 2.84-2.78 (m, 2H, H-3/4), 2.78-2.67 (m, 2H, H-3/4), 2.22-2.14 (m, 4H, H-3/4), 1.68-1.52 (m, 2H, H-2), 1.38 (m, 2H, H-1), 1.34 (d, *J* = 6.6 Hz, 6H, H-6);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 146.8 (s, C-7), 128.6 (d, C-8/9), 128.0 (d, C-8/9), 126.8 (d, C-10), 65.9 (d, C-5), 56.5 (t, C-3/4), 54.5 (t, C-3/4), 31.4 (t, C-1), 30.5 (d, C-2), 21.1 (q, C-6);

^{1}H (401 MHz, CD_3CN): δ 7.50 (d, *J* = 7.2 Hz, 4H, H-8/9), 7.31 (t, *J* = 7.5 Hz, 4H, H-8/9), 7.21 (t, *J* = 7.3 Hz, 2H, H-10), 3.24 (q, *J* = 6.7 Hz, 2H, H-5), 2.92 (d, *J* = 9.3 Hz, 2H, H-3/4), 2.69 (d, *J* = 10.6 Hz, 2H, H-3/4), 2.31 (dd, *J* = 10.6, 3.6 Hz, 2H, H-3/4), 2.22-2.20 (m, 2H, H-3/4), 1.84-1.78 (m, 2H, H-2), 1.46 (t, *J* = 3.0 Hz, 2H, H-1), 1.31 (d, *J* = 6.7 Hz, 6H, H-6);

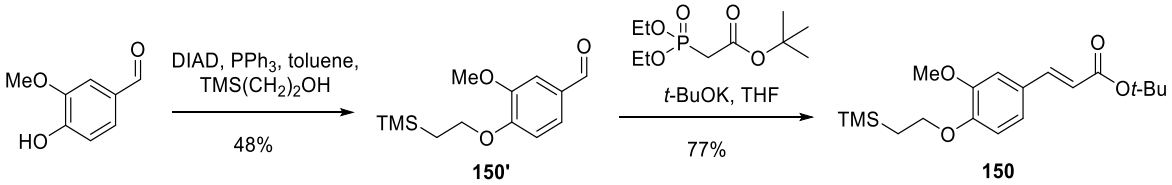
^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 147.4 (s, C-7), 129.1 (d, C-8/9), 128.5 (d, C-8/9), 127.4 (d, C-10), 66.2 (d, C-h), 57.2 (t, C-3/4), 54.9 (t, C-3/4), 32.0 (t, C-1), 31.1 (d, C-2), 21.1 (q, C-6);

MS (APCI+) *m/z*, (%): 468 (9, $[M + Na]^+$), 335 (100, $[M + H]^+$);

HRMS (APCI+) *m/z*: $[M + H]^+$ calcd. for $C_{23}H_{31}N_2$ 335.2482; found: 335.2485; HRMS (ESI+) *m/z*: $[M + H]^+$ calcd. for $C_{23}H_{31}N_2$ 335.2482; found: 335.2479.

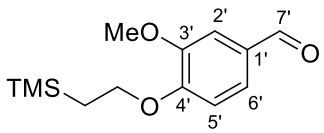
6.2.5. Addition of stilbene **157** to cinnamate **150**

Synthesis of cinnamate 150



Step 1. Vanillin (1.52 g, 10 mmol) and PPh_3 (5.25 g, 20 mmol) were suspended in dry toluene (50 mL) at −20 °C and stirred vigorously. Under an inert atmosphere, 2-(trimethylsilyl)ethanol (2.2 mL, 15 mmol) was added, followed by slow addition of diisopropyl azodicarboxylate (3.0 mL, 15 mmol) over 3 min. The suspension dissolved giving a clear yellow-red solution. The reaction was slowly warmed to 23 °C over 4 h followed by stirring at r.t. overnight. The reaction mixture was concentrated in vacuum and adsorbed on silica gel. Flash chromatography (pure cyclohexane to cyclohexane/EA 3:1) yielded 1.225 g (48%) of **150'** as a colourless oil. Toluene proved critical for obtaining an acceptable yield, reactions in THF generally yielded 10-20%.[180]

3-Methoxy-4-[2-(trimethylsilyl)ethoxy]benzaldehyde (**150'**)



R_f 0.47 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3079 (w), 3004 (w), 2952 (w), 2897 (w), 1681 (m), 1594 (w), 1584 (m), 1507 (m), 1465 (w), 1423 (w), 1395 (w), 1339 (w), 1262 (vs), 1236 (s), 1158 (m), 1133 (s), 1123 (m), 1061 (w),

1033 (m), 985 (w), 963 (w), 944 (w), 854 (s), 836 (vs), 807 (s), 780 (w), 753 (w), 729 (m), 693 (w), 645 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.84 (s, 1H, H-7'), 7.43 (dd, *J* = 8.1, 1.9 Hz, 1H, H-6'), 7.40 (d, *J* = 1.9 Hz, 1H, H-2'), 6.94 (d, *J* = 8.1 Hz, 1H, H-5'), 4.26-4.13 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.92 (s, 3H, OC*H*$_3$), 1.32-1.18 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.09 (s, 9H, Si(C*H*$_3$)$_3$);

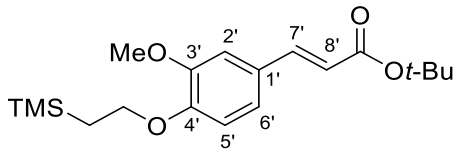
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 191.1 (d, C-7'), 154.1 (s, C-4'), 150.0 (s, C-3'), 129.9 (s, C-1'), 127.0 (d, C-6'), 111.4 (d, C-5'), 109.2 (d, C-2'), 66.8 (t, O*C*H$_2$CH$_2$TMS), 56.1 (q, O*C*H$_3$), 17.7 (t, OCH$_2$*C*H$_2$TMS), −1.3 (q, Si(*C*H$_3$)$_3$);

MS (CI+) *m/z*, (%): 253 (22, $[M + H]^+$), 225 (100, $[M + H - C_2H_2]^+$), 224 (48, $[M - C_2H_2]^{\bullet+}$), 209 (43, $[M - C_2H_2 - CH_3]^+$), 194 (18), 101 (5, $[TMSCH_2CH_2]^+$), 73 (16, $[TMS]^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd. for $C_{13}H_{21}O_3Si$ 253.1260; found: 253.1262.

Step 2. *tert*-Butyl diethylphosphonoacetate (2.4 mL, 10.27 mmol), followed by a solution of *t*-BuOK (17.1 mL, 1M in THF) were added to a solution of aldehyde **151'** (2.16 g, 8.56 mmol) in dry THF (40 mL). The mixture was stirred at r.t. for 2 h, then partitioned between water (100 mL) and DCM (70 mL). The aqueous layer was extracted twice with DCM (2×50 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by flash chromatography (pure PE to PE/EA 4:1) to yield 2.334 g (77%) of **150** as a colourless oil.

tert-Butyl (E)-3-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}acrylate (**150**)



R_f 0.60 (hexane/EA 5:1);

IR $\tilde{\nu}$[cm^{-1}]: 3002 (w), 2952 (w), 2929 (w), 2852 (w), 1702 (m), 1632 (w), 1598 (w), 1580 (w), 1510 (m), 1467 (w), 1421 (w), 1366 (w), 1307 (w), 1249 (s), 1133 (vs), 1036 (w), 979 (w), 945 (w), 837 (s), 805 (w), 753 (w), 693 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.52 (d, *J* = 15.9 Hz, 1H, H-7'), 7.08-7.01 (m, 2H, H-2', H-5'), 6.82 (d, *J* = 8.0 Hz, 1H, H-5'), 6.23 (d, *J* = 15.9 Hz, 1H, H-8'), 4.20-4.10 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.88 (s, 3H, OC*H*$_3$), 1.53 (s, 9H, OC(C*H*$_3$)$_3$), 1.29-1.16 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.08 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.8 (s, *C*OO*t*-Bu), 150.4 (s, C-4'), 149.6 (s, C-3'), 143.8 (d, C-7'), 127.5 (s, C-1'), 122.5 (d, C-6'), 117.8 (d, C-8'), 112.3 (d, C-5'), 109.8 (d, C-2'), 80.4 (s, O*C*(CH$_3$)$_3$), 66.5 (t, O*C*H$_2$CH$_2$TMS), 56.0 (q, O*C*H$_3$), 28.4 (q, OC(*C*H$_3$)$_3$), 17.8 (t, OCH$_2$*C*H$_2$TMS), −1.3 (q, Si(*C*H$_3$)$_3$);

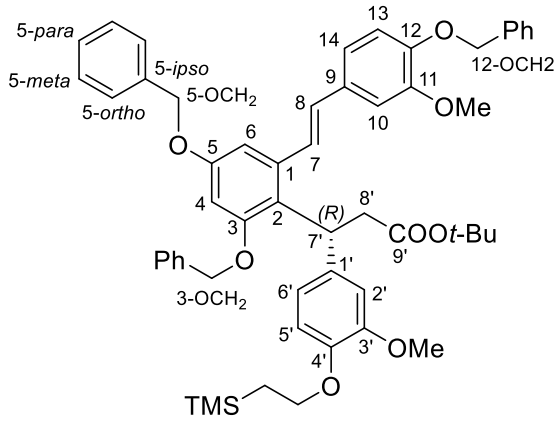
MS (ESI+) *m/z*, (%): 723 (100, $[2M + Na]^+$), 373 (97, $[M + Na]^+$), 317 (8, $[M$ – isobutene + $Na]^+$), 295 (38, $[M$ – isobutene + $H]^+$), 249 (42);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{19}H_{30}NaO_4Si$ 373.1806; found: 373.1805.

Conjugate addition of 157 to 150

The same procedure as for **148** was followed using starting with stilbene **157** (118.5 mg, 0.195 mmol), ligand (*R,R*)-**L1** (54.5 mg, 0.225 mmol), *n*-BuLi (130 µL, 0.208 mmol, 1.6 M in hexanes), TMSCl (49 µL, 0.390 mmol) and cinnamate **150** (29.4 mg, 0.10 mmol). Purification by flash chromatography (cyclohexane/EA 50: to 10:1) yielded 92.3 mg of **169** (70%) as a colourless film, 60% ee by chiral HPLC (Hexane/*i*-PrOH 90:10, 1.0 mL/min).

tert-Butyl (R,E)-3-{2,4-bis(benzyloxy)-6-[4-(benzyloxy)-3-methoxystyryl]phenyl}-3-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}propanoate (**169**)



R_f 0.15 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3063 (w), 3033 (w), 2952 (w), 2871 (w), 1722 (w), 1595 (w), 1511 (m), 1454 (w), 1418 (w), 1368 (w), 1249 (m), 1138 (s), 1057 (w), 1029 (w), 965 (w), 838 (m), 732 (vs), 696 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.24 (m, 16H, Ph, H-7), 7.02-6.98 (br. s, 1H, H-10), 6.94 (br. d, *J* = 8.2, H-14), 6.85 (d, *J* = 8.3 Hz, 1H, H-13), 6.78 (d, *J* = 15.9 Hz, 1H, H-8), 6.76 (d, *J* = 2.4 Hz, 1H, H-4/6), 6.75 (s, 1H, H-2'), 6.68 (s, 2H, H-5', H-6'), 6.54 (d, *J* = 2.5 Hz, 1H, H-4/6), 5.18 (s, 2H, C12-OC*H*$_2$Ph), 5.14-5.01 (m, 1H, H-7'), 5.06 (s, 2H, C5-OC*H*$_2$Ph), 4.99 (d, *J* = 11.6 Hz, 1H, C3-OC*H*$_a$H$_b$Ph), 4.90 (d, *J* = 11.6 Hz, 1H, C3-OCH$_a$*H*$_b$Ph), 4.08-4.04 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.93 (s, 3H, C11-OC*H*$_3$), 3.57 (s, 3H, C3'-OC*H*$_3$), 3.26-3.00 (br., 1H, H-8'a), 3.07 (dd, *J* = 14.2, 7.4 Hz, 1H, H-8'b), 1.27 (s, 9H, COOC(C*H*$_3$)$_3$), 1.19-1.15 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.05 (s, 9H, Si(C*H*$_3$)$_3$);

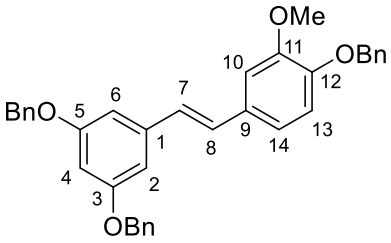
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.3 (s, C-9'), 158.30 (s, C-5), 158.26 (br. s, C-3), 149.9 (s, C-11), 149.2 (s, C-3'), 148.2 (s, C-12), 146.3 (s, C-4'), 139.7 (s, C-1), 137.2 (s, Ph^{ipso}), 137.1 (s, Ph^{ipso}), 137.0 (s, Ph^{ipso}), 136.5 (s, C-1'), 131.4 (br. d, C-8), 131.3 (s, C-9), 128.73 (d, 2×C, Ph^{meta}), 128.70 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.1 (d, Ph^{para}), 128.0 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.8 (d, 2×C, C3-OCH$_2$Ph^{ortho}), 127.7 (d, 2×C, C5-OCH$_2$Ph^{ortho}), 127.4 (d, 2×C, C12-OCH$_2$Ph^{ortho}), 126.6 (d, C-7), 123.3 (s, C-2), 119.9 (d, C-14), 119.4 (d, C-6'), 114.1 (d, C-13), 112.7 (d, C-5'), 111.3 (d, C-2'), 109.7 (d, C-10), 104.7 (d, C-4/6), 100.4 (d, C-4/6), 80.1 (s, COO*C*(CH$_3$)$_3$), 71.2 (t, C12-O*C*H$_2$Ph), 70.6 (t, C3-O*C*H$_2$Ph), 70.2 (t, C5-O*C*H$_2$Ph), 66.4 (t, O*C*H$_2$CH$_2$TMS), 56.1 (q, C11-OCH$_3$), 55.7 (q, C3'-OCH$_3$), 39.6 (t, C-8'), 38.3 (d, C-7', detected by HMBC), 18.0 (t, OCH$_2$*C*H$_2$TMS), –1.3 (q, Si(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 901 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{55}H_{63}O_8Si$ 879.4287; found: 879.4290.

(E)-4-[3,5-bis(benzyloxy)styryl]-1-(benzyloxy)-2-methoxybenzene (**157-H**)

Obtained in varying amounts from conjugate addition of **157** to various Michael acceptors.



R_f 0.30 (hexane/EA 5:1);

IR $\tilde{\nu}$[cm^{-1}]: 3063 (w), 3031 (w), 2926 (w), 2866 (w), 1719 (w), 1584 (s), 1510 (m), 1452 (m), 1375 (w), 1345 (w), 1288 (w), 1260 (s), 1236 (m), 1220 (m), 1139 (vs), 1080 (w), 1053 (m), 1027 (s), 957 (m), 845 (w), 822 (w), 798 (w), 733 (s), 694 (s), 681 (m), 630 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.52-7.28 (m, 15H, Ph), 7.08 (d, J = 2.0 Hz, 1H, H-10), 7.02 (d, J = 16.2 Hz, 1H, H-7/8), 6.98 (dd, J = 8.3, 1.9 Hz, 1H, H-14), 6.90 (d, J = 16.2 Hz, 1H, H-7/8), 6.86 (d, J = 8.2 Hz, 1H, H-13), 6.77 (d, J = 2.2 Hz, 2H, H-2,6), 6.56 (t, J = 2.2 Hz, 1H, H-4), 5.19 (s, 2H, C12-OCH_2Ph), 5.08 (s, 4H, C3,5-OCH_2Ph), 3.96 (s, 3H, OCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.3 (s, C-3, C-5), 149.9 (s, C-11), 148.3 (s, C-12), 139.7 (s, C-1/9), 137.1 (s, C12-OBn^{ipso}), 137.0 (s, C3,5-OBn^{ipso}), 130.8 (s, C-1/9), 129.2 (d), 128.7 (d, 4×C, C3,5-OBn), 128.7 (d, 2×C), 128.1 (d, 2×C), 128.0 (d), 127.7 (d, 4×C, C3,5-OBn), 127.4 (d, 2×C), 127.0 (d), 120.0 (d, C-14), 114.1 (d, C-13), 109.6 (d, C-10), 105.7 (d, C-2,6), 101.4 (d, C-4), 71.1 (t, C12-OCH_2Ph), 70.2 (t, C3-OCH_2Ph, C5-OCH_2Ph), 56.1 (q, OCH_3);

MS (APCI+) *m/z*, (%): 529 (100, $[M + H]^+$), 438 (29, $[M + H - Bn]^+$);

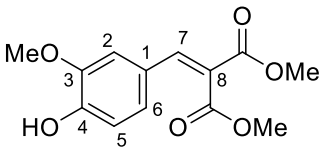
HRMS (APCI+) *m/z*: $[M + H]^+$ calcd. for $C_{36}H_{33}O_4$ 529.2373; found: 529.2372.

6.2.6. Synthesis of malonates **171a-d**, **188**, **195**

Synthesis of 171a

Step 1. A mixture of vanillin (6.09 g, 40 mmol), dimethyl malonate (6.4 mL, 56 mmol), piperidine (0.60 mL, 6 mmol) and acetic acid (0.23 mL, 4 mmol) in toluene (40 mL) was heated to reflux using a Dean-Stark trap for 3 h. After the azeotropic distillation of water ceased, the mixture was cooled to r.t., concentrated and dried in high vacuum. The semi-solid mixture was purified by flash chromatography (cyclohexane/EA 9:1 to 2:1) to yield 9.18 g (86%) of **170a** as a colourless solid, mp 93-94 °C.

Dimethyl 2-(4-hydroxy-3-methoxybenzylidene)malonate (**170a**)



R_f 0.08 (hexane/EA 5:1); R_f 0.60 (Et_2O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3250 (br.), 3057 (w), 3005 (w), 2953 (w), 2846 (w), 1720 (s), 1624 (w), 1590 (m), 1515 (m), 1432 (m), 1375 (w), 1291 (w), 1258 (s), 1209 (s), 1174 (s), 1158 (s), 1127 (m), 1068 (s), 1030 (m), 989 (w), 925 (w), 849 (w), 819 (w), 733 (m), 701 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.68 (s, 1H, H-7), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6), 6.98 (d, *J* = 2.0 Hz, 1H, H-2), 6.91 (d, *J* = 8.2 Hz, 1H, H-5), 5.94 (s, 1H, OH), 3.88 (s, 3H, C3-OMe), 3.86 (s, 3H, COOCH_3), 3.83 (s, 3H, COOCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.9 (s, *C*OOMe), 165.0 (s, *C*OOMe), 148.5 (s, C-4), 146.7 (s, C-3), 143.1 (d, C-7), 125.2 (s, C-1), 125.0 (d, C-6), 122.8 (s, C-8), 115.0 (d, C-5), 111.4 (d, C-2), 56.0 (q, C3-O*C*H_3), 52.8 (q, COO*C*H_3), 52.7 (q, COO*C*H_3);

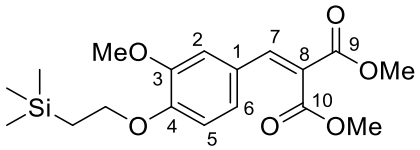
MS (ESI+) *m/z*, (%): 289 (100, $[M + Na]^+$), 235 (20, $[M + H - MeOH]^+$), 167 (7);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{14}NaO_6$ 289.0683; found: 289.0683;

Anal. calcd. for $C_{13}H_{14}O_6$ (266.25): C, 58.65; H, 5.30. Found: C, 58.51; H, 5.09.

Step 2. Phenol **170a** (5.32 g, 20 mmol) was suspended in dry toluene (200 mL) at 0 °C. Under a stream of dry nitrogen, PPh_3 (7.87 g, 30 mmol) and 2-(trimethylsilyl)ethanol (3.7 mL, 26 mmol) were added. The resulting suspension was stirred vigorously and diisopropyl azodicarboxylate (5.1 mL, 26 mmol) was added dropwise leading to gradual dissolution of the suspension producing clear yellow-red solution. After 20 min, the temperature was increased to 23 °C for 30 min. The solvent was removed under vacuum, THF (20 mL), water (4 mL) and acetic acid (4 mL) were added and the mixture was stirred for 30 min. The volatiles were stripped off in vacuum and the crude product was purified by flash chromatography (pure cyclohexane to cyclohexane/EA 9:1) to yield 5.73 g (78%) of **171a** as a colourless solid, mp 65-67 °C.

Dimethyl 2-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]benzylidene}malonate (**171a**)



R_f 0.34 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3000 (w), 2951 (w), 2899 (w), 2847 (w), 1724 (m), 1622 (w), 1596 (w), 1513 (m), 1465 (w), 1435 (w), 1423 (w), 1379 (w), 1336 (w), 1247 (s), 1217 (vs), 1192 (m), 1164 (m), 1140 (vs), 1067 (m), 1034 (w), 987 (w), 964 (w), 836 (s), 753 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.69 (s, 1H, H-7), 7.04 (dd, *J* = 8.4, 2.1 Hz, 1H, H-6), 6.98 (d, *J* = 2.1 Hz, 1H, H-2), 6.83 (d, *J* = 8.4 Hz, 1H, H-5), 4.20-4.12 (m, 2H, OC$H_2$$CH_2$TMS), 3.87 (s, 3H, COOC$H_3$), 3.85 (s, 3H, C3'-OC$H_3$), 3.84 (s, 3H, COOC$H_3$), 1.28-1.16 (m, 2H, OCH_2CH_2TMS), 0.08 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.9 (s, C-9/10), 165.0 (s, C-9/10), 151.1 (s, C-4), 149.4 (s, C-3), 143.1 (d, C-7), 125.2 (s, C-1), 124.4 (d, C-6), 122.8 (s, C-8), 112.2 (d, C-2/5), 111.9 (d, C-2/5), 66.6 (t, O*C*$H_2$$CH_2$TMS), 55.9 (q, O*C*$H_3$), 52.8 (q, O*C*$H_3$), 52.7 (q, O*C*$H_3$), 17.8 (t, OCH_2*C*H_2TMS), –1.3 (q, Si(*C*H_3)$_3$);

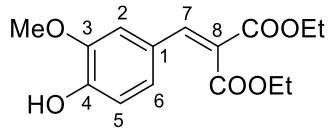
MS (ESI+) *m/z*, (%): 755 (9, $[2M + Na]^+$), 405 (9, $[M + K]^+$), 389 (100, $[M + Na]^+$), 367 (9, $[M + H]^+$), 307 (66, $[M + H - MeOH - CO]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{18}H_{26}NaO_6Si$ 389.1391; found: 389.1389.

Synthesis of 171b

Step 1. A mixture of vanillin (3.04 g, 20 mmol), diethyl malonate (4.3 mL, 28 mmol), piperidine (0.3 mL, 3 mmol) and AcOH (0.12 mL, 2 mmol) in toluene (20 mL) was heated to reflux using a Dean-Stark trap for 4 h. After the azeotropic distillation of water ceased, the solvent was distilled off to reduce the volume to ~1/3. After cooling, PE (10 mL) was added resulting in the formation of a precipitate. The solvent was decanted, and the solids were triturated with fresh PE (10 mL), and finally with a 10:1 mixture of PE and Et_2O (25 mL). Filtration and drying under vacuum yielded 5.88 g (99%) of **170b** as a light beige solid, mp 106-107 °C. Analytical data were in an agreement with the literature.[267] Note: A slight excess of diethyl malonate (1.4 equiv.) is required for complete conversion and gives analytically pure product without further purification. A stoichiometric amount malonate under otherwise identical conditions afforded lower yield (64-72%).

Diethyl 2-(4-hydroxy-3-methoxybenzylidene)malonate (**170b**)



R_f 0.18 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3200 (br.), 2982 (w), 2938 (w), 2904 (w), 2843 (w), 1717 (m), 1624 (w), 1589 (w), 1515 (m), 1464 (w), 1430 (w), 1379 (w), 1290 (m), 1257 (s), 1206 (vs), 1179 (s), 1157 (vs), 1127 (m), 1094 (w), 1063 (m), 1022 (m), 952. (w), 859 (w), 735 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.64 (s, 1H, H-7), 7.06-6.99 (m, 2H, H-2, H-6), 6.91 (d, J = 8.2 Hz, 1H, H-5), 5.90 (s, 1H, OH), 4.29 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 4.34 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 3.88 (s, 3H, OCH_3), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.31 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3);

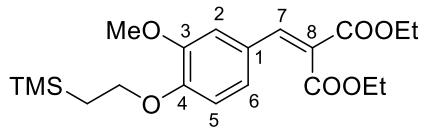
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.4 (s, *C*OOEt), 164.6 (s, *C*OOEt), 148.3 (s, C-4), 146.7 (s, C-3), 142.2 (d, C-7), 125.4 (s, C-1), 124.9 (d, C-6), 123.7 (s, C-8), 114.9 (d, C-5), 111.5 (d, C-2), 61.8 (t, O*C*H$_2$CH$_3$), 61.6 (t, O*C*H$_2$CH$_3$), 56.0 (q, O*C*H$_3$), 14.3 (q, OCH$_2$*C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 611 (27, [2M + Na]$^+$), 317 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{15}H_{18}O_6Na$ 317.0996; found: 317.0995.

Step 2. Following the procedure for **171a**, phenol **170b** (2.94 g, 10 mmol) was alkylated in dry toluene (80 mL) using PPh_3 (3.93 g, 15 mmol), 2-(trimethylsilyl)ethanol (1.9 mL, 13 mmol) and diisopropyl azodicarboxylate (2.6 mL, 13 mmol). Yield 3.159 g (80%) of **171b** as a soft colourless amorphous solid. A less polar solvent proved critical for obtaining high yield as the reaction in THF gives yields below 50%.[180]

Diethyl 2-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]benzylidene}malonate (**171b**)



R_f 0.43 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2981 (w), 2953 (w), 2903 (w), 2874 (w), 1719 (s), 1622 (w), 1596 (w), 1513 (m), 1465 (w), 1423 (w), 1379 (w), 1355 (w), 1275 (s), 1246 (s), 1224 (s), 1210 (m), 1190 (m), 1164 (m), 1141 (s), 1095 (m), 1062 (m), 1034 (w), 990 (w), 934 (w), 855 (s), 836 (s), 807 (m), 770 (w), 752 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.65 (s, 1H, H-7), 7.06 (dd, J = 8.3, 2.2 Hz, 1H, H-6), 7.02 (d, J = 2.1 Hz, 1H, H-2), 6.82 (d, J = 8.3 Hz, 1H, H-5), 4.35 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 4.29 (q, J = 7.1 Hz,

2H, OC*H*$_2$CH$_3$), 4.18-4.12 (m, 2H, OC*H*$_2$CH$_2$Si), 3.84 (s, 3H, OMe), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.25-1.18 (m, 2H, OCH$_2$C*H*$_2$Si), 0.08 (s, 9H, SiC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 167.4 (s, *C*OOEt), 164.6 (s, *C*OOEt), 150.9 (s, C-4), 149.3 (s, C-3), 142.2 (d, C-7), 125.4 (s, C-1), 124.4 (d, C-6), 123.6 (s, C-8), 112.14 (d, C-5), 112.07 (d, C-2), 66.5 (t, *C*H$_2$CH$_2$Si), 61.7 (t, O*C*H$_2$CH$_3$), 61.6 (t, O*C*H$_2$CH$_3$), 55.9 (q, OMe), 17.8 (t, OCH$_2$*C*H$_2$Si), 14.3 (q, OCH$_2$*C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$), −1.3 (q, SiC*C*H$_3$);

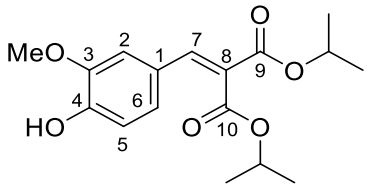
MS (ESI+) *m/z*, (%): 811 (24, [2M + Na]$^+$), 417 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{20}H_{30}NaO_6Si$ 417.1704; found: 417.1702.

Synthesis of 171c

Step 1. A mixture of vanillin (3.04 g, 20 mmol), diisopropyl malonate (5.3 mL, 28 mmol), piperidine (0.30 mL, 3 mmol) and AcOH (0.12 mL, 2 mmol) in toluene (20 mL) was heated to reflux using a Dean-Stark trap for 3 h. After the azeotropic distillation of water ceased, the mixture was cooled, concentrated and dried under high vacuum. The semi-solid mixture was purified by flash chromatography (PE/EA, 11:1 to 3:1) to yield 6.44 g (quant.) of **170c** white colourless solid, mp 60-62 °C.

Diisopropyl 2-(4-hydroxy-3-methoxybenzylidene)malonate (**170c**)



R_f 0.45 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3250 (br.), 2981 (w), 2938 (w), 2878 (w), 2842 (w), 1715 (m), 1624 (w), 1590 (w), 1515 (m), 1465 (w), 1453 (w), 1430 (w), 1374 (w), 1289 (m), 1257 (m), 1211 (s), 1178 (m), 1160 (m), 1129 (m), 1102 (s), 1061 (m), 1031 (w), 923 (w), 908 (w), 833 (w), 818 (w), 765 (w);

^{1}H (401 MHz, CDCl$_3$): δ 7.59 (s, 1H, H-7), 7.06 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6), 7.03 (d, *J* = 2.0 Hz, 1H, H-2), 6.90 (d, *J* = 8.2 Hz, 1H, H-5), 5.90 (s, 1H, O*H*), 5.24 (sept, *J* = 6.3 Hz, 1H, OC*H*(CH$_3$)$_2$), 5.14 (sept, *J* = 6.2 Hz, 1H, OC*H*(CH$_3$)$_2$), 3.88 (s, 3H, OC*H*$_3$), 1.31 (d, *J* = 6.3 Hz, 6H, OCH(C*H*$_3$)$_2$), 1.30 (d, *J* = 6.3 Hz, 6H, OCH(C*H*$_3$)$_2$);

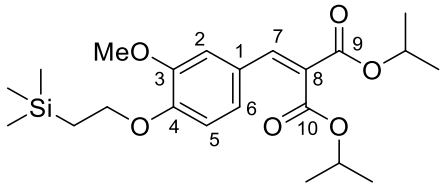
^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 167.0 (s, C-9/10), 164.2 (s, C-9/10), 148.2 (s, C-4), 146.6 (s, C-3), 141.6 (d, C-7), 125.5 (s, C-1/8), 124.9 (d, C-6), 124.5 (s, C-1/8), 114.8 (d, C-5), 111.6 (d, C-2), 69.3 (d, O*C*H(CH$_3$)$_2$), 69.2 (d, O*C*H(CH$_3$)$_2$), 56.0 (q, O*C*H$_3$), 22.0 (q, OCH(*C*H$_3$)$_2$), 21.8 (q, OCH(*C*H$_3$)$_2$);

MS (ESI−) *m/z*, (%): 321 (100, [M − H]$^-$), 306 (16);

HRMS (ESI−) *m/z*: [M − H]$^-$ calcd. for $C_{17}H_{21}O_6$ 321.1344; found: 321.1344.

Step 2. Following the procedure for **171a**, phenol **170c** (5.975 g, 18.5 mmol) was alkylated in dry toluene (125 mL) using PPh$_3$ (7.30 g, 27.8 mmol), 2-(trimethylsilyl)ethanol (3.45 mL, 24.1 mmol) and diisopropyl azodicarboxylate (4.74 mL, 24.1 mmol). Yield 6.59 g (84%) of **171c** as a colourless oil that slowly crystallizes on standing, mp 48-50 °C.

Diisopropyl 2-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]benzylidene}malonate (**171c**)



R_f 0.46 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2980 (w), 2952 (w), 2897 (w), 2832 (w), 1718 (s), 1623 (w), 1597 (w), 1513 (m), 1466 (w), 1423 (w), 1374 (w), 1333 (w), 1246 (vs), 1228 (vs), 1191 (m), 1165 (m), 1142 (s), 1105 (vs), 1059 (m), 1036 (m), 990 (w), 964 (w), 855 (m), 836 (s), 808 (w), 768 (w), 753 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.59 (s, 1H, H-7), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H, H-6), 7.03 (d, *J* = 2.1 Hz, 1H, H-2), 6.81 (d, *J* = 8.3 Hz, 1H, H-5), 5.24 (sept, *J* = 6.3 Hz, 1H, OC*H*(CH_3)$_2$), 5.13 (sept, *J* = 6.3 Hz, 1H, OC*H*(CH_3)$_2$), 4.18-4.09 (m, 2H, OC$H_2$$CH_2$TMS), 3.83 (s, 3H, O$CH_3$), 1.31 (d, *J* = 6.3 Hz, 6H, OCH(CH_3)$_2$), 1.29 (d, *J* = 6.3 Hz, 6H, OCH(CH_3)$_2$), 1.23-1.16 (m, 2H, OCH_2CH_2TMS), 0.07 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.0 (s, C-9/10), 164.2 (s, C-9/10), 150.7 (s, C-4), 149.3 (s, C-3), 141.5 (d, C-7), 125.5 (s, C-8), 124.4 (s, C-1), 124.3 (d, C-6), 112.2 (d, C-2/5), 112.1 (d, C-2/5), 69.2 (d, O*C*H(*C*H$_3$)$_2$), 69.1 (d, O*C*H(*C*H$_3$)$_2$), 66.5 (t, O*C*$H_2$$CH_2$TMS), 55.9 (q, O*C*$H_3$), 21.9 (q, OCH(*C*H$_3$)$_2$), 21.7 (q, OCH(*C*H$_3$)$_2$), 17.8 (t, OCH_2*C*H_2TMS), –1.3 (q, Si(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 867 (5, [2M + Na]$^+$), 445 (44, [M + Na]$^+$), 423 (12, [M + H]$^+$), 335 (25, [M – COO*i*-Pr]$^+$), 293 (100, [M – COO*i*-Pr – CH_3CHCH_2]$^+$);

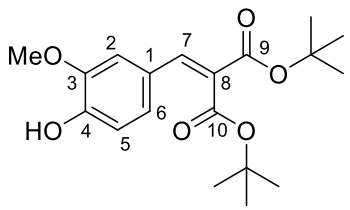
HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{22}H_{35}O_6Si$ 423.2197; found: 423.2195, [M + Na]$^+$ calcd. for $C_{22}H_{34}O_6NaSi$ 445.2017; found: 445.2013;

Anal. calcd. for $C_{22}H_{34}O_6Si$ (422.59): C, 62.53; H, 8.11. Found: C, 62.29; H, 8.06.

Synthesis of 171d

Step 1. A mixture of vanillin (3.04 g, 20 mmol), di-*tert*-butyl malonate (6.3 mL, 28 mmol), piperidine (0.30 mL, 3 mmol) and acetic acid (0.12 mL, 2 mmol) in toluene (20 mL) was heated to reflux using a Dean-Stark trap for 4 h. After the azeotropic distillation of water ceased, the mixture was cooled and concentrated and dried in high vacuum. The semi-solid mixture was purified by flash chromatography (silica, 11:1 to 5:1 PE/EA) to yield 4.36 g (62%) of **170d** as a colourless amorphous solid.

Di-tert-butyl 2-(4-hydroxy-3-methoxybenzylidene)malonate (**170d**)



R_f 0.60 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3300 (br.); 2978 (w), 2936 (w), 2847 (w), 1710 (s), 1625 (w), 1591 (w), 1516 (m), 1455 (w), 1431 (w), 1392 (w), 1367 (m), 1240 (s), 1146 (vs), 1128 (m), 1067 (m), 1031 (m), 954 (w), 848 (w), 818 (w), 772 (w), 744 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.46 (s, 1H, H-7), 7.12-7.03 (m, 2H, H-2, H-6), 6.89 (d, J = 8.7 Hz, 1H, H-5), 5.88 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 1.54 (s, 9H, O*t*-Bu), 1.53 (s, 9H, O*t*-Bu);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.7 (s, C-9/10), 164.0 (s, C-9/10), 147.9 (s, C-4), 146.6 (s, C-3), 140.2 (d, C-7), 126.7 (s, C-8), 125.9 (s, C-1), 124.7 (d, C-6), 114.7 (d, C-5), 111.7 (d, C-2), 82.2 (s, COO*C*Me$_3$), 81.9 (s, COO*C*Me$_3$), 56.1 (q, OCH_3), 28.3 (q, *t*-Bu), 28.1 (q, *t*-Bu);

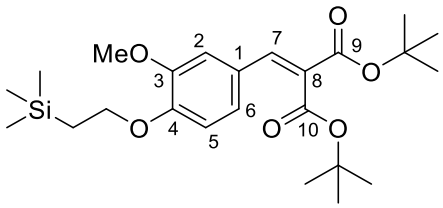
MS (ESI–) *m/z*, (%): 349 (100, [M – H]$^-$), 175 (12);

HRMS (ESI–) *m/z*: [M – H]$^-$ calcd. for $C_{19}H_{25}O_6$ 349.1657; found: 349.1657;

Anal. calcd. for $C_{19}H_{26}O_6$ (350.41): C, 65.13; H, 7.48. Found: C, 64.89; H, 7.59.

Step 2. Following the procedure for **171a**, from phenol **170d** (1.38 g, 3.94 mmol) was alkylated in dry toluene (30 mL) using PPh_3 (1.55 g, 5.91 mmol), 2-(trimethylsilyl)ethanol (0.73 mL, 5.12 mmol) and diisopropyl azodicarboxylate (1.00 mL, 5.12 mmol). Yield 1.57 g (88%) of **171d** as a colourless oil that forms an amorphous solid after two months at –18 °C.

Di-tert-butyl 2-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]benzylidene}malonate (**171d**)



R_f 0.40 (hexane/EA 11:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2977 (w), 2954 (w), 2935 (w), 2903 (w), 2833 (w), 1713 (m), 1624 (w), 1597 (w), 1513 (m), 1466 (w), 1423 (w), 1392 (w), 1367 (w), 1335 (w), 1247 (s), 1237 (s), 1139 (vs), 1064 (m), 1035 (m), 991 (w), 964 (w), 944 (w), 837 (s), 774 (w), 747 (w), 694 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.47 (s, 1H, H-7), 7.10 (m, 2H, H-2, H-6), 6.81 (d, J = 8.5, Hz, 1H, H-5), 4.19-4.10 (m, 2H, OCH_2CH$_2$TMS), 3.84 (s, 3H, OCH_3), 1.54 (s, 9H, OC(CH_3)$_3$), 1.53 (s, 9H, OC(CH_3)$_3$), 1.28-1.15 (m, 2H, OCH$_2$CH_2TMS), 0.07 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.7 (s, C-9/10), 164.1 (s, C-9/10), 150.5 (s, C-4), 149.3 (s, C-3), 140.2 (d, C-7), 126.6 (s, C-8), 125.9 (s, C-1), 124.0 (d, C-6), 112.6 (d, C-2), 112.1 (d, C-5), 82.2 (s, O*C*(CH$_3$)$_3$), 81.9 (s, O*C*(CH$_3$)$_3$), 66.4 (t, OCH$_2$CH$_2$TMS), 56.1 (q, O*C*H$_3$), 28.3 (q, OC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 17.8 (t, OCH$_2$*C*H$_2$TMS), –1.3 (q, Si(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 923 (33, [2M + Na]$^+$), 489 (5, [M + K]$^+$), 473 (30, [M + Na]$^+$), 451 (10, [M + H]$^+$), 395 (13, [M + H – isobutene]$^+$), 339 (42, [M + H – 2×isobutene]$^+$), 321 (17, [M + H – 2×isobutene – H_2O]$^+$), 293 (100, [M + H – 2×isobutene – H_2O – CO]$^+$);

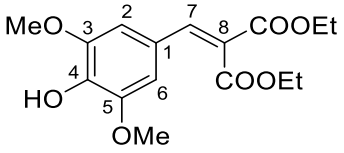
HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{24}H_{39}O_6Si$ 451.2510; found: 451.2509, [M + Na]$^+$ calcd. for $C_{24}H_{38}NaO_6Si$ 473.2330; found: 473.2327;

Anal. calcd. for $C_{24}H_{38}O_6Si$ (450.65): C, 63.97; H, 8.50. Found: C, 63.67; H, 8.38.

Synthesis of malonate 188

Step 1. A mixture of syringaldehyde (3.64 g, 20 mmol), diethyl malonate (4.3 mL, 28 mmol), piperidine (0.30 mL, 3 mmol) and AcOH (0.12 mL, 2 mmol) in toluene (20 mL) was heated to reflux using a Dean-Stark trap for 4 h. After the azeotropic distillation of water ceased, the mixture was cooled and concentrated in vacuum to ~1/2 volume. PE (50 mL) and Et_2O (5) were added, the resulting suspension was matured for 1 h and filtered. The solids were washed with PE (200 mL) and dried under vacuum affording 6.19 g (95%) of **194** as a pale-yellow solid, mp 111-112 °C.

Diethyl 2-(4-hydroxy-3,5-dimethoxybenzylidene)malonate (**194**)



R_f 0.15 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3250 (br.), 2979 (w), 2938 (w), 2842 (w), 1723 (s), 1623 (m), 1601 (m), 1514 (s), 1459 (m), 1429 (w), 1396 (w), 1382 (w), 1328 (w), 1217 (vs), 1157 (s), 1112 (s), 1067 (s), 1044 (w), 1023 (w), 989 (w), 830 (w), 623 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.63 (s, 1H, H-7), 6.77 (s, 2H, H-2, H-6), 6.10-5.50 (b. s, 1H, O*H*), 4.34 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.29 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.88 (s, 6H, OC*H*$_3$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.4 (s, *C*OOEt), 164.5 (s, *C*OOEt), 147.1 (s, C-3, C-5), 142.4 (d, C-7), 137.5 (s, C-4), 124.3 (s, C-1/8), 124.2 (s, C-1/8), 106.9 (d, C-2, C-6), 61.8 (t, O*C*H$_2$CH$_3$), 61.6 (t, O*C*H$_2$CH$_3$), 56.4 (q, 2×C, O*C*H$_3$), 14.3 (q, OCH$_2$*C*H$_3$), 14.2 (q, OCH$_2$*C*H$_3$);

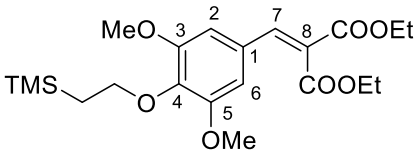
MS (ESI+) *m/z*, (%): 671 (43, [2M + Na]$^+$), 363 (23, [M + K]$^+$), 347 (100, [M + Na]$^+$), 325 (36, [M + H]$^+$), 279 (86, [M – EtO]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{16}H_{20}O_7Na$ 347.1101; found: 347.1099;

Anal. calcd. for $C_{11}H_{14}O_2$ (324.33): C, 59.25; H, 6.22. Found: C, 59.49; H, 6.27.

Step 2. Following the procedure for **171a**, phenol **194** (3.24 g, 10 mmol) was alkylated in dry toluene (45 mL) using PPh_3 (3.93 g, 15 mmol), 2-(trimethylsilyl)ethanol (1.9 mL, 13 mmol) and diisopropyl azodicarboxylate (2.6 mL, 13 mmol). Yield 3.57 g (84%) of **188** as a colourless solid, mp 44-45 °C.

Diethyl 2-{3,5-dimethoxy-4-[2-(trimethylsilyl)ethoxy]benzylidene}malonate (**188**)



R_f 0.45 (hexane/EA, 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2980 (w), 2953 (w), 2901 (w), 2841 (w), 1722 (s), 1626 (w), 1579 (m), 1503 (m), 1454 (w), 1421 (w), 1393 (w), 1377 (w), 1333 (w), 1241 (vs), 1209 (s), 1155 (w), 1124 (vs), 1064 (m), 1041 (w), 1025 (w), 966 (w), 945 (w), 856 (s), 834 (s), 762 (w), 693 (w), 620 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.64 (s, 1H, H-7), 6.73 (s, 2H, H-2, H-6), 4.39-4.25 (m, 4H, OCH_2CH$_3$), 4.17-4.05 (m, 2H, OCH_2CH$_2$TMS), 3.82 (s, 6H, OCH_3), 1.37-1.27 (m, 6H, OCH$_2$CH_3), 1.19-1.08 (m, 2H, OCH$_2$CH_2TMS), 0.02 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.2 (s, *C*OOEt), 164.3 (s, *C*OOEt), 153.7 (s, C-3, C-5), 142.2 (d, C-7), 139.3 (s, C-4), 128.0 (s, C-1), 125.2 (s, C-8), 107.1 (d, C-2, C-6), 71.2 (t, O*C*H$_2$CH$_2$TMS), 61.8 (t, O*C*H$_2$CH$_3$), 61.7 (t, O*C*H$_2$CH$_3$), 56.2 (q, 2×C, O*C*H$_3$), 18.9 (t, OCH$_2$*C*H$_2$TMS), 14.3 (q, OCH$_2$*C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$), −1.4 (q, Si(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 871 (4, [2M + Na]$^+$), 463 (7, [M + K]$^+$), 447 (100, [M + Na]$^+$);

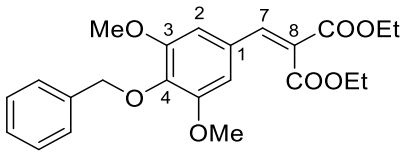
HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{21}H_{32}O_7NaSi$ 447.1810; found: 447.1804;

Anal. Calcd. for $C_{11}H_{14}O_2$ (424.56): C, 59.41; H, 7.60. Found: C, 59.30; H, 7.42.

Synthesis of benzylated malonate 195

A mixture of malonate **194** (6.5 g, 20 mmol), BnBr (4.8 mL, 40 mmol) and calcinated K_2CO_3 (5.53 g, 40 mmol) in DMF (40 mL) was stirred at r.t. for 2 days. The mixture was partitioned between water (250 mL) and EA (250 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by flash chromatography (pure cyclohexane to cyclohexane/EA 4:1) to yield 8.0 g of **195** (96%) as a colourless solid.

Diethyl 2-[4-(benzyloxy)-3,5-dimethoxybenzylidene]malonate (**195**)



R_f 0.46 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3031 (w), 2980 (w), 2936 (w), 2842 (w), 1720 (s), 1625 (w), 1579 (m), 1503 (m), 1454 (m), 1421 (w), 1377 (w), 1333 (w), 1239 (s), 1210 (s), 1155 (m), 1124 (vs), 1064 (m), 988 (w), 837 (w), 734 (m), 697 (m);

^{1}H (401 MHz, $CDCl_3$): δ 7.64 (s, 1H, H-7), 7.48-7.44 (m, 2H, Ph), 7.37-7.27 (m, 3H, Ph), 6.72 (s, 2H, H-2), 5.05 (s, 1H, OCH_2Ph), 4.32 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 4.30 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 3.81 (s, 6H, C3-OCH_3), 1.33 (t, J = 11.7, 7.2 Hz, 3H, OCH$_2$CH_3), 1.30 (t, J = 11.7, 7.2 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.1 (s, *C*OOEt), 164.3 (s, *C*OOEt), 153.7 (s, 2×C, C-3), 142.2 (d, C-7), 139.3 (s, C-4), 137.6 (s, Ph^{ipso}), 128.6 (d, Ph^{meta}), 128.5 (s, C-1), 128.3 (d, Ph^{ortho}), 128.1 (d, Ph^{para}), 125.5 (s, C-8), 107.1 (d, C-2), 75.2 (t, O*C*H$_2$Ph), 61.8 (t, O*C*H$_2$CH$_3$), 61.7 (t, O*C*H$_2$CH$_3$), 56.2 (q, 2×C, C-3), 14.3 (q, OCH$_2$*C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 851 (7, [M + Na]$^+$), 437 (100, [2M + Na]$^+$); MS (APCI+) *m/z*, (%): 415 (100, [M + H]$^+$), 369 (70, [M + H – EtOH]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{23}H_{26}O_7Na$ 439.1571; found: 437.1568; HRMS (APCI+) *m/z*: [M + H]$^+$ calcd. for $C_{23}H_{27}O_7$ 415.1751; found: 415.1750.

6.2.7. Optimization of asymmetric conjugate addition of **157** to malonates **171a-d**

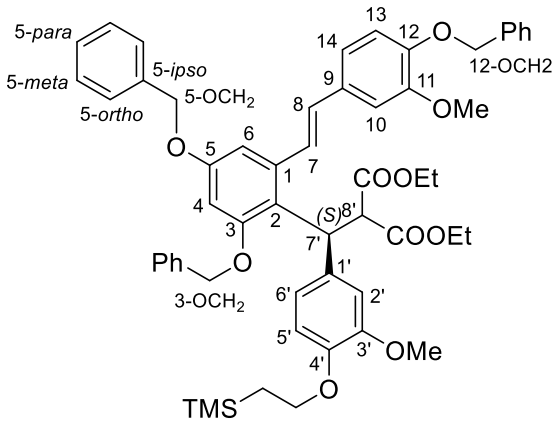
Conjugate addition of 157 to 171b in toluene at –78 °C

In a flame-dried Schlenk flask, stilbene **157** (39.5 mg, 65µmol) and (+)-sparteine (17 µL, 75 µmol) were dissolved in dry toluene (0.6 mL). Toluene was evaporated under vacuum using a rotary evaporator followed by drying in high vacuum for 20 min. Under a N_2 atmosphere, a stirring bar was added and the mixture was re-dissolved dry toluene (0.4 mL). The flask was heated gently until **157** fully dissolved. The reaction was quickly cooled to –78 °C, followed by addition of *n*-BuLi (41 µl, 65 µmol, 1.6 M in hexanes) after 1 min. A yellow colour developed immediately during the addition and persisted until quenching. The solution was stirred at –78 °C for 10 min. A solution of **171b** (19.7 mg, 50 µmol) in toluene (0.3 mL) was added dropwise, followed by stirring at –78 °C for 30 min and warming to r.t. The reaction was quenched by wet Et_2O (3 mL) and filtered through a pad of silica gel (4 cm, ø 2.5 cm) with Et_2O (130 mL). Concentration and drying under vacuum gave 59.1 mg of a yellow crude product. Purification by flash chromatography afforded 35.1 mg (76%) of **172b** as a colourless sticky solid, 49% ee by chiral HPLC (Hexane/*i*-PrOH 85:15, 1 mL/min).

Conjugate addition of 157 to 171b in toluene/ethylbenzene/pentane eutectic at –115 °C

In a flame-dried Schlenk flask, stilbene **157** (39.5 mg, 65µmol) and (+)-sparteine (46 µL, 200 µmol) were dissolved in dry toluene (0.6 mL). Toluene was evaporated under vacuum using rotary evaporator followed by drying under high vacuum for 20 min. Under N_2 atmosphere, stirring bar was added, followed by dry toluene (0.8 mL) and dry ethylbenzene (0.8 mL). The flask was heated gently until **157** fully dissolved, then dry pentane (0.8 mL) was added. The reaction was quickly cooled to –78 °C, followed by addition of *n*-BuLi (41 µl, 65 µmol, 1.6 M in hexanes) after 1 min. A yellow color developed immediately during the addition and persisted until quenching. The solution was stirred at –78 °C for 10 min followed by cooling to –115 °C (PE/liquid N_2 bath) while maintaining vigorous stirring. The solvent mixture became very viscous but remained homogenous. Note: when cooled below –120 °C, the mixture becomes glassy and eventually crystallizes after several minutes. A solution of **171b** (19.7 mg, 50 µmol) in toluene (0.3 mL) was added dropwise, followed by stirring at –115 °C for 10 min and gradually warming to –80 °C. The reaction was quenched by wet Et_2O (3 mL) and filtered through a pad of silica gel (4 cm, ø 2.5 cm) with Et_2O (130 mL). Concentration and drying under vacuum gave 125 mg of a yellow crude product. Purification by flash chromatography (cyclohexane/EA 20:1 to 2:1) afforded 36.3 mg (78%) of **172b** as a colourless sticky solid, 70% ee by chiral HPLC (Hexane/*i*-PrOH 85:15, 1 mL/min).

Diethyl (S,E)-2-({2,4-bis(benzyloxy)-6-[4-(benzyloxy)-3-methoxystyryl]phenyl}{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}methyl)malonate (**172b**)



R_f 0.14 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3089 (w), 3032 (w), 2952 (w), 2870 (w), 1752 (w), 1730 (w), 1595 (w), 1511 (m), 1454 (w), 1418 (w), 1370 (w), 1248 (s), 1228 (m), 1137 (vs), 1029 (m), 965 (w), 856 (m), 837 (m), 803 (w), 731 (s), 696 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.67 (d, *J* = 15.5 Hz, 1H, H-7), 7.50-7.29 (m, 15H, Ph), 7.15-7.03 (m, 2H, H-10, H-14), 6.89 (d, *J* = 8.3 Hz, 1H, H-13), 6.81 (d, *J* = 15.7 Hz, 1H, H-8), 6.72 (m, 2H, H-4/6, H-2'), 6.67 (dd, *J* = 8.4, 2.1 Hz, 1H, H-6'), 6.58 (d, *J* = 8.3 Hz, 1H, H-5'), 6.46 (s, 1H, H-4/6), 5.25-5.05 (br., 1H, H-7'), 5.21 (s, 2H, C12-OC*H*$_2$Ph), 5.06-4.90 (m, 3H, H-8', C3-OC*H*$_2$Ph), 5.01 (s, 2H, C5-OC*H*$_2$Ph), 4.07 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.03-3.93 (m, 4H, OC*H*$_2$CH$_3$, OC*H*$_2$CH$_2$TMS), 3.97 (s, 3H, C11-OC*H*$_3$), 3.40 (s, 3H, C3'-OC*H*$_3$), 1.16-1.12 (m, 2H, OCH$_2$C*H*$_2$TMS), 1.11 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.99 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.03 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.8 (s, *C*OOEt), 168.5 (s, *C*OOEt), 158.5 (s, C-5), 158.3 (s, C-3), 149.9 (s, C-11), 148.8 (s, C-3'), 148.3 (s, C-12), 146.4 (s, C-4'), 140.0 (s, C-1), 137.2 (s, Ph^{ipso}), 137.0 (s, Ph^{ipso}), 136.8 (s, Ph^{ipso}), 133.9 (s, C-1'), 132.3 (d, C-8), 131.3 (s, C-9), 128.74 (d, 2×C, Ph^{meta}), 128.72 (d, 4×C, Ph^{meta}), 128.18 (d, Ph^{para}), 128.17 (d, Ph^{para}), 128.04 (d, 2×C, C3-Ph^{ortho}), 128.01 (d, Ph^{para}), 127.8 (d, 2×C, C5-Ph^{ortho}), 127.4 (d, 2×C, C12-Ph^{ortho}), 126.7 (d, C-7), 120.8 (s, C-2), 120.3 (d, C-6'), 119.8 (d, C-14), 114.2 (d, C-13), 112.4 (d, C-5'), 111.6 (d, C-2'), 110.2 (d, C-10), 105.1 (d, C-4/6), 100.3 (d, C-4/6), 71.2 (t, C12-O*C*H$_2$Ph), 70.8 (t, C3-O*C*H$_2$Ph), 70.2 (t, C5-O*C*H$_2$Ph), 66.2 (t, O*C*H$_2$CH$_2$TMS), 61.4 (t, O*C*H$_2$CH$_3$), 61.3 (t, O*C*H$_2$CH$_3$), 56.2 (q, C11-O*C*H$_3$), 55.4 (q, C3'-O*C*H$_3$), 54.5 (d, C-8'), 43.3 (d, C-7'), 17.9 (t, OCH$_2$*C*H$_2$TMS), 14.1 (q, OCH$_2$*C*H$_3$), 14.0 (q, OCH$_2$*C*H$_3$), –1.3 (q, Si(*C*H$_3$)$_3$);

^{1}H NMR (401 MHz, CD_3CN): δ 7.71-7.54 (m, 1H, H-7), 7.49-7.28 (m, 15H, Ph), 7.19-7.06 (m, 2H, H-10, H-14), 7.02 (d, *J* = 8.3 Hz, 1H, H-13), 6.90 (d, *J* = 15.9 Hz, 1H, H-8), 6.76 (d, *J* = 2.4 Hz, 1H, H-4/6), 6.72 (d, *J* = 1.7 Hz, 1H, H-2'), 6.70 (d, *J* = 8.4 Hz, 1H, 5'), 6.66 (dd, *J* = 8.3, 1.7 Hz, 1H, H-6'), 6.54 (d, *J* = 2.4 Hz, 1H, H-4/6), 5.30-5.00 (br., 1H, H-7'), 5.12 (s, 2H, C5/C12-OC*H*$_2$Ph), 5.08 (s, 2H, C5/C12-OC*H*$_2$Ph), 5.03 (m, 2H, C3-OC*H*$_2$Ph), 4.97-4.80 (broad, 1H, H-8'), 4.03 (q, *J* = 7.3 Hz, 2H, OC*H*$_2$CH$_3$), 3.99-3.96 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.95-3.82 (m, 2H, OC*H*$_2$CH$_3$), 3.88 (s, 3H, 11-OC*H*$_3$), 3.42 (s, 3H, 3'-OC*H*$_3$), 1.08 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.07-1.01 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.94 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.03 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 169.5 (s, C-9'), 169.1 (s, C-9'), 159.5 (s, C-5), 159.1 (s, C-3), 150.9 (s, C-11), 149.4 (s, 2×C, C-12, C-3'), 147.8 (s, C-4'), 140.8 (s, C-1), 138.4 (s, C5/C12-Ph^{ipso}), 138.3 (s, C5/C12-Ph^{ipso}), 138.0 (s, C3-Ph^{ipso}), 134.9 (s, C-1'), 133.4 (d, C-8, detected by HSQC), 132.0 (s, C-9), 129.6 (d, 2×C, Ph^{meta}), 129.5 (d, 4×C, Ph^{meta}), 129.1 (d, Ph^{para}), 129.04 (d, Ph^{para}), 129.01 (d, Ph^{para}), 128.95 (d, 2×C, Ph^{ortho}), 128.94 (d, 2×C, Ph^{ortho}), 128.7 (d, 2×C, Ph^{ortho}), 126.8 (d, C-6'), 120.5

(d, C-14), 115.1 (d, C-13), 113.8 (d, C-2‘/5’), 112.7 (d, C-2’/5’), 111.1 (d, C-10), 106.0 (d, C-4/6), 101.2 (d, C-4/6), 71.6 (t, C5/C12-O*C*H$_2$Ph), 71.4 (t, C3-O*C*H$_2$Ph), 70.7 (t, C5/C12-O*C*H$_2$Ph), 67.1 (t, O*C*H$_2$CH$_2$TMS), 62.2 (t, O*C*H$_2$CH$_3$), 62.1 (t, O*C*H$_2$CH$_3$), 56.5 (q, C11-*C*H$_3$), 56.0 (q, C3’-*C*H$_3$), 55.3 (d, C-8’), 42.0 (d, C-7’, detected by HSQC), 18.3 (t, OCH$_2$*C*H$_2$TMS), 14.3 (q, OCH$_2$*C*H$_3$), 14.2 (q, OCH$_2$*C*H$_3$), –1.4 (q, Si(*C*H$_3$)$_3$);

Hindered rotation (presumably around C2-C7’ bond) leads to broadening of some ^{1}H and ^{13}C NMR signals. NMR spectra acquired at 52 °C in $CDCl_3$ show only marginally less broadening. Heating **172b** in C_6D_6 above 70 °C results in the formation of *cis*-**172b**, which is possibly driven by the release of strain associated with steric crowding around the C2-C7’ and C1-C7 bonds.

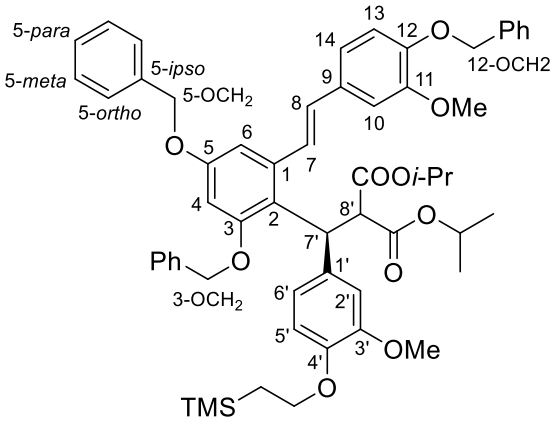
MS (ESI+) *m/z*, (%): 961 (6, [M + K]$^+$), 945 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{56}H_{62}NaO_{10}Si$ 945.4005; found: 945.4002.

Conjugate addition of 157 to 171c in toluene at –78 °C

The same procedure as for **172b** was followed, starting with **157** (39.5 mg, 65 µmol), (+)-sparteine (46 µL, 200 µmol) and **171c** (21.1 mg, 50 µmol), malonate addition at –78 °C. Yield 33.5 mg **172c** (70%) as a colourless film, 52% ee by chiral HPLC (Hexane/*i*-PrOH 85:15, 1 mL/min).

Diisopropyl (S,E)-2-({2,4-bis(benzyloxy)-6-[4-(benzyloxy)-3-methoxystyryl]phenyl}{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}methyl)malonate (**172c**)



R_f 0.20 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3065 (w), 3033 (w), 2979 (w), 2925 (m), 2850 (w), 1749 (w), 1727 (m), 1596 (m), 1511 (s), 1464 (w), 1450 (m), 1419 (w), 1374 (w), 1260 (s), 1249 (s), 1230 (s), 1179 (w), 1140 (vs), 1101 (s), 1039 (m), 1028 (m), 966 (w), 857 (m), 837 (s), 803 (w), 734 (m), 696 (s);

^{1}H (401 MHz, $CDCl_3$): δ 7.70 (br. d, *J* = 16.0 Hz, 1H, H-7), 7.48-7.30 (m, 15H, Ph), 7.17-7.03 (m, 2H, H-10, H-14), 6.90 (d, *J* = 8.3 Hz, 1H, H-13), 6.82 (d, *J* = 15.7 Hz, 1H, H-8), 6.74-72 (m, 2H, H-4/6, H-2’), 6.68 (dd, *J* = 8.3, 2.1 Hz, 1H, H-6’), 6.58 (d, *J* = 8.3 Hz, 1H, H-5’), 6.46 (br. s, 1H, H-4/6), 5.21 (s, 2H, C12-OC*H*$_2$Ph), 5.20-5.10 (br. m, 1H, H-7’), 5.05-4.90 (m, 3H, H-8’, C3-OC*H*$_2$Ph), 5.02 (s, 2H, C5-OC*H*$_2$Ph), 4.95-4.79 (m, 2H, OC*H*(CH$_3$)$_2$), 4.03-3.97 (m, 4H, OC*H*$_2$CH$_3$, OC*H*$_2$CH$_2$TMS), 3.97 (s, 3H, C11-OC*H*$_3$), 3.38 (s, 3H, C3’-OC*H*$_3$), 1.16-1.11 (m, 2H, OCH$_2$C*H*$_2$TMS), 1.11-1.07 (m, 6H, OCH(C*H*$_3$)$_2$), 1.04 (d, *J* = 7.1 Hz, 3H, OCH(C*H*$_3$)$_2$), 0.97 (d, *J* = 7.1 Hz, 3H, OCH(C*H*$_3$)$_2$), 0.03 (s, 9H, Si(C*H*$_3$)$_3$);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 168.3 (s, COO*i*-Pr), 168.1 (s, COO*i*-Pr), 158.5 (s, C-5), 158.4 (s, C-3), 149.9 (s, C-11), 148.8 (s, C-3'), 148.2 (s, C-12), 146.4 (s, C-4'), 140.0 (s, C-1), 137.2 (s, Ph^{ipso}), 137.0 (s, Ph^{ipso}), 136.9 (s, Ph^{ipso}), 134.0 (s, C-1'), 132.2 (d, C-8), 131.3 (s, C-9), 128.72 (d, 2×C, Ph^{meta}), 128.70 (d, 4×C, Ph^{meta}), 128.16 (d, Ph^{para}), 128.13 (d, Ph^{para}), 128.09 (d, 2×C, C3-Ph^{ortho}), 128.0 (d, Ph^{para}), 127.7 (d, 2×C, C5-Ph^{ortho}), 127.4 (d, 2×C, C12-Ph^{ortho}), 126.8 (d, C-7), 121.0 (s, C-2), 120.4 (d, C-6'), 119.8 (d, C-14), 114.2 (d, C-13), 112.4 (d, C-5'), 111.6 (d, C-2'), 110.0 (d, C-10), 105.1 (d, C-4/6), 100.4 (d, C-4/6), 71.2 (t, C12-OCH_2Ph), 70.8 (t, C3-OCH_2Ph), 70.2 (t, C5-OCH_2Ph), 68.72 (d, O$CH(CH_3)_2$), 68.66 (d, O$CH(CH_3)_2$), 66.2 (t, OCH_2CH_2TMS), 56.1 (q, C11-OCH_3), 55.4 (q, C3'-OCH_3), 54.7 (d, C-8'), 43.2 (d, C-7'), 21.7 (q, OCH(CH_3)$_2$), 21.6 (q, OCH(CH_3)$_2$), 21.5 (q, 2×C, OCH(CH_3)$_2$), 17.9 (t, OCH_2CH_2TMS), –1.3 (q, Si(CH_3)$_3$);

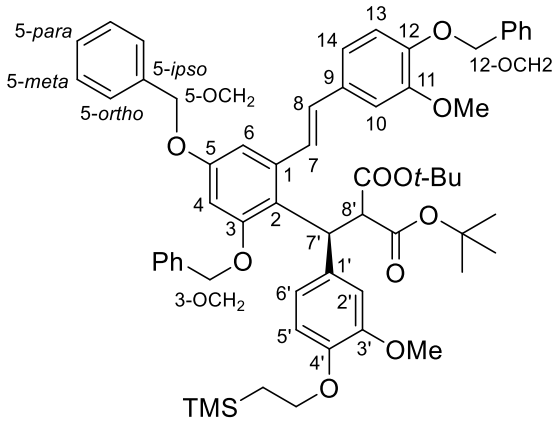
MS (ESI+) *m/z*, (%): 1918 (76, $[2M + NH_4]^+$), 973 (7, $[M + Na]^+$), 968 (100, $[M + NH_4]^+$);

HRMS (ESI+) *m/z*: $[M + NH_4]^+$ calcd. for $C_{58}H_{70}NO_{10}Si$ 968.4764; found: 968.4762.

Conjugate addition of 157 to 171d in toluene at –78 °C

The same procedure as for **172b** was followed, starting with **157** (39.5 mg, 65 µmol), (+)-sparteine (46 µL, 200 µmol) and **171d** (22.5 mg, 50 µmol), malonate addition at –78 °C. Yield 30.0 mg **172d** (61%) as a colourless film, 44% ee by chiral HPLC (Hexane/*i*-PrOH 79:3, 1 mL/min). Freeze-drying from C_6H_6 produced a solid foam.

Di-tert-butyl (S,E)-2-({2,4-bis(benzyloxy)-6-[4-(benzyloxy)-3-methoxystyryl]phenyl}{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}methyl)malonate (**172d**)



R_f 0.25 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3087 (w), 3063 (w), 3033 (w), 2951 (w), 2925 (m), 2855 (w), 1747 (w), 1726 (m), 1596 (m), 1511 (m), 1463 (w), 1454 (w), 1419 (w), 1367 (w), 1249 (s), 1136 (vs), 1028 (m), 965 (w), 911 (w), 838 (s), 802 (w), 732 (s), 696 (s);

^{1}H (401 MHz, $CDCl_3$): δ 7.69 (d, *J* = 15.9 Hz, 1H, H-7), 7.50-7.29 (m, 15H, Ph), 7.13 (br. s, 1H, H-10), 7.06 (br. d, *J* = 8.2 Hz, 1H, H-14), 6.89 (d, *J* = 8.3 Hz, 1H, H-13), 6.82 (d, *J* = 15.7 Hz, 1H, H-8), 6.74 (br. s, 1H, H-4/6), 6.68 (d, *J* = 2.0 Hz, 1H, H-2'), 6.65 (br. d, *J* = 8.4 Hz, 1H, H-6'), 6.57 (d, *J* = 8.5 Hz, 1H, H-5'), 6.47 (br. s, 1H, H-4/6), 5.20 (s, 2H, C12-OCH_2Ph), 5.09 (d, *J* = 12.3 Hz, 1H, H-7'), 5.05-4.80 (m, 3H, H-8', C3-OCH_2Ph), 5.04 (s, 2H, C5-OCH_2Ph), 4.03-3.97 (m, 2H, OCH_2CH_2TMS), 3.96 (s, 3H, C11-OCH_3), 3.40 (s, 3H, C3'-OCH_3), 1.31 (s, 9H, OC(CH_3)$_3$), 1.20 (s, 9H, OC(CH_3)$_3$), 1.15-1.11 (m, 2H, OCH_2CH_2TMS), 0.03 (s, 9H, SiCH_3);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 168.1 (s, C-9'), 167.9 (s, C-9'), 158.6 (s, C-3/5), 158.5 (s, C-3/5), 149.9 (s, C-11), 148.7 (s, C-3'), 148.2 (s, C-12), 146.1 (s, C-4'), 139.9 (s, C-1), 137.2 (s, Ph^{ipso}), 137.1 (s, Ph^{ipso}), 136.9 (s, Ph^{ipso}), 134.4 (s, C-1'), 132.1 (d, C-8), 131.3 (s, C-9), 128.7 (br. d, 6×C, Ph^{meta}), 128.3 (d, Ph^{para}), 128.2 (d, Ph^{para}), 128.1 (d, 2×C, C3-Ph^{ortho}), 128.0 (d, Ph^{para}), 127.7 (d, 2×C, C5-Ph^{ortho}), 127.4 (d, 2×C, C12-Ph^{ortho}), 126.8 (d, C-7), 121.3 (s, C-2), 120.4 (d, C-6'), 119.8 (d, C-14), 114.2 (d, C-13), 112.5 (d, C-5'), 111.4 (d, C-2'), 110.0 (d, C-10), 104.9 (d, C-4/6), 100.3 (d, C-4/6), 81.2 (s, O*C*$(CH_3)_3$), 81.1 (s, O*C*$(CH_3)_3$), 71.2 (t, C12-O*C*H_2Ph), 70.8 (t, C3-O*C*H_2Ph), 70.2 (t, C5-O*C*H_2Ph), 66.2 (t, O*C*H_2CH_2TMS), 56.1 (q, C3'-O*C*H_3), 56.1 (q, C11-O*C*H_3), 55.3 (d, C-8'), 43.0 (d, C-7'), 27.9 (q, OC(*C*$H_3)_3$), 27.7 (q, OC(*C*$H_3)_3$), 17.9 (t, OCH_2*C*H_2TMS), 14.1 (q, OCH_2*C*H_3), 14.0 (q, OCH_2*C*H_3), –1.3 (q, Si*C*H_3);

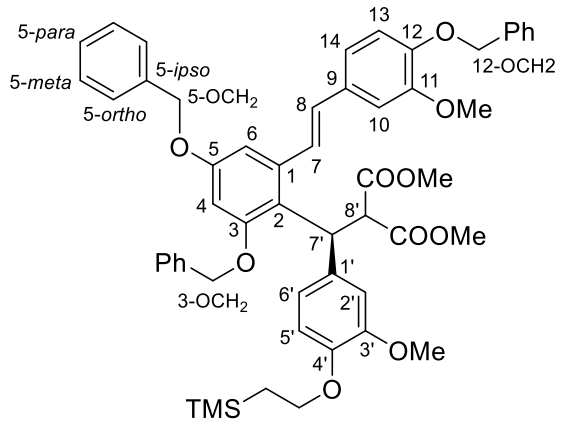
MS (ESI+) *m/z*, (%): 1078 (13), 1001 (4, $[M + Na]^+$), 996 (100, $[M + NH_4]^+$), 763 (4, [M – CH(COO*t*-Bu)$_2$]$^+$), 451 (3, [retro-Michael: **171d** + H]$^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{60}H_{70}NaO_{10}Si$ 1001.4631; found: 1001.4629; *m/z*: $[M + NH_4]^+$ calcd. for $C_{60}H_{74}NO_{10}Si$ 996.5077; found: 996.5080.

Conjugate addition of 157 to 171a in toluene at –78 °C

The same procedure as for **172b** was followed, starting with **157** (39.5 mg, 65 μmol), (+)-sparteine (46 μL, 200 μmol) and **171a** (18.3 mg, 50 μmol) addition of malonate at –78 °C. Yield 37.0 mg **172a** (82%) as a colourless film, 50% ee by chiral HPLC (Hexane/*i*-PrOH 85:15, 1 mL/min).

Dimethyl (S,E)-2-({2,4-bis(benzyloxy)-6-[4-(benzyloxy)-3-methoxystyryl]phenyl}{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}methyl)malonate (**172a**)



R_f 0.15 (hexane/EA x:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3062 (w), 3032 (w), 3004 (w), 2950 (w), 2871 (w), 2838 (w), 1757 (w), 1737 (m), 1595 (m), 1512 (m), 1454 (w), 1433 (w), 1419 (w), 1378 (w), 1249 (s), 1191 (w), 1140 (vs), 1029 (m), 966 (w), 911 (w), 857 (m), 839 (m), 803 (w), 738 (w), 698 (m), 641 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.75-7.50 (br., 1H, H-7), 7.50-7.28 (m, 15H, Ph), 7.14-7.02 (m, 2H, H-10, H-14), 6.89 (d, *J* = 8.3 Hz, 1H, H-13), 6.82 (d, *J* = 15.8 Hz, 1H, H-8), 6.73 (d, *J* = 2.4 Hz, 1H, H-4/6) 6.71 (d, *J* = 2.1 Hz, 1H, H-2'), 6.67 (dd, *J* = 8.3, 2.1 Hz, 1H, H-6'), 6.59 (d, *J* = 8.3 Hz, 1H, H-5'), 6.46 (d, *J* = 2.3 Hz, 1H, H-4/6), 5.35-5.10 (br., 1H, H-7'), 5.21 (s, 2H, C12-OC*H*$_2$Ph), 5.05-4.89 (m, 3H, H-8', C3-OC*H*$_2$Ph), 5.01 (s, 2H, C5-OC*H*$_2$Ph), 4.03-3.99 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.97 (s, 3H, C11-OC*H*$_3$), 3.61 (s, 3H, COOC*H*$_3$), 3.49 (s, 3H, COOC*H*$_3$), 3.42 (br. s, 3H, C3'-OC*H*$_3$), 1.17-1.12 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.04 (s, 9H, Si(C*H*$_3$)$_3$);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 169.3 (s, *C*OOMe), 168.8 (s, *C*OOMe), 158.6 (s, C-5), 158.2 (s, C-3), 149.9 (s, C-11), 148.9 (s, C-3'), 148.3 (s, C-12), 146.5 (s, C-4'), 140.1 (s, C-1), 137.2 (s, Ph^{ipso}), 136.9 (s, Ph^{ipso}), 136.8 (s, Ph^{ipso}), 133.7 (s, C-1'), 132.3 (d, C-8), 131.2 (s, C-9), 128.76 (d, 2×C, Ph^{meta}), 128.73 (d, 4×C, Ph^{meta}), 128.20 (d, 2×C, Ph^{para}), 128.01 (d, 3×C, Ph^{para}, C3-Ph^{ortho}), 127.8 (d, 2×C, C5-Ph^{ortho}), 127.4 (d, 2×C, C12-Ph^{ortho}), 126.6 (d, C-7), 120.7 (s, C-2), 120.1 (d, C-6'), 119.8 (d, C-14), 114.3 (d, C-13), 112.4 (d, C-5'), 111.6 (d, C-2'), 110.3 (d, C-10), 105.2 (d, C-4/6), 100.4 (d, C-4/6), 71.2 (t, C12-O*C*H_2Ph), 70.7 (t, C3-O*C*H_2Ph), 70.2 (t, C5-O*C*H_2Ph), 66.2 (t, O*C*$H_2$$CH_2$TMS), 56.2 (q, C11-O*C*$H_3$), 55.5 (q, C3'-O*C*$H_3$), 54.3 (d, C-8'), 52.7 (q, COO*C*H_3), 52.4 (q, COO*C*H_3), 43.3 (br. d, C-7'), 17.9 (t, OCH_2*C*H_2TMS), –1.3 (q, Si(*C*H_3)$_3$);

MS (ESI+) *m/z*, (%): 1806 (12, $[2M + NH_4]^+$), 933 (2, $[M + K]^+$), 917 (10, $[M + Na]^+$), 912 (100, $[M + NH_4]^+$), 895 (7, $[M + H]^+$);

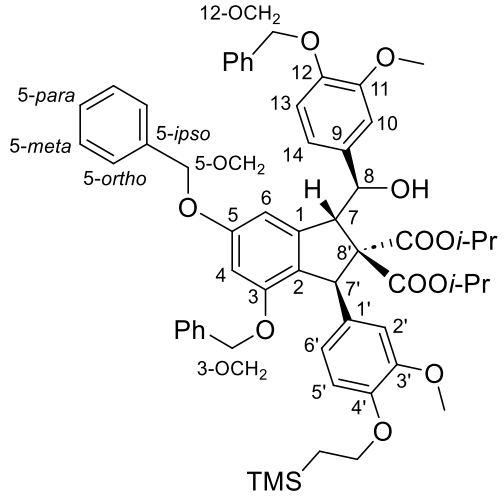
HRMS (ESI+) *m/z*: $[M + NH_4]^+$ calcd. for $C_{54}H_{62}NO_{10}Si$ 912.4138; found: 912.4137; *m/z*: $[M + Na]^+$ calcd. for $C_{54}H_{58}NaO_{10}Si$ 917.3692; found: 917.3690.

6.2.8. Tandem addition/oxidation of S4M3 (isolation of alcohol)

One-pot conjugate addition/oxidative bicyclisation of 157 with 171c in toluene

Stilbene **157** (39.5 mg, 65 µmol) and (+)-sparteine (34 µL, 150 µmol) were dissolved with gentle heating (~40 °C) in dry toluene (0.5 mL) in a Schlenk flask. The solution was cooled to –78 °C, followed by addition of *n*-BuLi solution (41 µL, 65 µmol, 1.6 M in hexanes). The resulting yellow solution was stirred at –78 °C for 10 min. A solution of **171c** (21.1 mg, 50 µmol) in toluene (0.4 mL) was added dropwise, followed by stirring at –78 °C for 30 min, then by gradual warming to –20 °C over 30 min. THF (2 mL) and calcinated LiBr (26 mg, 0.30 mmol) were added, followed by $FeCp_2PF_6$ (**52**) (100 mg, 0.30 mmol). The Schlenk flask was flushed with dry N_2 after each addition of solid reagent. The dark blue suspension was stirred for 10 min., followed by warming to r.t. over 20 min. The blue colour dissipated, giving dark brown/green solution. Quenching by saturated Na_2SO_3 (1 mL) caused quick decolouration, giving yellow emulsion, which was partitioned between diluted Na_2SO_3 (50 mL water, 8 mL sat. Na_2SO_3 solution), and EA (80 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give 197 mg of an orange solid. This material was adsorbed on a small amount of silica gel using Et_2O and loaded onto a 4 cm pad of silica (diameter 2.5 cm). PE (150 mL) was passed through the column, until all orange material ($FeCp_2$) eluted. The column was then washed with Et_2O (150 mL, fraction I) and EA (100 mL, fraction II). After concentration, fraction II yielded 35 mg of sparteine-related oxidation products containing no cyclisation product. Fraction, I yielded 81.7 mg of crude cyclisation product **175**, which was purified by flash chromatography to yield 26.9 mg of pure **175** (55%) as a colourless film, and 4.0 mg of lactone **176** (8%) as a colourless film; 59% ee by chiral HPLC of **175** (hexane/*i*-PrOH 85:15, 1.0 ml/min).

Diisopropyl (1S,3S)-4,6-bis(benzyloxy)-1-{(S)-[4-(benzyloxy)-3-methoxyphenyl](hydroxy)methyl}-3-{3-methoxy-4-[2-(trimethylsilyl)ethoxy]phenyl}-1,3-dihydro-2H-indene-2,2-dicarboxylate (**175**)



R_f 0.09 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3650-3350 (br.), 3063 (w), 3032 (w), 2977 (w), 2931 (m), 2872 (w), 1718 (m), 1602 (m), 1510 (m), 1463 (w), 1454 (w), 1421 (w), 1374 (w), 1336 (w), 1249 (vs), 1229 (m), 1179 (m), 1139 (vs), 1105 (s), 1077 (m), 1027 (s), 968 (w), 910 (w), 856 (m), 837 (s), 804 (m), 734 (vs), 695 (vs), 666 (w), 645 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.41-7.20 (m, 13H, Ph), 7.01 (d, *J* = 1.9 Hz, 1H, H-10), 6.98-6.91 (m, 2H, Ph), 6.92 (dd, *J* = 8.3, 1.8 Hz, 1H, H-14), 6.88 (d, *J* = 8.2 Hz, 1H, H-13), 6.66 (d, *J* = 8.4 Hz, 1H, H-5'), 6.64 (d, *J* = 1.8 Hz, 1H, H-2'), 6.50 (dd, *J* = 8.3, 1.9 Hz, 1H, H-6'), 6.32 (d, *J* = 1.7 Hz, 1H, H-4), 5.63 (dd, *J* = 1.9, 0.9 Hz, 1H, H-6), 5.15 (sept, *J* = 6.3 Hz, 1H, OCH(CH_3)$_2$[a]), 5.14 (s, 2H, C12-OCH_2Ph), 4.90 (s, 1H, H-7'), 4.83 (d, *J* = 11.8 Hz, 1H, C3-OCH_aH$_b$Ph), 4.78 (d, *J* = 9.4 Hz, 1H, H-7), 4.74 (d, *J* = 11.8 Hz, 1H, C3-OCH$_a$$H_b$Ph), 4.70-4.64 (m, 2H, H-8, OCH(CH$_3$)$_2$[b]), 4.64 (d, *J* = 11.6 Hz, 1H, C5-OCH_aH$_b$Ph), 4.60 (d, *J* = 11.6 Hz, 1H, C5-OCH$_a$$H_b$Ph), 4.08-4.03 (m, 2H, C4'-OCH_2CH$_2$TMS), 3.88 (s, 3H, C11-OCH_3), 3.80 (d, *J* = 5.3 Hz, 1H, C8-OH), 3.66 (s, 3H, C3'-OCH_3), 1.30 (d, *J* = 6.3 Hz, 3H, OCH(CH_3)$_2$[a]), 1.26 (d, *J* = 6.3 Hz, 3H, OCH(CH_3)$_2$[a]), 1.21-1.12 (m, 2H, C4'-OCH$_2$CH_2TMS), 1.10 (d, *J* = 6.2 Hz, 3H, OCH(CH_3)$_2$[b]), 0.73 (d, *J* = 6.3 Hz, 3H, OCH(CH_3)$_2$[b]), 0.05 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.7 (s, *C*OO*i*-Pr), 170.3 (s, *C*OO*i*-Pr), 159.6 (s, C-3), 154.7 (s, C-5), 150.1 (s, C-11), 148.8 (s, C-3'), 148.3 (s, C-12), 147.2 (s, C-4'), 141.6 (s, C-1), 137.2 (s, Ph^{ipso}), 137.0 (s, Ph^{ipso}), 136.9 (s, Ph^{ipso}), 136.4 (s, C-9), 133.4 (s, C-1'), 128.7 (d, Ph^{meta}), 128.6 (d, Ph^{meta}), 128.3 (d, Ph^{meta}), 128.0 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.70 (d, Ph^{para}), 127.68 (d, Ph^{ortho}), 127.3 (d, Ph^{ortho}), 127.2 (d, Ph^{ortho}), 126.8 (s, C-2), 120.7 (d, C-14), 120.5 (d, C-6'), 113.9 (d, C-13, C-2'), 112.7 (d, C-5'), 111.6 (d, C-10), 102.4 (d, C-6), 100.4 (d, C-4), 75.3 (d, C-8), 71.2 (t, C12-O*C*H$_2$Ph), 70.2 (s, C-8'), 70.0 (d, O*C*H(CH$_3$)$_2$), 69.9 (t, C3/5-O*C*H$_2$Ph), 69.8 (d, O*C*H(CH$_3$)$_2$), 69.6 (t, C3/5-O*C*H$_2$Ph), 66.4 (t, O*C*H$_2$CH$_2$TMS), 57.5 (d, C-7), 56.2 (q, C11-O*C*H$_3$), 55.9 (q, C3'-O*C*H$_3$), 54.2 (d, C-7'), 21.8 (q, OCH(*C*H$_3$)$_2$), 21.6 (q, OCH(*C*H$_3$)$_2$), 21.5 (q, OCH(*C*H$_3$)$_2$), 21.2 (q, OCH(*C*H$_3$)$_2$), 17.9 (t, OCH$_2$*C*H$_2$TMS), –1.3 (q, Si(*C*H$_3$)$_3$);

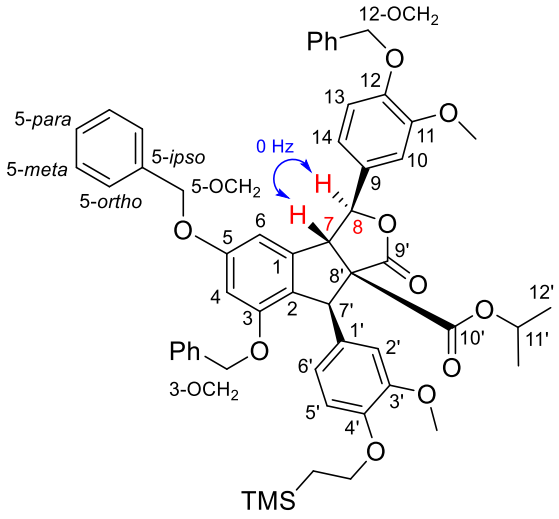
MS (ESI+) *m/z*, (%): 989 (70, [M + Na]$^+$), 949 (100, [M + H – H$_2$O]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{58}H_{66}NaO_{11}Si$ 989.4267; found: 989.4264.

Base induced lactonization of 175

DBU (2 µL, 17 µmol) was added to a solution of **175** (9.3 mg, 10 µmol) in THF-d8 (0.6 mL) in an NMR tube. The mixture was shaken and left at r.t. Monitoring by ^{1}H NMR showed 15% conversion after 10 min and full conversion to **176** after 20 h. The product was purified by prep. TLC (silica gel, PE/EA 3:1) yielding 7.8 mg of **176** (89%) as a colourless film.

O,O,O-Tribenzyl-8'-carbisopropoxy-9'-oxognetifolin F (**176**)



R_f 0.32 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3064 (w), 3033 (w), 2951 (w), 2934 (w), 2874 (w), 1781 (m), 1725 (w), 1601 (m), 1513 (m), 1464 (m), 1454 (w), 1420 (w), 1375 (w), 1248 (s), 1230 (s), 1152 (s), 1139 (vs), 1105 (m), 1029 (s), 1009 (m), 968 (w), 909 (m), 856 (m), 837 (m), 730 (vs), 695 (s), 646 (w);

^{1}H (401 MHz, $CDCl_3$): δ 7.48-7.28 (m, 10H, Ph), 7.25-7.19 (m, 3H, Ph), 6.98-6.95 (m, 2H, Ph), 6.90-6.81 (m, 3H, H-10, H-13, H-14), 6.69 (d, *J* = 2.0, Hz, 1H, H-6), 6.58-6.68 (m, 2H, H-2', H-5'), 6.48 (d, *J* = 2.0 Hz, 1H, H-4), 6.50-6.30 (br., 1H, H-6'), 5.66 (s, 1H, H-8), 5.14 (s, 2H, C12-OC*H*$_2$Ph), 5.08 (s, 3H, H-7', C5-OC*H*$_2$Ph), 4.89 (d, *J* = 11.9 Hz, 1H, C3-OC*H*^{a}H^{b}Ph), 4.82 (d, *J* = 11.9 Hz, 1H, C3-OCH^a*H*^{b}Ph), 4.68 (s, 1H, H-7), 4.33 (sept, *J* = 6.3 Hz, 1H, H-11'), 4.07-3.99 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.90 (s, 3H, C11-OC*H*$_3$), 3.68 (s, 3H, C3'-OC*H*$_3$), 1.19-1.10 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.69 (d, *J* = 6.2 Hz, 3H, H-12'), 0.56 (d, *J* = 6.2 Hz, 3H, H-12'), 0.03 (s, 9H, SiC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.9 (s, C-9'), 165.5 (s, C-10'), 161.5 (s, C-5), 155.8 (s, C-3), 150.1 (s, C-11), 149.0 (s, C-3'), 148.1 (s, C-12), 147.5 (s, C-4'), 143.2 (s, C-1), 137.1 (s, C12-OCH$_2$Ph^{ipso}), 136.7 (s, C5-OCH$_2$Ph^{ipso}), 136.5 (s, C3-OCH$_2$Ph^{ipso}), 132.3 (s, C-9), 131.9 (s, C-1'), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.4 (d, 2×C, Ph^{meta}), 128.4 (d, Ph^{para}), 128.0 (d, Ph^{para}), 127.8 (d, Ph^{para}), 127.8 (d, 2×C, C5-OCH$_2$Ph^{ortho}), 127.3 (d, 2×C, C12-OCH$_2$Ph^{ortho}), 127.1 (d, 2×C, C3-OCH$_2$Ph^{ortho}), 124.9 (s, C-2), 120.7 (d, C-6'), 117.2 (d, C-14), 114.1 (d, C-13), 113.3 (d, C-2'), 112.5 (d, C-5'), 108.6 (d, C-10), 100.9 (d, C-4), 100.7 (d, C-6), 84.3 (d, C-8), 71.2 (t, C12-O*C*H$_2$Ph), 70.8 (t, C5-O*C*H$_2$Ph), 69.8 (d, C-11'), 69.7 (t, C3-O*C*H$_2$Ph), 66.4 (t, O*C*H$_2$CH$_2$TMS), 66.2 (s, H-8'), 56.6 (d, H-7'), 56.27 (d, H-7), 56.27 (q, C11-OMe), 56.0 (q, C3'-OMe), 21.1 (q, C-12'), 21.0 (q, C-12'), 17.8 (t, OCH$_2$*C*H$_2$TMS), −1.3 (q, Si*C*H$_3$);

MS (ESI+) *m/z*, (%): 929 (100, [M + Na]$^+$), 924 (57, [M + NH$_4$]$^+$);

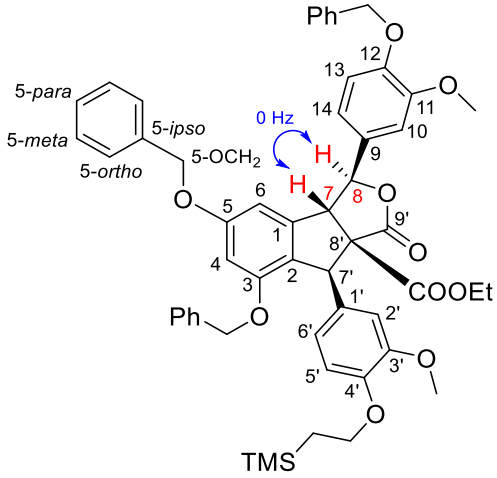
HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{55}H_{58}NaO_{10}Si$ 929.3692; found: 929.3684.

6.2.9. Total synthesis of gnetifolin F (**I**)

One-pot conjugate addition/oxidative bicyclisation of 157/171b in eutectic solvent mixture

A three-necked 250 mL round-bottom flask was charged with stilbene **157** (1.975 g, 3.25 mmol) and (+)-sparteine (1.7 mL, 7.5 mmol). A mechanical stirrer was installed at the central port and the flask was put under a dry N_2 atmosphere. Dry toluene (25 mL) and dry EtPh (25 mL) were added, followed by gentle heating (50 °C) to fully dissolve all solids. The solution was cooled to –78 °C, followed by addition of *n*-BuLi solution (2.0 mL, 3.25 mmol, 1.6 M in hexanes). The resulting yellow solution was stirred at –78 °C for 20 min. A second cooling bath with PE/Et_2O was prepared and cooled to –130 °C. The reaction mixture was quickly cooled to –115 °C using this bath, maintaining vigorous stirring. The solution became very viscous but remained homogeneous. After 2 min., a solution of **171b** (0.986 g, 2.50 mmol) in toluene (12 mL) was added over 2 min. Immediately after that, isohexane (3 mL) was added to reduce the viscosity of the solvent. The mixture was forcibly stirred for 10 min at –115 °C, then slowly warmed to –90 °C over 45 min. The bath was again replaced by acetone/dry ice and the reaction warmed to –50 °C. Dry THF (125 mL) and calcinated LiBr (1.74 g, 20 mmol) were added, followed by warming to –23 °C. Excess $FeCp_2PF_6$ (**52**) (5.0 g, 15 mmol) was added in a single portion, followed by flushing with dry N_2. The dark blue suspension was stirred for 10 min., followed by warming to r.t. over 20 min. The blue colour dissipated, giving a dark brown/green solution. Quenching by saturated Na_2SO_3 solution (50 mL) led to quick decolouration. The resulting yellow emulsion was partitioned between diluted Na_2SO_3 (400 mL water, 150 mL sat. Na_2SO_3 solution) and EA (500 mL). The aqueous layer was washed with EA (500 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The orange crude product was dissolved in dry EtOH (20 ml) and DCM (20 mL). TFA (1.5 mL) was added and the reaction was stirred for 30 min. All volatiles were stripped off in vacuum and the material was adsorbed to a small amount of silica gel using DCM. Flash chromatography (PE/Et_2O, 20:1 to 3:1) yielded 1.861 g of **177** (83%) as a colourless sticky paste, that slowly hardened in the freezer. The enantiomers of **177** were inseparable by chiral HPLC, analysis of **179a** after saponification showed 69% ee (hexane/*i*-PrOH 50/50, 1.0 ml/min).

O,O,O-Tribenzyl-8'-carbethoxy-9'-oxognetifolin F (**177**)



R_f 0.22 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3064 (w), 3033 (w), 2952 (w), 2902 (w), 2873 (w), 2836 (w), 1781 (m), 1735 (m), 1599 (m), 1513 (m), 1464 (w), 1453 (w), 1373 (w), 1336 (w), 1297 (w), 1231 (s), 1153 (vs), 1139 (vs), 1028 (s), 857 (m), 836 (s), 737 (s), 695 (s);

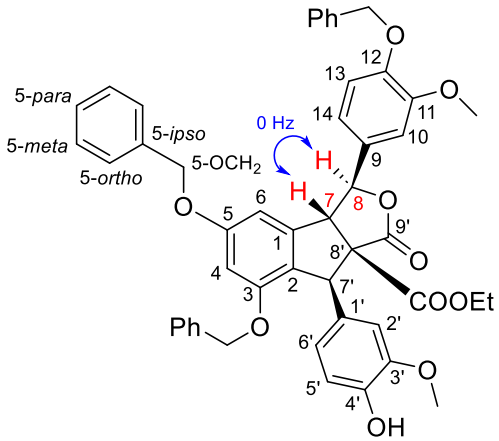
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49-7.19 (m, 13H, Ph), 7.00-6.93 (m, 2H, Ph), 6.89-6.83 (m, 3H, H-10, H-13, H-14), 6.68 (dd, *J* = 2.0, 0.9 Hz, 1H, H-4/6), 6.65 (m, 2H, H-2', H-5'), 6.48 (dd, *J* = 2.0, 0.7 Hz, 1H, H-4/6), 6.39 (d, *J* = 8.3 Hz, 1H, H-6'), 5.65 (s, 1H, H-8), 5.15 (s, 2H, C12-OCH_2Ph), 5.09 (s, 1H, H-7'), 5.08 (s, 2H, C5-OCH_2Ph), 4.90 (d, *J* = 11.9 Hz, 1H, C3-OCH_aH$_b$Ph), 4.83 (d, *J* = 11.9 Hz, 1H, C3-OCH$_a$$H_b$Ph), 4.70 (t, *J* = 0.7 Hz, 1H, H-7), 4.09-3.99 (m, 2H, OCH_2CH$_2$TMS), 3.89 (s, 3H, C11-OCH_3), 3.69 (s, 3H, C3'-OCH_3), 3.61-3.47 (m, 2H, OCH_2CH$_3$), 1.18-1.13 (m, 2H, OCH$_2$CH_2TMS), 0.72 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 0.04 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.8 (s, C-9'), 166.2 (s, *C*OOEt), 161.5 (s, C-5), 155.8 (s, C-3), 150.0 (s, C-11), 148.9 (s, C-3'), 148.1 (s, C-12), 147.4 (s, C-4'), 143.3 (s, C-1), 137.0 (s, C12-OCH$_2$Ph^{ipso}), 136.7 (s, C5- OCH$_2$Ph^{ipso}), 136.5 (s, C3-OCH$_2$Ph^{ipso}), 132.1 (s, C-9), 131.8 (s, C-1'), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.4 (d, 2×C, Ph^{meta}), 128.4 (d, Ph^{para}), 128.0 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.8 (d, 2×C, C5-OCH$_2$Ph^{ortho}), 127.4 (d, 2×C, C12-OCH$_2$Ph^{ortho}), 127.0 (d, 2×C, C3-OCH$_2$Ph^{ortho}), 124.7 (s, C-2), 120.4 (d, C-6'), 117.4 (d, C-14), 114.0 (d, C-13), 113.1 (d, C-2'), 112.4 (d, C-5'), 108.7 (d, C-10), 101.0 (d, C-4/6), 100.8 (d, C-4/6), 84.6 (d, C-8), 71.1 (t, C12-O*C*H$_2$Ph), 70.7 (t, C5-O*C*H$_2$Ph), 69.7 (t, C3-O*C*H$_2$Ph), 66.5 (s, H-8'), 66.3 (t, O*C*H$_2$CH$_2$TMS), 62.0 (t, O*C*H$_2$CH$_3$), 56.4 (d, H-7'), 56.3 (d, H-7), 56.2 (q, C11-O*C*H$_3$), 56.0 (q, C3'-O*C*H$_3$), 17.8 (t, OCH$_2$*C*H$_2$TMS), 13.7 (q, OCH$_2$*C*H$_3$), −1.3 (q, Si(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 1803 (35, [2M + H_3O]$^+$), 915 (16, [M + Na]$^+$), 910 (100, [M + NH_4]$^+$), 893 (4, [M + H]$^+$), 669 (37, [M – 3-methoxy-4-(2-(trimethylsilyl)-ethoxy)benzene]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{54}H_{57}O_{10}Si$ 893.3715; found: 893.3715, [M + NH_4]$^+$ calcd. for $C_{54}H_{60}NO_{10}Si$ 910.3981; found: 910.3980.

8'-Carbethoxy-9'-oxognetifolin F 3,5,12-O-tribenzyl ether (**178**)



Obtained from oxidative cyclisation along with **177**, when using 1 N HCl/EA for workup.

R_f 0.15 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3400 (br.), 3450 (w), 3088 (w), 3063 (w), 3032 (w), 2936 (w), 2872 (w), 2845 (w), 1779 (m), 1732 (m), 1601 (m), 1514 (s), 1454 (m), 1373 (w), 1327 (w), 1268 (s), 1232 (m), 1152 (vs), 1030 (s), 857 (w), 810 (w), 738 (m), 697 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.46-7.20 (m, 13H, Ph), 6.99-6.94 (m, 2H, Ph), 6.88-6.83 (m, 3H, H-10, H-13, H-14), 6.71 (d, *J* = 8.2 Hz, 1H, H-5'), 6.68 (d, *J* = 2.0 Hz, 1H, H-4), 6.62 (broad, 1H, H-2'), 6.48 (d, *J* = 2.0 Hz, 1H, H-6), 6.38 (broad, 1H, H-6'), 5.65 (s, 1H, H-8), 5.15 (s, 2H, C12-OCH_2Ph), 5.07 (s, 3H, H-7', C5-OCH_2Ph), 4.90 (d, *J* = 11.9 Hz, 1H, C3-OCH^aH^{b}Ph), 4.83 (d, *J* = 11.9 Hz, 1H,

C3-OCH^aH^bPh), 4.69 (t, J = 0.7 Hz, 1H, H-7), 3.89 (s, 3H, C11-OMe), 3.70 (s, 3H, C3'-OMe), 3.60-3.47 (m, 2H, OCH_2CH$_3$), 0.71 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 174.1 (s, C-9'), 166.1 (s, *C*OOEt), 161.5 (s, C-5), 155.8 (s, C-3), 150.0 (s, C-11), 148.1 (s, C-12), 146.0 (s, C-3'), 144.8 (s, C-4'), 143.3 (s, C-1), 137.0 (s, C12-OCH$_2$Ph^{ipso}), 136.7 (s, C5- OCH$_2$Ph^{ipso}), 136.5 (s, C3-OCH$_2$Ph^{ipso}), 132.0 (s, C-9), 131.3 (s, C-1'), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.38 (d, 2×C, Ph^{meta}), 128.36 (d, Ph^{para}), 128.0 (d, Ph^{para}), 127.8 (d, Ph^{para}), 127.8 (d, 2×C, C5-OCH$_2$Ph^{ortho}), 127.3 (d, 2×C, C12-OCH$_2$Ph^{ortho}), 127.1 (d, 2×C, C3-OCH$_2$Ph^{ortho}), 124.6 (s, C-2), 121.1 (d, C-6'), 117.4 (d, C-14), 114.0 (d, C-13), 113.9 (d, C-2'), 112.2 (d, C-5'), 108.7 (d, C-10), 101.0 (d, C-4/6), 100.8 (d, C-4/6), 84.6 (d, C-8), 71.1 (t, C12-O*C*H$_2$Ph), 70.7 (t, C5-O*C*H$_2$Ph), 69.7 (t, C3-O*C*H$_2$Ph), 66.4 (s, H-8'), 61.9 (t, O*C*H$_2$CH$_3$), 56.5 (d, H-7'), 56.3 (d, H-7), 56.2 (q, C11-O*C*H$_3$), 56.0 (q, C3'-O*C*H$_3$), 13.6 (q, OCH$_2$*C*H$_3$);

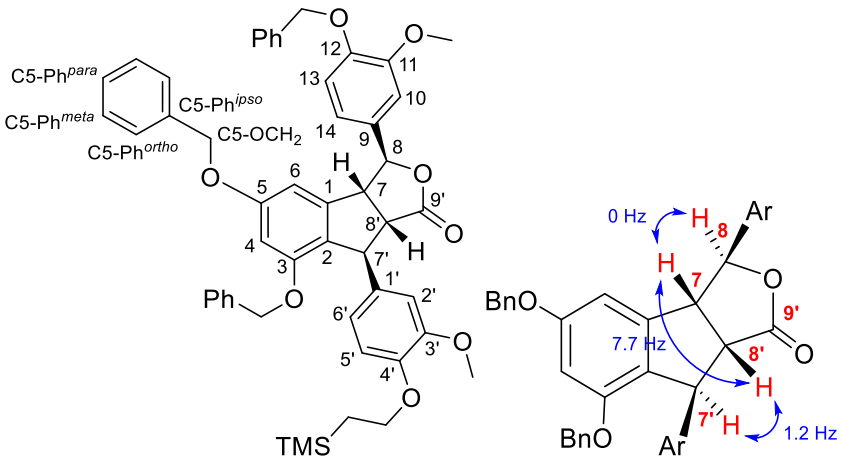
MS (ESI−) *m/z*, (%): 1583 (8, [2M − H]$^-$), 837 (15, [M + HCOO]$^-$), 827 (19, [M + Cl]$^-$), 791 (100, [M − H]$^-$);

HRMS (ESI−) *m/z*: [M − H]$^-$ calcd. for $C_{49}H_{43}O_{10}$ 791.2862; found: 791.2860.

Saponification-decarboxylation of 177

177 (120 mg, 134 µmol) was dissolved in dioxane (5 mL). A freshly prepared solution of KOH (490 mg, 8.7 mmol) in water (2 mL) was added. Vacuum was applied to the stirred reaction mixture until the solvent started to gently boil, followed by flushing with N_2. The vaccum-N_2 cycle was repeated 3 times. The reaction was then heated to reflux for 3 h. After cooling, the reaction mixture was partitioned between 30%$_w$ aqueous citric acid (20 mL) and DCM (30 mL). The aqueous layer was extracted with additional DCM (4×30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and resubmitted to the same saponification conditions. After three cycles of saponification/workup, the product was purified by flash chromatography (PE/EA, 11:1 to 3:1) to yield in order of elution 88.5 mg of **179a** (80%) as colourless amorphous solid and 20.0 mg of **182** (17%) as a colourless amorphous solid. When first analysed by ^{1}H NMR, **179a** contained an admixture, tentatively identified as **179b** (dr 8:1). This admixture disappeared when the CDCl$_3$ sample was remeasured after several hours.

Protected 9'-oxognetifolin F (**179a**)



R_f 0.52 (PE/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3089 (w), 3063 (w), 3032 (w), 2949 (w), 2931 (w), 2869 (w), 1766 (m), 1594 (m), 1512 (m), 1454 (w), 1420 (w), 1377 (w), 1332 (w), 1292 (w), 1250 (m), 1230 (m), 1138 (vs), 1069 (w), 1030 (s), 967 (w), 855 (m), 837 (m), 736 (m), 696 (m), 630 (w);

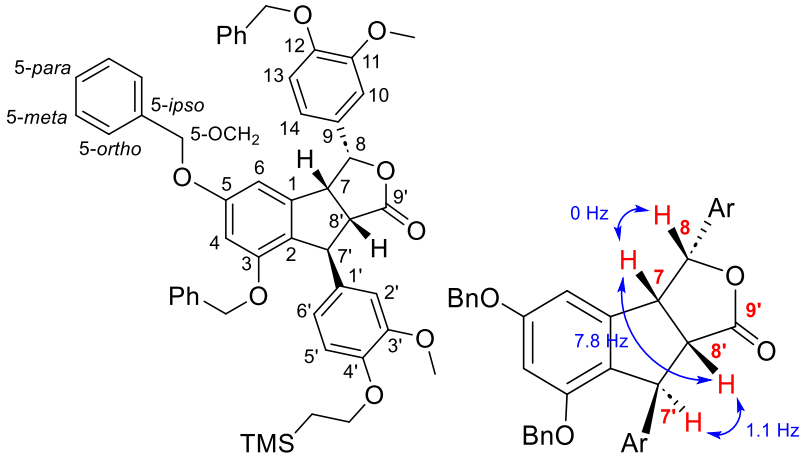
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49-7.23 (m, 13H, Ph), 7.06-7.08 (m, 2H, Ph), 6.90 (d, J = 8.2 Hz, 1H, H-13), 6.83-8.86 (m, 2H, H-10, H-14), 6.72-6.65 (m, 3H, H-2', H-5', H-6), 6.50 (d, J = 1.7 Hz, 1H, H-4), 6.44 (dd, J = 8.3, 2.1 Hz, 1H, H-6'), 5.58 (s, 1H, H-8), 5.17 (s, 2H, C12-OCH_2Ph), 5.07 (s, 2H, C5-OCH_2Ph), 4.95 (d, J = 12.0 Hz, 1H, C3-OCH_aH$_b$Ph), 4.88 (d, J = 12.0 Hz, 1H, C3-OCH$_a$$H_b$Ph), 4.86 (d, J = 1.1 Hz, 1H, H-7'), 4.15 (d, J = 7.6 Hz, 1H, H-7), 4.09-4.03 (m, 2H, OCH_2CH$_2$TMS), 3.92 (s, 3H, C11-OCH_3), 3.68 (s, 3H, C3'-OCH_3), 3.37 (dd, J =7.7, 1.2 Hz, 1H, H-8'), 1.20-1.14 (m, 2H, OCH$_2$$CH_2$TMS), 0.05 (s, 9H, Si(C$H_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 179.1 (s, C-9'), 161.3 (s, C-5), 156.1 (s, C-3), 150.2 (s, C-11), 149.5 (s, C-3'), 148.4 (s, C-12), 147.0 (s, C-4'), 144.4 (s, C-1), 137.0 (s, C12-Ph^{ipso}), 136.8 (s, C5-Ph^{ipso}), 136.7 (s, C3-Ph^{ipso}), 136.2 (s, C-1'), 133.2 (s, C-9), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.5 (d, 2×C, Ph^{meta}), 128.3 (d, Ph^{para}), 128.1 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.8 (d, 2×C, C5-Ph^{ortho}), 127.4 (d, 2×C, C12-Ph^{ortho}), 127.2 (d, 2×C, C3-Ph^{ortho}), 125.8 (s, C-2), 118.4 (d, C-6'), 117.4 (d, C-14), 114.3 (d, C-13), 113.0 (d, C-5'), 111.7 (d, C-2'), 109.0 (d, C-10), 101.4 (d, C-6), 100.5 (d, C-4), 85.5 (d, C-8), 71.2 (t, OCH_2Ph), 70.7 (t, OCH_2Ph), 69.8 (t, C3-OCH_2Ph), 66.5 (t, OCH_2CH$_2$TMS), 56.4 (q, C11-OCH_3), 56.0 (q, C3'-OCH_3), 54.1 (d, C-7), 52.7 (d, C-8'), 51.2 (d, C-7'), 17.9 (t, OCH$_2$$CH_2$TMS), −1.3 (q, Si($CH_3$)$_3$);

MS (ESI+) *m/z*, (%): 1659 (85, [2M + H_2O + H]$^+$), 1005 (66), 921 (100, [M + TMS(CH$_2$)$_2$]$^+$), 859 (74, [M + K]$^+$), 843 (89, [M + Na]$^+$), 838 (66, [M + NH_4]$^+$), 821 (66, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{51}H_{53}O_8Si$ 821.3504; found: 821.3497; [M + NH_4]$^+$ calcd. for $C_{51}H_{56}NO_8Si$ 838.3775; found: 838.3773; *m/z*: [M + Na]$^+$ calcd. for $C_{51}H_{52}NaO_8Si$ 843.3329; found: 843.3322.

Protected 8-epi-9'-oxognetifolin F (**179b**)

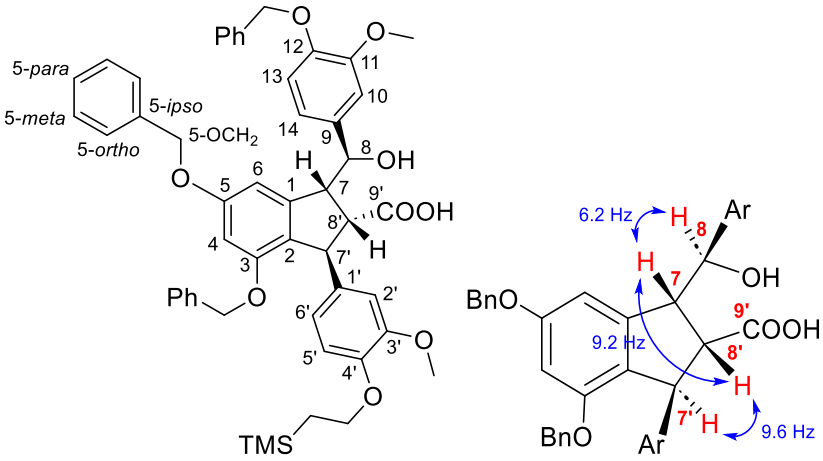


Minor unstable diastereomer observed in samples of **179a**, spontaneously converted to **179a** in $CDCl_3$.

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49-7.23 (m, 13H, Ph, overlaps with **179a**), 7.07-7.08 (m, 2H, Ph, overlaps with **179a**), 7.01 (d, J = 2.0 Hz, 1H, H-10), 6.96 (dd, J = 8.4, 2.1 Hz, 1H, H-14), 6.89 (d, J = 8.2 Hz, 1H, H-13), 6.72-6.65 (m, 3H, H-2', H-5', H-6, overlaps with **179a**), 6.51 (d, J = 2.2 Hz, 1H, H-4), 6.36 (dd, J = 8.1, 2.1 Hz, 1H, H-6'), 6.04 (s, 1H, H-8), 5.17 (s, 2H, C12-OCH_2Ph), 5.10 (s, 2H, C5-OCH_2Ph), 4.92 (d, J = 12.1 Hz, 1H, C3-OCH_aH$_b$Ph), 4.87 (d, J = 1.1 Hz, 1H, H-7'), 4.82 (d, J =

12.0 Hz, 1H, C3-OCH$_a$*H*$_b$Ph), 4.32 (d, *J* = 7.8 Hz, 1H, H-7), 4.08-4.02 (m, 2H, O*CH*$_2$CH$_2$TMS), 3.91 (s, 3H, C11-O*CH*$_3$), 3.67 (s, 3H, C3'-O*CH*$_3$), 3.39 (dd, *J* = 7.8, 1.1 Hz, 1H, H-8'), 1.20-1.14 (m, 2H, OCH$_2$*CH*$_2$TMS, overlaps with **179a**), 0.05 (s, 9H, Si(C*H*$_3$)$_3$, overlaps with **179a**);.

Protected 9'-oxognetifolin F hydrate (**182**)



Minor side product, formed during the cyclisation leading to **179a** in 2-17% yield. Stable in $CDCl_3$.

R_f 0.05 (hexane/EA 3:1);

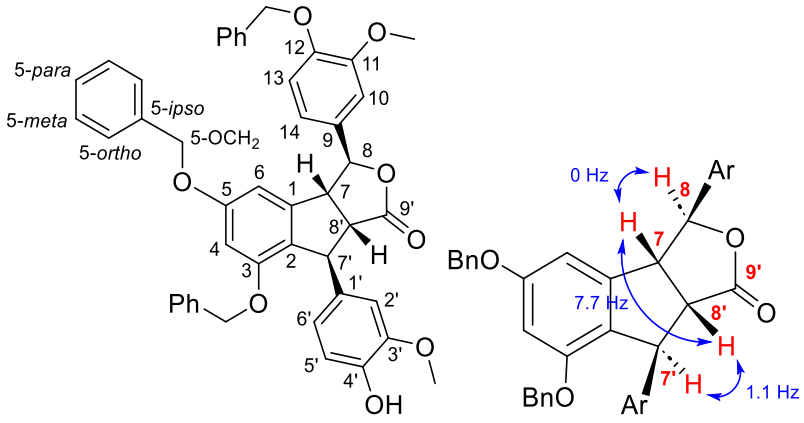
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.42-7.19 (m, 13H, Ph), 6.99 (d, *J* = 1.7 Hz, 1H, H-10), 6.92-6.90 (m, 2H, Ph), 6.86-6.87 (m, 2H, H-13, H-14), 6.65 (d, *J* = 8.3 Hz, 1H, H-5'), 6.56 (d, *J* = 2.0 Hz, 1H, H-2'), 6.41 (d, *J* = 2.0 Hz, 1H, H-4/6), 6.40 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6'), 6.20 (d, *J* = 2.0 Hz, 1H, H-4/6), 5.14 (s, 2H, C12-OC*H*$_2$Ph), 4.92 (d, *J* = 6.2 Hz, 1H, H-8), 4.88 (s, 2H, C5-OC*H*$_2$Ph), 4.87 (d, *J* = 12.0 Hz, 1H, C3-OC*H*$_a$H$_b$Ph), 4.79 (d, *J* = 12.0 Hz, 1H, C3-OCH$_a$*H*$_b$Ph), 4.75 (d, *J* = 9.6 Hz, 1H, H-7'), 4.25 (dd, *J* = 9.0, 6.2 Hz, 1H, H-7), 4.06-4.02 (m, 2H, O*CH*$_2$CH$_2$TMS), 3.87 (s, 3H, C11-OC*H*$_3$), 3.80 (dd, *J* = 9.5, 9.2 Hz, 1H, H-8'), 3.67 (s, 3H, C3'-OC*H*$_3$), 1.18-1.14 (m, 2H, OCH$_2$*CH*$_2$TMS), 0.04 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.8 (s, C-9'), 160.4 (s, C-5), 155.7 (s, C-3), 149.9 (s, C-11), 148.8 (s, C-3'), 147.4 (s, C-12), 147.1 (s, C-4'), 143.6 (s, C-1), 137.2 (s, Ph^{ipso}), 136.9 (s, Ph^{ipso}), 136.8 (s, Ph^{ipso}), 135.4 (s, C-9), 133.3 (s, C-1'), 128.73 (d, 2×C, Ph^{meta}), 128.67 (d, 2×C, Ph^{meta}), 128.4 (d, 2×C, Ph^{meta}), 128.2 (d, Ph^{para}), 128.0 (d, Ph^{para}), 127.76 (d, Ph^{para}), 127.73 (d, 2×C, Ph^{ortho}), 127.5 (d, 2×C, Ph^{ortho}), 127.1 (d, 2×C, Ph^{ortho}), 126.7 (s, C-2), 120.3 (d, C-6'), 119.4 (d, C-14), 114.0 (d, C-13), 112.9 (d, C-2'/5'), 112.4 (d, C-2'/5'), 110.4 (d, C-10), 101.5 (d, C-4/6), 100.4 (d, C-4/6), 76.0 (d, C-8), 71.2 (t, O*C*H$_2$Ph), 70.2 (t, O*C*H$_2$Ph), 69.6 (t, O*C*H$_2$Ph), 66.2 (t, O*C*H$_2$CH$_2$TMS), 56.4 (q, O*C*H$_3$), 56.0 (q, O*C*H$_3$), 53.6 (d, C-7), 51.8 (d, C-8'), 49.6 (d, C-7'), 18.0 (t, OCH$_2$*C*H$_2$TMS), −1.3 (q, Si(*C*H$_3$)$_3$);

MS (ESI−) *m/z*, (%): 1675 (8, [2M − H]$^-$), 837 (100, [M − H]$^-$), 529 (9);

HRMS (ESI−) *m/z*: [M − H]$^-$ calcd. for $C_{51}H_{53}O_9Si$ 837.3453; found: 837.3454.

9'-Oxognetifolin F 3,5,12-O-tribenzyl ether (**181**)



Side product from saponification of **177**, formed during acidic workup using 1 N aqueous HCl or 1% TFA in DCM.

R_f 0.12 (PE/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3250 (br.), 3062 (w), 3032 (m), 2928 (w), 2854 (w), 1764 (m), 1601 (m), 1513 (s), 1454 (m), 1376 (w), 1330 (w), 1263 (s), 1234 (m), 1212 (m), 1142 (vs), 1070 (w), 1030 (s), 851 (w), 811 (w), 737 (m), 697 (m), 629 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.24 (m, 13H, Ph), 7.10-7.06 (m, 2H, Ph), 6.90 (d, *J* = 8.2 Hz, 1H, H-13), 6.87-8.82 (m, 2H, H-10, H-14), 6.75 (d, *J* = 8.2 Hz, 1H, H-5'), 6.72 (d, *J* = 2.0 Hz, 1H, H-6), 6.67 (d, *J* = 1.9 Hz, 1H, H-2'), 6.50 (d, *J* = 1.9 Hz, 1H, H-4), 6.40 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6'), 5.59 (s, 1H, H-8), 5.49 (br. s, 1H, 4'-O*H*), 5.17 (s, 2H, C12-OC*H*$_2$Ph), 5.07 (s, 2H, C5-OC*H*$_2$Ph), 4.96 (d, *J* = 11.9 Hz, 1H, C3-OC*H*$_a$H$_b$Ph), 4.88 (d, *J* = 11.9 Hz, 1H, C3-OCH$_a$*H*$_b$Ph), 4.85 (d, *J* = 1.1 Hz, 1H, H-7'), 4.16 (d, *J* = 7.6 Hz, 1H, H-7), 3.92 (s, 3H, C11-OC*H*$_3$), 3.70 (s, 3H, C3'-OC*H*$_3$), 3.37 (dd, *J* =7.7, 1.3 Hz, 1H, H-8');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 179.1 (s, C-9'), 161.3 (s, C-5), 156.1 (s, C-3), 150.2 (s, C-11), 148.4 (s, C-12), 146.4 (s, C-3'), 144.4 (s, C-1), 144.3 (s, C-4'), 137.0 (s, C12-Ph^{ipso}), 136.8 (s, C5-Ph^{ipso}), 136.7 (s, C3-Ph^{ipso}), 135.7 (s, C-1'), 133.1 (s, C-9), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.5 (d, 2×C, Ph^{meta}), 128.3 (d, Ph^{para}), 128.1 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.8 (d, 2×C, C5-Ph^{ortho}), 127.4 (d, 2×C, C12-Ph^{ortho}), 127.2 (d, 2×C, C3-Ph^{ortho}), 125.8 (s, C-2), 119.0 (d, C-6'), 117.4 (d, C-14), 114.4 (d, C-13/5'), 114.3 (d, C-13/5'), 110.8 (d, C-2'), 109.0 (d, C-10), 101.4 (d, C-6), 100.5 (d, C-4), 85.5 (d, C-8), 71.2 (t, O*C*H$_2$Ph), 70.7 (t, O*C*H$_2$Ph), 69.8 (t, C3-O*C*H$_2$Ph), 56.4 (q, C11-O*C*H$_3$), 55.9 (q, C3'-O*C*H$_3$), 54.1 (d, C-7), 52.7 (d, C-8'), 51.4 (d, C-7');

MS (ESI−) *m/z*, (%): 1439 (6, [2M − H]$^-$), 765 (14, [M + HCOO]$^-$), 755 (22, [M + Cl]$^-$), 719 (100, [M − H]$^-$);

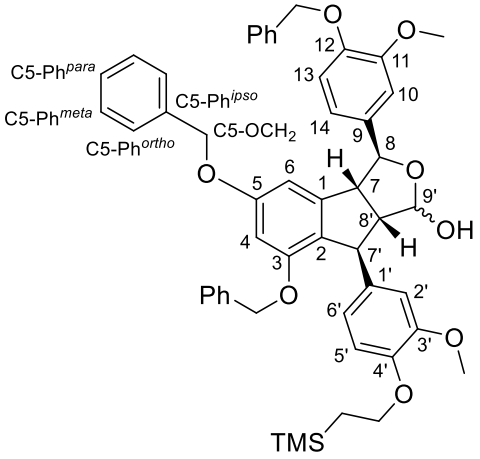
HRMS (ESI−) *m/z*: [M − H]$^-$ calcd. for $C_{46}H_{39}O_8$ 719.2650; found: 719.2647.

Reduction of 179a with DIBAL

A solution of DIBAL (51 µL, 51 µmol, 1 M in toluene) was added to a solution of **179a** (8.4 mg, 10 µmol) in dry THF (0.5 mL) at –78 °C. The mixture was stirred at –78 °C for 15 min., followed by gradual warming to –10 °C over 30 min. The reaction was quenched by a few drops of water. The mixture was partitioned between saturated potassium sodium tartrate (10 mL) and EA (50 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated

and dried in vacuum to give 10 mg of **183** (quant.) as a colourless film as 1:1 mixture of anomers A,B.

Protected 9'-hydroxygnetifolin F, mixture of anomers (**183**-A/B)



R_f 0.20 (hexane/EA 3:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.49-7.19 (m, 26H, Ph), 7.16 (d, *J* = 1.8 Hz, 1H, H-10^A), 7.03-6.99 (m, 2H, Ph), 6.99 (d, *J* = 1.8 Hz, 1H, H-10^B), 6.96-6.93 (m, 2H, Ph), 6.90-6.82 (m, 4H, H-13^{AB}, H-14^{AB}), 6.73 (d, *J* = 8.3 Hz, 1H, H-5'^{A}), 6.71 (d, *J* = 8.3 Hz, 1H, H-5'^{B}), 6.66-6.65 (m, 2H, H-2'^{AB}), 6.58 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6'^{A}), 6.55 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6'^{B}), 6.51-6.47 (m, 2H, H-4^A, H-6^A), 6.45 (d, *J* = 2.1 Hz, 1H, H-4/6^B), 6.44 (d, *J* = 1.9 Hz, 1H, H-4/6^B), 5.84 (d, *J* = 6.0 Hz, 1H, H-9'^{B}), 5.50 (d, *J* = 3.4 Hz, 1H, H-9'^{A}), 5.18 (s, 2H, C12-OCH_2Ph^B), 5.17 (s, 2H, C12-OCH_2Ph^A), 5.08 (d, *J* = 5.6 Hz, 1H, H-8^B), 5.03 (s, 3H, C5-OCH_2Ph^A), 5.01 (s, 3H, C5-OCH_2Ph^B), 4.98 (d, *J* = 4.4 Hz, 1H, H-8^A), 4.93 (d, *J* = 11.9 Hz, 1H, C3-OCH_aH$_b$Ph^B), 4.90 (d, *J* = 11.9 Hz, 1H, C3-OCH_aH$_b$Ph^A), 4.84 (d, *J* = 11.9 Hz, 1H, C3-OCH$_a$$H_b$Ph^B), 4.83 (d, *J* = 11.9 Hz, 1H, C3-OCH$_a$$H_b$Ph^A), 4.72 (d, *J* = 2.0 Hz, 1H, H-7'^{B}), 4.42 (d, *J* = 3.8 Hz, 1H, H-7'^{A}), 4.11-4.06 (m, 4H, OCH_2CH$_2$TMS^{AB}), 4.01-3.96 (m 2H, H-7^{AB}), 3.92 (s, 6H, C11-OCH_3^{AB}), 3.69 (s, 3H, C3'-OCH_3^{A}), 3.67 (s, 3H, C3'-OCH_3^{B}), 3.26 (ddd, *J* = 9.7, 5.8, 2.1 Hz, 1H, H-8'^{B}), 3.05 (ddd, *J* = 7.8, 3.7, 3.4 Hz, 1H, H-8'^{A}), 1.23-1.16 (m, 4H, OCH$_2$$CH_2$TMS^{AB}), 0.06 (s, 9H, Si(CH_3)$_3$^{A}), 0.06 (s, 9H, Si(CH_3)$_3$^{B});

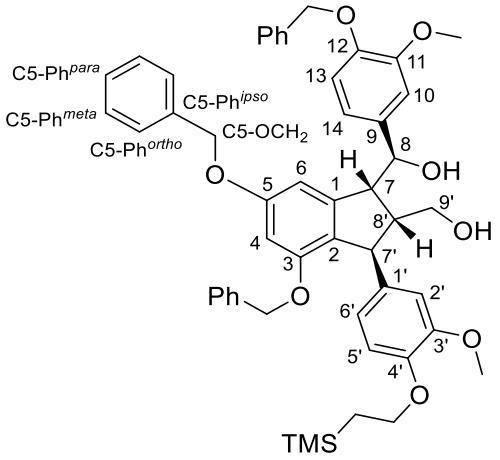
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.8 (s, C-5^A), 160.6 (s, C-5^B), 156.4 (s, C-3^A), 155.7 (s, C-3^B), 150.2 (s, C-11), 150.0 (s, C-11), 149.6 (s, C-3'^{A}), 149.4 (s, C-3'^{B}), 148.0 (s, C-12^B), 147.8 (s, C-12^A), 146.9 (s, C-4'^{A}), 146.8 (s, C-1^A), 146.6 (s, C-4'^{B}), 146.3 (s, C-1^B), 138.7 (s, C-1'^{B}), 137.6 (s, C-1'^{A}), 137.4 (s, Ph^{ipso}), 137.3 (s, Ph^{ipso}), 137.1 (s, Ph^{ipso}), 136.98 (s, Ph^{ipso}), 136.95 (s, Ph^{ipso}), 136.8 (s, Ph^{ipso}), 136.1 (s, C-9^A), 135.1 (s, C-9^B), 128.77 (d, 2×C, Ph^{meta}), 128.76 (d, 2×C, Ph^{meta}), 128.70 (d, 2×C, Ph^{meta}), 128.69 (d, 2×C, Ph^{meta}), 128.4 (d, 4×C, Ph^{meta}), 128.21 (d, Ph^{para}), 128.18 (d, Ph^{para}), 127.99 (d, Ph^{para}), 127.97 (d, Ph^{para}), 127.80 (s, C-2^B), 127.76 (d, Ph^{para}), 127.75 (d, Ph^{para}), 127.70 (d, 4×C, Ph^{ortho}), 127.39 (d, 2×C, Ph^{ortho}), 127.38 (d, 2×C, Ph^{ortho}), 127.2 (d, 2×C, Ph^{ortho}), 127.1 (d, 2×C, Ph^{ortho}), 125.3 (s, C-2^A), 119.2 (d, C-6'^{A}), 119.1 (d, C-6'^{B}), 118.9 (d, C-14^B), 118.7 (d, C-14^A), 114.1 (d, C-13^B), 114.0 (d, C-13^A), 113.2 (d, C-5'^{B}), 113.1 (d, C-5'^{A}), 111.9 (d, C-2'^{B}), 111.6 (d, C-2'^{A}), 110.3 (d, C-10^A), 109.9 (d, C-10^B), 104.7 (d, C-9'^{A}), 101.6 (d, C-4/6^A), 101.5 (d, C-4/6^B), 100.0 (d, C-4/6^A), 99.9 (d, C-4/6^B), 99.5 (d, C-9'^{B}), 88.0 (d, C-8^A), 85.0 (d, C-8^B), 71.25 (t, C12-OCH$_2$Ph^B), 71.24 (t, C12-OCH$_2$Ph^A), 70.55 (t, C5-OCH$_2$Ph^A), 70.53 (t, C5-OCH$_2$Ph^B), 69.7 (t, C3-OCH$_2$Ph^A), 69.6 (t, C3-OCH$_2$Ph^B), 66.5 (t, 2×C, OCH$_2$CH$_2$TMS^{AB}), 63.3 (d, C-8'^{A}), 59.2 (d, C-8'^{B}), 58.4 (d, C-7^B), 57.8 (d, C-7^A), 56.25 (q, C11-OCH$_3$^{B}), 56.21 (q, C11-OCH$_3$^{A}), 56.0 (q, C3'-OCH$_3$^{A}), 55.9 (q, C3'-OCH$_3$^{B}), 51.1 (d, C-7'^{A}), 47.1 (d, C-7'^{B}), 17.99 (t, OCH$_2$$CH_2$TMS^A), 17.98 (t, OCH$_2$$CH_2$TMS^B), –1.3 (q, 6×C, Si(CH$_3$)$_3$^{AB});

MS (ESI+) *m/z*, (%): 1667 (3, $[2M + Na]^+$), 845 (6, $[M + Na]^+$), 663 (100, [Irgafos 168 oxide + H]$^+$); HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{51}H_{54}O_8NaSi$ 845.3480; found: 845.3473.

Reduction of 179a with $LiAlH_4$

Step1. A solution of **179a** (88.0 mg, 107 µmol) in dry THF (5 mL) was cooled to −78 °C and treated with a solution of $LiAlH_4$ (450 µL, 1 mmol, 2.4 M in THF). The reaction was gradually warmed to r.t. over 2 hours, followed by quenching by 5 drops of water. The mixture was partitioned between water (20 mL) and DCM (50 mL). The organic layer was dried over Na_2SO_4, concentrated, and dried under vacuum to afford 88.6 mg of diol **184** (quant.) as a colourless film.

Protected gnetifolin F hydrate (**184**)



R_f 0.40 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3100 (br.), 3063 (w), 3034 (w), 2952 (w), 2925 (w), 2871 (w), 1596 (m), 1510 (m), 1453 (w), 1421 (w), 1377 (w), 1334 (w), 1285 (m), 1251 (s), 1225 (m), 1177 (w), 1139 (vs), 1035 (s), 1007 (w), 965 (w), 945 (w), 910 (w), 859 (m), 835 (s), 810 (w), 766 (w), 731 (vs), 694 (vs), 670 (w), 628 (w);

^{1}H (401 MHz, C_6D_6): δ 7.42-7.32 (m, 4H, Ar), 7.18-7.04 (m, 9H, Ar), 6.89-6.82 (m, 3H, Ar), 6.78-6.74 (m, 3H, Ar), 6.72-6.67 (m, 2H, H-10, H-14/6'), 6.49 (d, *J* = 2.0 Hz, 1H, H-4/6), 5.58 (d, *J* = 2.1 Hz, 1H, H-4/6), 4.84 (s, 2H, C12-OC*H*$_2$Ph), 4.73 (d, *J* = 9.2 Hz, 1H, H-8), 4.63 (d, *J* = 11.7 Hz, 1H, C3/5-OC*H*$_a$H$_b$Ph), 4.57 (d, *J* = 11.7 Hz, 1H, C3/5-OCH$_a$*H*$_b$Ph), 4.54 (d, *J* = 12.0 Hz, 1H, C3/5-OC*H*$_a$H$_b$Ph), 4.50 (d, *J* = 12.1 Hz, 1H, C3/5-OCH$_a$*H*$_b$Ph), 4.33 (d, *J* = 9.2 Hz, 1H, H-7'), 4.10-4.04 (m, 3H, H-9'a, OC*H*$_2$CH$_2$TMS), 3.97 (dd, *J* = 11.5, 4.1 Hz, 1H, H-9'b), 3.75 (dd, *J* = 9.2, 7.1 Hz, 1H, H-7), 3.45 (s, 3H, OC*H*$_3$), 3.39 (s, 3H, OC*H*$_3$), 3.05 (tdd, *J* = 9.2, 7.0, 4.1 Hz, 1H, H-8'), 0.06 (s, 9H, Si(C*H*$_3$)$_3$);

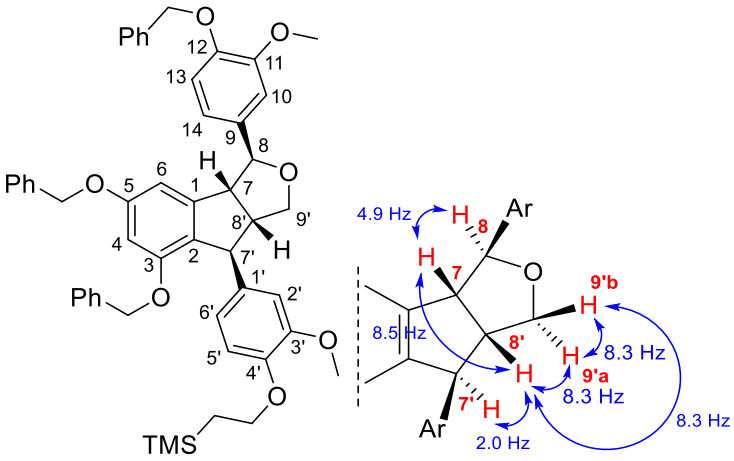
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 159.6 (s, C-5), 156.0 (s, C-3), 150.9 (s, C-11/3'), 150.4 (s, C-11/3'), 148.8 (s, C-12), 148.2 (s, C-4'), 146.6 (s, C-1), 138.1 (s, C-1'), 137.9 (s, Ph^{ipso}), 137.8 (s, Ph^{ipso}), 137.44 (s, C-9), 137.38 (s, Ph^{ipso}), 128.8 (d, Ph^{meta}), 128.7 (d, Ph^{meta}), 128.4 (d, Ph^{meta}), 128.2-127.8 (d, 3×C, Ph^{para}), 127.7 (d, Ph^{ortho}), 127.6 (d, Ph^{ortho}), 127.1 (d, Ph^{ortho}), 126.5 (s, C-2), 120.3 (d, C-14/6'), 120.2 (d, C-14/6'), 114.4 (d, C-10/13), 113.9 (d, C-10/13), 112.7 (d, C-2'/5'), 112.2 (d, C-2'/5'), 103.9 (d, C-4/6), 100.7 (d, C-4/6), 75.1 (d, C-8), 71.2 (t, C12-O*C*H$_2$Ph), 70.4 (t, C3/5-O*C*H$_2$Ph), 69.4 (t, C3/5-O*C*H$_2$Ph), 66.9 (t, O*C*H$_2$CH$_2$TMS), 61.6 (t, C-9'), 58.0 (d, C-8'), 55.8 (q, C11/3'-O*C*H$_3$), 55.7 (q, C11/3'-O*C*H$_3$), 55.4 (d, C-7), 49.9 (d, C-7'), 18.2 (t, OCH$_2$*C*H$_2$TMS), −1.2 (q, Si(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 1671 (24, $[2M + Na]^+$), 847 (100, $[M + Na]^+$), 807 (29, $[M + H - H_2O]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{51}H_{56}NaO_8Si$ 847.3637; found: 847.3642.

Step 2. After characterization, **184** was dissolved in 1% TFA in dry DCM (10 mL) and stirred at r.t. for 20 min. The mixture was evaporated and adsorbed onto silica. Flash chromatography (cyclohexane/EA 50:1 to 3:1) afforded 81.9 mg of **185** (94%) as a colourless film.

Protected gnetifolin F (**185**)



R_f 0.65 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3033 (w), 3003 (w), 2949 (w), 2930 (w), 2866 (w), 1594 (m), 1510 (m), 1453 (w), 1419 (w), 1377 (w), 1330 (w), 1260 (s), 1226 (m), 1177 (w), 1136 (vs), 1074 (w), 1028 (s), 968 (w), 910 (w), 837 (s), 810 (m), 734 (vs), 695 (vs), 631 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 7.41-7.30 (m, 4H, Ph), 7.21-6.74 (m, 17H, Ar), 6.73 (d, *J* = 2.1 Hz, 1H, H-4/6), 6.56 (d, *J* = 2.0 Hz, 1H, H-4/6), 5.05 (d, *J* = 4.8 Hz, 1H, H-8), 4.90 (s, 2H, C12-OC*H*$_2$Ph), 4.86 (d, *J* = 11.8 Hz, 1H, C5-OC*H*$_a$H$_b$Ph), 4.81 (d, *J* = 11.8 Hz, 1H, C5-OCH$_a$*H*$_b$Ph), 4.65 (d, *J* = 12.0 Hz, 1H, C3-OC*H*$_a$H$_b$Ph), 4.57 (d, *J* = 12.0 Hz, 1H, C3-OCH$_a$*H*$_b$Ph), 4.48 (t, *J* = 8.4 Hz, 1H, H-9'a), 4.37 (d, *J* = 1.9 Hz, 1H, H-7'), 4.15 (dd, *J* = 8.7, 4.9 Hz, 1H, H-7), 4.05-9.99 (m, 2H, OC*H*$_2$CH$_2$TMS), 3.71 (t, *J* = 8.5 Hz, 1H, H-9'b), 3.47 (s, 3H, C11-OC*H*$_3$), 3.40 (s, 3H, C3'-OC*H*$_3$), 3.28 (qd, *J* = 8.3, 2.2 Hz, 1H, H-8'), 1.12-1.06 (m, 2H, OCH$_2$*C*H$_2$TMS), 0.03 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 161.5 (s, C-5), 157.0 (s, C-3), 150.1 (s, C-11), 150.7 (s, C-3'), 148.8 (s, C-12), 148.0 (s, C-1/4'), 147.3 (s, C-1/4'), 139.3 (s, C-1'), 138.1 (s, Ph^{ipso}), 137.7 (s, Ph^{ipso}), 137.4 (s, Ph^{ipso}), 136.7 (s, C-9), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.1 (d, Ph^{para}), 127.90 (d, Ph^{para}), 127.88 (d, Ph^{para}), 127.8 (d, 2×C, Ph^{ortho}), 127.7 (d, 2×C, Ph^{ortho}), 127.5 (d, 2×C, Ph^{ortho}), 126.6 (s, C-2), 119.7 (d, C-6'), 118.9 (d, C-14), 114.9 (d, C-13), 114.6 (d, C-5'), 112.7 (d, C-2'), 111.0 (d, C-10), 102.1 (d, C-4/6), 100.4 (d, C-4/6), 88.0 (d, C-8), 74.4 (t, C-9'), 71.3 (t, C12-OCH$_2$Ph), 70.5 (t, C5-OCH$_2$Ph), 69.6 (t, C3-OCH$_2$Ph), 66.8 (t, OCH$_2$CH$_2$TMS), 60.3 (d, C-7), 55.7 (q, C-8'/OCH$_3$), 55.64 (q, C-8'/OCH$_3$), 55.61 (d, C-8'/OCH$_3$), 52.1 (d, C-7'), 18.1 (t, OCH$_2$CH$_2$TMS), −1.2 (q, Si(CH$_3$)$_3$);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.50-7.21 (m, 13H, Ph), 7.04-6.98 (m, 2H, Ph), 6.99 (d, *J* = 1.7 Hz, 1H, H-10), 6.87 (d, *J* = 8.2 Hz, 1H, H-13), 6.83 (dd, *J* = 8.3, 1.8 Hz, 1H, H-14), 6.72 (d, *J* = 8.2 Hz, 1H, H-5'), 6.60 (d, *J* = 2.1 Hz, 1H, H-2'), 6.54 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6'), 6.46 (d, *J* = 2.2 Hz, 1H, H-4/6), 6.45 (d, *J* = 2.2 Hz, 1H, H-4/6), 5.18 (s, 2H, C12-OC*H*$_2$Ph), 5.02 (s, 2H, C5-OC*H*$_2$Ph), 4.92 (d, *J* = 11.8 Hz, 1H, C3-OC*H*$_a$H$_b$Ph), 4.84 (d, *J* = 11.8 Hz, 1H, C3-OCH$_a$*H*$_b$Ph), 4.72 (d, *J* = 4.9 Hz, 1H, H-8), 4.50 (t, *J* = 8.3 Hz, 1H, H-9'a), 4.19 (d, *J* = 1.9 Hz, 1H, H-7'), 4.13-4.04 (m, 2H,

OC*H*$_2$CH$_2$TMS), 3.94 (dd, *J* = 8.5, 4.9 Hz, 1H, H-7), 3.92 (s, 3H, C11-OC*H*$_3$), 3.66 (s, 3H, C3'-OC*H*$_3$), 3.60 (t, *J* = 8.3 Hz, 1H, H-9'b), 3.18 (qd, *J* = 8.3, 2.0 Hz, 1H, H-8'), 1.20-1.17 (m, 2H, OCH$_2$*C*H$_2$TMS), 0.06 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 160.8 (s, C-5), 156.4 (s, C-3), 150.1 (s, C-11), 149.4 (s, C-3'), 147.8 (s, C-12), 146.6 (s, C-1/4'), 146.6 (s, C-1/4'), 138.4 (s, C-1'), 137.1 (s, Ph^{ipso}), 136.9 (s, Ph^{ipso}), 136.7 (s, Ph^{ipso}), 135.7 (s, C-9), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.4 (d, 2×C, Ph^{meta}), 128.2 (d, Ph^{para}), 127.0 (d, Ph^{para}), 127.8 (d, Ph^{para}), 127.7 (d, 2×C, Ph^{ortho}), 127.4 (d, 2×C, Ph^{ortho}), 127.3 (d, 2×C, Ph^{ortho}), 126.1 (s, C-2), 119.1 (d, C-6'), 118.7 (d, C-14), 114.1 (d, C-13), 113.1 (d, C-5'), 111.7 (d, C-2'), 109.9 (d, C-10), 101.8 (d, C-4/6), 99.9 (d, C-4/6), 87.6 (d, C-8), 74.3 (t, C-9'), 71.3 (t, C12-O*C*H$_2$Ph), 70.5 (t, C5-O*C*H$_2$Ph), 69.7 (t, C3-O*C*H$_2$Ph), 66.5 (t, O*C*H$_2$CH$_2$TMS), 59.4 (d, C-7), 56.2 (q, C11-O*C*H$_3$), 55.9 (q, C3'-O*C*H$_3$), 55.0 (d, C-8'), 51.3 (d, C-7'), 18.0 (t, OCH$_2$*C*H$_2$TMS), −1.3 (q, Si(*C*H$_3$)$_3$);

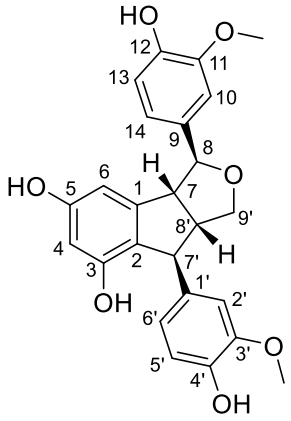
MS (ESI+) *m/z*, (%): 1636 (24, [2M + Na]$^+$), 829 (100, [M + Na]$^+$), 807 (7, [M + H]$^+$), 563 (33);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{51}H_{55}O_7Si$ 807.3712; found: 807.3715.

Global deprotection of 185 by BCl_3

Following a modified published method,[178,179] a solution of BCl_3 (0.15 mL, 0.15 mmol, 1 M in DCM) was added at –78 °C to a solution of **185** and *p*-xylene (0.10 mL, 0.84 mmol) in dry DCM (0.3 mL). The colour immediately changed to bright orange. After 20 min. at –78 °C, the reaction was quenched by addition of a 4:1 DCM/MeOH mixture, which led to immediate disappearance of the colour. The volatiles were evaporated in vacuum and the resulting crude product was purified by flash chromatography (PE/Et$_2$O, 9:1 to 1:1) to yield 7.9 mg of optically enriched (+)-**I** (86%) as a colourless film. The NMR data matched those of the natural product.[99]

Gnetifolin F (**I**)



R_f 0.50 (Et$_2$O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3100 (br.), 3059 (w), 3001 (w), 2926 (w), 2854 (w), 1601 (m), 1512 (s), 1463 (m), 1453 (m), 1432 (m), 1342 (m), 1265 (s), 1233 (m), 1207 (m), 1122 (w), 1073 (m), 1031 (s), 993 (m), 816 (vs), 770 (m), 735 (w), 699 (w);

^{1}H (401 MHz, acetone-d6): δ 8.15 (s, 1H, C5-O*H*), 7.84 (s, 1H, C3-O*H*), 7.51 (s, 1H, C12-O*H*), 7.26 (s, 1H, C4'-O*H*), 7.04 (d, *J* = 2.0 Hz, 1H, H-10), 6.90 (dd, *J* = 8.1, 1.9 Hz, 1H, H-14), 6.82 (d, *J* = 8.1 Hz, 1H, H-13), 6.73 (d, *J* = 2.1 Hz, 1H, H-2'), 6.66 (d, *J* = 8.1 Hz, 1H, H-5'), 6.50 (dd, *J* = 8.1, 2.0 Hz, 1H, H-6'), 6.35 (dd, *J* = 2.2, 1.0 Hz, 1H, H-4/6), 6.27 (dd, *J* = 2.1, 0.7 Hz, 1H, H-4/6), 4.72 (d, *J*

= 4.4 Hz, 1H, H-8), 4.46 (t, *J* = 8.3 Hz, 1H, H-9a), 4.18 (d, *J* = 1.6 Hz, 1H, H-7'), 3.86 (s, 3H, C11-OC*H*$_3$), 3.80 (dd, *J* = 8.4, 4.3 Hz, 1H, H-7), 3.74 (s, 3H, C3'-OC*H*$_3$), 3.50 (t, *J* = 8.7 Hz, 1H, H-9b), 3.04 (qd, *J* = 8.4, 1.7 Hz, 1H, H-8');

$^{13}C\{^1H\}$ NMR (101 MHz, acetone-d6): δ 159.9 (s, C-5), 155.9 (s, C-3), 148.4 (s, 2×C, C-11, C-1), 148.1 (s, C-3'), 146.8 (s, C-12), 145.6 (s, C-4'), 138.1 (s, C-1'), 135.6 (s, C-9), 122.8 (s, C-2), 120.3 (d, C-6'), 119.7 (d, C-14), 115.6 (d, C-5'), 115.5 (d, C-13), 112.0 (d, C-2'), 110.6 (d, C-10), 103.3 (d, C-6), 102.7 (d, C-4), 88.4 (d, C-8), 74.5 (t, C-9'), 59.7 (d, C-7), 56.3 (q, C11/3'-OCH_3), 56.2 (q, C11/3'-OCH_3), 55.9 (d, C-8'), 51.1 (d, C-7');

MS (ESI–) *m/z*, (%): 435 (100, $[M - H]^-$);

MS (ESI+) *m/z*, (%): 895 (13, $[2M + Na]^+$), 459 (100, $[M + Na]^+$), 437 (6, $[M + H]^+$), 313 (14, $[M - C_7H_7O_2]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{25}H_{24}NaO_7$ 459.1414; found: 459.1418, $[M + H]^+$ calcd. for $C_{25}H_{25}O_7$ 437.1595; found: 437.1596;

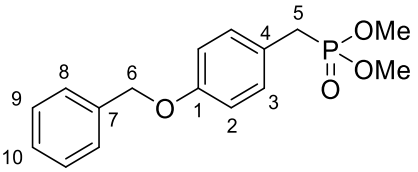
α_D^{20} = +33.4 (c 0.269, MeOH).

6.2.10. Total synthesis of (+) and (–)-11-deoxykompasinol A (**IV**)

Synthesis of protected resveratrol 186

Step 1. At 0 °C, dimethyl phosphite (3.1 mL, 34.3 mmol) was added dropwise over 2 min to a suspension of sodium hydride (1.27 g, 31.7 mmol, 60% in mineral oil) in THF (45 mL). A solution of KHMDS (0.86 mL, 0.86 mmol, 1M in THF) was added, followed by stirring at r.t. for 1 h. A solution of *para*-(benzyloxy)-benzyl chloride (3.99 g, 17.1 mmol) in THF (15 mL) was added dropwise over 2 min. KI (285 mg, 1.7 mmol) was added, followed by stirring at r.t. overnight. The mixture was partitioned between saturated NH_4Cl solution (100 mL) and DCM (150 mL). The aqueous layer was washed twice with DCM (2×100 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and dried under high vacuum at 65 °C for two days to yield 4.97 g of **187** (94%) as a pale-yellow solid, mp 60-60°C.

Diethyl [4-(benzyloxy)benzyl]phosphonate (**187**)



IR (film) $\tilde{\nu}$[cm^{-1}]: 3062 (w), 3034 (w), 2952 (w), 2922 (w), 2851 (w), 1610 (w), 1584 (w), 1510 (m), 1455 (w), 1382 (w), 1297 (w), 1240 (s), 1178 (w), 1053 (w), 1022 (vs), 859 (m), 827 (m), 803 (m), 733 (m), 697 (m);

^1H NMR (401 MHz, $CDCl_3$): δ 7.45-7.36 (m, 4H, H-8, H-9), 7.35-7.29 (m, 1H, H-10), 7.24-2.17 (m, 2H, H-3), 6.95-6.91 (m, 2H, H-2), 5.05 (s, 2H, H-6), 3.67 (d, $^3J_{HP}$ = 10.7 Hz, 6H, OCH_3), 3.11 (d, $^2J_{HP}$ = 21.1 Hz, 2H, H-5);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 158.0 (s, $^5J_{CP}$ = 3.5 Hz, C-1), 137.1 (s, C-7), 130.9 (d, $^3J_{CP}$ = 3.1 Hz, C-3), 128.6 (d, 2×C, C-9), 128.1 (d, C-10), 127.4 (d, 2×C, C-8), 123.5 (s, $^2J_{CP}$ = 3.1 Hz, C-4),

115.2 (d, $^{4}J_{CP}$ = 3.0 Hz, C-2), 71.2 (t, C-6), 53.0 (q, $^{2}J_{CP}$ = 4.9 Hz, O*C*H$_3$), 32.1 (t, $^{1}J_{CP}$ = 139.2 Hz, C-5);

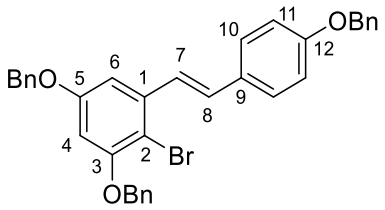
^{31}P NMR (162 MHz, CDCl$_3$): δ 29.20;

MS (ESI+) *m/z*, (%): 329 (92, [M + Na]$^+$), 307 (100, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{16}H_{20}O_4P$ 307.1094; found: 307.1093.

Step 2. Phosphonate **187** (4.00 g, 13.0 mmol) and aldehyde **165** (6.744 g, 17.0 mmol) were partially dissolved in dry DMF (40 mL). The resulting suspension was stirred vigorously and a *t*-AmONa solution (7.8 mL, 26.1 mmol, 40% in toluene) was slowly added. The solids dissolved giving a brown solution, which was stirred overnight at r.t. The reaction mixture was partitioned between water (250 mL) and DCM (150 mL). The aqueous layer was extracted twice with DCM (2×150 mL). The combined DCM extracts were dried over Na_2SO_4 and concentrated. The crude product was recrystallized from a Et_2O/MeOH mixture to give 5.387 g of pure **186** (71%) as a colourless solid, mp 110-111 °C.

2-Bromoresveratrol tribezyl ether (**186**)



R_f 0.33 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3088 (w), 3063 (w), 3032 (w), 2929 (w), 2867 (w), 1571 (s), 1508 (m), 1453 (w), 1425 (w), 1376 (w), 1311 (w), 1280 (w), 1263 (w), 1237 (m), 1163 (s), 1082 (w), 1067 (m), 1019 (m), 959 (m), 823 (m), 732 (vs), 694 (vs), 664 (w);

^{1}H (401 MHz, CDCl$_3$): δ 7.54-7.30 (m, 18H, H-7/8, H-10, Ph), 7.04-6.95 (m, 2H, H-11), 6.94 (d, *J* = 16.2 Hz, 1H, H-7/8), 6.91 (d, *J* = 2.7 Hz, 1H, H-4/6), 6.54 (d, *J* = 2.7 Hz, 1H, H-4/6), 5.13 (s, 2H, OC*H*$_2$Ph), 5.11 (s, 2H, OC*H*$_2$Ph), 5.08 (s, 2H, OC*H*$_2$Ph);

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 159.0 (s, C-12), 158.7 (s, C-3/5), 156.1 (s, C-3/5), 139.2 (s, C-1), 137.0 (s, Ph^{ipso}), 136.7 (s, Ph^{ipso}), 136.6 (s, Ph^{ipso}), 131.3 (d, C-7/8), 130.2 (s, C-9), 128.82 (d, 2×C, Ph^{meta}), 128.77 (d, 2×C, Ph^{meta}), 128.72 (d, 2×C, Ph^{meta}), 128.3 (d, 2×C, C-7/8, Ph^{para}), 128.2 (d, Ph^{para}), 128.1 (d, Ph^{para}), 127.8 (d, 2×C, Ph^{ortho}), 127.6 (d, 2×C, Ph^{ortho}), 127.1 (d, 2×C, Ph^{ortho}), 126.0 (d, 2×C, C-10), 115.3 (d, 2×C, C-11), 106.1 (s, C-2), 104.3 (d, C-4/6), 101.2 (d, C-4/6), 71.1 (t, O*C*H$_2$Ph), 70.6 (t, O*C*H$_2$Ph), 70.2 (t, O*C*H$_2$Ph);

MS (ESI+) *m/z*, (%): 617/615 (21/15, [M + K]$^+$), 601/599 (41/37, [M + Na]$^+$), 579/577 (100/99, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{35}H_{30}{}^{79}BrO_3$ 577.1373; found: 577.1371.

One-pot conjugate addition/oxidative bicyclisation of 186/188 at –115 °C

Using (+)-*sparteine*. The same procedure as for **177** was followed, using **186** (1.88 g, 3.25 mmol), **188** (1.06 g, 2.50 mmol) and (+)-sparteine (1.70 mL, 7.5 mmol). Conjugate addition at –115 °C.

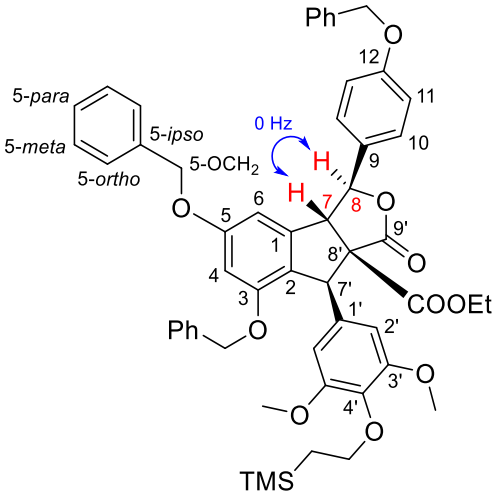
Purification by flash chromatography (cyclohexane/EA, 25:1 to 2:1) yielded in order of increasing polarity: 1.23 g of **189** (55%) as a colourless amorphous solid and 0.88 g of a mixture of **189** and unknown sideproducts. In the next step, this mixture was saponified separately from the bulk material (see prep. of **190**) to yield additional 5% of **190** with respect to starting **188**.

Enantiomers of **189** were inseparable by chiral HPLC, analysis of the saponification product **190** after the next step revealed 34% ee by chiral HPLC (Hexane/*i*-PrOH 50:50, flow 1.0 mL/min).

Using (–)-*sparteine.* Procedure and loadings identical as above, except (–)-sparteine (1.70 mL, 7.5 mmol). Purification by flash chromatography (cyclohexane/EA, 25:1 to 2:1) yielded 0.916 g of *ent*-**189** (41%) and 1.076 g of a mixture of **189** and unknown sideproducts. In the next step, this mixture was saponified separately from the bulk material (see prep. of **190**) to yield additional 10% of **190** with respect to starting **188**.

Analysis of the saponification product *ent*-**190** after the next step revealed 33% ee by chiral HPLC (Hexane/*i*-PrOH 50:50, flow 1.0 mL/min).

Protected 8'-carbethoxy-9'-oxo-11-deoxykompasinol A (**189**)



R_f 0.21 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3088 (w), 3064 (w), 3033 (w), 2951 (w), 2898 (w), 2838 (w), 1781 (m), 1732 (w), 1592 (m), 1511 (w), 1499 (w), 1455 (m), 1423 (w), 1376 (w), 1329 (w), 1298 (w), 1230 (s), 1177 (w), 1154 (vs), 1124 (vs), 1027 (s), 969 (w), 858 (w), 833 (s), 734 (s), 695 (s);

^{1}H (401 MHz, C_6D_6): δ 7.40-7.34 (m, 2H, Ph), 7.30-7.01 (m, 11H, H-10, Ph), 6.90-6.81 (m, 4H, H-11, Ph), 6.68 (d, J = 1.5 Hz, 1H, H-4), 6.60-6.44 (br. s, 2H, H-2', H-6'), 6.43 (d, J = 1.7 Hz, 1H, H-6), 5.70 (s, 1H, H-8), 5.69 (s, 1H, H-7'), 5.01 (s, 1H, H-7), 4.80 (s, 2H, C5-OCH_2Ph), 4.66 (s, 2H, C12-OCH_2Ph), 4.52 (d, J = 12.0 Hz, 1H, C3-OCH^aH^{b}Ph), 4.45 (d, J = 12.0 Hz, 1H, C3-OCH^aH^bPh), 4.25-4.19 (m, 2H, OCH_2CH$_2$TMS), 3.53-3.43 (m, 2H, OCH_2CH$_3$), 3.35 (s, 6H, C3'-OCH_3), 1.27-1.22 (m, 2H, OCH$_2$CH_2TMS), 0.58 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3); –0.01 (q, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 174.4 (s, C-9'), 166.4 (s, *C*OOEt), 162.1 (s, C-5), 159.1 (s, C-12), 156.3 (s, C-3), 154.2 (s, 2×C, C-3'), 144.1 (s, C-1), 137.7 (s, C-4'), 137.4 (s, Ph^{ipso}), 137.3 (s, Ph^{ipso}), 137.0 (s, Ph^{ipso}), 135.4 (s, C-1'), 132.1 (s, C-9), 128.9 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.41 (d, Ph^{para}), 128.38 (d, Ph^{para}), 128.0 (d, 2×C, Ph^{ortho}), 127.9 (d, Ph^{para}), 127.7 (d, 2×C, Ph^{ortho}), 127.3 (d, 2×C, Ph^{ortho}), 126.7 (d, 2×C, C-10), 125.0 (s, C-2), 115.4 (d, 2×C, C-11), 107.4 (br. d, 2xC, C-2'), 101.3 (d, C-4/6), 101.2 (d, C-4/6), 84.4 (d, C-8), 70.7 (t, C5-O*C*H$_2$Ph), 70.6 (t, O*C*H$_2$CH$_2$TMS), 70.0 (t, C12-O*C*H$_2$Ph), 69.6 (t, C3-O*C*H$_2$Ph), 66.9 (s, C-8'), 61.8 (t, O*C*H$_2$CH$_3$),

57.9 (d, C-7'), 57.2 (d, C-7), 55.9 (q, 2xC, C3'-O*C*H$_3$, 5'-O*C*H$_3$), 19.2 (t, OCH$_2$*C*H$_2$TMS), 13.6 (q, OCH$_2$*C*H$_3$), –1.3 (q, Si(*C*H$_3$)$_3$);

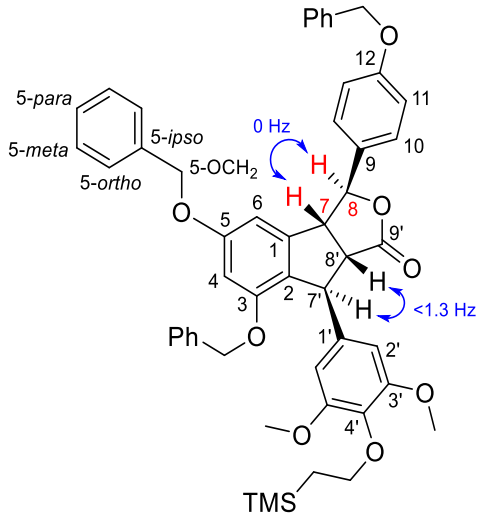
MS (ESI+) *m/z*, (%): 1807 (32, [2M + Na]$^+$), 918 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{45}H_{56}O_{10}NaSi$ 915.3535; found: 915.3529.

Saponification-decarboxylation of 189

The same procedure as for **179a** was followed starting with **189** (311 mg, 261 µmol), except that 2:1 EtOH/toluene mixture (21 mL) was used as a solvent. Purification by flash chromatography (cyclohexane/EA, 25:1 to 3:1) yielded in order of elution 111.9 mg of **190** (52%) as colourless amorphous solid and 30.1 mg of **191** (16%) as a colourless amorphous solid.

Protected 9'-oxo-11-deoxykompasinol A (**190**)



R_f 0.24 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3064 (w), 3033 (w), 3002 (w), 2948 (w), 2874 (w), 1766 (m), 1589 (m), 1511 (m), 1499 (m), 1454 (m), 1421 (w), 1374 (w), 1331 (m), 1294 (w), 1231 (s), 1149 (s), 1124 (vs), 1069 (w), 1039 (m), 1027 (m), 971 (w), 858 (m), 831 (s), 734 (s), 695 (s);

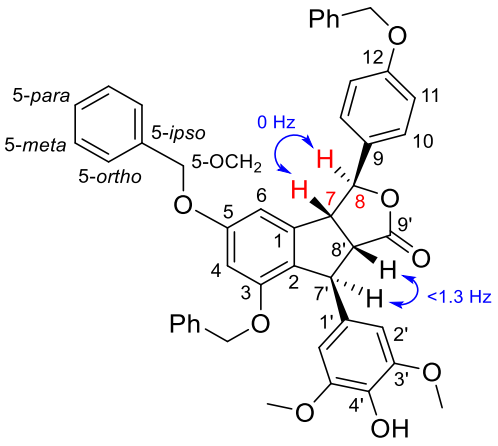
^{1}H (401 MHz, C_6D_6): δ 7.40-7.34 (m, 2H, Ph), 7.29-7.01 (m, 11H, H-10, Ph), 6.96-6.89 (m, 2H, Ph), 6.87-6.82 (m, 2H, H-11), 6.64 (d, *J* = 1.7 Hz, 1H, H-4), 6.48 (s, 2H, H-2'), 6.47 (d, *J* = 1.7 Hz, 1H, H-6), 5.55 (s, 1H, H-8), 5.36 (s, 1H, H-7'), 4.82 (s, 2H, C5-OC*H*$_2$Ph), 4.74 (s, 2H, C12-OC*H*$_2$Ph), 4.60 (d, *J* = 12.1 Hz, 1H, C3-OC*H*^{a}H^{b}Ph), 4.53 (d, *J* = 12.1 Hz, 1H, C3-OCH^a*H*^{b}Ph), 4.32-4.26 (m, 2H, OC*H*$_2$CH$_2$TMS), 4.06 (d, *J* = 7.8 Hz, 1H, H-7), 3.44 (dd, *J* = 7.7, 1.3 Hz, 1H, H-8'), 3.32 (s, 6H, C3'-OC*H*$_3$), 1.33-1.27 (m, 2H, OCH$_2$C*H*$_2$TMS), 0.02 (q, Si(C*H*$_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 178.4 (s, C-9'), 161.9 (s, C-5), 159.3 (s, C-12), 156.6 (s, C-3), 154.7 (s, 2×C, C-3'), 145.3 (s, C-1), 139.6 (s, C-1'), 137.40 (s, 2×C, Ph^{ipso}), 137.37 (s, C-4'), 137.1 (s, Ph^{ipso}), 133.2 (s, C-9), 128.9 (d, 2×C, Ph^{meta}), 128.8 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.4 (d, Ph^{para}), 128.2 (d, Ph^{para}), 127.9 (d, 3×C, Ph^{para}, Ph^{ortho}), 127.7 (d, 2×C, Ph^{ortho}), 127.3 (d, 2×C, Ph^{ortho}), 126.9 (d, 2×C, C-10), 125.8 (s, C-2), 115.7 (d, 2×C, C-11), 105.5 (d, 2xC, C-2'), 101.7 (d, C-4/6), 100.9 (d, C-4/6), 85.4 (d, C-8), 70.6 (t, 2×C, C5-O*C*H$_2$Ph, O*C*H$_2$CH$_2$TMS), 70.1 (t, C12-O*C*H$_2$Ph), 69.6 (t, C3-O*C*H$_2$Ph), 55.9 (q, 2xC, C3'-O*C*H$_3$), 54.6 (d, C-7), 53.1 (d, C-8'), 52.8 (d, C-7'), 19.2 (t, OCH$_2$*C*H$_2$TMS), –1.3 (q, Si(C*H*$_3$)$_3$);

MS (ESI+) *m/z*, (%):1663 (15, $[2M + Na]^+$), 843 (100, $[M + Na]^+$), 821 (5, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{51}H_{52}NaO_8Si$ 843.3324; found: 843.3319, $[M + H]^+$ calcd. for $C_{51}H_{53}O_8Si$ 821.3504; found: 821.3502.

9'-Oxo-11-deoxykompasinol A 3,5,12-O-tribenzyl ether (**191**)



R_f 0.79 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3200 (br.), 3065 (w), 3033 (w), 2955 (m), 2932 (m), 2869 (m), 1765 (m), 1602 (s), 1512 (m), 1455 (m), 1375 (w), 1329 (m), 1303 (m), 1216 (m), 1149 (s), 1113 (vs), 1068 (m), 1038 (m), 1027 (w), 988 (w), 914 (w), 830 (m), 811 (w), 735 (s), 696 (s), 635 (w);

^{1}H (401 MHz, C_6D_6): δ 7.49-7.34 (m, 2H, Ph), 7.28-7.00 (m, 11H, H-10, Ph), 6.95-6.90 (m, 2H, Ph), 6.88-6.82 (m, 2H, H-11), 6.65 (d, *J* = 1.7 Hz, 1H, H-4), 6.49 (d, *J* = 1.8 Hz, 1H, H-6), 6.42 (s, 2H, H-2'), 5.56 (s, 1H, H-8), 5.52-5.26 (br. s, C4'-O*H*), 5.33 (s, 1H, H-7'), 4.82 (s, 2H, C5-OCH_2Ph), 4.74 (s, 2H, C12-OCH_2Ph), 4.60 (d, *J* = 12.1 Hz, 1H, C3-OCH^aH^{b}Ph), 4.55 (d, *J* = 12.1 Hz, 1H, C3-OCH^aH^bPh), 4.05 (d, *J* = 7.7 Hz, 1H, H-7), 3.42 (dd, *J* = 7.7, 1.3 Hz, 1H, H-8'), 3.23 (s, 6H, C3'-OCH_3);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 178.5 (s, C-9'), 161.8 (s, C-5), 159.3 (s, C-12), 156.6 (s, C-3), 148.0 (s, 2×C, C-3'), 145.3 (s, C-1), 137.42 (s, Ph^{ipso}), 137.37 (s, C-4'), 137.1 (s, Ph^{ipso}), 135.12 (s, C-1'), 133.2 (s, C-9), 128.9 (d, 2×C, Ph^{meta}), 128.8 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.3 (d, Ph^{para}), 128.2 (d, Ph^{para}), 127.9 (d, 3×C, Ph^{para}, Ph^{ortho}), 127.7 (d, 2×C, Ph^{ortho}), 127.4 (d, 2×C, Ph^{ortho}), 126.9 (d, 2×C, C-10), 125.9 (s, C-2), 115.7 (d, 2×C, C-11), 105.1 (d, C-2', C-6'), 101.7 (d, C-4/6), 101.0 (d, C-4/6), 85.4 (d, C-8), 70.6 (t, C5-OCH$_2$Ph), 70.1 (t, C12-OCH$_2$Ph), 69.7 (t, C3-OCH$_2$Ph), 56.0 (q, C3'-OCH$_3$, C5'-OCH$_3$), 54.6 (d, C-7), 53.3 (d, C-8'), 52.8 (d, C-7');

MS (ESI+) *m/z*, (%): 743 (100, $[M + Na]^+$), 721 (9, $[M + H]^+$);

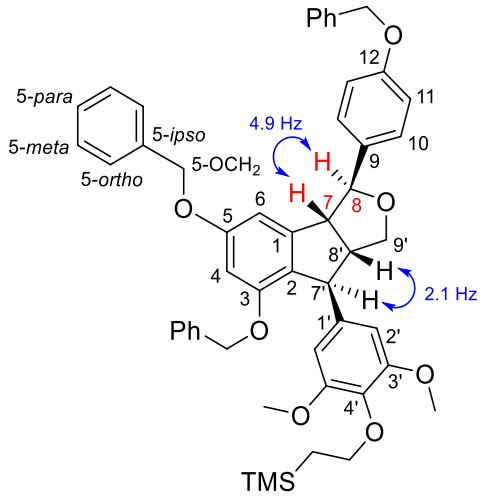
HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{46}H_{40}O_8Na$ 743.2615; found: 743.2609, $[M + H]^+$ calcd. for $C_{46}H_{41}O_8$ 721.2796; found: 721.2791.

Reduction of 190 with $LiAlH_4$

A solution of **190** (475 mg, 0.489 mmol) in dry THF (28 mL) was cooled to 0 °C and treated with a solution of $LiAlH_4$ (1.2 mL, 2.9 mmol, 2.4 M in THF). The reaction was warmed to r.t. for 30 min, followed by quenching with saturated solution of sodium potassium tartrate (1 mL). The mixture was

partitioned between water (100 mL) and DCM (200 mL). The organic phase separated, dried over Na_2SO_4, concentrated, and dried under vacuum. The residue was redissolved in 5% TFA in DCM (25 mL) and stirred for 20 min at r.t., followed by evaporation and drying under vacuum. Purification by flash chromatography (cyclohexane/EA 50:1 to 3:1) afforded 194 mg of **192** (41%) as a colourless film and 131 mg of **193** (32%) as a colourless amorphous solid.

Protected 11-deoxykompasinol A (**192**)



R_f 0.35 (hexane/EA 5:1), R_f 0.58 (hexane/EA 3:1), R_f 0.76 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3088 (w), 3063 (w), 3032 (w), 2949 (w), 2869 (w), 2837 (w), 1588 (s), 1508 (m), 1454 (m), 1421 (m), 1375 (w), 1331 (m), 1299 (w), 1226 (m), 1174 (w), 1125 (vs), 1075 (w), 1041 (m), 1027 (m), 971 (w), 950 (w), 858 (m), 827 (s), 734 (s), 695 (vs), 637 (w);

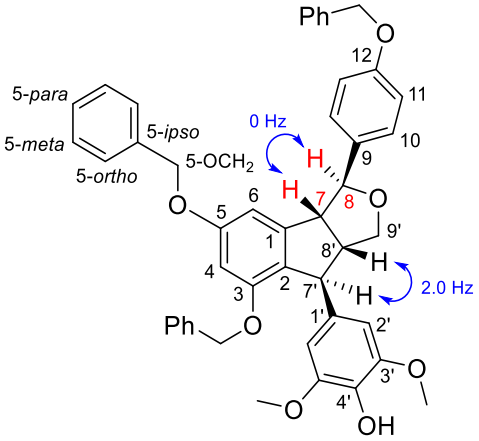
^{1}H (401 MHz, $CDCl_3$): δ 7.48-7.33 (m, 12H, Ph), 7.27-7.25 (m, 3H, Ph), 7.04-7.00 (m, 4H, H-11, H-13, Ph), 6.50 (d, J = 2.0 Hz, 1H, H-4/6), 6.47 (d, J = 2.0 Hz, 1H, H-4/6), 6.28 (s, 2H, H-2'), 5.11 (s, 2H, C12-OCH_2Ph), 5.09-5.03 (m, 2H, C5-OCH_2Ph), 4.94 (d, J = 11.8 Hz, 1H, C3-OCH^aH^{b}Ph), 4.86 (d, J = 11.8 Hz, 1H, C3-OCH^aH^bPh), 4.75 (d, J = 4.9 Hz, 1H, H-8), 4.52 (t, J = 8.5 Hz, 1H, H-9'a), 4.19 (d, J = 2.1 Hz, 1H, H-7'), 4.08-4.03 (m, 2H, OCH_2CH$_2$TMS), 3.95 (dd, J = 8.8, 4.9 Hz, 1H, H-7), 3.68 (s, 6H, C3'-OCH_3), 3.63 (t, J = 8.5 Hz, 1H, H-9'b), 3.23 (dtd, J = 8.8, 8.5, 2.1 Hz, 1H, H-8'), 1.22-1.17 (m, 2H, OCH$_2$CH_2TMS), 0.03 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.8 (s, C-5), 158.5 (s, C-12), 156.4 (s, C-3), 153.6 (s, 2xC, C-3'), 146.7 (s, C-1), 141.3 (s, C-1'), 137.13 (s, Ph^{ipso}), 137.07 (s, Ph^{ipso}), 136.8 (s, Ph^{ipso}), 135.2 (s, C-4'), 134.9 (s, C-9), 128.77 (d, 2×C, Ph^{meta}), 128.74 (d, 2×C, Ph^{meta}), 128.5 (d, 2×C, Ph^{meta}), 128.2 (d, Ph^{para}), 128.1 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.7 (d, 4×C, Ph^{ortho}, C-10), 127.6 (d, 2×C, Ph^{ortho}), 127.2 (d, 2×C, Ph^{ortho}), 125.7 (s, C-2), 115.1 (d, 2xC, C-11), 104.6 (d, 2xC, C-2'), 101.8 (d, C-4/6), 99.8 (d, C-4/6), 87.5 (d, C-8), 74.3 (t, C-9'), 70.8 (t, OCH_2CH$_2$TMS), 70.5 (t, C5-OCH_2Ph), 70.2 (t, C12-OCH_2Ph), 69.7 (t, C3-OCH_2Ph), 59.5 (d, C-7), 56.1 (q, 2xC, C3'-OCH_3), 54.9 (d, C-8'), 52.1 (d, C-7'), 18.9 (t, OCH$_2$CH_2TMS), –1.3 (q, Si(CH_3)$_3$);

MS (ESI+) *m/z*, (%): 1631 (292, [2M + H_2O + H]$^+$), 845 (32, [M + K]$^+$), 829 (53, [M + Na]$^+$), 807 (100, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{51}H_{54}NaO_7Si$ 829.3531; found: 829.3527, [M + H]$^+$ calcd. for $C_{51}H_{55}O_7Si$ 807.3712; found: 807.3709.

11-Deoxykompasinol A 3,5,12-O-tribenzyl ether (**193**)



R_f 0.41 (hexane/EA 3:1), R_f 0.67 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3100 (br.), 3088 (w), 3062 (w), 3032 (w), 3002 (w), 2936 (w), 2871 (w), 1601 (s), 1510 (s), 1454 (s), 1429 (w), 1374 (w), 1329 (m), 1303 (m), 1239 (m), 1214 (s), 1174 (m), 1140 (s), 1113 (vs), 1075 (w), 1041 (w), 1027 (m), 969 (w), 914 (w), 828 (m), 735 (s), 697 (s), 676 (w), 637 (w);

^{1}H (401 MHz, CD_3COCD_3): δ 7.53-7.46 (m, 4H, Ph), 7.43-7.23 (m, 11H, Ph, H-10/11), 7.17-7.12 (m, 2H, Ph), 7.07-7.00 (m, 2H, H-10/11), 6.95 (s, 1H, OH), 6.60-6.57 (m, 2H, H-4, H-6), 6.39 (s, 2H, H-2'), 5.14 (s, 2H, C12-OCH_2Ph), 5.12 (s, 2H, C5-OCH_2Ph), 5.05 (d, J = 12.3 Hz, 1H, C3-OCH^aH^{b}Ph), 4.96 (d, J = 12.3 Hz, 1H, C3-OCH^aH^bPh), 4.75 (d, J = 4.4 Hz, 1H, H-8), 4.45 (t, J = 8.4 Hz, 1H, H-9'a), 4.22 (d, J = 2.0 Hz, 1H, H-7'), 3.94 (dd, J = 8.6, 4.5 Hz, 1H, H-7), 3.65 (s, 6H, C3'-OMe), 3.54 (t, J = 8.5 Hz, 1H, H-9'b), 3.15 (qd, J = 8.3, 2.0 Hz, 1H, H-8');

^{13}C{^{1}H} NMR (101 MHz, CD_3COCD_3): δ 161.7 (s, C-5), 159.2 (s, C-12), 157.2 (s, C-3), 148.6 (s, C-1), 147.8 (s, C-3', C-5'), 138.51 (s, C-1'/4'), 128.49 (s, C-1'/4'), 138.3 (s, Ph^{ipso}), 137.3 (s, Ph^{ipso}), 136.3 (s, Ph^{ipso}), 135.3 (s, C-9), 129.3 (d, 4×C, Ph^{meta}), 129.1 (d, 2×C, Ph^{meta}), 128.64 (d, Ph^{para}), 128.61 (d, Ph^{para}), 128.5 (d, Ph^{para}), 128.41 (d, C-10/14), 128.35 (d, 2×C, Ph^{ortho}), 128.32 (d, C-10/14), 127.9 (d, 4×C, Ph^{ortho}), 126.6 (s, C-2), 115.6 (d, C-11, C-13), 105.9 (d, C-2', C-6'), 102.6 (d, C-4/6), 100.6 (d, C-4/6), 88.0 (d, C-8), 74.7 (t, C-9'), 70.8 (t, OCH$_2$Ph), 70.5 (t, OCH$_2$Ph), 70.0 (t, OCH$_2$Ph), 60.2 (d, C-7), 56.6 (q, 2xC, C3'-OCH$_3$), 55.7 (d, C-8'), 52.5 (d, C-7');

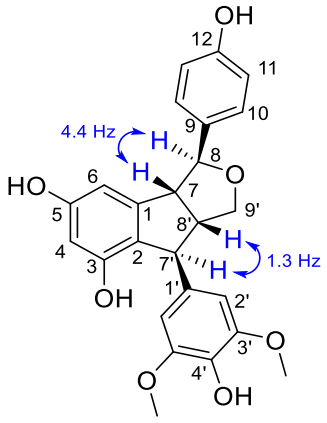
MS (ESI+) *m/z*, (%): 1435 (8, [2M + Na]$^+$), 745 (18, [M + K]$^+$), 729 (56, [M + Na]$^+$), 707 (100, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{46}H_{42}NaO_7$ 729.2823; found: 729.2819, [M + H]$^+$ calcd. for $C_{46}H_{43}O_7$ 707.3003; found: 707.3001.

Global deprotection of 192 by BCl_3

Following the procedure used for **185**, protected **192** was treated with BCl_3 (0.48 mL, 0.48 mmol, 1 M in DCM) in dry DCM (0.7 mL) and *p*-xylene (0.33 mL, 2.66 mmol) at –78 °C for 80 min. Flash chromatography (PE/Et_2O, 9:1 to 1:1) yielded 23.1 mg of optically enriched (+)-**IV** (quant.) as a colourless film. The scalemic mixture was separated by chiral HPLC using a YMC Chiral ART Cellulose-SC column (250 x 20.0 mm, 5µm), gradient elution with ternary mobile phase 30:70 to 40:60 (5% $CHCl_3$ in *i*-PrOH) : (heptane). Yield 5.6 mg of (+)-**IV**, 2.5 mg of (–)-**IV**.

11-Deoxykompasinol A (**IV**)



R_f 0.11 (Et_2O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3575-3050 (br.), 2954 (w), 2923 (s), 2853 (m), 1739 (w), 1709 (w), 1657 (w), 1633 (w), 1515 (w), 1462 (m), 1377 (w), 1261 (w), 1214 (w), 1114 (w), 1024 (w), 801 (w), 721 (w);

^{1}H (401 MHz, acetone-d6): δ 8.48 (s, 1H, O*H*), 8.30 (s, 1H, O*H*), 7.98 (s, 1H, O*H*), 7.30-7.24 (m, 2H, H-10), 6.97 (s, 1H, O*H*), 6.85-6.81 (m, 2H, H-11), 6.39 (s, 2H, H-2'), 6.32 (d, *J* = 2.1 Hz, 1H, H-4/6), 6.27 (d, *J* = 2.1 Hz, 1H, H-4/6), 4.71 (d, *J* = 4.4 Hz, 1H, H-8), 4.44 (t, *J* = 8.4 Hz, 1H, H-9'a), 4.17 (d, *J* = 1.3 Hz, 1H, H-7'), 3.78 (dd, *J* = 8.4, 4.3 Hz, 1H, H-7), 3.70 (s, 6H, C3'-OCH_3), 3.49 (t, *J* = 8.4 Hz, 1H, H-9'b), 3.05 (qd, *J* = 8.4, 1.4 Hz, 1H, H-8');

^{13}C{^{1}H} NMR (101 MHz, acetone-d6): δ 159.9 (s, C-5), 157.7 (s, C-12), 156.0 (s, C-3), 148.53 (s, 2xC, C-3'), 148.48 (s, C-1), 137.2 (s, C-1'), 135.2 (s, C-4'), 134.9 (s, C-9), 128.3 (d, 2xC, C-10), 122.6 (s, C-2), 116.0 (d, 2xC, C-11), 105.8 (d, 2xC, C-2'), 103.2 (d, C-4/6), 102.7 (d, C-4/6), 88.2 (d, C-8), 74.5 (t, C-9'), 59.6 (d, C-7), 56.6 (q, 2xC, C3'-O*C*H$_3$), 56.0 (d, C-8'), 51.5 (d, C-7');

^{1}H (401 MHz, DMSO-d6): δ 9.37 (s, 1H, O*H*), 9.10 (s, 1H, O*H*), 9.00 (s, 1H, O*H*), 8.01 (s, 1H, O*H*), 7.19 (d, *J* = 8.6 Hz, 2H, H-10), 6.75 (d, *J* = 8.6 Hz, 2H, H-11), 6.25 (s, 2H, H-2'), 6.13 (s, 2H, H-4, H-6), 4.61 (d, *J* = 4.2 Hz, 1H, H-8), 4.37 (t, *J* = 8.4 Hz, 1H, H-9'a), 4.01 (d, *J* = 1.1 Hz, 1H, H-7'), 3.68 (dd, *J* = 8.2, 4.0 Hz, 1H, H-7), 3.63 (s, 6H, C3'-OCH_3), 3.37 (t, *J* = 8.4 Hz, 1H, H-9'b), 2.91 (qd, *J* = 8.4, 1.2 Hz, 1H, H-8');

^{13}C{^{1}H} NMR (101 MHz, DMSO-d6): δ 158.6 (s, C-5), 156.7 (s, C-12), 154.9 (s, C-3), 147.7 (s, 2xC, C-3'), 146.9 (s, C-1), 136.0 (s, C-1'), 133.7 (s, C-4'), 132.9 (s, C-9), 127.5 (d, 2xC, C-10), 121.1 (s, C-2), 115.1 (d, 2xC, C-11), 104.8 (d, 2xC, C-2'), 101.7 (d, C-4/6), 101.6 (d, C-4/6), 86.8 (d, C-8), 73.3 (t, C-9'), 58.0 (d, C-7), 56.0 (q, 2xC, C3'-O*C*H$_3$), 54.2 (d, C-8'), 50.1 (d, C-7');

MS (ESI+) *m/z*, (%): 895 (15, [2M + Na]$^+$), 459 (100, [M + Na]$^{\cdot+}$), 437 (16, [M + H]$^+$); MS (ESI–) *m/z*, (%): 435 (100, [M – H]$^-$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{25}H_{24}O_7Na$ 459.1414; found: 459.1411; HRMS (ESI–) *m/z*: [M – H]$^-$ calcd. for $C_{25}H_{23}O_7$ 435.1449; found: 435.1147;

Scalemic mixture (33% ee): α_D^{20} = +9.3 (c 1.330, MeOH);

Major enantiomer: α_D^{20} = +30.3 (c 1.145, MeOH);

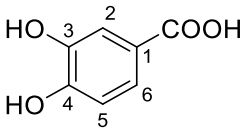
Minor enantiomer (containing impurity): α_D^{20} = –14.5 (c 1.117, MeOH).

6.2.11. Towards kompasinol A

Preparation of methyl protocatechuate from vanillin

Step 1. In a stainless steel container water (14 mL) was added to KOH pellets (133 g). The resulting slurry was stirred using mechanical stirrer with Teflon anchor until completely homogeneous. The vessel was then insulated against loss of heat by covering with several layers of Al foil and heated to 235 °C (internal bimetal probe). With constant stirring, vanillin (24 g, 0.158 mol) was added in portions, leading to melting and instant reaction with release of gas. The temperature was gradually raised to 270 °C over 25 min, and maintained at 270 °C for 10 min. After cooling, the mixture was carefully diluted with water (200 mL) and transferred into 2 L beaker. The base was neutralized with 30% H_2SO_4 to pH ~ 2 and additional water was added to give 1.7 L overall volume. The beaker was covered and stored overnight in at 4 °C during which a spongy precipitate formed. The gelatinous mixture was stirred for 5 min and then filtered. The solids were washed with water (200 mL) and dried to yield 23.8 g of a beige powder. The filtrate was extracted with EA (2×200 mL) to yield another 5.95 g after concentration and drying. Analysis of the combined solids by ^{1}H NMR in DMSO-*d6* showed a single product - protocatechuic acid. Combustion analysis showed 65% purity based on carbon content, the rest likely being inorganic salts.[185,268]

Protocatechuic acid



^{1}H (401 MHz, DMSO-*d6*): δ 9.73 (br. s, 1H, O*H*), 9.35 (br. s, 1H, O*H*), 7.32 (d, *J* = 2.1 Hz, 1H, H-2), 7.28 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6), 6.78 (d, *J* = 8.2 Hz, 1H, H-5);

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*): δ 167.5 (s, *C*OOH), 150.2 (s, C-4), 145.0 (s, C-3), 122.1 (d, C-6), 121.8 (s, C-1), 116.7 (d, C-2), 115.3 (d, C-5);

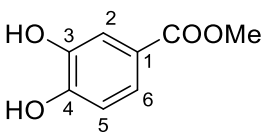
MS (ESI–) *m/z*, (%): 153 (100, $[M - H]^-$), 109 (59, $[M - CO_2 - H]^-$);

HRMS (ESI–) *m/z*: $[M - H]^-$ calcd. for $C_7H_5O_4$ 153.0193; found: 153.0194;

Anal. calcd. for $C_7H_6O_4$ (154.12): C, 54.55; H, 3.92. Found: C, 35.85; H, 3.17 (65% purity).

Step 2. The crude mixture from the previous step was dissolved in MeOH (600 mL), conc. H_2SO_4 (2 mL, 36 mmol) was added and the solution was heated to reflux overnight. The solvent was concentrated in vacuum to ~150 mL, 4% $NaHCO_3$ (350 mL) was added, and the mixture was extracted twice with EA (2×250 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated and dried under vacuum to give 21.4 g of **197** (80% over 2 steps) as a hard colourless solid.

Methyl protocatechuate (**197**)



^{1}H (401 MHz, DMSO-*d6*): δ 9.77 (br. s, 1H, O*H*), 9.36 (br. s, 1H, O*H*), 7.35 (d, *J* = 2.1 Hz, 1H, H-2), 7.30 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6), 6.80 (d, *J* = 8.2 Hz, 1H, H-5), 3.76 (s, 3H, COOC*H*$_3$);

$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d6*): δ 166.6 (s, *C*OOMe), 150.4 (s, C-4), 145.1 (s, C-3), 121.8 (d, C-6), 120.5 (s, C-1), 116.2 (d, C-2), 115.3 (d, C-5), 51.6 (q, COO*C*H_3);

MS (ESI–) *m/z*, (%): 167 (100, $[M - H]^-$), 109 (62, $[M - CO_2 - Me]^-$);

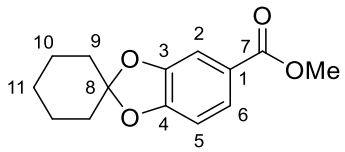
HRMS (ESI–) *m/z*: $[M - H]^-$ calcd. for $C_8H_7O_4$ 167.03498; found: 167.03530;

Anal. calcd. for $C_8H_8O_4$ (168.15): C, 57.14; H, 4.80. Found: C, 56.84; H, 4.59.

Synthesis of protected piceatannol 196

Methyl 2,2-(pentane-1,5-diyl)benzo[d][1,3]dioxole-5-carboxylate (**198**)

Methyl protocatechuate (**197**) (5.0 g, 29.7 mmol), *p*-TsOH (283 mg, 1.49 mmol) and cyclohexanone (4.3 mL, 41.6 mmol) were dissolved in benzene (15 mL) and heated to reflux using a Dean-Stark trap. Azeotropic distillation of water continued for more than 2 h, therefore the heating was continued overnight (16 h). After cooling, the reaction was quenched by saturated Na_2CO_3 solution (25 mL) and partitioned between 10% Na_2CO_3 (300 mL) and a 1:1 mixture of PE/Et_2O (400 mL). The organic layer was dried over Na_2SO_4, concentrated, and dried in vacuum to give 7.59 g of **198** (quant.) as a colourless oil, which was used without further purification.



R_f 0.58 (hexane/EA 11:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2935 (m), 2857 (w), 1714 (m), 1625 (w), 1606 (w), 1494 (m), 1444 (m), 1361 (w), 1279 (m), 1254 (vs), 1235 (m), 1198 (m), 1144 (w), 1113 (w), 1084 (m), 1058 (m), 980 (w), 911 (w), 880 (w), 847 (w), 834 (w), 800 (w), 760 (m);

^{1}H (401 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 8.1, 1.7 Hz, 1H, H-6), 7.38 (d, *J* = 1.7 Hz, 1H, H-2), 6.74 (d, *J* = 8.2 Hz, 1H, H-5), 1.96-1.89 (m, 4H, H-9), 1.82-1.69 (m, 4H, H-10), 1.55-1.45 (m, 2H, H-11);

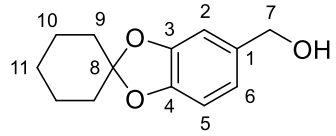
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 166.9 (s, *C*$OOCH_3$), 151.7 (s, C-4), 147.7 (s, C-3), 124.9 (d, C-6), 123.5 (s, C-1), 120.2 (s, C-8), 109.5 (d, C-2/5), 107.9 (d, C-2/5), 52.1 (q, O*C*H_3), 35.3 (t, C-9), 24.6 (t, C-11), 23.2 (t, C-10);

MS (ESI+) *m/z*, (%): 249 (100, $[M + H]^+$), 217 (87, $[M + H - MeOH]^+$), 123 (86);

HRMS (ESI+) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{17}O_4$ 249.1121; found: 249.1121.

[2,2-(Pentane-1,5-diyl)[d][1,3]dioxol-5-yl]methanol (**199**)

A commercial solution of $LiAlH_4$ (2.1 mL, 5 mmol, 2.4 M in THF) was added to a stirred solution of **198** (2.48 g, 10 mmol) in dry THF (20 mL) at r.t. After 10 min at r.t., the reaction was heated to reflux for 1 h. After cooling, a 25% NaOH solution (10 mL) was added and stirring was continued for 10 min. The mixture was partitioned between Et_2O (170 mL) and a 1:1 mixture of water (100 mL) and saturated sodium potassium tartrate solution (100 mL). The organic extract was dried over Na_2SO_4, concentrated and dried in vacuum to give 2.29 g of **199** (quant.) as a colourless oil that was used in the next step without purification. A small portion of this material was purified by flash chromatography (silica, 20 to 33% EA in PE) to obtain an analytically pure sample of **199**.



R_f 0.23 (hexane/EA 5:1), R_f 0.07 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3100 (br.), 2935 (m), 2863 (w), 1494 (s), 1443 (s), 1364 (w), 1339 (w), 1282 (w), 1245 (vs), 1209 (w), 1157 (w), 1115 (w), 1059 (s), 1009 (w), 971 (m), 931 (w), 901 (w), 839 (w), 806 (m), 776 (m), 759 (w), 646 (w);

^{1}H (401 MHz, $CDCl_3$): δ 6.80-6.71 (m, 2H, H-2, H-6), 6.68 (d, *J* = 7.8 Hz, 1H, H-5), 4.53 (s, 2H, H-7), 1.94-1.85 (m, 4H, H-9), 1.82 (s, 1H, OH), 1.78-1.67 (m, 4H, H-10), 1.55-1.44 (m, 2H, H-11);

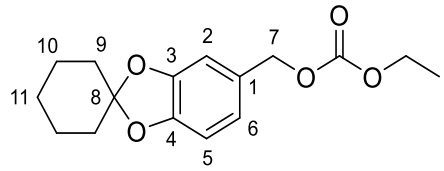
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.9 (s, C-3/4), 147.2 (s, C-3/4), 134.2 (s, C-1), 120.0 (d, C-6), 118.9 (s, C-8), 108.1 (d, C-2/5), 107.9 (d, C-2/5), 65.6 (t, C-7), 35.3 (t, C-9), 24.7 (t, C-11), 23.3 (t, C-10);

MS (ESI+) *m/z*, (%): 243 (8, [M + Na]$^+$), 203 (100, [M + H – H_2O]$^+$); MS (APCI+) *m/z*, (%): 220 (3, [M]$^{\cdot+}$), 203 (100, [M + H – H_2O]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{13}H_{16}NaO_3$ 243.0992; found: 243.0989; HRMS (APCI+) *m/z*: [M]$^{\cdot+}$ calcd. for $C_{13}H_{16}O_3$ 220.1094; found: 220.1090.

[2,2-(Pentane-1,5-diyl)[d][1,3]dioxol-5-yl]methyl ethyl carbonate (**200**)

Benzyl alcohol **199** (2.20 g, 10 mmol), pyridine (2.4 mL, 30 mmol) and dimethylaminopyridine (61 mg, 0.5 mmol) were dissolved in DCM (40 mL) and the reaction mixture was cooled to 0 °C. Ethyl chloroformate (1.2 mL, 12.5 mmol) was added dropwise. After at 20 min at 0 °C, saturated solution of $NaHCO_3$ (50 mL), water (50 mL) and PE (100 mL) were added, the layers were separated and the aqueous layer was extracted with PE (100 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and dried under high vacuum to yield 2.87 g of **200** (98%) as a colourless oil, which was used in the next step without further purification.



R_f 0.88 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2934 (w), 2857 (w), 1740 (s), 1497 (m), 1447 (w), 1365 (w), 1236 (vs), 1161 (w), 1119 (w), 1060 (m), 1010 (w), 991 (w), 972 (w), 941 (w), 902 (w), 849 (w), 808 (w), 790 (m), 765 (w);

^{1}H (401 MHz, C_6D_6): δ 6.87 (d, *J* = 1.7 Hz, 1H, H-2), 6.68 (ddt, *J* = 7.9, 1.7, 0.5 Hz, 1H, H-6), 6.59 (d, *J* = 7.9 Hz, 1H, H-5), 4.91 (s, 2H, H-7), 3.88 (q, *J* = 7.1 Hz, 2H, O*C*H_2CH$_3$), 1.72-1.69 (m, 4H, H-9), 1.53-1.44 (m, 4H, H-10), 1.15-1.09 (m, 2H, H-11), 0.89 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3);

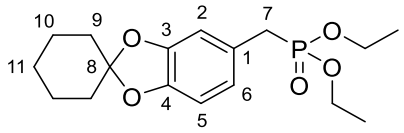
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 155.7 (s, *C*OOEt), 148.3 (s, C-3, C-4), 129.4 (s, C-1), 122.3 (d, C-6), 119.1 (s, C-8), 109.5 (d, C-2), 108.3 (d, C-5), 69.5 (t, C-7), 63.7 (t, O*C*H$_2$CH$_3$), 35.4 (t, C-9), 24.7 (t, C-11), 23.4 (t, C-10), 14.2 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 315 (26, [M + Na]$^+$), 203 (100, [M – CO_2 – EtO]$^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{16}H_{20}NaO_5$ 315.1203; found: 315.1204.

Diethyl {[2,2-(pentane-1,5-diyl)[d][1,3]dioxol-5-yl]methyl}phosphonate (**201**)

Following a modified published method,[176] allylpalladium(II) chloride dimer (146 mg, 0.4 mmol), DPEPhos (539 mg, 1.0 mmol) and diethyl phosphite (3.2 mL, 25 mmol) were added to a solution of carbonate **200** (2.92 g, 10 mmol) in dry DMF (15 mL). The reaction vessel was sealed and heated to 90 °C for 60 h. After cooling, the volatiles were stripped off under vacuum and the residue was purified by flash chromatography (PE/EA 2:1 to 1:1) to yield 2.394 g of **201** as a colourless oil, 70% yield over 4 steps based on methyl protocatechuate.



R_f 0.23 (hexane/EA 1:1), R_f 0.31 (Et_2O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3650-3350 (br.), 2981 (w), 2938 (m), 2866 (w), 1495 (s), 1445 (m), 1392 (w), 1359 (w), 1281 (w), 1244 (s), 1206 (w), 1159 (w), 1126 (w), 1098 (w), 1052 (s), 1022 (vs), 960 (vs), 939 (s), 903 (m), 849 (w), 835 (m), 816 (w), 750 (w), 728 (w), 629 (w);

^{1}H (401 MHz, $CDCl_3$): δ 6.73-6.62 (m, 3H, H-2, H-5, H-6), 4.08-3.96 (m, 4H, POCH_2CH$_3$), 3.02 (d, $^2J_{HP}$ = 21.2 Hz, 2H), 1.90-1.85 (m, 4H, H-9), 1.75-1.67 (m, 4H, H-10), 1.48 (m, 2H, H-11), 1.25 (t, *J* = 7.1 Hz, 6H, POCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.8 (s, J_{CP} = 3.1 Hz, C-3/4), 146.6 (s, J_{CP} = 3.7 Hz, C-3/4), 124.1 (s, $^2J_{CP}$ = 9.5 Hz, C-1), 122.2 (d, $^3J_{CP}$ = 7.7 Hz, C-2/6), 118.9 (s, C-8), 110.1 (d, $^3J_{CP}$ = 5.9 Hz, C-2/6), 108.2 (d, $^4J_{CP}$ = 2.9 Hz, C-5), 62.22 (t, $^3J_{CP}$ = 6.6 Hz, PO*C*H$_2$CH$_3$), 35.3 (t, C-9), 33.5 (t, $^1J_{CP}$ = 139.0 Hz, C-7), 24.7 (t, C-11), 23.3 (t, C-10), 16.6 (q, $^4J_{CP}$ = 5.9 Hz, POCH$_2$*C*H$_3$);

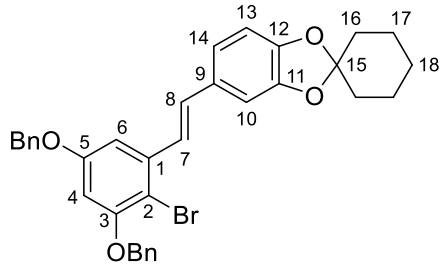
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 27.36 (85% H_3PO_4 standard; δ 0.00 ppm);

MS (ESI+) *m/z*, (%): 379 (5, $[M + K]^+$), 363 (100, $[M + Na]^+$), 341 (76, $[M + H]^+$), 203 (27, $[M – PO(OEt)_2]^+$); MS (APCI+) *m/z*, (%): 341 (100, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{17}H_{25}NaO_5P$ 363.1332; found: 363.1330; HRMS (APCI+) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{26}O_5P$ 341.1512; found: 341.1509.

(E)-5-[3,5-bis(benzyloxy)-2-bromostyryl]-2,2-(pentane-1,5-diyl)[d][1,3]dioxole (**196**)

A 100 mL round-bottomed flask containing a large magnetic stirring bar was charged with phosphonate **201** (1.65 g, 4.84 mmol), (2-bromo-3,5-bis(benzyloxy)benzaldehyde (2.50 g, 6.30 mmol) and dry DMF (10 mL). A solution of *t*-AmONa (2.9 ml, 9.7 mmol, 40% in toluene) was added while maintaining vigorous stirring. The mixture spontaneously warmed up to ~35 °C and turned homogeneous during the addition. After stirring for 1 h at r.t., the solvent was evaporated under vacuum and the residue was purified by flash chromatography (PE/EA 15:1 to 10:1) to yield 2.62 g (92%) of **196** as colourless solid, >95% purity by ^{1}H NMR. Crystallization from cyclohexane/Et_2O afforded 1.596 g of large colourless crystals, mp 137-139 °C, that were more suitable for storage.



R_f 0.47 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3063 (w), 3032 (w), 2937 (w), 2863 (w), 1575 (m), 1494 (s), 1447 (m), 1426 (m), 1361 (m), 1334 (m), 1281 (w), 1252 (s), 1211 (w), 1162 (s), 1115 (w), 1084 (m), 1058 (s), 1020 (m), 972 (m), 958 (m), 902 (m), 843 (w), 818 (w), 797 (w), 734 (s), 695 (s);

^{1}H (401 MHz, $CDCl_3$): δ 7.51-7.28 (m, 11H, Ph, H-7), 7.06 (d, *J* = 1.7 Hz, 1H, H-10), 6.93-6.85 (m, 3H, H-6, H-14, H-8), 6.72 (d, *J* = 8.0 Hz, 1H, H-13), 6.53 (d, *J* = 2.7 Hz, 1H, H-4), 5.12 (s, 2H, OC*H*$_2$Ph), 5.07 (s, 2H, OC*H*$_2$Ph), 1.96-1.90 (m, 4H, H-16), 1.78-1.69 (m, 4H, H-17), 1.53-1.48 (m, 2H, H-18);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.7 (s, C-3/5), 156.1 (s, C-3/5), 148.2 (s, C-11/12), 148.0 (s, C-11/12), 139.1 (s, C-1), 136.7 (s, *ipso*-Ph), 136.6 (s, *ipso*-Ph), 131.8 (d, C-8), 130.9 (s, C-9), 128.8 (d, 2×C, Ph^{meta}), 128.7 (d, 2×C, Ph^{meta}), 128.3 (d, Ph^{para}), 128.0 (d, Ph^{para}), 127.8 (d, 2×C, Ph^{ortho}), 127.1 (d, 2×C, Ph^{ortho}), 125.7 (d, C-7), 121.7 (d, C-14), 119.3 (s, C-15), 108.3 (d, C-13), 106.1 (s, C-2), 105.7 (d, C-10), 104.3 (d, C-6), 101.2 (d, C-4), 71.1 (t, O*C*H$_2$Ph), 70.5 (t, O*C*H$_2$Ph), 35.4 (t, C-16), 24.7 (t, C-18), 23.3 (t, C-17);

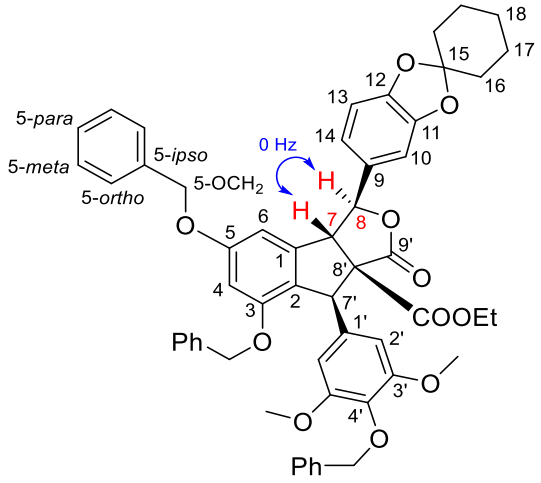
MS (ESI+) *m/z*, (%): 1191/1189/1187 (93, [2M + Na]$^+$), 623/621 (27, [M + K]$^+$), 607/605 (100, [M + Na]$^+$), 585/583 (27, [M + H]$^+$); MS (APCI+) *m/z*, (%): 585/583 (100, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{34}H_{31}{}^{79}BrNaO_4$ 605.1298; found: 605.1293; HRMS (APCI+) *m/z*: [M + H]$^+$ calcd. for $C_{34}H_{32}{}^{79}BrO_4$ 583.1479; found: 583.1473.

One-pot conjugate addition/oxidative bicyclisation of 196/195 at –120 °C

The procedure developed for **177** was followed. Lithiation of **196** (190 mg, 0.325 mmol) in toluene (2.5 mL) and EtPh (2.5 mL) by *n*-BuLi (203 µL) for 20 min at –78 °C. Conjugate addition: a solution of **195** (106 mg, 0.25 mmol) in toluene (1 mL) added at –120 °C, then isohexane (1.5 mL). LiBr (174 mg, 2.0 mmol) added at –50 °C. Oxidation at –25 °C by $FeCp_2PF_6$ (0.50 g, 1.5 mmol). Immediately after aqueous workup (no treatment with TFA) purified by flash chromatography to yield 80 mg of **202** (36%) as a colourless amorphous solid, 28% ee by chiral HPLC (hexane/*i*-PrOH 85/15, 1.0 ml/min).

Protected 8'-carbethoxy-9'-oxokompasinol A (**202**)



R_f 0.50 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3064 (w), 3032 (w), 2936 (w), 2864 (w), 1781 (m), 1732 (m), 1593 (m), 1497 (m), 1452 (m), 1423 (w), 1366 (w), 1331 (w), 1235 (s), 1153 (vs), 1122 (vs), 1059 (m), 1028 (m), 972 (w), 903 (w), 839 (w), 812 (w), 733 (s), 696 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.47-7.2 (m, 13H, Ph), 7.02-6.97 (m, 2H, Ph), 6.76-6.69 (m, 3H, H-10, H-13, H-14), 6.66 (d, *J* = 1.5 Hz, 1H, H-4), 6.49 (d, *J* = 1.6, Hz, 1H, H-6), 6.35-6.05 (br. s, 2H, H-2'), 5.59 (s, 1H, H-8), 5.09 (s, 2H, C5-OC*H*$_2$Ph), 5.06 (s, 1H, H-7'), 4.93 (s, 2H, C4'-OC*H*$_2$Ph), 4.91 (d, *J* = 11.7 Hz, 1H, C3-OC*H*^{a}H^{b}Ph), 4.82 (d, *J* = 11.7 Hz, 1H, C3-OCH^a*H*^{b}Ph), 4.67 (s, Hz, 1H, H-7), 3.69 (s, 6H, C3'-OC*H*$_3$), 3.62-3.55 (m, 2H, OC*H*$_2$CH$_3$), 1.92-1.85 (m, 4H, H-16), 1.77-1.68 (m, 4H, H-17), 1.53-1.47 (m, 2H, H-18), 0.78 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.8 (s, C-9'), 166.0 (s, *C*OOEt), 161.6 (s, C-5), 155.8 (s, C-3), 153.1 (s, 2×C, C-3'), 148.2 (s, C-11/12), 147.7 (s, C-11/12), 143.4 (s, C-1), 143.2 (s, C-4'), 138.0 (s, C4'-OCH$_2$Ph^{ipso}), 136.7 (s, C5-OCH$_2$Ph^{ipso}), 136.5 (s, C3-OCH$_2$Ph^{ipso}), 135.3 (s, C-1'), 132.1 (s, C-9), 128.8 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.5 (d, 2×C, Ph^{meta}), 128.4 (d, Ph^{para}), 128.2 (d, 2×C, Ph^{ortho}), 128.0 (d, Ph^{para}), 127.9 (d, Ph^{para}), 127.8 (d, 2×C, Ph^{ortho}), 127.2 (d, 2×C, Ph^{ortho}), 124.3 (s, C-2), 119.5 (s, C-15), 117.6 (d, C-14), 108.2 (d, C-13), 106.4 (br. d, 2xC, C-2', detected by HSQC), 105.4 (d, C-10), 100.9 (d, C-4/6), 100.8 (d, C-4/6), 85.0 (d, C-8), 75.1 (t, C4'-O*C*H$_2$Ph), 70.7 (t, C5-O*C*H$_2$Ph), 69.7 (t, C3-O*C*H$_2$Ph), 66.4 (s, H-8'), 62.0 (t, O*C*H$_2$CH$_3$), 57.1 (d, H-7'), 56.7 (d, H-7), 56.2 (q, 2xC, C3'-O*C*H$_3$), 35.3 (t, 2×C, C-16), 24.6 (t, C-18), 23.3 (t, 2×C, C-17), 13.7 (q, OCH$_2$*C*H$_3$);

^{1}H NMR (401 MHz, C_6D_6): δ 7.55-7.50 (m, 2H, Ph), 7.40-7.35 (m, 2H, Ph), 7.24-7.00 (m, 9H, Ph), 6.95 (d, *J* = 1.8 Hz, 1H, H-10), 6.96-6.93 (m, 2H, Ph), 6.83 (dd, *J* = 8.0, 1.9 Hz, 1H, H-14), 6.66 (d, *J* = 8.0 Hz, 1H, H-13), 6.63 (d, *J* = 1.5 Hz, 1H, H-4), 6.54-6.43 (br. s, 2H, H-2'), 6.43 (d, *J* = 1.6 Hz, 1H, H-6), 5.66 (s, 1H, H-8), 5.63 (s, 1H, H-7'), 5.08 (s, 2H, C4'-OC*H*$_2$Ph), 5.00 (s, 1H, H-7), 4.79 (s, 2H, C5-OC*H*$_2$Ph), 4.53 (d, *J* = 11.9 Hz, 1H, C3-OC*H*^{a}H^{b}Ph), 4.46 (d, *J* = 11.9 Hz, 1H, C3-OCH^a*H*^{b}Ph), 3.55-3.43 (m, 2H, OC*H*$_2$CH$_3$), 3.29 (s, 6H, C3'-OC*H*$_3$), 1.78-1.70 (m, 4H, H-16), 1.56-1.45 (m, 4H, H-17), 1.19-1.09 (m, 2H, H-18), 0.62 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 174.4 (s, C-9'), 166.4 (s, *C*OOEt), 162.1 (s, C-5), 156.3 (s, C-3), 153.9 (s, 2×C, C-3'), 148.7 (s, C-11/12), 148.1 (s, C-11/12), 144.2 (s, C-1), 139.1 (s, C4'-OCH$_2$Ph^{ipso}), 137.5 (s, C-4'), 137.3 (s, C3/5-OCH$_2$Ph^{ipso}), 136.9 (s, C3/5-OCH$_2$Ph^{ipso}), 135.8 (s, C-1'), 133.1 (s, C-9), 128.9 (d, 2×C, Ph^{meta}), 128.6 (d, 2×C, Ph^{meta}), 128.4 (d, 2×C, Ph^{meta}), 128.3-127.8 (s, 5×C, Ph), 127.7 (d, 2×C, Ph^{ortho}), 127.4 (d, 2×C, Ph^{ortho}), 124.9 (s, C-2), 119.4 (s, C-15), 118.3 (d, C-14), 108.5 (d, C-13), 107.3 (br. d, 2xC, C-2'), 106.0 (d, C-10), 101.3 (d, C-4/6), 101.2 (d, C-4/6), 84.8 (d, C-8), 74.9 (t, C4'-O*C*H$_2$Ph), 70.7 (t, C5-O*C*H$_2$Ph), 69.6 (t, C3-O*C*H$_2$Ph), 66.9 (s, H-8'), 62.9 (t, O*C*H$_2$CH$_3$),

57.9 (d, H-7'), 56.3 (d, H-7), 55.9 (q, 2xC, C3'-O*C*H$_3$), 35.46 (t, C-16), 35.43 (t, C-16), 24.7 (t, C-18), 23.4 (t, 2×C, C-17), 13.7 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 911 (100, [M + Na]$^+$), 906 (6, [M + NH$_4$]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{55}H_{52}NaO_{11}$ 911.3402; found: 911.3394.

6.2.12. Comparison of ^{1}H and ^{13}C NMR spectra of natural and synthetic FIS

Table 31a. Comparison of NMR data of semisynthetic and synthetic kompasinol A (**III**) and gnetifolin F (**I**) derivatives, $CDCl_3$ (only main skeleton atoms).

	Synthetic *Pentamethyl ether of* **III**		*Pentamethyl ether of* **III** [113]		*Pentaacetate of* **III** [113]		*Tetraacetate of* **I** [98]	
Atom no.	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm
1	-	147.0	-	146.8	-	146.0	-	146.2
2	-	124.3	-	124.1	-	133.5	-	133.7
3	-	157.7	-	157.5	-	147.5	-	142.0
4	6.36	97.9	6.36	97.7	6.78	115.8	6.77	115.6
5	-	161.9	-	161.7	-	151.1	-	147.5
6	6.41	100.4	6.42	100.3	6.9	115.8	6.86	115.6
7	**3.89**	**59.1**	**3.89**	**58.9**	**3.84**	**59.3**	**3.86**	**59.3**
8	**4.79**	**87.6**	**4.80**	**87.4**	**4.84**	**85.4**	**4.81**	**86.2**
9	-	135.2	-	134.9	-	140.6	-	139.3
10	6.98	109.4	6.98	109.2	7.23	121.0	7.02	110.0
11	-	149.4	-	149.2	-	142.2	-	151.3
12	-	148.7	-	148.5	-	141.5	-	140.5
13	6.89	111.2	6.89	111.0	7.22	123.6	7.05	118.1
14	6.98	118.6	6.99	118.5	7.3	123.8	6.97	122.7
1'	-	141.3	-	141.1	-	141.4	-	138.7
2'	6.24	104.3	6.24	104.0	6.31	104	6.62	111.5
3'	-	153.2	-	153.0	-	152.3	-	151.3
4'	-	136.2	-	136.4	-	127.4	-	151.1
5'	-	153.2	-	153.0	-	152.3	6.94	122.7
6'	6.24	104.3	6.24	104.0	6.31	104.0	6.69	119.8
7'	**4.17**	**51.3**	**4.17**	**51.1**	**4.27**	**55.0**	**4.30**	**54.2**
8'	**3.14**	**54.9**	**3.14**	**54.7**	**3.33**	**57.5**	**3.33**	**57.2**
9'α	**3.60**	**74.2**	**3.60**	**74.0**	**3.97**	**73.4**	**3.93**	**73.5**
9'β	**4.53**	-	**4.54**	-	**4.38**	-	**4.41**	-
$J_{(x,y)}$	J (Hz)		J (Hz)		J (Hz)		J (Hz)	
7-8	4.6	-	4.6	-	6.3	-	6.5	-
7-8'	8.5	-	8.5	-	8.6	-	n. a.	-
8'-7'	1.7	-	1.7	-	4.9	-	5.5	-

Table 31b. Comparison of NMR data of isolated and synthetic gnetifolin F (**I**), acetone-*d6* (only main skeleton atoms).

	Synthetic I		**I** from *Gnetum klossi*[99]		**I** from *G. cleistostachyum*[97]	
Atom no.	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm
1	-	148.4	-	148.3	-	147.9
2	-	122.8	-	122.8	-	122.7
3	-	155.9	-	155.8	-	159.7
4	6.27	102.7	6.27	102.7	6.26	102.5
5	-	159.9	-	159.8	-	155.8
6	6.35	103.3	6.35	103.3	6.34	103.1
7	**3.80**	59.7	**3.81**	**59.7**	**3.75**	**59.6**
8	**4.72**	88.4	**4.71**	**88.3**	**4.70**	**88.3**
9	-	135.6	-	135.5	-	135.5
10	7.04	110.6	7.03	110.5	7.02	110.4
11	-	148.4	-	148.3	-	148.3
12	-	146.8	-	146.7	-	146.7
13	6.82	115.5	6.82	115.5	6.82	115.3
14	6.90	119.7	6.89	119.6	6.89	119.6
1'	-	138.1	-	138.0	-	138.0
2'	6.73	112.0	6.73	111.9	6.72	111.8
3'	-	148.1	-	148.0	-	148.3
4'	-	145.6	-	145.5	-	145.5
5'	6.66	115.6	6.66	115.4	6.66	115.4
6'	6.50	120.3	6.50	120.3	6.49	120.2
7'	**4.18**	51.1	**4.18**	**51.0**	**4.17**	**50.9**
8'	**3.04**	55.9	**3.03**	**55.9**	**3.04**	**55.8**
9'α	**3.50**	74.5	**3.51**	**74.5**	**3.49**	**74.4**
9'β	**4.46**	-	**4.46**	-	**4.45**	**-**
$J_{(x,y)}$	*J* (Hz)		*J* (Hz)		*J* (Hz)	
7-8	4.3	-	4.0	-	4.5	-
7-8'	8.4	-	8.8	-	8.4	-
8'-7'	1.6	-	0	-	0	-

Table 31c. Comparison of NMR data of isolated and synthetic 11-deoxykompasinol A (**IV**), DMSO-*d6* (only main skeleton atoms).

	Synthetic IV		**IV** from *Orychophragmus violaceus*[110]	
Atom no.	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm
1	-	146.9	-	146.9
2	-	121.1	-	121.1
3	-	154.9	-	154.9
4	6.13	101.6	6.13	101.6
5	-	158.6	-	158.6
6	6.13	101.7	6.13	101.7
7	**3.68**	58.0	**3.69**	**58.0**
8	**4.61**	86.8	**4.61**	**86.8**
9	-	132.9	-	133.0
10, 14	7.19	127.5	7.20	127.5
11, 13	6.75	115.1	6.75	115.1
12	-	156.7	-	156.7
1'	-	136.0	-	136.0
2', 6’	6.25	104.8	6.25	104.7
3', 5’	-	147.7	-	147.7
4'	-	133.7	-	133.7
7'	**4.01**	50.1	**4.02**	**50.2**
8'	**2.91**	54.2	**2.91**	**54.3**
9'	**3.37, 4.37**	73.3	**3.37, 4.37**	**73.3**
$J_{(x,y)}$	J (Hz)		J (Hz)	
7-8	4.1	-	4.1	-
7-8'	8.3	-	8.4	-
8'-7'	1.2	-	1.4	-

6.3. Part C

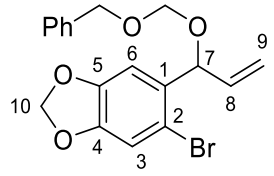
6.3.1. First generation radical 6-exo-tet approach to **11**

Initial study using BOM protecting group

5-{1-[(Benzyloxy)methoxy]allyl}-6-bromobenzo[d][1,3]dioxole (**207**)

A solution of vinylmagnesium bromide (3.3 mL, 2.3 mmol, 0.7 M in THF) was added dropwise to the solution of 6-bromoiperonal (504 mg, 2.2 mmol) in dry THF (3 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C. DIPEA (0.96 mL, 5.5 mmol) was added, followed by technical grade BOMCl (1.3 mL, 5.5 mmol, 60% purity). The mixture was stirred for 2 h at r.t., followed by filtration through a 4 cm pad of silica (2.5 cm diameter). The filter was washed with Et_2O (200 mL) and the combined

filtrate was concentrated and purified by repeated flash chromatography (PE/EA 15:1 to 10:1) to yield 468 mg (56%) of **207** as a colourless oil.



R_f 0.63 (hexane/EA 3:1);

^{1}H NMR (401 MHz, C_6D_6): δ 7.31-7.23 (m, 2H, Ph), 7.19-7.04 (m, 3H, Ph), 7.12 (s, 1H, H-3/6), 6.81 (s, 1H, H-3/6), 5.89-5.74 (m, 2H, H-7, H-8), 5.41-5.32 (m, 1H, H-9a), 5.16 (d, *J* = 1.3 Hz, 1H, C4-OC*H*$_a$H$_b$O), 5.15 (d, *J* = 1.3 Hz, 1H, C4-OCH$_a$*H*$_b$O), 5.08-5.02 (m, 1H, H-9b), 4.69 (d, *J* = 6.8 Hz, 1H, C7-OC*H*$_a$H$_b$OBn), 4.62 (d, *J* = 6.8 Hz, 1H, C7-OCH$_a$*H*$_b$OBn), 4.50 (s, 2H, COC*H*$_2$Ph);

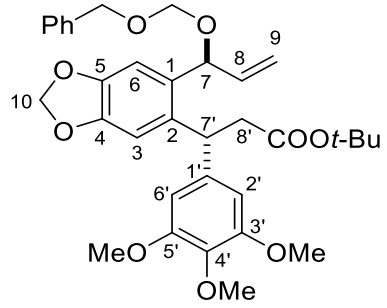
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 148.30 (s, C-4/5), 148.26 (s, C-4/5), 138.6 (s, Ph^{ipso}), 137.4 (d, C-8), 134.0 (s, C-1), 128.6 (d, 2×C, Ph), 128.1 (d, 2×C, Ph), 127.7 (d, Ph^{para}), 116.2 (t, C-9), 113.7 (s, C-2), 112.6 (d, C-3/6), 108.6 (d, C-3/6), 101.7 (t, C4-O*C*H$_2$O), 92.1 (t, O*C*H$_2$OBn), 77.1 (d, C-7), 69.7 (t, O*C*H$_2$Ph);

MS (EI+) *m/z*, (%): 378/376 (48/47, [M]$^{\cdot+}$), 257/255 (57/52, [M + H$_2$O – BnOH – CH$_2$O]$^{\cdot+}$), 160 (100, [M – BnOCH$_2$O – Br]$^{\cdot+}$), 148 (31), 131 (35);

HRMS (EI+) *m/z*: [M]$^{\cdot+}$ calcd. for $C_{18}H_{17}{}^{79}BrO_4$ 376.0310; found: 376.0309.

tert-Butyl (R)-3-(6-{(S)-1-[(benzyloxy)methoxy]allyl}benzo[d][1,3]dioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)propanoate* (**208**)

A solution of **207** (45 mg, 0.12 mmol) and TMEDA (18 µl, 0.12 mmol) in dry toluene (2 mL) was cooled to –78 °C. A solution of *n*-BuLi (75 µl, 0.12 mmol, 1.6 M in hexanes) was added dropwise. The clear solution turned light yellow. After stirring for 40 min at –78 °C, a solution of **146** (29 mg, 0.1 mmol) in toluene (0.5 mL) was added dropwise, followed by stirring at –78 ° for 10 min. The temperature was gradually increased to –55 °C over 40 min. The reaction was quenched by addition of 5 drops of wet THF, followed by water (5 mL). After warming, the mixture was partitioned between saturated NH_4Cl (20 mL) and DCM (80 ml). After separation of phases, the aqueous layer was washed twice with fresh DCM (2×80 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by flash chromatography (PE/EA 22:1 to 5:1) to yield 18 mg of **208** (30%) as a colourless oil, dr 4.5:1.



R_f 0.19 (hexane/EA 3:1);

^{1}H NMR (401 MHz, C_6D_6, A major diastereomer, B minor diast.): δ 7.40-7.02 (m, 10H, Ph^{AB}), 7.26 (s, 1H, H-3/6^B), 7.21 (s, 1H, H-3/6^A), 6.94 (s, 1H, H-3/6^A), 6.92 (s, 1H, H-3/6^B), 6.65 (s, 2H, H-2'^{B}),

6.51 (s, 2H, H-2'^{A}), 6.10 (ddd, *J* = 17.1, 10.3, 5.8 Hz, 1H, H-8^{B}), 5.95 (dt, *J* = 5.9, 1.4 Hz, 1H, H-7^{B}), 5.88-5.78 (m, 2H, H-7^{A}, H-8^{A}), 5.53 (dt, *J* = 17.2, 1.5 Hz, 1H, H-9a^{B}), 5.31 (d, *J* = 1.4 Hz, 1H, C4-OC*H*$_a$H$_b$O^{A}), 5.30 (d, *J* = 1.3 Hz, 1H, C4-OC*H*$_a$H$_b$O^{B}), 5.27 (d, *J* = 1.4 Hz, 2H, C4-OCH$_a$*H*$_b$O^{AB}), 5.21-5.09 (m, H, H-9a^{A}, H-9b^{B}, H-7'^{AB}), 4.97-4.91 (m, H, H-9b^{A}), 4.82 (d, *J* = 6.8 Hz, 1H, C7-OC*H*$_a$H$_b$OBn^{A}), 4.76 (d, *J* = 6.8 Hz, 1H, C7-OCH$_a$*H*$_b$OBn^{A}), 4.66 (d, *J* = 12.1 Hz, 1H, OC*H*$_a$H$_b$Ph^{A}), 4.61 (d, *J* = 11.8 Hz, 1H, OCH$_a$*H*$_b$Ph^{A}), 4.60 (d, *J* = 6.9 Hz, 1H, C7-OC*H*$_a$H$_b$OBn^{B}), 4.56 (d, *J* = 6.9 Hz, 1H, C7-OCH$_a$*H*$_b$OBn^{B}), 4.51 (d, *J* = 12.0 Hz, 1H, OC*H*$_a$H$_b$Ph^{B}), 4.33 (d, *J* = 11.9 Hz, 1H, OCH$_a$*H*$_b$Ph^{B}), 3.80 (s, 3H, C4'-OC*H*$_3$^{A}), 3.79 (s, 3H, C4'-OC*H*$_3$^{B}), 3.39 (s, 6H, C3'-OC*H*$_3$^{B}, C5'-OC*H*$_3$^{B}), 3.35 (s, 6H, C3'-OC*H*$_3$^{A}, C5'-OC*H*$_3$^{A}), 3.00-2.75 (m, 4H, H-8'^{AB}), 1.28 (s, 9H, OC(C*H*$_3$)$_3$^{A}), 1.27 (s, 9H, OC(C*H*$_3$)$_3$^{B});

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 170.75 (s, *C*OO*t*-Bu^{A}), 170.73 (s, *C*OO*t*-Bu^{B}), 154.3 (s, 2×C, C-3'^{B}, C-5'^{B}), 154.2 (s, 2×C, C-3'^{A}, C-5'^{A}), 147.93 (s, C-4/5^{A}), 147.92 (s, C-4/5^{B}), 147.2 (s, C-4/5^{B}), 147.1 (s, C-4/5^{A}), 139.77 (s, C-1'^{A}), 139.20 (d, C-8^{A}), 139.16 (s, C-1'^{B}), 138.9 (d, C-8^{B}), 138.8 (s, 2×C, Ph$^{ipso\text{-}AB}$), 138.4 (s, C-4'^{B}), 138.2 (s, C-4'^{A}), 136.1 (s, C-2^{B}), 136.0 (s, C-2^{A}), 132.8 (s, C-1^{A}), 132.4 (s, C-1^{B}), 128.6-128.7 (d, 10×C, Ph^{AB}, overlaps with C_6D_6), 115.7 (t, 2×C, C-9^{AB}), 108.8 (d, C-3/6^{A}), 108.1 (d, C-3/6^{B}), 107.8 (d, C-3/6^{B}), 107.6 (d, C-3/6^{A}), 106.1 (d, 2×C, C-2'^{A}, C-6'^{A}), 106.0 (d, 2×C, C-2'^{B}, C-6'^{B}), 101.2 (t, C4-O*C*H$_2$OBn^{A}), 101.1 (t, C4-O*C*H$_2$OBn^{B}), 91.8 (t, C7-O*C*H$_2$OBn^{A}), 91.6 (t, C7-O*C*H$_2$OBn^{B}), 80.2 (s, 2×C, O*C*(CH$_3$)$_3$^{AB}), 74.0 (d, C-8^{B}), 73.9 (d, C-8^{A}), 69.7 (t, 2×C, O*C*H$_2$Ph^{AB}), 60.54 (q, C4'-O*C*H$_3$^{A}), 60.51 (q, C4'-O*C*H$_3$^{B}), 55.91 (q, 2×C, C3'-O*C*H$_3$^{B}, C5'-O*C*H$_3$^{B}), 55.88 (q, 2×C, C3'-O*C*H$_3$^{A}, C5'-O*C*H$_3$^{A}), 42.9 (t, C-8'^{A}), 42.8 (d, C-7'^{A}), 42.7 (t, C-8'^{B}), 42.5 (d, C-7'^{B}), 28.0 (q, 2×C, O*C*(CH$_3$)^{AB});

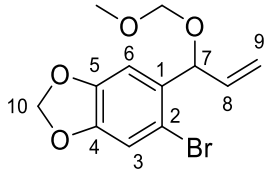
MS (ESI+) *m/z*, (%): 1207 (21, [2M + Na]$^+$), 615 (100, [M + Na]$^+$), 399 (19, [M – BnOCH$_2$O – isobutene]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{34}H_{40}O_9Na$ 615.25645; found: 615.25560.

Radical 6-exo-trig approach based on MOM-protected 210

Vinylmagnesium bromide (21.4 mL, 21.4 mmol, 1 M in THF) was added dropwise to the solution of 6-bromoiperonal (4.58 g, 20 mmol) in dry THF (20 mL) at 0 °C. The reaction was warmed to r.t. and stirred for 1 h. DIPEA (7.7 mL, 44 mmol) was added, followed by TBAI (369 mg, 1 mmol) and MOMCl (3.0 mL, 40 mmol). The mixture was stirred at r.t. for 2 h. Saturated $NaHCO_3$ solution (70 mL), water (70 mL) and PE (80 mL) were added. The layers were separated, and the aqueous layer was extracted with PE (3×70 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (PE/EA 22:1 to 5:1) to yield 5.254 g of **210** (87%) as a colourless oil.

5-Bromo-6-[1-(methoxymethoxy)allyl]benzo[d][1,3]dioxole (**210**)



R_f 0.67 (hexane/EA 5:1), R_f 0.47 (PE/Et_2O 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2985 (w), 2948 (w), 2889 (w), 2823 (w), 1502 (w), 1472 (s), 1407 (w), 1389 (w), 1369 (w), 1232 (s), 1149 (w), 1096 (w), 1023 (vs), 979 (w), 920 (s), 867 (m), 841 (m), 800 (w), 722 (w), 695 (w), 669 (w), 641 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.98 (s, 1H, H-3/6), 6.97 (s, 1H, H-3/6), 5.99-5.95 (m, 2H, H-10), 5.85 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, H-8), 5.46 (dt, *J* = 6.0, 1.4 Hz, 1H, H-7), 5.33 (dt, *J* = 17.2, 1.4 Hz, 1H, H-9a), 5.20 (dt, *J* = 10.4, 1.4 Hz, 1H, H-9b), 4.69 (d, *J* = 6.6 Hz, 1H, OC*H*$_a$H$_b$OMe), 4.60 (d, *J* = 6.7 Hz, 1H, OCH$_a$*H*$_b$OMe), 3.38 (s, 1H, OC*H*$_3$);

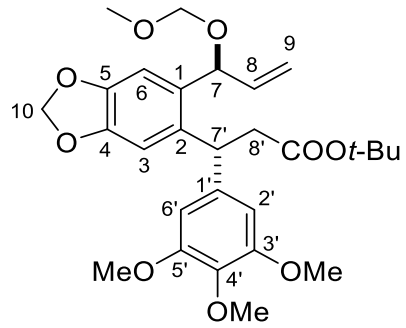
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.95 (s, C-4/5), 147.94 (s, C-4/5), 136.9 (d, C-8), 133.4 (s, C-1), 116.6 (t, C-9), 113.5 (s, C-2), 112.5 (d, C-3/6), 108.3 (d, C-3/6), 101.9 (t, C-10), 94.1 (t, O*C*H$_2$OMe), 76.7 (d, C-7), 55.8 (q, O*C*H$_3$);

MS (ESI+) *m/z*, (%): 325/323 (7/7, [M + Na]$^+$), 241/239 (11/12, [M + H – MeOH – CH$_2$O]$^+$), 215/213 (18/18, [M + H – MeOH – CH$_2$O – C$_2$H$_2$]$^+$), 188 (20), 160 (100, [M + H – MeOH – CH$_2$O – Br]$^+$), 130 (26);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{12}H_{13}{}^{79}BrO_4Na$ 322.9889; found: 322.9892.

tert-Butyl (R)-3-(6-((S*)-1-(methoxymethoxy)allyl)benzo[d][1,3]dioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)propanoate* (**211**)

A solution of *n*-BuLi (1.2 mL, 2 mmol, 1.6 M in hexanes) was added at –78 °C to a solution of **210** (600 mg, 2.0 mmol) and TMEDA (2.1 mL, 14.2 mmol) in dry toluene (7 mL). The reaction was stirred for at –78 °C 15 min, during which a bright yellow colour developed. A solution of **146** (418 mg, 1.42 mmol) in toluene (4 mL) was added dropwise over 50 s. The mixture was stirred at –78 °C for 60 min, followed by quenching by wet THF. The mixture was filtered through a 4 cm silica gel pad (3 cm diameter), and the sorbent was washed with Et_2O (100 mL). The combined solutions were concentrated to yield 1.01 g of crude product, dr 5.5:1. Purification by flash chromatography (PE/EA, 11:1 to 3:1) afforded 440 mg of **211** (60%) as colourless film, dr 8.3:1.



R_f 0.22 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2976 (w), 2935 (w), 2887 (w), 2838 (w), 2773 (w), 1728 (m), 1589 (w), 1504 (w), 1484 (m), 1457 (w), 1419 (w), 1392 (w), 1367 (w), 1331 (w), 1234 (m), 1146 (m), 1125 (vs), 1029 (vs), 933 (m), 871 (w), 846 (w), 805 (w), 764 (w), 730 (s), 695 (m), 661 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.91 (s, 1H, H-3/6), 6.68 (s, 1H, H-3/6), 6.39 (s, 2H, H-2', H-6'), 5.92 (d, *J* = 1.4 Hz, 1H, H-10a), 5.91 (d, *J* = 1.4 Hz, 1H, H-10b), 5.79 (ddd, *J* = 16.8, 10.7, 6.0 Hz, 1H, H-8), 5.47 (dt, *J* = 6.1, 1.4 Hz, 1H, H-7), 5.10-5.02 (m, 2H, H-9ab), 4.77 (dd, *J* = 8.8, 7.2 Hz, 1H, H-7'), 4.64 (d, *J* = 6.6 Hz, 1H, C7-OC*H*$_a$H$_b$OCH$_3$), 4.60 (d, *J* = 6.6 Hz, 1H, C7-OCH$_a$*H*$_b$OCH$_3$), 3.79 (s, 3H,

C4'-OCH_3), 3.77 (s, 6H, C3'-OCH_3, C5'-OCH_3), 3.40 (s, 3H, C7-OCH$_2$OCH_3), 2.94-2.75 (m, 2H, H-8'ab), 1.33 (s, 9H, OC(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.9 (s, *C*OO*t*-Bu), 153.2 (s, 2×C, C-3', C-5'), 147.3 (s, C-4/5), 146.5 (s, C-4/5), 139.4 (s, C-1'), 138.4 (d, C-8), 136.6 (s, C-4'), 135.3 (s, C-2), 131.9 (s, C-1), 116.0 (t, C-9), 108.1 (d, C-3/6), 107.3 (d, C-3/6), 105.2 (d, 2×C, C-2', C-6'), 101.2 (t, C-10), 93.6 (t, C7-O*C*H$_2$OCH$_3$), 80.7 (s, O*C*(CH$_3$)$_3$), 73.7 (d, C-8), 61.0 (q, C4'-O*C*H$_3$), 56.2 (q, 2×C, C3'-O*C*H$_3$, C5'-O*C*H$_3$), 55.7 (q, C7-OCH$_2$O*C*H$_3$), 42.6 (t, C-8'), 42.2 (d, C-7'), 28.1 (q, OC(*C*H$_3$)$_3$);

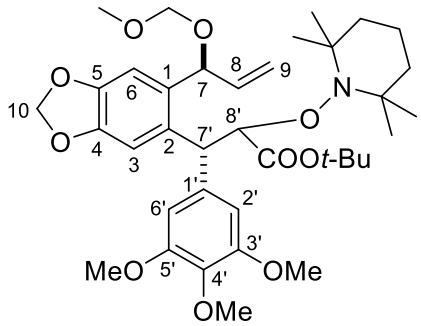
MS (ESI+) *m/z*, (%): 539 (100, [M + Na]$^+$), 399 (55, [M + H – MeOH – CH$_2$O – isobutene]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{28}H_{36}O_9Na$ 539.2252; found: 539.2244.

tert-Butyl (3R)-3-(6-((S*)-1-(methoxymethoxy)allyl)benzo[d][1,3]dioxol-5-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3-(3,4,5-trimethoxyphenyl)* (**212**)

A solution of *n*-BuLi (472 µL, 0.755 mmol, 1.6 M in hexanes) was added to a solution of diisopropylamine (124 µL, 881 mmol) in THF (5 mL) at –78 °C. The reaction was warmed to 0 °C for 5 min, followed by cooling to –78 °C. A solution of **211** (325 mg, 0.629 mmol) in THF (1 mL) was added dropwise, followed by stirring for 25 min. Solid 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (**109**) (184 mg, 0.755 mmol) was added, followed by stirring for 25 min. 5 drops of sat. Na_2SO_3 were added. After warming to r.t., the mixture was filtered through 4 cm silica pad (3 cm diameter), the sorbent was washed with EA (100 mL). The combined solutions were concentrated to yield 420 mg of crude product, dr 2:1. Purification by flash chromatography (PE/Et$_2$O 5:1) afforded 330 mg of **212** (78%) as colourless film, dr 2:1.

tert-Butyl (3R)-3-{6-[(S*)-1-(methoxymethoxy)allyl]benzo[d][1,3]dioxol-5-yl}-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-3-(3,4,5-trimethoxyphenyl)propanoate* (**212**)



R_f 0.34 (hexane/EA 3:1), R_f 0.21 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2974 (w), 2933 (w), 2838 (w), 1733 (m), 1590 (w), 1506 (w), 1484 (m), 1458 (w), 1421 (w), 1366 (w), 1328 (w), 1233 (m), 1183 (w), 1147 (s), 1126 (vs), 1031 (vs), 993 (w), 975 (w), 929 (m), 874 (w), 843 (w), 803 (w), 780 (w), 735 (m), 718 (w), 706 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.06 (s, 1H, H-6^B), 6.99 (s, 1H, H-6^A), 6.93 (s, 1H, H-3^A), 6.83 (s, 1H, H-3^B), 6.57 (s, 2H, H-2'^{B}), 6.53 (s, 2H, H-2'^{A}), 5.94 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH$_b$O^A), 5.93 (d, *J* = 1.4 Hz, 1H, C4-OCH$_a$$H_b$O^A), 5.92 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH$_b$O^B), 5.88 (d, *J* = 1.4 Hz, 1H, C4-OCH$_a$$H_b$O^B), 5.87 (ddd, *J* = 16.9, 10.3, 5.9 Hz, 1H, H-8^B), 5.56 (d, *J* = 6.1 Hz, 1H, H-7^B), 5.54 (ddd, *J* = 16.9, 10.3, 5.9 Hz, 1H, H-8^A), 5.46 (br. d, *J* = 6.1 Hz, 1H, H-7^A), 5.29-5.20 (m, 2H, H-9ab^B), 4.92-4.82 (m, 4H, H-8'^{AB}, H-9ab^A), 4.78 (d, *J* = 9.9 Hz, 1H, H-7'^{B}), 4.73 (d, *J* = 6.5 Hz, 1H, OCH_aH$_b$OCH$_3$^{B}), 4.71 (d, *J* = 6.5 Hz, 1H, OCH$_a$$H_bOCH_3$^{B}), 4.64 (d, *J* = 6.6 Hz, 1H, OCH_aH$_b$OCH$_3$^{A}),

4.62 (d, J = 6.5 Hz, 1H, $OCH_aH_bOCH_3^A$), 4.56 (d, J = 10.1 Hz, 1H, H-7'^{A}), 3.79 (s, 6H, C3'-OCH_3^B), 3.79 (s, 6H, C3'-OCH_3^A), 3.78 (s, 3H, C4'-OCH_3^A), 3.77 (s, 3H, C4'-OCH_3^B), 3.49 (s, 3H, $OCH_2OCH_3^A$), 3.42 (s, 3H, $OCH_2OCH_3^B$), 1.51-1.23 (m, 12H, TMP-CH_2^{AB}), 1.22 (s, 9H, $OC(CH_3)_3^A$), 1.16 (s, 12H, $OC(CH_3)_3^B$, TMP-CH_3^B), 1.14 (s, 3H, TMP-CH_3^A), 1.09 (s, 3H, TMP-CH_3^A), 1.06 (s, 3H, TMP-CH_3^B), 1.05-0.99 (br. s, 3H, TMP-CH_3^B), 0.97 (s, 3H, TMP-CH_3^A), 0.80 (s, 3H, TMP-CH_3^B), 0.66 (s, 3H, TMP-CH_3^A);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.9 (s, C-9'^{A}), 170.8 (s, C-9'^{B}), 152.9 (s, 2×C, C-3'^{B}, C-5'^{B}), 152.8 (s, C-3'^{A}, C-5'^{A}), 146.72 (s, C-4^B), 146.67 (s, C-4^A), 146.5 (s, C-5^A), 146.4 (s, C-5^B), 139.4 (d, C-8^B), 137.8 (d, C-8^A), 137.2 (s, C-1'^{A}), 137.0 (s, C-4'^{A}), 136.8 (s, C-4'^{B}), 136.2 (s, C-1'^{B}), 133.8 (s, C-2^A), 133.4 (s, C-1/2^B), 132.4 (s, C-1/2^B), 131.3 (s, C-1^A), 116.9 (t, C-9^B), 115.8 (t, C-9^A), 109.2 (d, C-3^B), 108.5 (d, C3/6^A), 108.3 (d, C-3/6^A), 107.6 (d, C-2'^{A}, C-6'^{A}), 107.1 (d,C-2'^{A}, C-6'^{B}), 107.0 (d, C-6^B), 101.2 (t, C4-OCH_2O^A), 101.1 (t, C4-OCH_2O^B), 95.04 (t, $OCH_2OCH_3^A$), 94.99 (t, $OCH_2OCH_3^B$), 87.4 (d, C-8'^{B}), 86.6 (d, C-8'^{A}), 81.14 (s, $OC(CH_3)_3^B$), 81.10 (s, $OC(CH_3)_3^A$), 75.5 (d, C-7^B), 73.4 (d, C-7^A), 61.07 (s, TMP-$NC(CH_3)_2^A$), 61.05 (s, TMP-$NC(CH_3)_2^B$), 61.00 (q, C4'-OCH_3^A), 60.98 (q, C4'-OCH_3^B), 59.8 (s, TMP-$NC(CH_3)_2^B$), 59.6 (s, TMP-$NC(CH_3)_2^A$), 56.4 (q, 2×C, C3'-OCH_3^A, C5'-OCH_3^A), 56.2 (q, 2×C, C3'-OCH_3^B, C5'-OCH_3^B), 56.0 (q, $OCH_2CH_3^A$), 55.8 (q, $OCH_2CH_3^B$), 49.2 (d, C-7'^{A}), 47.9 (d, C-7'^{B}), 41.0 (t, TMP-CH_2), 40.9 (t, TMP-CH_2), 40.5 (t, 2×C, TMP-CH_2), 34.2 (q, TMP-CH_3), 34.03 (q, TMP-CH_3), 33.95 (q, TMP-CH_3), 33.86 (q, TMP-CH_3), 27.8 (q, $OC(CH_3)_3^A$), 27.7 (q, $OC(CH_3)_3^B$), 20.7 (q, TMP-CH_3), 20.6 (q, TMP-CH_3), 20.32 (q, TMP-CH_3), 20.27 (q, TMP-CH_3), 17.20 (t, TMP-CH_2^B), 17.16 (t, TMP-CH_2^A);

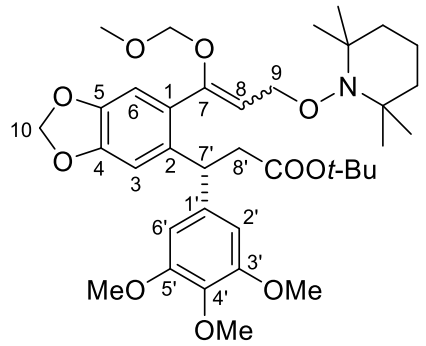
MS (ESI+) *m/z*, (%): 672 (100, $[M + H]^+$), 339 (33);

HRMS (ESI+) *m/z*: $[M + H]^+$ calcd. for $C_{37}H_{54}O_{10}N$ 672.3742; found: 672.3737.

PRE-mediated isomerization of 212 to 214

A solution of **212** (93 mg, 94 µmol) and TEMPO (6 mg, 37 µmol) in trifluorotoluene (1.0 mL) was degassed by bubbling dry N_2 for 10 min. The reaction vessel was sealed and heated to 140 °C for 35 min using microwave heating. After cooling, the mixture was separated by flash chromatography (PE/Et_2O 10:1 to 2:1) to yield 42.3 mg of **214** (67%) as colourless amorphous solid, dr 1:1.

tert-Butyl (R)-3-(6-{1-(methoxymethoxy)-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]prop-1-en-1-yl}benzo[d][1,3]dioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)propanoate* (**214**)



R_f 0.32 (hexane/EA 2:1), R_f 0.14 (hexane/EA 5:1);

^1H NMR (401 MHz, $CDCl_3$): δ 6.79 (s, 2H, H-3/6), 6.76 (s, 1H, H-3/6), 6.62 (s, 1H, H-3/6), 6.48 (s, 2H, H-2'), 6.47-6.39 (br. s, 2H, H-2'), 5.95-5.89 (m, 4H, C4-OH_2O), 5.33 (t, J = 7.7 Hz, 1H, H-8), 5.07 (s, 2H, OCH_2OCH_3), 4.92 (t, J = 6.6 Hz, 1H, H-8), 4.56 (dd, J = 9.5, 7.0 Hz, 1H, H-7'), 4.66-

4.50 (m, 4H, H-9, H-7', OCH_2OCH$_3$), 4.03-3.85 (br. s, 1H, H-9), 3.80 (s, 12H, C3'-OCH_3), 3.79 (s, 3H, C4'-OCH_3), 3.78 (s, 3H, C4'-OCH_3), 3.49 (s, 3H, OCH$_2$OCH_3), 3.43 (s, 3H, OCH$_2$OCH_3), 2.88-2.75 (m, 4H, H-8'), 1.55-1.23 (m, 12H, TMP-CH_2), 1.30 (s, 9H, OC(CH_3)$_3$), 1.28 (s, 9H, OC(CH_3)$_3$), 1.22 (s, 3H, TMP-CH_3), 1.19 (s, 3H, TMP-CH_3), 1.17-1.09 (br. s, 3H, TMP-CH_3), 1.09 (s, 3H, TMP-CH_3), 1.07 (s, 3H, TMP-CH_3), 1.06 (s, 3H, TMP-CH_3), 1.02 (s, 3H, TMP-CH_3), 0.95 (br. s, 3H, TMP-CH_3);

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 171.0 (s, C-9'), 170.8 (s, C-9'), 156.4 (s, C-7), 153.1 (s, 4×C, C-3', C-5'), 151.9 (s, C-7), 148.3 (s, 2×C, C-4/5), 145.8 (s, C-4/5), 145.6 (s, C-4/5), 139.5 (s, C-2/1'), 138.8 (s, C-2/1'), 137.3 (s, C-2/1'), 136.7 (s, C-2/1'), 136.6 (s, C-4'), 136.5 (s, C-4'), 127.8 (s, C-1), 127.2 (s, C-1), 111.9 (d, C-8), 111.1 (d, 2×C, C-3/6), 107.8 (d, C-3/6), 107.4 (d, C-3/6), 105.1 (d, 2×C, C-2', C-6'), 105.0 (d, 2×C, C-2', C-6'), 101.7 (br. d, C-8), 101.4 (t, C4-OCH$_2$O), 101.3 (t, C4-OCH$_2$O), 94.4 (t, OCH$_2$OCH$_3$), 93.3 (t, OCH$_2$OCH$_3$), 80.53 (s, OC(CH$_3$)$_3$), 80.50 (s, OC(CH$_3$)$_3$), 73.9 (t, C-9), 72.0 (t, C-9), 60.98 (q, C4'-OCH$_3$), 60.96 (q, C4'-OCH$_3$), 59.79 (s, TMP-NC(CH$_3$)$_2$), 59.77 (s, TMP-NC(CH$_3$)$_2$), 59.7 (s, TMP-NC(CH$_3$)$_2$), 59.6 (s, TMP NC(CH$_3$)$_2$), 56.7 (q, OCH$_2$CH$_3$), 56.4 (q, OCH$_2$CH$_3$), 56.22 (q, 2×C, C3'-OCH$_3^B$, C5'-OCH$_3$), 56.17 (q, 2×C, C3'-OCH$_3^B$, C5'-OCH$_3$), 44.3 (d, C-7'), 43.2 (d, C-7'), 42.7 (t, C-8'), 42.3 (t, C-8'), 39.8 (br. s, 4×C, TMP-CH$_2$), 33.3 (q, TMP-CH$_3$), 33.2 (q, TMP-CH$_3$), 33.1 (q, TMP-CH$_3$), 33.0 (q, TMP-CH$_3$), 28.1 (q, OC(CH$_3$)$_3$), 28.0 (q, OC(CH$_3$)$_3$), 20.3 (br. s, 4×C, TMP-CH$_3$), 17.3 (t, TMP-CH$_2$), 17.2 (t, TMP-CH$_2$);

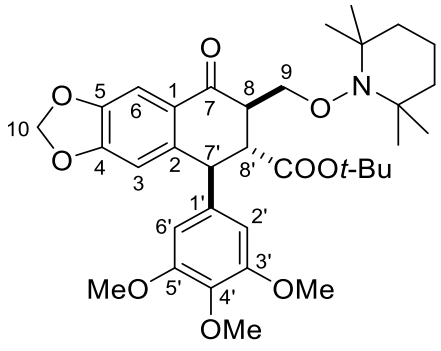
MS (ESI+) *m/z*, (%): 672 (100, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{37}H_{54}O_{10}N$ 672.3742; found: 672.3739.

Oxidative radical *6-endo-tri* cyclisation of 214

A solution of *n*-BuLi (167 µL, 0.268 mmol, 1.6 M in hexanes) was added at –78 °C to a solution of DIPA (44 µL, 0.312 mmol) in dry THF (1.5 mL). The solution was stirred for 15 min at –8 °C, followed by warming to 0 °C for 5 min and cooling back to –78 °C. A solution of **214** (150 mg, 0.223 mmol) in THF (0.7 mL) was added dropwise, followed stirring at –78 °C for 25 min and subsequent warming to –40 °C. Salt **52** (215 mg, 670 mmol) was added in one portion and the mixture was stirred for 45 min at –40 °C. The reaction was stopped by addition of saturated solution of Na_2SO_3 (5 mL). The mixture was partitioned between sat. Na_2SO_3 (30 mL) and DCM (60 mL). The phases were separated, and the aqueous phase was washed three times with fresh DCM (3×60 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by flash chromatography (PE/Et$_2$O 10:1 to 1:1) to yield 113 mg of a mixture of cyclic products. The cyclisation product **215a** and its diastereomer **215b** were inseparable from other products on repeated chromatography.

tert-Butyl (5S,6R*,7R*)-8-oxo-7-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}-5-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydronaphtho[2,3-d][1,3]dioxole-6-carboxylate* (**215a**)



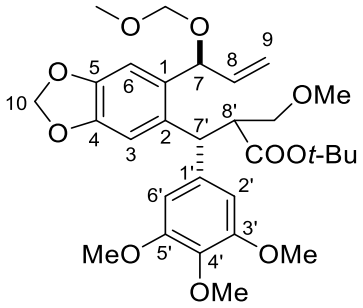
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.51 (s, 1H, H-6), 6.46 (s, 2H, H-2', H-6'), 6.21 (d, *J* = 1.0 Hz, 1H, H-3), 5.99 (d, *J* = 1.3 Hz, 1H, C4-OCH_aH$_b$O), 5.97 (d, *J* = 1.3 Hz, 1H, C4-OCH$_a$$H_b$O), 4.50 (dd, *J* = 8.5, 2.9 Hz, 1H, H-9a), 4.12 (dd, *J* = 11.9, 1.1 Hz, 1H, H-7'), 3.87 (s, 3H, C4'-OCH_3), 3.85-3.81 (m, 1H, H-9b), 3.82 (s, 6H, C3'-OCH_3, C5'-OCH_3), 3.58 (t, *J* = 12.0 Hz, 1H, H-8'), 3.02 (dt, *J* = 12.1, 2.9 Hz, 1H, H-8), 1.50-1.05 (m, 6H, TMP-CH_2), 1.18-0.95 (4×br. s, 12H, TMP-CH_3), 1.11 (s, 9H, OC(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.4 (s, C-7), 172.5 (s, C-9'),153.5 (s, 2×C, C-3', C-5'), 152.3 (s, C-4), 147.4 (s, C-5), 141.7 (s, C-2), 137.5 (s, C-4'), 135.8 (s, C-1'), 127.9 (s, C-1), 108.1 (d, C-3), 106.8 (d, 2×C, C-2', C-6'), 106.4 (d, C-6), 101.9 (t, C4-OCH_2O), 81.3 (s, OC(CH$_3$)$_3$), 73.9 (t, C-9), 61.1 (q, C4'-OCH_3), 60.1 (s, 2×C, TMP-NC(CH$_3$)$_2$), 56.2 (q, 2×C, C3'-OCH_3, C5'-OCH_3), 51.1 (d, C-8'), 49.8 (d, C-8), 49.0 (d, C-7'), 39.8 (t, 2×C, TMP-CH$_2$), 33.6 (q, TMP-CH$_3$), 32.7 (q, TMP-CH$_3$), 27.6 (q, 3×C, OC(CH$_3$)$_3$), 20.2 (q, 2×C, TMP-CH$_3$), 17.1 (t, TMP-CH$_2$).

6.3.2. Second generation approach based on RCM/conjugate addition

tert-Butyl (3R)-3-(6-((S*)-1-(methoxymethoxy)allyl)benzo[d][1,3]dioxol-5-yl)-2-(methoxymethyl)-3-(3,4,5-trimethoxyphenyl)propanoate* (**216a**)

A solution of tetramethylpiperidine (55 µl, 0.328 mmol) in THF (1 mL) was cooled to –78 °C. A solution of *n*-BuLi (180 µl, 1.7 M in hexanes, 0.289 mmol) was added dropwise, followed by gradual warming to 0 °C over 30 min. The reaction was again cooled to –78 °C. A solution of **211** (100 mg, 0.193 mmol) in THF (3 mL) was added dropwise, followed by stirring for 1 h at –78 °C. A solution of MOMCl (30 µl, 0.386 mmol) in THF (0.5 ml) was added dropwise. The temperature was increased to r.t. over 35 minutes, followed by stirring overnight at r.t. The reaction was quenched by adding a drop of water and Et_2O (5 mL). The mixture was partitioned between EA (150 mL) and aqueous NH_4Cl (150 mL). The aqueous phase was extracted again with EA (50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, concentrated, and purified by flash chromatography to yield 50 mg **211** (50%) and 40 mg of **216a** (41%), dr 2:1.



R_f 0.73 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2976.4 (w), 2934.1 (w), 2891.2 (w), 2836.2 (w), 1724.5 (m), 1589.1 (m), 1505.0 (m), 1484.2 (m), 1459.2 (m), 1421.2 (w), 1367.0 (w), 1328.0 (w), 1230.2 (m), 1147.7 (s), 1125.1 (vs), 1030.2 (vs), 910.7 (s), 846.0 (w), 728.3 (vs), 647.3 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.03 (s, 1H, H-3/6^{A}), 6.91 (s, 1H, H-3/6^{B}), 6.88 (s, 1H, H-3/6^{A}), 6.83 (s, 1H, H-3/6^{B}), 6.51 (s, 2H, H-2'^{B}), 6.43 (s, 2H, H-2'^{A}), 5.94 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH$_b$O^{B}), 5.92 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH$_b$O^{A}), 5.90 (d, *J* = 1.4 Hz, 1H, C4-OCH$_a$$H_b$O^{A}), 5.88 (d, *J* = 1.5 Hz, 1H, C4-OCH$_a$$H_b$O^{B}), 5.90-5.82 (m, 1H, H-8^{B}), 5.63 (ddd, *J* = 16.8, 10.3, 5.6 Hz, 1H, H-8^{A}), 5.57-5.52 (m, 2H, H-7^{AB}), 5.24-5.17 (m, 2H, H-9^{B}), 5.02-4.93 (m, 2H, H-9^{A}), 4.68 (d, *J* = 6.8 Hz, 1H, C7-

OCH_aH$_b$OCH$_3^B$), 4.65 (d, J = 6.6 Hz, 1H, C7-OCH_aH$_b$OCH$_3^A$), 4.60 (d, J = 6.6 Hz, 1H, C7-OCH$_a$$H_bOCH_3^A$), 4.56 (d, J = 6.6 Hz, 1H, C7-OCH$_a$$H_bOCH_3^B$), 4.37 (d, J = 11.3 Hz, 1H, H-7'^{B}), 4.34 (d, J = 10.7 Hz, 1H, H-7'^{A}), 3.79 (s, 6H, C3'-OCH_3^B), 3.79 (s, 6H, C3'-OCH_3^A), 3.77 (s, 3H, C4'-OCH_3^A), 3.75 (s, 3H, C4'-OCH_3^B), 3.66-3.58 (m, 1H, C8'-CH_aH$_b$OCH$_3^B$), 3.55-3.48 (m, 1H, C8'-CH_aH$_b$OCH$_3^A$), 3.46 (s, 3H, C7-OCH$_2$OCH_3^A), 3.42 (s, 3H, C7-OCH$_2$OCH_3^B), 3.35-3.27 (m, 1H, H-8'^{AB}, C8'-CH$_a$$H_bOCH_3^{AB}$), 3.25 (s, 3H, C8'-CH$_2OCH_3^A$), 3.24 (s, 3H, C8'-CH$_2OCH_3^B$), 1.25 (s, 9H, C(C$H_3$)$_3^A$), 1.23 (s, 9H, C(C$H_3$)$_3^B$);

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 172.9 (s, *C*OO*t*-Bu^B), 172.5 (s, *C*OO*t*-Bu^A), 153.2 (s, 2×C, C-3'^{A}, C-5'^{A}), 152.9 (s, 2×C, C-3'^{B}, C-5'^{B}), 147.7 (s, C-4/5^B), 147.0 (s, C-4/5^A), 146.7 (s, C-4/5^B), 146.4 (s, C-4/5^A), 138.6 (d, C-8^B), 138.4 (d, C-8^A), 137.8 (s, C-1'^{B}), 137.7 (s, C-1'^{A}), 136.8 (s, C-4'^{A}), 136.7 (s, C-4'^{B}), 133.6 (s, C-2^B), 133.5 (s, C-2^A), 133.0 (s, C-1^A), 132.1 (s, C-1^B), 117.0 (t, C-9^B), 115.8 (t, C-9^A), 108.3 (d, C-3/6^A), 107.7 (d, C-3/6^B), 107.1 (d, C-3/6^A), 106.5 (d, C-3/6^B), 105.8 (d, 2×C, C-2'B), 105.4 (d, 2×C, C-2'A), 101.3 (t, C4-O*C*H$_2$O^B), 101.2 (t, C4-O*C*H$_2$O^A), 93.9 (t, C7-O*C*H$_2$OCH$_3^A$), 93.6 (t, C7-O*C*H$_2$OCH$_3^B$), 80.78 (s, COO*C*(CH$_3$)$_3^B$), 80.77 (s, COO*C*(CH$_3$)$_3^A$), 73.8 (d, C-7^B), 73.5 (t, C8'-*C*H$_2$OCH$_3^A$), 73.2 (t, C8'-*C*H$_2$OCH$_3^B$), 73.0 (d, C-7^A), 61.0 (q, C-4'^{A}), 60.9 (q, C4'-O*C*H$_3^B$), 59.1 (q, C8'-CH$_2$O*C*H$_3^A$), 59.0 (q, C8'-CH$_2$O*C*H$_3^B$), 56.3 (q, 2×C, C3'-O*C*H$_3^A$), 56.2 (q, 2×C, C3'-O*C*H$_3^B$), 55.9 (q, C7-OCH$_2$O*C*H$_3^A$), 55.8 (q, C7-OCH$_2$O*C*H$_3^B$), 52.4 (d, C-8'^{B}), 52.0 (d, C-8'^{A}), 45.4 (d, C-7'^{A}), 44.7 (d, C-7'^{B}), 27.91 (q, *C*(CH$_3$)$_3^A$), 27.90 (q, O*C*(CH$_3$)$_3^B$);

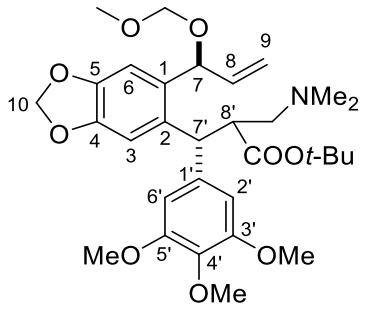
MS (ESI+) *m/z*, (%): 1143 (13, [2M + Na]$^+$), 583 (100, [M +Na]$^+$), 578 (17, [M + NH$_4$]$^+$), 339 (70);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{30}H_{40}O_{10}Na$ 583.25137; found: 583.25123.

One-pot conjugate addition of 210 to 146 followed by aminomethylation

A 250 mL flame-dried Schlenk flask was charged with **210** (7.2 g, 23.8 mmol), dry toluene (20 mL) and freshly distilled TMEDA (25.5 ml, 33.9 mmol). The mixture was cooled down to –78 °C and *n*-Bu-Li (16.6 ml, 23.8 mmol) was added dropwise, followed by stirring at –78 ° for 15 min, during which the solution turned bright yellow. A solution of **146** (5.0 g, 16.9 mmol) in toluene (20 mL) was added dropwise. The yellow solution turned orange and then yellow again. The mixture was stirred for 2 hours at –78 °C. Dry THF (50 mL) was added, followed by solid *N,N*-dimethyl-methyleneiminium iodide (Eschenmoser's salt) (6.3 g, 33.9 mmol). Vigorous stirring was maintained while the temperature was gradually increased to r.t. over 3 h. The reaction mixture was filtered through silica, the filter was washed with copious Et$_2$O. Concentration and purification by flash chromatography (cyclohexane/EA 3:1, then pure EA) yielded 6.0 g of **216b** (61%, dr 2:1) as a colourless viscous oil.

tert-Butyl (3R)-2-((dimethylamino)methyl)-3-(6-((S*)-1-(methoxymethoxy)allyl)benzo[d][1,3]dioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)propanoate* (**216b**)



R_f 0.15 (Et$_2$O);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3078 (w), 2974 (w), 2865 (w), 1726 (w), 1588 (w), 1505 (w), 1484 (m), 1367 (w), 1233 (m), 1125 (vs), 1030 (vs), 932 (m), 846 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 7.40 (s, 1H, H-3/6), 7.29 (s, 1H, H-3/6), 6.62 (s, 2H, H-2', H-6'), 5.99 (dt, *J* = 5.8, 1.4 Hz, 1H, H-7), 5.81 (ddd, *J* = 17.1, 10.3, 5.8 Hz, 1H, H-8), 5.37 (d, *J* = 1.3 Hz, 1H, C4-OC*H*$_a$H$_b$O), 5.28 (d, *J* = 1.3 Hz, 1H, C4-OCH$_a$*H*$_b$O), 5.21 (dt, *J* = 17.2, 1.6 Hz, 1H, H-9a), 4.97-4.90 (m, 2H, H-9b, C7-OC*H*$_a$H$_b$OCH$_3$), 4.74 (d, *J* = 6.5 Hz, 1H, C7-OCH$_a$*H*$_b$OCH$_3$), 4.61 (d, *J* = 11.4 Hz, 1H, H-7'), 3.78 (s, 3H, C4'-OC*H*$_3$), 3.57-3.50 (m, 1H, H-8'), 3.43 (s, 3H, C7-OCH$_2$OC*H*$_3$), 3.36 (s, 6H, C3'-OC*H*$_3$, C5'-OC*H*$_3$), 2.98 (t, *J* = 11.5 Hz, 1H, H-10'a), 2.32-2.23 (m, 1H, H-10'b), 2.12 (s, 6H, N(C*H*$_3$)$_2$), 1.32 (s, 9H, OC(C*H*$_3$)$_3$);

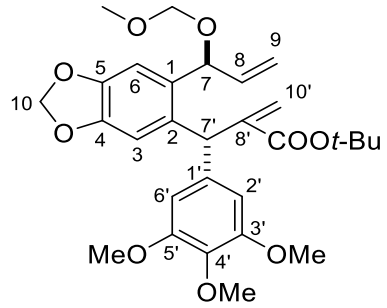
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 173.6 (s, C-9'), 154.2 (s, 2×C, C-3', C-5'), 147.5 (s, C-4/5), 147.0 (s, C-4/5), 139.5 (d, C-8), 138.3 (s, C-1'), 138.2 (s, C-4'), 134.6 (s, C-1/2), 133.8 (s, C-1/2), 115.9 (t, C-9), 108.6 (d, C-3/6), 108.0 (d, C-3/6), 106.3 (d, 2×C, C-2', C-6'), 101.1 (t, C4-O*C*H$_2$O), 94.3 (t, C7-O*C*H$_2$OCH$_3$), 80.0 (s, O*C*(CH$_3$)$_3$), 73.9 (d, C-7), 62.2 (t, C-10'), 60.5 (d, C4'-O*C*H$_3$), 55.9 (q, 2×C, C3'-O*C*H$_3$, C5'-O*C*H$_3$), 55.7 (q, C7-OCH$_2$O*C*H$_3$), 50.9 (d, C-8'), 47.5 (d, C-7'), 45.7 (q, 2×C, N(*C*H$_3$)$_2$), 28.0 (q, OC(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 574 (100, [M + H]$^+$), 512 (16, [M – CH$_3$OCH$_2$O]$^+$), 456 (32, [M – CH$_3$OCH$_2$O – isobutene]$^+$), 339 (35);

HRMS (ESI+) *m/z*: [M + H]$^+$ calcd. for $C_{31}H_{44}O_9N$ 574.3011; found: 574.3008.

tert-Butyl 2-((R)-(6-((S*)-1-(methoxymethoxy)allyl)benzo[d][1,3]dioxol-5-yl)(3,4,5-trimethoxyphenyl)methyl)acrylate* (**217**)

Amine **216b** (800 mg, 1.395 mmol) was dissolved in dry freshly distilled THF (1 ml). MeI (434 µl, 6.9 mmol) was added dropwise, followed by stirring for 2 h at r.t. The solvent and all volatiles were stripped off under vacuum. The residue was dissolved in THF/*t*-BuOH (1:1). A solution of *t*-BuOK (157 mg, 1.4 mmol) in dry THF/*t*-BuOH (1:1) mixture was added at r.t., and the reaction was stirred for 10 min. Additional *t*-BuOK (78 mg, 0.7 mmol) was added, followed by stirring for 30 minutes. The mixture was filtered through a 5 cm silica pad (2.5 cm diameter), the pad was washed with Et$_2$O (150 mL). The combined filtrates were concentrated and purified by flash chromatography (pure cyclohexane to cyclohexane/EA 3:1) to yield 617 mg of **217** (83%) as a colourless viscous oil.



R_f 0.52 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3057 (w), 2973 (w), 2935 (w), 2888 (w), 2838 (w), 1712 (w), 1628 (w), 1589 (w), 1504 (m), 1482 (w), 1462 (w), 1420 (w), 1367 (w), 1329 (w), 1254 (w), 1234 (m), 1125 (vs), 1028 (s), 933 (m), 849 (w), 734 (s), 701 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.01 (s, 1H, H-3/6), 6.45 (s, 1H, H-3/6), 6.31 (t, *J* = 1.2 Hz, 1H, H-10'a), 6.29 (s, 2H, H-2'), 5.93 (d, *J* = 1.4 Hz, 1H, C4-OC*H*$_a$H$_b$O), 5.91 (d, *J* = 1.4 Hz, 1H, C4-

OCH_aH_bO), 5.79 (ddd, *J* = 17.0, 10.2, 6.7 Hz, 1H, H-8), 5.46 (s, 1H, H-7'), 5.24 (dt, *J* = 6.8, 1.2 Hz, 1H, H-7), 5.19-5.10 (m, 3H, H-9, H-10'b), 4.65 (d, *J* = 6.5 Hz, 1H, C7-$OCH_aH_bOCH_3$), 4.57 (d, *J* = 6.5 Hz, 1H, C7-$OCH_aH_bOCH_3$), 3.82 (s, 3H, C4'-OCH_3), 3.76 (s, 6H, C3'-OCH_3), 3.35 (s, 3H, C7-OCH_2OCH_3), 1.37 (s, 9H, $C(CH_3)_3$);

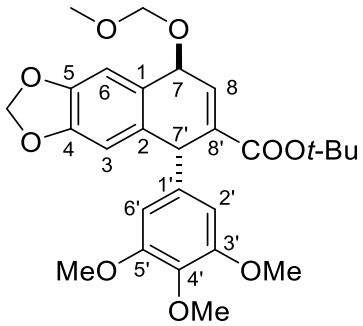
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1 (s, *C*OO*t*-Bu), 153.3 (s, 2×C, C-3'), 146.9 (s, C-4/5), 146.6 (s, C-4/5), 145.3 (s, C-8'), 138.3 (d, C-8), 137.7 (s, C-1'), 136.8 (s, C-4'), 133.5 (s, C-2), 132.5 (s, C-1), 126.5 (t, C-10'), 116.3 (t, C-9), 109.2 (d, C-3/6), 107.8 (d, C-3/6), 106.3 (d, 2×C, C-2'), 101.2 (t, C4-OCH_2O), 93.6 (t, C7-OCH_2OCH_3), 81.1 (s, COO$C(CH_3)_3$), 74.2 (d, C-7), 61.0 (q, C4'-OCH_3), 56.2 (q, 2×C, C3'-OCH_3), 55.5 (q, C7-OCH_2OCH_3), 47.9 (d, C-7'), 28.0 (q, $C(CH_3)_3$);

MS (ESI+) *m/z*, (%): 551 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{29}H_{36}O_9Na$ 551.2251; found: 551.2252.

tert-Butyl (5R,8S*)-8-(methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)-5,8-dihydronaphtho[2,3-d][1,3]dioxole-6-carboxylate* (**218**)

A flame-dried Schlenk flask was charged with Hoveyda-Grubbs II catalyst (242 mg, 0.386 mmol) and evacuated, followed by flushing with dry N_2. A solution of **217** (1020 mg, 1.930 mmol) in dry benzene (15 mL) was added. The reaction mixture was degassed by evacuating the mixture until the solvent started to gently boil, then flushing with N_2. The evacuation/N_2 flush cycle was repeated 5 times. The reaction was then stirred at 70 °C for 4 days, during which it was monitored by ^1H NMR. After reaching full conversion, the reaction was cooled to r.t. and directly loaded onto a column of silica and eluted with PE/PE (6:1), giving 500 mg of **218** (51%, dr 7:1) as colourless viscous oil.



R_f 0.45 (PE/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2936 (w), 2838 (w), 1706 (m), 1503 (w), 1483 (m), 1460 (m), 1303 (w), 1232 (m), 1142 (w), 1124 (vs), 1035 (m), 1007 (s), 934 (w), 848 (w), 736 (w);

^1H (401 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 2.7, 1.1 Hz, 1H, H-8), 6.99 (s, 1H, H-6), 6.67 (s, 1H, H-3), 6.30 (s, 2H, H-2', H-6'), 5.93 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH_bO), 5.91 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH_bO), 5.35 (dd, *J* = 3.4, 2.8 Hz, 1H, H-7), 4.98 (d, *J* = 7.0 Hz, 1H, C7-OCH_aH_bO), 4.89 (d, *J* = 7.0 Hz, 1H, C7-OCH_aH_bO), 4.88 (d, *J* = 3.5 Hz, 1H, H-7'), 3.78 (s, 9H, C3'-OCH_3, C4'-OCH_3, C5'-OCH_3), 3.54 (s, 3H, C7-OCH_2OCH_3), 1.39 (s, 9H, $C(CH_3)_3$);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.4 (s, C-9'), 153.3 (s, C-3', C-5'), 147.8 (s, C-4/5), 147.0 (s, C-4/5), 139.4 (s, C-1'), 136.8 (s, C-4'), 135.7 (d, C-8), 135.2 (s, C-8'), 131.5 (s, C-1/2), 126.7 (s, C-1/2), 108.1 (d, C-3), 106.8 (d, C-6), 105.3 (d, 2×C, C-2', C-6'), 101.3 (t, C4-OCH_2O), 96.2 (t, C7-OCH_2OMe), 80.3 (s, COOCMe$_3$), 71.7 (d, C-7), 61.0 (q, C4'-OCH_3), 56.3 (q, C3'-OCH_3, C5'-OCH_3), 56.2 (q, C7-OCH_2OCH_3), 45.8 (d, C-7'), 29.9 (q, $C(CH_3)_3$);

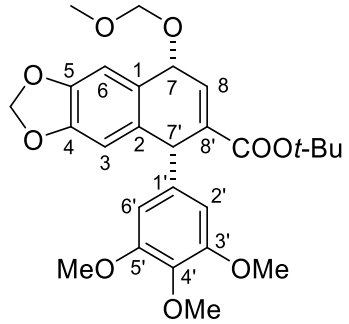
^{1}H (401 MHz, C_6D_6): δ 7.55 (dd, *J* = 2.6, 0.9 Hz, 1H, H-8), 7.23 (s, 1H, H-6), 6.76 (s, 1H, H-3), 6.49 (s, 2H, H-2', H-6'), 5.42 (t, *J* = 3.1 Hz, 1H, H-7), 5.32 (d, *J* = 1.3 Hz, 1H, C4-OCH_aH$_b$O), 5.24 (d, *J* = 1.3 Hz, 1H, C4-OCH$_a$$H_b$O), 5.09 (d, *J* = 3.5 Hz, 1H, H-7'), 4.71 (d, *J* = 6.9 Hz, 1H, C7-OCH_aH$_b$O), 4.59 (d, *J* = 6.9 Hz, 1H, C7-OCH$_a$$H_b$O), 3.75 (s, 3H, C4'-OCH$_3$), 3.36 (s, 6H, C3'-OCH$_3$, C5'-OCH$_3$), 3.22 (s, 3H, C7-OCH$_2OCH_3$), 1.30 (s, 9H, C(C$H_3$)$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 165.4 (s, C-9'), 154.2 (s, C-3', C-5'), 148.3 (s, C-4/5), 147.5 (s, C-4/5), 139.7 (s, C-1'), 138.5 (s, C-4'), 136.6 (d, C-8), 135.5 (s, C-8'), 131.9 (s, C-1/2), 127.7 (s, C-1/2), 108.5 (d, C-3), 107.2 (d, C-6), 106.4 (d, C-2', C-6'), 101.2 (t, C4-O*C*H$_2$O), 96.4 (t, C7-O*C*H$_2$OMe), 80.7 (s, COO*C*Me$_3$), 72.5 (d, C-7), 60.5 (q, C4'-O*C*H$_3$), 55.9 (q, C3'-O*C*H$_3$, C5'-O*C*H$_3$), 55.6 (q, C7-OCH$_2$O*C*H$_3$), 46.3 (d, C-7'), 28.0 (q, C(*C*H$_3$)$_3$);

MS (ESI+) *m/z*, (%): 1023 (55, [2M + Na]$^+$), 537 (10, [M + 2H$_2$O + H]$^+$), 523 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{27}H_{32}O_9Na$ 523.19385; found: 523.19409.

tert-Butyl (5R,8R*)-8-(methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)-5,8-dihydronaphtho[2,3-d][1,3]dioxole-6-carboxylate* (**218'**)



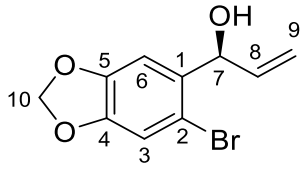
^{1}H (401 MHz, $CDCl_3$): δ 8.09 (m, Hz, 1H, H-8), 6.68 (s, 1H, H-3), 6.63-6.45 (br. s, 2H, H-2', H-6'), 6.14 (d, *J* = 1.1 Hz, 1H, H-6), 5.89 (d, *J* = 1.4 Hz, 1H, C4-OCH_aH$_b$O), 5.87 (d, *J* = 1.4 Hz, 1H, C4-OCH$_a$$H_b$O), 4.98 (m, *J* = 3.4, 2.8 Hz, 1H, H-7, overlaps with major isomer), 4.94 (d, *J* = 6.9 Hz, 1H, C7-OCH_aH$_b$O), 4.68 (d, *J* = 6.9 Hz, 1H, C7-OCH$_a$$H_b$O), 4.68 (m, *J* = 3.5 Hz, 1H, H-7', overlaps with major isomer), 3.46 (s, 3H, C4'-OCH$_3$), 3.85-3.77 (s, 6H, C3'-OCH$_3$, C5'-OCH$_3$), 3.41 (s, 3H, C7-OCH$_2$OCH_3), 1.22 (s, 9H, C(CH_3)$_3$).

Asymmetric vinylation of 6-bromopiperonal

Following a published procedure for enantioselective vinylation of benzaldehydes,[189] 6-bromopiperonal (153 mg, 670 µmol) was reacted with vinyltrimethoxysilane (205 µL, 1.34 mmol) in DMF (1 mL) at 55 °C. The catalyst was prepared as described from (*R*)-DTBM-SEGPHOS (50.0 mg, 42 µmol) and CuF_2 hydrate (3.0 mg, 25 µmol) in degassed MeOH (0.7 mL) and dried by co-evaporation with toluene. Thorough drying and strict exclusion of air during the catalyst transfer proved critical for maintaining catalyst activity. For work-up, the solution was poured into 10%$_w$ KOH (5 mL) and EtOH (10 mL). The mixture was heated to 50 °C for 20 min. The mixture was partitioned between water (40 mL) and a mixture of Et_2O/PE (1:1, 100 mL). The organic layer was washed with water (15 mL), dried over Na_2SO_4 and concentrated to give 207 mg of colourless solid, which was purified by flash chromatography (EA/PE, 11:1 to 5:1) to yield 142 mg of **221** (82%), er 97:3 (94% ee) by chiral HPLC. Recrystallization from EA/hexane 10:1 afforded 92 mg of **221** (53%), er 99:1

(98% ee). The crystals were suitable for X-ray analysis, which was used to the establish absolute configuration as (*S*)-**221**.

(S)-1-(6-Bromobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (**221**)



R_f 0.30 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3700-3100 (br.), 3380 (w), 3085 (w), 2980 (w), 2899 (w), 1502 (w), 1475 (vs), 1408 (w), 1390 (w), 1359 (w), 1234 (s), 1115 (w), 1039 (m), 987 (w), 932 (m), 870 (w), 840 (w), 799 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.01 (s, 1H, H-3/6), 6.98 (s, 1H, H-3/6), 6.01-5.93 (m, 1H, H-8), 5.98 (d, *J* = 1.4 Hz, 1H, H-10a), 5.97 (d, *J* = 1.4 Hz, 1H, H-10b), 5.58-5.52 (m, 1H, H-7), 5.40 (dt, *J* = 17.2, 1.5 Hz, 1H, H-9a), 5.22 (dt, *J* = 10.4, 1.4 Hz, 1H, H-9b), 2.01 (d, *J* = 3.8 Hz, 1H, C7-O*H*);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.97 (s, C-4/5), 149.92 (s, C-4/5), 138.6 (d, C-8), 135.0 (d, C-1), 115.6 (t, C-9), 113.1 (s, C-2), 112.7 (d, C-3/6), 107.9 (d, C-3/6), 101.9 (t, C4-OCH_2O), 73.5 (d, C-7);

MS (EI+) *m/z*, (%): 258/256 (50/51, $[M]^{\cdot+}$), 229 (20), 215/213(24/25), 177 (51, $[M - Br]^+$), 147 (55), 135 (48), 122 (100);

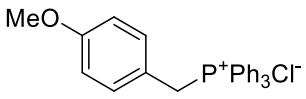
HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{10}H_9{}^{79}BrO_3$ 255.9730; found: 255.9728.

6.4. Part D

6.4.1. Synthesis of neopodophyllotoxin analogue by polar bicyclization

(4-Methoxybenzyl)triphenylphosphonium chloride (**226**)

A mixture of 4-methoxybenzyl chloride (1.43 g, 9.13 mmol) and PPh_3 (3.85 g, 14.7 mmol) in toluene (15 mL) was heated to 140 °C for 3 hours in a sealable pressure-resistant tube. After cooling, PE (20 mL) was added and the white precipitate was filtered off, washed with additional PE (100 mL) and dried under vacuum to give 2.65 g of phosphonium salt **226** (69%). ^{1}H and ^{13}C NMR spectra matched lit.[269]



^{1}H NMR (401 MHz, $CDCl_3$): δ 7.79-7.69 (m, 9H), 7.64-7.59 (m, 6H), 7.01 (dd, *J* = 8.9, 2.6 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 5.42 (d, *J* = 13.8 Hz, 2H, CH_2PPh$_3$), 3.71 (s, 3H, OCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.7 (s, J_{CP} = 3.7 Hz), 134.9 (d, J_{CP} = 3.0 Hz), 134.6 (d, J_{CP} = 9.7 Hz), 132.9 (d, J_{CP} = 5.5 Hz), 130.2 (d, J_{CP} = 12.5 Hz), 118.9 (s, J_{CP} = 8.8 Hz), 118.3 (s, J_{CP} = 85.4 Hz), 114.3 (d, J_{CP} = 3.2 Hz), 55.4 (q), 30.1 (t, J_{CP} = 46.3 Hz);

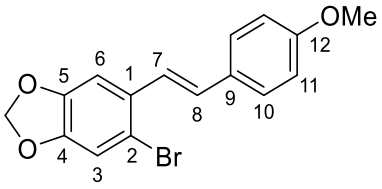
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 25.24.

(E)-5-Bromo-6-(4-methoxystyryl)benzo[d][1,3]dioxole (**225**)

Step 1. Salt **226** (2.65 g, 6.32 mmol, 1.03 equiv.) and 6-bromopiperonal (1.42 g, 6.20 mmol) were dissolved in dry DMF (20 mL). Sodium *tert*-pentoxide (3.7 mL, 40% in toluene, 12.2 mmol) was added dropwise, leading to noticeable evolution of heat and transient red coloration. The reaction vessel was sealed and stirred for 30 min after which the red colour disappeared. DMF was evaporated under vacuum and the mixture was separated using flash chromatography (cyclohexane/EA 20:1) giving 2.07 g of **225** (quant.) of stilbene as a mixture of isomers, *E*:*Z* 1:2.

Z-**225**: ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.15-7.07 (m, 2H), 7.05 (s, 1H), 6.79-6.71 (m, 2H), 6.68 (s, 1H), 6.55 (d, *J* = 12.0 Hz, 1H), 6.40 (d, *J* = 12.0 Hz, 1H), 5.93 (s, 2H), 3.78 (s, 3H).

Step 2. Ph_2Se_2 (39 mg, 0.124 mmol, 0.02 equiv.) was added to a solution of stilbenes (2.07 g, 6.20 mmol) in benzene (25 mL). The flask was evacuated until benzene started gently boiling, followed by flushing with dry N_2. The vacuum/N_2 cycle was repeated 7 times to remove dissolved O_2. The solution was irradiated by blue LED (450 nm) from a distance of 10 cm for 50 min. Concentration and purification by flash chromatography (cyclohexane/EA 20:1 to 15:1) yielded 1.91 g (92%) of (*E*)-**225** as a colourless powder.



R_f 0.55 (5:1, hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.52-7.43 (m, 2H, H-10), 7.28 (d, *J* = 16.1 Hz, 1H, H-7), 7.15 (s, 1H, H-6), 7.05 (s, 1H, H-3), 6.96-6.91 (m, 2H, H-11), 6.86 (d, *J* = 16.1 Hz, 1H, H-8), 6.01 (s, 2H, OC*H*$_2$O), 3.86 (s, 3H, C12-OCH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.6 (s, C-12), 147.9 (s, C-4/5), 147.8 (s, C-4/5), 131.0 (s, C-1/9), 130.1 (s, C-1/9), 129.5 (d, C-8), 128.0 (d, C×2, C-10), 125.4 (d, C-7), 115.1 (s, C-2), 114.3 (d, C×2, C-11), 112.9 (d, C-3), 105.8 (d, C-6), 101.9 (t, O*C*H_2O), 55.5 (q, C12-O*C*H_3);

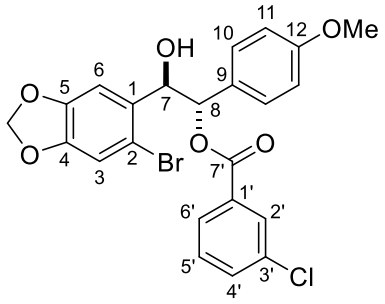
MS (EI+) *m/z*, (%): 334 (98, $[M]^+$), 332 (100, $[M]^{\cdot+}$), 253 (17, $[M - Br]^+$), 238 (14 $[M - Br - Me]^{\cdot+}$), 223 (35, $[M - Br - CH_2O]^+$), 210 (20, $[M - Br - Me - CO]^{\cdot+}$), 195 (54), 180 (20), 152 (37);

HRMS (EI+) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{13}O_3{}^{79}Br$ 332.0048; found: 332.0047.

Epoxidation of (*E*)-225 using *m*-CPBA

To a solution (*E*)-**225** (0.95 g, 2.85 mmol) in DCM (25 mL) at 0 °C was added $NaHCO_3$ (4.0 g), followed by *m*-CPBA (1.72 g, 7 mmol, 2.5 equiv.). The mixture turned purple. TLC analysis revealed incomplete consumption of the starting material after 1 h, therefore the increasingly dark suspension was warmed to r.t. After 30 min the mixture was partitioned between water (100 mL) and EA (100 mL), the organic phase was washed with brine and dried over Na_2SO_4, concentrated and purified by flash chromatography (cyclohexane/EA 0 to 25%) to obtain 802 mg of yellow solid, identified as a product of epoxide opening by *m*-chlorobenzoate based on ^{1}H, ^{13}C and 2D NMR. In the absence of $NaHCO_3$, reaction with *m*-CPBA in DCM only led to decomposition.[192]

(1S,2R*)-2-(6-Bromobenzo[d][1,3]dioxol-5-yl)-2-hydroxy-1-(4-methoxyphenyl)ethyl 3-chlorobenzoate* (**227**)



R_f 0.50 (2:1, hexane/EA 2:1), R_f 0.35 (hexane/EA 3:1), R_f 0.15 (hexane/EA 5:1);

^{1}H NMR (401 MHz, C_6D_6): δ 8.23 (t, *J* = 1.8 Hz, 1H, H-2'), 7.88 (dt, *J* = 7.8, 1.3 Hz, 1H, H-6'), 7.35-7.27 (m, 3H, H-10), 7.17 (s, 1H, H-3/6), 7.04 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H, H-4'), 6.73 (s, 1H, H-3/6), 6.73-6.64 (m, 3H, H-11, H-5'), 6.50 (d, *J* = 5.4 Hz, 1H, H-8), 5.37 (dd, *J* = 5.4, 4.2 Hz, 1H, H-7), 5.08 (d, *J* = 1.4 Hz, 1H, OC*H*$_a$H$_b$O), 5.02 (d, *J* = 1.4 Hz, 1H, OCH$_a$*H*$_b$O), 3.21 (s, 3H, C12-OC*H*$_3$), 1.73 (d, *J* = 4.1 Hz, 1H, C7-O*H*);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 164.3 (s, C-7'), 160.0 (s, C-12), 148.4 (s, C-4/5), 148.0 (s, C-4/5), 134.8 (s, C-3'), 133.1 (s, C-1/9), 133.0 (d, C-4'), 132.6 (s, C-1/9), 130.0 (d, C-2'/5'), 129.9 (d, C-2'/5'), 129.3 (s, C-1'), 129.0 (d, 2×C, C-10), 127.9 (d, C-6'), 114.1 (d, 2×C, C-11), 113.6 (s, C-2), 112.5 (d, C-3/6), 109.2 (d, C-3/6), 101.7 (t, O*C*H$_2$O), 79.0 (d, C-8), 75.3 (d, C-7), 54.7 (q, O*C*H$_3$);

MS (ESI+) *m/z*, (%): 545/543 (8, [M + K]$^+$), 531/529/527 (51, [M + Na]$^+$), 373/371 (37, [M + H – *m*CPBA]$^+$).

Preparation of DMDO

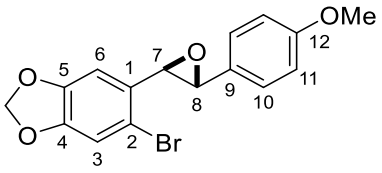
Acetone solution of DMDO was prepared following a modified published procedure.[270] In a three-necked 500 mL round-bottomed flask, $NaHCO_3$ (50 g), 60 mL acetone (70 mL) and water (92 mL) were stirred using a very large stirring bar. One side-neck was fitted with a venting tap (for emergency use) and the other was connected by short PVC tube to a two-necked 100 mL RBF immersed in dry-ice bath and equipped with dry-ice condenser. Membrane pump was connected to the top of the condenser via additional tap. Oxone (100 g) was added in 5 portions through the major inlet, each time followed by sealing and evacuation to ~150-300 mbar, until evolution of gas ceased (in about 10 min). 50-60 ml of yellow condensate was collected. After warming to room temperature to remove dissolved gasses, the solution was frozen and stored in a sealed flask at −20 °C.

Titration with *para*-methoxythioanisole (154.23 g/mol, 1.11 g/mL): To a solution of 4-MeO-thioanisole (40 μL) in 0.2 mL C_6D_6 was added 0.20 mL of DMDO solution in acetone. The mixture was shaken and allowed to stand for 10 min, then the solvents were stripped off under vacuum and the residue was analysed by ^{1}H NMR in C_6D_6. The ratio of *para*-methoxythioanisole to sulfoxide was 20:1, corresponding to a concentration of 0.072 M for the original DMDO solution.

Epoxidation of (*E*)-225 using DMDO

Stilbene (*E*)-**225** (285 mg, 0.855 mmol) was dissolved in acetone (10 mL) in an open flask and the solution of DMDO (17 mL, 0.072 M in acetone) was added at 0 °C. The water ice bath was allowed to slowly warm up and the solution was stirred at r.t. overnight, followed by concentration in vacuo and quick filtration through 3 cm of silica in benzene. Evaporation afforded 230 mg (77%) of epoxide **224** in the form of slowly crystallizing sticky paste that was immediately used in the next step.

5-Bromo-6-((2R,3R*)-3-(4-methoxyphenyl)oxiran-2-yl)benzo[d][1,3]dioxole* (**224**)



R_f 0.50 (hexane/EA 5:1), R_f 0.76 (benzene);

IR ν [cm^{-1}]: 3088 (w), 3048 (w), 2999 (w), 2969 (w), 2929 (w), 2835 (w), 1742 (w), 1683 (w), 1608 (w), 1513 (w), 1501 (m), 1476 (vs), 1440 (w), 1420 (w), 1392 (w), 1235 (vs), 1203 (w), 1172 (w), 1152 (m), 1111 (w), 1037 (s), 1021 (s), 977 (w), 933 (m), 903 (w), 881 (m), 858 (m), 839 (s), 812 (m), 784 (w), 758 (w), 671 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 7.20-7.15 (m, 2H, H-10), 6.99 (s, 1H, H-3/6), 6.80 (s, 1H, H-3/6), 6.79-6.70 (m, 2H, H-11), 5.17 (d, *J* = 1.4 Hz, 1H, OC*H*$_2$O), 5.14 (d, *J* = 1.3 Hz, 1H, OC*H*$_2$O), 4.16 (d, *J* = 1.9 Hz, 1H, H-7/8), 3.46 (d, *J* = 1.9 Hz, 1H, H-7/8), 3.26 (s, 3H, C12-OC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 160.4 (s, C-12), 148.5 (s, C-4/5), 148.3 (s, C-4/5), 131.2 (s, C-1/9), 129.3 (s, C-1/9), 127.3 (d, C-10), 114.4 (d, C-11), 112.4 (s, C-2), 112.7 (d, C-3/6), 106.6 (d, C-3/6), 101.8 (t, O*C*H$_2$O), 62.4 (d, C-7/8), 62.2 (d, C-7/8), 54.8 (q, O*C*H$_3$);

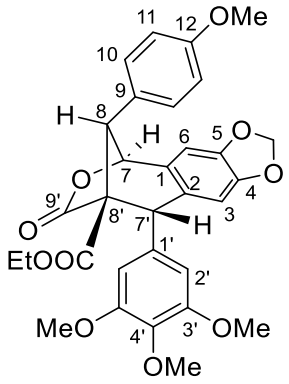
MS (ESI+) *m/z*, (%): 373/371 (100, $[M + Na]^+$), 349/451 (27, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{16}H_{13}O_4{}^{79}BrNa$ 370.98894; found: 370.98888; $[M + H]^+$ calcd. for $C_{16}H_{14}O_4{}^{79}Br$ 349.00700; found: 349.00677.

One-pot anionic annulation of 224 by the method of Florio et. al.

A solution of PhLi (0.42 mL, 1.8 M in Bu_2O, 0.756 mmol) was added dropwise at −78 °C to a solution of stilbene oxide **224** (220 mg, 0.63 mmol) in THF (4 mL). The resulting orange solution was stirred for 45 min. A solution of malonate (255 mg, 0.756 mmol) in THF (1.5 mL) was added dropwise, leading to slow discoloration of the mixture. After 30 min at −78 °C the reaction was warmed to 0 °C, followed by addition of EtOH (3 mL). HPLC/MS analysis (reverse phase, H_2O to MeCN, ESI+ detection) confirmed the formation of the desired product (*m/z* 563), although some of the non-cyclised intermediate after conjugate addition was still present (*m/z* 609). The reaction was stirred overnight at ambient temperature, then quenched with aqueous NH_4Cl and partitioned between saturated aqueous NH_4Cl (30 mL) and EA (40 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to afford 465 mg of crude product. Purification by flash chromatography (pure cyclohexane to cyclohexane/EA 1:1) afforded 148 mg (41%) of **229** as colourless crystals, mp 186-187 °C.

Ethyl (5S,8S*,9S*,11R*)-11-(4-methoxyphenyl)-7-oxo-9-(3,4,5-trimethoxyphenyl)-5,9-dihydro-5,8-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]oxepine-8(7H)-carboxylate* (**229**)



R_f 0.11 (hexane/EA 3:1);

IR ν [cm^{-1}]: 3025 (w), 2984 (w), 2944 (w), 2885 (w), 1737 (w), 1578 (w), 1502 (w), 1473 (m), 1441 (w), 1421 (w), 1389 (w), 1261 (w), 1234 (m), 1175 (w), 1113 (w), 1022 (m), 933 (m), 838 (s), 882 (w), 861 (w), 815 (w), 760 (w);

^{1}H NMR (401 MHz, $CDCl_3$): 6.81 (s, 1H, H-3), 6.80-6.74 (m, 4H, H-10, H-11), 6.70-6.05 (br. s, 2H, H-2'), 6.26 (s, 1H, H-6), 6.97-6.96 (m, 2H, OCH_2O), 5.46 (d, J = 5.0 Hz, 1H, H-7), 4.50 (d, J = 4.9 Hz, 1H, H-8), 4.49 (s, 1H, H-7'), 4.33-4.19 (m, 2H, OCH_2CH$_3$), 3.83 (s, 3H, C4'-OCH_3), 3.75(s, 9H, C12-OCH_3, C3'-OCH_3), 1.28 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 172.4 (s, C-9'), 168.8 (s, *C*OOEt), 159.2 (s, C-12), 153.0 (s, 2×C, C-3'), 149.1 (s, C-4/5), 146.8 (s, C-4/5), 137.3 (s, C-4'), 135.4 (s, C-1'), 132.1 (s, C-2), 129.3 (d, C-10), 126.9 (s, C-1), 124.6 (s, C-9), 114.2 (d, C-11), 110.8 (d, C-3), 107.7 (d, C-6), 101.6 (t, O*C*H$_2$O), 79.5 (d, C-7), 62.2 (t, O*C*H$_2$CH$_3$), 61.0 (q, C4'-O*C*H$_3$), 56.3 (q, 2×C, C3'-O*C*H$_3$), 55.3 (q, C12-O*C*H$_3$), 53.8 (d, C-8), 45.4 (d, C-7'), 14.2 (q, OCH$_2$*C*H$_3$), C-2' not detected at r.t. due to restricted rotation;

^{1}H NMR (401 MHz, C_6D_6): δ 6.91-6.87 (m, 1H, H-10), 6.85-6.65 (br. s, 2H, H-2'), 6.60-6.56 (m, 1H, H-11), 6.53 (s, 1H, H-3), 6.49 (s, 1H, H-6), 5.14-5.08 (m, 2H, OCH_2O), 4.95 (d, J = 5.0 Hz, 1H, H-7), 4.87 (s, 1H, H-7'), 4.50 (d, J = 4.9 Hz, 1H, H-8), 4.01-3.73 (m, 2H, OCH_2CH$_3$), 3.73 (s, 3H, C4'-OCH_3), 3.46 (s, 6H, C3'-OCH_3), 3.14 (s, 3H, C12-OCH_3), 0.88 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 172.2 (s, C-9'), 169.3 (s, *C*OOEt), 159.6 (s, C-12), 153.6 (s, 2×C, C-3'), 149.4 (s, C-4/5), 147.1 (s, C-4/5), 139.0 (s, C-4'), 135.7 (s, C-1'), 132.9 (s, C-2), 129.4 (d, C-10), 127.7 (s, C-1), 125.5 (s, C-9), 114.4 (d, C-11), 111.0 (d, C-3), 107.9 (d, C-6), 101.5 (t, O*C*H$_2$O), 79.2 (d, C-7), 61.9 (t, O*C*H$_2$CH$_3$), 60.4 (q, C4'-O*C*H$_3$), 55.9 (q, C3'-O*C*H$_3$), 54.7 (q, C12-O*C*H$_3$), 53.8 (d, C-8), 46.1 (d, C-7'), 14.0 (q, OCH$_2$*C*H$_3$), C-2' not detected at r.t. due to restricted rotation;

MS (ESI+) *m/z*, (%): 1147 (3, $[2M + Na]^+$), 601 (32, $[M + K]^+$), 585 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{31}H_{30}O_{10}Na$ 585.1731; found: 585.1727.

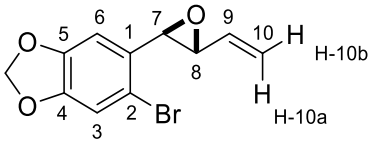
6.4.2. Rapid synthesis of neopodophyllotoxin core – racemic approach

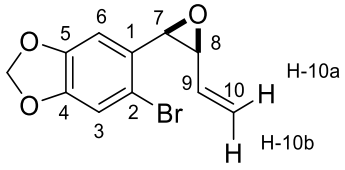
5-Bromo-6-[(2R,3R*)-3-vinyloxiran-2-yl]benzo[d][1,3]dioxole* and *5-bromo-6-[(2R*,3S*)-3-vinyloxiran-2-yl]benzo[d][1,3]dioxole* (**230**)

Following a published procedure,[193] allyl bromide (10.4 mL, 120 mmol) was added to a mixture of 6-bromopieronal (9.1 g, 40 mmol), K_2CO_3 (27.6 g, 200 mmol) and tetrahydrothiophene (0.71 mL) in *t*-BuOH (60 mL). The reaction vessel was sealed and stirred vigorously for 2 days at r.t. The solids were filtered off and washed with DCM (150 mL). Concentration of the filtrates under vacuum followed

by flash chromatography (pure cyclohexane to 20% EA) yielded 10.9 g (quant., dr 1.6:1) of **230** as a colourless oil. Due to limited stability, the epoxides were immediately used in the next step.

5-Bromo-6-[(2R,3R*)-3-vinyloxiran-2-yl]benzo[d][1,3]dioxole* and *5-bromo-6-[(2R*,3S*)-3-vinyloxiran-2-yl]benzo[d][1,3]dioxole* (**230**)





R_f 0.75 (hexane/EA 3:1);

IR ν [cm^{-1}]: 3087 (w), 2973 (w), 2900 (w), 2770 (w), 1502 (w), 1474 (vs), 1416 (m), 1251 (m), 1226 (s), 1111 (w), 1035 (s), 979 (w), 927 (s), 861 (m), 837 (m), 807 (w), 684 (w), 661 (w);

^{1}H (401 MHz, C_6D_6): δ 7.03 (s, 1H, H-3/6^{cis}), 6.82 (s, 1H, H-3/6^{trans}), 6.78 (s, 1H, H-3/6^{trans}), 6.76 (s, 1H, H-3/6^{cis}), 5.54 (ddd, *J* = 17.5, 10.4, 7.1 Hz, 1H, H-9^{cis}), 5.28-5.22 (m, 3H, H-9^{cis}, H-10a^{trans}), 5.12-5.15 (m, 4H, OC*H*$_2$O), 5.02 (ddd, *J* = 10.5, 1.4, 0.6 Hz, 1H, H-10b^{trans}), 4.96-4.91 (m, 1H, H-10b^{cis}), 4.05 (dd, *J* = 4.1, 0.6 Hz, 1H, H-7^{cis}), 3.95 (d, *J* = 1.8 Hz, 1H, H-7^{trans}), 3.40 (ddd, *J* = 6.8, 4.2, 1.1 Hz, 1H, H-8^{cis}), 2.88 (ddt, *J* = 7.2, 1.4, 0.7 Hz, 1H, H-8^{trans});

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 148.5 (s, C-4/5^{trans}), 148.3 (s, C-4/5^{cis}), 148.2 (s, C-4/5^{trans}), 147.7 (s, C-4/5^{cis}), 135.2 (d, C-9^{trans}), 132.2 (d, C-9^{cis}), 130.8 (s, C-1^{trans}), 129.0 (s, C-1^{cis}), 121.4 (t, C-10^{cis}), 119.3 (t, C-10^{trans}), 113.3 (s, C-2^{trans}), 113.1 (s, C-2^{cis}), 112.7 (d, C-3/6^{trans}), 112.6 (d, C-3/6^{cis}), 108.8 (d, C-3/6^{cis}), 106.5 (d, C-3/6^{trans}), 101.8 (t, O*C*H$_2$O^{trans}), 101.7 (t, O*C*H$_2$O^{cis}), 62.1 (d, C-8^{trans}), 60.2 (d, C-7^{trans}), 59.6 (d, C-7/8^{cis}), 59.5 (d, C-7/8^{cis});

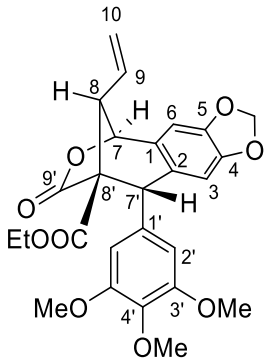
MS (EI+) *m/z*, (%): 270/268 (19, $[M]^{\cdot+}$), 215/231 (18, $[M - acryloyl]^+$), 189 (100, $[M - Br]^+$), 160 (24), 159 (23);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{11}H_9O_3{}^{79}Br$ 267.9735; found: 267.9731.

One-pot polar bicyclisation of 230

Epoxide **230** (5.11 g, 19 mmol) was dissolved in dry in benzene (30 mL). The solvent was evaporated, followed by drying under high vacuum. Under inert atmosphere, dry THF (160 mL) was added, and the flask was cooled to −78 °C. PhLi (12.1 mL, 21.8 mmol, 1.8 M in Bu_2O) was added over 2 min and the reddish mixture was stirred at −78 °C for 15 min. A solution of malonate **137** (7.39 g, 21.8 mmol) in THF (20 mL) was added dropwise over 4 min. The mixture was stirred at −78 °C for 30 min, then at r.t. for 2 h. Absolute EtOH (60 mL) was added, and the mixture was stirred at r.t. overnight. The mixture was partitioned between saturated aqueous NH_4Cl (200 mL) and EA (200 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The crude mixture contained the following compounds, as determined by ^{1}H NMR (concentration relative to **231a**): **231a** (1.00), **231b** (0.42), **233** (0.26), **234** (0.13), **232** (0.12). Purification by flash chromatography (cyclohexane/EA 10:1 to 2:1) yielded 4 fractions in order of increasing polarity: I) 4.71 g of an inseparable 2.7:1 mixture of **231a** and **233** (representing a non-isolated yield of 39% for **231a**); II) 1.60 g of a mixture of **231b**, **234** and **232**, further purified to obtain 300 mg of **232** (3.5%) as colourless solid and 1.10 g of a 3:1 inseparable mixture of **231b** and **234**; III) 0.51 g of predominantly **232**, further recrystallized (heptane/EA) to yield 250 mg of pure **232** (2.5%).

Ethyl (5S,8S*,9S*,11R*)-7-oxo-9-(3,4,5-trimethoxyphenyl)-11-vinyl-5,9-dihydro-5,8-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]oxepine-8(7H)-carboxylate* (**231a**)



R_f 0.21 (hexane/EA 5:1), R_f 0.84 (DCM/Et_2O 4:1);

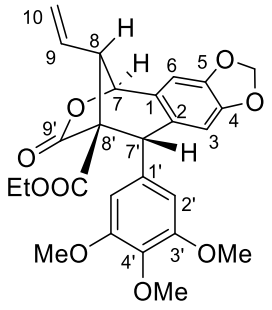
^{1}H NMR (401 MHz, C_6D_6): δ 6.85-6.62 (br. s, 2H, H-2'), 6.58 (s, 1H, H-3), 6.33 (s, 1H, H-6), 5.40 (ddd, *J* = 17.1, 10.4, 8.5 Hz, 1H, H-9), 5.22 (d, *J* = 1.3 Hz, 1H, OC*H*$_a$H$_b$O), 5.16 (d, *J* = 1.3 Hz, 1H, OCH$_a$*H*$_b$O), 5.01 (ddd, *J* = 17.1, 1.6, 1.0 Hz, 1H, H-10a), 4.94 (ddd, *J* = 10.4, 1.6, 1.0 Hz, 1H, H-10b), 4.87 (s, 1H, H-7'), 4.57 (d, *J* = 5.2 Hz, 1H, H-7), 3.94 (dq, *J* = 10.8, 7.1 Hz, 1H, OC*H*$_a$H$_b$CH$_3$), 3.82-3.74 (m, 1H, OCH$_a$*H*$_b$CH$_3$), 3.74 (s, 3H, C4'-OC*H*$_3$), 3.68-3.63 (m, 1H, H-8), 3.49 (s, 6H, C3'-OC*H*$_3$), 0.84 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 171.2 (s, C-9'), 168.2 (s, *C*OOEt), 153.6 (s, 2×C, C-3'), 149.4 (s, C-4/5), 146.9 (s, C-4/5), 139.3 (s, C-4'), 135.5 (s, C-1'), 132.4 (s, C-2), 130.3 (d, C-9), 127.1 (s, C-1), 121.7 (t, C-10), 110.8 (d, C-3), 110.1 (br. d, 2×C, C-2'), 108.0 (d, C-6), 101.4 (t, O*C*H$_2$O), 79.2 (d, C-7), 61.7 (t, O*C*H$_2$CH$_3$), 61.0 (s, C-8'), 60.4 (q, C4'-OC*H*$_3$), 56.0 (q, 2×C, C3'-OC*H*$_3$), 54.8 (d, C-8), 46.1 (d, C-7'), 14.0 (q, OCH$_2$C*H*$_3$);

MS (ESI+) *m/z*, (%): 521 (12, [M + K]$^+$), 505 (100, [M + Na]$^+$), 500 (9, [M + NH_4]$^+$), 483 (3, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{26}H_{26}O_9Na$ 505.1469; found: 505.1474.

Ethyl (5S,8S*,9S*,11S*)-7-oxo-9-(3,4,5-trimethoxyphenyl)-11-vinyl-5,9-dihydro-5,8-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]oxepine-8(7H)-carboxylate* (**231b**)



R_f 0.15 (hexane/EA 5:1), R_f 0.78 (DCM/Et_2O 4:1);

^{1}H NMR (401 MHz, C_6D_6): δ 6.63 (br. s, 2H, H-2'), 6.59 (d, *J* = 0.9 Hz, 1H, H-3), 6.33 (s, 1H, H-6), 5.87 (ddd, *J* = 17.0, 10.3, 9.4 Hz, 1H, H-9), 5.27 (d, *J* = 1.3 Hz, 1H, O*CH*$_2$O), 5.21 (d, *J* = 1.3 Hz, 1H, O*CH*$_2$O), 5.04 (d, *J* = 1.0 Hz, 1H, H-7'), 4.98 (ddd, *J* = 17.0, 1.5, 0.7 Hz, 1H, H-10), 4.93 (dd, *J* = 10.3, 1.5 Hz, 1H, H-10), 4.48 (s, 1H, H-7), 3.93 (dq, *J* = 10.7, 7.1 Hz, 1H, OCH$_a$*H*$_b$CH$_3$), 3.78 (dq, *J*

= 10.7, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.74 (s, 3H, C4'-OCH_3), 3.46 (br-s, 6H, C3'-OCH_3), 2.98 (d, *J* = 9.5 Hz, 1H, H-8), 0.83 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3);

$^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6): δ 169.6 (s, C-9'), 167.7 (s, *C*OOEt), 153.9 (s, 2×C, C-3'), 149.3 (s, C-4/5), 146.7 (s, C-4/5), 139.5 (s, C-4'), 135.3 (s, C-1'), 133.8 (d, C-9), 131.2 (s, C-2), 130.1 (s, C-1), 119.1 (t, C-10), 110.9 (d, C-3), 109.3 (d, 2×C, C-2'), 107.3 (d, C-6), 101.4 (t, OCH_2O), 79.7 (d, C-7), 62.2 (s, C-8'), 61.5 (t, OCH_2CH_3), 60.4 (d, C4'-OCH_3), 57.3 (q, C-8), 56.0 (q, 2×C, C3'-OCH_3), 52.1 (d, C-7'), 14.1 (q, OCH_2CH_3);

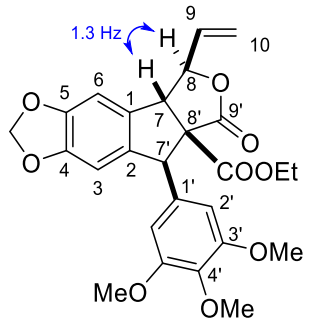
^1H NMR (401 MHz, $CDCl_3$): δ 6.72 (s, 1H, H-6), 6.40 (d, *J* = 1.0 Hz, 1H, H-3), 6.28 (br. s, 2H, H-2'), 5.97-5.88 (m, 1H, H-9), 5.95 (d, *J* = 1.3 Hz, 1H, OCH_2O), 5.94 (d, *J* = 1.3 Hz, 1H, OCH_2O), 5.31-5.24 (m, 2H, H-10), 4.99 (d, *J* = 1.0 Hz, 1H, H-7'), 4.94 (s, 1H, H-7), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 4.13 (dq, *J* = 10.8, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.83 (s, 3H, C4'-OCH_3), 3.74 (br. s, 6H, C3'-OCH_3), 3.33 (d, *J* = 9.4 Hz, 1H, H-8), 0.83 (t, J = 7.1 Hz, 3H, OCH_2CH_3);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.1 (s, C-9'), 167.3 (s, *C*OOEt), 152.8 (s, 2×C, C-3'), 149.0 (s, C-4/5), 146.5 (s, C-4/5), 137.8 (s, C-4'), 134.9 (s, C-1'), 132.8 (d, C-9), 130.3 (s, C-2), 129.3 (s, C-1), 120.1 (t, C-10), 110.6 (d, C-3), 108.0 (d, 2×C, C-2'), 107.2 (d, C-6), 101.6 (t, OCH_2O), 77.2 (d, C-7), 61.9 (s, C-8'), 61.8 (t, OCH_2CH_3), 60.9 (q, C4'-OCH_3), 57.2 (d, C-8), 56.3 (q, 2×C, C3'-OCH_3), 51.6 (d, C-7'), 14.3 (q, OCH_2CH_3);

MS (ESI+) *m/z*, (%): 505 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{26}H_{26}O_9Na$ 505.1469; found: 505.1463.

Ethyl (4bS,5R*,7aR*,8S*)-7-oxo-8-(3,4,5-trimethoxyphenyl)-5-vinyl-4b,8-dihydro-5H-furo[3',4':1,2]indeno[5,6-d][1,3]dioxole-7a(7H)-carboxylate* (**233**)

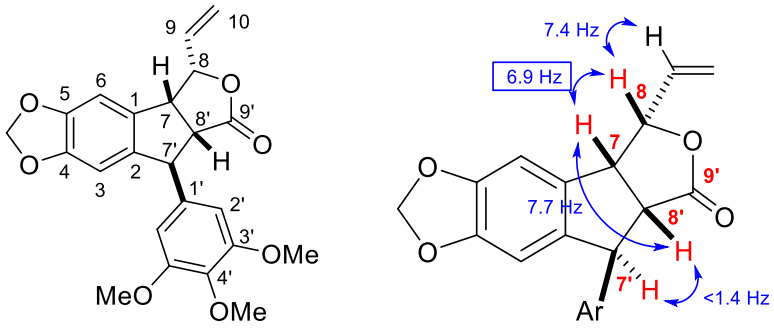


R_f 0.21 (hexane/EA 5:1), R_f 0.87 (DCM/Et_2O 4:1);

^1H (401 MHz, C_6D_6): δ 6.41 (d, *J* = 0.9 Hz, 1H, H-3/6), 6.36 (s, 1H, H-3/6), 6.21 (s, 2H, H-2'), 5.94 (ddd, *J* = 17.1, 10.5, 5.8 Hz, 1H, H-9), 5.31 (d, *J* = 1.3 Hz, 1H, OCH_aH_bO), 5.28 (dt, *J* = 17.2, 1.4 Hz, 1H, H-10a), 5.25 (d, *J* = 1.3 Hz, 1H, OCH_aH_bO), 5.16 (s, 1H, H-7'), 5.04-4.99 (m, 1H, H-10b), 4.79 (dq, *J* = 5.8, 1.3 Hz, 1H, H-8), 4.51 (dd, *J* = 1.3, 0.9 Hz, H-7), 3.76 (s, 3H, C4'-OCH_3), 3.66 (dq, *J* = 10.9, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.57 (dq, *J* = 10.9, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.35 (s, 6H, C3'-OCH_3), 0.68 (d, *J* = 7.1 Hz, 1H, OCH_2CH_3);

$^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6): δ 174.0 (s, C-9'), 166.7 (s, *C*OOEt), 154.0 (s, 2×C, C-3'),149.1 (s, C-4/5), 148.2 (s, C-4/5), 139.3 (s, C-1/2), 137.3 (s, C-4'), 136.3 (d, C-9), 136.1 (s, 1/2), 133.3 (s, C-1'), 117.3 (t, C-10), 106.8 (br. d, 2×C, C-2'), 105.9 (d, C-3/6), 104.0 (d, C-3/6), 101.6 (t, OCH_2O), 84.3 (d, C-8), 66.8 (s, H-8'), 62.0 (t, OCH_2CH_3), 60.5 (q, C4'-OCH_3), 59.7 (d, C-7'), 55.9 (q, 2×C, C3'-OCH_3), 53.5 (d, C-7), 13.6 (t, OCH_2CH_3);

(4bR,5S*,7aR*,8S*)-8-(3,4,5-Trimethoxyphenyl)-5-vinyl-4b,5,7a,8-tetrahydro-7H-furo[3',4':1,2]indeno[5,6-d][1,3]dioxol-7-one* **(234)**



Obtained in mixtures only. Relative configuration tentatively assigned on the basis of the value of the H7-H8 coupling constant (6.9 Hz).

R_f 0.15 (hexane/EA 5:1), R_f 0.67 (DCM/Et_2O 4:1);

^{1}H (401 MHz, C_6D_6): δ 6.66 (s, 1H, H-3/6), 6.48 (s, 1H, H-3/6), 6.25 (s, 2H, H-2'), 5.64 (ddd, *J* = 17.2, 10.5, 7.4 Hz, 1H, H-9), 5.32 (d, *J* = 1.2 Hz, 1H, O*CH*$_2$O), 5.28 (d, *J* = 1.3 Hz, 1H, O*CH*$_2$O), 5.13 (dt, *J* = 17.2, 1.3 Hz, 1H, H-10a), 4.92 (dt, *J* = 10.5, 1.2 Hz, 1H, H-10b), 4.80 (br. s, 1H, H-7'), 4.48 (ddt, *J* = 7.4, 6.9, 1.1 Hz, 1H, H-8), 3.83 (s, 3H, C4'-C*H*$_3$), 3.52 (ddt, *J* = 7.6, 6.8, 1.1 Hz, 1H, H-7), 3.37 (s, 6H, C3'-C*H*$_3$), 3.00 (dd, *J* = 7.7, 1.4 Hz, 1H, H-8');

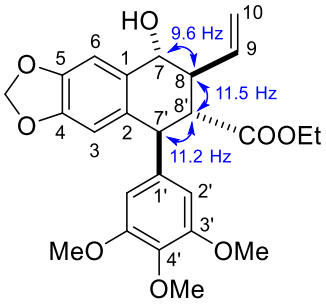
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 177.6 (s, C-9'), 154.6 (s, 2×C, C-3'), 149.1 (s, C-4/5), 148.0 (s, C-4/5), 140.3 (s, C-1/2/1'), 139.8 (s, C-1/2/1'), 138.7 (s, C-4'), 134.1 (d, C-9), 131.0 (s, C-1/2/1'), 118.6 (t, C-10), 106.8 (d, C-3/6), 106.2 (d, C-3/6), 105.4 (d, 2×C, C-2'), 101.6 (t, O*C*H$_2$O), 82.2 (d, C-8), 60.5 (q, C4'-*C*H$_3$), 56.0 (q, 2×C, C3'-*C*H$_3$), 55.2 (d, C-8'), 54.2 (d, C-7'), 49.5 (d, C-7);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.76 (s, 1H, H-3/6), 6.57 (s, 1H, H-3/6), 6.21 (s, 2H, H-2'), 5.97 (d, *J* = 1.3 Hz, 1H, OC*H*$_a$H$_b$O), 5.96 (d, *J* = 1.3 Hz, 1H, OCH$_a$*H*$_b$O), 5.69-5.87 (m, 1H, H-9), 5.50 (dt, *J* = 17.2, 1.2 Hz, 1H, H-10a), 5.43 (dt, *J* = 10.4, 1.0 Hz, 1H, H-10b), 5.16 (dt, *J* = 7.4, 1.1 Hz, 1H, H-8), 4.63 (t, *J* = 0.9 Hz, 1H, H-7'), 4.24-4.17 (m, 1H, H-7), 3.79 (s, 3H, C4'-C*H*$_3$), 3.76 (s, 6H, C3'-C*H*$_3$), 3.38 (dd, *J* = 7.7, 1.6 Hz, 1H, H-8');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 178.4 (s, C-9'), 153.6 (s, C-3'), 148.7 (s, C-4/5), 147.7 (s, C-4/5), 139.9 (s, C-1'), 138.8 (s, C-1/2), 137.1 (s, C-4'), 133.3 (d, C-9), 130.6 (s, C-1/2), 119.7 (t, C-10), 106.7 (d, C-3/6), 105.9 (d, C-3/6), 104.3 (d, C-2'), 101.7 (t, C-O*C*H$_2$O), 82.9 (d, C-8), 60.9 (q, C4'-*C*H$_3$), 56.3 (q, 2×C, C3'-*C*H$_3$), 55.3 (d, C-8'), 53.7 (d, C-7'), 49.3 (d, C-7);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{23}H_{22}O_7Na$ 433.12577; found: 433.12530.

Ethyl (7α,7'β,8α,8'β)-7-hydroxy-3',4',5'-trimethoxy-4,5-methylenedioxy-9a-homo-2,7'-cyclolign-9-eno-8'-oate (**232**)



Limited solubility in C_6H_6, Et_2O, well soluble in DCM, $CDCl_3$. Purified by precipitation from heptane/EA. Attempted recrystallization from C_6H_6, DCM/PE and $PhCF_3$/heptane resulted in fine cottony solid, unsuitable for X-ray. Relative configuration assigned based on ^{1}H-^{1}H coupling constants.

R_f 0.07 (hexane/EA 5:1), R_f 0.16 (hexane/EA 2:1), R_f 0.57 (DCM/Et_2O4:1);

^{1}H (401 MHz, $CDCl_3$): δ 7.12 (s, 1H, H-6), 6.30 (s, 2H, H-2'), 6.23 (d, *J* = 1.0 Hz, 1H, H-3), 5.90 (d, *J* = 1.4 Hz, 1H, OC*H*$_2$O), 5.89 (d, *J* = 1.4 Hz, 1H, OC*H*$_2$O), 5.74 (ddd, *J* = 17.1, 10.1, 9.4 Hz, 1H, H-9), 5.32 (ddd, *J* = 17.1, 1.7, 0.6 Hz, 1H, H-10a), 5.29 (dd, *J* = 10.1, 1.7, Hz, 1H, H-10b), 4.65 (br. d, *J* = 9.6 Hz, 1H, H-7), 4.27 (dt, *J* = 11.1, 1.4 Hz, 1H, H-7'), 3.96 (m, 2H, OC*H*$_2$CH$_3$), 3.83 (s, 3H, C4'-OC*H*$_3$), 3.79 (s, 6H, C3'-OC*H*$_3$), 2.87 (t, *J* = 11.4 Hz, 1H, H-8'), 2.64 (dt, *J* = 11.6, 9.5 Hz, 1H, H-8), 2.15 (br. s, 1H, C7-O*H*), 1.04 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.5 (s, *C*OOEt), 153.4 (s, 2×C, C-3'), 147.2 (s, C-4/5), 146.9 (s, C-4/5), 139.0 (s, C-1'), 137.1 (s, C-4'), 136.6 (d, C-9), 131.2 (s, C-1/2), 131.1 (s, C-1/2), 120.6 (d, C-10), 108.7 (d, C-3), 106.3 (d, C-6), 106.2 (d, 2×C, C-2'), 101.1 (t, O*C*H$_2$O), 71.6 (d, C-7), 61.0 (q, C4'-*C*H$_3$), 60.4 (t, O*C*H$_2$CH$_3$), 56.3 (q, 2×C, C3'-O*C*H$_3$), 53.8 (d, C-8'), 51.9 (d, C-8), 49.5 (d, C-7'), 14.3 (q, OCH$_2$*C*H$_3$);

^{1}H NMR (401 MHz, C_6D_6): δ 7.43 (d, *J* = 0.8 Hz, 1H, H-6), 6.58 (d, *J* = 0.8 Hz, 1H, H-3), 6.45 (s, 2H, H-2'), 5.57 (ddd, *J* = 17.0, 10.2, 9.2 Hz, 1H, H-9), 5.28 (d, *J* = 1.3 Hz, 1H, OC*H*$_2$O), 5.26 (d, *J* = 1.3 Hz, 1H, OC*H*$_2$O), 5.15 (dd, *J* = 17.0, 1.9 Hz, 1H, H-10a), 5.04 (dd, *J* = 10.2, 1.9, Hz, 1H, H-10b), 4.48 (dt, *J* = 11.1, 1.4 Hz, 1H, H-7'), 4.41 (ddt, *J* = 9.8, 5.3, 1.3 Hz, 1H, H-7), 3.89-3.75 (m, 2H, OC*H*$_2$CH$_3$), 3.81 (s, 3H, C4'-C*H*$_3$), 3.34 (s, 6H, C3'-C*H*$_3$), 3.03 (t, *J* = 11.4 Hz, 1H, H-8'), 2.67 (dt, *J* = 11.6, 9.5 Hz, 1H, H-8), 1.61 (d, *J* = 5.3 Hz, 1H, C7-O*H*), 0.78 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 172.0 (s, *C*OOEt), 154.0 (s, C-3'), 147.4 (s, C-4/5), 147.1 (s, C-4/5), 138.3 (s, C-1'), 137.1 (s, C-4'), 137.1 (d, C-9), 131.9 (s, C-1/2), 131.1 (s, C-1/2), 119.2 (d, C-10), 108.4 (d, C-3), 106.7 (d, C-2'), 106.6 (d, C-6), 100.8 (t, O*C*H$_2$O), 71.3 (d, C-7), 60.1 (q, C4'-*C*H$_3$), 59.6 (t, O*C*H$_2$CH$_3$), 55.5 (q, 2×C, C3'-O*C*H$_3$), 54.1 (d, C-8'), 51.7 (d, C-8), 49.7 (d, C-7'), 13.7 (q, OCH$_2$*C*H$_3$);

MS (ESI+) *m/z*, (%): 935 (7, [2M + Na]$^+$), 495 (11, [M + K]$^+$), 479 (100, [M + Na]$^+$), 439 (49, [M + H – H_2O]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{25}H_{28}O_8Na$ 479.16764; found: 479.16779.

6.4.3. Towards asymmetric synthesis of (2-fluoro)neopodophyllotoxin

Synthesis of organocatalysts

Isoselenocineole (**241**)

Prepared following a published procedure [201] from (*R*)-(+)-limonene (20 mL, 123 mmol), γ-terpinene (23 mL, 143 mmol) and black Se (8.0 g, 101 mmol). Yield 10 g (37%) of **241** as a yellowish liquid, bp 69-71 ° at 2.5 mbar.

IR (film) $\tilde{\nu}$[cm^{-1}]: 2940 (vs), 2918 (s), 2885 (s), 2868 (s), 1454 (vs), 1384 (w), 1365 (m), 1334 (w), 1301 (w), 1281 (w), 1225 (w), 1213 (w), 1195 (w), 1165 (w), 1149 (w), 1133 (s), 1112 (w), 1085 (m), 1065 (m), 1043 (w), 1018 (w), 979 (w), 932 (w), 863 (w), 804 (w), 704 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 3.72 (t, *J* = 4.0, 1H), 2.43 (tt, *J* = 13.9, 6.0 Hz, 1H), 2.34 (dt, *J* = 12.6, 1.6 Hz, 1H), 2.15-2.09 (m 1H), 2.03-1.94 (m, 1H), 1.83 (q, *J* = 1.8 Hz, 1H), 1.63 (s, 3H, SeCC*H*$_3$), 1.69-1.59 (m, 1 H), 1.54 (s, 3H, SeCC*H*$_3$), 1.56-1.47 (m, 1 H), 1.22-1.15 (m, 1H), 1.12 (d, *J* = 7.7 Hz, 3H, CHC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 50.4 (s), 50.0 (d), 48.9 (d), 36.2 (t), 35.8 (q), 35.5 (d), 27.1 (q), 24.6 (t), 23.8 (t), 18.9 (q);

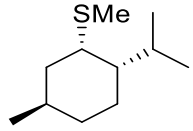
^{1}H NMR (401 MHz, C_6D_6): δ 3.47 (t, *J* = 4.0, 1 H), 2.55 (tt, *J* = 13.9, 5.9 Hz, 1H), 2.06 (dt, *J* = 12.5, 1.6 Hz, 1H), 2.00-1.93 (m 1 H), 1.93-1.84 (m, 1H), 1.52 (s, 3H, SeCC*H*$_3$), 1.49-1.44 (m, 1H), 1.47 (s, 3H, SeCC*H*$_3$), 1.43-1.39 (m, 1H), 1.27 (tdd, *J* = 14.2, 5.6, 3.4 Hz, 1H), 1.08-1.02 (m, 1H), 0.89 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 49.62 (s), 49.58 (d), 49.0 (d), 36.2 (t), 35.9 (q), 35.8 (d), 27.1 (q), 24.9 (t), 23.9 (t), 18.7 (q);

MS (EI+) *m/z*, (%): 218 (29, $[M]^{+\cdot}$), 137 (58, $[M - SeH]^{+}$), 121 (19, $[M - SeH_2 - Me]^{+}$), 95 (42, [M – SeH_2 – propenyl]), 81 (100), 67 (20), 55 (9);

HRMS (EI+) *m/z*: $[M + Na]^{+}$ calcd. for $C_{10}H_{18}{}^{80}Se$ 218.0568; found: 218.0568.

((1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl)(methyl)sulfane (**242**)



Prepared following a published procedure [202] from (–)-menthol tosylate (6.2 g, 20 mmol) using MeSNa (2.8 g, 40 mmol). Yield 1.67 g (44%) as a colourless oil.

IR (film) $\tilde{\nu}$[cm^{-1}]: 2946 (s), 2912 (vs), 2867 (m), 2839 (m), 1474 (w), 1455 (m), 1444 (m), 1382 (w), 1366 (w), 1314 (w), 1297 (w), 1281 (w), 1264 (w), 1241 (w), 1190 (w), 1169 (w), 1140 (w), 1125 (w), 1091 (w), 1061 (w), 1002 (w), 986 (w), 955 (w), 863 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 3.01 (qd, *J* = 3.2, 1.5 Hz, 1H, C*H*SCH$_3$), 2.06 (s, 3H, SC*H*$_3$), 1.96 (dtd, *J* = 13.2, 3.3, 2.2 Hz, 1H), 1.94-1.84 (m, 1H), 1.75-1.59 (m, 3H), 1.21-1.02 (m, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.88-0.81 (m, 1H);

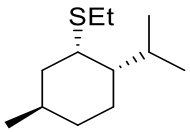
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 49.1 (d), 48.9 (d, *C*HSCH$_3$), 39.9 (t), 35.6 (t), 30.3 (d), 26.6 (d), 26.2 (t), 22.4 (q, *C*H$_3$), 21.3 (q, *C*H$_3$), 20.9 (q, *C*H$_3$), 15.3 (q, S*C*H$_3$);

MS (EI+) *m/z*, (%): 186 (34, $[M]^{\cdot+}$), 138 (35, $[M - MeSH]^{\cdot+}$), 123 (22, $[M - MeSH - Me]^{+}$), 95 (100, $[M - MeSH - i\text{-}Pr]^{+}$), 83 (58), 81 (67), 67 (40), 55 (47);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{11}H_{22}SO$ 186.1437; found: 186.1437;

α_D^{20} = +94.2 (c 0.467, $CHCl_3$).

Ethyl((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)sulfane (**243**)



Prepared following a published procedure [202] from (–)-menthol tosylate (6.2 g, 20 mmol) using EtSH (4.4 mL, 60 mmol) and K_2CO_3 (6.9 g, 50 mmol) in DMF (15 mL). Yield 1.31 g (32%) as a colourless oil.

IR (film) $\tilde{\nu}$[cm^{-1}]: 2946 (s), 2915 (vs), 2868 (s), 2839 (m), 1474 (w), 1454 (s), 1376 (w), 1366 (w), 1298 (w), 1281 (w), 1262 (m), 1239 (w), 1189 (w), 1169 (w), 1140 (w), 1125 (w), 1001 (w), 983 (w), 935 (w), 862 (w), 784 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 3.03 (qd, *J* = 3.2, 1.4 Hz, 1H, C*H*SCH_2CH_3), 2.39-2.24 (m, 2H, SCH_2CH_3), 2.15 (ddtd, *J* = 15.0, 11.9, 6.6, 3.1 Hz, 1H), 1.93-1.82 (m, 2H), 1.72-1.63 (m, 2H), 1.34 (tdd, *J* = 13.1, 12.2, 4.0 Hz, 1H), 1.11 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 1.09-1.03 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.99-0.93 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.87-0.75 (m, 1H);

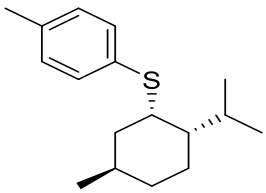
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 49.3 (d, *C*$HSCH_2CH_3$), 46.3 (d), 41.2 (t), 35.8 (t), 30.3 (d), 26.7 (d), 26.4 (t), 25.7 (t, SCH_2CH_3), 22.6 (q), 21.3 (q), 21.0 (q), 15.2 (q, SCH_2CH_3);

MS (EI+) *m/z*, (%): 200 (28, $[M]^{\cdot+}$), 138 (34, $[M - EtSH]^{\cdot+}$), 123 (27, $[M - EtSH - Me]^{+}$), 115 (14, $[M]^{\cdot+}$), 95 (100, $[M - EtSH - i\text{-}Pr]^{+}$), 83 (47), 81 (63), 67 (32), 55 (38);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{12}H_{24}S$ 200.1593; found: 200.1594;

α_D^{20} = +103.6 (c 0.505, $CHCl_3$).

((1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl)(p-tolyl)sulfane (**244**)



Prepared by the same procedure as **243** from (–)-menthol tosylate (6.2 g, 20 mmol) using *p*-TolSH (3.73 g, 30 mmol) and K_2CO_3 (5.53 g, 40 mmol) in DMF (20 mL). Yield 2.27 g (43%) as a colourless oil.

IR (film) $\tilde{\nu}$[cm^{-1}]: 3070 (w), 3018 (w), 2945 (s), 2918 (s), 2868 (m), 2839 (m), 1491 (m), 1474 (w), 1454 (w), 1444 (w), 1383 (w), 1366 (w), 1297 (w), 1280 (w), 1239 (w), 1189 (w), 1091 (w), 1018 (w), 984 (w), 863 (w), 808 (vs);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.32-7.29 (m, 2H), 7.10-7.08 (m, 2H), 3.56 (qd, *J* = 3.3, 1.3 Hz, 1H, C*H*S*p*-Tol), 2.32 (s, 3H, Ar-CH_3), 2.04 (dddt, *J* = 14.1, 12.1, 6.6, 3.3 Hz, 1H), 1.88 (dtd, *J* = 13.5, 3.3, 2.0 Hz, 1H), 1.82-1.71 (m, 3H), 1.32-1.11 (m, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.95-0.87 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 136.5 (s), 133.1 (s), 132.1 (d), 129.8 (d), 50.6 (d), 49.0 (d), 40.6 (t), 35.6 (t), 30.3 (d), 26.3 (d), 22.3 (q), 21.3 (q), 21.2 (q), 20.8 (q);

MS (EI+) *m/z*, (%): 262 (15, $[M]^{\cdot+}$), 124 (100, [*p*-TolSH]$^{\cdot+}$), 95 (22), 93 (22), 83 (30), 69 (16), 55 (25);

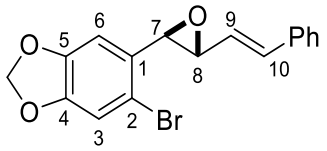
HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd. for $C_{17}H_{26}S$ 262.1750; found: 262.1752;

α_D^{20} = +91.3 (c 0.437, $CHCl_3$).

Asymmetric Corey-Chaykovsky epoxidation using cinnamyl bromide

Cinnamyl bromide (296 mg, 1.50 mmol), K_2CO_3 (242 mg, 1.75 mmol), isothiocineole (**ITC**) (17 mg, 0.1 mmol), *para*-xylene (12 µL, 0.10 mmol) and 6-bromopiperonal (114 g, 0.50 mmol) were added to a screw-top flask with a large stirring bar, followed by *t*-BuOH (0.8 mL) and DCM (0.2 mL). The flask was sealed, covered in aluminium foil and stirred at r.t. for 42 h. The reaction progress was monitored by taking small aliquots, diluting with C_6D_6, filtering and measuring ^{1}H NMR (integration vs. *para*-xylene internal standard). Dry benzene was added (5 mL), following filtration of the suspension, concentration, and flash chromatography (cyclohexane/EA 50:1 to 9:1) to yield 86.5 mg of **240** (50%, dr 40:1), 14% ee by chiral HPLC (hexane/*i*-Pr 99.3:0.7, 0.75 mL/min).

5-bromo-6-((2R,3R*)-3-((E)-styryl)oxiran-2-yl)benzo[d][1,3]dioxole* (**240**)



R_f 0.60 (cyclohexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3059 (w), 3026 (w), 2961 (w), 2900 (w), 1501 (w), 1474 (vs), 1412 (w), 1391 (w), 1362 (w), 1248 (m), 1226 (m), 1111 (w), 1035 (s), 963 (m), 932 (m), 869 (w), 838 (w), 825 (w), 743 (s), 691 (s);

^{1}H NMR (401 MHz, C_6D_6): δ 7.15-7.01 (m, 5H, Ph), 6.93 (d, *J* = 0.7 Hz, 1H, H-6), 6.81 (s, 1H, H-3), 6.56 (d, *J* = 16.0 Hz, 1H, H-10), 5.94 (dd, *J* = 16.0, 7.5 Hz, 1H, H-9), 5.17 (d, *J* = 1.3 Hz, 1H, C4-OC*H*$_a$H$_b$O), 5.14 (d, *J* = 1.3 Hz, 1H, C4-OCH$_a$*H*$_b$O), 4.12 (d, *J* = 1.9 Hz, 1H, H-7), 3.07 (ddd, *J* = 7.6, 1.9, 0.7 Hz, 1H, H-8);

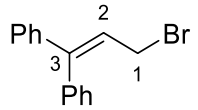
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 148.5 (s, C-4/5), 148.3 (s, C-4/5), 136.5 (s, Ph^{ipso}), 134.9 (d, C-10), 131.0 (s, C-1), 128.8 (d, 2×C, Ph), 128.4-127.7 (d, Ph^{para}, overlaps with solvent), 127.0 (d, 2×C, Ph), 126.2 (d, C-9), 113.4 (s, C-2), 112.8 (d, C-3), 106.6 (d, C-6), 101.8 (t, C4-O*C*H$_2$O), 62.5 (d, C-8), 60.6 (d, C-7);

MS (ESI+) *m/z*, (%): 387/385 (80/100, $[M + Na + H_2O]^+$), 369/367 (29/30, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{17}H_{13}{}^{79}BrO_3Na$ 366.99403; found: 366.99368.

3,3-Diphenylallyl bromide (**246**)

A solution of vinylmagnesium bromide (50 mL, 50 mmol, 1 M in THF) was added toa solution of benzophenone (7.29 g, 40 mmol) in dry THF (40mL) at r.t. The mixture was stirred for 2 days at r.t., then a saturated solution of potassium sodium tartrate was (25 mL) was added slowly. The mixture was partitioned between water (150 mL) and a 1:1 mixture of Et_2O/PE (250 mL), the organic phase was separated, washed with brine (25 mL), dried over Na_2SO_4 and concentrated to yield a yellowish oil. The crude oil was dissolved in Et2O (40 mL) and cooled to 0 °C. Phosphorus trichloride (4.1 mL, 44 mmol) was added slowly. The reaction flask was covered by aluminium foil and stirred for 3 h at 0 °C, then poured onto water ice. Et_2O (250 mL) was added. Still cold, the mixture was transferred to separatory funnel and the phases were separated. The organic phase was washed with water (100 mL), dried over N_2SO_4 (1 h, in the dark), concentrated and purified by flash chromatography (pure PE) to yield 7.25 g of **246** (66%) as a colourless oil, that solidified in the freezer, mp 41 °C.



R_f 0.6 (hexane);

IR (film) $\tilde{\nu}$[cm^{-1}]: (3080 (w), 3055 (w), 3021 (w), 2962 (w), 2922 (w), 2852 (w), 1620 (w), 1598 (w), 1574 (w), 1489 (m), 1443 (m), 1429 (w), 1357 (w), 1206 (m), 1149 (w), 1074 (w), 1029 (w), 936 (w), 886 (w), 843 (w), 770 (m), 758 (s), 696 (vs), 657 (w), 633 (w);

^{1}H NMR (401 MHz, C_6D_6): δ 7.18-7.00 (m, 10H, Ph), 6.11 (t, *J* = 8.6 Hz, 1H, H-2), 3.72 (d, *J* = 8.6 Hz, 2H, H-1);

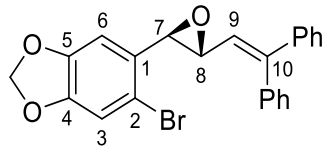
^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 146.4 (s, C-3), 141.6 (s, Ph^{ipso}), 138.6 (s, Ph^{ipso}), 128.7 (d, Ph), 128.5 (d, Ph), 128.11 (d, Ph), 128.08 (d, Ph), 128.0 (d, Ph), 124.2 (d, H-2), 31.0 (t, H-1);

MS (APCI+) *m/z*, (%): 193 (100, [M – Br]$^+$).

Asymmetric Corey-Chaykovsky epoxidation using 3,3-diphenylallyl bromide (246)

Bromide **246** (7.07 g, 25.9 mmol), K_2CO_3 (9.2 g, 67 mmol), isothiocineole (**ITC**) (315 mg, 1.85 mmol) and 6-bromopiperonal (4.24 g, 18.5 mmol) were added to a screw-top flask with a large stirring bar, followed by *t*-BuOH (37 mL) and DCM (7.5 mL). The flask was sealed, covered in aluminium foil and stirred at r.t. Monitoring by ^{1}H NMR showed 35% conversion after 14 h, 86% after 98 h and finally 95% after 168 h. Dry benzene was added (250 mL), followed by filtration of the suspension through a column of sand (7 cm) and Na_2SO_4 (4 cm). Additional benzene (250 mL) was used to wash the column. The clear filtrate was concentrated, dried under vacuum, and used immediately in the next step. Dr of **247** by ^{1}H NMR: *trans/cis* 6:1. The enantiomers of **247** could not be separated by HPLC, the enantiomeric excess (49%) was established after the next step. The absolute configuration of **247** was not assigned.

5-bromo-6-((2R,3R*)-3-(2,2-diphenylvinyl)oxiran-2-yl)benzo[d][1,3]dioxole* (**247**)



R_f 0.10 (cyclohexane/Et_2O 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3056 (w), 3028 (w), 2972 (w), 2897 (w), 1499 (w), 1474 (vs), 1444 (w), 1418 (w), 1390 (w), 1363 (w), 1250 (m), 1224 (m), 1194 (w), 1111 (w), 1074 (w), 1035 (s), 976 (w), 934 (w), 870 (w), 839 (w), 762 (s), 730 (w), 696 (vs), 677 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H, Ph), 7.23-7.18 (m, 2H, Ph), 7.10-7.00 (m, 5H, Ph), 6.97 (tt, *J* = 7.0, 1.4 Hz, 1H, Ph^{para}), 6.76 (s, 1H, H-3/6), 6.75 (s, 1H, H-3/6), 5.91 (d, *J* = 8.7 Hz, 1H, H-9), 5.09 (d, *J* = 1.4 Hz, 1H, C4-OC$H_a$$H_b$O), 5.06 (d, *J* = 1.4 Hz, 1H, C4-OC$H_a$$H_b$CO), 4.23 (d, *J* = 1.9 Hz, 1H, H-7), 3.42 (dd, *J* = 8.7, 2.0 Hz, 1H, H-8);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.5 (s, C-4/5), 148.4 (s, C-4/5), 148.2 (s, C-10), 141.9 (s, Ph^{ipso}), 139.2 (s, Ph^{ipso}), 130.7 (s, C-1), 130.6 (d, 2×C, Ph), 128.57 (d, 2×C, Ph), 128.56 (d, 2×C, Ph), 128.21 (d, 2×C, Ph), 128.20 (d, Ph^{para}), 128.1 (d, Ph^{para}), 126.2 (d, C-9), 113.0 (s, C-2), 112.6 (d, C-3/6), 106.5 (d, C-3/6), 101.7 (t, C4-O*C*H_2O), 60.6 (d, C-7), 60.5 (d, C-8);

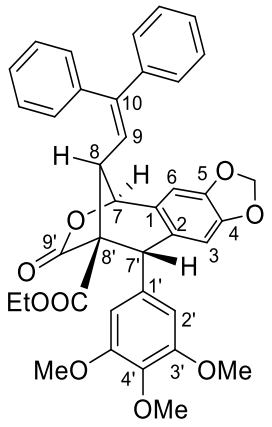
MS (ESI+) *m/z*, (%): 867/865/863 (3/5/3, $[2M + Na]^+$), 463/461 (33/48, $[M + Na + H_2O]^+$), 445/443 (96/100, $[M + Na]^+$), 423/421 (24/26, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{23}H_{17}{}^{79}BrO_3Na$ 443.02533; found: 443.02607.

One-pot polar bicyclisation of epoxide 247

Crude epoxide **247** (<18.5 mmol, *trans/cis* 6:1) from the previous step was dissolved in dry benzene (5 mL), followed by evaporation, and drying under high vacuum. Dry THF (200 mL) was added, and the solution was cooled to –78 °C. PhLi (12.3 mL, 22.2 mmol, 1.8 M in Bu_2O) was added dropwise, followed by stirring for 25 min at –78 °C. A solution of malonate **137** (7.51 mg, 22.2 mmol) in THF (15 mL) was added dropwise, followed by stirring for 30 min. at –78 °C. The reaction was warmed up to r.t. and stirred for 2 h. Absolute EtOH (40 mL) was added, followed by stirring for 16 h. The solvent was evaporated using rotary evaporator to reduce the volume to 1/3 of the original volume. The mixture was partitioned between 5% HCl (450 mL) and EA (300 mL). The aqueous phase was extracted with fresh EA (200 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (cyclohexane/EA 20:1 to 2:1) to yield 3.993 g of **248a/b** (38% over 2 steps, dr 3.5:1) as a yellow amorphous solid and 1.94 g of **249** (16%) as a yellow solid. **249** was separated by chiral HPLC (Hexane:*i*-PrOH 90:10, 1.50 ml/min) giving 49% ee.

Ethyl (5S,8S*,9S*,11R*)-11-(2,2-diphenylvinyl)-7-oxo-9-(3,4,5-trimethoxyphenyl)-5,9-dihydro-5,8-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]oxepine-8(7H)-carboxylate* (**248a**)



R_f 0.35 (Tol/Et_2O 4:1);

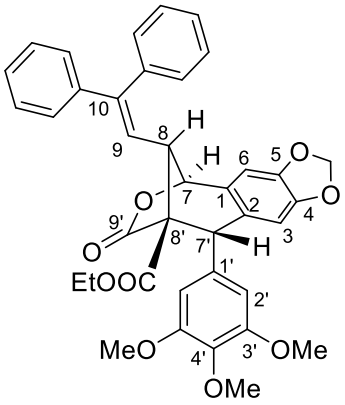
^{1}H NMR (401 MHz, C_6D_6): δ 7.22-6.87 (m, 10H, Ph), 6.91-6.73 (br. s, 2H, H-2'), 6.72 (s, 1H, H-3), 6.41 (s, 1H, H-6), 6.05 (d, *J* = 10.1 Hz, 1H, H-9), 5.32 (s, 1H, H-7'), 5.20 (s, 2H, C4-OC*H*$_2$O), 4.74 (d, *J* = 5.2 Hz, 1H, H-7), 4.25 (dd, *J* = 10.2, 5.2 Hz, 1H, H-8), 3.74 (s, 3H, C4'-OC*H*$_3$), 3.81-3.67 (m, 2H, OC*H*$_2$CH$_3$), 3.51 (br. s, 6H, C3'-OC*H*$_3$), 0.69 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 170.9 (s, C-9'), 168.4 (s, *C*OOEt), 153.7 (s, 2×C, C-3'), 150.2 (s, C-10), 149.5 (s, C-4/5), 147.0 (s, C-4/5), 142.0 (s, Ph^{ipso}), 139.6 (s, Ph^{ipso}), 139.3 (s, C-4'), 135.6 (s, C-1'), 132.3 (s, C-2), 129.7 (d, 2×C, Ph), 128.9 (d, 2×C, Ph), 128.7 (d, 2×C, Ph), 128.4 (d, Ph^{para}), 128.1 (d, Ph^{para}), 127.9 (d, 2×C, Ph), 127.4 (s, C-1), 119.6 (d, C-9), 110.9 (d, C-3), 110.2 (br. d, 2×C, C-2'), 108.2 (d, C-6), 101.5 (t, O*C*H$_2$O), 79.5 (d, C-7), 61.9 (t, O*C*H$_2$CH$_3$), 61.3 (s, C-8'), 60.4 (q, C4'-OC*H*$_3$), 56.0 (q, 2×C, C3'-OC*H*$_3$), 50.7 (d, C-8), 46.2 (d, C-7'), 13.7 (q, OCH$_2$C*H*$_3$);

MS (ESI+) *m/z*, (%): 1291 (11, [2M + Na]$^+$), 657 (100, [M + Na]$^+$), 652 (4, [M + NH$_4$]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{38}H_{34}O_9Na$ 657.20950; found: 657.21008.

Ethyl (5S,8S*,9S*,11S*)-11-(2,2-diphenylvinyl)-7-oxo-9-(3,4,5-trimethoxyphenyl)-5,9-dihydro-5,8-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]oxepine-8(7H)-carboxylate* (**248b**)

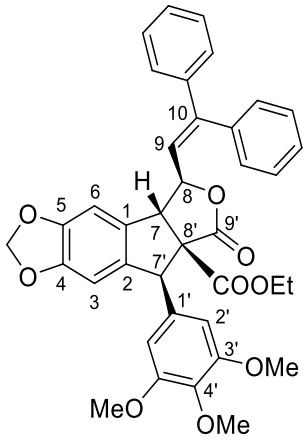


R_f 0.35 (Tol/Et$_2$O 4:1);

^{1}H NMR (401 MHz, C_6D_6): δ 7.26-6.87 (m, 10H, Ph), 6.62-6.53 (br. s, 2H, H-2'), 6.50 (d, *J* = 10.0 Hz, 1H, H-9), 6.35 (s, 2H, H-3, H-6), 5.20 (s, 1H, C4-OC*H*$_a$H$_b$O), 5.17 (s, 1H, C4-OCH$_a$*H*$_b$O), 4.95 (d, *J* = 1.0 Hz, 1H, H-7'), 4.62 (s, 1H, H-7), 3.96 (dq, *J* = 10.7, 7.1 Hz, 1H, OC*H*$_a$H$_b$CH$_3$), 3.80-3.67 (m, 2H, OC*H*$_a$H$_b$CH$_3$, H-8), 3.73 (s, 3H, C4'-OC*H*$_3$), 3.45 (br. s, 6H, C3'-OC*H*$_3$), 0.78 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 170.3 (s, C-9'), 168.2 (s, *C*OOEt), 153.8 (s, 2×C, C-3'), 149.2 (s, C-4/5), 146.6 (s, C-4/5), 146.0 (s, C-10), 141.7 (s, Ph^{ipso}), 139.3 (s, Ph^{ipso}), 139.3 (s, C-4'), 135.3 (s, C-1'), 131.1 (s, C-2), 130.1 (d, 2×C, Ph), 130.0 (s, C-1), 128.9 (d, 2×C, Ph), 128.7 (d, 2×C, Ph), 128.6 (d, Ph^{para}), 128.4 (d, Ph^{para}), 127.7 (d, 2×C, Ph), 123.6 (d, C-9), 111.1 (d, C-3), 109.3 (br. d, 2×C, C-2'), 107.0 (d, C-6), 101.3 (t, O*C*H$_2$O), 80.7 (d, C-7), 62.5 (s, C-8'), 61.8 (t, O*C*H$_2$CH$_3$), 60.4 (q, C4'-OC*H*$_3$), 56.0 (q, 2×C, C3'-OC*H*$_3$), 53.8 (d, C-8), 51.6 (d, C-7'), 14.1 (q, OCH$_2$C*H*$_3$);

Ethyl (4bS,5R*,7aR*,8S*)-5-(2,2-diphenylvinyl)-7-oxo-8-(3,4,5-trimethoxyphenyl)-4b,8-dihydro-5H-furo[3',4':1,2]indeno[5,6-d][1,3]dioxole-7a(7H)-carboxylate* (**249**)



R_f 0.45 (Tol/Et_2O 4:1);

^{1}H (401 MHz, C_6D_6): δ 7.27-7.03 (m, 10 Ph), 7.08 (s, 1H, H-3/6), 6.49 (s, 1H, H-3/6), 6.38 (d, *J* = 9.3 Hz, 1H, H-9), 6.36 (s, 2H, H-2'), 5.67 (dd, *J* = 9.4, 5.7 Hz, 1H, H-8), 5.33 (d, *J* = 1.3 Hz, 1H, OCH_aH_bO), 5.27 (s, 1H, H-7'), 5.21 (d, *J* = 1.3 Hz, 1H, OCH_aH_bO), 4.88 (d, *J* = 5.7 Hz, H-7), 3.74 (s, 3H, C4'-CH_3), 3.59 (dq, *J* = 11.1, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.40 (dq, *J* = 11.1, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.35 (s, 6H, C3'-CH_3), 0.52 (d, *J* = 7.1 Hz, 1H, OCH_2CH_3);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 173.7 (s, C-9'), 166.0 (s, *C*OOEt), 154.1 (s, 2×C, C-3'), 149.4 (s, C-4/5), 148.6 (s, C-4/5), 147.4 (s, C-10), 140.9 (s, Ph^{ipso}), 139.5 (s, C-1), 138.9 (s, 2×C, C-4', Ph^{ipso}), 136.9 (s, C-1'), 129.6 (d, 2×C, Ph), 129.4 (s, C-2), 128.9 (d, 2×C, Ph), 128.7 (d, 2×C, Ph), 128.6 (d, Ph^{para}), 128.4 (d, Ph^{para}), 128.0 (d, 2×C, Ph), 123.6 (d, C-9), 106.5 (br. d, 2×C, C-2'), 106.4 (d, C-3/6), 106.3 (d, C-3/6), 101.6 (t, C4-O*C*H_2O), 79.4 (d, C-8), 69.8 (s, H-8'), 62.0 (t, O*C*H_2CH_3), 60.5 (q, C4'-*C*H_3), 58.3 (d, C-7'), 55.9 (q, 2×C, C3'-*C*H_3), 54.1 (d, C-7), 13.5 (q, OCH_2*C*H_3);

^{1}H (401 MHz, CD_3CN): δ 7.53-7.32 (m, 10 Ph), 6.90 (s, 1H, H-3/6), 6.56 (s, 1H, H-3/6), 6.26 (s, 2H, H-2'), 6.12 (d, *J* = 9.2 Hz, 1H, H-9), 5.93 (d, *J* = 1.0 Hz, 1H, OCH_aH_bO), 5.91 (d, *J* = 1.0 Hz, 1H, OCH_aH_bO), 5.27 (dd, *J* = 9.1, 5.6 Hz, 1H, H-8), 4.78 (s, 1H, H-7'), 4.69 (d, *J* = 5.6 Hz, H-7), 3.81 (dq, *J* = 10.8, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.77-3.67 (m, 1H, $OCH_aH_bCH_3$), 3.72 (s, 6H, C3'-CH_3), 3.64 (s, 3H, C4'-CH_3), 0.80 (d, *J* = 7.1 Hz, 1H, OCH_2CH_3);

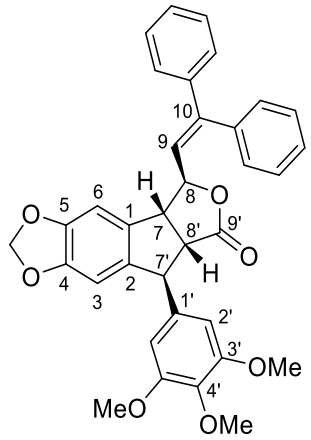
^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 174.7 (s, C-9'), 166.3 (s, *C*OOEt), 154.2 (s, 2×C, C-3'), 149.9 (s, C-4/5), 148.9 (s, C-4/5), 148.0 (s, C-10), 141.6 (s, Ph^{ipso}), 139.5 (s, Ph^{ipso}), 139.3 (s, C-1), 138.2 (s, C-4'), 137.6 (s, C-1'), 130.3 (d, 2×C, Ph), 129.9 (s, C-2), 129.6 (d, 2×C, Ph), 129.5 (d, 2×C, Ph), 129.4 (d, Ph^{para}), 129.3 (d, Ph^{para}), 128.6 (d, 2×C, Ph), 123.9 (d, C-9), 107.3 (d, C-3/6), 106.6 (br. d, 2×C, C-2'), 106.0 (d, C-3/6), 103.0 (t, C4-O*C*H_2O), 80.2 (d, C-8), 70.0 (s, H-8'), 62.8 (t, O*C*H_2CH_3), 60.8 (q, C4'-*C*H_3), 58.4 (d, C-7'), 56.8 (q, 2×C, C3'-*C*H_3), 54.4 (d, C-7), 13.9 (q, OCH_2*C*H_3);

MS (ESI+) *m/z*, (%): 1291 (13, $[2M + Na]^+$), 657 (100, $[M + Na]^+$), 439 (4);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd. for $C_{38}H_{34}O_9Na$ 657.20950; found: 657.20995.

(4bR,5R*,7aR*,8S*)-5-(2,2-diphenylvinyl)-8-(3,4,5-trimethoxyphenyl)-4b,5,7a,8-tetrahydro-7H-furo[3',4':1,2]indeno[5,6-d][1,3]dioxol-7-one* (**250**)

Detected in samples of **249** during attempted attempted crystallization from benzene.



R_f 0.45 (Tol/Et_2O 4:1);

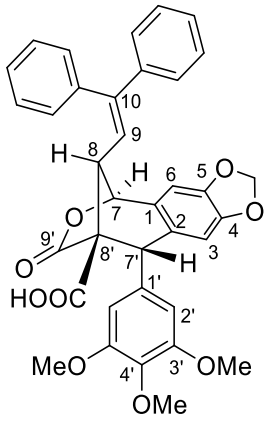
^1H (401 MHz, CD_3CN): δ 7.53-7.24 (m, 10 Ph), 6.86 (s, 1H, H-6), 6.62 (d, *J* = 1.2 Hz, 1H, H-3), 6.36 (s, 2H, H-2'), 6.01 (d, *J* = 9.5 Hz, 1H, H-9), 5.90 (d, *J* = 1.0 Hz, 1H, OCH_aH_bO), 5.87 (d, *J* = 1.0 Hz, 1H, OCH_aH_bO), 5.29 (dd, *J* = 9.5, 6.7 Hz, 1H, H-8), 4.58 (t, *J* = 1.3 Hz, 1H, H-7'), 4.34 (dd, *J* = 7.8, 6.6 Hz, H-7), 3.74 (s, 6H, C3'-CH_3), 3.66 (s, 3H, C4'-CH_3), 3.44 (dd, *J* = 7.8, 1.5 Hz, 1H, H-8'), 1.20 (d, *J* = 7.1 Hz, 1H, OCH_2CH_3);

$^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN): δ 179.5 (s, C-9'), 154.4 (s, 2×C, C-3'), 149.5 (s, C-4/5), 148.6 (s, C-4/5), 147.2 (s, C-10), 141.9 (s, Ph^{ipso}), 141.4 (s, C-1'), 140.3 (s, C-1), 139.6 (s, Ph^{ipso}), 137.8 (s, C-4'), 131.7 (s, C-2), 130.3 (d, 2×C, Ph), 129.6 (d, 2×C, Ph), 129.4 (d, 2×C, Ph), 129.3 (d, Ph^{para}), 129.1 (d, Ph^{para}), 128.5 (d, 2×C, Ph), 125.0 (d, C-9), 107.3 (d, C-3/6), 106.1 (d, C-3/6), 105.2 (d, 2×C, C-2'), 102.8 (t, C4-OCH_2O), 80.4 (d, C-8), 60.8 (q, C4'-CH_3), 56.7 (q, 2×C, C3'-CH_3), 55.2 (d, H-8'), 54.7 (d, C-7'), 51.0 (d, C-7).

Saponification of 248a/b

A solution of **248a/b** (16 mg, 25 µmol, dr 3:1) and LiOH (30 mg, 1.25 mmol) in THF (0.7 mL) and EtOH (3.0 mL) was heated to reflux for 5 h. After cooling, the reaction was stopped by addition of saturated NH_4Cl (1 mL). The mixture was partitioned between EA (10 mL) and water (10 mL). The organic phase was washed with brine (3 mL), dried over Na_2SO_4 and concentrated to give 21 mg of crude product. The product was dissolved in benzene (2 mL), leading to a cloudy solution which developed a colourless precipitate on standing. The precipitate was filtered off to give 5.0 mg of **251** (42%, based on **248a**). The filtrate was concentrated and purified by preparative TLC (silica, DCM/MeOH 40:1) to yield 1.5 mg of **252** (13%, based on **248a**) as a colourless amorphous solid.

(5S,8S*,9S*,11R*)-11-(2,2-diphenylvinyl)-7-oxo-9-(3,4,5-trimethoxyphenyl)-5,9-dihydro-5,8-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]oxepine-8(7H)-carboxylic acid* (**252**)



R_f 0.60 (DCM/MeOH 40:1);

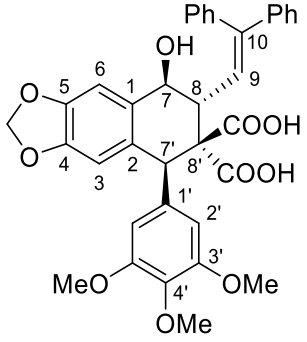
^{1}H (401 MHz, CD_3CN): δ 7.52-7.37 (m, 3H, Ph), 7.29-7.05 (m, 7H, Ph), 6.83 (s, 1H, H-3), 6.53-6.29 (br. s, 2H, H-2'), 6.45 (s, 1H, H-6), 5.97 (d, J = 1.1 Hz, 1H, C4-OCH_aH$_b$O), 5.95 (d, J = 1.1 Hz, 1H, C4-OCH$_a$$H_b$O), 5.75 (d, J = 10.1 Hz, 1H, H-9), 5.13 (d, J = 5.2 Hz, 1H, H-7), 5.04 (s, 1H, H-7'), 3.85 (dd, J = 10.2, 5.2 Hz, 1H, H-8), 3.70 (s, 3H, C4'-OCH_3), 3.68 (s, 6H, C3'-OCH_3);

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 172.9 (s, C-9'), 169.6 (s, *C*OOH), 153.4 (s, 2×C, C-3'), 150.2 (s, C-10), 149.9 (s, C-4/5), 147.6 (s, C-4/5), 142.2 (s, Ph^{ipso}), 139.8 (s, Ph^{ipso}), 138.3 (s, C-4'), 137.0 (s, C-1'), 132.3 (s, C-2), 130.3 (d, 2×C, Ph), 129.6 (d, 2×C, Ph), 129.3 (d, 2×C, Ph), 129.1 (d, Ph^{para}), 128.8 (d, Ph^{para}), 128.1 (d, 2×C, Ph), 127.6 (s, C-1), 120.2 (d, C-9), 111.1 (d, C-3), 110.0 (br. d, 2×C, C-2'), 108.7 (d, C-6), 102.8 (t, O*C*H$_2$O), 80.2 (d, C-7), 61.2 (s, C-8'), 60.8 (q, C4'-OCH_3), 56.7 (q, 2×C, C3'-OCH_3), 50.9 (d, C-8), 46.3 (d, C-7');

^{1}H (401 MHz, $CDCl_3$): δ 7.43-7.33 (m, 3H, Ph), 7.28-7.07 (m, 7H, Ph), 6.72 (s, 1H, H-3), 6.60-6.00 (br. s, 2H, H-2'), 6.52 (s, 1H, H-6), 6.00 (d, J = 1.4 Hz, 1H, C4-OCH_aH$_b$O), 6.01 (d, J = 1.4 Hz, 1H, C4-OCH$_a$$H_b$O), 5.92 (d, J = 9.3 Hz, 1H, H-9), 4.95 (d, J = 5.3 Hz, 1H, H-7), 4.92 (s, 1H, H-7'), 3.87 (dd, J = 8.8, 3.2 Hz, 1H, H-8), 3.82 (s, 3H, C4'-OCH_3), 3.74 (s, 6H, C3'-OCH_3);

MS (ESI–) *m/z*, (%): 605 (100, [M – H]$^-$).

(5S,7R*,8S*)-7-(2,2-diphenylvinyl)-8-hydroxy-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphtho[2,3-d][1,3]dioxole-6,6(5H)-dicarboxylic acid* (**251**)



R_f 0.20 (DCM/MeOH 40:1);

^{1}H (401 MHz, CD_3CN): δ 7.31-7.15 (m, 10H, Ph), 6.96 (s, 1H, H-3/6), 6.53 (d, J = 10.4 Hz, 1H, H-9), 6.30 (s, 1H, H-3/6), 6.12 (s, 2H, H-2'), 5.88 (d, J = 1.0 Hz, 1H, C4-OCH_aH$_b$O), 5.86 (d, J = 1.0 Hz, 1H, C4-OCH$_a$$H_b$O), 4.65 (s, 1H, H-7'), 4.53 (br. d, J = 9.9 Hz, 1H, H-7), 3.68 (s, 3H, C4'-OCH_3), 3.50-3.45 (m, 1H, H-8), 3.49 (s, 6H, C3'-OCH_3);

$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3CN): δ 171.9 (s, *C*OOH, detected by HMBC), 170.0 (s, *C*OOH, detected by HMBC), 153.4 (s, 2×C, C-3'), 148.1 (s, C-4/5), 147.6 (s, C-4/5), 145.9 (s, C-10), 144.8 (s, Ph^{ipso}), 141.3 (s, Ph^{ipso}), 137.5 (s, C-4'), 137.3 (s, C-1'), 132.4 (s, C-1/2), 131.9 (s, C-1/2), 131.2 (d, 2×C, Ph), 129.1 (d, 2×C, Ph), 128.5 (d, 2×C, Ph), 128.3 (d, C-9), 128.2 (d, 2×C, Ph), 127.9 (d, Ph^{para}), 127.6 (d, Ph^{para}), 108.8 (d, C-3/6), 108.5 (d, 2×C, C-2'), 107.4 (d, C-3/6), 102.2 (t, O*C*H_2O), 70.7 (d, C-7), 62.6 (s, C-8'), 60.7 (q, C4'-OCH_3), 56.3 (q, 2×C, C3'-OCH_3), 51.9 (d, C-7'), 42.5 (d, C-8);

^{1}H (401 MHz, CD_3OD): δ 7.30-7.25 (m, 3H, Ph), 7.22-7.13 (m, 7H, Ph), 6.95 (s, 1H, H-3/6), 6.69 (d, *J* = 10.2 Hz, 1H, H-9), 6.29 (s, 1H, H-3/6), 6.20 (s, 2H, H-2'), 5.86 (s, 2H, C4-OCH_2O), 4.72 (s, 1H, H-7'), 4.61 (d, *J* = 10.0 Hz, 1H, H-7), 3.73 (s, 3H, C4'-OCH_3), 3.61 (t, *J* = 10.0 Hz, 1H, H-8), 3.55 (s, 6H, C3'-OCH_3);

$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD): δ 173.8 (s, *C*OOH, detected by HMBC), 171.7 (s, *C*OOH, detected by HMBC), 153.6 (s, 2×C, C-3'), 148.6 (s, C-4/5), 148.1 (s, C-4/5), 146.3 (s, C-10), 145.5 (s, Ph^{ipso}), 142.0 (s, Ph^{ipso}), 138.3 (s, C-1'), 137.6 (s, C-4'), 133.0 (s, C-1/2), 132.7 (s, C-1/2), 131.7 (d, 2×C, Ph), 128.9 (d, C-9), 128.8 (d, 2×C, Ph), 128.59 (d, 2×C, Ph), 128.56 (d, 2×C, Ph), 127.7 (d, Ph^{para}), 127.5 (d, Ph^{para}), 109.4 (d, C-3/6), 108.8 (d, 2×C, C-2'), 107.7 (d, C-3/6), 102.2 (t, O*C*H_2O), 71.5 (d, C-7), 64.1 (s, C-8'), 61.0 (q, C4'-OCH_3), 56.4 (q, 2×C, C3'-OCH_3), 52.8 (d, C-7'), 42.8 (d, C-8);

MS (ESI–) *m/z*, (%): 623 (100, $[M - H]^-$), 579 (70, $[M - H - CO_2]^-$); MS (ESI+) *m/z*, (%): 625 (9, $[M + H]^+$), 607 (100, $[M + H - H_2O]^+$).

6.5. Part E

6.5.1. General experimental procedures

Preparation of LiHMDS: A solution of *n*-BuLi (1.5 mL, 2.4 mmol, 1.6 M in hexanes) was added to a solution of hexamethyldisilazane (503 µl, 2.4 mmol) in THF (20 mL) at −78 °C, followed by stirring at −78 °C for 30 min.

Co-generation of Li alkoxide: The base mixture was prepared *in situ* by addition of *n*-BuLi (1.9 mL, 3.0 mmol, 1.6 M in hexanes) to a solution of hexamethyldisilazane (503 µl, 2.4 mmol) and the respective alcohol (0.6 mmol) in THF (20 mL) at −78 °C, followed by stirring at −78 °C for 30 min.

Co-generation of Na/K alkoxide: The base was prepared by addition of NaHMDS or KHMDS solution (3.0 mL, 3.0 mmol, 1 M in THF) to a solution of the respective alcohol (0.6 mmol) in THF (20 mL) at −78 °C.

Nitrosative cleavage of Li, Na, K enolates generated by direct deprotonation (Method A): An oven-dried Schlenk flask equipped with a magnetic stirring bar was flushed with dry nitrogen, charged with a solution of the respective base (KHMDS, NaHMDS, LiHMDS with or without alkoxide) in freshly distilled THF (20 mL) and placed in a dry ice/acetone bath. A solution of the ketone (2.0 mmol) in THF (2 mL) was added dropwise over 2 min and the resulting solution was stirred at −78 °C for 15 min. Neat alkyl nitrite was added as a single portion while maintaining vigorous stirring. A slight turbidity usually developed at this point and the color changed to dark red for most aromatic ketones or to dark yellow for aliphatic ketones. After 30 min at −78 °C, the turbidity dissipated and the reaction progress was assessed by TLC. If not complete, the temperature was raised as indicated at the individual compounds.

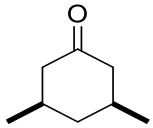
Workup: Saturated NH_4Cl solution (20 mL) was added followed by water (5 mL) and DCM (80 mL). The layers were separated and the aqueous was extracted with DCM (3×70 mL). The combined DCM extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EA/PE 1:20 to 1:1) and all non-volatile products including oximes were dried under high vacuum ($p < 1$ mbar). Variations are provided at the individual compounds.

Nitrosative cleavage of Li enolates generated by desilylation of TMS enol ethers (Method B): An oven-dried Schlenk flask equipped with a magnetic stirring bar was flushed with dry nitrogen, charged with a solution of the starting silyl enol ether (1.0 mmol) in freshly distilled THF (5 mL) and placed in a dry ice/acetone bath. A solution of MeLi (813 µl, 1.3 mmol, 1.6 M in diethyl ether) was added dropwise and the bath was warmed to −20 °C over 20 min. After the starting material was fully consumed as indicated by TLC, the bath was cooled to −78 °C. Neat isoamyl nitrite (202 µL, 1.5 mmol) was added as a single portion while maintaining vigorous stirring. No color change or turbidity was observed. The reaction mixture was stirred at −78 °C for 40 min after which the starting ketone was consumed as indicated by TLC. The reaction was quenched, worked up and purified following method **A**.

The *E*/*Z* configuration of oxime **274a** and oxime ether **272** was established by NOE and assigned by analogy for other oximes.

6.5.2. Synthesis and characterization of starting materials

(3R,5S*)-3,5-Dimethylcyclohexan-1-one* (**273a**)

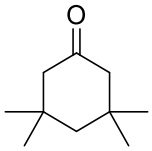


Prepared following a published procedure [271] by Jones oxidation of commercial (3*R**,5*S**)-3,5-dimethylcyclohexanol (10.22 g, 79.7 mmol). Distillation yielded 8.28 g (82%) as a colourless fragrant oil, bp 66-67 °C at 21 mbar. NMR data match those previously reported.

^{1}H NMR (401 MHz, $CDCl_3$): δ 2.40-2.22 (m, 2H), 1.91 (t, J = 12.8 Hz, 2H), 1.90-1.78 (m, 2H), 1.00 (d, J = 6.1 Hz, 6H);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 211.8 (s), 49.5 (t), 42.8 (t), 33.3 (d), 22.5 (q).

3,3,5,5-Tetramethylcyclohexanone (**273b**)



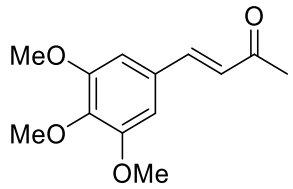
CuBr•DMS (308 mg, 1.5 mmol) was suspended in dry THF (15 mL) under a nitrogen atmosphere and cooled to −40 °C. Dry HMPA [272] (5.75 mL, 33 mmol) and MeMgCl solution (8.50 mL, 25.5 mmol, 3 M in THF) were subsequently added and the mixture was stirred at −40 °C for 10 min, during which the mixture turned from transparent yellow to cloudy grey. Isophorone (2.25 mL, 15 mmol) was added dropwise and the mixture was slowly warmed to 0 °C over 1 h. Saturated NH_4Cl solution (30 mL)

was added very slowly followed by pentane (150 mL). After separation, the organic layer was washed with water (3×50 mL), dried over Na_2SO_4 and concentrated at 50 mbar (30 °C). The crude oil was purified by column chromatography (PE/Et_2O 10:1) to yield 1.461 g (63%) of **273b** as a colourless oil. NMR data match those previously reported.

^{1}H NMR (401 MHz, $CDCl_3$): δ 2.15 (s, 4H), 2.01 (s, 2H), 1.03 (s, 12H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 212.7 (s), 54.1 (t), 51.8 (t), 36.3 (s), 31.5 (q).

(E)-1-(3,4,5-Trimethoxyphenyl)but-1-en-3-one (**147a**)



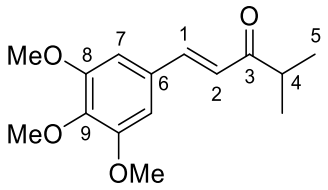
Prepared following a published procedure [233] from 3,4,5-trimethoxybenzaldehyde (9.81 g, 50 mmol) and acetone (50 mL, 0.68 mol). Recrystallization from EtOH and purification of the mother liquor by column chromatography (PE/EA 2:1) afforded a combined yield of 6.75 g (57%) of **147a** as colourless crystals, mp 90 °C (lit. 87-89 °C). The data match those previously reported.[233]

R_f 0.46 (hexane/EA 1:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.43 (d, J = 16.2 Hz, 1H), 6.77 (s, 2H), 6.63 (d, J = 16.2 Hz, 1H), 3.89 (s, 6H), 3.88 (s, 3H), 2.38 (s, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 198.4 (s), 153.6 (s, 2×C), 143.6 (d), 140.5 (s), 130.0 (s), 126.7 (d), 105.5 (d, 2C), 61.1 (q), 56.2 (q, 2C), 27.5 (q).

(E)-4-Methyl-1-(3,4,5-trimethoxyphenyl)pent-1-en-3-one (**147b**)



NaOMe solution (2 drops, 25 wt.% in MeOH) was added to a solution of 3,4,5-trimethoxy-benzaldehyde (1.95 g, 10 mmol) in MeOH (20 mL) containing 3-methylbutan-2-one (3.2 mL, 30 mmol). After stirring at 23 °C for 12 days, the mixture partitioned between water (120 mL) and Et_2O (150 mL). The aqueous layer was extracted again by Et_2O (4×100 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated. Recrystallization from aqueous MeOH afforded 1.98 g (74%) of **147b** as colourless crystals, mp 113 °C.

R_f 0.54 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3070 (w), 2961 (m), 2870 (w), 2845 (w), 2829 (w), 1685 (w), 1653 (m), 1622 (w), 1609 (w), 1580 (m), 1505 (m), 1460 (m), 1421 (m), 1336 (m), 1321 (m), 1253 (m), 1201 (vs), 1123 (w), 1092 (w), 1059 (w), 1003 (w), 992 (m), 843 (w), 734 (w), 701 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 7.52 (d, *J* = 15.9 Hz, 1H, H-1), 6.79 (s, 2H, H-7), 6.70 (d, *J* = 16.0 Hz, 1H, H-2), 3.90 (s, 6H, OCH_3), 3.89 (s, 3H, OCH_3), 2.96 (sept, *J* = 6.9 Hz, 1H, H-4), 1.19 (d, *J* = 6.9 Hz, 6H, H-5);

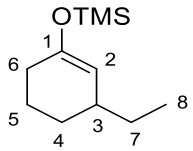
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 203.9 (s, C-3), 153.6 (s, C-8), 142.6 (d, C-1), 140.4 (s, C-9), 130.3 (s, C-6), 124.1 (d, C-2), 105.6 (d, C-7), 61.1 (q, C9-OCH_3), 56.3 (q, 2×C, C8-OCH_3), 39.2 (d, C-4), 18.7 (q, C-5);

MS (ESI+) *m/z*, (%): 551 (33, $[2M + Na]^+$), 287 (100, $[M + Na]^+$), 265 (4, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_4$ 287.1254; found: 287.1252;

Anal. Calcd for $C_{15}H_{20}O_4$ (264.32): C, 68.16; H, 7.63. Found: C, 68.10; H, 7.49.

((3-Ethylcyclohex-1-en-1-yl)oxy)trimethylsilane (**295a**)



Prepared by a published procedure:[238] A solution of EtMgBr (7.20 mL, 21.6 mmol, 3 M in Et_2O) was added to a mixture of CuBr•DMS (175 mg, 0.85 mmol) and HMPA (4.9 mL, 28 mmol) in THF (20 mL) at –40 °C. After 10 min, cyclohex-2-en-1-one (**294a**, 1.23 mL, 12.7 mmol) was added followed by TMSCl (3.2 mL, 25 mmol) and Et_3N (3.5 mL, 25 mmol). Chromatography in PE yielded 1.178 g (46%) of **295a** as a colourless oil. Spectroscopic data match those reported.[273]

R_f 0.86 (hexane/EA 22:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2960 (w), 2930 (m), 2875 (w), 2858 (w), 1663 (m), 1456 (w), 1367 (w), 1250 (m), 1184 (s), 1129 (w), 1058 (w), 1042 (w), 972 (w), 905 (m), 883 (w), 838 (vs), 750 (m), 689 (w);

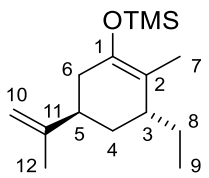
^{1}H NMR (401 MHz, C_6D_6): δ 4.95 (s, 1H, H-2), 2.08-2.01 (m, 3H, H-3, H-6), 1.63-1.56 (m, 2H, H-4a, H-5a), 1.52-1.41 (m, 1H, H-5b), 1.37-1.21 (m, 2H, H-7), 1.09-1.00 (m, 1H, H-4b), 0.89 (t, *J* = 7.4 Hz, 3H, H-8), 0.20 (s, 9H, Si(CH_3)$_3$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 151.0 (s, C-1), 108.9 (d, C-2), 36.7 (d, C-3), 30.6 (t, C-6), 30.2 (t, C-7), 28.9 (t, C-4), 22.2 (t, C-5), 11.6 (q, C-8), 0.5 (q, Si(CH$_3$)$_3$);

MS (EI+) *m/z*, (%): 198 (15, $[M]^{+\cdot}$), 183 (9, $[M - Me]^+$), 169 (100, $[M - Et]^+$), 130 (9), 73 (33, $[SiMe_3]^+$);

HRMS (EI+) *m/z*: $[M]^{+\cdot}$ calcd for $C_{11}H_{22}OSi$ 198.1440; found: 198.1439.

(3R,5R)-3-Ethyl-2-methyl-5-(prop-1-en-2-yl)-1-(trimethylsilyloxy)cyclohex-1-ene (**295b**)



Prepared following the procedure for **295a** from (*R*)-(−)-carvone (**294b**, 2.0 mL, 12.7 mmol), yield 1.54 g (48%) as a colourless oil.

R_f 0.71 (hexane/EA 22:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2960 (m), 2922 (m), 2862 (w), 1716 (w), 1683 (m), 1645 (w), 1447 (w), 1378 (w), 1342 (w), 1307 (w), 1250 (m), 1184 (s), 1127 (w), 1083 (w), 1018 (w), 980 (w), 924 (s), 888 (m), 838 (vs), 752 (m), 688 (w), 643 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 4.73 (s, 2H, H-10), 2.38-2.28 (m, 1H, H-5), 2.06-1.94 (m, 2H, H-6), 1.93-1.87 (m, 1H, H-3), 1.74 (s, 3H, H-12), 1.74-1.70 (m, 1H, H-4a), 1.66-1.58 (m, 1H, H-8a), 1.59 (t, J = 1.9 Hz, 3H, H-7), 1.41 (dddd, J = 13.2, 12.4, 5.6, 0.9 Hz, 1H, H-4b), 1.21 (ddq, J = 14.2, 10.1, 7.3 Hz, 1H, H-8b), 0.90 (t, J = 7.4 Hz, 3H, H-9), 0.17 (s, 9H, Si(CH_3)$_3$);

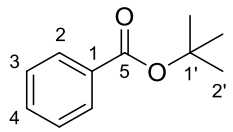
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.7 (s, C-11), 142.9 (s, C-1), 115.6 (s, C-2), 108.8 (t, C-10), 41.0 (d, C-3), 37.4 (d, C-5), 35.8 (t, C-6), 30.5 (t, C-4), 25.5 (t, C-8), 20.9 (q, C-12), 15.1 (q, C-7), 12.9 (q, C-9), 0.9 (q, Si(CH_3)$_3$);

MS (EI+) *m/z*, (%): 252 (22, [M]$^{+\cdot}$), 223 (100, [M − Et]$^+$), 195 (17), 181 (42), 165 (18), 73 (82, [$SiMe_3$]$^+$);

HRMS (EI) *m/z*: [M]$^{+\cdot}$ calcd for $C_{15}H_{28}OSi$ 252.1909; found: 252.1908.

6.5.3. Characterization data of cleavage products

tert-Butyl benzoate (**262a**)



Prepared by method **A** from propiophenone (**261a**, 266 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *t*-BuONO (333 µL, 2.8 mmol) at −15 °C, warmed to r.t. over 45 min, extracted with Et_2O (3×100 mL) instead of DCM, yield 294 mg (82%) as a colourless oil.

R_f 0.49 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2987 (w), 2942 (w), 1715 (s), 1609 (w), 1590 (w), 1483 (w), 1455 (m), 1397 (w), 1372 (m), 1318 (m), 1292 (vs), 1257 (m), 1168 (s), 1115 (vs), 1073 (m), 1029 (m), 850 (m), 759 (w), 710 (vs), 689 (m).

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.02-7.99 (m, 2H, H-2), 7.52 (tt, J = 7.4, 1.6 Hz, 1H, H-4), 7.42 (t, J = 7.6 Hz, 2H, H-3), 1.60 (s, 9H, H-2'');

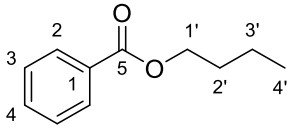
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.9 (s, C-5), 132.5 (d, C-4), 132.2 (s, C-1), 129.5 (d, C-2), 128.3 (d, C-3), 81.1 (s, C-1''), 28.3 (q, C-2'');

MS (EI+) *m/z*, (%): 178 (4, [M]$^{+\cdot}$), 163 (2, [M – CH_3]$^+$), 123 (100, [$PhCOOH_2$]$^+$), 105 (93, [PhCO]$^+$), 77 (27, [Ph]$^+$), 57 (31, [*t*-Bu]$^+$), 56 (11, [isobutene]$^{+\cdot}$);

HRMS (EI+) *m/z*: [M]$^{+\cdot}$ calcd for $C_{11}H_{14}O_2$ 178.0994; found 178.0993;

Anal. Calcd. for $C_{11}H_{14}O_2$ (178.23): C, 74.13; H, 7.92. Found: C, 73.97; H, 7.86.

Butyl benzoate (**262b**)



Prepared by method **A** from propiophenone (**261a**, 266 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *n*-BuONO (327 µL, 2.8 mmol) at −78 °C, warmed to –20 °C over 5 h, yield 356 mg (99%) as a colourless oil. Alternatively prepared from isobutyrophenone (**261d**, 300 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *n*-BuONO (327 µL, 2.8 mmol) at −78 °C, warmed to r.t.; yield 235 mg (66%).

R_f 0.63 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2969 (w), 2883 (w), 1721 (vs), 1607 (w), 1590 (w), 1456 (m), 1389 (w), 1318 (m), 1273 (vs), 1179 (m), 1111 (s), 1073 (m), 1030 (m), 967 (w), 942 (w), 709 (vs), 689 (m), 677 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H, H-2), 7.56 (tt, J = 7.4, 1.3 Hz, 1H, H-4), 7.45-7.42 (m, 2H, H-3), 4.33 (t, *J* = 6.6 Hz, 2H, H-1'), 1.76 (tt, *J* = 7.4, 6.6 Hz, 2H, H-2'), 1.53-1.44 (m, 2H, H-3'), 0.98 (t, *J* = 7.4 Hz, 3H, H-4');

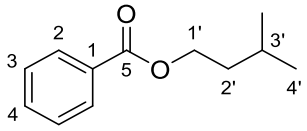
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.8 (s, C-5), 132.9 (d, C-4), 130.7 (s, C-1), 129.7 (d, C-2), 128.4 (d, C-3), 65.0 (t, C-1'), 30.9 (t, C-2'), 19.4 (t, C-3'), 13.9 (q, C-4');

MS (EI+) *m/z*, (%): 178 (11, $[M]^{\cdot+}$), 123 (98, $[PhCOOH_2]^+$), 105 (100, $[M - C_4H_9O]^+$), 77 (31, $[Ph]^+$), 56 (6, $[butene]^{\cdot+}$);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_{11}H_{14}O_2$ 178.0994; found 178.0992;

Anal. Calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13; H, 7.92. Found: C, 73.84; H, 7.78.

Isopentyl benzoate (**262c**)



Prepared by method **A** from propiophenone (**261a**, 266 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (376 µL, 2.8 mmol) at −78 °C, warmed to −20 °C over 15 min. Purification yielded 5 mg (1%) of **263** as a colourless solid and 370 mg (96%) of **262c** as a colourless oil. Alternatively prepared from isobutyrophenone (**261d**, 300 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (376 µL, 2.8 mmol), warmed to 0 °C over 15 min; yield 380 mg (98%).

R_f 0.60 (hexane/EA 22:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2958 (m), 2871 (w), 1716 (s), 1602 (w), 1452 (w), 1386 (w), 1314 (w), 1267 (vs), 1175 (w), 1109 (s), 1070 (w), 1026 (w), 951 (w), 707 (vs), 687 (w), 675 (w);

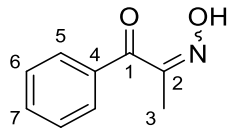
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.07-8.02 (m, 2H, H-2), 7.55 (tt, *J* = 7.4, 1.4 Hz, 1H, H-4), 7.55-7.41 (m, 2H, H-3), 4.36 (t, *J* = 6.8 Hz, 2H, H-1'), 1.80 (non, *J* = 6.7 Hz, 1H, H-3'), 1.67 (q, *J* = 6.8 Hz, 2H, H-2'), 0.98 (d, *J* = 6.6 Hz, 6H, H-4');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.8 (s, C-5), 132.9 (d, C-4), 130.7 (s, C-1), 129.7 (d, C-2), 128.4 (d, C-3), 63.8 (t, C-1'), 37.6 (t, C-2'), 25.4 (d, C-3'), 22.7 (q, C-4');

MS (ESI+) *m/z*, (%): 215 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_2$ 215.1042; found 215.1041.

2-(Hydroxyimino)-1-phenylpropan-1-one (**263**)



Formed by method **A** from propiophenone (**261a**, 266 µL, 2.0 mmol), LiHMDS (2.4 mmol), and *t*-BuONO (333 µL, 2.8 mmol) at −78 °C, warmed to r.t. and stirred for 16 h, yield 118 mg (33%) of **262a** and 188 mg (57%) of **263** as colourless crystals, mp 108-109 °C.

R_f 0.63 (hexane/EA 10:1);

IR (film) ν[cm^{-1}]: 3219 (br.), 2956 (w), 2923 (m), 2851 (w), 1718 (w), 1658 (m), 1647 (m), 1596 (w), 1446 (m), 1364 (w), 1320 (w), 1307 (w), 1278 (w), 1182 (m), 1012 (s), 998 (vs), 895 (s), 758 (w), 707 (s), 692 (vs), 665 (s);

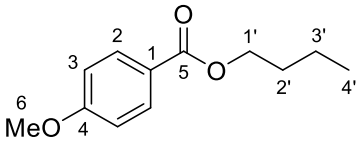
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.21 (br. s, 1H, NOH), 7.93-7.85 (m, 2H, H-5), 7.61-7.53 (m, 1H, H-7), 7.47-7.41 (m, 2H, H-6), 2.18 (s, 3H, H-3);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 192.0 (s, C-1), 156.9 (s, C-2), 136.5 (s, C-4), 133.0 (d, C-7), 130.3 (d, C-5), 128.3 (d, C-6), 10.3 (q, C-3);

MS (EI+) *m/z*, (%): 163 (38, $[M]^{+\cdot}$), 118 (11), 105 (100, $[PhCO]^+$), 77 (48, $[Ph]^+$);

HRMS (EI+) *m/z*: $[M]^{+\cdot}$ calcd for $C_9H_9NO_2$ 163.0633; found: 163.0634.

Butyl 4-methoxybenzoate (**264a**)



Prepared by method **A** from 4-methoxypropiophenone (**261b**, 350 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *n*-BuONO (327 µL, 2.8 mmol) at –78 °C for 75 min; yield 323 mg (77%) as a colourless oil.

R_f 0.70 (hexane/EA 7:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2959 (w), 2934 (w), 2874 (w), 2841 (w), 1707 (s), 1605 (m), 1581 (w), 1510 (w), 1460 (w), 1384 (w), 1315 (w), 1274 (s), 1250 (vs), 1165 (s), 1099 (s), 1028 (m), 964 (w), 846 (m), 769 (m), 696 (w), 612 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.00 (d, J = 8.9 Hz, 2H, H-2), 6.91 (d, J = 8.9 Hz, 2H, H-3), 4.29 (t, J = 6.6 Hz, 2H, H-1'), 3.86 (s, 3H, H-6), 1.77-1.70 (m, 2H, H-2'), 1.52-1.43 (m, 2H, H-3'), 1.02 (t, J = 7.4 Hz, 3H, H-4');

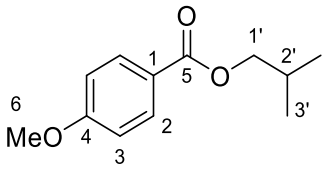
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.6 (s, C-5), 163.4 (s, C-4), 131.7 (d, C-2), 123.1 (s, C-1), 113.7 (d, C-3), 64.7 (t, C-1'), 55.6 (q, C-6), 31.0 (t, C-2'), 19.4 (t, C-3'), 13.9 (q, C-4');

MS (ESI+) *m/z*, (%): 439 (6, $[2M + Na]^+$), 231 (100, $[M + Na]^+$), 153 (6, $[MeOC_6H_4COOH_2]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_3$ 231.0992; found 231.0992;

Anal. Calcd for $C_{12}H_{16}O_3$ (208.26): C, 69.21; H, 7.74. Found: C, 69.01; H, 7.63.

Isobutyl 4-methoxybenzoate (**264b**)



Prepared by method **A** from 4-methoxypropiophenone (**261b**, 350 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-BuONO (332 µL, 2.8 mmol) at –78 °C, warmed to −40 °C over 15 min; yield 407 mg (97%) as a colourless oil.

R_f 0.65 (hexane/EA 11:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2971 (m), 2884 (w), 2850 (w), 1714 (s), 1611 (m), 1587 (w), 1515 (m), 1472 (m), 1380 (w), 1319 (w), 1276 (m), 1253 (s), 1168 (s), 1103 (s), 1032 (m), 1012 (w), 987 (w), 849 (m), 771 (m), 698 (m), 637 (w), 614 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.0 Hz, 2H, H-2), 6.92 (d, *J* = 8.9 Hz, 2H, H-3), 4.07 (d, *J* = 6.6 Hz, 2H, H-1'), 3.85 (s, 3H, H-6), 2.06 (non, *J* = 6.7 Hz, 1H, H-2'), 1.01 (d, *J* = 6.7 Hz, 6H, H-3');

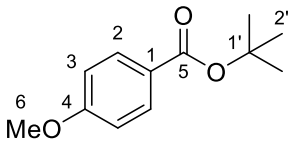
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.5 (s, C-5), 163.4 (s, C-4), 131.7 (d, C-2), 123.1 (s, C-1), 113.7 (d, C-3), 70.8 (t, C-1'), 55.5 (q, C-6), 28.1 (d, C-2'), 19.4 (q, C-3');

MS (CI+) *m/z*, (%): 209 (45, $[M + H]^+$), 153 (100, $[M + H - \text{isobutene}]^+$), 152 (86, $[M - \text{isobutene}]^{\cdot+}$), 135 (75, $[MeOC_6H_4CO]^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{17}O_3$ 209.1172; found: 209.1175;

Anal. Calcd for $C_{12}H_{16}O_3$ (208.26): C, 69.21; H, 7.74. Found: C, 69.23; H, 7.69.

tert-Butyl 4-methoxybenzoate (**264c**)



Prepared by method **A** from 4-methoxypropiophenone (**261b**, 350 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *t*-BuONO (333 µL, 2.8 mmol) at –78 °C; yield 382 mg (91%) as a colourless oil. The reaction progress was monitored by raising the temperature in 20 °C intervals, taking aliquots, quenching them by wet Et_2O, and running GCs, which showed: 1) complete consumption of **261b** after 3 min at −78 °C, 2) disappearance of an unidentified transient side-product above –40 °C, and 3) gradual intensity increase of the peak of **264c** relative to dodecane internal standard ceasing at −20 ºC.

R_f 0.40 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2985 (w), 2943 (w), 2849 (w), 1709 (m), 1610 (m), 1586 (w), 1515 (m), 1462 (w), 1397 (w), 1371 (m), 1319 (m), 1293 (m), 1254 (s), 1184 (w), 1158 (s), 1118 (m), 1104 (s), 1032 (m), 849 (m), 773 (m), 753 (w), 698 (w);

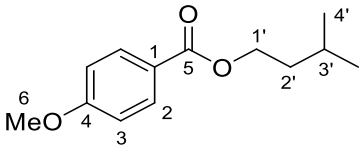
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.9 Hz, 2H, H-2), 6.90 (d, *J* = 8.9 Hz, 2H, H-3), 3.85 (s, 3H, H-6), 1.59 (s, 9H, H-2'');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.7 (s, C-5), 163.1 (s, C-4), 131.5 (d, C-2), 124.6 (s, C-1), 113.5 (d, C-3), 80.6 (s, C-1''), 55.5 (q, C-6), 28.4 (q, C-2'');

MS (EI+) *m/z*, (%): 208 (10, $[M]^{\cdot+}$), 152 (100, $[M - \text{isobutene}]^{\cdot+}$), 135 (72, $[MeOC_6H_4CO]^+$), 107 (5, $[MeOC_6H_4]^+$), 92 (9, $[M - t\text{-Bu} - CO_2 - CH_3]^{\cdot+}$), 77 (10, $[Ph]^+$), 57 (10, $[t\text{-Bu}]^+$), 41 (9, $[allyl]^+$);

Anal. Calcd for $C_{12}H_{16}O_3$ (208.26): C, 69.21; H, 7.74. Found: C, 69.23; H, 7.69.

Isopentyl 4-methoxybenzoate (**264d**)



Prepared by method **A** from 4-methoxypropiophenone (**261b**, 350 µL, 2.0 mmol), KHMDS (2.6 mL, 2.6 mmol, 1 M in THF), and *i*-AmONO (376 µL, 2.8 mmol) at −78 °C for 30 min; yield 444 mg (99%) as a colourless oil. Alternatively prepared from desoxyanisoin (see preparation of **265b**).

R_f 0.68 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2967 (m), 2881 (w), 2850 (w), 1713 (m), 1611 (m), 1587 (w), 1516 (m), 1467 (w), 1424 (w), 1390 (w), 1373 (w), 1319 (w), 1277 (m), 1240 (s), 1168 (s), 1115 (m), 1103 (s), 1032 (m), 1012 (w), 960 (w), 849 (m), 825 (w), 790 (w), 771 (m), 698 (m);

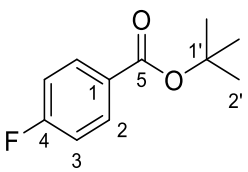
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 2H, H-2), 6.91 (d, *J* = 8.9 Hz, 2H, H-3), 4.32 (t, *J* = 6.8 Hz, 2H, H-1''), 3.86 (s, 3H, H-6), 1.80 (non, *J* = 6.6 Hz, 1H, H-3''), 1.66 (q, *J* = 6.8 Hz, 2H, H-2''), 0.97 (d, *J* = 6.6 Hz, 6H, H-4'');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.6 (s, C-5), 163.4 (s, C-4), 131.7 (d, C-2), 123.1 (s, C-1), 113.7 (d, C-3), 63.5 (t, C-1''), 55.5 (q, C-6), 37.6 (t, C-2''), 25.4 (d, C-3''), 22.7 (q, C-4'');

MS (EI+) *m/z*, (%): 222 (5, $[M]^{\cdot+}$), 152 (100, $[M - C_5H_{10}]^{\cdot+}$), 135 (92, $[MeOC_6H_4CO]^+$), 107 (6, $[MeOC_6H_4]^+$), 92 (11, $[C_6H_4O]^+$), 77 (13, $[Ph]^+$);

Anal. Calcd for $C_{13}H_{18}O_3$ (222.28): C, 70.24; H, 8.16. Found: C, 70.45; H, 8.29.

tert-Butyl 4-fluorobenzoate (**264e**)



Prepared by method **A** from 4-fluoropropiophenone (**261c**, 278 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *t*-BuONO (333 µL, 2.8 mmol) at –78 °C, warmed to –20 °C over 5 h; yield 326 mg (83%) as a colourless volatile oil.

R_f 0.22 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2989 (w), 2942 (w), 1716 (s), 1609 (m), 1511 (m), 1481 (w), 1462 (w), 1416 (w), 1398 (w), 1372 (m), 1309 (m), 1292 (s), 1259 (w), 1241 (m), 1177 (m), 1153 (s), 1116 (s), 1093 (m), 1018 (w), 853 (s), 811 (w), 770 (s), 754 (w), 689 (w), 635 (w), 613 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.02-7.97 (m, 2H, H-2), 7.10-7.05 (m, 2H, H-3), 1.60 (s, 9H, H-2'');

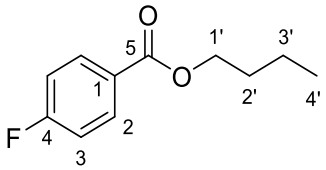
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.6 (s, $^1J_{(C\text{-}F)}$ = 253 Hz, C-4), 164.9 (s, C-5), 132.1 (d, $^3J_{(C\text{-}F)}$ = 9.2 Hz, C-2), 128.4 (s, $^4J_{(C\text{-}F)}$ = 3.0 Hz, C-1), 115.3 (d, $^2J_{(C\text{-}F)}$ = 21.9 Hz, C-3), 81.3 (s, C-1''), 28.3 (q, C-2'');

^{19}F (376 MHz, $CDCl_3$): δ –107.9;

MS (EI+) *m/z*, (%): 196 (1, $[M]^{\cdot+}$), 141 (66, $[FC_6H_4COOH_2]^+$), 123 (100, [M – *t*-BuO]$^+$), 95 (37, $[FC_6H_4]^+$), 75 (16, $[C_6H_3]^+$), 57 (60, [*t*-Bu]$^+$), 56 (53, [isobutene]$^{\cdot+}$), 41 (25, [allyl]$^+$);

Anal. Calcd for $C_{11}H_{13}FO_2$ (196.22): C, 67.33; H, 6.68. Found: C, 67.49; H, 6.79.

Butyl 4-fluorobenzoate (**264f**)



Prepared by method **A** from 4-fluoropropiophenone (**261c**, 278 µL, 2.0 mmol), KHMDS (2.3 mL, 2.3 mmol, 1 M in THF), and *n*-BuONO (281 µL, 2.4 mmol) at −78 °C, warmed to −20 °C over 80 min. Concentration at 75 mbar (25 °C) yielded the crude product (806 mg), which was purified using Et_2O/pentane; yield 374 mg (95%) as a colourless volatile oil.

R_f 0.46 (hexane/Et_2O 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2961 (w), 2935 (w), 2875 (w), 1716 (s), 1603 (m), 1507 (m), 1466 (w), 1411 (w), 1385 (w), 1304 (w), 1268 (vs), 1237 (s), 1152 (m), 1107 (s), 1089 (s), 1015 (w), 943 (w), 853 (m), 821 (w), 766 (s), 687 (w), 607 (m);

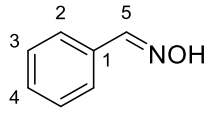
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.07-8.03 (m, 2H, H-2), 7.12-7.08 (m, 2H, H-3), 4.31 (t, *J* = 6.6 Hz, 2H, H-1''), 1.78-1.71 (m, 2H, H-2''), 1.52-1.43 (m, 2H, H-3''), 0.98 (t, *J* = 7.4 Hz, 3H, H-4''); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.9 (s, C-5), 165.8 (s, $^1J_{(C\text{-}F)}$ = 253 Hz, C-4), 132.2 (d, $^3J_{(C\text{-}F)}$ = 9.3 Hz, C-2), 126.9 (s, $^4J_{(C\text{-}F)}$ = 3.0 Hz, C-1), 115.6 (d, $^2J_{(C\text{-}F)}$ = 22.0 Hz, C-3), 65.1 (t, C-1''), 30.9 (t, C-2''), 19.4 (t, C-3''), 13.9 (q, C-4'');

^{19}F NMR (376 MHz, $CDCl_3$): δ −107.1;

MS (EI+) *m/z*, (%): 196 (4, $[M]^{\cdot+}$), 141 (91, $[FC_6H_4COOH_2]^+$), 140 (36, $[FC_6H_4COOH]^{\cdot+}$), 123 (100, $[FC_6H_4CO]^+$), 95 (55, $[FC_6H_4]^+$), 75 (13 $[C_6H_3]^+$), 56 (21, [butene]$^{\cdot+}$);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_{11}H_{13}FO_2$ 196.0900; found 196.0901.

Benzaldoxime (**265a**)



Prepared by method **A** from desoxybenzoin (**261f**, 392 mg, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (269 µL, 2.0 mmol) at –78 °C, warmed to 0 °C over 4 h. Purification yielded in order of increasing polarity 390 mg (99%) of **262c**, 100 mg (41%) of (*Z*)-**265a** and 114 mg (47%) of a 10:1 *E*/*Z* mixture of **265a** as a pale yellow sticky solid.

R_f 0.45, 0.36 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3150 (s), 3072 (w), 3038 (w), 2989 (w), 2903 (w), 2790 (w), 1636 (w), 1605 (w), 1583 (w), 1498 (m), 1450 (m), 1307 (m), 1292 (m), 1214 (m), 1078 (w), 949 (vs), 871 (s), 755 (vs), 691 (vs), 645 (s);

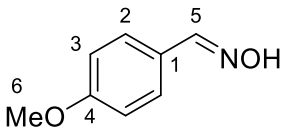
^{1}H NMR (401 MHz, $CDCl_3$): δ 10.22-8.71 (br. s, 1H, NOH^E), 8.85-8.54 (br. s, 1H, NOH^Z), 8.18 (s, 1H, H-5^Z), 7.98-7.95 (m, 2H, H-2^E), 7.60-7.58 (m, 2H, H-2^Z), 7.47-7.17 (m, 7H, H-3,4,5^E, H-3,4^Z);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.5 (d, C-5^Z), 146.9 (d, C-5^E), 132.0 (s, C-1^Z), 131.1 (d, C-2^E), 130.5 (s, C-1^E), 130.3 (d, C-4^E), 130.2 (d, C-4^Z), 128.9 (d, C-3^Z), 128.6 (d, C-3^E), 127.2 (d, C-2^Z);

MS (CI+) *m/z*, (%):122 (100, $[M + H]^+$), 121 (70, $[M]^{\cdot+}$), 104 (47, $[PhCN + H]^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for C_7H_8NO 122.0606; found 122.0604.

4-Methoxybenzaldehyde oxime (**265b**)



Prepared by method **A** from desoxyanisoin (513 mg, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (349 µL, 2.6 mmol) at –78 °C, warmed to –5 °C over 3 h; yield 392 mg (88%) of **264d** and 255 mg (84%) of **265b** as 1:10 *E*/*Z* mixture as a colourless solid, mp 56 °C.

R_f 0.14 (hexane/EA 4:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3290 (s), 3015 (w), 2974 (w), 2934 (w), 2848 (w), 1611 (s), 1580 (w), 1518 (s), 1462 (w), 1446 (w), 1422 (w), 1307 (m), 1252 (vs), 1215 (w), 1174 (s), 1113 (w), 1029 (s), 955 (s), 944 (s), 875 (m), 829 (s), 758 (m), 694 (m), 638 (m), 590 (s);

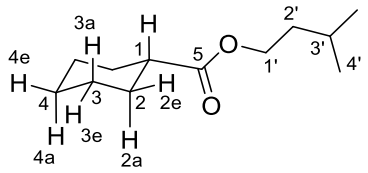
^{1}H NMR (401 MHz, $CDCl_3$): δ 10.00-5.00 (br. s, 2H, NOH^{EZ}), 8.12 (s, 1H, H-5^Z), 7.96 (d, J = 8.8 Hz, 2H, H-2^E), 7.52 (d, J = 8.7 Hz, 2H, H-2^Z), 7.34 (s, 1H, H-5^E), 6.94 (d, J = 9.0 Hz, 2H, H-3^E), 6.91 (d, J = 8.7 Hz, 2H, H-3^Z), 3.85 (s, 3H, H-6^E), 3.83 (s, 3H, H-6^Z);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.2 (s, C-4^Z), 161.0 (s, C-4^E), 150.0 (d, C-5^Z), 146.2 (d, C-5^E), 133.2 (d, C-2^E), 128.6 (d, C-2^Z), 124.6 (s, C-1^Z), 114.4 (d, C-3^Z), 113.9 (d, C-3^E), 55.46 (q, C-6^Z), 55.45 (q, C-6^E), C-1^E was not detected;

MS (CI+) *m/z*, (%): 152 (64, $[M + H]^+$), 151 (65, $[M]^{\cdot+}$), 136 (55, $[M + H - CH_4]^+$), 135 (43, $[M + H - OH]^+$), 134 (100, $[MeOC_6H_4CN + H]^+$), 109 (8, $[PhOMe + H]^+$), 108 (10, $[PhOMe]^{\cdot+}$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_8H_{10}NO_2$ 152.0712; found: 152.0713.

Isoamyl cyclohexanecarboxylate (**267**)



Prepared by method **A** from dicyclohexyl ketone (**266**) (394 µL, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C for 45 min; yield 184 mg (81%) of **268** as a yellow solid and 366 mg of an inseparable mixture of **266** (17%, calculated from ^{1}H NMR spectrum) and **267** (76% calculated from ^{1}H NMR spectrum) as a colourless oil. Alternatively, **7** was prepared by method **A** from cyclohexyl methyl ketone (275 µL, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C for 45 min. The crude extract was concentrated at 100 mbar (30 °C) and purified by column chromatography (benzene); yield 89 mg (35%) of recovered cyclohexyl methyl ketone and 124 mg (31%) of **267** as a colourless oil with flowery aroma.

R_f 0.68 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2939 (s), 2866 (m), 1736 (vs), 1470 (w), 1455 (m), 1391 (w), 1373 (w), 1316 (m), 1279 (w), 1250 (s), 1231 (w), 1195 (m), 1170 (vs), 1136 (s), 1058 (m), 965 (w), 897 (w), 849 (w);

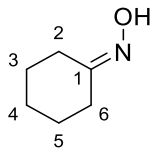
^{1}H NMR (401 MHz, $CDCl_3$): δ 4.08 (t, *J* = 6.8 Hz, 2H, H-1‘), 2.27 (tt, *J* = 11.3, 3.6 Hz, 1H, H-1), 1.92-1.86 (m, 2H, H-2e), 1.77-1.72 (m, 2H, H-3e), 1.70-1.65 (m, 1H, H-3‘), 1.65-1.60 (m, 1H, H-4e), 1.50 (q, *J* = 6.9 Hz, 2H, H-2‘), 1.47-1.38 (m, 2H, H-2a), 1.38-1.18 (m, 3H, H-3a, H-4a), 0.91 (d, *J* = 6.6 Hz, 6H, H-4‘);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 176.4 (s, C5), 62.9 (t, C-1’), 43.4 (d, C-1), 37.5 (t, C-2’), 29.2 (t, C-2), 25.9 (t, C-4), 25.6 (t, C-3), 25.2 (d, C-3’), 22.6 (q, C-4’);

MS (EI+) *m/z*, (%): 198 (1, $[M]^{\cdot+}$), 183 (2, $[M - Me]^{+}$), 155 (5, $[M - Pr]^{+}$), 143 (7), 129 (100, $[c\text{-}C_6H_{11}COOH_2]^{+}$), 111 (77, $[c\text{-}C_6H_{11}CO]^{+}$), 83 (82, $[c\text{-}C_6H_{11}]^{+}$), 81 (38, $[C_6H_9]^{+}$), 71 (84, $[Am]^{+}$), 70 (91, $[pentene]^{\cdot+}$), 67 (48), 54 (42, $[butadiene]^{\cdot+}$), 53 (39);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_{12}H_{22}O_2$ 198.1620; found: 198.1624; HRMS (ESI+) *m/z*: $[M + Na]^{+}$ calcd for $C_{12}H_{22}O_2Na$ 221.1512; found: 221.1512.

Cyclohexanone oxime (**268**)



mp 85 °C; R_f 0.30 (hexane/EA 2:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3189 (m), 3115 (m), 2938 (s), 2867 (s), 1668 (m), 1482 (m), 1452 (m), 1440 (m), 1355 (s), 1228 (s), 1143 (m), 1109 (m), 996 (vs), 962 (vs), 926 (w), 902 (s), 860 (s), 843 (s), 779 (s), 660 (m);

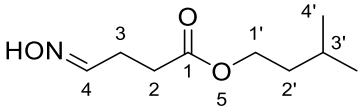
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.58 (br. s, 1H, NOH), 2.52-2.49 (m, 2H, H-2), 2.23-2.20 (m, 2H, H-6), 1.70-1.57 (m, 6H, H-3, H-4, H-5);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 160.9 (s, C-1), 32.3 (t, C-6), 27.0 (t, C-5), 25.9 (t, C-2), 25.7 (t, C-3), 24.6 (t, C-4);

MS (EI+) *m/z*, (%): 113 (100, $[M]^{\cdot+}$), 98 (28), 96 (20, $[M - OH]^+$), 85 (20, $[M - C_2H_4]^{\cdot+}$), 84 (15, $[M - Et]^+$), 81 (27), 79 (11), 72 (38, $[M - allyl]^+$), 68 (29, $[M - HCN - H_2O]^{\cdot+}$), 67 (30), 59 (35), 55 (34), 54 (31 $[butadiene]^{\cdot+}$), 53 (10);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_6H_{11}NO$ 113.0841; found: 113.0840.

Isopentyl 4-(hydroxyimino)butanoate (**270a**)



Prepared by method **A** from cyclobutanone (**269a**, 479 µL, 6.42 mmol), NaHMDS (7.36 mL, 7.36 mmol, 1 M in THF) in THF (75 mL), and *i*-AmONO (1.03 mL, 7.68 mmol) at −78 °C for 45 min, giving 932 mg of a mixture containing **270a** (*E*/*Z* 1.1:1) and a complex mixture of oxidized self-aldol products; yield 206 mg (17%) as 1.3:1 *E*/*Z* mixture as a colourless oil that solidified below 0 °C, mp 24-27 °C.

R_f 0.26, 0.20 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3354-3110 (br.), 2958 (m), 2930 (w), 2872 (w), 1732 (vs), 1465 (w), 1422 (w), 1389 (w), 1367 (w), 1260 (m), 1167 (vs), 1052 (w), 994 (w), 918 (s), 819 (w), 709 (w);

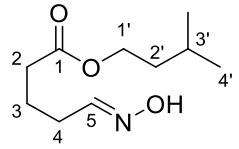
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.53 (s, 1H, NO*H*^{Z}), 8.05 (s, 1H, NO*H*^{E}), 7.50-7.45 (m, 1H, H-4^{E}), 6.78 (t, *J* = 5.3 Hz, 1H, H-4^{Z}), 4.121 (q, *J* = 6.9 Hz, 2H, H-1'^{Z}), 4.116 (q, *J* = 6.9 Hz, 2H, H-1'^{E}), 2.83-2.58 (m, 2H, H-3^{Z}), 2.55-2.49 (m, 6H, H-3^{E}, H-2^{EZ}), 1.67 (non, *J* = 6.7 Hz, 2H, H-3'^{EZ}), 1.51 (q, *J* = 6.9 Hz, 4H, H-2'^{EZ}), 0.91 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 172.7 (s, C-1^{Z}), 172.6 (s, C-1^{E}), 150.8 (d, C-4^{Z}), 150.3 (d, C-4^{E}), 63.62 (t, C-1'^{Z}), 63.59 (t, C-1'^{E}), 37.40 (t, C-2'^{Z}), 37.39 (t, C-2'^{E}), 31.0 (t, C-2^{E}), 30.7 (t, C-2^{Z}), 25.18 (d, C-3'^{Z}), 25.17 (d, C-3'^{E}), 25.1 (t, C-3^{E}), 22.6 (q, C-4'^{EZ}), 20.7 (t, C-3^{Z});

MS (ESI+) *m/z*, (%): 210 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_9H_{17}NNaO_3$ 210.1101; found: 210.1099.

Isopentyl 5-(hydroxyimino)pentanoate (**270b**)



Prepared by method **A** from cyclopentanone (**269b**, 177 µL, 2.0 mmol), NaHMDS (2.3 mL, 2.3 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C for 70 min, giving crude **270b** (385 mg, *E*/*Z* 2.8:1); yield 339 mg (84%) as 1.3:1 *E*/*Z* mixture as a colourless oil.

R_f 0.43, 0.35 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3490-3200 (br.), 3101 (w), 2957 (s), 2932 (w), 2871 (m), 1731 (vs), 1461 (m), 1395 (w), 1368 (w), 1315 (w), 1245 (m), 1162 (vs), 1051 (w), 921 (s), 888 (m), 824 (w), 728 (w), 694 (w);

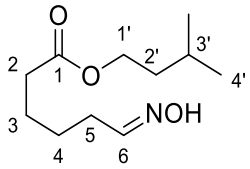
^{1}H NMR (401 MHz, $CDCl_3$): δ 9.08-8.36 (br. s, 1H, NOH^{Z}), 8.36-7.86 (br. s, 1H, NOH^{E}), 7.41 (t, J = 5.9 Hz, 1H, H-5^{E}), 6.71 (t, J = 5.5 Hz, 1H, H-5^{Z}), 4.105 (t, J = 6.9 Hz, 2H, H-1'^{Z}), 4.100 (t, J = 6.9 Hz, 2H, H-1'^{E}), 2.42 (td, J = 7.7, 5.6 Hz, 2H, H-4^{Z}), 2.35 (t, J = 7.4 Hz, 2H, H-2^{Z}), 2.34 (t, J = 7.4 Hz, 2H, H-2^{E}), 2.24 (td, J = 7.4, 5.9 Hz, 2H, H-4^{E}), 1.87-1.79 (m, 4H, H-3^{EZ}), 1.73-1.62 (m, 2H, H-3'^{EZ}), 1.51 (q, J = 6.9 Hz, 2H, H-2'^{EZ}), 1.50 (q, J = 6.9 Hz, 2H, H-2'^{EZ}), 0.91 (d, J = 6.6 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.3 (s, C-1^{EZ}), 151.7 (d, C-5^{Z}), 151.2 (d, C-5^{E}), 63.3 (t, C-1'^{EZ}), 37.4 (t, C-2'^{EZ}), 33.9 (t, C-2^{Z}), 33.6 (t, C-2^{E}), 29.0 (t, C-4^{E}), 25.2 (d, C-3'^{EZ}), 24.5 (t, C-4^{Z}), 22.6 (q, C-4'^{EZ}), 21.9 (t, C-3^{E}), 21.6 (t, C-3^{Z});

MS (ESI+) *m/z*, (%): 224 (100, $[M + Na]^+$), 202 (11, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{19}NNaO_3$ 224.1257; found: 224.1257.

Isopentyl 6-(hydroxyimino)hexanoate (**270c**)



Prepared by method **A** from cyclohexanone (**269c**, 1.65 mL, 16.0 mmol), *i*-AmOH (0.52 mL, 4.8 mmol), *n*-BuLi (16.0 mL, 25.6 mmol, 1.6 M in hexanes), HMDS (4.36 mL, 20.8 mmol) in THF (100 mL), and *i*-AmONO (3.43 mL, 25.6 mmol) at –78 °C for 60 min, giving crude **270c** (3.73 g, *E*/*Z* 1.3:1); yield 2.38 g (69%) as 1.2:1 *E*/*Z* mixture as a colourless, very viscous oil.

R_f 0.41 (hexane/EA 2:1);

IR ($CHCl_3$) $\tilde{\nu}$[cm^{-1}]: 3670 (w), 3587 (m), 3295 (br.), 3113 (m), 2961 (vs), 2935 (vs), 2871 (s), 2736 (w), 1726 (br.), 1464 (m), 1432 (w), 1419 (w), 1395 (m), 1388 (m), 1369 (m), 1353 (w), 1282 (s), 1263 (s), 1186 (s), 1169 (s), 1100 (m), 1063 (m), 966 (m), 948 (m), 921 (m), 902 (m), 841 (w), 825 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 10.00-5.00 (br. s, 2H, NOH^{EZ}), 7.40 (t, J = 6.0 Hz, 1H, H-6^{E}), 6.70 (t, J = 5.5 Hz, 1H, H-6^{Z}), 4.09 (t, J = 6.8 Hz, 4H, H-1'^{EZ}), 2.39 (td, J = 7.6, 5.5 Hz, 2H, H-5^{Z}), 2.32 (t, J = 7.0 Hz, 2H, H-2^{Z}), 2.31 (t, J = 7.0 Hz, 2H, H-2^{E}), 2.21 (td, J = 7.4, 6.1 Hz, 2H, H-5^{E}), 1.72-1.63 (m, 6H, H-3^{EZ}, H-3'^{EZ}), 1.56-1.47 (m, 8H, H-4^{EZ}, H-2'^{EZ}), 0.91 (d, J = 6.6 Hz, 12H, H-4'^{EZ});

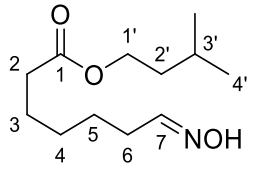
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.71 (s, C-1^{Z}), 173.68 (s, C-1^{E}), 152.3 (d, C-6^{Z}), 151.7 (d, C-6^{E}), 63.2 (t, C-1'^{EZ}), 37.4 (t, C-2'^{EZ}), 34.10 (t, C-2^{E}), 34.08 (t, C-2^{Z}), 29.3 (t, C-5^{E}), 26.1 (t, C-4^{E}), 25.7 (t, C-4^{Z}), 25.2 (d, C-3'^{EZ}), 24.76 (t, C-3^{E}), 24.74 (t, C-3^{Z}), 24.5 (t, C-5^{Z}), 22.6 (q, C-4'^{EZ});

MS (ESI+) *m/z*, (%): 238 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{21}NNaO_3$ 238.1414; found: 238.1414;

Anal. Calcd for $C_{11}H_{21}O_3N$ (215.29): C, 61.37; H, 9.83; N, 6.51. Found: C, 61.19; H, 9.89; N, 6.01.

Isopentyl 7-(hydroxyimino)heptanoate (**270d**)



Prepared by method **A** from cycloheptanone (**269d**, 473 µL, 4.0 mmol), *i*-AmOH (131 µL, 1.2 mmol), *n*-BuLi (4.0 mL, 6.4 mmol, 1.6 M in hexanes), HMDS (1.1 mL, 5.2 mmol) in THF (40 mL), and *i*-AmONO (859 µL, 6.4 mmol) at –78 °C for 20 min, giving crude **270d** (1.01 g, *E*/*Z* 1.3:1); yield 710 mg (77%) as 1.2:1 *E*/*Z* mixture as a colourless, very viscous oil.

R_f 0.63, 0.51 (hexane/EA 2:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3150 (br.), 3150-3000 (br.), 2965 (s), 2940 (s), 2877 (m), 1738 (s), 1468 (m), 1393 (w), 1372 (m), 1269 (m), 1172 (s), 972 (w), 923 (m), 825 (m), 734 (w);

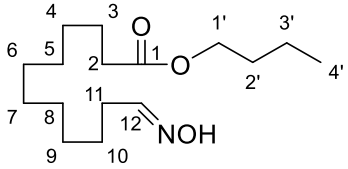
^{1}H NMR (401 MHz, $CDCl_3$): δ 9.00-8.35 (br. s, 1H, NO*H*^{Z}), 8.35-7.60 (br. s, 1H, NO*H*^{E}), 7.41 (t, *J* = 6.1 Hz, 1H, H-7^E), 6.70 (t, *J* = 5.6 Hz, 1H, H-7^Z), 4.09 (t, *J* = 6.8 Hz, 4H, H-1'^{EZ}), 2.38 (td, *J* = 7.6, 5.5 Hz, 2H, H-6^Z), 2.30 (t, *J* = 7.5 Hz, 2H, H-2^Z), 2.29 (t, *J* = 7.5 Hz, 2H, H-2^E), 2.20 (q, *J* = 6.2 Hz, 2H, H-6^E), 1.72-1.59 (m, 6H, H-3^{EZ}, H-3'^{EZ}), 1.63-1.47 (m, 8H, H-5^{EZ}, H-2'^{EZ}), 1.41-1.32 (m, 4H, H-4^{EZ}), 0.91 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.9 (s, C-1^{EZ}), 152.6 (d, C-7^Z), 152.0 (d, C-7^E), 63.2 (t, C-1'^{EZ}), 37.5 (t, C-2'^{EZ}), 34.32 (t, C-2^Z), 34.30 (t, C-2^E), 29.4 (t, C-6^E), 29.0 (t, C-4^Z), 28.7 (t, C-4^E), 26.3 (t, C-5^E), 25.8 (t, C-5^Z), 25.2 (d, C-3'^{EZ}), 24.9 (t, C-6^Z), 24.8 (t, C-3^{EZ}), 22.6 (q, C-4'^{EZ});

MS (ESI+) *m/z*, (%): 252 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{23}NNaO_3$ 252.1570; found: 252.1571.

Butyl 12-(hydroxyimino)dodecanoate (**270e**)



Prepared by method **A** from cyclododecanone (**269e**, 182 mg, 1.0 mmol), *n*-BuOH (55 µL, 0.6 mmol), *n*-BuLi (1.25 mL, 2.0 mmol, 1.6 M in hexanes), HMDS (293 µL, 1.4 mmol) in THF (15 mL), and *n*-BuONO (210 µL, 1.8 mmol) at –78 °C for 40 min, giving crude **270e** (356 mg, *E*/*Z* 1.1:1); yield 233 mg (82%) as 1.3:1 *E*/*Z* mixture as a colourless solid, mp 64 °C.

R_f 0.52 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3210 (m), 3100 (m), 3046 (s), 2926 (vs), 2883 (m), 2858 (s), 1730 (vs), 1672 (w), 1469 (m), 1447 (m), 1423 (m), 1367 (w), 1330 (m), 1320 (m), 1293 (m), 1264 (m), 1235 (m), 1205 (m), 1175 (vs), 1081 (m), 943 (m), 926 (m), 868 (m), 832 (m), 745 (w), 721 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.80-7.50 (br. s, 2H, NO*H*^{EZ}), 7.41 (t, *J* = 6.1 Hz, 1H, H-12^E), 6.71 (t, *J* = 5.5 Hz, 1H, H-12^Z), 4.04 (t, *J* = 6.7 Hz, 4H, H-1'^{EZ}), 2.34 (td, *J* = 7.6, 5.4 Hz, 2H, H-11^Z), 2.26 (t, *J* = 7.6 Hz, 4H, H-2^{EZ}), 2.18 (td, *J* = 7.5, 6.1 Hz, 2H, H-11^E), 1.61-1.55 (m, 8H, H-2'^{EZ}, H-3^{EZ}), 1.50-1.42 (m, 4H, H-10^{EZ}), 1.40-1.29 (m, 4H, H-3'^{EZ}), 1.29-1.23 (m, 24H, H-4^E to H-9^E, H-4^Z to H-9^Z), 0.90 (t, *J* = 7.4 Hz, 6H, H-4'^{EZ});

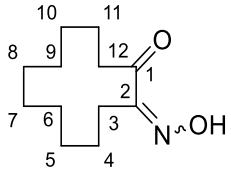
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 174.2 (s, C-1^{EZ}), 153.1 (d, C-12^{Z}), 152.4 (d, C-12^{E}), 64.3 (t, C-$1'^{EZ}$), 34.5 (t, C-2^{EZ}), 30.8 (t, C-$2'^{EZ}$), 29.6 (t), 29.53 (t), 29.51 (t), 29.49 (t), 29.47 (t), 29.37 (t, 2×C), 29.36 (t), 29.34 (t), 29.33 (t), 29.25 (t, 2×C), 29.16 (t), 26.7 (t, C-10^{E}), 26.2 (t, C-10^{Z}), 25.1 (t, C-3^{EZ}), 25.0 (t, C-11^{Z}), 19.3 (t, C-$3'^{EZ}$), 13.8 (q, C-$4'^{EZ}$);

MS (ESI+) *m/z*, (%): 609 (6, $[2M + K]^+$), 593 (6, $[2M + Na]^+$), 416 (14), 330 (7), 308 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{31}NNaO_3$ 308.2196; found: 308.2197;

Anal. Calcd for $C_{16}H_{31}NO_3$ (285.45): C, 67.33; H, 10.95; N, 4.91. Found: C, 67.69; H, 11.21; N, 4.74.

2-(Hydroxyimino)cyclododecan-1-one (**271a**)



Side-product of the cleavage of cyclododecanone (**269e**, 182 mg, 1 mmol) by KHMDS (1.2 mL, 1.2 mol, 1 M in THF), and *n*-BuONO (164 µL, 1.4 mmol) at −78 °C (table 3, entry 6); yield in order of elution 127 mg (44%) of **270e**, 15 mg (7%) of **271a**-A as a single unassigned isomer as a colourless solid, and 20 mg (9%) of **271a**-B as a single isomer as colourless crystals, mp 64-70 °C.

R_f 0.26, 0.18 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3260 (s), 3225 (s), 3041 (w), 2945 (s), 2928 (s), 2871 (m), 1665 (vs), 1432 (m), 1420 (s), 1377 (m), 1355 (m), 1344 (m), 1288 (w), 1240 (m), 1200 (m), 1122 (m), 1089 (w), 1045 (w), 1023 (s), 1001 (s), 988 (vs), 935 (m), 877 (m), 840 (w), 759 (s), 730 (m), 709 (m), 693 (w), 602 (s);

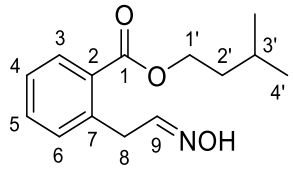
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.65-8.25 (br. s, 1H, OH^{B}), 8.35-7.80 (br. s, 1H, OH^{A}), 2.89-2.86 (m, 2H, H-12^{B}), 2.78-2.75 (m, 2H, H-12^{A}), 2.70-2.66 (m, 2H, H-3^{A}), 2.51-2.49 (m, 2H, H-3^{B}), 1.82-1.73 (m, 2H, H-11^{B}), 1.77-1.69 (m, 2H, H-11^{A}), 1.56-1.47 (m, 2H, H-4^{A}), 1.52-1.20 (m, 26H, H-5^{A} to H-10^{A}, H-4^{B} to H-10^{B});

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 203.1 (s, C-1^{B}), 201.2 (s, C-1^{A}), 160.4 (s, C-2^{A}), 158.2 (s, C-2^{B}), 43.5 (t, C-12^{B}), 38.5 (t, C-12^{A}), 30.7 (t, C-3^{B}), 26.7 (t, CH_2^{B}), 26.4 (t, CH_2^{A}), 26.3 (t, CH_2^{A}), 26.2 (t, CH_2^{B}), 25.9 (t, CH_2^{B}), 25.7 (t, CH_2^{B}), 25.4 (t, CH_2^{B}), 25.0 (t, CH_2^{A}), 24.6 (t, CH_2^{A}), 23.8 (t, CH_2^{A}), 23.6 (t, CH_2^{B}), 23.4 (t, CH_2^{A}), 23.3 (t, CH_2^{A}), 23.2 (t, CH_2^{A}), 22.9 (t, CH_2^{B}), 22.6 (t, CH_2^{B}), 22.0 (t, C-3^{A});

MS (CI+) *m/z*, (%): 212 (100, $[M + H]^+$), 210 (18, $[M – H]^+$), 194 (32, $[M – OH]^+$), 183 (13, $[M – CO]^{\cdot+}$), 166 (16, $[M – H_2O – HCN]^{\cdot+}$);

HRMS (CI+) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{22}NO_2$ 212.1651; found: 212.1653.

Isopentyl 2-(2-(hydroxyimino)ethyl)benzoate (**270f**)



Prepared by method **A** from 1-indanone (**269f**, 264 mg, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at –78 °C for 90 min, giving crude **270f** (528 mg, *E*/*Z* 1:1; yield 357 mg (71%) as 1:1.1 *E*/*Z* mixture as a colourless, very viscous oil.

R_f 0.32 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3000 (br.), 2967 (m), 2880 (w), 1718 (s), 1607 (w), 1469 (m), 1453 (m), 1391 (w), 1259 (vs), 1137 (s), 1084 (s), 946 (m), 804 (w), 752 (s), 709 (s), 665 (m);

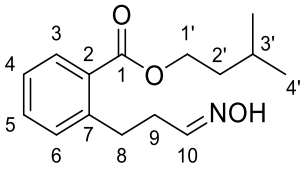
^{1}H NMR (401 MHz, $CDCl_3$): δ 11.00-5.00 (br. s, 2H, NO*H*^{EZ}), 7.99-7.94 (m, 2H, H-3^{EZ}), 7.63 (t, *J* = 5.9 Hz, 1H, H-9^{Z}), 7.46 (ddd, *J* = 7.5, 7.0, 1.4 Hz, 2H, H-5^{EZ}), 7.35-7.28 (m, 4H, H-4^{EZ}, H-6^{EZ}), 6.89 (t, *J* = 5.1 Hz, 1H, H-9^{E}), 4.34 (t, *J* = 6.8 Hz, 4H, H-1'^{EZ}), 4.07 (d, *J* = 5.0 Hz, 2H, H-8^{E}), 3.92 (d, *J* = 5.9 Hz, 2H, H-8^{Z}), 1.83-1.71 (m, 2H, H-3'^{EZ}), 1.66 (q, *J* = 6.7 Hz, 2H, H-2'^{Z}), 1.65 (q, *J* = 6.7 Hz, 2H, H-2'^{E}), 0.97 (d, *J* = 6.6 Hz, 6H, H-4'^{Z}), 0.96 (d, *J* = 6.6 Hz, 6H, H-4'^{E});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 167.4 (s, C-1$^{E/Z}$), 167.3 (s, C-1$^{E/Z}$), 151.1 (d, C-9^{Z}), 150.8 (d, C-9^{E}), 138.5 (s, C-7^{E}), 135.1 (s, C-7^{Z}), 132.5 (d, 2×C, Ar-CH), 131.9 (d, Ar-CH), 131.6 (d, Ar-CH), 131.2 (d, Ar-CH), 131.1 (d, Ar-CH), 130.0 (s, C-2$^{E/Z}$), 129.9 (s, C-2$^{E/Z}$), 127.2 (d, C-4/6$^{E/Z}$), 127.1 (d, C-4/6$^{E/Z}$), 64.0 (t, C-1'$^{E/Z}$), 63.9 (t, C-1'$^{E/Z}$), 37.5 (t, C-2'$^{E/Z}$), 37.4 (t, C-2'$^{E/Z}$), 34.8 (t, C-8^{Z}), 34.3 (t, C-8^{E}), 24.3 (d, C-3'^{EZ}), 22.6 (q, C-4'^{EZ});

MS (ESI−) *m/z*, (%): 248 (39, [M − H]), 160 (100, [M – H – *i*-AmOH]);

HRMS (ESI−) *m/z*: [M − H]$^-$ calcd for $C_{14}H_{18}NO_3$ 248.1292; found: 248.1288.

Isopentyl 2-(3-(hydroxyimino)propyl)benzoate (**270g**)



Prepared by method **A** from 1-tetralone (**269g**, 266 µL, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C, warmed to −40 °C over 1 h. A deep red colour developed on oxidation and persisted until quenching, giving a green crude product (525 mg); yield in order of elution 218 mg (41%) of **270g** as 1.8:1 *E*/*Z* mixture as a colourless oil, 113 mg (21%) of (*E*)-**270g** as colourless oil, and 117 mg (33%) of **271b** as a single unassigned isomer as colourless solid.

R_f 0.39 (hexane/EA 2.5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3267 (br.), 2957 (m), 2930 (w), 2871 (w), 1714 (s), 1601 (w), 1577 (w), 1449 (m), 1292 (w), 1250 (vs), 1132 (m), 1081 (s), 922 (m), 906 (m), 749 (s), 709 (m), 663 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.40-8.00 (br. s, 1H, NO*H*^{Z}), 7.91 (dd, *J* = 7.9, 1.0 Hz, 2H, H-3^{EZ}), 7.84 (br. s, 1H, NO*H*^{E}), 7.49 (t, *J* = 5.9 Hz, 1H, H-10^{E}), 7.43 (td, *J* = 7.5, 1.5 Hz, 2H, H-5^{EZ}), 7.30-7.24 (m, 4H, H-4^{EZ}, H-6^{EZ}), 6.80 (t, *J* = 5.4 Hz, 1H, H-10^{Z}), 4.33 (t, *J* = 6.8 Hz, 4H, H-1'^{EZ}), 3.18-3.11 (m, 4H, H-8^{EZ}), 2.75 (td, *J* = 7.9, 5.4 Hz, 2H, H-9^{Z}), 2.57-2.51 (m, 2H, H-9^{E}), 1.82-1.75 (m, 2H, H-

3'^{EZ}), 1.66 (q, *J* = 6.9 Hz, 2H, H-2'^{E}), 1.65 (q, *J* = 6.7 Hz, 2H, H-2'^{Z}), 0.97 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

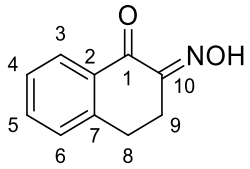
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 167.63 (s, C-1^{Z}), 167.57 (s, C-1^{E}), 152.0 (d, C-10^{Z}), 151.6 (d, C-10^{E}), 142.7 (s, C-7^{Z}), 142.6 (s, C-7^{E}), 135.6 (d, C-5^{Z}), 132.2 (d, C-5^{E}), 131.2 (d, C-6/3^{E}), 131.03 (d, C-6/3^{E}), 131.00 (d, C-6/3^{Z}), 130.98 (d, C-6/3^{Z}), 129.82 (s, C-2^{E}), 129.81 (s, C-2^{Z}), 126.49 (d, C-4^{E}), 126.46 (d, C-4^{Z}), 63.8 (t, C-1'^{EZ}), 37.5 (t, C-2'^{EZ}), 31.7 (t, C-8^{E}), 31.5 (t, C-9^{E}), 30.8 (t, C-8^{Z}), 26.7 (t, C-9^{Z}), 25.3 (d, C-3'^{EZ}), 22.6 (q, C-4'^{EZ});

MS (CI+) *m/z*, (%): 264 (17, $[M + H]^+$), 246 (45, $[M - OH]^+$), 176 (87, [M – *i*-AmO]$^+$), 158 (100, [M – H_2O – *i*-AmO]$^+$);

MS (ESI+) *m/z*, (%): 549 (19, $[2M + Na]^+$), 286 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{21}NNaO_3$ 286.1414; found: 286.1412.

2-(Hydroxyimino)-3,4-dihydronaphthalen-1(2H)-one (**271b**)



Prepared by method **A** from 1-tetralone (**269g**, 266 µL, 2.0 mmol), KHMDS (2.4 ml, 2.4 mmol, 1 M in THF), and *t*-BuONO (333 µL, 2.8 mmol) at −78 °C, warmed to −5 °C, giving a green crude product (358 mg); yield 253 mg (72%) as a single unassigned isomer as colourless crystals, mp >120 °C (dec.). Also obtained together with **270g** in cleavage reactions (table 23, entries 10-12). Unstable when stored at r.t.

R_f 0.16 (hexane/EA 2.5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3183 (br.), 2964 (w), 1701 (s), 1617 (w), 1602 (s), 1460 (s), 1412 (m), 1302 (s), 1263 (m), 1236 (m), 1052 (s), 1033 (m), 1021 (m), 906 (vs), 804 (s), 791 (m), 733 (vs), 707 (s), 659 (s), 627 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 11.00-10.30 (br. s, 1H, NO*H*), 8.12 (d, *J* = 7.7 Hz, 1H, H-3), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H, H-5), 7.38 (t, *J* = 7.4, Hz, 1H, H-4), 7.30 (d, *J* = 7.3 Hz, 1H, H-6), 3.20-3.17 (m, 2H, H-9), 3.08 (t, *J* = 6.6 Hz, 2H, H-8);

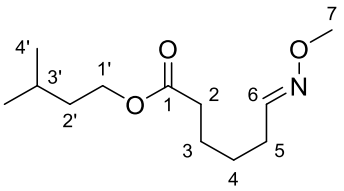
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 183.1 (s, C-1), 152.9 (s, C-10), 143.5 (s, C-7), 134.4 (d, C-5), 133.4 (s, C-2), 128.7 (d, C-3/6), 128.5 (d, C-3/6), 127.4 (d, C-4), 26.8 (t, C-8), 23.4 (t, C-9);

MS (CI+) *m/z*, (%): 176 (64, $[M + H]^+$), 175 (49, $[M]^{\cdot+}$), 158 (100, $[M - OH]^+$), 130 (10, $[M - OH - CO]^+$);

MS (ESI+) *m/z*, (%): 373 (42, $[2M + Na]^+$), 198 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9NNaO_2$ 198.0525; found: 198.0525.

Isopentyl 6-(methoxyimino)hexanoate (**272**)



Prepared by modified method **A** from cyclohexanone (**269c**, 1.04 mL, 10 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (1.55 mL, 11.5 mmol) in THF (40 mL) at –78 °C. After 60 min, calcinated K_2CO_3 (2.07 mg, 15 mmol) was added followed by MeI (1.87 mL, 30.0 mmol). After 5 min, the dry-ice bath was removed and vigorous stirring was continued overnight; yield 1.17 g (51%) as 1.4:1 *E:Z* mixture as a colourless oil.

R_f 0.75 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2959 (m), 2871 (w), 2816 (w), 1738 (vs), 1466 (m), 1369 (w), 1232 (w), 1183 (m), 1158 (s), 1114 (w), 1053 (vs), 865 (m);

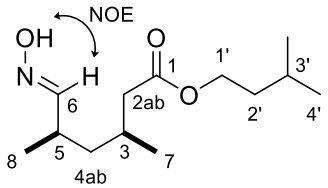
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.35 (t, *J* = 6.2 Hz, 1H, H-6^E), 6.62 (t, *J* = 5.4 Hz, 1H, H-6^Z), 4.10 (t, *J* = 7.0 Hz, 4H, H-1'^{EZ}), 3.86 (s, 3H, H-7^Z), 3.81 (s, 3H, H-7^E), 2.36-2.30 (m, 6H, H-2^{EZ}, H-5^Z), 2.20 (q, *J* = 6.9 Hz, 2H, H-5^E), 1.76-1.61 (m, 6H, H-3^{EZ}, H-3'^{EZ}), 1.59-1.45 (m, 8H, H-4^{EZ}, H-2'^{EZ}), 0.92 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.56 (s, C-1^Z), 173.54 (s, C-1^E), 151.2 (d, C-6^Z), 150.3 (d, C-6^E), 63.1 (t, C-4'^{EZ}), 61.7 (q, C-7^Z), 61.3 (q, C-7^E), 37.4 (t, C-2'^{EZ}), 34.1 (t, C-2^E), 34.0 (t, C-2^Z), 29.3 (t, C-5^E), 26.2 (t, C-4^E), 25.8 (t, C-4^Z), 25.3 (t, C-5^Z), 25.2 (d, C-3'^{EZ}), 24.7 (t, C-3^Z), 24.5 (t, C-3^E), 22.6 (q, C-4'^{EZ});

MS (ESI+) *m/z*, (%): 252 (100, [M + Na]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd for $C_{12}H_{23}NNaO_3$ 252.1570; found: 252.1571.

Isopentyl (3S,5R*)-6-(hydroxyimino)-3,5-dimethylhexanoate* (**274a**)



Prepared by method **A** from *cis*-3,5-dimethylcyclohexanone (**273a**, 252 mg, 2.0 mmol) and various base systems (table 24). Optimal is NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C for 30 min, giving crude **274a** (507 mg, *E*/*Z* = 3.7:1); yield 444 mg (91%) of **274a** as 3.5:1 *E*/*Z* mixture as a colourless oil.

R_f 0.30 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3100 (br.), 2968 (s), 2939 (s), 2881 (m), 1737 (vs), 1465 (s), 1389 (m), 1372 (m), 1300 (m), 1270 (m), 1231 (ws), 1180 (w), 1125 (w), 1097 (w), 1053 (m), 977 (m), 942 (s);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.75 (br. s, 1H, O*H*^{Z}), 8.39 (br. s, 1H, O*H*^{E}), 7.23 (d, *J* = 7.5 Hz, 1H, H-6^E), 6.48 (d, *J* = 7.8 Hz, 1H, H-6^Z), 4.09 (t, *J* = 6.9 Hz, 4H, H-1'^{EZ}), 3.31-3.21 (m, 1H, H-5^Z), 2.52-2.47 (m, 1H, H-5^E), 2.29-2.22 (m, 2H, H-2a^{EZ}), 2.16-2.10 (m, 2H, H-2b^{EZ}), 2.04-1.90 (m, 2H, H-3^{EZ}), 1.67 (non, *J* = 6.7 Hz, 2H, H-3'^{EZ}), 1.53-1.41 (m, 6H, H-2'^{EZ}, H-4a^{EZ}), 1.24-1.16 (m, 2H, H-4b^{EZ}),

1.06 (d, J = 6.8 Hz, 3H, H-8^{E}), 1.03 (d, J = 6.8 Hz, 3H, H-8^{Z}), 0.95 (d, J = 6.6 Hz, 3H, H-7^{Z}), 0.93 (d, J = 6.6 Hz, 3H, H-7^{E}), 0.90 (d, J = 6.6 Hz, 12H, H-4'^{EZ});

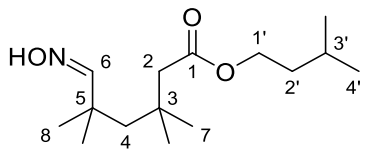
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 173.2 (s, C-1^{Z}), 173.1 (s, C-1^{E}), 156.9 (d, C-6^{Z}), 156.0 (d, C-6^{E}), 63.12 (t, C-1'^{E}), 63.09 (t, C-1'^{Z}), 42.2 (t, C-2^{Z}), 42.1 (t, C-2^{E}), 42.0 (t, C-4^{Z}), 41.7 (t, C-4^{E}), 37.46 (t, C-2'^{Z}), 37.45 (t, C-2'^{E}), 32.1 (d, C-5^{E}), 28.6 (d, C-3^{Z}), 28.1 (d, C-3^{E}), 27.3 (d, C-5^{Z}), 25.2 (d, C-3'^{EZ}), 22.6 (q, C-4'^{EZ}), 19.7 (q, C-7^{Z}), 19.6 (q, C-7^{E}), 18.9 (q, C-8^{E}), 18.1 (q, C-8^{Z});

MS (CI+) *m/z*, (%): 244 (72, $[M + H]^+$), 228 (96, $[M - Me]^+$), 226 (100, $[M - OH]^+$), 199 (43, $[M - OH - HCN]^+$), 156 (93, [M – *i*-AmO]$^+$), 140 (28, [M – Me – *i*-AmOH]$^+$), 138 (73, [M – *i*-AmO − $H_2O]^+$), 129 (48, $[M - OH - HCN - C_5H_{10}]^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{26}NO_3$ 244.1907; found: 244.1914;

Anal. Calcd for $C_{13}H_{25}NO_3$ (178.23): C, 64.16; H, 10.36; N, 5.76. Found: C, 64.13; H, 10.48; N, 5.69.

Isopentyl (E)-6-(hydroxyimino)-3,3,5,5-tetramethylhexanoate (**274b**)



Prepared by method **A** from 3,3,5,5-tetramethylcyclohexan-1-one (**273b**, 154 mg, 1.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF) in THF (8 mL), and *i*-AmONO (175 µL, 1.3 mmol) at −78 °C, warmed to r.t. over 1 h; yield 174 mg (64%) as single *E* isomer as a colourless oil.

R_f 0.23 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3150 (br), 2958 (s), 2931 (w), 2872 (w), 1730 (vs), 1465 (m), 1385 (m), 1368 (m), 1348 (w), 1316 (w), 1288 (w), 1223 (s), 1148 (m), 1106 (w), 1051 (w), 974 (w), 939 (vs), 866 (w);

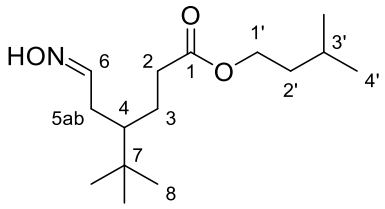
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.50-6.50 (br. s, 1H, NO*H*), 7.38 (s, 1H, H-6), 4.08 (t, J = 6.9 Hz, 2H, H-1'), 2.23 (s, 2H, H-2), 1.69 (non, J = 6.7 Hz, 1H, H-3'), 1.61 (s, 2H, H-4), 1.51 (q, J = 6.8 Hz, 2H, H-2'), 1.16 (s, 6H, H-8), 1.04 (s, 6H, H-7), 0.91 (d, J = 6.6 Hz, 6H, H-4');

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 172.3 (s, C-1), 159.9 (d, C-6), 62.9 (t, C-1'), 52.2 (t, C-4), 48.0 (t, C-2), 37.7 (s, C-5), 37.5 (t, C-2'), 34.7 (s, C-3), 29.3 (q, C-7), 27.9 (q, C-8), 25.2 (d, C-3'), 22.6 (q, C-4');

MS (ESI+) *m/z*, (%): 565 (18, $[2M + Na]^+$), 310 (6, $[M + K]^+$), 294 (100, $[M + Na]^+$), 272 (4, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{29}O_3NNa$ 294.2040; found: 294.2039.

Isopentyl 4-(2-(hydroxyimino)ethyl)-5,5-dimethylhexanoate (**274c**)



Prepared by method **A** from 4-(*tert*-butyl)cyclohexan-1-one (**273c**, 308 mg, 2.0 mmol), KHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C for 30 min, giving red-brown crude **274c** (555 mg, *E*/*Z* 1.1:1); yield 364 mg (67%) as 1:1.4 *E*/*Z* mixture as a colourless oil.

R_f 0.46, 0.41 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3100 (br.), 2967 (s), 2918 (m), 2880 (s), 1738 (s), 1473 (m), 1401 (w), 1371 (w), 1344 (m), 1286 (m), 1162 (s), 1063 (w), 953 (m), 924 (m), 899 (m), 694 (w), 609 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.45-8.05 (br. s, 1H, NO*H*^{Z}), 7.93-7.54 (br. s, 1H, NO*H*^{E}), 7.43 (t, *J* = 6.9 Hz, 1H, H-6^E), 6.77 (t, *J* = 6.8 Hz, 1H, H-6^Z), 4.09 (t, *J* = 6.9 Hz, 4H, H-2'^{EZ}), 2.48-2.21 (m, 7H, H-2^{EZ}, H-5a^{EZ}, H-5b^Z), 2.07 (dt, *J* = 15.3, 7.1 Hz, 1H, H-5b^E), 1.91-1.75 (m, 4H, H-3^{EZ}), 1.69 (non, *J* = 6.7 Hz, 2H, H-3'^{EZ}), 1.51 (q, *J* = 6.8 Hz, 4H, H-2'^{EZ}), 1.47-1.35 (m, 2H, H-4^{EZ}), 0.91-0.90 (m, 12H, H-4'^{EZ}), 0.91 (s, 18H, H-8^{EZ});

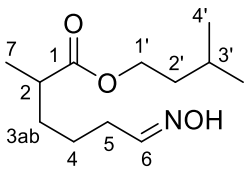
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.95 (s, C-1^Z), 173.86 (s, C-1^E), 153.5 (br. d, C-6^Z), 152.8 (br. d, C-6^E), 63.3 (t, C-1'^{EZ}), 46.3 (d, C-4^Z), 45.9 (d, C-4^E), 37.5 (t, C-2'^{EZ}), 34.08 (s, C-7^Z), 34.05 (s, C-7^E), 33.9 (t, C-2$^{Z/E}$), 33.7 (t, C-2$^{Z/E}$), 30.7 (t, C-5^E), 27.8 (q, C-8^Z), 27.7 (q, C-8^E), 26.5 (t, C-3$^{Z/E}$/5^Z), 26.2 (t, C-3$^{Z/E}$/5^Z), 25.9 (t, C-3$^{Z/E}$/5^Z), 25.2 (d, C-3'^{EZ}), 22.6 (q, C-4'^{EZ});

MS (CI+) *m/z*, (%): 272 (100, $[M + H]^+$), 256 (61, $[M - Me]^+$), 254 (43, $[M - OH]^+$), 214 (16, $[M - t\text{-Bu}]^+$), 198 (38, $[M - OH - \text{isobutene}]^+$), 184 (46, $[M - i\text{-AmO}]^+$), 166 (78, $[M - OH - i\text{-AmOH}]^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{30}NO_3$ 272.2226; found: 272.2228;

Anal. Calcd for $C_{15}H_{29}NO_3$ (271.40): C, 66.38; H, 10.77; N, 5.16. Found: C, 66.17; H, 10.87; N, 5.10.

Isopentyl 6-(hydroxyimino)-2-methylhexanoate (**279a**)



Prepared by method **A** from 2-methylcyclohexanone (**278a**, 243 µL, 2.0 mmol) and various base systems (table 5). Optimal is NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C for 50 min, giving crude **279a** (487 mg, *E*/*Z* 1.2:1); yield 314 mg (68%) of **279a** as 1.2:1 *E*/*Z* mixture as a colourless oil.

R_f 0.21 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3270 (br.), 2957 (s), 2871 (m), 1730 (vs), 1462 (s), 1387 (w), 1368 (w), 1256 (m), 1163 (vs), 1134 (w), 1078 (m), 922 (s), 824 (w), 742 (w), 600 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.51 (br. s, 1H, NO*H*^{E}), 8.10 (br. s, 1H, NO*H*^{Z}), 7.40 (t, *J* = 6.0 Hz, 1H, H-6^E), 6.69 (t, *J* = 5.5 Hz, 1H, H-6^Z), 4.10 (t, *J* = 6.9 Hz, 2H, H-1'^{Z}), 4.09 (t, *J* = 6.9 Hz, 2H, H-

1'^{E}), 2.49-2.35 (m, 4H, H-2^{EZ}, H-5^{Z}), 2.19 (td, *J* = 7.3, 6.1 Hz, 2H, H-5^{E}), 1.73-1.62 (m, 4H, H-3a^{EZ}, H-3'^{EZ}), 1.54-1.39 (m, 10H, H-2'^{EZ}, H-3b^{EZ}, H-4^{EZ}), 1.15 (d, *J* = 7.0 Hz, 3H, H-7^{Z}), 1.14 (d, *J* = 7.0 Hz, 3H, H-7^{E}), 0.91 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 176.76 (s, C-1^{Z}), 176.74 (s, C-1^{E}), 152.4 (d, C-6^{Z}), 151.8 (d, C-6^{E}), 63.2 (t, C-1'^{EZ}), 39.51 (d, C-2^{E}), 39.49 (d, C-2^{Z}), 37.5 (t, C-2'^{EZ}), 33.5 (t, C-3^{Z}), 33.2 (t, C-3^{E}), 29.5 (t, C-5^{E}), 25.2 (d, C-3'^{EZ}), 24.9 (t, C-4^{Z}), 24.4 (t, C-4^{E}), 23.9 (t, C-5^{Z}), 22.59 (q, C-4'^{E}), 22.58 (q, C-4'^{Z}), 17.26 (q, C-7^{Z}), 17.24 (q, C-7^{E});

MS (CI+) *m/z*, (%): 230 (22, $[M + H]^+$), 212 (13, $[M - OH]^+$), 142 (100, [M – *i*-AmO]$^+$), 124 (29, [M – OH – *i*-AmOH]$^+$), 115 (45, [*i*-AmOCO]$^+$), 96 (44, [M – OH – *i*-AmOH − CO]$^+$), 71 (53, [*i*-Am]$^+$);

MS (ESI+) *m/z*, (%): 481 (11, $[2M + Na]^+$), 252 (100, $[M + Na]^+$), 230 (12, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{23}NNaO_3$ 252.1570; found: 252.1571.

Cleavage of 2-methylcyclohexanone (278a) via thermodynamic enolate

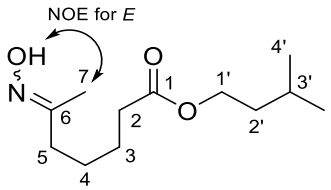
Step 1. ((2-Methylcyclohex-1-en-1-yl)oxy)trimethylsilane (**278a'**) was prepared from 2-methylcyclohexanone (**278a**, 1.21 mL, 10 mmol) as a 6:1 mixture of constitutional isomers, yield 1.5 g (80%).[273]

^{1}H NMR (401 MHz, C_6D_6): δ 2.04-1.97 (m, 2H), 1.94-1.89 (m, 2H), 1.69 (tt, *J* = 1.9, 1.0 Hz, 3H), 1.57-1.50 (m, 2H), 1.49-1.43 (m, 2H), 0.17 (s, 9H);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 143.5 (s), 111.3 (s), 30.8 (t), 30.5 (t), 24.2 (t), 23.5 (t), 16.8 (q), 0.9 (q).

Step 2. Cleavage by method **B** from silyl enol ether **278a'** (369 mg, 2.0 mmol), MeLi (1.6 mL, 2.6 mmol, 1.6 M in Et_2O), and *i*-AmONO (405 μL, 3.0 mmol), giving a crude oily 15:1 mixture of **280a/279a** (460 mg). Purification yielded 324 mg of **280a** as a 5:1 *E/Z* mixture and 53 mg of (*E*)-**280a** (82% based on global silyl enol ether, 95% based on the thermodynamic silyl enol ether) as colourless oils.

Isopentyl 6-(hydroxyimino)heptanoate (**280a**)



R_f 0.35 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3050 (br.), 2957 (s), 2929 (m), 2870 (m), 1733 (vs), 1462 (m), 1389 (w), 1367 (m), 1287 (w), 1251 (m), 1184 (m), 1167 (s), 1143 (s), 1084 (m), 1066 (m), 1050 (w), 949 (s), 741 (w), 645 (w);

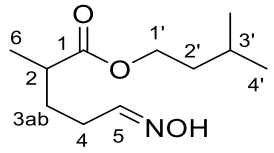
^{1}H NMR (401 MHz, C_6D_6): δ 10.00-8.75 (br. s, 2H, NO*H*^{EZ}), 4.053 (t, *J* = 6.9 Hz, 2H, H-1'^{E}), 4.046 (t, *J* = 6.9 Hz, 2H, H-1'^{Z}), 2.26 (t, *J* = 7.4 Hz, 2H, H-5^{Z}), 2.12 (t, *J* = 7.4 Hz, 2H, H-2^{Z}), 2.09 (t, *J* = 7.3 Hz, 2H, H-2^{E}), 1.94 (t, *J* = 7.2 Hz, 2H, H-5^{E}), 1.71 (s, 3H, H-7^{E}), 1.60 (s, 3H, H-7^{Z}), 1.57-1.46 (m, 6H, H-3^{EZ}, H-3'^{EZ}), 1.39-1.28 (m, 8H, H-2'^{EZ}, H-4^{EZ}), 0.783 (d, *J* = 6.6 Hz, 6H, H-4'^{E}), 0.780 (d, *J* = 6.6 Hz, 6H, H-4'^{Z});

$^{13}C\{^{1}H\}$ NMR (101 MHz, C_6D_6): δ 172.98 (s, C-1^{E}), 172.96 (s, C-1^{Z}), 157.3 (s, C-6^{Z}), 157.2 (s, C-6^{E}), 62.9 (t, C-1'^{EZ}), 37.8 (t, C-2'^{EZ}), 35.5 (t, C-5^{E}), 34.1 (t, C-2^{Z}), 34.0 (t, C-2^{E}), 28.4 (t, C-5^{Z}), 25.9 (t, C-4^{E}), 25.3 (d, C-3'^{EZ}), 25.2 (t, C-4^{Z}), 24.7 (t, C-3^{EZ}), 22.5 (q, C-4'^{EZ}), 19.6 (q, C-7^{Z}), 13.4 (q, C-7^{E});

MS (ESI+) *m/z*, (%): 481 (5, $[2M + Na]^+$), 252 (100, $[M + Na]^+$), 230 (4, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{23}NO_3Na$ 252.1570; found: 252.1568.

Isopentyl 5-(hydroxyimino)-2-methylpentanoate (**279b**)



Prepared by method **A** from 2-methylcyclopentanone (**278b**, 214 µl, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 m in THF), and *i*-AmONO (322 µl, 2.4 mmol) at −78 °C for 30 min; yield 374 mg of colourless oil containing by ^{1}H NMR 93:7 mixture of **279b** (80%) as 1.1:1 *E*/*Z* mixture and **280b** (6%), and 11 mg (2%) of pure **280b** as colourless oil (overall 10:1 cleavage selectivity).

R_f 0.53, 0.47 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3379-3263 (br.), 3110 (w), 2958 (m), 2933 (m), 2872 (w), 1730 (vs), 1463 (m), 1387 (w), 1368 (w), 1241 (w), 1167 (vs), 1133 (m), 1067 (w), 1048 (w), 970 (w), 905 (m), 755 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.13 (br. s, 1H, NO*H*^{E}), 8.71 (br. s, 1H, NO*H*^{Z}), 7.39 (t, *J* = 6.0 Hz, 1H, H-5^{E}), 6.69 (t, *J* = 5.5 Hz, 1H, H-5^{Z}), 4.093 (t, *J* = 6.9 Hz, 2H, H-1'$^{E/Z}$), 4.088 (t, *J* = 6.9 Hz, 2H, H-1'$^{E/Z}$), 2.49-2.36 (m, 4H, H-2^{EZ}, H-4^{Z}), 2.23-2.18 (m, 2H, H-4^{E}), 1.90-1.80 (m, 2H, H-3a$^{E/Z}$), 1.72-1.54 (m, 4H, H-3b^{EZ}, H-3'^{EZ}), 1.53-1.47 (m, 4H, H-2'^{EZ}), 1.16 (d, *J* = 7.0 Hz, 3H, H-6$^{E/Z}$), 1.15 (d, *J* = 7.0 Hz, 3H, H-6$^{E/Z}$), 0.90 (d, *J* = 6.7 Hz, 12H, H-4'^{EZ});

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 176.39 (s, C-1$^{E/Z}$), 176.36 (s, C-1$^{E/Z}$), 151.7 (d, C-5^{Z}), 151.2 (d, C-5^{E}), 63.29 (t, C-1'$^{E/Z}$), 63.27 (t, C-1'$^{E/Z}$), 39.3 (d, C-2^{Z}), 39.0 (d, C-2^{E}), 37.4 (t, C-2'^{EZ}), 30.4 (t, C-3^{E}), 29.9 (t, C-3^{Z}), 27.4 (t, C-4^{E}), 25.2 (d, C-3'^{EZ}), 23.0 (t, C-4^{Z}), 22.5 (q, C-4'^{EZ}), 17.10 (q, C-6^{E}), 17.06 (q, C-6^{Z});

MS (ESI+) *m/z*, (%): 453 (22, $[2M + Na]^+$), 238 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{21}O_3NNa$ 238.1414; found: 238.1414;

Anal. $C_{11}H_{21}NO_3$ (215.29): calc. C 61.37; H 9.83; N 6.51, found: 60.96; H 9.44; N 6.35.

Cleavage of 2-methylcyclopentanone (278b) via thermodynamic enolate

Step 1. ((2-Methylcyclopent-1-en-1-yl)oxy)trimethylsilane (**278b'**)was prepared from 2-methylcyclopentanone (**278b**, 750 µL, 7 mmol) as a 7.7:1 mixture of constitutional isomers, yield 573 mg (48%).[273]

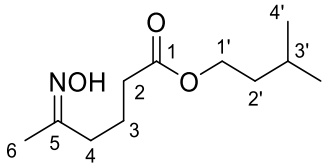
^{1}H NMR (401 MHz, C_6D_6): δ 2.32-2.25 (m, 2H), 2.21-2.14 (m, 2H), 1.76-1.68 (m, 2H), 1.62 (tt, *J* = 2.2, 1.1 Hz, 3H), 0.15 (s, 9H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, C_6D_6): δ 143.5 (s), 111.3 (s), 34.1 (t), 33.9 (t), 20.1 (t), 12.2 (q), 0.7 (q).

Step 2. Cleavage by method **B** from silyl enol ether **278b'** (340 mg, 2.0 mmol), MeLi (1.6 mL, 2.6 mmol, 1.6 M in diethyl ether), and *i*-AmONO (405 µL, 3.0 mmol), giving a crude oily 11:1 **280b**/**279b**

mixture (414 mg). Purification yielded 361 mg of 18:1 mixture of **280b** (*E/Z* 5:1) and **279b**, and 11 mg of **280b** (*E/Z* 3.4:1) as colourless oils. Yield of **280b**: 81% based on global silyl enol ether, 92% based on the thermodynamic silyl enol ether.

Isopentyl 5-(hydroxyimino)hexanoate (**280b**)



R_f 0.31, 0.23 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3050 (br.), 2957 (s), 2930 (m), 2872 (m), 1732 (vs), 1462 (m), 1386 (w), 1368 (s), 1312 (w), 1248 (m), 1169 (w), 1149 (s), 1068 (m), 948 (s), 825 (w), 768 (w);

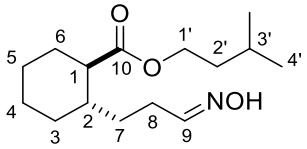
^{1}H NMR (401 MHz, C_6D_6): δ 9.25-8.50 (br. s, 2H, NO*H*^{EZ}), 4.053 (t, *J* = 6.9 Hz, 2H, H-1'$^{E/Z}$), 4.049 (t, *J* = 6.9 Hz, 2H, H-1'$^{E/Z}$), 2.29-2.25 (m, 2H, H-4^Z), 2.13 (t, *J* = 7.2 Hz, 2H, H-2^Z), 2.11 (t, *J* = 7.3 Hz, 2H, H-2^E), 1.96 (t, *J* = 7.5 Hz, 2H, H-4^E), 1.76-1.68 (m, 4H, H-3^{EZ}), 1.67 (s, 3H, H-6^E), 1.58 (s, 3H, H-6^Z), 1.56-1.47 (m, 2H, H-3'^{EZ}), 1.36 (q, *J* = 6.9 Hz, 2H, H-2'$^{E/Z}$), 1.35 (q, *J* = 6.9 Hz, 2H, H-2'$^{E/Z}$), 0.78 (d, *J* = 6.7 Hz, 6H, H-4'$^{E/Z}$), 0.77 (d, *J* = 6.7 Hz, 6H, H-4'$^{E/Z}$);

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 172.74 (s, C-1$^{E/Z}$), 172.67 (s, C-1$^{E/Z}$), 157.2 (s, C-5$^{E/Z}$), 156.8 (s, C-5$^{E/Z}$), 62.94 (t, C-1'$^{E/Z}$), 62.91 (t, C-1'$^{E/Z}$), 37.7 (t, C-2'^{EZ}), 35.2 (t, C-4^E), 34.0 (t, C-2^Z), 33.5 (t, C-2^E), 28.0 (t, C-4^Z), 25.33 (d, C-3'$^{E/Z}$), 25.31 (d, C-3'$^{E/Z}$), 22.5 (q, C-4'^{EZ}), 21.7 (t, C-3^E), 21.2 (t, C-3^Z), 19.5 (q, C-6^Z), 13.3 (q, C-6^E);

MS (CI+) *m/z*, (%): 216 (18, $[M + H]^+$), 214 (16, $[M - H]^+$), 200 (100, $[M - CH_3]^+$), 128 (18, [M – *i*-AmO]$^+$), 126 (19, [M – H – *i*-AmOH]$^+$), 112 (60, [M – CH_3 – *i*-AmOH]$^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{22}NO_3$ 216.1600; found: 216.1599.

Isopentyl (1R,2S*)-2-(3-(hydroxyimino)propyl)cyclohexane-1-carboxylate* (**279c**)



Prepared by method **A** from racemic *trans*-1-decalone (**278c**, 152 mg, 1.0 mmol), NaHMDS (1.15 mL, 1.15 mmol, 1 M in THF) in THF (5 mL), and *i*-AmONO (161 µL, 1.2 mmol) at −78 °C for 40 min, giving a crude product (283 mg, *E*/*Z* 1.5:1); yield 35 mg (13%) of (*E*)-**279c** and 154 mg (57%) of **279c** as 1.1:1 *E*/*Z* mixture as colourless oils.

R_f 0.33, 0.24 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3424-3255 (br.), 2928 (s), 2857 (m), 1729 (vs), 1711 (s), 1449 (m), 1388 (w), 1367 (w), 1320 (w), 1254 (m), 1231 (w), 1160 (vs), 1134 (m), 1051 (m), 991 (w), 912 (m), 736 (m), 705 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.58 (s, 1H, NO*H*^{E}), 8.12 (s, 1H, NO*H*^{Z}), 7.36 (t, *J* = 6.0 Hz, 1H, H-9^E), 6.66 (t, *J* = 5.3 Hz, 1H, H-9^Z), 4.11-4.07 (m, 4H, H-1'^{EZ}), 2.45-2.22 (m, 3H), 2.16-2.01 (m, 3H), 1.91-1.83 (m, 4H), 1.75-1.39 (m, 16H), 1.31-1.15 (m, 6H), 0.95-0.85 (m, 14H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 176.30 (s, C-10^{Z}), 176.26 (s, C-10^{E}), 152.7 (d, C-9^{Z}), 152.1 (d, C-9^{E}), 63.01 (t, C-1'$^{E/Z}$), 63.00 (t, C-1'$^{E/Z}$), 50.10 (d, C-$1^{E/Z}$), 50.09 (d, C-$1^{E/Z}$), 38.7 (d, C-2^{Z}), 38.5 (d, C-2^{E}), 37.5 (t, C-2'^{EZ}), 31.6 (t, C-7^{E}), 31.0 (t, C-7^{Z}), 30.6 (t, CH_2^{E}), 30.5 (t, CH_2^{Z}), 30.23 (t, CH_2^{Z}), 30.20 (t, CH_2^{E}), 26.7 (t, C-8^{E}), 25.67 (t, CH_2), 25.65 (t, CH_2), 25.56 (t, CH_2), 25.53 (t, CH_2), 25.2 (d, C-3'^{EZ}), 22.6 (q, C-4'^{EZ}), 22.1 (t, C-8^{Z});

MS (ESI+) *m/z*, (%): 561 (16, $[2M + Na]^+$), 292 (100, $[M + Na]^+$), 270 (25, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{27}NNaO_3$ 292.1883; found: 292.1881.

Cleavage of *trans*-1-decalone (278c) via thermodynamic enolate

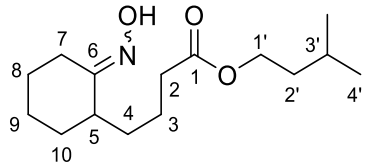
Step 1. Trimethyl((2,3,4,4a,5,6,7,8-octahydronaphthalen-1-yl)oxy)silane (**278c'**) was prepared from *trans*-1-decalone (**278c**, 704 mg, 4.6 mmol) as a 4:1 mixture of constitutional isomers, yield 1.00 g (96%). [273]

^{1}H NMR (401 MHz, C_6D_6, major isomer): δ 3.08 (dquint, *J* = 13.7, 2.1 Hz, 1H, H-$9_{equat.}$), 2.16-0.90 (m, 14H), 0.17 (s, 9H, Si(CH_3)$_3$);

$^{13}C\{^{1}H\}$ NMR (101 MHz, C_6D_6): δ 142.0 (s, C-1), 118.6 (s, C-10), 37.5 (d, C-5), 36.1 (t), 31.7 (t), 31.4 (t), 27.5 (t), 26.9 (t), 26.7 (t), 22.3 (t), 0.8 (q, Si(CH_3)$_3$).

Step 2. Cleavage by method **B** from silyl enol ether **278c'** (1.00 g, 4.46 mmol), MeLi (3.6 mL, 5.8 mmol, 1.6 M in diethyl ether), and *i*-AmONO (900 µL, 6.7 mmol), giving a crude solid 7:1 **280c**/**279c** mixture (1.11 g). Purification yielded 725 mg of a 10:1 mixture of (*E*)-**280c** and **279c** as a colourless solid and 91 mg of a 4:1 mixture of (*Z*)-**280c** and **279c**; overall yield of **280c**: 725 mg (58%) over 2 steps from **278c**.

Isopentyl 4-(2-(hydroxyimino)cyclohexyl)butanoate (**280c**)



R_f 0.42, 0.35 (hexane/EA 5:1);

(*E*)-**280c**: mp 55-56 °C;

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3050 (br.), 2954 (m), 2925 (s), 2857 (m), 1730 (vs), 1670 (w), 1462 (w), 1449 (w), 1418 (w), 1397 (w), 1386 (w), 1368 (w), 1316 (w), 1253 (m), 1162 (vs), 1145 (m), 1078 (w), 1051 (w), 981 (w), 910 (s), 880 (w), 682 (w), 736 (s), 704 (w), 666 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.75-8.25 (br. s, 1H, NO*H*), 4.08 (t, *J* = 6.9 Hz, 2H, H-1'), 2.66-2.59 (m, 1H, H-7a), 2.36-2.27 (m, 3H, H-7b, H-2), 2.28-2.19 (m, 1H, H-5), 1.87-1.80 (m, 1H, H-4a), 1.76-1.54 (m, 8H, H-3, H-8, H-9, H-10a, H-3'), 1.50 (q, *J* = 6.9 Hz, 2H, H-2'), 1.45-1.33 (m, 2H, H-4b, H-10b), 0.91 (d, *J* = 6.7 Hz, 6H, H-4');

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 173.9 (s, C-1), 162.7 (s, C-6), 63.1 (t, C-1'), 41.7 (d, C-5), 37.5 (t, C-2'), 34.4 (t, C-2), 32.8 (t, C-4), 30.4 (t C-10), 26.2 (t, C-8/9), 25.2 (d, C-3'), 23.6 (t, C-8/9), 23.1 (t, C-7), 22.8 (t, C-3), 22.6 (q, C-4');

MS (ESI+) *m/z*, (%): 561 (5, $[2M + Na]^+$), 308 (6, $[M + K]^+$), 292 (100, $[M + Na]^+$), 270 (7, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{27}NNaO_3$ 292.1883; found: 292.1883.

(*Z*)-**208c**:

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.75-7.75 (br. s, 1H, NO*H*), 4.08 (t, *J* = 6.9 Hz, 2H, H-1'), 3.52-3.45 (m, 1H, H-5), 2.33 (t, *J* = 6.6 Hz, 2H, H-2), 2.25-2.20 (m, 1H, H-7a), 2.15 (ddd, *J* = 14.1, 13.6, 4.9 Hz, 1H, H-7b), 1.90-1.83 (m, 1H, H-8a), 1.73-1.40 (m, 10H, H-3, H-4, H-9, H-8b, H-10, H-3'), 1.50 (q, *J* = 6.9 Hz, 2H, H-2'), 0.91 (d, *J* = 6.6 Hz, 6H, H-4');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.9 (s, C-1), 163.2 (s, C-6), 63.1 (t, C-1'), 37.5 (t, C-2'), 34.4 (t, C-2), 32.0 (d, C-5), 30.2 (t, C-4/10), 30.1 (t, C-4/10), 28.7 (t, C-7), 27.1 (t, C-8), 25.2 (d, C-3'), 22.8 (t, C-3), 22.6 (q, C-4'), 20.7 (t, C-9);

MS (ESI+) *m/z*, (%): 561 (10, $[2M + Na]^+$), 292 (100, $[M + Na]^+$), 270 (5, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{27}NNaO_3$ 292.1883; found: 292.1884.

Cleavage of 278d via kinetic enolate

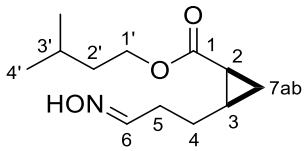
Step 1. The starting ketone **278d** was prepared by cyclopropanation of cyclohex-2-en-1-one (682 µL, 7.03 mmol).[232] The crude product (412 mg) was distilled using a Kugelrohr apparatus to yield 169 mg (21%) of clear light oil, bp 80-85 °C (15 mbar).

^{1}H NMR (401 MHz, $CDCl_3$): δ 2.29 (ddd, *J* = 18.3, 5.3, 3.7 Hz, 1H), 2.05 (dddd, *J* = 18.2, 11.5, 6.8, 0.8 Hz, 1H), 2.00-1.86 (m, 2H), 1.78-1.55 (m, 4H), 1.21 (q, *J* = 5.3 Hz, 1H), 1.05 (ddd, *J* = 9.8, 8.2, 5.3 Hz, 1H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 209.5 (s), 36.8 (t), 26.0 (d), 21.4 (t), 17.9 (t), 17.6 (d), 10.3 (t).

Step 2. Cleavage by method **A** from **278d** (165 mg, 1.49 mmol), NaHMDS (1.71 mL, 1.71 mmol, 1 M in THF) in THF (10 mL), and *i*-AmONO (240 µL, 1.79 mmol) at −78 °C for 20 min. The crude product (295 mg, *E*/*Z* = 2.8:1) was repeatedly purified by flash chromatography (hexane/EA 5:1 and CH_2Cl_2/Et_2O 10:1) yielding 95 mg (28%) of **279d** as 1.2:1 *E*/*Z* mixture as a colourless oil and 103 mg (49%) of **281** as separable 6:1 mixture of unassigned diastereomers as colourless solids.

Isopentyl (1S,2R*)-2-(3-(hydroxyimino)propyl)cyclopropane-1-carboxylate* (**279d**)



R_f 0.48, 0.37 (hexane/EA 2:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3450-3220 (br.), 2958 (m), 2928 (w), 2871 (w), 1720 (s), 1451 (w), 1404 (m), 1371 (m), 1278 (w), 1166 (vs), 1051 (w), 911 (s), 831 (w), 730 (s), 648 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.80 (br. s, 1H, NOH^Z), 8.35 (br. s, 1H, NOH^E), 7.40 (t, *J* = 6.1 Hz, 1H, H-6^E), 6.73 (br. t, *J* = 5.5 Hz, 1H, H-6^Z), 4.10 (t, *J* = 6.9 Hz, 4H, H-1'^{EZ}), 2.46-2.33 (m, 2H, H-5^Z), 2.31-2.18 (m, 2H, H-5^E), 1.83-1.63 (m, 8H, H-2^{EZ}, H-4^{EZ}, H-3'^{EZ}), 1.51 (q, *J* = 6.9 Hz, 4H, H-2'^{EZ}), 1.30-1.20 (m, 2H, H-3^{EZ}), 1.05-1.02 (m, 2H, H-7a^{EZ}), 0.98-0.92 (m, 2H, H-7b^{EZ}), 0.91 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

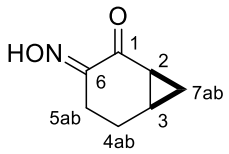
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.2 (s, C-1^{EZ}), 152.1 (d, C-6^Z), 151.6 (d, C-6^E), 63.3 (t, C-1'^{EZ}), 37.5 (t, C-2'^{EZ}), 29.6 (t, C-5^E), 25.2 (d, C-3'^{EZ}), 25.1 (t, C-5^Z), 24.3 (t, C-4^E), 23.8 (t, C-4^Z),

22.60 (q, C-4'^{Z}), 22.57 (q, C-4'^{E}), 21.4 (d, C-3^{Z}), 21.1 (d, C-3^{E}), 18.35 (d, C-2^{E}), 18.34 (d, C-2^{Z}), 13.58 (t, C-7^{Z}), 13.56 (t, C-7^{E});

MS (ESI+) *m/z*, (%): 493 (4, $[2M + K]^+$), 477 (7, $[2M + Na]^+$), 250 (100, $[M + Na]^+$), 228 (8, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{21}NNaO_3$ 250.1414; found: 250.1412.

(1S,6R*)-3-(hydroxyimino)bicyclo[4.1.0]heptan-2-one* (**281**)



281^{A}: mp 131-133 °C (dec.);

R_f 0.18 (hexane/EA 2:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-2700 (br.), 3024 (w), 2929 (w), 2874 (w), 1689 (vs), 1611 (m), 1430 (m), 1354 (w), 1335 (w), 1286 (m), 1233 (w), 1189 (w), 1090 (w), 1054 (w), 1020 (m), 1004 (w), 921 (vs), 903 (s), 854 (m), 831 (m), 799 (w), 747 (m), 728 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 10.58 (br. s, 1H, NO*H*), 3.04 (ddt, *J* = 19.1, 6.0, 1.4 Hz, 1H, H-5a), 2.24 (ddd, *J* = 19.3, 13.6, 6.6 Hz, 1H, H-5b), 2.13 (dddd, *J* = 13.9, 6.7, 2.5, 1.6 Hz, 1H, H-4a), 2.09-1.99 (m, 2H, H-4b, H-2), 1.99-1.89 (m, 1H, H-3), 1.41 (td, *J* = 6.0, 4.2 Hz, 1H, H-7a), 1.27 (ddd, *J* = 9.3, 8.0, 5.9 Hz, 1H, H-7b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 195.0 (s, C-1), 151.7 (s, C-6), 26.8 (d, C-2), 20.11 (d, C-3), 20.10 (t, C-5), 18.5 (t, C-4), 11.4 (t, C-7);

MS (EI+) *m/z*, (%): 139 (97, $[M]^{\cdot+}$), 122 (100, $[M - OH]^+$), 94 (30, $[M - CO - OH]^+$), 81 (25), 67 (25, [pentadienyl]$^+$);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_7H_9NO_2$ 139.0633; found: 139.0636.

281^{B}: colourless paste.

R_f 0.33 (hexane/EA 2:1);

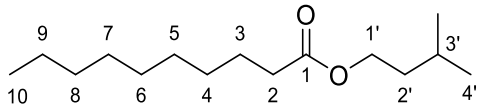
IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-2700 (br.), 3020 (w), 2929 (w), 2847 (w), 1634 (s), 1562 (m), 1415 (w), 1356 (m), 1337 (w), 1296 (w), 1182 (m), 1015 (s), 986 (m), 945 (vs), 922 (m), 868 (m), 832 (w), 796 (m), 760 (m), 673 (m), 635 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 15.27 (s, 1H, NO*H*), 2.64 (dddd, *J* = 16.7, 5.2, 2.2, 1.0 Hz, 1H, H-5a), 2.37 (ddd, *J* = 16.6, 14.0, 5.4 Hz, 1H, H-5b), 2.21 (ddt, *J* = 13.8, 5.1, 2.3 Hz, 1H, H-4a), 2.12-2.03 (m, 1H, H-4b), 2.03-1.94 (m, 2H, H-2, H-3), 1.61-1.55 (m, 1H, H-7a), 1.34 (ddd, *J* = 9.4, 8.0, 5.7 Hz, 1H, H-7b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 198.0 (s, C-1), 145.5 (s, C-6), 26.3 (d, C-2), 24.7 (t, C-5), 20.3 (t, C-4), 19.7 (d, C-3), 11.7 (t, C-7);

MS (EI+) *m/z*, (%): 139 (93, $[M]^{\cdot+}$), 122 (100, $[M - OH]^+$), 94 (28, $[M - CO - OH]^+$), 81 (31), 67 (24, [pentadienyl]$^+$).

Isopentyl decanoate (**283a**)



Prepared by method **A** from methyl nonyl ketone (**282b**, 413 µL, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C, warmed to −60 °C over 10 min. Purification yielded 365 mg of an inseparable 7:1 mixture of **283a** and diisoamyl carbonate (**276**) corresponding to 67% yield (by ^{1}H NMR) and 81 mg (25%) of nonanal oxime (**284a**) as 1.2:1 *E/Z* mixture. A trace amount of isoamyl acetate was also detected in the ^{1}H spectra but was not isolated because of its low boiling point.

R_f 0.86 (hexane/EA 5:1);

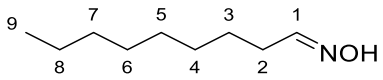
^{1}H NMR (401 MHz, $CDCl_3$): δ 4.09 (t, *J* = 6.9 Hz, 2H, H-1‘), 2.27 (t, *J* = 7.6 Hz, 2H, H-2), 1.75-1.63 (m, 1H, H-3‘), 1.63-1.56 (m, 2H, H-3), 1.51 (q, *J* = 6.9 Hz, 2H, H-2‘), 1.33-1.20 (br. s, 12H, H-4 to H-9), 0.92 (d, *J* = 6.8 Hz, 6H, H-4‘), 0.96 (t, *J* = 7.0 Hz, 3H, H-10);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.2 (s, C-1), 63.0 (t, C-1‘), 37.5 (t, C-2‘), 34.6 (t, C-2), 32.0 (t, C-4 to C-8), 29.6 (t, C-4 to C-8), 29.42 (t, C-4 to C-8), 29.40 (t, C-4 to C-8), 29.3 (t, C-4 to C-8), 25.22 (d, C-3‘), 25.17 (t, C-3), 22.8 (t, C-9), 22.6 (q, C-4‘), 14.3 (q, C-10);

MS (EI+) *m/z*, (%): 242 (4, $[M]^{\cdot+}$), 227 (2, $[M - Me]^{+}$), 199 (12, $[M - Pr]^{+}$), 173 (83, $[C_9H_{19}COOH_2]^{+}$), 172 (25, $[C_9H_{19}COOH]^{\cdot+}$), 155 (100, $[C_9H_{19}CO]^{+}$), 129 (24, $[M - octyl]^{+}$), 115 (16, $[M - Non]^{+}$), 85 (38, $[Hex]^{+}$), 71 (96, $[Am]^{+}$), 70 (74, $[C_5H_{10}]^{\cdot+}$), 60 (89, $[AcOH]^{\cdot+}$), 57 (91, $[Bu]^{+}$), 55 (91, $[methallyl]^{+}$);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_{15}H_{30}O_2$ 242.2246; found: 242.2243.

Nonanal oxime (**284a**)

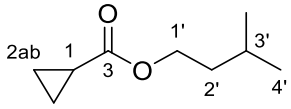


R_f 0.30 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): 7.42 (t, *J* = 6.2 Hz, 1H, H-1^{E}), 6.73 (t, *J* = 5.5 Hz, 1H, H-1^{Z}), 2.38 (td, *J* = 7.6, 5.4 Hz, 2H, H-2^{Z}), 2.19 (td, *J* = 7.5, 6.2 Hz, 2H, H-2^{E}), 1.53-1.44 (m, 4H, H-3^{EZ}), 1.35-1.23 (m, 20H, H-4^{EZ} to H-8^{EZ}), 0.87 (t, *J* = 6.6 Hz, 6H, H-9^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.1 (d, C-1^{E}), 152.5 (d, C-1^{Z}), 31.9 (t, C-7^{EZ}), 29.6 (t), 29.5 (t), 29.4 (t, 2×C), 29.29 (t), 29.28 (t), 29.20 (t), 26.7 (t, C-3^{Z}), 26.1 (t, C-3^{E}), 25.2 (t, C-2^{Z}), 22.8 (t, C-8^{EZ}), 14.2 (q, C-9^{EZ}).

Isopentyl cyclopropanecarboxylate (**283b**)



Prepared by method **A** from cyclopropyl methyl ketone (**282b**, 198 µL, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C, warmed to −35 °C over 25 min. Concentration at 200 mbar (32 °C) afforded an oily crude product (771 mg) that was purified by flash chromatography (pentane/Et_2O); yield 207 mg (66%) of **283b** as a colourless oil with pleasant flowery scent and 14 mg (6%) of hydroxyamino ketone **285b** as a colourless crystalline solid.

R_f 0.54 (DCM);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2958 (m), 2872 (w), 1725 (vs), 1464 (w), 1402 (m), 1371 (m), 1267 (m), 1199 (w), 1167 (vs), 1099 (w), 1076 (m), 1030 (w), 902 (w), 854 (w), 824 (w), 746 (w);

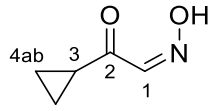
^{1}H NMR (401 MHz, $CDCl_3$): δ 4.10 (t, *J* = 6.9 Hz, 2H, H-1'), 1.69 (non, *J* = 6.7 Hz, 1H, H-3'), 1.59 (tt, *J* = 8.1, 4.6 Hz, 1H, H-1), 1.52 (q, *J* = 6.8 Hz, 2H, H-2'), 1.01-0.95 (m, 2H, H-2a), 0.92 (d, *J* = 6.6 Hz, 6H, H-4'), 0.87-0.81 (m, 2H, H-2b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.1 (s, C-3), 63.3 (t, C-1'), 37.5 (t, C-2'), 25.2 (d, C-3'), 22.6 (q, C-4'), 13.1 (d, C-1), 8.4 (t, C-2);

MS (CI+) *m/z*, (%): 157 (60, $[M + H]^+$), 115 (19, $[cPrCOOEt + H]^+$), 87 (83, $[i\text{-AmO}]^+$), 71 (100, $[i\text{-Am}]^+$), 70 (68, $[isopentene]^{\cdot+}$), 69 (64, $[cPrCO]^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_9H_{17}O_2$ 157.1229; found: 157.1230.

(Z)-2-cyclopropyl-2-oxoacetaldehyde oxime (**285b**)



mp 72-73 °C;

R_f 0.18 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3185 (br.), 3002 (w), 2961 (w), 2927 (w), 2871 (w), 2719 (w), 1765 (m), 1676 (w), 1640 (s), 1616 (w), 1514 (m), 1453 (s), 1425 (w), 1393 (s), 1273 (w), 1189 (s), 1090 (w), 1064 (w), 1030 (w), 996 (vs), 937 (w), 908 (vs), 865 (m), 810 (w), 772 (s), 717 (w), 674 (s);

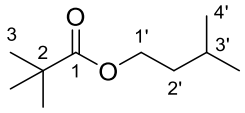
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.53 (s, 1H, NO*H*), 7.62 (s, 1H, H-1), 2.71 (tt, *J* = 7.9, 4.6 Hz, 1H, H-3), 1.19-1.15 (m, 2H, H-4a), 1.03-0.92 (m, 2H, H-4b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 198.7 (s, C-2), 150.1 (d, C-1), 16.7 (d, C-3), 12.2 (t, C-4);

MS (CI+) *m/z*, (%): 114 (100, $[M + H^+]^+$), 113 (7, $[M]^{\cdot+}$), 96 (22, $[M + H - H_2O]^+$), 72 (99, $[M - cPr]^+$), 69 (75, $[cPrCO]^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ calcd for $C_5H_8NO_2$ 114.0555; found: 114.0557.

Isopentyl pivalate (**283c**)



Prepared by method **A** from pinacolone (**282d**, 250 µL, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF) in THF (12 mL), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C, warmed to r.t over 35 min. Concentration at 200 mbar (32 °C) and purification by flash chromatography (pentane/Et_2O) yielded 53 mg (15%) of **283c** as a colourless oil with pleasant flowery scent and 117 mg (45%) of **285c** as a colourless solid.

R_f 0.87 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2958 (m), 2872 (w), 1730 (s), 1480 (w), 1465 (w), 1367 (w), 1284 (m), 1251 (w), 1152 (vs), 1094 (m), 1050 (w), 841 (m);

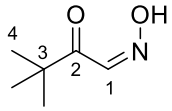
^{1}H NMR (401 MHz, $CDCl_3$): δ 4.08 (t, *J* = 6.7 Hz, 2H, H-1'), 1.68 (non, *J* = 6.7 Hz, 1H, H-3'), 1.51 (q, *J* = 6.8 Hz, 2H, H-2'), 1.19 (s, 9H, H-3), 0.92 (d, *J* = 6.6 Hz, 6H, H-4');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 178.8 (s, C-1), 63.2 (t, C-1'), 38.9 (s, C-2), 37.5 (s, C-2'), 27.4 (q, C-3), 25.3 (d, C-3'), 22.6 (q, C-4');

MS (CI+) *m/z*, (%): 173 (21, $[M+H]^+$), 131 (13, [*t*BuCOOEt+H]$^+$), 103 (76, [*t*BuCOOH+H]$^+$), 85 (19, [M+H−*i*AmOH]$^+$), 71 (100, [isopentyl$^+$]$^+$), 70 (61, [isopentene]$^+$), 57 (50, [*t*Bu]$^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{21}O_2$ 173.1542; Found: 173.1544.

(Z)-3,3-Dimethyl-2-oxobutanal oxime (**285c**)



Oxidation of the potassium enolate under otherwise identical conditions resulted in 23 mg (6%) of **283c** and 189 mg (73%) of **285c** as colourless solid, mp 48-49 °C.

IR (film) $\tilde{\nu}$[cm^{-1}]: 3324 (br.), 2972 (m), 2935 (w), 2907 (w), 2873 (w), 1699 (s), 1664 (s), 1595 (m), 1479 (s), 1459 (s), 1396 (w), 1367 (w), 1262 (w), 1159 (m), 1029 (w), 974 (vs), 939 (m), 892 (s), 844 (m), 802 (m), 725 (m), 619 (m);

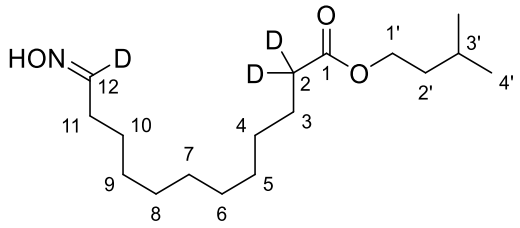
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.37 (br. s, 1H, NO*H*), 7.78 (s, 1H, H-1), 1.26 (s, 9H, H-4); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 202.2 (s, C-2), 147.1 (d, C-1), 44.1 (s, C-3), 26.5 (q, C-4);

MS (CI+) *m/z*, (%): 130 (44, $[M + H]^+$), 129 (14, $[M]^{\cdot+}$), 112 (28, $[M + H - H_2O]^+$), 88 (36), 85 (17, [pivaloyl]$^+$), 70 (100, $[M - CH_3 - CHNOH]^{\cdot+}$), 57 (99, [*t*-Bu]$^+$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_6H_{12}NO_2$ 130.0868; found: 130.0865;

Anal. Calcd for $C_6H_{11}NO_2$ (129.16): C, 55.80; H, 8.58; N, 10.84. Found: C, 55.89; H, 8.39; N, 10.90.

Isopentyl 12-(hydroxyimino)dodecanoate-2,2,12-d$_3$ (**287a**)



Step 1. Under inert atmosphere, a solution of NaOD (0.05 M) was prepared by dissolving sodium metal (12 mg, 0.5 mmol) in D_2O (10 mL), which was added to a stirred solution of cyclododecanone (**269e**, 730 mg, 4 mmol) in THF (10 mL) at 23 °C. After full deuteration as indicated by ^{1}H and ^{13}C NMR spectroscopy, hexane (50 mL) was added, the organic layer was separated, washed with D_2O (2×2 mL), dried over Na_2SO_4 and concentrated to give 689 mg (92%) of [2,2,12,12-D_4]-cyclododecanone (**286a**), which was used in the cleavage step without purification.

Step 1. Cleavage by method **A** from **286a** (186 mg, 1.0 mmol), *i*-AmOH (33 µL, 0.3 mmol), *n*-BuLi (0.90 mL, 1.4 mmol, 1.6 M in hexanes), HMDS (241 µL, 1.15 mmol) in THF (12 mL), and *i*-AmONO (186 µL, 1.4 mmol) at –78 °C for 120 min; yield 256 mg (85%) as 10:1 mixture of unassigned diastereomers as a colourless solid, mp 64-65 °C.

R_f 0.39, 0.33 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3205 (m), 3076 (m), 2963 (m), 2925 (s), 2858 (s), 1724 (vs), 1469 (m), 1439 (m), 1283 (s), 1263 (s), 1234 (m), 1128 (s), 1074 (m), 1056 (m), 964 (m), 878 (m), 828 (m), 716 (m), 641 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.25 (br. s, 1H, OH^A), 7.86 (br. s, 1H, OH^B), 4.09 (t, J = 6.9 Hz, 4H, H-1'^{AB}), 2.36 (t, J = 7.5 Hz, 2H, H-11^A), 2.18 (t, J = 7.4 Hz, 2H, H-11^B), 1.68 (non, J = 6.7 Hz, 2H, H-3'^{AB}), 1.62-1.56 (m, 4H, H-3^{AB}), 1.53-1.44 (m, 8H, H-2'^{AB}, H-10^{AB}), 1.27 (br. s, 24H, H-4^{AB} to H-9^{AB}), 0.91 (d, J = 6.6 Hz, 12H, H-4'^{AB});

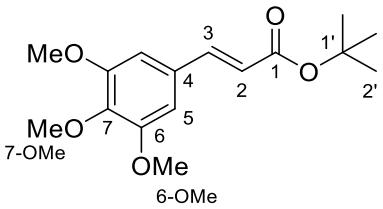
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, only isomer A): δ 174.2 (s, C-1), 152.8 (t, J = 26.9 Hz, C-12), 63.1 (t, C-1'), 37.5 (t, C-2'), 34.0 (quint, J = 19.0 Hz, C-2), 29.54 (t), 29.50 (t), 29.48 (t), 29.38 (t), 29.35 (t), 29.2 (t), 26.2 (t, C-10), 25.2 (d, 3'), 25.0 (t), 24.9 (t), 22.6 (q, C-4');

MS (CI+) *m/z*, (%): 303 (22, [M + H]$^+$), 287 (56, [M – Me]$^+$), 196 (100, [NC(C_9H_{18})CD_2CO]$^+$), 71 (12, [isopentyl]$^+$);

HRMS (CI+) *m/z*: [M + H]$^+$ calcd. for $C_{17}H_{31}D_3NO_3$ 303.2727, found: 303.2725;

Anal. Calcd for $C_{17}H_{30}D_3NO_3$ (302.47): C, 67.51; N, 4.63. Found: C, 67.63; N, 4.65.

tert-Butyl (E)-3-(3,4,5-trimethoxyphenyl)acrylate (**146**)



Prepared by method **A** from **147a** (1.44 g, 6.09 mmol), KHMDS (7.3 mL, 7.3 mmol, 1 M in THF) in THF (50 mL), and *t*-BuONO (0.94 mL, 7.9 mmol) at −78 °C, warmed to 23 °C over 70 min. Purification by flash chromatography (CH_2Cl_2/Et_2O 30:1) yielded 1.21 g (67%) of **146** as a soft colourless solid. Alternatively prepared by method **A** from **147b** (132 mg, 0.5 mmol), NaHMDS (600 µL, 0.6 mmol, 1 M in THF), and *t*-BuONO (83 µL, 0.7 mmol) at −78 °C, warmed to 23 °C over 60 min. Purification as above yielded 84 mg (57%) of **146** as colourless solid, mp 76-77 °C.

R_f 0.65 (hexane/EA 10:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3022 (w), 2968 (w), 2927 (m), 2850 (w), 2826 (w), 1696 (s), 1634 (s), 1582 (s), 1504 (s), 1467 (m), 1457 (m), 1448 (m), 1420 (s), 1312 (s), 1276 (s), 1247 (s), 1144 (vs), 1121 (vs), 1009 (s), 995 (m), 846 (m), 834 (s);

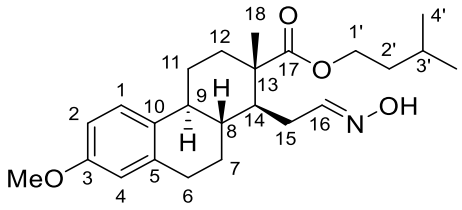
^{1}H NMR (401 MHz, C_6D_6): δ 7.85 (d, J = 15.8 Hz, 1H, H-3), 6.52 (d, J = 16.0 Hz, 1H, H-2), 6.50 (s, 2H, H-5), 3.78 (s, 3H, C7-OCH_3), 3.27 (s, 6H, C6-OCH_3), 1.52 (s, 9H, H-2');

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 166.2 (s, C-1), 154.3 (s, C-6), 144.3 (d, C-3), 141.2 (s, C-7), 130.3 (s, C-4), 119.7 (d, C-2), 105.8 (d, C-5), 80.0 (s, C-1'), 60.5 (q, C7-OCH_3), 55.7 (q, C6-OCH_3), 27.3 (q, C-2');

MS (CI+) *m/z*, (%): 295 (62, [M + H]$^+$), 294 (26, [M]$^{\cdot+}$), 239 (100, [M + H − isobutene]$^+$), 221 (26, [M – *t*-BuO]$^+$);

HRMS (CI+) *m/z*: [M + H]$^+$ calcd for $C_{16}H_{23}O_5$ 295.1545; found: 295.1541.

Isopentyl (2S)-1-(2-(hydroxyimino)ethyl)-7-methoxy-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-carboxylate (**287b**)



Prepared by method **A** from estrone 3-methyl ether (**286b**, 71 mg, 0.25 mmol), NaHMDS (325 µL, 0.325 mmol, 1 M in THF) in THF (5 mL), and *i*-AmONO (50 µL, 0.375 mmol) at −78 °C for 75 min. The oily crude product (108 mg, *E*/*Z* = 1:1.2) was purified to yield 79 mg (78%) of **287b** as a 1:1 *E*/*Z* mixture as a colourless viscous oil and 17 mg (21%) of **288a** as colourless sticky solid, which contained an unidentified impurity bearing the COO*i*-Am group (<15% by ^{1}H NMR spectroscopy).

R_f 0.45, 0.36 (CH_2Cl_2/Et_2O 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3100 (br.), 2958 (m), 2867 (w), 2834 (w), 1719 (s), 1610 (w), 1501 (m), 1466 (w), 1429 (w), 1386 (w), 1316 (w), 1283 (m), 1255 (m), 1235 (s), 1226 (vs), 1160 (m), 1115 (s), 1039 (s), 907 (s), 728 (vs), 648 (w);

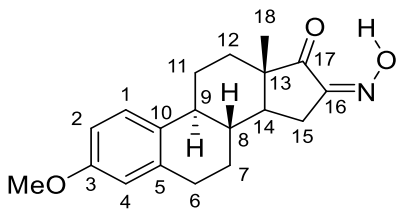
^{1}H NMR (401 MHz, $CDCl_3$): δ 9.50-7.50 (br. s, 2H, NO*H*^{EZ}), 7.42 (dd, *J* = 6.6, 5.7 Hz, 1H, H-16^{E}), 7.19 (d, *J* = 8.5 Hz, 1H, H-1$^{E/Z}$), 7.18 (d, *J* = 8.6 Hz, 1H, H-1$^{E/Z}$), 6.81 (br. s, 1H, H-16^{Z}), 6.74-6.70 (m, 2H, H-2^{EZ}), 6.62 (s, 2H, H-4^{EZ}), 4.15-4.11 (m, 4H, H-1'^{EZ}), 3.78 (s, 6H, C3-OC*H*$_3^{EZ}$), 2.86-2.84 (m, 4H, H-6^{EZ}), 2.62-2.54 (m, 1H, H-15a^{Z}), 2.46-2.38 (m, 2H, H-9^{EZ}), 2.35-2.26 (m, 3H, H-11a^{EZ}, H-15a^{E}), 2.21-2.09 (m, 5H, H-7a$^{E/Z}$, H-14^{EZ}, H-15b^{EZ}), 2.01-1.89 (m, 3H, H-7a$^{E/Z}$, H-12a^{EZ}), 1.85-1.79 (m, 2H, H-12b^{EZ}), 1.76-1.65 (m, 2H, H-3'^{EZ}), 1.57-1.50 (m, 4H, H-2'^{EZ}), 1.49-1.31 (m, 6H, H-7b^{EZ}, H-8^{EZ}, H-11b^{EZ}), 1.19 (s, 3H, H-18^{Z}), 1.18 (s, 3H, H-18^{E}), 0.94 (d, *J* = 6.6 Hz, 6H, H-4'^{Z}), 0.93 (d, *J* = 6.6 Hz, 6H, H-4'^{E});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 178.3 (s, C-17), 178.2 (s, C-17), 157.8 (s, C-3^{EZ}), 153.9 (d, C-16^{Z}), 152.9 (d, C-16^{E}), 137.9 (s, C-5), 137.8 (s, C-5), 132.0 (s, C-10), 131.8 (s, C-10), 126.6 (d, C-1), 126.5 (d, C-1), 113.59 (d, C-4), 113.57 (d, C-4), 112.0 (d, C-2), 111.9 (d, C-2), 63.63 (t, C-1'), 63.58 (t, C-1'), 55.4 (q, OCH_3^{EZ}), 47.9 (s, C-13), 47.5 (s, C-13), 44.6 (d, C-14^{Z}), 43.8 (d, C-14^{E}), 43.12 (d, C-9), 43.06 (d, C-9), 41.2 (d, C-8), 40.9 (d, C-8), 37.5 (t, 3×C, C-12, C-2'^{EZ}), 37.2 (t, C-12), 31.5 (t, C-15^{E}), 30.3 (t, C-6), 30.2 (t, C-6), 27.3 (t, C-15^{Z}), 27.2 (t, C-7), 26.8 (t, C-7), 26.1 (t, C-11), 25.9 (t, C-11), 25.32 (d, C-3'), 25.31 (d, C-3'), 22.65 (q, C-4'), 22.63 (q, C-4'), 15.3 (q, C-18^{EZ});

MS (ESI+) *m/z*, (%): 825 (85, [2M + Na]$^{+}$), 424 (100, [M + Na]$^{+}$);

HRMS (ESI+) *m/z*: [M + Na]$^{+}$ calcd. for $C_{24}H_{35}O_4NNa$ 424.2458, found: 424.2458.

16-hydroxyiminoestrone 3-methyl ether (**288a**)



R_f 0.17 (CH_2Cl_2/Et_2O 3:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.20 (br. s, 1H, NO*H*), 7.20 (dd, *J* = 8.7, 1.0 Hz, 1H, H-1), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1H, H-2), 6.95 (d, *J* = 2.7 Hz, 1H, H-4), 3.79 (s, 3H, OCH_3), 3.10-2.70 (m, 3H, H-6, H-15a), 2.48-1.90 (m, 5H, H-7a, H-9, H-11a, H-12a, H-15b), 1.72-1.29 (m, 5H, H-7b, H-8, H-11b, H-12b, H-14), 1.00 (s, 3H, H-18);

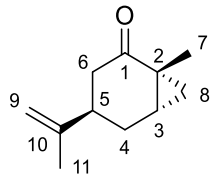
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 205.2 (s, C-17), 157.8 (s, C-3), 137.7 (s, C-5), 131.7 (s, C-10), 126.4 (d, C-1), 114.1 (d, C-4), 111.8 (d, C-2), 55.4 (q, O*C*H$_3$), 49.4 (s, C-13), 45.6 (d, C-14), 44.0 (d, C-9), 37.9 (d, C-8), 31.3 (t, C-12), 29.7 (t, C-6), 26.8 (t, C-7/11), 25.9 (t, C-7/11), 14.4 (q, C-18); C-15 and C-16 not detected;

MS (ESI+) *m/z*, (%): 336 (93, [M + Na]$^+$), 280 (100);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd for $C_{19}H_{23}O_3NNa$ 336.1570; found: 336.1572.

Cleavage of 286c

Step 1. Bicyclo[4.1.0]heptanone **286c** was prepared by cyclopropanation of *R*-(−)-carvone (1.10 mL, 7.03 mmol);[232] yield 1.17 g (quant.) as a yellow oil, used further without purification.



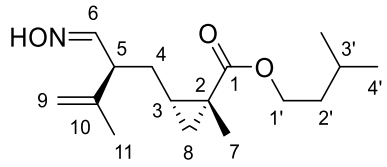
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (quint, *J* = 1.5 Hz, 1H, H-9a), 4.71 (br. s, 1H, H-9b), 2.44-2.32 (m, 2H, H-6a, H-5), 2.09-1.96 (m, 2H, H-6b, H-4a), 1.86 (ddd, *J* = 13.4, 11.6, 3.4 Hz, 1H, H-4b), 1.70 (s, 3H, H-11), 1.56 (dddd, *J* = 8.1, 5.9, 3.4, 2.6 Hz, 1H, H-3), 1.36 (dd, *J* = 5.9, 5.6 Hz, 1H, H-8a), 1.32 (s, 3H, H-7), 0.86 (dd, *J* = 7.9, 5.4 Hz, 1H, H-8b); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 210.4 (s, C-1), 147.1 (s, C-10), 110.2 (t, C-9), 41.9 (t, C-6), 36.8 (d, C-5), 29.3 (s, C-2), 27.0 (t, C-4), 25.3 (d, C-3), 20.6 (q, C-11). 19.9 (q, C-7), 17.7 (t, C-8);

MS (ESI+) *m/z*, (%): 351 (11, [2M+Na]$^+$), 329 (21, [2M+H]$^+$), 187 (19, [M+Na]$^+$), 165 (100, [M+H]$^+$);

HRMS (ESI+) *m/z*: [M+Na]$^+$ Calcd for $C_{11}H_{16}ONa$ 187.1093; Found: 187.1094.

Step 2. Cleavage by method **A** from **286c** (164 mg, 1.0 mmol) and NaHMDS (1.15 mL, 1.15 mmol, 1 M in THF) at −78 °C for 15 min, warmed to 0 °C for 5 min, *i*-AmONO (161 µL, 1.2 mmol) at −78 °C, warming to −20°C over 60 min. Purification yielded 102 mg (52%) of (*E*)-**288b** as a colourless solid and 68 mg (24%) of an inseparable 1:5 mixture of (*Z*)-**288b** and (*Z*)-**287c** as a colourless oil.

Isopentyl (1R,2S)-2-((S)-2-((Z)-(hydroxyimino)methyl)-3-methylbut-3-en-1-yl)-1-methylcyclopropane-1-carboxylate (**287c**)



(*Z*)-**287c**: R_f 0.28 (hexane/EA 5:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.29 (br. s, 1H, NO*H*), 7.31 (d, *J* = 7.3 Hz, 1H, H-6), 4.84 (quint, *J* = 1.5 Hz, 1H, H-9a), 4.78 (dq, *J* = 1.7, 0.9 Hz, 1H, H-9b), 4.13-4.03 (m, 2H, H-1'), 2.84 (qd, *J* = 7.4, 0.9 Hz, 1H, H-5), 1.80 (t, *J* = 7.4 Hz, 2H, H-4), 1.73-1.63 (m, 1H, H-3'), 1.68 (dd, *J* = 1.5, 0.9 Hz,

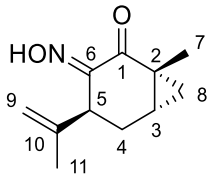
3H, H-11), 1.54-1.48 (m, 2H, H-2'), 1.25 (s, 3H, H-7), 1.15 (dd, *J* = 7.0, 4.3 Hz, 1H, H-8a), 0.99 (dq, *J* = 8.6, 7.0 Hz, 1H, H-3), 0.910 (d, *J* = 6.6 Hz, 3H, H-4'), 0.906 (d, *J* = 6.6 Hz, 3H, H-5'), 0.78 (dd, *J* = 8.6, 4.3 Hz, 1H, H-8b);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 174.4 (s, C-1), 153.2 (d, C-6), 144.2 (s, C-10), 112.6 (t, C-9), 63.5 (t, C-1'), 47.9 (d, C-5), 37.5 (t, C-2'), 29.2 (t, C-4), 28.2 (d, C-3), 25.2 (d, C-3'), 24.1 (s, C-2), 22.64 (q, C-4'), 22.56 (q, C-5'), 21.5 (t, C-8), 21.3 (q, C-7), 20.8 (q, C-11);

MS (ESI+) *m/z*, (%): 304 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{27}O_3NNa$ 304.1883; found: 304.1884.

(*1R,4S,6S)-3-(hydroxyimino)-1-methyl-4-(prop-1-en-2-yl)bicyclo[4.1.0]heptan-2-one* (**288b**)



(*E*)-**288b**: Colourless solid, mp 40-41 °C;

R_f 0.12 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3100 (br.), 3076 (w), 3007 (w), 2968 (m), 2929 (m), 2865 (w), 1685 (s), 1649 (w), 1604 (m), 1444 (s), 1376 (w), 1354 (m), 1220 (w), 1026 (w), 977 (m), 905 (s), 819 (w), 797 (w);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (br. s, 1H, NO*H*), 4.79 (quint, *J* = 1.4 Hz, 1H, H-9a), 4.76 (q, *J* = 0.9 Hz, 1H, H-9b), 3.63 (ddd, *J* = 8.9, 8.0, 0.8 Hz, 1H, H-5), 2.14-2.11 (m, 2H, H-4), 1.71 (ddt, *J* = 8.1, 6.4, 3.3 Hz, 1H, H-3), 1.66 (dd, *J* = 1.5, 0.8 Hz, 3H, H-11), 1.39 (dd, *J* = 6.2, 5.8 Hz, 1H, H-8a), 1.30 (s, 3H, H-7), 1.13 (dd, *J* = 8.1, 5.7 Hz, 1H, H-8b);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 198.6 (s C-1), 156.4 (s, C-6), 144.4 (s, C-10), 111.8 (t, C-9), 42.9 (d, C-5), 31.3 (s, C-2), 28.4 (d, C-3), 27.4 (t, C-4), 21.9 (t, C-8), 20.5 (q, C-11), 18.2 (q, C-7);

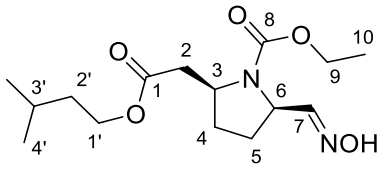
MS (ESI+) *m/z*, (%): 409 (4, $[2M + Na]^+$), 216 (100, $[M + Na]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{15}O_2NNa$ 216.0995; found: 216.0995.

(*Z*)-**288b**: ^{1}H NMR (401 MHz, $CDCl_3$): δ 14.95 (br. s, 1H, NO*H*), 4.90 (quint, *J* = 1.5 Hz, 1H, H-9a), 4.88-4.86 (m, 1H, H-9b), 3.30 (dd, *J* = 12.5, 5.6 Hz, 1H, H-5), 2.24 (ddd, *J* = 13.7, 12.9, 3.2 Hz, 1H, H-4a), 2.05 (ddd, *J* = 13.7, 5.6, 2.7 Hz, 1H, H-4b), 1.73-1.62 (m, 2H, H-3, H-8a), 1.68 (s, 3H, H-11), 1.31 (s, 3H, H-7), 1.16-1.14 (m, 1H, H-8b);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 200.3 (s, C-1), 147.2 (s, C-6), 143.3 (s, C-10), 114.7 (t, C-9), 45.5 (d, C-5), 31.2 (s, C-2), 27.8 (d, C-3), 26.5 (t, C-4), 20.8 (t, C-8), 18.9 (q, C-11), 18.4 (q, C-7).

Isopentyl 2-((2S,5R*)-5-((hydroxyimino)methyl)-1-(ethoxycarbonyl)pyrrolidin-2-yl)acetate* (**287d**)



Prepared by method **A** from *N*-carbethoxy-4-nortropinone (**286d**, 394 mg, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (322 µL, 2.4 mmol) at −78 °C, warmed to −20 °C over 45 min; yield 390 mg (62%) as 1.8:1 *E/Z* mixture as a colourless oil.

R_f 0.15 (hexane/EA 1:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3600-3200 (br.), 3200-3050 (br.), 2958 (m), 2935 (w), 2872 (w), 1731 (m), 1697 (s), 1676 (s), 1466 (w), 1412 (s), 1380 (s), 1344 (m), 1301 (m), 1169 (s), 1113 (s), 1053 (w), 1023 (w), 961 (m), 918 (m), 772 (w), 734 (m);

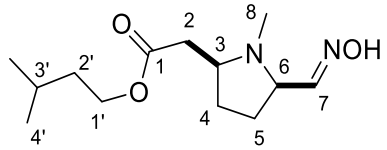
^{1}H NMR (401 MHz, CD_3CN): δ 8.71 (s, 1H, NO*H*^{Z}), 8.50 (s, 1H, NO*H*^{E}), 7.26 (d, *J* = 6.0 Hz, 1H, H-7^E), 6.67 (d, *J* = 5.6 Hz, 1H, H-7^Z), 4.78 (dt, *J* = 6.5, 5.8 Hz, 1H, H-6^Z), 4.35 (dt, *J* = 7.3, 5.9 Hz, 1H, H-6^E), 4.22-4.11 (m, 2H, H-3^{EZ}), 4.10-4.01 (m, 8H, H-9^{EZ}, H-1'^{EZ}), 2.86-2.70 (m, 2H, H-2a^{EZ}), 2.43-2.34 (m, 2H, H-2b^{EZ}), 2.29-2.22 (m, 1H, H-4a^Z/5a^Z), 2.12-1.99 (m, 3H, H-4a^Z/5a^Z, H-4a^E, H-5a^E), 1.93-1.86 (m, 1H, H-5b^E), 1.81-1.69 (m, 3H, H-4b^{EZ}, H-5b^Z), 1.68 (non, *J* = 7.1 Hz, 2H, H-3'^{EZ}), 1.50 (q, *J* = 6.8 Hz, 2H, H-2'^{Z}), 1.49 (q, *J* = 6.8 Hz, 2H, H-2'^{E}), 1.19 (t, *J* = 7.1 Hz, 6H, H-10^{EZ}), 0.91 (d, *J* = 6.7 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 172.34 (s, C-1^E), 172.28 (s, C-1^Z), 156.0 (s, C-8^E), 155.4 (d, C-7^Z), 152.6 (d, C-7^E), 64.0 (t, C-1'^{Z}), 63.9 (t, C-1'^{E}), 62.1 (t, C-9^Z), 62.0 (t, C-9^E), 58.4 (d, C-6^E), 56.8 (d, C-3^{EZ}), 55.3-54.5 (br. d, C-6^Z), 40.6-40.1 (br. t, C-2^{EZ}), 38.3 (t, C-2'^{EZ}), 31.2-28.7 (br. t, C-4^{EZ}, C-5^{EZ}), 26.1 (d, C-3'^{EZ}), 22.9 (q, C-4'^{EZ}), 15.2 (q, C-10^{EZ}), C-8^Z was not detected;

MS (ESI+) *m/z*, (%): 651 (45, $[2M + Na]^+$), 337 (100, $[M + Na]^+$), 315 (34, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{26}O_5N_2Na$ 337.1734; found: 337.1734.

Isopentyl 2-((2S,5R*)-5-((hydroxyimino)methyl)-1-methylpyrrolidin-2-yl)acetate* (**287e**)



Prepared by method **A** from tropinone (**286e**, 278 mg, 2.0 mmol), HMPA (487 µL, 2.8 mmol), NaHMDS (2.8 mL, 2.8 mmol, 1 M in THF), and *i*-AmONO (376 µL, 2.8 mmol) at −78 °C for 60 min; yield 221 mg (43%) of (*E*)-**287e** and 27 mg (5%) of **287e** as 1:3 *E/Z* mixture as colourless sticky oils.

R_f 0.33 (hexane/EA 1:1);

IR ($CHCl_3$) $\tilde{\nu}$[cm^{-1}]: 3584 (m), 3299 (br.), 3098 (w), 2961 (vs), 2931 (s), 2872 (s), 2796 (m), 1726 (vs), 1464 (s), 1459 (s), 1396 (m), 1388 (m), 1369 (m), 1347 (m), 1318 (w), 1295 (s), 1244 (w), 1191 (s), 1158 (s), 1132 (w), 1063 (m), 1043 (m), 952 (s), 923 (w), 907 (w), 845 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.68 (br. s, 1H, NO*H*^{Z}), 8.78 (br. s, 1H, NO*H*^{E}), 7.27 (d, *J* = 8.0 Hz, 1H, H-7^E), 6.80 (d, *J* = 5.7 Hz, 1H, H-7^Z), 4.124 (t, *J* = 6.9 Hz, 2H, H-1'^{Z}), 4.118 (t, *J* = 6.9 Hz, 2H, H-1'^{E}), 3.65-3.60 (m, 1H, H-6^Z), 2.97 (q, *J* = 8.1 Hz, 1H, H-6^E), 2.79-2.72 (m, 2H, H-3^{EZ}), 2.68 (dd, *J* = 15.0, 4.2 Hz, 1H, H-2a^Z), 2.67 (dd, *J* = 15.0, 4.2 Hz, 1H, H-2a^E), 2.39 (dd, *J* = 15.0, 8.8 Hz, 1H, H-2b^Z), 2.34 (dd, *J* = 15.0, 8.9 Hz, 1H, H-2b^E), 2.33 (s, 3H, H-8^Z), 2.28 (s, 3H, H-8^E), 2.15-2.04 (m, 3H, H-4a^{EZ}, H-5a^Z), 1.99-1.91 (m, 1H, H-5a^E), 1.79-1.59 (m, 6H, H-4b^{EZ}, H-5b^{EZ}, H-3'^{EZ}), 1.53 (q, *J* = 6.9 Hz, 4H, H-2'^{EZ}), 0.93 (d, *J* = 6.6 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.3 (s, C1^E), 172.1 (s, C-1^Z), 153.4 (d, C-7^Z), 153.1 (d, C-7^E), 65.9 (d, C-6^E), 63.4 (t, C-1'^{Z}), 63.3 (t, C-1'^{E}), 63.2 (d, C-3^E), 63.0 (d, C-3^Z), 62.3 (d, C-6^Z), 39.6 (t, C-

2^E), 39.5 (q, C-8^Z), 39.4 (t, C-2^Z), 38.7 (q, C-8^E), 37.4 (t, C-$2'^{EZ}$), 30.2 (t, C-4^Z), 29.9 (t, C-4^E), 27.7 (t, C-5^E), 27.0 (t, C-5^Z), 25.2 (d, C-$3'^{EZ}$), 22.6 (q, C-$4'^{EZ}$);

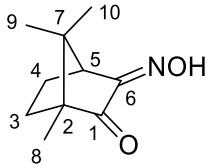
MS (ESI+) *m/z*, (%): 279 (100, $[M + Na]^+$), 257 (87, $[M + H]^+$), 212 (6, $[M + H - H_2O - HCN]^+$);

MS (CI+) *m/z*, (%): 257 (50, $[M + H]^+$), 212 (100, $[M + H - H_2O - HCN]^+$), 127 (87, [M + H – *i*-AmOAc]$^+$), 109 (15, $[M + H - i\text{-AmOAc} - H_2O]^+$), 82 (21, $[M + H - i\text{-AmOAc} - H_2O - HCN]^+$);

HRMS (ESI+) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{25}N_2O_3$ 257.1860; found: 257.1861;

Anal. Calcd for $C_{13}H_{24}N_2O_3$ (256.35): C, 60.91; H, 9.44; N, 10.93. Found: C, 61.05; H, 9.36; N, 10.69.

(1S,4S)-3-(Hydroxyimino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**290**)



Prepared by method **A** from (*1R*)-(+)-camphor (**289**, 304 mg, 2.0 mmol), NaHMDS (2.4 mL, 2.4 mmol, 1 M in THF), and *i*-AmONO (376 µL, 2.8 mmol) at −78 °C, warmed to 23 °C over 45 min; yield 206 mg (56%) as colourless crystalline solid, mp 147 °C (lit. 150 °C [235]).

R_f 0.45 (hexane/EA 2.5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3407 (s), 2968 (m), 2940 (m), 2882 (w), 1742 (vs), 1645 (s), 1450 (m), 1400 (s), 1379 (s), 1290 (m), 1179 (m), 1074 (m), 1003 (s), 951 (s), 930 (vs), 889 (s), 864 (m), 835 (m), 716 (s), 677 (m), 549 (m);

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.96 (br. s, 1H, NO*H*^{Z}), 8.62 (br. s, 1H, NO*H*^{E}), 3.25 (d, *J* = 6.7 Hz, 1H, H-5^E), 2.71 (d, *J* = 6.7 Hz, 1H, H-5^Z), 2.15-2.00 (m, 2H, H-4exo^{EZ}), 1.86-1.74 (m, 2H, H-3exo^{EZ}), 1.68-1.52 (m, 4H, H-3endo^{EZ}, H-4endo^{EZ}), 1.02 (s, 3H, H-8^E), 1.01 (s, 3H, H-8^Z), 1.00 (s, 6H, H-9,10), 0.92 (s, 3H, H-9^Z/10^Z), 0.88 (s, 3H, H-9^E/10^E);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 204.4 (s, C-1^Z), 204.3 (s, C-1^E), 160.0 (s, C-6^E), 156.3 (s, C-6^Z), 59.7 (s, C-7^Z), 58.7 (s, C-7^E), 49.7 (d, C-5^Z), 47.1 (s, C-2^Z), 46.8 (d, C-5^E), 45.0 (s, C-2^E), 30.8 (t, C-3^E), 30.1 (t, C-3^Z), 25.1 (t, C-4^Z), 23.9 (t, C-4^E), 20.8 (q, C-9^E/10^E), 20.7 (q, C-9^Z/10^Z), 18.1 (q, C-9^Z/10^Z), 17.8 (q, C-9^E/10^E), 9.1 (q, C-8^E), 8.5 (q, C-8^Z);

MS (CI+) *m/z*, (%): 182 (60, $[M + H]^+$), 181 (22, $[M]^{\cdot+}$), 164 (21, $[M - OH]^+$), 136 (100, $[M - OH - CO]^+$), 127 (29), 109 (40, $[M - OH - CO - HCN]^+$);

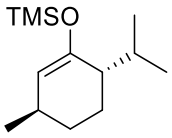
HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{16}NO_2$ 182.1181; found: 182.1181;

Anal. Calcd for $C_{10}H_{15}NO_2$ (181.24): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.16; H, 8.56; N, 7.51.

Cleavage of menthone (291a) via kinetic enolate

Step 1. Preparation of **291b**: *n*-BuLi (3.91 mL, 6.25 mmol, 1.6 M in hexanes) was added to diisopropylamine (988 µL, 7.0 mmol) in THF (20 mL) at −78 °C. After stirring for 20 min at −78 °C, (−)-L-menthone (**291a**, 864 µL, 5.0 mmol) was added dropwise over 2 min and the mixture was warmed to −20 °C for 10 min, followed by cooling to −78 °C. TMSCl (952 µL, 7.5 mmol) was added followed by warming to −30 °C over 30 min. Et_3N (2 mL, 14 mmol) was added followed by 2% aq.

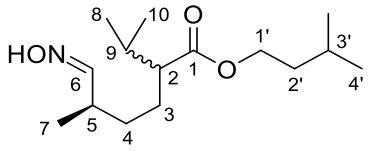
$NaHCO_3$ solution (30 mL) and PE (60 mL). The organic layer was separated, washed with 2% aq. $NaHCO_3$ (3×5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford 1.13 g (99%) of crude kinetic TMS enol ether **291b**.



^{1}H NMR (401 MHz, C_6D_6): δ 4.85 (dd, *J* = 3.3, 1.6 Hz, 1H, *H*C=C), 2.43-2.35 (m, 1H, C*H*), 2.23-2.11 (m, 2H, 2×C*H*), 1.71-1.62 (m, 1H, CH_2), 1.62-1.55 (m, 1H, CH_2), 1.31 (tdd, *J* = 13.0, 10.4, 2.8 Hz, 1H, CH_2), 1.03-0.95 (m, 1H, CH_2), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3), 0.94 (d, *J* = 7.1 Hz, 6H, *i*Pr), 0.20 (s, 9H, SiMe); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 152.7 (s), 112.0 (d), 44.8 (d), 32.1 (t), 30.6 (d), 27.9 (d), 23.2 (q), 23.0 (t), 20.3 (q), 17.2 (q), 0.4 (q). The NMR data match the lit.[274]

Step 2. Cleavage by method **B** from silyl enol ether **291b** (1.13 g, 5 mmol), MeLi (4.3 mL, 6.5 mmol, 1.5 M in Et_2O), and *i*-AmONO (1.0 mL, 7.5 mmol) at −78 °C, warmed to 0 °C over 30 min. Purification yielded 248 mg (27%) of **293** and 83 mg (6%) of **292a** as 1:1 mixture of epimers at C-2 and both as approx. 10:1 *E/Z* mixture as colourless oils.

Isopentyl (5R)-6-(hydroxyimino)-2-isopropyl-5-methylhexanoate (**292a**)



R_f 0.23 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3550-3100 (br.), 2959 (s), 2931 (m), 2872 (m), 1729 (vs), 1712 (s), 1462 (s), 1388 (m), 1370 (m), 1260 (m), 1230 (w), 1168 (s), 1052 (w), 1003 (w), 941 (s), 823 (w);

(*E*)-**292a**: ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.80 (br. s, 2H, NO*H*), 7.30 (d, *J* = 7.2 Hz, 1H, H-6), 7.28 (d, *J* = 7.6 Hz, 1H, H-6), 4.18-4.08 (m, 4H, H-1'), 2.42-2.32 (m, 2H, H-2), 2.11-2.07 (m, 2H, H-5), 1.92-1.81 (m, 2H, H-9), 1.76-1.48 (m, 10H, H-3/4, H-2', H-3'), 1.47-1.28 (m, 4H, H-3/4), 1.09 (d, *J* = 7.2 Hz, 6H, H-7), 0.95-0.91 (m, 24H, H-8, H-10, H-4');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.8 (s, 2×C-1), 156.3 (d, C-6), 156.2 (d, C-6), 62.8 (t, 2×C-1'), 53.0 (d, C-5), 52.8 (d, C-5), 37.6 (t, 2×C-2'), 34.7 (d, C-2), 34.4 (d, C-2), 32.82 (t, C-3/4), 32.77 (t, C-3/4), 30.79 (d, C-9), 30.75 (d, C-9), 27.3 (t, C-3/4), 27.1 (t, C-3/4), 25.2 (d, 2×C-3'), 22.6 (q, C-4'), 22.5 (q, C-4'), 20.67 (q, C-8/10), 20.62 (q, C-8/10), 20.35 (q, C-8/10), 20.33 (q, C-8/10), 18.3 (q, C-7), 18.0 (q, C-7).

(*Z*)-**292a** (detectable resonances): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (br. s, 2H, H-6^Z);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.90 (s, C-1^Z), 175.87 (s, C-1^Z), 156.16 (d, C-6^Z), 156.12 (d, C-6^Z);

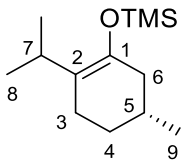
MS (CI+) *m/z*, (%): 272 (41, $[M + H]^+$), 254 (32, $[M - OH]^+$), 227 (27, $[M - OH - HCN]^+$), 199 (16, $[M - OH - HCN - C_2H_4]^+$), 184 (100, $[M - i\text{-AmO}]^+$), 166 (63, $[M - OH - i\text{-AmOH}]^+$), 157 (34, $[M - i\text{-AmO} - HCN]^+$), 138 (36, $[M - OH - i\text{-AmOH} - CO]^+$), 73 (11), 71 (13, $[i\text{-Am}]^+$), 70 (9);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{30}NO_3$ 272.2226; found: 272.2225.

Cleavage of menthone (291a) via thermodynamic enolate

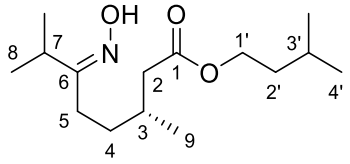
Step 1. Crude (*R*)-((2-isopropyl-5-methylcyclohex-1-en-1-yl)oxy)trimethylsilane (**291c**) was prepared from (−)-L-menthone **291a** (1.40 mL, 8 mmol) following a published procedure as a 7.2:1 mixture of constitutional isomers, yield 1.81 g (quant.). [273]

^{1}H NMR (400 MHz, C_6D_6): δ 3.28 (sept, *J* = 7.0 Hz, 1H, H-7), 2.12 (ddq, *J* = 16.1, 5.5, 1.6 Hz, 1H, H-6a), 1.98-1.92 (m, 2H, H-3), 1.77 (ddt, *J* = 16.1, 9.4, 1.6 Hz, 1H, H-6b), 1.70-1.54 (m, 2H, H-4a, H-5), 1.15-1.06 (m, 1H, H-4b), 1.04 (d, *J* = 7.0 Hz, 3H, H-8), 1.03 (d, *J* = 7.0 Hz, 3H, H-8), 0.89 (d, *J* = 7.0 Hz, 3H, H-9), 0.18 (s, 9H, SiMe); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 141.4 (s, C-1), 120.1 (s, C-2), 39.5 (t, C-6), 31.5 (t, C-4), 29.9 (d, C-5), 26.6 (d, C-7), 21.9 (t, C-3), 21.7 (q, C-9), 20.9 (q, C-8), 20.6 (q, C-8), 0.95 (q, SiMe). The NMR data matched lit.[274]



Step 2. Cleavage by method **B** from silyl enol ether **291c** (1.81 mg, 8 mmol), MeLi (6.0 mL, 9.6 mmol, 1.6 M in Et_2O) in THF (40 mL), and *i*-AmONO (1.40 mL, 10.4 mmol); yield 1.28 g (59%) of **292b** as 1:1.5 *E/Z* mixture as a colourless oil and 355 mg (16%) of **292a** as 3.4:1 *E/Z* mixture.

Isopentyl (R,Z)-6-(hydroxyimino)-3,7-dimethyloctanoate (**292b**)



R_f 0.43 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3500-3050 (br.), 2958 (s), 2931 (m), 2872 (m), 1733 (vs), 1653 (w), 1464 (m), 1385 (w), 1367 (w), 1310 (w), 1252 (m), 1197 (m), 1157 (s), 1084 (w), 1049 (w), 966 (m), 944 (m), 819 (w), 634 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.25-8.45 (br. s, 2H, NO*H*^{EZ}), 4.09 (t, *J* = 6.9 Hz, 4H, H-1'^{EZ}), 3.40 (sept, *J* = 7.0 Hz, 1H, H-7^Z), 2.47 (sept, *J* = 6.9 Hz, 1H, H-7^E), 2.37-2.09 (m, 8H, H-2^{EZ}, H-5^{EZ}), 2.03-1.94 (m, 2H, H-3^{EZ}), 1.67 (non, *J* = 6.8 Hz, 2H, H-3'^{EZ}), 1.62-1.37 (m, 4H, H-4^{EZ}), 1.50 (q, *J* = 6.9 Hz, 4H, 2'^{EZ}), 1.09 (d, *J* = 6.9 Hz, 6H, H-8^E), 1.06 (d, *J* = 7.0 Hz, 6H, H-8^Z), 0.98 (d, *J* = 6.7 Hz, 3H, H-9^E), 0.96 (d, *J* = 6.6 Hz, 3H, H-9^Z), 0.91 (d, *J* = 6.7 Hz, 12H, H-4'^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.32 (s, C-1^E), 173.27 (s, C-1^Z), 165.5 (s, C-6^E), 165.0 (s, C-6^Z), 63.07 (t, C-1'^{Z}), 63.05 (t, C-1'^{E}), 41.8 (t, C-2^Z), 41.7 (t, C-2^E), 37.5 (t, C-2'^{EZ}), 33.7 (d, C-7^E), 33.3 (t, C-4^Z), 32.7 (t, C-4^E), 31.1 (d, C-3^E), 30.5 (d, C-3^Z), 27.7 (t, C-5^Z), 26.5 (d, C-7^Z), 25.2 (d, C-3'^{EZ}), 24.3 (t, C-5^E), 22.6 (q, C-4'^{EZ}), 20.13 (q, C-8^E), 20.10 (q, C-8^E), 19.7 (q, C-9^Z), 19.6 (q, C-9^E), 19.1 (q, 2C-8^Z);

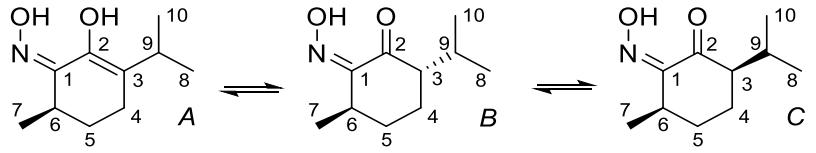
MS (ESI+) *m/z*, (%): 565 (11, $[2M + Na]^+$), 310 (6, $[M + K]^+$), 294 (100, $[M + Na]^+$), 272 (55, $[M + H]^+$);

HRMS (ESI+) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{29}NNaO_3$ 294.2040; found: 294.2040.

Anal. Calcd for $C_{15}H_{29}NO_3$ (271.40): C, 66.38; H, 10.79; N, 5.16. Found: C, 66.30; H, 10.61; N, 4.96;

$[\alpha]^{20}_D$ = +6.8 (c 0.47, MeOH).

(R,Z)-2-Hydroxy-3-isopropyl-6-methylcyclohex-2-en-1-one oxime (**293**)



Major component of the crude mixture resulting from nitrosation of directly generated Na and Li enolates of L-menthone (**289**) (method **A**) or prepared in 248 mg (27%) yield from silyl enol ether **291b** (method **B**) as partly separable 7:1 mixture of tautomers A and B, which are stable for hours in base-treated $CDCl_3$.

R_f 0.40, 0.15 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3450-3100 (br.), 2960 (s), 2931 (m), 2872 (m), 1701 (m), 1611 (w), 1559 (w), 1462 (m), 1388 (m), 1371 (m), 1312 (w), 1283 (m), 1194 (w), 1157 (s), 1105 (w), 1002 (vs), 941 (w), 892 (vs), 797 (m), 759 (w), 732 (m), 693 (w), 667 (w), 607 (w);

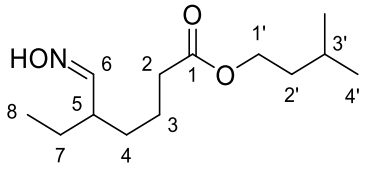
^{1}H NMR (401 MHz, $CDCl_3$): δ 7.81 (br. s, 1H, NO*H*^{A}), 5.87 (br. s, 1H, C2-O*H*^{A}), 3.62 (qdd, *J* = 7.1, 5.3, 1.6 Hz, 1H, H-6^B), 3.35 (qdd, *J* = 7.2, 4.9, 2.4 Hz, 1H, H-6^A), 3.19 (sept, *J* = 6.9 Hz, 1H, H-9^A), 2.51 (dsept, *J* = 6.9, 3.4 Hz, 1H, H-9^B), 2.29-2.24 (m, 1H, H-3^B), 2.23 (ddd, *J* = 17.3, 12.1, 5.1 Hz, 1H, H-4a^A), 2.04 (ddd, *J* = 17.4, 5.1, 2.4 Hz, 1H, H-4b^A), 1.92-1.74 (m, 4H, H-4^B, H-5^B), 1.72 (dddd, *J* = 13.3, 12.1, 5.0, 4.9 Hz, 1H, H-5a^A), 1.63 (ddt, *J* = 13.3, 4.9, 2.3 Hz, 1H, H-5b^A), 1.14 (d, *J* = 7.2 Hz, 3H, H-7^B), 1.10 (d, *J* = 7.1 Hz, 3H, H-7^A), 1.01 (d, *J* = 7.0 Hz, 3H, H-8/10^A), 0.99 (d, *J* = 7.0 Hz, 3H, H-8/10^A), 0.96 (d, *J* = 7.0 Hz, 3H, H-8/10^B), 0.86 (d, *J* = 6.8 Hz, 3H, H-8/10^B), NOH^B resonance was not detected;

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 198.9 (s, C-2^B), 158.2 (s, C-1^B), 156.8 (s, C-1^A), 136.7 (s, C-2^A), 126.1 (s, C-3^A), 56.7 (d, C-3^B), 29.4 (d, C-6^B), 28.9 (t, C-5^B), 27.8 (t, C-5^A), 26.8 (d, C-9^B), 26.7 (d, C-9^A), 26.3 (d, C-6^A), 20.5 (q, C-8/10^B), 20.4 (q, C-8/10^A), 19.9 (q, C-8/10^A), 18.5 (t, C-4^B), 18.0 (q, C-8/10^B), 17.9 (t, C-4^A), 16.0 (q, C-7^B), 15.0 (q, C-7^A);

MS (CI+) *m/z*, (%): 184 (100, $[M + H]^+$), 183 (47, $[M]^{\cdot+}$), 182 (16, $[M - H]^+$), 141 (18, [M − propene]$^{\cdot+}$);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{18}NO_2$ 184.1338; found: 184.1340.

Isopentyl 5-((hydroxyimino)methyl)heptanoate (**296a**)



Method C: A flame dried Schlenk flask connected to dry nitrogen was charged with CuBr•DMS (82 mg, 0.4 mmol) and dry THF (20 mL) and cooled to −78 °C. A solution of EtMgBr (0.80 mL, 2.4 mmol, 3M in Et_2O) was added dropwise. The resulting white suspension was stirred at −78 °C for 10 min until the precipitate dissolved. A solution of cyclohex-2-en-1-one (**294a**, 194 µL, 2.0 mmol) in THF (3.5 mL) was added over 3 min. During addition a yellow turbidity developed that turned progressively darker. After 7 min at −78 °C, *i*-AmONO (350 µL, 2.6 mmol) was added, followed by warming to 23 °C and work-up following method **A**. The dark oily crude product (536 mg) was

purified by column chromatography in PE/EA (10:1 to 3:1) to yield 120 mg (24%) of **296a** as 2.4:1 *E/Z* mixture as a colourless oil. A significant fraction of the crude mass consisted of baseline material.

R_f 0.22 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3400-3200 (br.), 3111 (br.), 2959 (s), 2931 (m), 2873 (m), 1733 (vs), 1460 (m), 1386 (w), 1367 (w), 1347 (w), 1276 (m), 1239 (m), 1167 (vs), 1134 (w), 1111 (w), 1052 (w), 940 (s), 885 (w), 785 (w);

^{1}H NMR (401 MHz, $CDCl_3$): δ 9.00-7.25 (br. s, 2H, NO*H*^{EZ}), 7.20 (d, *J* = 8.0 Hz, 1H, H-6^E), 6.46 (br. d, *J* = 8.2 Hz, 1H, H-6^Z), 4.09 (t, *J* = 6.9 Hz, 4H, H-1‘^{EZ}), 3.08-2.99 (m, 1H, H-5^Z), 2.33-2.27 (m, 4H, H-2^{EZ}), 2.20-2.11 (m, 1H, H-5^E), 1.72-1.56 (m, 6H, H-3^{EZ}, H-3‘^{EZ}), 1.55-1.29 (m, 12H, H-2’^{EZ}, H-4^{EZ}, H-7 ^{EZ}), 0.91 (d, *J* = 6.6 Hz, 12H, H-4‘^{EZ}), 0.89 (t, *J* = 7.4 Hz, 6H, H-8^{EZ});

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 173.8 (s, C-1^Z), 173.7 (s, C-1^E), 155.45 (d, C-6^Z), 155.44 (d, C-6^E), 63.18 (t, C-1’^{E}), 63.15 (t, C-1’^{Z}), 41.3 (d, C-5^E), 37.5 (t, C-2‘^{EZ}), 36.3 (d, C-5^Z), 34.34 (t, C-2^Z), 34.33 (t, C-2^E), 32.03 (t, C-3^E), 32.00 (t, C-3^Z), 25.9 (t, C-7^E), 25.8 (t, C-7^Z), 25.2 (d, C-3‘^{EZ}), 22.8 (t, C-4^Z), 22.62 (t, C-4^E), 22.59 (q, C-4‘^{EZ}), 11.8 (q, C-8^Z), 11.6 (q, C-8^E);

MS (EI+) *m/z*, (%): 243 (3, $[M]^{\cdot+}$), 226 (53, $[M - OH]^+$), 156 (57, [M – *i*-AmO]$^+$), 138 (100, [M – *i*-AmO − H_2O]$^+$), 110 (42, [M – *i*-AmO − H_2O − CO]$^+$), 87 (57, [*i*-AmO] $^+$), 71 (54, [*i*-Am]$^+$), 70 (46, $[C_5H_{10}]^{\cdot+}$);

HRMS (EI+) *m/z*: $[M]^{\cdot+}$ calcd for $C_{13}H_{25}NO_3$ 243.1834; found: 243.1836;

Anal. Calcd for $C_{13}H_{25}NO_3$ (243.34): C, 64.16; H, 10.36; N, 5.72. Found: C, 64.36; H, 10.34; N, 5.62.

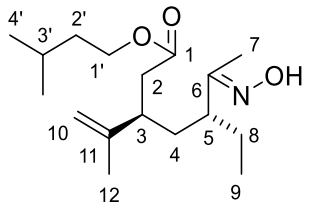
Method D: Silyl enol ether **295a** (198 mg, 1.0 mmol) was treated with MeLi (0.81 mL, 1.3 mmol, 1.6 M in Et_2O) at –20 °C and oxidized by *i*-AmONO (202 µL, 1.5 mmol) at –78 °C. The oily crude product (200 mg) was purified to yield 178 mg (73%) of **296a** as 13:1 *E/Z* mixture as a colourless oil. The NMR spectra match **296a** prepared by method C.

MS (CI+) *m/z*, (%): 244 (33, $[M + H]^+$), 228 (18, $[M - Me]^+$), 226 (50, $[M + H - H_2O]^+$), 199 (16, [M – OH − HCN]$^+$), 156 (79, [M + H – *i*-AmOH]$^+$), 138 (100, [M + H – *i*-AmOH − H_2O]$^+$), 129 (54), 111 (20), 110 (19, [M – *i*-AmO − H_2O − CO]$^+$), 87 (16), 71 (48);

HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{26}NO_3$ 244.1913; found: 244.1912;

Anal. Calcd for $C_{13}H_{25}NO_3$ (243.34): C, 64.16; H, 10.36; N, 5.72. Found: C, 64.07; H, 10.11; N, 5.70.

Isopentyl (3R,5R,E)-5-ethyl-6-(hydroxyimino)-3-(prop-1-en-2-yl)heptanoate (**296b**)



Method C: A solution of (*R*)-(−)-carvone (**294b**, 313 µL, 2.0 mmol) was cannulated to the cuprate solution prepared as for **296a** at −30 °C over 1 h. Quenched by 10% aq. EDTA solution (20 mL). The oily crude product (563 mg) was purified to yield 250 mg (42%) of **296b** as 4:1 *E*:*Z* mixture as a colourless oil and 48 mg (8%) of another oily substance that was identified based on NMR data as

isopentyl (3*R*,5*R*)-5-ethyl-6-oxo-3-(prop-1-en-2-yl)heptanoate resulting likely from copper assisted hydrolysis of the ketoxime.

Method D: Silyl enol ether **295b** (252 mg, 1.0 mmol) was treated with MeLi (0.81 mL, 1.3 mmol, 1.6 M in Et_2O) and oxidized by *i*-AmONO (202 µL, 1.5 mmol) followed by warming to −30 °C over 45 min; yield 260 mg (87%) of (*E*)-**296b** as a colourless oil. NMR spectra match the major (*E*) isomer of **296b** prepared by Method C.

R_f 0.39 (hexane/EA 5:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 3450-3200 (br.), 3076 (w), 2959 (s), 2930 (m), 2873 (m), 1734 (vs), 1647 (w), 1460 (m), 1368 (m), 1347 (w), 1265 (m), 1194 (w), 1152 (vs), 1104 (w), 1052 (w), 999 (m), 951 (m), 892 (s), 853 (w), 767 (m);

^{1}H NMR (401 MHz, $CDCl_3$): δ 8.31 (br. s, 1H, NO*H*), 4.80-4.74 (m, 2H, H-10), 4.09-4.01 (m, 2H, H-1'), 2.58 (tt, *J* = 8.6, 6.3 Hz, 1H, H-3), 2.39 (dd, *J* = 14.6, 6.3 Hz, 1H, H-2a), 2.32 (dd, *J* = 14.6, 8.7 Hz, 1H, H-2b), 2.19-2.12 (m, 1H, H-5), 1.77 (s, 3H, H-7), 1.72-1.57 (m, 1H, H-3'), 1.65 (s, 3H, H-12), 1.57-1.32 (m, 6H, H-4, H-8, H-2'), 0.90 (d, *J* = 6.6 Hz, 6H, H-4'), 0.81 (t, *J* = 7.4 Hz, 3H, H-9);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.7 (s, C-1), 160.6 (s, C-6), 146.1 (s, C-11), 112.6 (t, C-10), 63.1 (t, C-1'), 44.2 (d, C-5), 41.5 (d, C-3), 39.1 (t, C-2), 37.5 (t, C-2'), 35.7 (t, C-4), 25.2 (d, C-3'), 24.5 (t, C-8), 22.6 (q, C-4'), 18.8 (q, C-12), 11.7 (q, C-9), 10.4 (q, C-7);

MS (ESI+) *m/z*, (%): 617 (38, [2M + Na]$^+$), 336 (13, [M + K]$^+$), 320 (100, [M + Na]$^+$), 298 (16, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{31}O_3NNa$ 320.2196; found: 320.2194;

Anal. Calcd for $C_{17}H_{31}NO_3$ (297.44): C, 68.65; H, 10.51; N, 4.71. Found: C, 68.51; H, 10.23; N, 4.46;

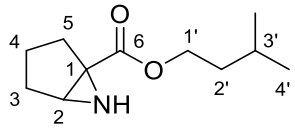
$[\alpha]^{20}_D$ = −0.3 (c 0.35, $CHCl_3$).

Mannich cyclisation of oxime ether 272

Method 1. A solution of $TiCl_4$ (1 mL, 1 mmol, 1M in DCM) was added at –78 °C to a solution of **272** (115 mg, 0.5 mmol) in dry DCM (1 mL), followed by Et_3N (0.56 mL, 4 mmol). The resulting black solution was stirred for 30 min at –78 °C, followed by addition of 3 drops of saturated solution of Na_2CO_3. The Mixture was partitioned between Na_2CO_3 (20 mL) and DCM (50 mL). The phases were separated, and the aqueous phase was washed with fresh DCM (2×25 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography (PE/EA 5:1) to yield 49 mg of **303** (49%) as a colourless oil and 13 mg of **304** (13%) as a colourless oil.

Method 2. A solution of $TiCl_4$ (0.75 mL, 0.75 mmol, 1M in DCM) was added to a solution of Ti(O*i*-Pr)$_4$ (74 µL, 0.25 mmol) in DCM (0.5 mL) at 0 °C. The mixture was warmed to r.t. for 10 min, followed by cooling to –20 °C. A solution of **272** (57 mg, 0.25 mmol) in DCM (0.5 mL) was added at –20 °C, followed by Et_3N (0.140 mL, 1 mmol). Work-up and purification as in method 1 afforded 32 mg of **304** (65%).

Isopentyl 6-azabicyclo[3.1.0]hexane-1-carboxylate (**303**)



R_f 0.34 (hexane/EA 3:1);

IR (film) $\tilde{\nu}$[cm^{-1}]: 2956 (m), 2871 (w), 1716 (s), 1465 (w), 1445 (w), 1399 (w), 1318 (w), 1282 (s), 1179 (vs), 1152 (w), 1115 (m), 1082 (w), 1064 (w), 957 (w), 920 (w), 877 (w), 853 (w), 796 (w), 751 (m);

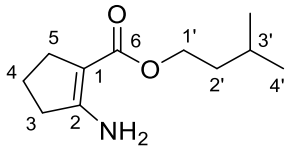
^{1}H NMR (401 MHz, $CDCl_3$): δ 4.23-4.12 (m, 2H, H-1'), 2.81 (d, *J* = 2.4 Hz, 1H, H-2), 2.12-2.04 (m, 1H, H-3a), 1.94 (dd, *J* = 13.0 Hz, 8.0 Hz, 1H, H-3b), 1.86 (dd, *J* = 12.4 Hz, 8.1 Hz, 1H, H-5a), 1.74-1.59 (m, 4H, H-3', N*H*, H-5b, H-4a), 1.55 (q, *J* = 7.0 Hz, 2H, H-2'), 1.46-1.39 (m, 1H, H-4b);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.9 (s, C-6), 64.2 (t, C-1'), 46.1 (d, C-2), 45.2 (s, C-1), 37.4 (t, C-2'), 27.4 (t, C-5), 26.7 (t, C-3), 25.3 (d, C-3'), 22.63 (q, C-4'), 22.61 (q, C-4'), 20.5 (t, C-4);

MS (ESI+) *m/z*, (%): 479 (25), 417 (25, [2M + Na]$^+$), 252 (20, [M + Na + MeOH]$^+$), 220 (100, [M + Na]$^+$), 198 (70, [M + H]$^+$);

HRMS (ESI+) *m/z*: [M + Na]$^+$ calcd. for $C_{11}H_{19}O_2NNa$ 220.1308; found: 220.1305.

Isopentyl 2-aminocyclopent-1-ene-1-carboxylate (**304**)



R_f 0.55 (hexane/EA 3:1);

^{1}H NMR (401 MHz, $CDCl_3$): δ 6.20-5.00 (br. s, 2H, NH_2), 4.13 (t, *J* = 6.8 Hz, 2H, H-1'), 2.60-2.41 (m, 4H, H-3, H-5), 1.88-1.77 (m, 2H, H-4), 1.76-1.65 (m, 1H, H-3'), 1.54 (q, *J* = 6.9 Hz, 2H, H-2'), 0.93 (d, *J* = 6.7 Hz, 6H, H-4');

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.4 (s, C-6), 161.7 (s, C-2), 95.8 (s, C-1), 61.6 (t, C-1'), 37.9 (t, C-2'), 35.3 (t, C-3/5), 29.7 (t, C-3/5), 25.3 (d, C-3'), 22.7 (q, C-4'), 20.9 (t, C-4).

6.6. X-ray crystallography

All crystal structures were deposited in the Cambridge Crystallographic Data Centre (CCDC) database under the following numbers:

Compound	Deposition number	a	b	c	Space group
(*S*)-**221**	2242138	4.6097(2)	11.0098(5)	18.9484(9)	$P2_12_12_1$
233	2242139	11.7116(3)	b 12.3179(3)	16.2012(5)	$P2_1/c$
139	2242141	17.8164(13)	11.3656(8)	14.4031(11)	$P2_1/c$
231a	2242142	10.2728(3)	11.1652(3)	11.3928(3)	*P*-1
133	2242143	7.9688(5)	14.5204(8)	14.7413(8)	*P*-1
124a	2242144	13.8586(6)	12.4142(5)	12.4074(6)	$P2_1/c$
revised-68a	2242145	9.3641(2)	10.1562(3)	11.5095(3)	*P*-1
231b	2242146	10.5666(3)	10.6697(3)	10.7791(3)	*P*-1
231a	2242147	8.4055(4)	10.2896(5)	14.8129(7)	*P*-1
229	2242148	11.5332(6)	21.4602(13)	11.7614(7)	$P2_1/n$

Cell lengths (a, b, c) in Å.

7. REFERENCES

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8. AUTHOR'S PUBLICATIONS AND SCIENTIFIC PRESENTATIONS

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