Synthesis of the Fijiolides Dihydropentalene Core and Amino Acid

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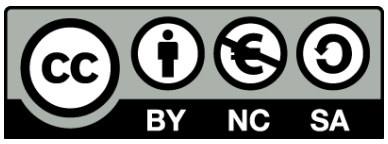

Your best teacher is your last mistake.

Ralph Nader

Acknowledgement

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List of Abbreviations

Å	ångström, 10^{-10} m
Ac	acetyl
ACA	asymmetric conjugate addition
acac	pentane-2,4-dione
Ad	6-aminopurine
aq.	aqueous
Ar	aromat
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert* butyloxy carbonyl
bod	bicyclo[2.2.2]octadiene
br	broad
brsm	*based on recovered starting material*
Bu	butyl
Bz	benzoyl
c	concentration (g · 100 mL^{-1})
cald.	calculated
cat.	catalytic
Cbz	benzyloxy carbonyl
CDI	carbonyl diimidazole
CoA	coenzyme A
cod	cycloocta-1,5-diene
COX	cyclooxygenase
cp*	pentamethyl cyclopentadiene
CSA	camphor sulfonic acid
Cy	cyclohexane
d	day(s)
dba	1,5-diphenyl penta-1,4-dien-3-one
DBU	diazabicycloundecene
DCE	1,2-dichloroethane
de	*diastereomeric excess*
δ	chemical shift (ppm)
$(DHQ)_2PHAL$	1,4-*bis*((1*R*)-((2*R*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl) methoxy)phthalazine
DIBAL	di*iso*butyl aluminum hydride
DIPT	di*iso*propyl tartrate
DMAP	dimethyl aminopyridine
DMDO	dimethyl dioxirane
DMF	dimethyl formamide
DM-Segphos	(5'-(*bis*(3,5-dimethylphenyl) phosphaneyl)-[4,4'-bibenzo[*d*] [1,3]dioxol]-5-yl)(2,4-dimethyl phenyl)(3,5-dimethylphenyl) phosphane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dosp	((4-dodecylphenyl)sulfonyl) proline
dppf	1,1'-bis(diphenylphosphino) ferrocene
d.r.	*diastereomeric ratio*
E	*entgegen*
EDCl	3-(ethyliminomethylene amino)-*N*,*N*-dimethylpropan-1-amine
ee	enantiomeric excess
equiv.	equivalents
ESI	electrospray ionization

esp	3,3'-(1,3-phenylene)bis(2,2-dimethylpropanoic acid)
espn	3,3'-(1,3-phenylene)bis(2,2-dimethylpropanamide)
Et	ethyl
et al.	*et alii*
FT-IR	Fourier-transform infrared spectroscopy
h	hour(s)
hυ	photon
HMDS	hexamethyl disilazide
HPLC	high pressure liquid chromatography
HR-MS	high resolution mass spectrometry
HWE	HORNER-WADSWORTH-EMMONS
Hz	hertz
i	*iso*
IC_{50}	half maximal inhibitory concentration
J	coupling constant
L	litre
LDA	lithium di*iso*propyl amine
$LiAlH_4$	lithium aluminum hydride
M	molar mass, $g \cdot mol^{-1}$
M	concentration, $mol \cdot L^{-1}$
m	milli, 10^{-3}
Me	methyl
MHz	megahertz, 10^6 Hz
µ	micro, 10^{-6}
min	minutes
mol	$6.022 \cdot 10^{23}$
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves
Ms	mesyl
n	normal
nap	4-methyl-*N*-(2-oxopiperidin-3-yl)benzenesulfonamide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nf	nonafluorobutane sulfonyl
NFκB	nuclear factor-κB
nm	nanometer, 10^{-9} m
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
$\tilde{\upsilon}$	vibration frequency (cm^{-1})
org.	organic
p	*para*
PCC	pyridinium chlorochromate
PCP	peptidyl-carrier protein
PG	protecting group
Ph	phenyl
pin	pinacol
Piv	pivaloyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
pTSA	*para* toluene sulfonic acid
py	pyridine
R	residue
R	*rectus*
rac.	racemic

rcm	ring closing metathesis
Red-Al	sodium bis(2-methox yethoxy)aluminium hydride
Ref.	reference
R_f	retention factor
ρ	Density ($g \cdot mL^{-1}$)
rt	room temperature
S	*sinister*
sat.	*saturated*
Sgc	*streptomycene globisporus cluster*
S_N	nucleophilic substitution
TBAF	tetra butyl ammonium fluoride
TBS	*tert* butyl dimethyl silyl
TBDPS	*tert* butyl diphenyl silyl
TDP	thymine diphosphate
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical
tert	*tertiary*
TES	triethyl silyl
Tf	trifluoromethane sulfonyl
TFDO	methyl(trifluoromethyl) dioxirane
TFA	trifluoro acetic acid
THF	tetrahydrofurane
TIPDS	1,1,3,3-tetra*iso*propyl disiloxane
TLC	thin layer chromatography
TMS	trimethyl silyl
TNF-α	tumor necrosis factor α
Tol	toluyl
TPA	triphenylacetate
t_R	retention time
Ts	*para* toluene sulfonyl
UV	ultra violett
Z	*zusammen*

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1 Introduction – Enediyne derived Natural Products

Cyclic nine- and ten-membered enediyne structures containing natural products have attracted attention of the synthetic and pharmacologic community over the past three decades.[1] They belong to a fascinating family of secondary metabolites, both in terms of molecular structure and biological activity. Although only a few examples have been discovered so far,[2] two of them (neocarzinostatin[3] **1** and calicheamicin[4] **2**) have been already approved for anticancer therapy. Another four are subject of ongoing drug development programs (C-1027 **3**,[5] unicialamycin **4**,[6] dynemicin **5**,[7] and esperamicin **6**,[8] figure 1).

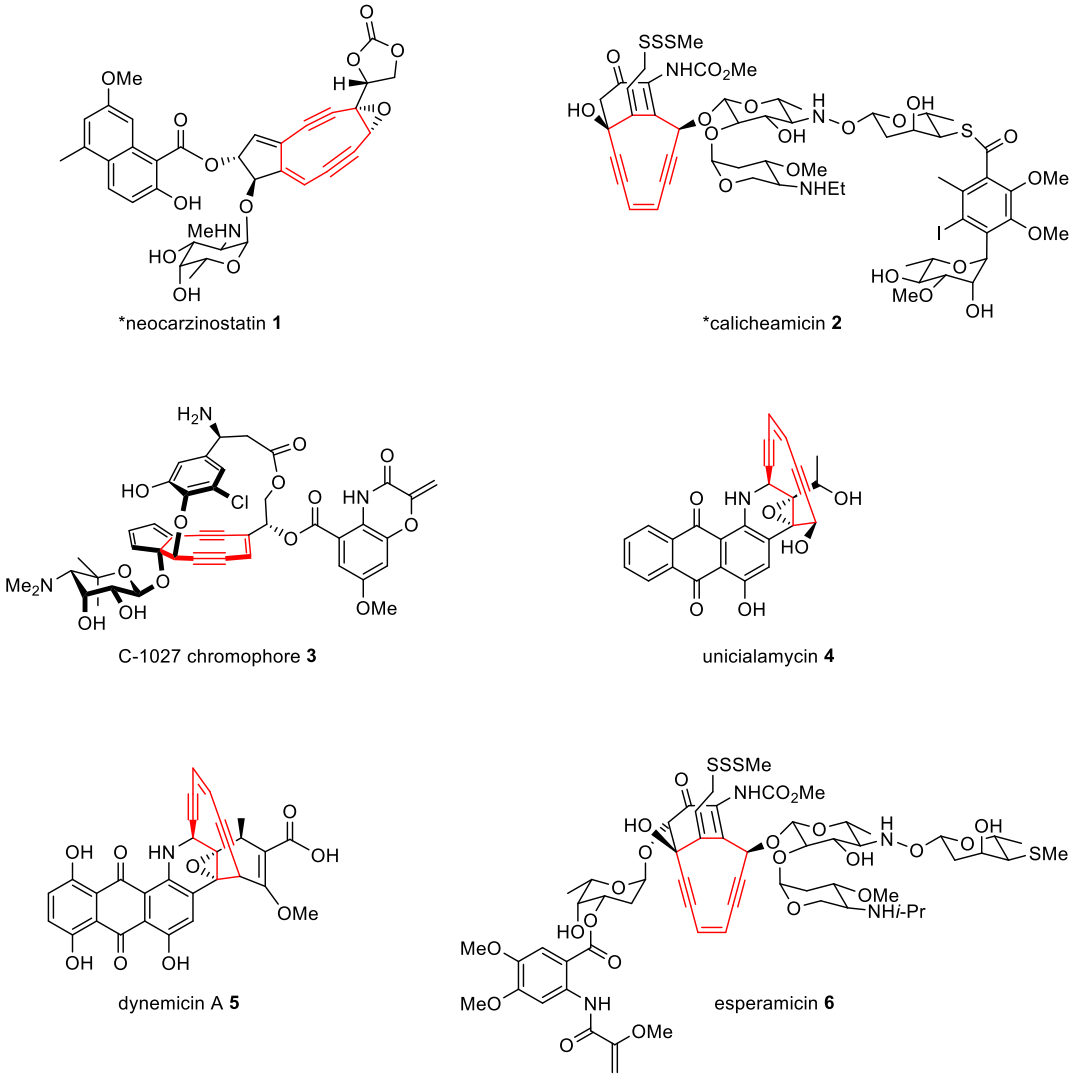
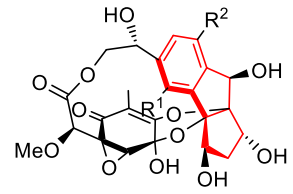
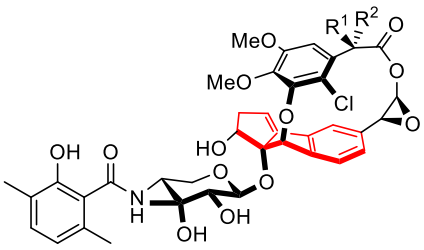


Figure 1: Examples of enediyne derived natural products as (*approved) anticancer therapeutic agents (enediyne core displayed in red).

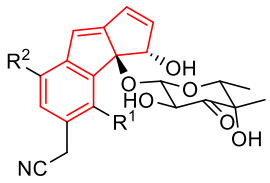
Albeit the gene clusters responsible for their biosynthesis have been identified in a whole number of *actinomycetes*,[9] the number of enediyne derived structures isolated so far appears quite limited. This might be due to their high tendency to undergo BERGMAN-cyclizations or MYERS-SAITO rearrangements,[10] for example upon attempts to isolate them (chapter 1.2). Consequently, some cyclization-derived natural products have been discovered in the past, including the sporolides **7**,[11] amycolamycins **8**,[12] cyanosporasides **9**,[13] and fijiolides[14], which are subject of this thesis (figure 2).



R^1 = Cl, R^2 = H sporolide A **7a**
R^1 = H, R^2 = Cl sporolide B **7b**



R^1 = OH, R^2 = H amycolamycin A **8a**
R^1 = H, R^2 = OH amycolamycin B **8b**

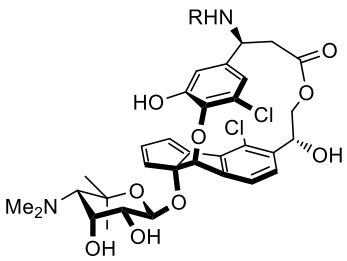


R^1 = Cl, R^2 = H cyanosporaside A **9a**
R^1 = H, R^2 = Cl cyanosporaside B **9b**

Figure 2: BERGMAN-cyclization derived natural products (former enediyne structure marked in red).

1.2 Isolation and Biological Origin of Fijiolides

Fijiolide A (**10a**) and B (**10b**) were isolated in 2010 by FENICAL *et al.* from marine-derived *actinomycete* strain CNS-653,[14a] which was found in sediment samples from Beqa Lagoon, Fiji. Their absolute structures could be determined by combination of 2D NMR spectroscopic data, circular dichroism and advanced MOSHER`s method (figure 3) and were found only to differ in acetylation of an amino acids substructure.



R = Ac fijiolde A **10a**
R = H fijiolide B **10b**

Figure 3: Structure of fijiolide A and B, elucidated by FENICAL.

Structurally, the fijiolides consist of an 8,9-dihydroxylated benzodihydropentalene core structure (red), a *β*-tyrosine moiety (green) forming the *ansa*-bridge in a *para*-cyclophane and an amino sugar (blue, figure 4). Key characteristics of **10** include an atrop-isomerism with restricted rotation regarding orientation of the tyrosine unit during cyclophane formation (alternatively leading to atrop-isomer **11**). Furthermore, the fijiolides feature a hindered tertiary glycosylated alcohol at C9 and a strained cyclopentadienol subunit incorporated in the tricylic indene fragment.

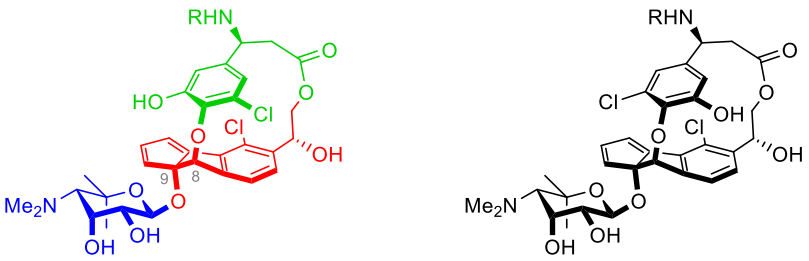
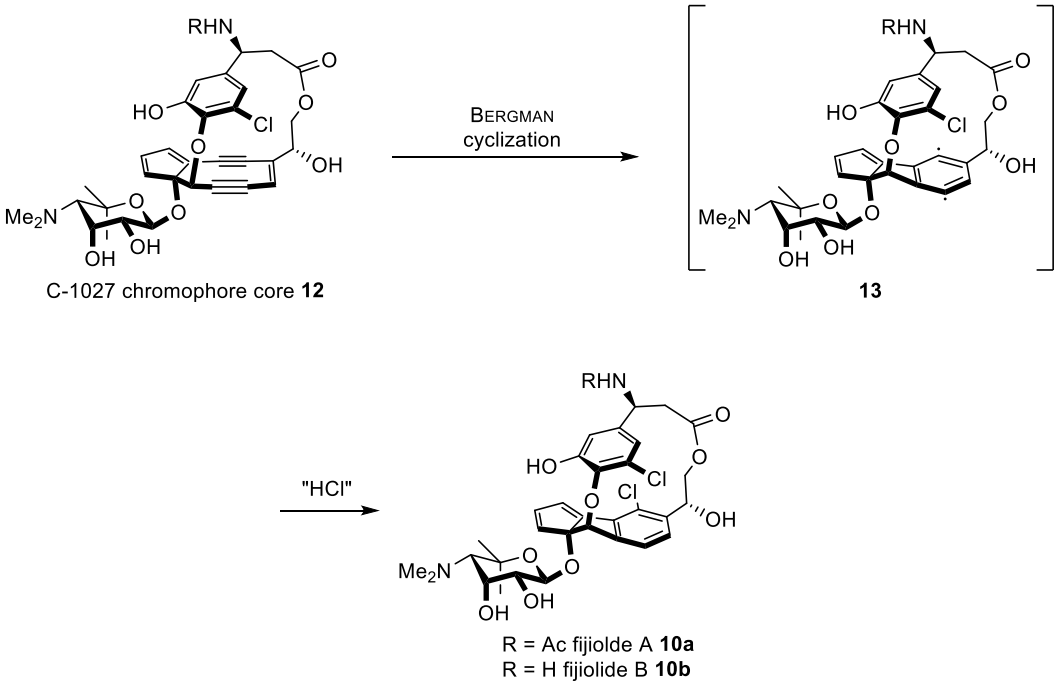


Figure 4: The fijiolides A and B and atrop-isomer **11**.

Biologically they seem to result from Bergman-cyclization of related enediyne precursor C-1027 chromophore **12**, where 3,6-biradical intermediate **13** would have to be formally quenched by a chlorine radical at C3 (scheme 1). The high tendency of cyclic enediyne structures to undergo BERGMAN-cyclizations was demonstrated by HIRAMA,[15] INOUE[16] and others[17] for a variety of substrates, often occurring spontaneously in solution within minutes. However, a regioselective mono-chlorination of **13**`s aglycon proved to be difficult when carried out using Cl-radical sources for several substrates, predominantly leading to chlorination at C6 or dichlorination. Only recently, the application of an ionic pathway using LiCl in DMSO to mimic the *actinomycete*`s seawater environment allowed to address the desired C3 position.[15a]



Scheme 1: BERGMAN-cyclization of **12** to form fijiolides A and B via biradical **13**.

Further evidence for a collective biosynthetic background of the fijiolides and C-1027 chromophores was provided by OH *et al.*, who isolated cyclized chromophore III (**14a**) and V (**14b**), together with fijiolides A and B from an arctic marine *actinomycete Streptomyces* strain ART5 (figure 5).[14b]

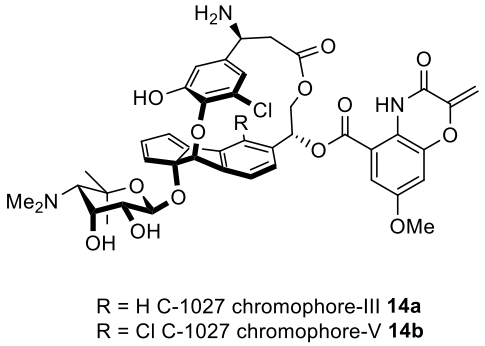
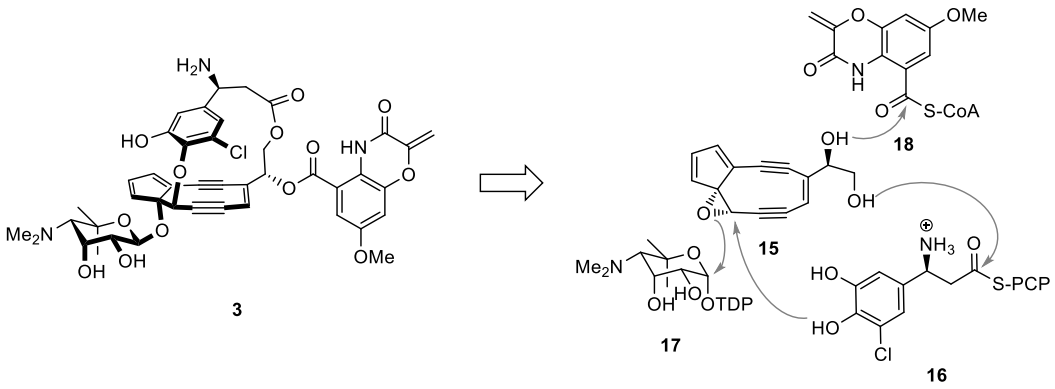


Figure 5: Structure of C-1027 chromophore III and V isolated by OH and coworkers.[14b]

1.3 Biosynthesis of C-1027

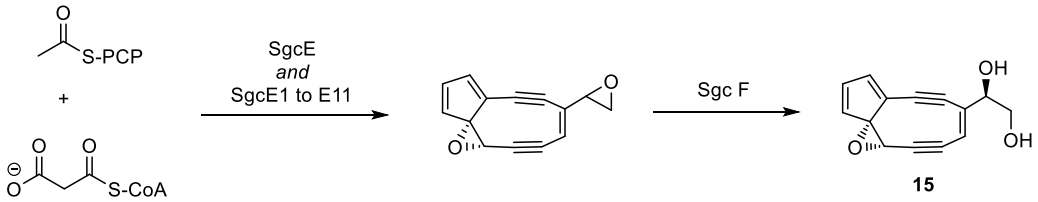
In 2002 SHEN and coworkers characterized the biosynthetic pathway for C-1027 (**3**),[18] which is likely to be quite similar for the fijiolides due to the already mentioned structural relationship between **3** and the fijiolides (chapter 1.2). SHEN *et al.* cloned and characterized

the 85-kilobase gene cluster from *streptomyces globisporus*, which revealed an iterative type I polyketide synthase leading to a highly convergent biosynthesis of four building blocks **15**-**18** (scheme 2).



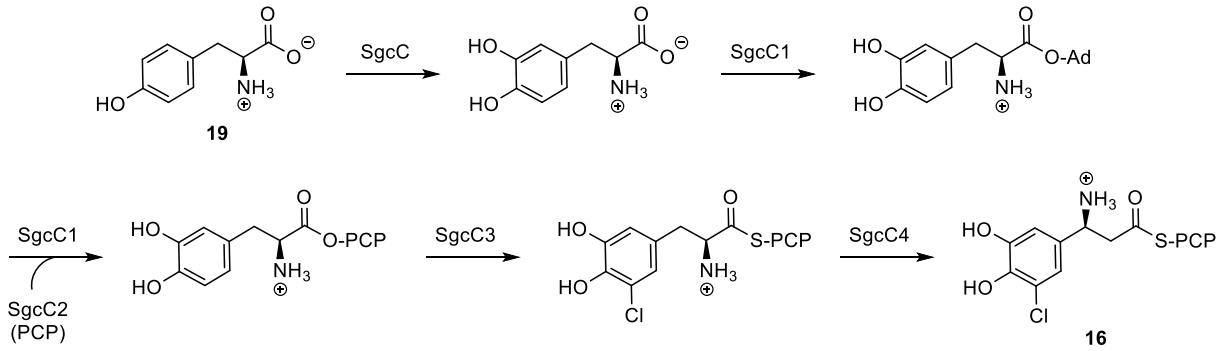
Scheme 2: Hypothesized biosynthetic assembly of the building blocks **15**-**18** towards C-1027 chromophore **3**.

In correlation with investigations on the gene cluster of neocarzinostatin[19] SHEN *et al.* concluded a group of open reading frames (ORFs, SgcE and SgcE1 to SgcE11) might be involved in the synthesis of enediyne structure **15**, together with epoxide hydrolase SgcF (scheme 3).



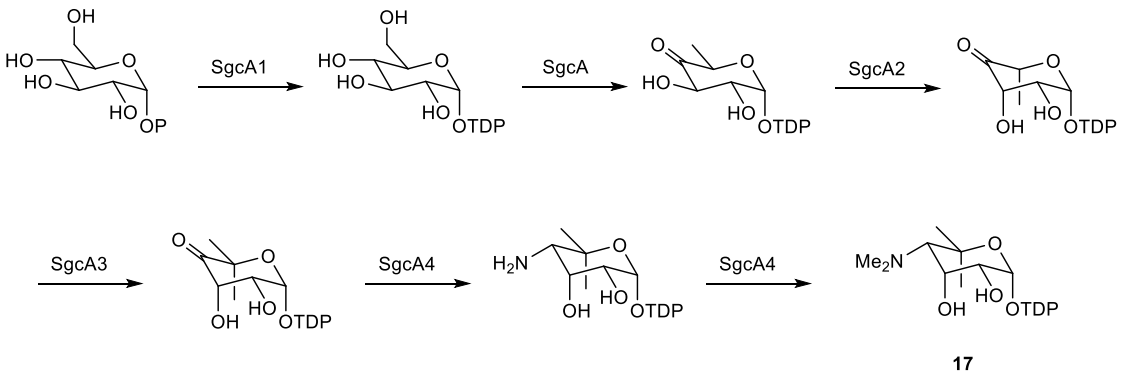
Scheme 3: Hypothetical biosynthetic pathway of enediyne fragment **15**.

Based on the set of enzymes found in the gene cluster the authors proposed a biosynthetic route towards amino acid **16** starting with hydroxylation of tyrosine **19**, followed by stepwise activation of the carboxylic acid. Subsequent chlorination of the catechol and migration of the amine might furnish amino acid building block **16** (scheme 4).



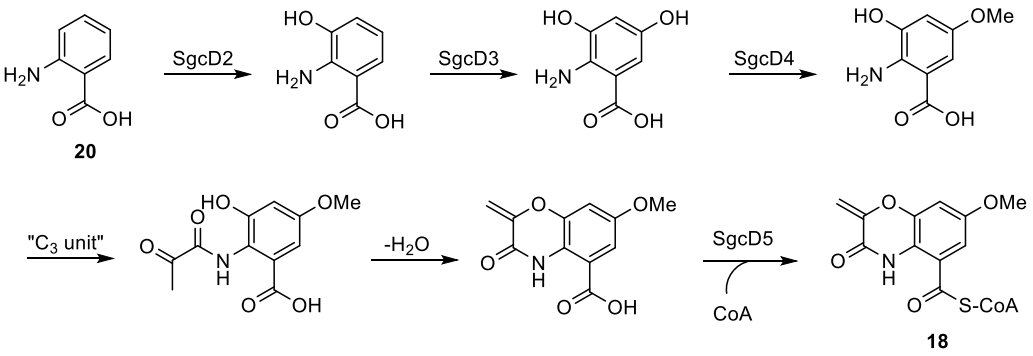
Scheme 4: Proposed biosynthetic pathways of the synthesis of amino acid **16**.

Biosynthesis of amino sugar **17** might start from glucose and rely on phosphorylation at C1 and reduction at C6. Oxidation at C4, epimerization and methylation at C5, followed by reductive amination and methylation of the resulting amine could furnish amino sugar **17** (scheme 5).



Scheme 5: Proposed biosynthetic pathways for the synthesis of amino sugar **17**.

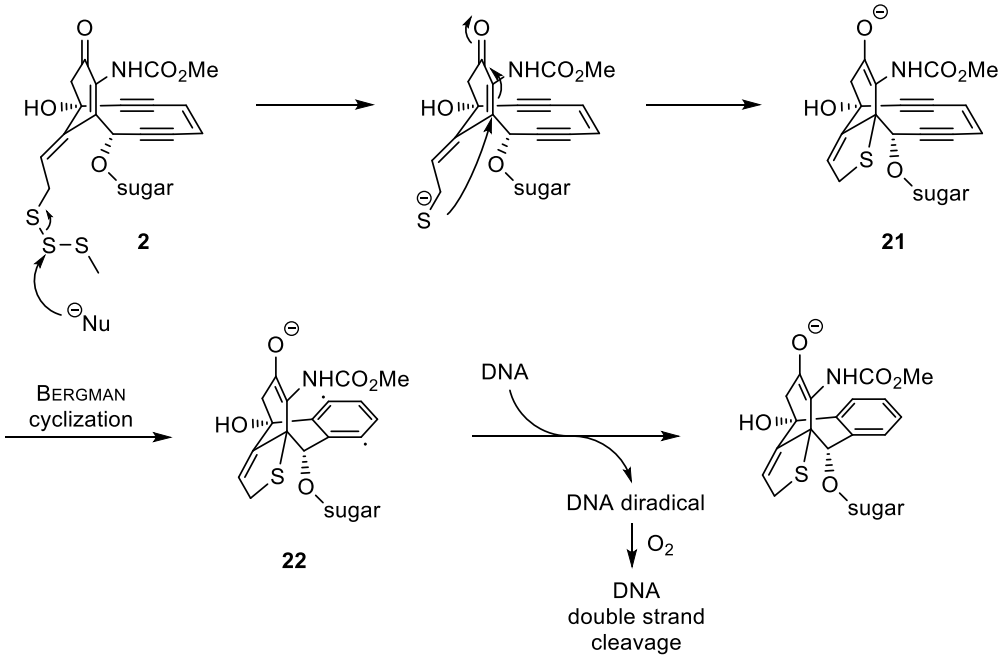
For benzoxazolinate **18** double hydroxylation of benzoic acid **20**, followed by mono-etherification was hypothesized to take place. Amide formation, condensation and activation of the benzoic acid would then give building block **18** (scheme 6).



Scheme 6: Proposed biosynthetic pathways for synthesis of benzoxazolinate **18**.

1.4 Biological Activity

The already mentioned tendency of enediyne containing natural products to cyclize is also responsible for their biological activity. While acyclic enediynes usually require harsh conditions for cyclization, natural occurring enediynes are often incorporated in cyclic skeletons and therefore undergo cyclization under much milder conditions.[15,16] As exemplified for calicheamicin **2**[20] in scheme 7, a nucleophilic attack cleaves the trisulfide`s S-S bond of the allylic trigger heterolytically, which induces intramolecular cyclization to **21** and facilitates subsequent BERGMAN-cyclization to yield biradical **22**. This highly reactive 1,4-biradical abstracts two H atoms from the DNA backbone which finally results in apoptosis. Alternatively, photoactivation, thiols, or non-neutral pH-values also induce cyclization.[20,21]



Scheme 7: Mechanism of DNA cleavage exemplified for calicheamicin.[20]

In contrast to other enediyne-containing natural products C-1027-derived cyclization products do not lose their biological activity upon rearrangement entirely, which makes them even more attractive targets for medicinal application, due to higher stability. In fact, FENICAL *et al.* found the fijiolides A and B to be potent inhibitors of TNF-α-induced NFκB activation.[14a] For fijiolide A, they found reduced activation by 70.3% with an IC_{50} value of 0.57 µM; fijiolide B showed dose-independent inhibition of 46.5%. This finding clearly demonstrates the importance of the amine`s acetylation. Furthermore, for fijiolide A an induction of

quinone reductase-1 (QR1) with a rate of 3.5 (28.4 μM) was observed; with a concentration of 1.8 μM necessary to double activity. Fijiolide B had no influence on QR1 activity. In contrast to the fijiolides, the structurally related cyclized C-1027 chromophores III (**14a**) and V (**14b**, figure 5, chapter 1.2) were also found to inhibit isocitrate lyase (ICL, IC_{50} of 25.6 μM for chromophore III, 37.9 μM for V), an enzyme playing a pivotal role in *Candida albicans* pathogenicity. In addition, for both chromophores moderate to high anti-proliferative activity was found against a variety of carcinoma cell lines.[14b]

The inhibitory effects against TNF-*α*-induced NF*κ*B activation of the fijiolides` bioactivity are of particular interest for medicinal chemistry. NF*κ*B (nuclear factor-*κ*B) is a transcription factor present in almost all cell types.[22] It is responsible for the immune response of over 400 genes in case of infections or inflammation and other stressful events.[23] While controlled by inhibitory proteins in the resting state, upon external stimuli these proteins get rapidly phosphorylated, ubiquitinated and degradated which liberates NF*κ*B for regulating gene transcription. However, a variety of viruses[24] tend to utilize NF*κ*B for activating their own genes for replication. Furthermore, its extraordinative activation in cancerous cells is well documented.[25]

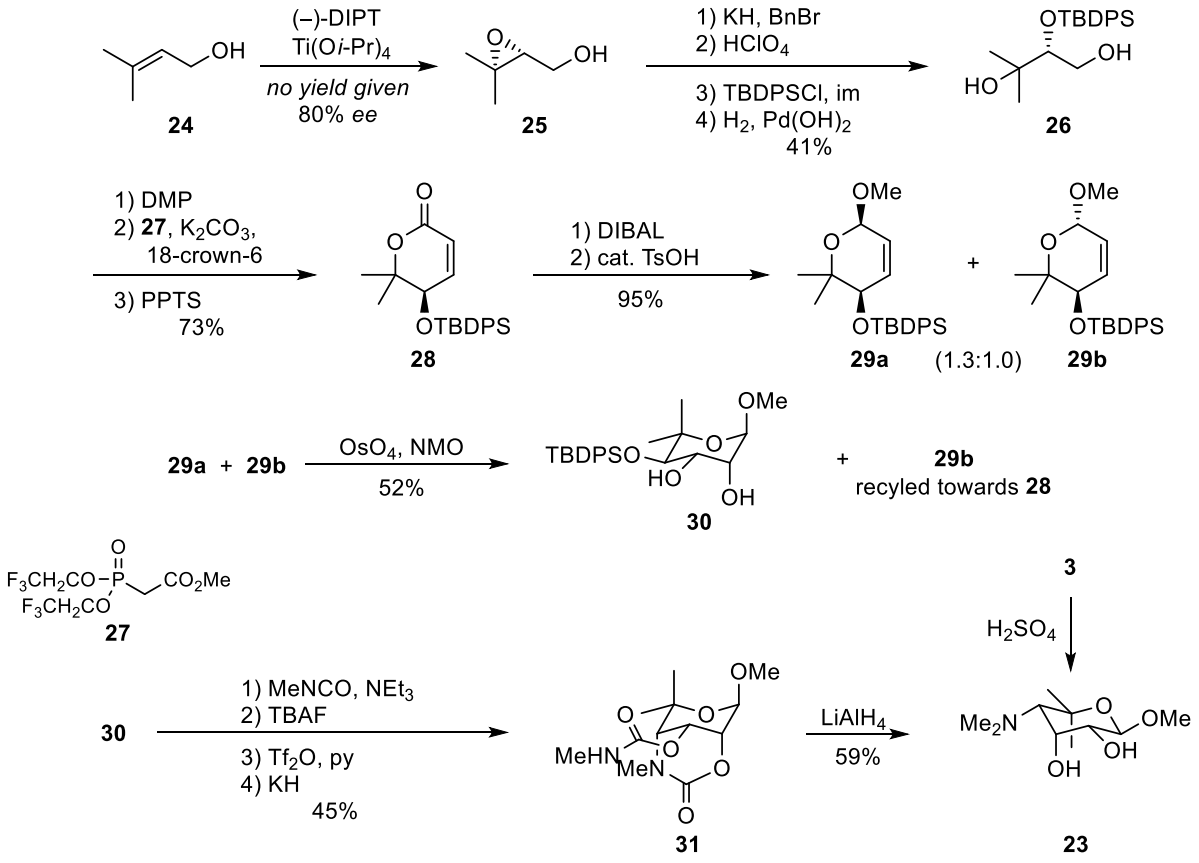
One of the most potent activators of NF*κ*B is tumor necrosis factor *α* (TNF-*α*). While TNF-*α* is essential part of the intact immune response, its misregulation can lead to a variety of diseases such as inflammatory or viral infections.[26] Therefore a selective inhibition of TNF-*α* does represent an interesting approach for cancer therapy.

1.5 Current State of Research

Due to their potential as lead structures for medicinal chemistry (chapter 1.4), numerous approaches towards synthesis of enediyne related natural products and their substructures have been published over the years,[3-14] the ones related to C-1027 and the fijiolides will be discussed in the following section.

1.5.1.1 Synthesis of the Amino Sugar: HIRAMA`s first Generation Synthesis

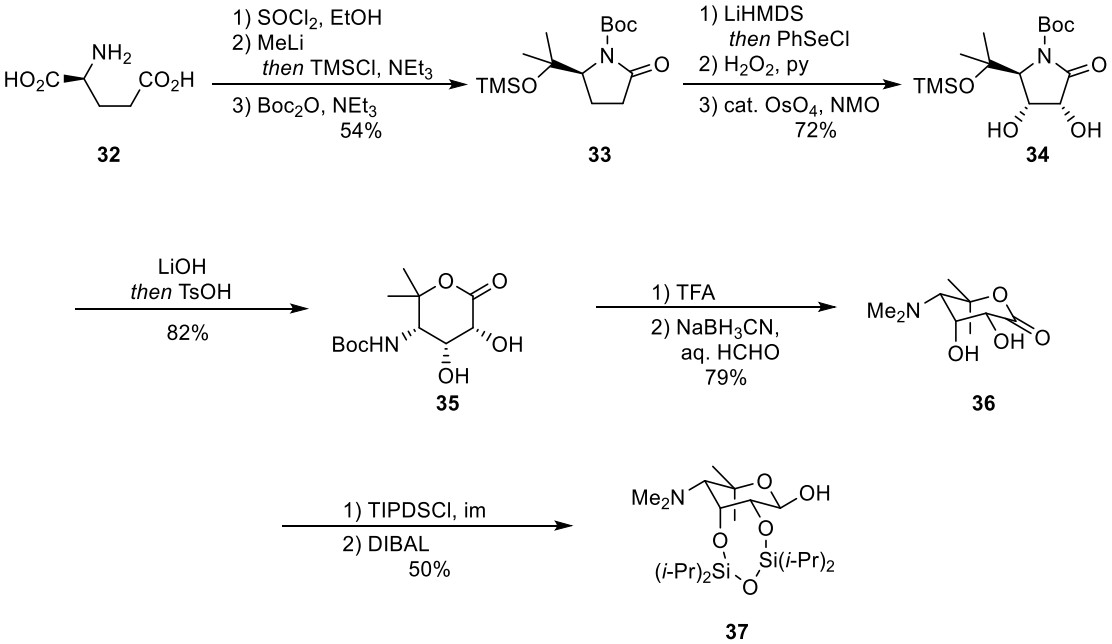
HIRAMA`s first generation synthesis[27] of amino sugar **23** started with SHARPLESS epoxidation of prenol **24** to give epoxide **25**. Benzylation of the primary alcohol, epoxide opening, silylation of the corresponding secondary alcohol and hydrogenolytic cleavage of the benzyl ether resulted in **26** in 41% yield over four steps. Oxidation of the primary alcohol and subsequent STILL-GENNARI olefination gave the (*Z*)-configured *α,β*-unsaturated ester, which was cyclized under acidic conditions to lactone **28**. Reduction using DIBAL and methylation furnished lactols **29a** and **29b** (scheme 10) with following dihydroxylation of this mixture yielding 1,4-*cis*-substituted diol **30** while unreacted lactol **29b** could be recycled. Diol **30** was converted into the biscarbamate, desilylated, triflated and cyclized under basic conditions to give **31**. Final reduction of cyclized carbamate **31** with $LiAlH_4$ gave methyl glycoside (–)-**23** (scheme 8) with identical spectroscopic data to those derived from acidic degradation of C-1027 (**3**). Overall this synthesis yielded (–)-**23** in 1-2% with 80% *ee* over 17 steps and helped to verify amino sugar **23**`s absolute configuration, which proved to be challenging using alternative methods.



Scheme 8: HIRAMA`s first generation synthesis[27] of amino sugar **23**.

1.5.1.2 HIRAMA`s second Generation Synthesis

HIRAMA`s second generation synthesis[28] of **23** started from *L*-glutamic acid (**32**), which was cyclized to the γ-lactam ethyl ester, followed by addition of methyl lithium, silylation of the resulting alcohol and Boc-protection of the amide to give **33** in 54% yield. Addition of PhSeCl to the enolate of **33**, GRIECO elimination and dihydroxylation resulted in diol **34** as a single diastereomer, which gave δ-lactone **35** after saponification and acidic lactonization. Boc-deprotection and reductive amination yielded *N*,*N*-dimethylamine **36** in 79%. Protection of the diol and DIBAL reduction furnished lactol **37** in 50% yield, which represents to this date the shortest synthesis with eleven steps and an overall yield of 13% (scheme 9). Furthermore, protection of the diol as disiloxanylidene was hypothesized to be beneficial in the stereoselective glycosylation of fijiolides aglycon and subsequent desilylation, which was later demonstrated by CRAMER (see chapter 1.5.3).[14c]

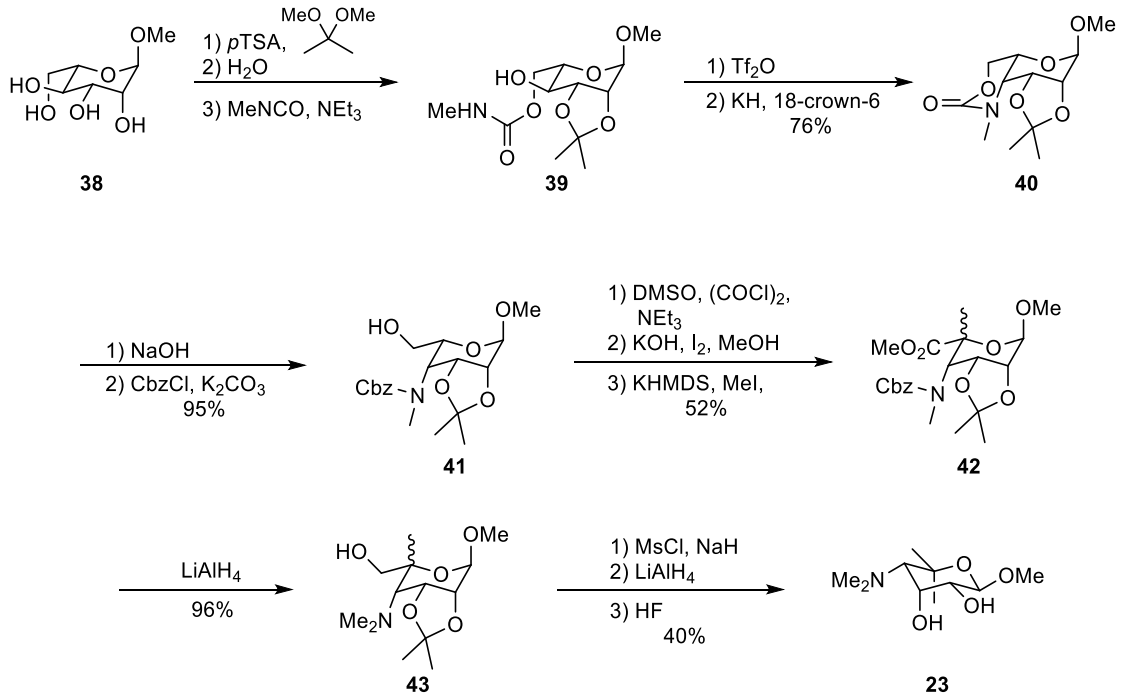


Scheme 9: HIRAMA`s second generation synthesis[28] of amino sugar **37**.

1.5.1.3 SEMMELHACK`s Synthesis of 23

In 2001 SEMMELHACK and coworkers published a synthesis[29] of **23** starting from enantiopure *α*-methyl-*L*-manno-pyranoside (**38**). Double acetonide formation and selective hydrolysis of the C4/C6 acetonide,[30] followed by carbamate formation at C6 gave **39**. Triflation of the alcohol and intramolecular S_N2 displacement of the latter gave oxazinanone **40**. Although

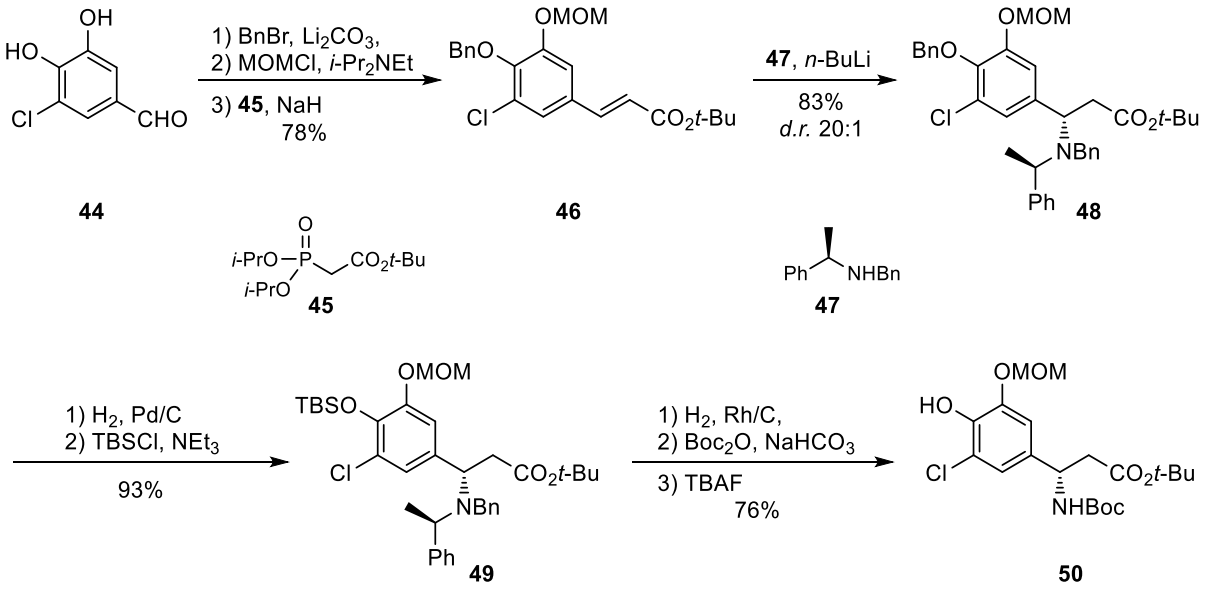
reduction of the oxazinone in **40** with $LiAlH_4$ gave the amino alcohol in excellent yield, subsequent oxidation resulted in competing elimination at C4, therefore the carbamate of **40** was cleaved under basic conditions followed by Cbz-protection of the amine to give **41** in 95% yield. A stepwise oxidation of the alcohol to the methyl ester and α-methylation resulted in **42** as a mixture of diastereomers, which were reduced to alcohol **43** using $LiAlH_4$. Mesylation of the alcohol, reduction of the mesylate and subsequent acetal deprotection gave (–)-**23** in 14 steps starting from **38** in 10% yield (scheme 10).



Scheme 10: SEMMELHACK`s synthesis[29] of amino sugar **23**.

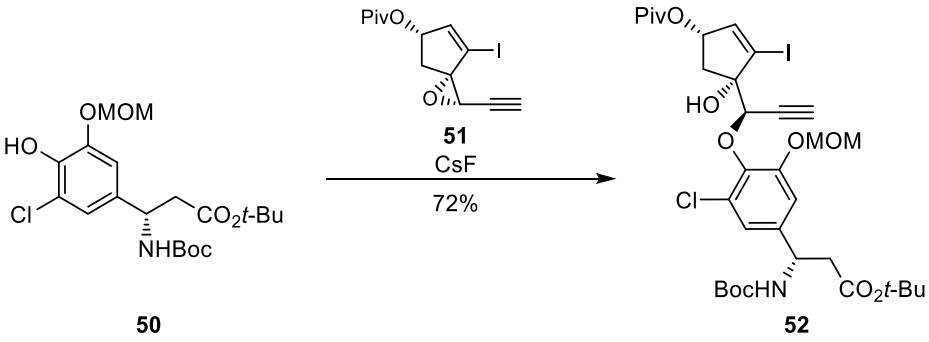
1.5.2.1 Synthesis of the Amino Acid: HIRAMA`s Synthesis

The group of HIRAMA developed a synthesis[31] for the β-tyrosine moiety of the fijiolides starting from benzaldehyde **44** (scheme 11). The catechol of **44** was orthogonal protected as benzyl and MOM ethers and following HWE-reaction gave cinnamic ester **46** in 78% yield. Asymmetric conjugate addition with DAVIES` lithium amide[32] **47** resulted in amino ester **48** with a *d.r.* of 20:1. Hydrogenolytic deprotection of **48** also caused elimination of the amine, so a change of the benzylic phenol protection to a TBS ether gave **49**. Subsequent amine deprotection, Boc-protection and desilylation gave **50** in nine steps and 46% yield starting from aldehyde **44**.



Scheme 11: HIRAMA`s synthesis of the *β*-tyrosine moiety of C-1027.

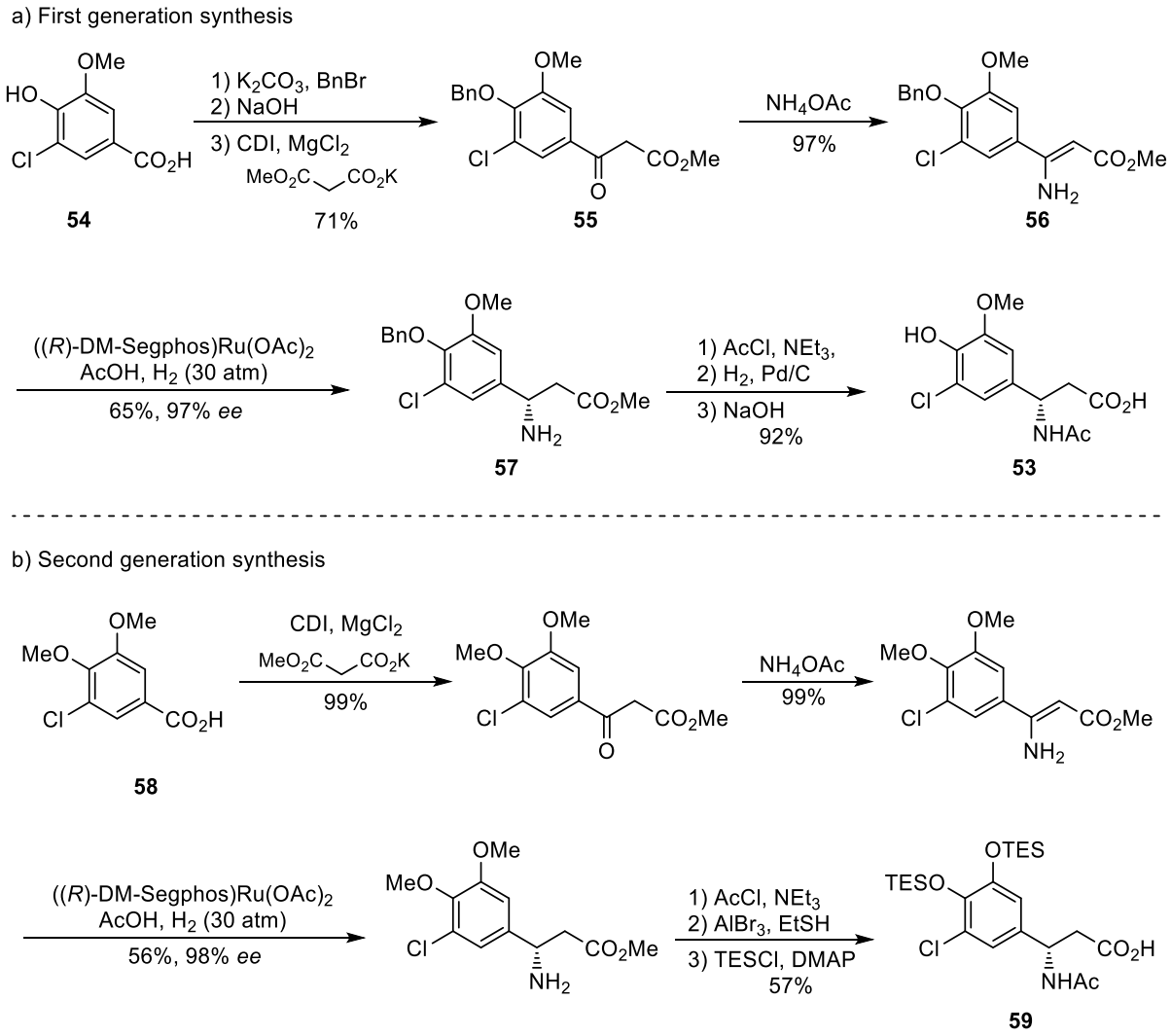
HIRAMA *et al*. then used amino acid **50** to investigate regioselective epoxide opening on C-1027 building block **51** utilizing CsF in DMF at 80 °C for their synthetic studies towards the C-1027 chromophore (**52**, scheme 12).[31]



Scheme 12: Epoxide opening by amino acid derivative **50** on C-1027 building block **51**.

1.5.2.2 CRAMER`s Synthesis of the Amino Acid moiety

CRAMER`s first generation synthesis[14d] of the *β*-tyrosine moiety **53** started with 5-chlorovanilic acid (**54**). *O*-benzylation of the phenol and a decarboxylative CLAISEN condensation gave *β*-keto ester **55**, which was subsequently converted into enamine **56**. A highly enantioselective hydrogenation using a $Ru(OAc)_2$/DM-Segphos combination yielded **57**. Subsequent acetylation of the amine, hydrogenolytic cleavage of the benzyl ether and saponification of the ester gave acid **53** in 41% yield over eight steps (scheme 13a).

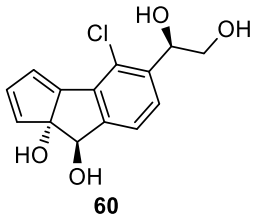


Scheme 13: CRAMER`s two generations of amino acid syntheses.

After their synthetic efforts had revealed that no orthogonal protection of the catechol was necessary (chapter 1.5.3), a slight modification of the protecting group strategy furnished *bis*-silylated amino acid **59** in 32% yield from 5-chloroveratric acid (**58**, scheme 13b).[14d]

1.5.3 CRAMER`s Total Synthesis of Fijiolide A

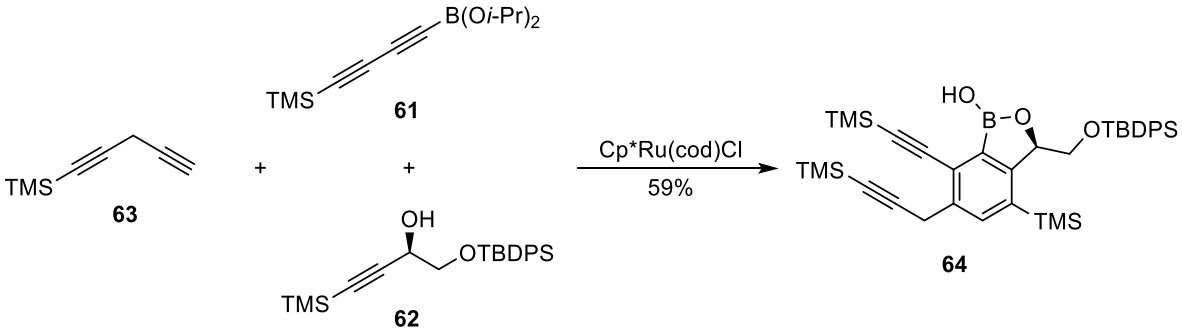
Synthesis of the tricyclic core structure **60** of the fijiolides (figure 6) represents the synthetically most challenging part of the synthesis together with the atrop-selective cyclophane formation. Trapping biradical intermediate **13** resulting from BERGMAN-cyclization of the enediyne precursor C-1027 would deliver **10** (scheme 1, chapter 1.2). However, synthetic work of INOUE and HIRAMA[5b-e] towards total synthesis of the C-1027 chromophore **3** revealed the required enediyne precursor required for this transformation to be synthetically equally challenging.



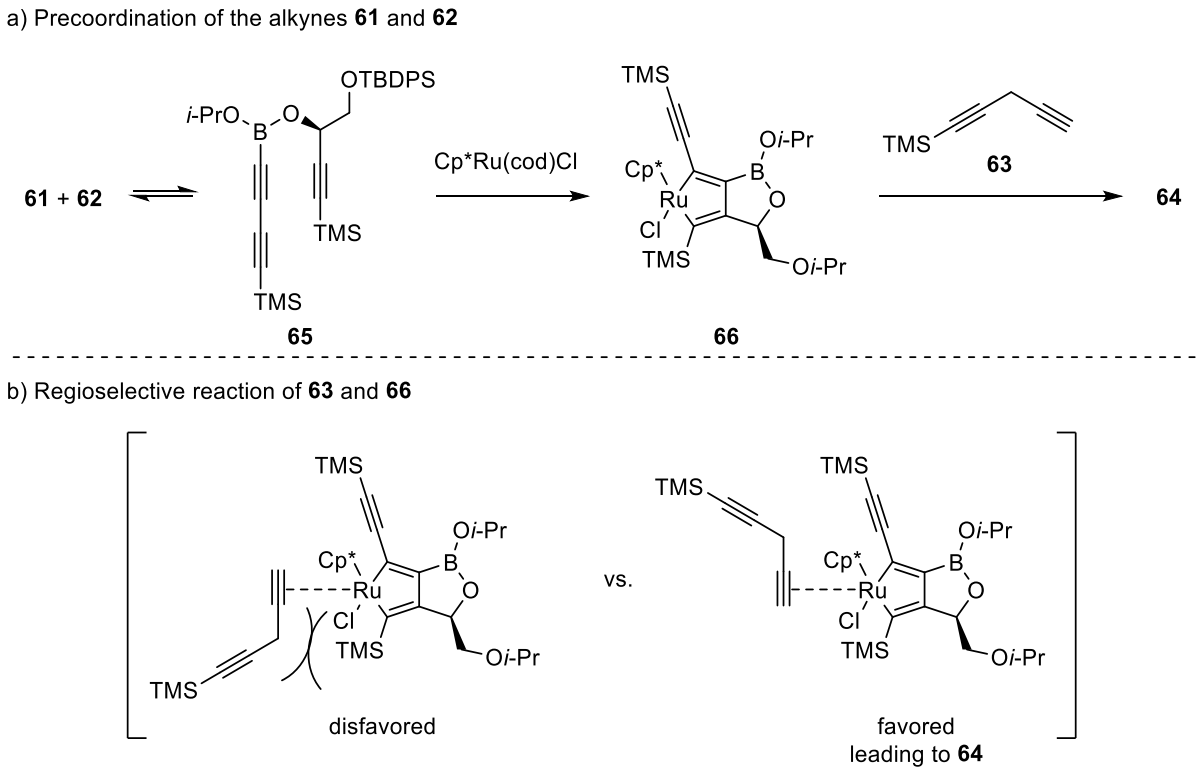
60

Figure 6: Benzodihydropentalene core of the fijiolides.

For their synthesis of fijiolide A, CRAMER and coworkers[14c] developed an elegant synthetic route towards tricyclic compound **60** via a highly regioselective [2+2+2]-cycloaddition of alkynes **61**, **62** and **63** (scheme 14), based on synthetic efforts of YAMAMOTO.[33] A preformation of boron-tethered triyne **65** gave under Ru(I)-catalysis **66** (scheme 15a), which could then react regioselectively with the unprotected alkyne of diyne **63** (scheme 15b) to form highly functionalized **64** in 59% yield as single diastereomer.

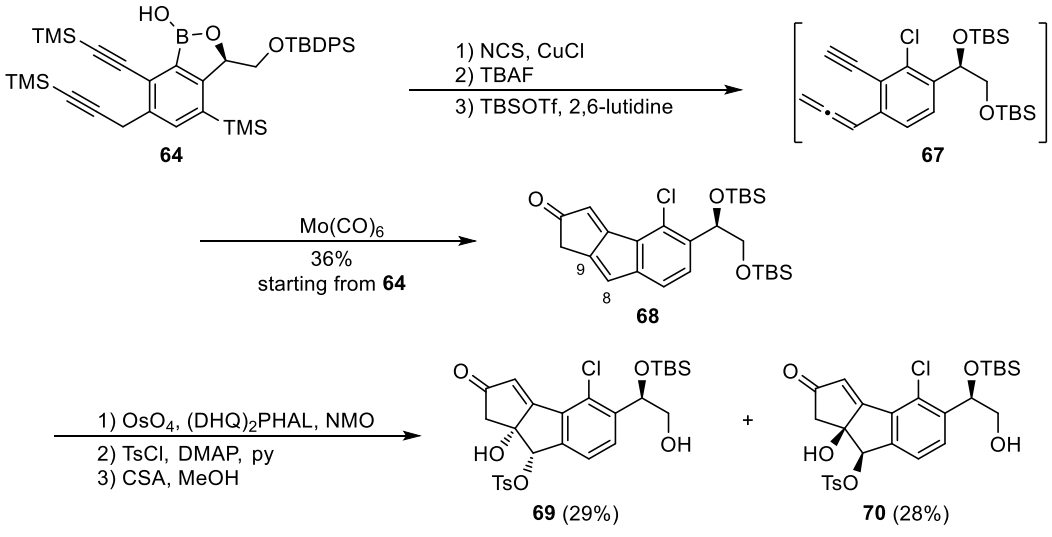


Scheme 14: CRAMER`s highly regioselective [2+2+2]-cycloaddition of alkynes **61** - **63** to yield **64**.



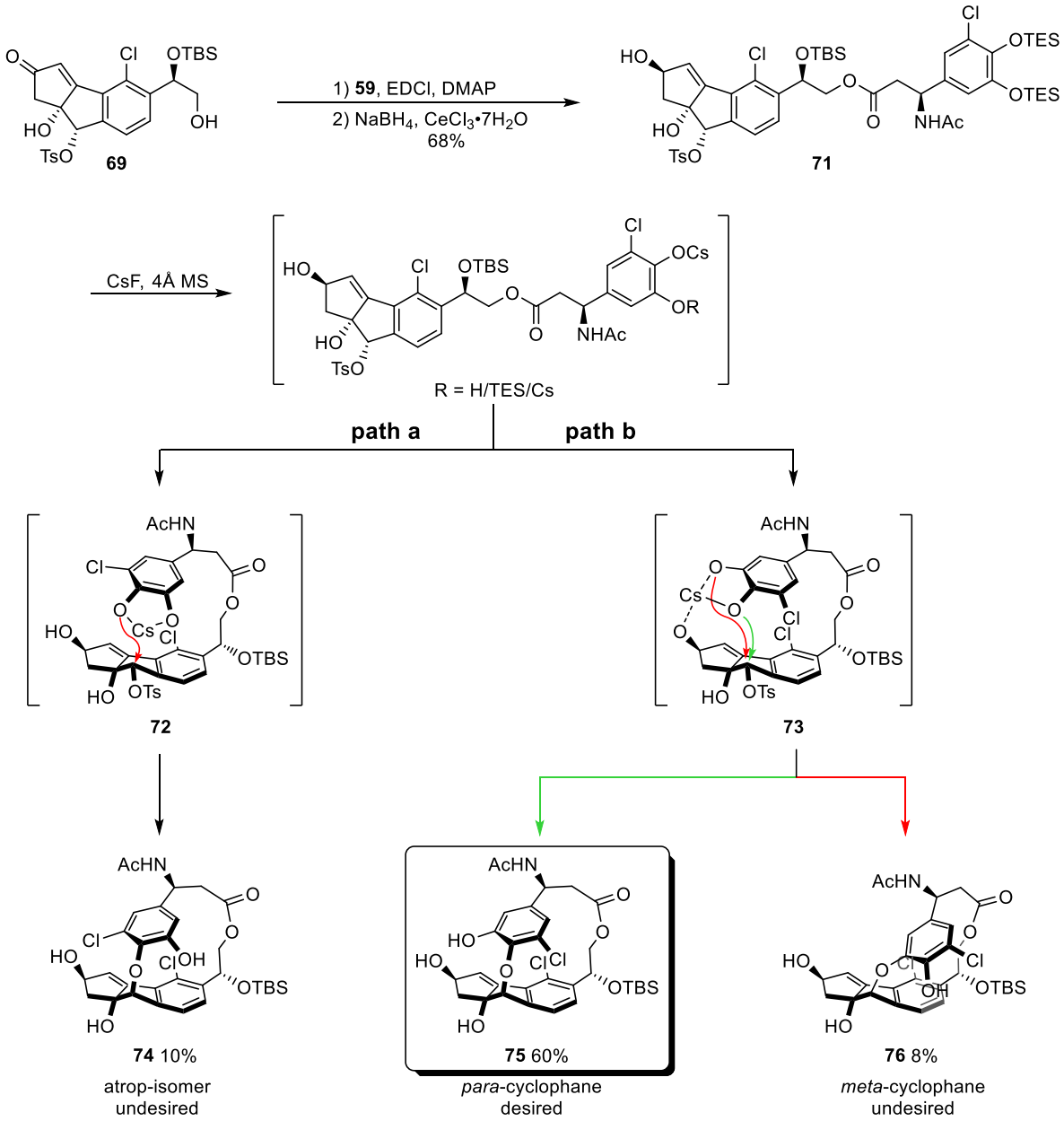
Scheme 15: Preformation of **71** explaining the regioselectivity observed.

With **64** in hand, chlorination, desilylation-induced allene formation and protection of the diol side chain gave precursor **67** for an allenic PAUSON-KHAND reaction,[34] which provided cyclopentenone **68** in 36% yield over four steps. Dihydroxylation at C8/C9, regioselective tosylation of the resulting alcohol at C8 and acidic deprotection of the side chain`s primary alcohol furnished diols **69** and **70** (scheme 16). With this impressive reaction sequence the cyclopentenone building block of the fijiolides was accessible to investigate atrop-selective cyclophane formation (scheme 17).



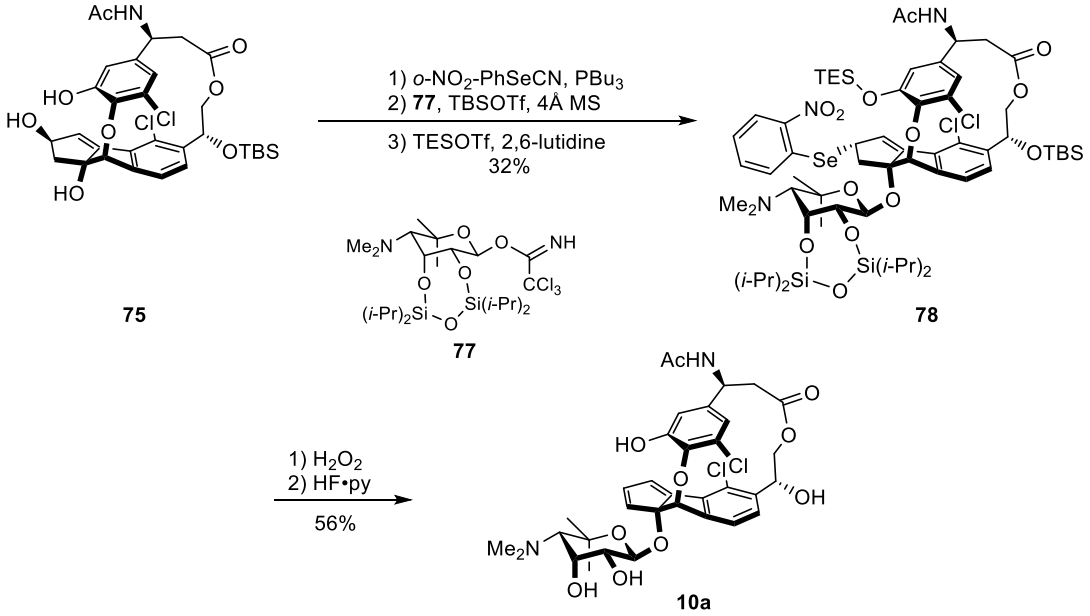
Scheme 16: Synthesis of diol **69** via PAUSON-KHAND reaction.

Esterification of **69** with *β*-amino acid **59** (chapter 1.5.2.2), followed by LUCHE reduction yielded ester **71** in 68%. Deprotection using CsF induced the desired cyclophane formation (scheme 17). The authors explained the observed atropselectivity of **75**:**74** ≥5:1 with a Cs-chelate **73** (**path b**) which assisted the nucleophilic attack of the *para*-hydroxy group at C8 to form **75** (green arrow). With formation of atropisomer **74** no coordination to the cyclopentenol would occur (intermediate **72**, **path a**). As a side product, formation of *meta*-cyclophane **76** was observed (red arrow). Studies using partially protected derivatives at any alcohol in **71** always led to lower regio- and atropselectivities in the cyclophane formation event, supporting the hypothesis of chelate **73**. Overall *para*-cyclophane **75** was isolated in 60% yield starting from **71**.



Scheme 17: Cs-chelate assisted *para*-cyclophane formation to yield **75**.

After successful construction of the cyclophane moiety, substitution of the allylic alcohol by a selenide, glycosylation at C9 with SCHMIDT donor **77** (chapter 1.5.1.2) and silylation of the phenol gave allyl selenide **78**. Final GRIECO elimination and global deprotection gave fijiolide A in 18% yield over five steps from **75** (scheme 18). A variety of other protocols investigated for dehydration of **75** to introduce the cyclopentadiene mostly resulted in decomposition of the starting material or no conversion at all.[14e]



Scheme 18: End-game of the synthesis of fijiolide A (**10a**).

Although CRAMER`s retrosynthetic approach remains unmatched in terms of elegance and efficiency there still exists one drawback. Albeit extensively studied, the dihydroxylation of indene **69** at C8/C9 could not be performed in diastereoselective fashion, effectively resulting in a significant loss of starting material at this relatively late stage, giving a low yield of 29% for the desired *cis*-diol (8*S*,9*R*)-**69**.

2 Objective of this Project

With CRAMER`s synthesis leaving only small room for improvement the major contribution to seem useful is a synthetic strategy offering selective introduction of the *trans*-configured (8*S*,9*R*)-diol incorporated in the benzodihydropentalene substructure. Furthermore, a synthetic access towards natural occurring analogous structures bearing stereochemistry at ring C might be opened by another strategy. In order to develop a stereoselective synthetic route to the diol in the fijiolides, benzodihydropentalene **79** should be targeted as test system (figure 7).

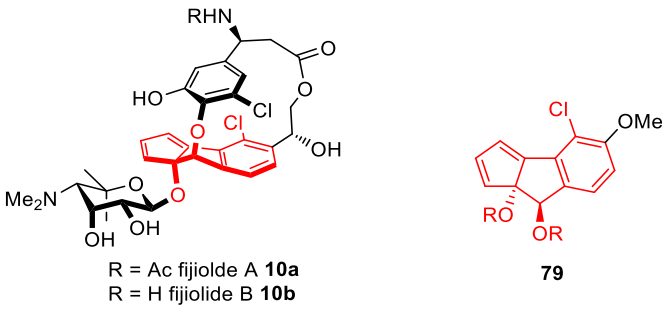
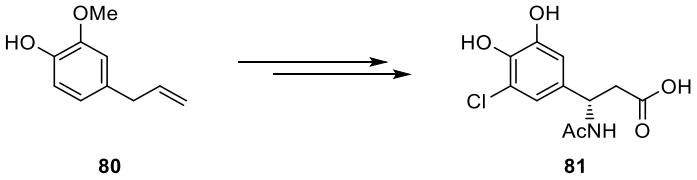


Figure 7: Benzodihydropentalene **79** as test system for diastereoselective introduction of the diol in fijiolides (substructure highlighted in red).

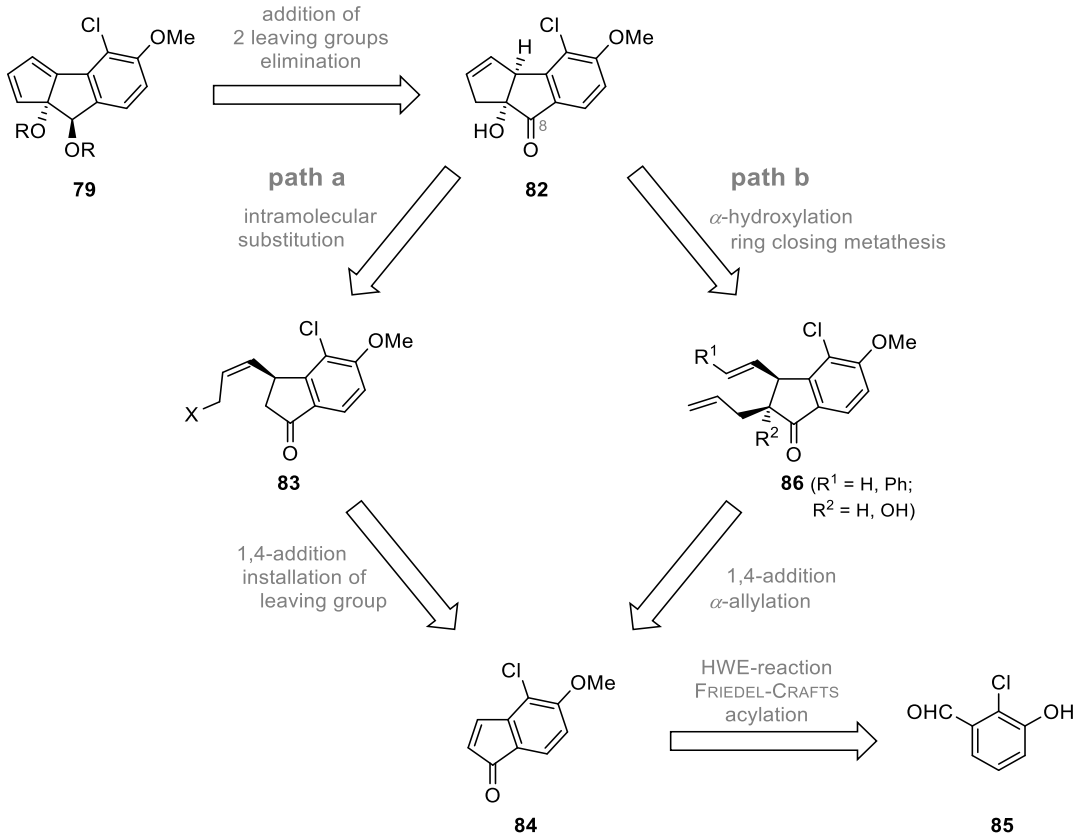
In addition, a synthetic access to the amino acid **81** should be developed, relying on cheap starting material. Therefore, a synthesis of **81** starting from eugenol (**80**) was to be encountered (scheme 19).



Scheme 19: Synthesis of amino acid **81** from eugenol (**80**).

3.1 Retrosynthetic Analysis – Benzodihydropentalene 79

The benzodihydropentalene core **79** should be accessible from cyclopentene **82** via substrate directed reduction at C8, addition of two leaving groups to the olefin and subsequent double elimination. Hydroxyketone **82** can be derived from indanone **83** by intramolecular enolate chemistry followed by α-hydroxylation. Indanone **83** should be accessible from indenone **84** via enantioselective 1,4-addition with subsequent installation of a leaving group. Indenone **84** can be obtained from aldehyde **85** via HWE-olefination and subsequent FRIEDEL-CRAFTS acylation (scheme 20, path a).



Scheme 20: Retrosynthetic analysis of benzodihydropentalene core **79**.

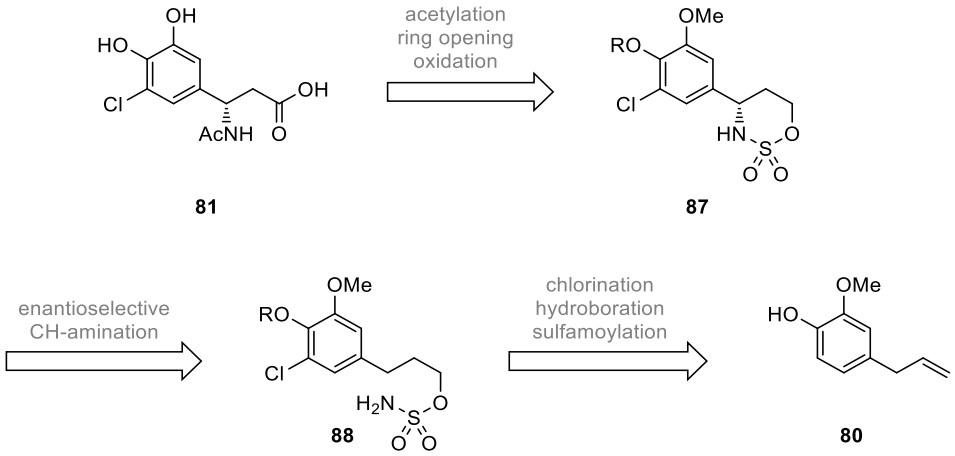
After attempts to close ring C via intramolecular enolate chemistry at the stage of ketone **83** proved to be not productive (chapter 4.3), the synthetic strategy was modified towards allylated 1,4-addition product **86** and to install the cyclopentene in **82** by ring closing metathesis (scheme 20, path b).

Overall, the retrosynthetic approach minimizes the use of protecting groups and furthermore relies only on enantioselective introduction of a stereogenic center in the asymmetric

conjugate addition (ACA) step. Given the manifold examples in literature demonstrating generality of this enantioselective conjugate additions (see chapter 4.2) it seemed to be a reasonable starting point, even if its application to indenones had to be developed. Although the stereocenter introduced in the 1,4-addition is not present in the final compound, it still allows substrate-controlled introduction of stereoinformation in all other relevant positions.

3.2 Retrosynthetic Analysis of Amino Acid 81

For the synthesis of amino acid **81** starting from eugenol (**80**), enantioselective introduction of the amine in benzylic position is the most challenging task. Based on the work of DU BOIS,[35] amino acid **81** might be obtained from oxathiazinane **87** by ring opening, followed by oxidation. Oxathiazinane **87** should be accessible from sulfamate **88** by enantioselective CH-amination. Sulfamate **88** itself origins from eugenol via chlorination, hydroboration with oxidative work-up and sulfamoylation of the resulting alcohol (scheme 21).



Scheme 21: Retrosynthetic analysis of amino acid **81**.

4.1 Synthesis of the Benzodihydropentalene core – Access to Indenone 89

In recent years a variety of indenone syntheses have been developed, due to their incorporation in a number of bioactive compounds such as neo-lignin[36] (**89**) or the COX-2 inhibitor **90** (figure 8).[37] Especially transition-metal catalyzed access from benzylic esters,[38] aldehydes,[39] and other derivatives[40] has been extensively studied. Unfortunately, the integration of halides in the starting material restricts the number of appropriate methods. Therefore, intramolecular FRIEDEL-CRAFTS acylation of cinnamic acid derivatives was chosen as strategy for the construction of indenone **84**.

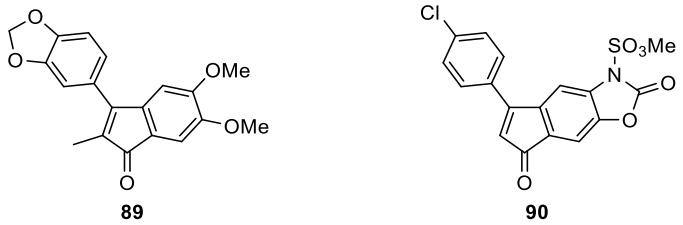
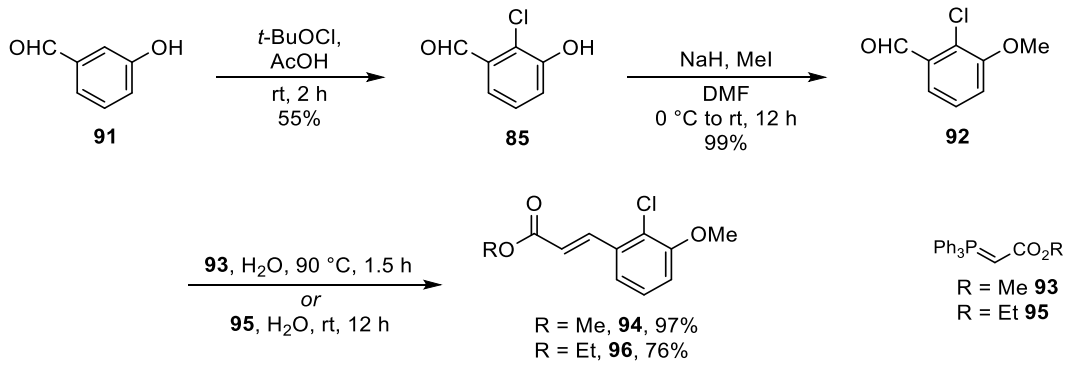


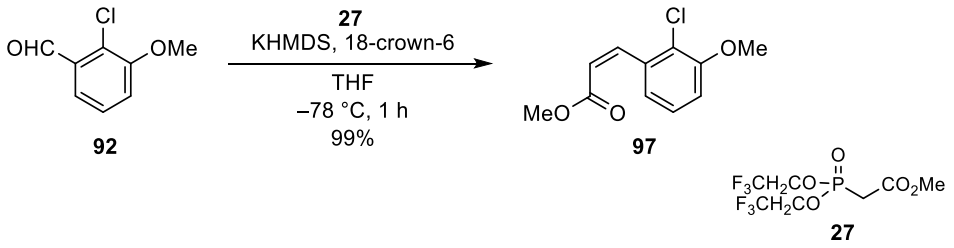
Figure 8: Examples of indenone-derived biological active compounds.

For the synthesis of the cinnamic acid precursors, literature known aldehyde **85** was selected as starting material. Although benzaldehyde **85** is commercially available, an access to decagram quantities was established following a procedure of GILES[41] by chlorinating *meta*-hydroxy benzaldehyde **91** with *tert*-butyl hypochlorite to yield **85** in 55% after recrystallization (scheme 22). That way, the costs for starting material could be reduced drastically (**91** 100 g 44.10 € vs. **85** 1 g 41.90 €)[42]. Aldehyde **85** was then methylated and used for WITTIG-reaction in water with stable ylide **93** to give (*E*)-configured cinnamic ester **94** in 97% yield. Using ylide **95**, the corresponding ethyl ester **96** was obtained in 76% yield.



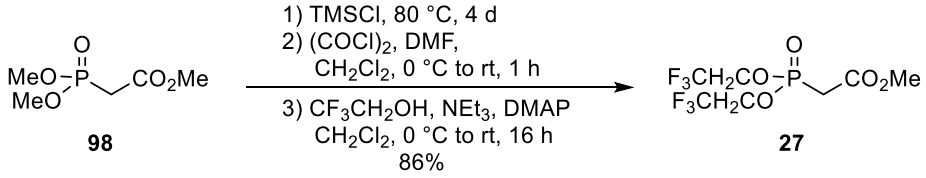
Scheme 22: Synthesis of cinnamic esters **94** and **96**.

After several failed attempts to isomerize (*E*)-configured cinnamic acid derivatives *in situ* to close ring B via FRIEDEL-CRAFTS acylation,[43] a (*Z*)-selective olefination was considered to be the most promising option. Therefore, STILL-GENNARI-olefination[44] using KHMDS and 18-crown-6 at low temperatures in THF was applied to afford (*Z*)-configured *α,β*-unsaturated ester **97** in 99% yield as the sole product (scheme 23).



Scheme 23: STILL-GENNARI-olefination of **92** to yield cinnamic acid ester **97**.

Since the use of reagents as costly as phosphono acetate **27** (5 g, 168 €, 15.7 mmol)[45] at such an early stage of the synthesis would limit its overall scalability, an expedient route towards **27** was established, following a procedure of OBERTHÜR.[46] Phosphonate **98** was *bis*-silylated with TMSCl and transformed into the dichloride using oxalyl chloride and catalytic amounts of DMF. Subsequent double esterification with trifluoroethanol and DMAP in CH_2Cl_2 yielded **27** in 86% overall yield. These operations could be performed on multigram-scale with only one final purification step necessary (scheme 24).

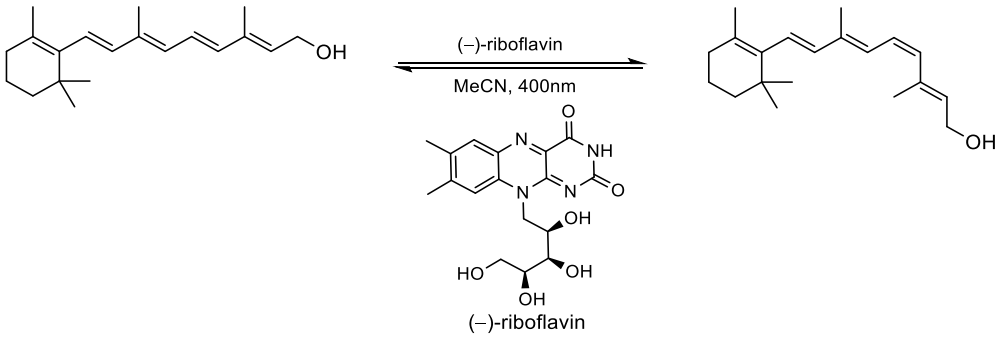


Scheme 24: Cost-efficient synthesis of phosphono acetate **27**.[46]

Even though the costs for generating gram quantities of (*Z*)-**97** could be significantly decreased by synthesis of phosphono acetate **27**, the 5.00 equiv. of 18-crown-6 required for this olefination still remained a limiting factor.[44] Use of 3.00 equiv. crown ether resulted in (*E*/*Z*)-mixtures of ~1:2 and for conversion of 3.10 g aldehyde **92** about 30.0 g of crown ether were needed (18-crown-6: 100 g, 325 €).[47]

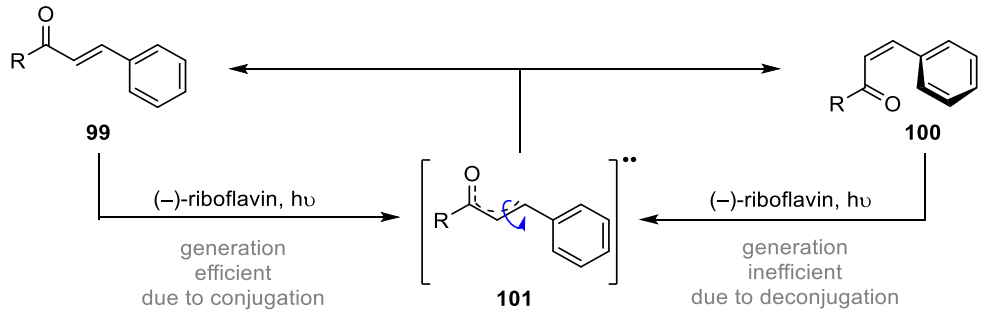
Therefore, another method to isomerize (*E*)-configured cinnamic ester **94** was investigated following a procedure developed by GILMOUR.[48] Detection of crystalline riboflavin in eyes of a broad range of vertebrates led to the finding that riboflavin may catalyze light-induced

isomerization of double bonds (as exemplified by WALKER and RADDA for 11-*cis*-retinol, scheme 25).[49]



Scheme 25: 11-*cis*-retinol isomerization catalyzed by (–)-riboflavin.[48]

GILMOUR *et al.* developed a protocol for isomerization of cinnamic esters (**99** → **100**) under catalysis of vitamin B2.[48] A biradical species **101** is formed by photo-excitation, which is efficiently generated from (*E*)-configured cinnamic esters but not from the (*Z*)-configuration due to a poor orbital overlap of the olefin with the π-system of the tilted aromatic ring. Consequently, this shifts the (*E*/*Z*) equilibrium, which leads to enriched formation of (*Z*)-configured esters **100** (scheme 26).

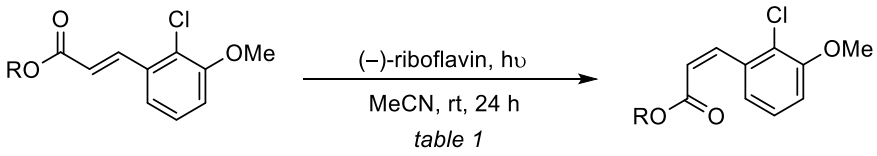


Scheme 26: Concept of light-induced *E* → *Z* isomerization under riboflavin catalysis.

However, unsubstituted cinnamic methyl ester only gave a (*Z*/*E*) ratio of 60:40 after being exposed to the reaction conditions (table 1, entry 1). Only cinnamic esters bearing a substituent in benzylic position gave satisfactory ratios of isomerization.[48b] Therefore, it was very surprising to find a ratio (*Z*/*E*) of up to 6.5:1 for **94** → **97** on a 0.1 mmol scale (entry 2 and 3), most likely due to the chloro substituent in *ortho* position also favoring a shift of the arene moiety out of plane (scheme 27).

On a 2.0 mmol scale the ratio (*Z*/*E*) dropped to 1.6:1 (entry 4), by increasing dilution a ratio of 8:1 could be restored on preparative useful scale of up to 11.0 mmol (entry 5 and 6). Use of

the corresponding acid **102** resulted in almost no conversion (entry 7). The ethyl ester **96** gave a ratio of 10:1 on a 1.3 mmol scale (entry 8).



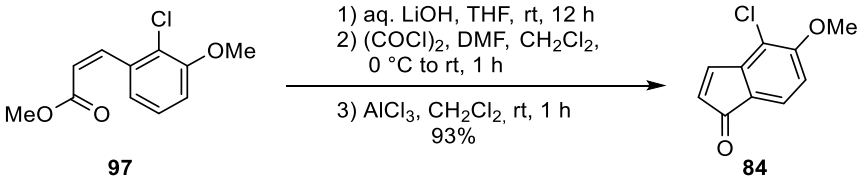
Scheme 27: Photo-induced (–)-riboflavin catalyzed isomerization.

Table 1: Light-induced $E \rightarrow Z$ isomerization of cinnamic acid derivatives.

entry	ester residue CO_2R	scale (mmol)	concentration (M)	comments	yield (%), (*Z*/*E*)-ratio
1[48b]	Me (**99**)	0.1	0.070	Unfunctionalized ester, 400 nm light	99, 1.5:1
2	Me (**94**)	0.1	0.070	435 nm light	87, 3.5:1
3	Me (**94**)	0.1	0.070	365 nm UV-light	93, 6.5:1
4	Me (**94**)	2.0	0.070	365 nm UV-light	91, 1.6:1
5	Me (**94**)	2.0	0.035	365 nm UV-light	96, 7:1
6	Me (**94**)	11.0	0.035	365 nm UV-light	98, 8:1
7	H (**102**)	0.1	0.070	365 nm UV-light	92, 1:10
8	Et (**96**)	1.3	0.044	365 nm UV-light	98, 10:1

Preliminary tests to further scale up the isomerization process via continuous flow implementation failed due to riboflavin`s poor solubility in MeCN. However, GILMOUR and coworkers recently reported a covalent immobilization strategy for (–)-riboflavin catalysts, which might allow an application of flow chemistry to further scale up of this isomerization process.[50] In addition, SEEBERGER and GILMORE could demonstrate the application of heterogeneous photocatalysis in continuous flow via serial micro-batch reactors.[51]

Having developed a reliable access to (*Z*)-configured cinnamic acid ester **97** the FRIEDEL-CRAFTS acylation was to be encountered. Saponification of **97** yielded the corresponding acid, which was converted without further purification into the acid chloride using oxalyl chloride/DMF. Following FRIEDEL-CRAFTS acylation with aluminum(III) chloride in CH_2Cl_2 gave rise to indenone **84** in 93% yield over three steps (scheme 28).

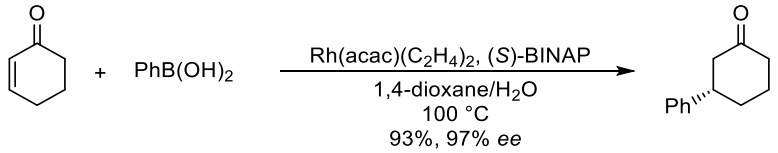


Scheme 28: Completion of ring B via FRIEDEL-CRAFTS acylation.

In order to install the missing C_3-fragment of ring C onto the indenone core of **84**, rhodium-catalyzed asymmetric conjugate addition (ACA) was hypothesized to allow introduction of ring fragment C in a highly enantioselective fashion. Furthermore, when performed with an indenone already bearing the diol side chain, a possible substrate`s influence on diastereoselectivity might be easier to overcontrol than by classical cuprate addition chemistry.[52] The theoretical background of rhodium-catalyzed ACA and application in natural product synthesis will be discussed in the following chapter.

4.2 Rhodium-Catalyzed Asymmetric Conjugate Additions

Asymmetric conjugate addition has emerged as one of the fundamental technics in organic synthesis to introduce stereochemistry onto MICHAEL acceptors. The groundbreaking work of ALEXAKIS,[53] FERINGA[54] and HAYASHI[55] in the 1990s paved the way for asymmetric copper- and rhodium-catalyzed conjugate additions (scheme 29). This powerful methodology has been applied in numerous total syntheses like HELMCHEN`s Baclofen synthesis,[56] COREY`s synthesis of platensimycin,[57] FÜRSTNER`s protecting group free synthesis of ecklonialactone B,[58] KOERT`s synthesis of phoslactomycin A[59] or INOUE`s hydroxyzinowol synthesis[60] (figure 9, bond formed during ACA depicted in red).



Scheme 29: HAYASHI`s first example of an Rh-catalyzed asymmetric conjugate addition.[55]

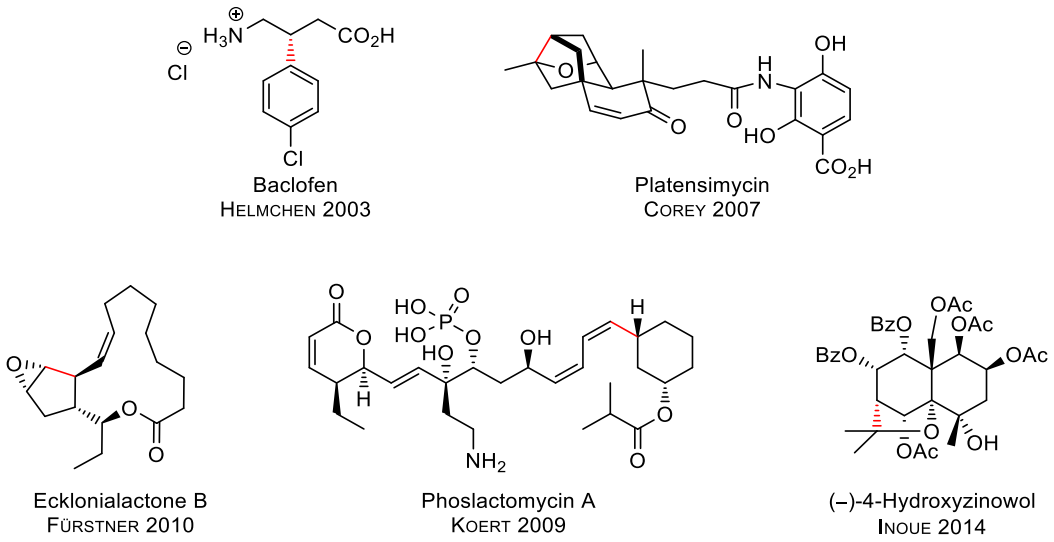
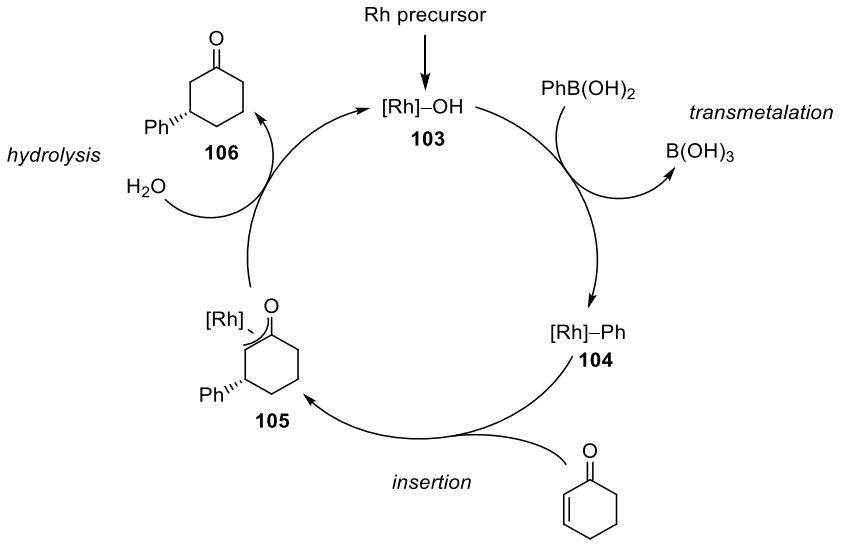


Figure 9: Selected natural products syntheses using this methodology.[56-60]

The generally accepted mechanism[61] of these asymmetric conjugate additions relies on transmetalation of the nucleophile onto the rhodium catalyst **103** to give **104**, which then coordinates the Michael acceptor. Insertion of the alkene into the Rh-C bond forms rhodium-oxa-π-allyl species **105** with the nucleophile enantioselectively connected to the former enone. Hydrolysis then liberates the product (**106**) and regenerates the catalyst (scheme 30 for the addition of $PhB(OH)_2$ to cyclohexenone).



Scheme 30: General mechanism of rhodium-catalyzed conjugate additions.

Since the first examples of conjugate additions emerged, a broad range of MICHAEL acceptors such as acyclic and cyclic enones,[62] α,β-unsaturated esters,[63] lactones,[58] nitroalkenes,[64] amides[65] and alkenyl sulfones[66] have been used for conjugate additions. Furthermore, the scope of nucleophiles has been significantly increased to all kinds of boronic acid derivatives,[67] silanes,[68] alkenyl zirconium reagents[69] and others.[70] In addition to aryl

nucleophiles also alkenyl,[71] some alkyl[72] and even alkynyl[73] nucleophiles were found to be transferred in conjugate additions.

As chiral ligands for rhodium-catalyzed asymmetric conjugate additions, there are three general types known in the literature: Phosphine derived compounds like BINAP **107** bearing axial chirality, chiral diene ligands like HAYASHI`s (*R*,*R*)-Ph-bod **108**[74] often derived from terpene feedstock, and sulfoxide-olefin hybrid ligands, as exemplified by a work of KNOCHEL and coworkers (**109**, figure 10a). Exemplified coordinative modes of the active catalysts are depicted in figure 10b for each ligand type.

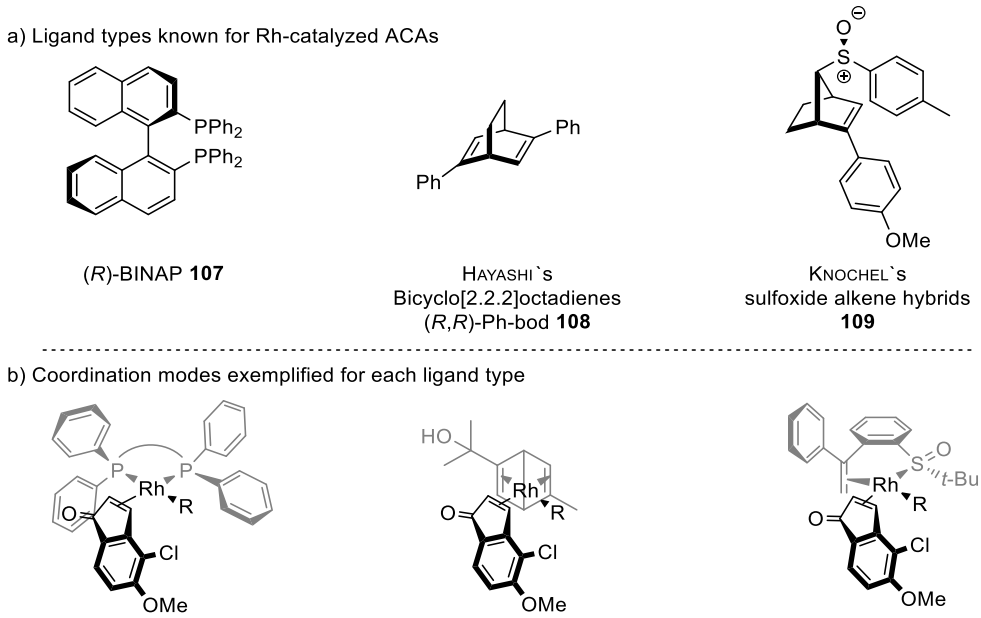
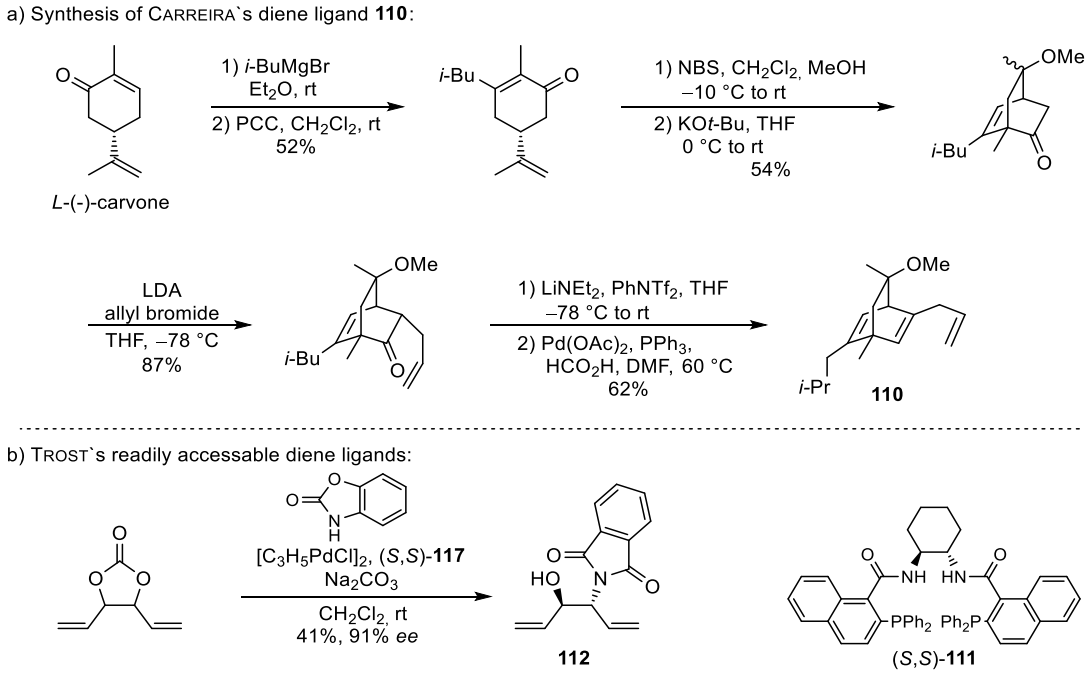


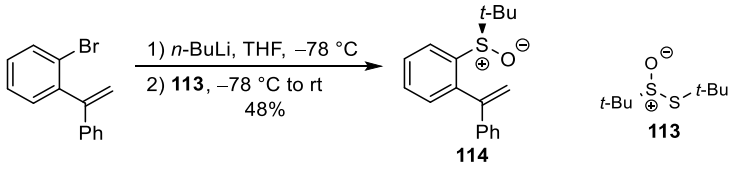
Figure 10: Ligand systems known for Rh-catalyzed asymmetric conjugate additions and their coordination modes in the enantioselectivity-inducing step (exemplified for indenone **84**).

While phosphine-based ligands are well established ligands for a broad range of transition metals and usually commercially available in both enantiomeric forms, they were among the first ligands to be tested in asymmetric conjugate additions and give satisfying results for simple substrates.[62] However, especially for more challenging substrates like cyclopentenones or for the addition of alkenyl nucleophiles, diene ligands often give superior results and operate at lower temperatures than phosphine based systems.[62] Since numerous diene ligands are derived from natural occurring terpenes like CARREIRA`s diene **110** from carvone[75] (scheme 31a), their main limitation is the availability of the respective terpene. Consequently, use of diene ligands is often limited to one enantiomer while the other one relies on step-intense synthesis. Exceptions like TROST`s divinyl ethylene carbonate derived dienes **112**[76] (scheme 31b) are obtained by catalytic asymmetric synthesis, chiral resolution[77] or separation of the enantiomers via chiral HPLC.[78]



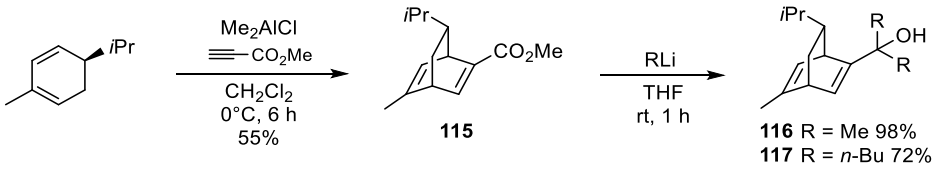
Scheme 31: Synthesis of selected diene ligands.

Examples of chiral sulfoxide olefin hybrid ligands are relatively rare in the literature compared to their diene and phosphine derived counterparts. Although both enantiomers can be easily obtained, as demonstrated by LIAO *et al.*, by addition of abundant chiral thiosulfinate **113** to lithiated aromatics to give **114**[79] (scheme 32), their application in organic synthesis to this date remains limited. Nevertheless, they offer relatively high coordination ability to transition metals and allow conjugate additions even at room temperature.[80]



Scheme 32: LIAO`s synthesis of sulfoxide alkene hybrid ligand **114**.[79]

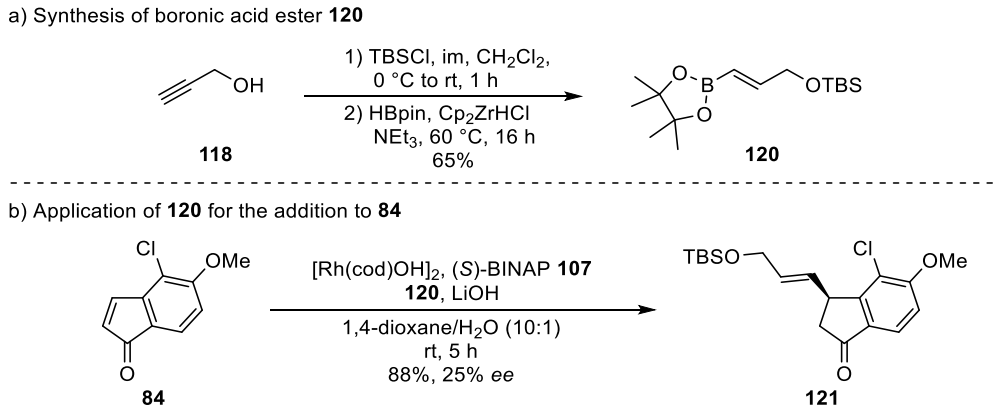
In this work, BINAP derivatives and HAYASHI`s phellandrene-derived dienes were mainly used as ligands for asymmetric conjugate addition to indenone **84**, due to their fast preparation[81] and proven application at room temperature. The synthesis of the latter was accomplished by DIELS-ALDER cycloaddition of (*R*)-(–)-*α*-phellandrene with methyl propiolate to give **115**. Addition of MeLi to the ester yielded **116** in 98%. Diene **117** was synthesized using *n*-BuLi (scheme 33). Experiments to further increase the steric bulk by addition of phenyl lithium or *t*-BuLi failed to give any product.



Scheme 33: Synthesis of HAYASHI`s phellandrene derived ligands **115** - **117**.[81]

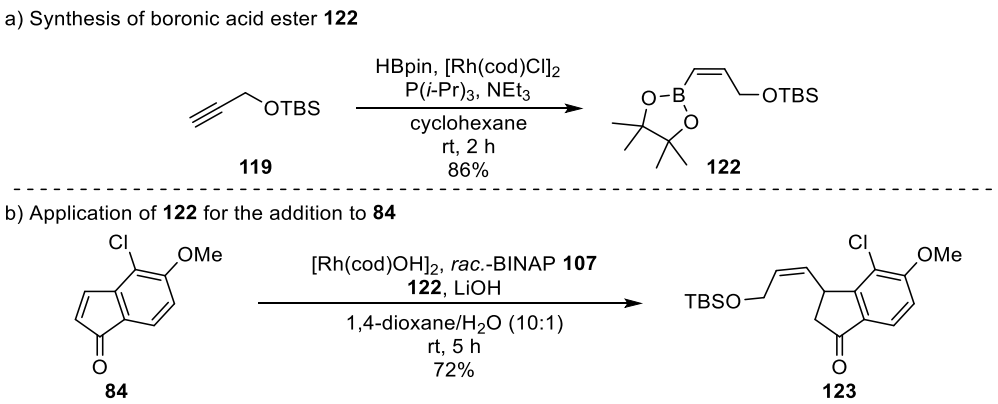
4.3 Installation of Ring C via intramolecular Enolate Chemistry

As model structure, boronic acid pinacol ester **120** was chosen to test feasibility of this strategy. After initial standard hydroboration procedures[82] failed to deliver **120**, WANG`s protocol gave (*E*)-**120** in 65% yield using 10 mol% of SCHWARTZ-reagent via hydrozirconation/transmetalation starting from propargylic alcohol (**118**) (scheme 34a).[83] Subjected to reaction conditions of rhodium-catalyzed asymmetric conjugate additions with indenone **84** as substrate using (*S*)-BINAP, vinylated indanone **121** was isolated in 88% yield, however, with only 25% *ee*. Nevertheless, the applicability of indenone **84** for Rh-catalyzed conjugate additions could be demonstrated (scheme 34b).



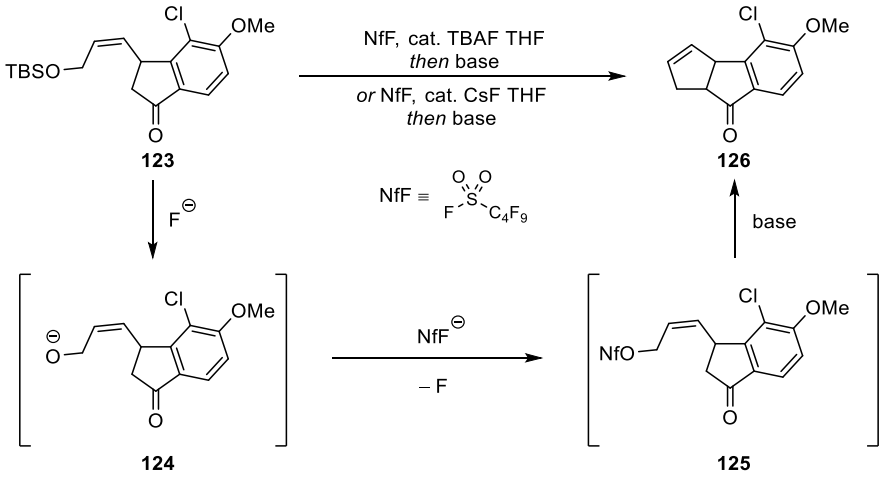
Scheme 34: Hydroboration of TBS-protected propargylic alcohol **119** and subsequent rhodium-catalyzed 1,4-addition of **120** to indenone **84**.

Since for strategic reasons a (*Z*)-configured double bond would be more suitable because it would facilitate following operations to close ring C, (*Z*)-configured pinacol ester **122** was synthesized via rhodium-catalyzed hydroboration using a $[Rh(cod)Cl]_2$/P(*i*-Pr)$_3$-combination[84] in 86% starting from TBS-protected propargylic alcohol **118** (scheme 35a). The adjacent 1,4-addition with indenone **84** gave rise to indanone **123** in 72% yield with full retention of double bond configuration (scheme 35b).



Scheme 35: Synthesis of pinacol ester **122** from propargylic alcohol and its use in rhodium-catalyzed conjugate addition to indenone **84**.

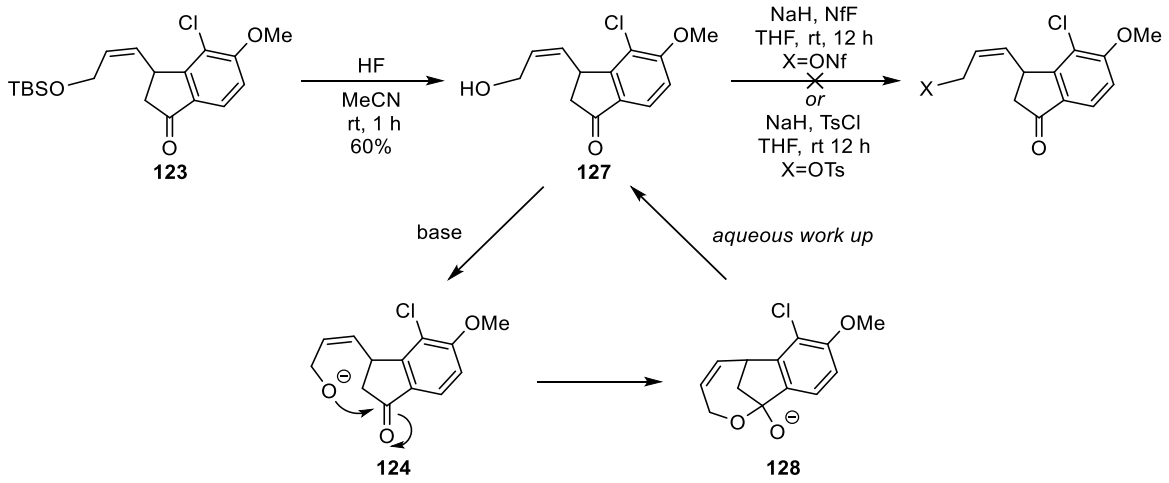
Initially, it was planned to perform a ring closure towards tricycle **126** in a one-pot desilylation-nonaflation-substitution procedure (scheme 36). Examples from literature[85] have already demonstrated the direct conversion of silyl enol ethers into nonaflates using nonafluorobutane sulfonyl fluoride (NfF). Even one-pot combinations with subsequent cross coupling reactions for a variety of substrates have been reported.[86] Herein, application of these protocols for silylated alcohol **123** was tested. It was hypothesized, that catalytic amounts of fluoride could partially deprotect the alcohol, forming alcoholate **124** with weakly coordinating tetra-*n*-butyl ammonium (or cesium) counter ion. Alcoholate **124** could then get sulfonylated by NfF to form **125**, liberating stoichiometric amounts of fluoride to deprotect the remaining alcohol. Enolate formation on **125** by addition of base might then allow an intramolecular S_N2-type substitution to afford tricyclic compound **126** (scheme 36).



Scheme 36: Initial strategy to close the cyclopentene ring.

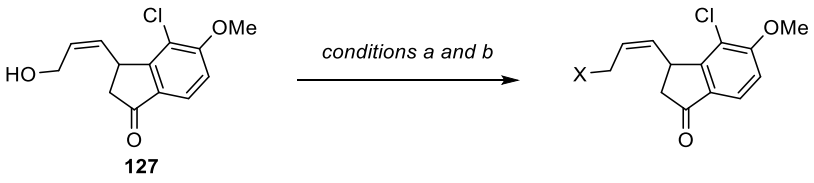
After several unsuccessful attempts to achieve desilylation of **123** with TBAF (1 M in THF or trihydrate) or CsF, deprotection using 48% HF in MeCN furnished alcohol **127** in 60% yield. Subsequent sulfonylation was neither possible using combination of NaH and NfF, nor NaH

and TsCl in THF, probably due to formation of hemi acetal **128** via intramolecular attack of alcoholate **124** towards the ketone. After aqueous work up, alcohol **127** was reisolated in all cases (scheme 37).



Scheme 37: Failed attempts to sulfonylate alcohol **127**.

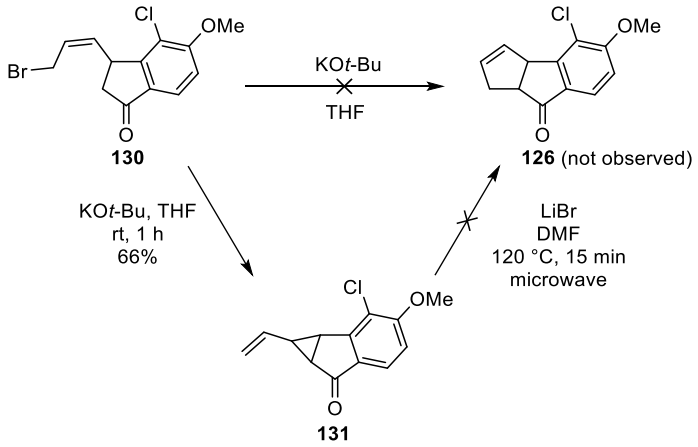
Installation of a leaving group in allylic position under non-basic conditions was achieved by BF_3**.**OEt_2-mediated iodination using KI in 1,4-dioxane, but the corresponding allyl iodide **129** decomposed upon removal of solvent. An APPEL-reaction with NBS and PPh_3 in CH_2Cl_2 furnished allyl bromide **130** in 96% yield (scheme 38).



conditions a: X=I **129***;* BF_3•OEt_2, KI 1,4-dioxane, 1 h, *product decomposed*
conditions b: X=Br **130**; NBS, PPh_3 CH_2Cl_2, 12 h, 96%

Scheme 38: Installation of the allyl halide.

Intramolecular substitution of bromine in **130** proceeded quite smoothly. However, only vinyl cyclopropane **131** was isolated in 66% yield, following an S_N2`-type ring closure (scheme 39). IKEGAMI *et al.* described a similar observation for their synthesis of bicyclo[3.3.0]oct-6-en-2-one.[87] Their solution, a LiI-promoted ring-expansion, only resulted in demethylation on the phenol (scheme 39).

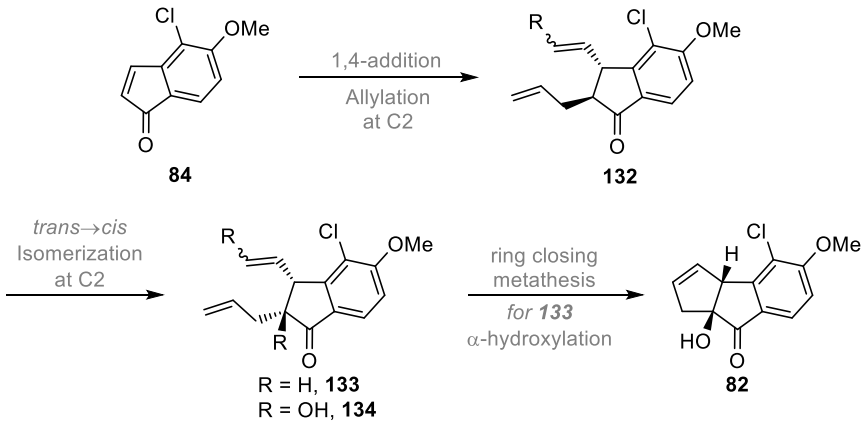


Scheme 39: Unexpected formation of vinyl cyclopropane **131**.

Even though other examples from literature offer alternative procedures to expand the cyclopropane ring, most of them rely on flash vacuum pyrolysis[88] or stoichiometric use of expensive transition metal catalysts,[89] both providing no appealing alternative for synthesis of tricycle **126** on preparatively useful scale. Therefore, no further experiments were conducted to rearrange vinyl cyclopropane **131**.

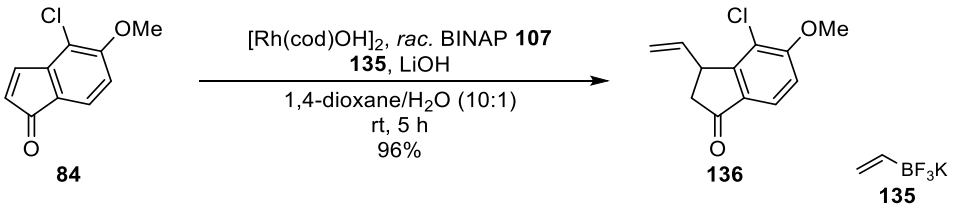
4.4 Installation of Ring C via Ring Closing Metathesis

After results from chapter 4.2 showed that competing S_N2`-type ring closure prevents cyclopentene formation, an alternative approach towards tricyclic compound **82** was developed (see chapter 3.1, retrosynthesis second generation). With access to vinylation of indenone **84** already established, *α*-allylation followed by isomerization at C2 to give a *cis*-arrangement of allyl and vinyl side chain in **133**/**134** should allow ring closing metathesis to form ring C (scheme 40).



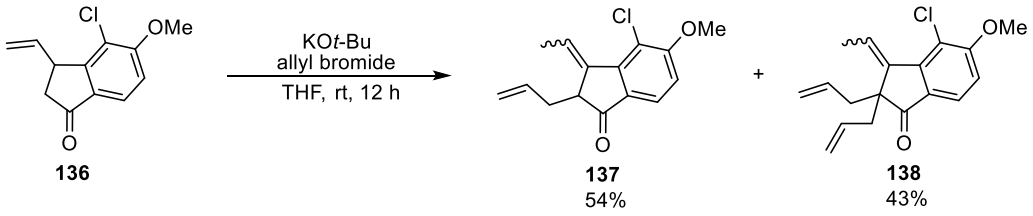
Scheme 40: Revised synthetic strategy for construction of cyclopentene **82**.

Previously established rhodium-catalyzed 1,4-addition conditions with trifluoroborate **135** gave vinylated indanone **136** in 96% yield (scheme 41). Unfortunately, the decreased reactivity of **135** led in some cases to formation of significant amounts of reduced indanone, which could not be separated from **136**. Alternative boronic acid-derived vinylation agents such as the anhydride or the pinacol ester are usually quite expensive and furthermore often suffer from low stability. Therefore, trifluoroborate **135** remained the nucleophile of choice.



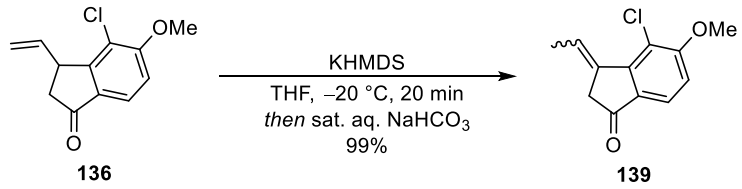
Scheme 41: Conjugate addition of **84** with trifluoroborate **135** and alternative vinylation agents.

When **136** was exposed to KO*t*-Bu and allyl bromide at rt in THF, a mixture of allylated (**137**) and doubly allylated (**138**) products was obtained, both with the double bond isomerized into benzylic position (scheme 42).



Scheme 42: α-Allylation of indanone **136**.

In order to investigate the double bond`s tendency to isomerize under basic conditions, indanone **136** was dissolved in THF, deprotonated using KHMDS and quenched after 20 min at –20 °C. Complete isomerization towards indanone **139** with an internal double bond was observed (scheme 43).



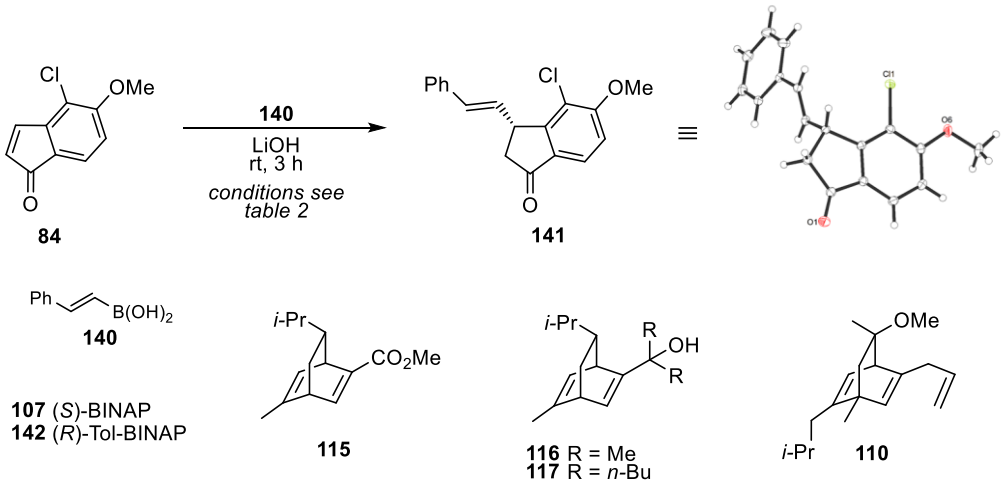
Scheme 43: Stability test of vinylated indanone **136**.

Since the lability of **136**`s double bond under basic conditions caused problems in allylation and probably in *trans*→*cis* isomerization at C2, the necessity for a more rigid double bond

was obvious. Therefore 1,4-addition of indenone **84** was performed using styrene boronic acid **140** (scheme 44).

The styrene moiety in addition product **141** might offer three main advantages compared to the simple vinyl unit in **136**. The increased reactivity of the boronic acid might suppress competing side reactions in the addition process. Moreover, addition of an internal olefin residue onto indenone **84** might reduce risk of isomerization. Furthermore, addition product **141**`s increased steric demand of the styryl chain in *β*-position should have a positive impact on substrate-controlled isomerization of the allyl moiety in *α*-position (scheme 49).

For addition of styrene boronic acid **140** to indenone **84** a screening of ligands and conditions revealed diene ligands to be more performant ligands than phosphine-based ligands (table 2, entry 1-3 vs. entry 4-8). No influence of the organic solvent was found (1,4-dioxane vs toluene, entry 1 and 2). HAYASHI`s phellandrene derived diene ligands (synthesis see chapter 4.2) were found to form competent catalysts with Rh-precursor B. However, using ligand **115**, only low conversions and enantiomeric induction were obtained (entry 4). Ligand **116** gave **141** in excellent yield with 59% *ee* at rt (entry 5), by decreasing temperature to 0 °C an *ee* of 74% was obtained, again with 99% yield (entry 6). Lowering temperature to –20 °C gave no conversion to **141**, probably due to solidified solvent mixture. Increasing steric bulk at the diene ligand from **116** to **117** resulted in decrease of yield and *ee* (entry 7). The best *ee* was obtained using CARREIRA`s diene **110**[90] with 85% yield and 95% *ee* (entry 8). In order to further increase the *ee* of indanone **141** it was recrystallized from *n*-pentane/CH_2Cl_2 to give >99% *ee*, whose structure and absolute configuration were verified by X-ray crystal structure (for representative HPLC-chromatograms see chapter 8.2.3, page 108).



Scheme 44: Asymmetric conjugate addition to indenone **84** with ligands **107**-**117** tested.

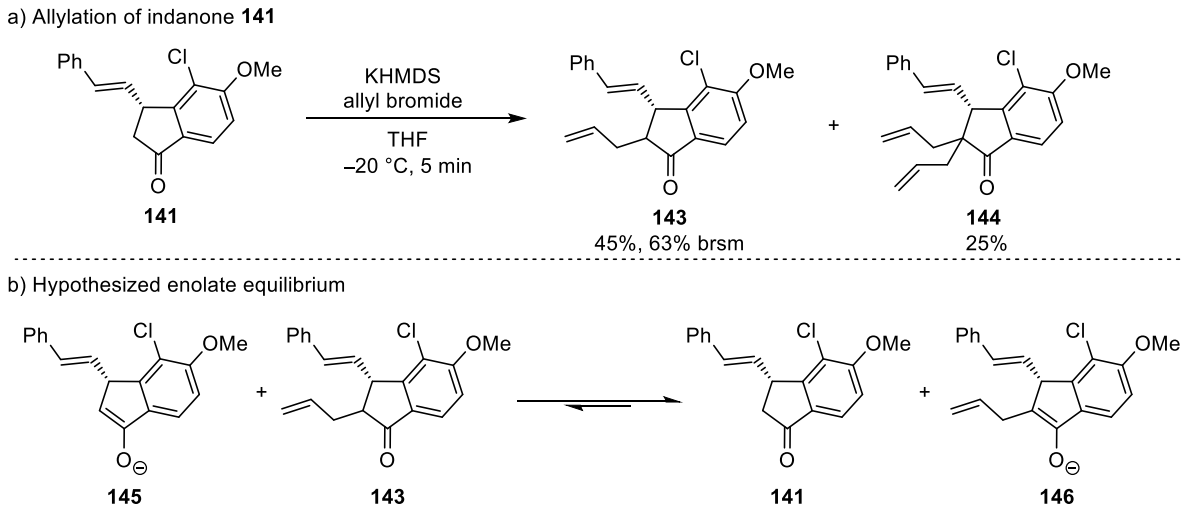
Table 2: Optimization of reaction conditions for the asymmetric conjugate addition to **84**.

entry	precursor cat.	ligand	solvent (xx/H_2O 10:1)	yield (%)[a]	*ee* (%)
1	A	**107**	1,4-dioxane	65	41
2	A	**107**	toluene	66	41
3	A	**142**	toluene	56	38[b]
4	B	**115**	toluene	62	44
5	B	**116**	toluene	99	59
6	B	**116**	toluene	99	74[c]
7	B	**117**	toluene	45	22
8	B	**110**	toluene	85	95

[a]isolated yields; catalyst precursor A: $[Rh(cod)OH]_2$ (5 mol%), catalyst precursor B: $[Rh(C_2H_4)_2Cl]_2$ (2 mol%); [b](*S*)-enantiomer was obtained; reactions were performed at 25 °C except [c]reaction was performed at 0 °C.

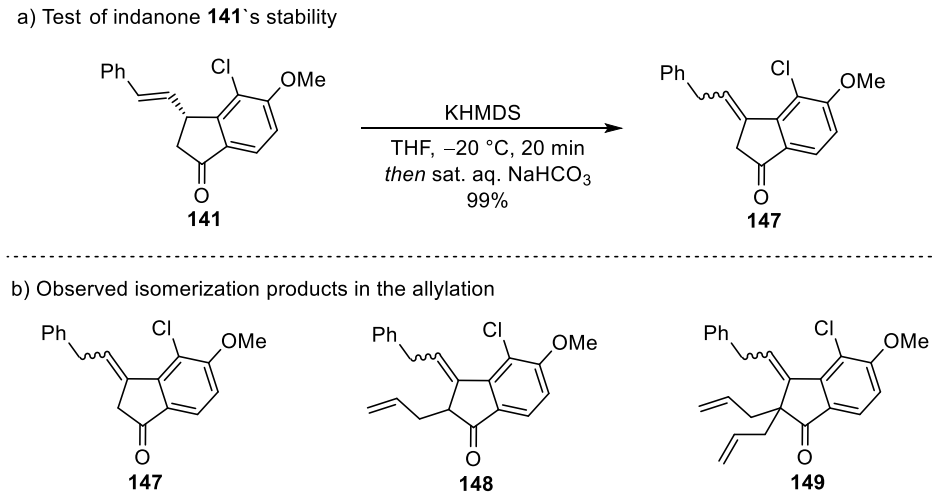
Due to better commercial availability of (*R*,*R*,*R*)-**116** (scheme 33, chapter 4.2), indanone (*R*)-**141** was synthesized and used for establishing synthetic access to dihydro pentalene **79**. For natural occurring fijiolides the respective (*S*)-enantiomer (*S*)-**141** would be required, which is accessible using enantiomeric ligand (*S*,*S*,*S*)-**116** (5 steps from (*R*)-(–)-carvone).[91] To the best of our knowledge these examples display the first reliable application[92] for asymmetric conjugate addition to an indenone.

Allylation of **141** gave again mixtures of mono- and double-allylated indanones **143** and **144** (scheme 45a). Variation of leaving group (X = Br, I), base (KHMDS, LDA) or temperature (ranging from –20 °C to –78 °C) had no influence on the ratio **143**/**144**. Slow addition of electrophile to the enolate only resulted in increased formation of doubly allylated product **144**. Since the ratio of **143**/**144** seemed to be almost unaffected by most parameters variated, the problem might be formation of an equilibrium between enolate **145** and **143** leading to **141** and **146** which causes significant double allylation due to lower pKa value of the product than the starting material (scheme 45b).



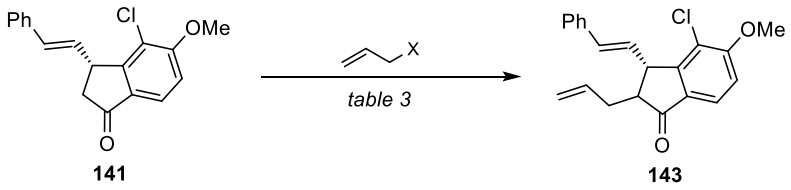
Scheme 45: Allylation of indanone and equilibrium between the enolates of product and starting material.

Furthermore, the stability of enolate **145** could not be increased; also for **141** complete isomerization of the double bond was observed at –20 °C after 20 min. In the allylation reaction, formation of isomerized products **147** - **149** was observed with the same product ratio **148**:**149**:**147** as without isomerization. In order to prevent isomerization, the allylation reaction had to be quenched 5 min after addition of base (scheme 46).



Scheme 46: Stability test of indanone **141** and isomerization products **147** – **149** in the allylation.

With the aim of increasing the yield of mono-allylated indanone **143** a series of conditions for TSUJI-TROST-type allylations (scheme 47, table 3, entries 1-5), or enamine additions (entry 6 and 7) were tested, all leading to double allylation, isomerization or no conversion.



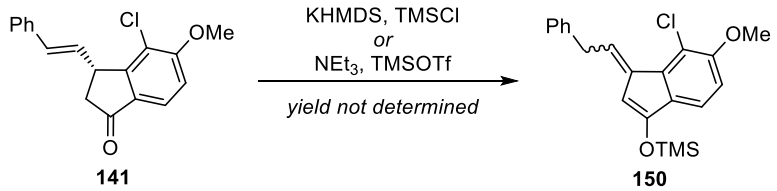
Scheme 47: Attempted TSUJI-TROST-type allylations using indanone **141**.

Table 3: Alternative allylation procedures tested for the sequence **141** → **143**.

entry	Pd-catalyst	base	X (allyl compound)	additive	temperature	solvent
1[b]	$Pd(dppf)Cl_2$	Pyrrolidine	OEt	-	rt	MeOH
2[b]	$Pd(dppf)Cl_2$	Pyrrolidine	OAc	-	rt	DMSO
3[b]	$Pd(dppf)Cl_2$	*rac.* Proline	Br	-	rt	DMSO
4[a]	Pd_2dba_3 + dppf	KHMDS	OCO_2Me	LiCl	0 °C	THF
5[a]	Pd_2dba_3 + dppf	KHMDS	OCO_2Me	-	–78 °C	THF
6[b]	-	Pyrrolidine	Br	-	rt	DMSO
7[b]	-	*rac.* Proline	Br	-	rt	DMSO

[a]isomerization observed; [b]no conversion.

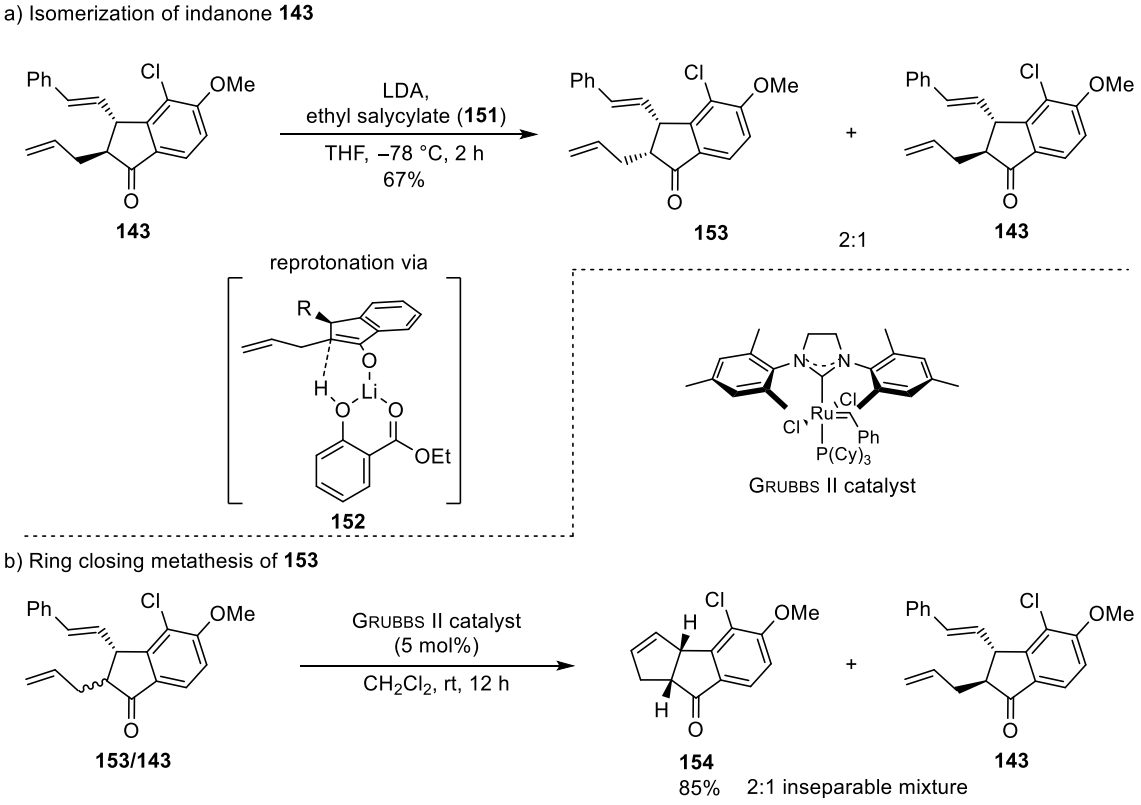
When indanone **141** was converted into the silyl enol ether only isomerized product **150** was observed (scheme 48). For mono-allylation of **141** without double-bond isomerization 63% brsm of **143** were the best results obtained (scheme 45a), which is in accordance with the literature for alkylation/allylation of indanones.[93]



Scheme 48: Synthesis of silyl enol ether **150** with isomerized double bond.

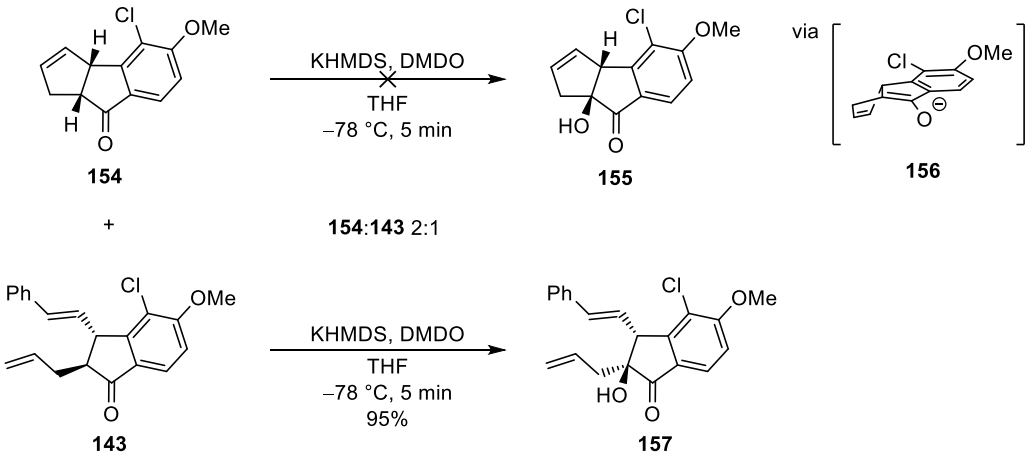
With mono-allylated indanone **143** in hand the isomerization was performed, following a procedure of KRAUSE,[94] using LiHMDS to generate the lithium enolate. The latter was subsequently reprotonated by ethyl salicylate (**151**) from the sterically less hindered side via chelate **152**. Overall, an *trans*→*cis* isomerization of the allyl group at C2 can be achieved that way, (scheme 49a). Although this isomerization process is known to give better results for

six- or seven-membered rings, also for five-membered rings remarkable *cis*/*trans*-ratios of 4:1 were reported. For **143** a *cis*/*trans*-ratio **143**:**153** of 2:1 was obtained, limited by the fast enolate addition necessary to prevent double-bond isomerization (scheme 46a). The subsequent ring closing metathesis (rcm) of the *cis*/*trans* mixture using GRUBBS II in CH_2Cl_2 yielded tricycle **154** in 70% together with unreacted *trans*-**143** as an inseparable mixture (scheme 49b).



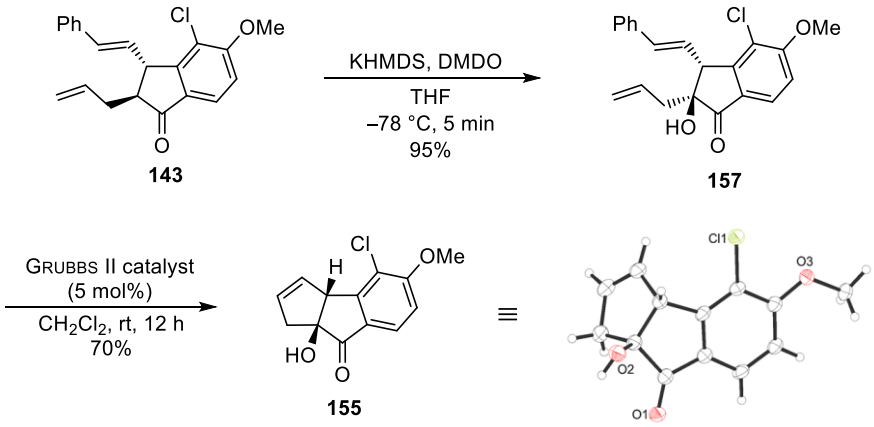
Scheme 49: *trans*→*cis* Isomerization of **143**`s allyl residue and subsequent rcm.

Subjecting this mixture to conditions for *α*-hydroxylation using modified conditions from ADAM[95] did not result in hydroxylated tricyclic compound **155**, probably due to poor formation of enolate **156**. Generation of **156** would require planarization at C9 and therefore it seems to be unlikely for this highly strained system (scheme 50). Nevertheless, hydroxylated indanone **157** was isolated with full preservation of the double bonds and without epoxidation or other side reactions observed.



Scheme 50: *α*-Hydroxylation of mixture **154**:**143**.

The obtained *cis*/*trans* ratio by isomerization was far from satisfactory and allowed no clean isolation of tricycle **154**, so installation of the *cis*-arrangement of allyl and styryl residue was combined with oxygenation at C2. Therefore, allylated **143** was deprotonated using KHMDS in THF at –78 °C and DMDO was added as *O*-electrophile to give *trans*-**157** exclusively, which was then subjected to ring closing metathesis conditions to yield tricycle **155** in 67% yield over two steps. The successful construction of **155** was verified by X-ray crystallography (scheme 51).



Scheme 51: Synthesis of *α*-hydroxyketone **155**:

The low stability of DMDO upon storage required the use of freshly prepared reagent and the large amount of acetone hindered the extraction process. $(TMSO)_2$ was synthesized following a procedure of BABIN[96] and tested as *O*-electrophile,[97] however, no improvement in comparison to DMDO was found. Other *O*-electrophiles such as VEDEJ`s reagent[98] or DAVIS` oxaziridines[99] (figure 11) were considered but their overall lower atom economy, price (DAVIS reagent) or toxicity (VEDEJ`s reagent) made them unattractive alternatives.

In situ formed TFDO[100] or O_2[101] were believed not to react fast enough with the enolate of **149** to prevent double bond isomerization or other unproductive side reactions.

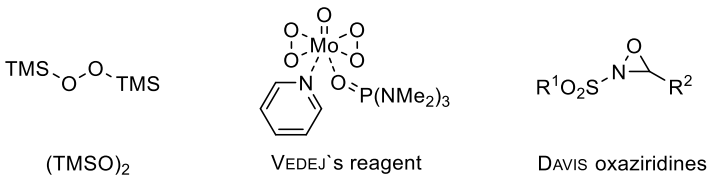
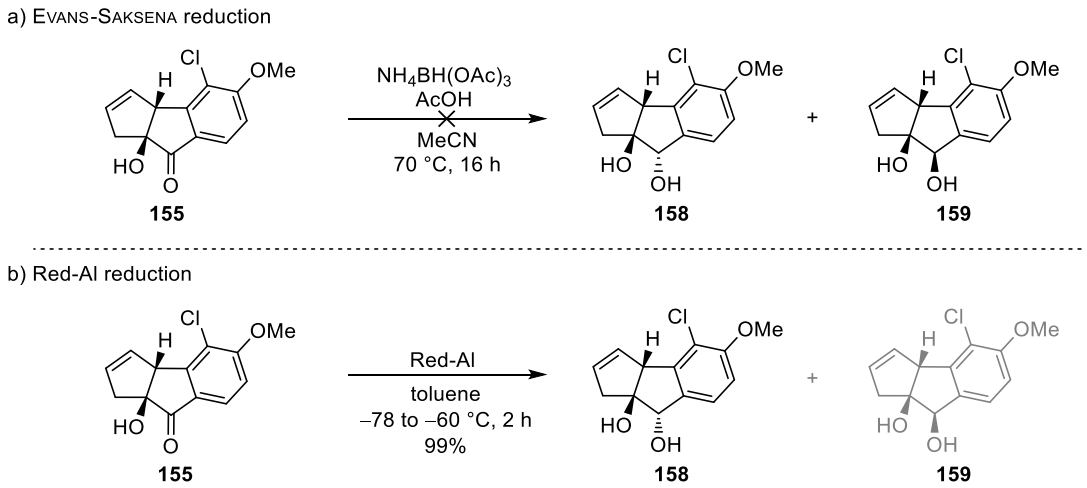


Figure 11: Alternative *O*-electrophiles considered for *α*-hydroxylation of **143**.

Due to the high lability of the styrilic double bonds in **141** and **143** (scheme 46a), the reaction sequence of allylation, oxygenation and metathesis was streamlined with only aqueous work up in between to give tricycle **155** from **141** in 25% yield over three steps on 1.55 mmol scale (scheme 51).

4.5 Installation of the Cyclopentadiene in Ring C

After successful assembly of the carbon core structure in **79**, adjustment of the oxidation states had to be carried out, starting with diastereoselective reduction at C8. Initially, a directed EVANS-SAKSENA reduction[102] was planned to establish *trans*-diol **158** (scheme 52a). However, subjected to typical reaction conditions no reduction of the ketone was observed even at 70 °C for 16 h. Instead, reduction using Red-Al[103] in toluene at –60 °C yielded almost exclusively *trans*-diol **158** (scheme 52b). At higher temperatures or with faster addition of Red-Al, a *cis*/*trans* mixture of up to 1:2 was observed. Although not productive for further synthesis, *cis*-**159** helped to verify the *trans*-relationship in its diastereomer *trans*-**158** by observing a correlation of the benzylic proton at C8 and the allyl proton at C10 in an NOESY experiment (figure 12).



Scheme 52: Directed reduction of **155**`s ketone at C8.

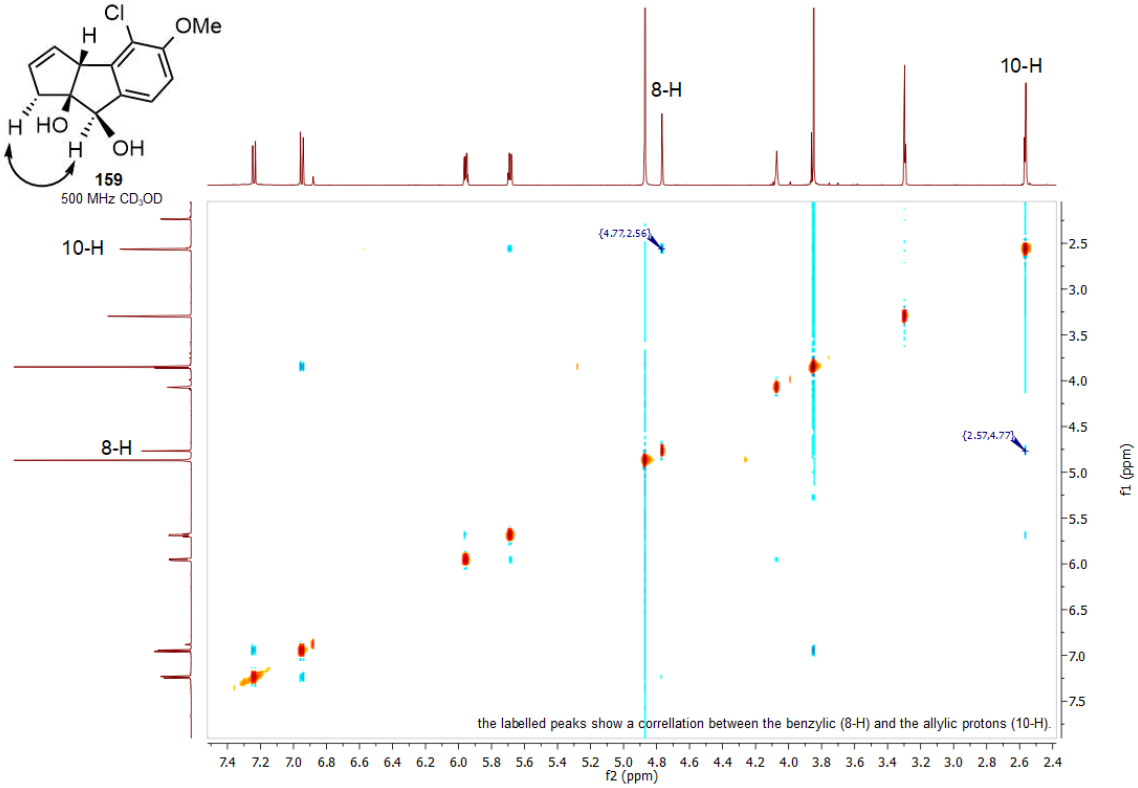
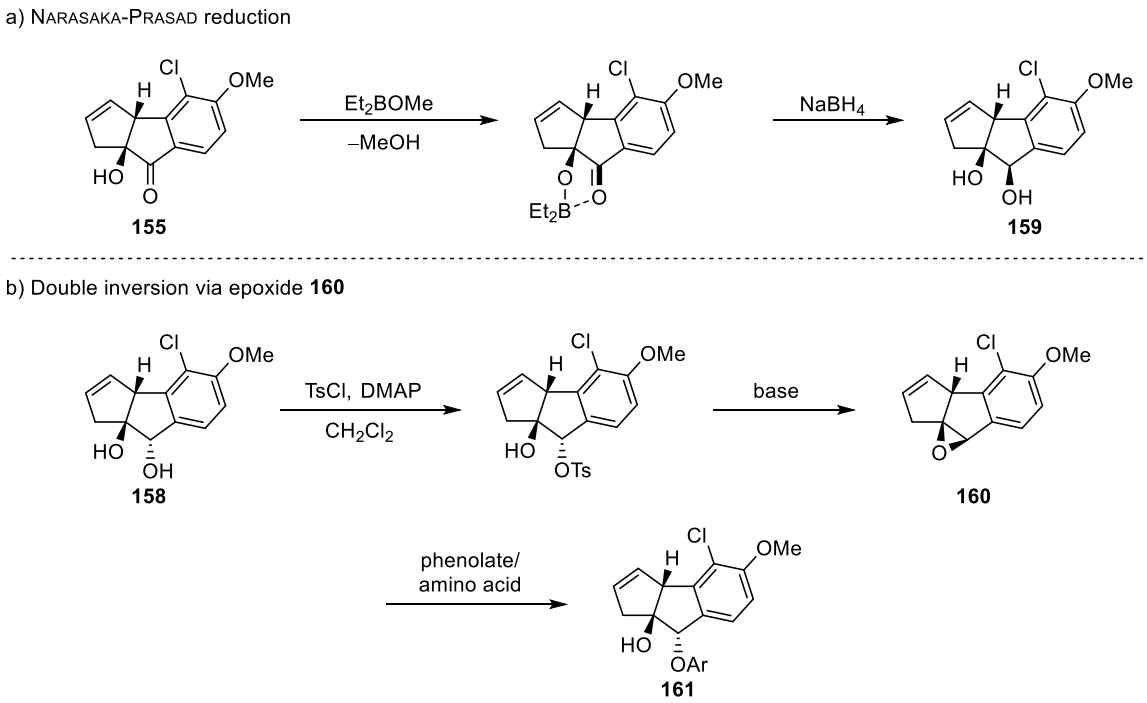


Figure 12: NOESY of *cis*-**159** showing a correlation of 8-H and 10-H.

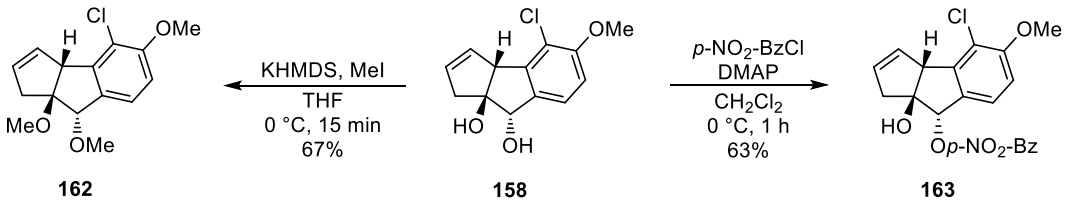
After several attempts to reproduce exclusive formation of *trans*-**158** and a series of varying temperature, time of addition and concentration it was found fundamental to solidify Red-Al at –78 °C first. Slow addition of ketone **155** as 0.03M solution at temperatures below –60 °C until complete consumption of **155** restored the *trans*/*cis* ratio of >15:1 on 1.0 mmol scale.

For synthesis of the natural product **10a** a *cis*-selective reduction would be more suitable since it allows a cyclophane-formation by substitution of an alcohol derived leaving group at C8 analogous to CRAMER`s strategy (scheme 17, chapter 1.5.3). A *cis*-selective reduction of **155** might be achieved by coordination of alcohol and ketone with LEWIS acids to shield the alcohol`s face from an attacking hydride (NARASAKA-PRASAD-type reduction,[104] scheme 53a) Alternatively, *trans*-**158** could be selectively tosylated at C8, the addition of base might lead to epoxide **160**, which could then be opened by an appropriate phenolate to achieve an overall double inversion at C8 to yield **161** (scheme 53b).



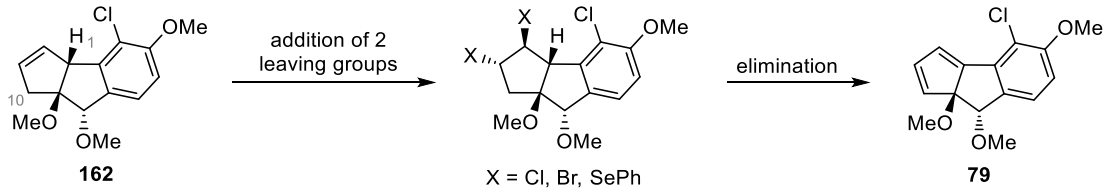
Scheme 53: NARASAKA-PRASAD reduction for ketone **155** and alternative strategy for installing a phenol ether at C8.

With the *trans*-relationship in diol **158** successfully installed, formation of the cyclopentadiene moiety was addressed next. Etherification of **158** to block both alcohols gave twice methylated olefin **162** in reasonable yield. In order to demonstrate a possible discrimination between both alcohols in **158**, the benzylic position (C8) was selectively esterificated to yield **163** using *para*-nitro benzoyl chloride which unfortunately did not crystallize to verify its structure by X-ray crystallography (scheme 54).



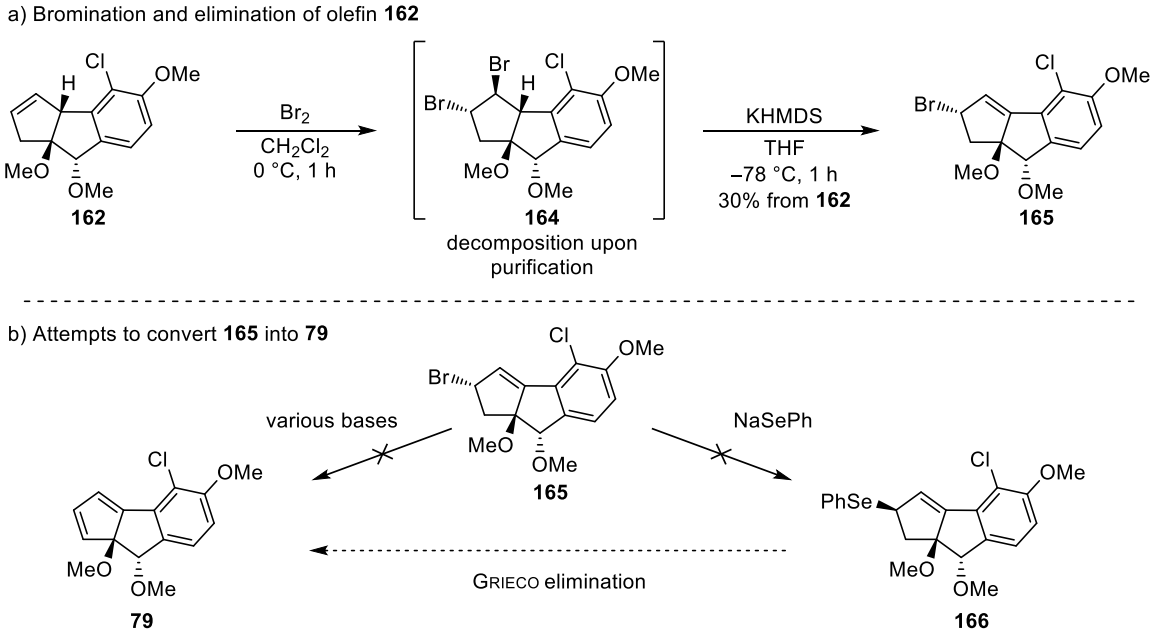
Scheme 54: Methylation and regioselective esterification of diol **158**.

With both alcohols protected, conversion of olefin **162** into dihydropentalene **79** was investigated. The general strategy for this formal oxidation at C1 and C10 relied on adding two leaving groups onto olefin **162** to allow double elimination towards cyclopentadiene **79** (scheme 55). As potential leaving groups, halides and selenides were identified to be the most promising options.



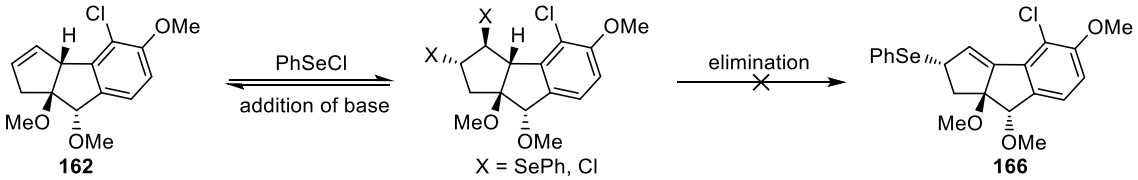
Scheme 55: General strategy for installing the cyclopentadiene moiety.

Bromination of **162** yielded unstable dibromide **164** which upon treatment with excess of KHMDS at low temperatures gave allyl bromide **165** in 30% yield (scheme 56a). A second HBr elimination towards **79** was unsuccessful as well as substitution of bromide in **165** by seleno phenolate towards **166** for a subsequent GRIECO elimination (scheme 56b).



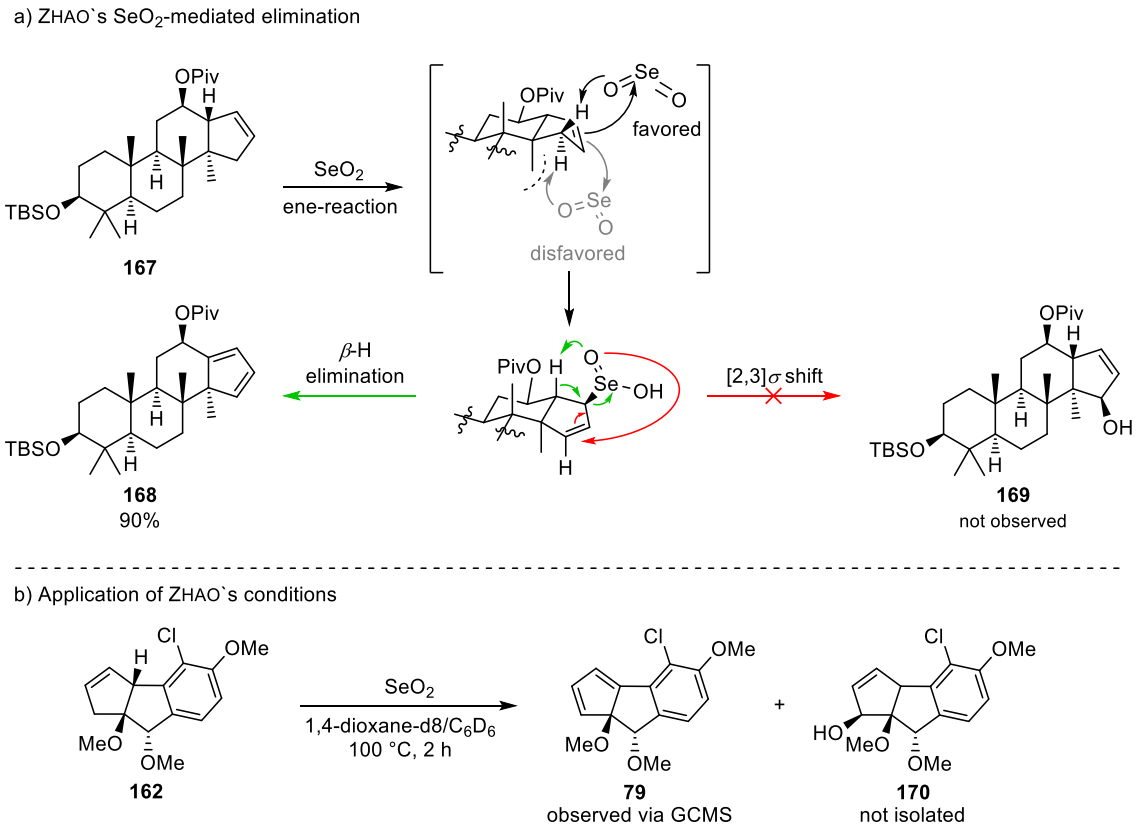
Scheme 56: Bromination of cyclopentene **162** and subsequent attempts to obtain **79**.

The addition of PhSeCl was found to be reversible (scheme 57), upon addition of base olefin **162** was reisolated. Addition of PhSeBr to **162** did not give any product at all, as well as a combination of $(PhSe)_2$/NCS following a procedure of SHARPLESS.[105]



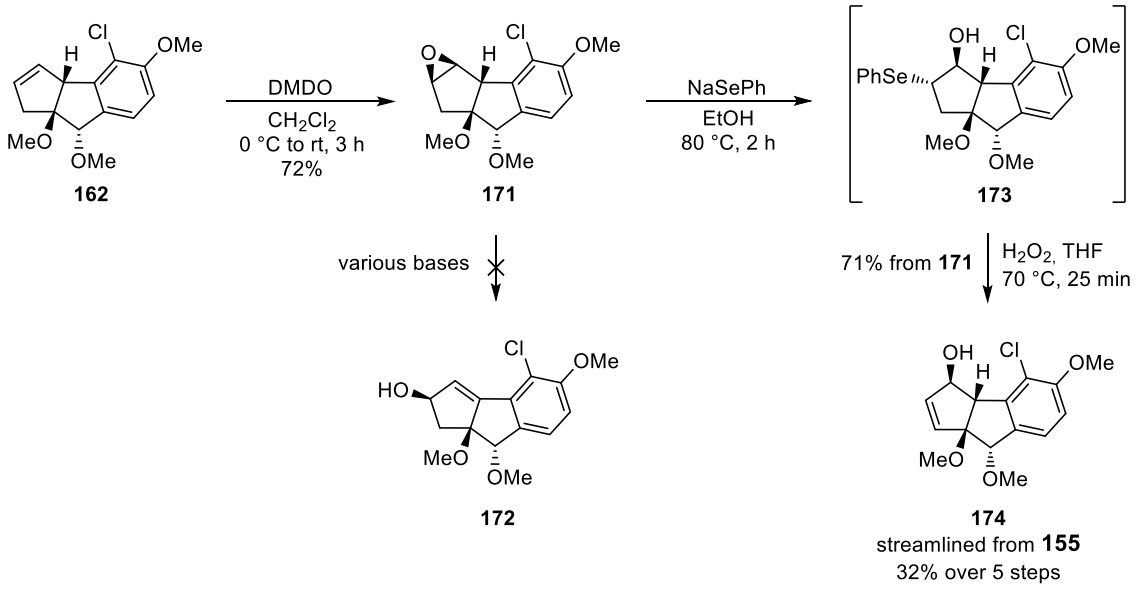
Scheme 57: Attempted addition of PhSeCl to olefin **162**.

For their synthesis of the hupehenols[106] ZHAO *et al.* found a SeO_2-mediated oxidation of highly substituted cyclopentene **167** to give cyclopentadiene **168** in 90% yield instead of the expected RILEY-oxidation product allyl alcohol **169** (scheme 58a). Their explanations for this finding was a competing β-H elimination (green path) instead of a [2,3]-sigmatropic shift (red path) taking place after the ene-reaction. When olefin **162** was subjected to ZHAO`s conditions the expected cyclopentadiene **79** was detected via GCMS, but neither **79** nor typical allylic oxidation product **170** were isolated (scheme 58b).



Scheme 58: Unexpected formation of cyclopentadiene **168** during attempted allylic oxidation of **167**[106] and SeO_2-mediated elimination of cyclopentene **162** to cyclopentadiene **79**.

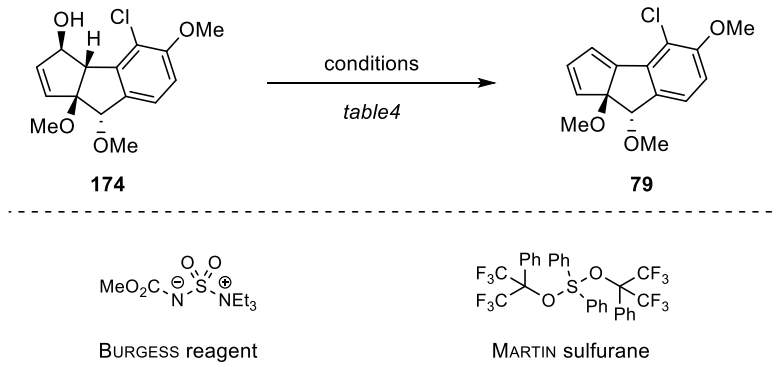
With the results from previous investigations suggesting a stepwise installation of leaving groups to be necessary, olefin **162** was stereoselectively epoxidized using DMDO in 72% yield to give **171**. Subsequent base-catalyzed epoxide opening towards allylic alcohol **172** was not achieved. A regioselective epoxide opening at C11 by seleno phenolate finally gave access to α-hydroxy selenide **173**, which was subsequently oxidized with H_2O_2 to give allyl alcohol **174** in 71% starting from epoxide **171** (scheme 59). The regioselectivity of the ring opening event was in accordance with previously observed trends for opening of the bromonium-ion transitioned in the formation of dibromide **164** (scheme 56).



Scheme 59: Synthesis of allyl alcohol **174** from cyclopentene **162** via epoxidation, epoxide opening and GRIECO elimination.

The tricyclic carbon skeleton was found to be prone to elimination of methanol under slightly acidic conditions. In order to minimize the risk of elimination taking place in synthesis of allylic alcohol **174**, the sequence of reduction of hydroxyketone **155**, methylation, epoxidation and GRIECO elimination was streamlined with one final purification to give **174** in 32% yield over five steps.

For *syn*-elimination of the alcohol in compound **174** (scheme 60) a screening of conditions began with BURGESS reagent,[107] which gave <10% yield of dihydropentalene **79** (table 4, entry 1). Neither with MARTIN sulfurane[108] (entry 2) nor using APPEL conditions (entry 3) from chapter 4.3 an elimination to **79** was observed. Finally, elimination of an *in situ* formed triflate[109] using an excess of KHMDS and $PhNTf_2$ as sulfonylating agent gave cyclopentadiene **79** in 82% yield. Diene **79** showed a remarkable stability, even after 10 d at rt in C_6D_6, only traces of product degradation were observed by TLC.

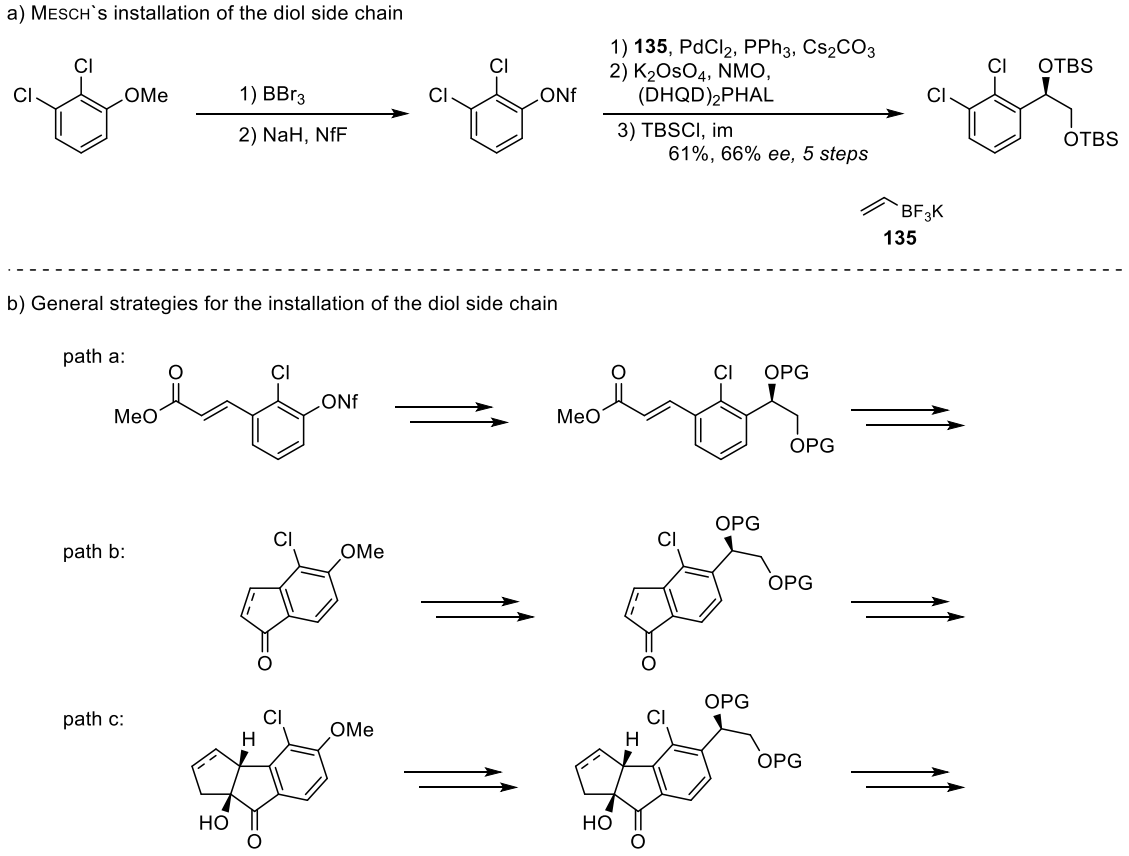


Scheme 60: Final elimination of the alcohol in **181** to yield cyclopentadiene **84**.

Table 4: Conditions screened for elimination of **174** → **79**.

entry	conditions	yield (%)
1	BURGESS reagent, C_6H_6, 80 °C, 2 h	<10
2	MARTIN sulfurane, CH_2Cl_2, 0 °C to rt, 24 h	-
3	PPh_3, NBS, CH_2Cl_2, rt, 2 d	-
4	KHMDS, $PhNTf_2$, THF, –78 °C, 20 min	82

With synthetic access to the fijiolide`s core structure **79** developed, a combination with MESCH`s protocol (scheme 61a)[110] for the construction of the diol side chain would be necessary for the total synthesis of the fijiolides. This might be realized by introduction of the side chain before the indenone is constructed, which would further increase the number of linear steps by four and would additionally require use of protecting groups tolerating aqueous basic as well as LEWIS-acidic conditions for indenone construction (path a). Alternative side-chain installation at the indenone stage would require masking the enone (path b). Overall installation after formation of the tricyclic core structure would be desirable since formation of ring C represents the reaction sequence bottleneck in synthesis of the pentalene core but would require protection of the cyclopentene for dihydroxylation as well (path c, scheme 61b).

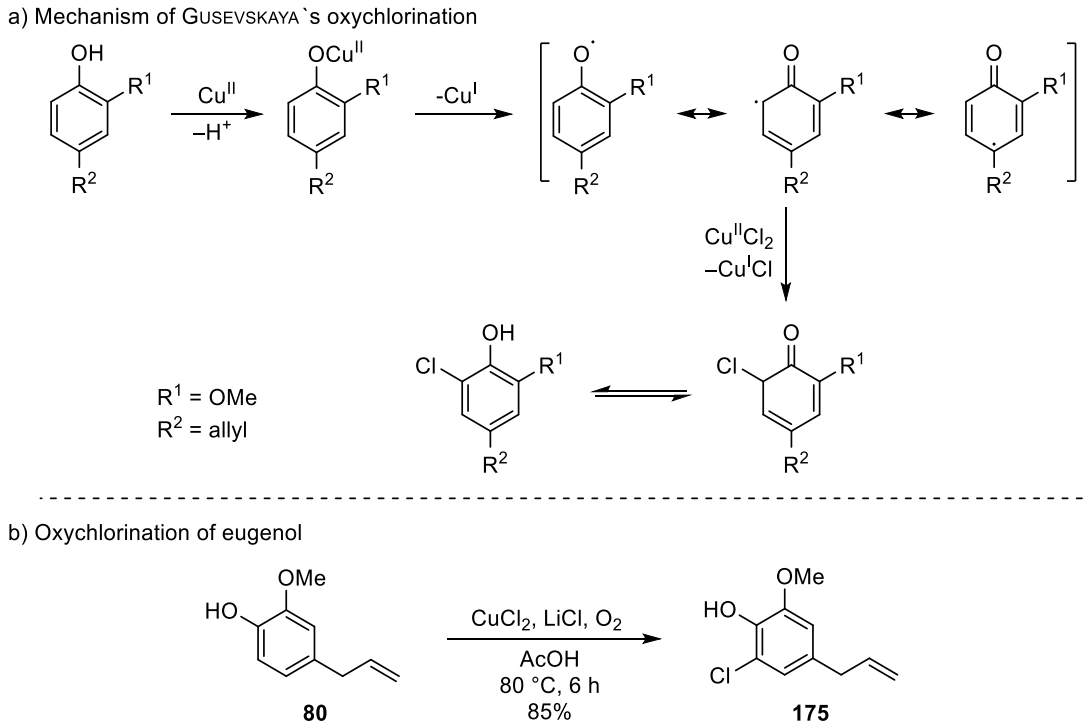


Scheme 61: a) MESCH`s installation of the diol side chain and strategies for the application in the total synthesis of the fijiolides.

5.1 Synthesis of Amino Acid 81

For the synthesis of the amino acid moiety eugenol (**80**) was identified to be the optimal starting material, due to its good availability (500 g 91.50 €)[111] and the fact, that for construction of amino acid **81** no C-C bonds need to be formed.

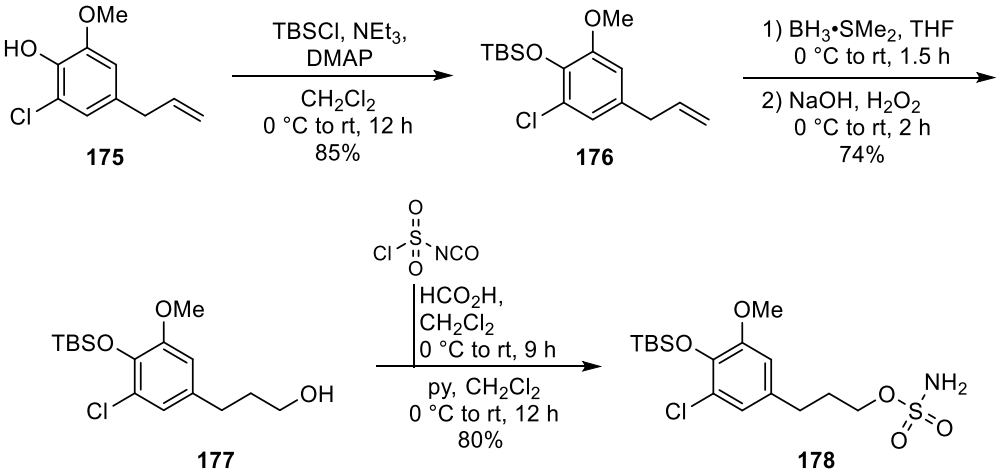
The synthesis of amino acid **81** started with oxychlorination of eugenol (**80**), following a procedure of GUSEVSKAYA.[112] Under O_2-atmosphere a copper-assisted radical formation in *ortho*/*para* position to the phenol is believed to take place, which subsequently reacts with $CuCl_2$ to afford the chlorinated species (scheme 62a). The *para*-position of eugenol is blocked by the allyl substituent, therefore the *ortho* chlorinated species is the only product observed. Following this protocol, chlorinated eugenol **175** was isolated in 85% yield (scheme 62b).



Scheme 62: Oxychlorination of eugenol (**80**).

In the beginning of the synthesis, an orthogonal protection strategy of both phenolic alcohols of amino acid **81** was believed to simplify regioselective cyclophane formation (scheme 17, chapter 1.5.3). Therefore, TBS-protection of the phenol of chlorinated eugenol **175** was performed to yield **176** in 85% (scheme 63). However, CRAMER`s synthesis[14c] demonstrated that no orthogonal protection is necessary. Hence, the synthetic route was later modified to methylate phenol **175** (see chapter 5.3). TBS-protection of **175** was followed by hydroboration of the allyl chain, which yielded alcohol **177** in 74% after oxidative work up

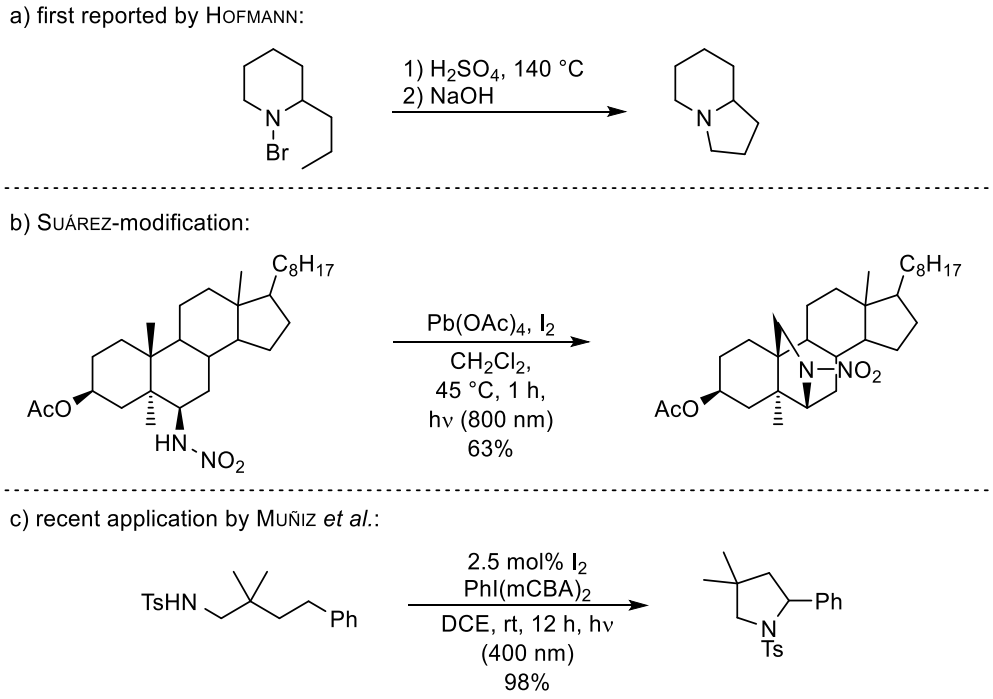
(scheme 63). Subsequent sulfamoylation of **177** using *in situ* formed sulfamoyl chloride[113] gave sulfamate **178** in 80% yield on gram scale as substrate for the rhodium-catalyzed enantioselective CH amination. The theoretical background of the amination strategy will be discussed in the following chapter.



Scheme 63: Synthesis of TBS-protected sulfamate **178**.

5.2 Rhodium-Catalyzed CH-Amination

Although synthetic utility of CH-amination on a broad scope only emerged in the past two decades, the first examples of CH-amination reactions reach back almost one and a half centuries to the development of the HOFMANN-LÖFFLER-FREYTAG reaction (scheme 64a).[114] While this long known methodology has been refined over the years (scheme 64b and c)[115,116] allowing it`s application under much milder conditions, CH-amination as a research field has matured to offer several fascinating solutions to this complex synthetic challenge.



Scheme 64: Examples of the HOFMANN-LÖFFLER-FREYTAG reaction.

One of the biggest challenges is not only to overcome the CH-bond`s high enthalpic stability (representative values see figure 13),[117] but also to selectively address one particular bond in the presence of several others in a comparable energy range.

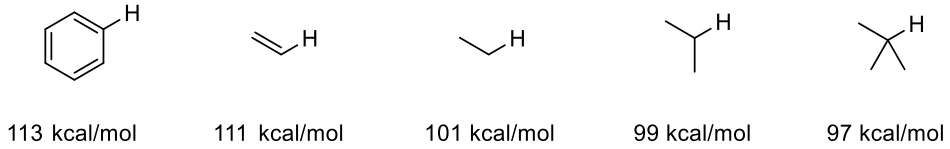
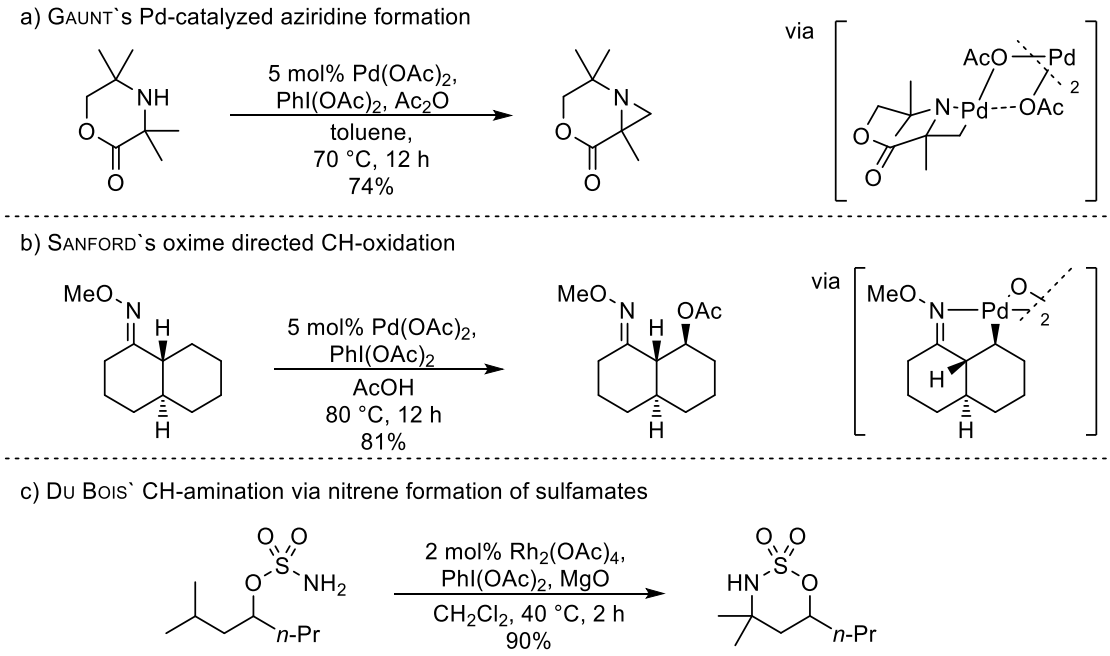


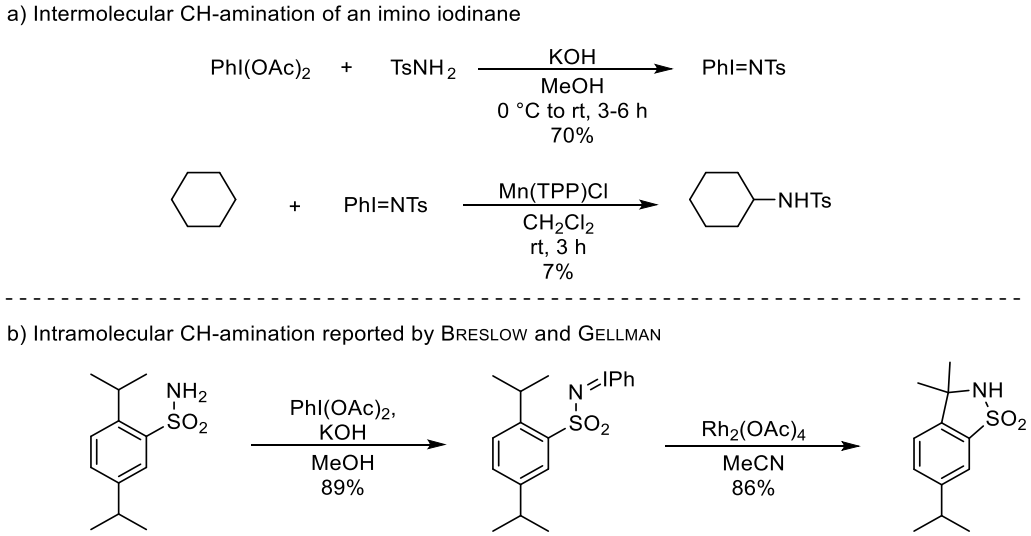
Figure 13: CH-bond-dissociation energies.

In order to resolve the selectivity issue of CH-functionalization three general concepts have been developed: Substrate-controlled reactions by offering certain privileged CH-bonds as exemplified by GAUNT *et al.*[118] (scheme 65a), via installation of a directing group (scheme 65b, demonstrated for oximes by SANFORD and coworkers)[119] or by intramolecular cyclization via nitrene-insertion[120] favoring a certain ring-size (scheme 65c). While the first two concepts rely on offering CH-bonds in close proximity to the coordinated transition metal complex on rigid substrates the nitrene insertions tolerates a broad range of substrates irrespective of their rotational degrees of freedom. Therefore, targeting an enantioselective CH-amination in benzylic position for the amine`s introduction via rhodium-catalyzed nitrene-based cyclization of DU BOIS` sulfamates seems to be predestinated (see scheme 65c).



Scheme 65: General concepts to achieve selectivity in CH-functionalization.

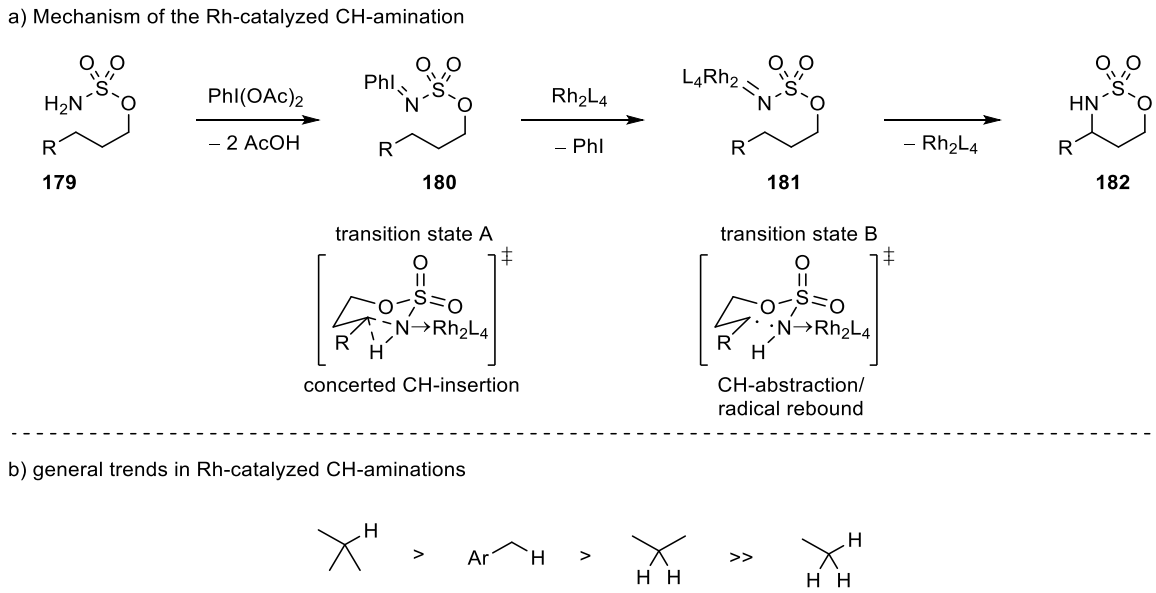
In the early 80s, BRESLOW and GELLMANN reported the first inter- and intramolecular transition metal-catalyzed CH-aminations of imino iodinane species in their efforts to mimic catalytic activity of cytochrome P-450 (scheme 66a).[121] Mechanistically, the formation of a rhodium-nitrenoid was proposed, which subsequently inserts into the benzylic tertiary CH-bond (scheme 66b).



Scheme 66: First examples of transition metal-catalyzed CH-amination by BRESLOW and GELLMAN.[121]

The main limitation to this method was the low stability of the starting material (exemplified synthesis in scheme 66a). Therefore, the utility of this transformation was underestimated for almost two decades.

In 2001, the groups of DU BOIS[120,122] and DAUBAN[123] demonstrated independently that sulfamates, carbamates and urea derivatives form imino iodinane species *in situ* in the presence of Iodine(III) containing oxidation agents. These can be directly used to achieve CH-amination of secondary, tertiary, and benzylic CH-bonds. Mechanistic investigations[124] and DFT-calculations[125] proposed the oxidation of the amine **179** to imino iodinane **180**, which subsequently forms the rhodium-nitrenoid species **181** that can insert into CH-bonds to produce oxathiazinane **182** (scheme 67a, transition state A). A radical-based CH-abstraction mechanism was also discussed (scheme 67a, transition state B), however, radical clock experiments[126] could exclude the formation of radicals with a lifetime of more than 200 fs. Nevertheless, empirical observations concerning reactivity of CH-bonds are in accordance with typical ones for radical processes (scheme 67b).



Scheme 67: Mechanism of the rhodium-catalyzed CH-amination and relative reactivity of CH-bonds therein.

Although a broad range of transition metals are able to catalyze CH-aminations, such as Cu-,[127] Ag-,[128] Fe-,[129] Mn-,[130] or Ru-complexes,[131] the use of dimeric Rh-carboxylate complexes was boosted by DU BOIS` development of $Rh_2(esp)_2$ (**183**) with tethered carboxylate units (figure 14a). Thereby, the catalysts` lability towards oxidation was overcome which strongly enhanced its performance and allowed reduction of catalyst loading in intramolecular cyclizations to 0.15 mol%.[132] Additionally, the first examples of intermolecular CH-amination with acceptable conversion were reported,[133] albeit with overall bigger selectivity issues than for intramolecular examples. The utility of this method

was demonstrated in a number of total syntheses such as manzacidine A and C,[134] saxitoxin,[135] or tetrodotoxin[136] and others[137] (figure 14b).

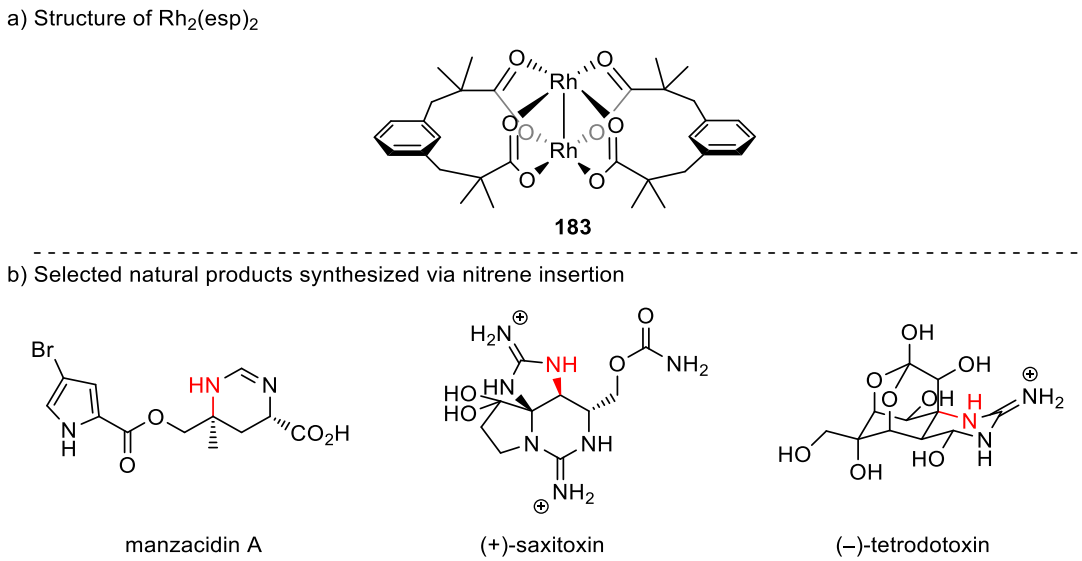
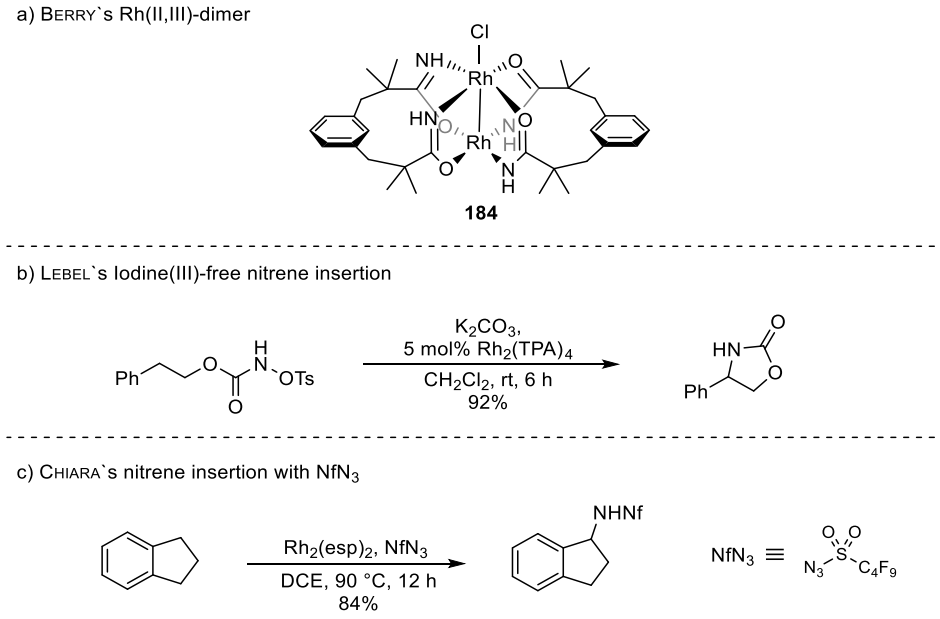


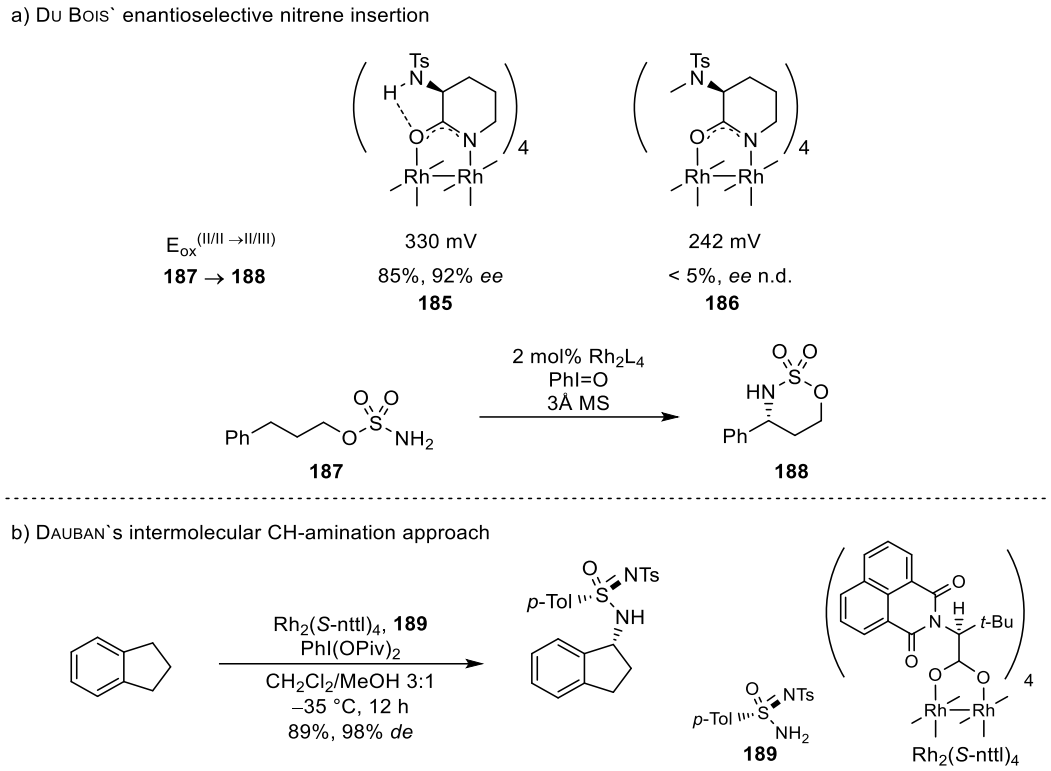
Figure 14: Structure of the $Rh_2(esp)_2$ catalyst and total syntheses relying on rhodium-catalyzed CH-aminations (CN-bond formed depicted in red).

With the major improvements in CH-amination in recent years, there are still some limitations remaining. First of all, the iodine(III) oxidant used also tends to oxidize labile substrates and, even worse, $Rh^{(II,II)}$-dimers to catalytical inactive $Rh^{(II,III)}$-dimers, which can be easily observed by change of the reaction color to red. One solution to this problem was proposed by BERRY *et al.* by introduction of the stable, catalytical active $Rh^{(II,III)}$-dimer $Rh_2(espn)_2Cl$ (**184**, scheme 68a),[138] which could increase the turnover number (TON) for the examples investigated by the factor 2-3 and allowed conversions with only 0.05 mol% catalyst loading. Another solution might be the invention of substrates not relying on iodine(III) oxidation prior to nitrene formation as exemplified by LEBEL and coworkers[139] or CHIARA[140] *et al.* (scheme 68b and c). The latter might be of particular interest, since most organic azides as nitrene precursors failed to react under typical CH-amination conditions.[139]



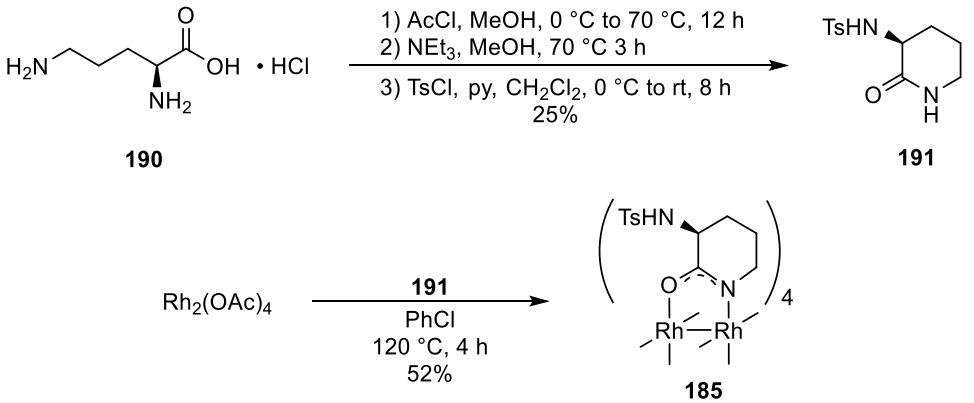
Scheme 68: BERRY`s $Rh^{(II,III)}$-dimer and examples of substrates not relying on oxidation prior to nitrene formation.

Another drawback of rhodium-catalyzed CH-aminations is enantioselectivity. While for tertiary CH-bonds a complete retention of configuration can be observed and substrate-directed reactions give high diastereoselectivity, as exemplified by DU BOIS` saxitoxin synthesis[135] (see figure 14b), application of chiral rhodium tetracarboxylate catalysts only gave poor enantioinduction. In 2008, DU BOIS published a series of rhodium carboxamidate dimers, demonstrating that Rh_2(*S*-nap)$_4$ (**185**)[35] could overcome this issue, mainly due to a hydrogen bridge significantly enhancing the catalyst`s redox potential (scheme 69a, comparison with its methylated analogue **186**). A solution for intermolecular CH-amination was proposed by DAUBAN and coworkers[141] by the use of Rh_2(*S*-nttl)$_4$ in combination with chiral sulfonimidamides **189** resulting in a matched/mismatched scenario giving benzylic amination products in up to 89% yield with excellent *de*`s (scheme 69b).



Scheme 69: Rh_2(*S*-nap)$_4$ and its methylated analogue, their application in enantioselective CH-amination and DAUBAN`s diastereoselective intermolecular amination.

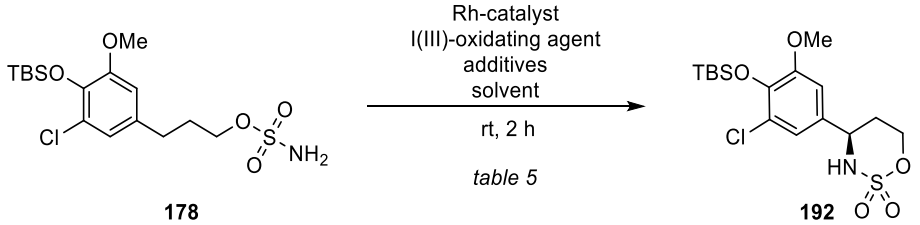
For synthesis of amino acid **81**, application of DU BOIS` Rh_2(*S*-nap)$_4$ catalyst **185** for intramolecular CH-amination was believed to offer sufficient enantiocontrol, given the comparable examples in literature (**187** → **188**, scheme 69a) demonstrating high enantiomeric induction by this catalyst. Synthesis of Rh_2(*S*-nap)$_4$ was achieved by cyclization of (*L*)-ornithine hydrochloride (**190**) to the lactam followed by tosylation in a single flask and subsequent ligand exchange onto $Rh_2(OAc)_4$ in (scheme 70). Further experiments to produce ligands with different sulfonylation patterns to vary the electronic and steric demand remained unsuccessful.



Scheme 70: Synthesis of Rh_2(*S*-nap)$_4$ from ornithine hydrochloride **185**.[35]

5.3 Synthesis of Oxathiazinane 193

After CH-amination of sulfamate **178** (scheme 71) with $Rh_2(esp)_2$ and $PhI(OPiv)_2$ gave racemic oxathiazinane **192** in 90% yield (table 5, entry 1), a transfer of the optimized reaction conditions towards the chiral Rh_2(*S*-nap)$_4$ gave only unsatisfactory 44% *ee* in CH_2Cl_2 and 53% *ee* in benzene, although excellent yields were achieved (entry 2-4). Use of Rh_2(*S*-dosp)$_4$ (figure 15a) resulted in 12% *ee* in favor of (*S*)-**192** (entry 5). It was reasoned that two in the activation of the sulfamate liberated carboxylate moieties (see mechanism, chapter 5.2) of the oxidating agent undertook a ligand exchange on the catalyst, causing a loss of stereoinformation at the catalyst and consequently a loss of enantioselectivity in the product.



Scheme 71: CH-Amination of sulfamate **178** to yield oxathiazinane **192**.

Indeed, the use of iodosobenzene as oxidating agent gave **192** with up to 87% *ee* (for representative HPLC-chromatograms see chapter 8.3.1, page 142). On the downside, the yield dropped drastically (entries 6 and 7). The general problem using iodosobenzene as oxidating reagent is the compounds` low solubility, which requires the addition of large amounts of oxidating agent at once, whereby side-reactions such as partial catalyst degradation or other unproductive oxidative processes get encouraged. In addition, H_2O is liberated in the activation of the sulfamate which seems to inhibit the reaction as well. A shortened reaction time of 2 h and the use of freshly activated 3 Å molecular sieves yielded **192** in acceptable 66% yield with 84% *ee* (entry 8). Nevertheless, the crystal structure of oxathiazinane **192** (figure 15b) revealed the opposite enantiomer had been formed, due to a wrong prediction of enantioselectivity in the original literature.[142]

Table 5: Enantioselective CH-amination using different catalyst and oxidation agents.

entry	Rh-catalyst	solvent	oxidating agent	additive	yield (%)[a]	*ee* (%)
1	$Rh_2(esp)_2$	CH_2Cl_2	$PhI(OPiv)_2$	MgO	90	-
2	Rh_2(*S*-nap)$_4$	CH_2Cl_2	$PhI(OPiv)_2$	MgO	82	44
3	Rh_2(*S*-nap)$_4$	CH_2Cl_2	$PhI(OPiv)_2$	MgO, 4Å MS	98	37
4	Rh_2(*S*-nap)$_4$	benzene	$PhI(OPiv)_2$	MgO, 4Å MS	99	53
5	Rh_2(*S*-dosp)$_4$	benzene	PhIO	MgO, 4Å MS	77	12[b]
6	Rh_2(*S*-nap)$_4$	CH_2Cl_2	PhIO	MgO, 4Å MS	37	82
7	Rh_2(*S*-nap)$_4$	benzene	PhIO	MgO, 4Å MS	30	87
8	Rh_2(*S*-nap)$_4$	CH_2Cl_2	PhIO	MgO, 3Å MS (powdered)	66	84
9	Rh_2(*S*-nap)$_4$	benzene	PhIO	MgO, 3Å MS (powdered)	45	79

[a]isolated yields; [b]the (*S*)-enantiomer was obtained.

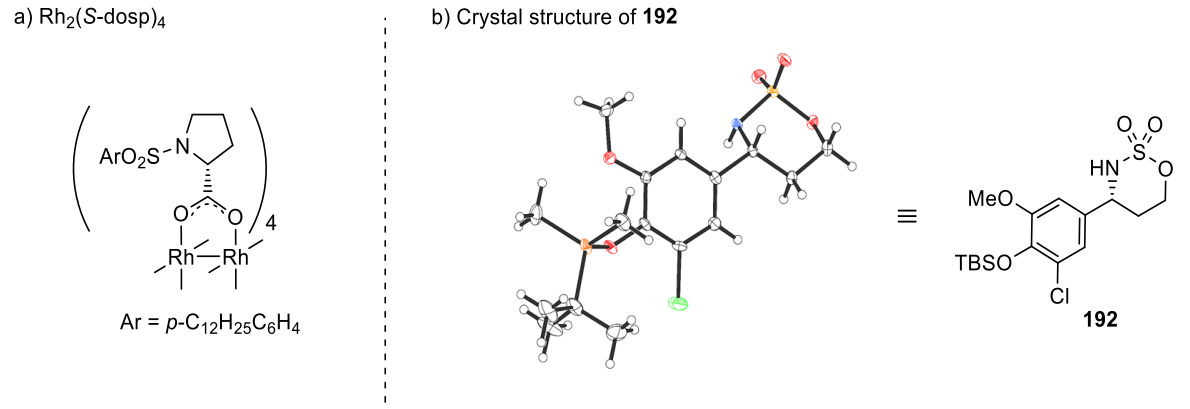
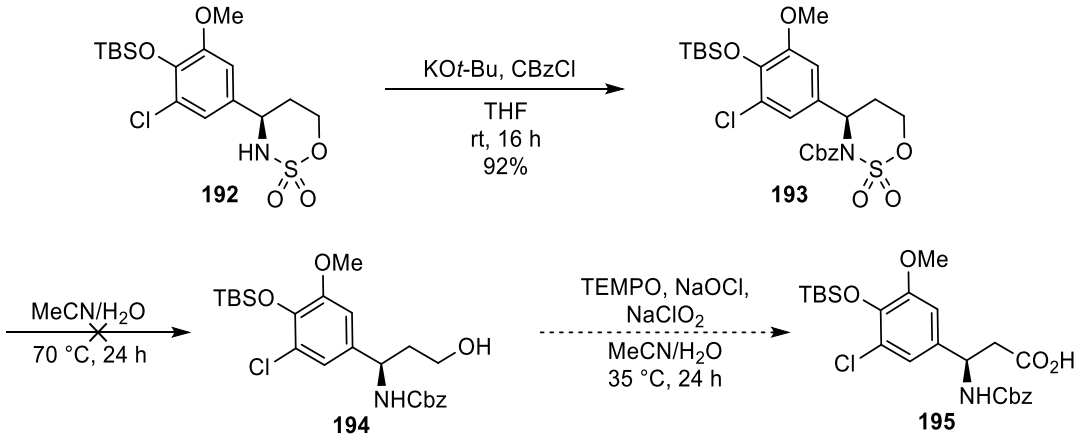


Figure 15: Rh_2(*S*-dosp)$_4$ and crystal structure of oxathiazinane **192**.

In order to establish synthetic access to amino acid **81** the route was further investigated with the (*R*)-enantiomer. However, by application of Rh_2(*R*-nap)$_4$ the (*S*)-enantiomer of **192** can be obtained. Cbz-protection of the amine was achieved in 92% yield, using KO*t*-Bu and CbzCl in THF (scheme 74). It is literature known, that the enhanced electrophilicity of the protected amine allows ring opening under much milder conditions, compared to unprotected oxathiazinanes.[122] DU BOIS could demonstrate that even weak nucleophiles such as water are able to open the ring towards the corresponding amino alcohol at slightly elevated temperatures. Following his procedure, oxathiazinane **193** was supposed to be opened by heating to 70 °C in MeCN/H_2O and a subsequent modified PINNICK oxidation would give raise to amino acid **195** (scheme 72). However, after several attempts, **195** could not be

isolated, probably due to the low stability of the TBS-phenol ether under the strong acidic reaction conditions. Modification of oxidation conditions for classical PINNICK conditions[143] also remained unsuccessful. Furthermore, isolation of the amino alcohol **194** for a separated oxidation was unsuccessful as well.



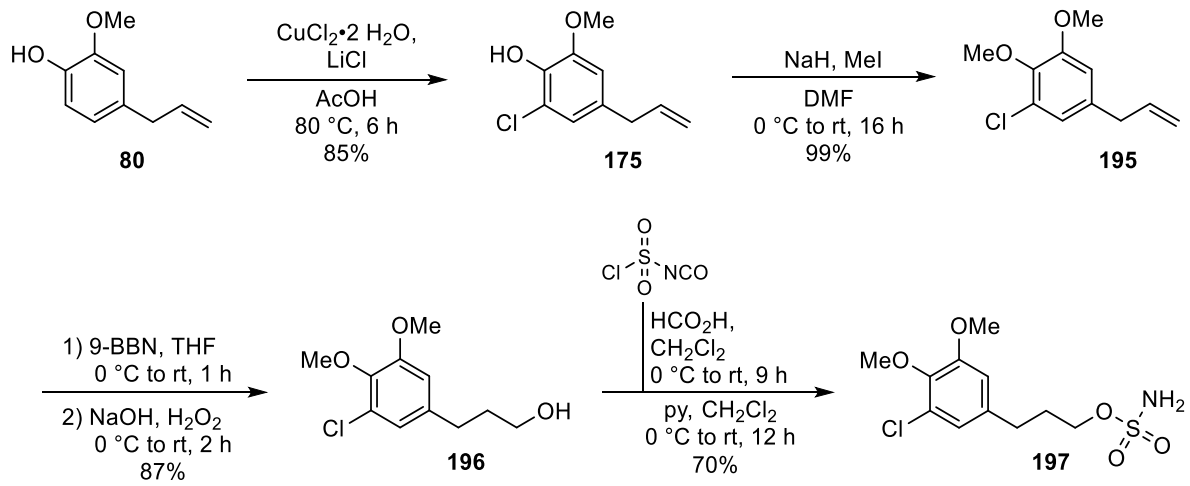
Scheme 72: Failed attempts to isolate amino alcohol **194**.

5.3 Second Generation Synthesis of the Amino Acid

Since the TBS-protecting group proved to be unstable in the oxidation step and in addition was hypothesized to be a possible cause for low yields in CH-amination of **187** using iodosobenzene, another protection for phenol **175** was investigated. CRAMER had shown that no orthogonal protection of the catechol`s alcohols in synthesis of the cyclophane is required (scheme 17, chapter 1.5.3), so a second methyl ether was chosen for its greater stability under acidic conditions and possible simultaneous deprotection of both alcohols.

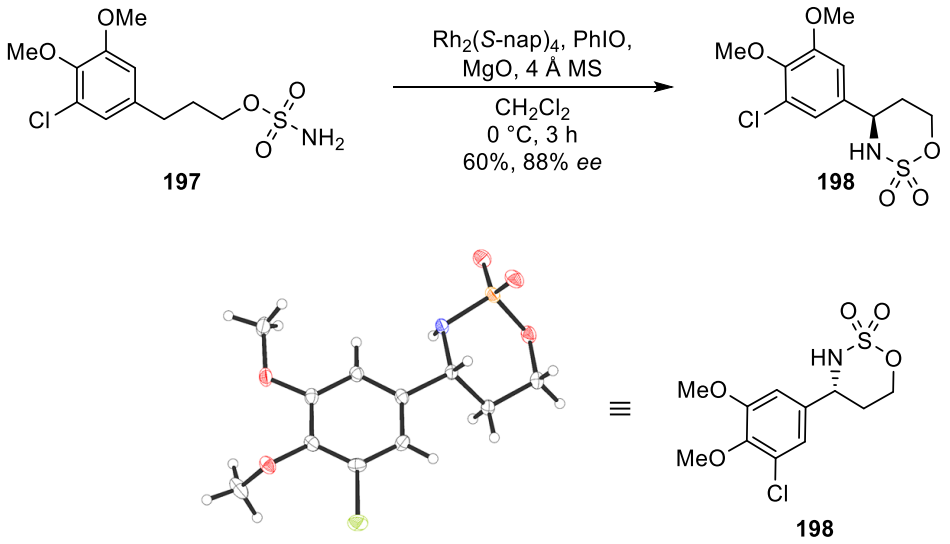
In addition, the oxathiazinane was to be acetylated instead of Cbz-protected, since the final product fijiolide A would feature the same substitution pattern.

With the revised protecting group strategy suggesting an overall greater stability, previously established transformations (chapter 5.1) furnished twice methylated sulfamate **197** in 52% yield over four steps on gram scale starting from eugenol (scheme 73).



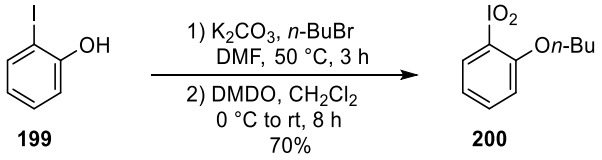
Scheme 73: Synthesis of doubly methylated sulfamate **197**.

CH-amination of **197** using $Rh_2(esp)_2$ gave oxathiazinane **198** in quantitative yield, however, using Rh_2(*S*-nap)$_4$/iodosobenzene again resulted in a significant loss of yield (scheme 74). Oxathiazinane **198** was isolated in 60% yield with 88% *ee*, structurally verified by X-ray crystallography (for representative HPLC-chromatograms see chapter 8.3.2, page 152).



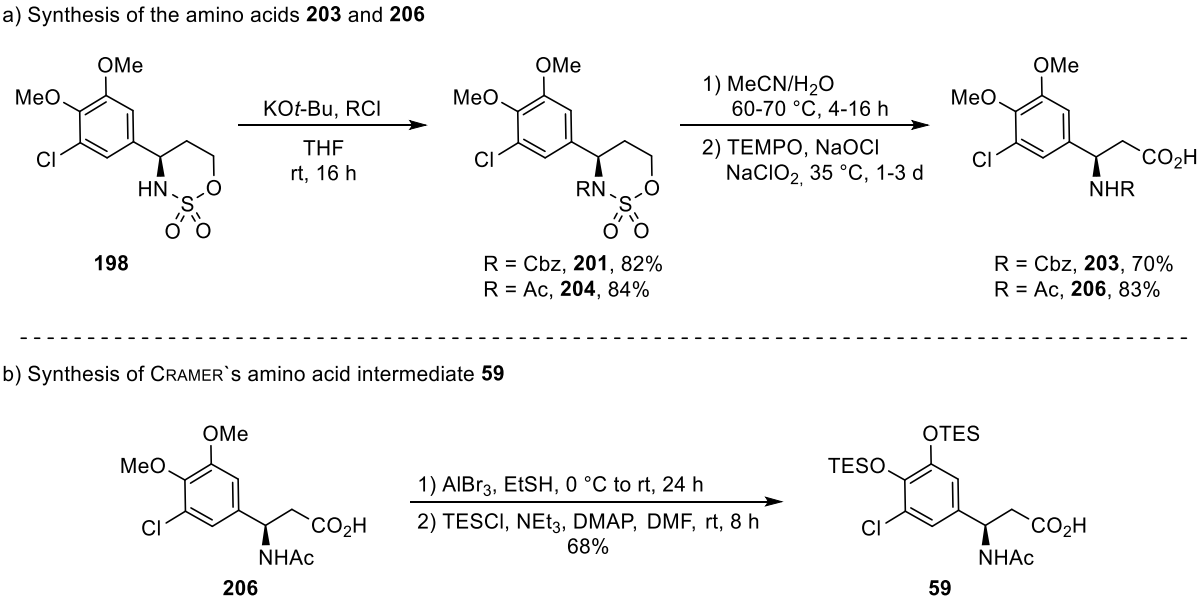
Scheme 74: CH-amination of sulfamate **197** to yield oxathiazinane **198**.

In order to increase the oxidation agent`s solubility an *ortho*-substituted derivative **200** was synthesized in two steps from *ortho*-iodo phenol (**199**) following a procedure of NEMYKIN and ZHDANKIN[144] (scheme 75). Iodosobenzene **200**`s secondary phenolic ether prevents it`s oligomerization and increases it`s solubility. Unfortunately, **200** was found to be no potent oxidating agent for this kind of transformation, therefore no further experiments were performed to increase the oxidation reagent`s solubility.



Scheme 75: Synthesis of *ortho*-substituted iodosobenzene analogue **200**.

For the purpose of testing the catechol`s stability using DU BOIS` conditions oxathiazinane **198** was Cbz-protected in 82% yield and the subsequent ring opening/PINNICK oxidation protocol gave Cbz-protected amino acid **203** in 70% yield (scheme 76a). In order to avoid a step-intensive Cbz-deprotection/acetylation sequence of amino acid **203**, oxathiazinane **198** was acetylated with AcCl and KO*t*-Bu in 84% yield. Employing Ac_2O as acetylation agent resulted in partial ring opening by the acetate rather than protection of the amine. DU BOIS` protocol then furnished acetylated amino acid **206** in 83% yield. However, lower temperatures and shorter reaction time in the ring opening were found to be fundamental to prevent deacetylation. The enantiomer of CRAMER`s amino acid intermediate **59** was then obtained by deprotection of **206** using $AlBr_3$/EtSH and subsequent TES-protection in 68% yield (scheme 76b).[145]



Scheme 76: Protection, ring opening and oxidation of **198** to yield amino acids **203** and **206** and synthesis of CRAMER`s intermediate **59**.

When comparing the NMR-spectroscopic data of **59** (figure 16 and 17) with that reported by CRAMER all signals were in accordance with the literature (see table 6 and 7). As expected, the opposite enantiomer was obtained, which led to a reversed optical rotation (see chapter 8.3.2, page 163).

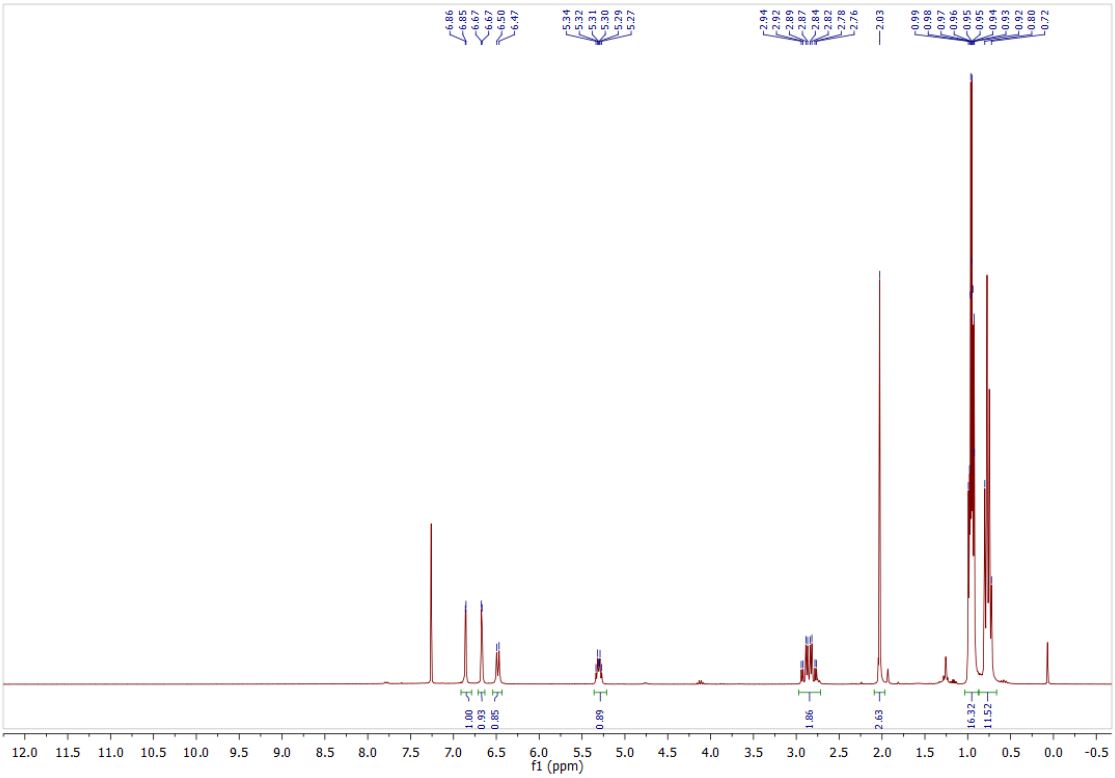
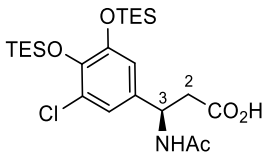


Figure 16: ^{1}H-NMR of amino acid **59**.



59

Table 6: ^{1}H-NMR-Spectroscopic comparison of **59** with data reported by CRAMER.

	Amino Acid **59**		CRAMER`s Amino Acid **59**		
Proton	δ_H [ppm]	multi. (*J*[Hz])	δ_H [ppm]	multi. (*J*[Hz])	Deviation Δδ [ppm]
TES	0.72-0.80	m	0.73-0.82	m	0.02
TES	0.96	td, (6.0, 7.8)	0.97	td, (6.0, 7.8)	0.01
Ac	2.03	s	2.04	s	0.01
2-H_A	2.80	dd, (5.8, 16.1)	2.82	dd, (5.8, 16.1)	0.02
2-H_B	2.91	dd, (5.8, 16.1)	2.91	dd, (5.8, 16.1)	0.00
3-H	5.30	dt, (5.8, 8.4)	5.32	dt, (5.8, 8.4)	0.02
NH	6.48	d, (8.5)	6.47	d, (8.5)	0.01
Ar	6.67	d, (2.3)	6.68	d, (2.3)	0.01
Ar	6.86	d, (2.3)	6.87	d, (2.3)	0.01

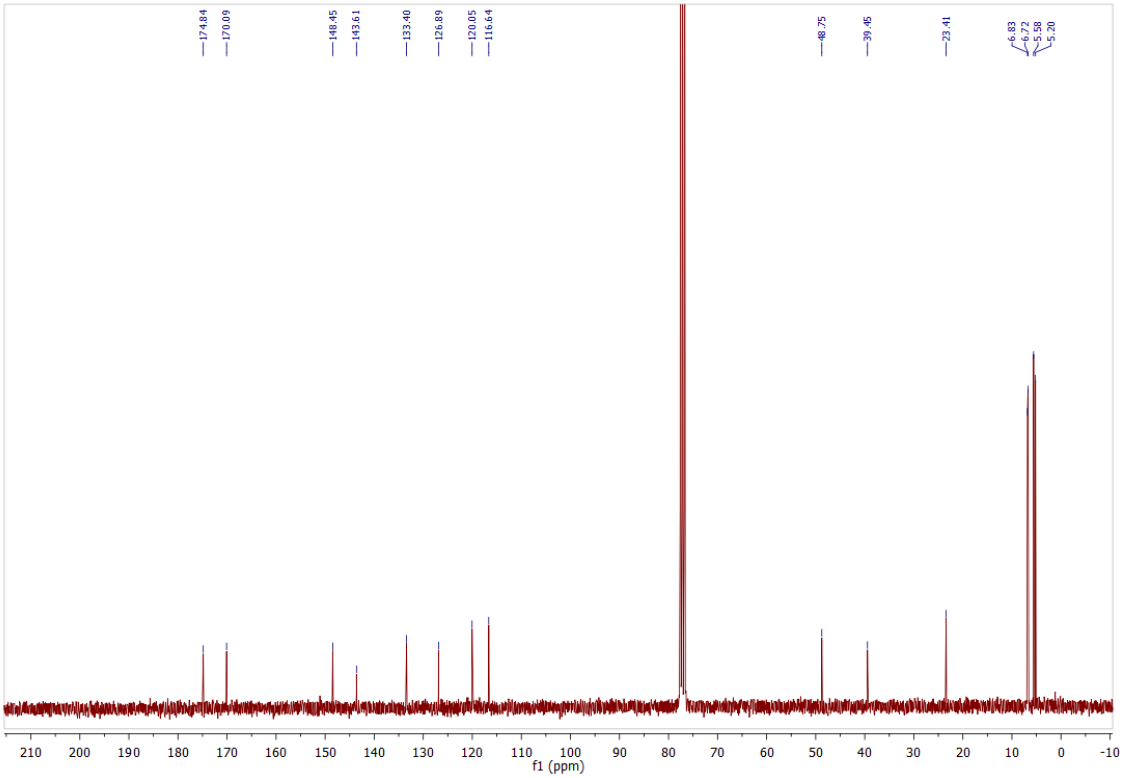


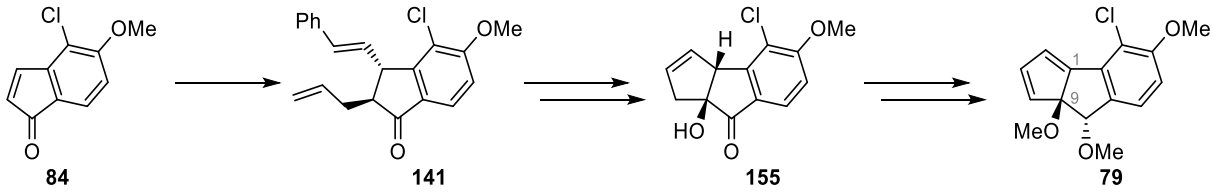
Figure 17: ^{13}C-NMR of amino acid **59**.

Table 7: ^{13}C-NMR-Spectroscopic comparison of **59** with data reported by CRAMER.

	Amino Acid **59**	CRAMER`s Amino Acid **59**	
Carbon	δ_C [ppm]	δ_C [ppm]	Deviation $\Delta\delta$ [ppm]
TES	5.2	5.0	0.2
TES	5.6	5.4	0.2
TES	6.7	6.6	0.1
TES	6.8	6.7	0.1
Me	23.4	23.2	0.2
C2	39.5	39.5	0.0
C3	48.8	48.6	0.2
Ar	116.6	116.4	0.2
Ar	120.0	119.8	0.2
Ar	126.8	126.6	0.2
Ar	133.4	133.3	0.1
Ar	143.6	143.4	0.2
Ar	148.4	148.2	0.2
NAc	170.1	170.1	0.0
CO_2H	174.8	175.0	0.2

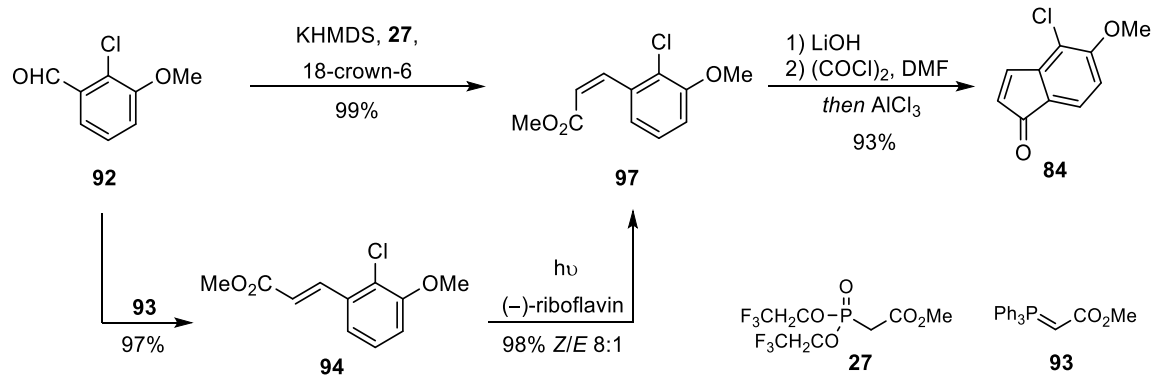
6 Summary and Outlook

In this thesis, a stereoselective access to the benzodihydropentalene core structure **79** and the amino acid fragment **81** of the fijiolides was developed. For benzodihydropentalene **79** the synthetic strategy relied on introduction of a styryl moiety onto indenone **84** allowing construction of ring C via ring closing metathesis. Essential for this strategy was the early introduction of the alcohol at C9, that enabled the *cis*-arrangement of the previously installed allyl and the styryl moiety. Although the fijiolides` core does not contain a stereocenter at C1, enantioselective introduction of the styryl residue in this position allowed to build up the cyclopentadienol in a stereocontrolled fashion with a high degree of substrate control (scheme 77).



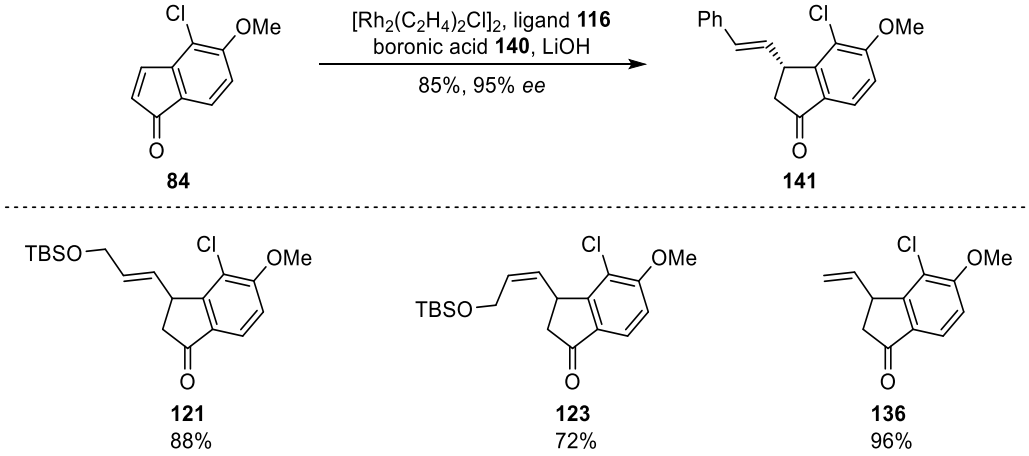
Scheme 77: Enantioselective conjugate addition to indenone **84** and following transformations leading to benzodihydropentalene **79**.

For construction of indenone **84**, a highly flexible route starting from literature known aldehyde **92** was established via FRIEDEL-CRAFTS acylation of an cinnamic acid. The corresponding ester **97** could be obtained by STILL-GENNARI-olefination from aldehyde **92**. In addition, an environmentally friendly alternative to direct (*Z*)-selective olefination of **92** was developed for construction of the FRIEDEL-CRAFTS precursor by riboflavin-catalyzed (*E*→*Z*)-isomerization of ester **94** under UV-light. Subsequent saponification of ester **97** and transformation into the acid chloride enabled aluminum(III) chloride promoted intramolecular acylation to yield **84** on gram scale (scheme 78).



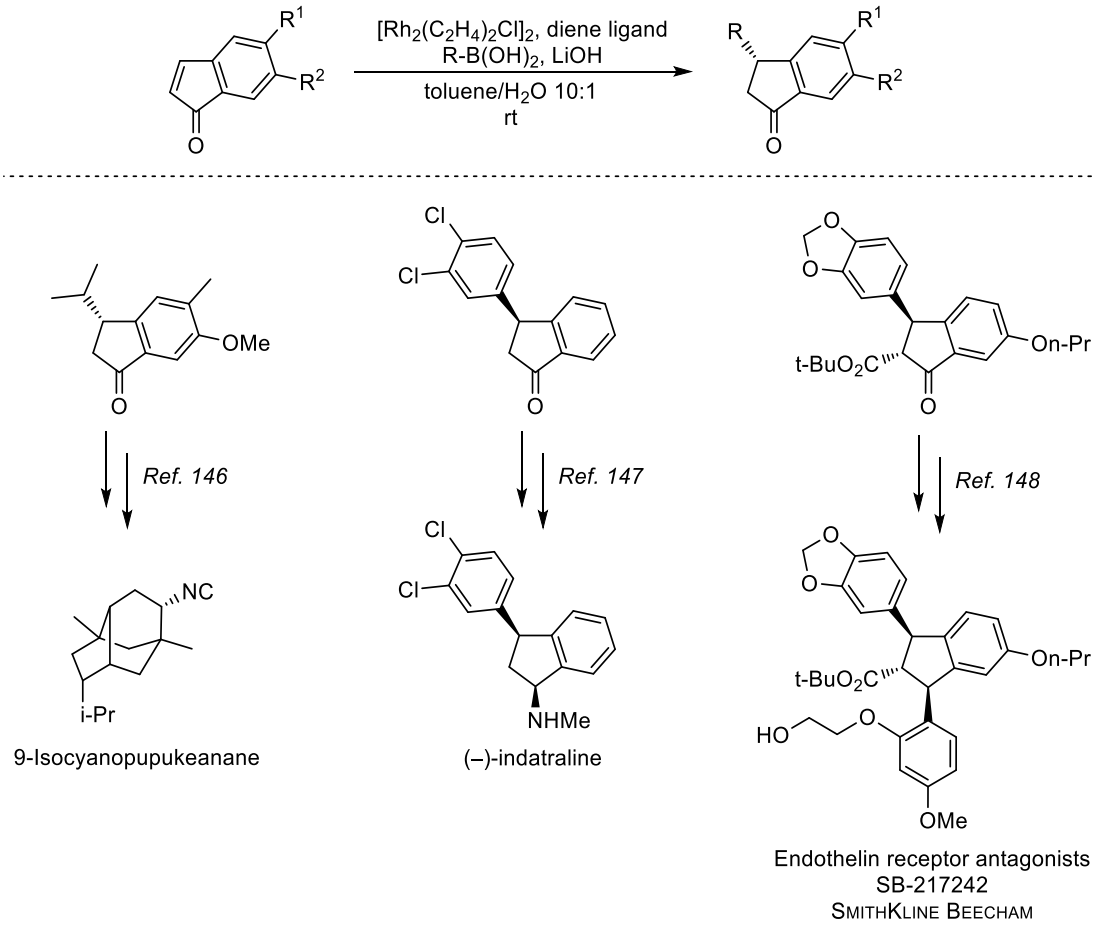
Scheme 78: Synthesis of Indenone **84** from aldehyde **85**.

Indenone **84** was then used for rhodium-catalyzed asymmetric conjugate addition with alkenyl boronic acid derivative **140** to yield indanone derivative **141**. With HAYASHI`s diene **116**, indanone (*R*)-**141** was obtained in 99% yield with 74% *ee*, which could be further increased by recrystallization to >99% *ee*, structurally secured by X-ray crystallography. The use of CARREIRA`s diene ligand **110** gave **141** in 85% with 95% *ee* (scheme 79). In addition, the conjugate addition of three more alkenyl nucleophiles could be achieved in good to excellent yield. However, synthesis of the resulting addition products proved to be not productive for the construction of benzodihydropentalene **79**.



Scheme 79: Conjugate addition of alkenyl boronic acid derivatives to indenone **84**.

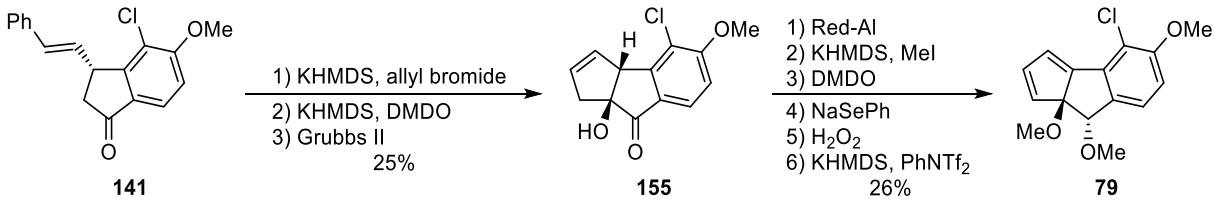
With the first reliable protocol for asymmetric conjugate addition on indenones developed, application of this method could be used for synthesis of a variety of biological active compounds. Formal syntheses of three different examples are depicted in scheme 80. By this method, functionalization of various biological active indenones should be possible.



Scheme 80: Proposed application of asymmetric conjugate additions for formal syntheses of biological active indanones.[146,147,148]

With indanone **141** in hand, allylation was performed to yield allylated indanone **143**. Although extensively studied, neither formation of the double allylated product **144**, nor the fast isomerization of the double bond could be effectively suppressed. *α*-Hydroxylation of **143** and subsequent ring closing metathesis gave *α*-hydroxy ketone **155**. Furthermore, the non-oxygenated tricyclic ketone **154** was obtained as inseparable mixture with **143** by *trans→cis* isomerization at C2 of **143** with subsequent ring closing metathesis. However, for **154**, installation of the alcohol at C9 towards ketone **155** remained unsuccessful. Ketone **155** was reduced to diol **158** in substrate-directed, highly diastereoselective fashion with a *trans*/*cis* ratio of >15:1. Methylation of **158** gave olefin **162**, which was then epoxidized. Regioselective epoxide opening with NaSePh at C11, followed by elimination of the selenide under oxidative conditions yielded allylic alcohol **174**. Cyclopentadiene **79** was then accessed via *syn*-elimination of an *in situ* formed triflate (scheme 81). Alternative routes for double elimination of cyclopentene **162**`s additions products towards **79** remained unsuccessful. Due to the apparent lability of various substrates en route to **79** the amount of purification steps

from indanone **141** to cyclopentadiene **79** was reduced to three column chromatographic separations.



Scheme 81: Synthesis of benzodihydropentalene **79** from ketone **141**.

Overall, the synthetic strategy does not rely on many non-strategic redox reactions or the use of various protecting groups. With eight steps of construction reactions and one step of strategic redox reactions in overall twelve steps a percent ideality of 75% can be calculated following BARAN`s definition[149] of ideal synthesis (equation 1) for construction of **79** starting from aldehyde **92**.

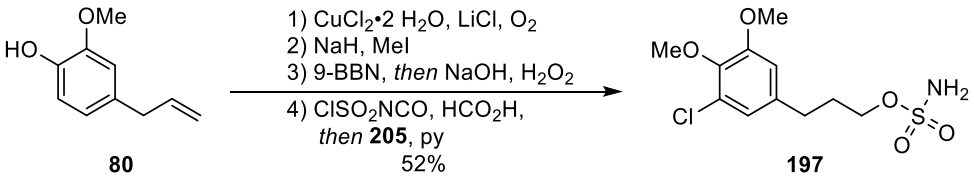
$$\%ideality = \frac{(number\ of\ construction\ reactions)+(number\ of\ strategic\ redox-reactions)}{(number\ of\ total\ steps)} * 100$$

Equation 1: BARAN`s definition of synthetic ideality.

Due to the tilted geometry of ring C in tricyclic compound **155** and the products resulting from it, a high degree of regio- and stereoselectivity could be observed for construction of diene **79**. This finding could be helpful for synthesis of tricyclic systems of a few similar natural products core structures (see figure 2, chapter 1.1). Furthermore, the synthetic strategy for construction of the cyclopentadiene from an cyclopentene might be applicable in general.

Synthesis of Amino Acid 59

Synthesis of amino acid **81** started with chlorination of eugenol (**80**) following a procedure of GUSEVSKAYA. Subsequent methylation of the phenol, hydroboration of the olefin with oxidative work up and sulfamoylation gave sulfamate **197** in 52% yield over four steps starting from **80** as substrate for rhodium-catalyzed CH-amination (scheme 82). The TBS protected sulfamate **178** was synthesized by analogous reactions but could not be oxidized to the respective amino acid.

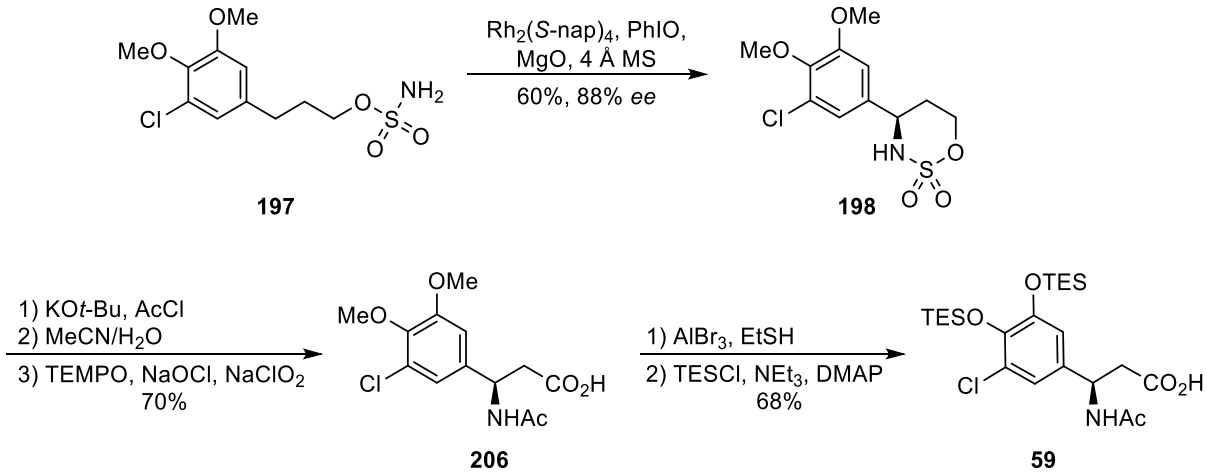


80 197

Scheme 82: Synthesis of sulfamate **197** from eugenol (**80**).

Sulfamate **197** was then cyclized under Rh_2(*S*-nap)$_4$-catalysis via enantioselective nitrene CH-insertion to give oxathiazinane **198** in 60% yield with 88% *ee*, structurally secured by X-ray crystallography. The choice of the oxidation agent utilized was found to be crucial. Although oxathiazinane **198** could be obtained in quantitative yield using PhI(OPiv)$_2$, a continuous ligand exchange of the liberated carboxylate moieties with the catalyst was hypothesized to be the cause for a significant loss of enantioinduction.

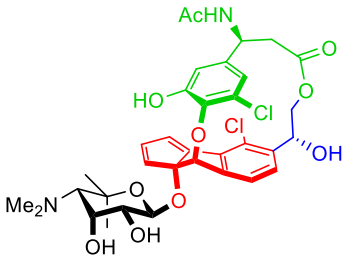
Acetylation of oxathiazinane **198**`s amine, ring opening and PINNICK oxidation then furnished amino acid **206**. Deprotection of the catechol and TES-protection gave the enantiomer of CRAMER`s intermediate **59** in 15% over eight steps with 88% *ee*. No C-C bonds have to be formed starting from cheap material, which should allow to perform the reaction sequence towards **59** on gram-scale (scheme 83).



197 198 206 59

Scheme 83: Synthesis of CRAMER`s amino acid derivative **59** from sulfamate **198**.

For synthesis of amino acid **59**, three steps of construction and two steps of strategic redox-reactions out of eight total steps give 63% ideality.



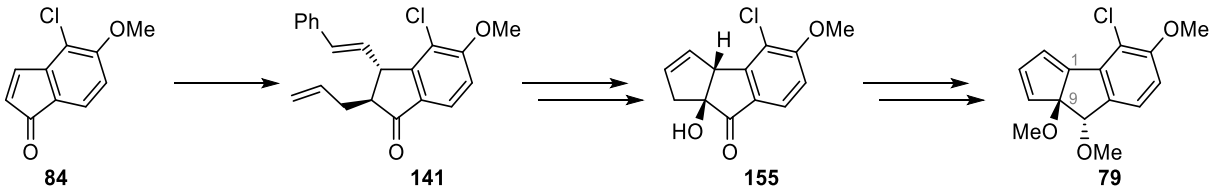
fijiolde A **10a**

Figure 18: Summary of the synthetic efforts.

Overall, a stereoselective access to the benzodihydropentalene structure (red) and the amino acid (green) could be developed (figure 18). Furthermore, MESCH could demonstrate in his Bachelor thesis how to achieve the installation of the diol side chain (blue) from a methoxy group on a test system. Combined with the amino sugar`s literature known synthesis (black, chapter 1.5.1) a new synthetic access to fijiolide A would be achieved.

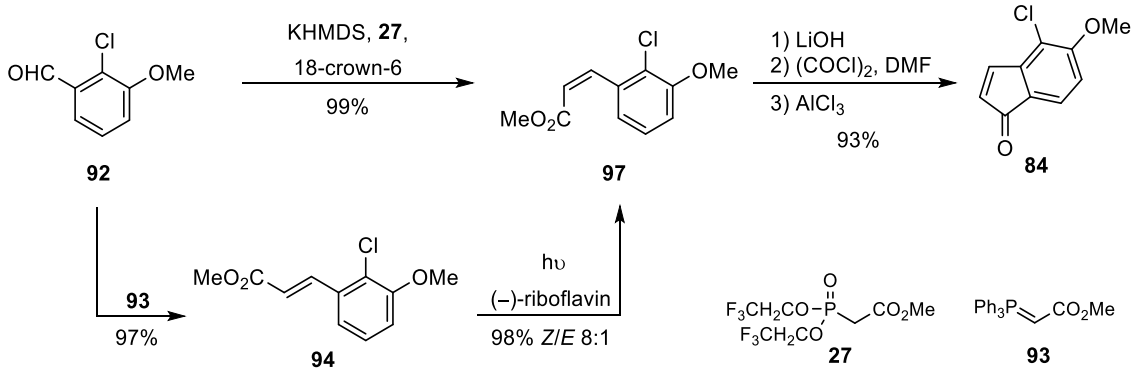
7 Zusammenfassung und Ausblick

In der vorliegenden Arbeit wurde ein stereoselektiver Zugang zum Benzodihydropentalenkern **79** und der Aminosäure **81** der Fijiolide entwickelt. Die Synthesestrategie für Dihydropentalen **79** beruhte auf der Addition eines Styrylrestes an Indenon **84** als Vorläufer für den Aufbau von Ring C via Ringschlussmetathese. Als entscheidend stellte sich dabei die frühzeitige Einführung des Alkohols an C9 heraus, durch den zuverlässig eine *cis*-Konfiguration des zuvor eingeführten Allyl- und Styrylsubstituenten erreicht werden konnte. Auch wenn die Fijiolide kein Stereozentrum an C1 besitzen, ermöglichte die enantioselektive Einführung des Styrylrestes den stereoselektiven Aufbau des Cyclopentadienols mit einem hohen Maß an Substratkontrolle (Schema 84).



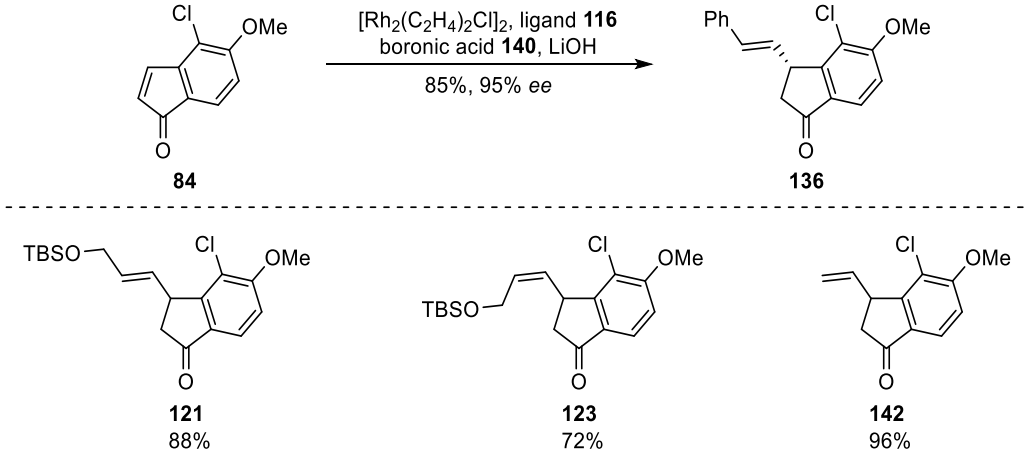
Schema 84: Enantioselektive 1,4-Addition an Indenon **84** und der darauffolgende Aufbau des Benzodihydropentalens **79**.

Der Zugang zu Indenon **84** gelang ausgehend vom literaturbekannten Aldehyd **92**, durch intramolekulare FRIEDEL-CRAFTS Acylierung von einem Zimtsäurederivat. Der entsprechende (*Z*)-konfigurierte Ester **97** konnte durch STILL-GENNARI Olefinierung erhalten werden. Alternativ zur (*Z*)-selektiven Olefinierung konnte unter UV-Licht eine Riboflavin-katalysierte (*E*→*Z*)-Isomerisierung durchgeführt werden ausgehend von Ester **94**. Die anschließende Verseifung von Ester **97** ermöglichte die intramolekulare Acylierung des entsprechenden Säurechlorids in Gegenwart von Aluminium(III)chlorid (Schema 85).



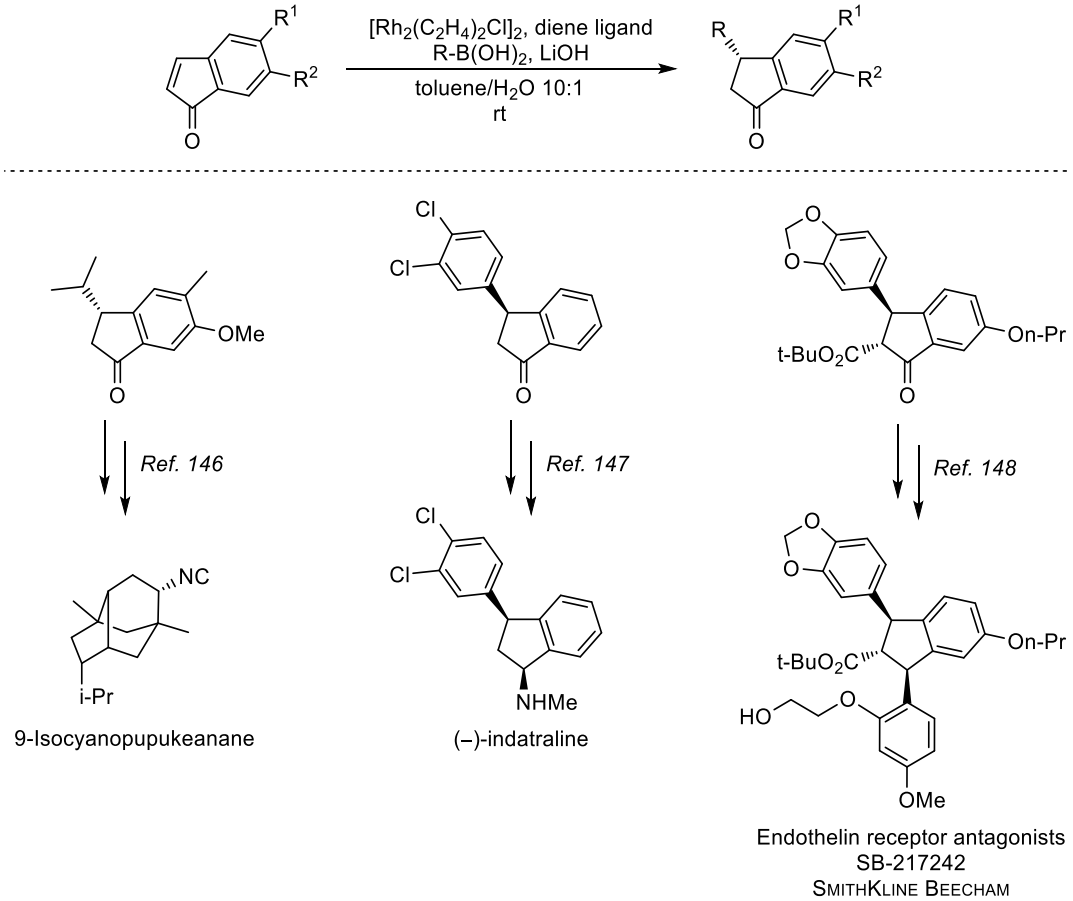
Schema 85: Synthese des Indenons **84** ausgehend von Aldehyd **92**.

Indenon **84** wurde dann in rhodiumkatalysierten 1,4-Additionen mit verschiedenen Alkenylboronsäure-Derivaten eingesetzt. Unter Verwendung von HAYASHI`s Dien Ligand **116** konnte Indanon (*R*)-**141** in 99% Ausbeute mit 74% *ee* erhalten werden. Durch Umkristallisation konnte der *ee* auf >99% erhöht werden, was via Kristallstrukturanalyse bestätigt wurde. Unter Verwendung von CARREIRA`s Dien Ligand **110** konnte (*R*)-**141** sogar mit 95% *ee* in 85% Ausbeute isoliert werden (Schema 86). Zusätzlich konnten die Additionsprodukte von drei weiteren Alkenylnukleophilen in guten bis sehr guten Ausbeuten erhalten werden, deren Addition für die Synthese von **79** jedoch nicht zielführend war.



Schema 86: Asymmetrische 1,4-Addition von Alkenylboronsäure-Derivaten an Indenon **84**.

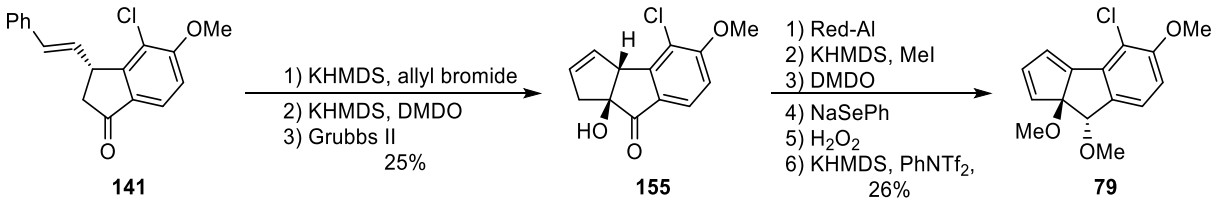
Durch die Entwicklung des ersten verlässlichen Protokolls für die asymmetrische 1,4-Addition an Indenone ist die Übertragung auf andere Indenone für die Darstellung einiger biologisch aktiver Substanzen denkbar. Formale Synthesen für drei Beispiele sind Schema 87 zu entnehmen. Auf diesem Wege sollte die Funktionalisierung von Indenonen als Bausteine einer Reihe von biologisch aktiver Verbindungen gelingen.



Schema 87: Vorschläge für die Anwendung der enantioselektiven 1,4-Addition in der formalen Synthese biologisch aktiver Indanone.[146-148]

Indanon **141** wurde anschließend *α*-allyliert, wodurch Indanon **143** erhalten wurde. Auch nach umfassenden Untersuchungen konnte dabei weder die doppelte Allylierung zu Indanon **144**, noch die Anfälligkeit der styrylischen Doppelbindung für Isomerisierungen unterbunden werden. Eine darauffolgende *α*-Hydroxylierung von **143** und Ringschlussmetathese lieferte *α*-Hydroxyketon **155**. Zudem konnte das nicht hydroxylierte tricyclische Keton **154** aus Indanon **143** durch *trans*→*cis* Isomerisierung an C2 und Ringschlussmetathese als untrennbares Gemisch mit **143** erhalten werden. Das Einführen des Alkohols an C9 hin zu **155** verblieb für Keton **154** jedoch erfolglos. Die anschließende substratkontrollierte Reduktion von **155** an C8 lieferte *trans*-Diol **158** mit einer Diastereoselektivität von *d.r.* >15:1. Durch Methylierung des Diols wurde das Cyclopenten **162** erhalten, das dann epoxidiert werden konnte. Die regioselektive Epoxidöffnung mit NaSePh an C11, gefolgt von einer oxidativen Eliminierung ergab Allylalkohol **174**. Dieser konnte anschließend durch *syn*-Eliminierung eines *in situ* erzeugten Triflats in das Cyclopentadien **79** überführt werden (Schema 88). Alternative Routen zur doppelten Eliminierung an Additionsprodukten von Cyclopenten **162** hin zu Dien **79** blieben erfolglos. Aufgrund der beobachteten Instabilität

diverser Intermediate in der Synthese von Cyclopentadien **79** wurde die Anzahl der chromatografischen Reinigungen ausgehend von Indanon **141** auf drei über neun Stufen reduziert.



Schema 88: Synthese des Benzodihydropentalens **79** ausgehend von Keton **147**.

Insgesamt konnte in der Synthese von Cyclopentadien **79** die Verwendung von Schutzgruppen oder nicht zielführenden Redox-Operationen minimiert werden. BARANs Definition der idealen Synthese entsprechend (Gleichung 2) konnte bei acht strategischen Bindungsknüpfungen und einer Reduktion bei zwölf gesamten Stufen 75% Idealität für den Aufbau von Cyclopentadien **79** ausgehend von Aldehyd **92** erreicht werden.

$$\%\, Idealität = \frac{(Anzahl\ der\ Bindungknüpfungen)+(Anzahl\ strategischer\ Redox-Reaktionen)}{(Anzahl\ der\ gesamten\ Stufen)} * 100$$

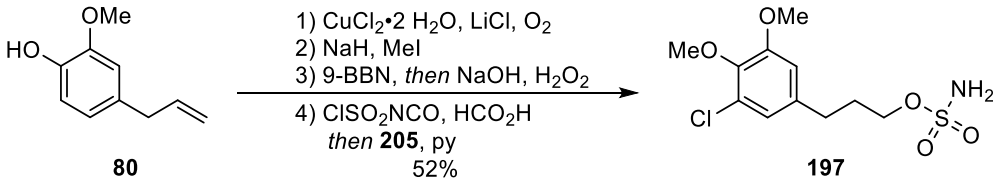
Gleichung 2: BARANs Definition der idealen Synthese.

Durch die gewinkelte Geometrie von Ring C des tricyclischen Ketons **155** und seiner Folgeverbindungen konnte zudem ein hohes Maß an Regio- und Diastereoselektivität bei den Operationen zum Aufbau des Diens **79** beobachtet werden. Dies könnte sich vor allem für den Aufbau der tricyclischen Systeme einer Reihe von ähnlich strukturierten Naturstoffgerüsten als nützlich erweisen. Die Strategie zum Aufbau des Cyclopentdiens ausgehend von Cyclopentenen sollte zudem auch auf andere Systeme übertragbar sein.

Synthese der Aminosäure 59

Die Synthese der Aminosäure **81** begann mit der Oxychlorierung von Eugenol (**80**) nach einer Vorschrift von GUSEVSKAYA. Durch anschließende Schützung des Phenols, Hydroborierung des Olefins mit oxidativer Aufarbeitung und Sulfamoylierung des resultierenden Alkohols konnte Sulfamat **197** in 52% über vier Stufen als Substrat für die Rhodium-katalysierte CH-Aminierung dargestellt werden (Schema 89). Über eine analoge Sequenz wurde zudem

das TBS-geschützte Sulfamat **178** erhalten, welches allerdings nicht zur entsprechenden Aminosäure oxidiert werden konnte.

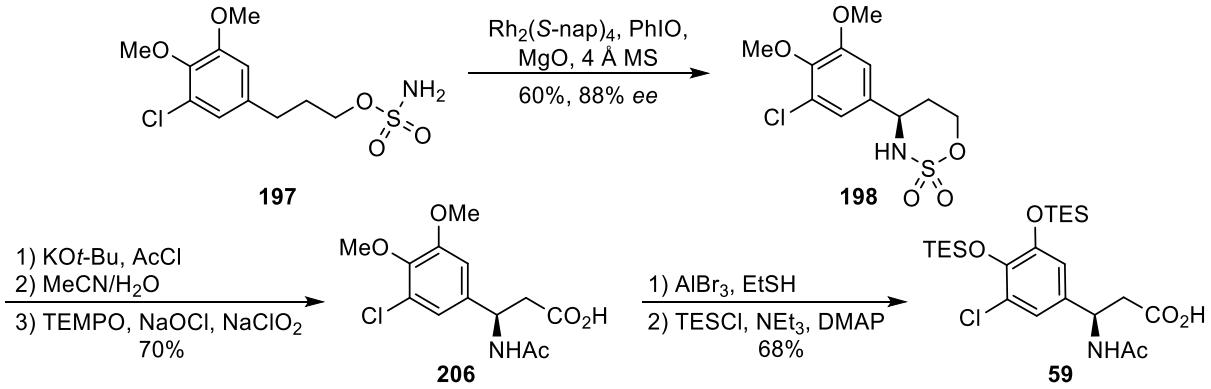


80 **197**

Schema 89: Synthese des Sulfamats **197** ausgehend von Eugenol (**80**).

Sulfamat **197** konnte anschließend unter Rh_2(*S*-nap)$_4$-Katalyse via Nitreninsertion nach DU BOIS in 60% Ausbeute mit 88% *ee* in das Oxathiazinan **198** überführt werden, dessen Struktur durch Kristallstrukturanalyse bestätigt werden konnte. Die Wahl des Oxidationsmittels war dabei von entscheidender Bedeutung. Obwohl unter Verwendung von $PhI(OPiv)_2$ Oxazinan **198** in quantitativer Ausbeute erhalten werden konnte, führte vermutlich ein kontinuierlicher Ligandenaustausch der Carboxylatreste mit dem Katalysator zu stark verminderten Enantiomerenüberschüssen.

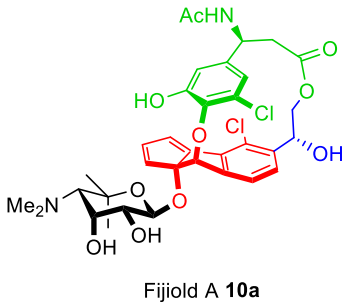
Durch Acetylierung von **198**, gefolgt von der Öffnung des Oxathiazinan-Rings durch Wasser und anschließender PINNICK-Oxidation des resultierenden Aminoalkohols, wurde Aminosäure **206** erhalten. Diese wurde durch Entschützen des Catechols und nachgelagerte TES-Schützung in CRAMER`s Aminosäure-Intermediat **59** überführt. So gelang die Synthese von Aminosäure **59** ausgehend von Eugenol in 15% Ausbeute über acht Stufen mit 88% *ee*. Dafür mussten ausgehend von ausgesprochen billigem Startmaterial keine C-C Bindungen geknüpft werden, was eine Synthese von **59** im Gramm-Maßstab ermöglichen sollte (Schema 90).



197 **198** **206** **59**

Schema 90: Synthese von CRAMERs Aminosäure Derivat **59** ausgehend von Sulfamat **197**.

Für die Synthese der Aminosäure **59** wurde mit drei Konstruktionsreaktionen und zwei essentiellen Redox-Reaktionen bei acht Stufen insgesamt eine prozentuale Idealität von 63% errechnet.



Fijiold A **10a**

Abbildung 19: Zusammenfassung der synthetisierten Bausteine.

Zusammengefasst konnte ein neuer stereoselektiver Zugang zur Benzodihydropentalen Struktur (rot) und der Aminosäure (grün) entwickelt werden (Abbildung 19). Zudem gelang es MESCH in seiner Bachelorarbeit, ausgehend von einem Methylether, die Diol-Seitenkette an einem Testsystem aufzubauen (blau). In Kombination mit der literaturbekannten Synthese des Aminozuckers (schwarz, Kapitel 1.5.1) sollte so ein neuer Zugang zu Fijiolid A gelingen.

8.1 Experimental Part – General Methods and Materials

All commercially available reagents and reactants were used without purification unless otherwise noted. The following reagents were prepared/dried as stated:

Phosphate puffer pH 7: 135.5 g KH_2PO_4 and 162.0 g $Na_2HPO_4 \cdot 2\,H_2O$ were dissolved in 1 L distilled H_2O.

NEt_3, *i*-Pr_2NH: Refluxing in the presence of CaH_2 with subsequent distillation under Ar-atmosphere.

All solvents were distilled by rotary evaporation. Solvents for non-aqueous reactions were dried as follows prior to use:

1,4-dioxane 99.5%, *Extra Dry*, stored over molecular sieves, purchased from *Acros Organics*, used without further purification.

CH_2Cl_2 was refluxed and distilled from CaH_2 under Ar-atmosphere.

Cyclohexane 99.8%, *Extra Dry*, stored over molecular sieves, purchased from *Acros Organics*, used without further purification.

DMF HPLC-grade, purchased from *Acros Organics*, used without further purification.

MeCN HPLC-grade, purchased from *Acros Organics*, used without further purification.

MeOH was dried by refluxing with Mg-turnings (5g/L) and subsequent distillation under Ar-atmosphere.

THF was dried with KOH and subsequently distilled from sodium/benzophenone. respectively from Solvona® under Ar-atmosphere.

Toluene was refluxed in the presence of Na with subsequent distillation under Ar-atmosphere.

All non-aqueous reactions were carried out using flame-dried glassware under argon atmosphere.

Reactions were monitored by thin layer chromatography (TLC) using *Merck* Silica Gel 60 F_{254}-plates and visualized by fluorescence quenching under UV-light. In addition, TLC-plates were stained using a $CeSO_4$/phosphomolybdic acid stain. Chromatographic purification of products was performed on *Merck* Silica Gel 60 (230-400 mesh) unless otherwise noted using

a forced flow of eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure and by exposing to high vacuum at room temperature if necessary.

NMR spectra were recorded on a *Bruker* AV II 300 MHz, AV III 500 MHz and AV III HD 500 MHz spectrometer at room temperature. Chemical shifts are reported in ppm with the solvent resonance as internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet.

Mass spectra were recorded by the mass service department of the Philipps-University Marburg. HR-ESI mass spectra were acquired with a LTQ-FT mass spectrometer (*Thermo Fischer Scientific*). The resolution was set to 100.000.

IR spectra were recorded on a *Bruker* IFS 200 spectrometer. The absorption bands are given in wave numbers (cm^{-1}), intensities are reported as follows: s = strong, m = medium, w = weak, br = broad band.

Melting points were determined on a *Mettler Toledo* MP70 using one end closed capillary tubes.

Optical rotations were determined at 25 °C for the Na-D wavelength (589 nm) with a *Krüss* P8000-T polarimeter.

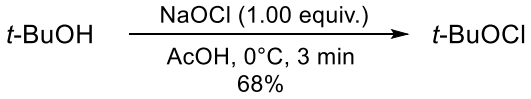
Light induced isomerizations were performed using High Power single chip LED H2A1-H365-r4 and H2A1-H435 from *Roithner Lasertechnik GmbH*.

HPLC measurements were performed using a 1200 combination from *Agilent Technologies* (G1312B Quat-pump, G1329B ALS-sampler, G1316A thermostat, G4212B Diodenarray-detector).

X-ray crystallographic analysis were performed by the X-ray crystallographic department of the Philipps-University Marburg on a *Bruker* D8 QUEST or STOE STADIVARI. Structures were solved by direct methods; all atoms were refined anisotropically (except H).

8.2 Synthetic Procedures for Preparation of the Benzodihydropentalene core

tert-Butyl hypochlorite



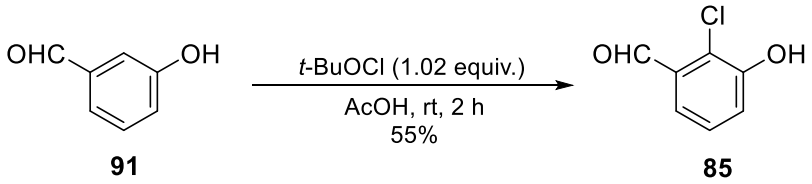
t-Butanol [M 74.12; ρ 0.78]	1.00 equiv.	558 mmol	52.4 mL
NaOCl [M 74.44; 12wt%]	1.00 equiv.	558 mmol	285 mL
AcOH [M 60.05; ρ 1.05]	1.10 equiv.	614 mmol	35.1 mL

At 0 °C *t*-BuOH (52.4 mL, 558 mmol, 1.00 equiv.) and AcOH (35.1 mL, 614 mmol, 1.10 equiv.) were added to aq. NaOCl (285 mL, 558 mmol, 12wt%, 1.00 equiv.) and the mixture was stirred for 3 min. The layers were separated, the org. layer was washed with H_2O (2x50 mL) and 10% aq. Na_2CO_3 (2x50 mL) and filtrated over $CaCl_2$ to yield *t*-BuOCl (41.1 g, 379 mmol, 68%) as yellow liquid.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.33 (s, 9 H, *t*-Bu) ppm.

The spectroscopic data obtained matched that reported in the literature.[150]

2-Chloro-3-hydroxybenzaldehyde 85



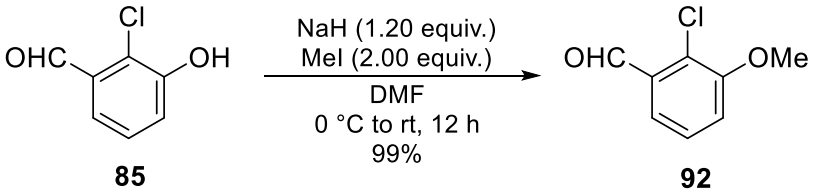
Aldehyde **91** [M 122.12]	1.00 equiv.	358 mmol	43.7 g
t-BuOCl [M 108.57; ρ 0.96]	1.02 equiv.	370 mmol	40.6 g

Aldehyde **91** (43.7 g, 358 mmol, 1.00 equiv.) was dissolved in aq. AcOH (100 mL, 90%) at rt. *t*-BuOCl (40.6 g, 370 mmol, 1.02 equiv.) was added dropwise and the mixture was stirred at rt for 2 h. After filtration the precipitate was recrystallized from 50% aq. AcOH to yield aldehyde **85** (30.8 g, 197 mmol, 55%) as colorless crystals.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 5.86 (s_{br}, 1 H, OH), 7.22-7.31 (m, 2 H, Ar), 7.48 (dd, *J* = 2.2, 7.1 Hz, 1 H, Ar), 10.35 (s, 1 H, CHO) ppm.

The spectroscopic data of **85** matched that reported in the literature.[41]

2-Chloro-3-methoxybenzaldehyde 92



Phenol **85** [M 122.12]	1.00 equiv.	31.9 mmol	5.00 g
NaH [60wt%, mineral oil; M 24.00]	1.20 equiv.	38.3 mmol	1.53 g
MeI [M 141.94; ρ 2.28]	2.00 equiv.	63.9 mmol	3.98 mL

Under Ar-atmosphere phenol **85** (5.00 g, 31.9 mmol, 1.00 equiv.) was dissolved in DMF (400 mL). At 0 °C NaH (1.53 g, 38.3 mmol, 60wt% in mineral oil, 1.20 equiv.) was added. After 15 min MeI (3.98 mL, 63.9 mmol, 2.00 equiv.) was added and the mixture was stirred at rt for 12 h. The reaction was quenched by the addition H_2O (200 mL), extracted with cyclohexane (3x100 mL), washed with brine (150 mL), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 8:1) methylated phenol **92** (5.44 g, 31.9 mmol, 99%) was obtained as colorless solid.

TLC: R_f = 0.28 (*n*-pentane/EtOAc 8:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.96 (s, 3 H, OMe), 7.16 (dd, *J* = 1.4, 8.0 Hz, 1 H, Ar), 7.34 (t, *J* = 8.0 Hz, 1 H, Ar), 7.54 (dd, *J* = 1.4 Hz, 8.0 Hz, 1 H, Ar), 10.53 (s, 1 H, CHO) ppm.

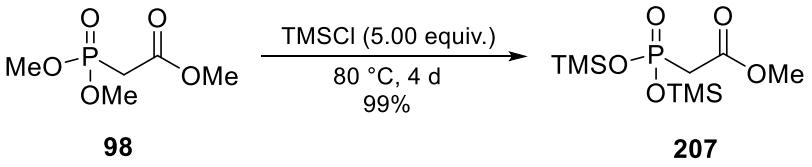
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 56.7 (OMe), 117.2 (Ar), 120.9 (Ar), 126.9 (Ar), 127.7 (Ar), 133.8 (Ar), 155.7 (Ar), 190.2 (CHO) ppm.

HR-MS: (ESI+); m/z calc. for $C_8H_7ClO_2Na$ $[M\text{-}Na]^+$ 193.0027, found 193.0027.

FT-IR: (neat); ϑ̃ = 2923 (m), 2853 (w), 1729 (w), 1696 (m), 1574 (m), 1470 (m), 1452 (w), 1434 (m), 1384 (w), 1359 (w), 1304 (w), 1272 (s), 1241 (w), 1193 (w), 1154 (w), 1113 (w), 1051 (m), 990 (w), 934 (w), 904 (w), 776 (m), 714 (w), 616 (w) cm^{-1}.

m.p.: 38 °C (EtOAc).

Methyl 2-(bis((trimethylsilyl)oxy)phosphoryl)acetate 207



98 **207**

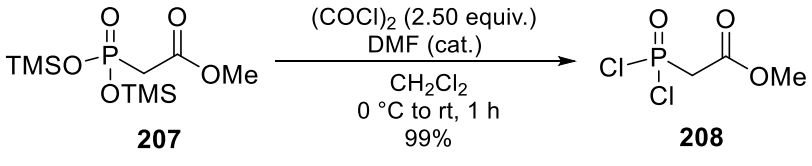
Phosphono acetate **98** [M 182.11]	1.00 equiv.	60.0 mmol	9.60 mL
TMSCl [M 108.64; ρ 0.85]	5.00 equiv.	300 mmol	38.1 mL

Under Ar-atmosphere phosphono acetate **98** (9.60 mL, 60.0 mmol, 1.00 equiv.) and freshly distilled TMSCl (38.1 mL, 300 mmol, 5.00 equiv.) were stirred at 80 °C for 4 d. All volatile compounds were removed under reduced pressure and the crude silylated phosphono acetate **207** was directly used for the next step without further purification.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.30 (s, 18 H, TMS), 2.89 (d, *J* = 22.5 Hz, 2 H, CH_2), 3.71 (s, 3 H, OMe) ppm.

The spectrum of **207** matched that reported in the literature.[46]

Methyl 2-(dichlorophosphoryl)acetate 208



207 **208**

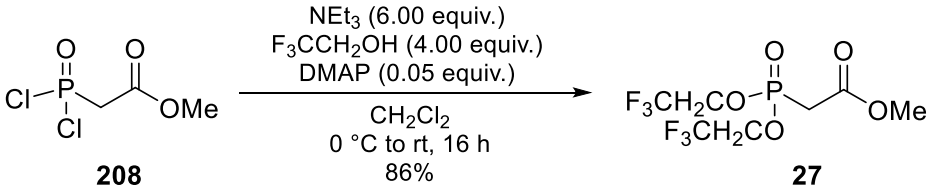
Silylated phosphono acetate **207** [M 298.42]	1.00 equiv.	60.0 mmol	17.9 g
Oxalyl chloride [M 126.93; ρ 1.48]	2.50 equiv.	150 mmol	13.1 mL
DMF [M 73.10, ρ 0.95]	0.01 equiv.		

Under Ar-atmosphere crude silylated phosphono acetate **207** (17.9 g, 60.0 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (120 mL). At 0 °C oxalyl chloride (13.1 mL, 150 mmol, 2.50 equiv.) and catalytic amounts of DMF (1 drop) were added slowly. The mixture was stirred at rt for 1 h, before all volatile compounds were removed *in vacuo*. The crude dichloride **208** was used for the next step without further purification.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.75 (d, *J* = 19.1 Hz, 2 H, CH_2), 3.84 (s, 3 H, OMe) ppm.

The spectrum of **208** matched that reported in the literature.[46]

Methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetate 27



Dichloride **208** [M 190.94]	1.00 equiv.	60.0 mmol	11.5 g
NEt_3 [M 101.19; ρ 0.73]	6.00 equiv.	360 mmol	50.4 mL
Trifluoroethanol [M 100.04; ρ 1.38]	4.00 equiv.	240 mmol	17.4 mL
DMAP [M 122.17]	0.05 equiv.	1.20 mmol	144 mg

Under Ar-atmosphere crude dichloride **208** (11.5 g, 60.0 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (60 mL). At 0 °C NEt_3 (50.4 mL, 360 mmol, 6.00 equiv.) and 2,2,2-trifluoroethanol (17.4 mL, 240 mmol, 4.00 equiv.) in CH_2Cl_2 (60 mL) were added slowly. Catalytic amounts of DMAP (144 mg, 1.20 mmol, 0.05 equiv.) were added and the mixture was stirred at rt for 16 h. The mixture was diluted with CH_2Cl_2 (1.00 L), washed with brine (450 mL), dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo*. After column

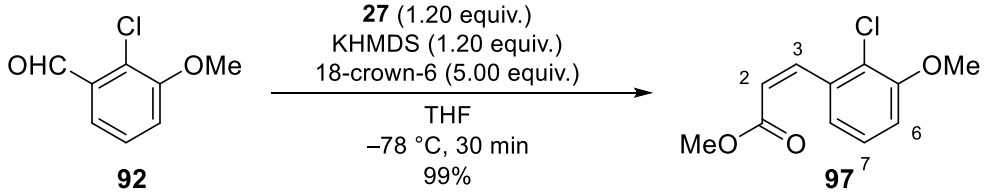
chromatography (*n*-pentane/EtOAc 2:1) phosphono acetate **27** (16.3 g, 51.2 mmol, 86%) was obtained as colorless oil.

TLC: R_f = 0.27 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.16 (d, *J* = 21.2 Hz, 2 H, CH_2), 3.96 (s, 3 H, OMe), 4.46 (m, 4 H, CH_2OP) ppm.

The spectroscopic data of **27** matched that reported in the literature.[46]

(*Z*)-2-Chloro-3-methoxy cinnamic acid methyl ester 97



Aldehyde **92** [M 170.59]	1.00 equiv.	18.2 mmol	3.10 g
Phosphono acetate **27** [M 318.19; ρ 1.50]	1.20 equiv.	22.7 mmol	4.80 mL
KHMDS [0.5 M, toluene; M 199.48]	1.20 equiv.	22.7 mmol	45.4 mL
18-crown-6 [M 264.32]	5.00 equiv.	114 mmol	30.0 g

Under Ar-atmosphere phosphono acetate **27** (4.80 mL, 22.7 mmol, 1.20 equiv.) and 18-crown-6 (30.0 g, 114 mmol, 5.00 equiv.) were dissolved in THF (250 mL). At –78 °C KHMDS (45.4 mL, 22.7 mmol, 0.5 M in toluene, 1.20 equiv.) and aldehyde **92** (3.10 g, 18.2 mmol, 1.00 equiv.) were added and the mixture was stirred for 30 min. Sat. aq. NH_4Cl (100 mL) was added to the reaction mixture, it was slowly warmed to rt, extracted with Et_2O (3x100 mL), the combined org. layers were dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 8:1) *α*,*β*-unsaturated ester **97** (4.10 g, 18.1 mmol, 99%) was obtained as colorless oil.

TLC: R_f = 0.23 (*n*-pentane/EtOAc 8:1).

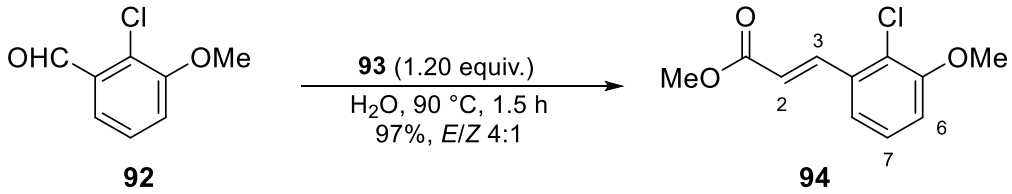
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.65 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 6.09 (d, *J* = 12.2 Hz, 1 H, 2-H), 6.91 (d, *J* = 8.0 Hz, 1 H, Ar), 7.06 (d, *J* = 8.0 Hz, 1 H, Ar), 7.15 (d, *J* = 12.2 Hz, 1 H, 3-H), 7.20 (t, *J* = 8.0 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 51.4 (OMe), 56.7 (OMe), 112.0 (Ar), 121.7 (C2), 121.8 (Ar), 122.6 (Ar), 126.6 (Ar), 135.7 (Ar), 140.9 (C3), 155.2 (Ar), 166.2 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{11}H_{11}ClO_3Na$ $[M\text{-}Na]^+$ 249.0289, found 249.0285.

FT-IR: (neat); ϑ̃ = 3214 (w), 2918 (w), 2853 (w), 1729 (m), 1640 (w), 1572 (w), 1471 (w), 1453 (w), 1433 (m), 1352 (w), 1267 (m), 1215 (w), 1164 (m), 1090 (w), 1066 (s), 960 (m), 903 (w), 832 (m), 777 (w), 721 (w), 654 (w), 614 (w), 554 (w), 527 (w), 470 (w), 445 (w) cm^{-1}.

(*E*)-2-Chloro-3-methoxy cinnamic acid methyl ester 94



Aldehyde **92** [M 170.59]	1.00 equiv.	10.0 mmol	1.70 g
Ylide **93** [M 334.35]	1.20 equiv.	12.0 mmol	3.99 g

Ylide **93** (3.99 g, 12.0 mmol, 1.20 equiv.) was dissolved in H_2O (80 mL), aldehyde **92** (1.70 g, 10.0 mmol, 1.00 equiv.) was added and the mixture was heated to 90 °C for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (2x20 mL), the combined org. layers were dried over $MgSO_4$, filtrated and all volatile compounds were removed under reduced pressure. After

column chromatography (*n*-pentane/EtOAc 8:1) *α*,*β*-unsaturated ester **94** (2.20 g, 9.71 mmol, 97%, *E*/*Z* 4:1) was obtained as colorless solid.

TLC: R_f = 0.23 (*n*-pentane/EtOAc 8:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.82 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 6.42 (d, *J* = 16.0 Hz, 1 H, 2-H), 6.94-6.97 (m, 1 H, Ar), 7.23-7.25 (m, 2 H, Ar), 8.14 (d, *J* = 16.0 Hz, 1 H, 3-H) ppm.

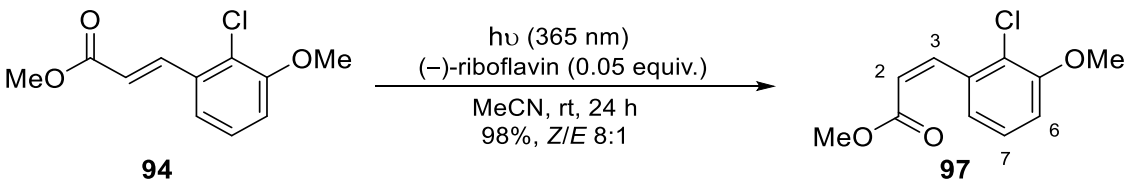
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 52.0 (OMe), 56.5 (OMe), 113.1 (Ar), 119.5 (C2), 121.1 (Ar), 126.6 (Ar), 127.4 (Ar), 134.4 (Ar), 141.0 (C3), 155.8 (Ar), 167.0 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{11}H_{11}ClO_3Na$ $[M-Na]^+$ 249.0289, found 249.0285.

FT-IR: (neat); ῡ = 2923 (m), 2949 (w), 2842 (w), 1716 (s), 1637 (w), 1571 (m), 1471 (w), 1430 (m), 1268 (s), 1170 (m), 1111 (w), 1070 (m), 1046 (w), 1015 (w), 981 (w), 941 (w), 864 (w), 826 (w), 783 (m), 735 (w), 702 (w), 652 (w) cm^{-1}.

m.p.: 74.6 °C (EtOAc).

Isomerization of (*E*)-2-chloro-3-methoxy cinnamic acid methyl ester 94



94 **97**

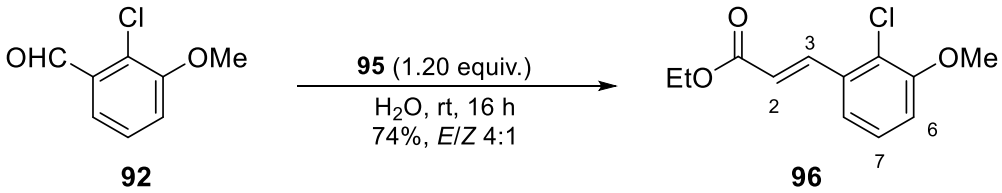
Cinnamic ester **94** [M 226.66]	1.00 equiv.	11.0 mmol	2.50 g
(–)-riboflavin [M 376.37]	0.05 equiv.	0.55 mmol	207 mg

Under Ar-atmosphere ester **94** (2.50 g, 11.0 mmol, 1.00 equiv.) and (–)-riboflavin (207 mg, 0.55 mmol, 0.05 equiv.) were dissolved in MeCN (300 mL) and stirred under irradiation with UV-light (365 nm) at rt for 24 h. The reaction mixture was filtrated through a plug of silica and concentrated *in vacuo* to yield cinnamic acid ester **97** (2.45 g, 11.0 mmol, 98%, *Z*/*E* 8:1) as colorless oil.

The *Z*/*E* ratio was determined by comparing the integrals of the olefinic protons at C2.

The spectroscopic data matched that of **8.2.7**.

(*E*)-2-Chloro-3-methoxy cinnamic acid ethyl ester 96



Aldehyde **92** [M 170.59]	1.00 equiv.	1.91 mmol	325 mg
Ylide **95** [M 334.35]	1.20 equiv.	2.29 mmol	796 mg

Ylide **95** (796 mg, 2.29 mmol, 1.20 equiv.) was dissolved in H_2O (15 mL), aldehyde **92** (325 mg, 1.91 mmol, 1.00 equiv.) was added and the mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (2x2 mL), the combined org. layers were dried over $MgSO_4$, filtrated and all volatile compounds were removed under reduced pressure. After column chromatography (*n*-pentane/EtOAc 8:1) *α*,*β*-unsaturated ester **96** (336 mg, 1.39 mmol, 74%, *E*/*Z* 4:1) was obtained as colorless oil.

TLC: R_f = 0.38 (*n*-pentane/EtOAc 8:1).

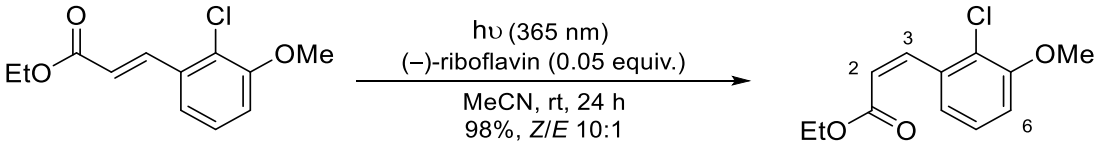
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.35 (t, *J* = 7.1 Hz, 3 H, Me), 3.92 (s, 3 H, OMe), 4.28 (q, *J* = 7.1 Hz, 2 H, OCH_2), 6.42 (d, *J* = 16.0 Hz, 1 H, 2-H), 6.95-6.97 (m, 1 H, Ar), 7.23-7.25 (m, 2 H, Ar), 8.13 (d, *J* = 16.0 Hz, 1 H, 3-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 14.5 (Me), 56.5 (OMe), 60.8 (OCH_2), 113.0 (Ar), 119.5 (C2), 121.5 (Ar), 123.6 (Ar), 127.3 (Ar), 134.4 (Ar), 140.7 (C3), 155.7 (Ar), 166.6 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{12}H_{13}ClO_3$ Na $[M\text{-}Na]^+$ 249.0445, found 263.0439.

FT-IR: (neat); ῡ = 3056 (w), 2981 (w), 1717 (m), 1638 (w), 1591 (w), 1570 (w), 1472 (w), 1436 (m), 1403 (w), 1270 (m), 1194 (s), 1118 (m), 1069 (w), 1031 (w), 997 (w), 832 (w), 785 (w), 751 (w), 721 (s), 696 (m), 644 (w), 541 (s), 506 (w), 438 (w) cm^{-1}.

Isomerization of (*E*)-2-chloro-3-methoxy cinnamic acid ethyl ester 209



96 **209**

Cinnamic ester **96** [M 240.68]	1.00 equiv.	1.33 mmol	321 mg
(-)-riboflavin [M 376.37]	0.05 equiv.	66.7 µmol	25.1 mg

Under Ar-atmosphere ester **96** (321 mg, 1.33 mmol, 1.00 equiv.) and (–)-riboflavin (25.1 mg, 66.7 µmol, 0.05 equiv.) were dissolved in MeCN (30 mL) and stirred under irradiation with UV-light (365 nm) at rt for 24 h. The reaction mixture was filtrated through a plug of silica and concentrated *in vacuo* to yield cinnamic acid ester **209** (316 mg, 1.31 mmol, 98%, *Z*/*E* 10:1) as colorless oil.

The *Z*/*E* ratio was determined by comparing the integrals of the olefinic protons at C2.

TLC: R_f = 0.38 (*n*-pentane/EtOAc 8:1).

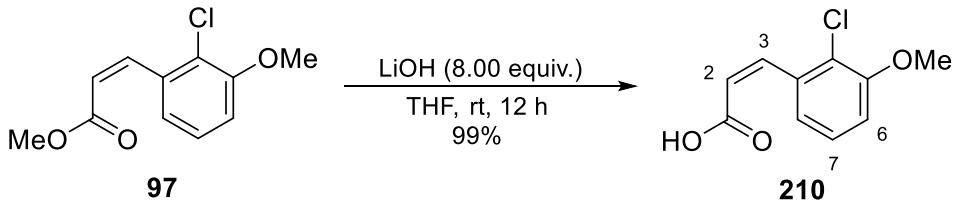
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.17 (t, *J* = 7.1 Hz, 3 H, Me), 3.91 (s, 3 H, OMe), 4.11 (q, *J* = 7.1 Hz, 2 H, OCH_2), 6.08 (d, *J* = 12.2 Hz, 1 H, 2-H), 6.91 (dd, *J* = 1.4, 8.0 Hz, 1 H, Ar), 7.06 (dd, *J* = 1.4, 8.0 Hz, 1 H, Ar), 7.13 (d, *J* = 12.2 Hz, 1 H, 3-H), 7.19 (dd, *J* = 8.0, 8.0 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 14.1 (Me), 56.4 (OMe), 60.4 (OCH_2), 111.9 (Ar), 121.7 (C2), 122.3 (Ar), 122.6 (Ar), 126.5 (Ar), 135.8 (Ar), 140.4 (C3), 155.1 (Ar), 165.8 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{12}H_{13}ClO_3Na$ $[M-Na]^+$ 249.0445, found 263.0442.

FT-IR: (neat); ῦ = 2980 (m), 2938 (w), 2841 (w), 1721 (s), 1638 (w), 1592 (w), 1570 (m), 1472 (s), 1432 (m), 1404 (w), 1386 (w), 1293 (w), 1269 (s), 1208 (w), 1181 (s), 1109 (w), 1069 (s), 1048 (w), 1031 (w), 982 (w), 955 (w), 899 (w), 831 (w), 783 (m), 723 (w), 639 (w) cm^{-1}.

(*Z*)-2-Chloro-3-methoxy cinnamic acid 210



97 **210**

Cinnamic ester **97** [M 226.66]	1.00 equiv.	15.4 mmol	3.50 g
LiOH [2.0 M, aq.; M 23.95]	8.00 equiv.	123 mmol	61.8 mL

Ester **97** (3.50 g, 15.4 mmol, 1.00 equiv.) was dissolved in THF (40 mL), aq. LiOH (61.8 mL, 123 mmol, 2.0 M, 8.00 equiv.) was added and the mixture was stirred at rt for 12 h. The reaction mixture was acidified with aq. HCl (1.0 M) to reach pH = 1, it was diluted with CH_2Cl_2 (50 mL) and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (2x25 mL), the combined org. layers were dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo* to yield acid **210** (3.28 g, 15.4 mmol, 99%) as pale-yellow solid. The crude product was directly used for the next step without further purification.

TLC: R_f = 0.25 (CH_2Cl_2/MeOH 15:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.91 (s, 3 H, OMe), 6.07 (d, *J* = 12.2 Hz, 1 H, 2-H), 6.91 (dd, *J* = 1.5, 8.0 Hz, 1 H, Ar), 7.06 (d, *J* = 8.0 Hz, 1 H, Ar), 7.17 (d, *J* = 8.0 Hz, 1 H, Ar), 7.23 (d, *J* = 12.0 Hz, 1 H, 3-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 56.4 (OMe), 112.2 (Ar), 121.0 (C2), 121.7 (Ar), 122.7 (Ar), 126.8 (Ar), 135.3 (Ar), 143.0 (C3), 155.1 (Ar), 170.1 (C1) ppm.

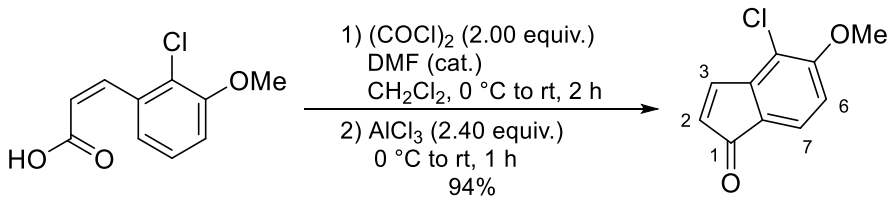
HR-MS: (ESI+); m/z calc. for $C_{10}H_9ClO_3Na$ $[M\text{-}Na]^+$ 235.0132, found 235.0128.

FT-IR: (neat); $\tilde{\upsilon}$ = 2968 (m), 2844 (w), 2740 (w), 2561 (w), 1709 (m), 1636 (m), 1571 (m), 1474 (m), 1456 (w), 1437 (w), 1420 (w), 1291 (w), 1270 (m), 1240 (s), 1211 (w), 1074 (m), 1048 (w), 913 (w), 826 (w), 802 (w), 763 (w), 720 (w), 643 (w), 614 (w) cm^{-1}.

m.p.: 163 °C (CH_2Cl_2).

When ethyl ester **209** (310 mg, 1.29 mmol) was saponificated under analogous conditions 270 mg (1.27 mmol, 99%) of cinnamic acid **210** were obtained.

4-Chloro-5-methoxyinden-1-one 84



210 **84**

Acid **210** [M 212.63]	1.00 equiv.	6.58 mmol	1.40 g
Oxalyl chloride [M 126.93; ρ 1.48]	2.50 equiv.	16.5 mmol	1.41 mL
DMF [M 73.10, ρ 0.95]	0.01 equiv.		
$AlCl_3$ [M 133.34]	2.40 equiv.	15.8 mmol	2.11 g

Under Ar-atmosphere crude acid **210** (1.40 g, 6.58 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL). At 0 °C oxalyl chloride (1.41 mL, 16.5 mmol, 2.00 equiv.) and DMF (1 drop) were added and the mixture was stirred at rt for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), $AlCl_3$ (2.11 g, 15.8 mmol, 2.40 equiv.) was added at 0 °C and it was further stirred at rt for 1 h. The mixture was diluted with sat. aq. ROCHELLE salt (150 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x30 mL) and the org. layer was washed with aq. NaOH (50 mL, 0.1 M) and brine (75 mL). The org. layer was dried over $MgSO_4$, filtrated and was concentrated *in vacuo*. After filtration over a short pad of neutral aluminum oxide (activity I) indenone **84** (1.20 g, 6.17 mmol, 94%) was obtained as yellow solid.

TLC: R_f = 0.25 (*n*-pentane/EtOAc 8:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.94 (s, 3 H, OMe), 5.99 (d, *J* = 6.0 Hz, 1 H, 2-H), 6.66 (d, *J* = 8.0 Hz, 1 H, 6-H), 7.33 (dd, *J* = 0.9, 8.0 Hz, 1 H, 7-H), 7.69 (dd, *J* = 0.9, 6.0 Hz, 1 H, 3-H) ppm.

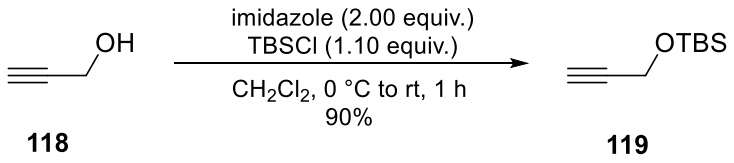
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 56.8 (OMe), 109.8 (C6), 118.0 (Ar), 122.5 (C2), 124.2 (7-H), 129.4 (Ar), 144.6 (Ar), 145.6 (C3), 160.0 (Ar), 196.4 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{10}H_8ClO_2H$ $[M-H]^+$ 195.0207, found 195.0206.

FT-IR: (neat); $\tilde{\upsilon}$ = 2941 (w), 2846 (w), 1711 (s), 1594 (s), 1571 (w), 1477 (m), 1437 (w), 1329 (m), 1284 (s), 1187 (w), 1166 (w), 1131 (w), 1061 (m), 970 (w), 921 (w), 882 (w), 824 (w), 794 (w), 763 (w), 733 (w), 645 (w), 610 (w), 509 (w) cm^{-1}.

m.p.: 240 °C decomposition (CH_2Cl_2).

8.2.2 *tert*-Butyl dimethyl(prop-2-yn-1-yloxy)silane 119



Propargyl alcohol **118** [M 56.06; ρ 0.97]	1.00 equiv.	89.1 mmol	5.15 mL
Imidazole [68.08]	2.00 equiv.	178 mmol	12.1 g
TBSCl [M 150.72]	1.10 equiv.	99.0 mmol	14.9 g

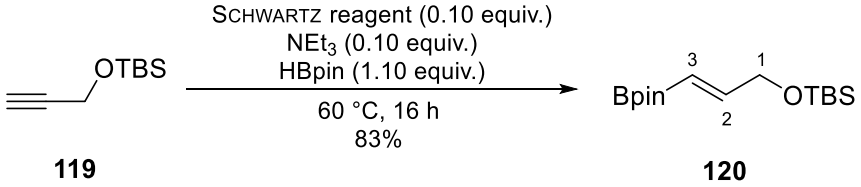
Under Ar-atmosphere propargylic alcohol **118** (5.15 mL, 89.1 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (80 mL). At 0 °C imidazole (12.1 g, 178 mmol, 2.00 equiv.) and TBSCl (14.9 g, 99.0 mmol, 1.10 equiv.) were added and the mixture was stirred at rt for 1 h. The reaction mixture was washed with H_2O (100 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. After column chromatography (*n*-pentane/EtOAc 40:1) TBS-protected propargylic alcohol **119** (13.6 g, 79.8 mmol, 90%) was isolated as colorless liquid.

TLC: R_f = 0.37 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.13 (s, 6 H, TBS), 0.91 (s, 9 H, TBS), 2.38 (t, *J* = 2.4 Hz, 1 H, CH), 4.31 (d, *J* = 2.4 Hz, 2 H, CH_2) ppm.

The spectroscopic data of **119** matched that reported in the literature.[151]

(*E*)-*tert*-Butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-oxy)silane 126



119 **120**

Propargyl alcohol **119** [M 170.32; ρ 0.84]	1.00 equiv.	14.7 mmol	2.50 mL
SCHWARTZ reagent [M 257.87]	0.10 equiv.	1.47 mmol	378 mg
NEt_3 [M 101.19; ρ 0.73]	0.10 equiv.	1.47 mmol	0.20 mL
Pinacolborane [M 127.98]	1.10 equiv.	15.4 mmol	1.97 mL

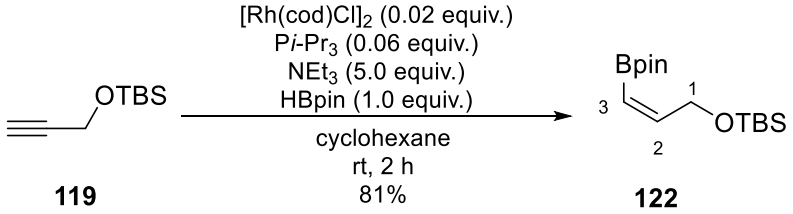
Under Ar-atmosphere TBS-protected propargylic alcohol **119** (2.50 mL, 14.7 mmol, 1.00 equiv.), SCHWARTZ reagent (378 mg, 1.47 mmol, 0.10 equiv.), NEt_3 (0.20 mL, 1.47 mmol, 0.10 equiv.) and pinacol borane (1.97 mL, 15.4 mmol, 1.10 equiv.) were stirred at 60 °C for 16 h. The reaction mixture was filtrated through a pad of silica to yield (*E*)-configured boronic pinacol ester **120** (3.40 g, 12.2 mmol, 83%) as yellow oil.

TLC: R_f = 0.50 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.06 (s, 6 H, TBS), 0.91 (s, 9 H, TBS), 1.27 (s, 12 H, Me), 4.25 (dd, *J* = 2.1, 3.6 Hz, 2 H, 1-H), 5.75 (dt, *J* = 2.1, 17.9 Hz, 1 H, 3-H), 6.68 (dt, *J* = 3.6, 17.9 Hz, 1 H, 2-H) ppm.

The spectroscopic data of **120** matched that reported in the literature.[83]

(*Z*)-*tert*-Butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) allyl)oxy)silane 122



Propargyl alcohol **119** [M 170.32; ρ 0.84]	1.20 equiv.	1.28 mmol	0.26 mL
$[Rh(cod)Cl]_2$ [M 493.08]	0.02 equiv.	16.0 µmol	7.90 mg
P*i*-Pr_3 [M 160.24; ρ 0.84]	0.06 equiv.	64.0 µmol	12.0 µL
NEt_3 [M 101.19; ρ 0.73]	5.00 equiv.	5.34 mmol	0.74 mL
Pinacolborane [M 127.98]	1.00 equiv.	1.07 mmol	0.16 mL

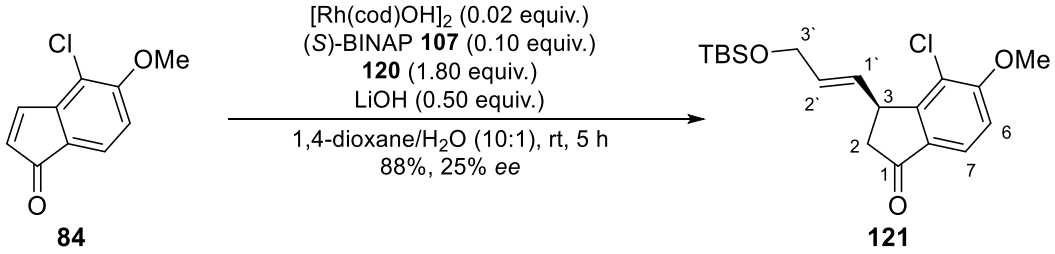
Under Ar-atmosphere $[Rh(cod)Cl]_2$ (7.90 mg, 16.0 µmol, 0.02 equiv.) was dissolved in cyclohexane (3 mL). P*i*-Pr_3 (12.0 µL, 6.40 µmol, 0.06 equiv.), NEt_3 (0.74 mL, 5.34 mmol, 5.00 equiv.) and pinacolborane (0.16 mL, 1.07 mmol 1.00 equiv.) were added and the mixture was stirred at rt for 30 min. TBS-protected propargylic alcohol **119** (0.26 mL, 1.29 mmol, 1.20 equiv.) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 20:1) (*Z*)-configured boronic pinacol ester **122** (242 mg, 0.87 mmol, 81%) was isolated as yellow-brown oil.

TLC: R_f = 0.50 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.07 (s, 6 H, TBS), 0.91 (s, 9 H, TBS), 1.26 (s, 12 H, Me), 4.50 (dd, *J* = 1.7, 6.1 Hz, 2 H, 1-H), 5.39 (dt, *J* = 1.7, 13.4 Hz, 1 H, 3-H), 6.51 (dt, *J* = 6.1, 13.4 Hz, 1 H, 2-H) ppm.

The spectroscopic data of **122** matched that reported in the literature.[84]

(*S*,*E*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-4-chloro-5-methoxy-2,3-dihydroinden-1-one 121



Indenone **84** [M 194.61]	1.00 equiv.	436 µmol	85.0 mg
$[Rh(cod)OH]_2$ [M 388.93]	0.02 equiv.	13.4 µmol	6.10 mg
(*S*)-BINAP **107** [M 622.67]	0.10 equiv.	67.0 µmol	41.7 mg
Boronic acid ester **120** [M 298.31]	1.80 equiv.	1.68 mmol	500 mg
$LiOH \cdot H_2O$ [M 31.96]	0.50 equiv.	335 µmol	14.1 mg

Under Ar-atmosphere $[Rh(cod)OH]_2$ (6.1 mg, 13.4 µmol, 0.02 equiv.), boronic acid ester **120** (500 mg, 1.68 mmol, 1.80 equiv.) and (*S*)-BINAP **107** (41.7 mg, 67.0 µmol, 0.10 equiv.) were stirred in degassed 1,4-dioxane/H_2O (2.2 mL, 10:1) at rt for 30 min. Indenone **84** (85.0 mg, 436 µmol, 1.00 equiv.) and $LiOH \cdot H_2O$ (14.1 mg, 335 µmol, 0.50 equiv.) were added and the reaction mixture was stirred at this temperature for 5 h. It was diluted with H_2O (5 mL), extracted with Et_2O (3x5 mL), dried over Na_2SO_4 and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) vinylated indanone **121** (142 mg, 387 µmol, 88%, 25% *ee*) was obtained as pale-yellow oil.

TLC: R_f = 0.15 (*n*-pentane/EtOAc 8:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.03 (s, 6 H, TBS), 0.88 (s, 6 H, TBS), 2.55 (dd, *J* = 2.1, 19.0 Hz, 1 H, 2-H_A), 2.99 (dd, *J* = 8.1, 19.0 Hz, 1 H, 2-H_B), 3.99 (s, 3 H, OMe), 4.09-4.17 (m, 3 H, 3-H, 3`-H), 5.68-5.64 (m, 2 H, 2`-H, 3`-H), 7.00 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.67 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

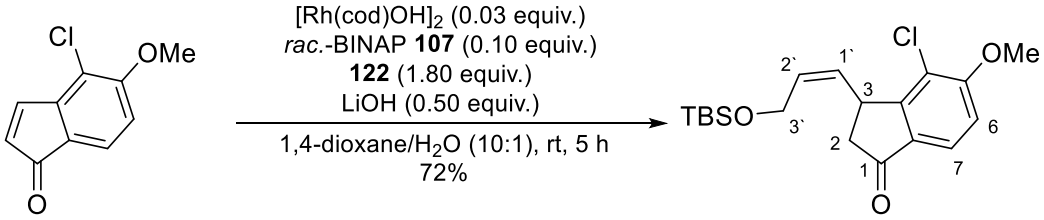
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –5.1 (TBS), 18.6 (TBS), 26.1 (TBS), 40.4 (C3), 44.6 (C2), 56.9 (OMe), 63.4 (C3`), 112.1 (C6), 120.8 (Ar), 123.5 (C7), 129.2 (C1`), 131.2 (C2`), 131.5 (Ar), 155.4 (Ar), 160.7 (Ar), 203.6 (CO) ppm.

HR-MS: (ESI+); m/z calc. for $C_{19}H_{27}ClO_3SiH$ $[M-H]^+$ 367.1491, found 367.1502.

FT-IR: (neat); ῡ = 2930 (m), 2854 (w), 1704 (s), 1597 (s), 1571 (w), 1478 (m), 1438 (w), 1329 (m), 1283 (s), 1251 (m), 1188 (w), 1166 (w), 1130 (w), 1067 (s), 1044 (w), 969 (w), 912 (w), 890 (w), 867 (w), 836 (w), 812 (m), 794 (w), 726 (w), 698 (w), 597 (w) cm^{-1}.

HPLC: (Chiralpac IC, *n*-hexane/EtOAc 9/1, 0.7 mL/min, 254 nm) t_R(major) = 12.1 min, t_R(minor) = 13.2 min.

(*Z*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-4-chloro-5-methoxy-2,3-dihydroinden-1-one 123



84 **123**

Indenone **84** [M 194.61]	1.00 equiv.	272 µmol	53.0 mg
$[Rh(cod)OH]_2$ [M 456.19]	0.03 equiv.	13.4 µmol	5.70 mg
rac.-BINAP **107** [M 622.67]	0.10 equiv.	42.0 µmol	26.1 mg
Boronic acid ester **122** [M 298.31]	2.00 equiv.	838 µmol	250 mg
$LiOH·H_2O$ [M 31.96]	0.50 equiv.	210 µmol	8.81 mg

Under Ar-atmosphere $[Rh(cod)OH]_2$ (5.70 mg, 13.4 µmol, 0.03 equiv.), boronic acid ester **122** (250 mg, 838 µmol, 2.00 equiv.) and *rac.* BINAP **107** (26.1 mg, 42.0 µmol, 0.10 equiv.) were

stirred in degassed 1,4-dioxane/H_2O (2.2 mL, 10:1) at rt for 30 min. Indenone **84** (53.0 mg, 272 µmol, 1.00 equiv.) and $LiOH \cdot H_2O$ (8.81 mg, 210 µmol, 0.50 equiv.) were added and the reaction mixture was stirred at this temperature for 5 h. It was diluted with H_2O (3 mL), extracted with Et_2O (3x3 mL), dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) vinylated indanone **123** (72.0 mg, 196 µmol, 72%) was obtained as pale-yellow oil.

TLC: R_f = 0.15 (*n*-pentane/EtOAc 4:1).

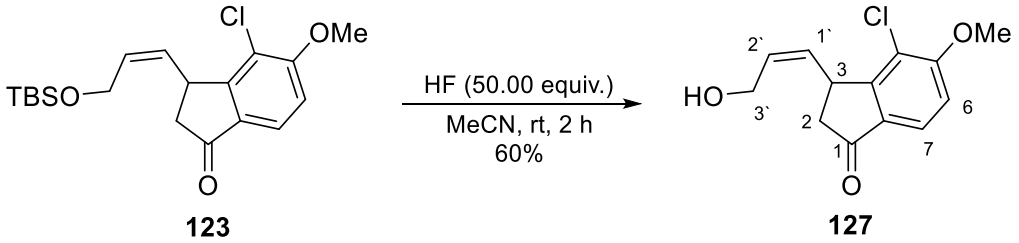
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.11 (s, 6 H, TBS), 0.93 (s, 9 H, TBS), 2.46 (dd, *J* = 1.9, 18.0 Hz, 1 H, 2-H_A), 3.01 (dt, *J* = 8.6, 18.0 Hz, 1 H, 2-H_B), 3.99 (s, 3 H, OMe), 4.34-4.41 (m, 2 H, 3`-H), 4.47 (ddd, *J* = 1.7, 5.8, 7.1 Hz, 1 H, 3-H), 5.21 (tt, *J* = 1.7, 10.7 Hz, 1 H, 1`-H), 5.67 (dt, *J* = 5.8, 10.7 Hz, 1 H, 2`-H), 7.01 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.68 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –5.1 (TBS), 18.6 (TBS), 26.1 (TBS), 40.4 (C3), 44.6 (C2), 56.9 (OMe), 63.4 (C3`), 112.1 (C6), 120.8 (Ar), 123.5 (C7), 129.2 (Ar), 131.2 (C1`), 131.5 (C2`), 155.4 (Ar), 160.7 (Ar), 203.6 (CO) ppm.

HR-MS: (ESI+); m/z calc. for $C_{19}H_{27}ClO_3SiH$ $[M-H]^+$ 367.1491, found 367.1502.

FT-IR: (neat); ϑ̃ = 3246 (s), 2943 (s), 2836 (m), 1601 (m), 1576 (s), 1496 (s), 1461 (s), 1423 (m), 1362 (m), 1305 (m), 1286 (s), 1241 (s), 1187 (m), 1147 (s), 1053 (s), 1023 (s), 993 (s), 922 (s), 871 (s), 785 (s), 618 (w), 573 (w), 549 (w), 522 (w) cm^{-1}.

(*Z*)-4-Chloro-3-(3-hydroxypropenyl)-5-methoxyindanone 127



123 **127**

Indanone **123** [M 366.96]	1.00 equiv.	382 µmol	140 mg
HF [48wt%, aq.; M 20.00]	50.00 equiv.	19.0 mmol	0.70 mL

The TBS-protected allyl silyl ether **123** (140 mg, 382 µmol, 1.00 equiv.) was dissolved in MeCN (1 mL). Aq. HF (0.70 mL, 19.0 mmol, 48%, 50.00 equiv.) was added and the mixture was stirred at rt for 2 h. Sat. aq. $NaHCO_3$ (15 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3x5 mL). The combined org. layers were dried over $MgSO_4$, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1 to 1:1) allylic alcohol **127** (58.0 mg, 0.23 mmol, 60%) was isolated as yellow oil.

TLC: R_f = 0.61 (EtOAc).

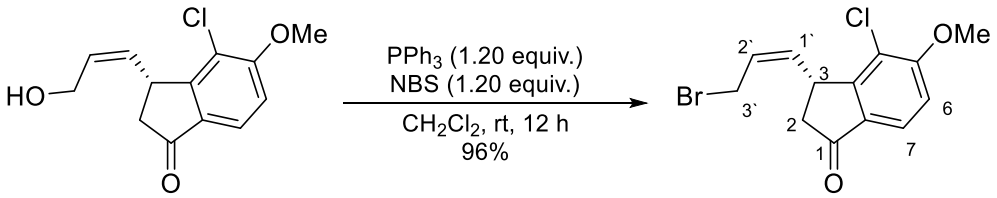
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.76 (s_{br}, 1 H, OH), 2.44 (dd, *J* = 2.2, 19.2 Hz, 1 H, 2-H_A), 3.03 (dd, *J* = 8.8, 19.2 Hz, 1 H, 2-H_B), 3.98 (s, 3 H, OMe), 4.39 (t, *J* = 8.8 Hz, 1 H, 3-H), 4.45 (ddd, *J* = 1.4, 2.2, 6.6 Hz, 2 H, 3`-H), 5.28 (t, *J* = 10.5 Hz, 1 H, 2`-H), 5.74 (dt, *J* = 6.6, 10.5 Hz, 1 H, 1`-H), 7.01 (d, *J* = 8.4 Hz, 1 H, Ar), 7.68 (d, *J* = 8.4 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 36.4 (C2), 44.7 (C3), 56.9 (OMe), 59.2 (C3`), 112.3 (C6), 120.5 (Ar), 123.7 (C7), 130.0 (C1`), 131.1 (Ar), 131.7 (C2`), 155.3 (Ar), 160.8 (Ar), 203.4 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{13}H_{13}ClO_3H$ $[M-H]^+$ 253.0626, found 253.0633.

FT-IR: (neat); ϑ̃ = 3246 (s), 2943 (s), 2836 (s), 1601 (m), 1576 (m), 1496 (s), 1461 (s), 1423 (s), 1362 (m), 1305 (m), 1286 (m), 1241 (s), 1187 (s), 1147 (s), 1053 (m), 1023 (m), 993 (m), 922 (s), 871 (m), 785 (s), 618 (s), 573 (s), 549 (w), 522 (w) cm^{-1}.

(*Z*)-3-(3-Bromopropenyl)-4-chloro-5-methoxyindanone 130



127 **130**

Allyl alcohol **127** [M 252.69]	1.00 equiv.	135 µmol	34.0 mg
PPh_3 [M 262.28]	1.20 equiv.	161 µmol	42.0 mg
NBS [M 177.99]	1.20 equiv.	161 µmol	29.0 mg

Under Ar-atmosphere allyl alcohol **127** (34.0 mg, 135 µmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (2 mL). In a separate flask PPh_3 (42.0 mg, 161 µmol, 1.20 equiv.) and NBS (29.0 mg, 161 µmol, 1.20 equiv.) were dissolved in CH_2Cl_2 (2 mL) and stirred under Ar-atmosphere at rt for 5 min. This mixture was then added to the allyl alcohol and stirred at rt for 12 h. All volatile compounds were removed under reduced pressure and after column chromatography (*n*-pentane/EtOAc 4:1) allyl bromide **130** (49.0 mg, 156 µmol, 96%) was isolated as colorless oil.

TLC: R_f = 0.12 (*n*-pentane/EtOAc 8:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.47 (dd, *J* = 2.4, 19.2 Hz, 1 H, 2-H_A), 3.10 (dd, *J* = 8.6, 19.2 Hz, 1 H, 2-H_B), 3.99 (s, 3 H, OMe), 4.11 (dd, *J* = 7.6, 10.5 Hz, 1 H, 3`-H_A), 4.31 (t, *J* = 9.7 Hz, 1 H, 3-H), 4.42 (ddd, *J* = 2.5, 8.2, 10.5 Hz, 1 H,

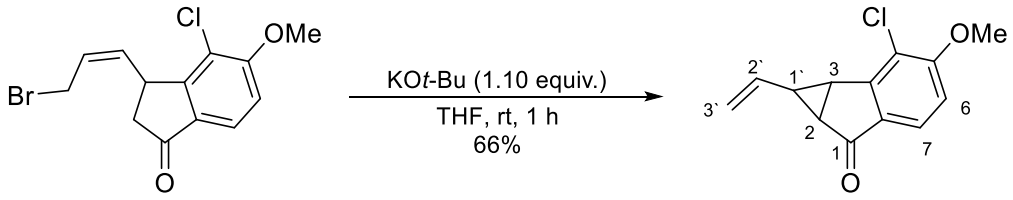
3`-$H_B$), 5.36 (t, *J* = 10.3 Hz, 1 H, 2`-H), 5.87 (ddd, *J* = 7.6, 8.2, 10.3 Hz, 1 H, 1`-H), 7.03 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.70 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 26.8 (CH_2Br), 35.9 (C2), 44.2 (C3), 57.0 (OMe), 112.5 (C6), 120.7 (Ar), 123.7 (C7), 126.7 (Ar), 131.1 (C1`), 134.3 (C2`), 154.8 (Ar), 160.8 (Ar), 202.9 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{13}H_{12}BrClO_2Na$ $[M\text{-}Na]^+$ 338.9580, found 338.9580.

FT-IR: (neat); ῡ = 3246 (s), 2943 (s), 2836 (s), 1601 (m), 1576 (m), 1496 (s), 1461 (s), 1423 (s), 1362 (m), 1305 (m), 1286 (m), 1241 (s), 1187 (s), 1147 (s), 1053 (m), 1023 (s), 993 (s), 922 (s), 871 (s), 785 (s), 618 (s), 573 (s), 549 (w), 522 (w) cm^{-1}.

4-Chloro-5-methoxy-1-vinyl-2,3-dihydrocyclopropainden-1-one 131



130 **131**

Allyl bromide **130** [M 315.59]	1.00 equiv.	111 µmol	35.0 mg
KO*t*-Bu [M 112.21]	1.10 equiv.	122 µmol	13.7 mg

Under Ar-atmosphere allyl bromide **130** (35.0 mg, 111 µmol, 1.00 equiv.) was dissolved in THF (1 mL). KO*t*-Bu (13.7 mg, 122 µmol, 1.10 equiv.) was added and the reaction mixture was stirred at rt for 1 h. It was diluted with H_2O (2 mL), extracted with CH_2Cl_2 (3x2 mL), dried over Na_2SO_4, filtrated and all volatile compounds were removed under reduced pressure. After column chromatography (*n*-pentane/EtOAc 4:1) vinyl cyclopropane **131** (17.0 mg, 72.4 µmol, 66%) was isolated as colorless oil.

TLC: R_f = 0.20 (*n*-pentane/EtOAc 4:1).

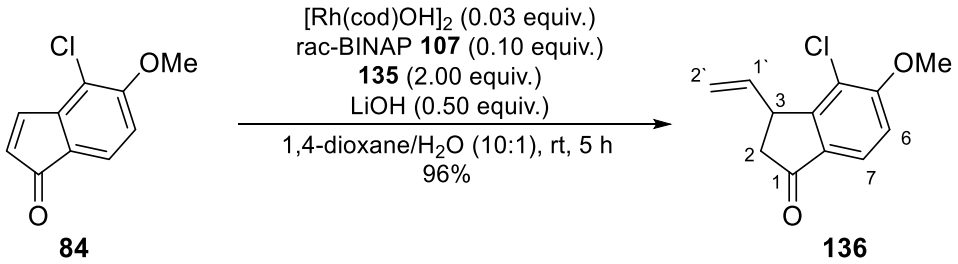
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.18 (dt, *J* = 3.1, 8.5 Hz, 1 H, 1`-H), 2.55 (dd, *J* = 3.1, 4.9 Hz, 1 H, 3-H), 3.09 (dd, *J* = 3.0, 4.9 Hz, 1 H, 2-H), 3.97 (s, 3 H, OMe), 5.09 (dd, *J* = 1.0, 10.3 Hz, 1 H, 3`-H_A), 5.21 (dd, *J* = 1.0, 17.0 Hz, 1 H, 3`-$H_B$), 5.55 (ddd, *J* = 8.5, 10.3, 17.0 Hz, 1 H, 2`-H), 6.86 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.55 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 27.6 (C3), 35.6 (C2), 48.7 (C1`), 56.9 (OMe), 110.7 (Ar), 116.4 (C3`), 118.9 (Ar), 124.5 (Ar), 128.2 (Ar), 135.7 (C2`), 152.9 (Ar), 159.7 (Ar), 199.2 (CO) ppm.

HR-MS: (ESI+); m/z calc. for $C_{13}H_{11}ClO_2Na$ $[M\text{-}Na]^+$ 235.0513, found 235.0520.

FT-IR: (neat); ῡ = 2952 (m), 2884 (w), 1716 (m), 1596 (w), 1459 (w), 1441 (w), 1365 (w), 1332 (w), 1285 (w), 1183 (m), 1117 (w), 1056 (w), 1033 (s), 983 (m), 919 (m), 847 (w), 760 (w), 602 (w) cm^{-1}.

8.2.3 4-Chloro-5-methoxy-3-vinyl-2,3-dihydro-1H-inden-1-one 136



84 **136**

Indenone **84** [M 194.61]	1.00 equiv.	187 µmol	36.0 mg
$[Rh(cod)OH]_2$ [M 456.19]	0.03 equiv.	5.60 µmol	2.60 mg
rac. BINAP **107** [M 622.67]	0.10 equiv.	19.0 µmol	11.6 mg
Trifluoroborate **135** [M 133.95]	2.00 equiv.	373 mmol	50.0 mg
$LiOH{\cdot}H_2O$ [M 31.96]	0.50 equiv.	93.3 µmol	3.00 mg

Under Ar-atmosphere $[Rh(cod)OH]_2$ (2.60 mg, 5.60 µmol, 0.03 equiv.), trifluoroborate **135** (50.0 mg, 373 µmol, 2.00 equiv.) and *rac.* BINAP **113** (11.6 mg, 19.0 µmol, 0.10 equiv.) were stirred in degassed 1,4-dioxane/H_2O (1.1 mL, 10:1) at rt for 30 min. Indenone **84** (36.0 mg, 187 µmol, 1.00 equiv.) and $LiOH \cdot H_2O$ (3.00 mg, 93.3 µmol, 0.50 equiv.) were added and the reaction mixture was stirred at this temperature for 5 h. It was diluted with H_2O (1.5 mL), extracted with Et_2O (3x1.5 mL), dried over Na_2SO_4 and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) vinylated indanone **136** (40.0 mg, 179 µmol, 96%) was obtained as pale-yellow oil.

TLC: R_f = 0.15 (*n*-pentane/EtOAc 4:1).

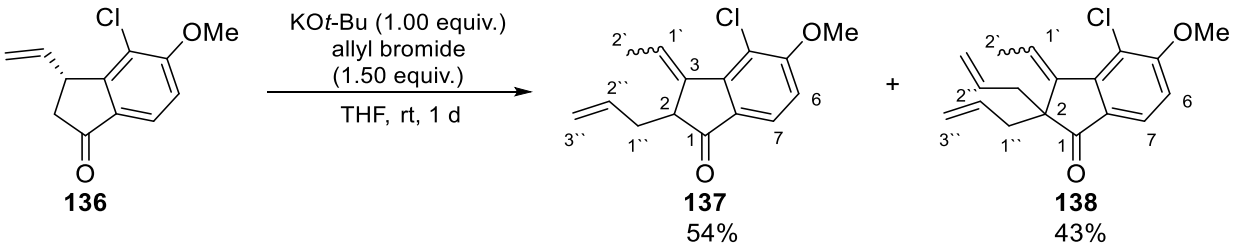
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.56 (dd, *J* = 2.1, 19.0 Hz, 1 H, 2-H_A), 3.00 (dd, *J* = 8.1, 19.0 Hz, 1 H, 2-H_B), 4.00 (s, 3 H, OMe), 4.13 (t, *J* = 7.7 Hz, 1 H, 3-H), 5.12-5.13 (m, 1 H, 2`-$H_A$), 5.15 (dd, *J* = 3.4, 17.5 Hz, 1 H, 2`-H_B), 5.84 (ddd, *J* = 7.7, 9.9, 17.5 Hz, 1 H, 1`-H), 7.02 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.69 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 41.6 (C3), 44.3 (C2), 56.9 (OMe), 111.7 (C6), 112.2 (C2`), 116.4 (Ar), 123.5 (C7), 131.2 (Ar), 137.5 (C1`), 155.1 (Ar), 160.7 (Ar), 203.5 (CO) ppm.

HR-MS: (ESI+); m/z calc. for $C_{12}H_{11}ClO_2H$ $[M-H]^+$ 223.0520, found 223.0525.

FT-IR: (neat); ϑ̃ = 3085 (w), 2940 (w), 2844 (w), 1709 (s), 1639 (w), 1596 (s), 1574 (w), 1480 (m), 1461 (w), 1439 (w), 1330 (m), 1284 (s), 1259 (w), 1189 (w), 1158 (w), 1128 (m), 1092 (w), 1062 (m), 988 (w), 920 (w), 835 (w), 810 (w), 694 (w), 604 (w), 522 (w) cm^{-1}.

Allylation of indanone 136



Indanone **136** [M 222.67]	1.00 equiv.	404 µmol	90.0 mg
KO*t*-Bu [M 112.21]	1.00 equiv.	404 µmol	45.0 mg
Allyl bromide [M 120.99, ρ 1.40]	1.50 equiv.	606 µmol	52.4 µL

Under Ar-atmosphere indanone **136** (90.0 mg, 404 µmol, 1.00 equiv.) was dissolved in THF (1 mL). KO*t*-Bu (45.0 mg, 404 µmol 1.00 equiv.) was added and the mixture was stirred at rt for 30 min. Freshly distilled allyl bromide (52.4 µL, 606 µmol, 1.50 equiv.) was added and the mixture was stirred at rt for 12 h. Sat. aq. $NaHCO_3$ (1 mL) was added, it was extracted with Et_2O (3x1 mL), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) allylated indanone **137** (57.0 mg, 217 µmol, 54%) and doubly allylated indanone **138** (55.0 mg, 173 µmol, 43%) were obtained as yellow oils.

2-Allyl-4-chloro-3-ethylidene-5-methoxy-2,3-dihydro-1H-inden-1-one 137:

TLC: R_f = 0.33 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.98 (d, *J* = 7.2 Hz, 3 H, 2`-H), 2.53-2.74 (m, 2 H, 1"-H), 3.33-3.35 (m, 1 H, 2-H), 4.00 (s, 3 H, OMe), 4.89 (d, *J* = 9.9 Hz, 1 H, 3"-$H_A$), 5.02 (dd, *J* = 1.7, 17.1 Hz, 1 H, 3"-$H_B$), 5.60 (tdd, *J* = 7.2, 9.9, 17.1 Hz, 1 H, 2"-H), 6.95 (d, *J* = 8.3 Hz, 1 H, 6-H), 7.31 (ddd, *J* = 2.0, 7.2, 7.5 Hz, 1 H, 1`-H), 7.69 (d, *J* = 8.3 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 16.1 (C2`), 35.8 (C1"), 49.9 (C2), 57.0 (OMe), 111.5 (Ar), 117.6 (Ar), 118.1 (C3"), 123.4 (Ar), 127.0 (C1`), 131.5 (Ar), 133.5 (C2"), 136.0 (Ar), 146.7 (C3), 161.1 (Ar), 203.4 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{15}H_{15}ClO_2H$ $[M-H]^+$ 263.0833, found 263.0840.

FT-IR: (neat); ϑ̃ = 3086 (w), 2941 (w), 1709 (s), 1592 (m), 1478 (m), 1438 (w), 1333 (w), 1281 (s), 1183 (w), 1132 (w), 1060 (m), 826 (w), 786 (w), 735 (w) cm^{-1}.

2,2-Diallyl-4-chloro-3-ethylidene-5-methoxy-2,3-dihydro-1H-inden-1-one 138:

TLC: R_f = 0.42 (*n*-pentane/EtOAc 4:1).

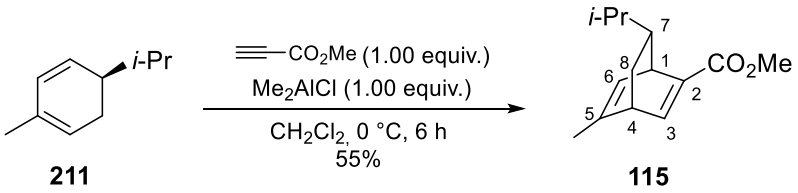
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.07 (d, *J* = 7.5 Hz, 3 H, 2`-H), 2.65 (d, *J* = 7.2 Hz, 4 H, 1"-H), 3.99 (s, 3 H, OMe), 4.79 (dd, *J* = 1.4, 10.0 Hz, 2 H, 3"-$H_A$), 4.97 (dd, *J* = 1.4, 17.0 Hz, 2 H, 3"-$H_B$), 5.39 (tdd, *J* = 7.2, 10.0, 17.0 Hz, 2 H, 2"-H), 6.95 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.60 (d, *J* = 7.5 Hz, 1 H, 1`-H), 7.69 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 15.3 (C2`), 41.0 (C1"), 57.7 (OMe), 57.4 (C2), 111.6 (C6), 117.8 (C3"), 118.0 (Ar), 123.1 (C7), 128.3 (Ar), 131.2 (Ar), 133.0 (C2"), 137.4 (C1`), 146.7 (C3), 161.3 (Ar), 205.8 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{18}H_{19}ClO_2H$ $[M-H]^+$ 303.1146, found 303.1154.

FT-IR: (neat); ϑ̃ = 3076 (w), 3005 (w), 2976 (w), 2919 (w), 2846 (w), 1706 (s), 1640 (w), 1590 (s), 1560 (m), 1464 (w), 1438 (m), 1413 (w), 1358 (w), 1325 (m), 1275 (s), 1253 (w), 1200 (w), 1178 (w), 1126 (m), 1097 (w), 1067 (s), 992 (w), 963 (w), 915 (m), 822 (m), 783 (w), 756 (m), 679 (w), 628 (w), 601 (m), 533 (w), 458 (w) cm^{-1}.

Methyl (1*R*,4*R*,7*R*)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate 211



211 **115**

(*R*)-α-Phellandrene **211** [50wt%; M 136.24]	1.05 equiv.	31.5 mmol	10.2 mL
Methyl propiolate [M 84.07; ρ 0.95]	1.00 equiv.	30.0 mmol	2.67 mL
Me_2AlCl [1.0 M, *n*-hexane; M 92.50]	1.00 equiv.	30.0 mmol	30.0 mL

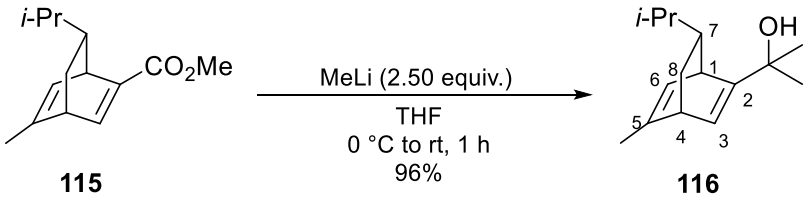
(*R*)-(–)-*α*-Phellandrene **211** (10.2 mL, 31.5 mmol, 50wt% technical grade, 1.05 equiv.) and methyl propiolate (2.67 mL, 30.0 mmol, 1.00 equiv.) were dissolved in CH_2Cl_2 (30 mL) under Ar-atmosphere. At 0 °C Me_2AlCl (30.0 mL, 30.0 mmol, 1.0 M in *n*-hexane, 1.00 equiv.) was added dropwise and the mixture was stirred at this temperature for 6 h. H_2O (30 mL) was added to quench the reaction, it was extracted with Et_2O (3x30 mL), the combined org. layers were dried over $MgSO_4$, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 20:1) diene **115** (3.80 g, 17.3 mmol, 55%) was obtained as colorless oil.

TLC: R_f = 0.45 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.81 (d, *J* = 5.9 Hz, 3 H, *i*-Pr), 0.80 (dd, *J* = 2.6, 6.8 Hz, 1 H, 8-H_A), 0.99 (d, *J* = 5.7 Hz, 3 H, *i*-Pr), 1.07-1.20 (m, 2 H, 7-H, *i*-Pr), 1.55 (ddd, *J* = 3.0, 8.8, 11.5 Hz, 1 H, 8-H_B), 1.81 (d, *J* = 1.7 Hz, 3 H, 5-Me), 3.38 (dq, *J* = 2.5, 6.8 Hz, 1 H, 4-H), 3.72 (s, 3 H, OMe), 4.07 (dt, *J* = 2.0, 6.1 Hz, 1 H, 1-H), 5.80 (dt, *J* = 1.7, 5.9 Hz, 1 H, 6-H), 7.29 (dd, *J* = 1.9, 6.4 Hz, 1 H, 3-H) ppm.

The spectroscopic data of **115** matched that reported in the literature.[81]

5-((1*R*,4*R*,7*R*)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-dien-2-yl)propan-5-ol 116



115 **116**

Ester **115** [M 220.31]	1.00 equiv.	4.54 mmol	1.00 g
MeLi [1.6 M, *n*-hexane; M 21.98]	2.50 equiv.	11.3 mmol	7.09 mL

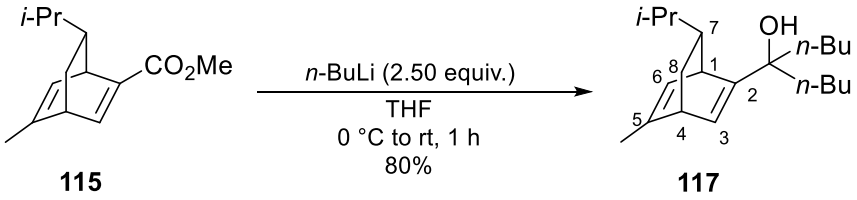
Under Ar-atmosphere ester **115** (1.00 g, 4.54 mmol, 1.00 equiv.) was dissolved in THF (25 mL). At 0 °C MeLi (7.09 mL, 11.3 mmol, 1.6 M in hexane, 2.50 equiv.) was added and the mixture was stirred at rt for 1 h. H_2O (60 mL) was added to quench the reaction, it was extracted with Et_2O (3x60 mL), the combined org. layers were dried over $MgSO_4$, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) alcohol **116** (1.03 g, 4.67 mmol, 96%) was obtained as pale-yellow oil.

TLC: R_f = 0.23 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.80 (d, *J* = 5.8 Hz, 3 H, *i*-Pr), 0.87 (ddd, *J* = 2.3, 4.3, 11.4 Hz, 1 H, 8-H_A), 0.96 (d, *J* = 5.8 Hz, 3 H, *i*-Pr), 1.04-1.13 (m, 2 H, 7-H, *i*-Pr), 1.32 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.56 (ddd, *J* = 3.0, 8.2, 11.4 Hz, 1 H, 8-H_B), 1.80 (d, *J* = 1.7 Hz, 3 H, 5-Me), 3.18 (dt, *J* = 2.3, 5.1 Hz, 1 H, 4-H), 3.61 (dt, *J* = 1.8, 6.1 Hz, 1 H, 1-H), 5.75 (dt, *J* = 1.8, 6.1 Hz, 1 H, 6-H), 6.02 (dd, *J* = 2.0, 6.1 Hz, 1 H, 3-H) ppm.

The spectroscopic data of **116** matched that reported in the literature.[81]

5-((1*R*,4*R*,7*R*)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-dien-2-yl)nonan-5-ol 117



115 **117**

Ester **115** [M 220.31]	1.00 equiv.	1.45 mmol	318 mg
n-BuLi [1.6 M, *n*-hexane; M 64.05]	2.50 equiv.	3.61 mmol	2.25 mL

Under Ar-atmosphere ester **115** (318 mg, 1.45 mmol, 1.00 equiv.) was dissolved in THF (5 mL). At 0 °C *n*-BuLi (2.25 mL, 3.61 mmol, 1.6 M in *n*-hexane, 2.50 equiv.) was added and the mixture was stirred at rt for 1 h. H_2O (20 mL) was added to quench the reaction, it was extracted with Et_2O (3x20 mL), the combined org. layers were dried over $MgSO_4$, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 20:1) alcohol **117** (353 mg, 1.16 mmol, 80%) was obtained as pale-yellow oil.

TLC: R_f = 0.40 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.80 (d, *J* = 5.8 Hz, 3 H, *i*-Pr), 0.84-0.91 (m, 7 H, 8-H_A, *n*-Bu), 0.94 (d, *J* = 5.8 Hz, 3 H, *i*-Pr), 1.05-1.09 (m, 2 H, 7-H, *i*-Pr), 1.21-1.34 (m, 8 H, *n*-Bu), 1.45-1.64 (m, 5 H, *n*-Bu, 8-H_B), 1.79 (d, *J* = 1.7 Hz, 3 H, 5-Me), 3.18 (dt, *J* = 2.2, 5.0 Hz, 1 H, 4-H), 3.43 (dt, *J* = 1.7, 6.0 Hz, 1 H, 1-H), 5.70 (dd, *J* = 1.7, 6.0 Hz, 1 H, 6-H), 5.99 (dd, *J* = 2.2, 6.1 Hz, 1 H, 3-H) ppm.

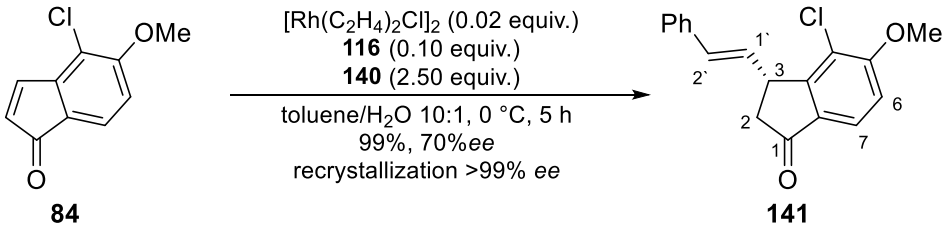
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 14.2 (*n*-Bu), 14.3 (*n*-Bu), 19.1 (5-Me), 21.7 (*i*-Pr), 22.0 (*i*-Pr), 23.3 (*n*-Bu), 23.3 (*n*-Bu), 25.7 (*n*-Bu), 25.9 (*n*-Bu), 32.9 (C8), 33.9 (*i*-Pr), 38.6 (*n*-Bu), 38.7 (*n*-Bu), 40.9 (C1), 43.2 (C4), 47.9 (C7), 76.9 (COH), 124.0 (C6), 126.7 (C3), 145.6 (C2), 153.9 (C5) ppm.

HR-MS: (ESI+); m/z calc. for $C_{21}H_{36}O$ $[M-H]^+$ 304.2718, found 304.2718.

FT-IR: (neat); $\tilde{\upsilon}$ = 3471 (w), 3034 (w), 2955 (w), 2931 (s), 2866 (w), 1709 (w), 1464 (m), 1380 (w), 1323 (w), 1290 (w), 1257 (w), 1206 (w), 1142 (w), 1011 (w), 884 (w), 861 (w), 816 (m), 789 (w), 733 (w), 687 (w), 637 (w) cm^{-1}.

[α]: 22 (c 0.71, EtOAc).

(*R*,*E*)-4-Chloro-5-methoxy-3-styryl-2,3-dihydroinden-1-one 141



Indenone **84** [M 194.61]	1.0 equiv.	5.41 mmol	1.05 g
$[Rh(C_2H_4)_2Cl]_2$ [M 388.93]	0.02 equiv.	0.11 mmol	42.1 mg
Diene **116** [M 220.35]	0.10 equiv.	0.54 mmol	119 mg
Boronic acid **140** [M 298.31]	2.50 equiv.	13.5 mmol	2.00 g
$LiOH \cdot H_2O$ [M 31.96]	0.50 equiv.	2.70 mmol	113 mg

Under Ar-atmosphere $[Rh(C_2H_4)_2Cl]_2$ (42.1 mg, 0.11 mmol, 0.02 equiv.), styrene boronic acid **140** (2.00 g, 13.5 mmol, 2.50 equiv.) and diene ligand **116** (119 mg, 0.54 mmol, 0.10 equiv.) were stirred in degassed toluene/H_2O (33 mL, 10:1) at rt for 30 min. At 0 °C indenone **84** (1.05 g, 5.41 mmol, 1.00 equiv.) and $LiOH \cdot H_2O$ (113 mg, 2.70 mmol, 0.50 equiv.) were added and the reaction mixture was stirred at this temperature for 5 h. It was diluted with H_2O (100 mL), extracted with Et_2O (3x75 mL), dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) styrylated indanone **141** (1.61 g, 5.39 mmol, 99%, 74%*ee*) was obtained as pale-yellow crystals. Recrystallization from *n*-pentane/CH_2Cl_2 (1:1) gave 1.01 g

(63%, >99% *ee*) of **141**.

TLC: R_f = 0.17 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.64 (dd, *J* = 2.0, 19.0 Hz, 1 H, 2-H_A), 3.09 (dd, *J* = 8.2 Hz, 19.0 Hz, 1 H, 2-H_B), 3.99 (s, 3 H, OMe), 4.29 (dt, *J* = 2.0, 8.2 Hz, 1 H, 3-H), 6.14 (dd, *J* = 8.2, 15.8 Hz, 1 H, 1`-H), 6.53 (dd, *J* = 0.8, 15.8 Hz, 1 H, 2`-H), 7.03 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.18-7.35 (m, 5 H, Ph), 7.72 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 41.2 (C3), 44.7 (C2), 56.9 (OMe), 112.3 (6-H), 120.9 (Ar), 123.5 (7-H), 126.4 (Ar), 127.7 (Ar), 128.7 (Ar), 129.3 (C2`), 131.2 (Ar), 131.9 (C1`), 137.0 (Ar), 155.4 (Ar), 160.7 (Ar), 203.4 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{18}H_{15}ClO_2Na$ $[M-Na]^+$ 299.0833, found 299.0828.

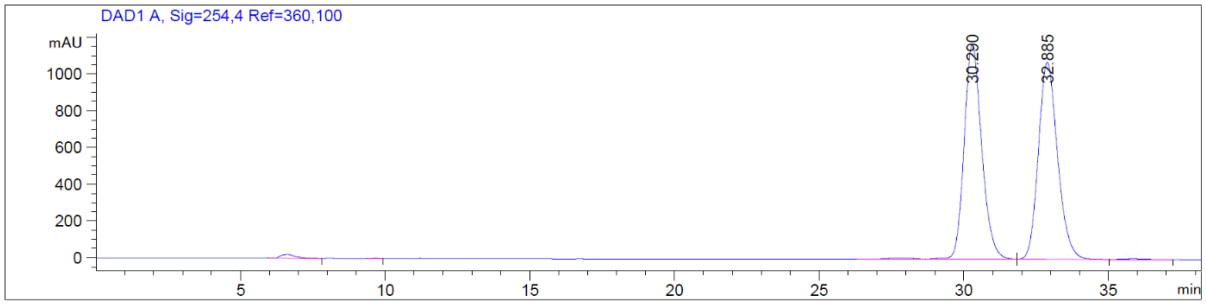
FT-IR: (neat); ῡ = 3025 (w), 2941 (w), 2843 (w), 1709 (s), 1595 (m), 1573 (w), 1479 (w), 1439 (w), 1328 (m), 1283 (s), 1254 (w), 1186 (w), 1157 (w), 1127 (w), 1061 (m), 965 (w), 813 (w), 749 (w), 695 (w), 606 (w), 542 (w) cm^{-1}.

m.p.: 138 °C (EtOAc).

HPLC: (Chiralpac IC, *n*-hexane/EtOAc 9/1, 0.7 mL/min, 254 nm) t_R(major) = 31.5 min, t_R(minor) = 34.9 min.

[α]: 82 (c 0.50, $CHCl_3$), for recrystallized compound with ee > 99%).

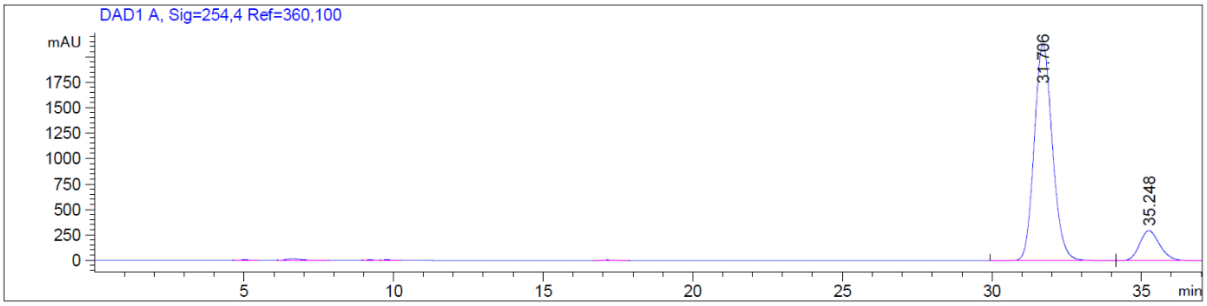
using *rac*-BINAP



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
4	30.290	BB	0.6425	4.90515e4	1166.78503	49.2656
5	32.885	BB	0.7055	4.92134e4	1072.20862	49.4281

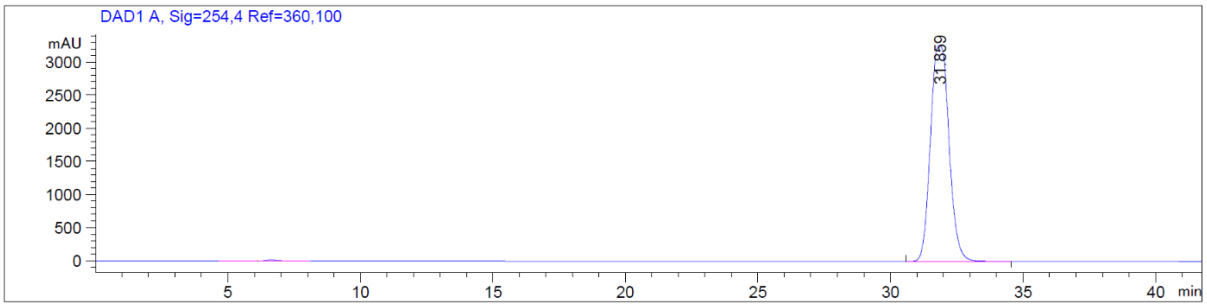
with diene **116**:



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
6	31.706	BB	0.6531	9.00579e4	2130.80151	85.8889
7	35.248	BBA	0.7269	1.38489e4	295.40579	13.2078

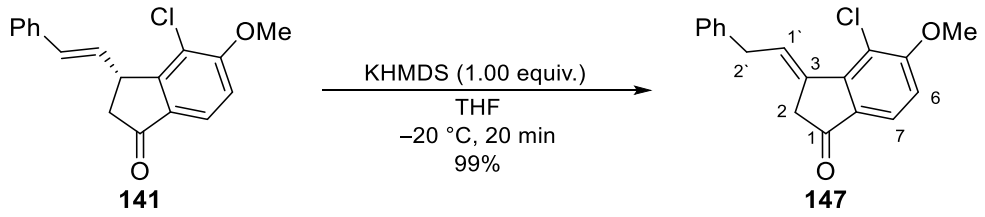
after recrystallization:



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
3	31.859	BB	0.7560	1.58158e5	3260.21729	99.6525

4-Chloro-5-methoxy-3-(2-phenylethylidene)-2,3-dihydroinden-1-one 147



Indanone **141** [M 298.77]	1.00 equiv.	335 µmol	100 mg
KHMDS [0.5 M, toluene; M 199.48]	1.00 equiv.	335 µmol	669 µL

Under Ar-atmosphere indanone **141** (100 mg, 335 µmol, 1.00 equiv.) was dissolved in THF (5 mL). At –20 °C KHMDS (669 µL, 335 µmol, 0.5 M in toluene, 1.00 equiv.) was added and the mixture was stirred at this temperature for 20 min. Sat. aq. $NaHCO_3$ (5 mL) was added, it was extracted with Et_2O (3x10 mL), the combined org. layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) indanone **147** (99.0 mg, 335 µmol, 99%) was obtained as yellow oil.

TLC: R_f = 0.17 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.33-3.34 (m, 2 H, 2-H), 3.61 (d, *J* = 7.5 Hz, 2 H, 2`-H), 3.98 (s, 3 H, OMe), 6.95 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.20-7.35 (m, 5 H, Ph), 7.40 (td, *J* = 2.0, 7.5 Hz, 1 H, 1`-H), 7.70 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

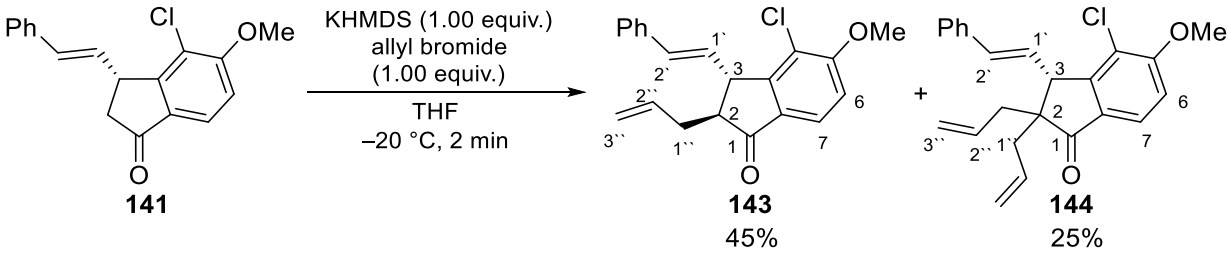
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 37.0 (C2`), 40.7 (C2), 57.0 (OMe), 111.7 (C6), 118.5 (Ar), 123.3 (Ar), 126.5 (C7), 128.5 (Ar), 128.8 (C1`), 130.2 (Ar), 139.6 (Ar), 146.5 (C3), 160.9 (Ar), 200.2 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{18}H_{15}ClO_2Na$ $[M\text{-}Na]^+$ 299.0833, found 299.0828.

FT-IR: (neat); ϑ̃ = 3060 (w), 3025 (w), 2939 (m), 2843 (w), 1705 (s), 1588 (s), 1561 (m), 1493 (w), 1464 (s), 1437 (w), 1418 (m), 1391 (w), 1324 (s), 1277 (w),

1258 (s), 1163 (w), 1126 (s), 1059 (s), 995 (w), 908 (s), 809 (s), 730 (s), 698 (s), 642 (m), 604 (m), 584 (w), 549 (w), 500 (w), 439 (w) cm^{-1}.

Allylation of Indanone 141



Indanone **141** [M 298.77]	1.00 equiv.	837 µmol	250 mg
KHMDS [0.5 M, toluene; M 199.48]	1.00 equiv.	837 µmol	1.67 mL
Allyl bromide [M 120.99, ρ 1.40]	1.00 equiv.	837 µmol	72.3 µL

Under Ar-atmosphere indanone **141** (250 mg, 837 µmol, 1.00 equiv.) was dissolved in THF (10 mL). At –20 °C KHMDS (1.67 mL, 837 µmol, 0.5 M in toluene, 1.00 equiv.) was added and the mixture was stirred for 2 min. Freshly distilled allyl bromide (72.3 µL, 837 µmol, 1.00 equiv.) was added and the mixture was stirred at –20 °C for further 2 min. Sat. aq. $NaHCO_3$ (5 mL) was added, it was extracted with Et_2O (3x10 mL), the combined org. layers were dried over Na_2SO_4, filtrated and all volatile compounds were concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) allylated indanone **143** (127 mg, 375 µmol, 45% *cis*/*trans* 1:6.5), doubly allylated indanone **144** (79.0 mg, 208 µmol, 25%) and recovered indanone **141** (70 mg, 237 µmol, 28%) were obtained as yellow oils.

(2*S*,3*S*)-2-Allyl-4-chloro-5-methoxy-3-((*E*)-styryl)-2,3-dihydroinden-1-one 143:

TLC: R_f = 0.32 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.32-2.43 (m, 1 H, 1"-H_A), 2.61-2.69 (m, 1 H, 1"-H_B), 3.10 (dd, *J* = 7.4, 7.4 Hz, 1 H, 2-H), 3.92-3.97 (m, 1 H, 3-H), 3.99 (s, 3 H, OMe), 5.09 (dd, *J* = 1.7, 9.9 Hz, 1 H, 3"-H_A), 5.17 (dd, *J* = 1.7, 16.7 Hz, 1 H, 3"-H_B), 5.80 (tdd, *J* = 6.7, 6.7, 13.4 Hz, 1 H, 2"-H), 6.14 (dd, *J* = 8.5, 15.8 Hz, 1 H, 1`-H), 6.51 (d, *J* = 15.8 Hz, 1 H, 2`-H), 7.04 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.21-7.34 (m, 5 H, Ph), 7.71 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 35.9 (C1"), 46.0 (C3), 47.2 (C2), 56.9 (OMe), 112.4 (C6), 117.8 (C3"), 121.1 (Ar), 123.7 (C7), 126.4 (Ar), 127.6 (Ar), 128.7 (Ar), 129.2 (C2`), 131.2 (Ar), 132.1 (C2`), 135.1 (C1"), 137.1 (Ar), 154.1 (Ar), 161.0 (Ar), 205.0 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{21}H_{19}ClO_2Na$ $[M-Na]^+$ 361.0966, found 361.0965.

FT-IR: (neat); ϑ̃ = 3060 (w), 3025 (w), 2940 (w), 2842 (w), 1706 (s), 1640 (w), 1590 (s), 1564 (w), 1493 (w), 1468 (m), 1437 (w), 1419 (w), 1326 (m), 1279 (s), 1257 (w), 1184 (w), 1163 (w), 1127 (m), 1061 (s), 995 (w), 966 (w), 919 (w), 812 (m), 749 (m), 698 (m), 641 (w), 606 (w) cm^{-1}.

Due to the low stability of **143** upon purification (double bond isomerization) no sample pure enough for a reliable measurement of optical rotation could be obtained.

(*S*,*E*)-2,2-Diallyl-4-chloro-5-methoxy-3-styryl-2,3-dihydro-*1H*-inden-1-one 144:

TLC: R_f = 0.41 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.22-2.56 (m, 4 H, 1"-H), 3.99 (s, 3 H, OMe), 4.07 (d, *J* = 9.4 Hz, 1 H, 3-H), 5.00-5.09 (m, 1 H, 3"-H), 5.58 (tdd, *J* = 7.4, 10.0, 17.5 Hz, 1 H, 2"-H), 5.86 (dddd, *J* = 6.5, 7.9, 10.0, 17.5 Hz, 1 H, 2"-H), 6.05 (dd, *J* = 9.4, 15.8 Hz, 1 H, 1`-H), 6.52 (d, *J* = 15.8 Hz, 1 H, 1`-H), 7.02

(d, J = 8.4 Hz, 1 H, 6-H), 7.21-7.34 (m, 5 H, Ph), 7.71 (d, J = 8.4 Hz, 1 H, 7-H) ppm.

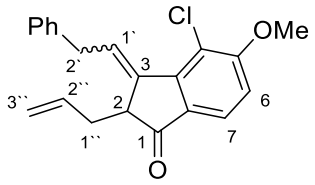
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 37.3 (C1"$_A$), 42.4 (C1"$_B$), 51.6 (C2), 56.8 (OMe), 57.9 (C3), 112.2 (C6), 118.5 (C3"$_A$), 118.9 (C3"$_B$), 120.8 (Ar), 123.7 (C7), 126.4 (Ar), 127.6 (Ar), 128.7 (Ar), 129.1 (C2`), 130.1 (C1`), 133.2 (C2"$_A$), 133.4 (C2"$_B$), 133.8 (Ar), 137.1 (Ar), 153.2 (Ar), 160.8 (Ar), 206.4 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{24}H_{23}ClO_2H$ $[M-H]^+$ 379.1459, found 379.1470.

FT-IR: (neat); ῡ = 3078 (w), 3024 (w), 2976 (w), 2939 (w), 2843 (w), 1707 (s), 1640 (w), 1595 (s), 1573 (w), 1479 (m), 1439 (w), 1330 (m), 1280 (s), 1161 (w), 1129 (w), 1064 (m), 992 (w), 966 (w), 919 (w), 818 (w), 789 (w), 750 (w), 696 (w), 661 (w), 612 (w), 590 (w) cm^{-1}.

If the enolate mixture of **141** was stirred for 20 min or more at –20 °C the isomerized allylated compounds **148** and **149** were isolated as yellow oils.

2-Allyl-4-chloro-5-methoxy-3-(2-phenylethylidene)-2,3-dihydro-*1H*-inden-1-one 148:



148

TLC: R_f = 0.32 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.63 (ddt, J = 1.3, 7.2, 14.0 Hz, 1 H, 1"-H$_A$), 2.70-2.79 (m, 1 H, 1"-H$_B$), 3.46 (ddd, J = 1.6, 4.6, 6.5 Hz, 1 H, 2-H), 3.70 (d, J = 7.6 Hz, 2 H, 2`-H), 3.99 (s, 3 H, OMe), 4.91 (ddt, J = 1.0, 1.7, 10.0 Hz, 1 H, 3"-H$_A$), 5.02 (dq, J = 1.7, 17.3 Hz, 1 H, 3"-H$_B$), 5.63 (tdd, J = 7.2, 10.0, 17.3 Hz, 1 H,

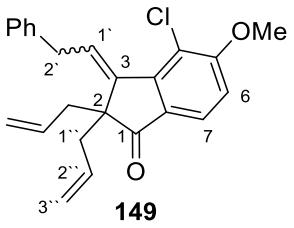
2"-H), 6.98 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.24-7.36 (m, 5 H, Ph), 7.42 (td, *J* = 1.7, 7.6 Hz, 1 H, 1`-H), 7.72 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 36.5 (C1"), 47.2 (C2), 50.1 (C2`), 57.0 (OMe), 111.8 (C6), 118.0 (C3"), 123.4 (C7), 126.4 (Ar), 127.6 (Ar), 128.5 (Ar), 128.7 (C1`), 128.9 (Ar), 130.3 (Ar), 135.9 (C2"), 139.7 (Ar), 146.6 (C3), 154.1 (Ar), 161.2 (Ar), 203.0 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{21}H_{19}ClO_2Na$ $[M\text{-}Na]^+$ 361.0966, found 361.0965.

FT-IR: (neat); ῡ = 3078 (w), 3025 (w), 2976 (w), 2939 (w), 2842 (w), 1708 (s), 1640 (w), 1592 (s), 1564 (w), 1468 (m), 1438 (w), 1417 (w), 1328 (m), 1278 (s), 1256 (w), 1184 (w), 1161 (w), 1128 (m), 1064 (s), 992 (w), 966 (w), 920 (m), 814 (w), 748 (m), 698 (m), 663 (w), 590 (w), 499 (w), 442 (w) cm^{-1}.

2,2-Diallyl-4-chloro-5-methoxy-3-(2-phenylethylidene)-2,3-dihydro-*1H*-inden-1-one 149:



149

TLC: R_f = 0.41 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.65 (dd, *J* = 1.2, 7.3 Hz, 4 H, 1"-H), 3.77 (d, *J* = 7.6 Hz, 2 H, 2`-H), 3.91 (s, 3 H, OMe), 4.74 (dd, *J* = 1.8, 10.1 Hz, 2 H, 3"-$H_A$), 4.91 (dd, *J* = 1.8, 17.0 Hz, 2 H, 3"-$H_B$), 5.36 (tdd, *J* = 7.2, 10.1, 17.0 Hz, 2 H, 2"-H), 6.90 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.16-7.31 (m, 5 H, Ph), 7.62 (d, *J* = 7.6 Hz, 1 H, 1`-H), 7.64 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

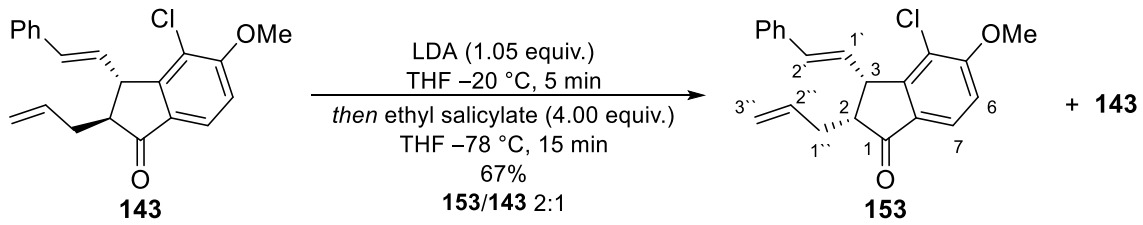
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 35.3 (C2`), 41.4 (C1"), 56.9 (C2), 57.2 (OMe), 111.8 (C6), 118.0 (C3"), 118.2 (Ar), 123.0 (C7), 126.4 (Ph), 128.4 (Ph), 128.7 (Ph),

131.2 (Ar), 131.9 (C2`), 132.6 (Ar), 137.1 (C1`), 139.8 (C2"), 146.3 (Ar), 161.2 (Ar), 205.3 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{24}H_{23}ClO_2H$ $[M-H]^+$ 379.1459, found 379.1470.

FT-IR: (neat); $\tilde{\upsilon}$ = 3076 (w), 3026 (w), 2976 (w), 2938 (w), 2841 (w), 1707 (s), 1640 (w), 1589 (s), 1561 (m), 1495 (w), 1464 (w), 1438 (m), 1413 (w), 1362 (w), 1325 (m), 1276 (w), 1253 (s), 1183 (w), 1160 (w), 1125 (m), 1067 (s), 1030 (w), 992 (w), 964 (w), 917 (m), 851 (w), 823 (m), 781 (w), 743 (m), 698 (m), 680 (w), 628 (w), 597 (w), 531 (w), 494 (w), 452 (w) cm^{-1}.

8.4.9 (2*R*,3*S*)-2-Allyl-4-chloro-5-methoxy-3-((*E*)-styryl)-2,3-dihydroinden-1-one 153



Indanone **143** [M 338.83]	1.00 equiv.	207 µmol	70.0 mg
i-Pr_2NH [M 101.19; ρ 0.72]	1.10 equiv.	227 µmol	31.9 µL
n-BuLi [1.6 M, *n*-hexane; M 64.05]	1.05 equiv.	217 µmol	86.8 µL
Ethyl salicylate [M 166.18; ρ 1.13]	4.00 equiv.	826 µmol	122 µL

Under Ar-atmosphere *n*-BuLi (86.8 µL, 217 µmol, 1.6 M in THF, 1.05 equiv.) was added to a solution of *i*-Pr_2NH (31.9 µL, 227 µmol, 1.10 equiv.) in THF (2 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min. At –20 °C indanone **143** (70.0 mg, 207 µmol, 1.00 equiv.) was added and the mixture was stirred for 2 min. The resulting enolate was added dropwise to a solution of ethyl salicylate (122 µL, 826 µmol, 4.00 equiv.) in THF (2 mL) at –78 °C and the mixture was stirred at this temperature for 15 min. The reaction mixture was warmed to rt and AcOH (50.0 µL, 0.83 mmol, 4.00 equiv.) was added. It was filtrated through a short pad of

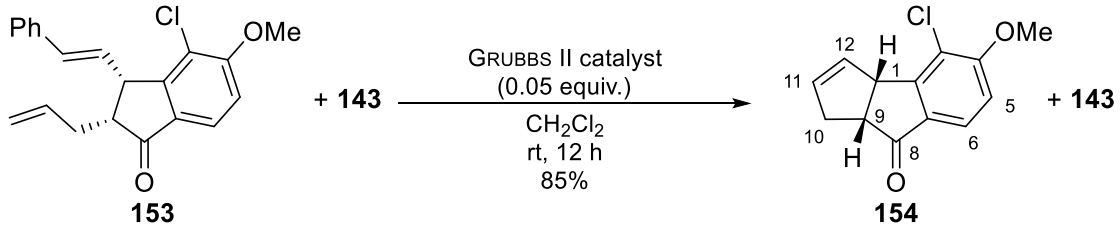
celite, washed with sat. aq. $NaHCO_3$ (3 mL) and H_2O (3x3 mL) and extracted with Et_2O (3x3 mL). The combined org. layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) allylated indanone mixture **153/143** (47.0 mg, 141 µmol, 67%, *cis*/*trans* 2:1) was obtained as yellow oil.

TLC: R_f = 0.32 (*n*-pentane/EtOAc 4:1).

The following signals could be assigned to the *cis*-configured indanone **153**.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.21-2.30 (m, 1 H, 1"-H_A), 2.80 (dtt, *J* = 1.9, 4.1, 15.5 Hz, 1 H, 1"-H_B), 2.98 (ddd, *J* = 4.1, 7.5, 10.4 Hz, 1 H, 2-H), 3.93-3.96 (m, 1 H, 3-H), 3.99 (s, 3 H, OMe), 5.09 (dd, *J* = 1.7, 9.9 Hz, 1 H, 3"-H_A), 5.17 (dd, *J* = 1.7, 17.0 Hz, 1 H, 3"-H_B), 5.95 (ddt, *J* = 6.7, 10.4, 17.0 Hz, 1 H, 2"-H), 6.14 (dd, *J* = 8.5, 15.8 Hz, 1 H, 1`-H), 6.42 (d, *J* = 15.8 Hz, 1 H, 2`-H), 7.02 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.19-7.35 (m, 5 H, Ph), 7.74 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

(8*R*,9*S*)-3-Chloro-4-methoxy-8,9-dihydrocyclopentainden-8-one 154



Indanone mixture **153/143** [M 338.83]	1.00 equiv.	139 µmol	47.0 mg
GRUBBS II catalyst [M 848.97]	0.05 equiv.	6.94 µmol	5.80 mg

Under Ar-atmosphere the allylated indanone mixture **153**/**143** (47.0 mg, 139 µmol, 1.00 equiv.) and GRUBBS II catalyst (5.80 mg, 6.94 µmol, 0.05 equiv.) were dissolved in CH_2Cl_2 (8 mL) and stirred at rt for 12 h. The reaction mixture was filtrated through a short pad of celite and all volatile compounds were removed under reduced pressure. After column

chromatography (*n*-pentane/EtOAc 4:1) an inseparable mixture of tricyclic compound **154** and *trans*-indanone **143** (32.0 mg, 121 µmol, 85%, 2:1) were obtained as yellow oil.

The following analytical data could be assigned to tricycle **154**:

TLC: R_f = 0.32 (*n*-pentane/EtOAc 4:1).

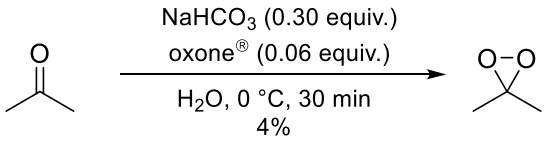
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.72 (ddd, *J* = 2.8, 6.5, 11.6 Hz, 1 H, 10-H_A), 2.82 (ddd, *J* = 2.3, 2.3, 10.5 Hz, 1 H, 10-H_B), 3.40 (ddd, *J* = 3.2, 7.0, 10.5 Hz, 1 H, 9-H), 3.99 (s, 3 H, OMe), 4.53 (dd, *J* = 2.3, 6.5 Hz, 1 H, 9-H), 5.68 (dd, *J* = 2.3, 5.5 Hz, 1 H, 11-H), 6.06 (dd, *J* = 2.3, 5.5 Hz, 1 H, 12-H), 6.96 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.66 (d, *J* = 8.4 Hz, 1 H, 6-H) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 35.5 (C10), 50.3 (C9), 51.7 (C13), 56.9 (OMe), 111.8 (C5), 124.3 (C6), 126.4 (Ar), 130.0 (Ar), 131.3 (C11), 135.11 (C12), 156.8 (Ar), 160.5 (Ar), 207.6 (C8) ppm.

HR-MS: (ESI+); m/z calc. for $C_{13}H_{11}ClO_2Na$ $[M\text{-}Na]^+$ 257.0339, found 257.0340.

Compound **154** could not be separated from **143** chromatographically, therefore no sample pure enough for a reliable measurement of optical rotation or an IR spectrum could be obtained.

3,3-Dimethyldioxirane



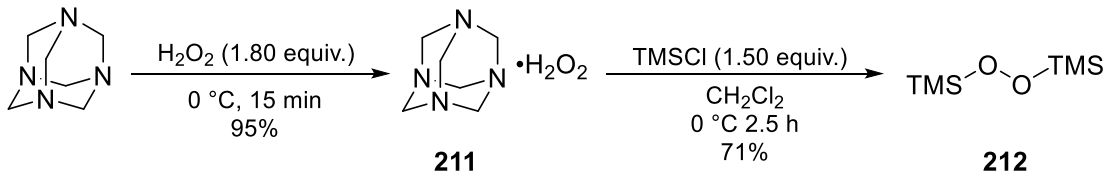
Acetone [M 58.08]	12.5 equiv.	2.58 mol	192 mL
$NaHCO_3$ [M 84.01]	3.75 equiv.	775 mmol	65.1 g
Oxone® [M 307.38]	1.00 equiv.	209 mmol	64.2 g

Acetone (192 mL, 2.58 mol, 12.5 equiv.) and $NaHCO_3$ (65.1 g, 775 mmol, 3.75 equiv.) were dissolved in H_2O (254 mL) under vigorous stirring. At 0 °C oxone® (64.2 g, 209 mmol, 1.00 equiv.) was added and the mixture was stirred at this temperature for 30 min. It was warmed to rt and DMDO (150 mL, 9.00 mmol, 0.06 M in acetone, 4%) was distilled off as pale-yellow solution into a precooled (–78 °C) flask at 120 mbar.

^{1}H-NMR: 300 MHz, $CDCl_3$; 1.67 (s, 6 H, Me) ppm.

The spectroscopic data obtained matched that reported in the literature.[152]

***Bis*(trimethylsilyl) peroxide 212**



Urotropine [M 140.19]	1.00 equiv.	143 mmol	20.0 g
H_2O_2 [30%, aq.; M 34.02; ρ 1.11]	1.80 equiv.	257 mmol	26.2 mL
TMSCl [M 108.64; ρ 0.85]	1.50 equiv.	202 mmol	25.8 mL

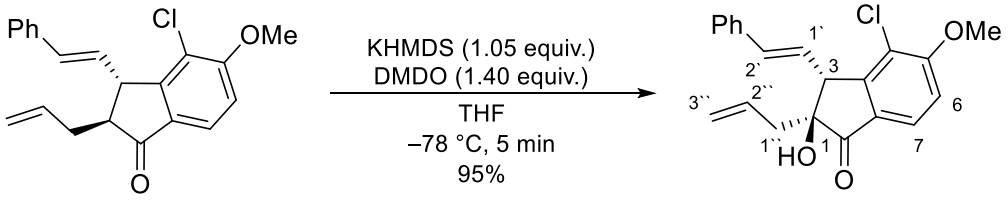
To finely powdered urotropine (20.0 g, 143 mmol, 1.00 equiv.) aq. H_2O_2 (26.2 mL, 256 mmol, 30%, 1.80 equiv.) was added slowly at 0 °C. The mixture was stirred until complete dissolution (15 min) and all volatile compounds were removed under reduced pressure. The crude H_2O_2-urotropine complex **211** (23.5 g, 135 mmol, 95%) was dried *in vacuo* and was directly used for the next step.

Under Ar-atmosphere crude **211** (23.5 g, 135 mmol, 1.00 equiv.) was suspended in CH_2Cl_2 (100 mL). At 0 °C TMSCl (25.8 mL, 202 mmol, 1.50 equiv.) was added over a period of 2 h and the mixture was stirred at this temperature for 30 min. The reaction mixture was filtrated and CH_2Cl_2 was removed at atmospheric pressure to yield *bis*(trimethylsilyl) peroxide **212** (18.0 g, 95.3 mmol, 71%) as colorless liquid.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 18 H, TMS) ppm.

The spectroscopic data of **212** matched that reported in the literature.[96]

(2*S*,3*R*)-2-Allyl-4-chloro-2-hydroxy-5-methoxy-3-((*E*)-styryl)-2,3-dihydroinden-1-one 157



143 **157**

Indanone **143** [M 338.83]	1.00 equiv.	177 µmol	60.0 mg
KHMDS [0.5 M, toluene; 199.48]	1.05 equiv.	186 µmol	370 µL
DMDO [0.06 M, acetone; M 74.08]	1.40 equiv.	248 µmol	6.16 mL

Under Ar-atmosphere allylated indanone **143** (60.0 mg, 177 µmol, 1.00 equiv.) was dissolved in THF (6 mL). At –78 °C KHMDS (370 µL, 186 µmol, 0.5 M in toluene, 1.05 equiv.) was added, the reaction mixture was stirred for 5 min, freshly prepared DMDO (6.16 mL, 248 µmol, 0.06 M in acetone, 1.40 equiv.) was added and the stirring was continued for further 2 min. Sat. aq. NH_4Cl was added to quench the reaction and it was slowly warmed to rt. The layers were separated and the aq. layer was extracted with Et_2O (3x5 mL), the combined org. layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 2:1) hydroxylated indanone **157** (60.0 mg, 173 µmol, 95%) was obtained as yellow oil.

TLC: R_f = 0.33 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.47-2.52 (m, 2 H, 1"-H), 4.00 (s, 3 H, OMe), 4.18 (d, *J* = 9.3 Hz, 1 H, 3-H), 5.18 (dd, *J* = 1.8, 11.5 Hz, 1 H, 3"-H_A), 5.22 (d, *J* = 3.2 Hz, 1 H, 3"-H_B), 5.89-6.03 (m, 1 H, 2"-H), 6.13 (dd, *J* = 9.3, 15.8 Hz, 1 H, 1`-H), 6.60 (d, *J* = 15.8 Hz, 1 H, 2`-H), 7.05 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.23-7.39 (m, 5 H, Ph), 7.76 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

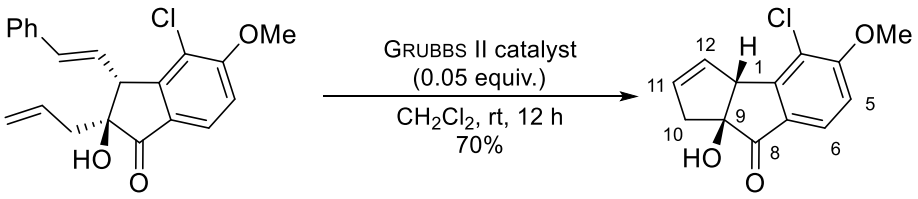
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 39.0 (C1"), 53.9 (C3), 56.8 (OMe), 81.9 (C2), 112.3 (C6), 120.5 (C3"), 121.1 (C7), 124.6 (Ar), 125.7 (Ar), 126.4 (Ar), 127.7 (Ar), 128.0 (C2`), 128.6 (Ar), 131.5 (C2`), 134.2 (C1"), 136.9 (Ar), 151.8 (Ar), 161.5 (Ar), 202.9 (C1) ppm.

HR-MS: (ESI+); m/z calc. for $C_{21}H_{19}ClO_3Na$ $[M-Na]^+$ 377.0915, found 377.0910.

FT-IR: (neat); ῡ = 3470 (w), 3403 (w), 2977 (w), 2925 (w), 2361 (m), 1713 (s), 1596 (s), 1572 (w), 1479 (w), 1438 (w), 1394 (w), 1332 (m), 1283 (s), 1158 (w), 1130 (w), 1062 (m), 996 (w), 968 (w), 920 (w), 787 (w), 755 (w), 696 (w), 456 (w) cm^{-1}.

Due to the low stability of **157** upon purification no sample pure enough for a reliable measurement of optical rotation could be obtained.

(1*R*,9*S*)-3-Chloro-9-hydroxy-4-methoxy-1,10-dihydrocyclopentainden-8-one 155



157 **155**

Indanone **157** [M 356.85]	1.00 equiv.	168 µmol	60.0 mg
GRUBBS II catalyst [M 848.97]	0.05 equiv.	8.45 µmol	7.18 mg

Under Ar-atmosphere **157** (60.0 mg, 168 µmol, 1.00 equiv.) and GRUBBS II catalyst (7.18 mg, 8.45 µmol, 0.05 equiv.) were dissolved in CH_2Cl_2 (8 mL) and stirred at rt for 12 h. The reaction mixture was filtrated through a short pad of celite and all volatile compounds were removed under reduced pressure. After column chromatography (*n*-pentane/EtOAc 2:1) tricyclic compound **155** (30.0 mg, 0.12 mmol, 70%) was obtained as colorless crystals.

TLC: R_f = 0.27 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 500 MHz, $CDCl_3$; δ = 2.67 (dtd, *J* = 1.1, 2.2, 18.5 Hz, 1 H, 10-H_A), 2.84 (dq, *J* = 2.4, 18.5 Hz, 1 H, 10-H_B), 4.00 (s, 3 H, OMe), 4.26 (s_{br}, 1 H, 1-H), 5.68 (dq, *J* = 2.2, 6.0 Hz, 1 H, 11-H), 6.19 (dq, *J* = 2.4, 6.0 Hz, 1 H, 12-H), 7.00 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.70 (d, *J* = 8.4 Hz, 1 H, 6-H) ppm.

^{13}C-NMR: 126 MHz, $CDCl_3$; δ = 43.9 (C10), 56.9 (OMe), 58.9 (C1), 86.5 (C9), 112.3 (C5), 119.8 (Ar), 125.3 (C6), 127.7 (Ar), 128.8 (C11), 129.9 (C12), 153.9 (Ar), 161.5 (Ar), 204.6 (C8) ppm.

HR-MS: (ESI+); m/z calc. for $C_{13}H_{11}ClO_3Na$ $[M\text{-}Na]^+$ 273.0289, found 273.0285.

FT-IR: (neat); ῡ = 3413 (w), 3058 (w), 3024 (w), 2930 (w), 2847 (w), 1710 (s), 1595 (s), 1571 (w), 1479 (w), 1438 (w), 1330 (m), 1283 (s), 1249 (w), 1164 (w),

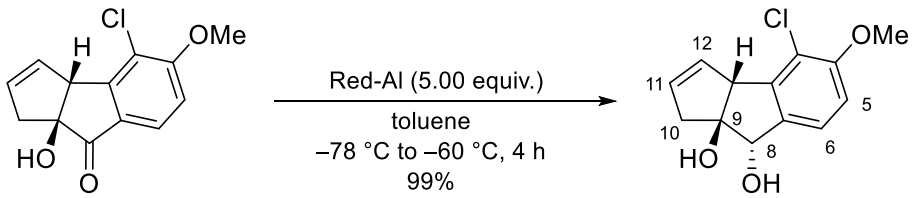
1131 (m), 1062 (m), 1002 (w), 966 (w), 924 (w), 899 (w), 820 (w), 780 (w), 754 (w), 695 (w), 642 (w), 598 (w), 544 (w) cm^{-1}.

m.p.: 135 °C (EtOAc).

[α]: 109 (c 0.50, $CHCl_3$).

When the reaction sequence of allylation, *α*-hydroxylation and ring closing metathesis was streamlined with the respective crude product mixtures 228 mg (25%) of tricycle **155** were obtained starting from **143** (1.10 g, 3.68 mmol).

8.2.4 Reduction of *α*-hydroxyketone 155



155 **158**

Ketone **155** [M 250.68]	1.00 equiv.	878 µmol	220 mg
Red-Al [3.5 M, toluene; 92.14]	5.00 equiv.	4.39 mmol	1.25 mL

Under Ar-atmosphere a solution of tricycle **155** (220 mg, 878 µmol, 1.00 equiv.) in toluene (24 mL) was added to precooled Red-Al (1.25 mL, 4.39 mmol, 3.5 M in toluene, 5.00 equiv.) at –78 °C. The mixture was slowly warmed to –60 °C and was stirred at this temperature for 4 h. Sat. aq. ROCHELLE salt (25 mL) was added and the mixture was slowly warmed to rt. The layers were separated and the aq. layer was extracted with EtOAc (3x25 mL). The combined org. layers were dried over Na_2SO_4, filtrated and all volatile compounds were removed under reduced pressure to yield *trans*-diol **158** (221 mg, 0.88 mmol, 99%) as colorless crystals which were used for the next step without further purification.

If the reaction was performed at temperatures above –60 °C up to 25% of *cis*-diol **159** were obtained as colorless oil.

(1*R*,8*S*,9*S*)-3-Chloro-4-methoxy-1,10-dihydrocyclopentaindene-8,9-diol 158

TLC: R_f = 0.17 (*n*-pentane/EtOAc 1:1).

^{1}H-NMR: 500 MHz, CD_3OD; δ = 2.31 (dt, *J* = 2.2, 17.7 Hz, 1 H, 10-H_A), 2.98 (dq, *J* = 2.2, 17.7 Hz, 1 H, 10-H_B), 3.86 (s, 3 H, OMe), 3.92 (d, *J* = 2.3 Hz, 1 H, 1-H), 4.98 (s, 1 H, 8-H), 5.72 (ddd, *J* = 2.2, 2.2, 6.0 Hz, 1 H, 11-H), 6.12 (dtd, *J* = 2.3, 2.6, 6.0 Hz, 1 H, 12-H), 6.98 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.23 (d, *J* = 8.3 Hz, 1 H, 6-H) ppm.

^{13}C-NMR: 126 MHz, CD_3OD; δ = 41.4 (C10), 56.9 (OMe), 65.5 (C1), 83.2 (C8), 92.6 (C9), 112.8 (C5), 119.7 (Ar), 125.0 (C6), 130.5 (C11), 131.4 (C12) 137.6 (Ar), 142.9 (Ar), 156.9 (Ar) ppm.

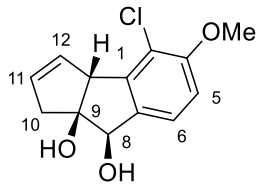
HR-MS: (ESI+); m/z calc. for $C_{13}H_{13}ClO_3Na$ $[M\text{-}Na]^+$ 275.0445, found 275.0441.

FT-IR: (neat); ῡ = 3399 (w), 3055 (w), 2923 (m), 2849 (w), 1707 (m), 1597 (m), 1572 (w), 1478 (m), 1437 (w), 1328 (w), 1283 (s), 1261 (w), 1164 (w), 1132 (w), 1066 (s), 957 (w), 926 (w), 897 (w), 809 (m), 721 (w), 699 (w), 601 (w) cm^{-1}.

m.p.: 145 °C (decomposition).

[α]: 208 (c 0.56, EtOAc).

(1*R*,8*R*,9*S*)-3-Chloro-4-methoxy-1,10-dihydrocyclopentaindene-8,9-diol 159



159

TLC: R_f = 0.23 (*n*-pentane/EtOAc 1:1).

^{1}H-NMR: 500 MHz, CD_3OD; δ = 2.56 (d, *J* = 2.2 Hz, 1 H, 10-H_A), 2.57 (d, *J* = 2.2 Hz, 1 H, 10-H_B), 3.85 (s, 3 H, OMe), 4.07 (d, *J* = 2.1 Hz, 1 H, 1-H), 4.77 (s, 1 H, 8-H), 5.69 (dq, *J* = 2.2, 6.0 Hz, 1 H, 11-H), 5.96 (dq, *J* = 2.1, 6.0 Hz, 1 H, 12-H), 6.95 (d, *J* = 8.2 Hz, 1 H, 5-H), 7.24 (dd, *J* = 0.9, 8.2 Hz, 1 H, 6-H) ppm.

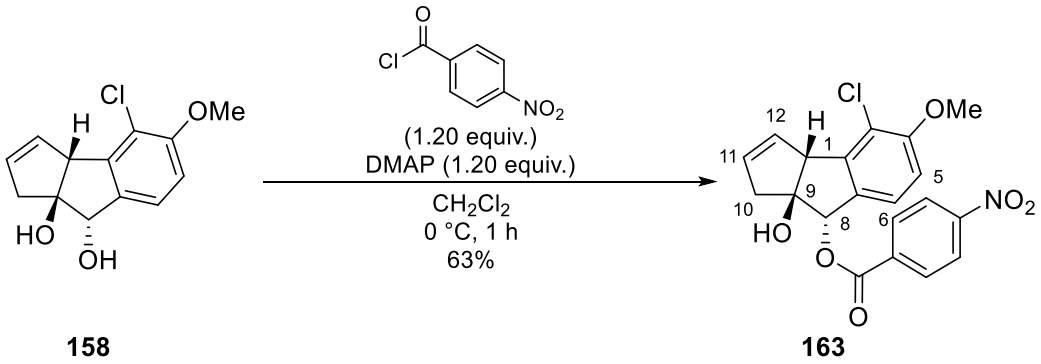
^{13}C-NMR: 126 MHz, CD_3OD; δ = 43.9 (C10), 55.5 (OMe), 61.4 (C1), 79.1 (C8), 88.5 (C9), 111.2 (Ar), 118.4 (Ar), 123.9 (Ar), 129.0 (C11), 129.3 (C12), 136.5 (Ar), 141.8 (Ar), 155.6 (Ar) ppm.

HR-MS: (ESI+); m/z calc. for $C_{13}H_{13}ClO_3Na$ $[M\text{-}Na]^+$ 275.0445, found 275.0441.

FT-IR: (neat); ῡ = 3357 (w), 3056 (w), 3006 (w), 2931 (w), 2841 (w), 2508 (w), 1721 (w), 1607 (w), 1574 (w), 1477 (m), 1436 (w), 1319 (w), 1260 (s), 1189 (w), 1164 (w), 1136 (w), 1067 (s), 1037 (w), 1009 (w), 952 (w), 897 (m), 810 (m), 771 (m), 747 (w), 720 (w), 677 (w), 654 (w), 602 (w) cm^{-1}.

The *cis*-diol **159** was obtained from a racemic sample of tricyclic compound **161**, therefore no measurement of optical rotation was performed.

(1*R*,8*S*,9*S*)-3-Chloro-9-hydroxy-4-methoxy-1,8,9,10-tetrahydrocyclopentainden-8-yl 4-nitrobenzoate 163



158 **163**

trans-Diol **158** [M 252.69]	1.00 equiv.	47.5 µmol	12.0 mg
DMAP [M 122.17]	1.50 equiv.	71.2 µmol	8.70 mg
para-Nitro benzoyl chloride [M 185.56]	1.20 equiv.	57.0 µmol	10.6 mg

Under Ar-atmosphere diol **158** (12.0 mg, 47.5 µmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (0.5 mL). At 0 °C DMAP (8.70 mg, 71.2 µmol, 1.50 equiv.) and *para*-nitro benzoyl chloride (10.6 mg, 57.0 µmol, 1.20 equiv.) were added and the mixture was stirred at this temperature for 1 h. The reaction was quenched by the addition of H_2O (2 mL), extracted with Et_2O (3x2 mL), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) ester **163** (12.0 mg, 29.9 µmol, 63%) was obtained as colorless oil.

TLC: R_f = 0.18 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, C_6D_6; δ = 2.22 (ddt, *J* = 2.2, 2.2, 17.5 Hz, 1 H, 10-H_A), 2.74 (ddt, *J* = 2.2, 2.2, 17.5 Hz, 1 H, 10-H_B), 3.23 (s, 3 H, OMe), 4.22 (s_{br}, 1 H, 1-H), 5.51 (ddt, *J* = 2.2, 2.2, 6.0 Hz, 1 H, 11-H), 6.18 (d, *J* = 0.9 Hz, 1 H, 8-H), 6.31 (dtd, *J* = 2.2, 2.2, 6.0 Hz, 1 H, 12-H), 6.40 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.03 (dd, *J* = 0.9, 8.3 Hz, 1 H, 6-H) ppm.

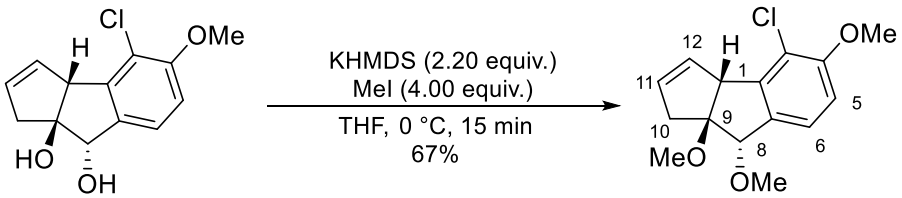
^{13}C-NMR: 75 MHz, C_6D_6; δ = 42.4 (C10), 55.9 (OMe), 63.3 (C1), 87.4 (C8), 91.1 (C9), 111.8 (C5), 119.8 (Ar), 123.6 (Ph), 124.3 (C6), 129.8 (C11), 130.0 (C12), 130.7 (Ph), 131.5 (Ph), 134.7 (Ph), 143.0 (Ar), 150.9 (Ar), 157.0 (Ar), 165.9 (CO) ppm.

HR-MS: (ESI+); m/z calc. for $C_{20}H_{16}ClNO_6Na$ $[M\text{-}Na]^+$ 424.0558, found 424.0569.

FT-IR: (neat); ῡ = 3246 (s), 2943 (s), 2836 (s), 1601 (s), 1576 (m), 1496 (m), 1461 (s), 1423 (m), 1362 (m), 1305 (s), 1286 (s), 1241 (m), 1187 (w), 1147 (s), 1053 (m), 1023 (m), 993 (m), 922 (s), 871 (s), 785 (s), 618 (m), 573 (s), 549 (m), 522 (s) cm^{-1}.

[α]: 121 (c 0.63, EtOAc).

(1*R*,8*S*,9*S*)-3-Chloro-4,8,9-trimethoxy-1,8,9,10-tetrahydrocyclopentaindene 162



158 **162**

trans-Diol **158** [M 252.69]	1.00 equiv.	772 µmol	195 mg
KHMDS [0.5 M, toluene; 199.48]	2.20 equiv.	1.70 mmol	3.39 mL
MeI [M 141.94; ρ 2.28]	4.00 equiv.	3.08 mmol	192 µL

Under Ar-atmosphere diol **158** (195 mg, 772 µmol, 1.00 equiv.) was dissolved in THF (15 mL). At 0 °C KHMDS (3.39 mL, 1.70 mmol, 0.5 M in toluene, 2.20 equiv.) and MeI (192 µL, 3.08 mmol, 4.00 equiv.) were added and the mixture was stirred at this temperature

for 15 min. The reaction was quenched by the addition of H_2O (15 mL), extracted with Et_2O (3x20 mL), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) methylated compound **162** (150 mg, 534 µmol, 67%) was obtained as colorless oil.

TLC: R_f = 0.50 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 500 MHz, CD_3OD; δ = 2.50 (ddt, *J* = 1.2, 2.5, 18.5 Hz, 1 H, 10-H_A), 2.87 (ddt, *J* = 2.0, 2.8, 18.5 Hz, 1 H, 10-H_B), 3.28 (s, 3 H, OMe), 3.54 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 4.09 (d, *J* = 2.1 Hz, 1 H, 1-H), 4.75 (s, 1 H, 8-H), 5.76 (ddt, *J* = 2.0, 2.5, 6.0 Hz, 1 H, 11-H), 6.19 (dtd, *J* = 2.1, 2.8, 6.0 Hz, 1 H, 12-H), 6.95 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.17 (d, *J* = 8.3 Hz, 1 H, 6-H) ppm.

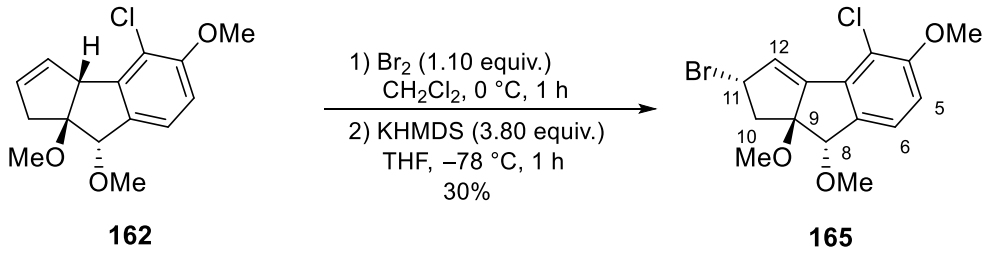
^{13}C-NMR: 126 MHz, CD_3OD; δ = 36.2 (C10), 51.8 (C1), 56.8 (OMe), 58.8 (OMe), 58.9 (OMe), 90.2 (C8), 98.6 (C9), 112.8 (C5), 119.4 (Ar), 125.3 (C6), 130.5 (C12), 131.7 (C11), 135.0 (Ar), 142.0 (Ar), 157.0 (Ar) ppm.

HR-MS: (ESI+); m/z calc. for $C_{15}H_{17}ClO_3Na$ $[M\text{-}Na]^+$ 303.0758, found 303.0758.

FT-IR: (neat); ϋ = 3051 (w), 2935 (m), 2830 (w), 1607 (w), 1576 (w), 1480 (m), 1440 (w), 1354 (w), 1324 (w), 1304 (w), 1274 (m), 1248 (w), 1195 (w), 1166 (w), 1140 (w), 1091 (w), 1069 (s), 1016 (w), 984 (w), 952 (w), 910 (w), 874 (w), 814 (w), 782 (w), 736 (w), 697 (w), 671 (w), 628 (w), 596 (w) cm^{-1}.

[α]: 117 (c 0.57, EtOAc).

(8*S*,9*S*,12*S*)-11-Bromo-3-chloro-4,8,9-trimethoxy-8,9,10,11-tetrahydrocyclopentaindene 165



162 **165**

Olefin **162** [M 280.75]	1.00 equiv.	74.8 µmol	21.0 mg
Bromine [0.26 M, CH_2Cl_2; M 159.81]	1.10 equiv.	82.5 µmol	317 µL
KHMDS [0.5 M, toluene; 199.48]	3.80 equiv.	279 µmol	559 µL

Under Ar-atmosphere olefin **162** (21.0 mg, 74.8 µmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (1 mL). At 0 °C Br_2 (317 µL, 82.5 µmol, 0.26 M in CH_2Cl_2, 1.10 equiv.) was added and the mixture was stirred at this temperature for 30 min. Phosphate puffer solution (1.5 mL, pH = 7) was added and the excess of Br_2 quenched by addition of 20% aq. $Na_2S_2O_3$ (3 mL). The reaction mixture was extracted with CH_2Cl_2 (3x5 mL) and dried over Na_2SO_4. It was filtrated and all volatile compounds were removed *in vacuo*. Since the resulting dibromide **164** decomposed upon purification the crude product was directly used for the next step.

The crude dibromide **164** was dissolved in THF (0.5 mL) under Ar-atmosphere. At –78 °C KHMDS (559 µL, 279 µmol, 0.5 M in toluene, 3.80 equiv.) was added and the mixture was stirred at this temperature for 1 h. Sat. aq. NH_4Cl (2 mL) was added, it was extracted with Et_2O (3x5 mL), the combined org. layers were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. After column chromatography (*n*-pentane/EtOAc 4:1) allyl bromide **165** (8.00 mg, 22.2 µmol, 30%) was obtained as colorless oil.

TLC: R_f = 0.23 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, acetone-d_6; δ = 2.66 (dd, *J* = 6.3, 14.4 Hz, 1 H, 10-H_A), 2.84 (dd, *J* = 6.3, 14.4 Hz, 1 H, 10-H_B), 3.14 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.25 (s, 1 H, 8-H), 5.69 (dt, *J* = 1.6, 6.3 Hz, 1 H, 11-H), 6.48

(d, J = 1.6 Hz, 1 H, 12-H), 7.09 (d, J = 8.3 Hz, 1 H, 5-H), 7.47 (d, J = 8.3 Hz, 1 H, 6-H) ppm.

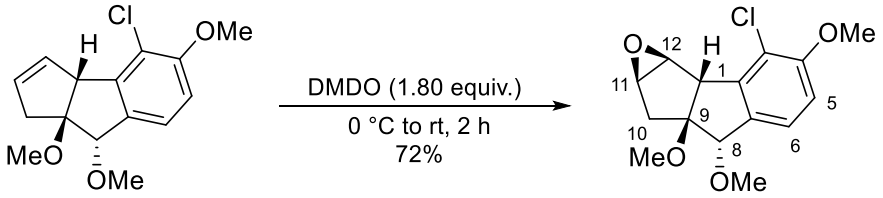
^{13}C-NMR: 75 MHz, acetone-d_6: δ = 40.3 (C10), 51.5 (C11), 56.7 (OMe), 57.0 (OMe), 57.0 (OMe), 57.8 (OMe), 83.2 (C8), 99.8 (C9), 113.5 (C5), 127.5 (C6), 130.0 (C12), 134.9 (Ar), 141.8 (Ar), 147.9 (Ar), 157.0 (Ar) ppm.

HR-MS: (ESI+); m/z calc. for $C_{15}H_{16}ClO_3$ $[M-H]^+$ 279.0793, found 279.0782.

FT-IR: (neat); ῡ = 3286 (m), 2925 (m), 2853 (w), 1604 (w), 1477 (m), 1432 (w), 1308 (w), 1282 (m), 1189 (w), 1165 (w), 1141 (w), 1101 (w), 1066 (s), 1037 (w), 975 (w), 891 (w), 817 (m), 789 (w), 721 (w), 697 (w), 669 (w) cm^{-1}.

The bromination/elimination sequence of **165** was performed using a racemic sample, therefore no measurement of optical rotation was done.

(1*S*,8*S*,9*S*,11*S*,12*R*)-3-Chloro-4,8,9-trimethoxy-1,8,9,10,11,12hexahydrobenzo[1,8]pentaleno[11,12]oxirene 171



162 **171**

Olefin **162** [M 280.75]	1.00 equiv.	594 µmol	150 mg
DMDO [0.06 M, acetone; M 74.08]	1.80 equiv.	1.06 mmol	17.8 mL

Under Ar-atmosphere olefin **162** (150 mg, 594 µmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL). At 0 °C freshly distilled DMDO (17.8 mL, 1.06 mmol, 0.06 M in acetone,

1.80 equiv.) was added and the mixture was stirred at rt for 2 h. All volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) epoxide **171** (126 mg, 428 µmol, 72%) was obtained as colorless oil.

TLC: R_f = 0.29 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, C_6D_6; δ = 2.10 (d, *J* = 15.9 Hz, 1 H, 10-H_A), 2.44 (dd, *J* = 2.4, 15.9 Hz, 1 H, 10-H_B), 2.95 (dd, *J* = 2.4, 2.4 Hz, 1 H, 11-H), 3.20 (s, 3 H, OMe), 3.22 (s, 3 H, OMe), 3.34 (s, 3 H, OMe), 3.93 (s_{br}, 1 H, 1-H), 4.02 (d, *J* = 2.4 Hz, 1 H, 12-H), 4.69 (d, *J* = 1.0 Hz, 1 H, 8-H), 6.37 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.14 (dd, *J* = 1.0, 8.3 Hz, 1 H, 6-H) ppm.

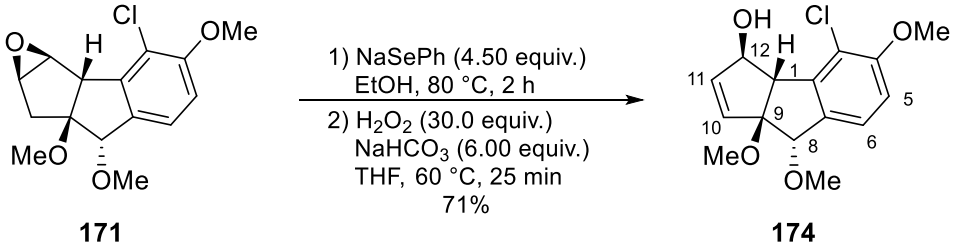
^{13}C-NMR: 75 MHz, C_6D_6; δ = 31.4 (C10), 51.6 (OMe), 52.5 (C1), 55.6 (C12), 57.6 (OMe), 57.8 (C11), 58.8 (OMe), 90.1 (C9), 97.7 (C8), 112.1 (C5), 124.2 (C6), 127.8 (Ar), 135.0 (Ar), 137.8 (Ar), 156.8 (Ar) ppm.

HR-MS: (ESI+); m/z calc. for $C_{15}H_{17}ClO_4Na$ $[M-Na]^+$ 319.0708, found 319.0707.

FT-IR: (neat); ῡ = 2939 (m), 2833 (w), 1715 (w), 1605 (w), 1576 (w), 1480 (m), 1439 (w), 1400 (w), 1355 (w), 1327 (w), 1307 (w), 1279 (m), 1251 (w), 1197 (w), 1168 (w), 1139 (w), 1099 (w), 1068 (s), 982 (w), 951 (w), 912 (w), 873 (w), 843 (m), 816 (w), 787 (w), 723 (w), 691 (w), 600 (w), 568 (w) cm^{-1}.

[α]: 24 (c 0.62, EtOAc).

(1*S*,8*S*,9*S*,12*R*)-3-Chloro-4,8,9-trimethoxy-1,8,9,12-tetrahydrocyclopentainden-12-ol 174



171 **174**

Epoxide **171** [M 296.75]	1.00 equiv.	118 µmol	35.0 mg
Diphenyl diselenide [M 312.13]	4.50 equiv.	531 µmol	165 mg
$NaBH_4$ [M 37.83]	8.80 equiv.	1.04 mmol	39.3 mg
$NaHCO_3$ [M 84.00]	6.00 equiv.	708 µmol	59.4 mg
H_2O_2 [30wt%, aq.; M 34.02]	30.0 equiv.	3.53 mmol	361 µL

Under Ar-atmosphere diphenyl diselenide (165 mg, 531 µmol, 4.50 equiv.) was dissolved in degassed EtOH (8 mL). At 0 °C $NaBH_4$ (39.3 mg, 1.04 mmol, 8.80 equiv.) was added. After 15 min the solution was added to epoxide **171** (35.0 mg, 118 µmol, 1.00 equiv.) and the mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt, THF (15 mL), $NaHCO_3$ (59.4 mg, 708 µmol, 6.00 equiv.) and aq. H_2O_2 (361 µL, 3.53 mmol, 30%, 30.00 equiv.) were added and the heating was continued for 25 min. Sat. aq. NH_4Cl was added to quench the reaction, it was extracted with Et_2O (3x15 mL), dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo* to yield allylic alcohol **174** (25.0 mg, 84.2 µmol, 71%) as colorless oil after column chromatography (*n*-pentane/EtOAc 2:1).

TLC: R_f = 0.27 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 300 MHz, C_6D_6; δ = 1.75 (s_{br}, 1 H, OH), 3.25 (s, 3 H, OMe), 3.27 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.53 (s, 1 H, 1-H), 4.66 (s_{br}, 1 H, 12-H), 4.94 (d, *J* = 1.1 Hz, 1 H, 8-H), 5.77 (dd, *J* = 2.4, 5.7 Hz, 1 H, 11-H), 5.84 (d, *J* = 5.7 Hz, 1 H, 10-H), 6.36 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.11 (dd, *J* = 1.1, 8.3 Hz, 1 H, 6-H) ppm.

^{13}C-NMR: 75 MHz, C_6D_6; δ = 52.1 (OMe), 55.9 (C1), 58.7 (OMe), 59.0 (OMe), 80.8 (C12), 91.9 (C8), 102.0 (C9), 112.2 (C5), 119.9 (Ar), 124.7 (C6), 132.8 (C10), 135.2 (Ar), 137.4 (C11), 141.2 (Ar), 156.1 (Ar) ppm.

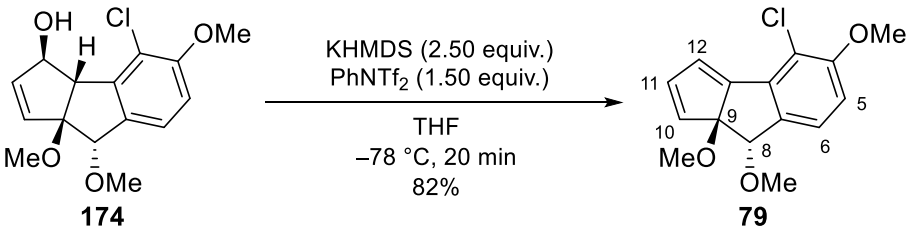
HR-MS: (ESI+); m/z calc. for $C_{15}H_{17}ClO_4Na$ $[M\text{-}Na]^+$ 319.0708, found 319.0709.

FT-IR: (neat); ῦ = 3433 (s_{br}), 2938 (w), 2830 (w), 2128 (w), 1716 (w), 1606 (w), 1577 (m), 1481 (w), 1439 (w), 1357 (m), 1321 (s), 1277 (s), 1239 (m), 1193 (m), 1171 (m), 1149 (m), 1089 (s), 1066 (s), 1036 (m), 1016 (m), 988 (w), 969 (w), 949 (w), 907 (w), 808 (s), 788 (m), 754 (m), 714 (w), 602 (m), 540 (w), 513 (w) cm^{-1}.

[α]: 129 (c 0.49, EtOAc).

If the reaction sequence of reduction, methylation, epoxidation and GRIECO elimination was streamlined with the respective crude products 21.0 mg (32%) of allyl alcohol **174** could be obtained starting from tricyclic compound **155** (55.0 mg, 224 µmol).

(8*S*,9*S*)-3-Chloro-4,8,9-trimethoxy-8,9-dihydrocyclopentaindene 79



Allyl alcohol **174** [M 296.75]	1.00 equiv.	43.8 µmol	13.0 mg
$PhNTf_2$ [357.25]	1.50 equiv.	65.7 µmol	23.5 mg
KHMDS [0.5 M, toluene; 199.48]	2.50 equiv.	110 µmol	219 µL

Under Ar-atmosphere allylic alcohol **174** (13.0 mg, 43.8 µmol, 1.00 equiv.) was dissolved in THF (1 mL). At –78 °C KHMDS (219 µL, 110 µmol, 0.5 M in toluene, 2.50 equiv.) and $PhNTf_2$ (23.5 mg, 65.7 µmol, 1.50 equiv.) were added. After stirring at this temperature for 20 min the solution was quenched by the addition of H_2O (2 mL), extracted with Et_2O (3x3 mL), dried over Na_2SO_4 and filtrated. All volatiles were removed *in vacuo* to yield cyclopentadiene **79** (10.0 mg, 35.9 µmol, 82%) as colorless oil after column chromatography (*n*-pentane/EtOAc 4:1).

TLC: R_f = 0.50 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 500 MHz, C_6D_6; δ = 3.00 (s, 3 H, OMe), 3.06 (s, 3 H, OMe), 3.22 (s, 3 H, OMe), 4.77 (s, 1 H, 8-H), 6.22 (d, *J* = 8.1 Hz, 1 H, 5-H), 6.27 (dd, *J* = 0.7, 5.4 Hz, 1 H, 10-H), 6.29 (dd, *J* = 1.9, 5.4 Hz, 1 H, 11-H), 6.59 (d, *J* = 1.9 Hz, 1 H, 12-H), 7.02 (d, *J* = 8.1 Hz, 1 H, 6-H) ppm.

^{13}C-NMR: 126 MHz, C_6D_6; δ = 51.3 (OMe), 55.4 (OMe), 55.9 (OMe), 85.8 (C8), 100.7 (C9), 110.2 (C5), 118.4 (Ar), 126.1 (C6), 126.9 (C12), 135.2 (C10), 136.1 (Ar), 138.1 (C11), 144.0 (Ar), 151.0 (C13), 156.5 (Ar) ppm.

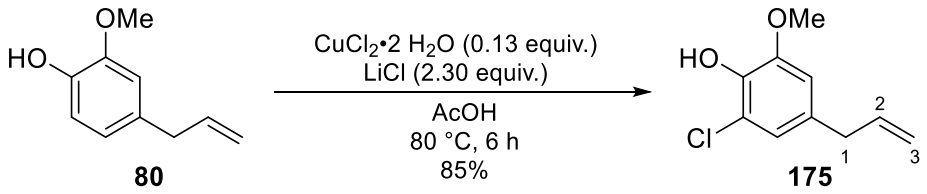
HR-MS: (ESI+); m/z calc. for $C_{15}H_{15}ClO_3Na$ $[M\text{-}Na]^+$ 301.0602, found 301.0603.

FT-IR: (neat); ϑ̃ = 3070 (w), 2933 (w), 2896 (w), 2824 (w), 1603 (w), 1563 (w), 1467 (m), 1437 (w), 1337 (w), 1277 (m), 1195 (w), 1172 (w), 1091 (s), 1055 (w), 1006 (w), 980 (w), 936 (w), 864 (w), 810 (w), 761 (w), 717 (w), 601 (w) cm^{-1}.

[α]: 126 (c 0.75, EtOAc).

8.3 Synthetic Procedures for Preparation of Oxathiazinane 192

8.3.1 4-Allyl-2-chloro-6-methoxyphenol 175



Eugenol (**80**) [M 164.20]	1.00 equiv.	50.0 mmol	7.65 mL
$CuCl_2 \cdot 2\ H_2O$ [M 170.48]	0.13 equiv	6.25 mmol	1.08 g
LiCl [M 42.39]	2.30 equiv.	112 mmol	4.25 g

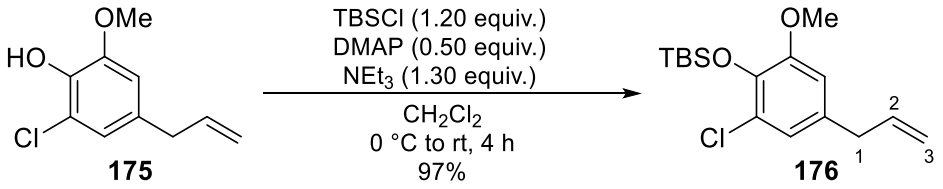
Under O_2-atmosphere eugenol (**80**) (7.65 mL, 50.0 mmol, 1.00 equiv.) was dissolved in AcOH (125 mL), $CuCl_2 \cdot 2\ H_2O$ (1.08 g, 6.25 mmol, 0.13 equiv.) and LiCl (4.25 g, 112 mmol, 2.30 equiv.) were added and the mixture was stirred at 80 °C for 6 h. Sat. aq. $NaHCO_3$ (100 mL) was added, the reaction mixture was extracted with Et_2O (3x150 mL), the combined org. layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 8:1) 6-chloroeugenol **175** (8.43 g, 42.4 mmol, 85%) was isolated as pale-yellow oil.

TLC: $R_f = 0.23$ (*n*-pentane/EtOAc 8:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.29 (ddt, $J = 0.7, 1.4, 6.7$ Hz, 2 H, 1-H), 3.86 (s, 3 H, OMe), 5.04-5.07 (m, 1 H, 3-H_A), 5.09-5.12 (m, 1 H, 3-H_B), 5.78 (s, 1 H, ArOH), 5.91 (ddt, $J = 6.7, 9.6, 17.5$ Hz, 1 H, 2-H), 6.59 (s, 1 H, Ar), 6.77 (s, 1 H, Ar) ppm.

The analytical data were in accordance with that reported in the literature.[112]

(4-Allyl-2-chloro-6-methoxyphenoxy)(*tert*-butyl)dimethylsilane 176



6-Chloroeugenol **175** [M 198.65]	1.00 equiv.	24.6 mmol	4.88 g
TBSCl [M 150.72]	1.20 equiv.	29.5 mmol	4.44 g
DMAP [M 122.17]	0.50 equiv.	12.3 mmol	1.50 g
NEt_3 [M 101.19; ρ 0.73]	1.30 equiv.	31.9 mmol	4.43 mL

Under Ar-atmosphere 6-chloroeugenol **175** (4.88 g, 24.6 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (100 mL). At 0 °C DMAP (1.50 g, 12.3 mmol, 0.50 equiv.), NEt_3 (4.26 mL, 31.9 mmol, 1.30 equiv.) and TBSCl (4.42 g, 29.5 mmol, 1.20 equiv.) were added and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (50 mL) and brine (50 mL) and was dried over Na_2SO_4. All volatiles were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 40:1) TBS-protected chloroeugenol **176** (7.43 g, 23.7 mmol, 97%) was obtained as colorless oil.

TLC: R_f = 0.65 (*n*-pentane/EtOAc 40:1).

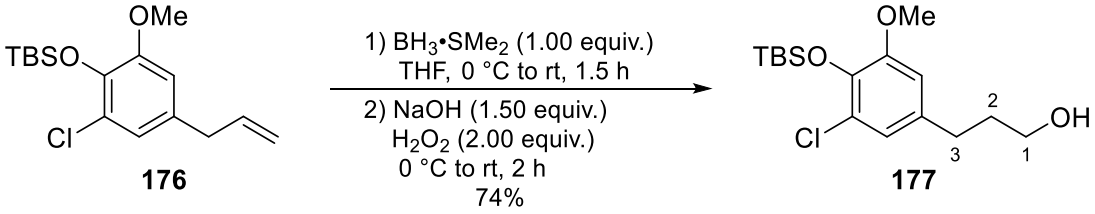
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 6 H, TBS), 1.04 (s, 9 H, TBS), 3.29 (d, *J* = 6.7 Hz, 2 H, 1-H), 3.78 (s, 3 H, OMe), 5.04-5.13 (m, 2 H, 3-H), 5.93 (ddt, *J* = 6.7, 9.6, 17.4 Hz, 1 H, 2-H), 6.57 (s, 1 H, Ar), 6.79 (s, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –4.0 (TBS), 19.0 (TBS), 26.1 (TBS), 39.8 (C1), 55.5 (OMe), 110.7 (Ar), 116.4 (C3), 122.0 (Ar), 133.4 (Ar), 137.1 (C2), 151.5 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{16}H_{25}ClO_2Na$ $[M\text{-}Na]^+$ 564.1244, found 564.1249.

FT-IR: (neat): $\tilde{\upsilon}$ = 2937 (w), 1598 (w), 1572 (m), 1490 (s), 1461 (w), 1415 (m), 1273 (m), 1235 (m), 1181 (w), 1140 (m), 1051 (s), 1001 (s), 968 (w), 913 (m), 837 (m), 778 (m), 686 (m), 598 (w), 3078 (w), 3002 (w), 2830 (w), 1639 (w) cm^{-1}.

3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-chloro-5-methoxyphenyl)propanol 177



TBS-protected 6-chloroeugenol **176** [M 312.91]	1.00 equiv.	23.7 mmol	7.43 g
BH_3•SMe [M 75.96; ρ 0.80]	1.00 equiv.	23.7 mmol	2.25 mL
NaOH [15wt% aq.; M 40.00]	1.50 equiv.	35.6 mmol	8.20 mL
H_2O_2 [30wt% aq.; M 34.02; ρ 1.11]	2.00 equiv.	47.4 mmol	4.90 mL

Under Ar-atmosphere olefin **176** (7.43 g, 23.7 mmol, 1.00 equiv.) was dissolved in THF (120 mL). At 0 °C $BH_3 \cdot SMe_2$ (2.25 mL, 23.7 mmol, 1.00 equiv.) was added, the mixture was stirred at this temperature for 10 min and at rt for 1 h. Aq. NaOH (8.20 mL, 35.6 mmol, 15wt%, 1.50 equiv.) and aq. H_2O_2 (4.90 mL, 47.4 mmol, 30%, 2.00 equiv.) were added at 0 °C and the reaction mixture was stirred for 2 h at rt. The reaction was quenched with brine (100 mL), extracted with Et_2O (3x50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 1:1) alcohol **177** (5.82 g, 17.6 mmol, 74%) was obtained as colorless oil.

TLC: R_f = 0.65 (EtOAc).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.18 (s, 6 H, TBS), 1.03 (s, 9 H, TBS), 1.71 (s, 1 H, OH), 1.84 (dt, *J* = 6.4, 13.5 Hz, 2 H, 2-H), 2.60 (dd, *J* = 6.8, 8.6 Hz, 2 H, 3-H),

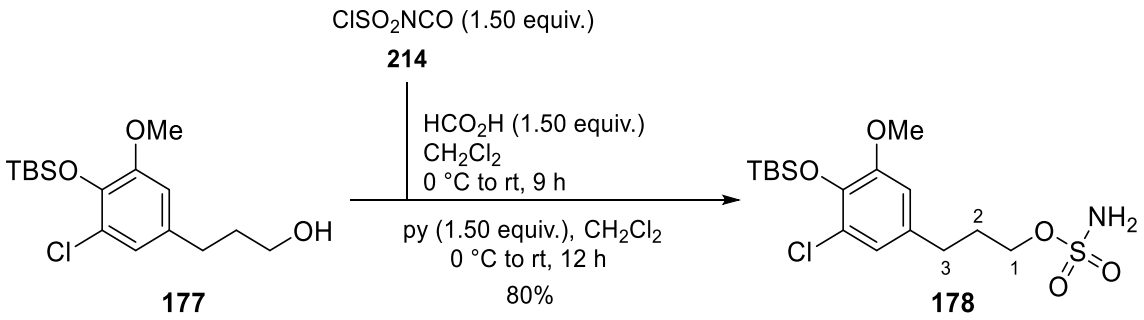
3.65 (t, *J* = 6.4 Hz, 2 H, 1-H), 3.77 (s, 3 H, OMe), 6.58 (d, *J* = 2.0 Hz, 1 H, Ar), 6.77 (d, *J* = 2.0 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –4.0 (TBS), 19.1 (TBS), 26.1 (TBS), 31.8 (C2), 34.2 (C3), 55.5 (OMe), 62.2 (C1), 110.6 (Ar), 121.7 (Ar), 125.7 (Ar), 135.1 (Ar), 139.9 (Ar), 151.5 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{16}H_{28}ClO_3Si$ $[M-H]^+$ 331.1491, found 331.1502.

FT-IR: (neat): ῡ = 3337 (w), 2931 (m), 2885 (w), 2857 (w), 1571 (w), 1495 (s), 1466 (w), 1415 (w), 1391 (w), 1361 (w), 1321 (w), 1249 (s), 1187 (w), 1149 (m), 1055 (s), 1010 (w), 906 (s), 837 (s), 804 (w), 782 (m), 738 (w), 695 (w), 660 (w), 600 (w) cm-^{1}.

3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-chloro-5-methoxyphenyl)propyl sulfamate



Chlorosulfonyl isocyante **214** [M 141.53; ρ 1.63]	1.50 equiv.	26.4 mmol	0.99 mL
Formic acid [M 46.04; ρ 1.22]	1.50 equiv.	26.4 mmol	2.29 mL
Alcohol **177** [M 330.92]	1.00 equiv.	17.6 mmol	5.82 g
Pyridine [M 79.10; ρ 0.98]	1.50 equiv.	26.4 mmol	2.13 mL

Under Ar-atmosphere formic acid (0.99 mL, 26.4 mmol, 1.50 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (**214**) (2.29 mL, 26.4 mmol, 1.50 equiv.) at 0 °C. After 5 min of vigorous stirring, CH_2Cl_2 (15 mL) was added and the mixture was stirred at 0 °C for 1 h and at rt for 8 h. At 0 °C alcohol **177** (5.82 g, 17.6 mmol, 1.00 equiv.) and pyridine (2.13 mL, 26.4 mmol, 1.50 equiv.) in CH_2Cl_2 (15 mL) were added dropwise. The reaction mixture was slowly warmed to rt and was stirred for 12 h. The mixture was diluted with EtOAc (60 mL), quenched with H_2O (60 mL) and the layers were separated. The aq. layer was extracted with EtOAc (2x30 mL) and the combined org. layers were washed with brine (2x20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. After column chromatography (*n*-pentane/EtOAc 2:1) sulfamate **178** (5.80 g, 14.2 mmol, 80%) was isolated as colorless solid.

TLC: R_f = 0.48 (*n*-pentane/EtOAc 1:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.18 (s, 6 H, TBS), 1.02 (s, 9 H, TBS), 2.01 (ddt, *J* = 4.9, 7.3, 8.4 Hz, 2 H, 2-H), 2.63 (dd, *J* = 6.7, 8.4 Hz, 2 H, 3-H), 3.78 (s, 3 H, OMe), 4.18 (t, *J* = 6.2 Hz, 2 H, 1-H), 6.58 (s, 1 H, Ar), 6.76 (s, 1 H, Ar) ppm.

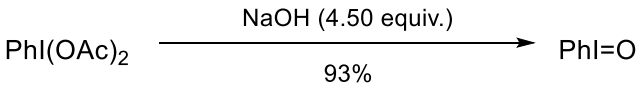
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –4.0 (TBS), 19.0 (TBS), 26.0 (TBS), 30.4 (C2), 31.1 (C3), 55.5 (OMe), 70.4 (C1), 110.8 (Ar), 121.6 (Ar), 125.7 (Ar), 133.7 (Ar), 140.1 (Ar), 151.5 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{16}H_{28}ClNO_5SSiNa$ $[M\text{-}Na]^+$ 432.1038, found 432.1049.

FT-IR: (neat): ῡ = 3282 (w), 2931 (m), 2895 (w), 2857 (w), 1570 (w), 1495 (s), 1466 (w), 1416 (w), 1360 (m), 1324 (w), 1272 (w), 1249 (s), 1179 (s), 1149 (w), 1054 (m), 1010 (w), 905 (m), 836 (m), 804 (w), 781 (s), 740 (w), 694 (w), 662 (w), 593 (w), 662 (w) cm^{-1}.

m.p.: 46 °C (EtOAc).

Iodosobenzene

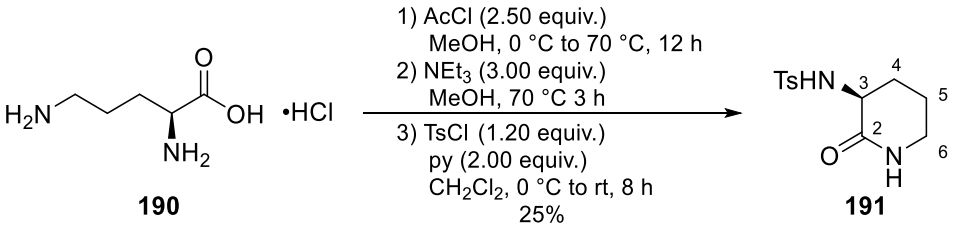


$PhI(OAc)_2$ [M 322.10]	1.00 equiv.	20.0 mmol	6.44 g
NaOH [3.0 M, aq.; M 40.00]	4.50 equiv.	90.0 mmol	40.0 mL

Aq. NaOH (30.0 mL, 90.0 mmol, 3.0 M, 4.50 equiv.) was added to $PhI(OAc)_2$ (6.44 g, 20.0 mmol, 1.00 equiv.) under vigorous stirring over a period of 5 min and was afterwards stirred for 1 h at rt. H_2O (40 mL) was added and the crude product was filtrated. The filter cake was washed with H_2O (2x20 mL) and $CHCl_3$ (15 mL) and dried *in vacuo* to give iodosobenzene (4.10 g, 18.6 mmol, 93%) as colorless solid.

C_6H_5IO (22.01)	calc.	C 32.76	H 2.29
	found	C 32.81	H 2.27

(*S*)-4-Methyl-*N*-(2-oxopiperidin-3-yl)benzenesulfonamide 191



L-(+)-Ornithine hydrochloride **190** [M 168.62]	1.00 equiv.	25.0 mmol	4.21 g
AcCl [M 78.50; ρ 1.10]	2.50 equiv.	62.5 mmol	4.46 mL
NEt_3 [M 101.19; ρ 0.73]	3.00 equiv.	75.0 mmol	10.4 mL
TsCl [M 190.64]	1.20 equiv.	30.0 mmol	5.72 g
Pyridine [M 79.10; ρ 0.98]	2.00 equiv.	50.0 mmol	4.04 mL

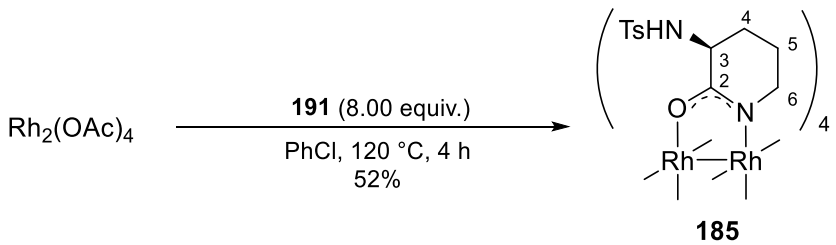
At 0 °C acetyl chloride (4.46 mL, 62.5 mmol, 2.50 equiv.) was added slowly to a solution of *L*-(+)-ornithine hydrochloride (**190**) (4.21 g, 25.0 mmol, 1.00 equiv.) in MeOH (100 mL). After 10 min the mixture was refluxed for 12 h. The reaction mixture was concentrated *in vacuo* and dried under high vacuum for 4 h. The colorless solid was dissolved in MeOH (100 mL), NEt_3 (10.4 mL, 75.0 mmol, 3.00 equiv.) was added and the solution was refluxed for 2 h. All volatile compounds were removed under reduced pressure and the crude product was dried under high vacuum for further 3 h. The resulting solid was suspended in CH_2Cl_2 (100 mL) and pyridine (4.04 mL, 50.0 mmol, 2.00 equiv.) was added. At 0 °C TsCl (5.72 g, 30.0 mmol, 1.20 equiv.) was added, the mixture was slowly warmed to rt and stirred for 8 h. The crude product was concentrated under reduced pressure, dissolved in warm EtOAc (100 mL) and washed with sat. aq. NH_4Cl (100 mL). The organic layer was dried over $NaSO_4$, filtrated and concentrated *in vacuo*. After recrystallization from EtOAc lactam **191** (1.67 g, 6.22 mmol, 25%) was obtained as colorless solid.

TLC: R_f = 0.48 (*n*-pentane/EtOAc 1:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.72-1.98 (m, 3 H, 4-H_A, 5-H), 2.42 (s, 3 H, Me), 2.46-2.53 (m, 1 H, 4-H_B), 3.27-3.32 (m, 2 H, 6-H), 3.44-3.51 (m, 1 H, 3-H), 5.67 (s_{br}, 1 H, TsNH), 5.82 (s_{br}, 1 H, NH), 7.31 (d, *J* = 8.0 Hz, 2 H, Ts), 7.78 (d, *J* = 8.0 Hz, 2 H, Ts) ppm.

The analytical data were in accordance with that reported in the literature.[35]

Rh_2(*S*-nap)$_4$ 185



185

$Rh_2(OAc)_4$ [M 441.99]	1.00 equiv.	0.11 mmol	49.3 mg
Lactam **191** [M 268.33]	8.00 equiv.	0.89 mmol	239 mg

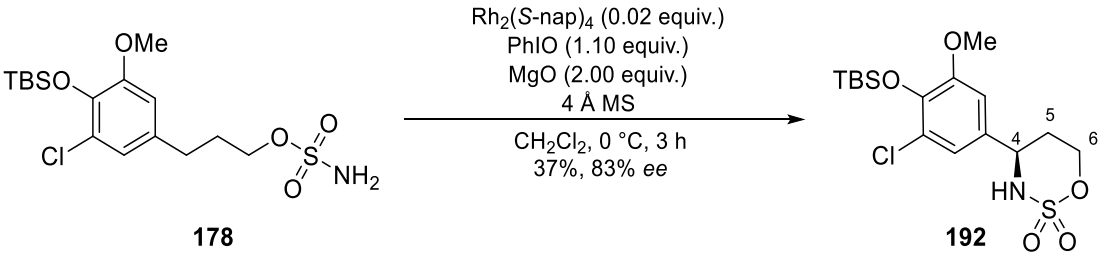
Under Ar-atmosphere lactam **191** (239 mg, 0.89 mmol, 8.00 equiv.) and $Rh_2(OAc)_4$ (49.3 mg, 0.11 mmol, 1.00 equiv.) were suspended in chlorobenzene (20 mL). The solvent was distilled off and replaced four times. The crude product was directly purified via column chromatography (CH_2Cl_2/MeCN 4:1). The resulting Rh_2(*S*-nap)$_4$ was dissolved in acetone (5 mL), concentrated under reduced pressure and dried *in vacuo* at 80 °C for 12 h to give catalyst **185** (73.0 mg, 57.1 µmol, 52%) as blue-green solid.

TLC: R_f = 0.19 (CH_2Cl_2/MeCN 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.22-1.61 (m, 14 H, 4-H_A, 5-H), 1.84-1.91 (m, 2 H, 4-H_B), 2.39 (s, 6 H, Me), 2.43 (s, 6 H, Me), 2.93-3.34 (m, 12 H, 6-H, 3-H), 5.79 (d, *J* = 2.7 Hz, 2 H, TsNH), 5.86 (d, *J* = 3.0 Hz, 2 H, TsNH), 7.32 (d, *J* = 7.8 Hz, 4 H, Ts), 7.40 (d, *J* = 7.8 Hz, 4 H, Ts), 7.68 (d, *J* = 8.4 Hz, 4 H, Ts), 7.76 (d, *J* = 8.4 Hz, 4 H, Ts) ppm.

The analytical data were in accordance with that reported in the literature.[35]

(*R*)-4-(4-((*tert*-Butyldimethylsilyl)oxy)-3-chloro-5-methoxyphenyl)-1,2,3-oxathiazinane 2,2-dioxide 192



178 **192**

Sulfamate **178** [M 409.11]	1.00 equiv.	235 µmol	96.3 mg
Rh_2(*S*-nap)$_4$ [M 1279.14]	0.02 equiv.	4.70 µmol	6.00 mg
Iodosobenzene [M 220.01]	1.30 equiv.	306 µmol	67.2 mg
MgO [M 40.32]	2.00 equiv	470 µmol	19.0 mg

Under Ar-atmosphere sulfamate **178** (96.3 mg, 235 µmol, 1.00 equiv.), MgO (19.0 mg, 470 µmol, 2.00 equiv.) and Rh_2(*S*-nap)$_4$ (6.00 mg, 4.70 µmol, 0.02 equiv.) were dissolved in CH_2Cl_2 (1 mL). Iodosobenzene (67.2 mg, 306 µmol, 1.30 equiv.) was added and the mixture was stirred at rt for 2 h. CH_2Cl_2 (3 mL) was added and the reaction mixture was filtrated through a pad of Celite. The crude product was concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 4:1) oxathiazinane **192** (35.0 mg, 85.8 µmol, 37%, 83%*ee*) was isolated as colorless solid.

TLC: R_f = 0.33 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 6 H, TBS), 1.02 (s, 9 H, TBS), 1.99 (ddd, *J* = 2.3, 4.2, 14.3 Hz, 1 H, 5-H_A), 2.22 (dtd, *J* = 5.0, 12.4, 14.3 Hz, 1 H, 5-H_B), 3.82 (s, 3 H, OMe), 4.39 (d, *J* = 9.6 Hz, 1 H, NH), 4.64 (ddd, *J* = 1.7, 5.0, 11.7 Hz, 1 H, 6-H_A), 4.75 (ddd, *J* = 2.5, 9.0, 12.4 Hz, 1 H, 4-H), 4.85 (dd, *J* = 2.3, 11.7 Hz, 1 H, 6-H_B), 6.78 (d, *J* = 2.2 Hz, 1 H, Ar), 6.91 (d, *J* = 2.2 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –3.9 (TBS), 19.0 (TBS), 26.0 (TBS), 30.1 (C5), 55.7 (OMe), 58.6 (C4), 71.9 (C6), 108.6 (Ar), 119.7 (Ar), 126.2 (Ar), 131.1 (Ar), 142.4 (Ar), 152.1 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{24}H_{32}ClNO_7SSiNa$ $[M\text{-}Na]^+$ 564.1249, found 564.1248.

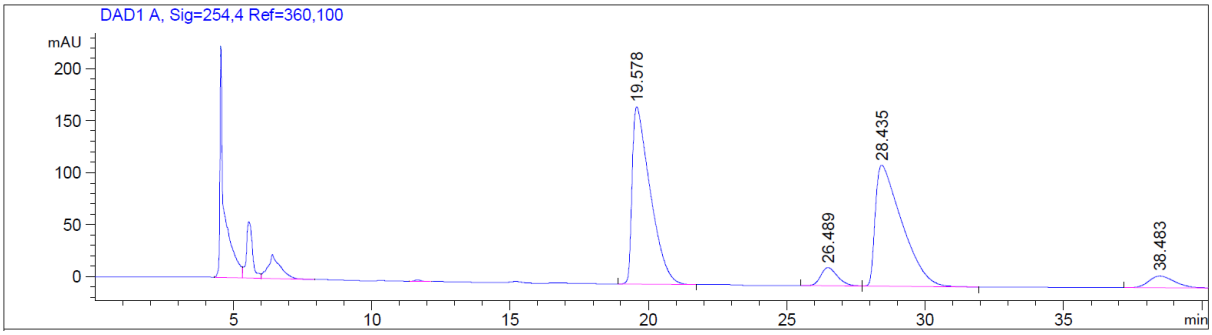
FT-IR: (neat): ϑ̃ = 3262 (w), 2931 (w), 2896 (w), 2857 (w), 1573 (w), 1500 (m), 1467 (w), 1420 (w), 1360 (w), 1333 (w), 1306 (w), 1251 (m), 1188 (s), 1155 (w), 1055 (m), 1022 (w), 988 (w), 909 (w), 884 (w), 870 (w), 840 (m), 782 (s), 742 (w), 714 (w), 742 (w), 714 (w), 681 (w), 600 (w), 579 (w) cm^{-1}.

m.p.: 169 °C (EtOAc).

HPLC: (Chiralpac IC, *n*-hexane/EtOAc 9/1, 0.7 mL/min, 254 nm) t_R(major) = 31.1 min, t_R(minor) = 21.9 min.

$[\alpha]_D^{23}$ –7.3 (c 0.5, EtOAc, for a sample with 82%*ee*).

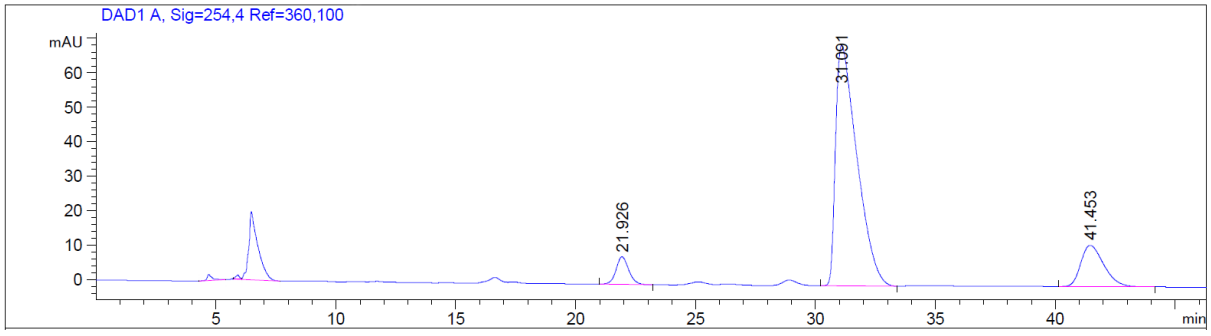
Using $Rh_2(esp)_2$



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
5	19.578	BB	0.6720	7755.37793	170.71292	36.9310
6	26.489	BB	0.6477	732.08136	17.51178	3.4862
7	28.435	BB	0.9645	7739.30078	116.27983	36.8544
8	38.483	BBA	0.9634	724.40222	11.24723	3.4496

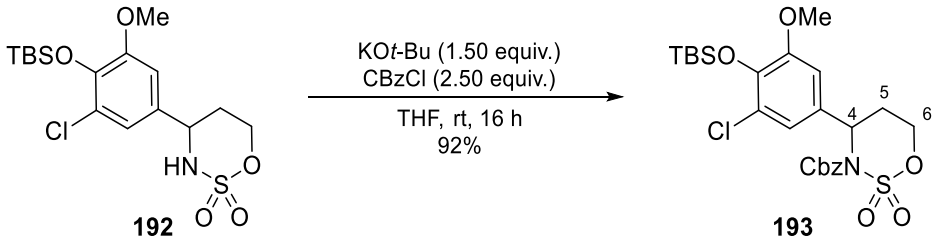
The peaks around 26.5 and 38.5 min belong to minor impurities of the non-chlorinated oxathiazinane

Using $Rh_2(S\text{-nap})_4$ under optimized conditions



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
4	21.926	BB	0.5537	295.50867	8.02411	4.9424
5	31.091	BB	0.9250	4321.79932	69.74007	72.2827

Benzyl (*S*)-4-(4-((*tert*-butyldimethylsilyl)oxy)-3-chloro-5-methoxyphenyl)-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide 193



Oxathiazinane **192** [M 407.98]	1.00 equiv.	90.0 µmol	36.7 mg
KO*t*-Bu [M 112.21]	1.50 equiv.	135 µmol	15.1 mg
CbzCl [M 170.60; ρ 1.20]	2.50 equiv.	225 µmol	32.0 µL

Under Ar-atmosphere oxathiazinane **192** (36.7 mg, 90.0 µmol, 1.00 equiv.) was dissolved in THF (1.5 mL). KO*t*-Bu (15.1 mg, 135 µmol, 1.50 equiv.) was added and the mixture was stirred at rt for 1.5 h. Benzyl chloroformate (32.0 µL, 225 µmol. 2.50 equiv.) was added and the mixture was stirred at rt for 16 h. H_2O (3 mL) was added to quench the reaction, it was extracted with EtOAc (3x2 mL), washed with brine (2 mL), dried over $MgSO_4$ and filtrated. All volatiles were removed under reduced pressure. After column chromatography (*n*-pentane/CH_2Cl_2 1:1) Cbz-*N*-protected oxathiazinane **194** (45.0 mg, 83.0 µmol, 92%) was isolated as colorless oil.

TLC: R_f = 0.10 (*n*-pentane/CH_2Cl_2 1:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 6 H, TBS), 1.03 (s, 9 H, TBS), 2.40 (dddd, *J* = 2.3, 3.5, 6.2, 14.7 Hz, 1 H, 5-H_A), 2.90 (dddd, *J* = 4.9, 7.4, 10.8, 14.7 Hz, 1 H, 5-H_B), 3.71 (s, 3 H, OMe), 4.46 (td, *J* = 6.2, 10.8 Hz, 1 H, 6-H_A), 4.70 (ddd, *J* = 2.3, 7.4, 10.8 Hz, 1 H, 6-H_B), 5.32 (s, 2 H, Cbz), 5.64 (t, *J* = 5.6 Hz, 1 H, 4-H), 6.78 (d, *J* = 2.2 Hz, 1 H, Ar), 6.91 (dd, *J* = 0.7, 2.2 Hz, 1 H, Ar), 7.31-7.38 (m, 5 H, Ph) ppm.

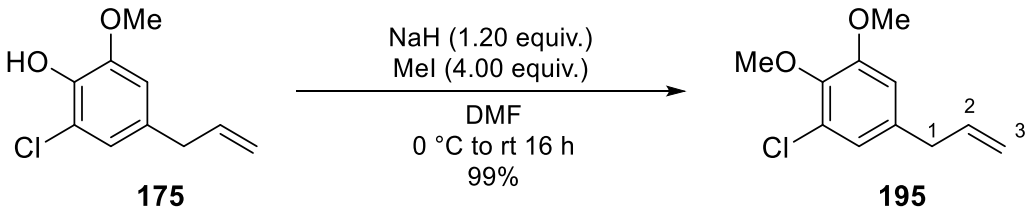
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –3.9 (TBS), 19.0 (TBS), 26.0 (TBS), 28.5 (C5), 55.5 (OMe), 60.4 (ArCN), 69.8 (C4), 70.1 (C6), 107.8 (Ar), 119.1 (Ar), 126.3 (Ar), 128.0 (Ph), 128.7 (Ph), 128.8 (Ph), 130. 9 (Ar), 134.8 (Ph), 151.8 (Ar), 152.2 (NCO_2) ppm.

HR-MS: (ESI+): m/z calc. for $C_{24}H_{32}ClNO_7SSiNa$ $[M\text{-}Na]^+$ 564.1249, found 564.1248.

FT-IR: (neat): ῡ = 3246 (s), 2943 (s), 2836 (m), 1601 (m), 1576 (s), 1496 (s), 1461 (s), 1423 (s), 1362 (m), 1305 (m), 1286 (m), 1241 (s), 1187 (s), 1147 (s), 1053 (m), 1023 (m), 993 (s), 922 (s), 871 (w), 785 (w), 618 (w), 573 (w), 549 (w), 522 (w) cm^{-1}.

Oxathiazinane **193** was synthesized using racemic oxathiazinane **192**, therefore no measurement of optical rotation was performed.

8.3.2 5-Allyl-1-chloro-2,3-dimethoxybenzene 195



6-Chloroeugenol **175** [M 198.65]	1.00 equiv.	5.28 mmol	1.05 g
NaH [60wt%, mineral oil; M 24.00]	1.20 equiv.	6.34 mmol	290 mg
MeI [M 141.94; ρ 2.28]	4.00 equiv.	21.1 mmol	1.50 mL

Under Ar-atmosphere 6-chloroeugenol **175** (1.05 g, 5.28 mmol, 1.00 equiv.) was dissolved in DMF (100 mL). At 0 °C NaH (290 mg, 6.34 mmol, 1.20 equiv.) was added. After 15 min MeI

(1.50 mL, 21.1 mmol, 4.00 equiv.) was added and the mixture was stirred at rt for 16 h. The reaction was quenched with H_2O (150 mL) and extracted with cyclohexane (3x40 mL), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 8:1) 5-allyl chloro-2,3-dimethoxybenzene **195** (1.12 g, 5.26 mmol, 99%) was isolated as colorless oil.

TLC: R_f = 0.55 (*n*-pentane/EtOAc 8:1).

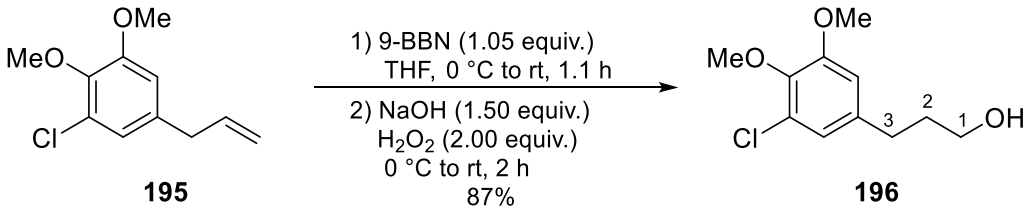
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.31 (dd, *J* = 1.4, 6.8 Hz, 2 H, 1-H), 3.84 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 5.07-5.14 (m, 2 H, 3-H), 5.92 (ddt, *J* = 6.8, 9.6, 17.4 Hz, 1 H, 2-H), 6.63 (d, *J* = 1.9 Hz, 1 H, Ar), 6.81 (d, *J* = 1.9 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 39.9 (C1), 56.2 (OMe), 60.8 (OMe), 111.6 (Ar), 116.6 (C3), 121.9 (Ar), 128.2 (Ar), 136.7 (C2), 143.9 (Ar), 153.8 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{11}H_{13}ClO_2Na$ $[M\text{-}Na]^+$ 235.0496, found 235.0497.

FT-IR: (neat): ῡ = 3078 (w), 3001 (w), 2934 (w), 2832 (w), 1681 (w), 1639 (w), 1598 (w), 1572 (m), 1490 (s), 1459 (w), 1415 (m), 1273 (m), 1235 (m), 1182 (w), 1140 (m), 1051 (s), 1001 (m), 968 (w), 913 (m), 837 (m), 777 (w), 745 (w), 686 (w), 598 (w), 548 (w) cm^{-1}.

3-(3-Chloro-4,5-dimethoxyphenyl) propanol 196



Olefin **195** [M 212.67]	1.00 equiv.	5.27 mmol	1.12 g
9-BBN [0.5 M, THF; M 122.02]	1.05 equiv.	5.53 mmol	11.1 mL
NaOH [15wt% aq.; M 40.00]	1.50 equiv.	7.90 mmol	1.80 mL
H_2O_2 [30wt% aq.; M 34.02; ρ 1.11]	2.00 equiv.	10.5 mmol	1.08 mL

Under Ar-atmosphere 5-allyl-1-chloro-2,3-dimethoxybenzene **195** (1.12 g, 5.27 mmol, 1.00 equiv.) was dissolved in THF (20 mL). At 0 °C 9-BBN (11.1 mL, 5.53 mmol, 0.5 M in THF, 1.05 equiv.) was added and the mixture was stirred at 0 °C for 10 min and at rt for 1 h. 15% aq. NaOH (1.80 mL, 7.90 mmol, 1.50 equiv.) and aq. H_2O_2 (1.08 mL, 10.5 mmol, 30%, 2.00 equiv.) were added at 0 °C and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with brine (40 mL), extracted with Et_2O (3x20 mL), dried over $MgSO_4$, filtrated and concentrated *in vacuo*. After column chromatography (*n*-pentane/EtOAc 1:1) alcohol **196** (1.05 g, 4.56 mmol, 87%) was obtained as colorless oil.

TLC: R_f = 0.30 (EtOAc).

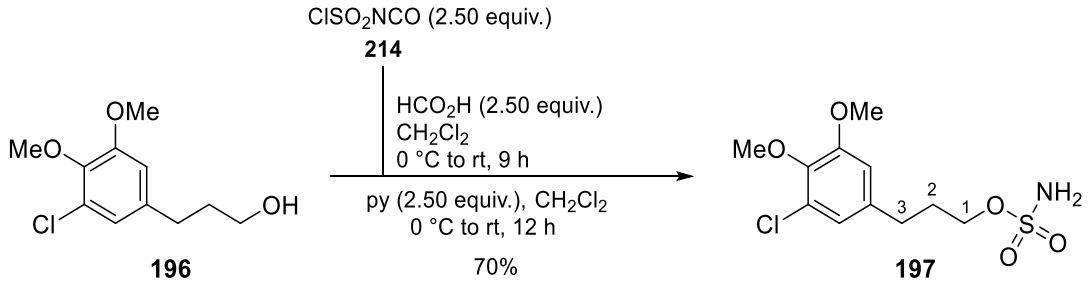
^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.82-1.91 (m, 2 H, 2-H), 2.65 (dd, *J* = 6.7, 8.7 Hz, 2 H, 3-H), 3.67 (t, *J* = 6.4 Hz, 2 H, 1-H), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 6.58 (d, *J* = 2.0 Hz, 1 H, Ar), 6.77 (d, *J* = 2.0 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 31.0 (C2), 34.1 (C3), 56.3 (OMe), 60.8 (OMe), 62.2 (C1), 111.5 (Ar), 121.7 (Ar), 128.2 (Ar), 138.6 (Ar), 143.8 (Ar), 153.8 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{11}H_{15}ClO_3Na$ $[M\text{-}Na]^+$ 253.0602, found 253.0603.

FT-IR: (neat): $\tilde{\upsilon}$ = 3387 (w), 3054 (w), 2939 (w), 2877 (w), 1599 (w), 1572 (m), 1491 (m), 1457 (w), 1414 (m), 1307 (w), 1270 (m), 1234 (m), 1183 (w), 1141 (m), 1049 (s), 1001 (m), 963 (w), 916 (w), 852 (m), 774 (w), 733 (s), 702 (w), 655 (w), 610 (w), 573 (w), 512 (w), 472 (w) cm^{-1}.

3-(3-Chloro-4,5-dimethoxyphenyl) propyl sulfamate 197



Chlorosulfonyl isocyante **214** [M 141.53; ρ 1.63]	2.50 equiv.	19.8 mmol	1.72 mL
Formic acid [M 46.04; ρ 1.22]	2.50 equiv.	19.8 mmol	0.75 mL
Alcohol **205** [M 230.69]	1.00 equiv.	7.90 mmol	1.82 g
Pyridine [M 79.10; ρ 0.98]	2.50 equiv.	19.8 mmol	1.59 mL

Under Ar-atmosphere formic acid (0.75 mL, 19.8 mmol, 2.50 equiv.) was added dropwise to neat chlorosulfonyl isocyanate **214** (1.72 mL, 19.8 mmol, 2.50 equiv.) at 0 °C. After 5 min of vigorous stirring, CH_2Cl_2 (8 mL) was added and the mixture was stirred at 0 °C for 1 h and at rt for 8 h. At 0 °C alcohol **196** (1.82 g, 7.90 mmol, 1.00 equiv.) and pyridine (1.59 mL, 19.8 mmol, 2.50 equiv.) in CH_2Cl_2 (10 mL) were added dropwise. The reaction mixture was slowly warmed to rt and was stirred for 12 h. The mixture was diluted with EtOAc (100 mL), quenched with H_2O (100 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3x50 mL) and the combined org. layers were washed with brine (2x20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. After column chromatography (*n*-pentane/EtOAc 2:1) sulfamate **197** (1.65 g, 5.40 mmol, 70%) was isolated as colorless oil.

TLC: R_f = 0.33 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.00-2.09 (m, 2 H, 2-H), 2.68 (t, *J* = 7.5 Hz, 2 H, 3-H), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.21 (t, *J* = 6.2 Hz, 2 H, 1-H), 4.74 (s_{br}, 1 H, NH), 6.65 (d, *J* = 1.8 Hz, 1 H, Ar), 6.80 (d, *J* = 1.8 Hz, 1 H, Ar) ppm.

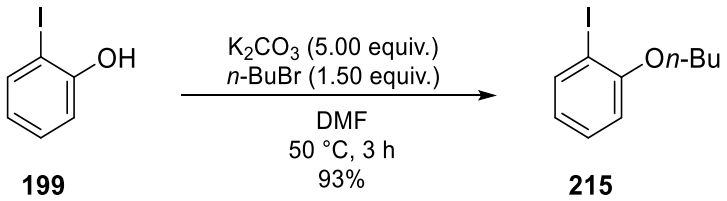
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 30.4 (C2), 31.4 (C3), 56.3 (OMe), 60.8 (OMe), 70.4 (C1), 111.7 (Ar), 121.7 (Ar), 128.3 (Ar), 137.2 (Ar), 144.1 (Ar), 154.0 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{11}H_{16}ClNO_5SNa$ $[M\text{-}Na]^+$ 332.0330, found 332.0333.

FT-IR: (neat): ῡ = 3361 (w), 3270 (w), 3106 (w), 2940 (w), 1599 (w), 1572 (m), 1492 (m), 1459 (w), 1416 (w), 1360 (s), 1309 (w), 1277 (w), 1234 (w), 1176 (s), 1141 (m), 1083 (w), 1048 (m), 996 (w), 927 (s), 818 (m), 777 (w), 734 (w), 657 (w), 590 (w), 552 (s) cm^{-1}.

m.p.: 66 °C (EtOAc).

1-Butoxy-2-iodobenzene 215



199 **215**

ortho-Iodophenol **199** [M 220.01]	1.00 equiv.	741 µmol	163 mg
K_2CO_3 [M 138.20]	5.00 equiv.	3.70 mmol	512 mg
n-BuBr [M 137.02; ρ 1.27]	1.50 equiv.	1.11 mmol	120 µL

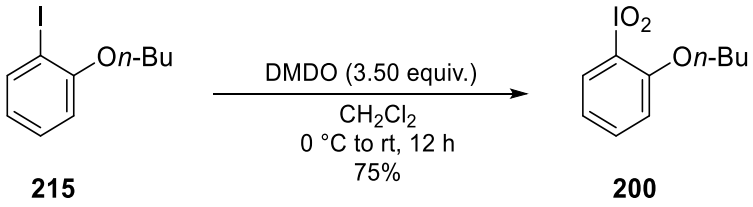
Under Ar-atmosphere 2-iodophenol (**199)** (163 mg, 741 µmol, 1.00 equiv.) was dissolved in DMF (4 mL), K_2CO_3 (512 mg, 3.70 mmol, 5.00 equiv.) was added and the mixture was stirred at rt for 10 min. *n*-BuBr (120 µL, 1.11 mmol, 1.50 equiv.) was added and the reaction mixture was heated to 50 °C for 3 h. H_2O (3 mL) was added to quench the reaction, it was extracted with CH_2Cl_2 (3x5 mL), the combined org. layer were dried over Na_2CO_3, filtrated and all volatile compounds were removed *in vacuo*. After column chromatography (*n*-pentane/EtOAc 20:1) ether **215** (189 mg, 685 µmol, 93%) was isolated as colorless oil.

TLC: R_f = 0.80 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.00 (t, *J* = 7.5 Hz, 3 H, Me), 1.56 (dq, *J* = 7.5, 14.5 Hz, 2 H, *n*-Bu), 1.83 (tt, *J* = 6.3, 8.4 Hz, 2 H, *n*-Bu), 4.02 (t, *J* = 6.3 Hz, 2 H, O*n*-Bu), 6.69 (td, *J* = 1.4, 7.5 Hz, 1 H, Ar), 6.80 (dd, *J* = 1.4, 8.2 Hz, 1 H, Ar), 7.28 (ddd, *J* = 1.6, 7.5, 8.2 Hz, 1 H, Ar), 7.76 (dd, *J* = 1.6, 7.5 Hz, Ar) ppm.

The analytical data were in accordance with that reported in the literature.[144]

1-Butoxy-2-iodosobenzene 200



215 **200**

n-Butoxy-2-iodbenzene **215** [M 276.12]	1.00 equiv.	684 µmol	189 mg
DMDO [0.06 M, acetone; M 74.08]	3.50 equiv.	2.40 mmol	39.9 mL

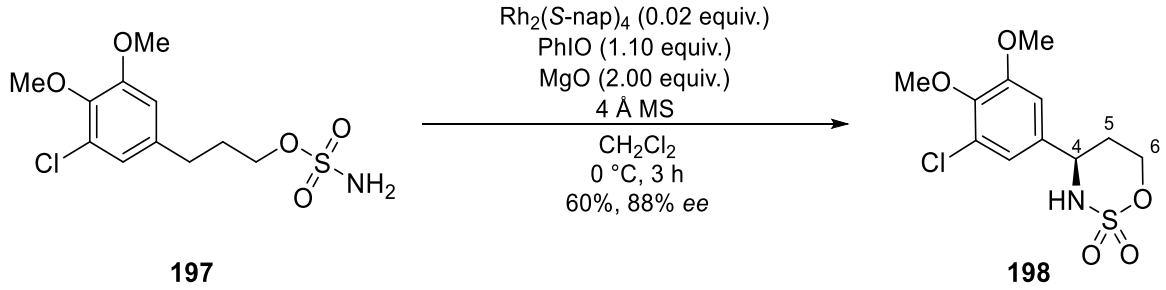
Under Ar-atmosphere ether **215** (189 mg, 684 µmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (4 mL). At 0 °C DMDO (39.4 mL, 2.40 mmol, 0.06 M in acetone, 3.50 equiv.) was added and the mixture was stirred at rt for 12 h. It was filtrated, Et_2O (15 mL) was added to the filtrate

and it was filtrated again. The precipitates were combined, washed with Et_2O (2x10 mL) and dried under reduced pressure to give **200** (157 mg, 409 µmol, 75%) as colorless solid.

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.99 (t, *J* = 7.3 Hz, 3 H, Me), 1.50 (dq, *J* = 7.3, 14.5 Hz, 2 H, *n*-Bu), 1.84 (tt, *J* = 6.6, 14.5 Hz, 2 H, *n*-Bu), 4.17 (t, *J* = 6.6 Hz, 2 H, O*n*-Bu), 7.04 (dd, *J* = 1.0, 8.2 Hz, 1 H, Ar), 7.24-7.30 (m, 1 H, Ar), 7.59 (ddd, *J* = 1.6, 7.4, 8.6 Hz, 1 H, Ar), 7.98 (dd, *J* = 1.6, 7.9 Hz, Ar) ppm.

The analytical data were in accordance with that reported in the literature.[143]

(*R*)-4-(3-chloro-4,5-dimethoxyphenyl)-1,2,3-oxathiazinane 2,2-dioxide 198



197 **198**

Sulfamate **197** [M 309.76]	1.00 equiv.	646 µmol	200 mg
Rh_2(*S*-nap)$_4$ [M 1279.14]	0.02 equiv.	12.9 µmol	16.5 mg
Iodosobenzene [M 220.01]	1.10 equiv.	710 µmol	156 mg
MgO [M 40.32]	2.00 equiv	1.29 mmol	52.1 mg

Under Ar-atmosphere sulfamate **197** (200 mg, 646 µmol, 1.00 equiv.), MgO (52.1 mg, 1.29 mmol, 2.00 equiv.) and Rh_2(*S*-nap)$_4$ (16.5 mg, 12.9 µmol, 0.02 equiv.) were dissolved in CH_2Cl_2 (5 mL). Iodosybenzene (156 mg, 710 µmol, 1.10 equiv.) was added and the mixture was stirred at rt for 3 h. CH_2Cl_2 (10 mL) was added and the reaction mixture was filtered through a pad of Celite. The crude product was concentrated *in vacuo*. After column

chromatography (*n*-pentane/EtOAc 2:1) oxathiazinane **198** (119 mg, 387 µmol, 60%, 88% *ee*) was isolated as colorless solid.

TLC: R_f = 0.28 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.02 (ddd, *J* = 2.3, 2.5, 14.4 Hz, 1 H, 5-H_A), 2.22 (ddt, *J* = 5.0, 12.5, 14.4 Hz, 1 H, 5-H_B), 3.86 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 4.40 (d, *J* = 9.3 Hz, 1 H, NH), 4.66 (ddd, *J* = 1.7, 5.0, 11.7 Hz, 1 H, 6-H_A), 4.78 (ddd, *J* = 2.5, 9.3, 12.5 Hz, 1 H, 4-H), 4.85 (dd, *J* = 2.3, 11.7 Hz, 1 H, 6-H_B), 6.82 (d, *J* = 2.0 Hz, 1 H, Ar), 6.93 (d, *J* = 2.0 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 29.9 (C5), 56.4 (OMe), 58.3 (C4), 60.9 (OMe), 71.8 (C6), 109.5 (Ar), 119.6 (Ar), 128.8 (Ar), 134.6 (Ar), 145.7 (Ar), 154.3 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{11}H_{14}ClNO_5SNa$ $[M\text{-}Na]^+$ 330.0173, found 330.0171.

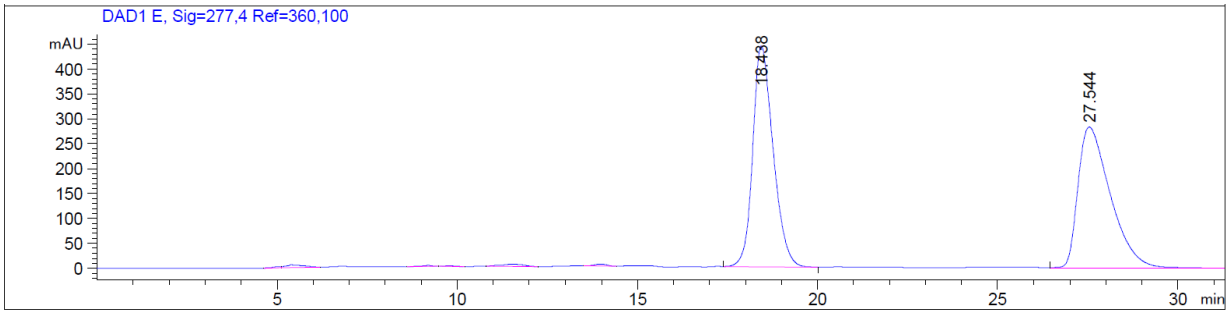
FT-IR: (neat): ϑ̃ = 3246 (w), 2943 (w), 2836 (w), 1601 (w), 1576 (w), 1496 (w), 1461 (w), 1423 (m), 1362 (m), 1305 (w), 1286 (w), 1241 (w), 1187 (s), 1147 (w), 1053 (m), 1023 (w), 993 (m), 922 (w), 871 (w), 785 (m), 618 (w), 573 (w), 549 (w), 522 (w) cm^{-1}.

HPLC: (Chiralpac IC, *n*-hexane/EtOAc 3/2, 0.7 mL/min, 277 nm) t_R(major) = 27.1 min, t_R(minor) = 18.3 min.

$[\alpha]_D^{23}$ –6.4 (c 0.6, EtOAc, for a sample with 88% *ee*).

m.p.: 66 °C (EtOAc).

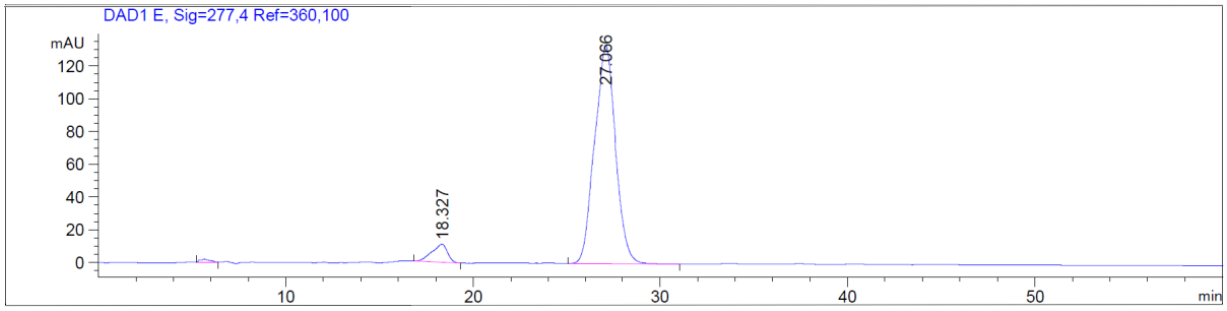
Using $Rh_2(esp)_2$



Signal 3: DAD1 E, Sig=277,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
7	18.438	BB	0.5992	1.74435e4	443.17221	49.1181
8	27.544	BBA	0.9461	1.74679e4	282.21152	49.1867

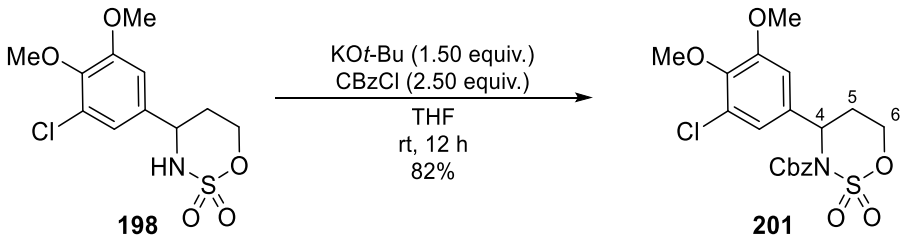
Using $Rh_2(S\text{-nap})_4$ under optimized conditions



Signal 3: DAD1 E, Sig=277,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
2	18.327	BB	0.8248	647.25354	11.09172	5.7553
3	27.066	BB	1.1355	1.05325e4	133.64407	93.6545

Benzyl 4-(3-chloro-4,5-dimethoxyphenyl)-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide 201



Oxathiazinane **198** [M 407.98]	1.00 equiv.	4.87 mmol	1.50 g
KO*t*-Bu [M 112.21]	1.50 equiv.	7.31 mmol	820 mg
CbzCl [M 170.60; ρ 1.20]	2.50 equiv.	12.2 mmol	1.73 mL

Under Ar-atmosphere oxathiazinane **198** (1.50 g, 4.87 mmol, 1.00 equiv.) was dissolved in THF (120 mL). KO*t*-Bu (820 mg, 7.31 mmol, 1.50 equiv.) was added and the mixture was stirred at rt for 1.5 h. Benzyl chloroformate (1.73 mL, 12.2 mmol. 2.50 equiv.) was added and the mixture was stirred at rt for 12 h. H_2O (100 mL) was added to quench the reaction and it was extracted with EtOAc (3x30 mL), washed with brine (20 mL), dried over $MgSO_4$, filtrated and all volatile compounds were removed under reduced pressure. After column chromatography (*n*-pentane/CH_2Cl_2 2:1) Cbz-*N*-protected oxathiazinane **201** (1.75 g, 3.96 mmol, 82%) was isolated as colorless oil.

TLC: R_f = 0.17 (*n*-pentane/CH_2Cl_2 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.33 (dddd, *J* = 2.3, 3.5, 6.2, 14.7 Hz, 1 H, 5-H_A), 2.82 (dddd, *J* = 5.0, 7.3, 10.9, 14.7 Hz, 1 H, 5-H_B), 3.70 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 4.38 (td, *J* = 6.2, 10.9 Hz, 1 H, 6-H_A), 4.61 (ddd, *J* = 2.3, 7.3, 9.9 Hz, 1 H, 6-H_B), 5.24 (s, 2 H, Cbz), 5.56 (t, *J* = 4.2 Hz, 1 H, 4-H), 6.76 (d, *J* = 2.2 Hz, 1 H, Ar), 6.85 (d, *J* = 2.2 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 28.2 (C5), 56.2 (OMe), 60.3 (C4), 60.8 (OMe), 69.9 (Cbz), 70.1 (C6), 108.6 (Ar), 118.9 (Ar), 128.0 (Ph), 128.7 (Ph), 128.8 (Ph), 128.9 (Ar), 134.4 (Ar), 134.7 (Ph), 145.0 (Ar), 152.1 (Ar), 154.2 (NCO_2) ppm.

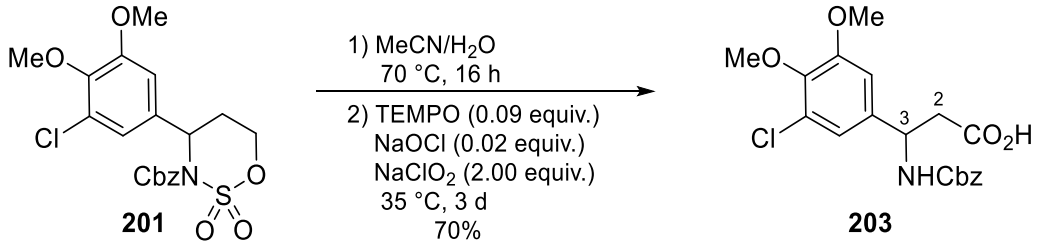
HR-MS: (ESI+): m/z calc. for $C_{19}H_{20}ClNO_7SNa$ $[M\text{-}Na]^+$ 464.0541, found 464.0542.

FT-IR: (neat): $\tilde{\upsilon}$ = 2942 (w), 2834 (2), 1734 (s), 1600 (w), 1573 (w), 1494 (m), 1457 (m), 1383 (s), 1274 (s), 1241 (m), 1177 (s), 1142 (m), 1095 (w), 1045 (m), 998 (s), 971 (s), 933 (m), 884 (w), 855 (w), 786 (m), 760 (m), 743 (m), 697 (m), 666 (m), 596 (m), 570 (m), 477 (w) cm^{-1}.

m.p.: 109 °C (EtOAc).

Oxathiazinane **201** was synthesized using racemic oxathiazinane **198**, therefore no measurement of optical rotation was performed.

3-(((Benzyloxy)carbonyl)amino)-3-(3-chloro-4,5-dimethoxyphenyl)propanoic acid 203



Oxathiazinane **201** [M 441.88]	1.00 equiv.	679 µmol	300 mg
TEMPO [M 156.25]	0.09 equiv.	58.4 µmol	9.10 mg
Na_2HPO_4•12 H_2O [M 358.14]	1.40 equiv.	950 µmol	340 mg
NaOCl [M 74.44; 12wt%]	0.02 equiv.	13.6 µmol	6.90 µL
$NaClO_2$ [M 90.44]	2.00 equiv.	1.36 mmol	123 mg
Na_2SO_3 [M 126.04]	2.40 equiv.	1.63 mmol	205 mg

Cbz-protected oxathiazinane **201** (300 mg, 679 µmol, 1.00 equiv.) was dissolved in MeCN/H_2O (6 mL, 4:3) and the mixture was stirred at 70 °C for 16 h. The mixture was cooled to 35 °C and Na_2HPO_4·12 H_2O (340 mg, 950 µmol, 1.40 equiv.) was added to reach pH~4. TEMPO (9.10 mg, 58.4 µmol, 0.09 equiv.) was added, aq. NaOCl (6.90 µL, 13.6 µmol, 12wt%, 0.02 equiv.) and $NaClO_2$ (123 mg, 1.36 mmol, 2.00 equiv.) were added in 7 portions over 3 h and the mixture was stirred at this temperature for 3 d. Aq. NaOH (2.0 M) was added to reach pH~8, aq. Na_2SO_3 (205 mg, 1.63 mmol, 2.40 equiv.) was added and stirring was continued at rt for 30 min. The reaction mixture was washed with EtOAc (10 mL), the pH was adjusted to ~3 by addition of HCl (1.0 M) and the layers were separated. The aq. layer was extracted with EtOAc (3x15 mL), the combined org. layers were washed with H_2O (2x10 mL) and brine (15 mL), dried over $MgSO_4$, filtrated and concentrated *in vacuo* to yield amino acid **203** (179 mg, 471 µmol, 70%) as colorless solid.

TLC: R_f = 0.29 (CH_2Cl_2/EtOAc:AcOH 100:20:1).

^{1}H-NMR: 300 MHz, DMSO-d_6; δ = 2.65 (d, *J* = 8.2 Hz, 2 H, 2-H), 3.72 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 4.90 (q, *J* = 7.7 Hz, 1 H, 3-H), 5.00 (s_{br}, 2 H, Cbz), 6.96 (d, *J* = 2.0 Hz, 1 H, Ar), 7.02 (d, *J* = 2.0 Hz, 1 H, Ar), 7.26-7.38 (m, 5 H, Ph), 12.29 (s_{br}, 1 H, CO_2H) ppm.

^{13}C-NMR: 75 MHz, DMSO-d_6; δ = 41.1 (C2), 51.3 (C3), 56.0 (OMe), 60.1 (OMe), 65.3 (Cbz), 110.2 (Ar), 118.2 (Ar), 126.5 (Ar), 127.6 (Ph), 127.7 (Ph), 128.3 (Ph), 137.0 (Ar), 139.8 (Ph), 143.5 (Ar), 153.3 (Ar), 155.3 (NCO_2), 171.4 (CO_2H) ppm.

HR-MS: (ESI+): m/z calc. for $C_{19}H_{20}ClNO_6Na$ $[M-Na]^+$ 416.0871, found 416.0883.

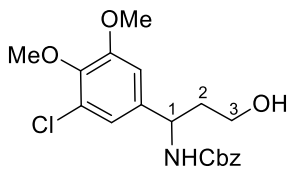
FT-IR: (neat); ϑ̃ = 3322 (w), 2940 (w), 2833 (w), 2483 (w), 2072 (w), 1692 (s), 1599 (m), 1574 (m), 1531 (s), 1492 (s), 1453 (s), 1414 (m), 1341 (s), 1271 (s), 1233 (s), 1180 (m), 1139 (m), 1044 (s), 997 (m), 909 (w), 848 (m), 774 (m), 738 (m), 696 (m), 666 (m), 581 (m), 466 (w) cm^{-1}.

m.p.: 177-178 °C (EtOAc, decomposition).

Amino acid **203** was synthesized using racemic oxathiazinane **201**, therefore no measurement of optical rotation was performed.

If only the ring opening was performed without oxidation amino alcohol **202** was obtained.

Benzyl (1-(3-chloro-4,5-dimethoxyphenyl)-3-hydroxypropyl)carbamate 202



202

TLC: R_f = 0.16 (CH_2Cl_2/EtOAc 5:1).

^{1}H-NMR: 300 MHz, MeOD-d_4; δ = 3.60 (ddq, *J* = 6.0, 11.0, 16.8 Hz, 2 H, 2-H), 3.82 (s, 6 H, OMe), 3.88 (s, 2 H, 3-H), 4.76 (t, *J* = 7.4 Hz, 1 H, 1-H), 5.10 (s_{br}, 2 H, Cbz), 6.96-6.98 (m, 2 H, Ar), 7.33-7.36 (m, 5 H, Ph) ppm.

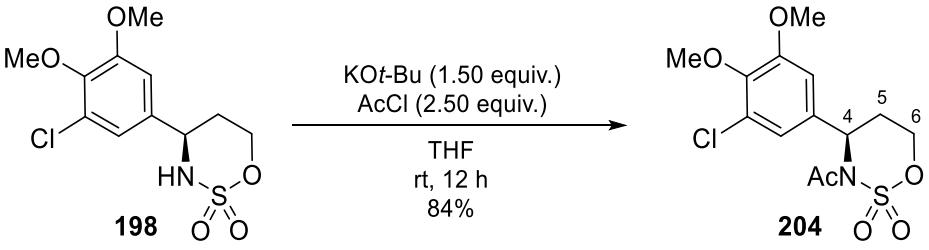
^{13}C-NMR: 75 MHz, MeOD-d_4; δ = 40.2 (C2), 53.3 (C1), 56.6 (OMe), 59.5 (C3), 60.9 (OMe), 67.5 (Cbz), 110.8 (Ar), 120.5 (Ar), 128.6 (Ar), 128.7 (Ph), 129.0 (Ph), 129.4 (Ph), 138.4 (Ar), 141.8 (Ph), 145.4 (Ar), 155.2 (Ar), 158.2 (NCO_2) ppm.

HR-MS: (ESI+): m/z calc. for $C_{19}H_{22}ClNO_5Na$ $[M-Na]^+$ 402.1079, found 402.1089.

FT-IR: (neat); ῡ = 3328 (w), 2940 (w), 2881 (w), 1691 (s), 1574 (w), 1517 (w), 1493 (m), 1455 (w), 1420 (w), 1342 (w), 1237 (m), 1136 (w), 1049 (s), 1000 (w), 899 (w), 853 (w), 740 (w), 698 (m), 654 (w), 584 (w), 457 (w), 421 (w) cm^{-1}.

Amino alcohol **202** was synthesized using racemic oxathiazinane **201**, therefore no measurement of optical rotation was performed.

(*R*)-1-(4-(3-Chloro-4,5-dimethoxyphenyl)-2,2-dioxido-1,2,3-oxathiazinan-3-yl)-ethan-1-one 204



Oxathiazinane **198** [M 407.98]	1.00 equiv.	260 µmol	80.0 mg
KO*t*-Bu [M 112.21]	1.50 equiv.	390 µmol	43.8 mg
AcCl [M 78.40; ρ 1.10]	2.50 equiv.	650 µmol	46.2 µL

Under Ar-atmosphere oxathiazinane **198** (80.0 mg, 260 µmol, 1.00 equiv.) was dissolved in THF (5 mL). KO*t*Bu (43.8 mg, 390 µmol, 1.50 equiv.) was added and the mixture was stirred at rt for 1.5 h. Acetyl chloride (46.2 µL, 650 µmol, 2.50 equiv.) was added and the mixture was stirred at rt for 12 h. H_2O (10 mL) was added to quench the reaction, it was extracted with EtOAc (3x10 mL), washed with brine (10 mL), dried over $MgSO_4$ and all volatile compounds were removed under reduced pressure. After column chromatography (*n*-pentane/EtOAc 2:1) *N*-acetylated oxathiazinane **204** (76.0 mg, 217 µmol, 84%) was isolated as colorless oil.

TLC: R_f = 0.20 (*n*-pentane/CH_2Cl_2 2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.47 (dddd, *J* = 2.3, 3.5, 6.2, 14.7 Hz, 1 H, 5-H_A), 2.59 (s, 3 H, Me), 2.87 (dddd, *J* = 4.6, 7.4, 10.8, 14.7 Hz, 1 H, 5-H_B), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.51 (td, *J* = 6.2, 10.8 Hz, 1 H, 6-H_A), 4.73 (ddd, *J* = 2.3, 7.4, 10.8 Hz, 1 H, 6-H_B), 5.89 (t, *J* = 4.6 Hz, 1 H, 4-H). 6.80 (d, *J* = 2.1 Hz, 1 H, Ar), 6.94 (dd, *J* = 0.8, 2.1 Hz, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 24.8 (Me), 28.2 (C5), 56.3 (OMe), 57.7 (C4), 60.8 (OMe), 70.9 (C6), 108.9 (Ar), 119.3 (Ar), 128.9 (Ar), 134.3 (Ar), 145.2 (Ar), 154.2 (Ar), 168.6 (CO) ppm.

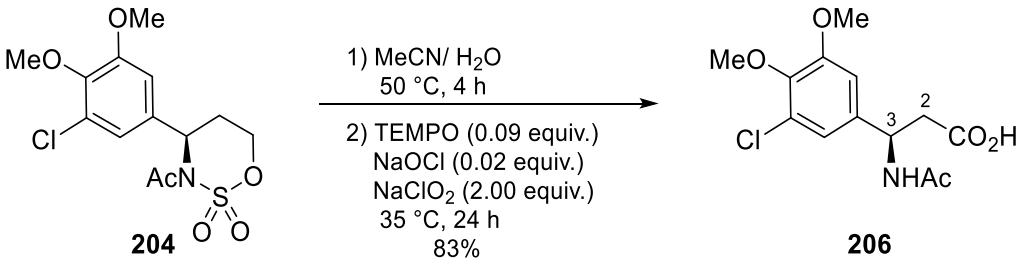
FT-IR: (neat): $\tilde{\upsilon}$ = 2942 (w), 2837 (w), 1705 (s), 1601 (w), 1574 (w), 1495 (w), 1462 (w), 1417 (w), 1372 (s), 1262 (s), 1177 (s), 1144 (w), 1113 (w), 1047 (m), 988 (s), 958 (w), 924 (m), 888 (w), 790 (s), 731 (m), 683 (w), 646 (w), 583 (s), 543 (w), 506 (w), 479 (w), 434 (w) cm^{-1}.

HR-MS: (ESI+): m/z calc. for $C_{13}H_{16}ClNO_6SNa$ [M-Na]+ 372.0279, found 372.0290.

m.p.: 102 °C (EtOAc).

$[\alpha]_D^{23}$ 20 (c 0.55, EtOAc).

(*R*)-3-acetamido-3-(3-chloro-4,5-dimethoxyphenyl)propanoic acid 206



Oxathiazinane **204** [M 349.78]	1.00 equiv.	198 µmol	69.3 mg
TEMPO [M 156.25]	0.09 equiv.	17.0 µmol	2.60 mg
Na_2HPO_4•12 H_2O [M 358.14]	1.40 equiv.	277 µmol	38.3 mg
NaOCl [M 74.44; 12wt%]	0.02 equiv.	4.00 µmol	2.01 µL
$NaClO_2$ [M 90.44]	2.00 equiv.	396 µmol	35.8 mg
Na_2SO_3 [M 126.04]	2.40 equiv.	475 µmol	59.7 mg

Acetylated oxathiazinane **204** (69.3 mg, 198 µmol, 1.00 equiv.) was dissolved in MeCN/H_2O (1.2 mL, 4:3) and the mixture was stirred at 50 °C for 4 h. The mixture was cooled to 35 °C and Na_2HPO_4·12 H_2O (38.3 mg, 277 µmol, 1.40 equiv.) was added to reach pH~4. TEMPO (2.60 mg, 17.0 µmol, 0.09 equiv.) was added, aq. NaOCl (2.01 µL, 4.00 µmol, 12wt%, 0.02 equiv.) and $NaClO_2$ (35.8 mg, 396 µmol, 2.00 equiv.) were added in 7 portions over 3 h and the mixture was stirred at this temperature for 24 h. Aq. NaOH (2.0 M) was added to reach pH~8, aq. Na_2SO_3 (59.7 mg, 475 µmol, 2.40 equiv.) was added and stirring was continued at rt for 30 min. The reaction mixture was washed with EtOAc (10 mL), the pH was adjusted to ~3 by addition of HCl (1.0 M) and the layers were separated. The aq. layer was extracted with EtOAc (3x15 mL), the combined org. layers were washed with H_2O (2x10 mL) and brine (15 mL), dried over $MgSO_4$, filtrated and concentrated *in vacuo* to yield amino acid **206** (50.1 mg, 166 µmol, 83%) as colorless solid.

TLC: R_f = 0.29 (CH_2Cl_2/MeOH/AcOH 100:20:1).

^{1}H-NMR: 300 MHz, DMSO-d_6; δ = 1.82 (s, 3 H, Me), 2.65 (d, *J* = 7.4 Hz, 2 H, 2-H), 3.71 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 5.11 (q, *J* = 7.6 Hz, 1 H, 3-H), 6.93 (d, *J* = 2.0 Hz, 1 H, Ar), 6.99 (d, *J* = 2.0 Hz, 1 H, Ar), 8.34 (d, *J* = 8.4 Hz, 1 H, NH), 12.17 (s_{br}, 1 H, CO_2H) ppm.

300 MHz, MeOD-d_4; δ = 2.00 (s, 3 H, Me), 2.81 (dd, *J* = 4.6, 7.4 Hz, 2 H, 2-H), 3.83 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 5.30 (t, *J* = 7.4 Hz, 1 H, 3-H), 7.02 (s_{br}, 1 H, Ar) ppm.

^{13}C-NMR: 75 MHz, MeOD-d_4; δ = 22.6 (Me), 41.4 (C2), 51.2 (C3), 56.7 (OMe), 60.9 (OMe), 111.3 (Ar), 120.7 (Ar), 129.0 (Ar), 139.9 (Ar), 145.8 (Ar), 155.2 (Ar), 171.4 (NAc), 173.8 (CO_2H) ppm.

HR-MS: (ESI+): m/z calc. for $C_{13}H_{16}ClNO_5Na$ $[M-Na]^+$ 324.0609, found 324.0617.

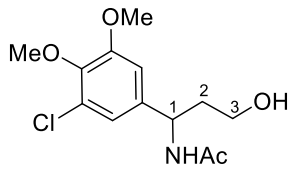
FT-IR: (neat); ῡ = 2939 (s), 2836 (w), 2470 (w), 1718 (m), 1620 (s), 1575 (w), 1491 (w), 1461 (w), 1418 (s), 1278 (s), 1236 (w), 1181 (w), 1143 (m), 1049 (s), 1000 (s), 911 (w), 851 (m), 778 (w), 669 (w), 628 (w), 492 (w) cm^{-1}.

m.p.: 174 °C (EtOAc).

$[\alpha]_D^{23}$ 26 (c 0.6, EtOAc).

If only the ring opening was performed without oxidation amino alcohol **205** was obtained as pale-yellow oil.

***N*-(1-(3-Chloro-4,5-dimethoxyphenyl)-3-hydroxypropyl)acetamide 205**



205

TLC: R_f = 0.59 (CH_2Cl_2/MeOH/AcOH 100:20:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.82 (ddt, *J* = 3.5, 10.0, 13.4 Hz, 2 H, 2-H), 2.05 (s, 3 H, Me), 3.60-3.76 (m, 2 H, 3-H), 3.85 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 5.13 (td, *J* = 3.9, 9.1 Hz, 1 H, 1-H), 6.04 (s_{br}, 1 H, NH), 6.75 (d, *J* = 2.1 Hz, 1 H, Ar), 6.91 (d, *J* = 2.1 Hz, 1 H, Ar) ppm.

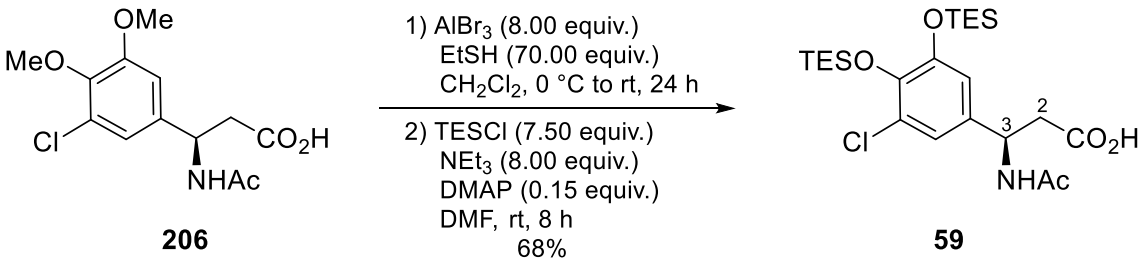
^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 23.4 (Me), 38.4 (C2), 50.8 (C3), 56.4 (OMe), 59.0 (OMe), 60.8 (C1), 110.3 (Ar), 119.5 (Ar), 119.6 (Ar), 138.4 (Ar), 144.9 (Ar), 154.1 (Ar), 170.9 (CO) ppm.

HR-MS: (ESI+): m/z calc. for $C_{13}H_{18}ClNO_4Na$ $[M-Na]^+$ 310.0817, found 310.0824.

FT-IR: (neat); $\tilde{\upsilon}$ = 3246 (s), 2943 (s), 2836 (s), 1601 (s), 1576 (m), 1496 (m), 1461 (m), 1423 (m), 1362 (m), 1305 (s), 1286 (m), 1241 (m), 1187 (m), 1147 (m), 1053 (m), 1023 (s), 993 (m), 922 (s), 871 (m), 785 (s), 618 (m), 573 (m), 549 (m), 522 (s) cm^{-1}.

Amino alcohol **205** was synthesized using racemic oxathiazinane **204**, therefore no measurement of optical rotation was performed.

(*R*)-3-acetamido-3-(3-chloro-4,5-bis((triethylsilyl)oxy)phenyl)propanoic acid 59



Amino acid **206** [M 301.72]	1.00 equiv.	67.0 µmol	20.2 mg
$AlBr_3$ [M 266.69]	8.00 equiv.	536 µmol	143 mg
EtSH [M 62.14; ρ 0.84]	70.00 equiv.	4.69 mmol	347 µL
TESCl [M 150.72; ρ 0.90]	7.50 equiv.	503 µmol	84.3 µL
NEt_3 [M 101.19; ρ 0.73]	8.00 equiv.	536 µmol	74.7 µL
DMAP [M 122.17]	0.15 equiv.	10.0 µmol	1.20 mg

Under Ar-atmosphere amino acid **206** (20.2 mg, 67.0 µmol, 1.00 equiv.) was suspended in CH_2Cl_2 (0.3 mL) and added to a solution of $AlBr_3$ (143 mg, 536 µmol, 8.00 equiv.) in EtSH (347 µL, 4.69 mmol, 70.00 equiv.) at 0 °C. The mixture was warmed to rt and stirred for 24 h at this temperature. It was quenched by the addition of 1.0 M HCl (0.3 mL) and diluted with EtOAc (0.5 mL). NaCl was added to saturate the aq. layer and it was extracted with EtOAc (5x10 mL). The combined org. layers were dried over Na_2SO_4, filtrated and all volatile compounds were removed *in vacuo* to yield crude amino acid **81** (18.0 mg), which was directly used for the next step without further purification.

Under Ar-atmosphere crude amino acid **81**, NEt_3 (74.7 µL, 536 µmol, 8.00 equiv.) and DMAP (1.20 mg, 10.0 µmol, 0.15 equiv.) were dissolved in DMF (0.4 mL). At 0 °C TESCl (84.3 µL, 503 µmol, 7.50 equiv.) was added and the mixture was stirred at rt for 8 h. Sat. aq. NH_4Cl was added to quench the reaction, it was extracted with Et_2O (3x7 mL), the combined layers were washed with brine (5 mL), dried over Na_2SO_4 and all volatile compounds were removed *in vacuo*. After column chromatography (CH_2Cl_2/MeOH/AcOH 100:2:1) TES-protected amino acid **59** (23.0 mg, 45.8 µmol, 68%) was isolated as colorless oil.

TLC: R_f = 0.11 (CH_2Cl_2/MeOH:AcOH 100:2:1).

^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.72-0.80 (m, 12 H, TES), 0.96 (td, *J* = 6.0, 7.8 Hz, 1 H, TES), 2.03 (s, 3 H, Me), 2.80 (dd, *J* = 5.8, 16.1 Hz, 1 H, 2-H_A), 2.91 (dd, *J* = 5.8, 16.1 Hz, 1 H, 2-H_B), 5.30 (dt, *J* = 5.8, 8.5 Hz, 1 H, 3-H), 6.48 (d, *J* = 8.5 Hz, 1 H, NH), 6.67 (d, *J* = 2.3 Hz, 1 H, Ar), 6.86 (d, *J* = 2.3 Hz, 1 H, Ar) ppm.

The carboxylic acid proton could not be detected.

^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 5.2 (TES), 5.6 (TES), 6.7 (TES), 6.8 (TES), 23.4 (Me), 39.5 (C2), 48.8 (C3), 116.6 (Ar), 120.0 (Ar), 126.8 (Ar), 133.4 (Ar), 143.6 (Ar), 148.4 (Ar), 170.1 (NAc), 174.8 (CO_2H) ppm.

HR-MS: (ESI+): m/z calc. for $C_{23}H_{40}ClNO_5Si_2H$ $[M-H]^+$ 502.2212, found 502.2206.

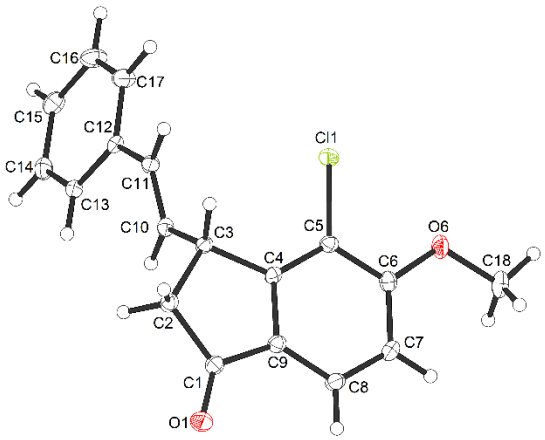
FT-IR: (neat); ῡ = 3246 (s), 2943 (m), 2836 (s), 1601 (s), 1576 (s), 1496 (s), 1461 (m), 1423 (m), 1362 (m), 1305 (s), 1286 (m), 1241 (m), 1187 (s), 1147 (s), 1053 (m), 1023 (m), 993 (m), 922 (s), 871 (s), 785 (w), 618 (s), 573 (s), 549 (s), 522 (w) cm^{-1}.

$[\alpha]_D^{23}$ 38 (c 1.0, $CHCl_3$).

The analytical data were in accordance with that reported in the literature.[14c]

8.4 Crystal structures

8.4.1 Crystal Structure of Indanone (*R*)-141:



Habitus, colour	nugget, colourless	
Crystal size	0.23 x 0.19 x 0.16 mm^3	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	Z = 4
Unit cell dimensions	a = 7.4545(3) Å	α= 90°.
	b = 8.5743(3) Å	β= 90°.
	c = 22.5355(9) Å	γ = 90°.
Volume	1440.40(10) $Å^3$	
Cell determination	9898 peaks with Theta 2.9 to 27.5°.	
Empirical formula	C_{18} H_{15} Cl O_2	
Moiety formula	C_{18} H_{15} Cl O_2	
Formula weight	298.75	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	0.266 mm^{-1}	
F(000)	624	

Data collection:

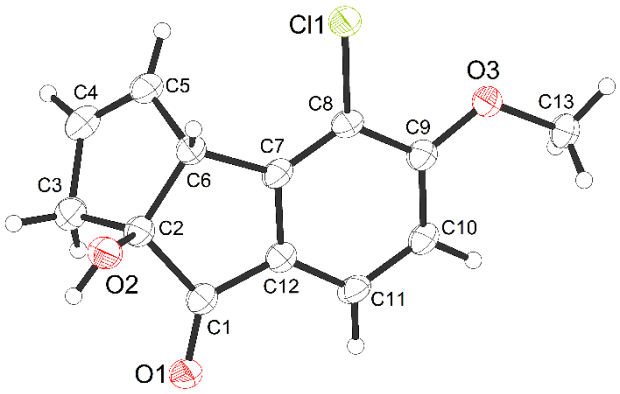
Diffractometer type	Bruker D8 QUEST area detector
Wavelength	0.71073 Å
Temperature	110(2) K
Theta range for data collection	2.542 to 27.510°.
Index ranges	-9<=h<=9, -11<=k<=11, -26<=l<=29
Data collection software	APEX3 (Bruker AXS Inc., 2015)[1]
Cell refinement software	SAINT V8.37A (Bruker AXS Inc., 2015)[2]
Data reduction software	SAINT V8.37A (Bruker AXS Inc., 2015)

Solution and refinement:

Reflections collected	25314
Independent reflections	3308 [R(int) = 0.0203]
Completeness to theta = 25.242°	99.9 %
Observed reflections	3253[I > 2σ(I)]
Reflections used for refinement	3308
Absorption correction	Semi-empirical from equivalents[3]
Max. and min. transmission	0.96 and 0.93
Flack parameter (absolute struct.)	0.019(8)[4]
Largest diff. peak and hole	0.224 and -0.264 $e.Å^{-3}$
Solution	Dual space algorithm

Refinement	Full-matrix least-squares on F^2
Treatment of hydrogen atoms	Calculated positions, constr. ref.
Programs used	XT V2014/1 (Bruker AXS Inc., 2014)[5]
	SHELXL-2014/7 (Sheldrick, 2014)[6]
	DIAMOND (Crystal Impact)[7]
	ShelXle (Hübschle, Sheldrick, Dittrich, 2011)[8]
Data / restraints / parameters	3308 / 0 / 191
Goodness-of-fit on F^2	1.080
R index (all data)	wR2 = 0.0632
R index conventional [I>2sigma(I)]	R1 = 0.0233

8.4.2 Crystal Structure of Indanone 155:



Habitus, colour	block, colorless	
Crystal size	0.12 x 0.07 x 0.05 mm^3	
Crystal system	Triclinic	
Space group	P-1	Z = 4
Unit cell dimensions	a = 9.1838(2) Å	α= 95.877(2)°.
	b = 9.3213(2) Å	β= 103.180(2)°.
	c = 14.8602(4) Å	γ = 109.791(2)°.
Volume	1142.83(5) $Å^3$	
Cell determination	15313 peaks with Theta 3.1 to 69.7°.	
Empirical formula	C_{13} H_{11} Cl O_3	
Moiety formula	C_{13} H_{11} Cl O_3	
Formula weight	250.67	
Density (calculated)	1.457 Mg/m^3	
Absorption coefficient	2.915 mm^{-1}	
F(000)	520	

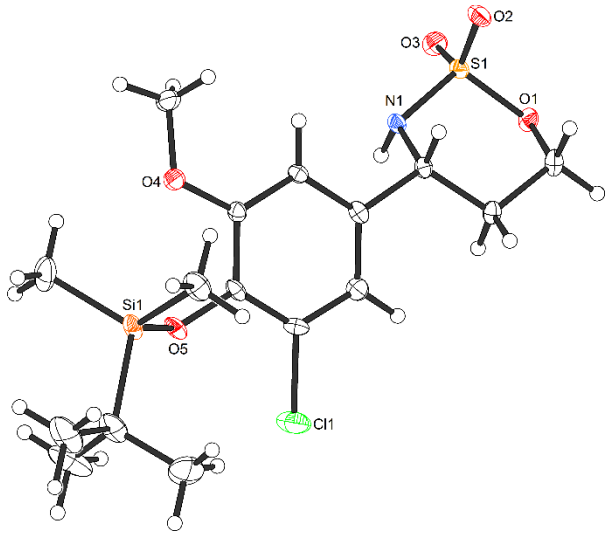
Data collection:

Diffractometer type	STOE STADIVARI
Wavelength	1.54184 Å
Temperature	100(2) K
Theta range for data collection	3.115 to 69.513°.
Index ranges	-11<=h<=9, -11<=k<=10, -8<=l<=17
Data collection software	X-Area Pilatus3_SV 1.31.127.0 (STOE, 2016)[1]
Cell refinement software	X-Area Recipe 1.33.0.0 (STOE, 2015)[2]
Data reduction software	X-Area Integrate 1.71.0.0 (STOE, 2016)[3]
	X-Area LANA 1.68.2.0 (STOE, 2016)[4]

Solution and refinement:

Reflections collected	17645
Independent reflections	4198 [R(int) = 0.0331]
Completeness to theta = 67.684°	99.0 %
Observed reflections	3366[I > 2σ(I)]
Reflections used for refinement	4198
Absorption correction	Semi-empirical from equivalents[4]
Max. and min. transmission	0.9695 and 0.2938
Largest diff. peak and hole	0.533 and -0.290 e.Å^{-3}
Solution	dual space algorithm
Refinement	Full-matrix least-squares on F^2
Treatment of hydrogen atoms	CH calculated, constr. ref., OH located, isotr. ref.
Programs used	XT V2014/1 (Bruker AXS Inc., 2014)[5] SHELXL-2016/6 (Sheldrick, 2016)[6] DIAMOND (Crystal Impact)[7] ShelXle (Hübschle, Sheldrick, Dittrich, 2011)[8]
Data / restraints / parameters	4198 / 0 / 317
Goodness-of-fit on F^2	1.015
R index (all data)	wR2 = 0.1185
R index conventional [I>2sigma(I)]	R1 = 0.0426

8.4.3 Crystal Structure of Oxathiazinane 192:



Habitus, colour	block, colourless	
Crystal size	0.60 x 0.19 x 0.17 mm^3	
Crystal system	Monoclinic	
Space group	$P2_1$	Z = 2
Unit cell dimensions	a = 6.6235(3) Å	α= 90°.
	b = 7.7531(3) Å	β= 92.834(2)°.
	c = 19.9152(8) Å	γ = 90°.
Volume	1021.45(7) Å^3	
Cell determination	9953 peaks with Theta 3.1 to 27.5°.	
Empirical formula	C_{16} H_{26} Cl N O_5 S Si	

Moiety formula	C_{16} H_{26} Cl N O_5 S Si
Formula weight	407.98
Density (calculated)	1.326 Mg/m^3
Absorption coefficient	0.37 mm^{-1}
F(000)	432

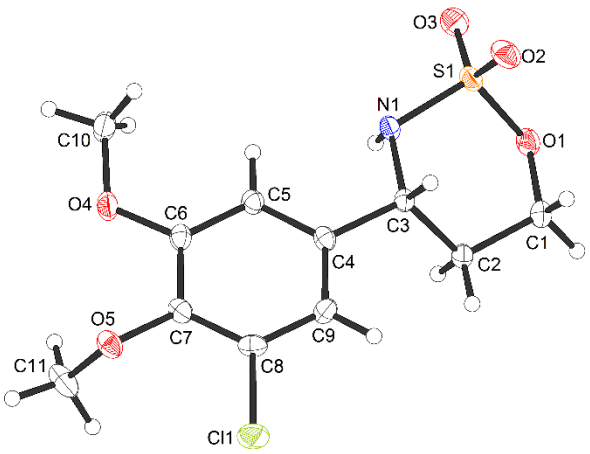
Data collection:

Diffractometer type	Bruker D8 QUEST area detector
Wavelength	0.71073 Å
Temperature	100(2) K
Theta range for data collection	2.820 to 27.528°.
Index ranges	-8<=h<=8, -10<=k<=9, -25<=l<=25
Data collection software	BRUKER APEX2 2014.9-0 [1]
Cell refinement software	BRUKER SAINT [2]
Data reduction software	SAINT V8.34A (Bruker AXS Inc., 2013) [2]

Solution and refinement:

Reflections collected	39159
Independent reflections	4545 [R(int) = 0.0344]
Completeness to theta = 25.242°	99.9 %
Observed reflections	4397[I>2sigma(I)]
Reflections used for refinement	4545
Absorption correction	Semi-empirical from equivalents [3]
Max. and min. transmission	0.7456 and 0.7033
Flack parameter (absolute struct.)	0.031(15)
Largest diff. peak and hole	0.262 and -0.464 $e.Å^{-3}$
Solution	Direct methods [4,4]
Refinement	Full-matrix least-squares on F^2 [4]
Treatment of hydrogen atoms	Calculated positions, constr. ref.
Programs used	XT V2014/1 (Bruker AXS Inc., 2014) [4,5] SHELXL-2014/7 (Sheldrick, 2014) [4,6] DIAMOND (Crystal Impact) [7]
Data / restraints / parameters	4545 / 1 / 236
Goodness-of-fit on F^2	1.083
R index (all data)	wR2 = 0.0777
R index conventional [I>2sigma(I)]	R1 = 0.0277

8.4.4 Crystal Structure of Oxathiazinane 198:



Habitus, colour	plate, colourless	
Crystal size	0.27 x 0.14 x 0.05 mm^3	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	Z = 4
Unit cell dimensions	a = 7.3554(3) Å	α= 90°.
	b = 8.3592(3) Å	β= 90°.
	c = 21.2995(8) Å	γ = 90°.
Volume	1309.61(9) $Å^3$	
Cell determination	18121 peaks with Theta 4.2 to 75.6°.	
Empirical formula	C_{11} H_{14} Cl N O_5 S	
Moiety formula	C_{11} H_{14} Cl N O_5 S	
Formula weight	307.74	
Density (calculated)	1.561 Mg/m^3	
Absorption coefficient	4.246 mm^{-1}	
F(000)	640	

Data collection:

Diffractometer type	STOE STADIVARI
Wavelength	1.54186 Å
Temperature	100(2) K
Theta range for data collection	4.151 to 74.787°.
Index ranges	-9<=h<=7, -8<=k<=10, -26<=l<=26
Data collection software	X-Area Pilatus3_SV 1.31.127.0 (STOE, 2016)[1]
Cell refinement software	X-Area Recipe 1.33.0.0 (STOE, 2015)[2]
Data reduction software	X-Area Integrate 1.71.0.0 (STOE, 2016)[3]
	X-Area LANA 1.68.2.0 (STOE, 2016)[4]

Solution and refinement:

Reflections collected	12779
Independent reflections	2647 [R(int) = 0.0449]
Completeness to theta = 67.686°	99.8 %
Observed reflections	2491[I > 2σ(I)]
Reflections used for refinement	2647
Absorption correction	Semi-empirical from equivalents[4]
Max. and min. transmission	0.8571 and 0.2602
Flack parameter (absolute struct.)	-0.006(9)[5]
Largest diff. peak and hole	0.358 and -0.327 $e.Å^{-3}$
Solution	intrinsic phasing[6]
Refinement	Full-matrix least-squares on F^2[7]
Treatment of hydrogen atoms	CH calculated, constr., NH located, isotr. ref.
Programs used	XT V2014/1 (Bruker AXS Inc., 2014)[6]
	SHELXL-2018/1 (Sheldrick, 2018)[7]
	DIAMOND (Crystal Impact)[8]
	ShelXle (Hübschle, Sheldrick, Dittrich, 2011)[9]
Data / restraints / parameters	2647 / 0 / 178
Goodness-of-fit on F^2	1.041
R index (all data)	wR2 = 0.0863
R index conventional [I>2sigma(I)]	R1 = 0.0328

[1] *X-Area Pilatus3_SV*, STOE & Cie GmbH, Darmstadt, Germany, **2016**.
[2] *X-Area Recipe*, STOE & Cie GmbH, Darmstadt, Germany, **2015**.
[3] *X-Area Integrate*, STOE & Cie GmbH, Darmstadt, Germany, **2016**.
[4] *X-Area LANA*, STOE & Cie GmbH, Darmstadt, Germany, **2016**.
[5] S. Parsons, H. D. Flack, T. Wagner, *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.* **2013**, *69*, 249.
[6] G. M. Sheldrick, *Acta Crystallogr A Found Adv* **2015**, *71*, 3.
[7] G. M. Sheldrick, *Acta crystallographica. Section C, Structural chemistry* **2015**, *71*, 3.
[8] K. Brandenburg, *Diamond - Crystal and Molecular Structure Visualization*, Crystal Impact - Dr. H. Putz & Dr. K. Brandenburg GbR, Bonn, Germany, **2014**.
[9] C. B. Hübschle, G. M. Sheldrick, B. Dittrich, *Journal of applied crystallography* **2011**, *44*, 1281.

9. References

[1] K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Ōtake, N. Ishida, *Tetrahedron Lett.* **1985**, *26*, 331–334.
[2] a) A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, *39*, 2103–2117;
b) M. Gredičak, I. Jerić, *Acta Pharmaceutica* **2007**, *57*, 133–150;
c) U. Galm, M. H. Hager, S. G. van Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.* **2005**, *105*, 739–758.
[3] For isolation see: a) K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Ōtake, N. Ishida, *Tetrahedron Lett.* **1985**, *26*, 331–334.
For synthetic studies studies see: b) A. G. Myers, R. Glatthar, M. Hammond, P. M. Harrington, E. Y. Kuo, J. Liang, S. E. Schaus, Y. Wu, J.-N. Xiang, *J. Am. Chem. Soc.* **2002**, *124*, 5380–5401.
[4] For isolation see: a) M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, D. B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3464–3466;
b) M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren, D. B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3466–3468.
For total a synthesis see: c) K. C. Nicolaou, C. W. Hummel, E. N. Pitsinos, M. Nakada, A. L. Smith, K. Shibayama, H. Saimoto, *J. Am. Chem. Soc.* **1992**, *114*, 10082–10084.
[5] For isolation see: a) J. Hu, Y.-C. Xue, M.-Y. Xie, R. U.I. Zhang, T. Otani, Y. Minami, Y. Yamada, T. Marunaka, *J. Antibiot.* **1988**, *41*, 1575–1579;
b) X. Yan, Hindra, H. Ge, D. Yang, T. Huang, I. Crnovcic, B. Shen *et al.*, *J. Nat. Prod.* **2018**, *81*, 594–599.
For synthetic studies see: c) M. Inoue, S. Hatano, M. Kodama, T. Sasaki, T. Kikuchi, M. Hirama, *Org. Lett.* **2004**, *6*, 3833–3836;
d) M. Inoue, T. Kikuchi, M. Hirama, *Tetrahedron Lett.* **2004**, *45*, 6439–6442;
e) M. Inoue, T. Sasaki, S. Hatano, M. Hirama, *Angew. Chem. Int. Ed.* **2004**, *43*, 6500–6505;
f) M. Inoue, I. Ohashi, T. Kawaguchi, M. Hirama, *Angew. Chem. Int. Ed.* **2008**, *47*, 1777–1779.
[6] For isolation see: a) J. Davies, H. Wang, T. Taylor, K. Warabi, X.-H. Huang, R. J. Andersen, *Org. Lett.* **2005**, *7*, 5233–5236;
For total syntheses see: b) K. C. Nicolaou, H. Zhang, J. S. Chen, J. J. Crawford, L. Pasunoori, *Angew. Chem. Int. Ed.* **2007**, *46*, 4704–4707;
c) K. C. Nicolaou, J. S. Chen, H. Zhang, A. Montero, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 185–189; d) K. C. Nicolaou, Y. Wang, M. Lu, D. Mandal, M. R. Pattanayak, R. Yu *et al*. *J. Am. Chem. Soc.* **2016**, *138*, 8235–8246.
[7] For isolation see: a) M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716;
b) H. Kamei, Y. Nishiyama, A. Takahashi, Y. Obi, T. Oki, *J. Antibiot.* **1991**, *44*, 1306–1311.
For a proposed biosynthesis see: b) Q. Gao, J. S. Thorson, *FEMS Microbiol. Lett.* **2008**, *282*, 105–114; c) D. R. Cohen, C. A. Townsend, *Nature Chemistry* **2018**, *10*, 231–236.
For total syntheses see: d) A. G. Myers, M. E. Fraley, N. J. Tom, S. B. Cohen, D. J. Madar, *Chem. Biol.* **1995**, *2*, 33–43;
e) M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525.
[8] For isolation see: a) J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462;
b) J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.* **1987**, *109*, 3462–3464.

For synthetic studies see: c) E. Da Silva, J. Prandi, J.-M. Beau, *J. Chem. Soc., Chem. Commun.* **1994**, 2127–2128;
d) G. Ulibarri, H. Audrain, W. Nadler, H. Lhermitte, D. S. Grierson, *Pure Appl. Chem.* **1996**, *68*, 601–604;
e) E. C. Sherer, K. N. Kirschner, F. C. Pickard, C. Rein, S. Feldgus, G. C. Shields, *J. Phys. Chem. B* **2008**, *112*, 16917–16934.
[9] X. Yan, H. Ge, T. Huang, Hindra, D. Yang, Q. Teng *et al. mBio* **2016**, 1–12.
[10] Xi, Z.; Goldberg, I. H, Comprehensive Natural Products Chemistry; Elsevier: New York, **1999**; *7*, 533–592.
[11] For isolation see: a) G. O. Buchanan, P. G. Williams, R. H. Feling, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* **2005**, *7*, 2731–2734.
For a proposed biosynthesis see: b) R. P. McGlinchey, M. Nett, B. S. Moore, *J. Am. Chem. Soc.* **2008**, *130*, 2406–2407.
For synthetic studies see: c) K. C. Nicolaou, J. Wang, Y. Tang, *Angew. Chem. Int. Ed.* **2008**, *47*, 1432–1435;
d) J. A. Gladding, J. P. Bacci, S. A. Shaw, A. B. Smith, *Tetrahedron* **2011**, *67*, 6697–6706;
e) P. Li, D. Menche, *Angew. Chem. Int. Ed.* **2009**, *48*, 5078–5080;
f) S. Yamashita, K. Terayama, E. Ozeki, Y. Hayashi, M. Hirama, *Org. Lett.* **2017**, *20*, 276–279.
For total a synthesis see: g) K. C. Nicolaou, J. Wang, Y. Tang, *Angew. Chem. Int. Ed.* **2008**, *47*, 1432–1435.
[12] For isolation see: S. Y. Ma, Y. S. Xiao, B. Zhang, F. L. Shao, Z. K. Guo, J. J. Zhang *et al. Org. Lett.* **2017**, *19*, 6208–6211.
[13] For isolation see: a) D.-C. Oh, P. G. Williams, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* **2006**, *8*, 1021–1024.
For a proposed biosynthesis see: b) A. L. Lane, S.-J. Nam, T. Fukuda, K. Yamanaka, C. A. Kauffman, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* **2013**, *135*, 4171–4174.
For total synthesis see: c) K. Yamada, M. J. Lear, T. Yamaguchi, S. Yamashita, I. D. Gridnev, Y. Hayashi, M. Hirama, *Angew. Chem. Int. Ed.* **2014**, *53*, 13902–13906.
[14] For isolation see: a) S.-J. Nam, S. P. Gaudêncio, C. A. Kauffman, P. R. Jensen, T. P. Kondratyuk, L. E. Marler, J. M. Pezzuto, W. Fenical, *J. Nat. Prod.* **2010**, *73*, 1080–1086;
b) K. Moon, C.-H. Ahn, Y. Shin, T. H. Won, K. Ko, S. K. Lee, K.-B. Oh, J. Shin, S.-I. Nam, D.-C. Oh, *Mar Drugs* **2014**, *12*, 2526–2538.
For total synthesis see: c) C. Heinz, N. Cramer, *J. Am. Chem. Soc.* **2015**, *137*, 11278–11281;
d) C. Heinz, N. Cramer, *Chimia* **2016**, *70*, 258–262;
e) C. Heinz, PhD thesis, ETH Zürich, **2016**.
[15] a) M. Hirama, *Proc. Jpn. Acad., Ser. B* **2016**, *92*, 290–329;
b) K.-i. Iida, M. Hirama, *J. Am. Chem. Soc.* **1995**, *117*, 8875–8876;
c) K. Yamada, M. J. Lear, T. Yamaguchi, S. Yamashita, I. D. Gridnev, Y. Hayashi, M. Hirama, *Angew. Chem. Int. Ed.* **2014**, *53*, 13902–13906;
d) M. Inoue, I. Ohashi, T. Kawaguchi, M. Hirama, *Angew. Chem. Int. Ed.* **2008**, *47*, 1777–1779.
[16] M. Inoue, S. Hatano, M. Kodama, T. Sasaki, T. Kikuchi, M. Hirama, *Org. Lett.* **2004**, *6*, 3833–3836.
[17] Y. Ken-ichiro, Y. Minami, R. Azuma, M. Saeki, T. Otani, *Tetrahedron Lett.* **1993**, *34*, 2637–2640.
[18] W. Liu, S. D. Christenson, S. Standage, B. Shen, *Science* **2002**, *297*, 1170–1173.
[19] S. van Lanen, B. Shen, *CTMC* **2008**, *8*, 448–459.
[20] U. Galm, M. H. Hager, S. G. van Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.* **2005**, *105*, 739–758.

[21] a) P. Bhattacharya, A. Basak, A. Campbell, I. V. Alabugin, *Mol. Pharm.* **2018**, *15*, 768–797.
b) A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, *39*, 2103–2117.
[22] M. Karin, Y. Ben-Neriah, *Annu. Rev. Immunol.* **2000**, *18*, 621–663.
[23] B. B. Aggarwal, *Cancer cell* **2004**, *6*, 203–208.
[24] M. M. Rahman, G. McFadden, *PLoS pathogens* **2006**, *2*, 66–77.
[25] T. D. Gilmore, *Oncogene* **2006**, *25*, 6680–6684.
[26] T. Hehlgans, K. Pfeffer, *Immunology* **2005**, *115*, 1–20.
[27] K.-I. Iida, T. Ishii, M. Hirama, T. Otani, Y. Minami, K.-i. Yoshida, *Tetrahedron Lett.* **1993**, *34*, 4079–4082.
[28] K. Hirai, Y. Tamura, I. Sato, M. Hirama, *Synlett* **2010**, *2010*, 2156–2158.
[29] M. F. Semmelhack, Y. Jiang, D. Ho, *Org. Lett.* **2001**, *3*, 2403–2406.
[30] M. E. Evans, F. W. Parrish, *Carbohydr. Res.* **1977**, *54*, 105–114.
[31] I. Sato, T. Kikuchi, M. Hirama, *Chem. Lett.* **1999**, *28*, 511–512.
[32] S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1991**, *2*, 183–186.
[33] Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713.
[34] S. Datta, R.-S. Liu, *Tetrahedron Lett.* **2005**, *46*, 7985–7988.
[35] D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220–9221.
[36] D. C. Harrowven, N. A. Newman, C. A. Knight, *Tetrahedron Lett.* **1998**, *39*, 6757–6760.
[37] T. Itoh, T. Mase, T. Nishikata, T. Iyama, H. Tachikawa, Y. Kobayashi, Y. Yamamoto, N. Miyaura, *Tetrahedron* **2006**, *62*, 9610–9621.
[38] H. Tsukamoto, Y. Kondo, *Org. Lett.* **2007**, *9*, 4227–4230.
[39] R. C. Larock, M. J. Doty, S. Cacchi, *J. Org. Chem.* **1993**, *58*, 4579–4583.
[40] a) Z. Qi, M. Wang, X. Li, *Org. Lett.* **2013**, *15*, 5440–5443;
b) J. Wen, W. Shi, F. Zhang, D. Liu, S. Tang, H. Wang, X.-M. Lin, A. Lei, *Org. Lett.* **2017**, *19*, 3131–3134;
c) X.-F. Wu, F. Zhu, A. Spannenberg, *Chem. Commun.* **2017**, *53*, 13149–13152;
d) X.-T. Zhu, Q. Zhao, F. Liu, A.-F. Wang, P.-J. Cai, W.-J. Hao, S.-J. Tu, B. Jiang, *Chem. Commun.* **2017**, *53*, 6828–6831.
[41] R. G. F. Giles, I. R. Green, S.-H. Li, *Aust. J. Chem.* **2005**, *58*, 565–571.
[42] Sigma Aldrich [prices from 9.4.2018]
[43] Failed attemps for *in situ* isomerization of cinnamic acid ester **94** and the corresponding acid included acidic conditions (TFA, PPTS), convertion into the acid chloride or mixed anhydride with addition of LEWIS acid.
[44] W.C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
[45] Sigma Aldrich, [price from 6.4.2018]
[46] F. Messik, M. Oberthür, *Synthesis* **2013** *45*, 167–170.
[47] Sigma Aldrich [price from 6.4.2018]
[48] a) J. B. Metternich, R. Gilmour, *J. Am. Chem. Soc.* **2015**, *137*, 11254–11257;
b) J. Metternich, R. Gilmour, *Synlett* **2016**, *27*, 2541–2552.
[49] A. G. N. Walker, G. K. Radda. *Nature* **1967**, *215*, 1483.
[50] J. Metternich, S. Sagebiel, A. Lückener, S. Lamping, B. J. Ravoo, R. Gilmour, *Chem. Eur. J.* **2018**, *24*, 4228–4233.
[51] B. Pieber, M. Shalom, M. Antonietti, P. H. Seeberger, K. Gilmore, *Angew. Chem. Int. Ed.* **2018**, ASAP. DOI: 10.1002/anie.201712568
[52] A. Kolb, S. Hirner, K. Harms, P. v. Zezschwitz, *Org. Lett.* **2012**, *14*, 1978–1981.
[53] A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2427–2430.
[54] B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed.* **1997**, *36*, 2620–2623.

[55] Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.
[56] a) O. Meyer, J.-M. Becht, G. Helmchen, *Synlett* **2003**, 1539–1541;
b) J.-M. Becht, O. Meyer, G. Helmchen, *Synthesis* **2003** 2805–2810.
[57] G. Lalic, E. J. Corey, *Org. Lett.* **2007**, *9*, 4921–4923.
[58] V. Hickmann, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11042–11044.
[59] C. M. König, B. Gebhardt, C. Schleth, M. Dauber, U. Koert, *Org. Lett.* **2009**, *11*, 2728–2731.
[60] H. Todoroki, M. Iwatsu, D. Urabe, M. Inoue, *J. Org. Chem.* **2014**, *79*, 8835–8849.
[61] T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844.
[62] For a recent review article about Rh- and Cu-catalyzed conjugate additions see: D. Müller, A. Alexakis, *Chem. Commun.* **2012**, *48*, 12037–12049.
[63] S. Sakuma, M. Sakai, R. Itooka, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 5951–5955.
[64] Z.-Q. Wang, C.-G. Feng, S.-S. Zhang, M.-H. Xu, G.-Q. Lin, *Angew. Chem. Int. Ed.* **2010**, *49*, 5780–5783.
[65] C. G. Frost, S. D. Penrose, R. Gleave, *Org. Biomol. Chem.* **2008**, *6*, 4340–4347.
[66] C.-Y. Wu, Y.-F. Zhang, M.-H. Xu, *Org. Lett.* **2018**, *20*, 1789–1793.
[67] a) A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045–8052;
b) Q. Chong, Z. Yue, S. Zhang, C. Ji, F. Cheng, H. Zhang, X. Hong, F. Meng, *ACS Catal.* **2017**, 5693–5698.
[68] K.-s. Lee, A. H. Hoveyda, *J. Org. Chem.* **2009**, *74*, 4455–4462.
[69] S. Oi, T. Sato, Y. Inoue, *Tetrahedron Lett.* **2004**, *45*, 5051–5055.
[70] a) S. J. Mahoney, A. M. Dumas, E. Fillion, *Org. Lett.* **2009**, *11*, 5346–5349;
b) D. E. van Horn, E. Negishi, *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254.
[71] M. K. Brown, E. J. Corey, *Org. Lett.* **2010**, *12*, 172–175.
[72] K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 1541–1544.
[73] T. Nishimura, X.-X. Guo, N. Uchiyama, T. Katoh, T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 1576–1577.
[74] N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584–13585.
[75] C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873–3876.
[76] B. M. Trost, A. C. Burns, T. Tautz, *Org. Lett.* **2011**, *13*, 4566–4569.
[77] N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584–13585.
[78] R. Shintani, Y. Ichikawa, K. Takatsu, F.-X. Chen, T. Hayashi, *J. Org. Chem.* **2009**, *74*, 869–873.
[79] G. Chen, J. Gui, L. Li, J. Liao, *Angew. Chem. Int. Ed.* **2011**, *50*, 7681–7685.
[80] S. Otocka, M. Kwiatkowska, L. Madalińska, P. Kiełbasiński, *Chem. Rev.* **2017**, *117*, 4147–4181.
[81] K. Okamoto, T. Hayashi, V. H. Rawal, *Org. Lett.* **2008**, *10*, 4387–4389.
[82] a) C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482–3485;
b) K. Shirakawa, A. Arase, M. Hoshi, *Synthesis* **2004**, 1814–1820.
[83] Y. D. Wang, G. Kimball, A. S. Prashad, Y. Wang, *Tetrahedron Lett.* **2005**, *46*, 8777–8780.
[84] T. Ohmura, Y. Yamamoto, N. Miyaura, *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991.
[85] a) E. Hirsch, S. Hünig, H.-U. Reissig, *Chem. Ber.* **1982**, *115*, 3687–3696;
b) U. Hertenstein, S. Hünig, H. Reichelt, R. Schaller, *Chem. Ber.* **1986**, *119*, 699–721.
[86] a) M. Webel, H.-U. Reissig, *Synlett* **1997**, 1141–1142;
b) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2002**, 3646–3658.
[87] S.-i. Hashimoto, T. Shinoda, S. Ikegami, *Tetrahedron Lett.* **1986**, *27*, 2885–2888.

[88] J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197–1212.
[89] T. Hudlicky, F. F. Koszyk, T. M. Kutchan, J. P. Sheth, *J. Org. Chem.* **1980**, *45*, 5020–5027.
[90] C. Müller generously provided us with a sample of diene ligand **110**.
[91] a) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, K. Tomer, *J. Am. Chem. Soc.* **1968**, *90*, 4762–4763;
b) A. Sen, W. Grosch, *Flavour Fragr. J.* **1990**, *5*, 233–234.
[92] One case of Rh-catalyzed 1,4-addition of an aryl boronic acid to an indenone is described in the literature furnishing the addition product in 27% with 8% *ee*, for additional informations see: T. Itoh, T. Mase, T. Nishikata, T. Iyama, H. Tachikawa, Y. Kobayashi, Y. Yamamoto, N. Miyaura, *Tetrahedron* **2006**, *62*, 9610–9621.
[93] a) E. Alcalde, N. Mesquida, S. Lopez-Perez, J. Frigola, R. Merce, J. Holenz, M. Pujol, E. Hernandez, *Bioorg. Med. Chem.* **2009**, *17*, 7387–7397;
b) J. M. Cid, J. L. Romera, A. A. Trabanco, *Tetrahedron Lett.* **2004**, *45*, 1133–1136.
[94] N. Krause, *Angew. Chem.* **1994**, *106*, 1845–1847.
[95] W. Adam, F. Prechtl, *Chem. Ber.* **1991**, *124*, 2369–2372.
[96] P. Babin, B. Bennetau, J. Dunoguès, *Synth. Commun.* **1992**, *22*, 2849–2852.
[97] Y. Choi, H. Ishikawa, J. Velcicky, G. I. Elliott, M. M. Miller, D. L. Boger, *Org. Lett.* **2005**, *7*, 4539–4542.
[98] D. Spitzner, K. Oesterreich, *Eur. J. Org. Chem.* **2001**, *2001*, 1883–1886.
[99] F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919–934.
[100] Y. Wang, A. Jäger, M. Gruner, T. Lübken, P. Metz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15861–15865.
[101] C. J. Gartshore, D. W. Lupton, *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116.
[102] D. L. Comins, S. Huang, C. L. McArdle, C. L. Ingalls, *Org. Lett.* **2001**, *3*, 469–471.
[103] N. Bajwa, M. P. Jennings, *J. Org. Chem.* **2008**, *73*, 3638–3641.
[104] For examples see: a) K. Narasaka, F.-C. Pai, *Tetrahedron* **1984**, *40*, 2233–2238;
b) K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repič, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155–158;
c) Q. Liu, Y. Deng, A. B. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 13668–13671.
[105] T. Hori, K. B. Sharpless, *J. Org. Chem.* **1979**, *44*, 4208–4210.
[106] L.-D. Shao, J. Xu, X.-N. Li, Z.-J. Zhang, X. Shi, J. Ren *et al. RSC Adv* **2016**, *6*, 35792–35803.
[107] B. R. Smith, J. T. Njardarson, *Org. Lett.* **2017**, *19*, 5316–5319.
[108] L. You, X.-T. Liang, L.-M. Xu, Y.-F. Wang, J.-J. Zhang, Q. Su *et al. J. Am. Chem. Soc.* **2015**, *137*, 10120–10123.
[109] N. Münster, P. Nikodemiak, U. Koert, *Org. Lett.* **2016**, *18*, 4296–4299.
[110] J. Mesch, B.Sc. thesis, Philipps-University Marburg, **2016**.
[111] Sigma Aldrich [price from 6.4.2108]
[112] L. Menini, E. V. Gusevskaya, *Appl. Catal. A Gen.* **2006**, *309*, 122–128.
[113] J. W. Timberlake, W. J. Ray, E. D. Stevens, C. L. Klein, *J. Org. Chem.* **1989**, *54*, 5824–5826.
[114] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 109–131.
[115] R. Hernández, A. Rivera, J. A. Salazar, E. Suárez, *J. Chem. Soc., Chem. Commun.* **1980**, 958–959.
[116] a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287–8291;
b) T. Duhamel, C. J. Stein, C. Martínez, M. Reiher, K. Muñiz, *ACS Catal.* **2018**, 3918–3925.
[117] J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62–101.
[118] A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129–133.
[119] L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543.
[120] C. G. Espino, P. M. Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936.

[121] a) R. Breslow, S. H. Gellman, *J. Chem. Soc., Chem. Commun.* **1982**, 1400–1401;
b) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729.
[122] C. G. Espino, J. Du Bois, *Angew. Chem. Int. Ed.* **2001**, *40*, 598–600.
[123] P. Dauban, L. Sanière, A. Tarrade, R. H. Dodd, *J. Am. Chem. Soc.* **2001**, *123*, 7707–7708.
[124] K. W. Fiori, C. G. Espino, B. H. Brodsky, J. Du Bois, *Tetrahedron* **2009**, *65*, 3042–3051.
[125] X. Lin, C. Zhao, C.-M. Che, Z. Ke, D. L. Phillips, *Chem. Asian J.* **2007**, *2*, 1101–1108.
[126] a) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220–9221;
b) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562–568.
[127] D. N. Barman, K. M. Nicholas, *Eur. J. Org. Chem.* **2011**, *2011*, 908–911.
[128] J. M. Alderson, A. M. Phelps, R. J. Scamp, N. S. Dolan, J. M. Schomaker, *J. Am. Chem. Soc.* **2014**, *136*, 16720–16723.
[129] E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591–595.
[130] J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *Acc. Chem. Res.* **1997**, *30*, 364–372.
[131] M. E. Harvey, D. G. Musaev, J. Du Bois, *J. Am. Chem. Soc.* **2011**, *133*, 17207–17216.
[132] C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379.
[133] a) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562–568;
b) J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem. Int. Ed.* **2013**, *52*, 11343–11346.
[134] P. M. Wehn, J. Du Bois, *J. Am. Chem. Soc.* **2002**, *124*, 12950–12951.
[135] J. J. Fleming, J. Du Bois, *J. Am. Chem. Soc.* **2006**, *128*, 3926–3927.
[136] A. Hinman, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511.
[137] a) S. Kang, H.-K. Lee, *J. Org. Chem.* **2010**, *75*, 237–240;
b) B. Darses, R. Rodrigues, L. Neuville, M. Mazurais, P. Dauban, *Chem. Commun.* **2016**, *53*, 493–508.
[138] K. P. Kornecki, J. F. Berry, *Chem. Commun.* **2012**, *48*, 12097–12099.
[139] H. Lebel, K. Huard, S. Lectard, *J. Am. Chem. Soc.* **2005**, *127*, 14198–14199.
[140] J. R. Suárez, J. L. Chiara, *Chem. Commun.* **2013**, *49*, 9194–9196.
[141] C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343–350.
[142] The prediction of enantioselective CH-amination using Rh_2(*S*-nap)$_4$ has already been corrected, for details see reference 137b
[143] L. A. Paquette, R. A. Roberts, G. J. Drtina, *J. Am. Chem. Soc.* **1984**, *106*, 6690–6693.
[144] A. Y. Koposov, R. R. Karimov, I. M. Geraskin, V. N. Nemykin, V. V. Zhdankin, *J. Org. Chem.* **2006**, *71*, 8452–8458.
[145] The unprotected catechol was obtained in ~80% purity analogous to CRAMER`s deprotection of the methyl ester. In order to compare the analytical data with that of CRAMER, the TES-protection of the catechol was performed.
[146] a) E. J. Corey, M. Behforouz, M. Ishiguro, *J. Am. Chem. Soc.* **1979**, *101*, 1608–1609;
b) M. K. Brown, E. J. Corey, *Org. Lett.* **2010**, *12*, 172–175.
[147] W.-T. Wei, J.-Y. Yeh, T.-S. Kuo, H.-L. Wu, *Chem. Eur. J.* **2011**, *17*, 11405–11409.
[148] T. Itoh, T. Mase, T. Nishikata, T. Iyama, H. Tachikawa, Y. Kobayashi, Y. Yamamoto, N. Miyaura, *Tetrahedron* **2006**, *62*, 9610–9621.
[149] T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657–4673.
[150] M. J. Mintz, C. Walling, *Org. Synth.* **1969**, *49*, 9–11.
[151] J. R. Falck, A. He, H. Fukui, H. Tsutsui, A. Radha, *Angew. Chem. Int. Ed.* **2007**, *46*, 4527–4529.
[152] Douglass F. Taber, Peter W. DeMatteo, Rasha A. Hassan, *Org. Synth.* **2013**, *90*, 350–357.