Université de Montréal

Acyclic Stereocontrol and Chemical Diversity

&

Application to the Total Synthesis of Bafilomycin A_1

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Abbreviations

$[\alpha]_D$	Specific rotation
Ac	Acetyl
AM1	Austin Model 1
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOM	Benzyloxymethyl
Bu	Butyl
t-Bu	*tert*-Butyl
δ	Chemical shift in ppm
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DEC	No reaction meanwhile decomposition of starting material
DIPEA	Diisopropylethyl amine
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Ethylene glycol dimethyl ether, 1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide, methyl sulfoxide

DPPA	Diphenyl phosphoryl azide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et	Ethyl
ether	Diethyl ether
eq	Equivalent
h	Hour (s)
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphoramide
HRMS	High resolution mass spectrum
Hz	Hertz
Imid	Imidazole
IR	Infrared spectroscopy
KHMDS	Potassium bis(trimethylsilyl)amide, Potassium hexamethyldisilane
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
μ	Micro 10^{-6}
μL	Microliter
mCPBA	*meta*-Chloroperbenzoic acid
MACIM	Methyl 1-acetylimidazolidin-2-one-(4*S*)-carboxylate
Me	Methyl
MEPY	Methyl-2-oxapyrrolidine-4(*S*)-carboxylate

mg	Milligram
min	Minute
MHz	Megahertz
mL	Milliliter
mmol	Millimole
MNDO	Modified negleft of diatomic overlap
MOM	Methoxymethyl
mp	Melting point
MPPIM	Methyl 1-(3-phenylpropanoyl)imidazolidin-2-one-4(*S*)-carboxylate
Ms	Methanesulfonyl
MS	Mass spectrum
NBS	*N*-Bromosuccinmide
NIS	*N*-Iodosuccinimde
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NMP	1-Methyl-2-pyrrolidinone
nOe	Nuclear Overhauser effect
NR	No reaction
OTf	Trifluoromethanesulfonate, Triflate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PLE	Pig Liver Esterase

Piv	Pivaloyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
PTSA	*para*-Toluenesulfonic acid monohydrate
Pyr	Pyridine
rt	Room temperature
sat.	Saturated
TBAF	Tetrabutylammonium fluoride
TBDPS	tert-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMPA	Trimethylphosphonoacetate
TPAP	Tetrapropylammonium perruthenate
TPS	*tert*-Butyldiphenylsilyl
Tr	Trityl, Triphenylmethyl
Trisyl	2,4,6-Triisopropylbenzenesulfonyl
Ts	Toluenesulfonyl

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Abstract

We have demonstrated that the stereocontrolled conjugate addition of organocuprates to γ-alkoxy-α.β-unsaturated esters proceeds with high diastereoselectivity in a two-directional strategy. This protocol affords acyclic chains that contain three contiguous substituents of the *anti*, *anti* propionate triad type and its phenylacetate equivalent. α-Alkylations and aldol type reactions on the cuprate adduct also proceed in a stereoselective manner.

Enolate hydroxylation with a chiral oxaziridine and cuprate additions can be done in an iterative manner to generate seven carbon acyclic motifs harboring five contiguous stereocenters consisting of alternating hydroxyl and phenyl substituents with complete stereocontrol. A series of 1,2-asymmetric inductions starting with a resident γ-alkoxy group propagate with excellent stereoselectivity through two successive conjugate additions and two enolate hydroxylations.

We have also demonstrated that the high degree of 1,2-induction in the α-alkylation and α-hydroxylation reactions can be also extended to solid phase. Polypropionate synthesis can be achieved on solid phase with excellent 1,2 induction through two cuprate additions and two enolate hydroxylation cycles. The stereoselectivities of these reactions on solid-phase are as good as in solution chemistry and the stereofacial selectivities are the same for solid–phase and solution chemistry.

The enantiopure indanes and tetrahydronaphthalenes were synthesized from the γ-alkoxy α,β-unsaturated ester with very high stereoselectivities and good yields using the stereocontrolled cuprate additions and Friedel-Crafts reactions as the key steps.

The natural macrolide Bafilomycin A_1 was successfully synthesized originally from D-mannitol and D-valine using stereocontrolled cuprate conjugate additions and α-hydroxylation to efficiently install all the chiral centers. The Stille coupling reaction was used to join the two fully assembled segments and macrolactonization was accomplished with a Keck reaction.

Keywords: 1,2 induction, cuprate addition, solid phase, total synthesis, Bafilomycin A_1

Résumé

Nous avons démontré que l'addition conjuguée d'organocuprates sur des γ-alkoxy esters α,β-insaturés est réalisée avec une haute diastéréosélectivité, dans une stratégie bidirectionnelle. Cette méthodologie permet d'obtenir des chaînes acycliques contenant trois substituants contigus, du type de la triade *anti, anti* propionate et de son équivalent phénylacétate. Les réactions de type α-alkylation et aldol sur l'adduit cuprate procèdent aussi de façon stéréosélective.

L'hydroxylation d'énolates au moyen d'une oxaziridine chirale et l'addition de cuprates peuvent être réalisées de façon itérative, de manière à générer des motifs de sept carbones acycliques contenant cinq stéréocentres chiraux contigus consistant en l'alternance de substituants hydroxyles et phényles, ce avec un complet stéréocontrôle. Ceci est réalisé au moyen de deux additions conjuguées et deux hydroxylations d'énolates successives, qui se propagent avec une excellente stéréosélectivité grâce à une série d'inductions asymétriques 1,2 débutant avec un groupe γ-alkoxy.

Nous avons aussi démontré que le haut degré d'induction 1,2 dans les réactions d'α-alkylations et α-hydroxylations peut être étendu à la phase solide. Ainsi la synthèse de polypropionates peut être réalisée sur support solide avec une excellente induction 1,2 par itération de deux additions de cuprates et deux hydroxylations d'énolates. Les stéréosélectivités et sélectivités stéréofaciales obtenues en phase solide sont identiques à celles obtenues pour la chimie en solution.

Des indanes et des tétrahydronaphtalènes énantiopurs ont été synthétisés avec une très haute stéréosélectivité et de bons rendements à partir de γ-alkoxy esters α,β-insaturés, en utilisant des additions de cuprates stéréocontrôlées et des réactions de Friedel-Crafts comme étapes clés.

Le macrolide naturel Bafilomycine A_1 a été synthétisé avec succès à partir du D-mannitol et de la D-valine; des réactions d'additions conjuguées de cuprates et d'α-hydroxylations ont permis d'installer efficacement tous les centres chiraux. Un couplage de Stille a été employé pour connecter les deux longs segments entièrement assemblés. La macrolactonisation a quant à elle été réalisée par une réaction de Keck.

Mots clés: induction-1,2, addition de cuprate, phase solide, synthèse totale, bafilomycin A_1

THEORETICAL PART

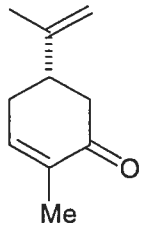
Chapter one Asymmetric synthesis

♦ 1-1 The (*R*)- and (*S*)- worlds

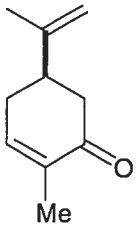
Organic compounds play an important role in life, not least in the area of pharmaceuticals and agrochemicals. The synthesis of an increasing number of compounds possessing specific structures is required to meet particular needs in the pharmaceutical industry. Today, a large number of organic compounds have to be synthesized and screened for biological activity in order to discover potential drug candidates.

The vastly different biological activities of enantiomers and enantiopure diastereomers in biological systems are well documented.[1] Examples (**Figure 1**) of the different physical properties of enantiomers and enantiopure diastereomers include the different odors of (*R*)-carvone (*spearmint*) and (*S*)-carvone (*caraway*), the different tastes of L-(*S*)-amino acids such as leucine, phenylalanine, tyrosine and tryptophan (*bitter*) and the corresponding D-(*R*)-enantiomers (*sweet*), (*S,S*)-aspartame (*sweet*) and its (*S,R*)-diastereomer (*bitter*). Further relevant examples to modern medicine include the different bioactivities of D-propoxyphene (analgesic) and L-propoxyphene (antitussive, no analgesic effect), (*R*)-thalidomide (sedative and hypnotic) and (*S*)-thalidomide (teratogenic, the culprit of the well-known tragedy of birth defects), and the profen-drugs (2-arylpropionic acids, non-steroidal anti-inflammatory drugs).

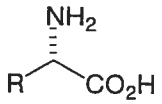
Figure 1 The (*R*)- and (*S*)- worlds



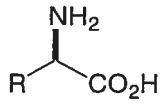
(*S*)-(+)-carvone
caraway



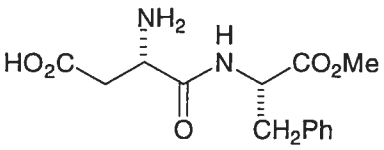
(*R*)-(-)-carvone
spearmint



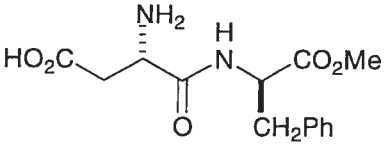
(*S*)-amino acids
bitter



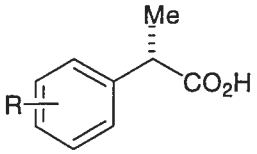
(*R*)-amino acids
sweet



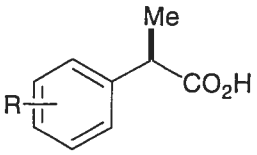
(*S*, *S*)-aspartame
sweet



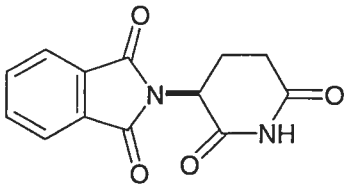
(*S*, *R*)-aspartame
bitter



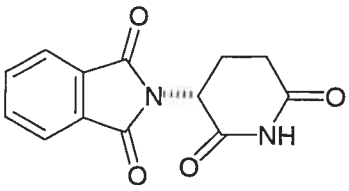
(2*S*)-2-arylpropionic acids
inactive



(2*R*)-2-arylpropionic acids
antiinflammatory



(*S*)-thalidomide
teratogenic



(*R*)-thalidomide
sedative and hypnotic

Often biological activity arises through the interaction of an organic compound with a biomolecule such as an enzyme or a receptor. When dealing with chiral non-racemic molecules, especially with single enantiomers, specificity becomes an important issue. If

an organic compound itself is chiral, then its two enantiomers are likely to interact differently with a given chiral biomolecule resulting in different biological responses. The levels of such biological activity for two enantiomers may be so different that the two enantiomers should be viewed as two distinct compounds. So using the racemate of a particular biologically active compound is equivalent to using a mixture of two different compounds.[2]

For several reasons, a racemic mixture of a drug is seldom used in the pharmaceutical industry.[2] Firstly, one enantiomer of the two may be more active than the other. Secondly, both enantiomers may have some side-effects. Thus it is better to use the most active and least toxic enantiomer in therapeutic practice. Therefore, enantiopure drugs are imperative.

There are two general methods for preparing enantiopure or diastereopure compounds, resolution of the racemate, and asymmetric synthesis.[3] Resolution, although apparently straightforward, may often be expensive because a stoichiometric amount of a suitable agrent is required and because the unwanted enantiomer has to be disposed of.[3] Therefore, asymmetric synthesis is invariably considered in the initial plans.

♦ 1-2 Asymmetric synthesis

Asymmetric synthesis is a process in which a chiral molecule in a mixture of molecules is converted into enantiopure or enantio-enriched units. For asymmetric synthesis, we divide substrates into two categories, cyclic systems and acyclic systems. In cyclic

systems, especially in six-membered ring systems, where the conformations are rigid and predictable,[4,5] diastereoselective synthesis with stereocontrolled introduction of substituents may be carried out by relying on conformational bias.[6]

In acyclic systems, the substrate can adopt numerous conformations depending on many electronic, steric, solvent, additive, and temperature effects.[7] It is therefore more difficult to achieve diastereoselective synthesis in these systems. High stereoselectivities were not achieved before 1970 though many studies had been carried out.[7] However in the last two decades, great progress has been made in acyclic stereocontrol. Many complex natural compounds such as Palytoxin,[8] Swinholide A,[9] Rapamycin[10] with over ten stereogenic centers have been synthesized. Virtually complete stereocontrol is quite a common feature of asymmetric synthesis today and obtaining enantiopure compounds with a few stereogenic centers is now an easy task.

In order to achieve high level of induction in asymmetric synthesis, at least one component of the reaction must be chiral.[11] If there is no asymmetric component in the reaction, then the transition state will be enantiomeric and equal in energy, resulting in the formation of a racemate. In principle, the use of a chiral, non-racemic substrate, reagent, solvent or catalyst should lead to asymmetric synthesis.

◆ 1-2-1 Chiral solvent control

In an organic reaction, using a chiral and non-racemic solvent may lead to asymmetric induction if the solvent is involved in the transition state.[12] Because the solvent is chiral

and non-racemic, the transition state of the organic reaction should be enantiomeric or diastereomeric and an asymmetric synthesis should become possible. Unfortunately, this approach has been of little use because the level of induction is often low and unpredictable.[13] In addition to their high costs, there are very few enantiomerically pure solvents which are available in sufficient quantity and which possess the properties required to be useful.

Involving a chiral and non-racemic substrate, auxiliary, reagent, or catalyst to obtain good stereoselectivity are more promising approaches.

♦ 1-2-2 Chiral non-racemic substrate control (chiron approach[14])

This approach is a basic strategy for asymmetric synthesis and uses chiral non-racemic molecules, where the chirality usually comes from a resident stereogenic carbon present in a natural compound. Because the chiral center is usually close to the site of reaction, the resulting transition state is chiral and then asymmetric induction is achieved. The advantage of this approach is that there is no need to take extra steps to attach and then remove a chiral auxiliary, nor are chiral reagents needed to control stereoselectivity. Nature provides many chiral compounds such as carbohydrates, amino acids, terpenes, steroids and alkaloids[15] for use in this approach. 1,2-Asymmetric induction gives the greatest control and is the most important and extensively studied case. 1,3-Asymmetric induction is often found in the biosynthesis of natural systems, such as 1,3-polyol compounds[16], and several highly stereocontrolled methodologies have been developed.[17] High stereocontrol of 1,4-asymmetric induction has been difficult to achieve and only a

few examples are documented.[18] So the limitation of this approach is that it is not possible to control the stereochemistry of the newly formed center(s) the further it is from the resident (usually over three carbon bonds) center(s). In this approach, the Felkin-Ahn[19] model and Cram's rule[20] are very important models for prediction of the stereochemical outcome of 1,2- and 1,3 –induction on reactions involving nucleophilic attack.

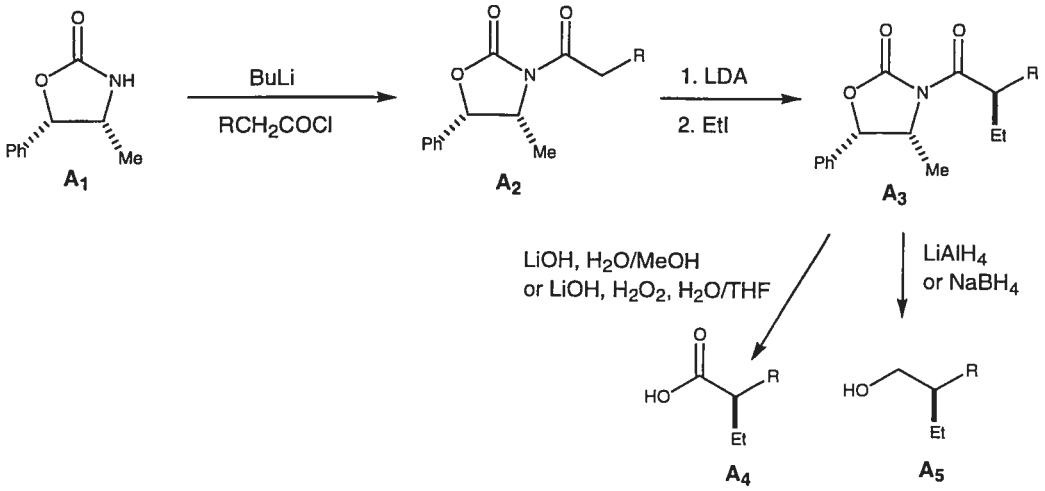
♦ 1-2-3 Chiral auxiliary control

In this approach the pro-chiral substrate is attached to a chiral, non-racemic group, known as a chiral auxiliary, prior to the reaction, and these chiral auxiliaries then control stereoselectivities of the asymmetric reaction. The chiral auxiliaries must be cheap and easy to obtain in quantity with high enantiomeric purity to insure high disoselectivity. Chiral auxiliaries must be easily attached to the pro-chiral substrates and the control of stereoselectivity must be high and predictable. The major diastereoisomers should be easily purified after the reaction. Chiral auxiliaries should be easily removed from the reaction products without jeopardizing the diastereoisomeric or enantiomeric purity of the products.

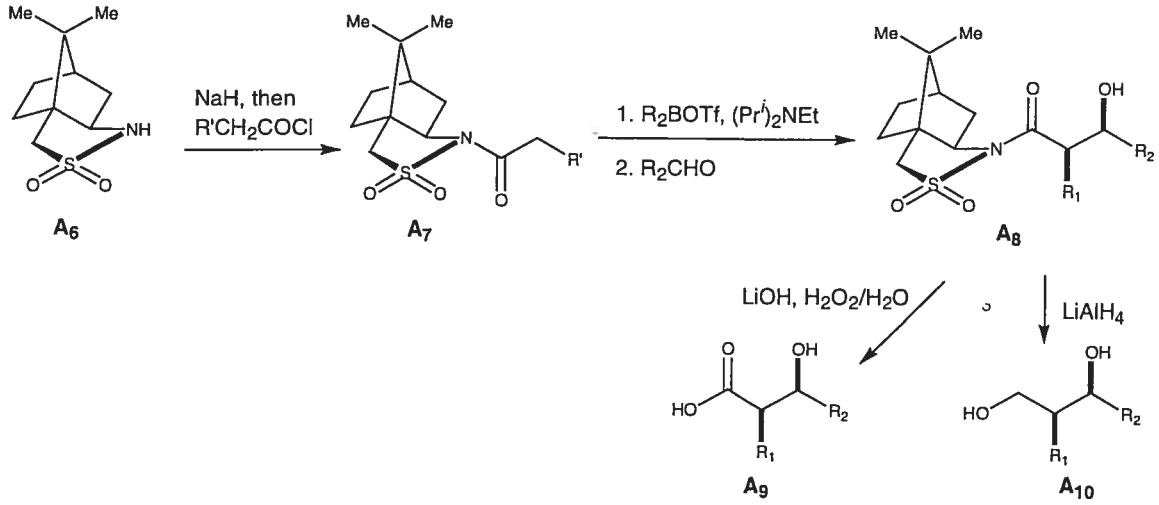
Finally, chiral auxiliaries should be easily separated and recovered after cleavage. Evans[21] and Oppolzer's[22] chiral auxiliaries are two excellent examples (**Scheme 1**) of what can be achieved using chiral auxiliaries.

Scheme 1 Evans' and Oppolzer's chiral auxiliaries in asymmetric synthesis

a: Evans' auxiliary



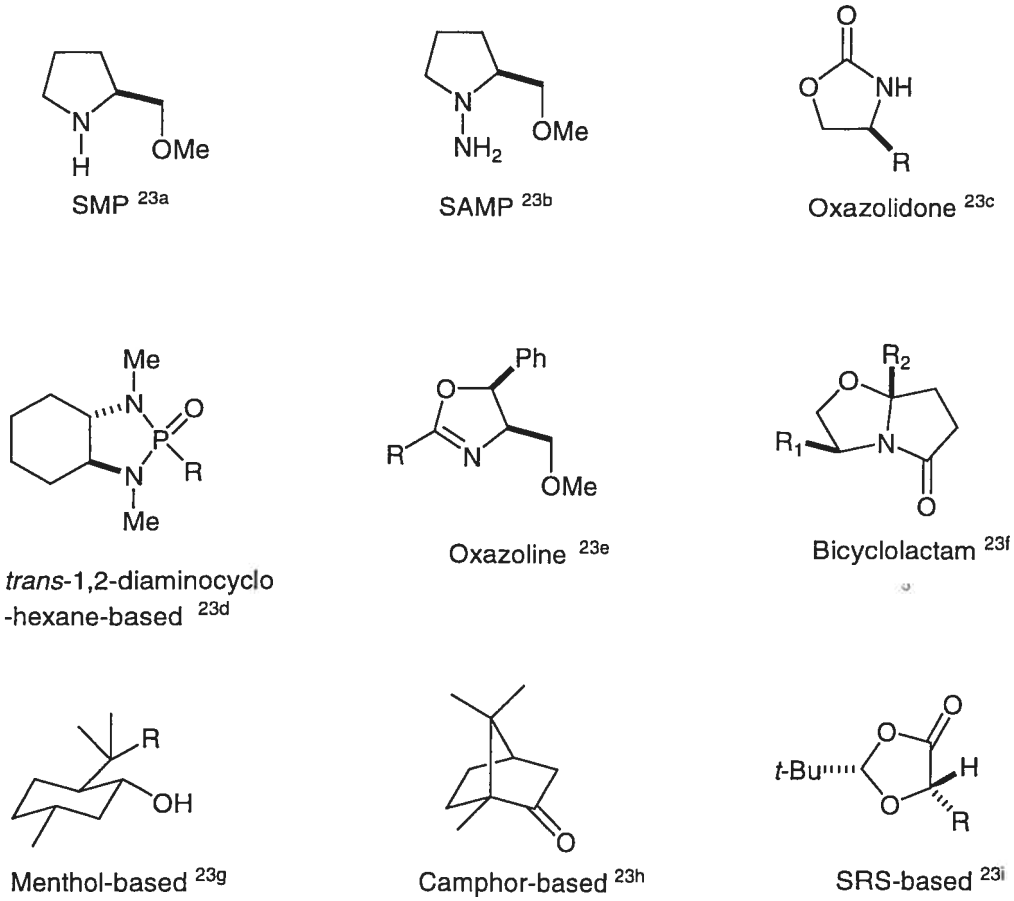
b: Oppolzer's auxiliary



The chiral auxiliaries $\mathbf{A_1}$ and $\mathbf{A_6}$ are easily attached to the pro-chiral substrates to form $\mathbf{A_2}$ and $\mathbf{A_7}$ respectively, which undergo the asymmetric reactions to give enantiopure products $\mathbf{A_3}$ and $\mathbf{A_8}$. In these two reactions, the stereoselectivities and stereochemistry are totally controlled by the two chiral auxiliaries $\mathbf{A_1}$ and $\mathbf{A_6}$ through rigid coordinated metal intermediate enolates. Finally, $\mathbf{A_1}$ and $\mathbf{A_6}$ can be cleaved from $\mathbf{A_3}$ and $\mathbf{A_8}$ by using

reduction or hydrolysis to give the $\mathbf{A_4}$ and $\mathbf{A_9}$ or $\mathbf{A_5}$ and $\mathbf{A_{10}}$ for further modifications. $\mathbf{A_1}$ and $\mathbf{A_6}$ can be separated and recovered from the reaction mixture for further usage.

Figure 2 Chiral auxiliaries



Extensive studies concerning this approach have been carried out and many chiral auxiliaries have been developed and tested (**Figure 2**[23]). At present, there are relatively few chiral auxiliaries which meet all the requirements.

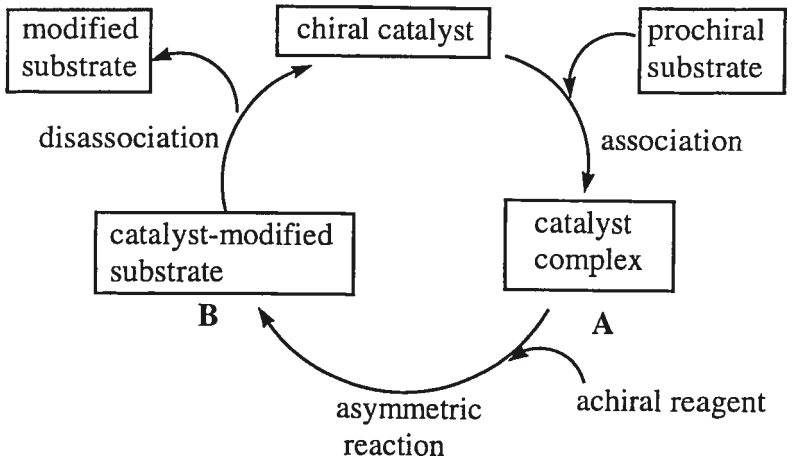
The advantage of this approach is that it can allow the generation of a chiral center (or centers) which is far from a chiral center. The reactions are often highly predictable and

reliable. The auxiliaries can be recycled. The limitation is that stoichiometric quantities of the chiral auxiliaries are required to be attached to the substrates before the reactions and to be cleaved after the reactions.

♦ 1-2-4 Chiral catalyst control

A chiral, non-racemic catalyst can be used to control the stereoselectivity in asymmetric synthesis. The principle of this approach is depicted in **Figure 3**. In this approach, the stoichiometric reagent is achiral but does not react with prochiral substrate in the absence of the catalyst. The catalyst associates with the prochiral substrate first to form the complex **A** which then reacts with the reagent to give the new complex **B** in which a new chiral center should be formed. Then the catalyst is disassociated from the modified substrate **B** and goes back into the catalytic cycle.

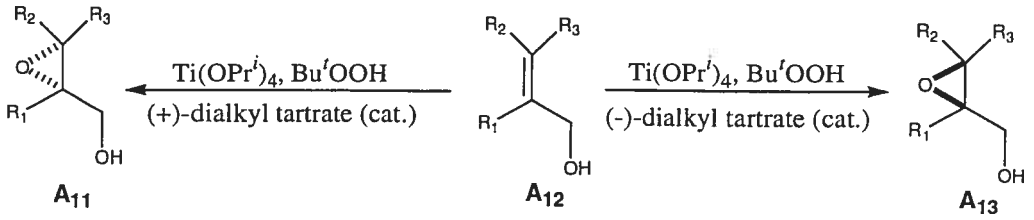
Figure 3 Protocol of chiral catalyst control



Because the chiral catalyst is involved in the transition state, asymmetric induction is expected. This approach is most promising for asymmetric synthesis because it can be

economic. A small amount of the chiral, non-racemic catalyst leads to stoichiometric amounts of the desired enantiomerically enriched product. This approach is most generally studied in asymmetric chemical synthesis, and synthetic catalysts[24] are used to achieve asymmetric synthesis in academic laboratories and in industry. One of the earlier representatives of this approach is the Sharpless epoxidation[25] which is shown in **Scheme 2**. Unfortunately, relatively few catalysts, which give a high enantiomeric excess within a class of substrates, are universally applicable.

Scheme 2 Chiral catalyst controlled-Sharpless epoxidation reaction



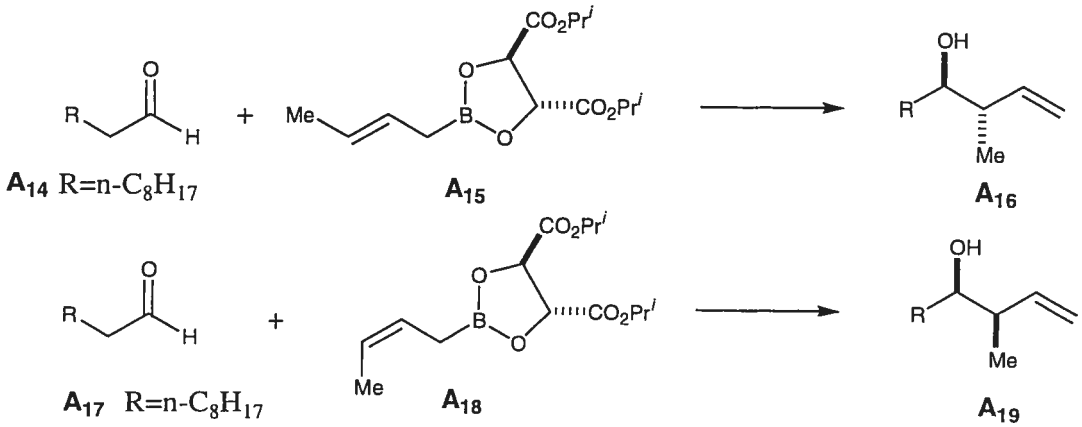
♦ 1-2-5 Chiral and non-racemic reagent control

In this approach, a stoichiometric amount, or more, of the chiral reagent is used to achieve stereochemical control. The stereogenic center(s) in the chiral non-racemic reagent(s) controls the stereochemistry of newly formed chiral center(s) in the product.

Roush's allyl boranes[26] (**Scheme 3**[27]) and Brown's crotylborane reagents[28] (**Scheme 3**[29]) are among the most successful examples of this approach. The stereoselectivities are high and stereochemistry predictable. Unfortunately, only a few of these reagents have been developed and most of them are usually expensive.

Scheme 3 Chiral and non-racemic reagent control

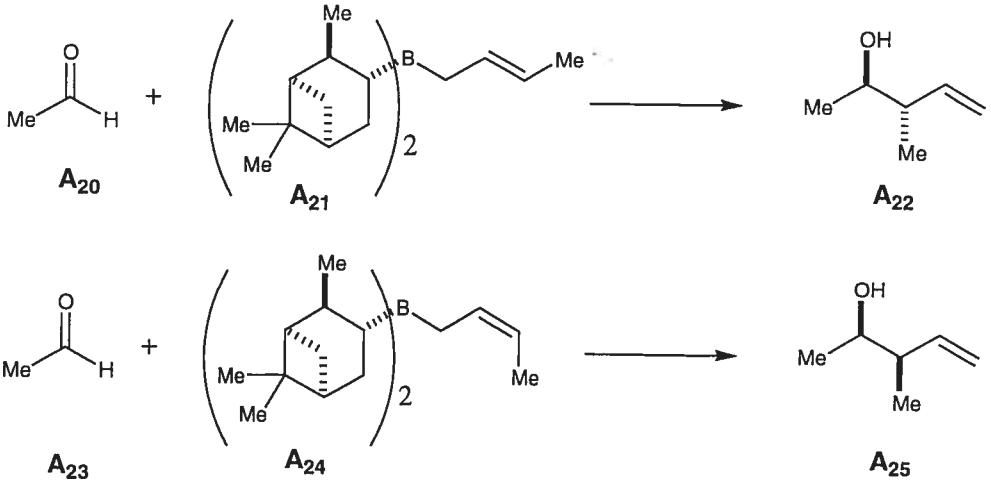
a: Roush's chiral allyl dialkoxy borane



A_{14} R=n-C_8H_{17} A_{15} A_{16}

A_{17} R=n-C_8H_{17} A_{18} A_{19}

b: Brown's chiral crotylboranes



A_{20} A_{21} A_{22}

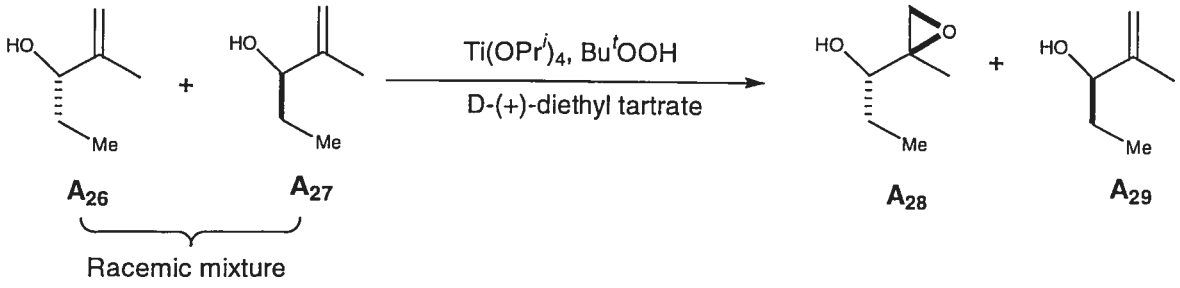
A_{23} A_{24} A_{25}

♦ 1-2-6 Kinetic resolution

In this approach, a resolution of a racemic substrate is achieved at the same time as an asymmetric reaction is carried out. This approach relies on the difference in the rate of reaction of the individual enantiomers of the racemate with an enantiomerically pure

reactant, reagent, or catalyst. In an ideal case this rate difference is so large that one enantiomer of the racemate does not react, while the other reacts rapidly. Routine separation of the product and the unreacted enantiomer would then provide both in an enantiomerically pure form. There are numerous examples of the use of Sharpless asymmetric epoxidation[30] for kinetic resolution in the asymmetric synthesis of various types of targets. An example of those is shown in **Scheme 4**.[30a]

Scheme 4 Kinetic resolution-Sharpless epoxidation



Under the above reaction conditions, the enantiomer $\mathbf{A_{26}}$ of the racemate reacts very fast with the reagents to form enantiomerically pure epoxide product $\mathbf{A_{28}}$, while the enantiomer $\mathbf{A_{27}}$ of the racemate reacts very slowly. At the end of the reaction, only the epoxide $\mathbf{A_{28}}$ and enantiomer $\mathbf{A_{27}}$ are left. These two different compounds may be separated easily by column chromatography or crystallization.

The above approaches are basic strategies actually used for asymmetric synthesis. In many cases, two or even three approaches are used at different stages of the total synthesis of natural and unnatural products.

Chapter two Cuprate reagents

♦ 2-1 Introduction

The conjugate addition of organometallic reagents (R-M) to α,β-unsaturated carbonyl compounds is one of the most important carbon-carbon bond formation reactions for organic synthesis. Although organometallic compounds such as M=Li,[31] B,[32], Al,[33], Al-Ni[34], Si-Ni[35], Zr-Ni[36], or Zn[37] have provided convenient methods for conjugate addition, organocopper derivatives are definitely the most widely used reagents. Collman and Hegedus[38] summed up the situation some years ago in their text on organometallic chemistry by stating, "Of all the transition-metal-organometallic reagents developed for application to organic synthesis, organocopper complexes are by far the most heavily used and enthusiastically accepted in synthetic chemistry, ..." Numerous publications and reviews have documented specific organocopper chemistry.[39]

♦ 2-2 Cuprate reagents

Numerous cuprate reagents have been developed and they are basically prepared by reacting either organolithium reagents (lithium-based) or Grignard reagents (magnesium-based) with different copper salts such as CuX (X=I, Br, Cl) or CuCN at certain stoichiometric ratios. The reactivities of these reagents can be dramatically changed by adding ligands and additives. A large number of diverse new cuprate reagents have been developed and they can be classified into three categories (R, alkyl group; M, metal ion, Li or Mg; X, halide from copper salts and Grignard reagents; L, ligand; A, additive as activators):

(I) RM + CuX·L·A (CuX, catalytic amount)

Using Grignard reagents alone as organometallic components in displacement reactions or conjugate addition reactions usually does not afford coupling products in synthetically useful yields or the reactions are very slow.[39e] The reaction can be significantly improved when these reactions are run in the presence of catalytic amount of copper(I) salt (such as Li_2CuCl_2 or CuI). Although the effectiveness and reproducibility may need to be improved, these catalytic processes are a very promising ways to reduce the amount of copper used in the reaction (which is a big problem on an industrial scale)[40] and to develop asymmetric version of this reaction.[41]

(II) RCu·M·X·L·A

Because the solubility of these kinds of cuprate reagents in organic solvents is low, RCu-type reagents are not usually reactive enough for synthetic use.[39e] The solubility can be increased, however, by using certain ligands (CN, R_3P, $(RO)_3P$, R_2S)[39e] and additives (BF_3, etc.).[39e]

(II) $R_1R_2Cu·M·X·L·A$

These cuprates are the most frequently used reagents in organic synthesis because they are soluble in THF and ether, their reactivity is greatly enhanced. In the reaction, only one R group (R_1 or R_2) of $R_1R_2Cu·M·X·L·A$ is transferred, therefore, selectively transferring only one group R (unless R_1 and R_2 are same) for a specific reaction has been the "holy grail" for this kind of cuprate. The two basic approaches to this problem have been the use of a non-transferable group R (or "dummy") bonded to Cu at an sp or sp^2 carbon (e.g., alkynyl[42] or 2-thienyl,[43]) or attached to Cu via a heteroatoms (S,[44] N,[45] or P[46]).

R_2CuLi (Gilman reagents, a low order cuprate, made from CuX and 2 equv. of RLi) are the original forms of this type of organocopper reagents. Many modifications of Gilman reagents have been made to increase the reactivity further or to meet the needs for some specific uses.

$R_2Cu(CN)Li_2$ (Lipshutz reagent, higher order cyanocuprate, made from CuCN and 2 equv. of RLi) is another frequently used cuprate whose reactivity is as good as that of the Gilman reagent.

◆ 2-3 Mechanism of cuprate addition

The popularity of organocopper complexes as reagents in organic synthesis, especially in conjugate addition reactions, has spawned numerous mechanistic investigations, as well as useful tools for carbon-carbon α-bond formation. However, the structure of organocopper reagents and detailed mechanisms of the reactions remain unclear. The aggregate structure and mechanism show a strong dependence on the substrates and the reaction conditions (solvents, temperature, additives). For all cuprate reagents, the basic structure R_2CuM remains.[47] The "higher order cuprate" (Lipshutz reagent)[48] seems to be $R_2CuLi{\cdot}LiCN$ and the Ashby reagent (R_3CuLi_2)[49] seems to be $R_2CuLi{\cdot}RLi$. Organocopper reagents (Gilman and Lipshutz reagents) are mostly used in the conjugate addition of carbonyl compounds.

Studies show that conjugate additions of cuprate to α,β-unsaturated carbonyls, or related compounds (cuprate addition) are greatly accelerated by additives such as BF_3 etherate,[50]

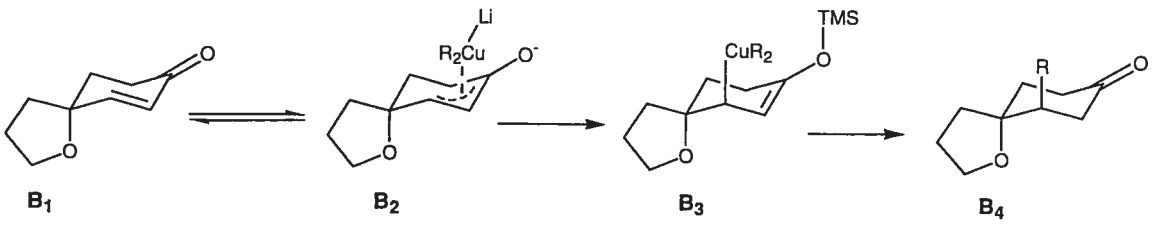
and TMSX (X=Cl, I, CN, OTf).[51] Its mildness and compatibility with many functional groups make TMSCl the most frequently used additive in cuprate additions.

It is generally agreed that the cuprate reagent and substrate initially react rapidly with each other to form a d-π* complex,[51a] followed by formation of a copper (III)-bond. Reductive elimination from this copper (III) species affords the enolate or enoates. Although the accelerating effect of TMS-Cl on cuprate additions remains unclear, some scientists do propose mechanisms for this reaction.

♦ 2-3-1 Corey's proposal[51a]

Corey proposed that TMS-Cl trapped an initial cuprate-substrate (d-π*) complex **B_2** (**Figure 4**) thus shifting the equilibrium towards the resultant silyl enol ether **B_3.** Reductive elimination then gave the 1,4 addition product **B_4**.

Figure 4 Corey's proposal for the Me_3SiCl-accelerated cuprate 1,4-conjugate addition reaction

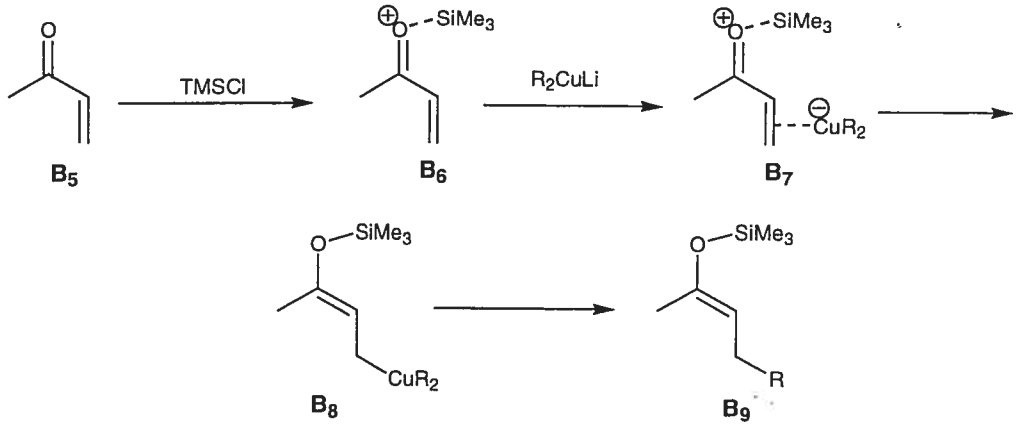


♦ 2-3-2 Kuwajima's proposal[52]

A second scenario suggested by Kuwajima (**Figure 5**) invokes a TMSCl-substrate interaction in a Lewis acid-Lewis base sense. TMSCl acts as a Lewis acid and binds the

oxygen of enone $\mathbf{B_5}$ giving $\mathbf{B_6}$ in which the β-carbon becomes more electrophilic and reacts with nucleophilic cuprates. In this way, the cuprate conjugate addition reactions are accelerated.

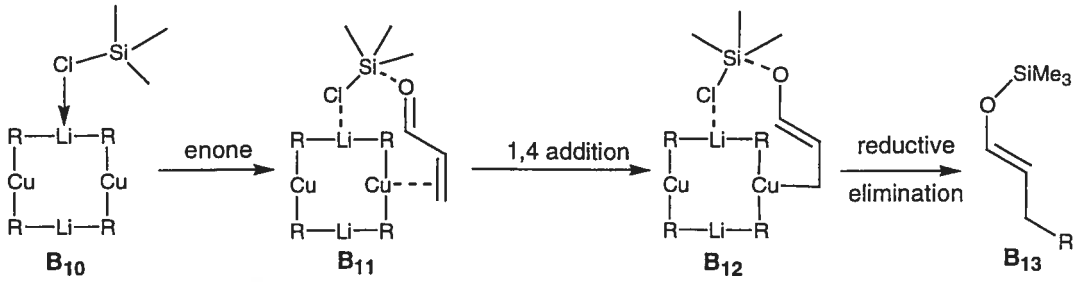
Figure 5 Kuwajima's proposal for the Me_3SiCl-accelerated cuprate 1,4-conjugate addition reaction



♦ 2-3-3 Lipshutz proposal[51b]

Lipshutz proposed (**Figure 6**) that an interaction between TMS-Cl and R_2CuLi might exist where TMS-Cl acts as a Lewis acid towards the cuprate. Interaction between the lithium cation and chlorine increase the Lewis acidity of the trimethylsilyl group itself. The Me_3Si residue is well-positioned within the cuprate cluster on an enhanced "push and pull" effect, which is generally regarded as essential for the activity of the cuprate as a Michael donor.

Figure 6 Lipshutz's proposal for Me_3SiCl-accelerated cuprate 1,4-conjugate addition reaction



♦ 2-3-4 Bertz's proposal[53]

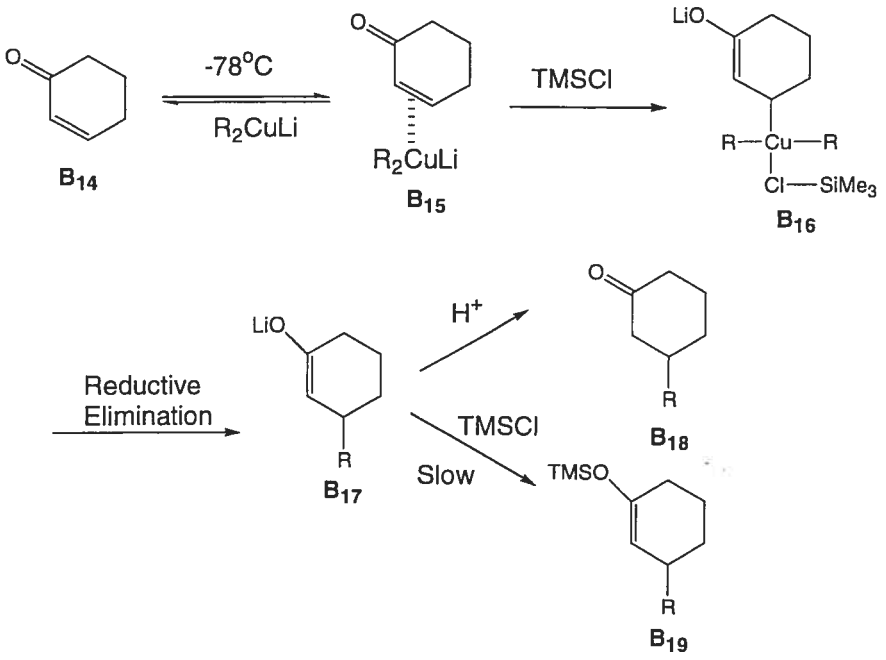
Bertz proposed a new mechanism (**Figure 7**) after he performed careful experiments on a cuprate-TMSCl-enone system and carried out a density functional theory (DFT) calculation. His proposal is consistent with both the experimental evidence and the theoretical results.

Bertz chose to react $Bu_2CuLi{\cdot}LiI$ with 2-cyclohexenone using TMSCl as an additive. The study shows that a short reaction time favors compound $\mathbf{B_{18}}$, while longer reaction times tends to favor compound $\mathbf{B_{19}}$. That means that TMSCl reacts very slowly with the enone and even the enolate. This evidence rules out the three mechanisms suggested before because they all suggested TMSCl reacts rapidly with enones to form TMS enol ethers.

Bertz proposed that TMSCl enhances the rate of cuprate addition by promoting conversion of the initially formed d-π^* complex $\mathbf{B_{15}}$ to a reactive copper species $\mathbf{B_{16}}$ capable of rapid reductive elimination to product $\mathbf{B_{17}}$. The presence of a bridging Cl

places the Si atom in the β-position relative to Cu (III), in analogy with β-silylcarbenium ion, thus stabilizing the transition state for reductive elimination.

Figure 7 Bertz's proposal for Me_3SiCl-accelerated cuprate 1,4-conjugate addition reaction



Bertz did experiments to test his proposal.[54] He prepared three cuprates, $BuCu(CH_2SiMe_3)Li$, $RCu[N(SiMe_3)_2]Li$ and $BuCu(SSiMe_3)Li$, all of which have silicon in the β position relative to copper and compared their reactivities towards 2-cyclohexenone with those for BuCu(Th)Li·LiCN and Bu_2CuLi· LiCN. The result shows that the $BuCu[(CH_2Si(CH_3)_3]$ Li·LiI is significantly more reactive towards 2-cyclohexenone than the corresponding 2-thienylcuprate and cyano Gilman reagents in both diethyl ether and THF. In fact, the yields of 3-butylcyclohexanone are quantitative

or nearly so (99-100%) from BuCu[($CH_2Si(CH_3)_3$] Li·LiI and BuCu[($CH_2Si(CH_3)_3$] Li·LiCN in both ether and THF even at the shortest time (4 seconds).

The result also shows that the yields appear to be independent of the nature of the lithium salt such as LiCN and LiI, but dependent on the atom to which silicon is bonded to (eg. N, S or C), carbon being the best. His other experiments on the thermal stability of the silicon containing cuprates show that cuprates are much more thermally stable than the corresponding 2-thienylcuprates and the cyano Gilman reagents.

♦ 2-4 Role of counter-cation, M^+

Although the exact nature of the counter-cation, M^+ of cuprate is still an open question,[55] it is very important for their reactivity. The reactivity of the cuprate can be adjusted, depending on the nature of M^+, and its removal results in loss of reactivity. Certain structural features such as the nature of M^+, the state of aggregation are vitally important to the reactivity.

♦ 2-5 Role of solvents

The choice of solvent also plays an important role in cuprate addition reaction, depending on differences in their solubility and coordinating effects.[54] Tetrahydrofuran and ether are the commonly used solvents for synthetic purposes.[54] The coordination of a solvent can facilitate cuprate formation and stabilize the Cu (III) intermediate species.

Chapter three Stereocontrolled cuprate additions to conjugated systems

♦ 3-1 Introduction

As already discussed, cuprate conjugate addition reactions are very versatile in organic synthetic chemistry. Stereocontrolled cuprate additions make this carbon-carbon bond forming reaction much more powerful. Numerous publications have documented these studies[56] and several approaches have been developed to reach this goal.

(a) Using cuprates with non-transferable chiral ligands to control enantioselective 1,4-additions, and in some cases, remarkable *e.e* (90%) have been achieved.[57] Because a stoichiometric amount of chiral ligand has to be used, this approach is expensive and not practical in industrial synthesis.

(b) Catalytic amount of chiral copper complex or external chiral ligands is used to control enantioselective 1,4-conjugate additions. Sometimes, as high as 95% e.e can be obtained.[57] This approach can only be used for Grignard or organozinc reagents and cannot be applied to Gilman reagents.

(c) Chiral auxiliary control. This approach is mostly used in enantioselective 1,4-conjugate addition of cuprate reagents to α,β-unsaturated esters or amides. The chiral auxiliaries are attached to the esters or amides to control the 1,4-conjugate addition, The most successful example of this approach so far is to use Oppolzer's camphorsultam[58] as the auxiliary, where the resulting e.e is high and different enantiomers of the camphorsultam auxiliary give different enantiomers of the product after hydrolysis. The limitation of this approach is the chiral auxiliaries have to be attached to the substrate and then removed after reaction.

(d) Conformational control is mostly used in cyclic systems.[59] Because of the relatively well-defined conformation of the cyclic systems, cuprate reagents approach the conjugate system from one favored face achieving stereoselectivity. This approach is of limited applicability in acyclic systems.

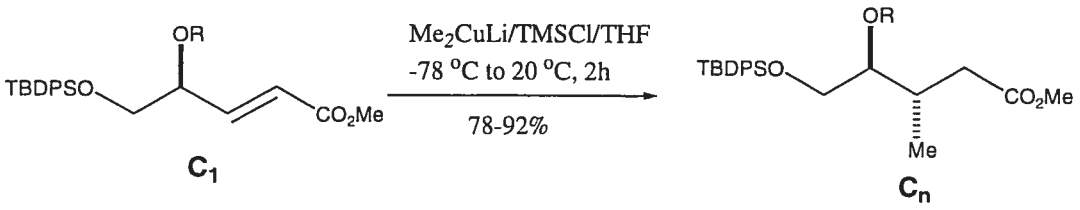
(e) Substrate control (especially 1,2 induction) is the most versatile methodology to achieve diastereoselective cuprate conjugate addition on carbonyl compounds.[60]

The conjugate addition of organocopper reagents to enones is a classical reaction in today's repertoire of stereocontrolled C-C bond forming reactions[60]. In contrast, stereocontrolled conjugate addition of organocopper reagents to acyclic α,β-unsaturated esters had remained less exploited until Yamamoto and co-workers[61] demonstrated that $MeCu{\cdot}BF_3$ addition to γ-substituted α,β-unsaturated esters gives quite good stereoselectivity.[62] More studies of cuprate addition to γ-alkoxy-α,β-unsaturated esters were published with pronounced stereoselectivity being observed.[63] Yamamoto and co-workers[64] have further shown that the γ,δ-dialkoxy, α,β-unsaturated esters and related compounds react with organocopper-Lewis acidic reagents with 1,3-chirality transfer, resulting in double bond transposition and α-alkylation with excellent stereoselectivity. Organocuprate additions to α,β-unsaturated esters in the presence of trimethylsilyl chloride were also studied and faster reactions and higher yields were observed.[65] There are conflicting reports on the dependence or non-dependence of the double-bond geometry on the stereochemical outcome of conjugate additions to γ-alkoxy α,β-unsaturated esters.[61, 63]

♦ 3-2 Conjugate addition of cuprate to γ-alkoxy α,β-unsaturated esters

Conjugate additions of cuprate to γ-alkoxy α,β-unsaturated ester (**Table 1**)[66] with lithium dimethylcuprate in THF in the presence of TMSCl has also been studied in our laboratory. Conjugate addition took place in excellent yields to give a high preponderance of the *anti* (3*S*)-methyl products in each series. The highest stereoselectivity was observed for the BOM ether with an *anti/syn* ratio of 14:1.

Table 1 Stereocontrolled addition to γ-alkoxy α,β-unsaturated ester (1, 2-induction)[66]

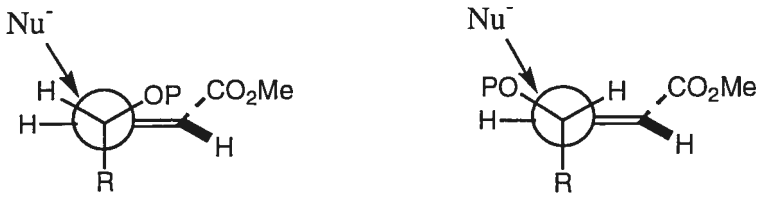


Substrate	R	Product	Ratio
1	BOM	*anti/syn*	14:1
2	MOM	*anti/syn*	11:1
3	MTM	*anti/syn*	9.8:1
4	Me	*anti/syn*	9.9:1

A modified Felkin-Ahn transition state model (**Figure 8**) for the γ-alkoxy series was proposed to interpret the observed stereoselectivity. The proposed *anti*-adduct model (OP-inside), which agrees with both the Morokuma[67] and Yamamoto proposals,[61c] has a number of positive features in its favor. It allows a favorable interaction of the alkoxy group with the π-system through a two-electron (p) and a four-electron (π) interaction[68]

in the ground state. In addition, the high-lying σR'-C orbital can interact with the low-lying π* orbital thus stabilizing the α,β-unsaturated fragment, and rendering the carbonyl of the ester a better chelation site. Furthermore, the *anti*-orientation of R group in the proposed model may also stabilize the incipient σ*C-Cu orbital in the d,π* complex-β-cuprio (III) adduct, through sigma bond donation (Cieplak effect).[69] The proposed model is also free of 1, 2-allylic strain.

Figure 8 Transition state model for cuprate addition

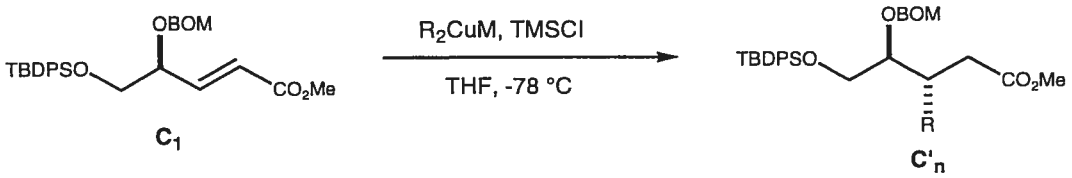


anti, major isomer *syn*, minor isomer

◆ 3-3 Further studies of conjugate addition of cuprates to γ-alkoxy α,β-unsaturated esters, and 1, 2 induction

Later, our group further explored the generality of this *anti*-conjugate addition of dimethyl cuprates to γ-alkoxy α,β-unsaturated esters and extended it to other organoalkyl[70] groups (shown in **Table 2**). Good to excellent *anti*-stereoselectivity was obtained for various cuprate reagents in the conjugate additions when the reactions were carried out at –78 °C. Thus, the generality of this methodology to prepare β-alkyl –γ-alkoxy esters was proved.

Table 2 Asymmetric cuprate additions to acyclic systems (1, 2-induction)[70]

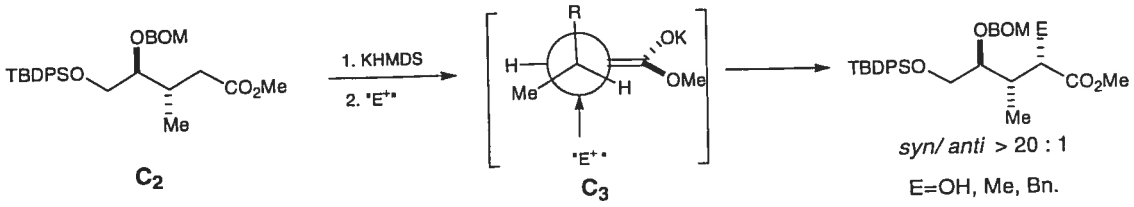


R	M	Yield	*Anti*/*Syn*
Methyl	Li	93%	>50 : 1
Ethyl	MgBr	73%	>50 : 1
Butyl	Li	90%	>50 : 1
Vinyl	MgBr	70%	>12 : 1
2-Propenyl	Li	60%	> 8 : 1

Having demonstrated the generality of 1,2 -induction in the γ-substituted α,β-unsaturated ester motif, we then explored the prospects of electrophilic additions of the corresponding enolates. Treatment of the adduct $\mathbf{C_2}$ obtained from lithium dimethylcuprate addition to the α,β unsaturated ester $\mathbf{C_1}$, with KHMDS and quenching with methyl iodide and benzyl bromide respectively (**Figure 9**) gave excellent yields of the 2*S*, 3*S*-dimethyl, and 2*S*-benzyl-3*S*-methyl substituted analogs essentially as single products as evidenced by ^{1}HNMR spectroscopy. No reaction occurred when LiHMDS or NaHMDS were used as base in this reaction. This method provides an expedient route to enantiomerically pure acyclic compounds that contain vicinal *syn*-related alkyl substituents. Treatment of the potassium enolate with the Davis oxaziridine reagent[71] provided enantiomerically pure α-hydroxy ester after chromatography. In each instance, and regardless of the nature or size of the γ-substituents on the chain, hydroxylation took place to give *syn*-selectivity. This is

another way to generate propionate biosynthetic triads. The *syn*-selectivities of these α-hydroxylation reactions were explained by the proposed model C_3 (in **Figure 9**)

Figure 9 Stereocontrolled α-hydroxylation[70]

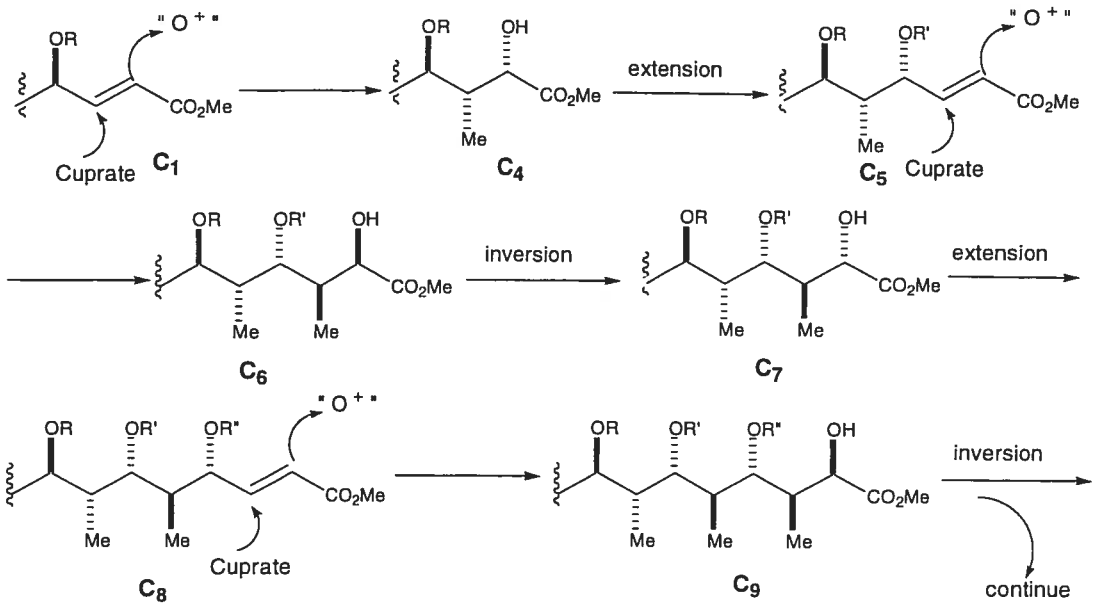


◆ 3-4 Polypropionate syntheses and application to the synthesis of the acyclic segment of Rifamycin S[72]

This methodology was further explored in our group to synthesize polypropionates,[72] a ubiquitous motif produced by biosynthesis in important classes of antibiotics such as macrolides and ionophores.[73]

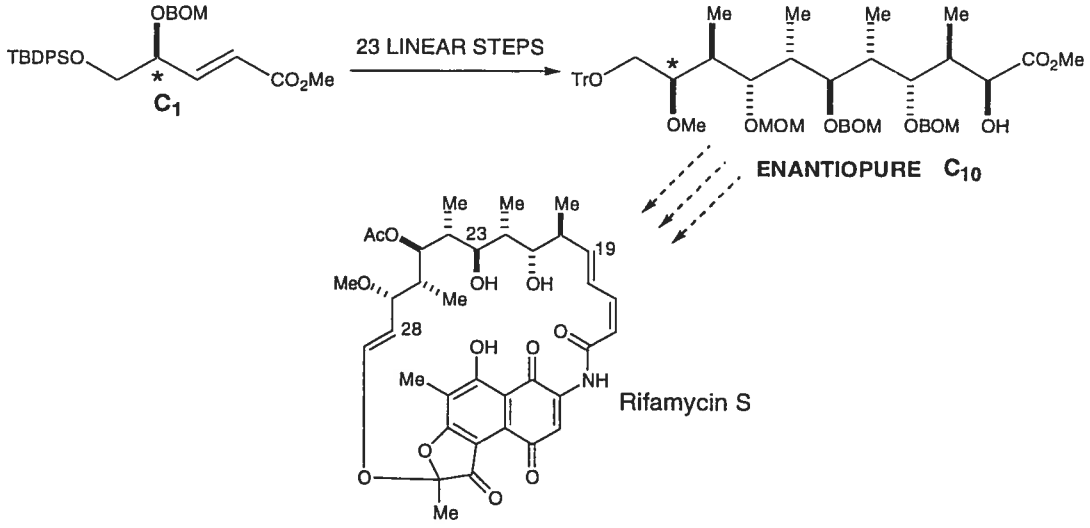
This methodology was exploited in the synthesis of the C_{19}-C_{28} polypropionate subunit of rifamycin S (**Figure 10**). Starting from γ-alkoxy-α,β-unsaturated ester C_1 and installing vicinal methyl/hydroxyl groups to give C_4, the chain was then extended via Wittig reaction[74] to generate a new γ-alkoxy-α,β-unsaturated ester motif C_5. A conjugate addition-hydroxylation protocol on C_5 completed the second propionate-type stereotriad to generate C_6 which was subjected to chain-extension and reiteration of the conjugate addition and hydroxylation process, provided an overall *anti/syn/anti/* polypropionate.

Figure 10 Strategy for the synthesis of polypropionates[72]



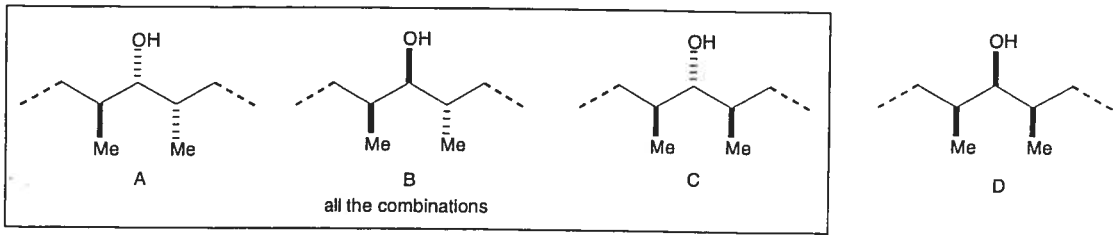
Four consecutive cuprate additions and four hydroxylations were performed to generate eight vicinal stereocenters (four propionate units) in a highly stereocontrolled manner on an acyclic system! The C_{19}-C_{28} segment of rifamycin S with 9 stereogenic centers was built from a single chiron in 23 linear steps (**Scheme 5**).[72]

Scheme 5 Stereocontrolled synthesis of C_{19}-C_{28} subunit of Rifamycin S[72]



The iteration could also be processed with an option to grow polypropionate stereotriads having diastereomeric relationships by inverting the configuration of the α-hydroxylation products via a Mitsunobu reaction. This simple protocol can give rise to combinations of stereotriads shown as types A, B, C (**Figure 11**). The *syn/syn* motif in D cannot be prepared by the above protocol because of the inherent stereochemical outcome of the conjugate addition and subsequent hydroxylation. This particular stereotriad, however, can be obtained indirectly by an oxidation-reduction sequence from a motif related to D, with functionally different ends.

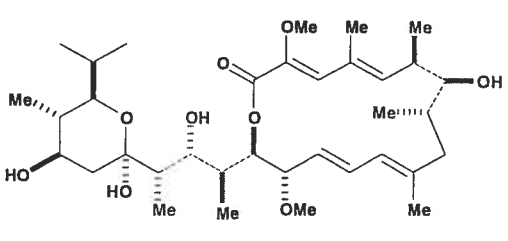
Figure 11 Propionate Stereotriads



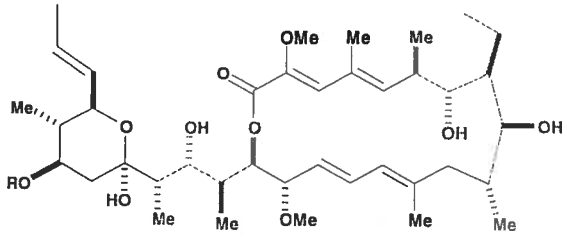
This powerful methodology may be used to synthesize many natural compounds, such as macrolides and ionophores. Some examples are shown in **Figure 12**, where the red area may be installed by the above methodology.

The above methodologies provide access to enantiopure propionate triads in acyclic systems in a one-directional chain extension. We then decided to explore the option of constructing triads in a two-directional way.

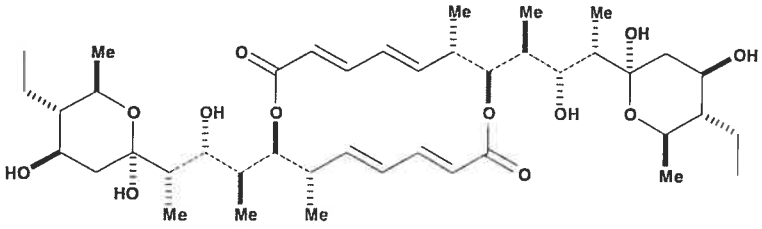
Figure 12 Macrolides and ionophores



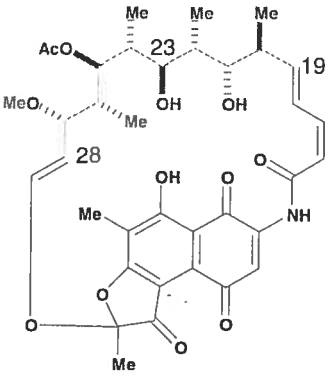
Bafilomycin A_1



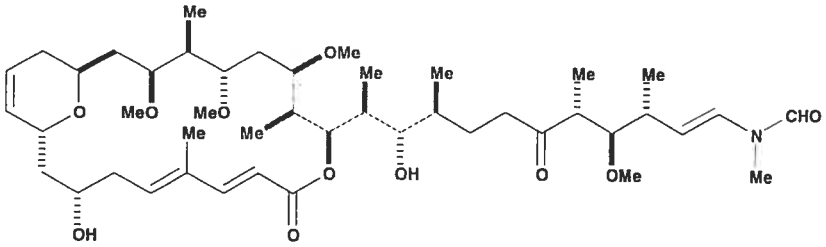
Concanamycin A



Elaiophylin aglycone



Rifamycin S



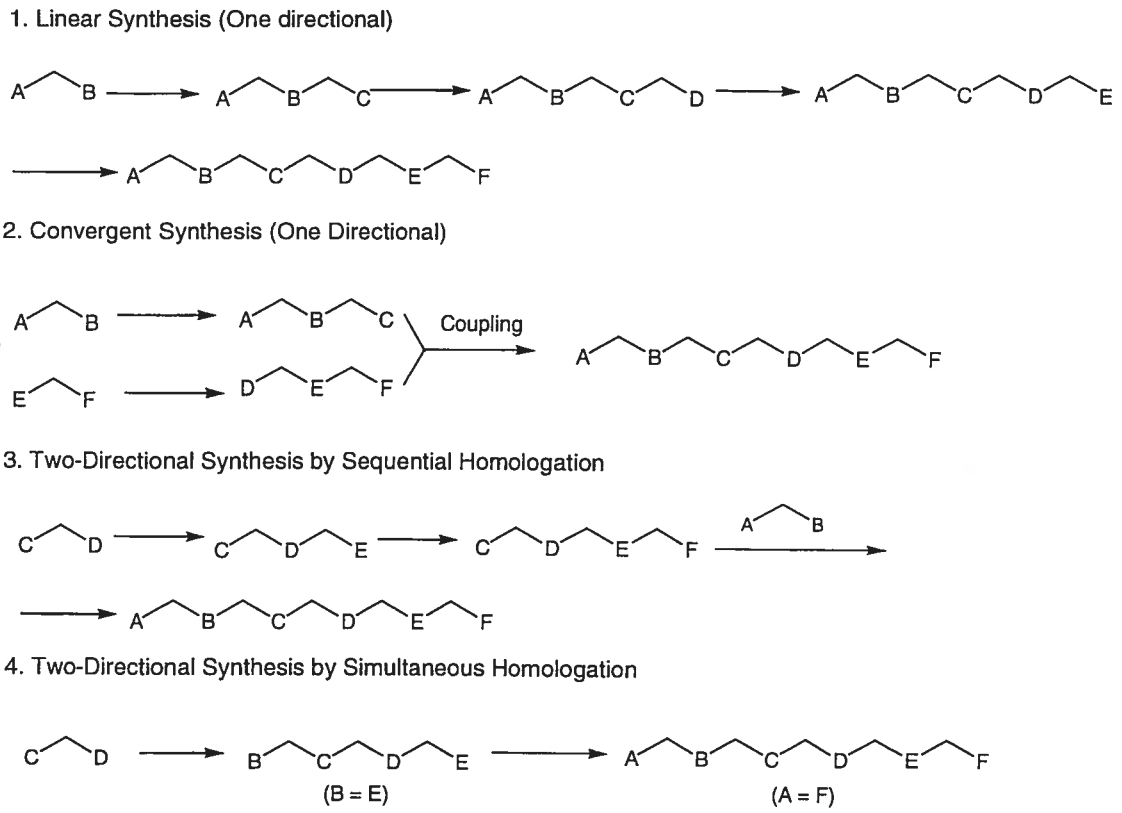
Scytophycin C

Chapter four Stereocontrolled cuprate addition in a two directional manner

◆ 4-1 Introduction

In organic synthesis, there are four main strategies to synthesize an acyclic chain (**Figure 13**), namely:

Figure 13 Strategies for the synthesis of acyclic chain



(1) *One-directional linear synthesis*: this strategy consists of building target acyclic chain from one end to the other and it can be used in any synthesis. This strategy may avoid the difficult coupling of two segments as in convergent synthesis; however, it possesses the limitation that as the chain grows, one may require carrying multiple protecting groups. Consequently, the synthetic sequence may be long with low overall yields.

(2) *One-directional convergent synthesis*: this strategy involves synthesizing the target acyclic chain by coupling two nearly equal-length segments together. The synthetic sequence may be shorter and the overall yield higher than in a linear synthesis. Whenever possible, this strategy is used in almost all multi-step syntheses. The major limitation of this approach is the need for the coupling of the two large segments which may be difficult, especially if they are densely functionalised.

The one-directional linear and convergent syntheses are the two most commonly used strategies in the literature.

(3) *Two-directional synthesis by sequential homologation*: This strategy is similar to the one-directional linear synthesis. As matter of fact, target chains are synthesized from the middle, finishing one half of the chain from one end, then building up the other half from the other end. Although the synthetic sequence is still longer than by one-directional convergent synthesis, it is comparable in efficiency to one-directional linear synthesis.

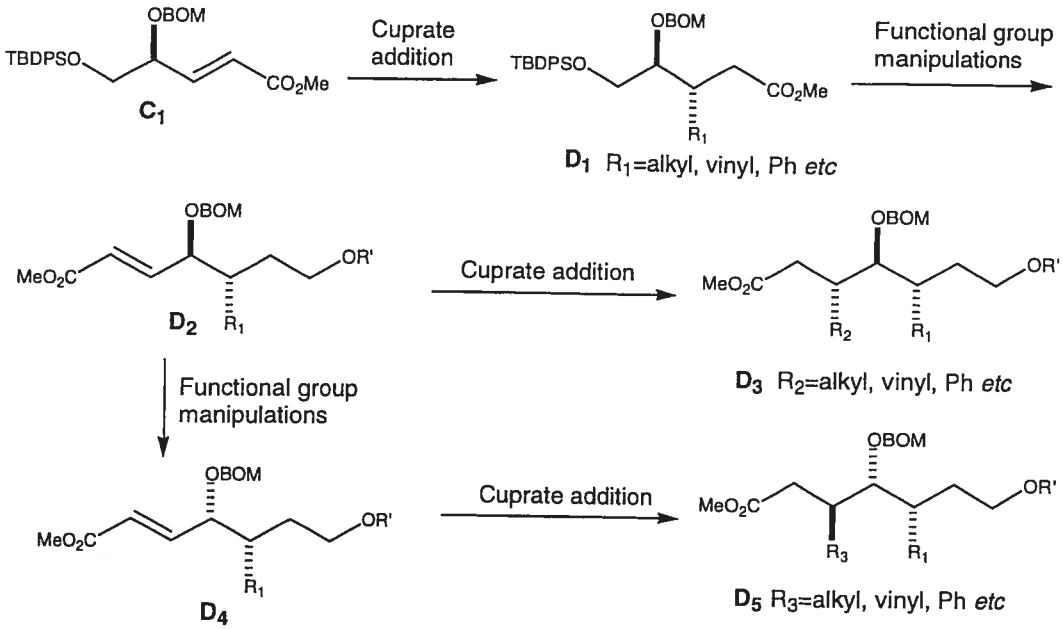
(4) *Two-directional synthesis by simultaneous homologation*: This strategy involves homologating both ends of the chain at the same time. The operational requirement necessitates that the two ends of the chain be symmetric, since desymmetrizing the ends is required in the end of a synthesis. This strategy has received considerable attention over the last few years, largely through the pioneering efforts of Schreiber[75]. This strategy offers a highly efficient route to synthesize the target in relatively few steps, compared with the above three strategies.[76] The limitation is that this strategy can only

apply to molecules which have a significant element of symmetry and desymmetrizing is difficult in many situations.

◆ 4-2 Stereocontrolled cuprate addition in a two directional manner

Having demonstrated the efficiency of asymmetric cuprate addition in one directional linear synthesis by previous members in this group,[72] we turned our attention to try two-directional asymmetric cuprate addition to α,β-unsaturated esters. In order to avoid the difficult desymmetrization of the two ends when using two-directional simultaneous homologation strategy, we considered two-directional synthesis by a *sequential homologation strategy* as shown in **Scheme 6.**

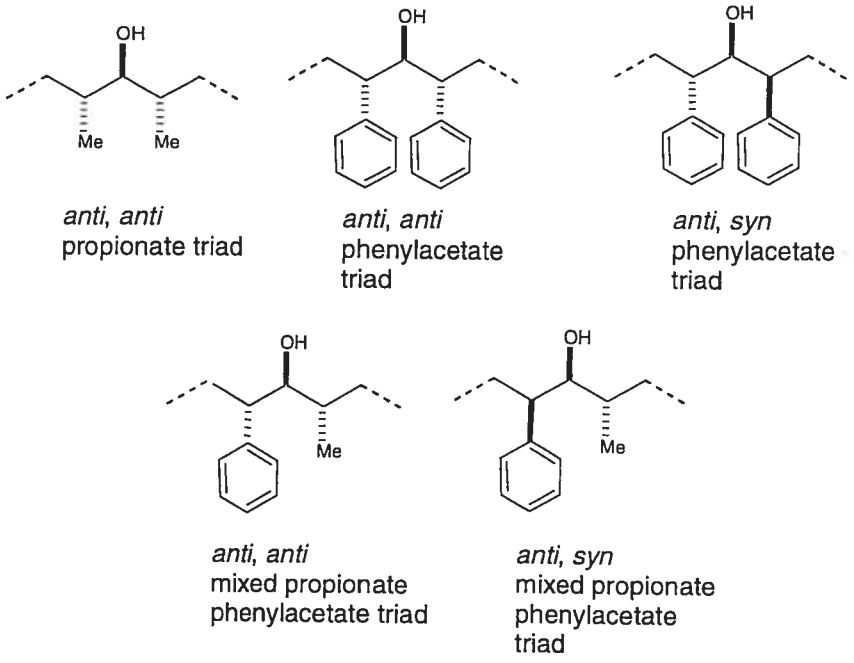
Scheme 6 Two-directional cuprate additions by sequential homologation



Starting with α,β-unsaturated ester $\mathbf{C_1}$, the first cuprate addition gave the product $\mathbf{D_1}$ with very good *trans*-stereoselectivity and yield.[64, 68] After several functional group manipulations, the chain of the first cuprate adduct was extended in the other direction to

form the second α,β-unsaturated ester $\mathbf{D_2}$. Analogously, cuprate addition on $\mathbf{D_2}$ afforded the desired products with high *trans*-selectivity in good yield. Several kinds of stereotriads may be synthesized by this method. The stereochemistry of the alkoxy group of α,β-unsaturated ester $\mathbf{D_2}$ may be inverted such that cuprate additions on the resulting ester $\mathbf{D_4}$ may give other stereotriads. Five kinds of triads may be synthesized by this protocol (**Scheme 7**) including *anti, anti* propionate, phenylacetate, and mixed propionate phenylacetate triads.

Scheme 7 Stereotriads



Of all the propionate triads, the *anti, anti* orientation appears to be the most difficult accessible[77]. To the best of our knowledge, the analogous phenyl-hydroxy-phenyl triads are not known and they could constitute interesting phenylacetate counterparts of the ubiquitous propionate assembly protocol.

◆ 4-2-1 Synthesis of *anti, anti* propionate triads and *anti, anti* mixed propionate phenylacetate triads

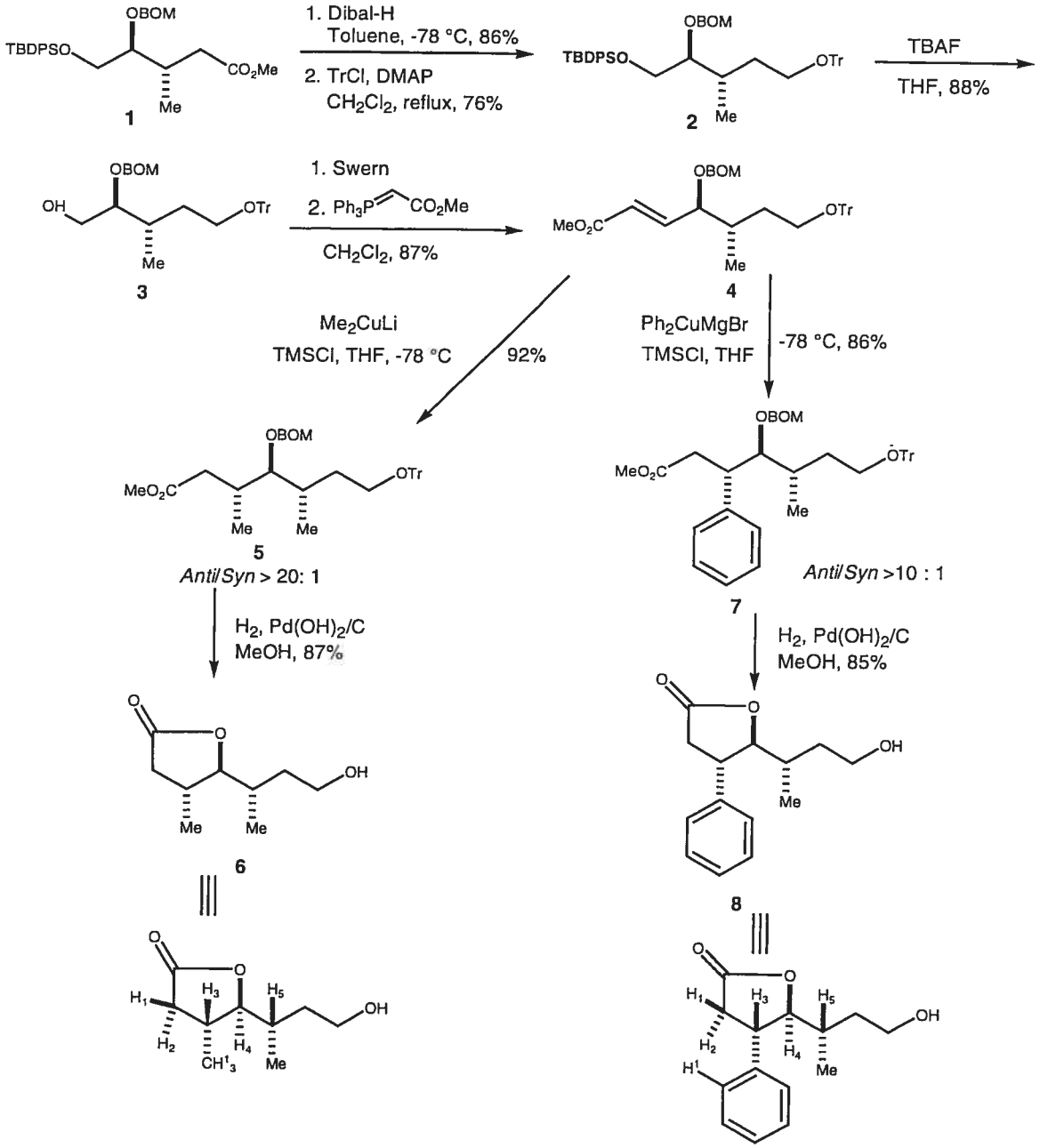
Our synthesis of the above triads (**Scheme 8**) began with ester **1** which was synthesized from D-mannitol in 100-mmol scale.[78] In order to differentiate the end groups in the intended seven-carbon acyclic motifs, the ester was reduced to the corresponding alcohol, which was then protected as trityl ether to provide **2** in 82% overall yield. Deprotection of the TBDPS with TBAF gave the primary alcohol **3**, which was then transformed to the α,β-unsaturated ester **4** using a Swern oxidation and a Wittig reaction. Dimethyl cuprate addition to **4** at – 78 °C with TMSCl as an additive provided the *anti, anti* triad **5** in 92% yield with over 20:1 stereoselectivity.

Reaction of diphenyl cuprate with the α,β-unsaturated ester **4** was found to be slower than corresponding dimethyl cuprate addition reaction possibly due to steric interactions. Thus, excess reagent and longer reaction times were needed to complete the reaction leading to **7** in 86% with over 10:1 stereoselectivity.

The stereochemistry of **5** and **7** was assigned according to the COSY and nOe studies of the corresponding lactones **6** and **8** which were obtained by hydrogenation of **5** and **7** respectively. The nOe spectra of **6** and **8** shows that one of H_1 and H_2 has no nOe effect with H_4, but another one has strong nOe effect with H_4. The first one must be H_1 and the second one must be H_2. The stronger nOe effects between H_1 and H_3, than that between H_2 and H_3, between H_2 and H^1 than that between H_1 and H^1 in the nOe spectra of **6** and **8**

indicate that the cuprate addition had proceeded with *anti*-stereoselectivity. The strong nOe effect between H_3 and H_5 futher proved the above conclusion.

Scheme 8 Synthesis of *anti, anti* propionate triads and *anti, anti* mixed propionate phenylacetate triads



Thus, by this method, *anti, anti* propionate and mixed propionate phenylacetate triads, which are usually very difficult to obtain, were synthesized from D-mannitol with good yields and high stereoselectivities. In these two cases, the cuprate additions proceded generally with good *anti*-selectivity.

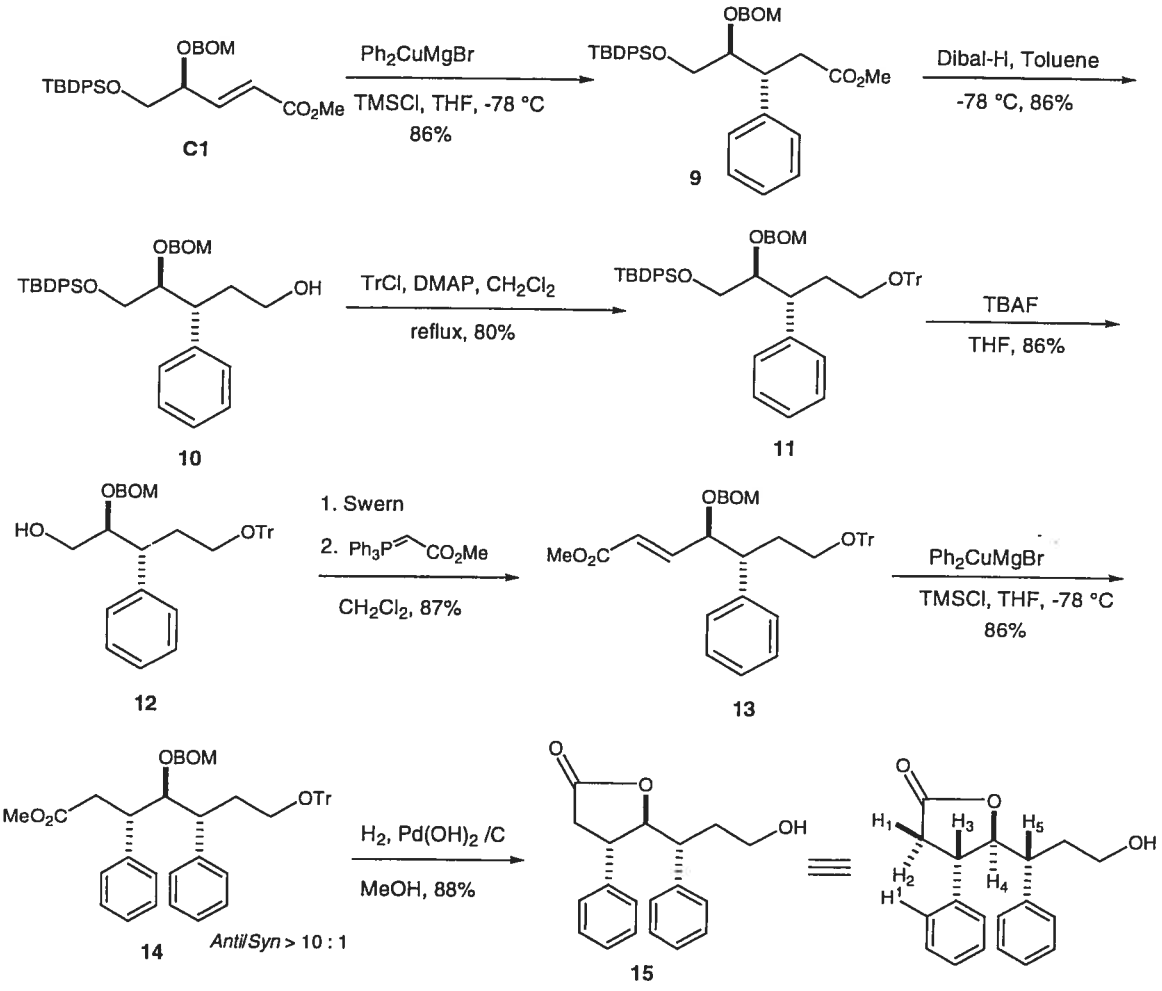
♦ 4-2-2 Synthesis of *anti, anti* phenylacetate triad

Our attention was focused on the synthesis of the *anti, anti* phenylacetate triad, which, to the best of our knowledge, was not synthesized before by any other protocols (**Scheme 9**). Thus, addition of diphenyl cuprate to the α,β-unsaturated ester $\mathbf{C_1}$ according to the procedure developed in our group[70] afforded the product **9** in 86% yield with over 15:1 *anti*-stereoselectivity. This compound was further reduced to alcohol **10** with Dibal-H in toluene, and **10** was then protected as the trityl ether to give **11**. Deprotection of the TBDPS group with TBAF, followed by Swern oxidation and Wittig reaction, afforded γ-alkoxy-α,β-unsaturated ester **13** in good yield.

The stage was now set for the second cuprate addition. The reaction turned out to be very slow. Twenty equivalents of reagents and over 10 h were needed to ensure the completion of the reaction. The desired product **14** was obtained in 86% with over 10:1 stereoselectivity. The stereochemistry of **14** was assigned according to the COSY and nOe experiment of the corresponding lactone **15** which was derived from **14** by hydrogenation. The nOe spectra of **15** shows that one of H_1 and H_2 has no nOe effect with H_4, but another one has strong nOe effect with H_4. The first one must be H_1 and the second one must be H_2. The stronger nOe effect between H_1 and H_3 than that between H_2

and H_3, between H_2 and H^1 than that between H_1 and H^1 in the nOe spectra of **15** indicate that the cuprate addition reaction also had *anti*-stereoselectivity. The strong nOe effect between H_3 and H_5 provides futher evidence.

Scheme 9 Synthesis of *anti, anti* phenylacetate triad

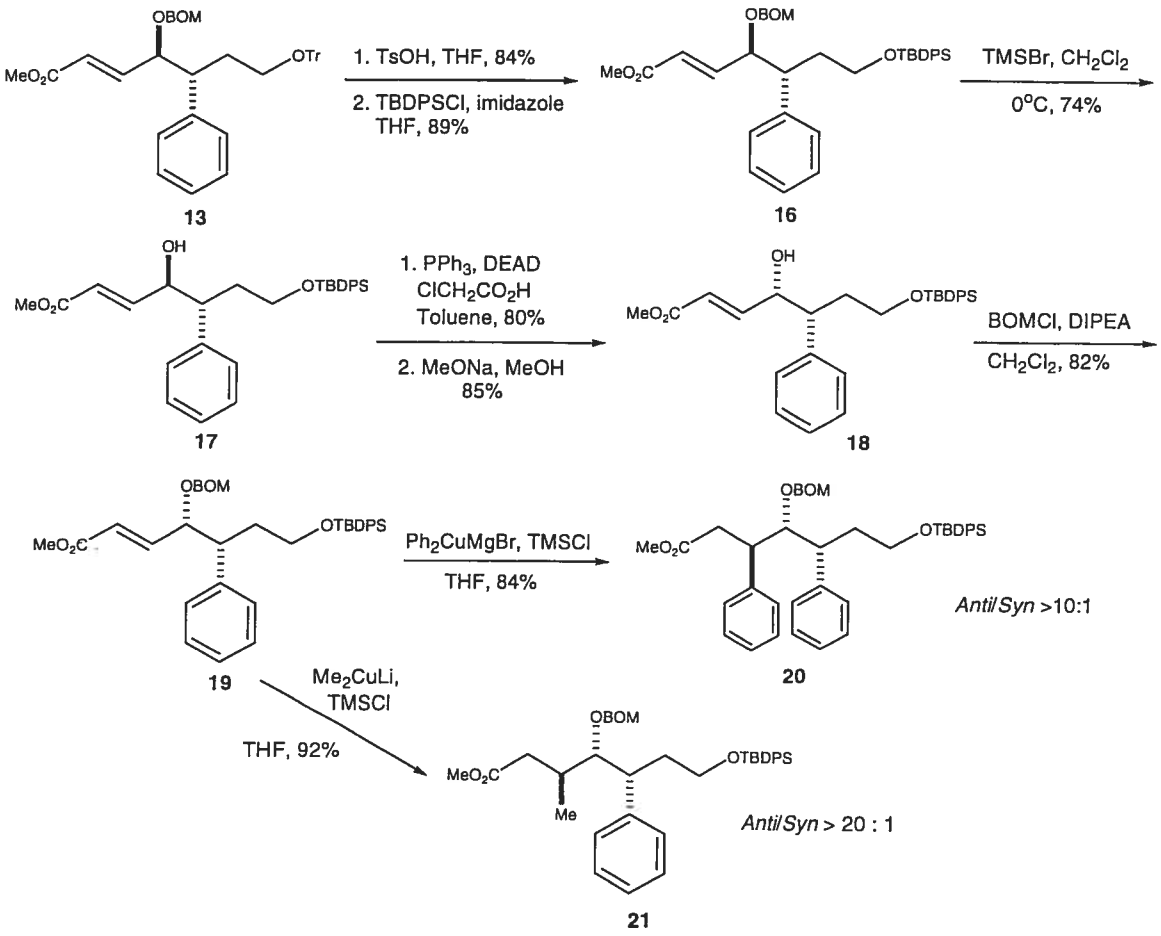


◆ 4-2-3 Syntheses of *anti, syn* phenylacetate triad and *anti, syn* mixed propionate phenylacetate triads

The *anti, syn* phenylacetate triad and *anti, syn* mixed propionate phenylacetate triads can not be synthesized directly by two-directional cuprate additions as shown in **Schemes 8**

and **9**. These syntheses may be realized by inverting the configuration of the alkoxy group in compound **13**, followed by cuprate addition (**Scheme 10**).

Scheme 10 Syntheses of *anti, syn* phenylacetate and *anti, syn* mixed propionate phenylacetate triads



We started out with the compound **13** in which the labile trityl group was changed to the bulky TBDPS group to give **16** in order to carry out functional group manipulations in the next several steps. The BOM group of **16** was removed with TMSBr[79] to generate the alcohol **17.** The configuration of the hydroxyl group was inverted using a Mitsunobu reaction to give **18**.[80]

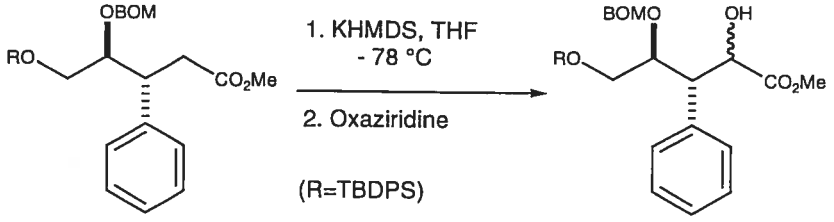
Protection of the γ-hydroxyl group of **18** as the BOM ether generated the new γ-alkoxy-α,β-unsaturated ester **19,** which underwent conjugate addition with the mixed diphenyl cuprate magnesium reagent to give the end-group differentiated C_2-symmetrical (3*R*, 5*R*)-diphenyl-(4*R*)-ol motif **20** in excellent yield and with over 10:1 distereoselectivity. Longer reaction time (12 h) and excess reagents (20 equiv.) were needed to complete the reaction. Lithium dimethyl cuprate addition to **19** afforded the adduct **21** in 92% yield and with over 20:1 diastereoselectivity. The *anti*-stereoselectivities were assigned based on previous experience in this series.

♦ 4-2-4 Stereocontrolled syntheses of phenylacetate triads

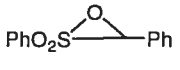
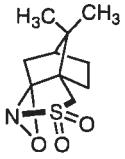
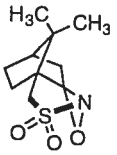
Previous work[70, 72] in the synthesis of propionate triads in an iterative manner from our group had shown that α-hydroxylation of the potassium enolate of the cuprate adduct with the Davis oxaziridine reagent[71] afforded a single isomer with an *anti, syn* γ-hydroxy-methyl-hydroxy unit on the chain. It was of interest to explore the stereoselectivity of the hydroxylation of the 3-phenyl analog.

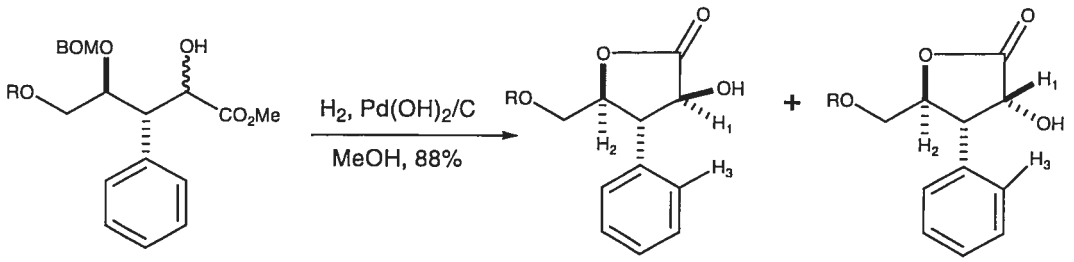
Surprisingly, treatment of the potassium enoate of ester **9** generated with KHMDS with the achiral Davis oxaziridine afforded a 1:1 mixture of distereoisomers (**Scheme 11**). High stereoselectivity (over 20:1) was found with the matched (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine[71] to afford the (2*S*)-hydroxy ester derivative **22** in 83% yield. Selectivity with the (1*R*)-(-)-(10-camphorsulfonyl)oxaziridine[71] was over 12:1.

Scheme 11 Stereocontrolled syntheses of phenylacetate triads



9 **22a + 22b**

entry	oxaziridine	structure	*syn* (**22a**)/*anti* (**22b**)	yield
1	(±)-*trans*-2-(phenyl -sulfonyl)-3-phenyl -oxaziridine		1 : 1	82%
2	(1*R*)-(-)-(10-camphor -sulfonyl)oxaziridine		12 : 1	80%
3	(1*S*)-(+)-(10-camphor -sulfonyl)oxaziridine		20 : 1	83%



22a + 22b **23a** **23b**

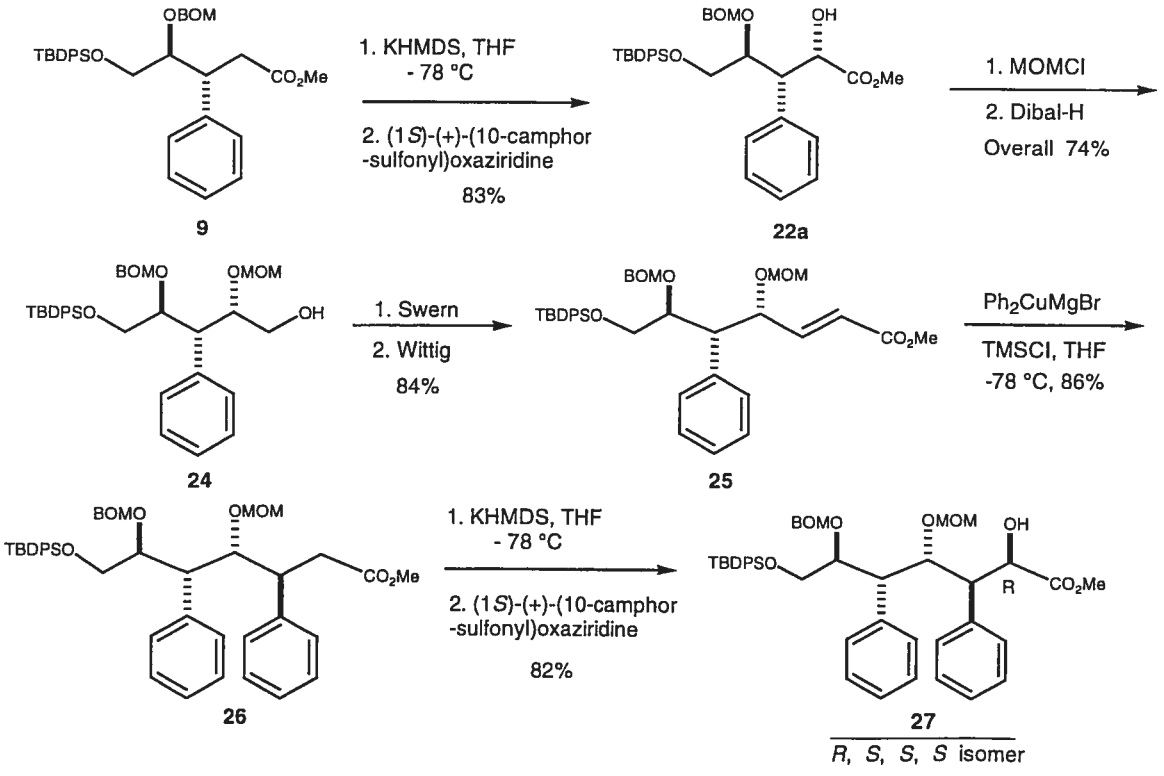
In order to prove the stereochemistry of the adducts, the 1:1 mixture of **22** was transformed into the corresponding lactones **23a** and **23b** by catalytic hydrogenation. The stronger nOe effect between H_1 and H_2 of **23a** than that between H_1 and H_2 of **23b**, and between H_1 and H_3 of **23a** than that between H_1 and H_3 of **23b** prove that hydroxy group of **23b** has a *syn*-relationship with the phenyl ring. The lactones derived from the α-hydroxylation product **22,** which were obtained from the reaction between the potassium

enolate of ester **9** with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine and (1*R*)-(-)-(10-camphorsulfonyl)oxaziridine, were identical in all aspects with **23a**. In this way, the *syn*-stereoselectivity of the α-hydroxylation reaction was secured. ^{19}F NMR of the corresponding Mosher ester of **23a** further proved the stereoselectivity of this reaction by comparing the intergration areas of the two isomers. By adopting our protocol, the synthesis of *anti, syn* phenylacetate triad was realized.

◆ 4-2-5 Synthesis of *R, S, S, S* phenylacetate triads

After the stereocontrolled synthesis of phenylacetate triad was successfully carried out (**Scheme 11**), we wanted to synthesize phenylacetate triads by iterative cuprate addition and hydroxylation in acyclic motifs as previously demonstrated for the propionate triads in our group.[72]

Scheme 12 Synthesis of *R, S, S, S* phenylacetate triads

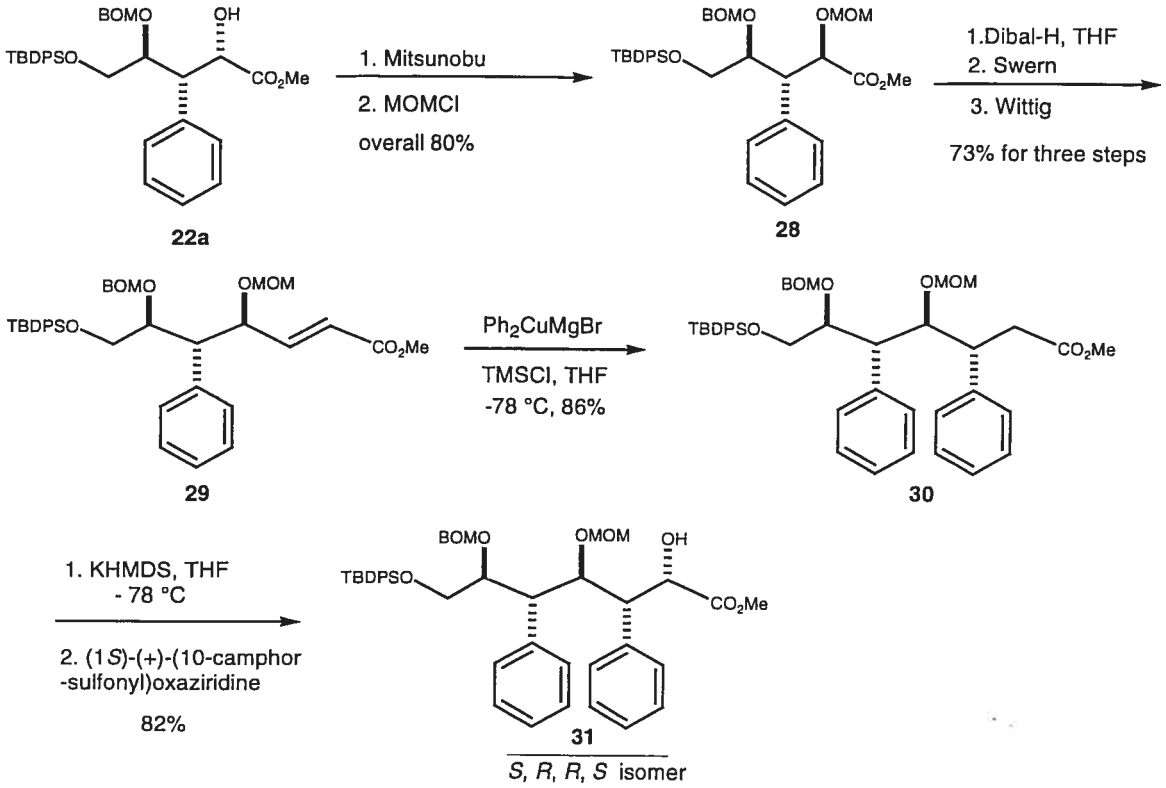


This work was successfully carried out as shown in **Scheme 12**. Protection of the hydroxy group of **22a** as the MOM ether and reduction of the ester with Dibal-H gave **24** in 74% overall yield. Swern oxidation, followed by Wittig reaction, provided the γ-alkoxy-α,β-unsaturated ester **25**, which underwent mixed diphenyl magnesium cuprate addition to afford the adduct **26** in 86% yield and with excellent stereoselectivity. α-Hydroxylation of the potassium enolate of ester **26** with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine generated **27** in 82 % yield (based on recovered starting material) with over 10:1 stereoselectivity by NMR spectroscopy. This reaction was found to be very slow. Although three equivalents of the reagents were used, 50% of the starting material was recovered after 7 h reaction. The stereoselectivity was also secured by the ^{1}H and ^{19}F proton spectroscopy of the corresponding Mosher ester of compound **26**. Thus, phenylacetate triads with the 2*R*, 3*S*, 4*S*, 5*S* configuration were synthesized by this protocol.

◆ 4-2-6 Synthesis of *S*, *R*, *R*, *S* phenylacetate triads

In order to extend the stereochemical versatility of the above protocol, the α-hydroxy function in **22a** was inverted via a Mitsunobu reaction.[80] After alcohol protection with a MOM group (**Scheme 13**), the ester **28** was reduced to the corresponding alcohol which was subjected to a Swern oxidation and a Wittig reaction to afford the new γ-alkoxy-α,β-unsaturated ester **29**. Conjugate addition to **29** with mixed diphenyl magnesium cuprate gave the corresponding *anti*, *anti* phenylacetate triad **30** as a single isomer in 86% yield.

Scheme 13 Synthesis of *S, R, R, S* phenylacetate triads



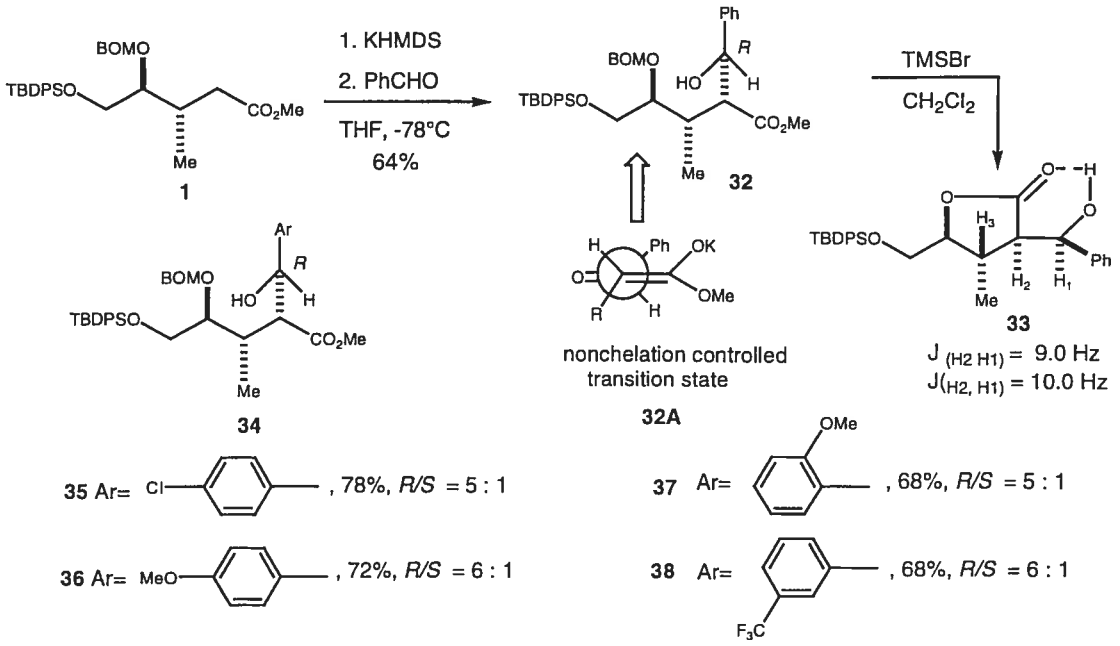
α-Hydroxylation of **30** was also found to be slow because of steric reasons. After 7 h, the reaction was quenched and the product **31** was obtained in 84% yield (based on 50% recovered material) and with over 12:1 stereoselectivity. Compared to the product synthesized in **Scheme 12**, which has 2*R*, 3*S*, 4*S*, 5*S* configurations, **31** has 2*S*, 3*R*, 4*R*, 5*S* configurations. The sequences shown in **Scheme 12** and **13** demonstrated that *anti*, *syn*, *anti* phenylacetate triads and *anti, anti, anti* phenylacetate triads can be synthesized with high yields and stereoselectivities. The drawback is that α-hydroxylation becomes more and more difficult with increasing chain length because of the increasing steric hinhrance.

In summary, we have demonstrated that the stereocontrolled conjugate addition of organocuprates to γ-alkoxy-α,β-unsaturated esters proceeds with high diastereoselectivity in a two-directional strategy. This protocol afforded acyclic chains that contain three contiguous substituents of the *anti*, *anti*, propionate triad type and their phenylacetate equivalents. Enolate hydroxylation and cuprate additions were performed in an iterative manner in these series to generate seven-carbon acyclic motifs harboring five contiguous stereocenters consisting of alternating hydroxyl and phenyl substituents with stereocontrol. A series of 1,2-asymmetric inductions were achieved starting with a resident γ-alkoxy group with excellent stereoselectivity through two successive conjugate additions and two enolate hydroxylations.

♦ 4-3 Polypropionates *via* the aldol reactions

The aldol reaction is another one of the most important and extensively studied carbon-carbon bond formation reactions in asymmetric synthesis[81]. It can generate two stereogenic centers in one step. The stereoselectivity of aldol reactions is usually controlled by using chiral auxiliaries or chiral reagents. In some cases, aldol reactions by 1,2-induction can give good to excellent stereoselectivity. This reaction[82] was also tried on compound **1** with benzaldehyde and selectivity was controlled by 1,2 asymmetric induction (**Scheme 14**). Treatment of the potassium enolate generated from the ester **1** with benzaldehyde at –78 °C gave a 6:1 ratio of diastereomers which were separable by column chromatography.[82]

Scheme 14 The aldol reaction



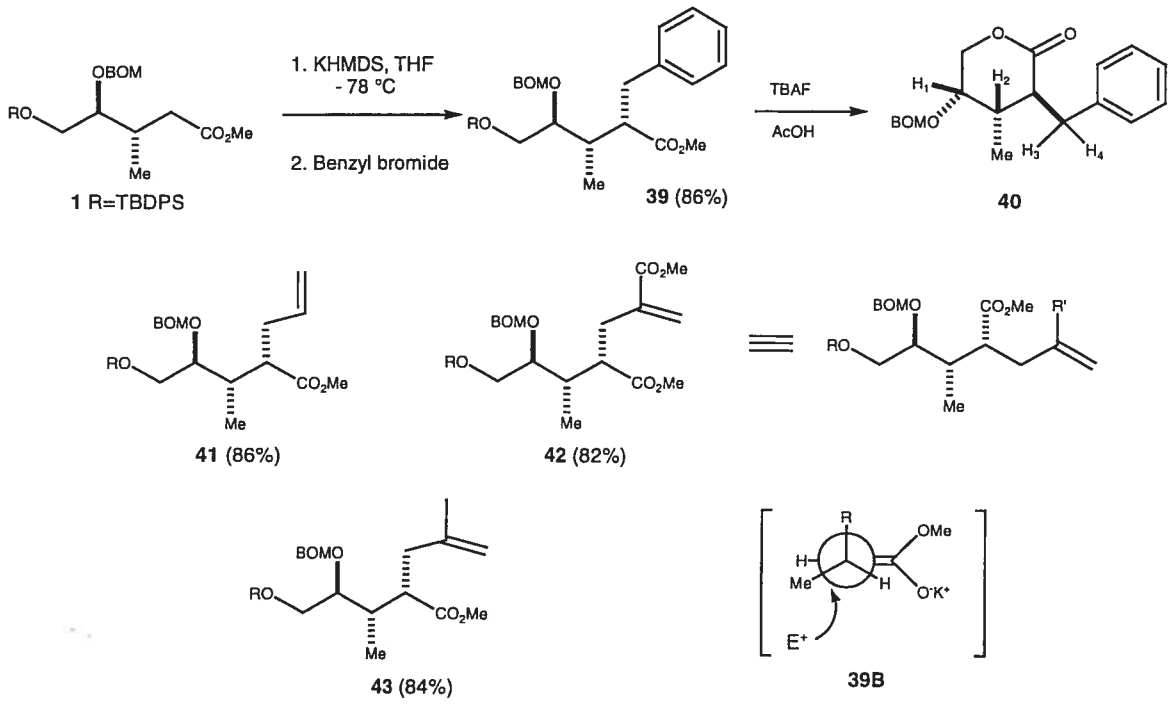
The stereochemistry of the major product was confirmed by detailed NMR studies of the corresponding lactone **33,** and the non-chelation controlled transition state **32A** was proposed for the outcome.[78] We then treated the potassium enolate of **1** with aromatic aldehydes with different substituents and moderate selectivity and yields were observed as shown in **Scheme 14**. All the diastereoisomers of **35**, **36**, **37**, **38** are separable by column chromatography. These reactions result from internal 1, 2- and 1,3 -asymmetric inductions from the resident group to a stereogenic carbon, although the selectivity was not high.[18,19]

♦ 4-4 α-Alkylations

α-Alkylation of ester enolates with reactive electrophiles such as allylic halides is another kind of carbon-carbon bond formation reaction in which a new chiral center is formed. It

is usually very difficult to realize high stereoselectivity in such alkylations, especially in acyclic systems.

Scheme 15 α-Alkylations



The most popular methods to achieve practical levels of stereocontrol in enolate alkylations normally rely on the use of chiral auxiliaries.[23] The alternative protocol is to use internal asymmetric induction (especially 1,2-induction). With the knowledge of α-hydroxylation and aldol reactions of the enolate of **1** giving high *syn*-stereoselectivity, we turned our attention to α-alkylation. To our delight, treatment of the potassium enolate of **1** with different kinds of allylic bromides gave only the corresponding *syn*-diastereoisomers with good to excellent yields (**Scheme 15**). Confirmation of the proposed *syn*-stereochemistry was secured by formation of the lactone **40.** The strong nOe effect between H_1 and H_3, and between H_1 and H_4 in lactone **40** proves that the benzyl group has *syn*-relationship with the methyl in compound **39**. This stereochemical

outcome can be rationalized based on a Felkin-type transition state **39B**. This protocol is important because manipulations of the alkene can generate other functional groups. This extends the versatility of the protocols developed during the course of our work.

Chapter five Stereocontrolled synthesis in acyclic systems on solid phase

♦ 5-1 Introduction

The techniques for solid-phase synthesis are based mainly on the pioneering work of Merrifield[83] which was followed by timely contribution in other areas of organic synthesis by Leznoff,[84] Camps,[85] and Frechet[86] during 1970-1985. It was Camps who, as early as 1974, published a synthesis of benzodiazepines using solid-phase chemistry. But this remained as a specialised and untapped area of research activity until the advent of combinatorial techniques for drug discovery and lead optimisation.[87] One of the reasons might be that medicinal chemists have recently been challenged by developments in biology and automation that allow the screening of large numbers of compounds.

The great advantage of combinatorial chemistry is that it has the potential to generate compounds faster than classical organic synthesis. Solid-phase chemistry is well suited for combinatorial chemistry because it can: (a) simplify work-up procedures, (b) provide high yields by employment excess reagent and be amenable to robotisation.

♦ 5-2 Comments on solid phase chemistry

The most-commonly-used polymer backbone is polystyrene, crosslinked with 1 or 2% divinylbenzene. This resin is frequently employed in reactions at higher temperatures as well as reactions with organometallic reagents. The following are some comments for solid phase chemistry:

▲ Solvent: resins are compatible with many polar and apolar solvents in which they can swell so that reactions can take place. Such solvents include DMF, NMP, alcohol, THF, acetonitrile, dichloromethane.

▲ Stirring: mixing is achieved by vortexing (by employing orbital shakers), ultrasonic or magnetic stirrers, or by bubbling gas through the suspension. Prolonged use of mechanical stirring can cause mechanical damage to the resin (pulverization).

▲ Temperature: the temperature for reactions ranges roughly from –78 °C to 155 °C, although room temperature is by far the most common.

▲ Reagents: a broad range of reagents is compatible with the conventional resins employed, including acids (*e.g.* TFA, $POCl_3$), bases (*e.g.* DBU, RLi), Lewis acids (*e.g.* $BF_3{\cdot}OEt$), reducing agents (e.g. $LiAlH_4$, Dibal-H, $NaCNBH_3$), homogenous transition metal complexes (e.g. $Pd(OAc)_2$, $Pd_2dba_3.CHCl_3$) and soluble salts (e.g. KO^tBu). Immobilized reagents are not usually used because of the inefficiency of solid-solid interactions. Sometimes a limiting factor in the choice of reagents is the nature of the linker attaching the molecule to the polymer.

▲ Work-up: after reactions are completed, resins are filtered and washed extensively with solvents (usually from polar solvents to apolar solvents) to remove excess reagents and high boiling solvents from their interior spaces.

▲ Linkers: Most of the linkers used in the beginning of solid-phase chemistry were originally developed for oligomer chemistry and afforded carboxylic acids and amides after cleavage which has severe limitations. Several attempts to circumvent this problem have led to alternative methods using the existing linkers to yield, after cleavage, alcohols[88] or amines[89] instead of carboxylic acids or amides. Also, strategies have been

developed in which the small molecules are released from the linker by a cyclization reaction.[90] Recently, linkers that are cleaved to other functionalities[91] have been reported.

▲ Reaction monitoring: solid phase reactions are generally more difficult to monitor, principally because the technique of "following a reaction by TLC" is not appropriate. Currently, the methods used for monitoring non-peptide solid-phase reactions include (a) analysing small amounts whilst the substrate and product are still bound to the resin, e.g. by FT-IR[83], ^{13}C gel NMR[92], MAS NMR,[93] color detection reagents for reactive functionalities[94] (*i.e*, NH_2, SH, COOH) (b) removing a small portion of the resin, cleaving small molecule fragments, followed by analysis.

♦5-3 Asymmetric syntheses on solid phase

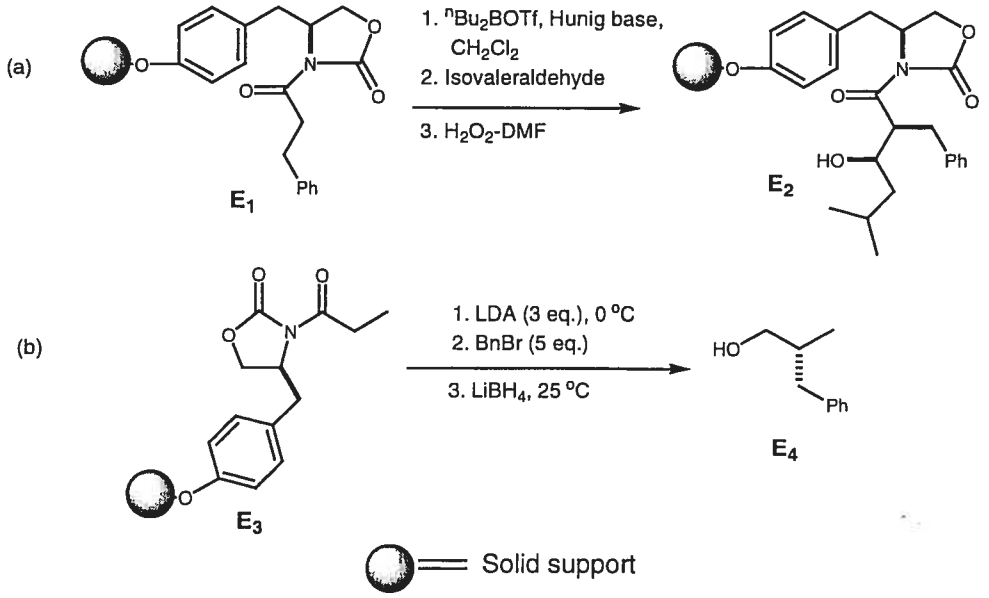
A current trend in solid-phase chemistry is to expand the repertoire of known organic reactions on solid-phase to achieve as much functional diversity as possible in the released substrate. Up to now, many known organic reactions can be used in solid-phase chemistry.[95] Furthermore, some asymmetric syntheses have been carried out on solid-phase.

♦ 5-3-1 Evans-type aldol reactions and α-alkylations using a solid supported auxiliary

Asymmetric syntheses controlled by a chiral auxiliary were first tried on solid phase and some examples are given in **Scheme 16**. In equation (a)[96] and (b)[97], enantioselective Evans-type aldol reaction and α-alkylation reaction with a solid supported auxiliary were

used for the synthesis of an α-substituted acid or ester. Solid phase synthesis proceeded with a high degree of enantioselectivity, as is observed in solution chemistry.

Scheme 16 Evans-type aldol reaction and α-alkylation using solid supported auxiliary[96, 97]



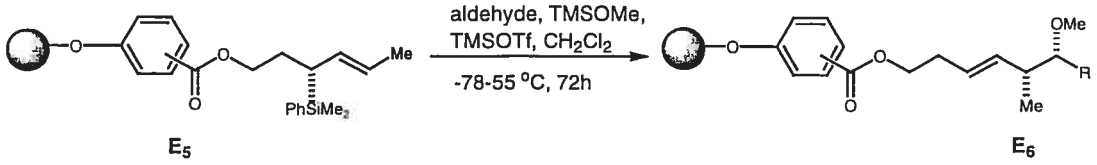
♦ 5-3-2 Panek's polypropionate synthesis by iterative crotylation on solid phase

Panek's group has successfully applied the (E)-crotysilane reagent-based asymmetric crotylation reaction on a solid support and provided functionalized chiral homoallylic ether $\mathbf{E_6}$ with high yield and diastereoselectivity (10:1 to 30:1, **Scheme 17**).[98] This methodology was further extended to the synthesis of polypropionate-like subunit through an iterative crotylation sequence. A polypropionate-like subunit $\mathbf{E_{11}}$, which contains three propionate units and six contiguous stereogenic centers, was synthesized from a solid-phase bounded achiral aldehyde $\mathbf{E_7}$ through iterative crotylation reactions. An overall yield of 37% for 10 steps and a *ds* of around 90% was reported. Their study

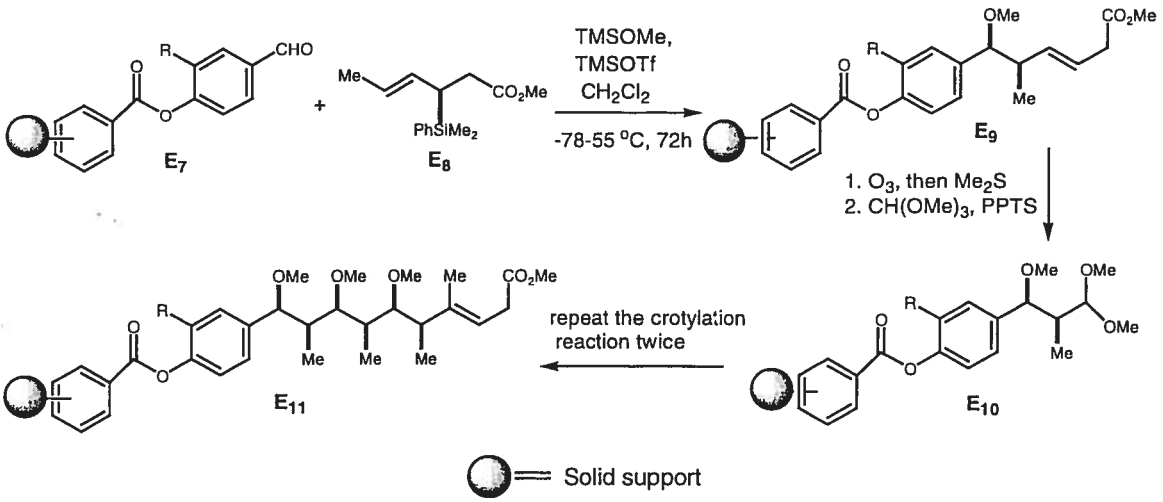
also shows that stereoselectivities for crotylation reactions on solid phase are similar or higher compared those in the solution reaction. This is a new and useful procedure for the preparation of stereochemically well-defined polypropionate-like subunits on solid-phase.

Scheme 17 Asymmetric crotylation reactions on a solid support[98]

(a) Stereocontrolled crotylation with a chiral crotylsilane:



(b) Enantioselective synthesis of polypropionate by crotylation:

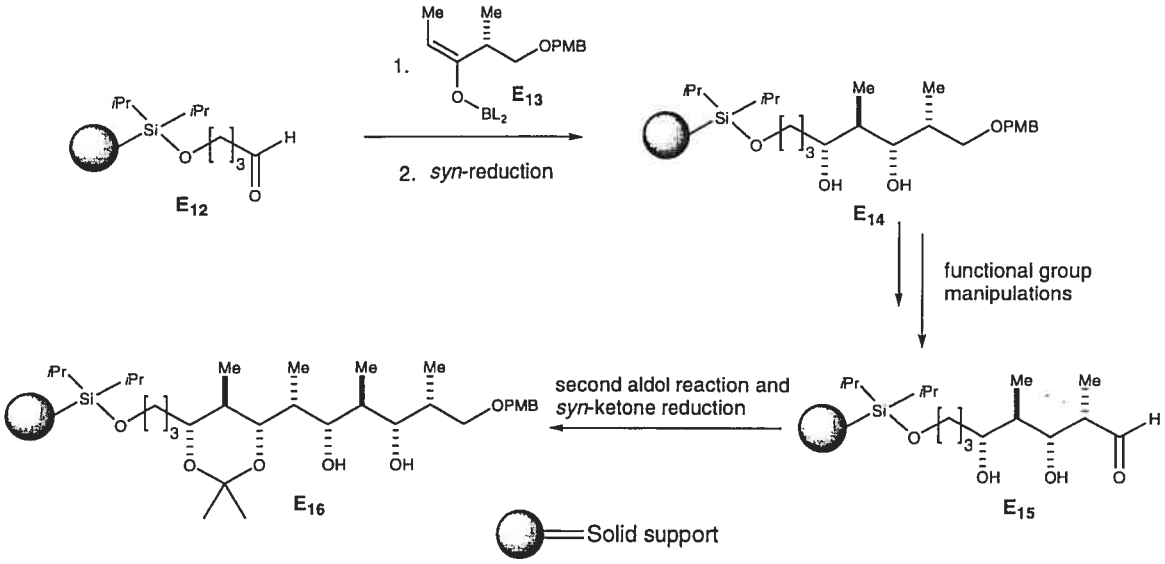


♦ 5-3-3 Paterson's polypropionate synthesis by iterative aldol reaction and ketone reduction on solid phase

Paterson's group has also synthesized polyketide-type sequences by iterative asymmetric boron-mediated aldol reactions and ketone reduction (**Scheme 18**).[99] The segment $\mathbf{E_{16}}$ with eight contiguous stereocenters, which was isolated in 37% overall yield and with 87% *ds* after cleavage, was synthesized from the achiral aldehyde $\mathbf{E_{12}}$ on solid phase in

eight steps. Notably, better yields and comparable diasteroselectivities can usually be achieved on solid-phase in comparison with the conventional solution-phase reactions. The methodology enables much greater structural and stereochemical diversification through the variation of both chain extension reagents and the stereochemistry of the aldol and reduction steps.

Scheme 18 Asymmetric boron-mediated aldol reactions on solid phase[99]

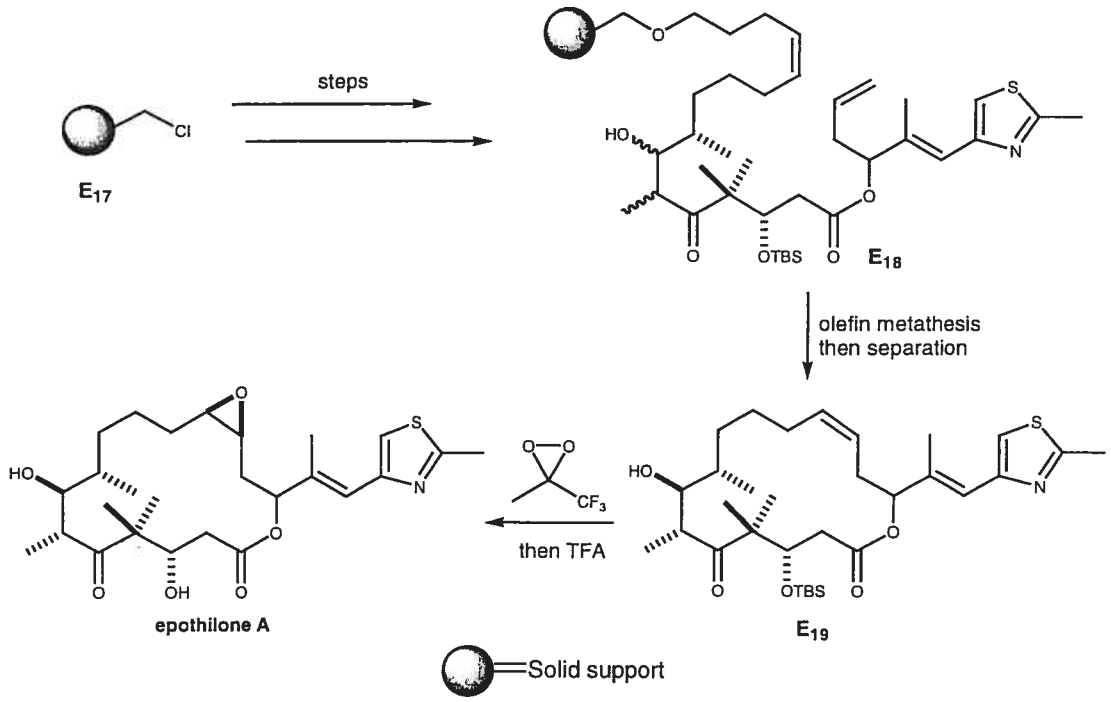


♦ 5-4 Total synthesis of epothilone A on solid phase

A most remarkable achievement in solid-phase chemistry has been the total synthesis of epothilone A on solid-phase by the Nicolaou group (**Scheme 19**).[100] The total synthesis of epothilone A started out with immobilized compound $\mathbf{E_{17}}$. After several steps of chain extensions, functional group manipulations and coupling reactions, the solid bound intermediate $\mathbf{E_{18}}$ was generated with good yield. A single olefin metathesis reaction simultaneously cyclized and liberated the product $\mathbf{E_{19}}$ from the solid support. A simple desilylation and an epoxidation reaction completed the total synthesis of epothilone A.

This was one of the first examples of solid-phase chemistry used in the total synthesis of a complex natural molecule. This study further proved the great potential of solid-phase chemistry.

Scheme 19 Total synthesis of epothilone A on solid phase[100]



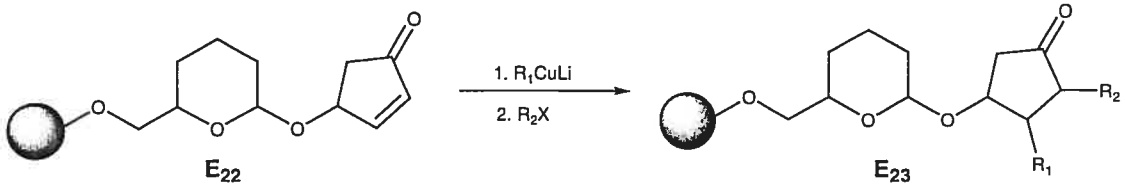
♦ 5-5 Cuprate reagents in asymmetric synthesis on solid-phase

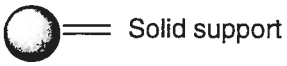
Cuprate reagents have also been used in asymmetric synthesis on solid phase as shown in **Scheme 20**. In example (a)[101], S_N2' reaction of organocopper reagents on solid support was successfully carried out and the yield and stereoselectivity were both very high. In example (b)[102], 1,4-cuprate additions to α,β-unsaturated ketone $\mathbf{E_{22}}$ followed by α-alkylation provided adduct $\mathbf{E_{23}}$. The two examples show that cuprates can be used on solid-phase even at low temperature such as –78 °C.

Scheme 20 Cuprate reagents used on solid phase chemistry[101, 102]

(a) S_N2' reaction by cuprate reagents

(b) Cuprate conjugate addition



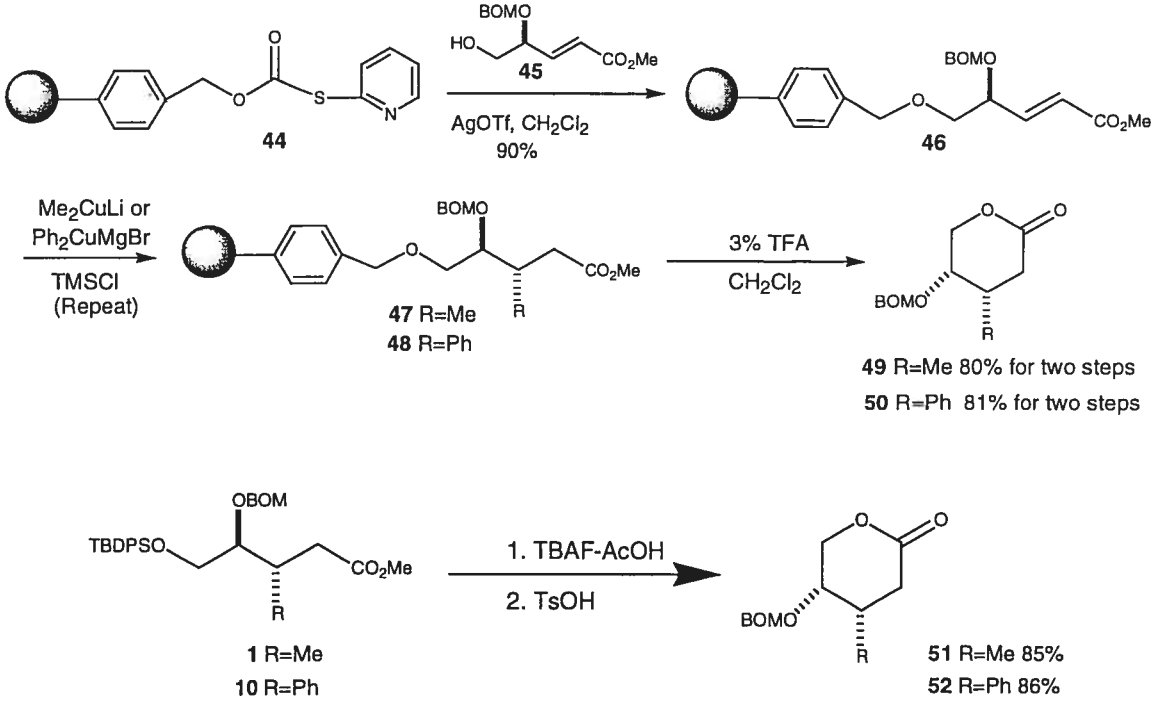


♦ 5-6 Cuprate additions to α, β-unsaturated esters on solid phase

In order to further explore the application of stereocontrolled cuprate conjugate additions developed by our group,[70, 72] we extended the protocol to solid phase and the initial results are shown in **Scheme 21**. The alcohol **45** was loaded on to Wang resin (4-Benzyloxybenzyl alcohol, polymer-bound, polystyrene cross-linked) through the thiocarbonate linkage[103] with 90% yield as monitored the reaction by infraed spectroscopy (1726 cm^{-1}). With the α,β-unsaturated ester **46** in hand, we then tried cuprate addition on solid phase. After treatment of **46** with dimethyl cuprate in the presence of TMSCl at –78 °C for six hours, we found that only a trace of the product was formed. The reaction was monitored by cleaving some of the compound from the solid phase and NMR analysis. Realizing that this reaction is very slow at –78 °C, we decided to raise the reaction temperature. The reaction was thus carried out at –78 °C for 2h, -40 °C for 2h and –20 °C for 2h. It was found that about only half of the starting material had

reacted. In order to ensure completion of the reaction, the resin was subjected to the same cuprate addition conditions again and all the starting material reacted this time as we expected. The product was cleaved from the solid phase and NMR characterization showed that the cyclized cuprate adduct **49** was formed and stereoselectivity was over 10:1. The stereochemistry was assigned by comparing the chemical and physical properties of the same compounds **51** and **52** made from known compounds **1** and **10** in solution. It was found that **49** and **51**, as well as **50** and **52,** were identical in every respect. Vinyl cuprate conjugate addition on solid-phase failed under these conditions because the cuprate reagent decomposed at –30 °C.

Scheme 21 Cuprate additions to α, β-unsaturated esters on solid phase

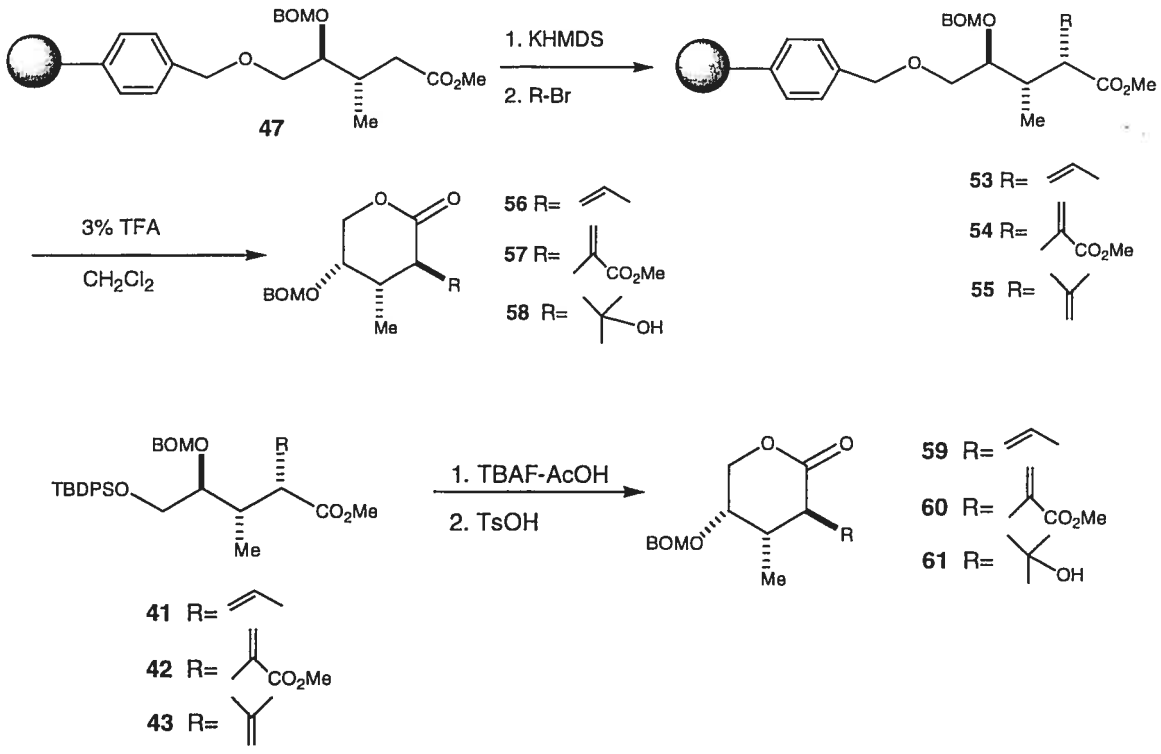


♦ 5-7 α-Alkylation reactions on solid phase

With the stereocontrolled cuprate conjugate additions on solid phase being successfully carried out, we then decided to try α-alkylation reactions on solid phase. Treatment of the

ester **47** with KHMDS in THF, as done in solution, followed by addition of the allylic halides or benzyl bromide, led to the corresponding α-substituted products **53**, **54,** and **55,** respectively, which were isolated as the corresponding β-lactones **56**, **57** and **58** in good yields and with over 10:1 stereoselectivity by ^{1}H NMR spectra after cleavage and column chromatography. The results show that solid phase reactions gave similar levels of diastereoselectivity compared to the solution phase reactions. The difference between the solid phase reactions and the corresponding solution phase reactions is that more reagents and longer reaction times were needed in order to complete the reactions in the solid phase.

Scheme 22 α-Alkylation reaction on solid phase



The stereochemical assignments were made by comparing chemical and physical properties of the compounds **56**, **57** and **58** made from solid-phase to those of compounds

59, **60** and **61** made from known compounds **40**, **41** and **42** in solution. They were identical in every respect, proving that the stereofacial selectivity for this kind of reaction either in solution or on solid phase is same.

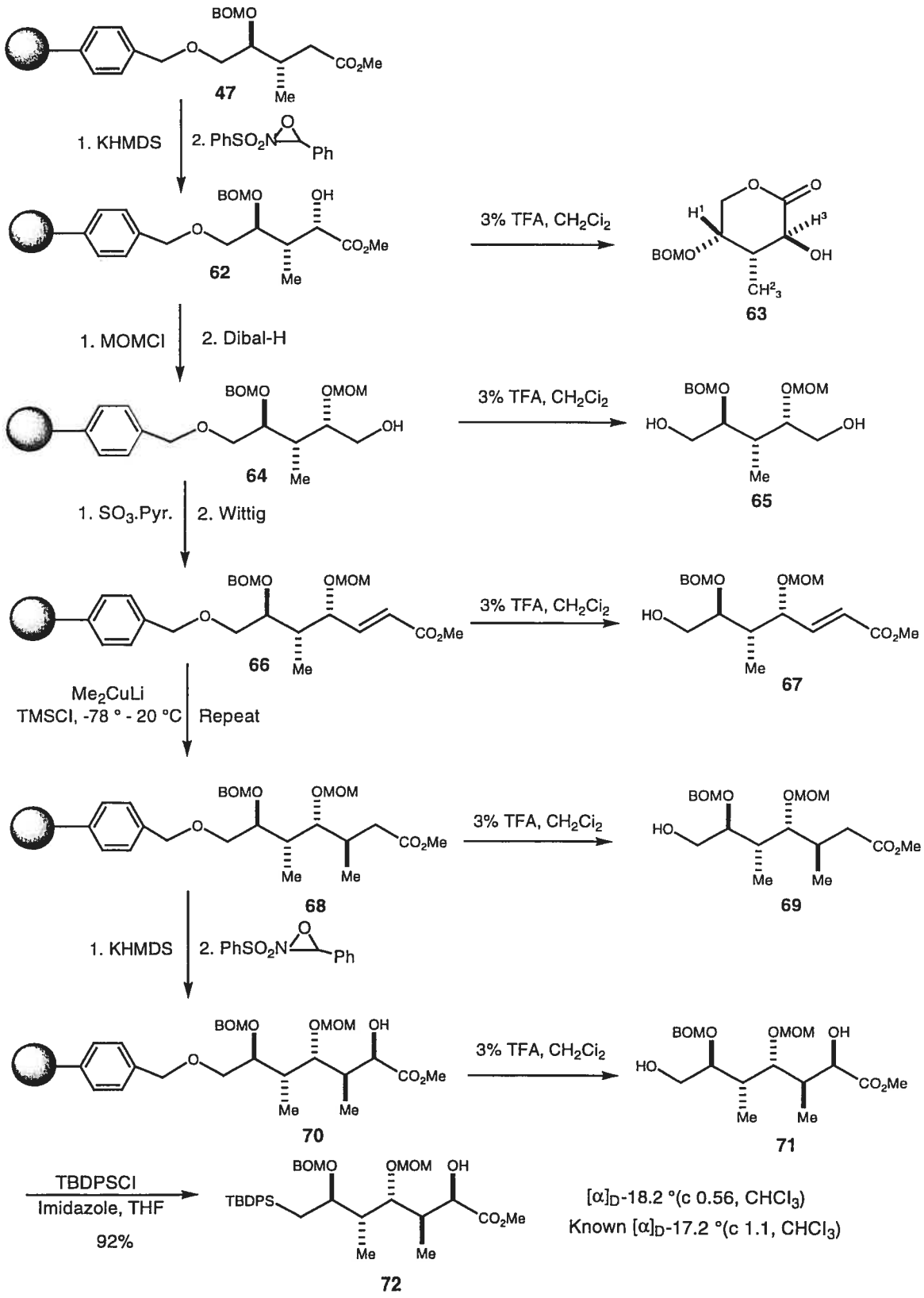
♦ 5-8 Stereocontrolled polypropionate synthesis on solid phase

After realizing the stereocontrolled cuprate conjugate addition and α-alkylation on solid phase, we studied α-hydroxylation (**Scheme 23**) as in solution chemistry.[70, 72] Indeed, treatment of the potassium enolate generated from **47** with Davis oxaziridine reagent[71] afforded the α-hydroxy ester **62** which, upon cleavage, gave an enantiopure lactone **63**. The strong nOe effect between H^2 and H^3, very weak nOe effect between H^1 and H^3 indicate that the hydroxyl group and methyl group in lactone **63** have *anti*-relationship.

Next, we decided to explore the possibility to synthesize polypropionate on solid phase as we did in solution chemistry. Protection of the hydroxy group of **62** with MOM group followed by the reduction of the ester with Dibal-H afforded the alcohol **64**, which was cleaved from solid phase to give **65**. Swern oxidation of the alcohol **64** to the corresponding aldehyde proved to be slow and to occur with moderate yield. The Doering-Parikh reagent[104] was found to be more efficient for this oxidation probably because the resin could swell better at room temperature than at lower temperature.

Treatment of the aldehyde with $Ph_3P{=}CHCO_2Me$ (10 eq.) in CH_2Cl_2 for two days provided the α,β-unsaturated ester **66** which underwent lithium dimethyl cuprate addition to give the adduct **68** (**Scheme 23**).

Scheme 23 Stereocontrolled polypropionate synthesis on solid phase



As we mentioned previously, this cuprate addition was also very slow at low temperature, so it was carried out at -78 °C for 2h, at –40 °C for 2 h and –20 °C for 2 h before it was quenched. In order to ensure the completion of this reaction, the same cuprate addition procedure was repeated and **69** was obtained after acidic cleavage. ^{1}H NMR showed that the stereoselectivity was over 10:1.

Finally, a second α-hydroxylation of **69** with Davis oxaziridine afforded the α-hydroxy ester **70**, which upon cleavage gave ester **71,** ^{1}H NMR shows that ds is over 10:1. Conversion of **71** to the TBDPS ether afforded **72**, which was identical in all the chemical and physical aspects to the known reference compound[105].

♦ 5-9 Summary

In conclusion, the high degree of 1,2-induction in the α-alkylation and α-hydroxylation reactions can be also extended to solid phase. Polypropionate synthesis can be achieved on solid phase with excellent 1,2 induction through two cuprate additions and two enolate hydroxylation cycles. The stereoselectivities of these reactions on solid-phase are as good as in solution chemistry and the stereofacial selectivities are same for solid–phase and solution chemistry. This methodology has several disadvantages. First, more reagents and longer reaction time are needed to ensure the completion of the reactions on solid phase than in solution reactions, and sometime, the reactions have to be repeated. Second, it is not easy to monitor the solid-phase reaction because compounds had to be cleaved from the solid phase in order to check the progress of the reaction. Finally, it is difficult to

measure the exact yield because several by-products can be formed when the products are cleaved from the solid support.

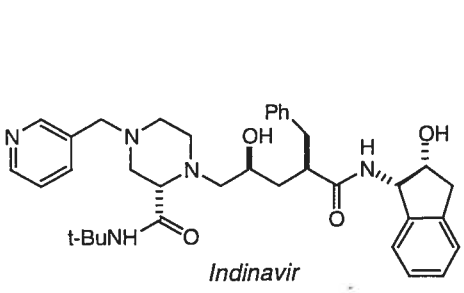
Chapter six Syntheses of enantiopure indanes and tetrahydronaphthalenes

Part one Synthesis of enantiopure indanes

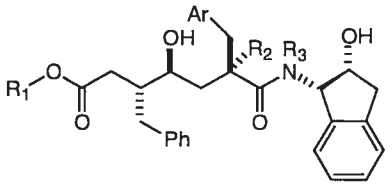
♦ 6-1 Introduction

Among the compounds containing a chiral indane subunit, none are more important than the orally active HIV protease inhibitor *indinavir* (L-735.524) and its analogs (**Figure 14**).[106]

Figure 14 HIV protease inhibitor *indinavir* and its analogs

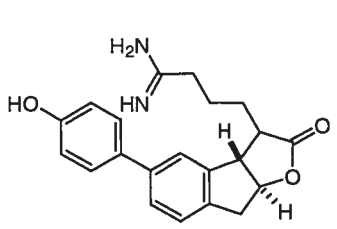


Indinavir

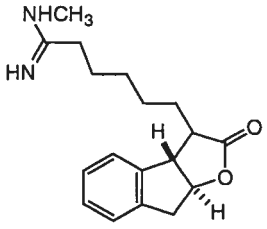


L-685.434 (-) R_1=*t*-Bu, R_2=R_3=H, Ar=Ph
L-697.807 (-) R_1=3-THF, R_2=R_3=H, Ar=Ph
L-687.965 (-) R_1=*t*-Bu, R_2=Me, R_3=H, Ar=Ph
L-689.428 (-) R_1=*t*-Bu, R_2=R_3=-$(CH_2)_2$-, Ar=Ph
(-) R_1=*t*-Bu, R_2=R_3=H, Ar=C_6H_4-*p*-OH

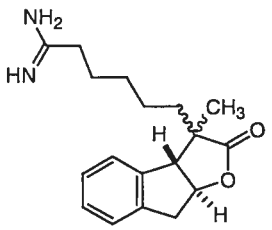
Figure 15 Trans-fused indane lactones as inhibitors of thrombin



F_1



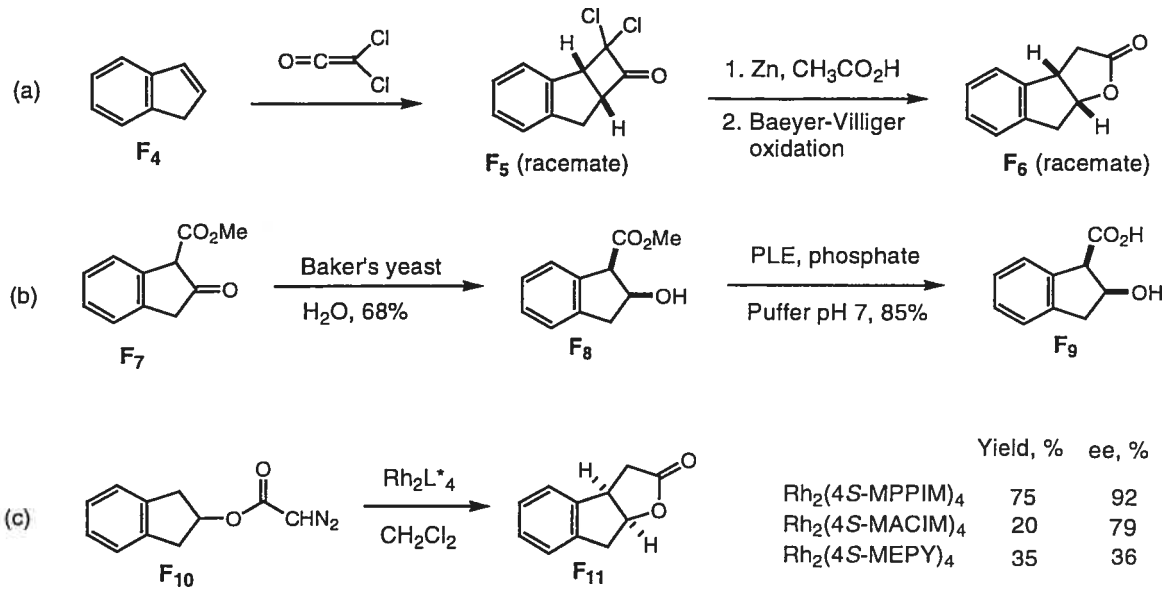
F_2



F_3

Trans-fused indane lactones (**Figure 15**) were found to be active inhibitors of the pro-coagulant serine protease thrombin.[107] Enantiopure indane derivatives were also used as chiral auxiliaries in asymmetric synthesis.[108] Some methodologies for the syntheses of chiral indanes are shown in **Scheme 24**.

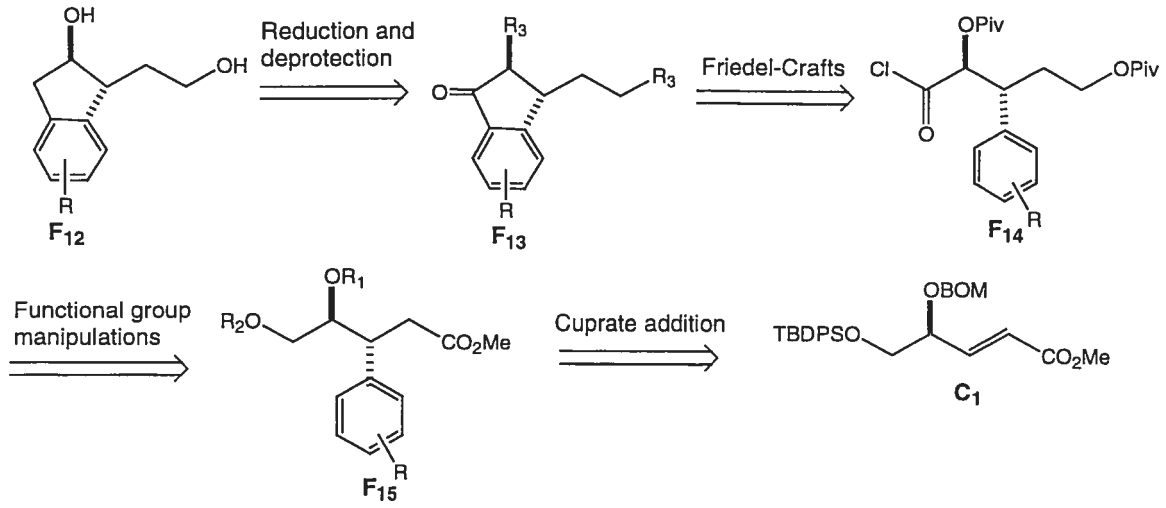
Scheme 24 Syntheses of indanes



In equation (a), the racemic indane **F$_6$** was synthesized from alkene **F$_4$** by a [2+2] cycloaddition with dichloroketene, followed by reductive dechlorination and Baeyer-Villiger oxidation.[109] In equation (b), indane **F$_9$** was obtained by Baker's yeast reduction of the corresponding β-ketoester **F$_7$** with high enantio- and diastereoselectivity but with low yield (34%).[110] In equation (c), carbon-hydrogen insertion reaction of diazoacetate **F$_{10}$** with Rh_2(4*S*-MPPIM)$_4$ provided the indane **F$_{11}$** in good yield and stereoselectivity, but the catalyst is very expensive.[111]

We therefore opted to synthesize the enantiopure indanes by a new protocol that uses substrate control to install the chiral centers as illustrated in the retrosynthetic plan in **Scheme 25**.

Scheme 25 Retrosynthetic plan for the synthesis of enantiopure indanes

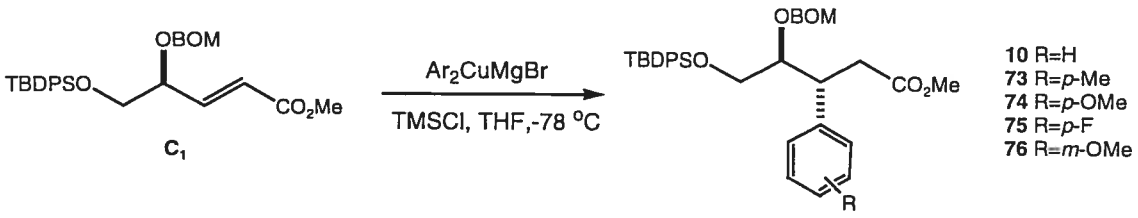


The enantiopure indanes $\mathbf{F_{12}}$ would be synthesized from the ketone $\mathbf{F_{13}}$ which could be derived from the acid chloride $\mathbf{F_{14}}$ using a Friedel-Crafts reaction.[112] $\mathbf{F_{14}}$ can be synthesized from $\mathbf{F_{15}}$ by several functional group manipulations and $\mathbf{F_{15}}$ would arise from $\mathbf{C_1}$ by stereocontrolled cuprate additions.

♦ 6-1-1 Stereocontrolled aryl cuprate additions to α,β-unsaturated esters

We started with studies of cuprate additions to α,β-unsaturated ester C_1 with different aryl cuprate reagents and the results are summarized in **Table 3**. The results in entries 1 and 2 indicate that stereoselectivity is not greatly influenced by whether the methoxy group is in the *para* or *meta* position of the benzene ring. The stereochemistry was *anti* as previously shown for other cuprate additions,[70, 72] and confirmed by single crystal X-ray analysis later in this work.

Table 3 Stereocontrolled aryl cuprate additions to α,β-unsaturated ester C_1



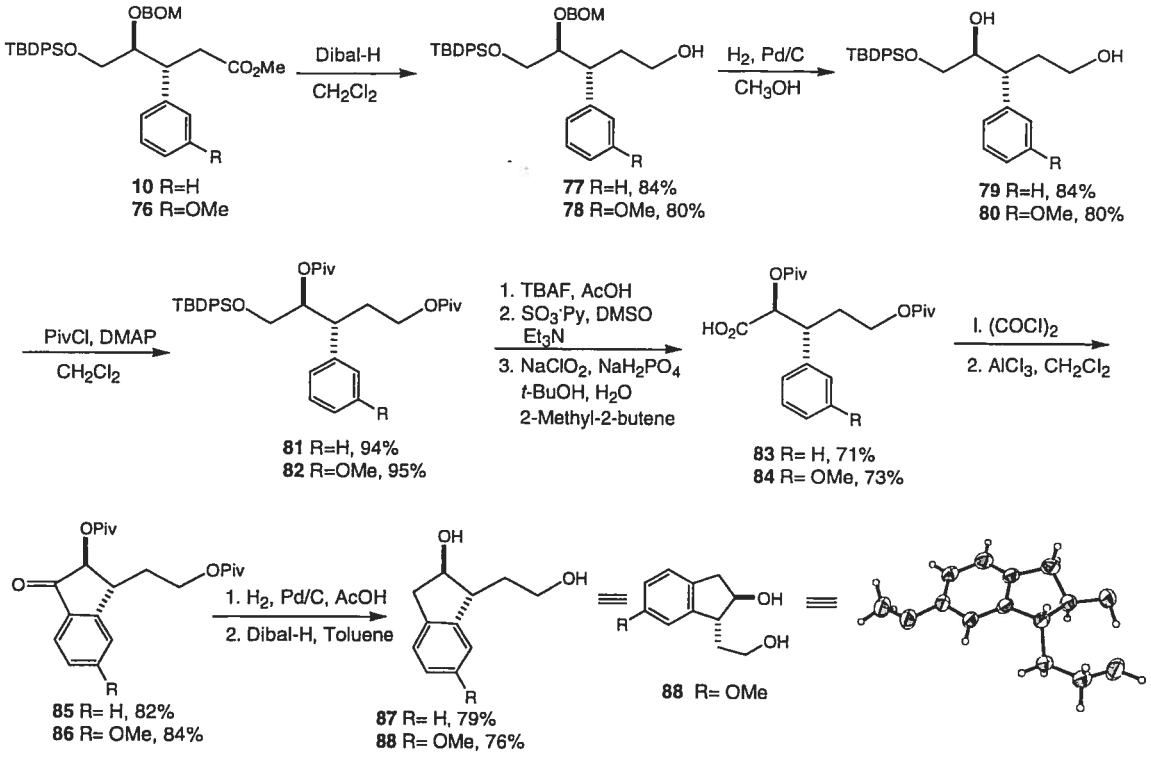
Entry	R	Yield	*anti/syn*
1	H	85%	16:1
2	*p*-Me	86%	14:1
3	*p*-OMe	84%	13:1
4	*p*-F	87%	14:1
5	*m*-OMe	84%	15:1

♦ 6-1-2 Synthesis of enantiopure indanes

We chose the cuprate addition adducts **10** and **76** for the synthesis of enantiopure indanes (**Scheme 26**). We worred that the BOM group cannot survive the Friedel-Crafts reaction conditions and may interfere with this reaction, it was removed by hydrogenation and replaced with the bulky pivaloyl group to give **81** and **82,** respectively. The TBDPS group was removed from **81** and **82** with TBAF in good respective yields and the resulting alcohols were oxidized to their aldehyde counterparts with the Doering-Parikh reagent.[104] Friedel-Crafts reaction of the resulting aldehydes proved to be low in yields and the stereoselectivities were poor. Alternatively, oxidation of the aldehydes using $NaClO_2$[113] gave the corresponding acids **83** and **84** in 71% and 73% overall yield for three steps. Treatment of the acids **83** and **84** with oxalyl chloride and a catalytic amount

of DMF[114] afforded the corresponding acid chlorides which were directly treated with $AlCl_3$ in CH_2Cl_2 at 0 °C to afford the Friedel-Crafts products **85** and **86** in 82% and 84% respectively. We were also pleased to find that no epimerization had occurred in this step. However, removal of the pivaloyl group of **85** and **86** at this stage with sodium methoxide did result in epimerization of the α-position of the ketones. Reduction of the carbonyl groups of **85** and **86** by hydrogenation in acetic acid, and removal of the pivaloyl groups with Dibal-H afforded the indanes **87** and **88** in excellent yield.

Scheme 26 Synthesis of enantiopure indanes



The *meta*-methoxy indane **88** afforded X-ray quality crystals after column chromatography and recrystallization from hexane-CH_2Cl_2 (**Scheme 26**).

♦ 6-1-3 Summary

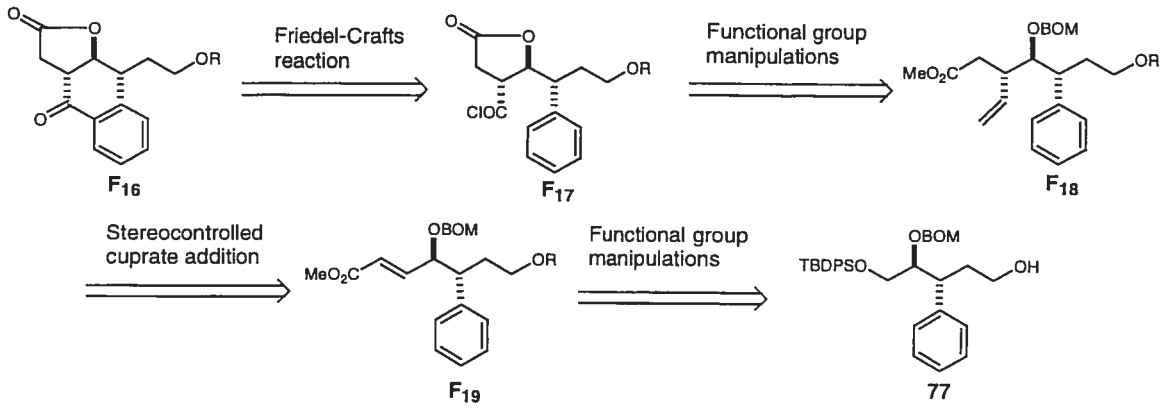
The indanes **87** and **88** were synthesized from the α,β-unsaturated ester $\mathbf{C_1}$ with very high stereoselectivities and good yields using stereocontrolled cuprate additions and Friedel-Crafts reactions as the key steps. Because **87** and **88** contain two hydroxy groups, they can be further manipulated for other purposes. This work also proved that the pivaloyl group is a very compatible protecting group in Friedel-Crafts reactions.

Part two Synthesis of enantiopure tetrahydronaphthalenes

♦ 6-2-1 The retrosynthetic plan

We wanted to synthesize enantiopure tetrahydronaphthalenes applying the same methodology as we used in the syntheses of enantiopure indanes. As shown in the retrosynthetic plan in **Scheme 27**, the enantiopure tetrahydronaphthalene $\mathbf{F_{16}}$ would be generated from the acid chloride $\mathbf{F_{17}}$ via a Friedel-Crafts reaction. The latter can be obtained by functional group manipulations of $\mathbf{F_{18}}$. The stereocontrolled introduction of a vinyl group in $\mathbf{F_{18}}$ would be accomplished using a cuprate addition to the α,β-unsaturated ester $\mathbf{F_{19}}$, which would originate from **77**.

Scheme 27 The retrosynthetic plan for the synthesis of enantiopure tetrahydronaphthalenes

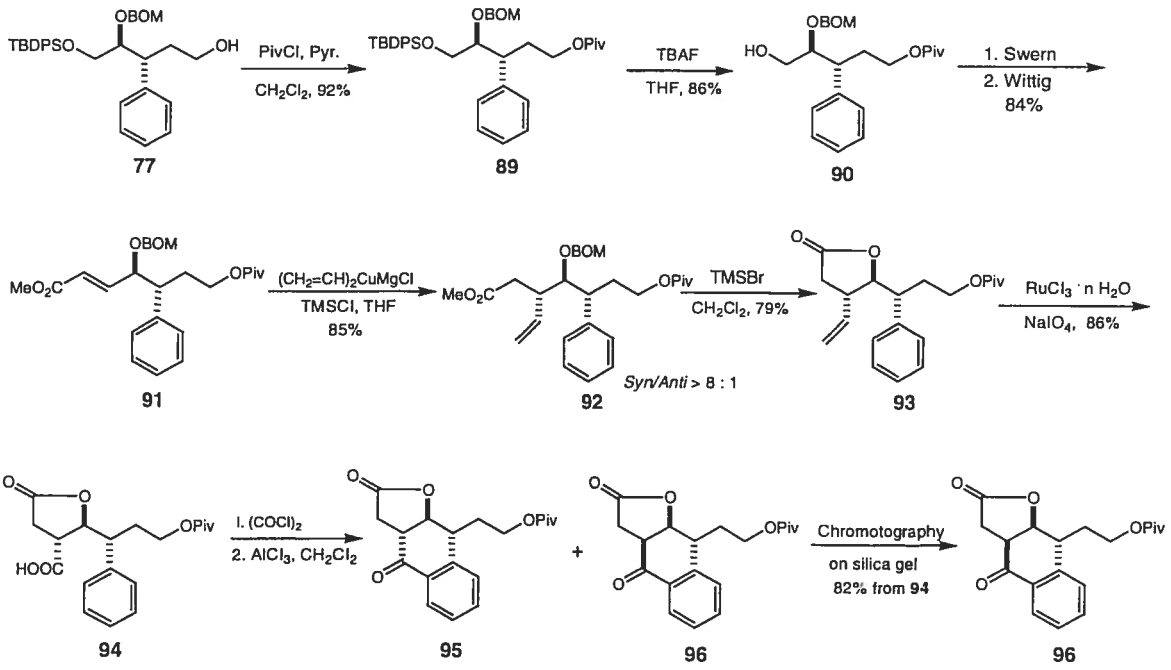


♦ 6-2-2 Synthesis of a *cis*-fused tetrahydronaphthalene

The alcohol **77** was protected with a pivaloyl group, and then the TBDPS group was removed with TBAF (**Scheme 28**). The resulting alcohol **90** was oxidized to the corresponding aldehyde which was treated with the Wittig reagent ($Ph_3P{=}CHCO_2Me$) to give the α,β-unsaturated ester **91** in good yield. Conjugate addition of the divinyl magnesium cuprate to the α,β-unsaturated ester **91** at –78 °C afforded the adduct **92** in 85% yield with a ratio over 8:1. The stereochemical outcome was expected to be *trans*-selectivity as in analogous cases[70, 72] which was confirmed later by X-ray analysis on compound **99**. As before, the BOM group was removed. Treatment of **92** with TMSBr[79] in CH_2Cl_2 afforded lactone **93**. The double bond of **93** was then cleaved and oxidized to the corresponding acid **94** in 86% yield using $NaIO_4$ and $RuCl_3.nH_2O$ as catalyst.[115] Treatment of **94** with oxalyl chloride and catalytic DMF, followed by Friedel-Crafts reaction with $AlCl_3$, afforded the cyclized products in good yield. TLC showed two products were formed and attempts to separate the two products by column

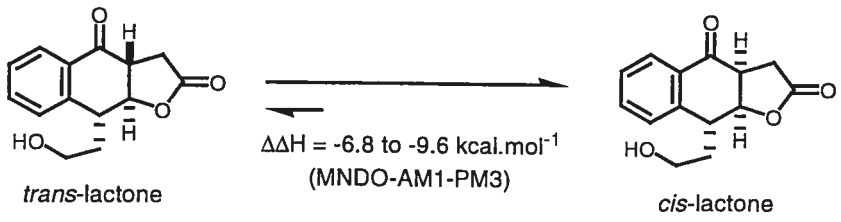
chromatography failed because the less polar product was changed to the more polar product on silica gel. We observed that the longer the column chromatography took, the more less-polar product was transformed to the more polar product. After we had run the column chromatography twice, almost all the less-polar product was changed to the more-polar product and nOe spectra revealed that this more polar compound was *cis*-lactone **96**, which was confirmed later by x-ray analysis on compound **99**.

Scheme 28 Synthesis of enantiopure tetrahydronaphathalene



MNDO-AM1-PM3 calculation[116] indicates that the *cis*-lactone **96** as the free alcohol is much more stable than corresponding *trans*-lactone **95** (**Scheme 29**).

Scheme 29 MNDO-AM1-PM3 calculated relative energy for *trans* and *cis* lactones



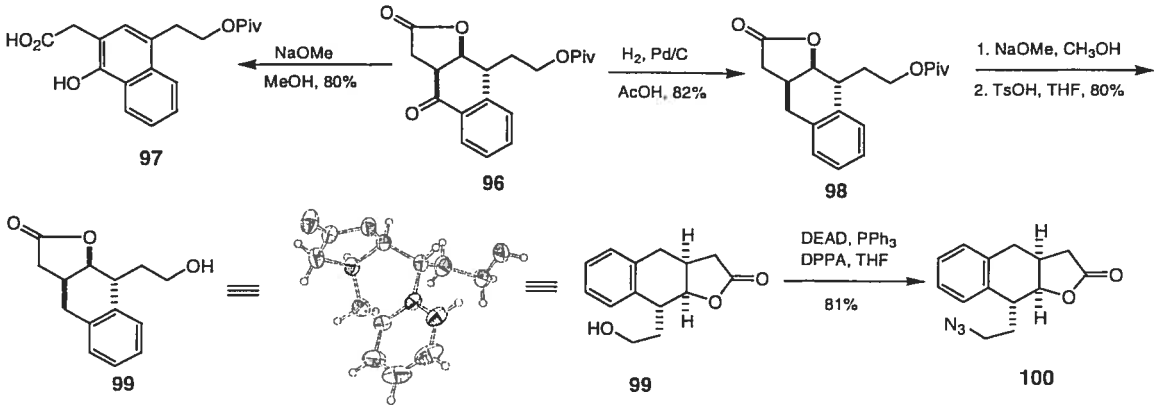
trans-lactone *cis*-lactone

♦ 6-2-3 Reduction and deprotection

Attempt to remove the pivaloyl group of **96** using NaOMe in MeOH led to the aromatized product **97** (**Scheme 30**). In order to avoid aromatization and epimerization, the benzylic carbonyl group was reduced to a methylene group. Hydrogenation in acetic acid with palladium on activated carbon as catalyst proved to be a very efficient for this purpose and the reduced product **98** was obtained in 82% yield.

The pivaloyl group was then removed with NaOMe in MeOH and some of hydrolyzed product was formed at the same time. The mixture was treated with TsOH in THF and the solid product **99** was obtained in 80% yield after column chromatography. Recrystallization in a mixture of hexane-CH_2Cl_2 gave X-ray quality crystals of **99** whose X-ray structure unambiguously proved the stereochemistry of the original *cis*-lactone **96**. Functional group manipulations were exemplified by transformation of the alcohol to the corresponding azide by treatment of the alcohol with DEAD, PPh_3, DPPA[80] to afford **100** in 81% yield.

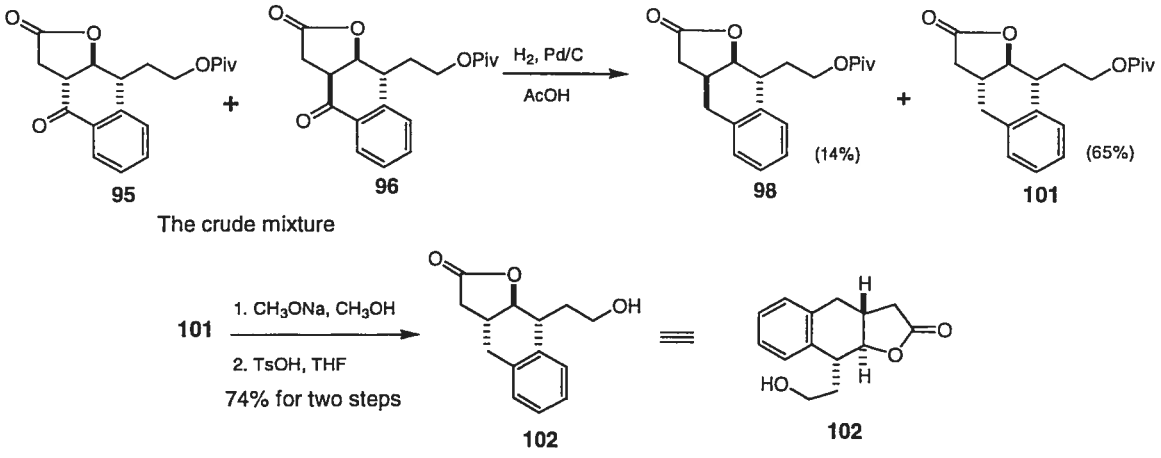
Scheme 30 Synthesis of *cis*-tetrahydronaphthalene **100**



♦ 6-2-4 Synthesis of a *trans*-fused tetrahydronaphthalene

Because the *trans*-lactone **95** epimerized to *cis*-lactone **96** on silica gel, we subjected the crude Friedel-Crafts products to hydrogenation directly in acetic acid with palladium on charcoal. This led to 14% of *cis*-lactone **98** and 65% of the *trans*-lactone **101** (**Scheme 31**).

Scheme 31 Synthesis of *trans*-tetrahydronaphthalene



Removal of the pivaloyl group with NaOMe in MeOH and treatment of the crude products with TsOH in THF, as we did before, afforded the *trans*-lactone **102** in 74% yield.

♦ 6-2-5 Summary

The *cis*- and *trans*-lactones **100** and **102** were synthesized from the α,β-unsaturated ester C_1 using stereocontrolled cuprate addition and Friedel-Crafts reactions as the key steps. The *trans*-lactone **94** was easily isomerized to *cis*-lactone **95** on silica gel. Column chromatography of the crude Friedel-Crafts products gave predominantly the *cis*-lactone **95** and hydrogenation of the crude Friedel-Crafts products provided predominantly *trans*-lactone **101**.

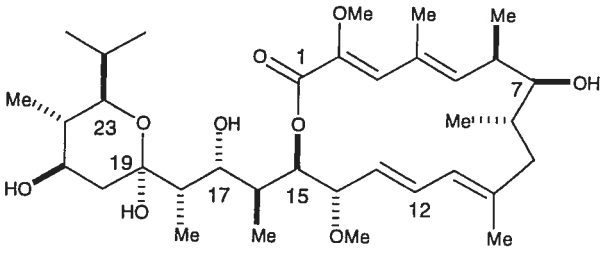
Chapter seven Total synthesis of Bafilomycin A_1

Part one Introduction

♦ 7-1-1 Background

The macrolide bafilomycin A_1 (**Figure 16**) was first isolated from the fermentation broth of *Streptomyces* griseus in 1983.[117] It exhibited activity against Gram-positive bacteria, and was also found to be a specific inhibitor of various membrane ATPases[118] with potential applications in the treatment of osteoporosis. Recently, studies showed that Bafilomycin A_1 potently reduced the production of Aβ, a peptide related to Alzheimer's disease.[119]

Figure 16 Bafilomycin A_1



Bafilomycin A_1

The Bafilomycins, Concanamycins[120] and Hygrolides[121] are closely related families of polyketide macrolide antibiotics characterized by a 16-membered or 18-membered tetraenic macrolactone ring and a six-membered hemiketal ring. Bafilomycin A_1 is a typical member of the Bafilomycins and its structure and absolute configuration were established by X-ray crystallographic analysis[122] which confirmed the earlier assignments made by Corey and Ponder based on NMR data and molecular modeling.[123] Inspection of

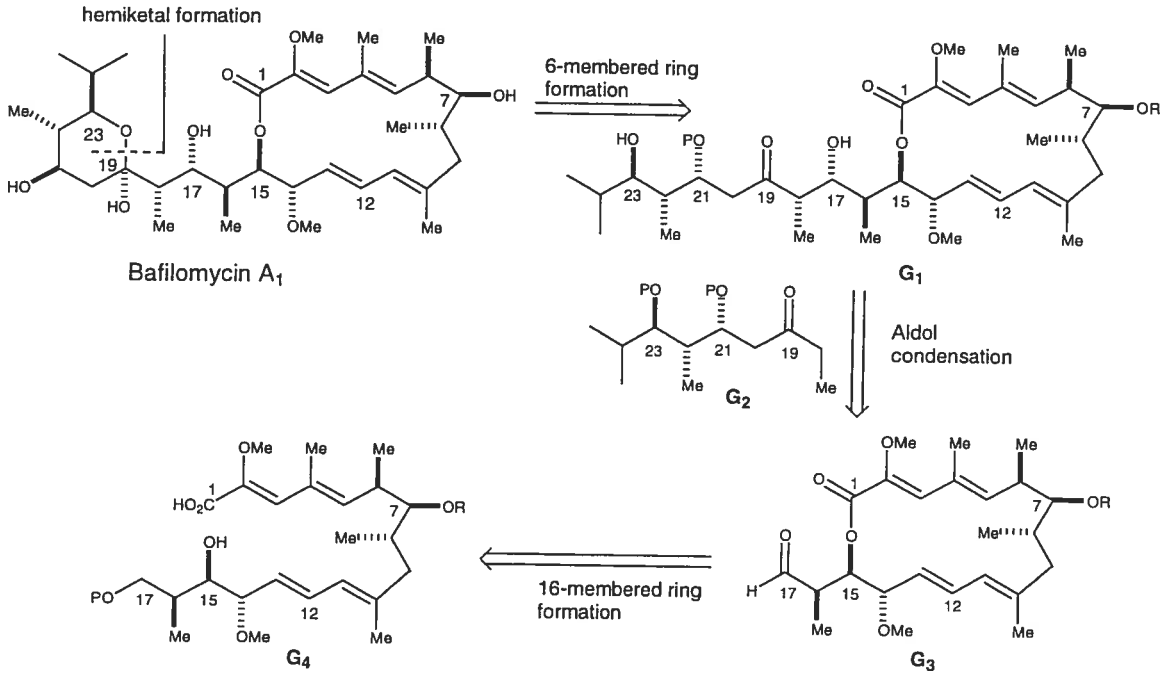
the fine functional features of the crystal structure of Bafilomycin A_1 reveals a unique H-bonding network involving the lactone carbonyl, the hemiacetal hydroxyl group, and the C_{17} hydroxyl group. This bonding may play an important role in its biological behavior. Indeed, a single crystal X-ray analysis of a ring-opened product[124], in which the macrolactone remained intact and the pseudosugar unit was transformed into an ester, maintained an H-bonding network similar to that of Bafilomycin A_1 between the C_{17} hydroxyl group and the lactone carbonyl. This product also retained substantial H^+-APTase inhibitory activity.[125] On the other hand, a ring expanded 18-membered lactone analog,[126] *iso*-Bafilomycin A_1, that possessed the hemiacetal-lactone carbonyl H-bond was inactive, no doubt due to the altered nature of the macrocycle.

Following the first report of total syntheses of Bafilomycin A_1 by Evans and Calter,[127] Toshima[128] and Roush[129] disclosed their total syntheses of Bafilomycin A_1. The syntheses of segments of Bafilomycin A_1 have also been reported by Paterson[130] and Marshall.[131] Total syntheses of Concanamycin F have been disclosed by Paterson[132] and Toshima[133] respectively. Yonemitsu[134] has also described the total synthesis of Hygrolidin.

♦ 7-1-2 General strategies for the total synthesis of Bafilomycin A_1

In all the studies towards the total synthesis of Bafilomycin A_1, the polypropionate subunits were constructed with different versions of the aldol approach. In general, these strategies formed the 16-membered lactone $\mathbf{G_3}$ first, and then used an aldol reaction between $\mathbf{G_2}$ and $\mathbf{G_3}$ to give $\mathbf{G_1}$. The 6-membered hemiketal ring was formed as the last step after all the protecting groups were removed. This general approach is outlined in **Scheme 32**.

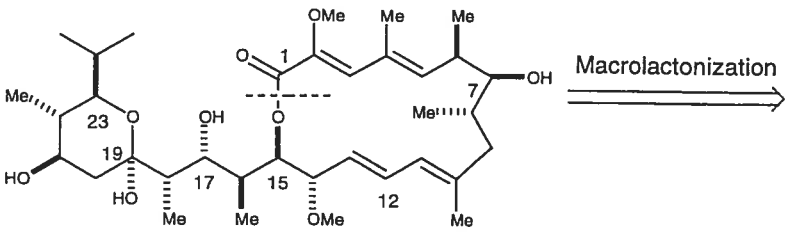
Scheme 32 General strategies for the total synthesis of Bafilomycin A_1



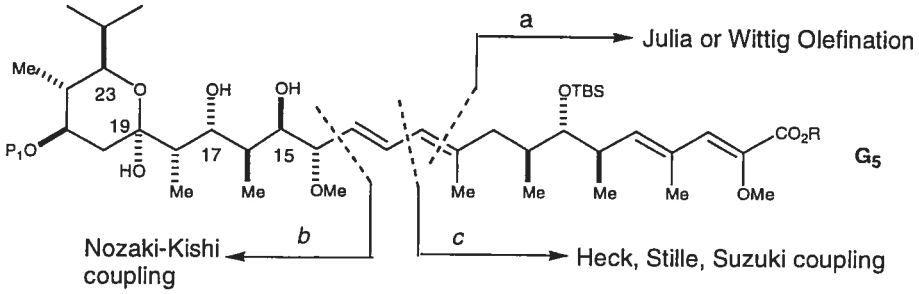
◆ 7-1-3 Retrosynthetic analysis of Bafilomycin A_1

Our approach to the synthesis of Bafilomycin A_1 relies on the generation of the polypropionate subunits with stereocontrolled cuprate additions and α-hydroxylation reactions developed in our group,[70,72] instead of using aldol reactions. We also planned to build the whole chain first, and then to form the 6-membered hemiketal ring and perform the macrolactonization at a later stage. Our retrosynthetic analysis of Bafilomycin A_1 is depicted in **Scheme 33**. Bafilomycin A_1 would be obtained by macrolactonization[135] of the acyclic precursor $\mathbf{G_5}$ which may be cut roughly into two equal pieces $\mathbf{G_6}$ and $\mathbf{G_7}$ (path a), or $\mathbf{G_8}$ and $\mathbf{G_9}$ (path b), or $\mathbf{G_{10}}$ and $\mathbf{G_{11}}$ (path c).

Scheme 33 Retrosynthetic analysis

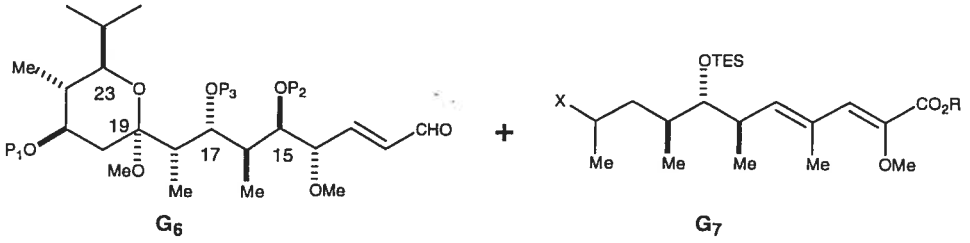


Bafilomycin A_1



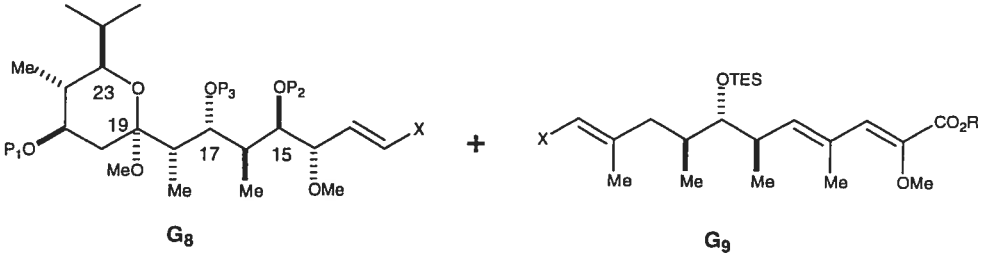
G_5

Path a



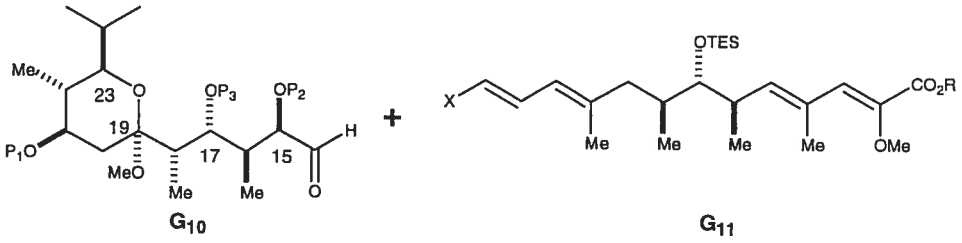
G_6 + G_7

Path b

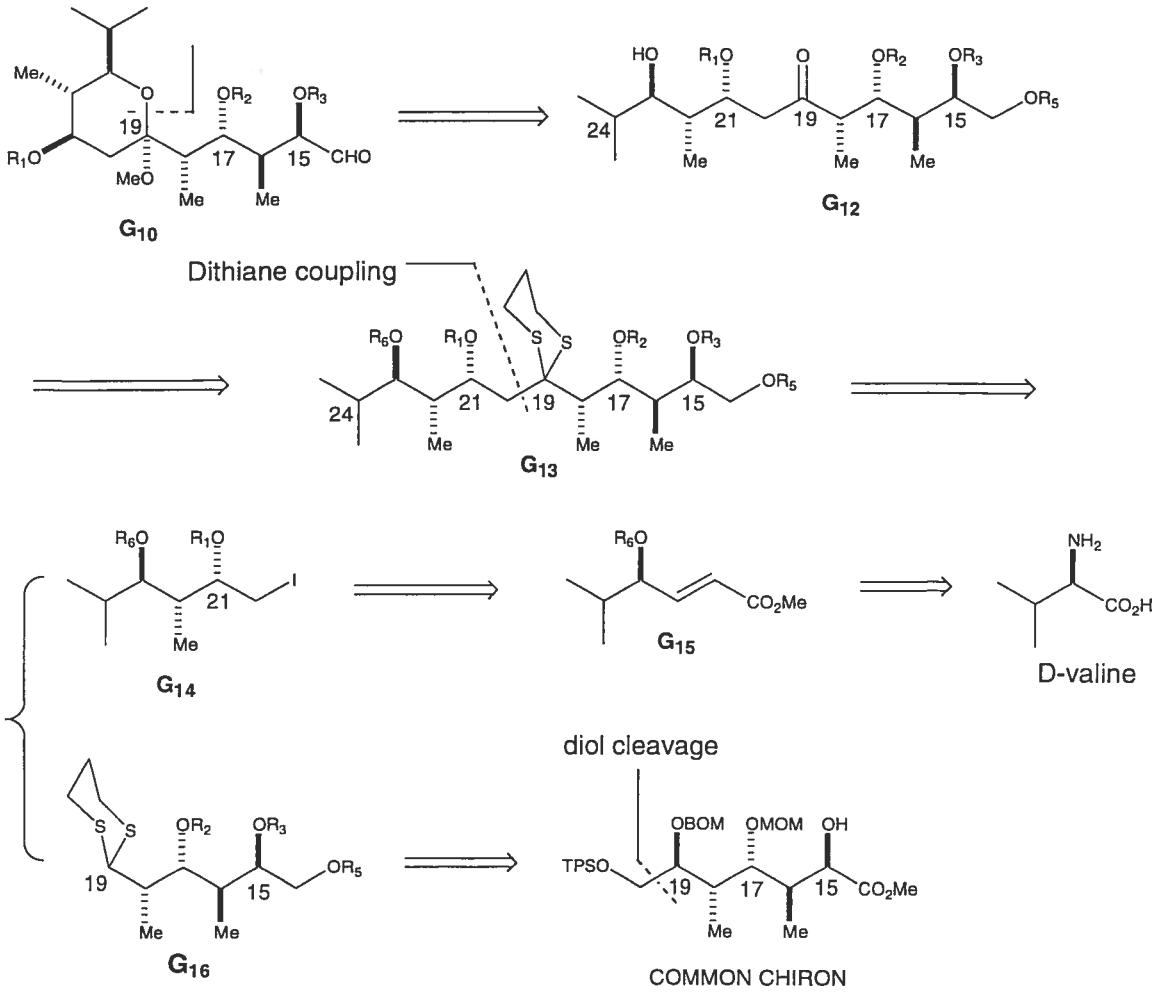


G_8 + G_9

Path c



G_{10} + G_{11}



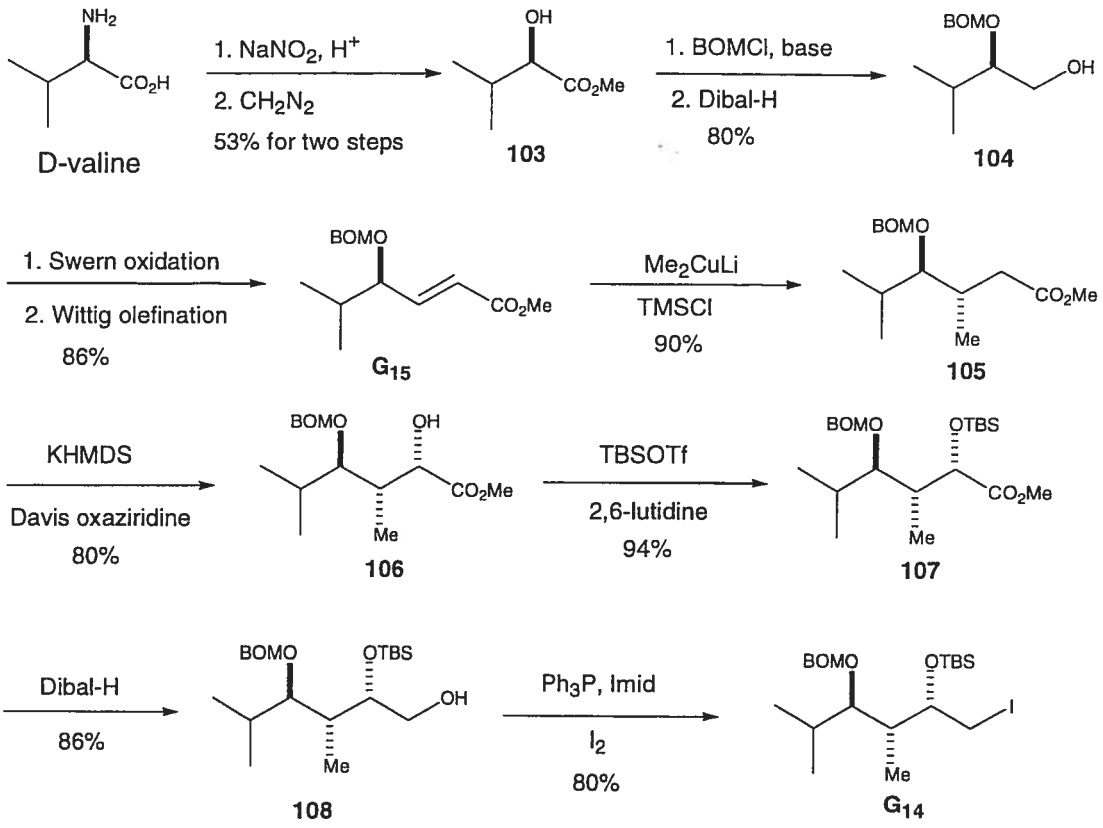
G_6 and G_7 could be coupled together by Julia[136] or Wittig olefination or other variants, G_8 and G_9 could be joined together by Heck[137], Stille[138], Suzuki[139] or some other palladium catalyzed coupling reactions, and G_{10} and G_{11} can be coupled together by Nozaki-Kishi reaction[140] or by nucleophilic attack on aldehyde G_{10} with dienic lithium or other metallic reagents derived from G_{11}. Further disconnection of G_6 and G_8 would provide G_{10}, which could be obtained from the acyclic ketone precursor G_{12}. Ketone G_{12} could arise from the dithiane precursor G_{13} by the selective removal of protecting groups. Disconnection of G_{13} could lead to the C21-C25 iodide segment G_{14}, and the C14-C19

dithiane segment G_{16}. All the stereocenters of G_{14} could be introduced from G_{15} by stereocontrolled cuprate addition and α-hydroxylation reactions and G_{15} can find its origin from D-valine. G_{16} would be obtained from a common chiron[72] by several functional group manipulations.

♦ 7-1-4 Syntheses of subunits G_{14} and G_{16}

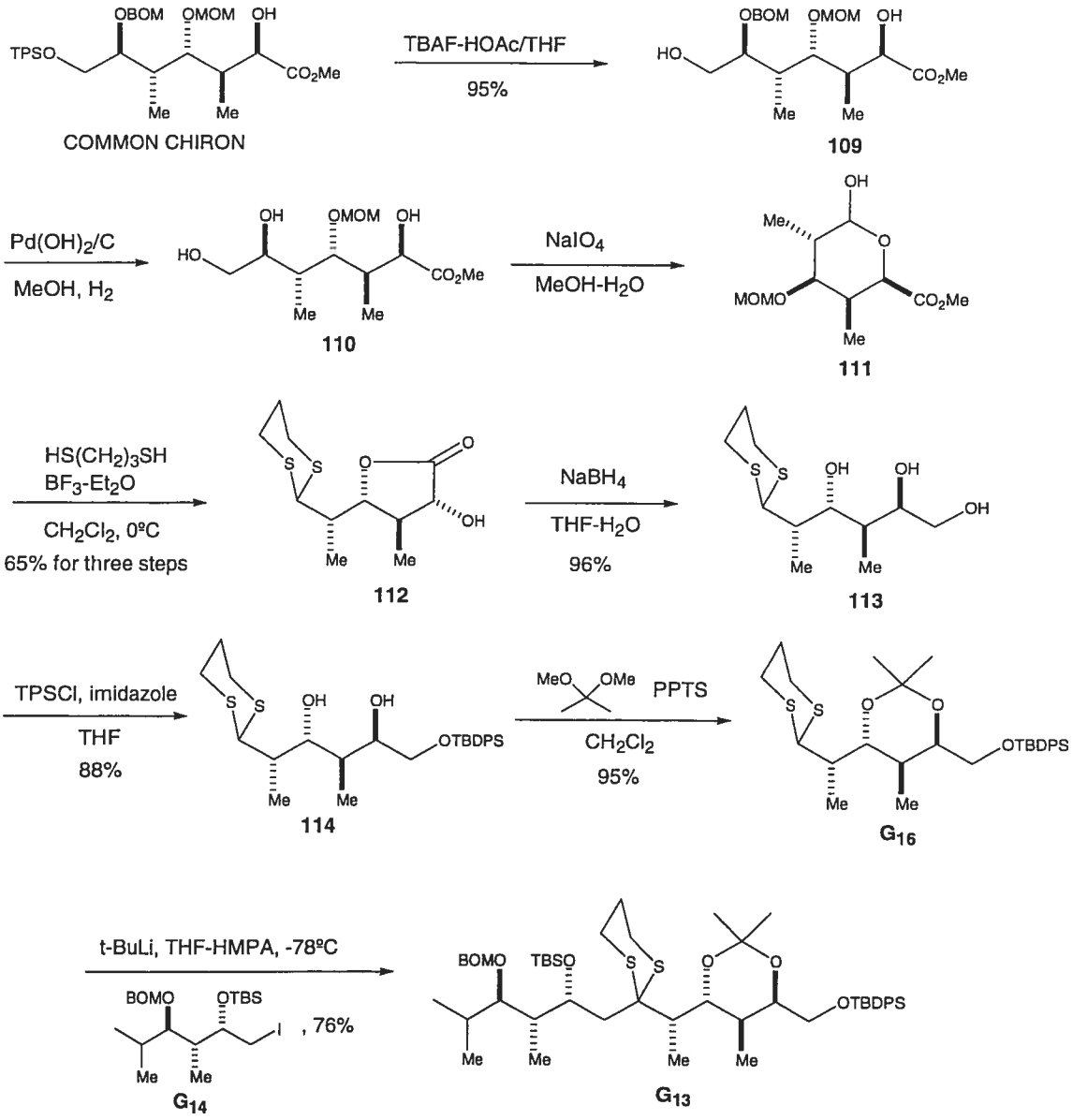
Subunits G_{14} and G_{16} have been previously synthesized in our group[141] and joined to give G_{13} as shown in **Schemes 34** and **35** respectively.

Scheme 34 Synthesis of subunit G_{14}



Intermediate $\mathbf{G_{15}}$ was obtained from D-valine by a sequence of functional group manipulations with very good overall yield. *Anti*-cuprate addition to $\mathbf{G_{15}}$ followed by *syn*-α-hydroxylation successfully introduced the β-methyl and α-hydroxy groups of **106** with the correct stereochemistry. Further functional group manipulations of **106** provided $\mathbf{G_{14}}$ (**Scheme 34**).

Scheme 35 Synthesis of subunit $\mathbf{G_{16}}$ and coupling reaction

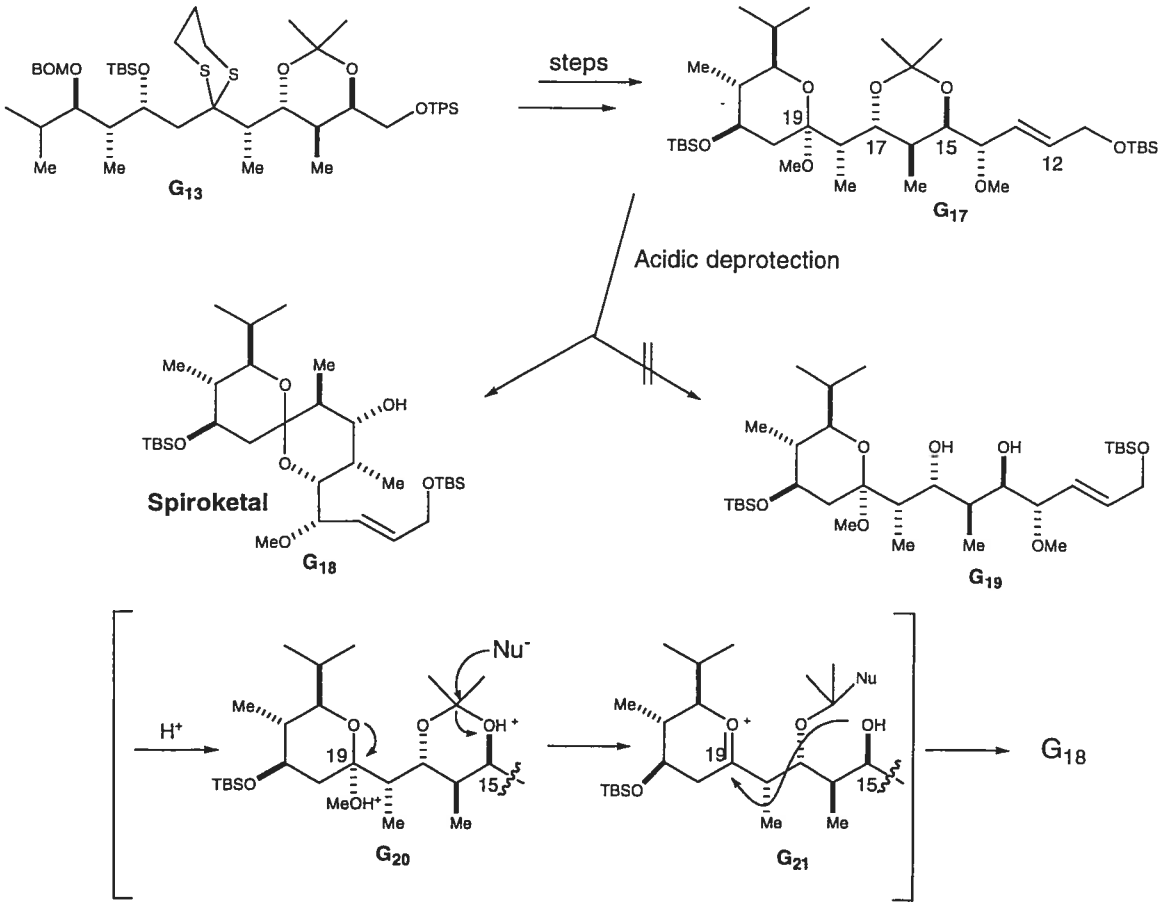


Scheme 35 shows how several functional group manipulations of the common chiron[142] provided the subunit $\mathbf{G_{16}}$ which was successfully joined with $\mathbf{G_{14}}$ to give the important subunit $\mathbf{G_{13}}$ in 76% yield.

♦ 7-1-5 Deprotection problems

Others[143] in this group planned to join two segments $\mathbf{G_6}$ and $\mathbf{G_7}$ using a Julia protocol and tried to synthesize $\mathbf{G_6}$ first. Compound $\mathbf{G_{17}}$ was successfully synthesized from $\mathbf{G_{13}}$ in 6 steps (**Scheme 36**). Unfortunately, the next step to remove the acetonide protecting group proved to be a problem.

Scheme 36 Deprotection problems



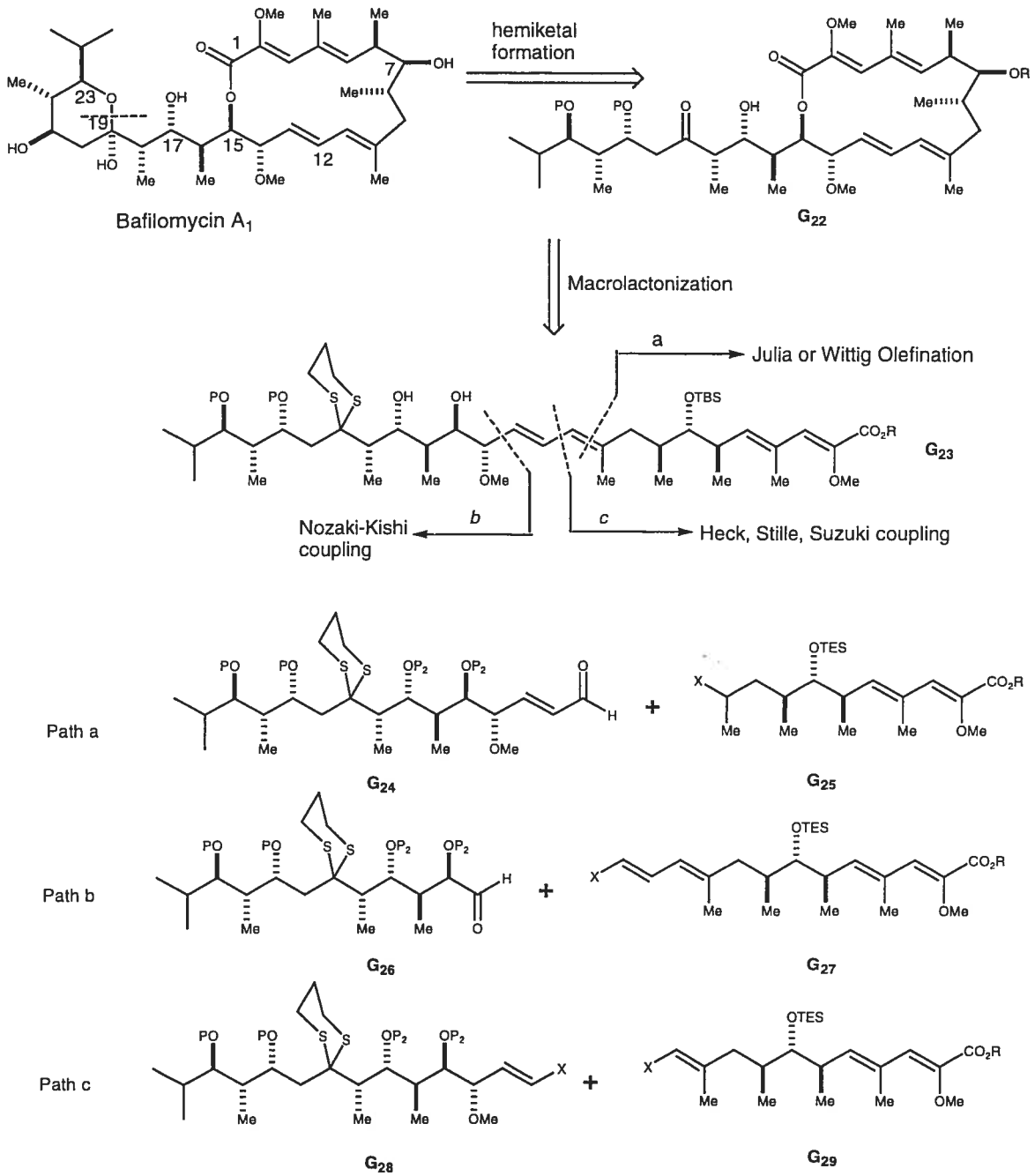
The acetonide protecting group was too stable to be removed without affecting other functionalities and all attempts under acidic and neutral conditions led to either no reaction or spiroketal $\mathbf{G_{18}}$. The latter was very stable and could not be converted to any useful compound. The mechanism for forming the spiroketal is shown **Scheme 36**.

♦ 7-1-6 Revised retrosynthetic analysis

Because efforts to replace the acetonide with other protecting groups were not fruitful, we decided that our strategy to form the six-membered hemiketal before macrolactonization was not practical.

To modify our strategy, we planned to do the macrolactonization before six-membered hemiketal ring formation as shown in **Scheme 37**. Bafilomycin A_1 would be obtained from $\mathbf{G_{22}}$ by a deprotection process with spontaneous hemiketal formation. Precusor $\mathbf{G_{22}}$ would arise from $\mathbf{G_{23}}$ after macrolactonization and dithiane deprotection. As in **Scheme 33**, $\mathbf{G_{23}}$ may be divided roughly into two equal segments for the coupling of which, the Julia coupling protocol of fragments $\mathbf{G_{24}}$ and $\mathbf{G_{25}}$, was first explored.

Scheme 37 Retrosynthetic analysis-2

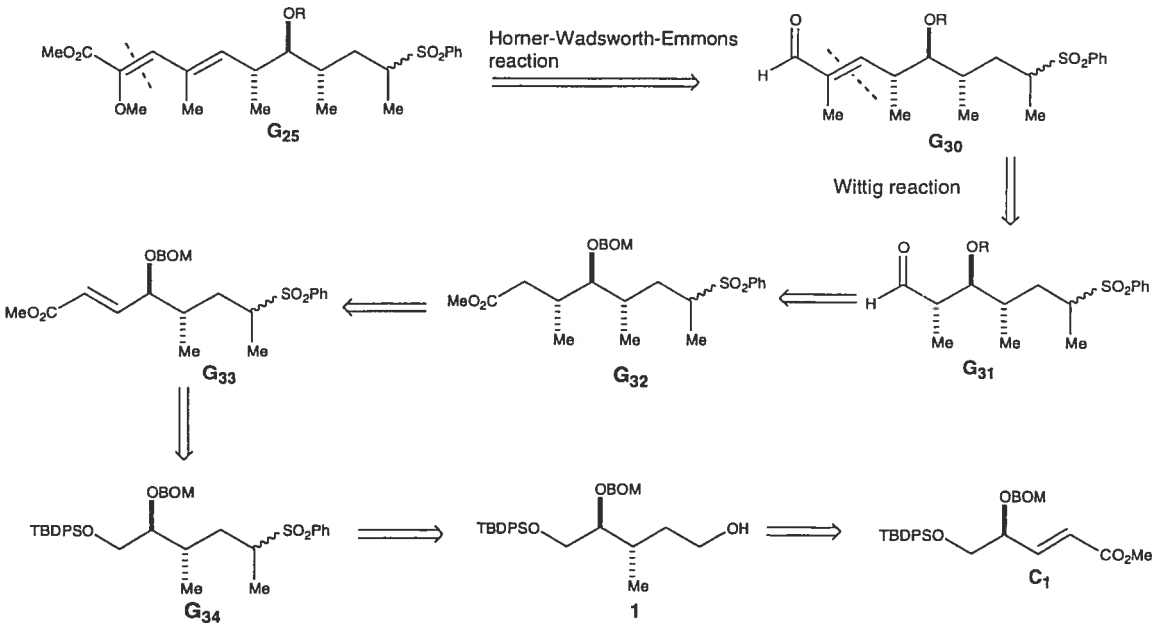


Part two Julia coupling method

♦ 7-2-1 Retrosynthetic analysis of G_{25}

For this strategy, two segments, G_{24} and G_{25} had to be synthesized. We decided to synthesize segment G_{25} first as shown in **Scheme 38**. G_{25} should be obtained from G_{30} by Horner-Wadworth-Emmons reaction.[144] Functional group manipulations of G_{32} should produce the aldehyde G_{31} which would undergo Wittig reaction to give G_{30}. Central to this synthetic plan was the introduction of the *trans*-propionate component in G_{32}, which would be accomplished from C_1 by the two-directional cuprate addition protocol developed in our group.[145]

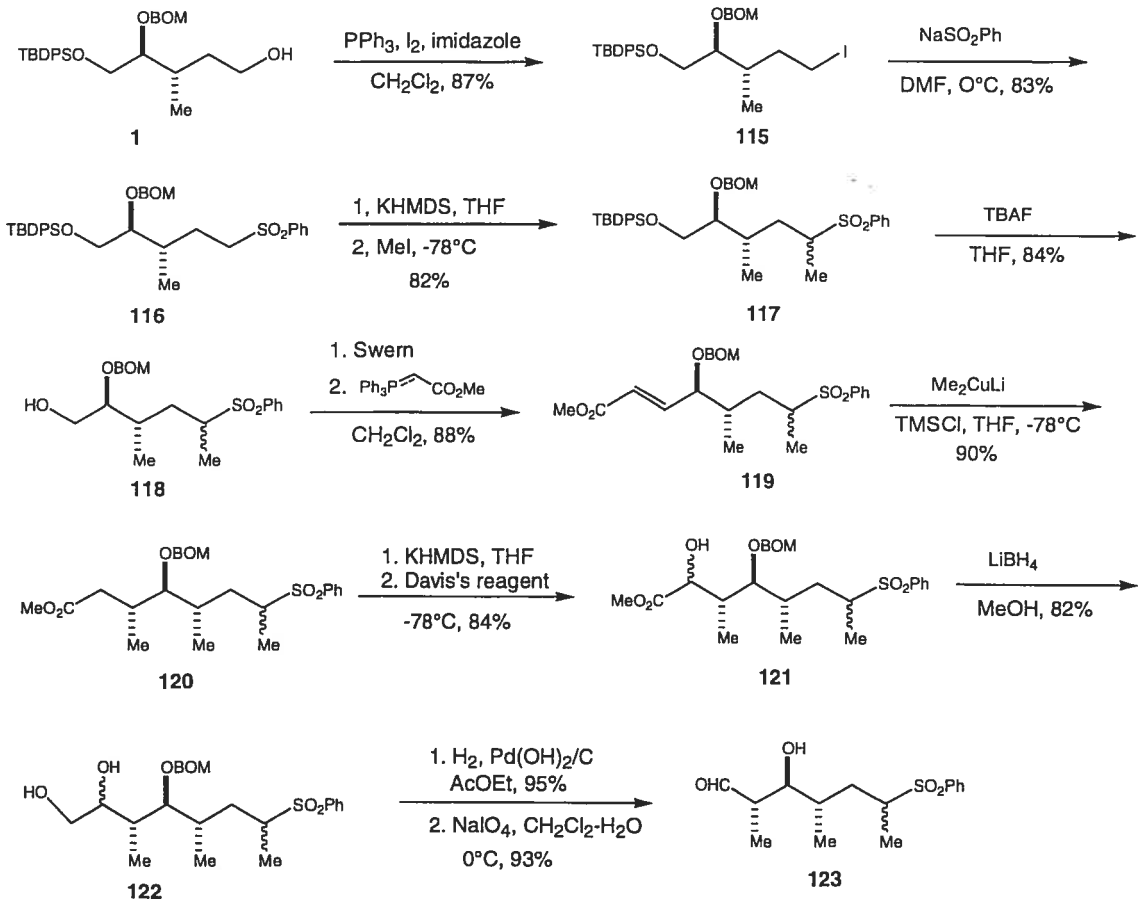
Scheme 38 Retrosynthetic analysis of G_{25}



♦ 7-2-2 Synthesis of aldehyde 123

The synthesis of the sulfone G_{15} started with the alcohol **1** which was transformed into the iodide **115** in 87% yield (**Scheme 39**). Treatment of the iodide **115** with $NaSO_2Ph$ in DMF at 0 °C successfully provided the sulfone **116**, which was treated with KHMDS at – 78 °C, followed with iodomethane, to give the isomeric mixture **117**. Because the two isomers of **117** would give the same product after Julia coupling reaction, they were carried on without separation.

Scheme 39 Synthesis of aldehyde **123**



The TBDPS protecting group of **117** was removed with TBAF to generate the alcohol **118** which underwent Swern oxidation[146] and Wittig reaction to give the α,β-unsaturated ester **119** in excellent yield. At this point, we had to introduce the methyl group with the correct stereochemistry using our stereocontrolled cuprate addition.

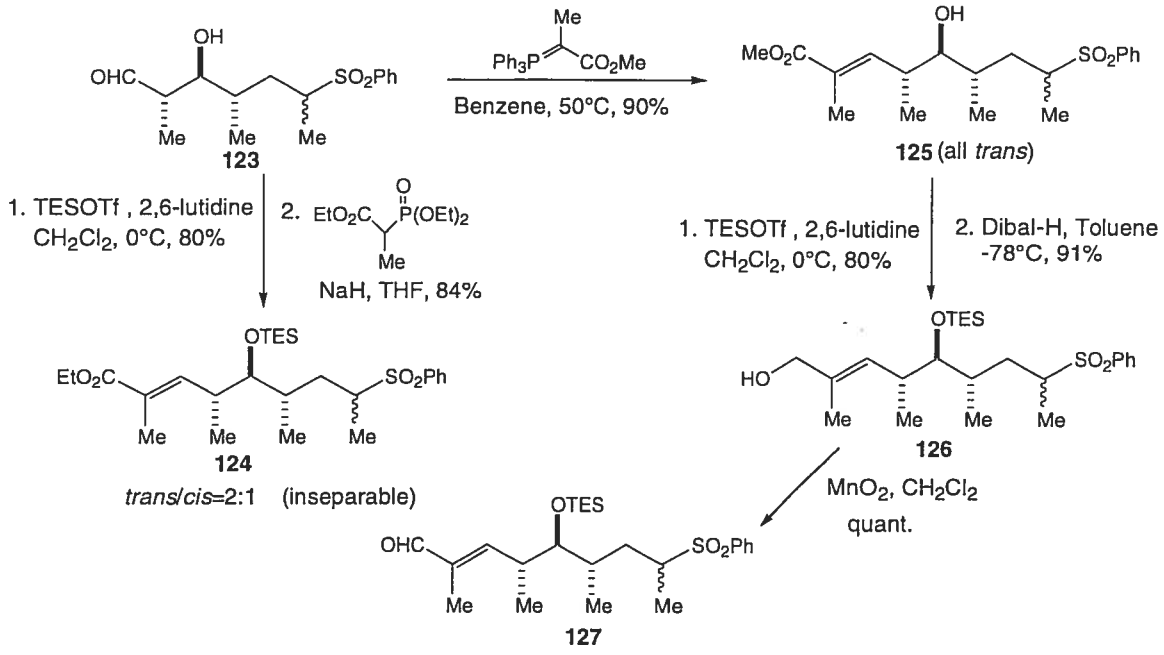
Treatment of the α,β-unsaturated ester **119** with lithium dimethyl cuprate at –78 °C with TMSCl as the additive afforded the adduct **120** in 90% and with a ratio of 20:1 by ^{1}H NMR spectroscopy. The stereochemistry should be *trans* as all the cuprate addition reactions which we tried before. Enolate formation of **120** with KHMDS followed by quenching with Davis oxaziridine reagent provided the α-hydroxy ester mixture **121**, which was further reduced to diol **122** with $LiBH_4$ in MeOH. The BOM protecting group of **122** was removed by hydrogenation to give the triol in 95% yield and the vicinal diol of the resulting triol was cleaved with $NaIO_4$ to provide the corresponding aldehyde **123** in excellent yield.

♦ 7-2-3 Synthesis of aldehyde 127

With the aldehyde **123** in hand, we wanted to extend the chain with a Wittig or Horner-Wadsworth-Emmons reaction. In order to safely carry out this reaction, the hydroxyl group of the aldehyde **123** was protected with TESOTf (**Scheme 40**). Unfortunately, Horner-Wadsworth-Emmons reaction of the aldehyde **123** provided a 2:1 mixture of inseparable *trans*/*cis* isomers **124**. (the *trans*- and *cis*-isomers were assigned later by comparing the ^{1}H NMR of compound **125** and its corresponding TES ether).

We then turned to the Wittig reaction to solve this problem. Treatment of the aldehyde **123** with the required Wittig reagent[147] in refluxing benzene for 48 h afforded exclusively the *trans*-isomer **125** in 90% yield. Protection of the hydroxy group of **125** with TESOTf followed by reduction with Dibal-H generated the allylic alcohol **126** which was then quantitatively oxidized to the corresponding allylic aldehyde **127** with MnO_2 in CH_2Cl_2.

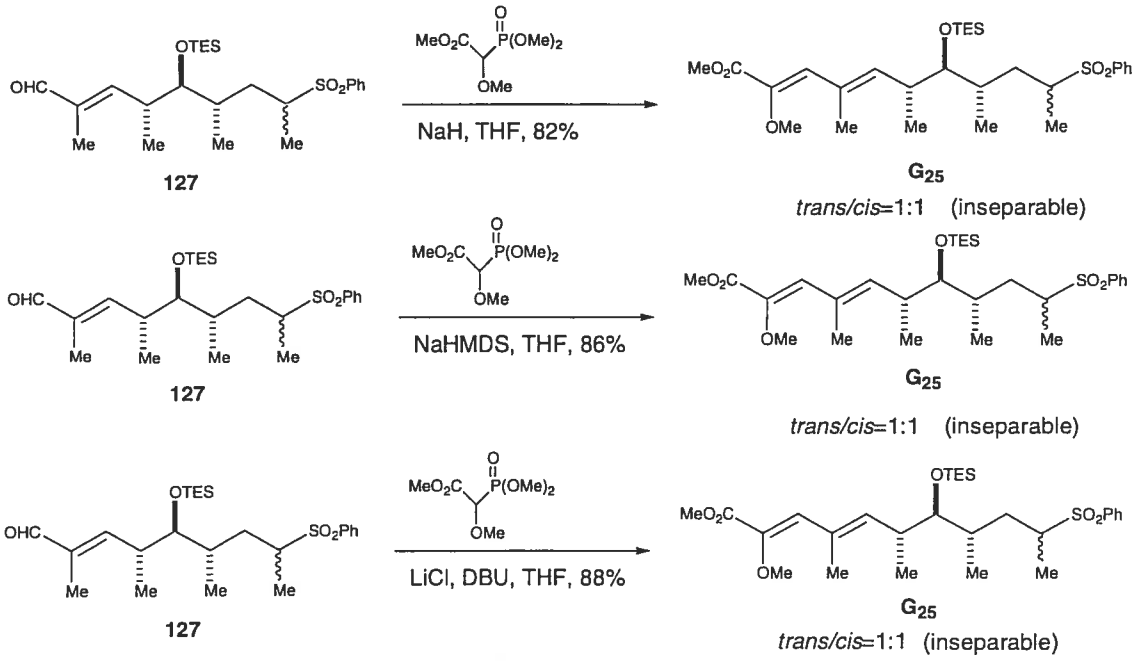
Scheme 40 Synthesis of aldehyde **127**



♦ 7-2-4 Problems with the Horner-Wadsworth-Emmons reaction

The chain extension of this allylic aldehyde with a Horner-Wadsworth-Emmons reaction proved not to be efficient (**Scheme 41**). Various conditions were tried for this reaction, but only 1:1 inseparable *trans/cis* isomers were isolated.

Scheme 41 Studies of Horner-Wadsworth-Emmons Reactions

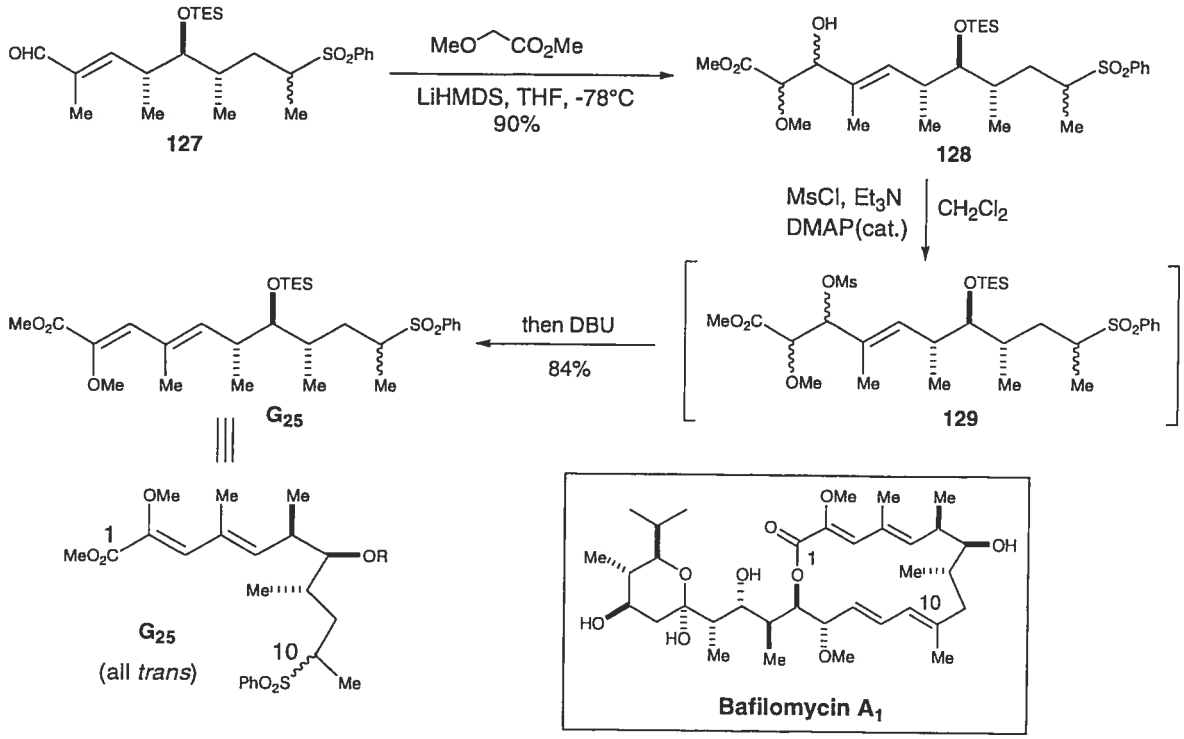


♦ 7-2-5 Synthesis of sulfone G_{25}

We decided to use another protocol to solve this problem (**Scheme 42**). Condensation of the allylic aldehyde **127** with the lithium enolate of methyl methoxyacetate gave the alcohol **128**, which was activated by forming mesylate **129** to effect elimination. After the mesylation reaction was complete, DBU was added to the reaction mixture and only the *trans*-product was formed in 84% yield.

The stereochemistry of the newly formed double bond was further confirmed by comparing ^{1}H NMR spectra of $\mathbf{G_{25}}$ with that of a segment obtained from degradation of Bafilomycin A_1. Thus, segment $\mathbf{G_{25}}$ was successfully synthesized for compound **1** and it is equivalent to the C_1-C_{10} segment of Bafilomycin A_1.

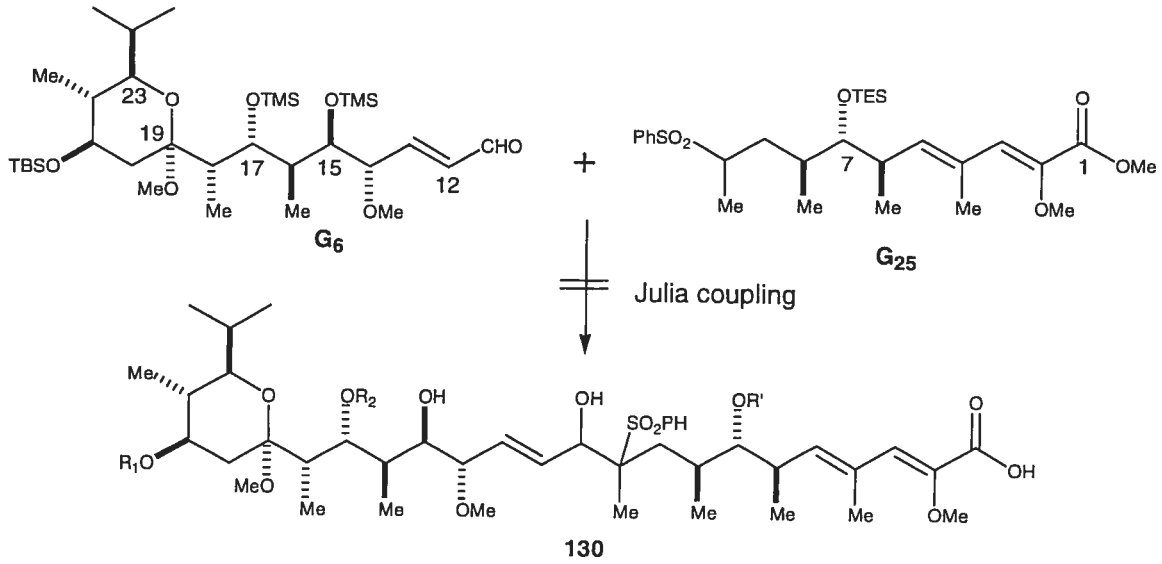
Scheme 42 Synthesis of sulfone G_{25}



♦ 7-2-6 Coupling problems

Unfortunately, attempts to join the sulfone G_{25} and the aldehyde G_6, which was obtained from degradation of Bafilomycin A_1, were unsuccessful (**Scheme 43**) using various conditions. We then decided to explore the Nozaki-Kishi coupling protocol[140] as a coupling method.

Scheme 43 Attempted Julia coupling

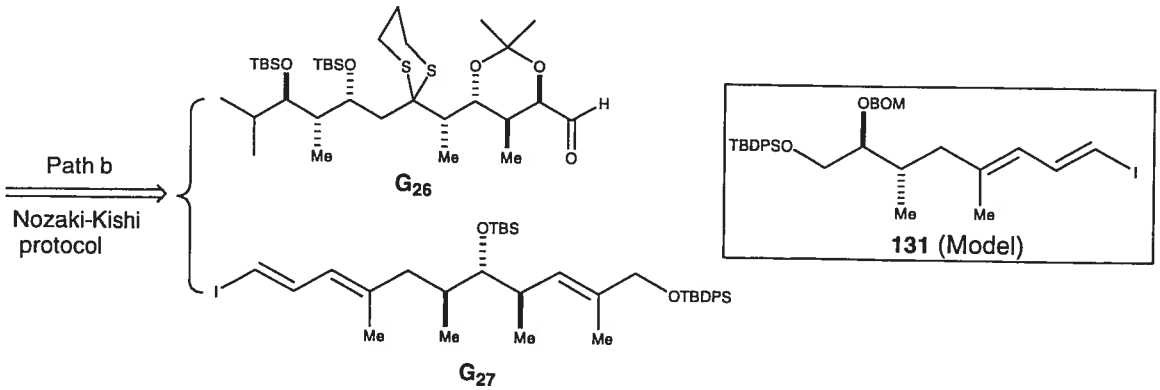


Part three Nozaki-Kishi coupling method

♦ 7-3-1 Synthesis of the model compound

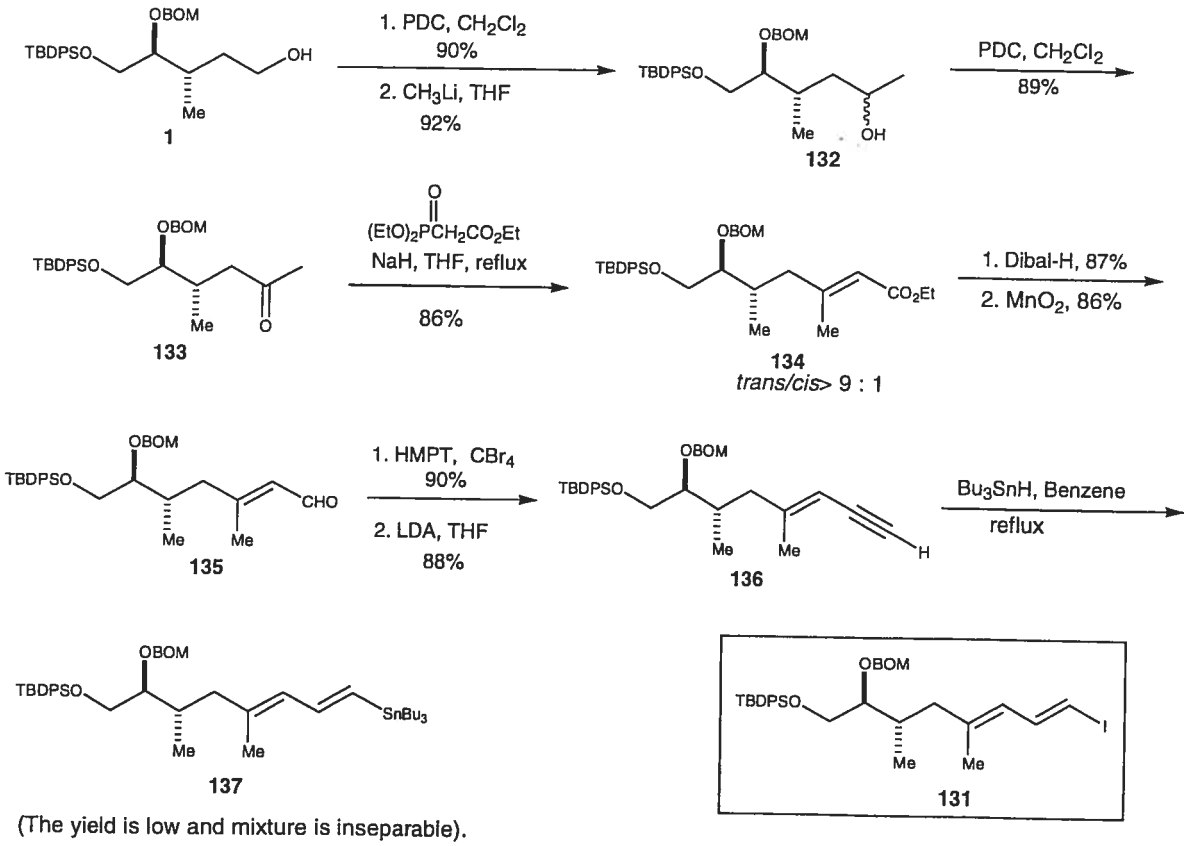
For this approach, the aldehyde G_{26} and dienic iodide G_{27} had to be synthesized (**Scheme 44**). This time, we decided to do some model studies using compound **131**.

Scheme 44 Nozaki-Kishi method



The attempted synthesis of the model compound **131** is shown in **Scheme 45**. Oxidation of alcohol **1** with PDC provided the corresponding aldehyde which was treated with MeLi to generate the secondary alcohol **132** in excellent yield. The alcohol **132** was oxidized to the ketone **133** which underwent a Horner-Wadsworth-Emmons reaction in refluxing THF, providing the α,β-unsaturated ester **134** with a ratio of *trans/cis* greater than 9:1. Reduction of the ester **134** with Dibal-H in toluene followed by oxidation with MnO_2 afforded α,β-unsaturated aldehyde **135** which was subjected to a Corey-Fuchs reaction[148] to give the enyne **136** in good yield.

Scheme 45 Synthesis towards model **131**

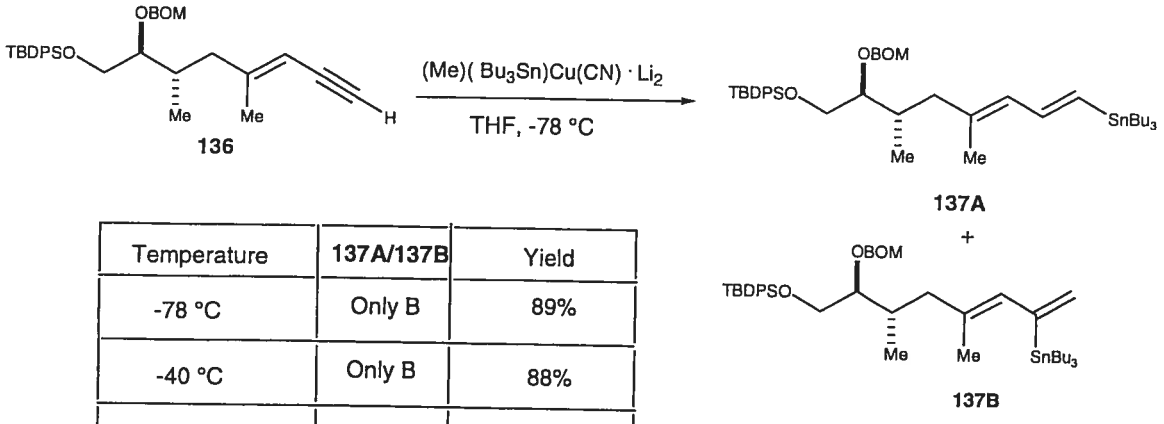


At this point, we tried to convert the enyne into dienic stannane **137**. First, we tried a radical hydrostannylation reaction with Bu_3SnH in refluxing benzene and unfortunately, the reaction turned out to be low yielding. Hydroboration[149] of **136** with catecholborane and 9-BBN was tried, but either no reaction occurred or complex products resulted. Hydrozirconation[150] of enyne **136** generated a mixture in which the BOM protecting group had been removed.

♦ 7-3-2 Synthesis studies towards the dienic iodide using cuprate reagents

We then decided to try a tributyltin cuprate addition reaction[151] to convert the enyne **136** to the dienic stannane **137A**. The methyl tributyltin cuprate was tested first and the results were summarized in **Scheme 46**. In the temperature range –78 °C to –20 °C, only the internal addition product **137B** was obtained in very good yield.

Scheme 46 Methyl tributyltin cuprate addition to enyne **137**

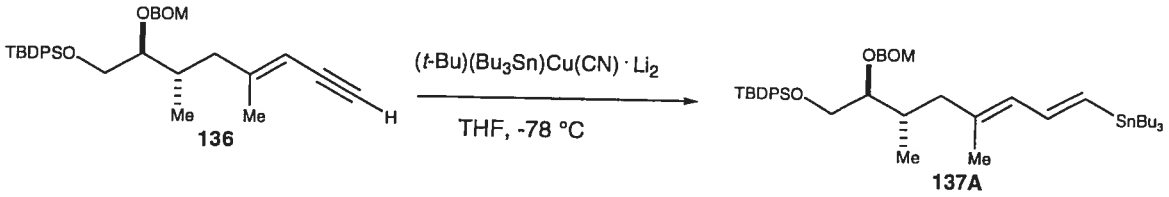


Temperature	137A/137B	Yield
-78 °C	Only B	89%
-40 °C	Only B	88%
-20 °C	Only B	86%

In the hope that increasing the size of the "R" group in the tributyltin cuprate would produce more **137A** instead of **137B**, we tried *t*-butyl tributyltin cuprate. Only the internal

addition product **137B** was produced in good yield when the reaction was carried out at –78 °C. As the reaction temperature was increased from –78 °C, more and more of the desired external addition product **137A** was obtained.

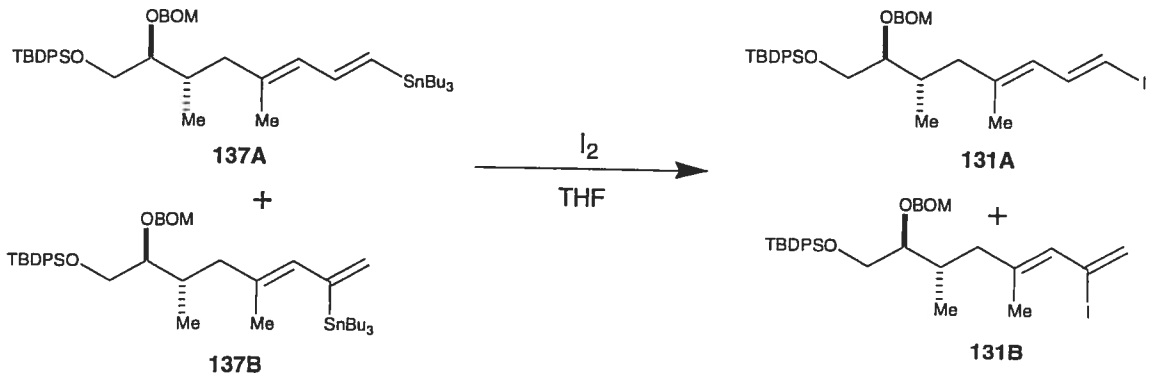
Scheme 47 *t*-Butyl tributyltin cuprate addition to enyne **136**



Temperature	137A/137B	Yield
-78 °C	Only B	90%
-40 °C	1 : 1	88%
-20 °C	2 : 1	87%
0 °C	3 : 1	85%
r. t	4 : 1	83%

The ratio of **137A** to **137B** could be increased to 4:1 when the reaction was carried out at room temperature. Unfortunately, **137A** and **137B** were inseparable by column chromatography and they were also unstable on silica gel even when 1% of Et_3N was used as stabilizer in the eluting solvent. Treatment of the crude mixture of **137A** and **137B** with iodine generated the corresponding mixture of the dienic iodides **131A** and **131B**, but the two isomers were inseparable by column chromatography and were also unstable on silica gel (**Scheme 48**). It became clear that it is not easy to synthesize the diennic iodide $\mathbf{G_{27}}$. Our next and final choice was to try a Stille coupling.

Scheme 48 Transformation of the dienic stannanes to dienic iodides

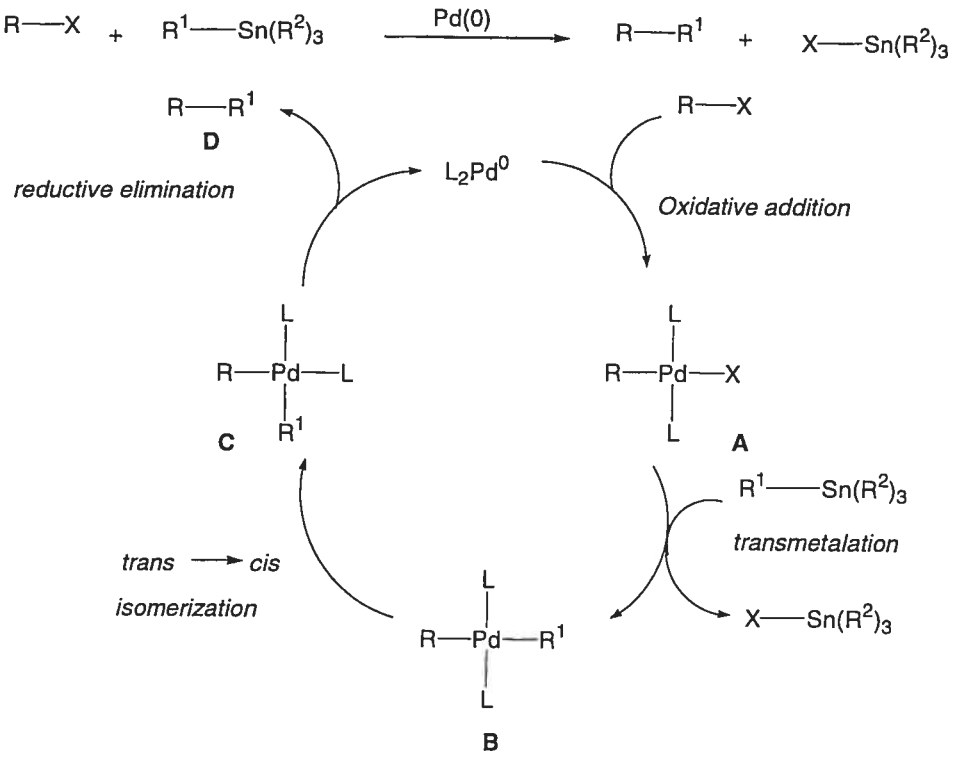


Part four The Stille coupling method

♦ 7-4-1 Mechanism of the Stille coupling

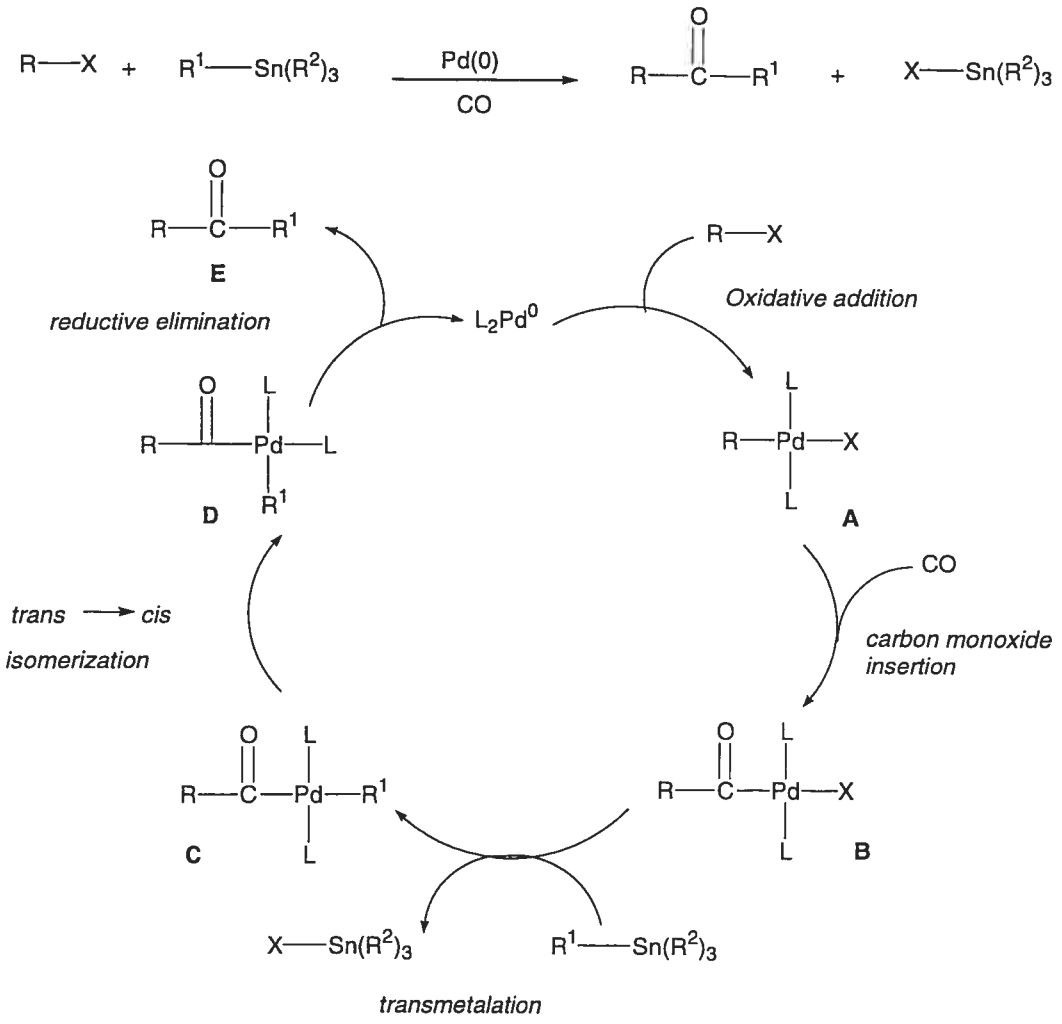
The late Professor J. K. Stille pioneered the development of a very effective and versatile palladium-mediated C-C bond forming method: the palladium-catalyzed cross-coupling of organic electrophiles with organostannanes.[152] This process continues to enjoy much success in organic synthesis because it proceeds in high yields under mild reaction conditions and because it tolerates a variety of functional groups (e. g. CO_2R, CN, OH and even CHO) on either coupling partner. An additional virtue of this palladium-catalyzed coupling process is that a wide variety of organic electrophiles and organotin reagents can be utilized. The catalytic cycle is shown in **Figure 17**.

Figure 17 Catalytic cycle of the Stille coupling reaction[152a]



It is presumed that a coordinatively unsaturated 14-electron palladium (0) complex such as bis(triphenylphosphine)palladium (0) serves as the catalytically active species.[152a] An oxidative addition of the organic electrophile, RX, to the palladium catalyst generates a 16-electron palladium (II) complex **A**, which then participates in a transmetalation with the organotin reagent (see **A**→**B**). After facial *trans*→*cis* isomerization (see **B**→**C**), a reductive elimination releases the primary organic product **D** and regenerates the catalytically active palladium (0) complex. If the coupling reaction is conducted in the presence of carbon monoxide, the two coupling partners become linked through a carbonyl bridge, giving rise to a ketone. The catalytic cycle presented in **Figure 18** serves as a working model for this variant.[152a]

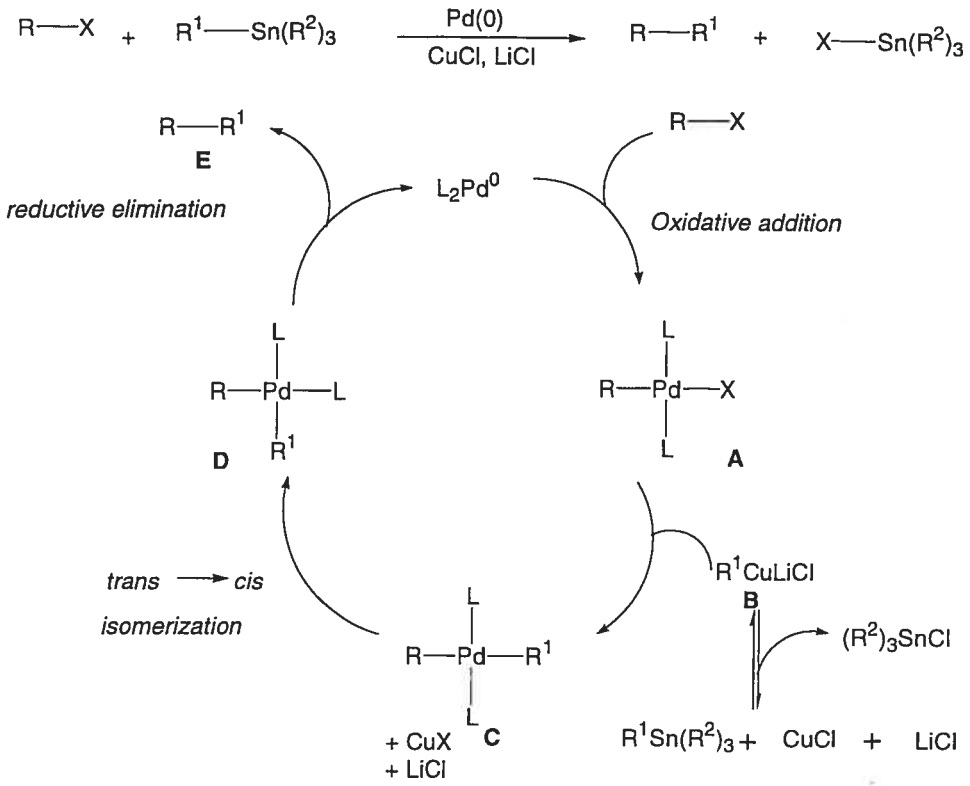
Figure 18 Catalytic cycle of the Stille reaction in the presence of carbon monoxide[152a]



♦ 7-4-2 Ligands and effects of copper in the Stille coupling

Later it was found that using $AsPh_3$ as ligand in place of PPh_3 greatly accelerated the Stille reaction because the weak chelation of $AsPh_3$ to palladium accelerates the rate-determining step, (transmetalation A→B in **Figure 17**).[153] Another modification that accelerates the Stille coupling is to add a copper salt like CuCl. The proposed mechanism[154] by Professor Corey is shown in **Figure 19**.

Figure 19 The effects of copper in the Stille coupling reaction[154]



According to the proposal, the function of the CuCl is to convert the vinystannane to a vinylcopper (I) species **B** (or a variant with respect to coordination/aggregation). Because species **B** is a more reactive metalloid (RCu) than the initial organostannane ($R^1SnR^2_3$), the rate-determining step (transmetallation) is greatly accelerated and the reaction proceeds faster. The $Pd(PPh_3)_4$/CuCl/LiCl system discovered by Professor Corey and his group is very efficient and many Stille coupling reactions which otherwise fail can be carried out efficiently.

Despite the great synthetic utility of the Stille coupling, a historic drawback of this reaction has been its reliance on stoichiometric quantities of toxic, costly and

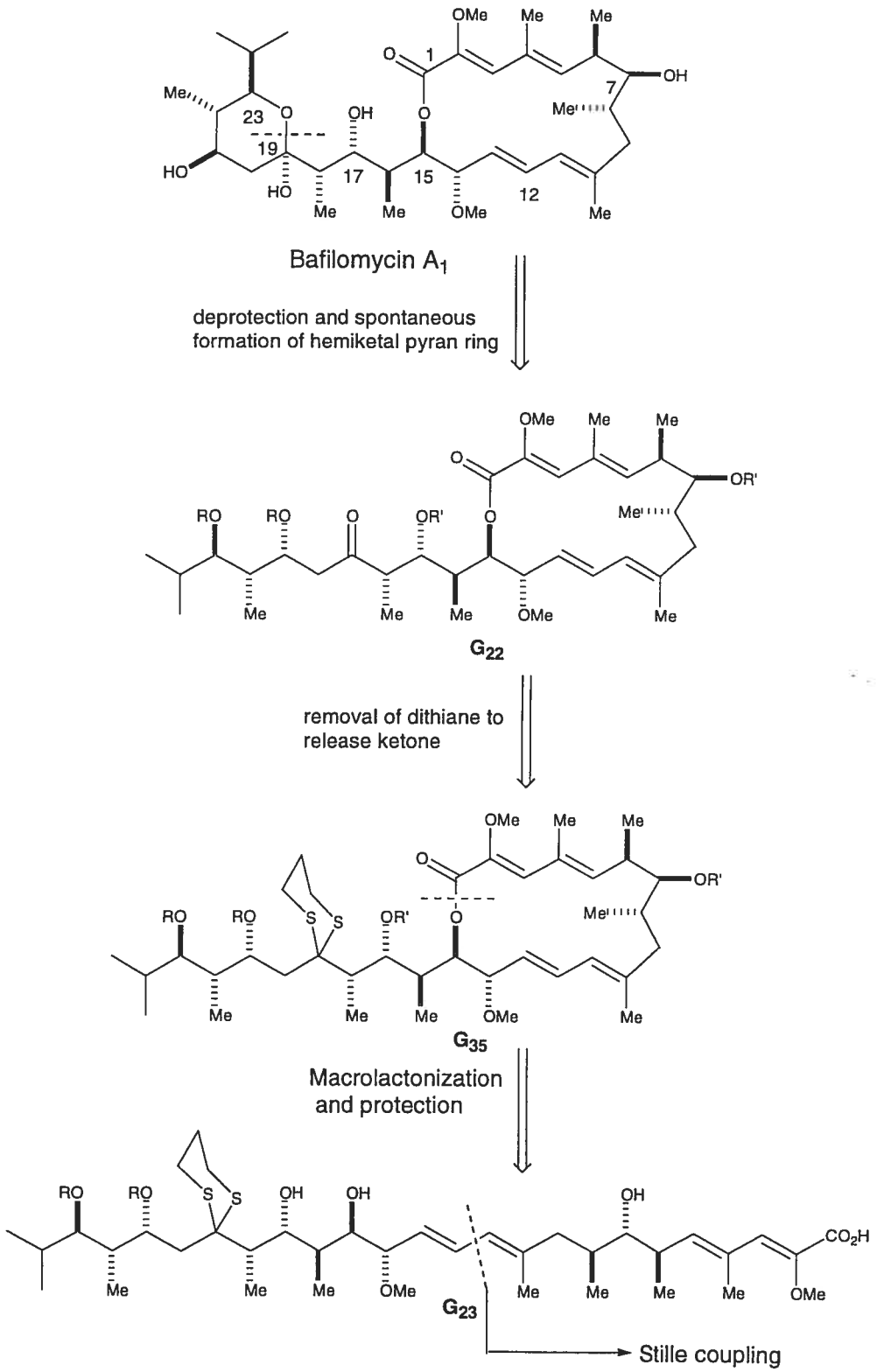
occasionally unstable organostannanes.[155] Therefore, a Stille reaction using catalytic amounts of tin would be of considerable benefit. Promising results have been reported by Professor Maleczka and his group.[156]

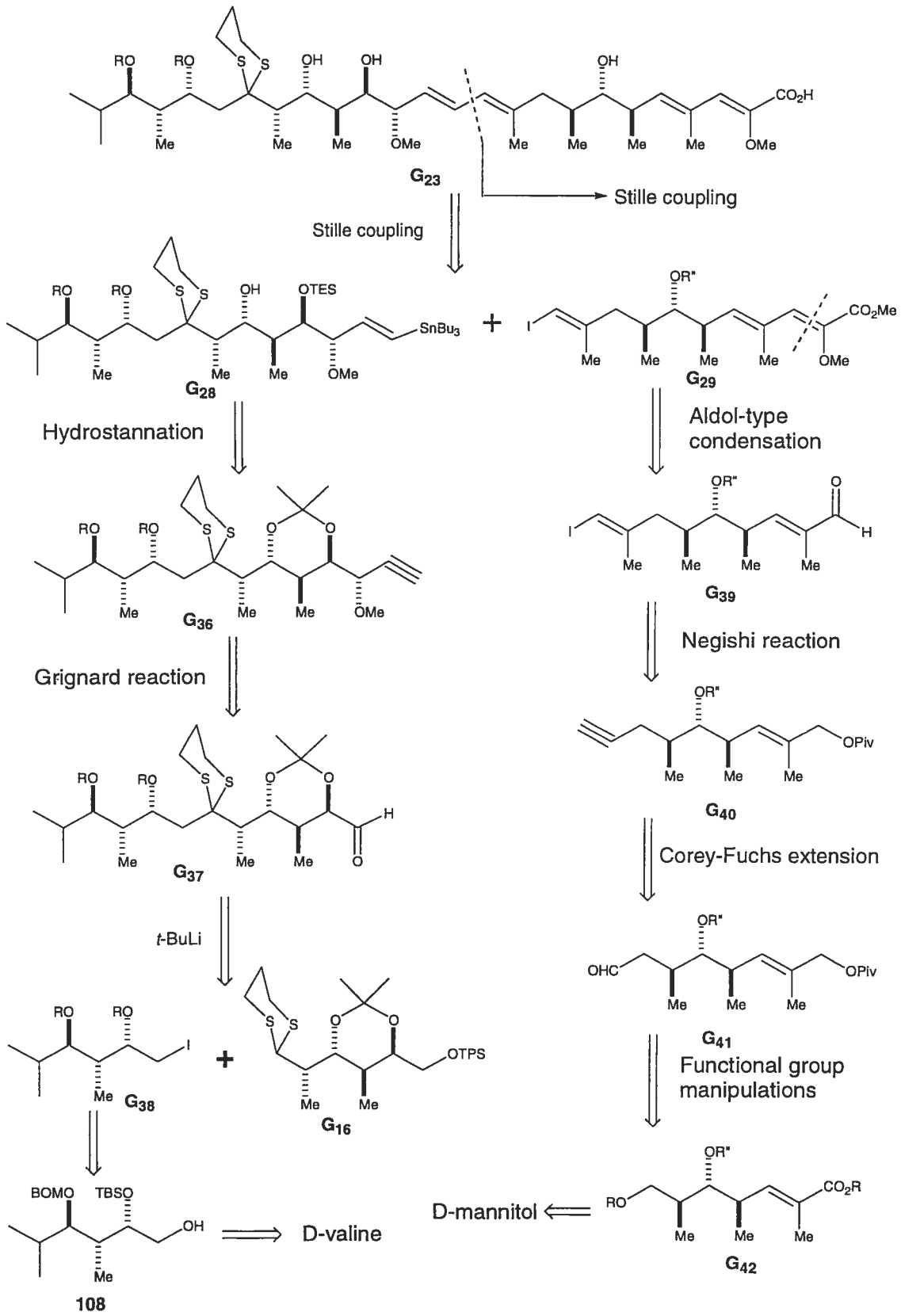
♦ 7-4-3 Retrosynthetic analysis of BafilomycinA_1 using the Stille coupling method

We decided to use the Stille coupling protocol for the total synthesis which would require the two segments $\mathbf{G_{28}}$ and $\mathbf{G_{29}}$ (in **Scheme 37**). In order to avoid spiroketal formation as described in **Scheme 36**, we decided to generate the pyran hemiketal in the last stage of the synthesis. This new strategy is depicted in **Scheme 49**. Bafilomycin A_1 would be obtained by deprotection of the ketone $\mathbf{G_{22}}$ and spontaneous formation of the hemiketal pyran ring. Ketone $\mathbf{G_{22}}$ could be generated by deprotection of the dithiane of $\mathbf{G_{35}}$ which would arise from the seco-acid $\mathbf{G_{23}}$ by macrolactonization followed by the protection of the two hydroxy groups at the C_{17} and C_7 positions. This strategy avoids the oxymercuration reaction that was observed during the chemical modification of Bafilomycin A_1.[157]

The seco-acid $\mathbf{G_{23}}$ was envisaged to arise from vinylstannane $\mathbf{G_{28}}$ and vinyl iodide $\mathbf{G_{29}}$ via a Stille coupling followed by deprotection and then hydrolysis. The vinylstannane $\mathbf{G_{28}}$ would be generated by palladium-catalyzed hydrostannylation of the acetylene $\mathbf{G_{36}}$, which would be obtained by nucleophilic addition of ethynylmagnesium bromide on the aldehyde $\mathbf{G_{37}}$ followed by protecting group adjustment. The aldehyde $\mathbf{G_{37}}$ would be generated by a condensation of the iodide $\mathbf{G_{38}}$ and the dithian $\mathbf{G_{16}}$ followed by deprotection and oxidation reactions.

Scheme 49 Retrosynthetic analysis-the Stille coupling method



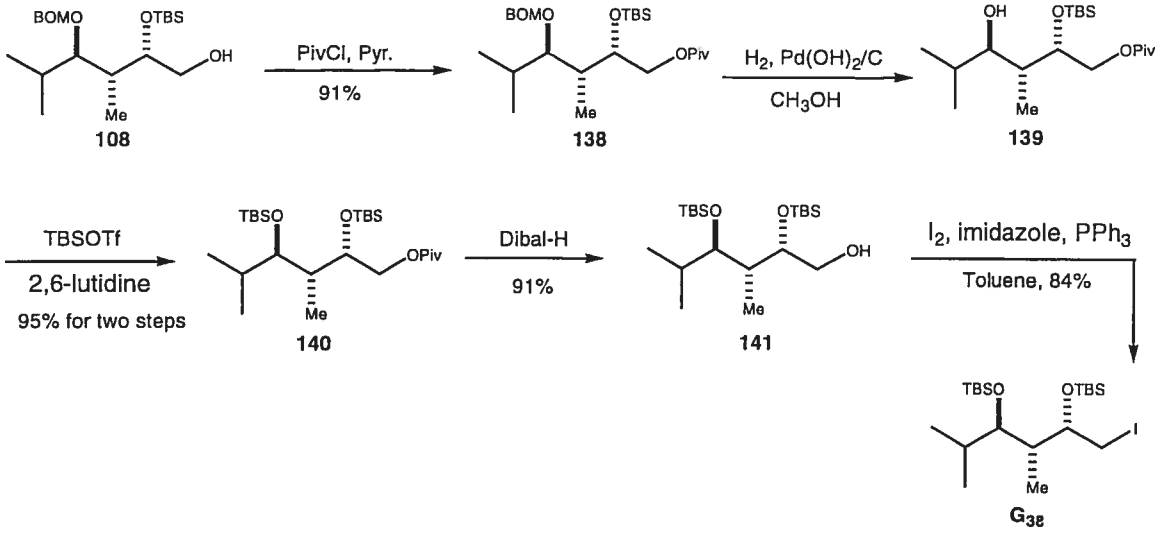

RO
RO
S
S
OH
OH
OH
CO2H
Me
Me
Me
OMe
Me
Me
Me
Me
OMe
G23
Stille coupling
Stille coupling
OTES
SnBu3
OR"
CO2Me
I
OMe
G28
G29
Hydrostannation
Aldol-type condensation
O
H
G36
G39
Grignard reaction
Negishi reaction
OPiv
G37
G40
t-BuLi
Corey-Fuchs extension
OHC
G41
G38
OTPS
G16
Functional group manipulations
BOMO
TBSO
D-mannitol
CO2R
D-valine
108
G42

Iodide G_{38} could be obtained from **108** by manipulations of the protecting groups. This time, we decided to replace the BOM protecting group with TBS because our early studies proved that removal of the BOM group at a later stage was difficult.[158] The ester G_{29} would be obtained from G_{39} by an aldol type condensation and α,β-elimination. Aldehyde G_{39} would be generated from the acetylene G_{40} by a Negishi reaction followed by deprotection and oxidation reactions. The acetylene G_{40} could arise from the aldehyde G_{41} by a Corey –Fuchs reaction[148] and G_{41} could be obtained by functional group manipulations of G_{42} which could be generated from D-mannitol.

♦ 7-4-4 Synthesis of iodide G_{38}

Scheme 50 summarizes the synthesis of the iodide compound G_{38} originally from D-valine.

Scheme 50 Synthesis of iodide compound G_{38}



Protection of the hydroxy group in **108** as the pivaloyl ester led to **138** from which the BOM group was removed with hydrogenation to generate the alcohol **139**. Without

purification, the crude alcohol **139** was reacted with TBSOTf to give **140,** and then the pivaloyl group in **140** was removed with Dibal-H to afford the primary alcohol **141**, which was treated with iodine, PPh_3 and imidazole to generate $\mathbf{G_{38}}$ in good yield.

♦ 7-4-5 Synthesis of vinyl iodide G_{29}

The construction of the vinyl iodide subunit $\mathbf{G_{29}}$ is shown in **Scheme 51**. This synthesis started out with alcohol **1** in which the hydroxy group was protected as a MOM ether to give **142**. Removal of the TBDPS group of **142** with TBAF followed by Swern oxidation and Wittig reagent provided the γ-alkoxy-α,β-unsaturated ester **144**. We were now in a position to try the pivotal two-directional cuprate additions for this synthesis.

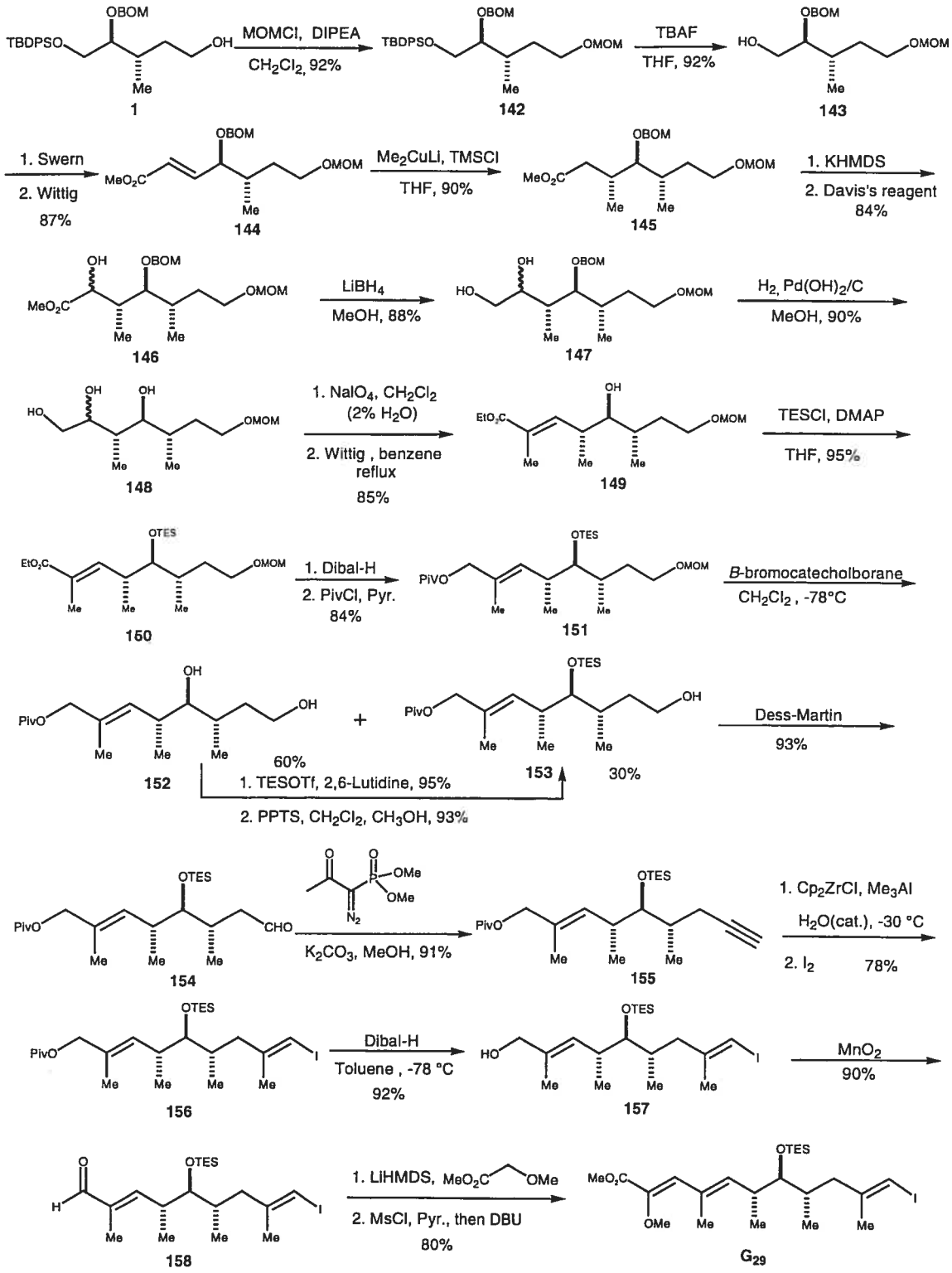
Conjugate addition of lithium dimethyl cuprate to **144** with TMSCl as an additive at –78°C afforded **145** in 90% and with a ratio over 20:1. Treatment of the potassium enolate of **145** with Davis reagent led to the α-hydroxy ester **146** which was further reduced to the diol **147** with $LiBH_4$. The BOM protecting group of **147** was removed at this stage to avoid functionality incompatibility.

Oxidative cleavage of the two vicinal hydroxy groups of the triol **148** with $NaIO_4$ afforded the corresponding aldehyde which, when treated with ethyl 2-(triphenylphosphoranylidene)propionate in benzene at refux,[147] led after TES protection to the *trans*-olefin **150**. Reduction of the ester **150** with Dibal-H followed by protection with pivaloyl group generated **151** in high yield.

In order to introduce the vinyl iodide functionality, the MOM protecting group of **151** had to be removed and B-bromocatecheborane was chosen for this purpose,[159] affording the desired alcohol **153** in 30% yield, accompanied by a major quantity of diol **152.** The diol **152** was efficiently converted to **153** in a two-step procedure: protection of the diol with TES groups and selective removal of the primary TES group with PPTS. Choosing the proper solvent is very important for the second step because no reaction was observed when only CH_2Cl_2 was used and both of the TES groups were removed in MeOH. After numerous experiments, it was found that a CH_2Cl_2-MeOH (3:1) system gave the best selectivity. Oxidation of alcohol **153** under Dess-Martin conditions generated aldehyde **154** which was further converted to the acetylenic intermediate **155** in high yield. Particularly the diazophosphonate method[160] (97%) proved much more efficient than the venerable Corey-Fuchs procedure[148] (72%).

Iodination utilizing the modified Negishi protocol[161] provided vinyl iodide **156** in 72% and was followed by deesterification with Dibal-H to give the alcohol **157**. Oxidation of the allylic alcohol **157** with MnO_2 afforded the α,β-unsaturated aldehyde **158** which underwent a simple aldol condensation with lithium 2-methoxyacetate, followed by mesylation of the resulting alcohol and β-elimination with DBU to introduce the α-methoxy ester group maintaining a *trans*-dienic geometry. Much to our satisfaction the resulting subunit $\mathbf{G_{29}}$ was stereochemically pure by ^{1}H NMR spectroscopy.

Scheme 51 Synthesis of vinyl iodide G_{29}



♦ 7-4-6 Synthesis of vinylstannane G_{28}

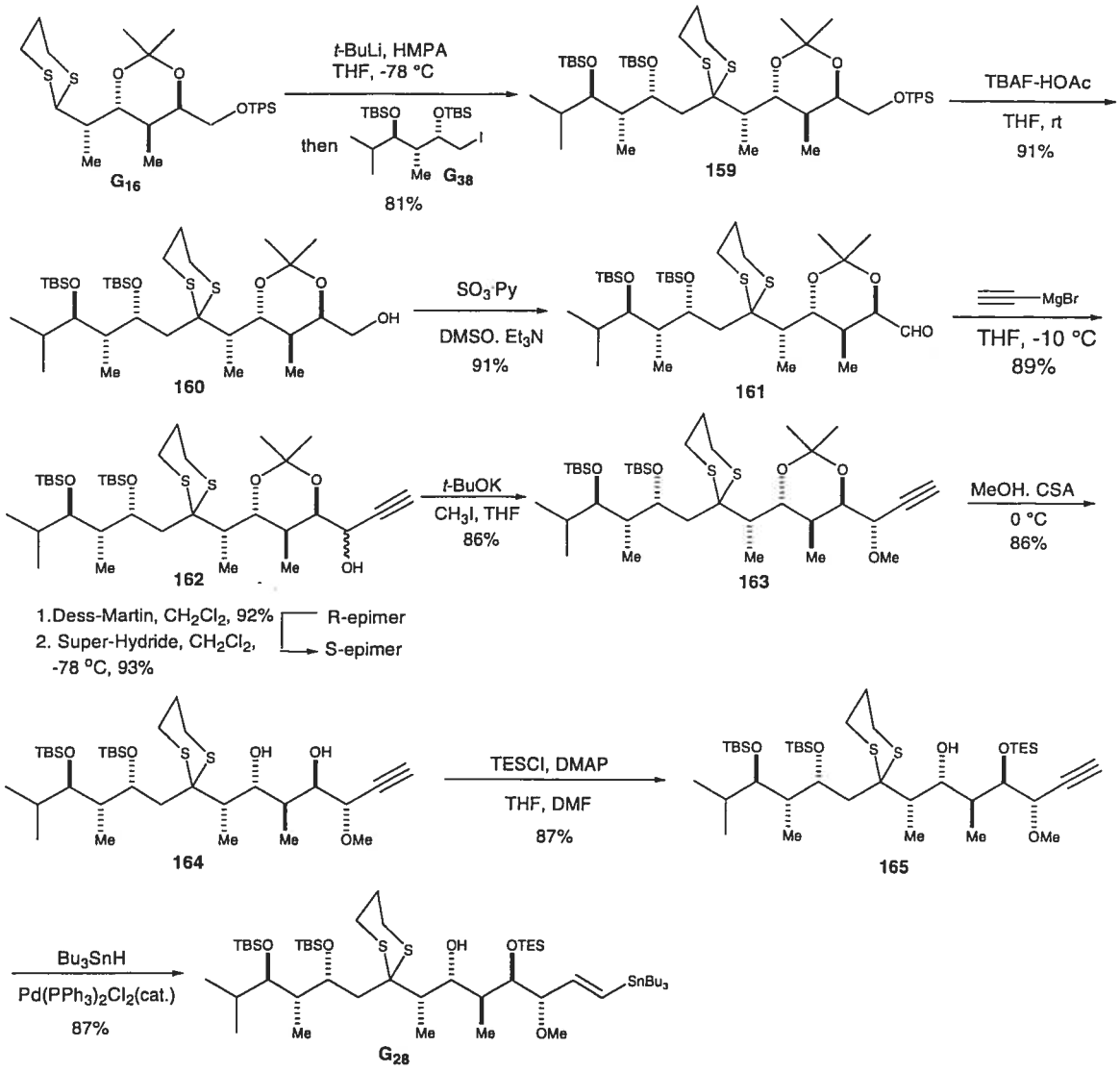
The elaboration of the entire vinylstannane subunit $\mathbf{G_{28}}$ is shown in **Scheme 52**. Thus, generation of the dithiane anion of $\mathbf{G_{16}}$ with *t*-butyllithium in a mixture of THF and HMPA, and condensation with the iodide $\mathbf{G_{38}}$ provided **159** in 84% yield. In order to introduce the vinylstannane group and an acetylenic alcohol having an *S*-configuration at C_{14}, the TBDPS ether of **159** was selectively cleaved with TBAF-AcOH complex and the resulting alcohol **160** was oxidized to the aldehyde **161** using the Doering-Parikh reagent.[104] Other oxidative methods such as Swern were also tried but the reactions either did not occur or the desired product was formed in low yield.

Treatment of the aldehyde **161** with ethynylmagnesium bromide in THF at –10 °C generated the separable acetylenic alcohols **162**. The undesired *R*-isomer of **162** was easily converted to the desired *S*-isomer of **162** by two step-sequence, oxidation of the alcohol to ketone and then reduction the ketone to desired S-isomer of **162.** For the oxidation, the Dess-Martin reagent proved more efficient because Swern and Doering-Parikh oxidations did not work. Although oxidation with MnO_2 resulted in an 80% yield of the corresponding ketone, the reaction was slow.

Reduction of the ketone to the desired *S*-isomer of **162** was successfully carried out with Super hydride. As reported in the original reference,[162] CH_2Cl_2 was found to be the best solvent because it does not interfere with the coordination between the ketone and the reagent. The oxidation-reduction sequence led to the desired isomer of **162**, which would be ascertained later through completion of the synthesis of Bafilomycin A_1. Methylation

of the hydroxy group of **162** with *t*-BuOK as base proved to be efficient, but using NaH as base gave a low yield.

Scheme 52 Synthesis of vinylstannane G_{28}



According to our previous work, it was necessary to remove the C_{15}-C_{17} isopropylidene acetal at this juncture and to use protective groups that would be removed easily without affecting the final target structure or intermediates leading to it. With this in mind, the acetonide group of **163** was carefully removed with CSA in MeOH. The reaction was

carefully monitored with TLC and the reaction was quenched when the by-product was formed. Treatment of the diol **164** with TESCl and imidazole in THF-DMF for 18 h provided the mono-TES ether **165** in very good yield. Finally, treatment of **165** with tributyltin hydride in the presence of a catalytic quantity of bistriphenylphosphine palladium (II) chloride led to the desired vinylstannane subunit $\mathbf{G_{28}}$ in a highly stereocontrolled manner. The coupling constant between H_1 and H_2 of the alkene was found to be 19.08 Hz, which confirmed the *trans*-alkene stereochemistry.

♦ 7-4-7 The Stille coupling and macrolactonization

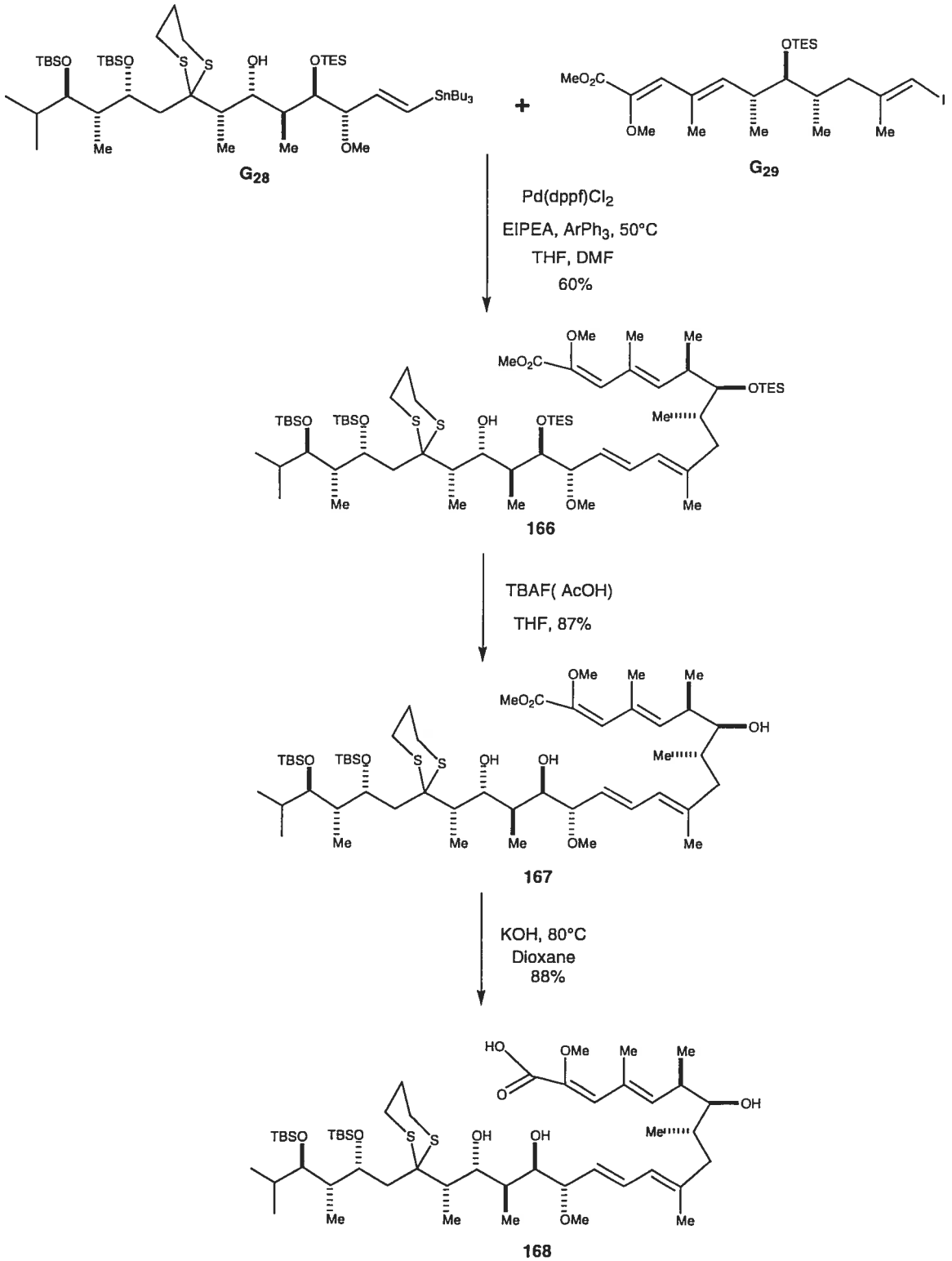
With chirons $\mathbf{G_{28}}$ and $\mathbf{G_{29}}$ in hand, we were in a position to try the Stille coupling reaction. Although the previous syntheses[127, 128] also used a Stille coupling protocol to join segments in the total synthesis of Bafilomycin A_1, their precursors for the coupling were not as fully functionalized as our segments $\mathbf{G_{28}}$ and $\mathbf{G_{29}}$. Furthermore, $\mathbf{G_{28}}$ contained the dithiane group in a Stille coupling, which has few precedents. The initial results using $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ or $Pd(dppf)Cl_2$ as the catalysts for this Stille coupling were discouraging and no coupling was observed. Curiously, $Pd(dppf)Cl_2$ in DMF was the catalyst used by Toshima[128] in the Stille coupling of two short segment in their work of total synthesis of Bafilomycin A_1. However, using a $Pd(dppf)Cl_2$, Hunig base[163] and triphenylarsine system for the Stille coupling was successful, providing the seco-ester **166** in 60% yield (**Scheme 53**). This reaction indicates that the dithiane group does not interfere with the Stille coupling reaction if present in the vinylstannane segment. Our results agree with Smith's work in their total synthesis of Rapamycin.[164] In their work, when the dithiane group was on the vinyl iodide segment, the Stille coupling reaction was

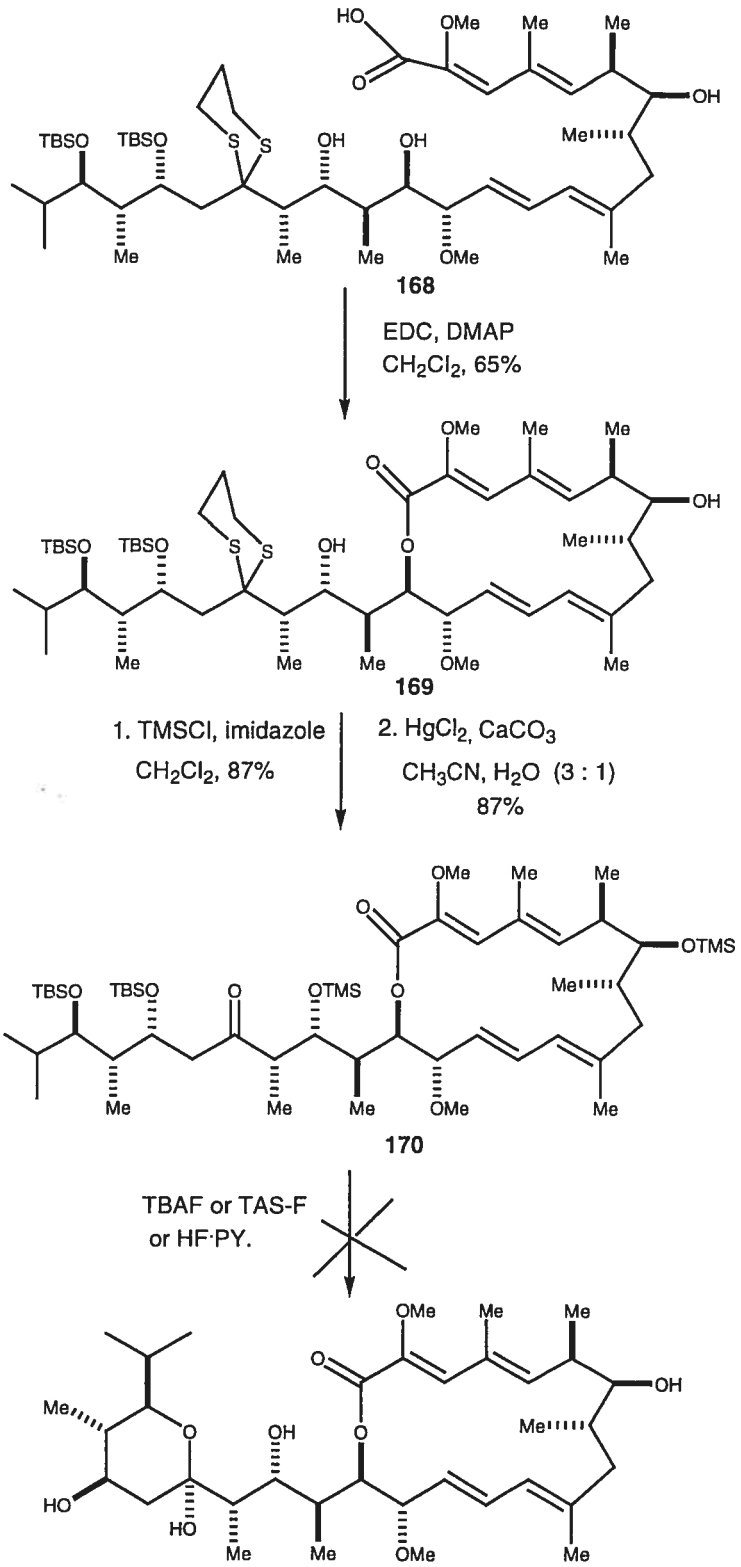
retarded. This is presumably because strong chelation between sulfur and palladium occurred after the oxidative addition (**Figure 17**), which hindered the transmetalation step. After they interchanged the vinylstannane and the vinyl-iodide groups, and the dithiane group was on the vinylstannane segment, the Stille coupling occurred without problem.

With the pivotal Stille coupling successfully carried out, we focused our attention on macrolactonization. To do this, we had to deprotect the C_{15} hydroxy group and to hydrolyze the ester. In this event, we found that a mixture of TBAF and acetic acid was highly effective in the selective cleavage of the C_7 and C_{15} TES ethers to afford **167** in the presence of the C_{21} and C_{23} TBS ethers. Hydrolysis of the ester was found to be easier when potassium hydroxide was used in aqueous dioxane at 80°C and afforded the desired seco-acid **168** in excellent overall yield. With the seco-acid in hand, we were now poised to try the macrolactonization reaction. The previous syntheses of the short subunit of Bafilomycin A_1 have succeeded in the macrolactonization reactions adopting the Yamaguchi protocol[165] to give the 16-membered lactone. We used the traditional EDC, DMAP coupling protocol[166] which afforded a 65% yield of the lactone **169**.

Up to this point, the only remaining problem was to remove all the protecting groups. We were aware that the previous work in the manipulation of Bafilomycin A_1 in the presence of mercuric chloride indicated that the oxymercuration reaction led to tetrahydrofuran ring involving the C_7 hydroxy group and the C_{10}-C_{11} double bond.[157]

Scheme 53 The Stille coupling and macrolactonization





Bafilomycin A_1

We decided to protect the hydroxy groups in the C_7 and C_{17} positions with TMS groups before we did the dethioacetalization reaction with mercuric chloride to generate the ketone **170**. The only task remaining for the total synthesis was to remove all the silyl protecting groups. Unfortunately, various fluoride reagents such as TBAF, TBAF-AcOH, TAS-F[167] and HF·Py did not lead the desired natural product.

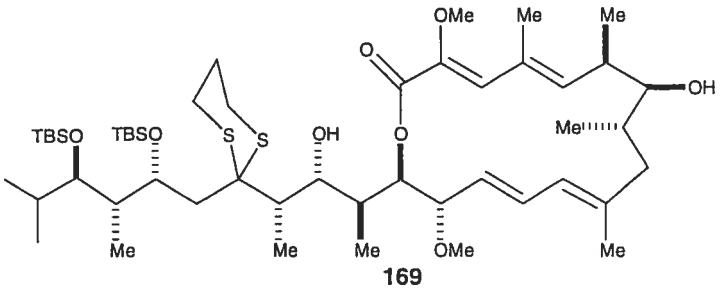
♦ 7-4-8 Total synthesis of Bafilomycin A_1

We figured that the α,β elimination reaction of the ketone was a fast reaction under these conditions and we decided that the ketone should be released in the last stage of the total synthesis (**Scheme 54**). Accordingly, the two TBS groups were removed with p-toluenesulfonic acid in methanol to give **171** in 86% yield. Finally, treatment of **171** with mercuric chloride and calcium carbonate in aqueous acetonitrile effected smooth dethioacetalization to afford crystalline Bafilomycin A_1, identical in all respects with an authentic sample.

♦ 7-4-9 Summary

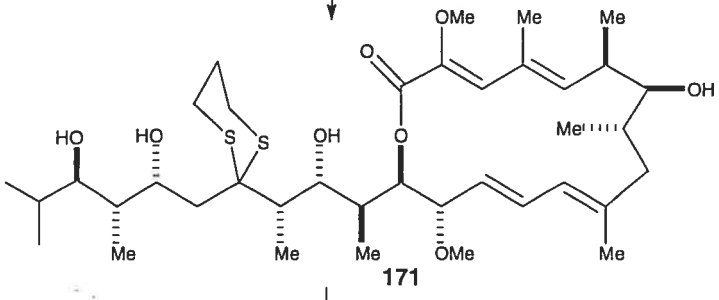
In summary, the natural macrolide BafilomycinA_1 was successfully synthesized originally from D-mannitol and D-valine using stereocontrolled cuprate conjugate additions and α-hydroxylation to efficiently install all the chiral centers. The Stille coupling reaction was used to join the two long fully assembled segments and macrolactonization was accomplished with a Keck reaction. This work further proves the power of stereocontrolled cuprate conjugate additions and α-hydroxylation developed in our group and used in the total synthesis of a natural compound.

Scheme 54 Total synthesis of Bafilomycin A_1



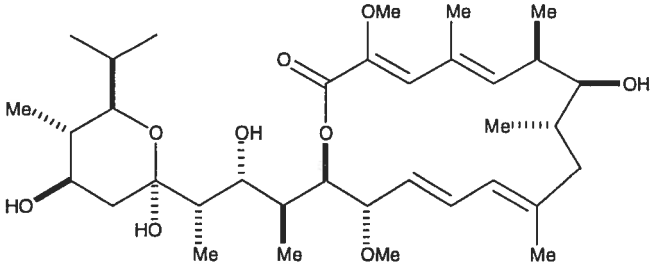
169

TsOH
MeOH, 86%



171

$HgCl_2$, $CaCO_3$
CH_3CN, H_2O (3 : 1)
85%



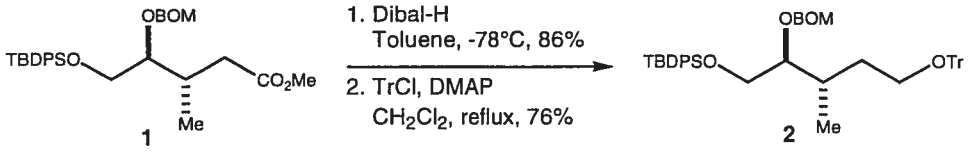
Bafilomycin A_1

EXPERIMENTAL PART

Materials and Methods. All commercially available reagents were used without further purification unless otherwise noted. All solvents were reagent grade and distilled under positive pressure of dry nitrogen before use. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Dichloromethane, benzene and diisopropylamine were distilled from calcium hydride. Triethylamine and diisopropylethylamine was freshly distilled from calcium hydride and stored over potassium hydroxide. Hexamethylphosphoramide was freshly distilled from calcium hydride and stored on 4Å molecule sieves. All reactions were performed under nitrogen atmosphere in oven or flame-dried glassware. Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography with 0.25-mm E. Merck pre-coated silica gel plates. Flash column chromatography was performed on E. Merck silica gel 60 (40-60 μm) using ethyl acetate/hexane (E/H) in different ratios. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR (^{1}H, ^{13}C) spectra were recorded on a Bruker AM-300 MHz or a Bruker AM-400 MHz spectrometer either in $CDCl_3$ with $CHCl_3$ (H, δ = 7.26 ppm: C, δ = 77.0 ppm) or in C_6D_6 with C_6H_6 (H, δ = 7.26 ppm: C, δ = 128 ppm) as internal reference. X-Ray analysis was performed using graphite monochromatized Mo Kα radiation, and the structure was solved using direct methods (MULTAN80) and difference Fourier calculations (SHELX76). Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were measured at the University of Montreal Mass Spectrometry Service Centre with desorption chemical ionization (CI) or fast atom bombardment (FAB). Infrared spectra (IR) were recorded either in a chloroform solution or neat with

sodium chloride cell with a Perkin-Elmer Model 283B spectromer. Optical rotations were measured at the sodium line with a Perkin-Elmer model 241 polarimeter at ambient temperature. Melting points are uncorrected.

[(2*S*, 3*S*)-2-Benzyloxymethoxy-3-methyl-5-trityloxypentyloxy]-*tert*-butyldiphenylsilane (2):



To a solution of ester **1** (2.00 g, 3.84 mmol) in toluene (50 mL) at –78 °C was added Dibal-H (0.50 M, 23.18 mL, 11.53 mmol). The reaction mixture was stirred at –78 °C for 1 h before a solution of HCl (1 M, 60 mL) was added. The resulting mixture was warmed to room temperature and then extracted with hexane-ethyl acetate (1:1, 40 mL x 2). The combined organic layers were washed with $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:4) to give the product (1.64 g, 86%).

To a solution of the above alcohol (1.20 g, 2.43 mmol) in CH_2Cl_2 (30 mL) was added DMAP (0.71 g, 5.83 mmol) and trityl chloride (1.35 g, 4.86 mmol). The reaction mixture was heated at reflux for 24 h before a solution of saturated NH_4Cl solution (20 mL) was added. The mixture was extracted with hexane (30 mL x 2) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was

purified by column chromatography on silica gel (E/H=1:20) to give product **2** (1.35 g, 76%) as a colorless oil;

$[\alpha]_D$-15.49 ° (c 1.2, $CHCl_3$);

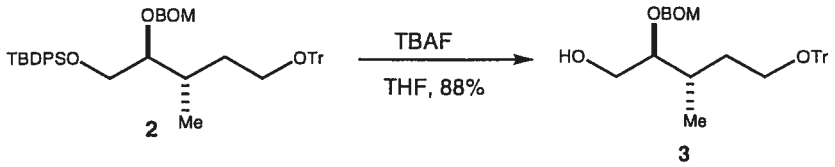
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J*=6.87 Hz, 1H), 1.12 (s, 9H), 1.40-1.54 (m, 1H), 1.90-2.02 (m, 1H), 2.06-2.17 (m, 1H), 3.06-3.14 (m, 1H), 3.20-3.28 (m, 1H), 3.66-3.70 (m, 1H), 3.74-3.90 (m, 2H), 4.60 (d, *J*=11.79 Hz, 1H), 4.73 (d, *J*=11.79 Hz, 1H), 4.87 (d, *J*=6.90 Hz, 1H), 4.97 (d, *J*=6.90 Hz, 1H), 7.20-7.50 (m, 26H), 7.73-7.77 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.77, 19.17, 26.84, 31.76, 32.17, 61.92, 64.39, 69.59, 82.47, 86.38, 94.74, 126.79, 127.51, 127.69, 127.79, 128.34, 128.67, 129.66, 133.47, 135.59, 135.63, 138.03, 144.47;

IR (thin film) νmax 2963, 2932, 2859, 1474, 1456, 1433, 1113, 846, 820, 743, 700 cm^{-1};

m/e: 732.1, 702.4, 689.2, 589.2, 484.1, 429.2, 386.4, 256.3.

(2*S*, 3*S*)-2-Benzyloxymethoxy-3-methyl-5-trityloxypentan-1-ol (3):



To a solution of ether **2** (1.50 g, 2.04 mmol) in THF (20 mL) at room temperature was added TBAF solution (1:1 complexed with acetic acid, 0.93 M, 6.00 mL, 5.58 mmol). The mixture was stirred at r.t for 6 h before a saturated solution of $NaHCO_3$ (30 mL) was added. The mixture was extracted with hexane-ethyl acetate (1:1, 50 mL x 2). The combined organic layers were washed with saturated $NaHCO_3$ solution, brine, dried over

Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:6) to afford product **3** (0.87 g, 88%) as a colorless oil;

$[\alpha]_D$ +16.77 ° (c 1.21, $CHCl_3$);

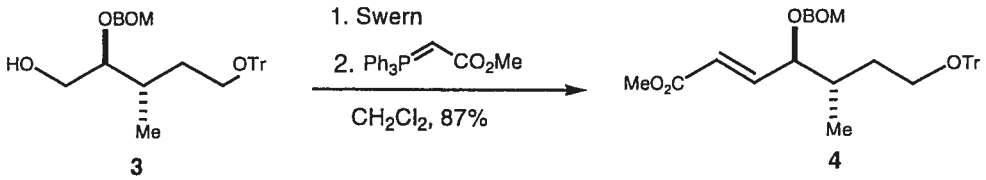
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J*=6.81 Hz, 3H), 1.40-1.50 (m, 1H), 1.82-2.04 (m, 2H), 3.04-3.14 (m, 1H), 3.18-3.24 (m, 1H), 3.42—3.50 (m, 1H), 3.60-3.82 (m, 2H), 4.60 (d, *J*=11.73 Hz, 1H), 4.73 (d, *J*=11.73 Hz, 1H), 4.74 (d, *J*=6.96 Hz, 1H), 4.90 (d, *J*=6.90 Hz, 1H), 7.24-7.52 (m, 20H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.63, 32.28, 32.48, 61.56, 63.33, 69.98, 86.34, 86.80, 95.51, 126.73, 127.59, 127.81, 128.39, 128.49, 137.65, 144.20;

IR (thin film) νmax 3340, 2935, 2863, 1471, 1429, 1113, 1028, 778, 701 cm^{-1};

m/e: 519.1, 487.1, 471.2, 429.1, 323.1, 243.1, 217.1, 197.1, 109.1, 91.1, 73.0.

(4*S*, 5*S*)-4-Benzyloxymethoxy-5-methyl-7-trityloxyhept-2-enoic acid methyl ester (4):



To a solution of oxalyl chloride (0.17 mL, 1.93 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added DMSO (0.21 mL, 2.89 mmol). The reaction mixture was stirred for 15 min before alcohol **3** (0.47 g, 0.96 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred and slowly warmed to –30 °C in about 30 min before triethylamine (0.54 mL. 3.85 mmol) was added. A white precipitate was formed and the mixture was stirred at this temperature for 15 min before being quenched by NH_4Cl solution (10 mL). The organic

layer was separated, dried and concentrated in *vacuo*. The crude aldehyde was dissolved in dry CH_2Cl_2 (15 mL) and $Ph_3P{=}CHCO_2CH_3$ (0.66 g, 1.93 mmol) was added to the solution. The mixture was stirred at r.t. for 6 h. The solvent was removed and the residue was purified by column chromatography (E/H=1:10) to give product **4** (0.46 g, 87%) as a colorless oil;

$[\alpha]_D$ -34.9 ° (c 0.96, $CHCl_3$);

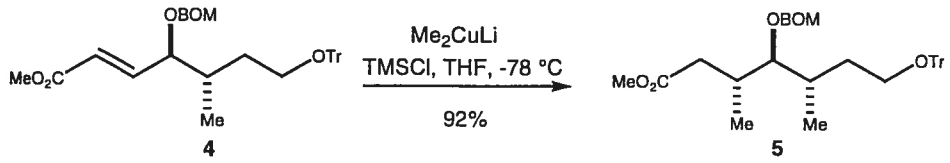
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J*=6.81 Hz, 3H), 1.38-1.50 (m, 1H), 1.79-1.91 (m, 1H), 1.92-2.09 (m, 1H), 3.02-3.13 (m, 1H), 3.13-3.23 (m, 1H), 3.76 (s, 3H), 4.10-4.16 (m, 1H), 4.54 (d, *J*=11.72 Hz, 1H), 4.65 (d, *J*=11.72 Hz, 1H), 4.71 (d, *J*=7.05 Hz, 1H), 4.74 (d, *J*=7.05 Hz, 1H), 5.95 (dd, *J*=1.23, 15.78 Hz, 1H), 6.84 (dd, *J*=6.60, 15.78 Hz, 1H), 7.20-7.38 (m, 14H), 7.42-7.50 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.22, 32.68, 34.56, 51.51, 61.51, 69.81, 79.48, 86.53, 92.90, 122.80, 126.88, 127.68, 127.74, 127.83, 128.39, 128.65, 137.72, 144.35, 146.26, 166.37;

IR (thin film) νmax 3033, 2950, 2865, 1724, 1494, 1452, 1278, 1027, 744, 700 cm^{-1};

m/e: 551.3 (M^++1), 503.1, 485.2, 429.0, 243.1, 165.1, 119.1, 77.0.

(3*R*, 4*S*, 5*S*)-4-Benzyloxymethoxy-3,5-dimethyl-7-trityloxyheptanoic acid methyl ester (5)



To a slurry of CuI (0.38 g, 1.99 mmol) in THF (8 mL) at –30 °C was added MeLi·LiBr (1.50 M, 2.65 mL, 3.98 mmol) and the reaction mixture was allowed to warm up to 0 °C

over 30 min. before it was cooled to –78 °C. To the resulting mixture were added Me_3SiCl (0.6 mL, 4.73 mmol) and ester **4** (0.22 g, 0.39 mmol) in THF (3 mL). The reaction mixture was stirred at –78 °C for 3 h before being quenched with saturated NH_4Cl solution (10 mL). The reaction mixture was diluted with hexane (30 mL), washed with NH_4Cl-NH_4OH (1:1, 30 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed in *vacuo* and the residue was subjected to column chromatography (E/H=1:30) to afford product **5** (0.21 g, 92%) as a colorless oil;

$[\alpha]_D$ -16.7 ° (c 0.42, $CHCl_3$);

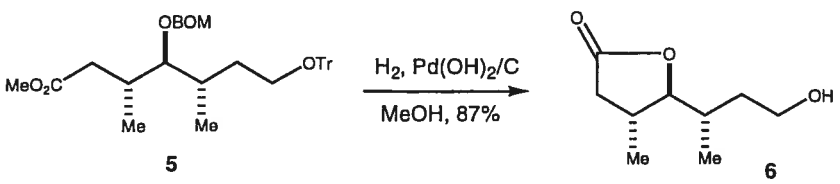
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J*=6.88 Hz, 1H), 1.02 (d, *J*=6.76 Hz, 1H), 1.37-1.45 (m, 1H), 1.94-2.05 (m, 2H), 2.16 (dd, *J*=9.52, 15.12 Hz, 1H), 2.23-2.38 (m, 1H), 2.64 (dd, *J*=3.80, 15.16 Hz, 1H), 3.01-3.09 (m, 1H), 3.15-3.22 (m, 2H), 3.68 (s, 3H), 4.64 (s, 2H), 4.77 (s, 2H), 7.22-7.47 (m, 15H), 7.49-7.52 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.87, 17.79, 31.55, 32.25, 32.69, 37.42, 51.30, 61.65, 70.02, 86.33, 88.51, 96.48, 126.73, 127.52, 127.66, 128.29, 128.56, 137.75, 144.33, 173.89;

IR (thin film) νmax 2951, 2877, 1737, 1491, 1449, 1381, 1277, 1161, 1073, 1037, 746, 706, 698 cm^{-1};

HRMS: $C_{37}H_{43}O_5$ (M^++1), calc.: 567.31104, found: 567.31280.

(4*R*, 5*S*)-[(1*S*)-3-Hydroxy-1-methylpropyl]-4-methyldihydrofuran-2-one (6):



A mixture of ester **5** (0.20 g, 0.35 mmol) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 30 mg) in MeOH (10 mL) was stirred under hydrogen at atmospheric pressure for 24 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The solvent was removed in *vacuo*. The product was purified by column chromatography (E/H=1:1) to give product **6** (0.074 g, 87%) as a colorless oil;

$[\alpha]_D$ –35.1 ° (c 0.50, $CHCl_3$);

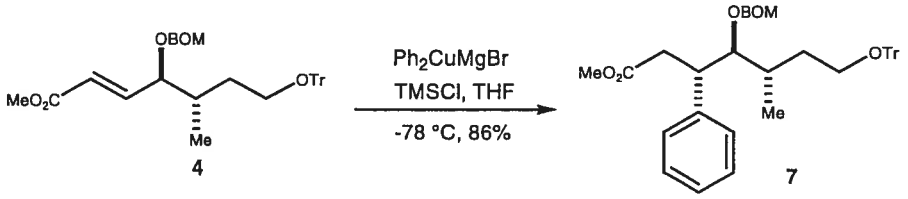
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J*=6.84 Hz, 3H), 1.17 (d, *J*=6.72 Hz, 3H) 1.40-1.52 (m, 1H), 1.59-1.70 (broad, 1H), 1.76-1.86 (m, 1H), 1.88-2.02 (m, 1H), 2.119 (dd, *J*=7.83, 11.52 Hz, 1H), 2.32-2.48 (m, 1H), 2.69 (dd, *J*=8.76, 17.55 Hz, 1H), 3.63-3.82 (m, 2H), 3.95 (t, *J*=6.30 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.51, 19.24, 32.24, 33.37, 34.57, 36.97, 60.26, 91.28, 172.50;

IR (thin film) νmax 3420, 2926, 1771, 1460, 1421, 1384, 1271, 1171, 1056, 978 cm^{-1};

HRMS: $C_9H_{17}O_3$ (M^++1), calc.: 172.10993, found: 172.10934.

(3*R*, 4*S*, 5*S*)-4-Benzyloxymethoxy-5-methyl-3-phenyl-7-trityloxheptanoic acid methyl ester (7):



To a slurry of CuI (0.33 g, 1.73 mmol) in THF (20 mL) at –78 °C was added PhMgBr solution (1M, 3.46 mL, 3.46 mmol). The reaction mixture was stirred at this temperature for 1 h before Me_3SiCl (0.60 mL, 4.73 mmol) and ester **4** (0.22 g, 0.39 mmol) in THF (3

mL) were added. The mixture was stirred at –78 °C for 6 h before NH_4Cl solution (15 mL) was slowly added. The resulting mixture was warmed to room temperature and then extracted with hexane (30 mL x 2). The combined organic layers were washed with NH_4Cl-NH_4OH solution (1:1, 30 mL x 2), brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (E/H=1:20) to give product **7** (0. 21 g, 85%) as a colorless oil;

$[\alpha]_D$ +7.8 ° (c 0.39, $CHCl_3$);

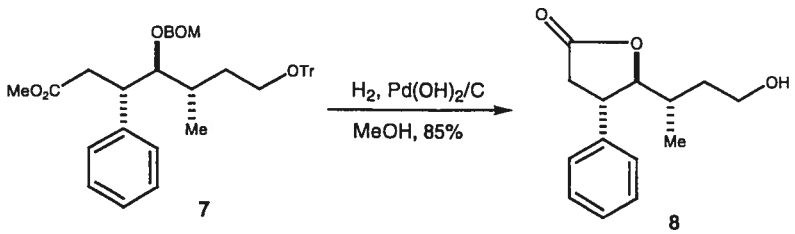
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, *J*=6.87 Hz, 3H), 1.28-1.40 (m, 1H), 1.70-1.83 (m, 1H), 1.90-2.04 (m, 1H), 2.64 (dd, *J*=9.69, 15.45 Hz, 1H), 2.85-2.95 (m, 1H), 3.02 (dd, *J*=5.10, 15.54 Hz, 1H), 3.08-3.15 (m, 1H), 3.45-3.54 (m, 1H), 3.54 (s, 3H), 3.62 (dd, *J*=2.61, 8.85 Hz, 1H), 4.62 (d, *J*=11.91 Hz, 1H), 4.67 (d, *J*=11.91 Hz, 1H), 4.69 (d, *J*=6.93Hz, 1H), 4.80 (d, *J*=6.93 Hz, 1H), 7.20-7.44 (m, 20H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.94, 30.68, 31.89, 38.04, 44.81, 51.26, 61.37, 70.20, 86.21, 87.95, 96.49, 126.66, 126.28, 127.56, 127.64, 127.67, 128.11, 128.32, 128.50, 128.55, 137.70, 144.36, 172.97;

IR (thin film) νmax 2933, 2849, 1737, 1455, 1429, 1272, 1164, 1110, 1053, 1028, 700 cm^{-1};

m/e: 537.5, 473.2, 269.1, 243.1, 183.1, 147.1, 135.1.

(4*S*, 5*S*)-5-[(1*S*)-3-Hydroxy-1-methylpropyl)-4-phenyldihydrofuran-2-one (8):



7 8

A mixture of ester **7** (0.23 g, 0.36 mmol) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 40 mg) in MeOH (10 mL) was stirred under hydrogen at atmospheric pressure for 24 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The solvent was removed in *vacuo*. The product was purified by column chromatography (E/H=1:5) to give product **8** (0.086 mg, 85%) as a colorless oil;

$[\alpha]_D$ –14.54 ° (c 0.35, $CHCl_3$);

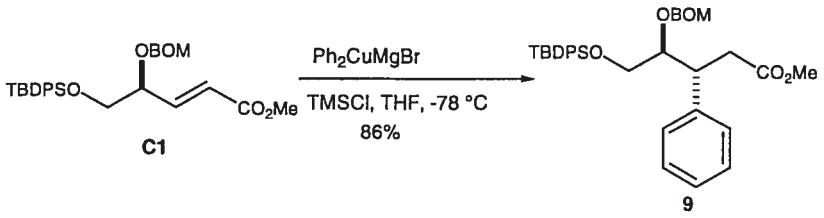
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J*=6.88 Hz, 3H), 1.43-1.52 (m, 1H), 1.77-1.87 (m, 1H), 2.01-2.10 (m, 1H), 2.67 (dd, *J*=9.04, 17.96 Hz, 1H), 2.99 (dd, *J*=9.36, 18.04 Hz, 1H), 3.47 (dd, *J*=8.88, 9.13 Hz, 1H), 3.60-3.70 (m, 1H), 3.70-3.80 (m, 1H), 4.45 (dd, *J*=5.96, 7.44 Hz, 1H), 7.26-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.54, 33.65, 34.51, 38.14, 44.11, 60.17, 90.61, 127.01, 127.42, 129.05, 140.62, 175.58;

IR (thin film) νmax 3401, 2932, 1773, 1497, 1457, 1417, 1208, 1171, 1056, 1002, 761, 700 cm^{-1};

HRMS: $C_{14}H_{19}O_3$ (M^++1), calc.: 235.12558, found: 235.12508.

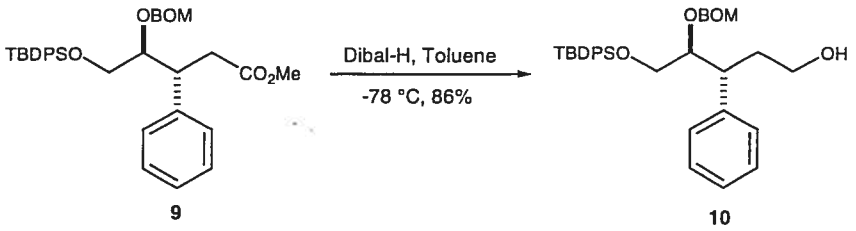
(3*R*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-3-phenylpentanoic acid methyl ester (9):



To a slurry of CuI (1.05 g, 5.51 mmol) in THF (30 mL) at –78 °C was added PhMgBr (1 M in THF, 11.03 mL, 11.03 mmol). The reaction mixture was stirred at –78 °C for 1 h

before TMSCl (3.00 mL, 2.57 g, 23.63 mmol) and ester $\mathbf{C_1}$ (0.56 g, 1.10 mmol) in THF (8 mL) were added. The reaction mixture was stirred at –78 °C for 5 h before NH_4Cl solution (50 mL) was added. The resulting mixture was allowed to warmed to room temperature before being extracted with hexane (70 mL x 2). The combined extracts were washed with NH_4Cl-NH_4OH (1:1, 60 mL x 3) and $NaHCO_3$ solution (40 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to column chromatograaphy (E/H=20:1) to give product **9** (0.55 g, 86%).

(3*R*, 4*S*)-4-Benzyloxymethoxy-5-(tert-butyldiphenylsilanyloxy)-3-phenyl-pentan-1-ol (10):



9 10

To a solution of ester **9** (0.70 g, 1.19 mmol) in toluene (20 mL) at –78 °C was added Dibal-H (0.50 M, 7.17 mL, 3.58 mmol). The reaction mixture was stirred at –78 °C for 1 h before HCl solution (1.00 M, 40 mL) was added. The resulting mixture was warmed to room temperature and then extracted with hexane-ethyl acetate (1:1, 40 mL x 2). The combined organic layers were washed with $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:5) to give the alcohol **10** (0.57 g, 86%);

$[\alpha]_D$ –21.41 ° (c 2.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.42-1.47 (broad, 1H), 1.89-1.95 (m, 1H), 2.23-2.28 (m, 1H), 3.13-3.19 (m, 1H), 3.42-3.36 (m, 4H), 3.86-3.90 (m, 1H), 4.49 (d,

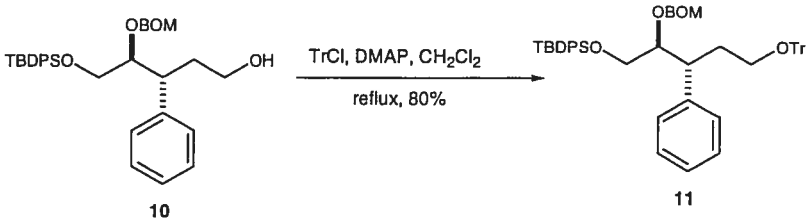
J=11.84 Hz, 1H), 4.62 (d, *J*=11.82 Hz, 1H), 4.73 (d, *J*=7.0 Hz, 1H), 4.86 (d, *J*=7.0 Hz, 1H), 7.19-7.66 (m, 20H) ppm;

^{13}C NMR (400 MHz, $CDCl_3$) δ 19.67, 26.84, 34.19, 43.76, 61.22, 64.05, 69.91, 81.75, 94.57, 126.58, 127.60, 127.67, 127.69, 127.73, 128.13, 128.28, 128.35, 128.43, 128.46, 129.21, 129.55, 129.62, 129.75, 133.22, 133.34, 135.48, 135.53, 135.54, 135.59, 137.85, 142.01 ppm;

IR (thin film) νmax 3376, 2930, 2858, 1472, 1428, 1115, 1028, 778, 700 cm^{-1};

m/e: 555.3 (M^++1), 485.2, 439.1, 243.1, 214.0, 165.1, 119.1, 77.0.

[(2*S*, 3*R*)-2-Benzyloxymethoxy-3-phenyl-5-trityloxypentyloxy]-*tert*-butyldiphenylsilane (11):



10 11

To a solution of alcohol **10** (0.70 g, 1.25 mmol) in CH_2Cl_2 (35 mL) was added DMAP (0.61 g, 5.02 mmol) and TrCl (1.05 g, 3.75 mmol). The mixture was heated at reflux for two days before being quenched with a solution of NH_4Cl (30 mL). The resulting mixture was extracted with hexane (30 mL x 2). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:25) to afford product **11** (0.80 g, 80%) as a colorless oil;

$[\alpha]_D$ -30.86 ° (c 1.16, $CHCl_3$);

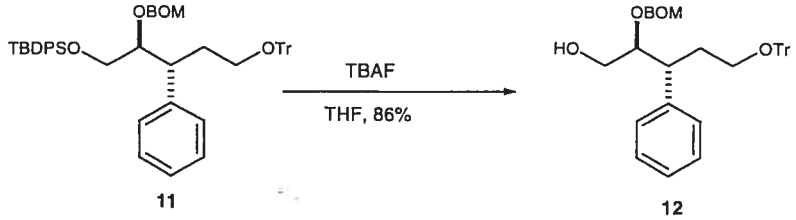
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.84-1.94 (m, 1H), 2.38-2.49 (m, 1H), 2.85 (dt, *J*=5.52, 8.98 Hz, 1H), 3.03-3.09 (m, 1H), 3.33-3.40 (m, 1H), 3.51 (dd, *J*=4.76, 11.0

Hz, 1H), 3.61 (dd, *J*=4.04, 10.96 Hz, 1H), 3.81-3.88 (m, 1H), 4.45 (d, *J*=11.76 Hz, 1H), 4.58 (d, *J*=11.76 Hz, 1H), 4.69 (d, *J*=6.96 Hz, 1H), 4.82 (d, *J*=6.96 Hz, 1H), 7.18-7.70 (m, 30H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.12, 26.79, 31.12, 43.51, 61.31, 63.98, 69.77, 82.60, 86.21, 94.51, 126.58, 127.49, 127.52, 127.56, 127.75, 127.85, 128.07, 128.28, 128.56, 133.27, 133.37, 137.88, 141.79, 144.38;

IR (thin film) νmax 2958, 2932, 2859, 1472, 1430, 1114, 8430, 820, 741, 700 cm^{-1};

(2*S*, 3*R*)-2-Benyloxymethoxy-3-phenyl-5-trityloxypentan-1-ol (12):



11 12

To a solution of ether **11** (1.80 g, 2.26 mmol) in THF (30 mL) at room temperature was added TBAF solution (1:1 complexed with acetic acid, 0.94 M, 14.42 mL, 13.56 mmol). The reaction mixture was stirred at room temperature for 6 h before a saturated solution of $NaHCO_3$ (40 mL) was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 50 mL x 2). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to afford product **12** (1.08 g, 86%) as a colorless oil;

$[\alpha]_D$ +1.69 ° (c 1.24, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80-1.92 (m, 1H), 2.28-2.39 (m, 1H), 2.80-2.97 (m, 2H), 2.99-3.08 (m, 2H), 3.35-3.45 (m, 1H), 3.45-3.58 (m, 1H), 3.68-3.74 (m, 1H), 4.64 (d,

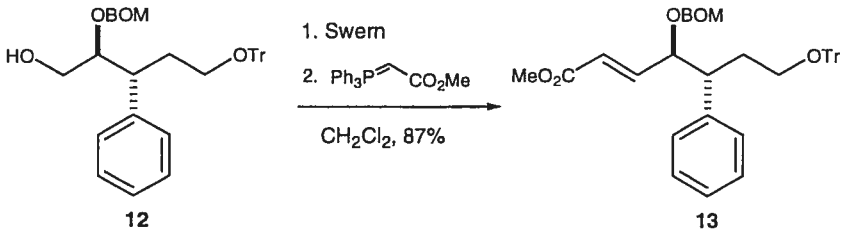
J=11.73 Hz, 1H), 4.74 (d, *J*=6.96 Hz, 1H), 4.76 (d, *J*=11.73 Hz, 1H), 4.97 (d, *J*=6.96 Hz, 1H), 7.08-7.12 (m, 2H), 7.18-7.24 (m, 23H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 31.93, 44.55, 61.23, 63.92, 70.18, 78.09, 86.31, 86.49, 95.68, 126.47, 126.64, 127.51, 127.56, 127.61, 127.86, 127.88, 128.21, 128.32, 128.46, 128.50, 129.54, 134.70, 137.06, 141.17, 144.22;

IR (thin film) νmax 3460, 3059, 2930, 2878, 1597, 1492, 1449, 1383, 1218, 1163, 1027, 746, 699 cm^{-1};

HRMS: $C_{38}H_{39}O_4$ (M^++1), calc.: 559.27697, found: 559.27657.

(4*S*, 5*R*)-4-Benzyloxymethoxy-5-phenyl-7-trityloxyhept-2-enoic acid methyl ester (13):



12 13

To a solution of oxaly chloride (0.17 mL, 0.24 g, 1.93 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added DMSO (0.19 mL, 0.21 g, 2.41 mmol). The reaction mixture was stirred for 15 min at –78 °C before alcohol **12** (0.36 g, 0.96 mmol) in CH_2Cl_2 (3 mL) was slowly added at –78 °C. The resulting mixture was stirred and slowly warmed to –30 °C in about 30 min before Et_3N (403 μL, 2.89 mmol) was added. The white precipitate was formed and the mixture was stirred at this temperature for 15 min before being quenched by NH_4Cl solution (10 mL). The organic layer was separated, dried and concentrated in *vacuo*. The crude aldehyde was dissolved in dry CH_2Cl_2 (15 mL) and $Ph_3P{=}CHCO_2CH_3$

(970 mg, 2.89 mmol) was added. The mixture was stirred at r.t. for 6 h. The solvent was removed and the residue was purified by column chromatography (E/H=1:10) to give product **13** (1.02 g, 87%) as a colorless oil;

$[\alpha]_D$ -34.92 ° (c 0.96, $CHCl_3$);

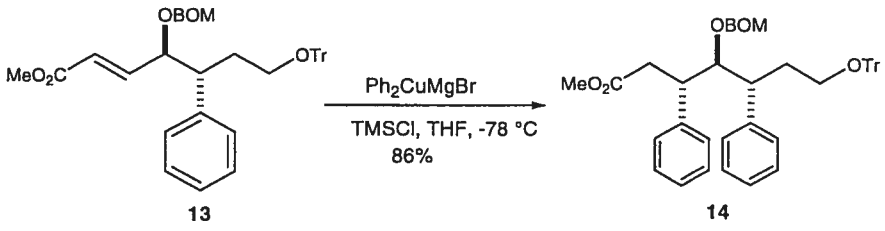
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92-2.26 (m, 1H), 2.22-2.37 (m, 1H), 2.86-2.97 (m, 1H), 3.05-3.18 (m, 2H), 3.72 (s, 3H), 4.41 (t, *J*=6.40 Hz, 1H), 4.46 (d, *J*=11.68 Hz, 1H), 4.52 (d, *J*=11.68 Hz, 1H), 5.88 (d, *J*=15.76 Hz, 1H), 6.79 (dd, *J*=6.56, 15.76 Hz, 1H), 7.10-7.39 (m, 20 H);

^{13}C NMR (100MHz, $CDCl_3$) δ 30.59, 47.04, 51.45, 60.97, 69.81, 79.29, 86.26, 92.79, 122.44, 126.62, 127.49, 127.61, 127.69, 127.83, 128.11, 128.27, 128.44, 128.75, 134.73, 135.41, 137.43, 140.21, 144.18, 146.54, 166.22;

IR (thin film) νmax 3031, 2950, 1726, 1492, 1450, 1275, 1167, 1027, 746, 699 cm^{-1};

m/e: 635.2 (M^++Na), 625.2, 611.2, 484.2, 429.0, 411.0, 243.1, 214.0, 165.1, 132.9.

(3*S*, 4*S*, 5*R*)-4-Benzyloxymethoxy-3,5-diphenyl-7-trityloxyheptanoic acid methyl ester (14):



13 14

To a slurry of CuI (2.00 g, 10.5 mmol) in THF (50 mL) at –78 °C was added PhMgBr solution (1 M, 21.00 mL, 21.00 mmol) and the mixure was stirred at this temperature for 1 h before TMSCl (4.00 mL, 31.50 mmol) and ester **13** (0.33 g, 0.52 mmol) in THF (5 mL) were added. The reaction mixture was stirred at –78 °C for 12 h before a saturated

solution of NH_4Cl (10 mL) was slowly added. The mixture was extracted with hexane (30 mL x 2). The combined organic layers were washed with NH_4Cl-NH_4OH solution (1:1, 30 mL x 2), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (E/H=1:30) to give product **14** (0.31 g, 86%) as a colorless oil;

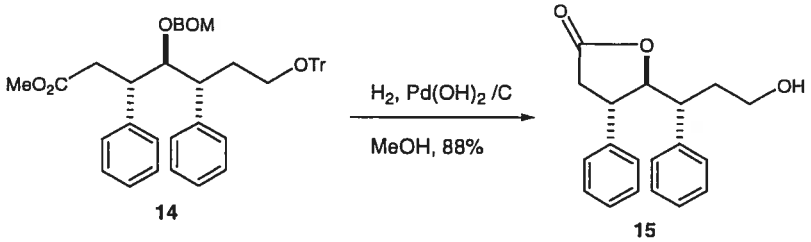
$[\alpha]_D$ –23.4 ° (c 1.35, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94-2.07 (m, 1H), 2.30-2.40 (m, 1H), 2.70-2.80 (m, 1H), 2.97-3.08 (m, 3H), 3.38-3.48 (m, 1H), 3.51 (s, 3H), 3.89 (dd, *J*=4.72, 7.02 Hz, 1H), 4.26 (d, *J*=6.92 Hz, 1H), 4.41 (d, *J*=6.92 Hz, 1H), 4.57 (d, *J*=11.89 Hz, 1H), 4.62 (d, *J*=11.84 Hz, 1H), 6.83 (dd, *J*=0.96, 8.64 Hz, 1H), 6.90-7.04 (m, 2H), 7.13-7.40 (m, 27 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 28.59, 36.43, 44.16, 44.73, 51.36, 60.79, 70.51, 86.04, 88.31, 96.95, 126.53, 127.44, 127.70, 128.02, 128.28, 128.34, 128.46, 128.59, 129.55, 141.80, 144.23, 173.15;

IR (thin film) νmax 2950, 1737, 1492, 1453, 1428, 1275, 1167, 1027, 736, 703 cm^{-1}.

(4*S*, 5*S*)-[(1*R*)-3-Hydroxy-1-phenylpropyl)-4-phenyldihydrofuran-2-one (15):



14 15

A mixture of ester **14** (0.20 g, 0.29 mmol) and $Pd(OH)_2$/C (20% Pd, Degussa type, 0.040 mg) in MeOH (12 mL) was stirred under hydrogen at atmospheric pressure for 24 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The solvent

was removed in *vacuo*. The product was purified by column chromatography (E/H=1:7) to give product **15** (0.068 g, 88%) as a colorless oil;

$[\alpha]_D$ -26.85 ° (c 0.35, $CHCl_3$);

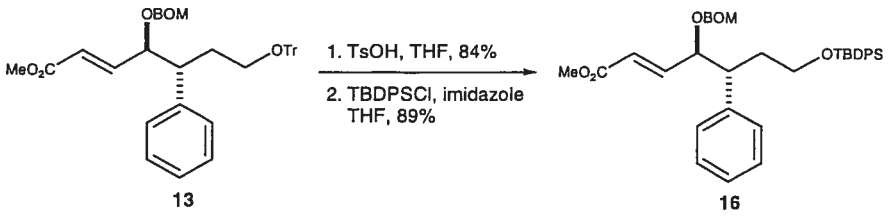
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.95 (m, 1H), 2.20-2.29 (m, 1H), 2.61 (dd, *J*=7.60, 18.12 Hz, 1H), 2.87 (dd, *J*=9.52, 18.16 Hz, 1H), 3.05-3.10 (m, 1H), 3.32-3.42 (m, 1H), 3.42-3.48 (m, 1H), 4.70 (dd, *J*=6.12, 7.52 Hz, 1H), 6.88-6.92 (m, 2H), 7.10-7.28 (m, 8H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 34.51, 37.01, 44.37, 46.88, 60.13, 89.99, 126.64, 127.03, 127.34, 128.49, 128.63, 128.79, 138.94, 140.87, 143.76, 144.07, 175.71;

IR (thin film) νmax 2917, 2849, 1777, 1496, 1455, 1173, 760, 700 cm^{-1};

HRMS: $C_{19}H_{21}O_3$ (M^++1), calc.: 296.14125, found: 296.12176.

(4*R*, 5*R*)-4-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-5-phenylhept-2-enoic acid methyl ester (16):



13 16

To a solution of ester **13** (2.40 g, 3.98 mmol) in THF (30 mL) at room temperature was added *p*-TsOH·H_2O (0.28 g, 1.45 mmol). The reaction mixture was stired for 30 min before a saturated solution of $NaHCO_3$ (30 mL) was added. The resulting mixture was extracted with ethyl acetate (30 mL x 2). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to column chromatography (E/H=1:3) to give the alcohol (1.00 g, 84%) which was used directly in the next step.

To a solution of the above alcohol (1.00 g, 2.70 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added imidazole (0.36 g, 5.4 mmol) and TBDPSCl (0.83 g, 0.83 mL, 3.00 mmol). The mixture was then stirred for 2 h at room temperature before being quenched by NH_4Cl solution (20 mL). The mixture was extracted with hexane (30 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to column chromatography (E/H=1:15) to afford product **16** (1.50 g , 89%) as a colorless oil;

$[\alpha]_D$ –28.7 ° (c 0.69, $CHCl_3$);

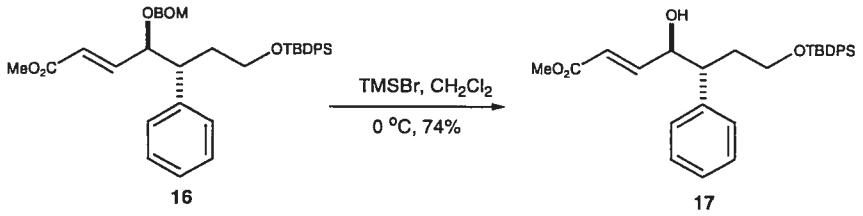
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.82-1.98 (m, 1H), 2.19-2.31 (m, 1H), 3.10-3.19 (m, 1H), 3.42-3.54 (m, 1H), 3.56-3.63 (m, 1H), 3.72 (s, 3H), 4.42 (dt, *J*=1.21, 6.30 Hz, 1H), 4.43 (d, *J*=11.58 Hz, 3H), 4.50 (d, *J*=11.58 Hz, 1H), 4.68 (d, *J*=7.08 Hz, 1H), 4.70 (d, *J*=7.08 Hz, 1H), 5.85 (dd, *J*=1.21, 15.78 Hz, 1H), 6.79 (dd, *J*=6.30, 15.78 Hz, 1H), 7.10-7.68 (m, 20 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.04, 26.71, 32.88, 46.51, 51.47, 61.31, 69.79, 79.33, 92.78, 122.41, 126.72, 127.43, 127.49, 127.64, 127.84, 128.22, 128.30, 128.77, 129.33, 129.42, 133.62, 133.69, 135.37, 135.44, 137.46, 140.17, 146.67, 166.25;

IR (thin film) νmax 2931, 2858, 1727, 1472, 1428, 1269, 1166, 1112, 1026, 701 cm^{-1};

m/e: 631.3 (M^++Na), 589.2, 567.2, 442.2, 409.1, 243.1, 136.0, 77.0.

(4*R*, 5*R*)-7-(*tert*-Butyldiphenylsilanyloxy)-4-hydroxy-5-phenylhept-2-enoic acid methyl ester (17):



16 17

To a solution of ester **16** (0.60 g, 1.0 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added TMSBr (0.37 g, 0.32 mL, 2.46 mmol). The reaction mixture was slowly warmed from –78 °C to –30 °C in 2 h and a saturated $NaHCO_3$ solution (30 mL) was then added. The mixture was extracted with ethyl acetate (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The oily residue was purified by column chromatography on silica gel (E/H=1:8) to give product **17** (0.35 g, 74%);

$[\alpha]_D$ +3.2 ° (c 0.75, $CHCl_3$);

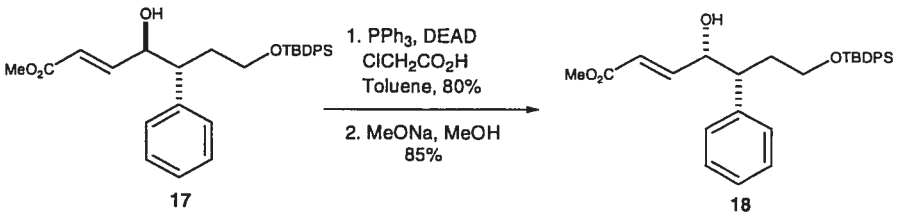
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.90-2.05 (m, 1H), 2.07-2.20 (m, 1H), 2.53 (d, *J*=5.67 Hz, 1H), 3.06-3.13 (m, 1H), 3.60-3.68 (m, 1H), 3.73 (s, 3H), 4.47-4.53 (m, 1H), 6.03 (dd, *J*=1.83, 15.63 Hz, 1H), 6.90 (dd, *J*=4.44, 15.63 Hz, 1H), 7.12-7.67 (m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.00, 26.69, 33.41, 48.52, 51.45, 61.65, 74.52, 120.70, 126.93, 127.53, 127.58, 128.43, 128.56, 128.71, 129.51, 129.59, 133.19, 133.24, 135.39, 135.49, 140.42, 148.69, 166.71;

IR (thin film) vmax 3449, 2933, 2859, 1726, 1429, 1276, 1169, 1119, 825, 703 cm^{-1}.

HRMS; $C_{30}H_{37}O_4Si$ (M^++1), calcd: 489.23826, found: 489.23856.

(4*S*, 5*R*)-7-(*tert*-Butyldiphenylsilanyloxy)-4-hydroxy-5-phenylhept-2-enoic acid methyl ester (18):



To a solution of alcohol **17** (0.33 g, 0.72 mmol) in toluene (4 mL) at 0 °C was added PPh_3 (0.37 g, 1.44 mmol), DEAD (0.24 g, 1.44 mmol), chloroacetic acid (0.14 g, 1.44 mmol). The reaction mixture was stirred at 0 °C for 1 h, and at room temperature for 16 h before saturated $NaHCO_3$ solution (20 mL) was added. The resulting mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:4) to give the ester (0.30 g, 80%) which was used directly in the next step.

To a solution of the above ester (0.30 g, 0.60 mmol) in MeOH (6 mL) was added NaOMe solution (1 M, 0.10 mL, 0.10 mmol). The reaction mixture was stirred at room temperature for 20 min before a saturated solution of NH_4Cl (20 mL) was added. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:6) to provid product **18** (0.25 g, 85%);

$[\alpha]_D$ –16.76 ° (c 1.01, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.90-2.01 (m, 1H), 2.06-2.18 (m, 1H), 2.44-

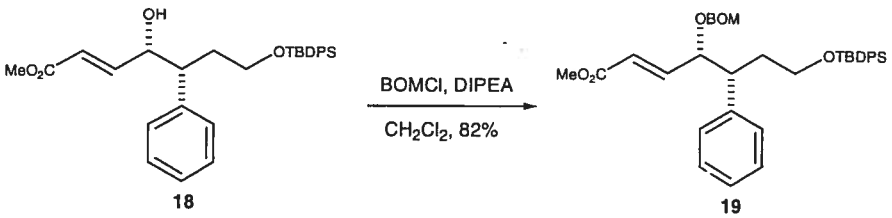
2.60 (broad 1H), 3.03-3.13 (m, 1H), 3.49-3.55 (m, 1H), 3.59-3.68 (m, 1H), 3.72 (s, 3H), 4.46-4.50 (m, 1H), 6.02 (dd, *J*=1.52, 15.64 Hz, 1H), 6.90 (dd, *J*=4.44, 15.64 Hz, 1H), 7.10-7.68 (m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 18.98, 26.67, 33.39, 48.49, 51.45, 61.61, 74.49, 120.66, 126.91, 127.51, 127.57, 128.41, 128.54, 129.49, 129.57, 133.14, 135.37, 135.46, 140.39, 148.69, 166.71;

IR (thin film) vmax 3448, 2931, 2857, 1725, 1428, 1277, 1168, 1117, 823, 701 cm^{-1};

HRMS; $C_{30}H_{37}O_4Si$ (M^++1), calcd: 489.23826, found: 489.23856.

(4*S*, 5*R*)-4-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-5-phenylhept-2-enoic acid methyl ester (19):



18 19

To a solution of ester **18** (0.18 g, 0.38 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added DIPEA (0.39 mL, 0.29 g, 2.27 mmol) and BOMCl (65%, 0.45 mL, 0.30 g, 1.89 mmol) with stirring. The reaction mixture was then warmed to room temperature and then stirred for 2 days. The reaction mixture was diluted with hexane (20 mL), washed wth NH_4Cl (15 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to column chromatography (E/H=1:20) to afford product **19** (189 mg, 82%) as a colorless oil;

$[\alpha]_D$ -24.8 ° (c 0.79, $CHCl_3$);

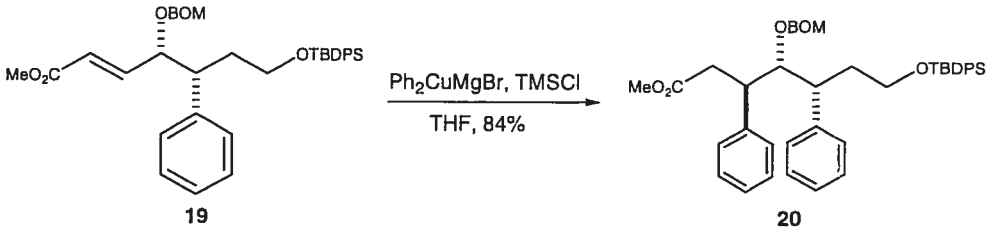
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.83-1.97 (m, 1H), 2.19-2.30 (m, 1H), 3.08-3.18 (m, 1H), 3.42-3.50 (m, 1H), 3.52-3.60 (m, 1H), 3.71 (s, 3H), 4.38-4.48 (m, 1H), 4.42 (d, *J*=10.50 Hz, 1H), 4.49 (d, *J*=10.50 Hz, 1H), 4.68 (d, *J*=6.87 Hz, 1H), 4.71 (d, *J*=6.87 Hz, 1H), 5.87 (dd, *J*=1.23, 15.78 Hz, 1H), 6.77 (dd, *J*=6.48, 15.78 Hz, 1H), 7.10-7.67 (m, 20H);

^{13}C NMR (400 MHz, $CDCl_3$) δ 19.00, 26.67, 32.81, 46.45, 61.25, 69.75, 79.26, 92.72, 122.37, 126.69, 127.39, 127.46, 127.61, 127.81, 128.19, 128.27, 128.73, 129.30, 129.39, 133.57, 133.64, 135.33, 135.41, 137.41, 140.12, 146.64, 166.23;

IR (thin film) νmax 2933, 2859, 1729, 1472, 1458, 1428, 1267, 1166, 1111, 1028, 700 cm^{-1};

m/e: 631.3 (M^++Na), 589.2, 567.2, 442.2, 409.1, 243.1, 136.0, 77.0.

(3*R*, 4*R*, 5*R*)-4-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-3,5-diphenyl-heptanoic acid methyl ester (20):



19 20

To a slurry of CuI (1.00 g, 5.25 mmol) in THF (20 mL) at –78 °C was added PhMgBr solution (1.00 M, 10.50 mL, 10.50 mmol) and the mixure was stirred at this temperature for 1 h. Then, to the mixture were added TMSCl (2.00 mL, 15.75 mmol) and ester **19** (0.20 g, 0.33 mmol) in THF (3 mL). The resulting mixture was stirred at –78 °C for 12 h before a saturated solution of NH_4Cl (10 mL) was slowly added. The mixture was extracted with hexane (30 mL). The organic layer was washed with NH_4Cl-NH_4OH

solution (1:1, 30 mL x 2), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (E/H=1:30) to give product **20** (0.18 g, 84%) as a colorless oil;

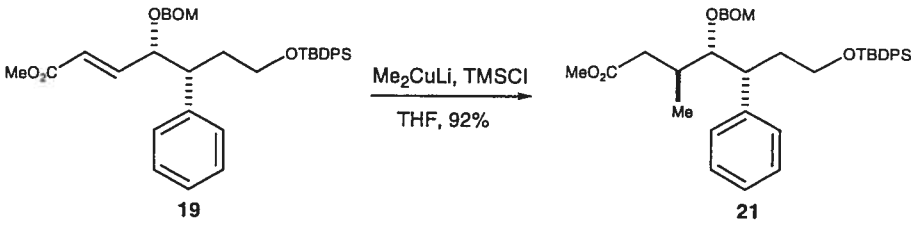
$[\alpha]_D$ -12.38 ° (c 0.42, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H),1.82-1.95 (m, 1H), 1.94-2.06 (m, 1H), 2.01 (dd, *J*=12.00, 15.00 Hz, 1H), 2.91-2.99 (m, 2H), 3.11-3.19 (m, 1H), 3.19-3.27 (m, 1H), 3.42 (s, 3H), 3.42-3.50 (m, 1H), 4.11 (dd, *J*=2.80, 7.90 Hz, 1H), 4.56 (s, 2H), 4.73 (d, *J*=8.60 Hz, 1H), 4.81 (d, *J*=8.60 Hz, 1H), 7.18-7.55 (m, 30H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 18.30, 26.61, 36.95, 37.87, 43.69, 45.60, 51.14, 60.86, 70.39, 87.04, 98.60, 126.29, 126.73, 127.34, 127.42, 127.59, 127.72, 128.29, 128.38, 129.34, 129.91, 133.65, 135.33, 137.62, 140.95, 143.20, 172.68;

IR (thin film) νmax 2931, 2848, 1734, 1472, 1465, 1428, 1260, 1112, 1022, 701 cm^{-1};

(3*S*, 4*S*, 5*R*)-4-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-3-methyl-5-phenylheptanoic acid methyl ester (21)



To a slurry of CuI (0.20 g, 1.05 mmol) in THF (8 mL) at –30 °C was added MeLi·LiBr (1.50 M, 1.40 mL, 2.10 mmol) and the reaction mixture was allowed to warm up to 0 °C over 30 min before it was cooled to –78 °C. To the resulting mixture were added Me_3SiCl (0.40 mL, 3.15 mmol) and ester **19** (0.20 g, 0.33 mmol) in THF (3 mL). The reaction was stirred at –78 °C for 3 h before being quenched with saturated NH_4Cl solution (10 mL).

The mixture was diluted with hexane (30 mL) and the organic layer was separated. The organic layer was washed with NH_4Cl-NH_4OH (1:1, 30 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to column chromatography (E/H=1:30) to afford product **21** (0.21g, 92%) as a colorless oil;

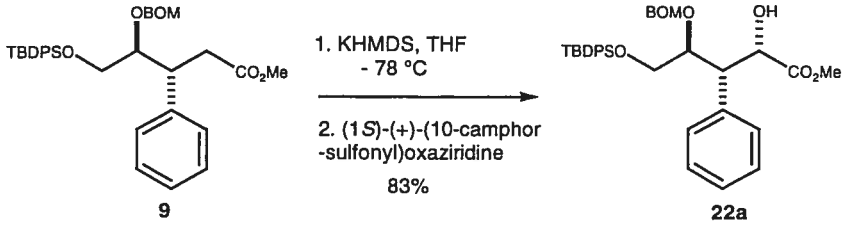
$[\alpha]_D$ –17.9 ° (c 0.69, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.02 (d, *J*=7.26 Hz, 3H), 1.81-1.92 (m, 1H), 2.02-2.18 (m, 2H), 2.20-2.32 (m, 1H), 2.53 (dd, *J*=2.10, 13.95 Hz, 1H), 3.09-3.18 (m, 1H), 3.32-3.46 (m, 1H), 3.51-3.58 (m, 1H), 3.63 (s, 3H), 4.47 (d, *J*=6.96 Hz,1H), 4.56 (d, *J*=11.85 Hz, 1H), 4.68 (d, *J*=11.85 Hz, 1H), 4.70 (d, *J*=6.96 Hz, 1H), 7.08-7.8 (m, 20H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 17.46, 19.07, 26.73, 32.86, 32.94, 36.94, 44.19, 51.29, 61.41, 70.24, 87.91, 96.59, 126.44, 127.41, 127.49, 127.71, 128.33, 128.41, 128.48, 129.31, 129.40, 135.40, 135.45, 141.84, 173.80;

IR (thin film) νmax 2931, 2849, 1736, 1454, 1428, 1270, 1163, 1111, 1053, 1028, 701 cm^{-1};

(2*S*, 3*R*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-3-phenylpentanoic acid methyl ester (22a):



9 22a

To a solution of ester **10** (3.06 g, 5.23 mmol) in THF (100 mL) at –78 °C was added KHMDS (0.50 M, 12 mL, 6.0 mmol). The reaction mixture was stirred at this temperature for 1 h before a solution of (1*S*)-(+)-10-camphorsulfonyloxaziridine (1.37 g,

6.00 mmol) in THF (30 mL) was added. The resulting mixture was stirred at –78 °C for another 2 h before being quenched with aquouos NH_4Cl solution (70 mL). The product was extracted with diethyl ether (100 mL x 3). The combined organic extracts were dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography (E/H=1:7) of the residue on silica gel provided product **22a** (2.61 g, 83%);

$[\alpha]_D$ -34.78 ° (c 0.92, $CHCl_3$);

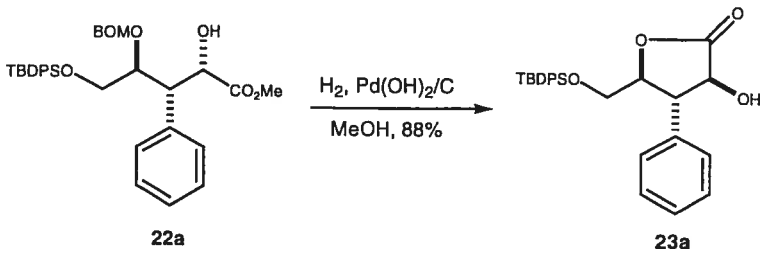
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 9H), 3.08 (d, *J*=5.72 Hz, 1H), 3.45 (dd, *J*=3.84, 11.52 Hz, 1H), 3.57 (dd, *J*=2.84, 10.80 Hz, 1H), 3.06 (s, 3H), 4.28-4.32 (m, 1H), 4.53 (d, *J*=11.80 Hz, 1H), 4.72 (d, *J*=11.80 Hz, 1H), 4.93 (d, *J*=6.76 Hz, 1H), 4.95 (d, *J*=6.76 Hz, 1H), 4.99 (dd, *J*=2.64, 5.28 Hz, 1H), 7.19-7.40 (m, 18 H), 7.58-7.62 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.06, 26.65, 49.84, 52.12, 60.28, 69.85, 70.25, 77.12, 94.25, 127.32, 127.41, 127.49, 127.60, 127.89, 128.05, 128.21, 128.30, 129.28, 129.35, 129.51, 133.00, 133.09, 135.30, 135.30, 136.20, 137.39, 174.59;

IR (thin film) νmax 3617, 3031, 2931, 2857, 1739, 1589, 1495, 1455, 1428, 1269, 1224, 1113, 1026, 702 cm^{-1};

HRMS: $C_{36}H_{42}O_6Si$ (M^++1), calc.: 599.28290, found: 599.28170.

(3*S*, 4*S*, 5*S*)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-3-hydroxy-4-phenyldihydrofuran-2-one (23a):



22a 23a

A mixture of ester **22a** (0.15 g, 0.25 mmol) and $Pd(OH)_2/C$ (0.040 g, 20% Pd, Degussa type) in MeOH (8 mL) was stirred under hydrogen at atmospheric pressure for 36 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The solvent was removed in *vacuo*. The product was purified by column chromatography (E/H=1:4) to give product **23a** (0.096 g, 86%) as colorless oil;

$[\alpha]_D$ –50.67 ° (c 1.14, $CHCl_3$);

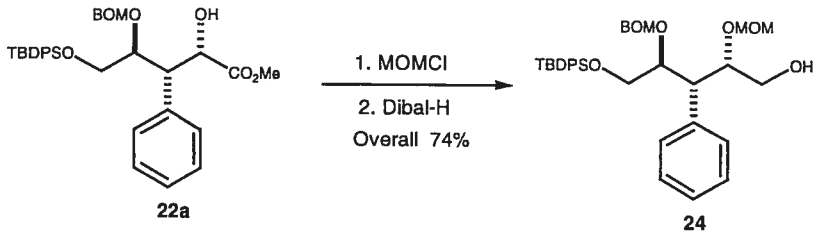
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.82-2.86 (broad, 1H), 3.69-3.78 (m, 2H), 3.97 (dd, *J*=2.36, 12.12 Hz, 1H), 4.50-4.58 (m, 2H), 4.66 (dd, *J*=2.88, 10.92 Hz, 1H), 6.76-7.48 (m, 11H), 7.58-7.67 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.09, 26.69, 49.90, 52.10, 63.59, 69.89, 70.29, 77.12, 94.33, 127.34, 127.43, 127.51, 127.61, 127.90, 128.06, 128.22, 128.31, 129.32, 129.37, 129.52, 133.07, 133.16, 135.34, 135.53, 136.28, 137.66, 174.59;

IR (thin film) νmax 3420, 2917, 2850, 1779, 1496, 1457, 1165, 760, 700 cm^{-1};

HRMS: $C_{27}H_{30}O_4SiNa$ (M^++Na), calc.: 469.18112, found: 469.18240.

(2*S*, 3*S*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-methoxymethoxy-3-phenylpentan-1-ol (24):



22a 24

To a solution of α-hydroxyl-ester **22a** (2.20 g, 3.66 mmol) in CH_2Cl_2 (50 mL) at room temperature was added *i*-Pr_2NEt (1.27 mL, 7.32 mmol) and MOMCl (0.55 mL, 7.32 mmol). The reaction mixture was stirred at room temperature for 16 h before being

quenched with NH_4Cl (50 mL x 2). The product was extracted with hexane (100 mL x 2). The combined organic extracts were dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:20) to give the MOM ether (2.06 g, 88%);

$[\alpha]_D$ –13.6° (c 0.88, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 3.37 (s, 3H), 3.54 (dd, *J*=3.52, 11.40 Hz, 1H), 3.64 (s, 3H), 3.73 (dd, *J*=4.16, 10.24 Hz, 1H), 3.78 (dd, *J*=2.20, 11.44 Hz, 1H), 4.18-4.24 (m, 1H), 4.52 (d, *J*=12.24 Hz, 1H), 4.63 (d, *J*=12.24 Hz, 1H), 4.70 (d, *J*=6.48 Hz, 1H), 4.76 (d, *J*=6.48 Hz, 1 H), 4.83 (d, *J*=4.16 Hz, 1H), 4.92 (d, *J*=6.60 Hz, 1H), 4.95 (d, *J*=6.60 Hz, 1H), 7.25-7.43 (m, 18H), 7.63-7.66 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.12, 26.74, 31.84, 49.91, 51.48, 56.73, 63.83, 69. 81, 76.54, 78.56, 94.81, 97.01, 127.13, 127.42, 127.46, 127.50, 127.61, 128.04, 128.25, 129.36, 129.52, 129.74, 133.14, 135.41, 135.63, 136.81, 137.81, 172.21;

IR (thin film) vmax 3069, 2931, 2893, 2857, 1748, 1496, 1472, 1428, 1389, 1361, 1210, 1152, 1114, 1072, 1039, 1026, 921, 823, 787, 740, 710 cm^{-1}.

To a solution of the above MOM ether (1.90 g, 2.96 mmol) in toluene (25 mL) at –78 °C was added Dibal-H (0.50 M, 17.76 mL, 8.88 mmol). The reaction mixture was stirred at –78 °C for 1.5 h before being quenched with NH_4Cl solution (30 mL). The mixture was extracted with diethyl ether (100 mL x 2). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:5) to give product **24** (1.50 g, 84%);

$[\alpha]_D$ +9.68 ° (c 0.96, $CHCl_3$);

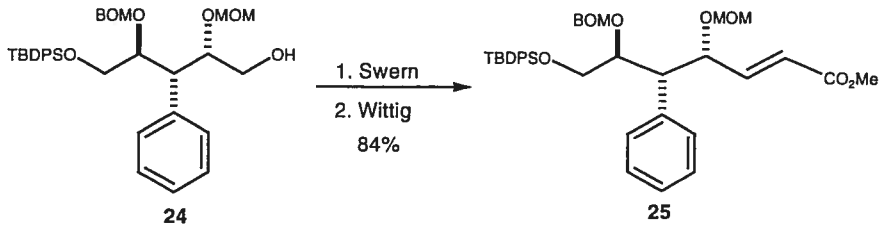
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 3.21-3.28 (m, 2H), 3.35 (s, 3H), 3.47 (dd, *J*=3.68, 11.44 Hz, 1H), 3.54 (dd, *J*=1.84, 11.36 Hz, 1H), 3.70 (dd, *J*=2.08, 11.36 Hz, 1H), 4.20-4.24 (m, 1H), 4.24-4.31 (m, 1H), 4.52 (d, *J*=12.08 Hz, 1H), 4.65 (d, *J*=12.08 Hz, 1H), 4.76 (d, *J*=6.84 Hz, 1H), 4.79 (d, *J*=6.84 Hz, 1H), 4.90 (d, *J*=6.60 Hz, 1H), 4.93 (d, *J*=6.60 Hz, 1H), 7.28-7.48 (m, 18H), 7.65-7.67 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.13, 26.76, 31.85, 49.56, 55.39, 63.86, 66.27, 69.85, 78.82, 82.76, 94.69, 97.81, 126.78, 127.44, 127.51, 127.56, 127.62, 127.94, 128.31, 129.39, 129.52, 129.88, 133.17, 133.23, 133.41, 135.60, 137.71, 137.82;

IR (thin film) νmax 3462, 3069, 3030, 2857, 1589, 1496, 1471, 1454, 1428, 1362 cm^{-1};

HRMS: $C_{37}H_{47}O_6Si$ (M^++1), calc.: 615.31421, found: 615.31600.

(4*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-4-methoxymethoxy-5-phenylhept-2-enoic acid methyl ester (25):



24 25

To a solution of oxalyl chloride (0.15 g, 0.10 mL, 1.15 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added DMSO (0.18 g, 0.20 mL, 2.30 mmol). The reaction mixture was stirred for 15 min before alcohol **24** (0.18 g, 0.29 mmol) in CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred and slowly warmed to –30 °C in about 30 min before triethylamine (0.29 g, 0.40 mL, 28.8 mmol) was added. The white precipitate was formed and the mixture was stirred at this temperature for 15 min before being quenched by a solution of NH_4Cl (10 mL). The organic layer was separated, dried and concentrated in *vacuo*. The

crude aldehyde was dissolved in dry CH_2Cl_2 (15 mL) and $Ph_3P{=}CHCO_2CH_3$ (0.20 g, 0.57 mmol) was added. The mixture was stirred at r.t. for 12 h. The solvent was removed and the residue was purified by column chromatography (E/H=10:1) to give product **25** (0.16 g, 84%) as a colorless oil;

R_f= 0.4 (E/H=1:8);

$[\alpha]_D$ -33.60 ° (c 0.86, $CHCl_3$);

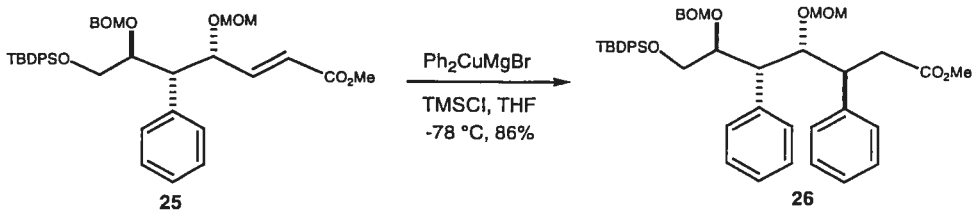
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 3.26-3.30 (m, 1H), 3.28 (s, 3H), 3.54 (dd, *J*=3.64, 11.32 Hz, 1H), 3.71 (s, 3H), 3.76 (dd, *J*=2.68, 11.32 Hz, 1H), 4.23-4.28 (m, 1H), 4.52 (d, *J*=12.16 Hz, 1H), 4.61 (d, *J*=12.16 Hz, 1H), 4,62 (d, *J*=6.6 Hz, 1H), 4.46 (d, *J*=6.60 Hz, 1H), 4.87-4.89 (m, 1H), 4.93 (d, *J*=6.64 Hz, 1H), 4.96 (d, *J*=6.64 Hz, 1H), 5.93 (dd, *J*=0.88, 15.76 Hz, 1H), 6.76 (dd, *J*=7.00, 15.76 Hz, 1H), 7.24-7.42 (m, 18 H), 7.62-7.69 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.08, 26.76, 51.40, 52.29, 55.96, 63.89, 69.79, 75.95, 78.61, 94.88, 95.67, 121.65, 126.84, 127.43, 127.49, 127.53, 127.58, 127.84, 128.26, 129.37, 129.54, 130.31, 133.08, 133.12, 135.39, 135.60, 137.03, 137.78, 148.24, 166.34;

IR (thin film) 3030, 2931, 2891, 2859, 1726, 1472, 1485, 1362, 1274, 1168, 1112, 1042, 719 cm^{-1};

HRMS: $C_{40}H_{49}O_7Si$ (M^++1), calc.: 669.32477, found: 669.32260.

(3S, 4*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyl-diphenylsilanyloxy)-4-methoxymethoxy-3,5-diphenylheptanoic acid methyl ester (26):



To a slurry of CuI (0.34 g, 1.78 mmol) in THF (10 mL) at -78 °C was added phenyl magnesium bromide solution (1.00 M, 3.56 mL, 3.56 mmol). The reaction mixture was stirred for 1 h at -78 °C before TMSCl (0.67 mL, 0.58 g, 5.34 mmol) and α,β-unsaturated ester **25** (0.12 g, 0.18 mmol) in THF (4 mL) were added. The reaction mixture was stirred at –78 °C for 7 h before being quenched with a solution of NH_4Cl-NH_4OH (1:1, 10 mL). The resulting mixture was extracted with hexane (20 mL x 3). The combined extracts were washed with NH_4Cl-NH_4OH solution (10 mL x 2), dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography of the residue (E/H=1:20) to give product **26** (0.11 g, 86%);

$[\alpha]_D$ +20.81 ° (c 0.86, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 9H), 2.52 (dd, *J*=10.12, 14.92 Hz, 1H), 2.92 (dd, *J*=4.56, 15.00 Hz, 1H), 2.98-3.42 (m, 2H), 3.24 (dd, *J*=3.88, 11.56 Hz, 1H), 3.41 (s, 3H), 3.49 (s, 3H), 3.54 (dd, *J*=1.40, 11.68 Hz, 1H), 4.04-4.07 (m, 1H), 4.49 (d, *J*=12.28 Hz, 1H), 4.57 (d, *J*=10.40 Hz, 1H), 4.66 (d, *J*=12.28 Hz, 1H), 4.85 (d, *J*=6.12 Hz, 1H), 4.87 (d, *J*=6.36 Hz, 1H), 4.88 (d, *J*=6.12 Hz, 1H), 4.98 (d, *J*=6.36 Hz, 1H), 7.14-7.41 (m, 23 H), 7.46-7.57 (m, 2H);

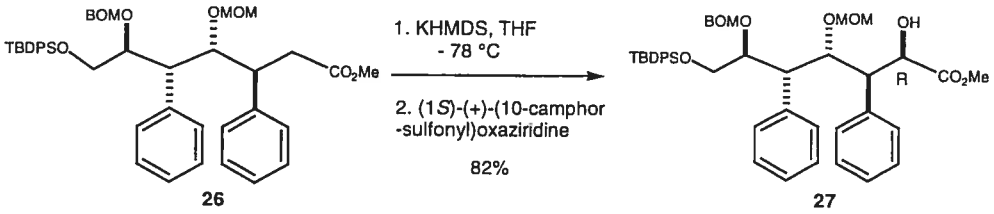
^{13}C NMR (100 MHz, $CDCl_3$) δ 18 97, 26.60, 39.37, 45.98, 48.24, 51.01, 50.39, 63.72, 69.97, 79.38, 82.01, 94.57, 99.54, 126.63, 126.74, 127.28, 127.35, 127.43, 127.55,

127.61, 128.24, 128.40, 128.57, 129.23, 129.35, 130.87, 133.14, 133.31, 135.32, 135.65, 137.26, 138.01, 141.21, 172.74;

IR (thin film) νmax 3030, 2931, 2857, 1738, 1496, 1454, 1428, 1362, 1260, 1155, 1113, 1104, 700 cm^{-1};

HRMS: $C_{46}H_{54}O_7SiNa$ (M^++Na), calc.: 769.35364, found: 769.35190.

(2*R*, 3*S*, 4*S*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-4-methoxymethoxy-3,5-diphenylheptanoic acid methyl ester (27):



26 **27**

To a solution of ester **26** (0.10 g, 0.13 mmol) in THF (3 mL) at –78 °C was added KHMDS (0.50 M, 0.54 mL, 0.28 mmol). The reaction mixture was stirred at this temperature for 1 h before a solution of (1*S*)-(+)-10-camphorsulfonyloxaziridine (0.064 g, 0.27 mmol) in THF (2 mL) was added. The resulting mixture was stirred at –78 °C for another 6 h before being quenched with NH_4Cl solution (70 mL). The product was extracted with diethyl ether (100 mL x 3). The combined organic extracts were dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography of the residue provided starting marterial (42 mg, with E/H=1:15 as eluents) and product **27** (0.049 g, 82% based on recorvered starting marterial, with E/H=1:8 as eluents);

$[\alpha]_D$ -12.56 ° (c 0.78, $CHCl_3$);

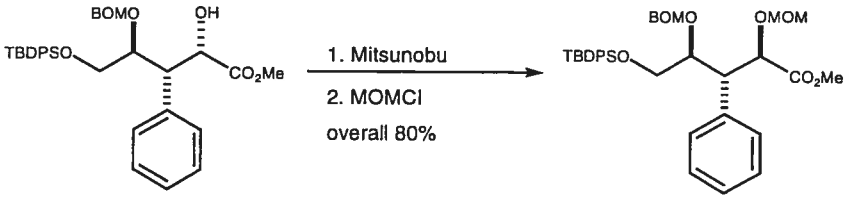
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 9 H), 2.84 (dd, *J*=2.64, 11.20 Hz, 1H), 2.94 (d, *J*=10.04 Hz, 1H), 3.28-3.35 (m, broad, 1H), 3.48 (s, 3H), 3.49 (s, 3H), 3.40-3.53 (m, 1H),

4.08-4.12 (m, 1H), 4.49 (d, *J*=12.16 Hz, 1H), 4.69 (d, *J*=12.06 Hz, 1H), 4.68-4.74 (m, 1H), 4.90-4.99 (m, 3H), 5.01 (d, *J*=6.28 Hz, 1H), 5.09 (d, *J*=6.28 Hz, 1H), 7.02-7.48 (m, 25 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 18.92, 26.52, 31.79, 47.94, 51.77, 52.43, 56.36, 63.75, 70.01, 70.65, 78.34, 79.31, 94.67, 99.56, 126.61, 127.23, 127.32, 127.42, 127.59, 127.66, 128.23, 129.16, 129.32, 129.55, 130.78, 133.30, 135.27, 135.54, 136.35, 137.17, 137.91, 171.19;

IR (thin film) 3511, 2930, 2849, 1778, 1495, 1492, 1453, 1407, 1261, 1225, 1113, 1041, 701 cm^{-1};

(2*R*, 3*R*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-methoxymethoxy-3-phenylpentanoic acid methyl ester (27):



22a **28**

To a solution of α-hydroxyl ester **22a** (1.50 g, 2.50 mmol) in toluene (20 mL) at 0 °C were added Ph_3P (3.28 g, 12.5 mmol), CH_2ClCO_2H (1.18 g, 12.5 mmol) and DEAD (2.17 g, 12.5 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 24 h before being quenched with NH_4CI solution (20 mL). The resulting mixture was extracted with diethyl ether (30 mL x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography of the residue provided the starting material (0.43 g, 29%, with E/H=1:6 as eluents) and the desired α-chloro-actoxyl

ester product (1.00 g, with E/H=1:10 as eluents, 85% based on recovered starting material).

To a solution of the α-chloro acetate product (1.00 g, 1.50 mmol) obtained from the above reaction in methanol (10 mL) was added sodium methoxide solution (0.50 M, 30 μL, 0.015 mmol). The reaction mixture was stirred ar room temperature for 1 h before being quenched with NH_4Cl solution (10 mL). The product was extracted with diethyl ether (20 mL x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:6) to give the alcohol (0.80 g, 90%);

$[\alpha]_D$ –35.9 ° (c 1.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 3.49 (dd, *J*=3.04, 11.48 Hz, 1H), 3.57-3.65 (broad, 1H), 3.67 (dd, *J*=1.84, 11.52 Hz, 1H), 3.84 (s, 3H), 3.98 (dd, *J*=1.68, 10.76 Hz, 1H), 4.22-4.28 (m, 1H), 4.38-4.44 (m, 1H), 4.46 (d, *J*=12.04 Hz, 1H), 4.61 (d, *J*=12.04 Hz, 1H), 4.74 (d, *J*=7.66 Hz, 1H), 4.78 (d, *J*=6.6 Hz, 1H), 7.26-7.48 (m, 18H), 7.64-7.66 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.23, 26.69, 49.13, 52.20, 63.29, 69.98, 73.03, 94.56, 127.13, 127.46, 127.54, 127.62, 128.30, 128.42, 128.98, 129.44, 129. 54, 133.18, 133.30, 135.39, 135.62, 137.65, 139.73, 174.88;

IR (thin film) 3498, 2931, 2857, 1735, 1495, 1472, 1454, 1428, 1258, 1234, 113, 1026, 701 cm^{-1};

HRMS: $C_{36}H_{42}O_6Si$ (M^++1), calc.: 599.28290, found: 599.28170.

To a solution of the above alcohol (0.80 g, 1.33 mmol) in CH_2Cl_2 (15 mL) at room temperature was added *i*-Pr_2NEt (0.46 mL, 2.66 mmol) and MOMCl (0.20 mL, 2.66 mmol). The mixture was stirred at room temperature for 16 h before being quenched with NH_4Cl solution (20 mL). The product was extracted with hexane (30 mL x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:20) to give **28** (0.79 g, 92%);

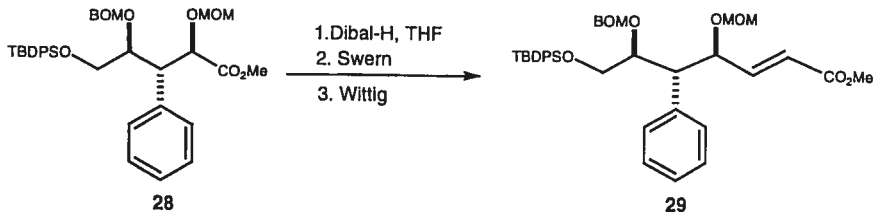
$[\alpha]_D$ -2.33 ° (c 0.85, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 3.16 (s, 3H), 3.55 (dd, *J*=2.80, 11.28 Hz, 1H), 3.74 (s, 3H), 3.80 (dd, *J*=2.12, 11.32 Hz, 1H), 4.09 (dd, *J*=2.64, 10.24 Hz,1H), 4.36 (dt, *J*=2.60, 10.48 Hz, 1H), 4.39 (d, *J*=2.64 Hz, 1H), 4.43 (d, *J*=12.04, 1H), 4.56 (d, *J*=2.00 Hz, 1H), 4.59 (d, *J*=7.04 Hz, 1H), 4.73 (d, *J*=7.08 Hz, 1H), 4.80 (d, *J*=6.84 Hz, 1H), 4.90 (d, *J*=7.04 Hz, 1H), 7.21-7.43 (m, 18H), 7.67-7.69 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.22, 26.67, 48.85, 51.44, 56.17, 63.58, 69.47, 76.64, 94.63, 96.37, 127.06, 127.31, 127.39, 127.40, 127.64, 128.17, 128.25, 129.26, 129.33, 129.52, 133.32, 134.71, 135.37, 135.46, 135.56, 135.67, 138.07, 139.32, 171.96;

IR (thin film) vmax 3071, 2933, 2893, 1746, 1499, 1474, 1378, 1364, 1155, 1072, 1032, 923, 789, 710 cm^{-1}.

(4*S*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-4-methoxymethoxy-5-phenylhept-2-enoic acid methyl ester (29):



28 29

To a solution of ester **28** (0.70 g, 1.09 mmol) in toluene (15 mL) at –78 °C was added Dibal-H (0.50 M, 6.54 mL, 3.27 mmol). The reaction mixture was stirred at –78 °C for 1.5 h before being quenched with NH_4Cl solution (15 mL). The resulting mixture was extracted with diethyl ether (30 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:5) to give the corresponding alcohol (0.58 g, 87%);

$[\alpha]_D$ –35.19 ° (c 0.85, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 3.37 (t, *J*=6.60 Hz, 1H), 3.41 (s, 3H), 3.50 (dd, *J*=7.12, 10.08 Hz, 1H), 3.60-3.70 (m, 2H), 3.78 (dd, *J*=3.92, 10.08 Hz, 1H), 4.11-4.18 (m, 1H), 4.28-4.30 (m, 1H), 4.55 (d, *J*=11.84 Hz, 1H), 4.69 (s, 2H), 4.70 (d, *J*=11.76 Hz, 1H), 4.90 (d, *J*=6.80 Hz, 1H), 4.96 (d, *J*=6.80 Hz, 1H), 7.20-7.48 (m, 6H), 7.50-7.53 (m, 2H), 7.68-7.70 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.08, 26.74, 48.99, 55.69, 64.55, 64.64, 69.95, 78.98, 83.51, 94.68, 97.51, 126.81, 127.52, 127.57, 127.69, 128.12, 128.30, 128.89, 129.48, 129.59, 129.76, 133.16, 133.18, 135.39, 135.55, 137.69, 139.51;

IR (thin film) νmax 3462, 2931, 2889, 2857, 1496, 1472, 1454, 1428, 1389, 1361, 1149, 1112, 1040, 823, 740, 702 cm^{-1}.

HRMS: $C_{37}H_{47}O_6Si$ (M^++1), calc.: 615.31421, found: 615.31600.

To a solution of oxalyl chloride (0.21 g, 0.15 mL, 1.73 mmol) in CH_2Cl_2 (15 mL) at –78 °C was added DMSO (0.27 g, 0.30 mL, 3.46 mmol). The reaction mixture was stirred for 15 min before the above alcohol (0.53 g, 0.86 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred and slowly warmed to –30 °C over 30 min before

triethylamine (0.87 g, 1.20 mL, 11.89 mmol) was added. The white precipitate was formed and the mixture was stirred at this temperature for 15 min before being quenched by NH_4Cl solution (20 mL). The organic layer was separated, dried and concentrated in *vacuo*. The crude aldehyde was dissolved in dry CH_2Cl_2 (25 mL) and $Ph_3P{=}CHCO_2CH_3$ (0.60 g, 1.72 mmol) was added. The mixture was stirred at r.t. for 12 h. The solvent was removed and the residue was purified by column chromatography (E/H=1:10) to give the product **29** (0.16 g, 84%) as a colorless oil;

R_f= 0.4 (E/H=1:8);

$[\alpha]_D$ -15.17 ° (c 0.85, $CHCl_3$);

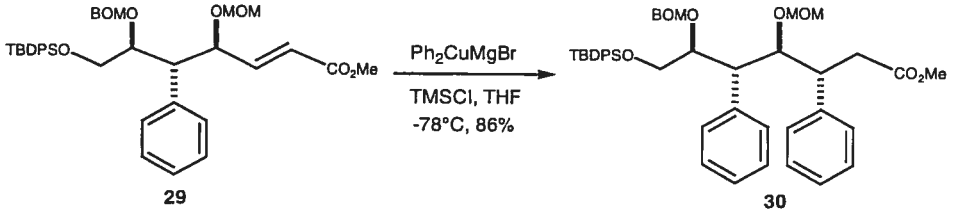
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H), 3.37 (s, 3H), 3.51 (dd, *J*=5.20, 9.28 Hz, 1H), 3.55 (dd, *J*=4.48, 11.16 Hz, 1H), 3.69 (s, 3H), 3.74 (dd, *J*=2.88, 11.08 Hz, 1H), 4.13 (m, 1H), 4.53 (d, *J*=11.96 Hz, 1H), 4.62 (d, *J*=6.80 Hz, 1H), 4.64 (d, *J*=6.80 Hz, 1H), 4.68 (d, *J*=11.96 Hz, 1H), 4.86 (d, *J*=6.88 Hz, 1H), 4.90-4.93 (m, 1H), 4.95 (d, *J*=6.88 Hz, 1H), 7.11-7.14 (m, 2H), 7.23-7.43 (m, 16H), 7.60-7.63 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.05, 26.66, 51.38, 55.78, 64.00, 70.06, 75.55, 78.66, 94.49, 94.79, 122.10, 126.89, 127.45, 127.51, 127.65, 127.97, 128.26, 129.40, 129.52, 133.06, 135.51, 137.64, 137.68, 146.41, 166.42;

IR (thin film) νmax 3030, 2931, 2891, 2859, 1726, 1472, 1485, 1362, 1274, 1168, 1112, 1042, 719 cm^{-1};

HRMS: $C_{40}H_{49}O_7Si$ (M^++1), calc.: 669.32477, found: 669.32260.

(3*R*, 4*S*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-4-methoxymethoxy-3,5-diphenylheptanoic acid methyl ester (30):



29 30

To a slurry of CuI (0.20 mg, 1.05 mmol) in THF (8 mL) at -78 °C was added PhMgBr (1.00 M, 2.10 mL, 2.10 mmol). The mixture was stirred for 1 h at -78 °C before TMSCl (0.56 mL, 0.48 g, 4.43 mmol) and α,β-unsaturated ester **29** (0.080 g, 0.12 mmol) in THF (2 mL) were added. The mixture was stirred at -78 °C for 7 h before being quenched with NH_4Cl-NH_4OH solution (1:1, 10 mL). The product was extracted with hexane (50 mL). The extract was washed with NH_4Cl-NH_4OH solution (10 mL x 2), dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography of the residue (silica gel, E/H=1:20) gave product **30** (0.076 g, 86%);

$[\alpha]_D$ -20.87 ° (c 0.91, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 2.62 (dd, *J*=10.64, 12.88 Hz, 1H), 2.83 (dd, *J*=4.64, 12.88 Hz, 1H), 3.37 (s, 3H), 3.40 (dd, *J*=3.76, 8.24 Hz, 1H), 3.47 (s, 3H), 3.50 (dd, *J*=3.72, 11.08 Hz, 1H), 3.74 (dd, *J*=2.84, 10.96 Hz, 1H), 3.76-3.82 (m, 1H), 4.01 (dd, *J*=3.80, 8.24 Hz, 1H), 4.32-4.37 (m, 1H), 4.51 (d, *J*=7.82 Hz, 1H), 4.53 (d, *J*=7.82 Hz, 1H), 4.54 (d, *J*=12.04 Hz, 1H), 4.63 (d, *J*=12.04 Hz, 1H), 4.91 (d, *J*=8.40 Hz, 1H), 4.93 (d, *J*=8.40 Hz, 1H), 6.90-93 (m, 2H), 7.16-7.42 (m, 21H), 7.62-7.68 (m, 2H);

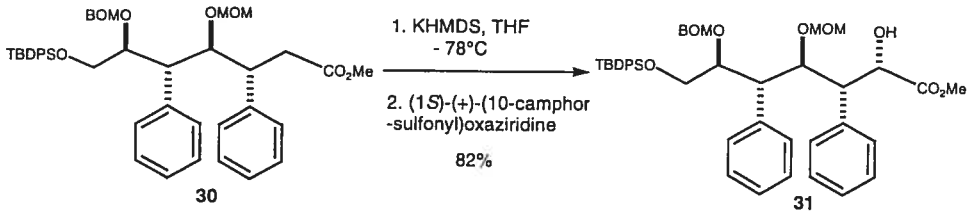
^{13}C NMR (100 MHz, $CDCl_3$) δ 18.98, 26.58, 36.79, 45.66, 48.03, 51.21, 56.44, 63.91, 69.51, 78.03, 86.97, 94.26, 99.23, 115.15, 120.50, 126.58, 127.29, 127.35, 127.45,

127.64, 128.20, 128.28, 128.26, 128.40, 128.59, 128.72, 129.18, 129.44, 129.51, 133.09, 133.21, 135.29, 135.59, 138.04, 140.98, 142.16, 173.10;

IR (thin film) νmax 3029, 2930, 2856, 1737, 1495, 1454, 1428, 1255, 1154, 1112, 1026, 701 cm^{-1};

HRMS: $C_{46}H_{54}O_7SiNa$ (M^++Na), calc.: 769.35364, found: 769.35190.

(2*S*, 3*R*, 4*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-4-methoxymethoxy-3,5-diphenylheptanoic acid methyl ester (31):



30 31

To a solution of ester **30** (0.050 g, 0.068 mmol) in THF (3 mL) at –78 °C was added KHMDS (0.50 M, 0.27 mL, 0.13 mmol). The reaction mixture was stirred at this temperature for 1 h before a solution of (1*S*)-(+)-10-camphorsulfonyloxaziridine (0.031 g, 0.13 mmol) in THF (1.5 mL) was added. The resulting mixture was stirred at –78 °C for another 6 h before being quenched with NH_4Cl solution (7 mL). The product was extracted with diethyl ether (15 mL x 3). The combined organic extracts were dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography of the residue provided starting marterial (0.024 g, with E/H=1:15 as eluents) and product **31** (0.022 g, 82 % based on recorved starting marterial, with E/H=1:7 as eluents);

$[\alpha]_D$ -45.00 ° (c 0.35, $CHCl_3$);

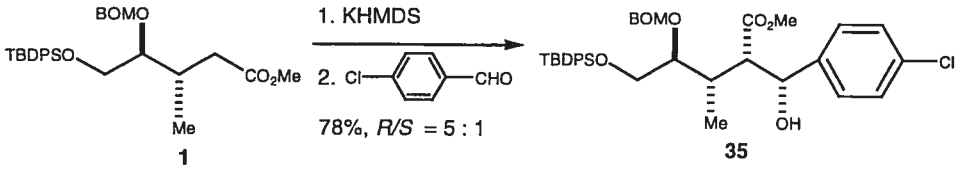
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 9H), 3.31-3.35 (m, 2H), 3.41 (s, 3H), 3.52-3.55 (m, 1H), 3.57 (s, 3H), 3.65 (d, *J*=11.48 Hz, 1H), 4.03-4.08 (m, 1H), 4.25 (d, *J*=11.12 Hz,

1H), 4.39 (d, *J*=10.60 Hz, 1H), 4.59 (d, *J*=12.08 Hz, 1H), 4.64 (d, *J*=6.32 Hz, 1H), 4.75 (d, *J*=12.08 Hz, 1H), 4.77 (d, *J*=6.32 Hz, 1H), 4.88-4.92 (m, 1H), 4.90 (d, *J*=6.76 Hz, 1H), 4.98 (d, *J*=6.76 Hz, 1H), 6.91-6.93 (m, 2H), 7.07-7.17 (m, 3H), 7.20-7.40 (m, 18H), 7.52-7.55 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 18.93, 26.45, 46.30, 51.69, 53.24, 56.54, 63.13, 69.66., 70.53, 93.55, 100.11, 126.43, 127.19, 127.36, 127.61, 128.21, 128.31, 128.36, 129.07, 129.38. 129.99, 135.57, 135.79, 174.90;

IR (thin film) 3515, 2932, 2851, 1776, 1495, 1494, 1455, 1401, 1257, 1113, 1046, 703 cm^{-1};

(2*S*, 3*S*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-[(*R*)-(4-chloro-phenyl)-hydroxymethyl]-3-methylpentanoic acid methyl ester (35):



To a solution of ester **1** in THF (0.22 g, 0.42 mmol) at –78 °C was added KHMDS solution (0.50 M, 1.26 mL, 0.63 mmol). The mixture was stirred at –78 °C for 1 h before a solution of 4-chlorobenzaldehyde (0.19 g, 1.27 mmol) in THF (3 mL) was added. The mixture was stirred at –78 °C for 2.5 h before a solution of NH_4Cl (15 mL) was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 50 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:8) to afford **35**-*R*-isomer (0.23 g, 78%) and **35**-*S*-isomer (0.046 g, 15.6%);

35-*R*-isomer

$[\alpha]_D$ -19.09 ° (c 0.99, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ1.07 (s, 9H), 1.15 (d, *J*=7.0 Hz, 3H), 1.15 (d, *J*=7.0 Hz, 1H), 2.50-2.60 (m, 1H), 2.88 (dd, *J*=3.96, 8.68 Hz, 1H), 3.45 (s, 3H), 3.61-3.65 (m, 1H), 3.76-3.86 (m, 2H), 4.56 (d, *J*=11.96 Hz, 1H), 4.63 (d, *J*=11.96 Hz, 1H), 4.78 (d, *J*=6.76 Hz, 1H), 4.86 (d, *J*=6.76 Hz, 1H), 5.04 (dd, *J*=3.76, 9.08 Hz, 1H), 7.20-7.48 (m, 15H), 7.67-7.70 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.52, 19.11, 26.71, 35.62, 51.38, 54.15, 64.16, 69.65, 71.12, 80.09, 94.40, 126.92, 127.50, 127.62, 128.25, 128.27, 129.67, 132.88, 133.13, 133.17, 135.51, 135.56, 137.75, 141.16, 175.27;

IR (neat) νmax 3479, 2956, 2863, 1734, 1592, 1518, 1456, 1432, 1181, 1111, 1041, 703 cm^{-1};

m/e: 683 (M^++Na), 673, 643, 603, 553, 445, 413, 385, 267, 235, 197, 135, 91, 77.

35-*S*-isomer

$[\alpha]_D$ +4.50 ° (c 0.86, $CHCl_3$);

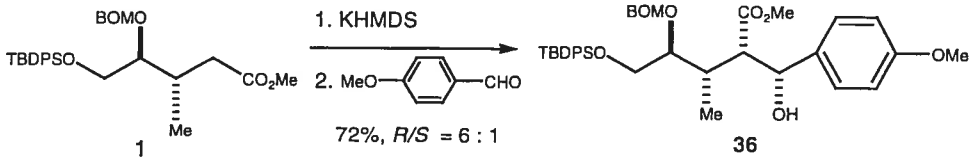
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.20 (d, *J*=7.20 Hz, 1H), 2.48-2.57 (m, 1H), 3.13 (dd, *J*=2.16, 9.64 Hz, 1H), 3.42 (s, 3H), 3.81 (dd, *J*=5.12, 11.16 Hz, 1H), 3.89 (dd, *J*=4.29, 11.04 Hz, 1H), 3.95-4.00 (m, 1H), 4.28 (d, *J*=4.04 Hz, 1H), 4.56 (d, *J*=11.84 Hz, 1H), 4.66 (d, *J*=11.84 Hz, 1H), 4.81 (d, *J*=6.52 Hz, 1H), 4.93 (d, *J*=6.52 Hz, 1H), 7.26-7.50 (m, 15H), 7.68-7.73 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.80, 19.12, 26.72, 34.94, 51.20, 53.93, 63.92, 70.17, 71.37, 81.50, 95.18, 127.66, 127.69, 127.72, 127.76, 128.16, 128.22, 128.39, 129.73, 133.06, 133.12, 135.51, 135.58, 137.09, 141.37, 173.36;

IR (neat) νmax 3481, 2963, 2863, 1733, 1589, 1517, 1455, 1433, 1184, 1112, 1044, 702 cm^{-1};

m/e: 683 (M^++Na), 643, 603, 553, 445, 413, 385, 267, 235, 197, 135, 91, 77.

(2*S*, 3*S*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-[(*R*)-hydroxy-(4-methoxyphenyl)-methyl]-3-methylpentanoic acid methyl ester (36):



To a solution of ester **1** (0.20 g, 0.38 mmol) in THF (6 mL) at –78 °C was added KHMDS solution (0.50 M in toluene, 1.15 mL, 0.58 mmol). The reaction mixture was stirred at –78 °C for 1 h before *p*-anisaldehyde (0.16 g, 0.14 mL, 1.14 mmol) was added. The reaction mixture was stirred at –78 °C for 2.5 h before a solution of saturated NH_4Cl solution (10 mL) was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 100 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to afford **36**-*R*-isomer (0.19 g, 72%) and **36**-*S*-isomer (0.031 g, 12%);

36-*R*-isomer

$[\alpha]_D$ -23.17 ° (c 1.10, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.05-2.11 (m 1H), 2.80-2.86 (broad, 1H), 3.23 (dd, *J*=3.92, 8.64 Hz, 1H), 3.57-3.60 (m, 1H), 3.63 (s, 3H), 3.71 (dd, *J*=4.40, 11.16 Hz, 1H), 3.77 (s, 3H), 3.77-3.86 (m, 2H), 4.49 (d, *J*=12.00 Hz, 1H), 4.57 (d, *J*=12.00 Hz, 1H), 4.73 (d, *J*=6.80 Hz, 1H), 4.77 (d, *J*=6.80 Hz, 1H), 4.96 (d, *J*=8.52 Hz, 1H), 6.85 (d, *J*=8.68 Hz, 2H), 7.23-7.45 (m, 13H). 7.56-7.63 (m, 4H);

^{13}C NMR (400 MHz, $CDCl_3$) δ 12.46, 19.04, 26.64, 34.20, 51.29, 51.99, 55.06, 63.34, 69.54, 73.65, 80.44, 94.65, 113.91, 127.39, 127.51, 127.55, 127.81, 128.21, 129.56, 133.24, 133.29, 133.45, 135.48, 135.56, 137.87, 159.23, 174.65;

IR (neat) νmax 3478, 2933, 2858, 1732, 1612, 1588, 1513, 1428, 1250, 1173, 1112, 1038, 703 cm^{-1};

m/e: 679 (M^++Na), 657, 609, 547, 517, 461, 441, 381, 323, 247, 217, 135, 91, 73.

36-*S*-isomer

$[\alpha]_D$ –23.78 ° (c 1.32, $CHCl_3$);

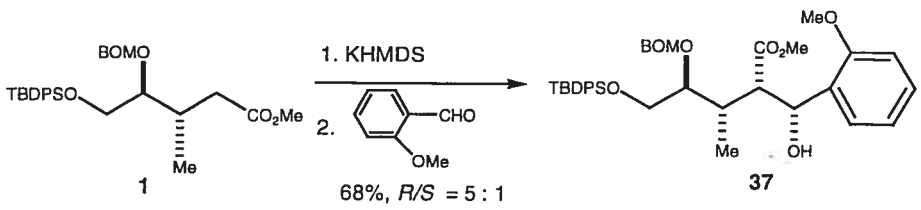
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.19 (d, *J*=7.24 Hz, 1H), 2.49-2.54 (m, 1H), 3.16 (dd, *J*=2.44, 9.76 Hz, 1H), 3.39 (s, 3H), 3.79 (s, 3H), 3.78-3.84 (m, 1H), 3.88 (dd, *J*=4.36, 11.08 Hz, 1H), 3.96 (d, *J*=6.36 Hz, 1H), 3.99 (d, *J*=6.36 Hz, 1H), 4.56 (d, *J*=11.88 Hz, 1H), 4.67 (d, *J*=11.88 Hz, 1H), 4.87 (d, *J*=6.60 Hz, 1H), 4.94 (d, *J*=6.60 Hz, 1H), 4.96 (dd, *J*=3.92, 9.72 Hz, 1H), 6.80 (d, *J*=8.68 Hz, 2H), 7.20-7.48 (m, 13H), 7.68-7.73 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ13.65, 19.11, 26.71, 35.06, 51.09, 53.93, 55.09, 64.07, 70.10, 71.64, 81.57, 95.17, 113.65, 127.62, 127.65, 127.71, 127.87, 128.34, 129.66, 133.13, 134.95, 135.51, 135.57, 137.26, 158.88, 173.59;

IR (neat) νmax 3479, 2954, 2856, 1733, 1591, 1514, 1432, 1240, 1176, 1111, 1039, 703cm^{-1};

m/e: 679 (M^++Na), 657, 609, 547, 517, 461, 441, 381, 323, 247, 217, 135, 91, 73.

(2*S*, 3*S*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-[(*R*)-hydroxy-(2-methoxyphenyl)-methyl]-3-methylpentanoic acid methyl ester (37):



To a solution of ester **1** (0.20 g, 0.38 mmol) in THF (6 mL) at –78 °C was added KHMDS solution (0.50 M in toluene, 1.15 mL, 0.58 mmol). The reaction mixture was stirred at –78 °C for 1 h before a solution of *o*-anisaldehyde (0.16 g, 1.14 mmol) in THF (2.5 mL) was added. The reaction mixture was stirred at –78 °C for 2.5 h before a solution of NH_4Cl (10 mL) was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 100 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to afford the **37**-*R* isomer (0.18 g, 68%) and **37**-*S* isomer (0.036 g, 13.5%);

37-*R*-isomer

$[\alpha]_D$ –12.6 ° (c 0.98, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 0.98 (d, *J*=7.22 Hz, 1H), 2.09-2,17 (m, 1H), 3.32 (dd, *J*=3.62, 8.68 Hz, 1H), 3.58 (s, 3H), 3.49-3.69 (m, 2H), 3.69 (s, 3H), 4.50 (d, *J*=11.86 Hz, 1H), 4.61 (d, *J*=11.96 Hz, 1H), 4.77 (d, *J*=6.68 Hz, 1H), 4.82 (d, *J*=6.72 Hz, 1H), 5.22 (t, *J*=8.08 Hz, 1H), 6.83 (d, *J*=8.28 Hz, 1H), 6.95 (t, *J*=7.48 Hz, 1H), 7.20-7.48 (m, 12H), 7.59-7.65 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.76, 19.06, 26.67, 34.77, 51.09, 51.15, 55.04, 63.67, 69.46, 70.22, 80.37, 94.75, 110.51, 120.73, 127.37, 127.50, 127.55, 127.62, 127.73, 128.21, 128.76, 129.35, 129.53, 129.66, 133.36, 135.50, 135.56, 137.96, 156.46, 174.62;

IR (neat) νmax 3498, 2933, 2858, 1735, 1602, 1589, 1492, 1463, 1428, 1242, 1167, 1112, 1027, 741, 702, 610 cm^{-1};

m/e: 550, 517, 461, 441, 381, 309, 267, 247, 197, 135, 91.

37-*S*-isomer

$[\alpha]_D$ –9.8 ° (c 1.24, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.19 (d, *J*=6.96 Hz, 3H), 2.49-2.69 (m, 1H), 2.96 (dd, *J*=3.36, 10.36 Hz, 1H), 3.36 (s, 3H), 3.60-3.68 (m, 1H), 3.72 (s, 3H), 3.76-3.81 (m, 2H), 4.56 (d, *J*=11.92 Hz, 1H), 4.63 (d, *J*=11.92 Hz, 1H), 4.79 (d, *J*=6.76 Hz, 1H), 4.87 (d, *J*=6.76 Hz, 1H), 5.32 (dd, *J*=3.32, 10.08 Hz, 1H), 6.82 (d, *J*=8.16 Hz, 1H), 6.95 (t, *J*=7.44 Hz, 1H), 7.20-7.49 (m, 13 H), 7.68-7.72 (m, 4H);

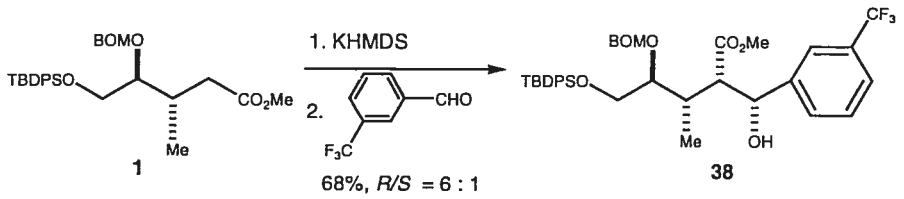
^{13}C NMR (100 MHz, $CDCl_3$) δ 12.90, 19.07, 26.65, 35.55, 51.05, 52.10, 55.10, 64.45, 67.24, 69.59, 80.83, 94.29, 109.89, 120.32, 125.94, 127.42, 127.55, 127.57, 127.64,

127.71, 128.13, 128.23, 129.53, 129.55, 130.51, 133.28, 133.34, 135.51, 135.55, 137.91, 155.54, 175.57;

IR (neat) νmax 3499, 2945, 2858, 1734, 1601, 1588, 1496, 1465, 1421, 1248, 1112, 1026, 744, 701 cm^{-1};

m/e: 550, 517, 461, 441, 381, 309, 267, 247, 197, 135, 91.

(2*S*, 3*S*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-2-[(*R*)-hydroxy-(3-trifluromethylphenyl)-methyl]-3-methylpentanoic acid methyl ester (38):



To a solution of ester **1** (0.16 g, 0.3 mmol) in THF (4 mL) at –78 °C was added KHMDS solution (0.50 M in toluene, 0.45 mmol). The reaction mixture was stirred at –78 °C for 1 h before a solution of α,α,α-trifluoro-*m*-tolualdehyde (0.10 g, 80 μL, 0.60 mmol) was added. The reaction mixture was stirred at –78 °C for 2.5 h before a solution of NH_4Cl (10 mL) was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 50 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:8) to afford **38**-*R*-isomer (0.14 g, 68%) and **38**-*S*-isomer (0.024 g, 11.33%);

38-*R*-isomer

$[\alpha]_D$ –1.29 ° (c 0.92, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.18 (d, *J*=7.00 Hz, 3H), 2.53-2.65 (m, 1H), 2.93 (dd, *J*=3.60, 9.88 Hz, 1H), 3.42 (s, 3H), 3.64 (dd, *J*=5.12, 10.28 Hz, 1H), 3.72-3.84 (m, 2H), 3.87 (d, *J*=9.44 Hz, 1H), 4.55 (d, *J*=11.96 Hz, 1H), 4.61 (d, *J*=11.96 Hz, 1H), 4.78 (d, *J*=6.72 Hz, 1H), 4.85 (d, *J*=6.76 Hz, 1H), 5.10-5.16 (m, 1H), 7.22-7.74 (m, 19H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.37, 19.05, 26.65, 35.65, 51.33, 54.05, 64.11, 69.67, 71.15, 79.96, 94.32, 122.21, 122.25, 124.01, 124.05, 127.50, 127.62, 128.26, 128.55, 128.96, 129.66, 129.68, 130.36, 130.68, 133.08, 133.10, 135.49, 135.54, 137.71, 143.82, 175.11;

IR (neat) νmax 3461, 2932, 2857, 1732, 1612, 1587, 1513, 1462, 1428, 1248, 1037, 830, 740, 702 cm^{-1};

38-*S*-isomer

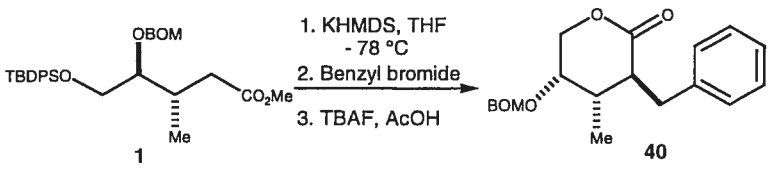
$[\alpha]_D$ −18.2 ° (c 1.40, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.22 (d, *J*=7.24 Hz, 3H), 2.56-2.65 (m, 1H), 3.14 (dd, *J*=2.32, 9.68 Hz, 1H), 3.40 (s, 3H), 3.20 (dd, *J*=5.08, 11.04 Hz, 1H), 3.89 (dd, *J*=4.92, 11.08 Hz, 1H), 3.98 (q, *J*=6.32 Hz, 1H), 4.51 (d, *J*=3.92 Hz, 1H), 4.57 (d, *J*=11.84 Hz, 1H), 4.66 (d, *J*=11.84 Hz, 1H), 4.87 (d, *J*=6.56 Hz, 1H), 4.92 (d, *J*=6.56 Hz, 1H), 5.08 (dd, *J*=3.80, 9.68 Hz, 1H), 7.27-7.77 (m, 19H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.94, 19.10, 26.69, 34.87, 51.17, 54.23, 63.79, 70.21, 71.49, 81.35, 95.07, 123.56, 123.60, 124.29, 124.33, 127.66, 127.69, 127.76, 128.38, 128.53, 129.75, 130.18, 130.53, 133.01, 135.50, 135.56, 137.03, 143.89, 173.22;

IR (neat) νmax 3461, 2932, 2857, 1732, 1612, 1587, 1513, 1462, 1428, 1248, 1037, 830, 740, 702 cm^{-1};

(3*S*, 4*S*, 5*S*)-3-Benzyl-5-benzyloxymethoxy-4-methyltetrahydropyran-2-one (40):



To a solution of ester **1** (0.30 g, 0.58 mmol) in THF (8 mL) at –78 °C was added KHMDS solution (0.50 M in toluene, 1.50 mL, 0.75 mmol). The reaction mixture was stirred at –78 °C for 1 h before a solution of benzyl bromide (0.35 mL, 0.51 g, 3.00 mmol) was added. The reaction mixture was stirred at –78 °C for 2.5 h and then a solution of saturated NH_4Cl solution was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 20 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:15) to afford the α-benzyl ester (0.30 g, 86%).

To a solution of the above α-benzyl ester (0.30 g, 0.49 mmol) in THF (9 mL) at room temperature was added TBAF-AcOH (1:1, 0.94 M, 2.28 mL, 2.15 mmol). The reaction mixture was stirred and monitored by TLC. After 2 h, the reaction was complete and the reaction mixture was acidified with acetic acid to pH 1. The mixture was then stirred for 1 h before being diluted with ethyl acetate (15 mL). The resulting mixture was washed with $NaHCO_3$ solution, NH_4Cl solution, brine and dried over Na_2SO_4. The solvent was

removed in *vacuo*. The residue was purified by column chromatography (E/H=1:3) to give lactone **40** (0.14 g, 82%);

$[\alpha]_D$ –31.57 ° (c 0.89, $CHCl_3$);

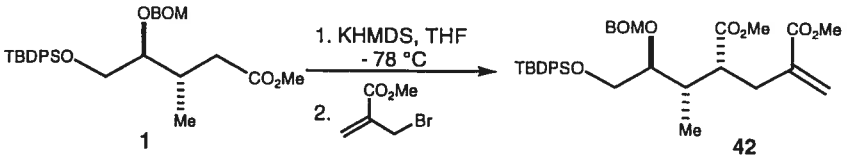
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J*=6.69 Hz, 1H), 1.87-1.98 (m, 1H), 2.82-2.92 (m, 1H), 2.92 (dd, *J*=5.25, 18.93 Hz, 1H), 3.50 (dd, *J*=4.26, 18.36 Hz, 1H), 3.73-3.80 (m, 1H), 3.88 (dd, *J*=1.53, 12.09 Hz, 1H), 4.44 (dd, *J*=2.58, 12.15 Hz, 1H), 4.61 (d, *J*=11.55 Hz, 1H), 4.67 (d, *J*=11.55 Hz, 1H), 4.79 (d, *J*=7.32 Hz, 1H), 4.91 (d, *J*=7.32 Hz, 1H), 7.20-7.45 (m, 10H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.99, 33.04, 34.79, 45.50, 69.84, 69.90, 72.67, 93.59, 126.63, 127.82, 127.85, 128.29, 128.42, 128.47, 129.38, 137.18, 138.13, 172.61;

IR (thin film) νmax 2937, 2896, 1729, 1603, 1496, 1454, 1399, 1252, 1209, 1164, 1103, 1044 cm^{-1};

HRMS; $C_{21}H_{25}O_4$ (M^++1), calcd: 341.16746, found: 341.16712.

(2*R*)-2-[(1*S*, 2*S*)-2-Benzyloxymethoxy-3-(*tert*-butyldiphenylsilanyloxy)-1-methyl-propyl]-4-methylenepentanedioic acid dimethyl ester (42):



To a solution of ester **1** (0.15 g, 0.29 mmol) in THF (5 mL) at –78 °C was added KHMDS solution (0.50 M, 0.75 mL, 0.37 mmol). The reaction mixture was stirred at –78 °C for 1 h before methyl (2-bromomethyl)acrylate (0.26 g, 0.17 mL, 1.44 mmol) was

added. The reaction mixture was stirred at –78 °C for 2.5 h before a solution of NH_4Cl (10 mL) was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 20 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:6) to afford product **42** (0.15 g, 82%);

$[\alpha]_D$ -3.71 ° (c 1.10, $CHCl_3$);

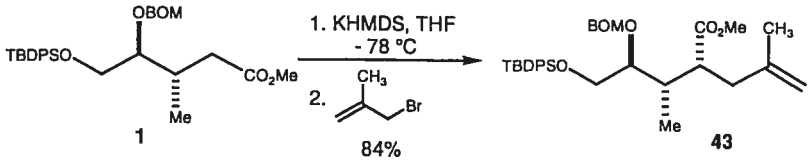
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J*=7.08 Hz, 1H), 1.09 (s, 9H), 2.37-2.46 (m, 1H), 2.55 (dd, *J*=11.72, 13.68 Hz, 1H), 2.67 (dd, *J*=1.96, 14.20 Hz, 1H), 2.98-3.05 (m, 1H), 3.63 (s, 3H), 3.72 (s, 3H), 3.71-3.78 (m, 1H), 3.80 (dd, *J*=5.36, 11.01 Hz, 1H), 4.55 (d, *J*=12.00 Hz, 1H), 4.62 (d, *J*=12.00 Hz, 1H), 4.81 (d, *J*=6.84 Hz, 1H), 4.88 (d, *J*=6.84 Hz, 1H), 5.57 (s, 1H), 6.13 (s, 1H), 7.27-7.46 (m, 11H), 7.68-7.73 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.27, 19.13, 26.73, 30.29, 37.12, 45.53, 51.16, 51.72, 64.19, 69.58, 80.50, 94.70, 110.51, 126.06, 127.40, 127.59, 127.62, 128.22, 129.61, 133.29, 135.55, 135.61, 137.89, 138.55, 167.09, 175.25;

IR (thin film) νmax 2951, 2888, 2858, 1732, 1631, 1590, 1472, 1439, 1428, 1389, 1362, 1306, 1196, 1149, 1112, 1039, 823, 740, 702 cm^{-1};

m/e: 619.3 (M^++1), 589.2, 561.2, 511.3, 481.3, 309.2, 239.1, 197.1, 135.1.

(2*R*, 3*S*, 4*S*)-5-Benzyloxymethoxy-4-methyl-3-(2-methylallyl)-tetrahydropyran-2-one (43):



To a solution of ester **1** (0.15 g, 0.29 mmol) in THF (5 mL) at –78 °C was added KHMDS solution (0.50 M in toluene, 0.75 mL, 0.37 mmol). The mixture was stirred at –78 °C for 1 h before a solution of 3-bromo-2-methyl propene (0.15 mL, 0.14 g, 1.44 mmol) was added. The mixture was stirred at –78 °C for 2.5 h before a solution of saturated NH_4Cl solution was added. The resulting mixture was extracted with hexane-ethyl acetate (1:1, 20 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:15) to afford product **43** (0.14 g, 84%);

$[\alpha]_D$ +1.18 ° (c 1.43, $CHCl_3$);

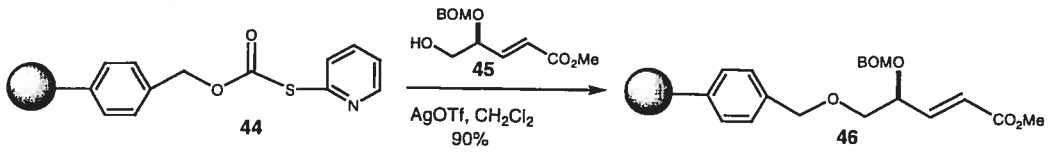
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J*=7.11 Hz, 3H), 1.07 (s, 9H), 1.70 (s, 3H), 2.15-2.23 (m, 1H), 2.29-2.40 (m, 2H), 2.91-3.00 (m, 1H), 3.60-3.64 (m, 1H), 3.64 (s, 3H), 3.76 (dd, *J*=5.28, 11.01 Hz, 1H), 3.83 (dd, *J*=4.14, 11.01 Hz, 1H), 4.53 (d, *J*=12.03 Hz, 1H), 4.03 (d, *J*=12.03 Hz, 1H), 4.68 (d, *J*=1.35 Hz, 1H), 4.73 (s, 1H), 4.77 (d, *J*=6.84 Hz, 1H), 4.87 (d, *J*=6.84 Hz, 1H), 7.29-7.49 (m, 11H), 7.68-7.74 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.18, 19.12, 22.66, 26.73, 35.69, 37.13, 44.84, 51.19, 64.11, 69.60, 79.96, 94.31, 111.10, 127.42, 127.58, 127.60, 127.62, 128.23, 129.62, 133.28, 135.54, 135.61, 137.89. 143.59, 175.69;

IR (thin film) νmax 3071, 2932, 2858, 1737, 1428, 1380, 1166, 1112, 1039, 891, 823, 739, 701 cm^{-1};

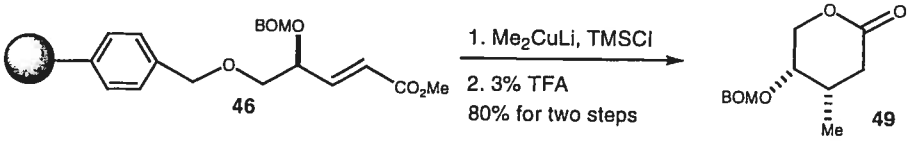
m/e: 575.3 (M^++1), 543.3, 523.3, 309.2, 197.1, 135.1, 121.1.

Synthesis of **46**



To a solution of alcohol **45** (1.37g, 5.16 mmol) in CH_2Cl_2 (35 mL) was added the resin **44** (3.00 g, 0.77 mmol/g, 2.31 mmol) and AgOTf (1.33 g, 5.16 mmol). The reaction mixture was stirred at r.t for 20 h (The reaction was monitored by infrared spectroscopy). The resin **46** was then washed with DMF, THF, CH_2Cl_2, hexane and dried in *vacuo*. The dried resin **46** (0.20 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (3 mL) for 1 h. The resin was then removed by filtration. The filtrate was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:4) afforded recovered alcohol **45** (0.037 g, 90%, so the loading was 0.69 mmol/g).

(4*S*, 5*S*)-5-Benzyloxymethoxy-4-methyltetrahydropyran-2-one (49):



To a solution of $MeCuLi_2$ at –78 °C [prepared by the addition of MeLi (complex with $MgBr_2$, 23.00 mL, 1.50 M in diethyl ether, 34.6 mmol) to CuI (2.88 g, 17.3 mmol) in THF (60 mL) at –15 °C, and the mixture was warmed to 0 °C in 0.5 h] was added TMSCl (72.9 mmol, 7.03 g, 8.03 mL) and resin **46** (2.50 g, 1.73 mmol) in THF (15 mL). The mixture was stirred at –78 °C for 2 h, -45 °C for 2 h, -25 °C for 2 h before being neutralized with acetic acid. NH_4Cl/NH_4OH (1:1, 100 mL) solution was added to dissolve all the copper salts. The resin was filtered and stirred in a mixture of NH_4Cl/NH_4OH (1:1, 7 mL) in THF (80 mL) for 20 min, after which, filtration was repeated. This procedure

was repeated two times. The resin was then washed with water, THF, DMF, CH_2Cl_2, hexane and dried in *vacuo* for 24 h. This cuprate reaction was repeated exactly as before to ensure high conversion. The dried resin **47** (0.15 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (5 mL) for 1 h. The resin was then removed by filtration. The filtrate was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated. Column chromatography of the residue (E/H=1:7) afforded lactone **49** (0.021 g, 80%, loading: 0.55 mmol/g);

$[\alpha]_D$ -53.45 ° (c 1.06, $CHCl_3$);

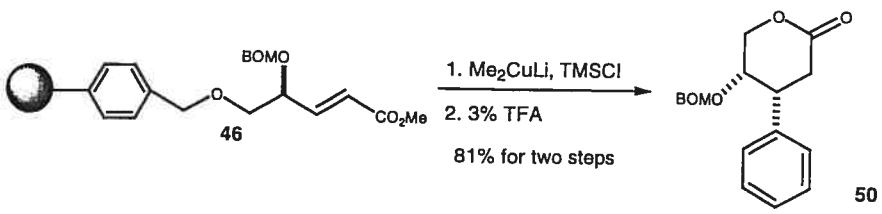
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, *J*=6.69 Hz, 3H), 2.17-2.30 (m, 1H), 2.53 (d, *J*=4.38 Hz, 1H), 2.56 (d, *J*=1.80 Hz, 1H), 3.81-3.85 (m, 1H), 4.27 (dd, *J*=2.07, 12.39 Hz, 1H), 4.59 (dd, *J*=2.28, 12.39 Hz, 1H), 4.64 (d, *J*=11.01 Hz, 1H), 4.68 (d, *J*=11.01 Hz, 1H), 4.82 (d, *J*=7.32 Hz, 1H), 4.94 (d, *J*=7.29 Hz, 1H), 7.32-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.83, 31.02, 33.65, 69.85, 71.35, 71.73, 93.70, 127.84, 128.45, 137.14, 170.13;

IR (thin film) νmax 2964, 2897, 1738, 1498, 1455, 1402, 1359, 1239, 1202, 1162, 1102, 1042, 913, 853, 802, 740, 699 cm^{-1};

HRMS: $C_{14}H_{19}O_4$ (M^++1), calcd: 251.12041, found: 251.12102.

(4*R*, 5*S*)-5-Benzyloxymethoxy-4-phenyltetrahydropyran-2-one (50):



To a slurry of CuI (3.00 g, 15.57 mmol) in THF (40 mL) was added PhMgBr (31.50 mL, 1.00 M in THF, 31.50 mmol). The reaction mixture was stirred at –78 °C for 1 h before TMSCl (5.86 mL, 47.25 mmol) and resin **46** (1.50 g, 1.04 mmol) in THF (15 mL) were added. The reaction mixture was stirred at –78 °C for 2 h, -45 °C for 2 h, -25 °C for 2 h before being quenched with acetic acid. NH_4Cl/NH_4OH (1:1, 150 mL) solution was added to dissolve all the copper salts. The resin was filtered and stirred in a mixture of NH_4Cl/NH_4OH (1:1, 10 mL) and THF (100 mL) for 20 min, after which, filtration was repeated. This procedure was repeated twice. The resin was then washed with water, DMF, THF, CH_2Cl_2, hexane and dried under vacuum for 24 h. This cuprate reaction was repeated exactly as before to ensure high conversion. The dried resin (150 mg) was added to a solution of 3% TFA in CH_2Cl_2 (5 mL) and was stirred for 1 h. The resin was then removed by filtration. The filtrate was diluted with ethyl acetate (10 mL), washed with $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:2) afforded the lactone **50** (0.026 g, 81%, loading: 0.56 mmol/g);

$[\alpha]_D$ -78.19 ° (c 0.77, $CHCl_3$);

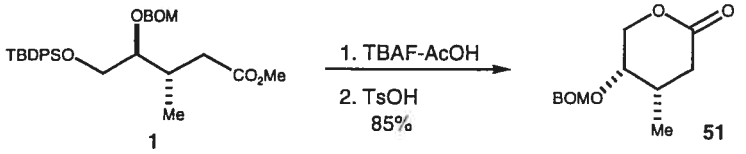
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, *J*=5.60, 17.20 Hz, 1H), 3.27 (dd, *J*=13.28, 17.24 Hz, 1H), 3.35-3.45 (m, 1H), 4.10-4.18 (m, 2H), 4.30 (d, *J*=11.56 Hz, 1H), 4.45 (dd, *J*=2.00, 12.48 Hz, 1H), 4.52 (d, *J*=7.32 Hz, 1H), 4.64 (dd, *J*=1.72, 12.48 Hz, 1H), 4.80 (d, *J*=7.36 Hz, 1H), 7.11-7.42 (m, 10H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 30.93, 41.63, 69.49, 71.31, 71.45, 92.99, 127.49, 127.65, 127.77, 127.84, 128.32, 128.58, 136.97, 138.98, 169.90;

IR (thin film) νmax 3006, 2949, 2895, 1737, 1604, 1498, 1454, 1401, 1201, 1160, 1095, 1036, 990,947, 842, 763, 699 cm^{-1};

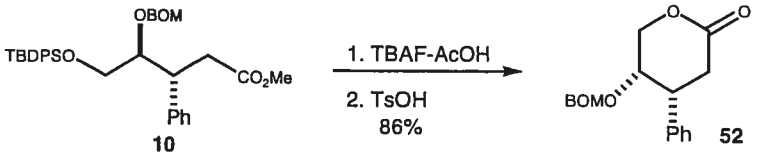
HRMS: $C_{19}H_{21}O_4$ (M^++1), calcd: 313.13611, found: 313.13507.

Solution phase synthesis of lactone 51:



To a solution of ester **1** (0.30 g, 0.57 mmol) in THF (5 mL) at r. t. was added TBAF-AcOH (1:1, 0.94 M, 3.06 mL, 2.88 mmol). The reaction mixture was stirred and monitored by TLC. After 1.5 h, the reaction was complete and the reaction mixture was acidified with $TsOH{\cdot}H_2O$ to pH 1. The reaction mixture was then stirred for further 1 h before being diluted with ethyl acetate (15 mL). The resulting mixture was nutralized with $NaHCO_3$ solution, washed with saturated NH_4Cl, brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to give lactone **51** (0.12 g, 85%).

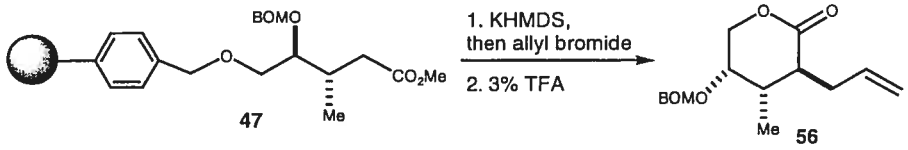
Solution phase synthesis of lactone 52:



To a solution of ester **10** (0.25 g, 0.43 mmol) in THF (5 mL) at room temperature was added TBAF-AcOH (1:1, 0.94 M, 2.28 mL, 2.15 mmol). The reaction mixture was stirred

and monitored by TLC. After 2 h, the reaction was complete and the reaction mixture was acidified with $TsOH{\cdot}H_2O$ to pH 1. The reaction mixture was then stirred for further 1 h before was diluted with ethyl acetate (15 mL). The resulting mixture was nutralized with $NaHCO_3$ solution, washed with saturated NH_4Cl, brine and dried over Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to give lactone **52** (0.12 g, 86%).

(3*S*, 4*S*, 5*S*)-3-Allyl-5-benzyloxymethoxy-4-methyltetrahydropyran-2-one (56):



To a suspension of resin **47** (0.30 g, 0.21 mmol) in THF (5 mL) at –78 °C was added KHMDS (1.26 mL, 0.50 M in toluene, 0.63 mmol). The mixture was stirred for 1 h before allyl bromide (91 μL, 0.13 g, 1.05 mmol) was added *via* syringe. The reaction mixture was stirred for further 1.5 h. The resin was then removed by filtration, washed with DMF, THF, ether, CH_2Cl_2 and dried in *vacuo*. The dried resin **53** (0.15 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (4 mL) and stirred for 1.5 h. The resin was then removed by filtration. The filtrate was washed with $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated. Column chromatography of the residue (E/H=1:3) afforded the lactone **56** (0.023 g, 75%, loading: 0.52 mmol/g);

$[\alpha]_D$ -44.97 ° (c 0.86, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J*=6.69 Hz, 1H), 1.02-1.13 (m, 1H), 2.34 (ddd, *J*=4.59, 9.07, 13.89 Hz, 1H), 2.66 (ddd, *J*=4.68, 4.71, 11.01 Hz, 1H), 2.84-2.93 (m, 1H), 3.82-3.85 (m, 1H), 4.21 (dd, *J*=1.71, 12.21Hz, 1H), 4.55 (dd, *J*=1.11, 12.21 Hz, 1H), 4.62

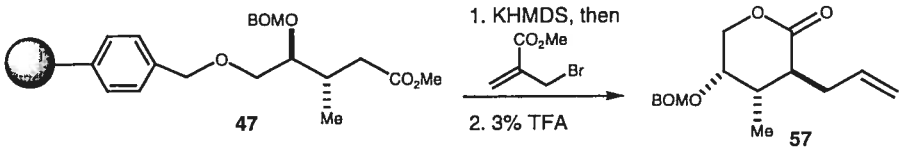
(d, *J*=11.61 Hz, 1H), 4.68 (d, *J*=11.61 Hz, 1H), 4.81 (d, *J*=7.32 Hz, 1H), 4.92 (d, *J*=7.62 Hz, 1H), 5.11 (d, *J*=1.62 Hz, 2H), 5.16 (dd, *J*=0.57, 8.61 Hz, 1H), 5.67-5.83 (m, 1H), 5.28-5.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.80, 32.96, 33.82, 43.21, 69.84, 70.35, 72.88, 93.65, 118.34, 127.82, 127.85, 128.43, 133.98, 137.18, 172.24;

IR (thin film) νmax 2968, 2897, 1732, 1640, 1455, 1400, 1255, 1205, 1163, 1102, 1043, 739, 699 cm^{-1};

HRMS: $C_{17}H_{23}O_4$ (M^++1), calcd: 291.15184, found: 291.15098.

(3*S*, 4*S*, 5*S*)-2-(5-Benzyloxymethoxy-4-methyl-2-oxo-tetrahydropyran-3-ylmethyl)-acrylic acid methyl ester (57):



To a suspension of resin **47** (0.30 g, 0.21 mmol) in THF (5 mL) at –78 °C was added KHMDS (1.26 mL, 0.50 M in toluene, 0.63 mmol). The reaction mixture was stirred for 1 h before methyl 2-(bromomethyl)acrylate (0.13 mL, 0.19 g, 1.05 mmol) was added *via* syringe. The reaction mixture was stirred for further 1.5 h. The resin was then removed by filtration, washed with DMF, THF, ether, CH_2Cl_2 and dried under vacuum. The dried resin **54** (0.15 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (4 mL) and stirred for 1.5 h. The resin was then removed by filtration. The filtrate was washed with $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:3) of the residue afforded the lactone **57** (0.022 g, 60%, loading: 0.42 mmol/g);

$[\alpha]_D$ -55.80 ° (c 0.83, $CHCl_3$);

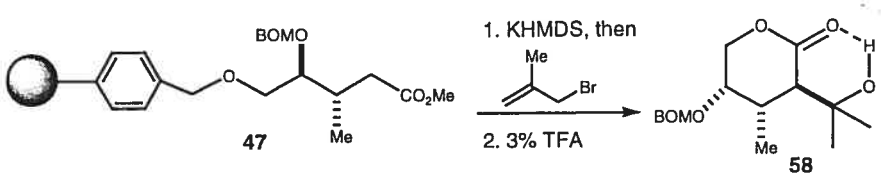
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J*=6.69 Hz, 1H), 1.89-1.98 (m, 1H), 2.70-2.89 (m, 2H), 3.76 (s, 3H), 3.80-3.84 (m,1H), 4.19 (dd, *J*=1.74, 12.06 Hz, 1H), 4.51 (dd, *J*=2.91, 12.12 Hz, 1H), 4.61 (d, *J*=12.01 Hz, 1H), 4.66 (d, *J*=12.09 Hz, 1H), 4.79 (d, *J*=7.29 Hz, 1H), 4.91 (d, *J*=7.32 Hz, 1H), 5.71 (s, 1H), 6.27 (s, 1H), 7.29-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.96, 31.78, 35.17, 43.78, 51.84, 69.82, 72.49, 93.62, 127.80, 127.85, 128.15, 128.41, 137.20, 137.31, 167.49, 172.09;

IR (thin film) νmax 2953, 2897, 1725, 1630, 1497, 144, 1441, 1399, 1302, 1207, 1165, 1142, 1103, 1041, 961, 906, 817, 743, 699 cm^{-1};

HRMS: $C_{19}H_{25}O_6$ (M^++1), calcd: 349.15729, found: 349.15688.

(3*R*, 4*S*, 5*S*)-5-Benzyloxymethoxy-3-(2-hydroxy-2-methylpropyl)-4-methyltetrahydropyran-2-one (58):



To a suspension of resin **47** (0.30 g, 0.21 mmol) in THF (5 mL) at –78 °C was added KHMDS (1.26 mL, 0.50 M in toluene, 0.63 mmol). The reaction mixture was stirred for 1 h before 3-bromo-2-methylpropene (0.11 mL, 0.14 g, 1.05 mmol) was added via syringe. The reaction mixture was stirred for further 1.5 h. The resin was removed by filtration, washed with DMF, THF, ether, CH_2Cl_2 and dried in *vacuo*. The dried resin **55** (0.15 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (4 mL) and was stirred for 1.5 h. The resin was then removed by filtration. The filtrate was washed with $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:3) of the residue afforded lactone **58** (0.018 g, 56%, loading: 0.39 mmol/g);

$[\alpha]_D$ -2.12 ° (c 0.80, $CHCl_3$);

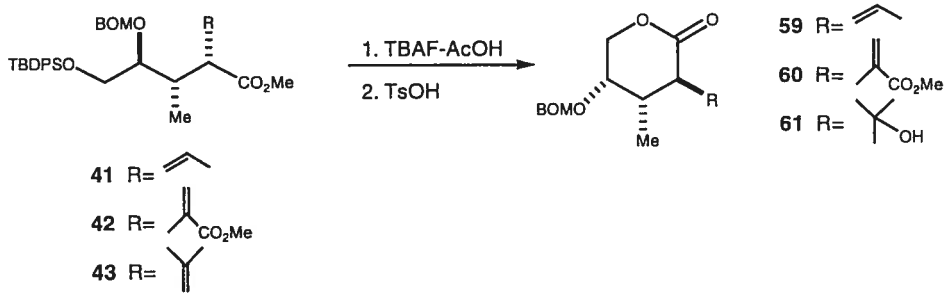
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J*=6.96 Hz, 3H), 1.33 (s, 3H), 1.45 (s, 3H), 1.73 (dd, *J*=9.03, 9.32 Hz, 1H), 2.00 (dd, *J*=9.32, 12.56 Hz, 1H), 2.38-2.44 (m, 1H), 3.19 (ddd, *J*=3.52, 8.82, 12.35 Hz, 1H), 3.41-3.48 (m, 1H), 3.59 (dd, *J*=6.28, 12.20 Hz, 1H), 3.75 (dd, *J*=2.60, 12.20 Hz, 1H), 4.63 (d, *J*=11.76 Hz, 1H), 4.73 (d, *J*=12.00 Hz, 1H), 4.74 (d, *J*=6.96 Hz, 1H), 4.93 (d, *J*=7.00 Hz, 1H), 7.30-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.71, 27.13, 28.84, 33.71, 36.07, 42.03, 63.60, 70.27, 81.91, 85.03, 95.51, 127.74, 127.87, 127.99, 128.49, 136.84, 178.09;

IR (thin film) vmax 3402, 2974, 2931, 1753, 1659, 1603, 1454, 1387, 1281, 1145, 1115, 1037 cm^{-1};

HRMS: $C_{17}H_{25}O_5$ (M^++1), calcd: 309.16233, found: 309.16198.

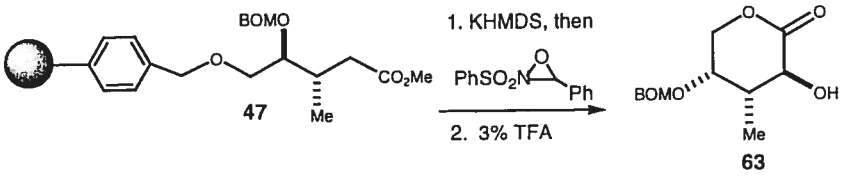
General procedure for the syntheses of lactones 59, 60, 61 in solution:



To a solution of ester **41,** or **42,** or **43** (0.30 g) in THF (5 mL) at room temperature was added TBAF-AcOH (1:1, 0.94 M, 4.00 mL, 3.76 mmol). The reaction mixture was stirred and monitored by TLC. After 1.5 h, the reaction was complete and the reaction mixture was acidified with $TsOH{\cdot}H_2O$ to pH 1. The reaction mixture was then stirred for further 1 h before being diluted with ethyl acetate (15 mL). The resulting mixture was nutralized with $NaHCO_3$ solution, washed with saturated NH_4Cl solution, brine and dried over

Na_2SO_4. The solvent was removed in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to give lactone **59**, or **60**, or **61** respectively.

(3*S*, 4*S*, 5*S*)- 5-Benzyloxymethoxy-3-hydroxy-4-methyltetrahydropyran-2-one (63):



To a suspension of resin **47** (3.00 g, 1.66 mmol) in THF (60 mL) at –78 °C was slowly added KHMDS (33.20 mL, 0.50 M in toluene, 16.60 mmol). The reaction mixture was stirred at –78 °C for 1 h and then slowly warmed to –40 °C in 30 min. The reaction mixture was then cooled to –78 °C and the Davis reagent (4.33 g, 16.60 mmol) in THF (25 mL) was added. The reaction mixture was stirred for 2 h and then warmed to –40 °C over 30 min before being quenched with acetic acid. The resin was then filtered, washed with DMF, THF, CH_2Cl_2, hexane and dried in *vacuo*. The dried resin **62** (0.15 g) was added to a solution of 3% TFA in CH_2Cl_2 (4 mL) and was stirred for 1 h before the resin was filtered. The filtrate was washed with $NaHCO_3$ solution, water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:2) of the residue afforded lactone **63** (0.016 g, 70%. Loading: 0.39 mmol/g);

$[\alpha]_D$ +3.0 ° (c 0.63 , $CHCl_3$);

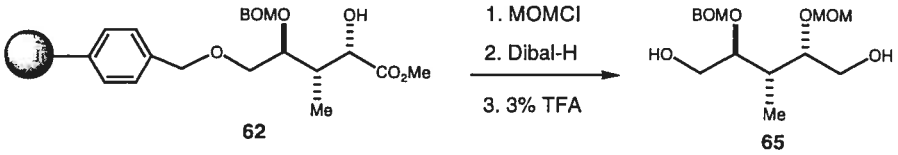
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, *J*=6.63 Hz, 3H), 2.18-2.29 (m, 1H), 3.95-4.01 (m, 1H), 4.24 (d, *J*=11.76 Hz, 1H), 4.33 (dd, *J*=7.36, 12.48 Hz, 1H), 4.58 (dd, *J*=2.04, 12.48 Hz, 1H), 4.65 (d, *J*=11.76 Hz, 1H), 4.68 (d, *J*=11.76 Hz, 1H), 4.82 (d, *J*=7.35 Hz, 1H), 4.94 (d, *J*=7.35 Hz, 1H), 7.32-7.45 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.11, 38.18, 68.95, 69.94, 71.78, 73.94, 94.05, 127.78, 127.89, 128.44, 136.91, 173.87;

IR (thin film) νmax 3469, 2931, 1735, 1455, 1208, 1160, 1114, 1037 cm^{-1};

HRMS: $C_{14}H_{19}O_5$ (M^++1), calcd: 267.11541, found: 267.11498.

(2*S*, 3*S*, 4*S*)-2-Benzyloxymethoxy-4-methoxymethoxy-3-methylpentane-1,5-diol (65):



To a suspension of resin **62** (4.00 g, 0.39 mmol/g, 1.52 mmol) in CH_2Cl_2 (120 mL) was added $^iPr_2NEt$ (4.05 mL, 3.08 g, 23.28 mmol) and MOMCl (1.52 mL, 1.61 g, 20 mmol). The reaction mixture was stirred at room temperature for 2 days. The resin was filtered, washed with water, DMF, THF, diethyl ether, CH_2Cl_2 and dried in *vacuo*. The dried resin (0.20 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (4 mL) and stirred for 1.5 h. The resin was then removed by filtration and the filtrate was washed with $NaHCO_3$, water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:3) of the residue afforded the α-MOM ether lactone (0.016 g, 67%, loading: 0.26 mmol/g);

$[\alpha]_D$ −181.97 ° (c 1.16, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.68 Hz, 3H), 2.20-2.28 (m, 1H), 3.45 (s, 3H), 3.89-3.91 (m, 1H), 4.21 (d, *J*=11.32 Hz, 1H), 4.22 (dd, *J*=2.28, 12.40 Hz, 1H), 4.46 (dd, *J*=2.36, 12.40 Hz, 1H), 4.59 (d, *J*=11.72 Hz, 1H), 4.63 (d, *J*=11.72 Hz, 1H), 4.72 (d, *J*=6.92 Hz, 1H), 4.77 (d, *J*=7.28 Hz, 1H), 4.88 (d, *J*=7.28 Hz, 1H), 5.10 (d, *J*=6.92 Hz, 1H), 7.26-7.38 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.35, 37.87, 56.32, 69.88, 70.78, 73.00, 73.88, 93.95, 97.30, 127.78, 127.81, 128.40, 137.12, 170.79;

IR (thin film) νmax 2996, 2896, 1747, 1497, 1455, 1402, 1383, 1356, 1251, 1144, 924, 747, 699 cm^{-1};

HRMS: $C_{16}H_{23}O_6$ (M^++1), calcd: 311.14948, found: 311.14850.

To a suspension of the above α-MOM ether lactone resin (3.80 g, 0.26 mmol/g, 0.99 mmol) in CH_2Cl_2 (120 mL) at –78 °C was added Dibal-H solution (0.50 M in toluene, 11.85 mL, 5.92 mmol) and the reaction mixture was stirred at this temperature for 2 h. The mixture was then slowly warmed to –40 °C in 1.5 h before it was recooled to –78 °C. A solution of NH_4Cl (20 mL) was added and the mixture was warmed to room temperature. The resin was quickly removed by filtration and then washed with NaOH solution (0.50 M), NH_4Cl solution, water, DMF, THF, diethyl ether, CH_2Cl_2 and dried in *vacuo*. The dried resin **64** (0.30 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (4 mL) and stirred for 1.5 h before the resin was removed by filtration. The filtrate was washed with $NaHCO_3$, water, dried over Na_2SO_4 and concentrated. Column chromatography of the residue (E/H=1:2) afforded alcohol **65** (0.017 g, 70%, so the loading was 0.18 mmol/g);

$[\alpha]_D$ +50.93 ° (c 1.07, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J*=7.08 Hz, 3H), 1.82-1.91 (m, 1H), 3.42 (s, 3H), 3.50-3.60 (m, 3H), 3.50-3.60 (m, 3H), 3.66-3.73 (m, 1H), 3.78-3.83 (m, 2H), 4.61 (d,

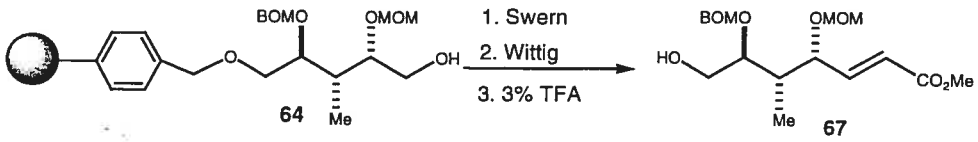
J=11.81 Hz, 1H), 4.64 (d, *J*=6.80 Hz, 1H), 4.70 (d, *J*=6.72 Hz, 1H), 4.74 (d, *J*=6.96 Hz, 1H), 4.75 (d, *J*=9.68 Hz, 1H), 4.92 (d, *J*=6.92 Hz, 1H), 7.28-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 10.97, 37.39, 55.56, 63.27, 65.07, 70.18, 83.09, 83.95, 95.44, 97.64, 127.83, 127.90, 128.45, 136.88;

IR (thin film) νmax 3427, 2935, 1455, 1083 cm^{-1};

HRMS: $C_{16}H_{27}O_6$ (M^++1), calcd: 315.18076, found: 315.18090.

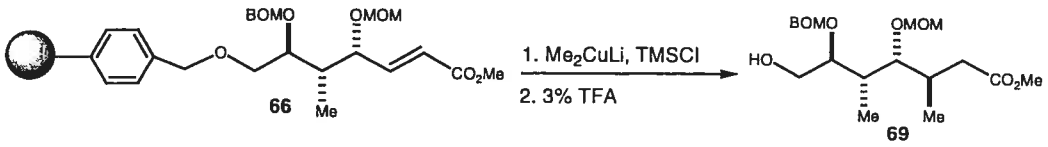
(4*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-7-hydroxy-4-methoxymethoxy-5-methyl-hept-2-enoic acid methyl ester (67):



To a suspension of resin **64** (3.50 g, 0.18 mmol/g, 0.63 mmol) in CH_2Cl_2 (120 mL) at room temperature was added DMSO (2 mL), Et_3N (1.52 g, 2.08 mL, 10.00 mmol), and SO_3·Py (1.51 g, 9.52 mmol). The reaction mixture was stirred at this temperature for 14 h before the resin was quickly removed by filtration, washed with water, DMF, THF, diethyl ether, CH_2Cl_2 and dried in *vacuo*. This resin was directly used in the next step.

To a suspension of the above resin in CH_2Cl_2 (50 mL) at room temperature was added the methyl (triphenylphosphoranylidene)acetate (2.19 g, 6.34 mmol) and the reaction mixture was stirred at this temperature for 24 h. The resin was quickly filtered, washed with DMF, THF, diethyl ether, CH_2Cl_2 and dried in *vacuo*.

(3*R*, 4*R*, 5S, 6*S*)-6-Benzyloxymethoxy-7-hydroxy-4-methoxymethoxy-3,5-dimethyl-heptanoic acid methyl ester (69):



To a solution of $MeCuLi_2$ at –78 °C [prepared by the addition of MeLi (complex with $MgBr_2$, 23 mL, 1.50 M in diethyl ether, 34.6 mmol) to CuI (2.88 g, 17.3 mmol) in THF (60 mL) at –15 °C, and the mixture was warmed to 0 °C in 0.5 h] was added TMSCl (7.03 g, 8.03 mL, 72.9 mmol) and resin **66** (2.50 g) in THF (25 mL). The reaction mixture was stirred at –78 °C for 2 h, -45 °C for 2 h, -25 °C for 2 h before being neutralized with acetic acid. NH_4Cl/NH_4OH (1:1, 100 mL) solution was added to dissolve all the copper salts. The resin was filtered and stirred in a mixture of NH_4Cl/NH_4OH(1:1, 7 mL) in THF (80 mL) for 20 min, after which, filtration was repeated. This procedure was repeated twice. The resin was then washed with water, THF, DMF, CH_2Cl_2, hexane and dried in *vacuo* for 24 h. This cuprate addition reaction was repeated exactly as before to ensure high conversion. The dried resin **68** (0.30 g) was suspended in a solution of 3% TFA in CH_2Cl_2 (5 mL) for 1 h. The resin was then removed by filtration. The filtrate was washed with $NaHCO_3$ solution, water, dried over Na_2SO_4 and concentrated. Column chromatography (E/H=1:7) of the residue afforded alcohol **69** (0.011 g, 50.8% for three steps, loading: 0.093 mmol/g);

$[\alpha]_D$ +8.07 ° (c 0.83, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J*=7.04 Hz, 3H), 0.92 (d, *J*=6.68 Hz, 1H), 1.18-1.19 (m, 1H), 2.11 (dd, *J*=8.56, 14.84 Hz, 1H), 2.19-2.27 (m, 1H), 2.53 (dd, *J*=4.80, 14.92 Hz, 1H), 3.33 (s. 3H), 3.50-3.55 (m, 3H), 3.65 (s, 3H), 3.77-3.82 (m, 1H), 4.57 (d,

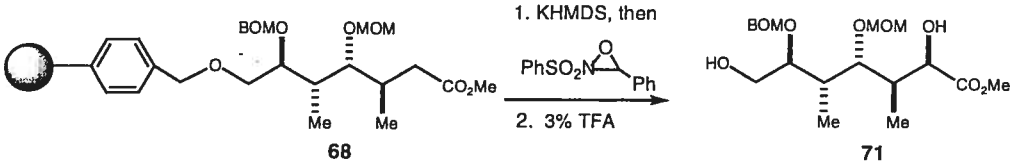
J=6.72 Hz, 1H), 4.58 (d, *J*=11.84 Hz, 1H), 4.59 (d, *J*=6.64 Hz, 1H), 4.75 (d, *J*=11.84 Hz, 1H), 4.83 (d, *J*=7.00 Hz, 1H), 4.92 (d, *J*=7.04 Hz, 1H), 7.28-7.39 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 10.10, 16.87, 33.70, 36.26, 38.21, 51.24, 55.71, 63.58, 70.12, 83.26, 84.11, 84.53, 95.68, 98.52, 127.77, 127.82, 128.40, 137.05, 173.54;

IR (thin film) νmax 3461, 2949, 1738, 1454, 1437, 1383, 1256, 1150, 1037, 952, 918, 739, 699 cm^{-1};

HRMS: $C_{20}H_{33}O_7$ (M^++1), calcd: 385.22263, found: 385.22390.

(2*R*, 3*S*, 4*S*, 5*S*, 6*S*)-6-Benzyloxymethoxy-2,7-dihydroxy-4-methoxymethoxy-3,5-dimethylheptanoic acid methyl ester (71):



To a suspension of resin **68** (2.00 g, 0.18 mmol) in THF (15 mL) at –78 °C was slowly added KHMDS (2.97 mL, 0.50 M in toluene, 1.48 mmol). The reaction mixture was stirred at –78 °C for 1 h before being slowly warmed to –40 °C in 30 min. The reaction mixture was then cooled to –78 °C and the Davis reagent (0.39 g, 1.48 mmol) in THF (4 mL) was added. The reaction mixture was stirred for 2 h and then warmed to –40 °C over 30 min before being quenched with acetic acid. The resin was then filtered, washed with DMF, THF, CH_2Cl_2, hexane and dried in *vacuo*. The dried resin **70** (1.00 g) was added to a solution of 3% TFA in CH_2Cl_2 (10 mL) and stirred for 1 h before the resin was removed by filtration. The filtrate was washed with $NaHCO_3$ solution, water, dried over Na_2SO_4

and concentrated. Column chromatography (E/H=1:1) of the residue afforded alcohol **71** (0.023 g, 62%. Loading: 0.057 mmol/g);

$[\alpha]_D$ +2.67 ° (c 0.98, $CHCl_3$);

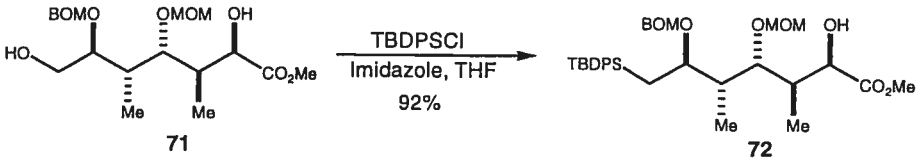
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, *J*=6.88 Hz, 3H), 0.90 (d, *J*=7.04 Hz, 1H), 1.76-1.86 (m, 1H), 2.07-2.16 (m, 1H), 3.37 (s, 3H), 3.51-3.58 (m, 2H), 3.80 (s, 3H), 3.82-3.89 (m, 2H), 4.54 (d, *J*=2.08 Hz, 1H), 4.61 (d, *J*=11.80 Hz, 1H), 4.68 (d, *J*=6.48 Hz, 1H), 4.73 (d, *J*=6.52 Hz, 1H), 4.77 (d, *J*=11.76 Hz, 1H), 4.86 (d, *J*=7.12 Hz, 1H), 4.96 (d, *J*=7.08 Hz, 1H), 7.28-7.39 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 9.52, 10.33, 35.93, 39.14, 52.35, 55.80, 63.79, 70.22, 70.55, 80.73, 84.29, 95.67, 98.99, 127.82, 128.41, 137.03, 175.67;

IR (thin film) νmax 3457, 2945, 2888, 1737, 1454, 1384, 1216, 1146, 1085, 1037, 955, 916, 740, 699 cm^{-1};

HRMS: $C_{20}H_{33}O_8$ (M^++1), calcd: 401.21753, found: 401.21670.

(2*R*, 3*S*, 4*S*, 5*S*, 6S)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-4-methoxymethoxy-3,5-dimethylheptanoic acid methyl ester (72):



To a solution alcohol **71** (0.020 g, 0.050 mmol) in THF (3 mL) at 0 °C were added imidazole (0.010 g, 0.14 mmol) and TBDPSCl (0.027 g, 0.10 mmol). The reaction mixture was stirred at 0 °C for 1.5 h before being quenched with saturated NH_4Cl solution (4 mL). The mixture was extracted with ethyl acetate (15 mL x 2). The

combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography of the residue afforded TBDPS ether **72** (0.027 g, 92%);

$[\alpha]_D$ –18.2 ° (c 0.56, $CHCl_3$);

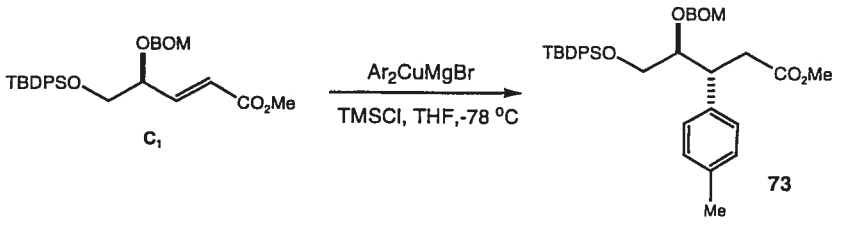
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.84 (d, *J*=6.81 Hz, 3H), 0.88 (d, *J*=7.12 Hz, 3H), 1.07 (s, 9H), 2.16-2.04 (m, 2H), 3.32 (s, 3H), 3.62-3.59 (m, 1H), 3.73-3.79 (m, 1H), 3.80 (s, 3H), 3.92-3.89 (m, 2H), 4.55 (d, *J*=11.2 Hz, 1H), 4.61-4.72 (m, 3H), 4.76 (d, *J*=6.31 Hz, 1H), 4.81 (d, *J*=6.96 Hz, 1H), 4.86 (d, *J*=6.96 Hz, 1H), 7.29-7.45 (m, 11H), 7.71-7.67 (m, 4H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.56, 10.62, 19.16, 26.72, 36.48, 39.38, 52.18, 55.73, 64.32, 69.88, 70.59, 80.63, 80.66, 94.90, 98.88, 127.40, 127.52, 127.57, 127.63, 128.19, 129.54, 133.30, 135.52, 137.78, 175.39;

IR (thin film): νmax 3520, 2950, 1738, 1430, 1384, 1086, 1036, 955, 917, 974, 701 cm^{-1};

HRMS: $C_{36}H_{50}O_8SiNa$ (M^++Na) calc.: 661.3172, found: 661.3202.

(3*R*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-3-*p*-tolyl-pentanoic acid methyl ester (73):



To a suspension of CuI (0.50 g, 2.63 mmol) in THF (20 mL) at –78 °C was added *p*-tolyl magnesium bromide solution (1.00 M in THF, 5.26 mL, 5.26 mmol). The mixture was stirred for 1 h at –78 °C before TMSCl (0.88 g, 0.76 mL, 7.00 mmol) and α,β-

unsaturated ester $\mathbf{C_1}$ (0.26 g, 0.50 mmol) in THF (3 mL) were added. The reaction mixture was stirred for 3 h at –78 °C, 2 h at –50 °C before being quenched with NH_4Cl solution (20 mL). The reaction mixture was warmed to room temperature and extracted with hexane (100 mL). The extract was washed with NH_4OH-NH_4Cl (1:1, 30 mL x 2), brine (20 mL), water (20 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:20) to give product **73** (0.25 g, 86%);

$[\alpha]_D$ 13.67 °(c 1.23, $CHCl_3$);

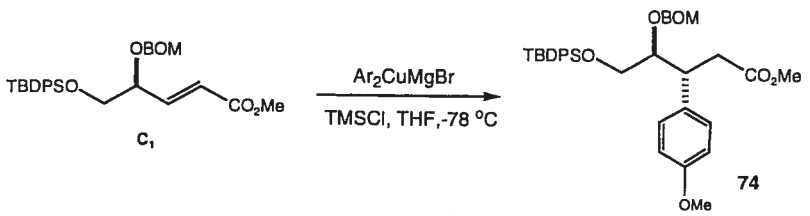
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9H), 2.35 (s, 3H), 2.69 (dd, *J*=10.08, 15.56 Hz, 1H), 3.03 (dd, *J*=5.04, 15.56 Hz, 1H), 3.59 (s, 3H), 3.59-3.68 (m, 3H), 3.91-3.95 (m, 1H), 4.48 (d, *J*=11.88 Hz, 1H), 4.59 (d, *J*=11.88 Hz, 1H), 4.72 (d, *J*=6.96 Hz, 1H), 4.86 (d, *J*=7.0 Hz, 1H), 7.10 (d, *J*=8.0 Hz, 1H), 7.15 (d, *J*=8.0 Hz, 1H), 7.26-7.46 (m, 8H), 7.57-7.68 (m, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.21, 21.10, 26.84, 36.77, 42.76, 51.44, 63.71, 69.90, 81.11, 94.40, 127.65, 127.72, 127.78, 128.11, 128.41, 129.16, 129.61, 129.65, 133.19, 133.31, 135.55, 135.67, 136.25, 138.21, 173.07;

IR (thin film) νmax 3021, 3030, 2932, 2858, 1740, 1515, 1472, 1455, 1428, 1362, 1259, 1158, 1113, 1027, 821, 740, 702, 613 cm^{-1};

M/e: 619.5 (M^++Na), 539.4, 501.2, 459.4, 431.3, 411.3, 385.2, 341.2, 197.1, 135.1.

(3*R*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-3-(4-methoxyphenyl)-pentanoic acid methyl ester (74):



To a suspension of CuI (0.50 g, 2.63 mmol) in THF (20 mL) at –78 °C was added 4-methoxylphenyl magnesium bromide solution (0.50 M in THF, 10.50 mL, 5.26 mmol). The reaction mixture was stirred for 1 h at –78 °C before TMSCl (0.88 g, 0.76 mL, 7 mmol) and α,β-unsaturated ester **C_1** (0.25 g, 0.5 mmol) in THF (4 mL) were added. The reaction mixture was stirred for 3 h at –78 °C, 2 h at –50 °C before being quenched with NH_4Cl solution (20 mL). The resulting mixture was warmed to r. t and extracted with hexane (100 mL). The extract was washed with NH_4OH-NH_4Cl (1:1, 30 mL x 2), brine (20 mL), water (20 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:20) to give product **74** (0.26 g, 84%);

$[\alpha]_D$ –42.1 ° (c 1.20, $CHCl_3$);

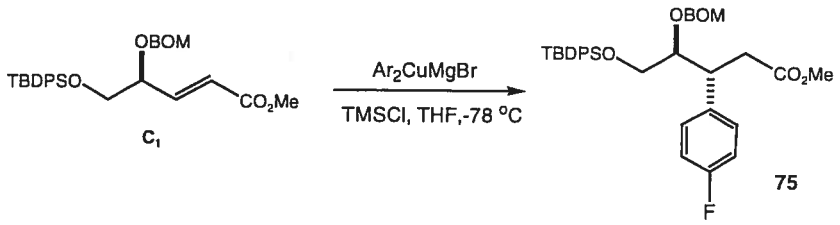
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 3H), 2.69 (dd, *J*=10.08, 15.56 Hz, 1H), 3.03 (dd, *J*=5.04, 15.56 Hz, 1H), 3.58 (s, 3H), 3.58-3.65 (m, 3H), 3.80 (s, 1H), 3.85-3.89 (m, 1H), 4.49 (d, *J*=11.88 Hz, 1H), 4.60 (d, *J*=11.88 Hz, 1H), 4.72 (d, *J*=6.90 Hz, 1H), 4.85 (d, *J*=6.96 Hz, 1H), 6.82 (d, *J*=8.72 Hz, 2H), 7.17 (d, *J*=8.68 Hz, 2H), 7.35 -7.45 (m, 1H), 7.56-7.66 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) 19.22, 26.84, 36.89, 42.38, 51.43, 55.17, 63.69, 69.91, 81.15, 94.40, 113.83, 127.64, 127.75, 128.40, 129.19, 129.64, 129.67, 133.29, 135.54, 135.66, 158.37, 173.05;

IR (thin film) νmax 2931, 1738, 1610, 1513, 1428, 1261, 1174, 1113, 1037, 702 cm^{-1};

m/e: 577.4, 565.4, 463.1, 391.1, 345.0, 325.1, 283.0, 197.0, 135.0.

(3*R*, 4*S*)-4-Benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-3-(4-fluorophenyl)-pentanoic acid methyl ester (75):



To a suspention of CuI (0.50 g, 2.63 mmol) in THF (20 mL) at –78 °C was added 4-fluorophenyl magnesium bromide solution (1.00 M in THF, 5.26 mL, 5.26 mmol). The reaction mixture was stirred for 1 h at –78 °C before TMSCl (0.88 g, 0.76 mL, 7.00 mmol) and α,β-unsaturated ester **C_1** (0.20 g, 0.39 mmol) in THF (3 mL) were added. The reaction mixture was stirred for 3 h at –78 °C, 2 h at –50 °C before being quenched with NH_4Cl solution (25 mL). The resulting mixture was warmed to room temperature and extracted with hexane (80 mL). The extract was washed with NH_4OH-NH_4Cl (1:1, 30 mL x 2), brine (20 mL), water (20 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:20) to give product **75** (0.20 g, 87%);

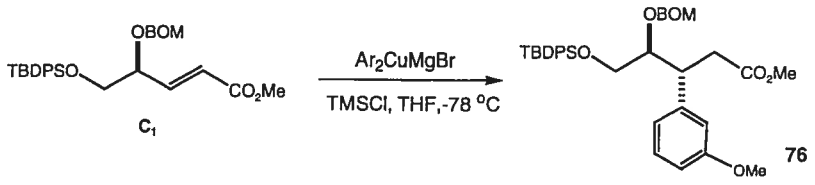
$[\alpha]_D$ –33.0 ° (c 1.56, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9H), 2.65 (dd, *J*=10.28, 15.72 Hz, 1H), 2.99 (dd, *J*=4.88, 15.72 Hz, 1H), 3.56 (s, 3H), 3.56-3.68 (m, 3H), 3.80-3.86 (m, 1H), 4.46 (d, *J*=11.92 Hz, 1H), 4.55 (d, *J*=11.92 Hz, 1H), 4.67 (d, *J*=6.96 Hz, 1H), 4.81 (d, *J*=6.96 Hz, 1H), 6.95 (t, *J*=8.72 Hz, 2H), 7.18-7.45 (m, 15H), 7.45-7.58 (m, 2H), 7.64-7.68 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.16, 26.79, 36.62, 42.41, 51.47, 63.47, 69.93, 80.83, 94.34, 115.13, 115.33, 127.65, 127.70, 128.41, 129.67, 129.72, 133.02, 133.13, 135.47, 135.61, 136.93, 137.67, 160.47, 162.91, 172.81;

IR (thin film) νmax 2931, 1739, 1604, 1510, 1428, 1260, 1232, 1172, 1113, 1037, 824, 740, 701 cm^{-1};

(3*R*, 4*S*)-4-Benyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-3-(3-methoxyphenyl)-pentanoic acid methyl ester (76):



To a suspension of CuI (7.56 g, 39.60 mmol) in THF (150 mL) at –78 °C was added meta-methoxy-phenyl magnesium bromide (1.00 M, 39.60 mL, 39.60 mmol). The reaction mixture was stirred at –78 °C for 1 h before TMSCl (8.20 mL, 7.16 g, 65.68 mmol) and ester **C_1** (3.0 g, 6.60 mmol) in THF (30 mL) was added dropwise under argon atmosphere. The reaction mixture was stirred at –78 °C for 3 h, at –50 °C for 3 h before being quenched with a solution of NH_4OH and NH_4Cl (1:1, 150 mL). The resulting mixture was warmed to room temperature and extracted with hexane (100 mL x 2). The combined extracts were washed with diluted NH_4OH solution (50 mL x 2), brine and

dried over Na_2SO_4. The solvent was removed in *vacuo*, and the residue was purified by column chromatography (E/H=1:20) to afford product **76** (3.42 g, 84%) as colorless oil;

$[\alpha]_D$ –28.59 ° (c 0.71, $CHCl_3$)

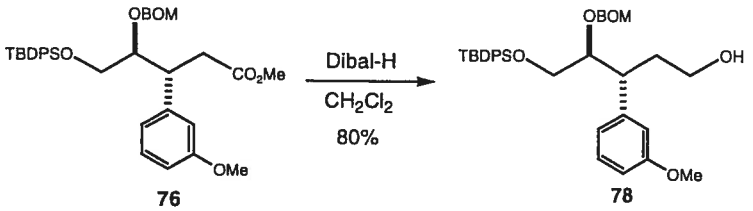
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (S, 9H), 2.72 (dd, *J*=9.80, 15.68 Hz, 1H), 3.02 (dd, *J*=5.12, 15.68 Hz, 1H), 3.59 (s, 3H), 3.59-3.70 (m, 3H), 3.77 (s, 3H), 3.88-3.93 (m, 1H), 4.48 (d, *J*=11.88 Hz, 1H), 4.58 (d, *J*=11.88 Hz, 1H), 4.70 (d, *J*=7.0 Hz, 1H), 4.83 (d, *J*=7.0 Hz, 1H), 6.78-6.89(m, 3H), 7.20 (t, *J*=7.48 Hz, 1H), 7.27-7.48 (m, 1H), 7.57 (d, *J*=7.96 Hz, 1H), 7.58 (d, *J*=8.04 Hz, 1H), 7.64 (d, *J*=8.04 Hz, 1H), 7.65 (d, *J*=7.96 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.20, 26.82, 36.65, 43.15, 51.46, 55.08, 63.65, 69.89, 80.94, 94.36, 112.23, 114.03, 120.57, 127.65, 127.76, 128.39, 129.41, 129.62, 129.68, 133.13, 133.30, 135.51, 135.64, 137.79, 143.00, 159.58, 172.94;

IR (thin film) νmax 2934, 1737, 1610, 1513, 1428, 1261, 1174, 1113, 1037cm^{-1};

HRMS: $C_{37}H_{44}O_6SiNa$ (M^++Na), calculated: 635.28052, found: 635.28040.

(3*R*, 4*S*)-4-Benyloxymethoxy-5-(*tert*-butyldiphenylsilanyloxy)-3-(3-methoxyphenyl)-pentan-1-ol (78):



76 78

To a stirred solution of ester **76** (3.30 g, 5.37 mmol) in toluene (50 mL) at –78 °C was added dropwise Dibal-H (1.50 M in toluene, 10.00 mL, 15.00 mmol) under nitrogen. The resulting mixture was stirred at this temperature for 1 h before being quenched with

saturated NH_4Cl solution (50 mL). The reaction mixture was warmed to room temperature and extracted with ether (100 mL x 2) immediately. The extracts were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was subjected to column chromatography (E/H=1:6) to afford alcohol **78** (2.50 g, 80%);

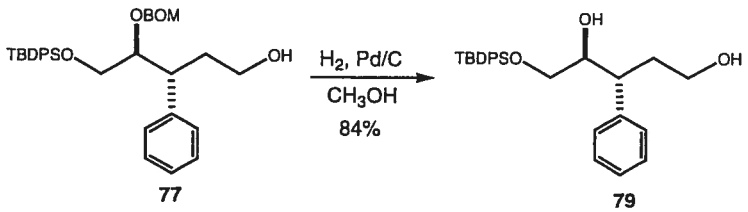
$[\alpha]_D$ –46.29 ° (c 0.89, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (m, 9H), 1.88-1.98 (m, 1H), 2.20-2.30 (m, 1H), 3.10-3.18 (m, 1H), 3.44-3.50 (m, 1H), 3.51-3.59 (m, 2H), 3.62 (dd, *J*=3.96, 11.08 Hz, 1H), 3.76 (s, 3H), 3.84-3.90 (m, 1H), 4.50 (d, *J*=11.84 Hz, 1H), 4.63 (d, *J*=11.84 Hz, 1H), 4.74 (d, *J*=6.96 Hz, 1H), 4.87 (d, *J*=6.96 Hz, 1H), 6.74-6.82 (m, 3H), 7.19 (dt, *J*=1.16, 7.48 Hz, 1H), 7.26-7.48 (m, 12 H), 7.52 (d, *J*=8.0 Hz, 1H), 7.53 (d, *J*=7.98 Hz, 1H), 7.61 (d, *J*=7.80 Hz, 1H), 7.62 (d, *J*=7.96 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.17, 26.81, 34.24, 43.84, 55.08, 61.44, 63.88, 69.96, 81.62, 94.54, 111.87, 114.17, 120.77, 127.62, 127.76, 128.38, 129.48, 129.56, 129.63, 133.20, 133.34, 135.48, 135.61, 137.81, 143.65, 159.67;

HRMS; $C_{36}H_{44}O_5SiNa$ (M^++Na), calculated: 607.28558, found: 607.28398.

(3*R*, 4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3-phenylpentane-1, 4-diol (79):



77 79

A mixture of alcohol **77** (2.80 g, 5.0 mmol) in methanol (20 mL) and Pd/C catalyst (0.070 g, 20% Pd, Degussa type) was stirred under hydrogen at atmospheric pressure for 20 h. The reaction mixture was filtered through Celite pad to remove the catalyst and the Celite

pad was washed with ethyl acetate (20 mL). The combined filtrates were dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the residue by column chromatography (silica gel, E/H=1:2) afforded product **79** (1.83 g, 84%);

$[\alpha]_D$ -10.45 ° (c 1.66, $CHCl_3$);

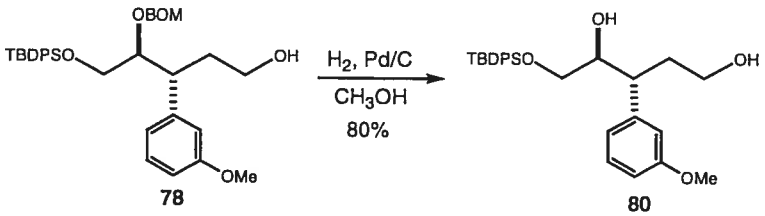
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.85-1.94 (m, 1H), 2.23-2.32 (m, 1H), 2.34-2.55 (broad, 2H), 2.28 (dt, *J*=5.66, 7.30 Hz, 1H), 3.37 (dd, *J*=6.72, 10.36 Hz, 1H), 3.42 (dd, *J*=3.36, 10.36 Hz, 1H), 3.48-3.55 (m, 1H), 3.58-3.64 (m, 1H), 3.83-3.88 (m, 1H), 7.02-7.06 (m, 2H), 7.14-7.24 (m, 3H), 7.32-7.46 (m, 6H), 7.52-7.58 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.63, 24.28, 33.98, 43.84, 58.81, 63.66, 72.85, 124.12, 125.16, 125.21, 125.29, 126.06, 127.21, 127.26, 130.27, 130.35, 132, 87, 132.89, 139.25;

IR (thin film) νmax 3370, 2930, 2857, 1493, 1471, 1427, 1073, 1048, 823, 689 cm^{-1};

m/e: 405.2, 377.2, 339.2, 309.2, 199.1, 154.1, 132.9, 91, 77, 57.

(3*R*, 4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3-(3-methoxyphenyl)-pentane-1, 4-diol (80):



A mixture of alcohol **78** (2.40 g, 5.16 mmol) in methanol (25 mL) and Pd/C catalyst (10%, 0.080 g) was stirred under hydrogen at atmospheric pressure for 20 h. The reaction mixture was filtered through Celite pad to remove the catalyst and the pad was washed with ethyl acetate (50 mL). The combined filtrates were dried over Na_2SO_4 and

concentrated in *vacuo*. Purification of the residue by column chromatography (silica gel, E/H=1:2) afforded product **80** (1.54 g, 80%);

$[\alpha]_D$ –32.46 ° (c 0.79, $CHCl_3$);

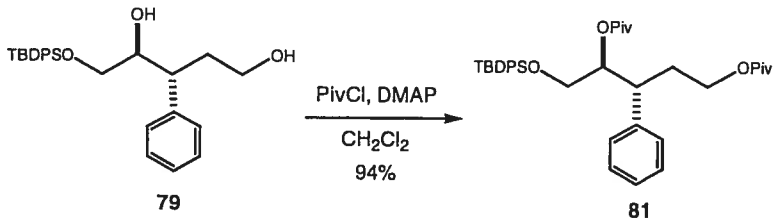
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.82-1.92 (m, 1H), 2.24-2.32 (m, 1H), 2.50-2.56 (broad, 2H), 2.73-2.80 (m, 1H), 3.39 (dd, *J*=6.68, 10.36 Hz, 1H), 3.45 (dd, *J*=3.28, 10.36 Hz, 1H), 3.48-3.53 (m, 1H), 3.59-3.64 (m, 1H), 3.74 (s, 3H), 3.81-3.88 (m, 1H), 6.63-6.67 (m, 2H), 6.71-6.74 (m, 1H), 7.12 (t, *J*=8.08 Hz, 1H), 7.31-7.48 (m, 6H), 7.53-7.60 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.19, 26.83, 36.42, 46.44, 55.05, 61.35, 66.21, 75.34, 111.76, 113.75, 120.19, 127.70, 127.75, 129.60, 129.75, 129.80, 132.81, 132.94, 135.42, 135.44, 143.46, 159.66;

IR (thin film) νmax 3376, 2936, 2857, 1495, 1475, 1111, 1073, 1048, 827, 690 cm^{-1};

m/e: 487.0(M^++Na), 445.0, 407.0, 369.0, 299.0, 199.0, 173.0, 135.0.

(1*S*, 2*R*)-2,2-Dimethylpropionic acid 1-(*tert*-butyldiphenylsilanyloxymethyl)-4-(2,2-dimethylpropionyloxy)-2-phenylbutyl ester (81):



79 81

To a stirred solution of alcohol **79** (2.20 g, 3.68 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added DMAP (1.34 g, 11.04 mmol) and pivaloyl chloride (0.90 mL, 0.88 g, 7.36 mmol). The reaction mixture was stirred at room temperature for 16 h before being quenched with saturated NH_4Cl solution (50 mL). The resulting mixture was extracted

with ether (50 mL x 3), and the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E:H=1:40) to afford product **81** (1.03 g, 93%) as a colorless oil;

$[\alpha]_D$ -45.82 ° (c 1.97, $CHCl_3$);

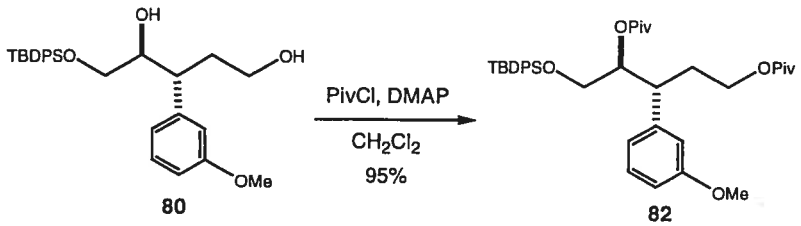
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 3H), 1.20 (s, 3H), 1.27 (s, 3H), 1.73-1.86 (m, 1H), 2.09-2.18 (m, 1H), 3.33 (m, 1H), 3.46 (dd, *J*=4.04, 11.44 Hz, 1H), 3.54 (dd, *J*=2.46, 11.44 Hz, 1H), 3.69-3.78 (m, 1H), 3.99-4.06 (m, 1H), 5.15-5.20 (m, 1H), 7.18-7.40 (m, 13H), 7.58-7.60 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.61, 24.16, 24.66, 24.75, 28.61, 36.16, 36.44, 40.06, 59.47, 60.51, 74.40, 124.49, 124.97, 125.05, 125.93, 126.16, 126.95, 127.11, 130.29, 1330.58, 132.82., 133. 02, 137.45, 175.53, 175.77;

IR (thin film) νmax 2960, 2932, 2858, 1729, 1480, 1462, 1428, 1283, 1154, 1113, 1042, 701cm $^{-1}$;

HRMS: $C_{37}H_{51}O_5Si$ (M^++1), calc.: 603.35059, found: 603.35340.

(1*S*, 2*R*)-2,2-Dimethyl-propionic acid 1-(*tert*-butyldiphenylsilanyloxymethyl)-4-(2,2-dimethylpropionyloxy)-2-(3-methoxyphnenylbutyl ester (82):



To a stirred solution of diol **80** (1.50 g, 3.23 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added DMAP (1.58 g, 12.92 mmol) and pivaloyl chloride (1.17 g, 1.19 mL, 9.68 mmol). The reaction mixture was then stirred at room temperature for 16 h before being

quenched with saturated NH_4Cl solution (50 mL). The resulting mixture was extracted with ether (30 mL x 2). The extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:40) to afford product **82** (1.94 g, 95%) as a colorless oil;

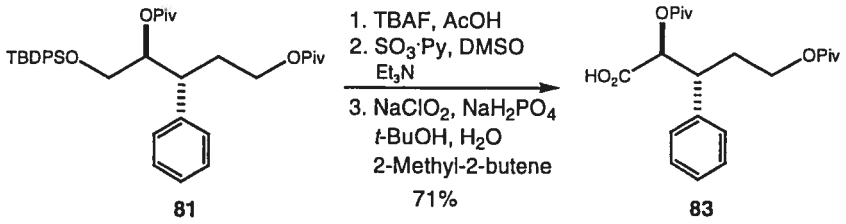
$[\alpha]_D$ –54.71 ° (c 1.38, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.21 (s, 9H), 1.27 (s, 9H), 1.74-1.82 (m, 1H), 2.08-2.18 (m, 1H), 3.28-3.38 (m, 1H), 3.48 (dd, *J*=3.84, 11.42 Hz, 1 H), 3.56 (dd, *J*=2.56, 11.42 Hz, 1H), 3.74 (s, 3H), 3.62-3.78 (m, 1H), 4.00-4.07 (m, 1H), 5.15 (dt, *J*=3.42, 9.76 Hz, 1H), 6.12-6.28 (m, 3H), 7.18-7.42 (m, 9H), 7.57 (d, *J*=6.4 Hz, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.97, 26.70, 27.21, 27.39, 31.17, 38.71, 39.00, 42.66, 55.04, 62.02, 63.07, 76.91, 112.41, 114.24, 120.69, 127.53, 127.59, 129.51, 129.67, 129.73, 132.78, 133.19, 135.37, 135.56, 141.59, 159.77, 178.08, 178.31;

IR (thin film) νmax 2959, 2900, 1727, 1596, 1480, 1463, 1432, 1281, 1255, 1153, 1110, 1038, 702 cm^{-1};

(2*S*, 3*R*)-2,5-Bis-(2,2-dimethylpropionyloxy)-3-phenylpentanoic acid (83):



81 **83**

To a solution of ester **81** (1.30 g, 2.15 mmol) in THF (10 mL) was added TBAF (complexed with acetic acid, 1:1, 11.46 mL, 10.78 mmol). The reaction mixture was stirred at room temperature for 16 h before being diluted with ethyl acetate (20 mL) and hexane (20 mL). The organic layer was washed with saturated $NaHCO_3$ solution (15 mL

x 3), brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:5) to give the alcohol (0.71 g, 90%) which was used directly in the next step.

To a solution of the above alcohol (0.69 g, 1.89 mmol), DMSO (1.00 mL) and Et_3N (1.49 mL, 1.09 g, 10.75 mmol)) in CH_2Cl_2 (15 mL) at 0 °C was added SO_3·Py (1.36 g, 8.40 mmol). The reaction mixture was stirred 2 h at room temperature before being quenched with NH_4Cl solution (20 mL). Hexane (50 mL) was added to the mixture and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to the column chromatography (E/H=1:7) to afford the aldehyde (0.62 g, 88%);

$[\alpha]_D$ –31.37 ° (c 0.86, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9H), 1.28 (s, 9H), 2.09-2.18 (m, 2H), 3.30-3.39 (m, 1H), 3.72-3.83 (m, 1H), 4.03-4.09 (m, 1H), 5.12 (d, *J*=7.88 Hz, 1H), 7.22-7.37 (m, 5H), 9.38 (d, *J*=0.64 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.07, 29.57, 38.63, 38.78, 42.59, 61.48, 80.63, 127.75, 128.23, 128.91, 138.10, 177.71, 178.18, 197.62;

IR (thin film) νmax 2973, 2934, 1731, 1480, 1283, 1146, 702 cm^{-1};

To a solution of the aldehyde (0.050 g, 0.14 mmol) in *t*-BuOH (1.5 mL) was added 2-methyl-butene (0.097 g, 0.15 mL, 1.38 mmol) and a solution of $NaClO_2$ (0.13 g, 1.38 mmol) and KH_2PO_4 (0.15 g, excess) in water (2 mL). The reaction mixture was stirred at room temperature for 2 h (the colour of the reaction became yellow). The reaction

mixture was then extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography of the residue (silica gel, E/H=1) afforded acid **83** (0.047 g, 90 %);

$[\alpha]_D$ -19.07 ° (c 0.87, $CHCl_3$);

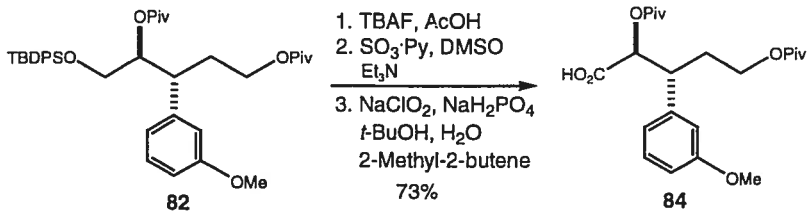
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9H), 1.25 (s, 9H), 2.08-2.19 (m, 1H), 2.21-2.31 (m, 1H), 3.42 (dt, *J*=3.76, 11.44 Hz, 1H), 3.75-3.82 (m, 1H), 4.06-4.12 (m, 1H), 5.11 (d, *J*=3.96 Hz, 1H), 7.24-7.35 (m, 5H), 8.8-9.20 (broad, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.45, 24.57, 26.01, 36.18, 36.22, 41.03, 59.36, 72.82, 125.11, 125.83, 126.11, 135.98, 171.67, 175.01, 175.90;

IR (thin film) νmax 3227, 2973, 1703, 1480, 1451, 1394, 1363, 1284, 1145 cm^{-1};

m/e: 401.3, 379.3, 361.2, 289.1, 277.2, 249.2, 193.1, 154.1, 137.1, 117.1, 85.0.

(2*S*, 3*R*)-2,5-Bis-(2,2-dimethylpropionyloxy)-3-(3-methoxyphenyl)pentanoic acid (84):



To a solution of ester **82** (2.20 g, 3.47 mmol) in THF (20 mL) was added TBAF (1:1 complexed with acetic acid, 0.94 M, 18.48 mL, 17.38 mmol). The reaction mixture was stirred at room temperature for 16 h before being diluted with ethyl acetate (20 mL) and hexane (20 mL). The resulting mixture was washed with saturated $NaHCO_3$ solution (15 mL x 3), brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected

to column chromatography (E/H=1:5) to give the alcohol (1.21 g, 92%). The product was used directly in the next step.

To a solution of the above alcohol (1.20 g, 3.19 mmol) in CH_2Cl_2 (30 mL) was added DMSO (1.00 mL, excess), Et_3N (3.37 mL, 2.46 g, 24.29 mmol) and SO_3·Py (2.80 g, 17.35 mmol). The mixture was stirred for 2 h at room temperature before being quenched with NH_4Cl solution (20 mL). Hexane (50 mL) was added to the mixture and the organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to the column chromatography (E/H=1:7) to afford the aldehyde (1.03 g, 86%) which was used directly in the next step.

To a solution of the aldehyde (0.54 g, 1.38 mmol) in *t*-BuOH (15 mL) was added 2-methyl-butene (0.96 g, 1.46 mL, 13.8 mmol) and a solution of $NaClO_2$ (1.25 g, 13.8 mmol) and KH_2PO_4 (1.00 g, excess) in water (20 mL). The reaction mixture was stirred at room temperature for 2 h (the colour of the reaction became yellow). The product was then extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the residue by column chromatography (silica gel, E/H=1:1) afforded acid **84** (0.49 g, 92 %);

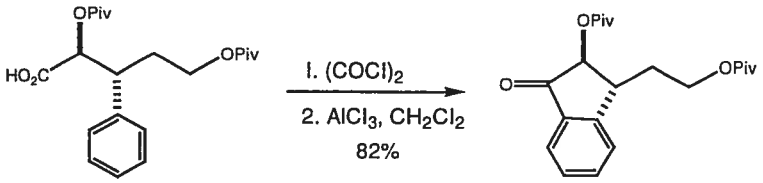
$[\alpha]_D$ –34.7 ° (c 1.24, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 1.25 (s, 9H), 2.04-2.13 (m, 1H), 2.14-2.27 (m, 1H), 3.40 (dt, *J*=3.26, 10.86 Hz, 1H), 3.79 (s, 3H), 3.74-3.88 (m, 1H), 4.02-4.12 (m, 1H), 5.11 (d, *J*=3.86 Hz, 1H), 6.78-6.88 (m, 3H), 7.20-7.26 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.22, 27.23, 28.56, 39.11, 44.00, 55.01, 60.20, 75.08, 113.21, 114.37, 120.98, 129.89, 140.46, 174.48, 178.11, 179.01;

IR (thin film) νmax 3410, 2935, 1727, 1595, 1483, 1466, 1436, 1282, 1257, 1155, 1111, 702 cm^{-1};

(1*R*, 2*S*)-2,2-Dimethylpropionic acid 1-[2-(2,2-dimethylpropionyloxy)ethyl]-3-oxo-indan-2-yl ester (85):



83 **85**

To a solution of acid **83** (0.040 g, 0.11 mmol) at 0 °C was added oxalyl chloride (0.14 g, 0.095 mL, 1.06 mmol). DMF (20 μL) was added dropwise to the reaction (the gas was evolved). The mixture was stirred for 30 min and the solvent was then removed in *vacuo*. The residue was dissolved in anhydrous CH_2Cl_2 (15 mL) and cooled to 0 °C before $AlCl_3$ (0.14 g, 1.06 mmol) was added in one potion. The mixture was then stirred at room temperature for 40 min before being quenched with HCl (1 M, 10 mL) solution at 0 °C. The product was extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with $NaHCO_3$ solution, water, dried over Na_2SO_4, filtered and concentrated in *vacuo*. Column chromatography of the residue (silica gel, E/H=1:5) afforded product **85** (0.031 g, 82%);

$[\alpha]_D$ -3.65 ° (c 0.57, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (s, 9H), 1.27 (s, 9H), 1.99-2.09 (m, 1H), 2.48-2.56 (m, 1H), 3.45-3.50 (m, 1H), 4.12-4.20 (m, 1H), 4.30-4.38 (m, 1H), 5.17 (d, *J*=4.92 Hz,

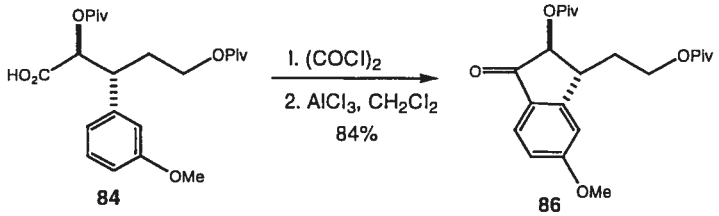
1H), 7.42 (dd, *J*=7.44, 7.80 Hz, 1H), 7.52 (dd, *J*=0.80, 7.80 Hz, 1H), 7.68 (dt, *J*=7.80, 7.68 Hz, 1H), 7.78 (d, *J*=7.68 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.50, 24.61, 29.41, 36.16, 59.49, 77.23, 121.72, 122.47, 125.83, 131.65, 133.23, 149.91, 175.21, 175.79, 196.59;

IR (thin film) νmax 2971, 1727, 1607, 1480, 1397, 1283 cm^{-1};

HRMS; $C_{21}H_{29}O_5$ (M^++1), calcd: 361.20151, found: 361.20290.

(2*S*, 3*R*)-2,2-Dimethylpropionic acid 3-[2-(2,2-dimethylpropionyloxy)ethyl]-5-methoxy-1-oxo-indan-2-yl ester (86):



To a solution of acid **84** (0.090 g, 0.22 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added oxalyl chloride (0.11 g, 79 μL, 0.88 mmol). DMF (20 μL) was added dropwise to the reaction (the gas was evolved). The reaction mixture was stirred for 30 min and then the solvent was removed in *vacuo*. The residue was dissolved in anhydrous CH_2Cl_2 (15 mL) and the resulting solution was cooled to 0 °C before $AlCl_3$ (0.15 g, 1.10 mmol) was added in one potion. The reaction mixture was then stirred at room temperature for 40 min before being slowly quenched with HCl (1 M, 10 mL) solution at 0 °C. The resulting mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed dilute $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in *vacuo*. Purification of

the residue by column chromatography (silica gel, E/H=1:5) afforded product **86** (0.072 g, 84%);

$[\alpha]_D$ –29.59 ° (c 1.58, $CHCl_3$);

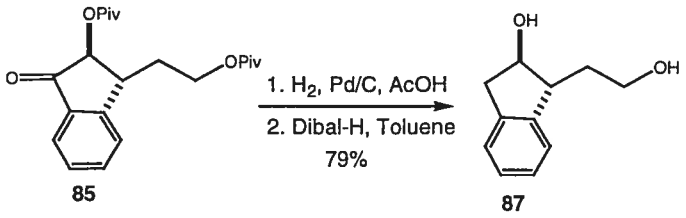
^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 9H), 1.24 (s, 9H), 1.90-2.04 (m, 1H), 2.39-2.52 (m, 1H), 3.32-3.42 (m, 1H), 3.88 (s, 3H), 4.10-4.19 (m, 1H), 4.30-4.37 (m, 1H), 5.16 (d, *J*=4.68 Hz, 1H), 6.89-6.96 (m, 2H), 7.68 (d, *J*=8.46 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.51, 24.60, 29.35, 36.18, 38.80, 53.25, 59.43, 77.07, 106.19, 113.34, 123.64, 124.87, 152.98, 163.60, 175.23, 175.81, 194.70;

IR (thin film) νmax 2971, 1723, 1600, 1480, 1432, 1281, 1147, 1037 cm^{-1};

HRMS; $C_{22}H_{31}O_6$ (M^++1), calcd: 391.21207, found: 391.21316.

(1*R*, 2*R*)-1-(2-Hydroxyethyl)-indan-2-ol (87):



A mixture of ketone **85** (0.020 g, 0.056 mmol) in acetic acid (1.50 mL) and Pd/C catalyst (10%, 10 mg) was stirred under hydrogen at atmospheric pressure for 2 h. The reaction mixture was filtered through a Celite pad to remove the catalyst and the pad was washed with ethyl acetate (20 mL). The combined filtrates were concentrated in *vacuo*. Column chromatography of the residue (silica gel, E/H=1:2) afforded the product (0.016 g, 85%);

$[\alpha]_D$ -28.24 ° (c 1.19, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9H), 1.21 (s, 9H), 1.88-1.98 (m, 1H), 2.04-2.13 (m, 1H), 2.83 (dd, *J*=4.20, 16.84 Hz, 1H), 3.30-3.36 (m, 1H), 3.44 (dd, *J*=6.84, 16.84 Hz, 1H), 4.12-4.28 (m, 2H), 5.20-5.26 (m, 1H), 7.21 (s, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.48, 24.64, 29.55, 35.57, 36.01, 36.17, 44.95, 59.59, 77.38, 121.44, 122.23, 124.34, 124.69, 137.37, 140.53, 175.85, 175.90;

IR (thin film) νmax 2971, 1728, 1480, 1459, 1283, 1153 cm^{-1};

HRMS: $C_{21}H_{31}O_4$ (M^++1), calc.: 347.22223, found: 347.22290.

To a solution of the above product (0.017 g, 0.049 mmol) in toluene (5 mL) at –78 °C was added Dibal-H (0.50 M, 0.39 mL, 0.20 mmol). The reaction mixture was stirred at –78 °C for 1.5 h before being quenched with NH_4Cl solution. The resulting mixture was warmed to room temperature and extracted with diethyl ether (20 mL x 2). The combined extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:2) to afford product **87** (0.009 g, 93%);

$[\alpha]_D$ –19.25 ° (c 0.81, $CHCl_3$);

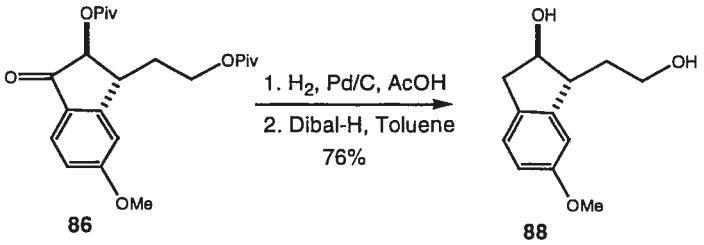
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70-1.81 (m, 1H), 2.26-2.37 (m, 1H), 2.91 (dd, *J*=8.32, 15.24 Hz, 1H), 3.03-3.09 (m, 1H), 3.22 (dd, *J*=7.28, 15.32 Hz, 1H), 3.40-3.50 (broad, 2H), 3.87 (dt, *J*=3.08, 10.2 Hz, 1H), 4.04-4.09 (m, 1H), 4.31 (dd, *J*=7.44, 15.92 Hz, 1H), 7.12-7.26 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.54, 37.24, 49.31, 59.95, 77.59, 120.67, 122.09, 124.16, 124.46, 137.62, 141.11;

IR (thin film) νax 3337, 2934, 1610, 1586, 1490, 1432, 1328, 1284, 1175, 1151, 1069, 1036 cm^{-1};

HRMS: $C_{11}H_{15}O_2$ (M^++1), calc.: 179.10721, found: 179.10810.

(1*R*, 2*R*)-1-(2-Hydroxyethyl)-6-methoxyindan-2-ol (88):



86 88

A mixture of ketone **86** (0.05 g, 0.13 mmol) in acetic acid (5 mL) and Pd/C catalyst (10%, 20 mg) was stirred under hydrogen at atmospheric pressure for 2 h. The reaction mixture was then filtered through a Celite pad which was then washed with ethyl acetate (20 mL). The combined filtrates were concentrated in *vacuo*. Purification of the residue by column chromatography (silica gel, E/H=1:2) afforded the indane (0.039 g, 81%);

$[\alpha]_D$ −13.90 ° (c 1.28, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 9H), 1.21 (s, 9H), 1.83-1.92 (m, 1H), 2.01-2.11 (m, 1H), 2.75 (dd, *J*=4.08, 16.5 Hz, 1H), 3.22-3.32 (m, 1H), 3.36 (dd, *J*=6.75, 16.5 Hz, 1H), 3.78 (s, 3H), 4.12-4.29 (m, 2H), 5.19-5.25 (m, 1H), 6.72-6.78 (m, 2H), 7.08-7.13 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.96, 27.12, 31.98, 37.24, 38.46, 38.63, 47.65, 55.28, 62.03, 80.23, 109.52, 112.95, 125.25, 131.66, 144.45, 159.05, 178.20, 178.26;

IR (thin film) νax 2970, 1728, 1611, 1596, 1480, 1462, 1433, 1480, 1462, 1397, 1366, 1284, 1157, 1034 cm^{-1};

HRMS: $C_{22}H_{31}O_6$ (M^++1), calculated: 391.21207, found: 391.21316.

To a solution of the above indane (0.070 g, 0.19 mmol) in toluene (10 mL) at –78 °C was added Dibal-H (1.50 M, 0.37 mL, 0.56 mmol). The reaction mixture was stirred at –78 °C for 1.5 h before being quenched with saturated NH_4Cl solution (10 mL). The resulting mixture was warmed to room temperature and extracted with ether (15 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to column chromatography (E/H=1:2) to afford product **88** (0.033 g, 86%) as a solid which was recrystallized from a mixture of hexane and CH_2Cl_2;

mp: 97 °C;

$[\alpha]_D$ –30.80 ° (c 1.18, $CHCl_3$);

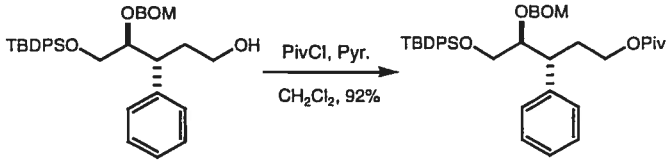
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66-1.76 (m, 1H), 2.21-2.28 (m, 1H), 2.82 (dd, *J*=8.44, 14.92 Hz, 1H), 2.99-3.04 (m, 1H), 3.15 (dd, *J*=7.28, 14.95 Hz, 1H), 3.70 (broad, 2H), 3.79 (s, 3H), 3.85 (dt, *J*=3.12, 10.68 Hz, 1H), 6.68 (s, 1H), 6.17-6.74 (m, 1H), 7.09 (d, *J*=8.16 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.50, 36.41, 49.42, 52.87, 59.78, 77.74, 106.81, 109.79, 122.68, 129.46, 142.57, 156.42;

IR (thin film) νmax 3340, 2934, 1611, 1587, 1491, 1431, 1284, 1175, 1151, 1069, 1036 cm^{-1};

HRMS: $C_{12}H_{17}O_3$ (M^++1), calculated: 209.10956, found: 209.10911.

2,2-Dimethylpropionic acid (3*R*, 4*S*)-4-benzyloxymethoxy-5-(*tert*-butyldiphenylsilanyl)-3-phenylpentyl ester (89):



77 89

To a stirred solution of alcohol **77** (3.00 g, 5.35 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (2.50 mL, 2.33 g, 16.2 mmol) and pivaloyl chloride (1.33 mL, 1.30 g, 10.81 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with ether (50 mL x 3). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:30) to afford **89** (3.22 g, 92%) as a colorless oil;

$[\alpha]_D$ -39.73 ° (c 2.23, $CHCl_3$);

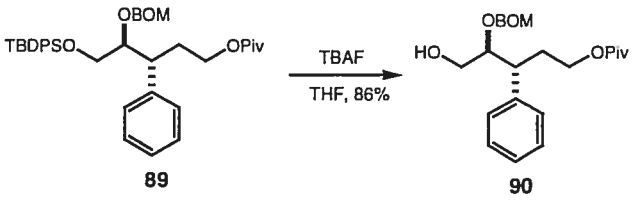
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 9H), 1.19 (s, 9H), 1.90-2.10 (m, 1H), 2.39-2.50 (m, 1H), 3.19-3.26 (m 1H), 3.52 (dd, *J*=4.44, 11.12 Hz, 1H), 3.63 (dd, *J*=4.00, 11.16 Hz, 1H), 3.78-3.83 (m, 1H), 3.84-3.89 (m, 1H), 3.99-4.05 (m, 1H), 4.49 (d, *J*=11.80 Hz, 1H), 4.62 (d, *J*=11.84 Hz, 1H), 4.72 (d, *J*=7.04 Hz, 1H), 4.84 (d, *J*=7.04 Hz, 1H), 7.20-7.47 (m, 8H), 7.50-7.52 (m, 1H), 7.62-7.67 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.09, 26.73, 27.11, 29.97, 38.58, 43.42, 62.76, 63.46, 69.81, 81.51, 94.29, 126.65, 127.52, 127.54, 127.67, 128.30, 128.36, 128.44, 129.48, 129.55, 133.11, 133.19, 135.39, 135.52, 137.71, 141.16, 178.36;

IR (thin film) νmax 3069, 2968, 2932, 2868, 1727, 1495, 1479, 1454, 1428, 1284, 1156, 11134, 1026, 823, 740, 701, 611 cm^{-1};

m/e: 655.5 (M^++1), 651.3, 603.5, 577.5, 551.5, 501.3, 453.2, 339.1, 263.1, 197.0, 135.0, 117.0.;

2, 2-Dimethylpropionic acid (3*R*, 4*S*)-4-benzyloxymethoxy-5-hydroxy-3-phenylpentyl ester (90):



89 90

To a solution of **89** (3.00 g, 4.62 mmol) in THF (40 mL) was added TBAF solution (1:1 complexed with AcOH, 0.94 M, 24.59 mL, 23.11 mmol). The resulting mixture was stirred for 6 h at ambient temperature and then diluted with hexane-ethyl acetate (1:1, 200 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (50 mL x 2), brine (50 mL x 2), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Purification of the crude product by column chromatography (E/H=1:6) provided alcohol **90** (1.59 g, 86%) as a clear, colorless oil;

$[\alpha]_D$ –8.90 ° (c 0.55, $CHCl_3$);

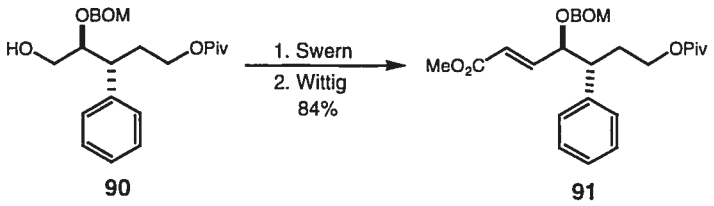
^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 9H), 1.88-1.99 (m, 1H), 2.31-2.43 (m, 1H), 2.89-2.97 (m, 1H), 3.36 (dd, *J*=6.18, 12.0 Hz, 1H), 3.49 (dd, *J*=2.07, 12.00 Hz, 1H), 3.69-3.82 (m, 2H), 3.92-4.00 (m, 1H), 4.65 (d, *J*=11.73 Hz, 1H), 4.77 (d, *J*=7.05 Hz, 1H), 4.78 (d, *J*=11.73 Hz, 1H), 4.99 (d, *J*=7.05 Hz, 1H), 7.12-7.43 (m, 10H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.08, 30.66, 38.56, 44.50, 62.57, 63.61, 70.24, 85.92, 95.56, 126.96, 127.83, 127.92, 128.08, 128.40, 128.48, 128.70, 136.99, 140.57, 178.32;

IR (thin film) νmax 3468, 2960, 1726, 1480, 1455, 1285, 1162, 1037, 701 cm^{-1}.

m/e: 401.1 (M^++1), 369.2, 293.1, 191.0, 154.0, 137.0, 91.0.

(4*R*, 5*R*)-4-Benzyloxymethoxy-7-(2,2-dimethylpropionyloxy)-5-phenylhept-2-enoic acid methyl ester (91):



90 **91**

To a solution of oxalyl chloride (1.27 g, 0.87 mL, 9.98 mmol) in CH_2Cl_2 (30 mL) at –78 °C was added DMSO (1.06 mL, 1.17 g, 14.97 mmol). The mixture was stirred for 15 min before alcohol **90** (2.00 g, 4.99 mmol) in CH_2Cl_2 (10 mL) was slowly added. The mixture was stirred and slowly warmed to –30 °C in about 30 min before triethylamine (2.78 mL, 2.02 g, 19.96 mmol) was added. The white precipitate was formed and the mixture was stirred at this temperature for 15 min before being quenched by saturated NH_4Cl solution (30 mL). The organic layer was separated, dried and concentrated in *vacuo*. The crude aldehyde was dissolved in dry CH_2Cl_2 (30 mL) and $Ph_3P{=}CHCO_2CH_3$ (3.34 g, 9.98 mmol) was added. The mixture was stirred at r.t. for 12 h and then the solvent was removed in *vacuo*. The residue was purified by column chromatography (E/H=1:10) to give **91** (1.90 g, 84%) as a colorless oil;

$[\alpha]_D$ -65.42 ^{0} (c 2.3, $CHCl_3$);

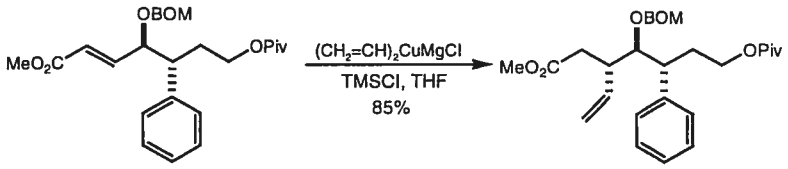
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9H), 1.96-2.07 (m, 1H), 2,29-2.39 (m, 1H), 2.90-2.98 (m, 1H), 3.69 (s, 3H), 3.77-3.83 (m, 1H), 4.00-4.06 (m, 1H), 4.41 (dt, *J*=1.10, 6.72 Hz, 1H), 4.47 (d, *J*=11.68 Hz, 1H), 4.69 (d, *J*=7.12 Hz, 1H), 4.72 (d, *J*=7.12 Hz, 1H), 5.86 (dd, *J*=1.10, 15.80 Hz, 1H), 6.73 (dd, *J*=6.60, 15.80 Hz, 1H), 7.17-7.39 (m, 10H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.05, 29.48, 38.56, 47.29, 51.51, 62.33, 69.91, 79.07, 92.79, 122.71, 127.11, 127.69, 127.78, 128.32, 128.46, 128.51, 137.35, 139.53, 146.19, 166.11, 178.24;

IR (thin film) vmax 3030, 2957, 2898, 1727, 1496, 1480, 1454, 1436, 1283, 1164, 1277, 1165, 1101, 1026, 700 cm^{-1}.

HRMS; $C_{27}H_{35}O_6$ (M^++1), calcd: 455.24338, found: 455.24240.

3-[(1*R*, 2*R*)-1-Benzyloxymethoxy-4-(2,2-dimethylpropionyloxy)-2-phenylbutyl]-pent-4-enoic acid methyl ester (92):



91 **92**

To a slurry of CuI (1.90 g, 10.00 mmol) in THF (50 mL) at –78 °C was added vinyl magnesium bromide solution (1.00 M in THF, 20.00 mL, 20.00 mmol). The resulting mixture was stirred at –78 °C for 1 h before TMSCl (3.79 mL, 3.26 g, 15 mmol) and ester **91** (1.10 g, 2.42 mmol) in THF (15 mL) were added. The reaction mixture was stirred at –78 °C for 6 h before being quenched with NH_4OH-NH_4Cl solution (1:1, 30 mL). The resulting mixture was warmed to room temperature and extracted with hexane (100 mL x

3). The combined extracts were washed with a dilute NH_4OH solution, brine, dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the residue by column chromatography (E/H=1:14) afforded **92** (0.99 g, 85%) as a colorless oil;

$[\alpha]_D$ -19.94 ° (c 1.78, $CHCl_3$);

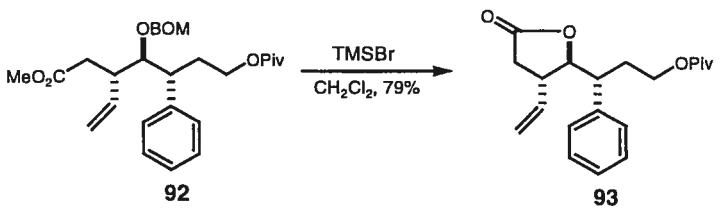
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9H), 1.98-2.90 (m, 1H), 2.29 (dd, *J*=10.00, 15.44 Hz, 1H), 2.31-2.38 (m, 1H), 2.55 (dd, *J*=4.04, 15.40 1H), 2.72-2.80 (m, 1H), 2.92-3.00 (m, 1H), 3.59 (s, 3H), 3.68 -3.77 (m, 2H), 3.95-4.04 (m, 1H), 4.45 (d, *J*=7.0 Hz, 1H), 5.04 (dd, *J*=1.32, 17.24, 1H), 5.09 (dd, *J*=1.32, 10.40 Hz, 1H), 5.77-5.87 (m, 1H), 7.17 - 7.38 (m, 10H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.06, 28.66, 34.82, 38.55, 43.13, 44.85, 51.31, 62.52, 70.32, 85.85, 96.39, 116.67, 126.89, 127.62, 128.22, 128.32, 128.65, 137.51, 138.14, 140.97, 172.91, 178.26;

IR (thin film) νmax 3030, 2958, 2900, 1727, 1660, 1496, 1480, 1454, 1365, 1283, 1163, 1037, 737, 700 cm^{-1};

m/e: 512.2, 495.2, 451.2, 421.2, 375.1, 273.1, 243.1, 211.1, 169.1, 117.

2,2-Dimethylpropionic acid (3*R*)-3-[(2*R*, 3*S*)-5-oxo-3-vinyltetrahydrofuran-2yl]-3-phenylpropyl ester (93):



92 93

To a solution of ester **92** (2.00 g, 4.13 mmol) in CH_2Cl_2 (40 mL) at –30 °C was added TMSBr (2.18 mL, 2.53 g, 16.52 mmol). The reaction mixture was stirred at –30 °C for 2.5 h before being quenched with saturated $NaHCO_3$ solution (15 mL). The resulting mixture was extracted with hexane (25 mL x 2). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:10) to give **93** (1.08 g, 79%) as a colorless oil;

$[\alpha]_D$ -49.34 ° (c 0.89, $CDCl_3$);

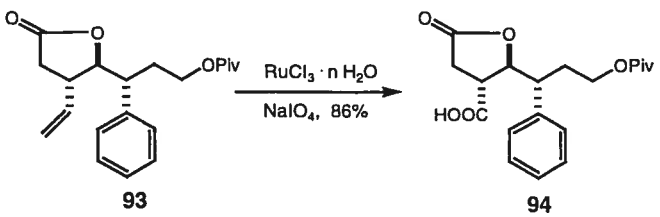
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 1.97-2.08 (m, 1H), 2.28-2.37 (m, 1H), 2.38 (dd, *J*=9.16, 17.76 Hz, 1H), 2.59 (dd, *J*=8.80, 17.76 Hz, 1H), 2,82-2.97 (m, 2H), 3.77-3.84 (m, 1H), 3.97-4.05 (m, 1H), 4.34 (t, *J*=7.00 Hz, 1H), 4.78 (dd, *J*=0.88, 17.00 Hz, 1H), 4.83 (dd, *J*=0.76, 10.24 Hz, 1H), 5.32-5.43 (m, 1H), 7.15-7.35 (m, 5 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.06, 30.27, 34.08, 38.57, 43.46, 46.57, 61.86, 87.46, 116.79, 127.55, 128.41, 128.77, 135.84, 138.67, 175.26, 178.18;

IR (thin film) νmax 2957, 1728, 1480, 1454, 1365, 1285, 1159, 1026 cm^{-1};

HRMS; $C_{20}H_{27}O_4$ (M^++1), calcd: 331.19095, found: 331.19000.

2-[3-(2,2-Dimethylpropionyloxy)-1-phenylpropyl]-5-oxo-tetrahydrofuran-3-carboxylic acid (94):



93 94

To a solution of ester **93** (0.40 g, 0.83 mmol) in a mixture of CCl_4 (10 mL), CH_3CN (5 mL) and H_2O (2 mL) at room temperature was added $NaIO_4$ (1.50 g, excess) and then $RuCl_3 \cdot nH_2O$ (8.0 mg, 0.038 mmol). The reaction mixture was stirred for 1.5 h at room temperature before being diluted with NH_4Cl solution. The mixture was extracted with ethyl acetate (30 mL x 2). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:1) to give **94** (0.25 g, 86%);

$[\alpha]_D$ -34.79 ° (c 1.9, $CHCl_3$);

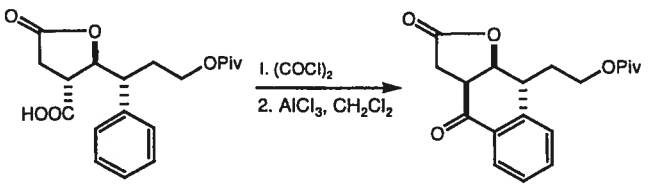
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 2.00-2.12 (m, 1H), 2.29-2.39 (m, 1H), 2.55 (dd, *J*=9.84, 17.95 Hz, 1H), 2.76 (dd, *J*=7.2, 17.95 Hz, 1H), 2.92-3.04 (m, 2H), 3.80-3.87 (m, 1H), 3.99-4.07 (m, 1H), 4.87 (dd, *J*=5.92, 7.8 Hz, 1H), 7.19-7.40 (m, 5H), 9.20-9.50 (broad, 1H) ppm;

^{13}C NMR ($CDCl_3$, 400 MHz) δ 26.99, 30.33, 31.72, 38.59, 43.34, 47.30, 61.78, 84.37, 127.94, 128.48, 128.95, 137.01, 174.05, 176.05, 178.46 ppm;

IR (thin film) νmax 3600, 2963, 1728, 1480, 1454, 1365, 1285, 1159, 1026 cm^{-1};

HRMS; $C_{19}H_{25}O_6$ (M^++1), calcd: 349.16510, found: 349.16600.

2.2-Dimethylpropionic acid 2-(2, 4-dioxo-2, 3, 3a, 4, 9, 9a -hexahydronaphtho [2, 3-b]-furan-9-yl)ethyl ester (96):



94 **96**

To a solution of acid **94** (0.12 g, 0.34 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added oxalyl chloride (0.28 g, 0.19 mL, 2.12 mmol). DMF (30 μL) was added dropwise to the reaction (the gas was evolved). The reaction mixture was stirred for 30 min and then the solvent was removed in *vacuo*. The residue was dissolved in anhydrous CH_2Cl_2 (8 mL) and the resulting solution was cooled to 0 °C before $AlCl_3$ (0.23 g, 1.72 mmol) was added in one potion. The reaction mixture was then stirred at room temperature for 40 min before being slowly quenched with HCl (1 M, 10 mL) solution at 0 °C. The product was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with dilute $NaHCO_3$ solution, water, dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the residue by column chromatography (silica gel, E/H=1:5) afforded **96** (0.093 g, 82%);

$[\alpha]_D$ –75.02 ° (c 0.85, $CHCl_3$);

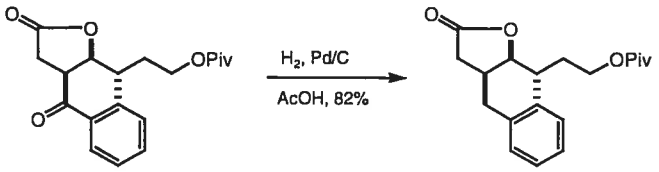
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 9H), 1.68-1.80 (m, 1H), 2.04-2.16 (m, 1H), 3.03 (dd, *J*=2.20, 24 Hz, 1H), 3.06 (dd, *J*=13.16, 24.12 Hz, 1H), 3.47-3.51(m, 1H), 3.55-3.61 (m, 1H), 3.97 -4.06 (m, 1H), 4.11-4.21 (m, 1H), 5.07 (dd, *J*=3.64, 7.04 Hz, 1H), 7.27 (dd, *J*=1.60, 10.28 Hz, 1H), 7.43 (ddd, *J*=1.60, 10.28, 10.28 Hz, 1H), 7.62 (ddd, *J*=1.92, 9.96, 10.78 Hz, 1H), 7.96 (dd, *J*=1.92, 9.96 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.08, 33.56, 34.76, 37.66, 38.67, 43.45, 60.77, 80.50, 127.97, 128.10, 129.71, 130.30, 134.94, 141.91, 174.11, 178.14, 195.57;

IR (thin film) νmax 2972, 1785, 1727, 1683, 1601, 1480, 1457, 1420, 1398, 1344, 1283, 1210, 1152, 1034, 988, 937, 770.cm^{-1};

HRMS; $C_{19}H_{23}O_5$ (M^++1), calcd: 331.15454, found: 331.15360.

2.2-Dimethylpropionic acid 2-(-oxo-2, 3, 3a, 4, 9, 9a -hexahydronaphtho [2, 3b]-furan-9-yl)-ethyl ester (98):



96 98

A mixture of ketone **96** (0.050 g, 0.15 mmol) in acetic acid (3 mL) and Pd/C (10%, 30 mg) was stirred under hydrogen at atmospheric pressure for 2 h. The reaction mixture was filtered through a Celite pad which was then washed with ethyl acetate (20 mL). The combined filtrates were concentrated in *vacuo*. Purification of the residue by column chromatography (E/H=1:2) afforded **98** (0.039 g, 82%);

$[\alpha]_D$ –49.6 ° (c 1.34, $CHCl_3$);

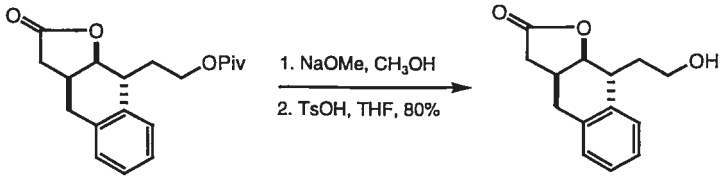
^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 9H), 1.98 -2.06 (m, 1H), 2.09-2.18 (m, 1H), 2.26 (dd, *J*=4.84, 18.40 Hz, 1H), 2.61 (dd, *J*=7.72, 17.12 Hz, 1H), 2.82 (dd, *J*= 0.16, 18.4 Hz, 1H), 2.92-3.19 (m, 3H), 4.00-4.09 (m, 1H), 4.18-4.27 (m, 1H), 4.75 (dd, *J*=4.44, 8.29 Hz, 1H), 7.15-7.26 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.65, 27.13, 30.14, 30.16, 32.21, 36.20, 38.54, 59.51, 80.75, 124.78, 124.83, 125.56, 125.98, 132.82, 135.53, 173.76, 175.92;

IR (thin film) νmax 2973, 2873, 1775, 1725, 1483, 1461, 1341, 1368, 1287, 1160, 1012, 941, 756 cm^{-1};

HRMS; $C_{19}H_{25}O_4$ (M^++1), calcd: 317.17529, found: 317.17300.

9-(2-Hydroxyethyl)-3a, 4, 9, 9a-tetrahydro-3H-naphtho [2, 3-b]furan-2-one (99):



98 99

To a solution of lactone **98** (0.03 g, 0.095 mmol) in MeOH (3 mL) was added sodium methoxide solution (1 M, 0.10 mL, 0.10 mmol). The reaction mixture was stirred at room temperature for 18 h before being quenched with TsOH (neutralized to PH=7). The solvent was removed in *vacuo* and the residue was dissolved in THF (5 mL). $TsOH{\cdot}H_2O$ (0.040 g, 0.21 mmol) was added and the mixture was stirred at room temperature for 1 h before being quenched with saturated $NaHCO_3$ solution (8 mL). The resulting mixture was extracted with ethyl acetate (20 mL x 2), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:2) to give **99** (0.018 g, 80%) as a solid which was recrystallized from a mixture of hexane and CH_2Cl_2;

mp: 104-105 °C;

$[\alpha]_D$ –31.87 ° (c 0.64, $CHCl_3$)

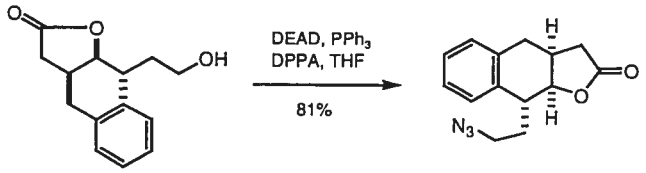
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.74 (Broad, 2H), 1.99-2.22 (m, 2H), 2.29 (dd, *J*=4.00, 17.72 Hz, 1H), 2.61 (dd, *J*=5.80, 14.08 Hz, 1H), 2.84 (dd, *J*=10.14, 17.84, 1H), 2.88-3.20 (m, 3H), 3.08-3.14 (m, 1H), 3.74-3.84 (m, 2H), 4.75 (dd, *J*=4.96, 8.12 Hz, 1H), 7.13-7.28 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.41, 30.61, 30.95, 32.22, 38.06, 57.99, 81.29, 124.56, 124.68, 124.99, 125.68, 133.36, 134.18, 173.93;

IR (thin film) νmax 3457, 2993, 2883, 1726, 1448, 1412, 1367, 1314, 1223, 1052, 997, 975 cm^{-1};

HRMS; $C_{14}H_{17}O_3$ (M^++1), calcd: 233.11777, found: 233.11870.

9-(2-Azidoethyl)-3a,4,9,9a-tetrahydro-3H-naphtho[2,3-b]furan-2-one (100):



99 **100**

To a solution of alcohol **99** (0.050 g, 0.22 mmol) and Ph_3P (0.22 g, .0.86 mmol) in THF (5 mL) was added DEAD (0.15 mL, 0.86 mmol) and then $(PhO)_2PON_3$ (0.19 mL, 0.86 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h before being diluted with hexane-ethyl acetate (1:1, 30 mL). The mixture was washed with a saturated NH_4Cl solution (15 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (E/H=1:8) to afford **100** (0.045 g, 81%) as a colorless oil;

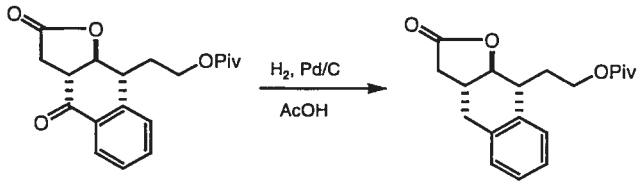
$[\alpha]_D$-2.37 ° (c 0.53, CH_3Cl);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (d, *J*=7.20 Hz, 1H), 1.52 (d, *J*=7.20 Hz, 1H), 1.74 (dd, *J*=4.35, 17.79 Hz, 1H), 2.08-2.23 (m, 2H), 2.58 (dd, *J*=7.29, 12.72 Hz, 1H), 2.85 (t, *J*=7.47 Hz, 2H), 3.86 (dd, *J*=5.22, 7.77 Hz, 1H), 6.83 (dd, *J*=5.16, 8.94 Hz, 2H), 7.03-7.06 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.91, 32.81, 32.89, 34.64, 41.38, 49.35, 83.42, 127.36, 127.43, 127.75, 128.52, 135.64, 135.71, 177.21;

IR (thin film) νmax 2928, 2854, 2093, 1774, 1488, 1458, 1416, 1346, 1259, 1181, 1012, 755 cm^{-1};

2.2-Dimethylpropionic acid 2-(-oxo-2, 3, 3a, 4, 9, 9a -hexahydronaphtho [2, 3b]-furan-9-yl)ethyl ester (101):



95 **101**

A mixture of the crude Friedel-Crafts product (**95** and **96**) (0.040 g, 0.13 mmol) in acetic acid (2 mL) and Pd/C (10%, 0.025 g) was stirred under hydrogen at atmospheric pressure for 2 h. The reaction mixture was filtered through a Celite pad which was then washed with ethyl acetate (20 mL). The combined filtrates were concentrated in *vacuo*. Purification of the residue by column chromatography (silica gel, E/H=1:2) afforded *cis*-product **101** (0.025 g, 65%) and its *trans* isomer **98** (0.006 g, 14%);

$[\alpha]_D$ +47.47 ° (c 1.28, $CHCl_3$);

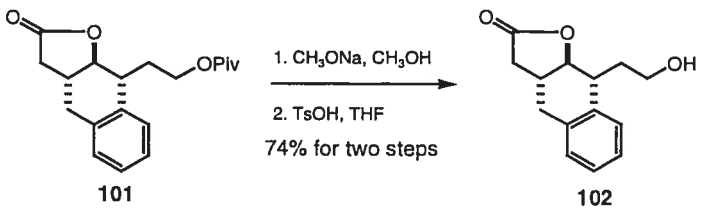
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9H), 2.20-2.28 (m, 1H), 2.38-2.50 (m, 33H), 2.73 (dd, *J*=12.8, 22.5 Hz, 1H), 2.78-2.88 (m, 1H), 3.08-3.13 (dd, *J*=3.80, 15.92 Hz, 1H), 3.22-3.30 (m, 1H), 4.10-4.18 (m, 2H), 4.26-4.32 (m, 1H), 7.12 (d, *J*=7.40 Hz, 1H), 7.19 (t, *J*=6.58, 1H), 7.25 (t, *J*=6.68 Hz, 1H), 7.38 (d, *J*=7.84 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.58, 28.63, 31.33, 33.04, 36.10, 37.57, 38.44, 59.28, 83.12, 124.23, 124.51, 125.32, 127.68, 132.48, 133.44, 173.42, 175.89;

IR (thin film) νmax 2971, 2873, 1776, 1726, 1481, 1459, 1416, 1399, 1366, 1285, 1159, 1011, 940, 755 cm^{-1};

HRMS; $C_{19}H_{25}O_4$ (M^++1), calcd: 317.17529, found: 317.17300.

9-(2-Hydroxyethyl)-3a, 4, 9, 9a-tetrahydro-3H-naphtho [2, 3-b]furan-2-one (102):



101 102

To a solution of lactone **101** (0.020 g, 0.063 mmol) in MeOH (5 mL) was added sodium methoxide solution (1 M in methanol, 30 μL, 0.030 mmol). The reaction mixture was stirred at room temperature for 18 h before being quenched with p-TsOH (neutralized to pH=7). The solvent was removed in *vacuo* and the residue was dissolved in THF (5 mL). *p*-TsOH·H_2O (0.030 g, 0.158 mmol) was added and the mixture was stirred at room temperature for 1 h before being quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate (20 mL x 2), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, E/H=1:2) to give alcohol **102** (0.011 g, 74%);

$[\alpha]_D$ –41.90 ° (c 0.76, $CHCl_3$);

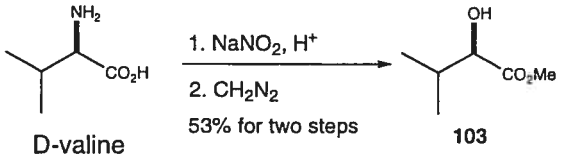
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58-2.72 (broad, 2H), 1.82-1.98 (m, 1H), 2.40-2.58 (m, 3H), 2.74 (dd, *J*=12.80, 22.44 Hz, 1H), 2.84 (dd, *J*=10.76, 14.84 Hz, 1H), 3.10 (dd, *J*=3.76, 15.88 Hz, 1H), 3.28 (t, *J*=9.16Hz, 1H), 3.85-3.95 (m, 2H), 4.15 (t, *J*=10.52 Hz, 1H), 7.13 (d, *J*=7.38 Hz, 1H), 7.19 (t, *J*=7.10 Hz, 1H), 7.25 (t, *J*=7.28 Hz, 1H), 7.40 (d, *J*=7.88 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.27, 32.84, 34.00, 37.62, 38.31, 57.87, 84.56, 124.07, 124.45, 125.48, 126.98, 132.35, 134.27, 173.56;

IR (thin film) νmax 3458, 2995, 2880, 1724, 1448, 1411, 1368, 1313, 1221, 1053, 998, 977 cm^{-1};

HRMS; $C_{14}H_{17}O_3$ (M^++1), calcd: 233.11777, found: 233.11870.

(2*R*)-2-Hydroxy-3-methylbutyric acid methyl ester (103)[168]:

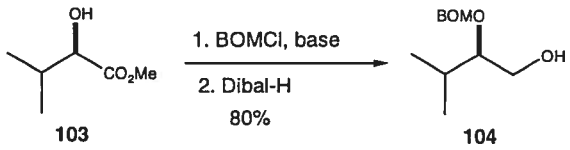


D-valine **103**

A three-neck flask, equipped with a thermometer, magnetic stirring bar, and dropping funnel, was charged with D-valine (12.00 g, 102.00 mmol) and 1N sulfuric acid (154 mL). A solution of sodium nitrite (10.50 g, 153.00 mmol) in water (40 mL) was added dropwise over 2 h while keeping the internal temperature below 0 °C with ice-salt bath. The resulting solution was stirred at room temperature for 20 h. The reaction solution was adjusted to pH 7 with solid $NaHCO_3$, and then the volume of the solution was reduced to 50-60 mL. The concentrated solution was adjusted to PH 2 with concentrated H_3PO_4, and then extracted with THF (200 mL x 3). The combined organic layers were washed with brine, and then dried over Na_2SO_4. The crude product was recrystallization from ether-hexane in a refrigerator to afford α-hydroxy acid **103** (6.50 g, 53%);

The α-hydroxy acid was esterified in ether by diazomethane generated from the diazald kit (from Aldrich) to give α-hydroxy methyl ester.

(2*R*)-2-Benzyloxymethoxy-3-methylbutan-1-ol (104):



103 104

To a solution of **103** (14.78 g, 112 mmol) in CH_2Cl_2 (22 mL) was added diisopropylethylamine (95.60 mL, 550 mmol) and BOMCl (65%, 76.00 mL, 550.00 mmol) at 0 °C. The resulting solution was stirred at room temperature for 52 h. The reaction mixture was diluted with EtOAc, washed with water, saturated NH_4Cl, and brine, then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:8) to afford the BOM-methyl ester as a syrup (24.00 g, 85%);

TLC: E/H = 1:5, R_f = 0.48;

$[\alpha]_D$ -58.40 ° (c 1.38, $CHCl_3$);.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 4.3 Hz, 3H), 1.01 (d, *J* = 5.6 Hz, 1H), 2.20-2.10 (m, 1H), 3.70 (s, 3H), 3.98 (d, *J* = 5.6 Hz, 1H), 4.64 (s, 2H), 4.81 (s, 2H), 7.37-7.26 (m, 5H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.60, 18.68, 31.35, 51.58, 69.89, 80.96, 94.50, 127.62, 127.72, 128.31, 137.50,172.70;

IR (neat) νmax 2960, 1750, 1270, 1170, 1050, 740, 700, cm^{-1};

m/e: 253 (M^++1), 223, 181, 145, 117;

HRMS: $C_{14}H_{21}O_4$ (M^++1), calcd: 253.14403: found: 253.14680.

To a solution of the above product (12.32 g, 48.00 mmol) in THF (150 mL) at –78 °C was added DIBAL-H (1.0 M in THF, 165.00 mL, 165.00 mmol). The resulting solution was stirred at 0 °C for 3 h, and then recooled to –78 °C. The reaction was quenched by adding methanol (25 mL), water (12 mL), EtOAc, Celite and Na_2SO_4. The mixture was filtered and washed with EtOAc. The crude product was purified by chromatography (E/H=1:3) to afford alcohol **104** (9.52 g, 87%);

TLC: E/H = 1:4, R_f = 0.40;

$[\alpha]_D$ -59.60 ° (c 1.4, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 5.1 Hz, 3H), 0.96 (d, *J* = 5.1 Hz, 3H), 1.89-1.84 (m, 1H), 3.05-3.02 (m, 1H), 3.38-3.34 (m, 1H), 3.67-3.57 (m, 2H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.94 (d, *J* = 6.9 Hz, 1H), 7.36-7.26 (m, 5H) ppm;

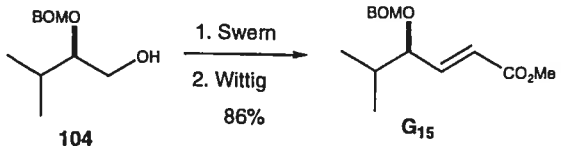
^{13}C-NMR (400 MHz, $CDCl_3$) δ 18.15, 18.72, 30.09, 63.56, 70.02, 87.62, 95.64, 127.85, 128.45, 137.11 ppm;

IR (thin film) νmax 3440, 2980, 1080, 760, 700 cm^{-1};

m/e: 225 (M^++1), 214, 207, 197, 181, 169, 149:

HRMS: $C_{13}H_{21}O_3$ (M^++1), calcd: 225.14913: found: 225.14667.

(4*R*)-4-Benzyloxymethoxy-5-methylhex-2-enoic acid methyl ester (G_{15}):



104 G_{15}

To a solution of oxalyl chloride (3.80 mL, 43.8 mmol) in CH_2Cl_2 (200 mL) at –70 °C was added DMSO (6.20 mL, 87.60 mmol). The resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to –55 °C, then a solution of alcohol **104** (6.5 g, 29 mmol) in CH_2Cl_2 (40 mL) was added. The reaction mixture was warmed to –40 °C over 20 min and diisopropylethylamine (20.30 mL, 117.00 mmol) was added, then temperature was allowed to rise further to –30 °C over 30 min. The reaction mixture was quenched with saturated NH_4Cl solution, diluted with CH_2Cl_2, washed with 2.5% HCl, saturated $NaHCO_3$ and brine, then dried over Na_2SO_4 for 2 h. After removing solvent, the residue was dried on an oil pump for 2 h. To a solution of the above crude aldehyde in CH_2Cl_2 (100 mL) was added methyl (triphenylphosphoranylidene) acetate (14.6 g, 44 mmol, solid). The resulting mixture was stirred for 14 h at room temperature. The reaction mixture after removing solvent was purified by chromatography (E/H=1:2) to afford $\mathbf{G_{15}}$ as colorless oil (7.00 g, 86% overall);

TLC: E/H = 1:4, R_f = 0.60;

$[\alpha]_D$ +106.00 ° (c 1.1, $CHCl_3$);

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.95-1.80 (m, 1H), 3.75 (s, 3H), 4.05 (t, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.80-4.65 (m, 3H), 6.00 (dd, *J* = 1.2, 15.8 Hz, 1H), 6.85 (dd, *J* = 6.7, 15.8 Hz, 1H), 7.40-7.30 (m, 5H);

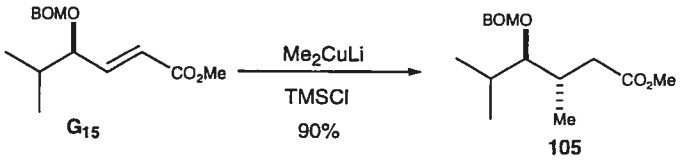
^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.27, 32.59, 51.58, 69.79, 80.53, 92.87, 122.68, 127.74, 127.89, 128.44, 137.72, 146.76, 166.52;

IR ($CDCl_3$) νmax 3020, 1725, 1230 cm^{-1};

m/e: 279 (M^++1), 237, 213, 181, 141, 109;

HRMS: $C_{16}H_{23}O_4$ (M^++1), calcd: 279.15969: found: 279.16292.

(3*S*, 4*R*)-4-Benzyloxymethoxy-3,5-dimethylhexanoic acid methyl ester (105):



To a suspension of CuI (9.60 g, 50.3 mmol) in THF (250 mL) was added MeLi·LiBr (1.5 M in ether, 67.00 mL, 101.00 mmol) at –15 °C. The reaction mixture was allowed to warm up to 0 °C over 30 min, then cooled to –78 °C. To the resulting mixture was added Me_3SiCl (25.40 mL, 201.00 mmol), and then a solution of **G_{15}** (7.00 g, 25.00 mmol) in THF (50 mL). Stirring was continued for 3.5 h at –78 °C, then the mixture was quenched with saturated NH_4Cl, diluted with EtOAc and washed with concentrated NH_4OH. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with saturated NH_4Cl-NH_4OH (1:1), saturated NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:16) to afford **105** as a colorless oil (7.00 g, 90%);

TLC: E/H = 1:5, R_f = 0.57;

$[\alpha]_D$ -17.90 ° (c 1.1, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 3.4 Hz, 3H), 0.97 (d, *J* = 3.4 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.90-1.80 (m, 1H), 2.16 (dd, *J* = 9.6, 15.0 Hz, 1H), 2.30-2.20 (m, 1H), 2.63 (dd, *J* = 3.6, 15.0 Hz, 1H), 3.11 (t, *J* = 5.4 Hz, 1H), 3.66 (s, 3H), 4.66 (dd, *J* = 11.8,

17.1 Hz, 2H), 4.79 (dd, J = 6.8, 12.3 Hz, 2H), 7.37-7.26 (m, 5H);

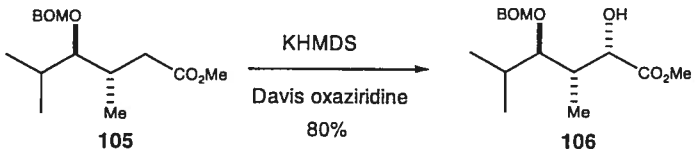
^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.52, 17.73, 20.03, 30.38, 32.76, 37.06, 51.33, 79.06, 88.83, 96.62, 127.51, 127.64, 128.29, 137.76, 173.98;

IR ($CDCl_3$): vmax 2960, 1760, 1215, 1060 cm^{-1};

m/e: 295 (M^++1), 217, 187, 157, 149, 109, 92;

HRMS: $C_{16}H_{23}O_4$ (M^++Na), calcd: 295.19101, found: 295.19447.

(2*S*, 3*S*, 4*R*)-4-Benzyloxymethoxy-2-hydroxy-3,5-dimethylhexanoic acid methyl ester (106):



To a solution of **105** (7.00 g, 25.00 mmol) in THF (220 mL) was added KHMDS (0.50 M in toluene, 60.00 mL, 30.00 mmol) at –78 °C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (9.80 g, 38.00 mmol) in THF (30 mL) was added. Stirring was continued for 3 h at –78 °C, and the mixture was quenched with saturated NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with saturated NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:6) to give **106** as colorless oil (6.50 g, 80%);

TLC: E/H = 1:4, R_f =0.37;

$[\alpha]_D$ -9.58 ° (c 2.4, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 1.90-1.80 (m, 1H), 2.20-2.10 (m, 1H), 3.38 (dd, J = 3.0, 9.1 Hz, 1H), 4.66 (d, J = 2.1 Hz, 1H), 3.79 (s, 3H), 4.67 (s, 2H), 4.80 (d, J = 6.5 Hz, 1H), 4.88 (d, J = 6.5 Hz, 1H), 7.37-7.26 (m, 5H);

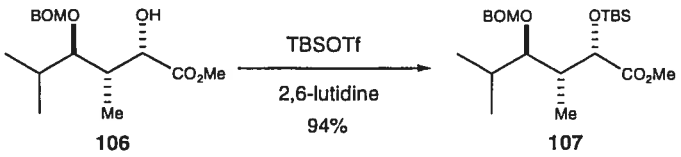
^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.62, 15.42, 20.40, 29.59, 39.04, 52.14, 70.26, 70.64, 85.86, 97.02, 127.60, 128.30, 137.54, 175.26;

IR (neat): νmax 3525, 2970, 1740, 1250, 1150, 1040 cm^{-1};

m/e: 311, 279, 257, 216, 203, 131, 108, 91, 73, 57;

HRMS: (M^++1), calcd: 311.18591, found: 311.18957.

(2*S*, 3*R*, 4*R*)-4-Benzyloxymethoxy-2-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexanoic acid methyl ester (107):



To a solution of **106** (9.20 g, 30.00 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added 2,6-lutidine (10.30 mL, 89.00 mmol) and TBSOTf (10.21 mL, 44.52 mmol). The resulting solution was stirred for 1 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:20) to give the TBS ether as a colorless oil (12.40 g, 94%);

TLC: E/H = 1:5, R_f = 0.80;

$[\alpha]_D$ -12.48 ° (c 1.5, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (d, *J*=7.0, 3H), 0.92 (s, 9H), 0.93 (d, *J*=6.9, 1H), 1.01 (d, *J*=6.92, 3H), 1.90 (m, 1H), 2.10 (m, 1H), 3.30 (dd, *J*=2.40, 8.79 Hz, 1H), 3.72 (s, 3H), 4.65 (d, *J*=11.9 Hz, 1H), 4.68 (d, *J*=11.9 Hz, 1H), 4.78 (d, *J*=6.72 Hz, 1H), 4.84 (d, *J*=6.72 Hz, 1H), 7.23 (m, 5H);

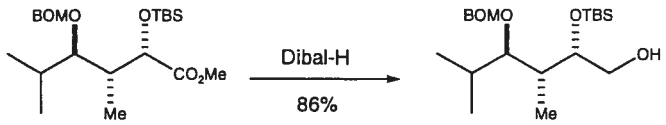
^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.99, -4.83, 10.84, 15.35, 18.32, 20.52, 25.83, 29.64, 41.24, 51.44, 69.87, 72.26, 86.74, 97.04, 127.46, 127.73, 129.22, 137.88, 174.61;

IR (neat): νmax 2940, 2850, 2710, 1406, 1250, 1150, 1040, 860, 780 cm^{-1};

m/e: 424, 317, 237, 216, 196, 149, 131, 108, 93;

HRMS: **$C_{23}H_{41}O_5Si$** (M^++1), calcd: 425.27243, found: 425.26974.

(2*S*, 3*R*, 4*R*)-4-Benzyloxymethoxy-2-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexan-1-ol (108):



107 108

To a solution of **107** (12.40 g, 29.00 mmol) in THF (150 mL) at –78 °C was added DIBAL-H (1.50 M in toluene, 43.00 mL, 64.50 mmol) dropwise over 30 min and the reaction mixture was stirred at 0 °C for 1 h. The mixture was cooled to –78 °C and quenched with saturated NH_4Cl, then diluted with EtOAc. HCl solution (2%, 100 mL) was added to dissolve inorganic gel. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with saturated $NaHCO_3$, saturated NH_4Cl and

brine, then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:6) to afford **108** as colorless oil (9.01 g, 86%);

TLC: E/H = 1:3, R_f = 0.30;

$[\alpha]_D$ -16.30 ° (*c* 2.5, $CHCl_3$);

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.95-0.90 (m, 15H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.94-1.82 (m, 3H), 2.28 (dd, *J* = 4.0, 7.1 Hz, 1H), 3.63-3.54 (m, 2H), 3.98 (dd, *J* = 4.9, 8.7 Hz, 1H), 4.66 (s, 2H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.84 (d, *J* = 6.7 Hz, 1H), 7.37-7.26 (m, 5H);

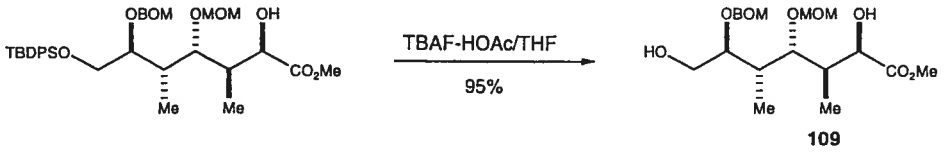
^{13}C-NMR (00 MHz, $CDCl_3$) δ -4.54, -4.18, 12.09, 16.52, 18.15, 20.74, 25.84, 29.93, 38.70, 65.82, 69.94, 73.11, 87.16, 95.59, 127.49, 127.69, 128.26, 137.86;

IR (neat): νmax 3450, 2950, 2880, 1460, 1380, 1250, 1140, 1090, 1080, 830, 770 cm^{-1};

m/e: 397 (M^++1), 289, 237, 216, 196, 149, 131, 108, 93;

HRMS: $C_{22}H_{41}O_4Si$ (M^++1), calcd: 397.27753, found: 397.27607.

(2*R*, 3*R*, 4*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-2,7-dihydroxy-4-methoxymethoxy-3,5-dimethylheptanoic acid methyl ester (109):



109

To a solution of the common chiron (3.40 g, 5.40 mmol) in THF (27 mL) was added a solution of TBAF-AcOH (8.51 mL, 0.95 M in THF, 8.00 mmol) at room temperature. The resulting mixture was stirred for 21 h at room temperature. The reaction mixture was

diluted with EtOAc and washed with saturated NH_4Cl, brine, and then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:2) to afford diol **109** as a colorless oil (2.00 g, 95%);

TLC: E/H = 1:1, R_f = 0.45;

$[\alpha]_D$ +1.70 ° (*c* 0.9, $CHCl_3$);

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 1.84-1.79 (m, 1H), 2.15-2.09 (m, 1H), 3.17 (broad, 2H), 3.35 (s, 3H), 3.58-3.52 (m, 2H), 3.77 (s, 3H), 3.90-3.78 (m, 2H), 4.52 (d, *J* = 2.1 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.86 (d, *J* = 7.1 Hz, 1H), 4.95 (d, *J* = 7.1 Hz, 1H), 7.35-7.27 (m, 5H);

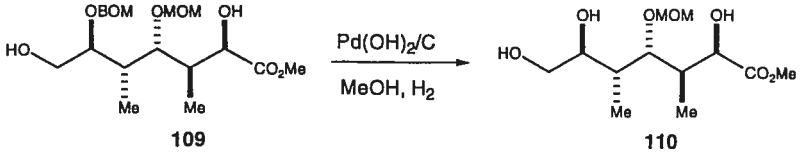
^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.60, 10.40, 35.97, 39.19, 52.43, 55.87, 63.87, 70.28, 70.60, 80.80, 84.39, 95.97, 99.06, 127.91, 128.46, 128.48, 128.49, 137.07, 175.74;

IR (neat) νmax 3490, 2980, 2950, 1745, 1460, 1390, 1250, 1220, 1150, 1050 cm^{-1};

m/e: 423 (M^++Na), 418, 383, 369, 339, 313, 261, 181, 165, 149, 133 ppm;

HRMS: $C_{20}H_{32}O_8$ (M^++Na), calcd: 423.19949, found: 423.20130.

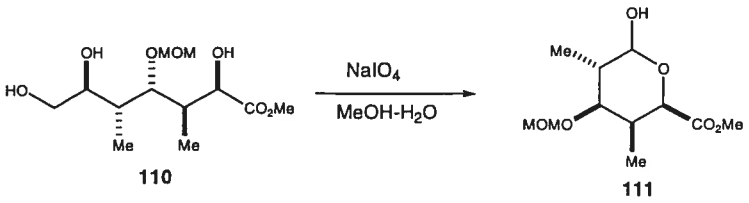
(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2,6,7-Trihydroxy-4-methoxymethoxy-3,5-dimethylheptanoic acid methyl ester (110):



109 **110**

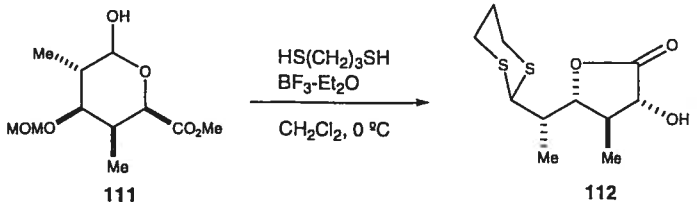
A mixture of **109** (2.00 g, 5.21 mmol) and $Pd(OH)_2/C$ (0.20 g, 20% Pd, Degussa type) in MeOH (26 mL) under 1 atm hydrogen was stirred at room temperature for 3 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The crude triol **110** was directly used for next step without purification. TLC: E/H = 1:0, R_f = 0.25.

6-Hydroxy-4-methoxymethoxy-3,5-dimethyltetrahydro-pyran-2-carboxylic acid methyl ester (111):



To a solution of crude triol **110** (5.20 mmol) in a mixture of MeOH (34 mL) and H_2O (17 mL) was added sodium periodate (1.60 g, 7.80 mmol, as solid) at room temperature. The resulting mixture was stirred for 2 h, then evaporated to remove MeOH. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl and brine, and dried over Na_2SO_4. The crude **111** after drying on oil pump was used for next step directly without purification. TLC: E/H = 1:0, R_f = 0.80.

(3*R*, 4*R*, 5*R*)-5-[(1*S*)-1-[1,3]Dithian-2-yl-ethyl)-3-hydroxy-4-methyldihydrofuran-2-one (112):



To a solution of crude **111** (5.20 mmol) in CH_2Cl_2 (40 mL) at 0 °C were added 1,3-propanedithiol (1.56 mL, 15.60 mmol) and boron trifluoride diethyl etherate (1.28 mL, 10.40 mmol). The resulting mixture was stirred for 3.5 h at 0 °C, diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, saturated NH_4Cl, brine, and then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:2) to afford **112** as a colorless oil (0.88 g, 65% for three steps);

TLC: E/H = 1:1, R_f = 0.40;

$[\alpha]_D$ -27.50 ° (*c* 0.4, $CHCl_3$);

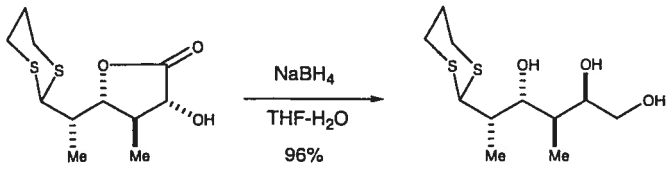
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.90-1.80 (m, 1H), 2.09-2.02 (m, 2H), 2.27-2.11 (m, 1H), 2.87-2.83 (m, 4H), 3.50 (broad, 1H), 4.13-4.07 (m, 2H), 4.40 (dd, *J* = 1.4, 10.0 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.89, 14.21, 25.73, 30.29, 30.35, 39.32, 41.61, 51.39, 81.74 176.23;

IR (neat) νmax 3390, 2982, 2947, 1765, 1462, 1393, 1220, 1150, 1050 cm^{-1};

HRMS: $C_{11}H_{19}O_3S_2$ (M^++1), calcd: 263.07758, found: 263.07730.

(2*R*, 3*S*, 4*R*, 5*S*)-5-[1,3]Dithian-2-yl-3-methylhexane-1,2,4-triol (113):



112 **113**

To a solution of **112** (0.24 g, 0.9 mmol) in a mixture of THF (8 mL) and H_2O (2 mL) was added sodium borohydride (0.17 g, 4.50 mmol, as solid) at room temperature. The resulting mixture was stirred for 2 h, then quenched with 2% aqueous HCl carefully. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, saturated NH_4Cl and brine. The aqueous phase was re-extracted with EtOAc four times. The combined organic phase was dried over Na_2SO_4. The crude product was purified by column chromatography (E/H=2:1) to give alcohol **113** (0.23 g, 95%);

TLC: E/H = 1:0, R_f = 0.40;

$[\alpha]_D$ -17.2 ° (*c* 2.5, $CHCl_3$);

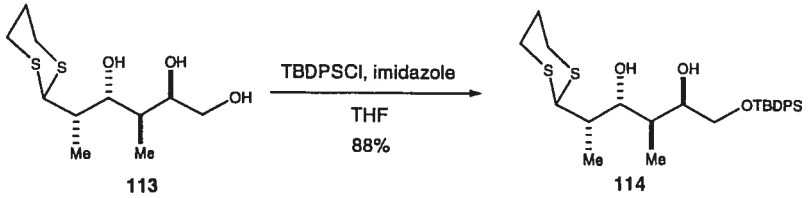
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.81 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 2.14-1.77 (m, 4H), 2.93-2.81 (m, 4H), 3.60 (dd, *J* = 3.40, 11.2 Hz, 1H), 3.67 (d, *J* = 8.4 Hz, 1H), 3.98 (d, *J* = 9.6 Hz, 2H), 3.73 (s, 3H), 4.14 (d, *J* = 7.1 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.08, 11.52, 226.02, 30.50, 30.75, 37.68, 39.87, 52.89, 64.85, 73.51, 73.62;

IR (neat) vmax 3490, 2990, 2970, 1790, 1470, 1440, 1205, 1140, 990, 940, 750 cm^{-1};

m/e: 262, 217, 181, 126, 109, 91.

(2*R*, 3*S*, 4*R*, 5*S*)-1-(*tert*-Butyldiphenylsilanyloxy)-5-[1,3]dithian-2-yl-3-methylhexane-2,4-diol (114):



113 114

To a solution of alcohol **113** (0.23 g, 0.85 mmol) and imidazole (0.24 g, 3.59 mmol) in THF (7 mL) was added TBDPSCl (0.25 mL, 0.94 mmol) at room temperature. The resulting mixture was stirred for 2 h, and then diluted with EtOAc, washed with saturated. NH_4Cl and brine. The aqueous phase was re-extracted with EtOAc. The combined organic phase was dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:3) to afford dithiane-diol **114** as an oil (0.34 g, 88%);

TLC: E/H = 1:3, R_f = 0.30;

$[\alpha]_D$ -4.0 ° (*c* 4.8, $CHCl_3$);

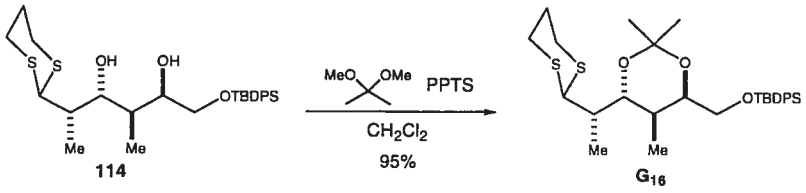
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.81 (d, *J* = 7.1 Hz, 3H), 1.09 (s, 9H), 1.14 (d, *J* = 6.9 Hz, 3H), 2.12-1.79 (m, 4H), 2.92-2.83 (broad, 6H), 3.67 (dd, *J* = 5.00, 10.1 Hz, 1H), 3.74 (dd, *J* = 7.5, 10.2 Hz, 1H), 3.98 (dd, *J* = 3.6, 8.0 Hz, 1H), 4.14-4.07 (m, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 7.47-7.27 (m, 6H), 7.71-7.67 (m, 4H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.55, 11.27, 19.11, 26.02, 26.79, 30.50, 30.87, 36.55, 40.43, 52.92, 65.45, 72.79, 74.54, 127.69, 129.71, 129.74, 132.99, 133.03, 135.43, 135.46;

IR (neat) νmax 3400, 2900, 1440, 1410, 1260, 1090, 800, 740, 680 cm^{-1};

HRMS: $C_{27}H_{41}O_3SiS_2$ (M^++1), calcd: 423.19949, found: 423.20130.

***tert*-Butyl-[(4*R*, 5*S*, 6*R*)-6-(1-[1,3]dithian-(2*S*)-yl-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-yl-methoxy]diphenylsilane (G_{16}):**



To a solution of dithane-diol **114** (0.34 g, 0.68 mmol) in dichloromethane (10 mL) were added 2,2-dimethoxypropane (1.00 mL, 8.20 mmol) and PPTS (0.033 g, 0.14 mmol, as solid) subsequently at room temperature. The resulting mixture was stirred for 2 h and then directly purified by chromatography to afford G_{16} as a colorless oil (0.35 g, 96%);

TLC: E/H = 1:5, R_f = 0.75;

$[\alpha]_D$ +19.74 ° (*c* 1.17, $CHCl_3$);

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 1.92-1.82 (m, 3H), 2.18-2.05 (m, 1H), 2.87-2.79 (m, 4H), 3.72-3.63 (m, 3H), 3.89 (dd, *J* = 6.50, 11.5 Hz, 1H), 4.08 (d, *J* = 8.0 Hz, 1H), 7.45-7.26 (m, 6H), 7.72-7.68 (m, 4H);

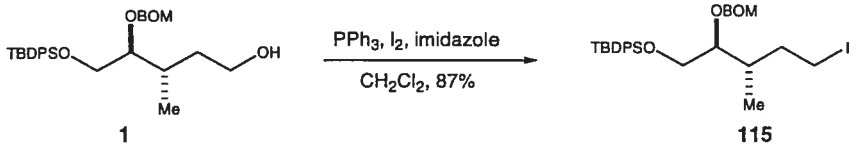
^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.45, 11.78, 20.00, 23.79, 26.69, 30.14, 30.29, 35.26, 40.62, 51,62, 63.28, 69.76, 73.51, 100.54, 127.47, 127.53, 129.53, 133.68, 135.45, 135.53;

IR (neat) νmax 2900, 1440, 1360, 1090, 1000 cm^{-1};

m/e: 545 (M^++1), 487, 429, 397, 339, 281, 241, 217, 181, 147;

HRMS: $C_{30}H_{45}O_3SiS_2$ (M^++1), calcd: 545.25792, found: 545.255600.

[(2*S*, 3*S*)-2-Benzyloxymethoxy-5-iodo-3-methylpentyloxy]-*tert*-butyldiphenylsilane (115):



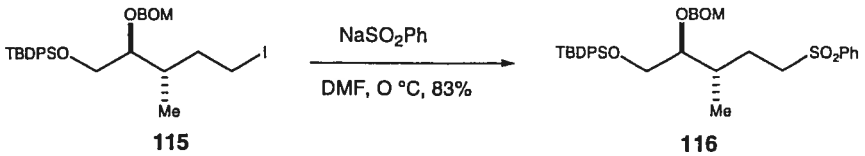
1 115

To a solution of **1** (1.50 g, 3.01 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added PPh_3 (1.58 g, 6.02 mmol), imidazole (0.41 g, 6.02 mmol) and I_2 (1.53 g, 6.02 mmol). The reaction mixture was stirred for 1.5 h before being quenched by an aqueous NH_4Cl solution (30 mL) and then diluted with hexane (60 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:50) to afford iodide **115** (1.57 g, 87%) as a colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J*=6.87 Hz, 3H), 1.07 (s, 9H), 1.64-1.78 (m, 1H), 1.98-2.17 (m, 2H), 3.08-3.18 (m, 1H), 3.58-3.80 (m, 3H), 4.54 (d, *J*=11.85 Hz, 1H), 4.67 (d, *J*=11.85 Hz, 1H), 4.78 (d, *J*=6.96 Hz, 1H), 4.88 (d, *J*=6.96 Hz, 1H), 7.28-7.49 (m, 10H), 7.65-7.75 (m, 5H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.07, 19.08, 26.76, 35.65, 35.96, 63.90, 69.68, 81.50, 94.61, 127.53, 127.65, 127.72, 128.31, 129.48, 129.63, 129.63, 129.68, 133.22, 135.49, 135.54, 137.78;

[(2*S*, 3*S*)-5-Benzenesulfonyl-2-benzyloxymethoxy-3-methylpentyloxy]-*tert*-butyldiphenylsilane (116):



115 116

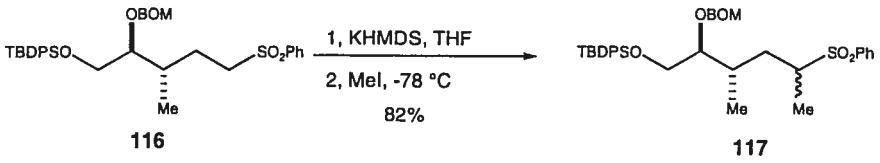
To a solution of **115** (1.50 g, 2.49 mmol) in DMF (40 mL) at room temperature was added $NaSO_2Ph$ (0.81 g, 4.98 mmol). The mixture was stirred for 24 h before being quenched with an aqueous NH_4Cl solution (30 mL). The mixture was extracted with diethyl ether (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:15) to give **116** (1.27 g, 83%) as a colorless oil;

$[\alpha]_D$ –25.7 ° (c 1.2, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J*=6.84 Hz, 3H), 1.05 (s, 9H), 1.62-1.72 (m, 1H), 1.91-2.10 (m, 2H), 3.09-3.14 (m, 1H), 3.18-3.28 (m, 1H), 3.49-3.54 (m, 1H), 3.66 (dd, *J*=4.22, 11.04 Hz, 1H), 3.72 (dd, *J*=5.56, 11.04 Hz, 1H), 4.48 (d, *J*=11.92 Hz, 1H), 4.58 (d, *J*=11.92 Hz, 1H), 4.69 (d, *J*=6.96 Hz, 1H), 4.80 (d, *J*=6.96 Hz, 1H), 7.28-7.54 (m, 12 H), 7.60-7.68 (m, 4H), 7.88-7.90 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.08, 19.09, 20.97, 24.89, 26.75, 33.29, 54.49, 63.72, 69.71, 81.43, 94.42, 127.57, 127.62, 127.68, 127.97, 128.33, 129.13, 129.70, 129.73, 133.12, 133.47, 135.46, 135.56, 137.69, 139.05;

[(2*S*, 3*S*)-5-Benzenesulfonyl-2-benzyloxymethoxy-3-methylhexyloxy]-*tert*-butyldiphenylsilane (117):

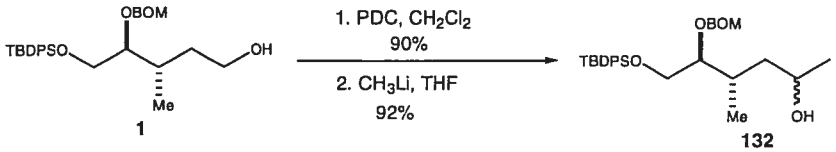


116 **117**

To a solution of **116** (1.20 g, 1.95 mmol) in THF (10 mL) at –78 °C was added LDA (2 M in THF, 1.95 mL, 2.53 mmol). The reaction mixture was stirred for 30 min before CH_3I (0.55 g, 0.24 mL, 3.89 mmol) was added. The resulting mixture was stirred at –78 °C for another 30 min before being quenched with NH_4Cl solution (20 mL) and diluted with diethyl ether (50 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (H/E=1:10) to provide **117** (0.99 g, 82%).

For synthetic procedures of compounds **118** to $\mathbf{G_{25}}$, please see the corresponding procedures of compounds **143** to $\mathbf{G_{29}}$.

(5*S*, 4*S*)-5-Benzyloxymethoxy-6-(*tert*-butyldiphenylsilanyloxy)-4-methylhexan-2-ol (132):

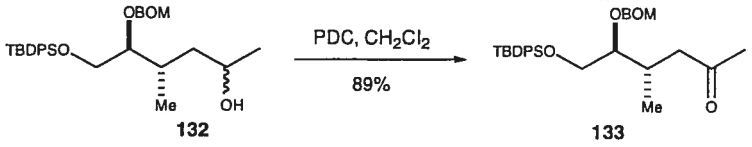


To a solution of alcohol **1** (1.00 g, 2.40 mmol) in CH_2Cl_2 (20 mL) was added pyridium chlorochromate (0.73 g, 3.36 mmol). The reaction mixture was stirred for 1.5 h and more pyridium chlorochromate (0.48 g, 2.24 mmol) was added. The mixture was stirred for 1 h before being diluted with diethyl ether (40 mL). The resulting mixture was filtered through a silica pad to remove the inorganic salts and the pad was washed with ether (20 mL x 2). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The

residue was purified by column chromatography (E/H=1:15) to give aldehyde (0.89 g, 90%) which was used directly in the next step.

To the above aldehyde (0.89 g, 2.16 mmol) in THF (15 mL) in –78 °C was added MeLi (1.5 M in ether, 2.88 mL, 4.32 mmol). The mixture was stirred for 30 min before being quenched with NH_4Cl solution (20 mL) and diluted with ether (40 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified with column chromatography (E/H=1:8) to afford alcohol **132** (0.88 g, 92%) as a colorless oil.

(3*S*, 4*S*)-5-Benzyloxymethoxy-6-(*tert*-butyldiphenylsilanyloxy)-4-methylhexan-2-one (133) :

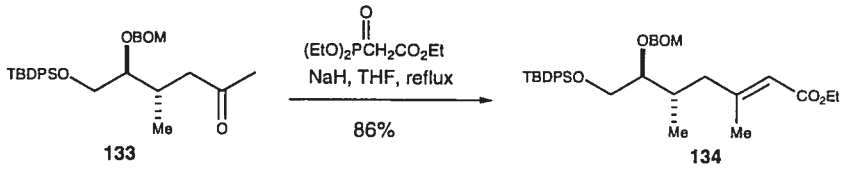


132 133

To a solution of alcohol **132** (0.88 g, 1.98 mmol) in CH_2Cl_2 (15 mL) was added pyridium chlorochromate (0.86 g, 3.96 mmol). The reaction mixture was stirred for 1 h and more pyridium chlorochromate (0.32 g, 1.49 mmol) was added. The mixture was stirred for 1 h before being diluted with diethyl ether (30 mL). The mixture was filtered through a silica pad to remove the inorganic salts and the pad was washed with ether (15 mL x 2). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:16) to give ketone **133** (0.78 g, 89%) as a colorless oil;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, *J*=6.76 Hz, 3H), 1.06 (s, 9H), 2.09 (s, 3H), 2.25 (dd, *J*=8.96 Hz, 16.28 Hz, 1H), 2.40-2.49 (m, 1H), 2.58 (dd, *J*=3.09, 16.68 Hz, 1H), 3.55-3.59 (m, 1H), 3.67 (dd, *J*=4.80, 10.88 Hz, 1H), 3.73 (dd, *J*=5.76, 10.88 Hz, 1H), 4.52 (d, *J*=11.92 Hz, 1H), 4.63 (d, *J*=11.92 Hz, 1H), 4.76 (d, *J*=6.92 Hz, 1H), 4.85 (d, *J*=6.92 Hz, 1H), 7.26-7.46 (m, 11H), 7.65-7.69 (m, 4H).

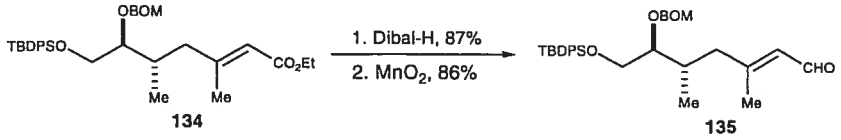
(5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-3,5-dimethylhept-2-enoic acid ethyl ester (134):



To a solution of triethyl phosphonateacetate (1.97 g, 8.81 mmol) in THF (30 mL) at –30 °C was added NaH (0.32 g, 60% in mineral oil, 8.00 mmol). The reaction mixture was stirred for 30 min before ketone **133** (0.77 g, 1.52 mmol) in THF (4 mL) was added. The reaction mixture was heated at reflux for 48 h before being cooled to room temperature and quenched with NH_4Cl solution (20 mL). The resulting mixture was extracted with ether (30 mL x 2). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:8) to afford **134** (0.75 g, 86%);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, *J*=6.78 Hz, 3H), 1.07 (s, 9H), 1.30 (t, *J*=6.81 Hz, 3H), 1.88 (dd, *J*=10.05, 13.56 Hz, 1H), 2.16 (s, 3H), 2.16-2.27 (m, 1H), 2.43 (dd, *J*=3.85, 13.56 Hz, 1H), 3.58-3.62 (m, 1H), 3.74-3.85 (m, 2H), 4.17 (q, *J*=6.81 Hz, 2H), 4.54 (d, *J*=11.79 Hz, 1H), 4.66 (d, *J*=11.79 Hz, 1H), 4.79 (d, *J*=6.76 Hz, 1H), 4.89 (d, *J*=6.89 Hz, 1H), 5.68 (s, 1H), 7.26-7.48 (m, 11H), 7.68-7.74 (m, 4H).

(5*S*, 6*S*)-6-Benzyloxymethoxy-7-(*tert*-butyldiphenylsilanyloxy)-3,5-dimethylhept-2-enal (135):

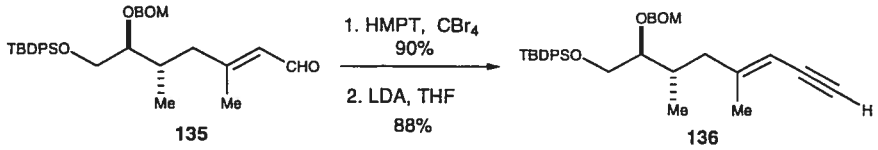


To a solution of ester **134** (0.70 g, 1.31 mmol) in toluene (20 mL) at –78 °C was added Dibal-H (0.5 M, 7.17 mL, 3.58 mmol). The reaction mixture was stirred at –78 °C for 1 h before a solution of HCl (1 M, 20 mL) was added. The resulting mixture was warmed to room temperature and then extracted with hexane-ethyl acetate (1:1, 20 mL x 2). The combined organic layers were washed with $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:5) to give the alcohol (0.61 g, 87%);

To the above alcohol (0.60 g, 1.10 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (0.48 g, 5.5 mmol). The reaction mixture was stirred for 4 h before the mixture was filtered through a Celite pad to remove the inorganic salts. The pad was washed with CH_2Cl_2 (10 mL x 2) and the combined filtrates were concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:12) to afford aldehyde **135** (0.51 g, 86%);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, *J*=6.84 Hz, 3H), 1.06 (s, 9H), 1.95 (dd, *J*=10.24, 13.59 Hz, 1H), 2.13 (s, 3H), 2.13-2.27 (m, 1H), 2.48 (dd, *J*=4.57, 13.59 Hz, 1H), 3.53-3.61 (m, 1H), 3.62-3.83 (m, 2H), 4.53 (d, *J*=11.97 Hz, 1H), 4.63 (d, *J*=11.97 Hz, 1H), 4.76 (d, *J*=7.02 Hz, 1H), 4.86 (d, *J*=7.02 Hz, 1H), 5.87 (d, *J*=7.92 Hz, 1H), 7.26-7.48 (m, 12 H), 7.62-7.73 (m, 3H), 9.99 (d, *J*=7.92 Hz, 1H) ppm.

[(2*S*, 3*S*)-2-Benzyloxymethoxy-3,5-dimethyloct-5-en-7-ynyloxy]-*tert*-butyldiphenylsilane (136):



To a solution of CBr_4 (1.56 g, 4.73 mmol) in THF (40 mL) at –30 °C was slowly added HMPT (0.77 g, 0.86 mL, 4.73 mmol). The color of the reaction changed from red to beige. The reaction mixture was stirred for further 15 min after addition, and then aldehyde **135** (0.50 g, 0.94 mmol) was added. Stirring continued for 1 h at –30 °C before $NaHCO_3$ solution was added to the mixture. The resulting mixture was extracted with hexane (30 mL x 2). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:70) to afford the dibromide compound (0.58 g, 90%) as a colorless oil;

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, *J*=6.82 Hz, 3H), 1.09 (s, 9H), 1.74 (s, 3H), 1.87 (dd, *J*=10.50, 13.58 Hz, 1H), 2.10-2.22 (m, 1H), 2.35 (dd, *J*=3.74, 13.58 Hz, 1H), 3.61-3.68 (m, 1H), 3.72-3.87 (m, 2H), 4.57 (d, *J*=11.76 Hz, 1H), 4.68 (d, *J*=11.76 Hz, 1H), 4.82 (d, *J*=6.93 Hz, 1H), 4.92 (d, *J*=6.93 Hz,.1H), 5.88 (d, *J*=10.50 Hz, 1H), 7.14 (d, *J*=10.5 Hz, 1H), 7.27-7.51 (m, 11H), 7.69-7.74 (m, 4H).

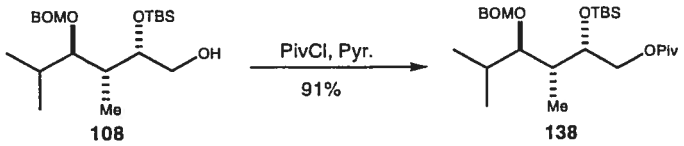
To a solution of the above dibromide compound (0.58 g, 0.84 mmol) in THF (15 mL) at –78 °C was added LDA (2.0 M in ether, 1.26 mL, 2.52 mmol). The reaction mixture was stirred for 15 min before being quenched with aqueous NH_4Cl solution. The resulting mixture was extracted with hexane (20 mL x 2). The combined extracts were washed

with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:80) to afford enyne **136** (0.39 g, 88%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 0.87 (d, *J*=6.81 Hz, 3H), 1.08 (s, 9H), 1.76 (s, 3H), 1.89 (dd, *J*=10.53, 13.68 Hz, 1H), 2.14-2.26 (m, 1H), 2.37 (dd, *J*=3.81, 13.68 Hz, 1H), 3.01 (s, 1H), 3.62-3.68 (m, 1H), 3.73-3.89 (m, 2H), 4.58 (d, *J*=11.29 Hz, 1H), 4.69 (d, *J*=11.29 Hz, 1H), 4.83 (d, *J*=6.93 Hz, 1H), 4.93 (d, *J*=6.93 Hz, 1H), 5.26 (s, 1H), 7.27-7.51 (m, 11H), 7.69-7.24 (m, 4H).

General procedure for stannyl cuprate additions to the enyne **136**:

To a slurry of dried CuCN (0.090 g, 1.00 mmol) in THF (5 mL) at –35 °C was slowly added the organometallic reagents (2.00 mmol). The resultant clear, yellow solution was stirred for 30 min at –35 °C, cooled to –78 °C, treated dropwise with tributyltin hydride (0.50 mL, 2.00 mmol), and stirred 30 min further. A solution of enyne **136** (0.063 g, 0.12 mmol) in THF (2 mL) was added. The reaction mixture was warmed to one specific temperature and stirred for 12 h before being carefully quenched with methanol and saturated aqueous NH_4Cl (10 mL). The dark brown solution was warmed to room temperature, stirred for an additional 1 h and then extracted with hexane (40 mL). The organic phase was washed with brine, dried over Na_2SO_4, concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:100, with 1% Et_3N as a stabilizer).

2,2-Dimethylpropionic acid 4-benzyloxymethoxy-2-(*tert*-butyldimethylsilanloxy)-3,5-dimethylhexyl ester (138):



108 **138**

To a solution of **108** (8.00 g, 20.00 mmol) and DMAP (4.87 g, 40.00 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added pivaloyl chloride (3.66 mL, 30.00 mmol). The resulting solution was stirred for 12 h at 0 °C. The reaction mixture was directly purified by chromatography (E/H=1:25) to give **138** as colorless oil (8.50 g, 88%);

TLC: E/H = 1:10, R_f = 0.70;

$[\alpha]_D$ –9.96 ° (c 1.2, $CHCl_3$);

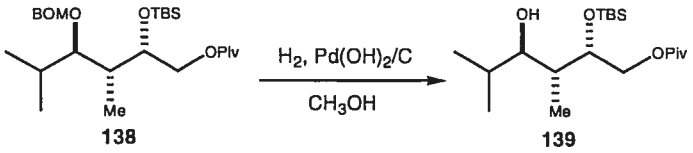
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.058 (s, 3H), 0.074 (s, 3H), 0.089 (s, 3H), 0.092 (s 3H), 0.84 (d, *J*=6.76 Hz, 3H), 0.86-0.93 (m, 24H), 1.19 (s, 9H), 1.75-1.85 (m, 2H), 3.46 (dd, *J*=3.04, 6.44 Hz, 1H), 3.98-4.20 (m, 2H), 4.01 (dd, *J*=6.88, 12.4 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.35, -4.12, -3.92, -3.57, 11.70, 16.39, 18.03, 18.38, 20.82, 25.69, 26.05, 27.10, 30.94, 38.59, 40.69, 66.68, 70.85, 78.57, 178.16;

IR (thin film) νmax 2958, 2858, 1732, 1472, 1389, 1367, 1282, 1254, 1147, 1094, 1052, 1006, 985, 836 cm^{-1};

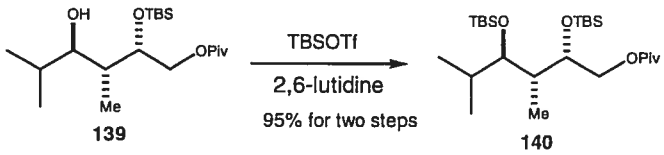
HRMS: $C_{23}H_{53}O_6Si_2$ (M^++1), calcd: 481.33807, found: 481.33590.

2,2-Dimethylpropionic acid 2-(*tert*-butyldimethylsilanyloxy)-4-hydroxy-3,5-dimethyl hexyl ester (139):



A mixture of **138** (3.00 g, 6.32 mmol) and 20% $Pd(OH)_2/C$ (0.40 g, Degussa type) in methanol (40 mL) under 1 atm of hydrogen was stirred at room temperature for 6 h. The reaction mixture was filtered through a pad of Celite to remove the catalyst and then washed with EtOAc. The crude alcohol **139** was subjected to next step without further purification.

2,2-Dimethyl-propionic acid 2,4-bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl ester (140):



To a solution of above alcohol **139** in CH_2Cl_2 (30 mL) at 0 °C were added 2,6-lutidine (1.66 mL, 14.23 mmol), then TBSOTf (2.19 mL, 9.49 mmol). The resulting solution was stirred for 1 h at this temperature. The reaction mixture was directly purified by chromatography (E/H=1:35) to afford **140** as colorless oil (2.86 g, 95%);

TLC: E/H = 1:10, R_f = 0.90;

$[\alpha]_D$ +2.82 ° (c 1.35, $CHCl_3$);

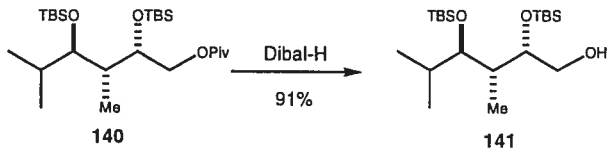
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.84 (d, *J*=6.76 Hz, 3H), 0.86-0.93 (m, 24H), 1.19 (s, 9H), 1.75-1.85 (m, 2H), 3.46 (dd, *J*=3.04, 6.44 Hz, 1H), 3.98-4.20 (m, 2H), 4.01 (dd, *J*=6.88, 12.40 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) –4.35, -4.12, -3.92, -3.57, 11.70, 16.39, 18.03, 18.38, 20.82, 25.69, 26.05, 27.10, 30.94, 38.59, 40.69, 66.68, 70.85, 78.57, 178.16;

IR (thin film) νmax 2958, 2858, 1732, 1472, 1389, 1362, 1282, 1254, 1147, 1094, 1052, 1006, 985, 836 cm^{-1};

HRMS: $C_{25}H_{55}O_4Si_2$ (M^++1), calcd: 475.36389, found: 475.36560.

2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3.5-dimethylhexan-1-ol (141):



140 **141**

To a solution of **140** (2.80 g, 5.86 mmol) in THF (20 mL) at –78 °C was added DIBAL-H (1.5 M in toluene, 10.00 mL, 15.00 mmol) dropwise. The resulting mixture was stirred for 1 h at –78 °C before being quenched with saturated NH_4Cl (25 mL). The reaction mixture was diluted with EtOAc (50 mL) and 2% HCl (20 mL) was added to dissolve inorganic salt. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with saturated $NaHCO_3$, saturated NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography (E/H=1:10) to afford alcohol **141** as a colorless oil (2.08 g, 91%);

TLC: E/H = 1:10, R_f = 0.47;

$[\alpha]_D$ +2.23 ° (c 0.81, $CHCl_3$);

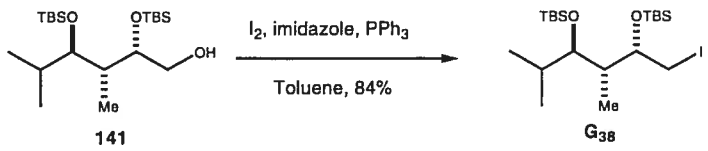
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.063 (s, 3H), 0.083 (s, 3H), 0.094 (s, 6H), 0.88-0.98 (m, 27H), 1.76-1.83 (m, 1H), 1.89-1.96 (m, 1H), 2.00-2.05 (m, 1H), 3.41 (t, *J*=4.64 Hz, 1H), 3.55-3.64 (m, 2H), 3.68 (dd, *J*=3.64, 7.22 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.44, -4.38, -4.26, -3.77, 14.38, 19.95, 18.04, 18.23, 20.87, 25.79, 25.96, 31.53, 40.03, 65.19, 74.47, 79.24;

IR (thin film) νmax 3400, 2961, 2856, 1476, 1368, 1280, 1256, 1173, 1088, 1053, 989, 841cm^{-1};

HRMS: $C_{20}H_{47}O_3Si_2$ (M^++1), calcd: 391.30637, found: 391.30580.

(2*S*, 3*R*, 4*R*)-2,4-Bis-(*tert*-butyldimethylsilanyloxy)-1-iodo-3,5-dimethylhexane (G_{38}):



To a solution of alcohol **141** (2.00 g, 5.00 mmol), dry imidazole (0.73 g, 10.0 mmol) and triphenylphosphine (2.69 g, 10.00 mmol) in toluene (20 mL) at 0 °C was added iodine (2.61g, 10.00 mmol). The resulting mixture was stirred for 1.5 h at this temperature. The reaction mixture was directly purified by chromatography (E/H=1:50) to afford **G_{38}** as a colorless oil (2.15 g, 84%);

TLC: E/H = 1:10, R_f = 0.95;

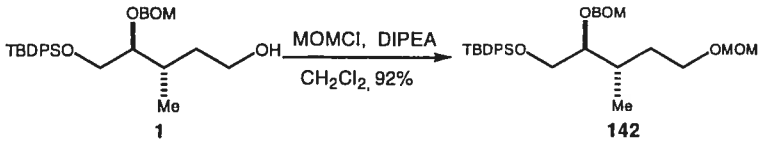
$[\alpha]_D$ –1.32 ° (c 1.21, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.097 (s, 6H), 0.12 (s, 3H), 0.14 (s, 3H), 0.88-0.95 (m, 27H), 1.72-1.82 (m, 1H), 1.98-2.20 (m, 1H), 3.28 (dd, *J*=5.92, 10.22 Hz, 1H), 3.35 (dd, *J*=2.60, 10.2 Hz, 1H), 3.42 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.32, -3.96, -3.39, 12.13, 14.04, 17.20, 18.04, 18.31, 21.31, 25.80, 26.05, 31.19, 42.73, 71.50, 78.25;

IR (thin film) νmax 2971, 2863, 1465, 1287, 1261, 1179, 1078, 1053, 990, 851 cm^{-1};

(2*S*, 3*S*)-(2-Benzyloxymethoxy-5-methoxymethoxy-3-methylpentyloxy)-*tert*-butyl-diphenyl-silane (142):



To a solution of **1** (18.00 g, 36 mmol) in dichloromethane (200 mL) at 0 °C under nitrogen atmosphere was added diisopropylethylamine (18.81 mL, 13.96 g, 108 mmol) and methyl chloromethyl ether (5.47 mL, 5.79 g, 72.00 mmol). The resultant mixture was stirred overnight at ambient temperature and then quenched by addition of saturated NH_4Cl (200 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the crude product by column chromatography (E/H=20:1) afforded MOM ether **142** (17.78 g, 92%) as a colorless oil;

TLC: R_f= 0.4 (E/H=1:10);

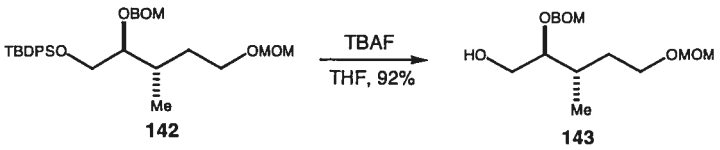
$[\alpha]_D$ -17.60 ° (c 0.71, CH_2Cl_2);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 6.92 Hz, 3H), 1.04 (s, 9H), 1.30-1.45 (m, 1H), 1.78-1.87 (m, 1H), 1.98-2.50 (m, 1H), 3.34 (s, 3H), 3.50-3.61 (m, 2H), 3.61-3.66 (m, 1H), 3.69-3.79 (m, 2H), 4.55 (d, J =11.84 Hz, 1H), 4.59 (d, J =1.44 Hz, 1H), 4.60 (d, J =1.44 Hz, 1H), 4.67 (d, J =11.84 Hz, 1H), 4.81 (d, J =6.92 Hz, 1H), 4.91 (d, J =6.92 Hz, 1H), 7.26-7.46 (m, 10H), 7.65-7.62 (m, 5H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.65, 19.06, 26.68, 31.65, 31.69, 55.01, 64.16, 65.93, 69.49, 82.09, 94.62, 96.23, 127.45, 127.57, 127.68, 128.25, 129.54, 129.56, 133.31, 134.68, 135.47, 135.51, 137.87;

IR (thin film) νmax 2931, 2884, 1472, 1428, 1388, 1112, 1041, 918, 740, 702 cm^{-1}; **HRMS**: $C_{32}H_{45}O_5Si$ (M^++1), calcd: 537.30365, found: 537.30490.

(2*S*, 3*S*)-2-Benzyloxymethoxy-5-methoxymethoxy-3-methylpentan-1-ol (143):



To a solution of **142** (15.00 g, 27.94 mmol) in THF (250 mL) was added TBAF solution (83.8 mL, 1 M, 83.83 mmol). The resulting mixture was stirred for 7 h at ambient temperature and then diluted with a mixture of hexane-ethyl acetate (1:1, 200 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL x 2) and brine (50 mL x 2), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Purification of the crude product by column chromatography (E/H=1:3) provided **143** (7.65 g, 92%) as a clear, colorless oil;

TLC: R_f= 0.4 (E/H=2:1);

$[\alpha]_D$ +24.20 ° (c 0.69, CH_2Cl_2);

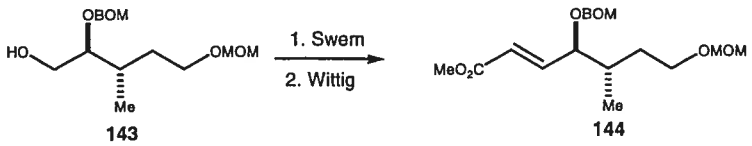
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, *J* = 6.88 Hz, 3H), 1.39-1.45 (m, 1H), 1.80-1.90 (m, 1H), 1.90-1.97 (m, 1H), 3.36 (s, 3H), 3.43-3.48 (m, 1H), 3.50-3.69 (m, 4H), 4.62 (d, *J* = 6.56 Hz, 2H), 4.68 (d, *J*= 11.72 Hz, 2H), 4.77 (d, *J*=6.96 Hz, 1H), 4.93 (d, *J* =6.96, 2H), 7.28-7.38 (m, 5H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.46, 32.01, 32.06, 55.02, 63.03, 65.69, 69.92, 86.08, 95.35, 96.26,127.80, 128.38, 137.1;

IR (thin film) νmax 3466, 2934, 2883, 1725, 1454, 1382, 1271, 1151, 1107, 1039, 918, 739, 699 cm^{-1};

HRMS: $C_{16}H_{27}O_5$ (M^++1), calcd: 299.18585, found: 299.18490.

(4*S*, 5*S*)-4-Benzyloxymethoxy-7-methoxymethoxy-5-methylhept-2-*trans*-enoic acid methyl ester (144):



To oxalyl chloride (21.00 g, 14.50 mL, 167.00 mmol) in CH_2Cl_2 (200 mL) at –78 °C was added DMSO (16.38 g, 14.90 mL, 209.70 mmol). The reaction mixture was stirred for 15 min, before **143** (25.00 g, 83.89 mmol) in CH_2Cl_2 (100 mL) was added slowly at –78 °C. The reaction mixture was stirred and slowly warmed to –30 °C in about 30 min before triethylamine (25.46 g, 251.67 mmol, 35 mL) was added. A white precipitate was formed

and the mixture was stirred at this temperature for 15 min before being quenched with saturated NH_4Cl (150 mL). The organic layer was separated, dried, filtrated and concentrated in *vacuo*. The crude aldehyde was dissolved in dry CH_2Cl_2 (270 mL) and $Ph_3P{=}CHCO_2CH_3$ (36.0 g, 334.36 mmol) was added to the solution. The resulting mixture was stirred at r.t. for 12 h. The solvent was removed and the residue was purified by column chromatography (E/H=1:10) to give **144** (26.85 g, 87%) as a colorless oil;

TLC: R_f= 0.4 (E/H=1:8);

$[\alpha]_D$ –53.8 ° (c 0.71, $CHCl_3$);

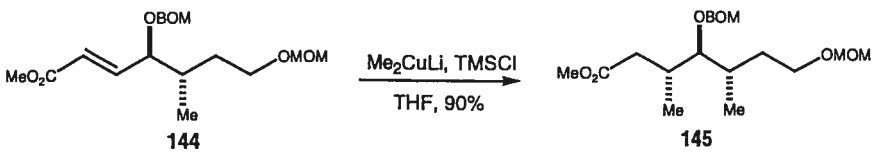
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, *J* = 6.84 Hz, 3H), 1.37-1.47 (m, 1H), 1.80-1.90 (m, 1H), 1.91-1.99 (m, 1H), 3.33 (s, 3H), 3.53-3.61 (m, 2H), 3.72 (s, 3H), 4.17 (t, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 11.72 Hz, 1H), 4.58 (d, *J* =6.6 Hz, 1H), 4.59 (d, *J*=6.6 Hz, 1H), 4.67 (d, *J* = 11.72 Hz, 1H), 4.71(d, *J* =7.08 Hz, 1H), 4.74 (d, *J* =7.08 Hz, 1H), 6.01 (dd, *J*= 1.04, 15.76 Hz, 1H), 6.84 (dd, *J*=6.6, 15.76 Hz, 1H), 7.22-7.35 (m, 5H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.03, 32.07, 34.39, 51.45, 55.01, 65.46, 69.66, 79.25, 92.67, 96.26, 122.78, 127.60, 127.71, 128.28, 137.52, 146.12, 166.25;

IR (thin film) νmax 2917, 1726, 1456, 1436, 1212, 1169, 1108, 1038 cm^{-1};

HRMS: $C_{19}H_{29}O_6$ (M^++1), calcd: 353.19642, found: 353.19547.

(3*R*, 4*S*, 5S)-4-Benzyloxymethoxy-7-methoxymethoxy-3, 5-methyl-heptanoic acid methyl ester (145):



To a stirred solution of the lithio dimethyl cuprate reagent (130.40 mmol) [prepared by treating a suspension of CuI (24.83 g, 130.40 mmol) in dry THF (250 mL) with MeLi-LiBr (1.5 M in ether, 173.00 mL, 260.00 mmol) at –5 °C] at –78 °C were added dropwise TMSCl (49.00 mL, 42.49 g, 391.00 mmol) and **144** (24.00 g, 65.20 mmol) in THF (150 mL). The reation mixture was stirred at –78 °C for 3 h before being quenched with a solution of NH_4OH/NH_4Cl (1:1, 300 mL). The resulting mixture was warmed to room temperature and extracted with hexane (200 mL x 2). The combined extracts were washed with diluted NH_4OH (100 mL x 2), brine and dried over sodium sulfate. The solvent was removed in *vacuo*, and the residue was purified by flashed chromatography (E/H=1:20) to afford **145** (22.50 g, 90%) as a colorless oil;

$[\alpha]_D$ +2.37 ° (c 0.76, $CHCl_3$);

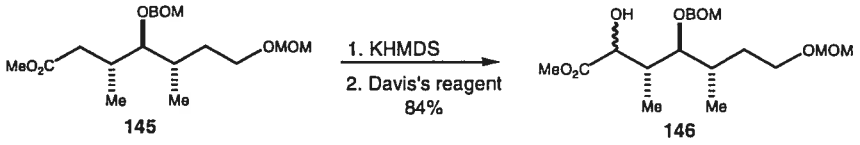
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, *J* =6.76 Hz, 3H), 1.01 (d, *J*=6.76 Hz, 3H), 1.38-1.46 (m, 1H), 1.84-1.96 (m, 2H), 2.16 (dd, *J* = 9.68, 14.98 Hz, 1H), 2.23-2.32 (m, 1H), 2.62 (dd, *J* = 3.76, 14.98 Hz, 1H), 3.20 (t, *J* = 5.12 Hz, 1H), 3.35 (s, 3H), 3.57-3.65 (m, 2H), 3.66 (s, 3H), 4.61 (dd, *J*= 0.64, 6.52 Hz, 1H), 4.62 (dd, *J*=0.64, 6.52 Hz, 1H), 4.64 (s, 2H), 4.78 (s, 2H), 7.26-7.36 (m, 5H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.70, 17.82, 31.35, 32.43, 32.60, 37.25, 51.27, 55.02, 65.89, 70.03, 88.33, 96.28, 96.46, 127.51, 127,63, 128.27, 137.72, 173.83;

IR (thin film) νmax 2950, 2881, 1737, 1455, 1439, 1383, 1276, 1194, 1108, 1037 cm^{-1};

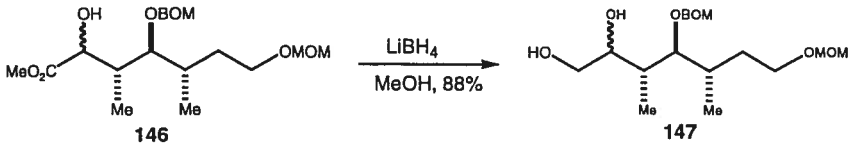
HRMS: $C_{20}H_{32}O_6$ (M^++1), calcd: 369.22772, found: 369.22690.

(2*S*, *R*, 3*R*, 4*S*, 5*S*)-4-Benzyloxymethoxy-2-hydroxy-7-methoxymethoxy-3, 5-dimethylheptanoic acid methyl ester (146):



To a stirred solution of **145** (25.00 g, 65.00 mmol) in THF (250 mL) at –78 °C was added KHMDS solution (0.50 M in toluene, 260.00 mL) under argon. After 30 min, a solution of *trans*-2-phenyl-sulfonyl-3-phenyloxaziridine (Davis' reagent, 38.61 g, 143 mmol) in THF (250 mL) was then added dropwise at –78 °C under argon. The reaction mixture was stirred at this temperature for 2.5 h. The reaction was quenched with saturate NH_4Cl solution (200 mL) and extracted with ether (200 mL x 3). The organic extracts were dried over sodium sulfate, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (E/H=1:3) to afford α-hydroxy ester **146** (21.89 g, 84%) as a colorless oil which was directly used in the next step.

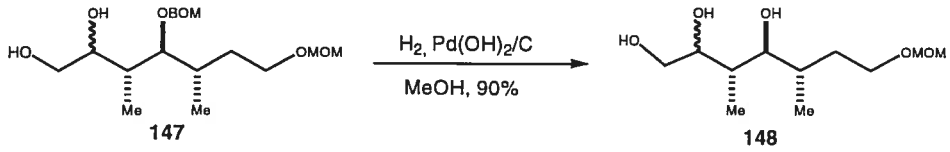
(2*S*, *R*, 3*R*, 4*S*, 5*S*)-4-Benzyloxymethoxy-2-hydroxy-7-methoxymethoxy-3,5-dimethylheptane-1,2-diol (147):



To a solution of **146** (7.00 g, 17.50 mmol) in THF (150 mL) at 0 °C was added $LiBH_4$ solution (2.0 M, 26.00 mL, 52.50 mmol). MeOH (4.00 mL) was added dropwise. The reaction mixture was then warmed to room temperature and allowed to stir for 2 h. The

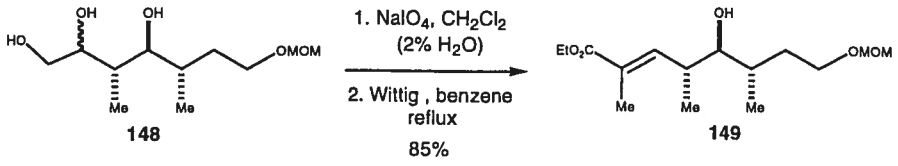
reaction was then quenched with saturated ammonium chloride solution (100 mL) and extracted with ether (200 mL x 2). The organic extracts were dried over $NaSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (E/H=1:1) to afford **147** (5.98 g, 92%) as a colorless oil which was directly used in the next step.

(2*S*,*R*, 3*S*, 4*S*, 5*S*)-7-methoxymethoxy-3, 5-dimethylheptane-1, 2, 4-triol (148):



A mixture of **147** (2.00 g, 7.93 mmol), 10% $Pd(OH)_2$ on active carbon (0.20 g, 20% Pd, Degussa type) in methanol (30 mL) was stirred under hydrogenation for 8 h, then filtered through Celite, washed completely with ether. The combined filtrates were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:2) to give **148** (1.68 g, 90%) which was used directly in the next step.

(4*R*, 5*S*, 6*S*)-5-Hydroxy-8-methoxymethoxy-2, 4, 6-trimethyloct-2-*trans*-enoic acid ethyl ester (149):



To a solution of **148** (1.68 g, 7.23 mmol) in CH_2Cl_2 (40 mL) were added $NaIO_4$ (6.79 g, 31.74 mmol) and H_2O (1.0 mL). The reaction mixture was stirred at room temperature for

1.5 h. The precipitate was filtered and washed with CH_2Cl_2 (20 mL x 2). The organic layer was dried over Na_2SO_4 and solvent was removed in *vacuo*. The crude aldehyle was used directly in the next step with out further purification.

To a solution of the above aldehyde from the previous reaction in benzene (40 mL) was added $Ph_3P{=}CHCO_2Et$ (5.60 g, 15.45 mmol). The mixture was heated at reflux for 2 days. The solvent was removed and the residue subjected to column chromatography (E/H=1:4) to afford **149** (1.94 g, 85%);

$[\alpha]_D$ +12.31 ° (0.58, $CHCl_3$);

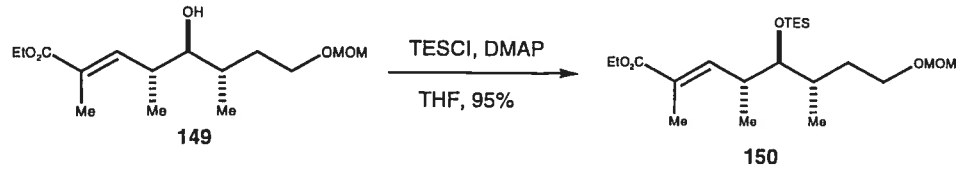
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (d, *J* = 6.84 Hz, 3H), 0.99 (d, *J* = 6.84 Hz, 3H), 1.23 (t, *J* = 6.84 Hz, 3H), 1.48-1.54 (m, 1H), 1.60-1.68 (m, 1H), 1.72-1.82 (m, 1H), 1.81 (d, *J* = 0.8 Hz, 3H), 2.60-2.70 (broad, 2 H), 3.23 (dd, *J* =5.08, 6.66 Hz, 1H), 3.31 (d, *J*= 0.64 Hz, 3H), 3.57-3.63 (m, 1H), 4.09-4.17 (m, 2H), 4.56 (s, 2H), 6.74 (dd, *J*=10.08, 0.96 Hz, 1H) ppm;

^{13}C NMR ($CDCl_3$, 400 MHz) δ 12.42, 14.06, 16.22, 16.68, 31.50, 33.91, 36.23, 55.03, 60.23, 65.47, 79.01, 96.19, 127.78, 143.20, 167.99 ppm;

IR (thin film) νmax 3502, 3061, 2991, 2879, 1708, 1461, 1388, 1270, 1236, 1138, 1108, 1037, 99, 918, 752 cm^{-1};

HRMS: $C_{15}H_{28}O_5Na$ (M^++Na), calcd: 311.18344, found: 311.18440.

(4*R*, 5*S*, 6*S*)--8-methoxymethoxy-2, 4, 6-trimethyl-5-(triethylsilanyloxy)-oct-2-*trans*-enoic acid ethyl ester (150):



To a solution of **149** (2.20 g, 7.23 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added imidazole (1.47 g. 21.69 mmol) and triethylsilyl chloride (2.43 mL, 2.18 g, 14.47 mmol). The resulting mixture was stirred for 24 h at ambient temperature and then diluted with hexane (100 mL) and ethyl acetate (20 mL). The organic layer was washed with saturated NH_4Cl (50 mL x 2) and brine (50 mL x 2), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Purification of the residue by column chromatography (E/H=1:9) on silica gel provided **150** (2.84 g, 95%) as a clear, colorless oil;

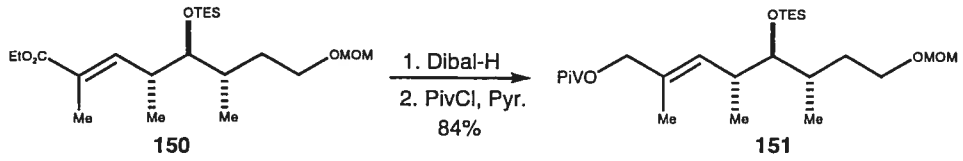
$[\alpha]_D$ +11.98 ° (c 1.11, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.59 (q, *J* =7.92 Hz, 6H), 0.88 (d, *J*=6.8 Hz, 3H), 0.94 (t, *J*=7.92 Hz, 9H), 0.96 (d, *J*=6.88 Hz, 3H), 1.27 (t, *J*=7.12 Hz, 3H), 1.28-1.40 (m, 1H), 1.72-1.81 (m, 2H), 1.82 (d, *J*=1.36 Hz, 3H), 2.60-2.73 (m, 1H), 3.35 (s. 1H), 3.48-3.63 (m, 3H), 4.10-4.23 (m, 2H), 4.60 (d, *J*=6.52 Hz, 1H), 4.61 (d, *J*=6.52 Hz, 1H), 6.83 (dd, *J*=10.2, 1.40 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.28, 6.90, 12.34, 14.11, 16.25, 17.56, 31.47, 34.89, 36.51, 54.99, 60.15, 66.11, 80.61, 96.27, 126.28, 145.36, 168.22;

IR (thin film) νmax 2957, 2877, 1711, 1650, 1459, 1414, 1384, 1356, 1292, 1238, 1037, 738 cm^{-1}.

2,2-Dimethylpropionic acid-(4*R*, 5*S*, 6*S*)--8-methoxymethoxy-2, 4, 6-trimethyl-5-(triethylsilanyloxy)-oct-2-*trans*-enyl ester (151):



150 151

To a stirred solution of **150** (5.60 g, 13.26 mmol) in toluene (150 mL) at –78 °C was added dropwise Dibal-H (1 M in toluene, 40.10 mL, 40.09 mmol)) under nitrogen. The reaction mixture was stirred at this temperature for 1 h before being quenched with saturated NH_4Cl solution (50 mL). The resulting mixture was warmed to room temperature and extracted with ether (75 mL x 3) immediately. The extracts were dried over Na_2SO_4, and then filtered. The solvent was removed in *vacuo* and the residue was subjected to the column chromatography (E/H=6:1) to afford the alcohol (4.28 g, 89%) as a colorless oil;

$[\alpha]_D$ -2.28 ° (c 1.32, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.57 (q, *J* =7.94 Hz, 6H), 0.86 (d, *J*=6.84 Hz, 3H), 0.91-0.95 (m, 12H), 1.22-1.33 (m, 1H), 1.63 (s, 3H), 1.79-1.86 (m, 1H), 2.1 (broad, 1H), 2.52-2.57 (m, 1H), 3.32 (s. 3H), 3.38 (t, *J*=4.48 Hz, 1H), 3.44-3.57 (m, 2H), 3.94 (s, 2H), 4.56 (d, *J*= 6.6 Hz, 1H), 4.57 (d, *J*=6.6 Hz, 1H), 5.43 (d, *J*=9.64 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.33, 6.96, 13.65, 16.59, 18.65, 31.73, 34.47, 35.59, 54.90, 66.28, 68.99, 80.89, 96.13, 129.13, 133.27;

IR (thin film) νmax 3426, 2929, 1473, 1463, 1387, 1361, 1253, 1149, 1106, 1037, 836, 773, 676 cm^{-1};

HRMS: $C_{19}H_{41}O_4Si$ (M^++1), calcd: 361.27742, found: 361.27677.

To a stirred solution of the above alcohol (4.81 g, 13.35 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added pyridine (3.42 mL, 3.34 g, 39.75 mmol) and pivaloyl chloride (3.28 mL, 3.20 g, 26.70 mmol). The reaction mixture was then stirred at room temperature for 16 h. The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with ether (50 mL x 3). The extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:40) afford **151** (5.64 g, 95%) as a colorless oil;

$[\alpha]_D$ -4.32 ° (c 1.23, CH_2Cl_2);

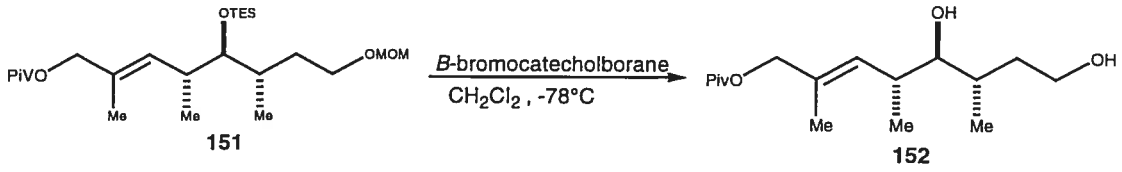
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.59 (q, *J* =7.88 Hz, 6H), 0.86 (d, *J*=6.84 Hz, 3H), 0.92 (d, *J*=6.96 Hz, 3H), 0.94 (t, *J*=7.88 Hz, 9H), 1.20 (s, 9H), 1.28-1.38 (m, 1H), 1.62 (s, 3H), 1.65-1.73 (m, 1H), 1.77-1.85 (m, 1H), 2.52-2.61 (m, 1H), 3.35 (s, 3H), 3.40 (t, *J*=4.64 Hz, 1H), 3.48-3.61 (m, 2H), 4.42 (d, *J*=12.52 Hz, 2H), 4.44 (d, *J*=12.52 Hz, 2H), 4.60 (d, *J*=5.84 Hz, 1H), 4.62 (d, *J*=5.84 Hz, 1H), 5.49 (d, *J*=9.64 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.34, 6.97, 13.85, 16.30, 18.50, 27.06, 31.69, 34.43, 35.42, 38.70, 54.94, 66.23, 69.67, 80.74, 96.24, 128.55, 131.61, 178.14;

IR (thin film) νmax 2958, 2877, 1732, 1481, 1460, 1283, 1238, 1153, 1107, 1035, 738 cm^{-1};

HRMS: $C_{24}H_{49}O_5Si$ (M^++1), calcd: 445.33493, found: 455.33350.

2,2-Dimethylpropionic acid-(4*R*, 5*S*, 6*S*)--5, 8-dihydroxy-2, 4, 6-trimethyl-oct-2-*trans*-enyl ester (152):



To a solution of **151** (0.70 g, 1.67 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added a solution of catecheolborane bromide (0.29 g, 1.67 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred and warmed to –30 °C in 30 min. H_2O (10 mL) was added and the mixture was stirred for 30 min before NaOH solution (1.0 M, 15 mL) was added at 0 °C. The mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with 1 M NaOH solution (15 mL x 2) and brine (15 mL x 2), dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography on silica-gel provided **153** (0.20 g, 30%, E/H=1:8), and **152** (0.21 g, 60%, E/H=1:2) as colorless oils;

$[\alpha]_D$ +14.70 ° (c 0.38, CH_2Cl_2);

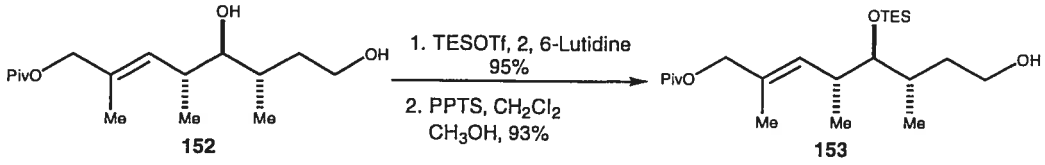
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, *J* = 6.84 Hz, 6H), 1.19 (s, 9 H), 1.60-1.72 (m, 1H), 1.67 (d, *J*=1.24 Hz, 3H), 1.73-1.86 (m, 1H), 2.60-2.70 (m, 1H), 2.62-2.67 (broad, 2H), 3.20 (t, *J*=5.88 Hz, 1H), 3.56-3.62 (m, 1H), 4.42 (d, *J*= 12.28 Hz, 1H), 4.52 (d, *J*=12.28 Hz, 1H), 5.39 (dd, *J* =9.72, 1.21 Hz, 1 H) ppm;

^{13}C NMR (CD_3Cl, 400 MHz) δ 14.06, 17.10, 17.29, 27.05, 33.18, 34.06, 35.53, 38.76, 59.81, 69.87, 79.27, 130.57, 131.57, 178.4 ppm;

IR (thin film) νmax 3370, 2961, 2931, 1728, 1480, 1459, 1397, 1284, 1156, 1060, 991 cm^{-1}.

HRMS: $C_{16}H_{31}O_4$ (M^++1), calcd: 287.22223, found: 287.22160.

2, 2-Dimethylpropionic acid-(4*R*, 5*S*, 6*S*)-8-hydroxy-2, 4, 6-trimethyl-5-(triethylsilanyloxy)-oct-2-*trans*-enyl ester (153):



To a solution of **152** (0.080 g, 0.28 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added 2,6-lutidine (0.089 mg, 0.83 mmol, 97 μL) and TESOTf (0.18 g, 0.70 mmol, 0.16 mL). The reaction mixture was stirred for 0.5 h at 0 °C before being quenched with saturated NH_4Cl (10 mL). The resulting mixture was extracted with hexane (10 mL x 2). The combined extracts were washed with brine (10 mL x 2), dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the crude product by column chromatography (E/H=50:1) on silica-gel provided the di-TES ether (0.14 g, 95%) as a colorless oil;

$[\alpha]_D$ -3.45 ° (c 0.52, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.54-0.61 (m, 12H), 0.85 (d, *J*=6.68 Hz, 3H), 0.90-0.96 (m, 21H), 1.21 (s, 9H), 1.23-1.36 (m, 1H), 1.62 (s, 3H), 1.64-1.74 (m, 1H), 2.54-2.59 (m,

1H), 3.40 (t, J = 4.28 Hz, 1H), 3.53-3.59 (m, 1H), 3.65-3.70, (m, 1H), 4.41 (d, J=12.6 Hz, 1H), 4.44 (d, J=12.6 Hz, 1 H), 5.50 (d, J=9.64 Hz, 1 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.28, 5.30,6.62, 6.93, 13.81, 16.17, 18.50, 27.04, 34.07, 34.98, 35.32, 38.69, 61.14, 68.75, 80.79, 128.24, 132.70, 178.16;

IR (thim film) νmax 2994, 2931, 1732, 1480, 1459, 1414, 1380, 1282, 1239, 1123, 1095, 1006, 972, 740 cm^{-1};

To a solution of the above di-TES ether (2.00 g, 3.89 mmol) in MeOH-CH_2Cl_2 solution (made from 15 mL of CH_2Cl_2 and 5 mL of MeOH) at –10 °C was added PPTS (0.20 g, 0.79 mmol). The reaction mixture was stirred for 1 h at –10 °C before being quenched with saturated NH_4Cl solution (50 mL), and then was extracted with ether (50 mL x 3). The extracts were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=40:1) to afford **153** (1.46 g, 93%) as a colorless oil;

$[\alpha]_D$ -16.10 ° (c 1.93, $CHCl_3$);

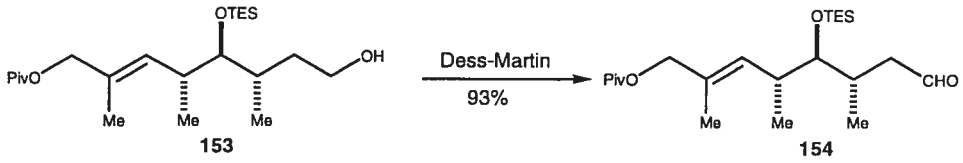
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.56 (q, J=7.92 Hz, 6H), 0.86-0.94 (m, 15H), 1.16 (s, 9H), 1.47-1.54 (m, 1H), 1.60 (d, J=1.12 Hz, 3H), 1.60-1.66 (m, 1H), 1.74-1.79 (m, 1H), 2.60-2.65 (m, 1H), 2.66-2.72 (broad, 1H), 3.38 (dd, J = 5.96, 5.92 Hz, 1H), 3.47-3.53 (m, 1H), 3.63-3.68 (m, 1H), 4.37 (d, J=12.48 Hz, 1H), 4.42 (d, J=12.48 Hz, 1H), 5.39 (dd, J=9.82, 1.04 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.26, 6.87, 13.79, 16.75, 18.07, 27.00, 33.71, 34.01, 35.98, 38.68, 59.79, 69.61, 80.96, 128.98, 131.76, 178.26;

IR (thin film) vmax 3401, 2962, 2931, 1728, 1480, 1458, 1397, 1284, 1156 cm^{-1};

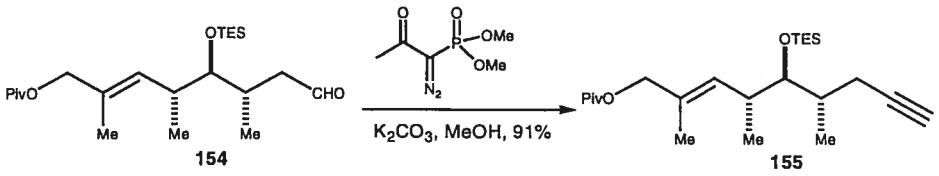
HRMS: $C_{22}H_{45}O_4Si$ (M^++1), calcd: 401.30872, found: 401.30872.

2, 2-Dimethylpropionic acid-(4*R*, 5*S*, 6*S*)-8-oxo-2, 4, 6-trimethyl-5-(triethylsilanyloxy)-oct-2-*trans*-enyl ester (154):



To a solution of **153** (1.35 g, 3.25 mmol) in dry CH_2Cl_2 (20 mL) at room temperature was added Dess-Martin reagent (2.37 g, 6.50 mmol). The mixture was stirred for 30 min, and then was diluted with hexane (20 mL) and ethyl acetate (5 mL). The mixture was filtered through a silica pad and the pad was washed with hexane-ethyl acetate solution (5:1, 50 mL). The filtrates were combined and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:10) to give **154** (1.20 g, 93%).

2, 2-Dimethylpropionic acid-(4*R*, 5*S*, 6*S*)-2, 4, 6-trimethyl-5-(triethylsilanyloxy)-non-2-*trans*-en-8ynyl ester (155):



To a solution of **155** (0.24 g, 0.60 mmol) in MeOH (8 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (0.35 g, 1.80 mmol) and K_2CO_3 (0.25 g, 1.8 mmol). The resulting mixture was stirred for 4 h at ambient temperature and then diluted with hexane

(20 mL) and ethyl acetate (8 mL). The organic layer was washed with saturated ammonium chloride (15 mL x 2) solution and brine (15 mL x 2), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue by column chromatography (E/H=60:1) on silica-gel provided **156** (0.22 g, 91%) as a clear, colorless oil.

$[\alpha]_D$ -4.36 ° (c 1.33, CH_2Cl_2);

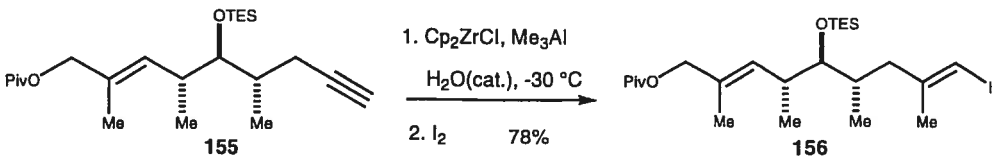
^{1}H NMR (C_6D_6, 400 MHz) δ 0.68 (q, *J* = 7.84 Hz, 6H), 0.97 (d, *J*=6.96 Hz, 3H), 0.98-1.06 (m, 12H), 1.23 (s, 9H), 1.56 (d, *J*=1.28 Hz, 3H), 1.82-1.85 (m, 1H), 1.85 (t, *J*=2.68 Hz, 1H), 2.21 (ddd, *J*=7.68, 2.68 Hz, 18.86 Hz, 1H), 2.31 (ddd, *J*=7.68, 2.68, 18.86 Hz, 1H), 2.52-2.56 (m, 1H), 3.52 (dd, *J* = 6.44, 6.44 Hz, 1H), 4.48 (d, *J* =17.3 Hz, 1H), 4.51 (d, *J* =17.3 Hz, 1H), 5.64 (dd, *J* =9.72, 1.16 Hz, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ 5.47, 6.99, 13.58, 16.17, 18.36, 21.78, 26.94, 35.39, 36.96, 38.45, 69.04, 69.66, 79.30, 82.96, 129.60, 129.85, 176.86;

IR (thin film) νmax 3312, 2959, 2876, 1731, 1480, 1459, 1379, 1283, 1152, 1102, 1034, 1009, 729 cm^{-1};

HRMS: $C_{23}H_{43}O_3Si$ (M^++1), calcd: 395.29816, found: 395.29740.

2, 2-Dimethylpropionic acid-(4*R*, 5*S*, 6*S*)-9-iodo-2, 4, 6, 8-tetramethyl-5-(triethylsilanyloxy)-nona-2, 8-*trans*-dienyl ester (156):



To a solution of Cp_2ZrCl_2 (0.22 g, 0.73 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added a solution of trimethylalane (2 M in hexane, 1.60 mL, 3.20 mmol). The reaction mixture was stirred for another 30 min at –20 °C before water (13.00 mg, 0.73 mmol) was added. After 30 min, a solution of **155** (0.45 g, 1.42 mmol) in CH_2Cl_2 (4 mL) was added. The reaction mixture was stirred for another 3 h at –20 °C before a solution of iodine (0.76 g, 3.00 mmol) in THF (3 mL) was added dropwise. After 10 min, the mixture was warmed to room temperature, and a saturated solution of $NaHCO_3$ (10 mL) was added slowly with vigorous stirring. The mixture was extracted with diethyl ether (30 mL x 3). The combined ether extract was dried over Na_2SO_4, concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:50) to afford **156** (0.59 g, 78%);

$[\alpha]_D$ -7.81 ° (c 0.84, CH_2Cl_2);

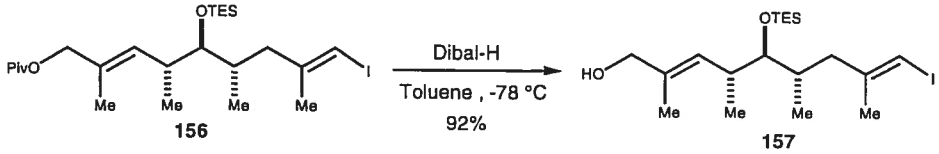
^{1}H NMR (C_6D_6, 400 MHz) δ 0.65 (q, *J* = 7.96 Hz, 6H), 0.76 (d, *J*=6.80 Hz, 3H), 0.95 (d, *J*=6.96 Hz, 3H), 1.06 (t, *J*=7.96 Hz, 9 H), 1.26 (s, 9H), 1.59 (d, *J*=1.21 Hz, 3H), 1.68-1.78 (m, 1H), 1.79 (s, 3H), 1.89 (dd, *J*=10.84, 12.90 Hz, 1H), 2.40 (dd, *J* = 12.9, 3.52 Hz, 1H), 2.50-2.57 (m, 1 H), 3.31 (t, *J* =4.76 Hz, 1H), 4.53 (d, *J* =12.56 Hz, 1H), 4.58 (d, *J*=12.52 Hz, 1H), 5.67 (d, *J*=9.48 Hz, 1H), 5.84 (s, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ 5.50, 7.00, 13.66, 15.81, 18.42, 23.01, 26.96, 35.44, 35.63, 38.43, 42.42, 69.06, 75.40, 80.63, 129.8, 130.2, 147.6, 178.9;

IR (thin film) νmax 2958, 2875, 1731, 1457, 1377, 1281, 1149, 1097, 1281, 1149, 1097, 1035, 735, 668 cm^{-1};

HRMS: $C_{24}H_{44}O_3Sil$ (M^++1), calcd: 535.21045, found: 535.21230.

(4*R*, 5*S*, 6*S*)-9-Iodo-2, 4, 6, 8-tetramethyl-5-(triethylsilanyloxy)-nona-2, 8-*trans*-dien-1-ol (157):



To a stirred solution of **156** (0.12 g, 0.22 mmol) in toluene (6 mL) at –78 °C was added dropwise Dibal-H (0.50 M in toluene, 1.10 mL, 0.56 mmol) under nitrogen. The reaction mixture was stirred at this temperature for 1 h before being quenched with saturated NH_4Cl solution (15 mL). The resulting mixture was warmed to room temperature and extracted with ether (25 mL x 3) immediately. The extracts were dried over Na_2SO_4, and then filtered. The solvent was removed in *vacuo* and the residue was subjected to the column chromatography (E/H=1:6) to afford **157** (0.10 g, 92%) as a colorless oil;

$[\alpha]_D$ -15.02 ° (c 1.0, hexane);

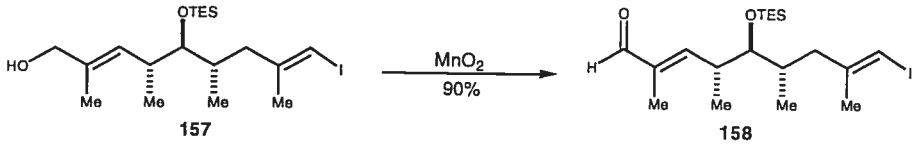
^{1}H NMR (C_6D_6, 300 MHz) δ 0.67 (q, *J* = 7.89 Hz, 6H), 0.78 (d, *J*=6.69 Hz, 3H), 0.99 (d, *J*=6.93 Hz, 3H), 1.06 (t, *J*=7.89 Hz, 9H), 1.65 (d, *J*=1.32 Hz, 3H), 1.77 (d, *J*=0.42 Hz, 3H), 1.72-1.79 (m, 1H), 1.91 (dd, *J*=10.71, 10.74 Hz, 1H), 2.43 (dd, *J*=12.99, 3.09 Hz, 1H), 2.56-2.60 (m, 1H), 3.34 (t, *J*=4.41 Hz, 1H), 3.87 (d, *J* = 0.87 Hz, 1H), 5.62 (dd, *J* =9.78, 0.84 Hz, 1H), 5.83 (s, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ 5.53, 7.03, 13.53, 15.97, 18.63, 23.25, 35.38, 35.62, 42.43, 68.34, 75.40, 80.89, 127.77, 134.07, 146.74;

IR (thin film) vmax 3326, 2957, 1480, 1457, 1414, 1377, 1272, 1238, 1142, 1096, 1038, 1000, 968, 851, 784, 737 cm^{-1};

HRMS: $C_{19}H_{36}O_2Sil$ (M^+-1), calcd: 451.15292, found: 451.15210.

(4*R*, 5*S*, 6*S*)-9-Iodo-2, 4, 6, 8-tetramethyl-5-(triethylsilanyloxy)-nona-2, 8-*trans*-dienal (158):



To a stirred solution of **157** (0.50 g, 1.10 mmol) in CH_2Cl_2 (18 mL) at room temperature was added MnO_2 (0.48 g, 5.50 mmol) in one portion. The mixture was stirred at room temperature for 2 h and then filtered through Celite. The Celite pad was washed with CH_2Cl_2 (40 mL) and the filtrate was concentrated in *vacuo*. The residue was purified by column chromatography (E/H=9:1) to give **158** (0.45 g, 90%);

$[\alpha]_D$ -0.96 ° (c 1.67, hexane);

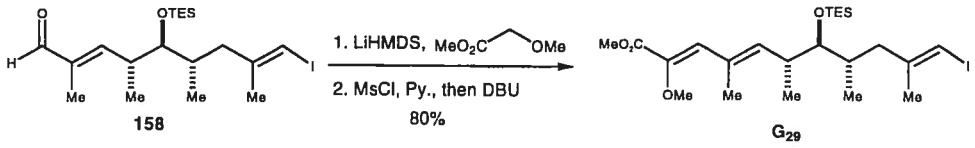
^{1}H NMR (C_6D_6, 300 MHz) δ 0.59 (q, *J* = 8.04 Hz, 6H), 0.64 (d, *J*=6.88 Hz, 3H), 0.85 (d, *J*=6.93 Hz, 3H), 1.00 (t, *J*=8.04 Hz, 9H), 1.56-1.64 (m, 1H), 1.71 (d, *J*=0.56 Hz, 3H), 1.75 (d, *J*=1.32 Hz, 3H), 1.75-1.85 (m, 1H), 2.23 (dd, *J*=13.08 Hz, 3.09 Hz, 1H), 2.61-2.66 (m, 1H), 3.31 (dd, *J*=3.56, 5.16 Hz, 1H), 5.80 (s, 1H), 6.48 (dd, *J*=9.48, 1.32 Hz, 1H), 9.40 (s, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ 5.39, 6.89, 9.17, 15.23, 17.62, 23.17, 36.08, 36.19, 42.62, 75.84, 79.87, 138.18, 146.06, 154.59, 193.68;

IR (thin film) νmax 2958, 2876, 1691, 1643, 1456, 1414, 1379, 1272, 1239, 1144, 1096, 1034, 1010, 968, 852, 739 cm^{-1};

HRMS: $C_{19}H_{34}O_2Sil$ (M^+-1), calcd: 449.13730, found: 449.13800.

(6*R*, 7*S*, 8*S*)-11-Iodo-2-methyl-4, 6, 8, 10-tetramethyl-7-(triethylsilanyloxy)-undeca-2, 4, 10 -*trans*-trienoic acid methyl ester (G_{29}):



To a stirred solution of methyl methoxy acetate (0.10 g, 0.10 mL, 1.00 mmol) in THF (3 mL) at –78 °C was added LiHMDS (1 M in THF, 0.60 mL, 0.60 mmol). The reaction mixture was stirred at –78 °C for 0.5 h before a solution of **158** (0.090 g, 0.20 mmol) in THF (1 mL) was added. The mixture was then stirred at –78 °C for 2 h, after which TLC indicated no aldehyde remained. The reaction mixture was quenched with dilute aqueous NH_4Cl and extracted with diethyl ether (15 mL x 3). The combined ether extracts were dried over sodium sulfate and concentrated in *vacuo*. Column chromatography (E/H=1:70) of the residue afforded the γ-hydroxy ester (0.096 g, 86%). The mixture was used for the next step directly.

To a solution of the above γ-hydroxy ester (0.10 g, 0.18 mmol) in CH_2Cl_2 (2 mL) was added MsCl (0.041 g, 27 μL, 0.36 mmol) and Et_3N (0.055 g, 75 μL, 0.54 mmol). The reaction mixture was stirred at room temperature for 3 h before DBU (0.054 g, 55 μL, 0.36 mmol) was added. The reaction mixture was stirred for another 2 h and then quenched with aqueous NH_4Cl. The resulting mixture was extracted with diethyl ether (5 mL x 3). The combined ether extracts were dried over Na_2SO_4 and then concentrated

under reduced pressure. Chromatography (E/H=1:4) of the residue afforded **4** (0.077 g, 80%);

$[\alpha]_D$ –1.24 ° (c 1,23, hexane);

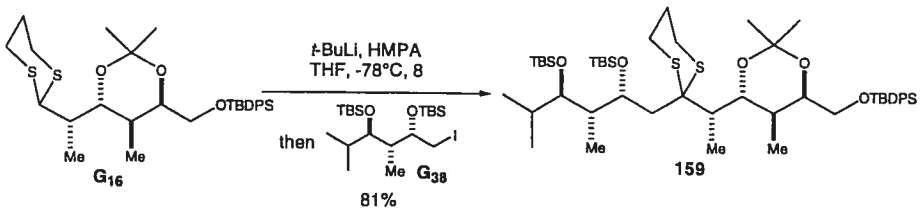
^{1}H NMR (C_6D_6, 400 MHz) δ 0.63 (q, *J* = 7.96 Hz, 6H), 0.74 (d, *J*=6.76 Hz, 3H), 0.96 (d, *J*=6.88 Hz, 3H), 1.02 (t, *J*=7.96 Hz, 9H), 1.62-1.68 (m, 1H), 1.72 (s. 3 H), 1.85 (dd, J_1=10.32, 13.34 Hz, 1H), 2.10 (d, *J*=1.24 Hz, 3H), 2.38 (dd, *J*=9.76, 3.98 Hz, 1H), 2.63-2.71 (m, 1H), 3.33 (dd, *J* = 5.02, 3.96 Hz, 1H), 3.40 (s, 3H), 3.60 (s, 3H), 5.81 (s, 1H), 6.05 (d, *J*=9.22 Hz, 1H), 6.91 (d, *J*=0.96 Hz, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ 5.48, 6.98, 14.83, 15.67, 18.19, 23.19, 35.76, 36.01, 42.57, 50.95, 59.43, 75.53, 80.56, 128.75, 130.69, 140.53, 143.45, 146.53, 164.45;

IR (thin film) νmax 2956, 2874, 1749, 1457, 1378, 1272, 1237, 1147, 1102, 1041, 1011 cm^{-1};

HRMS: $C_{23}H_{42}IO_4Si$ (M^++1), calcd: 537.18972, found: 537.18877.

4-(1-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]-dithian-2-yl}-ethyl)-6-(*tert*-butyldiphenylsilanyloxymethyl)-2,2,5-trimethyl-[1,3]-dioxane (159):



To a solution of $\mathbf{G_{16}}$ (0.58 g, 1.06 mmol) in THF (5 mL) at –78 °C were added HMPA (0.74 mL, 4.26 mmol) and *tert*-butyl lithium (1.70 M in pentane) until yellow color remained, and then more *tert*-butyl lithium (1.70 M in pentane, 0.75 mL, 1.27 mmol) was added. The resulting orange mixture was stirred for one hour at –78 °C before a solution of $\mathbf{G_{38}}$ (0.71 g, 1.41 mmol) in THF (3 mL) was added. The reaction was continued for 2 h at –78 °C, and then quenched with saturated NH_4Cl. The reaction mixture was extracted with EtOAc (15 mL x 3) and dried over Na_2SO_4. The residue was purified by column chromatography (E/H=1:30) to give **159** (0.79 g, 81%) as a foam;

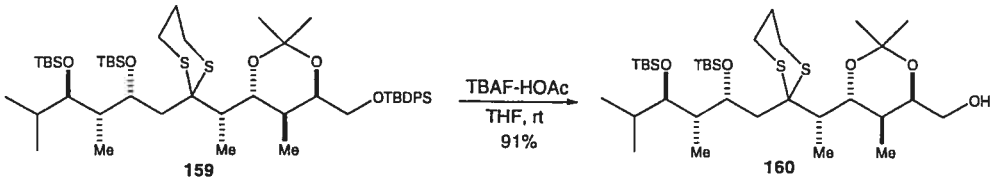
$[\alpha]_D$ +8.83 ° (c 1.18, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.105 (s, 3H), 0.173 (s, 3H), 0.21 (s, 3H), 0.23 (s, 3H), 0.84-1.0 (m, 30H), 1.09 (s, 9H), 1.117 (d, *J*=6.88 Hz, 3H), 1.29 (s, 3H), 1.30-1.37 (m, 2H), 1.38 (s, 3H), 1.75-2.0 (m, 4H), 2.1-2.18 (m, 1H), 2.23 (d, *J*=6.92 Hz, 1H), 2.52-2.62 (m, 2H), 2.90 (d, *J*=12.08 Hz, 2H), 3.64-3.74 (m, 3H), 3.88-3.91 (m. 1H), 4.06 (d, *J*=7.84 Hz, 1H), 4.41 (d, *J*=7.28 Hz, 1H), 7.4-7.5 (m, 6H), 7.11-7.76 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.41, -3.34, -2.92, -2.46, 9.23, 9.39, 11.92, 15.92, 18.34, 18.62, 19.11, 21.84, 23.13, 26.25, 26.73, 30.32, 37.12, 41.00, 41.41, 45.36, 57.49, 63.36, 69.65, 70.17, 73.50, 77.88, 100.30, 127.52, 127.56, 129.53, 129.56, 133.54, 133.68, 135.48, 135.56;

IR (thin film) νmax 2930, 2856, 1471, 1428, 1380, 1362, 1251, 1224, 1177, 1112, 1056, 1022, 835, 773, 736, 702 cm^{-1}.

[6-(1-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]-dithian-2-yl}ethyl)-2,2,5-trimethyl-[1,3]-dioxan-4-yl]-methanol (160):



To a solution of **159** (0.33 g, 0.35 mmol) in THF (3 mL) at room temperature was added TBAF-AcOH (0.95 M in THF, 0.75 mL, 0.71 mmol). The resulting mixture was stirred for 9 h before being diluted with EtOAc (15 mL), washed with saturated $NaHCO_3$ (10 mL x 3) and then dried over Na_2SO_4. The residue was purified by chromatography (E/H=1:4) to give the alcohol (0.22 g, 91%) as a colorless oil;

$[\alpha]_D$ +1.49 ° (c 0.87, $CHCl_3$);

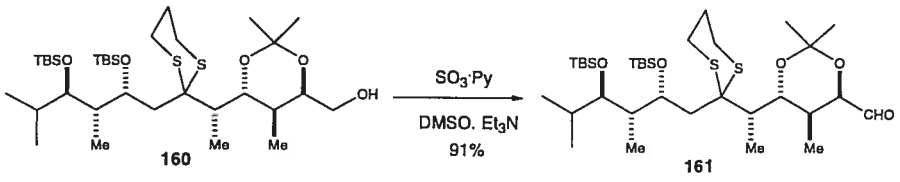
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.069 (s, 3H), 0.15 (s, 3H), 0.78 (s, 3H), 0.19 (s, 3H), 0.86-0.97 (m, 30H), 1.15 (d, *J*=9.36 Hz, 3H), 1.34 (s, 3H), 2.21 (d, *J*=9.41 Hz, 1H), 2.5-2.62 (m, 2H), 2.85 (d, *J*=2.6 Hz, 18.2 4Hz, 2H), 3.55 (dd, *J*=4.72, 15.22 Hz, 1H), 3.62-3.89 (m, 2H), 3.87-3.97 (m, 1H), 4.08 (d, *J*=10.6 Hz, 1H), 4.38 (dt, *J*=9.24, 2.28 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.46, -3.38, -3.01, -2.53, 9.20, 9.33, 12.09, 14.04, 15.87, 18.27, 18.54, 21.75, 23.89, 24.17, 25.05, 25.77, 25.88, 25.99, 26.17, 30.28, 37.04, 40.74, 41.35, 45.32, 57.34, 62.36, 70.12, 70.43, 73.33, 77.80, 100.48;

IR (thin film) νmax 3436, 2931, 2856, 1472, 1382, 1251, 1226, 1171, 1142, 1113, 1056, 1022, 835, 773 cm^{-1};

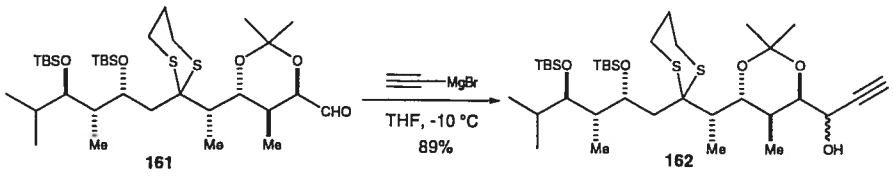
HRMS: $C_{34}H_{69}O_5Si_2S_2$ (M^+-1), calcd: 677.41248, found: 677.40990.

6-(1-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]dithian-2-yl}ethyl)-2,2,5-trimethyl-[1,3]dioxane-4-carbaldehyde (161):



To a solution of **160** (0.24 g, 0.36 mmol) in CH_2Cl_2 (4 mL) at room temperature were added dimethylsulfoxide (1.00 mL, excess), triethylamine (0.18 g, 0.25 mL, 1.80 mmol), SO_3·Py (0.23 g, 1.44 mmol) in that order. The reaction mixture was stirred for 2 h at room temperature before was quenched with saturated NH_4Cl (6 mL). The resulting mixture was extracted with ethyl acetate (15 mL x 2). The combined extracts were dried over Na_2SO_4 and then concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:7) to give the aldehyde (0.23 g, 91%) as a colorless oil which was used in the next step right away. TLC: E/H = 1:5, R_f = 0.35.

1-[6-(1-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]-dithian-2-yl}-ethyl)-2,2,5-trimethyl[1,3]-dioxan-4-yl]-prop-2-yn-1-ol (162):



To a solution of **161** (1.00 g, 1.47 mmol) in THF (15 mL) at –20 °C was added the ethynyl magnesium bromide (5.95 mL, 0.5 M, 2.95 mmol). The reaction mixture was stirred at –20 °C for 1 h before being quenched with saturated aqueous NH_4Cl (20 mL).

The mixture was extracted with EtOAc (30 mL x 3) and dried over Na_2SO_4. The solvent was removed in *vacuo* and the resulting residue was purified by column chromatography (E/H=1:15-1:10) to afford **162-*R***-isomer (0.40 g, 38.6%) and **162-*S***-isomer (0.52 g, 50.3%) as colorless oils;

For 161-*R*-isomer

$[\alpha]_D$ +9.86 ° (c 1.73, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.062 (s, 3H), 0.13 (s, 3H), 0.17 (s, 3H), 0.19 (s, 3H), 0.81-0.95 (m, 27H), 1.99 (d, *J*=6.76 Hz, 3H), 1.16 (d, *J*=6.64 Hz, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.70 (dd, *J*=2.44, 15.88 Hz, 1H), 1.78-1.90 (m, 2H), 1.93-2.15 (m, 4H), 2.23 (q, *J*=7.00 Hz, 1H), 2.47 (d, *J*=2.16 Hz, 1H), 2.50-2.62 (m, 2H), 2.78-2.92 (m, 2H), 3.68 (dd, *J*=1.04, 7.04 Hz, 1H), 3.81 (dd, *J*=4.64, 9.32 Hz, 1H), 4.09 (d, *J*=7.68 Hz, 1H), 4.31 (d, *J*=9.32 Hz, 1H), 4.37 (d, *J*=7.04 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.45, -3.37, -2.99, -2.53, 9.21, 9.31, 12.05, 13.97, 15.88, 18.28, 18.56, 21.73, 22.51, 22.55, 23.69, 24.15, 25.06, 25.74, 25.91, 25.99, 26.18, 30.32, 36.83, 41.02, 41.42, 45.43, 57.30, 62.03, 70.11, 73.19, 73.60, 74.14, 77.83, 80.48, 80.48, 101.10;

IR (thin film) νmax 3500, 2954, 2930, 1471, 1383, 1250, 1223, 1056, 1024, 835, 722 cm^{-1}.

For 162-*S*-isomer:

$[\alpha]_D$ +8.53 ° (c 0.91, $CHCl_3$);

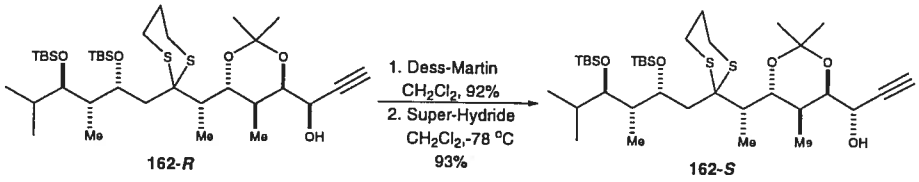
^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.007 (s, 3H), 0.14 (s, 3H), 0.18 (s, 3H), 0.19 (s, 3H), 0.80-0.92 (m, 27H), 1.05 (d, *J*=6.81 Hz, 3H), 1.17 (d, *J*=6.96 Hz, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 1.7-1.95 (m, 4H), 1.95-2.18 (m, 4H), 2.25 (q, *J*=7.02 Hz, 1H), 2.50 (d, *J*=2.07 Hz, 1H), 2.50-2.62 (m, 2H), 2.78-2.96 (m, 2H), 3.68 (dd, *J*=1.20, 7.11 Hz, 1H), 3.85 (dd, *J*=4.71, 8.28 Hz, 1H), 4.11 (d, *J*=7.74 Hz, 1H), 4.38 (dd, *J*=2.04, 8.23 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.45, -3.39, -2.99, -2.50, 9.17, 12.36, 15.89, 18.29, 18.57, 21.77, 23.68, 24.19, 24.90, 25.79, 25.91, 26.00, 26.19, 30.29, 36.97, 41.40, 45.39, 57.37, 61.91, 70.12, 71.51, 73.55, 76.57, 83.09, 100.90;

IR (thin film) νmax 3426, 3311, 2955, 2930, 2856, 1471, 1462, 1251, 1222, 1172, 1143, 1112, 1055, 1026, 836, 773 cm^{-1};

HRMS: $C_{36}H_{71}O_5Si_2S_2$ (M^++1), calcd: 703.42815, found: 703.42728.

Conversion of 162-*R*-isomer to 162-*S*-isomer:



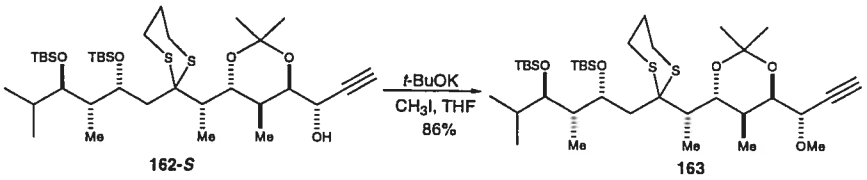
To a solution of the **162-*R*-isomer** (0.50 g, 0.71 mmol) in CH_2Cl_2 (15 mL) at room temperature was added Dess-Martin reagent (0.77 g, 2.13 mmol) in one portion. The reaction mixture was stirred for 1.5 h and TLC showed the reaction completed. The reaction mixture was concentrated in *vacuo* and the residue was subjected directly to column chromatography (H/E=30:1) to afford the ketone (0.46 g, 92%);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.068 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.19 (s, 3H), 0.84-0.95 (m, 27H), 0.99 (d, *J*=6.76 Hz, 3H), 1.21 (d, *J*=6.99 Hz, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.71 (dd, *J*=2.22, 15.72 Hz, 1H), 1.80-1.95 (m, 2H), 1.96-2.18 (m, 3H), 2.27 (q, *J*=7.05 Hz, 1H), 2.35-2.45 (m, 1H), 2.52-2.64 (m, 2H), 2.80-2.95 (m, 2H), 3.33 (s, 1H), 3.67 (d, *J*=7.17 Hz, 1H), 4.16 (d, *J*=7.68 Hz, 1H), 4.36-4.42 (m, 1H), 4.53 (d, *J*=4.89 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) -4.44, -3.35, -2.96, -2.54, 9.26, 9.30, 12.58, 14.00, 15.86, 18.29, 18.58, 21.71, 22.57, 23.56, 24.10, 25.03, 25.79, 25.88, 25.98, 26.19, 29.24, 29.54, 30.34, 31.80, 38.56, 40.96, 42.33, 45.35, 57.14, 70.06, 73.51, 76.37, 80.54, 101.65, 184.84;

To a solution of the above ketone (0.48 g, 0.68 mmol) in CH_2Cl_2 (19 mL) at –78 °C was added Super-hydride solution (1 M in THF, 2.65 mL, 2.65 mmol). The reaction mixture was stirred at –78 °C for 2 h before was quenched with saturated aqueous ammonium chloride solution (20 mL). The resulting mixture was warmed to room temperature, extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Column chromatography (H/E=20:1) of the residue afforded **162-*S*-isomer** (0.44 g, 93%).

4-(1-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]-dithian-2-yl}ethyl)-(1-methyoxyprop-2-ynyl)-2,2,5-trimethyl-[1,3]-dioxane (163):



162-*S* 163

To a solution of **162-*S*** isomer (0.41 g, 0.58 mmol) in THF (10 mL) at –20 °C was added *t*-BuOK (0.70 mL, 1 M, 0.70 mmol). The mixture was stirred 0.3 h before methyl iodide (0.099 g, 0.044 mL, 0.70 mmol) was added dropwise. The reaction mixture was stirred at –20 °C for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (H/E=15:1) to give **163** (0.36 g, 86%) as a colorless oil;

$[\alpha]_D$ +12.24 ° (c 0.2.96, $CHCl_3$);

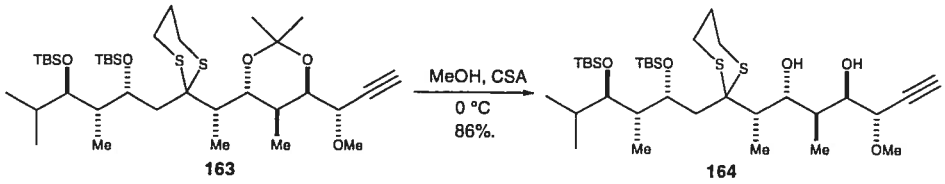
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.063 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.19 (s, 3H), 0.82-0.96 (m, 30H), 1.15 (d, *J*=6.96 Hz, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 1.72 (dd, *J*=2.04, 15.72 Hz, 1H), 1.1.82-2.04 (m, 4H), 2.05-2.16 (m, 2H), 2.23 (q, *J*=7.00 Hz, 1H), 2.44 (s, 1H), 2.50-2.62 (m, 2H), 2.80-2.96 (m, 2H), 3.44 (s, 3H), 3.67 (d, *J*=7.08 Hz, 1H), 3.88 (d, *J*=1.92 Hz, 1H), 4.07 (d, *J*=7.22 Hz, 1H), 4.37 (d, *J*=7.20 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) -4.46, -3.41, -3.00, -2.50, 9.12, 9.23, 11.85, 15.90, 18.29, 18.57, 21.78, 23.66, 24.20, 24.71, 25.76, 25.93, 26.00, 26.19, 30.28, 37.07, 41.15, 41.42, 45.46, 56.40, 57.42, 70.11, 70.32, 70.53, 73.41, 73.90, 77.87, 81.11, 100.83;

IR (thin film) νmax 2955, 2938, 1472, 1470, 1382, 1252, 1225, 1147, 1095, 1057, 1024, 836, 773, 668 cm^{-1};

HRMS: $C_{37}H_{73}O_5Si_2S_2$ (M^++1), calcd: 717.44379, found: 717.44170.

2-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]-dithian-2-yl}-6-methoxy-4-methyl-oct-7-yn-3,5-diol (164):



163 164

To a solution of **163** (0.25 g, 0.35 mmol) in MeOH (10 mL) at 0 °C was added CSA (0.081 g, 0.35 mmol) and the reaction mixture was stirred for 2 h, after which TLC indicated that a by-product began to form. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (15 mL), extracted with ethyl acetate (15 mL x 3). The combined organic extracts were dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (E/H=1:15) to give recovered **164** (0.10 g, 40%) and the diol (0.12 g, 86% based on recovered starting material) (H/E= 4:1);

$[\alpha]_D$ +5.20 ° (c 01.71, $CHCl_3$);

^{1}H NMR (C_6D_6, 400 MHz) δ 0.31 (s, 3H), 0.42 (s, 3H), 0.44 (s, 3H), 0.51 (s, 3H), 1.08 (d, *J*=7.0 Hz, 3H), 1.12-1.20 (m, 27H), 1.27 (d, *J*=7.0 Hz, 3H), 2.07 (d, *J*=2.00 Hz, 1H), 2.08-2.30 (m, 3H), 2.30-2.61 (m, 8H), 3.25 (s, 3H), 3.94 (d, *J*=7.48 Hz, 1H), 4.02 (dd,

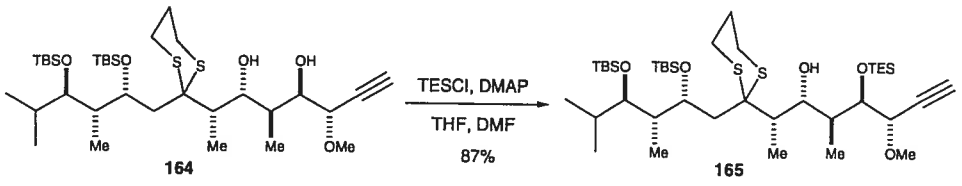
J=1.88, 7.68 Hz, 1H), 4.25 (d, *J*=7.0 Hz, 1H), 4.67 (t, *J*=6.52 Hz, 1H), 4.78 (d, *J*=8.52 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) -4.36, -3.27, -3.00, -2.33, 7.99, 9.01, 11.45, 15.65, 18.40, 18.54, 21.04, 24.39, 26.01, 26.12, 26.18, 26.27, 30.53, 38.75, 40.84, 41.13, 43.67, 56.66, 57.56, 770.53, 73.79, 73.41, 75.45, 78.11, 80.95;

IR (thin film) νmax 3469, 3309, 2955, 2929, 2856, 1471, 1387, 1360, 1252, 1112, 1088, 1055, 835, 772 cm^{-1};

HRMS: $C_{34}H_{68}O_5Si_2S_2$ (M^+), calcd: 676.40466, found: 676.40790

2-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]-dithian-2-yl}-6-methoxy-4-methyl-5-triethylsilanyloxy-oct-7-yn-3-ol (165):



To a solution of **164** (0.089 g, 0.13 mmol) in THF-DMF (3:1, 3 mL) at room temperature was added DMAP (0.36 g, 0.30 mmol) and TESCl (0.034 mL, 0.030 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 18 h before being quenched with saturated aqueous ammonium solution (8 mL). The resulting mixture was extracted with EtOAc (14 mL x 3) and dried over Na_2SO_4, The solvent was removed under reduced pressure and the residue was purified by column chromatography (E/H=1:8) to give **165** (0.36 g, 87%);

$[\alpha]_D$ +3.89 ° (c 0.54, CH_2Cl_2);

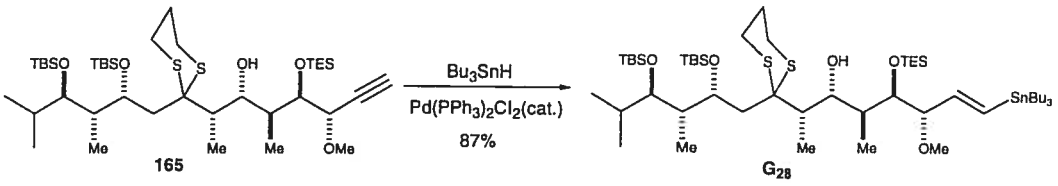
^{1}H NMR (C_6D_6, 300 MHz) δ 0.33 (s, 3H), 0.438 (s, 3H), 0.439 (s, 3H), 0.53 (s, 3H), 0.95 (t, *J*=7.55 Hz, 6H), 1.11 (d, *J*=6.93 Hz, 3H), 1.10-1.25 (m, 39H), 1.60-1.72 (m, 1H), 2.01-2.12 (m, 2H), 2.13 (d, *J*=2.04 Hz, 1H), 2.29-2.49 (m, 6H), 2.49-2.68 (m, 3H), 3.35 (s, 3H), 3.95 (dd, *J*=1.29, 7.72 Hz, 1H), 4.02 (dd, *J*=2.04, 6.81 Hz, 1H), 4.57 (dd, *J*=1.74, 6.81 Hz, 1H), 4.67 (dd, *J*=6.52, 12.3 Hz, 1H), 4.80 (dd, *J*=1.26, 9.09 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) -4.28, -3.34, -2.75, -2.36, 5.40, 6.40, 7.06, 7.31, 8.93, 11.20, 15.60, 18.43, 18.66, 21.51, 24.24, 25.78, 26.02, 26.12, 26.40, 30.56, 39.12, 40.08, 41.17, 44.25, 55.89, 57.88, 70.68, 72.01, 75.05, 74.04, 75.09, 78.50, 81.98;

IR (thin film) νmax 3436, 1472, 1470, 1382, 1253, 1056, 1027, 836, 773 cm^{-1};

HRMS; $C_{40}H_{83}O_5Si_3S_2$ (M^++1), calcd: 791.49898, found: 791.49803.

2-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethyl-hexyl]-[1,3]-dithian-2-yl}-6-methoxy-4-methyl-8-tributylstannanyl-5-triethylsilanyloxy-oct-7-en-3-ol (G_{28}):



To a solution of **165** (0.30 g, 0.38 mmol) in THF (10 mL) at 0 °C was added $Pd(PPh_3)_2Cl_2$ (0.013 g, 0.019 mmol). Bu_3SnH (0.17 g, 0.57 mmol) was then added dropwise and the reaction mixture was stirred at 0 °C for 1 h. TLC indicated that all the starting material reacted. The mixture was concentrated in *vacuo* and the residue was subjected to column chromatography (E/H=1:100, with 1% Et_3N as a stabilizer) to give **G_{28}** (0.36 g, 87%);

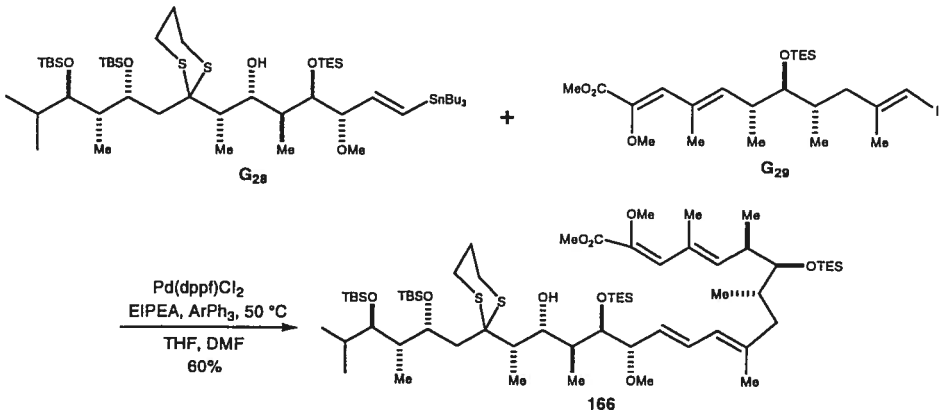
$[\alpha]_D$ -2.79 ° (c 0.43, $CHCl_3$);

^{1}H NMR (C_6D_6, 400 MHz) δ 0.23 (s, 3H), 0.35 (s, 3H), 0.37 (s, 3H), 0.70-0.83 (m, 6H), 0.94 (t, *J*=7.32 Hz, 9H), 0.97-1.16 (m, 45 H), 1.18 (d, *J*=6.96 Hz, 1H), 1.25-1.30 (m, 1H), 1.30-1.38 (m, 1H), 1.38 (q, *J*=7.28 Hz, 6H), 1.50-1.66 (m, 7H), 1.98-1.21 (m, 1H), 2.20-2.36 (m, 3H), 2.38-2.46 (m, 2H), 2.48-2.62 (m, 4H), 3.25 (s, 3H), 3.72 (t, *J*=7.0 Hz, 1H), 3.88 (d, *J*=7.62 Hz, 1H), 4.33 (d, *J*=7.0 Hz, 1H), 4.61 (dd, *J*=5.24, 10.44 Hz, 1H), 4.73 (d, *J*=8.32 Hz, 1H), 6.15 (dd, *J*=7.04, 19.08 Hz, 1H), 6.38 (d, *J*=19.08 Hz, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ -6.71, -5.77, -5.17, -4.78, 3.10, 4.63, 5.13, 6.43, 6.94, 9.94, 11.12, 13.29, 16.07, 16.24, 19.19, 21.83, 23.37, 23.63, 23.71, 23.97, 24.95, 26.82, 28.13, 36.77, 38.48, 38.83, 41.98, 53.20, 55.84, 68.27, 70.02, 73.52, 76.22, 85.28, 130.55, 140.74;

IR (thin film) νmax 2956, 2928, 2856, 1463, 1380, 1250, 1112, 1082, 1047, 835 cm^{-1};

18-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]dithian-2-yl}-17-hydroxy-2,14-dimethoxy-4,6,8,10,16-pentamethyl-7,15-bis-triethylsilanyloxynonadeca-2,4,10,12-tetraenoic acid methyl ester (166):



To a solution of $\mathbf{G_{29}}$ (0.050 g, 0.092 mmol) in THF-DMF (1:1, 3 mL) at 50 °C was added diisopropylethylamine (0.12 mL, 0.93 mmol), triphenylarsine (0.14 g, 0.46 mmol) and Pd(dppf)Cl_2 catalyst (0.022 g, 0.027 mmol). After 10 min, $\mathbf{G_{28}}$ (0.10 g, 0.092 mmol) in THF (1 mL) was added. The reaction mixture was stirred at 50 °C for 9 h (the color of the reaction changed from red to black), at which point, TLC indicated that no starting material remained. The reaction mixture was quenched with icy water (5 mL) and extracted with ethyl acetate (15 mL x 3). The combined extracts were dried over Na_2SO_4, concentrated in *vacuo*. Chromatography of the crude product (E/H=1:15) to afford **166** (0.066 g, 60 %) as a colorless oil;

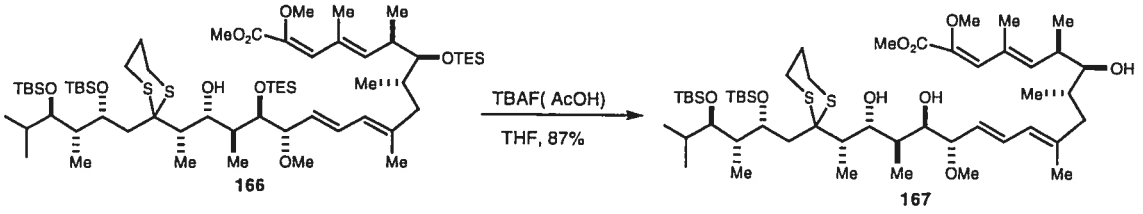
$[\alpha]_D$ +20.33 ° (c1.50, CH_2Cl_2);

^{1}H NMR (C_6D_6, 400 MHz) δ 0.33 (s, 3H), 0.45 (s, 3H), 0.47 (s, 3H), 0.54 (s, 3H), 0.71 (q, *J*=7.96 Hz, 6H), 0.81 (q, *J*=7.98 Hz, 6H), 0.98 (d, *J*=5.92 Hz, 3H), 1.04-1.22 (m, 51H), 1.27 (d, *J*=6.92 Hz, 3H), 1.30-1.51 (m, 2H), 1.61-1.72 (m, 1H), 1.26 (s, 3H), 1.88-1.98 (m, 1H), 2.12-2.26 (m, 2H), 2.16 (s, 3H), 2.30-2.38 (m, 3H), 2.42-2.52 (m, 2H), 2.53-2.74 (m, 3H), 2.80-2.90 (m, 1H), 3.30 (s, 3H), 3.19 (s, 3H), 3.49 (t, *J*=4.02 Hz, 1H), 3.61 (s, 3H), 3.88 (t, *J*=7.96 Hz, 1H), 3.97 (d, *J*=6.56 Hz, 1H), 4.34 (d, *J*=7.0Hz, 1H), 4.70 (dd, *J*=5.36, 10.04 Hz, 1H), 6.15 (dd, *J*=9.68, 15.72 Hz, 1H), 6.66 (dd, *J*=10.92, 15.22 Hz, 1H), 6.96 (s, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ -4.29, -3.34, -2.74, -2.37, 5.37, 5.57, 6.99, 7.01, 7.58, 8.85, 12.26, 14.85, 15.69, 15.73, 16.03, 18.33, 18.52, 18.67, 21.65, 24.26, 25.77, 26.05, 26.12, 26.41, 30.56, 36.06, 36.13, 39.23, 40.72, 41.26, 43.33, 44.51, 50.91, 55.49, 58.14, 59.42, 70.70, 72.37, 76.07, 78.68, 80.07, 84.25, 126.34, 128.88, 130.39, 130.63, 130.94, 137.81, 140.79, 143.44, 164.50;

IR νmax (thin film) 3468, 2955, 2875, 1722, 1617, 1459, 1382, 1343, 1249, 1105, 1047, 1018, 825, 773 cm^{-1}.

18-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]dithian-2-yl}-7,15,17-trihydroxy-2,14-dimethoxy-4,6,8,10,16-pentamethylnonadeca-2,4,10,12-tetraenoic acid methyl ester (167):



To a solution of **166** (0.035 g, 0.029 mmol) in THF (3 mL) at room temperature was added TBAF (complexed with AcOH, 1:1, 0.94 M, 0.45 mL, 0.44 mmol). The reaction mixture was stirred at room temperature for 1.5 h before was quenched with $NaHCO_3$ solution (5 mL). The resulting mixture was extracted with ethyl acetate (15 mL x 3) and the combined extracts were dried over Na_2SO_4. The solvent was removed in *vacuo* and the resulting residue was purified by column chromatography (E/H=1:6) to afford **167** (0.025 g, 88%) as a colorless oil;

$[\alpha]_D$ +12.64 ° (c 1.21, hexane);

^{1}H NMR (C_6D_6, 400 MHz) δ 0.33 (s, 3H), 0.46 (s, 3H), 0.50 (s, 3H), 0.54 (s, 3H), 0.89 (d, *J*=6.72 Hz, 3H), 0.93 (d, *J*=7.04 Hz, 3H), 1.14 (s, 9H), 1.14-1.24 (m, 21H), 1.36 (d, *J*=6.96 Hz, 3H), 1.67 (s, 3H), 1.75-1.85 (m, 1H), 1.91 (dd, *J*=10.16, 13.44 Hz, 1H), 2.09 (d, *J*=1.24 Hz, 3H), 2.12-2.32 (m, 4H), 2.39-2.60 (m, 6H), 2.60-2.80 (m, 3H), 3.01 (t, *J*=4.72 Hz, 1H), 3.19 (s, 3H), 3.44 (s, 3H), 3.55 (s, 3H), 3.73 (t, *J*=7.96 Hz, 1H), 3.98 (dd,

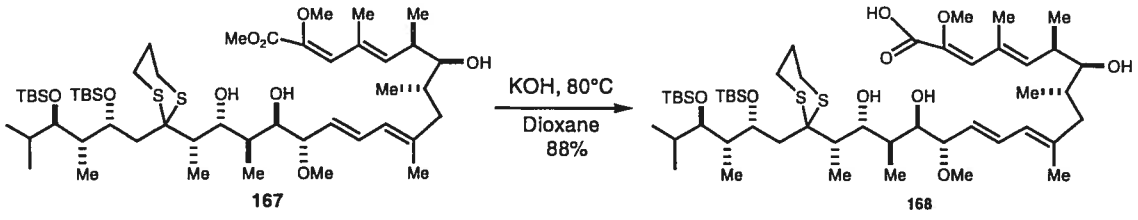
J=1.16, 7.36 Hz, 1H), 4.05 (d, *J*=8.40 Hz, 1H), 4.73 (t, *J*=6.76 Hz, 1H), 4.84 (d, *J*=7.16 Hz, 1H), 5.49 (dd, *J*=8.36, 15.12 Hz, 1H), 5.83 (d, *J*=9.88 Hz, 1H), 6.05 (d, *J*=11.00 Hz, 1H), 6.62 (dd, *J*=11.08, 15.28 Hz, 1H), 6.89 (d, *J*=0.72 Hz, 1H);

^{13}C NMR (C_6D_6, 100 MHz) δ -4.32, -3.42, -2.79, -2.42, 8.72, 9.03, 11.73, 13.94, 14.80, 15.85, 16.29, 16.33, 17.21, 18.46, 18.65, 21.79, 24.17, 25.78, 26.13, 26.38, 29.39, 29.68, 30.51, 31.90, 34.52, 35.72, 39.50, 40.53, 40.99, 42.43, 44.69, 50.99, 55.75, 58.17, 59.38, 70.64, 73.18, 73.76, 78.82, 79.59, 83.80, 125.72, 128.66, 128.28, 131.79, 132.09, 139.09, 139.35, 143.50, 164.34;

IR (thin film) νmax 3468, 2928, 2858, 1716, 1696, 1637, 1542, 1472, 1457, 1438, 1243, 1104, 1054, 835, 775 cm^{-1}.

HRMS; $C_{51}H_{97}O_9Si_2S_2$ (M^++1), calcd: 973.61126, found: 973.61031.

18-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]dithian-2-yl}-7,15,17-trihydroxy-2,14-dimethoxy-4,6,8,10,16-pentamethyl-nonadeca-2,4,10,12-tetraenoic acid (168):



To a solution of **167** (0.030 g, 0.031 mmol) in dioxane (2 mL) was added KOH solution (1 M, 0.31 mL, 0.31 mmol). The reaction mixture was heated at reflux for 1 h before being cooled to room temperature and carefully acidified with H_3PO_4 solution (1 N) to pH 4. The product was extracted with ethyl acetate (10 mL x 3). The combined extracts

were dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography (E/H=1:1) of the residue afforded **167** (0.026 g, 88%);

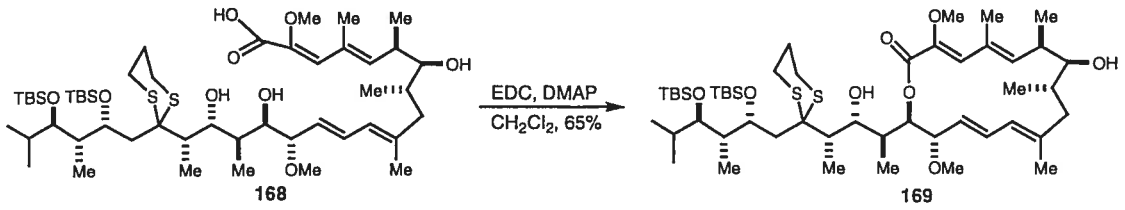
$[\alpha]_D$ +18.30 ° (c 3.75, CH_2Cl_2);

^{1}H NMR (400 MHz, C_6D_6) δ 0.33 (s, 3H), 0.46 (s, 3H), 0.50 (s, 3H), 0.54 (s, 3H), 0.89 (d, *J*=6.64 Hz, 3H), 0.95 (d, *J*=6.68 Hz, 3 H), 1.12-1.22 (m, 30H), 1.36 (d, *J*=7.04 Hz, 1H), 1.38-1.48 (m, 1H), 1.60-1.67 (m, 1H), 1.68 (s, 3H), 1.72-1.82 (m, 1H), 1.85-1.95 (m, 1H), 2.08 (s, 3H), 2.12-2.20 (m, 1H), 2.22-2.38 (m, 2H), 2.40-2.60 (m, 5H), 2.62-2.72 (m, 2H), 3.06 (t, *J*=6.16 Hz, 1H), 3.21 (s, 3H), 3.57 (s, 3H), 3.75 (t, *J*=8.00 Hz, 1H), 3.98 (d, *J*=7.12 Hz, 1H), 4.11 (dd, *J*=2.20, 7.84 Hz, 1H), 4.74 (d, *J*=7.60 Hz, 1H), 4.84 (d, *J*=7.04 Hz, 1H), 5.54 (dd, *J*=8.36, 15.26 Hz, 1H), 5.89 (d, *J*=9.56 Hz, 1H), 6.08 (d, *J*=11.0 Hz, 1H), 6.64 (dd, *J*=11.08, 15.24 Hz, 1 H), 7.04 (s 1H);

^{13}C NMR (100 MHz, C_6D_6) δ -4.40, -3.39, -2.76, -2.37, 8.77, 9.04, 11.70, 14.61, 15.84, 16.29, 16.38, 17.21, 18.51, 18.67, 21.81, 24.17, 25.78, 26.15, 26.40, 30.51, 34.49, 35.66, 39.25, 40.47, 41.02, 42.43, 44.75, 55.77, 58.16, 59.57, 70.61, 73.14, 73.81, 78.79, 79.89, 83.76, 125.82, 129.30, 130.63, 131.88, 132.19, 139.01, 10.43, 140.43, 142.94, 142,94, 168.43;

IR (thin film) νmax 3440, 2828, 1696, 1151, 1100, 1047, 976, 835, 773 cm^{-1};

16-(3-{2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyl]-[1,3]dithian-2-yl}-2-hydroxy-1-methylbutyl)-8-hydroxy-3,15-dimethoxy-5,7,9,11-tetramethyl-oxacyclohexadeca-3,5,11,13-tetraen-2-one (169):



To a solution of EDC·HCl (0.040 g, 0.021 mmol) and DMAP (0.030 g, 0.025 mmol) in CH_2Cl_2 (5 mL) at reflux was slowly added **168** (0.020 g, 0.021 mmol) in CH_2Cl_2 (3 mL) through syringe pump over 2.5 h. After the addition was completed, the mixture was heated at reflux for another 30 min. The solvent was then removed in *vacuo* and chromatography of the residue afforded **169** (0.013 g, 65%);

$[\alpha]_D$ +4.00 ° (c 0.33, CH_2Cl_2);

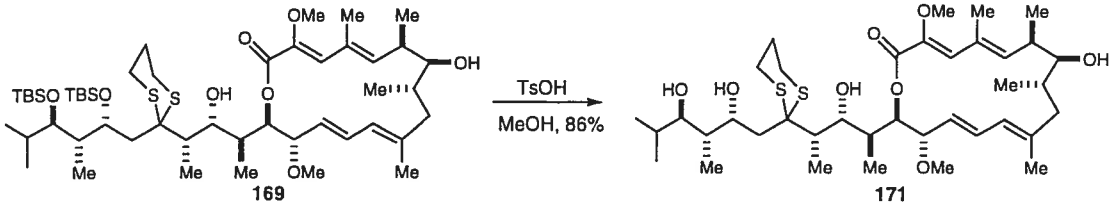
^{1}H NMR (400 MHz, C_6D_6) δ 0.34 (s, 3H), 0.50 (s, 3H), 0.54 (s, 3H), 0.58 (s, 3H), 0.79 (d, *J*=5.81 Hz, 3H), 0.93 (d, *J*=7.0 Hz, 3H), 1.10-1.22 (m, 30H), 1.51 (d, *J*=6.88 Hz, 3H), 1.64-1.84 (m, 4H), 1.94 (s, 3H), 2.06 (s, 3H), 2.12-2.32 (m, 4H), 2.48-2.74 (m, 6H), 2.83-2.93 (m, 2H), 3.18 (s, 3H), 3.73 (s, 3H), 4.01-4.06 (m, 2H), 4.51 (dd, *J*=5.12, 9.98 Hz, 1H), 4.73 (d, *J*=4.80 Hz, 1H), 4.89 (d, *J*=8.8 Hz, 1H), 5.22 (dd, *J*=9.28, 14.90 Hz, 1H), 5.63 (d, *J*=8.8 Hz, 1H), 5.68 (d, *J*=10.72 Hz, 1H), 5.88 (d, *J*=8.56 Hz, 1H), 6.60 (dd, *J*=10.84, 15.08 Hz, 1H), 6.88 (s, 1H);

^{13}C NMR (100 MHz, C_6D_6) δ -4.31, -3.34, -2.26, -2.26, 8.57, 8.77, 10.90, 13.94, 15.69, 16.91, 18.53, 18.71, 19.89, 21.56, 21.93, 24.13, 25.65, 25.84, 26.18, 26.44, 30.43, 36.65,

39.19, 39.57, 40.18, 40.97, 41.23, 44.85, 54.86, 58.48, 59.07, 70.51, 71.22, 76.93, 78.86, 80.35, 82.48, 125.18, 127.47, 131.83, 132.79, 133.06, 141.90, 142.14, 142.59, 166.60;

IR (thin film) νmax 3494, 2927, 2863, 1691, 1462, 1360, 1248, 1098, 1054, 965, 835, 772 cm^{-1};

16-(3-[2-(2,4-Dihydroxy-3,5-dimethylhexyl]-[1,3]dithian-2-yl}-2-hydroxy-1-methyl-butyl)-8-hydroxy-3,15-dimethoxy-5,7,9,11-tetramethyl-oxacyclohexadeca-3,5,11,13-tetraen-2-one (171):



169 171

To a solution of **169** (10 mg, 0.011 mmol) in MeOH (0.5 mL) was added TsOH .H_2O (6 mg, 0.32 mmol). The reaction mixture was stirred 4 h at room temperature and then was quenched with triethylamine. The solvent was removed in *vacuo*. The residue was purified by column chromatography (E/H=1:4) to afford **171** (6.5 mg, 86%);

$[\alpha]_D$ +2.82 ° (c 0.50, CH_2Cl_2) ;

^{1}H NMR (400 MHz, C_6D_6) δ 0.79 (d, *J*=5.88 Hz, 3H), 0.93 (d, *J*=7.04 Hz, 3H), 1.09 (d, *J*=6.76 Hz, 3H), 1.13 (d, *J*=7.08 Hz, 3H), 1.14 (d, *J*=6.92 Hz, 3H), 1.21 (d, *J*=6.56 Hz, 3H), 1.46 (d, *J*=7.08 Hz, 3H), 1.78-1.83 (m, 2H), 1.88-1.93 (m, 2H), 1.94 (s, 3H), 2.00-2.04 (m, 1H), 2.04 (d, *J*=1.16 Hz, 3H), 2.26-2.48 (m, 7H), 2.53-2.62 (m, 2H), 2.81 (dd, *J*=9.56, 15.64 Hz, 1H), 2.90-2.94 (m, 1H), 3.17 (s, 3H), 3.44-3.50 (m, 1H), 3.65 (s, 3H), 3.99 (t, *J*=8.8 Hz, 1H), 4.48-4.56 (m, 1H), 4.78-4.82 (m, 1H), 5.22 (dd, *J*=9.32, 15.66 Hz,

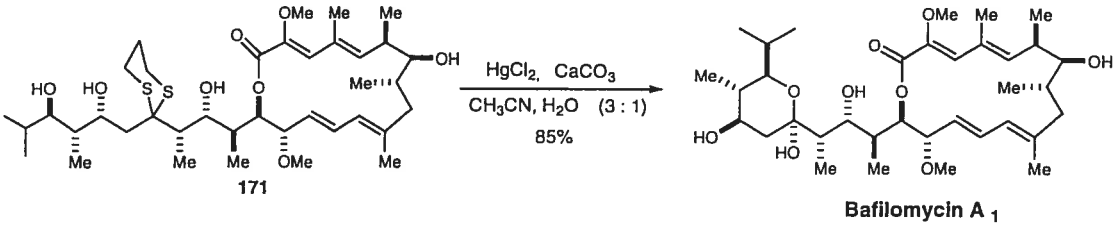
1H), 5.63 (d, *J*=8.68 Hz, 1H), 5.71 (d, *J*=10.92 Hz, 1H), 5.88 (d, *J*=8.92 Hz, 1H), 6.58 (dd, *J*=10.60, 15.24 Hz, 1H), 6.87 (s, 1H);

^{13}C NMR (100 MHz, C_6D_6) δ 8.58, 10.90, 11.95, 13.89, 16,95, 17,14, 19.77, 19.82, 21.62, 24.66, 25.71, 26.09, 29.81, 31.43, 36.70, 39.32, 39.87, 40.02, 40.14, 41.24, 42.25, 54.92, 57.88, 59.10, 70.18, 70.73, 76.94, 79.72, 80.35, 82.56, 125.21, 127.45, 131.89, 132.71, 132.96, 141.90, 142.11, 142.50, 166.56;

IR (thin film) νmax 3444, 2975, 2933, 2887, 1689, 1465, 1379, 1112, 967 cm^{-1};

HRMS: $C_{38}H_{65}O_8S_2$ (M^++1), calcd: 713.41211, found: 713.41470.

Bafilomycin A_1:



To a solution of **171** (6.4 mg, 0.009 mmol) in a solution (1 mL) of CH_3CN-H_2O (3:1) was slowly added a suspension of $CaCO_3$ (4.6 mg, 0.0455 mmol) and $HgCl_2$ (4.9 mg, 0.018 mmol) in CH_3CN-H_2O (3:1, 0.2 mL). The mixture was stirred at room temperature for 20 min, at which point, TLC indicated no starting material remained. The mixture was diluted with ethyl acetate (20 mL) and the two layers were separated. Organic layer was washed with saturated NaCl solution (10 mL x 3), dried over Na_2SO_4, and concentrated in *vacuo*. Column chromatography (E/H=1:2) of the residue afforded bafilomycin A_1 (4.8 mg, 85%);

$[\alpha]_D$ –3.27 ° (c 0.26, CH_2Cl_2) [reported[117] for natural bafilomycin A_1, $[\alpha]^{30}_D$ –3.07 ° (c 0.26, CH_2Cl_2)];

mp 96-97 °C [reported[117] for natural bafilomycin A_1, mp: 98.0-99.0 °C];

^{1}H NMR (600 MHz, C_6D_6) δ 0.84 (d, *J*=6.12 Hz, 3H), 0.96 (d, *J*=6.90 Hz, 3H), 0.99 (d, *J*=7.02 Hz, 3H), 1.02 (d, *J*=6.78 Hz, 3H), 1.04 (d, *J*=6.48 Hz, 3H), 1.19 (d, *J*=6.78 Hz, 3H), 1.28 (d, *J*=7.2 Hz, 3H), 1.46-1.54 (m, 1H), 1.80-1.88 (m, 2H), 1.94-1.99 (m, 2H), 1.97 (s, 3H), 2.07 (d, *J*=11.16 Hz, 1H), 2.11 (d, *J*=1.02 Hz, 3H), 2.37-2.42 (m, 1H), 2.46 (dd, *J*=4.68, 11.79 Hz, 1H), 2.51-2.58 (m, 1H), 2.96-3.00 (m, 1H), 3.17 (s, 3H), 3.74 (s, 3H), 3.86 (dd, *J*=2.72, 10.32 Hz, 1H), 3.92-3.95 (m, 1H), 4.00 (t, *J*=9.00 Hz, 1H), 4.60-4.63 (m, 1H), 5.17 (dd, *J*=9.42, 15.12 Hz, 1H), 5.26 (d, *J*=3.3 Hz, 1H), 5.47 (dd, *J*=1.21, 8.76 Hz, 1H), 5.72 (d, *J*=10.68 Hz, 1H), 5.89 (d, *J*=1.36 Hz, 1H), 5.92 (d, *J*=9.00 Hz, 1H) 6.57 (dd, *J*=10.74, 15.03 Hz, 1H), 6.92 (s, 1H);

^{13}C NMR (100 MHz, C_6D_6) δ 7.07, 9.72, 12.00, 13.91, 14.34, 16.91, 19.91, 21.27, 21.48, 28.05, 36.71, 37.16, 40.16, 41.17, 41.23, 42.37, 44.07, 54.83, 58.29, 70.41, 70.80, 75.86, 76.96, 80.35, 82.13, 99.01, 125.12, 127.35, 132.67, 132.79, 133.07, 141.66, 142.59, 167.19;

IR (thin film) νmax 3440, 2965, 2928, 2875, 1689, 1630, 1469, 1382, 1112, 967 cm^{-1};

HRMS: $C_{35}H_{59}O_9$ (M^++1), calcd: 623.4158, found: 623.4258.

[1] (a) Thall, E. "When Drug Molecules Look in the Mirror" *J. Chem. Educ.* **1996**, *73*, 481-484. (b) Caldwell, J. "Chiral Pharmacology and the Regulation of New Drugs", *Chem. Ind.* **1995**, 176-179. (c) Federsel, H-J. "Drug Chirality-Scale-up Manufacturing, and Control", *Chemtech.* **1993**, (Dec.), 23-24. (d) Coppola, G. M.; Schuster, H. F. "Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids" John Wiley & Sons, NY, **1987**.

[2] For a discussion of this and related problems see Ariens, E. J. "Chirality in Drug Design and Synthesis" (ed, C. Brown), **1990**, 29-43, Academic Press, London.

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Appendix

CRYSTAL AND MOLECULAR STRUCTURE OF

C12 H16 O3 COMPOUND (HAN278)

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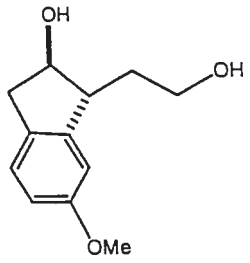
(1*R*, 2*R*)-1-(2-Hydroxy-ethyl)-6-methoxy-indan-2-ol (88):



Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C12 H16 O3.

Identification code	HAN278
Empirical formula	C12 H16 O3
Formula weight	208.248
Temperature	293(2)K
Wavelength	1.54178Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.0988(11)Å α = 90° b = 8.594(3)Å β = 94.82(3)° c = 12.516(6)Å γ = 90°
Volume	546.5(3)$Å^3$
Z	2
Density (calculated)	1.2655 Mg/m^3
Absorption coefficient	0.732 mm^{-1}
F(000)	224.0
Crystal size	0.67 x 0.25 x 0.19 mm
Theta range for data collection	3.54 to 69.89°
Index ranges	-6<=h<=6, -10<=k<=10, -15<=l<=15
Reflections collected	8611
Independent reflections	2058 [R(int) = 0.032]
Absorption correction	Integration
Max. and min. transmission	0.8932 and 0.7560
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2058 / 1 / 140
Goodness-of-fit on F^2	0.974
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.1109
R indices (all data)	R1 = 0.0448, wR2 = 0.1139
Absolute structure parameter	-0.1(3)
Extinction coefficient	0.061(5)
Largest diff. peak and hole	0.172 and -0.144 $e.Å^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for C12 H16 O3.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(2)	8997(4)	8844(2)	5376(2)	109(1)
O(6)	1452(3)	10327(2)	9916(1)	94(1)
O(11)	8424(5)	5876(2)	5702(1)	112(1)
C(1)	7144(4)	8537(2)	7143(1)	67(1)
C(2)	6930(5)	9247(2)	6016(1)	77(1)
C(3)	6800(5)	11003(2)	6189(2)	83(1)
C(4)	3743(5)	12252(2)	7526(2)	87(1)
C(5)	2411(5)	12041(2)	8455(2)	83(1)
C(6)	2658(4)	10647(2)	9000(2)	75(1)
C(7)	4187(4)	9441(2)	8636(1)	71(1)
C(8)	5467(4)	9666(2)	7714(1)	66(1)
C(9)	5249(4)	11074(2)	7158(2)	74(1)
C(10)	6360(4)	6823(2)	7214(2)	73(1)
C(11)	8315(5)	5682(2)	6821(2)	83(1)
C(12)	-474(5)	11414(3)	10202(2)	95(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C12 H16 O3.

	x	y	z	U(eq)
H(2)	9196	7897	5383	164
H(11)	9559	5303	5492	168
H(1)	8969	8644	7447	80
H(2A)	5262	8910	5641	93
H(3A)	8540	11451	6334	99
H(3B)	5891	11525	5578	99
H(4)	3603	13194	7159	104
H(5)	1374	12834	8700	100
H(7)	4344	8503	9006	85
H(10A)	6109	6582	7956	88
H(10B)	4683	6675	6801	88
H(11A)	10040	5863	7188	100
H(11B)	7783	4627	6974	100
H(12A)	365	12383	10403	143
H(12B)	-1346	11014	10795	143
H(12C)	-1742	11578	9602	143

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C12 H16 O3.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
O(2)	167(2)	74(1)	98(1)	5(1)	73(1)	-1(1)
O(6)	128(1)	75(1)	82(1)	-6(1)	38(1)	18(1)
O(11)	177(2)	80(1)	86(1)	-8(1)	49(1)	24(1)
C(1)	88(1)	51(1)	63(1)	-3(1)	18(1)	-4(1)
C(2)	110(1)	61(1)	65(1)	2(1)	22(1)	-4(1)
C(3)	117(2)	56(1)	77(1)	8(1)	22(1)	-5(1)
C(4)	112(2)	53(1)	96(1)	5(1)	14(1)	4(1)
C(5)	106(2)	54(1)	93(1)	-7(1)	19(1)	7(1)
C(6)	98(1)	60(1)	69(1)	-7(1)	15(1)	3(1)
C(7)	97(1)	52(1)	65(1)	-3(1)	15(1)	4(1)
C(8)	86(1)	48(1)	63(1)	-3(1)	8(1)	-1(1)
C(9)	98(1)	50(1)	74(1)	1(1)	13(1)	-4(1)
C(10)	96(1)	53(1)	75(1)	-1(1)	23(1)	-7(1)
C(11)	116(2)	55(1)	83(1)	-1(1)	31(1)	3(1)
C(12)	111(2)	87(2)	91(1)	-21(1)	26(1)	10(1)

Table 5. Bond lengths [Å] and angles [°] for C12 H16 O3

O(2)-C(2)	1.419(3)	O(6)-C(6)	1.375(2)
O(6)-C(12)	1.423(3)	O(11)-C(11)	1.417(3)
C(1)-C(8)	1.512(2)	C(1)-C(10)	1.531(2)
C(1)-C(2)	1.532(2)	C(2)-C(3)	1.527(3)
C(3)-C(9)	1.504(3)	C(4)-C(9)	1.373(3)
C(4)-C(5)	1.407(3)	C(5)-C(6)	1.379(3)
C(6)-C(7)	1.396(2)	C(7)-C(8)	1.385(3)
C(8)-C(9)	1.396(2)	C(10)-C(11)	1.509(3)
C(6)-O(6)-C(12)	116.45(18)	C(8)-C(1)-C(10)	115.39(15)
C(8)-C(1)-C(2)	100.40(14)	C(10)-C(1)-C(2)	116.01(15)
O(2)-C(2)-C(3)	111.40(17)	O(2)-C(2)-C(1)	115.05(19)
C(3)-C(2)-C(1)	105.27(14)	C(9)-C(3)-C(2)	100.77(15)
C(9)-C(4)-C(5)	120.28(18)	C(6)-C(5)-C(4)	119.33(19)
O(6)-C(6)-C(5)	123.89(18)	O(6)-C(6)-C(7)	115.17(17)
C(5)-C(6)-C(7)	120.95(18)	C(8)-C(7)-C(6)	118.90(17)
C(7)-C(8)-C(9)	120.81(17)	C(7)-C(8)-C(1)	128.98(16)
C(9)-C(8)-C(1)	110.19(16)	C(4)-C(9)-C(8)	119.73(18)
C(4)-C(9)-C(3)	130.30(19)	C(8)-C(9)-C(3)	109.97(17)
C(11)-C(10)-C(1)	115.02(16)	O(11)-C(11)-C(10)	109.15(19)

Table 6. Torsion angles [°] for C12 H16 O3.

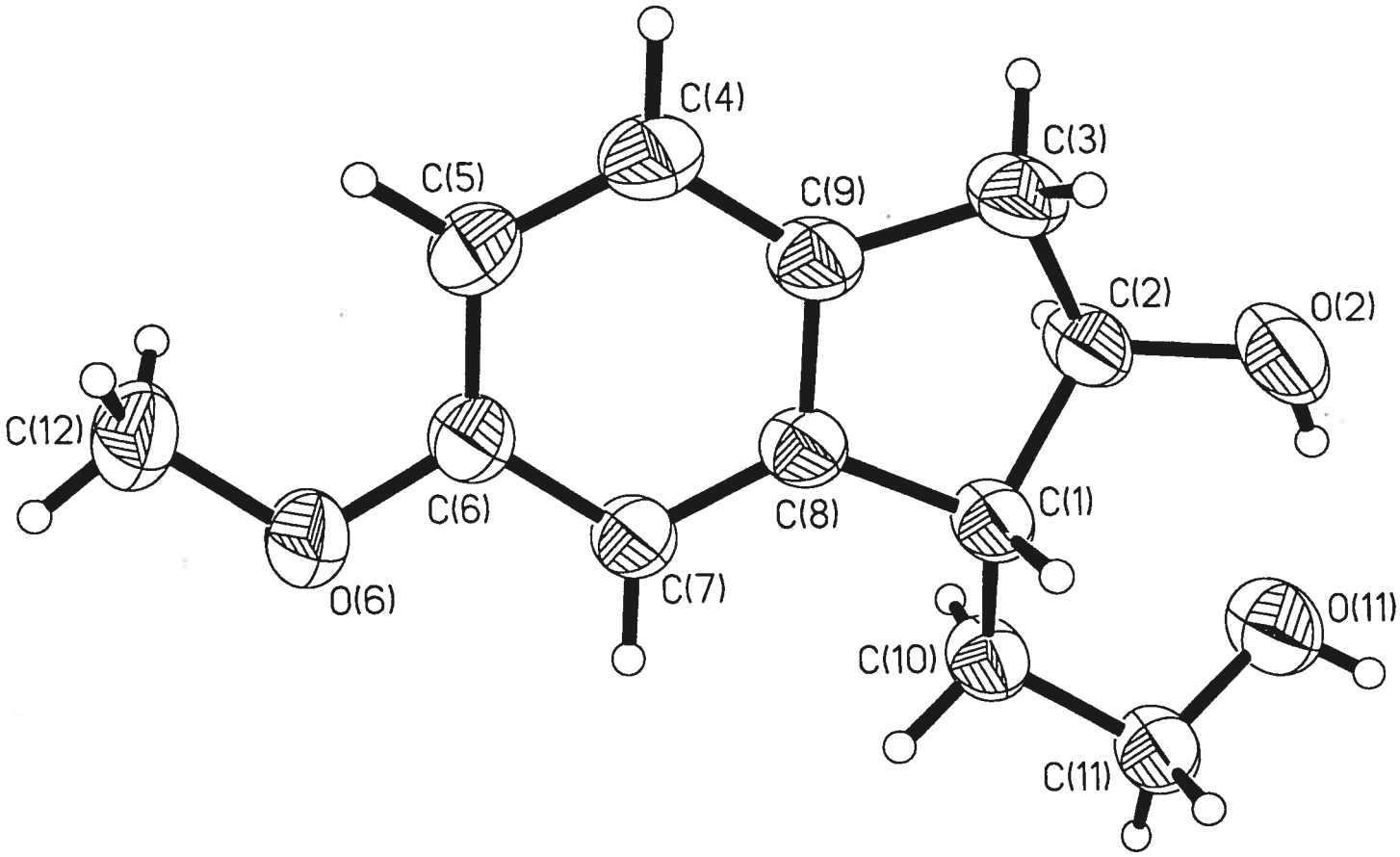
C(8)-C(1)-C(2)-O(2)	157.53(16)
C(10)-C(1)-C(2)-O(2)	-77.4(2)
C(8)-C(1)-C(2)-C(3)	34.5(2)
C(10)-C(1)-C(2)-C(3)	159.57(17)
O(2)-C(2)-C(3)-C(9)	-160.58(18)
C(1)-C(2)-C(3)-C(9)	-35.2(2)
C(9)-C(4)-C(5)-C(6)	0.7(3)
C(12)-O(6)-C(6)-C(5)	10.4(3)
C(12)-O(6)-C(6)-C(7)	-169.31(18)
C(4)-C(5)-C(6)-O(6)	179.7(2)
C(4)-C(5)-C(6)-C(7)	-0.6(3)
O(6)-C(6)-C(7)-C(8)	179.83(18)
C(5)-C(6)-C(7)-C(8)	0.1(3)
C(6)-C(7)-C(8)-C(9)	0.3(3)
C(6)-C(7)-C(8)-C(1)	-177.76(18)
C(10)-C(1)-C(8)-C(7)	31.9(3)
C(2)-C(1)-C(8)-C(7)	157.45(18)
C(10)-C(1)-C(8)-C(9)	-146.31(17)
C(2)-C(1)-C(8)-C(9)	-20.8(2)
C(5)-C(4)-C(9)-C(8)	-0.3(3)
C(5)-C(4)-C(9)-C(3)	178.8(2)
C(7)-C(8)-C(9)-C(4)	-0.2(3)
C(1)-C(8)-C(9)-C(4)	178.22(17)
C(7)-C(8)-C(9)-C(3)	-179.48(17)
C(1)-C(8)-C(9)-C(3)	-1.1(2)
C(2)-C(3)-C(9)-C(4)	-156.6(2)
C(2)-C(3)-C(9)-C(8)	22.5(2)
C(8)-C(1)-C(10)-C(11)	-169.34(17)
C(2)-C(1)-C(10)-C(11)	73.7(2)
C(1)-C(10)-C(11)-O(11)	-66.5(3)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C12 H16 O3.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	..A
O(2)-H(2)	0.82	1.83	156.1	2.603(3)	O(11)#1
O(11)-H(11)	0.82	1.85	157.0	2.626(2)	O(2)#2

Symmetry transformations used to generate equivalent atoms:

#1 x,y,z #2 -x+2,y-1/2,-z+1



ORTEP view of the C12 H16 O3

compound with the numbering scheme adopted. Ellipsoids drawn at

30% probality level. Hydrogens represented by sphere of arbitrary size.

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CRYSTAL AND MOLECULAR STRUCTURE OF

C14 H16 O3 COMPOUND (HAN273)

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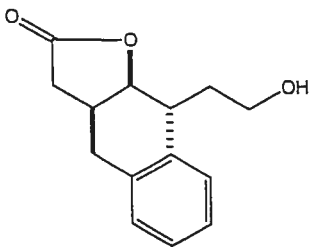
9-(2-Hydroxy-ethyl)-3a, 4, 9, 9a-tetrahydro-3H-naphtho [2, 3-b]furan-2-one (99):



Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C14 H16 O3.

Identification code	HAN273
Empirical formula	C14 H16 O3
Formula weight	232.268
Temperature	293(2)K
Wavelength	1.54056Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.68630(10)Å α = 90° b = 9.6974(2)Å β = 90° c = 21.9238(5)Å γ = 90°
Volume	1208.93(4)$Å^3$
Z	4
Density (calculated)	1.2761 Mg/m^3
Absorption coefficient	0.722 mm^{-1}
F(000)	496.0
Crystal size	0.76 x 0.34 x 0.33 mm
Theta range for data collection	4.03 to 72.64°
Index ranges	-6<=h<=5, -11<=k<=11, -24<=l<=27
Reflections collected	6036
Independent reflections	2292 [R(int) = 0.0249]
Absorption correction	Multi-scan
Max. and min. transmission	0.8488 and 0.5954
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2292 / 0 / 156
Goodness-of-fit on F^2	0.980
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0926
R indices (all data)	R1 = 0.0389, wR2 = 0.0952
Absolute structure parameter	-0.1(2)
Extinction coefficient	0.0195(13)
Largest diff. peak and hole	0.110 and -0.124 e.$Å^{-3}$

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C14 H16 O3.

	x	y	z	U(eq)
H(14)	689	-5031	9224	145
H(2A)	4462	2897	9438	71
H(2B)	3987	2655	8738	71
H(3)	6109	876	9494	57
H(4A)	6661	1089	8386	74
H(4B)	7015	-378	8671	74
H(6)	5119	636	7385	100
H(7)	2379	-386	6756	119
H(8)	-381	-1857	7145	111
H(9)	-487	-2311	8187	79
H(11)	711	-1671	9205	55
H(12)	3170	-290	9865	53
H(13A)	5565	-2308	9129	80
H(13B)	4118	-2522	9730	80
H(14A)	3274	-3954	8631	89
H(14B)	4407	-4611	9217	89

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C14 H16 O3.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
O(1)	54(1)	44(1)	108(1)	-6(1)	-4(1)	6(1)
O(12)	42(1)	39(1)	75(1)	-3(1)	7(1)	-3(1)
O(14)	134(1)	43(1)	112(1)	-7(1)	62(1)	-11(1)
C(1)	50(1)	39(1)	54(1)	-6(1)	-5(1)	-2(1)
C(2)	50(1)	45(1)	83(1)	6(1)	2(1)	-6(1)
C(3)	38(1)	47(1)	59(1)	-2(1)	-5(1)	-3(1)
C(4)	49(1)	65(1)	72(1)	-5(1)	13(1)	-12(1)
C(5)	59(1)	59(1)	51(1)	-5(1)	10(1)	3(1)
C(6)	96(2)	98(2)	55(1)	1(1)	16(1)	1(2)
C(7)	113(2)	138(2)	47(1)	-8(1)	2(1)	19(2)
C(8)	79(2)	132(2)	68(1)	-43(1)	-19(1)	14(1)
C(9)	56(1)	75(1)	67(1)	-24(1)	-6(1)	2(1)
C(10)	46(1)	44(1)	52(1)	-9(1)	-1(1)	6(1)
C(11)	46(1)	37(1)	55(1)	0(1)	-1(1)	-1(1)
C(12)	44(1)	41(1)	47(1)	2(1)	-3(1)	1(1)
C(13)	75(1)	47(1)	77(1)	5(1)	-6(1)	13(1)
C(14)	101(2)	43(1)	78(1)	5(1)	26(1)	14(1)

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C14 H16 O3.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	-309(2)	2981(1)	9258(1)	68(1)
O(12)	724(2)	808(1)	9422(1)	52(1)
O(14)	1023(4)	-4227(1)	9302(1)	97(1)
C(1)	1211(3)	2110(2)	9271(1)	48(1)
C(2)	3752(3)	2278(2)	9144(1)	59(1)
C(3)	4845(3)	848(2)	9191(1)	48(1)
C(4)	5860(3)	334(2)	8588(1)	62(1)
C(5)	4004(3)	-240(2)	8165(1)	56(1)
C(6)	4007(5)	37(3)	7548(1)	83(1)
C(7)	2360(5)	-573(3)	7172(1)	100(1)
C(8)	709(5)	-1445(3)	7403(1)	93(1)
C(9)	650(4)	-1722(2)	8029(1)	66(1)
C(10)	2290(3)	-1117(2)	8412(1)	48(1)
C(11)	2297(3)	-1374(1)	9090(1)	46(1)
C(12)	2828(3)	-54(2)	9440(1)	44(1)
C(13)	4014(4)	-2516(2)	9288(1)	67(1)
C(14)	3291(4)	-3927(2)	9073(1)	74(1)

Table 5. Bond lengths [Å] and angles [°] for C14 H16 O3

O(1)-C(1)	1.208(2)	O(12)-C(1)	1.334(2)
O(12)-C(12)	1.4598(18)	O(14)-C(14)	1.414(3)
C(1)-C(2)	1.481(3)	C(2)-C(3)	1.523(2)
C(3)-C(4)	1.526(2)	C(3)-C(12)	1.542(2)
C(4)-C(5)	1.511(3)	C(5)-C(6)	1.380(2)
C(5)-C(10)	1.402(2)	C(6)-C(7)	1.381(4)
C(7)-C(8)	1.361(4)	C(8)-C(9)	1.398(3)
C(9)-C(10)	1.386(2)	C(10)-C(11)	1.506(2)
C(11)-C(12)	1.523(2)	C(11)-C(13)	1.539(2)
C(13)-C(14)	1.505(3)		

C(1)-O(12)-C(12)	112.24(11)	O(1)-C(1)-O(12)	121.25(15)
O(1)-C(1)-C(2)	128.07(16)	O(12)-C(1)-C(2)	110.67(14)
C(1)-C(2)-C(3)	106.59(13)	C(2)-C(3)-C(4)	113.17(15)
C(2)-C(3)-C(12)	103.68(12)	C(4)-C(3)-C(12)	113.75(13)
C(5)-C(4)-C(3)	112.80(14)	C(6)-C(5)-C(10)	119.89(19)
C(6)-C(5)-C(4)	121.94(19)	C(10)-C(5)-C(4)	118.13(15)
C(5)-C(6)-C(7)	120.1(2)	C(8)-C(7)-C(6)	120.8(2)
C(7)-C(8)-C(9)	120.1(2)	C(10)-C(9)-C(8)	119.8(2)
C(9)-C(10)-C(5)	119.33(17)	C(9)-C(10)-C(11)	122.01(16)
C(5)-C(10)-C(11)	118.67(14)	C(10)-C(11)-C(12)	111.00(12)
C(10)-C(11)-C(13)	113.55(14)	C(12)-C(11)-C(13)	109.70(13)
O(12)-C(12)-C(11)	107.77(12)	O(12)-C(12)-C(3)	106.00(11)
C(11)-C(12)-C(3)	116.45(13)	C(14)-C(13)-C(11)	113.13(17)
O(14)-C(14)-C(13)	108.94(17)		

Table 6. Torsion angles [°] for C14 H16 O3.

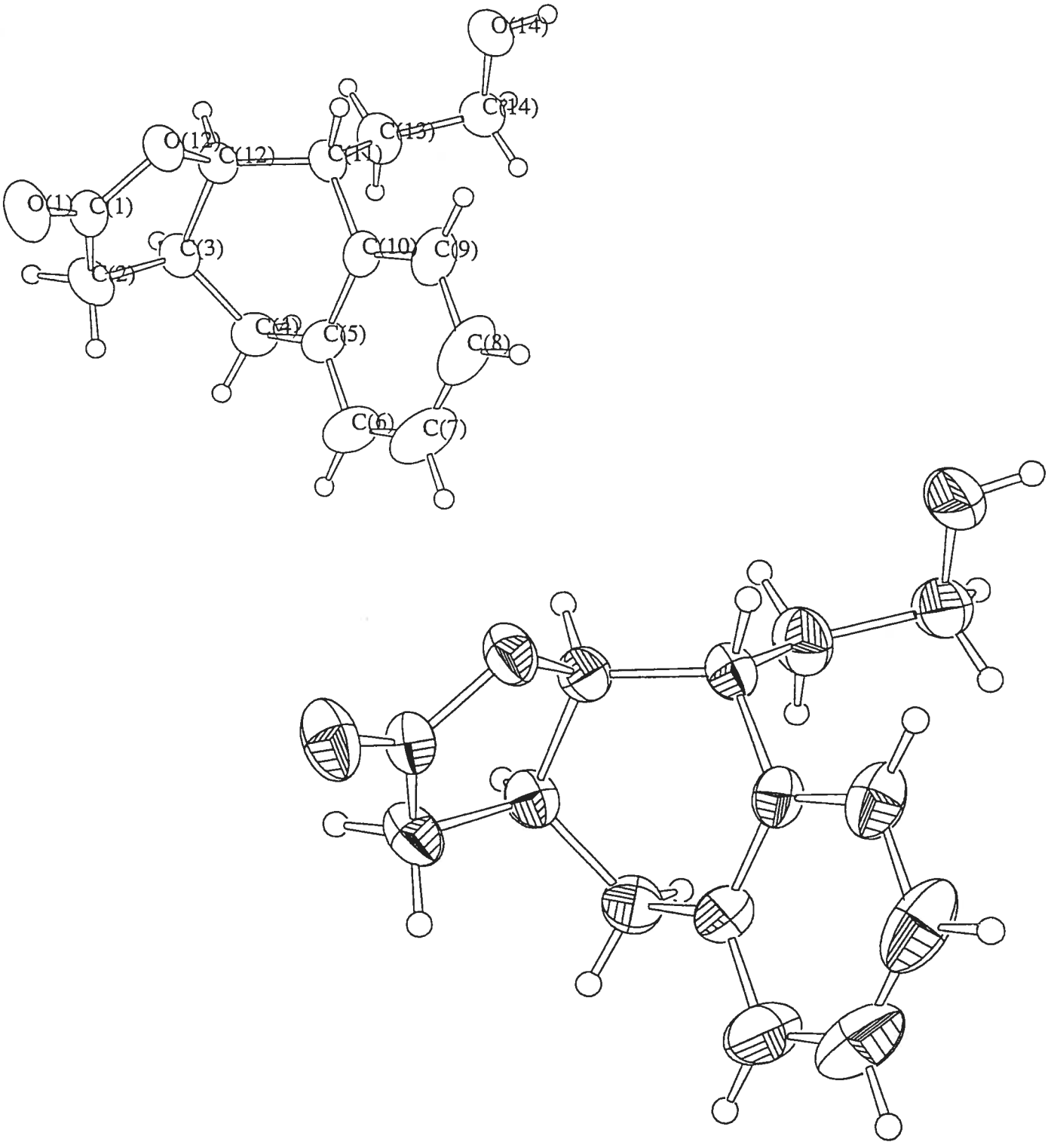
C(12)-O(12)-C(1)-O(1)	-176.93(15)
C(12)-O(12)-C(1)-C(2)	2.14(19)
O(1)-C(1)-C(2)-C(3)	-177.05(17)
O(12)-C(1)-C(2)-C(3)	4.0(2)
C(1)-C(2)-C(3)-C(4)	115.85(16)
C(1)-C(2)-C(3)-C(12)	-7.87(18)
C(2)-C(3)-C(4)-C(5)	-80.23(19)
C(12)-C(3)-C(4)-C(5)	37.8(2)
C(3)-C(4)-C(5)-C(6)	138.0(2)
C(3)-C(4)-C(5)-C(10)	-44.3(2)
C(10)-C(5)-C(6)-C(7)	-1.5(3)
C(4)-C(5)-C(6)-C(7)	176.2(2)
C(5)-C(6)-C(7)-C(8)	0.4(4)
C(6)-C(7)-C(8)-C(9)	0.6(4)
C(7)-C(8)-C(9)-C(10)	-0.6(4)
C(8)-C(9)-C(10)-C(5)	-0.5(3)
C(8)-C(9)-C(10)-C(11)	179.64(18)
C(6)-C(5)-C(10)-C(9)	1.6(3)
C(4)-C(5)-C(10)-C(9)	-176.25(16)
C(6)-C(5)-C(10)-C(11)	-178.57(18)
C(4)-C(5)-C(10)-C(11)	3.6(2)
C(9)-C(10)-C(11)-C(12)	-139.83(16)
C(5)-C(10)-C(11)-C(12)	40.30(19)
C(9)-C(10)-C(11)-C(13)	96.04(19)
C(5)-C(10)-C(11)-C(13)	-83.84(19)
C(1)-O(12)-C(12)-C(11)	-132.58(13)
C(1)-O(12)-C(12)-C(3)	-7.24(16)
C(10)-C(11)-C(12)-O(12)	74.81(16)
C(13)-C(11)-C(12)-O(12)	-158.89(14)
C(10)-C(11)-C(12)-C(3)	-44.04(18)
C(13)-C(11)-C(12)-C(3)	82.25(16)
C(2)-C(3)-C(12)-O(12)	8.99(16)
C(4)-C(3)-C(12)-O(12)	-114.34(15)
C(2)-C(3)-C(12)-C(11)	128.81(15)
C(4)-C(3)-C(12)-C(11)	5.47(19)
C(10)-C(11)-C(13)-C(14)	-67.9(2)
C(12)-C(11)-C(13)-C(14)	167.22(16)
C(11)-C(13)-C(14)-O(14)	-58.3(2)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C14 H16 O3.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	..A
O(14)-H(14)	0.82	2.01	165.7	2.813(2)	O(1)#1

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z



ORTEP view of the C14 H16 O3

compound with the numbering scheme adopted. Ellipsoids drawn at

40% probality level. Hydrogens represented by sphere of arbitrary size.

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