Université de Montréal

Acyclic Stereocontrol and Chemical Diversity
&
Application to the Synthesis of Macrolide and Ansa Antibiotics

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Application to the Synthesis of Macrolide and Ansa Antibiotics

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To my mother

my wife, Rui XIE

and my sons, Dimeng, Michael

&

To the memory of my father

Acknowledgments

I would like to take this opportunity to express my sincere gratitude to my supervisor, Professor Stephen Hanessian, for his guidance and inspiration throughout these years, for teaching me chemistry and life, and for helping me achieve such a great endeavor. I also heartily thank him for his support and understanding as a friend.

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Experimental Part

Abbreviation

$[\alpha]_D$	Specific rotation
Ac	Acetyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOM	Benzoxymethyl
Bu	Butyl
t-Bu	*tert*-Butyl
δ	Chemical shift in ppm
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DEC	No reaction meanwhile decomposition of starting material
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Ethylene glycol dimethyl ether, 1,2-Dimethoxy ethane
DMF	N,N-Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide, methyl sulfoxide
DPPA	Diphenyl phosphoryl azide
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
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
Me	Methyl
mg	Milligram
min	Minute
MHz	Megahertz
ml	Mililiter
mmol	Milimole
MOM	Methoxymethyl
mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrum
NBS	*N*-Bromosuccinmide
NIS	*N*-Iodosuccinimde
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NR	No reaction
OTf	Trifluoromethanesulfonate, Triflate

PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivaloyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
PTSA	*para*-Toluenesulfonic acid monohydrate
Pyr	Pyridine
rt	Room temperature
sat.	Saturated
TBAF	Tetrabutylamonium fluoride
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	Toluenesulfonate

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Abstract

We explored and exploited substrate-directed acyclic stereocontrol to address the synthesis of enantiopure molecules containing several stereocentres. We have demonstrated the high stereoselectivity, efficiency and practicality of cuprate conjugate addition to α,β-unsaturated esters with a variety of alkyl groups, in several systems. We studied the effects of different substituents on the stereoselectivity. We also demonstrated the high *syn*-stereoselectivity of functionalization of enolates: azidation, hydroxylation and alkylation. By employing these highly stereocontrolled reactions, we generated a large chemical diversity of enantiopure multi-chiral center compounds such as amino acids, hydroxy acids, and polyamino alcohols.

We have developed a highly stereocontrolled iterative methodology, the combination of *anti*-cuprate conjugate addition and *syn*-hydroxylation of enolates, to address the synthesis of enantiopure polypropionates. The remarkable features of our methodology are the predictability of the outcome of stereoselectivity, operational simplicity and efficiency. We have applied our methodology to the synthesis of the polypropionate of rifamycin S, which harbors eight contiguous stereocentres with an alternating methyl-hydroxy-methyl-hydroxy pattern. This represents the longest polypropionate chain in natural products. We synthesized an enantiopure nine stereocentre motif in 23 linear steps.

We also exploited this methodology to construct all the polypropionate subunits of bafilomycin A_1. We explored several approaches toward the total synthesis of bafilomycin A_1 by assembling of the polypropionate intermediates. We also did extensive studies on manipulation of protecting groups.

Résumé

Nous avons exploré et exploité en série acyclique la synthèse stéréocontrolée par le substrat de molécules possédant plusieurs stéréocentres. Nous avons démontré la grande stéréosélectivité, l'efficacité et la facilité de l'addition conjuguée du cuprate sur des esters α,β insaturés avec une variété de groupements alkyles et ce dans différents systèmes. Nous avons étudié les effets de différents substituants sur la stéréosélectivité. Nous avons aussi démontré la grande stéréosélectivité *syn* de la fonctionnalisation des énolates : azidation, hydroxylation et alkylation. Par l'utilisation de ces réactions hautement stéréosélectives, nous avons synthétisé une grande variété de composés possédant plusieurs centres chiraux énantiomériquement purs comme les acides aminés, les acides hydroxylés et les alcools polyaminés.

Nous avons développé une méthode itérative hautement stéréocontrolée par la combinaison de l'addition conjuguée *anti* du cuprate et l'hydroxylation *syn* de l'énolate pour conduire à la synthèse de polypropionates énantiomériquement purs. Les caractéristiques de notre méthodologie sont la prédiction de la stéréosélectivité obtenue, la simplicité et l'efficacité. Nous avons appliqué notre méthodologie à la synthèse de polypropionates de la rifamycine S qui contient huit stéréocentres contigus possédant le motif méthyl-hydroxy-méthyl-hydroxy. Ceci représente la plus longue chaîne de polypropionates connue dans les produits naturels. Nous avons synthétisé un motif contenant neuf stéréocentres énantiomériquement purs en vingt-trois étapes.

Nous avons aussi exploité cette méthodologie pour construire les sous-unités polypropionates de la bafilomycine A_1. Nous avons exploré plusieurs approches pour la synthèse totale de la bafilomycine A_1 par l'assemblage des différents intermédiaires polypropionates. Nous avons également réalisé une étude sur la manipulation des groupements protecteurs.

THEORETICAL PART

CHAPTER ONE

CHIRALITY, STEREOCHEMISTRY AND ASYMMETRIC SYNTHESIS

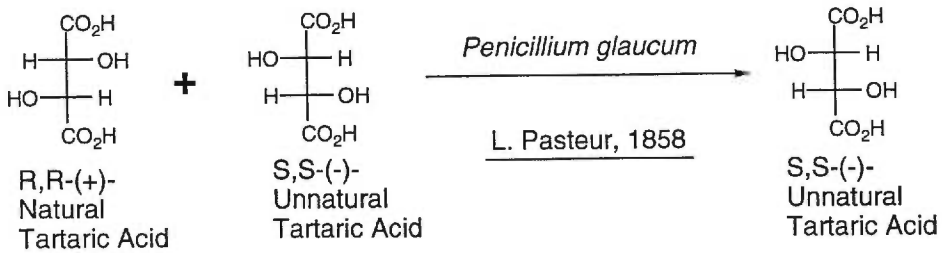
§1-1 Chirality

Chirality (handness) is the topological property of an object which can not be brought into congruence with its mirror image by translation and rotation.[1] Chirality exists in molecules like amino acids, sugars, proteins, RNAs, and DNAs as well as helical bacteria, helical plants, helical seashells and hands.[2] Chirality is a principal element of our universe and is a fundamental concept of chemistry and life science.[3]

Chirality in a chemistry sense treats not only the simple shape, but the shape with functionality and electronic properties. It is the basis of molecular recognition, which is the foundation of biological process. Most of the biological functions result from a strict matching of chirality of the molecules involved and the biological targets: enzymes, antigens, and receptors on the membrane of cells.

Even a hundred years ago, the profound influence of chirality in the life process was appreciated. In 1858, L. Pasteur demonstrated that microorganisms have no difficulty distinguishing between (*R,R*)- and (*S,S*)-tartaric acid. This was the first example of a biochemically enantioselective resolution of a racemate.[4]

Figure 1 BIOCHEMICALLY ENANTIOSELECTIVE RESOLUTION



In 1894, E. Fischer[5] discovered the specificity of yeast or enzymes to digest certain sugars during fermentation. He realized that enzyme transformations needed an exact match of chirality between the enzyme and the substrate, and he later expressed this chirality matching in his famous *lock-and-key* principle which has profoundly influenced many aspects of life science, medicine, immunology, and enzymology.[6]

§1-2 Stereochemistry[7]

Stereochemistry deals with the arrangement of atoms in a molecule in space. It is concerned with the detailed structural information of a molecule at all levels: constitution, configuration, conformation and molecular dynamics. The following are some historical events in the development of stereochemistry:[8]

In 1808, Malus discovered polarized light, a vitally important tool for the establishment of the stereochemistry.

In 1815, Biot made a landmark discovery when he found that some organic compounds, including turpentine, sucrose, camphor and tartaric acid, can rotate the plane of polarized light. He also recognized that the rotation is a property of the individual molecules, not that of the aggregate.

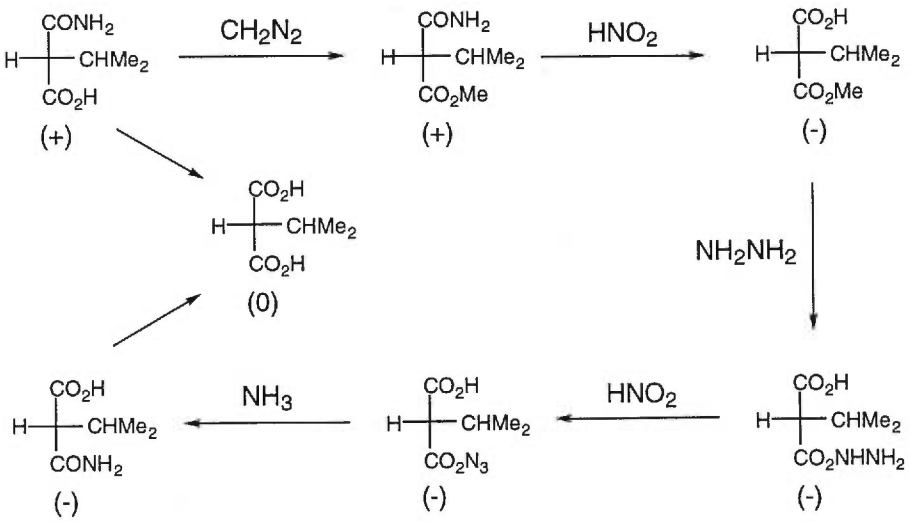
In 1848, Pasteur mechanically separated sodium ammonium tartrate crystals, demonstrating for the *first time* that an optically inactive racemate can be separated into two optically active enantiomers.

In 1860, Pasteur realized that optical activity is caused by an asymmetric grouping of the atoms in the optically active molecule. Molecules of the same substance rotating the plane of polarized light to the right or to the left are related to each other as is an object to its mirror image. However without valence theory, he could not figure out what the asymmetric grouping meant in a chemical sense.

After Kekulé[9] established the fundamental quadri-valence theory of carbon in 1858, Van't Hoff and Le Bel in 1874 simultaneously conceptualized the revolutionary tetrahedral nature of carbon which stated that the four valences of carbon are directed in three-dimensional space toward the four corners of a tetrahedron. The tetrahedral theory of carbon brought chemistry from a two-dimensional world to a three-dimensional world. Thus Van't Hoff and Le Bel laid down the foundation of stereochemistry.

The tetrahedral theory of carbon was experimentally supported by E. Fischer's work shown in Figure 2,[5c] along with his other work in carbohydrate synthesis. This theory was also supported by physical measurements and quantum mechanics.

Figaure 2 FISCHER'S PROOF OF TETRAHEDRAL THEORY



Fischer, E. and Brauns, F. *Ber.* **1914**, *47*, 3181

Configuration of carbon compounds originates from the different tetrahedral arrangement of the atoms or groups in a molecule. Configuration is a covalent property of a molecule and it cannot be changed without bond-breaking and forming. Initially, all the configurations of molecules were relative that of (*R*)-D-(+)-glyceraldehyde until the absolute configuration of sodium rubidium tartrate was determined by X-ray diffraction

method. The Cahn-Ingold-Prelog system,[10] (*R*)- and (*S*)- notation, was adopted for description of absolute configurations.

Conformations are the non-identical arrangements of the atoms in a molecule obtainable by rotation about one or more single bonds, although Sachse, in 1890, realized that six membered rings can exist in two non-planar forms and that the rigid chair form can have two mono-substitution products. The expression, conformation, was introduced in 1929 by Haworth, however, it took a long time to understand its importance and chemical meaning.

In the early 1950's Barton formulated the revolutionary and fundamental concept of conformational analysis[11] which was based on the large body of experimental data accumulated on the physical and chemical studies of cyclohexane derivatives, steroids and triterpenoids. He first pointed out *the chemical consequence of the difference between axial and equatorial substituents.*

Conformational analysis formulated the relationship between the preferred conformations and the chemical consequences: property, reactivity and selectivity. The function of a molecule in biological systems is associated with a specific, preferred conformation. Conformational analysis would provide the basis for rational design of structures with defined functions.

§1-3 Access to Enantiopure Compounds[12]

Basically, there are three ways to obtain enantiopure compounds.

First: Chirality Resolution

Chirality resolution generates no new stereogenic center. It simply separates two enantiomers, or destroys or transforms one enantiomer of the racemate. Chirality resolution is a very classical technique. In fact, Louis Pasteur had invented and used all three techniques even before the foundation of stereochemistry was laid down. Many

catalytic versions of chirality resolution have been developed recently. Chirality resolution can be accomplished by the following general procedures:

(A): Physical Separation via Enantiomeric Crystalline Forms

(a) Physical sorting of enantiomeric crystals, with the first resolution accomplished by Pasteur in 1848. Although the manual sorting of enantiomeric crystals of racemic sodium ammonium tartrate by Pasteur was very fortuitous and laborious, it is a monumental achievement in the history of chemistry and the starting point of stereochemistry.

(b) Seeding of a supersaturated solution of racemate with one enantiomeric crystal.[13]

(B): Physical Separation via Diastereomeric Forms

(a) Stable diastereomer formation (diastereomeric salts, diastereomeric molecules) followed by physical separation such as crystallization, chromatography, distillation, etc.

(b) Transient diastereomer formation such as chiral chromatography,[14] extraction with enantiopure solvents.

(C): Kinetic Controlled Resolution

Kinetic controlled resolution can be performed chemically or biochemically by using enantiopure environments (catalysts, enzymes, etc.) to differentiate the enantiomers.

(a) Kinetic resolution using chiral catalysts[15]

(b) Dynamic kinetic resolution using chiral catalysts under equilibrium conditions.[16]

(c) Biochemical transformations with enzymes, yeasts, or bacteria.[17]

(D): Desymmetrization Process by Using Enantiopure Reagents[18]

A symmetric enantiopure meso-compound is transformed into an asymmetric enantiopure compound by an enantiopure reagent through the chirality

differentiation, enantiopure diastereomer formation and following a chemical sequence.

Second: Chirality Transportation[19]

The chiral center or centers of an enantiopure compound from a natural source are embedded into the target molecule by a sequence of chemical reactions which do not perturb the chiral center or centers. This is a classical way to obtain enantiopure compounds with one or two chiral centers, especially before the sophisticated asymmetric synthesis technologies developed. No new stereogenic center is generated in this process.

Third: Asymmetric Synthesis

One or more new stereogenic centres are generated in enantiopure or enantioenriched fashion usually mediated by a chiral auxiliary, a chiral catalyst or related technique.

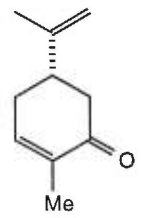
§1-4 The (*R*)- and (*S*)- Worlds

It has been known that enantiomers and enantiopure diastereomers possessed different properties in an asymmetric environment, such as a polarized light field or a biological system, since the Pasteur era. The vastly different biological activities of enantiomers and enantiopure diastereomers in biological systems are well-documented.[20] 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 their corresponding D-(*R*)-enantiomers (*sweet*), and (*S, S*)-aspartame (*sweet*) and its (*S, R*)-diastereomer (*bitter*). Further examples include the different bioactivities of (*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). Obviously, to obtain enantiopure products is an extremely important issue for industry, especially for the pharmaceutical and perfume

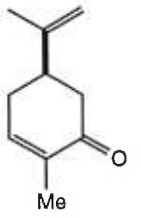
sectors. There is much to be learned on how to obtain these products efficiently and economically on an industrial scale.

Since the discovery of optical activity in organic molecules, chirality has been a fascinating and mysterious topic. Biological systems such as bacteria and yeasts have no difficulty differentiating enantiomers. Even more mysterious is the fact that biological systems can differentiate between two faces of a pro-chiral molecule and transform it into an enantiopure product. Most of the products made by organisms are enantiopure. On the other hand, the products made in laboratory were traditionally racemic, and chemists were faced with the challenge to control stereochemistry in the absolute sense.

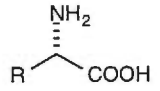
Figure 3 THE (*R*)- AND (*S*)- WORLDS



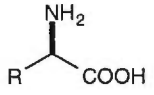
(*S*)-(+)-carvone
caraway



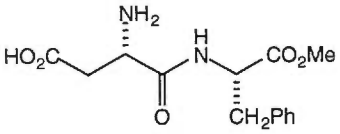
(*R*)-(-)-carvone
spearmint



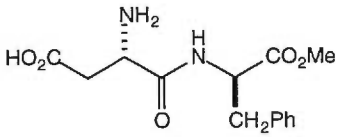
(*S*)-amino acids
bitter



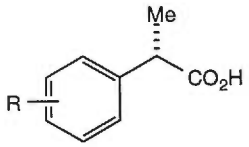
(*R*)-amino acids
sweet



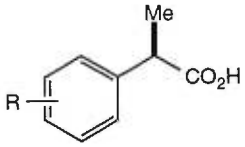
(*S, S*)-aspartame
sweet



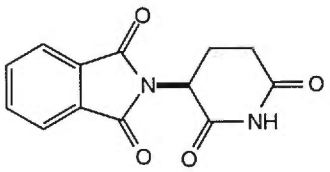
(*S, R*)-aspartame
bitter



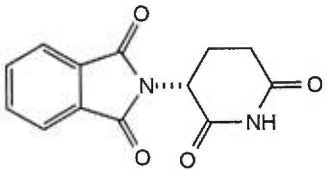
(*S*)-enantiomers
inactive



(*R*)-enantiomers
active



(*S*)-thalidomide
teratogenic



(*R*)-thalidomide
sedative and hypnotic

Industrial utility of chiral technology has had a much greater effect on the development of asymmetric synthesis. Chirality resolution was not a suitable approach to obtain enantiopure compounds since half of the products were undesired and had to be discarded. When the target contained *5* stereogenic centers, the separation and resolution of one enantiopure stereoisomer from a theoretical number of (*32*) stereoisomers were definitely not practical. The complete stereocontrol of every stereogenic center forming

step is the holy grail of organic chemists. Asymmetric synthesis is the most efficient and economical way to obtain enantiopure compounds if complete stereocontrol of the chemical process is to be achieved.

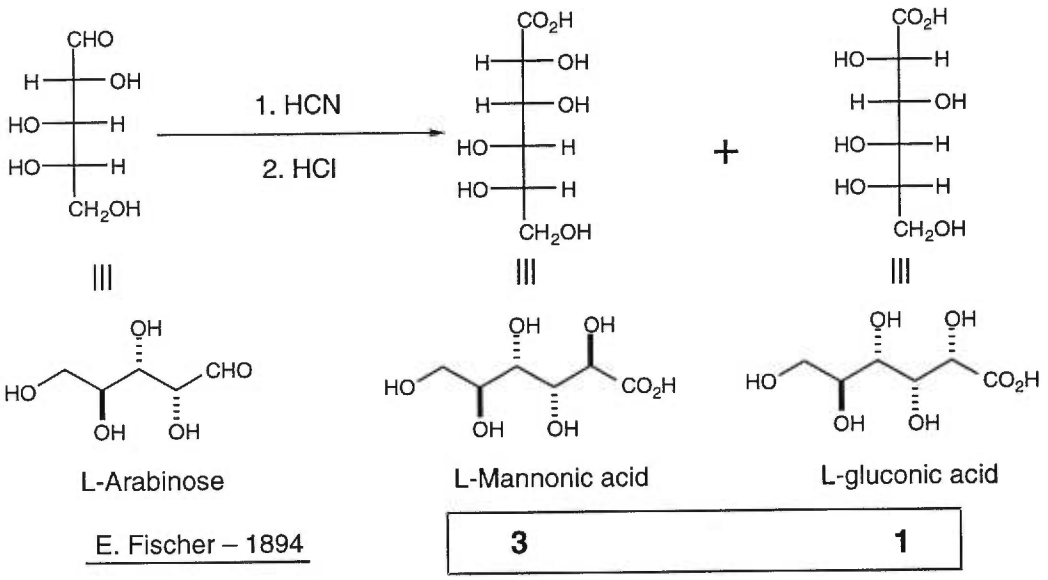
The number of chiral centers of drugs and biologically-interesting molecules increases constantly, however, the technology was not mature enough to address this very important issue until the late 1980's. The explosive growth of asymmetric synthesis, especially of catalytic asymmetric synthesis, in the last two decades has had an impact in the pharmaceutical industry. Stereoselective, efficient, economic and environmentally benign methods are very much in demand to meet the future challenge of drug discovery and development. The manufacture and dispensing of enantiopure drugs is an important issue with the federal regulation agencies.[21]

§1-5 Asymmetric Synthesis[12]

Asymmetric synthesis is a process in which an achiral unit in the ensemble of a substrate molecule is converted into an enantiopure or enantio-enriched unit.

As early as 1894, E. Fischer clearly outlined the concept of asymmetric synthesis based on his experiments in the conversion of one sugar to its next higher homologue via the cyanohydrin reaction. Actually, this is the first *substrate-controlled* asymmetric synthesis. During the following years the subject of asymmetric synthesis experienced great controversies over the roles of organism and vitalistic force.

Figure 4 FISCHER'S CONCEPT OF ASYMMETRIC SYNTHESIS



The foundations for the rational interpretation of the stereochemical course of asymmetric reactions, based upon conventional steric and electronic concepts were laid down around 1950 following the great effort of many prominent chemists including Prelog and Cram. However, the development of asymmetric synthesis was very slow in the beginning because of the lack of understanding and control of conformation issues. The selectivity was very low, far from practical utility until the end of the 1970's. All the known asymmetric organic reactions before 1970 were compiled in a one volume book by Morrison and Mosher. It is absolutely impossible to accomplish a similar task now.

Generally, asymmetric synthesis by purely chemical means[22] needs a chirality source to differentiate and control the reaction course. (Although racemic reactions follow the same stereochemical course, the newly formed stereogenic center is not enantiopure or enriched). The chirality source for stereocontrol can be from substrate and / or environment.

§1-5.1 The Chiron Approach[23] (Chiral Substrate Control)

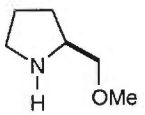
The basic idea of the chiron approach is to use enantiopure molecules, which Nature bestows on us, as the chirality source to control stereochemistry and obtain enantiopure products. Ideally the original chiral centers and carbons are assembled into target molecules.

There are a large variety of combinations of chirality and functionality in Nature: carbohydrates, amino acids, terpines, steroids and alkaloids.[24] These provide a broad space to play: recognizing the chiron in targets, selecting chiral templates and enantiopure materials from natural sources as starting points, designing the strategy with great freedom and executing in reaction vessels. Substrate control is a very basic strategy of asymmetric synthesis. Using the chiral center(s) existing in substrate to control the stereochemistry of the newly formed stereogenic center(s) is an ideal approach.

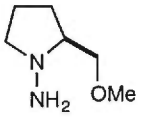
§1-5.2 Chiral Auxiliary Control

Chiral auxiliary control is at the borderline between substrate and environment control. The chiral auxiliary resides in the starting material and product, however, it is removed from the product after the stereocontrol process. A number of chiral auxiliaries have been developed for a variety of reactions (Figure 5).[25]

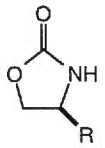
Figure 5 CHIRAL AUXILIARIES



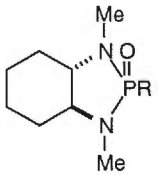
SMP [25(a)]



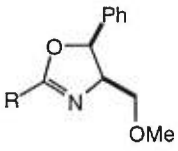
SAMP [25(b)]



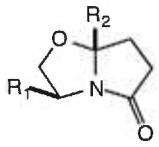
Oxazolidone [25(c)]



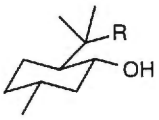
trans-1,2-diaminocyclo-hexane-based [25(d)]



Oxazoline [25(e)]

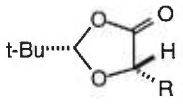


Bicyclolactam [25(f)]



Menthol-based [25(g)]

Camphor-based [25(h)]



SRS-based [25(i)]

§1-5.3 Chiral Environment Control

The chirality source of stereocontrol can reside in the environment in which the stereo-differentiating process takes place. Chiral reagent and chiral catalyst controls are the main means of this topic.

(A) Chiral Reagents Control –A stoichiometric amount, or more, of the chiral reagent is used to achieve stereochemical control. A number of strategies have been developed and high stereocontrol has been achieved.[26] Chiral boron reagents are among the most popular.[27]

(B) Chiral Catalyst Control – A chemzyme (abiological enzyme) is a long-sought holy grail of organic chemists.[28] The efforts, in the last two decades or so, have made the dream much closer to reality. The asymmetric catalytic systems for many reaction types have been developed and, in quite a few cases, high stereocontrol has been achieved. In the near future, catalytic asymmetric processes will dominate the field of asymmetric synthesis. Using small amounts of chiral catalyst to produce huge amounts of

enantiopure product will be a great objective for both economic and environmental considerations.[29]

§1-5.4 Chiral Substrate and Chiral Reagent or Catalyst Control–Double Induction[30]

When chiral substrate control alone does not yield with high stereoselectivity, double induction can be a good solution. Normally, double induction gives higher stereoselectivity, especially in matched cases.

§1-6 Transition State Models for Acyclic Stereocontrol

The stereoselectivity of an asymmetric reaction originates from a conformation bias in the transition state. The conformation bias results from subtle differences between conformers. The conformation analysis of the transition state concerns the dynamic process and differs from that of static molecules, although some principles could be applied in both cases. The unusually long and weak bonds and abnormal angles developed during transition state formation may lead to an unconventional conformational preference. Since the transition state is a crucial point of chemical bond forming and breaking, which involves electron rearrangement in molecular orbitals, greater electronic effects can be expected as compared to static conformational analysis. Transition states cannot be observed directly. They are formulated and revised based on the information deduced from products and theoretical consideration.[31]

§1-6.1 Transition State Models of Nucleophilic Attack

In the early 1950's, Prelog and Cram formulated the Prelog generalization[32] and the Cram rule[33], respectively, to interpret and predict the stereocontrolled course in acyclic systems based on extensive studies of asymmetric induction. Prelog's generalization concerns remote stereocontrol of 1,4 -asymmetric induction, and is the prototype of chiral auxiliary control. Although many highly stereoselective approaches

of chiral auxiliary control have been achieved, the conformational analyses of these chemical courses are much more complicated issues and are not fully established. Many unexpected stereoselectivities are still being reported.[34]

When strong chelation exists in reaction intermediates, Cram's chelate transition state model could be applied. The transition states are very similar to that of cyclic systems: the conformations are rigid and locked in relatively preferred conformers, the outcomes of stereochemistry are easily rationalized and predicted.[35]

The stereocontrol of 1,2-induction of nucleophilic addition to a carbonyl, one of the most important reactions for C-C bond forming, is of great interest and is relatively simple. A lot of experimental and theoretical work has been done in this area. The transition state model was first formulated as the Cram rule, shown in Figure 6. The carbonyl group was flanked by small (S) and medium (M) groups, while the substituent group on the carbonyl was eclipsed by the large (L) group. This transition state model provided the original ideals of using steric and electronic effects to interpret and predict the stereoselectivity.

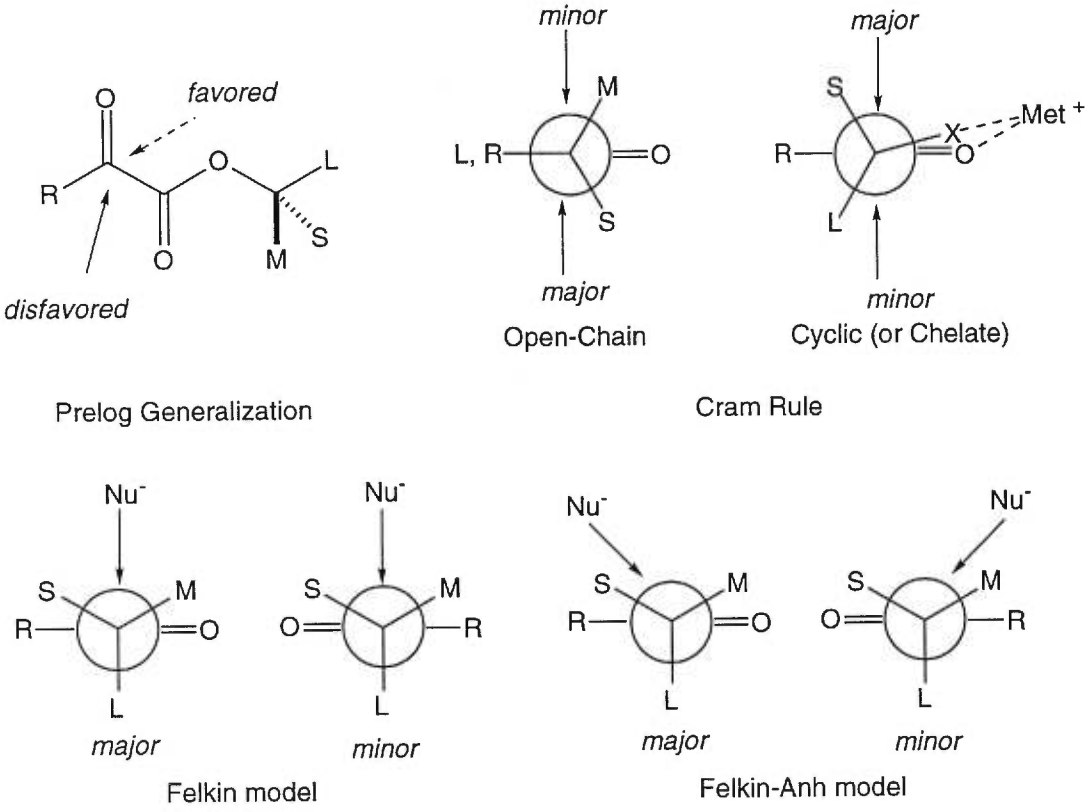
Felkin reformulated the transition state model by placing the large group at the anti-position to avoid the steric repulsion between the incoming nucleophile and the large group, and to provide electronic effects to facilitate bond formation. The medium and small groups were placed at the inside and outside positions, respectively.[36]

Anh introduced the Bürgi-Dunitz trajectory to modify the Felkin model.[37] The nucleophile attacks with an obtuse angle ($\alpha > 90°$) instead of a perpendicular angle ($\alpha = 90°$). The trajectory attack is mainly based on electronic and orbital interaction arguments. With trajectory attack, it seems more reasonable to place the medium group (M) inside to avoid the steric repulsion between the incoming nucleophile and the medium group. The Felkin-Anh model is the widely accepted transition state model for

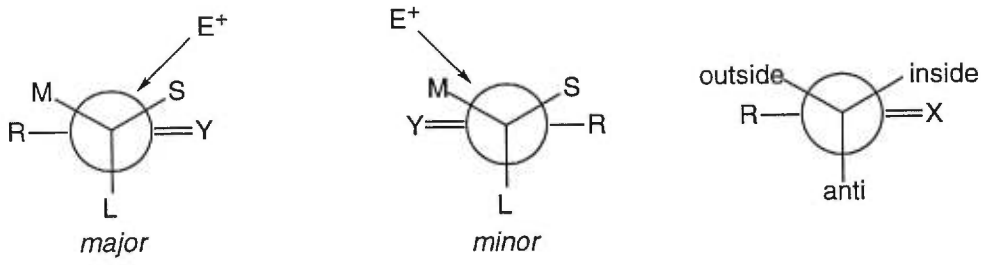
nucleophilic attack. Many experimental results and theoretical computation studies have given support to this model.[38]

Figure 6 TRANSITION STATE MODELS

A: Transition State Models of Nucleophilic Attack



B: Transition State Models of Electrophilic Attack



On the other hand, application of the Felkin-Anh model is still not an easy and obvious task. The order of L, M and S groups is determined not simply by volume or

steric sense, but by the combination of volume and electronic effects. Heathcock gave the order of the group preferred in anti-position as OMe > t-Bu > Ph > i-Pr > Et > Me > H.[38c] On the other hand, Eliel put alkoxy, OMe, OTES, OTBS and OTPS, at the inside position.[35c] The situation is not fully understood. We still need to find some special reasons to determine an order of L, M and S groups that rationalizes the observed stereoselectivities.

§1-6.2 Transition State Models of Electrophilic Attack[39]

Studies on the transition state model of an electrophilic attack are much less common than those of a nucleophilic attack, and the results are also very diversified. The transition state of an electrophilic attack is electron deficient instead of electron rich. This electronic effect may affect the order of the group that prefers the anti-position. The trajectory attack in the case of electrophilic attack is with an acute angle ($\alpha < 90°$) instead of with an obtuse angle in the case of nucleophilic attack. The large group still occupies the anti-position, however, the medium group has to occupy the outside position, contrary to the case of nucleophilic attack. The transition state for electrophilic attack is depicted in Figure 6.

§1-7 Substrate Directed Acyclic Stereocontrol

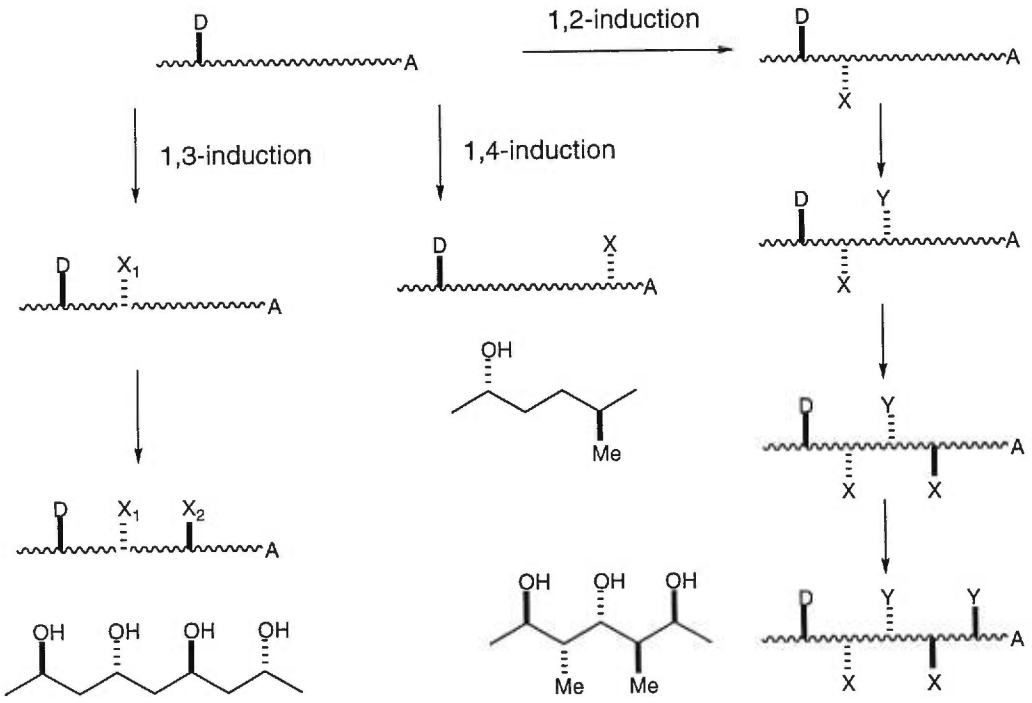
Stereocontrol in cyclic systems is a classical and well-understood topic, especially in five and six membered ring systems, where the conformations are rigid and predictable based on conformation analysis.[40]

The first asymmetric synthesis was a substrate directed acyclic stereocontrolled process, as demonstrated by E. Fischer. The outcome of stereochemistry is difficult to predict since the conformations are flexible and depend on many factors: electronic, steric, solvent, additive and temperature.

Although a lot of studies were carried out before 1970, high stereocontrol was not achieved.[41] The last two decades have witnessed a great advance in acyclic stereocontrol. Complete stereocontrol is a quite common feature of present asymmetric syntheses, obtaining enantiopure compounds with a few stereogenic centers is now trivial task.

Acyclic stereocontrol can be performed in 1,2-, 1,3-, 1,4-, or greater asymmetric induction versions (Figure 7). 1,2-Asymmetric induction gives the strongest control and is the most important and extensively studied case. 1,3-Asymmetric induction is quite popular in the biosynthesis of Nature, such as 1,3-polyol compounds[42], and several highly strereocontrolled methodologies have been developed.[43] The high stereocontrol of 1,4-asymmetric induction has been difficult to achieve. Only a few examples are documented.[44]

Figure 7 INTERNAL ASYMMETRIC INDUCTION IN ACYCLIC SYSTEMS



CHAPTER TWO

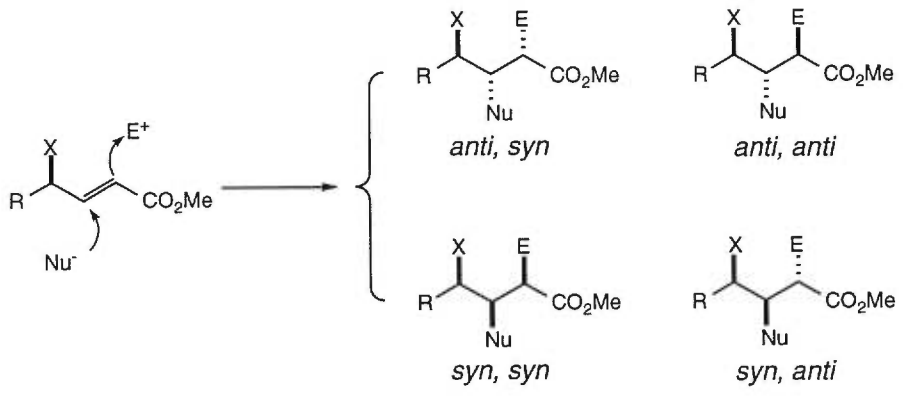
ACYCLIC STEREOCONTROL AND CHEMICAL DIVERSITY

§2-1 The Concept and the Starting Points

Carbon chains with consecutive chiral centers are prevailing in natural products and biologically interesting molecules. The number of chiral centers contained in the new drugs and drug-like molecules is constantly increasing. We just need to glance at natural products such as macrolide antibiotics,[45] polyether ionophores,[46] and the new protease inhibitors,[47] with their plethora of chiral centers, to realize why the demands for efficient synthesis of enantiopure motifs are so high.

Although a number of methodologies have recently been developed based on both cyclic and acyclic stereocontrol with high selectivity, the synthesis of enantiopure consecutive multi-chiral center motifs is still a very challenging task. Efficient, highly stereoselective and operationally simple approaches definitely need to be developed to meet the future synthetic standard and the economic and environmental requirements.

Figure 8 CONCEPT OF OUR RESEARCH



Our research objective is to explore and exploit *substrate-directed consecutive 1,2-asymmetric induction in acyclic systems* to achieve highly stereocontrolled syntheses

of motifs with multiple centers of chirality and apply this strategy in the syntheses of complex molecules, natural products or biologically interesting compounds. One of our initial targets was concerned with devising an approach to address the stereocontrolled synthesis of motifs with three chiral centers (Figure 8). Conjugate addition allows introduction, in a remote fashion, of various groups at the β-position as well as creating the opportunity of functionalization of the α-position with various functionalities. Using the γ-chiral center to direct the stereochemistry of conjugate addition, the nucleophile may be introduced in a highly stereocontrolled fashion. Subsequently, using the newly formed β-chiral center as the secondary chirality source to direct the stereochemistry of functionalization of the enolate, the electrophile may also be incorporated with high stereoselectivity. The hope is to obtain one pure or highly enriched diastereomer, out of the four possibilities, by this two-step sequence.

§2-2 Acyclic Stereocontrolled Conjugate Addition of Organocuprates

Organocopper reagents are among the most versatile and reliable reagents for the selective and efficient formation of carbon-carbon σ bonds and they are the most heavily-used reagents by synthetic organic chemists.[48] It is not a surprise that there are many reviews and treatises on the preparation, application, and mechanism of organocopper reagents.[49]

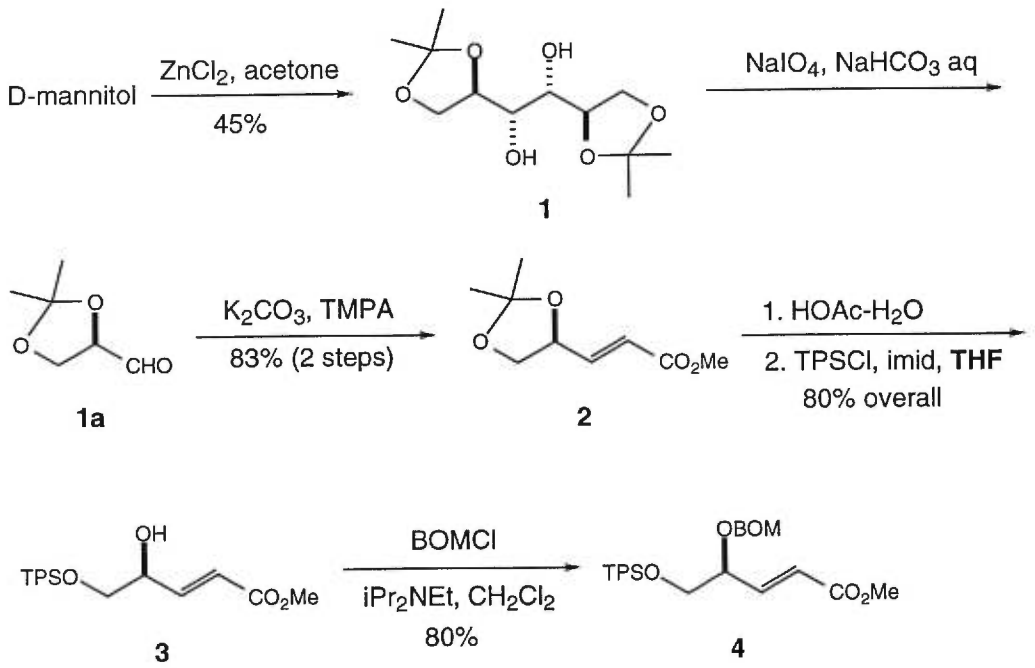
Figure 9 CHIRAL TEMPLATES

γ-Alkoxy series γ-Ureido series

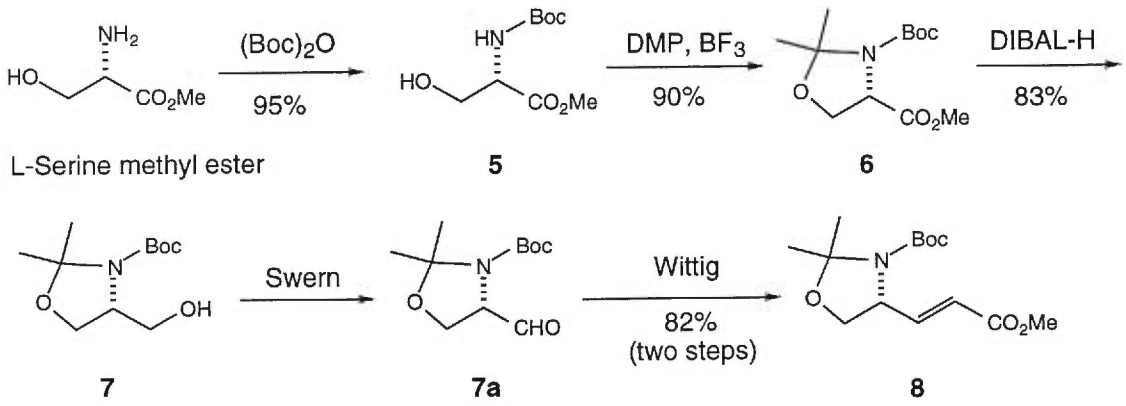
We chose two templates, shown in Figure 9, as our starting points. These templates have several advantages for application to the synthesis of complex molecules. They can be easily prepared in large quantity, their derivatives are easily functionalized, the functionalities easily differentiated, and two consecutive 1,2-inductions can be performed.

The γ-alkoxy α,β-unsaturated ester **4** can be conveniently prepared, in large quantity, from the glyceraldehyde derivative **1a**, which is a versatile and widely used molecule for asymmetric synthesis.[50] In turn, aldehyde **1a** can be obtained from D-mannitol.[51] The synthesis of chiral template **4**, shown in Scheme 1, was carried out following known procedures.[52] Only the selective protection[53] of the primary hydroxyl with TPS group need be mentioned here. Using THF (reaction time, 1 h; yield >90%; <5% di-TPS by-product) as the solvent proved to be much better than CH_2Cl_2 (~25% di-TPS by-product). Compound **4** was prepared on 100 mmol scale.

Scheme 1 SYNTHESIS OF γ-ALKOXY CHIRAL TEMPLATE



Scheme 2 SYNTHESIS OF γ-UREIDO CHIRAL TEMPLATE



The γ-ureido α,β-unsaturated ester, chiral template **8**, was prepared from L-serine methyl ester following known procedures.[52] The Garner aldehyde **7a**,[54] a configurationally stable intermediate, is a versatile building block for asymmetric synthesis. Compound **8** was prepared via the sequence shown in Scheme 2.

§2-2.1 General Consideration of Organocopper Reagents[49d,e]

Due to its synthetic significance, great efforts have been made to divulge the nature of the reactive species[55] and mechanism[56] since the 1960's, however, the structure of organocopper reagents and the detailed mechanisms of reaction remain unclear. The aggregate structure and mechanism show a strong dependence on the substrates and the reaction conditions (solvents, temperature, additives). It may not be possible to formulate a universal picture.

From a synthetic point of view, some significant results, conclusions and empirical guidelines are summarized here for a variety of organocopper reagents. There exists a large body of documents on a large number of organocopper reagents, usually prepared by reacting either organolithium reagents (lithium-based) or Grignard reagents (magnesium-based) with different copper salts at certain stoichiometric ratios. The

combination of organocopper reagents with different ligands and additives generates a large number of new organocopper reagents. Generally, organocopper reagents can be classified in three categories:

(**R**, alkyl groups; **M**, metal ions, Li or Mg; **X**, halides from copper salts and Grignard reagents; **L**, ligands; **A**, additives as activators)

(I) RM+CuX•L•A (catalytic) (Kharasch Reaction)

Grignard reagents are used almost exclusively in this catalytic process. Although the effectiveness and reproducibility need to improve, this catalytic process is a very promising way to reduce the amount of copper used in the reaction (it is a big problem for industrial scale)[57] and to develop the asymmetric versions of reactions.[58]

(II) RCu•M•X•L•A

Because of the solubility problems, RCu-type reagents are not usually reactive enough for synthetic use. The solubility and reactivity can be increased, however, by using certain ligands (CN, R_3P, $(RO)_3P$, R_2S) and additives (BF_3, etc.).

(III) R_1R_2CuM•X•L•A

Cuprates (Gilman reagent, R_2CuLi) are the original forms of this type of organocopper reagents. Cuprates are soluble in THF and ether, and form homogenous solutions so that the reactivity is greatly enhanced. Many modifications of Gilman reagents have been made to increase the reactivity further or to meet the needs for some specific uses.

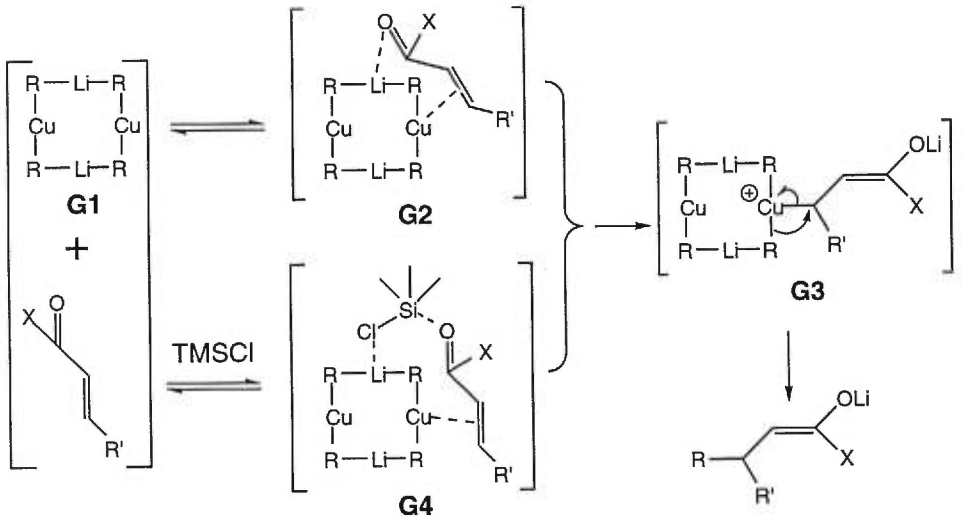
Although the reactivity and properties of cuprates can be changed dramatically by differing the ratio of lithium or Grignard reagent and copper salt, ligands and additives, the basic structure R_2CuM remains.[55] The "higher order cuprate" (Lipshutz reagent)[59] seems to be R_2CuLi•LiCN and the Ashby reagent (R_3CuLi_2)[60] seems to be R_2CuLi•RLi.

The detailed structures of aggregates are very important to their reactivity. The R group can also be heteroatom-functionalized, such as in amide cuprates.[61]

§2-2.2 Mechanism of Cuprate Addition[56]

Conjugate addition of organocuprates to an α,β-unsaturated carbonyl, or related compound, (cuprate addition) is a highly valuable and well-established synthetic tool for carbon-carbon σ bond formation. The accelerating effect by additives such as BF_3 etherate[62] and TMSX (X=Cl, I, Br, CN, OTf),[63] along with the highly stereoselective fashion[64] developed recently, has added more power to this remarkable reaction. However, the detailed mechanism and structure, especially that of the additive-accelerated version, remains unclear.

Figure 10 MECHANISM OF CUPRATE CONJUGATE ADDITION



(1): Cuprates exist predominantly as a dimer complex with a cyclic structure **G1** in solution. Kinetic studies have been shown that this complex $([R_1R_2Cu]^-M^+)_2$ is the kinetically reactive species.[56g] However, recent studies have revealed that the structure of

cuprates shows strong dependence on the solvents and the monomer can be the reactive species in some cases.[55f]

(2): During cuprate addition, the cuprate and the α,β-unsaturated carbonyl compound first form a Cu- π complex **G2** reversibly. This is followed by oxidative copper-carbon bond formation to give copper (III) intermediate **G3**, which undergoes reductive elimination to form the new carbon-carbon σ bond giving the enolate. There is a high probability that cuprate addition involves a redox process of Cu(I)/Cu(III). The oxidation potential (electron-donating ability) of the cuprate and the reduction potential (electron-accepting ability) of the α,β-unsaturated carbonyl system can be critical for reactivity and selectivity.[65] A similar mechanism of TMSCl-accelerating cuprate addition has been proposed. As shown in **G4**, TMSCl coordinates with the carbonyl oxygen and the lithium of the cuprate.[63b]

(3): The countercation, M^+, is very important for the reactivity of cuprates. 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 of aggregates containing M^+ are vitally important to the reactivity.

(4): The additives can also be critical for cuprate addition. Lewis acids such as BF_3 etherate and TMSX (X=Cl, Br, I, CN) have a remarkable accelerating effect on the reaction rate of cuprate addition and, in some cases, affect the stereochemical outcome.

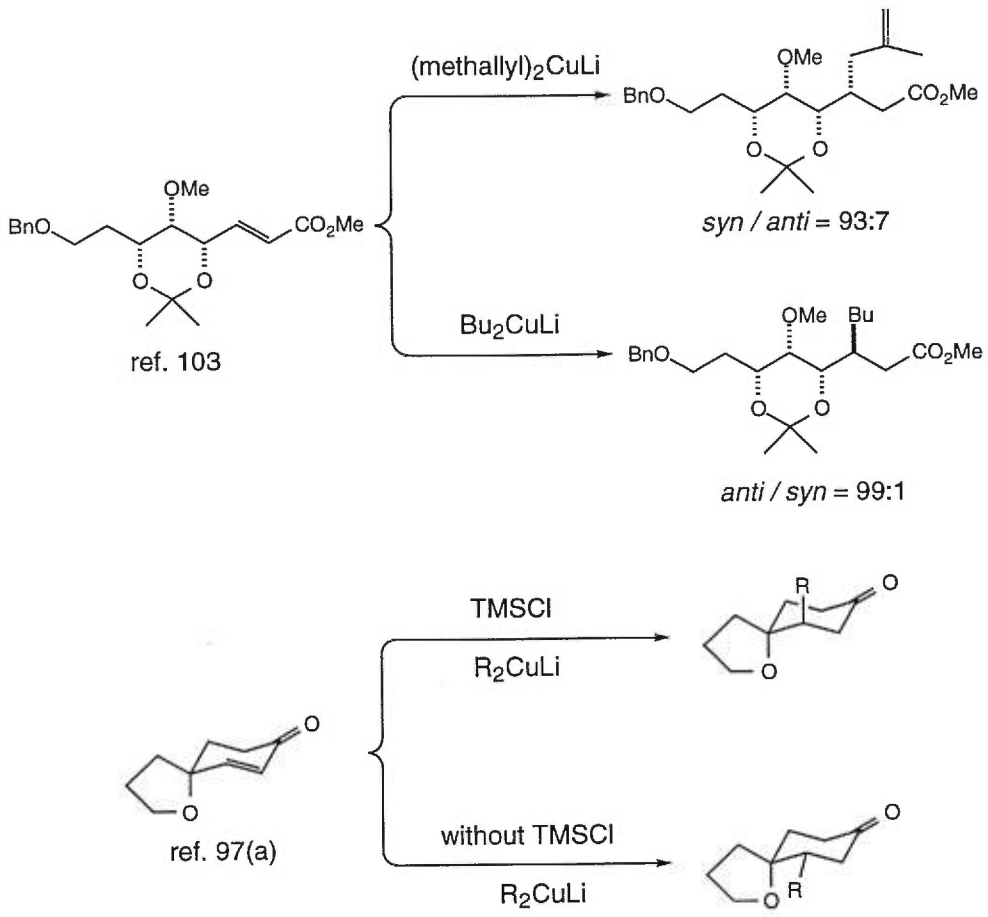
(5): The choice of solvent also has an important effect on cuprate addition, due to differences in their solubilities and coordinating effects. Tetrahydrofuran and ether (the former usually better than the latter) are commonly used solvents for synthetic purposes. The coordination of a solvent can facilitate the cuprate formation and stabilize the Cu(III) intermediate species.

§2-2.3 Stereochemical Considerations

Although great efforts have been made to interpret and predict the stereochemistry of cuprate addition to α,β-unsaturated esters bearing γ-chiral centers, the situation is still not fully established.

Syn-selectivity was obtained with dimethallylcuprate, meanwhile, *anti*-selectivity was obtained with dibutylcuprate on the same substrate.[66] Diallylcuprate was either unreactive to the α,β-unsaturated ester or reacted in a 1,2-addition fashion. Lithium reagent-based divinylcuprate reacted in a 1,4-addition fashion with high *anti*-selectivity, however, the reproducibility and yield were serious problems.[67] The results obtained from the addition of dimethylcuprate and divinylcuprate to 2-cyclohexen-1-one were even more intriguing.[63a] The stereoselectivity strongly depended on the solvent systems, additives and reagents. Remarkably, the additives, chlorotrialkylsilanes (TMSCl, TBSCl), greatly accelerated the reaction and completely reversed the stereoselectivity (Figure 11).

Figure 11 ABNORMALITY OF CUPRATE ADDITION



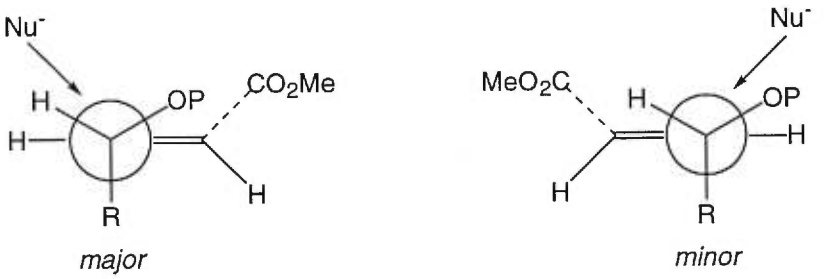
Extensive studies of stereoselectivity in the γ-alkoxy series, with R_2CuLi, RCu, $R_2CuLi{\bullet}BF_3$, and $RCu{\bullet}BF_3$ as reagents, have been reported by Yamamoto.[64b] Many theoretical computational studies have been documented.[64d] However, a full understanding of the diversified results has not been reached.

Generally, for the γ-alkoxy series of a variety of α,β-unsaturated systems, all organocopper reagents, except allylic ones, with monoesters gave *anti*-stereoselectivity and with diesters gave *syn*-stereoselectivity. Allylic copper reagents gave *syn*-stereoselectivity with both monoesters and diesters. *E*- and *Z*-configurations of the double bond resulted in no difference in the stereoselectivity.

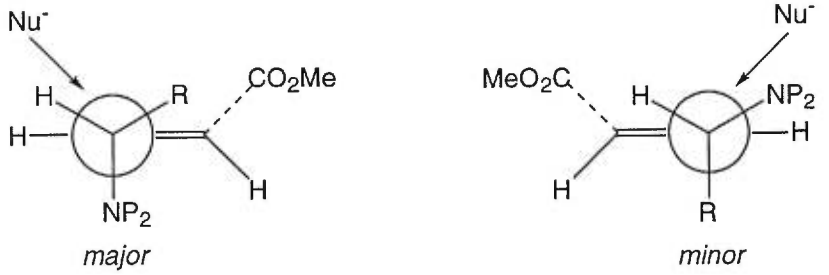
A modified Felkin-Anh transition state model, for the γ-alkoxy series was proposed to interpret the observed stereoselectivity.[52, 64b] This transition state model was rationalized based on the electronic and steric arguments (Figure 12).

Figure 12 TRANSITION STATE MODELS OF CUPRATE ADDITION

A: Transition State Models for the γ-Alkoxy Series



B: Transition State Models for the γ-Ureido Series



Surprisingly, the γ-ureido series of a variety of α,β-unsaturated systems gave the opposite stereoselectivity. All organocuprates (allylic ones were not tested) with monoesters gave *syn*-stereoselectivity, meanwhile, diesters gave *anti*-stereoselectivity. A transition state model for the γ-ureido series was also proposed and rationalized to explain the observed stereoselectivity (Figure 12).[52, 64c]

Although a lot of work has been done, obviously, there is a lot of work to be accomplished before there can be a clear understanding of the stereoselectivity, scope and limitations of γ-chirality directed conjugate additions of organocuprates.

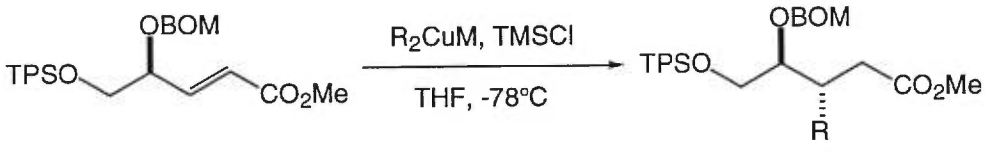
§2-2.4 General Considerations of Cuprate Addition

As demonstrated by the results from our laboratories[52] and others,[64, 66, 67] the high stereoselectivity of γ-chirality directed conjugate additions of organocuprates could be obtained. We intended to define the generality, the scope and the limitation of this highly stereocontrolled process, and to apply it as one key step in the synthesis of enantiopure consecutive multi-chiral center motifs .

We chose the combination of cuprate-TMSCl-THF as our reaction system to explore the stereochemistry of cuprate additions with a variety of chiral templates such as **4** and **8**. This system has several attracting features worth mentioning: (1) Cuprates can easily be prepared from a variety of readily available organolithium reagents (lithium-based) and Grignard reagents (magnesium-based), which can be made from the corresponding halides even when they are not commercially available. The reactivity of cuprates is generally high enough to react with cyclic or acyclic enones, enals, lactones and doubly activated olefins, such as diesters, but not high enough to readily react with acyclic enoates. (2) TMSCl is a very mild and weak Lewis acid. It is compatible with a variety of functionalities and can greatly accelerate the cuprate addition reaction, especially reactions between cuprates and enoates. Although other Lewis acids such as BF_3, TMSBr and TMSI also have great accelerating effects, their acidity may be too strong to be compatible with many sensitive functionalities. (3) THF is superior to ether and other solvents due to its dissolvability and coordinating effects. Usually THF gives better and more reproducible results.

§2-2.5 Cuprate Addition: γ-Alkoxy Series

Table 1 CUPRATE ADDITION OF γ-ALKOXY SERIES



4 **9 - 12**

Entry	R	M	Yield	*Anti/Syn*	Compound
1	Methyl	Li	93%	>20:1	**9**
2	Ethyl	Li	76%	>20:1	**10**
3	Ethyl	MgBr	73%	>20:1	**10**
4	Vinyl	MgBr	70%	>20:1	**11**
5	2-Propenyl	Li	60%	>20:1	**12**
6	2-Propenyl	MgBr	72%	>20:1	**12**
7	Ethyl	MgBr-BF_3	NR		
8	Allyl	MgBr	NR		
9	2-Propyl	MgCl	NR		

From our results in Table 1 we can see the generality of the excellent *anti*-stereoselectivity with good yields for the γ-alkoxy series. In the cases of methyl, ethyl (lithium-based[68] and magnesium-based), vinyl and 2-propenyl (lithium-based and magnesium-based), only the *anti*-isomers were detected by ^{1}H and ^{13}C NMR analysis.

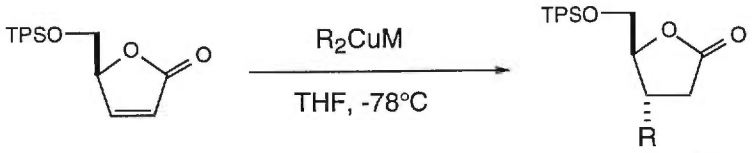
When BF_3 was used as the activator instead of TMSCl, no reaction occurred and the starting material decomposed when the temperature was increased.

Diallylcuprate magnesium bromide did not react with enoate **4** under these conditions and the starting material was recovered. Although dimethallylcuprate reacted

with enoate (see Figure 11), the stereoselectivity was completely reversed. Diallylcuprate either did not react or reacted in a 1,2-addition fashion. Successful examples for conjugate addition of diallylcuprate are very rare[69] and the reason for this abnormality is still unclear. Di-(2-propyl)cuprate magnesium chloride did not react and the starting material was recovered.

The different counterions, M^+, made quite a difference on the reproducibility, yield, stability and reactivity, however, no or very little difference on the stereoselectivity. The lithium-based cuprates usually show slightly higher reactivity, however, the reproducibility was disappointingly low, except for dimethylcuprate. In the cases of ethyl and 2-propenyl, the chances of geting low yields or 1,2-addition products were very high. Lithium-based divinylcuprate was reported to be very capricious and difficult to use.[70] *On the contrary, the magnesium-based cuprates were stable and gave the highly reproducible results of excellent stereoselectivity and high yield. Furthermore the procedures were also much simpler than those of the lithium counterparts.*[71]

Table 2 CUPRATE ADDITION OF A CYCLIC SYSTEM



12a **13 - 15**

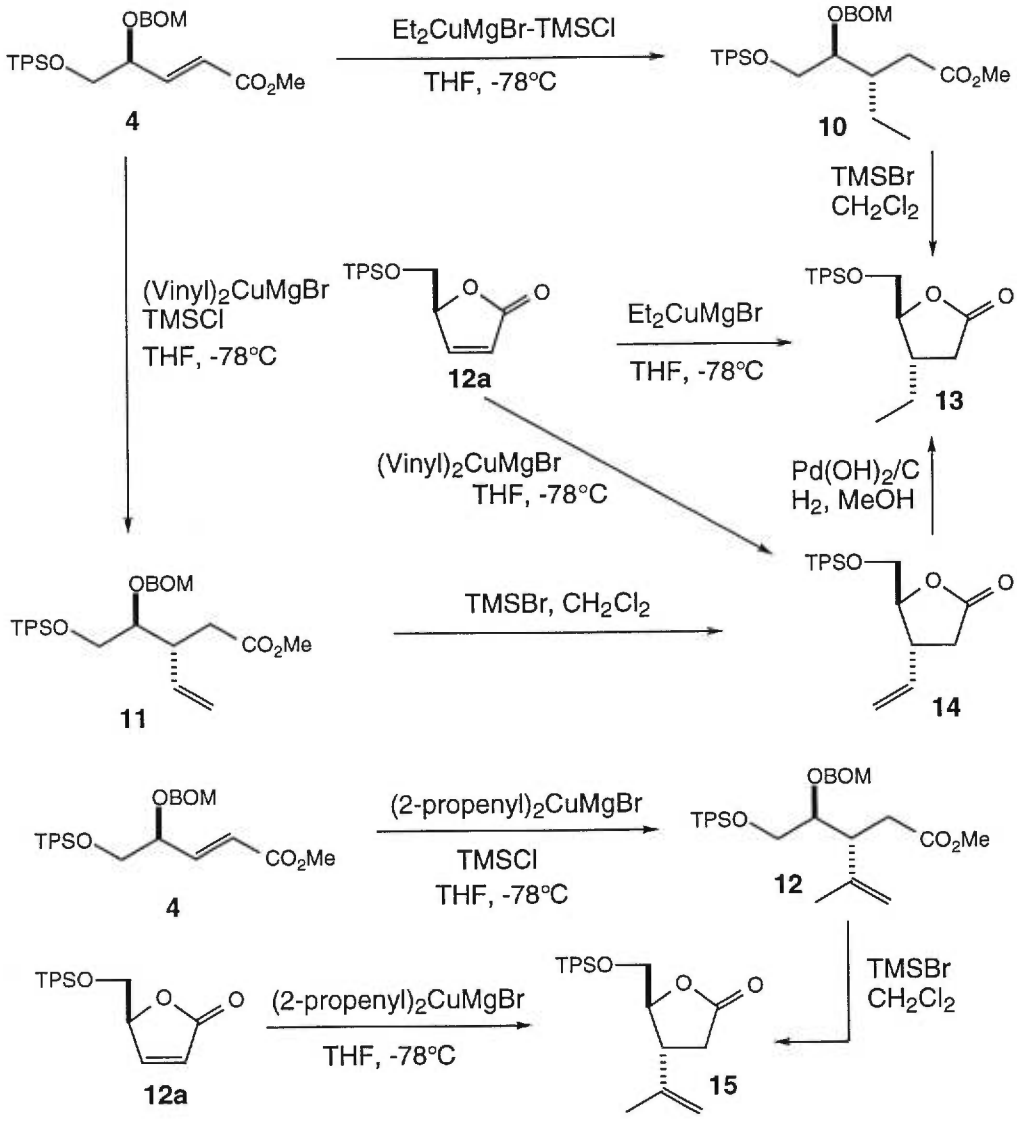
Entry	R	M	Yield	*Anti/Syn*	Compound
1	Ethyl	MgBr	60%	>10:1	**13**
2	Vinyl	MgBr	60%	>20:1	**14**
3	2-propenyl	MgBr	78%	>12:1	**15**
4	2-Propenyl	Li	Dec.		
5	Allyl	MgBr	70%	1,2-addition	
6	2-Propyl	MgCl	NR		

As we mentioned earlier, the stereocontrol in cyclic systems is well-established.[72] The *trans*-stereoselectivity of the reaction shown in Table 2 is doubtless. The reactivity of cuprates is high enough to react with α,β-unsaturated lactone **12a**[73] without an activator. All the magnesium-based cuprates of ethyl, vinyl and 2-propenyl reacted with lactone **12a** to give high stereoselectivity and good yield. However, the lithium-based cuprate of 2-propenyl never gave the desired product, diallylcuprate gave the 1,2-addition hydroxy product, and 2-propyl, with magnesium chloride as counterion, did not react.

From Tables 1 and 2, we can also see that the *stereoselectivity in acyclic systems overrides that in cyclic systems*, although, the sense of stereoselectivity is much easier to predict in cyclic systems than in acyclic systems.

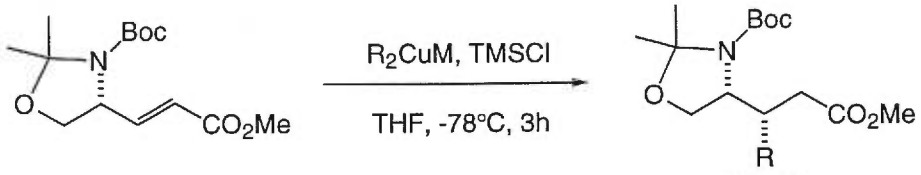
The *anti*-stereoselectivity for the acyclic-stereocontrolled cuprate addition was confirmed by a series of chemical transformations, shown in Scheme 3. Compounds **10** and **11** were transformed into lactones **13** and **14** respectively by using TMSBr.[74] Only one isomer was detected in both cases the acyclic and cyclic forms. Lactone **14** was transformed into lactone **13** by hydrogenation. Similarly, the stereochemistry of the 2-propenyl compound, **12,** was also confirmed. In the case of compound **9**, the stereochemistry was confirmed by X-ray diffraction analysis later.

Scheme 3 STEREOCHEMISTRY OF CUPRATE ADDITION IN γ-ALKOXY SERIES



§2-2.6 Cuprate Addition: γ -Ureido Series

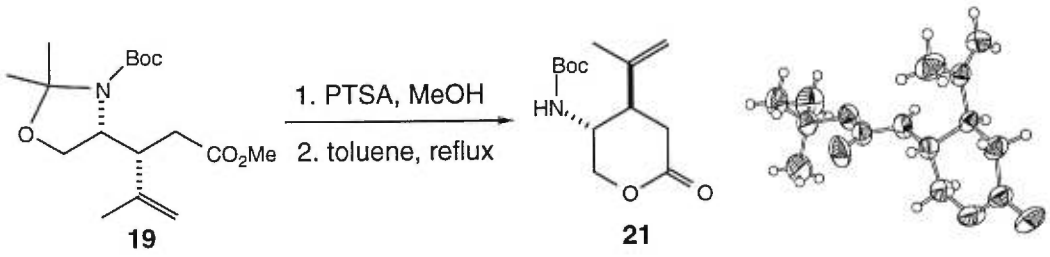
Table 3 CUPRATE ADDITION OF γ-UREIDO SERIES



8 **16 - 20**

Entry	R	M	Yield	*Syn/Anti*	Compound
1	Methyl	Li	97%	>20:1	**16**
2	Ethyl	MgBr	70%	>20:1	**17**
3	Vinyl	MgBr	80%	>20:1	**18**
4	2-Propenyl	Li	75%	>14:1	**19**
5	Phenyl	MgBr	80%	>8:1	**20**

Scheme 4 STEREOCHEMISTRY OF CUPRATE ADDITION IN γ-UREIDO SERIES



19 **21**

Table 3 summarizes the results of acyclic-stereocontrolled cuprate addition for the γ-ureido series. From Table 3, we can see cuprate addition of methyl, ethyl and vinyl groups occured in good yields with excellent *syn*-stereoselectivities. Only one isomer was detected by ^{1}H and ^{13}C NMR analyses in all cases. For the 2-propenyl and phenyl addition products, the *syn*-stereoselectivities dropped to 14:1 and 8:1, respectively. However, the yields were still very good.

The *syn*-selectivity was confirmed by chemical transformation of acyclic compound **19** to crystalline lactone **21** and X-ray diffraction analysis of a single crystal of **21** (Scheme 4). Later, X-ray diffraction analyses of the derivatives of compounds **12** (methyl) and **19** (2-propenyl) provided more evidence.

§2-2.7 Cuprate Addition: Transition State Model

We have demonstrated high stereoselectivities in both the γ -alkoxy and γ -ureido series. The sense of stereoselectivity, however, seems reversed, with *anti*-selectivity being favored in the γ -alkoxy series and *syn*-selectivity in the γ -ureido series. Although the transition states were rationalized, it was interesting to see the importance of both steric and electronic effects.

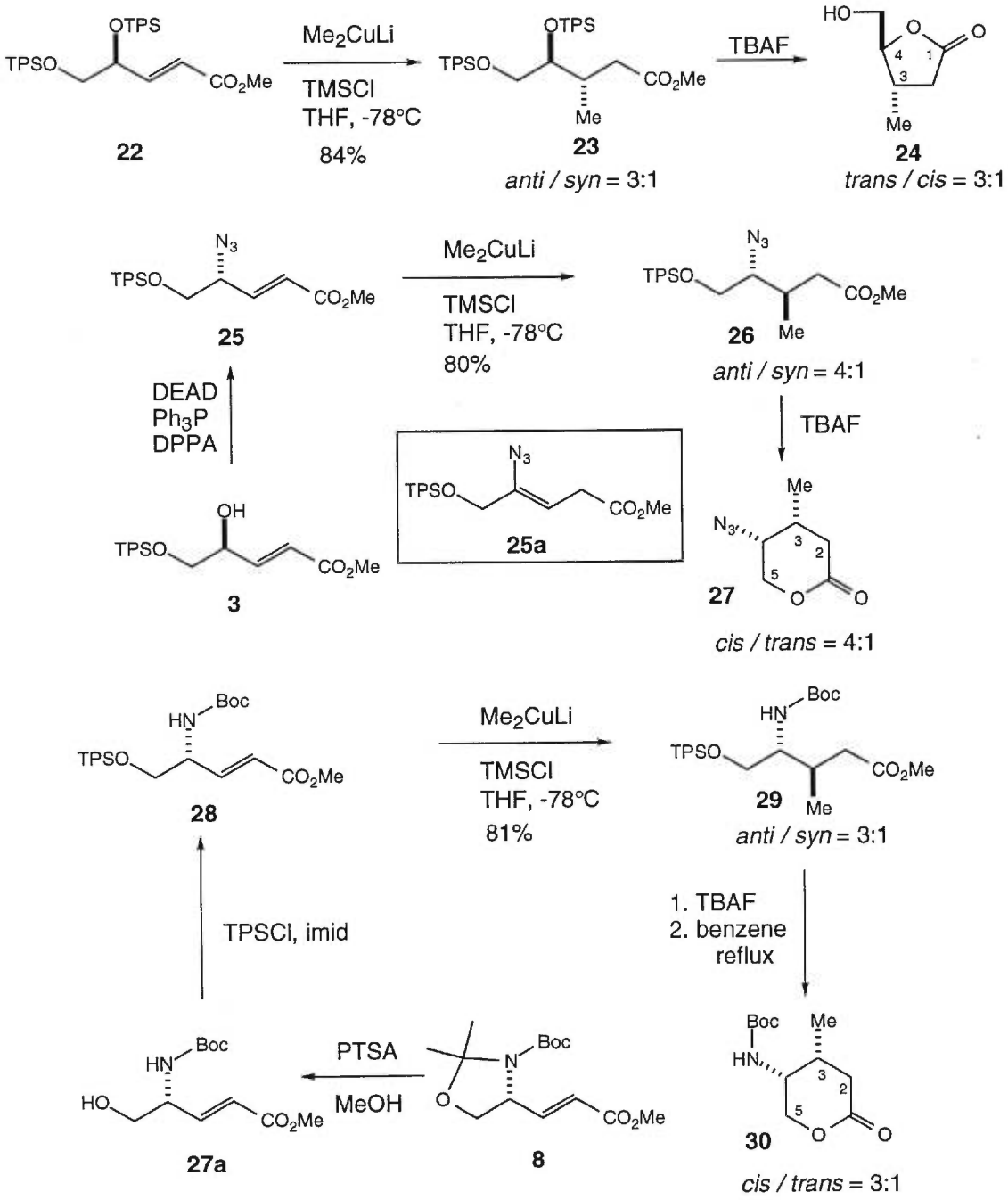
Several other different γ -substituents were studied, these are shown in Scheme 5.

γ -OTPS compound, **22**, obtained as a by-product as shown in Scheme 1, was subjected to cuprate addition. Compound **23** was obtained as the major isomer of a mixture (84% yield) of *anti / syn* = 3:1. The stereochemistry and selectivity was proved by transforming compound **23** into lactone **24** by treatment with TBAF and analyzing and comparing ^{1}H NMR data of **24** with that of the known analogues[75] [major, *trans*-**24**, δ = 4.20-4.13 (m); minor, *cis*-**24**, δ = 4.58-4.50 (m)].

γ-Azido compound, **25**, was prepared from the γ-hydroxy α, β-unsaturated ester **3** by employing Mitsunobu conditions[76] in 14% yield at 0°C. The major product was vinyl azide **25a**, the only product obtained at -78°C in 86% yield. γ-Azido α, β -unsaturated ester **25** was subjected to cuprate addition. Compound **26** was obtained as the major isomer of a mixture (80% yield) of *anti / syn* = 4:1. The stereochemistry and selectivity was proved by transforming **26** into lactone **27** by treating with TBAF and analyzing and

comparing the ^{1}H NMR data of **27** with that of the known analogues[77] (major, *cis*-**27**, H_2, J = 8.5, 8.9 Hz; H_5, J = 3.4, 5.0 Hz).

Scheme 5 TRANSITION STATE ASPECT OF CUPRATE ADDITION



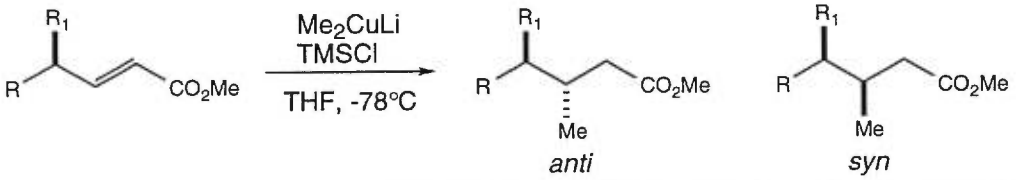
γ-*t*-Butoxy carbamic α, βunsaturated ester, **28**, was obtained by a two-step sequence from compound **8**, deprotecting the acetonide with PTSA / MeOH to give compound **27a**, followed protection of the hydroxy with TPS. Compound **28** was subjected to cuprate addition to yield compound **29** as the major isomer of a mixture (81% yield) of *anti / syn* = 3:1. The stereochemistry and selectivity was proved by transforming **29** into lactone **30** by treating with TBAF and then refluxing in benzene. The ^{1}H NMR data of **30** was analyzed and compared with that of known analogues[52] [major, *cis*-**30**, δ = 5.00-4.90 (br), 4.05-3.95 (br), 1.03 (d, J = 6.4 Hz); minor, *trans*-**30**, δ = 4.80-4.75 (br), 3.70-3.60 (br), 2.00-1.90 (m), 1.13 (d, J = 6.7 Hz)].

From the known data, summarized in Table 4, we could make some conclusions and predictions about the stereoselectivity of cuprate addition. The modified Felkin-Anh models, depicted in Figure 13, are taken as transition state models of cuprate addition.

(1) γ-Alkoxy groups have a strong tendency to occupy the inside position, the electronic interaction of the lone pairs of alkoxy and π*-bond orbital could be operative. Even with R_1 = OTPS, which is much more bulky than R = CH_2OTPS (Entry 7), the conformation of R-anti and R_1-inside still predominated. This reveals the electronic effect to be a much greater contributor to *anti*-stereoselectivity than the steric effect in the γ-alkoxy series.

(2) γ-Ureido groups do not show a significant electronic effect. The steric effect is the predominant contributor to the stereoselectivity. When R_1>>R, high *syn*-stereoselectivity will result (Entry 1, 2, 3 and 4).

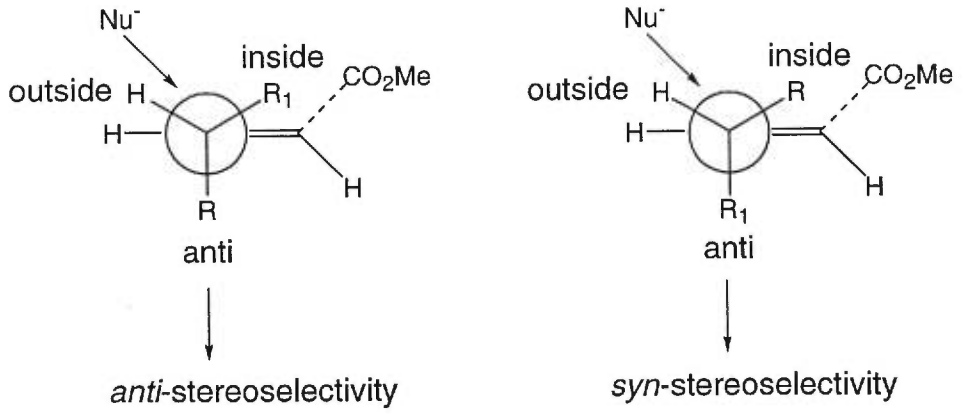
Table 4 TRANSITION STATE ASPECT OF CUPRATE ADDITION



Entry	R	R_1	*syn*	*Anti*	Yield
1 [a]	Me	NBn_2	16	1	80%
2 [a]	Me_2CHCH_2	NBn_2	13	1	87%
3 [a]	Bn	NBn_2	11	1	84%
4 [b]	CH_2OA	NABoc	20	1	97%
5	CH_2OTPS	N_3	1	3	80%
6	CH_2OTPS	NHBoc	1	4	81%
7	CH_2OTPS	OTPS	1	3	84%
8	CH_2OTPS	OBOM	1	20	93%
9 [c]	CHMeR	OBOM	1	20	90%
10 [d]	2-Propyl	OBOM	1	20	90%
11 [e]	Me	OBOM	1	2	

Note: a: see ref. 64(c); b: A-A, acetonide; c: see Scheme 11, 15, 17, 18 later; d: see ref. 87(b) e: see ref. 64(a)

Figure 13 GENERALIZATION OF TRANSITION STATE MODELS



(3) In the γ -alkoxy series where R_1 = OP, increasing the steric volume of R will increase the *anti*-stereoselectivity and decreasing the steric volume of R will decrease the *anti*-stereoselectivity.

(4) In the γ -ureido series where $R_1 = NP_2$, increasing the steric volume of R will decrease the *syn*-stereoselectivity, decreasing the steric volume of R will increase the *syn*-stereoselectivity.

(5) The CH_2OTPS is a more voluminous group than NHBoc and prefers the anti position.

§2-2.8 Cuprate Addition:Mechanism

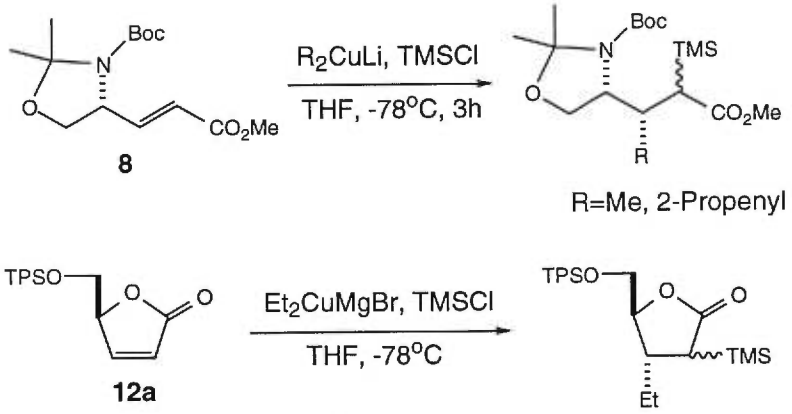
Although a lot of work has been done on the mechanism of cuprate addition, the final conclusion has not yet been reached, especially in the TMSCl-accelerated case. Since the combination of cuprate and TMSCl is a very powerful tool, the detailed mechanism deserves great attention.

In the cyclic enone cases, the coordination between the oxygen of the carbonyl and the silicon of TMSCl was proposed by Corey to interpret the accelerating effect, stereoselectivity reversal and TMS silyl enol ether formation. Lipshutz further proposed the π -complex structure **G4**, as depicted in Figure 10, whereby the TMSCl coordinates with both the oxygen of carbonyl and the lithium.

However, this proposal dose not seem to fit with our results in the cases of acyclic enoate **8** and cyclic lactone **12a** (Scheme 6). We always got C-silylated α -TMS products as coproducts. Silyl group migration from carbon to oxygen is well-known (Brook reaction), however, migration from oxygen to carbon is rare.[78] This seems to indicate the C-silylation product is originally generated and does not form from the migration of the O-silylation enolate product. On the other hand, direct silylation of the enolate usually

gives O-silylation, not C-silylation. There must exist a very favored condition for the generation of the C-silylated α -TMS product.

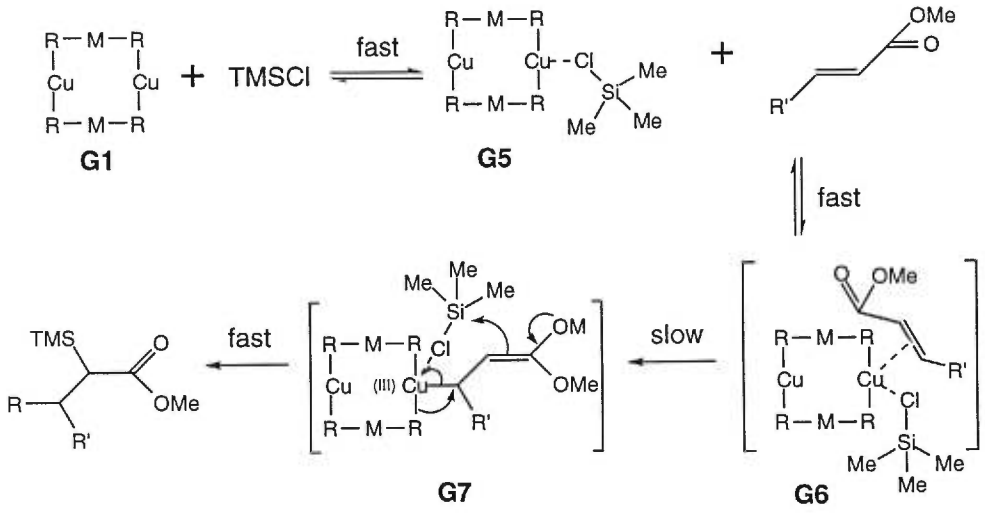
Scheme 6 MECHANISM OF CUPRATE ADDITION



Based on the new mechanism formulated by Bertz and Synder,[56c,d] we proposed the π-complex structure **G6** to account for our results (Figure 14). *TMSCl coordinates with copper directly through chlorine*, as in the new mechanism, based on several considerations. (1) Cuprate addition most likely involves a redox process Cu(I) / Cu(III) and a Cu(III) intermediate. (2) The stabilization of the β-cation is a well-known property of silicon (β-effect).[79] (3) The coordination of copper and silicon through chlorine could put copper at the β-position of silicon, thence stabilizing the Cu(III) intermediate, therefore facilitating the formation of the Cu(III) intermediate and accelerating the reaction. (4) TMSCl coordinated with copper is in proximity with the enolate carbon in **G6**. That could be the favored condition to form C-silylated α-TMS products. (5) From the kinetic point of view, the formation of the Cu(III) intermediate is the rate-controlling step. The concentration of π-complex is very high and once the Cu(III) intermediate is

formed, it collapses to product immediately. The great accelerating effect of TMSCl probably originates from TMSCl exerting direct interaction with copper at the rate-control step to stabilize and facilitate the formation of the Cu(III) intermediate.

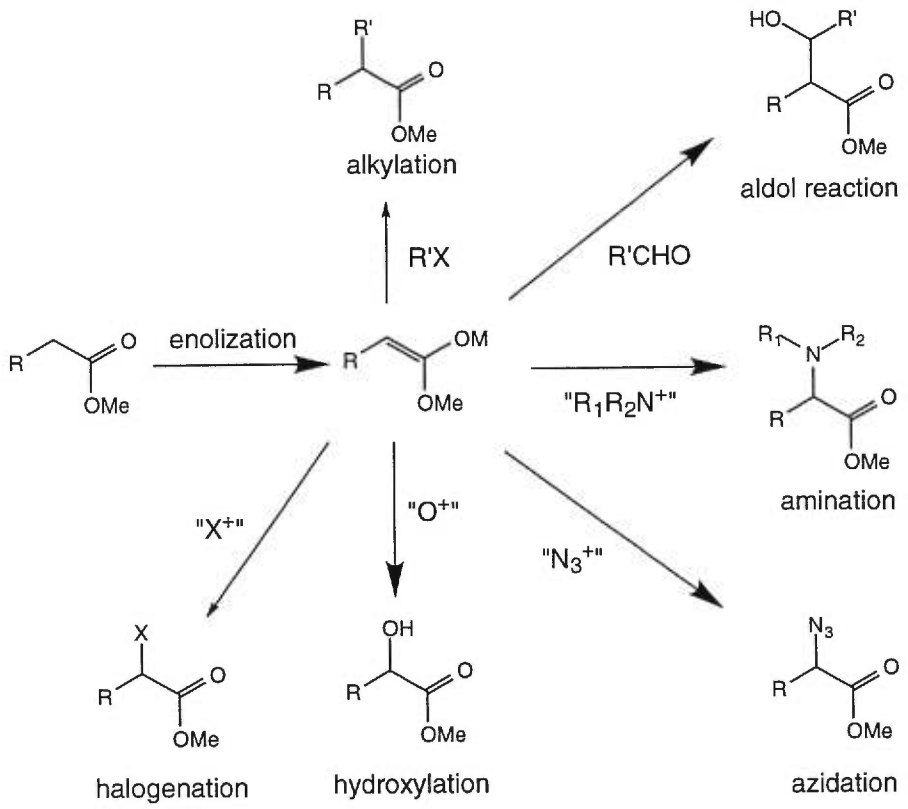
Figure 14 MECHANISM OF CUPRATE ADDITION



§2-3 Acyclic Stereocontrolled Functionalization of Enolates and the Generation of Chemical Diversity

Enolates are versatile intermediates in organic synthesis.[80] They can easily be generated from esters by deprotonation with bases and the specific configurations of enolates (*E*- or *Z*-) can be generated by employing specific conditions.[81] Alkylation and aldol reactions are two very classical and important carbon-carbon bond forming reactions and have been studied extensively.[82] The formation of carbon-oxygen and carbon-nitrogen bonds classically employs oxygen and nitrogen moieties as nucleophiles and carbon as electrophiles. The direct functionalization of enolates such as hydroxylation (Davis oxaziridine[83]), azidation (trisyl azide[84]), amination[85] and halogenation[86] (NBS, NIS) are relatively new reactions.

Figure 15 FUNCTIONALIZATION OF ENOLATES

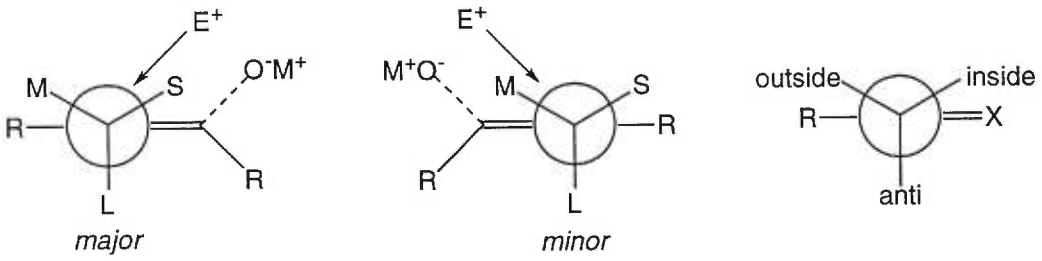


We have demonstrated the generality and feasibility of highly-stereocontrolled introduction of a variety of alkyl groups at the β-position by cuprate addition. This provided the ground work for the second part of our research objective, namely the internal-stereocontrolled functionalization of enolates.

Many studies on the stereocontrolled functionalization of enolates in cyclic systems and chiral auxiliary control cases have been documented. However, studies on the functionalization of enolates based on substrate-directed acyclic stereocontrol were rare before our initial work.[87]

Based on computational studies and with similar reasoning as the Felkin-Anh model for nucleophilic attack, Houk proposed the electrophilic rule for the transition state model of electrophilic attack. Fleming later proposed the transition state model,[88] as depicted in Figure 16, for electrophilic attack of enols, in acyclic systems, on trigonal carbons adjacent to a chiral center. This model was based on this electrophilic rule and his studies of alkylation and protonation of enols, although the stereoselectivities were poor.

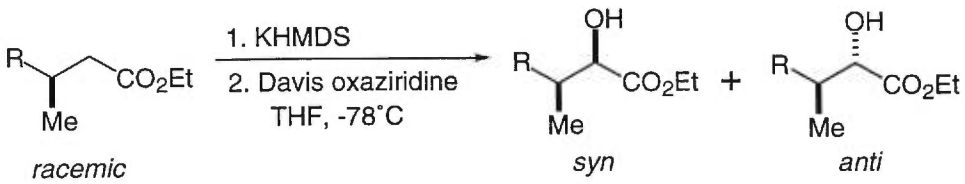
Figure 16 TRANSITION STATE MODEL FOR ELECTROPHILIC ATTACK

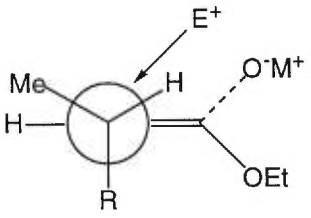


Houk-Fleming Model

Morizawa reported the highly *syn*-stereoselective hydroxylation of enolates with Davis oxaziridine. These results could be rationalized by the Houk-Fleming model of the enolate analogue (Figure 17).

Figure 17 HYDROXYLATION



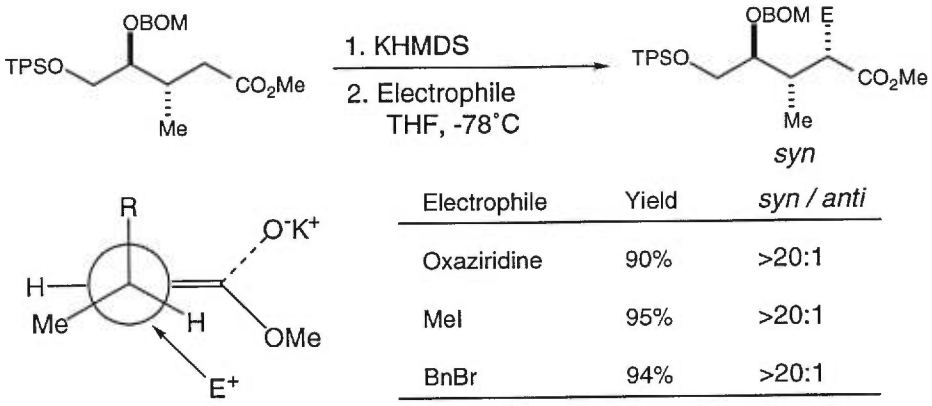


R	*syn*	*anti*
Ethyl	60	40
Phenyl	85	15
t-Butyl	95	5
CF_3	95	5

The seminal work from our laboratories also demonstrated the high *syn*-stereoselectivity (only one isomer was detected by ^{1}H and ^{13}C NMR analysis) of the alkylation and hydroxylation of enolates under optimized conditions: using KHMDS to form the enolate at -78°C in THF, and employing Davis oxaziridine, MeI and BnBr as electrophiles. The Houk-Fleming model held valid for interpreting these experimental results (Figure 18).

The superiority of KHMDS to NaHMDS and LiHMDS could result from several factors. KHMDS generates certain configurations (*E*- or *Z*-) of enolate in high purity which could affect the stereoselectivity. The aggregates of enolate[89] generated by KHMDS are in a much less chelated state than those generated by LiHMDS. This could enhance the reactivity of the enolates and the non-chelation controlled *syn*-stereoselectivity.

Figure 18 INITIAL WORK OF FUNCTIONALIZATION OF ENOLATES



Electrophile	Yield	*syn / anti*
Oxaziridine	90%	>20:1
MeI	95%	>20:1
BnBr	94%	>20:1

With this in mind, we intended to explore the generality and limitations of this process and to develop acyclic-stereocontrolled and chemically diversified methodologies to construct chemical libraries of enantiopure or enantio-enriched compounds.

§2-3.1 Azidation–Approach to Enantiopure Unnatural Amino Acids

The stereocontrolled synthesis of enantiopure unnatural amino acids has attracted great attention and effort[90] because of their importance in pharmaceutical-related research and practice such as peptidomimetics.[91]

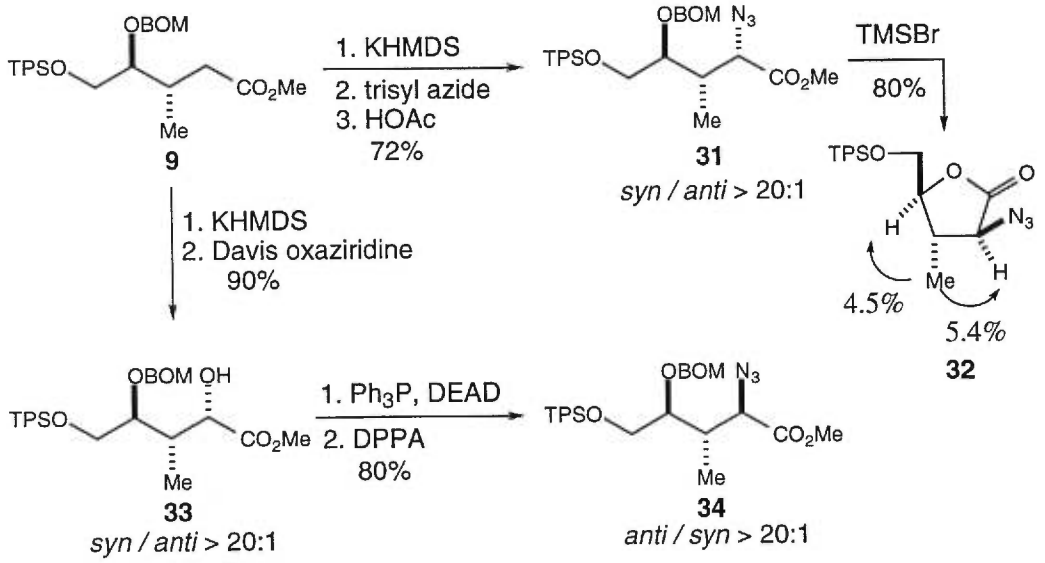
The use of the azido group as a latent amino group has some favored properties for organic synthesis. It can easily be transformed into an amino or protected amino group under mild conditions without disturbing other functionalities. It is stable under a variety of chemical transformations and performs as an ideal protected amino group. Amino groups usually have to be protected for these chemical transformations.

The conditions for direct azide transfer to an enolate were optimized by Evans.[84] The best results were obtained when KHMDS was used as the base, trisyl azide as the "N_3^+" source and acetic acid as the quench agent. Trisyl azide is a very stable solid and can be stored in the refrigerator for years without obvious detriment of quality.

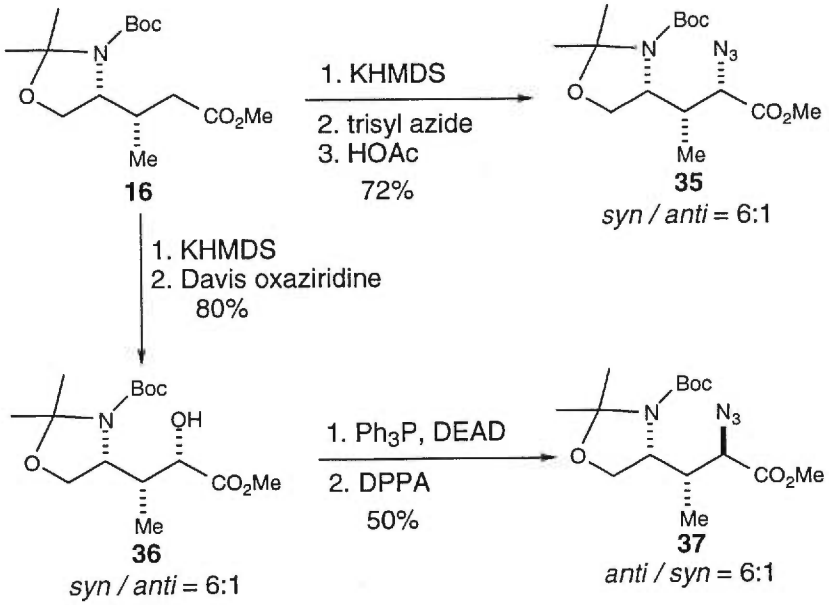
As shown in Scheme 7, the enantiopure ester **9**, obtained from acyclic stereocontrolled cuprate addition, was treated with KHMDS to form the enolate at -78°C, trisyl azide and acetic acid were then added as described in the detailed procedure. The α-azido ester **31** was obtained in enantiopure form after purification (*syn / anti* > 20:1, only one isomer was detected by ^{1}H and ^{13}C NMR analysis of the crude product). The stereochemistry was confirmed by transforming **31** to lactone **32** and carrying out NOE experimental studies.

In order to obtain the inverse α-azido ester **33**, we conceived a two step sequence as shown in Scheme 7. Hydroxylation, with Davis oxaziridine, of the enolate generated from ester **9** by KHMDS in THF at -78°C gave the enantiopure α-hydroxy ester **33** after chromatography (*syn / anti* > 20:1, only one isomer was detected by ^{1}H and ^{13}C NMR analysis of the crude product). To replace hydroxy with azido with inversion, several methods were tested unsuccessfully such as DBU-DPPA,[92] triflate-DPPA and mesylate-DPPA,[93] however, Mitsunobu conditions[76] proved excellently applicable in this case.

Scheme 7 FUNCTIONALIZATION OF ENOLATES IN γ–ALKOXY SERIES



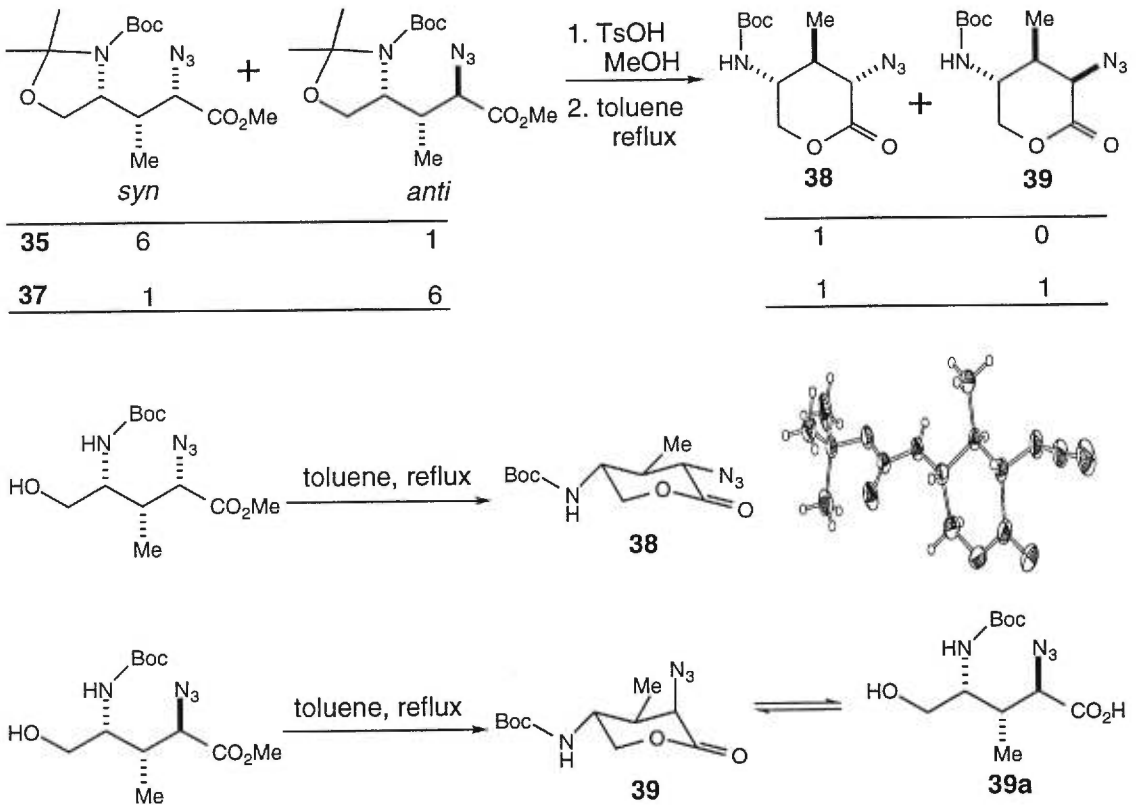
Scheme 8 FUNCTIONALIZATION OF ENOLATES IN γ–UREIDO SERIES



Treating α-hydroxy ester **33** with Ph_3P, DEAD and DPPA, under Mitsunobu conditions, afforded α-azido ester **34** in enantiopure form with 100% inversion of the α-chiral center.

The electrophilic azidation and hydroxylation processes were also applied to ester **16**, obtained in enantiopure form from acyclic stereocontrolled cuprate addition. Disappointingly the *syn*-stereoselectivity decreased (*syn / anti* = 6:1). Esters **35** and **36** represented the major isomers of the mixtures. Treatment of ester **36** (a mixture of *syn / anti* =6:1) with Ph_3P, DEAD and DPPA under Mitsunobu conditions afforded α-azido ester **37** as a mixture (*anti / syn* = 6:1), with inversion of the α-chiral center (Scheme 8).

Scheme 9 STEREOCHEMISTRY OF AZIDATION IN γ–UREIDO SERIES

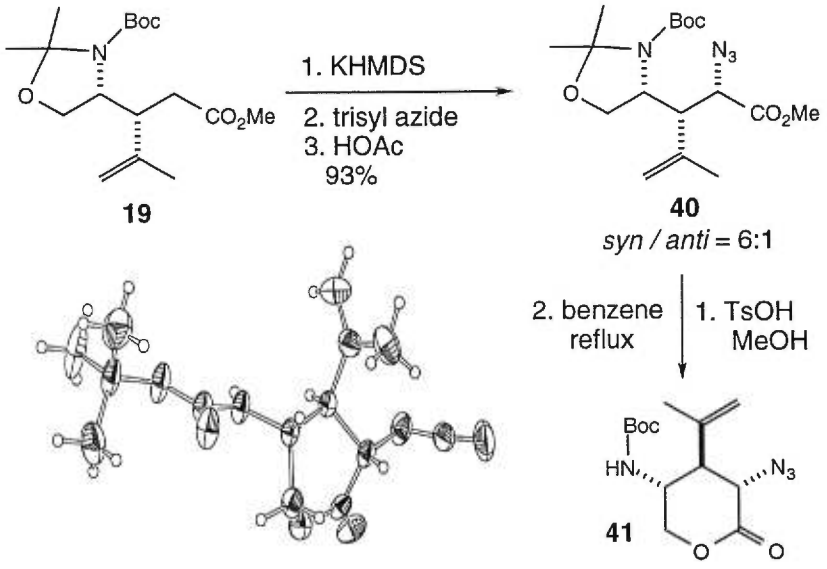


When we tried to confirm the stereochemistry of the α-azido esters, **35** and **37**, some unexpected results were obtained, as shown in Scheme 9. Transforming **35** (*syn / anti* = 6:1) to cyclic compounds, suprisingly gave only one isomer. Lactone **38** was obtained as a crystalline solid after chromatography and the stereochemistry was confirmed by X-ray diffraction analysis of a single crystal.

However, transforming **37** (*anti / syn* = 6:1) to cyclic compounds resulted in roughly a 1:1 mixture of lactones **38** and **39**. Under the reaction conditions no epimerization occurred. Lactone **39** could go through an acyclic hydroxy acid **39a** which could decompose during reaction or be lost during chromatography due to its polarity. Since all substituents are *equatorial*, lactone **38** is much more likely to exist in cyclic form than lactone **39,** which has one axial azido group.

Similarly azidation of enantiopure ester **19** afforded α-azido ester **40** as the major isomer of a mixture of *syn / anti* = 6:1. The stereochemistry was confirmed by transforming **40** to lactone **41**, which was again obtained as a crystalline solid of one single isomer, and X-ray diffraction analysis (Scheme 10).

Scheme 10 STEREOCHEMISTRY OF AZIDATION IN γ–UREIDO SERIES

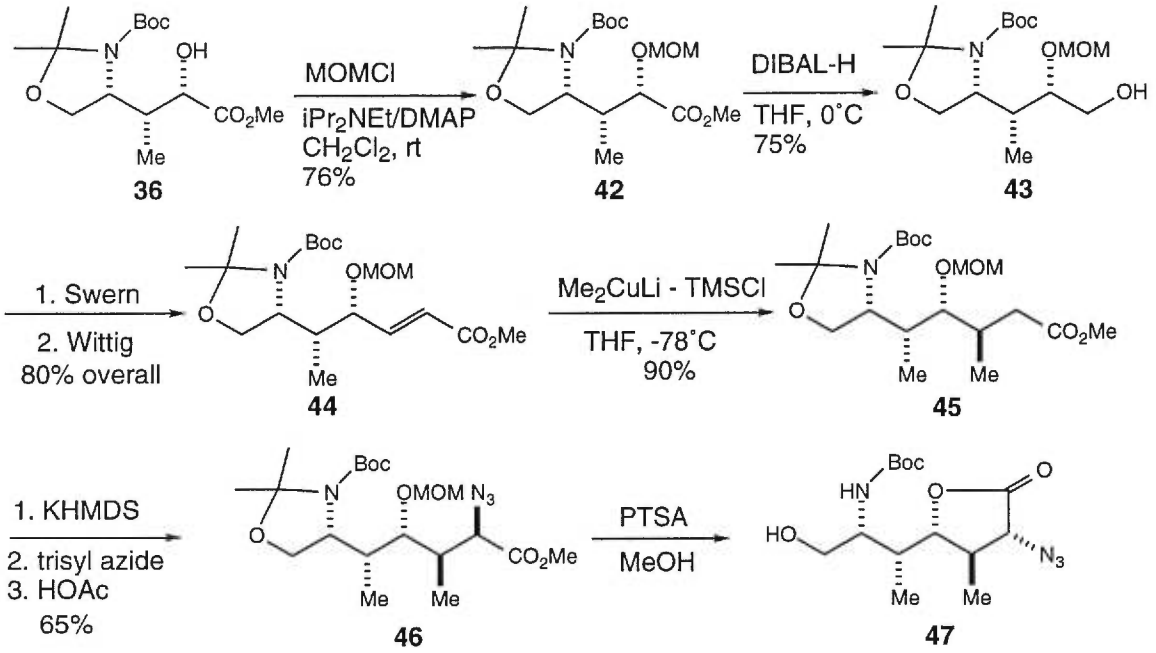


To test the feasibility of extending our acyclic-stereocontrolled methodology to an iterative process, on more complex molecules, we accomplished the sequence shown in Scheme 11.

The hydroxy group of α-hydroxy ester **36**, which was prepared by *anti*-cuprate addition (β-enantiopure) and *syn*-hydroxylation (α-, *syn / anti* = 6:1), was protected as the MOM ether. Ester **42** was subjected to DIBAL-H reduction to afford enantiopure alcohol **43** after removal of the minor epimer by chromatography. The secondary chiral template, γ-alkoxy α, β-unsaturated ester **44**, was prepared from alcohol **43** by Swern oxidation[94] and Wittig olefination.[95] We were now at the crucial point to test our methodology. The

secondary chiral template **44** is a hybrid molecule containing both nitrogen and oxygen moieties. We already knew that N-Boc group has great influence on the stereoselectivity (*syn / anti* = 6:1 comparing to alkoxy series *syn / anti* >20:1) of the hydroxylation step in a 1,3-remote fashion.

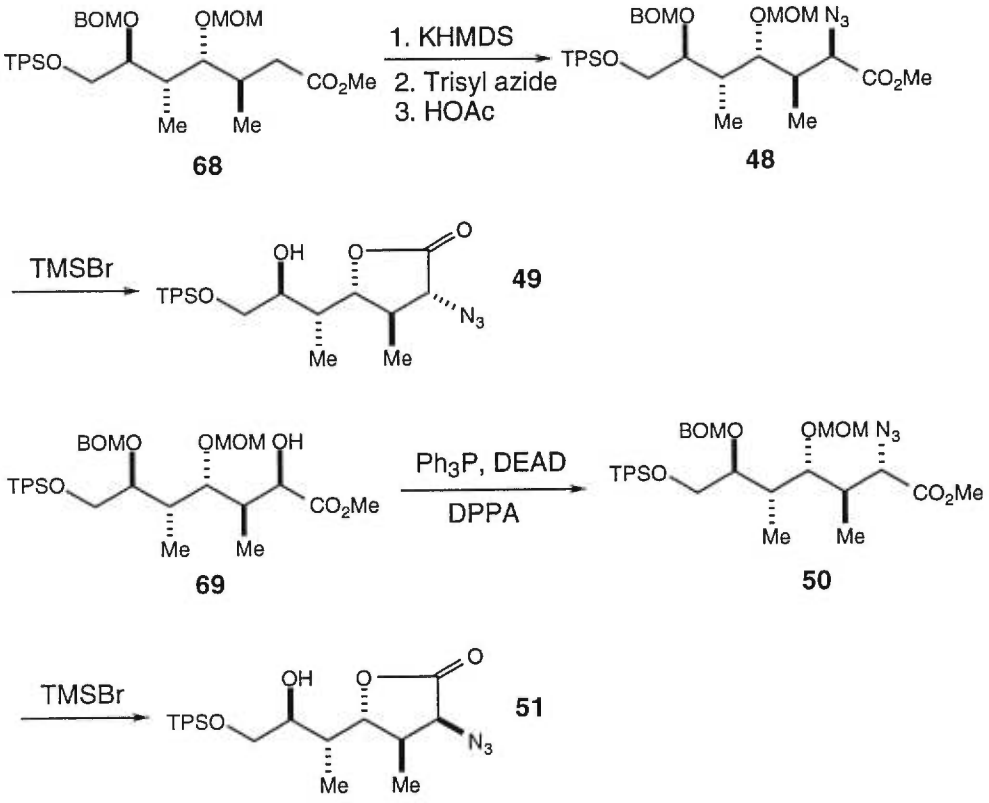
Scheme 11 ITERATIVE PROCESS OF OF AZIDATION IN γ–UREIDO SERIES



We were concerned whether the γ-alkoxy group could overcome the drawback to furnish high stereocontrol in the next cuprate addition. To our delight, when γ-alkoxy α, β-unsaturated ester **44** was subjected to cuprate addition, the γ-alkoxy group effectively directed the stereochemistry to furnish ester **45** with high *anti*-stereoselectivity (*anti / syn* > 20:1) and excellent yield. We were quite confident of high *syn*-stereoselectivity in the next step, azidation or hydroxylation. As expected, when ester **45** was subjected to electrophilic azide transfer process, α-azido ester **46** was obtained as an enantiopure

compound. α-Azido ester **46** was subsequently transformed into α-azido lactone **47**, the only isomer detectable by NMR analysis, by deprotecting the acetonide and MOM groups with PTSA in methanol. The stereochemistry was confirmed by detailed NMR analysis (see Figure 19).

Scheme 12 SECOND ROUND OF AZIDATION γ–ALKOXY SERIES

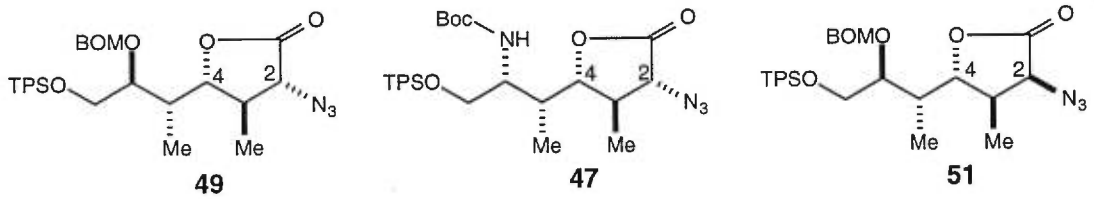


Ester **68** and α-hydroxy ester **69**, which were obtained from another iterative approach (see Chapter Three) in enantiopure form, were subjected to the azidation and Mitsunobu reaction, respectively. Both diastereomeric α-azido esters **48** and **50**, with opposite configurations at the α-chiral center, were obtained. These were transformed by TMSBr to α-azido lactones **49** and **51**, respectively. Both acyclic esters, **48** and **50**, and

both lactones, **49** and **51**, were enantiopure (only one isomer was detectable by NMR analysis in each case).

We were very confident about the stereochemistry of lactones **49** and **51**, therefore we can prove the stereochemistry of lactone **47** by comparing NMR spectra (Figure 19). ^{1}H NMR spectra of all three lactones, **47**, **49** and **51**, were very similar in terms of both chemical shift and coupling constant, except the α-proton (H2). The NMR data of the α-proton (H2) of lactone **47** were the same as that of lactone **49** and very different from that of lactone **51**. So lactone **47** must have the same stereochemistry as lactone **49**.

Figure 19 STEREOCHEMISTRY OF SECOND ROUND OF AZIDATION



49 **47** **51**

Proton	H2	H4	H2	H4	H2	H4
δ (ppm)	3.90	4.58	3.89	4.27	4.20	4.64
J (Hz)	11.2	1.4 10.3	11.0	1.6 10.0	7.4	2.3 7.9

In conclusion, we have demonstrated that highly stereocontrolled azidations can be achieved on a variety of different and complex acyclic substrates.

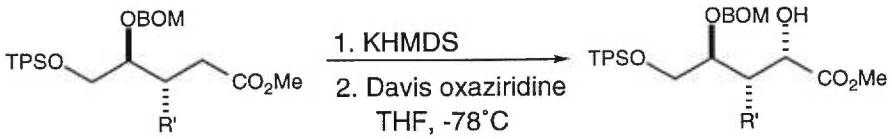
§2-3.2 Functionalization of Enolates: the Diversity

The detailed structures of the aggregates of enolates and the actual size of the substituents, which determine the reactivity and stereoselectivity, are very complex issues. A lot of work has been done and many principles and guidelines formulated,[89] however, accurate predictions are still difficult to make.

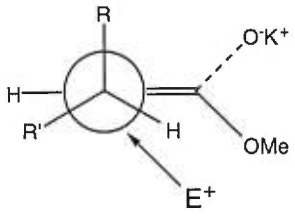
(A) Hydroxylation

The highly stereocontrolled hydroxylation of the β-methyl-γ-alkoxy enolate was achieved earlier. However, when we extended this procedure to the higher analogue, the *syn*-stereoselectivity disappointingly dropped dramatically. The results are summarized in Scheme 13. Enantiopure esters **10**, **11** and **12** were subjected to hydroxylation reactions to afford the corresponding α-hydroxy esters. The *syn*-stereoselectivities were obtained as 3:1, 4:1 and 3:1, respectively, although the yields were still good. Interestingly, hydroxylation of lactone **13** gave roughly a 1:1 mixture of *trans*- and *cis*-isomers. This revealed that stereocontrol in acyclic systems overrides the stereocontrol in cyclic systems. This is also true for the cases of cuprate addition (see **§2-2.5**), although the sense of stereoselectivity is much more predictable in cyclic systems. From these results we can also see that the stereoselectivity of hydroxylation is very sensitive to the steric change of R' (R' = Me, *syn* / *anti* > 20:1).

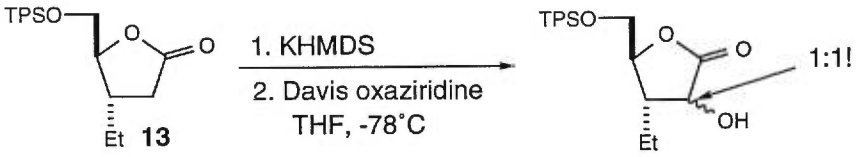
Scheme 13 HYDROXYLATION OF HIGHER ANALOGUES



10, Ethyl; **11**, Vinyl;
12, 2-propenyl



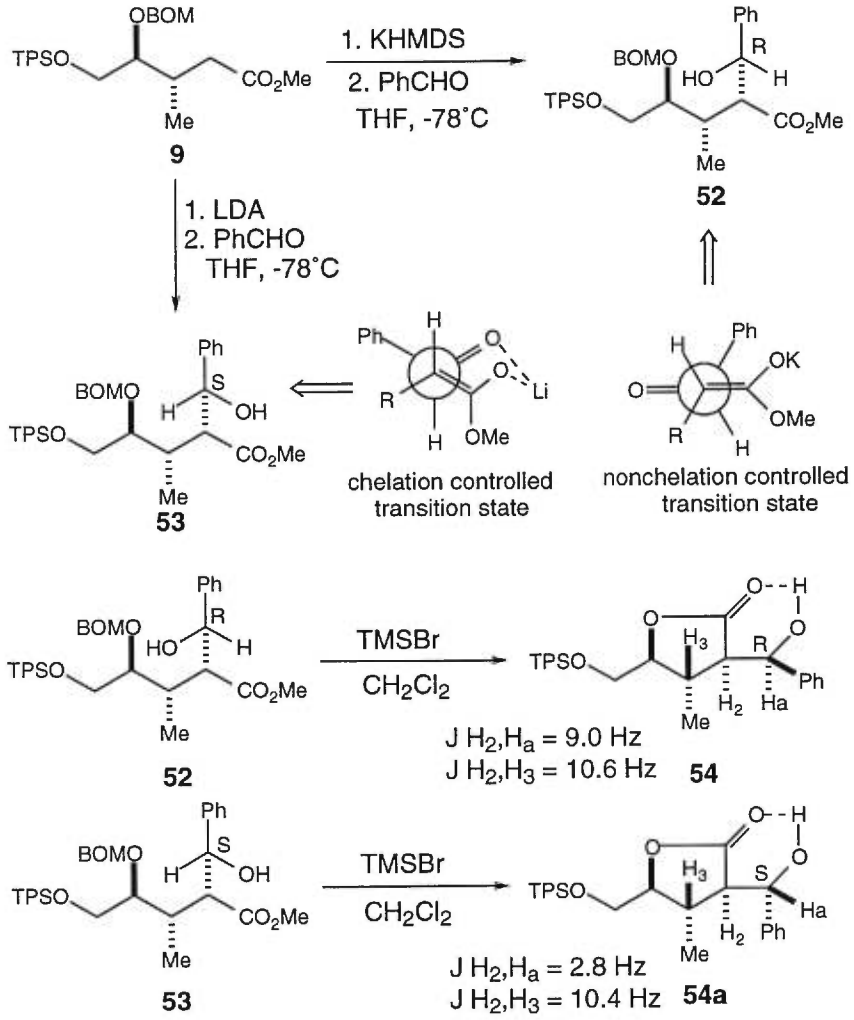
R'	Yield	*Syn/Anti*
Ethyl	70%	3:1
Vinyl	80%	4:1
Isopropenyl		3:1



(B) Aldol Reaction

The aldol reaction is one of the most important and extensively studied reactions in asymmetric synthesis.[96] It can generate one carbon-carbon bond and two stereogenic centers in one step.

Scheme 14 ALDOL REACTION



Our results are depicted in Scheme 14. Although the diastereofacial and enantio selectivities were not very high, the results were still quite interesting. Ester **9** was first treated with KHMDS in THF at -78°C to form enolate and then with benzaldehyde (2 equivalents). An enantiopure isomer **52** was isolated in 60% yield from a crude mixture

of three NMR detectable diastereomers (6:1:1.5). Interestingly, when LDA was used as the base instead of KHMDS, the enantioselectivity was reversed. An enantiopure isomer **53** was isolated in 60% yield from a crude mixture of three NMR detectable diastereomers (1:6:1.5). The *syn*-diastereofacial selectivities should have remained in both cases, as discussed in **§2-3.1** for functionalization of enolates.

The enantioselectivities were putatively assigned as (*R*)-**52** and (*S*)-**53**, as shown in Scheme 14, based on the nonchelation-controlled transition state for KHMDS and the chelation-controlled transition state for LDA. The diastereofacial selectivity was about 5:1 and the enantioselectivity about 6:1, in both cases.

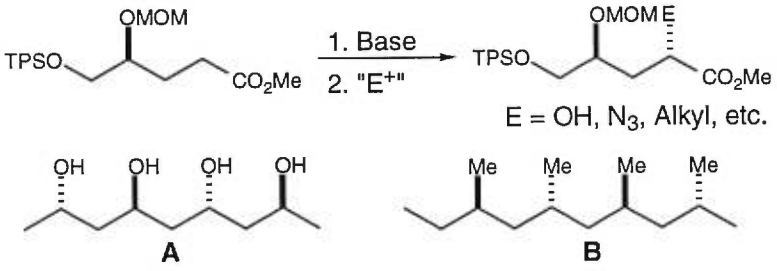
The *syn*-diastereofacial selectivity was confirmed by transforming both **52** and **53** into lactones (*R*)-**54** ($J_{H2,H3}$ = 10.6 Hz) and (*S*)-**54a** ($J_{H2,H3}$ = 10.4 Hz), respectively. The enantioselectivities were also supported by detailed NMR studies of lactones (*R*)-**54** and (*S*)-**54a**. If we assume that there exists hydrogen bonding between the carbonyl and the free hydroxy, we would expect the coupling constant for $J_{H2,Ha}$ of (*R*)-**54** to be much larger than that of (*S*)-**54a**, since the dihedral angle is near zero ($\Psi_{H2,Ha} \sim 0^\circ$) for (*R*)-**54** while $\Psi_{H2,Ha} \sim 90^\circ$ in (*S*)-**54a**. NMR experiments gave positive results, as $J_{H2,Ha}$ of (*R*)-**54** = 9.0 Hz and $J_{H2,Ha}$ of (*S*)-**54a** = 2.8 Hz.

When we tried to enhance the chelation control by adding $ZnBr_2$ to the enolate generated by KHMDS, the selectivity dropped to 1:1.8:1. We also tried to increase the conversion by employing 5 equivalents of benzaldehyde. Indeed, the yield was increased to 85%. The crude product was shown as a mixture with a ratio of 4:4:1 by ^1H NMR. The diastereofacial selectivity remained, however, *the enantioselectivity disappeared completely!*

(C): 1,3-Asymmetric Induction in Acyclic Systems

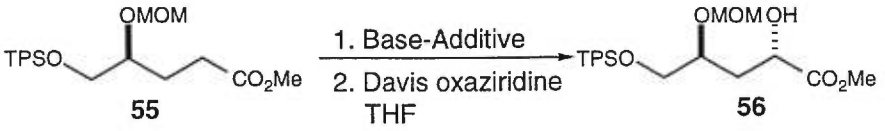
Enantiopure 1,3-skipped functionalities such as motifs **A** and **B**, shown in Figure 20, widely exist in natural products with interesting biological activities such as polyenes.[97] It is of great interest to develop acyclic-stereocontrolled methodologies to address the synthesis of such motifs.

Figure 20 1,3-ASYMMETRIC INDUCTION

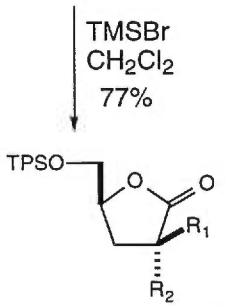


Our primary results are summarized in Table 5. Compound **55** was prepared by protecting the hydroxy group of compound **3** as the MOM ether yielding **55a**, and hydrogenating the olefin. The stereoselectivity was proved by transforming an acyclic mixture to a mixture of separable lactones, **57** and **57a.** The stereoselectivity proved to be low. It seemed difficult to improve by just changing base and temperature. It appears that the γ-directing groups have only a small effect on selectivity (γ-OMOM versus γ-OTPS, both the electronic and steric effects were changed).

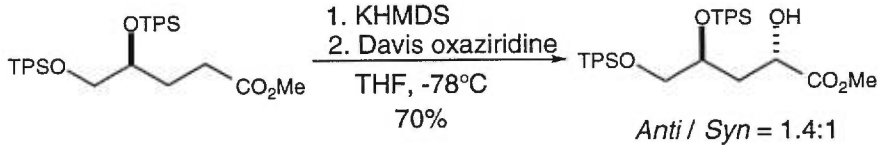
Table 5 1,3-ASYMMETRIC INDUCTION



Exp	Base-Additive	Temp.	Yield	*anti / syn*
1	KHMDS	-78°C	70%	3:1
2	LDA	-78°C	35%	1.5:1
3	KHMDS	-100°C	78%	1.5:1
4	KHMDS	-20°C	29%	3.5:1
5	KHMDS-$TiCl_4$	-78°C	DEC	
6	KHMDS-$ZnCl_2$	-78°C to 0°C	NR	
7	KHMDS	-48°C	39%	4:1



57 R_1=OH, R_2=H
57a R_1=H, R_2=OH

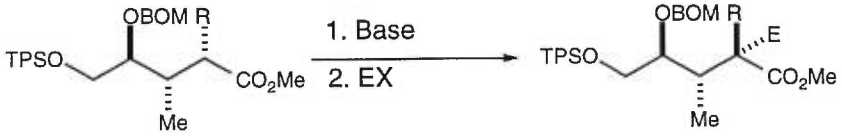


Anti / Syn = 1.4:1

(D): Quaternary Carbon Centers

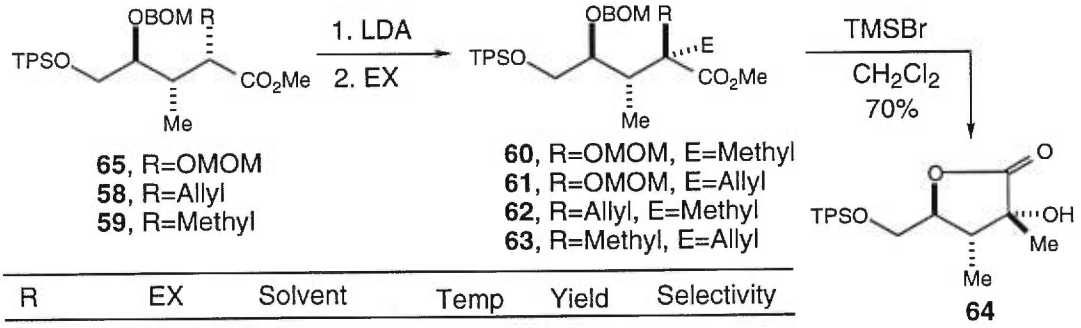
The construction of enantiopure quaternary carbon stereocenters, carbon centers with four different non-hydrogen substituents (tertiary alcohols, tertiary amines and all carbon quaternary centers), is a very challenging problem in natural product synthesis and drug design.[98] Great attention and effort have been paid and yielded many methodologies addressing one or two chiral center motifs. However, the creation of an enantiopure quaternary carbon center in a consecutive multi-chiral center motif is still a very demanding task. We intended to develop a flexible methodology by exploiting acyclic-stereocontrolled functionalization of enolates to address the construction of enantiopure quaternary carbon centers of consecutive multi-chiral center motifs as shown in Figure 21.

Figure 21 QUATERNARY CARBON STEREOCENTERS



R = OP, N_3, Alkyl, etc. E = OH, N_3, Alkyl, etc.

Table 6 QUATERNARY CARBON STEREOCENTERS



65, R=OMOM
58, R=Allyl
59, R=Methyl

60, R=OMOM, E=Methyl
61, R=OMOM, E=Allyl
62, R=Allyl, E=Methyl
63, R=Methyl, E=Allyl

64

R	EX	Solvent	Temp	Yield	Selectivity
OMOM	MeI	THF	-78°C	NR	*syn / anti*
OMOM	MeI	THF-HMPA (10eq)	-78°C	17%	8:1
OMOM	MeI	THF-HMPA (4:1)	-78°C	20%	8:1
OMOM	MeI	DME	-48°C	41%	8:1
OMOM	BnBr	DME	-48°C	NR	
OMOM	Allyl-I	DME	-5°C	63%	6:1
Allyl	MeI	DME	-5°C		5:1
Methyl	Allyl-I	DME	-5°C	83%	15:1

Our results are summarized in Table 6. α-MOM ether ester **65** was prepared by protecting the hydroxy group of compound **33** as the MOM ether (see Scheme 15). α-Allyl ester **58** and α-methyl ester **59** were prepared by alkylation of enolates generated by KHMDS from compound **9** with allyl iodide and methyl iodide, respectively. KHMDS

was not a suitable base for generating substituted enolates and commercial LDA was used as the base in all the reactions.

From Table 6 we can see that the reactivity of the enolate generated from **65** was very low at -78°C, in THF or in THF-HMPA. Using DME as the solvent at -48°C, the enolate generated from **65** reacted with MeI to afford compound **60** in 41% yield as an enantiopure product after purification (*syn / anti* = 8:1 by NMR analysis of the crude product). The stereochemistry was confirmed by transforming **60** into lactone **64** and comparing with a known compound.[99] However, the enolate reactivity was still not high enough to react with benzyl bromide under these conditions. The enolate generated from **65** at -5°C in DME reacted with allyl iodide to afford compound **61** in 63% yield (*syn / anti* = 6:1). Similarly, the enolate generated from allyl ester **58** reacted with methyl iodide to afford **62** (*syn /anti* = 5:1).

*Remarkably, when α-methyl ester **59** was subjected to the same conditions, compound **62** was obtained with excellent stereoselectivity (syn / anti >15:1 by NMR analysis) and yield (83%).* This can be rationalized with Houk-Fleming model shown in Figure 16.

§2-4: Summary and Perspectives

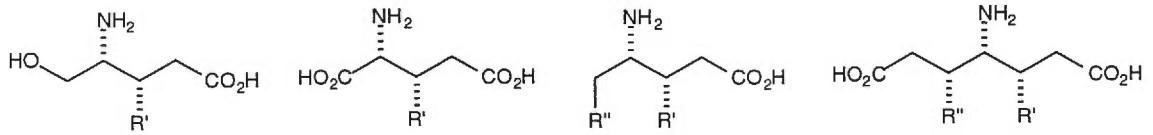
We have demonstrated the high stereoselectivity of cuprate-conjugate addition with a variety of alkyl groups, giving *anti*-selectivity in the γ-alkoxy series and *syn*-selectivity in the γ-ureido series. We also demonstrated high *syn*-stereoselectivity of functionalization of enolates in the γ-alkoxy series and moderate *syn*-stereoselectivity in the γ-ureido series. Combining these two stereocontrolled reactions, we have developed an acyclic-stereocontrolled methodology to address the synthesis of enantiopure or enantioenriched consecutive multi-chiral center units. We also proved this methodology

could be extended to an iterative process. The high stereoselectivity was retented on more complex molecules. After two rounds of cuprate addition and hydroxylation or azidation, an enantiopure five consecutive chiral center motif was obtained.

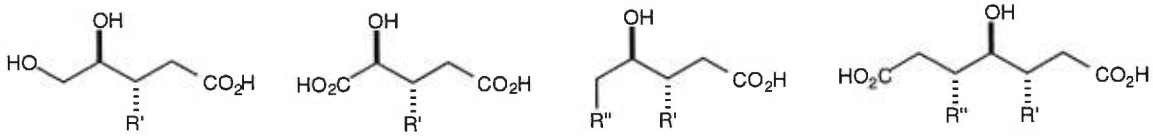
Employing our acyclic-stereocontrolled methodology, the combination of cuprate addition, hydroxylation, azidation, and Mitsunobu inversion, we could easily generate a large chemical diversity of enantiopure compounds with differentiable functionalities. These enantiopure compounds could be used as building blocks in peptidomimetics and combinatorial library construction. It is of special interest to use these molecules to build the combinatorial libraries of polypropionates, polyamino alcohols, and sugar-like molecules. Here are just a few examples shown in Figure 22.

Figure 22 ENANTIOPURE BUILDING BLOCKS

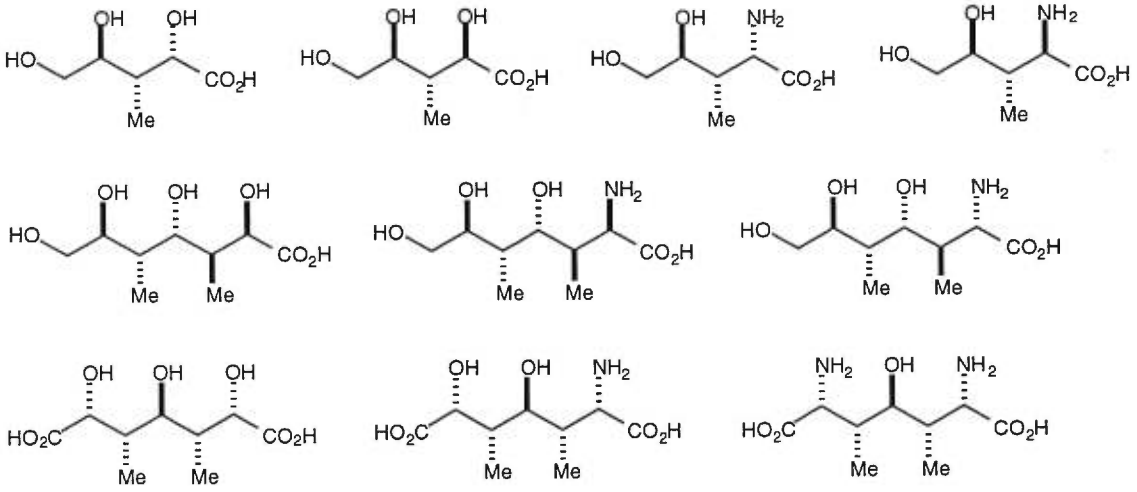
β-Substituted γ-amino acids



β-Substituted γ-hydroxy acids



Multi-chiral center motifs



CHAPTER THREE

Synthesis of Polypropionate Subunits of Natural Products

The polyketide pathway is a very important metabolic pathway in organisms.[100] It is responsible for the biosynthesis of many antibiotics, including macrolides, ansamycins, polyether ionophores, tetracyclines and polyenes. A huge number of these have been identified as having physiological activities. To date, however, only a few have found successful application in medicine, such as erythromycins, rifamycins, monensin, tetracyclines, FK506 and polyenes. Finding a drug out of these antibiotics is a great motivation for research.[101]

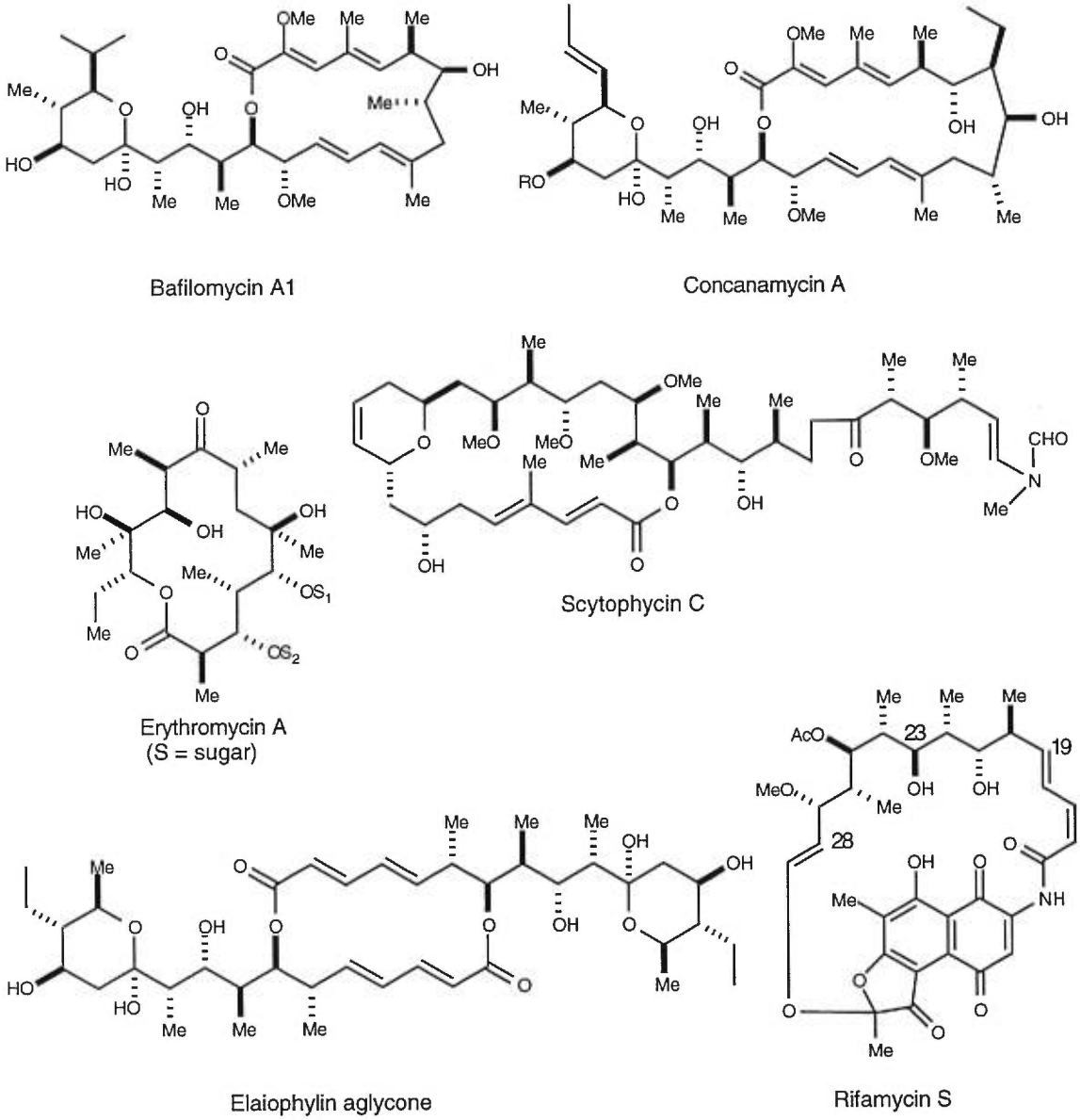
Polypropionates widely exist in the natural antibiotics of macrolides, ansamycins, polyether ionophores and polyenes. Because of their great importance in a basic understanding of biosynthesis and gene manipulation as well as commercial applications as medications, great attention and effort have been directed to the studies of polypropionate biosynthesis,[102] biogenetically combinatorial library construction,[103] chemical synthesis,[104] chemical modification and chemically combinatorial library construction.[105] Figure 23 shows just a few examples of macrolides, along with rifamycin S.[106]

§3-1 Polypropionates: Background of Chemical Synthesis

The plethora of chiral centers and the macrosize ring are the common structural features of polypropionate related compounds. In fact, these features have challenged synthetic organic chemists for several decades. The stereocontrolled construction of the consecutive multi-chiral centers of polypropionates, such as erythromycin A, was considered a hopeless task in 1956[107] by Woodward, the master of organic synthesis. The numerous chiral centers would result in a large number of different diastereomers having different chiralities, therefore different conformations and biological activities. It is

impractical to obtain one enantiopure isomer from a large number of diastereomers, even in an academic laboratory. Stereocontrol is the most

Figure 23 MACROLIDE AND ANSA ANTIBIOTICS

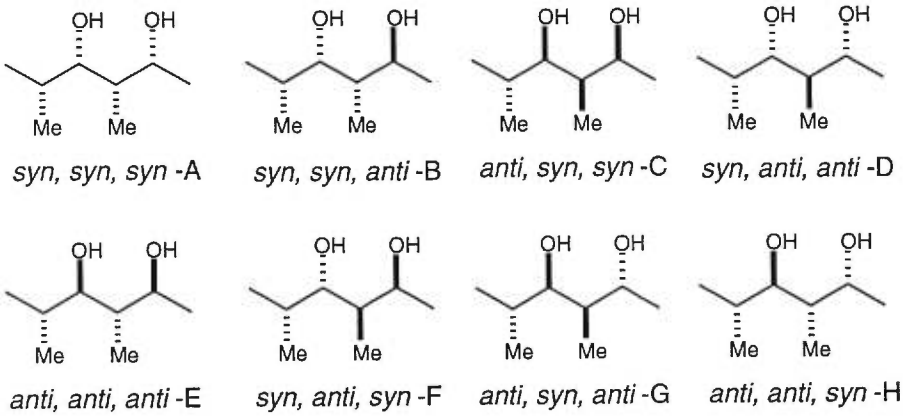


important issue in the chemical synthesis of polypropionates. In the last two decades or so, many stereocontrolled methodologies have been developed to address polypropionate

synthesis.[108] As result, many elegant total syntheses of macrolides and ansamycins have been achieved. On the other hand, every methodology has both advantages and limitations. The demand for highly stereocontrolled, efficient, predictable and operationally simple methodologies is very high. Furthermore, the recent rise of the chiral technology industry has made it even higher.

Polypropionate is an acyclic chain of consecutive multi-chiral centers which accommodate an alternating methyl-hydroxy-methyl-hydroxy pattern. In practice, all the stereochemical problems of stereocontrolled synthesis of polypropionates can be reduced to the stereochemical problems of tetrads, which contain four chiral centers. Eight tetrads, shown in Figure 24, can be conceived from the different combinations of four chiral centers (only relative stereochemistry was considered in the context of *anti-* and *syn-* notations).

Figure 24 POLYPROPIONATES - TETRADS



An ideal methodology would be one which can easily access all these tetrads, be performed in an iterative way to address longer chain synthesis, retain the high stereoselectivity in all rounds without modifications, be predictable in the outcome of stereochemistry at all stages, and be efficient and operationally simple.

Since an enormous body of studies have been documented, we can only summarize a few leading general methodologies (Figure 25).

(A): Aldol Approach[109]

The aldol reaction is probably the most efficient way to construct the polypropionate chain, since it can generate one carbon-carbon bond and two stereogenic centers in one step. As a direct result, the aldol reaction is the most extensively studied and used reaction in the synthesis of polypropionates. In the general frame of the aldol reaction, a large number of different versions have been developed. The stereochemistry could be controlled by a chiral substrate, auxiliary, reagent, or catalyst and by double induction. The aldol approach is very versatile, since the stereoselectivity can be altered by changing the configuration of the enolates (*E*- or *Z*-) and the transition states (chelation control or nonchelation control). However, these can make it more difficult to predict the stereochemistry. Furthermore, the already existing chiral centers could interfere with the stereocontrol of later stages. Chirality matching could be critical for the stereoselectivity of the second round or later.

(B) Cyclic Stereocontrol-Based Approach

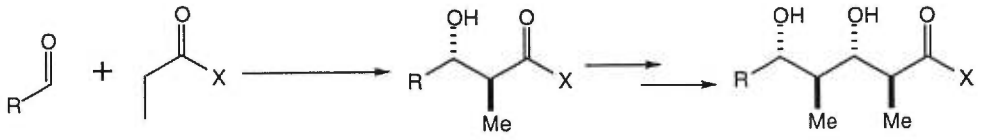
Cyclic stereocontrol is a classical and well-established strategy. Exploiting cyclic stereocontrol to solve the polypropionate synthesis problems has been exemplified by Corey, in his erythrolide synthesis,[110] and by Woodward, in his erythromycin A synthesis.[111] They elegantly demonstrated how to manipulate the stereochemistry and functionality in cyclic systems to achieve a long enantiopure polypropionate chain. Several other methodologies, based on manipulation of stereochemistry and functionality of cyclic systems, have been reported.[112]

(C) Epoxidation & Ring-Opening Approach

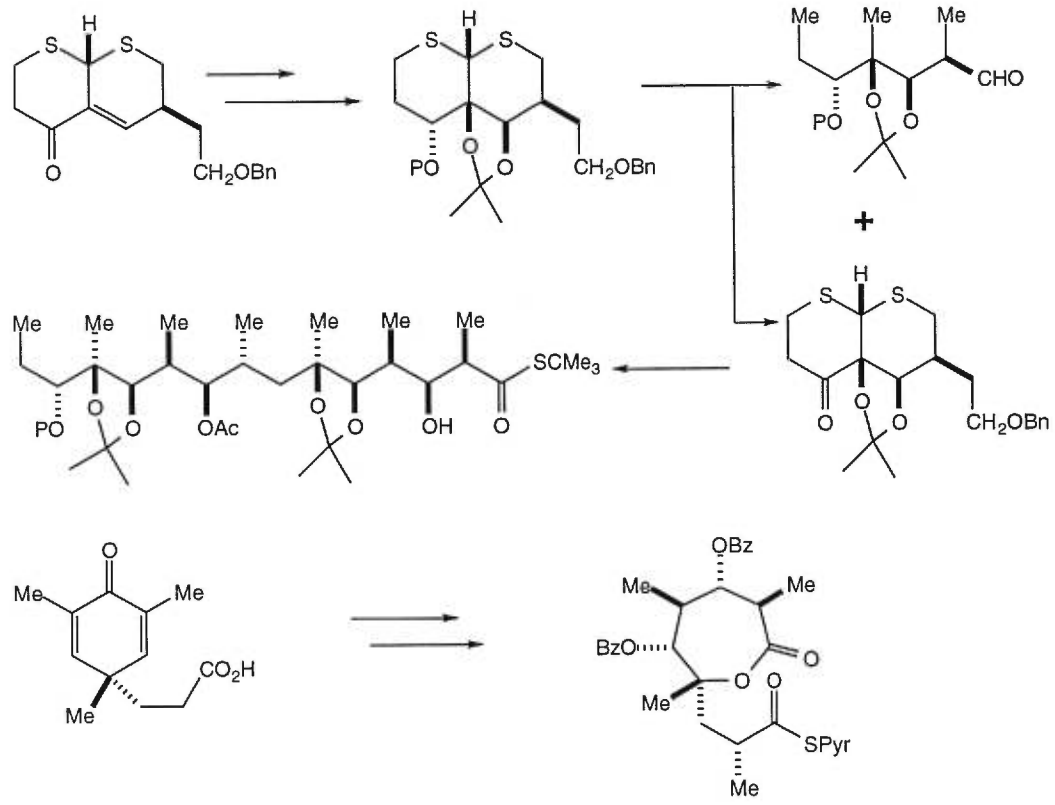
This approach consists of two stereocontrolled steps, stereocontrolled epoxidation and stereocontrolled opening of the epoxide with "Me⁻". Stereocontrolled epoxidation can be achieved by using catalytic asymmetric epoxidation[113] (Sharpless, Jacobsen, etc.)

Figure 25 GENERAL APPROACHES TO THE POLYPROPIONATES

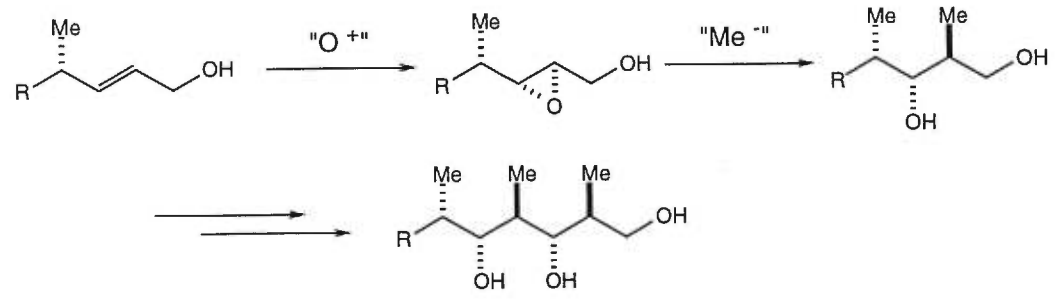
A: The Aldol Approach



B: The Cyclic Stereocontrol-Based Approach



C: Epoxidation and Ring Opening Approach



or substrate-directed asymmetric epoxidation.[114] The resulting enantiopure epoxides can be opened using Me_2CuLi,[115] Me_3Al,[116] etc.

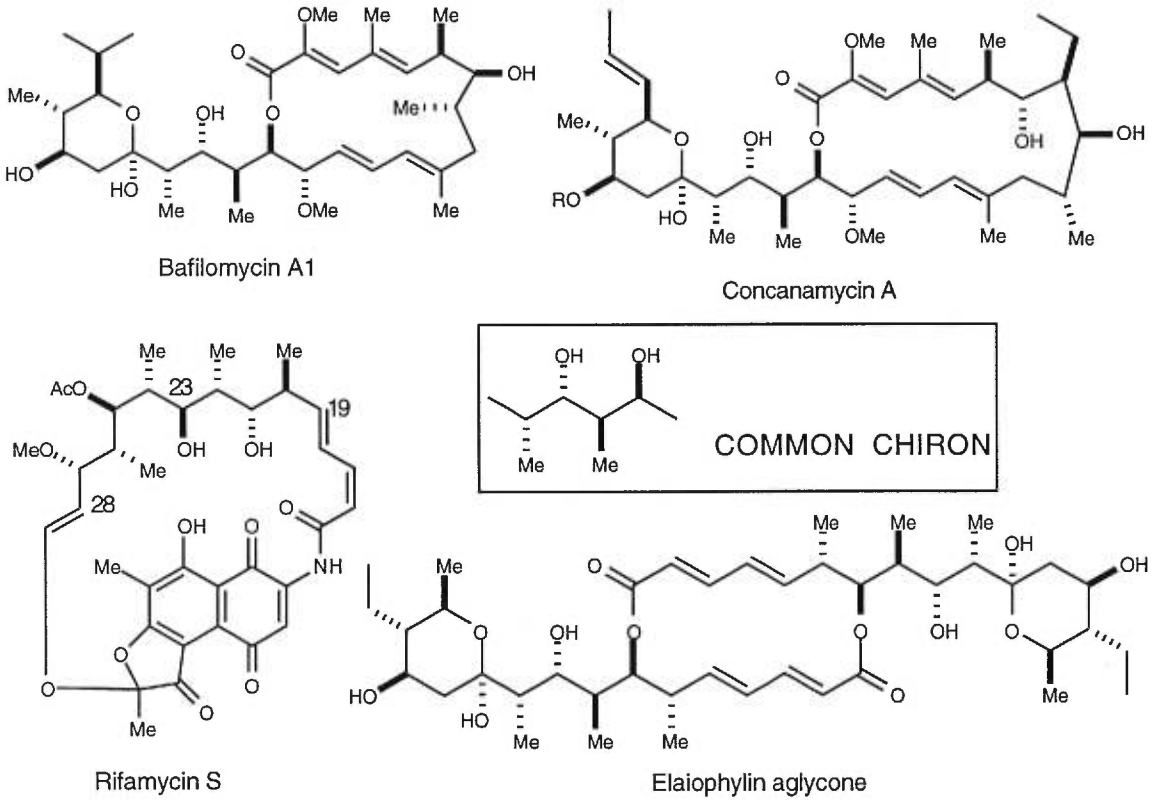
(D) Sugar-Based Approach[23]

Exploiting the plethora of combinations of chirality and functionality of sugars and their conformation bias is also a option. Manipulation of the stereochemistry and functionalities of already existing long carbon chains could afford enantiopure polypropionate chains.

§3-2 Polypropionate Synthesis: the Chiron Approach[23]

The Chiron (chiral synthon) approach is our basic philosophy. It pays special attention to the stereochemical pattern of target molecules and recognizes a variety of chirons. The chiron approach is guided by stereochemistry and provides more freedom for strategy design. We could easily identify polypropionates as chirons in the macrolide and ansa antibiotics shown in Figure 23. We could also easily recognize the common stereochemical pattern of these polypropionates (except for erythromycin A) as the *syn, anti, syn*-tetrad, referred to as the common chiron in Figure 26. This common chiron can easily be identified from many families of macrolide and ansa antibiotics such as rifamycins, bafilomycins, swinholides, misakinolides, scytophycins, aplyronines, etc., and a few examples are shown in Figure 26. The common precursor strategy[23] could greatly facilitate the family synthesis.

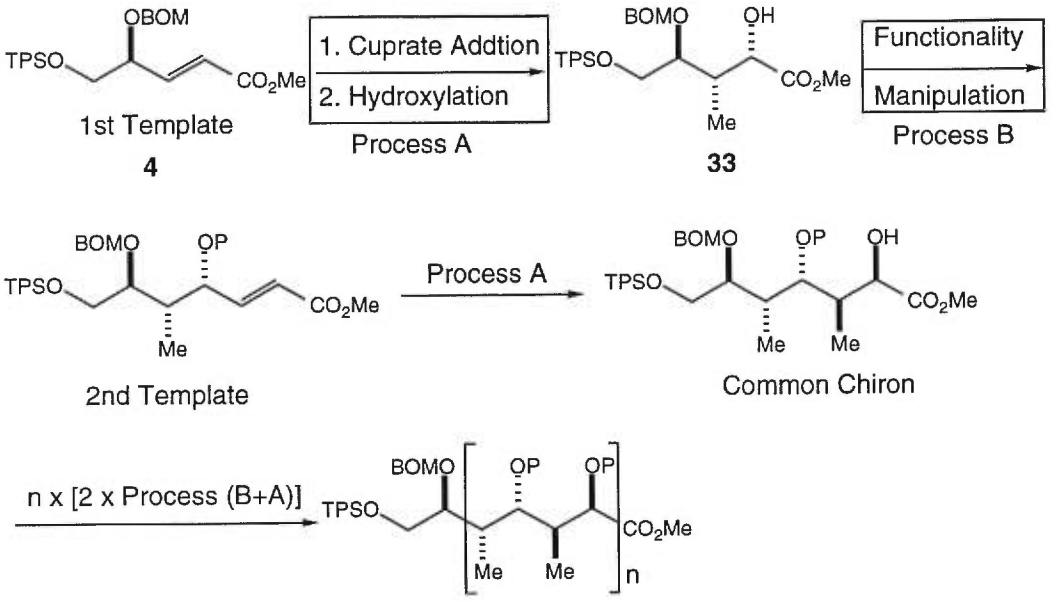
Figure 26 COMMON CHIRON FOR MACROLIDE AND ANSA ANTIBIOTICS



§3-3 New Methodology Based on Acyclic Stereocontrol

We have demonstrated the high stereoselectivities of cuprate-conjugate addition and hydroxylation of enolates. Combining these two highly stereocontrolled reactions, we could envision a novel iterative methodology based on acyclic stereocontrol to address polypropionate synthesis (Figure 27). By treating the 1st template **4** with highly stereocontrolled cuprate addition and hydroxylation (process A), we could obtain enantiopure intermediate **33**, as demonstrated earlier. Manipulation of the functionalities of **33** (process B) could result in the synthesis of the 2nd template. Application of process A on the 2nd template, if high stereoselectivity was retained, would result in a derivative of the common chiron mentioned before. In principle we could repeat processes B and A to achieve longer polypropionate chains.

Figure 27 NEW ITERATIVE METHODOLOGY FOR SYNTHESIS OF POLYPROPIONATES



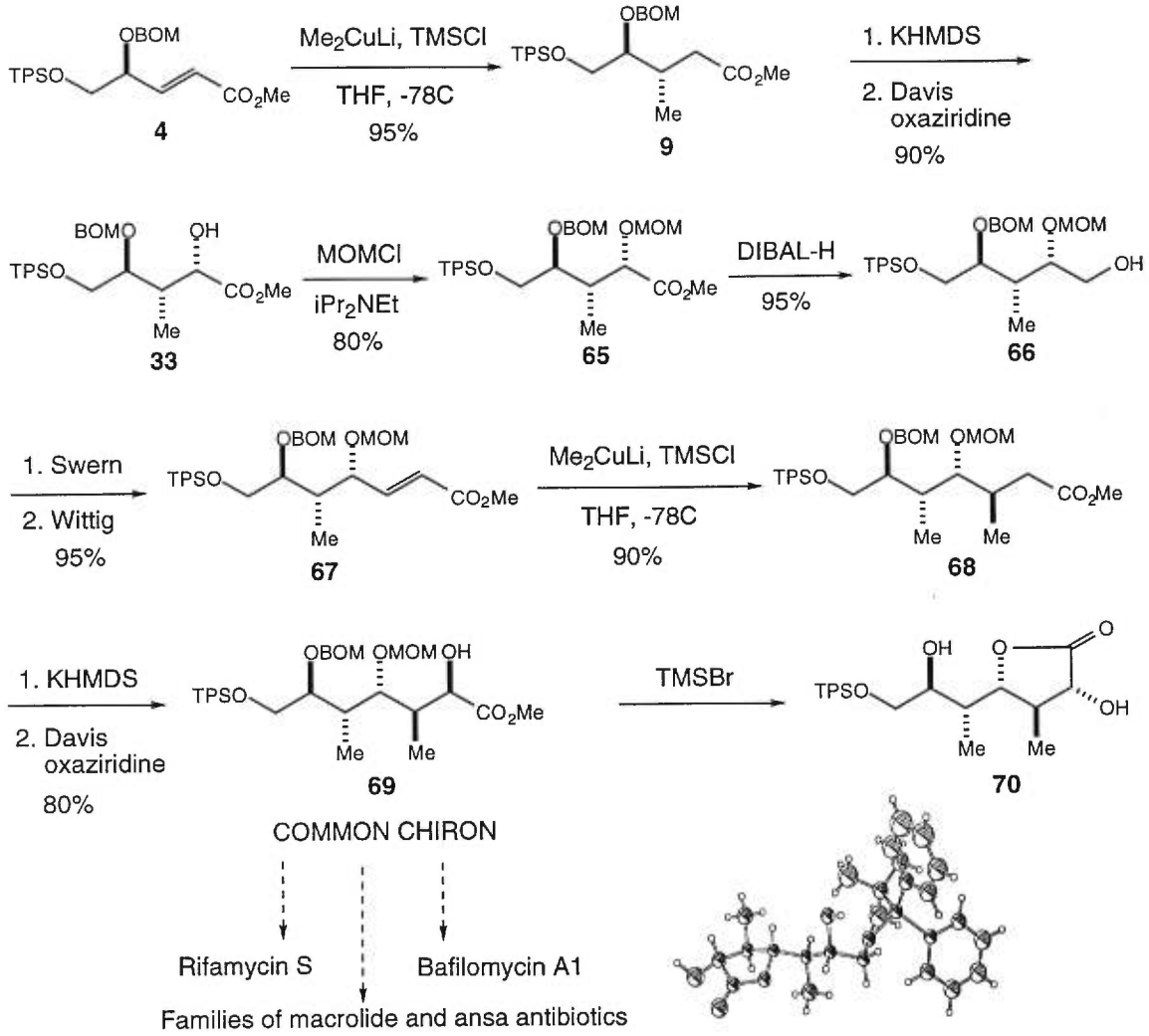
§3-4 Synthesis of the Common Chiron

As demonstrated by the initial work from our laboratories,[117] the highly stereocontrolled process A could be successfully applied to the 2nd template, in an iterative way, to reach the common chiron **69** (Scheme 15).

Starting from the 1st template **4** which could be prepared in large quantity on 100 mmol scale from D-mannitol, we could introduce the *anti*-methyl group in a highly stereocontrolled fashion by cuprate addition. Hydroxylation, with Davis oxaziridine, of the enolate generated from **9** by KHMDS afforded enantiopure compound **33** with high *syn*-stereoselectivity. Now, we simply needed to manipulate functionalities to reach the 2nd template **67**. Protection of the hydroxyl group to give the MOM ether **65**, reduction of the ester to afford alcohol **66**, followed by Swern oxidation and Wittig olefination, yielded the 2nd template **67** with high efficiency. To the 2nd template we applied stereocontrolled process A, introduction of an *anti*-methyl group and *syn*-hydroxy group, to give compound **68** and the common chiron **69**, respectively. This common chiron could be used as a precursor for the syntheses of many of the families of macrolide and

ansa antibiotics mentioned before. The stereochemistry of common chiron **69** was unequivocally confirmed by X-ray diffraction analysis of crystalline lactone **70** (Scheme 15).

Scheme 15 SYNTHESIS OF COMMON CHIRON



§3-5 Rifamycin S: the Longest Polypropionate Chain

The rifamycins are a family of ansamycin antibiotics which derive their name from the common structural features of a flat aromatic nucleus and a long aliphatic chain, shaped like a handle, joining two nonadjacent positions of the nucleus.[118] Rifamycins are

active against a large variety of organisms, bacteria, eukaryotes and viruses. Rifampicin, one derivative of the rifamycins, is one of only a few successful drugs for the treatment of tuberculosis. They exert their activity by the specific inhibition of bacterial DNA-dependent RNA polymerase. Structure and activity relationship studies have shown that the specific functionality pattern and conformation are critical for activity. Modification of the ansa chain of rifamycins resulted in the loss of activity. Specific bonding of the ansa chain to the β-sheet of the polymerase was proposed as a model to account for these results.[119] As illustrated, the stereochemistry and functionality pattern of the polypropionate chains are extremely important for biological activities.

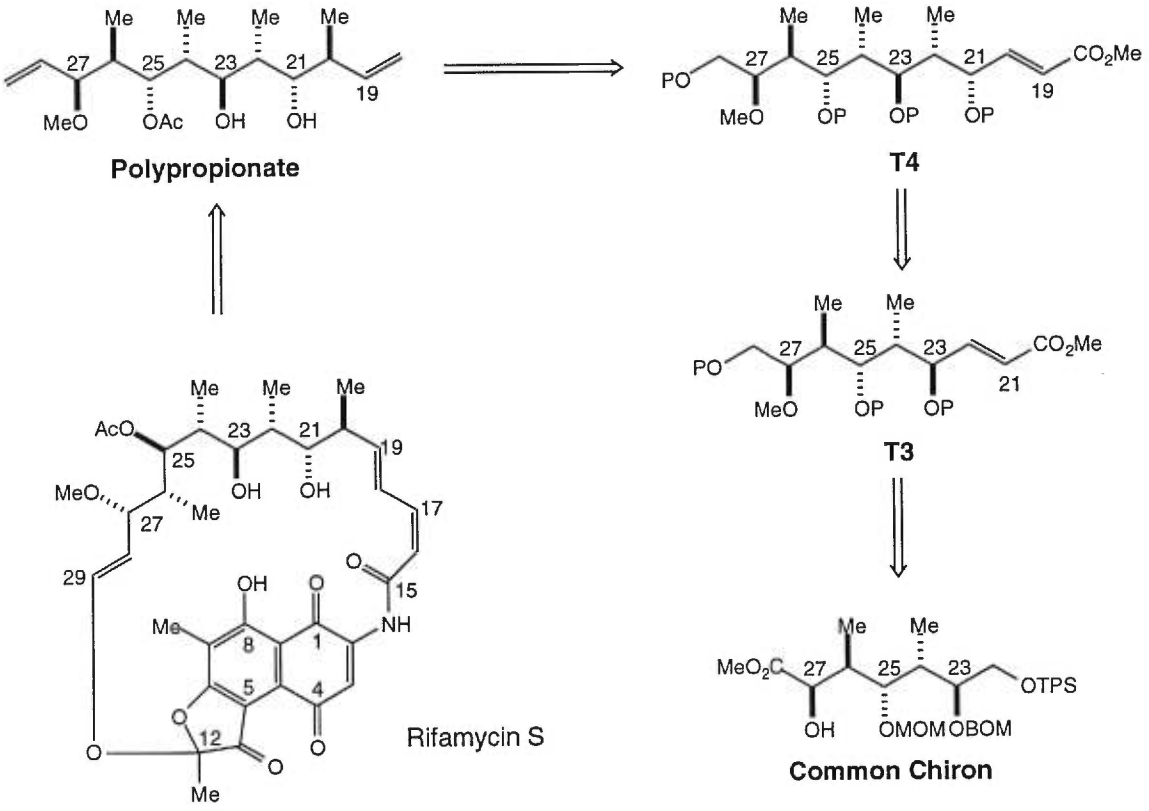
The ansa chain of rifamycin S is an ideal target to test the new stereocontrol methodologies. Its eight contiguous chiral center chain, having a complex stereochemical pattern, represents the longest polypropionate of any natural product and poses a great challenge for organic chemists. It could be considered a standard by which the efficiency of a stereocontrolled methodology can be measured. It is not surprising that there have been many syntheses of the ansa chain, however, only one total synthesis of rifamycin S has been documented.[120]

§3-6 Synthesis of the Polypropionate of Rifamycin S

Our retrosynthetic analysis of the polypropionate of rifamycin S is shown in Figure 28. The polypropionate, in principle, could be obtained by introducing a C20-*anti*-methyl group, with acyclic-stereocontrolled cuprate addition to a template **T4**. In turn, **T4** could be obtained by introducing a C22-*anti*-methyl group and a C21-*syn*-hydroxy group utilizing cuprate addition and hydroxylation, respectively, on **T3**, followed by functionality manipulation to elongate the chain. **T3** could be obtained by lengthening the chain in the opposite direction on the common chiron. However, in practice we have to consider the possible factors which could affect stereoselectivity. (1) The prospective templates contain several oxygen atoms which could form strongly

chelated aggregates, affecting the reactivity and stereoselectivity. (2) The different chirality of δ-position in **T3** may have some effect on stereoselectivity, especially the new pattern of relative stereochemistry in **T4**, possibly generating some unexpected effects.

Figure 28 RIFAMYCIN S: RETROSYNTHETIC ANALYSIS



Synthesis of the polypropionate of rifamycin S started from the common chiron **69**, which was obtained by a stereocontrolled sequence described in section **§3-4**. For the synthesis of the polypropionate we had to extend the chain in the opposite direction. This change would alter the relative stereochemistry between the newly introduced methyl group and the methyl at the δ-position from 1,3-*anti* to 1,3-*syn*.

Before elongating the chain, we had to reduce ester **69** to diol **71** by sodium borohydride. The selective protection of the primary alcohol with trityl group proved quite troublesome, the results are summarized in Table 7. The best result obtained was a 60% yield of product **72** and 20% recovered starting material, using TrDMAPCl (solid salt, prepared from trityl chloride and DMAP) as the reagent and heating at reflux in CH_2Cl_2 for 7 hours.

Scheme 16 RIFAMYCIN S: SYNTHESIS-1

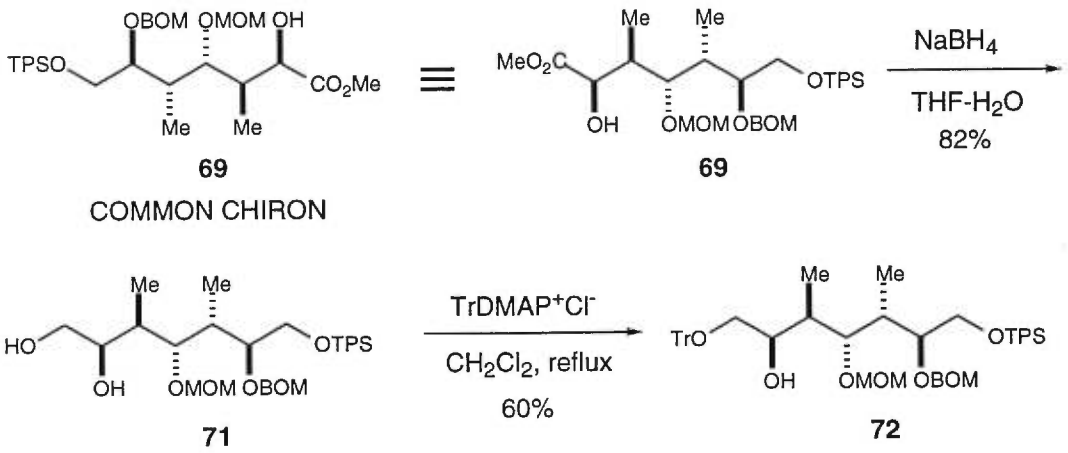


Table 7 RIFAMYCIN S: PROTECTION WITH TRITYL GROUP

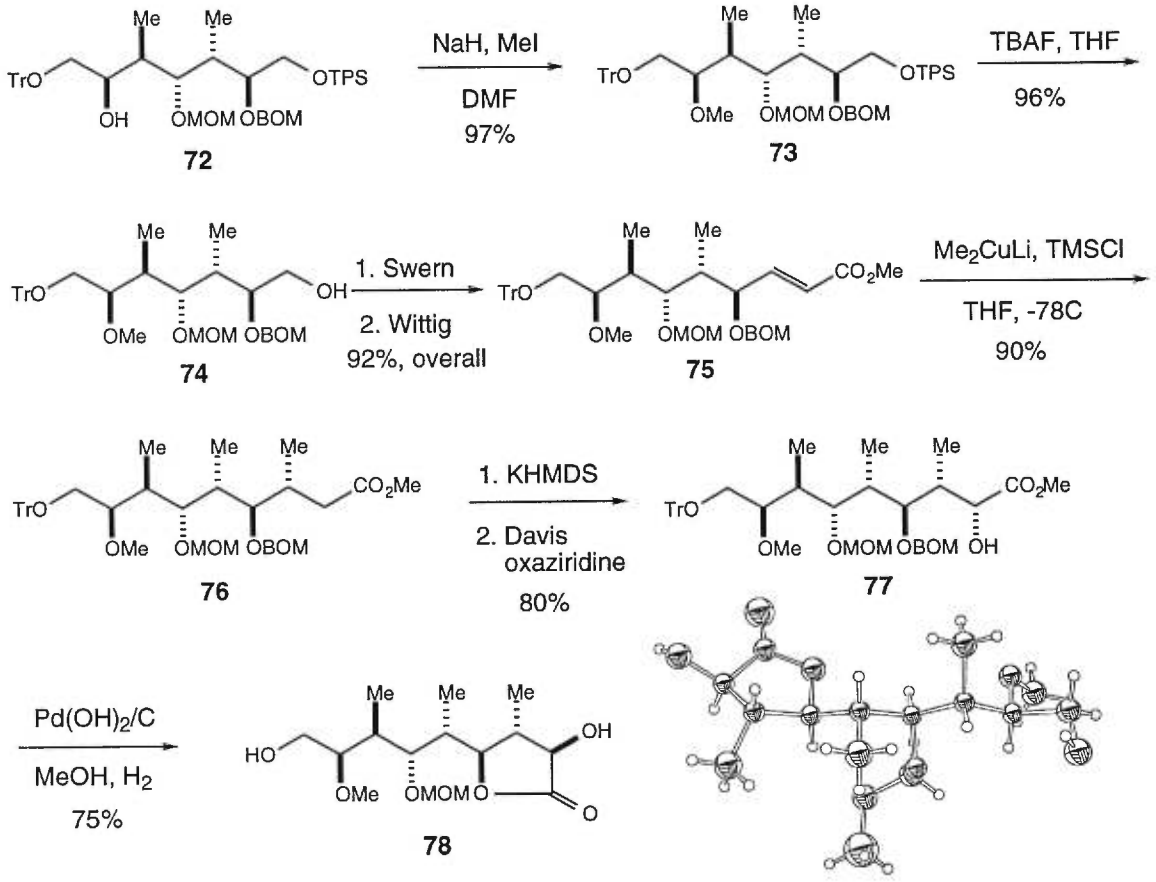
Reagent	Solvent	Temp	Time (h)	Yield	Recovered S.M.
$TrPyBF_4$	CH_2Cl_2	r.t.	29	22%	41%
	THF	r.t.	24	10%	64%
$TrDMAPClO_4$	CH_3CN	reflux		DEC	
TrDMAPCl	CH_2Cl_2	r.t.	days	NR	
	THF	r.t.	48	NR	
	CH_2Cl_2	reflux	7	60%	22%

The secondary hydroxy group of **72** was protected as a methyl ether, as for the C27-methoxy in rifamycin S. Treating **72** with NaH and MeI in DMF for 1 hour afforded compound **73** in 97% yield. Longer reaction times resulted in the loss of the TPS protecting group, an indication that the TPS group could be removed under these conditions.

It was then time to extend the chain in the opposite direction. The elongated third template, **75**, was obtained by a highly efficient sequence: removal of the TPS group with TBAF, followed by Swern oxidation and Wittig olefination.

Now the highly stereocontrolled sequence of cuprate addition and hydroxylation is ready to face the stereochemistry and reactivity tests in a much more complex system, in terms of the functionality and stereochemical pattern, to generate a new

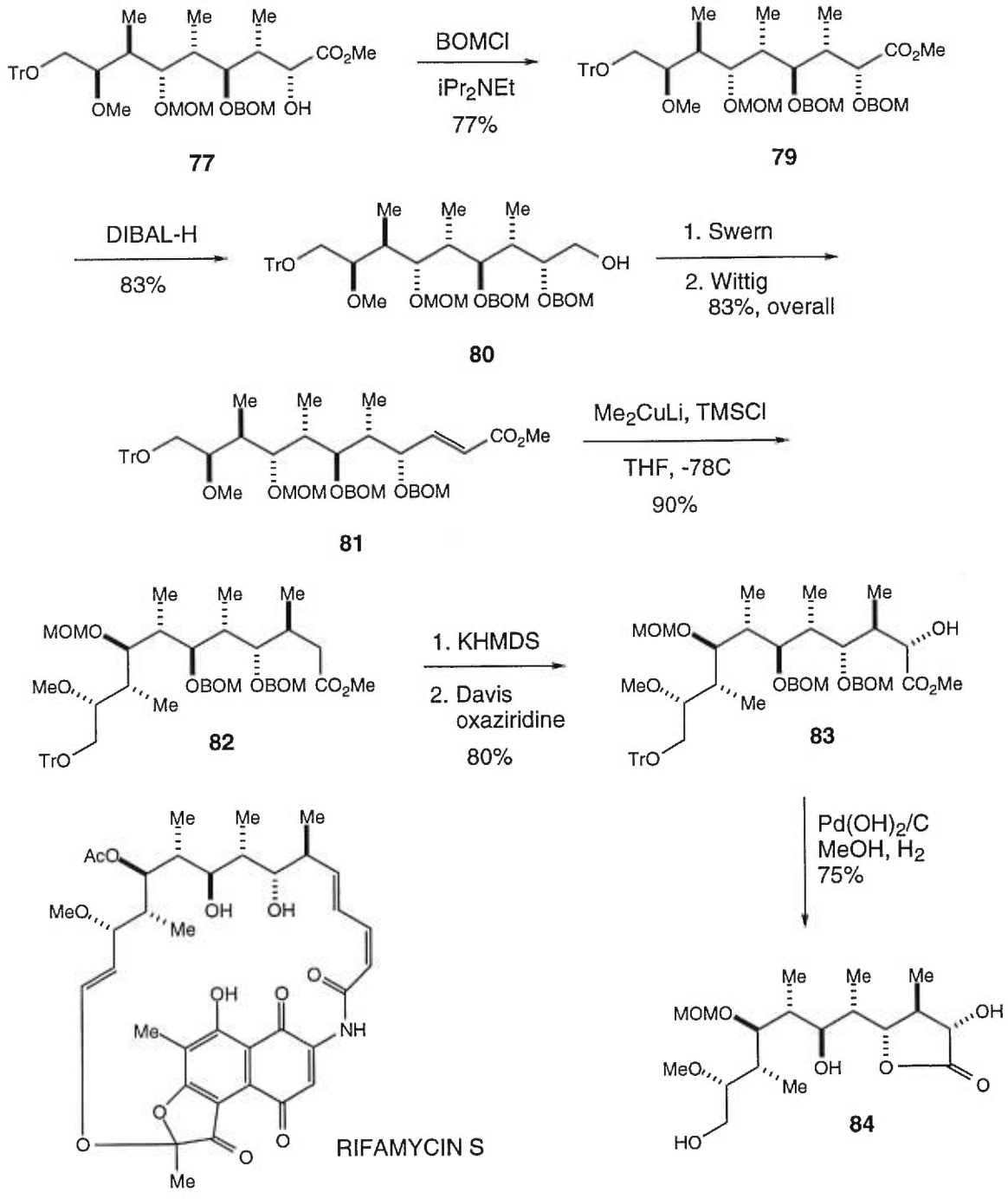
Scheme 17 RIFAMYCIN S: SYNTHESIS-2



relative stereochemical pattern (1,3-*syn*-di-methyl). Fortunately, everything went as anticipated, with no undesired effect showing up. So γ-alkoxy α,β-unsaturated ester **75**, the 3rd template, was treated under cuprate addition conditions to afford the adduct **76** in 90% yield. The *anti*-methyl group was introduced in a highly stereocontrolled fashion. Hydroxylation of the enolate generated from **76,** by KHMDS in THF at -78°C with Davis oxaziridine, afforded α-*syn*-hydroxy ester **77** in 80% yield as the only detectable isomer by NMR analysis. Hydrogenation of α-syn-hydroxy ester **77** afforded crystalline lactone **78** as the only detectable isomer by NMR analysis. The stereochemistry of lactone **78**, thence the stereochemistry of **77**, the *anti*-selectivity of cuprate addition and the *syn*-selectivity of hydroxylation, was confirmed by X-ray diffraction analysis.

For the synthesis of the polypropionate of rifamycin S, we needed to introduce one more *anti*-methyl at C-20. Although the molecule became even more complex, after three successful rounds of stereochemistry and reactivity tests, we were confident in the straightforward chemistry of the next round. Protecting the hydroxy group of **77** as the BOM ether gave **79**. Reduction of ester **79** to alcohol **80**, followed by Swern oxidation and Wittig olefination, gave the desired fourth template, γ-alkoxy α,β-unsaturated ester **81** with high efficiency. Treatment of the fourth template **81** under cuprate addition conditions introduced the *anti*-methyl group at C-20 to afford **82** as the only detectable isomer by NMR analysis. Compound **82** contains all eight contiguous chiral centers of the polypropionate required for rifamycin S. Further hydroxylation of compound **82** afforded the α-*syn*-hydroxy ester **83** as the only detectable isomer by NMR analysis, thence *an enantiopure nine contiguous chiral center motif with rich differentiable functionalities*. Compound **83** was transformed into lactone **84**, the only detectable isomer by NMR analysis. The stereochemistry was proved by comparing the NMR spectra of lactone **84** with that of lactone **70**.

Scheme 18 RIFAMYCIN S: SYNTHESIS -3

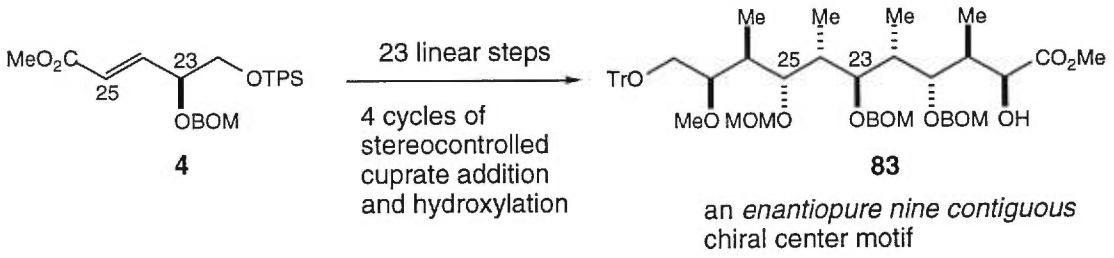


§3-7 Summary and Perspectives

We have developed a novel iterative methodology to address the polypropionate synthesis based on the chiron approach and substrate-directed acyclic stereocontrol. The

remarkable features of our methodology, as demonstrated before, are *(1) the consistency of high stereoselectivity in four cycles no matter how complex the systems were, (2) the reliable predictability of the outcome of stereochemistry which depends only on the adjacent chiral center, (3) and the operational simplicity and high efficiency.*

Figure 29 SYNTHESIS OF RIFAMYCIN S–CONCLUSION

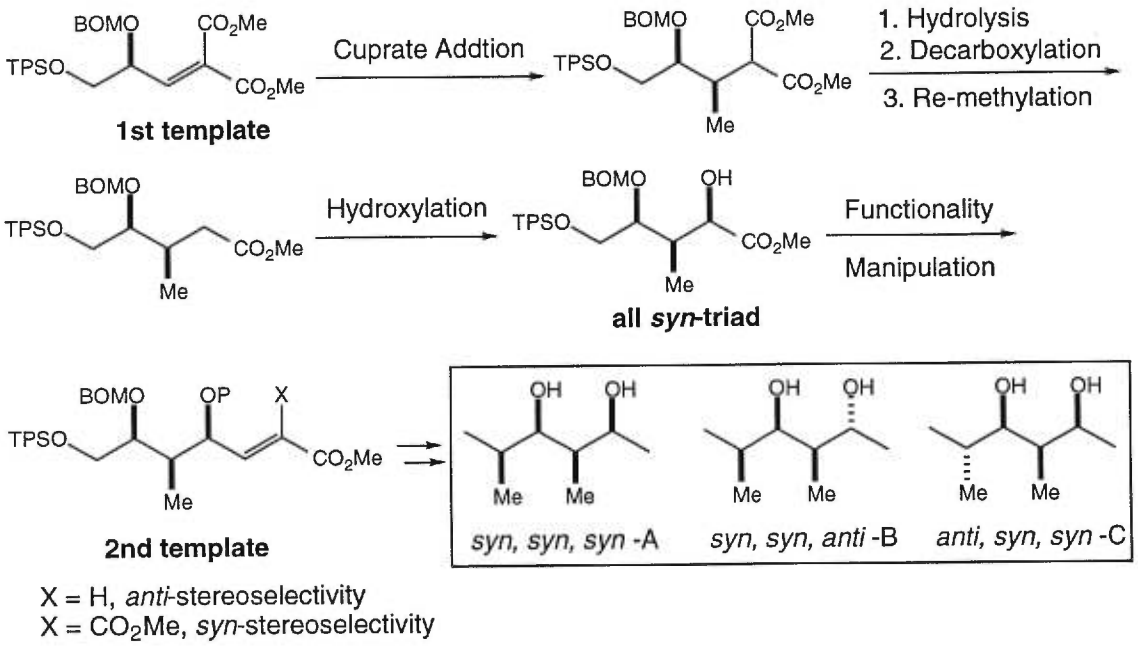


We have demonstrated the practicality and feasibility of our methodology by construction of *an enantiopure nine contiguous chiral center motif* ***83*** from a one chiral center template **4** through 23 linear steps. By this synthesis we have shown that we can *predict and control stereochemistry in an acyclic system, on a two directionally growing chain.* This synthesis also represents some sort of *atomic economy or ideal chiron approach by embedding all the original chirality and carbons of the 1st template* ***4*** *in the final target* ***83.***

Although we have proven our methodology to be greatly successful, in terms of stereoselectivity, chemical efficiency and predictability, we still have difficulty accessing all eight tetrads (Figure 24). On a one-directionally or two-directionally growing acyclic chain, by applying *anti*-cuprate addition and *syn*-hydroxylation, we could easily achieve *anti, anti, syn* -H, *anti, syn, anti* -G and *syn, anti, syn* -F. By incorporating Mitsunobu inversion of the hydroxy group, we could reach *anti, anti, anti* -E and *syn, anti, anti* -D. We cannot access *anti, syn, syn* -C, *syn, syn, anti* -B and *syn, syn, syn* -A because of the inherent stereochemical control.

We could conceive a longer sequence, still based on cuprate addition and hydroxylation of enolates to solve this problem (Scheme 19). If γ-alkoxy α, β unsaturated di-ester, the 1st template, is subjected to cuprate addition, *syn*-stereoselectivity is expected (many well-documented cases[64b,c]). Three extra steps, hydrolysis, decarboxylation and re-methylation, have to be added to the sequence to be ready for *syn*-hydroxylation. After hydroxylation, the all *syn*-triad could be obtained. The *syn*- or *anti*-stereoselectivity could be chosen by simply altering the X-group (X = H giving *anti*-, X = CO_2Me giving *syn*-) in the next cycle on the 2nd template. The tetrads, *syn, syn, syn*-A, *syn, syn, anti*-B and *anti, syn, syn*-C, could become accessible.

Scheme 19 PROPOSAL FOR ALL *syn* -TETRAD



X = H, *anti*-stereoselectivity
X = CO_2Me, *syn*-stereoselectivity

CHAPTER FOUR

Studies on the Total Synthesis of Bafilomycin A_1

Bafilomycin A_1 was first isolated from the fermentation broth of *streptomyces griseus* in 1983.[121] It exhibited activity against Gram-positive bacteria and fungi, and was found to be a specific inhibitor of various membrane ATPases.[122] Recently, studies showed that bafilomycin A_1 potently reduces Aβ production, a peptide related to Alzheimer's disease.[123]

Structurally, the bafilomycins, canamycins and hygrolides[124] are close relative families of polyketide macrolide antibiotics characterized by a 16- or 18-membered tetraenic macrolactone ring and a six-membered hemiketal ring. Bafilomycin A_1 is a prototypical member of the bafilomycins. Its structure, as shown in Figure 30, was established by X-ray diffraction analysis and chemical degradation.[125]

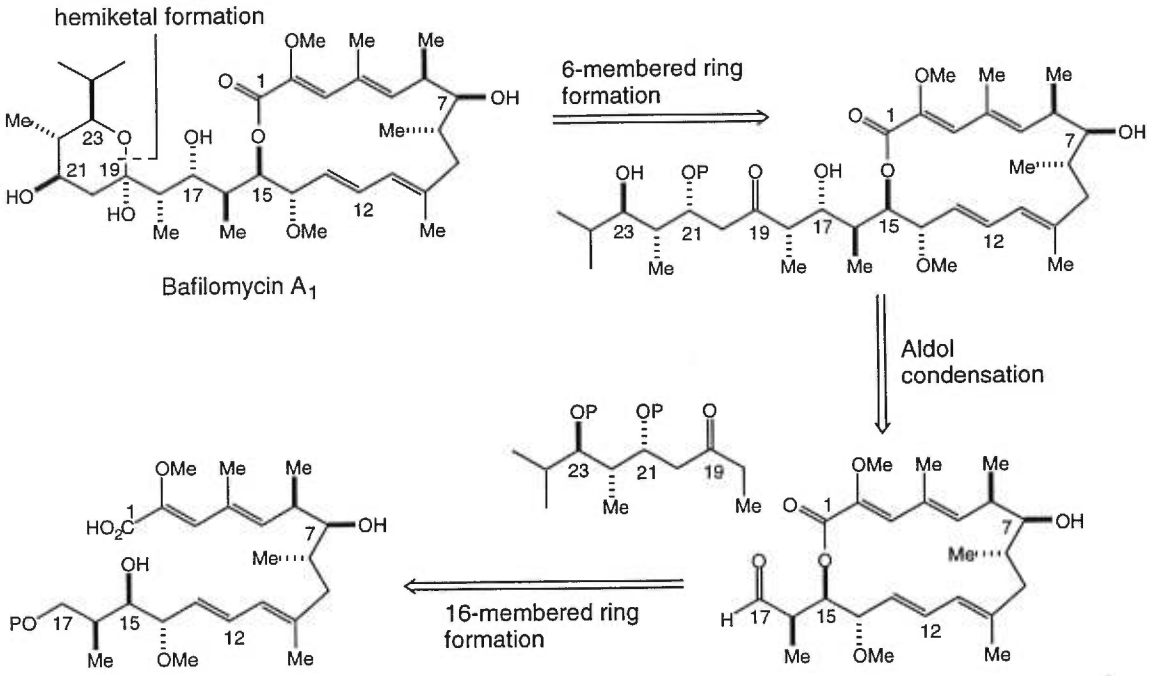
Due to the unusual structural features and unique bioactivities, great effort has been devoted to the total synthesis[126] and structural modification[127] of bafilomycin A_1 by many research groups.

Bafilomycin A_1 proved to be quite a challenging target to conquer because of its instability under various conditions.

§4-1 Bafilomycin A_1: Background and Retrosynthetic Analysis

Two total syntheses and several segment syntheses have been published. Different versions of the aldol approach were heavily employed to construct the polypropionate subunits in all these syntheses. The strategy was to form the 16-membered ring first and the 6-membered hemiketal ring as the last step (the 16-6-strategy). This general approach is outlined in Figure 30.

Figure 30 BAFILOMYCIN A1: GENERAL APPROACH



We were first interested in exploring another strategy, forming the 6-membered hemiketal ring first and the 16-membered macrolactone at a later stage, namely the 6-16-strategy.

Our retrosynthetic analysis of bafilomycin A_1 is depicted in Figure 31 and Figure 32. Macrolactonization[128] is the commonly used strategy to form the macrolactone ring since a large variety of methods are available to meet different requirements. We could reach bafilomycin A_1 by macrolactonization of acyclic precursor **P1**. For convergence, we wanted to cut **P1** in roughly two equal pieces, **P2** and **P3** (path *a*), **P4** and **P5** (path *b*), or **P6** and **P7** (path *c*). We could join **P2** and **P3** either by Julia[129] or Wittig olefination or other variants, **P4** and **P5** by Heck,[130] Stille,[131] Suzuki[132] or some other palladium-catalyzed coupling reactions, and **P6** and **P7** by Nozaki-Kishi[133] reaction or nucleophilic attack on aldehyde **P6** with dienic lithium or other metallic reagents derived from **P7**. Further disconnection of **P2** and **P4** would yield **P6**, which could be obtained from the

Figure 31 BAFILOMYCIN A1: RETROSYNTHETIC ANALYSIS 6-16-STRATEGY-1

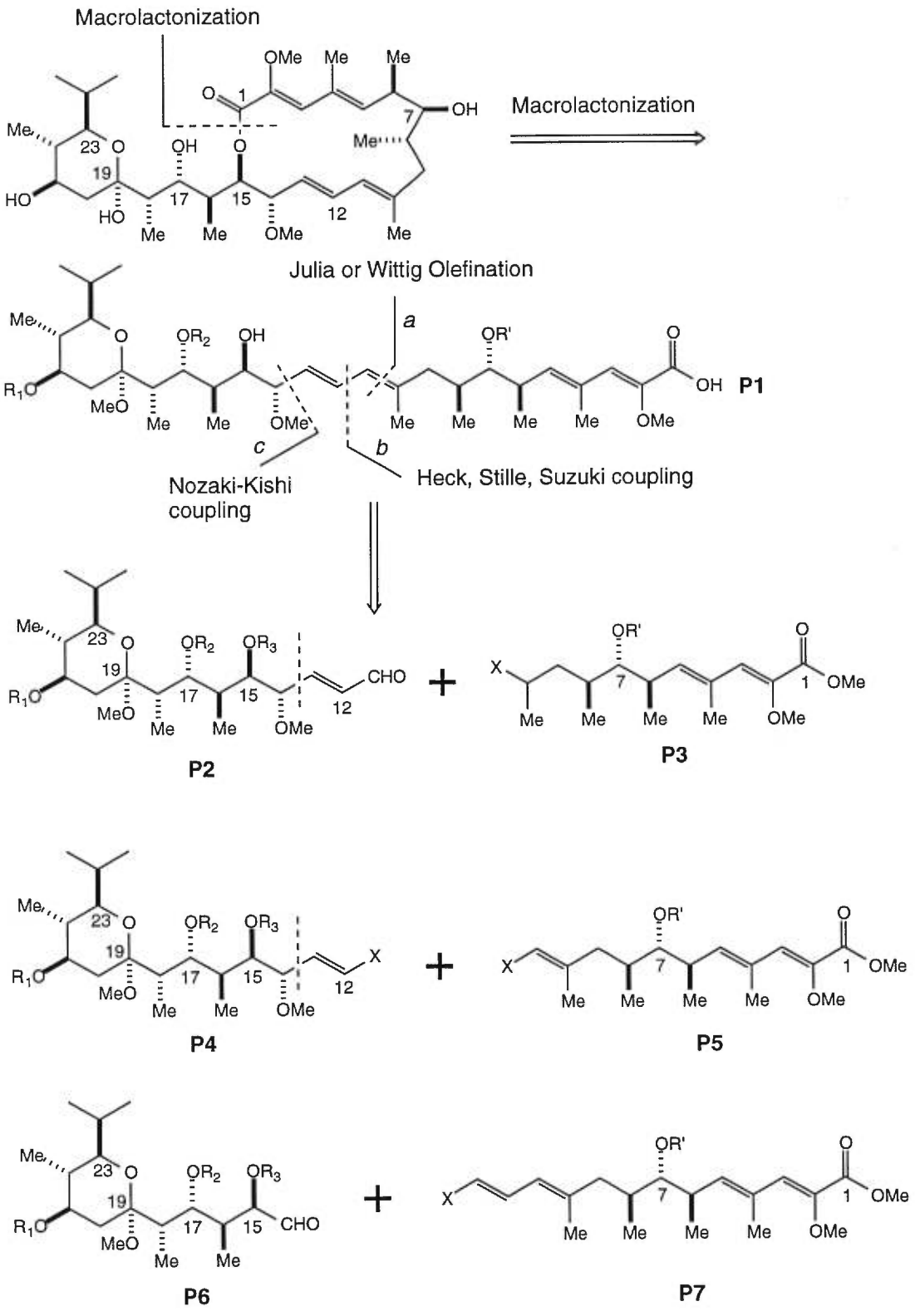
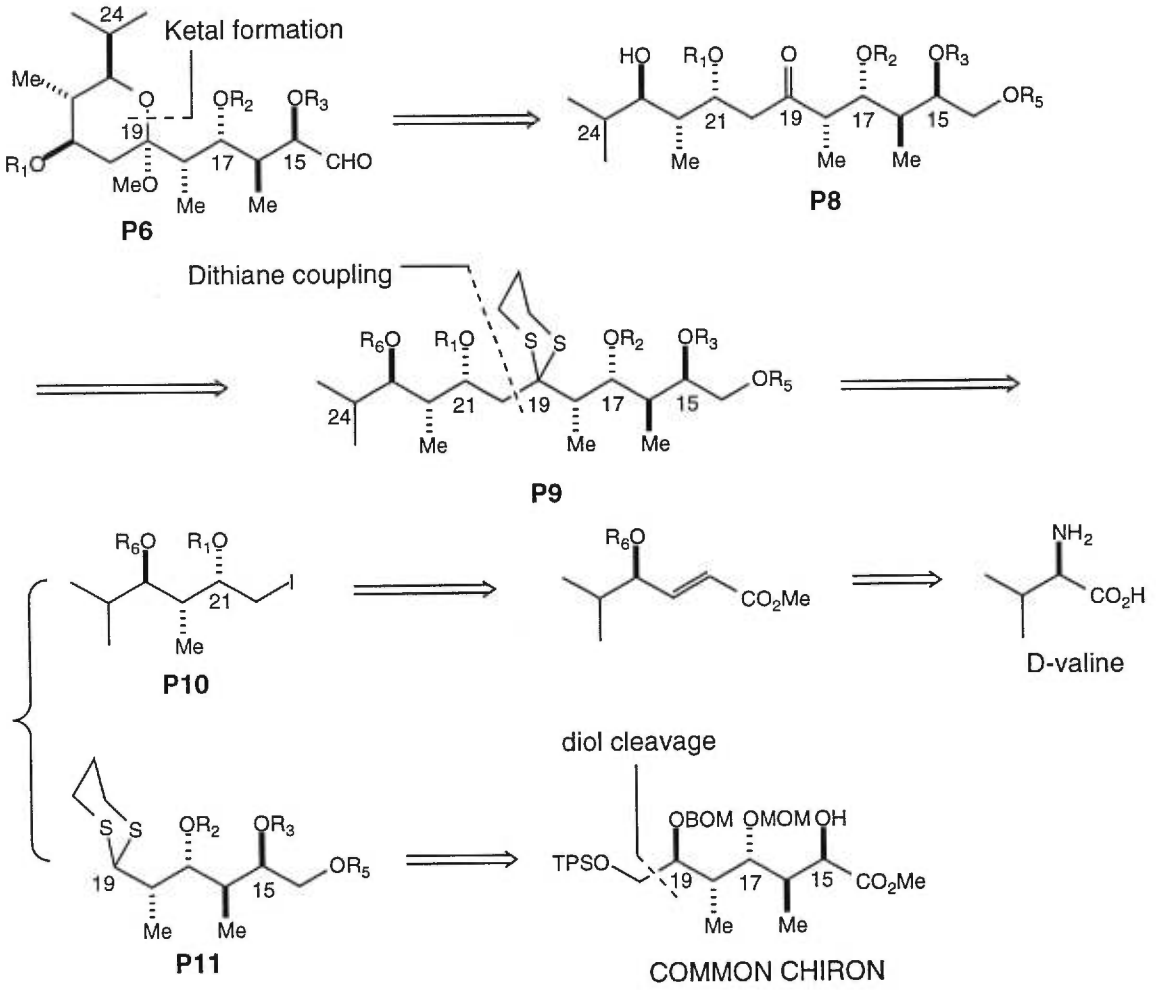


Figure 32 BAFILOMYCIN A1: RETROSYNTHETIC ANALYSIS 6-16-STRATEGY-2



acyclic ketone precursor, **P8**. Ketone **P8** could be obtained from dithiane precursor, **P9**, by the selective removal of several protecting groups. Dithiane **P9** could be obtained by coupling the C21-C25 iodide segment, **P10**, and the C14-C19 dithiane segment, **P11**.

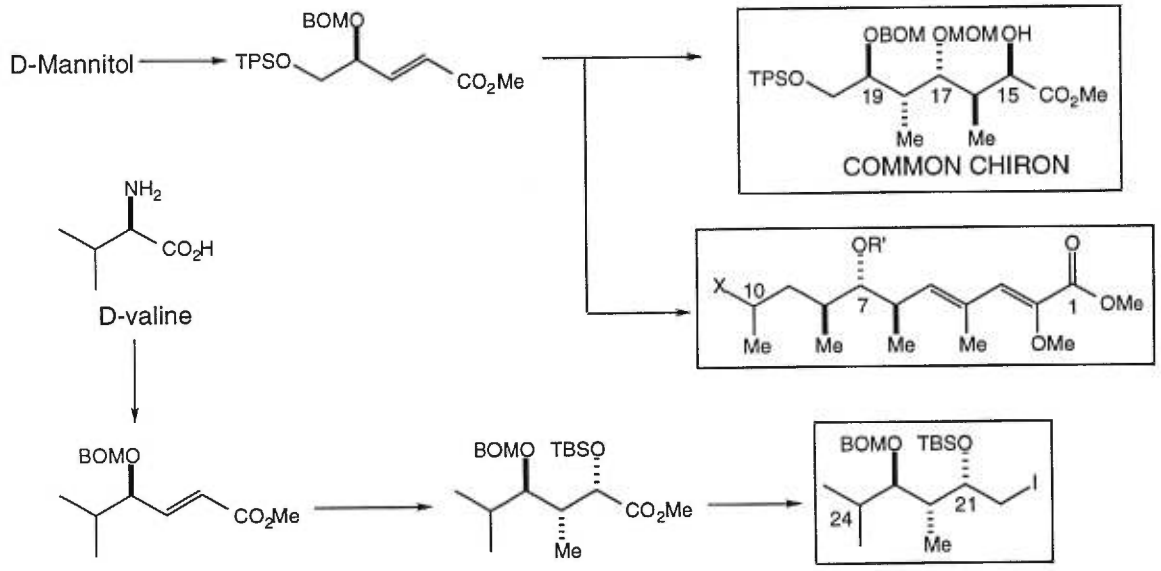
It is easy to conceive that **P10** could be obtained from D-valine by introducing an *anti*-methyl group and a *syn*-hydroxy group by stereocontrolled cuprate addition and hydroxylation, respectively, followed by functionality manipulation. Furthermore, **P11** could also be obtained from the common chiron by simple functionality manipulation.

§4-2 Bafilomycin A_1: Synthesis of the Intermediates

There are three polypropionate subunits in bafilomycin A_1 located at C6-C8, C15-C18 and C21-C23. The synthons containing these polypropionate subunits were synthesized as outlined in Figure 33.

Synthon **P3**, C1-C10 (X=SO_2Ph), has been obtained by two approaches,[134] either by a cuprate addition, hydroxylation, Mitsunobu inversion, cuprate addition sequence or by two cuprate additions on a two-directionally growing chain.

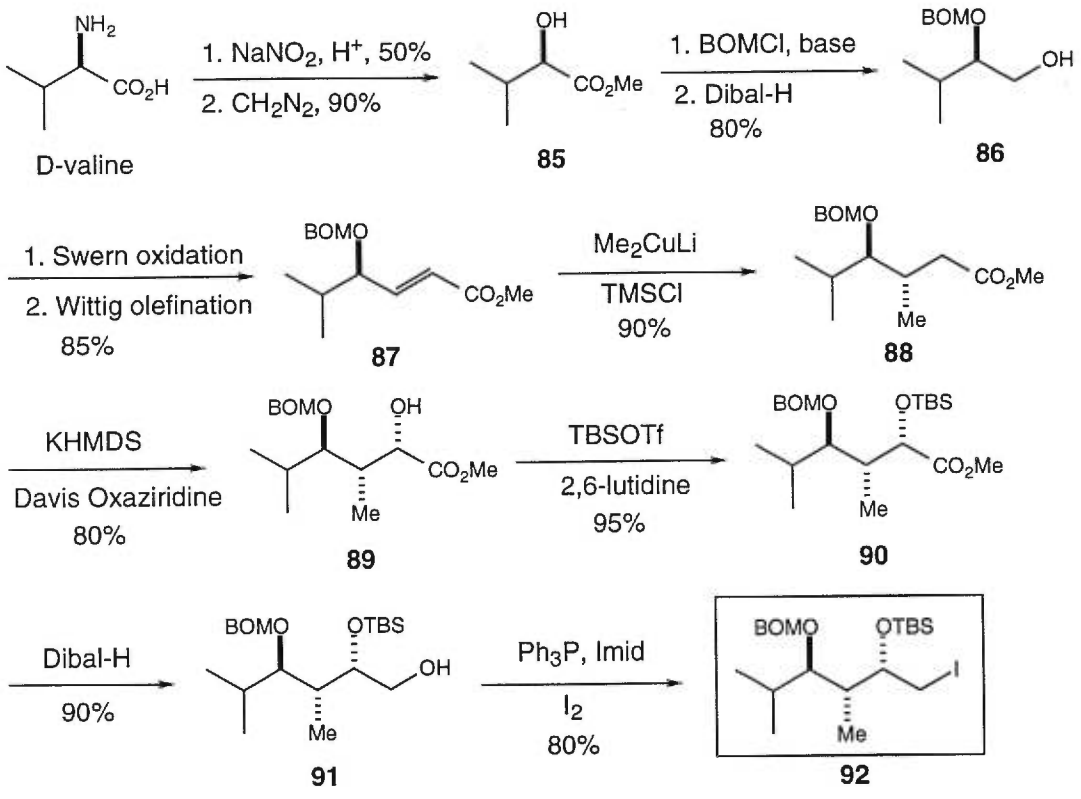
Figure 33 BAFILOMYCIN A1: INTERMEDIATES



Synthon **P10**, C20-C25, has been synthesized from D-valine,[135] as shown in Scheme 20. D-(*R*)-valine was transformed into the corresponding (*R*)-α-hydroxy acid by a double inversion sequence involving a diazonium intermediate and neighboring group participation. The acid was esterified with diazomethane to afford α-hydroxy methyl ester **85**. Protection of the hydroxy group as the BOM ether and reduction of the ester afforded alcohol **86**. Swern oxidation and Wittig olefination of **86** gave γ-alkoxy α,β-unsaturated ester **87** as a template for cuprate addition. Introduction of the *anti*-methyl

group afforded **88**, hydroxylation of the corresponding enolate generated by KHMDS with Davis oxaziridine introduced the *syn*-hydroxy group, affording α-hydroxy ester **89**. Protection of the hydroxy group as the TBS ether yielded **90** and reduction of the ester gave alcohol **91**. Treatment of alcohol **91** with triphenylphosphine, imidazole and iodine gave iodide **92** as the major isomer of a mixture (~3:1) in 80% yield. Iodide **92** is ready for coupling with dithiane synthon **P11**. Since iodide **92** is not stable for long periods, we keep alcohol **91** as the precursor. This sequence was carried out on a large scale; 25 mmol (10 grams) of alcohol **91** was obtained in one batch.

Scheme 20 BAFILOMYCIN A1: SYNTHESIS OF VALINE FRAGMENT

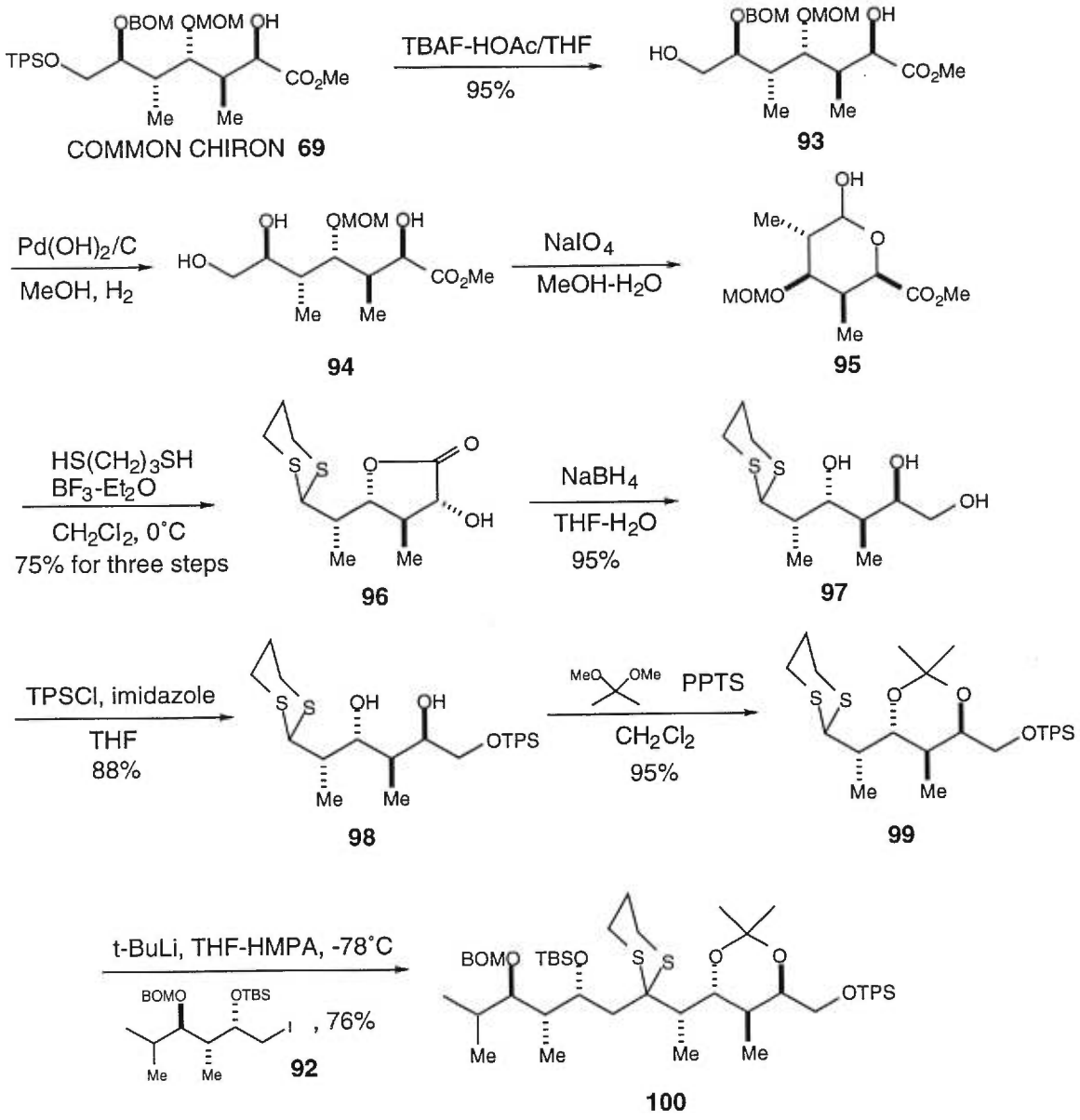


Synthon **P11**, C14-C19, was synthesized from the common chiron **69**, as shown in Scheme 21. The common chiron **69** was treated with TBAF-HOAc in THF to afford diol ester **93** in 95% yield. The TBAF-HOAc proved superior to TBAF for giving

reproducibly high yields. From **93** a three step sequence, removal of BOM by hydrogenation, diol cleavage by sodium periodate and protection of the aldehyde as dithiane **96**, was carried out without purification of neither **94** nor **95**. Dithiane-lactone **96** was reduced to dithiane-triol **97** using sodium borohydride. Dithiane-triol **97** was quite soluble in water and had to be extracted with ethyl acetate at least five times. Selectively protecting the primary hydroxy of **97** with TPS afforded diol **98**, and protection of this diol with acetonide gave dithiane **99**.

We were now ready to make synthon **P9**, C14-C25, by coupling dithiane **99** with iodie **92**. The anion generated from dithiane **99**, using tert-butyllithium in THF-HMPA at -78°C, reacted with iodide **92** to afford compound **100** in 76% yield.

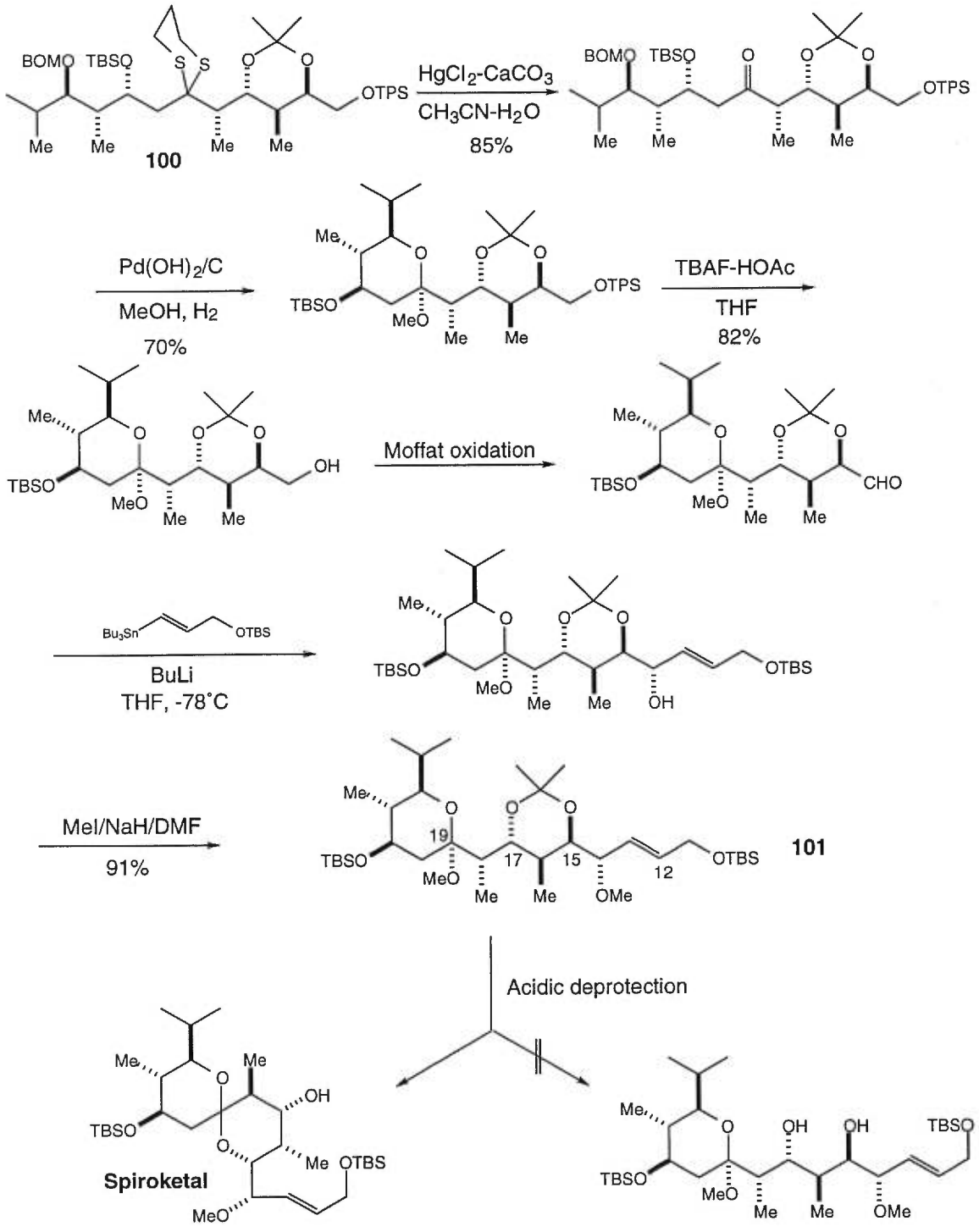
Scheme 21 BAFILOMYCIN A1: SYNTHESIS OF DITHIANE INTERMEDIATE



§4-3 Bafilomycin A_1: Problems from Protecting Groups

A sequence from compound **100** to **101**, the fully protected synthon **P2**, has been carried out (Scheme 22).[136] Disastrously, the acetonide protecting group was too stable to be deprotected without affecting other functionalities. All attempts under both acidic and neutral conditions led to either no reaction or spiroketal formation. The spiroketal was very stable and useless for this synthesis.

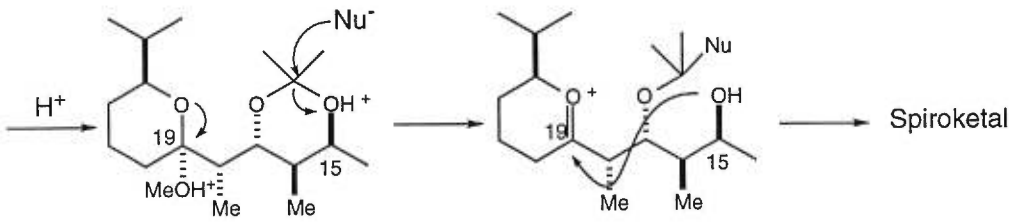
Scheme 22 BAFILOMYCIN A1: PROBLEMS OF DEPROTECTION



This situation is understandable if we consider the mechanism of deprotection (Figure 34). The acetonide ketal must be activated by acid before breaking the carbon-

oxygen bond. At same time the C19 mix ketal will be activated and will be waiting for the free hydroxyl of C15. Once the C15 free hydroxyl is generated, it reacts with the activated C19 ketal intramolecularly to form the spiroketal which has an all equatorial substituent pattern. Another alternative is based on the fact that the acetonide ketal is much more stable than the C19 mix ketal. Thus the equilibrium of the C19 mix ketal will start before the equilibrium of the acetonide ketal. The acetonide was not a viable protecting group to go further.

Figure 34 BAFILOMYCIN A1: SPIROKETAL FORMATION



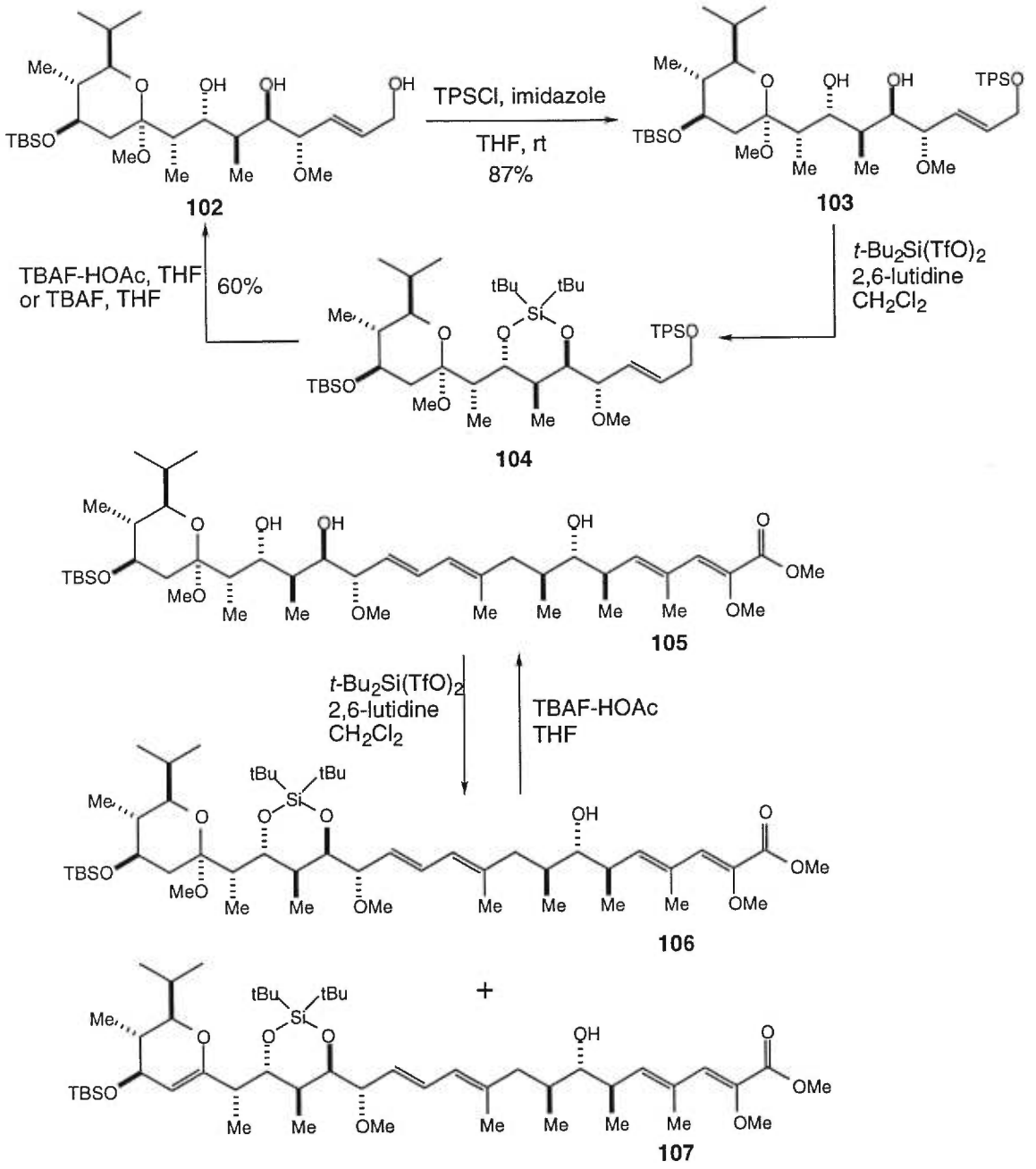
Now we had to find a pair of protecting groups for the diol, removable under basic conditions. Silyl protecting groups are suitable for this purpose and di-*tert*-butylsilylene seemed a good one to try first.

Indeed, di-*tert*-butylsilylene was a removable protecting group, as demonstrated in Scheme 23. The primary hydroxy group of triol **102**, obtained from controlled ozonolysis degradation of bafilomycin A_1,[137] was selectively protected with TPS to afford diol **103**. Treating diol **103** with 2,6-lutidine and di-*tert*-butylsilyl bistriflate in CH_2Cl_2 at 0°C afforded silylene **104**. The TPS and di-*tert*-butylsilylene of **104** could be removed in one step by using either TBAF or TBAF-HOAc to afford triol **102** in 60% yield without affecting the C21-OTBS or the C19 mix ketal.

In the second model, when triol-ester **105**, obtained from bafilomycin A_1, was treated with 2,6-lutidine and di-*tert*-butylsilyl bistriflate in CH_2Cl_2 at 0°C, both **106** (30% yield) and **107** (30% yield) were obtained. Compound **106** seemed unstable and changed

to **107** slowly. Silylene **106** was deprotected with TBAF-HOAc to afford triol-ester **105** in good yield.

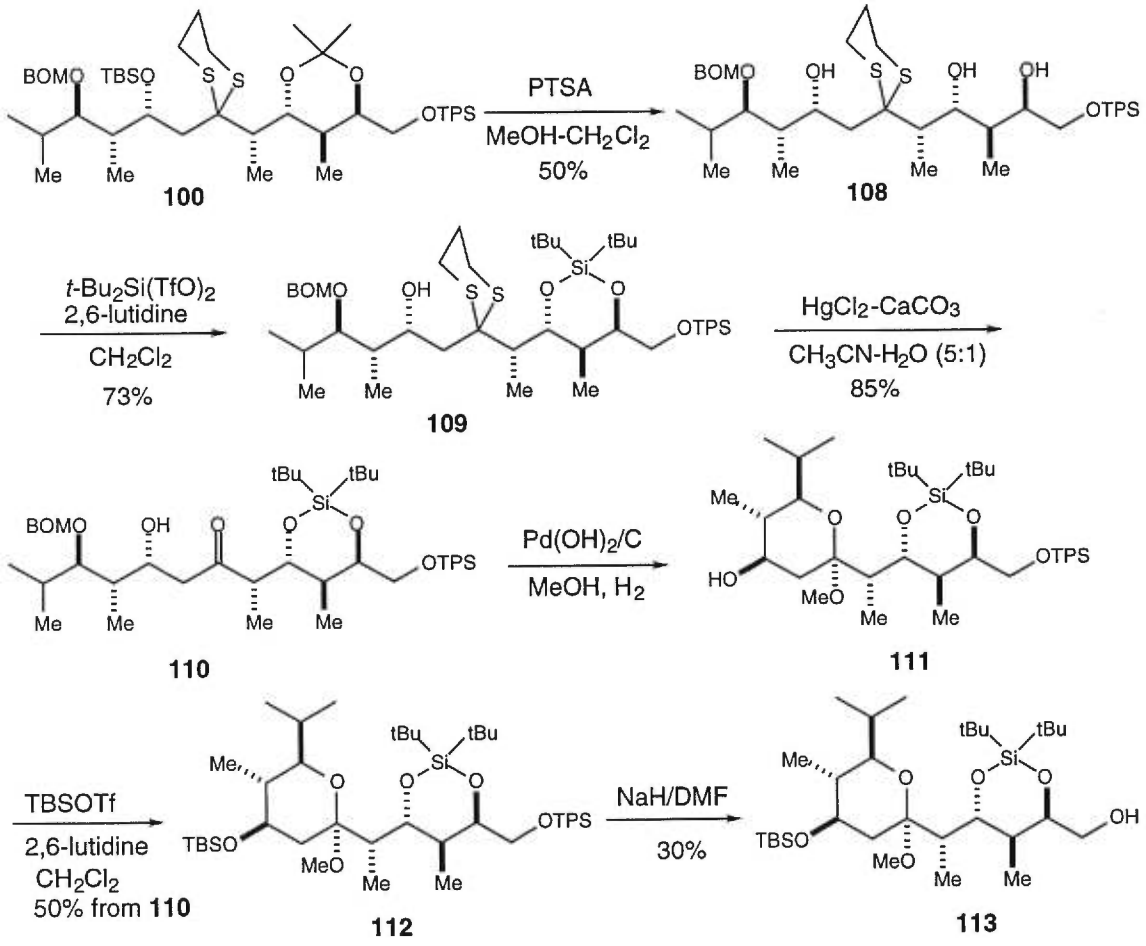
Scheme 23 BAFILOMYCIN A1: MODEL STUDIES OF SILYLENE AS PROTECTING GROUP



§4-4 Bafilomycin A_1: Manipulation of Protecting Groups

With coupling product **100** in hand, we first intended to test the di-*tert*-butylsilylene group on this compound. It proved impossible to selectively remove the acetonide without touching the TBS group. Treating **100** with PTSA in MeOH-CH_2Cl_2 afforded triol **108** in 40-50% yield.

Scheme 24 BAFILOMYCIN A1: MANIPULATION OF PROTECTING GROUPS-1

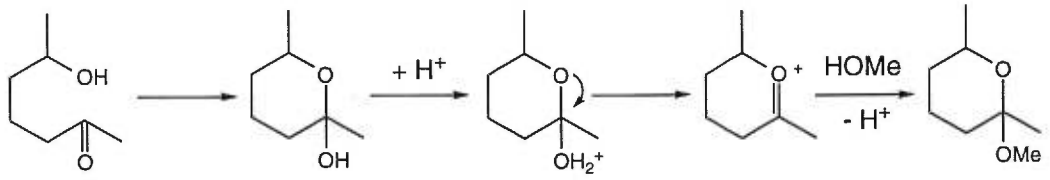


Triol **108** was treated with 2,6-lutidine and di-*tert*-butylsilyl bistriflate in CH_2Cl_2 at 0°C. The 1,3-diol was selectively protected to afford silylene **109**, however, the yield strongly depended on the batch of di-*tert*-butylsilyl bistriflate. Sometime the substrate was exclusively transformed into a unidentified by-product. Thus a pilot small scale

reaction had to be set up before a large scale one could be attempted using the same conditions (reagent, base and solvent). Dithiane **109** was treated with $HgCl_2$-$CaCO_3$ to afford ketone **110**. Since $HgCl_2$ could destroy the compound **109**, the procedure had to be followed carefully. Dithiane **109** was dissolved in CH_3CN-H_2O (5:1), the $CaCO_3$ added, stirred for 10-15 min, and the $HgCl_2$ added.

A two-step sequence was performed to transform **110** to **112**. The BOM group was removed by hydrogenolysis with $Pd(OH)_2/C$ in methanol. Spontaneously, the pyran ring and C19 mix ketal were formed. The mix ketal formation required an acidic

Figure 35 BAFILOMYCIN A1: PYRAN-MIXED KETAL FORMATION



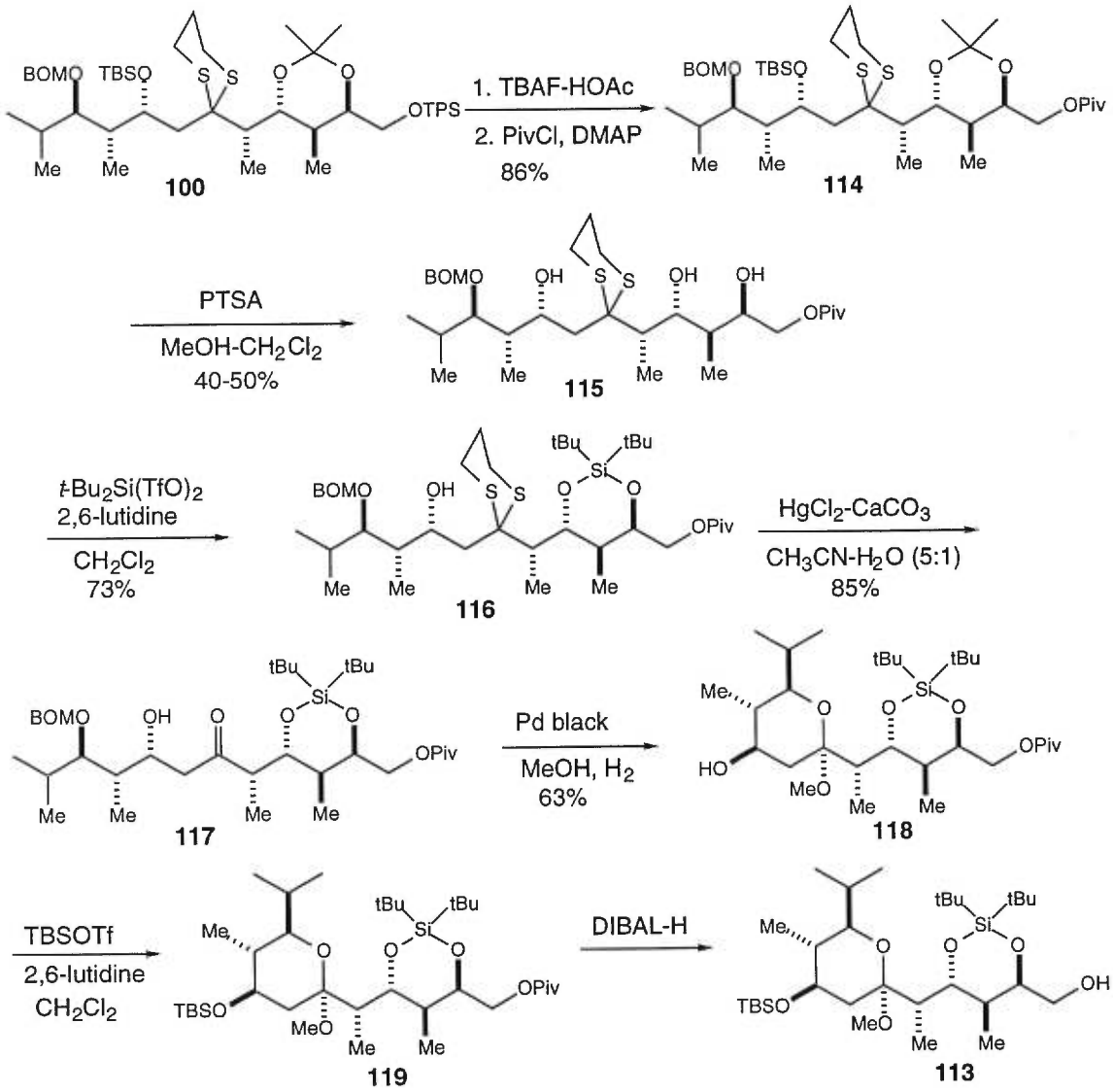
catalyst to generate an oxonium ion (Figure 35). It is not yet clear where the acid originates from. *This step turned out to be extremely difficult to control and reproduce.*

Protecting the hydroxy group of crude product **111** with 2,6-lutidine and TBSOTf in CH_2Cl_2 afforded **112** in 50% yield [the best yield ever obtained, usually a mixture (2:1) was obtained with an unidentified compound] from **110**.

Although the mechanism of using NaH in HMPA to selectively deprotect TPS in presence other silyl groups is not yet clear, this method was successfully used in a few cases with quite complex structures.[138] We also found that TPS group could be removed under NaH / DMF conditions, as mentioned in **§3-6**. In fact, in a model reaction we were able to selectively remove TPS group in the presence of the silylene in 68% yield (Scheme 30). Disappointingly, we only got 30% yield in the real system for the transformation of **112** into **113**.

To solve the problem of TPS removal, we thought a pivaloyl group could be better in terms of selective deprotection. We could remove pivaloyl by using reducing agents, such as DIBAL-H, without affecting other silyl groups (Scheme 25).

Scheme 25 BAFILOMYCIN A1: MANIPULATION OF PROTECTING GROUPS-2



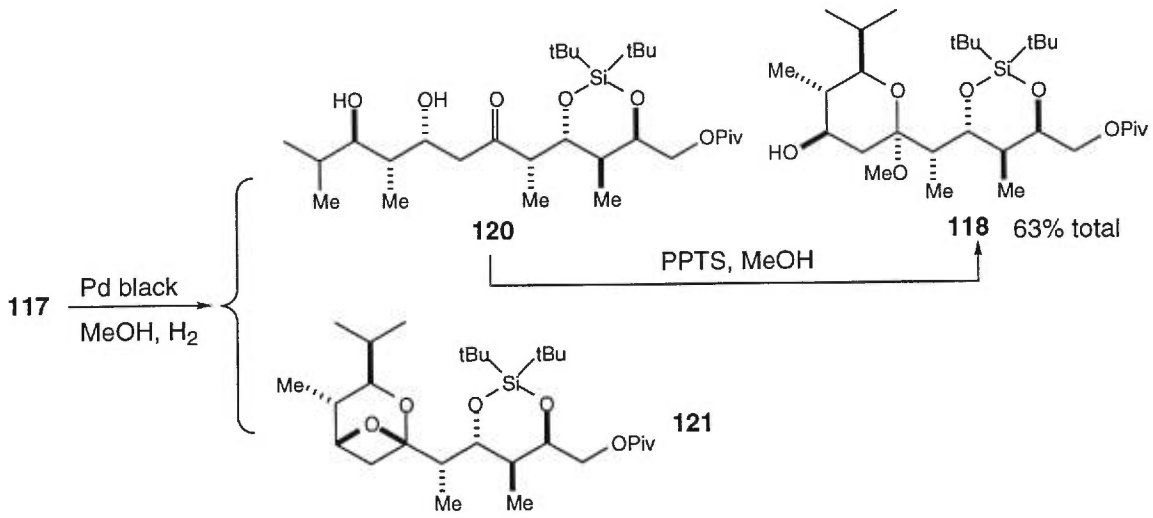
Starting from the coupling product **100**, the primary TPS group could be selectively removed, using TBAF-HOAc in THF in high yield, in presence of the secondary TBS group to afford **113a**. Protection of the newly generated primary

hydroxyl with pivaloyl chloride and DMAP, in CH_2Cl_2, afforded pivaloyl ester **114** in 86% yield from **100**.

From compound **114**, removal of the acetonide and TBS with PTSA afforded **115**. Protection of the diol with a silylene group gave **116** and removal of the dithiane afforded ketone **117**.

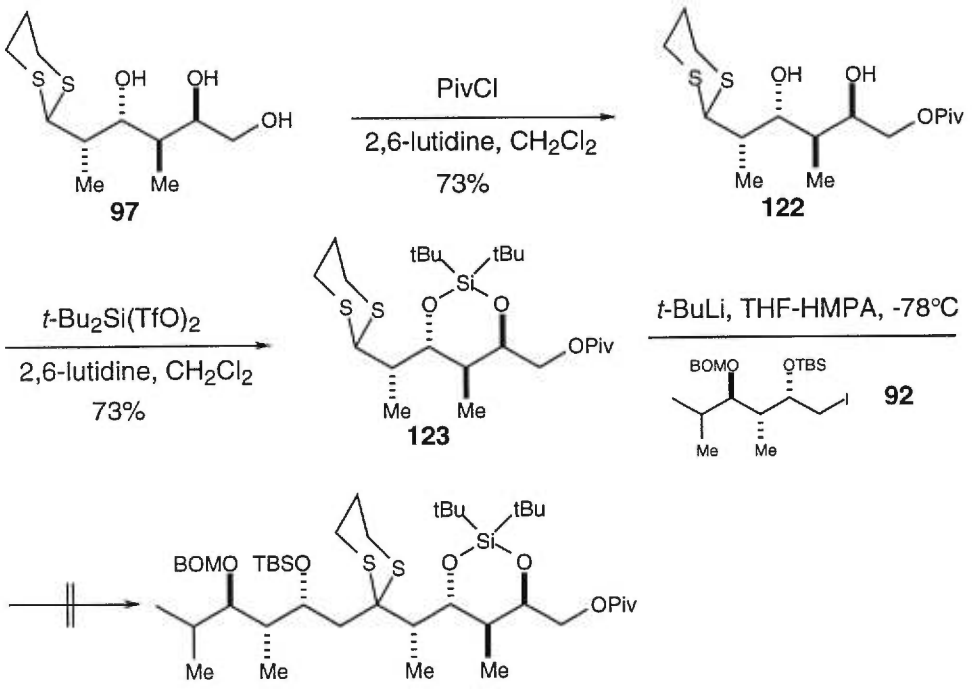
Again *the transformation from **117** to **118** under hydrogenolysis conditions proved very troublesome.* Using $Pd(OH)_2/C$ as the catalyst gave highly variable results. *Pd black gave much more reproducible results.* The TLC indicated three spots, which were identified as acyclic product **120**, the desired product **118** and a by-product **121** (putative structure), as shown in Scheme 26. We transformed the isolated acyclic compound, **120**, to **118** with PPTS in methanol in high yield, without the formation of by-product **121**. This implied palladium somehow was the culprit for the formation of **121**. However, it was still difficult to fully control the formation of **121**. When we protected the C21 hydroxy with TBS group, compound **119** was obtained as the major compound of a mixture (2:1) with an unidentified compound (one methoxy missing). Indeed, we selectively removed the pivaloyl group from **119** (as a mixture) with DIBAL-H to afford **113** (as a mixture) in good yield.

Scheme 26 BAFILOMYCIN A1: MANIPULATION OF PROTECTING GROUPS-3



The pivaloyl group was proven to be more compatible with silylene than the TPS group. It was interesting to see whether we could couple silylene-pivaloyl **123** and iodide **92** directly (Scheme 27). Compound **123** was prepared from dithiane-triol **97** by a two-step sequence, protecting the primary hydroxy with pivaloyl group and the diol with silylene. Unfortunately, when compound **123** was treated with *t*-BuLi and iodide **92**, using conditions identical to the acetonide case, no desired product appeared. Compound **123** decomposed to an unidentified product.

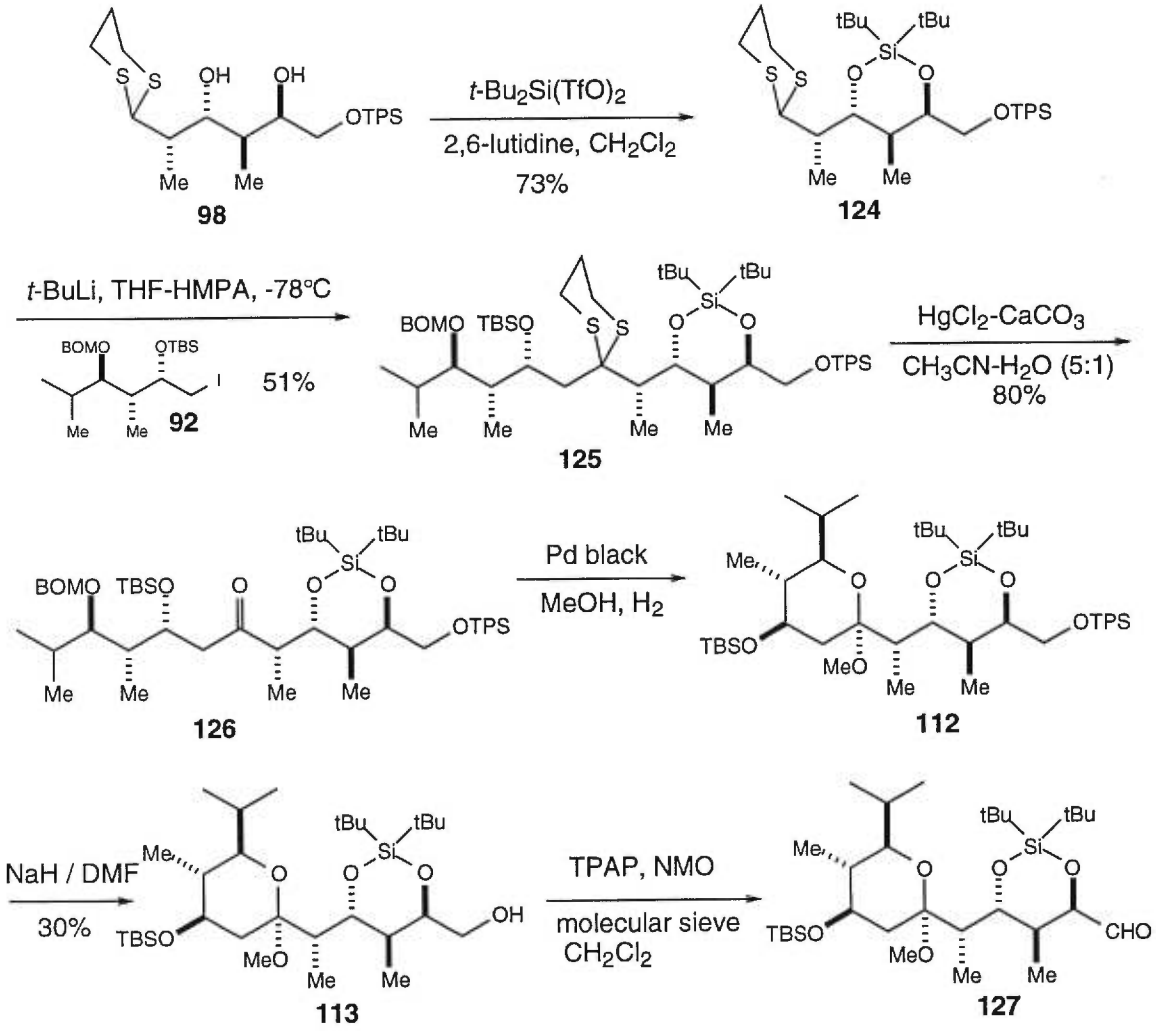
Scheme 27 BAFILOMYCIN A1: MANIPULATION OF PROTECTING GROUPS-4



§4-5 Bafilomycin A_1: Silylene Approach

Although we experienced great difficulty in selectively removing TPS in the presence of the silylene and in the formation of the pyran-ketal ring under hydrogenolysis conditions, it was quite an attractive approach to directly couple dithiane-silylene **124** and iodide **92** (Scheme 28). By this way, we hoped that we could save several steps toward reaching compound **112** and obtain substantial material to fully explore the elusive chemistry.

Scheme 28 BAFILOMYCIN A1: MANIPULATION OF PROTECTING GROUPS-5



Dithiane-diol **98** was treated with 2,6-lutidine and di-*tert*-butylsilyl bistriflate, in CH_2Cl_2 at 0°C, to afford dithiane-silylene **124** in 73% yield. The coupling of dithiane-silylene **124** and iodide **92** under the same conditions as used in the dithiane-acetonide case proceeded smoothly to afford coupling product **125** in 51% yield, lower than that of dithiane-acetonide case (76%). The transformation from **125** to ketone **126** went smoothly in high yield (>80%), however, ketone **126** needed to be extremely pure for the capricious hydrogenolysis step.

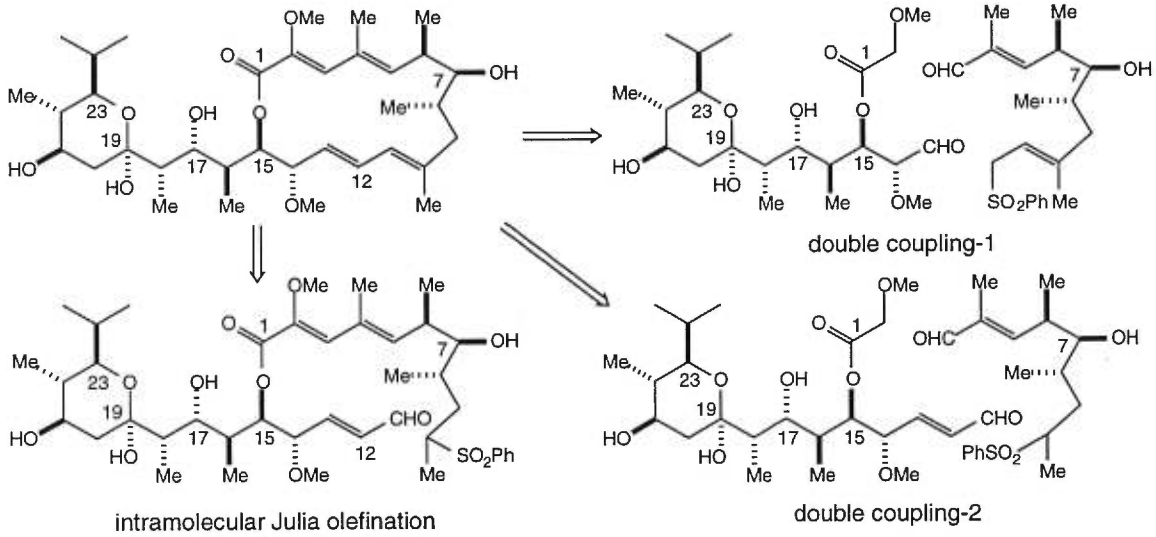
Again *the hydrogenolysis transformation from ketone **126** to pyran-ketal **112** proved even more troublesome and elusive*. Using $Pd(OH)_2/C$ as the catalyst, ketone **126** was almost completely transformed into an unidentified compound. Using Pd black as the catalyst, this transformation afforded a variable ratio (2:1, usually) and yield (60%) of a mixture of the desired product **112** and an unidentified one. Selective deprotection of the TPS, in the presence of the silylene, experienced the same problem of low yield (~30%).

Transformation from alcohol **113** to aldehyde **127** proved not to be simple. Swern oxidation resulted in the loss of the C19 methoxy group. This indicated silylene compounds, or more accurately, the C19 mix ketal was extremely sensitive to acidic conditions. We had to keep the environment basic at all times. The TPAP method[139] proved suitable for this transformation if we added triethylamine to keep a basic environment from the beginning. TLC and NMR showed the TPAP method gave good yield of aldehyde **127**.

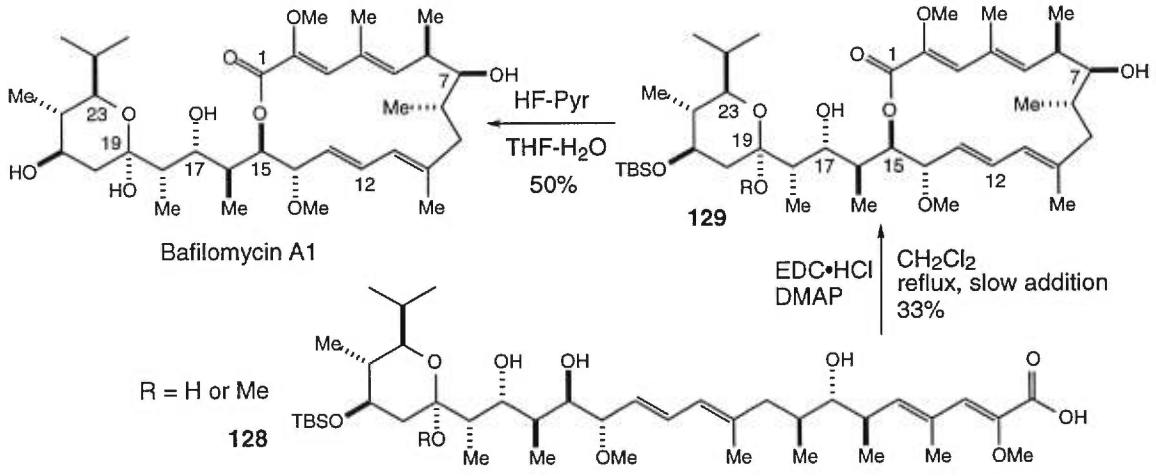
§4-6 Bafilomycin A_1: Retrospect

We experienced great difficulty in assembling the intermediates we readily obtained. Several strategies to form the 16-membered ring were tested[140] (Figure 36), with the macrolactonization approach proving to be the best one[141] (Scheme 29).

Figure 36 BAFILOMYCIN A1: GENERAL STRATEGIES FOR 16-MEMBERED RING

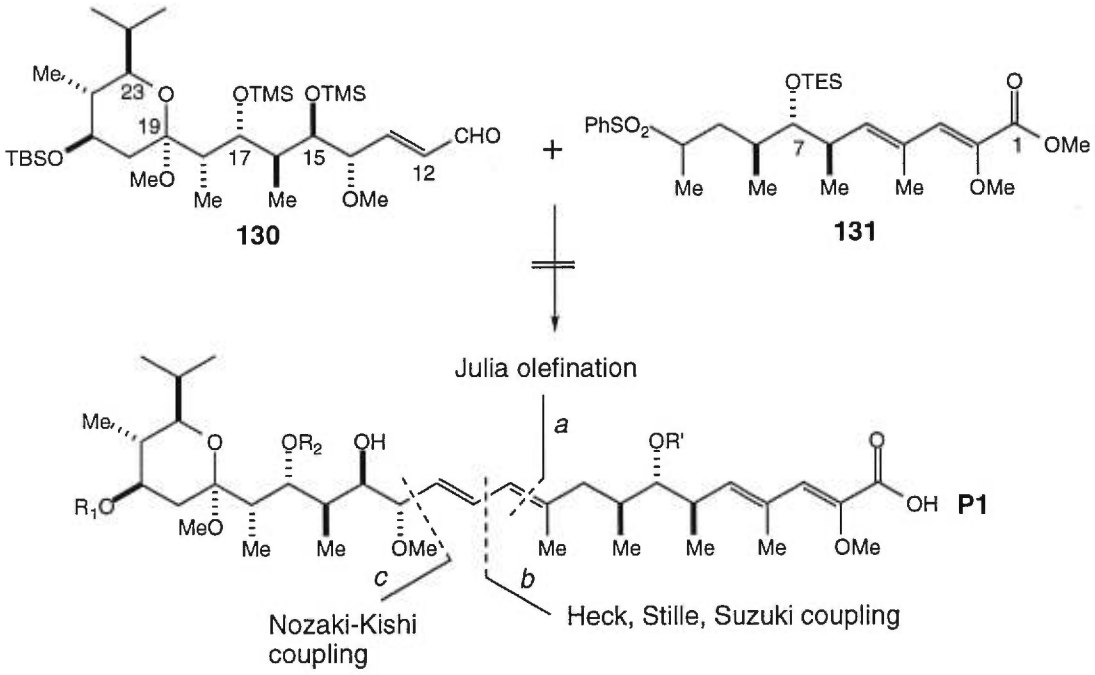


Scheme 29 BAFILOMYCIN A1: MACROLACTONIZATION



Acyclic acid **128** was macrolactonized under modified Keck conditions[142] (slow addition of a solution of the acyclic acid **128** in CH_2Cl_2 to a refluxing solution of EDC•HCl and DMAP in CH_2Cl_2) to afford the 16-membered macrolide **129**. Bafilomycin A_1 was achieved by deprotection of **129** by HF-pyridine in THF-H_2O. Thus, the synthetic target was reduced to acyclic acid **128**. Attempts to join aldehyde **130** and sulfone **131**, as indicated in Figure 37, were fruitless, at least up to now.

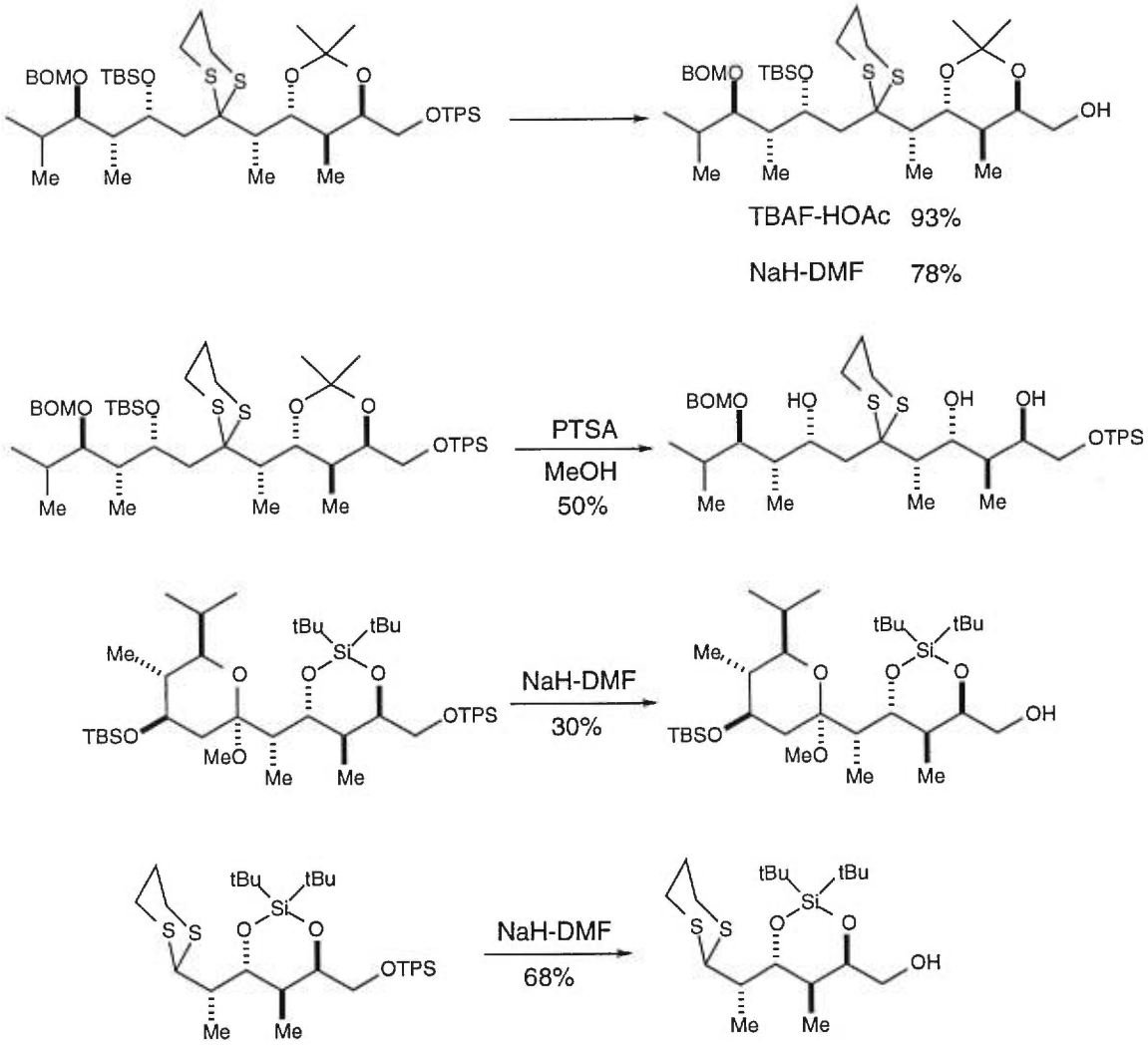
Figure 37 BAFILOMYCIN A1: JULIA OLEFINATION



Protecting groups created terrible problems. The acetonide was too stable to remove, di-*tert*-butylsilylene made the C19 mix ketal extremely sensitive to various conditions, with a mixture of the desired product and a by-product (one methoxy missing) being obtained. The compatibility of the silylene and TPS was very poor, resulting in a very low yield for the real molecule, **112**. Interestingly, TPS was selectively deprotected in the presence of TBS with TBAF-HOAc or NaH-DMF. However, under acidic

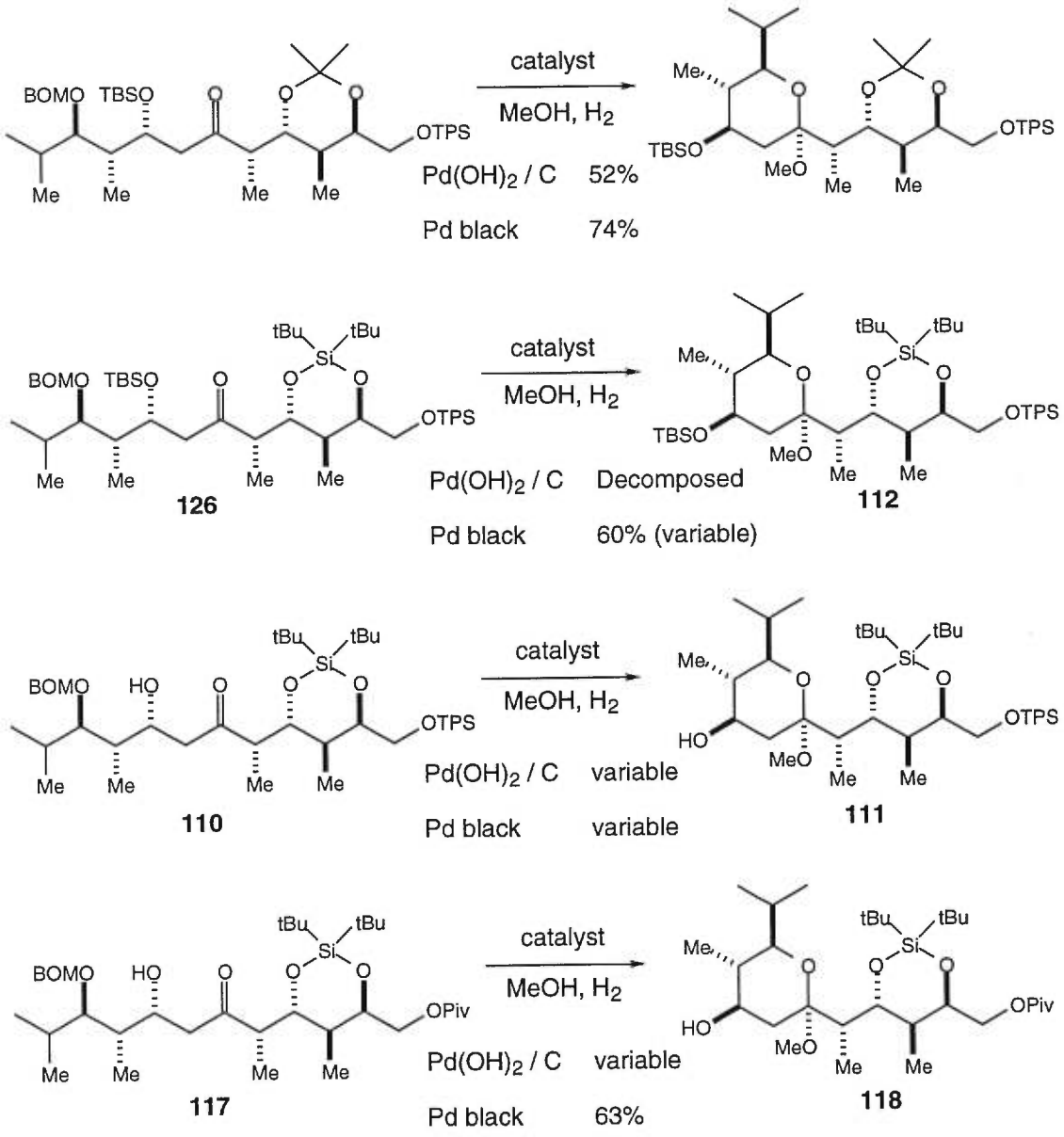
conditions the selectivity was reversed. The secondary TBS was deprotected in presence of the primary TPS.

Scheme 30 BAFILOMYCIN A_1: SUMMARY OF PROTECTING GROUP MANIPULATION



The formation of the pyran-ketal ring, by hydrogenolysis, was and still is a problem to be solved. *Generally, Pd black gave better results than $Pd(OH)_2/C$, which may be more acidic.* In the fully protected case, TBS-silylene-TPS **126** was extremely sensitive to palladium-catalyzed conditions. Even with Pd black, the results were still highly variable. Hydroxy-silylene-TPS **110** was less sensitive than compound **126**, however, the results were still variable. *The best results were obtained with hydroxy-silylene-Piv **117**.* $Pd(OH)_2/C$ was still not a good catalyst. Pd black gave reproducible results, although one more step was required.

Scheme 31 BAFILOMYCIN A_1: SUMMARY OF PYRAN KETAL FORMATION



§4-7 Bafilomycin A_1: Perspective and The 16-6-Strategy

Considering the difficulty encountered and the problems needed to be solved, the 6-16 strategy does not seem to be a viable one. To avoid the problems caused by the hemiketal pyran ring, its formation should be placed at the late stages of the synthesis.

Taking advantage of the chemistry accumulated during our studies, a new 16-6-strategy (formation of 16-membered macrolactone before that of pyran ring) was conceived, as depicted in Figure 38, Figure 39 and Figure 40. Bafilomycin A_1 could be obtained by deprotection of **132** and spontaneous formation of the hemiketal pyran ring. Ketone **132** could be obtained by deprotection of dithiane **133**. This step could be problematic since $HgCl_2$ may affect the olefins. By macrolactonization, acyclic-hydroxy acid **134** could be transformed into **133**. Compound **135** could be transformed into **134** by hydrolysis of ester and deprotection of hydroxyls. By aldol condensation and elimination, **135** could be obtained from **136**. Selective deprotection and oxidation of **137** could give **136**. Compound **137** could be disconnected by two paths, *a* and *b*. By path *a*, nucleophilic addition of a dienic lithium reagent to an aldehyde or Nozaki-Kishi reaction, aldehyde **138** and iodide **139** could be joined to afford **137**. At this stage, the desired stereochemistry of C14-hydroxy might be achieved by employing a chiral catalyst, such as CBS-Oxazaborolidine,[143] or by conducting an oxidation-reduction protocol.[144] Iodide **140** and dithiane **99** could be envisioned as the precursors of **138**. Iodide **140** could be obtained from **91** by manipulation of protecting groups. Dienic iodide **139** could be obtained from enyne **141** by hydrozirconation,[145] hydroboration[146] or hydrostannylation[147]. Enyne **141** could be accessable by a one-step Wittig-type reaction[148] from ketone **142** or by a Corey-Fuchs reaction[149] from aldehyde **143**. Aldehyde **143** could be accessible by a Wittig olefination-Dibal-H reduction-MnO_2 oxidation procedure from ketone **142**.

Figure 38 BAFILOMYCIN A1: RETROSYNTHETIC ANALYSIS 16-6-STRATEGY-1

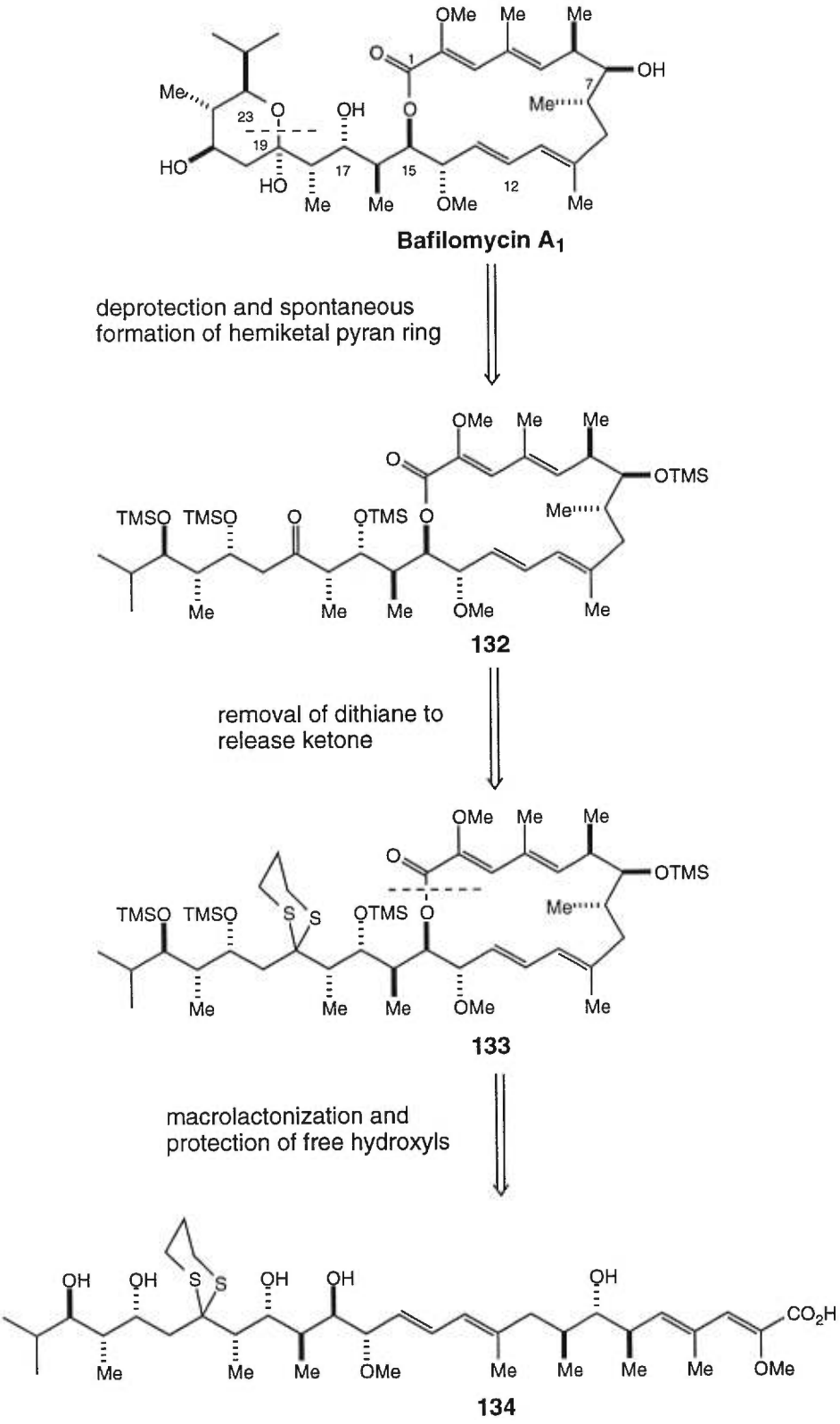


Figure 39 BAFILOMYCIN A1: RETROSYNTHETIC ANALYSIS 16-6-STRATEGY-2

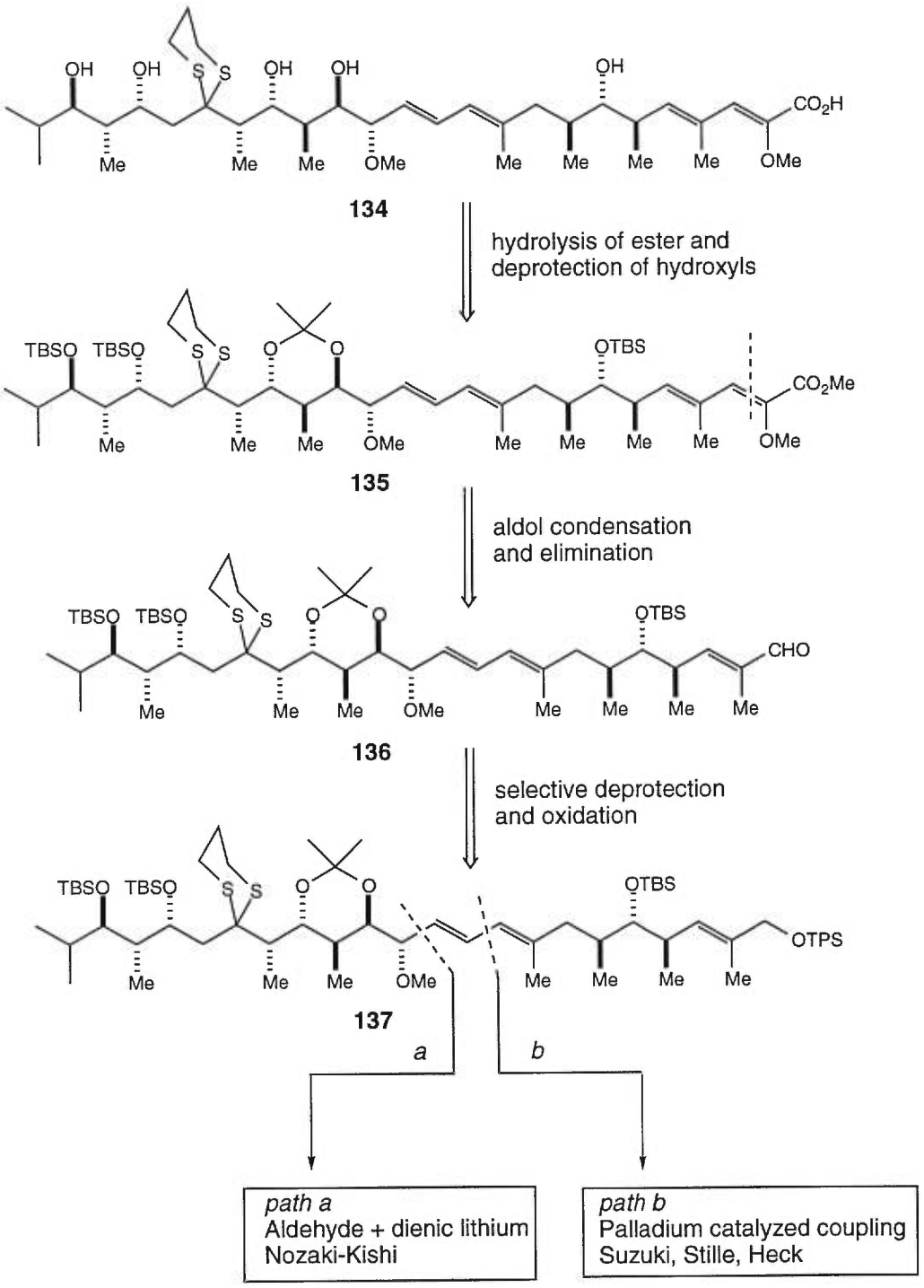
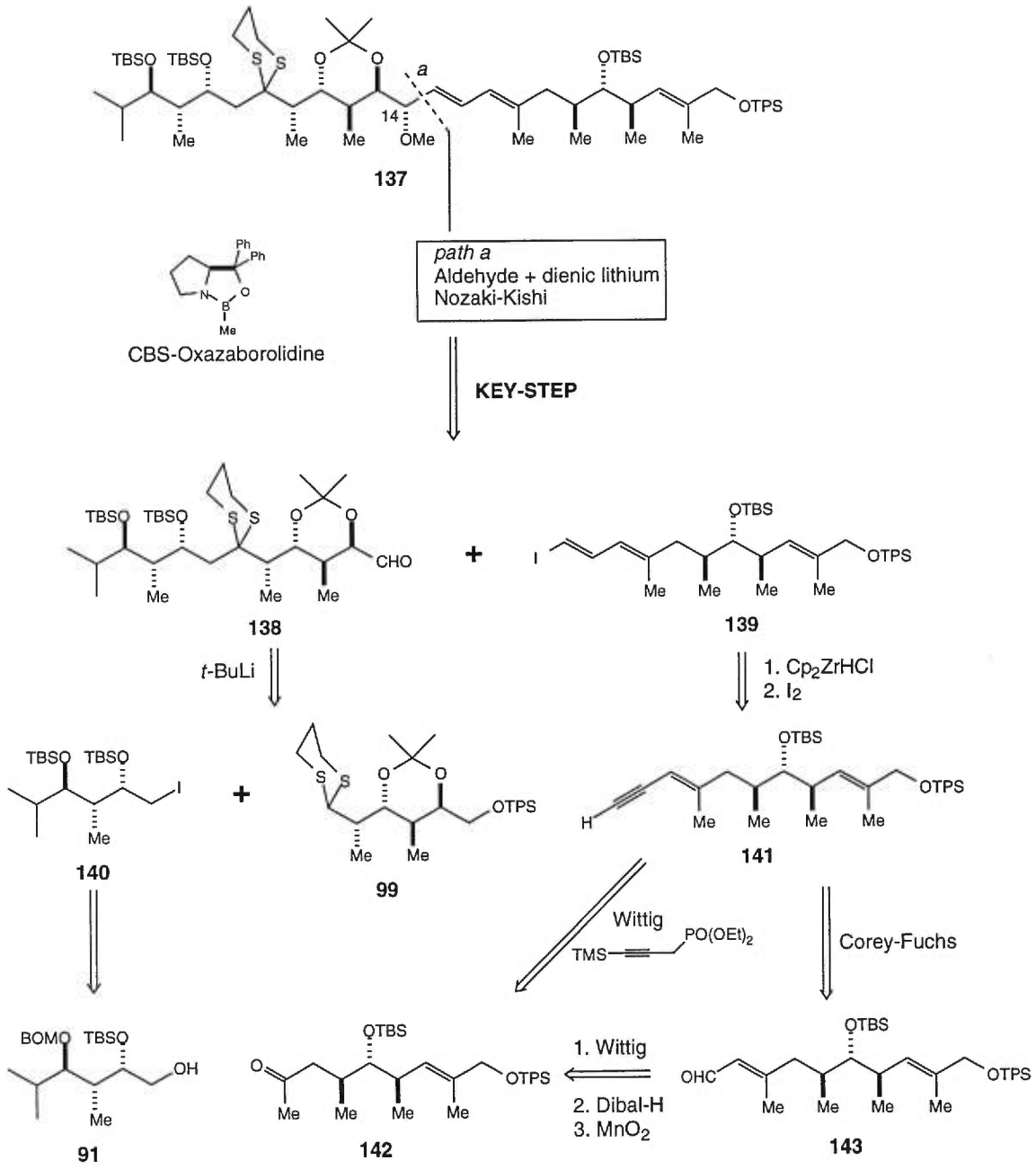
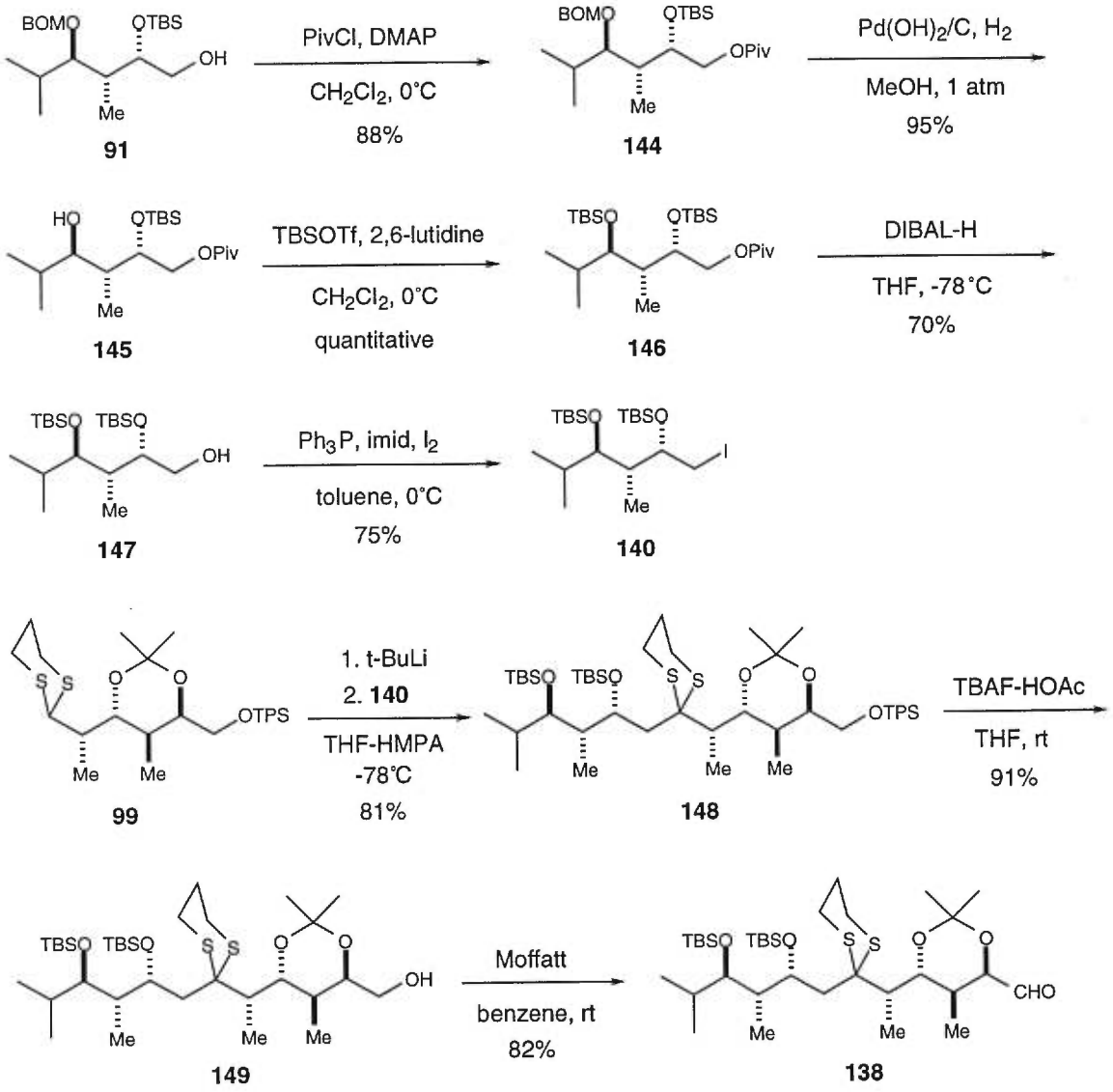


Figure 40 BAFILOMYCIN A1: RETROSYNTHETIC ANALYSIS 16-6-STRATEGY-3



A model synthetic sequence for the critical coupling of aldehyde **138** and a dienic derivative (X = I, or X = Bu_3Sn) was tested. Aldehyde **138** was prepared from **91** and **99** as shown in Scheme 32. Protection of the hydroxyl group of **91** as the pivaloyl ester gave **144**. Hydrogenolysis deprotection of the BOM group afforded **145**. Protection of the newly released hydroxyl group as TBS ether produced **146**, deprotection of pivaloyl protecting group with Dibal-H afforded **147**, and treatment of **147** with triphenylphosphine, imidazole and iodine afforded iodide **140**.

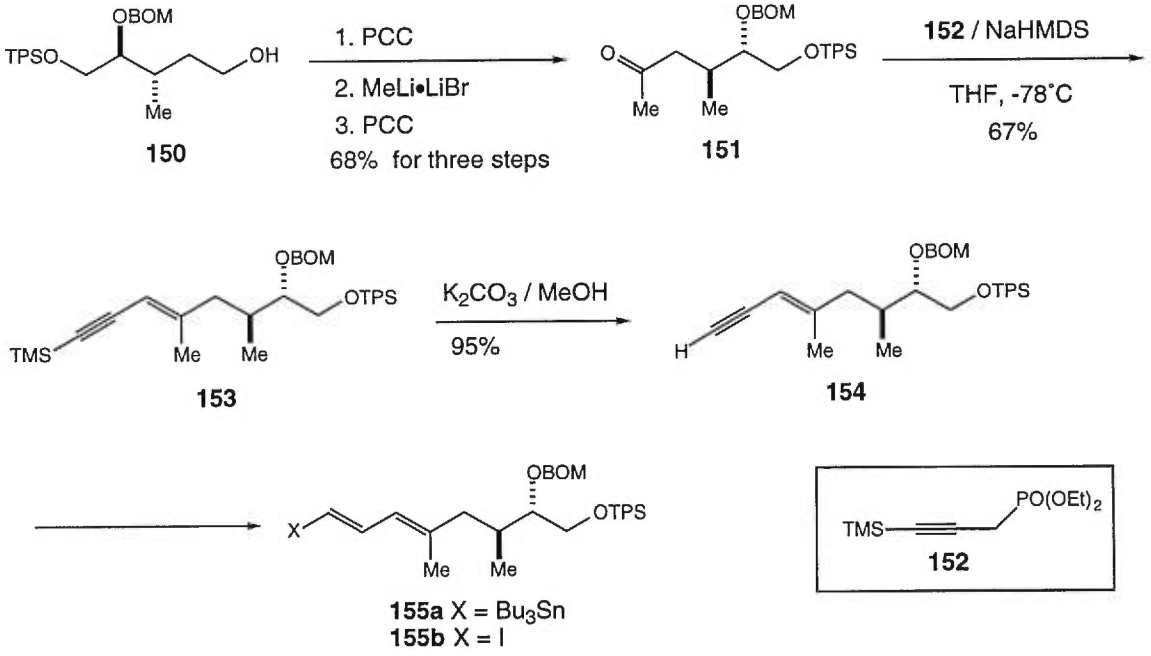
Scheme 32 BAFILOMYCIN A1: SYNTHESIS OF ALDEHYDE



Coupling of dithiane **99** and iodide **140** with *t*-BuLi, in THF-HMPA, produced **148** in high yield. Selective deprotection of TPS, in presence of di-TBS, using TBAF-HOAc, afforded alcohol **149** in excellent yield. Oxidation **149** to aldehyde **138** was proved very troublesome. Oxidation using the TPAP method[139] resulted in the clean formation of an unexpected product. Of the DMSO-based oxidations,[150] Swern and DMSO-TFAA gave complex mixtures, DMSO-Py-TFA-EDC afforded 32% **138** and 45% starting material. The best result was achieved with Moffatt oxidation,[151] DMSO-Py-TFA-DCC, which afforded 82% of the desired aldehyde **138**, although it suffered from difficulty of purification.

The model dienic derivative **155** (X = I, or X = Bu_3Sn) could be prepared from **150,**[152] which in turn was obtained from compound **9** by Dibal-H reduction. From compound **150**, a three-step sequence, oxidation with PCC to give the aldehyde, nucleophilic addition of MeLi to the aldehyde and oxidation with PCC once again,

Scheme 33 BAFILOMYCIN A1: SYNTHESIS OF DIENIC IODIDE

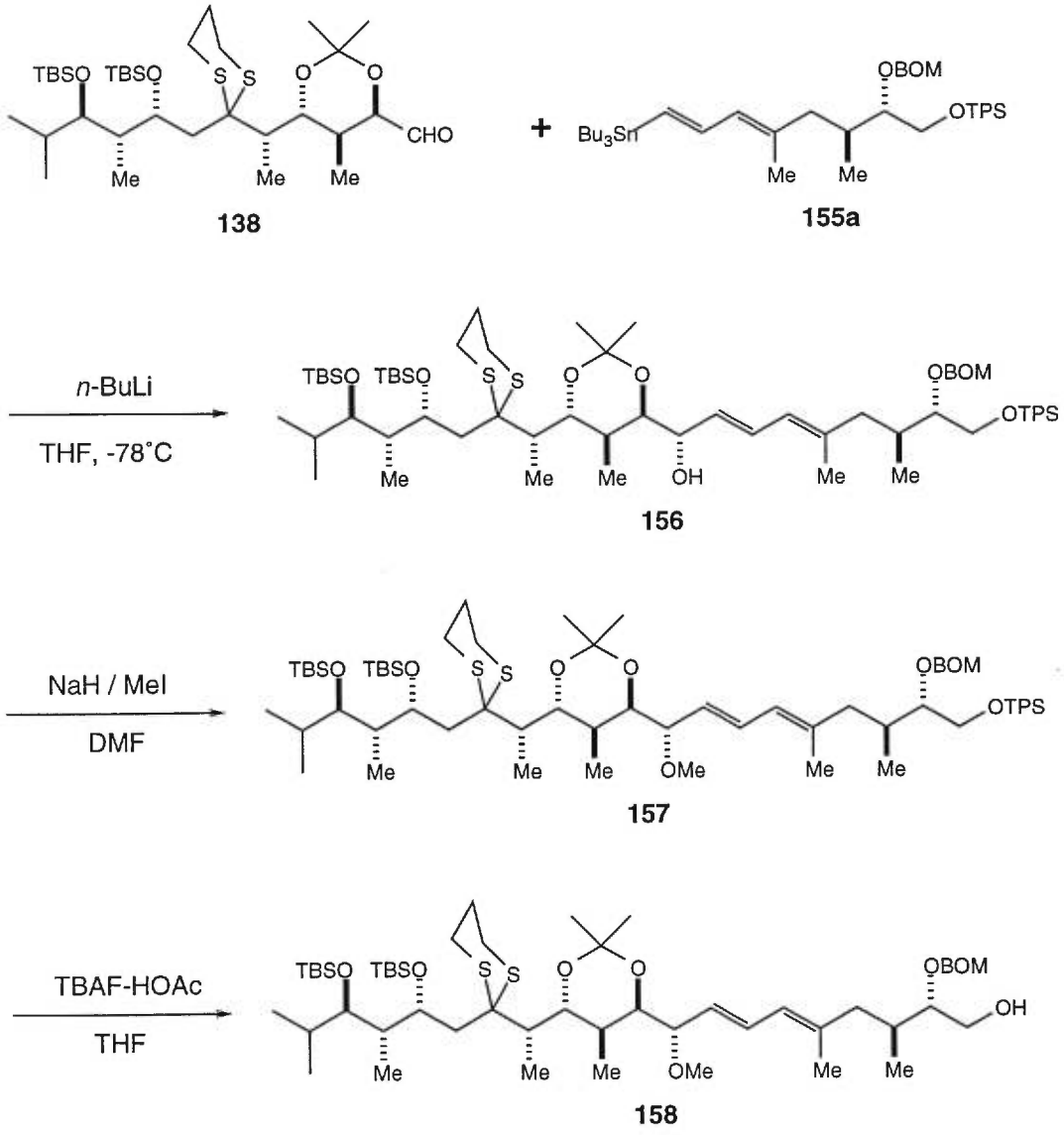


produced ketone **151**. A Wittig-type olefination with reagent **152,** prepared by a known procedure,[148] afforded TMS-protected enyne **153** as a mixture of *trans / cis* = 2:1. Deprotection of **153** with potassium carbonate afforded enyne **154** (2:1 mixture) in excellent yield.

Transformation of enyne **154** into dienic derivative **155** proved to be extremely challenging. Following the exact procedure of hydrostannylation under radical conditions (Bu_3SnH / AIBN, benzene, reflux) for a very similiar case[147], a strange tin compound, instead of the desired all-*trans* terminal dienic tin compound, was obtained. Although we went through the sequence shown in Scheme 34, coupling with aldehyde **138**, methylation of the hydroxyl and selective deprotection of the TPS group using this tin compound, NMR spectra did not match the desired spectra (bafilomycin A1 and acyclic derivatives). This tin compound could be an internal tin isomer. Hydroboration[146] of enyne **154** with catecholborane, in refluxing THF, gave no other products except starting material. Hydroboration with 9-BBN gave confusingly diene, instead of the expected dienic iodide, as the product. Hydrozirconation[145] of enyne **154** gave a mixture in which the BOM protecting group had been removed.

All these results indicated that the BOM group interfered with the reactions of this sequence. The hope is that the replacement of the BOM group with a TBS group in the real synthesis will alleviate these problems.

Scheme 34 BAFILOMYCIN A1: ATTEMPTED COUPLING OF ALDEHYDE AND DIENIC TIN



CHAPTER FIVE

GENERAL EXPERIMENTAL NOTES

§5-1 Instrumentation

All yields reported are isolated yields except where indicated. The stereo-selectivity was measured by ^{1}H-NMR analysis.

Melting points (mp) were measured on a Fisher-Johns melting point apparatus. All melting points are uncorrected.

Spectra of nuclear magnetic resonance of proton (^{1}H-NMR) and Carbon-13 (^{13}C-NMR) were recorded on a Varian VXR-300 (300 MHz), a Bruker AMX-300 (300 MHz) or a Bruker AMX-400 (400 MHz) spectrometer in a deuterated solvent as indicated with $CHCl_3$ (H, δ = 7.27 ppm; C, δ = 77.23 ppm) or C_6H_6 (H, δ = 7.16 ppm; C, δ = 128.39 ppm) as the internal reference. Chemical shifts (δ) and coupling constants (J) are expressed in ppm (part per million) and Hz (Hertz), respectively. The abbreviations used for the description of the peaks are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; dd, doublet of doublets; dt, doublet of triplets. DEPT experiments were performed routinely, methyl (CH_3) and methyne (CH) give positive signals, methylene (CH_2) gives a negative signal (-), and carbon without hydrogen gives no signal (0). ^{13}C-NMR and DEPT data are listed together. All chemical shifts are measured from the center of the resolved peaks, the unresolved multiplet and broad peaks are normally indicated as a range.

Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were determined on a VG Micro Mass 1212 and a Kratos MS-50 TCTA mass spectrometer, respectively, with desorption chemical ionization (CI), or fast atom bombardment (FAB).

Infrared spectra (IR) were recorded on a Perkin-Elmer 781 or Paragon 1000 infrared spectrophotometer in a chloroform solution with a sodium chloride cell.

Optical rotations ($[\alpha]_D$) were measured at the sodium line with a Perkin-Elmer 241 polarimeter at ambient temperature.

X-ray analysis was performed on the Enraf-Nonius CAD-4 diffractometer using graphite monochromatized Mo Kαradiation and the structure solved using direct methods (MULTAN80) and difference Fourier calculations (SHELX76).

All original data are available from Professor Stephen Hanessian, Université de Montréal.

§5-2 Chromatography

Flash chromatography was carried out according to the procedure of Still[153] using silica gel 60 (0.040-0.063 mm, 230-400 mesh ASTA) (E. Merck).

Thin layer chromatography (TLC) was performed using commercial precoated glass-backed Silica Gel 60 F254 plates with a layer thickness of 250 μm (E. Merck). This technique was used to follow the course of reactions, to determine the suitable solvent system for flash chromatography, and to check fractions of flash chromatography. A mixture of ethyl acetate-hexane on v/v basis, as indicated, was used as eluant.

TLC visualization

UV light

UV254 lamp was used to view TLC plates with UV light active compounds.

Stain solution

The TLC plate was dipped into the stain solution and heated to develop the colored spots.

(A) *Molybdate-Ceric solution*[154]

This solution was prepared by dissolving 50 g of ammonium molybdate (VI) tetrahydrate, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 20 g of ammonium cerium (IV) sulfate dihydrate,

$(NH_4)_4Ce(SO_4)\cdot 2H_2O$ in a solution of 1800 ml of distilled water and 200 ml of concentrated sulfuric acid.

(B) *Ninhydrin solution*

This solution was prepared by dissolving 2 g of ninhydrin dihydrate in a solution of 600 ml of butanol and 18 ml of acetic acid. This solution was used with nitrogen-containing compounds.

(c) *$KMnO_4$ solution*

A 10% aqueous solution of $KMnO_4$ was used with olefin-containing compounds.

§5-3 Solvents

Hexane, ethyl acetate and dichloromethane were distilled to remove any non-volatile material for chromatography and general use.

Anhydrous solvents were dried and distilled over suitable drying agents as listed below:

Solvent	Drying agent
THF	potassium/benzophenone
dichloromethane	calcium hydride
toluene	calcium hydride
triethylamine	calcium hydride
acetone	calcium chloride

§5-4 Reagents

All reagents were purchased from Aldrich, Sigma or Lancaster, and were used without further purification, except where indicated. All commercially unavailable reagents were prepared following the procedures listed below or known procedures.

(1). TBAF-HOAc (1:1 molar, 0.95 M in THF, pH~5.5)

This reagent was prepared by mixing of 10 ml TBAF solution (1.0 M in THF) and 572 μl HOAc.

(2). Anhydrous $ZnCl_2$

Zinc chloride was heated with flame molten and smoked for 15 min, then cooled down in a desiccator under vacuum. The anhydrous zinc chloride was grinded into powder before using.

§5-5 Anhydrous Reaction Conditions

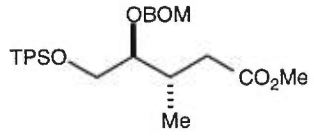
All anhydrous reactions were carried out under an atmosphere of dry nitrogen. The glass vessels, luer lock syringes, needles, and stirring bars were oven-dried at 110-140°C or flame-dried with a propane torch, and cooled to room temperature under a current of dry nitrogen. Micro-syringes were dried under vacuum using an oil pump at room temperature for at least 2 hours prior to use.

§5-6 Temperature Control

The temperatures expressed in the reaction schemes and in the text of the experimental part are the temperatures of the outside of reaction vessels except where indicated.

-78°C	acetone-dry ice bath
-40°C	acetone bath with liquid cooler
0°C (internal)	salt-ice-water bath
0°C	ice-water bath
room temperature	ambient temperature without any control

CHAPTER SIX
THE PROCEDURES AND DATA



(3S,4S)-4-benzyloxymethoxy-5-(tert-butyldiphenylsilanyloxy)-3-methyl-pentanoic acid methyl ester (9)

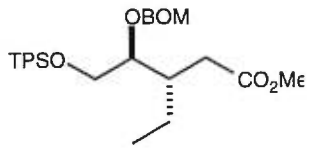
General procedure of cuprate addition

To a suspension of CuI (7.17 g, 37.7 mmol) in THF (400 ml) was added MeLi·LiBr (1.5 M in ether, 50.34 ml, 75.5 mmol) at -15°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (19.0 ml, 151 mmol), and then a solution of **4** (6.34 g, 12.5 mmol) in THF (60 ml). The reaction was continued for 3h at -78°C, then quenched with sat. NH_4Cl (100 ml). The reaction mixture was diluted with EtOAc (600 ml) and conc. NH_4OH (100 ml), then separated. The aqueous layer was extracted with EtOAc (3x200ml), and the combined organic extracts were washed with sat. NH_4Cl-NH_4OH (1:1, 200 ml), sat. NH_4Cl (200 ml) and brine (200 ml), then dried over Na_2SO_4. The crude product was purified by chromatography to afford **9** as an oil (6.04 g, 92%).

TLC: E/H = 1:5, R_f = 0.52.

$[\alpha]_D$ -21.7° (*c* 1.1, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.66 (m, 4H), 7.44-7.26 (m, 11H), 4.86 (d, J = 6.9 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 3.79-3.67 (m, 1H), 3.67 (s, 3H), 3.67-3.58 (m, 1H), 2.56 (dd, J = 4.36, 15.0 Hz, 1H), 2.41 (m, 1H), 2.17 (dd, J = 9.29, 15.0 Hz, 1H), 1.06 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H).



(3*S*, 4*S*)-4-Benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-3-ethyl-pentanoic acid methyl ester (10)

Procedure A

To a suspension of CuI (223 mg, 1.17 mmol) in THF (5 ml) at -40°C was added ethyl lithium (0.5 M in hexane, 4.7 ml, 2.35mmol), the resulting mixture was stirred for 30 min during which time the temperature was allowed to rise to -25°C, then cooled to -78°C. To the above mixture trimethylsilyl chloride (0.37 ml, 2.94 mmol) and a solution of **4** (98.8 mg, 0.19 mmol) in THF (5 ml) were added subsequently. The reaction was continued for 3 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated, the aqueous layer was extracted with EtOAc, the combined organic layer was washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **10** as an oil (78.4 mg, 75%).

Procedure B

To a suspension of CuI (202 mg, 1.06 mmol) in THF (5 ml) cooled to -78°C was added ethylmagnesium bromide (1.0 M in THF, 2.1 ml, 2.1 mmol). The resulting mixture was stirred for 30 min at -78°C, then trimethylsilyl chloride (0.34 ml, 2.66 mmol) and a solution of **4** (89.5 mg, 0.18 mmol) in THF (4 ml) were added subsequently. The reaction was continued for 3 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated, the aqueous layer was extracted with EtOAc, the combined organic layer was washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **10** as an oil (69 mg, 73%).

TLC: E/H = 1:5, R_f = 0.52.

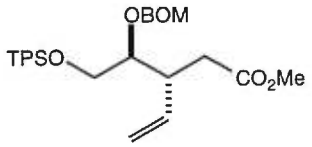
$[\alpha]_D$ -21.1° (*c* 4.3, $CHCl_3$)

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.7-7.55 (m, 4H), 7.45-7.20 (m, 11H), 4.85 (d, J = 6.9 Hz, 1H), 4.75 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 11.7 Hz, 1H), 4.50 (d, J = 11.8 Hz, 1H), 3.80-3.60 (m, 3H, s, 3H), 2.45 (dd, J = 4.7, 15.7 Hz, 1H), 2.25 (d, J = 8.1 Hz, 1H), 2.20 (m, 1H), 1.50 (m, 1H), 1.45 (m, 1H), 1.05 (s, 9H), 0.90 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.51 (0), 137.32 (0), 135.08, 135.03, 132.76 (0), 129.15, 127.81, 127.33, 127.18, 127.15, 127.02, 94.35 (-), 78.46, 69.18 (-), 64.02(-), 50.87, 37.80, 33.90 (-), 26.24, 23.34 (-), 18.60 (0), 11.06.

IR: ($CHCl_3$): 2940, 1970, 1840, 1740, 1600 cm^{-1}.

HRMS: $C_{32}H_{43}O_5Si$, calc.: 535.2879, found: 535.2848.



(3*R*,4*S*)-3-[1-Benzyloxymethoxy-2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-pent-4-enoic acid methyl ester (11)

To a suspension of CuI (141 mg, 0.74 mmol) in THF (5 ml) cooled to -78°C was added vinylmagnesium bromide (1.0 M in THF, 1.5 ml, 1.5 mmol). The resulting mixture was stirred for 30 min at -78°C, then trimethylsilyl chloride (0.28 ml, 2.23 mmol) and a solution of **4** (62.5 mg, 0.12 mmol) in THF (4 ml) were added subsequently. The reaction was continued for 3 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated, the aqueous layer was extracted with EtOAc, the combined organic layers were washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **11** as an oil (46 mg, 70%).

TLC: E/H = 1:5, R_f = 0.52.

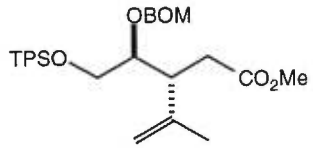
$[\alpha]_D$ -19.5° (*c* 2.1, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.65 (m, 4H), 7.45-7.27 (m, 11H), 5.74 (m, 1H), 5.15 (m, 2H), 4.86 (d, J = 6.9 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 4,64 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 3.73 (m, 3H), 3.65 (s, 3H), 3.00 (m, 1H), 2.67 (dd, J = 4.6, 15.3 Hz, 1H), 2.40 (dd, J = 9.6, 15.3 Hz, 1H), 1.07 (s, 9H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 172.06 (0), 137.35 (0), 137.21, 135.23, 135.15, 132.86 (0), 132.82 (0), 129.29, 129.26, 127.96, 127.90, 127.33, 127.26, 127.20, 116.50 (-), 94.14 (-), 79.41, 69.4 1(-), 63.84 (-), 51.02, 41.53, 34.89 (-), 26.38, 18.75 (0).

IR: ($CHCl_3$): 2950, 1970, 1830, 1745, 1650, 1600 cm^{-1}.

MS: 533.2 (m-1), 475.2, 425.3, 305.2.



(3*R*,4*S*)-3-[1-Benzyloxymethoxy-2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-4-methyl-pent-4-enoic acid methyl ester (12)

Procedure A

To a stirred solution of isopropenyl bromide (225 µl, 2.47 mmol) in THF (3 ml) cooled

to -78°C was added tert-butyllithium (1.7M in pentane, 4.64 ml, 7.89 mmol) dropwise via syringe until a deep yellow color remained. The resulting mixture was stirred for 60 min at -78 °C and then transferred via cannula to a suspension of CuI (235 mg, 1.23 mmol) in THF (5 ml) precooled to -78°C, the mixture was vigorously stirred for 30 min and the temperature was allowed to rise to -40°C during this time. The above solution was recooled to -78°C, then trimethylsilyl chloride (486 µl, 3.71 mmol) and a solution of **1** (104 mg, 0.21 mmol) in THF (5 ml) were added subsequently. The reaction was continued for 2 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated, the aqueous layer was extracted with EtOAc, the combined organic layer was washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **12** as an oil (68 mg, 60%).

Procedure B

To a suspension of CuI (151 mg, 0.79 mmol) in THF (1 ml) cooled to -78°C was added (2-propenyl)magnesium bromide (0.5 M in THF, 3.2 ml, 1.6 mmol). The resulting mixture was stirred for 30 min at -78°C, then trimethylsilyl chloride (0.30 ml, 2.39 mmol) and a solution of **4** (103 mg, 0.20 mmol) in THF (1 ml) were added subsequently. The reaction was continued for 3 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated, the aqueous layer was extracted with EtOAc, the combined organic layers were washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **12** as an oil (80 mg, 72%).

TLC: E/H = 1:5, R_f = 0.52.

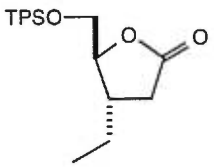
$[\alpha]_D$ -20.1° (*c* 3.7, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.65 (m, 4H), 7.44-7.26 (m, 11H), 4.87 (d, J = 11.9 Hz, 1H), 4.80 (m, 2H), 4.75 (d, J = 7.1 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 3.76-3.66 (m, 3H), 3.65 (s, 3H), 2.98-2.94 (m, 1H), 2.75 (dd, J = 4.7, 15.3 Hz, 1H), 2.45 (dd, J = 10.4, 15.3 Hz, 1H), 1.70 (s, 3H), 1.06 (s, 9H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 172.87 (0), 143.95 (0), 137.40 (0), 135.26, 135.16, 132.90 (0), 132.83 (0), 129.30, 129.26, 127.99, 127.49, 127.34, 127.27, 127.25, 112.92 (-), 94.35 (-), 78.36, 69.53 (-), 64.16 (-), 51.04, 44.01, 34.52(-), 26.40, 20.39, 18.76 (0).

IR: ($CHCl_3$): 2980, 1970, 1830, 1750, 1660, 1600 cm^{-1}.

MS: 547 (m+1), 489, 439, 409.



(4*S*,5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-4-ethyl-dihydro-furan-2-one (13)

Procedure A

To a suspension of CuI (155 mg, 0.82 mmol) in THF (4 ml) at -78°C was added ethyl magnesium bromide (1.0 M in THF, 1.6 ml, 1.6 mmol). The resulting mixture was stirred for 40 min at -78°C, then a solution of **12a** (48 mg, 0.14 mmol) in THF (4 ml) was added. The reaction was continued for 2 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **13** as an oil (31 mg, 60%).

$[\alpha]_D$ +27.4° (*c* 1.3, $CHCl_3$).

Procedure B

To a stirred solution of **10** (85 mg, 0.16 mmol) in CH_2Cl_2 (4 ml) at -60°C was added trimethylsilyl bromide (300 µl, 2.3 mmol). The resulting mixture was stirred and the temperature was allowed to gradually rise to 0°C over 90 min, then quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to give **13** as an oil (45.2 mg, 74%).

$[\alpha]_D$ +28.5° (*c* 2.3, $CHCl_3$).

procedure C

A mixture of vinyl lactone **14** (26.8 mg) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 20 mg) in MeOH (2 ml) under 1 atm of hydrogen was stirred at room temperature for 4 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The product was purified by chromatography to give **13** as an oil (26.8 mg, 100%).

$[\alpha]_D$ +27.7° (*c* 1.0, $CHCl_3$).

TLC: E/H = 1:4, R_f = 0.40.

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.65 (m, 4H), 7.48-7.38 (m, 6H), 4.21 (m, 1H), 3.88 (dd, J = 3.3, 11.4 Hz, 1H), 3.69 (dd, J = 3.5, 11.4 Hz, 1H), 2.81 (dd, J = 9.0, 17.6 Hz, 1H), 2.40 (m, 1H), 2.22 (dd, J = 6.2, 17.6 Hz, 1H), 1.55 (m, 1H), 1.40 (m, 1H),

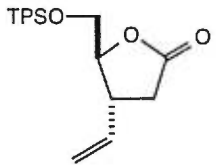
1.07 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 176.54 (0), 135.22, 135.12, 132.52 (0), 132.14 (0), 129.48, 127.41, 84.74, 64.38 (-), 37.70, 34.38 (-), 26.43 (-), 26.33, 18.77 (0), 11.14.

IR ($CHCl_3$): 2910, 1960, 1765, 1580, 1450 cm^{-1}.

MS: 325 ($M-C_4H_9$), 281.

HRMS: $C_{19}H_{21}O_3Si$ ($M-C_4H_9$), calc.: 325.1256, found: 325.1248.



(4*R*,5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-4-vinyl-dihydro-furan-2-one (14)

Procedure A

To a suspension of CuI (165 mg, 0.87 mmol) in THF (4 ml) at -78°C was added vinyl magnesium bromide (1.0 M in THF, 1.74 ml, 1.74 mmol). The resulting mixture was stirred for 40 min, then a solution of **12a** (51 mg, 0.14 mmol) in THF (4 ml) was added. The reaction was continued for 2 h at -78°C, then quenched with conc. NH_4OH-sat. NH_4Cl (1:1). The mixture was diluted with EtOAc and separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with conc. NH_4OH-sat. NH_4Cl (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **14** as an oil (33 mg, 60%).

$[\alpha]_D$ +33.1° (*c* 0.7, $CHCl_3$).

Procedure B

To a solution of **11** (40 mg, 0.07 mmol) in CH_2Cl_2(4 ml) at -70°C was added trimethylsilyl bromide (150 µl, 1.1 mmol). The resulting mixture was stirred and the temperature was allowed to gradually rise to 0°C over 90 min, then quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **14** as an oil (20 mg, 70%).

$[\alpha]_D$ +32.5° (*c* 1.0, $CHCl_3$).

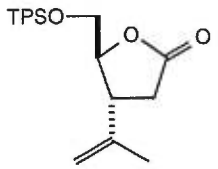
TLC: E/H = 1:5, R_f = 0.40.

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.65 (m, 4H), 7.46-7.27 (m, 6H), 5.80 (m, 1H), 5.15 (s, 1H), 5.10 (d, J = 6.3 Hz, 1H), 4.25 (m, 1H), 3.94 (dd, J = 3.8, 11.7 Hz, 1H), 3.74 (dd, J = 3.5, 11.7 Hz, 1H), 3.20 (m, 1H), 2.84 (dd, J = 8.9, 17.6 Hz, 1H), 2.60 (dd, J

= 8.5, 17.6 Hz, 1H), 1.07 (s, 9H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 175.38 (0), 135.85, 135.08, 134.98, 132.33 (0), 131.95 (0), 129.35, 127.27, 116.89 (-), 84.01, 62.76 (-), 40.19, 34.53 (-), 26.18, 18.67 (0).

IR ($CHCl_3$): 2900, 1950, 1880, 1760, 1630, 1570, 1450 cm^{-1}.



(4*R*,5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-4-isopropenyl-dihydro-furan-2-one (15)

Procedure A

To a suspension of CuI (252 mg, 1.3 mmol) in THF (1.5 ml) at -78°C was added isopropenylmagnesium bromide (0.5 M in THF, 5.3 ml, 2.6 mmol). The resulting grey-green mixture was stirred for 30 min and then a solution of **12a** (78 mg, 0.22 mmol) in THF (1.5 ml) was added. The reaction was continued for 2 h at -78 °C and quenched with sat. NH_4Cl-conc. NH_4OH (1:1). The reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl-conc. NH_4OH (1:1) and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford *trans*-**15** (68 mg, 78%) and *cis*-isomer.

Procedure B

To a solution of isopropenyl **12** (40 mg, 0.07 mmol) in dichloromethane (4 ml) at -60°C was added trimethylsilyl bromide (144 µl, 1.1 mmol), the mixture was stirred and the temperature allowed to rise gradually to 0°C over 90 min, the reaction was quenched with saturated ammonium chloride solution. The reaction mixture was diluted with dichloromethane and separated, the organic layer was washed with saturated sodium bicarbonate, brine and dried over sodium sulfate. The product was purified by chromatography to afford **15** as an oil (18 mg, 63%).

trans-**15**

TLC: E/H = 1:5, R_f = 0.65.

$[\alpha]_D$ +30.4° (*c* 3.3, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.70-7.66 (m, 4H), 7.48-7.26 (m, 6H), 4.85 (s, 1H), 4.81 (s, 1H)), 4.39-4.36 (m, 1H), 3.93 (dd, J = 3.0, 11.5 Hz, 1H), 3.73 (dd, J = 3.3, 11.5 Hz, 1H), 3.21-3.15 (m, 1H), 2.84 (dd, J = 9.5, 17.8 Hz, 1H), 2.49 (dd, J = 6.7, 17.8 Hz, 1H), 1.74 (s, 3H), 1.08 (s, 9H).

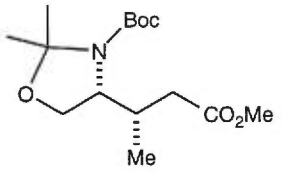
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 176.23 (-), 143.00 (0), 135.56, 135.46, 132.81

(0), 132.41 (0), 129.85, 127.76, 112.76 (-), 83.44, 64.25 (-), 43.39, 33.88 (-), 26.68, 19.48, 19.12 (0).

***cis*-isomer**

TLC: E/H = 1:5, R_f = 0.45.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.70-7.62 (m, 4H), 7.47-7.27 (m, 6H), 4.96-4.94 (m, 1H), 4.15-4.11 (m, 1H), 3.96 (dd, J = 2.2, 12.0 Hz, 1H), 3.68 (dd, J = 3.2, 12.0 Hz, 1H), 3.29 (dd, J = 9.6, 11.9 Hz, 1H), 2.89 (d, J = 12.0 Hz, 1H), 1.75 (s, 3H), 1.06 (s, 9H).



(4*R*)-4-[(1*S*)-2-Methoxycarbonyl-1-methyl-ethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (16)

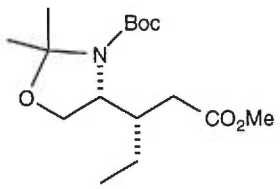
To a stirred suspension of CuI (2.0 g, 10.5 mmol) in THF (100 ml) was added MeLi·LiBr (1.5 M in ether, 14.1 ml, 21.0 mmol) at -25°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (4.0 ml, 31.6 mmol) and a solution of **8** (1.0 g, 3.5 mmol) in THF (50 ml) subsequently. The reaction was continued for 2.5 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-conc. NH_4OH (1:1), sat. NH_4Cl and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **16** as an oil (1.0 g, 95%).

TLC: E/H = 1:5, R_f = 0.45.

$[\alpha]_D$ -16.3° (*c* 0.54, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 3.95-3.86 (m, 2H), 3.80-3.75 (m, 1H), 3.65 (s, 3H), 2.55-2.45 (m, 2H), 2.10-2.00 (m, 1H), 1.60-1.40 (br, 6H), 1.45 (s, 9H), 0.90 (d, J = 8.1 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.1, 152.6, 93.4, 79.7, 63.7, 60.6, 51.0, 36.0, 32.1, 27.9, 26.0, 23.0, 16.2.



(4*R*)-4-[(1*S*)-1-Methoxycarbonylmethyl-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (17)

To a stirred suspension of CuI (188 mg, 0.99 mmol) in THF (10 ml) at -78°C was added ethylmagnesium bromide (1.0 M in THF, 2.0 ml, 2.0 mmol). The resulting mixture was stirred for 30 min, then trimethylsilyl chloride (0.37 ml, 3.0 mmol) and a solution of **8** (94 mg, 0.33 mmol) in THF (4 ml) were added subsequently. The reaction was continued for 3 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-conc. NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **17** as an oil (72 mg, 70%).

TLC: E/H = 1:5, R_f = 0.45.

$[\alpha]_D$ -20.5° (*c* 0.8, $CHCl_3$).

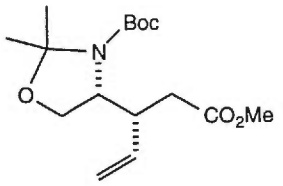
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.10-3.88 (br, 2H), 3.80-3.78 (br, 1H), 3.65 (s, 3H), 2.60-2.40 (br, 2H), 2.15-2.05 (br, 1H), 1.65-1.15 (br, s, 17H), 0.93 (t, J = 7.6 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.78, 152.34, 94.12, 79.89, 69.83, 63.53, 58.20, 51.34, 38.55, 34.12, 28.27, 25.98, 24.77, 22.81, 11.82.

IR ($CHCl_3$): 2965, 1730, 1690, 1470, 1460, 1430 cm^{-1}.

MS: 316.2 (m+1), 260.1, 216.2, 202.1.

HRMS: $C_{16}H_{30}NO_5$ (m+1), calc.: 316.2124, found: 316.2108.



(4*R*)-4-[(1*S*)-1-Methoxycarbonylmethyl-allyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (18)

To a stirred suspension of CuI (222 mg, 1.2 mmol) in THF (7 ml) at -78°C was added vinylmagnesiumbromide (1.0 M in THF, 2.3 ml, 2.3 mmol). The resulting mixture was stirred for 60 min, then trimethylsilyl chloride (0.147 ml, 1.2 mmol) and a solution of **8** (111 mg, 0.39 mmol) in THF (3 ml) were added subsequently. The reaction was continued for 2 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted

with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-conc. NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **18** as an oil (101 mg, 83%).

TLC: E/H = 1:5, R_f = 0.45.

$[\alpha]_D$ -12.4° (*c* 1.2, $CHCl_3$).

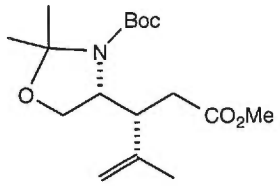
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 5.75-5.55 (br, 1H), 5.10-5.05 (br, 2H), 4.05-3.75 (br, 3H), 3.62 (s, 3H), 3.10 (br, 1H), 2.52 (dd, J = 4.0, 15.2 Hz, 1H), 2.31 (dd, J = 4.5, 15.2 Hz, 1H), 1.60-1.45 (br, 15H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) =172.21, 152.23, 136.77, 116.56, 93.72 79.50, 63.83, 59.11, 50.86, 41.97, 33.24, 27.68, 25.48, 21.86.

IR ($CHCl_3$): 3050, 2980, 1730, 1690, 1650 cm^{-1}.

MS: 314.2 (m+1), 258.1, 214.2, 200.1.

HRMS: $C_{16}H_{28}NO_5$ (m+1), Calc.: 314.1967, Found: 314.1979.



(4*R*)-4-[(1*R*)-1-Methoxycarbonylmethyl-2-methyl-allyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (19)

To a stirred solution of isopropenyl bromide (1.24 ml, 13.6 mmol) in THF (35 ml) at -78°C was added tert-butyllithium (1.7 M in pentane, 20 ml, 34 mmol) dropwise via syringe until a deep yellow color remained. The resulting mixture was stirred for 60 min at -78°C and then transferred via cannula to a suspension of CuI (1.3 g, 6.8 mmol) in THF (55 ml) precooled to -78°C. The mixture was vigorously stirred for 30 min and the temperature allowed to rise to -40°C. The resulting mixture was recooled to -78°C, and then trimethylsilyl chloride (2.6 ml, 20 mmol) and a solution of **8** (684 mg, 2.3 mmol) in THF (10 ml) were added subsequently. The reaction was continued for 2 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-conc. NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **19** as a solid (560 mg, 75%).

TLC: E/H = 1:5, R_f = 0.45.

$[\alpha]_D$ +5.75° (*c* 1.3, $CHCl_3$).

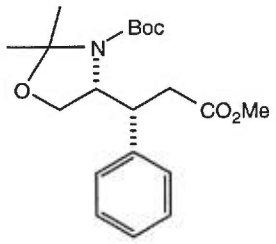
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.87 (s, 1H), 4.78 (s, 1H), 4.15-3.80 (br, 3H), 3.63 (s, 3H), 3.20 (br, 1H), 2.55 (br, 2H), 1.79 (br, 3H), 1.70-1.40 (br, m, 15H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) =173.19, 153.00, 144.52, 111.40, 94.52, 80.19, 63.29, 57.37, 51.41, 43.48, 31.88, 28.34, 25.99, 23.02, 22.22.

IR ($CHCl_3$): 2950, 1730, 1690, 1645 cm^{-1}.

MS: 328.2 (m+1), 272.1.

HRMS: $C_{17}H_{30}NO_5$ (m+1), calc.: 328.2124, found: 328.2110.



(4*R*)-4-[(1*R*)-2-Methoxycarbonyl-1-phenyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (20)

To a suspension of CuI (216 mg, 1.14 mmol) in THF (10 ml) was added phenylmagnesium bromide (1.0 M in THF, 2.3 ml, 2.3 mmol) at -78°C. The resulting mixture was stirred and the temperature was allowed to rise to -20°C over 50 min, then recooled to -78°C. To the reaction mixture trimethylsilyl chloride (0.43 ml, 3.42 mmol) and a solution of **8** (108 mg, 0.38 mmol) in THF (4 ml) were added subsequently. The reaction was continued for 3 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-conc. NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **20** as an oil (110 mg, 80%).

TLC: E/H = 1:5, R_f = 0.45.

$[\alpha]_D$ +36.0° (*c* 2.5, $CHCl_3$).

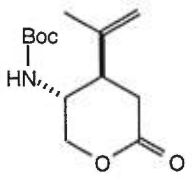
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.45-7.15 (m, 5H), 4.30-3.60 (br, 4H), 3.56 (s, 3H), 2.85 (d, J = 8.6 Hz, 2H), 1.70-1.45 (br, m, 15H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 172,30, 151.77, 139.66, 128.03, 127.92, 127.81, 127.38, 127.02, 126.22, 94.13, 79.73, 62.89, 60.93, 50.92, 42.14, 31.47, 27.80, 25.36, 23.16, 21.68.

IR ($CHCl_3$): 2960, 1955, 1880, 1810, 1745, 1690, 1610 cm^{-1}.

MS: 364.1(m+1), 264.1, 250.1.

HRMS: $C_{20}H_{30}NO_5$ (m+1), calc.: 364.2124, found: 364.2111.



[(3*R*,4*R*)-(4-Isopropenyl-6-oxo-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester (21)

To a solution of ester **19** (105 mg) in methanol (2 ml) was added PTSA (15 mg) and the resulting mixture was stirred for 18 h. The mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4. A crude product was obtained after removal of solvent and dried under vacuum.

A solution of the crude product in toluene (2 ml) was refluxed for 10 h. A solid product was obtained after removing solvent and was purified by chromatography to afford a crystalline lactone **21** suitable for X-ray analysis (49 mg, 60%).

TLC: E/H = 1:2, R_f = 0.50.

mp: 129-131°C.

$[\alpha]_D$ +24.2° (*c* 2.3, $CHCl_3$).

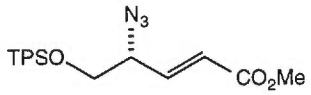
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 4.94 (s, 1H), 4.85 (s, 1H), 4.69 (d, J = 6.5 Hz, 1H), 4.47 (dd, J = 4.3, 11.4 Hz, 1H), 4.06-4.02 (m, 1H), 3.90 (br, 1H), 2.71-2.60 (m, 1H), 2.59-2.53 (m, 2H), 1.75 (s, 3H), 1.43 (s, 9H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm)= 171, 156, 143, 114, 82, 70, 48, 44, 33, 29, 19.

IR ($CHCl_3$): 3450, 1740, 1710, 1650 cm^{-1}.

HRMS: $C_{13}H_{22}NO_4$ (m+1), calc.: 256.1548, found, 256.1533.

X-Ray Diffraction Analysis Data.



(4*R*)-4-Azido-5-(tert-butyl-diphenyl-silanyloxy)-pent-2-enoic acid methyl ester (25)

To a solution of allylic alcohol **3** (207 mg, 0.54 mmol) and Ph_3P (424 mg, 1.62 mmol) in THF (5 ml) at 0°C were added DEAD (251 µl, 1.62 mmol) and DPPA (350 µl, 1.62 mmol) subsequently. The resulting solution was stirred at 0°C for 1 h, then room temperature for 1 h. The reaction mixture, after removing solvent, was directly purified by chromatography to afford azido **25** and **25a**.

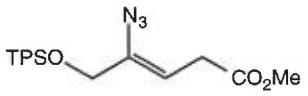
azido **25** (31 mg, 14%):

TLC: E/H = 1:5, R_f = 0.52.

$[\alpha]_D$ +35.5° (*c* 3.5, $CHCl_3$).

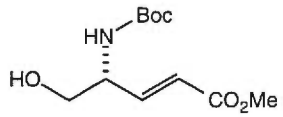
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.72-7.24 (m, 10H), 6.86 (dd, J = 5.2 15.6 Hz, 1H), 6.02 (dd, J = 1.5, 15.6 Hz, 1H), 4.48 (dd, J = 1.4, 5.0 Hz, 1H), 3.73 (s, 3H), 3.24 (dd, J=5.1, 12.5 Hz, 1H), 3.11 (dd, J = 4.7, 12.5 Hz, 1H), 1.13 (s, 9H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 166.27 (0), 146.41, 135.71, 132.94 (0), 132.51 (0), 129.96, 127.78, 127.70, 126.03, 126.01, 121.95, 120.15, 120.10, 71.77, 55.68 (-), 51.52, 26.84, 19.15 (0).
IR ($CHCl_3$): 3019, 2400, 2173, 2107, 1718, 1590, 1520, 1489, 1427 cm^{-1}.



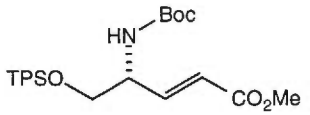
4-Azido-5-(tert-butyl-diphenyl-silanyloxy)-pent-3-enoic acid methyl ester (25a)

vinyl azide **25a** (86 mg, 39%):
TLC: E/H = 1:5, R_f = 0.60
$[\alpha]_D$ 0.0° (*c* 1.4, $CHCl_3$).
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.71-7.68 (m, 4H), 7.47-7.39 (m, 6H), 4.87 (t, J = 7.0 Hz, 1H), 4.34 (s, 2H), 3.68 (s, 3H), 3.10 (d, J = 7.0 Hz, 2H), 1.08 (s, 9H).
^{13}C-NMR (400MHz, $CDCl_3$): δ(ppm) =171.54 (0), 137.15 (0), 135.52, 132.63 (0), 129.82, 127.69, 108.82, 64.70 (-), 51.78, 31.53 (-), 26.56, 19.06 (0).
IR ($CHCl_3$): 2970, 2940, 2870, 2120, 1745, 1680, 1595, 1480, 1470, 1440 cm^{-1}.
HRMS: $C_{22}H_{26}O_3N_3Si$ (M-1), calc.: 408.1743; found: 408.1762.



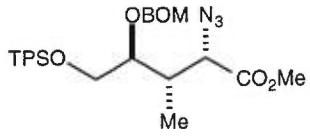
(4*R*)-4-tert-Butoxycarbonylamino-5-hydroxy-pent-2-enoic acid methyl ester (27a)

To a solution of acetonide **8** (367 mg, 1.28 mmol) in methanol (4 ml) was added PTSA (50 mg). The resulting solution was stirred for 20 h at room temperature. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford hydroxy **27a** as an oil (167 mg, 53%).
TLC: E/H = 1:2, R_f = 0.20
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 6.84 (dd, J = 4.9, 15.7 Hz, 1H), 5.92 (dd, J = 1.7, 15.7 Hz, 1H), 5.50-5.40 (br, 1H), 4.35-4.25 (br, 1H), 3.63 (s, 3H), 3.70-3.50 (m, 3H), 1.34 (s, 9H).



(4*R*)-4-tert-Butoxycarbonylamino-5-(tert-butyl-diphenyl-silanyloxy)-pent-2-enoic acid methyl ester (28)

To a solution of hydroxy 27a (167 mg, 0.68 mmol) and imidazole (162 mg, 2.4 mmol) in THF (5 ml) was added tert-butyldiphenylsilyl chloride (193 µl, 0.75 mmol) at room temperature. The resulting solution was stirred for 2 h at this temperature. The reaction mixture was diluted with EtOAc, washed with water and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford 28 as an oil (298 mg, 90%).
TLC: E/H = 1:5, R_f = 0.37.
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.64-7.60 (m, 4H), 7.45-7.26 (m, 6H), 6.92 (dd, J = 5.0, 15.7 Hz, 1H), 5.98 (dd, J = 1.8, 15.7 Hz, 1H), 4.95-4.85 (br, 1H), 4.50-4.40 (br, 1H), 3.75 (s, 3H), 3.80-3.60 (m, 2H), 1.45 (s, 9H), 1.05 (s, 9H).



(2*S*,3*S*,4*S*)-2-Azido-4-benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-3-methyl-pentanoic acid methyl ester (31)

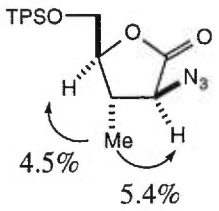
To a solution of ester **9** (147 mg, 0.28 mmol) in THF (8 ml) at -78°C was added KHMDS (0.5 M in toluene, 0.62 ml, 0.31 mmol). The mixture was stirred for 50 min and then a solution of trisyl azide (114 mg, 0.37 mmol) in THF (4 ml) was added. The resulting mixture was stirred further for 40 min at -78°C, and then HOAc (37 µl, 0,85 mmol) was added, and followed by immediately warming to 30°C and stirring for 1.5 h at this temperature. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give an azido ester **31** as an oil (110 mg, 70%).
TLC: E/H = 1:10, R_f = 0.30.
$[\alpha]_D$ -37.8° (*c* 3.0, $CHCl_3$).
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.65 (m, 4H), 7.46-7.25 (m, 11H), 4.83 (d, J = 6.7 Hz, 1H), 4.77 (d, J = 6.7 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 3.0 Hz,

1H), 4.55 (d, J = 12.0 Hz, 1H), 3.87 (dd, J = 2.8, 11.5 Hz, 1H), 3.82 (s, 3H), 3.80-3.66 (m, 1H), 3.60-3.55 (m, 1H), 2.59-2.53 (m, 1H), 1.06 (s, 9H), 0.83 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 170.81 (0), 137.25 (0), 135.26, 135.20, 132.79 (0), 129.37, 128.01, 127.33, 127.26, 94.01 (-), 78.61, 69.65 (-), 63.07 (-), 62.90, 52.18, 36.85, 26.42, 18.85 (0), 10.69.

IR ($CHCl_3$): 2940, 2100 (-N_3), 1960, 1890, 1820, 1720, 1590 cm^{-1}.

MS: 584 (m+23).



(3S,4S,5S)-3-Azido-5-(tert-butyl-diphenyl-silanyloxymethyl)-4-methyl-dihydro-furan-2-one (32)

To a solution of azido ester **31** (60 mg, 0.11 mmol) in CH_2Cl_2 (4 ml) at -60°C was added trimethylsilyl bromide (250 µl, excess). The mixture was stirred and the temperature was allowed to rise gradually to 0°C in 90 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2 and separated, the aqueous phase was extracted with CH_2Cl_2, the combined organic phase was washed with sat.$NaHCO_3$ and brine, dried over Na_2SO_4. The product was purified by chromatography to afford an azido lactone **32** as an oil (41 mg, 80%).

TLC: E/H = 1:5, R_f = 0.15.

$[\alpha]_D$ -53.5° (*c* 1.3, $CHCl_3$).

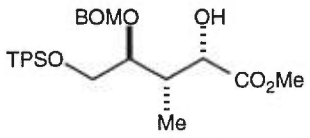
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.68-7.64 (m, 4H), 7.49-7.27 (m, 6H), 4.08-4.03 (m, 1H), 3,93 (dd, J = 3.0, 12.0 Hz, 1H), 3.89 (d, J = 11.7 Hz, 1H), 3.75 (dd, J = 3.8, 12.0 Hz, 1H), 2.51-2.42 (m, 1H), 1.17 (d, J = 6.6 Hz, 3H), 1.06 (s, 9H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 171.79, 135.22, 135.12, 132.32, 132.05, 129.56, 129.49, 127.45, 83.04, 63.95, 61.73, 37.42, 26.31, 18.82, 14.42.

NOE-NMR: as shown in picture.

IR ($CHCl_3$): 2910, 2850, 2110 (-N_3), 1960, 1890, 1780, 1590, 1470, 1460 cm^{-1}.

MS: 422.3 (m+23), 382.3, 352.2, 332.3.



(2*S*,3*S*,4*S*)-4-benzyloxymethoxy-5-(tert-butyldiphenylsilanyloxy)-2-hydroxy-3-methyl-pentanoic acid methyl ester (33)

General procedure of hydroxylation

To a solution of ester **9** (5.96 g, 11.5 mmol) in THF (120 ml) was added KHMDS (0.5 M in toluene, 27.5 ml, 13.7 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (4.48 g, 17.2 mmol) in THF (20 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give a hydroxy ester **33** as an oil (5.59 g, 91%).

TLC: E/H = 1:5, R_f = 0.25.

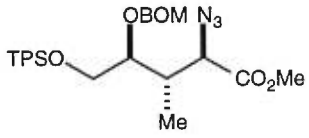
$[\alpha]_D$ -10.3° (*c* 0.7, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.65 (m, 4H), 7.46-7.26 (m, 11H), 4.84 (d, J = 6.7 Hz, 1H), 4.80 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 2.3 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.81 (s, 3H), 3.80-3.67 (m, 2H), 2.40 (m, 1H),1.06 (s, 9H), 0.83 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 175.12, 137.47, 135.52, 133.12, 129.62, 128.27, 127.70, 127.59, 94.56, 79.52, 70.44, 69.81, 63.95, 52.25, 37.71, 26.69, 19.10, 10.07.

IR ($CHCl_3$): 3530, 2960, 1780, 1460, cm^{-1}.

HRMS: $C_{31}H_{40}O_6SiNa$, calc.: 559.2492; found: 559.2518.



(2*R*,3*S*,4*S*)-(2-Azido-4-benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-3-methyl-pentanoic acid methyl ester (34)

To a solution of the hydroxy ester **33** (25 mg, 0.047 mmol) and Ph_3P (61.5 mg, 0.235 mmol) in THF (1 ml) at 0°C were added DEAD (37 µl, 0.235 mmol) and $(PhO)_2PON_3$ (50.9 µl, 0.235 mmol) subsequently. The resulting mixture was stirred at 0°C for 2 h and

then at room temperature for 16 h. The crude product after removing solvent was directly purified by chromatography to afford the azido ester **34** as an oil (21 mg, 80%).

TLC: E/H = 1:5, R_f = 0.50.

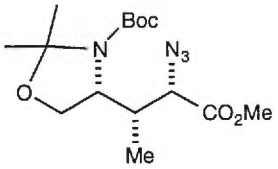
$[\alpha]_D$ +14.5° (*c* 1.2, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.65 (m, 4H), 7.46-7.21 (m, 11H), 4.71 (dd, J = 7.0, 8.9 Hz, 2H), 4.51 (dd, J = 12.0, 20.0 Hz, 2H), 4.13 (d, J = 4.1 Hz, 1H), 3.89 (dd, J = 3.3, 11.4 Hz, 1H), 3.82-3.73 (dd+s, 4H), 3.67-3.62 (m, 1H), 2.80-2.70 (m, 1H), 1.08 (s, 9H), 0.99 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 170.40, 137.83, 135.65, 135.56, 133.28, 129.68, 129.66, 128.24, 127.64, 127.58, 127.43, 94.62, 78.86, 69.67, 65.02, 63.49, 52.09, 37.16, 26.75, 19.24, 13.87.

IR ($CHCl_3$): 2960, 2110 ($-N_3$), 1960, 1900, 1820, 1745, 1605, 1590 cm^{-1}.

MS: 584.3 (m+23).



(4*R*)-4-[(1*R*,2*S*)-2-Azido-2-methoxycarbonyl-1-methyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (35)

To a solution of ester **16** (50 mg, 0.17 mmol) in THF (2 ml) at -78°C was added KHMDS (0.5 M in toluene, 0.37 ml, 0.18 mmol). The mixture was stirred for 40 min and then a solution of trisyl azide (68 mg, 0.22 mmol) in THF (2 ml) was added. The resulting mixture was stirred further for 50 min at -78°C, and then HOAc (37 µl, 0,85 mmol) was added, and followed by immediately warming to 30°C and stirring for 1.5 h at this temperature. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give a diastereomeric mixture of an azido ester **35** (*syn / anti* = 6:1) as an oil (41 mg, 72%).

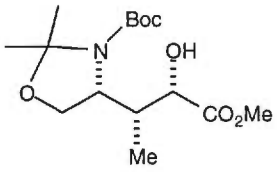
TLC: E/H = 1:4, R_f = 0.45.

Major *syn*-**35**

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.30-4.20 (br, 1H), 4.10-3.85 (br, 3H), 3.80 (s, 3H), 2.60-2.50 (m, 1H), 1.65-1.445 (br, 15H), 0.92 (d, J = 7.1 Hz, 3H).

IR ($CHCl_3$): 2960, 2105 ($-N_3$), 1740, 1690, 1450 cm^{-1}.

HRMS: $C_{15}H_{27}N_4O_5$ (m+1), calc.: 343.1981, found: 343.1970.



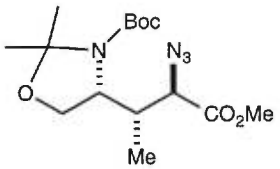
(4*R*)-4-[(1*R*,2*S*)-2-Hydroxy-2-methoxycarbonyl-1-methyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (36)

To a solution of ester **16** (184 mg, 0.61 mmol) in THF (4 ml) was added KHMDS (0.5M in toluene, 1.83 ml, 0.92 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (319 mg, 1.22 mmol) in THF (3 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give a diastereomeric mixture of **36** (*syn / anti* = 6:1) as an oil (178 mg, 90%).

TLC: E/H = 1:2, R_f = 0.40.

Major *syn*-**36**

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.40-4.30 (br, 1H), 4.10-3.80 (br, 3H), 3.70 (s, 3H), 2.45-2.35 (m, 1H), 1.60-1.40 (br, 15H), 0.81 (d, 3H).



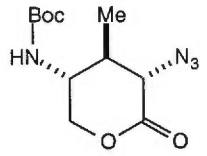
(4*R*)-4-[(1*R*,2*R*)-2-Azido-2-methoxycarbonyl-1-methyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (37)

To a solution of the hydroxy ester **36** (129 mg, 0.4 mmol) and Ph_3P (322 mg, 1.23 mmol) in THF (1 ml) was added DEAD (193 µl, 1.23 mmol) and then $(PhO)_2PON_3$ (266 µl, 1.23 mmol) at 0°C. The resulting mixture was stirred at 0°C for 2 h and then at room temperature for 21 h. The crude product after removing solvent was directly purified by chromatography to afford a diastereomeric mixture of azido ester **37** (*syn / anti* = 1:6) as an oil (77 mg, 55%).

TLC: E/H = 1:5, R_f = 0.45.

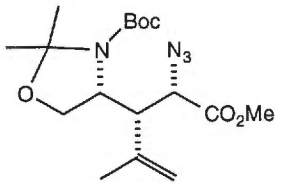
Major *anti*-**37**

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.25-4.15 (br, 1H), 4.10-3.85 (br, 3H), 3.80 (s, 3H), 2.30-2.15 (br, 1H), 1.65-1.45 (br, 15H), 1.05-0.9 (br, 3H).
IR ($CHCl_3$): 2995, 2110 ($-N_3$), 1750, 1700, 1600, 1460 cm^{-1}.
HRMS: 343.3 (m+1), 327.3, 287.3, 229.3.



(3*R*,4*R*,5*S*)-(5-Azido-4-methyl-6-oxo-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester (38)

To a solution of azido ester **35** (as a mixture) (43 mg, 0.12 mmol) in methanol (2 ml) was added PTSA (10 mg). The resulting mixture was stirred for 4.5 h and then diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4. A crude product (32 mg) was obtained after removing solvent.
A solution of the crude product in toluene (2 ml) was refluxed for 4 h. After removal of solvent, a crude product was obtained as solid, and purified by chromatography to afford a pure isomer **38** as crystalline product suitable for X-Ray analysis (10 mg, 30%).
TLC: E/H = 1:2, R_f = 0.50.
mp: 162-164°C.
$[\alpha]_D$ -17.9° (*c* 0.8, EtOAc).
^{1}H-NMR (300MHz, C_6D_6): δ (ppm) = 4.02-3.97 (br, 1H), 3.55 (dd, J = 4.2 , 11.7 Hz, 1H), 3.47-3.28 (m, 2H), 2.67 (d, J = 11.4 Hz, 1H), 1.44 (s, 9H), 1.13-1.01 (m 1H), 0.74 (d, J = 6.7 Hz, 3H).
^{13}C-NMR (300MHz, C_6D_6): δ (ppm) = 167.90, 154.74, 79.34, 68.65, 61.61, 50.09, 38.52, 27.94, 16.45.
MS: 271.4, 215.1, 171.2.
X-Ray Diffraction Analysis Data



(4*R*)-4-[(1*R*,2*S*)-1-(Azido-methoxycarbonyl-methyl)-2-methyl-allyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (40)

To a solution of ester **19** (62.5 mg, 0.19 mmol) in THF (4 ml) at -78°C was added KHMDS (0.5 M in toluene, 0.42 ml, 0.21 mmol). The mixture was stirred for 40 min and then a solution of trisyl azide (76.8 mg, 0.25 mmol) in THF (4 ml) was added. The resulting mixture was stirred further for 50 min at -78°C, and then HOAc (50 µl, 1.15 mmol) was added, and followed by immediately warming to 30°C and stirring for 1.5 h at this temperature. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give a diastereomeric mixture of an azido ester **40** (*syn / anti* = 6:1) as an oil (69 mg, 93%).

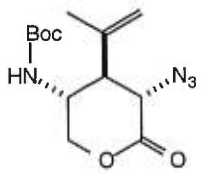
TLC: E/H = 1:5, R_f = 0.50.

Major *syn*-**40**

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.95-4.80 (br, 2H), 4.45-3.85 (br, 3H), 3.75 (s, 3H), 3.30-3.10 (br, 1H), 1.85-1.90 (br, 19H).

IR ($CHCl_3$): 2960, 2110 ($-N_3$), 1740, 1690, 1450 cm^{-1}.

HRMS: $C_{17}H_{29}N_4O_5$ (m+1), calc.: 369.2138, found: 369.2150.



(3*R*,4*R*,5*S*)-(5-Azido-4-isopropenyl-6-oxo-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester (41)

To a solution of azido ester **40** (86 mg, 0.233 mmol) in methanol (4 ml) was added PTSA (20 mg). The resulting mixture was stirred for 4.5 h and then diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4. A crude product (77 mg) was obtained after removing solvent.

A solution of the crude product in benzene (4 ml) was refluxed at 85°C for 6 h. After removal of solvent, a crude product was obtained as solid, and purified by chromatography to afford a pure isomer **41** as crystalline product suitable for X-Ray analysis (21 mg, 30%).

TLC: E/H = 1:1, R_f = 0.30.

mp: 115-117°C.

$[\alpha]_D$ -35.9° (*c* 0.9, CHCl3).

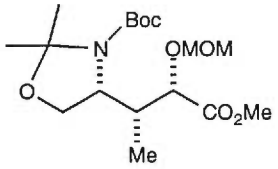
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 4.77 (s, 1H), 4.63 (s, 1H), 4.20 (br, 1H), 3.80-3.70 (m, 2H), 3.60-3.50 (m, 1H), 3.20 (d, J = 12.3 Hz, 1H), 1.90-1.80 (m, 1H), 1.43 (s, 3H), 1.40 (s, 9H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 168.00, 154.71, 140.06, 115.91, 79.41, 69.62, 58.23, 50.88, 47.37, 27.84, 17.42.

IR ($CHCl_3$): 3684, 3622, 3019, 2398, 2114, 1711, 1423 cm^{-1}.

MS: 319 (m+1), 254.

X-ray Diffraction Analysis Data



(*4R*)-4-[(1*R*,2*S*)-2-Methoxycarbonyl-2-methoxymethoxy-1-methyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (42)

To a solution of hydroxy ester **36** (228 mg, 0.72 mmol) and DMAP (43 mg, 0.35 mmol) in CH_2Cl_2 (6 ml) at 0°C were added diisopropylethylamine (1.87 ml, 10.8 mmol) and MOMCl (0.82 ml, 10.8 mmol) subsequently. The resulting mixture was stirred at room temperature for 51 h. The mixture was diluted with CH_2Cl_2, then washed with 2% HCl, sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. The crude product was purified by chromatography to afford **42** as an oil (232 mg, 89%).

TLC: E/H = 1:2, R_f = 0.60.

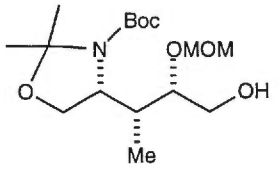
Major *syn*-**42**

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 4.64 (d, J = 6.8 Hz, 1H), 5.90 (d, J = 6.8 Hz, 1H), 4.15 (d, J = 1.4 Hz, 1H), 4.03-3.77 (m, 3H), 3.67 (d, 3H), 3.32 (s, 3H), 2.35-2.10 (br, 1H), 1.55 (s, 3H), 1.40 (s, 12H), 0.92 (d, J = 7.3 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 172.38, 152.0, 96.72, 93.69, 79.74, 7583, 64.46, 59.29, 56.23, 51.57, 38.81, 28.13, 26.52, 22.45, 11.00.

IR ($CHCl_3$): 2940, 1750, 1690, 1460 cm^{-1}.

HRMS: $C_{17}H_{32}NO_7$ (m+1), calc.: 362.2178, found: 362.2192.



(4*R*)-4-[(1*R*,2*S*)-3-Hydroxy-2-methoxymethoxy-1-methyl-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (43)

To a solution of ester **42** (238 mg, 0.66 mmol) in THF (10 ml) was added DIBAL-H at -78°C. The resulting mixture was stirred at 0°C for 2 h, then recooled to -78°C and quenched with sat. NH_4Cl. The mixture was diluted with EtOAc and 5% HCl, and separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with $NaHCO_3$, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford alcohol **43** as an oil [133 mg (pure isomer) and 47 mg (mixture of two isomers), 81%].

TLC: E/H = 1:1, R_f = 0.25.

$[\alpha]_D$ +23.6° (*c* 3.15, $CHCl_3$).

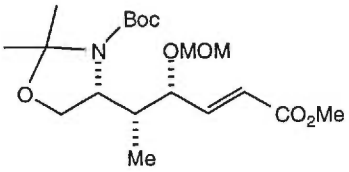
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4. 70 (s, 2H), 4.08 (d, J = 8.1 Hz, 1H), 3.98-3.89 (br, 1H), 3.85 (dd, J = 6.1, 8.9 Hz, 1H), 3.70-2.57 (m, 2H), 3.49-3.43 (m, 1H), 3.43 (s, 3H), 2.15-1.95 (br, 1H), 1.60 (s, 3H), 1.46 (s, 12H), 0.94 (d, J = 7.2 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 152.98, 97.97, 93.43, 83.61, 80.11, 65.92, 64.48, 60.31, 55.50, 37.20, 28.23, 27.02, 23.84, 11.36.

IR ($CHCl_3$): 3440, 2960, 1690, 1460 cm^{-1}.

MS: 356.1 (m+23), 334.2 (m+1).

HRMS: $C_{16}H_{32}NO_6$ (m+1), calc.: 334.2229, found: 334.2218.



(4*R*)-4-[(1*R*,2*R*)-4-Methoxycarbonyl-2-methoxymethoxy-1-methyl-but-3-enyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (44)

To a solution of oxalyl chloride (167 µl, 1.90 mmol) in CH_2Cl_2 (6 ml) at -78°C was added DMSO (270 µl, 3.8 mmol), and the resulting mixture was stirred for 10 min during which time the temperature was allowed to rise to -65°C, then a solution of alcohol **43** (127 mg, 0.38 mmol) in CH_2Cl_2 (4 ml) was added. The reaction mixture was warmed to -40°C

during 20 min, and then triethylamine (0.58 ml, 4.2 mmol) was added, the temperature was allowed to rise further to -30°C over 30 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, then washed with 2.5% HCl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4 for 2 h. The crude aldehyde, after removing solvent, was dried by an oil pump for 2 h.

To a solution of the above crude aldehyde in CH_2Cl_2 (4 ml) was added methyl (triphenylphosphoranylidene) acetate (382 mg, 1.14 mmol, as solid). The resulting mixture was stirred for 16 h at room temperature. The crude product, after removing solvent, was directly purified by chromatography to afford unsaturated ester **44** as an oil (112 mg, 76%).

TLC: E/H = 1:5, R_f = 0.45.

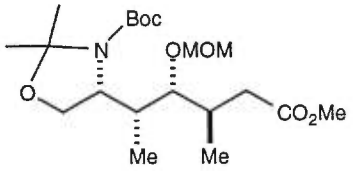
$[\alpha]_D$ -31.6° (*c* 3.8, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 6.88 (dd, J = 5.6, 15.7 Hz, 1H), 5.98 (d, J = 15.7 Hz, 1H), 4.57 (s, 2H), 4.28-4.27 (m, 1H), 4.10-4.00 (m, 1H), 4.00-3.90 (br, 1H), 3.58 (dd, J = 5.6, 8.9 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.10-2.00 (br, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.44 (s, 9H), 0.95 (d, J = 7.2 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 166.31, 146.87, 121.32, 95.40, 94.0, 79.79, 76.43, 66.61, 58.70, 56.01, 51.43, 40.65, 28.22, 26.75, 24.26, 22.75, 11.20.

IR ($CHCl_3$): 2970, 1720, 1690, 1480, 1460, 1440 cm^{-1}.

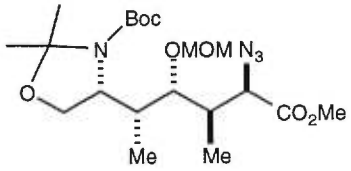
HRMS: $C_{19}H_{34}NO_7$ (m+1), calc.: 388.2335, found: 388.2348.



(4*R*)-4-[(1*R*,2*R*,3*R*)-4-Methoxycarbonyl-2-methoxymethoxy-1,3-dimethyl-butyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (45)

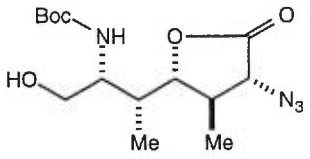
To a stirred suspension of CuI (315 mg, 1.66 mmol) in THF (15 ml) was added MeLi·LiBr (1.5 M in ether, 2.2 ml, 3.3 mmol) at -25°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (520 µl, 4.1 mmol) and a solution of **44** (107 mg, 0.28 mmol) in THF (5 ml) subsequently. The reaction was continued for 3 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were

washed with sat. NH_4Cl-NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **45** as an oil (104 mg, 90%).
TLC: E/H = 1:5, R_f = 0.50.
$[\alpha]_D$ -12.4° (*c* 0.8, $CHCl_3$).
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.70-4.60 (br, 2H), 4.00-3.85 (br, 4H), 3.66 (s, 2H), 3.40 (s, 3H), 3.40-3.35 (br, 1H), 2.50-2.00 (br, 4H), 1.58 (br, 3H), 1.47 (br, 12H), 1.00-0.90 (m, 6H).



(4*R*)-4-[(1*R*,2*R*,3*R*,4*R*)-4-Azido-4-methoxycarbonyl-2-methoxymethoxy-1,3-dimethyl-butyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (46)

To a solution of ester **45** (66 mg, 0.16 mmol) in THF (1.5 ml) at -78°C was added KHMDS (0.5 M in toluene, 393 µl, 0.19 mmol). The mixture was stirred for 30 min and then a solution of trisyl azide (76 mg, 0.24 mmol) in THF (1 ml) was added. The resulting mixture was stirred further for 20 min at -78°C, and then HOAc (43 µl, 0.98 mmol) was added, and followed by immediately warming to 30°C and stirring for 2.5 h at this temperature. The reaction mixture was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give an azido ester **46** as an oil (47 mg, 65%).
TLC: E/H = 1:5, R_f = 0.45.
$[\alpha]_D$ +45.8° (*c* 0.9, $CHCl_3$).
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.75-4.55 (m, 3H), 4.10-3.85 (br, m, 3H), 3.82 (s, 3H), 3.53-3.40 (m, s, 4H), 2.32-2.20 (br, 1H), 2.10-1.90 (br, 1H), 1.59 (s, 3H), 1.51 (s, 3H), 1.47 (s, 9H), 0.95 (d, J =7.2 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H).
^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 171.40, 164.45, 130.38, 99.29, 85.0, 81.70, 79.88, 77.15, 63.54, 59.74, 56.19, 52.57, 38.86, 28.31, 27.08, 11.52, 10.10.
IR ($CHCl_3$): 2970, 2110 ($-N_3$), 1745, 1690, 1480, 1460, 1430 cm^{-1}.
HRMS: $C_{20}H_{37}N_4O_7$ (m+1), calc.: 445.2662, found: 445.2647.

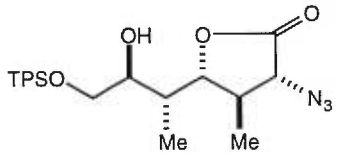


[(1*R*,2*R*)-2-[(4*R*,3*R*,2*R*)-4-Azido-3-methyl-5-oxo-tetrahydro-furan-2-yl)-1-hydroxymethyl-propyl]-carbamic acid tert-butyl ester (47)

To a solution of azido ester **46** (40 mg, 0.09 mmol) in methanol (2 ml) was added PTSA (17 mg). The resulting solution was stirred for 11 h at room temperature, then diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to afford the azido lactone **47** (20 mg, 67%).

TLC: E/H = 1:1, R_f = 0.22.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 5.09-5.08 (br, 1H), *4.27 (dd, J = 1.6, 10.0 Hz, 1H), 3.89 (d, J = 11.0 Hz, 1H, α-H)*, 3.82 (dd, J = 4.7, 11.7 Hz, 1H), 3.68 (dd, J = 4.2, 11.7 Hz, 1H), 3.64-3.59 (m, 1H), 2.38-2.25 (m, 1H), 2.22-2.10 (m, 1H), 1.44 (s, 9H), 1.20 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 7.2 Hz, 3H).



(3*R*)-3-Azido-(5*R*)-5-[3-(tert-butyl-diphenyl-silanyloxy)-(2*S*)-2-hydroxy-(1*R*)-1-methyl-propyl]-(4*R*)-4-methyl-dihydro-furan-2-one (49)

To a solution of ester **68** (110 mg, 0.17 mmol) in THF (2 ml) at -78°C was added KHMDS (0.5 M in toluene, 530 µl, 0.26 mmol). The mixture was stirred for 30 min and then a solution of trisyl azide (109 mg, 0.35 mmol) in THF (2 ml) was added. The resulting mixture was stirred further for 40 min at -78°C, and then HOAc (46 µl, 1.06 mmol) was added, and followed by immediately warming to 30°C and stirring for 2.5 h at this temperature. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give an azido ester **48** as an oil (100 mg, 80%).

TLC: E/H = 1:5, R_f = 0.42.

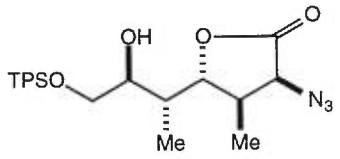
To a solution of azido ester **48** (100 mg) in CH_2Cl_2 (3 ml) at -60°C was added trimethylsilyl bromide (500 µl, excess). The mixture was stirred and the temperature

was allowed to rise gradually to 0°C over 90 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc, washed with sat.$NaHCO_3$ and brine, and then dried over Na_2SO_4. The product was purified by chromatography to afford an azido lactone **49** as an oil (41 mg, 49%, for two steps).

TLC: E/H = 1:3, R_f = 0.40.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.67-7.63 (m, 4H), 7.48-7.26 (m, 6H), *4.58 (dd, J = 1.4, 10.3 Hz, 1H), 3.90 (d, J = 11.2 Hz, 1H, α-H)*, 3.83 (dd, J = 3.0, 10.1 Hz, 1H), 3.68-3.63 (m, 1H), 3.58 (dd, J = 6.8, 10.1 Hz, 1H), 2.70-2.60 (br, 1H), 2.20-2.13 (m, 1H), 1.81-1.76 (m, 1H), 1.18 (d, J = 6.6 Hz, 3H), 1.07 (s, 9H), 1.07 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 172. 42, 135.40, 132.69, 132.57, 129.94, 127.81, 82.05, 72.27, 65.84, 64.35, 39.14, 36.13, 26.74, 19.15, 14.16, 8.20.



(3*S*)-3-Azido-(5*R*)-5-[3-(tert-butyl-diphenyl-silanyloxy)-(2*S*)-2-hydroxy-(1*R*)-1-methyl-propyl]-(4*R*)-4-methyl-dihydro-furan-2-one (51)

To a solution of hydroxy ester **69** (123 mg, 0.19 mmol) and Ph_3P (202 mg, 0.79 mmol) in THF (3 ml) was added DEAD (134 µl, 0.77 mmol) and then $(PhO)_2PON_3$ (167 µl, 0.77 mmol) at 0°C. The resulting mixture was stirred at 0°C for 30 min and then at room temperature for 2 h. The crude product, after removing solvent, was directly purified by chromatography to afford azido ester **50** as an oil.

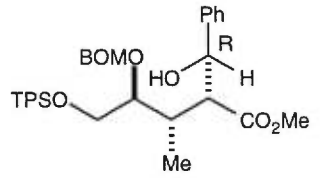
TLC: E/H = 1:5, R_f = 0.42.

To a solution of the above azido ester **50** in CH_2Cl_2 (3 ml) at -60°C was added trimethylsilyl bromide (500 µl, excess). The mixture was stirred and the temperature was allowed to rise gradually to 0°C over 90 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc, washed with sat.$NaHCO_3$ and brine, then dried over Na_2SO_4. The product was purified by chromatography to afford an azido lactone **51** as an oil (55 mg, 60%, for two steps).

TLC: E/H = 1:3, R_f = 0.47.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.67-7.64 (m, 4H), 7.48-7.25 (m, 6H), *4.64 (dd, J = 2.3, 7.9 Hz, 1H), 4.20 (d, J = 7.4 Hz, 1H, α-H)*, 3.80 (dd, J = 3.0, 10.0 Hz, 1H), 3.72-3.61 (m, 1H), 3.57 (dd, J = 6.7, 10.0 Hz, 1H), 2.70-2.60 (br, 1H), 2.49-2.43 (m, 1H),

1.83-1.79 (m, 1H), 1.09 (d, 3H), 1.07 (s, 9H), 0.72 (d, J = 7.0 Hz, 3H).



(4*S*)-4-Benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-(2*R*)-2-[(*R*)-hydroxy-phenyl-methyl]-(3*S*)-3-methyl-pentanoic acid methyl ester (52)

To a solution of ester **9** (65 mg, 0.12 mmol) in THF (2 ml) at -78 °C was added KHMDS (0.5 M in toluene, 300 µl, 0.15 mmol). The resulting solution was stirred for 30 min, then benzaldehyde (25 µl, 0.24 mmol) was added. The reaction was continued for 2 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc, washed with brine, and dried over Na_2SO_4. The crude product was purified by chromatography to afford alcohol **52** as an oil (47 mg, 60%).

TLC: E/H = 1:3, R_f = 0.32 (0.50, 0.55 for two minor isomers respectively).

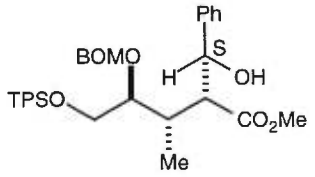
$[\alpha]_D$ -24.2° (*c* 2.0, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.69-7.65 (m, 4H), 7.43-7.24 (m, 16H), 5.05 (br, 1H), 4.85 (d, J = 6.8 Hz, 1H), 4.77 (d, J = 6.8 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 3.81-3.72 (m, 3H), 3.62-3.60 (m, 1H), 3.41 (s, 3H), 2.89 (dd, J = 4.0, 9.0 Hz, 1H), 2.60-2.50 (m, 1H), 1.15 (d, J = 7.1 Hz, 3H), 1.04 (s, 9H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 175 40 (0), 142.42 (0), 137.77, 135.53 (0), 135.50 (0), 135.49 (0), 133.17, 133.12, 129.61, 129.59, 128.23, 128.22, 128.09, 127.64, 127.59, 127.58, 127.57, 127.44, 127.16, 125.36, 94.33 (-), 80.09, 71.58, 69.53 (-), 64.20 (-), 54.36, 51.26, 35.61, 26.66, 19.07 (0), 13.32.

IR ($CHCl_3$): 3510, 2960, 1970, 1900, 1830, 1710, 1590 cm^{-1}.

MS: 649.4 (m+23), 627.3 (m+1).



(4*S*)-4-Benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-(2*R*)-2-[(*S*)-hydroxy-phenyl-methyl]-(3*S*)-3-methyl-pentanoic acid methyl ester (53)

To a solution of ester **9** (41 mg, 0.08 mmol) in THF (1 ml) at -78 °C was added LDA (2.0

M in heptane/THF/ethylbenzene, 3% diisopropylamine, 43 µl, 0.87 mmol). The resulting solution was stirred for 30 min, then benzaldehyde (16 µl, 0.15 mmol) was added. The reaction was continued for 2 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc, washed with brine, and dried over Na_2SO_4. The crude product was purified by chromatography to afford alcohol **53** as an oil (22 mg, 60% based recovered starting material).

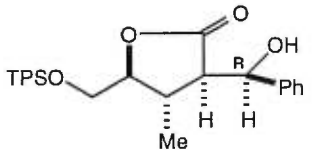
TLC: E/H = 1:3, R_f = 0.6 (0.55, 0.45 for two minor isomers respectively).

$[\alpha]_D$ +7.9° (*c* 1.0, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.66 (m, 4H), 7.47-7.21 (m, 16H), 5.03 (dd, J = 2.8, 9.5 Hz, 1H), 4.94 (d, J = 6.6 Hz, 1H), 4.88 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.17-4.10 (m, 1H), 4.00-3.95 (dd, J = 4.9, 16.3 Hz, 1H), 3.89 (dd, J = 4.7, 11.0 Hz, 1H), 3.80 (dd, J = 5.1, 11.0 Hz, 1H), 3.38 (s, 3H), 3.18 (dd, J = 2.4, 9.6 Hz, 1H), 2.58-2.49 (m, 1H), 1.20 (d, J = 7.2 Hz, 3H), 1.06 (s, 9H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.56, 142.75, 135.60, 135.53, 133.14, 129.70, 128.37, 128.11, 127.74, 127.68, 127.65, 127.50, 126.70, 95.16, 81.53, 72.15, 70.15, 64.05, 54.07, 51.10, 34.98, 26.73, 19.13, 13.58.

IR ($CHCl_3$): 3410, 2950, 1960, 1900, 1820, 1730, 1590, 1500 cm^{-1}.



5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-(3*R*)-3-[(*R*)-hydroxy-phenyl-methyl)-(4*S*)-4-methyl-dihydro-furan-2-one (54)

To a solution of ester **52** (44 mg, 0.07 mmol) in CH_2Cl_2 (1 ml) at -60°C was added trimethylsilyl bromide (185 µl, 1.4 mmol). The mixture was stirred and the temperature was allowed to rise gradually to 0°C over 2 h. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc, washed with sat.$NaHCO_3$ and brine, then dried over Na_2SO_4. The product was purified by chromatography to afford an hydroxy lactone **54** as an oil (24 mg, 72%).

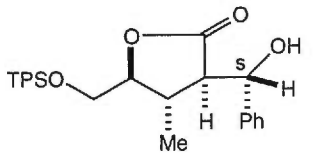
TLC: E/H = 1:3, R_f = 0.27.

$[\alpha]_D$ +19.0° (*c* 1.2, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.67-7.65 (m, 4H), 7.47-7.26 (m, 11H), *4.76 (d, J = 9.0 Hz, 1H),* 4.60 (br, 1H), 3.99-3.96 (dt, J = 3.3, 8.8 Hz, 1H), 3.91 (dd, J = 2.7, 11.9 Hz, 1H), 3.67 (dd, J = 3.6, 11.9 Hz, 1H), *2.53 (dd, J = 9.0, 10.6 Hz, 1H),* 2.25-2.20 (m,

1H), 1.08 (s, 9H), 0.33 (d, J = 6.6 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 178.80 (0), 139.87 (0), 135.55, 135.42, 132.81 (0), 132.32 (0), 129.83, 128.56, 128.45, 127.73, 127.72, 126.76, 85.62, 75.04, 62.28 (-), 54.11, 33.47, 26.68, 26.66, 19.16 (0), 16.09.



(5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-(3*R*)-3-[(*S*)-hydroxy-phenyl-methyl)-(4*S*)-4-methyl-dihydro-furan-2-one (54a)

To a solution of ester **53** (20 mg, 0.03 mmol) in CH_2Cl_2 (1 ml) at -60°C was added trimethylsilyl bromide (88 µl, 0.67 mmol). The mixture was stirred and the temperature was allowed to rise gradually to 0°C in 2 h. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, washed with sat.$NaHCO_3$ and brine, and dried over Na_2SO_4. The product was purified by chromatography to afford an hydroxy lactone **54a** as an oil (9.3 mg, 60%).

TLC: E/H = 1:3, R_f = 0.30.

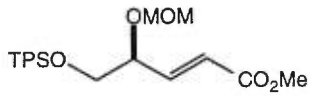
$[\alpha]_D$ +62.3° (*c* 0.8, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.67-7.65 (m, 4H), 7.45-7.26 (m, 11H), *5.41 (d, J = 2.8 Hz, 1H),* 3.98-3.94 (m, 1H), 3.84 (dd, J = 3.4, 11.7 Hz, 1H), 3.73 (dd, J = 4.7, 11.7 Hz, 1H), *2.67 (dd, J = 3.1, 10.4 Hz, 1H),* 2.63-2.55 (m, 1H), 1.05 (s, 9H), 0.54 (d, J = 6.5 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 176.95 (0), 140.64 (0), 135.54, 135.51, 135.50, 132.95 (0), 132.84 (0), 129.68, 128.41, 127.63, 127.62, 127.53, 125.26, 85.34, 70.48, 63.20 (-), 55.56, 30.78, 26.59, 19.10 (0), 16.96.

IR ($CHCl_3$): 3610, 2960, 2870, 1960, 1900, 1760, 1610, 1590 cm-1.

MS: 457.1 (M-OH).



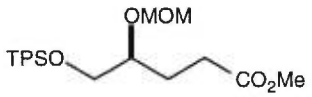
(4*S*)-5-(tert-Butyl-diphenyl-silanyloxy)-4-methoxymethoxy-pent-2-enoic acid methyl ester (55a)

To a solution of hydroxy ester **3** (944 mg, 2.46 mmol) and DMAP (300 mg, 2.45 mmol)

in CH_2Cl_2 (10 ml) at 0°C were added diisopropylethylamine (4.3 ml, 24.6 mmol) and MOMCl (1.88 ml, 24.6 mmol) subsequently. The resulting mixture was stirred at room temperature for 17 h. The crude product after removing solvent was directly purified by chromatography to afford **55a** as an oil (949 mg, 90%).

TLC: E/H = 1:5, R_f = 0.45.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.70-7.66 (m, 4H), 7.46-7.26 (m, 6H), 6.90 (dd, J = 5.5, 15.6 Hz, 1H), 6.08 (dd, J = 1.5, 15.6 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 4.38-4.36 (m, 1H), 3.78-3.74 (m, 1H), 3.74 (s, 3H), 3.68 (dd, J = 5.2, 10.5 Hz, 1H), 3.35 (s, 3H), 1.07 (s, 9H).



(4*S*)-5-(tert-Butyl-diphenyl-silanyloxy)-4-methoxymethoxy-pentanoic acid methyl ester (55)

A mixture of olefin **55a** (949 mg) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 45 mg) in MeOH (10 ml) under 1 atm of hydrogen was stirred at room temperature for 3 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The product was purified by chromatography to give **55** as an oil (880 mg, 92%).

TLC: E/H = 1:5, R_f = 0.44.

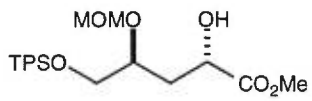
$[\alpha]_D$ -30.2° (*c* 0.9, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.68-7.66 (m, 4H), 7.45-7.26 (m, 6H), 4.72 (d, J = 6.7 Hz, 1H), 4.61 (d, J = 6.7 Hz, 1H), 3.71-3.60 (m, 3H), 3.67 (s, 3H), 3.33 (s, 3H), 2.44-2.40 (m, 2H), 2.05-1.95 (m, 1H), 1.84-1.81 (m, 1H), 1.06 (s, 9H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 173.84 (0), 135.48, 135.46, 133.24 (0), 133.23 (0), 129.59, 129.58, 127.58, 127.55, 96.09 (-), 76.76, 65.90 (-), 55.47, 51.41, 29.77 (-), 26.81 (-), 26.68, 19.06 (0).

IR ($CHCl_3$): 2960, 2940, 1960, 1900, 1735, 1590 cm^{-1}.

HRMS: $C_{24}H_{35}O_5Si$ (m+1), calc.: 431.2253, found: 431.2232.



5-(tert-Butyl-diphenyl-silanyloxy)-2-hydroxy-4-methoxymethoxy-pentanoic acid methyl ester (56)

General Procedure

To a solution of **55** (55 mg, 0.13 mmol) in THF (1 ml) was added KHMDS (0.5M in toluene, 383 µl, 0.19 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (66.7 mg, 0.25 mmol) in THF (1 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give a diastereomeric mixture of **56** (*anti / syn* = 3:1) as an oil (40 mg, 70%).

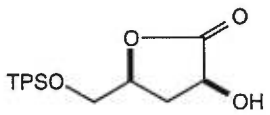
TLC: E/H = 1:1, R_f = 0.30.

anti-(2*S*,4*S*)- **56** (Major isomer)

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.66 (m, 4H), 7.47-7.27 (m, 6H), 4.76 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H), 4.48-4.42 (m, 1H), 3.97-3.90 (m, 1H), 3.78 (s, 3H), 3.75-3.63 (m, 2H), 3.36 (s, 3H), 3.26 (d, J = 5.8 Hz, 1H), 2.07-1.98 (m, 1H), 1.87-1.78 (m, 1H), 1.07 (s, 9H).

syn-(2R,4S)-**55** (Minor isomer)

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.60 (dd), 4.40-4.35 (m), 3.30 (s), 2.25-2.15 (dt).



(3*S*,5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-dihydro-furan-2-one (57)

To a solution of a diastereomeric mixture of ester 56 (84 mg, 0.19 mmol) in CH_2Cl_2 (2 ml) at -60°C was added trimethylsilyl bromide (372 µl, 2.8 mmol). The mixture was stirred and the temperature was allowed to rise gradually to 0°C over 90 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2 and separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed with sat.$NaHCO_3$ and brine, then dried over Na_2SO_4. The product was purified by chromatography to afford two lactone products **57** and **57a** (77%).

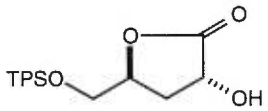
57 (32 mg)

TLC: E/H = 1:2, R_f = 0.25.

$[\alpha]_D$ +7.9° (*c* 1.7, $CHCl_3$).

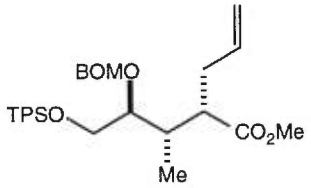
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.65 (m, 4H), 7.49-7.27 (m, 6H), 4.59-4.48 (m, 2H), 3.92 (dd, J = 3.3, 11.6 Hz, 1H), 3.75(dd, J = 4.2, 11.6 Hz, 1H), 3.40 (br, 1H), 2.65-2.55 (m, 1H), 2.29-2.18 (m, 1H), 1.07 (s, 9H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 177.04 (0), 135.55, 135.46, 132.67 (0), 132.44 (0), 129.87, 127.76, 77.00, 68.18, 64.35 (-), 32.25 (-), 26.63, 19.14 (0).
IR ($CHCl_3$): 3580, 2940, 2880, 1785, 1595, 1470 cm^{-1}.
MS: 393.2 (m+23), 371.2 (m+1).
HRMS: $C_{21}H_{27}O_4Si$ (m+1), calc.: 371.1678, found: 371.1666.



(3R,5S)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-dihydro-furan-2-one (57a)

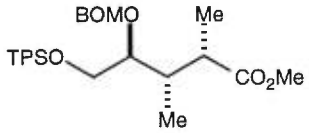
57a (22 mg)
TLC: E/H = 1:2, R_f = 0.35.
$[\alpha]_D$ +50.0° (*c* 1.0, $CHCl_3$).
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.67-7.62 (m, 4H), 7.50-7.27 (m, 6H), 4.81 (t, J = 8.9 Hz, 1H), 4.69 -4.63 (m, 1H), 3.91 (dd, J = 2.6, 11.5 Hz, 1H), 3.64 (dd, J = 2.4, 11.5 Hz, 1H), 3.00-2.85 (br, 1H), 2.68-2.60 (m, 1H), 2.41-2.31 (m, 1H), 1.05 (s, 9H).
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 177.83 (0), 135.50, 135.48, 135.37, 132.50 (0), 131.99 (0), 129.95, 127.83, 77.49, 67.40, 65.23 (-), 32.10 (-), 26.66, 19.03 (0).
IR ($CHCl_3$): 3590, 2950, 2880, 1790, 1600, 1470 cm^{-1}.
MS: 369.4 (m-1).



(2*S*)-2-[(2*S*)-2-Benzyloxymethoxy-3-(tert-butyl-diphenyl-silanyloxy)-(1*S*)-1-methyl-propyl]-pent-4-enoic acid methyl ester (58)

To a solution of ester **9** (123 mg, 0.24 mmol) in THF (3 ml) was added KHMDS (0.5 M in toluene, 0.586 ml, 0.28 mmol) at -78°C. The resulting mixture was stirred for 30 min and then treated with allyl iodide (108 µl, 1.2 mmol). The reaction was continued for 2 h at -78°C, and quenched with sat. NH_4Cl at this temperature. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl, brine, then dried over Na_2SO_4. The crude product was purified by chromatography to

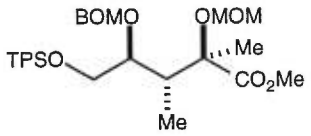
give allyl ester **58** as an oil (123 mg, 93%).
TLC: E/H = 1:5, R_f = 0.45.
$[\alpha]_D$ -7.5° (*c* 1.2, $CHCl_3$).
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.72-7.67 (m, 4H), 7.46-7.26 (m, 11H), 5.78-5.68 (m, 1H), 5.06-4.95 (m, 2H), 4.88 (d, J = 6.9 Hz, 1H), 4.78 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 3.83-3.60 (m, 3H), 3.66 (s, 3H), 2.85-2.75 (m, 1H), 2.40-2.20 (m, 3H), 1.06 (s, 9H), 0.91 (d, J = 7.1 Hz, 3H).
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 175.57 (0), 137.87 (0), 135.96, 135.61, 135.55, 133.27 (0), 129.64, 128.27, 127.63, 127.48, 116.24 (-), 94.37 (-), 79.97, 69.70 (-), 64.20 (-), 51.25, 46.04, 36.74, 31.77 (-), 26.74, 19.14 (0), 12.16.
IR ($CHCl_3$): 2950, 2900, 2880, 1740, 1650, 1600 cm^{-1}.
HRMS: $C_{34}H_{45}O_5Si$ (m+1), calc.: 561.3036, found: 561.3065.



(2*S*,3*S*,4*S*)-4-Benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-2,3-dimethyl-pentanoic acid methyl ester (59)

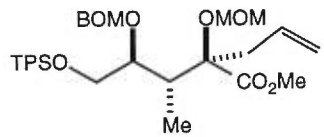
To a solution of ester **9** (139 mg, 0.27 mmol) in THF (3 ml) was added KHMDS (0.5 M in toluene, 0.64 ml, 0.32 mmol) at -78°C. The resulting mixture was stirred for 30 min and then treated with methyl iodide (85 µl, 1.34 mmol). The reaction was continued for 2 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give methyl ester 59 as an oil (138 mg, 96%).
TLC: E/H = 1:5, R_f = 0.45.
$[\alpha]_D$ -19.0° (*c* 1.2, $CHCl_3$).
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.75-7.71 (m, 4H), 7.49-7.28 (m, 11H), 4.95 (d, J = 7.0 Hz, 1H), 4.82 (d, J = 7.0 Hz, 1H), 4.71 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 3.88-3.84 (dd, J = 3.6, 11.2 Hz, 1H), 3.79-3.75 (dd, J = 5.3, 11.2 Hz, 1H), 3.71 (s, 3H), 3.61-3.57 (m, 1H), 2.97-2.91 (m, 1H), 2.48-2.43 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 1.14 (s, 9H), 0.87 (d, J = 7.1 Hz, 3H).
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 176.91 (0), 137.83 (0), 135.60, 135.55, 133.28 (0), 129.63, 128.30, 127.64, 127.51, 94.43 (-), 79.94, 69.86 (-), 64.41 (-), 51.44, 39.65,

36.41, 26.74, 19.13 (0), 11.75, 11.30.
IR ($CHCl_3$): 2960, 1960, 1900, 1820, 1730, 1590, 1470, 1480 cm^{-1}.
MS: 535 (m+1), 427.



(2R,3R,4S)-4-Benzyloxymethoxy-5-(tert-butyl-diphenyl-silanyloxy)-2-methoxymethoxy-2,3-dimethyl-pentanoic acid methyl ester (60)

To a solution of ester **65** (80 mg, 0.14 mmol) in DME (1.4 ml) was added LDA (2.0 M in hexane, 275 µl, 0.55 mmol) at -48°C. The resulting mixture was stirred for 30 min and then methyl iodide (86 µl, 1.38 mmol) was added. The reaction was continued for 2 h at -48°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give ester **60** as an oil (34 mg, 41%).
TLC: E/H = 1:5, R_f = 0.40.
$[\alpha]_D$ +51.6° (*c* 1.7, $CHCl_3$).
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.75-7.67 (m, 4H), 7.45-7.18 (m, 11H), 4.98 (d, J = 7.4 Hz, 1H), 4.75 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.65 (d, J = 7.4 Hz, 1H), 4.48 (s, 2H), 3.97 (dd, J = 2.2, 11.3 Hz, 1H), 3.83(dd, J = 4.4, 11.3 Hz, 1H), 3.68 (s, m, 4H), 3.31 (s, 3H), 2.67-2.57 (m, 1H), 1.46 (s, 3H), 1.08 (s, 9H), 0.94 (d, J = 7.0 Hz, 3H).
^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 175.71 (0), 138.13 (0), 135.72, 135.60, 133.68 (0), 133.63 (0), 129.54, 129.51, 128.19, 127.61, 127.57, 127.50, 127.31, 95.20 (-), 92.69 (-), 80.07, 79.77 (0), 69.29 (-), 65.07 (-), 55.46, 51.55, 42.60, 26.75, 21.12, 19.30 (0), 9.88.
IR ($CHCl_3$): 2980, 1970, 1900, 1830, 1740, 1590 cm-1.
HRMS: $C_{34}H_{46}O_7SiNa$ (m+23), calc.: 617.2910, found: 617.2924.



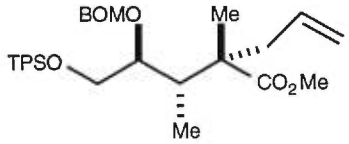
(2*R*)-2-[(2*S*)-2-Benzyloxymethoxy-3-(tert-butyl-diphenyl-silanyloxy)-(1*R*)-1-methyl-propyl]-2-methoxymethoxy-pent-4-enoic acid methyl ester (61)

To a solution of ester **65** (100 mg, 0.17 mmol) in DME (2 ml) at -10°C was added LDA (2.0 M in hexane/THF/ethylbenzene, 345 µl, 0.69 mmol). The resulting solution was stirred for 30 min and the temperature was maintained between -10°C and -5°C. To the reaction solution was added allyl iodide (157 µl, 1.7 mmol), and the resulting solution was stirred for 1 h and the temperature was allowed to rise to 0°C during this period. The reaction mixture was quenched with sat. NH_4Cl, diluted with EtOAc, washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give allyl ester **61** as an oil (68 mg, 63%).

(TLC: E/H = 1:5, R_f = 0.72).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.74-7.68 (m, 4H), 7.44-7.19 (m, 11H), 5.90-5.80 (m, 1H), 5.20 (d, J = 7.5 Hz, 1H), 5.15 (dd, J = 1.8, 17.0 Hz, 1H), 5.09 (dd, J = 2.0, 10.2 Hz, 1H), 4.75 (d, J = 7.0 Hz, 1H), 4.67 (d, J = 7.0 Hz, 1H), 4.64 (d, J = 7.4 Hz, 1H), 4.50 (dd, 2H), 3.98 (dd, J = 2.3, 11.3 Hz, 1H), 3.83 (dd, J = 4.1, 11.3 Hz, 1H), 3.67 (s, 3H), 3.66-3.62 (m, 1H), 3.34 (s, 3H), 2.76-2.70 (m, 2H), 2.57 (dd, J = 7.7, 14.5 Hz, 1H), 1.09 (s, 9H), 0.95 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 174.26 (0), 138.09 (0), 135.71, 135.69, 135.59, 133.66 (0), 133.63 (0), 133.36, 129.52, 129.48, 128.16, 127.59, 127.58, 127.54, 127.47, 127.28, 118.19 (-), 95.21 (-), 92.72 (-), 82.42 (0), 80.00, 69.26 (-), 64.91 (-), 55.47, 51.11, 41.41, 40.18 (-), 26.72, 19.28 (0), 9.68.



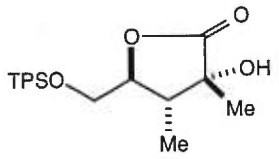
(2*S*)-2-[(2*S*)-2-Benzyloxymethoxy-3-(tert-butyl-diphenyl-silanyloxy)-(1*R*)-1-methyl-propyl]-2-methyl-pent-4-enoic acid methyl ester (63)

To a solution of ester **59** (59 mg, 0.11 mmol) in DME (1 ml) at -10°C was added LDA (2.0 M in hexane/THF/ethylbenzene, 220 µl, 0.44 mmol). The resulting solution was stirred for 30 min and the temperature was maintained between -10°C and -5°C. To the above solution was added allyl iodide (101 µl, 1.1 mmol), and the resulting solution was stirred for 1 h and the temperature was allowed to rise to 0°C during this period. The reaction mixture was quenched with sat. NH_4Cl, diluted with EtOAc, washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give allyl ester **63** as an oil (53 mg, 83%).

TLC: E/H = 1:5, R_f = 0.77.

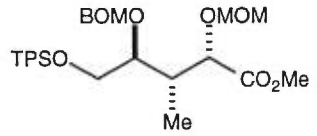
$[\alpha]_D$ 0.0° (*c* 1.8, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.72-7.67 (m, 4H), 7.45-7.23 (m, 11H), 5.78-5.60 (m, 1H), 5.07 (s, 1H), 5.03 (dd, J = 1.2, 8.5 Hz, 1H), 4.77 (d, J = 7.1 Hz, 1H), 4.65 (d, J = 7.1 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 3.90 (dd, J = 2.4, 11.6 Hz, 1H), 3.79 (dd, J = 3.9, 11.6 Hz, 1H), 3.63 (s, 3H), 3.43-3.40 (m, 1H), 2.70-2.65 (m, 1H), 2.38-2.27 (dd, 1H), 2.19-2.12 (dd, 1H), 1.09 (s, 9H), 1.05 (s, 3H), 0.81 (d, J = 7.0 Hz, 3H).
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 177.07 (0), 138.05 (0), 135.65, 135.59, 133.93 (0), 133.45, 129.57, 128.17, 127.57, 127.30, 117.73(-), 94.68 (-), 80.99, 69.91 (-), 64.81 (-), 50.97, 47.14 (0), 43.63 (-), 40.28, 26.73, 19.23 (0), 14.70, 10.80.
IR ($CHCl_3$): 3019, 2400, 1722, 1521, 1474, 1428 cm^{-1}.



(3*R*,4*R*,5*S*)-5-(tert-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-3,4-dimethyl-dihydro-furan-2-one (64)

To a solution of ester **60** (30 mg, 0.05 mmol) in CH_2Cl_2 (1 ml) at -60°C was added trimethylsilyl bromide (100 µl, 0.75 mmol). The mixture was stirred and the temperature was allowed to rise gradually to 0°C in 90 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2 and separated, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed with sat.$NaHCO_3$ and brine, dried over Na_2SO_4. The product was purified by chromatography to afford a hydroxy lactone **64** as an oil (14 mg, 70%).
TLC: E/H = 1:5, R_f = 0.20.
$[\alpha]_D$ +51.4° (*c* 0.7, $CHCl_3$).
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.68-7.65 (m, 4H), 7.47-7.26 (m, 6H), 4.26-4.22 (m, 1H), 3.98 (dd, J = 2.8, 11.9 Hz, 1H), 3.74 (dd, J = 3.7, 11.9 Hz, 1H), 2.28-2.24 (m, 1H), 2.12 (br, 1H), 1.44 (s, 3H), 1.05 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H).
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 177.53 (0), 135.55, 135.43, 132.96 (0), 132.61 (0), 129.79, 129.77, 127.70, 84.11, 74.29 (0), 62.14 (-), 40.91, 26.65, 22.32, 19.17 (0), 8.20.
IR ($CHCl_3$): 3600, 2950, 2880, 1970, 1900, 1780, 1600 cm^{-1}.
HRMS: $C_{23}H_{30}O_4SiNa$ (m+23), calc.: 421.1811, found: 421.1787.



(2S,3R,4S)-4-benzyloxymethoxy-5-(tert-butyldiphenylsilanyloxy)-2-methoxymethoxy-3-methyl-pentanoic acid methyl ester (65)

To a solution of **33** (16.3 g, 30.4 mmol) and diisopropylethylamine (52.8 ml, 304 mmol) and DMAP (1.8 g, 15.2 mmol) in CH_2Cl_2 (400 ml) at 0°C was added dropwise MOMCl (23.2 ml, 304 mmol). The resulting mixture was stirred at room temperature. After 24 h, more diisopropylethylamine (50.0 ml, 287 mmol) and MOMCl (20.0 ml, 262 mmol) was added at 0°C and the mixture was stirred for a further 24 h at room temperature. The mixture was diluted with CH_2Cl_2 (200 ml), then washed with 2% HCl (2x200 ml), sat. $NaHCO_3$ (200 ml) and brine (200 ml), then dried over Na_2SO_4. The crude product was purified by chromatography to afford **65** as an oil (16.2 g, 92%).

TLC: E/H = 1:5, R_f = 0.40.

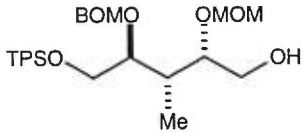
$[\alpha]_D$ -4.2° (*c* 1.4, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.73-7.67 (m, 4H), 7.44-7.25 (m, 11H), 4.84 (d, J = 6.8 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.70-4.54 (m, 4H), 4.50(d, J = 1.7 Hz, 1H), 3.93 (dd, J = 2.8, 11.3 Hz, 1H), 3.81-3.70 (m, s, 4H), 3.64-3.62 (m, 1H), 3.38 (s, 3H), 2.43-2.42 (m, 1H), 1.08 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.14, 137.73, 135.58, 135.54, 133.26, 133.22, 129.58, 128.22, 127.57, 127.53, 127.43, 96.93, 94.90, 79.70, 76.16, 69.72, 64.72, 56.29, 51.70, 38.47, 26.72, 19.15, 10.31.

IR ($CHCl_3$): 2960, 2940, 1750, 1430 cm^{-1}.

HRMS: $C_{33}H_{44}O_7SiNa$, calc.: 603.2754, found: 603.2784.



(2S,3S,4S)-4-benzyloxymethoxy-5-(tert-butyldiphenylsilanyloxy)-2-methoxymethoxy-3-methyl-pentan-1-ol (66)

To a solution of ester **65** (14.1 g, 24.3 mmol) in THF (250 ml) was added DIBAL-H (1.0 M in toluene, 55.9 ml, 55.9 mmol) at -78°C. The resulting mixture was stirred at 0°C for 2 h, then recooled to -78°C and quenched with sat. NH_4Cl. The mixture was diluted with EtOAc and 5% HCl, and separated, the aqueous phase was extracted with EtOAc, the

combined organic extracts were washed with sat. $NaHCO_3$, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford alcohol **66** as an oil (13.0 g, 97%).

TLC: E/H = 1:2, R_f = 0.45.

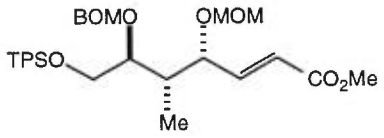
$[\alpha]_D$ +3.1° (*c* 1.6, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.73-7.67 (m, 4H), 7.44-7.25 (m, 11H), 4.84 (d, J = 6.8 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.70-4.54 (d+d+d+d+d, 4H), 4.50 (d, J = 1.7 Hz, 1H), 3.93 (dd, J = 2.8, 11.3 Hz, 1H), 3.81-3.70 (m+s, 4H), 3.64-3.62 (m, 1H), 3.38 (s, 3H), 2.43-2.42 (m, 1H), 1.08 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.14, 137.73, 135.58, 135.54, 133.26, 133.22, 129.58, 128.22, 127.57, 127.53, 127.43, 96.93, 94.90, 79.70, 76.16, 69.72, 64.72, 56.29, 51.70, 38.47, 26.72, 19.15, 10.31.

IR ($CHCl_3$): 2970, 2950, 2890, 1750, 1430 cm^{-1}.

HRMS: $C_{33}H_{44}O_7SiNa$, calc.: 603.2754, found: 603.2784.



(4R,5S,6S)-6-benzyloxymethoxy-7-(tert-butyldiphenylsilanyloxy)-4-methoxymethoxy-5-methyl-hept-2-enoic acid methyl ester (67)

To a solution of oxalyl chloride (3.8 ml, 43.5 mmol) in CH_2Cl_2 (100 ml) at -70°C was added DMSO (6.2 ml, 87.0 mmol), and the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to -55°C, then a solution of **66** (8.0 g, 14.5 mmol) in CH_2Cl_2 (50 ml) was added. The reaction mixture was warmed to -40°C over 20 min, and then triethylamine (20.2 ml, 145 mmol) was added, the temperature was allowed to rise further to -30°C over 30 min. The reaction was quenched with sat. NH_4Cl (100 ml). The reaction mixture was diluted with CH_2Cl_2 (400 ml), then washed with 2.5% HCl (2x200 ml), sat. $NaHCO_3$ (2x200 ml), and brine (200 ml), then dried over Na_2SO_4 for 2 h. The crude aldehyde after removing solvent was dried by an oil pump for 2 h.

To a solution of the crude aldehyde in CH_2Cl_2 (100 ml) was added methyl (triphenyl-phosphoranylidene) acetate (9.7 g, 29 mmol, as solid). The resulting mixture was stirred for 14 h at room temperature. The crude product after removing solvent was directly purified by chromatography to afford unsaturated ester **67** as an oil (8.73 g, 99%).

TLC: E/H = 1:5, R_f = 0.51.

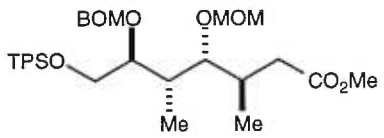
$[\alpha]_D$ -14.4° (*c* 1.0, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.66 (m, 4H), 7.44-7.24 (m, 11H), 6.06-6.91 (dd, J = 5.7, 15.7 Hz, 1H), 6.03-5.99 (dd, J = 1.4, 15.7 Hz, 1H), 4.87-4.81 (d+d, J = 6.8 Hz, 2H), 4.62- 4.50 (m, 4H), 3.89-3.86 (dd, J = 3.3, 11.2 Hz, 1H), 3.78-3.72 (s+m, 5H), 3.68-3.66 (m, 1H), 3.33 (s, 3H), 2.13-2.03 (m, 1H), 1.06 (s, 9H), 0.91 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 166.46, 148.36, 137.84, 135.56, 135.52, 133.33, 133.29, 129.56, 128.19, 127.56, 127.53, 127.51, 127.39, 121.47, 95.71, 94.95, 79.83, 76.28, 69.70, 64.30, 55.85, 51.36, 40.05, 26.77, 19.12, 9.91.

IR ($CHCl_3$): 2950, 1730, 1430 cm^{-1}.

HRMS: $C_{35}H_{46}O_7SiNa$, calc.: 629.2910, found: 629.2911.



(3R,4R,5S,6S)-6-benzyloxymethoxy-7-(tert-butyldiphenylsilanyloxy)-4-methoxymethoxy-3,5-dimethyl-heptanoic acid methyl ester (68)

To a suspension of CuI (14.3 g, 74.6 mmol) in THF (500 ml) was added MeLi·LiBr (1.5 M in ether, 100 ml, 150 mmol) at -15°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (25 ml, 211 mmol), and then a solution of **67** (8.5 g, 14.1 mmol) in THF (100 ml). The reaction was continued for 3 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **68** as an oil (8.2 g, 94%).

TLC: E/H = 1:5, R_f = 0.52.

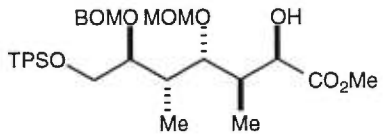
$[\alpha]_D$ -14.8° (*c* 1.0, $CHCl_3$);

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.72-7.68 (m, 4H), 7.44-7.26 (m, 11H), 4.89-4.82 (d+d, J = 6.8 Hz, 2H), 4.67-4.54 (m, 4H), 3.90-3.86 (dd, J = 3.2, 11.2 Hz, 1H), 3.78-3.73 (dd, J = 4.5, 11.2 Hz, 1H), 3.68-3.56 (s+m, 5H), 3.34 (s, 3H), 2.64-2.58 (dd, J = 4.1, 14.7 Hz, 1H), 2.30-2.05 (m, 3H), 1.08 (s, 9H), 0.97 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.64, 137.83, 135.81, 135.50, 135.46, 133.26, 129.51, 128.13, 127.79, 127.51, 127.47, 127.31, 98.24, 94.83, 82.86, 80.60, 69.62, 64.10, 55.61, 51.15, 37.85, 36.53, 33.83, 26.67, 19.08, 16.89, 10.14.

IR ($CHCl_3$): 2950, 1740, 1430, cm^{-1}.

HRMS: $C_{36}H_{50}O_7SiNa$, calc.: 645.3223, found: 645.3252.



(2R,3R,4R,5S,6S)-6-benzyloxymethoxy-7-(tert-butyldiphenylsilanyloxy)-2-hydroxy-4-methoxymethoxy-5-methyl-heptanoic acid methyl ester (69)

To a solution of **68** (3.58 g, 5.76 mmol) in THF (100 ml) was added KHMDS (0.5 M in toluene, 16.1 ml, 8.0 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (3.0 g, 115 mmol) in THF (20 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl, brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **69** as an oil (3.0 g, 80%).

TLC: E/H = 1:5, R_f = 0.40.

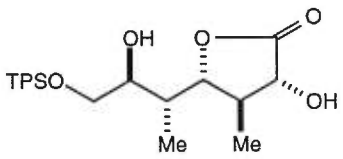
$[\alpha]_D$ -17.2° (*c* 1.1, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.70-7.66 (m, 4H), 7.43-7.27 (m, 11H), 4.88-4.81 (d+d, J = 6.9 Hz, 2H), 4.77-4.67 (d+d, J = 6.3 Hz, 2H), 4.69-4.52 (d+d, J = 11.0 Hz, 2H, d, J = 2.2 Hz,1H), 3.93- 3.88 (m, 2H), 3.80-3.72 (s+m, 4H), 3.61-3.58 (m, 1H), 3.32 (s, 3H), 2.17-2.05 (m, 2H), 1.06 (s, 9H), 0.87 (d, J = 7.1 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 175.38, 137.78, 135.51, 133.30, 129.55, 128.18, 127.63, 127.56, 127.51, 127.39, 98.86, 94.89, 80.66, 80.62, 70.58, 69.89, 64.32, 55.71, 52.17, 39.38, 36.45, 26.71, 19.14, 10.60, 9.53.

IR ($CHCl_3$): 3520, 2950, 1738, 1430 cm^{-1}.

HRMS: $C_{36}H_{50}O_8SiNa$, calc.: 661.3172, found: 661.3202.



(3R,4R,5S)-5-[(1R,2S)-3-(tert-butyldiphenylsilanyloxy)-2-hydroxy-1-methyl-propyl]-3-hydroxy-4-methyl-dihydro-furan-2-one (70)

To a solution of the common chiron **69** (36 mg, 0.056 mmol) in dry CH_2Cl_2 (1 ml) at -40°C was added trimethylsilyl bromide (75 µl, 0.56 mmol). The resulting mixture was

stirred for 2 h and the temperature was allowed to rise to 0°C. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, then dried over Na_2SO_4. The product was purified by chromatography to give crystalline **70** suitable for X-ray analysis (18.5 mg, 72%).

TLC: E/H = 1:2, R_f = 0.17.

$[\alpha]_D$ -8.5° (*c* 0.9, $CHCl_3$);

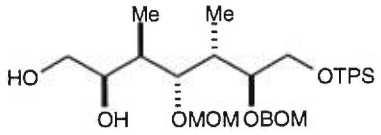
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.67-7.64 (m, 4H), 7,47-7.38 (m, 6H), 4.56 (d, J = 10.4 Hz, 1H), 4.08 (d, J = 10.7 Hz, 1H), 3.83 (dd, J = 3.1, 10.2 Hz, 1H), 3.69-3.65 (m, 1H), 3.60-3.56 (m, 1H), 2.29-2.22 (m, 1H), 1.84-1.80 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H), 1.07 (s, 9H), 0.73 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 176.72 (0), 135.40, 135.37, 132.72 (0), 132.61 (0), 129.89, 129.88, 127.78, 127.76. 81.29, 74.57, 72.34, 65.86 (-), 40.47, 35.93, 26.73, 19.14 (0), 13.81, 8.22.

IR ($CHCl_3$): 3580, 2940, 2870,1780, 1595, 1470 cm^{-1}.

HRMS: $C_{25}H_{34}O_5SiNa$, calc.: 465.2073, found: 465.2088.

X-Ray Diffraction Analysis Data



(2R,3R,4R,5S,6S)-6-benzyloxymethoxy-7-(tert-butyldiphenylsilanyloxy)-4-methoxymethoxy-3,5-dimethyl-heptan-1,2-diol (71)

To a solution of hydroxy ester **69** (632 mg, 1.0 mmol) in THF-H_2O (4:1, 10 ml) was added $NaBH_4$ (510 mg, 15 mmol) and the resulting mixture was stirred for 72 h at room temperature. The reaction was quenched with 2% HCl carefully and the reaction mixture was extracted with EtOAc. The combined organic extracts were washed with sat. $NaHCO_3$, sat. NH_4Cl and brine, then dried over Na_2SO_4. The product was purified by chromatography to afford diol **71** as an oil (495 mg, 82%).

TLC: E/H = 1:1, R_f = 0.25.

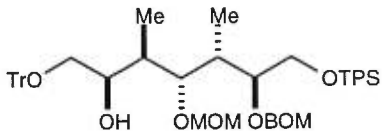
$[\alpha]_D$ -9.1° (*c* 1.8, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.73-7.66 (m, 4H), 7.47-7.26 (m, 11H), 4.86 (d, J = 6.94 Hz, 1H), 4.79 (dd, J = 4.4, 6.4 Hz, 2H), 4.70 (d, J = 11.9 Hz, 1H), 4.57 (dd, J = 6.3, 13.4 Hz, 2H), 4.10 (m, 1H), 3.86-3.64 (m, 4H), 3.59-3.47 (m, 2H), 3.34 (s, 3H), 2.65 (br, 2H), 2.15-2.10 (m, 1H), 1.77-1.71 (m, 1H), 1.07 (s, 9H), 0.90 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 137.66 (0), 135.61, 135.59, 135.56, 133.26 (0), 133.25 (0), 129.69, 128.33, 127.71, 127.66, 127.63, 127.59, 98.89 (-), 94.66 (-), 82.08, 80.58, 70.80, 70.01 (-), 65.17 (-), 64.06 (-), 56.02, 37.97, 37.03, 26.78, 19.16 (0), 10.54, 10.26.

IR ($CHCl_3$): 3460 (br), 1960, 1890, 1830, 1730, 1590, 1460 cm^{-1}.

HRMS: $C_{35}H_{50}O_7SiNa$, calc.: 633.3223, found: 633.3197.



(2R,3R,4R,5S,6S)-6-benzyloxymethoxy-7-(tert-butyldiphenylsilanyloxy)-4-methoxymethoxy-3,5-dimethyl-1-trityloxy-heptan-2-ol (72)

To a solution of diol **71** (495 mg, 0.81 mmol) in CH_2Cl_2 (15 ml) was added TrDMAP$^+$Cl$^-$ (trityl-4-dimethylaminopyridium chloride, 649 mg, 1.62 mmol, solid) and the resulting mixture was refluxed for 7 h. The reaction mixture after removing solvent was directly purified by chromatography to give **72** as an oil (418 mg, 60%) and starting material **71** (109 mg, 22%).

TLC: E/H = 1:5, R_f = 0.40.

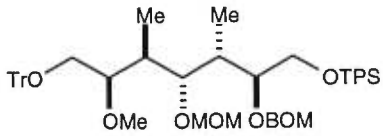
$[\alpha]_D$ -0.5° (*c* 1.2, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.68 (m, 4H), 7.51-7.22 (m, 26H), 4.89 (d, J = 6.9 Hz, 1H), 4.80 (t, J = 6.7 Hz, 2H), 4.69 (d, J = 12.1 Hz, 1H), 4.66 (d, J = 6.3 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.32 (br, 1H), 3.90-3.83 (m, 2H), 3.76 (dd, J = 4.8, 11.2 Hz, 1H), 3.63-3.61 (m, 1H), 3.38 (s, 3H), 3.37-3.31 (m, 1H), 3.23 (d, J = 3.6 Hz, 1H), 3.00 (dd, J = 6.0, 8.9 Hz, 1H), 2.13 (m, 1H), 1.87 (m, 1H), 1.08 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 144.14 (0), 137.88 (0), 135.64, 135.61, 133. 39 (0), 133.37, 129.63, 128.70, 128.30, 127.76, 127.73, 127.67, 127.63, 127.50, 126.88, 98.95 (-), 94.85 (-), 86.45 (0), 82.11, 80.81, 69.92 (-), 69.05, 65.84 (-), 64.39 (-), 55.96, 37.91, 37.18, 26.82, 19.20 (0), 10.20, 9.98.

IR ($CHCl_3$): 3460(br), 2950, 1960, 1890, 1830, 1730, 1590 cm^{-1};

HRMS: $C_{54}H_{64}O_7SiNa$, calc.: 875.4318, found: 875.4321.



(2R,3S,4R,5S,6S)-6-benzyloxymethoxy-6-(tert-butyldiphenylsilanyloxy)-2-methoxy-4-methoxymethoxy-3,5-dimethyl-1-trityloxy-heptane (73)

To a solution of **72** (411 mg, 0.48 mmol) in DMF (4 ml) at 0°C were added sodium hydride (60% in mineral oil, 191 mg, 4.8 mmol), and then methyl iodide (0.45 ml, 7.2 mmol). The reaction was continued for 1 h at room temperature and quenched with MeOH. The product was directly purified by chromatography to afford 73 as an oil (408 mg, 97%).

TLC: E/H = 1:5, R_f = 0.70.

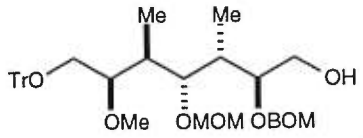
$[\alpha]_D$ -13.1° (*c* 1.9, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.73-7.68 (m, 4H), 7.50-7.22 (m, 26H), 4.87 (dd, J = 6.1, 7.4 Hz, 2H), 4.75 (d, J = 6.3 Hz, 1H), 4.70 (d, J = 6.4 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 4.57 (m, 2H), 3.94 (dd, J = 2.7, 11.3 Hz, 1H), 3.86 (d, J = 9.3 Hz, 1H), 3.79-3.74 (m, 2H), 3.68-3.64 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.10 (dd, J = 5.5, 9.5 Hz, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.08 (s, 9H), 0.84 (d, J = 7.1 Hz, 3H), 0.72 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 144.12, 138.14, 135.66, 135.62, 133.56, 129.57, 129.54, 128.68, 128.19, 127.70, 127.61, 127.59, 127.53, 127.31, 126.86, 98.67, 95.18, 86.70, 81.38, 81.16, 79.24, 69.67, 64.85, 58.19, 55.57, 38.38, 36.46, 26.80, 19.23, 10.21, 9.54.

IR ($CHCl_3$): 2930, 1960, 1890, 1830, 1730, 1600, 1500, 1450 cm^{-1}.

MS: 889 (m+23), 867 (m+1).



(2S,3S,4R,5S,6R)-2-benzyloxymethoxy-6-methoxy-4-methoxymethoxy-3,5-dimethyl-7-trityloxy-heptan-1-ol (74)

To a solution of **73** (404 mg, 0.47 mmol) in THF (4 ml) was added TBAF (1.0 M in THF, 0.93 ml, 0.93 mmol) at room temperature. The resulting mixture was stirred for 4.5 h at room temperature. The crude product was directly purified by chromatography to afford **74** as an oil (283 mg, 96%).

TLC: E/H = 1:3, R_f = 0.20.

$[\alpha]_D$ -0.9° (*c* 1.56, $CHCl_3$).

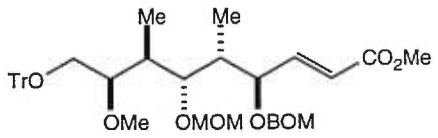
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.48-7.46 (m, 6H), 7.37-7.22 (m, 14H), 4.90 (dd, J = 7.0, 15.8 Hz, 2H), 4.78 (d, J = 11.8 Hz, 1H), 4.69 (dd, J = 6.5, 15.2 Hz, 2H), 4.60 (d, J = 11.9 Hz, 1H), 3.86 (br, 1H), 3.76 (d, J = 9.4 Hz, 1H), 3.67 (m, 1H), 3.61-3.44 (m, 2H), 3.41-3.59 (s+s+m, 3H+3H+ 2H), 3.10 (dd, J = 5.6, 9.6 Hz, 1H), 1.92-1.86 (m, 1H), 1.86-1.76 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H), 0.67 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 144.04 (0), 137.18 (0), 128.64, 128.47, 127.86, 127.73, 127.91, 98.76 (-), 95.64 (-), 86.74 (0), 84.97, 81.47, 79.18, 70.14 (-), 64.56 (-), 64.09 (-), 58.05, 55.67, 38.11, 36.13, 10.16, 9.85.

IR ($CHCl_3$): 3440 (br), 2950, 1960, 1830, 1600, 1500, 1450 cm^{-1}.

MS: 651.4 (m+23).

HRMS: $C_{39}H_{49}O_7$, calc.: 629.3478, found: 629.3473.



(4R,5R,6S,7S,8R)-4-benzyloxymethoxy-8-methoxy-6-methoxymethoxy-5,7-dimethyl-9-trityloxy-non-2-enoic acid methyl ester (75)

To a solution of oxalyl chloride (28 µl, 0.32 mmol) in CH_2Cl_2 (0.5 ml) at -70°C was added DMSO (45 µl, 0.62 mmol), and the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to -55°C, then a solution of **74** (40 mg, 0.06 mmol) in CH_2Cl_2 (1 ml) was added. The reaction mixture was warmed to -40°C during 20 min and triethylamine (178 µl, 1.28 mmol) was added, then temperature was allowed to rise further to -30°C over 30 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, then washed with 2.5% HCl, sat. $NaHCO_3$ and brine, then dried over Na_2SO_4 for 2 h. The crude aldehyde after removing solvent was dried by an oil pump for 2 h.

To a solution of the above crude aldehyde in CH_2Cl_2 (1 ml) was added methyl (triphenylphosphoranylidene) acetate (86 mg, 0.26 mmol, solid). The resulting mixture was stirred for 14 h at room temperature. The reaction mixture after removing solvent was directly purified by chromatography to afford **75** as an oil, (34 mg, 92%).

TLC: E/H = 1:3, R_f = 0.47.

$[\alpha]_D$ -15.8° (*c* 1.4, $CHCl_3$).

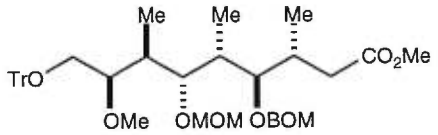
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.49-7.45 (m, 6H), 7.37-7.22 (m, 14H), 6.87 (dd, J = 7.9, 15.7 Hz, 1H), 5.99 (dd, J = 0.8, 15.7 Hz, 1H), 4.86-4.74 (m, 2H), 4.70 (d, J = 6.5

Hz, 1H), 4.63 (s, 2H), 4.13 (t, J = 8.3 Hz, 1H), 3.86 (d, J = 9.0 Hz, 1H), 3.75 (s, 3H), 3.73-3.64 (m, 2H), 3.43 (s, 3H), 3.40 (s, 3H), 3.38-3.35 (m, 1H), 3.09 (dd, J = 5.6, 9.6 Hz, 1H), 1.95-1.76 (m, 2H), 0.82 (d, J = 7.1 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 166.43 (0), 148.10 (0), 144.03, 137.68 (0), 128.64, 128.28, 127.77, 127.72, 127.59, 126.90, 122.57, 98.69 (-), 93.78 (-), 86.72 (0), 80.97, 79.31, 79.22, 69.91(-), 64.53 (-), 58.16, 55.67, 51.54, 39.33, 38.25, 10.08, 9.85.

IR ($CHCl_3$): 2950, 1960, 1820, 1725, 1665, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{42}H_{50}O_8Na$ (m+23), calc.: 705.3403, found: 705.3367.



(3R,4R,5R,6S,7S,8R)-4-benzyloxymethoxy-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxy-nonanoic acid methyl ester (76)

To a suspension of CuI (368 mg, 1.9 mmol) in THF (12 ml) was added MeLi·LiBr (1.5 M in ether, 2.6 ml, 3.87 mmol) at -15°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (0.73 ml, 5.8 mmol), and then a solution of **75** (220 mg, 0.32 mmol) in THF (5 ml). The reaction was continued for 3 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **76** as an oil (188 mg, 83%).

TLC: E/H = 1:5, R_f = 0.42.

[α] -37.5° (*c* 2.9, $CHCl_3$).

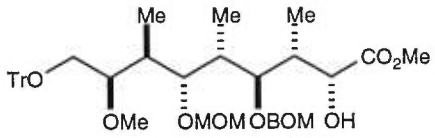
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.49-7.45 (m, 6H), 7.39-7.22 (m, 14H), 4.87 (dd, J = 6.7, 11.8 Hz, 2H), 4.76 (dd, J = 1.9, 8.5 Hz, 2H), 4.69 (d, J = 12.1 Hz, 1H), 4,63 (d, J = 12.1 Hz, 1H), 3,84 (d, J = 7.5 Hz, 1H), 3.74-3.72 (m, 1H), 3.69 (s, 3H), 3.58 (dd, J = 1.5, 9.4 Hz, 1H), 3.42 (s, 3H), 3.41- 3.36 (m, 1H), 3.30 (s, 3H), 3.08 (dd, J = 3.8, 5.7 Hz, 1H), 2.45 (dd, J = 2.6, 14.5 Hz, 1H), 2.32- 2.29 (m, 1H), 2.21 (dd, J = 10.1, 14.4 Hz, 1H), 1.89-1.86 (m, 1H), 1.76-1.71 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 174.11 (0), 144.06 (0), 138.00 (0), 128.65, 128.23, 127.72, 127.71, 127.39, 126.89, 98.65 (-), 97.22 (-), 86.72 (0), 86.44, 82.01, 79.06, 69.83 (-), 64.64 (-), 57.98, 55.36, 51.43, 38.37, 37.75, 35.12 (-), 32.38, 18.32,

10.29, 10.21.

IR ($CHCl_3$): 2950, 1960, 1820, 1735, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{43}H_{54}O_8Na$ (m+23), calc.: 721.3716, found: 721.3758.



(2R,3R,4R,5R,6S,7S,8R)-4-benzyloxymethoxy-2-hydroxy-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxy-nonanoic acid methyl ester (77)

To a solution of **76** (187 mg, 0.27 mmol) in THF (2 ml) was added KHMDS (0.5 M in toluene, 0.81 ml, 0.40 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (141 mg, 0.54 mmol) in THF (2 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **77** as an oil (145 mg, 76%).

TLC: E/H = 1:3, R_f = 0.20.

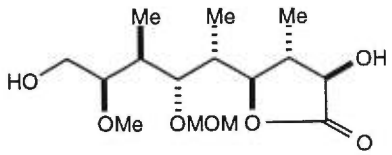
$[\alpha]_D$ -30°, (*c* 1.7, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.49-7.46 (m, 6H), 7.37-7.22 (m, 14H), 4.90 (dd, J = 6.7, 8.5 Hz, 2H), 4.76 (s, 2H), 4.68-4.64 (m, 3H), 3.82-3.70 (s+m, 3H+4H), 3.42 (s, 3H), 3.41-3,35 (m, 1H), 3.32 (s, 3H), 3.09 (dd, J = 6.0, 9.6 Hz, 1H), 2,34-2.31 (m, 1H), 1.96-1.89 (m, 2H), 1.04 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.88 (0), 144.02 (0), 137.31 (0), 128.63, 128.37, 128.35, 128.33, 127.83, 127.81, 127.80, 127.78, 127.74, 127.66, 126.92, 98.56 (-), 97.47 (-), 87.59 (0), 86.74, 81.44, 78.98, 70.99, 70.29 (-), 64.46 (-), 57.95, 55.47, 52.20, 38.46, 37.69, 37.21, 12.23, 10.83, 10.36.

IR ($CHCl_3$): 3480(br), 2950, 1960, 1830, 1760, 1740, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{43}H_{54}O_9Na$ (m+23), calc.: 737.3665, found: 737.3644.



(3R,4R,5R)-3-Hydroxy-5-[(1S,2S,3S,4R)-5-hydroxy-4-methoxy-2-methoxymethoxy-1,3-dimethyl-pentyl]-4-methyl-dihydro-furan-2-one (78)

A mixture of **77** (14 mg) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 20 mg) in MeOH (2 ml) under 1 atm hydrogen was stirred at room temperature for 20 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The product was purified by chromatography to give crystalline **78** suitable for X-ray analysis (5 mg, 80%).

TLC: E/H = 1:0, R_f = 0.47.

$[\alpha]_D$ -35.0° (*c* 0.1, $CHCl_3$);

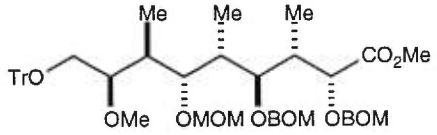
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.72 (dd, J = 6.4, 17.6 Hz, 2H), 4.16 (t, J = 9.2 Hz, 1H), 4.09 (d, J = 10.0 Hz, 1H), 3.83 (d, J = 8.9 Hz, 1H), 3.79-3.71 (m, 2H), 3.57-3.54 (m, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 270-2.60 (br, 2H), 2.24-2.21 (m, 1H), 1.97-1.80 (m, 2H), 1.35 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 4.9 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 175.94 (0), 99.13 (-), 83.96, 81.74, 80.05, 75.09, 63.18 (-), 58.25, 55.79, 43.13, 41.20, 37.82, 17.02, 10.34, 8.95.

IR ($CHCl_3$): 3580, 2940, 1780, 1610 cm^{-1}.

HRMS: $C_{15}H_{28}O_7Na$, calc.: 343.1732, found: 343.1740.

X-Ray diffraction Analysis Data



(2R,3S,4S,5S,6S,7S,8R)-2,4-bis-benzyloxymethoxy-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxy-nonanoic acid methyl ester (79)

To a solution of **77** (117 mg, 0.164 mmol) and diisopropylethylamine (0.87 ml, 4.9 mmol) in CH_2Cl_2 at 0°C was added BOMCl (0.68 ml, 4.9 mmol) dropwise and the resulting mixture was stirred at room temperature for 60 h. The product was purified by chromatography directly to afford **79** as an oil (106 mg, 77%).

TLC: E/H = 1:3, R_f = 0.70.

$[\alpha]_D$ -25.5° (*c* 0.8, $CHCl_3$);

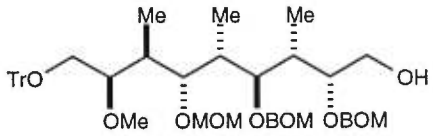
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.48-7.45 (m, 6H), 7.39-7.22 (m, 19H), 4.89-4.83 (m, 3H), 4.79- 4.70 (m, 4H), 4.66-4.61 (m, 3H), 4.41 (d, J = 3.1 Hz,1H), 3.82-3.64 (m+s, 2H+3H), 3,58 (dd, J = 3.9, 7.9 Hz, 1H), 3.43 (s, 3H), 3.42-3.36 (m, 1H), 3.33 (s, 3H), 3.06 (dd, J = 5.8, 9.4 Hz, 3H), 2.34-2.28 (m, 1H), 1.93-1.83 (m, 2H), 1.11 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.67 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 173.38, 144.06, 137.90, 137.73, 128.64, 128.30, 128.25, 127.74, 127.72, 127.56, 127.43, 126.88, 98.64, 96.97, 94.57, 86.68, 85.34, 81.40,

78.90, 76.01, 70.03, 69.91, 64.59, 58.02, 55.54, 51.83, 38.64, 38.51, 37.66, 13.10, 10.75, 10.37.

IR ($CHCl_3$): 2950, 1960, 1830, 1750, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{51}H_{62}O_{10}Na$, calc.: 857.4240, found: 857.4280.



(2R,3S,4S,5S,6S,7S,8R)-2,4-bis-benzyloxymethoxy-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxy-nonan-1-ol (80)

To a solution of the ester **79** (123 mg, 0.15 mmol) in THF (2 ml) at -78°C was added DIBAL-H (1.0 M in toluene, 0.36 ml, 0.36 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 sat. NH_4Cl, then diluted with EtOAc and 2% HCl to dissolve aluminum gel. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with sat. Na_HCO3, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford an **80** as an oil (98.4 mg, 83%).

TLC: E/H = 1:3, R_f = 0.22.

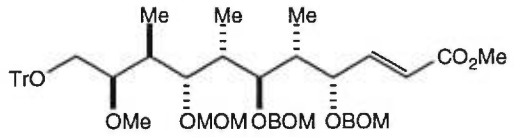
$[\alpha]_D$ -39.4° (*c* 1.2, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.51-7.48 (m, 6H), 7.41-7.23 (m, 19H), 4.90-4.88 (m, 3H), 4.83-4.75 (m, 4H), 4.67 (s, 2H), 4.60 (dd, J = 0.6, 11.8 Hz, 1H), 3.85-3.65 (m, 5H), 3.61 (dd, J = 3.2, 8.1 Hz, 1H), 3.45 (s, 3H), 3.45-3.31 (s+m, 3H+2H), 3.09 (dd, J = 5.7, 9.5 Hz, 1H), 2.08- 2.04 (m, 1H), 1.95-1.85 (m, 2H), 1.09 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 144.09 (0), 137.85 (0), 137.24 (0), 128.67, 128.49, 128.31, 127.86, 127.81, 127.79, 127.78, 127.75, 127.53, 126.91, 98.66 (-), 96.93 (-), 95.58 (-), 86.73 (0), 85.44, 82.74, 81.53, 79.04, 70.03 (-), 69.99 (-), 64.76 (-), 64.64 (-), 58.08, 55.60, 38.52, 37.58, 13.36, 11.11, 10.41.

IR ($CHCl_3$): 3460 2950, 1920, 1820, 1600, 1495, 1450 cm^{-1}.

HRMS: $C_{50}H_{62}O_9Na$, calc.: 829.4291, found: 829.4259.



(4S,5R,6R,7R,8S,9S,10R)-4,6-bis-benzyloxymethoxy-10-methoxy-8-methoxymethoxy-5,7,9-trimethyl-11-trityloxy-undec-2-enoic acid methyl ester (81)

To a solution of oxalyl chloride (53 µl, 0.6 mmol) in CH_2Cl_2 (2 ml) at -70°C was added DMSO (86 µl, 1.2 mmol), and the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to -55°C, then a solution of **80** (98 mg, 0.12 mmol) in CH_2Cl_2 (2 ml) was added. The reaction mixture was warmed to -40°C during 20 min and triethylamine (338 µl, 2.4 mmol) was added, then temperature was allowed to rise further to -30°C over 30 min.

To the above mixture was added a solution of methyl (triphenylphosphoranylidene) acetate (200 mg, 0.6 mmol) in CH_2Cl_2 (2 ml). The resulting mixture was stirred for 14 h at room temperature. The reaction mixture after removing solvent was directly purified by chromatography to afford **81** as an oil, (87 mg, 83%).

TLC: E/H = 1:5, R_f = 0.27.

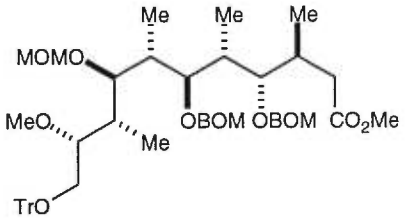
$[\alpha]_D$ +0.6° (*c* 1.6, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.49-7.46 (m, 6H), 7.34-7.22 (m, 19H), 6.99 (dd, J = 6.6, 15.7 Hz, 1H), 6.05 (d, J = 15.7 Hz, 1H), 4.88 (s, 2H), 4.77-4.69 (m, 4H), 4.67 (d, J = 8.6 Hz, 2H), 4.60 (d, J = 11.8 Hz, 1H), 4.44 (t, J = 6.1 Hz, 1H), 3.79 (d, J = 9.5 Hz, 1H), 3.74 (s, 3H), 3.61 (dd, J = 2.9, 9.7 Hz, 1H), 3.41 (s, 3H), 3.39-3.37 (m, 1H), 3.34 (s, 3H), 3.06 (dd, J = 5.6, 9.5 Hz, 1H), 2.13-2.08 (m, 1H), 1.95-1.83 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.66 (d, J = 6.9 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 166.53 (0), 148.24 (0), 144.07, 137.95 (0), 137.65 (0), 128.65, 128.35, 128.27, 127.80, 127.72, 127.63, 127.44, 126.89, 121.81, 98.64 (-), 97.04 (-), 92.95 (-), 86.72 (0), 85.06, 81.57, 78.97, 76.47, 69.94 (-), 69.86 (-), 64.71 (-), 58.02, 55.51, 51.52, 40.58, 38.44, 37.74, 13.36, 10.88, 10.26.

IR ($CHCl_3$): 2960, 1960, 1830, 1720, 1650, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{53}H_{64}O_{10}Na$, calc.: 883.4397, found: 883.4423.



(3S,4S,5R,6R,7R,8S,9S,10R)-4,6-bis-benzyloxymethoxy-10-methoxy-8-methoxymethoxy-3,5,7,9-tetramethyl-11-trityloxy-undecanoic acid methyl ester (82)

To a suspension of CuI (114 mg, 0.6 mmol) in THF (6 ml) was added MeLi·LiBr (1.5 M in ether, 0.8 ml, 1.2 mmol) at -15°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (227 µl, 1.8 mmol), and then a solution of **81** (86 mg, 0.1 mmol) in THF (2.5 ml). The reaction was continued for 3.5 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **82** as an oil (75 mg, 86%).

TLC: E/H = 1:5, R_f = 0.35.

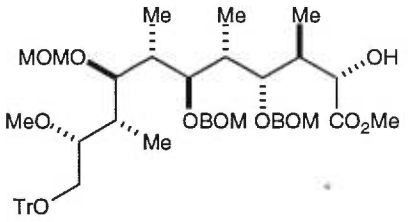
$[\alpha]_D$ -21.8° (*c* 1.6, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.49-7.47 (m, 6H), 7.35-7.23 (m, 19H), 4.89-4.84 (m, 3H), 4.79- 4.77 (m, 3H), 4.71 (d, J = 11.9 Hz, 1H), 4.64 (s, 2H), 4.59 (d, J = 11.9 Hz, 1H), 3,83-3.76 (m, 2H), 3.67 (s, 3H), 3.62-3.60 (m, 2H), 3.45 (s, 3H), 3.40-3.38 (m, 1H), 3.37 (s, 3H), 3.07 (dd, J = 5.8, 9.5 Hz, 1H), 2.71 (dd, J = 3.7, 15.2 Hz, 1H), 2.33-2.30 (m, 1H), 2.18 (dd, J = 9.8, 15.2 Hz, 1H), 2.09-2.06 (m, 1H), 1.88-1.83 (m, 2H), 1.05 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H);

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 173.89 (0), 144.04 (0), 137.93 (0), 137.91 (0), 128.61, 128.31, 128.30, 128.28, 128.27, 128.26, 128.25, 128.20, 127.67, 127.62, 127.61, 127.47, 127.38, 126.84, 98.62 (-), 96.95 (-), 96.51 (-), 86.66 (0), 85.69, 83.11, 81.24, 78.95, 70.05 (-), 69.75 (-), 64.64 (-), 58.05, 55.58, 51.28, 51.27, 38.48, 37.88, 37.12, 37.08 (-), 34.17, 17.54, 12.40, 10.90, 10.34.

IR ($CHCl_3$): 2950, 1960, 1830, 1730, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{54}H_{68}O_{10}Na$, calc.: 899.4710, found: 899.4720.



(2S,3S,4S,5R,6R,7R,8S,9S,10R)-4,6-bis-benzyloxymethoxy-2-hydroxy-10-methoxy-8-methoxymethoxy-3,5,7,9-tetramethyl-11-trityloxy-undecanoic acid methyl ester (83)

To a solution of **16** (43 mg, 0.05 mmol) in THF (1 ml) was added KHMDS (0.5 M in toluene, 147 µl, 0.07 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (26 mg, 0.1 mmol) in THF (20 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **17** as an oil (31 mg, 71%).

TLC: E/H = 1:4, R_f = 0.40.

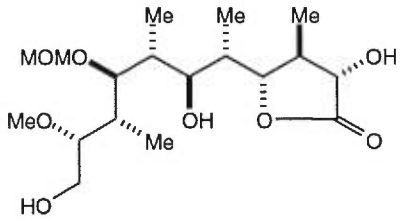
$[\alpha]_D$ -22.4° (*c* 1.6, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.48-7.46 (m, 6H), 7.33-7.22 (m, 19H), 4.91 (d, J = 6.5 Hz, 1H), 4.87 (s, 2H), 4.84 (d, J = 6.5 Hz, 1H), 4.75 (m, 3H), 4.67 (d, J = 12.1 Hz, 1H), 4.62 (s, 3H), 4.59 (d, J = 12.1 Hz, 1H), 3.86-3.76 (m+s, 3H+3H), 3.63-3.60 (m, 1H), 3.42 (s, 3H), 3.40-3.36 (m, 2H), 3.35 (s, 3H), 3.07 (dd, J = 5.8, 9.5 Hz, 1H), 2.25 (m, 1H), 1.97 (m, 1H), 1.86 (m, 2H), 1.04 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.1 Hz, 3H), 0.86 (d, J= 7.1 Hz, 3H), 0.68 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 175.18 (0), 144.04 (0), 137.90 (0), 137.50 (0), 128.61, 128.33, 128.17, 128.16, 127.69, 127.65, 127.61, 127.52, 127.36, 126.82, 98.58 (-), 97.16 (-), 96.83(-), 86.69 (0), 86.54, 81.08, 80.29, 78.88, 70.50, 70.22 (-), 69.82 (-), 64.54 (-), 57.98, 55.50, 52.11, 39.89, 38.54, 37.24, 36.58, 12.04, 10.97, 10.93, 10.43

IR ($CHCl_3$): 3500 (br), 2960, 1960, 1830, 1730, 1600, 1500, 1450 cm^{-1}.

HRMS: $C_{54}H_{68}O_{11}Na$, calc.: 915.4659, found: 915.4647.



(3S,4S,5R)-5-[(1S,2S,3R,4S,5S,6R)-2,7-dihydroxy-6-methoxy-4-methoxymethoxy-1,3,5-trimethyl-heptyl)]-3-hydroxy-4-methyl-dihydrofuran-2-one (84)

A mixture of **83** (12.4 mg) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 13 mg) in MeOH (1 ml) under 1 atm hydrogen was stirred at room temperature for 6 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The product was purified by chromatography to give a solid **84** (4 mg, 76%).

TLC: E/H = 1:0, R_f = 0.20.

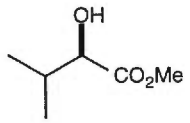
$[\alpha]_D$ -27.5° (*c* 0.4, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 4.76 (s, 2H), 4.50 (d, J = 10.2 Hz, 1H), 4.07 (d, J = 10.5 Hz, 1H), 3.90 (d, J = 9.4 Hz, 1H), 3.82-3.79 (m, 1H), 3.78-3.70 (m, 1H), 3.53-3.45 (m, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 2.90 (br, 2H), 2.34-2.27 (m, 1H), 2.04-1.98 (m, 1H), 1.90-1.80 (m, 2H), 1.65 (br, 1H), 1.23 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 7.3 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 176.63 (0), 99.10 (-), 81.79, 81.26, 79.83, 76.05, 74.35, 63.20 (-), 57.67, 55.88, 41.09, 38.41, 36.61, 36.34, 14.07, 10.74, 10.69, 10.50.

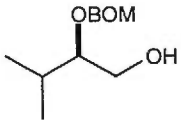
IR ($CHCl_3$): 3500 (br), 2950, 1780, 1740, 1600, 1465 cm^{-1}.

HRMS: $C_{18}H_{34}O_8$, calc.: 401.2151, found: 401.2155.



(2*R*)-2-Hydroxy-3-methyl-butyric acid methyl ester (85)

A three-neck flask, equipped with a thermometer, magnetic stirring bar, and dropping funnel, was charged with D-valine (12 g, 102 mmol) and 1N sulfuric acid (154 ml). A solution of sodium nitrite (10.5 g, 153 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 the pH to 7 with solid $NaHCO_3$, then reduced water under vacuum to 50-60 ml. The concentrated solution was adjusted the pH to 2 with concentrate H_3PO_4, then extracted with THF (3x200 ml). The combined organic layers were washed with brine, then dried over Na_2SO_4. The crude product was recrystallized from ether-hexane in refrigerator to afford α-hydroxy acid (6.5 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 **85**.



(2*R*)-2-Benzyloxymethoxy-3-methyl-butan-1-ol (86)

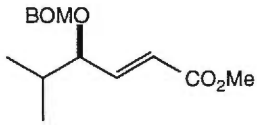
To a solution of the crude α-hydroxy methyl ester **85** (55 mmol) in CH_2Cl_2 (22 ml) were added diisopropylethylamine (95.6 ml, 550 mmol) and BOMCl (65%, 76 ml, 550 mmol) at 0°C. The resulting solution was stirred at room temperature for 52 h. The reaction mixture was diluted with EtOAc, washed with water, sat. NH_4Cl, and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford the BOM-methyl ester.
TLC: E/H = 1:5, R_f = 0.48.
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.37-7.26 (m, 5H), 4.81 (s, 2H), 4.64 (s, 2H), 3.98 (d, J = 5.6 Hz, 1H), 3.70 (s, 3H), 2.20-2.10 (m, 1H), 1.01 (d, J = 5.6 Hz, 1H), 0.99 (d, J = 4.3 Hz, 3H).
^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 172.70 (0), 137.50 (0), 128.31, 127.72, 127.62, 94.50 (-), 80.96, 69.89 (-), 51.58, 31.35, 18.68, 17.60.

To a solution of the BOM-methyl ester (55 mmol) in THF (150 ml) at -78°C was added DIBAL-H (1.0 M in THF, 165 ml, 165 mmol). The resulting solution was stirred at 0°C for 3 h, 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 to afford alcohol **86** (6.5 g, 53% for three steps from α-hydroxy acid).

TLC: E/H = 1:4, R_f = 0.40.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.36-7.26 (m, 5H), 4.94 (d, J = 6.9 Hz, 1H), 4.76 (d, J = 6.9 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.63 (d, J = 11.7 Hz, 1H), 3.67-3.57 (m, 2H), 3.38-3.34 (m, 1H), 3.05-3.02 (m, 1H), 1.89-1.84 (m, 1H), 0.96 (d, J = 5.1 Hz, 3H), 0.94 (d, J = 5.1 Hz, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 137.11 (0), 128.45, 127.85, 95.64 (-), 87.62, 70.02 (-), 63.56 (-), 30.09, 18.72, 18.15.



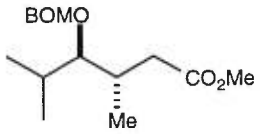
(4*R*)-4-Benzyloxymethoxy-5-methyl-hex-2-enoic acid methyl ester (87)

To a solution of oxalyl chloride (3.8 ml, 43.8 mmol) in CH_2Cl_2 (200 ml) at -70°C was added DMSO (6.2 ml, 87.6 mmol), and the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to -55°C, then a solution of **86** (6.5 g, 29 mmol) in CH_2Cl_2 (40 ml) was added. The reaction mixture was warmed to -40°C during 20 min and diisopropylethylamine (20.3 ml, 117 mmol) was added, then temperature was allowed to rise further to -30°C over 30 min. The reaction was quenched with sat. NH_4Cl. The reaction mixture was diluted with CH_2Cl_2, then washed with 2.5% HCl, sat. $NaHCO_3$ and brine, then dried over Na_2SO_4 for 2 h. The crude aldehyde after removing solvent was dried by an oil pump for 2 h.

To a solution of the above crude aldehyde in CH_2Cl_2 (1 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 directly purified by chromatography to afford **87** as an oil, (7.0 g, 86% overall).

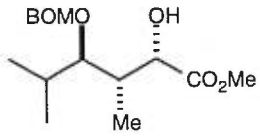
TLC: E/H = 1:4, R_f = 0.60.

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.40-7.30 (m, 5H), 6.85 (dd, J = 6.7, 15.8 Hz, 1H), 6.00 (dd, J = 1.2, 15.8 Hz, 1H), 4.80-4.65 (m, 3H), 4.55 (d, J = 11.7 Hz, 1H), 4.05 (t, J = 6.0 Hz, 1H), 3.75 (s, 3H), 1.95-1.80 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H).



(3*S*,4*R*)-4-Benzyloxymethoxy-3,5-dimethyl-hexanoic acid methyl ester (88)

To a suspension of CuI (9.6 g, 50.3 mmol) in THF (250 ml) was added MeLi·LiBr (1.5 M in ether, 67 ml, 101 mmol) at -15°C and the mixture was allowed to warm up to 0°C over 30 min, then cooled to -78°C. To the resulting mixture were added Me_3SiCl (25.4 ml, 201 mmol), and then a solution of **87** (7.0 g, 25 mmol) in THF (50 ml). The reaction was continued for 3.5 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and conc. NH_4OH, then separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with sat. NH_4Cl-NH_4OH (1:1), sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **88** as an oil (7.0 g, >90%).
TLC: E/H = 1:5, R_f = 0.57.
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.37-7.26 (m, 5H), 4.79 (dd, J = 6.8, 12.3 Hz, 2H), 4.66 (dd, J = 11.8, 17.1 Hz, 2H), 3.66 (s, 3H), 3.11 (t, J = 5.4 Hz, 1H), 2.63 (dd, J = 3.6, 15.0 Hz, 1H), 2.30-2.20 (m, 1H), 2.16 (dd, J = 9.6, 15.0 Hz, 1H), 1.90-1.80 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 3.4 Hz, 3H), 0.96 (d, J = 3.4 Hz, 3H).



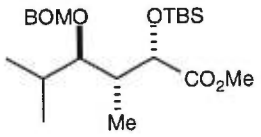
(2*S*,3*S*,4*R*)-4-Benzyloxymethoxy-2-hydroxy-3,5-dimethyl-hexanoic acid methyl ester (89)

To a solution of **88** (7.0 g, 25 mmol) in THF (220 ml) was added KHMDS (0.5 M in toluene, 60 ml, 30 mmol) at -78°C. The resulting mixture was stirred for 30 min and then a solution of Davis oxaziridine (9.8 g, 38 mmol) in THF (30 ml) was added. The reaction was continued for 3 h at -78°C, and quenched with sat. NH_4Cl. The reaction mixture was

extracted with EtOAc and the combined organic extracts were washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **89** as an oil (6.5 g, >80%).

TLC: E/H = 1:4, R_f = 0.37.

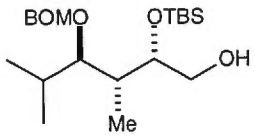
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.37-7.26 (m, 5H), 4.88 (d, J = 6.5 Hz, 1H), 4.80 (d, J = 6.5 Hz, 1H), 4.67 (s, 2H), 4.66 (d, J = 2.1 Hz, 1H), 3.79 (s, 3H), 3.38 (dd, J = 3.0, 9.1 Hz, 1H), 2.20-2.10 (m, 1H), 1.90-1.80 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H).



(2*S*,3*R*,4*R*)-4-Benzyloxymethoxy-2-(tert-butyl-dimethyl-silanyloxy)-3,5-dimethyl-hexanoic acid methyl ester (90)

To a solution of hydroxy ester **89** (9.2 g, 30 mmol) in CH_2Cl_2 (200 ml) at 0°C were added 2,6-lutidine (10.3 ml, 89 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.2 ml, 44.5 mmol). The resulting solution was stirred for 1 h at 0°C. The reaction mixture was diluted with CH_2Cl_2, washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give **90** as an oil (12.4 g).

TLC: E/H = 1:5, R_f = 0.80.



(2*S*,3*R*,4*R*)-4-Benzyloxymethoxy-2-(tert-butyl-dimethyl-silanyloxy)-3,5-dimethyl-hexan-1-ol (91)

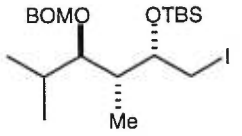
To a solution of the ester **90** (12.4 g, 29 mmol) in THF (150 ml) at -78°C was added DIBAL-H (1.5 M in toluene, 43 ml, 64.5 mmol) dropwise over 30 min and the reaction mixture was stirred at 0°C for 1 h. The mixture was cooled to -78°C and quenched with sat. NH_4Cl, then diluted with EtOAc and 2% HCl to dissolve aluminum gel. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with sat. Na_HCO3, sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford an **91** as an oil (9.0 g, 76% for two steps from **89**).

TLC: E/H = 1:3, R_f = 0.30.

$[\alpha]_D$ -16.3° (*c* 2.5, $CHCl_3$).

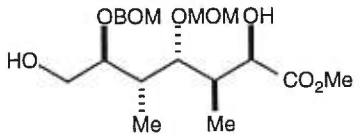
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.37-7.26 (m, 5H), 4.84 (d, J = 6.7 Hz, 1H), 4.79 (d, J = 6.7 Hz, 1H), 4.66 (s, 2H), 3.98 (dd, J = 4.9, 8.7 Hz, 1H), 3.63-3.54 (m, 2H), 2.28 (dd, J = 4.0, 7.1 Hz, 1H), 1.94-1.82 (m, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.95-0.90 (m, 15H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C-NMR (400MHz, $CDCl_3$): δ (ppm) = 137.86 (0), 128.26, 127.69, 127.49, 95.59 (-), 87.16, 73.11, 69.94 (-), 65.82 (-), 38.70, 29.93, 25.84, 20.74, 18.15(0), 16.52, 12.09, -4.18, -4.54.



[(1*S*,2*R*,3*R*)-3-Benzyloxymethoxy-1-iodomethyl-2,4-dimethyl-pentyloxy)-tert-butyl-dimethyl-silane (92)

To a solution of alcohol **91** (649 mg, 1.63 mmol), dry imidazole (178 mg, 2.61 mmol) and triphenylphosphine (685 mg, 2.61 mmol) in toluene (16 ml) at 0°C was added iodine (663 mg, 2.61 mmol). The resulting mixture was stirred for 1.5 h at this temperature. The reaction mixture was directly purified by chromatography to afford iodide **92** as an oil (762 mg, 80-90%) (a mixture with another unidentified compound)



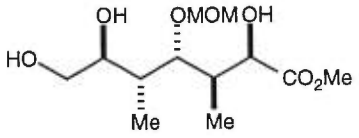
(2R,3R,4R,5S,6S)-6-Benzyloxymethoxy-2,7-dihydroxy-4-methoxymethoxy-3,5-dimethyl-heptanoic acid methyl ester (93)

To a solution of the common chiron **69** (3.4 g, 5.4 mmol) in THF (27 ml) was added a solution of TBAF-HOAc (8.5 ml, 0.95 M in THF, 8.0 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 sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to afford **93** as an oil (2.0 g, 95%).

TLC: E/H = 1:1, R_f = 0.45.

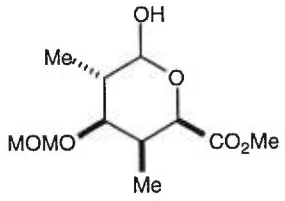
$[\alpha]_D$ +1.7° (*c* 0.9, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.35-7.27 (m, 5H), 4.95 (d, J = 7.1 Hz, 1H), 4.86 (d, J = 7.1 Hz, 1H), 4.76 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 6.5 Hz, 1H), 4.67 (d, J = 6.5 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 2.1 Hz, 1H), 3.90-3.78 (m, 2H), 3.77 (s, 3H), 3.58-3.52 (m, 2H), 3.35 (s, 3H), 3.17 (br, 2H), 2.15-2.09 (m, 1H), 1.84-1.79 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H).



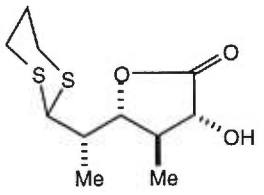
(2R,3R,4R,5R,6S)-2,6,7-Trihydroxy-4-methoxymethoxy-3,5-dimethyl-heptanoic acid methyl ester (94)

A mixture of diol **93** (2.0 g, 5.2 mmol) and $Pd(OH)_2/C$ (20% Pd, Degussa type, 200 mg) 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 **94** was directly used for next step without purification.
TLC: E/H = 1:0, R_f = 0.25.



6-Hydroxy-4-methoxymethoxy-3,5-dimethyl-tetrahydro-pyran-2-carboxylic acid methyl ester (95)

To a solution of the crude triol **94** (5.2 mmol) in MeOH (34 ml)-H_2O (17 ml) was added sodium periodate (1.6 g, 7.8 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 sat. NH_4Cl and brine, and dried over Na_2SO_4. The crude lactol **95** after drying by oil pump was used for next step directly without purification.
TLC: E/H = 1:0, R_f = 0.80.



(3R,4R,5R)-5-[(1S)-1-[1,3]Dithian-2-yl-ethyl)-3-hydroxy-4-methyl-dihydro-furan-2-one (96)

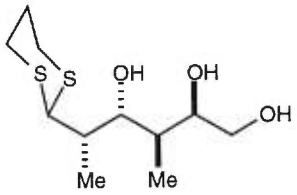
To a solution of the crude lactol **95** (5.2 mmol) in CH_2Cl_2 (40 ml) at 0°C were added 1,3-propanedithiol (1.56 ml, 15.6 mmol) and boron trifluoride diethyl etherate (1.28 ml, 10.4 mmol) subsequently. The resulting mixture was stirred for 3.5 h at 0°C, diluted with CH_2Cl_2, washed with sat. Na_HCO3, sat. NH_4Cl and brine, and then dried over Na_2SO_4. The crude product was purified by chromatography to afford hydroxy-lactone **96** as an oil (883 mg, 65% for three steps).

TLC: E/H = 1:1, R_f = 0.40.

$[\alpha]_D$ -27.5° (*c* 0.4, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.40 (dd, J = 1.4, 10.0 Hz, 1H), 4.13-4.07 (m, 2H), 3.50 (br, 1H), 2.87-2.83 (m, 4H), 2.27-2.11 (m, 1H), 2.09-2.02 (m, 2H), 1.90-1.80 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 176.23, 81.74, 51.39, 41.61, 39.32, 30.35, 30.29, 25.73, 14.21, 10.89.



(2R,3S,4R,5S)-5-[1,3]Dithian-2-yl-3-methyl-hexane-1,2,4-triol (97)

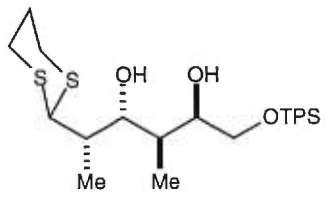
To a solution of dithiane-lactone **96** (235 mg, 0.9 mmol) in THF (8 ml)-H_2O (2 ml) was added sodium borohydride (174 mg, 4.5 mmol, as solid) at room temperature. The resulting mixture was stirred for 2 h, then quenched with 2% aqueous HCl carefully. The reaction mixture was diluted with EtOAc, washed with sat. Na_HCO3, sat. NH_4Cl and brine. The aqueous phase was re-extracted with EtOAc 4 times. The combined organic phase was dried over Na_2SO_4. The crude product **97** was directly used for next step without purification.

TLC: E/H = 1:0, R_f = 0.40.

$[\alpha]_D$ -17.2° (*c* 2.5, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 4.14 (d, J = 7.1 Hz, 1H), 3.98 (d, J = 9.6 Hz, 2H), 3.73 (s, 3H), 3.67 (d, J = 8.4 Hz, 1H), 3.60 (dd, J = 3.4, 11.2 Hz, 1H), 2.93-2.81 (m, 4H), 2.14-1.77 (m, 4H), 1.08 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 73.62, 73.51, 64.85 (-), 52.89, 39.87, 37.68, 30.75 (-), 30.50 (-), 226.02 (-), 11.52, 10.08.



(2R,3S,4R,5S)-1-(tert-Butyl-diphenyl-silanyloxy)-5-[1,3]dithian-2-yl-3-methyl-hexane-2,4-diol (98)

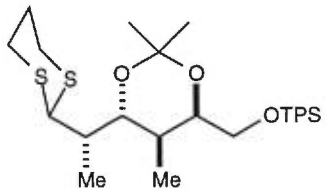
To a solution of the crude dithiane-triol **97** (0.89 mmol) and imidazole (243 mg, 3.59 mmol) in THF (7 ml) was added TPSCl (245 µl, 0.94 mmol) at room temperature. The resulting mixture was stirred for 2 h and then diluted with EtOAc, washed with sat. NH_4Cl and brine. The aqueous phase was re-extracted with EtOAc. The combined organic phase was dried over Na_2SO_4. The crude product was purified by chromatography to afford dithiane-diol **98** as an oil (343 mg, 76% for two steps).

TLC: E/H = 1:3, R_f = 0.30.

$[\alpha]_D$ -4.0° (*c* 4.8, $CHCl_3$).

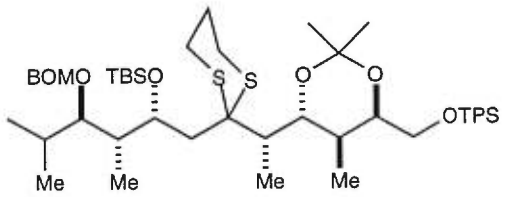
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.71-7.67 (m, 4H), 7.47-7.27 (m, 6H), 4.18 (d, J = 6.6 Hz, 1H), 4.14-4.07 (m, 1H), 3.98 (dd, J = 3.6, 8.0 Hz, 1H), 3.74 (dd, J = 7.5, 10.2 Hz, 1H), 3.67 (dd, J = 5.0, 10.1 Hz, 1H), 2.92-2.83 (br, 6H), 2.12-1.79 (m, 4H), 1.14 (d, J = 6.9 Hz, 3H), 1.09 (s, 9H), 0.81 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (300MHz, $CDCl_3$): δ (ppm) = 135.46, 135.43, 133.03 (0), 132.99 (0), 129.74, 129.71, 127.69, 74.54, 72.79, 65.45 (-), 52.92, 40.43, 36.55, 30.87 (-), 30.50 (-), 26.79, 26.02 (-), 19.11 (0), 11.27, 10.55.



tert-Butyl-[6-(1-[1,3]dithian-2-yl-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethoxy]-diphenyl-silane (99)

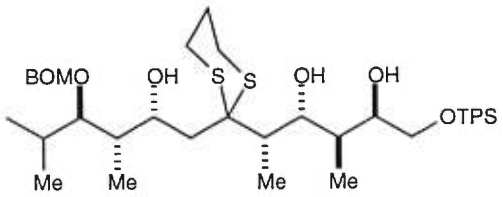
To a solution of dithane-diol **98** (343 mg, 0.68 mmol) in dichloromethane (10 ml) were added 2,2-dimethoxypropane (1.0 ml, 8.2 mmol) and PPTS (33 mg, 0.14 mmol, as solid) subsequently at room temperature. The resulting mixture was stirred for 2 h and then directly purified by chromatography to afford acetonide **99** as an oil (354 mg, 96%).
TLC: E/H = 1:5, R_f = 0.75.
^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.72-7.68 (m, 4H), 7.45-7.26 (m, 6H), 4.08 (d, J = 8.0 Hz, 1H), 3.89 (dd, J = 6.5,11.5 Hz, 1H), 3.72-3.63 (m, 3H), 2.87-2.79 (m, 4H), 2.18-2.05 (m, 1H), 1.92-1.82 (m, 3H), 1.36 (s,3H), 1.29 (s, 3H), 1.45 (d, J = 6.9 Hz, 3H), 1.07 (s, 9H), 0.83 (d, J = 6.8 Hz, 3H).



4-(1-{2-[4-Benzyloxymethoxy-2-(tert-butyl-dimethyl-silanyloxy)-3,5-dimethyl-hexyl]-[1,3]dithian-2-yl}-ethyl)-6-(tert-butyl-diphenyl-silanyloxymethyl)-2,2,5-trimethyl-[1,3]dioxane (100)

To a solution of dithiane **99** (318 mg, 0.58 mmol) in THF (4.5 ml) and HMPA (406 µl, 2.34 mmol) at -78°C was added tert-butyl lithium (1.7 M in pentane, 412 µl, 0.7 mmol) until yellow color remained. The resulting mixture was stirred for one hour at -78°C. To the above reaction mixture was added a solution of iodide comp (440 mg, 0.68 mmol, 75% purity) in THF (1.5 ml) at -78°C. The reaction was continued for 2.5 h at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc, the organic phase was washed with brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give the coupling product **100** as an oil (407 mg, 75%).
TLC: E/H = 1:15, R_f = 0.30.

^{1}H-NMR (300MHz, $CDCl_3$): δ (ppm) = 7.76-7.71 (m, 4H), 7.48-7.27 (m, 11H), 4.92 (s, 2H), 4.88 (d, J = 12.2 Hz, 1H), 4.81 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 6.0 Hz, 1H), 4.06 (d, J = 7.8 Hz, 1H), 3.89 (dd, J = 6.5, 11.3 Hz, 1H), 3.76-3.64 (m, 2H), 3.43 (dd, J = 1.3, 8.9 Hz, 1H), 2.94-2.81 (m, 2H), 2.61-2.55 (m, 2H), 2.31-2.10 (m, 4H), 1.98-1.74 (m, 6H), 1.39 (s, 3H), 1.29 (s, 3H), 1.18 (d, J = 6.9 Hz, 3H),1.10 (s, 9H), 1.07 (d, J = 6.9 Hz, 3H), 3.76 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 9.9 Hz, 3H), 0.90 (s, 9H), 0.86 (d, J = 6.9 Hz, 3H), 0.19 (s, 6H).



5-[2-(4-Benzyloxymethoxy-2-hydroxy-3,5-dimethyl-hexyl)-[1,3]dithian-2-yl]-1-(tert-butyl-diphenyl-silanyloxy)-3-methyl-hexane-2,4-diol (108)

To a solution of the coupling product **100** (196 mg, 0.21 mmol) in CH_2Cl_2 (3.3 ml)-MeOH (6.6 ml) was added PTSA (20 mg, 0.10 mmol). The resulting mixture was stirred for 2.5 h. The reaction was stopped by adding solid $NaHCO_3$. The reaction mixture was directly purified by chromatography to afford triol **108** as an oil (81 mg, 50%).

TLC: E/H = 1:2, R_f = 0.42.

$[\alpha]_D$ -28.4° (*c* 0.4, CCl_4).

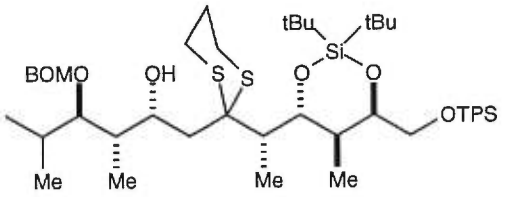
^{1}H-NMR (300MHz, C_6D_6): δ (ppm) = 7.89-7.85 (m, 4H), 7.38-7.10 (m, 11H), 4.86-4.78 (m, 4H), 4.67 (d, J = 6.6 Hz, 1H), 4.62 (d, J = 12.5 Hz, 1H), 4.44-4.42 (m, 1H), 3.97 (dd, J = 7.1, 10.1 Hz, 1H), 3.87 (dd, J = 5.3, 10.1 Hz, 1H), 3.71-3.60 (br, 2H), 3.77 (dd, J = 3.6, 8.1 Hz, 1H), 3.0-2.92 (br, 1H), 2.75 (dd, J = 7.9, 15.5 Hz, 1H), 2.65-2.51 (m, 1H), 2.50-2.30 (m, 4H), 2.15 (dd, J = 1.1, 15.5 Hz, 1H), 2.00-1.81 (m, 2H), 1.75-1.65 (m, 1H), 1.55-1.45 (m, 3H), 1.40 (d, J = 7.0 Hz, 3H), 1.22 (s, 9H), 1.02 (d, J = 6.9 Hz, 3H), 0.97-0.93 (m, 9H).

^{13}C-NMR (300MHz, C_6D_6): δ (ppm) = 138.19 (0), 135.72, 135.68, 133.68 (0), 133.60 (0), 129.65, 128.25, 127.81, 127.78, 127.76, 127.74, 127.55, 127.53, 127.50, 127.40, 97.25 (-), 87.43, 72.95, 72.41, 70.39 (-), 66.88, 66.40 (-), 58.58 (-), 42.21, 42.06, 41.87 (-), 39.46, 29.84, 26.80, 26.19 (-), 25.72 (-), 24.83 (-), 20.40, 19.14 (0), 15.80, 11.53, 10.07, 8.42.

IR (CCl_4): 3500, 2970, 2940, 1745, 1470, 1430 cm^{-1}.

MS: 791.4 (m+23), 769.4 (m+1).

HRMS: $C_{43}H_{65}O_6S_2Si$ (m+1), calc.: 769.3991, found: 769.3970.



4-Benzyloxymethoxy-1-(2-{1-[2,2-di-tert-butyl-6-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-[1,3,2]dioxasilinan-4-yl]-ethyl}-[1,3]dithian-2-yl)-3,5-dimethyl-hexan-2-ol (109)

To a solution of triol **108** (80 mg, 0.1 mmol) in CH_2Cl_2 (2 ml) at 0°C were added 2,6-lutidine (146 µl, 1.25 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (151 µl, 0.41 mmol). The resulting solution was stirred for 2 h at 0°C. The reaction mixture was directly purified by chromatography to afford the silylene **109** as an oil (70 mg, 74%).

TLC: E/H = 1:5, R_f = 0.62.

$[\alpha]_D$ -33.1° (*c* 1.9, CCl_4).

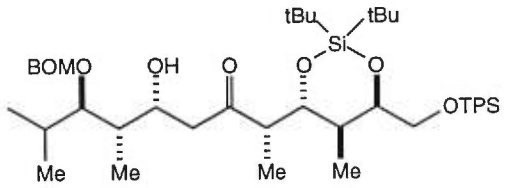
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.92-7.89 (m, 4H), 7.40-7.13 (m, 11H), 5.08 (d, J = 8.3 Hz, 1H), 5.01 (d, J = 12.6 Hz, 1H), 5.0-4.95 (br, 1H), 4.84 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 12.6 Hz, 1H), 4.48-4.40 (m, 1H), 4.16 (dd, J = 6.7, 10.6 Hz, 1H), 4.07 (dd, J = 5.4, 10.6 Hz, 1H), 3.43 (dd, J = 3.0, 8.5 Hz, 1H), 3.36 (d, J = 3.4 Hz, 1H), 2.88 (dd, J = 8.5, 15.7 Hz, 1H), 2.50-2.12 (m, 6H), 2.07 (d, J = 15.4 Hz, 1H), 1.95-1.85 (m, 1H), 1.80-1.70 (m, 1H), 1.55-1.45 (m, 2H), 1.42 (d, J = 6.9 Hz, 3H), 1.36 (s, 9H), 1.27 (s, 9H), 1.25 (s., 9H), 1.08 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 7.1 Hz, 6H), 0.81 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 138.46 (0), 135.75, 135.70, 133.95 (0), 133.54 (0), 129.63, 129.61, 128.17, 127.73, 127.68, 127.51, 127.49, 127.48, 127.27, 97.34 (-), 87.35, 76.21, 74.39, 70.43 (-), 66.53, 65.58 (-), 59.43 (-), 42.31, 41.,96, 41.88 (-), 39.41, 29.73, 27.69, 27.57, 26.74, 26.01 (-), 25.60 (-), 24.71 (-), 21.68 (0), 21.18 (0), 20.51, 19.11 (0), 15.59, 13.00, 9.90, 8.25.

IR (CCl_4): 3520, 2980, 1990, 1960, 1900, 1830, 1480, 1430 cm-1.

MS: 931.5 (m+23), 909.5 (m+10, 851.3, 801.4.

HRMS: $C_{51}H_{81}O_6S_2Si_2$ (m+1), calc.: 909.5013, 909.4969.



7-Benzyloxymethoxy-2-[2,2-di-tert-butyl-6-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-[1,3,2]dioxasilinan-4-yl]-5-hydroxy-6,8-dimethyl-nonan-3-one (110)

To a solution of dithiane **109** (67 mg, 0.07 mmol) in CH_3CN (3 ml) were added $CaCO_3$ (110 mg, 1.1 mmol) and H_2O (0.6 ml). The resulting suspension was vigorously stirred for 20 min, then $HgCl_2$ (140 mg, 0.52 mmol) was added. The mixture was vigorously stirred for 2 h. The reaction mixture was directly purified by chromatography to afford the ketone **110** as an oil (54.8 mg, 91%).

TLC: E/H = 1:5, R_f = 0.47.

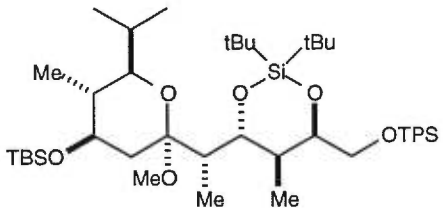
$[\alpha]_D$ -28.3° (*c* 1.4, CCl_4).

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.90-7.86 (m, 4H), 7.38-7.13 (m,11H), 4.97 (d, J = 7.5 Hz, 1H), 4.79 (d, J = 12.2 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.60 (dd, J = 3.6, 8.4 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.23 (dd, J = 5.5, 11.0 Hz, 1H), 4.02-3.90 (m, 2H), 3.58 (d, J = 2.7 Hz, 1H), 3.37 (dd, J = 3.5, 8.2 Hz, 1H), 3.00 (dd, J = 9.2, 16.7 Hz, 1H),, 2.50-2.40 (m, 2H), 2.15-2.05 (m, 1H), 1.95-1.85 (m, 1H), 1.80-1.75 (m, 1H), 1.26 (s, 9H), 1.19 (s, 9H), 1.17 (s, 9H), 1.17 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.6 Hz, 6H), 0.64 (d, J = 7.2 Hz, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 210.97 (0), 138.05 (0), 135.77, 135.71, 135.62, 133.64 (0), 133.39 (0), 129.73, 129.70, 128.22, 128.21, 128.00, 127.76, 127.72, 127.71, 127.70, 127.53, 97.29 (-), 87.45, 75.75, 75.47, 70.38 (-), 65.93, 65.56 (-), 51.26, 45.67 (-), 39.92, 37.67, 29.88, 27.41, 27.26, 26.79, 21.48 (0), 20.99 (0), 20.33, 19.07 (0), 15.81, 12.58, 10.20, 8.33.

IR (CCl_4): 3520, 2980, 1960, 1900, 1830, 1720, 1590, 1480, 1430 cm^{-1}.

HRMS: $C_{48}H_{75}O_7Si_2$ (m+1), calc.: 819.5051, fond: 819.5011.



2,2-Di-tert-butyl-4-{1-[4-(tert-butyl-dimethyl-silanyloxy)-6-isopropyl-2-methoxy-5-methyl-tetrahydro-pyran-2-yl]-ethyl}-6-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-[1,3,2]dioxasilinane (112)

Procedure A

A mixture of ketone **110** (18 mg, 0.02 mmol) and 20% $Pd(OH)_2/C$ (18 mg) in methanol (1.5 ml) under 1 atm of hydrogen was stirred at room temperature for 2 h. To the reaction mixture was added a few drops of triethylamine, then filtered through a pad of Celite to remove catalyst and washed with EtOAc. The crude product **111** after removal of solvent and drying under oil pump was subjected to next step directly.

TLC: E/H = 1:6, product **111**, R_f = 0.45; Starting material **110**, R_f = 0.37.

To a solution of the crude product **111** in CH_2Cl_2 (1.3 ml) at 0°C were added 2,6-lutidine (10.2 µl, 0.08 mmol), then TBSOTf (15.1 µl, 0.06 mmol). The resulting solution was stirred for 1 h at this temperature. To the reaction mixture was added a few drops of triethylamine, then directly purified by chromatography to afford **112** as an oil (9.2 mg, 50% for two steps from **110**).

TLC: E/H = 1:10, R_f = 0.80.

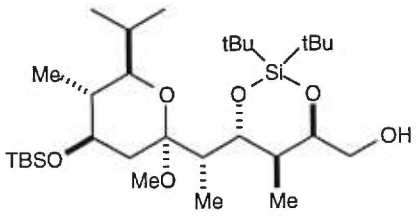
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.91-7.84 (m, 4H), 7.32-7.26 (m, 6H), 4.39 (dd, J = 5.6, 11.3 Hz, 1H), 4.32 (d, J = 7.7 Hz, 1H), 4.10 (dd, J = 6.5, 10.5 Hz, 1H), 4.00 (dd, J = 5.5, 10.5 Hz, 1H), 3.91 (ddd, J = 4.7, 4.3, 4.7 Hz, 1H), 3.19 (dd, J = 2.0, 10.4 Hz, 1H), 3.02 (s, 3H), 2.41 (dd, J = 4.8, 13.5 Hz, 1H), 2.12-2.00 (m, 2H), 1.91-1.87 (m, 1H), 1.82 (dd, J = 10.6, 13.5 Hz, 1H), 1.64-1.58 (m, 1H), 1.28 (s, 9H), 1.25 (s, 9H), 1.23 (s, 9H), 1.17 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.7 Hz, 3H), 1.09 (s, 9H), 1.01 (d, 3H), 0.99 (d, 3H), 0.76 (d, J = 7.3 Hz, 3H), 0.25 (s, 3H), 0.19 (s, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 135.75, 135.69, 133.82, 133.42, 129.68, 129.66,127.74, 127.69, 127.53, 102.91, 77.10, 75.82, 73.36, 71.61, 65.53, 45.97, 41.07, 40.64, 39.62, 38.43, 28.51, 27.72, 27.47, 27.34, 26.72, 25.75, 21.69, 21.14, 20.56, 19.07, 17.83, 14.00, 13.34, 12.69, 7.64, -4.03, -4.59.

Procedure B

A mixture of ketone **126** (60 mg, 0.058 mmol) and Pd black (90 mg) in methanol (2 ml) under 1 atm of hydrogen was stirred at room temperature for 5 h, then more Pd black (90

mg) was added and was stirred for further 20 h. To the reaction mixture was added a few drops of triethylamine, then filtered through a pad of Celite to remove catalyst and washed with EtOAc. The crude product was purified by chromatography to afford **112** as the major compound of a mixture (2:1, 33 mg, 62%) with an unidentified compound (one methoxy missing).
TLC: E/H = 1:15, R_f = 0.65.

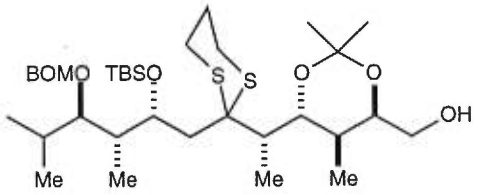


(2,2-Di-tert-butyl-6-{1-[4-(tert-butyl-dimethyl-silanyloxy)-6-isopropyl-2-methoxy-5-methyl-tetrahydro-pyran-2-yl]-ethyl}-5-methyl-[1,3,2]dioxasilinan-4-yl)-methanol (113)

Procedure A
To a solution of **112** (8.4 mg, 0.01 mmol) in DMF (1 ml) was added NaH (60% in mineral oil, 8 mg, 0.2 mmol). The resulting mixture was stirred for 1 h and quenched with sat. NH_4Cl. The reaction mixture was diluted with EtOAc and washed with brine, then dried over Na_2SO_4 with adding a few drops of triethylamine. The crude product was purified by chromatography to afford **113** (2 mg, 33%).
TLC: E/H = 1:10, R_f = 0.25.
^{1}H-NMR (300MHz, C_6D_6): δ (ppm) = 4.32 (d, J = 10.0 Hz, 1H), 4.10-4.00 (m, 1H), 3.91 (ddd, J = 4.6, 4.2, 4.8 Hz, 1H), 3.79 (t, J = 10.0 Hz, 1H), 3.67-3.63 (m, 1H), 3.19 (dd, J = 2.0, 10.4 Hz, 1H), 3.03 (s, 3H), 2.38 (dd, J = 4.8, 13.4 Hz, 1H), 2.30-2.20 (m, 1H), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 1H), 2.00-1.90 (m, 1H), 1.78 (dd, J = 10.6, 13.4 Hz, 1H), 1.64-1.50 (m, 1H), 1.22 (s, 9H), 1.16 (s, 9H), 1.12 (d, J = 7.2 Hz, 3H), 1.10 (s, 9H), 1.08 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 2.7 Hz, 3H), 0.98 (d, J = 2.5 Hz, 3H), 0.47 (d, J = 7.8 Hz, 3H), 0.25 (s, 3H), 0.20 (s, 3H).

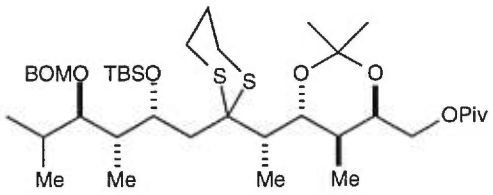
Procedure B
To a solution of the ester **119** (a mixture, 2:1, 5.0 mg, 0.007 mmol) in THF (1 ml) at 0°C was added DIBAL-H (1.0 M in toluene, 37 µl, 0.037 mmol). The resulting mixture was stirred for 1 h at this temperature. The reaction was quenched with methanol, water,

ethyl acetate and Na_2SO_4. The reaction mixture was purified by chromatography to afford **113** as a mixture (2:1, 3.0 mg, 68%).
TLC: E/H = 1:4, R_f = 0.50.



[6-(1-{2-[4-Benzyloxymethoxy-2-(tert-butyl-dimethyl-silanyloxy)-3,5-dimethyl-hexyl]-[1,3]dithian-2-yl}-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-yl]-methanol (113a)

To a solution of the coupling product **100** (179 mg, 0.19 mmol) in THF (2 ml) at room temperature was added TBAF-HOAc (0.95 M in THF, 245 µl, 0.23 mmol). The resulting mixture was stirred for 10 h. The reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl and brine, then dried over Na_2SO_4. The crude product was purified by chromatography to give alcohol **113a** as an oil (123 mg, 93%).
TLC: E/H = 1:4, R_f = 0.10.
$[\alpha]_D$ -6.9° (*c* 1.6, $CHCl_3$).
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.49 (d, J = 7.0 Hz, 2H), 7.26-7.13 (m, 3H), 5.09 (dd, J = 6.4, 11.1 Hz, 2H), 4.99-4.90 (m, 3H), 4.24 (d, J = 8.0 Hz, 1H), 3.96-3.90 (m, 1H), 3.68-3.61 (m, 2H), 3.49-3.45 (dd, J = 4.0, 11.1 Hz, 1H), 2.57-2.41 (m, 5H), 2.38-2.10 (m, 5H), 2.09-2.00 (m, 1H), 1.66-1.50 (m+s, 5H), 1.47, (s, 3H), 1.32 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.10 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H), 0.47 (s, 3H), 0.43 (s, 3H).
^{13}C-NMR (400MHz, C_6D_6): δ(ppm) = 138.92 (0), 128.11, 127.59, 127.58, 127.13, 100.39 (0), 96.67 (-), 86.50, 73.55, 70.36, 69.91 (-), 69.69, 62.18 (-), 57.62 (0), 43.13, 41.98 (-), 41.19, 37.17, 29.75, 26.10, 25.66 (-), 25.54 (-), 24.99, 24.26 (-), 24.17, 21.24, 18.43 (0), 15.24, 11.96, 10.20, 9.48, -2.69, -3.91.
IR ($CHCl_3$): 3600, 2950, 1730, 1470 cm^{-1}.
MS: 707 (m+23), 683 (m-1).
HRMS: $C_{35}H_{63}O_7Si_2S$ (m-1), calc.: 683.3833, found: 683.3805.



2,2-Dimethyl-propionic acid 6-(1-{2-[4-benzyloxymethoxy-2-(tert-butyl-dimethyl-silanyloxy)-3,5-dimethyl-hexyl]-[1,3]dithian-2-yl}-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (114)

To a solution of alcohol **113a** (94 mg, 0.14 mmol) and DMAP (100 mg, 0.83 mmol) in CH_2Cl_2 (1.5 ml) at 0°C was added pivaloyl chloride (67 µl, 0.55 mmol). The resulting solution was stirred for 2 h at 0°C. The reaction mixture was directly purified by chromatography to give the pivaloyl ester **114** as an oil (98 mg, 93%).

TLC: E/H = 1:4, R_f = 0.70.

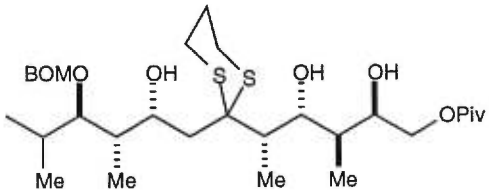
$[\alpha]_D$ -9.9° (*c* 2.0, $CHCl_3$).

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.47 (d, J = 7.2 Hz, 2H), 7.26-7.13 (m, 3H), 5.09-5.10 (m, 2H), 4.98-4.88 (m, 3H), 4.27-4.09 (m, 4H), 3.64 (d, J = 8.5 Hz, 1H), 2.55-2.40 (m, 4H), 2.20-2.08 (m, 4H), 2.06-1.95 (m, 1H), 1.70-1.65 (m, 1H), 1.60 (s, 3H), 1.59-1.50 (m, 1H), 1.43 (s, 3H), 1.40-135 (m, 1H), 1.31 (d, J = 6.7 Hz, 3H), 1.26 (s, 9H), 1.16-1.11 (m, 6H), 1.08 (s, 9H), 1.08-1.05 (m, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.44 (s, 3H), 0.41 (s, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 177.24 (0), 138.89 (0), 128.09, 127.57, 127.12, 100.49 (0), 96.67 (-), 86.50, 73.62, 69.89 (-), 69.66, 67.59, 63.71 (-), 57.52 (0), 43.05, 41.94 (-), 41.24, 38.45 (0), 37.54, 29.73, 26.96, 26.09, 25.66 (-), 25.54 (-), 24.82, 24.25 (-), 24.03, 21.22, 18.41 (0), 15.22, 11.53, 10.18, 9.50, -2.72, -3.94.

IR ($CHCl_3$): 2960, 1720, 1465 cm^{-1}.

MS: 769 (m+1).



2,2-Dimethyl-propionic acid 5-[2-(4-benzyloxymethoxy-2-hydroxy-3,5-dimethyl-hexyl)-[1,3]dithian-2-yl]-2,4-dihydroxy-3-methyl-hexyl ester (115)

To a solution of the pivaloyl ester **114** (186 mg, 0.24 mmol) in MeOH (8 ml)-CH_2Cl_2 (4 ml) was added PTSA (23 mg, 0.12 mmol). The resulting mixture was stirred for 9 h. The reaction was stopped by adding solid $NaHCO_3$. The reaction mixture was directly purified by chromatography to afford triol **115** as an oil (60 mg, 40%).

TLC: E/H = 1:2, R_f = 0.20.

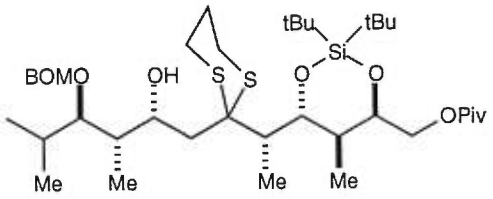
$[\alpha]_D$ -31.7° (*c* 0.7, $CHCl_3$).

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.37 (d, J = 8.3 Hz, 2H), 7.26-7.13 (m, 3H), 4.85 (d, J = 12.5 Hz, 1H), 4.80-4.75 (m, 3H), 4.63 (d, J = 6.6 Hz, 1H), 4.58 (d, J = 12.5 Hz, 1H), 4.48-4.40 (m, 2H), 4.31 (dd, J = 3.1, 9.7 Hz, 1H), 4.00-3.90 (br, 2H), 3.60-3.50 (br, 1H), 3.32 (dd, J = 3.5, 8.1 Hz, 1H), 2.72 (dd, J= 8.0, 15.6 Hz, 1H), 2.62-2.55 (m, 1H), 2.47-2.30 (m, 4H), 2.08 (d, J = 15.6 Hz, 1H), 1.92-1.82 (m, 2H), 1.67-1.64 (m, 1H), 1.52-1.45 (m, 2H), 1.36 (d, J = 7.0 Hz, 3H), 1.26 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H), 0.94-0.91 (d+d+d, 9H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 177.74 (0), 137.99 (0), 128.27, 127.51, 127.48, 97.23 (-), 87.46, 72.78, 71.14, 70.38 (-), 66.97, 66.74(-), 58.34 (0), 42.07, 42.00, 41.53 (-), 39.83, 38.48 (0), 29.84, 27.01, 26.18 (-), 25.65 (-), 24.75 (-), 20.29, 15.78, 11.90, 10.20, 8.08

IR ($CHCl_3$):3500 (br), 2980, 1740, 1470, 1400 cm^{-1}.

HRMS: $C_{32}H_{55}O_7S_2$ (m+1), calc.: 615.3389, found: 615.3376.

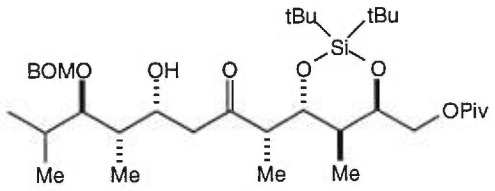


2,2-Dimethyl-propionic acid 6-{1-[2-(4-benzyloxymethoxy-2-hydroxy-3,5-dimethyl-hexyl)-[1,3]dithian-2-yl]-ethyl}-2,2-di-tert-butyl-5-methyl-[1,3,2]dioxasilinan-4-ylmethyl ester (116)

To a solution of the triol **115** (59 mg, 0.09 mmol) in CH_2Cl_2 (1 ml) at 0°C were added 2,6-lutidine (134 µl, 1.15 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (140 µl, 0.38 mmol). The resulting solution was stirred for 2 h at 0°C. The reaction mixture was directly purified by chromatography to afford the silylene **116** as an oil (48 mg, 66%).

TLC: E/H = 1:4, R_f = 0.47.

^{1}H-NMR (300MHz, C_6D_6): δ (ppm) = 7.45-7.42 (m, 2H), 7.27-7.13 (m, 3H), 5.15 (d, J = 9.2 Hz, 1H), 5.02 (d, J = 12.6 Hz, 1H), 4.99-4.95 (br, 1H), 4.81 (d, J = 6.8 Hz, 1H), 4.69 (s, 1H), 4.66 (d, J = 5.8 Hz, 1H), 4.55-4.40 (m, 3H), 4.44 (d, J = 3.3 Hz, 1H), 3.38 (dd, J = 3.6, 8.1 Hz, 1H), 2.93 (dd, J = 8.5, 15.6 Hz, 1H), 2.50-2.40 (m, 2H), 2.40-2.10 (m, 5H), 2.00-1.90 (m, 1H), 1.85-1.75 (m, 1H), 1.55-1.48 (m, 2H), 1.44 (d, J = 6.9 Hz, 3H), 1.39 (s, 9H), 1.29 (s, 9H), 1.26 (s, 9H), 1.12 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 7.2 Hz, 3H).



2,2-Dimethyl-propionic acid 6-(6-benzyloxymethoxy-4-hydroxy-1,5,7-trimethyl-2-oxo-octyl)-2,2-di-tert-butyl-5-methyl-[1,3,2]dioxasilinan-4-ylmethyl ester (117)

To a solution of the silylene-dithiane **116** (48 mg, 0.06 mmol) in CH_3CN (3 ml) were added $CaCO_3$ (126 mg, 1.26 mmol) and H_2O (0.6 ml). The resulting suspension was vigorously stirred for 20 min, then $HgCl_2$ (172 mg, 0.63 mmol) was added. The mixture was vigorously stirred for 14 h. The reaction mixture was directly purified by chromatography to afford the ketone **117** as an oil (33 mg, 78%).

TLC: E/H = 1:4, R_f = 0.30.

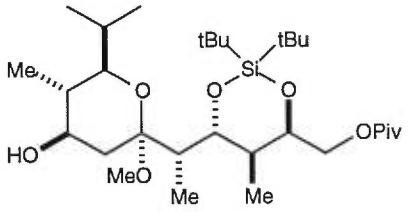
$[\alpha]_D$ -48.0° (*c* 0.3, CCl_4).

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.39-7.36 (m, 2H), 7.25-7.12 (m, 3H), 4.97 (d, J = 8.9 Hz, 1H), 4.79 (d, J = 12.2 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.58 (dd, J = 2.9, 9.6 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 4.29-4.24 (m, 2H), 3.65-3.55 (br, 1H), 3.36 (dd, J = 3.6, 8.1 Hz, 1H), 3.03 (dd, J = 9.3, 16.5 Hz, 1H), 2.47 (dd, J = 3.2, 16.5 Hz, 1H), 2.40-2.37 (m, 1H), 2.12-2.02 (m, 1H), 1.90-1.82 (m, 1H), 1.81-1.71 (m, 1H), 1.45-1.35 (m, 1H), 1.29 (s, 9H), 1.18 (s, 9H), 1.12 (s, 9H), 1.11 (d, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.45 (d, J = 7,3 Hz, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 210.56 (0), 177.40 (0), 138.10 (0), 128.22, 128.20, 127.78, 127.70, 127.69, 127.68, 97.32 (-), 87.53, 74.22, 73.58, 70.41 (-). 66.12, 65.32 (-), 50.59, 45.42 (-), 39.95, 38.46 (0), 37.47, 29.92, 27.28, 27.03, 21.33 (0), 20.66 (0), 20.28, 15.84, 12.02, 10.19, 7.62.

IR (CCl_4): 3510, 2995, 2960, 2880, 1740, 1480 cm^{-1}.

HRMS: $C_{37}H_{65}O_8Si$ (m+1), calc.: 665.4448, found: 665.4476.

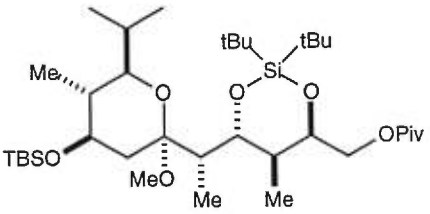


2,2-Dimethyl-propionic acid 2,2-di-tert-butyl-6-[1-(4-hydroxy-6-isopropyl-2-methoxy-5-methyl-tetrahydro-pyran-2-yl)-ethyl]-5-methyl-[1,3,2]dioxasilinan-4-ylmethyl ester (118)

A mixture of ketone **117** (10 mg, 0.015 mmol) and Pd black (22 mg) in methanol (1 ml) under 1 atm of hydrogen was stirred at room temperature for 1 h, then more Pd black (36 mg) was added and was stirred for further 2.5 h. The reaction was stopped by adding solid $NaHCO_3$. The reaction mixture was directly separated by chromatography to afford the desired product **118**, acyclic compound **120** and the by-product **121**. The acyclic compound **120** was transformed into **118** by PPTS in methanol in good yield. The desired product **118** (5.3 mg, 63%) was totally obtained.

TLC: E/H = 1:4, **121**, R_f = 0.80; **118**, R_f = 0.55; **120**, R_f = 0.25.

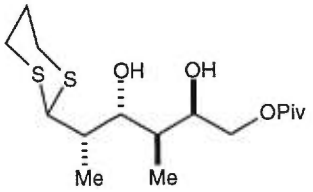
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 4.45-4.33 (m, 3H), 3.70-3.60 (br, 1H), 3.09 (dd, J = 2.0, 10.4 Hz, 1H), 2.99 (s, 3H), 2.53 (dd, J = 4.7, 13.3 Hz, 1H), 2.20-2.10 (m, 1H), 2.02 (dd, J = 6.9, 7.0 Hz, 1H), 1.90-1.80 (m, 1H), 1.57 (dd, J = 11.0, 13.4 Hz, 2H), 1.29 (s, 9H), 1.24 (s, 9H), 1.18 (s, 9H), 1.11 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.57 (d, J = 7.5 Hz, 3H).



2,2-Dimethyl-propionic acid 2,2-di-tert-butyl-6-{1-[4-(tert-butyl-dimethyl-silanyloxy)-6-isopropyl-2-methoxy-5-methyl-tetrahydro-pyran-2-yl]-ethyl}-5-methyl-[1,3,2]dioxasilinan-4-ylmethyl ester (119)

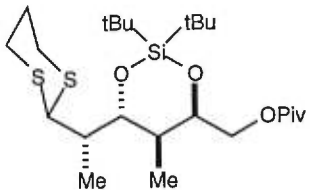
To a solution of hydroxy **118** (5.1 mg, 0.01 mmol) in CH_2Cl_2 (1 ml) at 0°C were added 2,6-lutidine (42.5 µl, 0.36 mmol), then TBSOTf (41.9 µl, 0.18 mmol). The resulting solution was stirred for 1 h at this temperature. The reaction mixture was directly

purified by chromatography to afford **119** as the major compound of a inseparable mixture (2:1, 5 mg, 80%) with an unidentified compound (one methoxy missing).
TLC: E/H = 1:10, R_f = 0.60.
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 4.50-4.30 (m, 3H), 3.91 (ddd, J = 4.8, 4.4, 4.6 Hz, 1H), 3.18 (dd, J = 1.9, 10.3 Hz, 1H), 3.02 (s, 3H), 2.84 (dd, J = 7.3, 14.5 Hz, 1H), 2.43-2.37 (m, 1H), 2.02 (dd, J = 6.7, 13.7 Hz, 1H), 2.00-1.90 (m, 1H), 1.88 (dd, J = 5.3, 7.1 Hz, 1H), 1.60-1.50 (m, 1H), 1.40 -1.00 (m, 56H), 0.59 (d, J = 7.1 Hz, 3H), 0.25 (s, 3H), 0.20 (s, 3H).



2,2-Dimethyl-propionic acid 5-[1,3]dithian-2-yl-2,4-dihydroxy-3-methyl-hexyl ester (122)

To a solution of the dithiane-triol **97** (98 mg, 0.37 mmol) and DMAP (224 mg, 1.84 mmol) in CH_2Cl_2 (3 ml) at 0°C was added pivaloyl chloride (150 µl, 1.22 mmol). The resulting solution was stirred for 2 h at 0°C. The reaction mixture was directly purified by chromatography to give the pivaloyl ester **122** as an oil (82 mg, 63%).
TLC: E/H = 1:4, R_f = 0.12.
^{1}H-NMR (300MHz, C_6D_6): δ (ppm) = 4.34-4.29 (m, 2H), 4.19-4.14 (m, 2H), 3.50-3.20 (br, 2H), 2.60-2.35 (m, 4H), 2.12-2.06 (m, 1H), 1.89-1.84 (m, 1H), 1.70-1.45 (m, 2H), 1.29 (d, J = 6.7 Hz, 3H), 1.24 (s, 9H), 0.78 (d, J = 7.0 Hz, 3H).



2,2-Di-tert-butyl-4-(tert-butyl-diphenyl-silanyloxymethyl)-6-(1-[1,3]dithian-2-yl-ethyl)-5-methyl-[1,3,2]dioxasilinane (123)

To a solution of **122** (81 mg, 0.23 mmol) in CH_2Cl_2 (3 ml) at 0°C were added 2,6-lutidine (267 µl, 2.3 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (252 µl, 0.69 mmol) subsequently. The resulting solution was stirred for 20 min at 0°C. The reaction

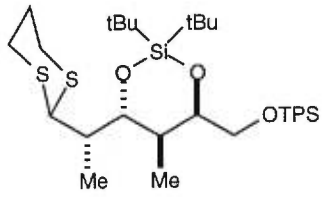
mixture was directly purified by chromatography to afford the silylene **123** as an oil (77 mg, 68%).

TLC: E/H = 1:4, R_f = 0.75.

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 4.63 (dd, J =1.6, 9.8 Hz, 1H), 4.35-4.20 (m, 4H), 2.52-2.42 (m, 4H), 2.20-2.10 (m, 1H), 2.00-1.90 (m, 1H), 1.70-1.60 (m, 1H), 1.60-1.50 (m, 1H), 1.28 (s, 9H), 1.27 (s, 9H), 1.20 (d, J = 6.7 Hz, 3H), 1.14 (s, 9H), 0.46 (d, J = 7.2 Hz, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 177.32 (0), 73.95, 72.25, 65.10 (-), 51.56, 40.23, 38.45 (0), 37.63, 29.88 (-), 29.82 (-), 27.43, 27.25, 27.04, 26.03 (-), 21.43 (0), 20.74 (0), 11.77, 9.98.

HRMS: $C_{24}H_{47}O_4S_2Si$ (m+1), calc.: 491.2684, found: 491.2667.



2,2-Di-tert-butyl-4-(tert-butyl-diphenyl-silanyloxymethyl)-6-(1-[1,3]dithian-2-yl-ethyl)-5-methyl-[1,3,2]dioxasilinane (124)

To a solution of the dithiane-diol **98** (238 mg, 0.47 mmol) in CH_2Cl_2 (10 ml) at 0°C were added 2,6-lutidine (219 µl, 1.89 mmol) and di-*tert*-butylsilyl bis(trifluoromethane-sulfonate) (258 µl, 0.71 mmol) subsequently. The resulting mixture was stirred at room temperature for 3 h, then diluted with CH_2Cl_2, washed with sat NH_4Cl and brine, and dried over Na_2SO_4. The crude product was purified by chromatography to afford the silylene **124** as an oil (235 mg, 77%).

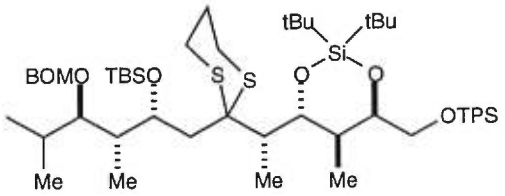
TLC: E/H = 1:5, R_f = 0.70.

$[\alpha]_D$ -22.4° (*c* 0.7, CCl_4).

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.90-7.84 (m, 4H), 7.33-7.21 (m, 6H), 4.64 (dd, J = 2.0, 8.8 Hz, 1H), 4.30 (d, J = 9.1 Hz, 1H), 4.26 (dd, J = 5.3, 11.8 Hz, 1H), 4.04 (dd, J = 6.6, 10.7 Hz, 1H), 3.96 (dd, J = 5.1, 10.7 Hz, 1H), 2.50-2.42 (m, 4H), 2.20-2.10 (m, 1H), 2.02-1.92 (m, 1H), 1.70-1.58 (m, 1H), 1.55-1.45 (m, 1H), 1.29 (s, 9H), 1.27 (d, J = 6.8 Hz, 3H), 1.25 (s, 9H), 1.19 (s, 9H), 0.61 (d, J = 7.3 Hz, 3H).

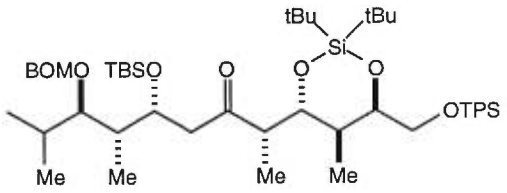
^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 135.73, 133.81 (0), 133.52 (0), 129.62, 127.73, 127.69, 76.21, 73.33, 65.33 (-), 51.77, 41.00, 37.80, 30.00 (-), 29.88 (-), 27.58, 27.47, 26.78, 26.08 (-), 21.58 (0), 21.05 (0), 19.12 (0), 12.33, 10.35.

IR (CCl_4): 3080, 2940, 2870, 2290, 1960, 1900, 1820, 1740, 1480, 1430 cm^{-1}.
MS: 645.4, 587.1, 567.0, 537.1, 509.1.
HRMS: $C_{35}H_{57}O_3S_2Si_2$ (m+1), calc.: 645.3288; found: 645.3273.



4-(1-{2-[4-Benzyloxymethoxy-2-(tert-butyl-dimethyl-silanyloxy)-3,5-dimethyl-hexyl]-[1,3]dithian-2-yl}-ethyl)-2,2-di-tert-butyl-6-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-[1,3,2]dioxasilinane (125)

To a solution of dithiane-silylene **124** (92 mg, 0.15 mmol) in THF (1.5 ml) and HMPA (103 µl, 0.6 mmol) at -78°C was added tert-butyl lithium (1.7 M in pentane, 130 µl, 0.22 mmol) until yellow color remained. The resulting mixture was stirred for 1 h at -78°C. To the above reaction mixture was added a solution of iodide **92** (129 mg, 0.18 mmol, 75% purity) in THF (1 ml) at -78°C. The reaction was continued for 2.5 at -78°C, then quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc, the organic phase was washed with brine and dried over sodium sulfate. The crude product was purified by chromatography to give the dithiane-silylene **125** as an oil (81 mg, 56%).
TLC: E/H = 1:10, R_f = 0.43.
^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 7.92-7.91 (m, 4H), 7.49 (d, J = 5.6 Hz, 2H), 7.31-7.15 (m, 9H), 5.11 (s, 2H), 5.05-4.86 (m, 4H), 4.49-4.46 (m, 1H), 4.14 (dd, J = 7.0, 10.4 Hz, 1H), 4.02 (dd, J = 5.4, 10.4 Hz, 1H), 3.70 (d, J = 8.8 Hz, 1H), 2.69-2.00 (m, 12H), 1.36 (d, J = 6.8 Hz, 3H), 1.33 (s, 9H), 1.27 (s, 9H), 1.26 (s, 9H), 1.18 (d, J = 6.9 Hz, 3H), 1.14 (s, 9H), 1.13-1.10 (m, 6H), 0.87 (d, J = 7.1 Hz, 3H), 0.55 (s, 3H), 0.49 (s, 3H).
^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 138.93 (0), 135,75, 135,67, 133.90 (0), 133.47 (0), 129.68, 129.65, 128.20, 128.12, 127.75, 127.72, 127.53, 127.14, 96.44 (-), 86.22, 75.56, 74.98, 69.84 (-), 65.51 (-), 58.70 (0), 44.98, 43.44 (-), 41.93, 39.82, 29.73, 27.76, 27.73, 26.72, 26.24, 25.86, 25.80 (-), 25.36 (-), 24.28 (-), 21.72, 21.39 (0), 21.31 (0), 19.09 (0), 18.55 (0), 15.44, 13.51, 9.97, 8.97, -2.20, -3.95.



7-Benzyloxymethoxy-5-(tert-butyl-dimethyl-silanyloxy)-2-[2,2-di-tert-butyl-6-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-[1,3,2]dioxasilinan-4-yl]-6,8-dimethyl-nonan-3-one (126)

To a solution of the dithiane-silylene **125** (73 mg, 0.07 mmol) in CH_3CN (4 ml) were added $CaCO_3$ (286 mg, 2.86 mmol) and H_2O (1 ml). The resulting suspension was vigorously stirred for 20 min, then $HgCl_2$ (387 mg, 1.43 mmol) was added. The mixture was vigorously stirred for 14 h. The reaction mixture was directly purified by chromatography to afford the silylene-ketone **126** as an oil (60 mg, 90%).

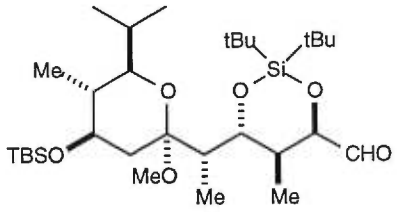
TLC: E/H = 1:10, R_f = 0.45.

$[\alpha]_D$ -18.5° (*c* 0.5, CCl_4).

^{1}H-NMR (300MHz, C_6D_6): δ (ppm) = 7.91-7.85 (m, 4H), 7.48-7.45 (m, 2H), 7.37-7.11 (m, 9H), 5.05 (dt, J = 1.8, 6.0 Hz, 1H), 4.94-4.87 (m, 3H), 4.76 (d, J = 12.4 Hz, 1H), 4.61 (dd, J = 3.4, 8.4 Hz, 1H), 4.26 (dd, J = 5.1, 10.5 Hz, 1H), 4.01-3.91 (m, 2H),. 3.52 (dd, J = 2.4, 8.5 Hz, 1H), 2.97-2.82 (m, 2H), 2.50-2.40 (m, 1H), 2.20-2.10 (m, 1H), 2.00-1.85 (m, 2H), 1.26 (s, 9H), 1.21 (d, 3H), 1.18 (s, 9H), 1.17 (s, 9H), 1.08 (d, 3H), 1.06 (s, 9H), 1.04 (d, J = 6.8 Hz, 6H), 0.65 (d, J = 7.3 Hz, 3H), 0.33 (s, 3H), 0.18 (s, 3H).

^{13}C-NMR (400MHz, C_6D_6): δ (ppm) = 208.18 (0), 138.65 (0), 135.76, 135.70, 133.66 (0), 133.39 (0), 129.73, 129.70, 128.12, 127.76, 127.74, 127.73, 127.53, 127.20, 96.78 (-), 86.73, 75.81, 75.14, 69.73 (-), 67.85, 65.53 (-), 50.97, 47.76 (-), 42.23, 37.46, 29.91, 27.40, 27.32, 26.78, 25.95, 21.46 (0), 20.99 (0), 20.78, 19.06 (0), 18.22 (0), 15.43, 12.74, 10.47, 8.52, -4.05, -4.58.

IR (CCl_4): 2940, 2880, 1750, 1480, 14709, 1430 cm^{-1}.



2,2-Di-tert-butyl-6-{1-[4-(tert-butyl-dimethyl-silanyloxy)-6-isopropyl-2-methoxy-5-methyl-tetrahydro-pyran-2-yl]-ethyl}-5-methyl-[1,3,2]dioxasilinane-4-carbaldehyde (127)

To compound **113** were a few drops of diisopropylethylamine, dichloromethane, 4Å molecular sieve and TPAP at room temperature. The resulting mixture was stirred for 1 h, then passed through a short silica gel pad to afford aldehyde 127. TLC and NMR showed a clean and high yield reaction

TLC: E/H = 1:0, R_f = 0.45.

^{1}H-NMR (400MHz, C_6D_6): δ (ppm) = 9.85 (s, 1H), 4.38 (d, 1H), 4.05 (dd, 1H), 3.95-3.85 (m, 1H), 3.65 (dd, 1H), 3.00 (s, 3H), 2.35 (dd, 1H), 2.15-2.05 (m, 1H), 1.95-1.85 (m, 1H), 1.80 (dd, 2H), 1.70-160 (m, 1H), 1.400.90 (m, 39H), 0.70 (d, 3H), 0.20 (s, 3H), 0.15 (s, 3H).

References and Notes

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[1] (a) Prelog, V. "Chirality in Chemistry (Nobel Lecture)", *Science*, **1976**, *193*, 17-24. (b) Mislow, K.; Siegel, J. "Stereoisomerism and Local Chirality", *J. Am. Chem. Soc.* **1984**, *106*, 3319-3328.

[2] For introductionary explaination see Hegstrum, R. A.; Kondepudi, D. K. "The Handness of the Universe", *Scientific American*, **1990**, *262*, 98-105.

[3] Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994.**

[4] Seebach, D. "Organic Synthesis-Where Now?", *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320-1367.

[5] For the historical account of the contribution of E. Fischer see (a) Lemieux, R.U.; Spohr, U. "How Emil Fischer Was Led to the Lock and Key Concept for Enzyme Specificity", *Advances in Carbohydrate Chemistry and Biochemistry* **1994**, *50*, 1-21. (b) Lichtenthaler, F.W. "Emil Fischer's Proof of the Configuration of Sugars: A Centennial Tribute", *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1541-1556. (c) Forster, M.O. "Emil Fischer Memorial Lecture", *J. Chem. Soc.* **1920**, 1157-1201.

[6] For the recent reviews on the lock-and-key principle see(a) Eschenmoser, A. "One Hundred Years Lock-and Key Principle", *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2363. (b) Lichtenthaler, F.W. "100 Years "Schlüssel–Schloss–Prinzip": What Made Emil Fischer Use this Analogy?", *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2364-2374. (c) Koshland, Jr., D.E. "The Key–Lock Theory and the Induced Fit Theory", *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2375-2378.

[7] For historic account see, Weyer J. "A Hundred Years of Stereochemistrythe Principal Development Phases in Retrospect" *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 591-598.

[8] These were extracted from (a) Ihde, A. J. "*The Development of Modern Chemistry* " **1984**, Dover Publications, Inc., NY. (b) Eliel, E. L. "*The Stereochemitry of Carbon Compounds*" **1962**, McGraw-Hill Book Company, Inc, NY.

[9] For historic account see, Hafner, K. "August Kekulé–the Architect of Chemistry Commemorating the 150th Anniversary of His Birth", *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 641-704.

[10] Prelog, V.; Helmchen, G. "Basic Principles of the CIP-System and Proposals for a Revision", *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567-583 and references cited therein.

[11] (a) "Conformational Analysis–The Fundamental Contributions of D.H.R. Barton and O. Hassel", *Topics in Stereochemistry*, **1971**, vol. *5*, 1-17. (b) Hanack, M. "*Conformation Theory*" **1965**, Academic Press, NY.

[12] General information was extracted from (a) Morrison, J. D., Mosher, H. S. *"Asymmetric Organic Reactions"*, Prentice-Hall. Inc., New Jersey, **1971**. (b) Morrison, J. D., Ed. *"Asymmetric Synthesis"*, Academic Press, New York; Vol. 1- Analytical Methods (**1983**), Vol. 2-Stereodifferentiating Addition Reactions, Part A (**1983**), Vol. 3-Stereodifferentiating Addition Reactions, Part B (**1984**), Vol. 4 -The Chiral Carbon Pool and Chiral Sulfur, Nitrogen, Phosphorus, and Silicon Centers (**1984**), Vol. 5-Chiral Catalysis (**1985**).

[13] Secor, R.M. "Seeding of a supersaturated solution ", *Chem. Rev.* **1963**, *63*, 297-309.

[14] (a) Okamoto, Y.; Yashima, E. "Polysaccharide Derivatives for Chromatographic Separation of Enantiomers", *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1020-1043. (b) "Chromatographic Chiral Separations", Vol. 40, **1988**, Zief, M.; Crane, L.J. Ed., Marcel Dekker, New York, NY. (c) Allenmark, S.G. "Chromatographic Enantioseparation: Methods and Applications", 2nd. ed., JohnWiley & Sons, New York, NY, **1992**.

[15] (a) Kagan, H.B.; Fiaud, J.C. "Kinetic Resolution", *Topics in Stereochemistry* **1988**, *18*, 249-330. (b) Tokunaga, M.; Larrow, J.F.; Kakiuchi, F.; Jacobsen, E.N. "Asymmetric

Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis", *Science*, **1997**, *277*, 936-938. (c) Vedjes, E.; Chen, X. "Parallel Kinetic Resolution", *J. Am. Chem. Soc.* **1997**, *119*, 2584-2585.

[16](a) Ward, R.S. "Dynamic Kinetic Resolution", *Tetrahedron: Asymmetry*, **1995**, *6*, 1475-1490. (b) Stürmer, R. "Enzymes and Transition Metal Complexes in Tandem-A New Concept for Dynamic Kinetic Resolution", *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1173-1174.

[17] The application of enzymes in chirality resolution see, (a) Faber, K. "Biotransformations of Non–Natural Compounds: State of the Art and Future Development", *Pure & Appl. Chem.* **1997**, *69*, 1613-1632. (b) Whitesides, G.M.; Wong, C.-H. "Enzymes as Catalysts in Synthetic Organic Chemistry", *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-718.

[18] (a) Poss, C.S.; Poss, C.S.; Schreiber, S. L. "Two-Directional Chain Synthesis and Terinus Differentiation", *Acc. Chem. Res.* **1994**, *27*, 9-17. (b) Magnuson, S. R. "Two-Directional Synthesis and its Use in Natural Product Synthesis", *Tetrahedron* **1995**, *51*, 2167-2213. (c) Harada, T., Oku, A. "Enantiodifferentiating Transformation of Prochiral Polyols By Using Menthone as Chiral Template" *SYNLETT* **1994**, (2), 95-154. (d) Nugent, W.A. "Desymmetrization of Meso Epoxides with Halides: A New Catalytic Reaction Based on Mechanistic Insight", *J. Am. Chem. Soc.* **1998**, *120*, 7139-7140.

[19] (a) Hanessian, S. "*The Total Synthesis of Natural Products: The Chiron Approach*", Pergamon Press, Oxford, **1984**. (b) Coppola, G.M.; Schuster, H.F. "Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids" John Wiley & Sons, NY, **1987**. (c) Sardina, F.J.; Rapoport, H. "Enantiosepecific Synthesis of Heterocycles from α-Amino Acids", *Chem. Rev.* **1996**, *96*, 1825-1872.

[20] (a) Thall, E. "When Drug Molecules Look in the Mirror" *J. Chem. Educ.* **1996**, *73*(6), 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.), 24-33. (d) Coppola, G.M.; Schuster, H.F. "Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids" John Wiley & Sons, NY, **1987**.

[21] For the highlight of the impact of chiral drugs and chiral technology see Stinson, S. C. *Chemical & Engneering News*, **1992**, (Sept. 28), 46-78; **1993**, (Sept. 27), 38-62; **1994**, (Sept. 19), 38-72; **1995**, (Oct. 9), 44-74; **1997**, (April, 28), 26; **1997,** (June 2), 28; **1997**, (July 14), 37; **1997**, (October 27), 15.

[22] Athough many non-chemical asymmetic reagents have been conceived and many experiments have been designed, no significant results have been obtained to date. See (a) Bonner, W.A. "Origins of Chiral Homogeneity in Nature", *Topics in Stereochemistry*, **1988**, *18*, 1-96. (b) *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 454 and 1207.

[23] (a) Hanessian, S. "*The Total Synthesis of Natural Products: The Chiron Approach*", Pergamon Press, Oxford, **1984**. (b) Hanessian, S. "Design and Implementation of Tactically Novel Strategies for Stereochemical Control Using the Chiron Approach", *Aldrichimica Acta* **1989,** *22,* 3-15. (c) Hanessian, S. "Reflections on the Total Synthesis of Natural Products: Art, Craft, Logic and the Chiron Approach", *Pure & Appl. Chem.* **1993**, *65*, 1189-1204. (d) Hanessian, S.; Franco, J.; Larouche, B. "The Psychobiological basis of Heuristic Synthesis Planning–Man, Machine and the Chiron Approach", *Pure & Appl. Chem.* **1990**, *62*, 1887-1910. (e) Hanessian, S.; Franco, J.; Gagnon, G.; Laramée, D.; Larouche, B. "Computer-Assisted Analysis and Perception of Stereochemical Features in Organic Molecules Using the CHIRON Program", *J. Chem. Inf. Comput. Sci.* **1990**, *30*, 413-425.

[24] There are many recent publications on this subject, see (a) Sardina, F.J.; Rapoport, H. "Enantiosepecific Synthesis of Heterocycles from α-Amino Acids", *Chem. Rev.* **1996**,

96, 1825-1872. (b) Ho, T.-L. "Enantioselective Synthesis: Natural Products from Chiral Terpenes", John Wiley & Sons, New York, **1992**.

[25] (a) Enders, D.; Klatt, M. "Asymmetric Synthesis with (*S*)-2-Methoxymethylpyrrolidine (SMP)–a Pioneer Auxiliary", *Synthesis*, **1996**, 1403-1418. (b) Enders, D. "Alkylation of Chiral Hydrazones", in "*Asymmetric Synthesis*" (Morrison, JD), **1984**, Vol. 3, 275-339. (c) Evans, D.A.; Takacs, J.M.; McGee, L.R.; Ennis, M.D.; Mathre, D.J.; Bartroli, J. "Chiral Enolate Design", *Pure & Appl. Chem.* **1981**, *53*, 1109-1127. (d) Bennani, Y.L.; Hanessian, S. "trans-1,2-Diaminocyclohexane Derivatives as Chiral Reagents, Scaffolds, and Ligands for Catalysis: Applications in Asymmetric Synthesis and Molecular Recognition", *Chem. Rev.* **1997**, *97*, 3161-3195. (e) Lutomski, K.A.; Meyers, A.I. "Asymmetric Synthesis via Chiral Oxazolines", in Asymmetric Synthesis (Morrison, JD), 1984, Vol 3, 213-274. (f) Romo, D.; Meyers, A.I. "Chiral Non-Racemic Bicyclic Lactams. Vehicles for the Construction of Natural and Unnatural Products Containing Quaternary Carbon Centers" *Tetrahedron* **1991**, *47*, 9503-9569. (g) Whitesell, J.M "Cyclohexyl-Based Chiral Auxilaries", *Chem. Rev.* **1992**, *92*, 953. (h) Oppolzer, W. "Camphor Derivatives as Chiral Auxilaries in Asymmetric Synthesis" *Tetrahedron* **1987**, *43*, 1969-2004. (I) Seebach, D.; Sting, A.R.; Hoffmann, M. "Self-Regeneration of Stereocenters (SRS)–Applications, Limitations and Abandonment of a Synthetic Principle" *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708-2748.

[26] Nógrádi, M. "*Stereoselective Synthesis–A Practical Approach*", VCH, Weinheim, **1995,** Chapter 3 and references cited therein.

[27] (a) Brown, H.C.; Jadhav, P.K.; Mandal, A.K. "Asymmetric Synthesis via Chiral Organoborane Reagents", *Tetrahedron*, **1981**, *37*, 3547-3587. (b) Brown, H.C.; Ramachandran, P.V. "The Boron Approach to Asymmetric Synthesis", *Pure & Appl. Chem.* **1991**, *63*, 307-316.

[28] Breslow, R. "Biomimetic Chemistry", *Chemical Society Reviews* **1972**, *1*, 553-580.

[29] Such as Sharpless asymmetric epoxidation, Sharpless asymmetric dihydoxylation, Jacobsen epoxidation, just name a few. See recent leading reviews: (a) Corey, E.J.; Guzman-Perez, A. "The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters", *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 388-401. (b) Trost, B.M. "Designing a Receptor for Molecular Recognition in a Catalytic Synthetic Reaction: Allylic Alkylation", *Acc. Chem. Res.* **1996**, *29*, 355-364. (c) Noyori, R. "Asymmetric Catalysis in Organic Synthesis", JohnWiley & Sons, NY, **1994**. (d) Noyori, R. "Organometallic Ways for the Multiplication of Chirality", *Tetrahedron*, **1994,** *50*, 4259-4292.

[30] For leading references see: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, R. "Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis", *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-30. (b) Hoffmann, R. W. "Stereoselective Syntheses of Building Blocks with Three Consecutive Stereogenic Centers: Important Precursors of Polyketide Natural Products", *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 489-503. (c) Roush, W. R. "Concerning the Diastereofacial Selectivity of the Aldol Reactions of α-Methyl Chiral Aldehydes and Lithium and Boron Propionate Enolates", *J. Org. Chem.* **1991**, *56*, 4151-4157.

[31] Houk, K.N.; Paddon-Row, M.N.; Rondan, N.G.; Wu, Y.-D.; Brown, F.K.; Spellmeyer, D.C.; Metz, J.T.; Li, Y.; Loncharich, R.J. "Theory and Modeling of Stereoselective Organic Reactions" *Science*, **1986**, *231*, 1108-1117.

[32] Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308.

[33] Cram, D.J.; Elhafez, F.A.A. *J. Am. Chem. Soc.* **1952**, *74*, 3210.

[34] (a) Crimmins, M.T.; King, B.W.; Tabet, E. A. "Asymmetric Aldol Additions with Titanium Enolates of Acyloxazolidinethiones: Dependence of Selectivity on Amine Base and Lewis Acid Stoichiometry", *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884. (b) Meyers,

A.I.; Seefeld, M.A.; Lefker, B.A.; Blake, J.F. "Origin of Stereochemistry in Simple Pyrrolidinone Enolate Alkylations", *J. Am. Chem. Soc.* **1997**, *119*, 4565-4566.

[35] For chelation-control see: (a) Still, W.C.; McDonald, III, J.H. "Chelation-Controled Nucleophilic Additions. 1. a Highly Effective System for Asymmetric Induction in the Reaction of Organometallics with α-Alkoxyketones", *Tetrahedron Lett.* **1980**, *21*, 1031-1034. (b) Reetz, M.T. "Structural, Mechanistic, and Theoretical Aspects of Chelation–Controlled Carbonyl Addition Reactions", *Acc. Chem. Res.* **1993**, *26*, 462-468. (c) Chen, X.; Hortelano, E.R.; Eliel, E.L.; Frye, S.V. "Chelates as Intermediates in Nucleophilic Additions to Alkoxy Ketones Aacording to Cram's Rule (Cyclic Model)", *J. Am. Chem. Soc.* **1992**, *114*, 1778-1784.

[36] (a) Cherest, M.; Felkin, H.; Prudent, N. "Torsional Strain Involving Partial Bonds. The Stereochemistry of the Lithium Aluminum Hydride Reduction of Some Simple Open-Chain Ketones", *Tetrahedron Lett.* **1968**, 2199-2204. (b) Cherest, M.; Felkin, H. "Torsional Strain Involving Partial Bonds. The Steric Course of the Reaction between Allyl Magnesium Bromide and 4-τ-Butyl Cyclohexanone" *ibid*, **1968**, 2205-2208.

[37] (a) Anh, N.T.; Eisenstein, O. "Theoretical Interpretation of 1,2 - Asymmetric Induction. the Importance of Antiperiplanarity" *Nouv. J. Chim.* **1977**, *1*, 61-69. (b) Anh, N.T. "Regio- and Stereo-selectivities in Some Nucleophilic Reactions" *Topics in Current Chemistry*, **1980**, *88*, 146-162.

[38] (a) Paddon-Row, M.N.; Rondan, N.G.; Houk, K.N. "Staggered Models for Asymmetric Induction: Attack Trajectories and Conformations of Allylic Bonds from ab Innitio Transtion Structures of Addition Reactions", *J. Am. Chem. Soc.* **1982**, *104*, 7162-. (b) Fleischer, J. M.; Gushurst, A. J.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluations of Organic Reactions. 26. Diastereoselective Additions: Cram's Rule" *J. Org. Chem.* **1995**, *60*, 490-498. (c) Lodge, E.P.; Heathcock, C.H. 'Steric Effects, as well

as σ*-Orbital Energies, Are Important in Diastereoface Differentiation in Additions to Chiral Aldehydes", *J. Am. Chem. Soc.* **1987**, *109,* 3353- 3361.

[39] Flemming, I.; Lewis, J.J. "A Paradigm for Diastereoselectivity in Electrophilic Attact on Trigonal Carbon adjacent to a Chiral Center: the Methylation and Protonation of Some Open-Chain Enolates" *Chem. Commun.* **1985**, 149-151 and references cited therein.

[40] Woodward demonstrated the power of stereocontrol in cyclic systems in his syntheses of quinine, reserpine, strychnine and Erythromycin. (a) Woodward, R.B.; Doering, W.E. "The Total Synthesis of Quinine", *J. Am. Chem. Soc.* **1945**, *67,* 860. (b) Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. "The Total Synthesis of Reserpine", *Tetrahedron*, **1958**, *2*, 1-57. (c) Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.;Daeniker, H.U.; Schenker, K. "The Total Synthesis of Strychnine", *Tetrahedron* **1963**, *19,* 247-288. (d) Woodward, R.B.; & coworkers, "Asymmetric Total Synthesis of Erythromycin", *J. Am. Chem. Soc.* **1981**, *103,* 3210-3213, 3213-3215 & 3215-3217.

[41] Bartlett, P.A. "Stereocontrol in the Synthesis of Acyclic Systems: Application to Natural Product Synthesis", *Tetrahedron*, **1980**, *36*, 2-72.

[42] For 1,3–polyol biosythesis see, Rychnovsky, S.D. "Oxo Polyene Macrolide Antibiotics" *Chem. Rev.* **1995**, *95*, 2021-2040 and references cited therein.

[43] For 1,3–induction see (a) Hanessian, S.; Vanasse, B. "Novel Access to (3R)- and (3S)-3-Hydroxy-L-Aspartic Acids, (4S)-4-Hydroxy-L-Glutamic Acid, and Related Amino Acids", *Can. J. Chem.* **1993**, *71*, 1401. (b) Gu, Z.-Q.; Hesson, D.P. "A highly Diastereoselective Synthesis of 4-Alkyl *Threo* Glutamic Acids", *Tetrahedron: Asymmetry* **1995**, *6*, 2101-2104. (c) Hanessian, S.; Schaum, R. "1,3-Asymmetric Induction in Enolate Alkylation Reactions of N-protected γ-Amino Acid Derivatives", *Tetrahedron Lett.* **1997**, *38*, 163-166.

[44] For 1,4–induction see (a) Narasaka, K.; Uktaka, Y.; Watanabe, K. "Selective 1,4-Chiral Induction in the Reaction of Enolates Generated from t-Butyl δ-Hydroxy Carboxylates",

Bull. Chem. Soc. Jpn. **1987**, *60*, 1457-1464. (b) Sato, T.; Kido, M.; Otera, J. "Acyclic 1,4-Diastereoselectivity in γ-Substituted α-Enones: Transmission of Chiral Information through Conjugation", *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2254-2256.

[45] For macrolide antibiotics see (a) "Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products", Lukacs, G., Ed., Springer-Verlag, Vol. 2, **1993**. (b) "Macrolides—chemistry, pharmacology and clinical uses", Bryskier, A. J., Butzler, J. -p., Neu, H. C., Tulkens, P. M., Ed., Arnette blackwell, Paris, **1993**. (c) "Antibiotics and Antiviral Compounds, Chemical Synthesis and Modification" Krohn, K.; Kisrt, H. A.; Maag, H., Ed., VCH, NY, **1993**.

[46] (a) "Polyether Antibiotics, Naturally Occurring Acid Ionophores-Chemistry", Vol. 2, Westley, J. W., Ed., Marcel Dekker, Inc., NY, **1982**. (b) Dutton, C. J.; Banks, B. J.; Cooper, C. B. "Polyether Ionophores", *Nat. Product Reports* **1995**, *12,* 165-181.

[47] For some Protease Inhibitors, (a) Wilson, E.K. "AIDS Conference Highlights Hope of Drug Cocktails, Chemokine Research", *Chemical & Engineering News* **1996**, (July 29), P42. (b) *Perspectives in Drug Discovery and Design*, **1995**, *2*, 427-436.

[48] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. "*Principles and Applications of Organotransition metal Chemistry*", p682, University Science, Mill Valley, CA, **1987**.

[49] For leading accounts see (a) Permuletter , P. "*Conjugate Addition Reactions in Organic Synthesis*", Pergamon, Oxford, **1992**. (b) Rossiter, B. E.; Swingle, N. M. "Asymmetric Conjugate Addition", *Chem. Rev.* **1992**, *92*, 771-806. (c) "*Organocopper Reagents, a Practical Approach*", Taylor, R. J. K., Ed., Oxford University Press, UK, **1994**. (d) Posner, G. H., " An Introduction to Synthesis Using Organocopper Reagents", John-Wiley & Sons, New York, **1980**. (e) Posner, G. H., "Conjugate Addition reactions of Organocopper Reagents", *Organic Reactions* **1972**, *19*, 1-113. (f) Lipshutz, B. H., Sengupta, S. "Organocopper Reagents: Substitution, Conjugate Addition, Carbo/Metallocupration, and Other Reactions", *Organic Reactions* **1992**, *41*, 135-631. (g)

Krause, N. Gerold, A. "Regio- and Stereoselective Syntheses With Organocopper Reagents", *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186-204.

[50] (a) Jurczak, J.; Pikul, S.; Bauer, T. "(R)- and (S)-2,3-O-Isopropylidene Glyceraldehyde in Stereoselective Organic Synthesis", *Tetrahedron* **1986**, *42*, 447-488. (b) Schmid C.R.; Bryant, J.D. "D-(R)-glyceraldehyde acetonide 1,3-dioxolane-4-carboxaldehyde, 2,2-dimethyl, (R)-)" *Organic Synthesis*, **1995**, *72*, 6-13.

[51] (a) Kuszmann, J.; Tomori, E.; Meerwald, I. "The Synthesis of 1,2:5,6-Di-O-Isopropylidene-D-Mannitol: a Comparative Study", *Carbohydrate Research* **1984**, *128*, 87-99. (b) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. "Practical Synthesis of Some Versatile Chiral Building Blocks from D-Mannitol", *Synthesis* **1986**, 403.

[52] Hanessian, S.; Sumi, K. "On the Stereochemical Divergence in the Conjugate Addition of Lithium Dimethylcuprate/ Trimethylsilyl Chloride to γ-Alkoxy and γ-Ureido α,β–Unsaturated Esters", *Synthesis* **1991,** 1083-1089.

[53] For the general information on the protecting groups see (a) Greene, T.W.; Wuts, P.G.M. "*Protective Groups in Organic Synthesis*", Wiley-Interscience, New York, **1991**. (b) Kocienski, P.J. "*Protecting Groups*", Thieme, Stuttgart, Germany, **1994**. (c) Nelson, T.D.; Crouch, R.D. "Selective Deprotection of Silyl Ethers", *Synthesis*, **1996**, 1031-1069.

[54] (a) Garner, P.; Park, J.M. "The synthesis and Configuration stability of differentially protected β-Hydroxy- α-Amino Aldehydes", *J. Org. Chem.* **1987**, *52*, 2361-2364. (b) McKillop, A.; Tayor, R.J.K.; Watson, R.J.; Lewis, N. "An Improved Procedure for the Preparation of the Garner Aldehyde and Its Use for the Synthesis of N-Protected 1-Halo-2-(*R*)-Amino-3-Butenes", *Synthesis*, **1994**, 31-33. (c) Dondoni, A.; Perrone, D. "Synthesis of N-tert-Butoxycarbonyl-N-Isopropylidene Serinal Methyl Ester by a Reduction-Oxidation Sequence", *Synthesis*, **1997**, 527-529.

[55] For recent studies on the structure of organocuprates see (a) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. "Structural Characterization of Organocopper Reagents by

EXAFS Spectroscopy", *J. Am. Chem. Soc.* **1993**, *115*, 348-350. (b) Snyder, J. P.; Spangler, D. P.; Behling, J. R.; Rossiter, B. E. "The Structure of "$R_2Cu(CN)Li_2$" Lithium Cuprates: Lower-Order Aggregates of Gilman Reagents and Organolithium Compounds", *J. Org. Chem.*, **1994**, *59*, 2665-2667. (c) Barnhart, T. M.; Huang, H.; Penner-Hahn, J. E. "Structural Characterization of Organocopper Compexes by EXAFS and XANES: Evidence That Cyanide Does Not Coordinate to Cu in Dimethyl Cuprate Solutions", *J. Org. Chem.*, **1995**, *60*, 4310-4311. (d) Snyder, J. P.; Bertz, S. H. "Higher Order" Cyanocuprate Structure: Cyanide Is Lithium Bond", *J. Org. Chem.*, **1995**, *60*, 4312-4313. (e) Bertz, S.H.; Nilsson, K.; Davidsson, Ö.; Snyder, J.P "The Use of ^{15}N NMR Spectroscpy to resolve the "Higher Order Cyanocuprtae" Controversy: ^{15}N, ^{6}Li, and ^{13}C NMR Spectroscopic Investigations of CuCN-drived Butyl Cuprates", *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 314-317. (f) Huang, H.; Liang, C.H.; Penner-Hahn, J.E. "X-Ray Absorption Spectroscopy of Dimethylcuprates: Evidence for Solvent-Dependent Aggregation", *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1564-1566.

[56] For studies on the mechanism see (a) Nakamura, E., Mori, S., Morokuma, K. "Theoretical Studies on the Addition of Polymetallic Lithium Organocuprate Clusters to Acetylene. Cooperative Effects of Metals in Trap-and-Bite Reaction Pathway", *J. Am. Chem. Soc.* **1997**, *119,* 4887-4899. (b) Nakamura, E., Mori, S., Morokuma, K. "Reaction Pathway of the Conjugate Addition of Lithium Organocuprate Clusters to Acrolein", *J. Am. Chem. Soc.* **1997**, *119,* 4900-4910. (c) Eriksson, M.; Johansson, A.; Nilsson, M.; Olsson, T. "The Role of Iodotrimethylsilane in the Conjugate Addition of Butylcopper·Lithium Iodide to α- Enones; Silylation of an Intermediate π-complex", *J. Am. Chem. Soc.* **1996**, *118,* 10904-10905. (d) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. "β- Silyl Organocuprates: The Grail of Organocuprate Chemistry", *J. Am. Chem. Soc.* **1996**, *118,* 10906-10907. (e) Krause, N., Wagner, R., Gerold, A. "New Insight into the Structure of Organocuprate π-complexes by Determination of 13C,13C

Coupling Constants", *J. Am. Chem. Soc.* **1994**, *116*, 381-382. (f) Kingsbury, C. L., Smith, R. A. "Some Observation onthe Mechanism of Diorganocuprate 1,4-Addition reactions with α,β,-Unsaturated Ketones: Effects of Diethyl Ether in Reactions of Butylcoppers in Toluene", *J. Org. Chem.* **1997**, *62*, 4629-4634. (g) Ullenius, C., Chritenson, B. "Organocuprate addition to α,β,-Unsaturated Compounds: Synthetic and Mechanistic Aspects", *Pure & Appl. Chem.* **1988**, *60*, 57-64.

[57] Lipshutz, B. H. "Downsizing Copper in Modern Cuprate Couplings", *Acc. Chem. Res.* **1997**, *30*, 277-282.

[58] (a) Krause, N. " Copper-Catalyzed Enantioselective Michael Additions: Recent Progress with New Phosphorus Ligands", *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 283-285. (b) Feringa, B. L., Pineschi, M., Arnold, L.A., Imbos, R., de Vries, A. H. M. "Highly Enantioselective Catalytic Conjugate Addition and Tandem Conjugate Addition-Aldol Reaction of Organozinc Reagents", *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620-2622.

[59] (a) Lipshutz, B. H. "Applications of Higher Order Mixed Organocuprates to Organic Synthesis", *Synthesis*, **1987**, 325-341. (b) Lipshutz, B. H. "The Evolution of Higher Order Cyanocuprates", *SYNLETT*, **1990**, 119-128.

[60] Ashby, E.C.; Lin, J.-J. *J. Org. Chem.* **1977**, *42*, 1099 and ibid, 2805.

[61] Yamamoto, Y.; Asao, N.; Uyehara, T. "Amide Cuprate Reagents as a New Class of Nitrogen Nucleophiles. Application to Asymmetric Synthesis of β-Lactams", *J. Am. Chem. Soc.* **1992**, *114*, 5427-5429.

[62] (a) Yamamoto, Y. "Selective Synthesis by Use of Lewis Acids in the Presence of Organocopper and Related Reagents", *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947-1038. (b) Ibuka, T.; Yamamoto, Y. "New Aspects of Organocopper Reagents: 1,3- and 1,2-Chiral Induction and Reaction Mechanism", *SYNLETT* **1992**, 769-777;

[63] (a) (i) Corey, E.J.; Boaz, N.W. "Evidence for a reversible d,π*-Complexation, β-Cupration sequence in the Conjugate Addition reaction of Gilman Reagents with α,β-Enones", *Tetrahedron Lett.* **1985**, *26*, 6015-6018. (ii) Corey, E.J.; Boaz, N.W. "The Recations of Combined Organocuprate-Chlorotrimethylsilane reagents with Conjugate Carbonyl Compounds", *Tetrahedron Lett.* **1985**, *26*, 6019-6022. (b) Lipshutz, B. H.; Dimock, S.H.; James, B. " The Role of TMSCl in Gilman Cuprate 1,4-Addition Reactions", *J. Am. Chem. Soc.* **1993**, *115*, 9283-9284. (c) Lipshutz, B. H.; Aue, D.H.; James, B. "An ab initio Molecular Orbital Study on the Lewis Acidity of TMS-Cl an TMS-CN Toward an α,β–Unsaturated aldehyde: Are These Acid-Base Interaction Important in Organocuprate 1,4-Adittion to Enones?", *Tetrahedron Lett.* **1996**, *37*, 8471-8474 and references cited therein.

[64] (a) Hanessian, S.; Sumi, K. "On the Stereochemical Divergence in the Conjugate Addition of Lithium Dimethylcuprate/ Trimethylsilyl Chloride to γ-Alkoxy and γ-Ureido α,β–Unsaturated Esters", *Synthesis* **1991,** 1083-1089. (b) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. "Diastereoselectivity of the Conjugate Addition of Organocopper Reagents to γ-Alkoxy α,β–Unsaturated Carbonyl Derivatives. Importance of the Reagent Type and the Double-Bond Geometry", *J. Am. Chem. Soc.* **1992**, *114*, 7652-7660. (c) Reetz, M. T.; Rohrig, D. "Stereoselective Synthesis of γ-Aminocarboxylates", *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1706-1709. (d) Dorigo, A. E.; Morokuma, K. "Stereoselectivity of the Nucleophilic Addition of Organocopper Reagents to Chiral α,β–Unsaturated Caronyl Compounds. Ab Initio Molecular Orbital Studies of Steric and Electronic Effects", *J. Am. Chem. Soc.* **1989**, *111*, 6524-6536.

[65] (a) House, H.O. "Use of Lithium Organocuprate Additions as Models for an Electron–Transfer Process", *Acc. Chem. Res.* **1976**, *9*, 59-67.

[66] (a) Nicolaou, K.C.; Pavai, M.R.; Seitz, S.P. *J. Am.Chem. Soc.* **1981**, *103*, 1224-1226 and ibid **1982**, *104*, 2027-2029. (b) Ziegler, F.E.; Gilligan, P.J. *J. Org. Chem.* **1981**, *46*, 3874-3880.

[67] (a) Roush, W.R.; Michaelides, M.R.; Tai, D.F.; Lesur, B.M.; Chong, W.K.M.; Harris, D.J. *J. Am.Chem. Soc.* **1989**, *111*, 2984-2995. (b) Roush, W.R.; Lesur, B.M. *Tetrahedron Lett.* **1983**, *24*, 2231-2234.

[68] Ethyllithium was prepared by using the known procedure see, Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A.; Parker, D. *J. Org. Chem.* **1984**, *49*,

[69] Lipshutz, B.H.; Ellsworth, E. L.; Dimock, S.H.; Smith, R.A.J. "New Methodology for Conjugate Additions of Allylic Ligands to α,β–Unsaturated Ketones: Synthetic and Spectroscopic Studies", *J. Am. Chem. Soc.* **1990**, *112*, 4404-4410.

[70] Ziegler, F.E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 426-427 and references cited therein.

[71] Our procedure was successfully employed by Ziegler see ref. 70.

[72] (a) Hanessian, S.; Murray, P.J. "Stereochemical Control of Nature's Biosynthetic Pathways: A General Strategy for the Synthesis of Polypropionate-Derived Structural Units from a Single Chiral Progenitor", *Tetrahedron* **1987**, *43*, 5055-5072. (b) Agyei-Aye, K.; Baker, D. *Carbohydrate Research* **1988**, *183*, 261-275.

[73] I thank Eric Olivier for providing this compound. For preparation, see, Mann, J.; Weymouth-Wilson, A.C. *Organic Synthesis* **1998**, *75*, 139.

[74] Hanessian, S.; Delorme, D.; Dufresne, Y. "Mild Cleavage of Methoxymethyl (MOM) Ethers with Trimethylsilyl Bromide", *Tetrahedron Lett.* **1984**, *25*, 2515-2518.

[75] Hanessian, S.; Murray, P.J. "Stereochemical Control of Nature's Biosynthetic Pathways: A General Strategy for the Synthesis of Polypropionate-Derived Structural Units from a Single Chiral Progenitor", *Tetrahedron* **1987**, *43*, 5055-5072.

[76] For Mitsunobu reaction and improvments see (a) Mitsunobu, O. "The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Matiral

Products", *Synthesis*, **1981**, 1-28. (b) Hughes, D.L. "The Mitsunobu Reaction", *Organic Reactions*, **1992**, *42*, 345. (c) Walker, M.A. "A High Yielding Synthesis of N-alkyl Maleimides Using a Novel Modification of the Mitsunobu Reaction", *J. Org. Chem.* **1995**, *60*, 5352-5355.

[77] (a) Ozgowoski, R.; Kunath, A.; Schick, H. *Liebigs Ann.* **1996**, 1443-1448. (b) Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *62*, 677.

[78] Colvin, E. "Silicon in Organic Synthesis", Butterworths, London, **1981**.

[79] Lambert, J.B. "The Interaction of Silicon with Positively Charged Carbon", *Tetrahedron* **1990**, *46*, 2677.

[80] Stowell, J.C. *Carbanions in Organic Synthesis*, JohnWiley & Sons, New York, **1979**.

[81] Morrison, J. D., Ed. *"Asymmetric Synthesis"*, Academic Press, New York, Vol. 3; Chapter 1, Evans, D.A. "Stereoselective Alkylation Reactions of Chiral Metal Enolates" and Chapter 2, Heathcock, C.H. "The Aldol Addition Reactions".

[82] Heathcock, C. H. "Understanding and Controlling Diasterofacial Selectivity in Carbon-Carbon Bond-Forming Reactions", *Aldrichimica Acta* **1990**, *23*, 99-111.

[83] (a) Davis, F. A.; Chen, B.-C. "Asymmetric Hydroxylation of Enolates with N-Sulfonyloxaziridines", *Chem. Rev.* **1992**, *92*, 919-934. (b) Vishwakarma, L.C.; Stringer, O.D.; Davis, F.A. "(*dl*)-trans-2-(Phenylsulfonyl)-3-Phenyloxaziridine (Oxaziridine, 3-Phenyl-2-(Phenylsulfonyl)", *Organic Synthesis*, **1988**, *66*, 203-210. (c) Davis, F. A.; Stringer, O. D. "Chemistry of Oxaziridine. 2. Improved Synthesis of 2-Sulfonyloxaziridines", *J. Org. Chem.* **1982**, *47,* 1774-1775.

[84] (a) Evans, D.A.; Britton, T.C. "Electrophilic Azide Transfer to Chiral Enolates. A General Approach to the Asymmetric Synthesis of α-AminoAcids", *J. Am. Chem. Soc.* **1987**, *109*, 6881-6883. (b) Evans, D.A.; Ellman, J.A. "The Total Synthesis of the Isodityrisine-Derived Cyclic Tripeptides OF4949-III and K-13. Determination of the Absolute Configuration of K-13", *J. Am. Chem. Soc.* **1989**, *111*, 1063-1072. For

preparation of trisyl azide see: (c) Leffler, J.E.; Tsun, Y. "Some Decomposition Reactions of Acid Azides", *J. Org. Chem.* **1963**, *28*, 902-906. (d) Harmon, R.E.; Wellman, G.; Gupta, S.K. "The Reaction of Arylsulfonyl Azides with N-Methylindole", *J. Org. Chem.* **1973**, *38*, 11-15.

[85] (a) Greck, C.; Genét, J.P. "Electrophilic Amination: New Synthetic Applications", *SYNLETT*, **1997**, 741-749. (b) Gennari, C.; Colombo, L.; Bertolini, G. "Asymmetric Electrophilic Amination: Synthesis of α-Amino and α-Hydrazino Acids with High Optical Purity", *J. Am. Chem. Soc.* **1986**, *108*, 6394-6395. (c) Evans, D. A.; Britton, T. C.; Dorow, R. L. Dellaria, J. F. "Stereoselective Amination of Chiral Enolates. A New Approach to the Asymmetric Synthesis of α-Hydrazino and α-AminoAcids Derivatives", *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397.(d) Trimnle, L.A.; Vederas, J. C. "Amination of Chiral Enolates by Dialkyl Azodiformates. Synthesis of α-Hydrazino Acid and α-AminoAcids", *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399. (e) Evans, D.A.; Nelson, S.G. *J. Am. Chem. Soc.* **1997**, *119*, 6452-6453.

[86] Evans, D.A.; Ellman, J.A.; Dorow, R.L. *Tetrahedron Lett.* **1987**, *28*, 1123-1126.

[87] (a) Morizawa, Y.; Yasuda, A.; Uchida, K. "Trifluoromethyl Group Induced highly Stereoselective Synthesis of α-Hydroxy Carbonyl Compounds", *Tetrahedron Lett.* **1986**, *27*, 1833-1836. Also see the initial work of our group (b) Hanessian, S.; Gai, Y.; Wang, W. *Tetrahedron Lett.* **1996**, *37*, 7473-7476.

[88] Flemming, I.; Lewis, J.J. "A Paradigm for Diastereoselectivity in Electrophilic Attack on Trigonal Carbon adjacent to a Chiral Center: the Methylation and Protonation of Some Open-Chain Enolates" *Chem. Commun.* **1985**, 149-151 and references cited therein.

[89] (a) Seebach, D. "Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficuties and Opportunities Afforded by Complex Structures", *Angew. Chem. Int. Ed. Engl.* **1988**, *27*,1724-1654. (b) Collum, D.B. *Acc.*

Chem. Res. **1992**, *25*, 448-454. (c) Rück, K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 433-435.

[90] For asymmetric synthesis of amino acids see, (a) Williams, R.M. *Aldrichimica Acta*, **1992**, *25*, 11-25. (b) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360-366 and references cited therein.

[91] (a) Giannis, A.; Kolter, T. "Peptidomimetics for receptor Ligands–Discovery, Development and Medical Perspectives", *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244-1267. (b) Gante, J. "Peptidomimetics–Tailored Enzyme Inhibitors", *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699-1720.

[92] Thompson, A.S.; Humphrey, G.R.; DeMarco, A.M.; Mathre, D.J.; Grabowski, E.J.J. "Direct Conversion of Activated Alcohols to Azides Using Diphenyl Phosphorazidate. A Practical Alternative to Mitsnobu Conditions", *J. Org. Chem.* **1993**, *58*, 5886-5888.

[93] Effenberger, F.; Burkard, U.; Willfahrt, J. "Trifluoromethanesulfonates of α-Hydroxycarboxylates–Educts for the Racemization–Free Synthesis of N-Substituted α-Amino Acids", *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 65-66.

[94] For DMSO-based oxidation see Tidwell, T.T. "Oxidation of Alcohols to Carbonyl Compounds via Alkoxysulfonium Ylides: the Moffatt, Swern, and Related Oxidations", *Organic Reactions*, **1990**, *39*, 297-572.

[95] For Wittig olefination see, (a) Vedejs, E. *Topics in Stereochemistry* **1994**, *21*, 1-157. (b) Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863-927.

[96] (a) Evans, D.A.; Bartroli, J.; Shih, T.L. "Enantioselective Aldol Condensations. 3. Erythro-Selective Chiral Aldol Condensations via Boron Enolates", *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129. (b) Evans, D. A.; McGee, L. R. "Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations via Zirconium Enolates", *J. Am. Chem. Soc.* **1981**, *103*, 2876-2878. (c) Evans, D. A.; Weber, A. E. "Asymmetric Glycine Enolate Aldol Reactions: Synthesis of Cyclosporine's Unusual

Amino Acid, MeBmt", *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, R. "Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis", *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-30. (e) Roush, W. R. "Concerning the Diastereofacial Selectivity of the Aldol reactions of α-Methyl Chiral Aldehydes and Lithium and Boron Propionate Enolates", *J. Org. Chem.* **1991**, *56*, 4151-4157. (f) Cowden, C.J.; Paterson, I. "Asymmetric Aldol Reactions Using Boron Enolates", *Organic Reactions* **1997**, *51*, 1-200.

[97] Rychnovsky, S.D. "Oxo Polyene Macrolide Antibiotics" *Chem. Rev.* **1995**, *95*, 2021-2040 and references cited therein..

[98] (a) Martin, S.F. "Methodology for the Construction of Quaternary Carbon Centers", *Tetrahedron* **1980**, *36*, 419-460. (b) Meyers, A.I.; Romo, D. *Tetrahedron* **1991**, *47*, 9503. (c) Fuji, K. "Asymmetric Creation of Quaternary Carbon Centers", *Chem. Rev.* **1993**, *93*, 2037-2066. (d) Åhman, J.; Wolfe, J.P.; Troutman, M.V.; Palucki, M.; Buchwald, S.L. "Asymmetric Arylation of Ketone Enolates", *J. Am. Chem. Soc.* **1998**, *120*, 1918-1919. (e) Enders, D.; Bartsch, M.; Backhaus, D.; Runsink, J.; Raabe, G. "Diastereo- and Enantioselective Synthesis of Polyfunctional Cyclic Ketones with Neighboring Quaternary and Tertiary Stereogenic Centers via [2,3]-Wittig Rearrangement", *Synthesis* **1996**, 1438-1442. (f) Tietze, L.F.; Schiemann, K.; Wegner, C. "Enantioselective Synthesis of Tertiary Homoallylic Alcohols via Diastereoselective Addition of Allylsilanes to Ketones", *J. Am. Chem. Soc.* **1995**, *117*, 5851-5852.

[99] Hanessian, S.; Murray, P.J. " A Versatile Protocol for the Stereocontrolled Elaboration of Vicinal Secondary and Tertiary Centers of Relevance to Natural Product Synthesis", *J. Org. Chem.* **1987**, *52*, 1170-1172.

[100] Metzler, D.E. "*Biochemistry - the Chemical Reactions of Living Cells*", Academic Prees, New York, **1977**.

[101] Cane, D.E. *Chem. Rev.* **1997**, *97*, 2463-2464.

[102] (a) Staunton, J.; Wilkinson, B. "The Biosynthesis of Aliphatic Polyketides", *Topics in Current Chemistry,* **1998**, *195,* 49-92.(b) "Polyketide and Nonribosomal polypeptide Biosynthesis", Cane, D. E., Ed., *Chem. Rev.* **1997**, *97*, No. 7 (special issue). (c) Cane, D. E. "Polyketide Biosynthesis -- Molecular Recognition or Genetic Programming", *Science* **1994**, *263*, 338-340.

[103] For biogenetically combinatorial library construction of polypropionate see, Cane, D.E. & coworkers, *J. Am. Chem. Soc.* **1995**, *117*, 9105-9106; *ibid*, **1996**, *118*, 9184-9185; *ibid*, **1998**, *120*, 2478-2479. See also Rawls, R.L. *Chemical & Engineering News* **1998**, (March 9), P29.

[104] (a) Mulzer, J. "Erythromycin Synthesis –A Never-ending Story?" *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1452-1454. (b) Norcross, R. D.; Paterson, I. "Total Synthesis of Bioactive Marine Macrolides", *Chem. Rev.* **1995,** *95*, 2041-2114. See also ref.

[105] (a) Paterson, I.; Scott, J.P. "Polyketide Library Synthesis: Iterative Assembly of Extended Polypropionates Using (*R*)- and (*S*)-1-(Benzyloxy)-2-Methylpentan-3-one", *Tetrahedron Lett.* **1997**, *38*, 7441-7444. (b) Paterson, I.; Scott, J.P. "Polyketide Library Synthesis: Conformation Control in Extended Polypropionates", *Tetrahedron Lett.* **1997**, *38*, 7445-7448.

[106] (a) Bafilomycin A1 see later for details. (b) Concanamycin A see Jyojima, T.; Katohno, M.; Miyamoto, N.; Nakata, M.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **1998**, *39*, 6003-6006 and references cited therein. (c) Erythromycin A see ref. Mulzer. (d) For synthesis of elaiophylin see (i) Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Lawson, K.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *J. Am. Chem. Soc.* **1985**, *107*, 5292; (ii) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369; (iii) Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454. (e) For rifamycin S see later for details. (f) For scytophycin C see, Paterson, I.; Watson, C.; Yeung, K.-S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452 references cited therein.

[107] Woodward, R.B. "Synthesis", in "*Perspectives in Organic Chemistry*", Todd, A., Ed.; Interscience, NY, p155-184, **1956.**

[108] (a) Hoffmann, R. W. "Stereoselective Syntheses of Building Blocks with Three Consecutive Stereogenic Centers: Important Precursors of Polyketide Natural Products", *Angew. Chem. Int. Ed. Engl.* **1987**, *26,* 489-503. (b) Hofmann, R. W.; Dahmann, G.; Anderson, M. A. "Stereoselective Synthesis of Alcohols, XLV: Recent Developments in the Generation of the Stereotriad 'D'", Synthesis, **1994,** 629-638. (c) Marshall, J. A.; Perkins, J. F.; Wolf, M.A. "Synthesis of syn, syn; anti, syn; syn, anti; anti, anti Stereotriads from a Single Pair of Enantiomeric Reagents", *J. Org. Chem.* **1995**, *60*, 5556-5559. (d) Jain, N. F.; Takenaka, N.; Panek, J.S. "Double-Stereodifferentiating Crotylation Reactions with Chiral (*E*)-Crotylsilanes. Evaluation of a New Approach for the Synthesis of Polypropionate-Derived Natural Products", *J. Am. Chem. Soc.* **1996**, *118*, 12475-12476.

[109] (a) Hoffmann, R. W.; Dahmann, G.; Anderson, M. A. "Stereoselective Synthesis of Alcohols, XLV: Recent Developments in the Generation of the Stereotriad 'D'", *Synthesis* **1994,** 629-638. (b) Paterson, I. "New Methods and Strategies for the Stereocontrolled Synthesis of Polypropionate-derived Natural Products", *Pure & Appl. Chem.* **1992**, *64*, 1821-1830. (c) Mukaiyama, T.; Kobayashi, S. "Tin(II) Enolates in the Aldol, Michael, and Related Reactions", *Org. React.* (NY), **1994**, *46*, 1-103. (d) Norcross, R. D.; Paterson, I. "Total Syethesis of Bioactive Marine Macrolides", *Chem. Rev.* **1995**, *95*, 2041-2114. and ref. 146.

[110] Corey, E.J.; Cheng, X.-M. *"The Logic of Chemical Synthesis"*, John-Wiley & Sons, New York, **1995**.

[111] Woodward, R.B. & coworkers, "Asymmetric Total Synthesis of Erythromycin A", *J. Am. Chem. Soc.* **1981**, *103,* 3210-3213, 3213-3215 & 3215-3217.

[112] (a) Lautens, M. "Ring Opening Reactions of Oxabicyclic Compounds as Route to Cyclic and Acyclic Compounds with Multiple Sterecenters", *SYNLETT* **1993**, 177-185. (b) Lautens, M. " New Methods for the Control of Multiple Stereocenters", *Pure & Appl. Chem.* **1992**, *64*, 1873-1882.(c) Vogel, P.; Sevin, A.-F.; Kernen, P.; Bialecki, M. *Pure & Appl. Chem.* **1996**, *68*, 719-722 and references cited therein. (d) Marchionni, C.; Vogel, P. Tetrahedron Lett. 1996, 37, 4149-4152.

[113] For asymmetric epoxidation see, Katsuki, T.; Martin, V.S. *Organic Reactions* **1996**, *48*, 1-299.

[114] Hoveyda, A.H.; Evans, D.A.; Fu, G.C. "Substrate-Directable Chemical Reactions", *Chem. Rev.* **1993**, *93*, 1307-1370.

[115] See Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

[116] Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483.

[117] Hanessian, S.; Gai, Y. unpublished results.

[118] Wehrli, W. "Ansamycins: Chemistry, Biosynthesis and Biological Activity", *Topics in Current Chemistry* **1977**, vol. *72*, 21.

[119] Hartmann, G. R.; Heinrich, P.; Kollenda, M. C.; Skrobranek, B.; Tropschug, M.; Weiβ, W. "Molecular Mechanism of Action of the Antibiotic Riampicin", *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1009-1074.

[120] For total synthesis of rifamycin S see (a) Nagaoka, H.; Rutsh, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. "Total Synthesis of Rifamycin S. 1. Stereocontrolled Synthesis of the Aliphatic Building Block", *J. Am. Chem. Soc.* **1980**, *102*, 7962-7965. (b) Iio, H.; Nagaoka, H.; Kishi, Y. "Total Synthesis of Rifamycin S. 2. Total Synthesis of Racemic Rifamycin S", *J. Am. Chem. Soc.* **1980**, *102*, 7965-7967. For syntheses of ansa chain of rifamycins see (c) Corey, E. J.; Hase, T. "Studies on the Total Synthesis of Rifamycin. Highly Stereoselective Synthesis of Intermediates for construction of the C(15) to C(29) Chain", *Tetrahedron Lett.* **1979**, 335-338. (d) Nakata, M.; Takao, H.; Ikeyyama, Y.;

Sakai, T.; Tatsuta, K.; Kinoshita, M. "Synthetic Studies of Rifamycins. IV. The Synthesis of Rifamycin Ansa-chain Compound Using Carbohydrate", *Bull. Chem. Soc. Jpn* **1981**, *54*, 1749-1756. (e) Masamune, ,S.; Imperiali, B.; Garvey, D. S. "Synthesis of Ansamycins: The Ansa Chain of Rifamycin S", *J. Am. Chem. Soc.* **1982**, *104*, 5528-5531. (f) Hanessian, S.; Pougny, J. -R.; Bossenkool, I. K. "Total Synthesis of the C19-C29 Aliphatic Segment of (+)-Rifamycin S", *J. Am. Chem. Soc.* **1982**, *104*, 6164-6166. (g) Still, W. C.; Barrish, J. "Stereoselective Synthesis of 1,3-Diol Derivatives and Application to the Ansa Bridge of Rifamycin S", *J. Am. Chem. Soc.* **1983**, *105*, 2487-2489. (h) Fraser-Reid, B.; Magdzinski, L.; Molino, B. "New Strategy for Carbohydrate-Based Synthesis of Multichiral Arrays: Pyranisidic Homologation", *J. Am. Chem. Soc.* **1984**, *106*, 731-734. (I) Rao, A.V.R.; Yadav, J. S.; Vidyasagar, V. "Stereoselective Synthesis of the C21-C27 Segment of Rifamycin S", *Chem. Commun.* **1985,** 55-56. (j) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. "Stereocontrolled Synthesis of an Epimer of the C(19)-C(27) Segment of Rifamycin S", *Helv. Chim. Acta* **1986**, *69,* 621-625. (k) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. "Expeditious Synthesis of the Polypropionate Sector of Rifamycin S by Reiterative Diene-Aldehyde Cyclocondensation Reactions", *J. Am. Chem. Soc.* **1987**, *109*, 862-867. (l) Roush, W. R.; Palkowitz, A. D. "Applications of Tartrate Ester Modified Allylic Boronates in Organic Synthesis: An Efficient, Highly Stereoselective Synthesis of the C(19)-C(29) Segment of Rifamycin S", *J. Am. Chem. Soc.* **1987**, *109*, 953-955. (m) Ziegler, F. E.; Cain W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. "Applications of the 3-Methyl-γ-Butyrolactone Strategy to the Synthesis of Polypropionates: The Prelog-Djerassi Lactonic Ester, ent-Invictolide, and the C19-C27 Fragment of Rifamycin S", *J. Am. Chem. Soc.* **1988**, *110*, 5442-5452. (n) Katsuki, T.; Hanamota, T.; Yamaguchi, M. "Synthesis of C19-C27 Fragment of Ansa Chain Part of Rifamycin S", *Chem. Lett.* **1989**, 117-118. (o) Peterson, I.; McClure C. K.; Schumann, R. C. "A Short Asymmetric Synthesis of a C19-C27 Segment of Rifamycin S.

Kinetic Resolution in the Aldol Reactions of Ethylketones Using Chiral Boron Reactions", *Tetrahedron Lett.* **1989**, *30*, 1293-1296. (p) Nakata, M.; Akiyama, N.; Kamata, J.-i.; Kojima, K.; Masuda, H.; Kinoshita, M.; Tasuta, K. "The Total Synthesis of Rifamycin W", *Tetrahedron* **1990**, *46*, 4629-4652. (q) Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. "A Highly Convergent Asymmetric Synthesis of the C(19)-C(27) Segment of Rifamycin S: An Application of Enantiodifferentiating Acetalization with Menthone", *J. Org. Chem.* **1992**, *57*, 1637-1639. (r) Lautens, M.; Belter, R. K. "The Effect of Remote Oxygens on the Ring-Opening Reactions of Oxabicyclic Compound with Organolithium Reagents. Synthesis of the C21-C27 Segment of Rifamycin S", *Tetrahedron Lett.* **1992**, *33*, 2617-2620. (s) Miashita, M.; Yoshihara, K.; Kawamine, K.; Hoshino, M.; Irie, H. "Synthetic Studies on Polypropionate Antibiotics Based on the Stereospecific Methylation of γ,δ-Epoxy Acrylates by Trimethylaluminum. A highly Stereoselective Construction of Eight Contiguous Chiral Centers of Ansa-chains of Rifamycins", *Tetrahedron Lett.* **1993**, *34*, 6285-6288.

[121] For isolation of bafilomycins see Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zähner, H. *J. Antibiotics* **1984**, *37*, 110-117 and references cited therein.

[122] (a) Bowman, E. J.; Siebers, A.; Altendorf, K. "Bafilomycins: A Class of Inhibitors of Membrane ATPase from Microorganisms, Animal Cells, and Plant Cells". *Proc. Natl. Acad. Sci. USA* **1988,** *85*, 7972-7976. (b) Knops, J.; Suomensaari, S.; Lee, M.; McConlogue, L.; Seubert, P.; Sinha, S. " Cell-type and Amyloid Precursor-type Specific Inhibition of Aβ Release by Bafilomycin A1, a Selective Inhibitor or Vacuolar ATPase", *J. Biol. Chem.* **1995,** *270*, 2419-2422.

[123] (a) Schenk, D. B.; Rydel, R. E.; May, P.; Little, S.; Panetta, J.; Lieberburg, I.; Sinha, S. "Therapeutic Approaches Related to Amyloid-β Peptide and Alzheimer's Disease", *J.*

Med. Chem. **1995**, *38,* 4143-4154. (b) Haass, C.; Capell, A.; Citron, M.; Teplow, D. B.; Selkoe, D. J. "The Vacuolar H^+-ATPase Inhibitor Bafilomycin A1 differentially Affects Proteolytic Pressing of Mutant and Wild Type β-Amyloid Precursor Protein", *J. Biol. Chem.* **1995,** *270*, 6186-6192.

[124] For the total synthesis of hygrolidin, see Makino, K.; Nakajima, N.; Hashimoto, S.-i.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077 and reference cited therein.

[125] Baker, G.H.; Brown, P.J.; Dorgan, R.J.J.; Everett, J.R,; Ley, S.V.; Slawin, A.M.Z.; Williams, D.J. *Tetrahedron Lett.* **1987**, *28*, 5565-5568.

[126] For total synthesis see (a) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Murase, H.; Yoshida, T.; Matsumura, S.; Nakata, M. "Total Synthesis of Bafilomycin A1. 1. Syntheses of the C5-C11, C12-C17, and C18-C25 Segments", *Tetrahedron Lett.* **1996**, *37*, 1069-1072. (b) Toshima, K.; Yamaguchi, H.; Jyojima, T.; Noguchi, Y.; Nakata, M.; Matsumura, S. "Total Synthesis of Bafilomycin A1. 2. The Assemblage and Completion of the Synthesis", *Tetrahedron Lett.* **1996**, *37*, 1073-1076. (c) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakata, M.; Matsumura, S. "Total Synthesis of Bafilomycin A1", *J. Org. Chem.* **1997,** *62*, 3271-3284 (full paper). (d) Calter, Ph.D. thesis, Harvard University. For synthetic studies see (e) Roush, W. R.; Bannister, T. D. "Stereoselective Synthesis of the C(13)-C(25) Segment of Bafilomycin A1", *Tetrahedron Lett.* **1992**, *33,* 3587-3590. (f) Roush, W. R.; Bannister, T. D.; Wendt, M. D. "Concerning the Diastereofacial Selectivity of Aldol Reactions of Chiral Methyl Ketone Enolates: Evidence for Remote Chelation in the Bafilomycin Aldol Reaction", *Tetrahedron Lett.* **1993**, *34,* 8387-8390. (g) Evans, D. A.; Calter, M. A. " Diastereoselective Aldol reactions of β-Silyloxy Ethyl Ketones. Application to the Total Synthesis of Bafilomycin A1", *Tetrahedron Lett.* **1993**, *34,* 6871-6874. (f) Paterson, I.; Bower, S.; Mcloed, M. D. "Stereocontrolled Aldol Additions to α-Methylene-β-Alkoxy

Aldehydes: Application to the Synthesis of a C13-C25 Segment of Bafilomycin A1", *Tetrahedron Lett.* **1995**, *36*, 175-178.

[127] For structural modification see (a) Hanessian, S.; Meng, Q.; Olivier, E. "An Unprecedented Ring Expansion in the Macrolide Series-Synthesis of Iso-bafilomycin A1", *Tetrahedron Lett.* **1994**, *35*, 5393-5396. (b) Hanessian, S.; Tehim, A.; Meng, Q. *Tetrahedron Lett.* **1996**, *37*, 9001-9004. (c) Gatti, P. A.; Gagliardi, S.; Cerri, A.; Visconti, M.; Farina, C. "Selective Oxidation of Hydroxy Group of Bafilomycin A1", *J. Org. Chem.* **1996**, *61*, 7185-7188. (d) Gagliardi, S,; Gatti, P. A.; Cerri, A.; Farina, C. *Tetrahedron Lett.* **1997**, *38*, 479-482. (e) Gatti, P. A.; Gagliardi, S.; Cerri, A.; Farina, C. *Tetrahedron Lett.* **1997**, *38*, 6949-6952.

[128] For general information on macrolactonization see (a) Meng, Q.; Hesse, M. "Ring Closure Methods in the Synthesis of Macrocyclic Natural Products", *Topics in Current Chemistry* **1991**, *161*, 107-170. (b) Bartra, M.; Urpf, F.; Vilarrasa, J. "Cyclization Methods Related to the Synthesis of Macrolide Antibiotics", p1-65 in Ref. 75 (a).

[129] For Julia olefination see, Hart, D.J.; Wu, W.-L. *Tetrahedron Lett.* **1996**, *37*, 5283-5286 and references cited therein.

[130] For Heck reaction see, de Meijere, A.; Meyer, F.E. "Fine Feathers Make Fine Birds: the Heck Reaction in Modern Garb", *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379-2411.

[131] Farina, V.; Krishmanurthy, V.; Scott, W.J. "The Stille Reaction", *Organic Reactions* **1997**, *50*, 1-652.

[132] For Suzuki reaction see, Miyaura, N.; Suzuki, A. "Palladium–Catalyzed Cross–Coupling Reactions of Organoboron Compounds", *Chem. Rev.* **1995**, *95*, 2457-2483.

[133] For Nozaki–Kiski reaction see, (a) Jin, H.; Uenishi, J.-i.; Christ, W.J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646. (b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386-5387 (An asymmetric process). For recent application see (c) Chen, X.-

T.; Gutteridge, C.E.R.; Bhattacharya, S.K.; Zhou, B.; Pettus, T.R.R.; Hascall, T.; Danishefsky, S.J. "Total Synthesis of Eleuthesides", *Angew. Chem. Int. Ed.* **1998**, *37*, 185-187. (d) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 1157-1160.

[134] Hanessian, S.; Olivier, E.; Ma, J. unpublished results.

[135] (a) Hanessian, S.; Gai, Y.; Wang, W. "Stereocontrolled Functionalization in Acyclic Systems by Exploiting Internal 1,2-Asymmetric Induction–Generation of Polypropionate and Related Motifs", *Tetrahedron Lett.* **1996**, *37*, 7473-7476. (b) Hanessian, S.; Gai, Y. unpublished results.

[136] Hanessian, S. Gai, Y. unpublished results

[137] Hanessian, S.; Meng,, Q. unpublished results.

[138] Smith, III, A.B.; Condon, S.M.; McCauley, J.A.; Leahy, J.W.; Leazer, Jr. J.L.; Maleczka, Jr.; R.E. *Tetrahedron Lett.* **1994**, *35*, 4907-4910.

[139] Griffith, W.P.; Ley, S.V. "TPAP: Tetra-*n*-Propylammonium Perruthenate, a Mild and Convenient Oxidant for Alcohols", *Aldrichimica Acta*, **1990**, *23*, 1-19.

[140] Hanessian, S.; Meng, Q. unpublished results.

[141] Hanessian, S.; Olivier, E.; Wang, W. unpublished results.

[142] Boden, E.P.; Keck, G.E. *J. Org. Chem.* **1985**, *50*, 2394.

[143] For application of CBS-Oxazaborolidine (Corey-Bakshi-Shibata) see, Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763 and references cited therein.

[144] (a) Oishi, T.; Nakata, T. "An Introduction of Chiral Centers into Acyclic Systems Based on Stereoselective Ketone Reduction", *Acc. Chem. Res.* **1984**, *17*, 338-344. (b) Narasimhan, S.; Balakumar, R. "Synthetic Applications of Zinc Borohydride", *aldrichimica Acta* **1998**, *31*, 19-26

[145] For hydrozirconation see, (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853-12910. (b) Wipf, P.; Coish, P.G. *Tetrahedron Lett.* **1997**, *38*, 5073-5076.(c) Lipshutz, B.H.; Wood, M.R. *J. Am. Chem. Soc.* **1993**, *115*, 12625-12626.

[146] For hydroboration see: (a) Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, Lodon, **1988.** (b) Lane, C.F.; Kabalka, G.W. *Tetrahedron* **1976**, *32*, 981-990. (c) Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Amer. Chem. Soc.* **1973**, *85*, 5786-5788. (d) Matsumoto, Y.; Naito, M.; Hayashi, T. *Organometallics* **1992**, *11*, 2732-2734 (Palladium (0) catalyzed).

[147] For hydrostannylation see (a) Smith III, A.B.; Condon, S.M.; McCauley, J.A. *Acc. Chem Res.* **1998**, *31*, 35. (b) Smith III, A.B.; Condon, S.M.; McCauley, J.A.; Leazer, Jr., J.L; Leahy, J.W.; Maleczka, Jr., R.E. *J. Am. Chem. Soc.* **1997**, *119*, 962.

[148] Gibson, A.W.; Humphrey, G.R.; Kennedy, D.J.; Wright, S.H.B. *Synthesis* **1991**, 414-416.

[149] Corey, E.J.; Fuchs, P.L. Tetrahedron Lett. **1972**, 3769-3772.

[150] For DMSO-based oxidation see Tidwell, T.T. "Oxidation of Alcohols to Carbonyl Compounds via Alkoxysulfonium Ylides: the Moffatt, Swern, and Related Oxidations", *Organic Reactions*, **1990**, *39*, 297-572.

[151] Moffatt, J.G. "Moffatt oxidation", *Organic Synthesis* **1973**, *Collective Vol. 5*, 242-245.

[152] I thank Jianguo Ma for providing this compound.

[153] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[154] El Khadem, H.; Hanessian, S. *Anal. Chem.* **1958**, *30*, 1965.