AN ABSTRACT OF THE DISSERTATION OF

Shan Wang for the degree of Doctor of Philosophy in Chemistry presented on Jannuary 23, 1997.

Title: Synthetic Studies on the Macrolide Antibiotic Rutamycin B

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Abstract approved: _____

James D. White

Part I. Five approaches, including two successful routes, toward the synthesis of the 1,7-dioxaspiro[5.5]undecanyl segment **7** of the macrolide antibiotic rutamycin B are described. The first plan for synthesis of **53** envisioned an aldol condensation of aldehyde **55** with ketone **57**. Aldehyde **55** was prepared from (*S*)-(-)-4-benzyl-2-oxazolidinone (**67**) in eight steps. Ketone **57** was obtained from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate (**65**) in fifteen steps.

The second approach to **53** was based on addition of a higher order cuprate derived from iodide **60** to epoxide **59**. Iodide **60** was produced from (*S*)-hydroxymethylpropionate **66** in eleven steps. Epoxide **59** was obtained from aldehyde **55** via a three step route.

A third advance toward **53** utilized the dianion of sulfone **61** and the epoxide **59**. Sulfone **61** was prepared from iodide **60** through straightforward displacement. The failure to obtain **53** by any of these three routes is rationalized.

The first successful pathway to **53** involved coupling of hydrazone **58** with amide **56**. Hydrazone **58** was formed in *situ* from the ketone **57**, while preparation of amide **56** required two steps from aldehyde **55**. Treatment of the coupled product **111** with acid gave dihydroxy spiroketal **112**.

The second successful route employed a Julia coupling of sulfone **63**, obtained from iodide **60**, with aldehyde **62**. Under mild acidic conditions, the ketone **124**, obtained from the Julia adduct **122** in two steps, underwent cyclization to trihydroxy spiroketal **1**. The structures of both **1** and **112** were confirmed by comparison with authentical samples.

Part II. Continuation of the sequence from **112** toward the total synthesis of rutamycin B is described. Wadsworth-Emmons reaction of phosphonate **7**, prepared from hydroxy ketone **125** in four steps, with keto aldehyde **10** afforded **158**. Aldehyde **10** was prepared in seven steps from **133**, obtained from (*R*)-3-hydroxy-2-methylpropionate (**65**). Aldehyde **9** was also obtained from **133** through a twelve-step sequence. The hydroxy ketone **159**, obtained from titanium tetrachloride-mediated aldol condensation of aldehyde **9** with **158**, was protected as its hexasilyl ether **160**. Strategies for the final conversion of **160** to rutamycin B are discussed.

SYNTHETIC STUDIES ON THE MACROLIDE ANTIBIOTIC RUTAMYCIN B

by

SHAN WANG

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This dissertation is dedicated to my Mother and Father,

Qi Yang and Huachao Wang

and my Sisters

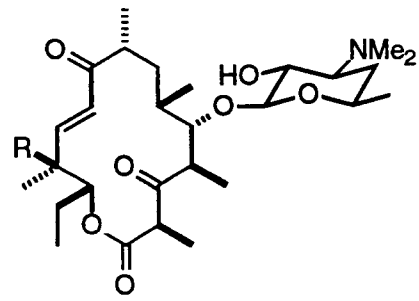
Fei Wang and Hua Wang

in appreciation of their unconditional love and support.

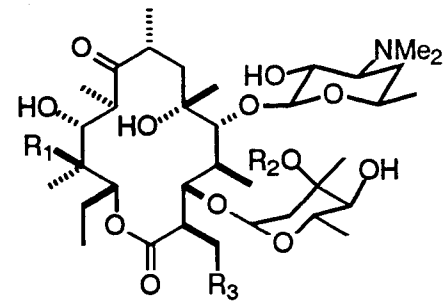
Synthetic Studies on the Macrolide Antibiotic Rutamycin B

Chapter I: General Introduction

Brockmann and Henkel isolated the first macrocyclic antibiotic, which they named pikromycin because of its bitter taste, from a strain of *Streptomyces* in 1950.[1] The structural characteristics of pikromycin and of other related antibiotics isolated subsequently showed a common feature - a macrocyclic lactone. Woodward proposed the term "macrolide" to describe this class of compounds.[2]



R = OH: Pikromycin
R = H: Narbomycin

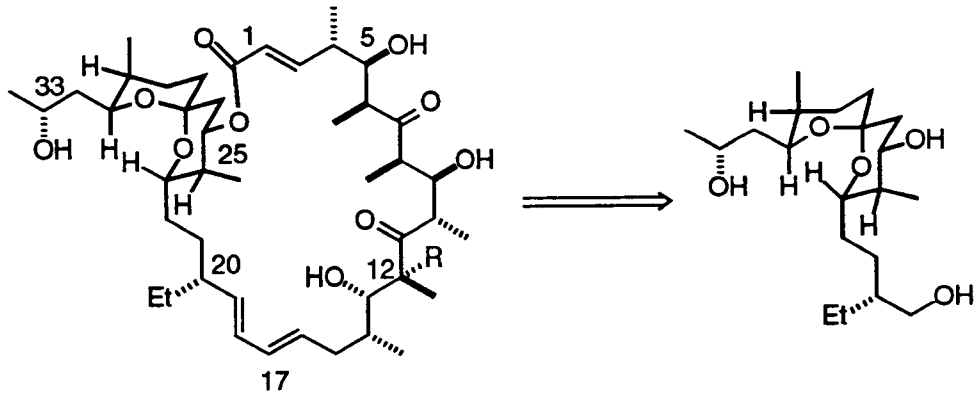


R_1 = OH, R_2 = CH_3, R_3 = H: Erythromycin A
R_1 = H, R_2 = CH_3, R_3 = H: Erythromycin B
R_1 = OH, R_2 = H, R_3 = H: Erythromycin C
R_1 = H, R_2 =H, R_3 = H: Erythromycin D
R_1 = OH, R_2 = CH_3, R_3 =OH: Erythromycin F

Macrolides are ubiquitous in nature, occurring in a very wide variety of organisms including marine species. Microorganisms of the *Streptomyces* family are an especially prolific source of macrolides. Many macrolides possess antibiotic activity, and a few, such as the erythromycins,[3] are highly valued for their medicinal properties. As a structural class, macrolides surpass even the steroids in their spectrum of biological activities. Not surprisingly, there has been a great deal of interest in the synthesis of macrolide antibiotics, with the result that many innovative strategies have been developed for assembling the complex architecture of these substances.

Two issues of paramount importance must be faced when considering the synthesis of a complex macrolide. First, there is the systematic creation of multiple chiral centers, some of which may be subject to stereomutation en route to the target. The second challenge is the closure of a seco acid to a highly functionalized, often labile lactone at or near the final stage of the synthesis. Our investigation of synthetic routes to the antibiotic rutamycin B have addressed these dual problems with interesting, and sometimes unexpected results. These studies have served not only as a test-bed for new methodology, but also as a stimulus for the invention of fresh synthetic strategies.

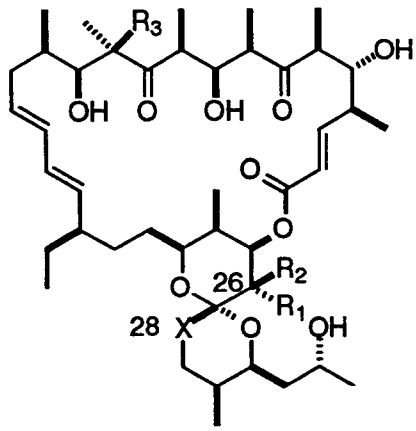
Thompson and co-workers[4] isolated rutamycin A in 1961 from cultures of *Streptomyces griseus*. Its structure and relative stereochemistry were elucidated by X-ray diffraction.[5] The discovery of this natural product was followed by the isolation of a close structural analogue, rutamycin B, from cultures of *Streptomyces aureofaciens* by Keller-Schierlein,[6] who assigned its relative stereostructure by NMR spectroscopy. The assignment of absolute configuration to the rutamycins is due to Evans and co-workers, who completed an asymmetric synthesis of the spiroketal segment **1**.[7]



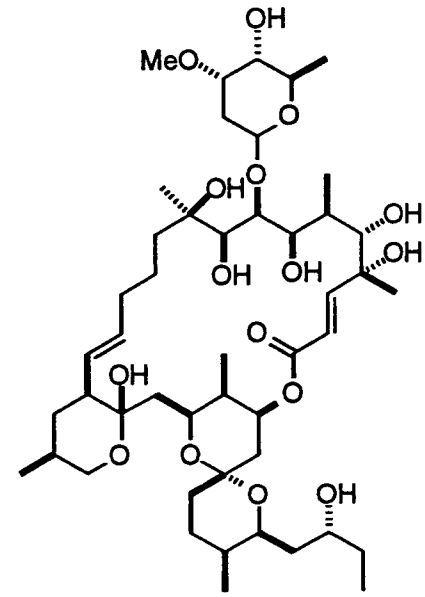
R = OH: Rutamycin A
R = H: Rutamycin B

1

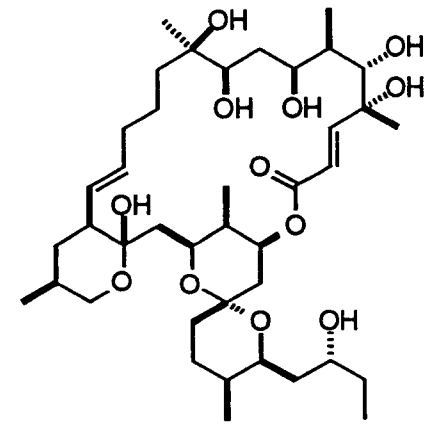
Like other members of the oligomycin[8] family of macrolide antibiotics,[9] rutamycin B possesses a 1,7-dioxaspiro[5.5]undecanyl ring system which is integrated into a 26-membered macrolactone ring biosynthesized largely from propionate units.



Macrolide	R_1	R_2	R_3	X
Oligomycin A	Me	H	OH	CH_2
Oligomycin B	Me	H	OH	CO
Oligomycin C	Me	H	H	CH_2
Oligomycin E	Me	OH	OH	CO
Rutamycin A	H	H	OH	CH_2
Rutamycin B	H	H	H	CH_2



Cytovaricin



Phthoramycin

Within this group, the structure of rutamycin B represents variations in the degree of oxidation at C28 and the substitution pattern at C26. This family of macrolides also

shares important structural similarities with cytovaricin[10] and the closely related macrolide phthoramycin.[11]

Like cytovaricin, the rutamycins are cytotoxic and have potent antifungal activity. Rutamycin B has been shown to prevent oxidative phosphorylation in mitochondria by inhibiting H^+-ATPase.[12,13] In almost every biological system ATP is used either directly or indirectly as an energy source. As most cell types are impermeable to ATP, it must be recycled in each cell. Consequently, every cell type throughout the biological world catalyzes an ATP synthesis-hydrolysis cycle of the

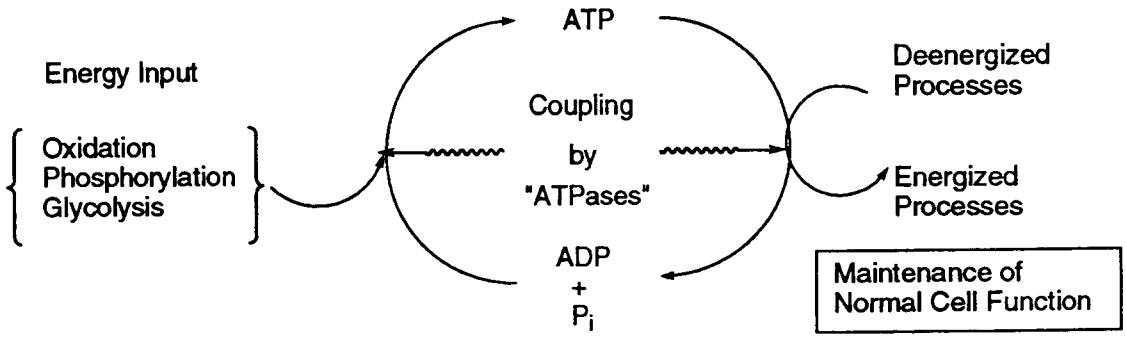


Fig. 1. ATP Synthesis-hydrolysis cycle catalyzed by most living cells

general type depicted in **Figure 1.**[12] This cycle is of critical importance to individual cell function and, therefore, to the function of intact prokaryotic or eukaryotic organisms. As a case in point, a 70 kg adult human while at rest may turn over as much as 50% of his/her body weight in ATP per day, a value that may increase under working conditions to almost 800kg, or roughly one ton. Consequently, the ATP synthesis-hydrolysis cycle of each cell type must be able to respond on demand to energy needs and to operate in a tightly coupled manner. This remarkable feat is accomplished by a diverse variety of 'ATPase' enzymes, of which at least three classes are 'ion motive' ATPases. The mode of action of rutamycin B is believed to involve

termination of the H^+ transferring process in mitochondria in order to prevent oxidative phosphorylation. This results in termination of the cycle and death of the cell, as illustrated in **Figure 2.**[12]

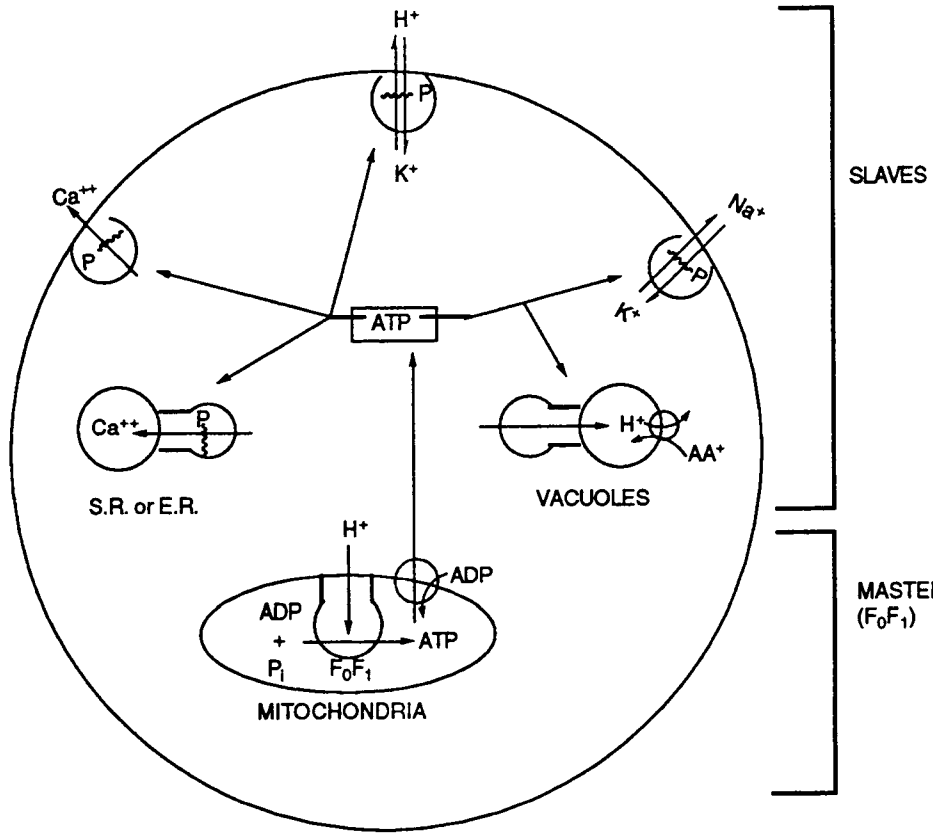
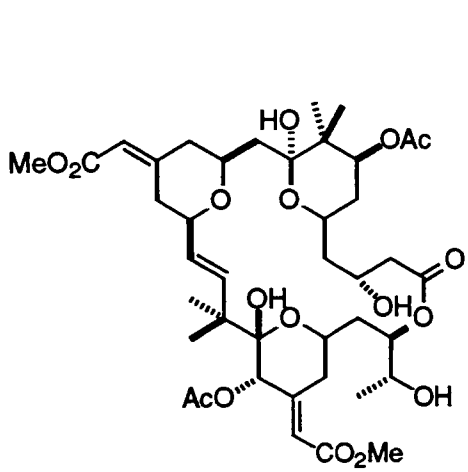


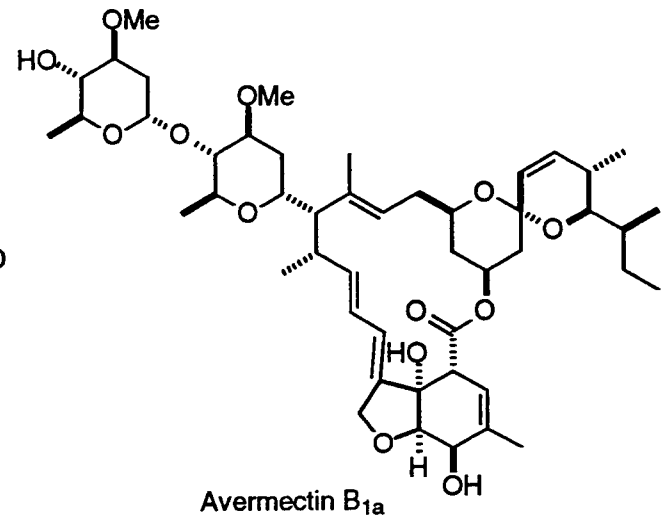
Fig. 2. Coupling relationship between the master 'ion motive' ATPase (F_0F_1) and the slave ATPase

The many important roles that macrolides perform in living systems, from regulatory functions to defense against predators, have led organic chemists to study these complex, naturally occurring structures in great detail. Most recently, these investigations have taken the form of synthetic exercises that have led to some notable achievements in the field, such as the total synthesis of bryostatin by Masamune,[13] the

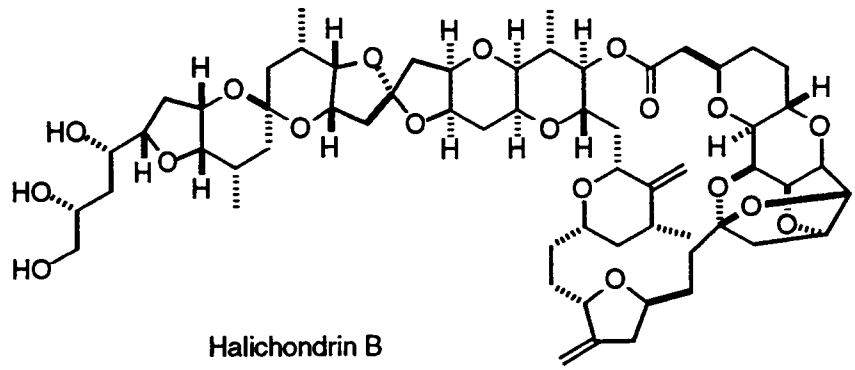
total synthesis of halichondrin B by Kishi,[14] and the total synthesis of avermectin B_{1a} by Hannessian, Ley and White.[15]



Bryostatin 7



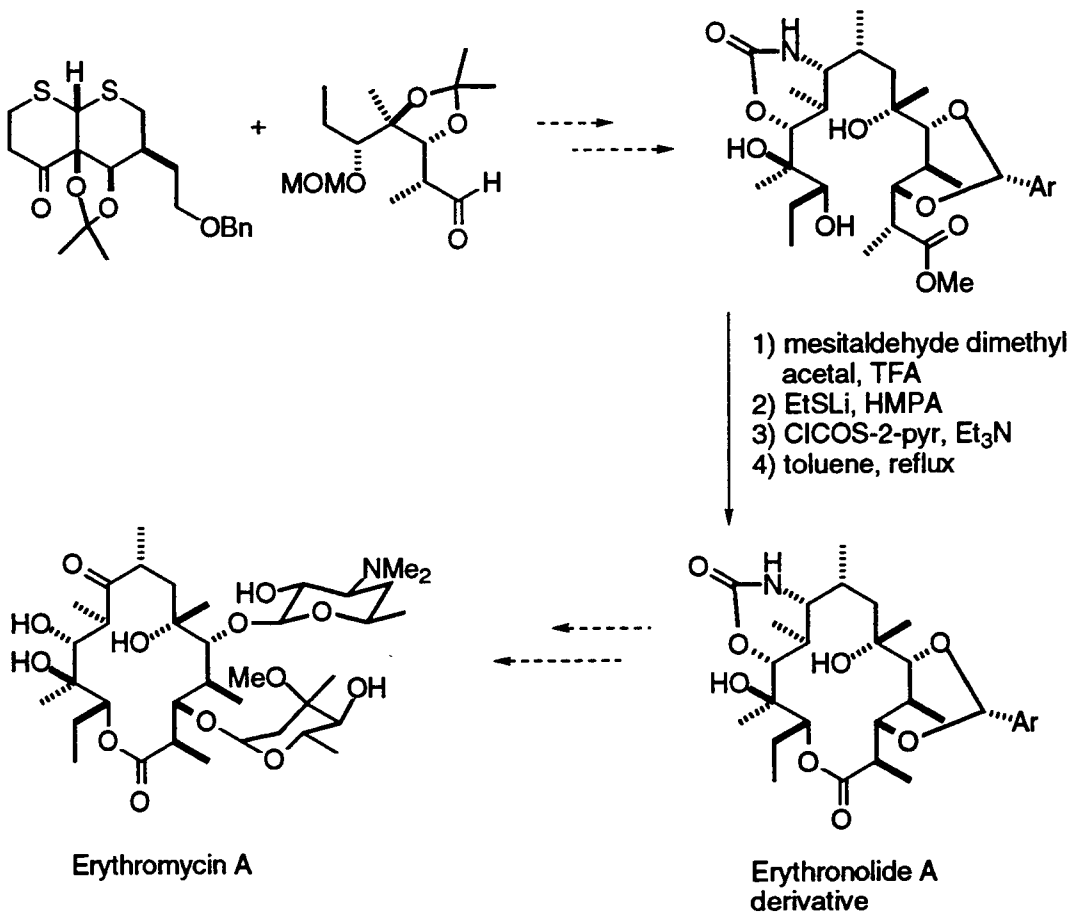
Avermectin B_{1a}



Halichondrin B

Forty years ago, one of the most distinguished organic chemists of this century made an often-quoted remark about the synthesis of erythromycin. The late Professor Woodward[16] stated: "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers...." A comparison of the nine stereocenters of erythromycin with the seventeen stereogenic carbons in rutamycin B puts Woodward's pessimism in a historical context that nicely illustrates the enormous progress made in stereoselective synthesis since his time. As a

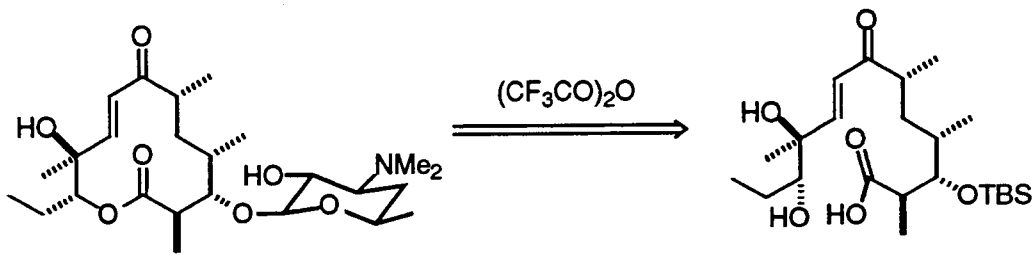
footnote, it should be added that Woodward achieved a brilliant synthesis of the "hopelessly complex" erythromycin shortly before his death in 1981 (**Scheme 1**).[17]



Scheme 1

The first synthesis of a polyoxomacrolide[18] antibiotic, methymycin, was accomplished in 1975 by Masamune and co-workers.[19] This was a significant event, as it catalyzed a vigorous level of subsequent activity in the area of macrolide synthesis. Extensive efforts in this arena have brought about new concepts, strategies, and methods for the construction of these structurally unique macrocyclic systems. Above all, the synthesis of methymycin demonstrated that medium- and large-ring lactones could be obtained from their corresponding seco acids, e.g. **2** (**Scheme 2**).

This was contrary to the then prevailing view, based mainly on Stoll's classic work,[20] which held that such intramolecular cyclization was inherently disfavored.



Methymycin

2

Scheme 2

The methymycin synthesis,[19] however, disclosed a fundamental problem associated with macrolide synthesis. Creation of the many chiral centers arrayed along the open-chain (acyclic) seco acid demanded a level of stereocontral that was unavailable at the time. Synthetic strategies designed to overcome this problem have developed primarily along three lines:[21]

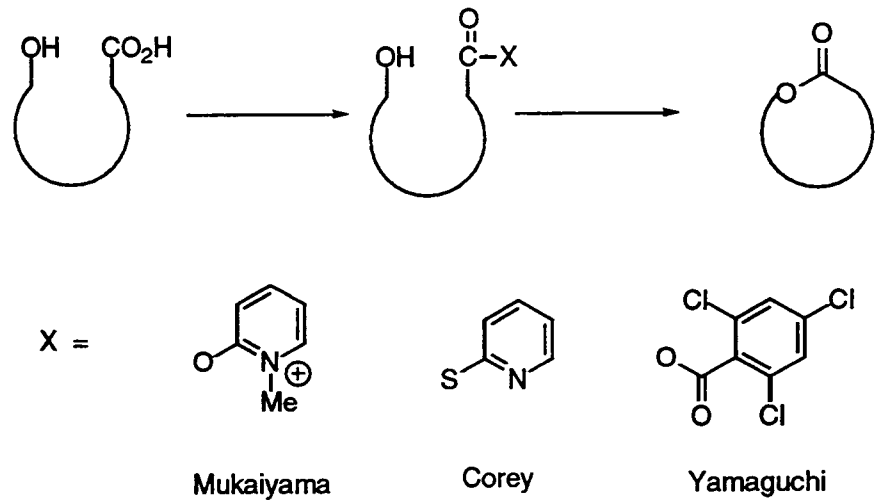
1. The Ring Approach. This traditional but still effective method makes use of the clearly defined *cis* and *trans* relationships of substituents on a cyclic system, often a five- or six-membered ring, that is amenable to stereocontrol. Ring cleavage transfers this stereochemistry to the resulting acyclic system.

2. The Carbohydrate Approach. The inherent stereochemistry of monosaccharides, such as glucose, is transferred to segments of macrolides through appropriate chemical operations. Thus, the many readily available monosaccharides conveniently serve as a "chiral pool".

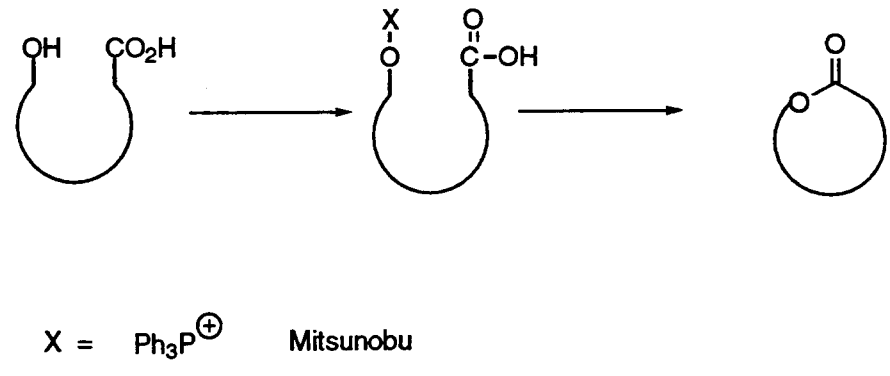
3. The Acyclic Approach. Chiral, open-chain segments of macrolides are stereoselectively constructed from acyclic precursors. This approach, which can be iterative, is a relatively new development in synthesis but has shown great promise.

The advantage of this last approach is obvious. Repetition of a synthetic operation, if executed with high diastereoselection (and enantioselection) at each step, would greatly simplify the synthetic design and minimize the number of steps leading to a seco acid. The challenge associated with acyclic stereoselection is formidable, but this technique has been investigated intensively in recent years and many new methods for the elaboration of chiral centers have been invented using this principle. This thesis will describe a convergent, acyclic approach toward the macrolide rutamycin B that will illustrate some of these methods.

1. Carboxyl Activation:

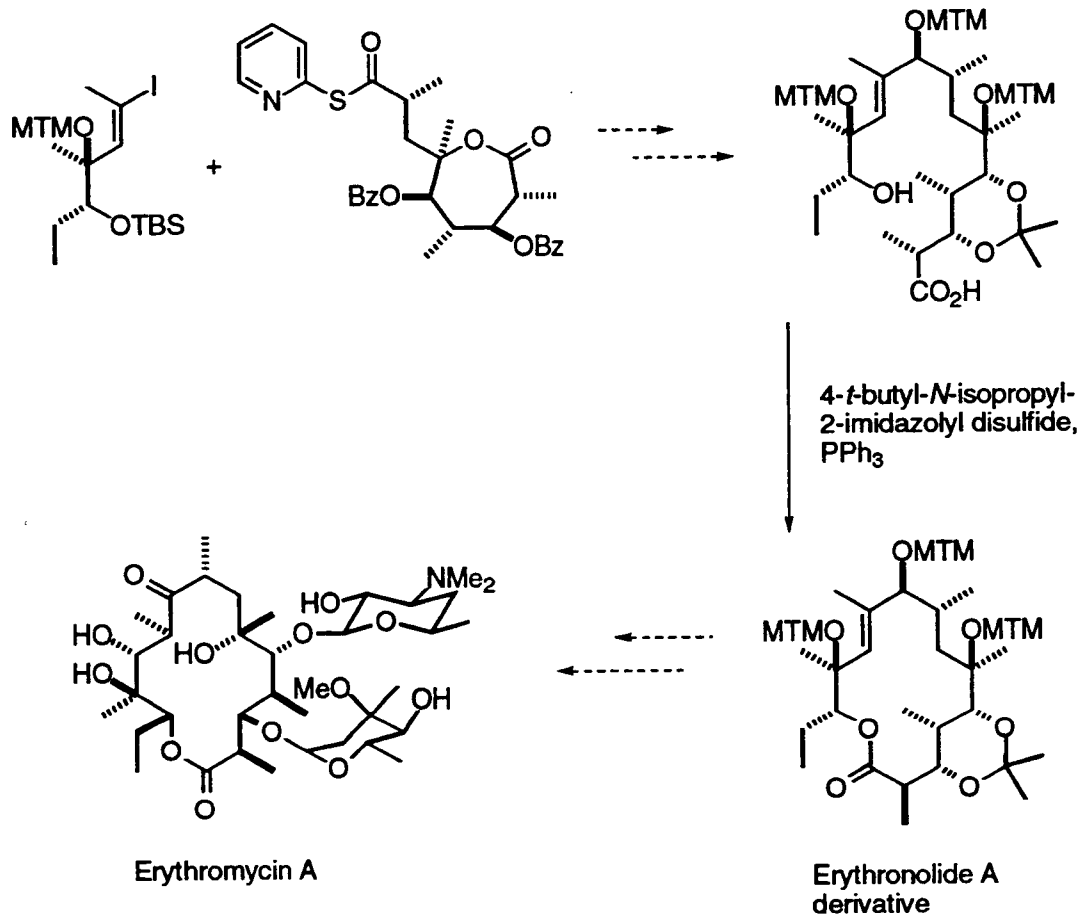


2. Hydroxyl Activation:



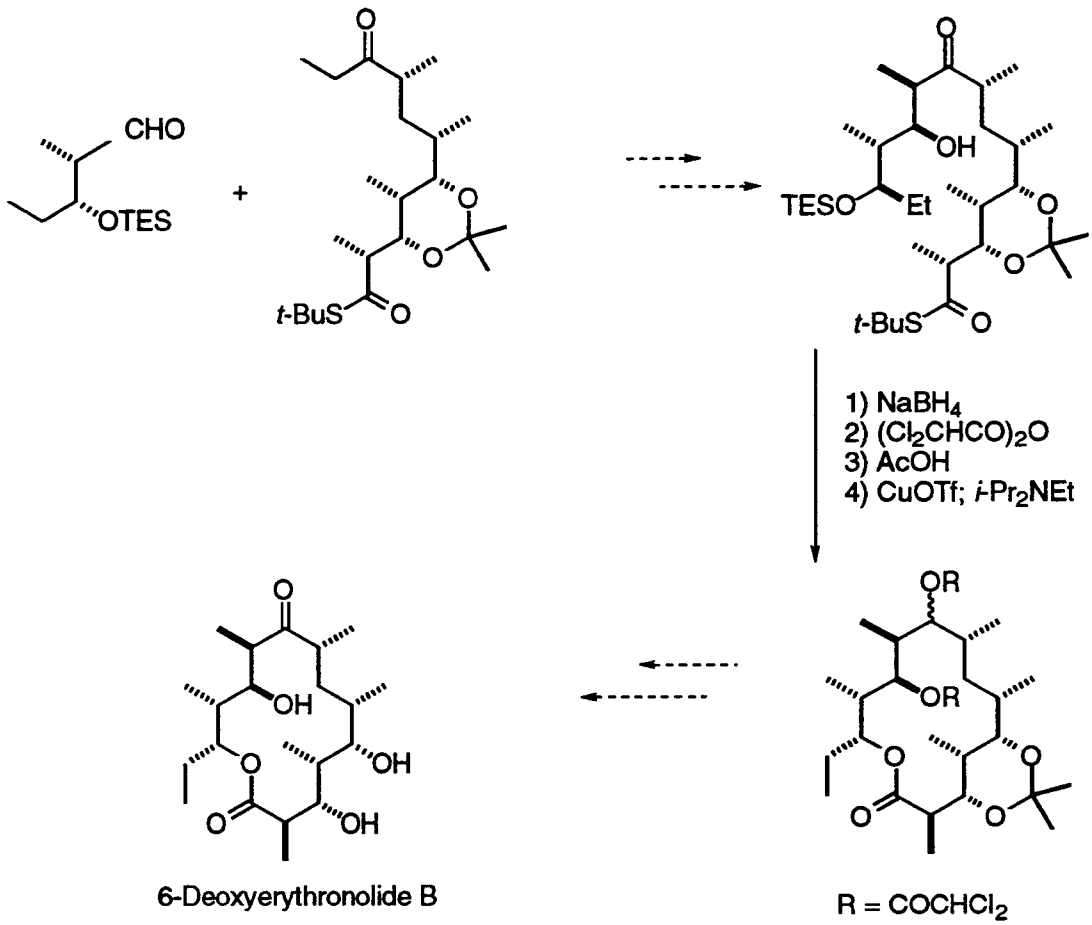
Scheme 3

Retrosynthetic analysis of rutamycin B suggests several plausible disconnections of the macrocycle. Two of these are at the bond between C17-C18 and at the lactone C-OR bond. This analysis permits two possible modes of ring closure involving either macrolactonization or connection of two (*E*)-alkene units to form the *trans*, *trans*-conjugated diene system. Conventionally, macrolide syntheses are completed by closing the ring from a seco hydroxy acid in the final step, as in the Evans' synthesis of rutamycin B.[19] The alternative approach to synthesis of rutamycin



Scheme 4

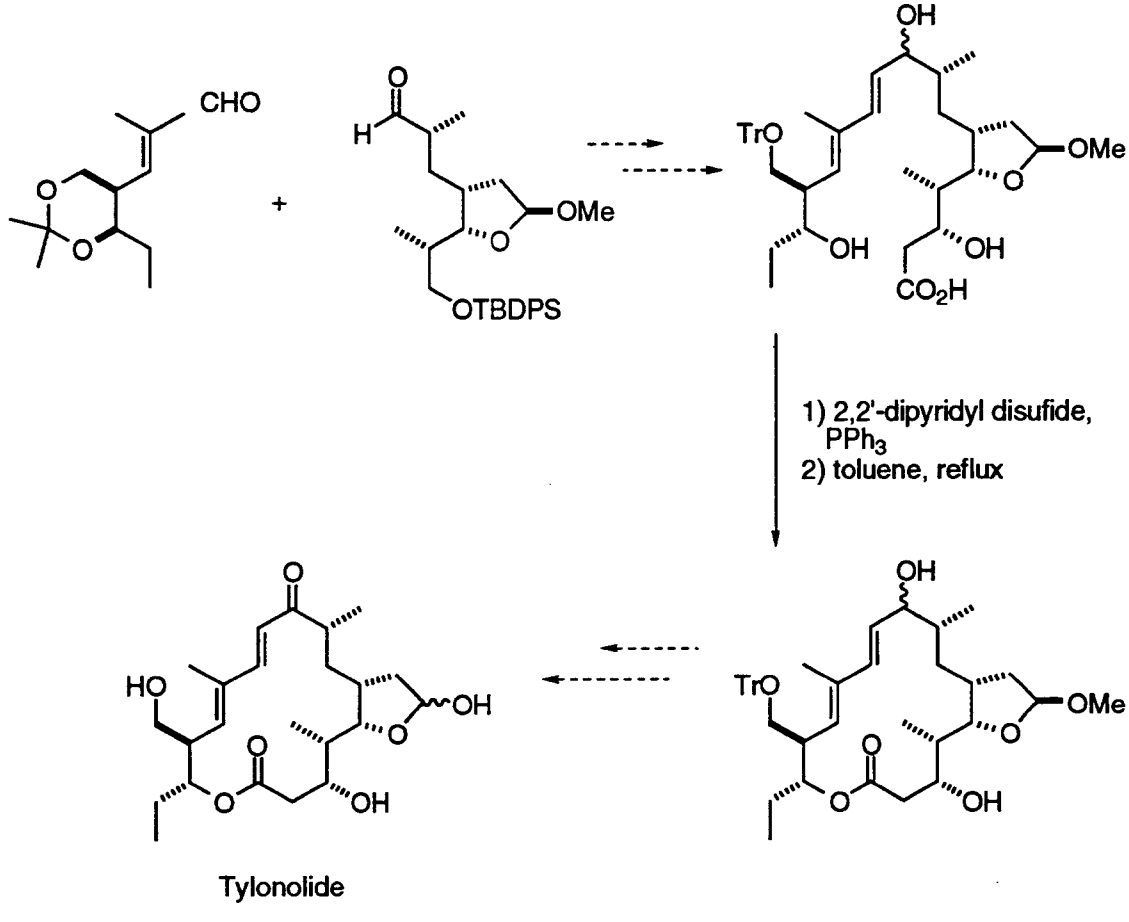
B, in which macrocyclization is envisioned by means of a diene construction, offers a novel but largely untested stratagem. Fortunately, many reagents based on organopalladium, organocopper and organotin species, to name a few, have become available to facilitate synthesis of 1,3-dienes. This approach to rutamycin B would provide a rigorous test of this methodology in an exceedingly complex venue.



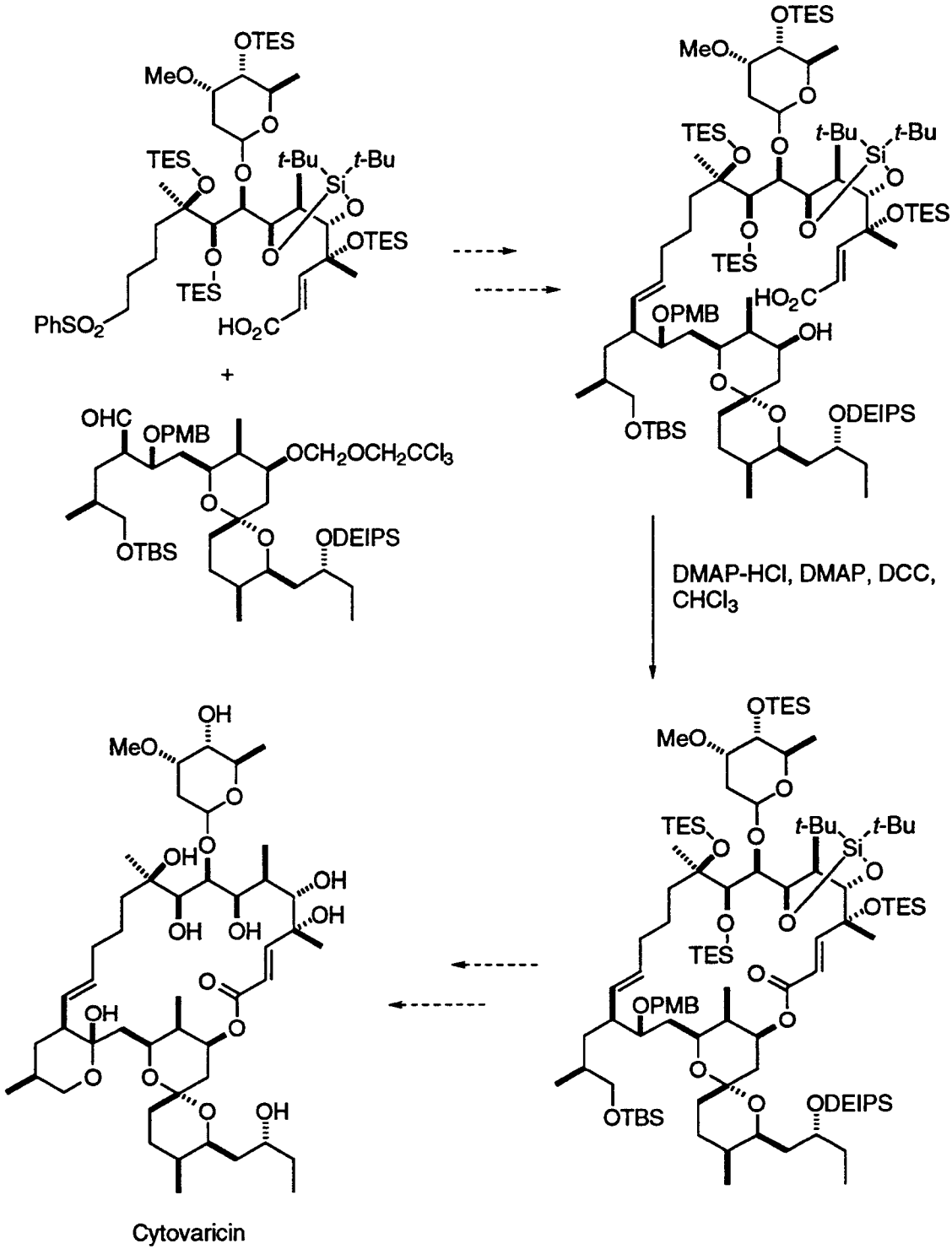
Scheme 5

As stated above, Masamune's[19] synthesis of methymycin first established the viability of the "seco acid" approach to macrolides. In the intervening years, macrolactonization methods[9] have greatly increased in scope and efficiency. Of the two most frequently employed techniques for macrolactone synthesis from ω-hydroxy-

carboxylic acids (**Scheme 3**), that invoking carboxyl activation is by far the most common.[18c,23,24,25] The Corey (**Scheme 4**),[26] Masamune (**Scheme 5**)[27] and Woodward (**Scheme 1**)[17] syntheses of erythronolide, Grieco's synthesis of tylonolide (**Scheme 6**),[28] and Evans' synthesis of cytovaricin (**Scheme 7**)[29] all exemplify this method. Hydroxyl activation, as in lactone synthesis based on the Mitsunobu reaction,[30] is the other more limited alternative. Few general techniques have been reported in the past three decades that have been able to increase the efficiency of macrolactone synthesis by this latter approach.

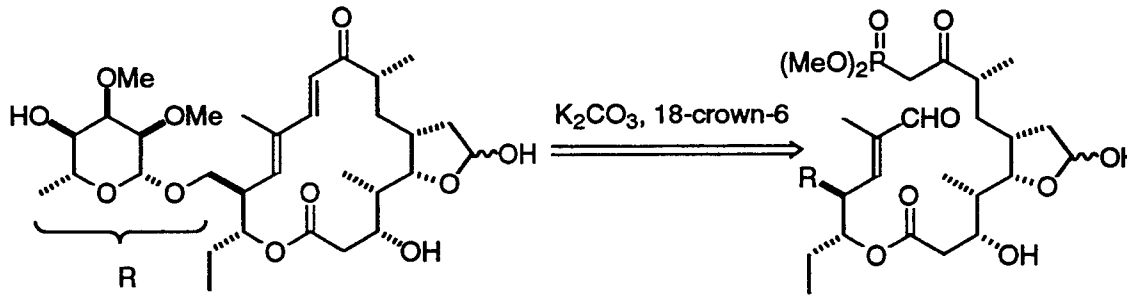


Scheme 6


OTES
MeO
TES
t-Bu
t-Bu
Si
OTES
TES
PhSO2
HO2C
+
OHC
OPMB
OCH2OCH2CCl3
OTBS
ODEIPS
OTES
MeO
TES
t-Bu
t-Bu
Si
OTES
TES
HO2C
OPMB
OH
OTBS
ODEIPS
DMAP-HCl, DMAP, DCC,
CHCl3
OH
MeO
OH
OH
OH
OH
OH
OH
OTES
MeO
TES
t-Bu
t-Bu
Si
OTES
TES
OPMB
OTBS
ODEIPS
Cytovaricin

Scheme 7

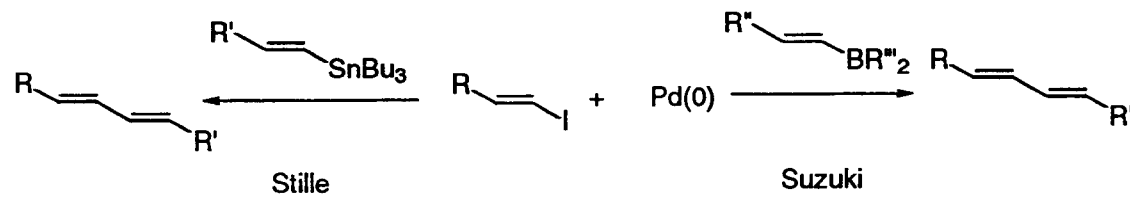
By contrast, many new methods for constructing conjugated diene systems have been devised that are both high yielding and broadly applicable. One of them was illustrated in Nicolaou's total synthesis of *O*-mycinosyltylonolide,[31] where an intramolecular Wadsworth-Emmons reaction[32] was used to produce a *trans,trans*-diene and close the ring (**Scheme 8**). Recently, much attention has been devoted to the



O-Mycinosyltylonolide

Scheme 8

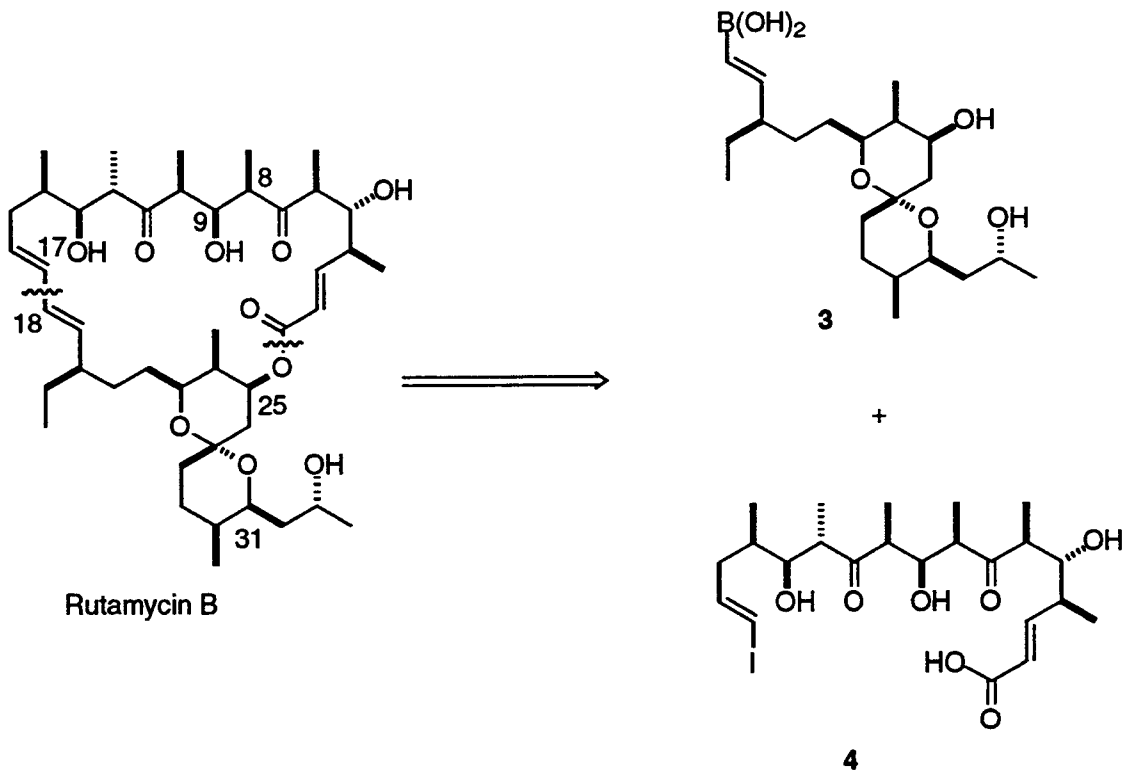
synthesis of conjugated dienes using the palladium(0)-catalyzed coupling of vinyl iodides with either vinylstannanes (Stille)[33] or vinyl boronates (Suzuki),[34] and it has been demonstrated that these processes can succeed with highly functionalized coupling partners (**Scheme 9**).



Scheme 9

Evans' strategy for the synthesis of rutamycin B[22] involved initial construction of the diene unit through a palladium(0)-catalyzed reaction of the vinyl iodide **4** with the vinyl boronate **3** (Suzuki coupling). The macrocycle was completed by connecting

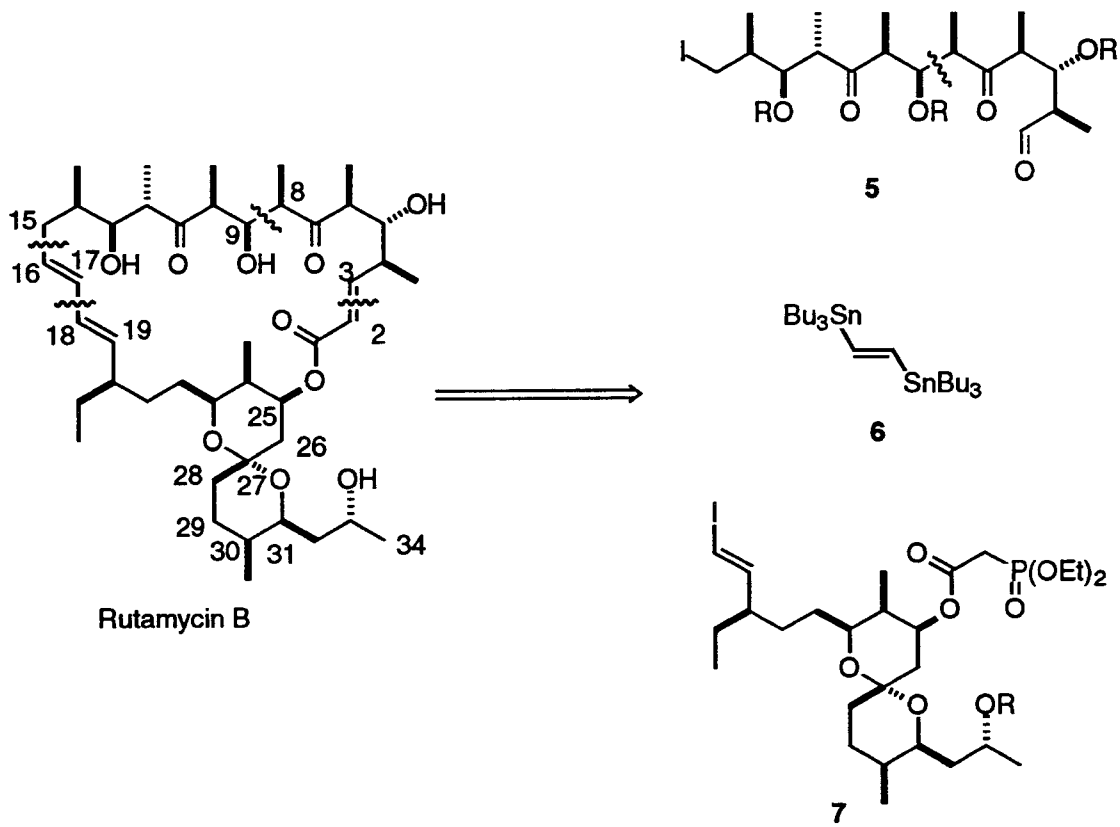
the secondary alcohol at C25 with the carboxyl moiety using the macrolactonization technique of Yonemitsu.[35] The latter is a modification of the Yamaguchi[25] macrolactonization method (**Scheme 10**).



Scheme 10

As pointed out above, our goal was not only to complete a total synthesis of rutamycin B, but also to use the route for the exploration of new synthetic strategies and as a test-bed for new methodology. Bypassing the more conventional approach in which lactonization is the ring forming step in macrolide synthesis, we chose to connect the diene unit of rutamycin B as the means for effecting closure of the macrolide. Our initial synthetic plan shown in **Scheme 11** divides the synthesis of rutamycin B into construction of two segments, the polypropionate fragment **5** and the spiroketal **7**. This retrosynthetic analysis arises through disconnection of the C15-C16, C17-C18 and C2-C3 bonds. It was originally intended that the C16-C17 unit **6** would

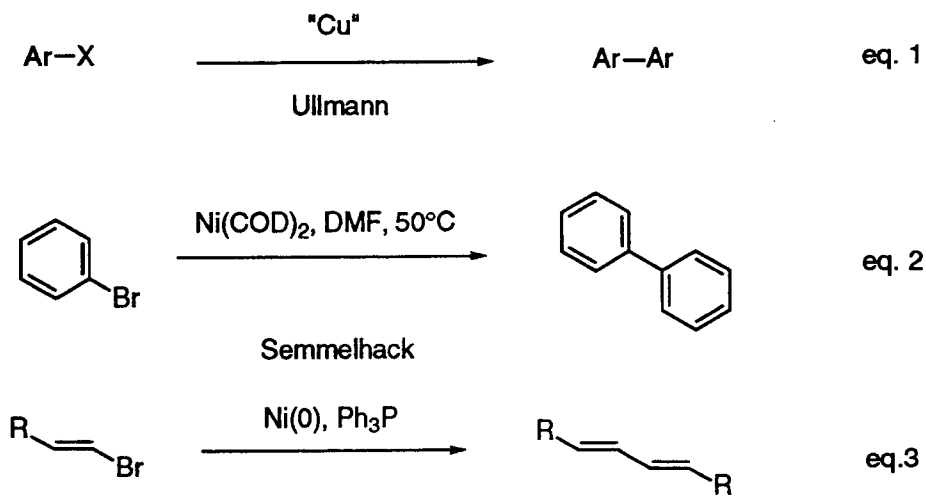
be inserted at the final step via a Stille[33] coupling. However, as events unfolded, we found that a plan incorporating the bis(stannyl)ethylene moiety in this manner was impractical. Furthermore, the presence of many functional groups in our synthesized precursors frustrated attempts to introduce the vinylstannane moiety early in the synthesis. These obstacles, ultimately led to a new synthetic strategy based on the conjugated diene construction mentioned above.



Scheme 11

The formation of a C-C bond by coupling sp^2 carbons owes its early development to studies carried out on the synthesis of biaryl systems. The most extensively exploited methodology for the elaboration of symmetrical biaryls is the classical Ullmann reaction,[36] usually defined as the copper-mediated self-coupling of an aryl halide (**Equation 1**). A major advance in this area was made in the early

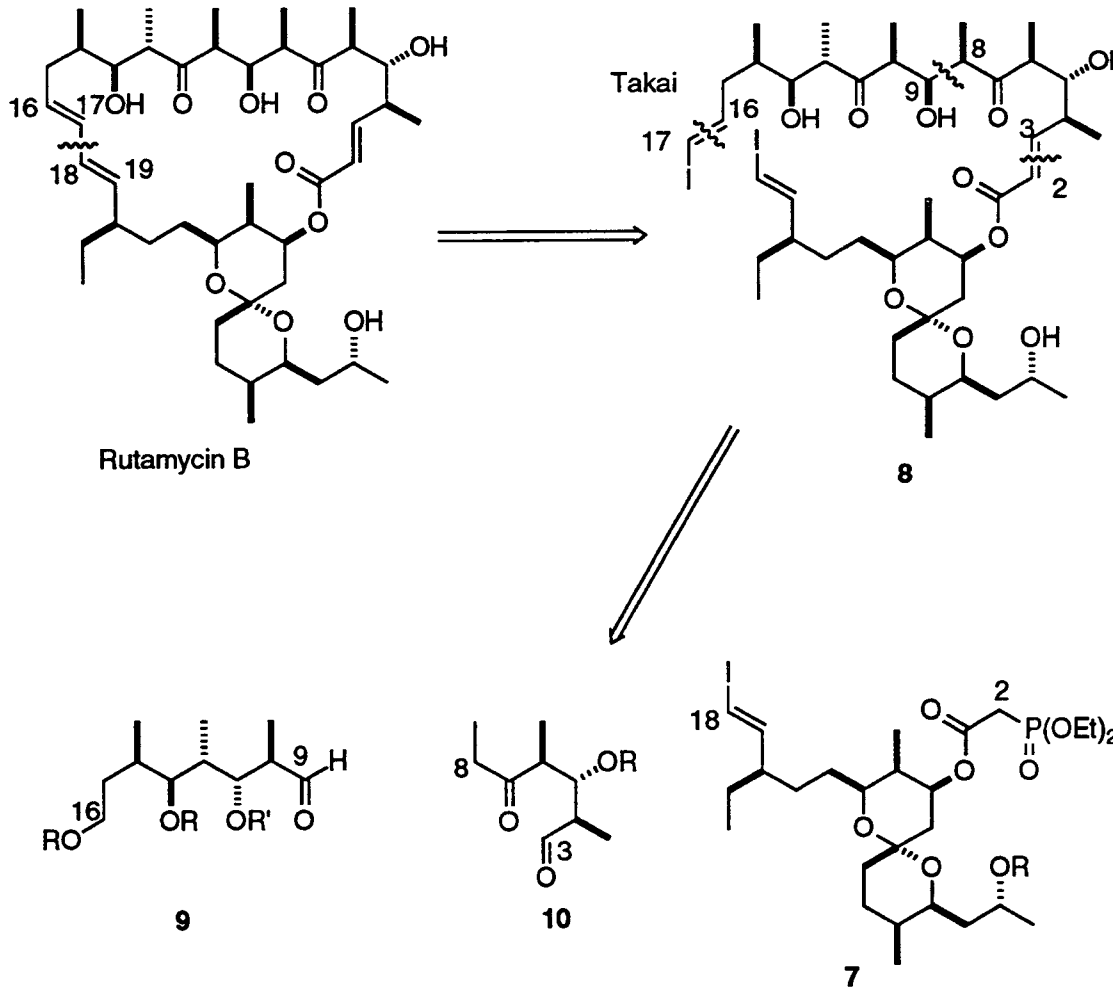
1970s, when Semmelhack and co-workers discovered that a nickel(0) reagent could be used in place of elemental copper (**Equation 2**).[37] Later, they used the same nickel(0) species in the presence of triphenylphosphine to form a *trans,trans*-diene through direct dimerization of an alkenyl halide (**Equation 3**)[38] (**Scheme 12**).



Scheme 12

Many improvements have been made since these original reports, including the introduction of more convenient reagents such as triphenyl-[39] and trialkylphosphinenickel(0) species[40] as well as a nickel(0) reagent prepared by reduction of nickel(II) chloride using zinc in the presence of potassium iodide and thiourea.[41] However, this nickel(0)-mediated *trans,trans*-1,3-diene construction has never been attempted in the context of a macrolide synthesis.

The synthetic plan in final form is illustrated in **Scheme 13.** It hinges on the initial connection of the spiroketal **7** with aldehyde **10** through a Wadsworth-Emmons olefination,[32] then on aldol coupling of the resulting ethyl ketone via its titanium enolate[42] with the aldehyde **9**. A Takai reaction[43] would be used to install the vinyl iodide at C16, and an ensuing ring closure with a nickel(0) reagent[44] would give rutamycin B.



Scheme 13

Both Evans' synthesis of rutamycin B (**Scheme 10**) and our own retrosynthetic plan (**Scheme 13**), make use of a 1,7-dioxaspiro[5.5]undecane moiety as a key building block. Our putative spiroketal **7** harbors eight of the seventeen stereogenic centers of the natural product, and therefore careful attention must be paid to the stereocontrolled construction of this complex intermediate. Prior to the discussion of its preparation, it is appropriate to first review the chemical properties of the 1,7-dioxaspiro[5.5]undecane ring system and how they can be used advantageously.

Spiroketals[45] enjoy widespread occurrence as substructures of natural substances from many sources, including insects, microbes, plants, fungi, and marine

organisms. The increasing pharmacological importance of compounds containing spiroketal assemblies has triggered intense interest in their synthesis. 1,7-Dioxaspiro[5.5]undecanes have been particularly well studied and are the most easily analyzed spiroketals for their preferred conformations. Where there is symmetrical substitution, there are four possible all-chair conformers of this system corresponding to

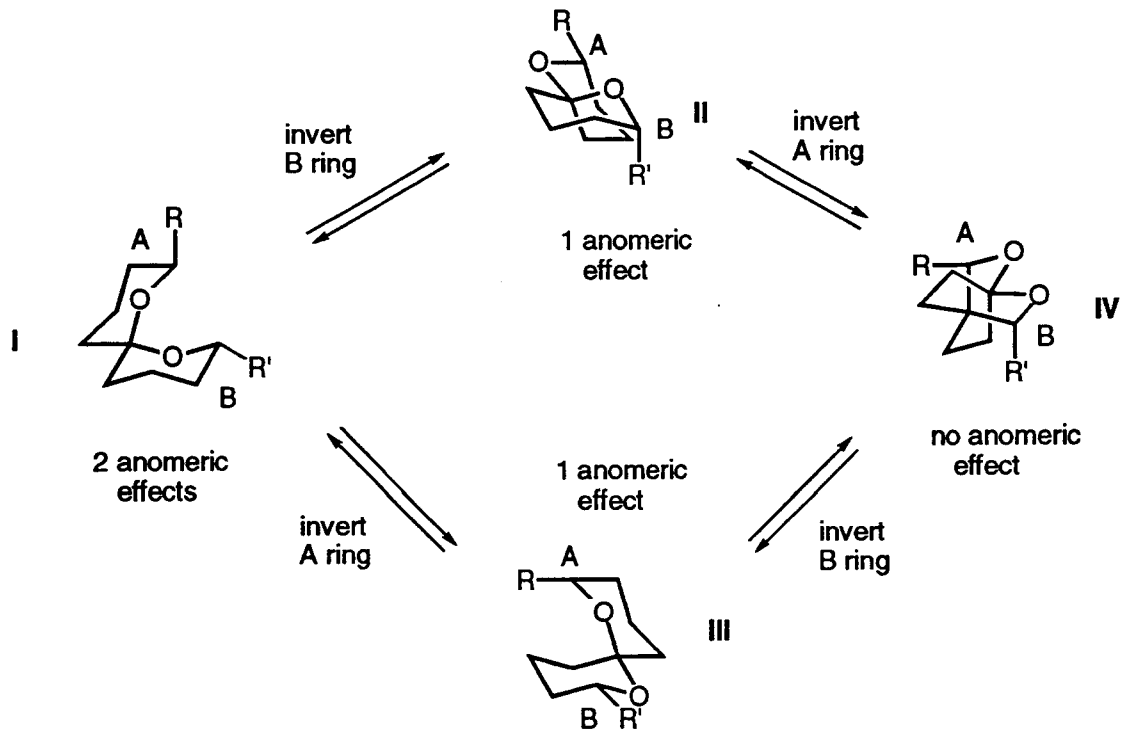
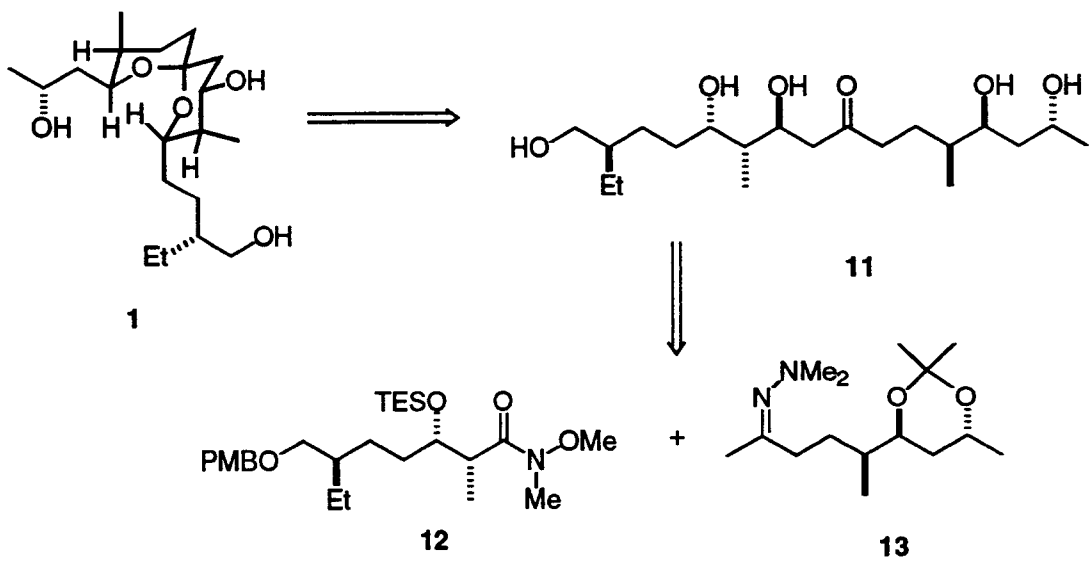


Fig. 3. All-chair conformations of 1,7-dioxaspiro[5.5]undecanes

independent inversion of each six-membered ring, as shown in **Figure 3.**[46] In the fully unsubstituted case, it has been shown that **I** is the most stable conformer of the dioxaspiro[5.5]undecane ring system. This has been ascribed to maximization of a thermodynamic anomeric effect,[47] resulting from the preference for a carbon-oxygen bond at the 2-position of a tetrahydropyran ring to reside in an axial orientation. The anomeric effect is known to have a profound influence on the conformation of

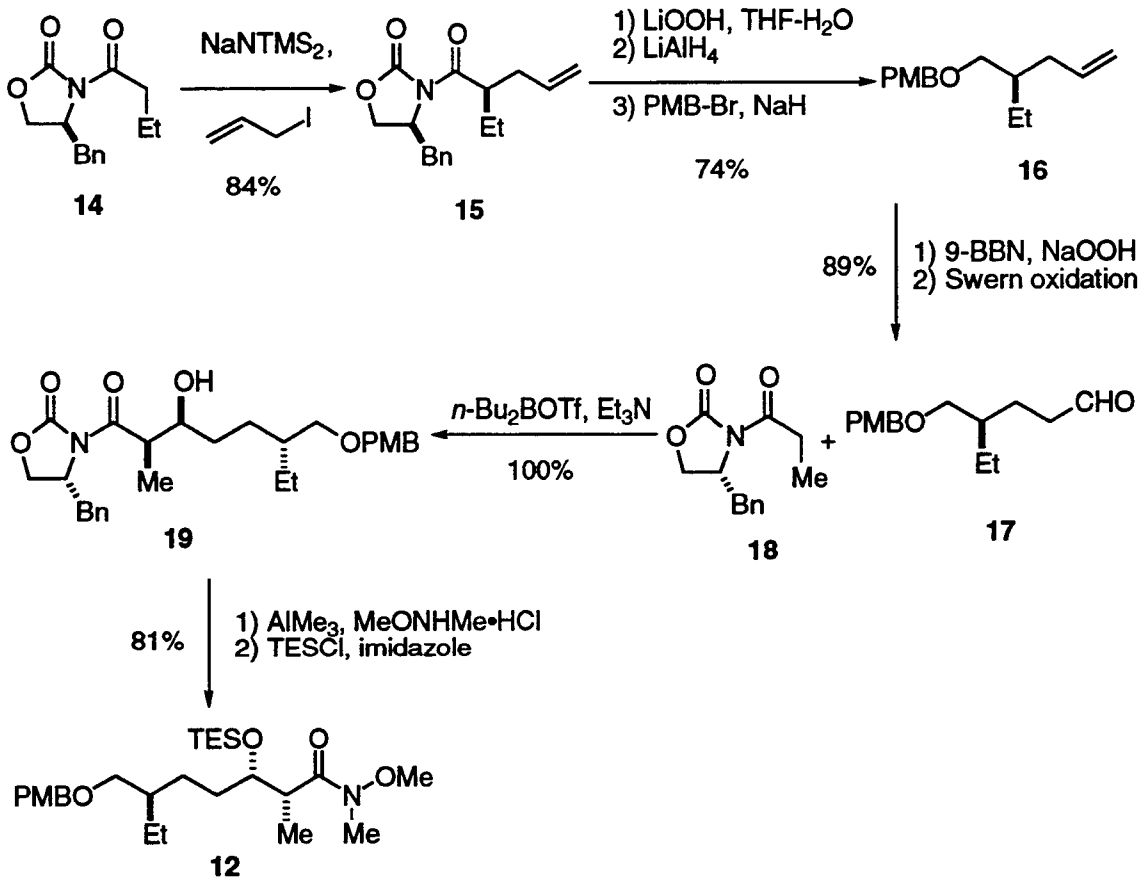
spiroketals. In the case of spiro[5.5] systems, the bisaxial arrangement of spiro C-O bonds is commonly observed in both saturated and unsaturated rings, a structural feature supported by the many synthetic compounds containing this ring system that have been characterized spectroscopically or crystallographically.[45,46,47]

Early work on the synthesis of spiroketals embedded in naturally occurring structures proceeded on the assumption that the configuration of the spiro carbon corresponded to the thermodynamically most stable form.[46,47] It was therefore presumed that acid-promoted spirocyclization of a dihydroxy ketone precursor should result in the desired configuration at the spiro center if the substitution pattern closely mimicked that of the natural product. This was indeed found to be a valid assumption. In fact, nowhere is the preference for axial C-O bonds in spirocyclic ketals more apparent than in the acid-catalyzed closure of a dihydroxy ketone to form a dioxaspiro[5.5]undecane. Our synthetic strategy as well as that of Evans takes advantage of this inherent thermodynamic bias in the formation of the 1,7-dioxaspiro[5.5]undecanyl segment of rutamycin B.



Scheme 14

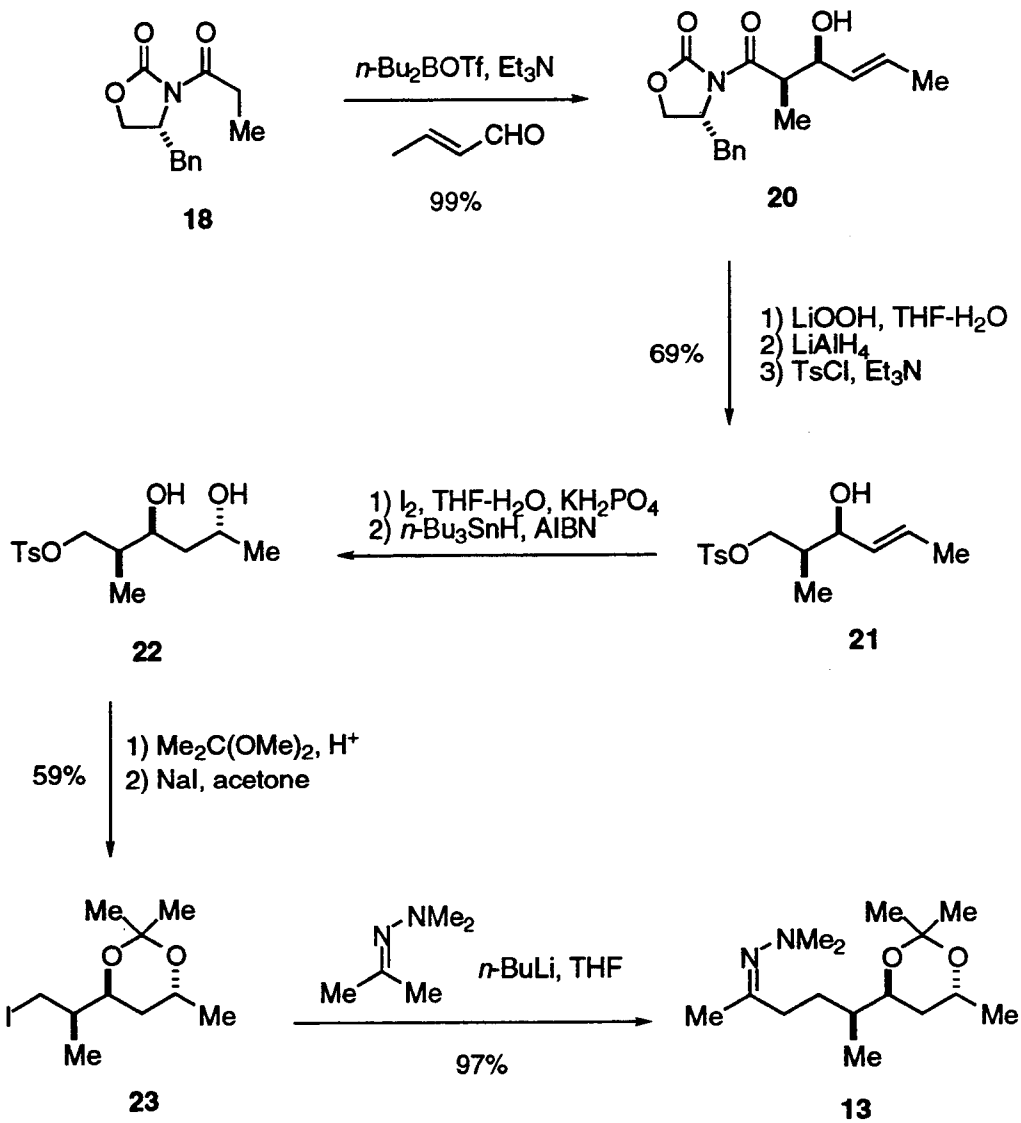
Evans' synthesis of the 1,7-dioxaspiro[5.5]undecanyl segment **1**[7] of rutamycin B (**Scheme 14**) employed, as one of the key steps, acylation of the metalated hydrazone **13** with the N-methoxy-N-methyl amide **12**. All of the absolute stereochemical relationships in **12** and **13** were established through alkylation and aldol bond constructions using N-acyloxazolidinone chiral auxiliaries. The equatorial alcohol of the spiroketal **1** was obtained through a samarium-catalyzed Meerwein-Ponndorf-Verley reduction.[48] Subsequent acid-catalyzed spirocyclization proceeded smoothly along with deprotection.



Scheme 15

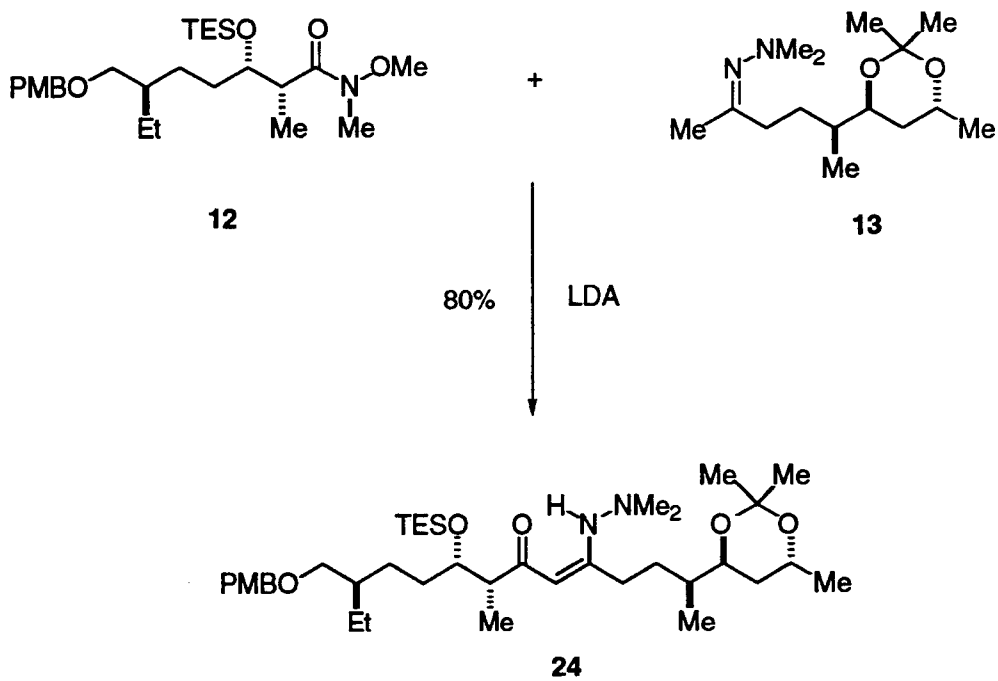
Evans' synthesis of amide **12** began with the acyloxazolidinone **14**, which had been prepared previously.[49] Alkylation of the sodium enolate derived from **14** with

allyl iodide afforded **15**, which was subjected to saponification and reduction. Protection of the resulting alcohol as the *p*-methoxybenzyl ether **16**, followed by hydroboration and Swern oxidation provided aldehyde **17**, which was subsequently employed in a boron-mediated aldol reaction with the N-propionyloxazolidinone **18** to afford the β-hydroxy imide **19**. Transamination of **19** and silylation of the resulting β-hydroxy imide gave the desired amide **12** in good yield (**Scheme 15**).



Scheme 16

Synthesis of the hydrazone **13** began with an asymmetric aldol addition of the boron enolate derived from N-propionyloxazolidinone **18** to crotonaldehyde. This provided imide **20** with excellent stereoselectivity. Subsequent saponification, reduction, and monotosylation afforded allylic alcohol **21**. Chamberlin's iodohydroxylation procedure,[50] followed by reductive removal of the iodide, yielded *anti* 1,3-diol **22**, which after ketalization gave acetonide **23** as a single diastereomer. The synthesis of **13** was completed by conversion of tosylate **23** to the corresponding iodide, which was treated with the lithio derivative of acetone dimethylhydrazone to furnish the desired hydrazone (**Scheme 16**).

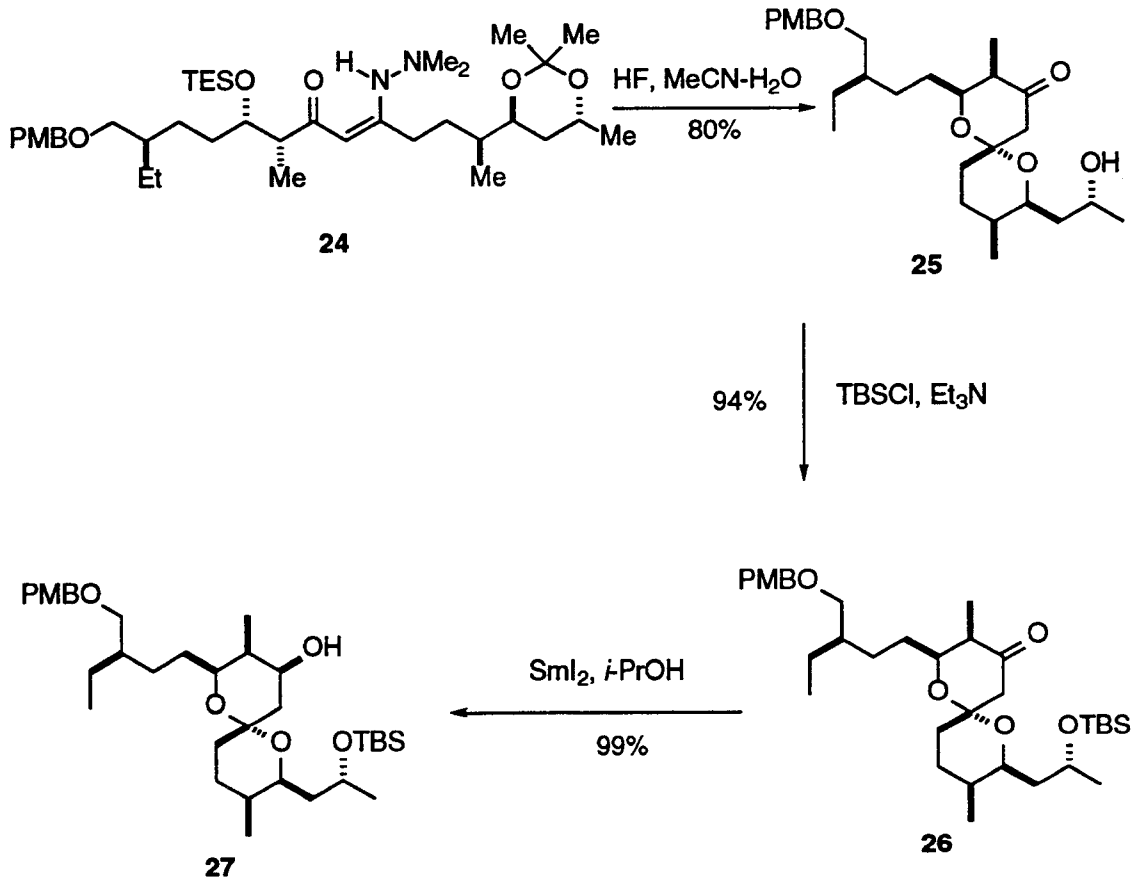


Scheme 17

The two subunits **12** and **13** were linked through an acylation process. The metalated hydrazone was added to amide **12** to yield the vinylogous amide **24**. Evans found that the correct choice of solvent and base was critical to the success of this reaction. The use of lithium diisopropylamide obtained from *n*-butyllithium in hexane

resulted in incomplete deprotonation of **13**, whereas lithium diisopropylamide prepared by addition of methyllithium in ether to a solution of diisopropylamine in tetrahydrofuran gave satisfactory results (**Scheme 17**).

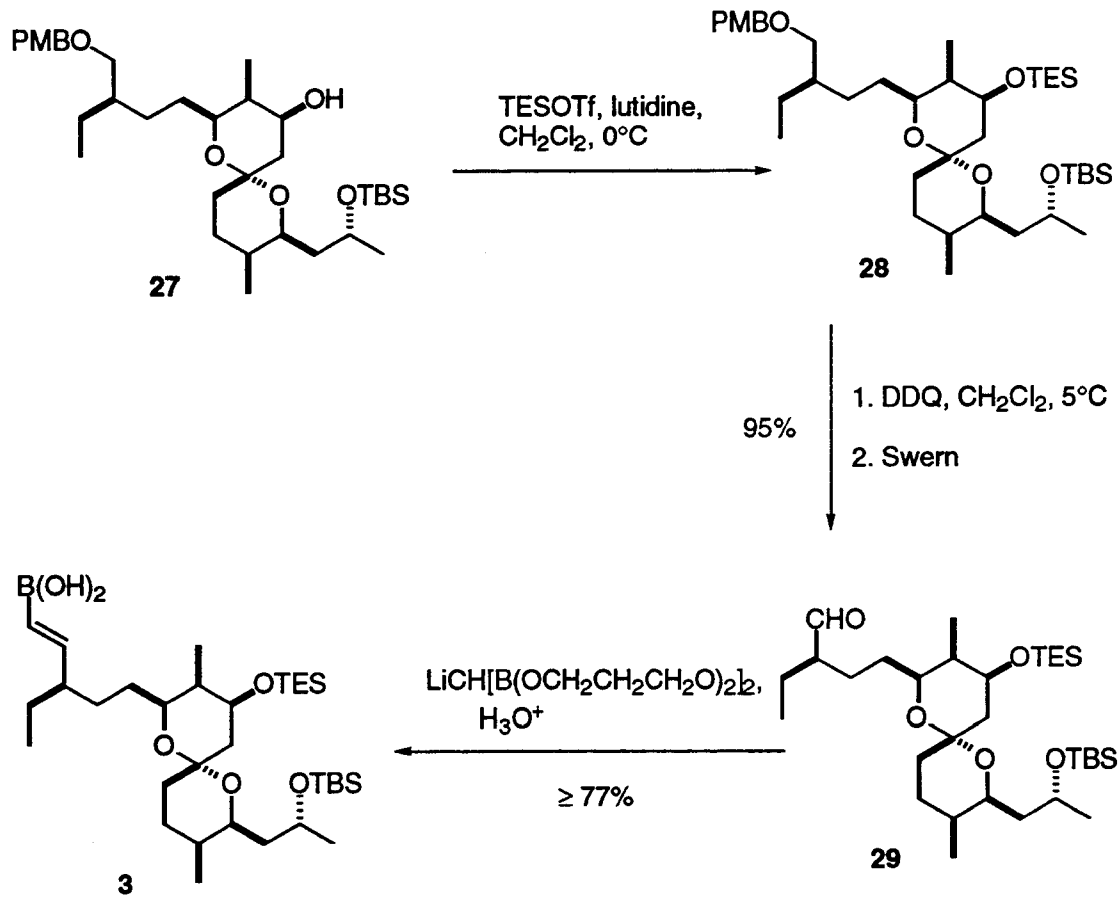
Complete deprotection of **24** and spiroketalization was carried out under mild acidic conditions. The resulting secondary alcohol **25** was protected as its *tert*-butyldimethylsilyl ether **26**, and the ketone was reduced to the equatorial alcohol **27** with samarium diiodide in isopropanol (**Scheme 18**).



Scheme 18

The spiroketal **3** was obtained from hydroxy ketal **27** through a four-step sequence initiated by silylation of the equatorial alcohol to give the protected ketal **28**. Subsequent removal of the *p*-methoxybenzyl group and Swern oxidation of the derived

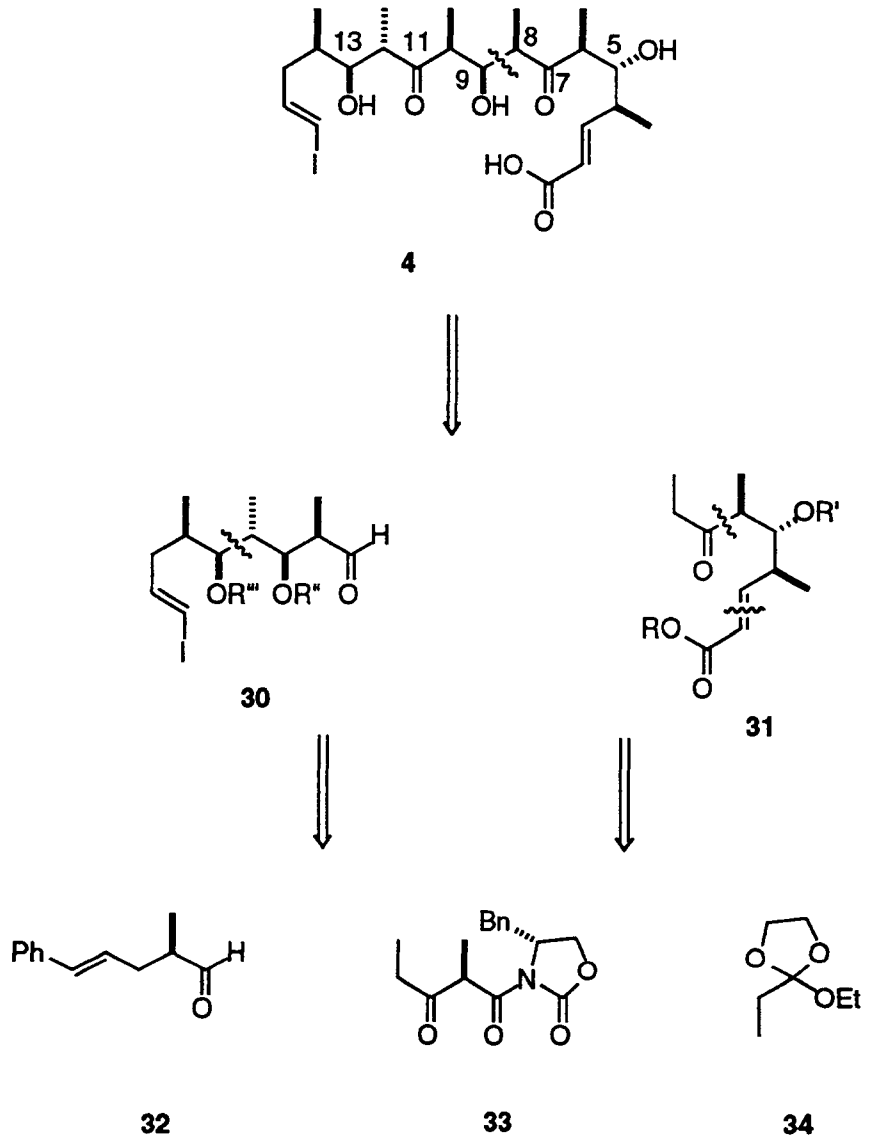
primary alcohol afforded aldehyde **29**, which was homologated to the vinylboronic acid **3** using Matteson's procedure[51] (**Scheme 19**).



Scheme 19

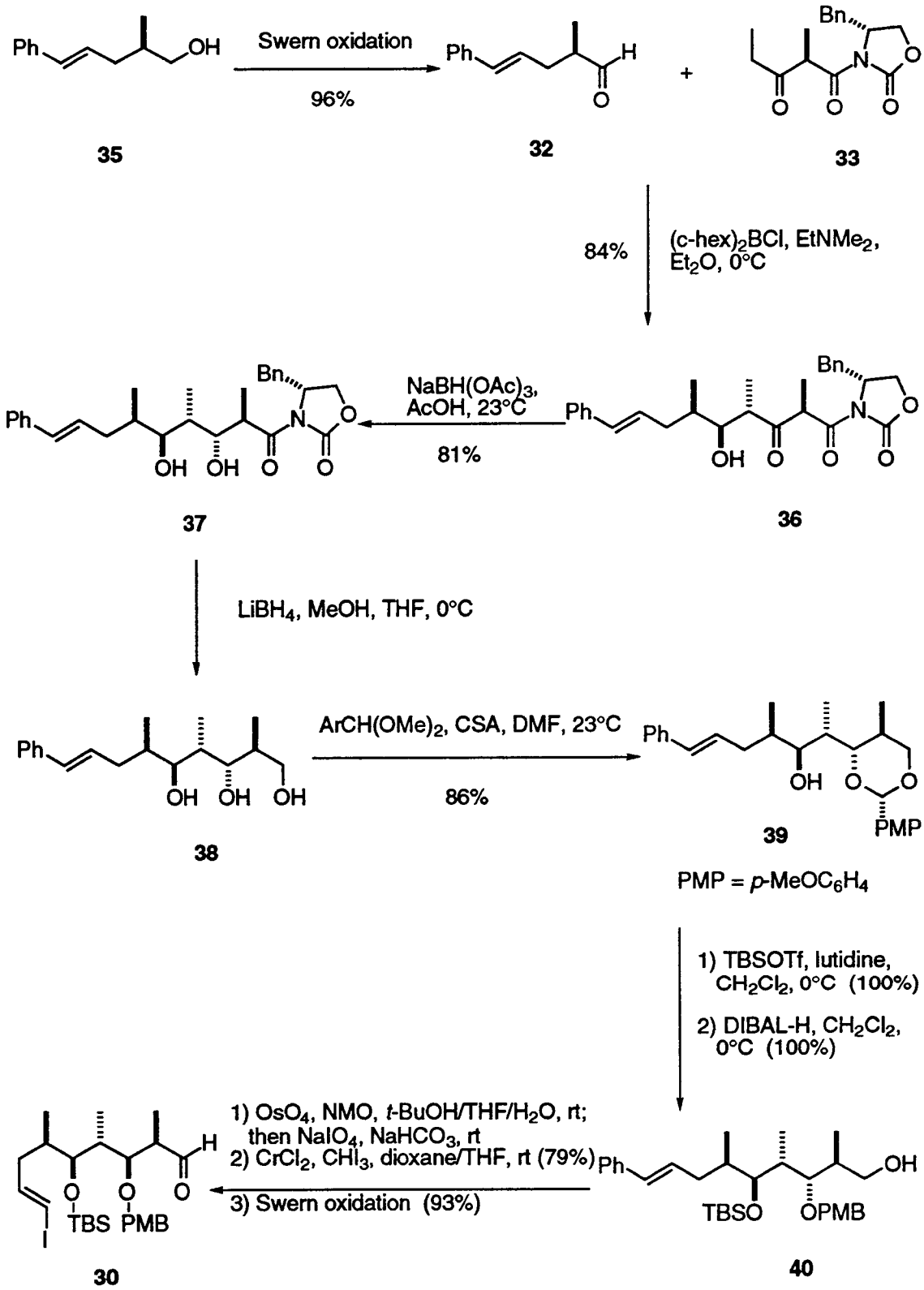
Analysis of the polypropionate segment **4** of rutamycin B, particularly the presence of carbonyl groups at C7 and C11, and hydroxyl functions at C5, C9, and C13 in **4**, suggested that this linear subunit could be considered the product of four aldol bond connections. Each of these projected reactions is a *syn* aldol construction, and each reaction is double-stereodifferentiating in nature. Precedence for the aldol linkage of C8 with C9 in *syn* fashion had been established with achiral aldehydes for titanium ketone enolates by Evans[52] and for boron enolates by Paterson.[53] Thus, **4** could be formed in principle by condensation of the aldehyde **30** and the enolate from ketone **31**.

The β-ketoimide **33**[54] in this scenario is the source of seven of the ten stereogenic centers in **4**, all of which are set in place by either aldol or acylative bond constructions (**Scheme 20**).

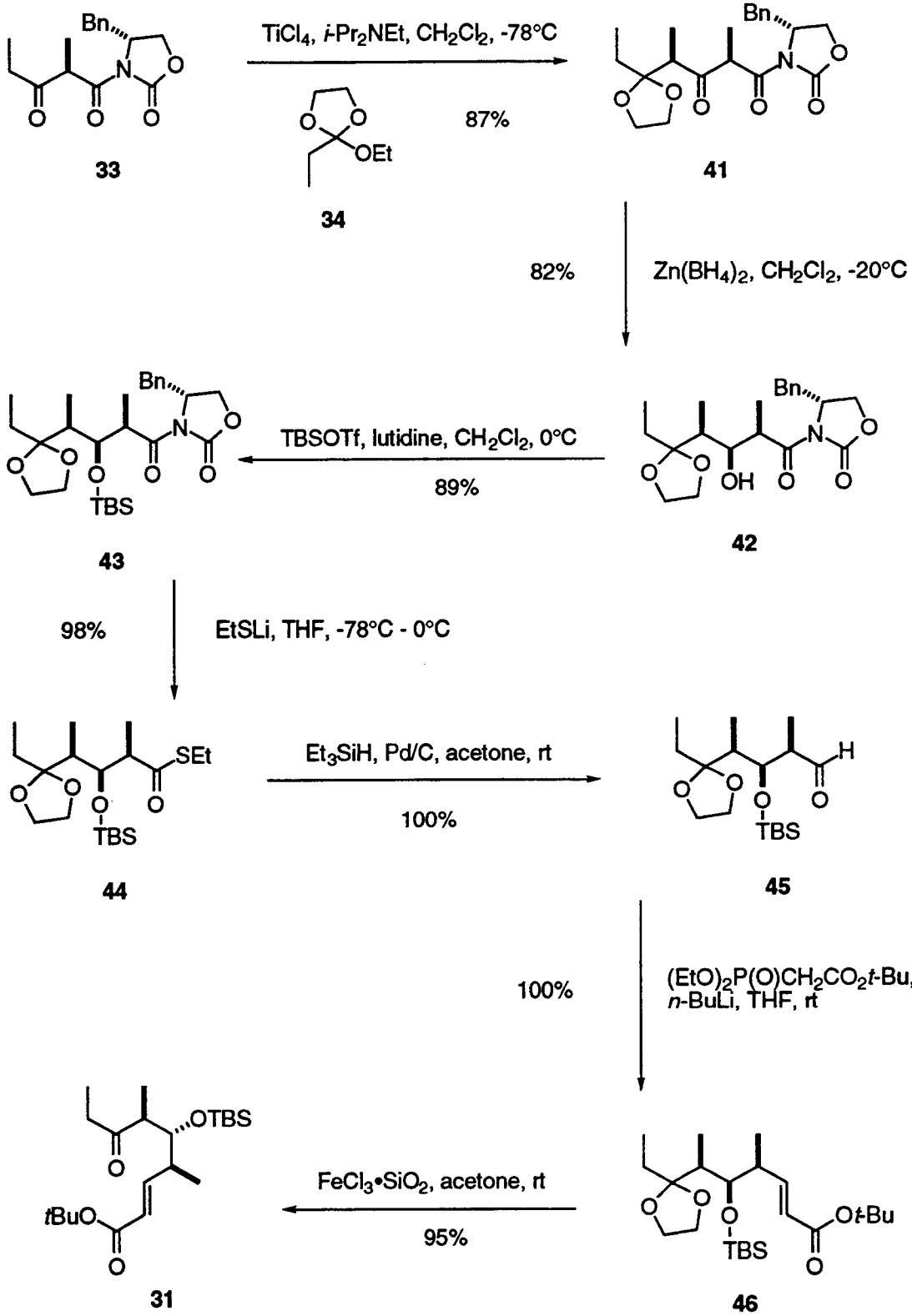


Scheme 20

Synthesis of aldehyde **30** began with Swern oxidation of alcohol **35**, which had been prepared previously.[55] Aldehyde **32** was treated with the (*E*)-boron enolate[56] derived from β-ketoimide **33** to provide the *anti* aldol adduct **36**. Directed reduction of


Swern oxidation
96%
35
32
33
84%
(c-hex)2BCl, EtNMe2,
Et2O, 0°C
NaBH(OAc)3,
AcOH, 23°C
81%
37
36
LiBH4, MeOH, THF, 0°C
ArCH(OMe)2, CSA, DMF, 23°C
86%
38
39
PMP = p-MeOC6H4
1) TBSOTf, lutidine,
CH2Cl2, 0°C (100%)
2) DIBAL-H, CH2Cl2,
0°C (100%)
1) OsO4, NMO, t-BuOH/THF/H2O, rt;
then NaIO4, NaHCO3, rt
2) CrCl2, CHI3, dioxane/THF, rt (79%)
3) Swern oxidation (93%)
30
40

Scheme 21

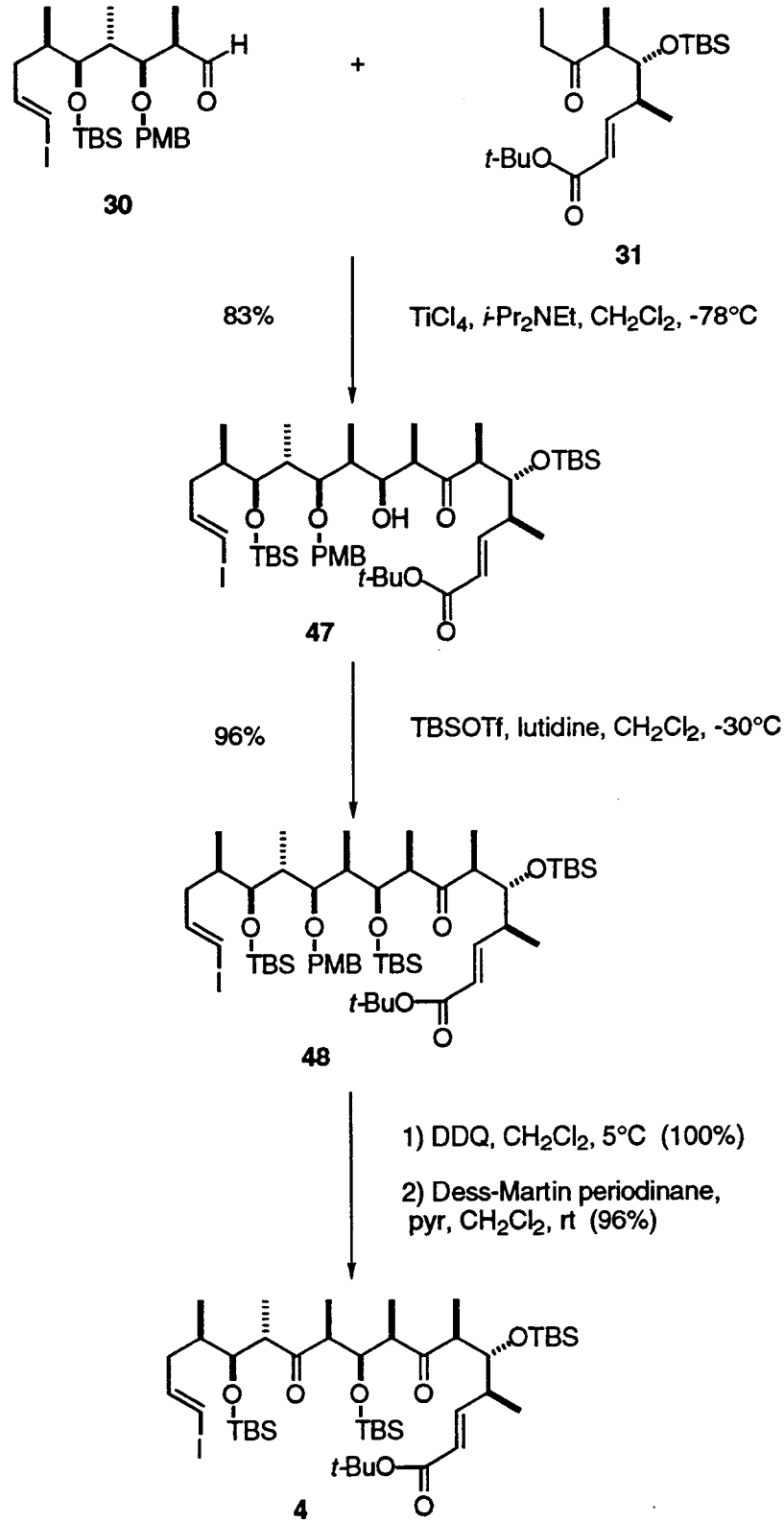

Bn
TiCl4, i-Pr2NEt, CH2Cl2, -78°C
87%
OEt
33
34
41
82%
Zn(BH4)2, CH2Cl2, -20°C
TBSOTf, lutidine, CH2Cl2, 0°C
89%
OH
TBS
42
43
98%
EtSLi, THF, -78°C - 0°C
SEt
Et3SiH, Pd/C, acetone, rt
100%
H
44
45
100%
(EtO)2P(O)CH2CO2t-Bu,
n-BuLi, THF, rt
OTBS
tBuO
FeCl3•SiO2, acetone, rt
95%
Ot-Bu
31
46

Scheme 22

β-hydroxyketone **36** using sodium triacetoxyborohydride afforded the *anti* diol **37**.[57] Reduction of **37** to the corresponding triol **38** using Penning's procedure[58] and regioselective protection with *p*-anisaldehyde dimethyl acetal yielded the *p*-methoxybenzylidene acetal **39**. Silylation of the remaining alcohol, followed by reductive cleavage of the acetal with diisobutylaluminum hydride,[59] gave **40**. The cinnamyl moiety was truncated by oxidation of the olefin[60] followed by diol cleavage. The resultant aldehyde was homologated to a vinyl iodide employing a modification of Takai's procedure.[43] Finally, Swern oxidation of the primary alcohol at the opposite terminus afforded the target aldehyde **30** (**Scheme 21**).

The next phase of Evans' approach to rutamycin B involved synthesis of ethyl ketone **31**, which was initiated by acylation of the titanium enolate of β-ketoimide **33** with the propionate-derived ortho ester **34**[61] to give ketal **41**. Chelate-controlled reduction of ketone **41** with zinc borohydride[62] afforded alcohol **42**, which was protected as its silyl ether **43**. Direct reduction of the terminal imide moiety gave a low yield of aldehyde **45**, but this problem was conveniently solved by transesterification[63] of the imide to provide thioester **44** which was reduced to **45** using Fukuyama's conditions.[64] The synthesis of **31** was completed by Horner-Emmons olefination[65] of **45** followed by deketalization[66] of the resultant α,β–unsaturated ester **46** (**Scheme 22**).

Reaction of aldehyde **30** with the titanium enolate[52] derived from ketone **31** provided the *syn* adduct **47**. Silylation of **47** gave **48**, from which the *p*-methoxybenzyl group was removed by oxidation. The resulting alcohol was oxidized under Dess-Martin conditions[67] to give the completed polypropionate fragment **4** (**Scheme 23**).

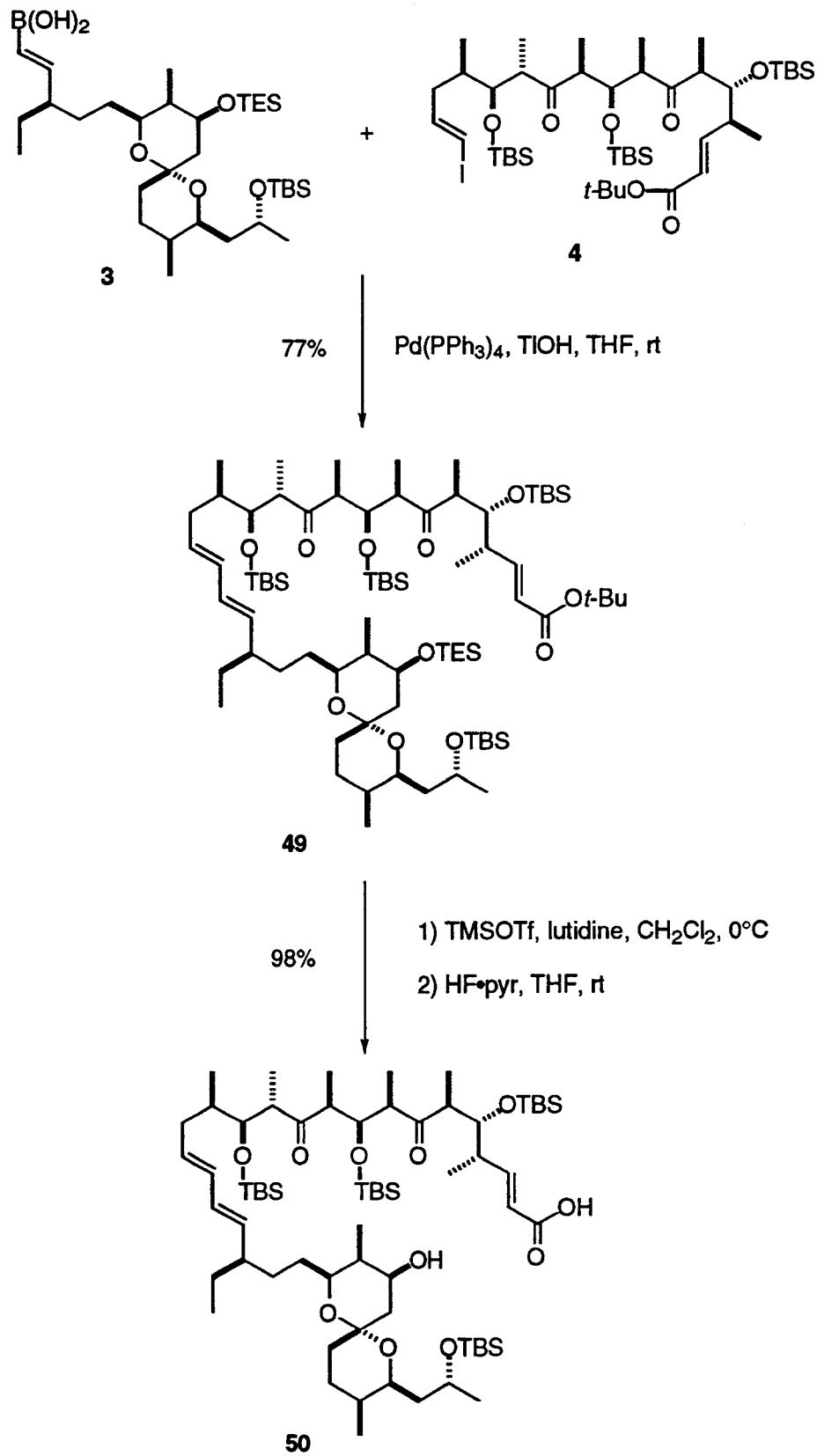

H
O
O
TBS PMB
O
30
+
OTBS
O
t-BuO
O
31
83%
TiCl4, i-Pr2NEt, CH2Cl2, -78°C
OTBS
O
O
OH
O
TBS PMB
t-BuO
O
47
96%
TBSOTf, lutidine, CH2Cl2, -30°C
OTBS
O
O
O
O
TBS PMB TBS
t-BuO
O
48
1) DDQ, CH2Cl2, 5°C (100%)
2) Dess-Martin periodinane,
pyr, CH2Cl2, rt (96%)
OTBS
O
O
O
O
TBS
TBS
t-BuO
O
4

Scheme 23

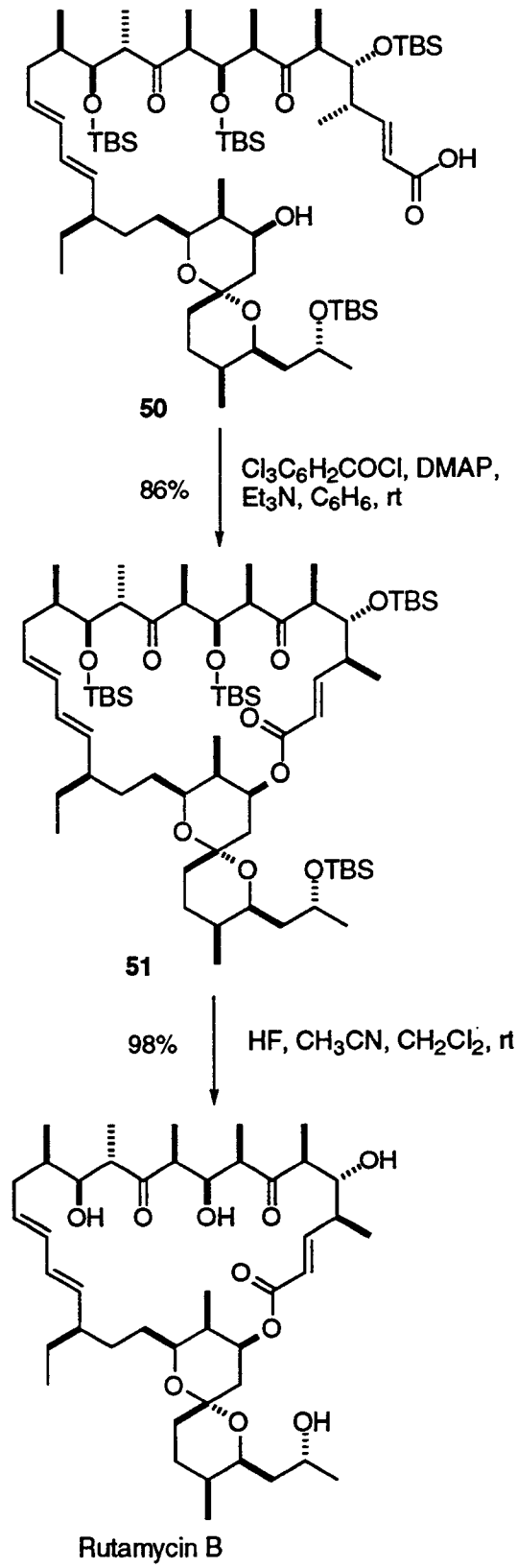
With both the spiroketal **3** and polypropionate segment **4** in hand, Kishi's modification[68] of the Suzuki coupling[34] was used to connect these subunits to give the diene **49**. The *tert*-butyl ester was converted to a carboxylic acid and the triethylsilyl protecting group was removed selectively to give the seco acid **50**. Yonemitsu macrolactonization conditions[35] were used to prepare the lactone **51**, and final deprotection with the hydrofluoric acid-acetonitrile complex afforded rutamycin B. This remarkable effort by a single student in the Evans laboratory completed the first and so far the only total synthesis of this macrolide (**Scheme 24, 25**).

Our own synthetic investigations on rutamycin B were begun well before the Evans' synthesis appeared in print. From the outset, our planned approach to both the polypropionate moiety and the spiroketal unit of rutamycin B was quite different from that of Evans. After Evans reported completion of his synthesis, we were able to take advantage of several strategic elements in his plan to advance our route. In fact, one of our two successful pathways to the spiroketal of **1** closely parallels that of Evans. However, a second and ultimately more practical route to this spiroketal was developed that is completely original. In particular, construction of the polypropionate backbone (C3-C17) follows a strategy that eschews the aldol methodology of Evans in favor of an iterative approach that employs asymmetric crotylation. Also, the sequence in which subunits are assembled again diverges from that used in Evans' rutamycin synthesis.

The first part of this thesis recounts the synthesis of the 1,7-dioxaspiro[5.5]undecanyl segment **7** of rutamycin B, while the second part describes our continuing studies toward completion of the total synthesis of this macrolide.


B(OH)2
OTES
OTBS
3
+
OTBS
TBS
TBS
t-BuO
I
4
77%
Pd(PPh3)4, TlOH, THF, rt
OTBS
TBS
TBS
Ot-Bu
OTES
OTBS
49
98%
1) TMSOTf, lutidine, CH2Cl2, 0°C
2) HF•pyr, THF, rt
OTBS
TBS
TBS
OH
OH
OTBS
50

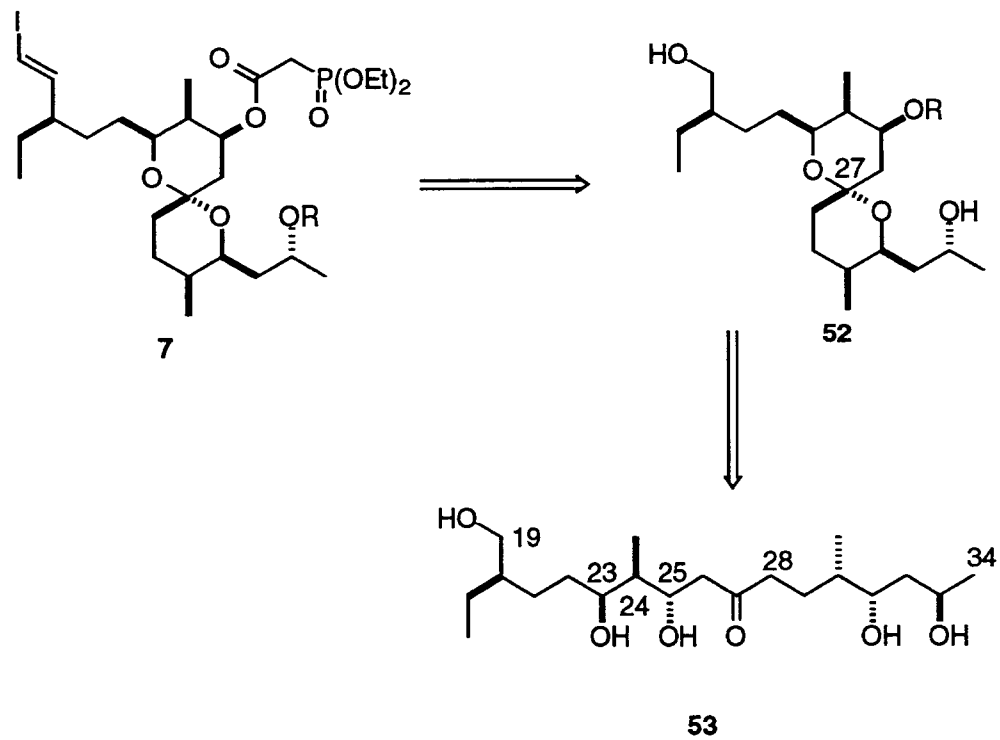
Scheme 24


OTBS
TBS
TBS
OH
O
OH
OTBS
50
86%
$Cl_3C_6H_2COCl$, DMAP,
Et_3N, C_6H_6, rt
OTBS
TBS
TBS
OTBS
51
98%
HF, CH_3CN, CH_2Cl_2, rt
OH
OH
OH
OH
Rutamycin B

Scheme 25

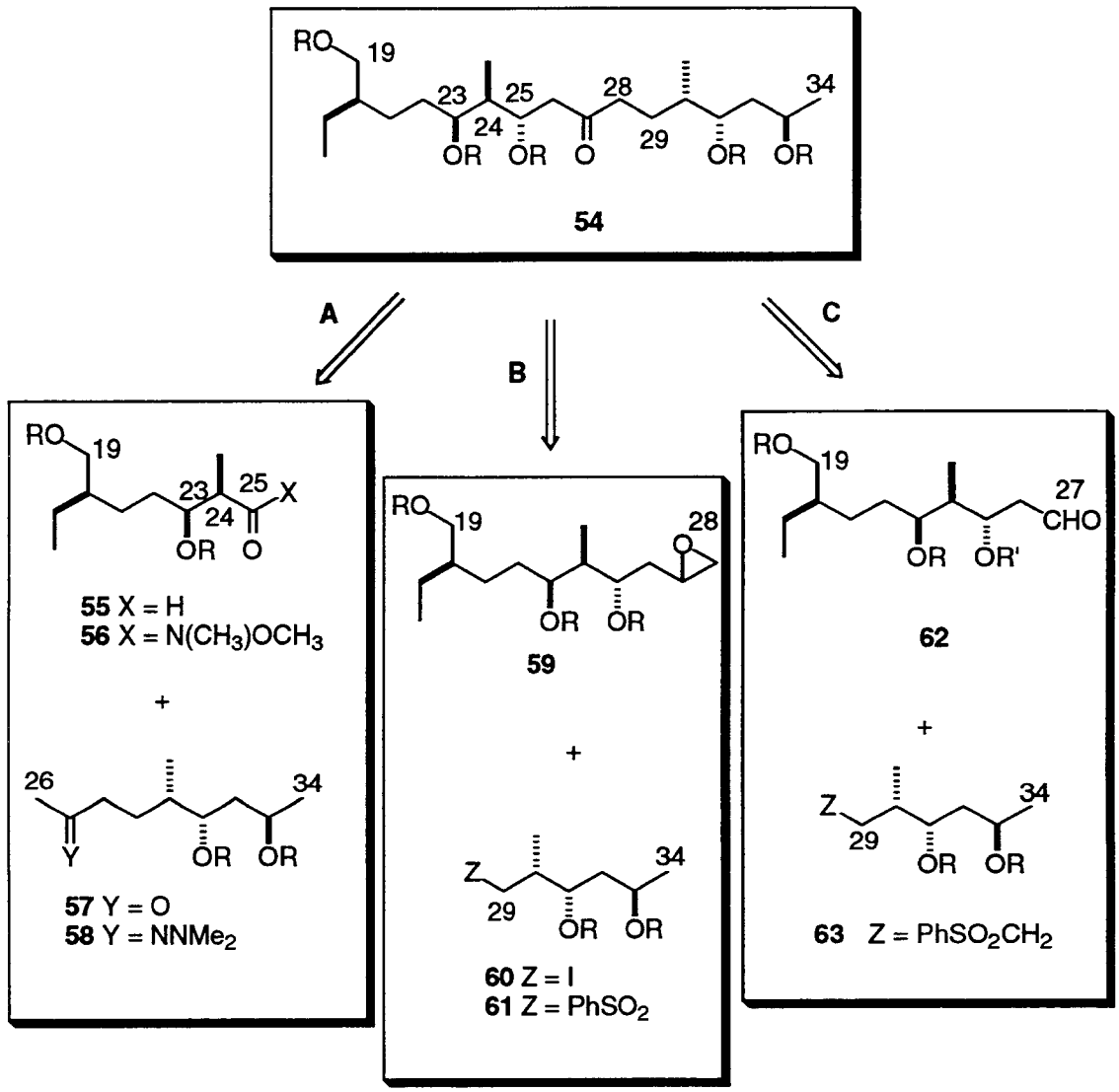
Chapter II: Total Synthesis of the 1,7-Dioxaspiro[5.5]undecanyl Segment of Rutamycin B

An important element in our synthetic plan for the spiroketal portion of rutymacin B is that it takes advantage of an inherent thermodynamic bias in the formation of the 1,7-dioxaspiro[5.5]undecane from an acyclic precursor. Uncoiling of the spiroketal **52** leads to a linear structure represented as the pentahydroxy ketone **53** (**Scheme 26**). Our expectation that this polyhydroxy ketone will close under mild acid catalysis to generate the spiroketal moiety of rutamycin B in the desired configuration is supported by Evans' construction of a similar ketal in his synthesis of cytovaricin.[29] A rationale for this outcome is based on the fact that the spiro center (C27) possessing the natural configuration of **1** places the larger alkyl groups in an equatorial orientation while conferring maximum anomeric stabilization.[46,47]



Scheme 26

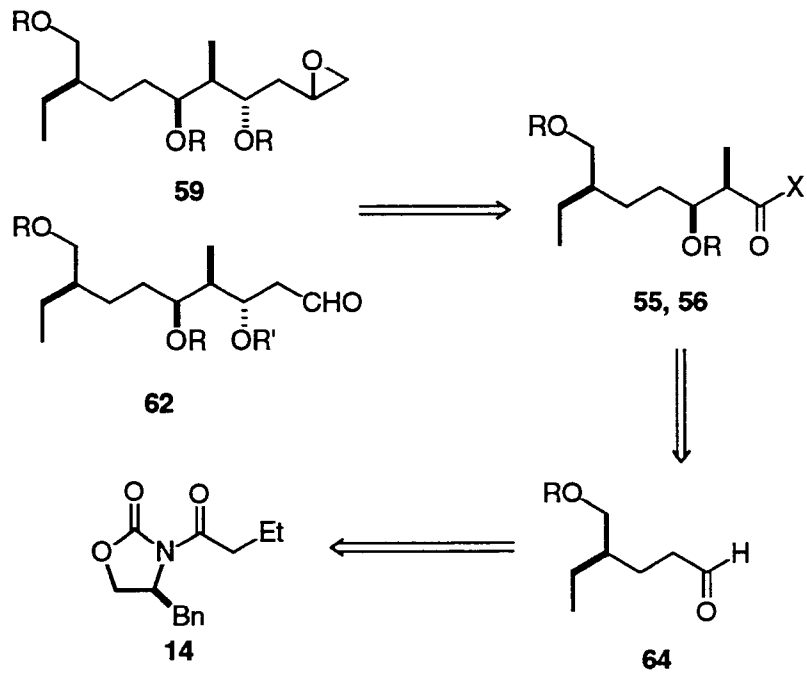
Three plausible retrosynthetic analyses of the linear structure **54** are outlined below. Pathway **A** postulates that **54** can arise from aldol condensation[69] of aldehyde **55** with the enolate of ketone **57** or alternatively, condensation of amide **56** with the enolate of hydrazone **58**.[70] Pathway **B** envisions **54** as the product of a reaction between epoxide **59** and either an organometallic nucleophile derived from iodide **60**[71] or the anion of sulfone **61**.[72] Finally in pathway **C**, Julia coupling[73] of aldehyde **62**



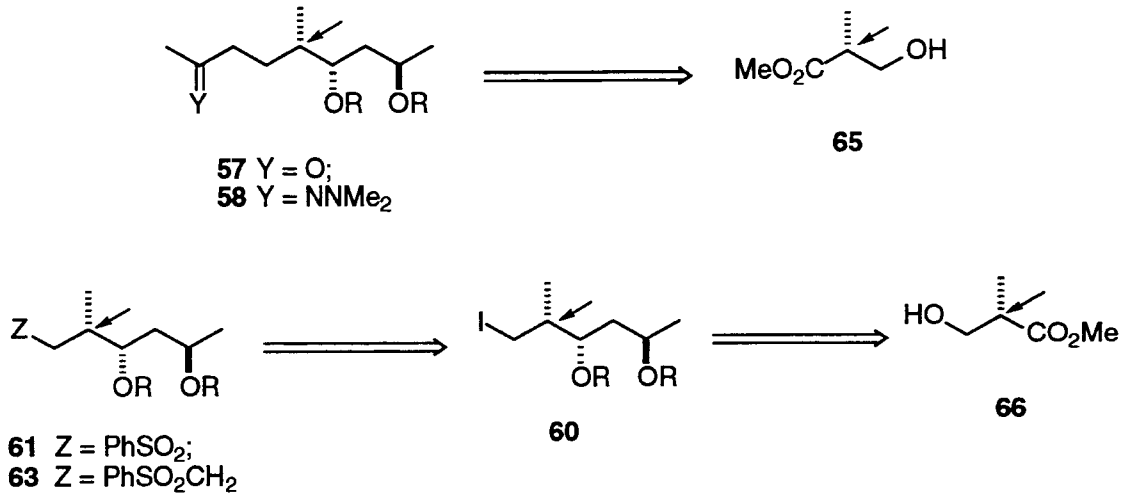
Scheme 27

with the sulfone **63**, a homolog of **61**, could also provide a route to the pentahydroxy ketone **54** (**Scheme 27**).

Aldehyde **55**, a key substance for preparing amide **56**, epoxide **59** and aldehyde **62**, can be derived, in principle, from crotylation[74] of aldehyde **64**, which in turn can be acquired from the N-butyryloxazolidinone **14** (**Scheme 28**).[49] Synthesis of ketone **57** and its hydrazone **58** was envisioned by a route which starts from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate (**65**).[75] On the other hand, sulfones **61** and **63** would be available from iodide **60**, which could originate from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**66**).[76] The advantage in choosing **65** and **66** as our starting materials was that both could provide the stereocenter at C30 of rutamycin B (**Scheme 29**).



Scheme 28

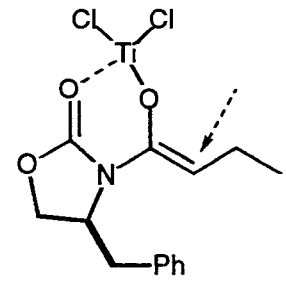


Scheme 29

Pathway A: The Aldol Approach

Synthesis of Aldehyde 55 (C19-C25 Segment)

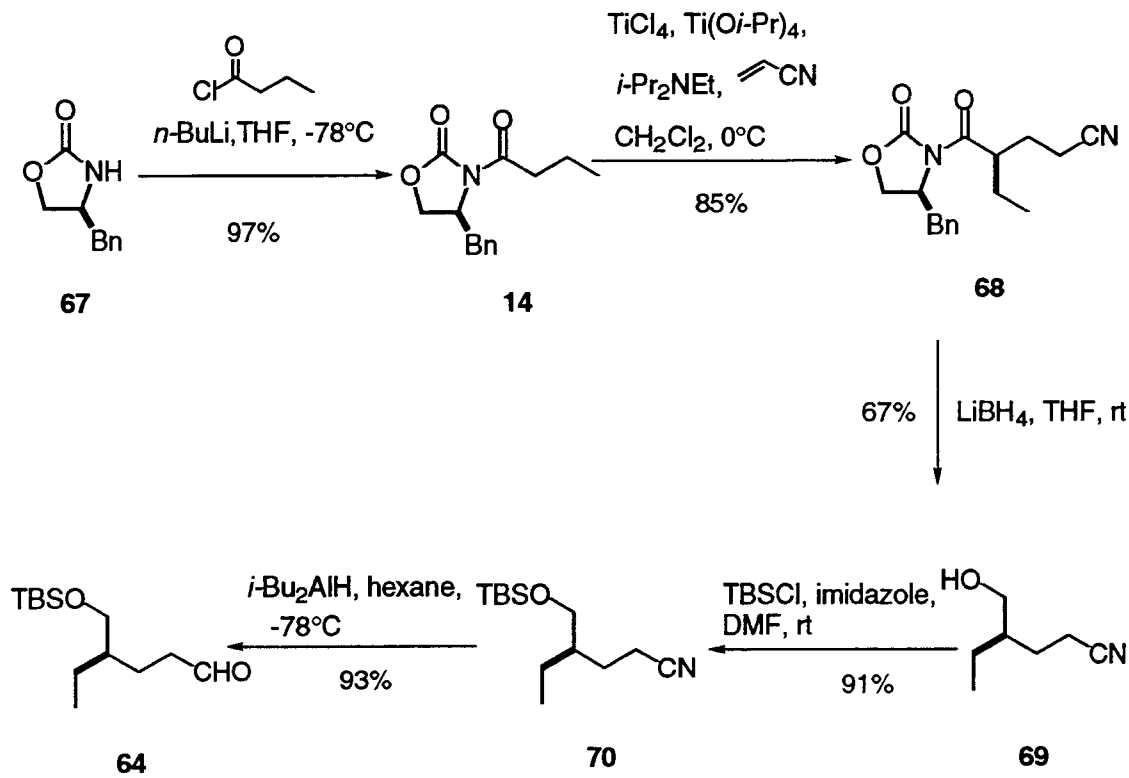
Synthesis of **55** began with (*S*)-(-)-3-butyryl-4-benzyloxazolidin-2-one (**14**),[49] a known compound obtained from acylation of (*S*)-(-)-4-benzyl-2-oxazolidinone (**67**) with butyryl chloride. An asymmetric Michael reaction of the titanium enolate of **14**



si-face alkylation

Fig. 4. Michael addition to oxazolidinone **14**

with acrylonitrile under Evans' conditions[52] furnished **68** as a single stereoisomer in high yield. Assignment of (*R*) configuration at the new stereogenic center of **68** is based on alkylation by acrylonitrile at the *si* face of the enolate of **14** as shown in **Figure 4**. The chiral auxiliary was cleaved from **68** by reduction with lithium borohydride, and the resulting hydroxy nitrile **69** was transformed to aldehyde **64** by protection of the alcohol as its *tert*-butyldimethylsilyl (TBS) ether **70** using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) followed by reduction of the

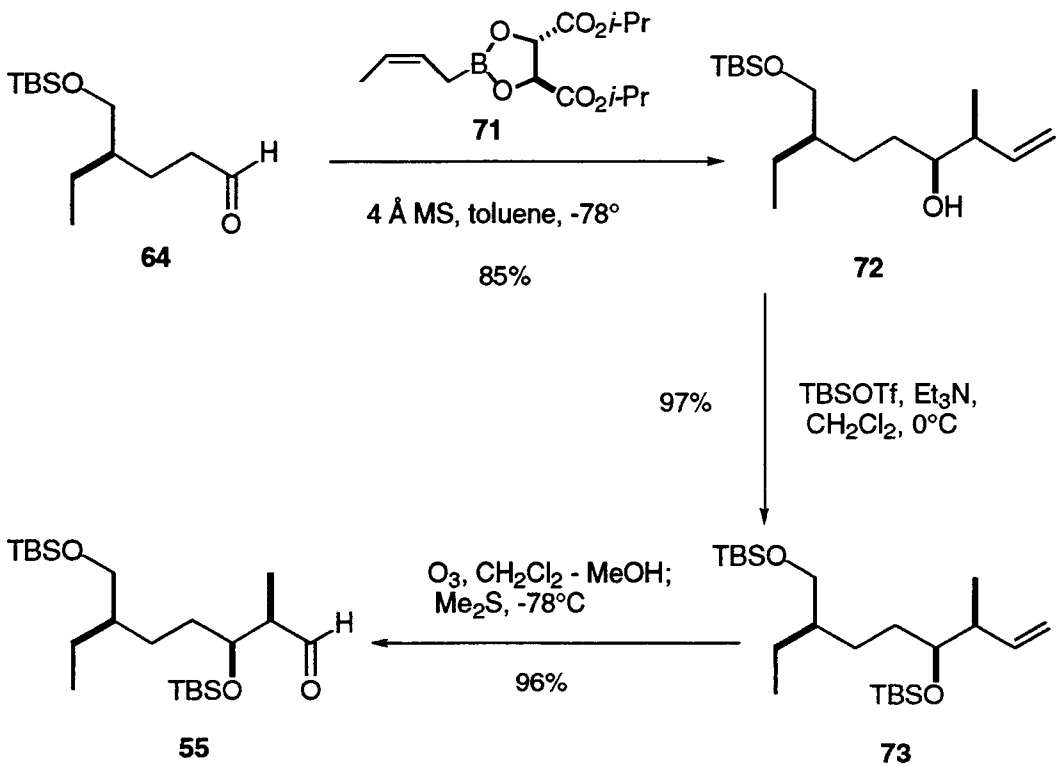


Scheme 30

nitrile with diisobutylaluminum hydride (DIBAL-H) (**Scheme 30**).[77]

Coupling of aldehyde **64** with the (*Z*)-crotylboronate **71**, prepared from (*S,S*)-diisopropyl tartrate (DIPT) according to Roush's procedure,[74] gave homoallylic alcohol **72** as a 5:1 mixture of two diastereomers. The mixture of alcohols was protected as their bis *tert*-butyldimethylsilyl ethers **73** and was subjected to ozonolysis

to yield **55** (**Scheme 31**).[78] The formation of the two new stereogenic centers at C23 and C24 can be explained by the cyclic transition state shown in **Figure 5**. The *(S,S)* chiral auxiliary in boronate **71** ensures that the crotyl group is directed to the *re* face of

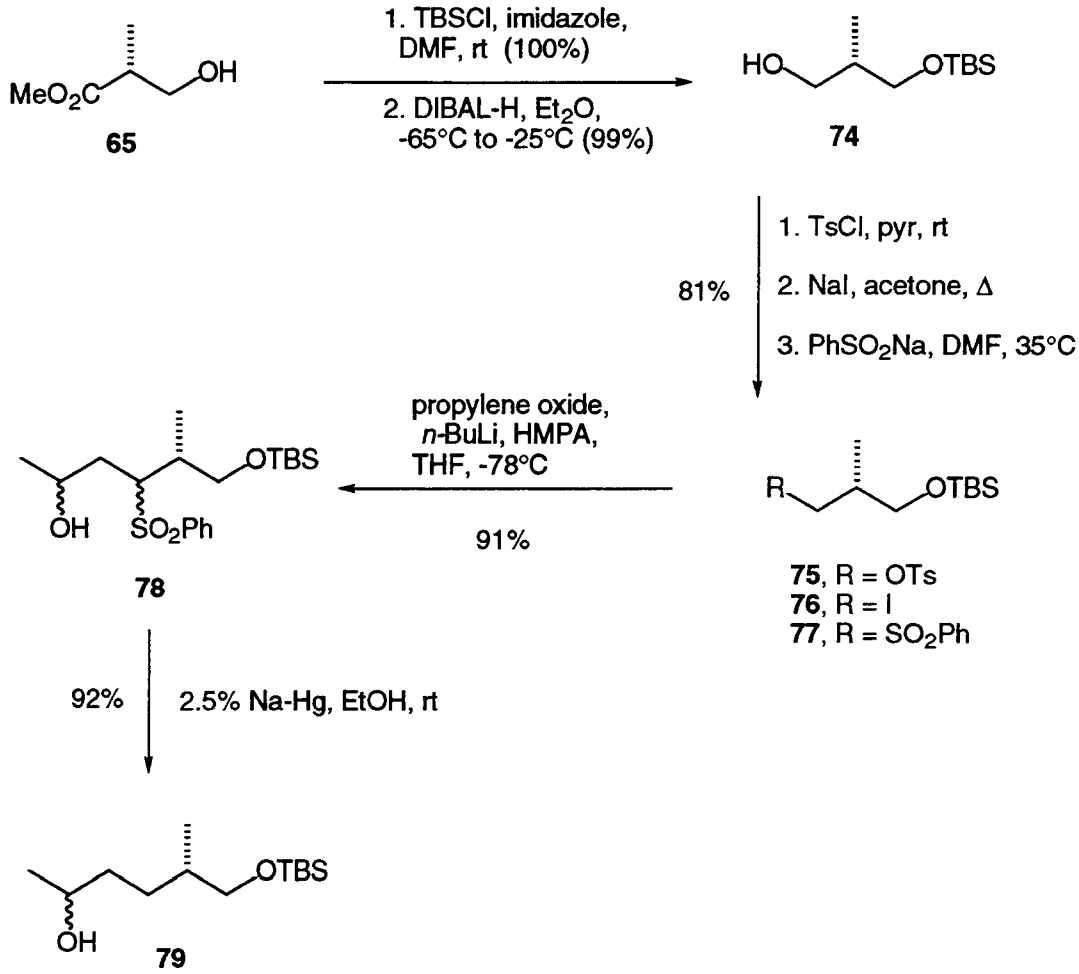


Scheme 31

the aldehyde carbonyl while *Z* configuration of the double bond dictates a *syn* relationship of C23 and C24.

Synthesis of Ketone 57 (C26-C34 Segment)

The route to **57** departed from (*R*)-(-)-2-methyl-1-[(*tert*-butyldimethylsilyl)oxy]propan-3-ol (**74**),[79] derived from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate (**65**) through standard silylation and reduction with diisobutyl aluminum hydride. Alcohol **74**, which provides the stereocenter at C30 of rutamycin



Scheme 32

B, was converted to sulfone **77** through tosylation to give tosylate **75**, followed by displacement with iodide and then a second displacement of **76** with sodium phenylsulfinate.[75] The anion of **77**, generated by treating the sulfone with *n*-butyllithium (*n*-BuLi) and hexamethylphosphoramide (HMPA) in tetrahydrofuran, was reacted with racemic propylene oxide to give hydroxy sulfone **78** as a mixture of stereoisomers.[80] Reductive removal of the sulfone group with sodium amalgam[81] yielded **79** as a 1:1 mixture of isomers at the center bearing the hydroxyl function (**Scheme 32**).

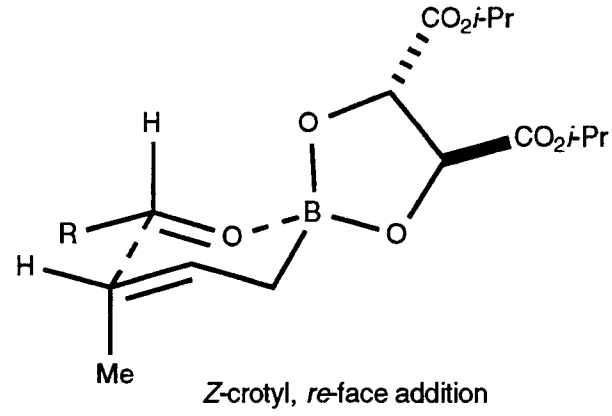
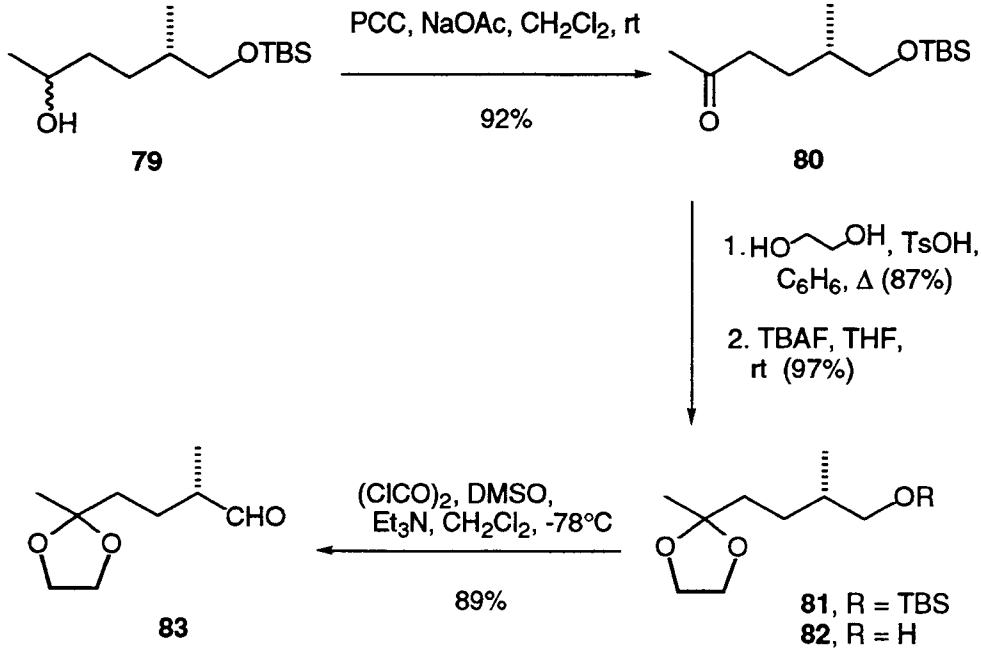


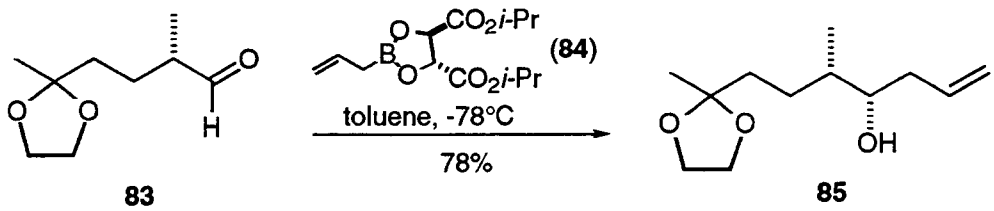
Fig. 5. Transition state for (*Z*)-crotylboronation of aldehyde **64** with (*S,S*)-Boronate **71**

Oxidation of **79** with pyridinium chlorochromate (PCC)[82] gave ketone **80** which was protected as its ketal **81** with ethylene glycol. Removal of the silyl group from **81** using tetra-*n*-butylammonium fluoride (TBAF), followed by Swern oxidation[83] of the alcohol **82**, afforded aldehyde **83** (**Scheme 33**).



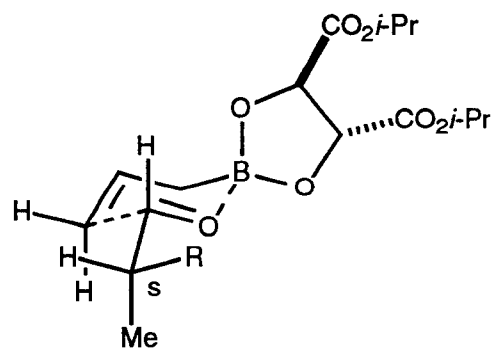
Scheme 33

Several methods appeared to be suitable for producing the *syn* relationship seen at C30 and C31 of rutamycin B,[69,84,85] and with aldehyde **83** in hand, it was decided to examine these options in the context of a route to the hydroxy ketone **89**. Treatment of **83** with the allylboronate **84** prepared from (*R,R*)-diisopropyl tartrate under Roush's conditions (**Scheme 34**),[84] or with the allylborane **86** generated from (+)-2-carene



Scheme 34

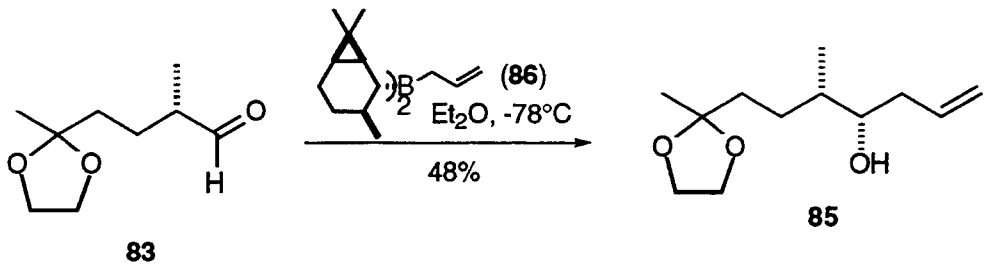
under Brown's conditions (**Scheme 35**),[85] provided **85** as a 4:1 (Roush's) and 8.6:1 (Brown's) mixture of two diastereomers. In both cases, the configuration of the secondary alcohol was the outcome of *si* face (Felkin)[86] attack of the allyl group. This resulted from stereocontrol by the (*R,R*) chiral auxiliary in boronate **84**, as shown in



si-face (Felkin) addition

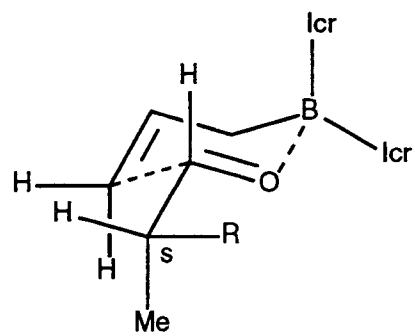
Fig. 6. Transition state for allylboronation of aldehyde **83** with (*R,R*)-Boronate **84**

Figure 6, and by the chiral diisocaranyl ligands in borane **86**, as shown in **Figure 7**. Protection of **85** furnished the silyl ether **87** which was subjected to a Wacker oxidation,[87] using palladium(II) chloride and copper(I) chloride as catalysts, to yield



Scheme 35

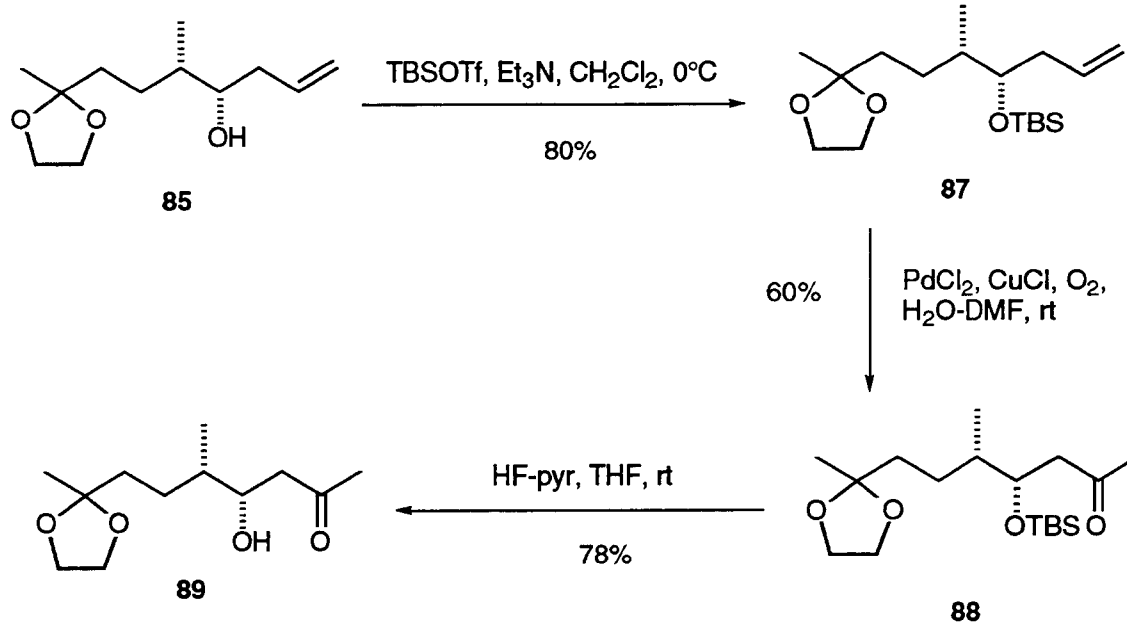
the methyl ketone **88**. The latter was desilylated with the hydrogen fluoride-pyridine complex to give hydroxy ketone **89** in good yield. On the other hand, when **85** was



si-face (Felkin) addition

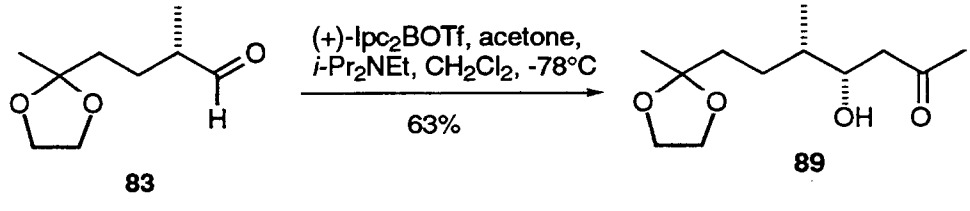
Fig. 7. Transition state for allylborination of aldehyde **83** with (-)-diisocaranylallylborane **86**

treated under the same Wacker oxidation conditions, only a minor quantity of **89** was obtained, confirming that the free hydroxyl group interferes with this process (**Scheme 36**).



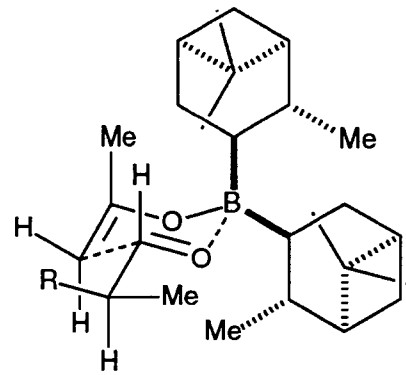
Scheme 36

The hydroxy ketone **89** could also be obtained in one step, in this case as a 10:1 mixture of stereoisomers by treating aldehyde **83** with the chiral enolate[69] prepared from acetone and (+)-diisopinocampheylborane trifluoromethanesulfonate (Ipc_2BOTf) (**Scheme 37**). Here, the (+)-isopinocampheyl ligands serve to furnish *syn* stereochemistry by promoting addition of the ketone enolate to the *si* face of **83**. The steric bias imparted by the isopinocampheyl substituents on boron is due principally to



Scheme 37

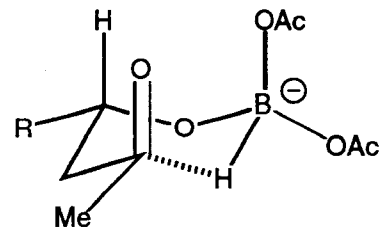
a protruding secondary methyl substituent of one of the isopinocampheyl groups, the second isopinocampheyl ligand providing a buttressing effect as shown in **Figure 8.**



si-face addition, no induction from α-chiral center

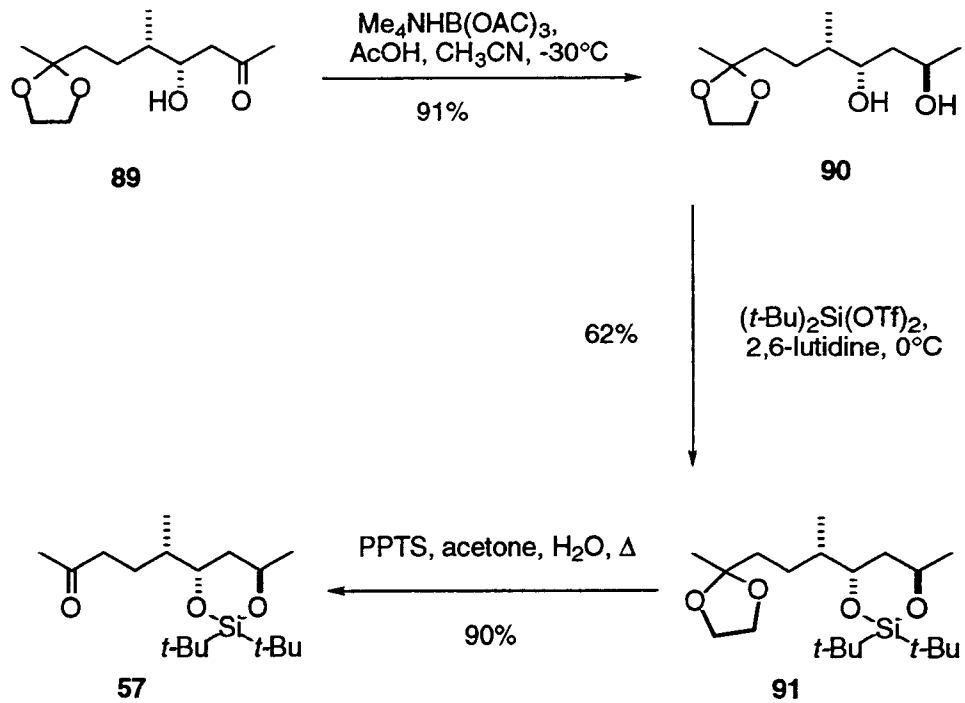
Fig. 8. Transition state for the asymmetric aldol reaction of **83** with acetone

The *anti*-1,3-diol moiety present in ketal **90** was set in place with excellent stereoselectivity by a directed reduction of the β-hydroxy ketone **89** with tetramethylammonium triacetoxyborohydride.[57] In this reduction, borohydride is first coordinated to the alcohol, and the alkoxyborohydride then transfers hydride in an intramolecular process to the *re* face of the ketone as shown in Figure 9. The resulting



Internally directed *re*-face addition of **89**
to give *anti*-1,3-diol **90**

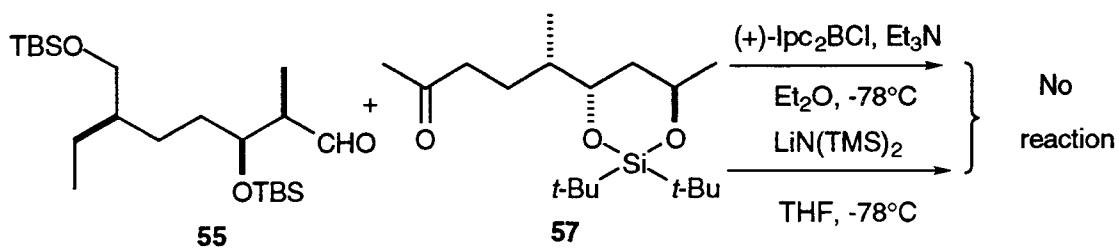
Fig. 9. Transition state for directed *anti* reduction of ketone **89**



Scheme 38

diol **90** was protected as its silylene derivative **91**,[88] and the ketal was selectively hydrolyzed in the presence of pyridinium *p*-toluenesulfonate (PPTS) to give ketone **57** (**Scheme 38**).

With **55** and **57** in hand, attention was turned towards linkage of these materials using aldol methodology. Unfortunately, all efforts along these lines were unproductive. Neither the conventional lithio enolate of **57** nor a chiral boron enolate[69] resulted in its successful coupling with **55**. In fact, only starting materials were recovered in all cases (**Scheme 39**).



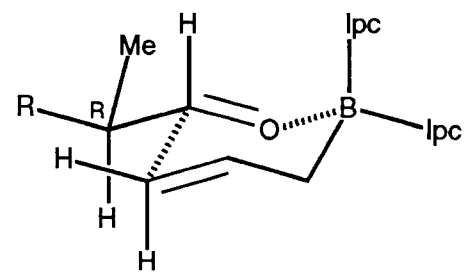
Scheme 39

Failure to effect the aldol condensation of **55** with **57** forced us to consider an alternative plan that would connect C28 with C29 instead of forming the C25-C26 bond. Two approaches based on this strategy were explored. These were coupling of epoxide **59** with iodide **60** using cuprate chemistry,[44] and reaction of **59** with the lithio derivative of sulfone **61**.[45]

Pathway B: Epoxide Approaches

Synthesis of Epoxide 59 (C19-C28 Segment)

Homoallylic alcohol **92** was prepared as a 4:1 mixture of two diastereomers by reaction of aldehyde **55** with Brown's[89] chiral borane derived from (-)-diisopinylcampheylmethoxyborane and allylmagnesium bromide. The (-)-diisopinocampheyl ligands on the boron atom served to furnish *anti* stereochemistry by

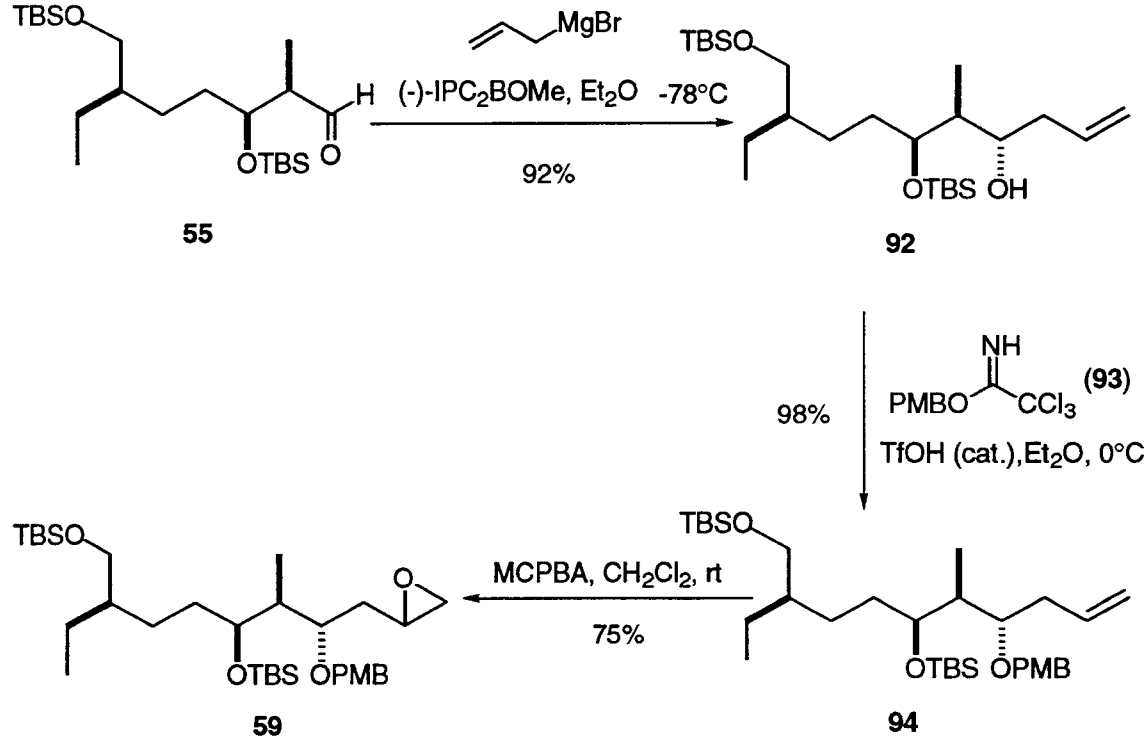


re-face (Felkin) addition

Fig. 10. Transition state for asymmetric allylborination of aldehyde **55** with (-)-diisopinylcampheylallylborane

addition to the *re* face of **55** as shown in **Figure 10**. Protection[90] of the alcohol of **92** as its *p*-methoxybenzyl (PMB) ether was carried out using *p*-methoxybenzyl

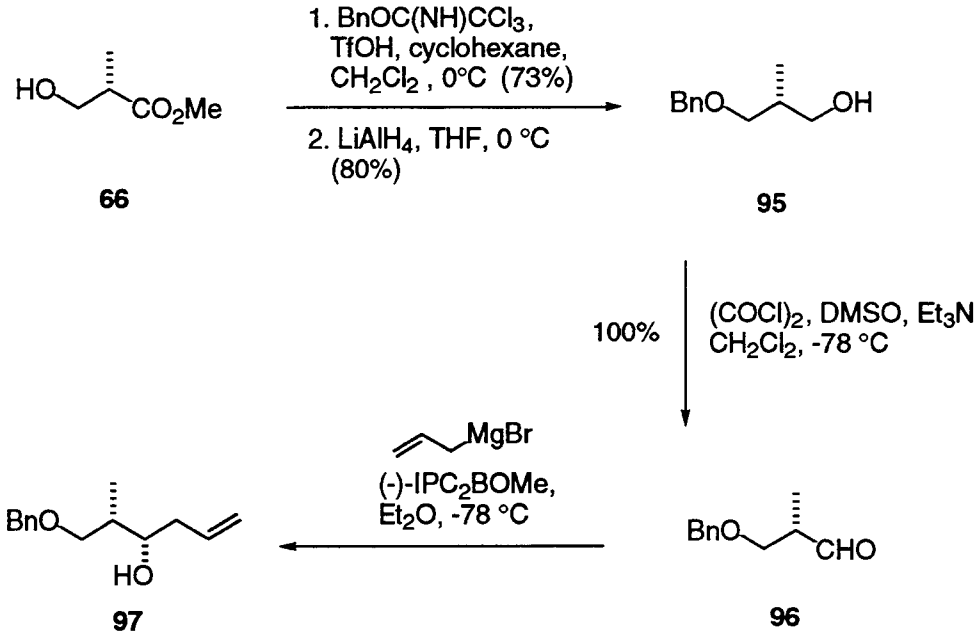
trichloroacetimidate (**93**) in the presence of a catalytic quantity of triflic acid and yielded **94**. Epoxidation of the terminal olefin of **94** with *m*-chloroperoxybenzoic acid (MCPBA) occurred with no stereoselection and furnished **59** as a 1:1 mixture of stereoisomers at the epoxide (**Scheme 40**).



Scheme 40

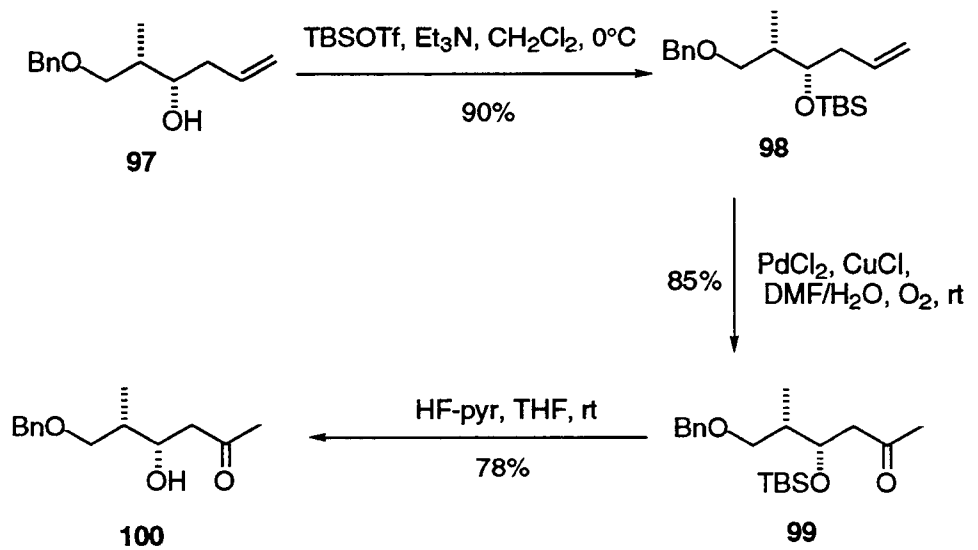
Synthesis of Iodide 60 (C29-C34 Segment)

The synthesis of iodide **60** started from (2*S*, 3*S*)-1-benzyloxy-2-methylhex-5-en-3-ol (**97**),[89] prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**66**) using literature methods. Protection of the primary alcohol with benzyl trichloroacetimidate, followed by reduction of the methyl ester with lithium aluminum hydride gave alcohol **95**.[76] A quantitative Swern oxidation of the primary alcohol afforded **96**. This aldehyde underwent asymmetric allylation using Brown's allylborane, again prepared



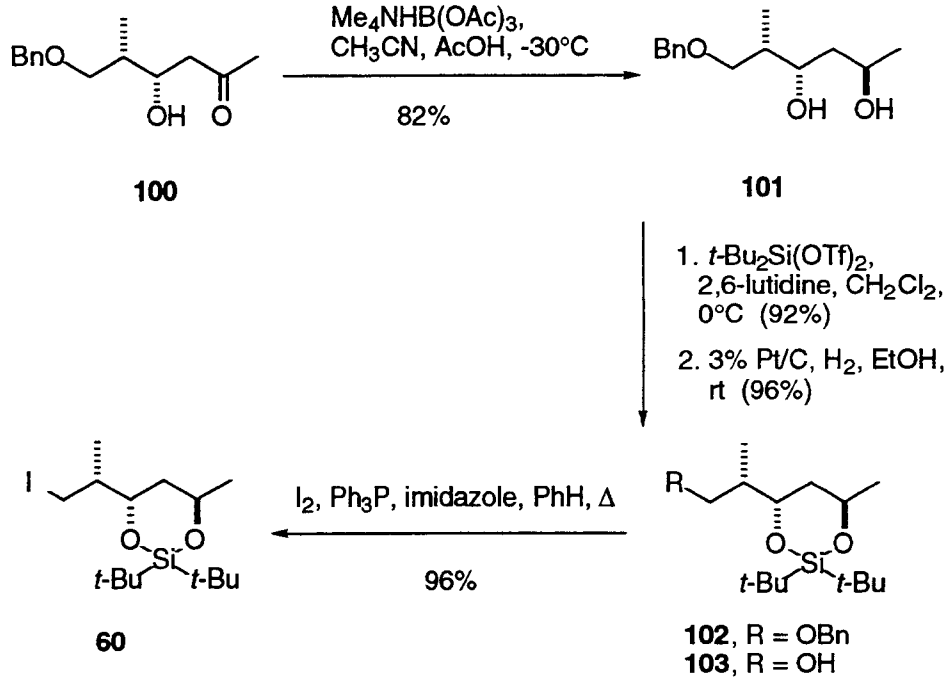
Scheme 41

from (-)-diisopinylcampheylmethoxyborane, to give homoallylic alcohol **97** containing the expected *syn* relationship between C30 and C31 of rutamycin B (**Scheme 41**).



Scheme 42

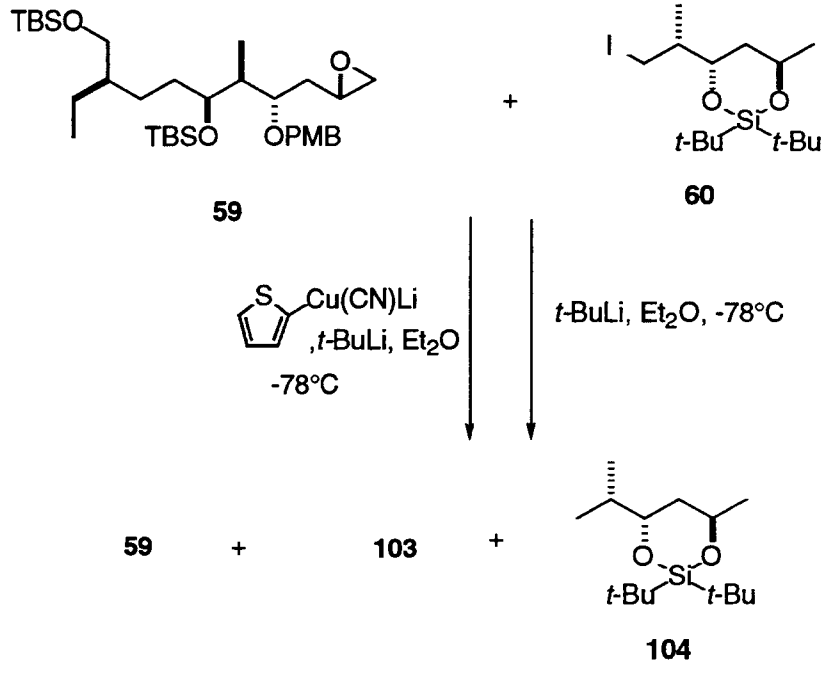
Protection of **97** as its *tert*-butyldimethylsilyl ether **98** was followed by a Wacker oxidation, which provided ketone **99**, and subsequent removal of the silyl protecting group[91] furnished β-hydroxy ketone **100**. When Wacker oxidation was attempted directly on **97**, the hydroxy ketone **100** was obtained in very low yield, thus confirming our previous observation that a free alcohol interferes with this process (**Scheme 42**).



Scheme 43

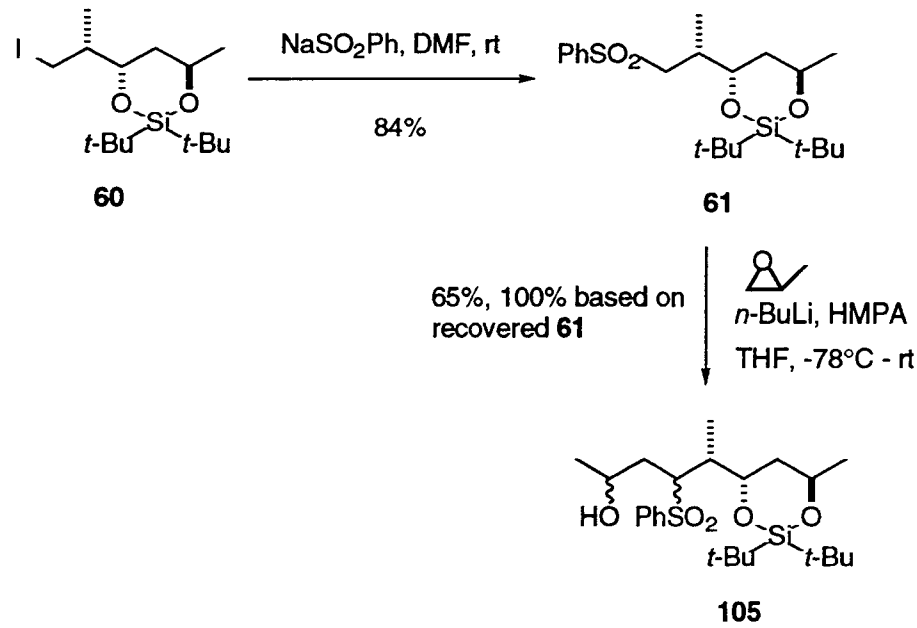
As with **89**, the *anti*-1,3-diol moiety of **101** was set in place by a directed reduction of **100** with tetramethylammonium triacetoxyborohydride. The diol of **101** was protected as its silylene derivative **102**, and the benzyl ether was cleaved by hydrogenolysis[92] to give the corresponding alcohol **103**. The latter was converted to **60** through iodination with triphenylphosphine diiodide in the presence of imidazole (**Scheme 43**).[93]

Several attempts were made to react epoxide **59** with both the higher order cuprate[71] derived from iodide **60** and directly with the organolithium derivative of **60**, all of which resulted in failure. Only the reduction product **104**, alcohol **103**, and recovered **59** were obtained from this reaction (**Scheme 44**).



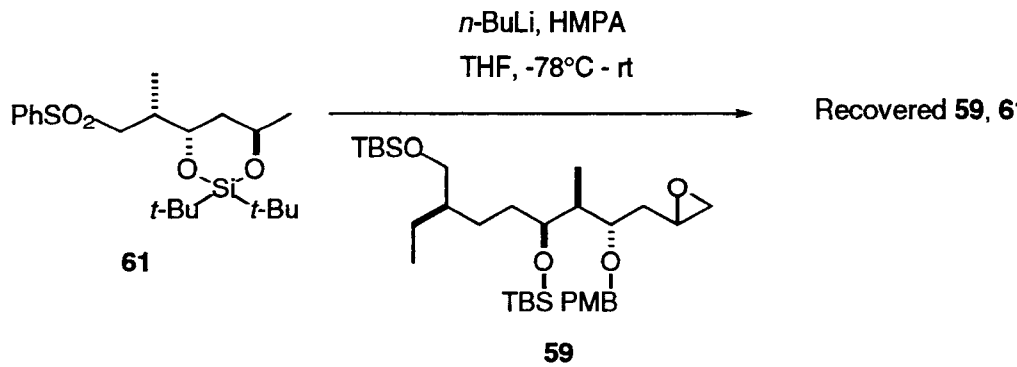
Scheme 44

In light of our earlier success in the reaction of propylene oxide with the α-lithio anion from sulfone **77** (**Scheme 32**), it was decided to examine a model reaction of the α-lithio anion of sulfone **61**, prepared directly from iodide **60** with sodium phenylsulfinate, with propylene oxide. We were encouraged to find that hydroxysulfone **105** was, in fact, obtained in good yield (**Scheme 45**). Based on this positive result, a variation of this approach using **59** as the epoxide component was next explored as a route to **54**. However, in contrast to the favorable outcome of the model reaction with **61**, its lithio derivative did not react with **59** (**Scheme 46**). Although there is good literature precedent[72] for predicting success from this reaction,



Scheme 45

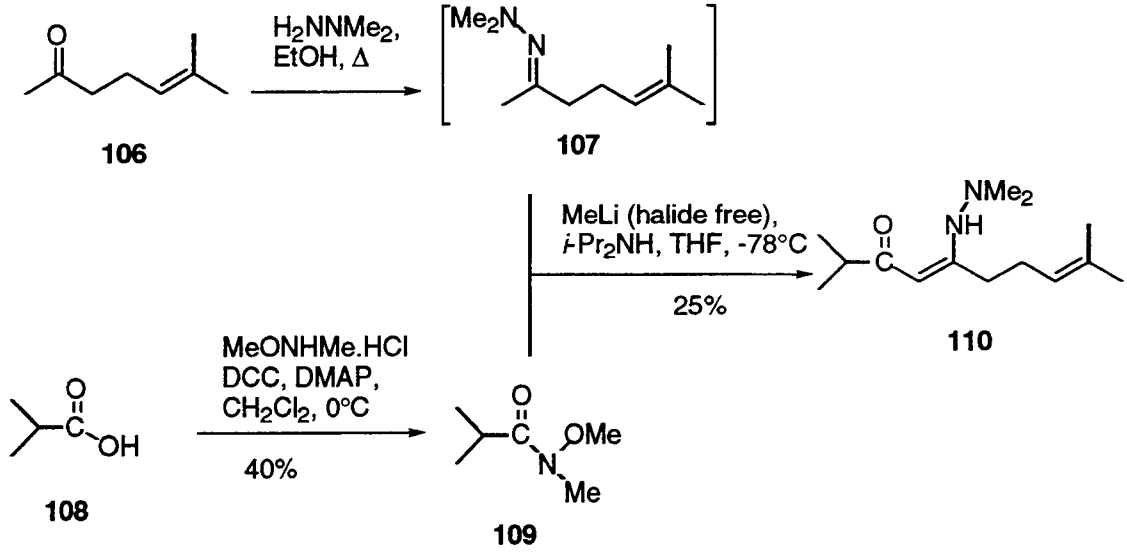
the process has been known to fail in circumstances[94] where large steric demand is present in the reacting components, or where the reactivity of the lithiosulfone may be reduced due to complexation of the metal. Either of these factors could provide a possible explanation for the lack of reactivity in our case.



Scheme 46

A Return to Pathway A: The Hydrazone Route

Evans' synthesis of the spiroketal segment **1** (**Scheme 14**) of rutamycin B[7] employed the lithium enolate of hydrazone **13** in a condensation with the Weinreb amide **12**.[70] A model study carried out in anticipation of a coupling analogous to that

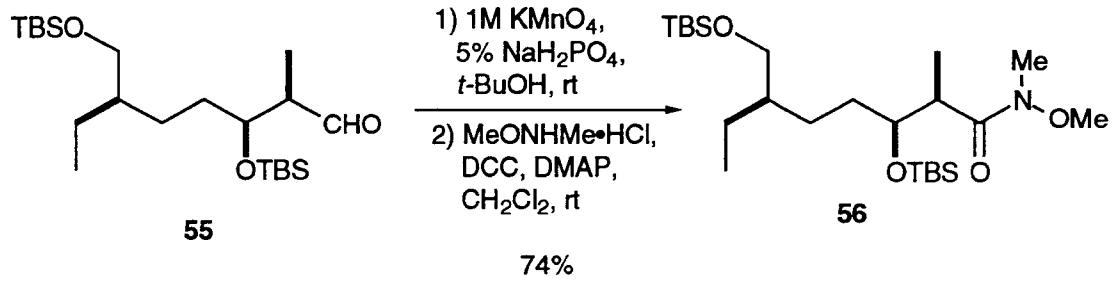


Scheme 47

of Evans demonstrated that the lithium enolate of hydrazone **107**, prepared from 6-methyl-5-heptene-2-one (**106**), reacted with the Weinreb amide **109**, prepared from butyric acid (**108**), to give the vinylogous amide **110**. As noted by Evans,[7] we found that halide-free methyllithium was necessary for generating the lithium diisopropylamide used to obtain the enolate of **107**. Unless this precaution was taken, no condensation with **109** occurred (**Scheme 47**).

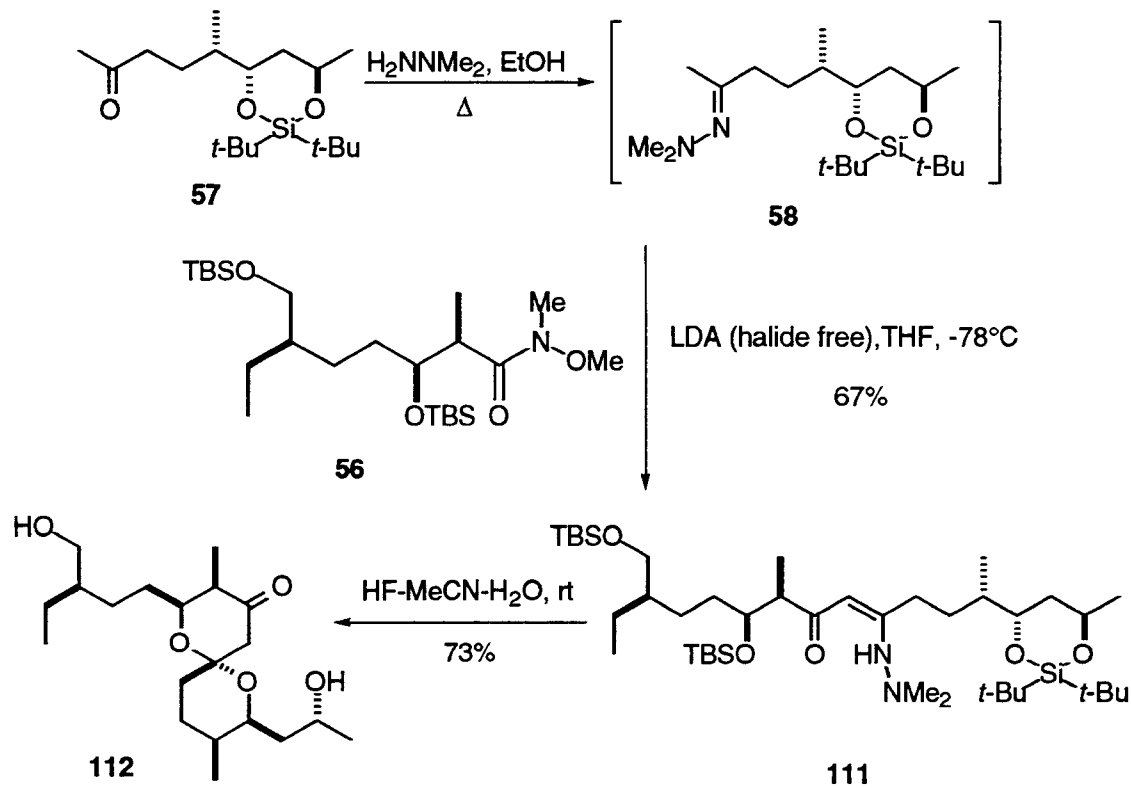
Encouraged by this result, we decided to extend this approach to the condensation of **56** with **58**. Oxidation[95] of aldehyde **55** with potassium permanganate, followed by treatment of the resultant acid with N,O-

dimethylhydroxylamine hydrochloride, 1,3-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP), afforded amide **56** (**Scheme 48**).[96]



Scheme 48

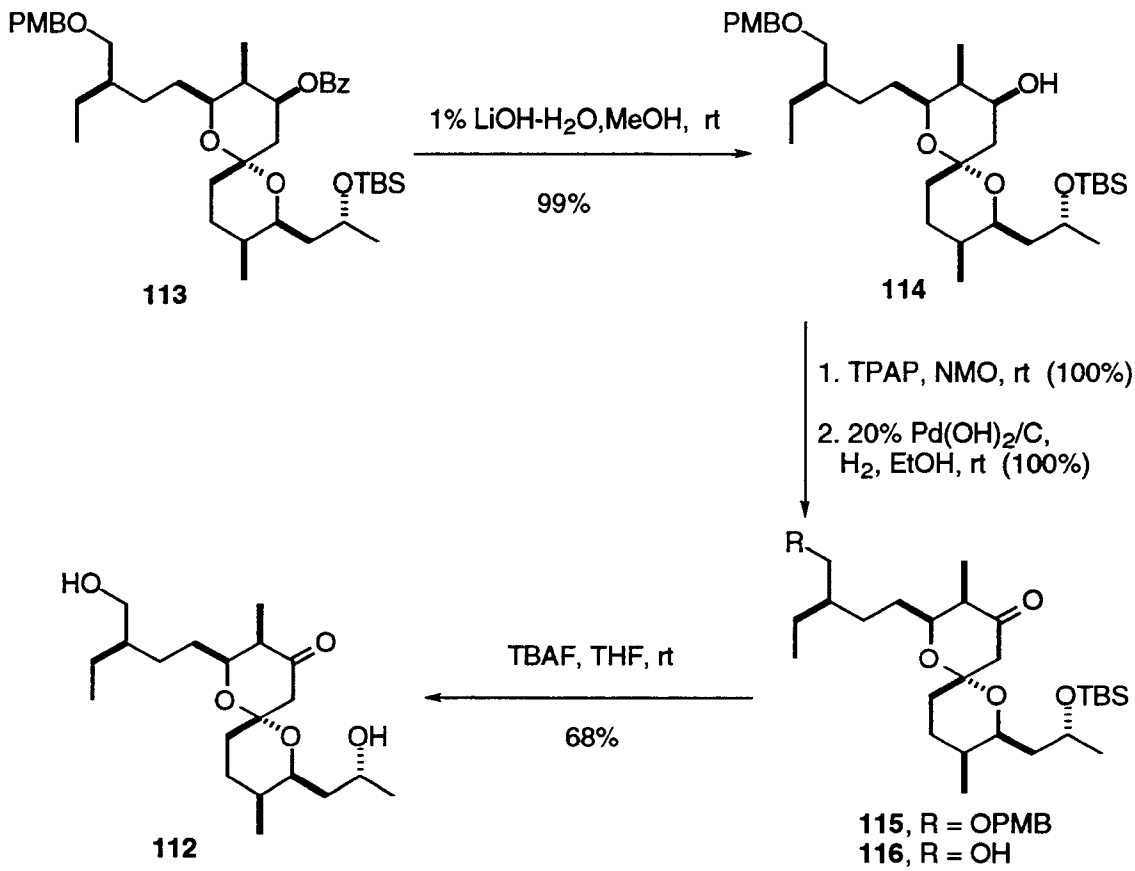
In a separate sequence, ketone **57** was converted to its N,N-dimethylhydrazone **58**,[97] and the lithium enolate of **58** was condensed with **56** under conditions used for



Scheme 49

the reaction of **107** with **109**.[29] Hydrolysis and spiroketalization[29] of the condensation product **111** proceeded smoothly in the presence of hydrofluoric acid-acetonitrile complex to give the desired dihydroxy spiroketal **112** (**Scheme 49**). The structure of this substance was confirmed by comparison with material prepared independently as described below.

A sample of benzoate **113**[7,98] provided by Professor Evans was saponified, and the resulting alcohol **114** was oxidized with tetra-*n*-propylammonium perruthenate



Scheme 50

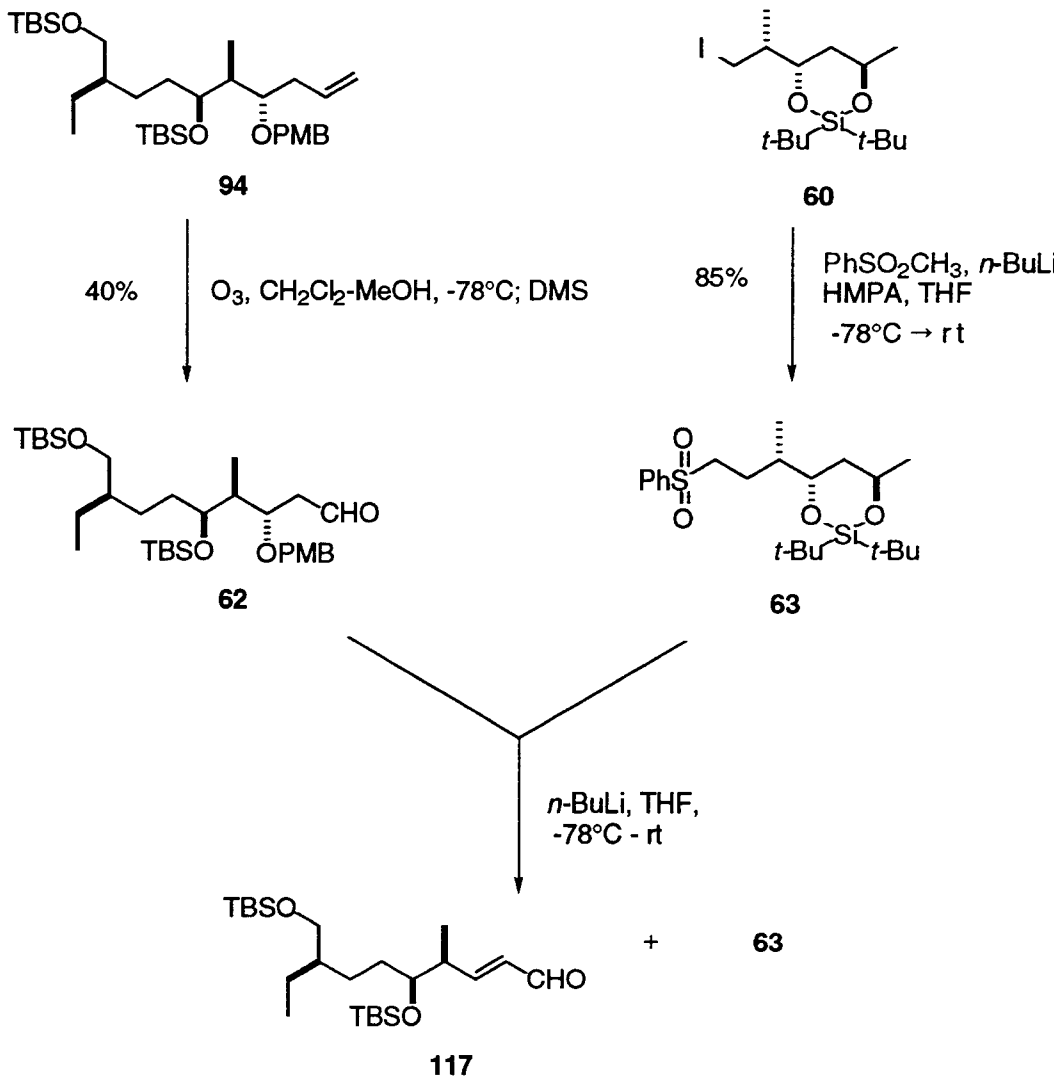
(TPAP)[99] and 4-methylmorpholine N-oxide (NMO) to yield ketone **115**. Reductive debenzylation[100] of this material gave hydroxy ketone **116** from which the silyl protecting group was removed with tetra-*n*-butylammonium fluoride to furnish **112**

(**Scheme 50**). The spiroketal **112** obtained from **113** was identical by comparison of TLC, IR, NMR, MS and optical rotation data with the material obtained from **111**. Since the structure of Evans' spiroketal **113**[7] was confirmed by comparing the spectral characteristics and optical rotation data of his triol **1** synthesized from **113** with the same spiroketal derived by degradation of rutamycins A and B, there remains no ambiguity with respect to the structure assigned to **112** obtained via linkage of **56** with **58**.

Pathway C: The Julia Route

Although our synthesis of the dihydroxy spiroketal **112** was successfully completed along lines pioneered by the Evans group, it was decided to explore other more innovative routes to this substance in the hope that they would be more efficient. To this end, we envisioned that a C27-C28 connection could be established via Julia coupling[73] of aldehyde **62** and sulfone **63**. In this scenario, the required equatorial orientation of the hydroxyl group attached to the spiroketal can be preset, thereby eliminating a reduction and a protection step.

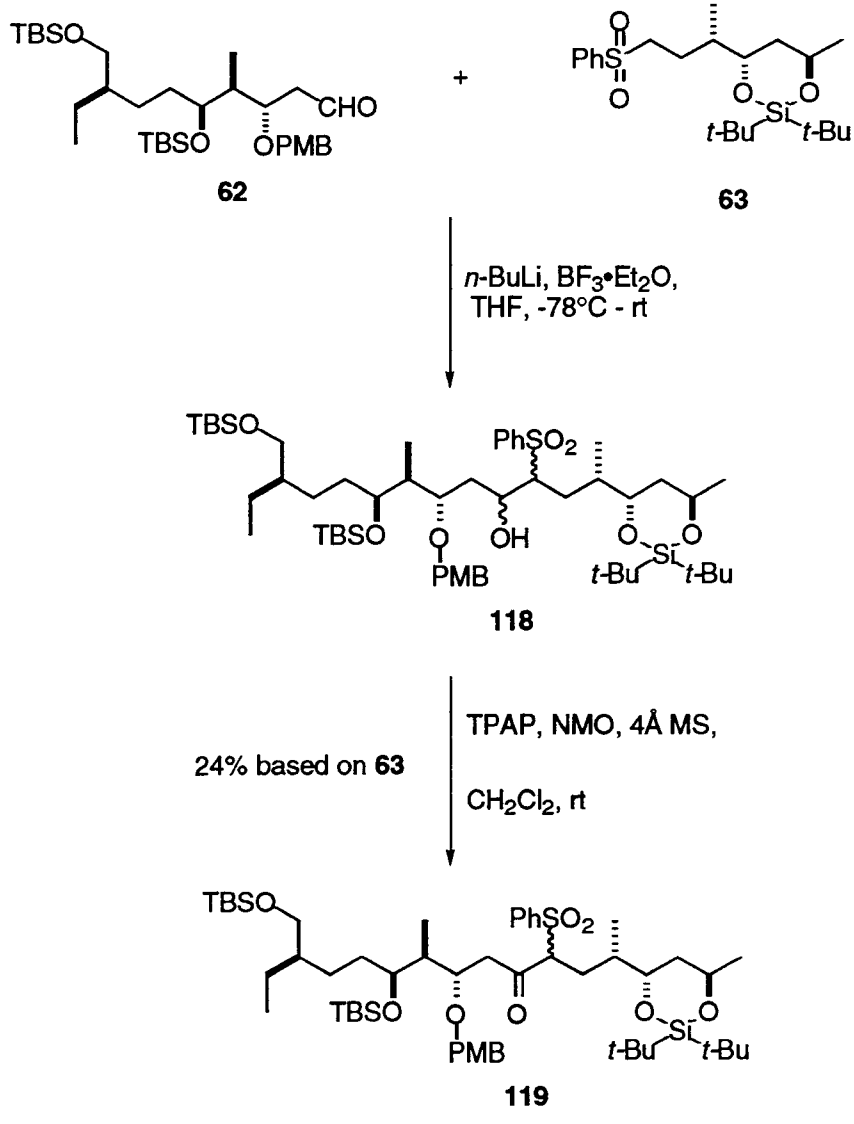
Sulfone **63** was easily accessed from iodide **60** through a displacement with the lithium anion of methyl phenyl sufone. Aldehyde **62** was obtained via ozonolysis of olefin **94**, although in a disappointingly low yield. An initial attempt to couple **62** with the lithium anion of **63** using standard Julia conditions[73] afforded none of the expected product. Instead, only recovered sulfone **63** and the α,β-unsaturated aldehyde **117** resulting from elimination of the *p*-methoxybenzyl ether were detected (**Scheme 51**). In further studies, it was found that the presence of a Lewis acid[101,102] promoted the



Scheme 51

condensation of **62** and **63**. For example, when boron trifluoride etherate[101] was added to the reaction mixture, the hydroxy sulfone **118** was obtained as a mixture of stereoisomers which underwent oxidation to produce the keto sulfone **119** in 24% yield over two steps (**Scheme 52**). Similarly, when magnesium bromide etherate[102] was employed as the Lewis acid, **119** was obtained in 15% yield over the same two steps (**Scheme 53**). When reductive desulfonation of **119** was attempted using 2.5% sodium

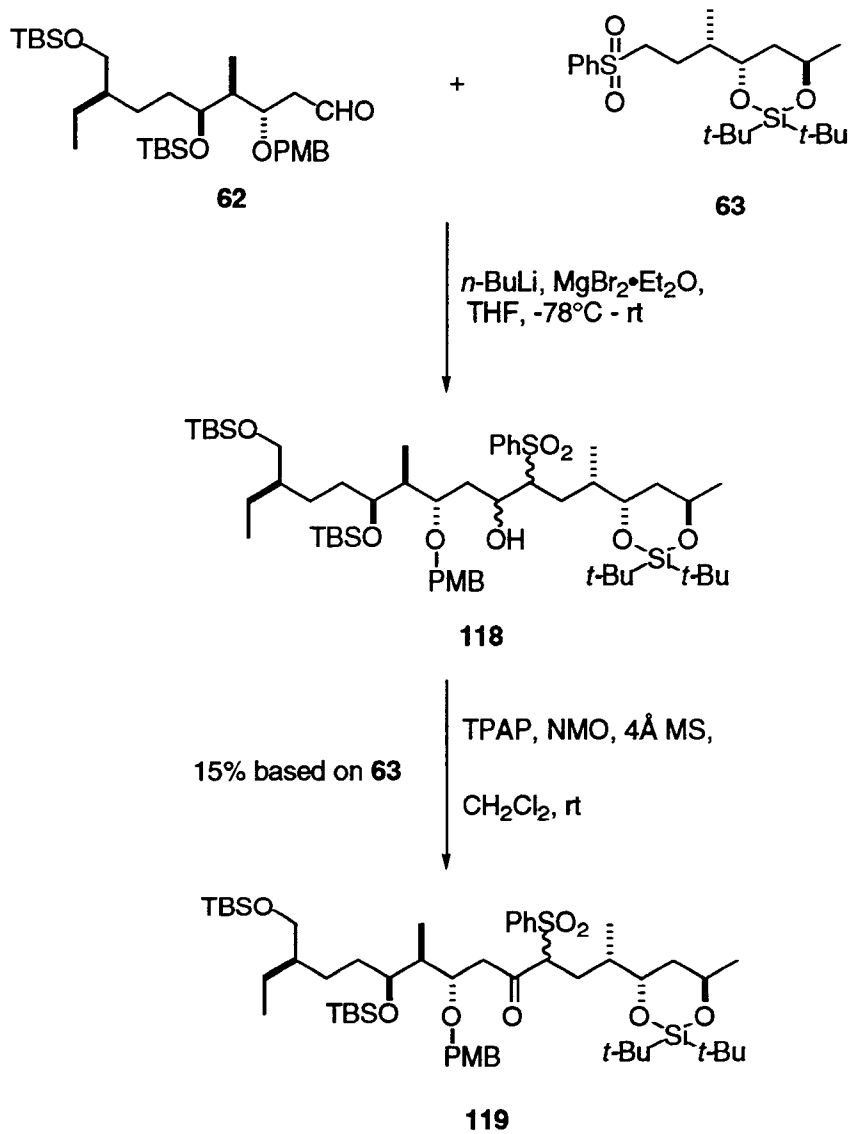
amalgam[81] in ethanol, four products of undetermined structure were isolated. However, it could be seen from their proton NMR spectra that these compounds contained neither the *p*-methoxybenzyl ether nor the sulfone group.



Scheme 52

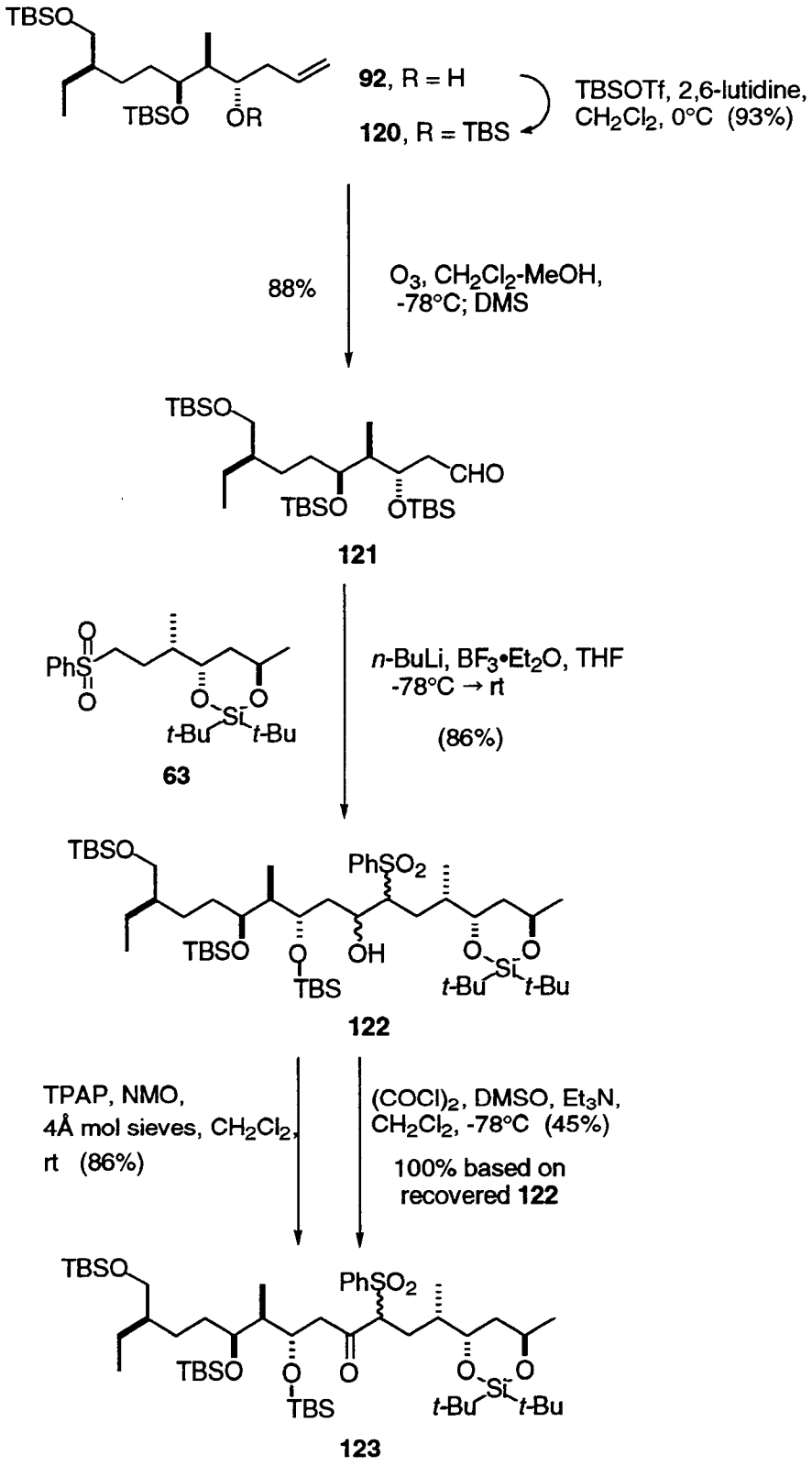
The unsatisfactory yields obtained in the ozonolysis of **94** and in the Julia coupling of **62** with **63**, along with the loss of the *p*-methoxybenzyl ether in the desulfonation step, forced us to reconsider our choice of the hydroxyl protecting group

for **92**. Specifically, a protecting group was needed which would be easy to install and remove, yet would be compatible with the synthetic sequence beyond **92**. With these requirements in mind, we returned to the *tert*-butyldimethylsilyl ether as a protecting group. Aldehyde **121** was prepared from homoallylic alcohol **92** through protection as



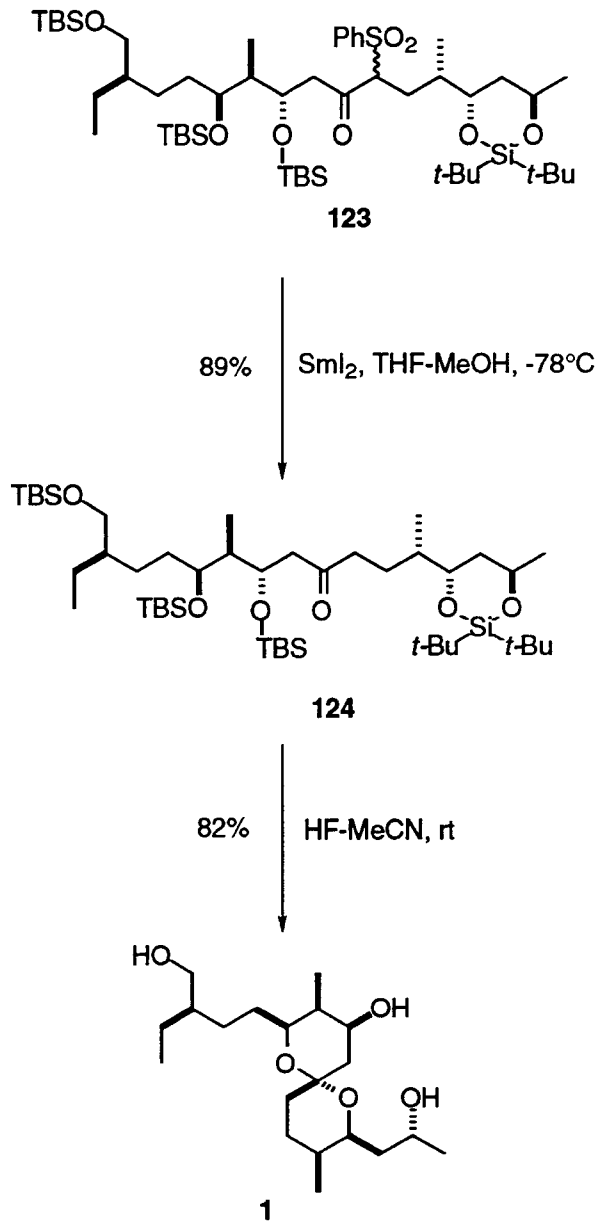
Scheme 53

its silyl ether **120** followed by ozonolysis. The yield of this sequence greatly exceeded that from **92** via its *p*-methoxybenzyl ether. To our delight, Julia coupling of **121** with


TBSO
TBSO
OR
92, R = H
120, R = TBS
TBSOTf, 2,6-lutidine,
CH2Cl2, 0°C (93%)
88%
O3, CH2Cl2-MeOH,
-78°C; DMS
TBSO
CHO
TBSO
OTBS
121
PhS
O
O
O
Si
t-Bu
t-Bu
63
n-BuLi, BF3•Et2O, THF
-78°C → rt
(86%)
TBSO
PhSO2
TBSO
O
OH
TBS
O
Si
O
t-Bu
t-Bu
122
TPAP, NMO,
4Å mol sieves, CH2Cl2,
rt (86%)
(COCl)2, DMSO, Et3N,
CH2Cl2, -78°C (45%)
100% based on
recovered 122
TBSO
PhSO2
TBSO
O
O
TBS
O
Si
O
t-Bu
t-Bu
123

Scheme 54

the lithium anion of sulfone **63** in the presence of boron trifluoride etherate afforded hydroxy sulfone **122** in excellent yield. Oxidation of **122** gave keto sulfone **123** as a mixture of two stereoisomers in 86% yield using tetra-*n*-propylammonium perruthenate and in quantitative yield (based on recovered starting material) using Swern conditions

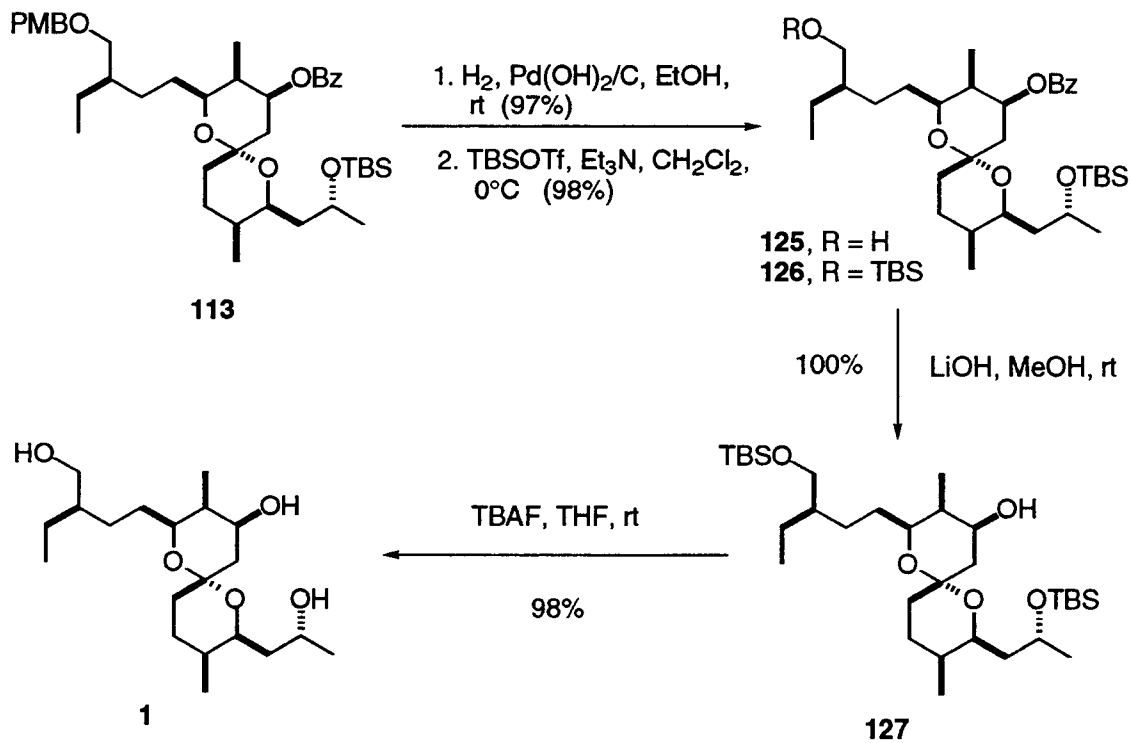


123 **124** **1**

Scheme 55

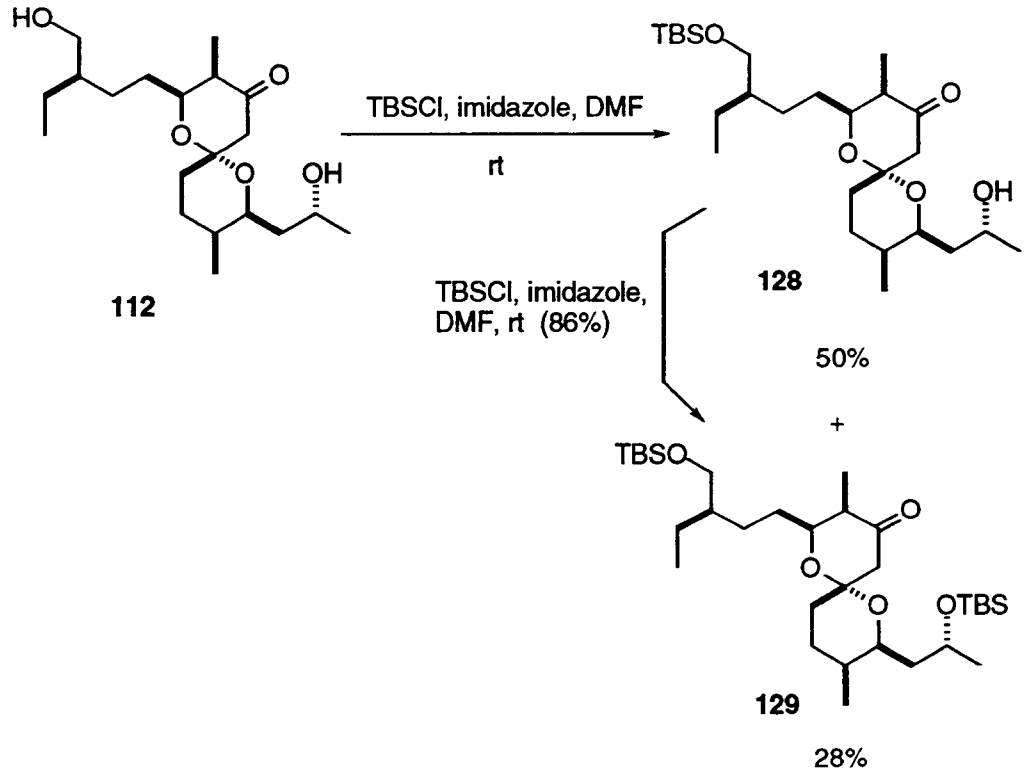
(**Scheme 54**). Clearly, the seemingly minor detail of the alcohol protecting group exercises a profound influence on the sequence of reactions from **92**. Replacement of the *p*-methoxybenzyl ether by a *tert*-butyldimethylsilyl ether not only permits more efficient ozonolysis of **92** but also facilitates Julia coupling of the derived aldehyde **121**.

Unexpectedly, reductive desulfonation of **123** was found to be problematic under the conventional conditions using either 2.5% sodium amalgam or aluminum amalgam[103] in ethanol. In the first case, a desulfonated olefin was isolated, whereas no reaction was observed in the second. However, when **123** was treated with samarium diiodide,[104] the desired pentahydroxy ketone **124** was obtained in excellent yield. Exposure of ketone **124** to hydrogen fluoride and acetonitrile effected removal of all silyl protecting groups and concomitant spiroketalization to give the trihydroxy spiroketal **1** (**Scheme 55**).



Scheme 56

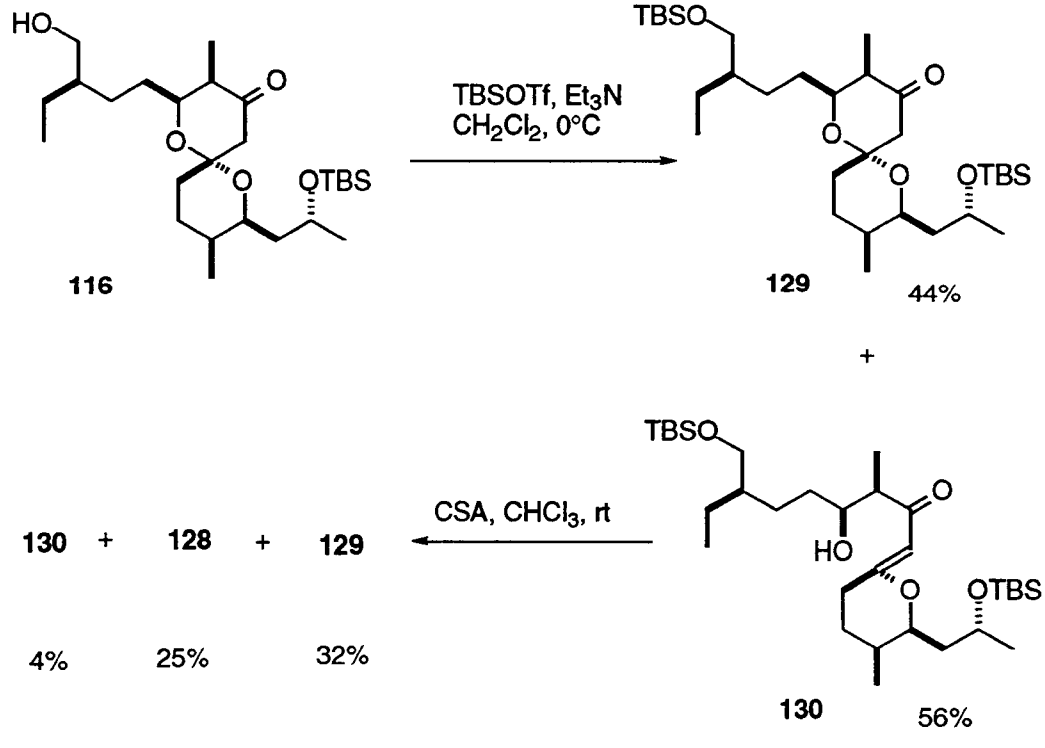
The structure of our synthesized spiroketal **1** was again confirmed by correlation with the same compound obtained from the benzoate **113** provided by Professor Evans. In this case, a modification of the previous sequence from **113** was employed that afforded an improved yield of **1**. Thus, reductive debenzylation[105] of **113** gave alcohol **125**, which was protected as its bissilyl ether **126**. The latter underwent saponification with 1% lithium hydroxide in methanol to yield alcohol **127**, which was deprotected using tetra-*n*-butylammonium fluoride to furnish **1**. This substance was identical by comparison of TLC, IR, ^{1}H and ^{13}C NMR, MS, and optical rotation data with the substance obtained from **124** (**Scheme 56**).



Scheme 57

Differentiation of Hydroxyl Functions (Further Elaboration) of Rutamycin Spiroketal

Our plan for attaching the polypropionate segment (C3-C15) of rutamycin B to the spiroketal portion and completion of the synthesis is shown in **Scheme 13**. It envisions initial formation of the ester linkage at C25 with final closure of the macrocycle across C17-C18. For this purpose, the C19 terminus of the spiroketal was to be transformed to a vinyl iodide in anticipation that the final macrocyclization would be accomplished via a Stille coupling with the polypropionate subunit. For practical reasons, including the fact that a vinyl iodide would be compatible with all subsequent chemistry, we chose to install this functionality before forming the ester linkage. The hydroxy benzoate **125** appeared to be an ideal substrate for developing this route, and efforts therefore focused on bringing forward our synthetic compounds **102** and **1** to this intermediate.

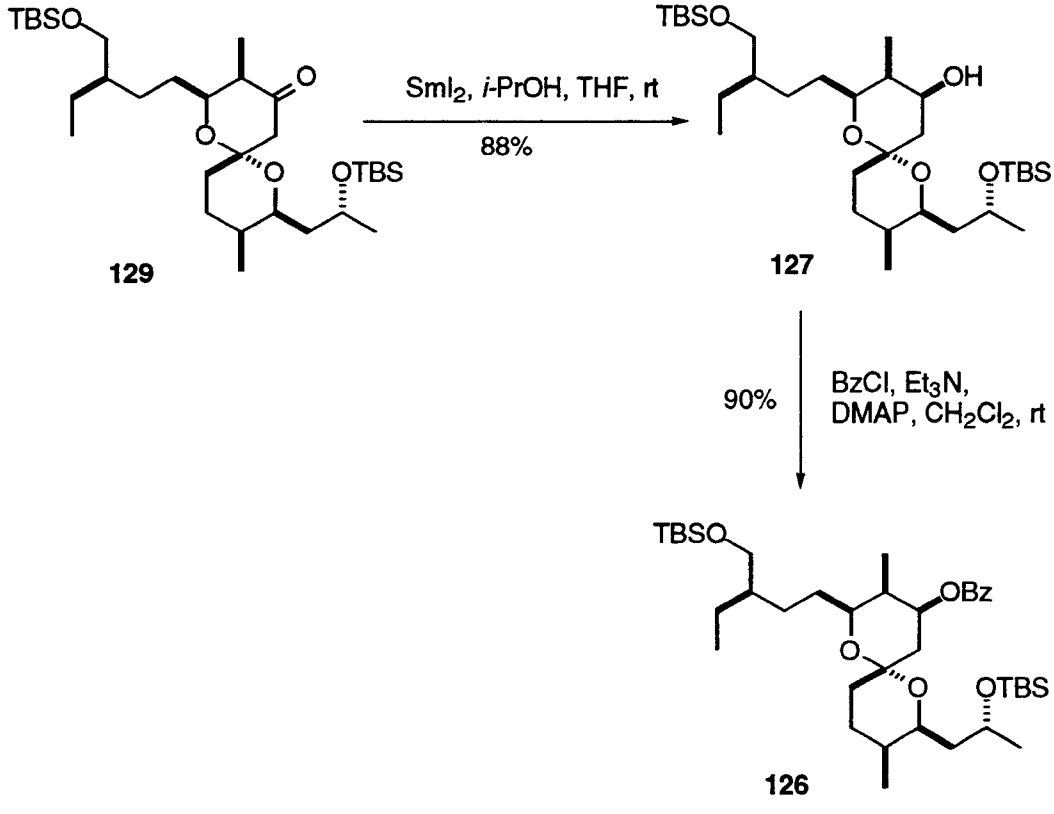


Scheme 58

Correlation of 112 with 125

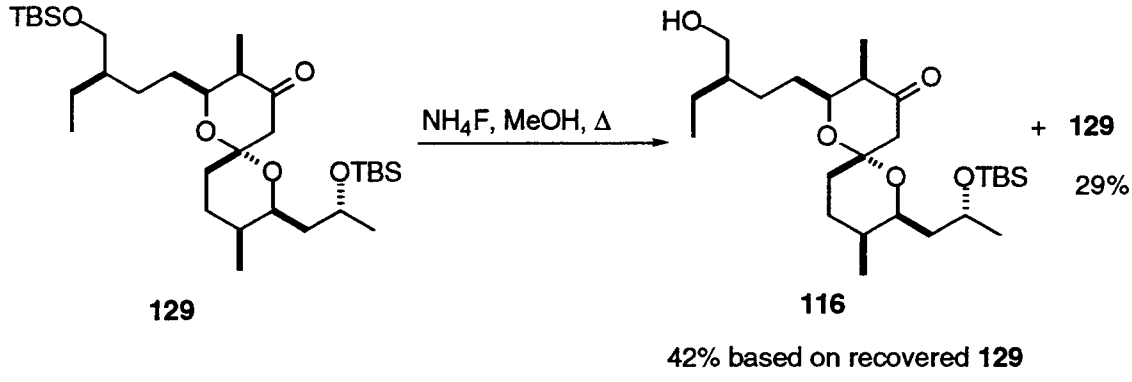
Silylation of dihydroxy ketone **112** with *tert*-butyldimethylsilyl chloride gave the desired bis *tert*-butyldimethylsilyl ether **129** as the minor product along with the monohydroxy ketone **128**. The latter was converted to **129** in good yield after a second silylation (**Scheme 57**). Surprisingly, silylation of **116** with *tert*-butyldimethylsilyl triflate in the presence of triethylamine gave the ring-opened product **130** resulting from elimination along with **129**. Upon treatment with camphorsulfonic acid (CSA), **130** was converted to **129** and the alcohol **128** (**Scheme 58**).

Reduction of ketone **129** with samarium diiodide[106] afforded the expected equatorial alcohol **127** as a single stereoisomer, and this was protected as its benzoate ester **126** (**Scheme 59**).[107]



Scheme 59

Exploratory studies on **129** indicated that selective deprotection of the primary *tert*-butyldimethylsilyl ether was possible with ammonium fluoride in methanol. This



129 **116**

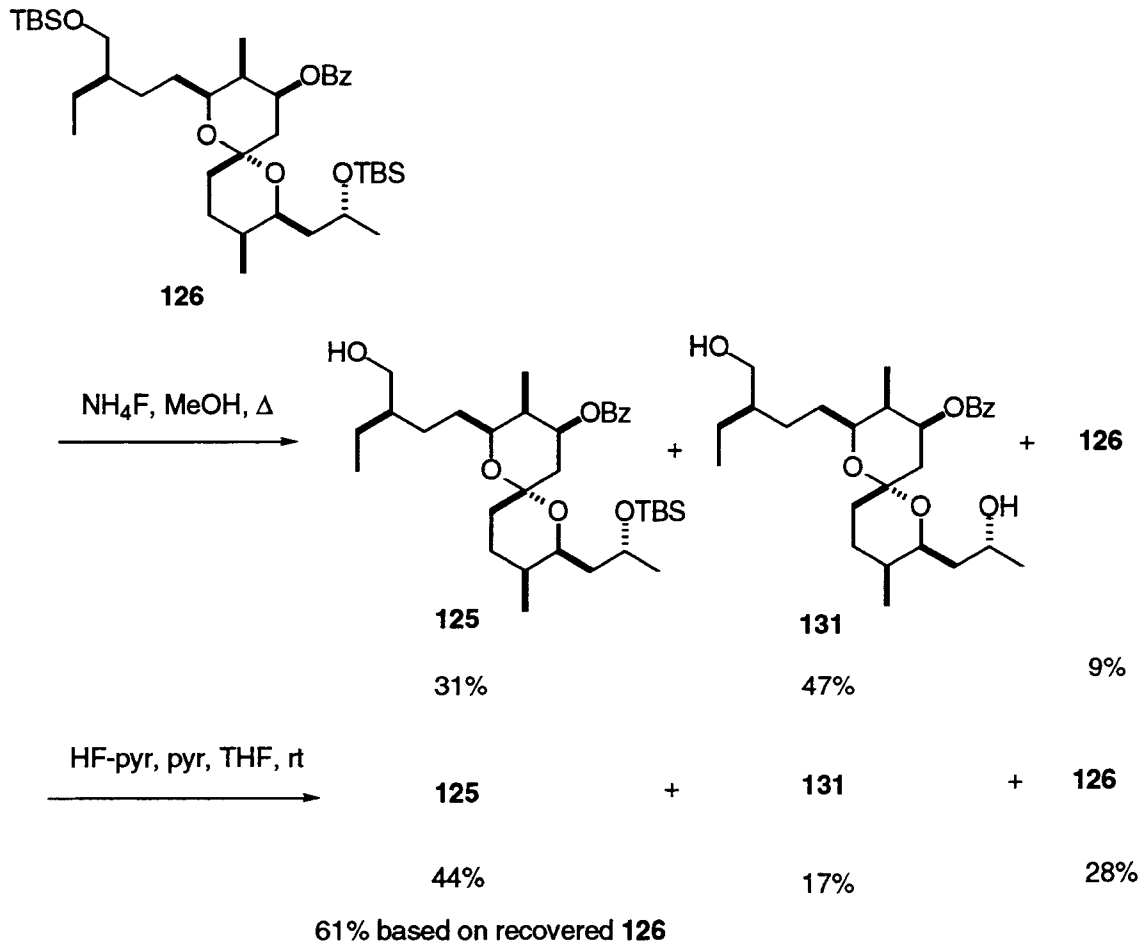
42% based on recovered **129**

Scheme 60

reaction afforded the alcohol **116** in modest, but acceptable yield (**Scheme 60**). However, similar deprotection of **126** was discouraging, diol **131** being the major product of this reaction. Fortunately, treatment of **126** with hydrogen fluoride-pyridine gave a much improved yield of the desired primary alcohol **125** (**Scheme 61**).

Correlation of 1 with 125

With our synthesized keto diol **112** successfully correlated with benzoate **125** derived from Evans' intermediate **113**, we next turned our attention to the convergence of triol **1** with the same hydroxy benzoate. Precedence suggested that, in the presence of silver nitrate,[108] a less hindered secondary alcohol can be selectively silylated in preference to a more crowded secondary alcohol. However, it was found that, although the primary hydroxyl group of **1** could be silylated to give diol **132**, the two secondary alcohols could not be easily distinguished. After considerable experimentation, it was discovered that silylation of **132** using *tert*-butyldimethylsilyl triflate and 2,6-lutidine at

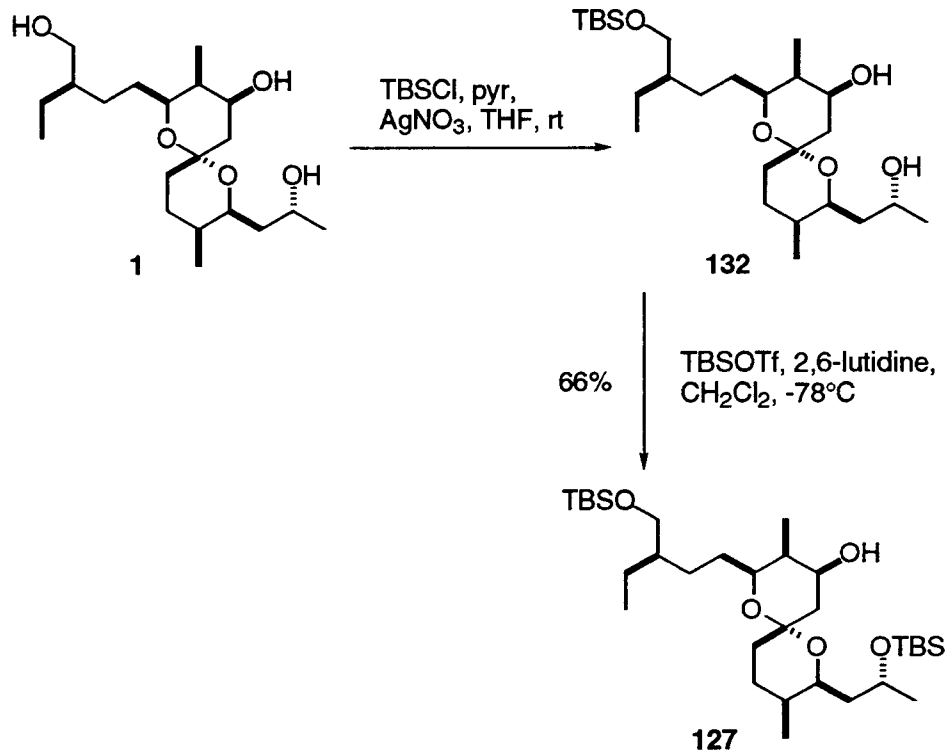


Scheme 61

low temperature[109] gave the desired bisilylated spiroketal **127** in acceptable yield (**Scheme 62**). This alcohol was shown to be identical with **127** obtained from reduction of **129** and was converted to **125** via **126** through the procedure described above.

With the acquisition of spiroketal **125**, a subunit of rutamycin B containing eight of its seventeen stereogenic centers has been prepared. The absolute configuration of these eight centers is firmly established by direct correlation of **125** with a substance, **113**, synthesized independently. Our routes to **125** via dihydroxy ketone **112** and triol **1** each permit synthesis of the spiroketal moiety of rutamycin B in

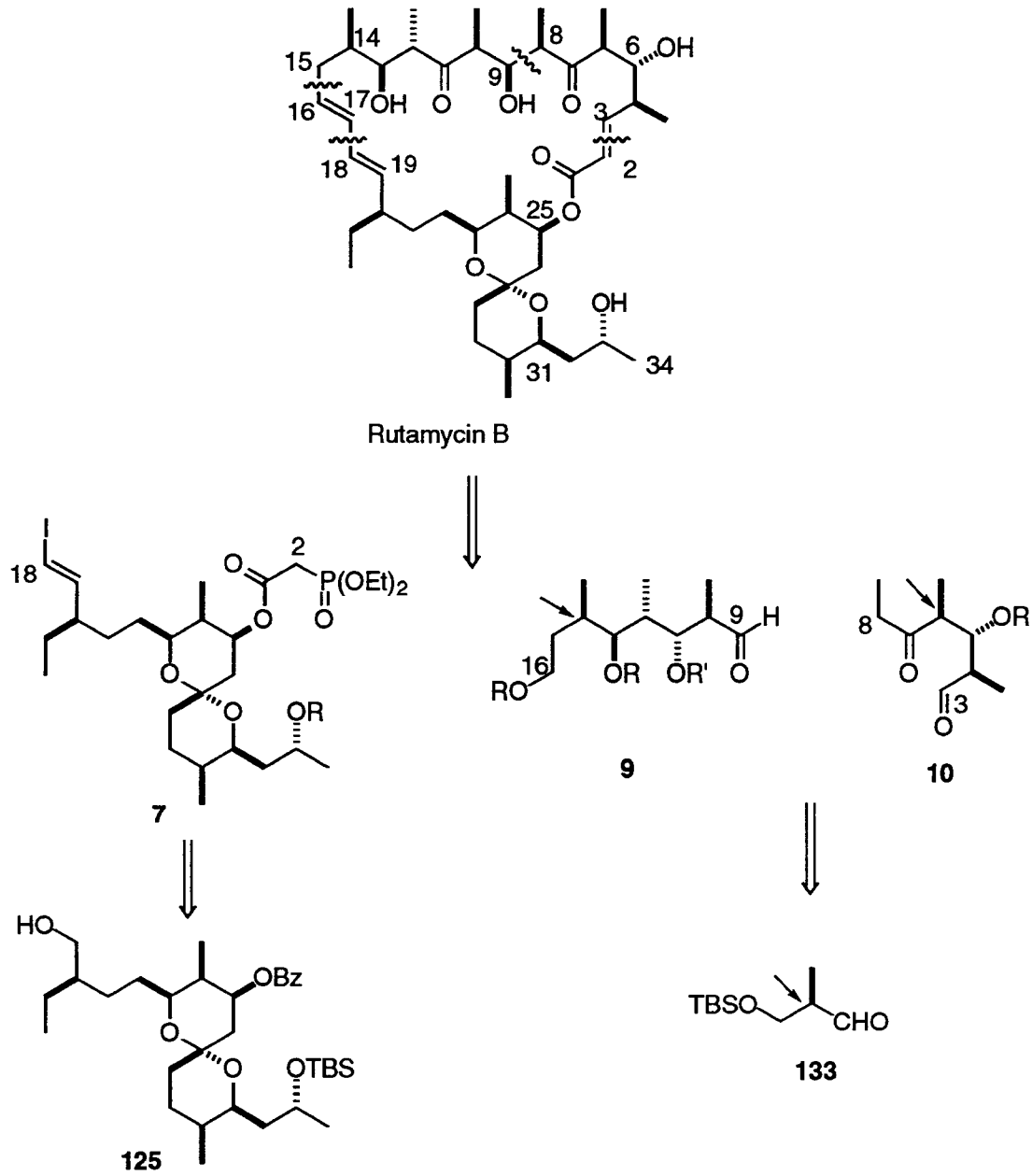
a form that differentiates the three hydroxyl substituents. This last feature becomes important in the context of further elaboration of rutamycin B spiroketal towards the complete macrolide.



Scheme 62

Chapter III: Approaches Toward the Total Synthesis of Rutamycin B

The finalized plan for synthesis of rutamycin B shown in **Scheme 13** calls for the condensation of phosphonate **7** with aldehyde **10** and subsequent aldol coupling of

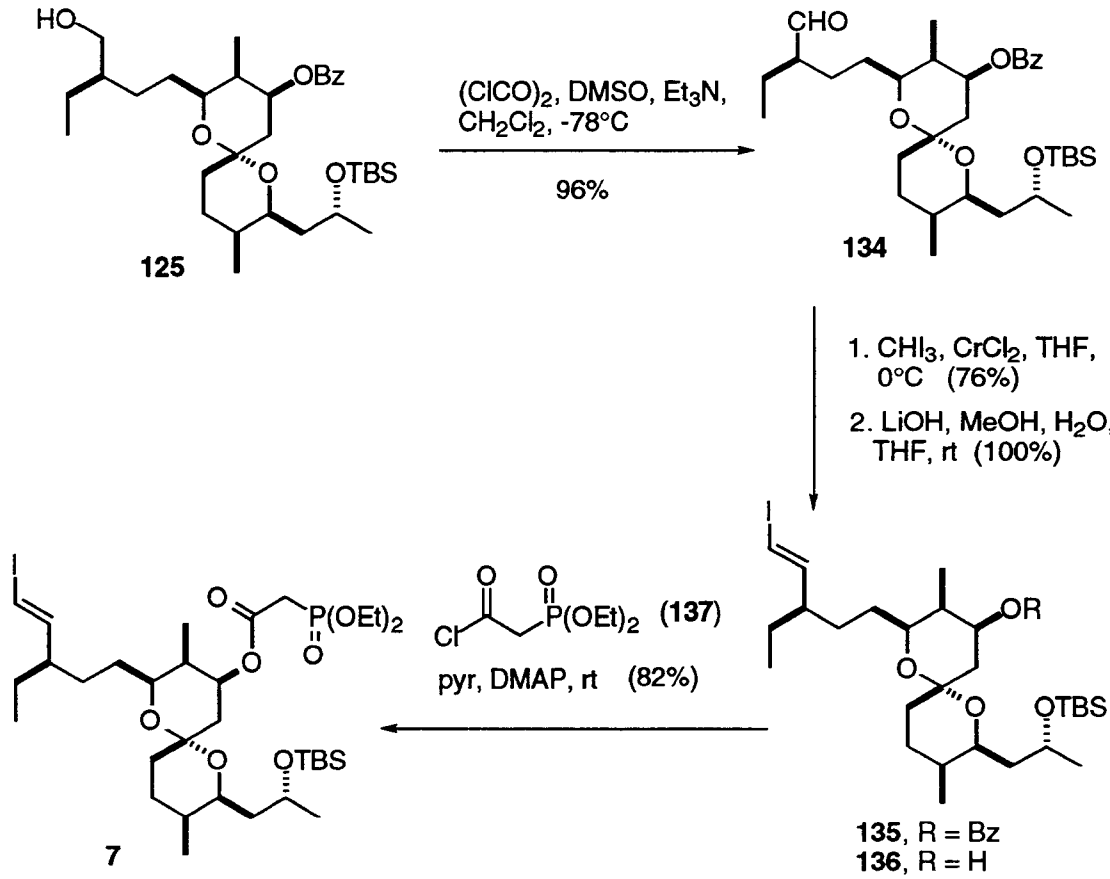


Scheme 63

this assembly with **9**. The spirofragment **7** should be accessible from the hydroxy benzoate **125**, whereas aldehydes **9** and **10** can both be generated from (*R*)-2-methylpropanal (**133**). The latter provides the stereocenters at C6 and C14 of rutamycin B (**Scheme 63**).

Synthesis of Phosphonate 7

The phosphonate **7** was obtained from hydroxy benzoate **125** through a four-step sequence in which aldehyde **134**, derived from Swern oxidation of **125**, underwent



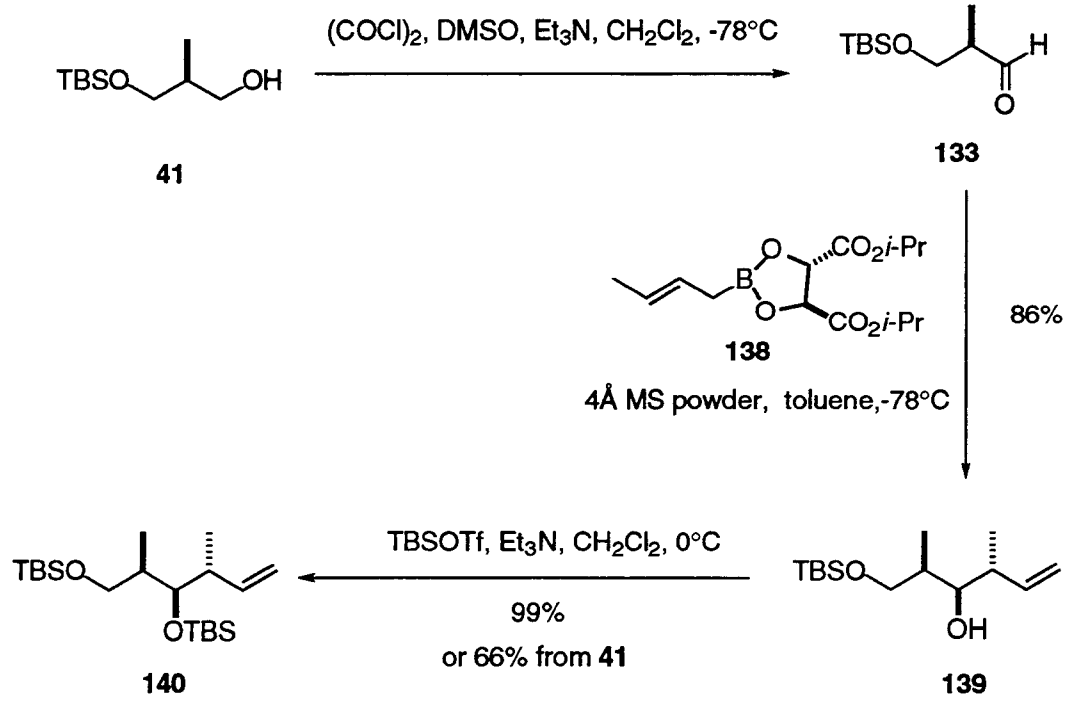
Scheme 64

a Takai[36] reaction with chromium(II) chloride and iodoform to give vinyl iodide **135**. The latter was obtained as a mixture of (*E*) and (*Z*) stereoisomers in the ratio 18:1,

respectively. Saponification of the benzoate of **135** gave alcohol **136**, which was acylated with the phosphonoacetyl chloride **137** to furnish **7** (**Scheme 64**).

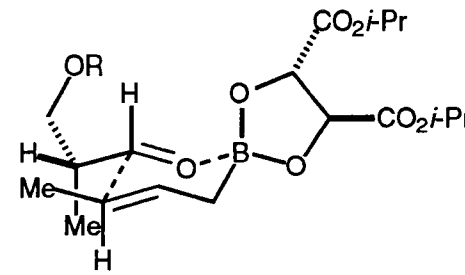
Synthesis of aldehyde 9 (C9-C16 Segment)

The synthesis of **9** began from alcohol **139**, prepared from the hydroxy silyl ether **41** of (2*S*) configuration by a literature procedure.[74b] Treatment of **133**, the product of Swern oxidation of **41**, with the (*E*)-crotylboronate **138**, derived from (*S*,*S*)-diisopropyl tartrate,[74] afforded the *syn, anti* homoallylic alcohol **139**. As shown in **Figure 11**, the ester substituents in the chiral boronate direct the attacking crotyl group towards the *re* face of the carbonyl in a Felkin mode of addition. The *anti* relationship is dictated by the (*E*) configuration of the crotyl double bond. Before proceeding further, the secondary hydroxyl group of **139** was protected as its *tert*-butyldimethylsilyl ether **140** (**Scheme 65**).



Scheme 65

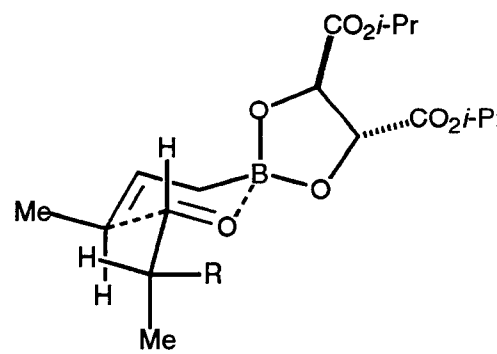
Selective cleavage of the primary silyl ether of **140** with ammonium fluoride gave the alcohol **141**, and a one-carbon homologation of this material was effected



(*E*)-crotyl, *re*- face (Felkin) addition

Fig. 11. Transition state for double asymmetric crotylation of aldehyde **133** with (*S,S*)-Boronate **138**

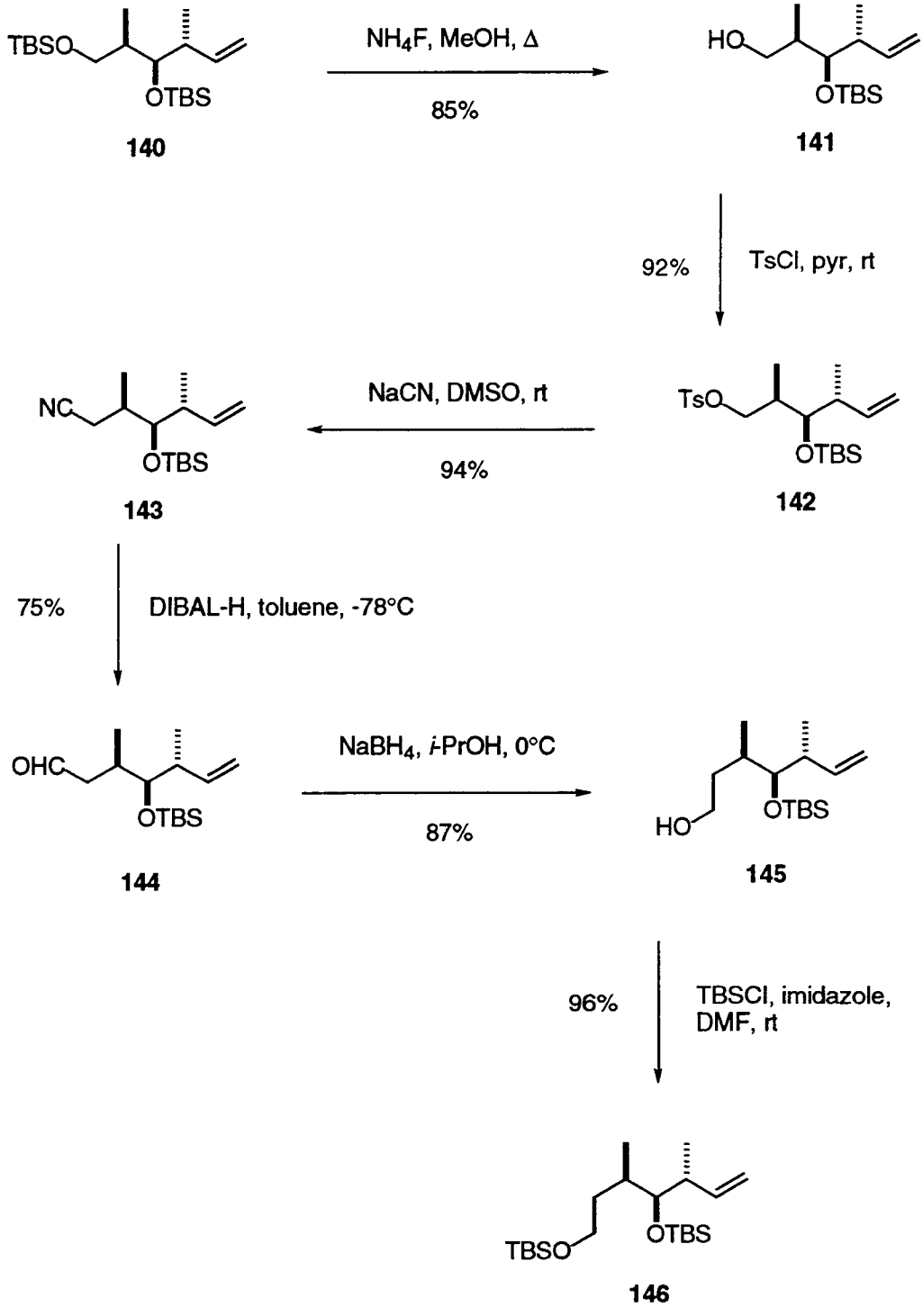
through a standard five-step sequence that led to the bissilyl ether **146**. Thus treatment of **141** with *p*-toluenesulfonyl chloride gave **142** and displacement of the primary tosylate with sodium cyanide in dimethyl sulfoxide yielded **143**. Reduction of this nitrile with diisobutylaluminum hydride afforded aldehyde **144**, which was further



(*E*)-crotyl, *si*- face (Felkin) addition

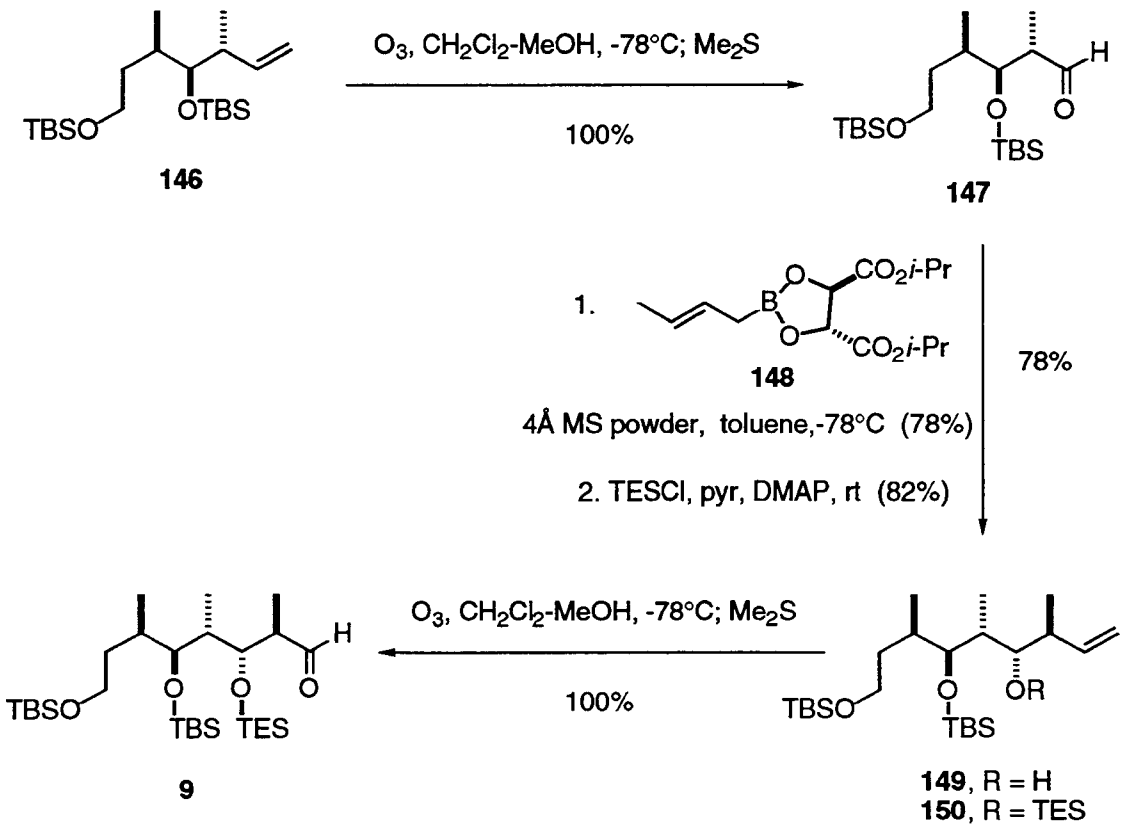
Fig. 12. Transition state for double asymmetric crotylation of aldehyde **147** with (*R,R*)-Boronate **148**

reduced to alcohol **145** with sodium borohydride in isopropyl alcohol. Final silylation of **145** furnished **146** (**Scheme 66**).



Scheme 66

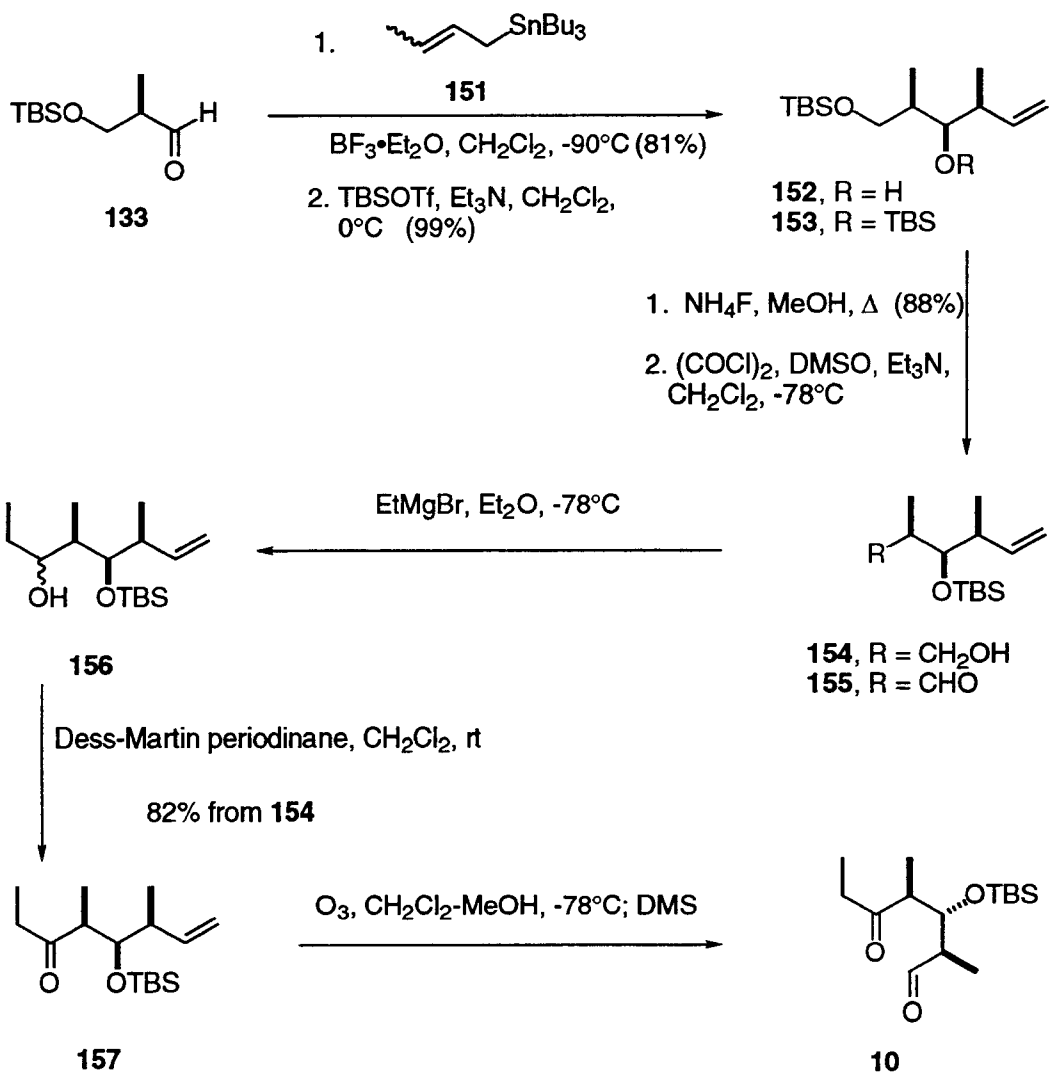
Ozonolytic cleavage of the vinyl group of **146** afforded aldehyde **147** in quantitative yield. A second double asymmetric crotylboronation, in this instance with the (*E*)-crotylboronate **148** derived from (*R*, *R*)-diisopropyl tartrate, gave **149**. Here, Felkin addition of the crotyl group is directed by the boronate to the *si* face of the aldehyde, the (*E*) configuration of the crotyl double bond again dictating an *anti* relationship as shown in **Figure 12**. Protection of the hydroxyl group of **149** as its triethylsilyl (TES) ether **150** was accomplished with triethylsilyl chloride (TESCl) and 4-dimethylaminopyridine in pyridine, and subsequent ozonolysis of the vinyl group delivered aldehyde **9** (**Scheme 67**).



Scheme 67

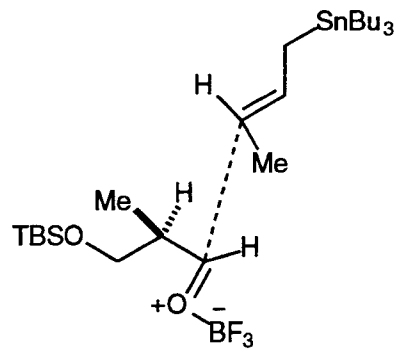
Synthesis of aldehyde 10 (C3-C8 Segment)

Aldehyde **133** was also the point of departure for the synthesis of **10**. Lewis acid promoted addition of a 1:1 mixture of (*E*) and (*Z*) tri-*n*-butylcrotylstannanes (**151**)[110] to **133** yielded the known *syn, syn* adduct **152**. In contrast to the cyclic transition state invoked for boronate addition, crotylstannylation of **133** is not under chelation control; product geometry is therefore decided by the Felkin-Anh rule as applied to the open transition state shown in **Figure 13**. Protection of the secondary



Scheme 68

alcohol of **152** using *tert*-butyldimethylsilyl triflate gave di-*tert*-butyldimethylsilyl ether **153**, which underwent selective removal of the primary silyl group with ammonium fluoride in methanol to give alcohol **154**. Swern oxidation of this alcohol



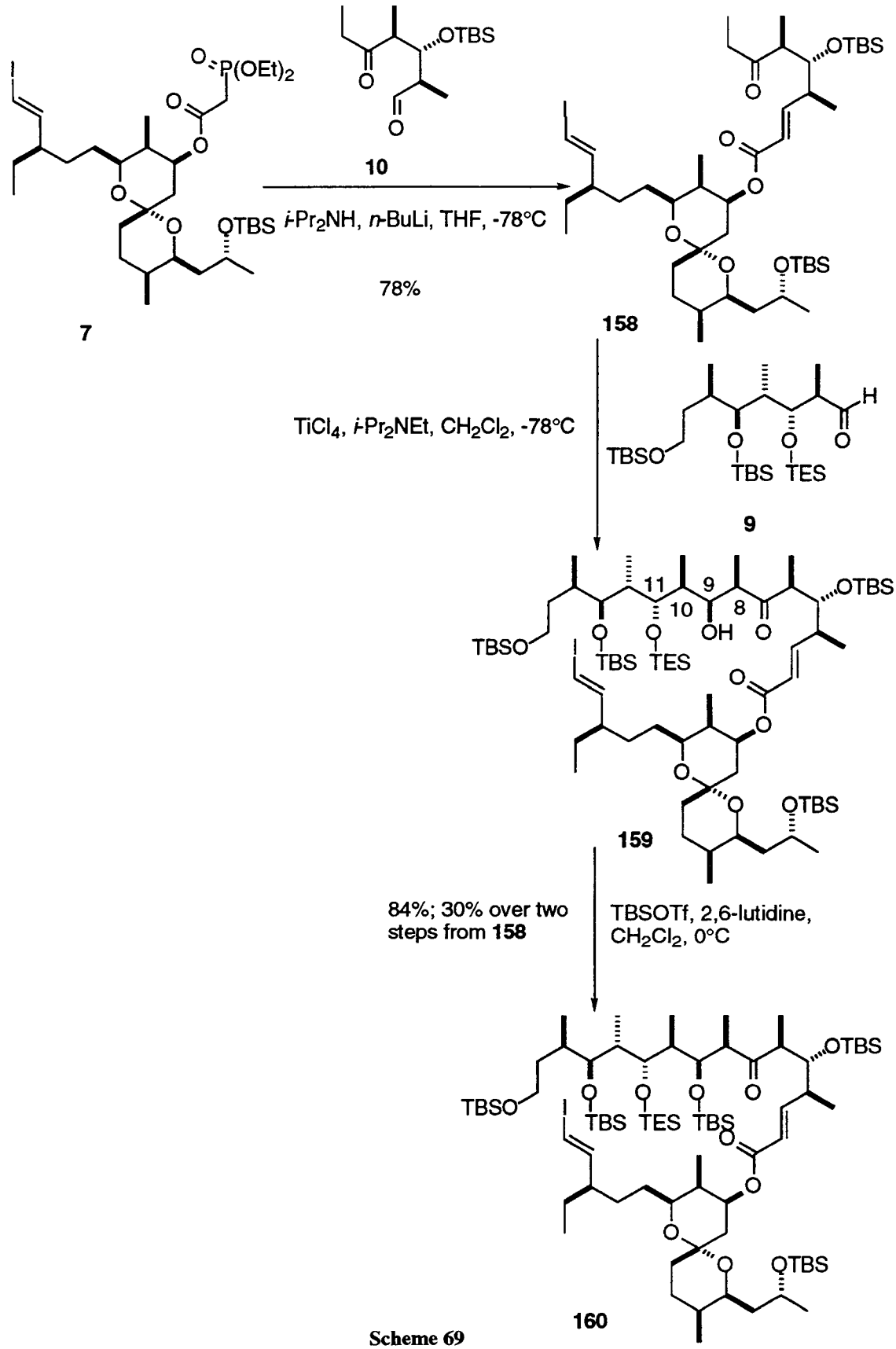
(*E*)-crotyl, *re*-face (Felkin) addition

Fig. 13. Open transition state for crotylstannylation of aldehyde **133** with stannane **151**

yield aldehyde **155**, which was subjected to a Grignard reaction with ethylmagnesium bromide to afford alcohol **156** as a 1:1 mixture of stereoisomers. The mixture was oxidized with Dess-Martin periodinane[111] to a single ketone **157**, which was ozonized to furnish the keto aldehyde **10** (**Scheme 68**).

Assembly of Rutamycin B Subunits

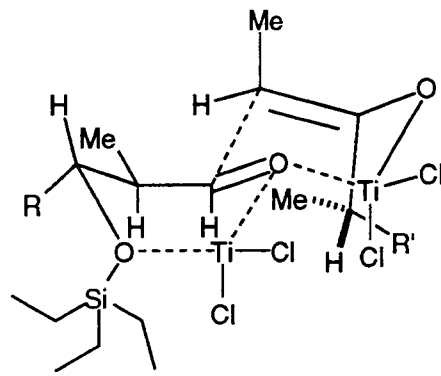
With synthesis of the three principal subunits of rutamycin B completed, attention was directed towards their assembly into a *seco* structure that would require only coupling of the chain ends to close the macrocycle. The sequence in which connection of the subunits **7**, **9** and **10** was envisioned has been discussed above and is formalized in **Scheme 63**. Specifically, our plan entailed initial formation of an ester linkage between **7** and **10**, which would become the lactone of the macrolide, with final


7
10
158
159
160
9
i-Pr2NH, n-BuLi, THF, -78°C
78%
TiCl4, i-Pr2NEt, CH2Cl2, -78°C
84%; 30% over two steps from 158
TBSOTf, 2,6-lutidine, CH2Cl2, 0°C

Scheme 69

closure of the 26-membered ring by connection of olefin termini to forge the diene moiety of rutamycin B.

Coupling of phosphonate **7** with aldehyde **10** was achieved by Wadsworth-Emmons olefination,[32] using lithium diisopropylamide as the base to form the anion of **7**. This yielded ethyl ketone **158**, which underwent aldol coupling as its titanium(IV) enolate[42] with aldehyde **9** to give **159**. The stereochemical outcome at C8 and C9 of **159** is rationalized by the transition state shown in **Figure 14** and reflects a convergence of effects which favor *re* (Felkin) attack at the aldehyde carbonyl of **9** by



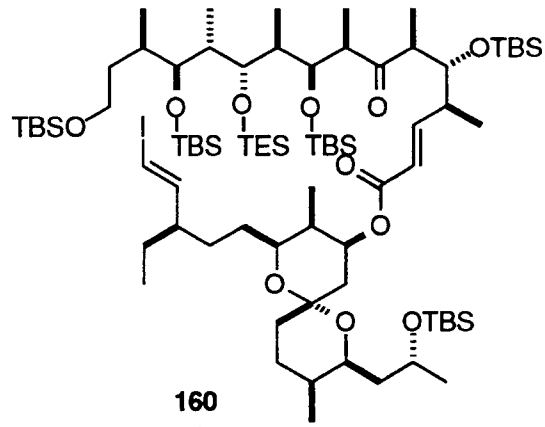
(*Z*) enolate, *re*-face (Felkin) addition

Fig. 14. Chelated transition state for aldol condensation of the titanium enolate of **158** with aldehyde **9**

the *si* face of the (*Z*) titanium enolate of **158**. This stereoselectivity is secured by an architecture that invokes complexation of the aldehyde oxygen of **9** with *two* titanium(IV) species to form a bicyclic array that blocks the *si* face of **9**. Our rational is based on the assumption that the aldehyde carbonyl of **9** is basic enough to coordinate two titanium cations simultaneously[112] and that greater stereocontrol and reactivity arise from a complex of this type. The factors that predispose this crucial aldol

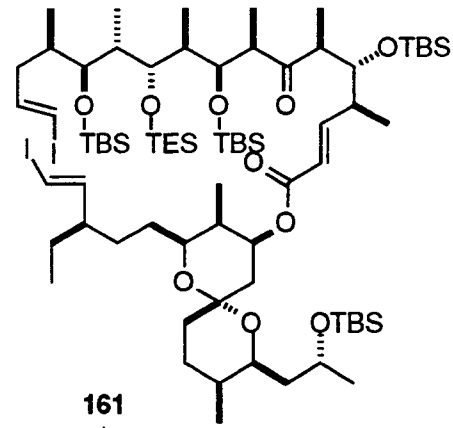
condensation to produce the *syn, syn* configuration across C8-C10 also include the presence of a bulky triethylsilyloxy substituent at the β carbon of the aldehyde component **158**. This substituent obstructs the *anti*-Felkin pathway that frequently attends aldol coupling with (*Z*) enolates.[113] Moreover, the configuration of the α' chiral center of ketone **158** reinforces the Felkin mode of attack on **9** since the largest substituent at this center remains *exo* in the chelated transition state shown in **Figure 14** whereas the methine hydrogen is *endo*.[52] The aldol condensation product **159** was converted to its *tert*-butyldimethylsilyl ether to provide the hexasilylated structure **160** in which the alcohol at C11 that must eventually be converted to a ketone is differentially protected (**Scheme 69**).

The hexasilyl ether **160**, which embodies all seventeen of the stereogenic centers of rutamycin B, is the furthest stage to which the synthesis has presently advanced. This highly functionalized substance now stands ready for conversion to a *seco* intermediate, for which a new macrocyclization protocol is envisioned. Our plan is to construct the bisvinyl iodide **161** through a sequence involving selective deprotection of the primary alcohol, oxidation to an aldehyde, and a Takai reaction with chromium(II) chloride and iodoform.[43] It is hoped that cyclization of the diiodo compound **161** can be accomplished via nickel(0) catalyzed intramolecular coupling using nickel bicyclooctadiene complex.[44] Selective removal of the triethylsilyl group[114] and oxidation of the resulting secondary alcohol with Dess-Martin periodinane (**Scheme 70**) should provide the tetrasilylated derivative **51** of rutamycin B, the final intermediate in Evans' synthesis of the macrolide. Simultaneous removal of all four *tert*-butyldimethylsilyl protecting group was achieved by Evans using hydrofluoric acid in dichloromethane with acetonitrile and gave synthetic rutamycin B (**Scheme 25**) in 98% yield.



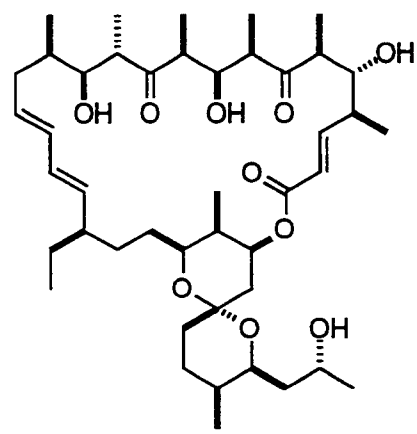
160

1) NH_4F, MeOH, Δ
2) Swern oxidation
3) CHI_3, $CrCl_2$, THF



161

1) $Ni(COD)_2$, bipy
2) TFA, THF-H_2O
3) Dess-Martin oxidation
4) HF-MeCN



Rutamycin B

Scheme 70

Chapter IV: Conclusion

In the course of this research, a convergent asymmetric approach towards the total synthesis of the macrolide rutamycin B was devised that included two successful and three failed asymmetric routes to the 1,7-dioxaspiro[5.5]undecanyl segment. Several methods for constructing multiple chiral centers were explored in the course of a sequence that led to the hydroxy ketone **54**. In particular, the allylboronates and crotylboronates of Roush proved to be invaluable for stereocontrolled elaboration of *syn* and *anti* relationships between vicinal centers, as was Brown's chiral isopinocampheylborane chemistry. In addition, important transformations were tested in complex structural settings that set new limits on their scope and functional group compatibility. These include an application of the Wacker oxidation to a terminal olefin, where the existence of a free β-hydroxy group clearly interfered with efficiency; selective removal of a primary *tert*-butyldimethylsilyl ether in the presence of a secondary silyl ether; directed reduction of a β-hydroxy ketone to an *anti*-1,3-diol with tetramethylammonium triacetoxyborohydride; reductive desulfonation of an α-sulfonyl ketone with samarium diiodide; and crotylstannylation of an α chiral aldehyde using a (*E*, *Z*) mixture of crotylstannanes to give a single isomer. Particularly noteworthy is the aldol coupling of **9** with the titanium enolate of **158** to furnish **159** with very high stereoselectivity. Finally, it can be said that the synthesis of rutamycin B, while not yet complete, has been advanced to a stage where a plausible conclusion can be foreseen.

Chapter V: Experimental Section

General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium or potassium and benzophenone under an argon atmosphere. Toluene, diisopropylamine, diisopropylethylamine, triethylamine, pyridine and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flamed dried under a stream of argon gas and glass syringes were oven dried at 120 °C prior to use.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at a pressure less than 0.25 mm of mercury.

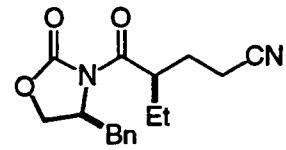
Analytical thin layer chromatography (TLC) was conducted using E. Merck precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, 10% ammonium molybdate in water, a 1% solution of vanillin in 0.1 M sulfuric acid in methanol or 2.5% *p*-anisaldehyde in 88% ethanol, 5% water, 3.5% concentrated sulfuric and 1% acetic acid. Flash chromatography was carried out using either Merck silica gel 60 (230-400 mesh ASTM) or Scientific Adsorbents Incorporated silica gel (40 micron partical size).

Radial chromatography was carried out on individually prepared rotors with layer thicknesses of 1, 2, or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, California.

Melting points were measured using a Büchi melting point apparatus. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at ambient temperature using a 0.9998 decimeter cell with 1 mL capacity. Infrared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order: chemical shift, number of protons, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad), and coupling constant (*J*) in Hertz.

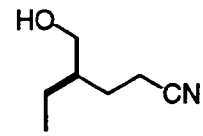
Chemical ionization (CI) high and low resolution mass spectra (HRMS and MS) were obtained using a Finnigan 4023 spectrometer or a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained with a Varian MAT311 or a Finnegan 4000 spectometer. Fast atom bombardment (FAB) mass spectra were obtained using a Kratos MS-50 spectometer. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

Experimental Data

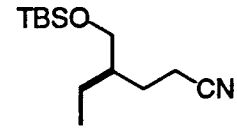


(4*S*)-3-[(2*R*)-4-Cyano-2-ethyl-1-oxobutan-1-yl]-4-(phenylmethyl)-1,3-oxazolidin-2-one (68). To a solution of titanium tetrachloride (1.0 M in dichloromethane, 15.45 mL, 15.45 mmol) in dichloromethane (15 mL) under argon at room temperature was added titanium(IV) isopropoxide (1.53 mL, 5.15 mmol). The resulting solution was stirred for 15 min at room temperature and cooled to 0°C. A solution of **14** (5.10 g, 20.6 mmol) in dichloromethane (30 mL) was added dropwise via cannula followed by diisopropylethylamine (4.33 mL, 24.8 mmol). This mixture was stirred for 1 h at 0°C and acrylonitrile (2.72 mL, 41.3 mmol) was added dropwise. The resultant mixture was stirred for 18.5 h at room temperature and dichloromethane (300 mL) and 1 N sodium bisufate solution (300 mL) were added. This mixture was stirred for 30 min and separated. The aqueous layer was extracted three times with dichloromethane (200 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, yielded 5.27 g (85%) of **68** as a colorless oil: $[\alpha]_D^{22}$ -20.1° (*c* 1.15, $CHCl_3$); IR (neat) 2970, 2936, 1778, 1693, 1454, 1391, 1214, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.93 (3H, t, *J* = 7 Hz), 1.48-1.62 (1H, m, *J* = 7 Hz), 1.68-1.81 (1H, m, *J* = 7 Hz), 1.82-1.93 (1H, m), 2.07-2.19 (1H, m, *J* = 8 Hz), 2.37 (2H, t, *J* = 7 Hz), 2.74-2.81 (1H, dd, *J* = 13, 10 Hz), 3.29-3.35 (1H, dd, *J* = 13, 4 Hz), 3.73-3.82 (1H, quint, *J* = 7 Hz), 4.19 (2H, t, *J* = 3 Hz), 4.64-4.71 (1H, dq, *J* = 7, 4 Hz), 7.19-7.22 (2H, m), 7.28-7.35 (3H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 11.2, 15.0, 24.8, 26.7, 37.9,

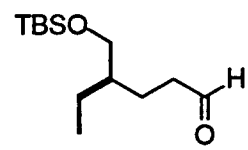
43.3, 55.5, 66.2, 119.1, 127.3, 128.9(2C), 129.3(2C), 135.1, 153.0, 174.6; Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.59; H, 6.66; N, 9.43.



(4*R*)-4-(Hydroxymethyl)pentanenitrile (69). To a solution of **68** (1.30 g, 4.30 mmol) in tetrahydrofuran (30 mL) under argon at 0°C was added a solution of lithium borohydride (2.0 M in tetrahydrofuran, 2.38 mL, 4.76 mmol). The resulting solution was stirred for 16 h at room temperature and quenched with methanol (3 mL). This mixture was stirred for 3 h and water (30 mL) was added. The resultant mixture was extracted three times with ether (50 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ether in hexane as eluant, yielded 578 mg (76%) of **67** and 369 mg (67%) of **69** as a colorless oil: $[\alpha]_D^{22}$ -7.1° (*c* 0.97, $CHCl_3$); IR (neat) 3419 (br), 2963, 2933, 2878, 2247, 1460, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.93 (3H, t, *J* = 7 Hz), 1.32-1.43 (3H, m), 1.54-1.60 (1H, m, *J* = 6 Hz), 1.61-1.81 (2H, m), 2.43 (2H, t, *J* = 8 Hz), 3.52-3.59 (1H, m, *J* = 5 Hz), 3.63-3.70 (1H, q, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 11.0, 15.0, 23.1, 26.8, 40.8, 64.2, 120.0; Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.52; H, 10.22; N, 10.86.

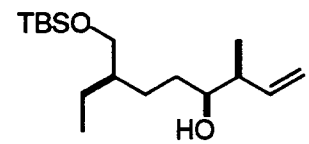


(4*R*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]pentanenitrile (70). To a solution of **69** (340 mg, 2.67 mmol) in dimethylformamide (6 mL) under argon at 0°C was added imidazole (254 mg, 3.74 mmol) followed by a solution of *tert*-butyldimethylsilyl chloride (483 mg, 3.20 mmol) in dimethylformamide (1.5 mL). The resulting solution was stirred for 2 d at room temperature and water (20 mL) was added. This mixture was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ether in pentane as eluant, yielded 585 mg (91%) of **70** as a colorless oil: $[\alpha]_D^{22}$ -3.5° (*c* 0.95, $CHCl_3$); IR (neat) 2958, 2932, 2883, 2860, 2247, 1467, 1255, 1097, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, s), 0.89 (9H, s), 0.91 (3H, t, *J* = 8 Hz), 1.20-1.41 (2H, m, *J* = 7 Hz), 1.49-1.58 (1H, m), 1.61-1.79 (2H, m), 2.41 (2H, t, *J* = 8 Hz), 3.45-3.51 (1H, dd, *J* = 10, 6 Hz), 3.57-3.62 (1H, dd, *J* = 10, 4 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.7, -5.6, 11.1, 15.0, 18.0, 23.2, 25.7(3C), 27.2, 40.9, 64.4, 120.1; Anal. Calcd for $C_{13}H_{27}NOSi$: C, 64.66; H, 11.27; N, 5.80. Found: C, 64.90; H, 11.32; N, 5.68.



(4*R*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]hexanal (64). To a solution of **70** (130 mg, 0.540 mmol) in hexane (6 mL) under argon at -78°C was added a solution of diisobutylaluminum hydride (1 M in hexane, 0.650 mL, 0.650 mmol) dropwise. The

resulting solution was stirred for 2 h at -78°C, quenched with methanol (1 mL) and saturated ammonium chloride solution (50 mL) was added. This mixture was stirred for 2 h at room temperature, diluted with ether (100 mL) and separated. The ether layer was washed with 0.6 N hydrochloric acid solution (60 mL) and brine (60 mL). The aqueous washings were extracted three times with ether (60 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent yielded 123 mg (93%) of **64** as a pale yellow oil which was used without purification: IR (neat) 2958, 2932, 2883, 2859, 1728, 1467, 1254, 1084, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.86-0.91 (3H, m), 0.89 (9H, s), 1.28-1.45 (3H, m), 1.59-1.73 (2H, m), 2.42-2.48 (2H, dt, J = 8, 2 Hz), 3.44-3.56 (2H, dq, J = 10, 6 Hz), 9.77 (1H, t, J = 2 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5(2C), 11.2, 18.2, 23.1, 23.5, 25.9(3C), 41.4, 41.5, 64.8, 202.9.



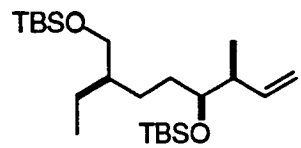
(3*S*,4*S*,7*R*)-7-[(*tert*-Butyldimethylsilyl)oxymethyl]-4-hydroxy-3-methyl-1-nonene (72). To a suspension of potassium *tert*-butyloxide (15.0 g, 0.134 mol) in tetrahydrofuran (70 mL) under argon at -78°C was added *cis*-2-butene (11.0 mL, 0.123 mol) dropwise via cannula, followed by *n*-butyllithium (1.6 M in hexane, 64.0 mL, 0.102 mol). The resulting mixture was stirred for 1 h at -78°C, allowed to warm to -25°C, and stirred for 45 min at -25°C. After the mixture was recooled to -78°C, triisopropyl borate (23.6 mL, 0.102 mol) was added dropwise. This mixture was stirred for 30 min at -78°C and quenched with 1 N hydrochloric acid solution (40 mL). The resultant mixture was thoroughly stirred with additional 1 N hydrochloric acid

solution (140 mL) and extracted with ethyl acetate, and the combined organic layers were added to powdered 4Å molecular sieves (50 g) and diethanolamine (8.66 mL, 89.0 mmol) under argon at room temperature. This mixture was stirred for 3 h and filtered with an ethyl acetate rinse. Removal of the organic solvent from the filtrate gave 11.4 g of crude (*Z*)-crotylamine complex as a white solid which was recrystallized from dichloromethane and ether. The colorless crystalline material was stored under argon.

To a rapidly stirred suspension of the (*Z*)-crotylamine complex (1.90 g, 11.2 mmol) in ether (36 mL) under argon at room temperature was added (*S,S*)-diisopropyl tartrate (2.39 mL, 11.2 mmol). The mixture was stirred for 5 min, brine (36 mL) was added, and rapid stirring was continued for 5 min. The mixture was extracted three times with ether (60 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent gave 3.29 g of **71** as a colorless oil which was used immediately.

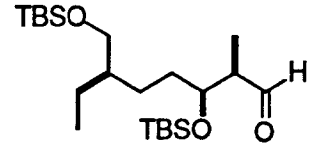
To a mixture of **71** (3.29 g, 11.0 mmol) and powdered 4Å molecular sieves (5 g) in toluene (20 mL) under argon at -78°C was added a solution of **64** (0.650 g, 2.66 mmol) in toluene (4 mL) dropwise. The resulting mixture was stirred for 2.5 d at -78°C. A 1 N sodium hydroxide solution (50 mL) was added and the mixture was stirred for 1.5 h at room temperature. The cloudy mixture was extracted three times with ether (80 mL), and the combined organic layers were washed with brine and dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 10% ethyl acetate in hexane as eluant, gave 0.676 g (85%) of **72** as a colorless oil: $[\alpha]_D^{22}$ -15.7° (*c* 0.85, $CHCl_3$); IR (neat) 3379 (br), 2958, 2932, 2890, 2860, 1466, 1253, 1094, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.88 (3H, d, *J* = 7 Hz), 0.89 (9H, s), 1.02 (3H, d, *J* = 7 Hz), 1.21-1.58 (8H, m), 2.23-2.34 (1H, m, *J* = 7 Hz), 3.45-3.50 (3H, m, *J* = 5 Hz), 5.05-5.12 (2H, dd, *J* = 12, 6, 1

Hz), 5.74-5.86 (1H, m, J = 7, 2 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5(2C), 11.1, 13.9, 18.2, 23.5, 25.8(3C), 26.8, 31.1, 41.9, 43.2, 65.1, 75.1, 115.0, 141.1; HRMS (CI) *m/z* 301.2561 (calcd for $C_{17}H_{36}O_2Si$ + H^+: 301.2564); Anal. Calcd for $C_{17}H_{36}O_2Si$: C, 67.93; H, 12.07. Found: C, 68.00; H, 12.23. This compound was contaminated by a small amount (*de* 5:1 by ^{13}C NMR) of a second stereoisomer.

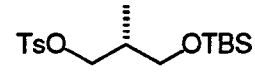


(3*S*,4*S*,7*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7-[(*tert*-butyldimethylsilyl)oxymethyl]-3-methyl-1-nonene (73). To a solution of **72** (116 mg, 0.390 mmol) in dichloromethane (4 mL) under argon at 0°C was added triethylamine (0.136 mL, 0.975 mmol) dropwise, followed by *tert*-butyldimethylsilyl triflate (0.125 mL, 0.546 mmol). The resulting mixture was stirred for 1 h at 0°C and saturated sodium bicarbonate solution (20 mL) was added. This mixture was extracted three times with ether (40 mL), and the combined organic layers were washed with water (100 mL) and dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 5% ethyl acetate in hexane as eluant, produced 153 mg (97%) of **73** as a pale yellow oil: $[\alpha]_D^{22}$ -11.7° (*c* 1.13, $CHCl_3$); IR (neat) 2967, 2934, 2891, 2859, 1473, 1306, 1090, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.03 (12H, m), 0.87 (3H, d, J = 7 Hz), 0.89 (18H, 2s), 0.96 (3H, d, J = 7 Hz), 1.19-1.43 (7H, m), 2.24-2.33 (1H, m, J = 7 Hz), 3.45-3.53 (3H, dd, J = 12, 5 Hz), 4.96-5.03 (2H, dd, J = 10, 1 Hz), 5.79-5.91 (1H, dq, J = 7, 3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -4.5, -4.3, -3.1, 11.1, 14.8, 18.1(2C), 23.4, 25.6(6C), 28.9, 31.0, 42.2, 42.5, 65.1, 76.2, 113.5,

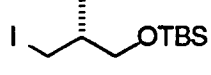
141.7; HRMS (CI) *m/z* 415.3426 (calcd for $C_{23}H_{50}O_2Si_2$ + H^+: 415.3429); Anal. Calcd for $C_{23}H_{50}O_2Si_2$: C, 66.59; H, 12.15. Found: C, 66.74; H, 12.29.



(2*R*,3*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-[(*tert*-butyldimethylsilyl)oxymethyl]-2-methyloctanal (55). A stream of ozone was passed through a solution of **73** (179 mg, 0.430 mmol) in dichloromethane (3.5 mL) and methanol (1.5 mL) at -78°C for 5 min. The excess ozone was purged with argon for 30 min, a catalytic amount of potassium bicarbonate and dimethyl sulfide (3 mL) was added, and the mixture was stirred at room temperature for 23 h. The solvent was removed under reduced pressure and the residue was purified on silica gel, using 2% ethyl acetate in hexane as eluant, to yield 173 mg (96%) of **55** as a colorless oil: $[\alpha]_D^{22}$ -18.7° (*c* 2.70, $CHCl_3$); IR (neat) 2957, 2932, 2889, 2859, 1729, 1467, 1254, 1089, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.05 (3H, d, *J* = 10 Hz), 0.86 (9H, s), 0.87 (3H, d, *J* = 7 Hz), 0.88 (9H, s), 1.05 (3H, d, *J* = 7 Hz), 1.10-1.59 (7H, m), 2.42-2.50 (1H, m), 3.42-3.52 (2H, dq, *J* = 10, 6 Hz), 4.05-4.11 (1H, dt, *J* = 7, 4 Hz), 9.76 (1H, s); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.6, -5.5, -4.8, -4.3, 7.4, 11.1, 17.9, 18.2, 23.3, (25.7, 25.8)(6C), 26.5, 31.6, 41.9, 51.0, 64.8, 72.4, 205.4; MS (CI) *m/z* 416 (M^+), 415, 401, 359, 343, 301, 227, 199, 173, 135, 119, 95; HRMS (CI) *m/z* 359.2438 (calcd for $C_{22}H_{48}O_3Si_2$ - C_4H_9: 359.2439).

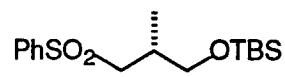


(2*R*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-(*p*-toluenesulfonyloxy)propane (75). To a solution of **74** (12.67 g, 62.10 mmol) in pyridine (120 mL) at 0°C was added *p*-toluenesulfonyl chloride (17.76 g, 93.15 mmol). The resulting mixture was stirred for 23 h at room temperature and was quenched with water (6 mL). This mixture was added to water (400 mL) and ether (700 mL), and the layers were separated. The aqueous layer was extracted three times with ether (400 mL), and the combined ethereal extracts were washed with 1 N hydrochloric acid solution (500 mL), saturated sodium bicarbonate solution (500 mL) and brine (500 mL), and was dried (magnesium sulfate). Removal of the solvent gave 20.39 g of crude **75** as a yellow oil. A small sample was purified on silica gel, using 10% ethyl acetate in hexane as eluant: IR (neat) 2956, 2932, 2885, 2858, 1364, 1307, 1025, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ -0.02 (6H, s), 0.81 (9H, s), 0.87 (3H, d, J = 7 Hz), 1.93 (1H, m), 2.44 (3H, s), 3.42 (1H, dd, J = 10, 7 Hz), 3.48 (1H, dd, J = 10, 5 Hz), 3.92 (1H, dd, J = 10, 6 Hz), 4.01 (1H, dd, J = 10, 6 Hz), 7.32 (2H, d, J = 8 Hz), 7.79 (2H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ -5.9(2C), 12.9, 18.1, 21.7, 25.7(3C), 35.5, 63.7, 72.1, 128.3(2C), 130.1(2C), 131.5, 144.6; Anal. Calcd for $C_{17}H_{30}O_4SSi$: C, 56.94; H, 8.43. Found: C, 56.98; H, 8.56.



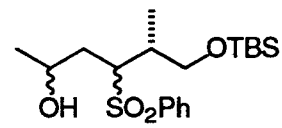
(2*R*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-iodopropane (76). A stirred solution of **75** (20.39 g) and sodium iodide (17.07 g, 113.9 mmol) in acetone (300 mL)

under argon was heated at reflux for 20 h and allowed to cool to room temperature. The mixture was filtered and the filtrate was washed with saturated sodium thiosulfate solution (100 mL), water (100 mL), and brine (100 mL) and was dried (magnesium sulfate). Removal of the solvent gave 16.89 g of crude **76** as a pale yellow oil. A small sample was purified on silica gel, using 10% ethyl acetate in hexane as eluant: IR (neat) 2956, 2929, 2896, 2858, 1471, 1257, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.06 (6H, s), 0.90 (9H, s), 0.96 (3H, d, J = 7 Hz),1.62 (1H, m), 3.22-3.33 (2H, m), 3.41 (1H, dd, J = 10, 7 Hz), 3.52 (1H, dd, J = 10, 5 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5(2C), 13.8, 17.2, 18.2, 25.8(3C), 37.9, 66.6.



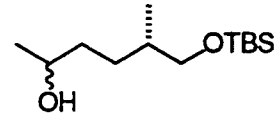
(2*R*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-propylphenylsulfone (77). A mixture of **76** (16.89 g) and sodium phenylsulfinate (17.66 g, 107.6 mmol) in dimethylformamide (250 mL) under argon was stirred at 37°C for 37 h and allowed to cool to room temperature. The solution was diluted with ether (500 mL), and saturated sodium bicarbonate solution (500 mL) was added. After separation, the aqueous layer was extracted three times with ether (400 mL), and the combined organic extract was washed with saturated sodium bicarbonate solution (500 mL) and brine (500 mL), and was dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 15% to 20% ethyl acetate in hexane, to yield 14.30 g (81% from **74**) of **77** as a pale yellow oil: $[\alpha]_D^{22}$ -2.5° (*c* 1.53, $CHCl_3$); IR (neat) 2956, 2930, 2885, 2858, 1472, 1307, 1025, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ -0.03 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.05 (3H, d, J = 7 Hz), 2.19 (1H, m), 2.84 (1H, dd, J = 14, 8 Hz), 3.34 (1H, dd, J = 10, 6

Hz), 3.40 (1H, dd, J = 14, 4 Hz), 3.53 (1H, dd, J = 10, 5 Hz), 7.53-7.66 (3H, m), 7.90-7.92 (2H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ -5.6(2C), 16.7, 18.1, 25.8(3C) 31.6, 59.0, 66.4, 127.8(2C), 129.2(2C), 133.5, 140.1; Anal. Calcd for $C_{16}H_{28}O_3SSi$: C, 58.49; H, 8.59. Found: C, 58.41; H, 8.76.

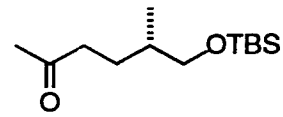


Hydroxy Sulfone (78). To a solution of **77** (7.00 g, 23.7 mmol) in tetrahydrofuran (70 mL) under argon at -78°C was added *n*-butyllithium (1.6 M in hexane, 17.5 mL, 26.1 mmol) dropwise. The resulting mixture was stirred for 20 min at -78°C and hexamethylphosphoramide (4.98 mL, 28.4 mmol) was added. The mixture was stirred for 10 min at -78°C and a solution of propylene oxide (2.24 mL, 32 mmol) in tetrahydrofuran (45 mL) was added dropwise via cannula. The reaction flask was placed in an ice-water bath and the mixture was stirred for 4 h at 0°C. The reaction was quenched with saturated ammonium chloride solution (161 mL), and the mixture was extracted three times with ether (200 mL). The combined ethereal extracts were washed with brine (500 mL) and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 20% to 40% ethyl acetate in hexane, to yield 12.7 g (92%) of **78** as a colorless oil: IR (neat) 2957, 2930, 2886, 2858, 1472, 1289, 1085, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ -0.08 (3H, s), -0.03 (3H, s), 0.82 (9H, s), 0.93 (3H, d, J = 7 Hz), 1.14 (3H, d, J = 6 Hz), 1.60-1.69 (1H, m), 2.11-2.20 (2H, m), 2.64 (1H, d, J = 4 Hz), 3.32 (1H, t, J = 10 Hz), 3.42 (1H, dd, J = 10, 5 Hz), 3.66 (1H, dt, J = 8, 2 Hz), 3.80-3.86 (1H, m), 7.53-7.67 (3H, m), 7.87-7.90 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ

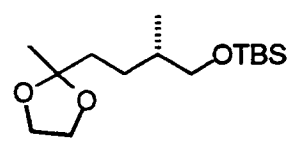
-5.6(2C), 10.4, 18.0, 23.4, 25.7(3C), 31.6, 34.4, 61.0, 64.9, 66.5, 128.5(2C), 129.2(2C), 133.6, 138.6; Anal. Calcd for $C_{19}H_{34}O_4SSi$: C, 59.02; H, 8.86. Found: C, 59.01; H, 9.01.



Hydroxy Silyl Ether (79). A mixture of **78** (5.36 g, 13.9 mmol) and sodium amalgam (2.5%, 192 g, 208 mmol) in ethanol (130 mL) under argon was stirred for 21 h at room temperature and the solvent was decanted. The residue was washed twice with ethanol (100 mL), and the combined ethanol washings were added to saturated ammonium chloride solution (250 mL). The mixture was extracted three times with ether (300 mL), and the combined ethereal extracts were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 20% to 40% ethyl acetate in hexane, to yield 2.80 g (92%) of **79** as a colorless oil: IR (neat) 3354 (bd), 2958, 2932, 2891, 2859, 1467, 1254, 1097, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, s), 0.87 (3H, d, J = 7 Hz), 0.89 (9H, s), 1.19 (3H, d, J = 6 Hz), 1.41-62 (5H, m), 3.37-3.43 (2H, m), 3.72-3.80 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5(2C), 16.7, 18.2, 23.2, 25.8(3C), 29.1, 35.6, 36.6, 68.1, 68.2; Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.46; H, 12.49.

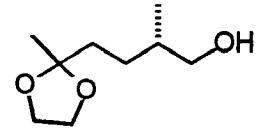


(5*S*)-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]hex-2-one (80). A solution of **79** (5.19 g, 21.1 mmol), pyridinium chlorochromate (7.28 g, 33.8 mmol), and sodium acetate (0.42 g, 5.00 mmol) in dichloromethane (250 mL) under argon was stirred for 5 h at room temperature and was diluted with ether (250 mL). The mixture was passed through a column of Florisil and the residue in the reaction flask was sonicated three times, each for 5 min, with ether (250 mL). The ethereal solution was passed through the same column of Florisil and combined with the previous column eluant. Removal of the solvent followed by chromatography of the residue on silica gel, using 15% ethyl acetate in hexane as eluant, yielded 4.70 g (92%) of **80** as a colorless oil: $[\alpha]_D^{22}$ -9.2° (*c* 2.13, $CHCl_3$); IR (neat) 2956, 2932, 2890, 2860, 1719, 1468, 1254, 1093, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.86 (3H, d, *J* = 7 Hz), 0.89 (9H, s), 1.32-1.44 (1H, m), 1.52-1.62 (1H, m, *J* = 6 Hz), 1.63-1.75 (1H, m), 2.13 (3H, s), 2.24-2.48 (2H, m), 3.40-3.42 (2H, dd, *J* = 6, 1 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5(2C), 16.4, 18.2, 25.8(3C), 27.3, 29.6, 35.2, 41.5, 67.9, 209.2; Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.54. Found: C, 63.81; H, 11.63.



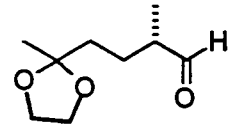
2-[(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutan-1-yl]-2-methyl-1,3-dioxalane (81). A stirred solution of **80** (304 mg, 1.24 mmol), ethylene glycol (310 mg, 6.20 mmol), and *p*-toluenesulfonic acid (2 mg) in benzene (60 mL) under argon was heated

at reflux for 5 d using a Dean-Stark trap to remove water. The mixture was allowed to cool to room temperature and was washed with 2.5% sodium bicarbonate solution (50 mL) and brine (50 mL), and was dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 8% ethyl acetate in hexane as eluant, gave 310 mg (87%) of **75** as a colorless oil: $[\alpha]_D^{22}$ -4.8° (*c* 0.85, $CHCl_3$); IR (neat) 2955, 2933, 2882, 2860, 1458, 1378, 1254, 1091, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.88 (3H, d, *J* = 4 Hz), 0.89 (9H, s), 1.08-1.20 (1H, m), 1.31 (3H, s), 1.43-1.74 (4H, m), 3.34-3.39 (1H, dd, *J* = 10, 6 Hz), 3.42-3.46 (1H, dd, *J* = 10, 6 Hz), 3.90-3.96 (4H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.4(2C), 16.7, 18.3, 23.7, 25.9(3C), 27.4, 35.9, 36.6, 64.6(2C), 68.1, 110.3; Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.44; H, 11.18. Found: C, 62.67; H, 11.39.

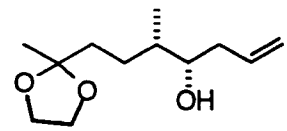


2-[(3*S*)-3-(Hydroxy)methylbutan-1-yl]-2-methyl-1,3-dioxalane (82). A solution of **81** (1.51 g, 5.22 mmol) and tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 11 mL, 11 mmol) in tetrahydrofuran (15 mL) under argon was stirred for 5 h at room temperature. The mixture was diluted with ether (50 mL) and was washed with brine (50 mL), and was dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ethyl acetate in hexane as eluant, yielded 876 mg (97%) of **82** as a colorless oil: $[\alpha]_D^{22}$ -8.1° (*c* 1.12, $CHCl_3$); IR (neat) 3419 (br), 2978, 2952, 2876, 1459, 1378, 1065, 859 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.91 (3H, t, *J* = 7 Hz), 1.20-1.27 (1H, m), 1.31 (3H, s), 1.46-1.65 (4H, m), 1.68-1.76 (1H, m), 3.44-3.49 (2H, dq, *J* = 13, 6 Hz), 3.89-3.97 (4H, m); ^{13}C NMR

($CDCl_3$, 100MHz) δ 16.5, 23.7, 27.1, 35.8, 36.3, 64.6(2C), 68.0, 110.2; MS (EI) *m/z* 173 (M^+-1), 157, 113, 95.



2-Methyl-2[(3*S*)-3-(methyl)butan-4-al-1-yl]-1,3-dioxalane (83). To a solution of oxalyl chloride (1.02 mL, 11.8 mmol) in dichloromethane (0.7 mL) under argon at -78°C was added dimethyl sulfoxide (1.68 mL, 23.5 mmol). The mixture was stirred for 5 min and a solution of **82** (280 mg, 1.61 mmol) in dichloromethane (10 mL) was added dropwise via cannula. Stirring was continued for 1 h at -78°C, after which triethylamine (9.07 mL, 58.8 mmol) was added. The mixture was stirred for 5 min at -78°C, allowed to warm to room temperature for 1 h, and was diluted with ether (50 mL). The solution was washed with brine (50 mL), the aqueous wash was extracted three times with ether (50 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ether in pentane as eluant, gave 228 mg (82%) of **76** as a pale yellow oil: $[\alpha]_D^{22}$ +13.7° (*c* 1.08, $CHCl_3$); IR (neat) 2981, 1725, 1378, 1220, 1068, 857 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.09 (3H, d, *J* = 7 Hz), 1.32 (3H, s), 1.42-1.89 (4H, m), 2.31-2.39 (1H, m), 3.89-3.96 (4H, m), 9.61 (1H, d, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.3, 23.7, 24.6, 36.2, 46.1, 64.6(2C), 109.6, 204.8. This aldehyde was taken to the next step without purification.



[2(3*S*,4*S*)]-2-[4-Hydroxy-3-(methyl)hept-6-en-1-yl]-2-methyl-1,3-dioxalane (85). Method A. To a stirred suspension of magnesium (1.40 g, 60.0 mmol) in ether (10 mL) under argon at room temperature was added a solution of allyl bromide (7.20 g, 60.0 mmol) in ether (30 mL) dropwise over a period of 1.5 h. The solution refluxed gently during addition and was used for the next step without purification.

To a flask containing ether (25 mL) under argon at -78°C was added simultaneously but separately a solution of trimethyl borate (2.84 g, 27.3 mmol) in ether (25 mL) and the freshly prepared solution of allylmagnesium bromide dropwise over 30 min with stirring. The mixture was stirred for 2 h at -78°C and was warmed to 0°C. A solution of 2 N hydrochloric acid (25 mL) was added dropwise, and the mixture was warmed to room temperature, stirred for 10 min, and partitioned. The aqueous layer was extracted once with dichloromethane (50 mL) and twice with ether (50 mL), and the combined organic layers were dried (sodium sulfate). After filtration, the volume of the solution was reduced to 100 mL. (*R,R*)-Diisopropyl tartrate (3.00 g, 128 mmol) was added and the mixture was stirred for 14 h at room temperature. Removal of the solvent followed by distillation under reduced pressure (115°-118°C at 1.5 mmHg) gave 2.18 g (30%) of **84** as a colorless oil.

To a mixture of **84** (1.32 g, 4.60 mmol) and powdered 4Å molecular sieves (1.0 g) in toluene (8 mL) under argon at -78°C was added a solution of **83** (400 mg, 2.32 mmol) in toluene (8 mL) via cannula. The mixture was stirred for 40 h at -78°C and was quenched with 2 N sodium hydroxide solution (20 mL). This mixture was stirred for 2 h at room temperature and extracted three times with ether (50 mL), and the combined organic layers were washed with water (50 mL) and dried (magnesium

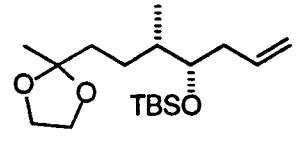
sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 25% ethyl acetate in hexane as eluant, gave 390 mg (78%) of **85** as a colorless oil: $[\alpha]_D^{22}$ -18.5° (*c* 0.85, $CHCl_3$); IR (neat) 3461 (br), 2978, 2940 2880, 1460, 1378, 1068, 857 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.89 (3H, d, *J* = 7 Hz), 1.22-1.29 (1H, m), 1.31 (3H, s), 1.47-1.76 (5H, m), 2.16-2.30 (2H, m), 3.52-3.56 (1H, m), 3.88-3.95 (4H, brs), 5.09-5.16 (2H, m), 5.75-5.88 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.8, 23.6, 27.2, 36.7, 37.8, 38.9, 64.5(2C), 73.6, 110.1, 117.6, 135.4; MS (CI) *m/z* 214 (M^+), 211, 153, 135, 95; HRMS (EI) *m/z* 214.1567 (calcd for $C_{12}H_{22}O_3$: 214.1570). This compound was contaminated by a small amount (*de* 4:1 by ^1H NMR) of a second stereoisomer.

Method B. To a solution of borane methyl sulfide (2.0 M in tetrahydrofuran, 1.2 mL, 2.4 mmol) in tetrahydrofuran (4.8 mL) under argon at -10°C was added (+)-2-carene (0.84 mL, 5.3 mmol) dropwise. The mixture was sealed under argon and stored for 24 h at 0°C, during which time a white solid formed. The supernatant liquid was removed via cannula and the residual solid was washed with ice-cold ether. The solid was dried under high vacuum at room temperature for 20 h.

To a suspension of this 2-isocaranylborane in tetrahydrofuran (1.1 mL) under argon at 0°C was added methanol (0.28 mL) dropwise over a period of 15 min with vigorous stirring. The mixture was stirred for 5 h, the solvent was removed, and the oily residue was dried under high vacuum for 16 h.

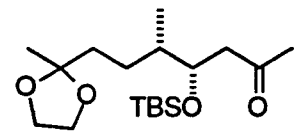
To a solution of this methoxyborane in ether (3 mL) under argon at -78°C was added a solution of allymagnesium bromide (1.0 M in ether, 2.1 mL, 2.1 mmol) dropwise over a period of 15 min. Stirring was continued for 15 min at -78°C and the mixture was allowed to warm to room temperature. The clear ethereal solution of **86** was used immediately in the next step.

To the solution of **86** in ether under argon at -78°C was added a solution of **83** (57 mg, 0.33 mmol) in ether (1.5 mL) dropwise. The mixture was stirred for 3 h at -78°C and quenched by addition of 3 N NaOH solution (0.5 mL) followed by 30% hydrogen peroxide solution (1 mL). The mixture was allowed to warm to room temperature and was heated at reflux for 3 h. After cooling to room temperature, the mixture was partitioned and the aqueous layer was extracted three times with ether (15 mL). The combined ethereal extracts were washed with water (20 mL) and brine (20 mL), and were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, produced 34 mg (48%) of **85** (*de* 8.6:1 by ^{13}C NMR) as a colorless oil.



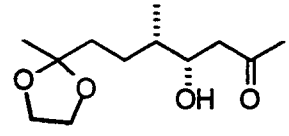
[2(3*S*,4*S*)]-2-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylhept-6-en-1-yl]-2-methyl-1,3-dioxalane (87). To a solution of **85** (51 mg, 0.24 mmol) in dichloromethane (2 mL) under argon at 0°C was added triethylamine (0.10 mL, 0.72 mmol) and *tert*-butyldimethylsilyl triflate (0.083 mL, 0.36 mmol). The solution was stirred for 1.25 h at 0°C and saturated sodium bicarbonate solution (20 mL) and ether (20 mL) were added. After separation, the aqueous layer was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 100% to 2% ethyl acetate in hexane to yield 62 mg (80%) of **87** as a colorless oil: $[\alpha]_D^{22}$ -10.2° (*c* 0.83, $CHCl_3$); IR (neat) 2954, 2929, 2883, 2857, 1472, 1376, 1254, 1065, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (3H, s), 0.06 (3H, s),

0.88 (9H, s), 0.82-0.90 (3H, m), 1.12-1.23 (1H, m), 1.31 (3H, s), 1.47-1.60 (3H, m), 1.63-1.68 (1H, m), 2.16-2.22 (2H, m), 3.54-3.61 (1H, m), 3.88-3.96 (4H, m), 4.98-5.01 (2H, m), 5.77 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.4, -4.6, 13.8, 18.0, 23.7, (25.8, 25.9)(3C), 37.3, 37.7, 38.2, 38.9, 64.5(2C), 75.3, 110.2, 116.3, 135.8; MS (CI) *m/z* 329 (M^++1), 313, 287, 275, 233, 185, 159, 153, 147, 95; HRMS (CI) *m/z* 329.2512 (calcd for $C_{18}H_{36}O_3Si + H^+$: 329.2513).



[2(3*S*,4*S*)]-2-[4-[(*tert*-butyldimethylsilyl)oxy]-3-methylhept-6-on-1-yl]-2-methyl-1,3-dioxalane (88). A stream of oxygen was passed through a stirred suspension of palladium chloride (3.4 mg, 0.019 mmol) and copper(I) chloride (19 mg, 0.19 mmol) in N, N-dimethylformamide (7 mL) and water (1 mL) for 2 h at room temperature. A solution of **87** (62 mg, 0.19 mmol) in N, N-dimethylformamide (3.5 mL) and water (0.5 mL) was added and was stirred for 3.5 h with oxygen passing through, during which the brown mixture became a clear pale brown solution containing green preciptate. Saturated ammoniun chloride solution (20 mL) was added, and the solution turned to a jade color and was extracted three times with ether (20 mL). The combined ethereal extracts were washed with brine (20 mL) and water (20 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatograghy of the residue on silica gel, with gradient elution from 10% to 20% ethyl acetate in hexane, to yield 40 mg (60%) of **88** as a colorless oil: $[\alpha]_D^{22}$ -29.1° (*c* 2.25, $CHCl_3$); IR (neat) 2958, 2930, 2881, 2860, 1726, 1384, 1263, 1076, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -0.02 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 0.81-0.88 (4H, m), 1.04-1.14 (1H, m),

1.31 (3H, s), 1.43-1.60 (2H, m), 1.61-1.74 (2H, m), 2.14 (3H, s), 2.34-2.41 (1H, dd, J = 15, 4 Hz), 2.55-2.62 (1H, dd, J = 16, 8 Hz), 3.90-3.97 (4H, m), 4.12 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.8(2C), 14.7, 17.9, 23.6, 25.7, 25.9(3C), 31.6, 37.3, 39.1, 47.1, 64.5(2C), 72.2, 110.0, 208.1; MS (CI) *m/z* 345 (M^++1), 329, 287, 213, 185, 169, 151, 87, 69; HRMS (CI) *m/z* 345.2461 (calcd for $C_{18}H_{36}O_4Si + H^+$: 345.2457).



[2(3*S*,4*S*)]-2-[4-Hydroxy-3-(methyl)hept-6-on-1-yl]-2-methyl-1,3-dioxalane (89). Method A. To a solution of **88** (24 mg, 0.070 mmol) in tetrahydrofuran (2 mL) in a Nalgene tube at 0°C was added a freshly prepared hydrofluoric acid-pyridine stock solution [Aldrich HF•pyridine solution (4 mL) in pyridine (5 mL) and tetrahydrofuran (20 mL), 6 mL]. The solution was stirred from 0°C to room temperature for 1.5 d, after which a saturated sodium bicarbonate solution (6 mL) was added and the mixture was stirred for 1 h. The mixture was diluted with ether and washed with saturated sodium bicarbonate solution (15 mL). The aqueous wash was extracted three times with ether (15 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 20% to 70% ethyl acetate in hexane, to yield 13 mg (78%) of **89** as a colorless oil: $[\alpha]_D^{22}$ -32.0° (*c* 0.50, $CHCl_3$); IR (neat) 3481 (br), 2958, 2938, 2881, 1713, 1361, 1066, 857 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.87 (3H, d, J = 7 Hz), 1.15-1.26 (1H, m), 1.28 (3H, s), 1.38-1.74 (4H, m), 2.16 (3H, s), 2.53-2.57 (2H, m), 2.88 (1H, brs), 3.85-3.96 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.3, 23.7, 26.8,

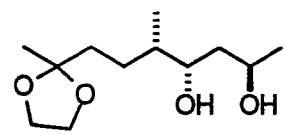
30.8, 36.7, 38.0, 47.2, 64.5(2C), 70.3, 110.1, 210.0; Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.70; H, 9.43.

Method B. To a solution of (1*S*)-(-)-(α)-pinene (10 mL, 63 mmol) (dried over calcium hydride and filtered through a plug of glass wool) in tetrahydrofuran (7 mL) under argon at room temperature was added a solution of borane-methylsulfide complex (10 M in dimethylsulfide, 5.4 mL, 54 mmol) over a period of 20 min, during which the internal temperature of the reaction was kept below 27°C. A small amount of the product crystalized during addition. Therefore, after addition, the mixture was heated to 50°C for 10 min to dissolve most of the solid particles and was allowed to stand under argon at room temperature for 20 h and then cooled to 0°C for 2 h. The supernatant was removed via cannula and the white crystals were broken up with a needle, washed twice with dry ice-cold ether, and dried under a stream of argon. This solid was stored under argon at -25°C.

To a suspension of the above (+)-diisopinocampheylborane (756 mg, 2.64 mmol) in hexanes (0.6 mL) under argon at 0°C was added trifluoromethanesulfonic acid (0.234 mL, 2.64 mmol) dropwise. The cooling bath was removed, and the two-phase mixture was stirred for 2.5 h at room temperature. A 60% conversion was assumed and an aliquot (0.428 mL, 0.813 mmol) of the upper layer was removed and used for the next step immediately.

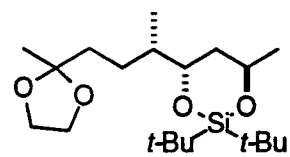
To a solution of (+)-diisopinocampheylborane trifluoromethanesulfonate (1.9 M in hexane, 0.428 mL, 0.813 mmol) in dichloromethane (3 mL) under argon at -78°C was added diisopropylethylamine (0.197 mL, 1.13 mmol) and acetone (0.053 mL, 0.723 mmol). The clear solution was stirred for 2.5 h at -78°C, and a solution of crude **83** (0.452 mmol) in dichloromethane (1.5 mL) was added via cannula. The mixture was allowed to slowly warm to -25°C and was stirred for 1.5 d at -25°C. The reaction was quenched by adding the mixture to a separatory funnel containing ether (20 mL)

and pH 7 buffer solution (20 mL). The phases were separated and the aqueous phase was extracted three times with ether (20 mL). The combined organic layers were concentrated and taken up in methanol (8 mL) and pH 7 buffer solution (1.5 mL) at 0°C. A 30% hydrogen peroxide solution (2 mL) was added and the cooling bath was removed. The mixture was stirred for 2 h at room temperature, diluted with water and extracted three times with dichloromethane (15 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (20 mL) and brine (20 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 25% to 75% ethyl acetate in hexane, to yield 65.7 mg (63% from **82**) of **89** as a colorless oil. This compound was contaminated by a small amount (*de* 9.7:1 by ^{13}C NMR) of a second stereoisomer.



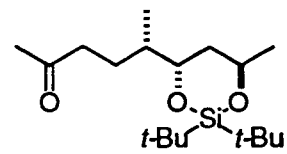
[2(3*S*,4*S*,6*R*)]-2-[4,6-Dihydroxy-3-(methyl)heptan-1-yl]-2-methyl-1,3-dioxalane (90). To a stirred solution of tetramethylammonium triacetoxyborohydride (189 mg, 0.720 mmol) in acetonitrile (1 mL) and acetic acid (1 mL) under argon at -40°C was added dropwise a solution of **89** (27.0 mg, 0.120 mmol) in acetonitrile (1.4 mL). The slurry was stirred for 30 min at -40°C and at -23°C for 20 h, after which it was quenched by addition of 0.5 N aqueous sodium potassium tartrate (2 mL). The mixture was stirred at room temperature for 30 min, diluted with dichloromethane (20 mL), and washed with saturated sodium bicarbonate solution (20 mL). The aqueous wash was extracted three times with dichloromethane (20 mL), and the combined organic layers

were dried (sodium sulfate). Removal of the sovent was followed by chromatography of the residue on silica gel, with gradient elution from 40% to 80% ethyl acetate in hexane, to yield 24.2 mg (91%) of **90** as a colorless oil: $[\alpha]_D^{22}$ -28.7° (*c* 0.65, $CHCl_3$); IR (neat) 3421, 3390, 2963, 2934, 2879, 1459, 1378, 1254, 1064 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.94 (3H, d, *J* = 6 Hz), 1.11 (3H, d, *J* = 6 Hz), 1.32 (3H, s), 1.24-1.82 (7H, m), 2.71 (2H, brs), 3.55 (4H, s), 3.67-3.88 (1H, m), 3.96-4.07 (1H, m); ^{13}C NMR (C_6D_6, 75MHz) δ 14.6, 23.7, 24.1, 27.6, 37.3, 39.4, 42.2, 64.6, 65.4(2C), 71.2, 110.4; MS (CI) *m/z* 231 (M^+-1), 215, 197, 171, 153, 135, 113; HRMS (CI) *m/z* 215.1646 (calcd for $C_{12}H_{24}O_4$ - OH: 215.1648). This compound was contaminated by a small amount (*de* 11:1 by ^{13}C NMR) of a second stereoisomer.



2(3*S*)-2-[3-[(4*S*,6*R*)-2,2-Di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]butan-1-yl]-2-methyl-1,3-dioxalane (91). To a solution of **90** (35 mg, 0.15 mmol) in dichloromethane (2.5 mL) under argon at 0°C was added dropwise 2,6-lutidine (0.052 mL, 0.45 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.066 mL, 0.18 mmol). The solution was stirred for 1.5 h at 0°C and for 2 h at room temperature, was recooled to 0°C, and was quenched by addition of saturated sodium bicarbonate solution (1 mL). The mixture was diluted with ether (20 mL) and was washed with saturated sodium bicarbonate solution (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 10% ethyl acetate in hexane as eluant, gave 35 mg (62%) of **91** as a colorless

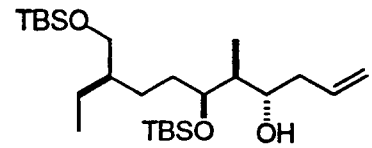
oil: IR (neat) 2965, 2935, 2882, 2860, 1473, 1379, 1136, 1102, 981 cm^{-1}; ^1H NMR (C_6D_6, 300MHz) δ 0.97 (3H, d, *J* = 6 Hz), 1.14 (18H, d, *J* = 3 Hz), 1.16 (3H, d, *J* = 8 Hz), 1.35 (3H, s), 1.39-1.44 (3H, m), 1.66-1.95 (4H, m), 3.52-3.59 (4H, m), 4.01-4.06 (1H, qd, *J* = 10, 2 Hz), 4.21-4.31 (1H, m, *J* = 7, 3 Hz); ^{13}C NMR (C_6D_6, 75MHz) δ 14.6, 21.1, 21.6, 23.7, 24.0, (27.5, 27.6)(6C), 27.7, 37.4, 37.9, 39.8, 64.7(2C), 67.8, 71.2, 110.3; MS (CI) *m/z* 373 (M^++1), 372 (M^+), 371, 358, 331, 315, 269, 229, 197, 153, 113; HRMS (CI) *m/z* 373.2773 (calcd for $C_{20}H_{40}O_4Si$ + H^+: 373.2775).



(5*S*)-5-[(4*S*,6*R*)-2,2-Di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]hexan-2-one (57)

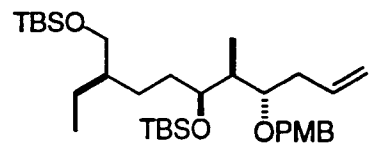
A stirred solution of **91** (18 mg, 0.048 mmol) and pyridinium *p*-toluenesulfonate (4.3 mg, 0.017 mmol) in acetone (1 mL) and water (0.2 mL) was heated at reflux for 4 h. The mixture was allowed to cool to room temperature and was extracted three times with ether (10 mL). The combined ethereal extracts were washed with water (20 mL) and dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 15% ethyl acetate in hexane as eluant, gave 15 mg (90%) of **57** as a colorless oil: IR (neat) 2965, 2934, 2888, 2856, 1718, 1472, 1140, 899; ^1H NMR ($CDCl_3$, 300MHz) δ 0.90 (6H, d, *J* = 6 Hz), 0.99 (18H, s), 1.29 (3H, d, *J* = 6 Hz), 1.36-1.49 (3H, m), 1.76-1.85 (1H, m), 2.00-2.10 (1H, ddd, *J* = 14, 10, 6 Hz), 2.15 (3H, s), 2.42-2.54 (2H, m), 4.00-4.05 (1H, qd, *J* = 12, 2 Hz), 4.36-4.45 (1H, m, *J* = 7, 2 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.8, 20.7, 21.3, 23.4, 27.0(6C), 27.2, 29.8, 37.5, 38.7, 41.5, 67.7, 71.1, 209.0; MS (CI) *m/z* 329

(M^++1), 313, 287, 271, 203, 153, 113; HRMS (CI) *m/z* 329.2512 (calcd for $C_{18}H_{36}O_3Si + H^+$: 329.2513).



(2*R*,5*S*,6*S*,7*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-ethyl-7-hydroxy-6-(methyl)dec-9-ene (92). To a suspension of (-)-B-methoxydiisopinocampheylborane (200 mg, 0.632 mmol) in ether (2.5 mL) under argon at -78°C was added dropwise allylmagnesium bromide solution (1.0 M in ether, 0.632 mL, 0.632 mmol). The mixture was stirred for 15 min at -78°C and for 1 h at room temperature, and was recooled to -78°C. A solution of **55** (201 mg, 0.482 mmol) in ether (4 mL) was added and the mixture was stirred for 2 h at -78°C and 2 h at room temperature. A 3 N sodium hydroxide solution (2.5 mL) followed by a 30% hydrogen peroxide solution (2.5 mL) were added, and the mixture was heated at reflux for 3 h. After cooling, the mixture was diluted with ether (20 mL) and washed with water (20 mL) and brine (20 mL). The aqueous washings were extracted three times with ether (30 mL), and the combined ethereal extracts were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 100% hexane to 2% ethyl acetate in hexane, to yield 203 mg (92%) of **92** as a colorless oil: $[\alpha]_D^{22}$ +16.4° (*c* 1.35, $CHCl_3$); IR (neat) 3466 (br), 2956, 2931, 2897, 2858, 1456, 1254, 1094, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.09 (6H, s), 0.87-0.91 (5H, m), 0.89 (18H, s), 1.09-1.38 (6H, m), 1.42-1.65 (3H, m), 2.16-2.35 (2H, m, *J* = 6 Hz), 2.82 (1H, br), 3.41-3.53 (2H, dq, *J* = 10, 5 Hz), 3.77-3.83 (2H, m), 5.06-5.14 (2H, m), 5.75-5.89 (1H, m, *J* = 7, 3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ

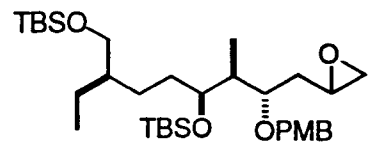
-5.5, -5.5, -4.7, -3.7, 5.5, 11.1, 17.9, 18.2, 23.1, 25.8(6C), 26.0, 31.7, 38.8, 39.7, 42.0, 64.9, 74.3, 77.9, 117.0, 135.4; MS (CI) *m/z* 459 (M^++1), 458, 457, 443, 401, 359, 309, 269, 227, 195, 177, 159, 115, 107; HRMS (CI) *m/z* 459.3690 (calcd for $C_{25}H_{54}O_3Si_2$ + H^+: 459.3691). This compound was contaminated by a small amount (*de* 3:1 by ^{13}C NMR) of a second stereoisomer.



(2*R*,5*S*,6*S*,7*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-ethyl-6-methyl-7-[[(4-methoxyphenyl)methoxy]methyl]dec-9-ene (94). To a slurry of sodium hydride (60% dispersion in mineral oil, 210 mg, 5.25 mmol) in ether (15 mL) under argon at 0°C was added *p*-methoxybenzyl alcohol (6.68 mL, 52.5 mmol) over a period of 15 min. The mixture was stirred for 15 min at 0°C until all solids had been dissolved. Trichloroacetonitrile (5.12 mL, 50.0 mmol) was added and the brown solution was stirred for 30 min at 0°C and 1 h at room temperature. The solvent was removed under reduced pressure and the residue was added to pentane (10 mL) and methanol (0.5 mL), and the mixture was shaken vigorously. The mixture was filtered through a short column of Celite which was rinsed with pentane. The combined organic solution was concentrated, and the residue was distilled under high vacuum to give 2.50 mL of **93** (135°C at 0.7 torr) as a colorless oil which was stored under argon at -25°C.

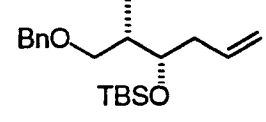
To a solution of **92** (45 mg, 0.098 mmol) in ether (1 mL) under argon at 0°C was added **93** (0.034 mL, 0.16 mmol), followed by 1% triflic acid solution (0.0043 mL, 0.00049 mmol). The solution was stirred for 10 min at 0°C and additional *p*-

methoxybenzyl trichloroacetimidate (0.034 mL) was added twice, at 10 min intervals. The reaction was quenched by addition of saturated sodium bicarbonate solution (3 mL), stirred for 10 min at room temperature, and diluted with ether (15 mL). The organic layer was separated and washed with saturated sodium bicarbonate solution (10 mL) and water (10 mL), and was dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 1% to 3% ethyl acetate in hexane, to yield 56 mg (98%) of **85** as a colorless oil: $[\alpha]_D^{22}$ -4.0° (*c* 1.32, $CHCl_3$); IR (neat) 2956, 2931, 2889, 2858, 1614, 1456, 1251, 1091, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.02 (6H, s), 0.04 (6H, d, *J* = 7 Hz), 0.83-0.96 (6H, m), 0.88 (9H, s), 0.89 (9H, s), 1.09-1.51 (7H, m), 1.69-1.74 (1H, m), 2.35-2.44 (2H, m, *J* = 7 Hz), 2.82 (1H, br), 3.44-3.50 (3H, m), 3.64-3.71 (1H, m), 3.78-3.81 (3H, m), 4.36 (1H, d, *J* = 11 Hz), 4.54 (1H, d, *J* = 11 Hz), 5.04-5.08 (2H, m), 5.78-5.90 (1H, m), 6.83-6.88 (2H, m, *J* = 9 Hz), 7.07-7.28 (2H, m, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -5.3, -4.6, -3.9, 9.5, 11.1, 18.0, 18.2, 23.2, 25.9(6C), 31.5, 35.9, 40.2, 42.1, 55.2, 65.0, 71.2, 73.5, 78.9, 113.5(2C), 116.7, 129.1(2C), 131.1, 135.2, 158.9; MS (CI) *m/z* 579 (M^++1), 578, 565, 564, 522, 521, 442, 401, 359, 309, 269, 227, 149, 121; HRMS (CI) *m/z* 521.3484 (calcd for $C_{33}H_{62}O_4Si_2$ - C_4H_9: 521.3484).



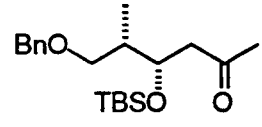
(4*S*,5*S*,6*S*,9*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldimethylsilyl)oxymethyl]-5-methyl-4-[[(4-methoxyphenyl)methoxy]methyl]-1,2-oxiranylundecane (59). A solution of **94** (41 mg, 0.071 mmol) and *m*-chloroperoxybenzoic acid (34 mg, 0.14 mmol) in dichloromethane (1 mL) under argon was stirred for 16 h at room

temperature. Ether (3 mL) and saturated sodium bicarbonate solution (3 mL) were added, and the mixtuer was stirred rapidly for 45 min. The mixture was diluted with additional ether (10 mL) and was partitioned. The aqueous layer was extracted three times with ether (10 mL), and the combined ethereal extracts were washed with saturated sodium bicarbonate solution (15 mL) and brine (15 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield 31 mg (75%) of **59** as a colorless oil: IR (neat) 2956, 2931, 2899, 2858, 1514, 1466, 1252, 1091, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.04 (6H, d, *J* = 6 Hz), 0.83-0.89 (3H, m), 0.89 (18H, s), 0.97 (3H, d, *J* = 7 Hz), 1.24-1.52 (6H, m), 1.75-1.90 (3H, m), 2.46-2.51 (1H, ddd, *J* = 8, 5, 4 Hz), 2.74-2.81 (1H, td, *J* = 12, 5 Hz), 2.98-3.08 (1H, m), 3.45-3.48 (2H, m), 3.57-3.72 (1H, m, *J* = 6 Hz), 3.78 (2H, s), 3.80 (3H, s), 4.38-4.56 (2H, m, *J* = 11, 8 Hz), 6.83-6.88 (2H, d, *J* = 9 Hz), 7.25-7.28 (2H, d, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-5.5, -4.5, -3.9)(4C), 10.0, 11.1, 18.0, 18.2, 23.2, 25.9(6C), 31.5, 35.7, 41.5, 42.1, 46.9, 49.9, 55.2, 64.9, 71.2, 72.1, 73.4, 78.0, 113.6(2C), 129.3(2C), 130.8, 159.0; MS (CI) *m/z* 595 (M^++1), 594, 593, 579, 559, 537, 501, 475, 459, 441, 413, 359, 305, 249, 149, 121; HRMS (CI) *m/z* 537.3431 (calcd for $C_{33}H_{62}O_5Si_2$ - C_4H_9: 537.3433).



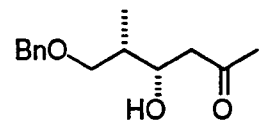
(2*S*,3*S*)-2-[(Benzyloxy)methyl]-3-[(*tert*-butyldimethylsilyl)oxy]hex-5-ene (98). To a solution of crude **97** (757 mg) in dichloromethane (20 mL) under argon at 0°C was added triethylamine (1.44 mL, 10.3 mmol) and *tert*-butyldimethylsilyl triflate (1.12 mL, 5.15 mmol). The solution was stirred for 1.75 h at 0°C and diluted with ether (50

mL), and saturated sodium bicarbonate solution (50 mL) was added. After separation, the aqueous layer was extracted three times with ether (50 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 100% hexane to 3% ethyl acetate in hexane, to yield 699 mg of **98** as a colorless oil: $[\alpha]_D^{22}$ -3.7° (*c* 3.58, $CHCl_3$); IR (neat) 2960, 2935, 2890, 2852, 1646, 1472, 1363, , 1254, 1094, 921, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (6H, d, *J* = 6 Hz), 0.91 (9H, s), 0.93 (3H, d, *J* = 6 Hz), 1.91-1.98 (1H, ddd, *J* = 10, 7, 3 Hz), 2.24-2.30 (2H, m), 3.28-3.33 (1H, ddd, *J* = 9, 7 Hz), 3.46-3.51 (1H, dd, *J* = 9, 7 Hz), 3.87-3.92 (1H, dt, *J* = 7, 3 Hz), 4.45-4.57 (2H, q, *J* = 10, 4 Hz), 5.02-5.10 (2H, m), 5.72-5.86 (1H, m, *J* = 10, 7 Hz), 7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.8, -4.1, 10.6, 18.1, 25.8(3C), 37.4, 39.5, 71.7, 72.9, 73.0, 116.6, 127.3, 127.5(2C), 128.2(2C), 135.3, 138.7; MS (CI) *m/z* 335 (M^++1), 334 (M^+), 333, 317, 301, 293, 277, 227, 187, 185, 145, 115; HRMS (CI) *m/z* 277.1623 (calcd. for $C_{18}H_{36}O_4Si$-C_4H_9: 277.1625).



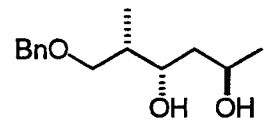
(4*S*,5*S*)-5-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsilyl)oxy]hexan-2-one (99). A stream of oxygen was passed through a stirred suspension of palladium chloride (13 mg, 0.073 mmol) and copper(I) chloride (73 mg, 0.73 mmol) in N, N-dimethylformamide (14 mL) and water (2 mL) at room temperature for 2.25 h. A solution of **98** (0.24 g, 0.73 mmol) in N, N-dimethylformamide in water (3.5:0.5 mL) was added and the brown mixture was stirred for 9 h with continuous passage of oxygen, during which the color turned to dark green. A saturated ammoniun chloride solution (20 mL) was added, and the mixture which had turned to a jade color was

extracted three times with ether (30 mL). The combined ethereal extracts were washed with brine (40 mL) and water (40 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatograghy of the residue on silica gel, with gradient elution from 100% hexane to 6% ethyl acetate in hexane to yield 0.15 g (85% based on recovered **98**) of **99** as a colorless oil: $[\alpha]_D^{22}$ -32.0° (*c* 2.20, $CHCl_3$); IR (neat) 2960, 2926, 2882, 2852, 1718, 1478, 1361, , 1256, 1077, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.00 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 0.90 (3H, d, *J* = 7 Hz), 1.84-1.91 (1H, dq, *J* = 7, 3 Hz), 2.13 (3H, s), 2.48-2.64 (2H, ddd, *J* = 10, 6, 4 Hz), 3.27-3.32 (1H, dd, *J* = 9, 7 Hz), 3.46-3.51 (1H, dd, *J* = 9, 7 Hz), 4.29-4.34 (1H, ddd, *J* = 6, 3, 2 Hz), 4.48 (2H, d, *J* = 4 Hz), 7.33 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.0, -4.6, 11.7, 18.0, 25.8(3C), 31.3, 39.1, 48.5, 69.1, 72.1, 72.8, 127.3, 127.5(2C), 128.2(2C), 138.5, 207.5; MS (CI) *m/z* 349 (M^+-1), 335, 293, 243, 201, 187, 159, 145, 96; HRMS (CI) *m/z* 293.1892 (calcd for $C_{18}H_{36}O_4Si$ - C_4H_9: 293.1574).



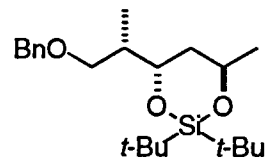
(4*S*,5*S*)-5-Benzyloxymethyl-4-hydroxyhexan-2-one (100). To a solution of **99** (34 mg, 0.097 mmol) in tetrahydrofuran (5 mL) in a Nalgene tube at 0°C was added a freshly prepared hydrofluoric acid-pyridine stock solution [Aldrich HF•pyridine solution (4 mL) in pyridine (5 mL) and tetrahydrofuran (20 mL), 8 mL]. The solution was stirred at 0°C to room temperature for 2 d, after which a saturated sodium bicarbonate solution (6 mL) was added and the mixture was stirred for 1 h. The mixture was added to ether (25 mL) and the solution was washed with additional saturated sodium bicarbonate solution (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined organic layers were dried (magnesium

sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 30% ethyl acetate in hexane, to yield 18 mg (78%) of **100** as a colorless oil: $[\alpha]_D^{22}$ -18.7° (*c* 1.57, $CHCl_3$); IR (neat) 3470, 2971, 2926, 2856, 1718, 1456, 1361, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.95 (3H, d, *J* = 7 Hz), 1.82-1.93 (1H, m, *J* = 5, 3 Hz), 2.17 (3H, s), 2.47-2.60 (1H, dt, *J* = 17, 3 Hz), 2.60-2.70 (1H, dd, *J* = 17, 10 Hz), 3.14 (1H, brs), 3.48 (2H, d, J = 6 Hz), 4.19-4.24 (1H, td, *J* = 9, 3 Hz), 4.50 (2H, s), 7.27-7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 11.3, 30.7, 37.9, 47.5, 69.3, 73.3, 73.5, 127.5, 127.6(2C), 128.3(2C), 138.0, 209.4; MS (CI) *m/z* 237 (M^++1), 219, 201, 189, 179, 159, 129, 119, 91; HRMS (CI) *m/z* 237.1491 (calcd for $C_{14}H_{20}O_3$+ H^+: 237.1491).



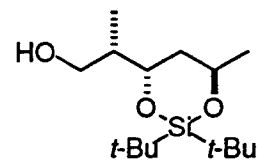
(2*S*,3*S*,5*R*)-1-Benzyloxy-2-methylhexan-3,5-diol (101). To a stirred solutiuon of tetramethylammonium triacetoxyborohydride (319 mg, 1.21 mmol) in acetonitrile (0.7 mL) and acetic acid (0.7 mL) under argon at -40°C was added dropwise a solution of **100** (53.0 mg, 0.224 mmol) in acetonitrile (1.6 mL). The slurry was stirred for 30 min at -40°C and at -28°C for 18 h, after which it was quenched by addition of 0.5 N sodium potassium tartrate solution (2 mL). The mixture was stirred at room temperature for 30 min, diluted with dichloromethane (20 mL), and washed with saturated sodium bicarbonate solution (20 mL). The aqueous wash was extracted three times with dichloromethane (20 mL), and the combined organic layers were dried (sodium sulfate). Removal of the sovent was followed by chromatography of the residue on silica gel, with gradient elution from 10% to 40% ethyl acetate in hexane, to yield 43.6 mg (82%) of **101** as a colorless oil: $[\alpha]_D^{22}$ -14.4° (*c* 1.85, $CHCl_3$); IR (neat)

3416, 3382, 2971, 2911, 2872, 1453, 1367, 1314, 1103, 1070, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (3H, d, *J* = 7 Hz), 1.20 (3H, d, *J* = 6 Hz), 1.34-1.43 (1H, ddd, *J* = 14, 8, 3 Hz), 1.57-1.70 (1H, ddt, *J* = 14, 6, 3 Hz), 1.84-1.97 (1H, m), 3.49 (1H, brs), 3.50 (1H, brs), 3.49 (2H, d, *J* = 6 Hz), 4.03-4.13 (2H, m), 4.49 (2H, s), 7.31 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 11.4, 23.4, 38.3, 41.4, 65.0, 70.5, 73.3, 74.2, 127.5, 127.6(2C), 128.3(2C), 137.9; MS (CI) *m/z* 239 (M^++1), 219, 203, 179, 160, 143, 113, 91; HRMS (CI) *m/z* 239.1648 (calcd for $C_{14}H_{22}O_3 + H^+$: 239.1648).



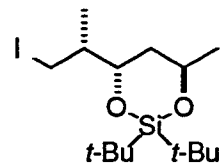
(2*S*)-1-(Benzyloxy)-2-[(4*S*,6*R*)-2,2-di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-propane (102). To a solution of **101** (100 mg, 0.420 mmol) in dichloromethane (6 mL) under argon at 0°C was added 2, 6-lutidine (0.196 mL, 1.68 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.184 mL, 0.504 mmol). The solution was stirred for 1.5 h at 0°C and 1h at room temperature, and was recooled to 0°C. The reaction was quenched with saturated sodium bicarbonate solution (3 mL), diluted with ether (30 mL), and washed with additional saturated sodium bicarbonate solution (30 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 3% to 15% ethyl acetate in hexane to yield 146 mg (92%) of **92** as a colorless oil: $[\alpha]_D^{22}$ +29.2° (*c* 2.03, $CHCl_3$); IR (neat) 2964, 2931, 2891, 2858, 1470, 1370, 1138, 1098, 985, 899, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.94 (3H, d, *J* = 7 Hz), 1.00 (18H, d, *J* = 3 Hz), 1.29 (3H, d, *J* = 7 Hz), 1.35-1.40 (1H, td, *J* = 14, 2 Hz), 1.75-1.82

(1H, m, J = 7 Hz), 2.07-2.15 (1H, m, J = 6 Hz), 3.33-3.37 (1H, dd, J = 9, 6 Hz), 3.52-3.56 (1H, m, J = 9, 8 Hz), 4.31-4.35 (1H, m, J = 11, 2 Hz), 4.38-4.44 (1H, m, J = 11, 4, 2 Hz), 4.46-4.55 (2H, q, J = 12 Hz), 7.27-7.32 (1H, m), 7.34-7.47 (4H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ 11.2, 20.8, 21.4, 23.6, (27.2, 27.3)(6C), 37.9, 39.8, 67.9, 68.2, 72.9, 73.3, 127.5, 127.7(2C), 128.3(2C), 138.6; MS (CI) *m/z* 379 (M^++1), 363, 321, 301, 229, 203, 119, 91; HRMS (CI) *m/z* 379.2667 (calcd for $C_{22}H_{38}O_3Si$ + H^+: 379.2669).

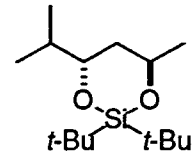


(2*S*)-2-[(4*S*,6*R*)-2,2-Di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]propan-1-ol (103). A round-bottom flask containing **102** (103 mg, 0.272 mmol) and 3% platinum on carbon (100 mg) in ethanol (3 mL) at room temperature was evacuated for 10 min, after which a hydrogen-filled balloon was attached. This process was repeated three times. The mixture was stirred under a hydrogen atmosphere at room temperature for 3.5 h, and was filtered through a short column of Celite which was rinsed with ethyl acetate. Removal of the combined organic solvent from the filtrate was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 20% ethyl acetate in hexane, to yield 70.0 mg (96%) of **103** as a colorless oil: $[\alpha]_D^{22}$ +34.2° (*c* 2.65, $CHCl_3$); IR (neat) 3363, 2964, 2938, 2891, 2858, 1469, 1384, 1145, 1045, 985, 899, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.97 (3H, d, J = 7 Hz), 1.00 (18H, d, J = 2 Hz), 1.30 (3H, d, J = 7 Hz), 1.20-1.40 (1H, m), 1.64-1.75 (1H, m, J = 4 Hz), 2.13-2.23 (1H, m, J = 10, 6 Hz), 2.69 (1H, m), 3.65-3.78 (2H, m, J = 10, 6 Hz), 4.39-4.48 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 10.3, 20.7, 23.3, 27.1(6C), 37.2, 40.2, 67.1,

67.7, 71.5; MS (CI) *m/z* 289 (M^++1), 288 (m^+), 287, 273, 269, 231, 203, 189, 113, 84, 77; HRMS (CI) *m/z* 289.2200 (calcd for $C_{15}H_{32}O_3Si + H^+$: 289.2200).



(2*S*)-[2(4*S*,6*R*)-2,2-Di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-1-iodopropane (60). A stirred suspension of **103** (58.0 mg, 0.201 mmol), triphenylphosphine (107 mg, 0.402 mmol), imidazole (55.0 mg, 0.804 mmol) and iodine (102 mg, 0.402 mmol) in benzene (dried over calcium hydride, 6.5 mL) under argon was heated at reflux for 6 h and allowed to cool to room temperature. The mixture was diluted with ether (40 mL) and was washed with saturated sodium thiosulfate solution (30 mL) and saturated sodium bicabonate solution (30 mL), and was dried (magnesium sulfate). Removal of the solvent followed by chromatography on silica gel, using 2% ethyl acetate in hexane as eluant, gave 76.0 mg (96%) of **60** as a pale yellow oil: $[\alpha]_D^{22}$ +35.2° (*c* 1.04, $CHCl_3$); IR (neat) 2972, 2932, 2890, 2859, 1473, 1144, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.00 (9H, s), 1.02 (9H, s), 1.04 (3H, d, *J* = 7 Hz), 1.33 (3H, d, *J* = 6 Hz), 1.35-1.54 (1H, td, *J* = 14, 2 Hz), 1.65-1.71 (1H, ddd, *J* = 14, 7, 4 Hz), 3.38-3.42 (1H, dd, *J* = 10, 7 Hz), 4.27-4.31 (1H, dt, *J* = 12, 2 Hz), 4.41-4.44 (1H, dq, *J* = 6, 2 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 12.3, 14.6, 20.8, 21.4, 23.5, (27.2, 27.3)(6C), 37.8, 42.0, 67.8, 69.9; HRMS (CI) *m/z* 399.1217 (calcd for $C_{15}H_{31}IO_2Si + H^+$: 399.1217).



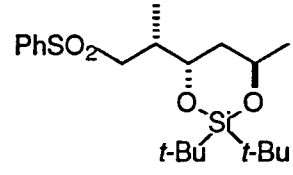
Attempted coupling reaction of 59 with 60.

(4*S*,6*R*)-2,2-Di-*tert*-butylsilylene-4-isopropyl-6-methyl-1,3-dioxane (104).

To a solution of copper(I) cyanide (0.18 g, 2.0 mmol) in tetrahydrofuran (6 mL) under argon at -78°C was added lithium thiophene (1.0 M in tetrahydrofuran, 2.0 mL, 2.0 mmol) dropwise. The solution was stirred for 10 min at -78°C and the cooling bath was removed. The mixture was allowed to warm over 10 min, the flask was placed in an ice-water bath, and stirring was continued for 2 h at 0°C. The dark brown 2-thienyl(cyano)copper lithium solution (0.25 M) was used immediately for the next step.

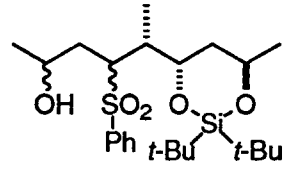
To a solution of **60** (41.0 mg, 0.103 mmol) in ether (1 mL) under argon at -78°C was added *tert*-butyllithium (1.7 M in pentane, 0.121 mL, 0.206 mmol) dropwise. The pale yellow solution was stirred for 5 min and the 2-thienyl(cyano)copper lithium solution (0.25 M in tetrahydrofuran, 0.412 mL, 0.103 mmol) was added. The dark brown solution was stirred for 10 min at -78°C, the cooling bath was removed partially, and the solution was allowed to warm slowly for 5 min. An ice-water bath was installed, and the turbid yellow mixture was stirred for 10 min at 0°C and recooled to -78°C, during which it became a slightly orange color. A solution of **59** (29.0 mg, 0.0490 mmol) in ether (0.6 mL) was added dropwise and the mixture was stirred for 10 min at -78°C. The cooling bath was removed partially and the mixture was allowed to warm slowly for 10 min. An ice-water bath was installed and the mixture was stirred for 40 min at 0°C. The reaction was quenched by addition of saturated ammonium chloride solution (1 mL), stirred for 30 min at room temperature, and ether (20 mL) and water (20 mL) were added. After separation, the aqueous layer was extracted three

times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield 23.0 mg of **59**, 5.00 mg of **103**, and 26.0 mg of **104**: IR (neat) 2965, 2933, 2891, 2860, 1472, 1382, 1105, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.90 (3H, d, *J*= 7 Hz), 0.92 (3H, d, *J* =7 Hz), 1.00-1.05 (18H, s), 1.26 (3H, d, *J* = 7 Hz), 1.40-1.50 (1H, m), 1.57-1.70 (1H, m), 1.87-2.01 (1H, m), 3.80-3.88 (1H, m), 4.32-4.42 (1H, m).

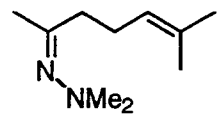


(2*S*)-[2(4*S*,6*R*)-2,2-Di-*tert*-butylsilyene-6-methyl-1,3-dioxan-4-yl]propyl-1-phenyl-sulfone (61). A solution of **60** (50.0 mg, 0.126 mmol) and sodium phenylsulfinate (33.0 mg, 0.200 mmol) in N,N-dimethylformamide (1 mL) under argon was stirred for 25 h at 37°C, allowed to cool to room temperature, and ether (15 mL) and saturated sodium bicarbonate solution (15 mL) were added. After separation, the aqueous layer was extracted three times with ether (15 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (30 mL) and brine (30 mL), and were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 12% ethyl acetate in hexane as eluant, gave 43.5 mg (84%) of **61** as a colorless oil: $[\alpha]_D^{22}$ +14.3° (*c* 0.87, $CHCl_3$); IR (neat) 2967, 2934, 2891, 2859, 1473, 1306, 1090, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.94 (9H, s), 0.96 (9H, s), 1.05 (3H, d, *J* = 7 Hz), 1.26 (3H, d, *J* = 7 Hz), 1.29-1.34 (1H, td, *J* = 14, 2 Hz), 1.94-2.05 (1H, dq, *J* = 11, 6 Hz), 2.14-2.22 (1H, m), 2.91-2.99 (1H, dd, *J* = 14, 7 Hz), 3.37-3.43 (1H, dd, *J* = 14, 5 Hz), 4.15-4.20 (1H, td, *J* = 11, 2 Hz), 4.33-4.42 (1H,

dquent, J = 6, 2 Hz), 7.53-7.59 (2H, m), 7.61-7.68 (1H, m), 7.91-7.94 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.9, 20.7, 21.3, 23.3, (27.1, 27.2)(6C), 34.8, 36.9, 59.6, 67.5, 70.1, 127.8(2C), 129.2(2C), 133.5, 140.0; MS (CI) *m/z* 413 (M^++1), 412, 355, 237, 203, 143, 95; HRMS (CI) *m/z* 413.2181 (calcd for $C_{21}H_{36}O_4SSi$ + H^+: 413.2183).

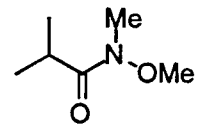


Hydroxy Sulfone (105). To a solution of **61** (10 mg, 0.024 mmol) in tetrahydrofuran (0.5 mL) under argon at -78°C was added *n*-butyllithium (1.6 M in hexane, 0.030 mL, 0.048 mmol) dropwise. The clear solution was stirred for 20 min and hexamethylphosphoramide (0.018 mL, 0.10 mmol) was added. The yellow solution was stirred for 15 min and propylene oxide (0.0080 mL, 0.12 mmol) was added. The mixture was stirred for 30 min at -78°C and for 1 h at 0°C. The reaction was quenched with saturated ammonium chloride solution (0.4 mL) and was extracted three times with ether (15 mL). The combined ethereal extracts were washed with brine (25 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography on silica gel, with gradient elution of 10% to 35% ethyl acetate in hexane, to yield 4.0 mg (40%) of **61** and 7.3 mg (65%, 100% based on recovered **61**) of **105** as a colorless oil. This material was a mixture of four stereoisomers: IR (neat) 3509, 2967, 2934, 2892, 1472, 1290 cm^{-1}; MS (CI) *m/z* 473, 472, 471 (M^++1), 413, 285, 229, 203, 151, 143; HRMS (CI) *m/z* 471.2599 (calcd for $C_{24}H_{42}O_5SSi$ + H^+: 471.2602).

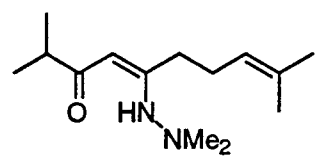


6-Methyl-5-hepten-2-one 1,1-Dimethylhydrazone (107). Method A. To a solution of 6-methyl-5-hepten-2-one (**106**, 0.50 mL) in dichloromethane (3.5 mL) under argon at 0°C was added 1,1-dimethylhydrazine (3.5 mL, 46 mmol) dropwise. The solution was stirred for 5 min and chlorotrimethylsilane (1.2 mL, 9.3 mmol) was added dropwise, during which the reaction temperature was kept below 7°C. The mixture was stirred for 50 min at room temperature, recooled to 0°C, and was poured onto crushed ice (20 g). The mixture was partitioned between water (20 mL) and dichloromethane (20 mL). The aqueous layer was extracted three times with dichloromethane (20 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent gave 0.24 g of crude **107**, which was unstable and hydrolyzed to **106** during chromatography on silica gel, using 10% ethyl acetate in hexane as eluant: IR (neat) 2973, 2839, 1667, 1471, 1386 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.60 (3H, s), 1.67 (3H, s), 1.92 (4H, 2s), 2.21 (3H, brs), 2.40 (6H, 2s), 5.10 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 16.5, 17.6, 25.6, 38.9, 46.9, 47.9, 123.1, 132.0, 167.5.

Method B. To a solution of **106** (1.5 mL) in ethanol (4.5 mL) under argon at room temperature was add 1,1-dimethylhydrazine (3.6 mL, 46 mmol). The solution was heated at reflux for 26 h and allowed to cool to room temperature. Excess 1,1-dimethylhydrazine was removed under reduced pressure to give 0.45 g of a 5:1 mixture of **107** and **106**, which was used for the next step without purification.

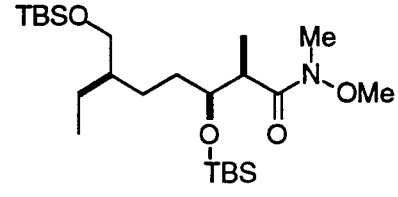


N,2-Dimethyl-N-(methoxy)propanamide (109). A solution of isobutyric acid (**108**, 1.05 mL, 11.4 mmol), N,O-dimethylhydroxylamine hydrochloride (3.38 g, 34.1 mmol), 1,3-dicyclohexylcarbodiimide (6.56 g, 31.8 mmol) and 4-dimethylaminopyridine (4.35 g, 35.2 mmol) in dichloromethane (25 mL) under argon was stirred at 0°C to room temperature for 12 hours and diluted with hexane (50 mL). The mixture was filtered through a pad of Celite which was rinsed with hexane. The organic layers were combined, and removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 25% ethyl acetate in hexane, to yield 589 mg (40%) of **109** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.10 (6H, d, J = 7 Hz), 2.95 (1H, m, J = 7 Hz), 3.17 (3H, s), 3.68 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.9, 29.6, 32.1, 178.1.



(4Z)-2,9-Dimethyl-5-[(2,2-dimethyl)hydrazino]octa-4,8-dien-3-one (110). To a solution of diisopropylamine (0.468 mL, 3.57 mmol) in tetrahydrofuran (2 mL) under argon at -30°C was added methyllithium (1.4 M in ether, containing less than 0.05 M halide, 2.30 mL, 3.17 mmol) dropwise. The colorless solution was warmed to 0°C, stirred for 10 min, recooled to -5°C, and a brown solution of crude **107** (445 mg) in tetrahydrofuran (2 mL) was added via cannula. The dark red mixture, which was bright yellow at the side, was stirred for 45 min at 0°C and was cooled to -78°C. The

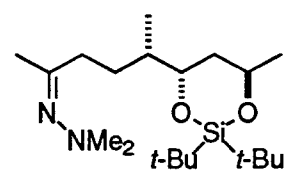
mixture was transferred dropwise into a precooled (-55°C) solution of **109** (465 mg, 3.55 mmol) in tetrahydrofuran (2.5 mL) via cannula. The mixture was stirred for 20 h at -45°C, cooled to -78°C, and was added to a rapidly stirred biphasic mixture consisting of saturated ammonium chloride solution (20 mL) and ether (20 mL) at 0°C via cannula, and was stirred for 15 min. After separation, the aqueous layer was extracted three times with ethyl acetate (20 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography on silica gel, with gradient elution from 5% to 40% ethyl acetate in hexane, to yield 51.0 mg (25% based on the purity of **107**) of **110** as a colorless oil: IR (neat) 2964, 1609, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.06 (6H, d, J = 7 Hz), 1.61 (3H, s), 1.68 (3H, s), 2.24 (2H, m), 2.35 (2H, m), 2.44 (1H, m, J = 7 Hz), 2.53 (3H, s), 4.85 (1H, s), 5.14 (1H, m), 11.13 (1H, brs); ^{13}C NMR ($CDCl_3$, 75MHz) δ 17.5, 19.7, 25.6, 27.1, 31.9, 39.3, 48.7, 90.4, 123.1, 132.5, 166.8, 202.4.



(2*R*,3*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-N,2-dimethyl-N-(methoxy)octanamide (56). A solution of **55** (108 mg, 0.259 mmol), 5% sodium phosphate monobasic solution (pH 4.17, 3.00 mL), and potassium permanganate solution (1 M, 4.50 mL) in *tert*-butanol (1.5 mL) was stirred vigorously for 5 h at room temperature. The reaction was quenched by addition of saturated sodium bisulfite solution (1.5 mL), dichloromethane (20 mL), and saturated ammonium chloride solution (20 mL). After separation, the aqueous layer was extracted three times with dichloromethane (20 mL), and the combined organic layers

were dried (sodium sulfate). Removal of the solvent gave 120 mg of a crude acid which was used without purification.

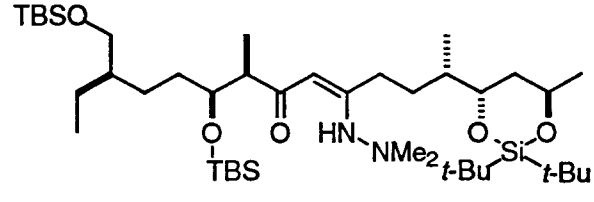
To a solution of the acid (120 mg) in dichloromethane (8 mL) under argon at 0°C was added N, O-dimethylhydroxylamine hydrochloride (86.0 mg, 0.860 mmol), 4-dimethylaminopyridine (110 mg, 0.890 mmol), and 1,3-dicyclohexylcarbodiimide (167 mg, 0.800 mmol). This homogeneous mixture was stirred for 9 h at room temperature, diluted with hexane (20 mL), filtered through a pad of Celite and rinsed with hexane. Removal of the combined organic solvent was followed by chromatography on silica gel, with gradient elution from 5% to 12% ethyl acetate in hexane, to yield 91.0 mg (74% from **55**) of **56** as a colorless oil: $[\alpha]_D^{22}$ -2.0° (*c* 0.82, $CHCl_3$); IR (neat) 2957, 2932, 2893, 1668, 1466, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.02 (6H, s), 0.05 (6H, s), 0.88 (20H, m), 1.13 (3H, d, *J* = 7 Hz), 1.32 (6H, m), 1.45 (2H, m), 2.96 (1H, br), 3.16 (3H, s), 3.45 (2H, m), 3.68 (3H, s), 3.92 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-5.5, -4.6, -4.2)(4C), 10.9, 11.1, 14.2, 18.2, 23.3, 24.8, 25.9(6C), 33.0, 40.3, 42.4, 61.2, 65.3, 73.5, 73.6, 176.5; MS (CI) *m/z* 476 (M^+), 460, 419, 418, 283, 260, 227, 115; HRMS (CI) *m/z* 418.2811 (calcd for $C_{24}H_{53}NO_4Si_2$ -C_4H_9: 418.2810).



(5*S*)-5-[(4*S*,6*R*)-2,2-Di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-2-hexanone 1,1-Di- methylhydrazone (58). Method A. To a solution of **57** (9.0 mg, 0.027 mmol) in dichloromethane (0.8 mL) under argon at 0°C was added 1,1-dimethylhydrazine (0.025 mL, 0.33 mmol) dropwise. The solution was stirred for 5 min and chlorotrimethylsilane (0.0070 mL, 0.054 mmol) was added dropwise, during which the

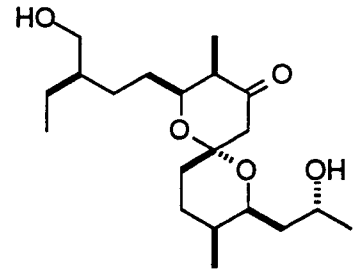
reaction temperature was kept below 7°C. The mixture was stirred for 50 min at room temperature, recooled to 0°C and was poured onto crushed ice (10 g). The mixture was partitioned between water (15 mL) and dichloromethane (15 mL). The aqueous layer was extracted three times with dichloromethane (15 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent gave 11 mg of a crude mixture of **57** and **58** as an oil, which was used without purification: IR (neat) 1729 (C=O), 1643 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.92 (3H, d, J = 7 Hz), 1.00 (18H, S), 1.29 (3H, d, J = 6 Hz), 1.29-1.52 (2H, m), 1.73 (2H, m), 1.92 (0.8H, s), 1.95 (2.2H, s), 2.03 (1H, m), 2.10-2.30 (2H, m), 2.40 (1.3H, s), 2.43 (4.7H, s), 3.85-4.12 (1H, m), 4.40 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.9, 16.3, 20.7, 21.3, 23.5, (27.2, 27.3)(6C), 30.1, 36.9, 37.4, 39.0, 47.0, 47.5, 67.7, 71.0, 167.9.

Method B. To a solution of **57** (23 mg, 0.070 mmol) in ethanol (1 mL) under argon at room temperature was added 1,1-dimethylhydrazine (0.022 mL, 0.28 mmol). The solution was heated at reflux for 21 h and allowed to cool to room temperature. Excess 1,1-dimethylhydrazine was removed under reduced pressure and the residue was dissolved in toluene (5 mL). Removal of the solvent gave 25 mg of a mixture of **57** and **58**, which was used without purification.



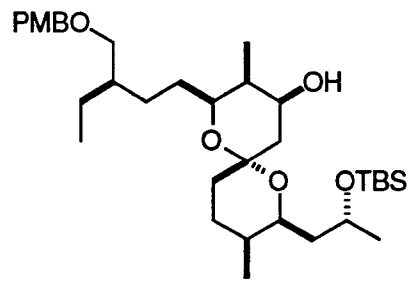
(*Z*)-(2*S*,8*R*,9*S*,12*R*)-9-[(*tert*-Butyldimethylsilyl)oxy]-12-[(*tert*-butyldimethylsilyl)oxymethyl]-2-[(4*S*,6*R*)-2,2-di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-8-methyl-5-(2,2-dimethylhydrazino)-5-tetradecan-7-one (111). To a solution of diisopropylamine (0.021 mL, 0.091 mmol) in tetrahydrofuran (0.7 mL) under argon at

-30°C was added methyllithium (1.35 M in ether, containing less than 0.05 M halide, 0.060 mL, 0.081 mmol) dropwise. The colorless solution was warmed to 0°C, stirred for 10 min, recooled to -4°C, and was added dropwise of a solution of crude **58** (25 mg, as a mixture with **57**) in tetrahydrofuran (0.7 mL). The yellow solution was stirred for 50 min at -2°C to 2°C, cooled to -78°C, and was transferred into a precooled (-57°C) solution of **56** (26 mg, 0.055 mmol) via cannula. The pale yellow solution was stirred for 20 h at -45°C, for 1.5 h at -30°C and for 19 h at -18°C. The mixture was recooled to -78°C and was transferred into a rapidly stirring biphasic solution of ether (20 mL) and saturated ammonium chloride solution (20 mL) at 0°C via cannula. The mixture was stirred for 15 min and was partitioned. The aqueous layer was extracted three times with ethyl acetate (20 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 30% ethyl acetate in hexane, to yield 5.6 mg (67% based on recovered **56**) of the unstable vinylogous amide **101** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (12H, s), 0.87 (21H, m), 0.91 (3H, d, J = 6 Hz), 0.95 (3H, d, J = 6 Hz), 1.01 (18H, s), 1.06 (3H, d, J = 7 Hz), 1.21-1.36 (8H, m), 1.41-1.51 (4H, m), 1.80 (1H, m), 2.01 (2H, m), 2.30-2.50 (3H, m), 2.53 (3H, s), 3.40-3.50 (2H, m), 3.86-3.95 (1H, m), 4.00-4.10 (1H, m), 4.40 (1H, m), 4.90 (1H, m), 11.29 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (-5.5, -4.8, -4.4)(4C), 11.1, 12.7, 13.9, 18.0, 18.2, 20.7, 21.3, 23.2, 23.4, 25.5, (25.9, 26.0)(6C), 26.1, (27.0, 27.1, 27.2)(6C), 37.5, 38.7, 39.2, 41.1, 41.5, 42.2, 48.7, 65.2, 67.7, 70.7, 71.1, 74.8, 92.1, 167.2, 200.1.



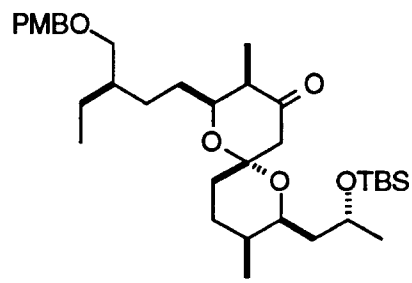
(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-one (112). Method A. A solution of **111** (3.6 mg, 0.0046mmol) in a hydrofluoric acid-acetonitrile-water stock solution {9:1 [95:5 (CH_3CN/48%HF)]/H_2O, 0.5 mL} was stirred for 5 d at room temperature, during which time an additional 0.2 mL of the stock solution was added at 20 h and 47 h. The solution was added to saturated aqueous sodium bicarbonate (2 ml) and water (8 ml). The mixture was extracted once with ethyl acetate (15 mL) and twice with ether (15 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 15% to 70% ethyl acetate in hexane, to yield 1.2 mg (73%) of **112** as a colorless oil: $[\alpha]_D^{22}$ -89.0° (*c* 0.10, $CHCl_3$); IR (neat) 3389, 3382, 2964, 2938, 2878, 1716, 1457, 1377, 1304, 1251, 1085, 972 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.89 (6H, m), 0.98 (1H, d, *J* = 7 Hz), 1.08 (3H, d, *J* = 7 Hz), 1.13 (3H, d, *J* = 6 Hz), 1.16-1.40 (3H, m), 1.41-1.49 (3H, m), 1.51-1.71 (7H, m), 2.08-2.22 (1H, m, *J* = 5 Hz), 2.26-2.60 (1H + 2'OH', m), 2.30 (1H, d, *J* = 14 Hz), 2.50 (1H, d, *J* = 14 Hz), 3.43-3.60 (2H, dtd, *J* = 24, 11, 6 Hz), 3.78-3.91 (1H, m, *J* = 6, 2 Hz), 3.98-4.06 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 10.5, 11.0, 11.3, 23.3, 24.8, 26.1, 26.5, 28.0, 29.4, 30.2, 41.8, 42.4, 47.9, 48.3, 63.9, 67.8, 70.6, 74.6, 98.9, 210.9; MS (CI) *m/z* 357 (M^++1), 355, 339, 268, 255, 227, 211, 197, 185, 173, 155, 95; HRMS (CI) *m/z* 357.2639 (calcd for $C_{20}H_{36}O_5$ + H^+: 357.2642).

Method B. A solution of **116** (460 mg, 0.977 mmol) and tetra-*n*-butylammonium fluoride (2.05 mL, 2.05 mmol) in tetrahydrofuran (15 mL) under argon was stirred for 8.5 h at room temperature. The mixture was added to ether (45 mL) and the solution was washed with brine (50 mL). The aqueous wash was extracted with ethyl acetate (50 mL) and twice with ether (50 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 30% to 60% ethyl acetate in hexane, to yield 236 mg (68%) of **112** as a colorless oil: $[\alpha]_D^{22}$ -105.5° (*c* 1.13, $CHCl_3$).



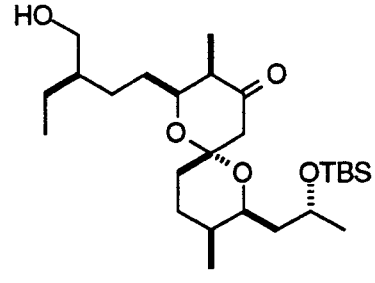
(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecan-4-ol (114). A suspension of **113** (1.24 g, 1.78 mmol) and lithium hydroxide monohydrate (0.618 g, 14.2 mmol) in methanol (80 mL) was stirred for 18 h at room temperature. The mixture was added to ether (120 mL) and the solution was washed with saturated ammonium chloride solution (150 mL) and brine (150 mL). The aqueous washs was extracted three times with ether (200 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 20% to 30% ethyl acetate in hexane, to yield 1.04 g (99%) of **114** as a colorless oil: $[\alpha]_D^{22}$ -43.7° (*c*

1.22, $CHCl_3$); IR (neat) 3436, 2957, 2938, 2858, 1616, 1516, 1463, 1377, 1251, 1178, 1091, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, s), 0.81 (3H, d, *J* = 7 Hz), 0.87 (9H, s), 0.88 (3H, d, *J* = 10 Hz), 0.92 (3H, d, *J* = 7 Hz), 1.16 (3H, d, *J* = 6 Hz), 1.23-1.42 (6H, m), 1.44-1.49 (2H, m), 1.50-1.67 (6H + OH, m), 1.68-1.74 (1H, dd, *J* = 12, 5 Hz), 1.80-1.85 (1H, m), 2.01-2.13 (1H, tt, *J* = 13, 4 Hz), 3.32 (2H, d, *J* = 6 Hz), 3.51-3.55 (1H, m), 3.72-3.82 (2H, m), 3.79 (3H, s), 4.15-4.19 (1H, m), 4.42 (2H, s), 6.84 (2H, d, *J* = 8 Hz), 7.24 (2H, d, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.7, -4.5, 3.9, 10.8, 10.9, 18.0, 23.5, 24.3, 25.8(3C), 26.4, 27.7, 29.5, 29.6, 29.7, 37.9, 39.0, 39.8, 43.2, 55.1, 67.1, 67.3, 69.1, 71.1, 72.5, 72.6, 97.4, 113.6(2C), 129.0(2C), 130.1, 158.9; MS (CI) *m/z* 592 (M^+), 591, 535, 517, 453, 439, 397, 325, 227, 159, 121, 95; HRMS (CI) *m/z* 591.4081 (calcd for $C_{34}H_{60}O_6Si$ - H^+: 591.4083).



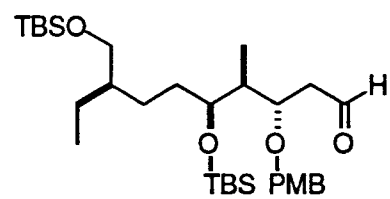
(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl] -2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecan -4-one (115). A suspension of **114** (1.03 g, 1.74 mmol), powdered activated 4Å molecular sieves (2.00 g), 4-methylmorpholine N-oxide (0.365 g, 2.61 mmol), and tetra-*n*-propylammonium perruthenate (34.0 mg, 0.0870 mmol) in dichloromethane (10 mL) under argon was stirred for 1.25 h at room temperature. The mixture was filtered through a short column of silica gel and the column was rinsed with dichloromethane. Removal of the combined organic solvent followed by chromatography of the residue

on silica gel, using 8% ethyl acetate in hexane as eluant, gave 1.02 g (100%) of **115**: $[\alpha]_D^{22}$ -56.9° (*c* 1.82, $CHCl_3$); IR (neat) 2975, 2931, 2884, 2858, 1722, 1516, 1463, 1251, 1091, 1038, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.02 (6H, d, *J* = 1 Hz), 0.86 (9H, s), 0.87 (3H, d, *J* = 5 Hz), 0.92 (3H, d, *J* = 7 Hz), 1.07 (3H, d, *J* = 7 Hz), 1.10 (3H, d, *J* = 6 Hz), 1.27 (3H, m), 1.30-1.53 (3H, m), 1.56-1.70 (7H, m), 2.04-2.16 (1H, m, *J* = 7 Hz), 2.25-2.34 (1H, m), 2.30 (1H, d, *J* = 13 Hz), 2.50 (1H, d, *J* = 14 Hz), 3.32 (2H, m, *J* = 4 Hz), 3.71-3.78 (2H, m), 3.80 (3H, s), 3.79-3.90 (1H, m), 4.42 (2H, s), 6.86 (2H, d, *J* = 9 Hz), 7.26 (2H, d, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.6, -4.4, 10.9, 11.0, 14.0, 18.0, 22.6, 23.5, 24.2, 25.8(3C), 26.4, 27.4, 28.7, 29.4, 31.5, 39.8, 42.9, 48.3, 55.2, 67.1, 70.0, 70.6, 72.5, 72.6, 99.0 113.6(2C), 129.0(2C), 130.7, 159.0, 210.4; MS (CI) *m/z* 591 (M^++1), 589, 575, 533, 471, 413, 341, 283, 229, 159, 121, 95; HRMS (CI) *m/z* 591.4081 (calcd for $C_{34}H_{60}O_6Si + H^+$: 591.4082).



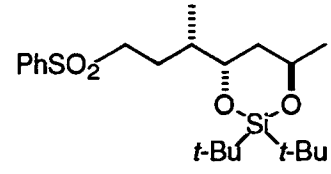
(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxymethyl]-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-one (116). A suspension of 20% palladium hydroxide on carbon (63 mg, 0.085 mmol) and 95% ethanol (7 mL) at room temperature was evacuated under reduced pressure for 10 min and the flask was filled with hydrogen using a balloon. This process was repeated three times. A solution of **115** (1.0 g,1.7 mmol) in 95% ethanol (7 mL) was added, and the solution was stirred under a hydrogen atmosphere for 1.75 h at room temperature,

filtered through a short column of Celite which was rinsed with ether. Removal of the combined organic solvent from the filtrate was followed by chromatography of the residue on silica gel, with gradient elution from 10% to 30% ethyl acetate in hexane, to yield 0.80 g (100%) of **116** as a colorless oil: $[\alpha]_D^{22}$ -68.7° (*c* 1.45, $CHCl_3$); IR (neat) 3449, 2957, 2931, 2884, 2864, 1716, 1464, 1384, 1251, 1085, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.02 (6H, s), 0.85 (9H, s), 0.88 (3H, d, *J* = 6 Hz), 0.91 (3H, d, *J* = 7 Hz), 1.08 (3H, d, *J* = 7 Hz), 1.11 (3H, d, *J* = 6 Hz), 1.22-1.34 (2H, m), 1.36-1.51 (6H, m), 1.54-1.79 (6H, m), 2.04-2.13 (1H, m, *J* = 6 Hz), 2.29 (1H, d, *J* = 14 Hz), 2.30-2.34 (1H, m), 2.48 (1H, d, *J* = 14 Hz), 3.53-3.59 (2H, m), 3.72-3.79 (2H, m), 3.83-4.11 (1H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ -4.6, -4.3, 10.7, 11.0, 15.2, 18.0, 23.2, 24.3, 25.8(3C), 26.4, 27.0, 28.9, 29.2, 29.4, 42.1, 43.0, 48.1, 48.3, 65.0, 65.8, 67.2, 70.7, 99.1, 210.3; MS (CI) *m/z* 471 (M^++1), 455, 413, 395, 369, 325, 297, 283, 229, 185, 159, 109; HRMS (CI) *m/z* 471.3507 (calcd for $C_{26}H_{50}O_5Si + H^+$: 471.3506).



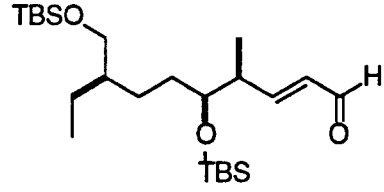
(3*S*,4*S*,5*S*,8*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-8-[(*tert*-butyldimethylsilyl)oxymethyl]-4-methyl-3-[(4-methoxyphenyl)methoxy]decanal (62). A stream of ozone was passed through a stirred solution of **94** (80 mg, 0.14 mmol) in dichloromethane (5 mL) and methanol (1 mL) at -78°C for 5 min. The excess ozone was purged with argon for 25 min, a catalytic amount of potassium bicarbonate and dimethyl sulfide (3 mL) were added, and the mixture was stirred at room temperature for 34 h. Removal of the solvent followed by chromatography of the residue on silica gel, using 5% ethyl acetate in hexane as eluant, gave 38 mg (47%) of **62** as a colorless oil: IR (neat) 2957, 2927,

2891, 2860, 1730, 1617, 1514, 1478, 1257, 1103, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.03 (12H, m), 0.86 (3H, m), 0.89 (18H, s), 0.96 (3H, d, *J* = 7 Hz), 1.33 (5H, m), 1.50 (2H, m), 1.82 (1H, m), 2.70 (2H, m), 3.46 (2H, m), 3.69 (1H, m), 3.80 (3H, s), 3.93 (1H, m), 4.45 (2H, m), 6.86 (2H, d, *J* = 9 Hz), 7.21 (2H, d, *J* = 8.7 Hz), 9.80 (1H, t, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ -5.5, -4.4, -4.4, -3.8, 10.4, 11.2, 18.1, 18.3, 23.3, (25.8, 25.9, 25.9) (6C), 26.4, 31.5, 41.4, 42.2, 46.8, 55.2, 65.0, 71.7, 73.4, 75.7, 113.8(2C), 129.4(2C), 130.4, 159.2, 202.0; MS (CI) *m/z* 580 (M^+), 579, 565, 523, 505, 427, 393, 385, 359, 301, 227, 121; HRMS (CI) *m/z* 579.3903 (calcd for $C_{32}H_{60}O_5Si_2$ - H^+: 579.3903).



(3*S*)-[3(4*S*,6*R*)]-2,2-Di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]butyl phenyl sulfone (63). To a solution of methyl phenyl sulfone (56 mg, 0.36 mmol) in tetrahydrofuran (1.5 mL) under argon at -78°C was added *n*-butyllithium (1.51 M in hexane, 0.24 mL, 0.36 mmol) dropwise. The pale yellow solution was stirred for 25 min at -78°C and an ice-water bath was installed. Hexamethylphosphoramide (0.10 mL, 0.84 mmol) was added, and the mixture was stirred for 35 min at 0°C and for 1 h at room temperature, and was recooled to 0°C. A solution of **60** (35 mg, 0.087 mmol) in tetrahydrofuran (1 mL) was added dropwise and the mixture was stirred for 1 h at 0°C and was quenched by addition of saturated ammonium chloride solution (1 mL). The mixture was extracted three times with ether (20 mL), and the combined ethereal extracts were washed with brine (40 mL) and dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient

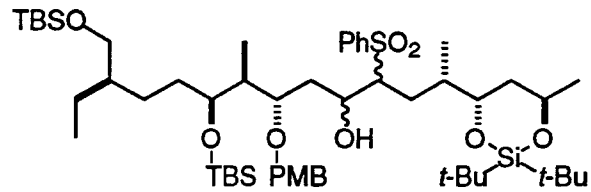
elution from 5% to 10% ethyl acetate in hexane, to yield 35 mg (95%) of **63** as a colorless oil: $[\alpha]_D^{22}$ +13.8° (*c* 1.11, $CHCl_3$); IR (neat) 2974, 2935, 2891, 2867, 1484, 1313, 1089, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88 (3H, d, *J* = 7 Hz), 0.94 (18H, s), 1.23-1.33 (1H, td, *J* = 20, 2 Hz), 1.26 (3H, d, *J* = 7 Hz), 1.50-1.71 (2H, m), 1.82-2.05 (2H, m), 3.07-3.26 (2H, m, *J* = 14, 6 Hz), 3.99-4.03 (1H, m, *J* = 10, 2 Hz), 4.34-4.42 (1H, dquent, *J* = 6, 2 Hz), 7.52-7.58 (2H, m), 7.61-7.67 (1H, m), 7.89-7.92 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.4, 20.6, 21.3, 23.3, 26.1, (27.1, 27.2)(6C), 37.1, 38.0, 54.5, 67.6, 70.5, 128.0(2C), 129.2(2C), 133.5, 139.1; MS (CI) *m/z* 427 (M^++1), 425, 369, 285, 251, 203, 109, 97; HRMS (CI) *m/z* 427.2338 (calcd for $C_{22}H_{38}O_4SSi + H^+$: 427.2339).



Attempted coupling of 62 with 63.

(4*S*,5*S*,8*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-8-[(*tert*-butyldimethylsilyl)oxymethyl]-4-methyldec-2-en-1-al (117). To a solution of **63** (10 mg, 0.024 mmol) in tetrahydrofuran (1 mL) under argon at -78°C was added *n*-butyllithium (1.55 M in hexane, 0.017 mL, 0.026 mmol) dropwise. The yellow solution was stirred for 30 min at -78°C and a solution of **62** (9.0 mg, 0.015 mmol) in tetrahydrofuran (1 mL) was added during a period of 10 min. The pale yellow solution was stirred for 10 min at -78°C and for 24 h at room temperature, and was quenched by addition of saturated ammonium chloride solution (0.5 mL). The mixture was diluted with ether (15 mL) and was washed with saturated ammonium chloride solution (15 mL) and brine (15 mL). The aqueous wash was extracted three time with ether (20 mL), and the

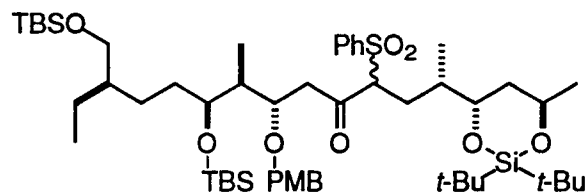
combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatogrphy of the residue on silica gel, with gradient elution from 2% to 10% ethyl acetate in hexane to yield 9.0 mg of **63** and 2.5 mg of **117** as a colorless oil: IR (neat) 2957, 2935, 2896, 2857, 1697, 1618, 1521, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.01-0.10 (12H, m), 0.91 (3H, m), 0.95 (18H, s), 1.04 (3H, m), 1.21-1.54 (6H, m), 2.63 (1H, m), 3.42 (2H, m), 3.62 (1H, m), 6.14 (1H, m), 6.87 (1H, m), 9.52 (1H, m).



Hydroxy Sulfone (118). Method A. To a solution of **63** (32 mg, 0.075 mmol) in tetrahydrofuran (1 mL) under argon at -78°C was added *n*-butyllithium (1.55 M in hexane, 0.048 mL, 0.075 mmol) dropwise. The yellow solution was stirred for 25 min at -78°C, freshly distilled trifluoroboron etherate (0.010 mL, 0.075 mmol) was added, and the solution was stirred for 10 min. A solution of **62** (35 mg, 0.060 mmol) in tetrahydrofuran (1 mL) was added dropwise over a period of 15 min, and the pale yellow solution was stirred for 3 h at -78°C and for 2 h at room temperature. The reaction was quenched by addition of saturated ammonium chloride solution (0.5 mL), diluted with ether (20 mL), and was washed with saturated ammonium chloride solution (15 mL) and brine (15 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatogrphy of the residue on silica gel, with gradient elution from 2% to 10% ethyl acetate in hexane, to yield 10.5 mg (30%) of **62**, 28 mg of a mixture of **118** and **63** which was used for the next step without

purification, and 6 mg of pure **118** as a colorless oil: IR (neat) 3537, 2963, 2935, 2900, 2857, 1518, 1478, 1254, 1154, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (12H, m), 0.68 (3H, m), 0.88 (27H, m), 0.96 (19H, m), 1.24 (14H, m), 1.60 (5H, m), 1.96 (1H, m), 3.48 (2H, m), 3.66 (1H, m), 3.80 (3H, s), 4.35 (2H, m), 6.85 (2H, d, J = 9 Hz), 7.18 (2H, d, J = 9 Hz), 7.56 (3H, m), 7.90 (2H, m); MS (FAB) *m/z* 1007 (M^++1), 1006 (M^+), 986, 950, 888, 868, 838, 812, 738, 720, 696, 642, 626, 596, 581, 538, 509, 463, 455, 419; HRMS (FAB) *m/z* 1007.632 (calcd for $C_{54}H_{98}O_9SSi_3+H^+$: 1007.632).

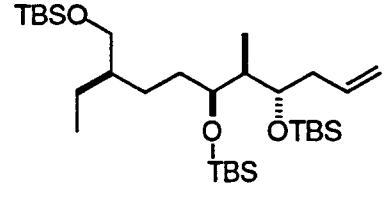
Method B. The same procedure was used as described above. A solution of **63** (17 mg, 0.040 mmol) in tetrahydrofuran (0.8 mL), a solution of **62** (10 mg, 0.017 mmol) in tetrahydrofuran (0.8 mL), *n*-butyllithium (1.50 M in hexane, 0.033 mL, 0.050 mmol) and magnesium bromide etherate (13 mg, 0.050 mmol), gave 5.1 mg of **62** and 15 mg of a mixture of **118** with **63** which was used for the next step without purification.



Keto Sulfone (119). Method A. A suspension of the mixture of **118** and **63** (34 mg), excess powdered activated 4Å molecular sieves, 4-methylmorpholine N-oxide, and tetra-*n*-propylammonium perruthenate in dichloromethane (2.5 mL) under argon was stirred for 2 h at room temperature. The solution was filtered through a short plug of Celite which was rinsed with dichloromethane. Removal of the combined organic solvent was followed by chromatography of the residue on silica gel, with gradient elution from 3% to 9% ethyl acetate in hexane to yield 17 mg (56%) of **63** and 7.3 mg (24% based on **63**, Method A) of **119** as a colorless oil: IR (neat) 2962, 2936, 2900, 2860, 1730, 1516, 1476, 1331, 1256, 1155, 1088, 844 cm^{-1}; ^1H NMR ($CDCl_3$,

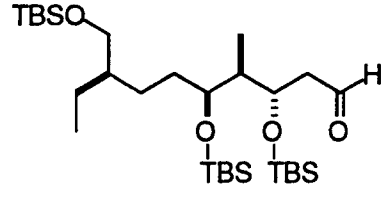
400MHz) δ 0.03 (12H, m), 0.88 (22H, m), 0.94 (22H, m), 1.22 (17H, m), 1.70 (4H, m), 3.11 (1H, m), 3.46 (2H, m), 3.69 (1H, m), 3.80 (3H, s), 3.94 (2H, m), 4.30 (2H, m), 4.42 (2H, m), 6.85 (2H, d, J = 8 Hz), 7.14 (2H, d, J = 8 Hz), 7.43 (1H, m), 7.52 (1H, m), 7.63 (1H, m), 7.74 (2H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ -5.4, -4.4, -4.3, -3.8, 9.9, 10.0, 11.1, 12.4, 15.0, 18.1, 18.3, 20.7, 21.4, 23.2, 23.3, 25.9 (9C), 27.2 (6C), 29.8, 31.8, 36.1, 36.8, 36.9, 40.9, 42.2, 55.2, 65.1, 67.6, 69.6, 71.3, 72.3, 75.4, 113.6, 113.7(2C), 128.8(2C), 129.1(2C), 129.5(2C), 130.9, 134.1, 159.0, 201.5; MS (FAB) *m/z* 1004 (M^+), 1003, 947, 890, 810, 736, 611, 553, 509, 477, 413; HRMS (FAB) *m/z* 1003.601 (calcd for $C_{54}H_{96}O_9SSi_3$-H^+: 1003.000);

Method B. The same procedure was used as described above. From 15 mg of the mixture of **118** and **63** there was obtained 4.2 mg (25%) of **63** and 1.5 mg (15% based on **63**, Method B) of **119**.



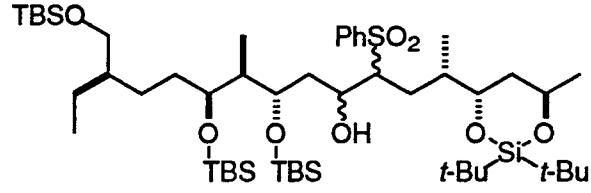
(2*R*,5*S*,6*R*,7*S*)-1,5,7-Tri-[(*tert*-butyldimethylsilyl)oxy]-2-ethyl-6-(methyl)dec-9-ene (120). To a solution of **92** (130 mg, 0.283 mmol) in dichloromethane (2.5 mL) under argon at 0°C was added 2,6-lutidine (0.132 mL, 1.13 mmol) and *tert*-butyldimethylsilyl triflate (0.100 mL, 0.425 mmol). The solution was stirred for 1 h at 0°C, diluted with ether (20 mL), and was washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 100% hexane as eluant, gave 151 mg (93%) of **120** as a colorless oil: $[\alpha]_D^{22}$ -4.4° (c 1.19, $CHCl_3$); IR (neat) 2958, 2928,

2892, 2857, 1474, 1261, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHZ) δ 0.02 (6H, s), 0.03 (6H, s), 0.04 (6H, s), 0.87 (27H, s), 0.88 (3H, s), 0.89 (3H, s), 1.26 (6H, m), 1.43 (2H, m), 1.62 (1H, m, *J* = 12, 7 Hz), 2.29 (2H, dd, *J* = 6 Hz), 3.47 (2H, d, *J* = 5 Hz), 3.68 (1H, q, *J* = 6 Hz), 3.75 (1H, q, *J* = 6 Hz), 5.00 (2H, dd, *J* = 12, 3 Hz), 5.76 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -5.5, -5.5, -4.6, -4.0, -3.9, -3.0, 9.2, 11.0, (18.0, 18.2)(3C), 23.3, 25.6, 25.9 (9C), 31.9, 39.5, 40.2, 42.3, 65.0, 72.2, 72.8, 116.6, 134.9; MS (CI) *m/z* 571 (M^+-1), 557, 515, 433, 383, 359, 259, 227, 185, 95; HRMS (CI) *m/z* 571.4397 (calcd for $C_{31}H_{64}O_5Si_2$-H^+: 571.4400).



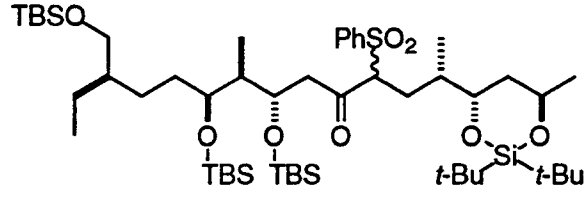
(3*S*,4*R*,5*S*,8*R*)-3,5-Di-[(*tert*-butyldimethylsilyl)oxy]-8-[[(*tert*-butyldimethyl)oxy]methyl]-4-(methyl)decan-1-al (121). A stream of ozone was passed through a stirred solution of **120** (45 mg, 0.078 mmol) in dichloromethane (3 mL) and methanol (0.6 mL) at -78°C for 5 min. The excess ozone was purged with argon for 25 min, a catalytic amount of potassium bicarbonate and dimethyl sulfide (2 mL) were added, and the solution was stirred at room temperature for 34 h. Removal of the solvent followed by chromatography of the residue on silica gel, using 5% ethyl acetate in hexane as eluant, gave 40 mg (88%) of **121** as a colorless oil: $[\alpha]_D^{22}$ +2.0° (*c* 3.50, $CHCl_3$); IR (neat) 2959, 2930, 2896, 2862, 1733, 1479, 1259, 1098, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (18H, m), 0.87 (3H, s), 0.88 (27H, s), 0.91 (3H, s), 1.31 (5H, m), 1.47 (2H, m), 1.71 (1H, m, *J* = 17, 7, 4 Hz), 2.61 (2H, dt, *J* = 5, 2 Hz), 3.46 (2H, d, *J* = 4 Hz), 3.76 (1H, dt, *J* = 6, 4 Hz), 4.15 (1H, q, *J* = 11, 5 Hz), 9.82 (1H, t, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -5.5, -4.5, -4.4, -4.4, -3.8, 9.9, 11.1,

17.9, 18.0, 18.2, 23.2, 25.6, (25.7, 25.8, 25.9)(9C), 31.9, 42.1, 42.2, 48.8, 64.9, 69.6, 72.4, 202.5; MS (CI) *m/z* 559 (M^+-13), 517, 443, 385, 359, 345, 301, 253, 227, 189, 171, 129; HRMS (CI) *m/z* 559.4036 (calcd for $C_{30}H_{66}O_4Si_3$ - CH_3: 559.4036).



Hydroxy Sulfone (122). To a solution of **63** (37 mg, 0.090 mmol) in tetrahydrofuran (1 mL) under argon at -78°C was added *n*-butyllithium (1.58 M in hexane, 0.057 mL, 0.090 mmol) dropwise. The yellow solution was stirred for 45 min, freshly distilled trifluoroboron etherate (0.011 mL, 0.090 mmol) was added dropwise, and the mixture was stirred for 5 min. A precooled (-78°C) solution of **121** (20 mg, 0.035 mmol) in tetrahydrofuran (0.8 mL) was added dropwise via cannula, and the pale yellow solution was stirred for 3 h at -78°C and for 1h at room temperature. The reaction was quenched by addition of saturated ammonium chloride solution (1 mL), diluted with ether (20 mL), and was washed with saturated ammonium chloride solution (20 mL) and brine (20 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatogrphy of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield 3.0 mg of **121**, 15 mg of **63**, and 30 mg (86%) of **122** as a colorless oil: IR (neat) 3535, 2956, 2933, 2899, 2859, 1480, 1263, 1260, 1160, 1093, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (18H, m), 0.71 (4H, dd, *J* = 13, 7 Hz), 0.89 (33H, m), 0.99 (18H, s), 1.26 (10H, m), 1.48 (4H, m), 1.75 (3H, m), 2.01 (3H, m), 3.04 (1H, m), 3.48 (2H, m), 3.75 (1H, m), 3.98 (2H, m), 4.29 (1H, m), 4.38 (1H, m), 7.56 (2H, m), 7.63 (1H, m), 7.88 (2H, m); ^{13}C NMR

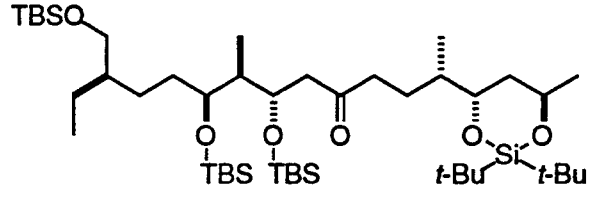
($CDCl_3$, 75MHz) δ -5.5, -4.7, -4.5, -4.3, -3.9, -3.8, 9.3, 9.8, 11.1, 12.9, 17.9, 18.0, 18.2, 20.7, 21.3, 23.3, 24.6, (25.8, 25.9) (9C), 26.5, (27.1, 27.2) (6C), 31.7, 37.3, 37.4, 42.5, 65.3, 66.1, 67.6, 70.0, 70.6, 70.9, 73.1, 128.5(2C), 129.1(2C), 133.7, 138.2; MS (FAB) *m/z* 1002 (M^++1), 1001 (M^+), 986, 943, 869, 812, 737, 679, 625, 595, 567, 463, 419, 359, 269, 227.



Keto Sulfone (123). Method A. A suspension of **122** (6.5 mg, 0.0065 mmol), an excess of powdered activated 4Å molecular sieves, 4-methylmorpholine N-oxide and tetra-*n*-propylammonium perruthenate in dichloromethane (1 mL) under argon was stirred for 2.5 h at room temperature. The mixture was filtered through a short plug of Celite which was rinsed with dichloromethane. Removal of the combined organic solvent from the filtrate was followed by chromatography of the residue on silica gel, with gradient elution from 3% to 9% ethyl acetate in hexane, to yield 5.6 mg (86%) of **123** as a colorless oil: IR (neat) 2959, 2938, 2892, 2867, 1723, 1475, 1331, 1264, 1149, 1097, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.02 (18H, m), 0.83 (9H, s), 0.88 (9H, s), 0.89 (9H, s), 0.94 (18H, s), 0.80-0.97 (8H, m), 1.24 (3H, d, *J* = 7 Hz), 1.21-1.40 (7H, m), 1.49 (3H, m), 1.65 (1H, m), 1.80 (1H, m), 2.03 (2H, m), 2.64-3.01 (1H, 2dd, *J* = 20, 6 Hz), 3.10-3.32 (1H, 2dd, *J* = 20, 6 Hz), 3.47 (2H, m), 3.84 (1H, m), 3.95 (1H, m), 4.13 (1H, dd, *J* = 11.7, 3.1 Hz), 4.25 (1H, m), 4.36 (1H, m), 7.53 (2H, m), 7.66 (1H, m), 7.77 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -4.7, -4.5, -4.3, -4.1, -3.7, 9.4, 11.1, 12.5, 17.9, 18.1, 18.2, 20.6, 21.3, 23.2, 23.3, 25.5, (25.8, 25.9) (9C), 26.0, (27.1, 27.2) (6C), 31.2, 36.9, 41.0, 42.3, 49.9, 51.4, 65.1, 67.9, 68.2, 69.8, 71.2,

72.9, 128.8, 129.2, 134.0, 136.5, 200.5; MS (FAB) *m/z* 999 (M^++1), 997, 941, 887, 867, 735, 728, 643, 611, 595, 575, 549, 519, 503, 429, 413, 323, 253, 217, 201, 181.

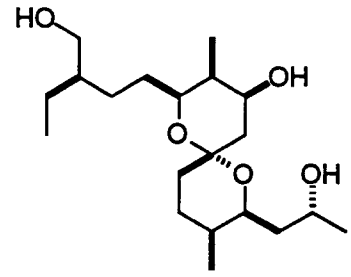
Method B. To a solution of oxalyl chloride (0.010 mL, 0.11 mmol) in dichloromethane (0.70 mL) under argon at -78°C was added dimethyl sulfoxide (0.061 mL, 0.22 mmol) and the solution was stirred for 5 min at -78°C. A solution of **122** (11 mg, 0.011 mmol) in dichloromethane (0.4 mL) was added and stirring was continued for 1 h. Triethylamine (0.039 mL, 0.28mmol) was added and the mixture was stirred for 5 min at -78°C and allowed to warm to room temperature for 1 h. The mixture was dissolved in ether (20 mL) and the solution was washed with brine (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 8% ethyl acetate in hexane, to yield 6.5 mg of **122** and 4.5 mg (45%, 100% based on recovered **122**) of **123** as a colorless oil.



(2*S*,7*S*,8*R*,9*S*,12*R*)-7,9-Di-[(*tert*-butyldimethylsilyl)oxy]-12-[(*tert*-butyldimethylsilyl)oxyme-thyl]-2-[(4*S*,6*R*)-2,2-di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-8-methyltetra-decan-5-one (124). A flame-dried flask under argon at room temperature was charged with samarium (900 mg, 6.00 mmol). The flask was evacuated under high vacuum for 15 min and was filled with argon. This process was repeated three times. Freshly distilled tetrahydrofuran (30 mL) and diiodomethane (0.244 mL, 3.00 mmol) were added with vigorous stirring under argon at room temperature and the dark blue

solution was stirred for an additional 1 h. This stock solution could be stored for 2.5 month under argon.

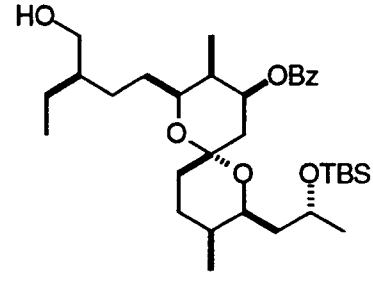
To a solution of **123** (14.5 mg, 0.0145 mmol) in tetrahydrofuran (1.6 mL) and methanol (0.8 mL) under argon at -78°C was added a freshly prepared solution of samarium diiodide (0.10 M in tetrahydrofuran, 0.580 mL, 0.0580 mmol). The reaction flask was covered with foil and the blue mixture was stirred for 30 min at -78°C and allowed to warm to room temperature for 1 h. The mixture was added to ether (20 mL) and the mixture was washed with saturated potassium carbonate solution (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2% to 5% ethyl acetate in hexane, to yield 11.0 mg (89%, 97% based on recovered **123**) of **124** as a colorless oil: $[\alpha]_D^{22}$ +19.8° (*c* 0.85, $CHCl_3$); IR (neat) 2963, 2932, 2896, 2860, 1715, 1476, 1386, 1257, 1103, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.01 (3H, s), 0.03 (6H, s), 0.06 (6H, s), 0.07 (3H, s), 0.83 (3H, d, *J* = 7 Hz), 0.84-0.91 (6H, m), 0.86 (9H, s), 0.89 (9H, s), 0.90 (9H, s), 1.00 (18H, s), 1.15-1.36 (5H, m), 1.29 (3H, d, *J* = 7 Hz), 1.37-1.53 (5H, m), 1.60-1.67 (1H, m), 1.70-1.81 (1H, m), 2.00-2.08 (1H, ddd, *J* = 16, 10, 6 Hz), 2.34-2.54 (2H, m), 2.56-2.68 (2H, ddd, *J* = 20, 16, 4 Hz), 3.48 (2H, ddd, *J* = 15, 10, 6 Hz), 3.83 (1H, q, *J* = 6 Hz), 4.00 (1H, td), 4.21 (1H, q, *J* = 6 Hz), 4.39 (1H, m, *J* = 12, 6, 2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.5, -5.4, -4.5, -4.4, -4.2, -3.6, 9.9, 11.1, 13.9, 18.0, 18.1, 18.3, 20.8, 21.3, 23.3, 23.5, 25.8, (25.9, 26.0)(9C), 26.8, 27.3(6C), 32.2, 37.7, 38.9, 41.9, 42.3, 42.4, 47.9, 65.1, 67.7, 70.1, 71.4, 72.1, 209.9; MS (CI) *m/z* 858 (M^+), 844, 802, 728, 670, 630, 596, 538, 498, 471, 359, 269, 227, 199, 147, 115; HRMS (CI) *m/z* 801.5738 (calcd for $C_{46}H_{98}O_6Si_4$-C_4H_9: 801.5739).



(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-ol (1). Method A. To a Nalgene vial containing **124** (10 mg, 0.010 mmol) at room temperature was added a stock solution of 48% hydrofluoric acid-acetonitrile (1:7, 3 mL). The mixture was stirred for 48 h, dissolved in ether (20 mL) and was washed with brine (15 mL) and water (15 mL). The aqueous wash was extracted with once ethyl acetate (20 mL) and twice with ether (20 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 40% to 95% ethyl acetate in hexane to yield 3.4 mg (82%) of **1** as a white solid: $[\alpha]_D^{22}$ -82.5° (*c* 0.16, $CHCl_3$).

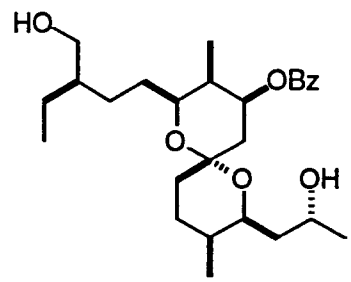
Method B. A solution of **127** (127 mg, 0.220 mmol) and tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.10 mL, 1.10 mmol) in tetrahydrofuran (8 mL) under argon was stirred for 24 h at room temperature. The solution was dissolved in ether (30 mL) and was washed with brine (30 mL). The aqueous wash was extracted once with ethyl acetate (30 mL) and twice with ether (30 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 40% to 90% ethyl acetate in hexane to yield 77.0 mg (98%) of **1** as a white solid: $[\alpha]_D^{22}$ -82.8° (*c* 1.01, $CHCl_3$); IR (neat) 3350 (br), 2964, 2940, 2876, 1455, 1386, 1059, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.82 (3H, d, *J* = 7 Hz), 0.87 (3H, m), 0.90 (3H, d, *J* = 8 Hz), 1.19 (3H, d, *J* = 6 Hz), 1.24 (2H, t, *J* = 7 Hz), 1.30-1.65 (12H, m), 1.68-1.74 (1H, dd, *J*

= 13, 5 Hz), 1.82-1.86 (1H, m), 2.03-2.16 (1H, m), 2.56-2.58 (3H, br), 3.44-3.50 (1H, dd, J = 11, 4 Hz), 3.55-3.60 (1H, dd, J = 11, 4 Hz), 3.71-3.97 (1H, m), 4.03-4.77 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 3.9, 11.1, 11.3, 23.3, 24.5, 26.4, 26.6, 29.0, 29.7, 30.7, 37.7, 38.9, 41.9, 42.3, 64.4, 64.5, 67.2, 67.3, 71.2, 97.4; MS (CI) *m/z* 358 (M^+), 341, 323, 270, 228, 211, 171, 113, 95; HRMS (CI) *m/z* 358.2717 (calcd for $C_{20}H_{38}O_5$: 358.2720).



(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsily-l)oxy]-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecane (125). Method A. From **113**: To a round-bottom flask containing 20% palladium hydroxide on carbon (9.00 mg, 0.0120 mmol) in 95% ethanol (1 mL) under hydrogen at room temperature was added a solution of **113** (130 mg, 0.187 mmol) in 95% ethanol (1 mL). The solution was stirred for 1 h at room temperature, the excess hydrogen was removed under reduced pressure, and the flask was filled with argon. The mixture was filtered through a pad of Celite and the pad was rinsed with ether. Removal of the combined organic solvents from the filtrate followed by chromatography of the residue on silica gel, using 20% ethyl acetate in hexane as eluant, furnished 105 mg (97%) of **113** as a colorless oil: $[\alpha]_D^{22}$ -57.6° (*c* 1.12, $CHCl_3$); IR (neat) 3442, 2956, 2933, 2881, 1720, 1276, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.06 (6H, s), 0.88 (9H, s), 0.92 (3H, m), 1.23 (6H, m), 1.42 (7H, m), 1.60

(7H, m), 1.74 (1H, d, J = 12 Hz), 1.92 (1H, dd, J = 12, 5 Hz), 2.03 (2H, s), 2.08 (1H, m), 2.18 (1H, m), 3.55 (2H, m), 3.80 (3H, m), 4.10 (1H, q, J = 7 Hz), 5.51 (1H, td, J = 12, 5 Hz), 7.43 (2H, m), 7.54 (1H, m), 8.02 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.6, -4.4, 5.0, 10.8, 10.9, 14.1, 18.0, 20.9, 23.1, 24.4, 25.8(3C), 26.3, 27.2, 29.5, 29.6, 35.1, 35.7, 42.1, 43.2, 60.3, 65.0, 67.2, 70.7, 71.2, 97.4, 128.2(2C), 129.3(2C), 130.5, 132.7, 165.5; MS (FAB) *m/z* 599 (M^++23), 577 (M^+), 559, 455, 397, 325, 223, 193, 159, 105; HRMS (FAB) *m/z* 599.3742 (calcd for $C_{33}H_{56}O_6Si$ + Na: 599.3745).



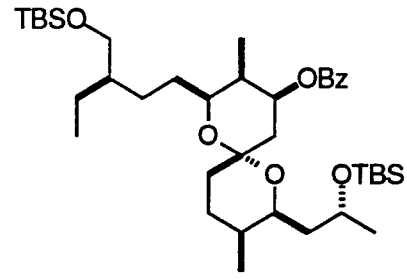
125 and **131**

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecane (125) and **(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecane (131).**

Method A. A stirred mixture of **126** (17 mg, 0.025 mmol) and ammonium fluoride (9.0 mg, 0.25 mmol) in methanol (4 mL) was heated at reflux for 2 d, allowed to cool to room temperature, and was concentrated under reduced pressure. The residue was dissolved in ether (10 mL) and the solution was washed with brine (10 mL). The aqueous wash was extracted three times with ether (10 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution

from 15% to 50% ethyl acetate in hexane, to yield 1.5 mg (9%) of **126**, 4.5 mg (31%) of **125** and 5.4 mg (47%) of **131**. Data for **131**: $[\alpha]_D^{22}$ -58.5° (*c* 0.22, $CHCl_3$); IR (neat) 3363, 3336, 2964, 2938, 2878, 1716, 1457, 1311, 1277, 1118, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.89 (3H, d, *J* = 7 Hz), 0.92 (3H, d, *J* = 6 Hz), 0.94(3H, d, *J* = 6 Hz), 1.24 (3H, d, *J* = 6 Hz), 1.21-1.29 (1H, m), 1.32-1.49 (7H, m), 1.50-1.76 (24H, m), 1.78 (3H, d, *J* = 12 Hz), 1.88-1.94 (1H, dd, *J* = 12, 5 Hz), 2.09-2.24 (2H, m), 3.50-3.64 (2H, dq, *J* = 16, 10, 5 Hz), 3.86-3.90 (1H, dt, *J* = 10, 6 Hz), 4.07-4.14 (2H, m), 5.47-5.54 (1H, td, *J* = 12, 5 Hz), 7.41-7.46 (2H, dd, *J* = 7 Hz), 7.53-7.59 (1H, m), 8.02-8.04 (2H, dd, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 5.0, 11.1, 11.2, 23.4, 24.8, 26.5, 26.7, 29.1, 29.7, 30.7, 35.0, 35.7, 41.9, 42.6, 64.5, 64.7, 67.3, 70.7, 71.5, 97.4, 128.2(2C), 129.4(2C), 130.5, 132.8, 165.6; MS (CI) *m/z* 462 (M^+), 445, 397, 374, 341, 323, 252, 211, 155, 123, 95; HRMS (CI) *m/z* 462.2890 (calcd for $C_{27}H_{42}O_6$: 462.2893).

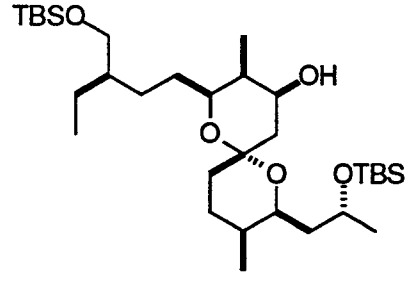
Method B. To a stirred solution of **126** (17 mg, 0.025 mmol) in tetrahydrofuran (1.5 mL) in a Nalgene tube at room temperature was added a freshly prepared hydrofluoric acid-pyridine stock solution [Aldrich pyr•HF (2.5 g) in pyridine (5.6 mL) and tetrahydrofuran (22.4 mL), 1 mL]. The mixture was stirred for 11 h at room temperature and quenched by addition of saturated sodium bicarbonate solution (2 mL). The mixture was extracted three times with ether (10 mL) and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 10% to 50% ethyl acetate in hexane, to yield 4.8 mg (28%) of **126**, 6.2 mg (44%, 61% based on recovered **126**) of **125**, and 1.9 mg (17%) of **131**.



(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsily-l)oxy]-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxymethyl]-1-pentyl]-1,7-dioxaspiro[5.5]undecane (126). Method A. From **125**. To a solution of **125** (50 mg, 0.087 mmol) in dichloromethane (2 mL) under argon at 0°C was added triethylamine (0.035 mL, 0.25 mmol) and *tert*-butyldimethylsilyl triflate (0.032 mL, 0.14 mmol). The solution was stirred for 1 h at 0°C, diluted with ether (15 mL), and was washed with saturated aqueous sodium bicarbonate (15 mL). The aqueous wash was extracted three times with ether (15 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 10% ethyl acetate in hexane as eluant, gave 58 mg (98%) of **126** as a colorless oil: $[\alpha]_D^{22}$ -43.4° (*c* 1.10, $CHCl_3$); IR (neat) 2953, 2930, 2890, 1723, 1467, 1276, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, s), 0.06 (6H, s), 0.87 (2H, m), 0.89 (18H, s), 0.93 (3H, d, *J* = 7 Hz), 0.94 (3H, d, *J* = 7 Hz), 1.22 (3H, d, *J* = 6 Hz), 1.23 (2H, m), 1.38 (6H, m), 1.62 (6H, m), 1.74 (1H, d, *J* = 12 Hz), 1.90 (1H, dd, *J* = 13, 5 Hz), 2.15 (1H, m), 2.20 (1H, m), 3.49 (2H, d, *J* = 5 Hz), 3.80 (3H, m), 5.51 (1H, td, *J* = 12, 5 Hz), 7.43 (2H, m), 7.54 (1H, m), 8.02 (2H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -4.6, -4.4, -3.0, 5.0, 10.9, 11.0, 18.0, 18.2, 23.1, 24.4, 25.6, (25.8, 25.9)(6C), 26.3, 27.4, 29.5, 29.6, 29.8, 35.2, 35.7, 42.0, 43.2, 65.3, 67.3, 69.4, 70.7, 71.3, 97.3, 128.2(2C), 129.4(2C), 130.6, 132.7, 165.6; MS (CI) *m/z* 690 (M^+), 675, 633, 569, 553, 511, 431, 389, 325, 267, 123; HRMS (CI) *m/z* 690.4709 (calcd for $C_{39}H_{70}O_6Si_2$:

690.4713). Anal. Calcd for $C_{39}H_{70}O_6Si_2$: C, 67.77; H, 10.21. Found: C, 67.97; H, 10.34.

Method B. From **127**. A solution of **127** (11.5 mg, 0.02 mmol), 4-dimethylaminopyridine (0.24 mg, 0.002 mmol), triethylamine (0.011 mL, 0.08 mmol), and benzoyl chloride (0.007 mL, 0.06 mmol) in dichloromethane (0.8 mL) under argon was stirred for 3 days. This solution was diluted with ether (5 mL) and saturated sodium bicarbonate solution (5 mL), and was stirred for 2 h. To this mixture was added water, the mixture was extracted with ether, and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 20% ethyl acetate in hexane, to yield 12.5 mg (90%) of **126** as a colorless oil.



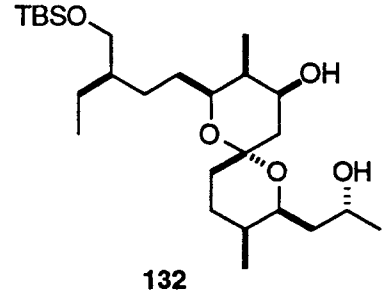
(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxy]methyl-1-pentyl]-1,7-dioxaspiro[5.5]undeca-n-4-ol (127). Method A. From **126**. A suspension of **126** (53 mg, 0.077 mmol) and lithium hydroxide monohydrate (32 mg, 0.53 mmol) in methanol (3 mL) was stirred for 10 h at room temperature. The mixture was added to ether (20 mL) and was washed with saturated ammonium chloride solution (20 mL) and brine (20 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by

chromatography of the residue on silica gel, using 17% ethyl acetate in hexane as eluant, to yield 45 mg (100%) of **127** as a colorless oil: $[\alpha]_D^{22}$ -40.9° (*c* 1.08, $CHCl_3$); IR (neat) 3376, 2957, 2932, 2894, 1467, 1384, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 300HMz) δ 0.03 (6H, s), 0.05 (6H, s), 0.83 (3H, d, *J* = 7 Hz), 0.84-0.87 (3H, d, *J* = 6 Hz), 0.88 (9H, s), 0.89 (9H, s), 0.93 (3H, d, *J* = 7 Hz), 1.17 (3H, d, *J* = 6 Hz), 1.12-1.44 (9H, m), 1.47-1.67 (6H, m), 1.69-1.75 (1H, dd, *J* = 13, 5 Hz), 1.80-1.90 (1H, quintet, *J* = 7 Hz), 2.02-2.14 (1H, tt, *J* = 13, 5 Hz), 3.47 (2H, d, *J* = 5 Hz), 3.53-3.57 (1H, m), 3.72-3.85 (2H, m), 4.15-4.22 (1H, td, *J* = 12, 5 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-5.5, -4.7, -4.5)(4C), 3.9, 10.9, 11.0, 18.0, 18.1, 23.1, 24.3, (25.8, 25.9)(6C), 26.3, 27.4, 29.5, 29.7, 29.8, 37.9, 39.0, 42.0, 43.2, 65.3, 67.2, 67.3, 69.1, 71.1, 97.3; MS (CI) *m/z* 588 (M^++2), 587 (M^++1), 586 (M^+), 571, 553, 529, 511, 453, 413, 325, 245, 113; HRMS (CI) *m/z* 587.4528 (calcd for $C_{32}H_{66}O_5Si_2 + H^+$: 587.4529).

Method B. From **129**: A foil-covered flask containing **129** (240 mg, 0.410 mmol) was evacuated under high vacuum and filled with argon at room temperature, and was charged with tetrahydrofuran (8 mL), isopropyl alcohol (degassed, 0.340 mL, 4.44 mmol) and samarium diiodide (0.10 M in tetrahydrofuran, 18.0 mL, 1.80 mmol). The blue solution was stirred for 5.5 h, diluted with ether (30 mL), and was washed with saturated sodium bicarbonate solution (30 mL). The aqueous washing was extracted three times with ether (30 mL), and the combined organic layers were washed with saturated sodium sulfite solution (50 mL) and brine (50 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 10% to 20% ethyl acetate in hexane, to yield 18.6 mg (8%) of **129** and 213 mg (88%) of **127** as a colorless oil.

Method C. From **132**: To a solution of **132** (42 mg, 0.089 mmol) in dichloromethane (2.5 mL) under argon at -78°C was added a solution of *tert*-butyldimethylsilyl triflate (0.021 mL, 0.089 mmol) and a solution of 2,6-lutidine (0.021 mL, 0.18 mmol) in

dichloromethane (0.7 mL) over a period of 10 min. The mixture was stirred for 2.5 h at -78°C, after which methanol (1 mL) was added and the solution was allowed to warm to room temperature. The mixture was diluted with dichloromethane (20 mL) and was washed with water (20 mL) and brine (20 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2% to 50% ethyl acetate in hexane, to yield 20 mg (48%) of **132** and 13 mg (25%, 50% based on recovered **132**) of **127**.

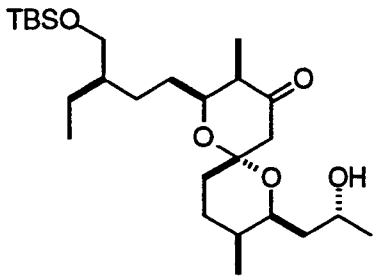


132

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxymethyl]-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-ol (132). A suspension of **1** (71 mg, 0.20 mmol), silver nitrate (74 mg, 0.44 mmol) and pyridine (0.080 mL, 0.99 mmol) in tetrahydrofuran (3.5 mL) under argon was stirred for 5 min at room temperature, and *tert*-butyldimethylsilyl chloride (64 mg, 0.44 mmol) was added. The cloudy mixture was stirred for 48 h at room temperature and was quenched by addition of 5% sodium bicarbonate solution (1 mL). The mixture was added to ether (20 mL) and the solution was washed with brine (20 mL) and water (20 mL). The aqueous wash was extracted once with ethyl acetate (30 mL) and twice with ether (30 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient

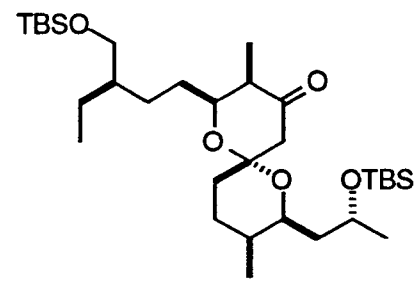
elution from 2% to 50% ethyl acetate in hexane to yield 43 mg (46%) of **132** and 19 mg (16%) of **127**.

Data for **132**: $[\alpha]_D^{22}$ -58.7° (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 300MHz) δ 0.02 (6H, s), 0.81-0.86 (3H, t, *J* = 7 Hz), 0.87-0.88 (3H, d, *J* = 3 Hz), 0.88 (9H, s), 0.91 (3H, d, *J* = 7 Hz), 1.21 (3H, d, *J* = 6 Hz), 1.24-1.45 (9H, m), 1.50-1.75 (7H, m), 1.82-1.90 (2H, m), 2.08-2.19 (1H, tt, *J* = 13, 4 Hz), 3.43-3.52 (2H, dq, *J* = 10, 6 Hz), 3.64-3.67 (1H, m), 3.95-4.08 (2H, m), 4.10-4.18 (1H, td, *J* = 12, 5 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5(2C), 3.9, 11.0, 11.2, 18.2, 23.1, 24.0, 25.9(2C), 26.4, 27.0, 29.7, 29.8, 30.6, 37.9, 38.9, 42.0, 42.0, 65.0, 65.4, 67.4, 67.5, 71.2, 97.3.



128

and



129

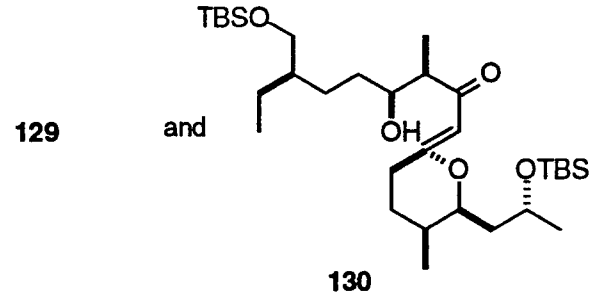
(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxymethyl]-1-pentyl]-1,7-dioxaspiro-[5.5]undecan-4-one (128) and **(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxymethyl]-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-one (129).** A solution of **112** (79 mg, 0.22 mmol), imidazole (42 mg, 0.62 mmol), and *tert*-butyldimethylsilyl chloride (80 mg, 0.53 mmol) in N, N-dimethylformamide (5 mL) under argon was stirred for 17 h at room temperature, after which additional imidazole (30 mg) and *tert*-butyldimethylsilyl chloride (48 mg) were added. Stirring was continued for 25 h, the mixture was added to ether (30 mL), and the solution was washed with brine (30 mL). The aqueous wash was extracted three times with ether

(30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 40% ethyl acetate in hexane to yield 52 mg (50%) of **128** and 36 mg (28%) of **129** as a colorless oil: $[\alpha]_D^{22}$ -54.9° (*c* 1.38, $CHCl_3$); IR (neat) 2957, 2931, 2891, 2858, 1722, 1463, 1384, 1251, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (6H, s), 0.04 (6H, s), 0.85 (3H, d, *J* = 6 Hz), 0.86 (9H, s), 0.89 (9H, s), 0.91 (3H, d, *J* = 7 Hz), 1.08 (3H, d, *J* = 7 Hz), 1.12 (3H, d, *J* = 7 Hz), 1.15-1.29 (2H, m), 1.30-1.53 (6H, m), 1.56-1.73 (6H, m), 2.04-2.17 (1H, m, *J* = 7, 2 Hz), 2.30 (1H, d, *J* = 14 Hz), 2.49 (1H, d, *J* = 14 Hz), 2.32-2.35 (1H, m), 3.44-3.55 (2H, ddd, *J* = 15, 10, 6 Hz), 3.71-3.78 (2H, dq, *J* = 7, 2 Hz), 3.80-3.85 (1H, m, *J* = 10, 5, 3 Hz); ^{13}C NMR ($CDCl_3$) δ (-5.5, -4.6, -4.4)(4C), 10.6, 10.9, 11.0, 18.0, 18.2, 23.1, 24.3, 25.8(6C), 26.3, 27.2, 28.9, 29.1, 29.4, 42.0, 42.9, 48.1, 48.3, 65.1, 67.1, 70.0, 70.7, 99.0, 210.5; MS (CI) *m/z* 585 (M^++1), 584 (M^+), 569, 527, 451, 437, 369, 341, 327, 283, 271, 241, 229, 187, 159, 137, 95; HRMS (CI) *m/z* 585.4372 (calcd for $C_{32}H_{64}O_5Si_2$+H^+: 585.4372). Anal. Calcd for $C_{32}H_{64}O_5Si_2$: C, 65.69; H, 11.03. Found: C, 65.58; H, 10.84.

Data for **128**: IR (neat) 3489 (br), 2957, 2931, 2884, 2864, 1716, 1463, 1384, 1251, 1091, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.02 (6H, s), 0.83-0.90 (3H, m), 0.86 (9H, s), 1.07 (3H, d, *J* = 7 Hz), 1.15 (3H, d, *J* = 6 Hz), 1.20-1.48 (8H, m), 1.51-1.75 (6H, m), 2.11-2.22 (1H, m), 2.27 (1H, d, *J* = 14 Hz), 2.27-2.36 (1H, m), 2.54 (1H, d, *J* = 14 Hz), 3.42-3.60 (2H, m), 3.89 (1H, brs), 3.93-4.04 (2H, m).

A solution of **128** (54 mg, 0.12 mmol), imidazole (50 mg, 0.73 mmol), and *tert*-butyldimethylsilyl chloride (95 mg, 0.61 mmol) in N, N-dimethylformamide (4 mL) under argon was stirred for 7 h at room temperature, diluted with ether (20 mL) and the solution was washed with brine (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium

sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 5% of ethyl acetate in hexane as eluant, gave 57.5 mg (86%) of **129**.

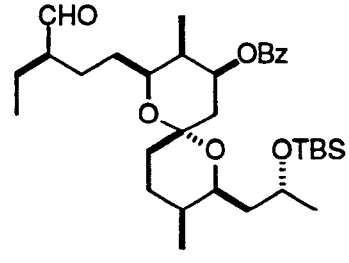


129 and **130**

(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-[(*tert*-butyldimethylsilyl)oxymethyl]-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-one (129) and **[2*S*,3*S*,6(4*R*,5*S*,8R)]-3-methyl-2-[(*R*)-2-[(*tert*-butyldimethylsilyl)-oxy]-1-propyl]-6-[(1*E*)-5-hydroxy-4-methyl-8-[(*tert*-butyldimethylsilyl)oxymethyl]-1-octe- nyl-3-one]tetrahydropyran (130).** To a solution of **116** (328 mg, 0.697 mmol) in dichloromethane (13 mL) under argon at 0°C was added triethylamine (0.254 mL, 1.81 mmol) and *tert*-butyldimethylsilyl triflate (0.223 mL, 0.975 mmol). The solution was stirred for 50 min at 0°C, was quenched by addition of saturated ammonium chloride solution (3 mL), and was extracted three times with ether (50 mL). The combined ethereal extracts were washed with brine (100 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 30% ethyl acetate in hexane, to yield 194 mg (56%) of **130** and 180 mg (44%) of **129**. Data for **130**: IR (neat) 3469, 2957, 2931, 2884, 2858, 1663, 1601, 1463, 1384, 1251, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (6H, s), 0.08 (6H, d, J = 2 Hz), 0.89 (18H, d, J = 1 Hz), 0.90-0.95 (6H, m), 1.02 (3H, m), 1.23 (3H, d, J = 6 Hz), 1.23-1.39 (5H, m), 1.40-1.51 (4H, m), 1.52-1.60 (2H, m, J = 5 Hz), 1.64-1.88 (3H, m), 2.19-2.37 (3H, m), 3.27 (1H, brs), 3.44-3.56 (2H, ddd,

J = 15, 10, 6 Hz), 3.90-3.93 (1H, m, J = 10 Hz), 4.18-4.27 (2H, m), 5.25 (1H, s); ^{13}C NMR ($CDCl_3$) δ (-5.5, -5.1, -4.6)(4C), 7.1, 9.6, 11.2, 13.9, 17.8, 18.2, 22.4, 23.3, 25.6, 25.7, 25.8(3C), 26.1, 27.5, 29.5, 32.6, 38.2, 40.6, 41.6, 42.7, 64.9, 67.6, 70.6, 82.1, 102.3, 177.3, 198.0; MS (CI) *m/z* 585 (M^++1), 584 (M^+), 569, 527, 469, 435, 383, 369 283, 229, 187, 159, 115, 95; HRMS (CI) *m/z* 585.4372 (calcd for $C_{32}H_{64}O_5Si_2$+H^+: 585.4372).

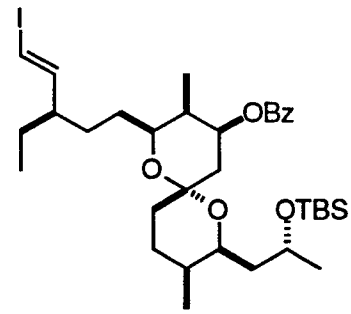
To a solution of **130** (194 mg, 0.390 mmol) in chloroform (4 mL) at room temperature was added (1*S*)-(+)-*O*-camphorsulfonic acid (8.00 mg, 0.0340 mmol). The mixture was stirred for 2 h at room temperature, after which additional (1*S*)-(+)-*O*-camphorsulfonic acid (12 mg) was added and the mixture was stirred for 3 d. The mixture was added to ether (30 mL) and the solution was washed with brine (30 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 20% ethyl acetate in hexane, to yield 63.0 mg (32%) of **129**.



(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsily-l)oxy]-1-propyl]-2-[(*R*)-3-ethyl-3-formylpropyl]-1,7-dioxaspiro[5.5]undecane (134)

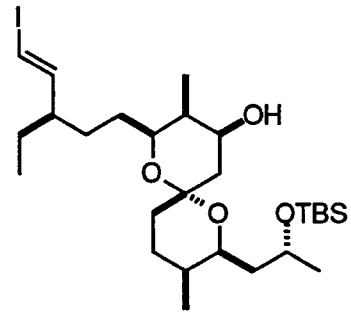
To a solution of oxalyl chloride (0.378 mL, 4.25 mmol) in dichloromethane (20 mL) under argon at -78°C was added dimethyl sulfoxide (0.603 mL, 8.50 mmol) and the

mixture was stirred for 15 min. A solution of **125** (490 mg, 0.850 mmol) in dichloromethane (6 mL) was added dropwise, stirring was continued for 30 min, and triethylamine (2.40 mL, 17.0 mmol) was added. The solution was stirred for 50 min at -78°C, allowed to warm to room temperature for 1 h, and was quenched by addition of water (1 mL). The mixture was diluted with ether (30 mL), and was washed with brine (30 mL) and water (30 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield 470 mg (96%) of **134** as a pale yellow oil: IR (neat) 2959, 2933, 2859, 1722, 1274, 1107, 1099, 990 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06 (6H, s), 0.89 (10H, s), 0.93 (9H, t, *J* = 8 Hz), 1.22 (3H, d, *J* = 6 Hz), 1.35-1.77 (13H, m), 1.84-1.95 (2H, m), 2.07-2.21 (3H, m), 3.74-3.86 (3H, m), 5.50 (1H, dt, *J* = 10, 5 Hz), 7.43 (1H, t, *J* = 7 Hz), 7.55 (1H, t, *J* = 7 Hz), 8.02 (1H, d, *J* = 7 Hz), 9.59 (1H, d, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.5, -4.3, 5.1, 10.9, 11.3, 18.0, 21.6, 24.4, 25.4, 25.8(3C), 26.3, 29.5, 29.6, 29.9, 35.2, 35.6, 43.1, 53.3, 67.2, 69.4, 70.3, 71.1, 97.4, 128.2(2C), 129.4(2C), 130.5, 132.7, 165.6, 204.8; MS (FAB) *m/z* 575 (M^++1), 574 (M^+), 557, 517, 469, 453, 395, 325, 267, 221, 193, 159, 137; HRMS (CI) *m/z* 575.3405 (calcd for $C_{33}H_{54}O_6Si + H^+$: 575.3769).



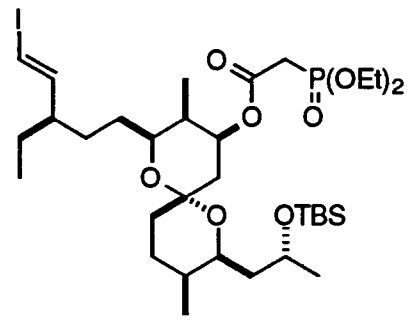
(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsily-l)oxy]-1-propyl]-2-[(*R*)-3-ethyl-5-(*E*)-iodo-4-pentenyl]-1,7-dioxaspiro[5.5]undecane (135). To a solution of chromium(II) chloride (994 mg, 8.09 mmol) in tetrahydrofuran (18 ml) under argon at 0°C was added dropwise a solution of **134** (465 mg, 0.809 mmol) and iodomethane (701 mg, 1.78 mmol) in tetrahydrofuran (18 mL) via cannula. The brown solution was stirred for 2 h at 0°C and for 1 h at room temperature, and was quenched by addition of water (5 mL). The resultant deep-green mixture was extracted three times with ether (80 mL), and the combined ethereal extracts were washed with water (150 mL) and brine (150 mL), and was dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2% to 4% ethyl acetate in hexane, to yield 431 mg (76%) of **135** as a colorless oil: $[\alpha]_D^{22}$ -62.7° (*c* 6.03, $CHCl_3$); IR (neat) 2958, 2931, 1720, 1275, 1255, 1098, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.07 (6H, s), 0.84-0.95 (18H, m), 1.22 (3H, d, *J* = 6 Hz), 1.25-1.94 (13H, m), 1.85-2.18 (4H, m), 3.71-3.87 (3H, m), 4.49 (1H, dt, *J* = 12, 5 Hz), 5.96 (1H, d, *J* = 14 Hz), 6.27 (1H, dd, *J* = 14, 9 Hz), 7.43 (2H, d, *J* = 7 Hz), 7.55 (1H, t, *J* = 7 Hz), 8.02 (2H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.4, -4.2, 5.1, 11.0, 11.5, 18.1, 24.5, 25.9(3C), 26.4, 27.9, 29.6 (2C), 30.2, 31.1, 35.8, 43.3, 48.7, 67.3, 69.5, 70.4, 71.3, 74.2, 97.5, 128.3(2C), 129.5(2C), 130.6, 132.8, 150.4, 165.7; MS (FAB) *m/z* 698 (M^+), 697, 683, 641, 577, 519, 451, 431, 389, 325, 267, 229, 205, 193, 159, 105; HRMS (FAB) *m/z* 698.2863 (calcd for $C_{34}H_{55}IO_5Si$:

698.2865). This compound was contaminated by a small amount of the *Z* stereoisomer (*E*/*Z* 18.4:1 by ^{13}C NMR).



(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl] -2-[(*R*)-3-ethyl-5-(*E*)-iodo-4-pentenyl]-1,7-dioxaspiro[5.5]undecan-4-ol (136). A suspension of **135** (65 mg, 0.093 mmol) and lithium hydroxide monohydrate (8.5 mg, 0.20 mmol) in methanol (0.4 mL), tetrahydrofuran (0.4 mL) and water (0.2 mL) was stirred for 20 h at room temperature. The mixture was added to ether (20 mL) and the solution was washed with water (20 mL) and brine (20 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silics gel, with gradient elution from 5% to 20% ethyl acetate in hexane, to yield 56 mg (100%) of **136** as a colorless oil: $[\alpha]_D^{22}$ -45.4° (*c* 2.08, $CHCl_3$); IR (neat) 3383 (br), 2957, 2932, 2885, 1459, 1253, 970, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.05 (6H, s), 0.80-0.94 (18H, m), 1.17 (3H, d, *J* = 6 Hz), 1.23-1.74 (14H, m), 1.80 (1H, m), 1.93-2.05 (2H, m), 3.55 (1H, m), 3.71 (1H, dt, *J* = 7, 2 Hz), 3.80 (1H, m), 4.17 (1H, dt, *J* = 12, 5 Hz), 5.95 (1H, d, *J* = 14 Hz), 6.26 (1H, dd, *J* = 14, 9 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.6, -4.4, 4.0, 10.9, 11.5, 18.0, 24.3, 25.8(3C), 26.4, 27.0, 29.5, 29.6, 30.2, 31.1, 38.0, 39.0, 43.2, 48.7, 67.1, 67.2, 69.2, 70.8, 74.0, 97.4, 150.4; MS

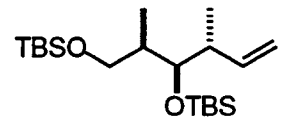
(FAB) *m/z* 595 (M^+), 577, 519, 443, 421, 345, 325, 227, 193, 159, 137; HRMS (FAB) *m/z* 595.2677 (calcd for $C_{27}H_{51}IO_4Si + H^+$: 595.2681).



(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-[(Diethylphosphonoacetyl)oxy]-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-ethyl-5-(*E*)-iodo-4-pentenyl]-1,7-dioxaspiro[5.5]undecane (7). A solution of triethyl phosphonoacetate (5.0 g, 22 mmol) and potassium hydroxide (1.5 g, 24 mmol) in ethanol (3.5 mL) and water (1.4 mL) was stirred for 15 h at room temperature. The volatile components were removed under reduced pressure and the residue was dissolved in water (20 mL). The mixture was extracted twice with ether (30 mL), and the combined organic layers were washed with water (40 mL) and acidified to pH 1 using 2 N hydrochloric acid, and brine (50 mL) was added. After separation, the aqueous layer was extracted three times with dichloromethane (50 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent gave 3.0 g (69%) of crude acid as a pale yellow oil.

To a solution of the acid (700 mg, 3.57 mmol) in dichloromethane (6 mL) at 0°C was added oxalyl chloride (0.477 mL, 5.36 mmol) dropwise and the mixture was stirred for 10 min at 0°C and for 22 h at room temperature. Removal of the solvent gave 766 mg of crude **137** which was used without purification.

To a solution of **136** (313 mg, 0.526 mmol), 4-(dimethylamino)pyridine (480 mg, 3.93 mmol), and pyridine (0.607 mL, 7.85 mmol) in dichloromethane (10 mL) under argon at 0°C was added dropwise a solution of crude **137** (766 mg) in dichloromethane (3 mL). The yellow solution was stirred for 1 h at 0°C and was quenched by addition of saturated sodium bicarbonate solution (5 mL). The mixture was diluted with dichloromethane (30 mL) and was washed with saturated sodium bicarbonate solution (30 mL), water (30 mL) and brine (30 mL). The aqueous wash was extracted three times with dichloromethane (80 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave 392 mg (96%) of **7** as a pale oil: $[\alpha]_D^{22}$ -42.8° (*c* 0.56, $CHCl_3$); IR (neat) 2958, 2952, 1735, 1273, 1257, 1057, 1028, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, s), 0.82-0.90 (18H, m), 1.17 (3H, d, J = 6 Hz), 1.24-1.63 (19H, m), 1.71-1.78 (2H, m), 1.86-2.08 (3H, m), 2.91 (1H, d, $J_{P,H}$ = 22 Hz), 3.62 (1H, m), 3.69 (1H, dt, J = 7, 2 Hz), 3.80 (1H, m), 4.15 (1H, quint, J = 7 Hz), 5.26 (1H, dt, J = 12, 5 Hz), 5.94 (1H, d, J = 14 Hz), 6.26 (1H, dd, J = 14, 9 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.5, -4.3, 4.8, 11.0, 11.5, 16.3 (d, $J_{P,C}$ = 6 Hz)(2C), 18.1, 24.4, 25.9(3C), 26.3, 27.0, 29.6, 30.1, 31.0, 34.5 (d, $J_{P,C}$ = 134 Hz), 35.0, 35.5, 43.2, 48.7, 62.6 (d, $J_{P,C}$ = 6 Hz)(3C), 67.1, 69.4, 70.2, 72.2, 74.2, 97.4, 150.3, 164.9 (d, $J_{P,C}$ = 6 Hz); MS (FAB) *m/z* 773 (M^++1), 772 (M^+), 771, 715, 672, 645, 577, 519, 345, 325, 253, 193; HRMS (FAB) *m/z* 773.3078 (calcd for $C_{33}H_{62}IO_8PSi + H^+$: 773.3074).



(2*R*,3*R*,4*R*)-1,3-Di-[(*tert*-butyldimethylsilyl)oxy]-2,4-(dimethyl)hex-5-ene (140).

To a solution of oxalyl chloride (18.3 mL, 205 mmol) in dichloromethane (350 mL) under argon at -78°C was added dimethyl sulfoxide (25 mL, 352 mmol). The mixture was stirred for 45 min at -78°C, and a solution of crude **41** (12.0 g, 58.7 mmol) in dichloromethane (100 mL) was added dropwise via cannula. Stirring was continued for 1 h, after which triethylamine (82.0 mL, 587 mmol) was added. The mixture was stirred for 45 min at -78°C, allowed to warm to room temperature for 1 h, quenched by addition of water (30 mL), and was diluted with pentane (800 mL). The solution was washed with brine (800 mL) and water (800 mL). The aqueous wash was extracted once with pentane (800 mL) and twice with ether (800 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent gave crude **133** as a yellow oil which was used without purification: $[\alpha]_D^{22}$ -7.5° (*c* 2.00, $CHCl_3$).

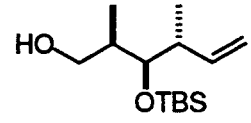
To a solution of the (*E*)-crotylboronate diethanolamine complex (18.8 g, 111 mmol) in ether (400 mL) under argon at room temperature was added D-(*S, S*)-diisopropyl tartrate (24.1 mL, 111 mmol). The mixture was rapidly stirred for 10 min and a saturated sodium chloride solution (400 mL) was added. Stirring was continued for 10 min and the mixture was partitioned. The aqueous layer was extracted three times with ether (400 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent gave **138** as a viscous pale yellow oil which was used immediately.

A mixture of crude **138** (111 mmol) and powdered activated 4Å molecular sieves (30.0 g) in toluene (400 mL) under argon was stirred for 15 min at room temperature and cooled to -78°C. A solution of crude **133** (58.7 mmol) in toluene (60

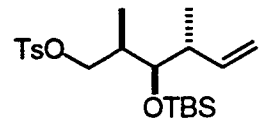
mL) was added dropwise via cannula over a period of 1 h, and the mixture was stirred for 2.5 d at -78°C and quenched by addition of 1 N sodium hydroxide solution (330 mL). The mixture was stirred for 2.5 h at room temperature and was diluted with ether (800 mL). The solution was washed with water (80 mL) and brine (800 mL), the aqueous wash was extracted three times with ether (800 mL), and the combined ethereal extracts were dried (sodium sulfate). Removal of the solvent gave crude alcohol **139** as a yellow oil which was used without purification: IR (neat) 3500, 2958, 2898, 1472, 1255, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.06 (6H, s), 0.89 (9H, s), 0.93 (3H, d, J = 3 Hz), 0.96 (3H, d, J = 3 Hz), 1.80 (1H, m), 2.27 (1H, m), 3.53 (1H, dd, J = 9, 2 Hz), 3.71 (2H, m), 5.10 (2H, m), 5.83 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.7, -5.7, 9.3, 16.5, 18.1, 25.7, 36.2, 41.6, 68.1, 76.5, 114.9, 141.9; MS (CI) *m/z* 259 (M^++1), 241, 205, 109; HRMS (CI) *m/z* 259.2094 (calcd for $C_{14}H_{30}O_2Si$ + H^+: 259.2093).

To a solution of crude **139** (58.7 mmol) and imidazole (8.10 g, 117 mmol) in dimethylformamide (60 ml) at room temperature was added a solution of *tert*-butyldimethylsilyl chloride (13.0 g, 83.7 mmol) in dimethylformamide (20 mL). The mixture was stirred for 4 d at room temperature, after which additional *tert*-butyldimethylsilyl chloride (3.00 g) and imidazole (2.00 g) were added. Stirring was continued for 2 d, the mixture was diluted with ether (200 mL), and the solution was washed with water (200 mL). The aqueous wash was extracted three times with ether (200 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2.5% to 10% ethyl acetate in hexane, to yield 13.0 g (66% from **41**) of **140** as a colorless oil: $[\alpha]_D^{22}$ -3.4° (*c* 5.94, $CHCl_3$); IR (neat) 2957, 2930, 2889, 2858, 1472, 1255, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.04 (6H, s), 0.84 (3H, d, J = 7 Hz), 0.89 (9H, s), 0.90 (9H, s), 0.99 (3H, d, J = 7 Hz), 1.76

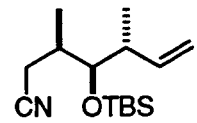
(1H, m), 2.34 (1H, m), 3.37 (1H, dd, J = 10, 7 Hz), 3.46 (1H, dd, J = 10, 7 Hz), 4.97 (2H, m), 5.83 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.3, -5.3, -4.1, -3.7, 11.7, 17.0, 18.3, 18.4, (25.9, 26.2)(6C), 39.2, 43.0, 66.0, 75.3, 113.9, 142.2; MS (CI) *m/z* 373 (M^++1), 357, 317, 257, 199, 109; HRMS (CI) *m/z* 373.2958 (calcd for $C_{20}H_{44}O_2Si_2$ + H^+: 373.2958). This compound was contaminated by *ca* 25% (4:1 by ^{13}C NMR) of a second stereoisomer.



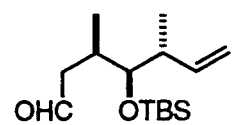
(2*R*,3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-2,4-(dimethyl)hex-5-ene (141). A stirred solution of **140** (13.0 g, 34.9 mmol) and ammonium fluoride (13.0 g, 349 mmol) in methanol (200 mL) was heated at reflux for 12 h and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 10% ethyl acetate in hexane (10 mL). The solution was chromatographed on silica gel, with gradient elution from 15% to 75% ethyl acetate in hexane, to yield 7.65 g (85%) of **141** as a colorless oil : $[\alpha]_D^{22}$ +0.97° (*c* 2.36, $CHCl_3$); IR (neat) 3355 (br), 2960, 2932, 2887, 2859, 1475, 1254, 1044, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.07 (6H, d, J = 3 Hz), 0.88 (3H, d, J = 7 Hz), 0.91 (9H, s), 1.03 (3H, d, J = 7 Hz), 1.86-1.96 (2H, m), 2.36-2.47 (1H, m), 3.46 (1H, dd, J = 11, 6 Hz), 3.61-3.68 (2H, m), 4.98-5.07 (2H, m), 5.86-5.97 (1H, ddd, J = 18, 10, 8 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.2, -4.1, 12.3, 18.0, 18.2, 25.9(3C), 39.6, 41.7, 65.7, 76.5, 114.3, 141.5; HRMS (CI) *m/z* 259.2094 (calcd for $C_{14}H_{30}O_2Si$ + H^+: 259.2093); Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.07; H, 11.71. Found: C, 65.15; H, 11.47. This compound was contaminated by *ca* 7% (13.4:1 by ^{13}C NMR) of a second stereoisomer.



(2*R*,3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethyl-1-(*p*-toluenesulfonyloxy)-hex-5-ene (142). To a solution of **141** (7.65 g, 29.6 mmol) in pyridine (80 mL) under argon at 0°C was added *p*-toluenesulfonyl chloride (8.46 g, 44.4 mmol). The mixture was stirred for 30 h at 0°C and was allowed to warm to room temperature. The reaction was quenched by addition of water (100 mL) and the mixture was stirred for 10 min. Ether (500 mL) and water (500 mL) were added and the layers were separated. The aqueous layer was extracted three times with ether (500 mL), and the combined ethereal extracts were washed with 1 N hydrochloric acid solution (500 mL), water (500 mL), and saturated sodium bicarbonate solution (500 mL), and were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield 11.2 g (92%) of **141** as a pale yellow oil: $[\alpha]_D^{22}$ -3.2° (*c* 3.65, $CHCl_3$); IR (neat) 3355 (br), 2959, 2929, 2884, 2859, 1605, 1475, 1373, 1259, 1189, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ -0.04 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 0.87 (3H, d, *J* = 7 Hz), 0.95 (3H, d, *J* = 7 Hz), 1.92-2.03 (1H, m), 2.24-2.33 (1H, m), 2.44 (1H, s), 3.43-3.57 (1H, m), 3.85-3.98 (2H, dd, *J* = 9, 6 Hz), 4.93-4.97 (2H, m), 5.70-5.81 (1H, m), 7.34 (2H, d, *J* = 8 Hz), 7.77 (2H, d, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ -4.3, -4.0, 12.1, 17.5, 18.2, 21.5, 25.9(3C), 36.9, 42.2, 73.3, 75.6, 114.7, 127.9(2C), 129.7(2C), 133.3, 140.9, 144.5; MS (CI) *m/z* 413 (M^++1), 401, 397, 355, 315, 271, 229, 185, 109; HRMS (CI) *m/z* 413.2181 (calcd for $C_{21}H_{36}O_4SSi + H^+$: 413.2182). This compound was contaminated by *ca* 25% (3:1 by ^{13}C NMR) of a second stereoisomer.

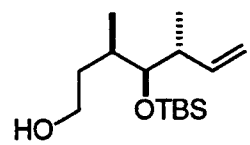


(2*R*,3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4-(dimethyl)hex-5-enenitrile (143). A solution of **142** (11.1 g, 27.0 mmol) and sodium nitrate (3.06 g, 59.4 mmol) in dimethyl sulfoxide (45 mL) under argon was stirred for 2.5 d at room temperature, and was diluted with water (50 mL). The mixture was extracted three times with hexane (50 mL), and the combined organic layers were washed with water (100 mL) and dried (magnesium sulfate). Removal of the solvent gave 6.81 g (94%) of **143** as a pale yellow oil: $[\alpha]_D^{22}$ -4.6° (*c* 1.61, $CHCl_3$); IR (neat) 2959, 2929, 2888, 2859, 2243, 1640, 1473, 1369, 1259, 1047, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.09 (6H, s), 0.92 (9H, s), 1.03 (3H, d, *J* = 7 Hz), 1.07 (3H, d, *J* = 7 Hz), 2.01-2.09 (1H, m), 2.24-2.31 (1H, dd, *J* = 17, 9 Hz), 2.38 (1H, m), 2.42-2.48 (1H, dd, *J* = 17, 9 Hz), 3.45-3.58 (1H, m), 5.00-5.06 (2H, m), 5.78-5.90 (1H, m, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ -4.1, -4.0, 15.3, 18.0, 18.2, 21.5, 26.0(3C), 35.5, 41.7, 77.4, 114.9, 119.4, 140.9; HRMS (CI) *m/z* 268.2097 (calcd for $C_{15}H_{29}NOSi + H^+$: 268.2098); Anal. Calcd for $C_{15}H_{29}NOSi$: C, 67.35; H, 10.93; N, 5.24. Found: C, 67.25; H, 11.12; N, 5.22. This compound was contaminated by *ca* 30% (2.5:1 by ^{13}C NMR) of a second stereoisomer.



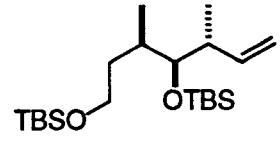
(3*R*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3,5-(dimethyl)hept-6-en-1-al (144). To a solution of **143** (5.20 g, 19.4 mmol) in toluene (80 mL) under argon at -78°C was

added diisobutylaluminum hydride (1.0 M in hexane, 58.3 mL, 58.3 mmol) dropwise over a period of 1 h. The solution was stirred for 3 h at -78°C and methanol (18 mL) was added dropwise. The mixture was stirred for 20 min at room temperature and transferred to a flask, via cannula, containing ether (300 mL) and saturated ammonium chloride solution (300 mL). The solution was stirred for 5 h, diluted with ether (300 mL), and partitioned. The ethereal layer was washed with 0.6 N hydrochloric acid solution (300 mL) and water (300 mL). The aqueous washings were extracted three times with ether (200 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2% to 5% ethyl acetate in hexane, to yield 3.87 g (75%) of **144** as a colorless oil: $[\alpha]_D^{22}$ -6.7° (*c* 0.93, $CHCl_3$); IR (neat) 2959, 2930, 2890, 2859, 1730, 1470, 1262, 1047, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.05 (6H, d, *J* = 5 Hz), 0.91 (9H, s), 0.93 (3H, d, *J* = 6 Hz), 1.02 (3H, d, *J* = 7 Hz), 2.21-2.32 (2H, m), 2.33-2.44 (1H, m), 2.58-2.67 (1H, m), 3.39-3.51 (1H, td, *J* = 26, 5 Hz), 4.95-5.03 (2H, m), 5.82-5.94 (1H, m), 9.71 (1H, t, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.1, -4.0, 15.8, 18.2, 18.8, 25.9(3C), 32.7, 41.4, 47.7, 78.5, 114.2, 141.5, 202.7; MS (CI) *m/z* 271 (M^++1), 255, 215, 199, 139, 121; HRMS (CI) *m/z* 271.2093 (calcd for $C_{15}H_{30}O_2Si$ + H^+: 271.2094). This compound was contaminated by *ca* 8% (12:1 by ^{13}C NMR) of a second stereoisomer.



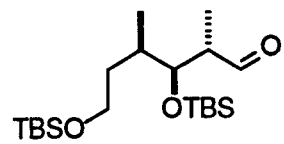
(3*R*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-3,5-(dimethyl)hept-6-ene (145). A suspension of **144** (3.23 g, 11.9 mmol) and sodium borohydride (1.38 g, 35.8

mmol) in isopropanol (70 mL) under argon was stirred for 1 h at 0°C. An aqueous solution of Rochelle salt (20 mL) in water (10 mL) was added, and the mixture was stirred for 40 min at room temperature and diluted with ether (150 mL). The organic layer was separated and was washed with aqueous Rochelle salt (100 mL) and water (100 mL). The aqueous wash was extracted three times with ether (100 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 10% ethyl acetate in hexane, as eluant, afforded 2.81 g (87%) of **145** as a colorless oil: $[\alpha]_D^{22}$ +6.1° (*c* 1.33, $CHCl_3$); IR (neat) 3340 (br), 2959, 2930, 2886, 2857, 1474, 1260, 1057, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, d, *J* = 5 Hz), 0.90 (9H, s), 0.91 (3H, d, *J* = 6 Hz), 0.99 (3H, d, *J* = 7 Hz), 1.34-1.50 (1H, m), 1.67-1.83 (2H, m), 1.85 (1H, s), 2.34-2.45 (1H, m), 3.37-3.43 (1H, m, *J* = 9, 5 Hz), 3.53-3.75 (2H, m), 4.93-5.01 (2H, m), 5.80-5.93 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -3.9, -3.8, 15.6, 17.1, 18.1, 26.0(3C), 34.4, 36.8, 41.9, 61.5, 79.5, 113.8, 142.0; MS (CI) *m/z* 271 (M^+-1), 255, 217, 199, 159, 141, 123; HRMS (CI) *m/z* 271.2094 (calcd for $C_{15}H_{32}O_2Si$ - H^+: 271.2095). This compound was contaminated by *ca* 30% (2.5:1 by ^{13}C NMR) of a second stereoisomer.



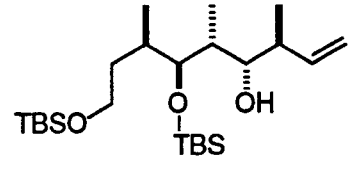
(3*R*,4*S*,5*R*)-1,4-Di-[(*tert*-butyldimethylsilyl)oxy]-3,5-(dimethyl)hept-1-ene (146). To a suspension of **145** (0.735 g, 2.70 mmol) and imidazole (0.743 g, 10.8 mmol) in dimethylformamide (20 mL) under argon at 0°C was added *tert*-butyldimethylsilyl chloride (0.839 g, 5.40 mmol). The mixture was stirred for 15 h at room temperature,

diluted with ether (100 mL), and washed with water (100 mL). The aqueous wash was extracted three times with ether (100 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 100% hexane to 1% ethyl acetate in hexane, to yield 1.00 g (96%) of **146** as a colorless oil: $[\alpha]_D^{22}$ +3.6° (*c* 1.75, $CHCl_3$); IR (neat) 2959, 2930, 2886, 2859, 1474, 1261, 1057, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04 (6H, s), 0.04 (6H, s), 0.88 (3H, d, *J* = 6.8 Hz), 0.89 (9H, s), 0.91 (9H, s), 1.01 (3H, d, *J* = 7 Hz), 1.30-1.39 (1H, m), 1.62-1.69 (1H, m), 1.70-1.81 (1H, m), 2.33-2.41 (1H, m), 3.38-3.42 (1H, m, *J* = 8, 4 Hz), 3.55-3.71 (2H, m), 4.91-4.99 (2H, m), 5.83-5.96 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-5.3, -3.8)(4C), 14.9, 16.5, 18.0, 18.3, (25.9, 26.1)(6C), 33.6, 37.3, 42.3, 61.6, 79.8, 113.7, 142.2; MS (CI) *m/z* 386 (M^+), 385 (M^+-1), 371, 329, 273, 255, 199, 159, 147, 123; HRMS (CI) *m/z* 385.2960 (calcd for $C_{21}H_{46}O_2Si$ 2- H^+: 385.2960). This compound was contaminated by *ca* 30% (2.5:1 by ^{13}C NMR) of a second stereoisomer.



(2*S*,3*S*,4*R*)-3,6-Di-[(*tert*-butyldimethylsilyl)oxy]-2,4-(dimethyl)hexan-1-al (147). A stream of ozone was passed through a solution of **146** (3.23 g, 8.35 mmol) in dichloromethane (120 mL) and methanol (27 mL) at -78°C for 25 min. The excess ozone was purged with argon for 40 min, a catalytic amount of potassium bicarbonate and dimethyl sulfide (35 mL) were added, and the mixture was stirred at room temperature for 2 d under argon. Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 100% hexane to

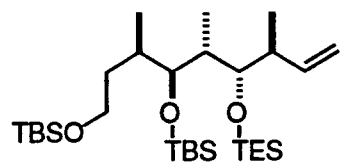
2% ethyl acetate in hexane, to yield 3.21 g (99%) of **147** as a colorless oil: $[\alpha]_D^{22}$ +27.3° (*c* 2.46, $CHCl_3$); IR (neat) 2957, 2932, 2887, 2859, 1730, 1473, 1257, 1102, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.06 (6H, s), 0.88 (18H, s), 0.90 (3H, d, *J* = 7 Hz), 1.07 (3H, d, *J* = 7 Hz), 1.24-1.35 (1H, m), 1.63-1.75 (1H, m), 1.80-1.93 (1H, m), 2.49-2.60 (1H, m), 3.55-3.59 (1H, m), 3.60-3.70 (1H, m), 3.76 (1H, t, *J* = 4 Hz), 9.76 (1H, d, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -5.4, -4.6, -4.0, 12.4, 14.4, 18.1(2C), 25.8(6C), 34.1, 35.9, 49.7, 61.0, 78.3, 205.1; MS (CI) *m/z* 387 (M^+-1), 373, 331, 315, 273, 257, 235, 199, 159, 125; HRMS (CI) *m/z* 373.2596 (calcd for $C_{20}H_{44}O_3Si_2$ - CH_3: 373.2595). This compound was contaminated by *ca* 20% (4.5:1 by ^{13}C NMR) of a second stereoisomer.



(3*R*,4*S*,5*R*,6*S*,7*S*)-1,4-Di-[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-3,5,7-trimethyl-non-8-ene (149). The (*E*)-crotylboronate **148** was prepared by the same procedure as was used for **138** except that (*R, R*)-diisopropyl tartrate replaced the (*S,S*) enantiomer.

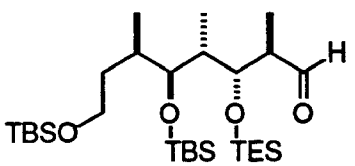
A suspension of crude **148** (34.3 mmol) and powdered activated 4Å molecular sieves (5.00 g) in toluene (100 mL) under argon was stirred for 15 min at room temperature and cooled to -78°C. A solution of **147** (3.13 g, 8.05 mmol) in toluene (30 mL) was added dropwise via cannula, and the slurry was stirred for 2.5 d at -78°C. The reaction was quenched by addition of 1 N sodium hydroxide solution (90 mL), and stirred for 2 h at room temperature. The mixture was diluted with ether (200 mL), and the solution was washed with water (200 mL) and brine (200 mL). The aqueous washing were extracted three times with ether (300 mL), and the combined ethereal

extracts were dried (magnesium sulfate). Removal of the solvent was followed by radial chromatography (4 mm plate) of the residue on silica gel, with gradient elution from 100% hexane to 1% ethyl acetate in hexane, to yield 2.79 g (78%) of **149** as a colorless oil: $[\alpha]_D^{22}$ +4.0° (*c* 4.74, $CHCl_3$); IR (neat) 3518 (br), 2957, 2931, 2887, 2859, 1473, 1390, 1257, 1100, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.05 (6H, s), 0.09 (6H, d, *J* = 8 Hz), 0.89 (9H, s), 0.89-0.99 (11H, m), 0.91 (9H, s), 1.24-1.31 (1H, m), 1.34-1.43 (1H, m), 1.71-1.80 (1H, m), 1.80-1.88 (1H, m), 1.88-1.96 (1H, m), 2.20-2.29 (1H, m, *J* = 7 Hz), 3.57-3.65 (2H, m), 3.67-3.75 (2H, m), 5.04-5.12 (2H, m), 5.79-5.90 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-5.4, -4.0, -3.7)(4C), 11.1, 15.0, 16.5, 18.2, 18.4, (25.9, 26.2)(6C), 33.7, 36.3, 37.0, 41.8, 61.4, 74.0, 81.0, 114.7, 142.5; HRMS (CI) *m/z* 444.3455 (calcd for $C_{24}H_{52}O_3Si_2$: 444.3457); Anal. Calcd for $C_{24}H_{52}O_3Si_2$: C, 64.80; H, 11.78. Found: C, 64.95; H, 11.74.



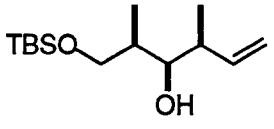
(3*R*,4*S*,5*R*,6*S*,7*S*)-1,4-Di-[(*tert*-butyldimethylsilyl)oxy]-6-(triethylsilyl)oxy-3,5,7-trimethylnon-8-ene (150). To a solution of **149** (250 mg, 0.560 mmol) and 4,4-dimethylaminopyridine (42.0 mg, 0.340 mmol) in pyridine (7 mL) under argon at room temperature was added triethylsilyl chloride (0.239 mL, 1.41 mmol). The mixture was stirred for 2 d, after which additional triethylsilyl chloride (0.210 mL) was added and stirring was continued for 2 d. The mixture was added to water (20 mL) and ether (20 mL), and was partitioned. The aqueous layer was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient

elution from 100% hexane to 3% ethyl acetate in hexane, to yield 258 mg (82%) of **150** as a colorless oil: $[\alpha]_D^{22}$ +1.6° (*c* 2.17, $CHCl_3$); IR (neat) 2952, 2928, 2880, 2859, 1473, 1254, 1100, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.02-0.08 (12H, m), 0.64 (6H, q, *J* = 8 Hz), 0.85-1.03 (25H, m), 0.98 (9H, t, *J* = 8 Hz), 1.25 (2H, m), 1.33-1.60 (2H, m), 1.63-1.84 (2H, m), 2.25-2.31 (1H, m), 3.51-3.70 (4H, m), 4.96-5.19 (2H, m), 5.83-5.95 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.4, -5.3, -4.5, -3.7, 5.6(3C), 7.1(3C), 12.2, 13.9, 18.1, 18.2, (25.8, 25.9, 26.0)(6C), 32.0, 34.4, 39.5, 42.6, 43.0, 61.0, 75.8, 78.0, 114.5, 140.6; MS (FAB) *m/z* 558 (M^+), 544, 501, 427, 397, 371, 331, 315, 273, 239, 199; HRMS (FAB) *m/z* 543.4083 (calcd for $C_{30}H_{66}O_3Si_3$ - CH_3: 543.4087); Anal. Calcd for $C_{30}H_{66}O_3Si_3$: C, 64.44; H, 11.90. Found: C, 64.51; H, 11.72.



(2*R*,3*R*,4*R*,5*S*,6*R*)-5,8-Di-[(*tert*-butyldimethylsilyl)oxy]-3-(triethylsilyl)oxy-2,4,6-trimethyloctan-1-al (9). A stream of ozone was passed through a solution of **150** (143 mg, 0.256 mmol) in dichloromethane (6 mL) and methanol (1 mL) at -78°C for 7 min. The excess ozone was purged with argon for 30 min, a catalytic amount of potassium bicarbonate and dimethyl sufide (2.6 mL) were added, and the mixture was stirred for 2 d at room temperature under argon. Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 1% to 3% ethyl acetate in hexane, to yield 144 mg (100%) of **9** as a colorless oil: $[\alpha]_D^{22}$ -9.5° (*c* 3.05, $CHCl_3$); IR (neat) 2957, 2932, 2880, 2860, 1730, 1473, 1257, 1052, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.04-0.08 (12H, m), 0.64 (6H, q, *J* = 8 Hz), 0.86-1.01 (24H,

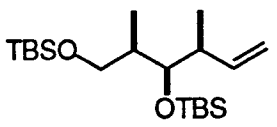
m), 0.98 (9H, t, J = 8 Hz), 1.10 (3H, d, J = 7 Hz), 1.37-1.47 (1H, m), 1.51-1.62 (1H, m), 1.68-1.80 (1H, m), 1.83-1.91 (1H, m, J = 7 Hz), 2.48-2.57 (1H, m), 3.54-3.68 (3H, m), 3.90-4.02 (1H, qd, J = 24, 6, 4 Hz), 9.75 (1H, d, J = 3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -5.4, -4.2, -4.1, 5.6(3C), 7.0(3C), 11.9, 12.3, 13.7, 18.2, 18.3, (25.8, 25.9, 26.0)(6C), 31.7, 38.5, 43.2, 50.8, 60.9, 76.1, 76.7, 205.1; MS (FAB) *m/z* 561 (M^++1), 560 (M^+), 559, 504, 487, 463, 447, 390, 371, 331, 315, 273, 239, 199.



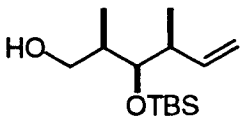
(2*R*,3*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4-dimethylhex-5-ene (152). An oven-dried 250 mL round-bottom three-neck flask equipped with an internal thermometer under argon at room temperature was charged with potassium *tert*-butoxide (8.00 g, 71.0 mmol) and tetrahydrofuran (50 mL). The solution was cooled to -78°C and *trans*-2-butene (7.40 mL, 80.0 mmol) was added dropwise via cannula while *n*-butyllithium (2.5 M in hexane, 28.4 mL, 71.0 mmol) was added via syringe pump. Addition took place over a period of 1.5 h in order that the internal temperature did not rise above -60°C. The flask which contained a the clear yellow-orange solution, was raised partially out of the cooling bath allowing the internal temperature to rise to -50°C, and the mixture was kept at this temperature for 25 min. The mixture was recooled to -78°C and tri-*n*-butylchlorostannane (17.6 mL, 65.0 mmol) was added dropwise over a period of 1 h via syringe pump in order that the internal temperature did not rise above -60°C. The mixture was stirred for 1.25 h at -78°C, quenched with 1 N hydrochloric acid solution (120 mL), and was diluted with hexane (200 mL). After separation, the aqueous layer was extracted three times with hexane (150 mL), and the

combined organic layers were dried (magnesium sulfate). Removal of the solvent gave crude **151** as a mixture of steoreisomers.

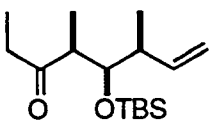
To a solution of crude **133** (9.19 mmol) in dichloromethane (40 mL) under argon at -90°C was added trifluoroboron etherate (10.1 mmol). The solution was stirred for 5 min and a solution of crude **151** (4.09 g, 10.1 mmol) in dichloromethane (15 mL) was added dropwise. The slightly turbid mixture was stirred for 4 h at -90°C and removed from the cooling bath. The reaction was quenched with saturated ammonium chloride solution (50 mL), and the mixture was stirred for 15 min. Water (20 mL) was added to dissolve precipitated solids, and after separation the aqueous layer was extracted three times with ether (20 mL) and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield (81%) of **152**. A second chromatography on silica gel, using 7% of ethyl acetate in hexane as eluant, afforded 1.70 g (75% from **41**) of **152** as a colorless oil: $[\alpha]_D^{22}$ -4.9° (*c* 1.05, $CHCl_3$); IR (neat) 3509, 2958, 2932, 2901, 2890, 2860, 1467, 1255, 1093, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.07 (6H, s), 0.90 (9H, s), 0.95 (3H, d, *J* = 7 Hz), 1.11 (3H, d, *J* = 7 Hz), 1.72-1.81 (1H, m), 2.23-2.35 (1H, m), 3.20 (1H, brd, *J* = 2 Hz), 3.57 (1H, dt, *J* = 9, 2 Hz), 3.67 (1H, dd, *J* = 10, 4 Hz), 3..79 (1H, dd, *J* = 10, 2 Hz), 4.97 (1H, dd *J* = 10, 2 Hz), 5.05 (1H, dd, *J* = 17, 1 Hz), 5.62 (1H, ddd, *J* = 17, 10, 9 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.8, -5.7, 9.2, 17.1, 18.1, 25.8(3C), 36.1, 42.1, 69.3, 78.2, 114.4, 141.2; MS (CI) *m/z* 259 (M^++1), 258 (M^+), 243, 203, 145, 127, 109; HRMS (CI) *m/z* 259.2093 (calcd for $C_{14}H_{30}O_2Si$ + H^+: 259.2093).



(2*R*,3*R*,4*S*)-1,3-Di-[(*tert*-butyldimethylsilyl)oxy]-2,4-dimethylhex-5-ene (153). To a solution of **152** (2.06 g, 7.98 mmol) in dichloromethane (45 mL) under argon at 0°C was added triethylamine (2.78 mL, 19.9 mmol) and *tert*-butyldimethylsilyl triflate (2.56 mL, 11.2 mmol). The mixture was stirred for 1.5 h at 0°C and the reaction was quenched by addition of saturated sodium bicarbonate solution (60 mL). The mixture was diluted with ether (250 mL), and after separation the organic layer was washed with water (150 mL) and was dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 100% hexane to 2% ethyl acetate in hexane, to yield 2.93 g (99%) of **153** as a colorless oil: $[\alpha]_D^{22}$ -17.2° (*c* 1.04, $CHCl_3$); IR (neat) 2957, 2931, 2889, 2859, 1488, 1254, 1105, 1052, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.03 (6H, s), 0.06 (6H, s), 0.78 (3H, d, *J* = 7 Hz), 0.89 (9H, s), 0.91 (9H, s), 1.00 (3H, d, *J* = 7 Hz), 1.71-1.84 (1H, m), 2.29-2.41 (1H, m), 3.33-3.47 (2H, m), 3.68 (1H, dd, *J* = 7, 2 Hz), 4.92-5.02 (2H, m), 5.81 (1H, ddd, *J* = 18, 10, 8 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.4, -5.4, -4.3, -3.8, 10.5, 16.8, 18.1, 18.4, (25.8, 26.1)(6C), 38.7, 42.7, 65.9, 74.8, 113.2, 142.1; HRMS (CI) *m/z* 373.2958 (calcd for $C_{20}H_{45}O_2Si_2$: 373.2957); Anal. Calcd for $C_{20}H_{45}O_2Si_2$: C, 64.44; H, 11.90. Found: C, 64.55; H, 11.79.



(2*R*,3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-2,4-dimethylhex-5-ene (154). A stirred solution of **153** (279 mg, 0.750 mmol) and ammonium fluoride (278 mg, 7.50 mmol) in methanol (10 mL) was heated at reflux for 12 h and allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in 10% ethyl acetate in hexane (10 mL). Chromatography on silica gel, with gradient elution from 10% to 75% ethyl acetate in hexane, yielded 170 mg (88%) of **154** as a colorless oil: $[\alpha]_D^{22}$ -21.3° (*c* 0.97, $CHCl_3$); IR (neat) 3540 (br), 2959, 2932, 2887, 2859, 1487, 1254, 1100, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.07 (6H, s), 0.08 (3H, s), 0.84 (3H, d, *J* = 7 Hz), 0.91 (9H, s), 1.03 (3H, d, *J* = 7 Hz), 1.88-1.94 (2H, m), 2.37-2.43 (2H, m), 3.43-3.61 (2H, m), 3.65 (1H, dd, *J* = 7, 2 Hz), 4.94-5.02 (2H, m), 5.80 (1H, ddd, *J* = 18, 10, 8 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -4.2, -3.9, 11.4, 17.1, 18.3, 26.1(3C), 39.5, 42.0, 66.1, 76.5, 113.6, 142.1; HRMS (CI) *m/z* 259.2093 (calcd for $C_{14}H_{30}O_2Si + H^+$: 259.2093); Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.07; H, 11.71. Found: C, 65.22; H, 11.81.



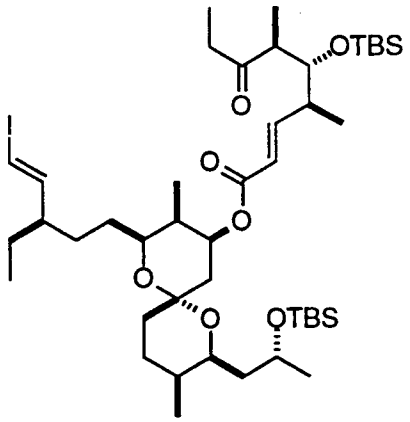
(4*S*,5*R*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4,6-dimethyloct-7-en-3-one (157). To a solution of oxalyl chloride (1.25 mL, 14.0 mmol) in dichloromethane (60 mL) under argon at -78°C was added dimethyl sulfoxide (1.99 mL, 28.0 mmol). The mixture was stirred for 35 min and a solution of **154** (725 mg, 2.80 mmol) in dichloromethane (10

mL) was added dropwise via cannula. Stirring was continued for 1 h and triethylamine (7.8 mL, 56 mmol) was added. The mixture was stirred for 40 min at -78°C and allowed to warm to room temperature for 1 h. The reaction was quenched by addition of water (2 mL), and the mixture was diluted with pentane (30 mL) and was washed with brine (30 mL) and water (30 mL). The aqueous wash was extracted with pentane (30 mL) and twice with ether (30 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent gave crude **155** as a yellow oil which was used without purification: ^{1}H NMR ($CDCl_3$, 300MHz) δ -0.01 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.03 (3H, d, J = 7 Hz), 1.10 (3H, d, J = 7 Hz), 2.32-2.44 (1H, m, J = 7 Hz), 2.48-2.56 (1H, dq, J = 7, 3 Hz), 4.04 (1H, dd, J = 7, 3 Hz), 4.99-5.07 (2H, m), 5.77 (1H, ddd, J = 18, 10, 8 Hz), 9.73 (1H, s).

To a solution of crude **155** (2.80 mmol) in ether (65 mL) under argon at -78°C was added ethylmagnesium bromide (3.0 M in ether, 3.73 mL, 11.2 mmol) dropwise. The solution was stirred for 2 h at -78°C and the reaction was quenched with saturated ammonium chloride solution (7 mL) followed by 1 N hydrochloric acid solution (7 mL). The mixture was stirred for 10 min and was diluted with ether (30 mL). The mixture was washed with saturated ammonium chloride solution (30 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (sodium sulfate). Removal of the solvent gave crude **156** as a yellow oil which was used without purification. A sample of **156** was purified for analysis: $[\alpha]_D^{22}$ -29.0° (c 1.09, $CHCl_3$); IR (neat) 3016, 2961, 2931, 2887, 2859, 1465, 1254, 1052, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.09 (6H, s), 0.89 (3H, d, J = 7 Hz), 0.91 (9H, s), 0.93 (3H, t, J = 7 Hz), 1.00 (3H, d, J = 7 Hz), 1.43-1.50 (2H, m), 1.63-1.69 (1H, m), 1.83 (1H, brs), 2.42-2.47 (1H, m), 3.51-3.55 (1H, m), 3.68 (1H, dd, J = 5, 3 Hz), 4.97-5.02 (2H, m), 5.94 (1H, ddd, J = 18, 11, 7 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ -4.1, -3.4, 8.4, 10.3, 15.7, 18.3, 26.1, 28.0, 40.1, 42.3, 76.0, 79.1, 113.5,

141.6; MS (CI) *m/z* 287 (M^++1), 286 (M^+), 285, 269, 257, 231, 201, 199, 173, 159, 155, 137, 109; HRMS (CI) *m/z* 287.2405 (calcd for $C_{16}H_{34}O_2Si + H^+$: 287.2407).

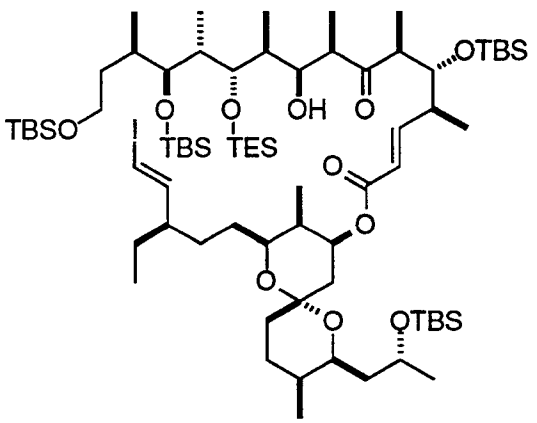
A solution of crude **156** (2.80 mmol) and Dess-Martin periodinane (3.13 g, 7.40 mmol) in wet dichloromethane (55 mL) was stirred for 1.5 h at room temperature, and ether (50 mL) and 1 N sodium hydroxide solution (50 mL) were added. After separation, the organic layer was washed with water (50 mL). The combined aqueous washes were extracted three times with ether (60 mL), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2% to 5% ethyl acetate in hexane, to yield 651 mg (82% from **154**) of pure **157** as a colorless oil: $[\alpha]_D^{22}$ -2.7° (*c* 2.25, $CHCl_3$); IR (neat) 2961, 2936, 2893, 2856, 1716, 1465, 1260, 1057, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ -0.05 (3H, s), 0.02 (3H, s), 0.85 (9H, s), 0.92 (3H, d, *J* = 7 Hz), 0.98 (3H, t, *J* = 7 Hz), 1.03 (3H, d, *J* = 7 Hz), 2.17-2.26 (1H, m), 2.36-2.49 (2H, m), 2.59-2.65 (1H, m), 3.92 (1H, dd, *J* = 5 Hz), 4.93-4.97 (2H, m), 5.71-5.80 (1H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ -4.1(2C), 7.6, 12.3, 15.5, 18.3, 26.0(3C), 35.0, 43.0, 49.8, 75.9, 114.3, 141.4, 213.5; HRMS (CI) *m/z* 285.2249 (calcd for $C_{16}H_{32}O_2Si + H^+$: 285.2251).



Ethyl Ketone 158. A stream of ozone was passed through a solution of **157** (30.0 mg, 0.105 mmol) in dichloromethane (3 mL) and methanol (0.5 mL) at -78°C for 5 min. The excess ozone was purged with argon for 15 min. Dimethyl sufide (0.8 mL) was added and the mixture was stirred for 2 h at room temperature under argon. Removal of the sovent gave 28.0 mg of crude **10** as a pale oil which was used immediately for the next step.

To a solution of diisopropylamine (0.037 mL, 0.026 mmol) in tetrahydrofuran (0.2 mL) under argon at 0°C was added *n*-butyllithium (1.33 M in hexane, 0.020 mL, 0.027 mmol) dropwise and the mixture was stirred for 15 min at 0°C. The solution was cooled to -78°C and a solution of **7** (20 mg, 0.026 mmol) in tetrahydrofuran (0.4 mL) was added dropwise. The solution was stirred for 45 min at -78°C and a solution of crude **10** (8.1 mg, 0.028 mmol) in tetrahydrofuran (0.2 mL) was added dropwise. The solution was stirred for 45 min at -78°C, slowly warmed to 0°C over a period of 15 min, and stirred for 30 min at 0°C. A saturated ammonium chloride solution (2 mL) was added, and the mixture was stirred for 15 min and was diluted with ether (20 mL). After separation, the aqueous layer was extracted three times with ether (10 mL), and the combined organic layers were washed with 5% hydrochloric acid solution (20 mL), water (20 mL) and brine (20 mL), and were dried (magnesium sulfate). Removal of the

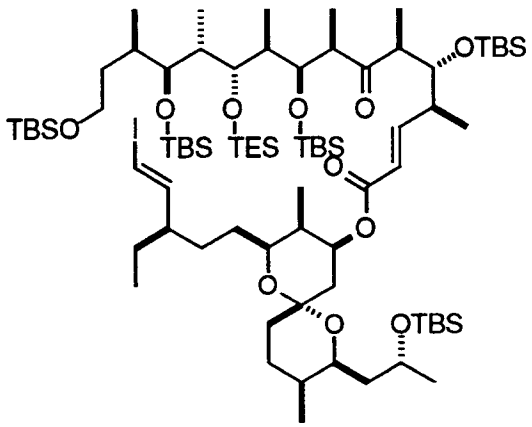
solvent followed by chromatography of the residue on silica gel, using 7% ether in hexane as eluant, afforded 17 mg (76%) of **158** as a colorless oil: $[\alpha]_D^{22}$ -52.9° (*c* 1.17, $CHCl_3$); IR (neat) 2958, 2930, 1716, 1254, 1095, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.01 (3H, s), 0.05 (9H, s), 0.80-1.00 (25H, m), 1.02-1.05 (6H, m), 1.07 (3H, d, *J* = 8 Hz), 1.18 (3H, d, *J* = 6 Hz), 1.25-1.66 (15H, m), 1.76 (1H, dd, *J* = 13, 5 Hz), 1.89-2.09 (3H, m), 2.37-2.51 (3H, m), 2.61 (1H, quint, *J* = 7 Hz), 3.64-3.74 (2H, m), 3.80 (1H, m), 4.03 (1H, t, *J* = 5 Hz), 5.28 (1H, dt, *J* = 12, 5 Hz), 5.75 (1H, dd, *J* = 16, 1 Hz), 5.94 (1H, d, *J* = 14 Hz), 6.25 (1H, dd, *J* = 14, 9 Hz), 6.96 (1H, dd, *J* = 16, 7 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-4.5, -4.3, -4.1)(4C), 4.9, 7.6, 11.0, 11.5, 13.3, 14.1, 18.1, 18.3, 24.5, (25.9, 26.0)(6C), 26.4, 27.0, 29.6, 29.7, 30.2, 31.0, 35.1, 35.3, 35.7, 41.5, 43.2, 48.7, 49.9, 67.2, 69.5, 70.3, 70.6, 74.2, 75.3, 97.5, 121.2, 150.4, 151.5, 165.6, 213.5; MS (FAB) *m/z* 904 (M^+), 890, 876, 847, 820, 759, 703, 637, 577, 519, 445, 403, 373, 345, 325, 267, 229, 193, 159; HRMS (FAB) *m/z* 577.2572 [calcd for $C_{44}H_{81}IO_7Si_2$ - OC(O)R ($C_{17}H_{31}O_4Si$) : 577.2572].



Hydroxy Ketone 159. To a solution of **158** (110 mg, 0.121 mmol) in dichloromethane (0.8 mL) under argon at -78°C was added dropwise a solution of titanium(IV) chloride (1.0 M in dichloromethane, 0.326 mL, 0.326 mmol) followed by diisopropylethylamine

(0.058 mL, 0.419 mmol). The deep red solution was stirred for 2 h at -78°C, after which a precooled (-78°C) solution of **9** (144 mg, 0.256 mmol) in dichloromethane (1.2 mL) was added via cannula. The resulting pale red solution was stirred for 1 h at -78°C, allowed to slowly warm, and was stirred at -45°C for 7 h. The reaction was quenched by addition of pH 7 phosphate buffer solution (2 mL) and was diluted with ether (20 mL). The solution was washed with saturated sodium bicarbonate solution (20 mL) and brine (20 mL), and the aqueous wash was extracted three times with ether (20 mL). The combined ethereal extracts were dried (magnesium sulfate) and the solvent was removed. Chromatography of the residue on silica gel, with gradient elution from 2% to 20% ethyl acetate in hexane yielded 79.0 mg (72%) of **158**, and 75.0 mg of a mixture of **159** and **9**. A purified sample of **159** was obtained by repeating the chromatographic separation described above: $[\alpha]_D^{22}$ -35.5° (*c* 0.77, $CHCl_3$); IR (neat) 3487 (br), 2956, 2930, 2884, 2857, 1724, 1713, 1481, 1464, 1254, 1095, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.01-0.17 (24H, m), 0.59-0.71 (6H, q, *J* = 5 Hz), 0.81 (6H, d, *J* = 8 Hz), 0.86-1.03 (19H, m), 0.87-0.88 (36H, m), 0.98 (9H, t, *J* = 8 Hz), 1.11-1.33 (20H, m), 1.38-1.53 (8H, m), 1.57-1.64 (5H, m), 1.70-1.80 (1H, m), 1.84-1.97 (1H, m), 1.98-2.10 (2H, m), 2.30-2.43 (1H, m), 2.60-2.64 (1H, m), 2.78-2.90 (1H, m), 3.52-3.74 (6H, m), 3.75-3.86 (1H, m), 3.92 (1H, d, *J* = 11 Hz), 4.08-4.19 (2H, m), 5.20-5.30 (1H, td, *J* = 11, 5 Hz), 5.75 (1H, d, *J* = 16 Hz), 5.94 (1H, d, *J* = 14 Hz), 6.22-6.30 (1H, dd, *J* = 14, 9 Hz), 6.94-7.00 (1H, dd, *J* = 16, 7 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ (-5.5, -5.3, -4.5, -4.4, -4.3, -4.0, -3.8)(8C), (4.9, 5.4)(3C), 7.0(3C), 10.9, 11.5, 12.1, 12.7, 13.0, 13.4, 14.0, 15.2, 15.8, (18.0, 18.1, 18.3)(4C), 22.6, 24.4, 25.7, (25.80, 25.83, 25.9, 25.97, 26.00)(12C), 26.3, 27.0, 29.4, 29.6, 30.1, 31.0, 31.5, 35.0, 35.6, 39.0, 41.4, 43.1, 48.7, 50.3, 55.5, 60.6, 67.1, 69.4, 70.2, 70.4, 73.5, 74.1, 75.8, 77.1, 78.9, 97.4, 120.9, 150.3, 151.7, 165.5, 214.9; MS (FAB) *m/z* 1487

(M^++Na), 1465 (M^++1), 1407, 1316, 1276, 1183, 1155, 1087, 989, 875, 819; HRMS (FAB) *m/z* 1407.8050 (calcd for $C_{73}H_{145}IO_{11}Si_5$-C_4H_9: 1407.7978).



Hexasilyl Ether 160. To a solution of **159** (74 mg) in dichloromethane (0.7 mL) under argon at 0°C was added 2,6-lutidine (0.048 mL, 0.40 mmol) and the mixture was stirred for 5 min at 0°C. *tert*-Butyldimethylsilyl triflate (0.048 mL, 0.20 mmol) was added dropwise and the mixture was stirred for 2.5 h at 0°C, after which an additional quantity of 2,6-lutidine (0.048 mL, 0.40 mmol) and *tert*-butyldimethylsilyl triflate (0.048 mL, 0.20 mmol) was added. Stirring was continued for 17 h at 0°C, and the reaction was quenched by addition of saturated sodium bicarbonate solution (2 mL). The mixture was diluted with ether (20 mL) and was washed with saturated sodium bicarbonate solution (20 mL) and water (20 mL). The aqueous wash was extracted three times with ether (20 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 2% to 5% ethyl acetate in hexane, to yield 41 mg of recovered impure **159** and 30 mg (84% based on recovered **159**, 30% from **158** based on recovered **158**) of **160** as a colorless oil: $[\alpha]_D^{22}$ -27.0° (*c* 1.40, $CHCl_3$); IR (neat) 2956, 2930, 2884, 2859, 1724, 1713, 1480, 1464, 1254, 1095, 834

cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ -0.05-0.13 (30H, m), 0.57-0.70 (6H, m, *J* = 5 Hz), 0.81 (6H, d, *J* = 7 Hz), 0.83-1.00 (6H, m), 0.87-0.88 (45H, m), 0.96 (9H, t, *J* = 8 Hz), 1.00-1.05 (5H, m), 1.09 (3H, d, *J* = 7 Hz), 1.18-1.34 (12H, m), 1.38-1.64 (12H, m), 1.67-1.82 (4H, m), 1.84-1.97 (1H, m), 1.98-2.10 (2H, m), 2.20-2.30 (1H, m), 2.64-2.73 (1H, d, *J* = 7 Hz), 2.92 (1H, t, *J* = 7 Hz), 3.41-3.51 (1H, m), 3.53-3.65 (4H, m), 3.71-3.75 (1H, m), 3.78-3.84 (2H, m), 4.06-4.09 (1H, dd, *J* = 7, 2 Hz), 4.15 (1H, d, *J* = 8 Hz), 5.24-5.31 (1H, td, *J* = 12, 5 Hz), 5.71-5.76 (1H, dd, *J* = 16, 2 Hz), 5.94 (1H, d, *J* = 14 Hz), 6.22-6.30 (1H, dd, *J* = 14, 9 Hz), 6.91-6.98 (1H, dd, *J* = 16, 6 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, -5.4, -4.5, -4.3, -4.2, -4.1, -4.0, -3.9, -3.7, -3.4, (4.8, 5.6)(3C), (7.1, 7.2)(3C), 10.7, 11.3, 11.8, 13.9, 14.5, 15.4, 18.0, 18.1, 18.31, 18.35, 18.5, 24.4, 25.6, (25.83, 25.87, 25.90, 26.0, 26.19, 26.23, 26.32)(15C), 27.0, 29.5, 29.6, 30.1, 31.0, 31.6, 35.0, 35.6, 39.4, 40.7, 42.2, 43.1, 43.5, 47.7, 48.7, 51.2, 60.8, 61.4, 67.1, 69.4, 70.2, 70.3, 71.2, 74.1, 75.2, 75.5, 76.1, 77.1, 78.2, 97.4, 121.0, 150.3, 152.4, 165.4, 213.8; MS (FAB) *m/z* 1579 (M^++1), 1578 (M^+), 1577 (M^+-1), 1521, 1448, 1390, 1316, 1276, 1183, 1155, 1087, 989, 875, 819; HRMS (FAB) *m/z* 1521.8788 (calcd for $C_{79}H_{159}IO_{11}Si_6$ - C_4H_9: 1521.8838).

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