7-(*p*-Cyanobenzyl)-5-[2-[(phenylthio)methyl]phenyl]naphthacene (8f): ^{1}H NMR ($CDCl_3$) δ 4.65 (s, 2 H), 3.77 (s, 2 H), 7.95 (d, 1 H, Ar), 7.0–8.72 (m, 22 H, remaining Ar); mass spectrum (FDMS) *m/e* 541.

8-(*p*-Cyanobenzyl)-5-[2-[(phenylthio)methyl]phenyl]naphthacene (8g): ^{1}H NMR ($CDCl_3$) δ 4.08 (s, 2 H), 3.77 (s, 2 H), 7.0–8.7 (m, 23 H, Ar); mass spectrum (FDMS) *m/e* 541.

9-(*p*-Cyanobenzyl)-5-[2-[(phenylthio)methyl]phenyl]naphthacene (8h): ^{1}H NMR ($CDCl_3$) δ 4.19 (s, 2 H), 3.77 (s, 2 H), 7.0–8.7 (m, 23 H, Ar); mass spectrum (FDMS) *m/e* 541.

10-(*p*-Cyanobenzyl)-5-[2-[(phenylthio)methyl]phenyl]naphthacene (8i): ^{1}H NMR ($CDCl_3$) δ 4.69 (s, 2 H), 3.77 (s, 2 H), 8.67 (s, 1 H, Ar), 8.78 (s, 1 H, Ar), 8.15 (s, 1 H, Ar), 8.00 (d, 1 H, Ar), 7.0–7.88 (m, 19 H, remaining Ar); mass spectrum (FDMS) *m/e* 541.

11-(*p*-Cyanobenzyl)-5-[2-[(phenylthio)methyl]phenyl]naphthacene (8j): ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 2 H), 3.77 (s, 2 H), 8.86 (s, 1 H, Ar), 7.99 (s, 1 H, Ar), 8.26 (d, 1 H, Ar), 7.0–7.88 (m, 20 H, remaining Ar); mass spectrum (FDMS) *m/e* 541.

12-(*p*-Cyanobenzyl)-5-[2-[(phenylthio)methyl]phenyl]naphthacene (8k): ^{1}H NMR ($CDCl_3$) δ 5.30 (s, 2 H), 3.77 (s, 2 H), 8.26 (s, 1 H, Ar), 8.82 (s, 1 H, Ar), 7.0–8.02 (m, 21 H, remaining Ar); mass spectrum (FDMS) *m/e* 541.

X-ray Crystallography.[6] A clear tabular crystal of **3** was mounted in a glass capillary and used for data collection on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo Kα radiation.[6] A summary of unit-cell data and refinement parameters are given in Table I. Unit-cell data were determined by least-squares refinement of 25 reflections ($12.0 < 2\theta < 20.6°$). Three standard reflections were remeasured every hour of X-ray exposure. Data were corrected for a maximum 8% variation in intensity over time.

The structure was solved by direct methods by using MULTAN 11/82. There are two molecules (A & B) in the assymetric unit. Refinement was by the full-matrix least-squares method. Hydrogen atoms were input at calculated positions in the final cycles of refinement but not refined.

Supplementary Material Available: Determination of the quantum yields of **4**, **5**, **6**, and **8** (2 pages). Ordering information is given on any current masthead page.

The Chemistry of Cyclic Vinyl Ethers. 6. Total Synthesis of Polyether Ionophore Antibiotics of the Calcimycin (A-23187) Class

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Abstract: An extremely convergent (longest linear sequence, 16 steps), fully stereoselective, and potentially general synthesis of the antibiotic ionophores of the Calcimycin (A-23187) class was devised. The key steps involve a coupling reaction between the chiral nonracemic subunits dihydropyran **41** (as the α-lithio anion) and bromide **49**. Subsequent acid-promoted cyclization directly produces the spirocyclic ring system found in the ionophore X-14885A (**3**). Alternatively, cyclopropanation of substituted vinyl ether **55** followed by acid treatment afforded the spiroketal **58** that was subsequently converted into the polyether ionophore Calcimycin (**1**) and also Cezomycin (**2**).

The first polyether ionophore antibiotics were isolated in 1951;[1] however, as a result of their structural complexities and the lack of sufficiently powerful spectroscopic techniques, 16 years passed before the first structure of a member of the class, Monensin, was elucidated.[2] The discovery in the late 1960's that these compounds possessed interesting biological and ionophoric properties resulted in a tremendous increase in interest in this class of substances. Over 80 new members of this class have been isolated and most of the structures fully established since that time.[3] Their remarkable structural complexities have stimulated the development of a variety of new synthetic methodologies based on acyclic stereocontrol for the efficient construction of these polyacetate and/or polypropionate derived materials.[4] In this paper, we present a full account of our efforts to apply new methodology, developed in our laboratories, involving the generation and subsequent reactions of cyclic vinyl ether anions to the enantioselective total synthesis of (−)-A-23187 and other members of that class such as Cezomycin (**2**).[5,6]

The antibiotic Calcimycin (**1**), also called A-23187, was isolated in 1974 by Chaney from the cultures of *Streptomyces chartreusis* (NRRL 3882) as a mixed calcium–magnesium salt.[7] Its structure was determined by a single-crystal X-ray analysis on the free acid. The absolute configuration was unequivocally established by the first total synthesis of (−)-**1** by Evans and co-workers in 1979, and several additional total syntheses of **1**, both in racemic and nonracemic form, have been recorded since that time.[8] Calcimycin (**1**) is active against Gram-positive bacteria and fungi, and the acute toxicity in mice is 10 mg/kg (intraperitoneal).[9] More importantly, Calcimycin was shown to form a 2:1 (antibiotic–cation) neutral complex with divalent metal cations and also to complex Ca^{2+} selectively over monovalent cations.[10] This unique

(1) Berger, J.; Rachlin, A. I.; Scott, W. E.; Sternbach, L. H.; Goldberg, M. W. *J. Am. Chem. Soc.* **1951**, *73*, 5295. Harned, R. L.; Hidy, P. H.; Corum, C. J.; Jones, K. L. *Antibiot. Chemother.* **1951**, *1*, 594.

(2) Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 5737.

(3) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1983. Dobler, M. In *Ionophores and Their Structures*; Wiley: New York, 1981.

(4) For a review on the construction of polypropionate and polyacetate subunits see: Hoffman, R. W. *Ang. Chem., Int. Ed. Engl.* **1987**, *26*, 489. The largest polyether ionophore to date was recently synthesized relying exclusively on asymmetric synthesis: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(5) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997 and references therein. (b) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187 and references therein. (c) Boeckman, R. K., Jr.; Bruza, K. J.; Heinrich, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 7101.

(6) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.

(7) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932.

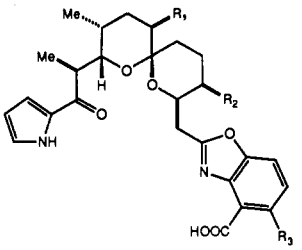
(8) (a) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Additional enantioselective total syntheses reported subsequently: (b) Nakahara, Y.; Fujita, A.; Beppu, K.; Ogawa, T. *Tetrahedron* **1986**, *42*, 6465. (c) Naegri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063. For a synthesis of racemic Calcimycin, see: (d) Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.-I.; Srinivasan, C. V. *J. Am. Chem. Soc.* **1982**, *104*, 1436. For a formal total synthesis see: Ziegler, F. E., Cain, D. M. *J. Org. Chem.* **1989**, *54*, 3347.

(9) Gale, R. M.; Higging, C. E.; Hoehn, M. M. U.S. Patent 3, 923, 823, 1975.

(10) Chaney, M. O.; Jones, N. D.; Debono, M. *J. Antibiot.* **1976**, *29*, 424.

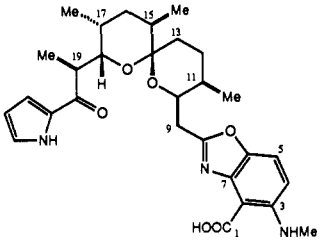
0002-7863/91/1513-5337$02.50/0

Table I



R_1	R_2	R_3	
Me	Me	NHMe	A-23187 (**1**)
Me	Me	H	Cezomycin (**2**)
H	Me	OH	X-14885A (**3**)
H	H	OH	CP-61,405 (**4**)
Me	Me	OH	AC7230 (**5**)

property has made it the agent of choice, thus far, for specific perturbation of transmembrane Ca^{2+} gradients in complex systems such as cells.[11]



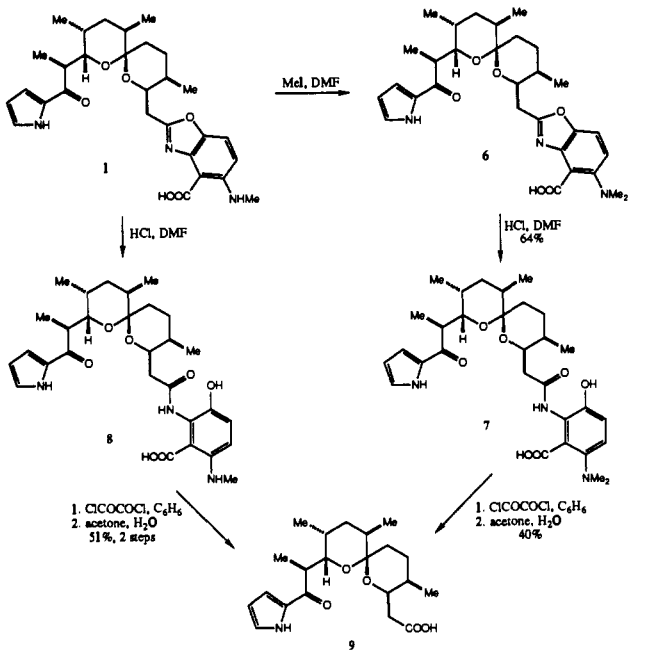
1

The structure of A-23187 reveals some novel features uncharacteristic of the known polyether ionophore antibiotics. A unique benzoxazole ring system along with a ketopyrrole are bridged by a 1,7-dioxaspiro[5.5]undecane ring system. Calcimycin contains seven stereogenic centers arrayed along the backbone of the 1,7-dioxaspiro[5.5]undecane skeleton, four of which are secondary methyl groups and two are masked hydroxyl groups. Four new natural products belonging to the Calcimycin class of ionophores were recently isolated: Cezomycin (**2**),[12] X-14885A (**3**),[13] and CP-61,405 (**4**)[14] from different strains of *Streptomyces* and AC7230 (**5**)[15] obtained from *Dactylosporangium* sp. AC7230, which are also active against Gram-positive bacteria and exhibit ionophoric properties similar to A-23187 (Table I).

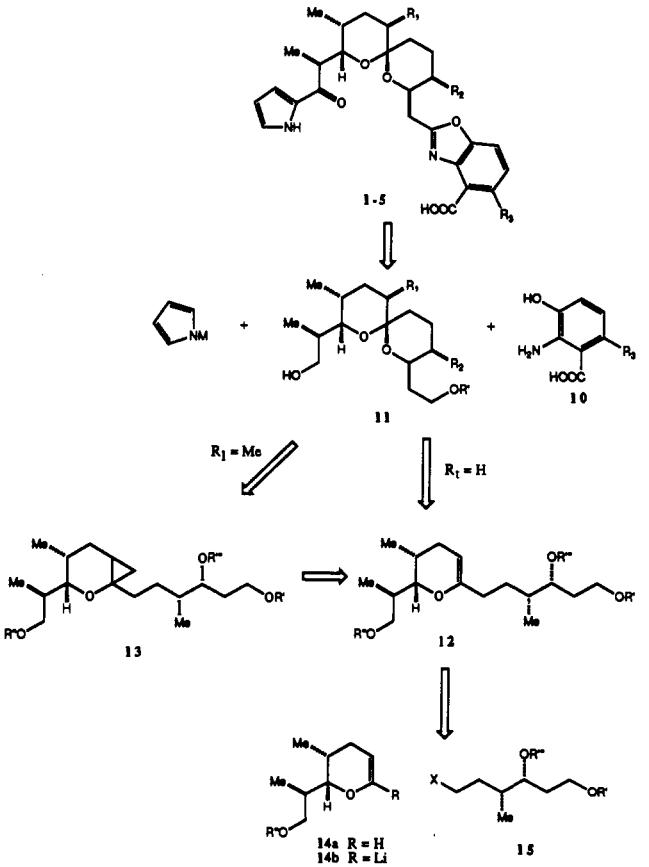
The unique biological properties of A-23187 and its congeners, as well as the challenges to contemporary synthetic methodology presented by the array of unusual structural and stereochemical features, led us to undertake the development of a general strategy for enantioselective total synthesis of members of this class of ionophores. It appeared that a single convergent, synthetic sequence could be evolved that would provide access to all currently known members of the class.

Degradation Studies on Natural (−)-A-23187. Prudhomme and Jeminet have reported that (−)-A-23187 (**1**) upon treatment with methyl iodide in the presence of potassium hydroxide in dimethylformamide led to methylation providing (−)-**6** (Scheme I).[16] Furthermore, acid treatment of (−)-**6**, unlike (−)-**1**, rapidly opened

Scheme I



Scheme II



the benzoxazole ring to give the amide (+)-**7** in 64% yield. Hydrolysis of the amide was accomplished upon addition of oxalyl chloride in benzene followed by aqueous acetone to give the pyrrole acid (+)-**9**. In our hands, we have found that direct treatment of natural (−)-**1** with 2 N aqueous hydrochloric acid in dimethylformamide led to a clean opening of the benzoxazole ring to give the amide **8**.[17] The amide bond was then smoothly cleaved

(11) For a review of ionophoric properties of A-23187 see: Taylor, R. W.; Kauffman, R. K.; Pfeiffer, D. R. In *Polyether Antibiotics. Naturally Occurring Acid Ionophores*, Marcel Dekker: New York, 1982; Vol. 1, p 103. For an interesting discussion of the structural requirements for ionophoric properties see: Gourcy, J.-G.; Prudhomme, M.; Dauphin, G.; Jeminet, G. *Tetrahedron Lett.* **1989**, *30*, 351.

(12) David, L.; Kergomard, A. *J. Antibiot.* **1982**, *35*, 1409.

(13) Westley, J. W.; Liu, C-M.; Blount, J. F.; Shello, L. H.; Troupe, N.; Miller, P. A. *J. Antibiot.* **1983**, *36*, 1275.

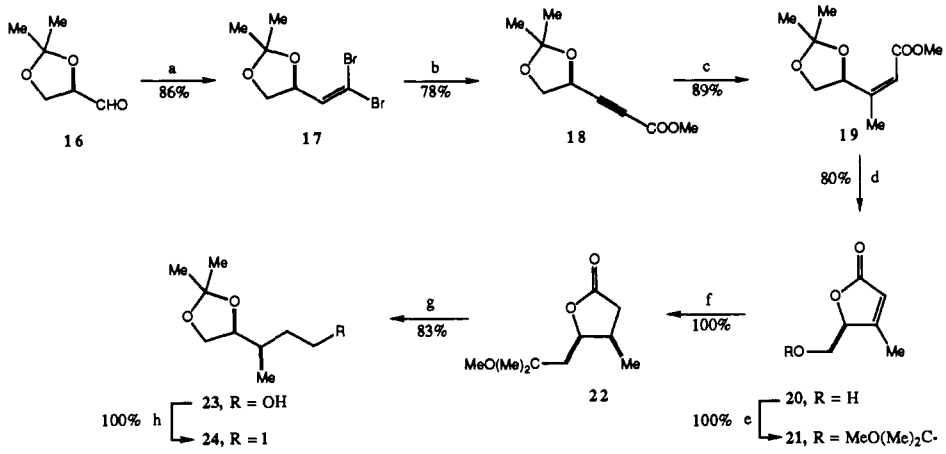
(14) Celmer, W. D.; Cullen, W. P.; Maeda, H.; Tone, J. U.S. Patent 4, 547, 523.

(15) The relative stereochemistry of AC7230 is not known. For isolation: Yaginuma, S.; Awata, M.; Muto, N.; Kinoshita, K.; Mizuno, K. *J. Antibiot.* **1987**, *40*, 239.

(16) Prudhomme, M.; Jeminet, G. *Experientia* **1983**, *39*, 256.

(17) It was noted that this reaction appears to be dependent on scale although conditions were never optimized. Conversion to (+)-**9** was complete on small scale (5–10 mg), but on larger scale (150 mg) approximately 40% of (−)-**1** was recovered.

Scheme III[a]



[a] Reagents: (a) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (b) *n*-BuLi, THF, −78 °C; $ClCO_2Me$, −78 °C; (c) MeCu, Et_2O–DMS, −78 °C; (d) aqueous HCl, THF; (e) $MeOC(Me)=CH_2$, $POCl_3$; (f) H_2, Rh–Al_2O_3, C_6H_6; (g) $LiAlH_4$, Et_2O, then *p*-TsOH·H_2O, acetone; (h) *N*-methyl-*N*,*N*′-dicyclohexylcarbodiimidinium-methyl iodide, THF, 35 °C.

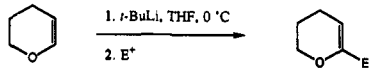
using oxalyl chloride to provide the naturally derived pyrrole acid (+)-**9** in 51% overall yield for the two steps.[18] The ketopyrrole (+)-**9**, containing all the stereogenicity of (−)-**1**, was identified as a key intermediate and became the initial goal of our synthetic effort.

Retrosynthetic Analysis

Our general strategy to access all the members of this class is depicted in Scheme II. We intended to introduce successively both aromatic moieties in the last steps of the synthesis from a monoprotected diol **11**. These disconnections would give us the flexibility required to synthesize compounds with different benzoxazole subunits simply by using the appropriate aminophenol **10** in the coupling reaction.

The spirocyclic ketal **11**, which incorporates all the stereogenic centers present in A-23187 or its analogues, could be derived from an acid-catalyzed cyclization of either the key substituted vinyl ether **12** (when R_1 = H), or by a tandem acid-catalyzed ring-opening spirocyclization of cyclopropane **13** (when R_1 = CH_3). The cyclopropane **13** could also be elaborated from vinyl ether **12**.

We intended to construct the substituted vinyl ether **12** via the coupling of the α-lithiovinyl ether anion **14b** derived from dihydropyran **14a** and a suitably protected halide **15** using the methodology developed both in our laboratories and in others for the formation of cyclic α-lithiovinyl ether anions from dihydropyrans.[5] In these studies, it was shown that a variety of substituted dihydropyrans, upon treatment with 1.1 equiv of *tert*-butyllithium in tetrahydrofuran (THF), were cleanly deprotonated at ~0 °C to afford the desired cyclic α-lithiovinyl ether anions which could be trapped with a variety of electrophiles such as aldehydes, ketones, or halides to give the corresponding coupling products in high yields (eq 1).[5]

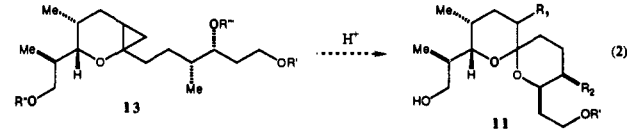


(1)

With this highly convergent route in mind, we first focused our attention on testing the feasibility of the acid-catalyzed cyclopropane opening and the subsequent ring closure to afford the spirocyclic ketal using a model compound.

Model Studies

The general approach under consideration for the assembly of the dioxaspirane skeleton relies on the cyclization shown in eq 2, wherein the cyclopropane **13** might be expected to undergo ring closure under acidic conditions to form potentially four diastereomers of **11**. Evans has shown that the potentially labile



(2)

asymmetric carbon at the spirane fusion in (−)-**1** as well as the adjacent C_{15} methyl group could be stereoselectively constructed under equilibrium conditions from a suitable precursor.[8a,19] The purpose of this model study was to test the feasibility of coupling of the precursors to afford the vinyl ester **12** and its elaboration via cyclopropane **13** to the spiroketal system related to A-23187.

We chose to model our key cyclization with substituted vinyl ether **25**, readily available from the coupling reaction of iodide **24** and the α-lithiovinyl ether derived from 3,4-dihydro-2*H*-pyran. The synthesis of optically pure iodide **24** from the known aldehyde **16**[20] is outlined in Scheme III.[21] Aldehyde **16** was converted to the acetylenic ester **18** following Corey's procedure.[22] Accordingly, **16** was treated with carbon tetrabromide and triphenylphosphine in methylene chloride (CH_2Cl_2) to afford dibromoolefin **17** in 86% yield, which in turn was treated with 2 equiv of *n*-butyllithium in THF at −78 °C followed by quenching with ethyl chloroformate to afford ester **18** in 68% overall yield for the two steps. Treatment of ester **18** with methylcopper[23] in THF at −78 °C and quenching at low temperature with saturated aqueous NH_4Cl afforded the unsaturated ester **19** as the sole product in 94% yield.[24] Acidic hydrolysis of ester **19** produced the naturally occurring butenolide **20** (umbelactone) as a crystalline material in 80% yield.[25] Catalytic hydrogenation of the butenolide **20** with 5% rhodium on alumina in benzene exhibited moderate asymmetric induction (cis–trans 6:1). The diastereoselectivity was markedly enhanced (>20:1) when the primary alcohol was pro-

(18) Shiozaki, M.; Ishida, N.; Iono, K.; Hiraoka, T. *Tetrahedron* **1980**, *36*, 2736.

(19) Calcimycin numbering is used throughout the discussion.

(20) Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463.

(21) We initially intended to use iodide **24** in the synthesis of A-23187 (disconnection at C_8–C_9 in retrosynthetic scheme), implying that C_8 would be part of the benzoxazole subunit; the coupling being achieved by a displacement reaction of an halide at C_9 and a lithiated benzoxazole. However it was later felt that this approach would not be as general and as mild as the one proposed in Scheme I.

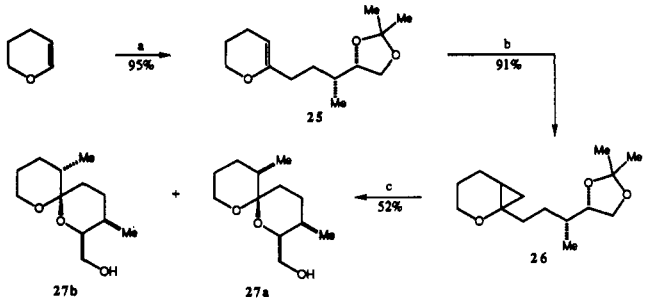
(22) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Ord, M. R.; Piggin, C. M.; Thaller, V. *J. Chem. Soc., Perkin Trans. 1* **1975**, *7*, 687.

(23) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240.

(24) The temperature at which the presumed vinylcopper intermediate is quenched is critical, since quenching at temperatures higher than −70 °C resulted in isomerization of this intermediate to afford a mixture of *E* and *Z* esters.

(25) Agarwal, S. K.; Rastogi, R. P. *Phytochem.* **1978**, *17*, 1663.

Scheme IV[a]



[a] Reagents: (a) *t*-BuLi, THF, −78 to 0 °C, **24**, 0 °C; (b) Et_2Zn, CH_2I_2, Et_2O; (c) *p*-TsOH·H_2O, C_6H_6, 80 °C.

tected with the bulky *tert*-butyldimethylsilyl (TBDMS) group. At this juncture in the synthesis we sought to incorporate a bulky protecting group that could also serve ultimately to produce the isopropylidene protecting group in the final product.

This was accomplished by treating butenolide **20** with 2-methoxypropene in the presence of a catalytic amount of $POCl_3$ to afford the acid-sensitive protected alcohol **21** in quantitative yield.[26] Catalytic hydrogenation of lactone **21** with 5% rhodium on alumina afforded lactone **22** with high level of diastereoselectivity (>20:1 cis-trans) in quantitative yield. Reduction of lactone **22** with lithium aluminum hydride (LAH) in ether at room temperature provided the corresponding diol, which upon exposure to a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in acetone afforded acetonide **23** in 71% overall yield from **22**. Treatment of **23** with cyclohexylcarbodiimidinium methiodide in THF then provided the iodide **24** in quantitative yield.[27]

6-Lithio-3,4-dihydro-2*H*-pyran generated from 3,4-dihydro-2*H*-pyran with *tert*-butyllithium in THF at 0 °C was reacted with the previously prepared iodide **24** to afford the optically active vinyl ether **25** in 91% yield (Scheme IV).[5] Treatment of **25** with diethylzinc and diiodomethane[28] gave a 1:1 mixture of cyclopropyl ethers **26** in 88% yield. When the mixture of cyclopropanes **26** was subjected to *p*-TsOH in benzene at reflux, a 4:1 mixture of dioxaspiranes **27a** and **27b** was obtained in 52% yield (unoptimized). ^1H NMR spectroscopy showed that the major product possessed the relative stereochemistry present in the A-23187 ring system, thus confirming the apparent feasibility of this approach.

The formation of the minor product is consistent with the relative thermodynamic stabilities of the two products. It can be predicted that the energy difference between **27a** and **27b** would be approximately 0.8 kcal/mol favoring **27a** owing to the presence of a 1,3-diaxial interaction between the axial methyl group and the axial proton in **27b**.[29] Such an interaction would be substantially larger in the case of A-23187 because of the presence of a methyl group at C-4 instead of a proton. The CH_3–CH_3 1,3-diaxial interaction is known to be ~3.7 kcal/mol. Thus, the desired isomer should be preferred by ≥2.9 kcal/mol, which corresponds to an equilibrium ratio >95:5 at room temperature.

Having, therefore, demonstrated the feasibility of the tandem cyclopropane ring opening/spiroketalization, we then focused our attention on the efficient synthesis of the three major subunits of A-23187.

Stereoselective Sequences to Chiral Nonracemic Dihydropyran Synthons (C_{14}–C_{20}). Initial Routes to 29 via an Antiselective Aldol Condensation. A series of routes to dihydropyran derivatives corresponding to C_{14}–C_{20} were initially investigated based on an anti-selective aldol condensation as described by Heathcock.[30] The first of these is depicted in Scheme V. Unfortunately, the diastereofacial selectivity observed for the key aldol condensation was modest providing a 2:1 mixture of β-hydroxy esters **28a** and **28b**. This mixture of diastereomers was converted by means of standard chemistry to the required chiral nonracemic dihydropyran **29**.[31]

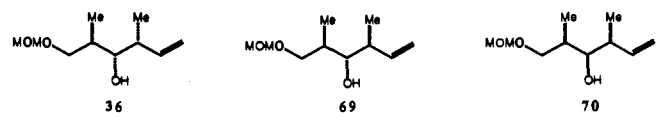
A related approach to the dihydropyran **29**, which was more amenable to scale up, was later developed as shown in Scheme VI. This route created the required chiral nonracemic aldehyde **30** via alkylation of a chiral oxazolidone enolate derived from norephedrine.[32] The required aldol condensation was conducted as described previously using the lithium enolate of 2,6-dimethylphenyl propionate to again afford a 2:1 mixture of diastereomers **31a** and **31b**.[33] Again, standard processing of this mixture as above afforded the required chiral nonracemic dihydropyran **29**.

The previous two synthetic routes developed for the preparation of the chiral nonracemic dihydropyran synthon **29** were concise, but suffered from unacceptably low stereoselectivity in the key aldol condensation. To circumvent that problem, an even more efficient and stereoselective approach was sought to assemble the C_{14}–C_{20} synthon.

Alternative Routes to the Chiral Nonracemic Dihydropyran 41 via Crotyl Metal Chemistry. A most efficient construction of the C_{14}–C_{20} synthon was achieved by employing a crotylstannane addition to an aldehyde to establish the three contiguous stereogenic centers. A 1-carbon homologation then provides the tetrahydropyran ring system. As shown in Scheme VII, the required aldehyde **32** is readily available in three steps from (*R*)-(−)-2-methyl-3-hydroxypropionate. Unlike in the two previous routes, a methoxymethyl ether (MOM) protecting group was chosen as the best alternative for the protection of the alcohol. This preference was based on several criteria: (1) availability of an adjacent oxygen for chelation of the Lewis acid during the crotylstannane addition reaction; (2) stability to strong bases such as *t*-BuLi (vide infra); and (3) sufficient lability to permit removal under mild acidic conditions.

Treatment of commercially available hydroxy ester **33** with chloromethyl methyl ether in the presence of diisopropylethylamine in CH_2Cl_2 afforded the desired protected alcohol **34**, which was then reduced to give monoprotected diol **35** in 89% yield for the two steps.[34] Subsequent Swern oxidation[35] afforded the required β-alkoxy aldehyde **32** in 94% yield. This extremely sensitive aldehyde was directly treated without any purification with crotyltri-*n*-butylstannane in the presence of $MgBr_2$–etherate[36] to afford the desired adduct **36** as the major diastereomer (6.7:1).[37] With the required three contiguous stereogenic centers in place, the one-carbon homologation of the olefin in **36** was then ad-

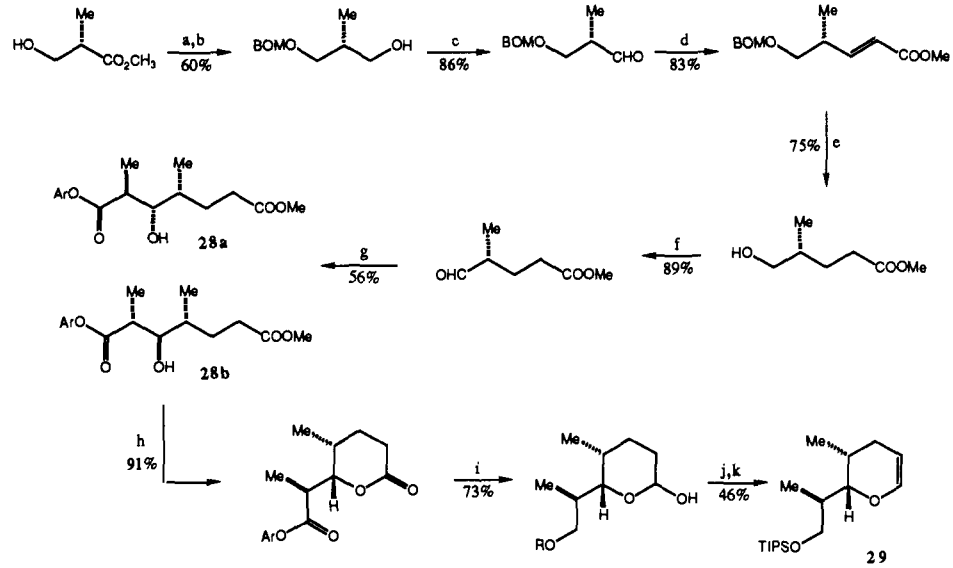
(26) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.
(27) Scheffold, R.; Saladin, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 229.
(28) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.
(29) For a discussion of stereoelectronic effects in spirocyclic ketals see: Deslongchamps, P. *Stereoelectronic Effects in Organic Synthesis*; Pergamon Press, New York; 1983. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Spring-Verlag, Berlin; 1983. For a table listing a variety of 1,3-diaxial interaction energies see: Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765.
(30) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.
(31) The two diastereomers were cleanly separated by flash chromatography at the stage of the vinyl ether **29**. For the sake of clarity only the desired diastereomer is shown in the scheme in the subsequent reactions. More recent studies of the aldol reaction suggest that higher diastereoselectivity may be possible: Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, New York, 1984; Vol. 3, pp 111–212.
(32) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(33) The diastereomers were easily separated by flash chromatography at the stage of the β-(triisopropylsilyl)oxy esters. For the sake of clarity, only the desired diastereomer is shown on the scheme.
(34) Boeckman, R. K., Jr.; Enholm, E. J.; Demko, D. M.; Charette, A. B. *J. Org. Chem.* **1986**, *51*, 4743.
(35) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(36) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.
(37) Ratio was determined to be 87:11:2 (**36**:**69**:**70**) by capillary gas chromatography. The diastereomers were easily



36 69 70

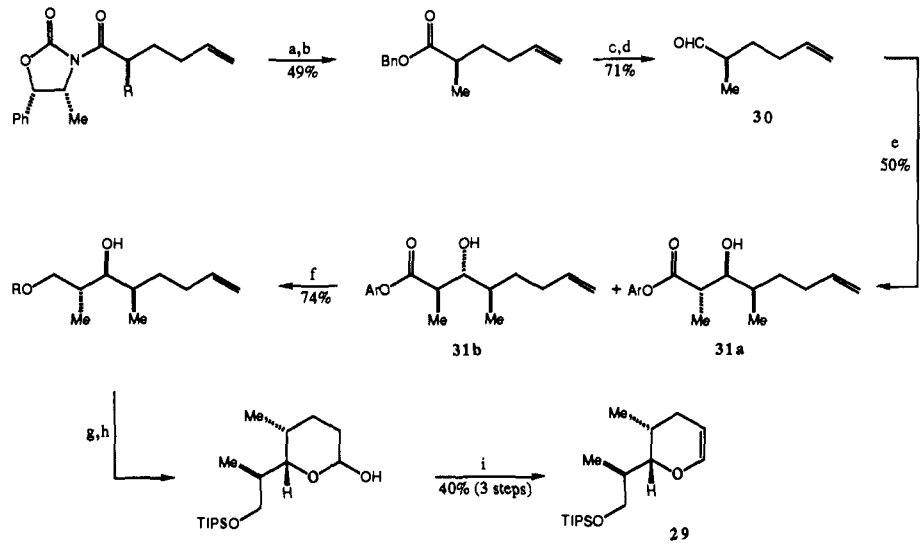
separated by flash chromatography after conversion to vinyl ether **41** or at several earlier stages.

Scheme V[a]



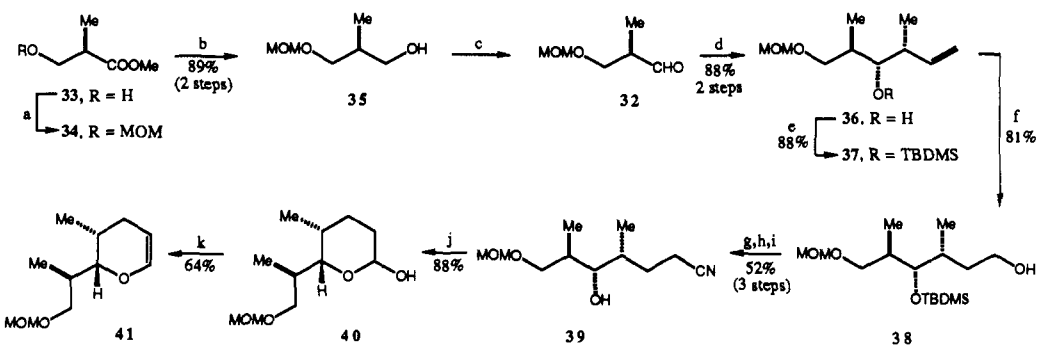
[a] Reagents: (a) BOMCl, i-Pr_2NEt, DMF; (b) $LiAlH_4$, Et_2O; (c) ClCOCOCl, DMSO, CH_2Cl_2, −78 °C; Et_3N; (d) $Ph_3P{=}CHCO_2Me$, DMF; (e) H_2, Pd/C, HCl, CH_3OH; (f) ClCOCOCl, DMSO, CH_2Cl_2, −78 °C; Et_3N; (g) 2,6-$(CH_3)_2PhOC(OLi){=}CHCH_3$, THF, −78 °C; (h) *p*-TsOH·H_2O, C_6H_6, 80 °C; (i) DIBAL-H, $PhCH_3$, −78 °C; (j) TIPSCl, imidazole, DMF; (k) MsCl, Et_3N, CH_2Cl_2.

Scheme VI[a]



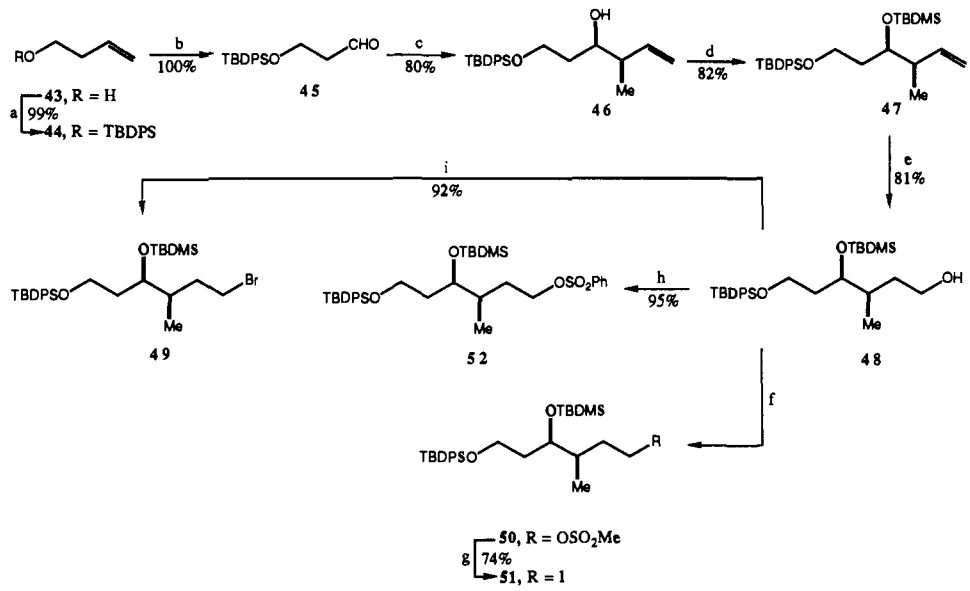
[a] Reagents: (a) LDA, THF, −78 °C; MeI; (b) BnOLi, THF, 0 °C; (c) $LiAlH_4$, Et_2O, 0 °C; (d) PCC, NaOAc, CH_2Cl_2; (e) $ArOC(OLi){=}CH$-CH_3, THF, −78 °C; (f) $LiAlH_4$, Et_2O, 0 °C; (g) TIPSCl, imidazole, DMF; (h) O_3, CH_2Cl_2, MeOH, −78 °C; Zn, HOAc; (i) MsCl, Et_3N, CH_2Cl_2.

Scheme VII[a]



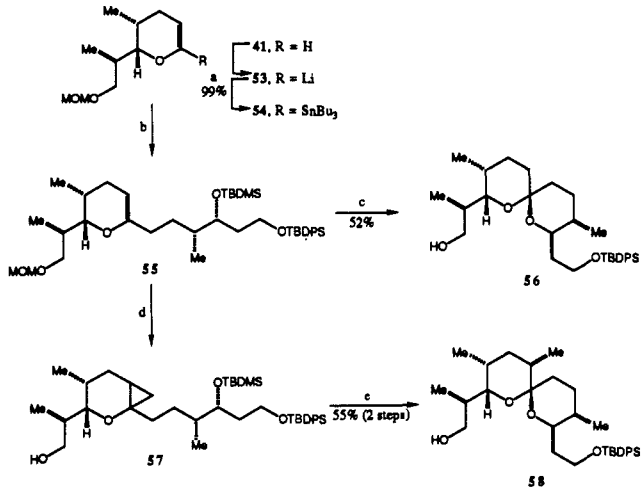
[a] Reagents: (a) MOMCl, i-Pr_2NEt, DMF; (b) $LiAlH_4$, Et_2O; (c) ClCOCOCl, DMSO, CH_2Cl_2, −78 °C, Et_3N; (d) $CH_3CH{=}CHCH_2SnBu_3$, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −30 °C; (e) TBDMSOTf, Et_3N, CH_2Cl_2; (f) BH_3·THF, THF, 0 °C to rt; H_2O_2, NaOH; (g) $PhSO_2Cl$, pyr, CH_2Cl_2; (h) KCN, DMSO, Et_3N, 55 °C; (i) TBAF, THF; (j) DIBAL-H, THF, −78 °C to 0 °C; (k) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt.

Scheme VIII[a]



[a] Reagents: (a) TBDPSCl, imidazole, DMF; (b) O_3, CH_2Cl_2, MeOH, −78 °C; DMS; (c) (*Z*)-$CH_3CH{=}CHCH_2BiPc_2$, THF, −78 °C; (d) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C; (e) BH_3·THF, THF, 0 °C; H_2O_2, NaOH; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C; (g) NaI, acetone; (h) $PhSO_2Cl$, pyr; (i) CBr_4, PPh_3, Et_2O.

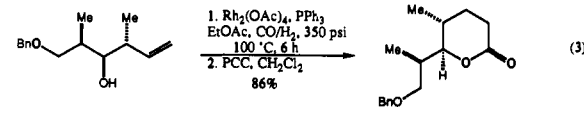
Scheme IX[a]



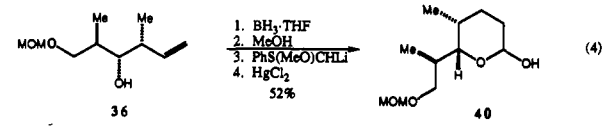
[a] Reagents: (a) KO*t*-Bu, *n*-BuLi, THF, −78 °C; Bu_3SnCl; (b) *n*-BuLi, THF, −78 °C; **49**, HMPA; (c) *p*-TsOH·H_2O, C_6H_6, 0 °C to 80 °C; (d) Et_2Zn, CH_2I_2, Et_2O; (e) *p*-TsOH·H_2O, C_6H_6, 80 °C.

dressed. A six-step sequence was developed as shown in Scheme VII. Protection of the secondary alcohol as TBDMS ether **37** followed by hydroboration produced the corresponding alcohol **38**. Benzenesulfonation, cyanide displacement, and desilylation afforded hydroxy nitrile **39**. Reduction of the nitrile with DIBAL-H in THF provided after acidic workup the desired lactols **40** as a mixture of anomers (1.4:1 = α:β). Even though the conversion of olefin **36** to lactols **40** was accomplished in six steps in good overall yield (33%), the actual transformation only consists of a hydroformylation of the double bond (Scheme VII). Therefore, we sought a more efficient method to effect this conversion.

Recently, Wuts reported that homoallylic alcohols similar to **36** could be efficiently converted into lactones via a hydroformylation–oxidation sequence employing rhodium acetate in the presence of triphenylphosphine, carbon monoxide, and hydrogen, followed by in situ oxidation of the intermediate lactols (eq 3).[38]

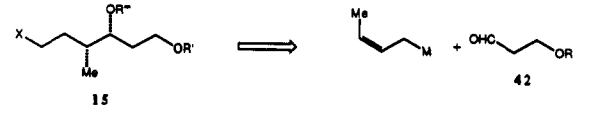


The homologation was successfully accomplished by a Lewis acid induced 1,2-migration of the organoborate complex derived from **36**.[39] Treatment of hydroxyolefin **36** with 1 equiv of borane–THF complex in THF followed by in situ treatment with 1 equiv of methanol and 3 equiv of [methoxy(phenylthio)-methyl]lithium afforded, after treatment with mercuric chloride and subsequent oxidation, the desired lactols **40** as a mixture of anomers (1.4:1 = α:β) in 52% overall yield for the one-pot homologation (eq 4). The synthesis of the key dihydropyran was then completed by submitting the mixture of lactols to methanesulfonyl chloride/triethylamine in CH_2Cl_2 to provide dihydropyran **41** in 64% yield.



Thus, the route to dihydropyran **41** that ultimately evolved is general, extremely short (six steps), and fully stereocontrolled. With a suitable C_{14}–C_{20} synthon in hand, the synthesis of the enantiomerically pure halide required for the coupling reaction was then addressed.

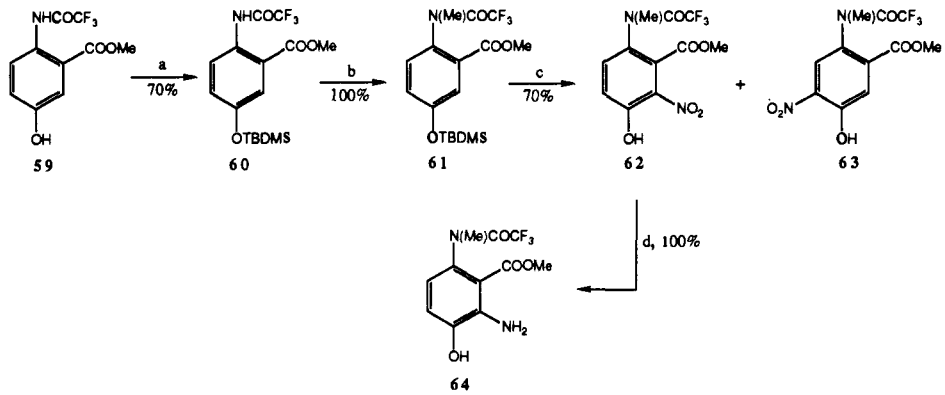
Enantioselective Synthesis of the C_8–C_{13} Halide Synthon. The most expedient way to create synthon **15**, which contains two adjacent syn stereogenic centers, would be to couple a suitably protected β-alkoxy aldehyde **42** with a chiral nonracemic crotyl metal reagent (eq 5).[40]



(38) Wuts, P. G.; Obrzut, M. L.; Thompson, P. A. *Tetrahedron Lett.* **1984**, *25*, 4051.

(39) For a conceptiually related strategy see: Brown, H. C.; Imai, T. *J. Am. Chem. Soc.* **1983**, *105*, 6285.

Scheme X[a]



[a]Reagents: TBDMSCl, imidazole, DMF; (b) MeI, K_2CO_3, acetone, 50 °C; (c) HNO_3, HF, CH_3NO_2; (d) H_2, Pd/C, MeOH.

The starting material, 3-buten-1-ol (**43**) was treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) under standard conditions[41] to afford the protected olefin **44**, which upon exposure to ozone afforded, after reductive workup, the desired β-silyloxy aldehyde **45** (Scheme VIII). Subsequent treatment of aldehyde **45** with (*Z*)-crotyldiisopinocampheylborane derived from (+)-α-pinene[42] in THF followed by oxidative work up afforded the desired homoallylic alcohol **46** as a single diastereomer, as judged by 300-MHz ^1H and 470-MHz ^{19}F NMR spectroscopy on the Mosher ester derivative,[43] in 80% yield.[44,45]

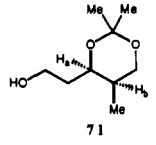
Protection of the secondary alcohol as a TBDMS ether provided the bis(silyl ether) **47**, which was directly followed by hydroboration to afford alcohol **48**. This alcohol could then be converted to a variety of halides or sulfonates. Treatment of **48** with carbon tetrabromide/triphenylphosphine in ether afforded the bromide **49** in 92% yield.[46] Alternatively, the iodide **51** could be obtained in 74% overall yield by mesylation to **50** and subsequent displacement of the mesylate by iodide. Finally, alcohol **48** could be converted to benzenesulfonate **52** in 90% yield using standard conditions.

Assembly of C_{14}–C_{20} Synthon and C_8–C_{13} Synthon. The dihydropyran **41** was then subjected to the standard deprotonation conditions (1 equiv of *t*-BuLi, THF, 0 °C), and subsequent quenching with D_2O showed ≤5% deuterium incorporation at the 2-position (Scheme IX). Increasing the number of equivalents of *tert*-butyllithium did not improve the amount of deuterium incorporation and resulted in decomposition of the base by deprotonation of THF.

Since it appeared that *t*-BuLi was not suitable to effect quantitative metalation, a stronger base was therefore investigated.[47] Treatment of dihydropyran **41** with 3 equiv of Schlosser base (*n*-BuLi/KO-*t*-Bu)[48] in THF at −78 °C followed by quenching of the anion with tri-*n*-butyltin chloride resulted in the quantitative formation of the vinylstannane **54** (Scheme IX).[49] After purification, the vinylstannane smoothly underwent transmetalation upon treatment with a stoichiometric amount of *n*-butyllithium at −78 °C for 10 min to produce the α-lithiovinyl ether anion **53**.[50] Unexpectedly, it appears that certain protecting groups, such as triisopropylsilyl (as in dihydropyran **29**) and benzyl ethers, are incompatible with anion **53**, leading to self-quenching of the anion either by intra- or intermolecular proton transfer from the protecting group.[51]

With suitable methodology to quantitatively generate the cyclic α-lithiovinyl ether anion derived from **41** in hand, the key coupling reaction to build the A-23187 carbon skeleton was then examined (Scheme IX). Treatment of the lithio species **53** with iodide **51** at −78 °C followed by warming to room temperature led to ≤10% yield of the desired coupling product **55**. The two major products of this reaction were dihydropyran **41** and the dimer derived from iodide **51**, the latter of which appeared to have resulted from either transmetalation or electron transfer. When the anion was warmed to 0 °C prior to the addition of a solution of iodide **51** in THF, the yield of the coupling product went up to ca. 30%. The use of alternative leaving groups to facilitate the S_N2 displacement was then investigated. The benzenesulfonate **52** led exclusively to protonated vinyl ether **41** and unchanged sulfonate. The in-

(40) For a review on allyl and crotyl metal addition to carbonyl compounds see: Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.
(41) Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1975**, *53*, 2975.
(42) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
(43) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(44) Since Brown had not reported addition of crotylboranes to β-hydroxy aldehydes, a proof of stereochemistry was necessary. Mosher ester formation using the *R*-(+) Mosher acid chloride gave only one diastereomer by examination of the methoxy peaks (δ 3.51 (3*R*,4*R*), δ 3.47 (3*S*,4*S*) for the racemate) in the 300-MHz ^1H NMR and the fluorine resonance (δ 82.24 (3*R*,4*R*), δ 82.03 (3*S*,4*S*) for the racemate) in the 470-MHz ^{19}F NMR indicating an enantiomeric purity ≥95%. The syn relationship between the substituents was confirmed by conversion of alcohol **46** into acetonide **71** via ozonolysis followed by in situ reduction (O_3, $NaBH_4$), ketalization (acetone, TsOH), and desilylation (TBAF, THF). The coupling constant between H_a and H_b was shown to be 3 Hz, which is consistent with an axial–equatorial relationship between the two hydrogens.



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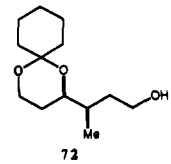
(45) As an additional structure proof, alcohol **46** was converted into the known cyclohexylidine ketal **72**: (1) TBAF; (2) cyclohexanone, TsOH; (3) 9-BBN; H_2O_2. These material were shown to be identical in all respects (^1H NMR, $[\alpha]_D$). For the synthesis of **72** see ref 8b.

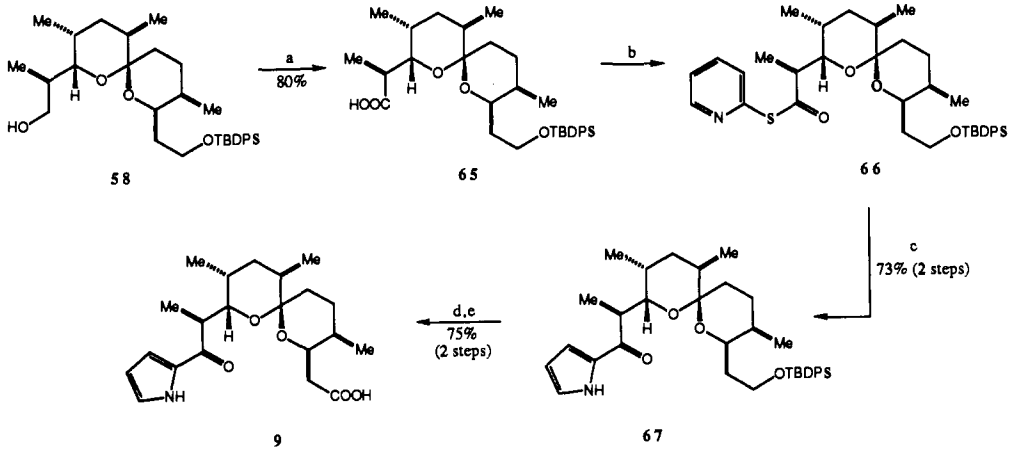


72

(46) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

(47) Asberom, T. Ph.D. Dissertation, University of Rochester, Rochester, NY, 1984.
(48) (a) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741. (b) Lehmann, R.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 745.
(49) During the course of our studies, similar difficulties were also encountered by several groups during attempts to effect deprotonation of protected glycals and similar deprotonation protocols were developed: (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 925. (b) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926. (c) Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinay, P. *Tetrahedron Lett.* **1986**, *27*, 6201.
(50) The anion could be trapped with benzaldehyde to afford the secondary alcohol adduct in 90% yield.
(51) Boeckman, R. K., Jr.; Charette, A. B. Unpublished results.

Scheme XI[a]



[a] Reagents: (a) H_2CrO_4, acetone, −25 °C; (b) 2,2′-dipyridyl disulfide, PPh_3, CH_2Cl_2; (c) pyrryl magnesium chloride, toluene, −78 °C; (d) TBAF, THF; (e) H_2CrO_4, acetone, −20 °C.

stantaneous appearance of a deep red color upon addition of a solution of the sulfonate to the anion at −78 or 0 °C, along with complete recovery of the starting materials, seemed to indicate that quenching of the α-lithiovinyl ether anion was occurring through deprotonation of the phenyl group of the phenylsulfonyl leaving group.

In light of the previous results, which suggest that the anion **53** is rather basic, we reasoned that the use of a less reactive alkylating agent that was also less prone to electron transfer or transmetalation chemistry, such as a bromide, in a more polar medium should favor the substitution reaction over the other undesired pathways. Accordingly, the anion **53**, generated as before, was warmed to 0 °C and a solution of bromide **49** in hexamethylphosphoramide was then added, producing a 70% yield of the desired coupling product **55**.

Treatment of vinyl ether **55** with *p*-toluenesulfonic acid monohydrate in benzene led to the desired spiroketal **56** present in the ionophore X-14885A in 52% yield (unoptimized). Alternatively, the key vinyl ether **55** was treated with excess diethylzinc and diiodomethane in ether at room temperature for 5 h to afford a homogeneous mixture of cyclopropanes **57** (ca. 80% yield). This inconsequential mixture of diastereomers was found to be ca. 1:1 (α:β) as determined by ^{13}C NMR analysis. Interestingly and conveniently, the methoxymethyl ether was simultaneously cleaved, presumably by the zinc iodide byproduct, under these conditions to liberate the primary alcohol.[52] Practically, the crude mixture of cyclopropanes **57** was then directly exposed to *p*-toluenesulfonic acid monohydrate in benzene at reflux to afford the desired key dioxaspirocyclic ketal **58** as a single diastereomer as established by ^1H NMR in 55% overall yield (from **55**).[53] The acidic conditions induced the opening of the cyclopropane, equilibration of the methyl group at C_{15}, selective desilylation at C_{10}, and spiroketalization with the required stereochemistry. The use of excess *p*-toluenesulfonic acid monohydrate was essential to obtain a reasonable yield for this conversion. A variety of other aqueous and nonaqueous acids of differing pK_a's were also investigated, but the desired dioxaspirane **58** was only obtained in low yields. With all the stereogenic centers in place, the incorporation of both aromatic subunits was then investigated.

Synthesis of Aminophenol 64. The protected aminophenol **64** is required for the synthesis of the benzoxazole subunit of A-23187 (Scheme X). The carboxyl group was to be protected as a methyl ester and the *N*-methylamino group as a trifluoroacetamide so that base treatment would allow both deprotections in a single step. The synthetic route employed was a modification of Evans' synthesis.[8a]

The known phenol **59**, available in 6 steps from *m*-aminobenzoic acid, afforded upon treatment with TBDSCl, silyl ether **60**, which underwent subsequent methylation to ester **61** (Scheme X).[54] Treatment of **61** with concentrated nitric acid in the presence of concentrated hydrofluoric acid in nitromethane produced a 2:1 mixture of 2-nitro **62** and 4-nitrophenol **63** in 70% overall yield. The desired 2-nitrophenol **62**, readily separable by chromatography, was hydrogenated to provide the required aminophenol **64**. Since the synthesis of the aminophenol was fairly straightforward and the starting material was available in large quantities, no attempts were made to improve the regioselectivity of the nitration.

Completion of the Enantioselective Total Synthesis of (−)-A-23187 (1). The final assembly of the two aromatic subunits in (−)-A-23187 (**1**) from spirocyclic ketal **58** was then addressed (Scheme XI). Chromic acid oxidation of the monoprotected diol **58** afforded the acid **65** in 80% yield. Employing methodology developed by Nicolaou, the pyrrole moiety was then introduced.[55] Displacement of the 2-thiopyridyl ester **66**, obtained upon treatment of acid **65** with 2,2′-dipyridyl sulfide in the presence of triphenylphosphine, with pyrrylmagnesium chloride in toluene provided the ketopyrrole **67** in 73% overall yield. It was found that an excess of the pyrryl Grignard reagent (ca. 10 equiv) was needed to obtain complete consumption of starting material. Standard deprotection and chromic acid oxidation afforded the labile pyrrole acid **9** (75% from **67**), which was identical in all respects (^1H NMR, IR, TLC, $[\alpha]_D$, MS, HRMS) with material obtained by degradation of Calcimycin, thereby further confirming the successful incorporation of the six stereogenic centers. With the synthesis of pyrrole acid (+)-**9**, our initial goal was achieved and a formal total synthesis of Cezomycin (**2**) completed since **2** has been obtained from **9** by the French group.[56]

A variety of carbonyl activation reagents were investigated to convert the carboxylic acid into a more reactive species in order to facilitate nucleophilic addition of the aminophenol **64** as a means to introduce of the aromatic moiety of A-23187.[57] The most effective reagent was found to be the [(benzotriazo-1-yl)oxy]-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), which had been previously employed for the synthesis of A-23187 analogues.[58] Treatment of acid (+)-**9** with BOP initially afforded

(52) The methoxymethyl ether protected **57** also undergoes cyclization with deprotection of the MOM-protected primary alcohol to afford **58**.

(53) The remainder of the material consisted mainly of the diol obtained by deprotection of the TBDPS ether.

(54) Stelt, V. *Recl. Trav. Chim. Pays-Bas* **1953**, *72*, 195. Zeitier, H. J. Z. *Physiol. Chem.* **1965**, *340*, 73.

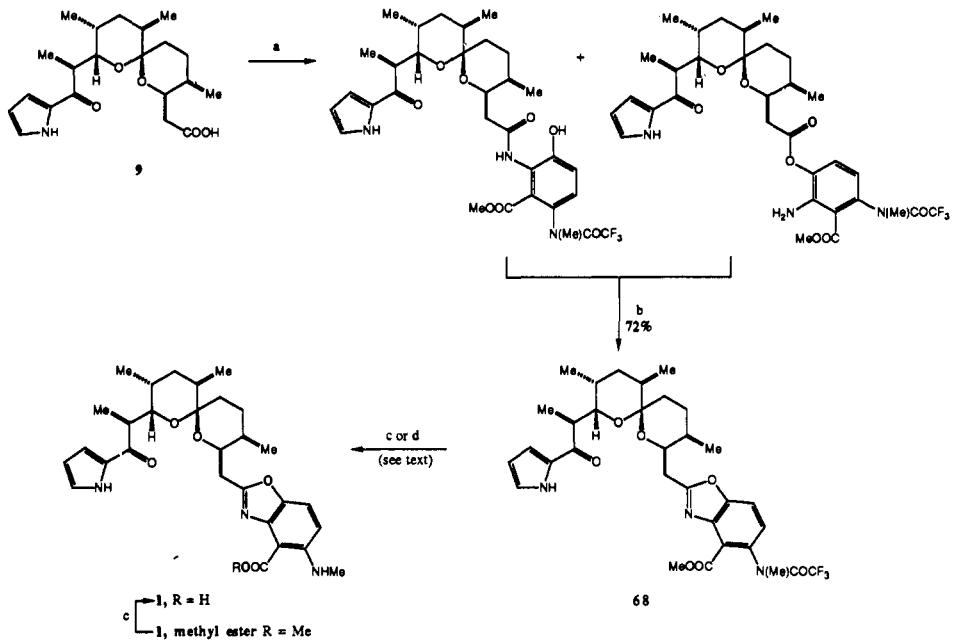
(55) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647.

(56) (a) Prudhomme, M.; Dauphin, G.; Jeminet, G. *J. Antibiot.* **1986**, *39*, 922. (b) Prudhomme, M.; Dauphin, G.; Jeminet, G. *J. Antibiot.* **1986**, *39*, 934.

(57) Conversion into the mesylate (MsCl, Et_3N, CH_2Cl_2), the acid chloride (ClCOCOCl, C_6H_6), or the mixed anhydride ($ClCO_2Et$, Et_3N, CH_2Cl_2) followed by subsequent treatment with aminophenol **64** gave either uncharacterizable products or low yields of the coupling product.

(58) Prudhomme, M.; Dauphin, G.; Guyot, J.; Jeminet, G. *J. Antibiot.* **1984**, *37*, 627. See also ref 16.

Scheme XII[a]



[a]Reagents: (a) BOP, **64**, Et_3N, DMF, 65 °C; (b) PPTS, 4-Å molecular sieves, $ClCH_2CH_2Cl$, 80 °C; (c) LiS-*n*-Pr, HMPA; (d) TBAF, THF.

a mixture of both the desired ester and amide coupled materials. However, exposure of this crude mixture of coupling products to the acidic dehydration conditions cleanly produced the desired benzoxazole **68** in 73% overall yield from **9** (Scheme XII). Benzoxazole **68** was also identical in all respects with material obtained by protection of authentic (−)-A-23187.[59]

Direct treatment of benzoxazole **68** using Evans' conditions for the saponification of (−)-A-23187 methyl ester (LiSPr, HMPA) effected, in one pot, both the saponification of the ester and the cleavage of the amide to afford (−)-A-23187 (**1**, R = H) which was identical in all respects with authentic material.[8a] Alternatively, treatment of 68 with tetrabutylammonium fluoride led to the exclusive cleavage of the amide providing (−)-A-23187 methyl ester (**1**, R = CH_3), which was also identical with material obtained from authentic Calcimycin. Conversion of synthetic (−)-A-23187 methyl ester (**1**, R = CH_3) to A-23187 (**1**, R = H) was again cleanly effected in quantitative yield using lithium *n*-propyl sulfide in hexamethylphosphoramide.

Conclusions

An extremely convergent (longest linear sequence, 16 steps), fully stereoselective, and potentially general synthesis of antibiotic ionophore (−)-A-23187 was devised. The key synthons **41** and **49** were obtained in six steps, respectively, from (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate and 3-buten-1-ol. A key coupling reaction between the α-lithiovinyl ether anion derived from **41** and bromide **49** provided, in an extremely efficient manner, the carbon framework required for the synthesis of the spirocyclic ketal subunit of A-23187. Furthermore, acid-catalyzed cyclization of **55** directly afforded the spiroketal **56**, which can be, in principle, converted into ionophore antibiotic X-14885A (**3**) by a sequence involving the incorporation of the aromatic subunits analogous to the one employed for (−)-A-23187.

Experimental Section

General Methods. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN). Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent on EM Reagents silica gel 60 (230–400 mesh). Tetrahydrofuran, diethyl ether (ether), toluene, and benzene were distilled from sodium–benzophenone ketyl. Dichloromethane and 1,2-dichloroethane were distilled from phosphorous pentoxide. Pyridine, diisopropylethylamine, triethylamine, and diisopropylamine were distilled from calcium hydride. Dimethylformamide was distilled under reduced pressure from calcium hydride and stored over activated 5-Å molecular sieves under an argon atmosphere. Methanol was distilled from magnesium methoxide. Dimethyl sulfide and dihydropyran were distilled from sodium. Reagent-grade anhydrous dimethyl sulfoxide was stored over activated 4-Å molecular sieves under argon. When necessary, other reagents were purified according to Perrin (Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd Ed.; Pergamon Press: New York, 1988). All air- or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware.

(−)-Calcimycin Methyl Ester (1, Methyl Ester). To a solution of calcimycin (**1**) (261 mg, 0.499 mmol) in ether (5 mL) at 0 °C was added a solution of diazomethane (4.99 mmol) (prepared from *N*-nitrosomethylurea (0.514 g) and 10% aqueous KOH (5 mL)) in ether (5 mL). The yellow solution was stirred at 0 °C for 30 min, and the excess diazomethane was destroyed by adding acetic acid (0.5 mL). The mixture was diluted with ether (30 mL), washed with 10% aqueous NaOH (10 mL) and saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the methyl ester as a yellow solid (266 mg, 99%). The resulting methyl ester was used directly in the next step without further purification: mp 104–106 °C; $[\alpha]_D$ −11.2° (*c* 0.035, $CHCl_3$) (lit. $[\alpha]_D$ −10° (*c* 0.011, $CHCl_3$)); IR ($CHCl_3$) 3420, 3340, 2940, 2900, 1660, 1630, 1400, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.08 (br s, 1 H), 7.85 (br s, 1 H), 7.62 (d, *J* = 9.0 Hz, 1 H), 6.90 (m, 2 H), 6.66 (d, *J* = 9.0 Hz, 1 H), 6.21 (m, 1 H), 3.98 (s, 3 H), 3.67 (dd, *J* = 10.3, 2.4 Hz, 1 H), 3.18 (m, 1 H), 3.09 (dd, *J* = 14.4, 8.1 Hz, 1 H), 2.97 (d, *J* = 4.6 Hz, 3 H), 2.84 (dd, *J* = 14.4, 6.8 Hz, 1 H), 1.75–1.00 (m, 10 H), 0.96 (d, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 6 H); MS (EI) 538 (M^+ + 1, 22), 537 (M^+, 67), 332 (22), 319 (15), 318 (44), 220 (31).

[6*S*,2*R*-[3*R*,9*R*,11*R*]-8*S*-[1*S*]]-(+)-Methyl 5-(*N*-Methyltrifluoroacetamido)-2-[[3,9,11-trimethyl]-8-[1-methyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2-yl]methyl-4-benzoxazolecarboxylate (68). To a solution of A-23187 methyl ester (**1**) (38.5 mg, 0.072 mmol) in dichloromethane (300 μL) at 0 °C was added triethylamine (20 μL, 0.14 mmol) followed by trifluoroacetic anhydride (12 μL, 0.086 mmol). The resulting solution was stirred at 0 °C for 25 min. The mixture was diluted with ether (5 mL), washed successively with H_2O (2 mL) and saturated aqueous NaCl (2 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography on Biosil-A using 40% ethyl acetate–hexanes as eluent to give the desired amide **68** (36.72 mg, 81%) as a white solid: mp 80–81 °C; R_f 0.40 (40% ethyl acetate–hexanes); $[\alpha]_D$ +6.6° (*c* 0.076, $CHCl_3$); IR ($CHCl_3$) 3440, 2960, 2920, 1720, 1700, 1640, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (br s, 1 H), 7.74 (m, 1), 7.00 (m, 1 H), 6.87 (m, 1 H), 6.21 (m, 1 H), 4.08 (m, 1 H), 3.96–3.94 (s, 3 H), 3.14–3.06 (m, 2 H), 3.48 (m, 1 H), 3.35–3.31 (m, 3 H), 2.94–2.89 (m, 1 H), 1.75–0.98 (m, 9 H), 0.94–0.73 (m, 12 H); MS (EI) 633 (M^+, 6), 429 (10), 372 (5), 316 (14),

(59) Obtained by esterification (CH_2N_2) and subsequent N-trifluoroacetylation (TFAA, CH_2Cl_2, Et_3N) of A-23187.

284 (8), 205 (7), 163 (8), 123 (15), 94 (63).

[2*R*,3*R*,6*S*,8*S*,9*R*,11*R*,1′*R*]-2-(Carboxymethyl)-8-[1′-methyl-2′-oxo-2′-(1*H*-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undecane (9). To a solution of A-23187 (209 mg, 0.400 mmol) in dimethylformamide (5 mL) was added 2 N aqueous HCl (3 mL). The solution was stirred at room temperature for 7 h. The mixture was diluted with chloroform (30 mL), and the pH of the aqueous layer was brought to 7 with phosphate buffer (30 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in benzene (10 mL), and oxalyl chloride (1.0 mL, 11.5 mmol) was added dropwise over 2 min. The resulting mixture was stirred at room temperature for 1 h. The solution was then cooled to 0 °C and a solution of acetone–H_2O (1:1, 10 mL) was slowly added. The resulting mixture was stirred at room temperature for 10 h. The organic layer was diluted with chloroform (30 mL), washed successively with H_2O (15 mL) and saturated aqueous NaCl (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by chromatography on Biosil-A using 50% ethyl acetate–hexanes as eluent to give the desired labile pyrrole acid **9** (77 mg, 51%) as a light brown oil: R_f 0.40 (10% methanol–chloroform); $[\alpha]_D$ +116° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3200, 2940, 2900, 1710, 1610, 1400, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.05 (br s, 1 H), 7.05 (m, 1 H), 7.01 (m, 1 H), 6.26 (m, 1 H), 3.95 (m, 2 H), 3.25 (m, 1 H), 2.54 (dd, J = 15.4, 8.3 Hz, 1 H), 2.37 (dd, J = 15.4, 6.0 Hz, 1 H), 1.83–1.23 (m, 9 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.80 (d, J = 6.9 Hz, 3 H).

(4*S*)-4-(2,2-Dibromoethenyl)-2,2-dimethyl-1,3-dioxolane (17). A solution of carbon tetrabromide (76.0 g, 0.26 mol) in methylene chloride (400 mL) was cooled in an ice bath, and a solution of triphenylphosphine (121.0 g, 0.46 mol) in methylene chloride (15 mL) was added rapidly. To the resulting bright orange solution was added a solution of aldehyde **16** (13.0 g, 0.10 mol) in methylene chloride (50 mL) over 10 min. The resulting mixture was stirred for 1 h at 0 °C while the disappearance of starting material was monitored by TLC. Isolation of the product was accomplished, at minimum exposure to air, by pouring the reaction mixture into pentane (4 volumes) and filtration through a bed of Celite to remove insoluble material. The insoluble fraction was reextracted with additional portions of methylene chloride followed by pentane precipitation to remove all of the olefinic product. The combined filtrates were evaporated under reduced pressure. The dibromoolefin **17** thus obtained was in essentially pure form (49.5 g, 86%). An analytical sample was prepared by distilling the crude product to afford a clear liquid: bp 80–85 °C (3 mmHg) [lit.[23b] bp 70–73 °C (0.5 mmHg)].

(4*S*)-(+)-4-(2-Carbomethoxy-1-ethynyl)-2,2-dimethyl-1,3-dioxolane (18). A solution of dibromoolefin **17** (30.0 g, 0.10 mol) in tetrahydrofuran (850 mL) was cooled to −78 °C, and *n*-butyllithium (134 mL, 1.57 M in hexane, 0.21 mol) was slowly added. After being stirred for 1 h, the reaction mixture was allowed to gradually warm to room temperature and was maintained at 23 °C for 1 h. After the mixture was cooled to −60 °C, a solution of methyl chloroformate (1.04 g, 0.11 mol) in tetrahydrofuran (30 mL) was slowly added. After the mixture was stirred for 1 h at −60 °C, the reaction temperature was gradually raised to 23 °C over 1 h. The mixture was then recooled to 0 °C and quenched with water (125 mL). The layers were separated, and the aqueous layer was saturated with sodium chloride and extracted with several portions of 67% ether–methylene chloride (50 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was distilled to afford the acetylenic ester **18** (14.4 g, 78%) as a colorless oil: bp 68–75 °C (0.8 mmHg); $[\alpha]_D$ +56.4° (*c* 19.5, C_6H_6); IR (film) 2240, 1720, 1430, 1380, 1370, 1070, 890, 745 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 4.81 (dd, J = 6.4, 6.4 Hz, 1 H), 4.12 (m, 2 H), 3.80 (s, 3 H), 1.52 (s, 3 H), 1.40 (s, 3 H); HRMS calcd for $C_9H_{12}O_4$ 184.0735, found 184.0713.

(4*S*)-4-[(*Z*)-2-(Carbomethoxy-1-methylethenyl)-2,2-dimethyl-1,3-dioxolane (19). A solution of dimethyl sulfide–cuprous bromide complex (20.9 g, 102 mmol) in diethyl ether (180 mL) and dimethyl sulfide (130 mL) was cooled in an ice bath, and methyllithium (78.5 mL, 1.3 M in ether, 102 mmol) was added over 30 min. The mixture was stirred at 0 °C for 10 min and then cooled to −78 °C. A solution of acetylenic ester **18** (14.4 g, 78.2 mmol) in ether (70 mL) was slowly added, and the resulting mixture was stirred for 1 h before being quenched with a pH 8 buffer solution of NH_4OH/NH_4Cl (50 mL) at −78 °C. The reaction mixture was allowed to warm gradually to 25 °C. The phases were separated, and the organic layer was washed with additional pH 8 buffer solution (5 × 25 mL). The combined aqueous layers were then saturated with solid sodium chloride and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude ester **19** (16.0 g). Purification was effected by chromatography on silica gel with a Waters Prep 500 system using 5% ethyl acetate–hexanes as eluent to afford the pure ester **19** (14.0 g, 89%): IR (film) 2980, 2930, 1715, 1640, 1440, 1375, 1310, 1240, 1210, 1150, 1090, 1050, 950 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.70 (m, 1 H), 4.30 (dd, J = 7.0, 7.0 Hz, 1 H), 1.95 (s, 3 H), 1.48 (s, 3 H), 1.39 (s, 3 H). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.43; H, 8.26.

(4*S*)-(−)-4,5-Dihydroxy-3-methyl-2-butenoic Acid 1,4-Lactone (20). A solution of acetonide **19** (15.0 g, 75 mmol) in tetrahydrofuran (100 mL) was treated with 3 N aqueous HCl (75 mL), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was cooled in an ice bath and carefully neutralized with solid $NaHCO_3$. After filtration to remove the solids and concentration of the filtrate under reduced pressure, the residue was saturated with solid NaCl and extracted with small portions of methylene chloride several times. The combined organic layers were dried over $MgSO_4$, and solvent was evaporated under reduced pressure to give a viscous yellow oil, which upon trituration with petroleum ether (bp 30 °C) afforded the known butenolide **20** (7.63 g, 80%) as a white solid: mp 64–66 °C (lit.[26] mp 65 °C); $[\alpha]_D$ −67.8° (*c* 4.28, EtOH); IR (film) 3580, 3400, 2930, 1750, 1640, 1300 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (s, 1 H), 4.92 (s, 1 H), 4.08 (d, J = 13.4 Hz, 1 H), 3.78 (d, J = 9.9 Hz, 1 H), 2.38 (s, 1 H), 2.12 (s, 3 H).

(4*S*)-(−)-4-Hydroxy--5-[(2-methoxypropyl)oxy]-3-methyl-2-butenoic Acid Lactone (21). To a mixture of butenolide **20** (2.9 g, 22.7 mmol) and methyl isopropenyl ether (7.1 g, 98.4 mmol) was introduced a trace of phosphorus oxychloride in a capillary. The reaction flask was stoppered and stirred at room temperature for 6 h. Two drops of triethylamine were then added, and the mixture was concentrated under reduced pressure to afford the desired protected alcohol **21** (4.5 g, 100%) as a white solid: mp 59–61 °C; $[\alpha]_D$ −29.5° (*c* 21.1, CCl_4); IR (film) 2920, 1765, 1640, 1680, 1210, 1150, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1 H), 4.92 (b s, 1 H), 3.80 (dd, J = 3.7, 3.7 Hz, 1 H), 3.60 (dd, J = 4.7, 4.7 Hz, 1 H), 3.21 (s, 3 H), 2.11 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.88; H, 8.05. Found: C, 59.79; H, 7.88.

(3*R*,4*S*)-(+)-4-Hydroxy-5-[(2-methoxypropyl)oxy]-3-methylbutanoic Acid Lactone (22). To a solution of olefin **21** (210 mg, 1.05 mmol) in benzene (2 mL) was added a catalytic amount (20 mg) of 5% rhodium on alumina. Hydrogenation was carried out at atmospheric pressure and a theoretical amount of hydrogen uptake was observed after 4 h. The mixture was passed through a short column of $MgSO_4$ to remove the catalyst and the filtrate concentrated under reduced pressure to afford the desired ketone **22** (213 mg, 100%) as a colorless liquid (cis:trans > 20:1): $[\alpha]_D$ +28.5° (*c* 42.3, C_6H_6); IR (film) 1765, 1475, 1460, 1210, 1160, 1090, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (m, 1 H), 3.65 (dd, J = 12.1, 3.1, 1 H), 3.16 (s, 3 H), 2.70 (m, 1 H), 2.50 (dd, J = 17.2, 8.0 Hz, 1 H), 2.32 (dd, J = 17.2, 8.0 Hz, 1 H), 1.29 (d, J = 4.0 Hz, 6 H), 1.12 (d, J = 7.0 Hz, 3 H).

[4*S*-[1*R*]]-(+)-4-[3-Hydroxy-1-methylpropyl]-2,2-dimethyl-1,3-dioxolane (23). To a suspension of lithium aluminum hydride (114 mg, 2.85 mmol) in anhydrous ether (10 mL) was added a solution of lactone **22** in ether (5 mL) over 10 min. The resulting mixture was stirred for 1.5 h at 25 °C. The mixture was cooled in an ice bath and quenched with successive addition of water (0.11 mL), 15% aqueous NaOH (0.11 mL), and H_2O (0.33 mL). After the mixture was stirred at 0 °C for 30 min and at room temperature for another 30 min, the white granular solid was filtered through a pad of $MgSO_4$. The precipitate was thoroughly rinsed with ethyl acetate, and the combined filtrate was evaporated to dryness under reduced pressure. The crude product was used in the next step without further purification.

To a solution of the above diol derived from lactone **22** (470 mg, 2.3 mmol) in dry acetone (15 mL) was added *p*-toluenesulfonic acid monohydrate (50 mg), and the mixture was stirred at room temperature overnight. Acetone was removed under reduced pressure, and the yellow oily residue was taken up in ether (25 mL), washed with H_2O (3 × 10 mL) and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure to afford the desired alcohol **23** (374 mg, 83%): $[\alpha]_D$ +13.6° (*c* 6.4, C_6H_6); IR (film) 3400, 2925, 2880, 1455, 1380, 1370, 1210, 1060, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03–3.99 (m, 2 H), 3.76–3.72 (m, 1 H), 3.68–3.62 (m, 2 H), 2.08–1.9 (br s, 1 H), 1.89–1.61 (m, 2 H), 1.49–1.42 (m, 4 H), 1.35 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.96, H, 10.44.

[4*S*-[1*R*]]-(+)-4-[3-Iodo-1-methylpropyl]-2,2-dimethyl-1,3-dioxolane (24). A stirred solution of alcohol **23** (1.32 g, 7.6 mmol) and *N*-methyl-*N*,*N*′-dicyclohexylcarbodiimidium methyl iodide (5.3 g, 15.2 mmol) in tetrahydrofuran (40 mL) was heated to 35 °C for 2 h. The resulting colorless solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in hexane (50 mL) and washed with 80% methanol–H_2O (3 × 15 mL) to remove *N*-methyl-*N*,*N*′-dicyclohexylurea. The combined aqueous washings were

back-extracted with hexane (3 × 15 mL). The combined organic layers were then dried over $MgSO_4$ and filtered through a plug of silica gel (2 g). The clear filtrate, after removal of solvent under reduced pressure, afforded the desired iodide **24** (2.15 g, 100%): $[\alpha]_D$ +13.2° (*c* 18.0, C_6H_6); IR (film) 2960, 2920, 2860, 1378, 1370, 1070, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02–3.95 (m, 2 H), 3.66–3.63 (m, 1 H), 3.34–3.29 (m, 1 H), 3.19–3.13 (m, 1 H), 1.95–1.90 (m, 1 H), 1.88–1.65 (m, 2 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H). Anal. Calcd for $C_9H_{17}IO_2$: C, 38.04; H, 6.03. Found: C, 38.25; H, 6.03.

[4*S*-[1*R*]]-4-[3-[6-(3,4-Dihydropyranyl)]-1-methylpropyl]-2,2-dimethyl-1,3-dioxolane (25). To a stirred solution of 3,4-dihydro-2*H*-pyran (0.89 g, 10.56 mmol) in THF (4 mL) at −78 °C was added a solution of *tert*-butyllithium (4.4 mL, 1.58 M in hexane, 6.9 mmol), and the resulting mixture was rapidly warmed to −5 to +5 °C (ice bath) and maintained at this temperature range for 45 min. The clear bright yellow solution of the anion was then treated with a solution of iodide **24** (1.50 g, 5.28 mmol) in THF (1 mL). The yellow color of the anion was rapidly discharged, and the resulting solution was stirred at 0 °C for 1 h and at 25 °C overnight. The reaction mixture was quenched with water (6 mL) and diluted with ether (30 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 5% ethyl acetate–hexanes as eluent to afford 1.2 g (95%) of the desired dihydropyran **25**: $[\alpha]_D$ +7.69° (*c* 2.6, CH_2Cl_2); IR (film) 2905, 2870, 1670, 1375, 1160, 1060, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 3.5, 3.4 Hz, 1 H), 4.03–3.95 (m, 4 H), 3.92–3.86 (m, 2 H), 3.62–3.58 (m, 2 H), 2.48–2.44 (m, 1 H), 2.11–2.06 (m, 1 H), 1.99–1.90 (m, 2 H), 1.80–1.74 (m, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H); HRMS calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1734.

Cyclopropanes (26). To a stirred mixture of dihydropyran **25** (635 mg, 2.65 mmol) and diethylzinc (4.0 mL, 15% v/v in hexane, 3.4 mmol) in ether (4 mL) at room temperature was added diiodomethane (1.42 g, 5.3 mmol) over 30 min, producing an exothermic reaction. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 8 h. The reaction mixture was then poured into 1% aqueous HCl (10 mL), and the organic phase was successively washed with water and dilute aqueous $NaHCO_3$. After the mixture was dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was chromatographed using 5% ethyl acetate–hexane as eluent to afford the desired cyclopropanes **26** as a 1:1 mixture of diastereomers (612 mg, 91%): IR (film) 2920, 1450, 1370, 1320, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04–4.01 (m, 1 H), 3.99–3.88 (m, 1 H), 3.66–3.58 (m, 1 H), 3.29–3.23 (m, 1 H), 1.90–1.84 (m, 2 H), 1.65–1.51 (m, 2 H), 1.49–1.40 (m, 4 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.93–0.84 (m, 2 H), 0.58–0.47 (m, 2 H); HRMS calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1913.

[2β(*S*),3β(*R*),6α,11α]-3,11-Dimethyl-2-(hydroxymethyl)-1,7-dioxaspiro[5.5]undecane (27a) and [2β(*S*),3β(*R*),6α,11α]-3,11-Dimethyl-2-(hydroxymethyl)-1,7-dioxaspiro[5.5]undecane (27b). To a solution of cyclopropyl ethers **26** (645 mg, 2.5 mmol) in benzene (5 mL) was added *p*-toluenesulfonic acid monohydrate (6 mg), and the mixture was heated under reflux for 5 h. The reaction mixture was cooled to room temperature, diluted with ether, and extracted with water (5 mL) and saturated aqueous NaCl (5 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The diastereomers (4:1 by ^1H NMR) were separated by chromatography using 20% ether–hexane as eluent to afford the pure spiroketals **27a** (231 mg, 43%) and **27b** (48 mg, 9%). **27a**: R_f 0.40 (20% ether–hexanes); IR (film) 3400, 2920, 2875, 1090, 990, 945 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92–3.89 (m, 1 H), 3.68–3.55 (m, 3 H), 3.50–3.48 (m, 1 H), 2.15–2.06 (m, 1 H), 1.99–1.91 (m, 2 H), 1.72–1.62 (m, 2 H), 1.59–1.47 (m, 3 H), 1.40–1.32 (m, 1 H), 1.30–1.18 (m, 2 H), 0.95 (d, *J* = 5.9 Hz, 3 H), 0.89 (d, *J* = 7.1 Hz, 3 H); HRMS calcd for $C_{12}H_{22}O_3$ 214.1569, found 214.1604.

27b: R_f 0.36 (20% ether–hexanes); IR (film) 3400, 2930, 2880, 1075, 1030, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94–3.90 (m, 1 H), 3.75–3.64 (m, 2 H), 3.59–3.55 (m, 1 H), 3.51–3.49 (m, 1 H), 2.14–2.10 (m, 1 H), 2.04–1.99 (m, 1 H), 1.85–1.73 (m, 2 H), 1.72–1.67 (m, 2 H), 1.55–1.25 (m, 5 H), 1.01 (d, *J* = 7.2 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H); MS (EI) *m/e* 214 (M^+).

(*S*)-(+)-(Benzyloxy)methyl 3-[(Benzyloxy)methoxy]-2-methylproplonate. To a solution of the (*S*)-(+)-3-hydroxy-2-methylpropionic acid (14.3 g, 0.14 mol) and diisopropylethylamine (53.5 g, 0.41 mol) in dimethylformamide (300 mL) at 0 °C was added chloromethyl benzyl ether (64.6 g, 0.41 mol) via a syringe. The resulting turbid solution was stirred at 0 °C for 30 min and at room temperature for 8 h. The reaction mixture was diluted with ether (600 mL), and the organic phase was washed with H_2O (3 × 200 mL), 15% aqueous $Cu(NO_3)_2$ (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography afforded the title bis BOM hydroxy ester (34.0 g, 70%) as a clear yellow oil: $[\alpha]_D$ +7.40° (*c* 7.3 EtOH); IR (film) 1740, 1455, 740, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.6 Hz, 10 H), 5.41–5.37 (m, 2 H), 4.75 (s, 2 H), 4.69 (s, 2 H), 4.58 (s, 2 H), 3.79 (dd, *J* = 7.8, 7.8 Hz, 1 H), 3.66 (dd, *J* = 5.0, 5.0 Hz, 1 H), 2.85–2.77 (m, 1 H), 1.20 (d, *J* = 6.9 Hz, 3 H).

(*R*)-(+)-3-[(Benzyloxy)methoxy]-2-methylpropanol. To a suspension of lithium aluminum hydride (3.0 g, 80 mmol) in anhydrous ether (100 mL) at 0 °C was added a solution of the bis BOM ether ester (25.0 g, 72.7 mmol) in anhydrous ether (100 mL) dropwise at a rate to maintain a gentle reflux. The reaction mixture was stirred at room temperature for 20 h. The mixture was then cooled to 0 °C and quenched by successive addition of H_2O (3.0 mL), 15% aqueous NaOH (3.0 mL), and H_2O (9.0 mL). After 1 h of stirring at room temperature, the precipitated aluminum salts were removed by filtration through a short pad of anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure, and the residue was chromatographed using 20% ether–hexanes as eluent to afford the title alcohol (13.7 g, 90%): $[\alpha]_D$ +6.37° (*c* 6.0, $CHCl_3$); IR (film) 3400, 1055, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H), 4.74 (s, 2 H), 4.59 (s, 2 H), 3.65–3.50 (m, 4 H), 2.18 (br s, 1 H), 2.17–2.02 (m, 1 H), 0.90 (d, *J* = 7.0 Hz, 3 H).

(*S*)-(+)-3-[(Benzyloxy)methoxy]-2-methylpropanal. A solution of oxalyl chloride (6.2 mL, 68.1 mmol) in dichloromethane (155 mL) was cooled to −78 °C, and a solution of dry dimethylsulfoxide (10.5 mL, 148 mmol) in dichloromethane (30 mL) was added dropwise from a pressure-equalizing addition funnel. After being stirred at −78 °C for 5 min, a solution of the BOM ether alcohol (13.0 g, 61.9 mmol) in dichloromethane (60 mL) was introduced within 5 min. The reaction was stirred at −78 °C for 30 min and then quenched with triethylamine (43 mL, 307 mmol). The reaction mixture was allowed to gradually warm to room temperature over 1 h. The mixture was diluted with dichloromethane (300 mL), and the organic layer was washed with H_2O (3 × 300 mL), cold 10% aqueous HCl (100 mL), and brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography using 20% ether–hexanes produced the title benzyl ether aldehyde (11.1 g, 86%) as a pale yellow oil: $[\alpha]_D$ +3.34° (*c* 10.7, EtOH); IR (film) 1720, 1450, 1045, 735, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.67 (s, 1 H), 7.28 (s, 5 H), 4.68 (s, 2 H), 4.53 (s, 2 H), 3.42 (d, *J* = 5.7 Hz, 2 H), 2.82–2.38 (m, 1 H), 1.13 (d, *J* = 6.94 Hz, 3 H).

(*R*)-(+)-Methyl 5-[(Benzyloxy)methoxy]-4-methylhex-2-enoate. To a suspension of the carbomethoxymethylenetriphenylphosphorane (18.0 g, 53 mmol) in dimethylformamide (50 mL) was added a solution of the BOM ether aldehyde (10.15 g, 48.8 mmol) in dimethylformamide (50 mL). The resulting white suspension gradually went into solution to give a pale yellow clear solution. The reaction mixture was stirred at 25 °C overnight. After being diluted with ether (200 mL), the organic phase was washed successively with H_2O (2 × 100 mL), 15% aqueous $Cu(NO_3)_2$ (2 × 50 mL), and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was triturated with hexane and passed through a column of silica gel using hexane followed by 50% ether–hexane to afford the title BOM unsaturated ester (11.1 g, 83%) as a pale yellow oil: $[\alpha]_D$ +2.26° (*c* 6.85, EtOH); IR (film) 1720, 1650, 1260, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 5 H), 6.94 (dd, *J* = 7.1, 7.1 Hz, 1 H), 5.86 (dd, *J* = 15.9, 0.9 Hz, 1 H), 4.73 (s, 2 H), 4.57 (s, 2 H), 3.71 (s, 3 H), 3.51 (d, *J* = 6.4 Hz, 2 H), 2.71–2.56 (m, 1 H), 1.08 (d, *J* = 6.8 Hz, 3 H).

(*R*)-(+)-Methyl 5-Hydroxy-4-methylpentanoate. A solution of the BOM unsaturated ester (6.40 g, 24.2 mmol) in a solution of 3% HCl in methanol (50 mL) containing 0.64 g of 10% palladium on carbon was placed under hydrogen and stirred for 12 h. The catalyst was removed by filtration through a plug of cotton and washing with ether. The clear filtrate was cooled to 0 °C and carefully neutralized by addition of small portions of solid $NaHCO_3$. After being filtered to remove the solids, the filtrate was evaporated in vacuo. The residue was chromatographed using 33% ether–hexane to afford the title hydroxy ester (2.70 g, 75%) as a pale yellow liquid: $[\alpha]_D$ +1.61° (*c* 11.5, EtOH); IR (film) 3440, 1740, 1465, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3 H), 3.33 (br s, 2 H), 2.92 (br s, 1 H), 2.39–2.20 (m, 2 H), 2.0–1.15 (m, 3 H), 1.88 (d, *J* = 2.8 Hz, 3 H); HRMS calcd for $C_7H_{14}O_3$ 115.0759, found 115.0773.

(*R*)-5-Carbomethoxy-2-methylpentanal. By the method described for the preparation of the preceding BOM aldehyde, the preceding hydroxy ester (200 mg, 1.37 mmol) was transformed to the aldehyde ester (176 mg, 89%). The aldehyde ester being somewhat sensitive was directly converted to aldol adducts **28a** and **28b**: IR (film) 2970, 2710, 1735 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 3.63 (s, 3 H), 2.46–2.27 (t, *J* = 7.5 Hz, 3 H), 2.23–1.5 (m, 2 H), 1.0 (d, *J* = 6.0 Hz, 3 H); HRMS calcd for $C_7H_{12}O_3$ 144.0786, found 144.0757.

(2*S*,3*S*,4*R*)-2,6-Dimethylphenyl 6-Carbomethoxy-2,4-dimethyl-3-hydroxyhexanoate (28a) and (2*R*,3*R*,4*R*)-2,6-Dimethylphenyl 6-Carbomethoxy-2,4-dimethyl-3-hydroxyhexanoate (28b). To a stirring solution

of lithium diisopropylamide (1.27 mmol; prepared by addition of 0.9 mL of a 1.46 M hexane solution of *n*-butyllithium to a solution of 0.18 mL of diisopropylamine in 1 mL of tetrahydrofuran) in tetrahydrofuran (1 mL) at −78 °C was added 2,6-dimethylphenyl propionate (226 mg, 1.27 mmol) in tetrahydrofuran (1 mL). After being stirred for 20 min at −78 °C, a solution of the preceding aldehyde ester (200 mg, 1.39 mmol) in tetrahydrofuran (0.5 mL) was added slowly. The resulting solution was stirred at −78 °C for 1 h before being quenched with saturated aqueous NH_4Cl solution. The layers were separated, and the organic layer was washed with H_2O (1 × 2 mL) and brine (2 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed using 20% ether–hexane to afford a 2:1 mixture of diastereomeric aldol adducts **28a** and **28b** (231 mg, 56%): IR (film) 3500, 1740, 1460, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 3 H), 3.81–3.76 (m, 1 H), 3.69 (s, 3 H), 3.59–3.54 (m, 0.5 H), 3.11–3.02 (q, *J* = 7.4 Hz, 0.5 H), 3.00–2.91 (q, *J* = 7.4 Hz, 1 H), 2.53–2.28 (m, 3 H), 2.17 (s, 6 H), 1.93–1.83 (m, 1 H), 1.80–1.60 (m, 3 H), 1.46 (d, *J* = 6.7 Hz, 1 H), 1.34 (d, *J* = 6.7 Hz, 2 H), 1.04 (d, *J* = 6.7 Hz, 1 H), 0.96 (d, *J* = 6.7 Hz, 2 H).

(2*S*,3*S*,4*R*)-6-[(2,6-Dimethylphenyl)carboxy]-5-hydroxy-4-methylheptanoic Acid 1,5-Lactone. A solution of esters **28a** and **28b** (500 mg, 1.55 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg) in benzene (5 mL) was heated under reflux for 8 h. After being cooled to room temperature, the solvent was evaporated under reduced pressure. The residue was taken up in dichloromethane (5 mL), washed with H_2O (2 × 3 mL) and brine (3 mL), and dried over $MgSO_4$. Evaporation of the solvent gave the title δ-lactone ester as a yellow oil. Chromatography using 75% ethyl acetate–hexane afforded the pure lactone (410 mg, 91%): IR (film) 1750, 1480, 1460, 1240, 1165, 1150, 760, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 3 H), 4.83 (dd, *J* = 10.7, 3.3 Hz, 1 H), 4.20 (dd, *J* = 8.0, 3.3 Hz, 0.5 H), 3.09–2.98 (m, 1 H), 2.68–2.47 (m, 2.5 H), 2.20 (s, 3 H), 2.16 (s, 3 H), 2.00–1.90 (m, 0.5 H), 1.78–1.70 (m, 1 H), 1.57 (d, *J* = 6.7, 1.3 Hz, 1.3 H), 1.37 (d, *J* = 6.7 Hz, 1.7 H), 1.15 (d, *J* = 6.7 Hz, 1.3 H), 1.05 (d, *J* = 6.7 Hz, 1.7 H); MS (EI) 290 (M^+).

(1*S*,2*R*,5*R*)-1-[(1*S*)-1-Methyl-2-[(triisopropylsilyl)oxy]ethyl]-2-methyl-5-hydroxytetrahydropyran and (1*S*,2*R*,5*S*)-1-[(1*S*)-1-Methyl-2-[(triisopropylsilyl)oxy]ethyl]-2-methyl-5-hydroxytetrahydropyran. A solution of the preceding δ-lactone (210 mg, 0.72 mmol) in toluene (2 mL) was cooled to −78 °C and was treated with diisobutylaluminum hydride (2.4 mL, 1.5 M in toluene, 3.6 mmol). The reaction mixture was stirred at −78 °C for 1 h. The excess diisobutylaluminum hydride was decomposed with acetone (0.2 mL). A saturated aqueous solution of sodium sulfate (1 mL) was then added, and the reaction mixture was allowed to warm to room temperature. To the resulting gelatenous precipitate was added small portion of anhydrous magnesium sulfate to obtain a grannular precipitate after stirring for 2 h. The precipitate was filtered and washed with a mixture of 50% ether–dichloromethane several times, and the filtrate was concentrated under reduced pressure. The residue was chromatographed using 50% ether–hexane as eluent to afford the desired hydroxy lactol (92 mg, 73%). This lactol was then dissolved in dimethylformamide (2 mL), and the resulting solution was stirred at room temperature for 2 h after the addition of imidazole (80 mg) and triisopropylsilyl chloride (120 mg). The reaction mixture was then diluted with saturated aqueous NaCl solution (2 mL) and extracted with ether. The combined ether extracts were washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using 5% ethyl acetate–hexane to afford the title TIPS-protected lactols as a mixture of diastereomers: IR (film) 3430, 2950, 2870, 1460, 1380, 885, 780, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25–5.05 (m, 1 H), 3.92–3.40 (m, 3 H), 1.90–1.33 (m, 7 H), 1.14–1.03 (m, 21 H), 0.96–0.75 (m, 6 H).

(2*S*,3*R*)-(+)-2-[(1*S*)-1-Methyl-2-[(triisopropylsilyl)oxy]ethyl]-3-methyl-3,4-dihydropyran (29). Procedure A. A solution of the preceding lactols (160 mg, 0.48 mmol) and excess triethylamine (774 mg, 7.7 mmol) in dichloromethane (2 mL) was cooled to 0 °C. Methanesulfonyl chloride (72 mg, 0.63 mmol) was added to the reaction mixture over 10 min. After being stirred at 0 °C for 1 h, the reaction mixture was warmed to room temperature and maintained at 25 °C overnight. The resulting white suspension was diluted with ether (10 mL), washed successively with chilled 5% aqueous HCl (3 × 5 mL) and 5% aqueous $NaHCO_3$ (2 × 5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The mixture was concentrated under reduced pressure, and the residue was passed through a short plug of Florisil using hexane as eluent to obtain a colorless oil. The desired diastereomer **29** (60% based on 2:1 mixture of starting lactol) was isolated by flash chromatography using hexane as eluent: $[\alpha]_D$ +18.38° (*c* 2.72, CH_2Cl_2); IR (film) 2940, 2860, 1720, 1640, 1460, 1380, 1260, 1210, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, *J* = 5.7 Hz, 1 H), 4.56 (t, *J* = 4.0 Hz, 1 H), 3.82–3.73 (m, 2 H), 3.59 (d, *J* = 10.3 Hz, 1 H), 2.35–2.29 (m, 1 H), 2.04–2.01 (m, 1 H), 1.77–1.63 (m, 2 H), 1.22–0.97 (m, 21 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H); HRMS calcd for $C_{18}H_{36}O_2Si$ (M^+ − 43) 262.1936, found 262.1912.

Procedure B. A solution of the 2*R*,3*S* monosilylated 1,3-diol, as prepared in the following text (4.21 g, 12.8 mmol), in 50% dichloromethane–methanol (100 mL) was cooled to −78 °C, and a steady stream of ozone was passed through the solution until the solution turned slightly blue. Zinc dust (12.0 g) was then added followed by acetic acid. The reaction mixture was allowed to warm to room temperature and stirred until a negative starch–iodide test for peroxides was obtained. The excess zinc dust was removed by filtration and the filtrate concentrated under reduced pressure. The residue was dissolved in ether, and the organic layer was successively washed with H_2O, 5% aqueous $NaHCO_3$, and H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The crude lactols were used directly in the next step without further purification.

To a mixture of the preceding lactols (72 mg, 0.22 mmol) and excess triethylamine (330 mg, 3.3 mmol) in dichloromethane (1 mL) at 0 °C was added methanesulfonyl chloride (38 mg, 0.33 mmol) over 5 min. The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. The resulting mixture was dilted with ether (5 mL), washed with H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was passed through a short pad of Florisil and eluted with hexane to afford the dihydropyran **29** as a colorless oil (27 mg, 40%, 2 steps): $[\alpha]_D$ +18.38° (*c* 2.72, CH_2CL_2); IR (film) 2940, 2860, 1720, 1640, 1460, 1380, 1260, 1210, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (d, *J* = 5.7 Hz, 1 H), 4.56 (t, *J* = 4.0 Hz, 1 H), 3.82–3.73 (m, 2 H), 3.59 (d, *J* = 10.3 Hz, 1 H), 2.35–2.29 (m, 1 H), 2.04–2.01 (m, 1 H), 1.77–1.63 (m, 2 H), 1.22–0.97 (m, 21 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H); HRMS calcd for $C_{18}H_{36}O_2Si$ 262.1936 (M^+ − 43), found 262.1912.

(4*R*,5*S*)-(+)-3-(1-Oxo-5-hexenyl)-4-methyl-5-phenyloxazolidone. To a stirred solution of (4*R*,5*S*)-4-methyl-5-phenyloxazolidone (3.54 g, 0.2 mol) in tetrahydrofuran (300 mL) was added a solution of *n*-butyllithium (133 mL, 1.5 M in hexane, 0.2 mol) at −78 °C, and the resulting mixture was stirred for 1 h. To this solution was slowly added a solution of 5-hexenyl chloride (26.9 g, 0.20 mol) in tetrahydrofuran (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and slowly warmed to 25 °C and maintained at this temperature for 8 h. The resulting solution was cooled at 0 °C and quenched with saturated aqueous NH_4Cl and then extracted with ether (3 × 100 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography using 10% ethyl acetate–hexanes to afford the title imide (53.4 g, 98%) as white crystals: mp 46–49 °C; $[\alpha]_D$ +32.04° (*c* 3.72, CH_2Cl_2); IR ($CHCl_3$) 1790, 1715, 1645, 1465, 1360, 1210 cm1−1; ^1H NMR (90 MHz, $CDCl_3$) δ 7.5–7.3 (m, 5 H), 6.05–5.50 (m, 2 H), 5.25–4.55 (m, 3 H), 3.1–2.85 (m, 1 H), 2.3–1.95 (m, 2 H), 1.9–1.6 (m, 2 H), 0.9 (d, *J* = 5.5 Hz, 3 H); HRMS calcd for $C_{16}H_{19}O_3N$ 273.1364, found 273.1372.

(4*R*,5*S*)-(+)-3-((2*R*)-2-Methyl-1-oxo-5-hexenyl)-4-methyl-5-phenyloxazolidone. A solution of diisopropylamine (26.4 mL, 0.175 mol) in tetrahydrofuran (180 mL) was stirred at 0 °C while a solution of *n*-butyllithium (117 mL, 1.5 M in hexane, 0.175 mol) was added dropwise. The resulting solution was stirred for an additional 10 min and cooled to −78 °C. To this solution of lithium diisopropylamide was added a solution of the preceding N-acylated imide (48 g, 0.176 mol) in tetrahydrofuran (180 mL) and the reaction mixture was stirred for 30 min. To the resulting lithium enolate solution was added freshly distilled methyl iodide (124 g, 0.874 mol) over a period of 30 min. After the addition, the reaction mixture was stirred at −78 °C for 2 h and then transferred to a −20 °C bath and maintained at this temperature overnight. The resulting white suspension was quenched with saturated aqueous NH_4Cl (90 mL) and extracted with ether (3 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by chromatography using 10% ethyl acetate–hexanes to afford the title methylated imide (33.2 g, 66%) as a yellow oil: $[\alpha]_D$ +7.5° (*c* 31.7, $CHCl_3$); IR (film) 1775, 1690, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5 H), 5.87–5.75 (m, 1 H), 5.64 (d, *J* = 8.4 Hz, 1 H), 5.04 (d, *J* = 17.4 Hz, 1 H), 4.98 (d, *J* = 10.2 Hz, 1 H), 4.77 (quintet, *J* = 6.0 Hz, 1 H), 3.75 (sextet, *J* = 6.6 Hz, 1 H), 2.16–2.07 (m, 2 H), 1.95–1.84 (m, 1 H), 1.59–1.49 (m, 1 H), 1.22 (d, *J* = 9.0 Hz, 3 H), 0.90 (d, *J* = 9.0 Hz, 3 H); MS (EI) 287 (M^+).

(2*R*)-(−)-Benzyl 2-Methyl-5-hexenoate. To a stirred solution of benzyl alcohol (25.0 g, 0.23 mol) in tetrahydrofuran (250 mL) at 0 °C was added *n*-butyllithium (117 mL, 1.5 M in hexane, 0.175 mol). The reaction mixture was stirred at 0 °C for 45 min, and then a solution of the preceding methylated imide (33.2 g, 0.116 mol) in tetrahydrofuran

(100 mL) was slowly added. After being stirred at 0 °C for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether (3 × 100 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was triturated with hexane and the white precipitate filtered to recover the oxazolidone (15.6 g, 76%). The filtrate was concentrated and subjected to flash chromatography on silica gel using hexane to afford the title benzyl ester (18.6 g, 74%): $[\alpha]_D$ −11.3° (*c* 2.89, $CHCl_3$); IR (film) 1730, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 5.83–5.70 (m, 1 H), 5.13 (s, 2 H), 5.04–4.93 (m, 2 H), 2.52 (quintet, *J* = 6.0 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.89–1.74 (m, 1 H), 1.58–1.47 (m, 1 H), 1.19 (d, *J* = 9.0 Hz, 3 H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.10; H, 8.20.

(2*R*)-(+)-2-Methyl-5-hexen-1-ol. To a stirred suspension of lithium aluminum hydride (5.6 g, 0.14 mol) in ether (300 mL) was added a solution of the preceding benzyl ester (27.6 g, 0.13 mol) in ether (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched by successive addition of H_2O (5.6 mL), 15% aqueous NaOH (5.6 mL), and H_2O (16.8 mL). The resulting white suspension was stirred at 0 °C for 30 min and at 25 °C for 1 h. The mixture was filtered through a plug of Florisil to remove aluminum salts, and the filtrate was concentrated. The resulting clear liquid was chromatographed using 10% ethyl acetate–hexane as eluent to afford the pure primary alcohol (11.8 g, 82%): $[\alpha]_D$ +9.1° (*c* 3.03, $CHCl_3$); IR (film) 3360, 3080, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86–5.76 (m, 1 H), 5.04 (d, *J* = 17.1 Hz, 1 H), 4.96 (d, *J* = 10.2 Hz, 1 H), 3.55–3.42 (m, 2 H), 2.15–2.02 (m, 2 H), 1.68–1.61 (m, 1 H), 1.54–1.49 (m, 1 H), 1.31–1.14 (m, 2 H), 0.93 (d, *J* = 6.7 Hz, 3 H); HRMS calcd for $C_7H_{14}O$ 97.1018, found 97.1021.

(2*R*)-(−)-2-Methyl-5-hexenal. To a stirred suspension of pyridinium chlorochromate (24.0 g, 110 mmol) and anhydrous sodium acetate (5.6 g, 69 mmol) in dichloromethane (90 mL) was added, in one portion, a solution of the preceding primary alcohol (7.8 g, 69 mmol) in dichloromethane (20 mL) at room temperature. After 2 h at room temperature, the reaction mixture was poured into ether (900 mL) and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly with ether (3 × 250 mL), whereupon it became a black granular solid. The combined organic solutions were passed through a short pad of Florisil and the solvent removed by distillation. Distillation of the residual oil through a short Vigreux column gave the title aldehyde (6.70 g, 87%): bp 60–62 °C (760 mm); $[\alpha]_D$ −12.4° (*c* 17.8, CH_2Cl_2); IR (film) 1720, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1 H), 5.69–5.59 (m, 1 H), 5.04 (d, *J* = 18.9 Hz, 1 H), 5.01 (d, *J* = 9.8 Hz, 1 H), 2.38–2.27 (m, 1 H), 2.16–2.05 (m, 2 H), 1.71–1.63 (m, 1 H), 1.38–1.32 (m, 1 H), 1.10 (d, *J* = 7.6 Hz, 3 H).

(2*S*,3*S*,4*R*)-2,6-Dimethylphenyl 2,4-Dimethyl-3-hydroxyoct-7-enoate (31a) and (2*R*,3*R*,4*R*)-2,6-Dimethylphenyl 2,4-Dimethyl-3-hydroxyoct-7-enoate (31b). To a stirring solution lithium diisopropylamide (9.4 mmol; prepared by addition of 6.0 mL of a 1.5 M solution of *n*-butyllithium in hexane to a solution of 1.3 mL of diisopropylamine in 4 mL of tetrahydrofuran) in tetrahydrofuran (4 mL) kept at −78 °C was added 2,6-dimethylphenyl propionate (1.70 g, 9.4 mmol) in tetrahydrofuran (2 mL). After the mixture was stirred at −78 °C for 20 min, a solution of the preceding aldehyde (956 mg, 8.5 mmol) in tetrahydrofuran (2 mL) was slowly added. The resulting solution was stirred at −78 °C for 1 h before being quenched with saturated aqueous NH_4Cl and extraction with ether (5 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by chromatography on Florisil and eluted with 10% ethyl acetate–hexane to afford the desired aldol products **31a** and **31b** (1.21 g, 50%) as a 2:1 mixture of diastereomers: IR (film) 3530, 1740, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.08 (s, 3 H), 6.91–5.77 (m, 1 H), 5.04 (d, *J* = 17.1 Hz, 1 H), 4.96 (d, *J* = 10.1 Hz, 1 H), 3.8–3.76 (m, 0.6 H), 3.54–3.50 (m, 0.3 H), 3.06–3.03 (m, 0.3 H), 2.99–2.92 (m, 0.6 H), 2.56 (d, *J* = 8.0 Hz, 0.34 H), 2.37 (d, *J* = 6.3 Hz, 0.6 H), 2.32–2.00 (m, 9 H), 1.78–1.69 (m, 1 H), 1.44 (d, *J* = 7.2 Hz, 1.5 H), 1.36 (d, *J* = 7.2 Hz, 1.9 H), 1.04 (d, *J* = 6.8 Hz, 0.8 H), 0.95 (d, *J* = 6.8 Hz, 1.74 H). MS (EI) 290 (M^+). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.27; H, 9.02.

(2*R*,3*S*,4*R*)-2,4-Dimethyloct-7-ene-1,3-diol and (2*S*,3*R*,4*R*)-2,4-Dimethyloct-7-ene-1,3-diol. By the method described for the preparation of (2*R*)-(+)-2-methyl-5-hexen-1-ol, the preceding 2:1 mixture of aldols **31a** and **31b** was transformed to a corresponding 2:1 mixture of the title diastereomeric diols. Purification was effected by chromatography using 30% ethyl acetate–hexane as eluent to afford the pure title diols (3.2 g, 74%): IR (film) 3340, 3060, 2920, 1630, 1450, 1020, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84–5.78 (m, 1 H), 5.03 (d, *J* = 17.1 Hz, 1 H), 4.96 (d, *J* = 10.2 Hz, 1 H), 3.80–3.62 (m, 2 H), 3.49 (dd, *J* = 8.9, 2.6 Hz, 1.3 H), 3.40–3.38 (m, 0.4 H), 2.22–1.21 (m, 8 H), 0.97 (d, *J* = 6.9 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3.3 H), 0.81 (d, *J* = 6.9 Hz, 1 H); HRMS calcd for $C_{10}H_{20}O_2$ (M^+ − 18) 154.1358, found 154.1349.

(2*R*,3*S*,4*R*)-(−)-2,4-Dimethyl-1-[(triisopropylsilyl)oxy]-7-octen-3-ol and (2*S*,3*R*,4*R*)-2,4-Dimethyl-1-[(triisopropylsilyl)oxy]-7-octen-3-ol. To a stirred solution of preceding 2:1 mixture of 1,3-diols (3.04 g, 17.7 mmol) and imidazole (2.5 g, 37.1 mmol) in dimethylformamide (30 mL) was added, in one portion, triisopropylsilyl chloride (3.60 g, 18.6 mmol). The resulting homogenous solution was stirred at room temperature for 8 h. The reaction mixture was diluted with ether (75 mL), washed with H_2O (75 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography using 20% dichloromethane–hexane afforded the 2*R*,3*S* hydroxy silyl ether (2.13 g, 37%) and its 2*S*,3*R* diastereomer (1.18 g, 20%). 2*R*,3*S* diastereomer: R_f 0.68 (60% dichloromethane–hexane); $[\alpha]_D$ −29.45° (*c* 7.5, CH_2Cl_2); IR (film) 3510, 3070, 2950, 2890, 1630, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87–5.77 (m, 1 H), 5.00 (d, *J* = 17.3 Hz, 1 H), 4.92 (d, *J* = 10.1 Hz, 1 H), 3.96 (s, 1 H), 3.85 (dd, *J* = 9.8, 2.2 Hz, 1 H), 3.68 (dd, *J* = 9.1, 8.9 Hz, 1 H), 3.46 (d, *J* = 8.3 Hz, 1 H), 2.14–2.05 (m, 2 H), 1.85–1.83 (m, 1 H), 1.60–1.36 (m, 3 H), 1.17–0.99 (m, 21 H), 0.89 (d, *J* = 6.2 Hz, 3 H), 0.76 (d, *J* = 0.7 Hz, 3 H); MS (EI) 285 (M^+ − 43). Anal. Calcd for $C_{19}H_{40}O_2Si$: C, 69.47; H, 12.27. Found: C, 69.72; H, 12.05.

2*S*,3*R* diastereomer: R_f 0.60 (60% dichloromethane–hexane); IR (film) 3500, 3170, 2940, 2880, 1630, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88–5.78 (m, 1 H), 5.04 (d, *J* = 17.1 Hz, 1 H), 4.95 (d, *J* = 10.1 Hz, 1 H), 3.92–3.85 (t, *J* = 3.6 Hz, 2 H), 3.68 (t, *J* = 7.4 Hz, 1 H), 3.34–3.32 (m, 1 H), 2.23–2.17 (m, 1 H), 2.02–1.95 (m, 1 H), 1.93–1.84 (m, 1 H), 1.71–1.60 (m, 3 H), 1.22–1.06 (m, 21 H), 0.96 (m, 21 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H); MS (EI) 285 (M^+ − 43).

(*R*)-(−)-Methyl 3-(Methoxymethoxy)-2-methylpropionate (34). To a solution of 10.0 g (0.084 mol) of (*R*)-(−)-methyl 2-methyl-3-hydroxypropionate (**33**) in dichloromethane (200 mL) was added diisopropylamine (30 mL, 0.169 mol) followed by chloromethyl methyl ether (9.6 mL, 0.127 mol). The solution was stirred at room temperature for 16 h. The resulting orange solution was diluted with ether (300 mL), washed with 10% aqueous HCl (2 × 100 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the desired product **34** (13.7 g, 99%) as a colorless liquid that was used without further purification: $[a]_D$ −13.97° (*c* 3.16, $CHCl_3$); IR (neat) 2940, 2870, 1750, 1460, 1440, 1210, 1030, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, 2 H), 3.67 (s, 3 H), 3.57–3.40 (m, 2 H), 2.75 (m, 1 H), 1.16 (d, *J* = 7.3 Hz, 3 H).

(*S*)-(−)-3-(Methoxymethoxy)-2-methylpropanol (35). To a suspension of lithium aluminum hydride (6.42 g, 0.169 mol) in anhydrous ether (300 mL) at 0 °C was added dropwise a solution of protected ester **34** (13.7 g, 0.083 mol) in ether (100 mL) over ca. 30 min. When the addition was completed, the reaction mixture was allowed to warm to room temperature and stir for 36 h. The reaction was quenched by slow addition of $Na_2SO_4 \cdot 10H_2O$ until the evolution of hydrogen stopped. The mixture was then filtered through Celite, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The resulting liquid was distilled under vacuum to provide the desired alcohol **35** (10.15 g, 89%) as a colorless liquid: bp 53–55 °C (0.18 mmHg); $[\alpha]_D$ −12.2° (*c* 2.66, $CHCl_3$); IR (neat) 3440, 2960, 2930, 2880, 1450, 1380, 1150, 1100, 1050, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2 H), 3.58–3.42 (m, 4 H), 3.34 (s, 3 H), 2.31 (br s, 1 H), 1.98 (m, 1 H), 0.88 (d, *J* = 7.0 Hz, 3 H).

(*R*)-(−)-3-(Methoxymethoxy)-2-methylpropanal (32). To a solution of freshly distilled oxalyl chloride (0.527 g, 4.15 mmol) in dry dichloromethane (25 mL) at −78 °C was added dimethyl sulfoxide (0.708 g, 9.06 mmol) dropwise over 3 min. The resulting mixture was stirred at −78 °C for 10 min, and a solution of the alcohol **35** (0.506 g, 3.77 mmol) in dichloromethane (2 mL) was added over ca. 2 min. The reaction was stirred at −78 °C for 30 min. Triethylamine (2.6 mL, 18.87 mmol) was then added, and the solution was warmed to 0 °C and stirred at that temperature for 15 min. The organic layer was washed with H_2O (2 × 5 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and used directly in the next reaction. The optical purity of **32** was checked by reducing an aliquot with lithium aluminum hydride in ether followed by Mosher ester formation. A sample of aldehyde **32** for spectroscopic analysis was obtained by carefully evaporating the solvent under reduced pressure (water bath ~25 °C). Aldehyde **32**, thus obtained, was shown to be ≥95% pure by ^1H NMR: $[\alpha]_D$ −12.6° (*c* 2.00, $CHCl_3$); IR (neat) 2940, 2895, 1730, 1050, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.2 Hz, 1 H), 4.59 (s, 2 H), 3.72 (d, *J* = 5.7 Hz, 2 H), 3.32 (s, 3 H), 2.62 (m, 1 H), 1.12 (d, *J* = 7.2 Hz, 3 H).

(2*R*,4*R*,3*S*)-(+)-1-(Methoxymethoxy)-2,4-dimethylhex-5-en-3-ol (36). A mixture of magnesium bromide etherate (5.24 g, 20.28 mmol) and aldehyde **32** (1.34 g, 10.14 mmol) in dichloromethane (50 mL) was cooled to −35 °C. A solution of tri-*n*-butylcrotylstannane (4.90 g, 14.19

mmol) in dichloromethane (50 mL) was added dropwise over ca. 15 min. The resulting solution was stirred at −30 °C for 2 h and overnight at room temperature. The mixture was then diluted with ether (250 mL), washed with H_2O (2 × 125 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow liquid. Chromatography using 15% ethyl acetate–hexanes as eluent afforded the alcohols **36**, **69**, and **70** (1.68 g, 88%) as a colorless liquid containing a mixture of diastereomers (6.7:1 **36**–(**69**+**70**)) homogeneous by TLC. Major isomer **36**: R_f 0.36 (20% ethyl acetate–hexanes); $[\alpha]_D$ +3.1° (*c* 1.49, $CHCl_3$) (mixture); IR (neat) 3500, 3060, 2960, 2920, 2860, 1640, 1450, 1140, 1100, 1040, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1 H), 5.08–5.01 (m, 2 H), 4.59 (s, 2 H), 3.69 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.55 (dd, *J* = 9.5, 5.5 Hz, 1 H), 3.40–3.33 (m, 1 H), 3.35 (s on m, 3 H), 2.70 (d, *J* = 5.8 Hz, 1 H), 2.38 (m, 1 H), 1.90 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H).

(2*R*,4*R*,3*S*)-1-(Methoxymethoxy)-2,4-dimethyl-3-[(*tert*-butyldimethylsilyl)oxy]hex-5-ene (37). To a solution of alcohol **36** (2.92 g, 15.5 mmol) in dichloromethane (25 mL) at 0 °C was added triethylamine (6.5 mL, 46.5 mmol) followed by *tert*-butyldimethylsilyl triflate (4.6 mL, 20.0 mmol). The yellow solution was stirred at 0 °C for 1 h. The resulting orange mixture was then poured into H_2O (10 mL) and diluted with ether (50 mL). The layers were separated, and the organic layer was washed with H_2O (15 mL) and saturated aqueous NaCl (15 mL), dried over $MgSO_4$, evaporated under reduced pressure to give an orange residue. Chromatography using 5% ethyl acetate–hexanes gave the protected alcohol **37** (4.15 g, 88%) as a colorless liquid: R_f 0.52 (10% ethyl acetate–hexanes); IR (neat) 3060, 2960, 2920, 2880, 1630, 1460, 1260, 1150, 1110, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 1 H), 4.96 (m, 2 H), 4.57 (s, 2 H), 3.68 (m, 1 H), 3.49 (m, 1 H), 3.32 (s, 3 H), 3.27 (m, 1 H), 2.38 (m, 1 H), 1.95 (m, 1 H), 0.95 (m, 6 H), 0.85 (s, 9 H), 0.03 (s, 6 H). Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.50; H, 11.23. Found: C, 63.73; H, 11.37.

(3*R*,5*R*,4*S*)-(+)-6-(Methoxymethoxy)-3,5-dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]hexan-1-ol (38). To a solution of alkene **37** (3.58 g, 11.8 mmol) in tetrahydrofuran (10 mL) at 0 °C was added a solution of borane–tetrahydrofuran complex (1.0 M, 24 mL, 24.0 mmol). The clear solution was warmed to room temperature (ca. 5 min) and stirred for 10 h. The reaction was then cooled to 0 °C, and excess borane was quenched by slow addition of methanol until the evolution of hydrogen had completely stopped. The resulting mixture was then cooled to −20 °C, and aqueous sodium hydroxide (2.5 M, 2 mL) was added dropwise followed by hydrogen peroxide (9.8 M, 2 mL). The cloudy solution was heated under reflux for 1 h. The cooled mixture was then diluted with ether (100 mL), washed with H_2O (2 × 50 mL) and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product as a colorless liquid that was purified by chromatography using 20% ethyl acetate–hexanes to afford the desired alcohol **38** (3.07 g, 81%) as a colorless liquid: R_f 0.34 (30% ethyl acetate–hexanes); $[\alpha]_D$ +5.5° (*c* 1.55, $CHCl_3$); IR (neat) 3440, 2980, 2880, 1460, 1380, 1260, 1150, 1100, 1050, 840, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, 2 H), 3.62 (m, 4 H), 3.69–3.48 (m, 4 H), 3.30 (m, 1 H), 1.94 (m, 1 H), 1.80–1.60 (m, 4 H), 1.42 (m, 1 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.87 (m, 12 H), 0.03 (s, 6 H). Anal. Calcd for $C_{16}H_{36}O_4Si$: C, 59.99; H, 11.33. Found: C, 59.96; H, 11.33.

(2*R*,4*R*,3*S*)-6-(Methoxymethoxy)-2,4-dimethyl-3-[(*tert*-butyldimethylsilyl)oxy]hexylbenzenesulfonate. To a solution of alcohol **38** (2.40 g, 7.49 mmol) in dichloromethane (20 mL) at room temperature was added pyridine (2.4 mL, 30.0 mmol) followed by benzenesulfonyl chloride (1.15 mL, 8.99 mmol). The clear solution was stirred at room temperature overnight (10 h), after which TLC analysis showed complete consumption of starting material. The reaction mixture was diluted with ether (100 mL), washed with H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the colorless oily benzenesulfonate (3.39 g, 98%), which was used directly in the next step without further purification: IR (neat) 2960, 2840, 1450, 1375, 1190, 1050, 840, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87–7.52 (m, 5 H), 4.57 (s, 2 H), 4.07 (m, 2 H), 3.58 (m, 1 H), 3.40 (m, 1 H), 3.33 (s, 3 H), 3.25 (m, 1 H), 1.88–1.63 (m, 3 H), 1.50 (m, 1 H), 0.89 (d, 3 H), 0.87 (s, 9 H), 0.78 (d, 3 H), 0.02 (s, 3 H), −0.02 (s, 3 H).

(4*R*,6*R*,5*S*)-(+)-7-(Methoxymethoxy)-4,6-dimethyl-5-[(*tert*-butyldimethylsilyl)oxy]heptanenitrile. To a solution of the preceding benzenesulfonate (3.39 g, 7.36 mmol) in dimethyl sulfoxide (25 mL) was added triethylamine (12 mL) followed by potassium cyanide (1.44 g, 22.1 mmol). The mixture was heated at 55 °C, and after 6 h TLC analysis showed complete consumption of starting material. The solution was then cooled to room temperature, diluted with ether (120 mL), washed successively with H_2O (3 × 50 mL) and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography using 10% ethyl acetate–hexanes to give the title nitrile (1.75 g, 71%, 2 steps from **38**) as a colorless liquid: R_f 0.25 (10% ethyl acetate–hexanes); $[\alpha]_D$ +2.4° (*c* 1.85, $CHCl_3$); IR (neat) 2940, 2920, 2220, 1450, 1250, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2 H), 3.58 (m, 1 H), 3.50 (m, 1 H), 3.33 (s, 3 H), 3.31 (m, 1 H), 2.35 (m, 2 H), 1.87 (m, 1 H), 1.73 (m, 2 H), 1.51 (m, 1 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.90 (d, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H). Anal. Calcd for $C_{17}H_{35}NO_3Si$: C, 61.99; H, 10.71. Found: C, 62.16; H, 10.73.

(4*R*,6*R*,5*S*)-(−)-7-(Methoxymethoxy)-4,6-dimethyl-5-hydroxyheptanenitrile (39). To the preceding nitrile (1.05 g, 3.17 mmol) was added a solution of tetra-*n*-butylammonium fluoride in THF (1.0 M, 9.5 mL, 9.5 mmol). The resulting orange solution was stirred at room temperature for 21 h. The reaction mixture was then diluted with ether (50 mL), and the organic phase was washed successively with H_2O (2 × 25 mL) and saturated aqueous NaCl (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 50% ethyl acetate–hexanes to afford the desired hydroxy nitrile **39** (509 mg, 75%) as a colorless liquid: R_f 0.31 (50% ethyl acetate–hexanes); $[\alpha]_D$ −35° (*c* 1.97, $CHCl_3$); IR (neat) 3500, 2980–2880, 2220, 1450, 1150, 1100, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 2 H), 3.66 (m, 1 H), 3.51 (m, 1 H), 3.41 (m, 1 H), 3.36 (s, 3 H), 2.39 (m, 2 H), 1.90 (m, 1 H), 1.79 (m, 1 H), 1.66 (m, 1 H), 0.89 (d, *J* = 6.3 Hz, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H); MS (EI) 184 (M^+ − 31, 1), 112 (59), 101 (49).

[3*R*,2*S*-[1*R*]]-3-Methyl-2-[1-methyl-2-(methoxymethoxy)ethyl]-6-(*R*)-hydroxytetrahydropyran and [3*R*,2*S*-[1*R*]]-3-Methyl-2-[1-methyl-2-(methoxymethoxy)ethyl]-6(*S*)-hydroxytetrahydropyran (40). To a solution of hydroxy nitrile **39** (2.83 g, 13.1 mmol) in THF (50 mL) at −78 °C was added dropwise diisobutylaluminum hydride (1.0 M in THF, 39.4 mL, 39.4 mmol). When the addition was completed, the clear solution was warmed to 0 °C and stirred at that temperature for 6 h. Excess diisobutylaluminum hydride was quenched by slow addition of H_2O. The resulting aluminate was hydrolyzed using 2 N aqueous HCl (50 mL), and the resulting clear solution was stirred at room temperature for 3 h to ensure complete hydrolysis of the aluminum salts. The aqueous layer was saturated with NaCl and extracted with ether (2 × 50 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 30% ethyl acetate–hexanes as eluent to give the desired lactols **40** (2.53 g, 88%) as a mixture of anomers (1.4:1 α:β): R_f 0.50 (5% ethyl acetate–hexanes); IR (neat) 3450, 2920, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (m, 0.3 H), 4.63–4.56 (m, 2.5 H), 3.80 (dd, *J* = 10.4, 1.8 Hz, 0.4 H), 3.66–3.60 (m, 1 H), 3.54–3.49 (m, 0.7 H), 3.46–3.41 (m, 0.7 H), 3.33–3.25 (m, 3.4 H), 2.10–1.35 (m, 7 H), 0.95–0.87 (m, 6 H).

[3*R*,2*S*-[1*R*]]-3-Methyl-2-[1-methyl-2-(methoxymethoxy)ethyl]-6-(*R*)-hydroxytetrahydropyran and [3*R*,2*S*-[1*R*]]-3-Methyl-2-[1-methyl-2-(methoxymethoxy)ethyl]-6(*S*)-hydroxytetrahydropyran (40). To a solution of alcohol **36** (1.40 g, 7.44 mmol) in tetrahydrofuran (4 mL) at 0 °C was added borane–tetrahydropyran complex (1.0 M in THF, 7.4 mL, 7.4 mmol). The clear solution was stirred at room temperature overnight (14 h). The solution was then recooled to 0 °C, and methanol (0.30 mL, 7.44 mmol) was added dropwise. The ice bath was removed, and the resulting mixture was stirred at room temperature for 2 h. The resulting clear solution was then added via a syringe to a solution of α-lithio(phenylthio)methoxymethane (prepared by addition of *n*-butyllithium (1.60 M in hexanes, 14.0 mL, 22.4 mmol) to a solution of (phenylthio)methoxymethane (3.43 g, 22.3 mmol) in tetrahydrofuran (20 mL) at −78 °C followed by warming to −40 °C and stirring at that temperature for 1 h) in tetrahydrofuran at −40 °C. The resulting yellow solution was warmed to −10 °C over 2 h. Solid mercuric chloride (6.06 g, 22.3 mmol) was added to the solution at −10 °C, and the cooling bath was removed. The resulting black mixture was allowed to stir at room temperature for 3 h. The reaction mixture was then cooled to 0 °C, and a solution of phosphate buffer (pH = 7, 30 mL) was added followed by hydrogen peroxide (9.8 M, 9 mL). The oxidation appeared complete after 3 h of stirring at room temperature. The mixture was poured in ether (150 mL) and the organic phase subsequently washed with H_2O (2 × 50 mL). The combined aqueous layers were saturated with NaCl and extracted with ether (2 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), and hydrogen sulfide was bubbled gently through the solution for 5 min to precipitate the mercuric salts. After an additional 30 min, the mixture was filtrated through Celite. The filtrate was then dried over $MgSO_4$ and evaporated under reduced pressure to give an orange residue that was purified by chromatography using 30% ethyl acetate–hexanes as eluent to afford the desired lactols **40** (844 mg, 52%) identical with that obtained previously: R_f 0.50 (5% ethyl acetate–hexanes); IR (neat) 3450, 2920, 1050 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (m, 0.3 H), 4.63–4.56 (m, 2.5 H), 3.80 (dd, J = 10.4, 1.8 Hz, 0.4 H), 3.66–3.60 (m, 1 H), 3.54–3.49 (m, 0.7 H), 3.46–3.41 (m, 0.7 H), 3.33–3.25 (m, 3.4 H), 2.10–1.35 (m, 7 H), 0.95–0.87 (m, 6 H).

[3*R*,2*S*-[1*R*]]-(+)-3-Methyl-2-[1-methyl-2-(methoxymethoxy)ethyl]-3,4-dihydro-2*H*-pyran (41). To a solution of the lactols **40** (1.181 g, 5.41 mmol) in dichloromethane (10 mL) at 0 °C was added triethylamine (2.3 mL, 16.2 mmol) followed by methanesulfonyl chloride (0.54 mL, 7.03 mmol). The mixture was allowed to warm to room temperature (ca. 1 h) and stir overnight (13 h). The resulting yellow solution was diluted with ether (50 mL), and the phases were successively washed with H_2O (2 × 20 mL) and saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 5% ethyl acetate–hexanes as eluent to afford the desired dihydropyran **41** (691 mg, 64%) as a colorless liquid: R_f 0.24 (5% ethyl acetate–hexanes); $[\alpha]_D$ +68° (*c* 1.20, $CHCl_3$); IR (neat) 3040, 2980, 2940, 1650, 1240, 1150, 1110, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (m, 1 H), 4.61 (s, 2 H), 4.55 (m, 1 H), 3.66 (dd, J = 9.1, 2.9 Hz, 1 H), 3.53 (m, 2 H), 3.33 (s, 3 H), 2.30 (m, 1 H), 2.03 (m, 1 H), 1.86 (m, 1 H), 1.65 (m, 1 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 7.0 Hz, 3 H); HRMS calcd for $C_9H_{15}O_2$ (M^+ – 31) 169.1228, found 169.1267.

3-[(*tert*-Butyldiphenylsilyl)oxy]-1-butene (44). A solution of 2.1 g (29.1 mmol) of 3-buten-1-ol (**43**), imidazole (5.7 g, 83.7 mmol), and *tert*-butylchlorodiphenylsilane (9.1 g, 33.1 mmol) in dimethylformamide (50 mL) was stirred at room temperature for 17 h. The solution was then diluted with ether (150 mL), washed with H_2O (3 × 50 mL) and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 5% ethyl acetate–hexanes to afford the desired protected alcohol **44** (9.02 g, 99%) as a colorless liquid: R_f 0.71 (10% ethyl acetate–hexanes); IR (neat) 3080, 2960, 2920, 2860, 1640, 1580, 1470, 1430, 1110, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 4 H), 7.37 (m, 6 H), 5.88–5.74 (m, 1 H), 5.06–4.98 (m, 2 H), 3.68 (t, J = 6.7 Hz, 2 H), 2.29 (m, 2 H), 1.02 (s, 9 H); MS (EI) 269 (3.6, M^+ – 41), 253 (100), 225 (38), 223 (60), 183 (32), 175 (35), 145 (31), 105 (35). Anal. Calcd for $C_{20}H_{26}OSi$: C, 77.29; H, 8.37. Found: C, 77.20; H, 8.44.

3-[(*tert*-Butyldiphenylsilyl)oxy)]propanal (45). Ozone was bubbled through a solution of protected alcohol **44** (0.514 g, 1.66 mmol) in methylene chloride–methanol (10 mL, 7:3) at –78 °C until the color of the solution remained light blue. Dimethyl sulfide (5 mL) was then added, and the clear solution was warmed to room temperature. Decomposition of the ozonide was monitored by TLC and was complete after 6 h. The mixture was then diluted with ether (40 mL), washed with H_2O (3 × 20 mL) and saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to afford the desired aldehyde **45** as a colorless liquid (0.513 g, 100%), pure enough to be used directly in the next step. An analytical sample was purified by chromatography using 10% ethyl acetate–hexanes as eluent: R_f 0.35 (10% ethyl acetate–hexanes); IR (neat) 3060, 2940, 2910, 2840, 1720, 1420, 1110, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.10 (t, J = 2.1 Hz, 1 H), 7.64 (m, 4 H), 7.39 (m, 6 H), 4.00 (t, J = 6.0 Hz, 2 H), 2.58 (dt, J = 6.0, 2.1 Hz, 2 H), 1.02 (s, 9 H); MS (EI) 255 (25, M^+ – 57), 225 (30), 199 (100), 183 (23); HRMS calcd for $C_{15}H_{16}O_2Si$ 255.0841, found 255.0850.

(3*R*,4*R*)-(+)-3-Methyl-4-hydroxy-6-[(*tert*-butyldiphenylsilyl)oxy]-hex-1-ene (46). To a suspension of freshly sublimed potassium *tert*-butoxide (1.96 g, 17.5 mmol) in tetrahydrofuran (30 mL) at –78 °C was added a solution of *cis*-2-butene (2 mL) in tetrahydrofuran (5 mL). *n*-Butyllithium (1.60 M in hexanes, 10.9 mL, 17.5 mmol) was added, and the yellow mixture was stirred at –78 °C for 5 min and at –45 °C for 15 min. The resulting orange solution was recooled to –78 °C, and a solution of diisopinocampheylmethoxyborane (0.50 M in ether, 41.9 mL, 21.0 mmol) derived from (+)-α-pinene was added dropwise over ca. 15 min. The resulting colorless solution was stirred at –78 °C for 30 min. Boron trifluoride etherate (2.9 mL, 23.2 mmol) was added dropwise followed immediately by the addition of a solution of the aldehyde **45** (6.00 g, 19.2 mmol) in tetrahydrofuran (10 mL) over ca. 5 min. The resulting solution was stirred at –78 °C for 4 h. The reaction was then quenched by addition of 2.5 N aqueous NaOH (22 mL) followed by 30% aqueous H_2O_2 (6 mL). The acetone–dry ice bath was removed, and the mixture was heated at 45 °C for 45 min. The cloudy solution was cooled to room temperature, diluted with ether (150 mL), washed with H_2O (3 × 50 mL) and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give a colorless liquid. Chromatography using 7% ethyl acetate–hexanes as eluent produced the desired alcohol **46** as a colorless liquid (5.12 g, 80%): R_f 0.35 (10% ethyl acetate–hexanes); $[\alpha]_D$ +3.3° (*c* 1.06, $CHCl_3$); IR (neat) 3500, 3060, 2960, 2840, 1640, 1580, 1470, 1420, 1110, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 4 H), 7.39 (m, 6 H), 5.76 (m, 1 H), 5.02 (m, 2 H), 3.85 (m, 2 H), 3.72 (m, 1 H), 3.18 (d, J = 2.8 Hz, 1 H), 2.26 (m, 1 H), 1.66 (m 2 H), 1.05–1.03 (m, 12 H); MS (EI) 311 (M^+ – 57, 2.1), 255 (17.2), 225 (21.6), 199 (86.1), 183 (21.6), 95 (100).

(3*R*,4*R*)-(+)-3-Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]hex-1-ene (47). To a solution of alcohol **46** (0.507 g, 1.44 mmol) in methylene chloride (30 mL) at 0 °C was added triethylamine (0.40 mL, 2.88 mmol) followed by *tert*-butyldimethylsilyl triflate (0.40 mL, 1.73 mmol). The resulting mixture was stirred at room temperature for 2 h, followed by dilution with ether (25 mL), washing with H_2O (2 × 10 mL) and saturated aqueous NaCl (10 mL), and drying over $MgSO_4$. After concentration under reduced pressure, the light brown residue was purified by chromatography using 3% ethyl acetate–hexanes as eluent to afford the desired protected alcohol **47** as a colorless liquid (0.548 g, 82%): $[\alpha]_D$ +21.0° (*c* 1.01, $CHCl_3$); IR (neat) 3160, 2940, 2860, 1260, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 4 H), 7.36 (m, 6 H), 5.84 (m, 1 H), 4.98–4.91 (m, 2 H), 3.76 (m, 1 H), 3.68 (t, J = 6.5 Hz, 2 H), 2.27 (m, 1 H), 1.65–1.52 (m, 2 H), 1.02 (s, 9 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.82 (s, 9 H), 0.00 (s, 3 H), –0.02 (s, 3 H). Anal. Calcd for $C_{29}H_{46}O_2Si_2$: C, 72.19; H, 9.61. Found: C, 71.78; H, 9.61.

(3*R*,4*R*)-(+)-3-Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-(*tert*-butyldiphenylsiloxy)hexan-1-ol (48). To a solution of olefin **47** (448 mg, 0.961 mmol) in tetrahydrofuran (0.2 mL) at 0 °C was added a solution of borane–tetrahydrofuran (1.0 M, 1.4 mL, 1.4 mmol). The mixture was warmed to room temperature and stirred for 4 h. The excess borane was quenched by addition of methanol to the reaction mixture at 0 °C until the evolution of hydrogen had ceased. The intermediate organoborane was then oxidized by successive addition of 2.5 N aqueous NaOH (2.5 mL, 0.6 mL) and H_2O_2 (9.8 M, 0.15 mL) to the mixture at –20 °C. After being stirred at room temperature for 45 min, the cloudy solution was diluted with ether (20 mL), washed with H_2O (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography using ethyl acetate–hexanes (1:9) as eluent to give the desired alcohol **48** (390 mg, 81%) as a colorless liquid: R_f 0.42 (20% ethyl acetate–hexanes); $[\alpha]_D$ +12.5° (*c* 1.20, $CHCl_3$); IR ($CDCl_3$) 3400, 3040, 2940, 2840, 1110, 1080, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 4 H), 7.35 (m, 6 H), 3.84 (m, 1 H), 3.72–3.58 (m, 4 H), 2.68 (br s, 1 H), 1.71 (m, 2 H), 1.63 (m, 2 H), 1.36 (m, 1 H), 1.04 (s, 9 H), 0.85 (m, 12 H), 0.05 (s, 3 H), 0.01 (s, 3 H). Anal. Calcd for $C_{29}H_{48}O_3Si_2$: C, 69.59; H, 9.67. Found: C, 69.26; H, 9.63.

(3*R*,4*R*)-(+)-1-Bromo-3-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]hexane (49). To a solution of alcohol **48** (600 mg, 1.20 mmol) and carbon tetrabromide (795 mg, 2.40 mmol) in ether (10 mL) was added triphenylphosphine (629 mg, 2.40 mmol). The resulting mixture was stirred at room temperature for 6 h. Hexanes (100 mL) were added, and the resulting mixture was filtered through Celite. The filtrate was evaporated under reduced pressure, and the residue was purified by chromatography using 2% ethyl acetate–hexanes as eluent to give the desired bromide **49** (621 mg, 92%) as a colorless liquid: R_f 0.41 (3% ethyl acetate–hexanes); $[\alpha]_D$ +14.2° (*c* 2.04, $CHCl_3$); IR (neat) 3060, 2960, 2840, 1470, 1260, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4 H), 7.41 (m, 6 H), 3.82 (m, 1 H), 3.70 (t, J = 6.4 Hz, 2 H), 3.51–3.38 (m, 2 H), 2.00 (m, 1 H), 1.78 (m, 1 H), 1.58 (m, 3 H), 1.06 (s, 9 H), 0.86 (s on d, 9 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H); HRMS calcd for $C_{25}H_{38}O_2Si_2Br$ (M^+ – 37) 506.1450, found 506.1421. Anal. Calcd for $C_{29}H_{47}Si_2O_2Br$: C, 61.82; H, 8.41. Found: C, 62.40; H, 8.50.

(3*R*,4*R*)-3-Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]hexane-1-methanesulfonate (50). To a solution of alcohol **48** (183 mg, 0.365 mmol) in dry dichloromethane (1.5 mL) at 0 °C was added triethylamine (0.2 mL, 1.45 mmol) followed by methanesulfonyl chloride (56 mL, 0.730 mmol). The clear yellow solution was warmed to room temperature and stirred for 2 h. The mixture was then diluted with ether (10 mL), washed with H_2O (2 × 5 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give mesylate **50** as a light yellow liquid, which was used in the next step without further purification: R_f 0.44 (20% ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 4 H), 7.36 (m, 6 H), 4.24 (m, 2 H), 3.79 (m, 1 H), 3.68 (t, J = 6.7 Hz, 2 H), 2.94 (s, 3 H), 1.96 (m, 1 H), 1.72 (m, 1 H), 1.62 (m, 1 H), 1.55–1.46 (m, 2 H), 1.03 (s, 9 H), 0.83 (m, 12 H), 0.01 (s, 3 H), –0.01 (s, 3 H).

(3*R*,4*R*)-(+)-1-Iodo-3-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]hexane (51). To a solution of crude mesylate **50** in acetone (3 mL) was added sodium iodide (274 mg, 1.83 mmol) with protection from light. The light yellow mixture was stirred at room temperature for 26 h. The reaction mixture was then diluted with ether (10 mL), washed successively with H_2O (2 × 5 mL), 5% aqueous $NaHSO_3$ (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give a colorless liquid. Chromatography of the liquid residue using 5% ethyl acetate–hexanes as eluent gave the desired colorless iodide

51 (166 mg, 74%, 2 steps from **48**): R_f 0.48 (5% ethyl acetate–hexanes); $[\alpha]_D$ +20.4° (*c* 1.10, $CHCl_3$); IR (neat) 3080, 2980, 2860, 1470, 1430, 1260, 1110, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (m, 4 H), 7.36 (m, 6 H), 3.78 (m, 1 H), 3.67 (t, *J* = 6.4 Hz, 2 H), 3.26 (m, 1 H), 3.12 (m, 1 H), 2.00 (m, 1 H), 1.68–1.52 (m, 4 H), 1.03 (s, 9 H), 0.83 (s, 9 H), 0.78 (d, *J* = 6.6 Hz, 3 H), 0.02 (s, 3 H), –0.01 (s, 3 H). Anal. Calcd for $C_{29}H_{47}O_2Si_2I$: C, 57.01; H, 7.76. Found: C, 57.59; H, 7.98.

[3*R*,2*S*-[1*R*]]-(+)-3-Methyl-2-[1-methyl-2-(methoxymethoxy)ethyl]-6-tri-*n*-butylstannyl-3,4-dihydro-2*H*-pyran (54). To a solution of dihydropyran **41** (674 mg, 3.37 mmol) in tetrahydrofuran (10 mL) at –78 °C was added freshly sublimed potassium *tert*-butoxide (1.13 g, 10.1 mmol) followed by *n*-butyllithium (1.60 M in hexane, 6.3 mL, 10.1 mmol). The orange mixture was stirred at –78 °C for 1 h. Tributyltin chloride (2.9 mL, 10.8 mmol) was then added rapidly, and after the addition, the acetone–dry ice bath was removed and the mixture was stirred for an additional 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with ether (50 mL), and the organic layer was washed with H_2O (2 × 20 mL) and saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The organotin byproducts were carefully evaporated (120 °C (0.2 mmHg)), and the residue after the distillation was purified by chromatography using 5% ethyl acetate–hexanes as eluent to give the desired vinylstannane **54** (1.64 g, 99%) as a colorless liquid: R_f (5% ethyl acetate–hexanes) 0.33; $[\alpha]_D$ +31° (*c* 1.31, $CHCl_3$); IR (neat) 2960, 1600, 1450, 1375, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62–4.57 (m, 3 H), 3.70 (dd, *J* = 9.0, 2.9 Hz, 1 H), 3.45 (m, 2 H), 3.33 (s, 3 H), 2.33 (m, 1 H), 1.99 (m, 1 H), 1.79 (m, 1 H), 1.62 (m, 1 H), 1.54–1.40 (m, 6 H), 1.34–1.22 (m, 6 H), 1.03–0.76 (m, 21 H); HRMS calcd for $C_{19}H_{37}O_3Sn$ (M^+ – 57) 433.1765, found 433.1770.

[2*S*-[1*R*]-3*R*,6-[3*R*,4*R*]]-(+)-2-[1-Methyl-2-(methoxymethoxy)ethyl]-3-methyl-6-[3-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]-1-hexyl]-3,4-dihydro-2*H*-pyran (55). To a solution of vinylstannane **54** (164 mg, 0.335 mmol) in tetrahydrofuran (1.0 mL) at –78 °C was added *n*-butyllithium (1.60 M in hexanes, 0.21 mL, 0.335 mmol). The resulting yellow solution was stirred at –78 °C for 10 min and at 0 °C for an additional 10 min. A solution of bromide **49** (0.226 g, 0.402 mmol) in hexamethylphosphoramide (1.0 mL) was added via a syringe over ca. 15 s. The resulting brown solution was stirred at 0 °C for 3 h and at room temperature overnight. The mixture was diluted with ether (15 mL) and washed successively with H_2O (3 × 5 mL), saturated aqueous $Cu(NO_3)_2$ (5 mL), saturated aqueous NH_4Cl (5 mL), and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 3% ethyl acetate–hexanes as eluent to provided the desired dihydropyran **55** (160 mg, 70%) as a colorless liquid: R_f 0.45 (5% ethyl acetate–hexanes); $[\alpha]_D$ +33.2° (*c* 0.56, $CHCl_3$); IR ($CDCl_3$) 2940, 2920, 2860, 2840, 1670, 1110, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4 H), 7.41 (m, 6 H), 4.64 (m, 2 H), 4.35 (d, *J* = 4.8 Hz, 1 H), 3.79 (m, 1 H), 3.73–3.67 (m, 3 H), 3.62–3.51 (m, 2 H), 3.37 (s, 3 H), 2.30 (m, 1 H), 2.02–1.88 (m, 4 H), 1.69–1.59 (m, 4 H), 1.49–1.45 (m, 1 H), 1.31–1.23 (m, 1 H), 1.07 (s, 9 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.86 (s on m, 9 H), 0.93–0.80 (m, 6 H), 0.04 (s, 3 H), 0.01 (s, 3 H).

[1*S*,3*S*-[1*R*],4*R*,1-[3*R*,4*R*],6*S*]-3-(1-Methyl-2-hydroxyethyl)-4-methyl-1-[3-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]hexyl]bicyclo[4.1.0]-2-oxyheptane and [1*R*,3*S*-[1*R*],4*R*,1-[3*R*,4*R*],6*R*]-3-(1-Methyl-2-hydroxyethyl)-4-methyl-1-[3-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]-hexyl]bicyclo[4.1.0]-2-oxyheptane (57). To a solution of dihydropyran **55** (49.1 mg, 0.0072 mmol) in ether (1.0 mL) at room temperature was added successively diethylzinc (1.0 M in hexanes, 0.36 mL, 0.359 mmol) and freshly distilled diiodomethane (60 μL, 0.744 mmol). The resulting cloudy mixture was stirred at room temperature temperature for 5 h. Ether (10 mL) was added followed by 2% aqueous HCl (5 mL). The organic layer was separated and washed with 2% aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and concentrated to give alcohols **57** (46.9 mg), which were used directly in the next step without further purification: R_f 0.55 (10% ethyl acetate–hexanes); IR ($CHCl_3$) 2960, 2860, 1450, 1110, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.41 (m, 6 H), 3.82 (m, 1 H), 3.72–3.56 (m, 4 H), 3.08 (m, 1 H), 1.95 (m, 1 H), 1.80–1.20 (m, 10 H), 1.06 (s, 9 H), 0.90–0.79 (m, 9 H), 0.86 (s, 9 H), 0.60 (m, 1 H), 0.53 (m, 1 H), 0.36 (m, 1 H), 0.04 (s, 3 H), 0.00 (s, 3 H).

(2*R*,3*R*,6*S*,8*S*,9*R*,11*R*,1*R*)-(+)-2-[[(2′-*tert*-Butyldiphenylsilyl)-oxy]ethyl]-8-(2-hydroxy-1-methylethyl)-3,9,11-trimethyl-1,7-dioxaspiro-[5.5]undecane (58). A solution of the crude cyclopropanes **57** (17.89 mg, 0.026 mmol) in benzene (0.5 mL) containing *p*-toluenesulfonic acid monohydrate (10.0 mg, 0.053 mmol) was stirred at 50–55 °C for 5 h. The resulting light brown solution was cooled to room temperature, diluted with ether (10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 10% ethyl acetate–hexanes, which afforded the desired spiroketal **58** (7.59 mg, 55% 2 steps from **55**) as a colorless oil: R_f 0.58 (20% ethyl acetate–hexanes); $[\alpha]_D$ +37.0° (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3460, 2960, 2920, 1450, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4 H), 7.38 (m, 6 H), 3.84–3.73 (m, 2 H), 3.68–3.64 (m, 1 H), 3.62–3.53 (m, 1 H), 3.45–3.33 (m, 2 H), 1.90–1.18 (m, 13 H), 1.08 (s, 9 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 6 H), 0.60 (d, *J* = 6.9 Hz, 3 H); MS (EI) 482 (M^+ – 56, 4), 481 (M^+ – 57, 11), 351 (12), 319 (15), 199 (86), 95 (100); HRMS calcd for $C_{29}H_{41}O_4Si$ 481.2774, found 481.2790.

(2*R*,3*R*,6*S*,8*S*,9*R*,1*R*)-(+)-2-[[(2′-*tert*-Butyldiphenylsilyl)oxy]-ethyl]-8-(2-hydroxy-1-methylethyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (56). To a solution of dihydropyran **55** (8.4 mg, 0.012 mmol) in benzene (300 μL) was added *p*-toluenesulfonic acid monohydrate (4.1 mg, 0.022 mmol). The solution was stirred at room temperature for 1 h and at 55 °C for 3 h. The light brown mixture was diluted with ether (10 mL), washed with saturated aqueous $NaHCO_3$ (2 × 3 mL) and saturated aqueous NaCl (3 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 7% ethyl acetate–hexanes to give the desired spirocyclic ketal **56** (3.35 mg, 52%) as a colorless liquid: IR ($CHCl_3$) 3480, 2920, 2820, 1450, 1110, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.35 (m, 6 H), 3.79–3.70 (m, 3 H), 3.53–3.35 (m, 3 H), 1.91–1.75 (m, 4 H), 1.64–1.49 (m, 4 H), 1.41–1.19 (m, 5 H), 1.03 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.58 (d, *J* = 7.0 Hz, 3 H); MS (EI) 467 (M^+ – 57, 11), 379 (17), 337 (22), 199 (100), 95 (87); HRMS calcd for $C_{28}H_{39}O_4Si$ 467.2618, found 467.2598.

Methyl 2-(Trifluoroacetamido)-5-[(*tert*-butyldimethylsilyl)oxy]-benzoate (60). To a solution of phenol **59** (10.0 g, 38.0 mmol) in dimethylformamide (100 mL) was added imidazole (5.17 g, 76.0 mmol) followed by *tert*-butylchlorodimethylsilane (6.3 g, 41.8 mmol), and the resulting solution was stirred at room temperature for 16 h. The solution was diluted with ether (150 mL) and washed with H_2O (2 × 50 mL), 10% aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the protected alcohol **60** (9.93 g, 70%) as a waxy white solid: mp 79–82 °C; IR (neat) 3220, 3160, 2940, 2840, 1710, 1700, 1600, 1520, 1240, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 9.1 Hz, 1 H), 7.50 (s, *J* = 2.9 Hz, 1 H), 7.07 (dd, *J* = 9.1, 2.9 Hz, 1 H), 3.94 (s, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H); MS (EI) 377 (M^+, 14.2), 320 (28), 288 (100); HRMS calcd for $C_{16}H_{22}F_3NO_4Si$ 377.1270, found 377.1232.

Methyl 2-(*N*-Methyltrifluoroacetamido)-5-[(*tert*-butyldimethylsilyl)-oxy]benzoate (61). To a solution of protected phenol **60** (2.0 g, 5.30 mmol) in acetone (50 mL) was added methyl iodide (10 mL, 159.0 mmol) followed by anhydrous potassium carbonate (3.7 g, 27 mmol). The resulting mixture was heated to 50 °C for 5 h after which TLC analysis showed complete consumption of starting material. The mixture was then cooled to room temperature and diluted with ether (75 mL), washed with H_2O (20 mL), and saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give *N*-methylamide **61** as a yellow oil (2.02 g, 98%) that was used without further purification. An analytical sample was purified by flash chromatography using 10% ethyl acetate–hexanes as eluent and gave the desired compound as a colorless oil: IR ($CDCl_3$) 2950, 2850, 1730, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.7 Hz, 1 H), 7.13 (d, *J* = 8.6 Hz, 1 H), 6.98 (dd, *J* = 8.6, 2.8 Hz, 1 H), 3.85 (s, 3 H), 3.26 (s, 3 H), 0.97 (s, 9 H), 0.22 (s, 6 H); MS (EI) 391 (M^+, 18), 334 (37), 302 (83), 113 (49), 99 (49); HRMS calcd for $C_{17}H_{24}F_3NO_4Si$ 391.1427, found 391.1412.

Methyl 3-Hydroxy-6-(*N*-methyltrifluoroacetamido)-2-nitrobenzoate (62) and Methyl 5-Hydroxy-2-(*N*-methyltrifluoroacetamido)-4-nitrobenzoate (63). To a solution of silyl ether **61** (221 mg, 6.57 mmol) in nitromethane (3 mL) was added concentrated hydrofluoric acid (1 mL) followed by concentrated nitric acid (1 mL, 16 mmol). The resulting solution was stirred at room temperature for 1.5 h. The orange solution was diluted with H_2O (10 mL) and ethyl acetate (10 mL). The organic layer was washed with H_2O (10 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The yellow oil, consisting mainly of a mixture of 2-nitro **62** and 4-nitro **63** regioisomers (105 mg, 70%) was purified by chromatography using 30% ethyl acetate–hexanes as eluent to give the desired 2-nitro **62** compound as a yellow oil that crystallized on standing (37 mg, 29%): mp 77.5–79 °C; R_f 0.54 (10% MeOH–$CHCl_3$); IR ($CHCl_3$) 3220, 3000, 1740, 1700, 1610, 1540, 1480, 1440, 1250, 1200, 1160 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.68 (d, *J* = 8.9 Hz, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 3.80 (s, 3 H), 3.23 (s, 3 H); MS (EI) 322 (M^+, 8), 304 (18), 262 (83), 148 (21), 110 (100); HRMS calcd for $C_{11}H_9F_3N_2O_6$ 322.0413, found 322.0365.

Methyl 3-Hydroxy-6-(*N*-methyltrifluoroacetamido)anthranilate (64). To a solution of nitrophenol **62** (172 mg, 0.537 mmol) in methanol (5 mL) was added a catalytic amount (20 mg) of 10% Pd–C. The mixture was stirred under an hydrogen atmosphere (balloon) for 16 h. Filtration through Celite followed by evaporation of the filtrate under reduced pressure gave aminophenyl **64** (156 mg, 100%) as an oil that crystallized on standing: mp 120–121 °C; IR ($CHCl_3$) 3400, 3250, 1690, 1270, 1160 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.15 (br s, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 6.42 (d, J = 8.0 Hz, 1 H), 6.10 (br s, 2 H), 3.76 (s, 3 H), 3.13 (s, 3 H); MS (EI) 292 (M^+, 37), 260 (21), 195 (33), 163 (66), 110 (31); HRMS calcd for $C_{11}H_{11}F_3N_2O_4$ 292.0671, found 292.0688.

(2*R*,3*R*,6*S*,8*S*,9*R*,11*R*,1*R*)-2-[[(2′-*tert*-Butyldiphenylsilyl)oxy]ethyl]-8-(1-methyl-2-carboxyethyl)-1,7-dioxaspiro[5.5]undecane (65). To a solution of alcohol **58** (50.4 mg, 0.094 mmol) in acetone (2 mL) at −25 °C was added Jones reagent (0.30 mL) (prepared from chromium trioxide (11.1 g) and concentrated sulfuric acid (9.2 mL) in H_2O (45 mL)). The cooling bath was allowed to warm to −5 °C over ca. 2 h. Excess oxidant was destroyed by addition of saturated aqueous $NaHSO_3$ (2 mL). The organic layer was diluted with ether (10 mL), washed with H_2O (2 × 3 mL) and saturated aqueous NaCl (3 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was filtered through a short column of silica gel using 10% ethyl acetate–hexanes followed by 50% ethyl acetate–hexanes as eluents. The filtrate obtained from the more polar eluent was evaporated under reduced pressure to give the desired carboxylic acid **65** (41.4 mg, 80%) that was employed without further purification in the next step: R_f 0.42 (20% ethyl acetate–hexanes); IR ($CHCl_3$) 2920, 2840, 1710, 1450, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.40 (m, 6 H), 3.87–3.65 (m, 3 H), 3.58 (dd, J = 9.5, 2.0 Hz, 1 H), 2.45 (m, 1 H), 1.98–1.20 (m, 12 H), 1.07 (s, 9 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.86 (m, 6 H).

(2*R*,3*R*,6*S*,8*S*,9*R*,11*R*,1*R*)-2-[[(2′-*tert*-Butyldiphenylsilyl)oxy]ethyl]-8-[1-methyl-2-oxo-(1*H*-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undecane (67). To a solution of acid **65** (27.15 mg, 0.049 mmol) in dichloromethane (0.5 mL) was added 2,2′-dipyridyl disulfide (43.3 mg, 0.196 mmol) followed by triphenylphosphine (51.5 mg, 0.196 mmol), and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with hexanes (5 mL) and filtered through Celite, and the organic layer was washed with 10% aqueous $NaHCO_3$ (2 × 2 mL) and saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. The crude residue was dissolved in toluene and cooled to −78 °C. An ca. 0.58 M solution of pyrryl magnesium chloride (1.5 mL, 0.87 mmol) (prepared by treatment of a solution of pyrrole (0.36 mL, 5.19 mmol) in toluene (5 mL) at −40 °C with methylmagnesium chloride (3.0 M in THF, 1.25 mL, 3.75 mmol) and warming to 0 °C for 10 min) was added dropwise over ca. 1 min. The clear solution was stirred at −78 °C for 90 min and then quenched by addition of saturated aqueous NH_4Cl (1 mL). The resulting mixture was warmed to room temperature, and the organic layer was diluted with ether (20 mL), washed with H_2O (2 × 5 mL), 10% aqueous $NaHCO_3$ (2 × 5 mL), and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 10% ethyl acetate–hexanes as eluent to give the desired ketopyrrole **67** (21.6 mg, 73%): R_f 0.38 (10% ethyl acetate–hexanes); $[\alpha]_D$ +52° (c 0.2, $CHCl_3$); IR ($CHCl_3$) 3440, 2920, 1630, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.15 (br s, 1 H), 7.72 (m, 4 H), 7.38 (m, 6 H), 6.89 (m, 1 H), 6.84 (m, 1 H), 6.19 (m, 1 H), 3.85 (m, 2 H), 3.55 (dd, J = 10.5, 2.1 Hz, 1 H), 3.31 (m, 1 H), 3.11 (m, 1 H), 1.71–1.11 (m, 11 H), 1.06 (s, 9 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.1 Hz, 3 H), 0.75 (d, J = 5.9 Hz, 3 H), 0.70 (d, J = 6.8 Hz, 3 H); MS (EI) 601 (M^+, 1), 545 (42), 544 (75), 199 (64), 94 (89); HRMS calcd for $C_{33}H_{42}NO_4Si$ 544.2883, found 544.2895.

(2*R*,3*R*,6*S*,8*S*,9*R*,11*R*,1′*R*)-2-(Hydroxyethyl)-8-[1′-methyl-2′-oxo-2′-(1*H*-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undecane. To protected ketopyrrole **67** (10.77 mg, 0.018 mmol) was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.5 mL, 0.5 mmol). The solution was stirred at room temperature for 2 h. The organic layer was diluted with ether and washed with H_2O (3 × 3 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography using 20% ethyl acetate–hexanes to afford the desired title alcohol (6.1 mg, 94%) as a colorless oil: R_f 0.36 (30% ethyl acetate–hexanes); $[\alpha]_D$ +123° (c 0.09, $CHCl_3$); IR ($CHCl_3$) 3430, 2910, 1630, 1400, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (br s, 1 H), 7.05 (m, 1 H), 7.03 (m, 1 H), 6.31 (dd, J = 5.1, 2.8 Hz, 1 H), 4.22 (m, 1 H), 3.99–3.92 (m, 2 H), 3.77–3.68 (m, 2 H), 3.30 (m, 1 H), 1.90–1.27 (m, 11 H), 1.07 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.8 Hz, 3 H); MS (EI) 363 (M^+, 6), 286 (3), 94 (100); HRMS calcd for $C_{21}H_{33}O_4N$ 363.2410, found 363.2395.

(2*R*,3*R*,6*S*,8*S*,9*R*,11*R*,1′*R*)-2-Carboxymethyl-8-[1′-methyl-2′-oxo-2′-(1*H*-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undecane (9). To a solution of the preceding alcohol (4.12 mg, 0.011 mmol) in acetone (0.3 mL) at −20 °C was added Jones reagent (30 μL) (prepared from chromium trioxide (11.1 g) and concentrated sulfuric acid (9.2 mL) in H_2O (45 mL)). TLC analysis showed that the starting material was completely consumed after 1 h of stirring at −20 °C. Excess oxidant was discharged by addition of saturated aqueous $NaHSO_3$ until the color of the solution became green. The mixture was diluted with 50% ethyl acetate–ether (15 mL) and washed with H_2O (3 mL) and saturated aqueous NaCl (3 mL) and dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by chromatography on Biosil-A using ethyl acetate–hexanes (1:1) as eluent to give the desired acid **9** (3.92 mg, 92%) as a brownish oil: R_f 0.40 (10% methanol–chloroform); $[\alpha]_D$ +116° (c 0.15, $CHCl_3$); IR ($CHCl_3$) 3200, 2940, 2900, 1710, 1610, 1400, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.05 (br s, 1 H), 7.05 (m, 1 H), 7.01 (m, 1 H), 6.26 (m, 1 H), 3.95 (m, 2 H), 3.25 (m, 1 H), 2.54 (dd, J = 15.4, 8.3 Hz, 1 H), 2.37 (dd, J = 15.4, 6.0 Hz), 1.83–1.23 (m, 9 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.80 (d, J = 6.9 Hz, 3 H); HRMS calcd for $C_{21}H_{31}NO_5$ 377.2202, found 377.2223.

[6*S*,2*R*-[3*R*,9*R*,11*R*]-8*S*-[1*S*]]-(+)-Methyl 5-(*N*-Methyltrifluoroacetamido)-2-[3,9,11-trimethyl-8-[1-methyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2-yl]methyl-4-benzoxazolecarboxylate (68). A solution of acid **9** (15.80 mg, 0.042 mmol), [(benzotriazo-1-yl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate (19.43 mg, 0.044 mmol), aminophenyl **64** (12.23 mg, 0.042 mmol) and triethylamine (30 μL) in dimethylformamide (0.2 mL) was heated at 65 °C for 18 h. The mixture was cooled to room temperature, diluted with ether (10 mL), washed with H_2O (2 × 5 mL) and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in 1,2-dichloroethane (3 mL) and pyridinium p-toluenesulfonate (30 mg) was added followed by freshly dried 4-Å molecular sieves (50 mg). The reaction mixture was heated at 80 °C for 24 h. After being cooled the solution was filtered and diluted with ether (10 mL), washed with H_2O (2 mL) and saturated aqueous NaCl (2 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Chromatography on Biosil-A using 30% ethyl acetate–hexanes as eluent afforded the desired benzoxazole **68** (15.86 mg, 73%) as a light yellow solid: mp 80–81 °C; R_f 0.51 (8% methanol–chloroform); IR ($CHCl_3$) 3440, 2960, 2920, 1720, 1700, 1640, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (br s, 1 H), 7.74 (m, 1 H), 7.26 (m, 1 H), 7.00 (m, 1 H), 6.87 (m, 1 H), 6.21 (m, 1 H), 4.08 (m, 1 H), 3.96 (s, 3 H), 3.48 (m, 1 H), 3.35–3.31 (m, 3 H), 3.14–3.06 (m, 2 H), 2.94–2.89 (m, 1 H), 1.75–0.98 (m, 9 H), 0.94–0.73 (m, 12 H); MS (EI) 633 (M^+, 6), 429 (10), 372 (5), 316 (14), 284 (8), 205 (7), 163 (8), 123 (15), 94 (63).

(−)-Calcimycin (A-23187) (1). To protected benzoxazole **68** (5.82 mg, 0.0092 mmol) was added a solution of LiS-n-Pr in HMPA (0.5 M, 0.2 mL, 0.10 mmol). The solution was stirred at room temperature for 3.5 h. The dark red mixture was diluted with ether (15 mL) and washed with H_2O (5 mL), saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was filtered through Biosil-A using 50% ethyl acetate–hexanes as eluent. The yellow oil, thus obtained, was diluted with ether (5 mL), washed with 10% aqueous H_3PO_4 (2 × 2 mL) and saturated aqueous NaCl (2 mL), dried over Na_2SO_4, and evaporated under reduced pressure to afford A-23187 (**1**; 4.75 mg, 99%) as a foamy solid that was identical in all respects with authentic material: mp 185–187 °C (natural 186–187 °C); R_f 0.47 (8% methanol–chloroform); $[\alpha]_D$ = −48.4° (c 0.3, $CHCl_3$) [lit.[7] −53.4° (c 0.5, $CHCl_3$), −45.1° (c 0.3, $CHCl_3$)]; IR ($CHCl_3$) 3420, 3360, 2990, 2920, 1700, 1630, 1550, 1420, 1250, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (br s, 1 H), 8.06 (m, 1 H), 7.56 (d, J = 9.1 Hz, 1 H), 7.03 (m, 1 H), 6.90 (m, 1 H), 6.62 (d, J = 9.1 Hz, 1 H), 6.23 (dd, J = 5.8, 2.4 Hz, 1 H), 4.24 (m, 1 H), 3.66 (dd, J = 10.4, 1.6 Hz, 1 H), 3.17 (m, 1 H), 3.09–2.87 (m, 2 H), 2.95 (m, 3 H), 1.78–1.20 (m, 9 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 5.8 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H); MS (EI) 524 (23), 523 (69), 479 (41), 318 (36), 246 (18), 206 (66).

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