# Synthesis of the Proposed Penultimate Biosynthetic Triene Intermediate of Monensin A

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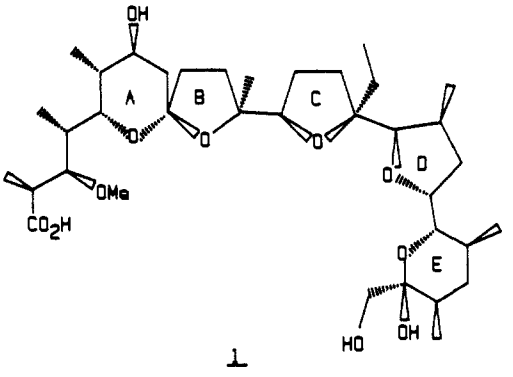
**Abstract:** A convergent chiral synthesis of the putative biosynthetic triene precursor, **2b**, has been accomplished. Our strategy entails the successive assembly of three key chiral synthons, prepared by enzymatic and microbial techniques.

The discovery of the naturally occurring polyether antibiotics has raised many questions concerning various aspects of their interesting biochemical properties, their complex chemistry, and their intricate mechanism of biosynthesis.[1] For instance, monensin A[2] (**1**) is a compound of considerable commercial importance. It




**1**

was first introduced as a coccidiostat in poultry and has since proved to be of great utility in the improvement of feed usage in ruminating livestock. These and other remarkable biochemical effects can presumably all be attributed to the ability of monensin A to disrupt the ionic gradients set up across various biological membranes. However it is not clear that this is monensin's only biochemical mode of action, and many investigators are pursuing this question.[3] The simple biosynthetic precursors of many of the polyether antibiotics have been proposed, and an elegant and comprehensive biosynthetic hypothesis has been formulated by Cane, Celmer, and Westley[4] based mainly on empirical observations.

This hypothesis states that the biosynthesis of the polyether ionophores occurs in a number of phases. First a series of condensations, reductions, and dehydrations takes place leading to a penultimate polyene, which finally in the oxidative phase undergoes stereoselective epoxidation and cyclization to the polyether natural product. As exemplified in Scheme I for monensin A, the sequential addition of acetate, propionate, and butyrate subunits[5] followed by appropriate reductions and dehydrations (requiring some 33 enzyme-catalyzed steps) would provide the speculative uncyclized polyene **2**.[6] This (*all-E*)-triene would then undergo enantiospecific epoxidation to the (12*R*,13*R*,16*R*,17*R*,20*S*,21*S*)-triepoxide **3** after which attack of the C-5 hydroxyl of **3** would initiate a cascade of ring closures generating the pentacyclic polyether monensin A. Support for this hypothesis has been obtained by Cane's incorporation studies[6a,b] showing that the ether oxygens of the C, D, and E rings of monensin all originate from molecular $O_2$. Furthermore, this polyene–polyether model has been put forward[4b] to account for the stereochemical similarities of a large number of polyether antibiotics.

Direct proof for or against these intriguing hypothetical final stages of polyether biosynthesis could be accomplished by either isolation of these proposed intermediates (or incompatible intermediates) from a fermentation or by the synthesis and metabolic studies of a labeled intermediate in a polyether synthesizing organism. However, the proposed intermediates have not been isolated as byproducts from fermentations, and their molecular complexity poses formidable synthetic challenges, making direct incorporation studies very difficult. We have recently accomplished the first successful total synthesis[7] of one of these proposed intermediates, **2b**, and a detailed account of our synthetic explorations leading to **2b** is described below. Crucial to this convergent synthesis was the availability of key chiral synthons which we obtained by making use of enzymatic and microbial methodology that has been developed in these labs for the synthesis of chiral compounds.

## Retrosynthetic Analysis

The proposed monensin precursor **2b** poses a challenging synthetic target due to the presence of nine chiral centers (six contiguous and three widely separated) and three geometrically defined "*E*" olefins on its highly oxygenated 26-carbon framework. The magnitude of such a linear molecule as well as the remote nature of the chiral centers requires several levels of convergency starting with optically pure chiral synthons at each level.

Retrosynthetic analysis of triene **2b** reveals the two strategic bonds indicated in Scheme II. Disconnection of these leads to the left fragment, which would lactonize to **4a**, a middle bifunctional diene fragment **5**, and a protected right fragment **6**, which possesses functionality necessary to couple with **5** in the desired *E* fashion. By using the existing chiral centers to control the stereochemistry about the newly created asymmetric centers and employing aldol and Claisen methodology, each of these fragments could be elaborated from the three biochemically derived chirons **7**, **8**, and **9**, respectively. Thus the construction of **2b** is reduced to the synthesis of three optically pure subtargets

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(3) Ledger, P. W.; Tanzer, M. L. *Trends Biochem. Sci. (Pers. Ed.)* **1984**, *9*, 313.

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(5) (a) Day, L. E.; Chamberlain, J. W.; Gordee, E. Z.; Chen, S.; Gorman, M.; Hamill, R. L.; Ness, T.; Weeks, R. E.; Stroshane, R. *Antimicrob. Agents Chemother.* **1973**, 410. (b) Sood, G. R.; Robinson, J. A.; Ajaz, A. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1421. (c) Gani, D.; O'Hagan, D.; Reynolds, K.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1002.

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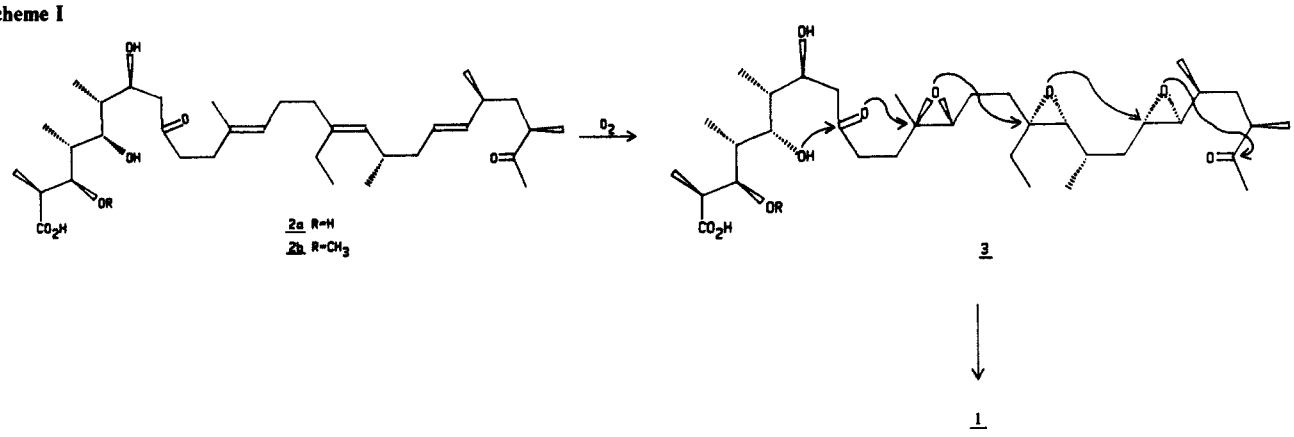
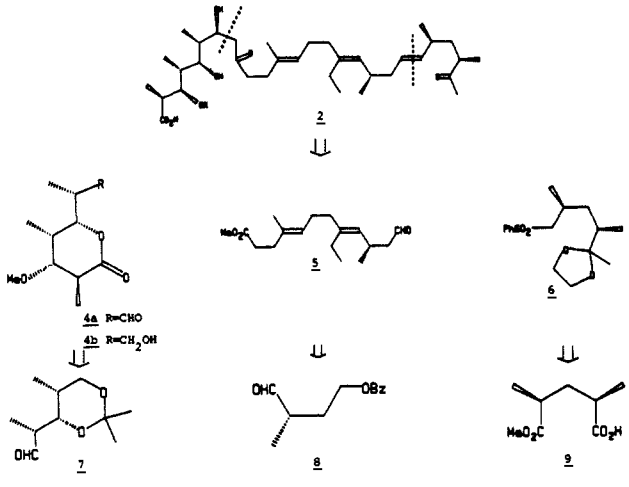
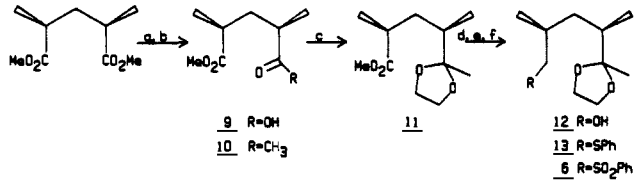
**Scheme I**



**Scheme II**



**Scheme III**[a]



[a] (a) *Gliocladium roseum*. (b) (i) $(COCl)_2$, $C_6H_6$, room temperature; (ii) $Me_2CuLi$, THF, −78 °C. (c) $(CH_2OH)_2$, PPTS, $C_6H_6$, 6-h reflux. (d) $LiAlH_4$, $Et_2O$. (e) Pyridine, PhSSPh, *n*-$Bu_3P$, room temperature. (f) mCPBA, $NaHCO_3$, $CH_2Cl_2$, room temperature.

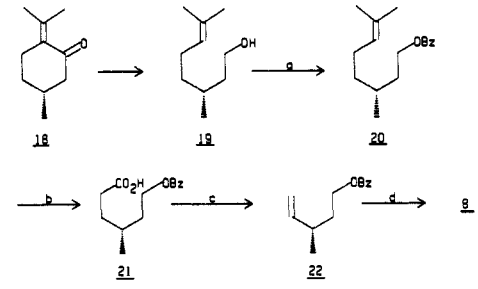
**4a**, **5**, and **6** from chiral synthons **7**, **8**, and **9** followed by stereospecific coupling reactions.

## Synthesis of Chiral Sulfone 6

The synthetic challenge inherent in obtaining the right fragment **6** consisted of introducing the two chiral centers and maintaining their asymmetry throughout the sequence of reactions depicted in Scheme III. Enantiotopic selective hydrolysis[8] of the *pro-R* ester group of *meso*-2,4-dimethylglutarate by *Gliocladium roseum* (5 g/L) served admirably to furnish multigram quantities of half-ester **9**, in optically pure form (86%, >0.98 ee).

Addition of dimethylcopper lithium to the acid chloride, derived from **9** (92%), gave **10**.[9] Ketalization (80%) to **11** using *p*-TsOH as an acid catalyst caused epimerization of the $\alpha$-methyl group, but was avoided by using the less acidic catalyst pyridinium tosylate (PPTS).[10] $LiAlH_4$ reduction of **11** gave alcohol **12** (98%) which was converted to sulfide **13** (91%) by treatment with diphenyl disulfide and tributylphosphine in the presence of pyridine.[11] Oxidation of **13** with MCPBA afforded the desired sulfide to sulfone transformation, but the chlorobenzoic acid byproduct caused deketalization and epimerization to the diastereomeric $\alpha$-methyl ketones (distinguishable by $^{13}C$ NMR). Buffering the oxidation with $NaHCO_3$ cleanly eliminated this hydrolysis and completed the synthesis of the right fragment of the biosynthetic precursor **6**.

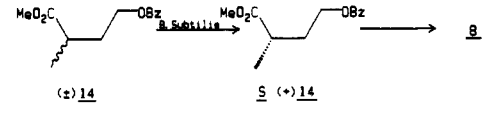
**Scheme IV**[a]



[a] (a) NaH, $PhCH_2Br$. (b) $O_3$, Jones [O]. (c) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine. (d) $O_3$, Zn, AcOH.

## Synthesis of Chiral Bifunctional Diene 5

As evident from Scheme II, synthesis of the middle fragment **5** required an easy access to the five-carbon chiral aldehyde **8**.[12] Three approaches were successfully devised: (a) kinetic resolution of a racemate, (b) asymmetric synthesis from a prochiral substrate, and (c) chemical degradation of a natural product. a kinetic resolution of ester **14** was developed by obtaining an esterase-producing microorganism which could hydrolyze one enantiomer much faster than the other.



When (±)-**14** was incubated with *Bacillus subtilis*, the undesired *R*-enantiomer was hydrolyzed preferentially ($E$ = 14)[13] and pure *S*-(+)-**14** (ee = 0.97) could be obtained at 63% conversion (yield of isolated product = 31%). Conversion of ester *S*-(+)-**14** to aldehyde (+)-**8** was accomplished by using a reduction–oxidation sequence [(a) $LiAlH_4$, (b) $(COCl)_2$, $Me_2SO$].[14] $\alpha$-Methyl

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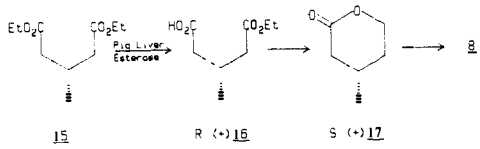
(13) The enantiomeric ratio ($E$) value) is calculated from $E = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)]$, where $c = ee_s/(ee_s + ee_p)$. For a comprehensive treatment of the principles involved in biochemical kinetic resolutions, see: Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(14) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

aldehyde **8** suffers epimerization extremely easily, as evidenced




by the complete loss of chirality if the oxidation was carried out by using slightly acidic reagents such as pyridinium chlorochromate or if the aldehyde was not used within 24 h.

An asymmetric synthesis of **8** was devised, employing prochiral substrate diethyl 3-methylglutarate, **15**, as the starting material. Commercially available pig liver esterase (PLE) is able to distinguish[13] between the enantiotopic ligands of **15** and preferentially hydrolyzes the *pro-R* ester, affording the half-ester *R*(+)-**16** (81%, ee = 0.69). Chemoselective ester reduction [(a) LiOH, (b) $LiBH_4$, (c) TsOH] furnished the (*S*)-lactone **17**. The enhancement of optical purity of **17** (ee = 0.91) by a combination of enantiotopic hydrolysis and kinetic resolution techniques[13] and its conversion to *S*-(+)-**9**[15] have been reported previously.

The final sequence leading to chiron **8** employs (*R*)-(+)-pulegone (**18**) as a readily available chiral (ee > 0.98[16]) starting material (Scheme IV).

(*R*)-(+)-Pulegone (**18**) was first converted to (*R*)-(+)-citronellol (**19**) according to known procedures.[17] The alcohol was protected as the benzyl ether (88%),[18] and the resulting benzyloxy olefin **20** on ozonolysis followed by Jones oxidation afforded the benzyloxy acid **21**.[19] Oxidative decarboxylation with lead tetraacetate (54% yield at 51% conversion)[20] and ozonolysis of the resulting **22** led to *S*-(+)-**8**. This approach is direct and readily amenable to scale-up.

Conversion of (+)-**8** to diene **5** (Scheme V) required the introduction of two *E*-trisubstituted olefins. This was achieved by use of the ortho ester Claisen rearrangement[21] which is known to give the required *E* olefin in a diastereomerically convergent fashion irrespective of the configuration of the allylic alcohol used.

Addition of the Grignard reagent, derived from 2-bromobutane to *S*-(+)-**8**, produced a diastereomeric mixture of allylic alcohols **23** (94%). On heating with excess trimethyl orthoacetate in the presence of catalytic amounts of propionic acid, the *E*-trisubstituted olefin, (+)-**24**, was produced (88%). Reduction of **24** (96%) with $LiAlH_4$ gave **25**, which upon PCC oxidation[22] (80%) afforded **26**. The latter was subjected to a second sequence of the Grignard addition/ortho ester Claisen rearrangement to form ester diene **27** (72% from **26**). A methyl substituent was desired on the second olefin, and hence the addition was carried out with 2-propenylmagnesium bromide. In order to avoid overreduction, the ester group of **27** was hydrolyzed to its acid before deprotecting the alcohol group and was regenerated on $CH_2N_2$ treatment after reductive debenzylation (68% at 75% conversion). It was convenient to store the middle fragment as the alcohol, **28**, and to oxidize it to **5**[14] (87%) immediately prior to its union with the right fragment, **6**.

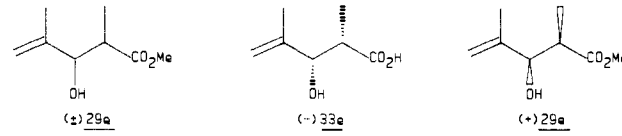
### Synthesis of Chiral Lactone 4

Lactone aldehyde **4** is a highly sensitive compound possessing five chiral centers, two of which are epimerizable and two more contain labile hydroxyls which are $\beta$ to a carbonyl. As alluded to earlier, our retrosynthetic analysis of **4** was based on the premise that aldol methodology could control the relative stereochemistry at C-2 and C-3 once chiral synthon **7** was obtained. Scheme VI shows the sequence of reactions used to introduce the erythro[23] stereochemistry present in chiral synthon **7**.

Reformatsky condensation of methyl 2-bromopropionate with methacrolein gave a 4:1 mixture of the erythro ((±)-**29e**) and threo ((±)-**29t**) isomers in 89% yield. The diastereomeric mixture was oxidized [$(COCl_2)$, $Me_2SO$, 83%], and the resulting $\beta$-keto ester (±)-**30** was stereoselectively reduced with zinc borohydride[24] in ether, yielding essentially pure erythro isomer (±)-**29e** (96% yield; erythro/threo ≥ 99:1). The overall yield of (±)-**29e** from methacrolein by this route was quite acceptable (71%), but the limited solubility of the zinc borohydride reagent in ether (the only solvent providing good selectivity) sets practical limits on the scale-up of this sequence.

A more direct route to **29e** was devised by making use of a directed aldol condensation. Treatment of *S*-phenyl thiopropionate **31** with 9-BBN triflate forms the cis boron enolate which undergoes condensation with methacrolein in a highly stereospecific manner.[25] The resulting erythro (±)-**32e** could then be transesterified[26] ($HgCl_2$, $CaCO_3$, $CH_3CN$, 85%), giving rise exclusively to the desired erythro (±)-**29e**.

Initially, it was decided to introduce chirality at this stage by a microbial kinetic resolution of (±)-**29e**. Thus, on incubation of racemic (±)-**29e** with *Gliocladium roseum* (2 g/L) under the




previously reported conditions,[13] the desired (2*S*,3*S*) enantiomer was preferentially hydrolyzed ($E$ = 20) and (−)-**33e** of good optical purity (ee = 0.90) could be obtained by terminating the hydrolysis at 25% conversion. With chiral (−)-**33e** in hand, the problem of introducing asymmetry at the $sp^2$ center of C-4 was next addressed as shown in Scheme VII. Stereospecific hydroboration of the olefin of (−)-**33e** required a rigid conformation; therefore (−)-**33e** was reduced with $LiAlH_4$ (90%) to (−)-**34**, and the resulting diol was protected as the cyclic acetonide[27] (−)-**35** ([(trimethylsilyl)oxy]propene, $Me_3SiCl$, $CH_2Cl_2$, 92%). The asymmetric centers of (−)-**35** direct the hydroboration–oxidation in a highly stereospecific manner, leading to the desired erythro alcohol **36** as the major isomer (85% yield, erythro:threo > 95:5), nicely solving the problem of relative stereochemistry. However, to our dismay, chiral (−)-**35** produced racemic **36**. This enigma presumably arises due to the meso symmetry inherent in an intermediate in the oxidative workup if the acetonide is partially cleaved.[28]

No attempts were made to modify the reaction conditions to eliminate this problem, since an enzymatic kinetic resolution of (±)-**36** could be performed more conveniently at a later stage in the sequence. Secondly, the overall synthesis of (±)-**36** could now be greatly improved by direct LAH reduction of $\beta$-hydroxy thioester (±)-**32** to diol (±)-**34** (98%).

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(16) Valentine, D.; Chan, C. C.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 62.
(17) a Plesek, J. *Collect. Czech. Chem. Commun.* **1957**, *22*, 644.
(18) (a) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225. (b) Stork, G.; Nakamura, E. *J. Am. Chem. Soc.* **1983**, *105*, 5510.
(19) The ozonolysis must be carefully monitored to avoid benzyl ether to benzoate oxidation: Hirama, M.; Shimizu, M. *Syn. Commun.* **1983**, *13*(9), 781.
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(23) The "erythro" and "threo" designations for the diastereomeric aldol products is in accord with the following: (a) Evans, D. A.; Takacs, J. M.; Mcgee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109. (b) House, H. H.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1972**, *95*, 3310. For alternative nomenclature see: (c) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. (d) Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.
(24) (a) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*(9), 338.
(25) (a) Hirama, M.; Garvey, D. S.; Linda, D. L.; Masamune, S. *Tetrahedron Lett.* **1979**, *20*, 3937. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
(26) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.
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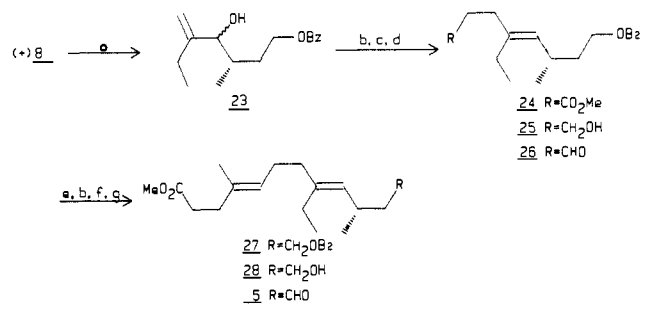
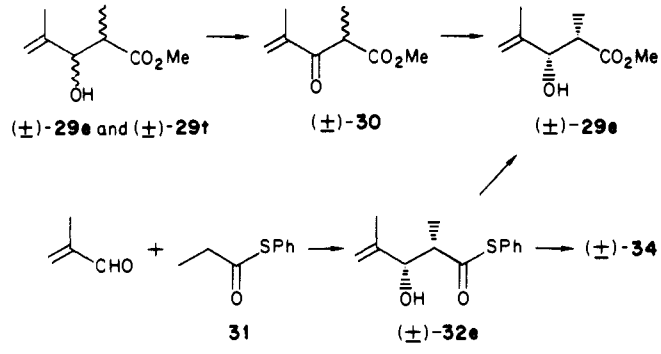
**Scheme V**[a]

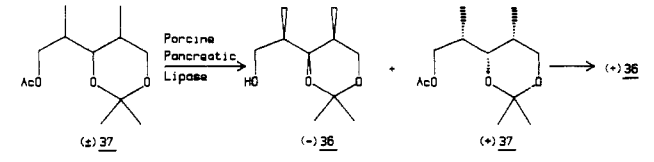


[a] (a) 2-Bromobutene, Mg, THF. (b) $CH_3(COMe)_3$, toluene, reflux. (c) $LiAlH_4$, THF. (d) PCC, $CH_2Cl_2$. (e) 2-Bromopropene, Mg, THF. (f) (i) LiOH; (ii) Na, $NH_3$, THF; (iii) $CH_2N_2$. (g) $(COCl)_2$, $Me_2SO$.

**Scheme VI**

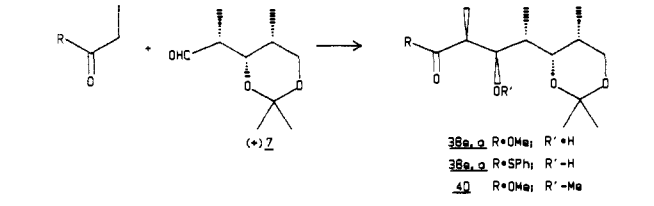


Acetylation of (±)-**36** ($Ac_2O$, $Et_3N$, DMPa,[29] 95%) afforded racemic (±)-**37**, which upon incubation with porcine pancreatic



lipase (PPL) in the presence of 0.5 to 1% by weight of α-toluenesulfonyl fluoride (PMSF) (to inhibit serine proteases) in phosphate buffer (pH 7.2) underwent hydrolysis with excellent enantioselectivity ($E$ = 18). At 40% conversion, the alcohol (−)-**36** could be obtained in 35% isolated yield [ee > 0.97 by HPLC analysis of (+)-MTPA[30] ester] whereas at 65% conversion, the unhydrolyzed (+)-**37** acetate was isolated in 30% yield and high optical purity [ee > 0.95 by HPLC analysis of (+)-MTPA ester of (+)-**36**]. The absolute stereochemistry of the two enantiomers of **36** was undefined at this stage. Hence, each enantiomer was converted to the lactone alcohol **4b**, and their optical rotations were compared with the (−)-**4b** lactone alcohol ($[\alpha]^{25}_D$ −110.0° ($CHCl_2$)) obtained from degradation of Monensin A. Thus, (−)-**36** alcohol led to the opposite enantiomer, (+)-**4b** ($[\alpha]^{25}_D$ +110.0° ($CHCl_3$)), indicating its 2*R*,2*S*,4*S* stereochemistry, whereas the alcohol derived from acetate (+)-**37** gave the correct enantiomer, (−)-**4b** ($[\alpha]^{25}_D$ −102.0° ($CHCl_3$)), confirming its 2*S*,3*R*,4*R* configuration.

Hydrolysis of acetate (+)-**37** (1 M LiOH, 4:1 THF:$H_2O$, reflux 12 h, 95%) followed by oxidation of the resulting alcohol (+)-**36** [$(COCl)_2$, $Me_2SO$, 86%] afforded aldehyde (+)-**7**. The remaining

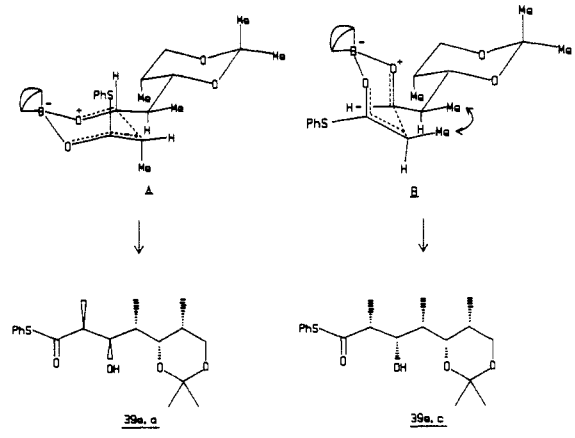


(29) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(30) Dale, J. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

segment of the carbon framework could be constructed by aldol condensation of (+)-**7** with an ethyl carbonyl anion equivalent. This reaction generates two new chiral centers and requires simultaneous control of the 2,3-erythro/threo and the 3,4-Cram/anti-Cram stereoselectivity. We had anticipated the preparation of the desired erythro selectivity to be relatively straightforward due to the availability of a variety of erythro selective reagents. Initial experimentation had suggested the use of boron enolate chemistry to be useful for this purpose.[32]

Thus, condensation of aldehyde (+)-**7** with Masamune's erythro-selective boron enolate of *S*-phenyl thiopropionate,[31,32] gave only one major condensation product which was characterized as the β-hydroxy thio ester **39e,a** exhibiting both the erythro and the anti-Cram stereochemistry. The 2,3-erythro configuration was expected on the basis of the cis geometry of the boron enolate, and the 3,4-anti-Cram stereochemistry can be explained by considering the transition state of this condensation. Assuming that **7** occurs predominantly in its most stable conformation,[33] either face of aldehyde should be available for attachment by the boron enolate of *S*-phenyl thiopropionate.

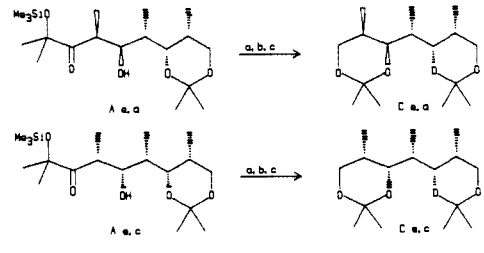
Attack on the *si* face of the aldehyde proceeds through transition state A which does not suffer from unfavorable steric interactions in contrast to transition state B. This leads eventually to formation



Erythro/anti-Cram Erythro/Cram

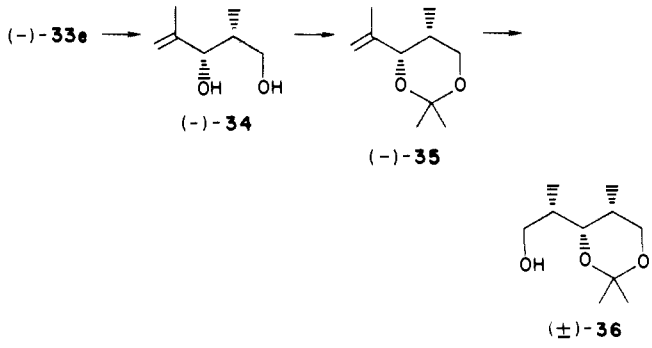
of the desired *erythro* anti-Cram product **39e,a**. On the other hand, attack on the *re* face resulting in **39e,c** must proceed through transition state B, which is destabilized by the indicated 1,3-

(31) (a) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24(1)*, 1, and references cited therein. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Reference 25b. (d) Heathcock, C. H.; Base, C. T. *J. Am. Chem. Soc.* **1977**, *99*, 8109. (e) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.
(32) Aldol condensation of aldehyde **7** with Heathcock's erythro selective reagent (ref 31d) exhibited excellent 2,3-erythro selectivity but surprisingly, very little 3,4-anti-Cram stereoselectivity, i.e., both the erythro anti-Cram (A e,a) and the erythro-Cram (A e,c) products were produced in comparable



amounts [A e,a vs. A e,c: (a) LDA 1:1, (b) LDA/$MgBr_2$ 2:1]. The conclusions regarding the relative stereochemistry were made by converting the isomers to their respective bis(acetonides) as shown in the scheme below [(a) $NaIO_4$; (b) $LiAlH_4$; (c) $H^+$, acetone]. Thus, $^1H$ NMR of the bis(acetonide) C e,a, obtained from A e,a, showed three methyl doublets [0.8 (d, 3 H), 1.07 (d, 3 H), 1.13 (d, 3 H)] illustrating the nonequivalence of the three methyl groups, whereas the bis(acetonide) C e,c, showed only two methyl doublets [1.0 (d, 3 H), 1.22 (d, 6 H)].
(33) For an analysis of the lowest energy conformations of aldehyde 7, see: Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.

**Scheme VII**



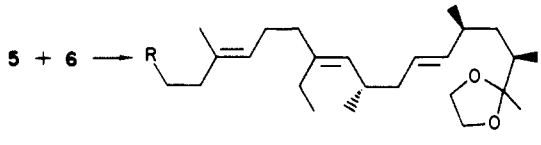

methyl–methyl interaction. Thus, **39e,a** could be expected and furthermore was the only adduct isolated.[34] This configuration was further confirmed by structure correlation with the naturally derived (−)-**4b**.

Transesterification of **39e,a** ($HgCl_2$, $CdCO_3$, 92%) resulted in β-hydroxy ester **38e,a**. The desired O-methylation of **38e,a** required extensive experimentation to find conditions reactive enough to form **40** while mild enough to avoid retro aldol degradation. This obstacle was finally surmounted by using methyl iodide and freshly prepared $Ag_2O$ in DMF as the Lewis acid (90%).[35] Upon mild acid treatment, deketalization of **40** was followed by spontaneous lactonization to afford lactone alcohol (−)-**4b** identical in all respects with (−)-**4b** obtained from degradation of natural monensin. Swern oxidation of (−)-**4b** yielded aldehyde (−)-**4a** which was extremely unstable and was made only prior to its use.

### Coupling of Fragments and Synthesis of 2b

The union of **5** and **6** was achieved by employing the Kocienski–Lythgo–Julia procedure,[36] which has been shown to give rise predominantly to the *E* olefin.[36d]

Condensation of aldehyde **5** with the anion of sulfone **6** (*n*-BuLi, THF, −78 °C) followed by in situ benzoylation gave the benzoyloxy sulfone as a mixture of diastereomeric products. Reductive elimination with sodium amalgam at low temperatures led to **41**,

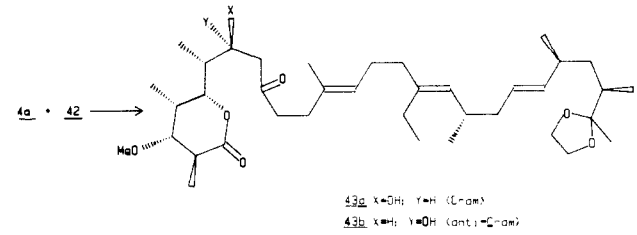



**41**, R = $CO_2CH_3$ **49**, R = CHO
**42**, R = $COCH_3$ **50**, R = $CH(OH)^{14}CH_3$
**48**, R = $CH_2OH$ **51**, R = $CO^{14}CH_3$

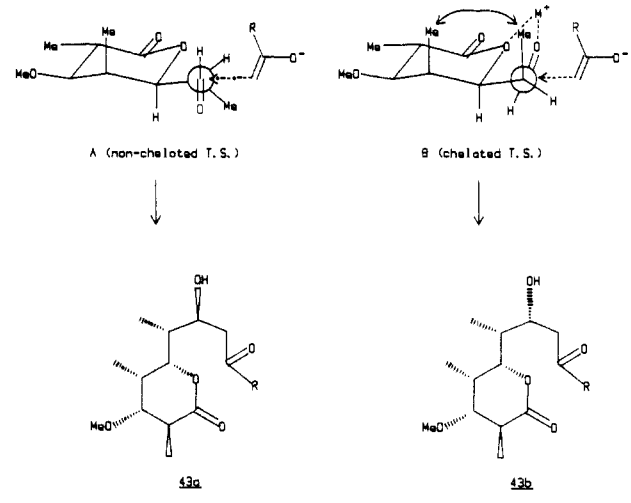
generating the disubstituted olefin with the desired *E* geometry (35% overall). Ester **41** was then hydrolyzed to the acid (NaOH, $CH_3OH$) and treated with oxalyl chloride in benzene (30 min, room temperature) to form the acid chloride which on treatment with $Me_2CuLi$ in THF furnished methyl ketone **42** in 85% overall yield.

A radiolabel in the final precursor **2b** would be of great assistance in following its fate in the final incubation experiments. Hence, it was found appropriate to introduce the $^{14}C$ label in the molecule at this stage. However, a different approach was taken for conversion of **41** to **42** because of the inefficiency of preparing labeled $Me_2CuLi$ on smaller scales from $^{14}CH_3I$. Methyl ester **41** was reduced to its aldehyde **49** in two steps [$LiAlH_4$ reduction followed by a Swern oxidation of the resulting alcohol **48**: 65.1% overall yield from ester **41**] and $^{14}CH_3MgI$ (prepared from $^{14}CH_3I$ and Mg) was added to it (54%). The resulting diastereomeric secondary alcohols, **50**, were oxidized (Collins reagent, $CrO_3$, pyridine, 67%) to generate the radioactive methylketone **51** (110 μCi, 1.72 mCi/mmol radioactivity).

This brings us to the final stage of the synthesis, i.e., the coupling of the left fragment (**4a**) with the right half (**42**) for the precursor




of Monensin. Aldol condensation of the kinetic enolate of methyl ketone **42** (LDA, THF, −78 °C) with lactone aldehyde **4a** gave a mixture of two diastereomeric aldols in the ratio of 9:1 in 80% yield at 81% conversion. As discussed below, the β-hydroxy ketone **43a** with the desired Cram stereochemistry was expected to be the major isomer in this reaction.




In accordance with the Felkin–Anh model,[37] the kinetic enolate of **42** would be expected to attack aldehyde **4a** from its sterically less hindered *si* face (transition state A) leading to the Cram diastereomer **43a**. The aldehyde **4a** also bears a β-alkoxy functionality, capable of coordinating with the lithium cation. The possible existence of a chelated transition state B, leading to the undesired anti-Cram product **43b**, however, appears unlikely because there is a severe 1,3-nonbonded steric interaction between the two methyl groups. Thus, the steric bulk of the lactone ring in transition state B should be expected to override the moderate chelating ability of lithium cations, suggesting that it is more likely for the reaction to proceed through nonchelated transition state A to form the Cram product **43a** as the major isomer.

A further chemical correlation was also achieved in support of our prediction regarding the Cram stereochemistry of the major isomer.

Still and co-workers[2c] had utilized the open chain silyloxy aldehyde **44** in their synthesis of monensin A and it was prepared in five steps from alcohols **4b**. They had obtained a 3:1 diastereoselection of **45a**:**45b** and had predicted the major isomer **45a** to bear the desired Cram stereochemistry, reasoning that the steric bulk of the silyloxy group should override the chelating ability of the lithium and/or magnesium cations. The final proof regarding the stereochemistry was obtained in their case by suc-

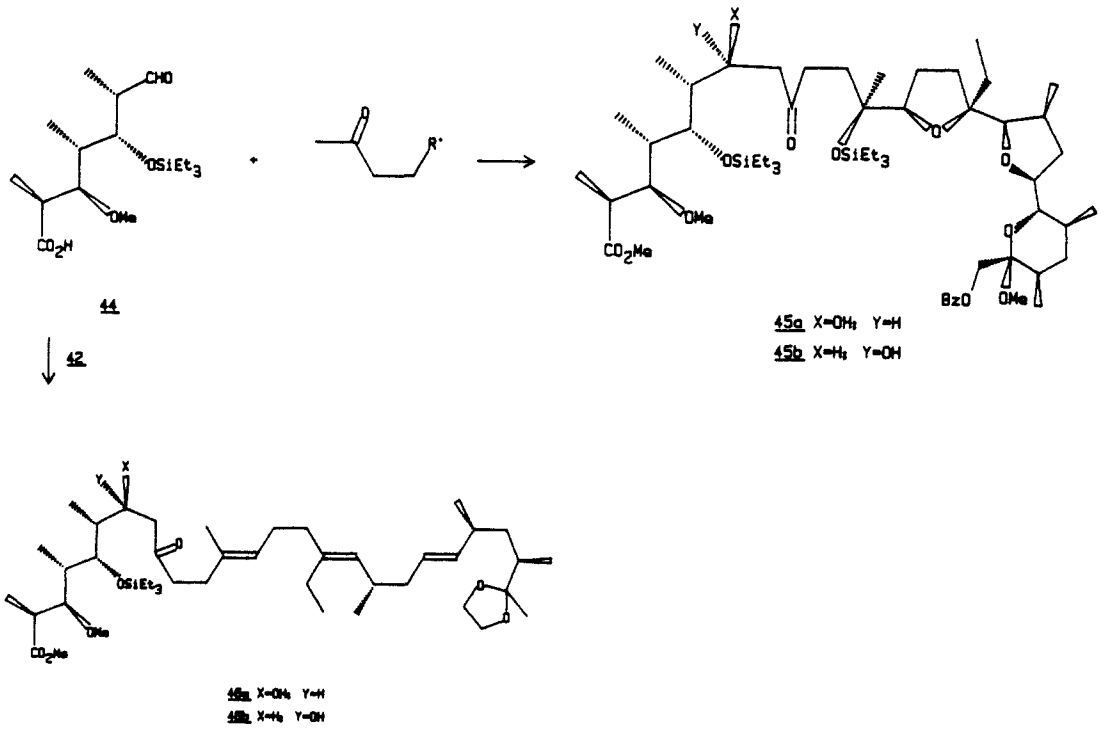
(34) The transesterification product **38e,a** derived from the major aldol condensation product **39e,a** on $LiAlH_4$ reduction followed by acetonide formation gave the acetonide C e,a identical with the one obtained from A e,a (see ref 32); $^1H$ NMR 0.8 (d, 3 H), 1.07 (d, 3 H), 1.13 (d, 3 H).

(35) (a) Kohn, R.; Trishmann, H.; Low, I. *Angew. Chem.* **1955**, *67*, 32. (b) Ferguson, A. C.; Haines, A. H. *J. Chem. Soc. C* **1969**, 2372.

(36) (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (c) Kocienski, P. J.; Lythgoe, B.; Roberts, D. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 834. (d) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

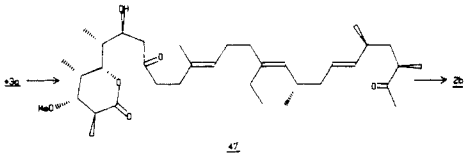
(37) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

Scheme VIII



cessful conversion of the major aldol **45a** to monensin A. The condensation of our ketone **42** with **44** gave a 2.8:1 mixture of diastereomeric aldols **46a**:**46b** (88% yield at 76% conversion). The major isomer, supposedly the Cram product **46a**, on treatment with $n$-$Bu_4N^+F^-$ desilylated and lactonized spontaneously to give a product identical in all respects with **43a**, the major diastereomer obtained from condensation of **4a** and **42**. This leaves us with very little doubt regarding the Cram stereochemistry of the major isomer **43a**.

All of the stereochemical and functional features of the target molecule **2b** exist in a suitably protected form in **43a**. Deketalization (PPTS, 5:1 acetone:$H_2O$, reflux, 8 h, 95%) afforded **47**.



In view of the sensitivity of the $\beta$-hydroxy ketone functionality of **47**, the mildest possible conditions for lactone opening were desired. After various unsuccessful attempts via chemical ($Et_3N$ or $i$-$Pr_2NEt$ or DMAP, MeOH, 25 °C; 0.1 M aqueous $K_2CO_3$, THF) and enzymatic (pig liver esterase or pig pancreatic lipase, 0.1 M phosphate buffer, pH 8) methods, it was finally effected by treatment with 4:1 THF–0.05 N NaOH for 10 min at 25 °C. Attempted isolation of the sodium salt of **2b** from the aqueous media either as the free acid or its methyl ester was unsuccessful. The formation of **2b** was however confirmed by its successful conversion to **47** upon acidification.

The synthesis was followed through in a similar fashion with radioactive ketone **51** to afforded radioactive precursor **2b**. This successful synthesis of **2b** provides all the tools necessary for a multitude of investigations regarding the biosynthesis of the polyether natural products. With synthetic **2b** in hand, different types of fermentations which have been mutagenized or treated with specific inhibitors can be assayed for accumulation of even minute quantities of natural **2b**. Access to radiolabeled **2b** also makes possible direct incorporation studies as well as assays for biosynthetic enzyme purifications.

This convergent synthesis not only provides access to both labeled and nonlabeled **2b**, it also vividly demonstrates the power of microbial and enzymatic methods in complex natural product synthesis.

## Experimental Section

$^1H$ NMR spectra were recorded on a Varian EM-390 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Chemical shifts are reported in $\delta$ (peak multiplicity, coupling constant if appropriate, number of protons). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. $^{13}C$ NMR spectra were obtained on a Jeol FX-90Q spectrometer operating at a frequency of 22.5 MHz. Infrared spectra were obtained on a Perkin-Elmer Model 599B spectrophotometer. Data are given in $cm^{-1}$. Ultraviolet spectra were recorded in methanol on a Cary 14 UV-VIS spectrophotometer. High-resolution mass spectroscopy were performed by the Analytical Instrument Center of The Ohio State University, Columbus, OH. Carbon–hydrogen analyses were performed by Galbraith Laboratories. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in the indicated solvents.

All solvents were purified before use. Thin-layer chromatography (TLC) was performed on plates coated with 0.25-mm thickness of silica gel 60F-254 (E. Merck). Column chromatography was performed by using MN-Kieselgel 60 (0.05–0.2 mm/70-270 mesh ASTM, Brinkman Instruments, Inc.).

**(2*S*,4*R*)-Methyl 2,4-Dimethyl-5-oxohexanoate (10).** Monoester acid 9[8] (4.06 g, 23.3 mmol) was dissolved in 25 mL of benzene, and excess oxalyl chloride (20.32 mL, 233 mmol) was added at 0 °C. After the mixture had been stirred for 4 h at room temperature, benzene and excess oxalyl chloride were removed in vacuo to give the crude acid chloride.

In another flask, dimethylcopper lithium was prepared by addition of $CH_3Li$ (104 mL of a 1.7 M soln, 177 mmol) to a suspension of CuI (17.75 g, 93.2 mmol) in 150 mL of THF at 0 °C. After being stirred at room temperature for 10 min, it was cooled to −78 °C, and the crude acid chloride was added dropwise as a solution in 10 mL of THF. After 30 min, the reaction was quenched with 10 mL of $CH_3OH$ at −78 °C. After the mixture had been warmed to room temperature, 100 mL of saturated $NH_4Cl$ was added, THF and $CH_3OH$ were removed, and the aqueous phase was extracted with $Et_2O$ (3 × 100 mL). Drying ($Na_2SO_4$), concentration, and column purification (4:1 hexane:EtOAc) gave 3.68 g (92%) of pure **10**. $[\alpha]^{25}_D$ +14.7° ($c$ 7.6, $CHCl_3$). $^1H$ NMR: 1.07 (d, $J$ = 6, 3 H), 1.15 (d, $J$ = 6, 3 H), 1.05–1.6 (m, 2 H), 1.87–2.3 (m, 1 H), 2.13 (s, 3 H), 2.3–2.76 (m, 1 H), 3.67 (s, 3 H). IR: ($CHCl_3$) 3020, 2975, 2950, 1725, 1710, 1460, 1435, 1380, 1355, 1270, 1225, 1195, 1170, 1130, 1080. $^{13}C$ NMR: 16.4, 17.7, 27.8, 36.6, 37.5, 45.1, 51.5, 176.4, 211.3.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.53; H, 9.49.

**(2*S*,4*R*)-Methyl-2-Methyl-4-(2′-methyl-1′,3′-dioxolan-2′-yl)penta-**

**noate (11).** Methyl ketone **10** (3.44 g, 20 mmol), pyridinium tosylate (502.6 mg, 2 mmol), and ethylene glycol (2.48 g, 40 mmol) in 100 mL of benzene were refluxed with water separation by a Dean–Stark trap for 6 h. Benzene was removed and the residue was dissolved in 250 mL of $Et_2O$. The solution was then washed sequentially with saturated aqueous $NaHCO_3$ (2 × 75 mL) and saturated aqueous NaCl (1 × 75 mL), dried ($Na_2SO_4$), and concentrated to give a residue weighing 3.96 g which after short-path distillation afforded 3.724 g (86%) of pure ketal **11** boiling at 75–78 °C (0.6 mmHg). $[\alpha]^{25}_D$ +24.5° (*c* 8.14, $CHCl_3$). $^1H$ NMR: 0.95 (d, *J* = 6.5, 3 H), 1.14 (d, *J* = 6.5, 3 H), 1.20 (s, 3 H), 1.33–2.75 (m, 4 H), 3.67 (s, 3 H), 3.90 (s, 3 H). IR ($CHCl_3$): 2980, 2950, 2880, 1725, 1460, 1435, 1380, 1270, 1230, 1200, 1195, 1170, 1125, 1090, 1040, 950, 870, 830. $^{13}C$ NMR: 14.6, 18.8, 20.8, 36.6, 37.5, 38.9, 51.5, 64.5, 112.4, 177.5.

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.93; H, 9.20.

**(2*S*,4*R*)-2-Methyl-4-(2′-methyl-1′,3′-dioxolan-2′-yl)pentan-1-ol (12).** A solution of ester ketal **11** (3.24 g, 15 mmol) in 10 mL of $Et_2O$ was added carefully to a suspension of $LiAlH_4$ (570 mg, 15 mmol) in 25 mL of $Et_2O$ at 0 °C. After stirring for 12 h at room temperature, the excess reagent was quenched by dropwise addition of $H_2O$. Finally, 50 mL saturated aqueous $NH_4Cl$ was added, and the two layers were separated. The aqueous layer was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated to give an oily residue which after column purification (9:1 to 4:1 hexane:EtOAc) gave alcohol **12**, 2.76 g (98%). $[\alpha]^{25}_D$ +20.3° (*c* 9.78, $CHCl_3$). $^1H$ NMR: 0.97 (d, *J* = 6, 6 H), 1.20 (s, 3 H), 0.7–2.03 (m, 4 H), 2.83 (br, s, 1 H), 3.47 (apparent t, 2 H), 3.95 (s, 4 H). IR ($CHCl_3$): 3620, 3460, 2960, 2930, 2880, 1465, 1370, 1230, 1160, 1090, 1085, 1040, 980, 945, 870.

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.87; H, 10.58.

**(2*S*,4*R*)-1-(Phenylthio)-2-methyl-4-(2′-methyl-1′,3′-dioxolan-2′-yl)-pentane (13).** Alcohol **12** (2.5 g, 13.3 mmol) was treated with diphenyl disulfide (4.36 g, 20 mmol) in the presence of tri-*n*-butylphosphine (5.0 mL, 20 mmol) in dry pyridine (3.2 mL, 40 mmol) at room temperature for 24 h. Water and $Et_2O$ were then added and the layers separated. The $Et_2O$ layer was washed with dilute $NaHCO_3$ and brine and dried ($MgSO_4$), and the solvents were removed, leaving a foul smelling residue (5.12 g).[4] Column purification (hexane to 9:1 hexane:ethyl acetate) afforded pure sulfide **13**, 3.42 g (91%). $[\alpha]^{25}_D$ +29.7° (*c* 4.96, $CHCl_3$). $^1H$ NMR: 0.93 (d, *J* = 6, 3 H), 1.12 (d, *J* = 6, 3 H), 1.23 (s, 3 H), 1.10–2.16 (m, 4 H), 2.53–3.20 (m, 2 H), 3.93 (s, 4 H), 7.13–7.50 (m, 5 H). IR ($CHCl_3$): 2960, 2925, 2880, 2850, 1585, 1480, 1460, 1440, 1380, 1220, 1160, 1140, 1100, 1085, 1060, 1040, 1025, 1000, 950, 860, 755, 730, 690. $^{13}C$ NMR: 15.4, 20.2, 20.8, 31.2, 39.0, 40.7, 64.5, 112.4, 125.7, 128.8, 129.2, 137.7.

Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63; S, 11.43. Found: C, 68.63; H, 8.60; S, 11.17.

**(2*S*,4*R*)-1-(Phenylsulfonyl)-2-methyl-4-(2′-methyl-1′,3′-dioxolan-2′-yl)pentane (6).** *m*-CPBA (4.5 g, 20.7 mmol) was added slowly to an ice-cooled and well-stirred heterogeneous solution of sulfide **13** (2.64 g, 9.43 mmol) and $NaHCO_3$ (3.5 g, 41.4 mmol) in 30 mL of $CH_2Cl_2$. After being stirred 3 h at room temperature, it was quenched with aqueous $NH_4OH$. The organic layer was separated and washed with saturated aqueous $NH_4OH$ (2 × 25 mL), dried ($Na_2SO_4$), and concentrated to give 2.93 g of yellow oil. Column purification (5:1 hexane:ethyl acetate) yielded pure sulfone **6**, 2.55 g (87%). $[\alpha]^{25}_D$ +18.9° (*c* 2.17, $CHCl_3$). $^1H$ NMR: 0.82 (d, *J* = 6.5, 3 H); 1.10 (d, *J* = 6.5, 3 H); 1.18 (s, 3 H); 0.97–1.8 (m, 3 H); 1.8–2.43 (m, 1 H); 2.67–3.27 (m, 2 H); 3.90 (s, 4 H); 7.3–8.2 (m, 5 H). IR ($CHCl_3$): 2980, 2960, 2930, 2880, 1460, 1450, 1400, 1380, 1300, 1220, 1160, 1145, 1100, 1080, 995, 950, 905, 860, 830. 740, 720, 685, 650, 600, 580, 535. $^{13}C$ NMR: 15.2, 20.1, 21.5, 26.9, 38.9, 39.5, 62.0, 64.5, 64.6, 112.0, 127.9, 129.3, 133.5, 140.3.

Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74; S, 10.26. Found: C, 61.27; H, 7.69; S, 10.04.

**(3*R*)-1-(Benzyloxy)-3,7-dimethyl-6-octene [(+)-20].** A solution of (3*R*)-citronellol (**19**) (88.3 g, 0.566 mol) in 100 mL of THF was added dropwise via a pressure equilibrating funnel to a suspension of oil-free sodium hydride (24.9 g, 60% suspension, 0.623 mol) in 500 mL of THF. The mixture was refluxed 2 h and cooled to room temperature, and benzyl bromide (70.7 mL, 0.594 mol) was added with concomitant formation of a white precipitate. The mixture was refluxed 36 h, cooled to room temperature, and carefully quenched with a minimum quantity of water. The THF was removed by rotary evaporator, and 500 mL of $H_2O$ was added to the residue. The aqueous solution was extracted with ether (3 × 300 mL). Drying ($Na_2SO_4$), concentration, and distillation of the residue gave **20** as a colorless oil (138 g, 99%), bp 125–130 °C at 0.5 mmHg. $[\alpha]^{25}_D$ +2.5° (*c* 4.83, $CHCl_3$). $^1H$ NMR: 0.8 (d, *J* = 5, 3 H), 0.8–1.8 (br m, 5 H), 1.6 (s, 3 H), 1.66 (s, 3 H), 2.0 (m, 2 H), 3.5 (t, *J* = 6.5, 2 H), 4.47 (s, 2 H), 5.1 (m, 1 H), 7.3 (s, 5 H). IR ($CHCl_3$): 3000, 2960, 2920, 1730, 1495, 1450, 1375, 1365, 1250, 1215, 1100, 1040, 1025, 905, 720, 695, 650, 605.

**(4*R*)-Methyl-6-(benzyloxy)hexanoic acid (21).** An acetone (500 mL) solution of **20** (20.0 g, 82 mmol) was subjected to ozonolysis by bubbling $O_3$ through the solution via a gas dispersion inlet while cooling at −78 °C. The reaction was monitored by TLC, and when disappearance of starting material was complete (90 min), the gas inlet was replaced with an $N_2$ bubbler for 15 min. The intermediate ozonide was then oxidized with Jones reagent while warming at 0 °C. The oxidation was worked up by filtering the chromium salts followed by removal of most of the acetone in vacuo. Acid **2** was purified by dissolving the residue in 1 N NaOH, washing the aqueous layer with ether, reacidifying the aqueous layer, and extracting the acid into EtOAc. Removal of the solvents provided **21** (15.5 g, 81%). $[\alpha]^{25}_D$ +3.87° (*c* 7.4, $CHCl_3$). $^1H$ NMR: 0.9 (d, *J* = 3, 3 H), 1.1–1.9 (br m, 5 H), 2.33 (t, *J* = 7.5, 2 H), 3.5 (t, *J* = 7.0, 2 H), 4.46 (s, 2 H), 7.27 (s, 5 H), 10.1 (br s, 1 H). IR ($CHCl_3$): 3000, 2960, 2935, 2870, 1710, 1605, 1585, 1495, 1450, 1410, 1380, 1365, 1285, 1225, 1175, 1095, 1025, 940, 910, 710, 695, 655, 605.

**(3*S*)-3-Methyl-5-(benzyloxy)-1-pentene [(+)-22].** A solution of acid **21** (62 g, 263 mmol) in benzene was added to a suspension of $Pb(OAc)_4$ (184 g, 416 mmol), $Cu(OAc)_2$ (9.6 g, 48 mmol), and pyridine (25 mL, 307 mmol) in benzene (1 L). The reaction was flushed with $N_2$, and while mechanically being stirred, was carefully warmed to avoid rapid and uncontrollable liberation of $CO_2$. After the initial evolution of gases had subsided, the reaction was refluxed for 2 h. Ethylene glycol (75 mL) and $H_2O$ (300 mL) were then added and the layers separated. The organic layer was then washed sequentially with 10% $HNO_3$ (3×) and $H_2O$ (3×). Unreacted acid **21** could then be removed for recycling by washing the organic layer with 1 N NaOH followed by reacidification and extraction to yield 30 g of unreacted **21**. The original benzene layer was dried ($Na_2SO_4$) and the benzene removed to yield a crude oil. Chromatography (100% hexane to 90% hexane–10% EtOAc) provided **22** (13.9 g, 54% yield with 51% conversion) as a clear colorless oil. $[\alpha]^{25}_D$ +22.5° (*c* 8.78, $CHCl_3$). $^1H$ NMR: 1.0 (d, *J* = 6, 3 H), 1.60 (apparent q, 2 H), 2.3 (m, 1 H), 3.5 (t, *J* = 6, 2 H), 4.5 (s, 2 H), 4.73–5.13 (m, 2 H), 5.5–5.9 (m, 1 H), 7.33 (s, 5 H). IR ($CHCl_3$): 3070, 3000, 2960, 2925, 2860, 2795, 1640, 1495, 1450, 1415, 1360, 1205, 1090, 1025, 995, 915, 695, 605.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.22; H, 9.54.

**(2*S*)-2-Methyl-4-(benzyloxy)-1-butanal [(+)-8].** Olefin **22** (5.0 g, 26.3 mmol) was dissolved in $CH_3OH$ (100 mL) and $O_3$ was passed through the solution while cooling at −78 °C. After 30 min, a blue color appeared and only traces of starting **21** remained according to TLC, at which time the ozone bubbler was replaced with a $N_2$ bubbler for 10 min. Zinc dust (3.9 g, 60.5 mmol) and acetic acid (10 mL, 163 mmol) were then added while stirring, and the reaction was allowed to warm to ambient temperature. After 2 h the reaction was diluted with $H_2O$ and extracted with ether (3×). Removal of the solvents yielded 5.03 g of crude yellow oil. Silica gel chromatography (95% hexane–5% EtOAc) provided (+)-**8** (3.6 g, 72%) as a clear colorless oil: bp 100–120 °C at 0.4 mmHg; $[\alpha]^{25}_D$ +15.8° (*c* 3.01, $CHCl_3$).[38] The optical purity of (+)-**8** was determined by $^1H$ NMR analysis of the derived ester (+)-**14**. Ester (+)-**14** was obtained from a sample of **8** by oxidation with Jones reagent for less than 30 s while cooling at 0 °C followed by esterification of the derived acid with $CH_2N_2$. The ester (+)-**14** derived in this manner $[\alpha]^{25}_D$ +24.9° (*c* 9.5, $CHCl_3$) was found to be optically pure by $^1H$ NMR analysis in the presence of Eu(hfc)$_3$. $^1H$ NMR: 1.13 (d, *J* = 6, 3 H), 1.37–2.27 (m, 2 H), 2.37–2.77 (m, 1 H), 3.53 (t, *J* = 6.5, 2 H), 4.5 (s, 2 H), 7.33 (s, 5 H).

**(6*S*)-Methyl 4-Ethyl-6-methyl-8-(benzyloxy)oct-4(*E*)-enoate (24).** A solution of 2-bromo-1-butene (10.389 g, 77 mmol) (Pfaltz & Bauer) in 10 mL of THF was added to a suspension of magnesium pieces (3.024 g, 84 mmol, freshly sanded), in 100 mL of THF. (The reaction was instantaneous in most cases; occasionally, initiation of the vigorous reaction was achieved by mild heating.) The reaction mixture was then heated to reflux for 2 h to ensure complete formation of the Grignard reagent. After the reagent had been cooled to room temperature, a solution of aldehyde **8** (13.44 g, 70 mmol) in 20 mL of THF was added dropwise and the reaction mixture stirred for an additional 90 min; the reaction was quenched with saturated $NH_4Cl$ (50 mL) followed by 10% HCl (50 mL) to dissolve all the precipitate. THF was removed by rotary evaporator and the aqueous phase extracted with ether (2 × 50 mL). The organic layer was washed sequentially with 10% HCl (2 × 50 mL) and saturated NaCl (2 × 50 mL), dried ($Na_2SO_4$), and concentrated to give

(38) For a recent synthesis of 2*R*-(−)-7 from S. Citronellol, see: Uneyama, K.; Matsuda, H.; Torii, S. *J. Org. Chem.* **1984**, *49*, 4315. (−)-4, $[\alpha]^{25}_D$ −11.61 (*c* 3.28, hexane).

16.8 g of a diastereomeric mixture of allylic alcohols. Column purification yielded 16.24 g (94%) of diastereomeric **23** which was subjected to the ortho ester Claisen rearrangement. $^1$H NMR: (high $R_f$ diastereomer) 0.83 (d, $J$ = 6, 3 H), 1.05 (t, $J$ = 7, 3 H), 1.35–2.25 (br m, 6 H), 3.5 (apparent t, $J$ = 6, 2 H), 3.93 (m, 1 H), 4.45 (s, 2 H), 4.92 (d, $J$ = 11, 2 H), 7.27 (s, 5 H); (low $R_f$ diastereomer) 0.87 (d, $J$ = 6, 3 H), 1.07 (t, $J$ = 7, 3 H), 1.23–2.33 (br m, 6 H), 3.55 (m, 2 H), 3.8–3.9 (m, 1 H), 4.52 (s, 2 H), 4.93 (d, $J$ = 8, 2 H), 7.33 (s, 5 H).

Trimethyl orthoacetate (44.56 mL, 350 mmol) and propionic acid (0.522 mL, 7 mmol) were added to a solution of **23** (16.24 g) in 150 mL toluene. The reaction mixture was set to gentle reflux, and nitrogen was constantly swept just above the surface of the solution to remove the methanol formed during the course of the reaction. After 15 h, the toluene was removed and the residue distilled under vacuum to give 17.52 g (88%, 82% overall from **8**) of pure benzyloxy ester **24**. $[\alpha]^{25}_D$ +24.6° ($c$ 2.76, $CHCl_3$). $^1$H NMR: 0.9 (d, $J$ = 6, 3 H), 0.93 (t, $J$ = 6, 3 H), 1.07–2.7 (br m, apparent s at 2.33, 9 H), 3.4 (t, $J$ = 7, 2 H), 3.63 (s, 3 H), 4.47 (s, 2 H), 4.86 (d, $J$ = 9, 1 H), 7.33 (s, 5 H). IR ($CHCl_3$): 3000, 2970, 2925, 2870, 1730, 1490, 1455, 1445, 1410, 1380, 1350, 1295, 1240, 1235, 1205, 1150, 1110, 1100, 1075, 1040, 1020, 930, 910, 865, 840, 830, 695, 660.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.00; H, 9.03.

**(6*S*)-1-Hydroxy-4-ethyl-6-methyl-8-(benzyloxy)oct-4(*E*)-ene (25).** A solution of ester **24** (14.56 g, 47.8 mmol) in 25 mL of ether was added dropwise to a suspension of $LiAlH_4$ (1.9 g, 50 mmol) in 100 mL of ether at 0 °C. After the mixture had stirred overnight at room temperature, the excess reagent was carefully quenched with 10% aqueous HCl at 0 °C. The solution was extracted repeatedly with ether (5 × 50 mL), dried ($Na_2SO_4$), concentrated, and purified by column chromatography to give 12.65 g (96%) pure alcohol **25**. $[\alpha]^{25}_D$ +15.6° ($c$ 5.62, $CHCl_3$). $^1$H NMR: 0.91 (d, $J$ = 6, 3 H), 0.96 (t, $J$ = 7, 3 H), 1.21–1.86 (m, 4 H), 1.86–2.35 (m, 5 H), 2.35–2.87 (m, 1 H), 3.42 (t, $J$ = 6, 2 H), 3.55 (t, $J$ = 6, 2 H), 4.48 (s, 2 H), 4.88 (d, $J$ = 9.5, 1 H), 7.35 (s, 5 H). IR ($CHCl_3$): 3620, 3000, 2960, 2930, 2870, 2860, 1495, 1455, 1360, 1210, 1100, 1090, 1080, 1070, 1025, 945, 910, 780, 760, 750, 740, 725, 695.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.81; H, 10.16.

**(6*S*)-4-Ethyl-6-methyl-8-(benzyloxy)oct-4(*E*)-en-1-al (26).** Pyridinium chlorochromate (14.55 g, 67.5 mmol) and NaOAc (1.1 g, 13.5 mmol) were suspended in 100 mL $CH_2Cl_2$ and stirred vigorously by using an overhead stirrer. A solution of the above alcohol **25** (12.42 g, 45 mmol) in 15 mL $CH_2Cl_2$ was added, and the mixture was left stirring overnight. After 15 h, it was diluted with ether (250 mL) and filtered through a short pad of silica gel. The sticky residue was treated repeatedly with ether (3 × 100 mL) and the ethereal solution filtered each time through silica gel. The combined ethereal extracts were concentrated and the residue chromatographed to yield 9.58 g (80%) pure aldehyde **26**. $[\alpha]^{25}_D$ +32.6° ($c$ 1.26, $CHCl_3$). $^1$H NMR: 0.93 (d, $J$ = 6, 3 H), 0.98 (t, $J$ = 8, 3 H), 1.2–1.77 (m, 2 H), 1.8–2.7 (m, 7 H), 3.4 (t, $J$ = 6, 2 H), 4.45 (s, 2 H), 4.87 (d, $J$ = 9, 1 H), 7.33 (s, 5 H), 9.77 (apparently s, 1 H). IR ($CHCl_3$): 3000, 2960, 2930, 2865, 2720, 1720, 1495, 1450, 1370, 1215, 1205, 1130, 1120, 1100, 1090, 1080, 1025, 730, 725, 695, 660.

**(10*S*)-Methyl 4,10-Dimethyl-8-ethyl-12-(benzyloxy)dodeca-4(*E*),8-(*E*)-dienoate (27).** The procedure was essentially the same as that for the preparation of ester **24**. Thus, reaction of the Grignard reagent derived from 2-bromopropene (3.99 g, 33 mmol) with aldehyde **26** (8.22 g, 30 mmol) gave after column purification, a diastereomeric mixture of the allylic alcohols (7.61 g, 80.17%). $^1$H NMR: 1.05 (d, $J$ = 6, 3 H), 1.07 (t, $J$ = 7, 3 H), 1.3–1.97 (m, 5 H), 1.83 (s, 3 H), 1.97–2.43 (m, 4 H), 2.43–2.9 (m, 1 H), 3.53 (t, $J$ = 7, 2 H), 4.17 (t, $J$ = 6, 4.17), 4.6 (s, 2 H), 5.02 (d, $J$ = 9, 2 H), 7.43 (s, 5 H). These (7.61 g, 24.1 mmol) upon ortho ester Claisen rearrangement and usual workup afforded ester **27** (8.01 g, 90%, 72% from **25**) after column purification (20:1 hexane:EtOAc). $[\alpha]^{25}_D$ +30.0° ($c$ 0.79, $CHCl_3$). $^1$H NMR: 0.93 (d, $J$ = 6, 3 H) 0.97 (t, $J$ = 7, 3 H), 1.6 (br s, 6 H), 2.0 (br s, 6 H), 2.33 (br s, 4 H), 3.43 (t, $J$ = 7, 2 H), 3.66 (s, 3 H), 4.47 (s, 2 H), 4.85 (d, $J$ = 9, 1 H), 5.03–5.3 (m, 1 H); 7.33 (s, 5 H). IR ($CHCl_3$): 3020, 3005, 2960, 2930, 2870, 1730, 1495, 1455, 1440, 1365, 1300, 1265, 1230, 1210, 1160, 1090, 1030, 940, 920, 860, 725, 700, 610.

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.10; H, 9.34.

**(10*S*)-Methyl 4,10-Dimethyl-8-ethyl-12-hydroxydodeca-4(*E*),8(*E*)-dienoate (28).** Benzyloxy ester **27** (3.72 g, 10 mmol) was dissolved in 50 mL of acetone and 50 mL of 1 M LiOH solution. After refluxing 4 h, the acetone was removed on rotary evaporator, and the reaction was acidified and extracted with ethyl acetate (3 × 100 mL). Drying ($Na_2SO_4$), concentration, and column purification (1:1 hexane:ether) gave 3.185 g of benzyloxy acid. The acid was then taken up in 2 mL of THF and added to a refluxing (−33 °C) solution of liquid ammonia. Sodium (1.7 g, 74 mmol) was added in small portions over a period of 4 h; the blue color persisted throughout the course of the reaction. The reaction was quenched with solid $NH_4Cl$, and ammonia was evaporated by overnight stirring at room temperature. Water (250 mL) and ether (100 mL) were added to the residual solids and the layers separated. The aqueous layer was carefully acidified and reextracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated, and the crude residue was then treated with ethereal $CH_2N_2$ and chromatographed (4:1 to 1:1 hexane:ether) to give 953 mg of unreacted benzyloxy ester **27** and 1.355 g of hydroxy ester **28** (68% yield based on 74.5% conversion). $[\alpha]^{25}_D$ +27.4° ($c$ 0.90, $CHCl_3$). $^1$H NMR: 0.97 (d, $J$ = 6, 3 H), 0.99 (t, $J$ = 7.5, 3 H), 1.63 (br, s, 6 H), 2.03 (br s, 6 H), 2.37 (br s, 5 H), 3.62 (t, $J$ = 7, 2 H), 3.69 (s, 3 H), 4.9 (d, $J$ = 9, 1 H), 5.03–5.3 (m, 1 H). IR ($CHCl_3$): 3625, 3545, 2965, 2925, 2875, 1730, 1455, 1440, 1375, 1350, 1300, 1270, 1240, 1210, 1160, 1100, 1070, 1050, 1040, 990, 890, 860, 725. $^{13}$C NMR: 173.9, 139.9, 133.3, 130.7, 125.1, 61.7, 51.4, 40.7, 36.2, 34.7, 33.1, 29.2, 26.8, 23.3, 21.9, 15.9, 13.5.

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.04; H, 10.61.

**(10*S*)-Methyl 4,10-Dimethyl-6-ethyl-12-oxododeca-4(*E*),8(*E*)-dienoate [(+)-5].** $Me_2SO$ (960 μL, 13.5 mmol) was added to a solution of oxalyl chloride (590 μL, 6.75 mmol) in 15 mL of $CH_2Cl_2$ at −60 °C. After 2 min, a 2-mL $CH_2Cl_2$ solution of alcohol **28** (1.27 g, 4.5 mmol) was added and stirring was continued at −50 to −60 °C for 30 min. The reaction was warmed to −10 °C and triethylamine (3.14 mL, 22.5 mmol) was added. After warming to room temperature, water (50 mL) was added and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and saturated NaCl, dried ($Na_2SO_4$), and concentrated to give a residue weighing 1.323 g. Column purification (4:1 hexane:ether) yielded 1.12 g (89%) pure aldehyde **5**. $[\alpha]^{25}_D$ +32.14° ($c$ 2.37). $^1$H NMR: 0.93–1.02 (m, 6 H), 1.648 (br s, 1 H), 2.043 (br s, 6 H), 2.397 (br s, 3 H), 3.702 (s, 3 H), 4.92 (d, $J$ = 9, 1 H), 5.03–5.25 (m, 1 H), 9.727 (t, $J$ = 2, 1 H). IR ($CHCl_3$): 3030, 2980, 2940, 2885, 2740, 1730, 1465, 1445, 1385, 1355, 1305, 1270, 1225, 1170, 1100, 1080, 1020, 860, 800, 785, 750. $^{13}$C NMR: 198.01, 169.3, 136.2, 128.99, 124.22, 120.54, 46.92, 31.64, 30.18, 28.60, 24.87, 23.08, 22.27, 18.91, 17.17, 11.48, 8.88.

**Methyl 2,4-Dimethyl-3-oxopent-4-enoate [(±)-30].** To a mechanically stirred suspension of PCC[22] (4.3 g, 20 mmol) in $CH_2Cl_2$ (40 mL) was added **29**[13] (mixture of **29e** and **29t**, 0.316 g, 2 mmol) in $CH_2Cl_2$. The resulting mixture was stirred overnight, diluted with $Et_2O$ (120 mL), filtered through celite/florisil, concentrated, and chromatographed (silica gel, 50 g/g, 9:1 hexane/$Et_2O$), giving rise to **30** (0.262 g, 83%). The oxidation can be monitored by GC (AT-1000, column temperature 160 °C, injector and detector temperature 245 °C, $N_2$ flow 15 mL/min (**29t** 5.5 min, **29e** 6 min, **30** 3.3 min). **30**: $^1$H NMR ($CDCl_3$) ppm 1.4 (d, 3 H), 1.87 (s, 3 H), 3.66 (s, 3 H), 4.15 (q, 1 H), 5.83 (q, 1 H, $J \simeq 1$ Hz), 6.0 (bs, 1 H); $^{13}$C NMR ($CDCl_3$) 13.9 (q), 17.8 (q), 47.2 (d), 52 (q), 125.6 (t), 143.9 (s), 171.5 (s).

**Methyl 3-Hydroxy-2,4-dimethylpent-4-enoate [(±)-29e from (±)-30]. $Zn(BH_4)_2/Et_2O$ solution:**[24] "Anhydrous" $ZnCl_2$ (5 g, 36.7 mmol) was refluxed 2–3 h with $SOCl_2$ (30 mL) to remove the last traces of moisture. The bulk of the $SOCl_2$ was removed by distillation; the last traces were removed at reduced pressure (aspirator). To 4 g (29.4 mmol) of $ZnCl_2$ prepared above was added $Et_2O$ (50 mL) and this mixture refluxed until nearly all $ZnCl_2$ was dissolved (~1 h). The resulting solution was filtered under $N_2$ into a flask containing $NaBH_4$ (2.7 g, 69 mmol, 1.17 eq) in $Et_2O$ (150 mL) and this mixture stirred overnight at room temperature. The resulting mixture was centrifuged to remove suspended solids (under $N_2$!) and titrated with a gas buret by adding aliquots of the $Zn(BH_4)_2/Et_2O$ solution into water/EtOH (1:1). Typical concentration of solutions prepared as above were 0.1 M (0.09–0.12 M, theoretical concentration 0.147 M). Solutions of $Zn(BH_4)_2$/DME were prepared in a similar manner except that the total volume of DME was 42.5 mL, and typical concentration of $Zn(BH_4)_2$/DME was 0.45 M.

**Reduction of 30 with $Zn(BH_4)_2/Et_2O$.** To a solution of **30** (202 mg, 1.3 mmol) in $Et_2O$ (1.5 mL) was added a $Zn(BH_4)_2/Et_2O$ solution (0.12 M, 10 mL) at 0 °C. The resulting mixture was stirred at 0 °C 1 h and excess $Zn(BH_4)_2$ destroyed by the addition of 30% (aqueous) $Na_2C_4H_4O_4$ (20 mL). The layers were separated, the aqueous layer was extracted with ether (3 × 20 mL), the combined organic extracts were washed with saturated brine (1 × 20 mL), dried ($Na_2SO_4$), and filtered, the filtrate was concentrated, and the residue was chromatographed (solvent being removed from appropriate fractions by distillation and chromatography on silica gel with 9:1, hexane/$Et_2O$) to yield **29e** (197 mg, 96%). (Note, **29e** is fairly volatile and some will be lost if solvent is removed on the rotovap.) GC analysis and $^{13}$C NMR indicate the diastereoselectivity of the reaction to be >99%. **29t**: $^1$H NMR ($CDCl_3$) ppm 1.06 (d, 3 H),

1.72 (bs, 3 H), 2.6 (m, 1 H), 4.1 (m, 1 H), 3.35 (s, 3 H), 4.96 (m, 2 H). $^{13}$C NMR ($CDCl_3$) 14.4 (q), 17.0 (q), 43.2 (d), 51.8 (q), 78.1 (d), 113.9 (q), 144.5 (s), 176.2 (s). IR ($CCl_4$) 3610 (s), 3510 (b), (OH), 3065 (C=CH), 2940 (C-H), 1732, 1718 (C=O), 1645 (C=C). **29e**: $^1$H NMR ($CDCl_3$) ppm 1.13 (d, 3 H), 1.73 (bs, 3 H), 2.7 (m, 1 H), 1.72 (s, 3 H), 4.4 (br, 1 H), 4.96 (m, 1 H), 5.07 (bs, 1 H). $^{13}$C NMR ($CDCl_3$) 10.7 (q), 18.7 (q), 42.8 (d), 51.7 (q), 75.3 (d), 112.0 (t), 144.5 (s), 176.0 (s). IR ($CCl_4$) 3610 (s), 3520 (b), (OH), 3070 (C=CH), 1715, 1731 (C=O), 1645 (C=C).

**(2*RS*,3*RS*)-*S*-Phenyl 3-Hydroxy-2,4-dimethylthioprop-4-enoate [(±)-32e].** A solution of diisopropylethylamine (850 mg, 6.58 mmol) and *S*-phenyl thiopropionate (**31**) (1.09 g, 6.58 mmol) in anhydrous $Et_2O$ (15 mL) was cooled to 0 °C and added during 5 min to a 0.25 M solution of 9-BBNOTf in $Et_2O$ (26.3 mL) at 0 °C. The cooling bath was removed, and the mixture was allowed to warm to 20 °C. Methacrolein (365 μL, 4.43 mmol) was added in one portion, and the reaction mixture was stirred for 30 min. After being cooled to 0 °C MoOPH (2.86 g, 6.58 mmol) was added in one portion. The reaction was stirred 15 min at 0 °C and then 45 min later the cooling bath was removed. The resulting mixture was poured into sufficient 1 N NaOH to dissolve all of the solids, the layers were separated, and the clear blue aqueous phase was extracted with $Et_2O$ (2 × 50 mL). The organic extracts were combined, extracted with dilute and saturated brine, and dried ($MgSO_4$). The solvent was removed in vacuo and the bright yellow-green residue was purified by flash chromatography (100 g/g, 4.5:1 hexane:EtOAc) to give 890 mg (85% yield) of (±)-**32e**. $^1$H NMR (90 MHz, $CDCl_3$): 1.25 (d, $J$ = 6 Hz, 3 H), 1.76 (br s, 3 H), 2.43 (br s, 1 H), 3.00 (m, 1 H), 5.00 (br s, 1 H), 5.13 (br s, 1 H). IR (neat): 3500, 3060, 2990, 2910, 1695, 1480, 1440. $^{13}$C NMR (22.5 MHz, $CDCl_3$): 11.4 (q), 19.0 (q), 50.9 (d), 75.1 (d), 112.8 (d), 127.5 (d), 128.4 (d), 129.3 (d), 129.5 (d), 134.6 (s), 201.5 (s). Mass spectrum: $m/z$ 237 ($M^+$ + 1, .07), 236 ($M^+$, .04), 166 ($M^+ - C_4H_7O$, 2.4).

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.06; H, 6.84; S, 13.56. Found: C, 66.10; H, 7.05; S, 13.49.

**(2*RS*,3*RS*)-Methyl 3-Hydroxy-2,4-dimethylprop-4-enoate [(±)-29e from (±)-32e].** (±)-**32e** (207 mg, 0.88 mmol) was dissolved in a mixture of $CH_3CN$ (10 mL) and $CH_3OH$ (10 mL). $HgCl_2$ (1.95 g, 7.18 mmol) and $CdCO_3$ (2.7 g, 15.7 mmol) were added. The reaction mixture was left to stir for 24–48 h. The solvents were removed in vacuo using $CCl_4$ as an entroping agent. The residue was suspended in hexane, and the solids were filtered off using scintered glass. The solvent was removed in vacuo, and the residue was purified by flash chromatography (50 g/g, 3:1 benzene:EtOAc) to give 118 mg (85% yield) of (±)-**29e**. $^1$H NMR (90 MHz, $CDCl_3$): 1.13 (d, $J$ = 7 Hz, 3 H), 1.70 (br s, 3 H), 2.59 (m, 1 H), 3.68 (s, 3 H), 4.28 (br s, 1 H), 4.87 (br s, 1 H), 5.04 (br s, 1 H). IR (neat): 3610, 3520, 3070, 1731, 1715, 1645. $^{13}$C NMR (22.5 MHz, $CDCl_3$): 10.7 (q), 18.7 (q), 42.8 (q), 51.7 (d), 75.3 (d), 112.0 (t), 144.5 (s), 176.0 (s). Mass spectrum: $m/z$ 158 ($M^+$, 2.8), 88 ($M^+ - C_4H_7O$, 100).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.94. Found: C, 60.68; H, 9.04.

**(2*R*,3*S*)-1,3-Dihydroxy-2,4-dimethylpent-4-ene [(−)-34].** A solution of (−)-**29e** (1.0 g, 6.32 mmol) in anhydrous $Et_2O$ (5 mL) [obtained by $CH_2N_2$ treatment of (−)-**33**[13]] was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (957 mg, 25.2 mmol) in $Et_2O$ (15 mL). After the addition was complete, the cooling bath was removed and the reaction was stirred for 3 h. After the reaction was again cooled to 0 °C, water (1 mL), 15% NaOH (1 mL), and water (3 mL) were added carefully. This mixture was stirred for 1 h. $Na_2SO_4$ was added, the solids were filtered and washed with EtOAc, and the solvents were removed in vacuo. The residue was purified by flash chromatography (75 g/g, 30:1 $CH_2Cl_2$:$CH_3OH$) to give 741 mg. (−)-**34** (90%): $[\alpha]_D$ −14° ($c$ 3.3), ee = 0.82 by HPLC analysis (Dextran column, 6:1 hexane:$Et_2O$, 1.0 mL/min) of the di-(+)-MTPA ester.

**(2*RS*,3*SR*)-1,3-Dihydroxy-2,4-dimethylpent-4-ene [(±)-34].** A solution of (±)-**32e** (647 mg, 2.95 mmol) in anhydrous $Et_2O$ (12 mL) was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (450 mg, 11.8 mmol) in $Et_2O$ (25 mL). The cooling bath was removed and the reaction mixture was stirred 1 h. After the mixture was again cooled to 0 °C, water (0.5 mL), 15% NaOH (0.5 mL), and water (1.5 mL) were added carefully. This mixture was stirred for 1 h. $Na_2SO_4$ was added and the solids were filtered and washed with EtOAc. After the solvents were removed in vacuo the residue was purified by flash chromatography (75 g/g, 30:1 $CH_2Cl_2$:$CH_3OH$) to give 375 mg (98% yield) of (±)-**34**. $^1$H NMR (90 MHz, $CDCl_3$): 0.87 (d, $J$ = 6 Hz, 3 H), 1.70 (s, 3 H), 2.72 (br s, 2 H), 3.68 (d, $J$ = 4 Hz, 2 H), 4.24 (br d, 1 H), 4.95 (br s, 1 H), 5.04 (br s, 1 H). IR (neat): 3615, 3380, 3085, 2965, 1650. $^{13}$C NMR (22.5 MHz, $CDCl_3$): 9.9 (q), 19.3 (q), 37.4 (d), 66.7 (t), 76.8 (d), 110.6 (t), 146.4 (s). Mass spectrum: $m/z$ 130 ($M^+$, 3.4), 112 ($M^+ - H_2O$, 25), 97 ($M^+ - CH_5O$, 71; $M^+ - C_3H_7O$, 100).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.56; H, 10.86. Found: C, 62.96; H, 10.87.

**(2*RS*,3*RS*)-1,3-Dihydroxy-2,4-dimethylpent-4-ene 1,3-Acetonide [(±)-35].** To a solution of compound (±)-**34** (613 mg, 4.71 mmol) and 2-[(trimethylsilyl)oxy]propene (83%, 890 mg, 5.65 mmol) in dry $CH_2Cl_2$ (20 mL) was added two drops of chlorotrimethylsilane. The reaction mixture was warmed almost to reflux and was stirred for 1 h. After being diluted with $Et_2O$, the mixture was extracted with 10% HCl and saturated $NaHCO_3$ and dried ($MgSO_4$). The residue was purified by flash chromatography (50 g/g, 30:1 hexane:$Et_2O$) to give 738 mg (92% yield) of (±)-**35**; bp 80 °C at 0.1 mmHg. $^1$H NMR (90 MHz, $CDCl_3$): 0.92 (d, $J$ = 7 Hz, 3 H), 1.45 (br s, 6 H), 1.67 (br s, 3 H), 1.69 (br s, 3 H), 3.62 (dd, $J$ = 1.5, 12 Hz, 1 H), 4.20 (dd, $J$ = 3, 12 Hz, 1 H), 4.35 (br s, 1 H), 4.92 (br s, 1 H), 5.05 (br s, 1 H). IR ($CCl_4$): 3090, 2980, 1650, 1440, 1445. $^{13}$C NMR (22.5 MHz, $CDCl_3$): 10.7 (q), 19.0 (q), 29.7 (q), 30.5 (d), 66.5 (t), 73.5 (d), 98.7 (s), 110.0 (t), 142.8 (s).

**(2*RS*,3*RS*,4*RS*)-1,3,5-Trihydroxy-2,4-dimethylpentane 3,5-Acetonide [(±)-36].** $BH_3$·THF (1 M, 5.3 mL) was added dropwise during 5 min to a solution of compound (±)-**35** (3.0 g, 17.6 mmol) in anhydrous THF (360 mL) at 0 °C. The cooling bath was removed, and the reaction mixture was stirred 3 h. After the mixture was cooled again to 0 °C, 3 N NaOH (11 mL) and 30% $H_2O_2$ (11 mL) were added carefully. The cooling bath was removed and the mixture was stirred for 1 h. The mixture was diluted with a saturated NaCl solution and extracted with $Et_2O$. After drying ($MgSO_4$) the solvent was removed in vacuo, and the residue was purified by flash chromatography (100 g/g, 40:1 $CH_2Cl_2$:$CH_3OH$) to give 2.19 g (66% yield) of (±)-**36** and 0.59 g (19% yield) of the undesired isomer. $^1$H NMR (90 MHz, $CDCl_3$): 1.15 (t, overlapping doublets, 6 H), 1.35 (br s, 6 H), 1.62 (m, 2 H), 2.5 (br s, 1 H), 3.50 (m, 2 H), 3.4–3.7 (m, 2 H), 4.09 (dd, $J$ = 3, 12 Hz, 1 H). IR ($CCl_4$): 3480, 2975, 2945, 1460, 1380. $^{13}$C NMR (22.5 MHz, $CDCl_3$): 11.1 (q), 13.5 (q), 19.1 (q), 29.7 (q), 30.6 (d), 64.4 (t), 67.2 (t), 73.7 (d), 99.1 (s). Mass spectrum: $m/z$ 189 ($M^+$ + 1, 1), 188 ($M^+$, .04), 173 ($M^+ - CH_3$, 13), 130 ($M^+ - C_3H_6O$, 3), 129 ($C_7H_{13}O_2$, 5), 112 ($M^+ - C_7H_{13}O_2$, 100).

**Acetate (±)-37.** 4-(Dimethylamino)pyridine (2.5 mg) was added to a solution of alcohol (±)-**36** (1.88 g, 10 mmol) in 20 mL of $CH_2Cl_2$. This was followed by addition of $Ac_2O$ (1.42 mL, 15 mmol) and triethylamine (1.67 mL, 12 mmol) sequentially at room temperature. After 6 h, the reaction mixture was washed with 10% aqueous HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), and aqueous NaCl (1 × 15 mL), dried, and concentrated, and the residue was purified by flash chromatography to yield 2.21 g (96%) of acetate (±)-**37**. $^1$H NMR: 1.0 (d, $J$ = 6, 3 H), 1.10 (d, $J$ = 6, 3 H), 1.40 (s, 6 H), 0.9–2.2 (br m, 2 H), 2.07 (s, 3 H), 3.4–4.33 (br m, SH). IR ($CHCl_3$): 3000, 2880, 1730, 1520, 1380, 1240, 1100, 1010, 850.

**Kinetic Resolution of Acetate (±)-37. Preparation of Inhibited PPL.** Crude lipase (30 g, Sigma, L3126, Type II) was stirred in 100 mL of 0.2 M phosphate buffer (pH 7.2) 30 min at 0–5 °C, after which a solution of 60 mg of (phenylmethyl)sulfonyl fluoride (PMSF) in 1.5 mL of EtOH was added dropwise over a period of 5 min. The mixture was stirred for an additional 2 h at this temperature and lyophilized overnight (12 h) to give solid inhibited PPL. It was crushed into a fine powder and stored in the refrigerator for future use.

**(−)-(2*R*,3*S*,4*S*)-1,3,5-Trihydroxy-2,4-dimethylpentane 3,5-Acetonide (36).** Acetate (±)-**37** (988 mg, 4.29 mmol) were suspended in 200 mL of 0.2 M phosphate buffer (pH 7.2), and 127 of inhibited PPL was added to the solution. The mixture was stirred vigorously and the progress of the reaction was monitored by GC [1.5% OV-101 on Chromosorb WHP, 6 ft, 140°; alcohol = 2.45 min, acetate = 3.88 min; 2 h, 16% conversion; 2.75 h, 22%; 3.75 h, 29%; 6 h, 40%]. The reaction was terminated at 40% conversion by adding 50 mL $Et_2O_3$ to the solution and separating the layers. The aqueous layer was reextracted with $Et_2O$ (2 × 50 mL), and the combined organic extracts were dried and concentrated to give a residue which after column separation yielded 554 mg (56%) of acetate (+)-**37** and 283 mg (35%) alcohol (−)-**36** ($[\alpha]^{25}_D$ −7.9° ($c$ 4.5, $CHCl_3$)) whose optical purity was ee > 0.95 by HPLC analysis of the (+)-MTPA ester (cyclobond I column, flow rate = 1.0 mL/min, 4:1 hexane/ether, $R_t$ = 7.39).

**(+)-(2*S*,3*R*,4*R*)-1,3,5-Trihydroxy-2,4-dimethylpentane 3,5-Acetonide (36).** Acetate (±)-**37** (500 mg (2.17 mmol)) was suspended in 100 mL of 0.2 M phosphate buffer (pH 7.2), and 150 mg of inhibited PPL was added to the solution. The mixture was stirred continuously and the progress of the reaction was monitored by GC. An additional 200 mg and 150 mg of inhibited PPL were added after 1.5 h and 3 h, respectively. The reaction was terminated at 65% conversion after 4 h total reaction time and worked up in the usual manner to afford, after chromatographic purification, 249 mg of alcohol (−)-**36** (61%, $[\alpha]^{25}_D$ −4.7° ($c$ = 4.0), $CHCl_3$) and 150 mg of acetate (+)-**37** (30%, $[\alpha]^{25}_D$ +3.3 ($c$ 3.5, $CHCl_3$)). Acetate (+)-**37** was hydrolyzed by refluxing in a solution of

10 mL of THF and 2 mL of 2 N LiOH for 3 h and removing THF on the rotavapor, extracting the aqueous layer with EtOAc (3 × 20 mL), and concentrating, drying, and purifying the residue by column chromatography. The alcohol (120 mg) (+)-**36** thus obtained ($[\alpha]^{25}_D$ +7.73° ($c$ = 4.7, $CHCl_3$)) had *ee* > 0.95 by HPLC analysis of its (+)-MTPA ester (same conditions as that for (−)-**36**; 7.84 min).

**(2*R*,3*S*,4*R*)-(−)-3,5-Dihydroxy-2,4-dimethylpentanal 3,5-Acetonide (7).** A solution of $Me_2SO$ (0.16 mL, 2.25 mmol) in 0.5 mL of $CH_2Cl_2$ was added to a solution of oxalyl chloride (0.144 g, 1.13 mmol) in 3 mL of $CH_2Cl_2$ at −50 °C. After 5 min, a solution of the alcohol (+)-**36** (94 mg, 0.5 mmol) in 1 mL of $CH_2Cl_2$ was added dropwise over a period of 5 min. After 30 min at −50 °C, 0.7 mL (5.1 mmol) of triethylamine was added, and the reaction mixture was allowed to warm to ambient temperature. Water (5 mL) was added, the two layers were separated, and the aqueous layer was extracted (2 × 10 mL) with $CH_2Cl_2$. The combined organic layers were dried and concentrated in vacuo, and the residue was purified by flash chromatography (4:1 hexane:$Et_2O$) to yield 80 mg (86%) pure **7**. $[\alpha]^{25}_D$ −2.3° ($c$ = 1.6, $CHCl_3$). $^1H$ NMR: 1.07 (d, $J$ = 5 Hz, 3 H), 1.14 (d, $J$ = 5 Hz, 3 H), 1.38 (s, 3 H), 1.44 (s, 3 H), 2.62 (m, 1 H), 1.59 (m, 1 H), 3.55 (dd, $J$ = 1.0, 12 Hz, 1 H), 4.00–4.23 (m, two overlapping dd, 2 H). IR (neat): 2990, 2930, 2870, 2710, 1725, 1460, 1380. $^{13}C$ NMR (22.5 MHz, $CDCl_3$): 10.7 (q), 11.4 (q), 19.1 (q), 29.6 (q), 30.9 (d), 48.8 (d), 66.7 (t), 72.0 (d), 99.1 (s), 202.9 (s).

**(+)-(2*S*,3*R*,4*R*,5*S*,6*R*)-*S*-Pbenyl 3,5,7-Trihydroxy-2,4,6-trimethylthioheptanoate 5,7-Acetonide (39e,a).** A solution of diisopropylethylamine 77 μL, 0.44 mmol) and *S*-phenyl propanethioate (**31**) (73 mg, 0.44 mmol) in 2 mL of anhydrous $Et_2O$ was cooled to 0 °C and added during 5 min to a 0.25 M solution of 9BBN-OTf in $Et_2O$ (1.76 mL) at 0 °C. The cooling bath was removed, and the mixture was allowed to warm to 20 °C. A solution of aldehyde **7** (75 mg, 0.4 mmol) in 1 mL of $Et_2O$ was added, and the reaction mixture was stirred for 30 min. After cooling to 0 °C, MoOPH (191 mg, 0.44 mmol) was added in one portion. The reaction mixture was stirred 15 min at 0 °C and then 45 min at room temperature. The yellow-green mixture was poured into sufficient 1 N NaOH to dissolve all the solids, the layers were separated, and the clear blue aqueous phase was reextracted with $Et_2O$ (2 × 10 mL). The combined organic extracts were dried and concentrated, and the residue was purified by flash chromatography to give 91.5 mg (65%) pure **39e,a**. HPLC of the alcohol **39e,a** and its (+)-MTPA derivative indicated ee > 0.95. $[\alpha]^{25}_D$ +34.16° ($c$ 1.7, $CHCl_3$). $^1H$ NMR: 0.95 (d, $J$ = 7 Hz, 3 H), 1.20 (d, $J$ = 7 Hz, 3 H), 1.30 (d, $J$ = 7 Hz, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.70 (m, 2 H), 1.95 (m, 1 H), 3.55 (dd, $J$ = 1.5, 12 Hz, 1 H), 3.90 (m, 1 H), 4.08 (m, 1 H), 4.00–4.20 (m, 2 H). IR (neat): 3470, 2995, 2940, 2880, 1695, 1480, 1460, 1440. $^{13}C$ NMR (22.5 MHz, $CDCl_3$): 11.8 (q), 12.1 (q), 12.5 (q), 29.8 (q), 33.0 (d), 38.8 (d), 50.8 (d), 72.8 (d), 74.6 (d), 99.1 (s), 127.5 (d), 129.6 (d), 134.6 (s), 202.2 (s). Mass spectrum: $m/z$ 353 ($M^+$ + 1, .11), 337 ($M^+ - CH_3$), 1), 276 ($M^+ - H_2O - C_3H_6O$, 4), 129 ($C_7H_{13}O_2$, 100).

Anal. Calcd for C, 64.73; H, 8.02; S, 9.09. Found C, 64.44; H, 7.96; S, 9.10.

**(−)-(2*S*,3*R*,4*R*,5*S*,6*R*)-Methyl 3,5,7-Trihydroxy-2,4,6-trimethylpentanoate 5,7-Acetonide (38e,a).** Thioester **39e,a** (77.5 mg, 0.22 mmol) was dissolved in 5 mL of a 1:1 mixture of $CH_3CN$ and $CH_3OH$. $HgCl_2$ (89.6 mg, 0.33 mmol) and $CdCO_3$ (113.5 mg, 0.66 mmol) were added. The reaction mixutre was stirred at room temperature 12–15 h, after which the solvents were removed azeotropically in vacuo by using $CCl_4$. The residue was suspended in hexane and filtered, the filtrate concentrated, and the resulting residue purified by flash chromatography to give 55.5 mg (92%) of **38e,a**. HPLC of the alcohol **38e,a** and its (+)-MTPA ester indicated an ee > 0.95. $[\alpha]^{25}_D$ −6.3° ($c$ 1.9, $CHCl_3$). $^1H$ NMR (90 MHz, $CDCl_3$): 0.93 (d, $J$ = 7 Hz, 3 H), 1.19 (d, $J$ = 7 Hz, 3 H), 1.12 (d, $J$ = 7 Hz, 3 H), 1.39 (br s, 3 H), 1.43 (br s, 3 H), 1.72 (m, 2 H), 2.65 (m, 1 H), 3.55 (dd, $J$ = 1, 12 Hz, 1 H), 3.71 (3, 3 H), 3.90 (m, 1 H), 4.11 (m, 2 H). IR (neat) 3500, 2995, 2940, 2880, 1735, 1460, 1435, 1380. $^{13}C$ NMR (22.5 MHz, $CDCl_3$): 4 (q), 12.0 (q), 12.5 (q), 19.3 (q), 29.8 (q), 33.1 (d), 38.7 (q), 42.1 (q), 51.9 (d), 68.0 (t), 73.2 (d), 74.3 (d), 99.1 (s), 176.9 (s). Mass spectrum: $m/z$ 275 ($M^+$ + 1, 2), 259 ($M^+ - CH_3$, 4), 216 ($M^+ - C_3H_6O$, 3), 215 ($M^+ - C_3H_6O$ − H, 6), 129 ($C_7H_{13}O_2$, 50), 100 ($C_6H_{12}O$, 11), 71 ($C_4H_7O$, 84), 59 ($C_3H_7O$, 100).

Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.28; H, 9.57. Found C, 60.84; H, 9.62.

**(+)-(2*S*,3*R*,4*R*,5*S*,6*R*)-Methyl 3,5,7-Trihydroxy-2,4,6-trimethylheptanoate 3-Methyl ether, 5,7-Acetonide (40).** To a solution of (−)-**38e,a** (41 mg, 0.15 mmol) and $CH_3I$ (20 μL, 0.32 mmol) in anhydrous DMF (0.75 mL) was added freshly prepared $Ag_2O$ (32 mg, 0.14 mmol). The mixture was heated at 40–45 °C. At 1 h intervals, portions of $Ag_2O$ (32 mg, 0.14 mmol) and $CH_3I$ (40 mL, 0.64 mmol) were added, and the progress of the reaction was continuously monitored by TLC. The reaction was found complete after 15 h. The reaction mixture was diluted with $Et_2O$ (10 mL), and the solids were filtered. The filtrate was extracted with water, dried, and concentrated, and the resulting residue on column purification gave 38.7 mg (90%) of **40**, judged to be pure (>0.95) by HPLC. $[\alpha]^{25}_D$ +6.7° ($c$ 3.5, $CHCl_3$). $^1H$ NMR (90 MHz, $CDCl_3$): 1.00 (d, $J$ = 7 Hz, 3 H), 1.14 (t, two overlapping doublets, 6 H), 1.47 (br s, 6 H), 1.65 (m, 1 H), 1.98 (m, 1 H), 2.70 (m, 1 H), 3.40 (s, 3 H), 3.4–3.7 (m, 3 H), 3.80 (s, 3 H), 4.08 (dd, $J$ = 3, 12 Hz, 1 H). IR (neat) 2630, 1735, 1455, 1375. $^{13}C$ NMR (22.5 MHz, $CDCl_3$) 11.5 (q), 11.6 (q), 12.4 (q), 19.4 (q), 29.8 (q), 32.0 (d), 38.2 (d), 41.5 (q), 51.6 (d), 58.8 (q), 67.6 (t), 72.6 (d), 82.9 (d), 99.1 (s), 176.3 (s).

HRMS: calcd for $C_{14}H_{25}O_4$ ($M^+$ −31), 257.1753; found, 257.1745.

**(−)-(2*S*,3*R*,4*R*,5*S*,6*R*)-3,5,7-Trihydroxy-2,4,6-trimethyl-1-pentanoic Acid Lactone, 3-Methyl Ether (4b).** Ester (+)-**40** (29 mg, 0.1 mmol) was dissolved in $CH_3OH$ (2.0 mL). Water (2.0 mL) and HOAc (0.3 mL) were added, and the reaction mixture was stirred at room temperature for 1 h. Solid $NaHCO_3$ was then added to the reaction mixture, and it was extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and concentrated, and the residue was purified by flash chromatography (40:1 $CH_2Cl_2$:$CH_3OH$) to give 18 mg (80%) of pure **4b**. $[\alpha]^{25}_D$ −102.0° ($c$ 1.3, $CHCl_3$).

The (+)-MTPA ester of synthetic lactone alcohol (−)-**4b** indicated ee > 0.95 and matched completely with (+)-MTPA ester of lactone alcohol (−)-**4b** obtained from degradation of monensin [cyclobond column, 1.8:1 hexane:$Et_2O$, flow rate = 2.0 mL/min; 8.72 min; $[\alpha]^{25}_D$ −110.0° ($c$ 1.3, $CHCl_3$ of lactone alcohol obtained from degradation of monensin].

The (+)-**4b** lactone alcohol synthesized in an analogous manner from alcohol (−)-**36** had $[\alpha]^{25}_D$ +110.0° ($c$ 1.3, $CHCl_3$) and its (+)-MTPA ester had a retention time of 9.79 min under identical conditions on HPLC. $^1H$ NMR (90 MHz, $CDCl_3$): 0.91 (d, $J$ = 7 Hz, 3 H), 1.18 (d, $J$ = 7 Hz, 3 H), 1.38 (d, $J$ = 7 Hz, 3 H), 1.83 (br s, 1 H), 2.05 (m, 1 H), 2.51 (m, 2 H), 3.26 (m, 1 H), 3.40 (s, 3 H), 3.69 (dd, $J$ = 2, 11 Hz, 2 H), 3.83–4.3 (m, 1 H). IR (neat) 3450, 2920, 1725, 1455. $^{13}C$ NMR (22.5 MHz, $CDCl_3$): 5.1 (q), 14.0 (q), 15.2 (q), 31.7 (d), 37.6 (d), 39.3 (d), 56.7 (q), 81.5 (d), 83.9 (d), 173.6 (s).

HRMS: calcd for $C_{10}H_{17}O_3$ ($M^+$ − 31), 185.1178; found, 185.1184.

**Lactone Aldehyde 4a.** A solution of oxalyl chloride (20 μL, 0.225 mmol) in 1 mL of $CH_2Cl_2$ was cooled to −50 °C and $Me_2SO$ (32 μL, 0.45 mmol) was added at this temperature. After 2 min, a solution of the alcohol (−)-**4b** (32.4 mg, 0.15 mmol) in 250 μL of $CH_2Cl_2$ was added, and the stirring was continued for 20 min at −50 °C. Triethylamine (105 μL, 0.75 mmol) was added, and the flask was gradually warmed to room temperature. Solvents were removed on a rotary evaporator, and the resulting residue was washed thoroughly with $Et_2O$ (10 mL). The organics were then filtered through a short pad of celite, and $Et_2O$ was removed on the rotary evaporator. The residue was then dissolved in $CHCl_3$ (15 mL) and washed thoroughly with water (3 × 20 mL). The organic layer was dried ($Na_2SO_4$) and concentrated to give 27.6 mg (86%) of pure aldehyde **4a** (one spot by TLC, 86%) which was stored at −78 °C under argon and used immediately for the next reaction. $^1H$ NMR: 0.89 (d, $J$ = 7.5, 3 H), 1.32 (d, $J$ = 7, 3 H), 1.37 (d, $J$ = 7, 3 H), 2.0–3.1 (m, 3 H), 3.22 (d, $J$ = 4.5, 1 H), 3.37 (s, 3 H), 4.33 (dd, $J$ = 2, 10, 1 H), 9.77 (d, $J$ = 1.5, 1 H).

**(+)-(10*S*,14*S*,16*R*)-Methyl 4,10,14,16-Tetramethyl-8-ethyl-16-(2′-methyl-1′,3′-dioxolan-2′-yl)heptadeca-4(*E*),8(*E*),12(*E*)-trienoate (41).** *n*-BuLi (2.62 mL, 1.83 M solution, 4.8 mmol) was added to a solution of phenyl sulfone (+)-**6** (1.373 g, 4.4 mmol) in 15 mL of THF at −78 °C. The solution was warmed to −30 °C, held at that temperature for 40 min, and cooled back to −78 °C. A solution of aldehyde (+)-**5** (1.12 g, 4 mmol) in 4 mL of THF was added dropwise at −78 °C. The solution was warmed to 0 °C and stirred for 1.5 h, after which it was cooled back to −78 °C and quenched with benzoyl chloride (603 μL, 5.2 mmol). The reaction was stirred overnight at room temperature, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). Drying ($Na_2SO_4$), concentration, and column purification (4:1 to 1:1 hexane:$Et_2O$) yielded 1.7 g (61%) of diastereomeric sulfone benzoates. Reductive elimination (1.7 g, 2.44 mmol) was achieved by dissolving the mixture in 14 mL of $CH_3OH$ and 7 mL of EtOAc, cooling the flask to −30 to −40 °C, and gradually adding portions of 5.77% Na–Hg to the solution. Thus, a total of 7.5 g of 5.77% Na–Hg was added at −30 to −40° over a period of 18 h. The reaction mixture was then allowed to stand at this temperature for 20 h. The reaction was worked up by pouring into saturated NaCl solution (250 mL) and extracting with $Et_2O$ (7 × 50 mL). Drying ($Na_2SO_4$), concentration, and column purification (9:1 hexane:$Et_2O$) yielded 611 mg pure **41** (57%, 35% overall from **20**). $[\alpha]^{25}_D$ +20.6° ($c$ 0.78, $CHCl_3$). $^1H$ NMR: 0.47–1.13 (m, 14 H), 1.20 (s, 3 H), 1.60 (s, 3 H), 1.40–2.17 (br m, 10 H), 2.34 (br s, 5 H), 3.67 (s, 3 H), 3.90 (s, 4 H), 4.77–5.53 (m, 4 H). IR: 2960, 2930, 2880, 1730, 1455, 1440, 1380, 1375, 1345, 1295, 1265, 1210, 1210, 1160, 1090, 1085, 1070, 1045, 970, 950, 860, 755, 730. $^{13}C$ NMR: 173.8, 139.0, 136.8, 133.1, 130.7, 127.7, 125.4, 112.5, 64.5 (2c), 51.4, 40.9, 39.1, 38.8, 36.2,

34.7, 33.1, 32.6, 29.5, 26.9, 23.4, 22.6, 21.0, 20.2, 15.9, 14.3, 13.5. Exact HRMS: calcd for $C_{27}H_{46}O_4$ ($M^+$), 434.3396; found 434.3387.

Anal. Calcd for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found: C, 74.46; H, 10.55.

**(+)-(11*S*,15*S*,16*R*)-5,11,15,17-Tetramethyl-9-ethyl-17-(2′-methyl-1′,3′-dioxolan-2′-yl)octadeca-5*E*,9*E*,13*E*-trien-2-one (42).** LiOH (0.5 mL, 2 M) was added to a solution of methyl ester **41** (145 mg, 0.33 mmol) in 4 mL of THF and the solution refluxed 10 h. THF was removed on a rotary evaporator, and the residue was diluted with 10 mL of $H_2O$. The aqueous solution was neutralized with $NaH_2PO_4$ and extracted with EtOAc (3 × 20 mL). Drying ($Na_2SO_4$) and concentration gave a residue which was taken up in 2 mL of benzene and oxalyl chloride (292 μL, 3.3 mmol). After the mixture had stirred 30 min at room temperature, benzene and excess oxalyl chloride were removed on a rotary evaporator to give the crude acid chloride.

In another flask, dimethylcopper lithium was prepared by addition of $CH_3Li$ (9.53 mL, 1.7 M, 16.2 mmol) to a suspension of CuI (1.9 g, 10 mmol) in 25 mL of $Et_2O$ at 0°. After stirring at room temperature for 10 min, it was cooled to −78 °C, and the crude acid chloride was added dropwise as a solution in 1 mL of $Et_2O$. After 30 min, the reaction was quenched with 1 mL of MeOH at −78 °C. On warming to room temperature, 15 mL saturated $NH_4Cl$ was added; THF and MeOH were removed on the rotary evaporator and the aqueous phase was extracted with $Et_2O$ (3 × 25 mL). Drying ($Na_2SO_4$), concentration, and column purification (4:1 hexane:$Et_2O$) gave 115 mg pure methyl ketone **42** (82%). $[\alpha]^{25}_D$ +24.92° (*c* 1.55, $CHCl_3$). $^1H$ NMR: 0.73–1.05 (m, 12 H), 1.23 (s, 3 H), 1.60 (s, 3 H), 2.14 (s, 3 H), 1.0–2.7 (m, 17 H), 3.90 (s, 4 H), 4.87 (d, *J* = 8, 1 H), 5.03–5.20 (m, 2 H), 5.25–5.40 (m, 1 H). IR: 2965, 2930, 2900, 2880, 1710, 1455, 1380, 1360, 1230, 1210, 1160, 1100, 1090, 1065, 1045, 970, 950, 870. $^{13}C$ NMR: 208.4, 138.9, 136.8, 133.4, 130.8, 127.7, 125.1, 112.6, 64.5 (2c), 42.5, 40.8, 39.1, 38.8, 36.3, 34.8, 33.6, 32.6, 29.8, 26.9, 23.4, 22.6, 20.9, 20.3, 16.1, 14.3, 13.5.

HRMS: calcd for $C_{27}H_{46}O_3$, 418.3426; found, 418.3412.

**43a and 43b.** LDA was prepared by adding *n*-BuLi (93 μL, 1.55 M, 0.144 mmol) to a solution of diisopropylamine (20 μL, 0.144 mmol) in 1 mL of THF at −78 °C and then stirring for 15 min at room temperature. A solution of methyl ketone (+)-**42** (50 mg, 0.120 mmol) in 1 mL THF was added to LDA at −78 °C. After stirring for 20 min at −78 °C, a solution of freshly prepared aldehyde **4a** (25.7 mg, 0.12 mmol) in 1 mL of THF was added. The reaction mixture was stirred for 45 min at −78° and quenched with saturated aqueous $NH_4Cl$ (50 μL) at this temperature. On warming to room temperature, the solution was filtered through a short pad of $Na_2SO_4$. The solvents were removed, and the residue was absorbed on silica gel (230–400 mesh), which was then subjected to column purification (4:1 to 1:1 hexane:$Et_2O$). The following products were obtained ($R_f$ values in solvent 1:1 hexane:EtOAc): unreacted methyl ketone (+)-**42** (8.94 mg, $R_f$ 0.67), unidentified product (6 mg, $R_f$ 0.5), minor isomer **43b** (5 mg, $R_f$ 0.4), major isomer **43a** (44.5 mg, $R_f$ 0.33), and unidentified product (4 mg, $R_f$ 0.25). Thus, the diastereomers **43a** and **43b** were obtained in a ratio of 9:1 and 80% yield based on 81% conversion of the methyl ketone (+)-**5**.

**43a**: $[\alpha]^{25}_D$ −41.38° (*c* 0.098, $CHCl_3$); $^1H$ NMR 1.13 (d, *J* = 7, 3 H), 1.27 (s, 3 H), 1.40 (d, *J* = 7, 3 H), 1.57 (s, 3 H), 0.9–2.7 (br m, 38 H), 3.1 (apparent s, 1 H), 3.42 (s, 3 H), 3.93 (br s, 4 H), 4.1–4.5 (m, 3 H), 4.8–5.5 (m, 3 H).

HRMS calcd for $C_{38}H_{64}O_7$ ($M^+$) 632.4651, found 632.4637.

**43b**: HRMS calcd for $C_{38}H_{64}O_7$ ($M^+$) 632.4651; found 632.4645.

**Aldols 46a and 46b.** THF (1 mL) was added in a 5-mL round-bottomed flask and cooled to −78 °C, after which 10 μL diisopropylamine (.07 mmol) was added. This was followed by addition of 22 μL of 1.55 M *n*-BuLi (.04 mmol). The flask was warmed to room temperature, stirred for 10 min, and cooled back to −78 °C. The methyl ketone (+)-**42** (14 mg, .033 mmol) in 200 μL of THF was added to this freshly prepared LDA at −78 °C. After stirring for 20 min at −78 °C, silyloxy aldehyde **44**[2c] (12 mg, .033 mmol) was added dropwise as a solution in 200 μL of THF. The reaction mixture was stirred 45 min at −78 °C after which it was quenched with 50 μL of saturated aqueous $NH_4Cl$ and warmed to room temperature. The solvents were removed on a rotary evaporator and the residue was directly subjected to short-pad flash chromatography using 230–400 mesh silica gel (4:1 to 1:1 hexane:$Et_2O$). The following products were obtained ($R_f$ values in 1:1 hexane:$Et_2O$): unreacted methyl ketone (+)-**42** (3.4 mg, $R_f$ 0.53, 24.3%), minor aldol product **46b** (4.5 mg, $R_f$ 0.44), and the major aldol product **46a** (12.7 mg, $R_f$ 0.35). Thus, the diastereomers **46a** and **46b** were obtained in a ratio of 2.8:1 and an 88% yield based on 76% conversion of the methyl ketone (+)-**5**.

**46a**: $^1H$ NMR 0–2.8 (m, roughly 72 H), 3.33 (s, 3 H), 3.74 (s, 3 H), 3.93 (s, 4 H).

**Conversion of 46a to 43a.** The major aldol product **46a** (10 mg, 0.0128 mmol) was dissolved in 1 mL of THF and 0.1 mL of a 1 M tetrabutylammonium fluoride solution in THF was added. A TLC check after 30 min of stirring at room temperature indicated total disappearance of the starting material. The solvents were removed, the residue preabsorbed on silica gel and subjected to flash chromatography yielding 8.1 mg of a single product (**46a**, $R_f$ 0.35 in 1:1 hexane:$Et_2O$, $R_f$ 0.62 in 1:1 hexane:EtOAc and the product $R_f$ 0.33 in 1:1 hexane:EtOAc) shown to be **43a** (100% yield) by cospotting on TLC and by $^1H$ NMR.

**Deketalization of 43a to 47.** 8.5 mg (0.013 mmol) of **43a** was dissolved in 2 mL of acetone and 0.4 mL of water, and 25 mg of pyridinium tosylate was added to this solution. After refluxing 7.5 h, acetone was removed on the rotary evaporator and water was azeotropically removed using $CCl_4$. The residue was purified using a short pad of silica gel (230–400 mesh) yielding 7.5 mg (95%) methyl ketone **47**, $[\alpha]^{25}_D$ −34.2 (*c* 0.052, $CHCl_3$). $^1H$ NMR: showed total disappearance of the ketal singlet 3.93 and appearance of a new methyl ketone singlet 2.03; 0.76–2.51 (broad multiplets), 2.03 (s, 3 H), 3.33 (s, 3 H), 4.08 (m, 2 H), 4.73 (m, 1 H), 4.97–5.20 (m, 4 H).

**Sodium Salt of 2b.** Lactone **47** (5 mg) ($R_f$ 0.33 in 1:1 hexane:EtOAc, $R_f$ 0.86 in EtOAc) was dissolved in 0.5 mL of 4:1 THF–0.05 N NaOH. A TLC check after 10 min at RT revealed total disappearance of starting material and the appearance of a new spot ($R_f$ 0.12 in EtOAc). This should be the sodium salt of **2b** since upon acidification, the starting material **47** ($R_f$ 0.33 in 1:1 hexane:EtOAc) was regenerated which was isolated and characterized in the usual fashion ($^1H$ NMR, $[\alpha]^{25}_D$).

**Synthesis of Radioactive ($^{14}C$) Methyl Ketone (51). 48.** A solution of ester (+)-**41** (117 mg, 0.269 mmol) in 2 mL of $Et_2O$ was added dropwise to a suspension of $LiAlH_4$ (31 mg, 0.81 mmol) in 10 mL of $Et_2O$ at 0 °C. After the mixture had stirred for 2 h at room temperature, the excess reagent was carefully quenched with 10% aqueous HCl at 0 °C. The two layers were separated, and the aqueous solution was extracted repeatedly with $Et_2O$ (4 × 15 mL). The combined organic extracts were dried and concentrated, and the residue was purified by column chromatography to yield 105 mg (95%) of the derived alcohol, **48**. $^1H$ NMR ($CDCl_3$): 0.92 (d, *J* = 6, 3 H), 1.23 (s, 3 H), 1.65 (s, 3 H), 0.8–2.35 (br m, 27 H), 3.66 (t, *J* = 6, 2 H), 3.93 (s, 4 H), 4.91 (d, *J* = 9, 1 H), 4.93–5.5 (m, 3 H).

**49.** $Me_2SO$ (91 μL, 1.29 mmol) was added to a solution of oxalyl chloride (45 μL, 0.517 mmol) in 2 mL of $CH_2Cl_2$ at −60 °C. After 1 min, 0.5 mL of $CH_2Cl_2$ solution of the above alcohol, **48** (81.2 mg, 0.2 mmol), was added and stirring was continued at −50 °C for 45 min. The reaction mixture was then quenched with triethylamine (180 μL, 1.3 mmol) and warmed to room temperature. Water (15 mL) was added, the two layers were separated, and the aqueous layer was extracted with $CH_3Cl_2$ (3 × 10 mL). The combined organic extracts were dried and concentrated, and the residue was purified by column chromatography to yield 69.5 mg (86%) of aldehyde, **49**. $^1H$ NMR: 0.81 (d, *J* = 6, 3 H), 0.9 (d, *J* = 6, 3 H), 1.13 (s, 3 H), 1.53 (s, 3 H), 0.8–2.6 (m, 23 H), 3.82 (s, 4 H), 4.8 (d, *J* = 10, 1 H), 4.8–5.35 (m, 3 H), 9.70 (t, *J* = 2, 1 H).

**50.** Freshly sanded Mg (40 mg, 1.74 mmol) was cut into small pieces and transferred to a 25-mL three-neck round-bottom flask with a finger tip condensor attached, which opened to a three way stopcock fitted with an argon balloon and a rubber septum. The flask was flame-dried and purged with argon for 15 min. $Et_2O$ (2 mL), 1,2-dibromoethane (10 μL), and $Br_2$ (1 drop) were added, and the red colored solution was refluxed for 5 min. The solution decolorized and became cloudy and was cooled to room temperature. The neck of the vial containing $^{14}CH_3I$ (5.5 mg, 0.038 mmol, 2 mCi radioactivity) was flame-dried and connected to the main flask via a canula. An argon atmosphere was strictly maintained during this operation. The flask was cooled to −78 °C, the seal of the vial was broken, $Et_2O$ (2 mL) was added, and the ethereal solution of $^{14}CH_3I$ was transferred by vaporizing it with a heat gun. The vial was rinsed twice with 2-mL portions of $Et_2O$, and the rinsings were added to the flask in a similar manner. This was followed by addition of $^{13}CH_3I$ (25 μL, 0.4 mmol). The flask was then warmed gradually and finally, after refluxing for 15 min, cooled back to room temperature. Addition of $Br_2$ (1 μL) resulted in its decolorization, confirming the formation of the Grignard reagent. A solution of the above aldehyde, **49** (48 mg, 0.119 mmol), in 3 mL of $Et_2O$ was added to the flask, and the solution was refluxed for 15 min. After additional stirring at room temperature for 30 min, the reaction was quenched with water (15 mL) and extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were dried and concentrated, and the residue was chromatographed (10:1 hexane:EtOAc) to yield 27 mg (54%) of a diastereomeric mixture of radioactive alcohols, **50** (total radioactivity = 110 μCi, $3.7 \times 10^9$ cpm/mmol). $^1H$ NMR: 0.91 (d, *J* = 6, 3 H), 1.23 (s, 3 H), 1.63 (s, 3 H), 0.8–2.6 (m, 3 H), 3.93 (s, 4 H), 4.9 (d, *J* = 9, 1 H), 4.9–5.5 (m, 3 H).

**51**. A solution of $CrO_3$ (65 mg, 0.65 mmol) and pyridine (10 μL, 0.13 mmol) in 5 mL of $CH_2Cl_2$ was stirred at room temperature for 15 min (persistent red color) after which a solution of $^{14}C$- and $^{13}C$-labeled alcohol (27 mg, 0.64 mmol) in 5 mL of $CH_2Cl_2$ was added dropwise. After 15 min, $Et_2O$ (25 mL) was added and the solution was decanted. The residue was washed with $Et_2O$ (2 × 20 mL). Drying and concentration under vacuo gave 40 mg of residue which after column purification yielded 18 mg (67%) of methyl ketone **51** (total radioactivity = 70 μCi).

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# Role of Retinal Isomerizations and Rotations in the Photocycle of Bacteriorhodopsin

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**Abstract:** Artificial bacteriorhodopsin (bR) pigments based on synthetic retinal analogues with selectively blocked single and double bonds were prepared. It was shown that rotations around single bonds $C_{12}$–$C_{13}$ and $C_{10}$–$C_{11}$ and isomerizations of $C_{11}$=$C_{12}$ and $C_9$=$C_{10}$ are not required either for initiating the photocycle of *all-trans*-bR or for forming its $M_{412}$ intermediate. The results are discussed in light of mechanisms for the primary event (based on the $C_{13}$=$C_{14}$ isomerization) involving a concerted double-bond and single-bond rotation around adjacent C,C bonds. Similarly, the photoreaction of the 13-cis isomer of bacteriorhodopsin does not require isomerization about the $C_{11}$=$C_{12}$ double bond or rotation around $C_{12}$–$C_{13}$. It is also shown that 13-cis ⇔ all-trans (light–dark adaptation) reaction of bacteriorhodopsin does not involve additional rotations or isomerizations involving the $C_9$–$C_{13}$ section of the molecule.

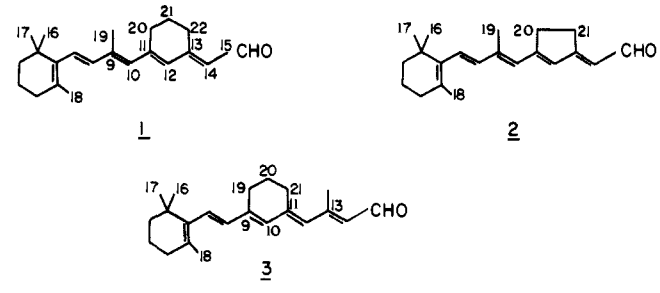
The light-adapted modification of bacteriorhodopsin (bR—the protein pigment in the purple membrane of *Halobacterium halobium*) contains an *all-trans*-retinyl chromophore bound to the protein via a protonated Schiff base linkage with a lysine residue.[1] The photosynthetic activity of $bR_t$ is associated with a light-driven proton pump induced by a photoprocess centered in the polyene chromophore.[1] In analogy to visual pigments [characterized by a similar (11-cis) retinal–protein complex], light absorption is followed by a sequence of structural transformations involving both the polyene and the protein.[2] A detailed description of all these events is required for formulating a molecular model for the function of bacteriorhodopsin.

Of major importance is the primary event, associated with the red-shifted $K_{610}$ intermediate, analogous to bathorhodopsin in the visual photocycle.[2] By use of artificial bacteriorhodopsins based on synthetic retinal analogues, it was recently concluded that only the terminal $C_{12}$–N part of the polyene is essential for initiating the bR photocycle, directly implying that the freedom to isomerize about the $C_{13}$=$C_{14}$ double bond is the major prerequisite for generating $K_{610}$.[3,4]

Several studies have previously led to the suggestion that both visual and bateriorhodopsin photocycles are initiated by isomerization around at least two bonds. Such studies include arguments based on the observation of two independent photocycles for $bR_t$ and for its 13-cis isomer, $bR_{13\text{-cis}}$,[5] Warshel's bicycle-pedal model for isomerization in a constrained medium,[6] and the approaches of Schulten[7] and Liu,[8] requiring simultaneous twisting of two adjacent bonds. The suggested combinations are $C_{11}$=$C_{12}$ and $C_{10}$–$C_{11}$ in the case of visual pigments[8a] and $C_{13}$=$C_{14}$ and $C_{14}$–$C_{15}$ for $bR_t$.[7,8b]

In addition to establishing the critical role of the $C_{13}$=$C_{14}$ isomerization in generating the photocycle, our previous work with $bR_t$[4,9] has excluded the need of isomerizations and rotations about all other polyene bonds, except for $C_{12}$–$C_{13}$, $C_{14}$–$C_{15}$, and $C_{15}$=N, for formation of the primary (K) intermediate. In the present work, based on synthetic retinals **1** and **2** (Chart I), we directly analyze the role played by the $C_{12}$–$C_{13}$ single bond in initiating the photocycle. These chromophores, which maintain the basic

**Chart I**

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