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Sequential Application of Stereoselective *Syn*-Oxidation Methodologies to Natural Product Synthesis: A Potentially Biomimetic Approach to the C_{12}-C_{21} Bistetrahydrofuran Region of Monensin

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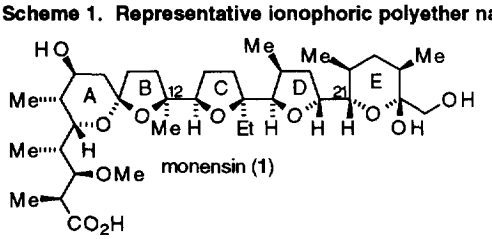
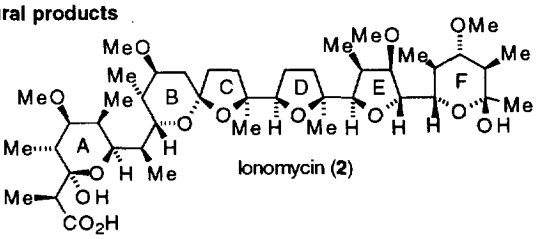
Abstract: The preparation of an all-Z-triene corresponding to an acyclic premonensin triene is described. In analogy to the Townsend *syn*-oxidative cyclization hypothesis for natural product biosynthesis, a sequence of regioselective and enantioselective *syn*-dihydroxylation of the triene, *cis*-selective *syn*-oxidative cyclization of the diol-diene, and *trans*-selective *syn*-oxidative cyclization of the remaining hydroxyalkene gives the correct stereochemical pattern corresponding to the C and D ring tetrahydrofurans of monensin. © 1997 Elsevier Science Ltd.

INTRODUCTION

The polyether antibiotics monensin (**1**) and lonomycin (**2**, Scheme 1) are two examples of a relatively large family of bioactive polyether ionophoric natural products isolated from *Streptomyces*. These compounds have commercial applications as coccidiostatic agents, and exhibit other useful antibiotic activities. The biological activities of these and structurally related ionophoric natural products result from their abilities to efficiently and selectively coordinate to monovalent ions, especially Na^+, and to facilitate their transport across biomembranes by encapsulating the metal ion by a relatively lipophilic shell.

Scheme 1. Representative ionophoric polyether natural products

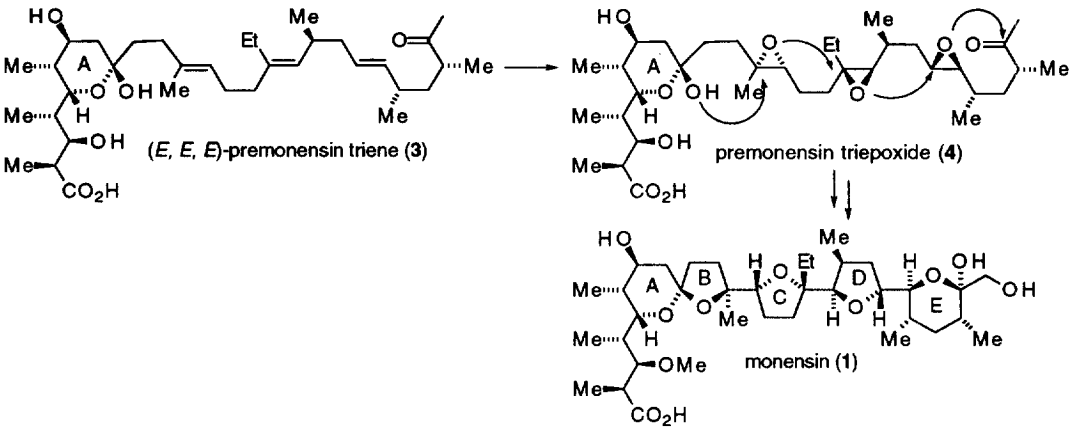




Although several total syntheses of these and related polyether natural products have been reported, the large-scale commercial preparation of these compounds is achieved by harnessing the synthetic power of microorganisms, i.e. by fermentation. To this end Cane has demonstrated the biosynthetic origins of the carbon chain of monensin from polyketide precursors (specifically acetate, propionate, and butyrate) and has also shown that the oxygen atoms of the C, D, and E rings of monensin arise from atmospheric oxygen and *not* from the polyketide carboxyl groups.[1] These results support an elegant hypothesis disclosed in 1983 by Cane, Celmer, and Westley, who proposed that polyether natural products such as monensin were derived from an all-

E-hydroxypolyene (**3**, Scheme 2). This polyene **3** is then presumably enzymatically stereoselectively epoxidized to the triepoxide **4**, followed by a cascade of regioselective and stereospecific *anti*-opening events by intramolecular alcohol addition to afford the polyether skeleton of monensin (**1**).[2]

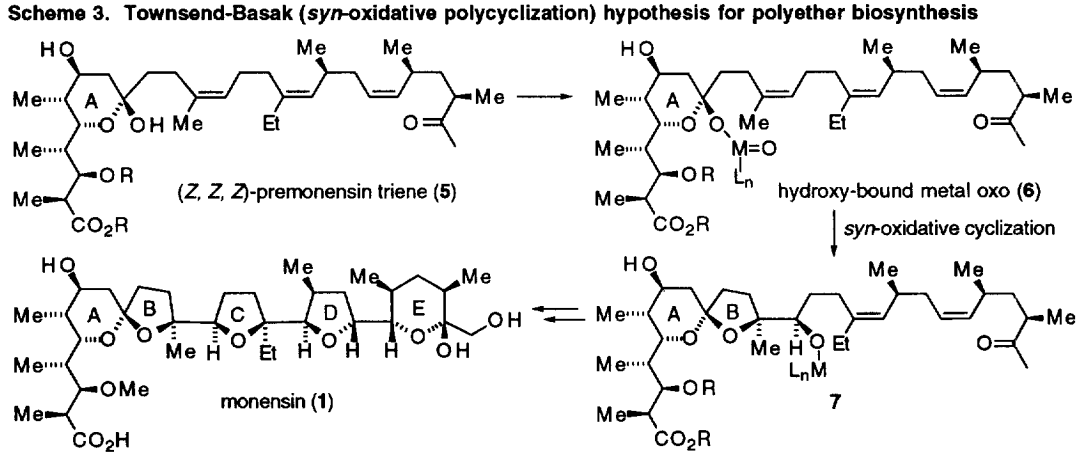
Scheme 2. Cane-Celmer-Westley (polyepoxidation/*anti*-cyclization) hypothesis for polyether biosynthesis



The putative premonensin triene **3** has not yet been found as a natural product, but **3** has been synthesized in several laboratories.[3] The only reported study of feeding experiments of *Streptomyces cinnamonensis* with synthetic radiolabeled (*E*, *E*, *E*)-premonensin triene derivatives failed to demonstrate isotopic incorporation in the monensin produced,[4] thus the Cane-Celmer-Westley hypothesis remains unproven.

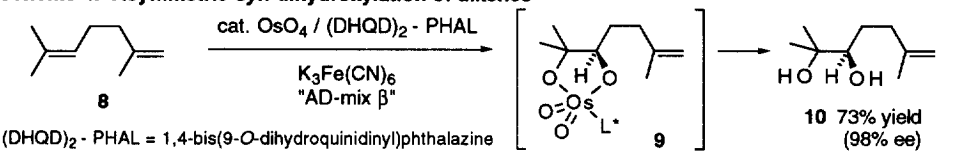
In the 1991 *Tetrahedron* Symposium-In-Print "Recent Advances in Bioorganic Chemistry", Townsend and Basak suggested a mechanistic alternative to the Cane-Celmer-Westley hypothesis, in which they proposed that *syn*-oxidative polycyclization of the (*Z*, *Z*, *Z*)-isomer (**5**) of premonensin triene might be operative (Scheme 3).[5] This *syn*-oxidative cyclization biosynthesis hypothesis also provides for late-stage introduction of oxygen atoms for the C, D, and E rings, and in the absence of further information on the biosynthesis pathway is equally plausible along with the stereocomplementary polyepoxide *anti*-cyclization hypothesis.

Scheme 3. Townsend-Basak (*syn*-oxidative polycyclization) hypothesis for polyether biosynthesis



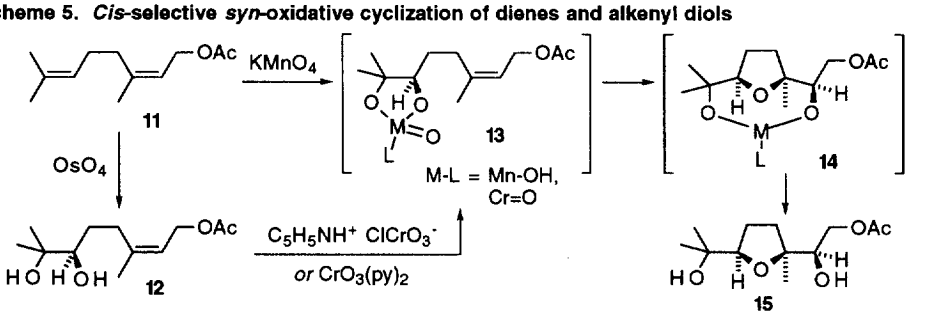
Although this reaction type is not currently known for biological systems, a number of examples of *syn*-oxidative cyclization reactions are documented in the chemical literature. A mechanistically related process is the well-known *syn*-dihydroxylation reaction, for which a highly enantioselective version has been developed as shown in Scheme 4.[6] In many cases the asymmetric dihydroxylation reaction is not only stereoselective but also highly regioselective, exhibiting particular affinity for trisubstituted alkenes.[7]

Scheme 4. Asymmetric *syn*-dihydroxylation of alkenes



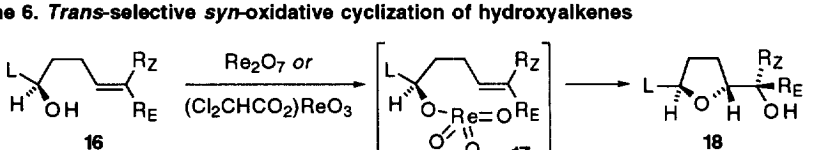
The prototype *syn*-oxidative cyclization reaction is the stereospecific permanganate-mediated conversion of 1,5-dienes such as **11** to *cis*-tetrahydrofuranyl diol **15** (Scheme 5).[8] Chromium oxos also mediate stereospecific *syn*-oxidative cyclizations of alkenyl diols including **12** to afford *cis*-substituted tetrahydrofuran products **15**.[9] The oxo ligands of the cyclic manganate or chromate ester intermediates are geometrically constrained from oxidation of the secondary carbinol hydrogen in favor of oxo transfer to the neighboring alkene. The synthetic utility of these reactions is somewhat limited, as a major side reaction of both manganese and chromium-promoted processes is oxidative carbon-carbon bond cleavage of alkenes and/or the 1,2-diol.

Scheme 5. *Cis*-selective *syn*-oxidative cyclization of dienes and alkenyl diols

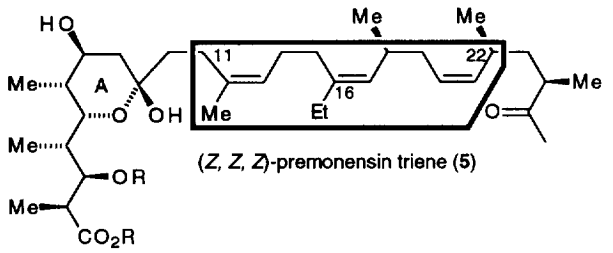


Syn-oxidative cyclizations directed by a single hydroxyl group consistently provide *trans*-tetrahydrofuranyl alcohols with high stereoselectivity when conducted with chromium[10] or rhenium oxide[11] reagents. Although the chromium (VI)-induced cyclizations are limited to tertiary alcohol substrates, the rhenium (VII) *syn*-oxidative cyclizations are compatible with primary and secondary alcohols **16** (Scheme 6). Oxidative cleavage of alkenes is not observed with the rhenium oxide procedures. We recently discovered that acylperrhenate reagents afford high-yielding *syn*-oxidative cyclizations of acid-sensitive substrates.[12]

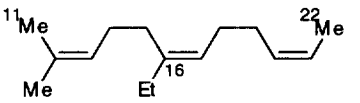
Scheme 6. *Trans*-selective *syn*-oxidative cyclization of hydroxyalkenes



In this paper we present the successful serial application of these *syn*-oxidation methodologies to the preparation of the bistetrahydrofuran section corresponding to the polyether ionophores monensin and lonomycin. We chose to initiate this study with the triene **19**, which would serve as a model for all-*Z*-premonensin triene (**5**).



(*Z, Z, Z*)-premonensin triene (**5**)

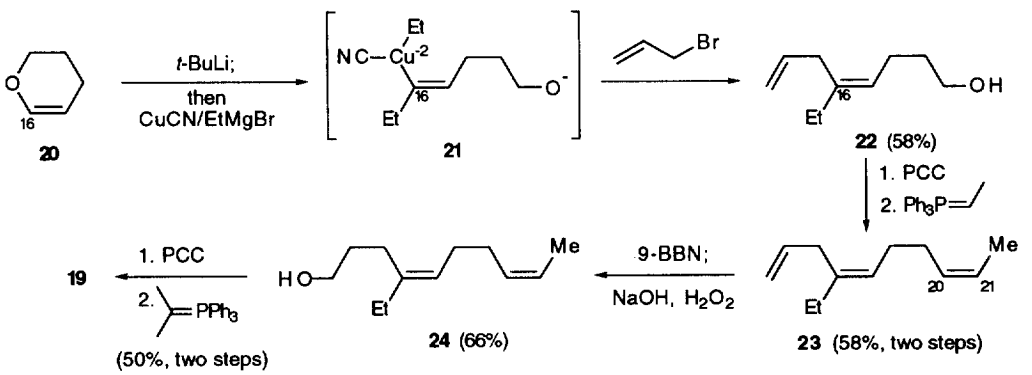


C_{11} - C_{22} triene fragment (**19**)

RESULTS

The synthesis of the triene fragment **19** began with the stereoselective preparation of the central trisubstituted *Z*-alkene, using the 1,2-metallate rearrangement methodology pioneered by Kocieński.[13] Deprotonation of dihydropyran (**20**) was followed by addition of the higher-order cuprate reagent generated from ethylmagnesium bromide and copper cyanide; 1,2-metallate rearrangement afforded the *Z*-vinylic cuprate intermediate **21** which was stereospecifically alkylated by allyl bromide to give **22** (Scheme 7). Pyridinium chlorochromate (PCC) oxidation of **22** followed by Wittig olefination under "salt-free" conditions[14] provided the $C_{20\text{-}21}$ alkene of **23** with high *cis*-stereoselectivity. Hydroboration of the triene substrate **23** with 9-BBN proceeded with complete regioselectivity for the monosubstituted alkene,[15] which upon oxidation of the organoborane provided the primary alcohol **24**. PCC oxidation and Wittig reaction with isopropyltriphenylphosphonium ylide then provided the desired C_{11}-C_{22} triene fragment **19**.

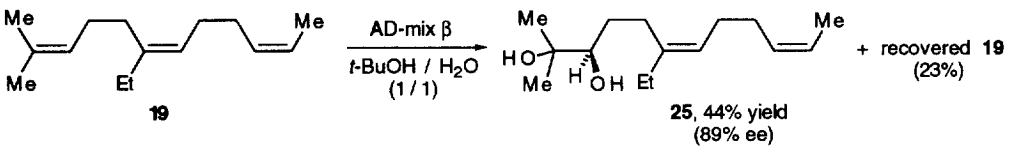
Scheme 7. Preparation of all-*Z*-triene 19



Asymmetric *syn*-dihydroxylation of triene **19** with AD-mix β [6] gives the diol **25** as the only significant regioisomer in 57% yield based on recovered triene **19** (Scheme 8). The relative inertness of the *cis*-disubstituted alkene of **19** is in consonance with the observed 23-fold difference in the relative rate constants for

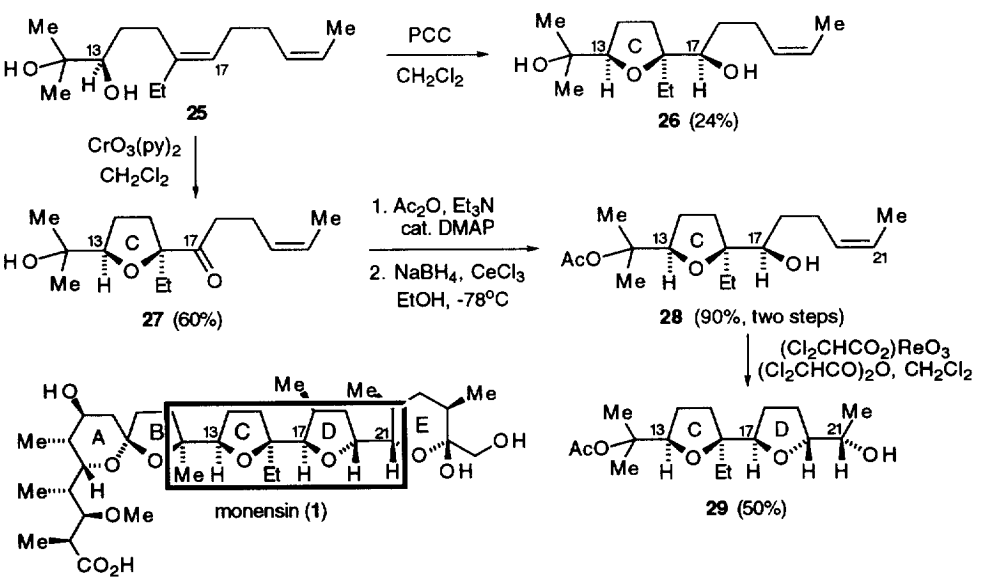
$(DHQD)_2PHAL$ / OsO_4-catalyzed dihydroxylation of 2-methyl-2-octene (trisubstituted alkene) vs. *cis*-5-decene.[16] However, the regioselectivity observed for the terminal trisubstituted alkene over the internal trisubstituted alkene is more surprising, in light of the more modest regioselectivities observed in the mono-dihydroxylation of squalene.[17,18]

Scheme 8. Regioselective asymmetric dihydroxylation of triene 19



PCC-induced *syn*-oxidative cyclization of **25** affords the *cis*-tetrahydrofuran diol **26** as a single stereoisomer; the relatively low yield is attributed to oxidative cleavage of carbon-carbon bonds. In contrast to precedent,[9a] reaction of **25** with Collins oxidant (CrO_3-py_2) gives a 60% yield of the tetrahydrofuranyl ketone **27** and only approximately 5% of the secondary alcohol **26** (Scheme 9). Apparently overoxidation of **26** to ketone **27** "protects" one of the oxygenated carbon-carbon bonds from oxidative cleavage. This unanticipated oxidation product also provides an opportunity for selective protection of the tertiary alcohol,[19] after which sodium borohydride / cerium chloride reduction[20] of the ketone selectively gives the secondary alcohol **28** consistent with Felkin-Anh stereocontrol.[21] *Syn*-oxidative cyclization of the hydroxyalkene **28** with dichloroacetylperrhenate[12] affords the *trans*, *cis*-bistetrahydrofuranyl alcohol **29**, thus completing the stereoselective synthesis of a general model system which corresponds to the C and D rings of monensin (**1**) as well as the D and E rings of lonomycin (**2**).

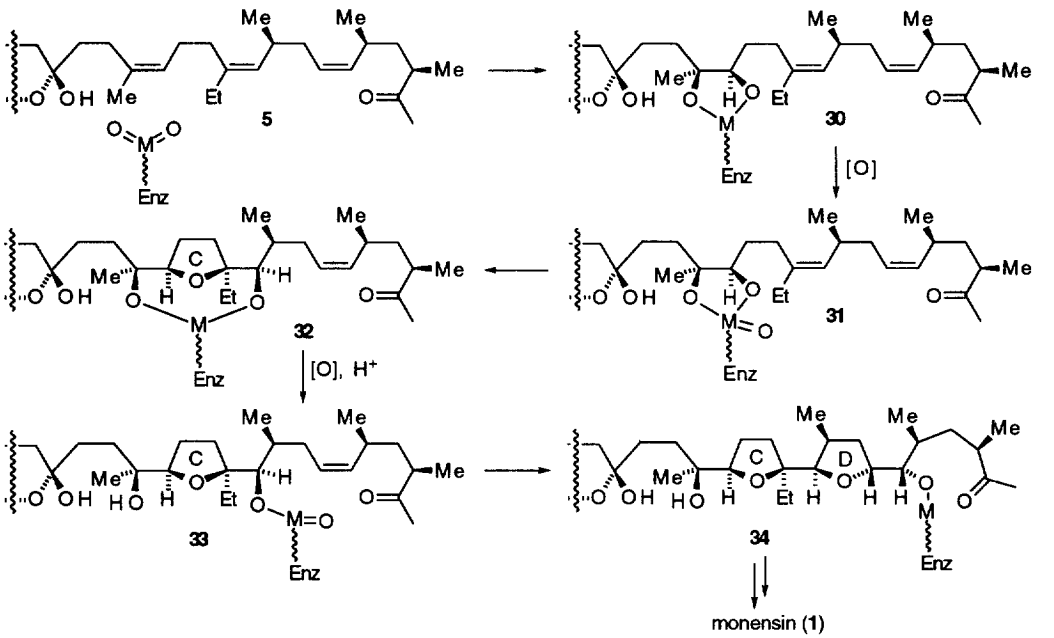
Scheme 9. Preparation of the C-D ring model 29 by sequential *syn*-oxidative cyclizations



DISCUSSION

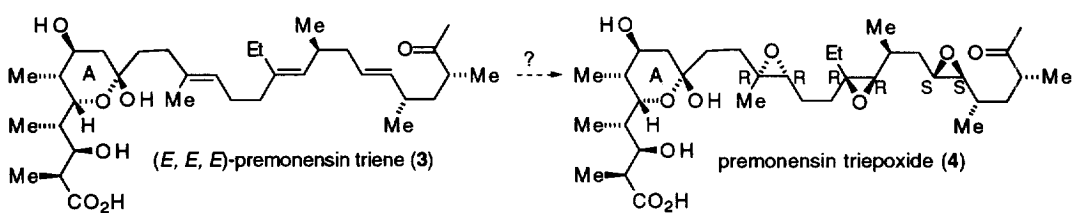
Our results demonstrate that the sequence of *syn*-dihydroxylation, diol-alkene *syn*-oxidative cyclization, and monohydroxyalkene *syn*-oxidative cyclization affords the correct stereochemical oxygenation pattern corresponding to the bistetrahydrofuran regions of monensin and lonomycin. Although our non-enzymatic process requires three different metal oxo reagents (Os, Cr, Re) perhaps we can speculate that a single biosynthetic enzyme containing a metal oxo site might catalyze all three transformations, if coupled with an external oxidizing agent (Scheme 10).

Scheme 10. Proposed tandem *syn*-oxidative cyclization of (*Z*, *Z*, *Z*)-premonensin triene (5)



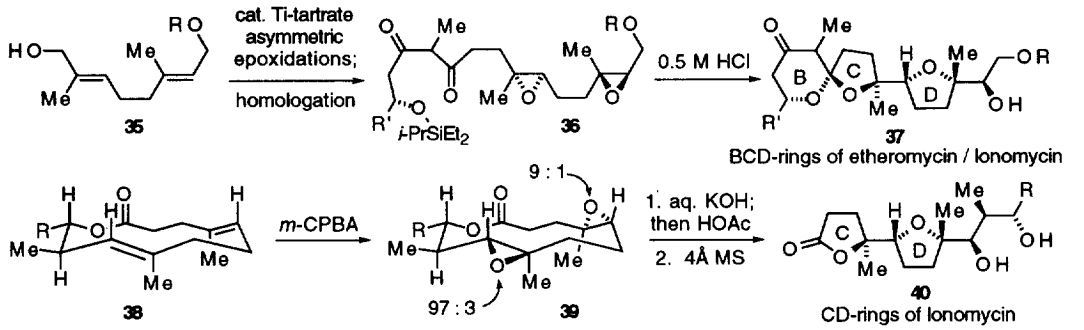
Is the polyepoxide cyclization route equally plausible? Although all-*E*-premonensin triene (**3**) has been prepared by three research groups,[3] the attempted chemical synthesis of monensin from **3** has never been reported. The key obstacle would appear to be stereoselective epoxidation of each alkene of triene **3** (Scheme 11). Note that preparation of triepoxide **4** requires epoxidation of both trisubstituted alkenes from the *re* face, whereas the disubstituted alkene requires epoxidation from the opposite (*si*) face.[22,23]

Scheme 11. Hypothetical polyepoxidation of triene (3)



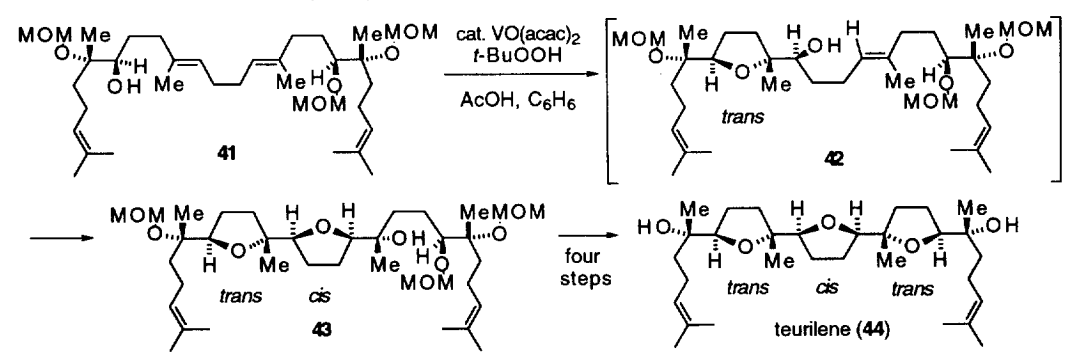
Successful strategies to the preparation of polyepoxides leading to the synthesis of polyketides bearing the stereochemical pattern of the monensin / lonomycin natural products have relied on asymmetric epoxidations of allylic alcohols coupled with multistep homologation pathways (**35** → **37**),[24] or the application of macrocyclic stereocontrol in the epoxidation as exemplified in the Evans synthesis of lonomycin (**38** → **40**, Scheme 12).[25] Although *anti*-cyclization of both bisepoxide compounds **36** and **39** proceeded with high stereospecificity, neither approach to polyepoxide synthesis could reasonably be considered to be biomimetic.[26]

Scheme 12. Alternative approaches to polyepoxide synthesis and *anti*-cyclization



Shirahama has applied sequential hydroxyl-directed vanadium-catalyzed epoxidations of bishomoallylic alcohols coupled with *anti*-cyclization of the hydroxyepoxides for the preparation of two of the three tetrahydrofuran rings of the polyether natural product teurilene (**44**) from an acyclic polyene precursor **41** (Scheme 13).[27] This work clearly demonstrated that the direction of hydroxyl-directed stereoinduction of epoxide formation was dependent on the substitution pattern of the alkene. For example, note that the first epoxidation / cyclization to the *trans*-tetrahydrofuran **42** exhibits a different mode of stereoinduction from the second epoxidation / cyclization, which afforded the *cis*-tetrahydrofuran of **43**.

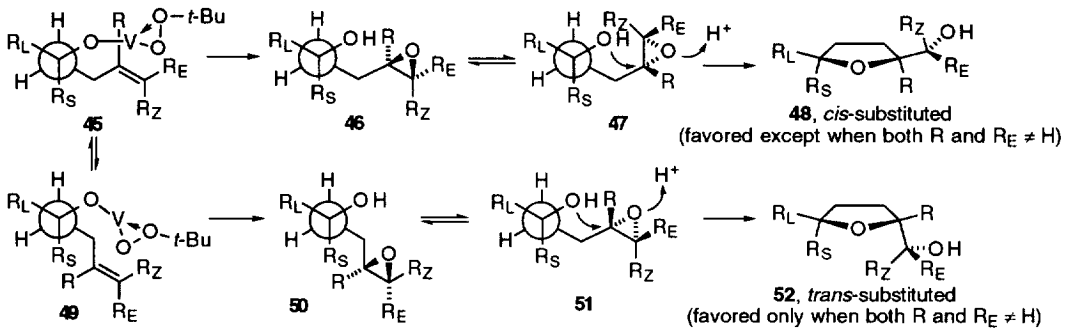
Scheme 13. Stereoselective hydroxyl-directed epoxidations in the synthesis of teurilene



In general the hydroxyl-directed vanadium-catalyzed epoxidation / *anti*-cyclization of bishomoallylic alcohols gives *cis*-tetrahydrofurans. Specifically, the conversion of **42** to **43** (Scheme 13) presumably proceeds via conformation **45** (Scheme 14).[27,28] However, *trans*-tetrahydrofurans are consistently produced from trisubstituted *E*-hydroxyalkenes which are disubstituted at the alkene carbon proximal to the hydroxyl group (i.e.

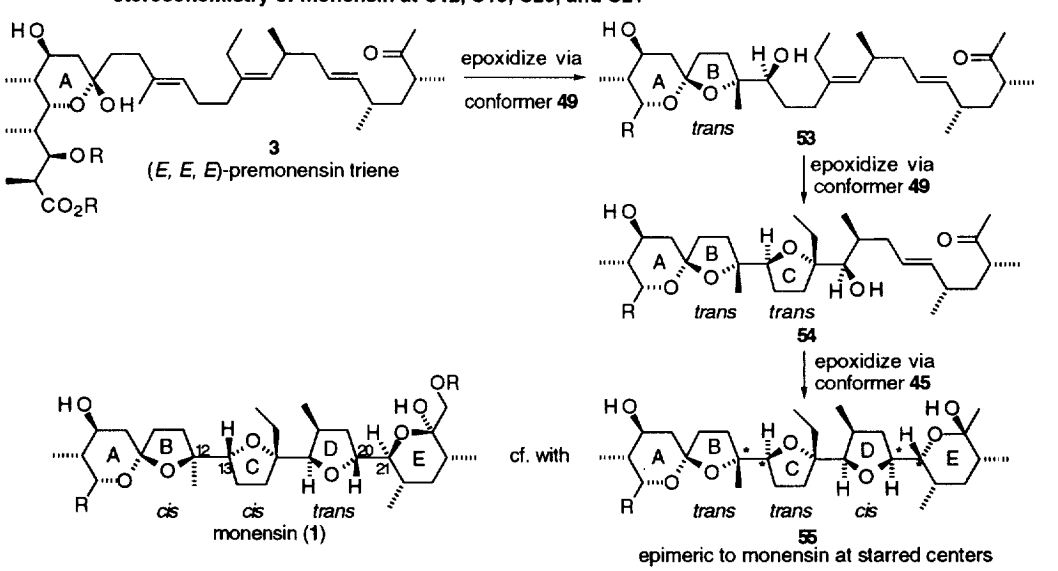
41 → **42**, via conformation **49**).[29] Note that when both R and R_E are substituted with alkyl groups (i.e. methyl or ethyl), the all-equatorial conformation **45** suffers a 1,3-non-bonding interaction between **R** and a homoallylic methylene hydrogen as well as between R_E and the vanadium-peroxo complex, and therefore epoxidation proceeds preferentially via the alternate conformation **49**.

Scheme 14. Conformational models for hydroxyl-directed epoxidations



We predict that application of these stereoinduction models to the hypothetical tandem hydroxyl-directed vanadium-catalyzed epoxidation of (*E,E,E*)-premonensin triene (**3**) would produce the *trans*, *trans*, *cis*-BCD ring diastereomer **55** (Scheme 15) instead of the desired *cis*, *cis*, *trans*-stereoisomer corresponding to the BCD rings of monensin (**1**). Specifically, both the A-ring hemiketal hydroxyl anomer **3** and the hydroxyl group of diene **53** are expected to direct epoxidation via conformation **49**, resulting in the undesired *trans*-tetrahydrofuran rings. In the case of D-ring formation, stereoinduction as modelled by conformation **45** should be operative for the hydroxyalkene **54**, once again resulting in an unwanted stereochemical outcome as the *cis*-D-ring of **55**.

Scheme 15. Stereoinduction models for hydroxyl-directed epoxidation are inconsistent with the stereochemistry of monensin at C12, C13, C20, and C21



CONCLUSIONS

Our synthetic conversion of the acyclic triene **19** into the bistetrahydrofuran compound **29** is consistent with the Townsend-Basak (*syn*-oxidative cyclization) model for polyether biosynthesis for the general case of polyether ionophores represented by the monensin / lonomycin polyketide families. Although our successful experiments with nonbiological reagents do not prove the Townsend biosynthesis hypothesis, our results do indicate that the Townsend model is mechanistically viable with regard to the stereochemical pattern consistently observed in this family of polyether natural products.

We also proposed that the stereochemical pattern of the polyether regions of these polyketide natural products cannot be correctly produced by application of hydroxyl-directed epoxidation methodology with the achiral, nonbiological catalyst $VO(acac)_2$. This prediction remains to be demonstrated by experiment (perhaps from a laboratory which has already synthesized the necessary all-*E*-premonensin triene?) but suggests that if an enzyme-catalyzed epoxidation manifold is truly operative in the biosynthesis of monensin, then this process does not involve chirality induction from stereogenic hydroxyl groups.

EXPERIMENTAL SECTION

***(Z)*-5-ethyl-4,7-octadien-1-ol (22):** *t*-BuLi (35.5 mL, 1.7 M in hexanes) was added to a 250 mL round bottom flask containing THF (15 mL) and 2,3-dihydropyran (**20**, 5.044 g, 60 mmol) at -78°C. The reaction mixture was then stirred at 0°C for 1 h. In a second flask, THF (300 mL) was added to CuCN (5.340 g, 60 mmol), which had been azeotropically dried with benzene. The solution was then cooled to -78°C and EtMgBr (300 mL, 1.0M in THF) was added via syringe. After complete addition of the EtMgBr, the lithiated dihydropyran was added to the cuprate via cannula at -78°C. The reaction was then allowed to warm to room temperature and was stirred overnight. (The reaction turned black as it warmed.) In the morning, the reaction was cooled to 0°C and allyl bromide (24 mL, 277 mmol) was added. The reaction was stirred for 1 h at 25°C, then the solution was quenched with saturated ammonium chloride. The resulting layers were separated, and the aqueous layer extracted with ether. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo*, and the product purified by flash chromatography (4 / 1, pentane / ethyl ether) to provide **22** as a colorless oil (5.390 g, 35 mmol, 58% yield). IR (neat) 3306, 2895, 1636, 1448, 1056, 909, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81-5.68 (1H, m), 5.20 (1H, t, J = 7.2 Hz), 5.03-4.96 (2H, m), 3.64 (2H, t, J = 6.6 Hz), 2.79 (2H, d, J = 6.6 Hz), 2.10 (2H, dd, J = 7.5, 15.0 Hz), 2.01 (2H, dd, J = 7.2, 14.4 Hz), 1.63 (2H, m), 0.98 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 136.8, 124.0, 115.3, 62.9, 35.2, 33.2, 30.0, 24.3, 13.0; MS (70 eV, EI) 154, 136, 121, 107, 95, 79, 67, 55, 41; HRMS (EI) calcd for $C_{10}H_{18}O$ 154.1358, found 154.1351.

***(Z)*-5-ethyl-4,7-octadienal:** Dienol **22** (2.495 g, 16 mmol) was dissolved in CH_2Cl_2 (40 mL). Celite (7.253 g) was added followed by the addition of pyridinium chlorochromate (5.160 g, 24 mmol), and the resulting mixture was stirred for 3 h at 25°C. Pentane / ethyl ether (1 / 1) was added, the mixture was filtered through silica gel and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography with

pentane / ethyl ether (50 / 1) to yield *(Z)*-5-ethyl-4,7-octadienal as a colorless oil (1.966 g, 13 mmol, 78%). IR (neat) 3064, 2962, 2721, 1727, 1636, 1439, 1055, 994, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (1H, s), 5.81-5.68 (1H, m), 5.16 (1H, t, J = 7.2 Hz), 2.80 (2H, d, J = 3.6 Hz), 2.49 (2H, m), 3.36 (2H, q, J = 7.2 Hz), 2.01 (2H, q, J = 6.3 Hz), 1.00 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 140.3, 136.0, 122.0, 115.2, 44.1, 34.9, 29.7, 20.6, 12.6; MS (70 eV, EI) 152, 137, 134, 123, 108, 93, 79, 67, 55, 41.

(Z,Z)-4-ethyl-1,4,8-decatriene (23): Ethyltriphenylphosphonium bromide (4.823 g, 13 mmol) in THF (80 mL) and toluene (10 mL) were cooled to -30°C and NaHMDS (13 mL, 1.0 M in THF) was added. The resulting orange solution was stirred for 2 h and then cooled to -90°C. Freshly prepared *(Z)*-5-ethyl-4,7-octadienal (1.966 g, 13 mmol) in THF (5 mL) was added and the reaction was allowed to slowly warm to room temperature overnight. H_2O (20 mL) was added, the layers were separated, and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over sodium sulfate. The solvent was evaporated, and the product purified by flash chromatography (50 / 1, pentane / ethyl ether) to provide **23** as a colorless oil (1.529 g, 9.3 mmol, 74% yield). IR (thin film CH_2Cl_2) 2946, 1636, 1436, 993, 910, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81-5.68 (1H, m), 5.49-5.37 (2H, m), 5.30 (1H, m), 4.95 (2H, m), 2.78 (2H, d, J = 6.0 Hz), 2.08-1.96 (6H, m), 1.58 (3H, d, J = 9.5 Hz), 1.00 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 136.9, 130.7, 124.4, 124.3, 115.3, 35.4, 30.0, 28.1, 27.7, 13.2, 13.1; MS (70 eV, EI) 164, 153, 109, 81, 67, 55, 49, 41; HRMS (EI) calcd for $C_{12}H_{20}$ 164.1565; found 164.1559.

(Z,Z)-4-ethyl-4,8-decadien-1-ol (24): 9-BBN (32 mL, 0.5 M in THF) was added to neat triene **23** (2.570 g, 16 mmol) in a round bottom flask fitted with a reflux condensor and stirred for 2.5 h. NaOH (10 mL, 3.0M) was added to the flask followed by slow addition of H_2O_2 (10 mL). The reaction mixture was heated to 50°C for 1.5 h, and then cooled to room temperature. The aqueous layer was saturated with potassium carbonate, and the layers were separated. The aqueous layer was extracted with ethyl ether, and the combined organic layers were dried over sodium sulfate. The solvent was evaporated, and the product purified by flash chromatography (4 / 1, pentane / ethyl ether) to provide **24** as a colorless oil (1.911 g, 10.5 mmol, 66% yield). IR (neat) 3324, 3011, 2654, 1690, 1447, 1057, 619 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (2H, m), 5.15 (1H, m), 3.64 (2H, t, J = 6.0 Hz), 2.39 (8H, m), 1.64 (6H, m), 0.99 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 130.6, 124.4, 124.0, 63.4, 31.7, 29.8, 28.0, 27.7, 26.8, 13.2, 13.17; MS (70 eV, EI) 182, 153, 127, 109, 95, 81, 67, 55, 41; HRMS (EI) calcd for $C_{12}H_{22}O$ 182.1670; found 182.1666.

(Z,Z)-6-ethyl-2-methyl-2,6,10-dodecatriene (19): Dienol **24** (1.066 g, 5.9 mmol) was dissolved in CH_2Cl_2 (30 mL). Celite (4.023 g) was added followed by the addition of pyridinium chlorochromate (1.935 g, 9.0 mmol), and the resulting mixture was stirred for 3 h at 25°C. Pentane / ethyl ether (1 / 1) was added, and the mixture was filtered through silica gel and concentrated *in vacuo* . The resulting pale yellow oil, (Z,Z)-4-ethyl-4,8-decadienal, was used for the next step. ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (1H, s), 5.50-5.36 (2H, m), 5.19 (1H, t, J = 6Hz), 2.52-2.46 (2H, m), 2.30-2.32 (2H, m), 2.08-1.96 (6H, m), 1.60 (3H, d, J = 7.5 Hz), 1.00 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 139.0, 130.0, 124.5, 124.3, 42.9, 29.3, 27.7, 27.2, 22.8, 12.9, 12.8. Isopropyltriphenylphosphonium bromide (2.227 g, 6.0 mmol) was dissolved in ethyl ether (15 mL). *n*-BuLi (2.4 mL, 2.5 M in pentane) was added and the resulting orange mixture was stirred at room temperature for 1.5 h. Crude (Z,Z)-4-ethyl-4,8-decadienal in ethyl ether was then introduced and the

reaction mixture was stirred overnight. H_2O (20 mL) was added and the biphasic solution was filtered through Celite. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over sodium sulfate, the solvent was removed *in vacuo*, and the product purified by flash chromatography (50 / 1, pentane / ethyl ether) to provide triene **19** as a colorless oil (0.865 g, 4.2 mmol, 50% yield for two steps). IR (neat) 2934, 1666, 1452, 1375, 929, 847, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.49-5.39 (2H, m), 5.13 (2H, m), 2.15 (10H, m), 1.69 (3H, s), 1.61 (6H, br s), 1.00 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 131.5, 130.4, 124.5, 123.9, 123.2, 30.5, 29.6, 27.8, 27.5, 27.2, 25.8, 17.7, 12.9, 12.8; MS (70 eV, EI) 206, 177, 163, 151, 137, 123, 109, 95, 81, 69, 55, 41; HRMS (EI) calcd for $C_{15}H_{26}$ 206.2034, found 206.2068. Anal. calcd 87.73% C, 12.27% H, found 86.54% C, 12.22% H.

(*Z,Z*)-6-ethyl-2-methyl-6,10-dodecadien-2,3-diol (25): AD-mix β (2.360 g, 1.4 g / mmol)[30] was dissolved in *t*-BuOH / H_2O (8 mL, 1 / 1). Methanesulfonamide (139 mg, 1.5 mmol) was added and the mixture was cooled to 0°C. Triene **19** (314 mg, 1.5 mmol) dissolved in *t*-BuOH (1 mL) was added. The mixture was stirred at 0°C for 7.5 h. Sodium sulfite (2.035 g) was added, the reaction was warmed to 25°C and stirred for 1 h. The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, the solvent was evaporated, and the product purified by flash chromatography (4 / 1, pentane / ethyl acetate) to provide starting material **19** (72.0 mg, 0.35 mmol, 23%) as a pale yellow oil and diol **25** as a colorless oil (0.159 g, 0.66 mmol, 44% yield; 57% yield based on recovered **19**). $[\alpha]^{23}_D$ +13.7 ($CHCl_3$, c = 0.336), 89% ee based on Mosher ester analysis, ^{19}F δ -71.08 Hz, -71.03 Hz (16 / 1); IR (neat) 3421, 2952, 1652, 1495, 1377, 1160, 1079, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.49-5.41 (2H, m), 5.18 (1H, t, J = 6.6 Hz), 3.34 (1H, dd, J = 1.8, 8.0 Hz), 2.27 (1H, br s), 2.11 (4H, m), 2.00 (4H, m), 2.11 (4H,m), 1.56 (5H, m), 1.34 (1H, br s), 1.18 (3H, s), 1.13 (3H, s), 0.98 (3H, t, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 130.5, 124.6, 124.5, 78.9, 73.4, 30.5, 29.7, 28.0, 27.7, 26.8, 23.5, 13.2; MS (70 eV, EI) 240, 222, 181, 167, 149, 136, 121, 109, 95, 81, 71, 59, 43; HRMS (EI) calcd for $C_{15}H_{28}O_2$ 240.2089, found 240.2091.

Tetrahydrofuranyl diol (26): Diene-diol **25** (239 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (2 mL). Pyridinium chlorochromate (0.214 g, 1.0 mmol) was added and the resulting mixture was stirred at 20° C for 5 min. Ethyl ether was added and the reaction was filtered through Celite. The filtrate was stirred with silica gel for 1.5 h, and then filtered to remove the silica gel. The silica gel was then washed with ethyl acetate to remove the remaining product. The solvent was concentrated *in vacuo*, and the product purified by flash chromatography (2 / 1, pentane / ethyl acetate) to provide **26** as a colorless oil (61.2 mg, 0.24 mmol, 24% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.52-5.38 (2H, m), 3.76 (1H, dd, J = 6.9, 8.4 Hz), 3.67 (1H, dd, J = 2.4, 10.2 Hz), 2.30-2.04 (4H, m), 1.95-1.81 (2H,m), 1.64 (3H, d, J = 5.1 Hz), 1.60-1.30 (4H, m), 1.29, (3H, s), 1.13 (3H, s), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5, 124.9, 88.9, 85.7, 75.6, 72.3, 32.1, 30.2, 29.8, 28.0, 27.6, 25.9, 24.2, 13.1, 8.2.

Tetrahydrofuranyl ketoalcohol (27): Chromium trioxide (3.029 g, 30 mmol) was dissolved in CH_2Cl_2 (12 mL). Pyridine (1 mL) was added and the reaction was stirred for 15 min.[31] Dienol **25** (0.486 g, 2.0 mmol) was then added. After stirring for 5 min, ethyl ether was added and the reaction mixture was filtered through Celite. The filtrate was stirred with silica gel for 1.5 h, and then filtered to remove the silica gel. The

silica gel was then washed with ethyl acetate to remove the remaining product. The solvent was removed *in vacuo*, and the product purified by flash chromatography (4 / 1, pentane / ethyl acetate) to provide **27** as a colorless oil (305 mg, 1.2 mmol, 60% yield). $[\alpha]^{23}_D$ -7.0 ($CHCl_3$, c = 0.430); IR (thin film CH_2Cl_2) 3439, 2970, 2897, 1710, 1451, 1362, 1138, 1043, 957 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51-5.41 (1H, m), 5.35-5.29 (1H, m), 3.83 (1H, dd, *J* = 5.1, 5.7 Hz), 3.18 (1H, br s), 2.61-2.54 (2H, m), 2.32 (2H, q, *J* = 4.2 Hz), 1.95-1.61 (9H, m), 1.32 (3H, s), 1.10 (3H, s), 0.87 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 128.7, 125.1, 91.3, 86.9, 70.5, 37.4, 33.9, 30.2, 27.8, 25.6, 24.6, 21.0, 12.6, 8.3; MS (70 eV, EI) 255, 239, 221, 195, 157, 139, 97, 85, 69, 57, 43; HRMS (EI) calcd for $C_{14}H_{23}O_3$ (M-CH_3) 239.1647, found 239.1628; Anal. calcd for $C_{15}H_{26}O_3$ 70.83% C, 10.30% H, found 70.16% C, 10.01% H.

Acetate ester of 27: **27** (242 mg, 0.95 mmol) was dissolved in triethylamine (2 mL). Acetic anhydride (0.25 mL) and DMAP (25.0 mg) were added and the mixture was stirred for 30 h. The reaction was diluted with ethyl ether (20 mL) and H_2O (3 mL) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9 / 1, pentane / ethyl acetate) to yield a pale yellow oil (271 mg, 0.91 mmol, 97% yield). $[\alpha]^{23}_D$ -14.7 ($CHCl_3$, c = 0.150); IR (thin film CH_2Cl_2) 2971, 2921, 1738, 1459, 1366, 1238, 1161, 1091, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (1H, m), 5.34 (1H, m), 3.93 (1H, t, *J* = 7.5 Hz), 2.70 (2H, m), 2.33-2.17 (2H, m), 1.94 (3H, s), 1.88-1.71 (2H, m), 1.61-1.57 (10H, m), 1.44 (3H, s), 0.80 (3H, t, *J* = 7.5Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 170.7, 129.6, 125.1, 92.5, 86.5, 82.6, 38.0, 33.4, 30.8, 26.5, 22.9, 22.8, 22.7, 21.2, 13.1, 8.7; MS (70 eV, EI) 281, 267, 239, 199, 157, 139, 97, 85, 69, 57, 43; HRMS (EI) calcd for $C_{16}H_{25}O_4$ (M-CH_3) 281.1753, found 287.1732; Anal. calcd for $C_{16}H_{25}O_4$ 68.89% C, 9.52% H, found 68.99% C, 9.28% H.

Tetrahydrofuranyl hydroxyalkene (28): $CeCl_3 \cdot H_2O$ (79.4 mg, 0.21 mmol) in EtOH (2 mL) was added to a 25 mL round bottom flask containing the above ketoacetate (56.1 mg, 0.17 mmol) and EtOH (2 mL). The mixture was cooled to -78°C. A solution of $NaBH_4$ (12.4 mg, 0.54 mmol) in EtOH (2 mL) was added over 20 min, and then stirred for 1 h at -78°C. The reaction was allowed to warm to 20°C over 1 h. Acetone was added to quench any remaining $NaBH_4$. The solvent was evaporated and the residue redissolved in H_2O and ethyl acetate. The layers were separated and the aqueous layer was extracted several times with ethyl acetate. The solvent was removed *in vacuo* and the product purified by flash chromatography (4 / 1, pentane / ethyl acetate) to provide a colorless oil (52.9 mg, 0.16 mmol, 94% yield). $[\alpha]^{23}_D$ +2.0 ($CHCl_3$, c = 0.628); IR (thin film CH_2Cl_2) 3518, 2936, 2870, 1741, 1461, 1367, 1234, 1154, 1086, 944 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51-5.38 (2H, m), 3.73 (1H, t, *J* = 7.5 Hz), 3.64 (1H, dd, *J* = 4.2, 8.5 Hz), 3.10 (1H, br s), 2.33-2.05 (6H, m), 2.00 (3H, s), 1.92 (2H, q, *J* = 9 Hz), 1.70-1.33 (13H, m), 0.90 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 130.5, 124.8, 89.3, 85.8, 83.0, 75.1, 31.8, 30.2, 29.4, 27.7, 24.3, 23.5, 23.0, 22.7, 13.2, 8.3; MS (70 eV, EI) 239, 199, 157, 139, 85, 69, 57, 43; HRMS (EI) calcd for $C_{17}H_{28}O_3$ (M-H_2O) 280.2038 found 280.2023; Anal. calcd for $C_{17}H_{30}O_4$ 68.42% C, 10.13% H, found 68.23% C, 10.18% H.

preparation of dichloroacetylperrhenate: Dirhenium heptoxide (160 mg, 0.32 mmol) was dissolved in THF (7 mL) in a 25 mL Schlenk flask. Dichloroacetic anhydride (0.07 mL, 0.46 mmol, 1.4 equiv based on Re_2O_7) was added, and the resulting mixture was stirred for 1 h at 20°C. The solution was cooled to 0°C,

concentrated *in vacuo*, rinsed with cold pentane (2 x 3 mL) and concentrated to give dichloroacetylperrhenate, $(Cl_2CHCO_2)ReO_3$.

Bistetrahydrofuran (29): Dichloroacetic anhydride (0.07 mL, 0.46 mmol, 1.4 equiv based on Re_2O_7) was added to the preparation of $(Cl_2CHCO_2)ReO_3$ followed by CH_2Cl_2 (1 mL). Hydroxyalkene **28** (60.1 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added to the flask. The resulting dark purple solution was allowed to slowly warm to room temperature overnight. The crude reaction mixture was diluted with pentane / ethyl acetate (1 / 1), filtered through silica gel and concentrated *in vacuo*. The residue was dissolved in acetone (1 mL) and sodium carbonate (1 mL, 10% in H_2O) was added. After stirring for 1 h the acetone was evaporated. The residue was extracted with ethyl acetate, dried over sodium sulfate and purified by silica gel chromatography with pentane / ethyl acetate (2 / 1) to provide **29** (29.9 mg, 0.10 mmol, 50% yield). $[\alpha]^{23}_D$ +10 ($CHCl_3$, c = 0.582); IR (thin film CH_2Cl_2) 3453, 2967, 2870, 1731, 1465, 1367, 1267, 1072, 946, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (2H, q, *J* = 7.5 Hz), 3.98-3.80 (2H, m), 1.97 (3H, s), 1.93-1.61 (8H, m), 1.56 (2H, q, *J* = 7.8 Hz), 1.47 (3H, s), 1.45 (3H, s), 1.09 (3H, d, *J* = 6.6 Hz), 0.90 (3H, t, *J* = 7.5 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 170.8, 88.0, 84.9, 84.1, 83.8, 83.6, 68.2, 30.7, 28.7, 27.5, 27.3, 25.7, 22.9, 22.8, 22.3, 18.3, 8.6; MS (70 eV, EI) 299, 254, 213, 199, 157, 139, 121, 85, 71, 57,43; HRMS (EI) calcd for $C_{16}H_{27}O_5$ (M-CH_3) 299.1859, found 299.1856; Anal. calcd for $C_{17}H_{30}O_5$ 64.94% C, 9.62% H, found 64.88% C, 9.44% H.

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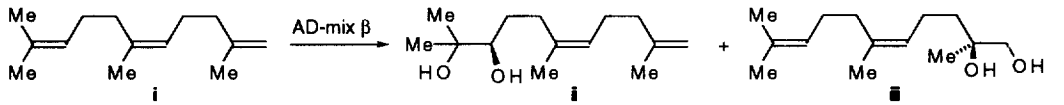
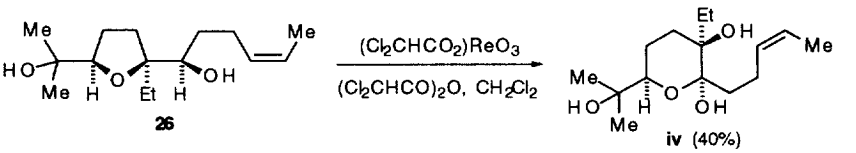
18. We originally attributed this regioselective outcome to additional steric hindrance provided by the ethyl substituent of triene substrate **19**. However, the asymmetric dihydroxylation of triene **i** also provided a 5 : 1 mixture of dihydroxylation products **ii** and **iii**, and dihydroxylation of the internal trisubstituted alkene of **i** was not observed. Presumably the internal trisubstituted alkenes of substrates **19** and **i** are protected from dihydroxylation by polyene folding in the protic solvent medium. See also: Van Tamelen, E. E.; Sharpless, K. B. *Tetrahedron Lett.* **1967**, 2655.



i ii iii

19. Initial attempts to achieve *syn*-oxidative cyclization by reaction of diol-alkene **26** with acylperrhenate reagents were unsuccessful and appeared to give product **iv** as a single diastereomer. This unexpected product presumably arises from secondary alcohol oxidation and acid-catalyzed pinacol-type rearrangement. The principal difference between substrate **26** and other substrates which we had previously successfully cyclized (ref. 12) appears to be the presence of the tertiary hydroxyl group.



26 **iv** (40%)

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