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Sequential Application of Stereoselective Syn-Oxidation Methodologies to Natural Product Synthesis: A Potentially Biomimetic Approach to the C12-C21 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, cisselective syn-oxidative cyclization of the diol-diene, and trans-selective syn-oxidative cyclization of the remaining hydroxylakene gives the correct sterochemical 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.





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.





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



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 transtetrahydrofuranyl alcohols with high stereoselectivity when conducted with chromium¹⁰ or rhenium oxide¹¹ 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).



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" conditions¹⁴ provided the C₂₀-21 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 C₁₁-C₂₂ 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





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, 9^a reaction of 25 with Collins oxidant (CrO₃-py₂) 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 tetrahydroful, ¹⁹ after which sodium borohydride / cerium chloride reduction²⁰ of the ketone selectively gives the secondary alcohol 28 consistent with Felkin-Anh stereocontrol.²¹ Syn-oxidative cyclization of the hydroxyalkene 28 with dichloroacetylperrhenate¹² 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).





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}





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 $(35 \rightarrow 37)$,²⁴ or the application of macrocyclic stereocontrol in the epoxidation as exemplified in the Evans synthesis of lonomycin ($38 \rightarrow 40$, 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





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.





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 \rightarrow 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 hydroxylakene 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



epimeric to monensin at starred centers

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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) & 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 C₁₀H₁₈O 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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. H₂O (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 CH₂Cl₂) 2946, 1636, 1436, 993, 910, 730 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₂₀ 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 H₂O₂ (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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₂₂O 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 CH₂Cl₂ (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, CDCl₃) & 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); ¹³C NMR (75 MHz, CDCl₃) & 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. H₂O (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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₆ 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 / H₂O (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 (CHCl₃, c = 0.336), 89% ee based on Mosher ester analysis, ¹⁹F 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₈O₂ 240.2089, found 240.2091.

Tetrahydrofuranyl diol (26): Diene-diol 25 (239 mg, 1.0 mmol) was dissolved in CH₂Cl₂ (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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 CH₂Cl₂ (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 (CHCl₃, c = 0.430); IR (thin film CH₂Cl₂) 3439, 2970, 2897, 1710, 1451, 1362, 1138, 1043, 957 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₄H₂₃O₃ (M-CH₃) 239.1647, found 239.1628; Anal. calcd for C₁₅H₂₆O₃ 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 H₂O (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 (CHCl₃, c = 0.150); IR (thin film CH₂Cl₂) 2971, 2921, 1738, 1459, 1366, 1238, 1161, 1091, 929 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₂₅O₄ (M-CH₃) 281.1753, found 287.1732; Anal. calcd for C₁₆H₂₅O₄ 68.89% C, 9.52% H, found 68.99% C, 9.28% H.

Tetrahydrofuranyl hydroxyalkene (28): CeCl₃·H₂O (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 NaBH₄ (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 NaBH₄. The solvent was evaporated and the residue redissolved in H₂O 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). $[\alpha]^{23}D +2.0$ (CHCl₃, c = 0.628); IR (thin film CH₂Cl₂) 3518, 2936, 2870, 1741, 1461, 1367, 1234, 1154, 1086, 944 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₈O₃ (M-H₂O) 280.2038 found 280.2023; Anal. calcd for C₁₇H₃₀O₄ 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 Re₂O₇) 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, (Cl2CHCO2)ReO3.

Bistetrahydrofuran (29): Dichloroacetic anhydride (0.07 mL, 0.46 mmol, 1.4 equiv based on Re₂O₇) was added to the preparation of (Cl₂CHCO₂)ReO₃ followed by CH₂Cl₂ (1 mL). Hydroxyalkene 28 (60.1 mg, 0.20 mmol) in CH₂Cl₂ (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 H₂O) 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). $[\alpha]^{23}D + 10$ (CHCl₃, c = 0.582); IR (thin film CH₂Cl₂) 3453, 2967, 2870, 1731, 1465, 1367, 1267, 1072, 946, 736 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C (75 MHz, CDCl₃) 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 C₁₆H₂₇O₅ (M-CH₃) 299.1859, found 299.1856; Anal. calcd for C17H30O5 64.94% C, 9.62% H, found 64.88% C, 9.44% H.

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