syn-Oxidative Polycyclizations of Hydroxypolyenes: Highly Stereoselective and Potentially Biomimetic Syntheses of *all-trans*-Polytetrahydrofurans

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Abstract: Acylperrhenate reagents promote hydroxyl-directed *syn*-oxidative polycyclizations of primary and secondary hydroxypolyenes, forming bis- and tristetrahydrofuranyl alcohols with excellent *trans*-stereoselectivity for each tetrahydrofuran ring. The combination of dichloroacetylperrhenate/dichloroacetic anhydride affords stereoselective *syn*-oxidative bicyclization to bistetrahydrofuranyl alcohol products, whereas trifluoroacetylperrhenate/trifluoroacetic anhydride or trichloroacetylperrhenate/trichloroacetic anhydride are more suitable for stereoselective formation of tristetrahydrofuranyl alcohols from acyclic hydroxytrienes. In the tricyclization reaction chirality induction from a single stereogenic hydroxyl group affords diastereoselective formation of six additional stereocenters in a single step. However, we have found that the growing polytetrahydrofuran chain can exert chelation effects upon the alkoxyrhenium intermediate, thus diminishing the degree of product diastereoselectivity. These *syn*-oxidative cyclization synthesis strategies mimic a possible pathway for the biosynthesis of many polycyclic ether natural products, including the tristetrahydrofuran acetogenin goniocin (**1**).

Introduction and Background

Polycyclic ether-containing substances have been isolated from a variety of terrestrial and marine sources, and scientific interest in these natural product structures has been motivated by their potent biological activities. The annonaceous acetogenins are a large family of plant-derived C_{35} or C_{37} compounds generally possessing one to three tetrahydrofuran rings attached to a common (*S*)-butenolide by a linear carbon chain which may be variously hydroxylated. These compounds display a wide range of biological activities including cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal, and immunosuppressive effects.[1] These activities are apparently related to ionophore properties, which are ultimately coupled to inhibition of mitochondrial electron transport.[2] Over 220 annonaceous acetogenin natural products have been structurally characterized, and approximately 90% of these compounds exhibit *trans*-tetrahydrofuran stereochemistry. Goniocin (**1**) was isolated from the bark of the Thai tree *Goniothalamus giganteus* and was the first tristetrahydrofuran-containing annonaceous acetogenin to be characterized (Figure 1, vide infra).[3]

Our program for polycyclic ether synthesis has been inspired by a novel biosynthesis hypothesis proposed by Townsend and Basak, who suggested that several families of polyether natural products might arise from a cascade of hydroxyl-directed *syn*-oxidative cyclizations[4] rather than the classical *anti*-opening of polyepoxy alcohols[5] (Scheme 1). Note that these two reaction types are mechanistically complementary with regard to the relative stereochemistry of the cyclic products; hydroxyl-directed variants of these reactions can also exhibit stereoinduction from chiral alcohols.

Although no examples of enzyme-induced *syn*-oxidative cyclizations have been reported, several nonenzymatic reagents are known to promote this type of reaction (Scheme 2). Alkenyl diols including **7** (from *syn*-dihydroxylation of geranyl acetate **6**) react with chromium(VI) oxidants to afford the *cis*-tetrahydrofuran diol **8** resulting from stereospecific *syn*-oxidative cyclization directed by the bidentate diol of substrate **7** rather than alcohol oxidation.[6] The mechanism of this process is undoubtably related to the single-step manganese(VII) or ruthenium(VIII)-induced oxidative cyclization of 1,5-dienes (i.e., **6** → **8**).[7] In contrast, the rhenium(VII) oxide-promoted *syn*-oxidative cyclizations of alkenyl alcohols bearing a single hydroxyl group such as **9** afford *trans*-tetrahydrofuranyl alcohol products **10**.[8]

In this paper we describe our explorations of metal-oxo-induced hydroxyl-directed *syn*-oxidative polycyclizations, which have resulted in the development of more general reagents for the stereoselective preparation of *all-trans*-polytetrahydrofurans from acyclic hydroxypolyenes.

[†] Condensed from the Ph.D. thesis of T.B.T., Northwestern University, 1996.

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

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(3) (a) Gu, Z.-M.; Fang, X.-P.; Zeng, L.; McLaughlin, J. L. *Tetrahedron Lett.* **1994**, *35*, 5367. (b) Goniodenin, a bis-THF acetogenin has been converted to an isomeric mixture of tristetrahydrofuran acetogenins with *m*-CPBA: Zhang, Y.; Zeng, L.; Woo, M.-H.; Gu, Z.-M.; Ye, Q.; Wu, F.-E.; McLaughlin, J. L. *Heterocycles* **1995**, *41*, 1743.

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(5) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.

(6) (a) Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 379. (b) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727. (c) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171.

(7) (a) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353. (b) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396. (c) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. M. *J. Chem. Soc., Chem. Commun.* **1979**, 918. (d) Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, *21*, 3531. (e) Carlsen, P. H. J.; Katsuki, T.; Martin, V. M.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (f) Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624. (g) Bertrand, P.; Gesson, J.-P. *Tetrahedron Lett.* **1992**, *33*, 5177. (h) Brown, R. C. D.; Kocienski, P. J. *Synlett* **1994**, 415.

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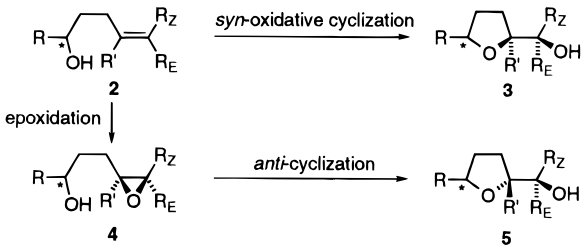
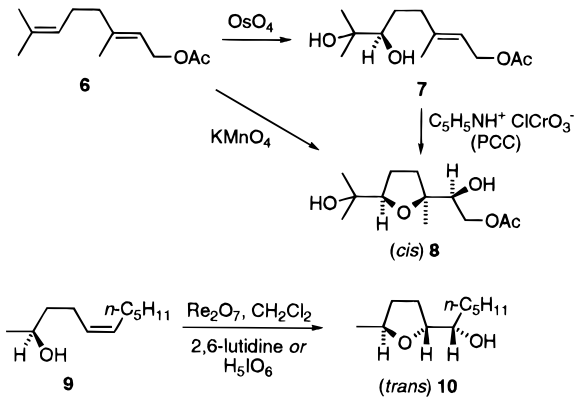
Scheme 1. Comparison of *syn*-Oxidative Cyclization vs Epoxidation/*anti*-Cyclization



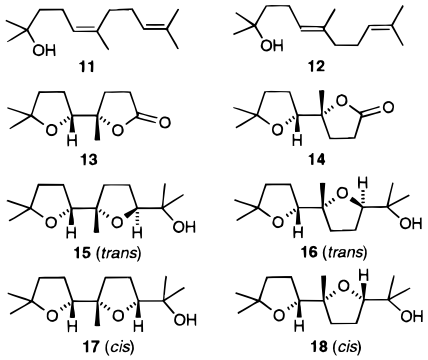
Scheme 2. Hydroxyl-Directed *syn*-Oxidative Cyclization Methodologies



Results and Discussion

***syn*-Oxidative Polycyclizations Induced by Chromium(VI) Oxo Complexes.** Our initial studies on the reaction of *Z*-tertiary hydroxydiene **11**[9] with pyridinium chlorochromate (PCC) in the presence of acetic acid[10] indicated the formation of bicyclic lactone **13** as the major product (Table 1). Similarly, the *E*-substrate **12** gave the diastereomeric lactone **14**, demonstrating the high stereospecificity of these reactions.[11] Further examination of the product mixtures from these reactions also revealed the formation of the tertiary alcohols **15** (from **11**) and **16** (from **12**), each as predominantly one tetrahydrofuran diastereomer.

Table 1. Oxidative Polycyclizations of Hydroxydienes **11** and **12**



hydroxydiene	reagents	products (isolated yield, ratio)
11	PCC, HOAc CH_2Cl_2	**13** / **14** (38%, 9.9 / 1) + **15** / **17** (9%, 11 / 1)
12	PCC, HOAc CH_2Cl_2	**14** / **13** (24%, 17 / 1) + **16** / **18** (19%, 3.7 / 1)
11	$VO(acac)_2$, *t*-BuOOH, HOAc, CH_2Cl_2	**18** / **16** (35%, 9.4 / 1)
12	$VO(acac)_2$, *t*-BuOOH, HOAc, CH_2Cl_2	**17** / **15** (45%, 2.7 / 1)

In all cases the crude reaction mixtures contained monocyclic 4,4-dimethyl-γ-butyrolactone resulting from *syn*-oxidative monocyclization of hydroxydiene **11** or **12** followed by oxidative cleavage of the monotetrahydrofuranyl alcohol. Purified samples of bicyclic tertiary alcohol product **15** underwent oxidative cleavage to the lactone **13** upon further reaction with PCC/HOAc; alcohol **16** was similarly converted into **14**, thus confirming the stereochemical connection between bicyclic lactone and alcohol products from each hydroxydiene **11**/**12**.

The relative stereochemistry of the chromium *syn*-oxidative cyclization products could not be unambiguously determined by spectroscopic methods alone, but assignments were made by comparisons with bicyclic tetrahydrofuranyl alcohol products obtained from vanadium-catalyzed hydroxyl-directed epoxidations coupled with acid-catalyzed intramolecular *anti*-opening of hydroxyepoxide intermediates.[12] Specifically, vanadium-catalyzed tandem epoxidation/*anti*-cyclization of the *Z*-hydroxydiene substrate **11** afforded *cis*-diastereomer **18** as the major product which exhibited identical spectroscopic characteristics and chromatographic retention times to the minor diastereomer obtained by *syn*-oxidative bicyclization of the *E* substrate **12**; the minor epoxidation/cyclization product from **11** was determined to be identical with compound **16** which was the major diastereomeric bistetrahydrofuranyl alcohol from chromium-induced *syn*-oxidative cyclization of **12**. Similar comparisons were made between epoxidation products of *E*-**12** and *syn*-oxidative bicyclization products from *Z*-**11**, thus confirming that *syn*-oxidative cyclization and epoxidation reactions are stereocomplementary not only in the mode of oxygen addition across the alkene but also in the formation of *trans*- vs *cis*-tetrahydrofuran products.

Although this study provided the first reports of *syn*-oxidative polycyclizations of hydroxypolyenes, the relatively rapid rate of primary and secondary alcohol oxidation by chromium(VI) oxo complexes and the significant occurrence of oxidative cleavage byproducts detracted from the general utility of PCC-induced *syn*-oxidative polycyclizations. Our studies turned to

(8) (a) Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303. (d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133. (e) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447. (f) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257. (g) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640.

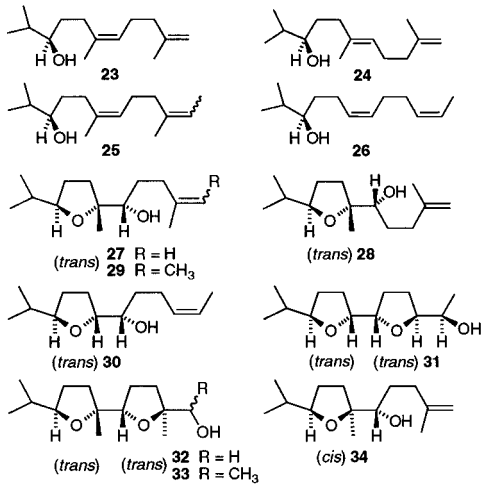
(9) All hydroxypolyene substrates were produced with >95% *E* or *Z* purity, with the exception of compound **29**, which was prepared as a 1.5:1 mixture of *E*/*Z* isomers at the terminal alkene. Please see the Supporting Information for the preparation and characterization of hydroxypolyene substrates.

(10) (a) Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2895. (b) Schlecht, M. F.; Kim, H.-J. *Tetrahedron Lett.* **1985**, *26*, 127. (c) Chakraborty, T. K.; Chandrasekaran, S. *Chem. Lett.* **1985**, 551. (d) Schlecht, M. F.; Kim, H. *Tetrahedron Lett.* **1986**, *27*, 4889. (e) Schlecht, M. F.; Kim, H.-J. *J. Org. Chem.* **1989**, *54*, 583. (f) Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Org. Chem.* **1990**, *55*, 891. (g) Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* **1990**, *31*, 2775. (h) Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Chem. Res., Miniprint* **1992**, 2213. (i) Waddell, T. G.; Carter, A. D.; Miller, T. J.; Pagni, R. M. *J. Org. Chem.* **1992**, *57*, 381. (j) McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921.

(11) Small amounts of the diastereomeric lactones produced in each case (**14** from the reaction of **11**; **13** from the reaction of **12**) may be attributed to either chromium-mediated epoxidation or alkene isomerization prior to *syn*-oxidative cyclization. Gas chromatography analysis of commercial neryl- and geranylacetone (precursors to **11** and **12**) revealed that each were contaminated with only 1.2−1.5% of the other isomeric compound, which accounts for some but not all of the slight loss of stereospecificity observed in these reactions.

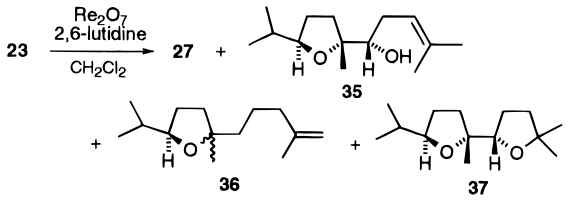
(12) (a) Nozaki, K.; Shirahama, H. *Chem. Lett.* **1988**, 1847. (b) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5947. (c) Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. (d) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299. (e) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. I* **1994**, 1975.

Table 2. Oxidative Cyclizations of Hydroxydienes **23**−**26**



entry	hydroxyalkene	reagents	products (isolated yield)
1	**23**	$(F_3CCO_2)ReO_3$ 2,6-lutidine, CH_2Cl_2	**27** (84%)
2	**24**	$(F_3CCO_2)ReO_3$ 2,6-lutidine, CH_2Cl_2	**28** (80%)
3	**25**	$(F_3CCO_2)ReO_3$ 2,6-lutidine, CH_2Cl_2	**29** (90%)
4	**26**	$(F_3CCO_2)ReO_3$ 2,6-lutidine, CH_2Cl_2	**30** (80%)
5	**30**	$(F_3CCO_2)ReO_3$ $(F_3CCO)_2O$, CH_2Cl_2	**31** (22%)
6	**30**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**31** (60%)
7	**26**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**31** (31%)
8	**27**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**32** (6%)
9	**29**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**33** (51%)
10	**24**	$VO(acac)_2$, *t*-BuOOH, NaOAc, CH_2Cl_2	**27** (50%)
11	**23**	$VO(acac)_2$, *t*-BuOOH, NaOAc, CH_2Cl_2	**34** (25%)

Scheme 3. Multiple Products from Re_2O_7-Induced Oxidative Bicyclization

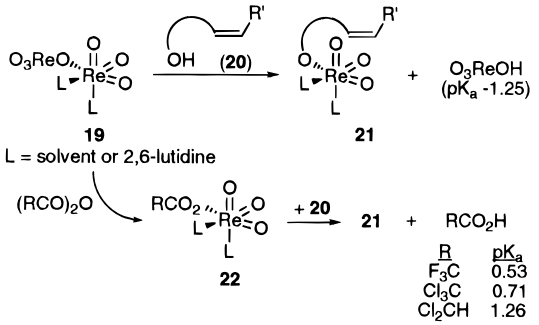


the development of a reagent which would be compatible with primary and secondary alcohols and allow *syn*-oxidative polycyclization in good yields and with high stereoselectivity.

***syn*-Oxidative Polycyclizations Induced by Rhenium(VII) Oxo Complexes.** Reaction of hydroxydiene **23** (see Table 2 for structure) with the combination of rhenium oxide and 2,6-lutidine[8] gave complex mixtures of the *syn*-oxidative monocyclization product **27** and its alkene isomer **35** as well as the acid-catalyzed (nonoxidative) cyclohydration byproduct **36**. The only bicyclic material produced was compound **37**, resulting from oxidative monocyclization followed by acid-catalyzed cyclohydration, even in the presence of lutidine (Scheme 3).

Kennedy has proposed that rhenium(VII) oxide-promoted *syn*-oxidative cyclizations require the intermediacy of the alkoxyperrhenate **21**;[8] note that formation of alkoxyperrhenate intermediate **21** results in production of 1 equiv of perrhenic acid ($HOReO_3$, pK_a −1.25;[13] Scheme 4). Although lutidine might be expected to neutralize this acid, we realized that 2 equiv of

Scheme 4. Formation of AlkoxyPerrhenate **21**



lutidine could be incorporated in the coordination sphere of each Lewis acidic rhenium atom (cf. **19** and **21**) instead of acting as a Brønsted−Lowry base. As Sinha and Keinan have noted that the presence of lutidine significantly inhibits *syn*-oxidative bicyclization processes,[8e] our goal was to develop base-free *syn*-oxidative polycyclization reagents which would be compatible with acid-sensitive alkenes. We proposed that the formation of acid-catalyzed byproducts might be disfavored by changing the leaving group from perrhenate (O_3ReO^-) to a less acidic carboxylate (RCO_2^-),[14] so that the pK_a of the reaction medium could be modified by varying the leaving group of the acylperrhenate RCO_2ReO_3 (**22**), which is ultimately controlled by the choice of carboxylic acid anhydride utilized in the metathesis reaction with Re_2O_7 (**19**).

We found that *syn*-oxidative cyclizations of the acid-sensitive hydroxydiene substrates **23**−**25**[9] with trifluoroacetylperrhenate **22** (R = F_3C) proceeded in excellent yields but required the presence of 2,6-lutidine. In each case monocyclic tetrahydrofuranyl alcohols **27**−**29** were formed with high *trans*-diastereoselectivity (Table 2, entries 1−3). Although bicyclizations of **23**−**26** were inhibited in the presence of lutidine or pyridine, we found that bicyclic product **31** could be obtained by reaction of **30** (product of entry 4) with trifluoroacetylperrhenate *in the presence of the corresponding carboxylic acid anhydride* (entry 5). Apparently the additional anhydride reacts with traces of perrhenic acid, regenerating the acylperrhenate reagent and thus further reducing the acidity of the reaction medium. After screening several acylperrhenates from commercially available acid anhydrides, we found that good yields of the bicyclic alcohol **31** could be obtained from **30** with the combination of dichloroacetylperrhenate and dichloroacetic anhydride, followed by deacylation of the dichloroacetate ester of **31** with methanolic sodium methoxide (entry 6). Bicyclization could also be achieved in one pot from acyclic substrate **26**, albeit in slightly lower yield (entry 7). Although the formation of bicyclic alcohol **32** from dichloroacetylperrhenate-promoted cyclization of **27** was accompanied by acid-catalyzed cyclohydration **37** and alkene migration products **35** (see Scheme 3 for structures), the more highly substituted substrate **29** gave a satisfactory yield of product **33** (entries 8 and 9).[15]

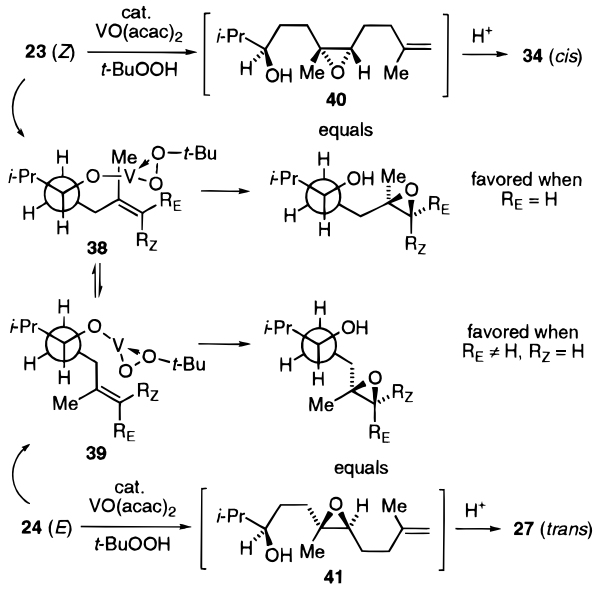
Stereochemical assignments for monocyclic products **27** and **28** were also determined by comparison with the epoxidation products obtained from the complementary alkene substrates. As expected from precedent,[16] the trisubstituted *E*-alkene **24** which is disubstituted at the alkene carbon proximal to the hydroxyl group afforded a *trans*-tetrahydrofuran product **27** (entry 10), which was indistinguishable in all respects (^1H, ^{13}C

(13) Bailey, N.; Carrington, A.; Lott, K. A. K.; Symons, M. C. R. *J. Chem. Soc.* **1960**, 290.

(14) (a) Edwards, P.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1984**, 2695. (b) Herrmann, W.; Thiel, W. R.; Kühn, F. E.; Fischer, R. W.; Kleine, W.; Herdtweck, E.; Scherer, W.; Mink, J. *Inorg. Chem.* **1993**, *32*, 5188.

(15) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750.

Scheme 5. Conformational Models for Hydroxyl-Directed Epoxidations



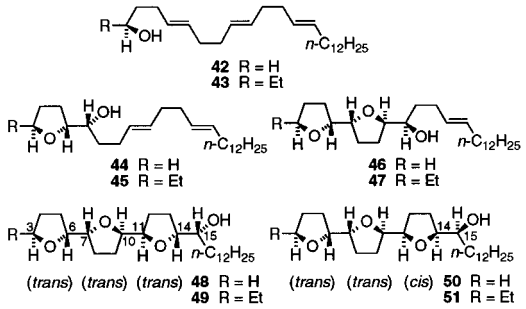
NMR and IR spectroscopy, gas chromatograph retention time) from the product obtained from *syn*-oxidative monocyclization of the *Z*-alkene **23** (entry 1). In contrast, epoxidation of the *Z*-isomer **23** yielded the *cis*-tetrahydrofuran **34** (entry 11). This assignment was supported by NOE difference studies, which revealed a positive NOE between the methyl group and the hydrogen atom across the tetrahydrofuran ring, whereas no such NOE could be observed in *trans*-tetrahydrofuran product **27**. In summary, the chair-like conformation **38** is normally favored (including substrates **11**, **12**, **23**, and **25**) except when the alkene not only bears disubstitution at the carbon proximal to the hydroxyl group but also is substituted with an alkyl group R_E (i.e., **24**) so that steric hindrance with the alkoxyvanadium peroxo species in conformation **38** can only be relieved by rotation into the more open conformation **39** (Scheme 5).[16a]

A projected synthesis of the tricyclic acetogenin goniocin (**1**) will require stereoselective *syn*-oxidative tricyclization of an *all-E*-hydroxytriene (Figures 1 and 2, vide infra). Reaction of the achiral primary hydroxytriene **42**[9] with trifluoroacetylperrhenate in the presence of lutidine gave the monocyclic *trans*-tetrahydrofuranyl hydroxydiene **44** in 49% (unoptimized) yield (Table 3, entry 1), whereas use of the dichloroacetylperrhenate reagent and dichloroacetic anhydride followed by methoxide deacylation afforded a tristetrahydrofuranyl alcohol product in 63% yield as a 4/1 mixture of diastereomers, and the major product was assigned as structure **48** (entry 2). Small amounts of the monocyclic compound **44** (7%) and starting material **42** were also recovered; apparently acid-catalyzed dichloroacetylation of hydroxyl groups prevented complete conversion of reactants and intermediates. Interestingly, we could find no trace of the bicyclic intermediate **46** in the crude product mixture.

Polycyclization of the chiral nonracemic secondary hydroxytriene **43**[9] with dichloroacetylperrhenate/dichloroacetic anhydride gave a 49% yield of tricyclization product. Examination of the ^{13}C NMR spectrum of this product revealed that an inseparable mixture of two diastereomers had been formed (entry 3). We also evaluated the reaction of **43** with dirhenium heptoxide/periodic acid and obtained only one of the tristetrahydrofuranyl alcohol diastereomers, which was assigned as structure **49** (entry 4). Although these conditions provided **49** in only 17% yield, we surmised that a reasonable chemical yield and high diasteroselectivity for the tricyclic alcohol might be obtained with acylperrhenate reagents which produced byproducts more acidic than dichloroacetic acid (pK_a 2.85) but less acidic than perrhenic acid (pK_a −1.25). This study resulted in the finding that trifluoroacetylperrhenate/trifluoroacetic anhydride (entry 5) and trichloroacetylperrhenate/trichloroacetic anhydride (entry 6) are the optimal reagents for completely diastereoselective tricyclization of **43** (as determined by ^{13}C NMR), whereas the combination of chloroacetylperrhenate/chloroacetic acid (entry 7) gave a mixture of diastereomers, consistent with the decreased acidity of the chloroacetic acid byproduct. We have also determined that the breakdown in diastereoselectivity appears to occur in the formation of both the second and third rings, as reaction of the monotetrahydrofuranyl alcohol **45** (product of entry 8) with 1.4 equiv of dichloroacetylperrhenate/dichloroacetic anhydride yielded bicyclic alcohol **47** in 21% yield (4/1 mixture of diasteromers by ^{13}C NMR) accompanied by a 30% yield of the tristetrahydrofuranyl alcohol **49** (apparently as a single diastereomer by ^{13}C NMR, entry 9) and recovered **45**.[17] Further reaction of bicyclic hydroxyalkenes **47** with dichloroacetylperrhenate/dichloroacetic anhydride afforded a 3/1 mixture of diastereomeric alcohols **49** and **51** (entry 10).[18]

As acylated products result from perrhenate-induced *syn*-oxidative cyclizations in the presence of carboxylic acid anhydrides, the polycyclization products are generally deacylated with sodium methoxide. In exploring milder conditions for

Table 3. *syn*-Oxidative Cyclizations of Hydroxytrienes **42** and **43**



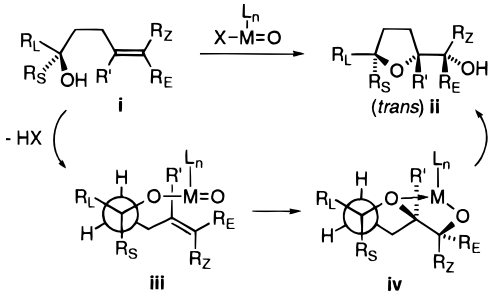
entry	hydroxypolyene	reagents	products (isolated yield, ratio)
1	**42**	$(F_3CCO_2)ReO_3$ 2,6-lutidine, CH_2Cl_2	**44** (49%)
2	**42**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**48** / **50** (63%, 4 / 1)
3	**43**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**49** / **51** (49%, 1 / 1)
4	**43**	Re_2O_7, H_5IO_6	**49** (17%)
5	**43**	$(F_3CCO_2)ReO_3$ $(F_3CCO)_2O$, CH_2Cl_2	**49** (39%)
6	**43**	$(Cl_3CCO_2)ReO_3$ $(Cl_3CCO)_2O$, CH_2Cl_2	**49** (32%)
7	**43**	$(ClCH_2CO_2)ReO_3$ $(ClCH_2CO)_2O$, CH_2Cl_2	**49** / **51** (42%, 1 / 1)
8	**43**	$(F_3CCO_2)ReO_3$ 2,6-lutidine, CH_2Cl_2	**45** (67%)
9	**45**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**47** (21%, 4 / 1) + **49** (30%)
10	**47**	$(Cl_2CHCO_2)ReO_3$ $(Cl_2CHCO)_2O$, CH_2Cl_2	**49** / **51** (36%, 3 / 1)

(16) Kishi first showed that *E*-trisubstituted alkenyl alcohols analogous to **24** afford *trans*-tetrahydrofuranyl alcohols via vanadium-catalyzed epoxidation/*anti*-cyclization. (a) Fukuyama, T.; Vranesic, B.; Negri, P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *31*, 2741. (b) Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582. (c) Reference 12d.

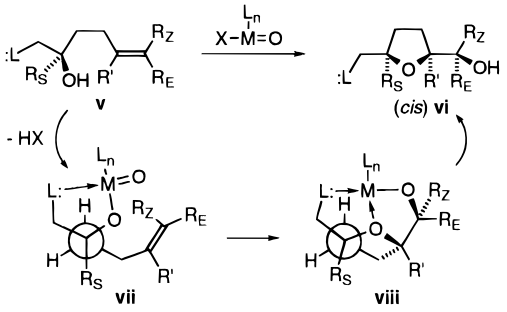
(17) A similar experiment with 1.4 equiv of $(F_3CCO_2)ReO_3/(F_3CCO)_2O$ afforded **47** and **49** as single diastereomers.

(18) We have noticed that the diastereomer ratios obtained with the dichloroacetylperrhenate reagents varied slightly between experiments, suggesting that there may be a concentration dependence of acid on the stereoselectivity of *syn*-oxidative cyclization reactions.

Scheme 6. Conformational Models for Hydroxyl-Directed *syn*-Oxidative Cyclizations



Scheme 7. Conformational Models for Bidentate-Directed *syn*-Oxidative Cyclizations



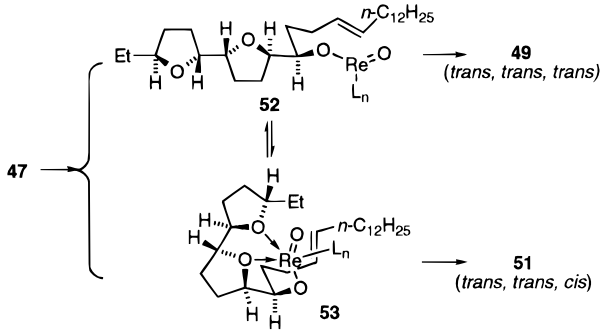
deacylation of the diastereomeric mixture of tricyclic products arising from dichloroacetylperrhenate-induced tricyclization of **43**, we discovered that Na_2CO_3 in acetone selectively deacylated the dichloroacetate of diastereomer **51**, which exhibited ^{13}C NMR spectra different from the product obtained from reaction of **43** with Re_2O_7/H_5IO_6. Alcohol **51** could be easily separated from the remaining dichloroacetate derivative by flash chromatography; deacylation of the dichloroacetate ester gave structure **49** (identical in all respects to the product from reaction of **43** with Re_2O_7/H_5IO_6).

PCC oxidation of each tristetrahydrofuranyl alcohol **49** and **51** afforded the expected ketone products. Each ketone exhibited a different ^{13}C NMR spectrum, demonstrating that compounds **49** and **51** differed in stereochemistry at C14. Although H14 could be clearly distinguished in the ^1H NMR spectrum for each ketone, neither compound exhibited NOEs with other hydrogens in the cyclic ether range (δ 3.7−4.0) upon irradiation of H14. Epoxidation/acid-catalyzed cyclization of the bistetrahydrofuran-hydroxyalkene **47** with peracetic acid in dichloromethane gave a mixture of two tristetrahydrofuranyl alcohols. Direct comparison of the ^{13}C NMR spectrum of this difficultly separable mixture showed that these epoxidation products differed from each perrhenate-derived product **49** and **51**, thus ruling out the possibility of an epoxidation side reaction with the perrhenate reagents. Furthermore, PCC oxidations of the alcohols resulting from peracid epoxidation/cyclization furnished ketones which were identical by ^1H and ^{13}C NMR spectroscopy to the ketones obtained from PCC oxidation of **49**/**51**, which proved that isomerization had not occurred elsewhere in the polycyclic ether structure.[19]

The formation of *trans*-tetrahydrofurans from chromium- and rhenium-promoted oxidative cyclizations of monodentate hydroxyalkenes is consistent with a chair-like conformation of the alkoxymetal oxo complex **iii** (Scheme 6). However, our results demonstrate that the diastereoselectivity of *syn*-oxidative *polycyclizations* is dramatically dependent on the acidity of the reaction medium. We attribute the loss of diastereoselectivity with dichloro- or monochloroacetylperrhenate reagents to bidentate or multidentate coordination of rhenium to the growing polytetrahydrofuran chain. Intramolecular coordination of an additional ligand constrains the geometry of the alkoxy-metal-oxo such that the alkene must rotate into alignment **vii** for reaction to give **vi** (R_S and R′ are *cis*, Scheme 7). This model is also consistent with Cr(VI)-promoted *syn*-oxidative cyclizations of 1,2-diol alkenes such as **7** (Scheme 2), which consistently afford *cis*-tetrahydrofuran products (i.e., **8**).[6] Although

(19) After considerable difficulty we obtained small amounts of the Mosher esters from reaction of **49** with (*R*)- and (*S*)-MTPA (Rieser, M. J.; Hui, Y.-h.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203); however, the chemical shift differences at H14 for each Mosher ester were less than 0.01 ppm. A similarly minute difference in chemical shift was observed in goniocin (ref 3a).

Scheme 8. Conformational Models for *syn*-Oxidative Cyclization of **47**



the Cr(VI)-promoted *syn*-oxidative polycyclizations of monohydroxydienes are apparently insensitive to coordination with neighboring ether substituents, the more Lewis acidic Re(VII) reagents can coordinate with the adjacent ether groups. This coordination effect could be enhanced with two tetrahydrofuran rings, as shown in structure **53** (Scheme 8) leading to *cis*-tetrahydrofuran product **51**; if intramolecular coordination is disfavored under acidic conditions, conformer **52** leading to *trans*-product **49** would be expected. Although we are unable to unequivocably prove the stereochemical assignment for **49** as *all-trans* and **51** as *all-cis* by spectroscopic methods, these assignments are consistent with the observed dependence of diastereoselectivity on the acid strength of the reaction medium.

Summary and Conclusions

This work demonstrates the stereoselective formation of *all-trans* bis- and tristetrahydrofuran compounds via tandem, hydroxyl-directed *syn*-oxidative cyclization reactions. Although chromium(VI)-promoted reactions are limited to tertiary alcohol substrates, the use of acylperrhenate(VII) reagents permits the formation of polycyclic ether products from primary and secondary alcohol substrates. One particular advantage of the acylperrhenate reagents over other rhenium reagent combinations is the compatibility with many acid-sensitive alkene substrates. However, the seemingly trivial extension of this methodology to the synthesis of tristetrahydrofuran compounds can be complicated by greatly decreased levels of *trans*-diastereoselectivity unless the more acidic trichloro- or trifluoroacetylperrhenate reagents are utilized.

The stereochemistry of our synthetic tristetrahydrofuranyl alcohol **49** matches the structure reported for the polyether region of the acetogenin goniocin (**1**), which suggests that a similar hydroxyl-directed cascade of *syn*-oxidative cyclization reactions could be involved in the biosynthesis of this and other *trans*-tetrahydrofuran natural products.[4] Although the tandem polyepoxidation/*anti*-cyclization biosynthesis hypothesis[5] cannot be dismissed, note that hydroxyl-directed epoxidations would

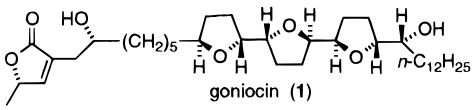


Figure 1.

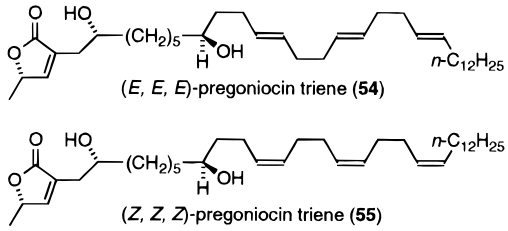


Figure 2.

afford predominantly *cis*-tetrahydrofuran products rather than the *trans*-diastereomers.[12e] The answer to this biosynthesis question may ultimately be determined by feeding experiments with isotopically labeled pregoniocin trienes **54** and **55** (Figure 2), and we are currently engaged in the chemical synthesis of these compounds.

Experimental Section

General Methods. All reactions were magnetically stirred in oven-dried glassware under an inert atmosphere. Unless otherwise indicated, reagents were obtained from commercial suppliers and used without further purification. The solvents diethyl ether and tetrahydrofuran (THF) were distilled from sodium metal/benzophenone ketyl prior to use; dichloromethane and toluene were distilled from calcium hydride prior to use.

General Procedure for PCC-Induced *syn*-Oxidative Bicyclizations: Hydroxydiene **11** or **12** (0.5 mmol) was dissolved in CH_2Cl_2 (5.5 mL). Celite (10× weight of hydroxypolyene), PCC (2.5 mmol), and HOAc (2.1 mL) were added, and the resulting heterogeneous mixture was stirred under N_2 at 20 °C for 14 h. The product mixture was diluted with pentane/ether (1/1) and filtered through 4 cm of silica gel. The products were purified by flash chromatography (pentane/ethyl acetate) to give a colorless oil.

Bicyclic lactone 13: IR (free film from CH_2Cl_2) 2972, 2876, 1777, 1463, 1386, 1302, 1238, 1161, 1071, 949, 885, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (1H, app t, J = 6.6, 7.6 Hz), 2.68−2.47 (2H, m), 2.32−2.22 (1H, m), 1.98−1.84 (2H, m), 1.81−1.65 (3H, m), 1.34 (3H, s), 1.24 (3H, s), 1.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 87.5, 82.4, 81.5, 38.2, 29.5, 29.0, 28.4, 27.6, 27.3, 22.9; MS (70 eV, EI) 198, 183, 165, 141, 125, 112, 99, 81, 71, 55, 43; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1255. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.33; H, 8.91.

Bicyclic lactone 14: IR (free film from CH_2Cl_2) 2972, 2876, 1777, 1456, 1386, 1238, 1154, 1065, 949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (1H, app t, J = 7.2, 7.4 Hz), 2.80−2.70 (1H, m), 2.46−2.32 (2H, m), 2.00−1.82 (3H, m), 1.73−1.64 (2H, m), 1.31 (3H, s), 1.17 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 86.1, 84.2, 81.7, 38.0, 32.0, 29.9, 27.8, 27.7, 26.5, 23.9; MS (70eV, EI) 198, 183, 165, 125, 112, 99, 81, 71, 55, 43; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1253.

Bistetrahydrofuranyl alcohol 15: IR (free film from CH_2Cl_2) 3474, 2970, 2930, 2871, 1457, 1366, 1146, 1063, 953, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (1H, app t, J = 6.8, 7.2 Hz), 3.78 (1H, app t, J = 7.4, 7.5 Hz), 2.20 (1H, s), 1.98−1.65 (8H, m), 1.25 (3H, s), 1.23 (3H, s), 1.21 (3H, s) 1.16 (3H, s), 1.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.8, 84.5, 84.3, 81.1, 70.6, 38.5, 34.7, 28.6, 28.0, 27.7, 27.6, 26.4, 24.0, 23.2; MS (70 eV, EI) 241, 227, 209, 183, 143, 125, 107, 97, 85, 71, 59, 43; HRMS calcd for $C_{13}H_{23}O_3$ $(M - CH_3)^+$ 227.1647, found 227.1656.

Bistetrahydrofuranyl alcohol 16: IR (free film from CH_2Cl_2) 3467, 2979, 2876, 1463, 1373, 1154, 1071, 956, 905 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (1H, app t J = 7.4, 7.5 Hz), 3.82 (1H, app t, J = 7.2, 8.4 Hz), 2.29 (1H, s), 2.16−2.06 (1H, m), 1.96−1.84 (2H, m), 1.82−1.55 (5H, m), 1.25 (6H, s), 1.22 (3H, s), 1.13(3H, s), 1.12 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.1, 84.6, 83.9, 81.1, 70.5, 38.8, 34.6, 28.4, 28.2, 27.8, 27.4, 26.4, 24.1, 24.0; MS (70 eV, EI) 242, 227, 209, 183, 143, 125, 97, 85, 71, 59, 43; HRMS calcd for $C_{14}H_{25}O_3$ $(M - H)^+$ 241.1804, found 241.1799; HRMS calcd for $C_{13}H_{23}O_3$ $(M - CH_3)^+$ 227.1647, found 227.1645.

General Procedure for Vanadium Catalyzed Epoxidation/Acid-Catalyzed *anti*-Cyclization Reactions. Hydroxypolyene (1.2 mmol) was dissolved in CH_2Cl_2 (18 mL). $VO(acac)_2$ (0.015 mmol), *t*-BuOOH (3.6 mmol, 3.0 M in isooctane), and HOAc (0.1 mL, 1.7 mmol) were added, and the resulting dark red reaction mixture was stirred under N_2 at 20 °C for 4 h. The reaction was quenched with water followed by extraction with chloroform. The combined chloroform extracts were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The products were purified by flash chromatography (pentane/ethyl acetate) to give a colorless oil.

Bistetrahydrofuranyl alcohol 18: IR (free film from CH_2Cl_2) 3442, 2966, 2934, 2876, 1463, 1379, 1231, 1149, 1071, 956, 905 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90−3.84 (3H, m), 2.30−2.20 (1H, m), 2.09−1.86 (3H, m), 1.84−1.68 (3H, m), 1.58−1.50 (1H, m), 1.30 (3H, s), 1.25 (3H, s), 1.21 (3H, s), 1.13 (3H, s), 1.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.7, 83.5, 83.0, 80.9, 72.0, 38.5, 34.4, 28.7, 27.8, 27.1, 25.7, 25.1, 24.4; MS (70 eV, EI) 243, 227, 209, 183, 143, 125, 99,85, 71, 59, 43; HRMS calcd for $C_{13}H_{23}O_3$ $(M - CH_3)^+$ 227.1647, found 227.1651.

Bistetrahydrofuranyl alcohol 17: IR (free film from CH_2Cl_2) 3441, 2971, 2933, 2873, 1457, 1368, 1151, 1071, 952, 897 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (1H, br s), 4.06 (1H, dd, J = 9.1, 6.3 Hz), 3.86 (1H, dd, J = 8.1, 3.0), 2.15−2.10 (2H, m), 1.96−1.90 (2H, m), 1.78−1.72 (2H, m), 1.63−1.48 (2H, m), 1.25 (9H, s),1.15 (3H, s), 1.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.8, 85.5, 84.0, 81.2, 72.0, 38.6, 30.8, 28.9, 28.5, 28.1, 28.0, 26.3, 25.3, 25.0; MS (70 eV, EI) 227, 209, 183, 166, 143, 125, 107, 85, 71, 59, 43; HRMS calcd for $C_{13}H_{23}O_3$ $(M - CH_3)^+$ 227.1647, found 227.1646; HRMS calcd for $C_{14}H_{25}O_2$ $(M - OH)^+$ 225.1854, found 225.1855.

Representative Example of Monocyclization with Trifluoroacetylperrhenate. Rhenium oxide (155.6 mg, 0.32 mmol, 1.9 equiv based on acyclic hydroxydiene) was dissolved in THF (6.0 mL) in a 50 mL Schlenk flask, trifluoroacetic anhydride (55 μL, 0.39 mmol, 2.3 equiv) was added, and the resulting mixture was stirred under nitrogen at room temperature for 1 h. The solution was cooled to 0 °C, concentrated *in vacuo*, rinsed with cold pentane (2 × 4 mL) and concentrated to give trifluoroacetylperrhenate as a white solid.

A solution of hydroxydiene **23** (35.3 mg, 0.17 mmol) and 2,6-lutidine (50 μL, 0.43 mmol, 2.5 equiv) in CH_2Cl_2 (6 mL) was added to the above preparation of $(F_3CCO_2)ReO_3$. The resulting dark purple solution was allowed to slowly warm to room temperature overnight. The crude reaction mixture was diluted with pentane/ethyl ether (1/1), filtered through silica gel, concentrated *in vacuo*, and purified by flash chromatography with pentane/ethyl ether (10/1) to yield monocyclic product **27** as a clear oil (32.1 mg, 0.14 mmol, 84% yield).

Monotetrahydrofuranyl alcohol 27: IR (free film from CH_2Cl_2) 3478, 3072, 2965, 2871, 1648, 1449, 1374, 1315, 1043, 865 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (2H, s), 3.66−3.58 (1H, m), 3.52 (1H, app dd, J = 10.4, 1.9 Hz), 2.36−2.27 (2H, m), 2.14−2.01 (2H, m), 1.93−1.85 (1H, m), 1.73 (3H, s), 1.72−1.33 (5H, m), 1.11 (3H, s), 0.94 (3H, d, J = 6.7 Hz), 0.86 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 109.8, 86.4, 82.3, 76.0, 34.7, 33.5, 31.0, 29.5, 28.9, 24.2, 22.5, 19.4, 17.9; MS (70 eV, LREI) 227, 209, 183, 170, 147, 139, 127, 109, 81, 69, 55, 43; HRMS calcd for $C_{14}H_{27}O_2$ $(M + H)^+$ 227.2011, found 227.2012.

Monotetrahydrofuranyl alcohol 28: IR (free film from CH_2Cl_2) 3460, 3074, 2966, 2871, 2366, 1648, 1447, 1375, 1292, 1086, 1042, 884, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (2H, s), 3.60−3.53 (1H, m), 3.40 (1H, t, J = 6.0 Hz), 2.55 (1H, br s), 2.36−2.26 (1H, m), 2.11−2.01 (1H, m), 1.90−1.83 (1H, m), 1.72 (3H, s), 1.70−1.58 (4H, m), 1.48−1.40 (2H, m), 1.11 (3H, s), 0.93 (3H, d, J = 6.6 Hz), 0.84 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 109.9, 84.8, 84.5, 76.3, 34.9, 34.8, 33.0, 29.5, 29.3, 22.5, 20.7, 19.4,

18.1; MS (70 eV, LREI) 225, 208, 183, 170, 147, 139, 127, 109, 81, 69, 55, 43; HRMS calcd for $C_{14}H_{24}O$ $(M - H_2O)^+$ 208.1827, found 208.1827.

Monotetrahydrofuranyl alcohol 29: (1.5/1.0 mixture of alkene isomers) IR (free film from CH_2Cl_2) 3452, 2962, 2936, 2871, 2357, 1653, 1556, 1456, 1374, 1110, 1041, 899, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.28−5.20 (1H, m), 3.67−3.59 (1H, m), 3.48 (1H, dd, J = 10.4, 1.7 Hz), 2.44−2.40 (1H, m), 2.22 (1H, t, J = 7.7 Hz), 2.11−2.01 (2H, m), 1.93−1.85 (1H, m), 1.72−1.49 (9H, m), 1.47−1.26 (2H, m), 1.11 (3H, s), 0.95 (3H, d, J = 6.8 Hz), 0.86 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 135.7, 119.6, 118.7, 86.5, 85.4, 76.3, 76.2, 36.7, 33.6, 31.06, 30.95, 29.9, 29.5, 29.0, 28.5, 24.4, 24.3, 23.4, 19.5, 18.0, 15.7, 13.4, 13.3; MS (70 eV, LREI) 240, 197, 153, 127, 109, 83, 69, 55, 43; HRMS calcd for $C_{15}H_{28}O_2$ 240.2089, found 240.2072.

Monotetrahydrofuranyl alcohol 30: IR (free film from CH_2Cl_2) 3442, 3011, 2961, 2926, 2871, 1469, 1366, 1318, 1063, 944, 875, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.52−5.34 (2H, m), 3.87−3.78 (2H, m), 3.64 (1H, app br dd, J = 7.3, 6.3 Hz), 2.27−2.09 (3H, m), 2.01−1.75 (3H, m), 1.72−1.50 (2H, m), 1.62 (3H, d, J = 6.3 Hz), 1.49−1.39 (2H, m), 0.95 (3H, d, J = 6.6 Hz), 0.85 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 124.4, 85.4, 81.9, 71.3, 33.2, 32.2, 29.5, 25.2, 23.3, 19.3, 18.1, 12.7; MS (70 eV, LREI) 212, 169, 149, 126, 113, 95, 81, 69, 55, 41; HRMS calcd for $C_{13}H_{24}O_2$ 212.1776: found 212.1773.

Representative example for dichloroacetylperrhenate-induced formation of bistetrahydrofuranyl alcohols:

Bistetrahydrofuranyl Alcohol 31 (Oxidative Cyclization of Monocyclic Alcohol 30 with Dichloroacetylperrhenate). Dirhenium heptoxide (108.7 mg, 0.22 mmol, 2.0 equiv based on monocyclic alcohol **30**) was dissolved in THF (6.0 mL) in a 25 mL Schlenk flask. Dichloroacetic anhydride (42 mL, 0.28 mmol, 1.2 equiv based on Re_2O_7) was added, and the resulting mixture was stirred under nitrogen at room temperature for 1 h. The solution was cooled to 0 °C, concentrated *in vacuo*, rinsed two times with cold pentane (4 mL), and concentrated to give dichloroacetylperrhenate as a purple oil.

Dichloroacetic anhydride (0.1 mL, 0.66 mmol, 6.0 equiv based on monocyclic alcohol **30**) in CH_2Cl_2 (3 mL) was added to the above preparation of $(Cl_2CHCO_2)ReO_3$ followed by the hydroxyalkene **30** (22.9 mg, 0.11 mmol) in CH_2Cl_2 (6 mL). The resulting dark purple solution was allowed to slowly warm to room temperature overnight. The crude reaction mixture was diluted with pentane/ethyl ether (1/1), filtered through silica gel, and concentrated *in vacuo*. The residue was dissolved in ethyl ether, and sodium methoxide in methanol was added to destroy excess dichloroacetic anhydride. The solution was quenched with saturated ammonium chloride, extracted with ethyl ether, dried with brine and sodium sulfate, and purified by flash chromatography with pentane/ethyl ether to yield bicyclic product **31** as a clear oil (16.1 mg, 0.71 mmol, 65% yield): IR (free film from CH_2Cl_2) 3422, 2960, 2876, 2361, 1704, 1653, 1554, 1456, 1062, 940, 667cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04−3.85 (4H, m), 3.67−3.60 (1H, m), 2.17 (1H, br s), 2.07−1.43 (9H, m), 1.10 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.84 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.2, 83.5, 82.1, 81.1, 67.8, 33.1, 29.2, 28.61, 28.57, 24.7, 19.4, 18.1, 17.9; MS (70 eV, LREI) 210, 183, 147, 113, 95, 81, 69, 57, 41; HRMS calcd for $C_{13}H_{22}O_2$ $(M - H_2O)^+$ 210.1620, found 210.1626.

Bistetrahydrofuranyl alcohol 32: IR (free film from CH_2Cl_2) 3414, 2966, 2925, 2856, 2360, 1740, 1706, 1653, 1558, 1456, 1373, 1116, 1047, 906, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92−3.87 (1H, m), 3.71−3.66 (1H, m), 3.52−3.44 (2H, m), 2.05−1.80 (3H, m), 1.79−1.50 (5H, m), 1.48−1.03 (8H, m), 0.94 (3H, d, J = 7.8 Hz), 0.86 (3H, d, J = 6.7 Hz); MS (70 eV, LREI) 211, 127, 109, 97, 81, 69, 55, 43; HRMS calcd for $C_{13}H_{23}O_2$ $(M - CH_2OH)^+$ 211.1698, found 211.1693.

Bistetrahydrofuranyl alcohol 33: (inseparable mixture of alkene isomers) IR (free film from CH_2Cl_2) 3422, 2969, 2872, 2363, 1653, 1456, 1373, 1290, 1047, 907, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96−3.86 (1H, m), 3.76−3.63 (2H, m), 2.55 (1H, br s), 2.11−1.84 (3H, m), 1.78−1.50 (6H, m), 1.14 (6H, s), 1.12−1.08 (3H, m), 0.93 (3H, d, J = 6.7 Hz), 0.85 (3H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.0, 86.5, 85.9, 85.6, 85.2, 83.7, 83.5, 72.6, 72.4, 34.5, 33.5, 33.2, 33.0, 32.9, 30.1, 28.5, 28.2, 28.0, 24.3, 24.1, 24.0, 20.0, 19.5, 17.8, 17.3, 17.0; MS (70 eV, LREI) 257, 211, 153, 127, 109, 85, 69, 43; HRMS calcd for $C_{13}H_{23}O_2$ $(M - CH_3CHOH)^+$ 211.1698, found 211.1698.

Monotetrahydrofuranyl Alcohol 45 (Trifluoroacetylperrhenate-Induced Oxidative Monocyclization of 43). A solution of ethyltrienol **43** (405.1 mg, 1.0 mmol) and 2,6-lutidine (0.37 mL, 3.18 mmol, 3.0 equiv based on trienol) in CH_2Cl_2 (16 mL) was added to solid trifluoroacetylperrhenate [4.1 mmol: prepared from Re_2O_7 (0.99 g, 2.05 mmol), $(F_3CCO)_2O$ (0.1 mL, 0.70 mmol, 1.4 equiv based on Re_2O_7) in THF (9 mL)] at 0 °C. The resulting dark purple solution was allowed to slowly warm to room temperature overnight. The crude reaction mixture was diluted with pentane/ ethyl ether (1/1), filtered through silica gel (5 cm), and concentrated *in vacuo*. The residue was purified by flash chromatography with pentane/ethyl acetate (4/1) to yield monocyclic product **45** as clear oil (284.3 mg, 0.70 mmol, 67% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.43−5.37 (4H, m), 3.84−3.75 (2H, m), 3.41−3.35 (1H, m), 2.41 (1H, br s), 2.26−1.94 (10H, m), 1.67−1.37 (6H, m), 1.25 (20H, br s), 0.93−0.85 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7, 130.3, 129.9, 129.5, 81.9, 80.6, 73.5, 33.2, 32.7, 32.6, 32.56, 31.9, 29.7, 29.6, 29.58, 29.5, 29.3, 29.1, 28.6, 28.4, 28.3, 22.7, 14.1, 10.3.

Tristetrahydrofuranyl alcohol 48: IR (free film from CH_2Cl_2) 3449, 2924, 2853, 1465, 1115, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89−3.74 (7H, m), 3.35 (1H, m), 1.89−1.69 (8H, m), 1.64−1.35 (6H, m), 1.23 (21H, br s), 0.84 (3H, t, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.9, 82.5, 82.0, 81.2, 81.1, 74.3, 68.4, 34.3, 30.9, 29.6, 29.3, 28.2, 28.1, 27.8, 25.9, 25.8, 22.6, 14.1; MS (70 eV, LREI) 321, 241, 211, 193, 141, 110, 97, 71, 43; HRMS calcd for $C_{25}H_{46}O_4$ 410.3396; found 410.3386. Anal. Calcd for $C_{25}H_{46}O_4$: 73.12 C, 11.29 H. Found 72.84 C, 11.04 H.

Representative Procedure for *syn*-Oxidative Polycyclization. Tristetrahydrofuranyl Alcohol 49 (Tricyclization of Chiral Trienol 43). Trifluoroacetic anhydride (0.13 mL, 0.92 mmol, 6.7 equiv based on acyclic substrate **43**) in CH_2Cl_2 (3 mL) was added to a preparation of $(F_3CCO_2)ReO_3$ [Re_2O_7 (395.7 mg, 0.82 mmol, 6.0 equiv), THF (13 mL), and $(F_3CCO)_2O$ (0.15 mL, 1.1 mmol, 1.3 equiv based on Re_2O_7)] followed by hydroxytriene **43** (53.5 mg, 0.137 mmol) in CH_2Cl_2 (3 mL). The resulting dark purple solution was allowed to slowly warm to room temperature overnight. The crude reaction mixture was diluted with pentane/ethyl ether (1/1), filtered through silica gel (2 cm), and concentrated *in vacuo*. The residue was dissolved in ethyl ether and sodium methoxide in methanol was added to destroy excess trifluoroacetic anhydride. The solution was quenched with saturated ammonium chloride, extracted with ethyl ether, dried with brine and sodium sulfate, and purified by flash chromatography with pentane/ethyl acetate (4/1) to yield tristetrahydrofuranyl alcohol **49** as a clear oil (23.2 mg, 39% yield): $[\alpha]^{23}_D$ −2.4° ($CHCl_3$, c = 0.42); IR (free film from CH_2Cl_2) 3486, 2915, 2854, 1646, 1457, 1066, 948, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96−3.50 (6H, m), 3.48−3.35 (1H, m), 2.04−1.77 (8H, m), 1.69−1.51 (3H, m), 1.49−1.35 (4H, m), 1.24 (22H, br s), 0.88 (6H, app q, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.5, 82.3, 81.2, 81.1, 80.5, 74.4, 34.2, 31.9, 31.5, 29.8, 29.7, 29.6, 29.3, 28.7, 28.5, 28.2, 28.1, 27.9, 27.8, 25.9, 22.7, 14.1, 10.2; MS (70 eV, LREI) 438, 409, 339, 321, 308, 269, 239, 169, 138, 125, 110, 99, 98, 97, 81, 71, 69, 57, 55, 43, 41; HRMS calcd for $C_{27}H_{50}O_4$ 438.3709: found 438.3704. Anal. Calcd for $C_{26}H_{50}O_4$: 73.92 C, 11.49 H. Found: 73.80 C, 11.14 H.

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Supporting Information Available: Preparation and characterization data for hydroxypolyene substrates **11** and **12**, **23**−**26**, **42** and **43** (10 pages). See any current masthead page for ordering and Internet access instructions.

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