syn-Oxidative Polycyclization of Hydroxy Polyenes: A New Approach to Polyether Synthesis

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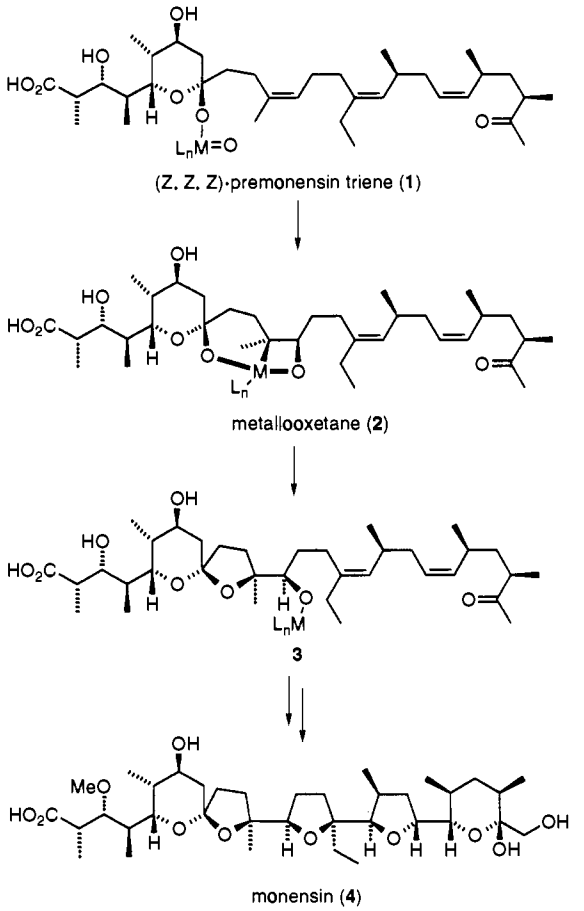
The Cane–Celmer–Westley model for polyether biosynthesis[2] features enzymatic polyepoxidation of an acyclic hydroxy polyene (i.e., (*E*,*E*,*E*)-premonensin triene → triepoxide), followed by a cascade of intramolecular *anti* epoxide-opening events to afford the polyether skeleton.[3,4] Townsend and Basak have recently advanced an alternative biosynthetic hypothesis which proposes an alkoxy-tethered, non-heme metal oxo as the active oxidative cyclization species.[5] Their mechanism involves initial [2 + 2] cycloaddition to a putative metallooxetane **2**,[6] which then undergoes reductive elimination of the metal, resulting in overall *syn*-addition of both oxygens to the alkene in compound **3** (Scheme 1).

Chromium[7] and rhenium[8] oxo reagents will induce *syn*-oxidative cyclizations of monoalkene substrates when tethered to a bishomoallylic alcohol, but *syn*-oxidative polycyclization with a reagent mechanism corresponding to the Townsend–Basak biosynthesis hypothesis has not been previously reported. We found that oxochromium(VI) compounds such as commercially

Scheme 1. Townsend–Basak Hypothesis



available pyridinium chlorochromate (PCC) will induce oxidative bicyclizations of terpene-derived hydroxydienes (Table 1). For instance, nerol-derived *Z* hydroxy diene **5**[9] reacts with PCC in the presence of acetic acid to provide oxidative bicyclization product alcohols **10** and **11**[10] as well as the bicyclic lactone **12**[10] in 47% combined yield (entry 1).[11] The isomeric *E* hydroxy diene **6**[9] similarly gives the corresponding diastereomeric alcohols **13** and **14**[10] and lactone **15**[10] (43% combined yield), demonstrating the high *syn*-stereospecificity of these reactions (entry 2).[12] Pyridinium dichromate (PDC)–acetic acid also promotes *syn*-oxidative bicyclization, although yields are slightly lower.

Stereochemical assignments for **10** and **11** and for **13** and **14** were conclusively determined by comparison with the products obtained from vanadium-catalyzed alkene epoxidation in tandem with acid-catalyzed cyclization[3b-d] (entries 3 and 4). These two reaction types are stereocomplementary not only in oxygenation of the alkene carbons but also in formation of *trans*-tetrahydrofuran **10** obtained from chromium-mediated *syn*-bicyclization

(1) (a) Camille and Henry Dreyfus New Faculty Awardee, 1992–1997. (b) This work was presented at the 207th ACS National Meeting, San Diego, CA, 1994; ORGN 168.

(2) (a) Westley, J. W.; Blount, J. F.; Evans, R. H.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 597. (b) Westley, J. W. In *Antibiotics*; Corcoran, J. W., Ed.; Springer-Verlag: New York, 1981; Vol. 4, pp 41–73. (c) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594. Feeding experiments have failed to detect radiolabeled monensin (**4**) upon incubation of tritiated synthetic (*E*,*E*,*E*)-premonensin triene with the monensin-producing organism *Streptomyces cinnamonensis*. (d) Holmes, D. S.; Sherringham, J. A.; Dyer, U. C.; Russell, S. T.; Robinson, J. A. *Helv. Chim. Acta* **1990**, *73*, 239. (e) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1.

(3) Conformational models have been developed for reliable prediction of stereoinduction in vanadium-catalyzed epoxidations of acyclic bishomoallylic alcohols. From 4-substituted 4-alken-1-ols, see: (a) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741. From 5-substituted 4-alken-1-ols, see: (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.

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(5) Townsend, C. A.; Basak, A. *Tetrahedron* **1991**, *47*, 2591.

(6) Jørgensen, K. A.; Schiøtt, B. *Chem. Rev.* **1990**, *90*, 1483.

(7) (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) Waddell, T. G.; Carter, A. D.; Miller, T. J.; Pagni, R. M. *J. Org. Chem.* **1992**, *57*, 381. (e) Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Chem. Res., Miniprint* **1992**, 2213. For *syn*-oxidative cyclization of alkenyl diols, see: (f) Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 379. (g) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727. (h) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171.

(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.

(9) Compounds **5**, **6**, and **8** were prepared by the addition of methylmagnesium bromide in ether to nerylacetone, geranylacetone, or farnesylacetone, respectively. **7** was prepared by addition of isopropylmagnesium bromide to nerylacetone, followed by sodium borohydride reduction of undesired aldol byproducts (ref 3d).

(10) This compound was characterized by ^{1}H and ^{13}C NMR, IR, and elemental analysis or high-resolution mass spectrometry.

(11) *Monocyclic* lactones corresponding to oxidative cleavage after one cyclization event are generally found in 10–20% isolated yields (ref 7a–e). Minor byproducts also include alkenyl-containing monocyclization products. The proportion of *anti*-lactone stereoisomers increases when a large excess of PCC (10 equiv) is present or when acetic acid is used as the bulk solvent.

(12) The reaction of **5** with chromium trioxide, acetic acid, and *tert*-butyl hydroperoxide (Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 2133) gives a 1/3 mixture of lactones **12** and **15** in 11% combined yield (unoptimized), indicating that chromium-mediated epoxidation and *anti*-opening (**5** → **15**) is competing with *syn*-oxidative bicyclization (**5** → **12**). Cyclization of **5** with chromium(V) oxidants (refs 9a,c) also gives predominantly lactone **15** in 6% yield (unoptimized) resulting from epoxidation–cyclization pathways.

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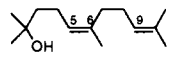
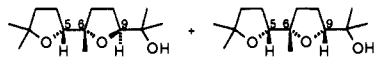
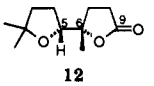
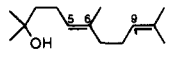
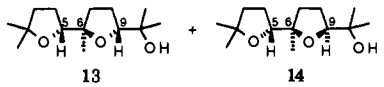
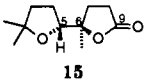
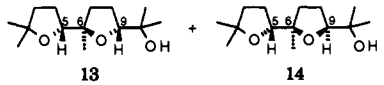
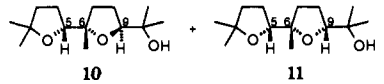
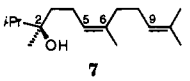
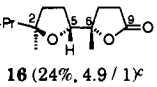
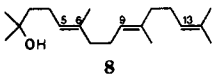
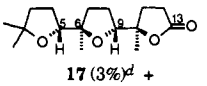
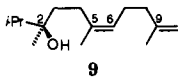
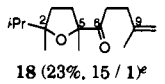
Table 1. Product Distributions from Oxidative Polycyclizations of Hydroxy Polyenes

entry	substrate	conditions	polycyclic alcohols (combined yield, ratio trans / cis)	polycyclic lactone (ratio syn / anti)
1	 **5**	PCC, HOAc[a]	 **10** + **11** (9%, 11 / 1)	 **12** (38%, 9.9 / 1)
2	 **6**	PCC, HOAc[a]	 **13** + **14** (19%, 3.7 / 1)	 **15** (24%, 17 / 1)
3	**5**	$VO(acac)_2$, *t*-BuOOH, HOAc[b]	 **13** + **14** (35%, 1 / 9.4)	(not observed)
4	**6**	$VO(acac)_2$, *t*-BuOOH, HOAc[b]	 **10** + **11** (45%, 1 / 2.7)	(not observed)
5	 **7**	PCC, HOAc[a]	(not observed)	 **16** (24%, 4.9 / 1)[c]
6	 **8**	PCC, HOAc[a]	(not observed)	 **17** (3%)[d] + **15** (25%)
7	 **9**	PCC, HOAc[a]	 **18** (23%, 15 / 1)[e]	

[a] Representative procedure: Hydroxy polyene (0.5 mmol) was dissolved in CH_2Cl_2 (5.5 mL). Celite (10× weight of hydroxy polyene), 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 1:1 pentane/ether and filtered through 2 in. of silica gel to remove chromium compounds. Cyclized products were purified by silica gel chromatography (pentane/ethyl acetate). [b] Representative procedure: Hydroxy polyene (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. After aqueous quench followed by extraction with chloroform and evaporation, cyclized products were purified by silica gel chromatography (pentane/ethyl acetate). [c] Stereochemistry of the major isomer is assigned by analogy to entry 1. We have not determined whether the minor isomer is a *cis*-tetrahydrofuran or *anti*-oxidation product. [d] Stereochemistry of the major isomer is assigned by analogy to entry 2. [e] Stereochemistry of the major isomer has not been assigned.

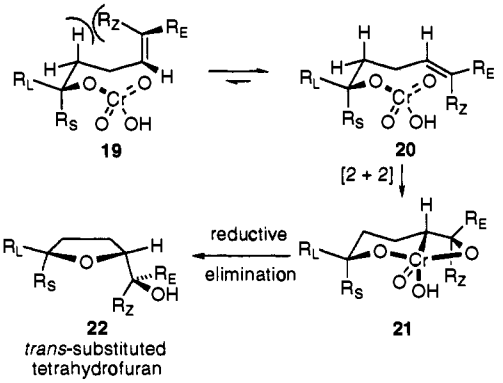
of **5** (entry 1, identical to the minor bicyclic alcohol product obtained in entry 4).

The reaction of hydroxy triene substrate **8**[9] provides the tricyclic lactone **17** as a minor product (entry 6), with significant amounts of bicyclic **13** also formed by oxidative cleavage after two cyclization events. Hydroxy diene **9**[13] was studied to determine if oxidative cyclization of a chromate ester arising from a secondary alcohol might occur more rapidly than simple oxidation. However, the only cyclic product found was monocyclic ketone **18** (entry 7).

These bicyclization reactions proceed with high stereoinduction for (*Z*)-alkene substrates, with the larger substituents located *trans* across the tetrahydrofuran rings in the major products **10** and **13** from hydroxy dienes **5** and **6**. The *trans*-substituted tetrahydrofuran products of entries 1, 2, 5, and 6 (Table 1) are consistent with cyclization of a chair-like conformer **20** in which the alkene is pseudoequatorially positioned (Scheme 2).[3b-d] The lower degree of *trans*-cross-ring stereoselectivity observed for (*E*)-alkene substrates is consistent with this model, since smaller R_Z substituents would lead to less disfavoring of the conformation **19** which would lead to *cis*-tetrahydrofuran product (not shown).

Our tandem polycyclization results provide unique insights into the stereochemical potential of the chromium-mediated oxidative cyclization reaction for forming *trans*-tetrahydrofuran rings. Furthermore, this demonstrates the possible biomimetic synthesis of chain polycyclic ethers according to the Townsend–Basak biosynthetic hypothesis. We are currently exploring other metal oxo reagents and catalysts for the *syn*-oxidative polycyclization reaction.

Scheme 2. Conformational Model for *syn*-Oxidative Cyclization



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Supplementary Material Available: Tabulated spectral data for compounds **10–16** and **18** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Compound **9** was prepared in six steps from nerylacetone: (1) AD-mix β (contains $K_2OsO_2(OH)_4$, dihydroquinidine 1,4-phthalazinediyl diether, K_2CO_3, and $K_3Fe(CN)_6$), $CH_3SO_2NH_2$, aqueous *t*-BuOH, (30%); (2) $CH_2{=}PPh_3$, THF (54%); (3) $NaIO_4$, Et_2O/H_2O (81%); (4) *i*-PrMgCl, Et_2O, 0 °C (73%); (5) PCC, CH_2Cl_2 (93%); (6) CH_3MgBr, Et_2O, 0 °C (84%).