Acylperrhenate-Induced Tandem *syn*-Oxidative Cyclizations of Hydroxydienes

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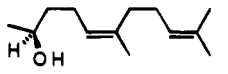
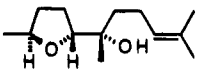
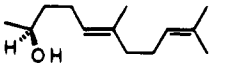
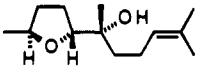
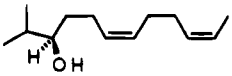
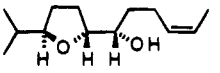
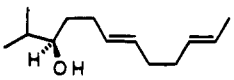
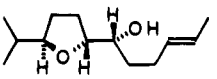
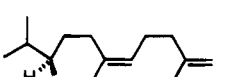
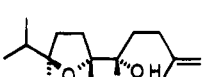
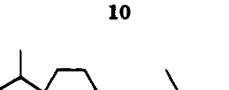
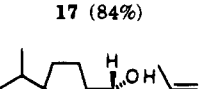
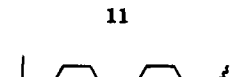
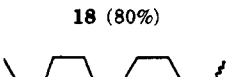
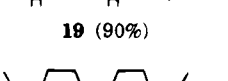
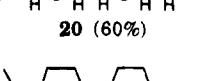
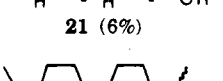
Tandem *syn*-oxidative polycyclizations of acyclic hydroxypolyenes represent efficient and possibly biomimetic[1] strategies for the chemical synthesis of polyether natural products. Hydroxyl-directed *syn*-oxidative cyclizations of bishomoallylic alcohols provide access to *trans*-tetrahydrofurans, whereas hydroxyl-directed epoxidation strategies generally produce *cis*-tetrahydrofurans[2] upon acid-catalyzed *anti*-cyclization.[3] Although chromium(VI)-induced *syn*-oxidative cyclizations are limited to tertiary alcohols,[4] Kennedy has developed a dirhenium heptoxide-mediated *syn*-oxidative cyclization method which produces predominantly *trans*-tetrahydrofuranyl alcohols and is compatible with primary and secondary hydroxyalkenes.[5] More recently, Sinha *et al.* have reported that mixtures of Re_2O_7 and periodic acid promote tandem *syn*-oxidative bicyclization of a *vic*-disubstituted diene to give synthetically useful yields of a *trans,trans*-bis-tetrahydrofuran product.[6] However, we found that application of these published rhenium oxide methodologies[5,6] to trisubstituted diene substrates **6** and **10** (*vide infra*) gave complex reaction mixtures including oxidative cyclization and acid-catalyzed (nonoxidative) cyclohydration byproducts, even in the presence of an amine base.

A plausible mechanism for hydroxyl-directed *syn*-oxidative cyclization (Scheme 1) requires formation of perrhenate ester **3** from the alcohol and Re_2O_7 (**1**),[7] which also generates 1 equiv of perrhenic acid (pK_a −1.25)[8] presumably responsible for nonoxidative cyclohydration of trisubstituted alkene substrates via tertiary carbenium ion intermediates. We hypothesized that a more general reagent for *syn*-oxidative cyclization might require changing the leaving group from perrhenate (O_3ReO^-) to a less acidic organic carboxylate (RCO_2^-), as in the acylperrhenates **2**.

Reaction of acyclic hydroxydienes **6**–**12**[9] with (trifluoroacetyl)perrhenate (**2**, R = CF_3)[10] gave good yields (65–90%) of monocyclic *trans*-tetrahydrofurfuryl alcohols **13**–**19** with excellent stereoselectivity (Table 1, procedure A). In the presence of amine base (both pyridine and 2,6-lutidine are satisfactory) monocyclization proceeds cleanly and without formation of acid-catalyzed cyclohydration products, even with the acid-sensitive substrates **6**, **7**, and **10**–**12**. The absence of bicyclic products is presumably due to a coordinative interaction between the Lewis acidic rhenium atom of the perrhenate ester and the tetrahydrofuran oxygen of monocyclic products **13**–**19**. Although we reasoned that the trifluoroacetic acid byproduct produced in perrhenate ester formation might break up this interaction, we observed that omission of base resulted in complex reaction mixtures, possibly due to trace amounts of perrhenic acid still present. We then found that additional trifluoroacetic anhydride apparently traps perrhenic acid (regenerating trifluoroacetylperrhenate) and the trifluoroacetic acid byproduct promotes formation of bicyclic *trans,trans*-tetrahydrofurfuryl

Table 1. Acylperrhenate-Induced Hydroxyl-Directed *syn*-Oxidative Cyclizations

hydroxyalkene	procedure[a]	product (yield, isomer ratio)
 **6**	A	 **13** (66%, 6 : 1)
 **7**	A	 **14** (66%, 9 : 1)
 **8**	A	 **15** (80%, 9 : 1)
 **9**	A	 **16** (65%)
 **10**	A	 **17** (84%)
 **11**	A	 **18** (80%)
 **12**	A	 **19** (90%)
15	B	 **20** (60%)
18	B	 **21** (6%)
19	B	 **22** (51%)

[a] Key: (A) $(CF_3CO_2)ReO_3$, 2,6-lutidine, CH_2Cl_2, 20 °C; (B) $(Cl_2CHCO_2)ReO_3$, $(Cl_2CHCO)_2O$, CH_2Cl_2, 20 °C.

(1) (a) Townsend, C. A. *Tetrahedron* **1991**, *47*, 2591. (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 298.

(2) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. I* **1994**, 1975.

(3) For an alternative biosynthesis hypothesis featuring tandem polyepoxide cyclizations, see: (a) Westley, J. W.; Blount, J. F.; Evans, R. H.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 597. (b) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594. (c) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1. For synthetic applications of tandem hydroxyl-directed epoxidations coupled with *anti*-selective cyclizations, see: (d) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299.

(4) McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921.

(5) (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.

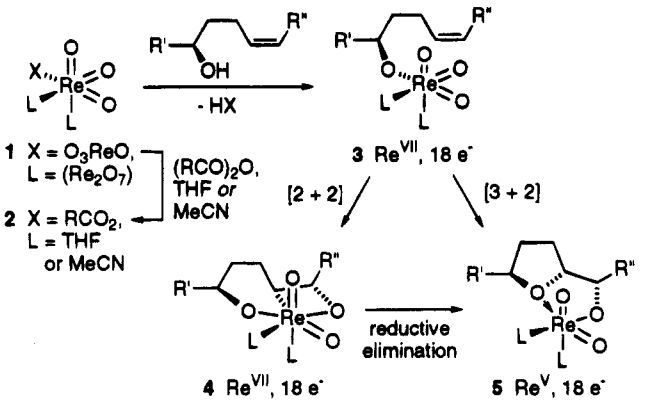
(6) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447.

(7) Krebs, B.; Müller, A.; Beyer, H. *J. Chem. Soc., Chem. Commun.* **1968**, 263.

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

0022-3263/95/1960-5750$09.00/0

Scheme 1. Mechanism of Re^{VII}-Induced *syn*-Oxidative Cyclizations



alcohol product **20** from tetrahydrofuran-containing hydroxyalkene **15** in 22% yield.

The optimal reagent combination for bicyclization was determined by correlating yields of bis-tetrahydrofuran alcohol products with carboxylic acid pK_a. We have found that (dichloroacetyl)perrhenate (**2**, R = Cl_2CH)[11] combined with excess dichloroacetic anhydride is a more effective reagent for cyclization of tetrahydrofuranyl hydroxyalkene **15** to the corresponding bistetrahydrofuran alcohol **20** (Table 1, procedure B).[12] Although these reaction conditions with the *vic*-disubstituted alkene **18** still give acid-catalyzed cyclohydration and alkene isomerization byproducts in addition to a low yield of the bicyclic alcohol **21**,[13] the more electron-rich trisubstituted alkene **19** gives satisfactory conversion to **22**. Note that the overall conversion of **12** to **22** represents a more relevant model for biomimetic polyether synthesis than does a less substituted substrate (i.e., **10** or **11**).

Although both [2 + 2] and [3 + 2] mechanisms have been proposed for *syn*-oxidative cyclizations,[5b,d] we currently favor a [3 + 2] cyclization of perrhenate **3** with the pendant alkene to give the tetrahydrofuranyl alcohol product complexed with rhenium(V) (**5**, Scheme 1). The consistently high degree of *trans*-stereoinduction is also compatible with a [3 + 2] mechanism, suggesting that the stereoinducing center must be relatively near the stereocenter being formed. Examination of space-filling models indicates that the [3 + 2] adduct leading to *cis*-tetrahydrofuran products suffers severe steric congestion relative to the isomeric [3 + 2] adduct providing *trans*-tetrahydrofurans. In contrast, models of the rhenia-oxetanes **4** do not exhibit much discrimination between the isomers leading to *cis*- or *trans*-products.

In summary, acylperrhenate reagents provide a more general solution to the problem of tandem *syn*-oxidative cyclizations of acid-sensitive hydroxydiene models for biomimetic synthesis routes to chain polyethers. We are currently exploring applications of acylperrhenate-induced cyclizations to the chemical synthesis of polycyclic ether natural products.

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Supporting Information Available: Representative experimental procedures and tabulated spectral data for compounds **6**–**22** (7 pages).

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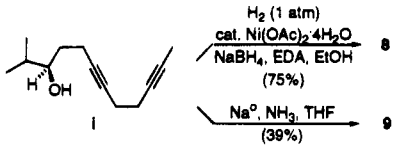
(9) Compounds **6** and **7** were prepared by sodium borohydride reduction of nerylacetone and geranylacetone, respectively (Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461). Compounds **8** and **9** were both prepared from the diynyl alcohol **i**, which was obtained from deca-4,8-diyn-1-ol (Bao, J.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616) in two steps: (1) PCC, CH_2Cl_2; (2) *i*-PrMgBr, Et_2O. *Cis,cis*-Dienyl alcohol **8** was synthesized by nickel-catalyzed partial hydrogenation of **i** (Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226), whereas the *trans, trans*-isomer **9** was prepared by sodium/ammonia reduction (Henrich, C. A. *Tetrahedron* **1977**, *33*, 1845). Compound **10** was prepared in four steps from nerylacetone: (1) AD-mix β, $CH_3SO_2NH_2$, 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%). The identical sequence of reactions from geranylacetone afforded the *E*-isomer **11**. Compound **12** was obtained as a 1/1 mixture of alkene isomers by a similar series of reactions in which the Wittig reaction (step 2) was conducted with CH_3CH=PPh_3.



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

(11) Prepared by metathesis of Re_2O_7 with dichloroacetic anhydride.

(12) Reaction of **15** with Re_2O_7/H_5IO_6 (refs 5c, 6) gave a 32% yield of bis-tetrahydrofuranyl alcohol **20**. However, reaction of **15** with $(CF_3CO_2)ReO_3/H_5IO_6$ gave a low-yielding mixture of **20** and the monotetrahydrofuranyl ketone resulting from simple alcohol oxidation.

(13) Reaction of **18** with Re_2O_7/H_5IO_6 resulted in rapid formation of the acid-catalyzed (non-oxidative) cyclohydration product **ii** (61% yield); the desired product **21** was not observed by ^1H NMR or GC analysis of the crude product mixture.