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Syn-Oxidative Cyclizations of Trishomoallylic Alcohols: Stereoselective and Stereospecific Synthesis of *trans*-Tetrahydropyranyl Alcohols

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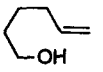
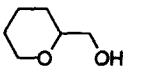
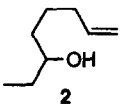
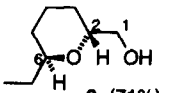
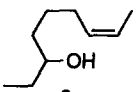
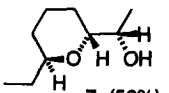
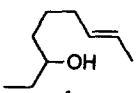
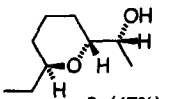
Abstract: Trifluoroacetylperrhenate promotes the hydroxyl-directed *syn*-oxidative cyclization of trishomoallylic alcohols. The cyclization reaction is highly stereospecific and stereoselective, providing a novel and efficient synthesis of *trans*-2,6-disubstituted tetrahydropyranyl alcohols.

Our laboratory has been engaged in studying stereospecific *syn*-oxidative cyclization reactions of hydroxyalkenes and -polyenes to cyclic ether products. Most synthetic approaches to tetrahydropyrans via hydroxyalkene cyclizations afford mixtures of isomeric products or favor the *cis*-2,6-disubstituted tetrahydropyran stereoisomer.[1] Several high-valent metal oxos (Cr, Mn, Re, Ru) are known to mediate hydroxyl-directed *syn*-oxidative cyclizations, but all reaction products reported from these reactions are limited to the formation of five-membered rings.[2] Kennedy's original report[3] on the discovery of Re_2O_7 / lutidine-promoted oxidative cyclizations to prepare *trans*-2,5-disubstituted tetrahydrofuranyl alcohols specifically indicated that the reaction was limited to bishomoallylic alcohol substrates, as trishomoallylic alcohols failed to undergo the title reaction. This reagent combination also fails to induce tandem bicyclizations of 1-hydroxy-4,8-dienes, as the reactivity of rhenium (VII) oxides for polycyclization processes is apparently diminished in the presence of amine bases. However, the combination of Re_2O_7 and periodic acid permits *syn*-oxidative bicyclization of 1-hydroxy-4,8-diene substrates.[4] We have previously reported that acylperrhenate reagents also show enhanced reactivity for the synthesis of polytetrahydrofurans and are superior reagents for *syn*-oxidative polycyclizations of acid-sensitive alkenes.[5] Herein we show that six-membered ring tetrahydropyranyl alcohols can be obtained by acylperrhenate-induced *syn*-oxidative cyclizations of trishomoallylic alcohols. Furthermore, these reactions proceed with a remarkably high degree of stereoinduction with chiral secondary alcohols.

Initial cyclization experiments on 5-hexen-1-ol (**1**) with dichloroacetylperrhenate or trifluoroacetylperrhenate in the presence of an equimolar amount of the corresponding carboxylic acid anhydride[5] demonstrated that a six-membered ring product **5** could be formed. Although competitive acylation of the alkenol substrate resulted in less than quantitative conversion, a good yield of cyclic product was obtained when

only 1.1 equiv of anhydride was employed (table 1). Workup with sodium methoxide converted the rhenium byproducts into water-soluble form and simultaneously provided deacylated product **5**. The racemic secondary alkenol **2**[6] gave an excellent yield of compound **6**[7] *as a single diastereomer*. Similar findings were observed with the *Z* and *E*-disubstituted alkene substrates **3** and **4**,[8] confirming the general stereospecificity of the *syn*-oxidative cyclization pathway for six-membered ring products as well as providing additional examples of the extremely high *trans*-stereoinduction for this cyclization reaction.

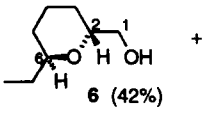
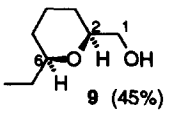
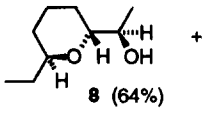
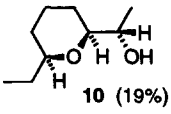
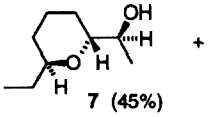
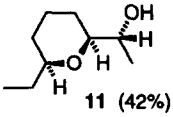
Table 1. Trifluoroacetylperrhenate-promoted *syn*-oxidative cyclizations[a]

alkenol substrate	tetrahydropyranyl alcohol product (isolated yield)
 **1**	 **5** (54%) (47%)[b]
 **2**	 **6** (71%)
 **3**	 **7** (52%)
 **4**	 **8** (47%)

[a] $(CF_3CO_2)ReO_3$, $(CF_3CO)_2O$, CH_2Cl_2, 20°C; $NaOCH_3$, CH_3OH.
[b] This yield was obtained with $(Cl_2CHCO_2)ReO_3$ / $(Cl_2CHCO)_2O$.

In contrast, *m*-CPBA epoxidation of **2** and acid-catalyzed intramolecular *anti*-addition / cyclization of the hydroxyepoxide intermediate provided an approximately equal mixture of the *trans*- and *cis*-diastereomeric tetrahydropyranyl alcohols **6** and **9** (table 2).[7] These epoxidation experiments provided a sample of the *cis*-tetrahydropyran **9**, which was demonstrated to be absent (< 1%) in the crude product extract from the acylperrhenate-induced *syn*-oxidative cyclization reaction of **2**. The *trans*-tetrahydropyran structure of **6** was consistent with the presence of nuclear Overhauser enhancement (nOe) between H-6 and H-1 as well as the absence of nOe's between H-6 and H-2; the *cis*-tetrahydropyran **9** exhibited nOe's between H-6 and H-2 but not between H-6 and H-1. The stereochemistry of product **7** was assigned as described above not only by nOe studies on this products but also by comparison to the *cis*-diastereomer **11**,[7] produced in the non-stereoselective but unambiguously stereospecific epoxidation and acid-catalyzed *anti*-addition / cyclization of the *E*-hydroxyalkene substrate **4** (table 2). Similar stereocomplementarity studies verified the stereochemical assignment of tetrahydropyranyl alcohol product **8**.[7]

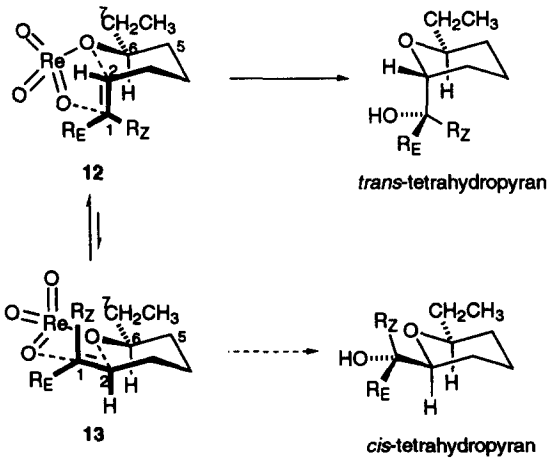
Table 2. Epoxidations / *anti*-cyclizations of alkenols **2** - **4**[c]

alkenol substrate	tetrahydropyranyl alcohol products (isolated yield)	
2	 **6** (42%)	 **9** (45%)
3	 **8** (64%)	 **10** (19%)
4	 **7** (45%)	 **11** (42%)

[c] *m*-CPBA, CH_2Cl_2, 20°C; cat. *p*-TsOH, CH_2Cl_2

In each case only the *trans*-tetrahydropyran diastereomers are formed via perrhenate-promoted *syn*-oxidative cyclization. We propose that the stereochemistry of the observed *trans*-tetrahydropyran products arises from alkene conformation in the transition state for cyclization, as shown in Scheme 1. In a [3 + 2] cycloaddition mechanism for *syn*-oxidative cyclization, three atoms of the hydroxyl-linked rhenium trioxo moiety (O—Re=O) must become aligned with the π-bond of the alkene moiety. Conformation **12** exhibits only one gauche interaction of Re with C7, whereas the conformation **13** required for *cis*-tetrahydrofuran products exhibits gauche interactions of Re with C5 as well as C7.

Scheme 1. Conformational models for *syn*-oxidative cyclization



The higher reactivity of the acylperrhenate reagents permits, for the first time, the general and stereoselective preparation of *trans*-tetrahydropyranyl alcohols via hydroxyl-directed *syn*-oxidative cyclization, greatly extending the scope and synthetic value of this chemical transformation. The excellent stereoinduction observed in this reaction efficiently increases structural complexity in a single step, and is complementary to other cyclization methods which generally afford predominantly *cis*-tetrahydropyran isomers. Further extensions of this strategy to the preparation of larger ether rings and applications to complex molecule synthesis are in progress.

Acknowledgment. This research was funded by the National Institutes of Health (GM53764). F. E. M. also acknowledges support from Lilly Research Laboratories, the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.

References and Notes

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5. (a) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750. (b) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022.
6. Prepared from 5-hexen-1-ol: (a) $(ClCO)_2$, DMSO, CH_2Cl_2; Et_3N (70%); (b) EtMgBr, THF (90%).
7. **6**: IR (free film from CH_2Cl_2) 3407, 2935, 2872, 1461, 1360, 1204, 1104, 1035, 966, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 - 3.75 (1H, m), 3.71 - 3.65 (1H, m), 3.49 - 3.44 (2H, dd, J = 3.6, 2.4 Hz), 2.00 - 1.85 (1H, s), 1.77 - 1.56 (5H, m), 1.47 - 1.19 (3H, m), 0.97 - 0.85 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.2, 70.7, 64.2, 29.1, 26.4, 25.3, 18.4, 10.3; MS (70eV, LREI) 145, 127, 113, 95, 79, 69, 57, 41; HRMS calcd for $C_8H_{15}O$ (M^+ - OH) 127.1122: found 127.1133. **7**: IR (free film from CH_2Cl_2) 3405, 2961, 2934, 2870, 1460, 1375, 1264, 1205, 1123, 1073, 1054, 1041, 998, 889 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 - 3.75 (1H, q, J = 6.4 Hz), 3.74 - 3.68 (1H, m), 3.42 - 3.38 (1H, m), 1.82-1.24 (9H, m), 1.19 - 1.10 (3H, d, J = 5.5 Hz), 0.95-0.83 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.4, 73.0, 68.9, 28.6, 24.7, 24.0, 18.1, 10.4. Anal. Calcd for $C_9H_{18}O_2$: C, 68.30; H, 11.47. Found: C, 68.47; H, 11.70. **8**: IR (free film from CH_2Cl_2) 3449, 2960, 2934, 2870, 2855, 1461, 1377, 1258, 1205, 1123, 1040, 998, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 - 3.63 (2H, m), 3.34 - 3.26 (1H, dt, J = 7.5, 4.1 Hz), 1.81 - 1.57 (5H, m), 1.42 - 1.19 (4H, m), 1.17 - 1.09 (3H, d, J = 5.3 Hz), 0.95 - 0.82 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.4, 73.7, 68.2, 29.8, 29.0, 26.4, 25.2, 18.4, 10.5. **9**: IR (free film from CH_2Cl_2) 3520, 2954, 2923, 2853, 1458, 1375, 1227, 1178, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 - 3.42 (3H, m), 3.29 - 3.19 (1H, m), 1.88 - 1.82 (1H, m), 1.69 - 1.42 (5H, m), 1.28 - 1.14 (3H, m), 1.11 - 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.1, 77.9, 66.5, 31.1, 29.3, 27.3, 23.1, 10.1. **10**: ^1H NMR (300 MHz, $CDCl_3$) δ 3.61 - 3.52 (1H, q, J = 6.0 Hz), 3.25 - 3.15 (1H, m), 3.10 - 3.01 (1H, dt, J = 7.5, 2.3 Hz), 1.89 - 1.81 (1H, d, J = 11.2 Hz), 1.64 - 1.38 (5H, m), 1.37 - 1.17 (3H, m), 1.17 - 1.13 (3H, d, J = 5.5 Hz), 0.91 - 0.83 (3H, t, J = 7.5 Hz). **11**: IR (free film from CH_2Cl_2) 3424, 2960, 2934, 2875, 2855, 1458, 1366, 1260, 1204, 1126, 1094, 1045, 1002, 907, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 - 3.77 (1H, q, J = 5.2 Hz), 3.29 - 3.23 (2H, m), 1.91 - 1.83 (1H, d, J = 9.1 Hz), 1.60 - 1.24 (8H, m), 1.17 - 1.13 (3H, d, J = 5.5 Hz), 0.94 - 0.89 (3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.7, 79.3, 69.7, 31.2, 29.4, 24.8, 23.2, 17.7, 10.0. Anal. Calcd for $C_9H_{18}O_2$: C, 68.30; H, 11.47. Found: C, 67.72; H, 11.54.
8. Compounds **3** and **4** were prepared from 5-hexyn-1-ol: (a) cat. PPTS, dihydropyran, CH_2Cl_2 (92%); (b) *n*-BuLi, THF, then CH_3I; (c) cat. *p*-TsOH, CH_3OH (61%, two steps); (d) $(ClCO)_2$, DMSO, CH_2Cl_2; Et_3N (62%); (e) EtMgBr, THF (88%); for **3**: (f) cat. $Ni(OAc)_2$, $NaBH_4$, $NH_2CH_2CH_2NH_2$, EtOH (89%); for **4**: (f) $LiAlH_4$, diglyme, 160°C (45%).

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