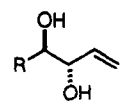
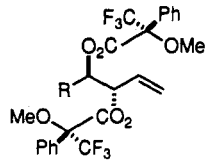
(*R*)-Mosher diester 11.[17] The diols 13 and 14 were also



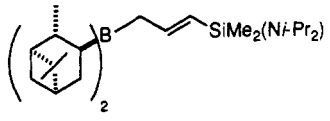
10

a R = 2-thienyl
b R = Ph
c R = *n*-$C_6H_{13}$
d R = cyclohexyl



11

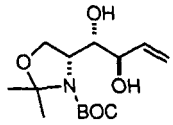
a R = 2-thienyl
b R = Ph



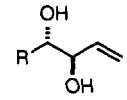
12

prepared from the reaction of the aldehydes with reagent **12**.[12] Again, the diastereoselectivity of the reaction was determined from the $^1$H NMR spectra and the enantioselectivity from an examination of the derived Mosher diester **15**. All these results are also included in Table I. It is interesting to note that although the reaction of the aldehyde **6** with reagent **5** gave only a single diol **8**, reaction with the antipodal reagent **12** gave both anti diols **8** and **13** (entry 2).[18] Clearly in this second case, the reagent and substrate (Felkin–Ahn control) stereochemical biases are mismatched. The entries 3–8 show that simple aldehydes are converted into the corresponding anti diols **10a–d** and **14a,b**, all with excellent relative stereochemical control.[19]

Additionally, formation of the Mosher diesters **11a,b** and **15a,b** clearly showed that, at least for entries 3–6, the enantioselectivity of reaction[20] was also impressive.

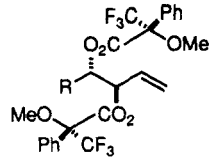


13



14

a R = 2-thienyl
b R = Ph



15

a R = 2-thienyl
b R = Ph

This study further demonstrates the utility of pinene-derived compounds in asymmetric synthesis. The direct conversion of aldehydes into anti diols via an experimentally simple one-pot process should be of very considerable use in synthesis. It is germane to compare the reactivity of the allylboranes **5** and **12** with the analogous tartrate reagents described by Roush.[13] Although the overall yields of diols from the allylsilane precusors were comparable with both methods, reagents **5** and **12** showed superior enantioselectivities in their reactions with aldehydes.

**Acknowledgment.** We thank the National Institutes of Health for support of this program (AI-20644) and G.D. Searle & Company for unrestricted support and microanalyses.

(17) For the preparation of Mosher esters, see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(18) The relative stereochemistry of diol **13** was determined from comparison of the chemical shift and *J* values for the C*H*(OH)CH=$CH_2$ proton in the $^1$H NMR spectrum with the corresponding data for diol **8**. Corresponding syn diols show larger C*H*(OH)C*H*(OH) coupling constants, see ref 11 and references therein.

(19) The relative stereochemical assignments for the anti diols **10a**, **14a**, **10b**, and **14b** was determined by comparisons of $^1$H NMR data observed with that reported for the corresponding racemic diols. See: Dana, G.; Chuche, J.; Monot, M.-R. *Bull. Soc. Chim. Fr.* **1967**, 3308. The assignments of relative stereochemistries for the diols **10c** and **10d** followed from the comparisons of the C*H*(OH)CH=$CH_2$ protons in the $^1$H NMR spectra with the corresponding resonances for diols **10a** and **10b**.

(20) The absolute stereochemistry of reaction was rigorously established only for the diol **8**. All other absolute stereochemical assignments are based upon comparisons of the $^1$H NMR spectra of the derived Mosher esters **11a** and **15a** and **11b** with **15b** (see ref 15). The absolute stereochemistries of **10c** and **10d** are based upon analogy with the other examples in Table I and on the basis of the known absolute stereochemical bias of (+)-$\alpha$-pinene-derived reagents (see ref 1).

## Cyclization of Alkoxymethyl Radicals

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*Received June 4, 1991*

*Summary:* Alkoxymethyl radicals, generated conveniently from phenylseleno precursors, cyclize to afford substituted tetrahydrofurans and tetrahydropyrans in excellent yield and with good stereoselectivity.

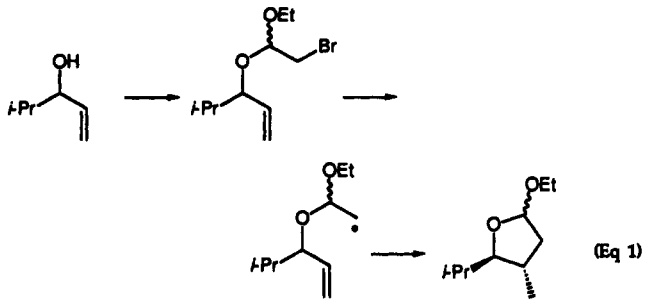
Cyclization of hexenyl radicals to cyclopentylmethyl radicals represents one of the most useful and thoroughly studied reactions in radical chemistry.[1] The analogous cyclization where carbon 3 in the hexenyl chain is replaced by an oxygen (or a nitrogen) is of considerable importance for the synthesis of heterocycles. In this process, illustrated by Stork's classic example (eq 1),[2] an allylic alcohol is extended by a two-carbon unit capable of forming a radical at the terminus. The resulting 2-alkoxyethyl radical undergoes a smooth cyclization to afford 2-alkoxytetrahydrofurans. This process has been studied extensively and nicely incorporated in the synthesis of complex substances.[1,3]

(1) For leading general references, see: (a) Beckwith, A. L. J.; Ingold, K. U. In *Free Radical Rearrangements*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 161–310. (b) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. (c) Giese, B. *Radicals in Organic Synthesis: Formation of C–C Bonds*; Pergamon Press: New York, 1986. (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (e) Curran, D. P. *Synthesis* **1988**, 417 and 489.

(2) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. For related studies, see: (a) Tada, M.; Okabe, M. *Chem. Lett.* **1980**, 201 and 831. (b) Okabe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 5382. (c) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.

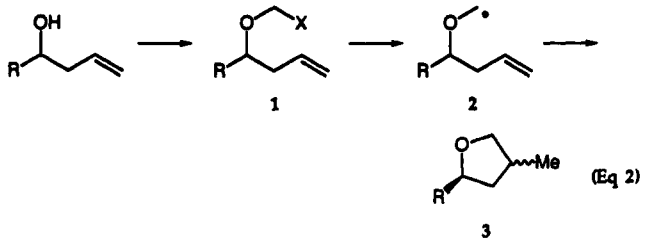
(3) The cyclization of the 2-alkoxyalkyl radical has been utilized extensively. Recent examples include the following: (a) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. (b) Hutchinson, J. H.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1987**, *28*, 1313. (c) Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

0022-3263/91/1956-5245$02.50/0 



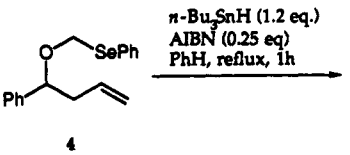

(Eq 1)

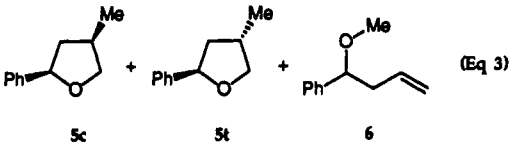
In connection with a project directed toward the synthesis of tetrahydrofuran- and tetrahydropyran-containing natural products, we required the cyclization of an alkoxymethyl radical derived from a homoallylic alcohol. We were surprised to find that in spite of the prevalence of such heterocycles, this fundamental ring construction remains unexplored (eq 2).[4-7] We describe here the results of our preliminary studies, which offer insight on the reactivity of alkoxy-substituted radicals and demonstrate the scope of this cyclization.




(Eq 2)

The required cyclization precursor was prepared in two steps from the corresponding alcohol by first conversion to the (tri-*n*-butylstannyl)methyl ether followed by a Sn–Li exchange[8] and quenching with $(PhSe)_2$.[9] Unlike $\alpha$-halo ethers, the $\alpha$-phenylseleno ethers were found to be relatively stable, easily surviving chromatography. Under standard radical cyclization conditions (0.015 M in substrate and 0.017 M in $n$-$Bu_3SnH$), substrate 4 gave an excellent yield of the desired tetrahydrofuran product in >90% isolated yield, as a 2.6:1 mixture of cis and trans isomers **5c** and **5t** (eq 3), with essentially none of the uncyclized reduction product 6 (by NMR).[10] The observed preponderance of the cis isomer over the trans isomer resembles that obtained for 3-substituted hexenyl radicals and can be rationalized by invoking a chair-like transition state for the ring closure.[11]




(Eq 3)

The high efficiency of the cyclization reaction is particularly noteworthy in light of the slow cyclization rate predicted for such radicals.[5] Cyclization of alkoxymethyl radicals are expected to have higher activation energy than simple alkyl radicals because of conjugation of the unpaired electron with the adjacent oxygen's lone pairs, an interaction that imparts partial double bond character to the C–O $\sigma$-bond, resulting in restricted rotational freedom. The total absence of reduced starting material under the standard conditions (i.e., without syringe pump conditions, cf. ref 6) suggests that the cyclization is quite fast compared to reduction. This supposition was confirmed when we carried out the cyclization under higher tin hydride concentration (Table I). Indeed, although the amount of reduction product increased as the tin hydride concentration was increased, even at 1.16 M tin hydride concentration, the major product was still the cyclized material.[12]

We also examined the effect of temperature on the stereoselectivity of the cyclization. We found that the cis to trans ratio increased steadily as the reaction temperature was decreased.[13] To our surprise, even at −70 °C (bath), the cyclization reaction was extremely fast. It is noteworthy that at this temperature the cyclization was highly cis selective (11/1), making this a synthetically useful radical cyclization reaction. The cyclized product was easily separated by flash chromatography from the uncyclized reduced material. Structurally this ring closure resembles the anionic cyclization recently reported by Broka.[14] Our results suggest that the high cis selectivity (~11/1) observed by Broka may be due, at least to a considerable extent, to temperature effects rather than to inherent differences between anionic cyclizations and the radical cyclizations.

In order to ascertain the scope of this ring construction, we examined the cyclization of several different alkoxymethyl radicals (Table II). The mono(selenoacetal) precursors were prepared as described above. As the examples illustrate, the cyclization is quite general and can be used to synthesize tetrahydrofurans and tetrahydropyrans. The tetrahydrofuran-forming reactions are extremely efficient

(4) When we began our studies we found no reports of cyclization of alkoxy-substituted methyl radicals. The process that came closest was Beckwith's cyclization of acyloxymethyl radicals to lactones: Beckwith, A. L. J.; Pigou, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 85.

(5) For discussion of the rates of ring closure of oxygen-containing analogues of hex-5-enyl cyclization, see: Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157.

(6) During the course of our work two independent reports described the cyclization of alkoxymethyl radicals. In each case, however, the radical center was further stabilized by the presence of an ester group: (a) Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335. (b) Lolkema, L. D. M.; Himenstra, H.; Al Ghouch, A. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 1491.

(7) For isolated examples of generation and cyclization of $\alpha$-oxygen-substituted alkyl radicals, see: (a) Yadav, V. K.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 897. (b) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064 and references cited therein. (c) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt, T.; Hug, P.; Winkler, T. *Synlett* **1990**, 687. (d) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263. (e) Keck, G. E.; Tafesh, A. M. *Synlett* **1990**, 257.

(8) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

(9) Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Perkin Trans. II.* In press.

(10) All compounds are >95% homogeneous by TLC and NMR and their structure assignments are consistent with spectroscopic data (250-, 300-, or 500-MHz $^1H$ NMR, IR, HRMS). The stereochemical assignments are based on NOE difference experiments.

(11) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925 and references cited therein. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (c) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

(12) Under comparable concentrations cyclization of the parent hex-5-enyl radical generates more of the reduction product. See: Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 5361.

(13) Low temperature reactions were catalyzed with $Et_3B$ and air. (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547 and references cited therein. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6125 and 6127.

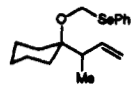
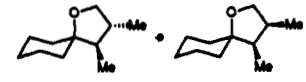
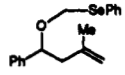
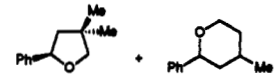
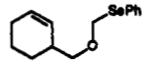
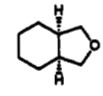
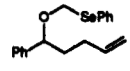
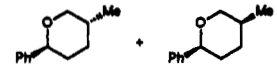
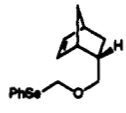
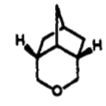
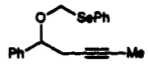
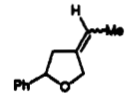
(14) (a) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. (b) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981.

**Table I. Effect of $n$-$Bu_3SnH$ Concentration and Temperature on Product Distribution (4 → 5 + 6)**

| [RSe]/[$Bu_3SnH$], M | temp (°C) | initiator[a]/solvent | cycliztn:reductn | 5c:5t[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 0.015/0.017 | 80 | A/benzene | >100:1 | 2.6:1 | 95 |
| 0.031/0.035 | 80 | A/benzene | 40:1 | 3.1:1 | 90 |
| 0.1/0.116 | 80 | A/benzene | 8:1 | 2.8:1 | 92 |
| 1.0/1.16 | 80 | A/benzene | 4:1 | 2.6:1 | 92 |
| 0.015/0.017 | 25 | B/benzene | 16:1 | 4.6:1 | 96 |
| 0.015/0.017 | -20 | B/toluene | 15:1 | 6:1 | 95 |
| 0.015/0.017 | -70 | B/toluene | 10:1 (88%:9%)[d] | 11:1 | 98 |

[a] Conditions: A = AIBN (0.25 equiv), reflux. B = $Et_3B$ (0.4 equiv), bath temperature indicated (see ref 13). [b] Ratios determined by capilary GC, which also indicated the presence of minor side products (1–4%) of as yet undetermined structure. In all cases clean, cyclized material was easily obtained by flash chromatography. [c] Combined yield of products isolated by a quick silica gel filtration. [d] Isolated yields.

**Table II. Cyclization of Various Alkoxymethyl Radical Intermediates**

| entry | substrate | conditions[a] | cyclization products | isomer ratio[b] | cyclization: reduction[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 4 | A | 5c + 5t | 2.6:1 (to 11:1)[d] | >100:1 | 90 |
| 2 |  | A |  | 4.3:1 (77%:18%) | >100:1 | 95 |
| 3 |  | A<br>B |  | 3.2:1<br>2.4:1 | 11:1<br>22:1 | >98<br>97 |
| 4 |  | A |  | | >100:1 | 80 |
| 5 |  | A<br>B |  | 8.2:1<br>14:1 | 3.5:1<br>60:1 | >98<br>>98 |
| 6 |  | B |  | | 12.4:1 | 73 |
| 7 |  | A |  | 1.5:1 | 39:1 | 83 |

[a] Conditions: A = RSePh [0.015 M], $n$-$Bu_3SnH$ (1.25 equiv, 0.017 M), AIBN (0.25 equiv), PhH, reflux, 1–3 h. B = $n$-$Bu_3SnH$ and AIBN solution added by syringe pump over ~4 h. [b] Ratios determined by capillary GC. Yield of chromatographically separated isomers shown in parentheses. [c] Combined yield of products isolated by quick silica gel filtration. [d] See Table I.

and give essentially none of the reduction products (entries 1, 2, 4, and 7).[15] The cyclization of the 5-methyl-substituted chain gave, as expected, a mixture of the 5-membered and the 6-membered ring compounds (entry 3). In contrast to the all carbon system, however, the exo-cyclization product predominated.[11a] Entry 2 demonstrates that 4-methyl-substituted 2-oxahex-5-enyl radicals cyclize with good stereoselectivity, comparable to that obtained for the all carbon system.[11a] As was illustrated for the example in entry 1 (vide supra, Table I), it should be possible to enhance the stereoselectivity of entry 2 and the regioselectivity of entry 3 by conducting the reaction at low temperature. The cyclization of 2-oxahept-6-enyl units (entry 5) under the standard conditions was accompanied by appreciable amounts of the reduced starting material, a problem easily overcome by adding the tin hydride with a syringe pump. The high trans selectivity presumably results from the cyclization taking place via a chair conformation, in which the phenyl group and the alkene are in an equatorial orientation.[11] Entries 4 and 6 demonstrate the use of the alkoxymethyl radical cyclization for the synthesis of bicyclic systems. The lower yields for these examples appear to be due to loss during isolation of the volatile products.

The results summarized above demonstrate that the cyclization of alkoxymethyl radicals provides an expedient and potentially stereoselective route to substituted tetrahydrofurans and tetrahydropyrans.

**Acknowledgment.** This work was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society. V.H.R. thanks the American Cancer Society for a Junior Faculty Research Award. We thank Dr. Dirk Friedrich and Professor Leo A. Paquette for providing us details of their mono(selenoacetal) preparation.

(15) For comparison, authentic samples of the uncyclized reduction products were prepared by methylation of the corresponding alcohols.