Scope of Alkoxymethyl Radical Cyclizations

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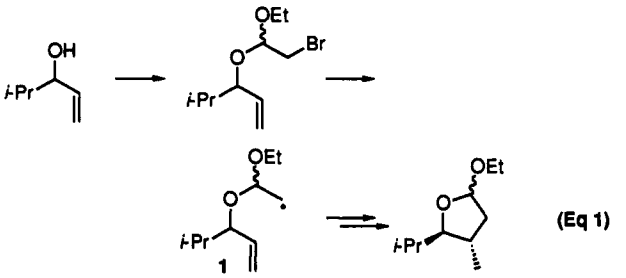
We have explored different aspects of the cyclization capability of alkoxymethyl radicals and report here a full account of our investigations. The required radicals were generated from (phenylseleno)-methyl ethers (e.g., **6**), which were prepared from homoallylic or bis-homoallylic alcohols by a two-step process. The alcohols were alkylated with (iodomethyl)tributylstannane. The stannanes were reacted with *n*-BuLi, and the resulting α-alkoxyanions were trapped with diphenyldiselenide to give the (phenylseleno)methyl ethers, which were stable to chromatography. When treated with tributyltin hydride, in the presence of a radical initiator, these precursors undergo a smooth cyclization to substituted tetrahydrofurans and tetrahydropyrans. Formation of the cyclization product was found to be the primary pathway even at relatively high tin hydride concentration. The diastereoselectivity of this cyclization was comparable to that observed in other radical cyclizations. The cis selectivity in cyclization of **6** increased gradually (up to 11:1) as the reaction temperature was lowered. The cyclization can be used for the synthesis of bicyclic and tricyclic compounds and can be incorporated in systems capable of tandem cyclizations.

Tetrahydrofuran and tetrahydropyran backbones are among the most common heterocyclic units found in natural products.[1] These frameworks can be seen in polyether and ionophore natural products and constitute the identifying skeleton of cyclic carbohydrates. General strategies for the synthesis of substituted tetrahydrofurans and tetrahydropyrans are still emerging.[2] We were interested in developing stereoselective routes to these skeletons, particularly to the tetrahydropyran unit found in the antifungal agent restricticin[3a] and in the pseudomonic acids.[3b] In this paper, we describe the details of a radical cyclization based construction of tetrahydrofurans and tetrahydropyrans.[4]

Background

The resurgence of interest in radical chemistry has included the development of approaches to various heterocycles.[5] For example, a widely used method for synthesizing tetrahydrofurans involves the cyclization of a hexenyl-type radical in which carbon 3 has been replaced by an oxygen atom.[6] This construction has proven valuable since the required precursor is assembled from simple components. A two-carbon unit capable of forming a radical at the terminus is coupled to an allylic alcohol. The 2-alkoxyethyl radical that is formed undergoes a smooth cyclization to a 2-alkoxytetrahydrofuran (eq 1).



(Eq 1)

Such cyclizations have been studied extensively and have been applied in the synthesis of several complex substances.[7]

In contrast to the extensive amount of work on these cyclizations, the related closure where the oxygen is in the 2-position (eq 2),which we refer to as an alkoxymethyl radical cyclization, had been relatively unexplored when we began our studies.[8-10] Beckwith had, however, reported

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(1) For general references to THF- and THP-containing natural products: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251, 551. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1.

(2) Review: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 411. (c) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330 and references cited therein.

(3) (a) Hensens, O. D.; Wichmann, C. F.; Liesch, J. M.; Vanmiddlesworth, F. L.; Wilson, K. E.; Schwartz, R. E. *Tetrahedron* **1991**, *47*, 3915. (b) For leading references on synthetic approaches to the pseudomonic acids, see: Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989; pp 425.

(4) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1991**, *56*, 5245.

(5) 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. (f) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.3.

(6) 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.; Abe, 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.

(7) 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.

(8) 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 (acyloxy)methyl radical to lactones: Beckwith, A. L. J.; Pigou, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 85. See also: Ahmad-Juhan, S. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 418 and references cited therein.

(9) During the course of this 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.

(10) A recent report described the use of alkoxymethyl radical cyclizations in complex substrates: Kim, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1991**, *113*, 9864.

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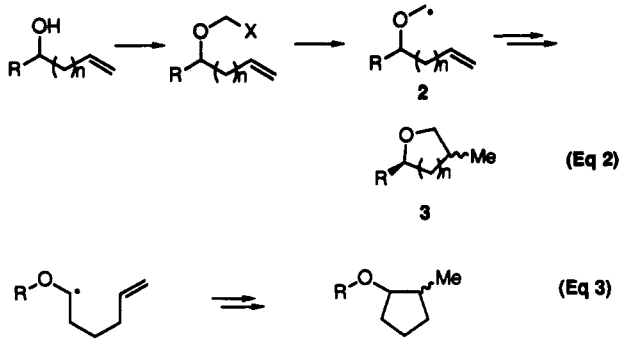
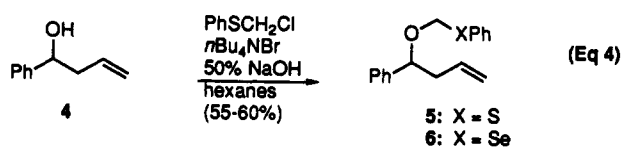


the kinetic parameters for this fundamental process (eq 2, $n = 1$).[11] The construction appeared quite promising since the required precursors were available by connecting a one-carbon radical synthon onto a homoallylic or a bis-homoallylic alcohol. It should be recognized that several synthetically useful cyclizations of radicals α to an oxygen had been investigated. However, the oxygen atom in these systems was external to the ring being formed rather than being part of it (eq 3).[12] We have explored different aspects of the alkoxymethyl radical cyclization and report here a full account of our investigations, including details on the preparation of the required cyclization precursors and the actual radical cyclizations.[4]

It should be noted that although the alkoxymethyl radical cyclization was not well known, the corresponding anionic process had been reported by Broka.[13] Our study afforded us the opportunity to compare the scope and selectivity in these two modes of cyclization.

Results and Discussion

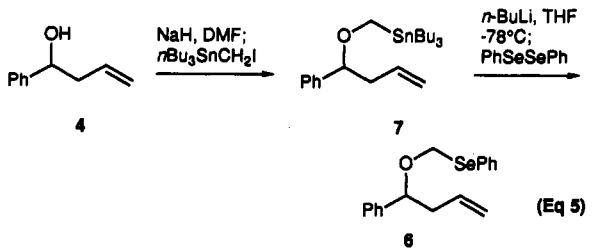
(a) Synthesis of Cyclization Precursors. We considered several precursors for the generation of the required alkoxymethyl radical. The initial cyclization studies were conducted on the phenylthio-substituted precursor, **5**, which proved surprisingly difficult to prepare. The required alcohol was prepared in quantitative yield from benzaldehyde and allyl bromide.[14] In concurrence with Beckwith's observations,[15] alkylation of the secondary alcohol with chloromethyl phenyl sulfide under standard conditions (NaH or KH, THF or DMF or DME) gave the desired monothioether in only 10–30% yield, along with large quantities of bis(phenylthio)methane. The desired transformation can, however, be accomplished in acceptable yields under phase-transfer conditions (eq 4).[16]



Unfortunately, even under these conditions, the alkylation proceeded in low yields with more hindered alcohols. We briefly explored the possibility of using the methoxymethyl (MOM) ether of the homoallylic alcohol as a precursor to the desired monothioacetals. However, under the conditions required to exchange the methoxy group with the phenylthio group (BF_3-Et_2O, CH_2Cl_2, PhSH),[17] the substrate underwent a cyclization to the 4-phenylthio-substituted tetrahydropyran.[18]

We prepared the corresponding monoseleno acetal, **6**, since it was expected to be a more reactive substrate for the radical formation.[15] The synthesis of this compound by a one-step process was, however, a nontrivial problem. Direct alkylation of alcohol **4** with $PhSeCH_2Cl$[15] gave acetal **6** in low yield (10–30%), along with a considerable amount of bis(phenylseleno)methane. Our efforts to optimize the alkylation reaction were to no avail. The main problem is that under basic conditions the chloride undergoes various side reactions,[15,19] which forced us to consider a two-step route to the monoseleno acetals.

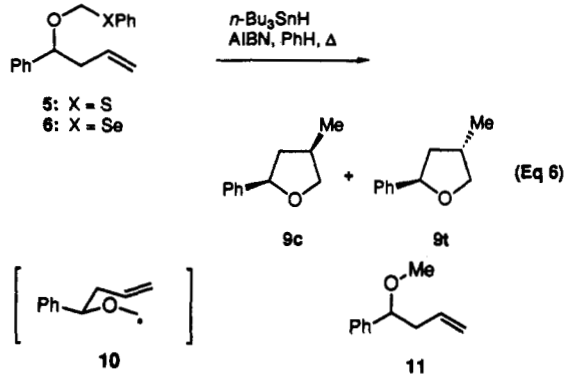
The most reliable route to the required monoseleno-acetals was through the corresponding (tri-*n*-butylstannyl)methyl ethers (eq 5).[20] Alkylation of the sodio-



anion of alcohol **4** in DMF with (iodomethyl)tributylstannane gave the expected ether **7** in moderate yield.[13,21] Following the procedure reported by Still,[21] the stannane was treated with a slight excess of *n*-BuLi to afford the α-alkoxymethyl lithio species. Upon quenching the reaction with PhSeSePh the desired selenoacetals were formed in good yield. This two-step process was quite reliable and was used to make all the other selenoacetals described here. In contrast to α-halo ethers, the α-thio and α-seleno ethers were found to be relatively stable and survived normal handling, including silica gel chromatography.

(b) Radical Cyclization of Phenylthio vs Phenylseleno Precursors. The initial cyclization studies were conducted on the monothioacetals. Treatment of substrate **5** with *n*-Bu_3SnH and AIBN (toluene, syringe pump) resulted in a slow formation of the desired tetrahydrofuran as the sole product in 63% yield as a 2.7:1 mixture of cis and trans diastereomers, along with recovered starting material (97% yield based on recovered starting material; eq 6). We were pleased to see that the reaction worked well, particularly with the absence of the uncyclized reduction product, **11**. Moreover, the high material balance indicated that the potentially problematic β-scission of the precyclization radical intermediate, to give

(11) (a) Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157. (b) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1988**, *53*, 1632.
(12) (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. (f) Lopez, J. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 3450.
(13) (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.
(14) Petrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910.
(15) Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77.
(16) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; 2nd ed.; Verlag Chemie: Weinheim, 1983.
(17) (a) Morton, H. E.; Guindon, Y. *J. Org. Chem.* **1985**, *50*, 5379. (b) Corey, E. J.; Hua, D. H.; Seitz, S. P. *Tetrahedron Lett.* **1984**, *25*, 3.
(18) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.
(19) In an effort to block the nucleophilic selenium, we examined the use of chloromethyl mesityl selenide. Unfortunately, the same results were obtained: the bis(mesitylseleno) methane was the major product.
(20) Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1621.
(21) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. Also see ref 13.



formaldehyde and a stable benzylic radical, had not occurred.[22] One problem with this reaction was that it proceeded slowly and did not go to completion, indicating that the phenylthio group was not the ideal precursor for this transformation. Much better results were obtained with the phenylseleno precursor, which Beckwith had shown was about 3 orders of magnitude more reactive than the phenylthio group toward attack by tributyltin radicals.

The phenylseleno precursors were found to be much more reactive under the cyclization conditions. When a benzene solution of selenoacetal **6** (0.015 M), *n*-Bu_3SnH (1.2 equiv), and AIBN (0.25 equiv) was heated to reflux, the starting material was consumed within 1 h and the desired tetrahydrofuran product was formed in 95% isolated yield, as a 2.6:1 mixture of **9c** and **9t** (eq 6). The stereochemistry assignment is based on NOE difference experiments on a sample of the cyclized product enriched in **9c**. The observed preponderance of the *cis* isomer over the *trans* isomer was rather modest, analogous to that obtained for simple 3-substituted hexenyl radicals, and can be rationalized by invoking a chairlike transition state (**10**) for the ring closure.[23] As with the phenylthio cyclization, we saw essentially none of the simple reduction product.

(c) Effect of Tin Hydride Concentration on Cyclization Yield. The high efficiency of the cyclization, particularly the absence of reduction product **11** (by NMR), is noteworthy in light of the kinetics data on such radicals. Beckwith found the cyclization of 2-oxahexenyl radical (*cf.* **10**) to be 1 order of magnitude slower than for the hexenyl radical and 3 orders of magnitude slower than for the 3-oxahexenyl radical.[12] The difference can be seen in the activation energies for the cyclization, which were highest for the 2-oxahexenyl radical. The low-temperature ESR spectrum of this radical showed considerable line broadening, indicating partial double-bond character through spin delocalization of the radical onto the adjacent oxygen, an interaction which restricts the rotational freedom of the CO σ-bond. The higher activation energy is believed to represent the energy required to disrupt this interaction while attaining the optimum overlap required for cyclization in the chairlike transition state.[12]

Although the alkoxymethyl radical cyclizes more slowly than a hexenyl radical, it also abstracts a hydrogen more slowly, about four times more slowly at 298 K.[12] The cyclization of selenide **6** was carried out under standard radical cyclization conditions, without resorting to syringe pump conditions, and gave essentially none of the reduction product, **11**. Thus, although the cyclization of alkoxymethyl radicals may be slow, it is still sufficiently fast compared with reduction to make it a synthetically useful ring construction. We have examined the cyclization under a range of tin hydride concentrations to see at what point the reduction becomes a problematic side reaction (Table I). As expected, the amount of reduction product increased as the tin hydride concentration was increased. However, even at high tin hydride concentration (1.16 M), the major product was still the cyclized product.[24]

Table I. The Effect of *n*-Bu_3SnH Concentration and the Cyclization/Reduction Ratio[a]

[6]/[Bu_3SnH], M	cyclization:reduction	9c:9t[b]	yield[c] (%)
0.015/0.017	>100:1	2.6:1	95
0.031/0.035	40:1	3.1:1	90
0.1/0.116	8:1	2.8:1	92
1.0/1.16	4:1	2.6:1	92

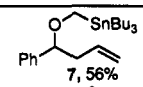
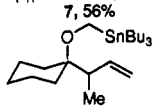
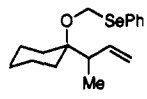
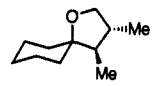
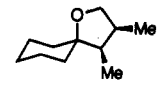
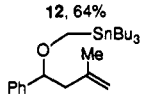
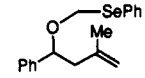
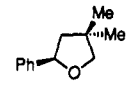
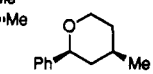
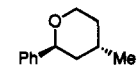
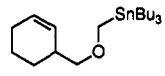
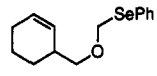
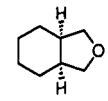
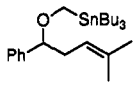
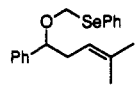
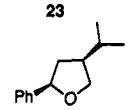
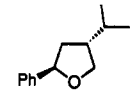
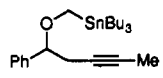
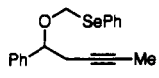
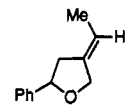
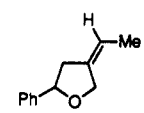
[a] Conditions: AIBN (0.25 equiv), benzene, reflux. [b] Ratios determined by capillary GC, which also indicated the presence of minor side products (1–4%) of as yet undetermined structure. In all cases clean, cyclized material was easily obtained by flash chromatography. [c] Combined yield of products isolated after a quick chromatographic separation.

(d) Scope of the 2-Oxahexenyl Radical Cyclization. We have explored the scope of this tetrahydrofuran synthesis by examining the cyclization of several related monoselenoacetal precursors (Table II). These precursors were readily synthesized from the corresponding homoallylic alcohols via the two-step process described above, namely alkylation with (iodomethyl)(tri-*n*-butyl)stannane followed by Li–Sn exchange and trapping with diphenyl diselenide. Both steps proceeded in fair to good yield, as shown in Table I. The radical cyclizations were usually carried out under the standard conditions mentioned earlier (conditions A). The cyclization of entry 3 was also examined using syringe pump conditions (conditions B).

As can be seen from Table II, the alkoxymethyl radical cyclization provides a direct and efficient route to tetrahydrofurans. Only small amounts of the reduction products (i.e., the methylated alcohols) were seen.[25] The cyclization of the 4-substituted 2-oxahexenyl radical gave a 4.3:1 mixture of two chromatographically separable tetrahydrofurans (entry 2). The observed diastereoselectivity can be rationalized by considering the more stable chairlike transition state for the closure (*cf.* **10**).[23] Substitution at the 5-position of the hexenyl chain resulted in the formation the exo-cyclization product **18**, along with the endo-cyclization products, tetrahydropyrans **19** and **20** (entry 3). In contrast to the all-carbon system,[23a] the exo-cyclization product predominated under the reaction conditions. Bicyclic compounds can be synthesized by cyclization onto a cycloalkenyl chain, as illustrated in entry 4. The lower yield here appears to be due to loss of material during isolation of this volatile compound. Cyclization of the alkynyl substrate afforded a nearly equal mixture of the exocyclic olefins (entry 6). The low selectivity for the hydrogen abstraction step is understandable given the similarity in the steric environment of the intermediate vinyl radical. As was illustrated for the example in entry 1 (Table III), it may be possible to enhance the stereoselectivity of entry 2 and the regioselectivity of entry 3 by conducting the reaction at a lower temperature.

(22) Choe, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959.
(23) (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.
(24) To assess the effect of tinhydride concentration on the cyclization of the parent hex-5-enyl radical, see: Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 5361.
(25) For comparison, authentic samples of the uncyclized reduction products were prepared by methylation of the corresponding alcohols.

Table II. Synthesis of Tetrahydrofurans via Cyclization of Alkoxymethyl Radicals

entry	$ROCH_2SnBu_3$ yield	$ROCH_2SePh$ yield	cyclization condns[a]	cyclization products		isomer ratio[b]	cyclization: reduction[b]	yield[c] (%) of cyclized product
1	 7, 56%	6 73%	A	9c	9t	2.6:1	>100:1	95
2	 12, 64%	 13, 74%	A	 14	 15	4.3:1 (77%:18%)	>100:1	95
3	 16, 94%	 17, 83%	A B	 18	 19  20	15:5:1 (63%:16%:2%) 16:5.6:1	18:1 23:1	82
4	 21, 60%	 22, 67%	A	 23		*d*	>100:1	80
5	 24, 80%	 25, 62%	A	 26	 27	2.2:1	14:1	83
6	 28, 81%	 29, 71%	A	 30	 31	1.5:1	39:1	73

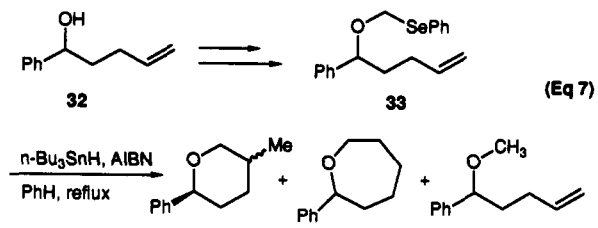
[a] Conditions: A = RSePh [0.015 M], *n*-Bu_3SnH (1.25 equiv, 0.017 M), AIBN (0.25 equiv), PhH, reflux, 1–3 h; B = *n*-Bu_3SnH and AIBN solution added by syringe pump over ~4 h. [b] Ratios determined by capillary GC. Yield of chromatographically separated isomers shown in parentheses. [c] Isolated yield of products. [d] A single isomer was observed.

Table III. The Effect of Temperature on Product Distribution

entry	substrate	T (°C)	conds[a]/solvent	cyclizn products	isomer ratio[b]	cyclized product yield[d] (%)	reduced product yield[d] (%)
1	6	25	A/benzene	9c + 9t	4.6:1	88	10
2		−20	A/toluene	9c + 8t	6:1	89	6
3		−70	A/toluene	9c + 9t	11:1	88	10
4		−70	B/toluene	9c + 9t	8:1	63	23
5	46	−70	B/toluene	47+ 48	5:1[c]	64	

[a] Conditions: A = R-SePh [0.015 M], *n*-Bu_3SnH (1.25 equiv, 0.017 M), Et_3B (0.4 equiv), PhH, reflux, 1–3 h. B = *n*-Bu_3SnH solution added by syringe pump over ~4 h. [b] Ratios determined by capillary GC. [c] Ratio determined by ^1H NMR. [d] Isolated yields.

(e) Synthesis of Tetrahydropyrans. The alkoxymethyl radical cyclization can provide a good route to tetrahydropyrans. It should be noted that this aspect of these cyclizations has also been investigated by others, albeit in systems where the alkoxymethyl radical is further stabilized by an electron-withdrawing group.[10] We prepared the required substrate from bis-homoallylic alcohol **32** in good overall yield (eq 7).



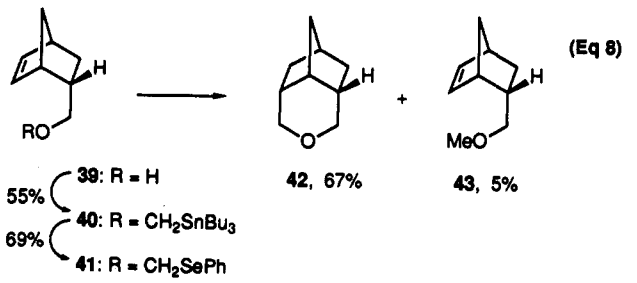
	34 : 35 : 36 (GC)	34 (trans/cis, NMR)
Bu_3SnH (0.017M), 1.5h, (97%)	69 : 8.5 : 22	4 : 1
Bu_3SnH by syringe pump	92 : 6.4 : 1.6	5 : 1

Cyclization of the 2-oxahept-6-enyl radical precursor **33** under the standard conditions gave a ~4:1 mixture (by GC) of cyclized to uncyclized products.[25] Formation of the reduction product was easily avoided by adding the tin hydride by syringe pump. The cyclized compounds consisted of a mixture of the six- and seven-membered ring products, with the former predominating by a 8:1 to 15:1 ratio (GC). In the preliminary report this ratio had been incorrectly labeled as representing the two tetrahydropyran diastereomers.[4] The NMR spectrum of the tetrahydropyran fraction clearly showed the presence of two diastereomers. Unfortunately, these diastereomers were inseparable by standard chromatographic techniques, including MPLC and GC. From decoupling and NOE experiments on the mixture, the major component was assigned the trans configuration. The predominance of the latter can be rationalized by considering the cyclization as taking place via a chair conformation, in which the phenyl group and the alkene are in an equatorial orientation (**37**).

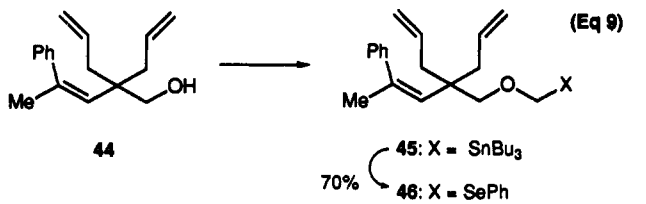
The formation of bridged systems was also possible by this cyclization process. Norbornenyl substrate **41**, formed in good yield from alcohol **39**, underwent a smooth cyclization to symmetrical ether **42**. As in the previous example, competitive reduction was minimized under

37 38

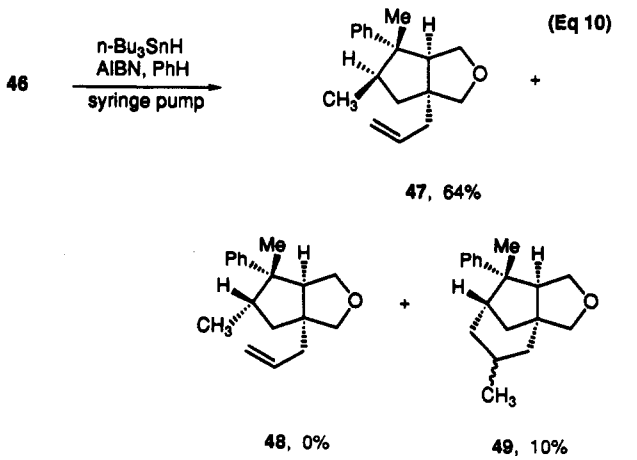
syringe pump conditions. It may be noted that anionic cyclization appears to not allow access to such bicyclic compounds.[13a]



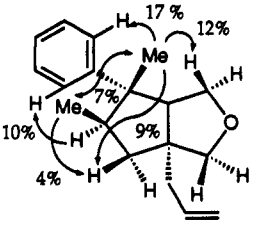
(f) Application to a Tandem Cyclization. We have also incorporated alkoxymethyl radical cyclization in a system where further cyclizations are possible.[26] The required alcohol **44** was prepared, as described, by a bisallylation of the appropriate α,β-unsaturated ester, followed by reduction with $LiAlH_4$.[26d] The standard two-step sequence afforded the cyclization precursor (eq 9).



44



The radical cyclization of **46** was carried out under low tin hydride concentration conditions to promote sequential cyclizations (eq 10). Under these conditions (conditions B in Table II) the major product was the double cyclization product, **47**, formed in 64% yield, with no detectable amount of the diastereomer where the two methyl groups are in a trans arrangement (**48**). Interestingly, a small amount of the triple cyclization product, **49**, was also formed, as a 2.8:1 mixture (by NMR) of inseparable diastereomers. Evidently, the *exo*-methyl radical intermediate of the double cyclization, which would have given product **48**, cyclized further to afford the [3.2.1]bicyclic substructure. The structure assigned to the major product was confirmed by NOE difference experiments and was consistent with earlier observations on the cyclization of xanthate-derived radicals.[26d] The prominent NOE enhancements are summarized below.



(g) Temperature Effects. We have found that the diastereoselectivity of some of these cyclizations can sometimes be altered dramatically by lowering the reaction temperature (Table III). The low-temperature reactions were conducted using the Et_3B (1.16 equiv of n-Bu_3SnH, 0.4 equiv of Et_3B) protocol, in either benzene or toluene.[27] Cyclization of the simple alkoxymethyl radical precursor, **6**, at room temperature gave the cyclized product in high yield, in a 4.6:1 cis to trans ratio, along with a small amount of the reduction product. The cyclized product was easily separated by flash chromatography from the uncyclized reduced material. To our surprise, even at lower temperatures the cyclization reaction was sufficiently fast that only a small amount of the reduction product was formed. When the temperature was lowered further, the cis/trans selectivity gradually increased, to 6:1 at −20 °C and to 11:1 at −70 °C. The cis selectivity was, however, a bit lower under low tin hydride concentration conditions (syringe pump, 1 h).

As was mentioned above, these radical cyclizations resemble the anionic cyclizations reported by Broka.[13] Our results suggest that the high cis selectivity (~11:1) observed by Broka may be due, at least in large part, to temperature effects rather than to inherent differences between anionic and radical cyclizations. In general, the radical cyclization proceeds in good yield, regardless of the substituents on the alkene.[13]

In addition to the simple system, we also examined the tandem cyclization reaction at low temperature (Table III, entry 5). The cyclization of substrate **46** was carried out under syringe pump conditions and afforded the cyclization products, bicyclic compounds **47** and **48**, in good yield. It is interesting to note that the third cyclization to **49** did not take place at −70 °C. In contrast to the simple system discussed above, the diastereoselectivity of this reaction, specifically the second cyclization, decreased at lower temperature. This outcome suggests that at higher temperature the second cyclization may be reversible, reforming the stable tertiary benzylic radical.

These results summarize our investigations on the scope and usefulness of the alkoxymethyl radical cyclization. Such radicals are reported to be more stable and, as a result, to undergo cyclization more slowly than simple alkyl radicals. Our results, however, show that alkoxymethyl

(26) (a) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (b) Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349. (c) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (d) Iwasa, S.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Org. Chem.* **1991**, *56*, 2849.

(27) (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.

radicals undergo cyclizations in good to excellent yield to afford tetrahydrofuran and tetrahydropyran products. The stereoselectivity of these cyclizations is comparable to that found in simple hexenyl systems but can sometimes be quite high, particularly at low temperature. The substrates required for these reactions are readily prepared from an appropriate alcohol.

Experimental Section[28]

General Procedure for the Synthesis of Radical Cyclization Precursors. Preparation of 4-[[Phenylthio)methyl]-oxy]-4-phenyl-1-butene (5). A mixture of 4-phenyl-1-buten-4-ol[14] (148 mg, 1.0 mmol), 50% aqueous NaOH (0.5 mL), hexanes (2 mL), and tetrabutylammonium bromide (0.032 g, 0.1 mmol) was treated with $PhSCH_2Cl$[15] (317 mg, 2.0 mmol). The resulting cloudy mixture was stirred at room temperature, and progress of the reaction was monitored by TLC. After 8 h, water (20 mL) was added, and the product was extracted three times with 1:1 hexanes–ether. The combined organic phase was washed sequentially with water and brine, dried over Na_2SO_4, and concentrated to afford the crude product as a pale yellow oil. Purification by flash chromatography (CH_2Cl_2–hexanes (1:5 then 1:3)) afforded **5** (163 mg, 60%) as a colorless oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.45 (m, 1H), 2.60 (m, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.83 (dd, J = 7.75, 5.77 Hz, 1H), 4.94–5.1 (m, 2H), 5.08 (d, J = 11.6 Hz, 1H), 5.63–5.79 (m, 1H), 7.30 (m, 8H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 42.1 (t), 73.2 (t), 78.3 (d), 117.1 (t), 126.6 (d), 127.2 (d), 127.9 (d), 128.5 (d), 128.8 (d), 130.2 (d), 134.6 (s), 136.0 (s), 140.5 (s); HRMS m/z calcd for $C_{17}H_{18}OS$ (M^+) 270.1078, found 270.1058 (M^+).

Preparation of Tributyl[[(1-phenyl-3-butenyl)oxy]-methyl]stannane (7). A stirred suspension of sodium hydride (60% dispersion, 208 mg, 5.2 mmol), washed free of oil, in dry DMF (2 mL) was treated dropwise with a solution of 4-phenyl-1-buten-4-ol[14] (592 mg, 4.0 mmol) in DMF (1 mL). After the mixture was stirred at room temperature for ca. 1 h, n-Bu_3SnCH_2I[21] (2.150 g, 5.0 mmol) was added, and the resulting slurry was allowed to stir overnight. Methanol (1 mL) was then added to destroy excess sodium hydride. The reaction mixture was diluted with hexanes (100 mL), washed twice with water and once with brine, and dried over Na_2SO_4. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (elution with hexanes) yielded stannane **7** (1.00 g, 56%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 7.0 Hz, 9H), 1.10–1.65 (m, 18H), 2.40 (m, 2H), 3.45 (d, J = 10.0 Hz, 1H), 3.62 (d, J = 10.0 Hz, 1H), 4.05 (m, 1H), 4.98 (m, 1H), 5.05 (m, 1H), 5.70 (ddd, J = 16.5, 9.3, 9.3 Hz, 1H), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8 .9, 13.7, 27.3, 29.1, 42.9, 59.6, 86.4, 116.4, 126.8, 127.3, 128.1, 135.3, 142.6.

Preparation of [[[(1-Phenyl-3-butenyl)oxy]methyl]-seleno]benzene (6). A solution of n-BuLi (1.12 mL of 2.5 M in hexanes, 2.8 mmol) was added over 2 min to a cooled (dry ice–acetone bath), stirred solution of stannane **7** (900 mg, 2.0 mmol) in dry THF (5 mL). After 5 min, a solution of diphenyl diselenide (911 mg, 2.91 mmol) in THF (2.5 mL) was added over 1 min. The cooling bath was removed after 20 min, and the reaction was quenched with saturated aqueous NH_4Cl. The product was isolated by extraction with hexanes. Purification of the crude product by flash chromatography on silica gel (elution with hexanes then hexanes–ether (50:1)) gave selenide **6** as colorless oil (461 mg, 73%): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (m, 1H), 2.58 (m, 1H), 4.80 (dd, J = 7.5, 5.6 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.98 (dm, J = 9.3 Hz, 1H), 5.05 (dm, J = 16.5 Hz, 1H), 5.39 (d, J = 11.2 Hz, 1H), 5.70 (ddd, J = 16.5, 9.3, 9.3 Hz, 1H), 7.28 (m, 8H), 7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.0, 69.8, 79.1, 117.1, 127.0, 127.2, 127.9, 128.5, 128.9, 130.7, 132.9, 134.5, 140.2; MS (70 eV) m/z (relative intensity) 317 (M^+ – 1, 0.4), 161 (M^+ – PhSe, 8).

General Procedure for Radical Cyclization. Procedure A: Cyclization of [[[(1-Phenyl-3-butenyl)oxy]methyl]-seleno]benzene (6) in the Presence of n-Bu_3SnH and AIBN. To a solution of selenide **6** (100 mg, 0.315 mmol) in benzene (20 mL) was added AIBN (16 mg, 0.09 mmol) and n-Bu_3SnH (107 mg, 0.36 mmol) at room temperature. The flask was carefully evacuated, flushed with argon three times, and then lowered into an oil bath preheated to 90 °C. After the solution was refluxed for 1.5 h, TLC showed complete absence of starting material. The flask was cooled to room temperature, and the benzene was removed in vacuo. The crude product was purified by flash chromatography (elution with 5% ethyl ether in hexanes) to afford a mixture of **9c** and **9t** (48 mg, 95% yield). GC analysis (capillary column at 120 °C oven temperature) of the product showed as 2.6:1 *ratio of diastereomers* **9c**/**9t**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (d, J = 7.5 Hz, 3H), 1.48 (m, 1H), 1.95 (m, 0.6 H), 2.48 (m, 1.4 H), 3.45 (t, J = 7.5 Hz, 0.3 H), 3.56 (t, J = 7.5 Hz, 0.7 H), 4.07 (t, J = 7.5 Hz, 0.7H), 4.2 (dd, J = 7.5, 7.5 Hz, 0.3H), 4.9 (dd, J = 7.5, 9.4 Hz, 0.7H), 5.01 (t, J = 7.5 Hz, 0.3H), 7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ (cis isomer) 17.4, 33.2, 43.9, 75.4, 81.5, 125.6, 127.0, 128.3, 143.4; (trans isomer) 17.7, 34.9, 42.7, 75.6, 80.0, 125.5, 126.9, 128.2, 144.0; HRMS calcd for $C_{11}H_{14}O$ (M^+) 162.1044, found 162.1044 (M^+).

Et_3B-Mediated Cyclization. Air was bubbled into a cooled (–20 °C) solution of substrate **6** (100 mg, 0.315 mmol) in dry benzene (20 mL) for ca. 2 min. The solution was treated with n-Bu_3SnH (107 mg, 0.36 mmol) followed by Et_3B (0.12 mL of 1 M solution in hexanes, 0.13 mmol). The mixture was stirred at –20 °C for 0.5 h, at which time no starting material was present. The benzene was removed in vacuo, and the crude product was purified by flash chromatography, which afforded the products, **9c** and **9t** (48 mg, 95%), in a 6:1 ratio (by GC at 120 °C oven temperature).

Procedure B: Syringe Pump Method. Substrates of entries 3 (Table II) and 4 and 5 (Table III) were cyclized according to procedure A except that the solution of n-Bu_3SnH and AIBN in benzene was added by syringe pump over approximately 3–5 h to a refluxing solution of substrate in benzene. A typical procedure is described below for the cyclization of **6**.

Air was bubbled into a cooled (–70 °C) solution of selenide **6** (70 mg, 0.22 mmol) in dry toluene (4 mL) for ca. 2 min. The solution was then treated with Et_3B (0.1 mL of 1 M solution in hexanes, 0.12 mmol). Bu_3SnH (0.07 mL, 0.25 mmol) in toluene (10.6 mL) was then added by a syringe pump over 1 h. After the addition no starting material was seen by TLC. The benzene was removed in vacuo, and the crude product was purified by flash chromatography to afford a mixture of **9c** and **9t** (17 mg, 63%) in a 8:1 ratio (GC) and reduced product **11** (6 mg, 22%).

The general procedures described above were used for the preparation and cyclization of the other substrates used in this study. The details of the specific experiments are presented below in an abbreviated format.

Preparation of 4-Methoxy-4-phenyl-1-butene[29] (Reduction Product). Samples of this methyl ether and all analogous "reduction products" were prepared by methylation of the alcohol as follows. The sodium salt of the alcohol (NaH, THF, room temperature) was treated with excess MeI. After the mixture was stirred for 1 h, the reaction was quenched with water and the product extracted and purified by chromatography: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.4 (m, 1H), 2.55 (m, 1H), 3.2 (s, 3H), 4.2 (t, J = 6.7 Hz, 1H), 5.05 (m, 2H), 5.75 (m, 1H), 7.3 (m, 5H).

Preparation of 1-(1-Methyl-2-propenyl)cyclohexan-1-ol. Following the procedure of Luche,[14] a mixture of saturated aqueous NH_4Cl (10 mL), THF (2 mL), and cyclohexanone (1.04 mL, 10 mmol) was treated with Zn dust (1.31 g, 20 mmol), added in small portions at room temperature. After 2 h, ether (100 mL) was added, and the layers were separated. The aqueous layer was reextracted with ether. The combined organic layers were

(28) **General Methods.** Nuclear magnetic resonance spectra (^1H NMR) were recorded on either Bruker 200, 250, or 300 MHz spectrometers. ^{13}C spectra were recorded at 50, 63, or 75 MHz. Gas chromatography analyses were performed on a Hewlett-Packard 5890 series II gas chromatograph equipped with a flame ionization detector, using 25-cm × 0.2-mm × 0.33-μm 5% PhMe silicone capillary column. Peak areas were recorded on a Hewlett-Packard 3396 series II integrator. High-resolution and low-resolution mass spectra were obtained on VG 70-250S under EI or CI condition. All reactions were performed in flame-dried apparatus and maintained under a positive pressure of argon, using freshly distilled solvents. Thin-layer chromatography was carried out on 0.25-mm E. Merck silica gel plates (60 F-254) and visualized using both UV light and an anisaldehyde indicator. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous material, unless stated otherwise.

(29) Mukaiyama, T.; Nagoaka, H.; Murakami, M.; Ohshima, M. *Chem. Lett.* **1985**, 977.

dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (1:1 hexanes–CH_2Cl_2) to afford the 1-(1-methyl-2-propenyl)cyclohexan-1-ol (1.43 g, 95%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 (d, J = 7.0 Hz, 3H), 1.50 (m, 10H), 2.13 (q, J = 7.0 Hz, 1H), 5.05 (m, 2H), 5.82 (m, 1H).

Preparation of Tributyl[1-(1-methyl-2-propenyl)cyclohexyl]oxy]methyl]stannane (12). To a suspension of oil-free KH (765 mg, 35 wt % in mineral oil, 6.5 mmol) in DMF (10 mL) was added 1-(1-methyl-2-propenyl)cyclohexan-1-ol (1.00 g, 6.5 mmol) at room temperature. After the mixture was stirred at 60 °C (bath) for 10 min and at room temperature for 40 min, it was treated with neat Bu_3SnCH_2I (2.15 g, 5 mmol). The resulting slurry was allowed to stir at room temperature for 2.5 h (TLC check) and then quenched with saturated NH_4Cl solution (20 mL). The mixture was extracted twice with 1:1 ether–hexanes, and the combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes) to afford (1.45 g, 64%) of stannane **12** as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (m, 12H), 1.40 (m, 22H), 2.45 (m, 1H), 3.35 (s, 2H), 4.95 (m, 2H), 5.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.9 (q), 13.7 (q), 21.5 (t), 21.8 (t), 26.2 (t), 27.4 (t), 29.3 (t), 29.9 (t), 41.9 (d), 47.9 (t), 108.2 (s), 114.1 (t), 141.6 (d).

Preparation of [[[1-(1-Methyl-2-propenyl)cyclohexyl]oxy]methyl]seleno]benzene (13). A solution of n-BuLi (1.27 mL of a 2.5 M in hexanes, 3.18 mmol) was added dropwise to a chilled (dry ice–acetone bath) solution of stannane **12** (1.00 g, 2.19 mmol) in THF (20 mL). After the mixture was stirred for 10 min, a THF solution (4 mL) of diphenyl diselenide (1.10 g, 3.50 mmol) was added dropwise. The resulting yellow solution was stirred further for 30 min and then quenched with saturated NH_4Cl (1.5 mL). The organic phase was separated, and the aqueous phase was extracted three times with ether. The organic layers were combined, dried over Na_2SO_4, and concentrated. Purification of the resulting crude product by flash chromatography (10:1 hexanes–CH_2Cl_2) yielded selenide **13** (505 mg, 74%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, J = 7.2 Hz, 3H), 1.50 (m, 10H), 2.42 (q, J = 7.2 Hz, 1H), 5.00 (m, 4H), 5.78 (m, 1H), 7.20 (m, 3H), 7.65 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.2 (q), 21.5 (t), 21.7 (t), 25.8 (t), 30.7 (t), 30.8 (t), 43.5 (d), 62.0 (t), 80.6 (s), 114.9 (t), 126.9 (d), 128.8 (d), 131.2 (s), 133.2 (d), 140.5 (d); HRMS calcd for $C_{17}H_{24}OSe$ (M^+) 324.0992, found 324.0992 (M^+).

Cyclizationof[[[1-(1-Methyl-2-propenyl)cyclohexyl]oxy]methyl]seleno]benzene (13). A solution of selenide **13** (250 mg, 0.77 mmol), n-Bu_3SnH (0.25 mL, 0.90 mmol), and AIBN (35.5 mg, 0.216 mmol) in dry benzene (51 mL) was heated to reflux. The reaction was monitored by TLC, which showed the absence of starting material after 70 min. The cooled solution was concentrated and the product purified by flash chromatography (2:1, hexanes–EtOAc) to afford the diastereomeric cyclization products **14** (100 mg, 77%) and **15** (18 mg, 18%).

***trans*-3,4-Dimethyl-1-oxaspiro[4.5]decane (14):** ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J = 7.1 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 1.20 (m, 5H), 1.52 (m, 7H), 3.28 (t, J = 8.0 Hz, 1H), 3.91 (t, J = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.6 (q), 15.9 (q), 21.7 (t), 23.1 (t), 26.0 (t), 31.1 (t), 36.5 (t), 40.2 (d), 51.4 (d), 72.3 (t), 83.7 (s); IR (neat) 2925, 1420, 865, 680 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_{20}O$ (M^+) 168.1514, found 168.1488 (M^+, 2).

***cis*-3,4-Dimethyl-1-oxaspiro[4.5]decane (15):** ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, J = 7.4 Hz, 3H), 0.92 (d, J = 7.4 Hz, 3H), 1.40 (m, 10H), 1.90 (m, 1H), 2.50 (m, 1H), 3.40 (t, J = 8.0 Hz, 1H), 3.91 (t, J = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.8 (q), 13.50 (q), 23.1 (t), 23.6 (t), 25.8 (t), 32.9 (t), 36.3 (d), 37.5 (t), 43.5 (d), 71.8 (t), 84.2 (s); IR (neat) 2925, 1420, 845, 680 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_{20}O$ (M^+) 168.1514, found 168.1488 (M^+, 2).

Preparation of Tributyl[[(3-methyl-1-phenyl-3-butenyl)oxy]methyl]stannane (16). A solution of 2-methyl-4-phenyl-1-buten-4-ol[14] (1.26 g, 7.78 mmol) in DMF (3 mL) was added slowly to a suspension of oil-free NaH (60%, 0.335 g, 8.39 mmol) in DMF (12 mL) at room temperature. After the solution was stirred for 1 h, n-Bu_3SnCH_2I (2.58 g, 5.99 mmol) in DMF (2 mL) was added and stirring continued for another 1 h. The reaction mixture was quenched with saturated NH_4Cl and extracted twice with 1:2 ether–hexanes. Evaporation of solvent followed by flash chromatography (1:8, CH_2Cl_2–hexanes) gave stannane **16** (2.6 g, 94%) as colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.8–1.00 (m, 15H), 1.25–1.35 (m, 6H), 1.40–1.60 (m, 6H), 1.74 (s, 3H, CH_3), 2.26 (dd, J = 5.2, 14.0 Hz, 1H), 2.48 (dd, J = 8.1, 14.0 Hz, 1H), 3.44 (d, J = 10.0 Hz, 1H), 3.60 (d, J = 10.0 Hz, 1H), 4.16 (dd, J = 5.3, 8.1 Hz, 1H), 4.65 (m, 1H), 4.74 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 8.9 (t), 13.7 (q), 23.1 (q), 27.3 (t), 29.2 (t), 46.8 (t), 59.6 (t), 85.8 (d), 112.3 (t), 126.8 (d), 127.2 (d), 128.1 (d), 142.8 (s), 142.9 (s); IR (neat) 3020, 3035, 2930, 1650, 1490, 1455, 1445, 1375, 1060, 880, 750 cm^{-1}.

Preparation of [[[(3-Methyl-1-phenyl-3-butenyl)oxy]methyl]seleno]benzene (17). A solution of n-BuLi (3.10 mL of 2.5 M in hexanes, 7.75 mmol) was added dropwise over 2 min to a cooled (dry ice–acetone) solution of stannane **16** (2.45 g, 5.27 mmol) in THF (50 mL). After 10 min, a solution of diphenyl diselenide (2.7025 g, 8.66 mmol) in THF (10 mL) was added over 4 min. The resulting mixture was stirred for 35 min and then quenched with saturated ammonium chloride (5 mL). Standard workup and flash chromatography (elution with CH_2Cl_2–hexanes (1:10)) gave **17** (1.459 g, 84%) as colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3H), 2.32 (dd, J = 5.15, 14.2 Hz, 1H), 2.57 (dd, J = 8.6, 14.2 Hz, 1H), 4.74 (m, 2H), 4.83 (d, J = 9.9 Hz, 1H), 4.90 (dd, J = 5.2, 8.6 Hz, 1H), 5.35 (d, J = 9.9 Hz, 1H), 7.15–7.35 (m, 8H), 7.52–7.60 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.6 (q), 46.2 (t), 69.8 (t), 77.8 (d), 113.1 (t), 126.9 (d), 127.2 (d), 127.8 (d), 128.4 (d), 128.9 (d), 130.9 (s), 132.8 (d), 140.6 (s), 141.8 (s); IR (neat) 3060, 2960, 2900, 1645, 1580, 1470, 1440, 1270, 1050, 885, 730, 690 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{15}O$ (M^+ – PhSe) 175.1122, found 175.1131 (M^+ – PhSe, 24).

Radical Cyclization of [[[(3-Methyl-1-phenyl-3-butenyl)oxy]methyl]seleno]benzene (17). A solution of selenide **17** (342 mg, 1.034 mmol), n-Bu_3SnH (0.25 mL, 1.265 mmol), and AIBN (45.4 mg, 0.28 mmol) in benzene (67 mL) was heated to reflux. Additional n-Bu_3SnH (0.05 mL, 0.253 mmol) was added after 2.5 h and refluxing continued for another 2.5 h. The concentrated reaction mixture was purified by flash chromatography (CH_2Cl_2–petroleum ether (1:3)) to afford a mixture of the cyclization products **18–20** (161 mg, 88%) along with a trace of the reduction product (2%). Further purification by MPLC (CH_2Cl_2–petroleum ether (1:3)) of 97 mg of this mixture gave **18** (63%), **19** (16%), and **20** (2%).

Tetrahydro-4,4-dimethyl-2-phenylfuran (18): ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.71 (dd, J = 9.4, 12.3 Hz, 1H), 2.15 (dd, J = 6.8, 12.3 Hz, 1H), 3.69 (d, J = 8.0 Hz, 1H), 3.79 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 6.8, 9.4 Hz, 1H), 7.4–7.6 (m, 5H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 26.4 (q), 26.5 (q), 40.1 (s), 49.2 (t), 80.7 (d), 80.9 (t), 125.4 (d), 126.9 (d), 128.2 (d), 143.7 (s); IR (neat) 3060, 3030, 2960, 2860, 1605, 1495, 1460, 1370, 1150, 900, 750, 695 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1205 (M^+, 51), 175.1132 (M^+ – 1, 35), 159.0845 (18).

***cis*-Tetrahydro-4-methyl-2-phenyl-2*H*-pyran (19):** ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J = 6.40 Hz, 3H), 1.3–1.45 (m, 2H), 1.6–1.7 (m, 1H), 1.72–1.9 (m, 2H), 3.61 (ddd, J = 2.2, 11.6, 12.7 Hz, 1H), 4.16 (ddd, J = 1.4, 4.5, 11.6 Hz, 1H), 4.31 (dd, J = 1.9, 11.3 Hz, 1H), 7.4–7.6 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.3 (q), 30.8 (d), 34.4 (t), 42.7 (t), 68.5 (t), 79.8 (d), 125.8 (d), 127.2 (d), 128.3 (d), 143.2 (s); HRMS calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1201 (M^+).

***trans*-Tetrahydro-4-methyl-2-phenyl-2*H*-pyran (20):** ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 7.1 Hz, 3H), 1.30–1.40 (m, 1H), 1.55–1.65 (m, 1H), 1.82–2.0 (m, 2H), 2.05–2.15 (m, 1H), 3.80–3.85 (m, 2H), 4.67 (dd, J = 2.9, 9.6 Hz, 1H), 7.4–7.6 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.5 (q), 25.3 (d), 32.1 (t), 38.9 (t), 63.1 (t), 73.9 (d), 126.1 (d), 127.1 (d), 128.3 (d), 142.9 (s); IR (neat, cm^{-1}) 2960, 2920, 1490, 1450, 1315, 1250, 1170, 905, 730; HRMS calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1201 (M^+).

2-Methyl-4-methoxy-4-phenyl-1-butene (reduction product): ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3H), 2.30 (dd, J = 5.5, 14.1 Hz, 1H), 2.55 (dd, J = 8.3, 14.1 Hz, 1H), 3.21 (s, 3H), 4.28 (dd, J = 5.5, 8.3 Hz, 1H), 4.70 (bs, 1H), 4.77 (bs, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.7 (q), 46.6 (t), 56.7 (q), 82.6 (d), 112.5 (t), 126.7 (d), 127.6 (d), 128.3 (d), 142.1 (s), 142.4 (s); HRMS calcd for $C_{12}H_{15}O$ (M^+ – 1) 175.1102, found 175.1128 (M^+ – 1).

Preparation of Tributyl[[2-cyclohexen-1-ylmethoxy)-

methyl]stannane (21). A solution of 2-cyclohexenylmethanol[30] (225 mg, 2.0 mmol) in THF (1 mL) was added slowly to a suspension of oil-free NaH (60%, 96 mg, 2.4 mmol) in THF (2 mL), maintained in an ice bath. After the addition was complete, the cold bath was removed, and the mixture was stirred for 1 h at room temperature and then treated with a solution of *n*-Bu_3SnCH_2I (688 mg, 1.6 mmol) in THF (1 mL). The progress of the alkylation was monitored by TLC. After 40 h, the reaction was worked up as before. Purification of the product by flash chromatography (elution with hexanes) gave the desired stannane **21** as colorless oil (400 mg, 60% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7 Hz, 9H), 1.20–1.80 (m, 22H), 1.98 (bs, 2H), 2.35 (m, 1H), 3.20 (d, J = 6.8 Hz, 2H), 3.72 (m, 2H), 5.58 (ddd, J = 9.4, 4.0, 2.0 Hz, 1H), 5.72 (ddd, J = 9.4, 4.0, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.1, 13.7, 20.9, 25.4, 26.0, 27.3, 29.1, 62.1, 79.7, 128.2, 128.7.

[[(2-Cyclohexen-1-ylmethoxy)methyl]seleno]benzene (22). A chilled (dry ice–acetone bath) solution of stannane **21** (470 mg, 1.14 mmol) in THF (4 mL) was treated dropwise with *n*-BuLi (0.6 mL of 1.5M in hexanes, 1.5 mmol). After 5 min, a solution of diphenyl diselenide (512 mg, 1.6 mmol) in THF (2.5 mL) was added dropwise. The mixture was allowed to stir for 20 min, at which point the cooling bath was removed (TLC check). The reaction was quenched with saturated NH_4Cl solution, worked up as before, and purified by flash chromatography (elution with CH_2Cl_2–hexanes (1:10)) to afford selenide **22** as a colorless liquid (213 mg, 67%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (m, 1H), 1.5 (m, 1H), 1.70 (m, 2H), 1.98 (bs, 2H), 2.4 (m, 1H), 3.48 (d, J = 6.8 Hz, 2H), 5.28 (s, 2H), 5.58 (ddd, 10.0, 2.1, 1.3 Hz, 1H), 5.75 (ddd, J = 10.0, 2.3, 2.5 Hz, 1H), 7.25 (m, 3 H), 7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 25.2, 25.9, 35.3, 73.1, 73.6, 127.0, 127.9, 128.9, 130.9, 132.9; MS (FAB) m/z (relative intensity) 282 (M^+, 3), 125 (M^+ – PhSe, 26.1); HRMS calcd for $C_{14}H_{18}OSe$ (M^+) 282.0522, found 282.0522 (M^+, 4.9).

Radical Cyclization of [[(2-Cyclohexen-1-ylmethoxy)methyl]seleno]benzene (22). A solution of selenide **22** (174 mg, 0.62 mmol), *n*-Bu_3SnH (0.2 mL, 1.16 equiv, and AIBN (28 mg, 0.3 equiv) in benzene (41 mL, 0.017M in *n*-Bu_3SnH) was heated to reflux for 1 h (TLC check). Evaporation of benzene and purification of the residue by flash chromatography (CH_2Cl_2–hexanes (1:2)) afforded **23** (73 mg, 80%) as a colorless volatile liquid. GC analysis (120 °C oven temperature) of the product showed single diastereomer: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (m, 2H), 1.46 (m, 4H), 1.60 (m, 2H), 2.18 (m, 2H), 3.60 (dd, J = 7.8, 5.4 Hz, 2H), 3.79 (dd, J = 7.8, 5.4, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 25.2, 38.0, 71.8; HRMS calcd for $C_8H_{13}O$ (M^+) 125.0966, found (M^+) 125.0966.

Preparation of 2-Methyl-5-phenyl-2-penten-5-one.[31] To a solution of LDA, prepared from diisopropylamine (0.35 mL, 2.6 mmol) and *n*-BuLi (1.25 mL of 2.5 M solution in hexanes, 2.5 mmol), in THF (4 mL) was added dropwise a solution of *O*-(trimethylsilyl)benzaldehyde cyanohydrin (410 mg, 2 mmol) in THF (2 mL). After 20 min, 4-bromo-2-methyl-2-butene (0.35 mL, 3 mmol) in THF (2 mL) was added. The reaction mixture was allowed to warm to room temperature, stirred for 2 h (TLC check), and quenched with saturated ammonium chloride (2 mL). Ether (10 mL) and aqueous HCl (5%, 2 mL) were added, and stirring was continued overnight to allow hydrolysis of silyl ether. The organic phase was separated and stirred with 1.0 N KOH (5.0 mL) for 1 h. The organic phase was separated, and the aqueous phase was reextracted with ether. The combined organic phase was concentrated and the residue purified by flash chromatography (CH_2Cl_2–hexanes (1:1)), giving 2-methyl-5-phenyl-2-penten-5-one as a colorless oil (200 mg, 57%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.58 (s, 3H), 1.77 (s, 3H), 2.72 (m, 2H), 5.25 (m, 1H), 7.38 (m, 3H), 7.55 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.0, 25.9, 42.7, 73.7, 115.7, 120.7, 124.9, 128.6, 128.8, 139.5.

Preparation of 2-Methyl-5-phenyl-2-penten-5-ol. This alcohol was prepared by reduction of 2-methyl-5-phenyl-2-penten-5-one (1.00 g, 5.75 mmol) with $NaBH_4$ (106 mg, 2.8 mmol) in methanol (5 mL) at 0 °C for 0.5 h. Usual workup and purification by flash chromatography (elution with methylene chloride–hexanes (1:1)) gave the desired alcohol (810 mg, 80%) as colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H), 1.70 (s, 3H), 2.1 (bs, 1H), 2.50 (m, 2H), 4.65 (dd, J = 8.0, 5.0 Hz, 1H), 5.15 (m, 1H), 7.3 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.9, 25.8, 38.2, 73.9, 119.7, 125.8, 127.3, 128.3, 135.5, 144.2; HRMS calcd for $C_{12}H_{16}O$ (M^+) 176.12 01, found 176.1201 (M^+).

Preparation of Tributyl[[(4-methyl-1-phenyl-3-pentenyl)oxy]methyl]stannane (24). A solution of 2-methyl-5-phenyl-2-penten-5-ol (176 mg, 1.00 mmol) in THF (3 mL) was added slowly to a suspension of oil-free NaH (60%, 50 mg, 1.25 mmol) in DMF (3 mL) at 0 °C. After the solution was stirred for 1 h at room temperature, *n*-Bu_3SnCH_2I (473 mg, 1.1 mmol) in THF (1.0 mL) was added dropwise, and the resulting mixture was heated to 80 °C for 3 h. The usual workup and chromatographic purification (elution with hexanes) afforded stannane **24** (296 mg, 62%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (m, 15H), 1.20–1.60 (m, 15H), 1.65 (s, 3H), 2.35 (m, 2H), 3.55 (m, 2H), 3.89 (dd, J = 8.7, 5.0 Hz, 1H), 5.20 (m, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.9, 13.7, 17.7, 25.7, 27.3, 29.2, 29.3, 37.2, 59.6, 86.6, 120.8, 126.8, 127.1, 128.0, 132.9, 143.4.

Preparation of [[[(4-Methyl-1-phenyl-3-pentenyl)oxy]methyl]seleno]benzene (25). *n*-BuLi (0.35 mL of 2.2 M in hexanes, 1.3 equiv) was added dropwise to a cooled (–78 °C) solution of stannane **24** (280 mg, 0.58 mmol) in THF (4 mL). After 5 min, a solution of diphenyl diselenide (253 mg, 0.81 mmol) in THF (2 mL) was added dropwise. The cold bath was removed and the solution stirred for 20 min and then quenched with saturated NH_4Cl solution. Standard workup and chromatographic purification (elution with hexanes) gave **25** (122 mg, 61%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3H), 1.62 (s, 3H), 2.45 (m, 2H), 4.78 (dd, J = 8.7, 5.0 Hz, 1H), 4.85 (d, J = 11.2 Hz, 1H), 5.1 (m, 1H), 5.38 (d, J = 11.2 Hz, 1H), 7.3 (m, 8H), 7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.8, 25.6, 36.4, 36.9, 69.9, 79.6, 120.1, 126.9, 127.2, 127.4, 127.7, 128.4, 128.9, 130.7, 13 3.0, 140.8; HRMS calcd for $C_{19}H_{22}OSe$ (M^+) 346.0835, found 346.0835 (M^+, 0.5), 189.13 (M^+ – PhSe, 7).

Cyclization of [[[(4-Methyl-1-phenyl-3-pentenyl)oxy]methyl]seleno]benzene (25). A solution of selenide **25** (122 mg, 0.35 mmol), *n*-Bu_3SnH (0.11 mL, 0.4 mmol), and AIBN (11.5 mg, 0.07 mmol) in benzene (25.3 mL, 0.017 M in *n*-Bu_3SnH) was refluxed for 45 min at 80 °C. Evaporation of benzene under vacuum followed by chromatographic purification (elution with methylene chloride–hexanes (1:2)) afforded the cyclization products, 4-isopropyl-2-phenyltetrahydrofurans **26** and **27** (56 mg, 83%), in a 2.2:1 ratio (by GC, 150 °C column temperature). A small amount of the reduced starting material was also isolated (4.0 mg, 6%) and its structure confirmed by comparison with an authentic sample: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (m, 6H), 1.50 (m, 2H), 1.95–2.25 (m) and 2.40 (m, total 2H), 3.55 (t, J = 10.0 Hz) and 3.70 (t, J = 8.5 Hz, total 1H), 4.10 (t, J = 8.5 Hz, cis) and 4.20 (t, J = 8.5 Hz, trans, total 1 H), 4.90 (dd, J = 10 Hz, 5.0 Hz) and 5.05 (t, J = 8.5 Hz, total 1H), 7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 21.6, 31.7, 32.0, 39.17, 40.8, 46.1, 48.2, 72.9, 73.1, 80.5, 81.7, 125.2, 125.6, 127.2, 128.2, 128.3, 143.2; HRMS calcd for $C_{13}H_{18}O$ (M^+) 190.1357, found 190.1358 (M^+). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.89; H, 9.59.

Reduction product: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.49 (s, 3H), 1.66 (s, 3H), 2.32 (m, 1H), 2.50 (m, 1H), 3.22 (s, 3H), 4.1 (t, J = 6.7 Hz, 1H), 5.12 (m, 1H), 7.30 (m, 5H).

5-Phenyl-2-pentyn-5-ol. To a solution of TMEDA (3.1 mL, 20.5 mmol) and THF (80 mL), maintained at –20 °C, was added 2-butyne (1.6 mL, 20.4 mmol) followed by *n*-BuLi (9.4 mL of 2.15 M in hexanes, 20.2 mmol). The solution was allowed to stir for 2.5 h at this temperature and then cooled to –78 °C (dry ice–acetone bath) and treated dropwise with a solution of benzaldehyde (2.5 mL, 24.6 mmol) in THF (20 mL). After the solution was stirred for 30 min at –78 °C, 1 h at –20 °C, and 1.5 h at room temeprature, 2 N HCl was added to acidify the solution. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phase was washed with aqueous sodium bisulfite, dried over Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (elution with ether–hexanes (1:5)) afforded the desired alcohol as colorless oil (1.37 g, 42%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.77 (t, J = 2.5 Hz, 3H), 2.50–2.57 (m, 2H), 4.75 (t, J = 6.5 Hz, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$)

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Degradative Routes to Electrophilic CD-Substructures of Taxol

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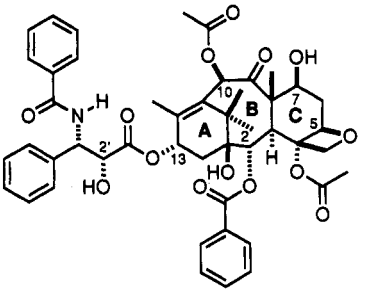
Various electrophilic derivatives containing the CD-substructure of taxol and bearing suitable appendages for joining to potential A-ring synthons have been prepared. This chemistry points to the stability of the oxetane to a variety of reaction conditions.

One of the synthetic routes to taxol (1),[2,3] and analogs thereof, involves joining A and CD constructs in a bimolecular fashion and generating the B-ring via a cyclization reaction.[4,5] In previous reports from this laboratory we have described methods for the presentation of extensively functionalized versions of the A-ring either as an electrophile at a pendant C-2 carbon[6] or as a nucleophile at C-1 or C-11 carbon (taxol numbering).[4d,6] Furthermore, we have also reported the synthesis of ketone **2**,[4a] which contains the full CD-substructure of taxol and can be obtained in enantiomerically pure form from chiral Wieland–Miescher ketone.[7] In this report we describe experiments, starting from ketone **2**, which allow for presentation of the CD segment as an electrophile suitable for coupling to appropriate A-ring constructs. These results demonstrate the remarkable stability of the oxetane to a variety of chemical operations.

Regioselective α-hydroxylation of the ketone function of **2** was accomplished through deprotonation with KHMDS and treatment of the resultant enolate with the known oxaziridine **3** (Scheme 1).[8] There was obtained a 63% yield of α-hydroxy ketone **4** accompanied by a 10% yield of its C-4 regioisomer. This mixture was then oxidized with lead tetraacetate (LTA)[9] in benzene–MeOH followed by chromatographic purification to yield the aldehyde ester **5** (68%).



Taxol
1

An alternative degradative mode started with the reaction of enone **6b** with catalytic OsO_4.[10] By using the conditions outlined in Scheme I, a 77% yield of the 1α,2α-diol **7** was obtained. Oxidation of this compound with LTA results, not unexpectedly,[11] in excision of C-2 and formation of the noraldehyde ester **8**.

Appropriate processing of enone **6a** also allows for access to a more functionalized version of aldehyde ester **5** (Scheme 2). Thus, nucleophilic epoxidation of this enone afforded an 82% yield of epoxy ketone **9**. Subjection of this compound to a Wharton rearrangement sequence[12] led to diol **10**. Two-fold silylation of the hydroxyl groups produced allylic silyl ether **11** which upon ozonolysis in methanol followed by dehydration with Ac_2O–Et_3N gave rise, predictably,[13] to the aldehyde ester **12** (65% overall).

We have also prepared CD coupling candidates from enone **6a**, where fragmentation has occurred between C-3 and C-4 (decalin numbering). In this way the CD-substructure is presented as a three-carbon ester and a one-carbon aldehyde. Two permutations are described (Scheme 3). Reaction of alcohol **6a** with NaH followed by benzyl bromide afforded benzyl ether **6c** in good yield. Hydroxylation of the latter via oxaziridine **3** afforded the 4α-hydroxy enone **13** in 83% yield. This compound on oxidation with LTA in benzene–MeOH yielded enoate aldehyde **14**. Alternatively, hydroxylation of the double bond of enone **13** gave rise to triol **15** in 49% yield. The vicinal 1α,2α-diol linkage was engaged through the agency

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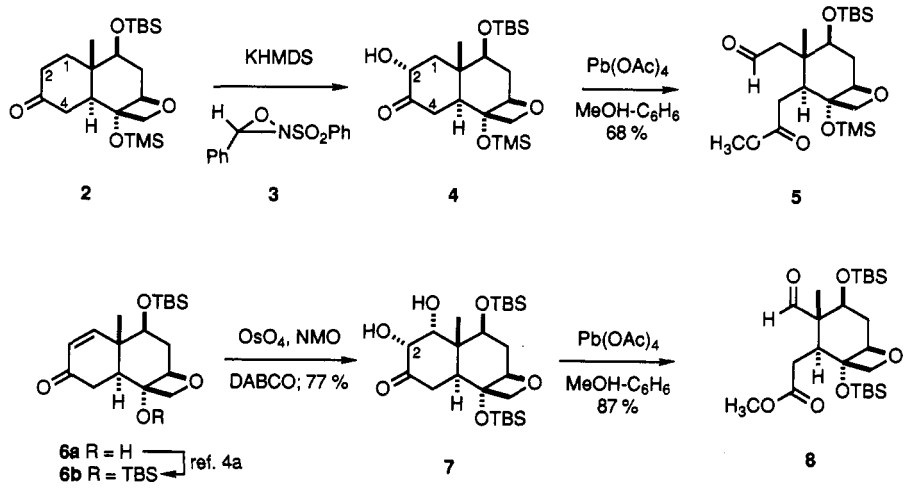
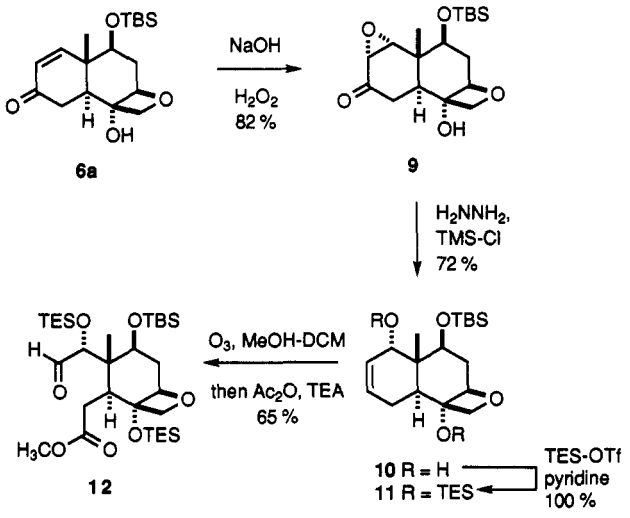
Scheme 1



Scheme 2



of dimethoxy propane affording acetonide **16a** (68%) and the fully protected compound **16b** (31%). The latter was converted to **16a** on treatment with TsOH in benzene at rt. Oxidation of α-hydroxy ketone **16a** with LTA under the usual conditions led to aldehyde ester **17** in 80% yield.

In summary these sequences illustrate the versatility of ketone **2** and enones **6** as intermediates for the preparation of electrophilic CD substrates for coupling with suitable A-ring nucleophiles. These findings also serve to underscore the stability of the oxetane linkage and suggest that this moiety can be incorporated at an early stage of the synthesis and sustained for many operations. Though the chemistry reported above was in fact carried out on racemic material, enantiomerically pure precursors of ketone **2** and ultimately enone **6** have been prepared on a substantial scale. The use of oxetane constructs described here and related structures, in coupling reactions with various A-ring based nucleophiles, are the subject of continuing investigations.

Experimental Section

General. Air and/or moisture-sensitive reactions were conducted under an atmosphere of dry nitrogen or argon using either flame-dried or oven-dried glassware and standard syringe/septa techniques. Methylene chloride was distilled from calcium hydride and THF was distilled from sodium/benzophenone. All other reagents were commercial reagent grade and were used without further purification unless otherwise stated. Melting points were measured using an Electrothermal IA 9100 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using neat samples on a Perkin-Elmer 1600 Series Fourier Transform spectrophotometer. NMR (^{1}H and ^{13}C) spectra were recorded in the indicated solvents using a Bruker AMX-400 spectrometer. Flash chromatography was performed using EM Science silica gel 60 (230–400) mesh.

Aldehyde Ester 5. Ketone **2** (55.5 mg; 0.13 mmol) in dry THF (3 mL) was cooled to −78 °C whereupon KHMDS in toluene (0.5 M; 0.40 mL; 0.20 mmol) was added dropwise. After 1 h, oxaziridine **3** (53.2 mg; 0.22 mmol) was added as a THF solution (2 mL) via cannula. This solution was stirred further at −78 °C for 1 h and then quenched with saturated NH_4Cl (10 mL). After warming to rt, the reaction was extracted with ether (2 × 15 mL), and the combined ether layers were washed with saturated NaCl (1 × 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The semisolid crude product was chromatographed on SiO_2, eluting with 1:4/EtOAc:hexanes to give the desired C-2 α-hydroxy ketone **4** contaminated with approximately 10–15% of the C-4 regioisomer (42.1 mg; 73%).

This mixture of α-hydroxy ketones (15.8 mg; 0.037 mmol) was dissolved in a 1:1/MeOH:benzene mixture (2 mL) and cooled to 0 °C, and solid LTA (17.8 mg; 0.040 mmol) was added. TLC indicated the reaction was complete within 5 min of stirring. Ether and Celite were added, and the cold suspension was filtered through a silica gel pad (ether wash). Crude NMR analysis revealed the product to be composed of a mixture of regioisomeric aldehyde esters in a ratio of 7.5:1. Purification on SiO_2, eluting with 1:9/Et_2O:petroleum ether gave pure aldehyde ester **5** (11.5 mg; 68%). The other regioisomer (approximately 10–15% by NMR) was not isolated. TLC:R_f = 0.35 (1:4/EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 9.76 (br s, 1H), 4.88–4.91 (m, 1H), 4.47–4.49 (d, 1H, J = 7.3 Hz), 4.37–4.39 (d, 1H, J = 7.3 Hz), 4.05–4.10 (m, 1H), 3.62 (s, 3H), 2.15–2.55 (m, 5H), 1.85–1.95 (m, 1H), 1.19 (s, 3H), 0.87 (s, 9H), 0.19 (s, 9H), 0.06 (s, 3H), 0.007 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 201.3, 173.3, 85.6, 79.1, 72.0, 51.8, 50.4, 46.7, 42.3, 36.9, 31.1, 29.7, 25.9, 18.0, 13.9, 1.8, −3.9, −4.8. IR (cm^{-1}): 1740, 1719, 1252, 1094. HRMS: calcd for $C_{22}H_{42}O_6Si$ (M^+ + 1) 459.2598; found 459.2597.

Dihydroxy Ketone 7. Enone **6b** (18.3 mg; 0.040 mmol), DABCO (16.8 mg; 0.15 mmol), and NMO (28.6 mg; 0.24 mmol) were dissolved in a 4:1 mixture of THF–H_2O (1 mL) and treated with OsO_4 in tBuOH (2.5 wt%; 0.023 mL; 0.0023 mmol). The resulting orange-brown solution was stirred in a preheated oil bath (temp = 40 °C) for 5 h. The reaction was then cooled to rt, quenched with 1:1/saturated $NaHSO_3$:saturated NaCl (10 mL) and extracted with CH_2Cl_2 (6 × 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography on SiO_2 using 1:4/EtOAc:hexanes as an eluant gave pure dihydroxy ketone **7** (15.1 mg; 77%). TLC: R_f = 0.75 (1:24/MeOH:CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 4.84–4.86 (d, 1H, J = 8.1 Hz), 4.40–4.42 (d, 1H, J = 7.2 Hz), 4.36–4.37 (m, 1H), 4.33–4.35 (d, 1H, J = 7.2 Hz), 4.15–4.20 (m, 1H), 4.09–4.10 (m, 1H),