($CHCl_3$) 1760, 1730, 1650, cm^{-1}; MS, *m/e* (relative intensity) 224 (M, 3.9), 152 (43.7), 121 (43.8), 93 (100.0); 250-MHz ^1H NMR ($CDCl_3$) δ 1.24 (3 H, d, J = 6.3 Hz), 1.36 (3 H, d, J = 7.4 Hz), 2.29 (H_5, m), 2.98 (H_1, H_6, m), 3.01 (H_2, m), 3.72 (3 H, s), 4.07 (H_9, m), 5.84 (H_4, ddd, $J_{3,4}$ = 9.3 Hz, J' = 3.4 Hz, J'' = 3.0 Hz), 6.14 (H_3, ddd, $J_{3,4}$ = 9.3 Hz, J' = 3.3 Hz, J'' = 2.6 Hz); 63-MHz ^{13}C NMR ($CDCl_3$) δ 16.3, 22.1, 30.5, 41.6, 44.0, 44.9, 51.7, 78.0, 125.6, 136.1, 172.2, 176.2. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19. Found: C, 64.24; H, 7.25.

Methyl (1*R,2*S**,5*R**,6*R**)-5-methyl-7-oxobicyclo[4.3.0]-non-3-ene-2-carboxylate (25)**: entry 16, Table I; yield, 273 mg (20%); bath temperature 100 °C (0.01 Torr); IR (film) 1730 (br), 1660 cm^{-1}; MS *m/e* (relative intensity) 208 (M, 22.3), 148 (37.9), 106 (37.8), 105 (100.0), 93 (85.2); the structure of adduct **25** has been unambiguously established by using ^1H-^1H and ^1H-^{13}C 2D NMR spectroscopy; 250-MHz ^1H NMR ($CDCl_3$) δ 0.96 (3 H, d, J = 7.5 Hz), 1.50 (H_9, m), 1.73 ($H_{9'}$, m), 2.00 (H_8, $H_{8'}$, m), 2.29 (H_5, m), 2.44 (H_6, dd, $J_{1,6} = J_{5,6}$ = 8.0 Hz), 2.80 (H_1, dddd, $J_{1,9}$ = 9.6 Hz, $J_{1,6} = J_{1,9'}$ = 8.0 Hz, $J_{1,2}$ = 6.6 Hz), 3.20 (H_2, ddd, $J_{1,2}$ = 6.6 Hz, $J_{2,3}$ = 3.2 Hz, $J_{2,4}$ = 2.5 Hz), 3.61 (3 H, s), 5.63 (H_3, ddd, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 3.2 Hz, $J_{3,5}$ = 3.1 Hz), 5.84 (H_4, ddd, $J_{3,4}$ = 10.0 Hz, $J_{2,4} = J_{4,5}$ = 2.5 Hz); 63-MHz ^{13}C NMR ($CDCl_3$) δ 18.1, 23.8, 28.1, 36.8, 38.5, 41.4, 48.7, 51.5, 122.9, 133.5, 172.9, 219.3; HRMS calcd for $C_{12}H_{16}O_3$ *m/e* 208.1099, found 208.1087. This compound is accompanied by ca. 15% of an unidentified isomer (^1H and ^{13}C NMR). The proton and ^{13}C NMR spectra are available as supplementary material for this work.

Methyl 3-[(1*R,2*R**)- and -(1*S**,2*R**)-2-(methoxycarbonyl)cyclohex-3-en-1-yl]-(*E*)-propenoate (27)**: entry 17, Table I; yield, 34 mg, (8%); IR (film) 1740 (sh), 1730, 1660, 1655 (sh) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.9 (1 H, m), 1.96 (1 H, m), 2.11 (2 H, m), 2.83 (1 H, m), 3.30 (1 H, m), 3.64 (3 H, s), 3.70 (3 H, s), 5.86 (3 H, m), 7.00 (1 H, dd, J = 15.75 Hz, J' = 8.0 Hz); 63-MHz ^{13}C NMR ($CDCl_3$) δ 16.7, 20.7, 33.8, 40.4, 47.0, 47.3, 117.3, 118.7, 125.5, 144.7, 162.5, 168.2. This compound has been previously described by House.[27]

Acknowledgment. Financial support from DGICYT, Spain (Project PB88-0241), and "Acción Integrada Hispano-Francesa" (1989 and 1990) is gratefully acknowledged.

Supplementary Material Available: Copy of HRMS for **25** and copies of ^{13}C and ^1H NMR spectra for **22** and **25** (5 pages). Ordering information is given on any current masthead page.

(27) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1963**, *28*, 27.

Stereochemical Control in Reactions of Nucleophiles with Oxocarbenium Ions Formed by Intramolecular Opening of Activated Epoxides by Neighboring Carbonyl Groups

Christopher H. Fotsch and A. Richard Chamberlin*

Department of Chemistry, University of California, Irvine, California 92717

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Tandem cyclization/reduction and cyclization/alkylation processes for the stereoselective synthesis of 2,5-disubstituted tetrahydrofurans, 2,6-disubstituted tetrahydropyrans, and 2,7-disubstituted oxepanes are described. In the presence of Lewis acids or TMSOTf, γ,δ-, δ,ϵ- and ϵ,ζ-epoxy ketones and esters undergo cyclization to the corresponding oxocarbenium ions, which react in situ with a variety of organosilanes and organoaluminum reagents to give the substituted oxacyclic products. For the synthesis of substituted tetrahydrofurans, the stereochemical control of the addition process was much higher with TMSOTf than BF_3·OEt_2.

Introduction

The synthesis of functionalized tetrahydrofuran and tetrahydropyran rings has received considerable attention because of the many biologically active compounds that contain these ring systems.[1] The polyether antibiotics, which perhaps best exemplify this group, contain an array of tetrahydrofuran and tetrahydropyran rings interconnected at the carbons adjacent to the oxacyclic ring oxygens.[2] The synthesis of these ionophores has spawned the development of many methods for the synthesis of 2,5-disubstituted tetrahydrofurans and 2,6-disubstituted tetrahydropyrans.[3] For instance, the synthesis of one tetrahydrofuran ring of lasalocid A relies on the acid-induced ring closure of an epoxy alcohol[14] prepared by hydroxyl-directed epoxidation of the corresponding bishomoallylic alcohol (eq 1). In this case the ratio of the tetrahydrofuran diastereomers is determined in the epoxidation step, which requires good long-range acyclic stereochemical control. An alternative strategy that avoids this requirement makes use of C-glycosylation techniques (eq 2)[3i,k,l] to join one

(1) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982. *Chemical Structures of Interest to the Division of Cancer Treatment*, Vol. VI, Compounds in Development-Drugs with Clinical Activity, Lomax, N. R.; Narayanan, V. L.; National Cancer Institute, Washington, D. C., 1988. For a review on macrolide antibiotic synthesis see: Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, 1984; pp 127-198.

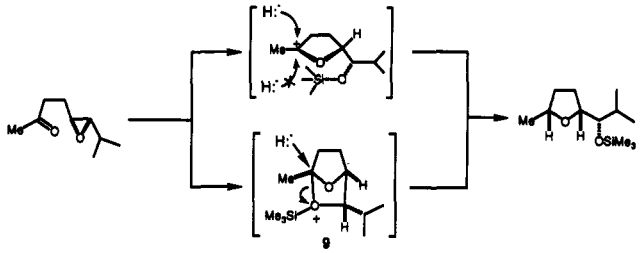
(2) Wierenga, W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1981; pp 287-351. Westly, J. W. In *Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control*; Grayson, M., Ed.; John Wiley and Sons: New York, 1982; pp 301-318.

(3) For a general review, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825. For recent examples of cyclization techniques see: (b) Tamooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6339. (c) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204. (d) Nicolaou, K. C.; Hwang, C. K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. (e) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483. (f) McCormick, M.; Monahan, R. III; Soria, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1989**, *54*, 4485. (g) Bartlett, P. A.; Chapuis, C. *J. Org. Chem.* **1986**, *51*, 2799. (h) Bartlett, P. A.; Ting, P. C. *J. Am. Chem. Soc.* **1984**, *106*, 2668. For recent examples of noncyclization techniques see: (i) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698. (j) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034. (k) Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc. Chem. Comm.* **1984**, 1153 and 1155. (l) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

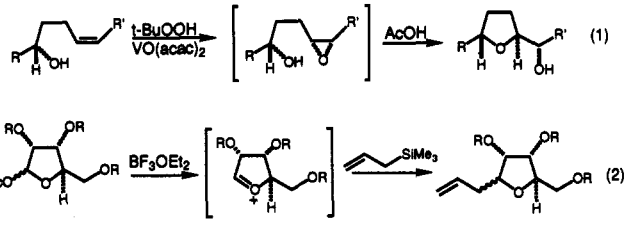
(4) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933.

0022-3263/91/1956-4141$02.50/0

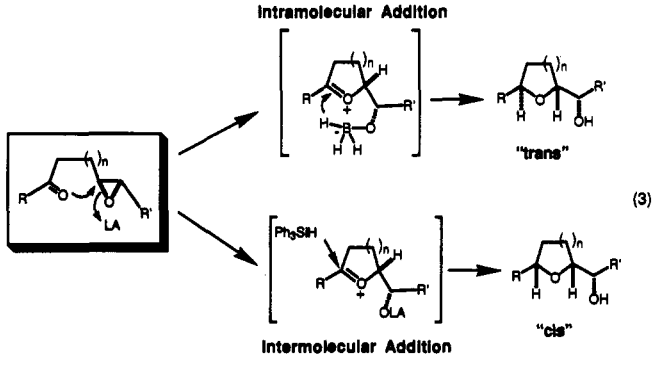
Scheme I



appendage to a preformed ring[5] in the step that determines the 2,5-stereochemistry.

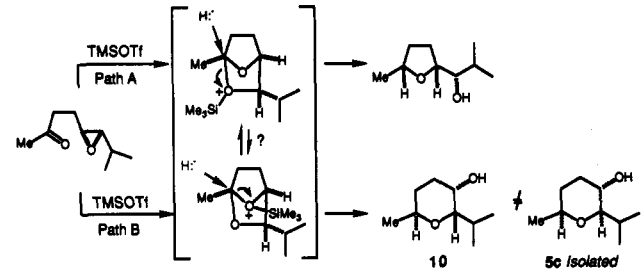


We have previously reported a hybrid of these two techniques in which treatment of γ,δ-substituted epoxy ketones with Lewis acids gives intermediate cyclic oxocarbenium ions (eq 3) that are stereoselectively reduced in situ.[6] The tetrahydrofuran stereochemistry in this case is controlled by the appendage in the 2-position and is a function of whether the reduction is intra- or intermolecular. Thus, $BH_3{\cdot}SMe_2$ acts as both a Lewis acid and a hydride source to give intramolecular reduction favoring the formation of "trans" tetrahydrofuran derivatives. On the other hand, intermolecular reduction from the opposite face of the oxocarbenium ion gives predominantly the "cis" product. The stereochemical relationship between the exocyclic hydroxyl group and the C2 appendage is determined by the geometry of the epoxide since opening of the Lewis acid complexed form is stereospecific.[7]



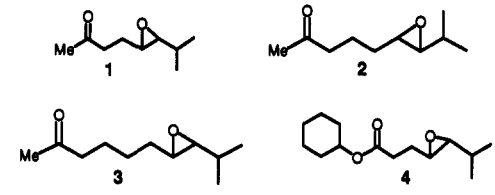
Because the stereoselectivity of the intermolecular reductions was not particularly high (~5:1), we have examined the process in more detail in hopes of improving the selectivity for 2,5-disubstituted tetrahydrofuran formation. In addition, we have investigated other nucleophiles in the addition process, so that not only reductions but also carbon–carbon bond formation might be accomplished. Formation of the homologous six- and seven-membered rings has also been tested successfully, as has the use of esters rather than ketone groups as internal nucleophiles.

Scheme II



Results and Discussion

In order to investigate more extensively the intermolecular reactions, four cyclization precursors were prepared by standard methods (see the Supplementary Material for details): the ketones **1**, **2**, and **3** and the ester **4**. With



these in hand, we reevaluated the hydride addition reaction for the five-membered ring precursor **1**. When treated with Ph_3SiH followed by the addition of $BF_3{\cdot}OEt_2$, the γ,δ-epoxy ketone **1** cyclized to give predominantly the cis 2,5-disubstituted tetrahydrofuran **5a**, along with the trans product **5b** and the six-membered ring product **5c**, in a 6:1:2 ratio (Table I). Interestingly, the stereoselectivity (cis vs trans) and the regioselectivity (five-membered ring formation vs six-membered ring formation) of this reaction improved a great deal when TMSOTf was employed in place of $BF_3{\cdot}OEt_2$. Cyclization and reduction with TMSOTf and Ph_3SiH gave 81% of cyclization products **5a**, **5b**, and **5c** favoring the formation of the cis isomer in a 20:1:1.3 ratio over trans isomer **5b** and six-membered ring product **5c**.

The enhancement observed with TMSOTf might be explained by the greater steric hindrance of hydride attack by the bulkier silyl substituent[8] or by the intermediacy of a cyclic ketal **9**, which could open with inversion (see Scheme I).[9] If the latter is true, the six-membered ring product (**5c**) would be formed from the same ketal intermediate through a ring cleavage of the alternative C–O bond (see Scheme II, path B), and the product generated by this process would be the trans 2,6-disubstituted tetrahydropyran **10**. Through decoupling experiments on the isolated six-membered ring product **5c** (see the Experimental Section), we were able to determine that the relative stereochemistry at the C2 and C6 positions is cis, which indicates that the isolated six-membered ring product **5c** was *not* derived by an S_N2-like addition process to the cyclic ketal **9**. We therefore conclude that the stereochemistry of the major 2,5-disubstituted tetrahydrofuran product is most likely established by attack of the reducing agent on the oxocarbenium ion, rather than the silylated ketal.

(5) Cuppe, T. L.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115.

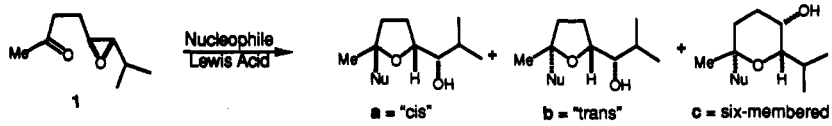
(6) Chamberlin, A. R.; Mulholland, R. L., Jr. *J. Org. Chem.* **1988**, *53*, 1082.

(7) Examples of opening epoxides with clean inversion are summarized in a review: Gorzynski Smith, J. *Synthesis* **1984**, 629.

(8) For an example of a large ether group hindering attack onto a five-membered ring, see: Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733. For a review on the steric influences of a TMS group, see: Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599.

(9) Denmark and co-workers observed that TMSOTf gave higher selectivities than $BF_3{\cdot}OEt_2$ in addition to acetals. See: Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

Table I. Products from Lewis Acid Catalyzed Cyclizations of Ketone 1 with Various Silyl and Organoaluminum Nucleophiles



entry	nucleophile	Lewis acid	no.	Nu	a:b:c[d]	yield (%)
1	Ph_3SiH	$F_3B{\cdot}OEt_2$[a]	5	H	6:1:2	67
2	Ph_3SiH	TMSOTf[a]	5	H	20:1:1.3	81
3		TMSOTf[b]	6		12:2:1	80
4		TMSOTf[c]	7		20:1	62
5	TMSCN	TMSOTf[a]	8		4:1	68
6	$AlMe_3$	$F_3B{\cdot}OEt_2$[a]	11		-	59
7	$AlEt_3$	$F_3B{\cdot}OEt_2$[a]	12 (5)		7:1:4 (3:1)	68[e]
8	$Et_2AlC{\equiv}CPh$	$F_3B{\cdot}OEt_2$[a]	13	C≡CPh	7:1	60
9	Et_2AlCN	$F_3B{\cdot}OEt_2$[a]	8	CN	1:1	65

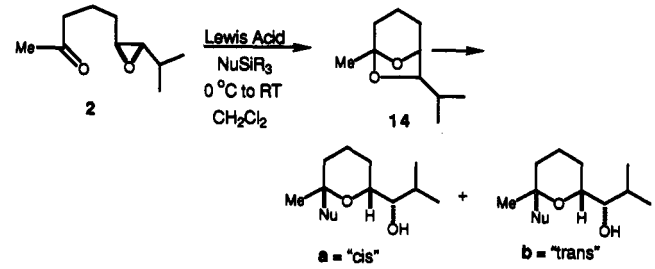
[a] -78 to 0 °C, CH_2Cl_2. [b] -45 to 0 °C, CH_3CN. [c] -98 to 0 °C, CH_2Cl_2. [d] Relative stereochemistry was determined by difference NOE and decoupling experiments that are described in the Experimental Section and supplementary material. [e] Yield of ethyl addition products **12**.

In addition to these hydride additions, three other nucleophiles, allyltrimethylsilane, α-(trimethylsiloxy)styrene, and trimethylsilyl cyanide, also added well under the TMSOTf conditions. Interestingly, only during the addition of allyltrimethylsilane were any six-membered ring products observed (determined by examination of ^1H NMR spectra of crude reaction mixtures). Addition of the trimethylsilyl enol ether of acetophenone gave the best selectivity (20:1 cis vs trans), while TMSCN was only moderately selective (4:1 cis vs trans). Addition of the nitrile may in fact be reversible, which could account for the lower selectivity.

Besides these silane-based nucleophiles, organoaluminum reagents were tested, since they are known to add to other stabilized carbocations such as iminium ions.[10] However, only a 6% yield of the dimethyltetrahydrofuran **11** was produced when the γ,δ-epoxy ketone **1** was treated with Me_3Al. If, however, $BF_3{\cdot}OEt_2$ was added to the organoaluminum prior to addition of the ketone, the yield of **11** increased dramatically, to 59% (TMSOTf gave lower yields). Besides adding alkyl groups, aluminum reagents with β-hydrogens (e.g. iBu_3Al, Et_3Al)[11] donated hydride to the oxocarbenium ion, giving the reduction products **5a** and **5b** along with alkylation products **12a** and **12b**. Diethylaluminum phenylacetylide added in fair yield with good stereoselectivity (60%, 7:1 cis vs trans), but Et_2AlCN—although transferring cyanide fairly cleanly (65%)—gave no selectivity.

Returning to the optimized TMSOTf conditions, we tested the process for the formation of larger rings. In contrast to the five-membered ring cases, the precursor **2** when treated with TMSOTf and $HSiPh_3$ at 0 °C afforded the cyclic ketal **14**, rather than the tetrahydropyran, as the only product. When treated with $BF_3{\cdot}OEt_2$ and Ph_3SiH at 0 °C for 18 h; however, the ketone **2** was converted into the desired cis tetrahydropyran product **15a** in 81% yield (trans isomer could not be detected by ^1H NMR or GC–MS analyses). Under the $BF_3{\cdot}OEt_2$ conditions, the ketal **14** was also converted into **15a**, which indicates that the cyclic ketal could be an intermediate in this process. The high level of stereochemical induction in this example is most likely due to the well-known stereoelectronic preference for axial attack on endocyclic six-membered ring π-bonds.[12] A similarly high degree of stereochemical control (49:1) was also observed in the addition of allyltrimethylsilane to the oxocarbenium ion derived from **2**.

Table II. Products from Lewis Acid Catalyzed Cyclizations of Ketone 2 with Various Silyl Nucleophiles



entry	Lewis acid	$NuSiR_3$	no.	a:b[a]	yield (%)
1	TMSOTf	$HSiPh_3$	14	-	47
2	$F_3B{\cdot}OEt_2$	$HSiPh_3$	15	>99:1	81
3	$F_3B{\cdot}OEt_2$		16	49:1	74
4	$F_3B{\cdot}OEt_2$	$NCSiMe_3$	17	1:2	47
5	$F_3B{\cdot}OEt_2$	$NCSiMe_3$[b]	17	1:20	87

[a] Relative stereochemistry was determined by difference NOE and decoupling experiments that are described in the Experimental Section and supplementary material. [b] Reaction conditions: -78 °C, 8 h; slow warming to -19 °C, 40 h.

High levels of selectivity were not observed with TMSCN under similar conditions. When treated with $BF_3{\cdot}OEt_2$ and TMSCN at 0–20 °C for 18 h, the δ,ε-epoxy ketone **2** afforded a meager 2:1 mixture of diastereomers with **17b**, the trans isomer being the major product, a result which is not consistent with the kinetically controlled stereochemical preferences observed for most other nucleophiles. To check for possible equilibration of an initially formed mixture, the ketone **2** was treated with TMSCN and $BF_3{\cdot}OEt_2$ at lower temperatures (-78 to -19 °C). Under these conditions the stereoselectivity of the reaction increased to >20:1 favoring **17b**, which indicates that CN addition is reversible. Why the trans isomer **17b** is favored over the cis isomer **17a** is still not clear, but energy minimization of the two isomers (QUANTA)[13] does

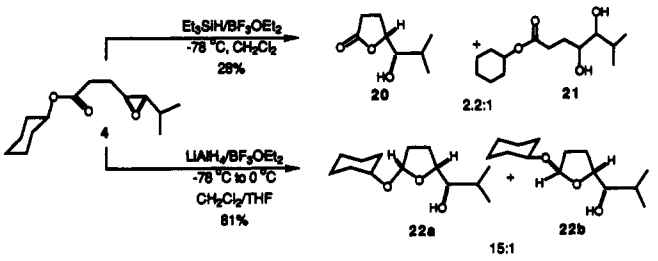
(10) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sukane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

(11) Both iBu_3Al and Et_2Al can act as reducing agents by delivering the β-hydrogen and eliminating isobutene and ethylene, respectively. See: House, H. O. *Modern Synthetic Reactions*; Benjamin/Cummings Publishing; Menlo Park, CA 1972; p 67.

(12) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 211.

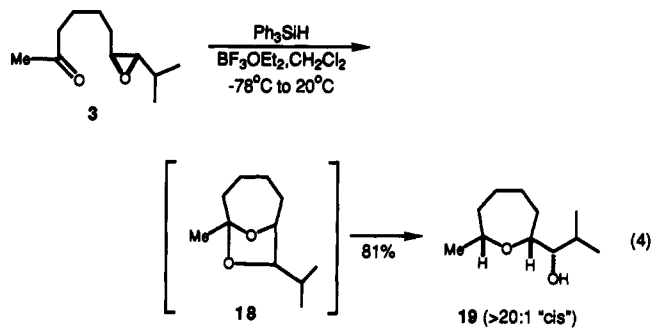
(13) Minimizations were calculated from Polygen's QUANTA using the CHARM minimization routine.

Scheme III



show that **17b** is indeed more stable than **17a**.

Seven-membered rings could also be prepared under the BF_3·OEt_2/$HSiPh_3$ conditions (eq 4). Again, longer reaction times and higher temperatures were required to complete the cyclization; otherwise the major product was a cyclic ketal, **18**. The stereoselectivity for this addition again was very good (>20:1). Unfortunately, attempts to add allyltrimethylsilane or TMSCN resulted in the isolation of <5% of desired products.



(4)

Besides testing ketone precursors in these studies, we were interested in the stereoselective formation of cyclic acetals from γ,δ-epoxy esters. Initial attempts with ethyl esters[14] resulted in dealkylation of the cationic intermediate to give the corresponding lactone **20** and none of the desired acetal. To circumvent this problem, the cyclohexyl ester **4** was prepared, anticipating that the corresponding oxocarbenium ion intermediate would be less likely to undergo dealkylation than its methyl or ethyl counterpart (Scheme III). Interestingly, initial attempts to cyclize/reduce the precursor **4** with Et_3SiH and BF_3·OEt_2 still give significant amounts of the lactone **20**, as well as the diol **21**. Believing that perhaps this more stabilized oxocarbenium ion might be slow to undergo reduction with the weak hydride sources normally employed, lithium aluminum hydride was added to a solution of the ester **4** and BF_3·OEt_2. It was gratifying to observe under these condition the formation of the cis acetal **22a** in a 15:1 preponderance over the trans isomer **22b**, in an 81% yield. Although this is the only example attempted thus far, this procedure is a potentially useful one for accomplishing the sometimes difficult task of controlling cyclic stereochemistry.[15]

Conclusions

The success or failure of nucleophilic addition to an oxocarbenium ion intermediate generated by the cyclization process described in the paper depends on the size of the ring being formed. Many different nucleophiles (Ph_3SiH, (allyl)$SiMe_3$, TMSCN, $Ph(Me_3SiO)CCH_3$, $AlMe_3$, $AlEt_3$, $Et_2AlC{\equiv}CPh$) could be added to the five-membered oxocarbenium ion intermediate; presumably, a ketal intermediate is quickly opened by TMSOTf and the resultant cation undergoes nucleophilic addition. However, for the six-membered ring precursor, a more stable ketal intermediate is formed, which requires more vigorous reaction conditions to re-form the oxocarbenium ion that ultimately reacts with the nucleophile. Nonetheless, several highly stereoselective cyclization/additions were observed. With the seven-membered ring precursor, the ketal intermediate was so unreactive that only triphenylsilane under forcing reaction conditions would produce the desired product in good yields. Finally, the process can be extended to carbonyl precursors other than ketones leading to the stereoselective synthesis of a cyclic acetal from a γ,δ-epoxy ester. These and other carbonyl precursors (e.g. amides, imines, thioesters, etc.) are currently under investigation.

Experimental Section

General. Unless otherwise mentioned, starting materials were obtained from commercial sources and used without further purification. When a solvent is specified as being dry, it has been distilled from CaH_2 or benzophenone ketyl. When air-water-sensitive reagents were used, an inert atmosphere was maintained by using argon with an on-line Ca_2SO_4 drying tube, and reactions were performed in flame-dried or oven-dried glassware. Analytically pure samples were obtained by flash chromatography (FC) on ICN 200–400-mesh silica, or for small scale purification, Chromatotron radial chromatography (RC) on Kieselgel 60 PF_{254} silica was used. Thin-layer chromatography (TLC) was performed on 0.25-mm Merck precoated silica plates (60 F-254). Gas chromatography (GC) analysis was done using a Hewlett-Packard Model 5830A GC equipped with a cross-linked 50% phenyl methyl silicone capillary column. Nonstandard abbreviations for ^1H NMR multiplicities are as follows: app = apparent, qn = quintet, sex = sextet, sep = septet, ovrlp = overlapping.

General Procedure Notes for Cyclizations. All reactions were carried out in base-washed and flame-dried glassware and were run under a positive Ar flow. CH_2Cl_2 was dried by storing over activated 3-Å sieves. Acetonitrile was distilled from CaH_2 and stored over activated 3-Å sieves. BF_3·OEt_2 was distilled and stored over CaH_2. Except where mentioned, all reactions were quenched with $NaHCO_3$, extracted three times with ether, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. When TMSCN was used, 1 M HCl was also used to wash the organic phase. All products obtained were clear to faint yellow oils.

***rel*-(2*R*,5*R*,α*S*)-α-(1-Methylethyl)-5-methyltetrahydrofuran-2-methanol (5a).** Triphenylsilane (dried for 18 h under heat and vacuum, 210 mg, 0.8 mmol) in 1.9 mL of CH_2Cl_2 was added to a solution of ketone **1** (31 mg, 0.2 mmol) in 1 mL of CH_2Cl_2 at −78 °C. After 5 min, trimethylsilyl triflate (TMSOTf, 0.09 mL, 0.44 mmol) was added dropwise to the solution. The temperature was maintained at −78 °C for 6 h and then slowly warmed to 0 °C over 12 h. Saturated $NaHCO_3$ (1 mL) was added, and the crude reaction was purified using the workup conditions described above. A ^1H NMR spectrum of the sample before purification indicated that the product ratio was 20:1:1.3 cis:trans:six-membered ring. Purification by RC (10:1 pentane–ether and then 5:1 pentane–ether) afforded two samples. The cis diastereomer **5a** was separated from a mixture of the trans isomer **5b** and six-membered ring product **5c** (trans and six-membered ring products could be partially separated on RC by using 9.2:1.6:1 pentane–ether–CH_2Cl_2). The overall yield of five-membered ring products was 81% (26 mg, 0.18 mmol). Data for **5a**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (2 H, m, H-5, H-2), 3.43 (1 H, dd, J = 8, 3 Hz, H-α), 2.17 (1 H, br s, OH), 1.99 (1 H, m, H-4(β)), 1.88 (1 H, m, H-3(α)), 1.75 (1 H, m, H-3(β)), 1.65 (1 H, m, H-β), 1.43 (1 H, m, H-4(α)), 1.23 (3 H, d, J = 6 Hz), 1.02 (3 H, d, J = 6 Hz), 0.87 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.48, 76.45, 75.16, 33.16, 30.47, 23.83, 21.01, 19.18, 18.61; IR (neat) 3450 (br), 2970, 2880, 1300, 1250, 1185 cm^{-1}; MS (EI, 70 eV) m/e 158 (M^+, 0.04), 115 (M − C_3H_7, 4.49), 85 (100); HRMS (CI, 70 eV) m/e

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(15) *Carbohydrate Chemistry*; Williams, N. R., Ed.; Royal Society of Chemistry, 1988; Vol. 20, pp 62–66. See also: Kobayashi, S.; Koide, K.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 2435 and references therein.

159.1385 (159.1369 calcd for $C_9H_{18}O_2$ + H). Data for **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (2 H, m, H-5, H-2), 3.43 (1 H, dd, J = 8, 3.8 Hz, H-α), 2.14 (1 H, br s, OH), 2.06 (1 H, m, H-4(β)), 1.87 (2 H, m, H-3), 1.64 (1 H, m, H-β), 1.49 (1 H, m, H-4(α)), 1.22 (3 H, d, J = 6 Hz), 1.01 (3 H, d, J = 6 Hz), 0.88 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 79.69, 76.96, 75.68, 34.15, 30.34, 25.12, 21.29, 19.04, 18.72; IR (neat) 3460 (br), 2970, 2880, 1305, 1250, 1080 cm^{-1}; MS (EI, 70 eV) m/e 158 (M^+, 0.13) 116 (4.48), 115 (M - C_3H_7, 2.89), 85 (100); HRMS (CI, 70 eV) m/e 159.1387 (159.1369 calcd for $C_9H_{18}O_2$ + H). ***rel*-(2*R*,3*S*,6*S*)-6-Methyl-2-(1-methylethyl)tetrahydro-2*H*-pyran-3-ol (5c)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.45 (1 H, ddd, J_{H-H6} = 10.5 Hz, J_{H-H2} = 10 Hz, J_{H-H4a} = 4 Hz, H-3), 3.37 (1 H, ovrlp dd of q, J_{H-H5a} = 10.5 Hz, $J_{H-H\alpha}$ = 6 Hz, J_{H-H5b} = 2 Hz, H-6), 2.92 (1 H, dd, J_{H-H3} = 9.5 Hz, $J_{H-H\alpha}$ = 2.5 Hz, H-2), 2.08–2.05 (1 H, m, H-4(α)), 2.05–2.01 (1 H, m, $HCMe_2$) 1.66 (1 H, d of m, J = 14 Hz, H-5(β)), 1.59 (1 H, br s, OH), 1.43 (1 H, m, H-4(β)), 1.28 (1 H, m, H-5(α)), 1.14 (3 H, d, J = 6.5 Hz), 1.01 (3 H, d, J = 7 Hz), 0.91 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.49, 73.28, 67.62, 33.46, 32.97, 27.87, 21.31, 19.78, 15.33; IR (neat) 3356 (br), 2934, 1388, 1366, 1087, 1034 cm^{-1}; MS (CI, 70 eV) m/e 159 (MH^+, 28.24), 141 (M - OH, 24.93), 85 (100); HRMS (CI, 70 eV) m/e 159.1372 (159.1385 calcd for $C_9H_{18}O_2$ + H).

***rel*-(2*R*,5*S*,α*S*)-5-Methyl-5-(2-propenyl)-α-(1-methylethyl)tetrahydrofuran-2-methanol (6a).** A solution of ketone 1 (31 mg, 0.20 mmol) and allyltrimethylsilane (0.13 mL, 0.8 mmol) in CH_3CN (0.6 mL) was stirred at −40 °C for 5 min. TMSOTf (0.09 mL, 0.44 mmol) was added dropwise. The reaction mixture was stirred at −45 °C for 2 h and quenched with saturated $NaHCO_3$ (ca. 1 mL). The product was isolated by the standard method. Following radial chromatography (12:1 pentane–ether) an inseparable mixture of cis and trans isomers **6a** and **6b** were collected along with six-membered ring isomer **6c** in an overall yield of 80% (26 mg, 16 mmol, ratio **6a**:**6b**:**6c** 12:2:1). Data for **6a** (the trans isomer appeared as small "shadows" to the left of the cis isomer peaks): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (1 H, m, alkene-H(β)), 5.11 (1 H, app d, alkene-H(γ)), 5.06 (1 H, app d, J = 3 Hz, alkene-H(γ)), 4.04 (1 H, ddd, J = 3.5, 6, 10 Hz, H-1), 3.40 (1 H, dd, J = 3, 8.4 Hz, *H*COH), 2.28 (2 H, m, allylic-H), 2.0–1.5 (6 H, m), 1.21 (3 H, s), 1.02 (3 H, d, J = 7 Hz), 0.86 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 117.5, 82.29, 80.37, 76.00, 45.59, 36.44, 30.43, 26.66, 24.14, 19.42, 18.56 (in the ^{13}C NMR, peaks for the trans isomer were identified as the following: 134.4, 118.0, 81.98, 79.62, 76.53, 45.87, 36.33, 30.46, 26.38, 24.09, 19.45, 18.53); IR (neat) 3455 (br), 3074, 2964, 1640, 1467, 1375, 1038, 913 cm^{-1}; MS (CI, 70 eV) m/e 199 (MH^+, 100), 181 (MH - H_2O, 25.50), 157 (M - C_3H_7, 57.27), 125 (M - C_4H_9O, 73.68); HRMS (CI, 70 eV) m/e 199.1701 (199.1698 calcd for $C_{12}H_{22}O_2$ + H). Data for ***rel*-(2*R*,3*S*,6*S*)-6-methyl-6-(2-propenyl)-2-(1-methylethyl)tetrahydro-2*H*-pyran-3-ol (6c)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.8 (1 H, m, alkene-H(β)), 5.08 (1 H, m, alkene-H(γ)), 5.03 (1 H, app d, alkene-H(γ)), 3.45 (1 H, ovrlp ddd, J_{H-H2} = 9.5 Hz, $J_{H-H4\beta}$ = 9.5 Hz, $J_{H-H4\alpha}$ = 5 Hz, H-3), 3.16 (1 H, dd, J_{H-H3} = 9.5 Hz, $J_{H-H\alpha}$ = 2.5 Hz, H-2), 2.62 (1 H, dd, J = 14, 6.5 Hz, allylic-H), 2.10 (1 H, dd, J = 14, 8 Hz, allylic-H) 2.01 (1 H, d of sep, $J_{H-H\beta}$ = 7, J_{H-H2} = 2.5 Hz, H-α), 1.89 (1 H, m), 1.66–1.42 (3 H, m), 1.25 (1 H, br s, OH), 1.10 (3 H, s), 0.97 (3 H, d, J = 7 Hz), 0.88 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2, 117.0, 77.54, 72.20, 68.10, 38.01, 34.39, 29.34, 27.96, 27.58, 19.85, 14.98; IR (neat) 3354 (br), 3079, 2930, 1640, 1460, 1375, 1036, 911 cm^{-1}; MS (CI, 70 eV) m/e 199 (MH^+, 20.55), 181 (MH - H_2O, 12.44), 157 (M - C_3H_5, 16.55), 125 (M - C_4H_9O, 100); HRMS (CI, 70 eV) m/e 199.1721 (199.1698 calcd for $C_{12}H_{22}O_2$ + H).

***rel*-(2*R*,5*R*,α*S*)-5-Cyano-5-methyl-α-(1-methylethyl)-tetrahydrofuran-2-methanol (8a).** Via the procedure for hydride addition product **5**, nitrile addition was carried out by adding TMSCN (0.11 mL, 0.8 mmol) and TMSOTf (0.9 mL, 0.44 mmol) to ketone 1 (31 mg, 0.2 mmol) in 2.5 mL of CH_2Cl_2 at −78 °C. After 3 h, the reaction mixture stirred for −30 °C for 1.5 h and for 1 h at 0 °C. Finally, saturated $NaHCO_3$ was added and the crude product was isolated using the standard workup procedure. An inseparable mixture of diastereomers **8a** and **8b** was isolated after RC (3:1 pentane–ether, pretreated plate with 10% triethylamine). ^{1}H NMR of the product indicated that a 4:1 ratio, presumably favoring cis isomer **8a**, was formed in a 68% overall yield (25 mg, 0.14 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (1 H, ddd, J = 7.5, 7, 3.5 Hz, H-2), 3.46 (1 H, dd, J = 7.5, 3.5 Hz, H-α), 2.40 (1 H, app qn, J = 6.5 Hz), 2.05 (2 H, app q, J = 8 Hz), 1.88 (3 H, m), 1.65 (3 H, s), 1.01 (3 H, d, J = 6.5 Hz), 0.91 (3 H, d, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.3, 81.72, 78.18, 75.54, 38.83, 30.52, 25.31, 23.73, 18.69, 18.65; IR (neat) 3500 (br), 2960, 2235 (weak), 1117, 1017 cm^{-1}; MS (EI, 70 eV) m/e 157 (M - CN, 0.45), 111 (M - CN and C_2H_4O, 25.04), 83 (45.88), 73 (55.60), 68 (77.37), 55 (100); MS (CI, 70 eV) m/e 184 (MH^+, 0.21), 1.66 (MH - H_2O, 1.43), 157 (MH - HCN, 100); MS (CI, negative ion, 70 eV) m/e 182 (M - H, 7.66) 181 (M - H_2, 11.46), 139 (100); HRMS (CI, 70 eV) m/e 184.1329 (183.1337 calcd for $C_{10}H_{17}NO_2$ + H). Minor diastereomer **8b**: ^{1}H NMR (partial) (500 MHz, $CDCl_3$) δ 4.19 (1 H, ddd, J = 9.5, 5, 5 Hz, H-2), 3.51 (1 H, dd, J = 7, 4.5 Hz, H-α), 1.65 (3 H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.8, 82.79, 76.26, 75.75, 39.72, 30.25, 25.98, 25.80, 18.88, 18.18.

***rel*-(2*R*,5*R*,α*S*)-5-Methyl-α-(1-methylethyl)-5-(1-oxo-2-phenylethanyl)tetrahydrofuran-2-methanol (7a).** Ketone 1 (31 mg, 0.2 mmol) in 2.5 mL of CH_2Cl_2 was cooled in a −100 °C bath, and 80 mg (0.4 mmol) of α-(trimethylsiloxy)styrene and 0.07 mL of TMSOTf (0.4 mmol) were added sequentially. After keeping the reaction temperature at ca. −95 °C for 4 h, the reaction flask was warmed to −78 °C and stirred for 14 h, slowly warming to 20 °C. Following the established workup procedure, the ^{1}H NMR spectrum of the crude isolate indicated that <5% of trans diastereomer was present in the sample. After radial chromatography (10:2:1 pentane–CH_2Cl_2–ether) only cis diastereomer **7a** was isolated in a 62% yield (34 mg, 0.13 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2 H, app d, J = 7.5 Hz, ArH), 7.56 (1 H, t, J = 7.5 Hz, ArH), 7.46 (2 H, t, J = 8 Hz, ArH), 4.15 (1 H, m, H-2), 3.43 (1 H, dd, J = 8.5, 3 Hz, H-α), 3.40 (1 H, br s, OH), 3.34 (1 H, d, J = 14.5 Hz, HCC(O)Ph), 3.11 (1 H, d, J = 14.5 Hz, HCC(O)Ph), 2.1 (2 H, m), 1.85 (2 H, m), 1.59 (1 H, app d of qn, J = 8.5, 6.5 Hz), 1.33 (3 H, s), 1.04 (3 H, d, J = 6.5 Hz), 0.86 (3 H, d, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0, 137.7, 133.1, 128.5, 128.4, 81.32, 80.40, 76.12, 47.45, 37.47, 30.53, 27.32, 23.79, 19.59, 18.73; IR (neat) 3442 (br), 3056, 2961, 1672, 1094, 1021, 748, 690 cm^{-1}; MS (EI, 70 eV) m/e 105 (C_5H_7O, 100); MS (CI, 70 eV) m/e 277 (MH^+, 5.14), 157 (M - C_8H_7O, 100); HRMS (CI, 70 eV) m/e 277.1795 (277.1804 calcd for $C_{17}H_{24}O_3$ + H). In another experiment, an inseparable mixture of diastereomers **7a** and **7b** formed. Some key chemical shifts of minor diastereomer **7b** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ aromatic protons buried underneath major diastereomer 3.99 (1 H, ddd, J = 9.3, 6, 3.3 Hz, H-2), 3.34 (1 H, dd, J = 7.5, 3.6 Hz, H-a), 3.33 (1 H, d, J = 14.7 Hz, HCC(O)Ph), 3.09 (1 H, d, J = 14.7 Hz, HCC(O)Ph), 2.19 (1 H, br s, OH), 2.3–1.4 (5 H, buried underneath major diastereomer), 1.32 (3 H, s), 1.03 (3 H, d, J = 6.6 Hz), 0.85 (3 H, d, J = 6.6 Hz); IR and MS data was similar to that reported for cis diastereomer **7a**.

rel-(2*S*,α*S*)-5,5-Dimethyl-α-(1-methylethyl)tetrahydrofuran-2-methanol (11). Trimethylaluminum (0.25 mL of a 2 M solution in toluene) was added dropwise to BF_3·OEt_2 (0.06 mL, 0.48 mmol) in 1.5 mL of CH_2Cl_2 at −78 °C and stirred for 5 min. A solution of ketone 1 (31 mg, 0.2 mmol) in 1 mL of CH_2Cl_2 at −78 °C in was added. In 1 h the reaction mixture was quenched with saturated $NaHCO_3$. The product was isolated by the standard method. Desired product 11 was isolated after RC (11:1 pentane–ether) (59% yield, 20 mg, 0.12 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (1 H, ddd, J = 8, 5.7, 3.5 Hz, H-2), 3.40 (1 H, dd, J = 9, 3 Hz, α-H), 2.18 (1 H, br s, OH), 2.2–1.5 (5 H, m), 1.27 (6 H, s), 1.03 (3 H, d, J = 6.6 Hz), 0.88 (3 H, d, J = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.53, 79.74, 76.21, 38.68, 30.43, 28.61, 27.90, 24.28, 19.46, 18.57; IR (neat) 3480 (br), 2980, 1465, 1385, 1360, 1040 cm^{-1}; MS (CI, 70 eV), m/e 173 (MH^+, 56.37), 155 (MH - H_2O, 82.45), 99 (100); HRMS (CI, 70 eV) m/e 173.1554 (173.1541 calcd for $C_{10}H_{20}O_2$ + H).

***rel*-(2*R*,5*S*,α*S*)-5-Ethyl-5-methyl-α-(1-methylethyl)tetrahydrofuran-2-methanol (12a).** Via a similar procedure that was described for the synthesis of 11, a Et_3Al/BF_3·OEt_2 solution was generated by adding 0.06 mL of BF_3·OEt_2 (0.48 mmol) to Et_3Al (0.5 mL of a 1 M solution in hexanes, 0.5 mmol) in 1.5 mL of CH_2Cl_2 at −78 °C. After 5 min a solution of ketone 1 (31 mg, 20 mmol) in 1 mL of CH_2Cl_2 at −78 °C was added. The reaction mixture was stirred at −78 °C for 4 h after which the reaction was quenched with $NaHCO_3$. The product was isolated by the standard method. Two samples were collected after RC (14:1

pentane–ether): the major product was an inseparable mixture of cis and trans ethyl addition products (**12a** and **12b**) and the minor product was a mixture of cis and trans *hydride* addition products **5a** and **5b** along with six-membered ring isomer **5c** (68% yield of ethyl addition products **12a** and **12b**, 26 mg, 0.14 mmol; ratio of all products 7:1:4:1 cis:trans:six-membered ring: hydride addition products). Data for **12a** (predominant isomer is the cis isomer): ^{1}H NMR (500 MHz, $CDCl_3$)[16] δ 4.01 (1 H, ddd, J = 9, 5.5, 3.5 Hz, H-2), 3.39 (1 H, dd, J = 8, 3 Hz, H-α), 2.28 (1 H, br s, OH), 1.92 (1 H, m, H-3(α)), 1.76 (2 H, m, H-3(β), H-4(β)), 1.66 (1 H, m, H-4(α)), 1.58 (1 H, m, $HCMe_2$), 1.55 (2 H, m, HCMe), 1.18 (3 H, s), 1.03 (3 H, d, J = 6.5 Hz), 0.90 (3 H, t, J = 7 Hz), 0.86 (3 H, d, J = 6.5 Hz) (most of the peaks in the ^{1}H NMR for trans isomer **12b** were buried underneath the peaks of the major isomer except for the following: δ 4.07 (1 H, ddd, J = 3, 6.5, 9 Hz, H-2), 2.1 (1 H, br s, OH), 1.02 (3 H, d, J = 6.5 Hz), 0.91 (3 H, t, J = 7.5 Hz), 0.87 (3 H, d, J = 6.5 Hz)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.15, 80.20, 75.96, 36.42, 33.62, 30.46, 25.87, 24.09, 19.54, 18.57, 8.82 (^{13}C NMR peaks for trans isomer **12b**: δ 83.08, 79.15, 76.46, 38.28, 34.00, 29.58, 29.30, 25.03, 19.38, 18.53, 8.92); IR (neat) 3462, 2865, 1063, 1039 cm^{-1}; MS (CI, 70 eV) m/e 187 (MH^+, 100), 169 (M-OH, 20.62); HRMS (CI, 70 eV) m/e 187.1700 (187.1698 calcd for $C_{11}H_{22}O_2$ + H). **Minor Products.** GC–MS of the higher polarity material revealed three different products: two having a mass equivalent to the hydride addition products **5a** and **5b**, and one having the same mass the major product of **12a** (presumably this is the six-membered ethyl addition product): GC–MS (CI, 70 eV, T_1 = 10 °C, t_1 = 5 min, rate = 10 deg/min, T_2 = 200 °C, t_2 = 10 min); fraction 1 and 2 (5.87 min, 27%, 6.13 min, 7%) 159 ($C_9H_{18}O_2$ + H, 86.38), 141 ($C_9H_{18}O_2$ – OH, 57.59), 85 ($C_9H_{18}O_2$ – C_4H_9O, 100); fraction 3 (9.11 min, 64) 187 ($C_{11}H_{22}O_2$ + H, 16.25), 169 ($C_{11}H_{22}O_2$ – OH, 18.08), 113 ($C_9H_{18}O_2$ – C_4H_9O, 100).

***rel*-(2*R*,5*R*,α*S*)-5-Methyl-α-(1-methylethyl)-5-(2-phenylethynyl)tetrahydrofuran-2-methanol (13a).** BuLi (0.4 mL, 1.5 M solution in hexanes, 0.6 mmol) was added to phenylacetylene (0.07 mL, 0.64 mmol) in 1.5 mL of dry ether at 0 °C and stirred for 30 min. Et_2AlCl (0.6 mL, 1 M solution in hexanes, 0.6 mmol) was added, and the reaction mixture was stirred for 20 min. The reaction mixture was then cooled to –78 °C, and 1 mL of CH_2Cl_2, 0.07 mL of BF_3·OEt_2 (0.56 mmol), and ketone **1** in 1 mL of CH_2Cl_2 were added sequentially to the reaction mixture. The reaction mixture stirred for 2.5 h at –78 °C and 30 min at –30 °C, after which the reaction was quenched with saturated $NaHCO_3$. Following the standard workup procedure, cis and trans diastereomers **13a** and **13b** were separated by RC (7:1 pentane–ether) in an overall yield of 60% (7:1 ratio cis:trans, 31 mg, 0.12 mmol). Data for **13a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (2 H, m, *o*-ArH), 7.29 (3 H, m, *m,p*-ArH), 4.31 (1 H, overlp ddd, J = 7.5, 7, 3.5 Hz, H-2), 3.49 (1 H, dd, J = 5.3, 4 Hz, H-α), 2.31 (1 H, m, H-4(β)), 2.11 (1 H, br s, OH), 2.0 (2 H, app q, J = 7.5 Hz, H-3), 1.90 (1 H, m, H-4(α)), 1.67 (1 H, m, H-β), 1.64 (3 H, s), 1.04 (3 H, d, J = 6.5 Hz), 0.91 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8, 128.3, 123.0, 92.20, 83.06, 80.55, 77.41, 40.63, 30.79, 28.14, 24.20, 19.47, 18.93; IR (neat) 3456, 3056, 2960, 1101, 1025, 756, 691 cm^{-1}; MS (EI, 70 eV) m/e 258 (M^+, 0.74), 185 (M – C_4H_9O, 18.69), 142 (100), 129 (88), 105 (100); HRMS (EI, 70 eV) m/e 258.1615 (258.1620 calcd for $C_{17}H_{22}O_2$). Data for **13b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2 H, m, ArH), 7.28 (3 H, m, ArH), 4.26 (1 H, ddd, J = 8.7, 6, 3 Hz, H-2), 3.52 (1 H, dd, J = 8.4, 3-H-α), 2.5 (1 H, br s, OH), 2.35 (2 H, m), 1.95 (2 H, m), 1.65 (3 H, s), 1.6 (1 H, m), 1.04 (3 H, d, J = 6.6 Hz), 0.90 (3 H, d, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.5, 128.2, 128.1, 122.4, 92.50, 83.67, 81.91, 76.23, 41.17, 30.36, 28.18, 24.86, 19.43, 18.76; MS (CI, 70 eV) m/e 259 (MH^+, 4.35), 157 (M – C_8H_5, 100): HRMS (CI, 70 eV) m/e 259.1708 (259.1698 calcd for $C_{17}H_{12}O_2$ + H).

***rel*-(2*R*,6*R*,α*S*)-α-(1-Methylethyl)tetrahydro-6-methyl-2*H*-pyran-2-methanol (15a).** To a solution of ketone **2** (45 mg, 0.25 mmol) in 0.5 mL of CH_2Cl_2 was added triphenylsilane (260 mg in 0.5 mL of CH_2Cl_2, 1 mmol) at 0 °C. After the mixture was stirred for 5 min, BF_3·OEt_2 (0.06 mL, 0.5 mmol) was added dropwise to the reaction mixture. The reaction mixture was warmed to 20 °C (ca. 3 h) and then quenched with saturated $NaHCO_3$. The product was isolated using the standard workup. Following radial chromatography (17:1 then 15:1 pentane–ether) and distillation using a Kugelrohr apparatus, cyclic product **15** was isolated in 81% yield (35 mg, 0.20 mmol). GC/MS indicated that only one peak in the GC trace of the crude product corresponds to the mass of **15a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (1 H, overlp dd of q, $J_{H\text{-}H5\beta}$ = 2 Hz, $J_{H\text{-}H5\alpha}$ = 11 Hz, $J_{H\text{-}H\alpha}$ = 6 Hz, H-6), 3.40 (1 H, ddd, $J_{H\text{-}H3\beta}$ = 2 Hz, $J_{H\text{-}H3\alpha}$ = 11 Hz, $J_{H\text{-}H\alpha}$ = 4 Hz, H-2), 3.31 (1 H, dd, J = 4.2, 7.8 Hz, *H*COH), 2.24 (1 H, br s, OH), 1.85 (1 H, m), 1.71 (1 H, m, H-β), 1.6–1.4 (3 H, m), 1.15 (3 H, d, J = 6.3 Hz, CH_3), 0.99 (3 H, d, J = 6.6 Hz), 0.86 (3 H, d, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.47, 78.02, 74.01, 33.31, 29.04, 23.48, 23.06, 22.13, 18.71, 18.65; IR (neat) 3473 (br), 2931, 1470, 1382, 1075, 1042, 1005, 895 cm^{-1}; MS (CI, 70 eV) m/e 173 (MH^+, 100), 155 (MH – H_2O, 63.62), 99 (45.60); HRMS (CI, 70 eV) m/e 173.15338 (173.15415 calcd for $C_{10}H_{20}O_2$ + H). Data for ***rel*-(1*R*,5*S*,7*S*)-5-methyl-7-(1-methylethyl)-6,8-dioxabicyclo[3.2.1]octane (14)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (1 H, m, H-1), 3.52 (1 H, dd, J = 4, 9 Hz, H-α), 2.0–1.5 (7 H, m), 1.44 (3 H, s), 1.09 (3 H, d, J = 6 Hz), 0.84 (3 H, d, J = 6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 106.9, 86.28, 76.12, 34.48, 27.72, 25.02, 23.64, 20.75, 19.04, 17.73; IR (FT, neat) 2958, 2938, 2872, 1463, 1382, 1104, 1038, 1007, 852 cm^{-1}: MS (EI, 70 eV), m/e 170 (M^+, 0.01) 128 (M – C_3h_6, 1.41), 98 (7.58), 85 (10.08), 59 (100); MS (CI, 70 eV) m/e 171 (MH^+, 99.40), 98 (100); HRMS (CI, 70 eV) 171.1380 (173.1385 calcd for $C_{10}H_{20}O_2$ + H).

***rel*-(2*R*,6*R*,α*S*)-6-Methyl-α-(1-methylethyl)-6-(2-propenyl)tetrahydro-2*H*-pyran-2-methanol (16a).** Via the procedure outlined for tetrahydropyran **15**, 0.43 mg of ketone **2** (0.25 mmol) was reacted with 0.16 mL of allyltrimethylsilane (1 mmol) and 0.08 mL of BF_3·OEt_2 (0.63 mmol) in 0.5 mL of CH_2Cl_2. Chromatography (RC, 11:1 to 5:1 pentane–ether) afforded two products in a 49:1 ratio (overall yield 74%, 39 mg, 0.18 mmol). The less polar sample gave the following data and is assigned as isomer **16a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (1 H, m, alkene-H(β)); 5.08 (1 H, app s, alkene-H(γ)), 5.03 (1 H, app dm, alkene-H(γ)), 3.61 (1 H, ddd, J = 11, 3.6, 3.6 Hz, H-2) 3.19 (1 H, dd, J = 3.9, 7.8 Hz, *H*COH), 2.52 (1 H, dd, J = 6.6, 14 Hz, allylic-H), 2.33 (1 H, br s, OH), 2.18 (1 H, dd, J = 6.8, 14 Hz, allylic-H), 1.7–1.6 (3 H, m), 1.52 (2 H, app d, J = 12 Hz), 1.33 (2 H, m), 1.13 (3 H, s), 0.97 (3 H, d, J = 6.6 Hz), 0.84 (3 H, d, J = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.1, 117.2, 78.61, 73.65, 70.47, 38.24, 34.70, 28.92, 28.49, 23.17, 18.85, 18.83, 18.72; IR (neat) 3471 (br), 3076, 2932, 2871, 1640, 1463, 1444, 1376, 1045, 913 cm^{-1}; MS (CI, 70 eV) m/e 213 MH^+, 100), 195 (MH – H_2O, 40.68), 177 (6.74), 171 (M – C_3H_5, 17.18), 139 (22.39); HRMS (CI), 213.1843 (213.1855 calcd for $C_{13}H_{24}O_2$ + H). Data for **16b**: ^{1}H NMR (300 MHz, $CDCl_3$, small quantities isolated that contained ether and water) δ 5.76 (1 H, m, alkenyl-H(β)), 5.03 (2 H, m, alkenyl-H(γ)), 3.5 (buried underneath solvent peaks, H-α), 3.2 (1 H, dd, J = 14.5, 4.5 Hz, H-2), 2.4–1.9 (4 H, m), 1.6–1.1 (peaks buried by solvent), 1.07 (3 H, s), 0.96 (3 H, d, J = 6.9 Hz), 0.88 (3 H, d, J = 6.9 Hz); MS (CI, 70 eV, GC (t_1 = 5 min, T_1 = 100 °C, rate = 10 °C/min, T_2 = 200 °C) retention time = 8:45 min) m/e 213 (M + 1, 20.06), 195 (MH – H_2O, 64.42), 171 (14.16), 139 (100).

***rel*-(2*R*,6*R*,α*S*)-6-Cyano-6-methyl-α-(1-methylethyl)-tetrahydro-2*H*-pyran-2-methanol (17a).** Via the procedure described for the synthesis of hydride addition product **15**, ketone **2** (34 mg, 0.2 mmol) in 0.4 mL of CH_2Cl_2 was treated with 0.06 mL of BF_3·OEt_2 (0.5 mmol) and 0.11 mL of TMSCN (0.8 mmol) to form a mixture of nitrile addition products **17a** and **17b**. The two diastereomers were separated by RC (5:1 and then 4:1 and then 1:1.5 pentane–ether) in a 47% overall yield (23 mg, 0.12 mmol, ratio of cis to trans is 1:2 as determined by ^{1}H NMR of crude product). Data for minor diastereomer **17a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (1 H, ddd, $J_{H\text{-}H3\alpha}$ = 11.5 hz, $J_{H\text{-}H\alpha}$ = 4.5 Hz, $J_{H\text{-}H3\beta}$ = 2.5 Hz, H-2), 3.34 (1 H, dd, $J_{H\text{-}H\beta}$ = 7.5 Hz, $J_{H\text{-}H2}$ = 4.5 Hz, H-α), 1.93 (2 H, H-5, 1.79 (1 H, m, H-4(α)), 1.76 (1 H, app sex, J = 7 Hz, Hβ), 1.69 (1 H, d of m, J = 14.5 Hz, H-3(β)), 1.59 (3 H, s), 1.53–1.45 (1 H, m, H-4(β)), 1.45–1.38 (1 H, m, H-3(α)), 1.25 (1 H, br s, OH), 0.99 (3 H, d, J = 7 Hz), 0.91 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.8, 77.95, 76.18, 72.05, 35.90, 29.03, 27.65, 22.96, 20.09, 18.73, 18.11; IR (neat) 3474 (br), 2858, 2368 (w), 1045, 1006 cm^{-1}; MS (CI, 70 eV) m/e 198 (MH^+, 0.01) 180 (MH – H_2O, 5.73), 171 (MH – HCN, 100); HRMS (CI,

(16) Chemical shift assignments were determined in part by 2D homonuclear decoupling experiments (see the supplementary material).

70 eV) m/e 198.1517 (198.1494 calcd for $C_{11}H_{19}NO_2$ + H).

***rel*-(2*R*,6*S*,α*S*)-6-Cyano-6-methyl-α-(1-methylethyl)-tetrahydro-2*H*-pyran-2-methanol (17b).** A solution of ketone **2** (0.34 mg, 0.2 mmol) in 2 mL of CH_2Cl_2 was stirred and cooled at −78 °C as TMSCN (0.08 mL, 0.6 mmol) and BF_3·OEt_2 (0.06 mL, 0.5 mmol) were added. The temperature was maintained at −78 °C for ca. 8 h and then slowly warmed to −19 °C (in a cold room) over 40 h. Ether and saturated $NaHCO_3$ were added, and the crude product was isolated by the standard method. ^1H NMR spectrum of the isolate indicated that <5% of cis diastereomer **17a** was present in the crude product. Trans diastereomer **17b** was isolated in 87% yield (34 mg, 0.17 mmol) using RC (3.5:1 and then 1:1 pentane–ether, pretreated plate with 7% triethylamine in 3.5:1 pentane–ether): ^1H NMR[16] (500 MHz, $CDCl_3$) δ 3.63 (1 H, ddd, $J_{H\text{-}H\alpha}$ = 8.5 Hz, J = 10, 7.5 Hz, H-2), 3.46 (1 H, dd, $J_{H\text{-}H_2}$ = 8.5 Hz, $J_{H\text{-}Hb}$ = 3 Hz, H-α), 2.1 (2 H, m, H-3(α), H-5(α)), 2.08 (1 H, d of sep (partially buried under 2.1 δ), J = 2.5, 1.5 Hz, H-β), 1.94 (1 H, app dd, J = 8, 8 Hz, H-5(β)), 1.69 (1 H, m, H-4(β)), 1.6 (1 H, br s, OH), 1.53 (3 H, s), 1.49–1.38 (2 H, m, H-4(α) and H-3(β)), 1.07 (3 H, d, J = 7 Hz), 0.88 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.8, 83.08, 73.27, 71.37, 39.79, 28.83, 26.99, 19.65, 17.32, 14.86; IR (neat) 3450 (br), 2963, 2234 (w), 1083, 1071, 1045 cm^{-1}; MS (EI, 70 eV) m/e 125 (M − C_4H_9O, 14.73), 96 (82), 82 (70.53), 68 (C_3H_6CN, 100); MS (CI, 70 eV) m/e 198 (MH^+, 3.40), 171 (MH − HCN, 100); HRMS (CI, 70 eV) m/e 198.1515 (198.1495 calcd for $C_{11}H_{19}NO_2$ + H).

***rel*-(2*R*,7*R*,α*S*)-7-Methyl-α-(1-methylethyl)oxepane-2-methanol (19).** Triphenylsilane (420 mg, 1.6 mmol) in 0.9 mL of CH_2Cl_2 was added to ketone **3** (37 mg, 0.2 mmol) at 20 °C. The solution was cooled to −45 °C, and BF_3·OEt_2 (0.11 mL, 0.89 mmol) was added dropwise. After being stirred for 1.5 h at −45 °C and for 6 h at −25 °C, the solution was warmed to 20 °C and stirred for 14 h. Ether and saturated $NaHCO_3$ were added, and the crude product was isolated following the standard workup procedure. Less than 5% of the minor diastereomer was present in the crude sample as indicated by the ^1H NMR spectrum. Purified oxepane **19** was isolated in an 81% yield (30 mg, 16 mmol) after RC (19:1 pentane–ether): ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (1 H, m, H-7), 3.45 (1 H, m, H-2), 3.31 (1 H, t, J = 6 Hz, H-α), 2.01 (1 H, br s, OH), 1.79 (1 H, sep, J = 6.6 hz, H-β), 1.78–1.4 (8 H, m, ring H), 1.16 (3 H, d, J = 7.8 Hz, H-α), 0.95 (3 H, d, J = 6.9 Hz), 0.89 (3 H, d, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 79.74, 79.41, 76.75, 37.93, 29.78, 29.18, 25.71, 24.51, 22.88, 19.22, 17.52; IR (neat) 3462 (br), 2928, 1101, 1002 cm^{-1}; MS (EI, 70 eV) m/e 143 (M − C_3H_7, 120), 113 (M − C_4H_9O, 51.56), 95 (100); MS (CI, 70 eV) m/e 187 (MH^+, 3.90), 169 (MH − H_2O, 5.41), 117 (MH − C_4H_6O, 100); HRMS (CI, 70 eV) m/e 187.1697 (187.1698 calcd for $C_{11}H_{22}O_2$ + H).

***rel*-(1*R*,6*S*,8*S*)-6-Methyl-8-(1-methylethyl)-7,9-dioxabicyclo[4.2.1]nonane (18).** Ketone **3** (37 mg, 0.2 mmol) in 1 mL of CH_2Cl_2 was cooled in a −40 °C bath, and BF_3·OEt_2 (0.05 mL, 0.4 mmol) was added. After being stirred for 1 h, the reaction mixture was warmed to 0 °C over 2 h and then quenched using saturated $NaHCO_3$. Following the standard workup procedure, ketal **18** was isolated in a 70% yield (26 mg, 14 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (1 H, app t, J = 4.8 Hz, H-1), 3.48 (1 H, dd, J = 10.5, 4.5 Hz, H-8), 1.9–1.51 (9 H, m), 1.36 (3 H, s), 1.05 (3 H, d, J = 6.6 Hz), 0.83 (3 H, d, J = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 110.2, 84.26, 77.36, 38.83, 29.93, 27.63, 27.02, 24.23, 24.00, 20.55, 19.03; IR (neat) 2928, 1469, 1449, 1151, 1053 cm^{-1}; MS (EI, 70 eV) m/e 184 (M^+, 1.15), 142 (M − C_3H_6, 55.17), 127 (60.73), 100 (75.19), 85 (100); MS (CI, 70 eV) m/e 185 (MH^+, 100), 167 (MH − H_2O, 2.97), 117 (82.42); HRMS (EI, 70 eV) m/e 184.1474 (184.1463 calcd for $C_{11}H_{22}O_2$).

***rel*-(2*R*,5*S*,α*S*)-5-Cyclohexoxy-α-(1-methylethyl)tetrahydrofuran-2-methanol (22a).** BF_3·OEt_2 (0.03 mL, 0.22 mmol) was added dropwise to epoxy ester **4** (48 mg, 0.2 mmol) in 2.5 mL of CH_2Cl_2 at −78 °C. After 5 min, 0.44 mL of a freshly prepared 0.5 M solution of $LiAlH_4$ in THF (0.22 mmol) was added over 5 min and the reaction mixture was stirred for 3 h at −78 °C. The reaction was warmed to 20 °C over 14 h, and the product was isolated using the standard workup procedure. Following RC (10:1 hexanes–ether pretreated with 1% triethylamine), 33 mg of cis acetal **22a** was isolated (81%, 39 mg, 0.18 mmol) with a small amount of the other diastereomer. Diastereomeric ratio (15:1 cis:trans) was determined by GC. Data for **22a**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (1 H, d, J = 3.5 Hz, H-5), 4.31 (1 H, d of t, J = 7.8, 2.5 Hz, H-2), 3.56 (1 H, m, (cyclohexyl)CHOR), 3.47 (1 H, d, J = 8.5 Hz), 3.15 (1 H, br s, OH), 2.15–1.1 (15 H, m), 1.04 (3 H, d, J = 7 Hz), 0.88 (3 H, d, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.8, 82.41, 76.65, 75.84, 33.70, 33.47, 31.97, 30.61, 25.45, 24.15, 24.01, 21.14, 19.50, 18.81; IR (neat) 3490, 2940, 2860, 1470, 1455, 1090, 1040, 1000 cm^{-1}; MS (EI, 70 eV) m/e 169 (M − C_4H_9O, 6.36), 143 (M − $C_6H_{11}O$, 6.93), 99 ($C_6H_{11}O$, 9.82), 87 ($C_5H_{11}O$, 100), 55 (44.64); MS (CI, 70 eV) m/e 143 (M − $C_6H_{11}O$, 100); MS (CI, negative ion, 70 eV) m/e 242 (M^+, 7.97), 241 (M − 1, 63.14), 141 (100); HRMS (EI, 70 eV) m/e 169.1223 (169.1228 calc for $C_{14}H_{26}O_3$ − C_4H_9O). Spectral data for minor diastereomer **22b**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (1 H, dd, J = 6.1, 1.8 Hz, H-5), 4.19 (1 H, app sex, J = 1.8 Hz, H-2), 3.53 (1 H, m, (cyclohexyl)CHOR), 3.47 (1 H, dd, J = 9, 3 Hz, H-α), 2.02–1.07 (16 H, m), 1.02 (3 H, d, J = 6.6 Hz), 0.90 (3 H, d, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.7, 78.51, 74.85, 33.89, 32.83, 31.94, 30.57, 25.61, 24.40, 24.24, 22.21, 19.14, 18.66; IR ($CHCl_3$) 3500, 2940, 1470, 1455, 1090, 1025, 990 cm^{-1}; MS (EI, 70 eV) m/e 169 (M − C_4H_9O, 11.43), 143 (M − $C_6H_{11}O$, 17.88), 87 ($C_5H_{11}O$, 84.62), 57 (100); MS (CI, 70 eV) m/e 243 (M + 1, 0.01), 143 (M − $C_6H_{11}O$, 100); MS (CI, negative ion, 70 eV) m/e 242 (MH^+, 0.84), 2.41 (M − 1, 6.10), 218 (100); HRMS (EI, 70 eV) m/e 169.1232 (169.1228 calcd for $C_{14}H_{28}O_3$ − C_4H_9O).

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Supplementary Material Available: Experimental procedures for the synthesis of compounds 1–4 along with the ^1H and ^{13}C NMR spectra for all new compounds and DNOE data and 2-D homonuclear decoupling spectra (74 pages). Ordering information is given on any current masthead page.

Reactions of Bridgehead Halides. A Synthesis of Modhephene, Isomodhephene, and *epi*-Modhephene

George A. Kraus* and Jianmin Shi

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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A synthesis of modhephene has been achieved, the key feature of which is the use of a novel nucleophilic addition/rearrangement reaction to develop the carbon framework. Stereochemical control of the stereogenic center bearing the methyl group was accomplished by variation of the hydrogenation conditions. As a byproduct of this work, we have clarified structural assignments of intermediates from previous syntheses.

The discovery of the novel sesquiterpene modhephene (1) has led to a renewed interest in the synthesis of propellanes. Total syntheses of this naturally occurring hydrocarbon have been recorded by a number of researchers.[1]

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