yield **24** (1.54 g, 50%) as colorless crystals: mp 46-47 °C; ^{19}F NMR ($CDCl_3$) δ -82.2 (3, s), -119.5 (2, s); ^1H NMR ($CDCl_3$) δ 1.22 (1, m, H-6n), 1.32 (1, m, H-5n), 1.49 (t, ddt, J = 10, 2.5, 1 Hz, H-7a), 1.53 (1, s, OH), 1.63 (1, br d, J = 13 Hz, H-3x), 1.67-1.79 (2, m, H-6x,5x), 1.89 (1, ddm, J = 13, 7 Hz, H-3n), 1.97 (1, dq, J = 10, 2 Hz, H-7s), 2.26 (1, br d, J = 4 Hz, H-4), 3.94 (1, br d, J = 7 Hz, H-2); IR (CCl_4) δ 3622, 3550-3300 cm^{-2} (OH). Anal. C, H.

1-(Pentafluoroethyl)-2-deuterio-2-norbornanols (2-*d*-19 and 2-*d*-21). Reduction of **20** (2.5 g of ether solution) with $LiAlD_4$ (250 mg, 6.6 mmol) as in the preparation of **21** and separation by GC gave 2-*d*-**19** and 2-*d*-**21**, whose ^1H NMR spectra resembled those of **19** and **21** less the signals at δ 4.52 and 3.99, respectively. These were converted to the respective triflates 2-*d*-*exo*-**25** and 2-*d*-*endo*-**25** as for the undeuterated analogs.

Product Studies. Solvolysis of *exo*-**11** (20 mg, 0.045 mmol) in 1 mL of acetone/H_2O (8/2) was conducted in a sealed ampule at 70 °C for 1 h. The ampule was cooled to 0 °C and then opened, and the volatile products were distilled off through a short-path column. The residue was analyzed by HPLC, and the volatile products were analyzed by analytical GC using a 61.5-m tri-2,4-xylyl phosphate column.

For hydrolysis of **17** and *exo*- and *endo*-**25**-OTf 15 mg (0.041 mmol) of the triflate was solvolyzed in 1 mL of acetone/H_2O (8/2) containing 17.5 mg (0.163 mmol) 2,6-lutidine. The product was extracted with ether, and the organic phase was washed with 0.5 mL of 2 N HCl and dilute $NaHCO_3$, dried over $MgSO_4$, and analyzed by GC.

For trifluoroacetolysis of **17** and *exo*- and *endo*-**25**-OTf 15 mg (0.041 mmol) triflate was solvolyzed in 1 mL of CF_3CO_2H containing 28 mg (0.203 mmol) K_2CO_3. The product was cooled to 0 °C, 10 mL of 2 N NaOH was added, and the mixture was stirred for 15 min. The product was extracted with 2 mL of ether which was washed with water, dried over $MgSO_4$, and analyzed by GC.

For preparative hydrolysis of 2-*d*-*exo*-**25**-OTf (220 mg, 0.61 mmol) in 6.1 mL of acetone/H_2O (8/2) containing 2,6-lutidine (260 mg, 2.42 mmol) was kept for 30 min at 60 °C and then cooled and extracted with 10 mL of ether, which was washed with HCl and $NaHCO_3$ solution and H_2O and dried over $MgSO_4$. The ether was distilled, and the product was separated by preparative GC (1.8-m DC 200 column, 120 °C).

For preparative trifluoroacetolysis 2-*d*-*exo*-**25**-OTf (150 mg, 0.41 mmol) in 4.1 mL of CF_3CO_2H containing K_2CO_3 (285 mg, 2.06 mmol) was kept for 45 min at room temperature. Then 40 mL of ice-cold 2 N NaOH was added, and the solution was stirred 30 min and then extracted with 10 mL of ether. The organic phase was washed to neutrality with H_2O and dried over $MgSO_4$, and the ether was distilled. The residue was analyzed by GC. Hydrolysis and trifluoroacetolysis of 2-*d*-*endo*-**25**-OTf were carried out similarly at 80 °C and room temperature, respectively.

1-(Pentafluoroethyl)-1-phenylethyl Tosylate (9). Pentafluoropropiophenone (PCR, Inc.; 2 g, 8.91 mmol) in 2 mL of ether was added to an ice-cooled solution of MeLi (9.8 mmol) in 22 mL of ether, and the solution was stirred 1 h. To the ice-cooled solution was added recrystallized TsCl (1.79 g, 9.4 mmol) in 15 mL of ether, and the solution was stirred overnight at room temperature. Water was added, the solution was extracted three times with ether, and the combined ether layers were washed with $NaHCO_3$ and NaCl, dried over Drierite, and evaporated. Successive purification by radial chromatography, recrystallization from pentane, and further radial chromatography (2.5/97.5 EtOAc/petroleum ether) gave pure **9** (34 mg, 0.086 mmol, 1%) along with larger fractions still containing alcohol: mp 59-60 °C; ^1H NMR ($CDCl_3$) δ 2.30 (3, br s, Me), 2.48 (3, s, CH_3Ar), 7.61 (4, AB, Ar), 7.43 (5, s, Ph); MS m/z (rel intensity) 394 (5, M^+), 275 (56, $M^+ - C_2F_5$), 223 (69, M^+ - OTs), 222 (100, M^+ - TsOH); HRMS m/z 394.0659 (M^+ requires 394.0662).

Kinetic Measurements. Rates in alcoholic solvents were usually measured by injecting 10 μL of 0.01-0.014 M solutions of the brosylate in CH_3CN into 1.2 mL of solvent in a thermostatted quartz cell (1.0-mm pathlength) and observing the decrease in absorbance (0.25-1.0 unit) at 242 nm. For rates in acids, 10 μL of 0.12-0.14 M solutions of brosylate in 1.2 mL of solvent was used, and the decrease in absorbance (0.1 unit) at 262 nm was measured. For reactions of *endo*-**11** at 74.8 °C the reaction solution of 17 μL of 0.014 M brosylate in 2.6 mL of solvent was contained in a pressure tube with a Teflon-brand stopcock in the constant temperature bath. At intervals the tube was removed from the bath and cooled in an ice bath, and the absorption of the solution was measured at 25 °C.

For reaction of *endo*-**12** in TFA 0.0132 g (2.93×10^{-5} mol) of brosylate was dissolved in 15 mL of TFA to give a 2.0×10^{-3} M solution, and 1.2-mL aliquots were placed in ampules which were then sealed. The samples were heated in the constant temperature bath and removed at intervals and cooled, and the absorbance was measured at 267 nm at 25 °C. Two tubes were used for the infinity value, and an absorbance change of 0.3 unit was observed. Rates for *exo*-**12** in TFE at 90.1 °C were measured similarly using 14 mL of 8×10^{-5} M brosylate.

Good first-order rate constants were obtained in each case with either measured infinity values or the Guggenheim method. At least duplicate runs with a maximum deviation of ±9% were obtained in each case.

Acknowledgment. Support of the work by the Natural Sciences and Engineering Research Council of Canada and by the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Hoechst AG for generous donations of pentafluoroethyl iodide.

Electrostatic Modulation of Hydroxyl Group Ionization in Acidic Media. Evidence for the Competitive Operation of Intramolecular S_N2 Reactions

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Abstract: The acid-catalyzed cyclodehydration of the cis and trans isomers of 2-substituted 1-(3-hydroxypropyl)cyclohexanols results in the formation of spirocyclic tetrahydrofurans. The stereochemical course of these reactions is highly varied, ranging from a dominant preference for retention when R = OCH_3 to modestly favored inversion when R = CH_3. Experiments with ^{18}O-labeled diols show that in the methoxyl series most of the isotope is retained irrespective of relative stereochemistry. On the other hand, the pair of phenyl-substituted isomers responds by losing approximately 50% of the label. The isotopic level in the product erodes further when R = CH_3. The stereochemical and isotopic labeling results are interpreted in terms of competing intramolecular S_N2 and classical S_N1 pathways. The extent to which cooperative nucleophilic attack with loss of the primary hydroxyl is facilitated reaches a maximum in the methoxyl-substituted diols, as a consequence of electrostatic inhibition of tertiary carbocation formation. As this effect is progressively lessened, the percentage of S_N1 response rises. At no time, however, do the stereoisomeric carbocations interconvert conformationally prior to cyclization.

Acid-catalyzed cyclodehydration reactions of diols have seen widespread use in cyclic ether formation,[1-5] yet little is known about structural effects on the stereochemistry of this reaction. Mihailovic and co-workers demonstrated that the cyclization of

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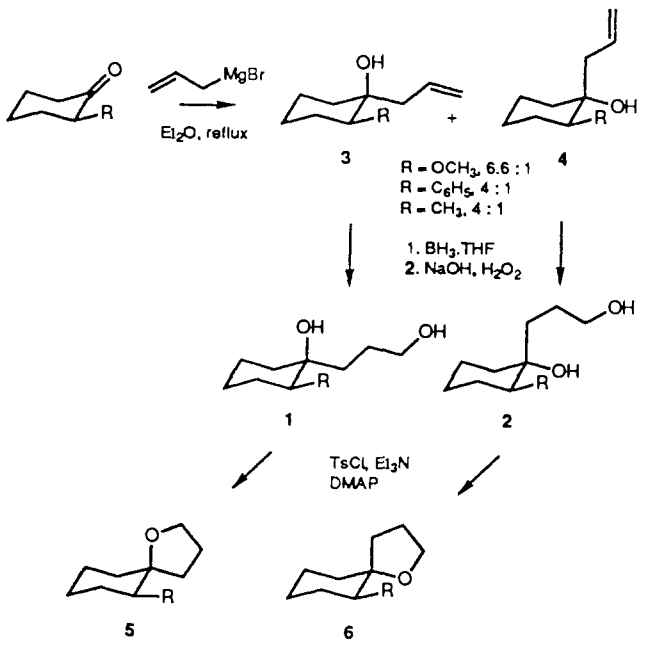
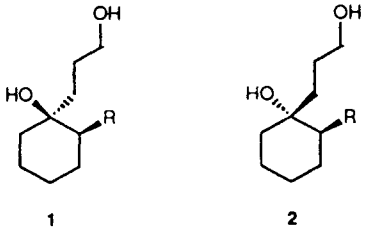
Scheme I



dl- and *meso*-hexane-2,5-diol with H_2SO_4 or H_3PO_4 proceeds with high stereoselectivity.[6,7] Any departure from the disecondary to lower levels of substitution demands more forcing conditions, and stereochemical control is thereby lost.[5,8] In 1,3-diols, a Wagner–Meerwein shift must operate prior to ring closure. The necessary involvement of carbocations causes any attempt at stereochemical definition to be inconclusive.[9]

Primarily because of our involvement with belted spirocyclic tetrahydrofurans,[10] we have targeted for study the possible modulation of competitive neighboring group participation by primary and tertiary hydroxyl groups in diastereomeric 1,4-diols such as **1** and **2**.[11] The remarkable discovery has been made that



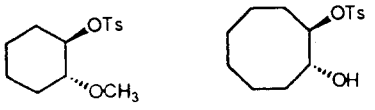
an α-heteroatom effect, e.g., when R = OCH_3, can strongly inhibit ionization of the neighboring tertiary hydroxyl in these systems. High levels of stereochemical retention are seen because an intramolecular S_N2 reaction becomes kinetically dominant. Isotopic labeling studies have confirmed that the primary alcohol functionality is selectively displaced by the tertiary hydroxyl group without wholesale concurrent heterolysis to give the trisubstituted carbocation. This mechanistic bias wanes in favor of the classical S_N1 ionization pathway as R is made phenyl and then methyl.

Results

Stereochemistry of Cyclodehydration. The preparation of diols **1** and **2** began by addition of allylmagnesium bromide to the individual cyclohexanones. Equatorial attack by the organometallic was invariably favored, leading to greater amounts of **3** relative to **4**. The proportion of less polar axial alcohol was greatest when R = OCH_3 (see Scheme I), presumably as a result of favorable ether oxygen coordination to Mg(II).[12] In the case of 2-methylcyclohexanone, recourse to allyltri-*n*-butylstannane and boron trifluoride etherate is reported to give **3**-CH_3 and **4**-CH_3 in a ratio of 94:6.[13]

After their chromatographic separation, **3** and **4** were hydroborated and the targeted diols were isolated as clear viscous oils or colorless solids. Subsequently, authentic samples of the spirocyclic tetrahydrofurans **5** and **6** were made available via cyclization of the primary monotosylates.[14,15] The infrared spectra of **5** and **6**, recorded on neat samples, showed distinctively different C–O–C stretching vibrations. Axial orientation of the ether linkage as in **5** is reflected in the appearance of a medium-intensity band at 1050–1055 cm^{-1}. In the equatorial diastereomers **6**, the stretching vibration is seen at 1075–1080 cm^{-1}.[16] Additionally, stereoisomer **5** proved to be less polar, except when R = OCH_3.

The acid-catalyzed cyclodehydration of **1** and **2** can occur through initial protonolysis and loss of either hydroxyl group. Since innumerable experiments have shown the relative ease of carbocation formation via the S_N1 reaction to be tertiary > secondary > primary, one's initial expectation might be that ionization within **1** and **2** to give the trisubstituted carbocation should be kinetically favored.[17,18] While this pathway might well operate in the parent diol of this series,[19] the possible electrostatic impact of a neighboring R group should not be considered inconsequential. This is especially true for **1**-OCH_3 and **2**-OCH_3, where application of the Taft equation to limiting S_N1 ionization of the tertiary carbinol predicts that a 10^{-2} rate-retarding influence should operate.[20] Roberts has, in fact, unequivocally demonstrated that the solvolysis reactions of **7**[21] and **8**[22] are indeed retarded by approximately 100-fold relative to cyclohexyl and cyclooctyl tosylates, respectively. Consequently, inductive electron withdrawal gains considerable importance in these systems, while anchimeric assistance via neighboring group participation by the α-oxygen center,[23] if operational, is ineffective in achieving even modest rate enhancement.



For these reasons, **1**-OCH_3 and **2**-OCH_3 were selected first to be heated with a catalytic quantity of *p*-toluenesulfonic acid in toluene. Dehydration of **1**-OCH_3 in this manner led reproducibly,

(1) Haggis, G. A.; Owen, L. N. *J. Chem. Soc.* **1953**, 389.
(2) Birch, S. F.; Dean, R. A.; Whitehead, E. V. *J. Org. Chem.* **1954**, *19*, 1449.
(3) Reppe, W. *Justus Liebigs Ann.* **1955**, *596*, 84, 111.
(4) Kotlyarevskii, I. L.; Shvartsberg, M. S.; Trotsenko, Z. P. *Zh. Obshch. Khim.* **1960**, *30*, 440.
(5) Carr, G.; Dean, C.; Whittaker, D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 351.
(6) Mihailovic, M. Lj.; Gojkovic, S.; Cekovic, Z. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2460.
(7) See also: Molnár, A.; Felföldi, K.; Bartók, M. *Tetrahedron* **1981**, *37*, 2149.
(8) Carr, G.; Whittaker, D. *J. Chem. Soc., Perkin Trans. 2* **1989**, 359.
(9) Olah, G. A.; Grant, J. L.; Spear, R. J.; Bollinger, J. M.; Serianz, A.; Sipos, G. *J. Am. Chem. Soc.* **1976**, *98*, 2501.
(10) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.
(11) Preliminary communication: Paquette, L. A.; Negri, J. T. *J. Am. Chem. Soc.* **1991**, *113*, 5072.
(12) Review: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
(13) Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* **1979**, 919.
(14) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.
(15) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669.
(16) Picard, P.; Moulines, J. *Tetrahedron Lett.* **1970**, *11*, 5133.
(17) Vogel, P. *Carbocation Chemistry*; Elsevier: Amsterdam, 1985.
(18) Creary, X. *Advances in Carbocation Chemistry, Volume 1*; Jai Press, Inc.; Greenwich, CT, 1989.
(19) (a) Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947. (b) Mudryk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657.
(20) (a) Winstein, S.; Grunwald, E. *J. Am. Chem. Soc.* **1948**, *70*, 828. (b) Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4935.
(21) (a) Roberts, D. D.; Hendrickson, W. *J. Org. Chem.* **1969**, *34*, 2415. (b) Roberts, D. D. *J. Org. Chem.* **1968**, *33*, 118.
(22) Roberts, D. D.; Traynham, J. G. *J. Org. Chem.* **1967**, *32*, 3177.
(23) Capon, B.; McManus, S. P. *Neighboring Group Participation, Volume 1*; Plenum Press: New York, 1976.

Table I. Acid-Promoted Cyclizations of Specifically C-1/^{18}O-Labeled Diols **1** and **2**[a]

starting diol	percent ^{18}O at C-1	combined product yield, %	extent of isotopic label present, %	
			5	**6**
1-OCH_3	40	47[b]	40, 39	11[c]
2-OCH_3	39	52[b]	16[c]	38, 39
1-C_6H_5	45	84	20, 25	0, 0
2-C_6H_5	45	73	0, 0	19, 22
1-CH_3	39	68	9, 11	0, 0
2-CH_3	38	53	0, 0	6, 10

[a] Analyses were performed by the ^{13}C NMR method described in the text. [b] Yields in these cases refer to major product only. [c] High-resolution mass spectral analysis was made necessary because of limited quantities. Percentages were obtained by analysis of *combined* minor products from duplicate runs.

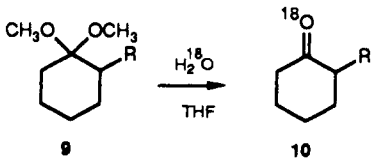
with high stereoselectivity, to a 96:4 mixture of **5**-OCH_3 and **6**-OCH_3 as determined by capillary GC analysis. The response of **2**-OCH_3 was to display equally impressive stereochemical retention (8% of **5**-OCH_3, 92% of **6**-OCH_3). Control experiments conducted independently on both tetrahydrofurans showed them to be stable to the reaction conditions.[24] Therefore, the product distributions necessarily reflect the operation of kinetic and not thermodynamic control. The preferred formation of different diastereomers requires that this pair of diols give rise to different intermediates. A logical rationalization of the results would be to involve selective intramolecular displacement of the primary hydroxyl functionality, without concurrent heterolysis of the tertiary C–O bond, as the predominant reaction pathway.

If electrostatic influences are of the degree of importance suggested, then replacement of OCH_3 by C_6H_5 should result in a lessening of the electronegativity influence. The extent of this change can be most readily gauged by comparison of the σ_m values of the two substituents: 0.12 for OCH_3 and 0.06 for C_6H_5.[25] Acid-catalyzed cyclization of **1**-C_6H_5 in the predescribed manner afforded a 67:33 mixture of **5**-C_6H_5 and **6**-C_6H_5, showing that stereochemical retention still predominates but to a lesser degree. By comparison, **2**-C_6H_5 underwent dehydration with a slight bias for inversion: 55% of **5**-C_6H_5 and 45% of **6**-C_6H_5. The distinction between the response of the methoxyl and phenyl compounds is consequently notable.

In the methyl derivatives, further erosion in the ability to control stereoselection was noted. When comparably transformed into their spiro tetrahydrofurans, both diols were observed to give mixtures somewhat enriched in the inverted stereoisomer (for **1**-CH_3, 40% of **5**-CH_3 and 60% of **6**-CH_3; for **2**-CH_3, 55% of **5**-CH_3 and 45% of **6**-CH_3). As before, the cyclized products in all four instances were recovered unchanged when resubmitted to the dehydration conditions. This insensitivity is taken as evidence that kinetic control is at play throughout the series.

Several possible explanations can be advanced to account for the preceding results. In order to distinguish between these mechanistic options, the specific origin of the resident ethereal oxygen in **5** and **6** was ascertained by ^{18}O labeling of the tertiary hydroxyl in the six diols.

Isotopic Labeling Studies. Incorporation of oxygen-18 was achieved by hydrolysis[26] of the cyclohexanone dimethyl acetals **9** in 50% isotopically enriched $H_2{}^{18}O$. The levels of ^{18}O incor-



9 **10**

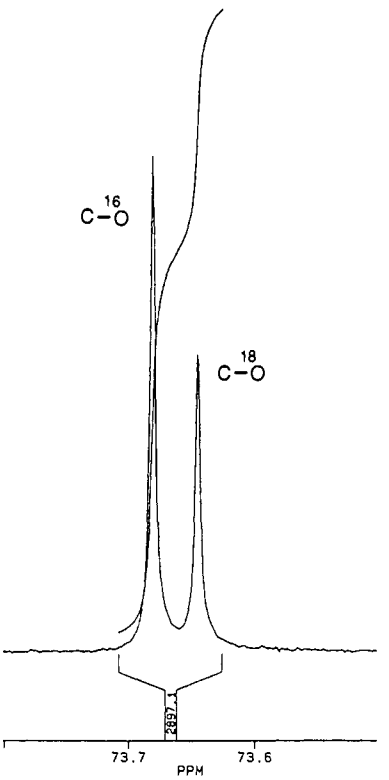


Figure 1. Partial expanded ^{13}C NMR spectrum of isotopically labeled **2**-CH_3 showing the extent of peak separation achieved by this technique.

poration into the carbonyl group were determined by making recourse to the ^{16}O/^{18}O isotopic effect on the chemical shift of the attached ^{13}C atom.[27] Analogous integration of the 75-MHz natural abundance carbon spectra of the derived diols revealed that no dilution of the isotopic concentrations had occurred during the two-step sequence (see Figure 1).[28] The relevant findings have been compiled in Table I.

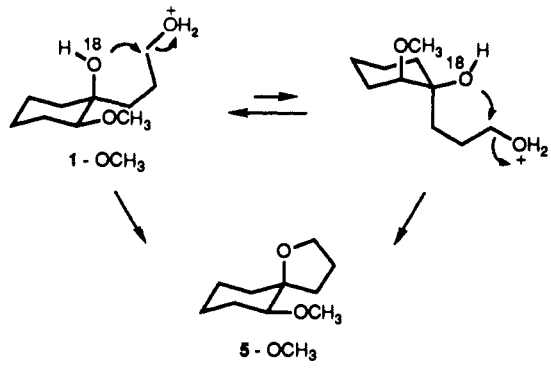
In six sets of duplicate experiments, these specifically labeled diols were cyclized as before. The tetrahydrofurans were isolated as pure isomers and analyzed by the ^{13}C NMR method except in those two instances where the amount of stereoisomeric product was below 10%. The extent of isotopic labeling in these minor components was ascertained by high-resolution mass spectral analysis of a sample resulting from combination of the two runs.

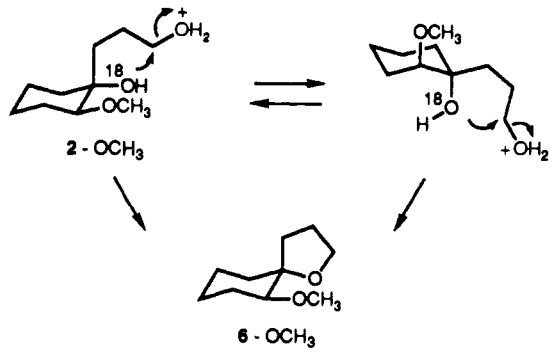
One consequence of the methoxyl substituent is immediately evident: the major tetrahydrofuran produced in each closure is formed not only stereoselectively but also with complete retention of the isotopic label. Thus, the tertiary hydroxyl group remains resident during the ring closures. The liberated water must therefore originate from loss of the primary hydroxyl group. Of additional interest is the fact that the quite minor products of inverted stereochemistry have retained 28–41% of the original ^{18}O label. These observations indicate that, although a very modest amount of ionization to give the tertiary cyclohexyl carbocation does occur, the liberated $H_2{}^{18}O$ does not completely leave the environment of the charged intermediate before being partly reassimilated on the opposite face.

The influence of a neighboring phenyl group has less dramatic consequences. The products of stereochemical retention now contain only approximately 50% of the original label. Although the levels of ^{18}O that persist are quite respectable, the increased incursion of competitive S_N1 ionization with loss of oxygen-18 has become significant. This modification in the extent to which

(24) Tetrahydrofurans are customarily stable to such acidic conditions; see ref 7. The presence of a 3-phenylselenenyl substituent facilitates stereochemical scrambling: Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995.
(25) Kosower, E. M. *An Introduction to Physical Organic Chemistry*; Wiley: New York, 1968; p 49.
(26) Creary, X.; Inocencio, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 5979.
(27) (a) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252. (b) Risley, J. M.; Van Etten, R. L.; Uncuta, C.; Balaban, A. T. *J. Am. Chem. Soc.* **1984**, *106*, 7836. (c) Wilgis, F. P.; Neumann, T. E.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4435.
(28) Signal resolution was routinely improved by use of a narrow sweep width and 128K of computer memory.

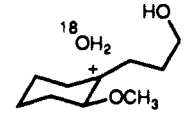
Scheme II





96% intramolecular S_N2 1 - OCH_3 S_N1 4%

92% intramolecular S_N2 2 - OCH_3 S_N1 8%



competitive mechanisms are operative is further revealed by the complete loss of ^{18}O on the spirocyclic tetrahydrofurans of inverted stereochemistry.

In the methyl-substituted systems, a further dimunition was seen in the level of isotopic content within the retention products. No detectable ^{18}O could again be found in the inverted stereoisomers.

The combined results show heteroatom substitution α to a potential carbocationic center to exert an electron-withdrawing effect which is sufficiently powerful to reverse traditional chemical behavior at a remarkable level. Experiments showing the relative ease of carbocation formation to follow the order tertiary > secondary > primary abound, as detailed in all introductory organic chemistry texts. However, the electrostatic circumstances present most notably in **1**-OCH_3 and **2**-OCH_3 impede classical S_N1 behavior sufficiently to allow preferred operation of the *intramolecular S_N2 mechanism.*

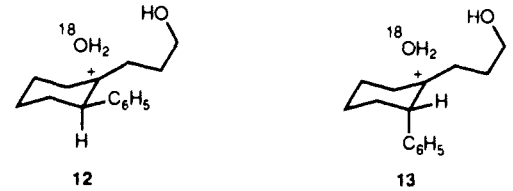
Discussion

Methoxyl Series. Favored Operation of the Intramolecular S_N2 Pathway. The observation that **1**-OCH_3 and **3**-OCH_3 cyclize with 96% and 92% retention of stereochemistry, respectively, without loss of the ^{18}O label originally present within the C-1 hydroxyl

Scheme III

34% intramolecular S_N2 1 - C_6H_5 S_N1 66%

22% intramolecular S_N2 2 - C_6H_5 S_N1 78%



group cannot be accommodated by a carbonium ion mechanism in its simplest form. Since the pair of stereoisomers undergoes dehydration with high stereoselectivity, these reactions clearly do not proceed through a common intermediate. Rather, the full range of the present findings can be explained in terms of kinetically favored operation of an intramolecular S_N2 reaction. As denoted in Scheme II, the process entails cooperative nucleophilic attack by a tertiary hydroxyl lone pair with displacement of water at the primary center of the diol. The previously unrecognized ability of this intramolecular reaction to be highly competitive vis-a-vis conventional S_N1 ionization may give rise to an initial impression that nontraditional chemical behavior is at play. However, five-ring cyclizative reactions are known to be especially favorable for entropic reasons.[23]

Although anchimeric assistance on the part of the tertiary hydroxyl certainly occurs and the same electrostatic effects operate in **1**-OCH_3 and **2**-OCH_3, allowance should be made for the possibility that the reacting conformer of a particular diol may differ from the preferred ground-state topography.[29] In the present circumstances, either chair conformer would appear to be quite capable of giving rise to the tetrahydrofuran (Scheme II). A minor difference is manifested in the partitioning of the mechanistic alternatives, however, with **1**-OCH_3 demonstrating a slightly greater (4%) predilection than **2**-OCH_3 for proceeding to product via the intramolecular S_N2 pathway. This trend is evident in all three pairs of stereoisomeric diols. Nevertheless, we choose not to speculate on its origins at this time, but simply call attention to the fact that axial cyclohexyl derivatives have long been recognized to ionize about three times faster than their equatorial conformers.[30]

The very high levels of ^{18}O retained during the **1**-OCH_3 → **5**-OCH_3 and **2**-OCH_3 → **6**-OCH_3 conversions facilitate analysis of the extent to which the two reaction channels operate. A control experiment in which labeled **1**-OCH_3 was dehydrated to only the 30% level and recovered showed that the isotopic label had not shifted to the primary position. Consequently, there appear to be no "hidden" mechanistic alternatives operating.

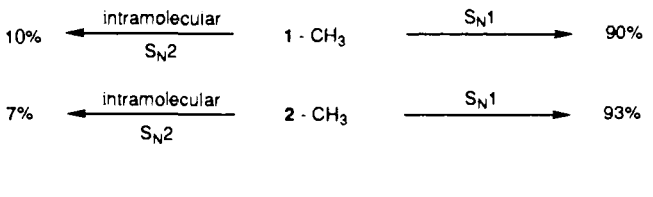
With both **1**-OCH_3 and **2**-OCH_3, the formation of inverted product is accompanied by significant amounts of recaptured $H_2{}^{18}O$. An obvious corollary of the picture developed thus far is that tertiary cation **11** is differently solvated by $H_2{}^{18}O$ in relation to its stereoisomeric precursors and is so inductively destabilized that its finite existence is short-lived. This translates into an inability on the part of the system to await nucleophilic attack by the tethered primary hydroxyl substituent exclusively. Instead, intramolecular capture finds itself competing with rebonding to $H_2{}^{18}O$ from the opposite face of the cationic carbon.[31] In both

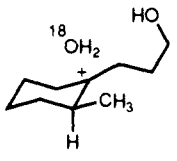
(29) (a) Lambert, J. B.; Putz, G. J. *J. Am. Chem. Soc.* **1973**, *95*, 6313. (b) Nordlander, J. E.; McCrary, T. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5132; **1974**, *96*, 4066 and relevant references cited in these papers.

(30) Winstein, S.; Holness, S. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.

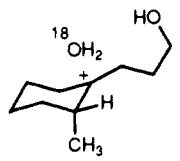
(31) Obviously, we are not in a position to assess the extent to which S_N1 ionization occurs with recapture of $H_2{}^{18}O$ from the original surface. Accordingly, the values given for the extent of S_N1 ionization must be regarded as minimal percentages.

Scheme IV





14



15

examples, the intramolecular cyclization occurs strictly by inversion. This necessitates that conformational interconversion between the carbocations not operate prior to C–O bond formation and that the departing $H_2{}^{18}O$ molecule be sterically shielding the surface on which it is originally located.

Impact of 2-Phenyl Substitution. The results show that the reduced electron-withdrawing ($-I$) effect of phenyl leads **1**-C_6H_5 and **2**-C_6H_5 to experience a greater proportion of S_N1 ionization than their methoxyl analogues (Scheme III). All things considered, the assumption that carbocations **12** and **13** are longer lived than **11** seems reasonable. As a result, the $H_2{}^{18}O$ has a greater opportunity to escape from the immediate environment, thereby facilitating ring closure via capture of the primary hydroxyl. Although neither inverted product contains residual ^{18}O, the sites on each side of the planar cations still do not give evidence of being totally comparable when accessed from the two directions. The cation from **1**-C_6H_5 undergoes closure to give equal amounts of ^{18}O-free **5**-C_6H_5 and **6**-C_6H_5. When starting with **2**-C_6H_5, more unlabeled **5**-C_6H_5 (55%) is produced than unlabeled **6**-C_6H_5 (23%). Thus, cyclization occurs more rapidly than full equilibration between conformers **12** and **13**. Furthermore, the presence of an axial phenyl group in **13** provides considerably more incentive to axial attack than does the equatorial phenyl in **12**.

Methyl Effect. Since methyl is an electron-releasing substituent, its role regarding carbocations **14** and **15** is to provide some measure of inductive stabilization. As is apparent from the product and isotopic labeling results, the relative rates of the two competing reactions now favor the S_N1 option quite heavily (Scheme IV). It is noteworthy, however, that the intramolecular S_N2 process does continue to play a role, albeit at a low level.

As has been emphasized earlier with the phenyl examples, cations **14** and **15** are necessarily formed in different geometric arrangements and with contrasting face-selective steric shielding by the departing water molecule. These features continue to be apparent in the chemistry of **1**-CH_3 and **2**-CH_3. Product distributions are clearly sensitive to the relative stereochemistry of the starting diol. For **1**-CH_3, loss of isotopic label materializes 9 out of every 10 times that a water molecule is lost. Although S_N1 behavior is adopted to generate **14** 90% of the time,[31] intramolecular closure of this intermediate occurs twice as fast when proceeding to **6**-CH_3 (60%) compared to **5**-CH_3 (30%). Since configurational inversion is more readily achieved, the water molecule involved in the reaction must continue to reside in the solvation shell to such an extent that intramolecular attack by the primary hydroxyl from the opposite face is kinetically facilitated.[32] This conclusion is supported by the complementary behavior of **2**-CH_3, which undergoes S_N1 ionization to the extent of 93%[31] and gives rise to more **5**-CH_3 (55%) than to stereochemically retained **6**-CH_3 (38%). Since inversion of configuration is obviously preferred in these two examples with formation of inverse ratios of the spirocyclic tetrahydrofurans, **14** and **15**, like **12** and **13**, cannot be equilibrating prior to covalent C–O bond formation. However, the internal return of $H_2{}^{18}O$ has become noticeably reduced, presumably as a consequence of the more favorable electronic state of affairs within these longer lived tertiary carbocations.

(32) (a) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779. (b) Finne, E. S.; Gunn, J. R.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7816. (c) Kirchen, R. P.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7811. (d) Buffam, D. J.; Sorensen, T. S.; Whitworth, S. M. *Can. J. Chem.* **1990**, *68*, 1889.

Conclusions

This study has demonstrated that the S_N1 response to tertiary alcohols is clearly subject to electrostatic modulation and to a significant degree. The rate retardation experienced by systems carrying a nearby methoxyl group is of sufficient magnitude to allow the previously unappreciated intramolecular S_N2 mechanistic alternative to dominate at levels in excess of 90%. Isotopic labeling data have provided convincing insight into the operation of this otherwise hidden pathway. The extent of its operation is dependent on the electronic characteristics of the nearby substituent. Its adoption continues to persist (at or below the 10% level) even when R is methyl.

The intriguing departure from traditional carbocation reactivity documented herein illustrates the potential promise offered by α-heteroatom substitution as a tool for effecting highly stereocontrolled intramolecular reactions under seemlingly improbable circumstances. Further studies are planned to more extensively quantify the magnitude of the effect and to demonstrate applications in stereocontrolled intramolecular processes.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC-300 instrument as indicated. Mass spectra were recorded on a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Isotropic levels determined by the intensity of $(M + 2)^+$ peaks were conducted for the appropriate natural abundances. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All separations were carried out under flash chromatography conditions on Merck silica gel HF_{254}. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

1-Allyl-2-methoxycyclohexanols (3-OCH_3 and 4-OCH_3). Allylmagnesium bromide was prepared from allyl bromide (7.74 g, 64 mmol) and magnesium turnings (2.67 g, 0.11 mol) in anhydrous ether (40 mL). A solution of 2-methoxycyclohexanone (3.0 g, 23.4 mmol) in ether (30 mL) was introduced dropwise to the Grignard solution. After 30 min, the reaction mixture was partitioned between saturated ammonium chloride solution (100 mL) and diethyl ether (100 mL). The ether layer was dried and concentrated to leave a mixture of alcohols (3.0 g). Column chromatography (silica gel, elution with ether–petroleum ether, 1:9) gave 2.95 g (74%) of **3**-OCH_3, 92 mg of a mixed fraction (63:37 favoring **3**-OCH_3 by ^1H NMR), and 259 mg (7%) of **4**-OCH_3.

For **3**-OCH_3: colorless oil; IR (neat, cm^{-1}) 3575–3400, 3065, 2980–2920, 1675, 1445, 1100, 990, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.00 (m, 2 H), 3.28 (s, 3 H), 2.93 (dd, J = 8.8, 3.8 Hz, 1 H), 2.21 (m, 3 H), 1.80–1.05 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.12, 117.32, 81.87, 72.72, 56.29, 43.33, 34.27, 25.01, 22.65, 21.12; MS m/z (M^+) calcd 170.1306, obsd 170.1322. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.45; H, 10.70.

For **4**-OCH_3: colorless oil; IR (neat, cm^{-1}) 3600–3300, 3045, 2980–2820, 1640, 1450, 1195, 1050, 1110, 925; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1 H), 5.12 (m, 2 H), 3.36 (s, 3 H), 3.06 (dd, J = 8.1, 3.5 Hz, 1 H), 2.44 (dd, J = 14.1, 6.7 Hz, 1 H), 2.25 (dd, J = 14.1, 8.1 Hz, 1 H), 2.00 (br s, 1 H), 1.90 (m, 1 H), 1.86–1.25 (series of m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.84, 118.46, 84.43, 73.47, 56.92, 39.18, 33.96, 25.33, 22.26, 21.78; MS m/z (M^+) calcd 170.1306, obsd 170.1292.

1-Allyl-2-phenylcyclohexanols (3-C_6H_5 and 4-C_6H_5). Reaction of 2-phenylcyclohexanone (3.0 g, 17.2 mmol) with the allyl Grignard reagent as above gave rise to a 3.8:1 mixture of **3**-C_6H_5 and **4**-C_6H_5 (GC analysis). The isomers were separated by silica gel chromatography (elution with ether–petroleum ether, 1:9) to give 2.678 g (72%) of **3**-C_6H_5 and 670 mg (18%) of **4**-C_6H_5.

For **3**-C_6H_5: colorless oil: IR (neat, cm^{-1}) 3480 (br); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 5.75 (m, 1 H), 5.07 (br d, J = 10 Hz, 1 H), 4.96 (br d, J = 17 Hz, 1 H), 2.55 (dd, J = 12.8, 3.6 Hz, 1 H), 2.13–1.84 (m, 3 H), 1.81–1.59 (m, 5 H), 1.55–1.26 (m, 3 H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 142.81, 133.73, 129.06, 128.01, 126.36, 118.26, 72.24, 52.06, 46.48, 29.09, 26.32, 21.49; MS *m/z* (M^+) calcd 216.1514, obsd 216.1522. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.09; H, 9.33.

For 4-C_6H_5: colorless solid, mp 55–56 °C (from cold diethyl ether–petroleum ether); IR (neat, cm^{-1}) 3585; ^1H NMR (300 MHZ, $CDCl_3$) δ 7.26 (m, 5 H), 5.76 (m, 1 H), 5.03 (m, 2 H), 2.81 (dd, *J* = 11.9, 4.2 Hz, 1 H), 2.50 (dd, *J* = 14.3, 8.3 Hz, 1 H), 2.08–1.66 (m, 6 H), 1.60–1.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.02, 133.68, 129.36, 127.88, 126.53, 117.83, 73.51, 54.61, 36.96, 36.70, 28.92, 26.11, 23.17; MS *m/z* (M^+) calcd 216.1514, obsd 216.1554. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.26; H, 9.41.

1-Allyl-2-methylcyclohexanols (3-CH_3 and 4-CH_3). Reaction of 2-methylcyclohexanone (3.0 g, 28.7 mmol) with the allyl Grignard reagent gave rise to a stereoisomeric mixture of 3-OCH_3 and 4-OCH_3 in a 4:1 ratio by ^1H NMR (3.82 g), which was subjected to silica gel chromatography (elution with ether–petroleum ether, 5:95). Isolated were 2.625 g (64%) of 3-CH_3, 512 mg of a mixed fraction, and 175 mg (4%) of 4-CH_3.

For 3-CH_3: colorless oil; IR (neat, cm^{-1}) 3480; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1 H), 5.05 (m, 2 H), 2.22 (dd, *J* = 7.5, 1.0 Hz, 2 H), 1.63–1.10 (m, 10 H), 0.86 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.06, 117.80, 72.53, 45.26, 38.05, 36.41, 30.45, 25.55, 21.62, 14.79; MS *m/z* ($M^+ - H$) calcd 153.1280, obsd 153.1253. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.51; H, 11.74.

For 4-CH_3: colorless oil; IR (neat, cm^{-1}) 3560–3200; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1 H), 5.13 (m, 2 H), 2.20 (dd, *J* = 12.6, 7.0 Hz, 2 H), 1.75–1.10 (m, 10 H), 0.93 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.81, 118.51, 73.64, 40.93, 38.52, 36.19, 30.92, 23.96, 22.98, 15.09; MS *m/z* (M^+) calcd 154.1357, obsd 154.1371.

***cis*-1-(3-Hydroxypropyl)-2-methoxycyclohexanol (1-OCH_3).** A solution of 3-OCH_3 (500 mg, 2.94 mmol) in dry tetrahydrofuran (10 mL) cocled to 0 °C was treated with a borane-THF complex (1.0 M, 3.0 mL, 3.0 mmol). The reaction mixture was stirred at 0 °C for 1 h, at which point 3 M sodium hydroxide (3.0 mL, 9 mmol) was added rapidly, followed by hydrogen peroxide (30%, 1 g). The resulting solution was stirred at 0 °C for an additional 1 h and poured into ether. The separated organic phase was washed with brine, dried, and evaporated. Column chromatography of the residue (silica gel, elution with ether–petroleum ether) furnished 313 mg (57%) of 1-OCH_3 as a thick, colorless oil: IR (neat, cm^{-1}) 3590–3160; ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (t, *J* = 5.3 Hz, 2 H), 3.35 (s, 3 H), 3.01 (dd, *J* = 7.1, 4.3 Hz, 1 H), 2.60 (br s, 2 H), 1.77–1.46 (m, 9 H), 1.44–1.18 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.72, 72.71, 62.90, 56.47, 34.56, 33.66, 26.20, 25.04, 21.99, 21.44; MS *m/z* (M^+) calcd 188.1412, obsd 188.1454.

***trans*-1-(3-Hydroxypropyl)-2-methoxycyclohexanol (2-OCH_3).** A 240-mg (1.4 mmol) sample of 4-OCH_3 was similarly hydroborated. Purification by column chromatography as before gave 2-OCH_3 as a thick, colorless oil (151 mg, 57%); IR (neat, cm^{-1}) 3600–3100; ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (t, *J* = 5.7 Hz, 2 H), 3.32 (s, 3 H), 3.05 (dd, *J* = 8.4, 3.6 Hz, 1 H), 2.92 (br s, 2 H), 2.80–1.35 (m, 9 H), 1.35–1.20 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.89, 73.58, 63.25, 56.81, 33.77, 30.92, 25.54, 25.33, 22.38, 21.87; MS *m/z* (M^+) calcd 188.1413, obsd 188.1444.

***cis*-1-(3-Hydroxypropyl)-2-phenylcyclohexanol (1-C_6H_5).** A 200-mg (0.925 mmol) sample of 3-C_6H_5 was similarly hydroborated to give 165 mg (76%) of 1-C_6H_5 as colorless needles: mp 96–97 °C (from ether–petroleum ether); IR ($CHCl_3$, cm^{-1}) 3605, 3420; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 3.46 (m, 2 H), 2.53 (dd, *J* = 12.8, 3.4 Hz, 1 H), 2.07 (qd, *J* = 12.8, 3.4 Hz, 1 H), 2.07 (qd, *J* = 12.8, 3.0 Hz, 1 H), 1.94–1.50 (m, 9 H), 1.45–1.10 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.87, 129.00, 128.16, 126.46, 72.40, 63.24, 52.60, 38.54, 36.14, 29.09, 26.39 (2 C), 21.62; MS *m/z* (M^+) calcd 234.1620, obsd 234.1623. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.78; H, 9.50.

***trans*-1-(3-Hydroxypropyl)-2-phenylcyclohexanol (2-C_6H_5).** In the manner described above, 4-C_6H_5 (207 mg, 0.95 mmol) was hydroborated and chromatographed (silica gel, elution with ether–petroleum ether, 1:1) to give 3-C_6H_5 as fine, colorless crystals; mp 137–138 °C (from ether–petroleum ether), 182 mg (81%); IR ($CHCl_3$, cm^{-1}) 3575, 3400; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.12 (m, 5 H), 3.44 (m, 2 H), 2.66 (dd, *J* = 12.5, 3.6 Hz, 1 H), 2.10–1.63 (m, 8 H), 1.55–1.20 (m, 5 H), 0.93 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.97, 129.47, 128.02, 126.63, 73.79, 63.22, 55.43, 36.25, 29.14, 28.73, 26.23, 25.81, 23.44; MS *m/z* (M^+) calcd 234.1620, obsd 234.1611. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.60; H, 9.50.

***cis*-1-(3-Hydroxypropyl)-2-methylcyclohexanol (1-CH_3).** Comparable treatment of 3-CH_3 (500 mg, 3.22 mmol) and silica gel chromatography of the diol (elution with ether–petroleum ether, 1:1) gave 1-CH_3 as granular white crystals: mp 78–79 °C (from CH_2Cl_2–petroleum ether), 435 mg (78%); IR ($CHCl_3$, cm^{-1}) 3500–3420; ^1H NMR (300 MHz, $CDCl_3$) δ 3.63 (m, 2 H), 2.08 (s, 2 H), 1.70–1.14 (series of m, 13 H), 0.87 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.69, 63.34, 38.74, 37.15, 35.70, 30.59, 26.66, 25.52, 21.80, 14.85; MS *m/z* (M^+) calcd 172.1464, obsd 172.1464. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.90; H, 11.73.

***trans*-1-(3-Hydroxypropyl)-2-methylcyclohexanol (2-CH_3).** From 148 g (0.96 mmol of 4-CH_3, 96 mg (58%) of 2-CH_3 was obtained as fine, granular crystals: mp 71–72 °C (from diethyl ether–petroleum ether); IR ($CHCl_3$, cm^{-1}) 3600; ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (m, 2 H), 2.95 (s, 2 H), 1.81 (m, 1 H), 1.73–1.35 (m, 8 H), 1.35–1.10 (m, 4 H), 0.88 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.84, 63.11, 41.26, 35.90, 30.99, 30.38, 25.54, 24.00, 23.03, 14.96; MS *m/z* (M^+) calcd 172.1464, obsd 172.1486. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.65; H, 11.81.

Base-Promoted Cyclization of the Primary Monotosylates. General Procedure. To a solution of the diol (0.37 mmol) and a catalytic quantity of 4-(dimethylamino)pyridine in dry triethylamine was added via cannula a solution of *p*-toluenesulfonyl chloride (78 mg, 0.4 mmol) in dry CH_2Cl_2 (1.4 mL). The reaction mixture was stirred at room temperature for 16 h and poured into ether and water (50 mL each). The ether layer was washed with 2 M HCl (3×) and then brine, dried, and concentrated. Column chromatography on silica gel followed.

For 5-OCH_3: colorless oil (73%); IR (neat, cm^{-1}) 2980–2820, 1400, 1195, 1140, 1110, 1065, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (m, 2 H), 3.35 (s, 3 H), 2.98 (dd, *J* = 7.4, 4.8 Hz, 1 H), 2.00–1.50 (m, 9 H), 1.42–1.15 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.86, 83.32, 67.74, 57.03, 35.18, 34.15, 26.51, 26.03, 22.67, 22.62; MS *m/z* (M^+) calcd 170.1307, obsd 170.1307. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.38; H, 10.72.

For 6-OCH_3: colorless oil (70%); IR (neat, cm^{-1}) 2980–2828, 1450, 1110, 1080, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (t, *J* = 6.5 Hz, 2 H), 3.39 (s, 3 H), 3.06 (dd, *J* = 8.8, 3.7 Hz, 1 H), 2.07–1.77 (m, 4 H), 1.69–1.49 (m, 4 H), 1.45–1.16 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.88, 67.65, 57.69, 35.99, 30.43, 28.37, 26.34, 23.45, 22.65; MS *m/z* (M^+) calcd 170.1306, obsd 170.1282.

For 5-C_6H_5: colorless oil (71%); IR (neat, cm^{-1}) 3060, 3040, 2960–2860, 1600, 1490, 1440, 1305, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 3.63 (m, 2 H), 2.50 (dd, *J* = 12.8, 3.5 Hz, 1 H), 2.05 (qd, *J* = 12.9, 3.4 Hz, 1 H), 1.90–1.55 (m, 7 H), 1.53–1.28 (m, 3 H), 0.94 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.86, 129.55, 127.67, 126.06, 83.58, 68.00, 52.74, 38.98, 36.35, 30.48, 26.43, 25.58, 22.81; MS *m/z* (M^+) calcd 216.1514, obsd 216.1507. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.18; H, 9.44.

For 6-C_6H_5: colorless oil (83%); IR (neat, cm^{-1}) 3080, 2975–2850, 1490, 1450, 1075; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.08 (m, 5 H), 3.56 (m, 1 H), 3.05 (m, 1 H), 2.77 (dd, *J* = 12.8, 3.0 Hz, 1 H), 1.84–1.44 (m, 9 H), 1.30 (m, 2 H), 0.95 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.40, 129.48, 127.40, 125.96, 85.79, 67.34, 51.72, 40.20, 29.81, 29.37, 26.20, 25.09; MS *m/z* (M^+) calcd 216.1514, obsd 216.1525. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.98; H, 9.40.

For 5-CH_3: colorless, volatile oil (50%); IR (neat, cm^{-1}) 2975–2865, 1725, 1460, 1440, 1070, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (m, 2 H), 1.91–1.18 (m, 13 H), 0.87 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.71, 67.55, 39.14, 36.76, 35.86, 31.61, 26.30, 24.69, 23.25, 15.18; MS *m/z* (M^+) calcd 154.1176, obsd 154.1354. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.98; H, 11.72.

For 6-CH_3: colorless, volatile oil (64%); IR (neat, cm^{-1}) 2995–2850, 1450, 1015; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (t, *J* = 6.6 Hz, 2 H), 2.00–1.50 (m, 9 H), 1.43–1.21 (m, 3 H), 1.05 (m, 1 H), 0.85 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.67, 67.21, 40.34, 37.91, 32.80, 29.15, 26.79, 25.03, 24.70, 24.48, 15.49; MS *m/z* (M^+) calcd 154.1358, obsd 154.1342. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.56; H, 11.72.

Acid-Promoted Cyclization of the Unlabeled Diols. General Procedure. The diol (0.17 mmol) was heated at reflux in an argon atmosphere in dry toluene (15 mL) containing a catalytic quantity of *p*-toluenesulfonic acid under a Soxhlet extractor containing CaH_2 for the removal of water. After 16 h, the reaction mixture was cooled and then poured into ether (30 mL) and saturated $NaHCO_3$ solution (20 mL). The organic phase was washed with brine, dried, and concentrated. The composition of the stereoisomeric spirocyclic tetrahydrofurans was determined by capillary GC, and separation was achieved by silica gel chromatography (elution with ether–petroleum ether, 10:90). For added details, see the section dealing with the isotopically labeled diols.

Preparation of Dimethyl Acetals 9. The ketone was stirred at room temperature with 1.2 equiv of trimethyl orthoformate in anhydrous methanol (ca. 3 mmol/mL) in the presence of *p*-toluenesulfonic acid (100–200 mg) for 16 h. The mixture was partitioned between ether and saturated $NaHCO_3$ solution, and the organic phase was washed with water and brine, dried, and evaporated. The pure acetals were obtained

by distillation under reduced pressure (**9**-OCH_3, 91%; **9**-CH_3, 76%) or by silica gel chromatography (**9**-C_6H_5, 26%). The last reaction was noted to proceed sluggishly.

Hydrolytic Incorporation of Oxygen-18. To a solution of the acetal in anhydrous THF (10 mL) was added 1.2 equiv of $H_2{}^{18}O$ (50% isotopically enriched) followed by 2 drops of concentrated H_2SO_4. The reaction mixture was stirred at room temperature, and the progress of the hydrolysis was monitored by TLC. When complete, triethylamine (4 drops) was added, stirring was continued for 5 min, and solvents were carefully removed on a rotary evaporator. The labeled ketone was distilled from the flask under reduced pressure. For R = OCH_3: reaction time of 24 h; 4.8 equiv of $H_2{}^{18}O$ utilized; 3.0 g of acetal furnished 1.59 g (72%) of 2-methoxycyclohexanone containing 40% of ^{18}O. For R = C_6H_5: reaction time of 20 min; 1.08 g of acetal gave 806 mg (94%) of 2-phenylcyclohexanone containing 45% of ^{18}O. For R = CH_3: reaction time of 25 min; 3.0 g of acetal afforded 1.999 g (94%) of 2-methylcyclohexane containing 39% of ^{18}O.

Alkylation and Hydroboration of the Labeled 2-Substituted Cyclohexanones. These reactions were performed in the previously described manner with essentially identical efficiencies. For **1**-OCH_3: ^{13}C-^{16}O, 72.72 ppm; ^{13}C-^{18}O, 72.69 ppm. For **1**-C_6H_5: ^{13}C-^{16}O, 72.26 ppm; ^{13}C-^{18}O, 72.22 ppm. For **1**-CH_3: ^{13}C-^{16}O, 72.68 ppm; ^{13}C-^{18}O, 72.65 ppm. For **2**-OCH_3: ^{13}C-^{16}O, 73.56 ppm; ^{13}C-^{18}O, 73.53 ppm. For **2**-C_6H_5: ^{13}C-^{16}O, 73.79 ppm; ^{13}C-^{18}O, 73.75 ppm. For **2**-CH_3: ^{13}C-^{16}O, 73.68 ppm; ^{13}C-^{18}O, 73.65 ppm.

Acid-Catalyzed Cyclization of the Labeled Diols. These cyclizations were carried out as described previously. The product ratios were determined by GC analysis. The diastereomeric tetrahydrofurans were separated by column chromatography on silica gel. All reactions were performed in duplicate. See Table I. For **5**-OCH_3: $^{13}CH_2$-^{16}O, 67.77 ppm; $^{13}CH_2$-^{18}O, 67.75 ppm. For **5**-C_6H_5: $^{13}CH_2$-^{16}O, 67.97 ppm; $^{13}CH_2$-^{18}O, 67.95 ppm. For **5**-CH_3: $^{13}CH_2$-^{16}O, 67.55 ppm; $^{13}CH_2$-^{18}O, 67.52 ppm. For **6**-OCH_3: $^{13}CH_2$-^{16}O, 67.67 ppm; $^{13}CH_2$-^{18}O, 67.65 ppm. For **6**-C_6H_5: $^{13}CH_2$-^{16}O, 67.34 ppm; $^{13}CH_2$-^{18}O, 67.32 ppm. For **6**-CH_3: $^{13}CH_2$-^{16}O, 67.21 ppm; $^{13}CH_2$-^{18}O, 67.18 ppm.

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Acid-Catalyzed Cyclization of 1,4-Diols Tethered to (Butadiene)iron Tricarbonyl Segments. Isotopic Labeling as a Mechanistic Probe of Stereochemical Retention during Tetrahydrofuran Formation

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Abstract: 1,4-Butanediols can undergo acid-catalyzed dehydrative cyclization by either of two pathways. Selected 1-(3-hydroxypropyl)cyclohexanols have previously been shown to prefer the intramolecular S_N2 option where displacement of water by the more highly substituted carbinol oxygen atom operates. All four ^{18}O-labeled 1,4-diols prepared in this study, constructed so as to carry the secondary hydroxyl immediately adjacent to a tricarbonyliron-complexed diene, choose the alternative S_N1 option. As a consequence, all of the isotopic content is absent in the tetrahydrofuran products, and stereochemical integrity is not preserved. Control experiments performed under the same mild conditions reveal product equilibration to be facile. Consequently, the opposite mechanistic extreme is followed by these systems. Other ground-state and transition-state considerations are discussed.

The ability of selected 1-(3-hydroxypropyl)cyclohexanols carrying electron-withdrawing 2-substituents to undergo acid-catalyzed conversion to spirocyclic tetrahydrofurans preferentially via an intramolecular S_N2 mechanism is now an established fact.[2] Even in those cases where the resident proximal group is capable of favorable inductive contributions (e.g., methyl), the alternative S_N1 option is not adopted exclusively. This remarkable departure from conventional mechanistic behavior has prompted us to examine structural building blocks other than cyclohexane rings for their capability to promote ionization via one or the other of these competing processes.

A systematic extension to tricarbonyl(*trans*-π-pentadienyl)iron systems forms the basis of the present report. Unsymmetrically substituted dienes selectively complexed to $Fe(CO)_3$ are playing increasingly utilitarian roles in organic synthesis.[3] Their intrinsic chirality and ability to be produced conveniently in optically pure condition have further broadened the range of interest.[3b,4]

No less impressive is the recent report[5] that the epimeric alcohols **1** and **4** are transformed in the presence of ethereal tetrafluoroboric acid to the optically active cyclized products **3** and **6**, respectively, with clean retention of stereochemistry. These results were attributed to the intervention of intermediate Fe$(CO)_3$-complexed pentadienyl cations **2** and **5**, which were formed stereoselectively because of anchimerically assisted departure of the protonated tertiary hydroxyl group with recapture of the ethereal oxygen from the same face as the departed water molecule. These observations are, however, also consistent with operation of the intramolecular S_N2 pathway.

Considerably earlier, the solvolytic studies of Clinton and Lillya showed definitively that the ionization of 3,5-dinitrobenzoates **7**

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(2) (a) Negri, J. T.; Paquette, L. A. *J. Am. Chem. Soc.*, preceding paper in this issue. (b) Paquette, L. A.; Negri, J. T. *J. Am. Chem. Soc.* **1991**, *113*, 5072.
(3) (a) Fatiadi, A. J. *J. Res. Natl. Inst. Stand. Technol.* **1991**, *96*, 1. (b) Franck-Neumann, M. *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Eds.; Springer-Verlag: Berlin, 1987; pp 247-264. (c) Koerner von Gustorf, E. A.; Grevels, F. W.; Fischler, I. *The Organic Chemistry of Iron*; Academic Press: New York, 1981; Vol. 2, pp 1-154.
(4) Grée, R. *Synthesis* **1989**, 341.
(5) Teniou, A.; Toupet, L.; Grée, R. *Synlett* **1991**, 195.

0002-7863/92/1514-8841$03.00/0