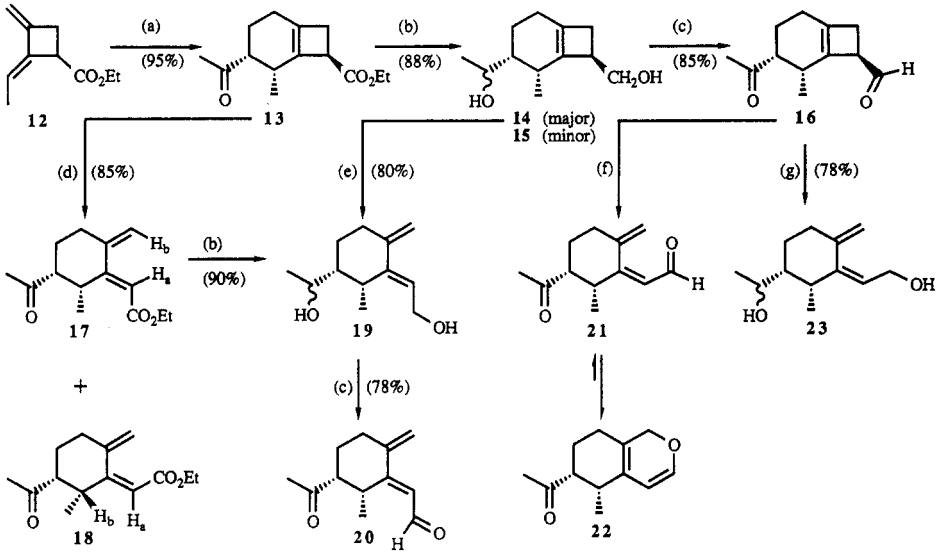
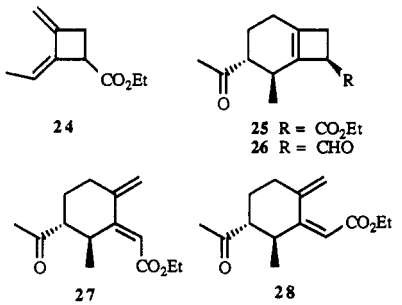
Scheme I[a]



[a] (a) 3-Buten-2-one, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C; (b) *i*-Bu_2AlH, Et_2O; (c) $(COCl)_2$, Me_2SO, CH_2Cl_2; Et_3N; (d) mesitylene, reflux, 1 h; (e) neat, 160 °C, 30 min; (f) C_6D_6, reflux, 3 h; (g) PhMe, reflux, 30 min; cool to −78 °C; add *i*-Bu_2AlH in PhMe; stir at −78 °C for 30 min, at 0 °C for 30 min, and at room temperature for 2 h.

are epimeric with the previously studied substances **13** and **16**, respectively.



Thermolysis of **26** produced results essentially identical with those described above for the ring opening of **16** (Scheme I, steps f and g). On the other hand, thermally induced ring opening of **25** gave a result significantly different from that derived from thermolysis of **13**. Thus, while ring opening of **13** produced a 11:1 mixture of **17** and **18**, treatment of **25** under identical conditions afforded a 1:1 mixture of the isomeric esters **27** and **28**.

The results summarized above show that functionalized 3-formylcyclobutene systems (e.g. **16**, **26**), like the parent compound **4**,[3] undergo electrocyclic ring opening with exclusive inward rotation of the formyl group. Interestingly, in accord with the theoretical predictions of Buda, Wang, and Houk,[5] thermolysis of the bicyclic ester **13** results in preferential outward rotation of the CO_2Et function. However, in the ring opening of **25**, the rates of inward and outward rotation of the ester group are equal. It is possible to rationalize the stereochemical difference between the ring openings of **13** and **25** as follows. Molecular models indicate that, in the conversion of **25** into **27** (outward rotation), it is necessary for the CO_2Et group to slide past the (pseudoequatorial) secondary Me group on the six-membered ring. The resultant steric strain, which is absent in the conversion of **13** into **17**, would cause an increase in the transition state energy for the **25** → **27** transformation relative to that for the **13** → **17** conversion. Thus, the stereochemistry of the thermal ring opening of **13** might be considered "normal", while that of the corresponding reaction involving substrate **25** can be classified as being somewhat "abnormal".

Acknowledgment. We thank Professor K. N. Houk for helpful discussions and for informing us regarding unpublished results from his laboratory. We are grateful to NSERC of Canada for financial support and to the University of British Columbia for a Graduate Fellowship (to Y.-F.L.).

Supplementary Material Available: Experimental procedures for the preparation of compound **13** and for the thermolysis of compounds **13** and **16**; spectral data for compounds **13**, **16**–**18**, and **21**–**23** (4 pages). Ordering information is given on any current masthead page.

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Intramolecular Radical Cyclizations of 2-Deoxy-2-iodohexopyranoside Derivatives: Routes to Densely Functionalized Carbocycles[1]

Summary: 2-Deoxy-2-iodohexopyranosides containing appropriate traps at C6 or C7 undergo radical cyclization to give oxabicyclo[2.2.1] or -[2.2.2] systems whose glycosidic bonds are readily cleaved to afford densely functionalized cyclopentanes or cyclohexanes.

Sir: The use of carbohydrates for the synthesis of carbocycles has been an area of protracted interest in our research group.[3] The well-documented annulation of carbohydrates through Diels–Alder methodology[4] and other techniques[5] has provided convenient access to optically

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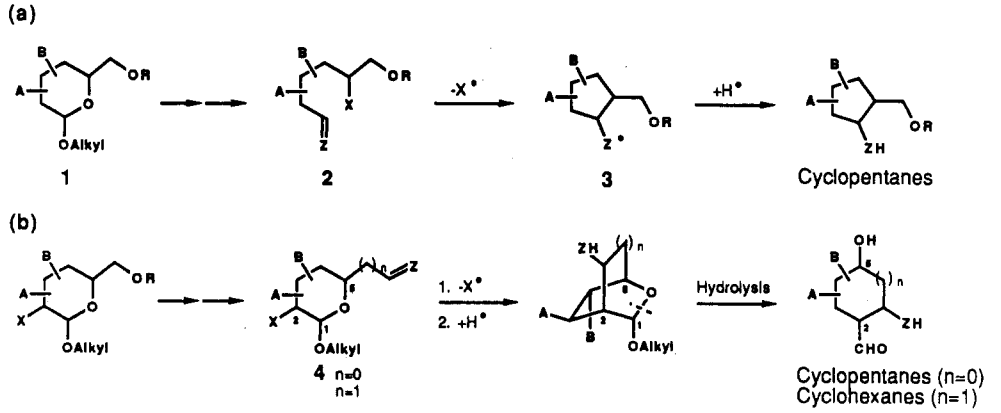
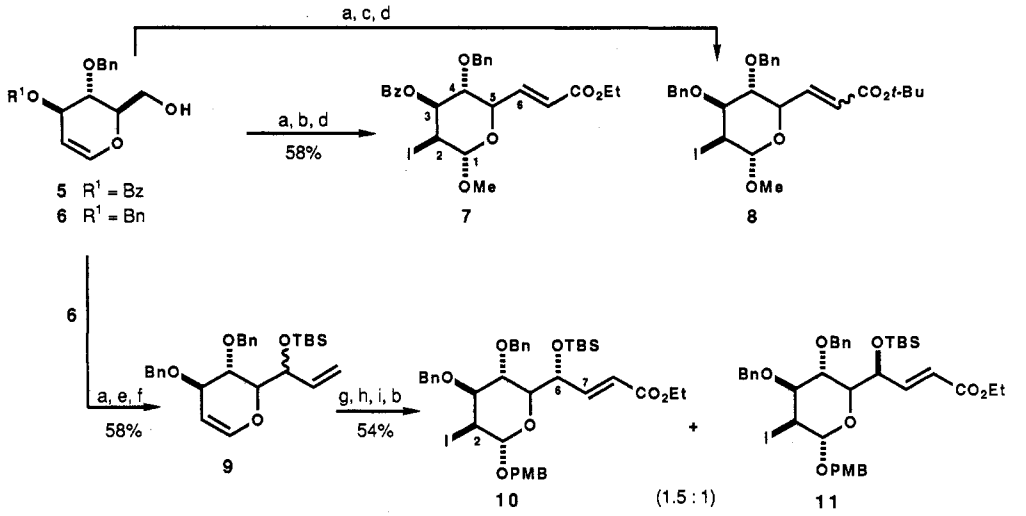
Scheme I



Scheme II[a]



[a] (a) PCC; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (c) $Ph_3P{=}CHCO_2t\text{-}Bu$ (d) *N*-iodosuccinimide (NIS), MeOH, CH_3CN; (e) vinylmagnesium bromide; (f) *tert*-butyldimethylsilyl chloride (TBSCl); (g) NIS, *p*-methoxybenzyl (PMB) alcohol, CH_3CN; (h) OsO_4, *N*-methylmorpholine oxide (NMMO); (i) $Pb(OAc)_4$.

pure carbocyclic derivatives. Recently, the application of free-radical methods for carbon–carbon bond formation in sugar derivatives has been explored in our laboratory, resulting in the formation of some potentially useful annulated pyranosides.[6] However, methods for the conversion of a carbohydrate to a carbocycle involving predominantly the carbon atoms of the starting sugar are rare,[7] an example of which is Ferrier's transformation of 6-deoxyhex-5-enopyranosides into deoxyinoses.[7a] A valuable contribution to this area was recently made by Wilcox and co-workers[8] that demonstrated the preparation of cyclopentane rings via radical cyclization of unsaturated acyclic halo sugars. Subsequent studies, reported by RajanBabu[9] and Bartlett,[10] have established the generality and versatility of this concept. The underlying methodology in the three aforementioned cases, summarized in Scheme I, part a, involves the transformation of an aldoside **1** into an acyclic species **2** that is equipped with a radical trap (e.g., Z = $CHCO_2R$,[8] CHOR,[9] or NOR[10]) and a radical progenitor (e.g., X = halogen, xanthate, or thiocarbonate). Cyclization then results in the intermediate **3**, which is reduced to the cyclopentane derivative.

(1) This work was supported by a grant from the National Institutes of Health (Grant GM 37380).

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(3) See for example: Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347; **1975**, *8*, 192.

(4) Rahman, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576. Fraser-Reid, B.; Underwood, R.; Osterhout, M.; Grossman, J. A.; Liotta, D. *J. Org. Chem.* **1986**, *51*, 2152.

(5) Sun, K. H.; Fraser-Reid, B.; Tam, T. F. *J. Am. Chem. Soc.* **1982**, *104*, 367. Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4661. Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Commun.* **1987**, 6.

(6) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102. Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484.

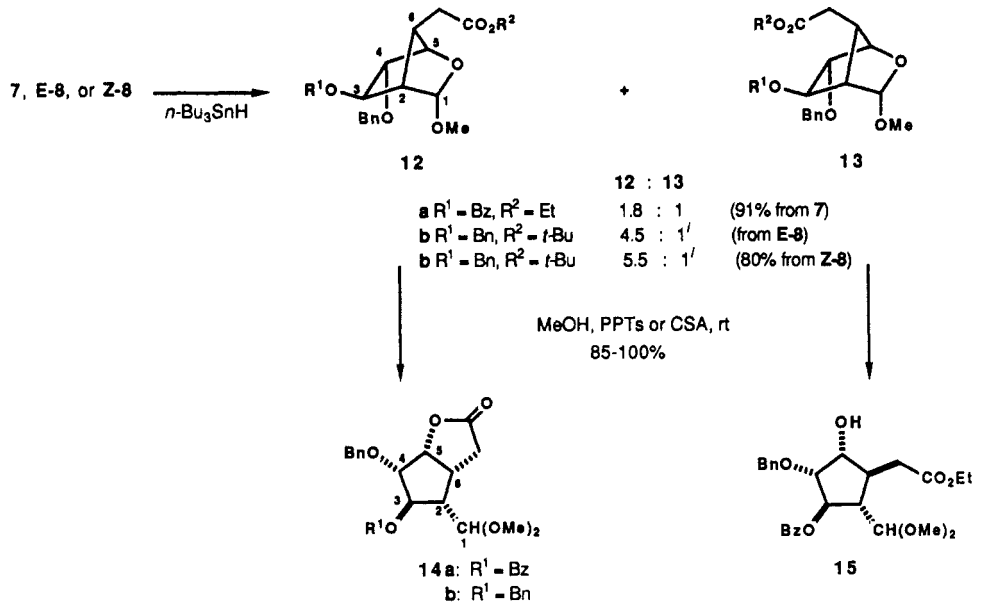
(7) (a) Blattner, R.; Ferrier, R. J. *Carbohydr. Res.* **1986**, *150*, 151 and previous papers in this series. (b) Belanger, P.; Prasit, P. *Tetrahedron Lett.* **1988**, *29*, 5521. (c) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. For two examples where a five-membered carbocyclic ring is obtained by trapping the radical at C-1 or C-2 in a pyranose with a suitable chain elaborated from C-3, see: Groninger, K. S.; Jager, K. F.; Giese, B. *Justus Liebigs Ann. Chem.* **1987**, 731. Hashimoto, H.; Furuichi, K.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1002 (respectively).

(8) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546.

(9) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522. RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609.

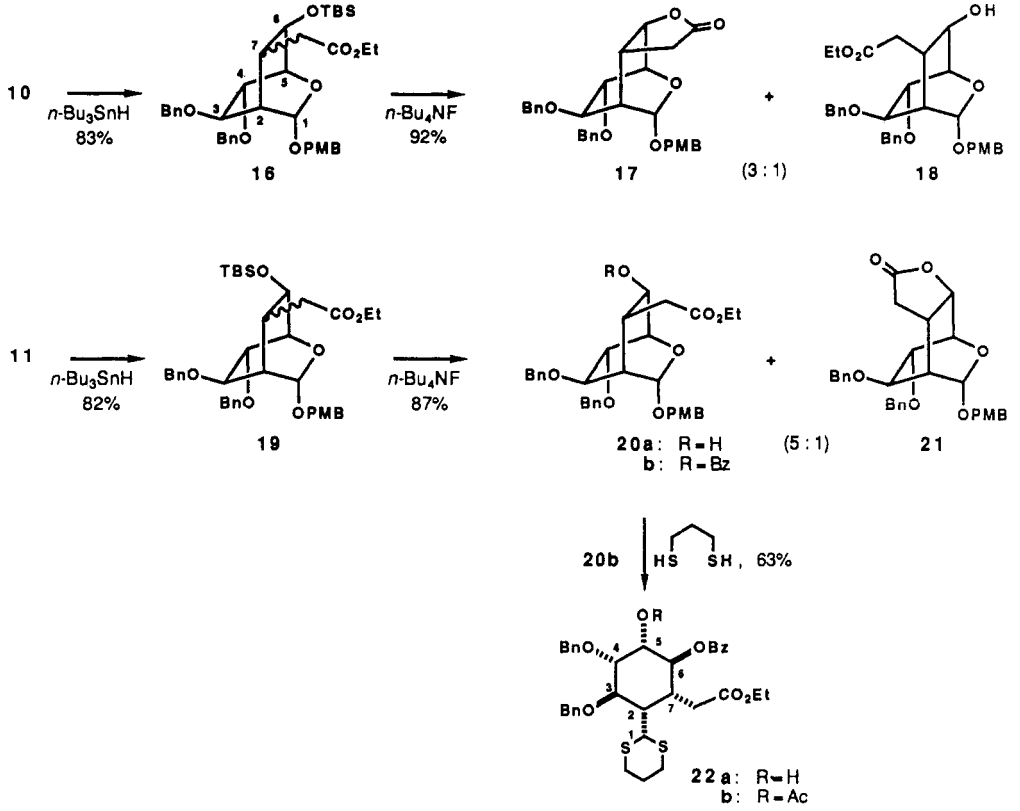
(10) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1638.

Scheme III



[i] Ratio determined by ^{1}H NMR integration of crude reaction mixture (average of two experiments).

Scheme IV



We have chosen to investigate an alternative strategy (postulated in Scheme I, part b) which envisages the development of the radical progenitor and trap (X and Z, respectively) in 4 without tampering with the anomeric center. The latter feature is an extremely versatile synthon[11] and this, combined with its stereoregulating properties,[12] commend its preservation as long as possible. However, cyclization of a monocycle (e.g., 4) is potentially disfavored since energy-demanding conformational changes are required prior to cyclization, which may involve overcoming the anomeric effect. This worrisome prognosis notwithstanding, we have tested the concept illustrated in Scheme I, part b, and in this paper we report its successful application to the formation of highly functionalized cyclopentane and cyclohexane ring systems.

(11) Fraser-Reid, B.; Anderson, R. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983. Inch, T. D. *Tetrahedron* **1984**, *40*, 3161. Seebach, D. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag: Frankfurt, 1980; Vol. 2.

(12) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer Verlag: New York, 1983. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983.

As our radical progenitors, we decided to employ 2-deoxy-2-halogeno glycosides, which are readily prepared from glycals by routine transformations, the iodine atom being introduced by the stereoselective process developed by Thiem and co-workers.[13] Thus, substrates **7** and **8** were prepared from the known glycals **5**[14] and **6**[15] in three steps as shown in Scheme II. In a similar fashion, the homologated analogues **10** and **11** were prepared from glycal **6** in seven steps in 31% combined overall yield.

Treatment of **7** with tri-*n*-butyltin hydride[16] led to the desired oxabicyclo[2.2.1]heptanes **12a** and **13a** (R^1 = Bz, R^2 = Et) as a 1.8:1 isomeric mixture in a surprising 91% isolated yield (Scheme III). The crystalline bicyclic products were easily separated by flash chromatography, and the stereochemical assignments derived from NMR experiments (COSY, HETCOR, NOE) indicated that in the major isomer the ester group lay on the less crowded side of the bicyclic structure. An expected increase in the stereoselectivity of the cyclization was achieved with the corresponding *tert*-butyl ester (*E*)-**8** which afforded a 4.5:1 mixture of bicyclic compounds **12b** and **13b** (R^1 = Bn, R^2 = *t*-Bu). No appreciable difference in the diastereomeric ratio was observed on changing to the cis isomer (*Z*)-**8**, which gave a 5.5:1 ratio of **12b** and **13b**.

Cleavage of the pyranose rings of **12** and **13** gave the cyclopentane derivatives **14** and **15**, respectively, in nearly quantitative yields under extremely mild conditions (MeOH, pyridinium *p*-toluenesulfonate [PPTs], or camphor sulfonic acid [CSA], room temperature), indicative of the strain inherent in these molecules. The latter products corroborated the configurational assignments of precursors **12** and **13**, which had been based on NMR data.

Next, we turned our attention to the preparation of six-membered ring carbocycles (Scheme IV). The homologated substrate **10** underwent cyclization[16] to afford the corresponding oxabicyclo[2.2.2]octanes **16** in 83% isolated yield as a 3:1 mixture of epimers, desilylation of which afforded the easily separable lactone **17** and hydroxy ester **18** in a 3:1 ratio. In the case of compound **11**, a similar reaction sequence led to **20a** and **21** (5:1).

Solvolytic cleavage of the oxabicyclo[2.2.2]octyl acetals proved to be much more difficult than with the oxabicyclo[2.2.1]heptyl counterparts. However, as typified with the benzoate **20b**, reaction with 1,3-propanedithiol and boron trifluoride–etherate led to the dithioacetal **22a** in good yields.

In conclusion, the results in Schenes III and IV show that a ready and highly efficient route to cycloalkanes is available which preserves all of the rich functionality of the carbohydrate precursor, the versatile anomeric center being masked to facilitate further manipulations. This valuable strategy, successfully applied here to the formation of cyclopentanes and cyclohexanes, appears to be well-suited for further development. Accordingly, employment of other radical traps and/or the selection of different starting sugars would lead to a variety of functionalized carbocycles and brings forth the interesting possibility of forming larger ring systems. These two factors together with the use of the bicyclic framework as a template to perform stereoselective transformations are currently under consideration.

Supplementary Material Available: Spectral data for bicyclic products **12** (**a** and **b**), **13** (**a** and **b**), **17**, **18**, **20a**, and **21** and for cycloalkanes **14** (**a** and **b**), **15**, and **22** (**a** and **b**) are provided (5 pages). Ordering information is given on any current masthead page.

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(13) (a) Thiem, J.; Karl, H. *Tetrahedron Lett.* **1978**, 4999. Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (b) For two recent reports on radical cyclization where the Thiem protocol is used for the generation of the precursors, see: Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691. Mesmacker, A. D.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57.

(14) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.

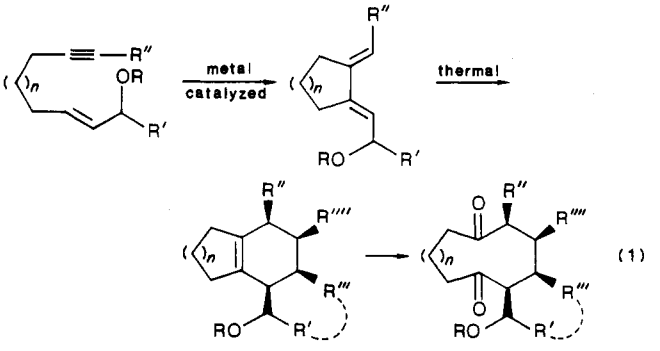
(15) Blackburne, I. D.; Burfitt, A. I. R.; Fredericks, P. F.; Guthrie, R. D. In *Synthetic Methods for Carbohydrates*; El Khadem, H. S., Ed.; American Chemical Society: Washington, DC, 1977.

(16) Typical cyclization procedure: A solution of the iodide (5.0 mM in dry toluene) was degassed with Argon and heated to reflux. *n*-Bu_3SnH (1.5 equiv) and catalytic AIBN in toluene were added via syringe pump over 2–4 h. Rotary evaporation of the solvent followed by flash chromatography (silica gel, EtOAc–petroleum ether) afforded the bicyclic products.

Hydroxy Group as a Regio- and Stereochemical Control Element for Sequential Metal-Catalyzed and Thermal Cyclizations

Summary: Stereocontrolled creation of fused ring systems from acyclic precursors invokes the powerful directive effect of the hydroxy group in which regioselectivity of a metal-catalyzed reaction totally changes and diastereofacial selectivity of the thermal step shows an unusual dependence on dienophile.

Sir: Rapid development of molecular complexity can simplify synthetic strategy.[1,2] Proceeding from acyclic substrates to polycyclic rings in two steps as outlined in eq 1 would constitute a useful approach toward such a goal.



(1)

In invoking this sequence, the allylic hydroxy or alkoxy group must serve (1) as a regiochemical control element in the metal-catalyzed cyclization to generate the conjugated 1,3-dienes rather than the nonconjugated 1,4-dienes

(1) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801; *Stud. Phys. Theor. Chem.* **1983**, *28*, 206; *Bull. Math. Biol.* **1983**, *45*, 849.

(2) For an excellent illustration, see: Wender, P. A.; vonGeldern, T. W. "Aromatic Compounds: Isomerization and Cyclization" In *Photochemistry in Organic Synthesis*; 1987; 226–55; Spec. Publ. R. Soc. Chem. 57.

0022-3263/89/1954-2271$01.50/0