on a Mel-Temp apparatus and are uncorrected. The ^1H (200.13 MHz) and ^{13}C (50.28 MHz) NMR spectra were obtained on a Bruker WH-200 instrument and the chemical shifts are reported in ppm downfield from internal tetramethylsilane. A Perkin-Elmer Model 467 spectrometer was used for infrared spectra. The field desorption/mass spectra were acquired on a Finnigan MAT 311A instrument. The TGA data were obtained on a Perkin-Elmer Model TGS-2 instrument.

Preparation of 3. 2,2'-Di-*tert*-butyl-4,4'-isopropylidenebis(phenol)[2] (100 g, 0.29 mol), paraformaldehyde (10.6 g, 0.35 mol), and xylene (1 L) are charged into a 1780-mL stainless steel autoclave and heated at 175 °C for 12 h. The reaction is cooled and filtered, and the solvent is removed under vacuum. The resulting yellow friable glass is stirred in a minimum amount of acetonitrile for 1–1.5 h, after which time a white powder remains. Filtration affords **3**, mp 325–330 °C. Second and third crops can be obtained by concentrating the acetonitrile. Total yield is 20 g (20%) of **3**.

An analytical sample of **3** is obtained by column chromatographing 2 g of **3** on 150 g of 0.063–0.2-mm silica gel (ICN Pharmaceuticals, Inc.) using as eluent 1:3 hexane:chloroform in a 4 × 30 cm column: IR (Nujol) 3460, 3570, 3615 cm^{-1} (hydroxyl), 1180–1220 cm^{-1} (Ar–O); FD/MS, *m/e* 704 (M^+); high-resolution mass spectrum, 704.4787 (calcd 704.4804); ^1H NMR ($CDCl_3$) δ 1.42 [s, 36 H, $C(CH_3)_3$], 1.56 [s, 12 H, $C(CH_3)_2$], 1.58 (s, 2 H_2O),[3] 3.68 (s, 4 H, CH_2), 5.24 (s, 4 H, OH),[3] 6.40 (d, 4 H, J = 2.4 Hz, Ar H), 7.24 (d, 4 H, J = 2.4 Hz, Ar H); VPO molecular weight (THF solvent at 45 °C), 747 (calcd 740). Anal. Calcd for $C_{48}H_{64}O_4 \cdot 2H_2O$: C, 77.84; H, 9.19. Found: C, 78.05; H, 9.13.

Preparation of 2. **3** is heated at 110 °C (2 mm) for 3 h in a vacuum oven: IR (Nujol) 3510, 3550, 3625 cm^{-1} (hydroxyl); ^1H NMR ($CDCl_3$) δ 1.42 [s, 36 H, $C(CH_3)_3$], 1.56 [s, 12 H, $C(CH_3)_2$], 3.68 (s, 4 H, CH_2), 5.24 (s, 4 H, OH), 6.40 (d, 4 H, J = 2.4 Hz, Ar H), 7.24 (d, 4 H, J = 2.4 Hz, Ar H); FD/MS, *m/e* 704 (M^+). Anal. Calcd for $C_{48}H_{64}O_4$: C, 81.81; H, 9.09. Found: C, 81.25; H, 9.11.

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(3) These absorptions disappeared upon addition of D_2O.

Communications

New Syntheses of Carbocycles from Carbohydrates. Cyclization of Radicals Derived from Unsaturated Halo Sugars

Summary: The cyclization of radicals derived from unsaturated aldoses promises to constitute an efficient and general preparation of hydroxylated cyclopentane and cyclohexane derivatives. The first example of this powerful new strategy for the preparation of polyhydroxylated carbocycles from aldoses is described. The effect of olefin geometry and hydroxyl group derivatization on product geometry is reported.

Sir: In the past decade, the potential use of carbohydrates as readily available polyhydroxylated structural units (chiral synthons) has been vigorously developed in several research groups.[1] The preparation of acyclic and heterocyclic products from aldoses has received great attention. In contrast, technology for the preparation of *carbocycles* from carbohydrates by the cyclization of acyclic aldose derivatives is in need of further development.[2] We report here the successful cyclization of an aldose derivative by a process that maintains all of the stereogenic carbon nuclei present in the original aldose. This powerful new strategy should find wide application in the preparation of biologically active polyhydroxylated carbocyclic natural products.

The formation of carbocycles by cyclization of unsaturated radicals is a well-known process that is undergoing rapid development.[3] Because the conditions required for such carbon–carbon bond formations are mild and asymmetric carbon nuclei can be retained immediately next to the sites of bond formation,[4] it appeared that this general strategy would be an especially effective technique for the cyclization of carbohydrate derivatives. Problems associated with carbanionic methods (regiospecific anion generation and stabilization, β-elimination) are avoided by using radical or cationic processes. On this basis it was hypothesized that polyhydroxylated carbocycles might be readily prepared from unsaturated halo sugars (Chart I).

To test this concept the hydroxy lactone **1**[5] was converted by the action of *N*-bromosuccinimide and triphenylphosphine[6] into the corresponding bromide **2** ($[\alpha]^{25}$ −39.5°, *c* 1.02)[7] and reduced to afford lactol **3** ($[\alpha]^{25}$ −37.5°, *c* 1.02)[7] in 82% overall yield. Treatment of this lactol with (carbethoxymethylidene)triphenylphosphorane afforded the olefinic halides (*Z*)-**4a** ($J_{2,3}$ = 12 Hz; $[\alpha]^{25}$ +87.4°, *c* 1.26)[7] and (*E*)-**4a** ($J_{2,3}$ = 16 Hz; $[\alpha]^{25}$ +29.1°, *c* 1.34)[7] in

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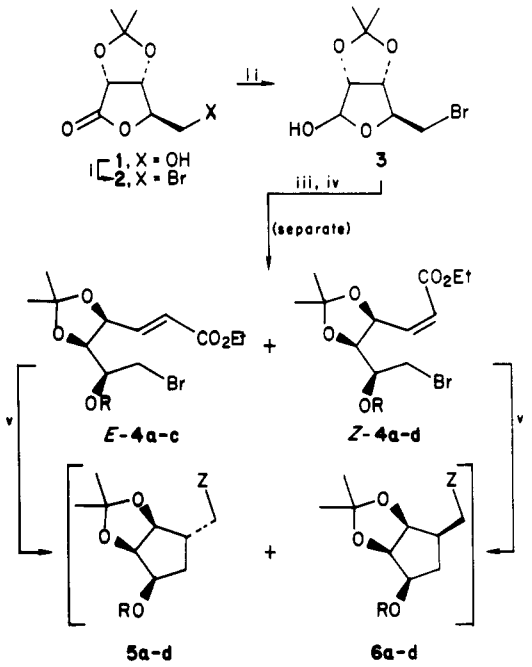
(7) Elemental analysis (combustion or mass spectrometric), magnetic resonance spectra (^1H and ^{13}C), and infrared spectra were consistent with the indicated structure for this molecule. Optical rotations were measured in ethanol free chloroform. Concentration (*c*) is given as g/100 mL.

0022-3263/85/1950-0546$01.50/0

Chart I



[a] (i) Ph_3P/NBS, CH_2Cl_2; (ii) Dibal-H, −78 °C; (iii) Ph_3P=C(H)CO_2Et, DME, 25 °C; (iv) RCOCl, pyridine; (v) Bu_3SnH/AIBN, C_6H_6, 80 °C.

Table I. Experimental Results for the Cyclization of Radicals Obtained from Unsaturated Aldose Derivatives

entry	starting material	R	yield,[a] %	ratio[b] (5/6)
1	(*Z*)-**4a**	H	80	6/1
2	(*E*)-**4a**	H	80	2/1
3	(*Z*)-**4b**	$COCH_3$	80	5/1
4	(*E*)-**4b**	$COCH_3$	82	1/1
5	(*Z*)-**4c**	COC_6H_5	89	10/1
6	(*E*)-**4c**	COC_6H_5	87	1/1.2
7	(*Z*)-**4d**	$COC(CH_3)_3$	87	11/1

[a] Isolated yield for the mixture of diastereomers. [b] Ratios determined by analysis of 200-MHz ^1H NMR spectra of unfractionated product.

67% and 13% yields, respectively.[8] These isomers were separated by medium pressure chromatography on silica and each was acylated to afford derivatives **4b**, **4c**, and **4d**.

When heated with tributyltin hydride and AIBN in benzene, each geometrical isomer of **4a** afforded the same two isomeric products, **5a** and **6a**. The yields and ratios of products obtained from these olefins or from the acylated derivatives of these olefinic alcohols are shown in Table I. The ratio of **5** to **6** depended on the olefin geometry and the nature of the protecting group on the C-6 hydroxyl. The assignment of relative configuration at the newly formed stereogenic carbon follows from the ^{13}C NMR spectra of the products (Table II).

It is apparent that the cyclization of these readily available unsaturated halo sugars affords good yields of the expected hydroxylated cyclopentanoid derivatives. Several interesting facts may be noted concerning the stereocontrol in this cyclization. The *Z* olefins afford consistently greater stereocontrol when compared with corresponding *E* isomers. The major product has the side chain in an exo orientation. The data also indicate that a degree of control in this cyclization is exerted by the oxygen substituent at C-4: while the cis alcohol affords a 6/1 ratio of products, the corresponding benzoate offers

(8) The conditions for olefination were essentially as reported by Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Theaker, P. D. *Carbohydr. Res.* **1974**, *38*, C22.

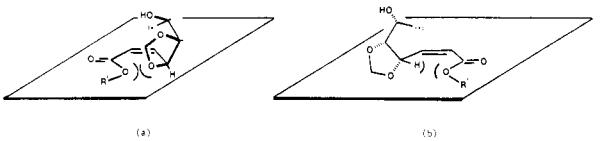
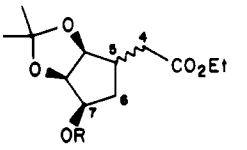


Figure 1. Illustration of potential steric interactions in ring closures to provide endo (a) or exo (b) products. Geminal methyl groups, which have been omitted for clarity, may also influence the outcome of these reactions.

Table II. Carbon-13 NMR Data (ppm) for Isomeric Cyclopentanoid Products



	C			
	4	5	6	7
R = OH				
5a	34.79	36.80	38.17	84.41
6a	33.16	35.70	36.93	80.18
R = Ac				
5b	33.36	37.00	37.84	84.21
6b	31.73	32.77	34.59	79.92
R = Bz				
5c	33.23	37.00	38.04	84.28
6c	29.78	31.99	34.59	80.25

selectivity 10/1 in favor of the exo isomer. The close correspondence between the results for the benzoate and pivalate esters indicates the probable insignificance of the potential electronic effects of the aryl ester.

Hypothetical transition states (major and minor pathways) for the cyclization of the cis ester are illustrated in Figure 1.

The difference in stereocontrol for the cis and trans esters suggests that the control mechanism is probably predominantly steric in origin. The transition states illustrated in Figure 1 emphasize the importance of the interactions of the ester with either the ethereal oxygen or the hydrogen on the γ-carbon. The idea here (which should be further tested) is that a through-space interaction between the ethoxycarbonyl group and the oxygen on the γ-carbon destabilizes the transition state leading to the endo product.

These experiments establish that the promising applications of radical–olefin cyclization may be extended into the realm of polyoxygenated substrates without complication. One expedient strategy for the synthesis of unsaturated halo sugars has been developed. On the basis of this exploratory effort, short syntheses of chiral, highly oxygenated synthons for the preparation of biologically active organic molecules can now be planned. Further reports from this lab will deal with new approaches to unsaturated halo sugars and additional aspects or applications of the cyclization of radicals derived from unsaturated halo sugars.

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