Stereochemical Control in Hex-5-enyl Radical Cyclizations: From Carbohydrates to Carbocycles. 3[1]

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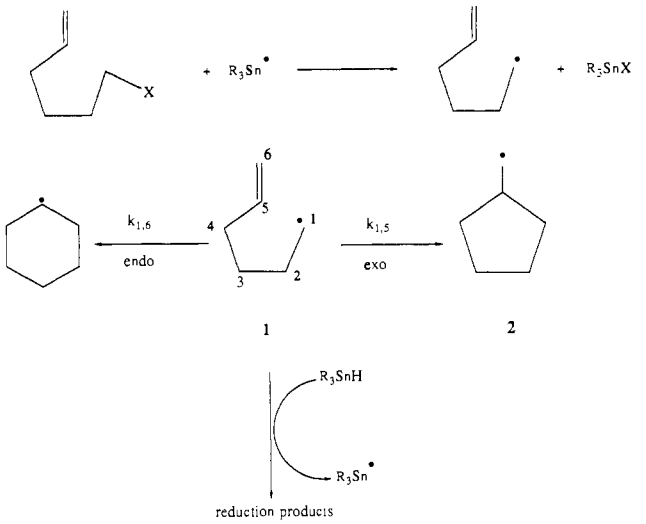
Abstract: The hex-5-enyl radical cyclization reaction was applied to prepare highly oxygenated cyclopentanoids from aldopyranose sugars. The Wittig reaction of the sugars readily provides hex-5-en-1-ols which were converted to hex-5-enyl radicals via one of the variations of the Barton deoxygenation reaction. The stereochemistry of the newly formed carbon–carbon bond, i.e., 1,5 stereochemistry, is controlled primarily by the configuration of the C_4 center of the radical. Unprecedented and exclusive 1,5-*trans* selectivity is realized in the gluco series, whereas the manno system leads to almost exclusive 1,5-*cis* stereochemistry. The C_4-deoxy system gives a mixture of both 1,5-*cis* and -*trans* products, with the former predominating. The stereochemical outcomes are rationalized by the cyclohexane-like transition state whose conformation, chair- or boatlike, is determined by both steric and stereoelectronic effects of substituent groups.

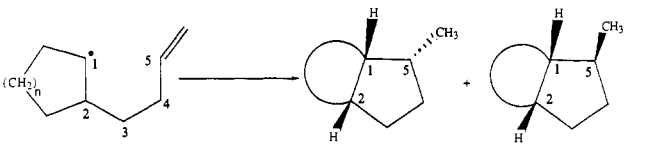
Although free-radical reactions forming carbon–carbon bonds have long been recognized as being widely applicable for polymer synthesis, only the past 15 years have witnessed impressive applications of these reactions in the synthesis of complex molecules.[2,3] Among the radical reactions, the exo cyclization of hex-5-enyl radical to cyclopentylmethyl radical and subsequent trapping by various reagents (Scheme I) have attracted the greatest attention. Also, it was during this period that detailed physical organic investigations were carried out[4] and kinetic and thermodynamic parameters were delineated for the individual steps as depicted in Scheme I. The stereochemical outcome of the ring closure of alkyl-substituted hex-5-enyl radicals has been studied[5] in some detail, and general guidelines to predict the stereochemistry have been proposed.[5b] The cyclization of 1- and 3-substituted

Scheme I[a]



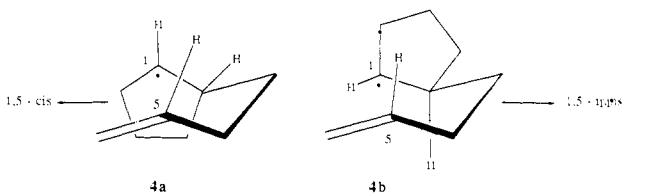
[a] At 60 °C, $k_{1,5}$ is approximately 10^5–10^6 s^{-1}; $k_{1,5}/k_{1,6} = 50$.

Scheme II



n=1	cyclopentyl	8.3	1
n=2	cyclohexyl	3.5	1

Scheme III



(1) Preliminary reports of portions of this work have appeared. See: (a) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. (b) RajanBabu, T. V. *Abstract of Papers*, 193rd National Meeting of the American Chemical Society Denver, CO; American Chemical Society: Washington, DC, 1987; ORGN 225.

(2) (a) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973. (b) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (d) Barton, D. H. R.; Motherwell, W. B. In *Organic Synthesis Today and Tomorrow*; Trost, B. M., Ed.; Pergamon Press: New York, 1981. (e) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, England, 1983. (f) Hart, D. J. *Science* **1984**, *223*, 883. (g) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (h) See also: *Selectivity and Synthetic Applications of Radical Reactions, Tetrahedron*: Symposia-in-Print No. 22; Giese, B., Ed.; Pergamon Press: Oxford, 1985; Vol. 41. (i) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986.

(3) (a) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. (b) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991. (c) Curran, D. P.; Rakiewicz, D. M., p 3943 in ref 2h. (d) Corey, E. J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425. (e) Reference 2d. (f) See also: Clive, D. L. J.; Beaulieu, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 307. Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, 2489. Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708. Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545. Begley, M. J.; Bhandal, H.; Hutchinson, J. H.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1317, and referenced cited therein. Stork, G. ; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826. For earlier examples from Stork's group, see: Reference 2e. Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. Snyder, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. Fox, D. P.; Little, D. R.; Baizer, M. M. *J. Org. Chem.* **1985**, *50*, 2202. Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349. Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *Tetrahedron Lett.* **1985**, *26*, 957. Ikeda, T.; Yue, S.; Hutchinson, C. R. *J. Org. Chem.* **1985**, *50*, 5193. Degueil-Casting, M.; Dejeso, B.; Kraus, G. A.; Landgrebe, K.; Maillard, B. *Tetrahedron Lett.* **1986**, *27*, 5927. Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484.

(4) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Pergamon Press: New York, 1980; Vol. 1. (b) For a compilation of other relevant references, see: Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240.

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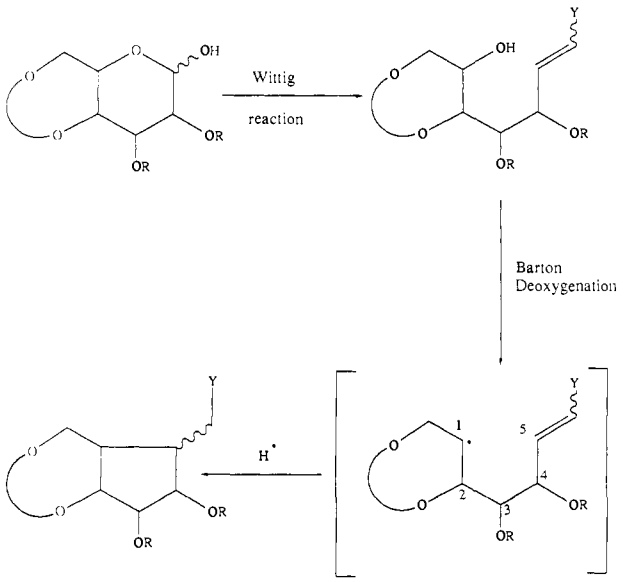
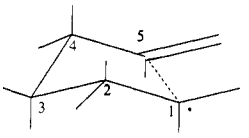
Scheme IV



hex-5-enyl radicals leads mostly to *cis*-disubstituted cyclopentyl products, whereas 2- and 4-substituted radicals predominantly give *trans* products. Beckwith[5] rationalized the observed stereochemical results by the transition-state structure **3**, in which

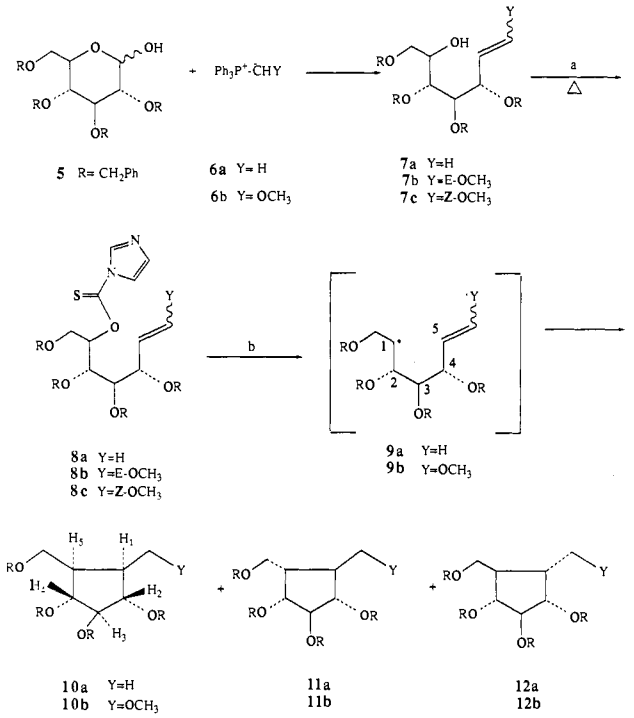


3

substituents occupy quasi-equatorial positions. The ring closure of cyclic 2-(but-3-enyl)cycloalkyl radicals is similar to that of the open-chain system, except that the constraints of the ring impose an almost exclusive 1,2-*cis* stereochemistry[6,7] (Scheme II). Curran[3c] argued that the 1,5-*cis* cyclization is favored because the chairlike transition structure **4a** (Scheme III) can achieve effective overlap between the SOMO of the radical center and the olefin orbitals with less strain than the other possible chair **4b**. Regardless of the underlying reasons for the stereochemical preference, it is this 1,5-*cis* stereochemical control in the cyclization of 1-substituted hex-5-enyl radicals that has been used in all the elegant synthetic schemes devised for complex molecules to date, and no attempts had been made to widen the scope of this potentially powerful reaction before we observed our initial results.[1,7c]

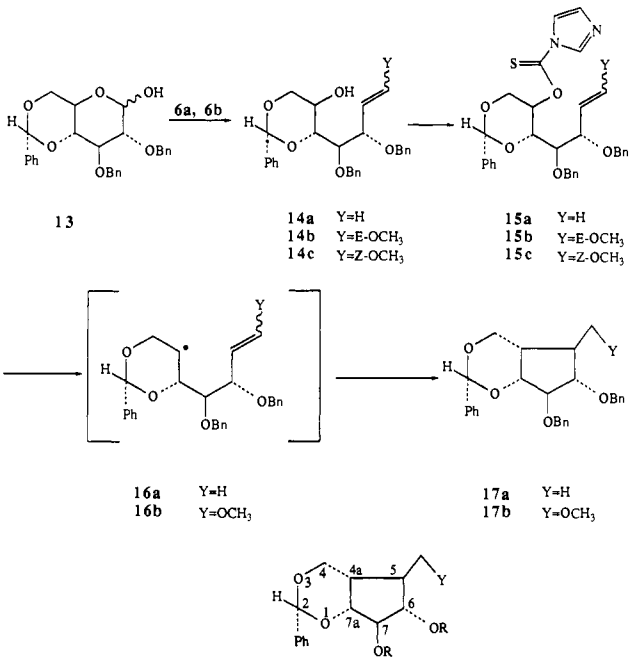
Our interest began in an exploratory program directed to the synthesis of carbocycles from carbohydrates.[8] We reasoned that

Scheme V[a]



[a] (a) Im_2CS, heat; (b) AIBN, Bu_3SnH, 110 °C.

Scheme VI



aldopyranoses that readily undergo the Wittig reaction to give hex-5-en-1-ols can be converted to highly functionalized hex-5-enyl radicals by any one of the variations of the Barton deoxygenation reaction,[9] as shown in Scheme IV. Because of the ready

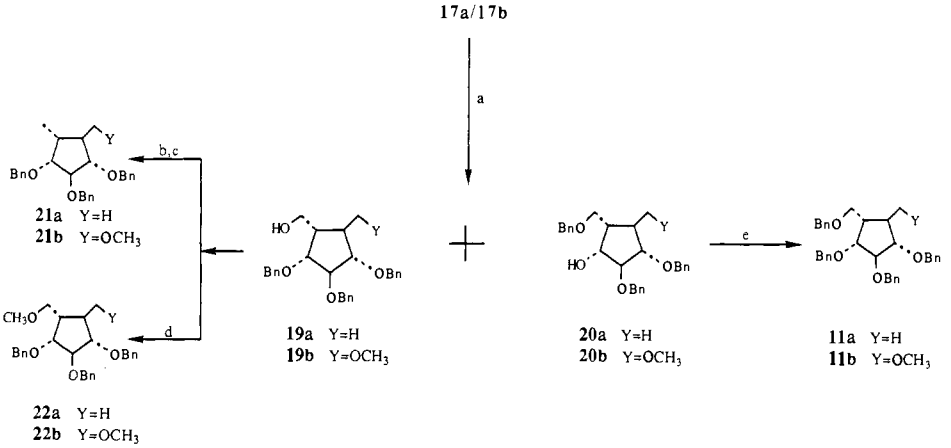
(5) (a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482, and references cited therein. (c) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545. (d) For rules for ring fusion stereochemistry in bicyclo[*n*.3.0] system, see: Clive, D. L. J.; Cheshire, D. R.; Set, L. *J. Chem. Soc., Chem. Commun.* **1987**, 353. (e) For exception to the rules possibly due to unusual steric crowding or electronic effects, see: Bradney, M. A. M.; Forbes, A. D.; Wood, J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1655. Brace, N. O. *J. Org. Chem.* **1966**, *31*, 2879. (f) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (g) Spellmeyer, D. C.; Houk, K, N. *J. Org. Chem.* **1987**, *52*, 959.

(6) (a) Wolff, S.; Agosta, W. C. *J. Chem. Res. (S)* **1981**, 78. (b) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811. (c) For an exceptional case where a 1,5-*cis* product would be precluded by steric crowding, see: Leonard, W. R.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 6431.

(7) For conformationally rigid systems: (a) Pradhan, S. K.; Kolhe, J. N.; Mistry, J. S. *Tetrahedron Lett.* **1982**, *23*, 4481. (b) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (c) RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296.

(8) While our study was in progress, the first example of a free-radical route to cycloalkanes from carbohydrates was reported by Wilcox et al.: (a) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546. (b) For an elegant application of this chemistry for the synthesis of pseudo-fructose see: Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. For examples of radical-based pyranoside annulations: (c) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. (d) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102. However, these systems involve the use of primary radicals, and the stereochemical questions we are addressing are not relevant to these cases.

Scheme VII[a]



[a](a) LAH, $AlCl_3$; (b) NBS, Ph_3P; (c) Bu_3SnH; (d) NaH, MeI; (e) NaH, BnBr.

availability of pyranose sugars of various configurations, such a protocol would provide a facile entry into highly oxygenated cyclopentanes and cyclopentanoid natural products, e.g., prostaglandins, iridoids, and brefeldin, as demonstrated by a synthesis of Corey lactone from 3-deoxyglucopyranose.[10] This protocol is also uniquely suited to study the effect of 1-, 2-, 3-, and 4-substituents on the stereochemistry of the cyclization reaction, and furthermore, the well-established protecting group strategies in carbohydrate chemistry would permit the study of open-chain as well as cyclic radicals with known absolute and relative stereochemistry. We hoped that these investigations would shed new insight into the nature of transition states and possibly provide useful stereochemical guidelines for the conversion of carbohydrates to carbocycles by this methodology. These expectations have been largely met, and in this paper we report the details of our investigations.

Results

Acyclic Radicals. The protocol for the conversion of hexopyranose sugars to functionalized cyclopentanes was first established by using readily available tetra-*O*-(phenylmethyl)-D-glucopyranose **5** (Scheme V). Upon treatment with 2 equiv of methylenetriphenylphosphorane (**6a**), **5** yields the Wittig product **7a** in high yield.[11] In the case of reaction with the methoxymethylene Witting reagent (**6b**), the stereochemistry of the vinyl ethers is readily established by their respective ^1H NMR spectra. In **7b** (the *E* isomer), H_1 appears at δ 6.32 as a doublet with $J_{1,2}$ = 13 Hz, while in the *Z* isomer **7c**, the corresponding peak is at δ 6.14 with J = 7 Hz. The ratio of **7b** to **7c** was 88 to 12. The radical **9a** was generated from the 1-*H*-imidazole-1-carbothioate **8a**, which in turn was prepared from the enitol **7a** by treating it with thiocarbonylbisimidazole in refluxing 1,2-dichloroethane. Even though crude **8a** can be used in subsequent reactions, we have routinely purified this intermediate before cyclization. Upon refluxing this precursor in toluene with tributyltin hydride in the presence of azobis(isobutyronitrile) as an initiator, **9a** is generated, which goes on to give products of **10a**, **11a**, and **12a** in overall 61% from **7a**. The structures of the cyclic products were established by comparison and correlation of ^1H and ^{13}C chemical shifts and difference NOE spectra of a number of related compounds prepared during this study (Table I). Some of these compounds were prepared by alternate routes from compounds whose structures were first established by degradation studies. For example, in **10a**, irradiation of the CH_3 signal results in the enhancement of H_1, H_2, H_4, and CH_2OBn peaks (see structure **10a** for proton labels). Likewise, irradiation of H_2 results in CH_3 enhancement. In **12a**, irradiation of CH_3 causes enhancement of signals due to H_1 and H_5. H_1 has a similar effect on H_2 and vice versa. Strong NOE is observed for the signals of H_4 and H_5 upon irradiation of CH_2OBn. An authentic sample of **11a** was prepared from **17a**, whose structure has been unequivocally established by degradation (Scheme VII). Reactions of **17a** shown in Scheme VII also yield **21b**, a methoxy compound stereochemically related to the optical antipode of **12a**. Comparison of ^{13}C chemical shifts of CH_3, C_1, and C_5 clearly shows this stereochemical relationship. Thus, in **12a** these are δ 13.40, 36.13, and 48.98; in **21b** the shifts are at δ 13.46, 36.16, and 48.93, respectively. Relative chemical shifts of the respective carbons in **10a** and **11a** also give an indication of the stereochemistry of these compounds.[12] In **10a**, which is the most congested (the "1,5-*cis*" isomer) system, these values are δ 13.46, 36.84, and 44.27, while in **11a** (the "1,5-*trans*" isomer) these carbons appear at δ 17.45, 39.20, and 47.20. The "steric shielding" in ^{13}C chemical shifts of 1,2-*cis* cyclopentanes has been well recognized.[12] Shielding due to the C_2 benzyloxy is responsible for the high-field methyl shift in **12a** as compared to the other *trans* isomer **11a**.

The enol ethers **7b** and **7c** can also be subjected to the cyclization[13] sequence to obtain similar products in a yield of 61%. The ratio of **10b** to **11b** to **12b** is 75:23:2. We have separated the *Z* and *E* isomers **7b** and **7c** and carried out the cyclization on individual radical precursors only to find that the stereochemical outcome remains invariant. The structure of the 2% product has not been established conclusively. Those of the others were confirmed by the techniques just outlined. An authentic sample of **11b** was prepared from **17b**, whose structure had been independently confirmed (Scheme VII). The relative chemical shifts of C_1 and C_5 in **10b** and **11b** are characteristic of the 1,5 stereochemical relationship.[12a,e] In **10b** they appear at δ 42.85 and 42.89, while in **11b** they are at δ 42.43 and 45.35.

Cyclic Radicals. In contrast to acyclic radicals, cyclic radicals exhibited much better stereoselectivities. Cyclization of radical

(9) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) In all radical cyclizations reported here using the Barton intermediate, varying amounts of starting alcohols were isolated. We have since found that the Robins procedure is considerably better in some cases: Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

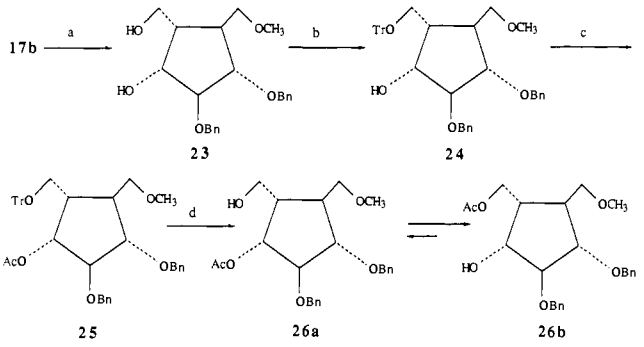
(10) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522.

(11) Pougny, J.-R.; Nassar, M. A. M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375.

(12) (a) Breitmaier, E.; Voelter, W. *^{13}C NMR Spectroscopy: Methods and Applications*; Verlag Chemie: Weinheim, Federal Republic of Germany, 1987. (b) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878. (c) Schneider, H.-J.; Nguyen-ba, N.; Thomas, F. *Tetrahedron* **1982**, *38*, 2327. (d) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294. (e) In cyclopentyl systems 1,2-substituents have the most pronounced effect on each other's chemical shifts, and this can be used reliably for stereochemical assignments. The 1,3-substituents appear to have minimal effect on each other. For a critical evaluation of these relative effects and reliability of ^{13}C methods see ref 12c.

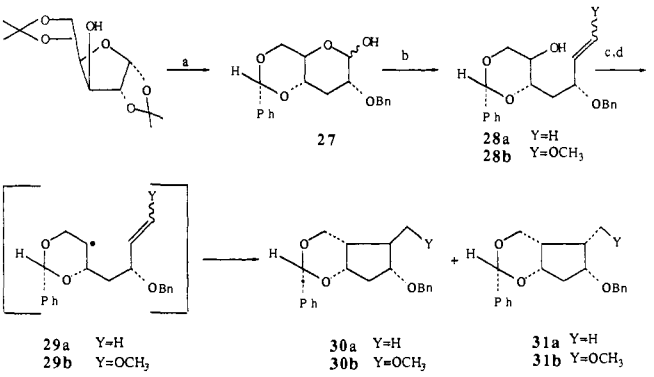
(13) (a) For the only other examples of intramolecular radical additions to enol ethers, see: Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317. Reference 4b. (b) *E* or *Z* geometry or the electronic nature of the olefin appears to have little effect on the stereochemistry of the cyclization. See: Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. See also: Reference 3a.

Scheme VIII[a]



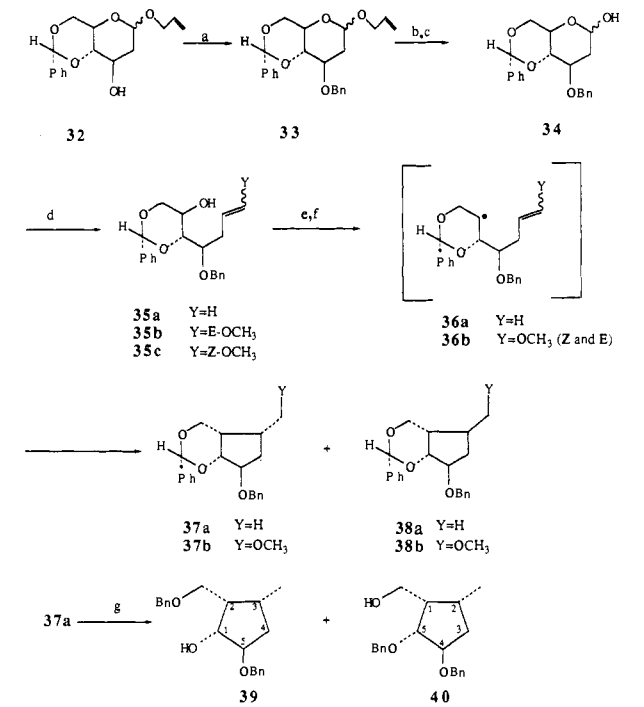
[a] (a) H_3O^+; (b) TrCl, Pyr; (c) Ac_2O, Pyr; (d) H_3O^+.

Scheme IX[a]



[a] (a) See ref 10; (b) Ph_3P^+–CHY; (c) $(Im)_2CS$, heat; (d) Bu_3SnH, AIBN, $PhCH_3$, heat.

Scheme X[a]



[a] (a) BnBr, NaH; (b) $Ir^+(COD)Ph_2PMe\ PF_6^+$; (c) $HgCl_2$, HgO, H_2O; (d) Wittig; (e) $(Im)_2CS$, heat; (f) Bu_3SnH, AIBN, $PhCH_3$, heat; (g) LAH, $AlCl_3$.

16a prepared from 4,6-*O*-benzylidene-2,3-bis-*O*-(phenylmethyl)-D-glucopyranose (**13**) yielded a single 1,5-*trans* product, **17a**, in 57% yield based on the corresponding radical precursor **15a** (Scheme VI). Likewise, the vinyl ether precursors **15b** and **15c** gave almost exclusively the product **17b** in moderate yield. Since in trial runs using the pure *Z* and *E* isomers same product was obtained, separation of the individual isomers is not needed.

Because the exclusive formation of 1,5-*trans* product is unprecedented in radical cyclization reactions, we have examined the structure of the products **17a** and **17b** in detail by both chemical degradations and spectroscopic techniques. In the NOE difference spectra of **17a** one observes enhancements of signals due to H_5 and H_6 upon irradiation of CH_3.[14] Similar signal enhancements for H_4, H_6, and H_{7a} are seen by irradiating H_{4a}; H_5 has related effects on CH_3 and H_7, and H_6 on CH_3, and H_{4a}. The ^{13}C resonance signals of C_{4a} and C_5 appear at δ 41.31 and 36.82, respectively. As we shall see later in this section, a comparison of these numbers to the corresponding values for *cis* compounds (**57a**, δ 35.05 and 37.16; **66**, δ 34.38 and 37.78) also suggests the indicated *trans* structure for **17a**.

Even though NOEs and relative ^{13}C shifts are highly reliable in assigning stereochemistry in bicyclic systems, because of the unusual and unprecedented *trans* nature of the 1,5-exo cyclization, we sought to confirm the structures of **17a** and **17b** by chemical means as well. An added impetus for this would be a better understanding of the chemistry of these highly functionalized molecules useful for further elaboration.

Treatment of **17a** with $LiAlH_4$ and $AlCl_3$ yields **19a** and **20a** in a ratio of 1 to 10 (Scheme VII). The primary alcohol **19a** may be converted into **21a**, a 1,2-dimethylcyclopentane, whose ^1H and ^{13}C NMR spectra clearly show that it has an unsymmetrical structure. This is possible only if the cyclization stereochemistry is *trans*. A similar set of transformations converts **17b** into an unsymmetric 1,2-bis(methoxymethyl)cyclopentane, **22b**, thereby also confirming a similar stereochemical outcome in this case. Further, **19a** may be transformed into a methyl ether **22a** which is used as a standard for ^{13}C and NOE measurements. For example, the methyl carbon in **22a** appears at 17.41 ppm, whereas the more sterically crowded methyl carbon of **21b** appears at 13.46 ppm. A comparison of these values with those of **11a** (17.45 ppm) and **12a** (13.40 ppm) unequivocally supports those assignments. Finally, an authentic sample of **11a** may be prepared from **20a** or **19a** by benzylation. Likewise, an authentic sample of **11b** may be prepared from **17b** by $LiAlH_4/AlCl_3$ treatment followed by benzylation.

The transformations described in Scheme VIII confirm the *cis* ring fusion in **17b**. The *cis* ring fusion in 2-(but-3-enyl)cycloalkyl radical cyclization products is well-precedented.[3,6,7] Hydrolysis of the benzylidene ring followed by selective protection of the primary alcohol yielded the trityl derivative **24**. Formation of secondary acetate followed by detritylation gives **26a** which undergoes isomerization by a 1,3 acetate migration that is possible only if the hydroxymethyl and the secondary acetate are in a 1,2-*cis* geometry.[15] The isomers **26a** and **26b** may be separated by column chromatography. Purified **26a** establishes an equilibrium (1:1) with **26b** in 4 days in $CDCl_3$, and this reaction can be readily followed by NMR.

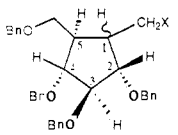
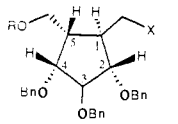
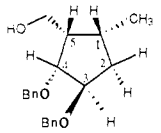
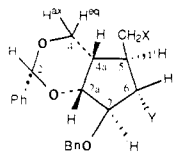
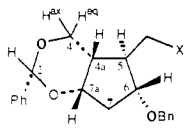
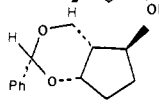
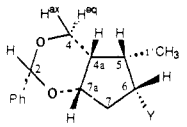
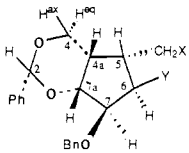
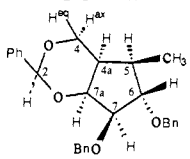
The 3-deoxy radical **29a** gives cyclic products identified as a mixture of **30a** and **31a** in a ratio of 11:1 (Scheme IX). The methyl signals in the ^{13}C spectrum appear at δ 16.12 and 11.40, as expected, the more crowded *cis* compound **31a** showing the upfield shift. The difference NOE spectrum of **30a** (see Experimental Section) is also consistent with the assigned structure. The stereochemistry of products derived from **29b** has been confirmed not only by physical measurements but also by its conversion to Corey lactone.[10]

Cyclic 4-deoxy radicals **36a** and **36b**, generated by similar routes, cyclize with predominantly 1,5-*cis* stereochemical outcome (Scheme X). Cyclization of **36a** proceeds in an overall yield of

(14) For numbering of hexahydrocyclopenta-1,3-dioxin see structure **18**.

(15) Ample precedent exists in the literature to suggest that this ready equilibration is possible only if the acetoxy and hydroxymethyl groups are *cis* to one another. (a) Jones, G.; Raphael, R. A.; Wright, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1676. (b) Doria, G.; Gaio, P.; Gandolfi, C. *Tetrahedron Lett.* **1972**, 4307.

Table I. Selected NOEs and ^{13}C Chemical Shifts

compound		NOE[a]	^{13}C shifts(ppm) CH_3	C_1	C_5
		Monocyclic Products			
	**10a** (X = H)	$CH_3 \rightarrow H_1, H_2, H_4, CH_2OBn$	13.46	36.84	44.27
	12a (X = H)	$CH_3 \rightarrow H_1, H_5$; $H_1 \rightarrow H_2$; $CH_2OBn \rightarrow H_4, H_5$	13.40	36.13	48.98
	10b (X = OMe)			42.85	42.89
	**11a** (R = Bn, X = H)		17.45	39.20	47.20
	11b (R = Bn, X = OMe)			42.43	45.35
	22a (R = OMe, X = H)	$CH_3 \rightarrow H_2$	17.41	39.13	47.13
	**40**	$CH_3 \rightarrow H_1, H_{2\alpha}, CH_2OH$	16.41	37.88	46.30
		Bicyclic products (4a,5-*trans*)			
	**17a** (X = H,Y = OBn)	$H_{4a} \rightarrow H_4, H_6, H_{7a}$; $CH_3 \rightarrow H_5, H_6$; $H_5 \rightarrow CH_3, H_7$	15.64	41.31	36.82
	17b (X = OMe, Y = OBn)	$H_2 \rightarrow H_{4ax}, H_{7a}$; $H_{4ax} \rightarrow H_{4a}, H_2$; $H_{4a} \rightarrow H_{7a}, H_{4ax}$; $H_7 \rightarrow H_5$			
	38a (X = Y = H)		18.69	(31.80, 40.13, 44.40, 65.80)[b]	
	38b (X = OMe, Y = H)	$H_{4ax} \rightarrow H_{4a}$; $H_{6\alpha} \rightarrow H_5, H_7$; $H_{4a} \rightarrow CH_2OMe, H_{7a}$	76.94	40.47	37.24
	**30a** (X = H)	$CH_3 \rightarrow H_5, H_6$; $H_5 \rightarrow H_4, CH_3$	16.12	44.32	38.30 (37.98)[b]
	30b (X = OMe)		78.57(?)	39.52	44.81
	**45**		18.67	(31.36, 32.01, 32.28, 47.27)[b]	
		Bicyclic Products (4a,5-*cis*)			
	**31a** (Y = OBn)		11.40	(37.15, 37.50, 41.46)[b]	
	44 (Y = H)	$CH_3 \rightarrow H_{4eq}$	18.80	(32.15, 33.41, 34.17, 40.24)[b]	
	**37a** (X = Y = H)	$CH_3 \rightarrow H_5, H_{6\alpha}, H_{4eq}$; $H_5 \rightarrow H_{4a}, H_{6\beta}, CH_3$; $H_{7a} \rightarrow H_{4a}$	18.80	(33.00, 37.60, 39.84)[b]	
	37b (X = OCH_3, Y = H)	$H_{4eq} \rightarrow CH_2OMe, H_{4ax}$; $H_{4a} \rightarrow H_{4ax}, H_5, H_{7a}$; $H_5 \rightarrow H_{4a}, H_{6\beta}$; $H_7 \rightarrow H_{6\alpha}$	76.57	36.99	38.27
	57a (X = H, Y = OBn)	$CH_3 \rightarrow H_{4eq}, H_5, H_6$; $H_{7a} \rightarrow H_2, H_{4a}$	15.45	35.05	37.16
	**66**	$CH_3 \rightarrow H_{4eq}, H_5, H_6$; $H_{7a} \rightarrow H_2, H_{4ax}, H_{4a}, H_7$	17.19	34.38	37.78

[a] Irradiation of the proton on the left of the arrow causes NOE of the one on the right. [b] Not unambiguously assigned.

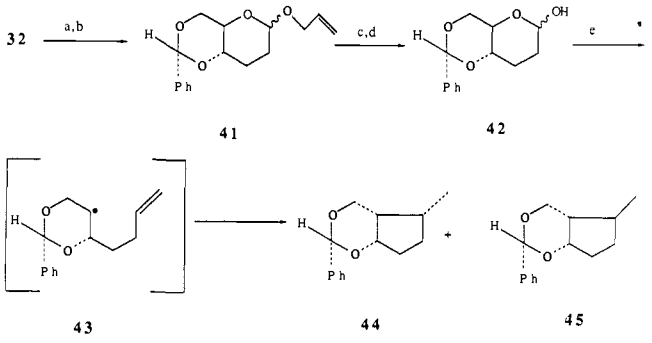
32% (from **35a**), giving **37a** and **38a** in a ratio of 77 to 23. The corresponding yield of the cyclization of **36b** is 51%, and the ratio of **37b** to **38b** is 86 to 14. The starting sugar **34** was prepared according to a procedure described in the literature[16] with a minor modification. In this scheme, the anomeric oxygen is protected as an allyl ether (e.g., **33**) and it is liberated at the end by an Ir(I) assisted 1,3 H migration to form a vinyl ether followed by hydrolysis.[17] As will be seen later, this general scheme has been used in the preparation of a number of radical precursors (**42**, **54**, and **63**). The ^1H, difference NOE, and ^{13}C spectra of the major product **37a** are consistent with the assigned structure. The shifts of the methyl carbon atoms are anomalous, but as expected the methine and methylene carbon signals in the major product are considerably shifted upfield as compared to that of the minor product **38a**. In the difference NOE spectrum of **37a**,[14] H_5 irradiation results in an enhancement of signals due to H_{4a}, $H_{6\beta}$, and CH_3. Irradiation of CH_3 has similar effects on H_5, $H_{6\alpha}$, and H_{4eq}; H_{7a} causes the enhancement of the peak of H_{4a}. All these confirm the structural assignment of **37a** and this points to a 1,5-*cis* cyclization mode en route to the major product. Structures of **37b** and **38b** were established by similar experiments. Careful examination of ^{13}C and NOE difference spectra of **40** prepared from **37a** by $LiAlH_4/AlCl_3$ reaction also supports the stereochemical assignments.

The effect of C-3 (radical numbering) substituents was further probed by the cyclization of the 3,4-dideoxy radical **43**. The precursor sugar is readily prepared (Scheme XI) from **32** whose synthesis was outlined earlier (Scheme X). Barton deoxygenation of **32** yielded **41**, which was readily converted into **42** as described earlier. Cyclopentanes **44** and **45** are prepared in 55% yield from the corresponding 1-*H*-imidazole-1-carbothioate. Integration of

(16) Reed, L. A.; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 6468, and references cited therein.

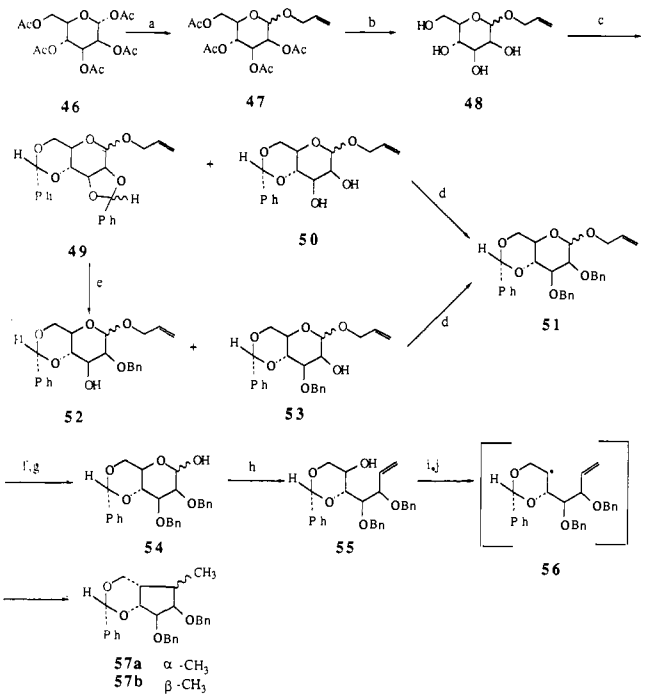
(17) Oltvoort, J. J.; Van Boeckel, J. H.; De Koning, J. H.; Van Boom, J. H. *Synthesis* **1981**, 305.

Scheme XI[a]



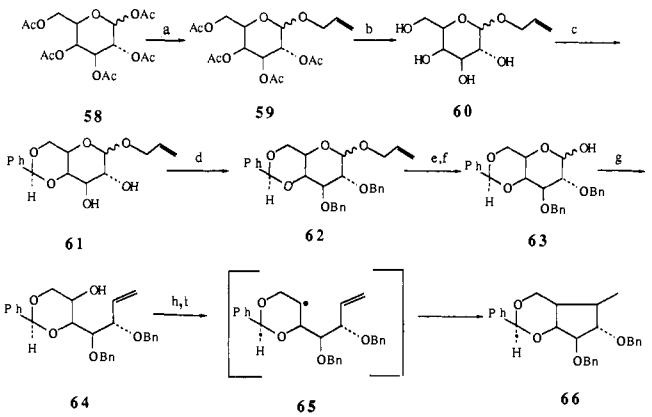
[a] (a) Im_2CS, heat; (b) Bu_3SnH, AIBN; (c) Ir^+, H_2; (d) $HgCl_2$, HgO, H_2O; (e) see Scheme X.

Scheme XII[a]



[a] (a) Allyl alcohol, $SnCl_4$; (b) OH^-; (c) $PhCHBr_2$, Pyr, (d) BnBr, NaH; (e) LAH, $AlCl_3$; (f) Ir^+; (g) $HgCl_2$, HgO, H_2O; (h) Wittig; (i) Im_2CS; (j) Bu_3SnH, AIBN, heat.

Scheme XIII[a]



[a] (a) Allyl alcohol, $SnCl_4$; (b) OH^-; (c) PhCHO, $ZnCl_2$; (d) BnBr, NaH; (e) Ir^+; (f) $HgCl_2$, H_2O; (g) Wittig; (h) Im_2CS; (i) Bu_3SnH, AIBN.

the methyl signals of the two compounds (δ 1.28 and 1.05, respectively) gives a ratio of 7 to 3 for *cis* vs *trans* cyclization products.

The synthesis of a radical precursor having the manno configuration (**54**) is shown in Scheme XII. Upon reaction with allyl alcohol in the presence of tin(IV) chloride[18] in dichloromethane, β-D-mannosepentaacetate gave the allyl glycosides **47** as a mixture of anomers. Hydrolysis of the acetates[19] followed by treatment with benzal bromide[20] in refluxing pyridine gave a mixture of mono- and bisbenzylidenes. The strained five-membered acetal may be cleaved by treating with $LiAlH_4$ and $AlCl_3$ to give a mixture of alcohols[21] **52** and **53**, both of which in turn may be transformed into desired product **51** by subsequent benzylation. The diol monoacetal can be directly converted to **51**. The major cyclization product **57a** (25% from the corresponding 1-*H*-imidazolecarbothioate) is readily identified as the one arising via 1,5-*cis* cyclization mode from **56**. The NOE difference spectrum is characterized by enhancement of signals due to H_5, H_6, and H_{4eq} upon irradiation of the CH_3 signal.[14] Also seen are similar effects on the signals of H_2 and H_{4a} upon irradiation of H_{7a}. The methyl peak in the major isomer appears at δ 1.30 and in the minor isomer at δ 1.15. This minor product, which is obtained only in less than 2%, has not been fully characterized even though it can be tentatively assigned the 1,5-*trans* structure **57b** based on the CH_3 chemical shift. We have observed similar chemical shift changes in several related systems (vide supra).

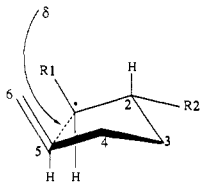
Scheme XIII outlines the synthesis of the precursor (**64**) to the radical **65** of the galacto configuration. The chemistry is similar to the one described for the manno system. The cyclization proceeds in 24% yield. Significant amounts (20%) of the starting alcohol **64** were recovered in this case under typical Barton deoxygenation conditions. The structure of the only cyclic product, **66**, has been assigned by NMR experiments. As expected NOEs are observed for the signals of H_{4eq}, H_5, and H_6 upon irradiation of the CH_3 resonance.[14] Irradiation of H_{7a} causes similar changes in the peaks corresponding to the H_2, H_{4ax}, H_{4a}, and H_7. The methyl signal as in the other 1,5-*cis* cases (e.g., δ 1.34 in **31a**, 1.28 in **37a**, 1.28 in **44**, and 1.30 in **57a**) appears at δ 1.40. In the *trans* series the chemical shifts range from δ 1.04 in **17a** to δ 1.15 in **57b**. The ^{13}C chemical shifts of C_{4a} and C_5 are also very diagnostic of this stereochemistry. For example a comparison of **57a** (*cis*, δ 35.05 and 37.16) and **57b** (*trans*, δ 35.65 and 42.10) clearly shows the well-recognized trend of upfield shift in sterically encumbered *cis* systems. The values of chemical shifts in **66** (δ 34.38 and 37.78) are closest to those of the *cis* compound **57a** (δ 35.05 and 37.16) rather than to those of the *trans* compound **57b** (δ 42.10 and 35.65), **17a** (δ 41.31 and 36.82), and **30a** (δ 44.32 and 38.30).

Discussion

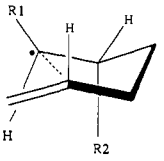
The stereochemistry of hex-5-enyl radical cyclization has been studied by Beckwith in great detail, and general guidelines with considerable predictive power have been proposed.[5b,5c] A number of theoretical studies based on ab initio and semiempirical methods have also appeared.[5f,5g] According to these studies, simple alkylsubstituted hex-5-enyl radicals cyclizations, 1- and 3-substituents, lead to mostly *cis* dialkylcyclopentanes, whereas 2- and 4-substituted hex-5-enyls, give predominantly *trans* products. Beckwith also recognized that the *cis* vs *trans* selectivity is most profoundly affected by 4-substituents.[22] Except in the case of the C-1 substituted radical, these results have been rationalized on the basis of a theoretically derived transition state **67** (Chart

(18) Hanessian, S.; Banoub, J. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1980.
(19) Watanabe, T.; Katayama, S.; Nakashita, Y.; Yamauchi, M. *J. Chem. Soc., Chem. Commun.* **1981**, 761.
(20) Garegg, P. J.; Swahn, C.-G. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1980.
(21) Liptak, A.; Jodal, I.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1.
(22) This effect, which was originally recognized by Beckwith, has since been used in synthesis: (a) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (b) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351. (c) Little, R. D.; Wolin, R. L. *Abstract of Papers*, 193rd National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, DC, 1987; ORGN 134.

Chart I

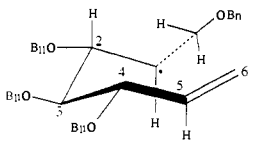


67a

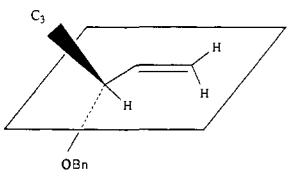


67b

δ for TS ca. 2.3 A; for cyclohexane 2.5 A

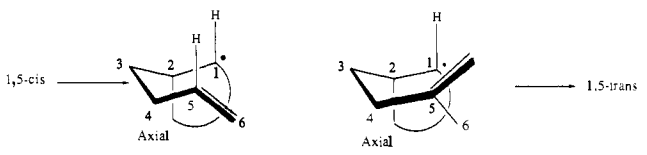


68a



68b

Scheme XIV



72a 72b

I), which has a long incipient bond (ca. 2.3 Å). It is argued that this distance (and other geometric parameters) is not much different from that between C_1–C_3 in cyclohexane, and therefore, conformational features that are well-known in this system can be used to rationalize stereochemical results in the hex-5-enyl radical cyclizations. Thus, in the absence of special effects a "chairlike" transition state would be preferred over a "boatlike" one (Scheme XIV). Of the two possible chairlike transition states (**67a** and **67b**), **67a** with substituents in quasi-equatorial position is favored leading to 2,5-*trans* product. Similar arguments can be made for the 3- and 4-substituted radical. The predominance of *cis* products from C_1-substituted radicals, has been explained on the basis of stereoelectronic[2c] as well as steric grounds.[3c]

The cyclization of the acyclic radical **9a** (or **9b**) giving rise mainly to 1,5-*cis* product **10** can be accounted for by a transition state **68a**. Note that in this transition state the (phenylmethoxy)methyl substituent at the C_1 position and the C_2, C_3, and C_4 phenylmethoxy groups are all in an equatorial orientation and the local allylic conformation (C_3–C_6) is the sterically most favorable one (**68b**).[23] Inversion at C_1 in **68a** or boatlike transition states would lead to the minor products. Theoretical calculations done by Houk and Spellmeyer[5g] estimate boatlike transition states to be only approximately 0.5 kcal/mol above the chairlike structure in these reactions (vide infra).

The boatlike transition state, however, appears to be favored in the cyclization of the cyclic radical **16** (Scheme VI). The exclusive formation of the 1,5-*trans* product **17** is totally unexpected, especially in view of the fact that other related radicals (e.g., **36** or **43**) and similar carbocyclic radicals give mostly 1,5-*cis* products.[6,7,24] If one assumes that the dioxan ring maintains the chair conformation and the bulky phenyl and butenyl groups occupy equatorial sites, the 1,5-*trans* product can only be rationalized by a boatlike cyclization transition state depicted by structure **69a** in Scheme XV, in which the pseudoaxial radical attacks the C=C bond in the pseudoequatorial butenyl side chain. This is in stark contrast to Beckwith's suggestion[6b] that 2-(but-3-enyl)cyclohexyl radical cyclizes via a transition state in which pseudoequatorial radical attacks an axial butenyl group. It was argued then that the orbital overlap required for the cyclization would be optimal in that arrangement.[24] It was also suggested[3c] that in the case of 2-(but-3-enyl)cyclopentyl radicals, chairlike transition state **4a** (Scheme III) en route to the 1,5-*cis* product can, with much less strain, accommodate effective overlap between the SOMO of the radical and the olefin π orbitals than the alternate chair **4b** that would lead to the *trans* product.[25] Another way of looking at this problem may be to consider *the cycloalkyl portion of the radical as having a fixed conformation while changing the conformation of the carbon atoms in the hexenyl segment* as shown in Scheme XIV. According to this scheme, the chairlike transition state **72a** gives a 1,5-*cis* product and the boatlike transition state **72b** gives a 1,5-*trans* product.

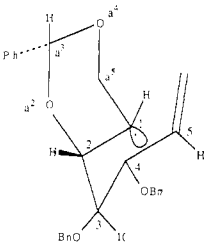
The exact origin of this preference for a boatlike transition state in the radical **69a** is unknown. Some relief of steric compression between the C-2 oxygen (i.e., dioxan O) and the C-4 phenylmethoxy group is expected as the *cis* decalin-like structure changes its conformation to **69a** from **69b**. However, the conformational studies[26] of various sugar derivatives suggest that this alone would not be sufficient to make such a dramatic effect. We propose that the local conformation of the allyl ether portion of the molecule (viz. C_3–C_6) is an important factor in controlling the stereochemistry. The boatlike transition state contains the most favorable allylic conformation[23] for the C_3–C_6 portion of the molecule, whereas the allylic segment in the chairlike transition state **69b** is considerably strained[23] because a bulky group (X = OBn) eclipses one of the vinylic hydrogen atoms. Since alkyl radical appears to add to olefins as a nucleophile,[2g] an activation of the olefin π^* orbital by the allylic β-CO-σ^* may also play an important role.[27]

In fact, in the absence of the allylic oxygen (as in **36** and **43**), the normal reaction via a chairlike transition state predominates (Scheme XVI); *cis*/*trans* ratios of 77–23 from **36a** (Scheme X), and 70–30 from **43**,[28] (Scheme XI) are obtained. The fact that the control element is the C_4 oxygen is further confirmed by the results of cyclization of the mannose-derived radical **56** (Scheme XII). In this case the configuration of the key C_4 center is inverted as compared to the glucose-derived radical **16**, and in accord with

(23) (a) Karabatsos, G. J.; Fenglio, D. *J. Top. Stereochem.* **1970**, *5*, 167. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (c) For a theoretical treatment of staggered models, see: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.

(24) Results from other laboratories[7] have since shown that the preference for 1,5-*cis* selectivity is noticed even when the butenyl group is equatorial. We have found that if the butenyl group is forced into an axial orientation [for example in radicals derived from *trans*-4-*tert*-butyl-2-(but-3-enyl)cyclohexanone] the major product indeed has 1,5-*trans* stereochemistry (ref 7c). Considering this reaction's long history, it is surprising that this control element had so far gone unrecognized; a casual examination of molecular models would have revealed this outcome.

(25) On somewhat similar grounds, earlier we[1a] raised the possibility that the dioxan ring of **16** may exist in a flexible boat form (**71**)



71

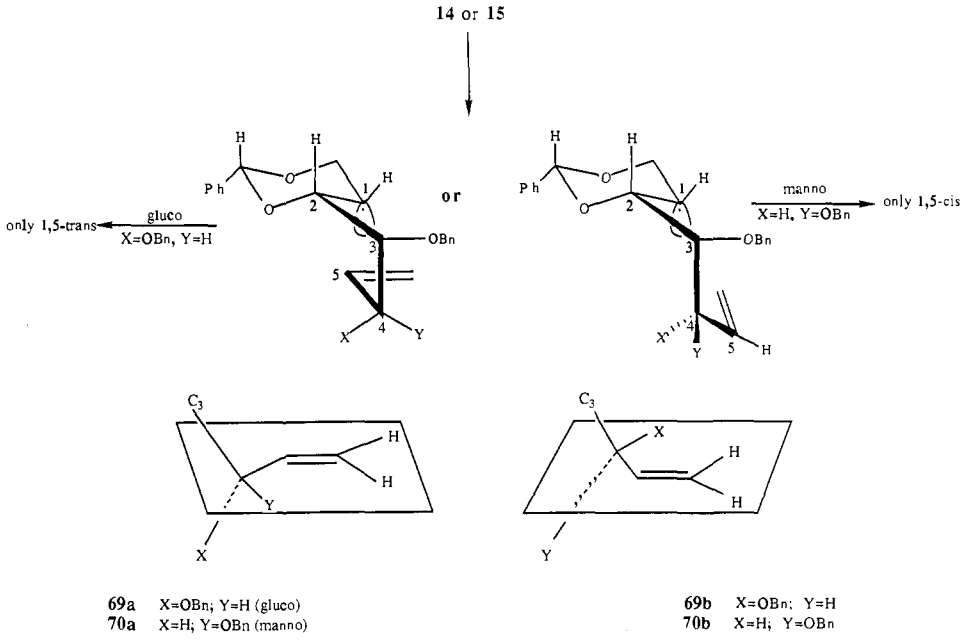
and in the $B_{a2,a5}$ conformation the bulky phenyl and butenyl groups might occupy the pseudoequatorial position with the lone-pair repulsions minimized. Then it was argued, the observed *trans* product could arise from a chairlike transition state as shown in the structure. Note that this structure is also characterized by the most favorable conformation of the allylic segment C_3–C_6. In the light of the studies of the manno (Scheme XV) and 2-deoxygluco (Scheme XVI) systems, we now feel that this was probably incorrect.

(26) Auge, J.; David, S. *Tetrahedron* **1984**, *40*, 2101.

(27) For a critical evaluation of the effect of allylic substituents on the stereochemistry of electrophilic additions to olefins, see: Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094, and references cited therein.

(28) The all-carbon analogue of **43** viz. *cis*-[2-(but-3-enyl)-4-phenyl]-cyclohexyl radical cyclizes to give a mixture of bicyclic products of which the major component (83%) has been identified as resulting from 1,5-*cis* cyclization (ref 7c).

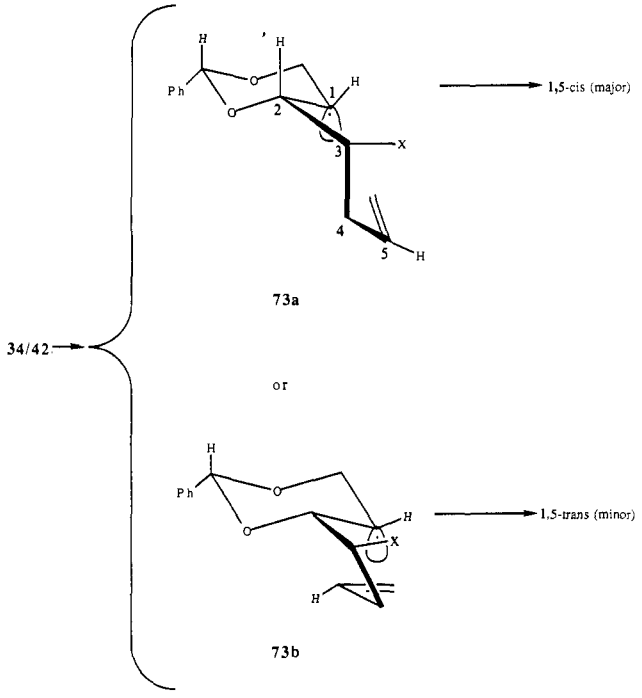
Scheme XV



69a X=OBn; Y=H (gluco)
70a X=H; Y=OBn (manno)

69b X=OBn; Y=H
70b X=H; Y=OBn

Scheme XVI



the prediction, only the 1,5-*cis* product is formed almost exclusively. As shown in the Scheme XV, the chairlike conformation of the transition state **70b** incorporates the low-energy and reactive conformation of the allylic (C_3–C_6) segment.

In order to evaluate the role of the C_3 oxygen (radical numbering) we examined the 3-deoxyglucose-derived radicals. Radical **29a** gave a mixture of *trans* (**30a**) and *cis* (**31a**) products in a ratio of 11 to 1 and radical **29b** gave almost exclusively the *trans* product **30b**. Thus the C_3 oxygen substituent does not exert strong effects on the stereoselectivity.

Finally, the galactose-derived radical **65** provided an additional test for the rationale just outlined (Scheme XIII). It should be noted that the transition state **74** in the galactose series is closely related to the enantiomer of the mannose-derived radical **70b** except for the configuration at C_3 (Scheme XVII). This allowed us to examine the effect of the C_3 configuration on the 1,5-*cis* cyclization. The fact that galactose-derived radical **65** gives exclusively the 1,5-*cis* product **66** also supports the above conclusion that the C_3 oxygen has very little influence on the stereochemical course of the reaction.

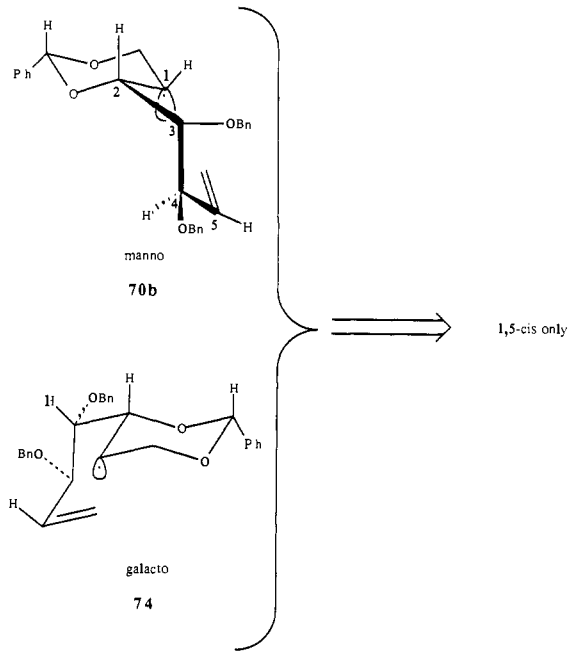
In conclusion, our studies show that the 1,5 stereochemistry in the cyclization of hex-5-enyl radicals is controlled by the nature of the substituent and the configuration at the C_4 center. In the presence of a C_4 oxygen substituent the local allylic conformation dictates the preference between the chairlike and boatlike transition state. The chairlike transition state leading to 1,5-*cis* products is generally favored. However, in the glucose series the low-energy, local allylic C_3–C_6 conformation can be accommodated only in the boatlike transition state which, we believe, leads to the unprecedented and exclusive 1,5-*trans* selectivity observed in the cyclization of radicals **16** and **29**. In contrast to the critical role of C_4 substituents, no significant effects to the 1,5 stereoselection are observed with C_3 substituents.

Experimental Section

General Procedure for the Wittig Reaction. A three-necked flask fitted with a dropping funnel, thermocouple lead, and serum stopper was thoroughly flame dried and was charged with a suspension of recrystallized, powdered, and *dried* phosphonium salt in anhydrous THF (0.5 M). The mixture was cooled to −20 °C and from the dropping funnel was added 0.98 equiv of 1.6 M *n*-BuLi in hexane. After all the butyllithium was added, the dropping funnel was washed with more THF. The mixture was stirred at −20 °C to room temperature until all the solid disappeared (~1 h). A solution of the pyranose (0.5 equiv, 0.5 M in THF) was added to the reaction mixture at −20 °C from the dropping funnel, and the mixture was stirred for 16 h while the temperature gradually came to room temperature. A dry condenser was connected to the flask, and the reaction mixture was heated to 50 °C for 15 min. It was subsequently cooled to room temperature, and excess reagent-grade acetone was added. After the mixture was stirred for 5 min, ether (120 mL/mmol of sugar) was added and the precipitated solid was filtered off with the aid of Celite. The Celite pad was washed with excess ether, and the combined ether solutions were washed with saturated sodium bicarbonate, sodium chloride, and water. It was dried and concentrated. The products were collected by flash[29] chromatography on silica gel using ethyl acetate/hexane as the solvent. In the case of the methyl vinyl ethers the *Z* and *E* isomers can be separated by careful chromatography for further experiments.

General Procedure for Radical Generation and Cyclization. A flame-dried single-necked flask with a reflux condenser was charged with a 0.2–0.3 M solution of the enitol (for example, **14**) in distilled dry 1,2-dichloroethane. To this solution was added 2 equiv of thiocarbonylbisimidazole (99+%, pure; Fluka), and the mixture was refluxed under nitrogen until all starting material disappeared as judged by thin-layer chromatography. In certain instances where the reaction was incomplete after 2 h, an additional 1 equiv of thiocarbonylbisimidazole was added and the reaction was heated further. The product was extracted into methylene chloride after adding excess water to destroy the thio-

Scheme XVII



carbonylbisimidazole. The combined CH_2Cl_2 layer was washed with *ice-cold* 1 N HCl, saturated sodium bicarbonate, and brine. The product was purified by flash chromatography on silica gel using an ethyl acetate/hexane solvent system. The yields of the product in general are ~75–85%.

The above product was transferred into a single-necked flask and was further dried by azeotroping with toluene. It was dissolved in freshly distilled toluene to make a 0.1–0.2 M solution, and 10–20 mg of azobis(isobutyronitrile) (AIBN) per mmol of starting material and 0.5 equiv of tributyltin hydride were added. The mixture was brought to reflux, and a solution of 1.5 equiv more of tributyltin hydride and AIBN (10–20 mg) dissolved in toluene was added from a syringe in about ~2 h. After all the hydride had been added, the reaction was further refluxed for 1 h and subsequently cooled. Excess ether was added, and the organic layer was washed with 1 N HCl, saturated sodium bicarbonate, and potassium fluoride. The dried organic extract was concentrated, and the products were isolated by chromatography on silica gel. Individual fractions were analyzed by ^1H and ^{13}C NMR to ascertain the presence (or absence) of cyclic products. The yields are reported under each specific example.

[1*R*-(1α,2β,3α,4β,5α)]-1-Methyl-2,3,4-tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]cyclopentane (10a) and Its Isomers 11a and 12a. A mixture of 0.668 g (1.24 mmol) of 1,2-dideoxy-3,4,5,7-tetrakis-*O*-(phenylmethyl)-D-hept-1-enitol (**7a**) and 0.442 g (2.48 mmol) of thiocarbonylbisimidazole in 6 mL of distilled, dry 1,2-dichloroethane was refluxed for 4 h under nitrogen, and 0.800 g (99%) of the 1-*H*-imidazolecarbothioate **8a** was isolated. A mixture of **8a**, 32 mg of AIBN, and 0.736 mL (2.72 mmol) of distilled tributyltin hydride in 12 mL of freshly distilled toluene was refluxed for 30 min, resulting in complete disappearance of the starting sugar. Workup and chromatography using 10–20% ethyl acetate/hexanes as the solvent yielded 0.395 g (61% as a mixture based on **7a**) of cyclic product **10a**, **11a**, and **12a** in a ratio of 74:14:12. These isomers were separated by careful chromatography and analyzed by high-resolution NMR spectroscopy (see supplementary material for detailed spectroscopic data, and for selected NMR data see Table I).

(*E*)-2-Deoxy-1-*O*-methyl-3,4,5,7-tetrakis-*O*-(phenylmethyl)-D-*gluco*-hept-1-enitol (7b). The title compound and its *Z* isomer were prepared by the general procedure in 61% yield: ^1H NMR (360 MHz) δ 2.90 (s, br, 1 H), 3.45 (s, 3 H), 3.61 (m, 2 H), 3.77 (m, 2 H), 4.00–4.10 (m, 2 H), 4.30–4.86 (m, 8 H), 6.32 (d, *J* = 13 Hz, 1 H), 7.20–7.35 (aromatic). The *Z* compound **7c** has a similar spectrum with the H_1 appearing at δ 6.14 as a doublet (*J* = 7 Hz). The ratio of *E* to *Z* isomer was 88:12. The unstable enol ethers were converted immediately into the cyclic products.

[1*S*-(1α,2β,3α,4β,5α)]-1-(Methoxymethyl)-2,3,4-tris(phenylmethoxy)-5-[(phenylmethoxy)methyl]cyclopentane (10b) and Its Isomer 11b. The general procedures described previously for generation and cyclization yielded 61% of a mixture of **10b** and **11b** in a ratio of 3:1. **10b** + **11b**: oil, $[\alpha]^{25}_D$ +1.6 ± 0.8°. Another compound **12b** (~2%) having an OCH_3 peak at δ 3.03 has only been tentatively identified based on the earlier structure **12a**.

(*R*)-1,2-Dideoxy-3,4-bis-*O*-(phenylmethyl)-5,7-*O*-(phenylmethylene)-D-*gluco*-hept-1-enitol (14a). The title compound was prepared in 82% yield from 2,3-bis-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-glucopyranose (**13**).[30]

(*R*)-1-*O*-Methyl-2-deoxy-3,4-bis-*O*-(phenylmethyl)-5,7-*O*-(phenylmethylene)-D-*gluco*-hept-1-enitol (14b/14c). The standard Wittig conditions afforded 81% of **14b** and **14c** in a ratio of 69:31): ^1H NMR inter alia δ 6.20 (dd, *J* = 6 Hz, 1 Hz, H_1 of *Z* isomer, 31%), 6.54 (d, *J* = 14 Hz, H_1 of *E* isomer, 69%).

[(2*R*)-(2α,4aβ,5β,6α,7β,7aβ)]-Hexahydro-5-methyl-2-phenyl-6,7-bis(phenylmethoxy)cyclopenta-1,3-dioxin (17a). The radical precursor **15a** prepared from **14a** in 68% yield was subjected to the deoxygenation reaction to get a single compound **17a** in 57% yield: mp 76–78 °C; $[\alpha]^{25}_D$ −10.4 ± 0.8° ($CHCl_3$, *c* 1).

[(2*R*)-(2α,4aβ,5β,6α,7β,7aβ)]-Hexahydro-5-(methoxymethyl)-2-phenyl-6,7-bis(phenylmethoxy)cyclopenta-1,3-dioxin (17b). The title compound was prepared in 62% yield by refluxing a mixture of 3.61 g (6.2 mmol) of **15b/15c**, 3.32 mL (12 mmol) of tributyltin hydride, and 91 mg of AIBN in 40 mL of dry toluene for 90 min followed by standard workup; $[\alpha]^{25}_D$ −15.2 ± 0.8° ($CHCl_3$, *c* 1).

A minor (<5%) cyclic product characterized by a OCH_3 peak at δ 3.36 remains uncharacterized.

[1*S*-(1α,2β,3α,4β,5α)]-2-Methyl-3,4,5-tris(phenylmethoxy)cyclopentanemethanol (19a) and [1*R*-(1α,2α,3β,4α,5β)]-3-Methyl-4,5-bis(phenylmethoxy)-2-[(phenylmethoxy)methyl]cyclopentanol (20a). To a solution of 0.430 g (1 mmol) of **17a** in 20 mL of anhydrous ether and 20 mL of anhydrous methylene chloride was added 0.042 g (1.10 mmol) of LAH. In a separate vial 0.147 g (1.10 mmol) of sublimed aluminum chloride was dissolved in 10 mL of ice-cold anhydrous ether. The aluminum chloride solution was added dropwise to the sugar and LAH suspension. The mixture was stirred for 40 min. Five grams of a mixture (3:3:1) of Celite, sodium sulfate, and water was added, and stirring was continued for 15 min. The insolubles were filtered off through a pad of $MgSO_4$, and the filter cake was washed with excess THF. The organic layer was washed with saturated sodium bicarbonate and brine and was concentrated. Column chromatography yielded 0.0190 g (4.5%) of **19a** and 0.184 g (44%) of **20a**.

19a: ^1H NMR δ 1.50 (d, *J* = 6 Hz, 3 H, CH_3), 1.80 (m, 1 H), 2.28 (m, 1 H), 2.53 (q, *J* = 4 Hz, 1 H, exchange with D_2O, O*H*), 3.55 (dd, *J* = 8, 4 Hz, 1 H), 3.75 (m, 1 H), 3.85 (m, 1 H), 3.95–4.05 (m, 2 H), 4.45–4.72 (6 H, CH_2Ph), 7.20–7.41 (m, aromatic H); FBMS 432.95 (M^+ + H; calcd for $C_{28}H_{33}O_4$ 433.24).

20a: ^1H NMR δ 1.02 (d, *J* = 7 Hz, 3 H), 1.90 (m, 1 H), 2.12 (m, 1 H), 3.08 (d, *J* = 4 Hz, exchange with D_2O, O*H*), 3.45 (dd, *J* = 9, 4 Hz, 1 H, H_4), 3.68 (ABX, J_{AB} = 10 Hz, J_{AX} = 4 Hz, J_{BX} = 7 Hz, 2 H, CH_2OBn), 3.83 (dd, *J* = 4, 2 Hz, 1 H, H_5), 4.25 (m, 1 H, H_1, upon exchange of OH becomes dd, *J* = 7, 2 Hz), 4.43–4.80 (6 H, CH_2Ph), 7.20–7.40 (m, aromatic); ^{13}C NMR δ 16.79, 37.57, 46.50, 68.49, 71.69, 72.01, 73.32, 76.30, 89.39, 90.33; FBMS 432.95 (M + H; calcd for $C_{28}H_{23}O_4$ 433.24); HRMS 341.1754 ($M^+ - C_7H_7$; calcd for $C_{21}H_{25}O_4$ 341.1753).

[1*S*-(1α,2β,3α,4β,5α)]-2-(Methoxymethyl)-3,4,5-tris(phenylmethoxy)cyclopentanemethanol (19b) and [1*R*-(1α,2β,3β,4α,5β)]-3-(Methoxymethyl)-4,5-bis(phenylmethoxy)-2-[(phenylmethoxy)methyl]cyclopentanol (20b). The title compounds were prepared as described in the previous experiment in yields of 16% and 64%, respectively, from **17b**.

19b: ^1H NMR δ 2.32 (m, 1 H), 2.40 (m, 1 H), 3.11 (q, *J* = 4 Hz, 1 H, exchange with D_2O), 3.32 (s, 3 H), 3.35 (m, 1 H), 3.50 (dd, *J* = 10, 4 Hz, 1 H), 3.69–3.82 (m, 3 H), 3.95 (m, 2 H), 4.45–4.70 (m, CH_2Ph, 6 H), 7.25–7.40 (m, aromatic); FBMS 463.00 (M^+ + H; calcd from $C_{29}H_{35}O_5$ 463.25); HRMS 371.1874 ($M^+ - C_7H_7$; calcd for $C_{22}H_{27}O_5$ 371.1859).

20b: ^1H NMR (360 MHz) δ 2.25 (m, 2 H, H_2, H_3), 3.07 (d, *J* = 5 Hz, 1 H, exchange with D_2O), 3.21 (s, 3 H), 3.37 (t, *J* = 5 Hz, 2 H), 3.75 (m, 3 H), 3.87 (t, m, *J* = 3 Hz, 1 H), 4.22 (m, 1 H), 4.50–4.80 (m, CH_2Ph), 7.20–7.35 (m, aromatic H); ^{13}C NMR δ 42.56, 44.16, 58.72, 69.30, 71.58, 71.80, 72.80, 73.28, 76.31, 83.98, 89.24; FBMS 463.03 (M + H; calcd for $C_{29}H_{35}O_5$ 463.25); HRMS 371.1879 ($M^+ - C_7H_7$; calcd for $C_{22}H_{27}O_5$ 371.1859).

[1*R*-(1α,2β,3α,4β,5β)]-1,5-Dimethyl-2,3,4-tris(phenylmethoxy)cyclopentane (21a). A solution 0.0298 g of the tosylate of **19a** (tosyl chloride, pyridine, 0 °C, overnight) in 2 mL of THF was treated with 0.10 mL of a 1 M solution of lithium triethylborohydride at 55 °C for 18 h. Water (10 mL) was added, and the product **21a** was extracted into ether and further purified by preparative thin-layer chromatography: ^1H NMR

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(30) Liptak, A.; Imre, J.; Harangi, J.; Nanasi, P. *Carbohydr. Res.* **1983**, *116*, 217.

(360 MHz) δ 1.04 (d, J = 4 Hz, 3 H), 1.06 (d, J = 4 Hz, 3 H), 1.70 (m, 1 H), 1.91 (m, 1 H), 3.46 (dd, J = 8, 4 Hz, 1 H), 3.68 (dm, J = 4 Hz, 1 H), 3.90 (dd, J = 4, 2 Hz, 1 H), 4.45–4.65 (3 AB q, 6 H), 7.20–7.46 (m, aromatic).

This product may also be prepared by the procedure outlined in the next experiment for the preparation of **21b**.

[1*S*-(1α,2β,3α,4β,5β)]-1-(Methoxymethyl)-5-methyl-2,3,4-tris(phenylmethoxy)cyclopentane (21b). To a solution of 0.056 g (0.12 mmol) of **19b** and 0.043 g (0.24 mmol) of freshly recrystallized *N*-bromosuccinimide in 3 mL of DMF was added 0.063 g (0.24 mmol) of triphenylphosphine. The mixture was maintained at 50 °C under nitrogen for 1 h, and 3 mL of methanol was added. The solvents were evaporated on the pump, and the residue was dissolved in 50 mL of ether. The ether layer was washed with saturated sodium chloride, dried, and concentrated. The product was isolated by preparative TLC and was used for the subsequent experiment.

A solution of 0.261 g (0.05 mmol) of the bromide from the previous experiment, 0.134 mL of tributyltin hydride, and 10 mg of AIBN in 3 mL of toluene was refluxed for 90 min. Saturated KF (10 mL) was added, and the product was extracted into ether. The major product, **21b**, was isolated in nearly quantitative yield by preparative TLC: ^{1}H NMR (360 MHz) δ 1.04 (d, J = 7 Hz, 3 H, CH_3), 1.32 (m, 1 H, H_5), 2.05 (m, 1 H, H_1), 3.30 (s, 3 H, CH_3O), 3.39 (d, AB q, J = 5 Hz, J_{AB} = 10 Hz, 2 H, CH_2OCH_3), 3.75 (m, 2 H, H_2, H_4), 3.97 (t, J = 4 Hz, 1 H, H_3), 4.30–4.65 (6 H, CH_2Ph), 7.20–7.40 (m, aromatic); ^{13}C NMR δ 13.46, 36.16, 48.93, 58.90, 71.23, 71.80, 71.82, 72.48, 83.71, 85.36, 87.49.

[1*R*-(1α,2β,3α,4β,5β)]-5-(Methoxymethyl)-1-methyl-2,3,4-tris(phenylmethoxy)cyclopentane (22a). To a solution of 0.023 g of **19a** in 2 mL of DMF was added 0.030 g of sodium hydride, and the mixture was stirred at 0 °C to room temperature for 30 min. The reaction was cooled to 0 °C, and 0.020 mL of methyl iodide was added. The reaction mixture was allowed to come to room temperature, and it was further stirred for 1 h. The product was isolated by the usual techniques and purified by preparative TLC.

[1*S*-(1α,2β,3α,4β,5β)]-1,5-Bis(methoxymethyl)-2,3,4-tris(phenylmethoxy)cyclopentane (22b). The title compound was prepared in 75% by methylation of **19b** by the procedure outlined in the previous experiment. ^{1}H NMR (360 MHz) δ 2.15–2.32 (m, 2 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 3.37 (m, 2 H), 3.47 (dd, J = 10, 6 Hz, 1 H), 3.62 (m, 1 H), 3.78 (m, 1 H), 3.90 (m, 1 H), 4.45–4.61 (m, CH_2Ph, 6 H), 7.20–7.42 (m, aromatic); ^{13}C NMR δ 42.230, 45.134, 58.709, 58.732, 71.171, 71.590, 71.705, 71.753, 73.146, 81.551, 85.178, 87.317; HRMS 385.1995 ($M^+ - C_7H_7$; calcd for $C_{23}H_{29}O_5$ 385.2015).

Preparation of Authentic 11a and 11b. These compounds were prepared from **20a** and **20b**, respectively, by benzylation of the secondary alcohol with benzyl bromide in DMF using NaH as a base to generate the alcoholate. These compounds were identical with the minor products obtained from the cyclization of radicals **9a** and **9b** (^{1}H NMR, ^{13}C NMR, HRMS, vide supra).

[1*S*-(1α,2α,3β,4α,5β)]-2-Hydroxy-5-(methoxymethyl)-3,4-bis(phenylmethoxy)cyclopentanemethanol (23). In a 50-mL flask 3 g of silica gel was suspended in 5 mL of CH_2Cl_2 and to it was added 0.5 mL of 6% oxalic acid solution. After the suspension was stirred for 5 min, 0.070 g of **17b** dissolved in 2 mL of CH_2Cl_2 was added. The reaction was stirred until all starting material was consumed, and the product was isolated first by filtering off the silica gel and then evaporation of the solvent followed by preparative thin-layer chromatography: ^{1}H NMR (360 MHz) δ 2.10 (m, 1 H), 2.30 (m, 1 H), 2.60 (s, br, 1 H, exchange with D_2O), 2.84 (s, br, 1 H, exchange with D_2O), 3.32 (s, superimposed on m, 5 H), 3.47 (dd, J = 8, 5 Hz, 1 H), 3.65 (ddd, J = 6, 3, 1 Hz, 1 H), 3.86 (m, br, 3 H), 4.50–4.70 (4 H, CH_2Ph), 7.25–7.40 (m, aromatic); HRMS 281.1386 ($M^+ - C_7H_7$; calcd for $C_{15}H_{21}O_5$ 281.1389).

[1*R*-(1α,2α,3β,4α,5β)]-3-(Methoxymethyl)-4,5-bis(phenylmethoxy)-2-[(triphenylmethoxy)methyl]cyclopentanol (24). A solution of 0.212 g (0.57 mmol) of **23** in 3 mL of anhydrous pyridine was treated with 0.190 (0.68 mmol) of triphenylmethyl chloride and 0.020 g of 4-(dimethylamino)pyridine. The mixture was stirred under nitrogen at room temperature for 72 h. It was then added to 50 mL of ice-cold water, and the product was extracted into ether. Column chromatography on silica gel using 10–20% ethyl acetate/hexanes yielded 0.253 (72%) of **24**: ^{1}H NMR (360 MHz) δ 2.21 (m, br, 2 H), 2.89 (d, J = 5 Hz, 1 H, exchange with D_2O), 3.21 (s, 3 H), 3.23 (m, br, 1 H), 3.36 (m, 3 H), 3.77 (m, 1 H), 3.87 (t, J = 4 Hz, 1 H), 4.25 (m, 1 H), 4.50–4.78 (CH_2Ph, 4 H), 7.18–7.47 (m, aromatic).

[1*R*-(1α,2α,3β,4α,5β)]-1-Acetoxy-3-(methoxymethyl)-4,5-bis(phenylmethoxy)-2-[(triphenylmethoxy)methyl]cyclopentane (25). The title compound was prepared by acetylation of **24** with acetic anhydride in pyridine in the presence of 4-(dimethylamino)pyridine at 0 °C. The product (95%) was purified by column chromatography on silica gel using 20% ethyl acetate/hexanes as the eluant: ^{1}H NMR δ 1.82 (s, 3 H), 2.03 (m, 1 H, H_3), 2.45 (m, 1 H, H_2), 3.10–3.35 (m, 4 H), 3.20 (s, 3 H), 3.76 (m, 1 H, H_4), 3.87 (t, J = 3 Hz, 1 H, H_5), 4.45 (AB q, 2 H, CH_2Ph), 4.62 (AB q, J_{AB} = 15 Hz, 2 H), 5.30 (m, 1 H, H_1), 7.18–7.75 (m, aromatic).

Equilibration of [1*S*-(1α,2α,3β,4α,5β)]-2-Acetoxy-5-(methoxymethyl)-3,4-bis(phenylmethoxy)cyclopentanemethanol (26a) and [1*R*-(1α,2α,3β,4α,5β)]-2-(Acetoxymethyl)-3-(methoxymethyl)-4,5-bis(phenylmethoxy)cyclopentanol (26b). A solution of 0.258 g of the trityl ether **25** in 80% acetic acid was stirred at room temperature until all the starting material disappeared. The reaction mixture was added to 40 mL of saturated sodium bicarbonate, and the product was extracted into ether. The ether layer was washed with saturated sodium chloride, dried, and concentrated. The primary product of detritylation (**26a**) underwent ready acetyl migration to establish an equilibrium mixture of **26a** and **26b** under the reaction conditions. These isomers were separated by column chromatography on silica. Purified **26a** establishes a 1:1 equilibrium with **26b** in 4 days in $CDCl_3$/TMS.

26a: ^{1}H NMR δ 2.07 (s, 3 H, $OCOCH_3$), 2.25 (m, 2 H), 3.30–3.40 (m, 1 H), 3.35 (s, 3 H, OCH_3), 3.52–3.70 (m, 4 H), 3.84 (dd, J = 4, 2 Hz, 1 H), 4.35–4.80 (4 H, CH_2Ph), 5.19 (d, br, J = 5 Hz, 1 H, H_1), 7.20–7.40 (m, aromatic); FABMS 415.23 (M + H; $C_{24}H_{31}O_6$).

26b: ^{1}H NMR δ 2.06 (s, 3 H, $OCOCH_3$), 2.17 (m, 2 H), 2.74 (d, J = 7 Hz, 1 H, OH), 3.30 (s, 3 H, OCH_3), 3.38 (m, 2 H), 3.79 (m, 1 H), 3.89 (t, br, J = 2 Hz, 1 H), 4.10 (m, br, 1 H), 4.22 (dd, J = 11, 4 Hz, 1 H), 4.42 (dd, J = 11, 8 Hz, 1 H) together CH_2OCOCH_3, 4.50–4.62 (m, CH_2Ph, 4 H), 7.21–7.50 (m, aromatic).

[2*R*-(2α,4aβ,5β,6α,7aβ)]-Hexahydro-5-methyl-2-phenyl-6-(phenylmethoxy)cyclopenta-1,3-dioxin (30a) and Its Isomer 31a. Reductive cyclization of **29a** by the procedures outlined earlier gave a mixture of **30a** and **31a** (11:1) in 67% yield from the corresponding 1-*H*-imidazolecarbothioate. For physical data on **30a** and **31a** see Table I and supplementary material.

[2*R*-(2α,4aα,5β,6α,7aβ)]-Hexahydro-5-(methoxymethyl)-2-phenyl-6-(phenylmethoxy)cyclopenta-1,3-dioxin (30b). See ref 10.

Cyclization of Radical 36a: [2*R*-(2α,4aβ,5α,7β,7aβ)]-Hexahydro-5-methyl-2-phenyl-7-(phenylmethoxy)cyclopenta-1,3-dioxin (37a) and Its Isomer 38a. Generation of the 1-*H*-imidazole-1-carbothioate of **35a** and its subsequent reaction with tributyltin hydride in the presence of AIBN gave a mixture of two cyclic products **37a** and **38a** in a ratio of 77:23 in an overall yield of 32% for **35a**.

[2*R*-(2α,4aβ,5α,7β,7aβ)]-Hexahydro-5-(methoxymethyl)-2-phenyl-7-(phenylmethoxy)cyclopenta-1,3-dioxin (37b). The title compound (86% of the mixture) and its isomer **38b** were prepared in 51% total yield from a mixture of **35b** and **35c**. They were readily separated by flash chromatography on silica gel using 20–30% ethyl acetate/hexanes as the solvent system.

[1*R*-(1α,2α,3α,5β)]-3-Methyl-5-(phenylmethoxy)-2-[(phenylmethoxy)methyl]cyclopentanol (39) and [1*S*-(1α,2α,4β,5β)]-2-Methyl-4,5-bis(phenylmethoxy)cyclopentanemethanol (40). These compounds were prepared by treatment of **37** with $LAH/AlCl_3$ in CH_2Cl_2/ether according to the procedure described earlier (for the preparation of **19a** and **20a**) in 96% combined yield.

(*R*)-Allyl 2,3-Dideoxy-4,6-*O*-(phenylmethylene)-D-glucopyranoside (41). This compound was prepared in 68% by deoxygenation of **32** by the procedure of Robins et al.[9b]

(*R*)-2,3-Dideoxy-4,6-*O*-(phenylmethylene)-D-glucopyranose (42). The title compound was prepared by (a) Ir^+-catalyzed 1,3 H shift to form a vinyl glycoside from **41** and (b) $HgCl_2$/HgO-assisted hydrolysis of this vinyl glycoside. **42**: IR (KBr) 3400, 3060, 3030, 1500, 1090, 750, 695 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.56–2.19 (m, 4 H), 2.51 (dd, J = 4, 2 Hz), 2.95 (d, J = 6 Hz) together 1'H, 3.40–3.81 (m, 3 H), 4.06 (m), 4.19 (dd, J = 10, 5 Hz), 4.28 (dd, J = 11, 4 Hz), 4.06–4.30 together 1 H, 4.92 (m), 5.28 (m) together 1 H, 5.50 (s), 5.57 (s) togehter 1 H, 7.30–7.55 (m, aromatic H); HRMS 236.1034 (M^+; calcd 236.1048).

[2*R*-(2α,4aβ,5α,7aβ)]-Hexahydro-5-methyl-2-phenylcyclopenta-1,3-dioxin (44) and Its Isomer (45). These compounds were prepared in 55% yield by cyclization of the radical **43**, which in turn was prepared from the corresponding alcohol via the Barton methodology. The ratio of **44** to **45** as ascertained by integration of the CH_3 signals was 7:3: ^{1}H NMR δ inter alia 1.28 (d, J = 7 Hz, 3 H, CH_3), 4.25 (ABX, J_{AB} = 12 Hz, J_{BX} = 4 Hz, J_{AX} = 0, 2 H), 4.38 (m, 1 H), 5.44 (s, 1 H). The minor isomer **45** has the CH_3 signal at δ 1.05. Irradiation of CH_3 in the major product causes $H_{4\,equatorial}$ signal enhancement. Major isomer: ^{13}C NMR δ 18.80, 32.15, 33.41, 34.17, 40.24, 66.23, 80.56, 100.17. Minor isomer ^{13}C NMR δ 18.67, 31.36, 32.01, 32.28, 47.27, 65.99, 80.85, 100.46; HRMS (done on the mixture) 218.1290 (M^+; calcd for $C_{14}H_{18}O_2$ 218.1307).

Allyl 2,3,4,6-Tetra-*O*-acetyl-D-mannopyranosides (47). The procedure described in the literature[18] was followed for the preparation of these glycosides. Thus, starting with 19.51 g (50 mmol) of α-D-mannopentaacetate, 5.80 mL of distilled stannic chloride, and 3.42 mL of dry allyl

alcohol, 15.64 g (80%) of the mixture of glycosides **47** was obtained after column chromatography.

Allyl 2,3-Bis-*O*-(phenylmethyl)-4,6-(phenylmethylene)-D-mannopyranosides (51). A solution of 14.02 g of the allyl glycosides (**47**) in 100 mL of anhydrous methanol was treated with 4 g of AGMP(OH^-) resin for 18 h. The reaction appeared incomplete by TLC (50% ethyl acetate/hexanes). The resin was filtered off, and the sugar was redissolved in 100 mL of fresh anhydrous methanol. Five grams of the AGMP(OH^-) resin was added, and the mixture was stirred under nitrogen until the completion of the reaction. The resin was filtered off, and the solvent was removed on the rotary and then on a high-vacuum pump. The organic product **48** was used for subsequent reaction without purification.

A mixture of 3.79 g (17.22 mmol) of **48** and 3.13 mL (18.94 mmol) of benzal bromide in 80 mL of anhydrous pyridine was maintained at 135 °C for 90 min. After being cooled to room temperature, the mixture was added to 500 mL of CH_2Cl_2 and the organic layer was repeatedly washed with 1 N HCl and sodium bicarbonate. Drying, concentration, and flash chromatography yielded four fractions containing varying amounts of mixtures of bisacetals (**49**), the desired 4,6-monoacetals (**50**), and a mixture of undesired 2,3-monoacetals. Further chromatography on silica gel using 30–50% ethyl acetate/hexanes yield 2.14 g of **49** and 1.16 g of **50**.

50: IR (neat) 3350, 3070, 3030, 2900, 1645, 1495, 1100, 750, 695 cm^{-1}; ^1H NMR (360 MHz) inter alia δ 2.52 (d, br, 1 H), 2.58 (d, br, 1 H), 3.75–4.35 (m), 4.92 (s, 1 H), 5.30 (m, 2 H), 5.57 (s, 1 H), 5.92 (m, 1 H), 7.35–7.52 (m, aromatic); HRMS 308.1252 (M^+; calcd for $C_{16}H_{20}O_6$ 308.1260).

The diol **50** was transformed into the bis-*O*-benzyl ether **51** by treatment of its sodium salt with benzyl bromide in DMF under previously described conditions in 93% yield. The ^{13}C NMR clearly indicates it is a single compound and as identified by the small $J_{1,2}$ coupling constant it is an α anomer.

51: IR (KBr) 3090, 3070, 3030, 1645, 1605, 1100 cm^{-1}; ^1H NMR (360 MHz) δ 3.80–4.02 (m, 5 H), 4.14 (m, 1 H), 4.22–4.30 (m, 2 H), 4.62–4.86 (2 AB q and d, $J_{1,2}$ = 2 Hz, 5 H), 5.18 (m, 2 H), 5.65 (s, 1 H), 5.84 (m, 1 H), 7.22–7.55 (m, aromatic); ^{13}C NMR δ 64.13, 67.84, 68.72, 73.05, 73.48, 76.25, 76.34, 79.08, 98.44, 101.32, 117.48, 125.93; FABMS 489.25 (M + H; calcd for $C_{30}H_{32}O_6$ 489.23).

The bisacetals **49** can be transformed into **51** via $LAH/AlCl_3$ cleavage of the strained five-membered acetal in preference to the six-membered one followed by benzyl ether formation by procedures described earlier. This way **49** was converted in two steps into **51** in about 80% yield.

49: ^1H NMR inter alia δ 5.52 (s, 0.16 H), 5.65 (s, 0.34 H), 5.97 (s, 0.16 H), 6.30 (s, 0.34 H) all peaks corresponding to the phenylmethylene (acetal) protons. This clearly indicates exo–endo isomers of the five-membered (2,3-acetal) ring in a ratio of 2:1.

52: ^1H NMR δ 2.36 (d, J = 8 Hz, 1 H), 3.76–4.30 (m, 8 H), 4.70 (AB q, J_{AB} = 12 Hz, 2 H), 4.90 (s, br, 1 H anomeric), 5.22 (m, 2 H), 5.58 (s, 1 H), 5.87 (m, 1 H), 7.30–7.50 (m, aromatic).

53: ^1H NMR δ 1.25 (d, J = 2 Hz, 1 H), 3.70–4.40 (m, 8 H), 4.75 (AB q, J_{AB} = 12 Hz, 2 H), 4.88 (d, J = 1 Hz, 1 H, anomeric), 5.24 (m, 2 H), 5.60 (s, 1 H), 5.88 (m, 1 H), 7.20–7.52 (m, aromatic).

2,3-Bis-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-mannopyranose (54). The title compound was prepared by the procedures described earlier. The allyl ether **51** was transformed into a vinyl ether by Ir^+ catalysis, and the resulting product was hydrolyzed by aqueous acetone in the presence of $HgCl_2/HgO$ in 95% yield: IR (neat) 3410, 3030, 1600, 1585, 1495, 1100, 750, 695 cm^{-1}; FABMS 449.26 (M^+ + H; calculated for $C_{23}H_{29}O_6$ 449.20).

(*R*)-1,2-Dideoxy-3,4-bis-*O*-(phenylmethyl)-5,7-*O*-(phenylmethylene)-D-*manno*-hept-1-enitol (55). The title compound was prepared by the standard Wittig procedure in 70% yield from **54**. **55**: IR (neat) 3410, 3010, 3060, 3030, 2970, 2530, 2870, 1600, 1495, 1100, 750, 695; ^1H NMR δ 1.70 (d, J = 4 Hz, 1 H), 3.50 (m, 1 H), 3.85 (m, 3 H), 4.24 (m, 2 H), 4.58 (AB q, J_{AB} = 12 Hz, 2 H), 4.62 (AB q, J_{AB} = 12 Hz, 2 H), 5.36 (s, 1 H), 5.45 (m, 2 H), 6.05 (ddd, J = 18, 11, 7 Hz, 1 H), 7.10–7.40 (m, aromatic); ^{13}C NMR δ 61.88, 70.52, 71.00, 73.81, 78.65, 78.96, 80.79, 101.15, 119.65, 126.14.

Deoxygenation of 55: Cyclization of Radical 56 to [2*R*-(2α,4aβ,5α,6β,7β,7aβ)]-Hexahydro-5-methyl-2-phenyl-6,7-bis(phenylmethoxy)cyclopenta-1,3-dioxin (57). The radical **56** was generated as described earlier, and the cyclic products **57a** and **57b** were isolated in 25% yield by column chromatography. In addition, a significant amount of **55** was also recovered. **57a**: oil, $[\alpha]^{25}_D$ +42.3 ± 2°. (See Supplementary Material for full data.)

The minor product (0.003 g, 1.7%), of higher R_f, (contaminated with inseparable impurities), was tentatively identified by its ^1H and ^{13}C NMR spectra. The methyl signal at δ 1.15 and ^{13}C spectrum with signals at δ 13.72, 35.65, 42.10 and 66.63 points to the 5β isomer, **57b**.

Allyl 2,3,4,6-Tetra-*O*-acetyl-D-galactopyranosides (59) (β-Isomer Major). This compound was prepared by $SnCl_4$-mediated glycosidation of a mixture of α and β-D-galactosepentacetate according to the procedure[18] described in the literature: ^1H NMR (360 MHz) δ 1.98 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.15 (s, 3 H), 3.84 (dt, J = 2, 7 Hz, 1 H), 4.05–4.25 (m, 3 H), 4.35 (ddt, J = 13, 4, 2 Hz, 1 H), 4.52 (d, J = 8 Hz, 1 H), 5.03 (dd, J = 10, 4 Hz, 1 H), 5.12–5.35 (m, 3 H), 5.40 (dd, J = 4, 1 Hz, 1 H), 5.86 (m, 1 H).

Allyl 2,3-Bis-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-galactopyranosides (62). The tetraacetate **59** was deacetylated with AGMP(OH^-) resin in methanol, and the acetal **61** was prepared by treatment of **60** with benzaldehyde in the presence of $ZnCl_2$, yield 0.50 g (21% from **58**). **61**: IR (KBr) δ 3420, 2930, 1645, 1495, 1170–1000 cm^{-1}; ^1H NMR (360 MHz) δ 2.45–2.50 (2 d, J = 2, 9 Hz, 2 H, OH), 3.49 (m, 1 H), 3.65–3.83 (m, 2 H), 4.05–4.18 (m, 2 H), 4.23 (d, m, J = 4 Hz, 1 H), 4.35 (m, 2 H), 4.45 (ddm, J = 12, 5 Hz, 1 H), 5.20–5.38 (m, 2 H), 5.56 (s, 1 H), 5.90 (m, 1 H), 7.38 (m, 3 H), 7.50 (m, 2 H); HRMS 307.1142 (M^+ − 1; calcd for $C_{16}H_{19}O_6$ 307.1182), 267.0864 ($M^+ - C_3H_5$; calcd 267.0868).

Benzylation of **61** in DMF using benzyl bromide and sodium hydride followed by chromatography gave **62** in nearly quantitative yield. **62**: ^1H NMR (360 MHz) δ 3.30 (s, 1 H), 3.55 (dd, J = 9, 4 Hz, 1 H), 3.88 (dd, J = 10, 8 Hz, 1 H), 4.02 (dd, J = 12, 2 Hz, 1 H), 4.15 (m, 2 H), 4.30 (dd, J = 13, 1 Hz, 1 H), 4.45 (m, 2 H), 4.78 (m, 3 H), 4.95 (d, J = 11 Hz, 1 H), 5.19 (dd, J = 10, 2 Hz, 1 H), 5.34 (dd, J = 17, 2 Hz, 1 H), 5.50 (s, 1 H), 5.96 (m, 1 H), 7.20–7.60 (m, aromatic).

2,3-Bis-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-galactopyranose (63). The allyl glycosides **62** were converted into **63** by the procedure described earlier by first converting it into a vinyl glycoside by the Ir^+-catalyzed 1,3 H shift and then hydrolyzing the vinyl ether in a $HgCl_2$-assisted reaction: mp 148–151 °C; $[\alpha]^{25}_D$ 108.5 ± 2°; IR (KBr) 3420, 3060, 3030, 1495, 1100, 740, 695 cm^{-1}; HRMS 357.1361 ($M^+ - C_7H_7$; calcd for $C_{20}H_{21}O_6$ 357.1338).

(*S*)-1,2-Dideoxy-3,4-bis-*O*-(phenylmethyl)-5,7-*O*-(phenylmethylene)-D-*galacto*-hept-1-enitol (64). This compound was prepared from **63** by the standard Wittig procedure described earlier in 69% yield: ^1H NMR (360 MHz) δ 2.85 (d, J = 11 Hz, 1 H), 3.75 (dd, J = 9, 3 Hz, 1 H), 3.85 (dm, J = 11 Hz, 1 H), 4.00–4.37 (m, 5 H), 4.70 (d, J = 12 Hz, 1 H), 4.75 (AB q, J_{AB} = 11 Hz, 2 H), 5.26–5.38 (m, 2 H), 5.41 (s, 1 H), 5.96 (ddd, J = 18, 10, 9 Hz, 1 H), 7.15–7.45 (m, aromatic H); ^{13}C NMR δ 63.29, 70.39, 72.69, 75.50, 77.65, 78.11, 79.74, 101.03, 118.54, 125.83.

Cyclization of Radical 65: [2*S*-(2α,4aβ,5α,6β,7α,7aβ)]-Hexahydro-5-methyl-2-phenyl-6,7-bis(phenylmethoxy)cyclopenta-1,3-dioxin (66). The imidazole-1-carbothioate prepared from 0.24 g (0.53 mmol) of **64** was refluxed in 3 mL of dry toluene containing 0.072 mL (0.5 equiv) of tributyltin hydride and 10 mg of AIBN. To the refluxing solution was added 0.213 mL more of tributyltin hydride and 20 mg of AIBN dissolved in 2 mL of toluene. The mixture was refluxed for a total of 100 min, and the product was isolated by standard procedure. Careful column chromatography on silica gel of the crude mixture yielded 0.040 g of **66** (18% from **64**). A major side product of the reaction was the starting alcohol **64**. *No trace of any other cyclization products were detected in either the ^1H or ^{13}C NMR spectra of the crude products*; oil, $[\alpha]^{25}_D$ +58.2 ± 2°. (See Supplementary Material for full data.)

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Supplementary Material Available: High-resolution proton and carbon NMR and mass spectrometry data with relevant assignments for **10a**, **10b**, **11a**, **11b**, **12a**, **14a**, **17a**, **17b**, **22a**, **28a**, **30a**, **31a**, **35a**, **35b/c**, **37a**, **37b**, **38a**, **38b**, **39**, **40**, **57a**, and **66** described in the Experimental Section (7 pages). Ordering information is given on any current masthead page.