Stereoselectivity of Electrophile-Promoted Cyclizations of γ-Hydroxyalkenes. An Investigation of Carbohydrate-Derived and Model Substrates

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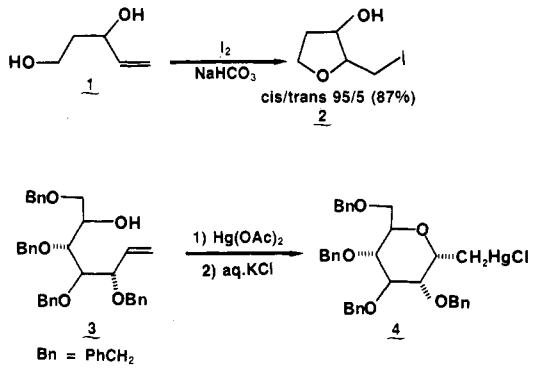
We have investigated cyclization reactions of γ-hydroxyalkenes bearing an alkoxy or alkyl substituent on the allylic carbon. A variety of electrophiles [*N*-bromosuccinimide, *N*-iodosuccinimide, iodine, mercury(II) acetate, mercury(II) trifluoroacetate, mercury(II) triflate, benzeneselenenyl chloride, and *N*-(phenylselenenyl)phthalimide] were employed. Alkenol **5** was prepared from D-arabinose and methylenetriphenylphosphorane, and alkenol **27** was synthesized in five steps from 2,3-isopropylidene-D-glyceraldehyde. Noncarbohydrate alkenols **1**, **17**, **23**, **35**, and **40** were prepared to analyze the cyclization stereoselectivity in simplified systems. Electrophile-mediated cyclizations of **5**, **1**, and **17** generally gave a tetrahydrofuran with a great preference for cis stereochemistry of the 2,3-ring substituents. The highest stereoselectivity was observed for reaction of mercury(II) acetate or iodine with **1** and **17** (cis/trans = >95:5). Reactions of **5**, **1**, and **17** with phenylselenonium reagents were anomalous in that the high selectivity observed with halonium and mercuronium reagents was absent. Cyclizations of **27**, **35**, and **40** proceeded without cis stereoselectivity. These results point to the allylic oxygenated substituents of **5**, **1**, and **17** as being the crucial stereodeterminant. Cyclization of **23** and **40** proceeded with trans stereoselectivity, due to the buttressing effect of the *Z* methyl group, irrespective of the presence of an allylic benzyloxy group (viz. **23**).

Electrophile-mediated cyclizations of γ-hydroxyalkenes offer a versatile means of preparing tetrahydrofuran ring systems.[1,2] The stereochemistry of the newly formed stereogenic center(s) is an important feature of these reactions. Yoshida and co-workers[1b] have systematically studied the directing effect of an allylic hydroxyl group in the iodoetherification of 4-pentene-1,3-diols. The products of these reactions are predominantly those with a cis arrangement of the hydroxyl and the substituent on the newly formed stereogenic center (e.g., **1** → **2**). Similar stereocontrol directed by allylic ethers has also been observed in reactions of alkenes derived from carbohydrates.[2] A key example is the cyclization of **3** with mercuric acetate to give only **4**.[2a]



Analogous halolactonization reactions of pentenoic acids have been examined in detail, especially with regard to stereoselectivity in the formation of the new carbon–carbon bond.[1a,3] Chamberlain and co-workers[3a] have investigated the importance of an allylic hydroxyl in directing these cyclizations to form the 2,3-cis products. The reactions are probably kinetically controlled.[3a] If the substituent on the allylic position is an alkyl group, conditions can be varied to give predominantly the 2,3-cis or 2,3-trans product, presumably representing the kinetic and thermodynamic products, respectively.[3b]

Since publication of the cyclization of **3** to **4**,[2a] other reports on electrophile-promoted cyclizations of various carbohydrate-derived alkenols have appeared;[2b–h] these generally demonstrated the same pattern of high cis stereoselectivity. Our preliminary communication described studies with arabinose-derived alkenol **5**, which we performed during the synthesis of a novel carbohydrate phosphonate.[2g,4] We have explored in greater detail the stereoselectivity of electrophile-promoted cyclizations of alkenols to shed more light on this chemistry. Our new results include a more complete investigation of the reactions of **5** and important experiments with model substrates.

Results and Discussion

Cyclization experiments were conducted on alkenes **1**, **5**, **17**, **23**, **27**, **35**, and **40**, which bear an allylic substituent.

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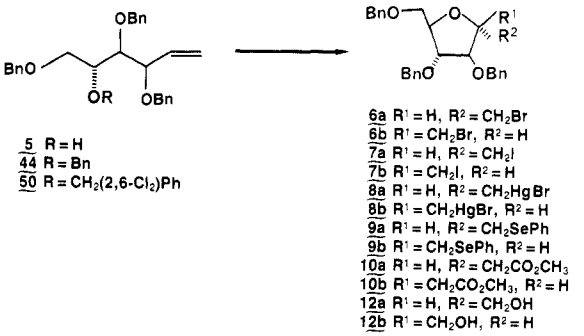
Table I. Results of Cyclization Reactions

no.	substr	THF product	cyclizn[a] reagent	% yield	2,3-trans: cis (α:β)
1	5	6	NBS	90	11:89
2	5	6	Br_2	50	12:88
3	5	7	NIS	90	11:89
4	5	8	$Hg(OAc)_2$	82	14:86
5	5	8	$Hg(OTfa)_2$	84	7:93
6	5	9	PhSeCl	70	65:35
7	5	9	*N*-PhSePhth	90	31:69
8	5	8	$Hg(OTf)_2$	90	46:54
9	5	10	$PdCl_2$, $CuCl_2$, CO	18	67:33
10	5	9	PhSeCl, K_2CO_3	80	53:47
11	5	9	PhSeCl, TEA	40	45:55
12	5	8	PhHgOTfa	55	8:92
13	5	12	MCPBA	65	45:55
14	1	14	I_2	85	<5:95
15	1	15	$Hg(OAc)_2$	96	<5:95
16	1	16	PhSeCl	87	38:62
17	17	20	I_2	89	<5:95
18	17	21	$Hg(OAc)_2$	87	<5:95
19	17	22	PhSeCl	73	20:80
20	23	24	I_2	80	>95:5
21	23	25	$Hg(OAc)_2$	85	67:33
22	23	26	PhSeCl	84	75:25
23	27	32	NBS	92	67:33
24	27	33	$Hg(OTfa)_2$	75	47:53
25	27	34	MCPBA	42	50:50
26	35	37	I_2	93	32:68
27	35	38	$Hg(OAc)_2$	86	40:60
28	35	39	PhSeCl	87	60:40
29	40	41	I_2	84	>95:5
30	40	42	$Hg(OAc)_2$	84	>95:5
31	40	43	PhSeCl	88	>95:5
32	44	6	NBS, Me_2SO/H_2O	74	13:87
33	44	6	Br_2, CCl_4	60	10:90
34	50	6	Br_2, CH_2Cl_2	90	4:96
35	50	6	Br_2, CH_3CN	90	7:93

[a] Abbreviations: Tfa = trifluoroacetyl; Phth = phthalimidyl; Tf = triflate; TEA = triethylamine.

The results of these studies are listed in Table I.

Alkenes with an Allylic Oxygen Group. Compound **5** was prepared from 2,3,5-tri-*O*-benzyl-D-arabinose and methylenetriphenylphosphorane.[4] Stereochemistry at the newly formed stereogenic center of the cyclized products was assigned by ^{13}C NMR,[5] or by conversion to compounds **6a** and **6b**, whose structure had already been unambiguously assigned.[4] Reaction of **5** with *N*-bromosuccinimide (NBS) gave bromides **6a** (**a** designates the α or 2,5-anhydro-D-mannitol configuration) and **6b** (**b** designates the β or 2,5-anhydro-D-glucitol configuration) in a ratio of 11:89 (entry 1). Similar stereoselectivity was observed with bromine (entry 2; **6a**/**6b** = 12:88), *N*-iodosuccinimide (NIS) (entry 3; **7a**/**7b** = 11:89), mercuric acetate (entry 4; **8a**/**8b** = 14:86, after conversion to the mercuric bromides), and mercuric trifluoroacetate (entry 5; **8a**/**8b** = 7:93). Treatment of **5** with either benzeneselenenyl chloride or *N*-(phenylselenenyl)phthalimide (entries 6 and 7) resulted in the expected phenyl selenides **9a** and **9b** in ratios of 65:35 and 31:69, respectively.[6] The lack of stereoselectivity with the selenonium electrophiles was surprising based on literature precedent[1,2] and on our own experience,[2g,4] although Bartlett had reported poor stereoselectivity for selenium electrophiles in some lactonization reactions.[3d] We have investigated the selenium-mediated cyclization of **5** in more detail (see below), although our initial result suggested variability in the stereoselectivity produced by different electrophiles. In a similar fashion, the reaction of **5** with mercuric triflate[7] did not exhibit 2,3-cis selectivity of the tetrahydrofuran substituents; rather, a mixture containing nearly equal amounts of **8a** and **8b** was produced (entry 8; **8a**/**8b**, 46:54).



5 R = H
44 R = Bn
50 R = CH_2(2,6-Cl_2)Ph

6a R^1 = H, R^2 = CH_2Br
6b R^1 = CH_2Br, R^2 = H
7a R^1 = H, R^2 = CH_2I
7b R^1 = CH_2I, R^2 = H
8a R^1 = H, R^2 = CH_2HgBr
8b R^1 = CH_2HgBr, R^2 = H
9a R^1 = H, R^2 = CH_2SePh
9b R^1 = CH_2SePh, R^2 = H
10a R^1 = H, R^2 = $CH_2CO_2CH_3$
10b R^1 = $CH_2CO_2CH_3$, R^2 = H
12a R^1 = H, R^2 = CH_2OH
12b R^1 = CH_2OH, R^2 = H

The palladium-mediated cyclization of alkenols, incorporating carbon monoxide, has also been reported to exhibit high stereocontrol when an allylic hydroxyl is present.[8] We conducted experiments on **5** under these conditions, but considerable decomposition occurred, possibly due to lability of the benzyl ethers. In any event, our best result (entry 9) was a 2:1 mixture of **10a** and **10b** in low yield (18%), another instance in which high 2,3-cis selectivity for cyclization of **5** was not achieved. However, in the majority of cases, the stereoselectivity was analogous to that reported for reactions of alkenols derived from glucose[2a] and ribose.[2b] The high selectivity with NBS (**6a**/**6b** = 1:8) was sufficient for our synthetic purposes.[2g,4]

The experiment with benzeneselenenyl chloride (PhSeCl) produced **9a** and **9b** in a ratio of 65:35. Structural proof was obtained by conversion of a 1:8 mixture of bromides **6a**:**6b**[4] to a 1:8 mixture of selenides **9a**:**9b** (using sodium phenyl selenide,[9] 64% yield; material was identical with **9a** and **9b** prepared by direct cyclization). In the same manner, a 1:1 mixture of **6a**:**6b** was converted to a 1:1 mixture of **9a**:**9b** (85% yield). To test if the 65:35 ratio of **9a** and **9b** came from direct cyclization or from equilibration of the selenide products, a 1:8 mixture of **9a**/**9b** was treated with 0.5 equiv of PhSeCl at 23 °C for 24 h in THF. There was no increase in the level of **9a** on analysis by ^{13}C NMR. By the same token, treatment of 1:1 or 1:8 mixtures of **9a**/**9b** with excess HCl (ethereal) in THF for 24 h resulted in only a minimal change of isomer ratio (2% and 6%, respectively). In the latter case, the change from 88:12 to 82:18 is hardly sufficient to account for a lack of cis stereoselectivity in the PhSeCl cyclizations. For confirmation of the unimportance of HCl as a source of epimerization, **5** was reacted with PhSeCl in the presence of either potassium carbonate or triethylamine (entries 10 and 11), producing mixtures of **9a** and **9b** in ratios of 53:47 (80%) and 45:55 (40%), respectively. Thus, HCl formed in the reaction of PhSeCl with **5** would have little effect on impairing 2,3-cis stereoselectivity, if it existed.

We supposed that the lack of high cis stereoselectivity in the phenylselenoetherification might be associated with the phenyl ring attached to the electrophilic selenium

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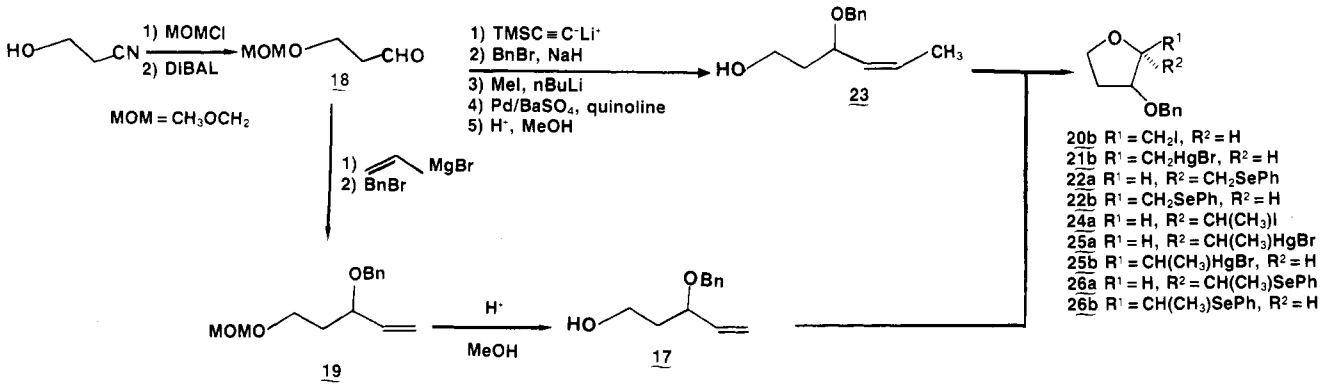
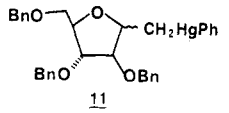
Scheme I



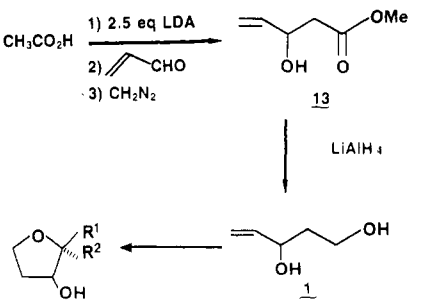
atom. A possible consequence of this notion was that a phenylmercuronium electrophile would also react in a stereochemically nonselective manner. Therefore, we prepared phenylmercuric trifluoroacetate[10] (PhHgOTfa) and reacted it with **5** in refluxing THF for 16 h, intending to prepare **11** (entry 12). However, a 55% yield of an 8:92 mixture of **8a** and **8b** was obtained. We believe that the PhHgOTfa is disproportionating to mercuric trifluoroacetate and diphenylmercury in the reaction mixture. If the reaction of PhHgOTfa was carried out for a longer period of time (19 days, ambient temperature, THF), then a 64% yield of a mixture of **8a** and **8b** was obtained, along with 9% of **11** (unassigned stereochemistry) and 5% of diphenylmercury. The stereochemistry of **11** is relatively unimportant, because **11** could have arisen under these extended reaction conditions by disproportionation of the isomeric mercuric trifluoroacetates related to **8a** and **8b** with diphenylmercury or PhHgOTfa.



11

Treatment of **5** with *m*-chloroperbenzoic acid (MCPBA) gave the hydroxymethyl compounds **12a** and **12b** in a ratio of 45:55 (entry 13). The ratio of **12a** and **12b** was accurately determined by 360-MHz ^{1}H NMR after converting them to bromides **6a** and **6b** by using zinc bromide and triphenylphosphine. The reaction with MCPBA presumably proceeded through an epoxide, in a virtually stereorandom manner; the epoxide then spontaneously cyclized to give **12a** and **12b**. Several attempts at forming the epoxide by using conditions[11] known to give stereocontrol in the presence of allylic ethers were unsuccessful. The double bond in **5** was fairly inert to epoxiding agents; for example, it reacted with MCPBA only at elevated temperature (refluxing 1,2-dichloroethane).

Model alkenol **1**, identical with that prepared by Yoshida,[1b] was prepared by reacting the dianion of acetic acid with acrolein, esterifying the resulting product with diazomethane, and reducing the ester (**13**) with lithium aluminum hydride (36% overall yield). Cyclization of **1** with iodine and mercuric acetate gave only (>95%) cis isomers **14b** and **15b** (determined by ^{1}H and ^{13}C NMR; entries 14 and 15). This high cis selectivity was even greater than that observed for carbohydrate-derived alkenol **5**, dramatizing the directing influence of the allylic oxygenated group. Our stereochemical results for cyclization of **1** with iodine are basically identical with those of Yoshida and co-workers.[1b]



Compound **17** was prepared for study because it is more analogous to **5** than is **1** (see Scheme I). 3-Hydroxypropionitrile was protected with the methoxymethyl (MOM) ether group and converted to the corresponding aldehyde, **18**. Reaction of **18** with vinylmagnesium bromide and benzylation of the resulting hydroxyl functionality gave **19**. Removal of the MOM group of **19** produced **17** in 58% overall yield from 3-hydroxypropionitrile. Cyclization of **17** with either iodine or mercuric acetate gave only the 2,3-cis isomers, **20b** or **21b** (>95%; entries 17, 18), similar to the behavior of **1**. However, reaction of **17** with benzeneselenenyl chloride gave a 80:20 mixture of **22b** to **22a** (entry 19). In a similar manner, reaction of **1** with benzeneselenenyl chloride gave a 38:62 mixture of **16a** to **16b** (entry 16). Thus, the selenonium ion mediated cyclizations were less cis selective, analogous to what was observed in the reactions of **5**.

Substitution of the alkene with a *Z* alkyl group has been reported to influence the cyclization to give predominantly the trans product (see discussion below and ref 1f and 1g). We prepared provocative model compound **23**, which incorporates both an allylic benzyloxy group and a *Z* methyl substituent on the alkene (Scheme I). Compound **23** was synthesized from **18** by reaction with the anion of (trimethylsilyl)acetylene, benzylation of the resulting alcohol, methylation of the acetylene, Lindlar reduction, and removal of the MOM group. Reaction of **23** with iodine, mercuric acetate, or benzeneselenenyl chloride gave largely the trans products (entries 20–22). For example, upon reaction with iodine, **23** produced solely trans isomer **24a**. Cyclization of **23** with mercuric acetate was less selective, giving a 67:33 mixture of **25a**:**25b**. Also, reaction of **23** with benzeneselenenyl chloride gave a 75:25 mixture of **26a**:**26b**. Thus, the *Z* methyl group was more effective in directing the cyclization than the allylic benzyl ether, although a

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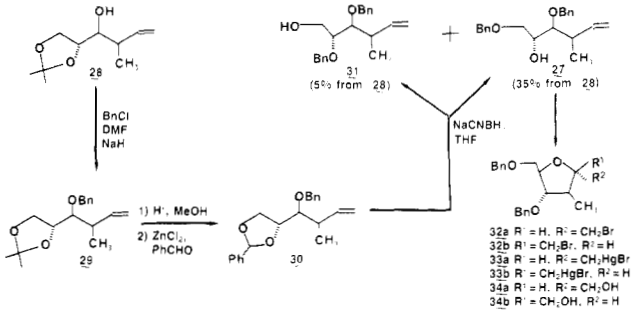
Scheme II



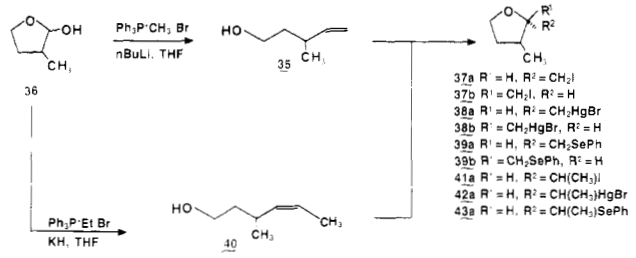
balance of competitive forces is evident. Here, again, the final ratios were somewhat electrophile dependent.

Alkenes with an Allylic Methyl Group. Literature precedent[1-3] suggests that the high stereoselectivity of halonium and mercuronium electrophiles in cyclization reactions of **5** is caused by the allylic benzyl ether substituent. To test this hypothesis in an unequivocal manner, for our systems, we prepared model alkenol **27**, in which this benzyl ether is replaced with a methyl group (see Scheme II). Compound **28**, which had been prepared by Hoffmann and co-workers[12] via condensation of a boronate ester with 2,3-isopropylidene-D-glyceraldehyde, was a logical starting point. Rousch and co-workers[13] recently reported a stereoselective synthetic procedure involving pinacol boronate esters, which are easier to prepare than Hoffmann's camphor-derived reagents.[12] Thus, we synthesized enantiomerically pure **28** according to Rousch and converted it to benzyl ether **29**. Removal of the isopropylidene group and incorporation of a benzylidene acetal in its place gave an equal mixture of the diastereomers of **30**. Reductive opening of the benzylidene ring of **30** with $NaBH_3CN$ under acidic conditions[14] led mainly to desired secondary alcohol **27** (35% from 28); there was also a small amount of the other regioisomer **31** (5% from 28). This synthetic sequence provided **27** for model studies, albeit with unoptimized yields.

Cyclization of **27** with NBS and mercuric trifluoroacetate gave expected products **32** and **33** (entries 23 and 24). The ^{13}C NMR resonances for some of the ring carbons of the products were far downfield, around 85–87 ppm. This indicates a tetrahydrofuran ring, rather than a tetrahydropyran ring.[15] The stereochemistry was assigned by inspection of the ^{13}C NMR data, by using the upfield shift of carbons in the 2,3-cis derivatives (**32b** and **33b**). The reactions with NBS and mercuric trifluoroacetate were not selective for the 2,3-cis isomer; the ratios were **32a**:**32b** = 67:33 and **33a**:**33b** = 47:53. Reaction with MCPBA, as expected, resulted in a 1:1 mixture of **34a** and **34b** (entry 25). Comparison of the results for cyclizations of **27** with those for **5** indicate that the cyclization stereoselectivity observed with **5** is due to the allylic benzyl ether group.

Alkenol **35** was prepared by reacting 2-methylbutyrolactol (**36**) with methylenetriphenylphosphorane (see Scheme III). Cyclization of **35** with iodine, mercuric acetate, or benzeneselenenyl chloride furnished mixtures of trans:cis isomers in ratios of 32:68 (**37a**:**37b**), 45:55 (**38a**:**38b**), and 40:60 (**39a**:**39b**), respectively (entries 26–28). The allylic methyl group clearly does not have a significant directing influence on the cyclization stereochemistry.

Scheme III



Z methyl derivative **40** was also investigated. Compound **40** was prepared by reaction of **36** with ethylidenetriphenylphosphorane. Cyclization of **40** with iodine, mercuric acetate, or benzeneselenenyl chloride produced exclusively (>98%) trans isomers, **41a**, **42a**, or **43a** (entries 29–31). Models indicate that the *Z* methyl group exerts a significant buttressing effect in the cyclization, which biases the system to the trans isomer (see ref 1g).

We tried to separate the selectivity in the ring closure from that in the initial electrophilic addition to the alkene by blocking the hydroxyl group of **5** with various groups (*t*-$BuMe_2Si$, *t*-$BuPh_2Si$, $Me_3SiCH_2CH_2OCH_2$, *p*-methoxybenzyl, and benzyl)[2g] and then reacting these masked derivatives with electrophiles. Instead of a completely intermolecular reaction, we observed electrophile-mediated cyclization, accompanied by dealkylation, to form **6**. Results with tetrabenzyl ether **44** are typical. Treatment of **44** with NBS in dimethyl sulfoxide/water,[16] or bromine in carbon tetrachloride, gave **6a** and **6b** in ratios of 13:87 and 10:90, respectively (entries 32 and 33). Trapping of the initially formed bromonium ion with an intermolecular nucleophile (water or Br^-) was much slower than intramolecular addition with subsequent debenzylation. It is interesting to note that **44** *did not react with mercuric acetate or NBS* in refluxing methylene chloride. This provides evidence for reversible formation of tetrahydrofuranonium ion **45**, insofar as the bromine and NBS reactions are identical, except that Br^- is able to intercept ion **45** whereas the succinimidyl ion is not.

Bartlett has investigated[1c] stereoselectivity in the cyclization reactions of alkenols and benzyl ethers such as **46** and **47**. These molecules reacted with iodine to give **48a** and **48b**.[1c] The highest 2,5-cis selectivity (21:1) in this reaction was seen for 2,6-dichlorobenzyl ether **47**, possibly because of steric compression at the stage of tetrahydrofuranonium ion **49**. Presumably, the larger the pendant group on the oxygen, the more the two ring substituents are compelled to adopt a cis arrangement relative to each other. We prepared 2,6-dichlorobenzyl ether **50** and examined the stereoselectivity upon cyclization. It did not react with NBS in methylene chloride, although it readily reacted with bromine in methylene chloride (at 22 °C) or in acetonitrile (at −5 °C) to give mixtures of **6a**:**6b** in ratios of 4:96 and 7:93, respectively (entries 34 and 35). In this case as well, the bulky 2,6-dichlorobenzyl ether facilitated greater stereoselectivity.

Mechanistic Analysis

Stereoselectivity in electrophile-induced cyclizations of alkenols can arise from several key factors: (1) the kinetic ratio of onium ion intermediates; (2) the degree of reversibility of intermediates (onium ions); (3) the trajectory requirements imposed by the presence of an internal nucleophile (preference for cyclization of one of the onium

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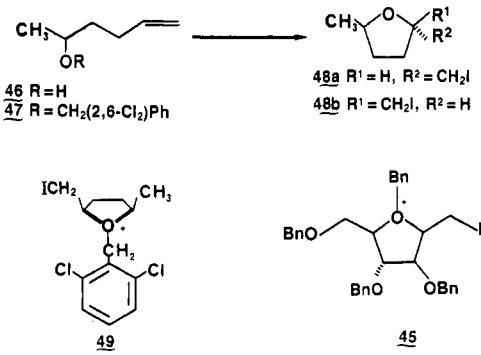

49

45

ions); and (4) the relative rates of decomposition of the two diastereomeric tetrahydrofuranonium ions. The presence of an allylic stereogenic center could impact on all of these parameters. For example, the first factor could include the directing ability of the allylic substituent in a particular conformation and the relative importance of such conformations as determined by structural or electronic constraints. From our studies on the electrophile-mediated cyclizations of a variety of alkenols, we can gain some appreciation for interplay of these effects in determining the stereochemistry of the products.

Figure 1 depicts a mechanistic pathway for these reactions. The first step is the formation of three-centered onium species. In the case of halogen additions, such intermediates are generally freely reversible.[17] There may be a kinetic preference for formation of one of the diastereomeric ions, although reactions with MCPBA, which are irreversible, clearly show no selectivity. One can argue whether, in these electrophile-mediated cyclizations, a full onium-type species really has time to form or whether a charge-transfer complex makes the alkene suitably electron deficient for cyclization to ensue. In either case, stereoselectivity could have a kinetic component.

The three-centered ion then cyclizes to a tetrahydrofuranonium intermediate. The special role that equilibrtion of this later ion may play in determining stereochemistry was pointed out by Bartlett.[1c] A bulky ether (such as 2,6-dichlorobenzyl) could buttress against the substituents on C-2 and C-5. Also, the bulky group would stabilize the tetrahydrofuranonium ion (**45**) against dealkylation to products, allowing thermodynamic equilibration to occur. The fact that **5**, but not **50**, cyclizes with NBS, whereas both **5** and **50** do cyclize with Br_2, shows that *formation of 45 must be reversible.*

The key role that the cyclization step plays in determining the stereochemistry of the products can be appreciated by an examination of the intermolecular addition of electrophiles to the double bond of allylic alcohols. Experiments reported in the literature[3a,18] reveal stereoselectivity in intermolecular additions opposite to that seen in intramolecular cyclizations.[1-4]

The rapidity of the cyclizations of **44**, relative to intermolecular reaction, suggests that they are kinetically controlled. Such a kinetic preference may be due to through-space coordination of the electrophile with the allylic benzyl ether oxygen.[2a,19] Alternatively, we have discussed[2g] the application of Houk's "inside-alkoxy" effect.[20]

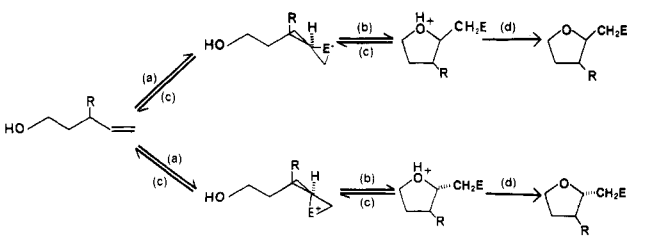

Figure 1. Mechanistic pathway for the cyclization of 4-penten-1-ols that bear an allylic substituent on carbon 3. Factors that may affect the stereochemistry are (a) kinetic selectivity of bromonium ion formation, (b) constraints imposed during cyclization, (c) degree to which equilibration of intermediates proceeds to decomposition, and (d) relative rates of decomposition of diastereomeric tetrahydrofuranonium ions.

Substrates **5**, **1**, and **17** contain highly directing allylic oxygen substituents. In these cases, the electrophile adds to the face of the double bond which is syn to the electron-rich allylic substituent. This can afford some coulombic (electrostatic) stabilization as expected from ab initio calculations,[19,20] as well as through-space stabilization of the electron-deficient onium species by the allylic oxygen atom. However, since these effects would, in principle, be achieved en route to both diastereomeric onium ions, they cannot alone explain the observed preference for 2,3-cis tetrahydrofurans. Other factors mentioned above must also come into play. Bromonium ions from **5**, **1**, and **17** may equilibrate between diastereomeric forms. Examination of the two possible transition states for ring closure also offers some insight. The stabilizing coulombic interactions are maintained throughout the cyclization process. In approaching the transition state leading to the 2,3-trans geometry (minor product), the C–O bond begins to form and the C–X bond stretches. The net effect is a displacement of the partially charged X substituent beyond the stabilizing effects of the electron-rich allylic substituent. Conversely, in approaching the transition state leading to the 2,3-cis geometry (major product), the X substituent actually moves closer to the allylic substituent as the reaction proceeds. Thus, this latter scenario may provide a reason for selective cyclization to the 2,3-cis isomer.

Substrate **23** has an added conformational constraint imposed by the presence of a *Z* methyl group. The *Z* methyl group has been shown[1f,g] to give trans products in reactions of this type and does so readily in the absence of an allylic substituent. In the case of **23**, steric factors and coulombic interactions oppose each other, although the steric factors are dominant.

The role that reversibility of onium ion intermediates may play in the cyclization stereoselectivity is demonstrated by reactions with MCPBA. These produce nearly equal mixtures of stereoisomers. As the reversibility of the onium ions increases, the reaction stereoselectivity will be increasingly determined by the relative energies of the diastereomeric transition states for ring closure. These relative energies will primarily be a function of conformational and trajectory factors. Since these factors are partially determined by the bond lengths and bond angles present in a given onium ion, the degree of stereoselectivity observed in these cases can be electrophile-dependent. The lower stereoselectivity with benzeneselenonium ions (entries 6, 7, 16, and 19) could be associated with such an effect.

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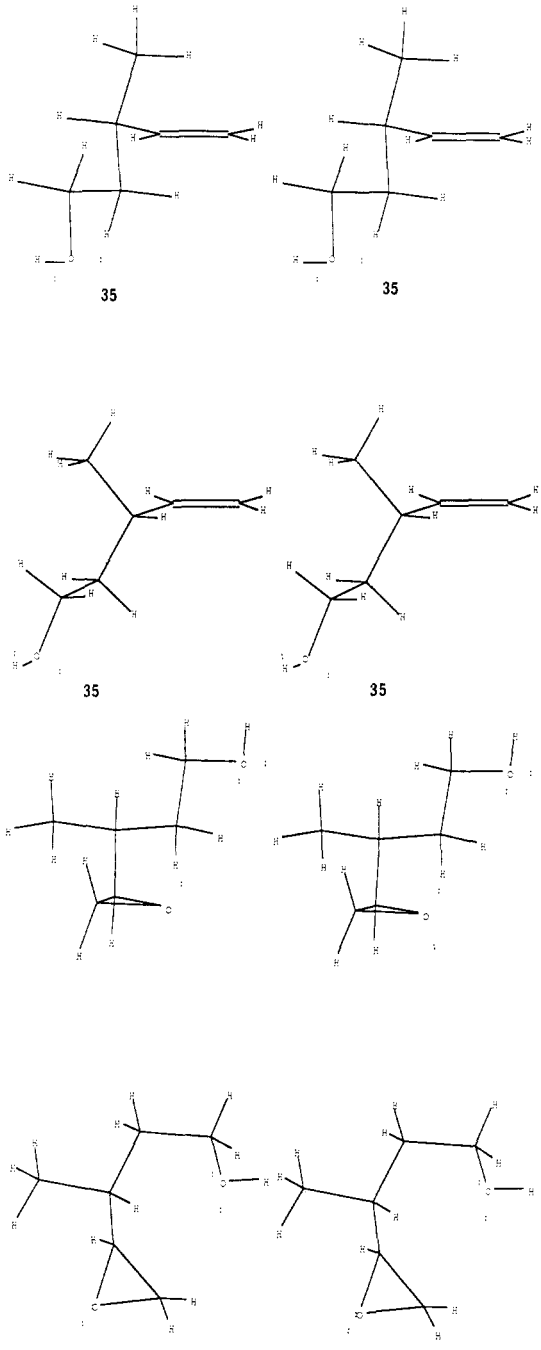

Figure 2. Stereodrawings of low-energy conformers of **35**, and the two diastereomeric epoxides derived from **35**, as determined by MM2 calculations.

Alkenols **27** and **35** bear a methyl group on the allylic carbon, replacing the critical benzyloxy group of **5** and **17**. There was only a minor diastereofacial preference in cyclizations of **27** and **35**. An evaluation of some of the factors involved was obtained theoretically by performing molecular mechanics calculations (MM2) on the relevant conformations of alkenol **35** and its corresponding diastereomeric epoxides. These two models represent reactant-like and product-like onium ion extremes and range in relative energy from 0.45 (±0.50) kcal/mol for the two monosubstituted olefin conformers to 3.14 (±0.50) kcal/mol for their corresponding epoxides. Drawings of the low energy conformer of **35**, and the two diastereomeric epoxides derived from **35**, are given in Figure 2. Therefore, depending upon the nature of the onium ion, one might observe selectivities that vary from 1:1 to >99:1. In practice, the selectivities observed with these simple substrates are modest, suggesting that the electrophile may be only weakly associated with the double bond (perhaps as in a charge-transfer complex) or that solvation may have a major role in the stabilization of one or both of the diastereomeric onium ions. At the least, *these results call for caution when generalizing about electrophile-induced alkenol cyclizations based on the behavior of a limited set of electrophiles.*

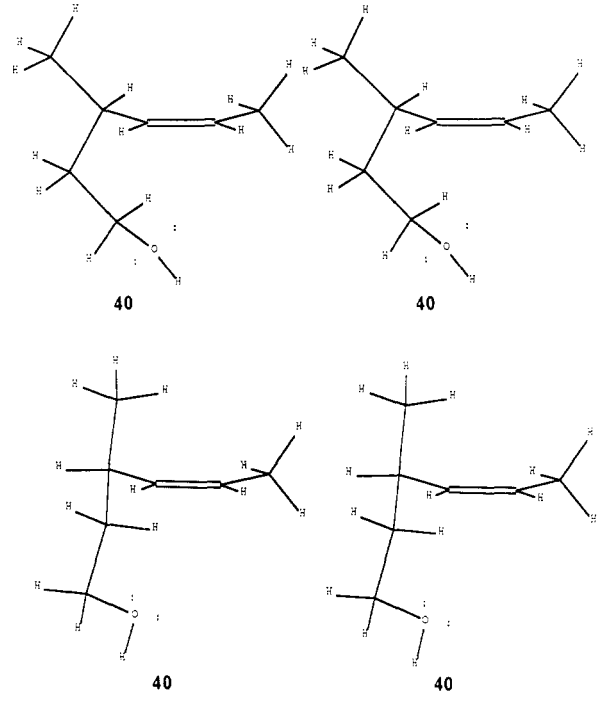

Figure 3.

Finally, alkenol **40** contains a *Z* methyl group on the alkene and a nondirecting allylic methyl group. This substrate gave exclusively trans products. As with **27** and **35**, there is no inherent diastereofacial preference for electrophilic additions to the double bond. Therefore, irreversible addition reactions, such as epoxidation, are nonselective. However, the stereoselectivity observed with electrophiles that can add reversibly may be influenced by steric interactions. These interactions are less severe in the transition state leading to the 2,3-trans structure than in that for the cis product. This hypothesis is consistent with MM2 calculations on the two relevant conformations of the olefin (Figure 3). This is an extreme model of the transition state because the effect of the electrophile is not included. However, the relative energy difference is 1.46 (±0.50) kcal/mol, favoring the conformation in which the *Z*-propenyl group eclipses the allylic hydrogen. This intermediate eventually leads to the formation of the trans-disubstituted ring.

The stereocontrol in cyclizations of this type is due to several different factors, suggested in the complexity of Figure 1. Our inability to determine the relative amounts of the diastereomeric onium ions, and the degree to which they can revert, means that the relative importance of the factors discussed above cannot be readily estimated. There is clearly, though, the capacity for thermodynamic equilibration of three-centered onium and tetrahydrofuranonium ions. Kinetic siphoning of species in the reaction manifold is also a possibility.

Conclusions

A series of γ-hydroxyalkenes bearing an allylic stereogenic center was prepared and cyclized with a variety of

electrophiles. The stereochemical composition of the resulting tetrahydrofuran ring systems was then determined. In the cases where the allylic substituent was an oxygenated group, the 2,3-cis product predominated. Selenonium ion mediated cyclizations were anomalous in that they gave less stereoselectivity compared with halonium ion and mercuronium ion reactions. A *Z* methyl group on the alkene induced trans product formation regardless of the allylic substituent. An allylic methyl group provided no stereocontrol, which points to the special influence of allylic oxygenated groups.

Consideration of our results, along with data in the literature, brings certain important points to the surface. (1) Tetrahydrofuranonium intermediates, such as those in reactions of **5** and **50** with Br_2 or NBS, are formed *reversibly*. This fact has wide-ranging implications to other work in this field. For example, in Bartlett's study[1c] involving **49**, support is given to the suggestion that inhibition of debenzylation by the bulky 2,6-dichloro substituent could lead to thermodynamic control by reversible tetrahydrofuranonium ion formation. (2) In trying to form generalized rules for electrophile-induced cyclizations, be they etherifications or lactonizations, a broad range of electrophiles needs to be considered. Generalizations should not be based on just two or three reagents.

Experimental Section

General Methods. ^1H NMR spectra were recorded on either a Varian EM-390 (90-MHz), Bruker AM-360WB (360-MHz), or Nicolet 360NB (360-MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX-60Q (15.0 MHz), General Electric QE-300 (75.5 MHz), or Bruker AM-360WB spectrometer (90.6 MHz). For NMR work, $CDCl_3$ was used as a solvent unless noted otherwise. Isomer ratios from ^{13}C NMR data were determined under conditions suitable for quantitation. Tetramethylsilane was used as an internal standard. NMR abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. ^{13}C NMR multiplities were determined by using INEPT. Elemental analyses were performed primarily by Galbraith Laboratories (Knoxville, TN). Capillary GLC analysis was performed on a Hewlett-Packard 5890 instrument with a flame ionization detector, using a Hewlett-Packard Model 3392A integrator. A fused silica column (26 m × 0.22 mm i.d. with a 0.12-mm film thickness) with a methyl silicone liquid phase (CPSil 5) was employed. Chemical ionization mass spectra (CI-MS) were recorded on a Finnigan 3300-6100 system with methane as the reagent gas, except where indicated otherwise. Solvents were reagent grade and used as purchased, except where indicated.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-iodo-D-mannitol (7a) and 2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-iodo-D-glucitol (7b). To a solution of **5** (15.17 g, 36 mmol) in 60 mL of dichloromethane was added *N*-iodosuccinimide (8.03 g, 36 mmol). The mixture was stirred at ambient temperature for 4 h, concentrated, and then redissolved in 60 mL of anhydrous ether. The solid was filtered off and the filtrate was concentrated to give 18.9 g (97%) of a 1:9 mixture of **7a** and **7b** (determined by 360-MHz ^1H NMR) as a pale yellow syrup, pure by TLC: CI-MS, *m/e* 545 (M + 1); 360-MHz ^1H NMR δ 3.25 (m, 2 H), 3.4–3.5 (m, 1 H), 3.55 (m, 1 H), 3.9–3.96 (m, 0.89 H, **7b**), 4.0–4.06 (m, 1 H), 4.08–4.10 (t, 0.11 H, **7a**), 4.18–4.26 (m, 1 H), 4.28–4.36 (m, 1 H), 4.4–4.59 (m, 6 H), 7.3 (m, 15 H); 15.0-MHz ^{13}C NMR (peaks for **7b**) δ 0.43 (C1); 70.44, 71.41, 72.06, 73.2 (CH_2); 82.00, 82.50, 83.17, 83.75 (CH); 127.7, 127.9, 128.4, 137.5, 138.2 (aromatic).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-(bromomercurio)-1-deoxy-D-mannitol (8a) and 2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-(bromomercurio)-1-deoxy-D-glucitol (8b). A. Cyclization of 5 with Mercuric Trifluoroacetate. A solution of **5** (300 mg, 0.72 mmol) in 5 mL of THF was treated with $CaCO_3$ (160 mg) and mercuric trifluoroacetate (460 mg, 1.08 mmol). After stirring for 2 h under nitrogen, TLC indicated that **5** had completely converted to an origin spot (EtOAc/hexane, 1:4). The solution was treated with saturated aqueous KBr, and the product was extracted into ether. The ether layer was washed with saturated aqueous KBr and water, dried ($MgSO_4$), filtered, and concentrated to give a clear oil, pure by TLC (490 mg, 98%): 360-MHz ^1H NMR δ 1.79 (dd, 1 H, H_{1a}, J = 2.5, 12.3 Hz), 2.20 (dd, 1 H, H_{1b}, J = 5.8, 12.3 Hz), 3.46 (dd, 1 H, J = 6, 9 Hz), 3.57 (dd, 1 H, J = 6, 8 Hz), 3.72 (d, 1 H, J = 2 Hz), 3.89 (d, 1 H, J = 2 Hz), 4.1 (m, 1 H), 4.3–4.7 (m, 7 H), 7.2–7.4 (m, 15 H) [Although minor peaks presumably due to **8a** could be seen, they were not clearly resolved, and assignments were not made.]; 15.0-MHz ^{13}C NMR δ 31.3 (ca. 1 C, C1 of **8b**), 38.4 (ca. 0.05 C, C1 of **8a**), 70.4, 71.5 (2 C), 73.2, 81.5–83.5 (4 C), 125.5–129 (15 C), 136.6, 137.4, 137.9. Anal. Calcd for $C_{27}H_{29}O_4HgBr$: C, 46.46; H, 4.19. Found: C, 46.73; H, 4.25.

B. Cyclization of 5 with Mercuric Acetate. A solution of **5** (10 g, 23.9 mmol), 5.23 g of $CaCO_3$, and 12.0 g of mercuric acetate in 70 mL of THF was heated at reflux for 1 h and then allowed to stir at ambient temperature for 16 h. Saturated aqueous KBr was added and the product was extracted into ether, washed with saturated aqueous KBr (twice) and water, dried ($MgSO_4$), filtered, and concentrated to give 15.5 g of a yellow oil. A portion of this oil (14.6 g) was purified by chromatography (dry gel column; EtOAc/hexane, 1:4) to give 12.9 g of a pure mixture of **8a** and **8b** (82%). Anal. Calcd for $C_{27}H_{29}O_4HgBr$: C, 46.46; H, 4.19. Found: C, 46.70; H, 4.23.

C. Cyclization of 5 with Mercuric Triflate. A solution of 100 mg of **5** (0.24 mmol) in 1 mL of THF was treated with 50 mg of $CaCO_3$ and 143 mg of mercuric triflate[7] (0.29 mmol) under N_2 at −5 °C. After 5 min, saturated aqueous KBr was added and the product was extracted into ether, washed with saturated aqueous KBr, dried ($MgSO_4$), filtered, and concentrated to give 160 mg (95%) of **8a** and **8b** pure by TLC.

Conversion of Mercurials 8a and 8b to Bromides 6a and 6b. The best means of accurately determining the ratio of **8a** and **8b** was by conversion into bromides **6a** and **6b** by the procedure described below. A solution of **8a** and **8b** (100 mg, 0.144 mmol) in 2 mL of pyridine was treated with bromine (10 μL, 0.20 mmol). After 16 h, the product was purified on a 2000-μm preparative TLC plate (EtOAc/hexane, 15:85) to give 60 mg of **6a** and **6b** pure by TLC (84%). The stereochemistry of this mixture was then determined by 360-MHz ^1H NMR.[4]

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-(phenylselenenyl)-D-mannitol (9a) and 2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-(phenylselenenyl)-D-glucitol (9b). A. Cyclization of 5 with *N*-(Phenylselenenyl)phthalimide. A solution of 335 mg of **5** (0.8 mmol) in 5 mL of dichloromethane was treated with 18 mg of D-camphorsulfonic acid (0.08 mmol) and 290 mg of *N*-(phenylselenenyl)phthalimide (0.96 mmol). After 2 h, water was added and the solution was extracted into ether, washed twice with water, dried ($MgSO_4$), filtered, and concentrated. The product was purified on two 2000-μm preparative TLC plates (EtOAc/hexane, 15:85) to give 410 mg of **9a** and **9b** (90%): 15.0-MHz ^{13}C NMR δ 25.6 (C1 for **9b**, 0.69 C), 30.2 (C1 for **9a**, 0.31 C), 70–87 (8 C, CH_2's and ring C's), 126–139 (24 C, aromatics). Anal. Calcd for $C_{33}H_{34}O_4Se$: C, 69.10; H, 5.97. Found: C, 68.74; H, 6.05.

B. Cyclization of 5 with PhSeCl. Compounds **9a** and **9b** were also prepared from **5** by using PhSeCl as described below. A solution of 1 g of **5** (2.4 mmol) in 20 mL of THF was cooled to −78 °C under nitrogen and treated with 687 mg of PhSeCl (recrystallized, 3.6 mmol). The solution was allowed to slowly warm to ambient temperature and stir for a total of 5 h. Water was then added and the product was extracted into ether, washed with water (twice), dried ($MgSO_4$), filtered, and concentrated. The major spot by TLC prior to workup appeared to be benzyl alcohol; however, it diminished during workup probably because some of it was extracted into the aqueous layer. The benzyl alcohol may have been formed by decomposition of **5** or **9**; it did not appear in reaction of **5** with *N*-(phenylselenenyl)phthalimide. Chromatography on silica gel led to 960 mg (70%) of pure **9a** and **9b** in a ratio of 65:35 by ^{13}C NMR. A small amount of benzyl alcohol was also purified and identified by GLC-MS.

C. Cyclization of 5 with PhSeCl in the Presence of K_2CO_3. To a solution of 310 mg of **5** (0.74 mmol) in 6 mL of THF was added 400 mg of K_2CO_3 (finely pulverized and dried under high vacuum for 4 h). The solution was then cooled to −78 °C and treated with 213 mg of PhSeCl (1.1 mmol). The dry ice bath was removed and the solution was allowed to slowly warm to ambient temperature. After a total of 16 h, water was added and the

product was extracted into ether, washed with water, dried ($MgSO_4$), filtered, and concentrated. As with the reaction in the absence of base, the major TLC spot by UV inspection during the course of the reaction was due to benzyl alcohol which diminished during workup. The product was purified on silica gel to give 347 mg of **9a** and **9b** (80%) in a ratio of 53:47 as determined by ^{13}C NMR.

D. Cyclization of 5 with PhSeCl in the Presence of Triethylamine. To a solution of **5** (310 mg, 0.74 mmol) in 6 mL of THF was added 103 μL of triethylamine (1.1 mmol). The solution was cooled to −78 °C and treated with 213 mg of PhSeCl (1.1 mmol). The solution was allowed to slowly warm to ambient temperature. The TLC of the reaction mixture after 16 h showed **9a** and **9b**, benzyl alcohol, and several other spots that had not been observed in the reactions described above. Water was added, and the product was extracted into ether, washed with 0.2 N HCl and water, dried ($MgSO_4$), filtered, and concentrated. The product was purified on silica gel (EtOAc/hexane, 1:9) to give 171 mg of **9a** and **9b** (45:55 ratio by ^{13}C NMR) pure by TLC (40%).

E. Treatment of 6a and 6b with Sodium Phenyl Selenide.[9a] A representative example is given here. A solution of 234 mg of diphenyl diselenide (0.75 mmol) and 30 mg of a 60% dispersion of NaH in oil (0.75 mmol) in 4 mL of THF was heated at reflux under N_2 for 50 min. The solution was cooled to ambient temperature and treated with 0.2 mL of HMPA, after which the yellow, cloudy suspension turned clear and red. This solution was treated with 497 mg of a 45:55 mixture of **6a** and **6b** (1.0 mmol) and heated at reflux. After 2.5 h, MeOH and ether were added, and the solution was washed with water, dried ($MgSO_4$), filtered, and concentrated. The product was purified on silica gel to give 510 mg of a 54:46 mixture of **9a** and **9b** (89%, ratio determined by ^{13}C NMR) which was pure by TLC.

Attempted Equilibration of 9a and 9b with PhSeCl. A mixture of 100 mg of a 15:85 mixture of **9a** and **9b** and 17 mg of PhSeCl (0.09 mmol) in 4 mL of THF was stirred at ambient temperature for 18 h, after which **9a** and **9b** was purified on silica gel as described above.

Attempted Equilibration of 9a and 9b with HCl. These experiments were done in the manner of the following example. A solution of 107 mg of a 54:46 mixture of **9a** and **9b** in 0.5 mL of THF was treated with 85 μL of saturated HCl in ether. After 16 h, the solution was treated with 1 N NaOH, and the product was extracted into ether. Purification was carried out as described above.

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-D-galacto-D-glyceroheptonate (10a) and Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-D-glycero-D-guloheptonate (10b). A mixture of **5** (560 mg, 1.3 mmol), cupric chloride (540 mg, 4 mmol), and palladium chloride (23 mg, 0.13 mmol) in 6.5 mL of MeOH was stirred for 18 h while gaseous carbon monoxide was bubbled in.[8a] The solution was filtered and the filtrate concentrated to an oil, which was redissolved in dichloromethane, washed with water and saturated aqueous NaCl, dried (K_2CO_3), and concentrated to a dark, brown syrup. It was purified on a 1500-μm preparative TLC plate (EtOAc/hexane, 4:1) to give 0.11 g (18%) of a 67:33 mixture of **10a** and **10b**, identical with **10** prepared previously:[4] CI-MS, m/e 477 (M + 1); 60-MHz ^1H NMR δ 2.6 (d, 2 H), 3.3–3.5 (m, 2 H), 3.6 (s, 3 H, CH_3), 3.75–4.0 (m, 2 H), 4.1–4.4 (m, 2 H), 4.45–4.65 (m, 6 H), 7.2 (m, 15 H); 90.6-MHz ^{13}C NMR δ 34.0 (0.33 C, C2 of **10b**); 38.0 (0.67 C, C2 of **10a**); 51.5 (0.33C, CH_3 of **10b**); 51.6 (0.67C, CH_3 of **10a**); 70.4, 70.5, 71.6, 71.7, 71.9, 73.4, 76.8, 77.1 (CH_2's); 79.2, 82.2, 82.7, 83.1, 83.8, 85.2, 86.9 (CH); 127.6, 127.7, 127.8, 128.3, 128.4, 137.9, 138.2 (aromatic); 171.2 (C=O).

Cyclization of 5 with Phenylmercuric Trifluoroacetate. A solution of 160 mg of **5** (0.38 mmol) in 5 mL of THF was treated with 84 mg of $CaCO_3$ and 238 mg of phenylmercuric trifluoroacetate[10] (0.6 mmol). The solution was refluxed for 16 h. Saturated aqueous KBr was added and the product was extracted into ether, washed with water, dried ($MgSO_4$), filtered, and concentrated. Purification was carried out on silica gel (EtOAc/hexane, 15:85) to give 147 mg of a 8:92 mixture of **8a** and **8b** (55%), identified as described above. Alternatively, a solution of 172 mg of **5** (0.41 mmol) in 2 mL of THF was treated with 84 mg of $CaCO_3$ and 225 mg of phenylmercuric trifluoroacetate (0.58 mmol). The solution was not heated at reflux, but allowed to stir for 19 days at ambient temperature. Workup as described above gave 7 mg of diphenylmercury (5%, identified by GLC and CI-MS), 185 mg of a 42:58 ratio of **8a** to **8b** (64%), and 25 mg of **11** (9%). Fast atom bombardment MS of **11**: m/e 696 (M + 1).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-mannitol (12a) and 2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-glucitol (12b). To a solution of **5** (200 mg, 0.47 mmol) in 5 mL of 1,2-dichloroethane was added 145 mg of 85% *m*-chloroperoxybenzoic acid and 1 mg of 4,4'-thiobis(2-*tert*-butyl-6-methylphenol).[21] The solution was refluxed for 16 h. Water was added and the product was extracted into EtOAc, washed with water and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a 2000-μm preparative TLC plate (EtOAc/hexane 35:65) to give 130 mg of a clear oil (63%) as a mixture of **12a** and **12b**. Upon scale-up (25 g of **5**), a 45% yield of pure **12a** and **12b** was obtained: 360-MHz ^1H NMR δ 2.4 (br s, 1 H, OH), 3.5–3.9 (m, 4 H), 4.0–4.14 (m, 4 H), 4.5–4.6 (m, 6 H), 7.2–7.4 (m, 15 H); 15.0-MHz ^{13}C NMR δ 61.6 (C1 for **12b**, ca. 0.5 C), 62.6 (C1 for **12a**, ca. 0.5 C), 70.0, 71.8 (2 C), 73.3, 80.1, 81.7, 83.0, 83.8, 127.6–128.4 (15 C, aromatic), 137.4–137.7 (3 C); CI-MS 435 (M + 1). The ratio of **12a** and **12b** was best determined by conversion to bromides **6a** and **6b** as described below and analysis of the 360-MHz ^1H NMR spectrum.

4-Pentene-1,3-diol (1). Diisopropylamine (20.7 g, 0.21 mol), dissolved in 20 mL of THF, was cooled to −78 °C and *n*-BuLi (131 mL of a 1.6 M solution in hexane 0.20 mol) was added dropwise. To the resulting solution of LDA was added 5.36 g (89.3 mmol) of glacial acetic acid. The reaction was warmed to room temperature and stirred for 24 h. The acetic acid dianion solution was cooled to −78 °C and 5.0 g (89.3 mmol) of acrolein was added. Stirring was continued for 2 h. The reaction was very gently quenched with saturated aqueous NH_4Cl. THF was removed and the residue was acidified with 10% aqueous HCl, extracted with ether, dried ($MgSO_4$), filtered, and concentrated. The crude product (4.6 g, 44%) was utilized in the next step without further purification: 360-MHz ^1H NMR δ 1.9 (br s, 1 H, OH), 2.5 (d, 2 H, J = 7.5 Hz), 4.95 (d, 1 H, J = 10.5 Hz), 5.25 (d, 1 H, J = 16.5 Hz), 5.8 (ddd, 1 H, J = 16.5, 10.5, 7.5 Hz). In a 500-mL flask was added 100 mL of 30% aqueous KOH and 100 mL of ether. The flask was cooled in an ice bath and 2.84 g (27.5 mmol) of *N*-nitroso-*N*-methylurea was added. After evolution of CH_2N_2 from the aqueous layer ceased, the ethereal layer was decanted and dried over KOH pellets. The ethereal CH_2N_2 solution was then added to 1.6 g (13.8 mmol) of the previously prepared acid dissolved in 20 mL of ether at 0 °C. After 20 min, the reaction mixture was then warmed to room temperature and glacial acetic acid was added to remove the excess CH_2N_2. The solution of ester was dried ($MgSO_4$), filtered, and concentrated. Bulb-to-bulb distillation (bp 50–60 °C, 0.1 mmHg) yielded ester **13** (1.62 g, 90%): 360-MHz ^1H NMR δ 2.4 (br s, 1 H, OH), 2.55 (d, 2 H, J = 6.5 Hz), 3.70 (s, 3 H), 4.75 (m, 1 H), 5.18 (d, 1 H, J = 10.9 Hz), 5.30 (d, 1 H, J = 17.5 Hz), 5.9 (ddd, 1 H, J = 17.5, 10.9, 6.4 Hz). Lithium aluminum hydride (405 mg, 10.65 mmol) was suspended in 10 mL of ether and cooled to −40 °C. Compound **13** (1.85 g, 14.23 mmol) was dissolved in 5 mL of ether and added dropwise to the LAH solution. After 20 min the reaction was quenched with wet ether followed by two drops of concentrated aqueous HCl. The solution was dried ($MgSO_4$), filtered, and concentrated. Bulb-to-bulb distillation (bp 80–85 °C, 0.1 mmHg) afforded diol **1** (1.30 g, 90%): 360-MHz ^1H NMR δ 1.8 (m, 2 H), 3.2–3.4 (br s, 2 H, OH), 3.8 (m, 2 H), 4.4 (m, 1 H), 5.15 (d, 1 H, J = 10.8 Hz), 5.3 (d, 1 H, J = 17.3 Hz), 5.90 (ddd, 1 H, J = 17.3, 10.8, 6.5 Hz).

Cyclization Procedure for Alkenols 1, 17, 23, 27, and 35 with Iodine. Alkenol **35** (44 mg, 0.39 mmol) was dissolved in 1.5 mL of ether and 0.5 mL of water. $NaHCO_3$ (49 mg, 0.58 mmol) and 147 mg (0.579 mmol) of I_2 were then added at 0 °C. The reaction was allowed to warm to room temperature and stirring was continued for 4 h. The mixture was diluted with ether, washed with saturated aqueous $Na_2S_2O_3$, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by preparative TLC (hexane–ether, 10:1) to afford product **37** (78 mg, 93%) as a 2:1 mixture of **37b:37a**. NMR and mass spectral data for the products of these reactions are listed below.

(21) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 65.
(22) Ho, P.-T.; Davies, N. J. *J. Org. Chem.* **1984**, *49*, 3027.

37: 360-MHz ^{1}H NMR δ 0.90 (d, 3 H, J = 7.1 Hz), 1.03 (d, 1.5 H, J = 6.6 Hz), 1.6–1.72 (m, 2 H), 2.05 (m, 0.5 H), 2.1–2.2 (m, 1.5 H), 2.4–2.45 (m, 1 H), 3.04 (dd, 1 H, J = 6.7, 9.9 Hz), 3.10–3.18 (m, 1.5 H), 3.26–3.36 (m, 1.5 H), 3.48 (m, 0.5 Hz), 3.74–3.86 (m, 2 H), 3.93 (q, 1 H, J = 7.6 Hz), 4.30 (q, 1 H, J = 6.8 Hz); 75.5-MHz ^{13}C NMR δ 5.30 (C1 of **37b**), 10.26 (C1 of **37b**), 13.96, 18.37, 34.6, 35.5, 36.35, 40.15, 67.70, 68.19, 82.40, 85.27; high-resolution mass spectrum, m/e calcd for $C_6H_{11}IO$ 225.9855, found 225.9855.

41a: 360-MHz ^{1}H NMR δ 1.08 (d, 3 H, J = 6.1 Hz), 1.65 (m, 1 H), 1.95 (d, 3 H, J = 7.1 Hz), 2.04–2.2 (m, 2 H), 2.86 (dd, 1 H, J = 3.57, 6.70 Hz), 3.85–3.95 (m, 2 H), 4.2–4.26 (m, 1 H); 75.5-MHz ^{13}C NMR δ 18.18 (C1), 25.54, 32.53, 35.06, 39.07, 67.99, 89.65; high-resolution mass spectrum, m/e calcd for $C_7H_{13}IO$ 240.0011, found 240.0036.

14b: 360-MHz ^{1}H NMR δ 1.85 (br s, 1 H), 2.05 (m, 1 H), 2.20 (m, 1 H), 3.30 (m, 2 H), 3.95 (dt, 1 H, J = 3.7, 8.7 Hz), 4.0–4.1 (m, 1 H), 4.14 (dd, 1 H, J = 8.4, 15.8 Hz), 4.5–4.6 (m, 1 H); 75.5-MHz ^{13}C NMR δ 1.51 (C1), 35.58, 67.31, 72.12, 82.85.

20b: 360-MHz ^{1}H NMR δ 2.0–2.1 (m, 1 H), 2.15–2.25 (m, 1 H), 3.25–3.42 (m, 2 H), 3.95–4.0 (m, 1 H), 4.05–4.10 (m, 2 H), 4.20–4.25 (m, 1 H), 4.50 (d, 1 H, J = 8.2 Hz), 4.65 (d, 1 H, J = 8.2 Hz), 7.25–7.40 (m, 5 H); 75.5-MHz ^{13}C NMR δ 2.26 (C1), 31.94, 67.20, 71.74, 78.58, 82.81, 127.68, 128.33; high-resolution mass spectrum, m/e calcd for $C_{12}H_{15}IO_2$ 318.0117, found 318.0105.

24a: 360-MHz ^{1}H NMR δ 1.82 (d, 3 H, J = 8.0 Hz), 1.90–2.15 (m, 2 H), 3.48 (m, 1 H), 3.93 (m, 2 H), 4.05 (m, 1 H), 4.18 (m, 1 H), 4.50 (d, 1 H, J = 12.0 Hz), 4.45 (d, 1 H, J = 12.0 Hz), 7.20–7.35 (m, 5 H); 75.5-MHz ^{13}C NMR δ 24.98 (C1), 29.92, 32.67, 67.92, 71.63, 83.25, 88.21, 127.76, 127.83, 128.49; high-resolution mass spectrum, m/e (MH^+) calcd for $C_{13}H_{17}IO_2$ 333.0352, found 333.0335.

Cyclization Procedure for Alkenols 1, 17, 23, 27, and 35 with Mercuric Acetate. Alkenol **35** (25 mg, 0.22 mmol) was dissolved in 1 mL of THF. $CaCO_3$ (40 mg) and 105 mg (0.330 mmol) of $Hg(OAc)_2$ were then added at room temperature. The reaction was allowed to stir for 6 h. Saturated aqueous KBr (3 mL) was added to the reaction mixture. After 15 min THF was removed and the crude reaction mixture was diluted with ether, washed with saturated aqueous KBr, and dried ($MgSO_4$). Flash chromatography (hexane–ether, 4:1) afforded **38** (75.3 mg, 87%) as a 2:3 mixture of **38a**:**38b**. NMR data for mercurials prepared in this manner are given below.

38: 360-MHz ^{1}H NMR δ 0.9 (d, 3 H, J = 6.0 Hz), 1.0 (d, 2 H, J = 6.8 Hz), 1.5–1.65 (m, 2.5 H), 2.0–2.2 (m, 3 H), 2.35 (m, 1 H), 3.6–3.95 (m, 5 H), 4.15 (dd, 1 H, J = 6.9, 13.2 Hz); 75.5-MHz ^{13}C NMR δ 13.68 (CH_3 of **38b**), 15.94 (CH_3 of **38a**), 33.45, 34.21, 35.82, 36.38, 39.32 (C1 of **38b**), 43.08 (C1 of **38a**), 65.52, 65.72, 79.13, 83.84; high-resolution mass spectrum, m/e calcd for $C_6H_{11}{}^{200}Hg^{79}BrO$ 377.9676, found 377.9683.

42a: 360-MHz ^{1}H NMR δ 1.10 (d, 3 H, J = 6.6 Hz), 1.55 (d, 3 H, J = 7.6 Hz), 1.55–1.65 (m, 1 H), 1.7–1.8 (m, 1 H), 2.10–2.18 (m, 1 H), 2.88 (qd, 1 H, J = 7.6, 3.5 Hz), 3.60 (dd, 1 H, J = 3.5, 7.8 Hz), 3.8–3.93 (m, 2 H); 75.5 MHz ^{13}C NMR δ 17.31, 19.55, 34.68, 41.39, 57.37 (CHHgBr), 66.49, 90.90.

15b: 360-MHz ^{1}H NMR δ 1.60 (br s, 1 H), 1.85–2.0 (m, 2 H), 2.15–2.20 (m, 2 H), 3.70–3.75 (m, 1 H), 3.75–3.85 (m, 1 H), 4.03–4.10 (m, 1 H), 4.15–4.25 (m, 1 H); 75.5-MHz ^{13}C NMR δ 31.47, 36.35 (CH_2HgBr), 67.50, 72.41, 80.90.

21b: 360-MHz ^{1}H NMR δ 1.85 (dd, 1 H, J = 3.3, 11.8 Hz), 2.0–2.15 (m, 3 H), 3.7–3.8 (m, 1 H), 3.85–3.90 (m, 1 H), 4.0 (apparent q, 1 H, J = 6.6 Hz), 4.30 (m, 1 H), 4.38 (d, 1 H, J = 12.4 Hz), 4.65 (d, 1 H, J = 12.4 Hz), 7.25–7.35 (m, 5 H); 75.5-MHz ^{13}C NMR δ 31.83, 32.01 (CH_2HgBr), 66.01, 71.34, 128.05, 128.61.

25: 360-MHz ^{1}H NMR δ 1.40 (d, J = 7.7 Hz), 1.41 (d, J = 7.7 Hz, resonances at 1.40 and 1.41 integrate to 3 H), 1.95–2.10 (m, 2 H), 2.50 (m, 0.33 H), 2.70 (apparent q, 0.67 H, J = 6.12 Hz). 3.65–3.70 (m, 0.67 H), 3.70–3.95 (m, 2.66 H), 3.95–4.10 (m, 0.67 H), 4.30 (d, 0.33 H, J = 10.7 Hz), 4.45 (d, 0.67 H, J = 12.3 Hz), 4.55 (d, 0.67 H, J = 12.3 Hz), 4.65 (d, 0.33 H, J = 10.7 Hz), 7.2–7.4 (m, 5 H); 75.5-MHz ^{13}C NMR δ 17.79, 19.63 (C1), 32.23, 47.97 (CHHgBr for **25b**), 54.70 (CHHgBr for **25a**), 66.09, 66.60, 71.30, 71.76, 79.06, 82.94, 87.48, 88.01, 127.94, 128.01, 128.10, 128.21, 128.62; high-resolution mass spectrum, m/e calcd for $C_{13}H_{18}{}^{200}Hg^{79}BrO_2$ 485.0173, found 485.0235.

Cyclization Procedure for Alkenols 1, 17, 23, 27, and 35 with Phenylselenenyl Chloride. To 50 mg (0.5 mmol) of alkenol **35** in 3 mL of dry dichloromethane at −78 °C was added a solution of 115 mg (0.6 mmol) of benzeneselenenyl chloride in 3 mL of dichloromethane. After 15 min the reaction mixture was diluted with dichloromethane, washed with dilute aqueous $NaHCO_3$ and water, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane–ether, 4:1) afforded **39** (101 mg, 86%) as a 60:40 mixture of **39a**:**39b**. NMR and mass spectral data for products prepared in this fashion are listed below.

39: 360-MHz ^{1}H NMR δ 0.95 (d, J = 8.8 Hz), 1.05 (d, J = 5.3 Hz, combined integration of resonances at 0.95 and 1.05 is 3 H), 1.5–1.7 (m, 1 H), 2.0–2.2 (m, 2 H), 3.0–3.2 (m, 2 H), 3.6–3.7 (m, 1 H), 3.7–4.1 (m, 2 H), 7.3–7.7 (m, 5 H); 75.5-MHz ^{13}C NMR δ 14.01 (CH_3 of **39b**), 17.54 (CH_3 of **39a**), 27.36 (C1 of **39b**), 28.24 (C1 of **39a**), 32.24, 34.74, 35.70, 39.12, 58.63, 60.70, 66.57, 67.30, 79.26, 84.15, 126.70, 128.98, 129.45, 132.43, 132.69; high-resolution mass spectrum, m/e calcd for $C_{12}H_{16}OSe$ 256.0366, found 256.0340.

43a: 360-MHz ^{1}H NMR δ 1.10 (d, 3 H, J = 7.0 Hz), 1.55 (d, 3 H, J = 7.0 Hz), 1.55–1.7 (m, 1 H), 2.10–2.20 (m, 1 H), 2.3–2.4 (m, 1 H), 3.4–3.5 (m, 1 H), 3.55 (dd, 1 H, J = 3.5, 7.0 Hz), 3.85–3.95 (m, 2 H), 7.25–7.35 (m, 2 H), 7.60–7.68 (m, 3 H); 75.5-MHz ^{13}C NMR δ 18.34, 20.18, 35.14, 36.80, 43.93 (CH_2SePh), 67.70, 89.31, 127.06, 127.65, 128.86, 129.09 (aromatics).

16: 360-MHz ^{1}H NMR δ 1.70 (br s, 1 H, O*H*), 1.90–2.05 (m, 1 H), 2.15–2.25 (m, 1 H), 2.94 (dd, 0.38 H, J = 8.1, 11.8 Hz), 3.08–3.25 (m, 1.62 H), 3.8–3.95 (m, 2 H), 3.95–4.04 (m, 0.38 H), 4.10 (apparent q, 0.62 H, J = 8.10 Hz), 4.21 (m, 0.38 H), 4.40 (m, 0.62 H), 7.25–7.3 (m, 2 H), 7.5–7.6 (m, 3 H).

22: 360-MHz ^{1}H NMR δ 2.0–2.3 (m, 2 H), 2.98 (dd, 0.2 H, J = 7.2, 12.6 Hz), 3.08 (dd, 0.2 H, J = 6.5, 12.6 Hz), 3.18 (dd, 0.8 H, J = 6.5, 11.5 Hz), 3.25 (dd, 0.8 H, J = 7.6, 11.5 Hz), 3.65–3.90 (m, 2 H), 4.0–4.1 (m, 16 H), 4.18–4.2 (m, 0.4 H), 4.45 (d, 1 H, J = 11.5 Hz), 4.80 (d, 1 H, J = 11.5 Hz), 7.2–7.4 (m, 7 H), 7.5–7.85 (m, 3 H); 75.5-MHz ^{13}C NMR δ 26.39 (C1 of **22b**), 30.94 (C1 of **22a**), 31.90 (C4 of **22b**), 32.31 (C4 of **22a**), 66.34 (C5 of **22a**), 66.52 (C5 of **22b**), 71.38 ($PhCH_2$ of **22b**), 72.15 ($PhCH_2$ of **22a**), 78.87 (C3 of **22b**), 79.76 (C3 of **22a**), 81.70 (C2 of **22b**), 82.84 (C2 of **22a**), 126.67, 126.90, 127.54, 127.66, 127.91, 127.98, 128.28, 128.53, 128.97, 129.08, 129.20, 129.74, 131.33, 131.51, 132.29, 132.50; high-resolution mass spectrum, m/e calcd for $C_{18}H_{20}O_2Se$ 348.0629, found 348.0602.

The 75:25 mixture of **26a** and **26b** were separated by chromatography (silica gel, ether/hexane, 1:4) to give pure isomers. Data for **26b**: 360-MHz ^{1}H NMR δ 1.30 (d, 3 H, J = 7.6 Hz), 2.0–2.25 (m, 2 H), 3.25–3.40 (m, 1 H), 3.65–3.75 (m, 1 H), 3.82–3.95 (m, 1 H), 4.05–4.15 (m, 2 H), 4.40 (d, 1 H, J = 12.3 Hz), 7.2–7.4 (m, 7 H), 7.5–7.65 (m, 3 H); 75.5-MHz ^{13}C δ 19.08 (CH_3), 31.76 (CH_2), 38.22 (CHSePh), 66.42, 71.01, 78.47, 85.93, 127.44, 127.71, 127.96, 128.35, 128.68, 129.34, 133.30, 134.56, 135.75.

Data for **26a**: 360-MHz ^{1}H NMR δ 1.40 (d, 3 H, J = 7.2 Hz), 1.95–2.05 (m, 2 H), 3.25–3.35 (m, 2 H), 3.80–3.90 (m, 1 H), 3.95–4.0 (m, 1 H), 4.05–4.10 (m, 1 H), 4.40 (d, 1 H, J = 12.0 Hz), 4.50 (d, 1 H, J = 12.0 Hz), 7.15–7.25 (m, 7 H), 7.40–7.45 (m, 3 H); 75.5-MHz ^{13}C NMR δ 19.59 (CH_3), 32.98, 42.79 (CHSePh), 67.70, 71.49, 82.01, 87.77, 127.34, 127.75, 128.42, 128.97, 134.45; high-resolution mass spectrum for **26a**, m/e calcd for $C_{19}H_{22}O_2Se$ 362.0785, found 362.0815.

3-(Benzyloxy)-4-penten-1-ol (17). 3-Hydroxypropanenitrile (10 g, 0.14 mol) was dissolved in 80 mL of dichloromethane and diisopropylethylamine (46 g, 0.35 mol) was added. The mixture was cooled to 0 °C and methoxymethyl chloride (16.4 g, 0.17 mol) was added dropwise. The reaction was allowed to continue for 12 h with warming to room temperature. The reaction mixture was diluted with dichloromethane, washed with 5% HCl, dried ($MgSO_4$), filtered, and concentrated. The crude product was distilled, giving 3-(methoxymethoxy)propanenitrile (14.3 g, 86%; bp 75–79 °C, 0.1 mmHg): 360-MHz ^{1}H NMR δ 2.64 (t, 2 H, J = 7.3 Hz), 3.4 (s, 3 H), 3.76 (t, 2 H, J = 7.3 Hz), 4.68 (s, 2 H). 3-(Methoxymethoxy)propanenitrile (2.5 g, 21.7 mmol) was dissolved in 125 mL of dry ether at −78 °C. Dibal-H (26.1 mL of a 1.0 M solution in THF) was added dropwise. Stirring was continued at −78 °C for 3 h. The reaction was carefully quenched by adding water at −78 °C, followed by concentrated H_2SO_4. After stirring at room temperature for 30 min, the aluminum salts dissolved in the aqueous phase. The layers were then separated and the aqueous layer was exhaustively extracted with ether. The organic layers were combined, dried ($MgSO_4$), filtered, and con-

centrated. Distillation (bp 73–76 °C, 0.08 mmHg) yielded pure **18** (2.2 g, 86%): 90-MHz ^{1}H NMR δ 2.63, (t, 2 H, J = 5.7 Hz), 3.3 (s, 3 H), 3.8 (t, 2 H, J = 5.7 Hz), 4.6 (s, 2 H), 9.65 (t, 1 H). Compound **18** (3.1 g, 32.3 mmol) was dissolved in 20 mL of THF and cooled to −78 °C. Vinylmagnesium bromide (42 mL of a 1.0 M solution in THF) was added dropwise, and the resulting solution was stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the THF was evaporated. The crude product was acidified with 5% aqueous HCl, and the product was extracted into ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The material was purified on silica gel (hexane–ether, 3:1) to afford the expeected allylic alcohol (4.21 g, 91%): 360-MHz ^{1}H NMR δ 1.8 (dt, 2 H, J = 6.4, 6.2 Hz), 2.22 (br s, 1 H, OH), 3.35 (s, 3 H), 3.65 (t, 2 H, J = 6.2 Hz), 4.3 (q, 1 H, J = 6.4 Hz), 4.6 (s, 2 H), 5.1 (d, 1 H, J = 11.6 Hz), 5.25 (d, 1 H, J = 14.1 Hz), 5.8 (ddd, 1 H, J = 14.1, 11.6, 6.4 Hz). NaH (50% dispersion in oil, 1.5 g, 31.2 mmol) was suspended in 25 mL of anhydrous THF and cooled to 0 °C. A THF solution of 3.5 g (24.0 mmol) of the alcohol prepared above was added dropwise, and the mixture was warmed to room temperature. Tetra-*n*-butylammonium iodide (1.77 g, 4.8 mmol) and benzyl bromide (4.51 g, 26.4 mmol) were added. The reaction was stirred for 12 h at room temperature, and then the THF was removed. The crude residue was acidified with 10% aqueous HCl, and the product was extracted into Et_2O. The organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography (hexane–ether, 6:1) yielded **19** (4.93 g, 87%): 360-MHz ^{1}H NMR δ 1.8 (m, 2 H), 3.35 (s, 3 H), 3.60 (m, 2 H), 3.95 (q, 1 H, J = 6.9 Hz), 4.3 (d, 1 H, J = 14 Hz), 4.55 (s, 2 H), 4.60 (d, 1 H, J = 14 Hz), 5.25 (d, 1 H, J = 10 Hz), 5.30 (d, 1 H, J = 16.8 Hz), 5.75 (ddd, 1 H, J = 16.8, 10, 6.9 Hz), 7.26–7.35 (br m, 5 H). A portion of this material (2.2 g, 9.32 mmol) was dissolved in 50 mL of MeOH and five drops of concentrated HCl were added. The reaction was refluxed for 2.5 h. The methanol was removed and the product was dissolved in ether, washed with 5% aqueous $NaHCO_3$ and water, dried ($MgSO_4$), filtered, and concentrated to afford **17** (1.77 g, 99%), which did not require further purification: 360-MHz ^{1}H NMR δ 1.85 (m, 2 H), 2.4 (br s, 1 H, OH), 3.8 (m, 2 H), 4.05 (m, 1 H), 4.4 (d, 1 H, J = 11.5 Hz), 4.65 (d, 1H, J = 11.5 Hz), 5.3 (d, 1 H, J = 9.8 Hz), 5.35 (d, 1 H, J = 11.5 Hz), 4.65 (d, 1 H, J = 11.5 Hz), 5.3 (d, 1 H, J = 9.8 Hz), 5.35 (d, 1 H, J = 14.7 Hz), 5.75 (ddd, 1 H, J = 14.7, 9.8, 6.5 Hz), 7.27–7.40 (br m, 5 H).

(*Z*)-3-(Benzyloxy)-4-hexen-1-ol (23). (Trimethylsilyl)-acetylene (1.0 g, 10.2 mmol) was dissolved in 10 mL of THF at −78 °C and *n*-BuLi (7.1 mL of a 1.6 M solution in hexanes, 10.7 mmol) was added dropwise. The solution was stirred for 20 min and then **18** (1.2 g, 10.2 mmol) dissolved in THF (5 mL) was added. After 45 min the reaction mixture was quenched at −78 °C with saturated aqueous NH_4Cl. THF was removed and the residue was acidified with 5% aqueous HCl and extracted with ether. The ethereal solution was washed with water, dried ($MgSO_4$), filtered, and concentrated to yield the expected alcohol (1.36 g, 62%), which was suitable for use in the next step without additional purification: 360-MHz ^{1}H NMR δ 0.1 (s, 9 H), 1.95 (br s, 1 H, OH), 2.0 (m, 2 H), 3.4 (s, 3 H), 3.8 (m, 2 H), 4.6 (t, 1 H, J = 5.5 Hz), 4.65 (s, 2 H). This material was benzylated in the same manner as for the preparation of **17**. The product obtained (76%), which was completely desilylated, was purified by flash chromatography (hexane–ether, 6:1): 360-MHz ^{1}H NMR δ 2.1 (dt, 2 H, J = 8.2, 7.0 Hz), 2.5 (d, 1 H, J = 2.1 Hz), 3.35 (s, 3 H), 3.7 (t, 2 H, J = 8.2 Hz), 4.3 (dt, 1 H, J = 7, 2.1 Hz), 4.5 (d, 1 H, J = 11.3 Hz), 4.6 (s, 2 H), 4.8 (d, 1 H, J = 11.3 Hz), 7.28–7.40 (br m, 5 H). This benzylated acetylene (2.96 g, 12.65 mmol) was dissolved in 25 mL of THF and cooled to −78 °C. *n*-BuLi (11.8 mL of a 1.6 M solution in hexanes, 16.4 mmol) was added dropwise and the solution was stirred for 30 min. Methyl iodide (2.7 g, 19.0 mmol) was added via syringe, and the mixture was warmed to room temperature for 2 h. After removal of THF, the product was dissolved in ether, washed with brine, and dried (Na_2SO_4). Flash column chromatography (hexane–ether, 5:1) produced the expected methylalkyne (2.67 g, 85%): 360-MHz ^{1}H NMR δ 1.8 (s, 3 H), 1.95 (m, 2 H), 3.25 (s, 3 H), 3.6 (t, 2 H, J = 7.8 Hz), 4.15 (m, 1 H), 4.6 (d, 1 H, J = 11.7 Hz), 4.45 (s, 2 H), 4.7 (d, 1 H, J = 11.7 Hz), 7.27–7.42 (br m, 5 H). The material (840 mg, 3.4 mmol) was dissolved in 20 mL of MeOH and 350 mg of 5% Pd on $BaSO_4$ and one drop quinoline were added. After TLC indicated complete consumption of alkyne, nitrogen was bubbled through the mixture. The catalyst was removed, the solution was concentrated, and the product was purified by column chromatography (hexane–ether, 4:1; 730 mg, 86%): 360-MHz ^{1}H NMR δ 1.65 (d, 3 H, J = 7.8 Hz), 1.95 (m, 2 H), 3.34 (s, 3 H), 3.665 (m, 2 H), 4.30 (d, 1 H, J = 11.7 Hz), 5.60 (s, 2 H), 5.35 (t, 1 H, J = 9.7 Hz), 5.7 (dq, 1 H, J = 9.7, 7.8 Hz), 7.28–7.40 (br m, 5 H). The MOM ether was removed in the same manner as in the preparation of **17**, and the product (**23**) was purified by column chromatography (hexane–ether, 3:1; 100%): 360-MHz ^{1}H NMR δ 1.65 (d, 3 H, J = 7.6 Hz), 1.95 (m, 2 H), 3.7 (m, 2 H), 4.3 (d, 1 H, J = 11.4 Hz), 4.4 (m, 1 H), 4.6 (d, 1 H, J = 11.4 Hz), 5.4 (t, 1 H, J = 10.9 Hz), 5.7 (dq, 1 H, J = 10.9, 7.6 Hz), 7.28–7.40 (br m, 5 H); high-resolution mass spectrum; m/e calcd for $C_{11}H_{13}O$ (M − 45) 161.0966, found 161.0974.

Conversion of Alcohols 12a and 12b to Bromides 6a and 6b. A mixture of **12a** and **12b** (15.0 g, 34.6 mmol) in 130 mL of THF was treated with 27 g of triphenylphosphine (103 mmol) and 7.8 g of zinc bromide (35 mmol).[21] To the resultant mixture was then slowly added 16.3 mL of diethyl azodicarboxylate (103 mmol). After being stirred for 18 h, the solution was treated with water, and the product was extracted into ether, washed twice with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography (Waters preparative HPLC; EtOAc/hexane 1:9) to give 11.2 g of a 45:55 mixture of **6a** and **6b** (65%).

4-*O*-Benzyl-1,2,3-trideoxy-5,6-isopropylidene-3-methyl-D-gluc-1-enitol (29). Compound **28** was prepared by the procedure of Rousch et al.[13] The diastereomeric purity (after chromatography) was >99% as determined by capillary GC: 360-MHz ^{1}H NMR δ 1.09 (d, 3 H, J = 6.8 Hz), 1.34 (s, 3 H), 1.41 (s, 3 H), 1.8–2.0 (br s, 1 H, OH), 2.23 (m, 1 H, H3), 3.63 (dd, 1 H, H4, J = 4.5, 7.2 Hz),[13] 3.8 (dd, 1 H, H6a, J = 7.5, 7.5 Hz), 3.96 (dd, 1 H, H6b, J = 6.3, 8.0 Hz), 4.10 (m, 1 H, H5), 5.03 (d, 1 H, H1a, J = 0.6 Hz), 5.07 (dd, 1 H, H1b, J = 0.9, 5.5 Hz), 5.72 (m, 1 H, H2). A solution of 1.05 g of **28** (5.65 mmol) was dissolved in 8 mL of DMF (distilled) under nitrogen and treated with 270 mg of a 60% dispersion of NaH in oil (7 mmol). After 10 min, the bubbling had ceased and benzyl bromide (737 μL, 6.2 mmol) was added to the grey suspension. After 30 min, water was added, and the product was extracted into ether, washed with water, dried ($MgSO_4$), filtered, and concentrated. This product was purified on 100 g of dry silica gel (ether/hexane, 1:10), resulting in 1.08 g of **29** pure by TLC (69% yield): 360-MHz ^{1}H NMR δ 1.07 (d, 3 H, J = 6.8 Hz), 1.34 (s, 3 H), 1.41 (s, 3 H), 2.38 (m, 1 H, H3, J_{3,CH_3} = 6.8 Hz, $J_{1a,3}$ = 1.1 Hz, $J_{1b,3}$ = 1.3 Hz, $J_{2,3}$ = 7.7 Hz, $J_{3,4}$ = 6.0 Hz), 3.52 (dd, 1 H, H4, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 4.7 Hz), 3.90 (dd, 1 H, H6a, $J_{6a,6b}$ = 7.9 Hz, $J_{5,6a}$ = 7.2 Hz), 3.98 (dd, 1 H, H6b, J = 7.9, 6.3 Hz), 4.17 (ddd, 1 H, H5, $J_{4,5}$ = 4.7 Hz, $J_{5,6a}$ = 7.2 Hz, $J_{5,6b}$ = 6.3 Hz), 4.61 (d, 1 H, $PhCH_2$a, J = 11.2 Hz), 4.72 (d, 1 H, $PhCH_2$b, J = 11.2 Hz), 5.01 (dd, 1 H, H1a, $J_{1a,2}$ = 10.4 Hz, $J_{1a,3}$ = 1.1 Hz), 5.05 (dd, 1 H, H1b, $J_{1b,2}$ = 17.3 Hz, $J_{1b,3}$ = 1.3 Hz), 5.84 (ddd, 1 H, H2, $J_{1a,2}$ = 10.4 Hz, $J_{1b,2}$ = 17.3 Hz, $J_{2,3}$ = 7.7 Hz), 7.3 (m, 5 H). Anal. Calcd for $C_{17}H_{34}O_3$: C, 73.88; H, 8.75. Found: C, 74.70; H, 8.74.

4-*O*-Benzyl-5,6-benzylidene-1,2,3-trideoxy-3-methyl-D-gluc-1-enitol (30). Compound **29** (0.70 g, 2.54 mmol) was dissolved in 10 mL of MeOH and treated with 70 mg of *p*-toluenesulfonic acid. After stirring for 2 days, TLC analysis indicated that ca. 25% of the starting material remained. An additional 70 mg of *p*-toluenesulfonic acid was added. The solvent was evaporated and fresh MeOH was added seven consecutive times, during which process the starting material was seen to be converted nearly completely to product by TLC. The solution was then treated with saturated aqueous $NaHCO_3$, and the product was extracted into $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to give 660 mg of a clear oil. This material was dissolved in 15 mL of THF and treated with 1 mL of benzaldehyde, 4.3 g of anhydrous $ZnCl_2$, and 0.4 mL of HOAc. The solution was heated at 50 °C under N_2 for 18 h. The clear solution was treated with saturated aqueous $NaHCO_3$, and the product was extracted into ether, washed with water, dried ($MgSO_4$), filtered, and concentrated. This produced the two diastereomers of **30** in near quantitative yield, but it was contaminated by a small amount of benzaldehyde that had a slightly lower R_f than **30**. The bulk of the material was carried

on to the next step, but a small quantity of **30** was rigorously purified by preparative TLC (EtOAc/hexane, 1:19): 360-MHz ^{1}H NMR δ 1.10 (d, 3 H, J = 6.9 Hz), 2.34 (m, 0.5 H, H3 of one diastereomer), 2.47 (m, 0.5 H, H3 of the other diastereomer), 3.64 (m, 1 H, H4), 4.01 (m, 1 H), 4.12 (ddd, 1 H), 4.27 (m, 1 H), 4.5–4.8 (m, 2 H), 5.0 (m, 2 H), 5.71 (s, 0.5 H), 5.75–5.95 (m, 1.5 H); CI-MS (NH_3), m/e 323 (M − 1). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.87; H, 7.68.

4,6-Di-*O*-benzyl-1,2,3-trideoxy-3-methyl-D-gluc-1-enitol (27). Compound **30** obtained from the preceding procedure was dissolved in 10 mL of THF to which had been added ca. 2 g of 3A molecular sieves. This solution was treated with 2.4 g of $NaCNBH_3$ under nitrogen at 0 °C. Saturated HCl/ether was added slowly until gas evolution had ceased. TLC analysis revealed that a minor amount of starting material remained, so an additional 0.5 g of $NaBH_3CN$ was added, followed by sufficient ethereal HCl to decompose it. TLC then revealed complete lack of starting material and predominant formation of two lower spots. After a total period of 0.5 h since the first addition of $NaCNBH_3$, water was added, and the product was extracted into ether, washed with 1 N HCl, saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The two products were purified by silica gel chromatography (EtOAc/hexane, 1:4) to yield 260 mg of **27** (upper spot, 35% from **28**) and 37 mg of **31** (lower spot, 5% from **28**). For **27**, capillary GC (SE-30 column) analysis showed that **27** contained only one component and was devoid of **31** (<0.5%): 360-MHz ^{1}H NMR δ 1.09 (d, 3 H, J = 6.7 Hz), 2.0–2.4 (br s, 1 H, OH), 2.55 (m, 1 H, H3), 3.45 (dd, 1 H, H4, J = 5.8, 5.8 Hz), 3.58 (dd, 1 H, H6a, $J_{6a,6b}$ = 9.5 Hz, $J_{5,6a}$ = 7.0 Hz), 3.67 (dd, 1 H, H6b, J = 3.0, 9.6 Hz), 3.87 (ddd, 1 H, H5, J = 3.0, 6.6, 6.6), 4.50–4.64 (m, 4 H), 5.00 (dd, 1 H, H1a, $J_{1a,2}$ = 10.3 Hz, $J_{1a,3}$ = 2.4 Hz), 5.06 (dd, 1 H, H1b, $J_{1b,2}$ = 15.8 Hz, $J_{1b,3}$ = 1.4 Hz), 5.88 (ddd, 1 H, H2, J = 7.5, 10.3, 17.6 Hz), 7.2–7.4 (m, 10 H); CI-MS, m/e 339 (M + 1). Anal. Calcd for $C_{22}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.01; H, 8.03.

5,6-Di-*O*-benzyl-1,2,3-trideoxy-3-methyl-D-gluc-1-enitol (31). Compound **31** obtained above was characterized as follows. Capillary GC (SE-30 column) analysis showed that this sample was 98.5% pure and contained 1.5% of **27**: 360-MHz ^{1}H NMR δ 1.05 (d, 3 H, J = 6.7 Hz), 2.50 (m, 1 H, H3), 3.50–3.62 (m, 2 H, H4 and H5), 3.83 (d, 2 H, H6a and H6b, $J_{5,6}$ = 3.8 Hz), 4.52–4.78 (m, 4 H), 5.01 (dd, 1 H, H1a, J = ca. 0.8, 10.3 Hz), 5.07 (dd, 1 H, H1b, J = 1.3, 7.1 Hz), 5.81 (ddd, 1 H, H2, J = 7.6, 10.1, 17.6 Hz), 7.2–7.4 (m, 10 H). Anal. Calcd for $C_{22}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.96; H, 8.09.

2,5-Anhydro-4,6-di-*O*-benzyl-1-bromo-1,3-dideoxy-3-methyl-D-mannitol (32a) and 2,5-Anhydro-4,6-di-*O*-benzyl-1-bromo-1,3-dideoxy-3-methyl-D-glucitol (32b). A solution of compound **27** (40 mg, 0.123 mmol) in 3 mL of dichloromethane was treated with 44 mg of *N*-bromosuccinimide (2 mmol). After 1 h, the product was purified on a 2000-μm preparative TLC plate (EtOAc/hexane, 1:4). This resulted in 46 mg of a clear oil (92% yield): 360-MHz ^{1}H NMR δ 0.92 (d, 1 H, J = 7.4 Hz), 1.10 (d, 2 H, J = 6.8 Hz), 2.2–2.38 (m, 0.7 H, C3 of **32a**), 2.38–2.5 (m, 0.3 H, C3 of **32b**), 3.2–4.4 (m, 7 H), 4.4–4.6 (m, 4 H), 7.3 (m, 10 H); 90.6-MHz ^{13}C NMR δ 11.8 (0.33 C, CH_3 of **32b**); 16.5 (0.67 C, CH_3 of **32a**); 30.0 (0.30 C, C1 of **32b**); 34.5 (0.70 C, C1 of **32a**); 41.7 (0.35 C, C3 of **32b**); 44.4 (0.65 C, C3 of **32a**); 70.7, 72.3, 73.5 (CH_2 of **32a**); 70.8, 71.5, 73.5 (CH_2 of **32b**); 80.3, 82.8, 84.0, 87.2, 87.5 (unassigned ring carbons); 127–128 (10 C, aromatics), 138.2 (2 C, quaternary carbons) [The fact that ring carbons appear as far downfield as 85–87 ppm indicates that the structure is a furanose (and not a pyranose) derivative.[15]]; CI-MS (NH_3), m/e 403 (M − 1), 404 (M^+), 405 (M + 1), 406 (M + 2). Anal. Calcd for $C_{21}H_{25}O_3Br$: C, 62.23; H, 6.22. Found: C, 62.46; H, 6.34.

2,5-Anhydro-4,6-di-*O*-benzyl-1-(bromomercurio)-1,3-dideoxy-3-methyl-D-mannitol (33a) and 2,5-Anhydro-4,6-di-*O*-benzyl-1-(bromomercurio)-1,3-dideoxy-3-methyl-D-glucitol (33b). A solution of compound **27** (40 mg, 0.123 mmol) in 4 mL of THF was treated with 22 mg of $CaCO_3$ and 63 mg of $Hg(OTfa)_2$ (0.15 mmol). After stirring under N_2 for 2 h, TLC showed complete loss of starting material. The solution was then treated with saturated aqueous KBr, and the product was extracted into ether, washed with saturated aqueous KBr, dried ($MgSO_4$), filtered, and concentrated to give a light yellow oil, pure by TLC (70 mg, 94% crude yield): 360-MHz ^{1}H NMR δ 0.96 (d, 1.5 H, J = 7.4 Hz), 1.05 (d, 1.5 H, J = 6.8 Hz), 1.3–2.4 (m, 3 H), 3.45–4.19 (m, 5 H), 4.5 (m, 4 H), 7.2 (m, 10 H); 90.6-MHz ^{13}C NMR δ 12.5 (0.51 C, CH_3 of **33b**); 15.4 (0.49 C, CH_3 of **33a**); 35.6 (0.53 C, C1 of **33b**); 40.2 (0.47 C, C1 of **33a**); 43.7 (0.56 C, C3 of **33b**); 50.5 (0.44 C, C3 of **33a**); resonances for **33b** and **33a** (ca. 0.5 C each) 70.4, 71.1, 71.8, 72.3, 73.4, 73.5, 79.0, 81.9, 83.1, 83.4; 87.5 (1 C); 127–129 (10 C, aromatic carbons), 138.0 (2 C, quaternary carbons); CI-MS, m/e 603 (M^+), 604 (M + 1), 605 (M^+ of ^{202}Hg isotope), 606 (M + 1 of ^{202}Hg isotope). A small amount of the crude material was purified by preparative TLC (EtOAc/hexane, 15:85) to give a sample for elemental analysis. Anal. Calcd for $C_{21}H_{25}O_3HgBr$: C, 41.63; H, 4.16. Found: C, 42.06; H, 4.33.

2,5-Anhydro-4,6-di-*O*-benzyl-3-deoxy-3-methyl-D-mannitol (34a) and 2,5-Anhydro-4,6-di-*O*-benzyl-3-deoxy-3-methyl-D-glucitol (34b). To a solution of **27** (46.2 mg, 0.14 mmol) in 1 mL of 1,2-dichloroethane was added 40 mg of 85% MCPBA and 1 mg of 4,4′-thiobis(2-*tert*-butyl-6-methylphenol).[21] The solution was stirred overnight. Water was added and the product was extracted into dichloromethane, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified on a 1500-μm preparative TLC plate (EtOAc/hexane, 1:2) to give 20 mg (42%) of a 1:1 mixture of **34a** and **34b** as a pale yellow oil: 360-MHz ^{1}H NMR δ 1.07 (d, 1.5 H, CH_3 of **34a** or **34b**), 1.13 (d, 1.5 H, CH_3 of **34a** or **34b**), 2.45 (m, 1 H, C3H), 3.2–4.2 (m, 8 H), 4.4–4.6 (m, 4 H), 7.25 (m, 10 H).

3-Methyl-4-penten-1-ol (35). To a suspension of methyltriphenylphosphonium bromide (21.9 g, 61.30 mmol) in 80 mL of anhydrous THF at 0 °C under nitrogen atmosphere was added via syringe *n*-BuLi (40.9 mL of a 1.6 M solution in hexanes, 61.3 mmol). The resulting red-orange solution was allowed to stir at 0 °C for 30 min. A solution of **36** (2.5 g, 24.51 mmol) in 10 mL of THF was then added dropwise. The reaction mixture was allowed to warm to 25 °C and stir for 8 h. Saturated aqueous NH_4Cl was added, the THF was removed, and the residue was acidified with 5% HCl. The product was extracted into ether, dried ($MgSO_4$), filtered, and concentrated. Bulb-to-bulb distillation (bp 50–53 °C, 20 mmHg) yielded **35** (1.62 g, 65%): 360-MHz ^{1}H NMR δ 1.0 (d, 3 H, J = 7.5 Hz), 1.2 (br s, 1 H, OH), 1.6 (m, 2 H), 2.3 (m, 1 H), 3.7 (t, 2 H, J = 5.7 Hz), 4.95 (d, 1 H, J = 11.4 Hz), 5.1 (d, 1 H, J = 13.3 Hz), 5.7 (ddd, 1 H, J = 13.3, 11.4, 7.6 Hz).

(*Z*)-3-Methyl-4-hexen-1-ol (40). Ethyltriphenylphoshonium bromide (6.8 g, 18.4 mmol) was suspended in 20 mL of anhydrous THF under nitrogen and KH (764 mg, 19.1 mmol) was added carefully via Gooch tubing. The reaction was brought to reflux for 1 h (to ensure complete ylide formation) and then cooled to 0 °C. 2-Methylbutyrolactol (**36**, 750 mg, 7.4 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stir for 12 h. The reaction was quenched with saturated aqueous NH_4Cl, the THF was removed, and the residue was acidified with 5% HCl. The product was extracted into ether, washed with water, dried ($MgSO_4$), filtered, and concentrated. Bulb-to-bulb distillation (bp 62–64 °C, 20 mmHg) afforded pure **40** (712 mg, 85%): 360-MHz ^{1}H NMR δ 0.95 (d, 3 H, J = 7.5 Hz), 1.25 (br s, 1 H, OH), 1.45 (m, 2 H), 1.6 (d, 3 H, J = 6.0 Hz), 2.6 (m, 1 H), 3.6 (t, 2 H, J = 6.9 Hz), 5.15 (t, 1 H, J = 9.0 Hz), 5.4 (dt, 1 H, J = 9.0, 6.0 Hz).

3,4,5,6-Tetra-*O*-benzyl-1,2-dideoxy-D-gluc-1-enitol (44). A solution of **5** (1.0 g, 2.4 mmol) in 2 mL of dimethylformamide was treated with 184 mg of a 50% dispersion of NaH in oil (3.8 mmol). After 15 min, bubbling in the gray solution had ceased and 400 μL of benzyl chloride (3.4 mmol) was added. After 2 h, water was added and the product was extracted into ether, washed with water (3×), dried ($MgSO_4$), filtered, and concentrated. Compound **44** was purified on 140 g of silica gel (EtOAc/hexane, 1:9) to yield 1.0 g of an oil that was pure by TLC (82%): 90-MHz ^{1}H NMR δ 3.5–4.7 (m, 13 H), 5.1–5.4 (m, 2 H), 5.6–5.8 (m, 1 H), 7.3 (br s, 2 OH); CI-MS, m/e 509 (M + 1). Anal. Calcd for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13. Found: C, 79.48; H, 7.13.

Cyclization of 44 with NBS/Water.[16] A solution of 200 mg of **44** (0.394 mmol) in 1 mL of dried Me_2SO was treated with 28 μL of water and 140 mg of recrystallized NBS (0.8 mmol). After 2 h, water was added and the product was extracted into ether, washed three times with water, dried ($MgSO_4$), filtered, and concentrated. Purification on a 2000-μm preparative TLC plate (EtOAc/hexane, 14:86) gave a 13:87 mixture of **6a** and **6b** as

determined by 360-MHz ^{1}H NMR[4] (74%). Also, a 21% yield of benzyl alcohol was obtained from the preparative plate.

Cyclization of 44 with Bromine. A solution of 220 mg of **44** (0.43 mmol) in 2 mL of CCl_4 was treated with 25 μL of bromine (0.45 mmol). After 1 h, the solution was loaded onto a 2000-μm preparative TLC plate and eluted with EtOAc/hexane, 1:9. This resulted in 140 mg (65%) of pure **6a** and **6b** in a ratio of 10:90 (by 360-MHz ^{1}H NMR) and 45 mg (60%) of benzyl bromide.

Attempted Cyclization of 44 with Mercuric Acetate. A solution of 200 mg (0.394 mmol) of **44** in 4 mL of THF was treated with 200 mg of mercuric acetate (200 mg, 0.63 mmol) and 90 mg of $CaCO_3$. After refluxing for 16 h, very little change in the TLC of the solution had occurred; starting material was largely unchanged.

Attempted Cyclization of 44 with *N*-Bromosuccinimide. A solution of 100 mg (0.2 mmol) of **44** and 71 mg of freshly recrystallized NBS (0.4 mmol) in 10 mL of methylene chloride was heated at reflux. After 24 h, the predominant spot by TLC was still starting **44**.

3,4,6-Tri-*O*-benzyl-5-(dichlorobenzyl)-1,2-dideoxy-D-gluc-1-enitol (50). This material was prepared in the same manner as described for **44**, giving **50** (30% yield) after recrystallization from MeOH/H_2O (mp 69–79 °C): 90-MHz ^{1}H NMR δ 3.6–4.2 (m, 5 H), 4.2–4.9 (m, 8 H), 4.9–6.2 (m, 3 H), 6.9–7.3 (m, 18 H); fast atom bombardment (FAB-MS), *m/e* 577. Anal. Calcd for $C_{34}H_{34}Cl_2O_4$: C, 70.71; H, 5.93. Found: C, 70.01; H, 5.87.

Cyclization of 50 with Bromine. To a solution of **50** (20 mg, 0.035 mmol) in 0.5 mL of methylene chloride was added 2.2 μL of bromine (0.043 mmol) via syringe. After 10 min, the solution was loaded onto a 1000-μm preparative TLC plate and chromatographed with EtOAc/hexane (15/85) to give 16 mg (90% yield) of a 3.7:96.3 ratio of **6a**:**6b**.

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Registry No. 1, 57445-90-6; **5**, 102208-53-7; **6a**, 102208-56-0; **6b**, 102093-88-9; **7a**, 109065-80-7; **7b**, 109121-38-2; **8a**, 109065-81-8; **8b**, 109121-39-3; **9a**, 109065-82-9; **9b**, 109121-40-6; **10a**, 109065-83-0; **10b**, 109065-84-1; **12a**, 102208-55-9; **12b**, 102208-54-8; **13**, 80959-53-1; **14b**, 100590-12-3; **15b**, 109066-14-0; **16a**, 109066-00-4; **16b**, 109066-01-5; **17**, 109065-85-2; **18**, 109066-05-9; **19**, 109066-06-0; **20b**, 109065-92-1; **21b**, 109066-15-1; **22a**, 109066-02-6; **22b**, 109066-03-7; **23**, 109065-86-3; **24a**, 109065-93-2; **25a**, 109066-16-2; **26a**, 109066-04-8; **27**, 109065-87-4; **28**, 88406-01-3; **29**, 109121-41-7; **30** (isomer 1), 109066-07-1; **30** (isomer 2), 109121-42-8; **31**, 109066-08-2; **32a**, 109066-09-3; **32b**, 109121-43-9; **33a**, 109066-17-3; **33b**, 109121-45-1; **34a**, 109066-10-6; **34b**, 109121-44-0; **35**, 51174-44-8; *cis*-**36**, 109066-11-7; *trans*-**36**, 109066-12-8; **37a**, 109065-89-6; **37b**, 109065-88-5; **38a**, 109065-94-3; **38b**, 109065-95-4; **39a**, 109065-97-6; **39b**, 109065-98-7; **40**, 109065-91-0; **41a**, 109065-90-9; **42a**, 109065-96-5; **43a**, 109065-99-8; **44**, 102093-89-0; **50**, 109066-13-9; acetic acid, 64-19-7; acrolein, 107-02-8; 3-hydroxypropanenitrile, 109-78-4; 3-(methoxymethoxy)propanenitrile, 52406-33-4; vinylmagnesium bromide, 1826-67-1; (trimethylsilyl)acetylene, 1066-54-2; methyltriphenylphosphonium bromide, 1779-49-3; ethyltriphenylphosphonium bromide, 1530-32-1.

Uncharged Stereoregular Nucleic Acid Analogues. 1. Synthesis of a Cytosine-Containing Oligomer with Carbamate Internucleoside Linkages

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The uncharged, stereoregular nucleic acid analogue **18**, with carbamate internucleoside linkages, was prepared. A block synthesis scheme was used to prepare **18**, using the dimer **11** as the basic unit. The oligomer **18** was shown to strongly bind to p(dG_6) and poly(G).

A variety of nucleic acid analogues containing wholly or substantially uncharged backbones have been shown to enter living animal cells and to be resistant to nucleolytic degradation therein.[1-3] Paul Miller has shown that one class of uncharged nucleic acid analogues significantly inhibit the intracellular activity of genetic sequences to which the analogues are complementary.[3] These results suggest that uncharged nucleic acid analogues may be of value for the study of genetic mechanisms, for the treatment of viral diseases, and possibly as anticancer agents. Further, suitable nucleic acid analogues lacking charges on their backbones can be exploited to considerable advantage in a diagnostic system having high specificity and sensitivity.

For analogues of nucleic acids to be suitable for such applications as mentioned above, we postulated that certain structural criteria are required to effect efficient hybridization of the analogue with its targeted genetic sequence. These criteria include a stereoregular backbone (required for a homogeneous binding constant between the analogue and its complementary genetic sequence), proper spacing and orientation of the component bases for hybridization, and analogue affinities for targeted genetic sequences that are sufficient to effect the desired biological or physical action. We believe certain internucleoside linkages containing carbonyl moieties, particularly carbamates **4**, satisfy the above criteria and should constitute

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