column chromatography with hexane as eluant, giving 100 mg of clear oil (99 % yield): ^{1}H NMR ($CDCl_3$) δ 1.90–1.60 (m, 13 H), 1.47 (d, J = 11.7 Hz, 2 H), 1.11 (d, J = 10.4 Hz, 1 H), 0.86 (d, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 51.7 (d), 39.5 (t), 38.5 (t), 31.9 (t), 29.4 (d), 28.1 (d), 27.9 (d), 27.1 (d), 20.9 (q).

Dihydroaromatic Trapping of B$^{\bullet+}$ from Biadamantylidene (1) (Table II) and from Dioxetane 2. The trapping experiments were performed by adding concentrated solutions of $9^{\bullet+}$ in CH_2Cl_2 (0.02 M) dropwise to solutions of 1 or 2 in oxygen-saturated CH_2Cl_2 at −78 °C containing 5.0 equiv of 11 or 12. The reactions were quenched with Et_3N, warmed to room temperature, and evaporated. The crude materials were tritrated thoroughly with hot pentane, filtered, and evaporated. Analysis of the product mixtures by ^{1}H NMR was facilitated by comparison to spectra of known materials, and product ratios were measured by integration.

Acknowledgment. We thank the donors of Petroleum Research Fund, administered by the American Chemical Society, for partial financial support of this work, and Amoco Oil Co. for a fellowship to M.F.T.

Registry No. 1, 30541-56-1; 2, 35544-39-9; 7, 73321-28-5; 8, 73679-39-7; 11, 628-41-1; 12, 613-31-0; 13, 53862-33-2; 15, 15914-95-1; 16, 20441-18-3; 19, 29186-07-0.

Halogenation of 1,5-Anhydrohex-1-enitols (Glycals). Influence of the C-6 Substituent[1]

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Received February 12, 1986

The stereochemistry of addition of chlorine and bromine to 3,4-di-*O*-acetyl-L-rhamnal (1), 3,4-di-*O*-acetyl-L-fucal (2), and other glycals has been investigated. Variations in the reaction conditions lead to dihalides having different configurations at C-1 and C-2. Chlorination in nonpolar solvents appears to proceed via stabilized syn ion pairs, selectively affording cis addition products. The product distribution from the bromination reactions suggests the participation of different ionic intermediates. In both chlorination and bromination, the product distribution is affected by the polarity of the solvent, the structure of the enol ether, and the nature of the halogen. The product distribution in the bromination reactions depends on the electron-withdrawing or -donating effect of the substituent at C-6. This result was interpreted in terms of the effect that the 6-substituent may exert on a nonbonding electron pair of the ring oxygen atom, affecting the stabilization of the carbocation at the anomeric center. The C-6 substituent exerts no significant effect on the chlorination reaction. Changes in the configuration of the substituents of the glycal may also modify the stereochemical course of the reaction. Thus, a change in the orientation of the acetoxy group at C-4 from equatorial (1) to axial (2) influenced the side of attack by halogen upon the double bond, leading to different ratios of cis and trans addition products from 1 and 2.

The addition of halogens to cyclic enol ethers was earlier investigated by Lemieux and Fraser-Reid,[2,3] who proposed a general mechanism involving polar attack of halogen on the double bond, resulting in formation of carbonium ions, which upon attack by halide ion lead principally to products of thermodynamic control. However, Igarashi et al.[4] established that product formation is under kinetic not thermodynamic control and that the stereoselectivity of the addition is dependent on the polarity of the solvent. Boullanger and Descotes[5] studied comparatively the addition of chlorine and bromine to acetylated and benzylated derivatives of D-glucal. The product distribution was explained on the basis of Igarashi's mechanism and a quantitative correlation established between the polarity of the solvents and the stereospecificity of the addition of chlorine. A general mechanism of chlorination of 3,4-dihydro-2*H*-pyran in several solvents, consistent with the observed solvent dependency, was proposed by Stone and Daves.[6]

In the present work, chlorination and bromination of 3,4-di-*O*-acetyl-L-rhamnal (1), 3,4-di-*O*-acetyl-L-fucal (2), and other substituted glycals has been studied as part of a synthetic program targeted toward 2′-halo derivatives of anthracycline antibiotics.[7] The 1,2-dihalides constitute useful synthetic intermediates or starting materials.[8] Product distribution obtained by halogenation of glycals under controlled conditions is discussed in terms of solvent polarity, the nature of the halogen, and the influence of steric effects in the alkene. The factors discussed here as being responsible for the product distribution during the halogenation reactions may help to explain the course of other electrophilic additions to alkenes.

Results and Discussion

Structural Assignments for the Products. Halogenation of the glycal derivatives was performed in the dark at 0 °C. The composition of the mixtures was determined by ^{1}H NMR spectroscopy and, in some instances, confirmed by analytical LC. The main products formed by the addition of chlorine or bromine (Scheme I) to the double bond of 3,4-di-*O*-acetyl-L-rhamnal (1) and 3,4-di-*O*-acetyl-L-fucal (2) were isolated by column chromatography and the minor ones purified by semipreparative LC. The structures of the resultant 2,6-dideoxy-2-haloglycosyl halides were established on the basis of their ^{1}H NMR spectra and optical rotations. It was carefully verified that

(1) Supported, in part, by Grant No. GM-11976 from the National Institute of General Medical Sciences. For a preliminary report, see: Horton, D.; Priebe, W.; Varela, O. *Abstr. Pap.-Am. Chem. Soc.* **1982**, *184th*, CARB-33.

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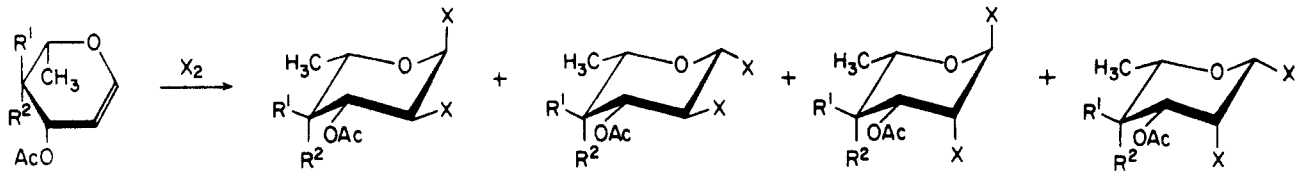
0022-3263/86/1951-3479$01.50/0

Scheme I



	α-L-*gluco*	β-L-*gluco*	α-L-*manno*	β-L-*manno*
1, R^1 = OAc; R^2 = H				
X = Cl	**1a**	**1b**	**1c**	**1d**
X = Br	**1e**		**1f**	
2, R^1 = H; R^2 = OAc	α-L-*galacto*	β-L-*galacto*	α-L-*talo*	β-L-*talo*
X = Cl	**2a**	**2b**	**2c**	**2d**
X = Br	**2e**		**2f**	

no anomerization or other isomerization of the products took place during the isolation procedures.

Derivatives of L-rhamnal diacetate (**1a**, **1b**, **1c**, **1d**, **1e**, and **1f**) showed large $J_{4,5}$ values (9.5–10.0 Hz), indicating the trans disposition of these protons in the favored $^1C_4$(L) conformation. A small value of $J_{2,3}$ (3.3–4.5 Hz) indicates a cis-equatorial–axial relationship for these two protons and thus the L-*manno* configuration for **1c**, **1d**, and **1f**; larger values of $J_{2,3}$ (~10.0 Hz) denote a trans-diaxial disposition for H-2 and H-3 and, therefore, the L-*gluco* configuration for **1a**, **1b**, and **1e**. Thus, from the four isomers obtained by chlorination of L-rhamnal diacetate (**1**), two of them (**1a** and **1b**) have the L-*gluco* configuration and the two others the L-*manno* (**1c** and **1d**).

The configuration at the anomeric center was established by ^{1}H NMR by considering a combination of the following factors: (a) the $J_{1,2}$ coupling constant; (b) the chemical shift of H-1; (c) the variation of chemical shift of H-3 and H-5; and (d) long-range coupling constants. Optical rotation was used to confirm proposed assignments. The orientation of H-1 and H-2 in **1b** was readily established as trans-diaxial because of the large value of $J_{1,2}$ (9.1 Hz), demonstrating that compound **1b** is the β anomer ($[\alpha]_D$ −45°) of 3,4-di-*O*-acetyl-2-chloro-2,6-dideoxy-L-glucopyranosyl chloride and the other *gluco* isomer (**1a**) is the α anomer ($[\alpha]^{20}_D$ −219°). The chemical shift of H-1 (6.08 ppm for **1a** and 5.26 for **1b**) confirmed these assignments, because equatorial protons at C-1 are generally shifted to lower field than axial ones.[9,10] Furthermore, the difference in chemical shift of H-3 ($\Delta\delta_{H-3^{a-b}}$) and H-5 ($\Delta\delta_{H-5^{a-b}}$) between **1a** and **1b** is, respectively, 0.27 and 0.58 ppm, indicating a downfield shift of H-3 and H-5 in **1a** because of the parallel 1,3-interaction with axial chlorine at C-1. Finally it was observed that all α anomers show a long-range $J_{1,5}$ coupling constant of 0.5–0.8 Hz (in some instances also $J_{1,3}$ of 0.5 Hz was observed); this last finding constitutes one more line of proof for the assigned configuration at the anomeric center. Compound **1a** showed $J_{1,5}$ = 0.7 Hz and $J_{1,3}$ = 0.5 Hz.

The $J_{1,2}$ coupling constants for the L-*manno* anomers **1c** and **1d** are very similar and give no information about the configuration at C-1. However, on the basis of the difference of chemical shifts of H-1, compound **1c** ($[\alpha]_D$ −78°) was established as the α anomer (H-1, 6.13 ppm) of 3,4-di-*O*-acetyl-2-chloro-2,6-dideoxy-L-mannopyranosyl chloride and **1d** ($[\alpha]_D$ +58°) as the β anomer (H-1, 5.57 ppm). In support of this, the $\Delta\delta_{H-5^{c-d}}$ value of 0.57 ppm indicates that isomer **1c**, exhibiting a downfield shift, is the α anomer. This conclusion was additionally confirmed by the long-range coupling constants $J_{1,5}$ (0.7 Hz) and $J_{1,3}$ (0.5 Hz). The specific rotations of −78° for **1c** and +58° for **1d** provide classical confirmation of these anomeric assignments.

In the dihalo derivatives **2a**, **2b**, **2c**, and **2d**, the $^1C_4$(L) conformation is also to be expected,[11] and this was confirmed by the large $J_{2,3}$ (10.7) values for **2a** and **2b**. The trans-diaxial orientation of H-2 and H-3 is only possible for the *galacto* isomers in the anticipated $^1C_4$(L) conformation. The configuration at C-1 of compound **2b** was established on the basis of the large $J_{1,2}$ value (9.1 Hz), which indicates that **2b** ($[\alpha]_D$ −32°) is the β anomer of 3,4-di-*O*-acetyl-2-chloro-2,6-dideoxy-L-galactopyranosyl chloride. The smaller value of $J_{1,2}$ (3.7 Hz) and the higher chemical shift for H-1 and H-5 ($\Delta\delta_{H-5^{a-b}}$ 0.59 Hz) than in compound **2b** support the assignment of **2a** ($[\alpha]_D$ −230°) as the α anomer. Furthermore, compound **2a**, as for the other α anomers, shows long-range coupling between H-1 and H-5 ($J_{1,5}$ = 0.7 Hz). The similar values of $J_{1,2}$ for **2c** and **2d** do not permit configurational assignment at the anomeric center, but the chemical shifts of H-1 (6.30 ppm for **2c** and 5.55 for **2d**) and H-5 ($\Delta\delta_{H-5^{c-d}}$ = 0.58 ppm) indicate compound **2c** to be the α anomer of 3,4-di-*O*-acetyl-2-chloro-2,6-dideoxy-L-talopyranosyl chloride, and **2d** ($[\alpha]_D$ +4°) the β anomer. The $J_{1,5}$ coupling of 0.8 Hz in **2c** supports these assignments.

Bromination of L-rhamnal diacetate (**1**) afforded two compounds, **1e** and **1f**. The $J_{2,3}$ coupling constant of 10.7 Hz for **1e** indicates the L-*gluco* configuration. The value of $J_{2,3}$ (3.8 Hz) for **1f** dictates a cis-equatorial–axial orientation for H-2 and H-3 and the L-*manno* configuration. The L-*gluco* isomer **1e** ($[\alpha]_D$ −283°) is the α anomer because the $J_{1,2}$ value of 3.6 Hz demonstrates a cis relationship between H-1 and H-2; the β anomer should display a much larger coupling constant, similar to that in **1b** (9.1 Hz). The α configuration assigned at C-1 for **1e** was confirmed by the chemical shift of H-1 (6.39 ppm), which shows downfield shielding of 0.31 ppm because of the effect of bromine, and by the chemical shift of H-5 in **1e**, which is very similar to that of **1a** (4.30 and 4.29 ppm, respectively). The chemical shift of H-1 in **1f**, downfield by 0.47 ppm with respect to H-1 of **1c**, suggests the α configuration for **1f** ($[\alpha]_D$ −125°). Both compounds (**1c** and **1f**) have identical chemical shifts for H-5 (4.21 ppm). Finally, the dibromides **1e** and **1f** show long-range $J_{1,5}$ coupling constants of 0.5 and 0.7 Hz. These couplings are observed only for the α anomers of the 1,2-dichlorides, and this observation constitutes yet one more proof for the anomeric assignments.

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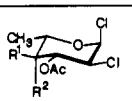
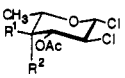
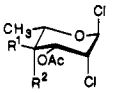
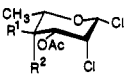
Table I. Chemical Shifts (δ, ppm) and Coupling Constants (Hz) for the Dihalides 1a–d, 2a–d, 1e, 1f, 2e, and 2f

	H-1		H-2		H-3		H-4		H-5			
compd	$J_{1,2}$	$J_{1,5}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{1,3}$	$J_{4,5}$	$J_{1,4}$	$J_{5,6}$		H-6	CH_3CO
1a	6.08		4.13		5.47		4.82		4.29		1.24	2.07, 2.05
	3.7	0.7	10.5		9.3	0.5	10.0		6.2			
1b	5.26		3.91		5.20		4.83		3.71		1.29	2.09, 2.04
	9.1		10.1		9.4		9.8		6.2			
1c	6.13		4.64		5.56		5.25		4.21		1.28	2.10, 2.09
	1.5	0.7	3.8		9.9	0.5	9.8		6.3			
1d	5.57		4.57		5.01		5.21		3.64		1.31	2.10, 2.06
	1.2		3.6		9.8		9.5		6.2			
2a	6.19		4.41		5.39		5.33		4.53		1.20	2.16, 2.05
	3.7	0.7	10.7		3.2	0.5	1.2	0.4	6.5			
2b	5.28		4.09		5.05		5.25		3.94		1.26	2.19, 2.07
	9.1		10.7		3.3		1.1		6.4			
2c	6.30		4.40		5.62		5.27		4.49		1.27	2.17, 2.09
	1.1	0.8	4.4	1.1	3.6	0.5	1.8	0.4	6.5			
2d	5.55		4.34			5.14—5.21			3.91		1.30	2.10, 2.04
	1.6		3.3	1.6			1.5		6.4			
1e	6.39		4.11		5.51		4.83		4.30		1.25	2.07, 2.06
	3.6	0.5	10.7		9.2	0.4	9.9		6.2			
1f	6.60		4.87		5.45		5.31		4.21		1.31	2.10, 2.09
	1.3	0.7	3.8		9.8	0.5	9.6		6.3			
2e	6.52		4.37		5.41		5.31		4.53		1.20	2.16, 2.05
	3.4	0.7	11.2		3.2	0.4	1.3	0.4	6.5			
2f	6.80		4.65		5.59		5.32		4.47		1.28	2.18, 2.09
	1.0	0.7	4.5	1.0	3.6	0.5	1.7	0.4	6.5			

Table II. Product Distribution in the Chlorination of 1 and 2 in Various Solvents[a]

							
		α-L-*gluco*	β-L-*gluco*	α-L-*manno*	β-L-*manno*		
solvent	b	**1a**	**1b**	**1c**	**1d**	cis:trans	gluco:manno
CCl_4	2.23	76	3	4	17	93:7	79:21
$(CH_2Cl)_2$	10.37	55	10	14	21	76:24	65:35
CH_3NO_2	38.57	35	23	24	18	53:47	58:42
		α-L-*galacto* **2a**	β-L-*galacto* **2b**	α-L-*talo* **2c**	β-L-*talo* **2d**	cis:trans	galacto:talo
CCl_4	2.23	65	17	6	12	77:23	82:18
$(CH_2Cl)_2$	10.37	55	30	10	5	60:40	85:15
CH_3NO_2	38.57	53	35	12	<1	53:47	88:12

[a] Determined from integrated ^1H NMR spectra or by analytical liquid chromatography. [b] Dielectric constant.

A similar situation exists with the compounds **2e** and **2f** obtained by bromination of 3,4-di-*O*-acetyl-L-fucal (**2**). The $J_{2,3}$ values of 11.2 Hz for **2e** and 4.5 Hz for **2f** indicate respectively the axial and equatorial orientations of the proton at C-2. In the L-*galacto* isomer (**2e**), the magnitude of $J_{1,2}$ (3.4 Hz) is very close to that observed for the chloro analogue **2a**. The difference in chemical shift of H-1 is 0.33 ppm, a magnitude similar to the difference between dichlorides **1a** and **1e** (0.31 ppm). The absence of differences in the chemical shift of H-5 for **2a** and **2e** (both 4.53 ppm) and the long-range $J_{1,5}$ coupling (0.7 Hz) supported additionally the assigned α-L-*galacto* configuration for **2e** ($[\alpha]_D$ −224°). Similar values for differences in the chemical shift of H-1 of **2c** vs. **2f** ($\Delta\delta_{H\text{-}1^{t-e}}$ = 0.50 ppm) and for **1c** vs. **1f** ($\Delta\delta_{H\text{-}1^{t-e}}$ = 0.47 ppm) suggest that the configuration at the anomeric center of both compounds is identical. Furthermore, as with other α anomers of the 1,2-dihalide series, a long-range $J_{1,5}$ coupling constant of 0.7 Hz was observed for **2f** ($[\alpha]_D$ −77°), confirming the assigned configuration at C-1. An additional important observation was that compounds having the α-L-*galacto* (**2a**, **2e**) and α-L-*talo* (**2c**, **2f**) configuration showed H-1–H-4 long-range coupling ($J_{1,4}$ = ~0.4 Hz). Finally, the structure of the L-*talo* derivatives was confirmed by the observed H-2–H-4 long-range coupling of ($J_{2,4}$ = 1.0–1.6 Hz) characteristic of the "W" disposition for these protons.

Results of Halogenation. Chlorination. Chlorination of L-rhamnal diacetate (**1**) in nonpolar solvents is very selective; in carbon tetrachloride the ratio of cis addition (**1a**, **1d**) to trans addition (**1b**, **1c**) products was 93:7. The compound having the α-L-*gluco* configuration (**1a**) is the main product (76%). An increase in the solvent polarity leads to a higher proportion of trans addition products (from 3 to 23% for **1b**, and from 4 to 24% for **1c**; Table II). Similar changes in product distribution were observed by Igarashi and co-workers[4] in the chlorination of D-glucal triacetate.

Addition of halogen to double bonds is expected to occur by a bimolecular process, with the approach of a halogen molecule perpendicularly to the π system of the enol ether[6,12,13] from above or below the plane of the molecule leading to charge-transfer complexes that may rearrange, in the rate-limiting step,[14,15] to intermediate ions (syn ion pairs, halonium ions, or open carbocations) which, according to their relative stabilities, control the stereochemical course of the reaction.

There are several examples in the literature showing that the presence of substituents which stabilize a positive charge favor the formation of open carbonium ions.[16-18]

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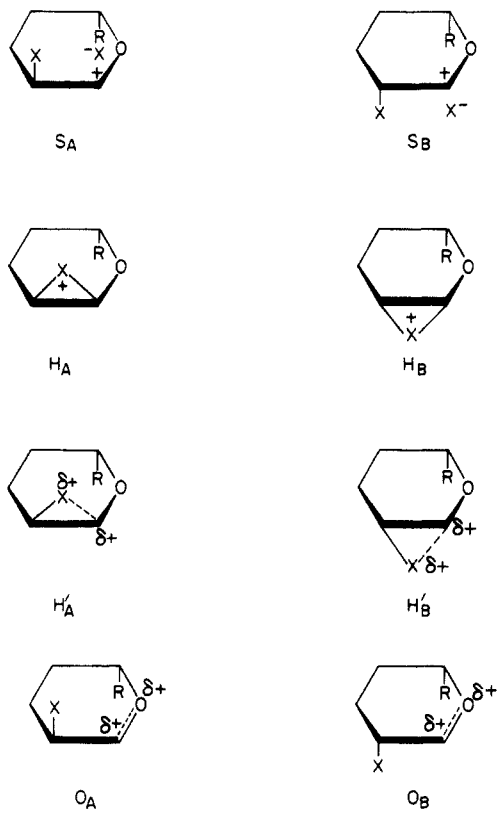
Chart I



Such stabilization in enol ethers is provided by electron donation from the ring oxygen atom.[19]

In solvents of weak solvating ability (nonpolar solvents), the stabilized syn ion pairs (SA and SB) can collapse directly to the *cis*-dichlorides **1a** and **1d**. The fact that the α-L-*gluco* isomer (**1a**) preponderates over the β-L-*manno* product (**1d**) may be attributed to the higher stability[4] of the syn ion pair SA as compared with SB. It is well-known that solvents play a large effect in reactions involving dipolar transition states,[20] and in the case of halogenation reactions they may exert an important role in solvating ionic species.[5] Thus, for chlorination in more polar solvents where separation of charges is favored, the possibility of forming oxonium ions OA and OB is increased, leading to a higher proportion of products **1b** and **1c**.

Chlorination of 3,4-di-*O*-acetyl-L-fucal (**2**) was also selective in nonpolar solvents; as with the chlorination of the rhamnal analogue **1**, higher proportions of the trans addition products were observed in solvents of higher polarity. However, an important difference was noted: the total proportion of compounds having the L-*galacto* configuration (**2a** + **2b**), formed during the addition of chlorine to **2**, increases only slightly (from 82 to 88%) in more polar solvents, whereas the proportion of L-*gluco* anomers (**1a** + **1b**) formed by chlorination of **1** decreases significantly (from 79 to 58%), indicating that the addition of chlorine to the double bond of **2** occurs preferentially from above the molecular plane, regardless of the solvent polarity. Compounds **1** and **2** exist mainly in the $^5H_4$(L) conformation[21] (Scheme I), as do other configurationally related glycals.[22,23] In the $^5H_4$(L) conformation, all of the substituents in **1** have quasiequatorial orientations, but in **2**, the acetoxyl group at C-4 is in quasiaxial disposition, and this should decrease the attack of chlorine from below the molecular plane, by avoidance of parallel interactions between chlorine and the 4-acetoxyl group. A similar effect of the orientation of substituents on the stereochemistry of halogenation in nonpolar solvents was observed with phenyl- and alkyl-substituted 2,3-anhydrofuran derivatives.[24]

Increasing the solvent polarity increases the proportion of β-L-*galacto* (**2b**) and α-L-*talo* (**2c**) isomers formed. The ratio of *cis*- (**2a**, **2d**) to *trans*-dihalides (**2b**, **2c**) changes with the polarity of the solvent from 77:23 (carbon tetrachloride) to 53:47 (nitromethane, a ratio identical with that observed for the L-rhamnal derivative **1**), suggesting again that, in both instances, chlorination in polar solvents proceeds through the stabilized carbocations OA and OB.

Bromination. Bromination of L-rhamnal diacetate (**1**) gave two products, having the α-L-*gluco* (**1e**) and α-L-*manno* (**1f**) configurations. As in the chlorination reaction, the proportion of α-L-*gluco* isomer **1e** decreases with polarity of the solvent from 64 (carbon tetrachloride) to 45% (nitromethane).

Bromination of L-fucal diacetate (**2**) gave mainly the α-L-*galacto* (**2e**) and α-L-*talo* (**2f**) dihalides, with traces of the β-L-*galacto* isomer, detectable only by ^{1}H NMR (<5% in all instances). As in the chlorination reaction, an increase in solvent polarity in the bromination of **2** causes an increase in the proportion of the L-*galacto* isomer (**2e**); however, the relationship is not simple. The α isomers were the primary products (95–100%) in the bromination of **1** and **2**.

Bromination of a double bond may proceed through the formation of strongly bridged "bromonium" ions HA and HB,[25] whose existence was proposed a long time ago,[26] and later proved by NMR spectroscopy[27] and by isolation[28] of a bromonium ion as its tribromide salt. However, other intermediates whose formation is dependent on reaction conditions and the structure of the alkene are possible, such as weakly bridged bromonium ions H'A and H'B, or stabilized carbocations OA, and OB. The product distribution should largely depend on the relative stabilities of these ionic intermediates. The inductive effect of the substituent at C-6 of the glycal may effectively control the charge distribution in the intermediate ions and therefore the products formed.

A strongly electron-withdrawing substituent at C-6, which would disfavor the formation of oxonium ions (OA, OB), would cause stronger interactions between bromine at C-2 with the positive charge at C-1 ("more-symmetrical bromonium ions", HA and HB). On the other hand, a weak inductive effect I(−) or I(+) of the group at C-6 would, by increasing the availability of electrons from the ring oxygen atom, decrease the interactions between the bromine atom at C-2 and the carbocation ion at C-1.

Changes in the reaction conditions, for instance an increase in the solvent polarity, may additionally decrease the interaction between bromine at C-2 and C-1, leading to asymmetrically bridged bromonium ions (H'A and H'B).

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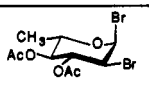
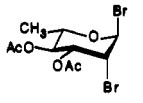
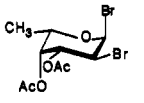
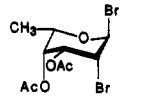
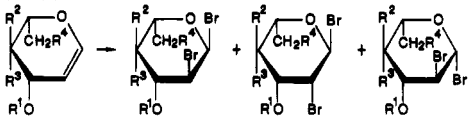
Table III. Product Distribution in the Bromination of 1 and 2 in Various Solvents[a]

solvent	b	 α-L-*gluco* 1e	 α-L-*manno* 1f	 α-L-*galacto* 2e	 α-L-*talo* 2f
CCl_4	2.23	64	36	60	40
Et_2O	4.22	60	40	71	29
$(CH_2Cl)_2$	10.37	57	43	78	22
CH_3NO_2	38.57	45	55	66	34

[a,b] See Table II.

Table IV. Product Distribution in the Bromination of Different C-6-Substituted Glycals in Carbon Tetrachloride[a]


α-cis (e) (α-L-*gluco*) α-trans (f) (α-L-*manno*) β-trans (g) (β-L-*gluco*)

3,[b] R^1 = Ac; R^2,R^4 = OAc; R^3 = H	8	62	30
4, R^1 = X;[c] R^2,R^4 = OX;[c] R^3 = H	trace	70	30
5,[d] R^1 = Y;[e] R^2,R^4 = OY;[e] R^3 = H	69	31	
1, R^1 = Ac; R^2 = OAc; R^3,R^4 = H	64 (α-L-*galacto*)	36 (α-L-*talo*)	(β-L-*galacto*)
6, R^1 = Ac; R^2 = H; R^3,R^4 = OAc	16	56	28
2, R^1 = Ac; R^2,R^4 = H; R^3 = OAc	60	40	

[a] The formulas depicted are the L enantiomers; compounds **3**, **4**, **5**, and **6** were actually the D enantiomers. [b] The values were for an initial glycal concentration of 0.2 M; for a more dilute solution (0.05 M), the ratio of products was[5] 7:67:26. [c] X = *p*-nitrobenzoyl. [d] See ref 5. [e] Y = benzyl.

This approach was used to rationalize our results on the bromination of L-rhamnal (**1**) and L-fucal (**2**) as well as other bromination reactions reported in the literature. Boullanger and Descotes[5] observed that bromination of 3,4,6-tri-*O*-benzyl-D-glucal (**5**, Table IV) gave exclusively two 1,2-dibromides having the α-D-*gluco* (**5e**, 69%) and α-D-*manno* (**5f**, 31%) configurations, in contrast to the results of bromination of 3,4,6-tri-*O*-acetyl-D-glucal (**3**), where the composition of the mixture was 8% α-D-*gluco* (**3e**), 30% β-D-*gluco* (**3g**), and 62% α-D-*manno* (**3f**). The higher proportion of the α-D-*gluco* isomer (**5e**) in the bromination of the benzyl ether **5** was attributed by these authors[5] to the bulkiness of the substituent at C-6. In order to confirm or reject the hypothesis of the existence of this proposed steric effect, we brominated 3,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucal (**4**). The bulkiness of both types of substituent is comparable, but the *p*-nitrobenzoyl group has a stronger electron-withdrawing effect than the benzyl group. Bromination of **4** gave only traces of the α-D-*gluco* isomer. The main product, as in the bromination of the glycal **3**, was compound **4f** (70%) having the α-D-*manno* configuration. The overall results were very close to those for bromination of tri-*O*-acetyl-D-galactal (**6**), indicating that electronic effects rather than purely steric effects of the C-6 substituent are responsible for the product distribution during bromination of differently substituted glycals. Thus, compounds **3**, **4**, and **6** (which have electron-withdrawing substituents at C-6) gave ~90% of trans addition products. This result may be explained by the formation of bridged bromonium ions (type HA or HB) that induce the attack of bromide from the opposite side (trans opening), affording β-trans (β-*gluco*) and α-trans (α-*manno*) products. The approach of bromine from below the molecular plane will lead to an intermediate energetically more favorable than when the attack is from above the plane of the molecule, for the same reasons as those involved in the chlorination reactions[4] for which the preponderance of α-D-*manno* isomers (**3f**, **4f**, and **6f**) over β-D-*gluco* (**3g**, **4g**, and **6g**) is to be expected.

The situation is different in the case of glycals **1**, **2**, and **5**, which have groups at C-5 of low inductive effect,[29] which allow the electrons of the ring oxygen atom to participate in the stabilization of the positive charge at C-1, leading to oxonium ions and decreasing the tendency of bromine at C-2 to form bromonium ions. In this instance, the attack of bromine from above the molecular plane will lead to the syn ion pair SA, which, as in the case of chlorine addition, may readily collapse to the α-cis isomers (**1e**, **2e**, and **5e**).

The approach of bromine from below the plane of the molecule could afford the syn ion pair SB; however, its conversion into the β-cis-dihalide not only opposes the driving force of the anomeric effect but also involves the attack of bromine from a more-hindered side. So, the alternative route, with trans-axial approach[14,30] to α-trans products (**1f**, **2f**, and **5f**) is to be expected. Furthermore, when brominations are performed in more polar solvents, the formation of oxonium ions (OA, OB) should be favored. The attack on bromine to OB is expected to be favorable[14,15,30] as compared with attack on OA, and when the polarity of the solvents is higher, the bromination reaction may proceed through oxonium ions, leading to higher proportions of α-trans addition product.

Conclusions

The combined results of chlorination and bromination of the glycals studied allow us to conclude that the bromination reactions, depending on the stabilizing factors of the alkene, may proceed through syn ion pairs, differently distorted cyclic bromonium ions, or open oxocations. The course of the reaction is significantly influenced by the substituent at C-6. Strongly electron-withdrawing substituents decrease the ability of electrons of the ring oxygen atom to stabilize the positive charge at C-1, which,

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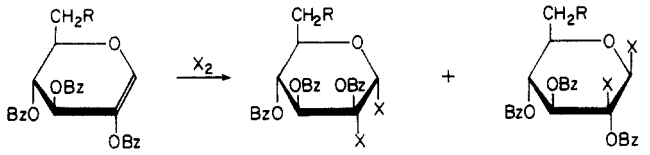
we presume, would lead to more-symmetrical bromonium ions of the type HA and HB and, in consequence, to trans addition products.

The effect of the substituents at C-6 seems to be unimportant in the chlorination reactions, unless the substituent at C-2 can participate in stabilization of the carbocation at C-1. Thus, in the addition of chlorine to 3,4-di-*O*-acetyl-L-rhamnal (1) and 3,4,6-tri-*O*-acetyl-D-glucal[4] (3), where the chlorine atom introduced at C-2 cannot stabilize the positive charge generated at C-1, a similar product distribution was observed.

On the other, the product distribution during the chlorination[31-33] of 2,3,4-tri-*O*-benzoyl-L-rhamnal (7) and 2,3,4,6-tetra-*O*-benzoyl-D-glucal (8) may be rationalized by considering the stabilization of the carbocation at C-1 by the 2-benzoate group;[31,33] the extent of this could also be affected by the nature of the substituent at C-6.

The addition of chlorine to compound 7 gave a product distribution similar to that observed for the chlorination of 1, 3, 4, and 5, suggesting a similar course of the reaction,



7[a] R = H; X = Cl
8 R = OBz; X = Cl

[a] D enantiomers are depicted; compound 7 and products obtained from it are actually the L enantiomers.

involving stabilized syn ion pair intermediates (SA, SB) that lead to the normal α-cis addition product, in preponderance over the β-*cis*-dihalide. However, the presence of a benzoate group at C-6 in compound 8, by decreasing the stabilization of the carbocation at C-1 by the electrons of the ring oxygen atom, will induce the participation of the 2-benzoate group, leading to the formation[31,33] of the stable benzo-oxonium ion, which undergoes trans-opening affording mainly the β-cis isomer.

Several other examples reported in the literature show the combined effect of the substituent at C-6 and the nature of the halogen introduced at C-2 during the addition of XF (X = Br or I) to glycals.[34]

Stereochemical factors in the alkene, such as the orientation of a substituent, may influence the mode of attack of the halogen to the double bond. Thus, the differently oriented acetoxy group in glycals 1 and 2 seems to affect the product distribution.

By considering the effects of substituents at C-6 on the stability of the intermediate ions formed during the addition of such electrophilic reagents as halogens, sulfenyl halides, mercury salts, and the like to alkenes, it is possible to rationalize the product distribution of these reactions.

Experimental Section

General Methods. 3,4-Di-*O*-acetyl-L-rhamnal (1) (Pfanstiehl Laboratories) was purified by column chromatography (5:1 hexane–ethyl acetate) before use. 3,4-Di-*O*-acetyl-L-fucal (2) was prepared by the procedure of Iselin and Reichstein,[35] mp 50 °C, $[\alpha]^{20}_D$ +9° (*c* 1.0, acetone), in accord with the literature. Solvents were dried and redistilled just prior to use. Melting points were determined in open glass capillaries by using a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 200-MHz and 50-MHz, respectively, with a Bruker WP-200 spectrometer by Dr. O. Mols and Dr. M. G. Schweitzer. The samples were dissolved in chloroform-*d* and the chemical shifts (ppm) refer to an internal standard of tetramethylsilane (δ = 0.00 ppm). Mass spectra were obtained by C. R. Weisenberger with an AEI MS9 double-focusing instrument equipped with direct-inlet probe. TLC was performed on precoated aluminum sheets (0.2 mm) and glass plates (0.25 mm) coated with silica gel 60F-254 (E. Merck, Darmstadt, GFR); components were detected by spraying the plates with 0.1 M ceric sulfate in 2 M sulfuric acid, with subsequent heating. Column chromatography was performed with silica gel 60 (230–400 mesh) (E. Merck, Darmstadt, GFR). High-pressure liquid chromatography (LC) was performed with a Waters apparatus equipped with a Model 6000A solvent-delivery system and Model 440 absorbance detector. Elemental analyses were determined by Dr. O. Mols.

Halogenation of Glycals. General Procedure for Data Recorded in Tables I–III. A solution of 0.2 mmol of the glycal derivative (1, 2, 3, 4, or 6) in the dry solvent (1 mL) was protected from light and cooled in an ice–water bath. Bromine was added dropwise, or chlorine was bubbled in, with stirring, until the color of excess halogen persisted. The solution was kept for 10 min at 0 °C and argon was then bubbled through it, to remove the excess of halogen. Highly volatile solvents were evaporated at ~40 °C by a stream of argon; less-volatile ones were removed under diminished pressure at the same temperature. Samples were then dried for 0.5 h under vacuum, at room temperature, and immediately analyzed by ^{1}H NMR spectroscopy, and, in most instances by analytical LC. The mixtures were composed exclusively of dihalides. It was verified by ^{1}H NMR spectroscopy that the preparatively isolated halides had not undergone anomerization or isomerization during the isolation procedure.

3,4-Di-*O*-acetyl-2-chloro-2,6-dideoxy-α-L-gluco- and -β-L-mannopyranosyl Chlorides (1a and 1b). 3,4-Di-*O*-acetyl-L-rhamnal (1, 3.0 g, 14 mmol) was dissolved in carbon tetrachloride (70 mL) and chlorine was bubbled through the solution (at 0 °C) until a slight yellow color persisted. The mixture was stirred for 10 min in a ice–water bath and the solvent was evaporated at 40 °C under diminished pressure to afford a crystalline product. TLC examination of the solid showed it to contain two main components (R_f 0.42 and 0.34; 2:1 hexane–acetone). The mixture was resolved by column chromatography on silica gel (180 g), using 6:1 hexane–acetone as eluant. The faster moving component, identified as the α-L-*gluco* isomer (**1a**), was isolated crystalline. Recrystallization from ether–hexane yielded 1.80 g (45%) of **1a**: mp 135–136 °C; $[\alpha]^{20}_D$ −219° (*c* 1.2, dichloromethane); IR (Nujol) 1755 (C=O), 735 (C—Cl) cm^{-1}; ^{13}C NMR δ 169.9 (C=O), 92.7 (C-1), 73.7 (C-4), 71.4 (C-3), 69.0 (C-5), 58.2 (C-2), 20.4 (OAc), and 16.9 (C-6).

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.12; H, 4.95; *m/z* (M^+ − Cl) 249.052968. Found: C, 42.07; H, 4.97; *m/z* 249.053660.

The slower moving component (β-L-*manno* isomer, **1d**) was recrystallized from ether–hexane: yield 0.41 g (10%); mp 146–148 °C; $[\alpha]^{20}_D$ +58.3° (*c* 0.4, dichloromethane); IR (Nujol) 1750 (C=O), 725 (C—Cl) cm^{-1}; ^{13}C NMR δ 170.1, 169.4 (C=O), 86.1 (C-1), 75.3 (C-5), 72.2, 69.3 (C-3, C-4), 62.5 (C-2), 20.5 (OAc), and 17.3 (C-6).

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.12; H, 4.95; *m/z* (M^+ − Cl) 249.052968. Found: C, 41.78; H, 4.96; *m/z* 249.053660.

3,4-Di-*O*-acetyl-2-chloro-2,6-dideoxy-α-L-mannopyranosyl Chloride (1c). Through a solution of 3,4-di-*O*-acetyl-L-rhamnal (1, 0.64 g, 3 mmol) in carbon tetrachloride (25 mL) was bubbled a continuous stream of dry argon for 15 min. The solution was protected from light, and iodobenzene dichloride[36] (0.86 g, 3.1 mmol) was added. Argon was bubbled for 5 more min and the suspension was vigorously stirred under argon while being irradiated by a 300-W incandescent light bulb.[37] After 15 min, no starting material was detected by TLC. The mixture was diluted with carbon tetrachloride, washed with 5% sodium thiosulfate and water, dried over magnesium sulfate, and evaporated. The

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residue was purified on a short column (15 × 3 cm), which was developed with hexane (to remove iodobenzene) and then with 8:1 hexane–ethyl acetate. The syrup thus obtained (0.36 g, 42%), which showed a single spot in TLC (R_f 0.66, 3:1 toluene–acetone), crystallized on storage (1 week at −14 °C) as colorless needles; mp 71–72 °C; $[\alpha]^{23}_D$ −78° (c 1.1, dichloromethane); IR (Nujol) 1755 (C=O), 735 (C—Cl) cm^{-1}; ^{13}C NMR δ 169.9 (C=O), 91.4 (C-1), 70.0 (C-3), 69.8 (C-4), 68.6 (C-5), 60.3 (C-2), 20.5 (OAc), and 17.0 (C-6).

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.12; H, 4.95; m/z (M^+ − Cl$^·$) 249.052968. Found: C, 42.33; H, 5.11; m/z 249.053660.

3,4-Di-*O*-acetyl-2-chloro-2,6-dideoxy-β-L-glucopyranosyl Chloride (1b). Compound **1** (0.081 g, 0.38 mmol) was chlorinated in nitromethane (2 mL) under the conditions described for the preparation of **1a** and **1d**. The syrup obtained after evaporation of the solvent was purified by LC (μPorasil column, 0.78 × 30 cm, at a flow rate of 3.0 mL/min) with 8:1 hexane–ethyl acetate as solvent. The fractions containing the compound having t_R 6.6 min were pooled, evaporated, and dried at room temperature at 3.3 torr to afford a crystalline sample of **1b**: yield 9.0 mg (8%); mp 67–69 °C; $[\alpha]^{23}_D$ −45° (c 0.7, dichloromethane); IR (Nujol) 1755 (C=O), and 735 (C—Cl) cm^{-1}.

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: m/z (M^+ − Cl$^·$) 249.052968. Found: m/z 249.053660.

3,4-Di-*O*-acetyl-2-bromo-2,6-dideoxy-α-L-gluco- and -α-L-mannopyranosyl Bromides (1e and 1f). L-Rhamnal diacetate (1, 0.856 g, 4 mmol) dissolved in carbon tetrachloride (20 mL) was treated for 10 min at 0 °C with a slight excess of bromine. Evaporation of the solvent under diminished pressure at 40 °C afforded a colorless syrup that crystallized after a few hours at −14 °C. TLC revealed the solid to be a mixture of two compounds (R_f 0.35 and 0.30, 4:1 hexane–ethyl acetate) that were separated by column chromatography (silica gel, 80 g) with 5:1 hexane–ethyl acetate. The compound having R_f 0.35 (α-L-*manno* isomer, **1f**) crystallized from ether–hexane: yield 0.138 g (9%); mp 92 °C; $[\alpha]^{22}_D$ −125° (c 0.5, dichloromethane); ^{13}C NMR δ 170.0, 169.7 (C=O), 86.0 (C-1), 72.0 (C-5), 70.3 (C-4), 68.6 (C-3), 52.3 (C-2), 20.5 (OAc), and 16.8 (C-6).

Anal. Calcd for $C_{10}H_{14}Br_2O_5$: C, 32.11; H, 3.77; m/z (M^+ − ^{79}Br$^·$) 293.002505. Found: C, 31.78; H, 3.82; m/z 293.002978. Evaporation of the later fractions from the column afforded the crystalline α-L-*gluco* isomer **1e**. Recrystallization from ether–hexane gave colorless crystals: yield 0.43 g (29%); mp 128–129 °C; $[\alpha]^{22}_D$ −283° (c 0.5, dichloromethane) (in good agreement with values reported[38] in the literature); ^{13}C NMR δ 170.0 (C=O), 89.3 (C-1), 79.3, 71.0, 69.0 (C-3,4,5), 49.1 (C-2), 20.5 (OAc), and 16.8 (C-6).

Anal. Calcd for $C_{10}H_{14}Br_2O_5$: m/z (M^+ − ^{79}Br$^·$) 293.002505. Found: m/z 293.002978.

3,4-Di-*O*-acetyl-2-chloro-2,6-dideoxy-α-L-galacto- and -β-L-talopyranosyl Chlorides (2a and 2d). 3,4-Di-*O*-acetyl-L-fucal (**2**, 0.642 g, 3 mmol) was chlorinated in carbon tetrachloride (15 mL) as described for compound 1. Evaporation of the solvent afforded a syrup that showed two main spots in TLC (R_f 0.5 and 0.3, 4:1 hexane–ethyl acetate). The mixture was separated by column chromatography (5:1 hexane–ethyl acetate). From the first fractions, the α-L-*galacto* isomer **2a** was isolated as a colorless syrup that failed to crystallize: yield 0.55 g (64%); $[\alpha]^{22}_D$ −230° (c 1.1, dichloromethane); IR (film) 1755 (C=O), 735 (C—Cl) cm^{-1}; ^{13}C NMR δ 170.2, 169.8 (C=O), 94.3 (C-1), 70.6, 69.6 (C-3,4), 68.4 (C-5), 55.6 (C-2), 20.3 (OAc), and 15.4 (C-6).

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.12; H, 4.95; m/z (M − Cl$^·$) 249.052968. Found: C, 41.73; H, 5.25; m/z 249.052660.

Evaporation of the later fractions from the column afforded the β-L-*talo* isomer **2d**, as a colorless syrup: yield 0.068 g (8%); $[\alpha]^{23}_D$ +4.0° (c 0.4, dichloromethane); IR (film) 1755 (C=O), 730 (C—Cl) cm^{-1}.

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: m/z (M^+ − Cl$^·$) 249.052968. Found: C, m/z 249.053660.

3,4-Di-*O*-acetyl-2-chloro-2,6-dideoxy-β-L-galactopyranosyl Chloride (2b). Chlorination of 3,4-di-*O*-acetyl-L-fucal (**2**, 50 mg) in 1,2-dichloroethane afforded a mixture of dihalides that was separated by LC (μPorasil column, 0.78 × 30 cm, at a flow rate of 3.5 mL/min) with 8:1 hexane–ethyl acetate. Fractions containing the product having t_R 11 min were pooled and evaporated to give the crystalline title compound: mp 91–93 °C; $[\alpha]^{25}_D$ −32° (c 0.2, dichloromethane).

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: m/z (M^+ − Cl$^·$) 249.052968. Found: m/z 249.053660.

3,4-Di-*O*-acetyl-2-bromo-2,6-dideoxy-α-L-galacto- and -α-L-talopyranosyl Bromides (2e and 2f). L-Fucal diacetate (**2**, 0.054 g, 0.25 mmol) dissolved in carbon tetrachloride (1.3 mL) was treated with bromine as already described for the glycal **1**. The mixture was monitored by ^{13}C NMR and separated by LC (μPorasil column, 0.78 × 30 cm, at a flow rate of 3 mL/min) with 6:1 hexane–ethyl acetate. Fractions containing the product having t_R 7.5 min were pooled and evaporated, and the α-L-*talo* isomer **2f** was obtained as a colorless syrup: yield 16 mg (17%); $[\alpha]^{22}_D$ −77° (c 1.4, dichloromethane); ^{13}C NMR δ 170.5, 169.7 (C=O), 91.6 (C-1), 47.3 (C-2), 20.3 (OAc), and 15.3 (C-6).

Anal. Calcd for $C_{10}H_{14}Br_2O_5$: m/z (M^+ − ^{79}Br$^·$) 293.002505. Found: m/z 293.003148.

The product having t_R 8.3 min was identified as the α-L-*galacto* isomer **2e**: yield 28 mg (30%); $[\alpha]^{22}_D$ −224° (c 2.0, dichloromethane); ^{13}C NMR δ 170.2, 169.6 (C=O), 88.7 (C-1), 47.0 (C-2), 20.4 (OAc), and 15.5 (C-6).

Anal. Calcd for $C_{10}H_{14}Br_2O_5$: m/z (M^+ − ^{79}Br$^·$) 293.002505. Found: m/z 293.003242.

The ^{13}C NMR signals of C-3, -4, and -5 in a mixture of **2e** and **2f** were not specifically differentiated. Their chemical shifts were 70.9, 70.7, 70.4, 70.3, 67.8, and 64.9.

Registry No. **1**, 34819-86-8; **1a**, 103321-18-2; **1b**, 103321-21-7; **1c**, 103321-20-6; **1d**, 103321-19-3; **1e**, 65784-91-0; **1f**, 103321-22-8; **2**, 54621-94-2; **2a**, 72864-45-0; **2b**, 103321-24-0; **2d**, 103321-23-9; **2e**, 103321-26-2; **2f**, 103321-25-1; **3**, 2873-29-2; **3f**, 62098-48-0; **3g**, 103475-53-2; **4**, 98044-32-7; **4f**, 103321-27-3; **4g**, 103321-28-4; **6**, 4098-06-0; **6f**, 103420-22-0; **6g**, 103420-23-1.

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Enantioselective Synthesis and Absolute Configuration of Both Enantiomers of *endo*-Brevicomin

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Received January 24, 1986

(1*R*,5*S*,7*S*)-(+)- and (1*S*,5*R*,7*R*)-(−)-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane ((+)- and (−)-*endo*-brevicomin, **5**) were synthesized in high enantiomeric purity in three steps starting from the (2*S*,3*S*)-(+)- and (2*R*,3*R*)-(−)-*erythro*-1-bromopentane-2,3-diol (**1**), respectively, with 60% overall yield. The key reaction is a stereoselective cycloacetalization of **1a** or **1b** with 4-(phenylsulfonyl)-2-butanone dimethyl acetal **2** or the corresponding ketone **2′**, respectively.

endo-Brevicomin is one of the attractant pheromones in the chemical communication system of several pine beetle species belonging to the genera *Dendroctonus* and *Dryocetes*.[1]

0022-3263/86/1951-3485$01.50/0