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Iodoalkoxylation of 1,5-anhydro-2-deoxy-hex-1-enitols (glycals)*

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ABSTRACT

Exclusive *trans*-addition is observed in the iodoalkoxylation of the 6-membered cyclic enol ethers 3,4-di-*O*-acetyl-L-rhamnal (**1**), 3,4-di-*O*-acetyl-L-fucal (**2**), and related glycal derivatives. The main products from **1** and from 3,4,6-tri-*O*-acetyl-D-glucal (**3**) thus had the α-*manno* configuration. Similarly, α-*talo* products were obtained from **2** in 87–93% yield. The product distribution is not affected by the electronegativity of the 5-substituent. It is concluded that steric factors in the glycal and the nucleophile affect only the step of *trans*-diaxial opening of the intermediate iodonium ion. Enhanced yields of the desired *trans*-diaxial products were observed in reactions of glycals having the *lyxo* configuration when the reactions were conducted in tetrahydrofuran or methanol.

INTRODUCTION

Our earlier reports[1,2] on the synthesis and *in vivo* antitumor activity of 2′-halo-substituted anthracycline glycosides, together with more recent studies[3,4], demonstrate significant activity in only those glycosides of suitable 6-deoxy-α-L-hexoses having the 2-halo group axially disposed. Improved methods were therefore sought for preparing 2-halo glycosides having the *trans*-diaxial disposition of substituents at C-1 and C-2.

Appropriately substituted glycals (1,5-anhydro-2-deoxy-hex-1-enitols) are particularly attractive synthetic precursors for this purpose. Functionalization of the double bond in such cyclic vinyl ethers usually leads to mixtures of *cis*- and *trans*-substituted products. We have studied the stereochemistry of the electrophilic addition of chlorine and bromide to various glycals[5] in an effort to maximize the yield of the required 2-chloro and 2-bromo products. The resultant 1,2-dihalides were then coupled with anthracyclinones under Koenigs–Knorr conditions to generate the desired analogs[4] of the natural anthracycline antibiotics.

A one-step reaction between an acylated glycal and daunomycinone in the presence of *N*-iodosuccinimide (NIS) leads[3] in to 2′-iodo anthracycline glycosides without the need for heavy-metal catalysis. Use of the method described by Thiem *et al.*[6] gave, exclusively, mixtures of *trans*-addition products, but significant production of the diequatorial (β-L glycoside) product in addition to the desired diaxial (α-L) glycoside led to diminished yields and necessitated tedious separations.

In this report we evaluate the NIS-mediated addition of alcohols to the double

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bond of glycals with the goal of exerting a higher degree of control on the stereochemistry of the products formed. Factors examined are the nature of the solvent, the nucleophile, and the structure of the glycal, in relation to the ratio of the final products. In contrast to our previous work[5] on chlorination and bromination of glycals, it was not expected that the substituent at C-6 of the glycal would have a significant effect, because the iodonium ion intermediate in iodoalkoxylation is more stable than the corresponding bromonium or chloronium ion.

2-Deoxy-2-halo glycosides are also useful intermediates for the preparation of 2-deoxy glycosides[7–9] and 2-isotopically labeled glycosides and their derivatives[10].

RESULTS AND DISCUSSION

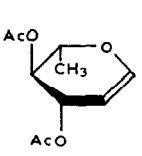
Structural assignments for the products. — Selected glycal derivatives were subjected to iodoalkoxylation in the dark at room temperature, and the compositions of the resultant mixtures were determined by ^{1}H-n.m.r. spectroscopy. Column chromatography was used to separate the pairs of isomers formed by the addition of NIS and various alcohols (Table I) to the double bond of 3,4-di-*O*-acetyl-L-rhamnal (**1**, products **1a** and **1b**, **1c** and **1d**, and **1e** and **1f**); 3,4-di-*O*-acetyl-D-arabinal (**5**, products **5a** and **5b**); and the *tert*-butyl 2-iodoglycosides **2c** and **2d** obtained from 3,4-di-*O*-acetyl-L-fucal (**2**). For the additions to 3,4-di-*O*-acetyl-L-xylal (**4**), the products (**4a** and **4b**) were separated by high-performance liquid chromatography (l.c.). Some of the products are new and

TABLE I

Product distribution in the iodoalkoxylation of glycals **1**, **2**, **3**, **4**, and **5**[a]

Expt.	*Starting glycal*	*Alcohol*	*Solvent*	*Products (%)*	
A	**1**	CH_3OH	CH_3CN	**1a** (82)	**1b** (18)
B	**1**	CH_3OH	CH_3OH	**1a** (66)	**1b** (34)
C	**1**	CH_3OH	THF	**1a** (77)	**1b** (23)
D	**1**	*i*-PrOH	CH_3CN	**1c** (82)	**1d** (18)
E	**1**	*i*-PrOH	THF	**1c** (80)	**1d** (20)
F	**1**	*tert*-BuOH	CH_3CN	**1e** (82)	**1f** (18)
G	**1**	*tert*-BuOH	THF	**1e** (85)	**1f** (15)
H	**2**	CH_3OH	CH_3CN	**2a** (87)	**2b** (13)
I	**2**	CH_3OH	CH_3OH	**2a** (91)	**2b** (9)
J	**2**	CH_3OH	THF	**2a** (93)	**2b** (7)
K	**2**	*tert*-BuOH	CH_3CN	**2c** (87)	**2d** (13)
L	**3**	CH_3OH	CH_3CN	**3a** (82)	**3b** (18)
M	**3**	CH_3OH	CH_3OH	**3a** (71)	**3b** (29)
N	**3**	CH_3OH	THF	**3a** (77)	**3b** (23)
O	**4**	CH_3OH	CH_3CN	**4a** (47)	**4b** (53)
P	**4**	CH_3OH	CH_3OH	**4a** (40)	**4b** (60)
Q	**5**	CH_3OH	CH_3CN	**5a** (56)	**5b** (44)
R	**5**	CH_3OH	CH_3OH	**5a** (47)	**5b** (53)

[a] Determined by ^{1}H-n.m.r. spectroscopy.



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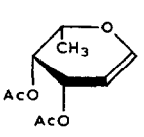

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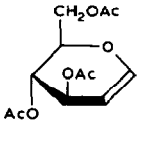

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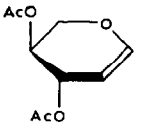

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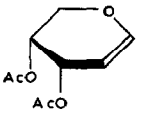

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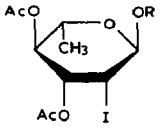
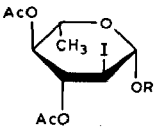


1a R = Me
1c R = Me_2CH
1e R = Me_3C



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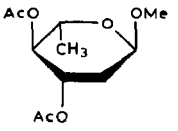
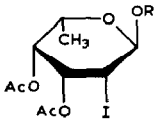
1d R = Me_2CH
1f R = Me_3C



1g



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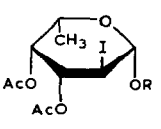
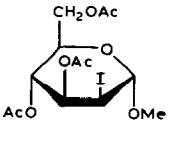
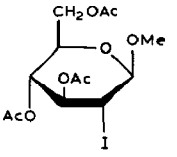


2b R = Me
2d R = Me_3C



3a



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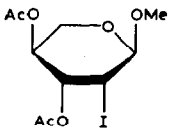

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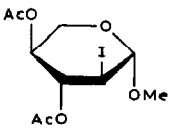

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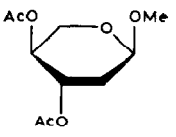

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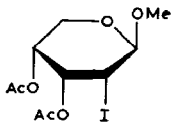
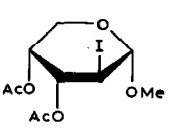


5a



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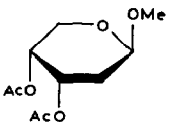


5c

others have been described; for the latter [**2a** and **2b** (ref. 11), and **3a** and **3b** (ref. 12)], no separation was undertaken.

The derivatives obtained from L-rhamnal diacetate (**1a**, **1b**, **1c**, **1d**, **1e**, and **1f**) showed large $J_{3,4}$ (9.0–9.4 Hz) and $J_{4,5}$ (9.2–9.5 Hz) values, indicating the *trans*-diaxial disposition between H-3–H-4 and H-4–H-5 in the favored $^1C_4$(L) conformation. The small values of $J_{2,3}$ (4.2–4.5 Hz) in compounds **1a**, **1c**, and **1e** indicate the L-*manno* configuration. Large values of $J_{2,3}$ (11.1 Hz) in compounds **1b**, **1d**, and **1f** signify the L-*gluco* configuration.

The anomeric configurations of all products were firmly established. The large

values of $J_{1,2}$ (8.9–9.0 Hz) for compounds **1b**, **1d**, and **1f** accord with their having the β-L *gluco* configuration.

Small (1.0–1.2 Hz) $J_{1,2}$ coupling constants indicate the α-L-*manno* configuration for compounds **1a**, **1c**, and **1e**. Interestingly, H-1 and H-2 in compounds **1a**, **1c**, and **1e** resonate at lower fields than the corresponding axial protons (H-1 and H-2) in compounds, **1b**, **1d**, and **1f**, respectively[13,14] (Table II), and H-5 in compounds **1a**, **1c**, and **1e** is shifted downfield as compared to H-5 in **1b**, **1d**, and **1f**, respectively, probably because of a parallel 1,3-interaction with the axial alkoxy group in the former compounds. Furthermore, the 1-methoxyl resonance (3.35 p.p.m.) in **1a** is shifted upfield as compared with that[15] in **1b** (3.52 p.p.m.).

For positive verification of the anomeric configuration, compounds **1a**, **1c**, and **1e** were deiodinated by using $HSnBu_3$. The deoxy derivative **1g** was obtained from **1a** in 80% yield. Its ^{1}H-n.m.r. spectrum (see Tables IV and V) shows two small coupling constants between H-1 and the C-2 protons ($J_{1,2eq}$ 1.2, $J_{1,2ax}$ 3.7 Hz), showing that H-1 is equatorial. As no anomerization is to be expected during the dehalogenation reaction, it is concluded that H-1 in compound **1a** is also equatorial, confirming the α-L-*manno* configuration previously proposed. As compounds **1a**, **1c**, and **1e** have almost identical ^{1}H-n.m.r. parameters it is obvious that they have the same (α-L-*manno*) configuration.

Among the two pairs of products from L-fucal diacetate (compounds **2a** and **2b**, **2c** and **2d**), the methyl glycosides **2a** and **2b** have already been described[11], and their absolute configurations established as α-L-*talo* and β-L-*galacto*, respectively. The ^{1}H-n.m.r. spectra of these compounds, as well as those of the *tert*-butyl glycosides **2c** and **2d**, confirm these assigned structures.

Compounds **2a** and **2c** show the same downfield shifts of H-1 and H-2 as compounds **1a**, **1c**, and **1e** with respect to the corresponding H-1 and H-2 signals in compounds **2b** and **2d** (Table III). There is also a downfield shift of H-5 in compounds **2a** and **2c** with respect to H-5 in compounds **2b** and **2d**, and an upfield shift of the 1-methoxyl signal in **2a** as compared with that in **2b**. Overall, this pattern establishes the α-L-*talo* configuration for **2a** and **2c**.

The two derivatives from D-glucal triacetate, methyl glycosides **3a** and **3b**, have already been described[12], and their absolute configurations have been established as α-D-*manno* and β-D-*gluco*, respectively, with ^{1}H-n.m.r. parameters consistent with these assignments.

The methyl glycosides (**4a** and **4b**) derived from L-xylal were inseparable by column chromatography and so were resolved by l.c. Their structures were established as follows: Compound **4b** shows large couplings (Table III) between H-1 and H-2, H-2 and H-3, H-3 and H-4, and H-4 and H-5′, which establishes the β-L-*xylo* configuration in the $^1C_4$ (L) conformation. The relatively weak axial-directing effect[16] of the methoxyl group at C-1 would generate only a little of the all-axial conformer, in equilibrium with the all-equatorial form. For compound **4a**, the α-L-*xylo* configuration was assigned, but this configurational and $^1C_4$ (L) conformational attribution were open to question because of the relatively small ("intermediate") coupling constants observed, indicative of conformational equilibration[17,18]. Accordingly, a confirmatory experiment was performed.

TABLE II

^{1}H-N.m.r. chemical shifts and multiplicities[a] for compounds **1a–f**, **2a–d**, **3a–b**, **4a–b**, and **5a–b**

Compound	*Chemical shifts (δ, p.p.m.) and multiplicities*											
	H-1	*H-2*	*H-3*	*H-4*	*H-5*[b]	*H-5'*[b]	*H-6*[c]	*H-6'*[c]	OCH_3	*OCH*	CH_3	$C(CH_3)_3$	CH_3CO
1a	4.97bs	4.50d	4.55dd	5.09t	3.86dq		1.21d		3.35s				2.04s, 2.02s
1b	4.47d	3.84dd	5.23dd	4.68t	3.58dq		1.23d		3.52s				2.06s, 2.00s
1c	5.15bs	4.45d	4.56dd	5.10t	3.95dq		*d*			3.87m	*d*		2.04s, 2.02s
1d	4.61d	3.83dd	5.23dd	4.67t	3.56dq		*e*			3.95m	*e*		2.05s, 1.99s
1e	5.32bs	4.40d	4.60dd	5.11t	4.10dq		1.18d					1.25s	2.06s, 2.05s
1f	4.80d	3.86dd	5.27dd	4.68t	3.58dq		1.21d					1.31s	2.07s, 2.01s
2a[f]	5.20bs	4.29d	4.90t	5.24dd	4.17dq		1.22d		3.42s				2.20s, 2.08s
2b[f]	4.54d	4.05dd	5.10dd	5.08bs	3.85dq		1.23d		3.58s				2.16s, 2.07s
2c	5.52bs	4.15d	4.94t	5.21bs	4.38dq		1.16d					1.24s	2.20s, 2.06s
2d	4.77d	4.04dd	5.10dd	5.05d	3.80dq		1.19d					1.33s	2.14s, 2.06s
3a[f]	5.03s	*g*	4.61dd	5.31t	4.02dd		*h*	*g*	3.42s				2.10s, 2.10s, 2.04s
3b[f]	*h*	3.88dd	5.29dd	4.95t	3.76ddd		4.34dd	4.12dd	3.57s				2.10s, 2.10s, 2.04s
4a	4.83d	4.46t	4.89dd	5.01m	3.91dd	3.81dd			3.45s				2.14s, 2.08s
4b	4.48d	3.84dd	5.28dd	4.90ddd	4.14dd	3.38dd			3.53s				2.11s, 2.02s
5a	4.75d	4.20dd	5.47t	5.10ddd	3.97dd	3.82dd			3.50s				2.17s, 2.02s
5b	4.48d	*i*	3.07dd	3.12bs	*i*	3.72d			3.57				2.15s, 2.10s

[a] Multiplicities are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. [b] The proton resonating at lower field is designated H-5, and that resonating at higher field H-5'. [c] Item *b* but for H-6 and H-6'. [d] These signals are overlapped between 1.1 and 1.3 p.p.m. [e] Same as *d*. [f] The spectra of these compounds were determined as a mixture at 500 MHz. [g] These signals are overlapped at 4.20 p.p.m. [h] Same as *g* except at 4.54 p.p.m. [i] These signals are overlapped between 4.2 and 4.0 p.p.m.

TABLE III

^{1}H-N.m.r. coupling constants for compounds **1a–f**, **2a–d**, **3a–b**, **4a–b**, and **5a–b**

Compound	*Coupling constants (Hz)*									
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	J_{CH,CH_3}
1a	1.0	4.5	9.2	9.2			6.3			
1b	9.0	11.1	9.1	9.3			6.1			
1c	1.1	4.3	9.2	9.4			6.3			6.1
1d	9.0	11.1	9.3	9.3			6.2			6.1
1e	1.2	4.2	9.4	9.5			6.3			
1f	8.9	11.1	9.0	9.4			6.2			
2a	1.1	4.8	3.5	1.7			6.5			
2b	9.0	12.2	3.0	1.0			6.6			
2c	0.7	4.1	4.1	1.3			6.6			
2d	8.9	11.7	3.3	0.8			6.5			
3a	0.3	4.0	9.5	9.2			5.0	3.0	Not determined	
3b	9.0	11.1	9.5	9.2			6.0	3.0	14.0	
4a	4.5	4.5	6.8	4.0	6.8	11.9				
4b	8.6	11.0	8.9	5.4	10.0	11.6				
5a	7.5	3.0	3.0	5.0	8.0	11.5				
5b	9.0	11.5	4.5	<1.0	<1.0	12.5				

Compound **4a** was deiodinated with $HSnBu_3$ and the corresponding deoxyglycoside **4c** was obtained in 75% yield. The large couplings between H-2*ax*–H-3, H-3–H-4, and H-4–H-5*ax* (Table V) indicate the favored $^1C_4$ (L) conformation. Small values of $J_{1,2eq}$ (2.9 Hz) and $J_{1,2ax}$ (3.1 Hz) indicate that H-1 is equatorial, and therefore compound **4c** has the α-L-*threo* configuration. It follows that compound **4a** has the α-L-*lyxo* configuration and, from the observed coupling constants, it may be concluded[16] that it is in conformational equilibrium between the $^1C_4$ (L) and $^4C_1$ (L) forms, with the former weakly preponderating.

The iodomethoxylation of D-arabinal diacetate (**5**) gave two compounds, **5a** and **5b**. Compound **5b** showed small couplings between H-4 and both H-5 and H-5′, indicating the equatorial orientation of H-4 in the $^1C_4$ (D) conformation, and large couplings between H-1–H-2 and H-3, thus establishing the α-D-*arabino* configuration. Compound **5a** appears to be an equilibrium mixture of conformers. The relatively large values of $J_{1,2}$ (7.5 Hz) and $J_{4,5'}$ (8.0 Hz) and the small couplings between H-3–H-4 and H-2–H-3 indicate the β-D-*ribo* configuration, with the compound in a chair–chair conformational equilibrium in which the $^4C_1$ (D) form preponderates.

To confirm the *ribo* configuration, compound **5a** was deiodinated with $HSnBu_3$, whereupon the deoxy glycoside **5c** was obtained. The ^{1}H-n.m.r. data for the derivative (Tables IV and V) indicate the stable $^1C_4$ (D) conformation and the β-D-*erythro* configuration, in accord with the structure assigned to its precursor.

The conformational tendency in the deoxy glycoside **5c** parallels that in methyl β-D-ribopyranoside triacetate[16,18] in favoring the $^1C_4$ (D) form, in contrast to the 2-iodo

TABLE IV

^{1}H-N.m.r. chemical shifts and multiplicities for compounds **1g**, **4c**, and **5c**

Compound	*Chemical shifts (δ, p.p.m.) and multiplicities*[a]									
H-1	*H-2*eq	*H-2*ax	*H-3*	*H-4*	*H-5*eq	*H-5*ax	*H-6*	OCH_3	CH_3CO	
1g	4.75d	2.22ddd	1.77ddd	5.24ddd	4.74t		3.83dq	1.18d	3.33s	2.04s, 2.00s
4c	4.72t	2.18ddd	1.75m	5.24ddd	4.87td	3.78dd	3.64dd		3.36s	2.04s, 2.03s
5c	4.84dd	1.87m	2.11td	5.28ddd	5.16bs	3.90dd	3.71dd		3.36s	2.13s, 2.01s

[a]Abbreviations: s, singlet; d, doublet; t, triplet; q: quartet; m, multiplet.

TABLE V

^{1}H-N.m.r. coupling constants for compounds **1g**, **4c**, and **5c**

Compound	*Coupling constants (Hz)*										
	$J_{1,2eq}$	$J_{1,2ax}$	$J_{2eq,2ax}$	$J_{2eq,3}$	$J_{2ax,3}$	$J_{3,4}$	$J_{4,5eq}$	$J_{4,5ax}$	$J_{5eq,5ax}$	$J_{5,6}$	$J_{2eq,4}$
1g	1.2	3.7	12.9	5.7	11.7	9.6		9.8		6.3	
4c	2.9	3.1	13.1	5.0	10.0	8.8	5.0	9.1	11.2		
5c	1.6	3.8	13.5	4.8	11.8	3.2	1.5	2.7	12.8		1.3

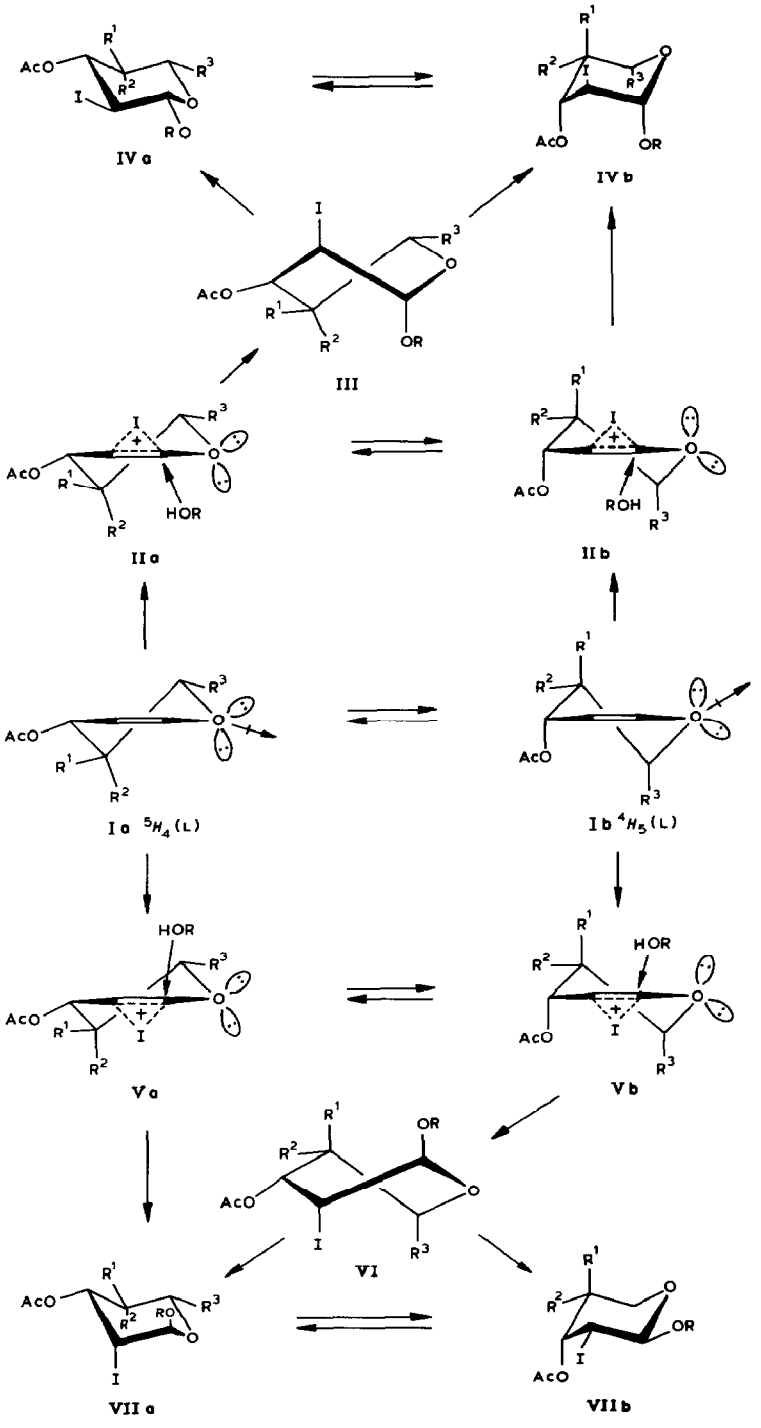
derivative **5a** in which the reverse $^4C_1$ (D) form preponderates. The behavior of **5a** may be attributed to the greater steric bulk of the iodo group, which would tend to destabilize the $^1C_4$ (D) conformation because of *syn*-diaxial interaction with the 3-acetoxy group. Similar steric arguments may account for the fact that the $^1C_4$ (L) conformation of compound **4a** (axial 2-iodo group), although weakly preponderant, is not so strongly favored as it is in the 2-acetoxy analog[16].

RESULTS OF IODOALKOXYLATION

Mechanistic aspects. — It is well known that the addition of NIS (or other equivalent source of iodine, such as I_2–AgOAc) and an alcohol to the double bond of an

Fig. 1 Proposed mechanism of iodoalkoxylation of glycals.

		R^1	R^2	R^3	R
Ia, Ib	= **1**	OAc	H	Me	
	= **2**	H	OAc	Me	
	= **3** (L)	OAc	H	CH_2OAc	
	= **4**	OAc	H	H	
IVa, IVb	= **1b**	OAc	H	Me	Me
	= **1d**	OAc	H	Me	Me_2CH
	= **1f**	OAc	H	Me	Me_3C
	= **2b**	H	OAc	Me	Me
	= **2d**	H	OAc	Me	Me_3C
	= **3b** (L)	OAc	H	CH_2OAc	Me
	= **4b**	OAc	H	H	Me
	= **5b**	H	OAc	H	Me
VIIa, VIIb	= **1a**	OAc	H	Me	Me
	= **1c**	OAc	H	Me	Me_2CH
	= **1e**	OAc	H	Me	Me_3C
	= **2a**	H	OAc	Me	Me
	= **2c**	H	OAc	Me	Me_3C
	= **3a** (L)	OAc	H	CH_2OAc	Me
	= **4a**	OAc	H	H	Me
	= **5a**	H	OAc	H	Me


IV a
IV b
III
II a
II b
I a $^5H_4$ (L)
I b $^4H_5$ (L)
V a
V b
VI
VII a
VII b

acylated glycal gives exclusively alkyl 2-iodoglycosides having the iodine and the alkoxy groups *trans*-disposed[7,15,19–22]. The results are explained in terms of a two-step mechanism (Fig. 1): electrophilic addition of iodine to the double bond gives a cyclic iodonium ion and then nucleophilic attack by the alcohol takes place regiospecifically at C-1 because of electronic assistance by the lone pair of the neighboring oxygen atom.

In order to delineate the factors influencing the proportions of stereoisomers formed, we examined the reaction employing various glycals, different nucleophiles, and several solvents. The results (Table I) confirm that only the 1,2-*trans* pair of 1-alkoxy-2-iodo products is formed in each instance, but the ratio of the two products varied from 93:7 (**2a**:**2b**, experiment J) to 2:3 (**4a**:**4b**, experiment P).

Effect of the nucleophile. — It is not possible to generalize as to which step is rate-determining in the haloalkoxylation reaction[15,19,23–26]. The specific process appears to depend mainly upon the nature of the halogenating reagent and the solvent. The process may be studied by varying the nucleophile while maintaining all other conditions constant. If the electrophilic attack by iodonium ion is irreversible, the proportion of resultant stereoisomers will remain the same, regardless of the nucleophile used. If the electrophilic step is reversible, the proportion of stereoisomers will change with the nucleophile. Experimentally, treating L-rhamnal diacetate (**1**) in acetonitrile with various alcohols (Table I, entries A, D, and F) and NIS showed the ratio of resultant stereoisomers to remain the same (41:9), thus indicating that the first step is irreversible under these conditions. The same conclusion may be drawn from the comparable reaction of L-fucal diacetate (**2**) in acetonitrile with methanol (entry H) and *tert*-butyl alcohol (entry K).

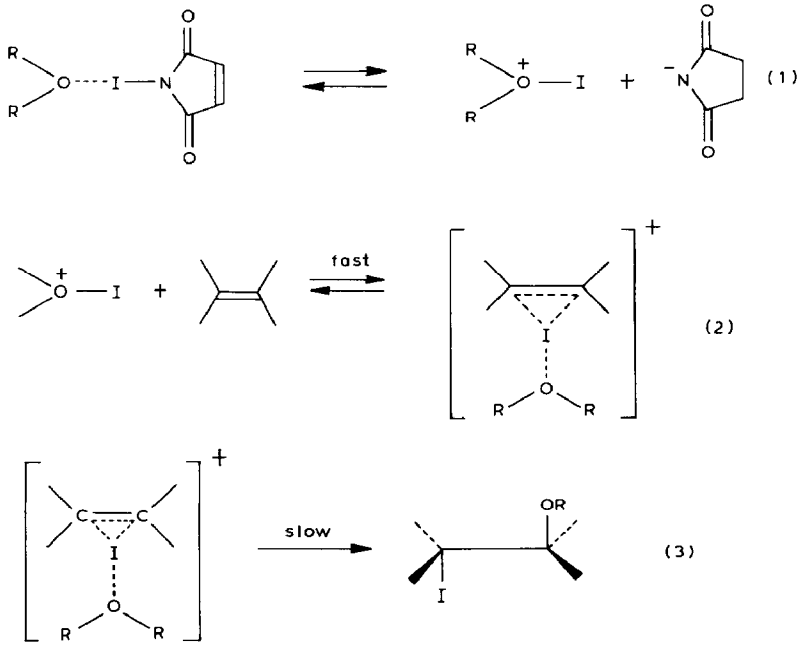


Fig. 2 Effect of oxygenated solvent.

However, some differences were observed when oxolane was used as the solvent (entries C, E, and G), and these results are discussed next.

Solvent effect. — The nature of the solvent has a strong to moderate influence on the final ratio of stereoisomers (see entries A, B, and C; D and E; F and G; H, I, and J; L, M, and N; O and P; and Q and R). These differences cannot be attributed simply to solvent polarity, because methanol and acetonitrile have almost the same dielectric constants. A possible explanation is that either methanol or oxolane (tetrahydrofuran, THF) forms a complex with iodine (eq. *1*, Fig. 2), so that the first step will be fast and reversible (eq. *2*, Fig. 2), and this complex then collapses slowly to give the final product (eq. *3*, Fig. 2). In such a situation, the ratio of stereoisomers will depend on the nucleophile (ROH).

Similar interpretations have been offered to explain the results of bromination of cyclohexene with different reagents and solvents[23,27]. To corroborate this proposal, L-rhamnal diacetate (**1**) was treated in THF with different alcohols (entries C, E, and G). In each instance, different proportions of stereoisomers were obtained; the bulkier the aglycon, the higher the proportion of *trans*-diaxial stereoisomers. When the stereochemistry of the reaction is controlled by the second step, two factors must be taken into account: first, the preference for the cyclic ion to open in a manner leading initially to diaxial substitution on a chair-form ring (see Fig. 1), and second, steric factors. The first consideration explains the higher proportion of *α-trans* products obtained from glycals **1**, **2**, and **3**, mainly through pathway Ia→Va→VIIa. The second could explain the increase of *trans*-diaxial products with increasing size of the alcohol (entries C, E, and G); most of the *α-trans* isomers should be formed through intermediate Va, as already mentioned. On the other hand, *β-trans* isomers should pass through either IIa or IIb. It is in the latter structure (IIb) where steric effects arise through 1,3-diaxial interactions between ROH and OAc, and ROH and R^3. As the R group of ROH becomes larger, attack from the underside becomes progressively disfavored, resulting in a higher proportion of *α-trans* isomers.

Effect of the glycal structure. — Previous studies[28,30] showed that glycals exist in solution as mixtures of the $^5H_4$ and $^4H_5$ conformers (Fig. 1) in proportions depending on the substituents R^1, R^2, and R^3 and their stereochemistry. L-Glucal triacetate (R^1 = OAc, R^2 = H, R^3 = CH_2OAc) exists almost 60% in the $^5H_4$ (L) conformation (D-glucal,**3**, was actually used but L-glucal is shown in Fig. 1 for homomorphic convenience). L-Rhamnal diacetate (**1**, R^1 = OAc, R^2 = H, R^3 = CH_3) shows similar behavior[30]. Similarly, L-galactal triacetate (R^1 = H, R^2 = OAc, R^3 = CH_2OAc) and L-fucal diacetate (**2**, R^1 = H, R^2 = OAc, R^3 = CH_3) exist mainly in the $^5H_4$ conformation. On the other hand, D-arabinal diacetate (**5**, R^1 = H, R^2 = OAc, R^3 = H) and L-xylal diacetate (**4**, R^1 = OAc, R^2 = H, R^3 = H), are mainly in the $^4H_5$ (D) and $^4H_5$ (L) conformations, respectively.

Our results already establish that, in acetonitrile, the addition of iodine to the double bond is irreversible, and the proportion of final products reflects the proportion of attack of iodine from below or above the plane of the bond. As L-fucal diacetate (**2**), which in the favored $^5H_4$ (L) conformation (Fig. 1) has an axial acetoxy group at C-4, is

iodinated mainly from below the plane of the molecule (giving compounds **2a** and **2c** in higher proportion than **2b** and **2d**, respectively), it appears that steric factors do not exert a major influence on formation of the iodonium ion; electrostatic effects might be responsible for the stereochemistry of the first step. In L-fucal diacetate (**2**), in the $^5H_4$ conformation, the dipole moment of the ring oxygen atom, the equatorial acetoxy group at C-3, and especially the axial acetoxy group at C-4 combine to give the molecule a net dipole moment with the negative pole below the plane, favoring electrophilic attack from this side. L-Rhamnal diacetate has its C-4 acetoxy group equatorial, and so the net dipole moment should be smaller and this would explain the decrease in reaction from below the plane of the molecule, as compared with L-fucal (see entries A and H, Table I). D-Glucal has the same relative configuration as L-rhamnal, and consequently behaves similarly (entries A and L).

L-Xylal diacetate (**4**) and D-arabinal diacetate (**5**), which exist respectively in the $^4H_5$ (L) and $^4H_5$ (D) conformations, have an axial acetoxy group at C-3 facing down and the dipole of the oxygen atom facing up. These similarities may explain the similar proportions of adducts obtained for both stereoisomers (entries O and Q). An increase in the reactivity of iodine from the top side in L-xylal diacetate (compared to D-arabinal diacetate) is attributable to the axial orientation of the 4-acetoxy group.

Conclusion. — The stereochemistry of NIS–alcohol addition to the double bond of acetylated glycals is controlled at either the electrophilic or nucleophilic step, according to the nature of the solvent.

In CH_3CN, where the first step seems to be irreversible, the stereochemistry of the reaction is controlled mainly by the dipole moment of the glycal. The final product distribution thus reflects the proportion of cyclic iodonium ion formed on each side of the molecule. In THF or CH_3OH, where the first step seems to be reversible, the distribution of product stereoisomers is controlled by the tendency for *trans*-diaxial opening of the cyclic ion, and by steric factors in the glycal and in the nucleophile.

EXPERIMENTAL

General methods. — 3,4-Di-*O*-acetyl-L-rhamnal (**1**) (Pfanstiehl Laboratories) was purified by column chromatography (5:1 hexane–ethyl acetate) before use. 3,4,6-Tri-*O*-acetyl-D-glucal (**3**) (Pfanstiehl Laboratories) was used without previous purification. 3,4-Di-*O*-acetyl-L-fucal (**2**) was prepared by the procedure of Iselin and Reichstein[31]. 3,4-Di-*O*-acetyl-L-xylal (**4**) and 3,4-di-*O*-acetyl-D-arabinal (**5**) were prepared as already described in the literature[32,33].

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. ^{1}H-N.m.r. spectra were recorded at 200 MHz with a Bruker WP-200 spectrometer by P. Shah and W. K. Berlin, and at 500 MHz with a Bruker AM-500 instrument by Dr. C. E. Cottrell. The samples were dissolved in chloroform-*d* and chemical shifts

(p.p.m.) refer to an internal standard of tetramethylsilane (δ = 0.00 p.p.m.). T.l.c. was performed on precoated aluminum sheets (0.2 mm) and glass plates (0.25 mm) coated with Silica Gel 60F-254 (E. Merck, Darmstadt, F.R.G.); components were detected by spraying the plates with 0.1M ceric sulfate in 2M sulfuric acid, with subsequent heating. Column chromatography was performed with Silica Gel 60 (230–400 mesh, E. Merck, Darmstadt, F.R.G.). High-performance liquid chromatography (l.c.) was performed with a Waters apparatus equipped with a Model 6000 A solvent delivery system and a Model 440 absorbance detector. Elemental analyses were done by Atlantic Microlabs, Inc., Atlanta, Georgia.

Iodoalkoxylation of glycals. — (a) General procedure for data recorded in Table I. Each glycal derivative (**1**, **2**, **3**, **4**, or **5**, 0.47 mmol) was dissolved in 2 mL of dry solvent (acetonitrile, methanol, or oxolane). The appropriate alcohol (MeOH, isopropyl alcohol, or *tert*-butyl alcohol; 0.86 mmol) was then added followed by 0.75 mmol of NIS. The mixtures were kept overnight at room temperature. T.l.c. (hexane–EtOAc) showed in most instances two spots of similar R_F value, and in some instances only one. The solution was diluted with CH_2Cl_2 and washed with 10% aqueous $Na_2S_2O_3$ and water. The organic layer was dried (Na_2SO_4) and evaporated to afford mixtures that contained only two compounds. The residues were analyzed by ^{1}H-n.m.r. spectroscopy (500 MHz) to determine the proportions of the two stereoisomeric products.

(b) Synthesis, isolation, and purification of the final products **1a**,**1b**; **1c**,**1d**; **1e**,**1f**; **2c**,**2d**; **4a**,**4b**; and **5a**,**5b**. The procedure used was the same as in section (*a*) except that the reaction was done on a 10 times larger scale. The solvent was CH_3CN in each instance. The mixtures were resolved by column chromatography on silica gel (100 g), with 15:1 hexane–EtOAc as eluant. The isomeric pairs **2a**,**2b** and **3a**,**3b** have already been described in the literature[14,15]; for these no separation was attempted. The ^{1}H-n.m.r. spectra of both mixtures were completely coincidental with those already described for the pure compounds[14,15].

*Methyl 3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-*L*-manno- and -β-*L*-gluco-pyranosides* (**1a** *and* **1b**). — The two compounds were isolated by column chromatography. The faster-moving component, identified as the α-L-*manno* isomer (**1a**), was crystalline. Recrystallization from ether–hexane yielded 1.05 g (60%) of **1a**, m.p. 63–65°, $[\alpha]_D^{20}$ −2.5° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{11}H_{17}IO_6$: C, 35.50; H, 4.60; I, 34.10. Found: C, 35.58; H, 4.61; I, 34.12.

The slower-moving β-L-*gluco* isomer (**1b**) was also isolated crystalline. Recrystallization from ether–hexane yielded 0.22 g (13%) of **1b**, m.p. 93–95°, $[\alpha]_D^{25}$ −84.7° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{11}H_{17}IO_6$: C, 35.50; H, 4.60; I, 34.10. Found: C, 35.61; H, 4.61; I, 34.03.

*Isopropyl 3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-*L*-manno- and -β-*L*-gluco-pyranosides* (**1c** and **1d**). — The two products were isolated by column chromatography. The faster-moving component, identified as the α-L-*manno* isomer (**1c**), was obtained as a syrup. Distillation at 100° (0.04 torr) yielded 1.21 g (65%) of **1c**, $[\alpha]_D^{20}$ −23° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{13}H_{21}IO_6$: C, 39.01; H, 5.29; I, 31.71. Found: C, 39.04; H, 5.31; I, 31.81.

The slower-moving component, identified as the *β*-L-*gluco* isomer (**1d**), was crystalline. Recrystallization from ether–hexane yielded 0.24 g (13%) of **1d**, m.p. 59–61°, $[\alpha]_D^{20}$ −63.4° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{13}H_{21}IO_6$: C, 39.01; H, 5.29; I, 31.71. Found: C, 39.09; H, 5.31; I, 31.77.

tert-*Butyl 3,4-di*-O-*acetyl-2,6-dideoxy-2-iodo-α*-L-*manno- and -β*-L-*gluco-pyranosides* (**1e** *and* **1f**). — The two compounds were isolated by column chromatography. The faster-moving component, the *α*-L-*manno* isomer (**1e**), was obtained as a syrup. Distillation at 100° (0.04 torr) yielded 1.11 g (57%) of **1e**, $[\alpha]_D^{20}$ −29.1° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{14}H_{23}IO_6$: C, 40.59; H, 5.60; I, 30.64. Found: C, 40.67; H, 5.61; I, 30.71.

The slower-moving component, identified as the *β*-L-*gluco* isomer (**1f**), was crystalline. Recrystallization from ether–hexane yielded 0.20 g (10%) of **1f**, m.p. 116–118°, $[\alpha]_D^{20}$ −61.2° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{14}H_{23}IO_6$: C, 40.59; H, 5.60; I, 30.64. Found: C, 40.70; H, 5.63; I, 30.53.

tert-*Butyl 3,4-di*-O-*acetyl-2,6-dideoxy-2-iodo-α*-L-*talo- and -β*-L-*galacto-pyranosides* (**2c** *and* **2d**). — The two compounds were isolated by column chromatography. The faster-moving *α*-L-*talo* isomer (**2c**), was a syrup. Distillation at 100° (0.04 torr) yielded 1.12 g (58%) of **2c**, $[\alpha]_D^{20}$ −53.4° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{14}H_{23}IO_6$: C, 40.59; H, 5.60; I, 30.64. Found: C, 40.64; H, 5.65; I, 30.73.

The slower-moving component, identified as the *β*-L-*galacto* isomer (**2d**), was isolated crystalline. Recrystallization from EtOH yielded 0.17 g (8.8%) of **2d**, m.p. 167–169°, $[\alpha]_D^{20}$ −23.0° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{14}H_{23}IO_6$: C, 40.59; H, 5.60; I, 30.64. Found: C, 40.64; H, 5.63; I, 30.61.

Methyl 3,4-di-O-*acetyl-2-deoxy-2-iodo-α*-L-*lyxo- and -β*-L-*xylo-pyranosides* (**4a** *and* **4b**). — Compounds **4a** and **4b** were not separable by column chromatography, but a 100-mg sample was resolved by l.c. (Zorbaxsil, 0.94 × 25 cm) with 5:1 hexane–ethyl acetate as solvent, flow rate of 2.5 mL.min^{-1}.

The first fraction (t_R 10.0 min), identified as the *α*-L-*lyxo* isomer (**4a**), was isolated as a solid. Recrystallization from ethyl ether–hexane yielded **4a**, m.p. 115–117°, lit.[34] 116° for the D enantiomer, $[\alpha]_D^{20}$ +14.9° (*c* 1, $CHCl_3$), lit.[34] −17° for the D enantiomer; ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{10}H_{15}IO_6$: C, 33.54; H, 4.22; I, 35.42. Found: C, 33.62; H, 4.23; I, 35.35.

The second fraction (t_R 10.8 min), identified as the *β*-L-*xylo* isomer (**4b**), was crystalline. Recrystallization from Et_2O–hexane yielded **4b**, m.p. 110–112°, $[\alpha]_D^{20}$ −49.2° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{10}H_{15}IO_6$: C, 33.54; H, 4.22; I, 35.43. Found: C, 33.61; H, 4.25; I, 35.36.

*Methyl 3,4-di-*O*-acetyl-2-deoxy-2-iodo-β-*D*-ribo- and -α-*D*-arabino-pyranosides* (**5a** *and* **5b**). — Separation by column chromatography gave two compounds. The faster-moving component, identified as the *β*-D-*ribo* isomer (**5a**), was isolated as a syrup. Distillation at 90° (0.04 torr) yielded 0.47 g (39%) of **5a**, $[\alpha]_D^{20}$ +10.7° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{10}H_{15}IO_6$: C, 33.54; H, 4.22; I, 35.43. Found: C, 33.54; H, 4.24; I, 35.35.

The slower-moving component, identified as the α-D-*arabino* isomer (**5b**), was crystalline. Recrystallization from Et_2O–hexane yielded 0.37 g (30%) of **5b**, m.p. 100–101°, $[\alpha]_D^{20}$ −51.2° (*c* 1, $CHCl_3$); ^{1}H-n.m.r.: see Tables II and III.

Anal. Calc. for $C_{10}H_{15}IO_6$: C, 33.54; H, 4.22; I, 35.43. Found: C, 33.49; H, 4.25; I, 35.50.

*Methyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-*L*-*arabino*-hexopyranoside* (**1g**). — Methyl 3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-mannopyranoside (**1a**; 100 mg, 0.27 mmol) was dissolved in 1 mL of dry benzene, 0.1 mL of $HSnBu_3$ (0.37 mmol) was added, and the mixture was kept at 60°. The reaction was complete after 1 h. The solution was evaporated under vacuum, redissolved in CH_3CN, and washed four times with hexane (to remove the excess of $HSnBu_3$ and $ISnBu_3$)[35]. The CH_3CN solution was concentrated to a syrup that was purified by vacuum distillation (60°, 0.04 torr), $[\alpha]_D^{20}$ −153° (*c* 1, $CHCl_3$), lit.[36] −156.1°, lit.[37] −150°. The ^{1}H-n.m.r. data (see Tables IV and V) were identical with values in the literature[36]. The final yield was 53 mg (80%).

*Methyl 3,4-di-*O*-acetyl-2-deoxy-α-*L*-threo-pentopyranoside* (**4c**). — Methyl 3,4-di-*O*-acetyl-2-deoxy-2-iodo-α-L-*lyxo*-pentopyranoside (**4a**, 96 mg, 0.27 mmol) was deiodinated with $HSnBu_3$ under the same conditions as just described to afford 47 mg (75%) of a syrup, which was distilled at 60° (0.04 torr), $[\alpha]_D^{20}$ −91° (*c* 1, $CHCl_3$), lit.[38] +86.5° and[39] +85.7° for the D enantiomer; ^{1}H-n.m.r.: see Tables IV and V.

Anal. Calc. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.62; H, 6.98.

*Methyl 3,4-di-*O*-acetyl-2-deoxy-β-*D*-erythro-pentopyranoside* (**5c**). — Methyl 3,4-di-*O*-acetyl-2-deoxy-2-iodo-β-D-ribopyranoside (**5a**, 96 mg, 0.27 mmol) was deiodinated with $HSnBu_3$ under the conditions just described to give 51 mg (82%) of a syrup, which was purified by distillation at 60° (0.04 torr), $[\alpha]_D^{20}$ −193° (*c* 1, $CHCl_3$), lit.[40] +193.6° for the L enantiomer; ^{1}H-n.m.r. see Tables IV and V.

Anal. Calc. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.83; H, 6.96.

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