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STEREOSELECTIVITIES IN THE REACTION OF METHYL 4,6-*O*-BENZYLIDENE-α- AND -β-D-HEXOPYRANOSID-2-ULOSES WITH DIAZOMETHANE*

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ABSTRACT

The stereoselectivities in the reaction with diazomethane of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**2**), its 3-epimer (**3**), its β anomer (**5**), and the corresponding 3-*O*-benzoyl derivative (**4**) have been examined in comparison with those in the Grignard reaction and in reduction with sodium borohydride. The opposite stereoselectivity of the diazomethane reaction, with equatorial attack on α anomers (**2** and **3**) and axial attack on β anomers (**4** and **5**), to that of the other reactions, is explained by an attractive, electrostatic interaction in the transition state between the diazomethyl cation and either the axial O-1 of the methoxyl group or lone-pair electrons of O-5.

INTRODUCTION

In previous papers, we examined the stereoselectivities in nucleophilic reactions of methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose[1] (**1**) and a few glycosid-3-uloses[2,3], and found a complementry stereoselectivity between the Grignard and diazomethane reactions. The abnormality of the latter reaction was deduced to be mainly controlled by an attractive, electrostatic interaction between vicinal and neighboring axial oxygen atoms and the diazomethyl cation in the zwitterionic intermediate. This presumption was strongly supported by the fact that stereoselectivity in the reaction of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*arabino*-hexopyranosid-3-ulose with diazomethane was controlled by the axial O-2 of the 2-methoxyl group, whereas that of the D-*ribo* derivative was controlled by the axial 1-methoxyl oxygen atom[4].

In this paper, the stereoselectivities in the Grignard and diazomethane reactions of the 3-*O*-methyl derivative[5,6] (**2**) of **1**, its 3-epimer[7] (**3**), the β anomer[8] (**4**) of **1**, and its 3-*O*-methyl derivative[5] (**5**) have been further examined. Compound **3** was synthesized by oxidation[9] of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-altropyranoside[10] with

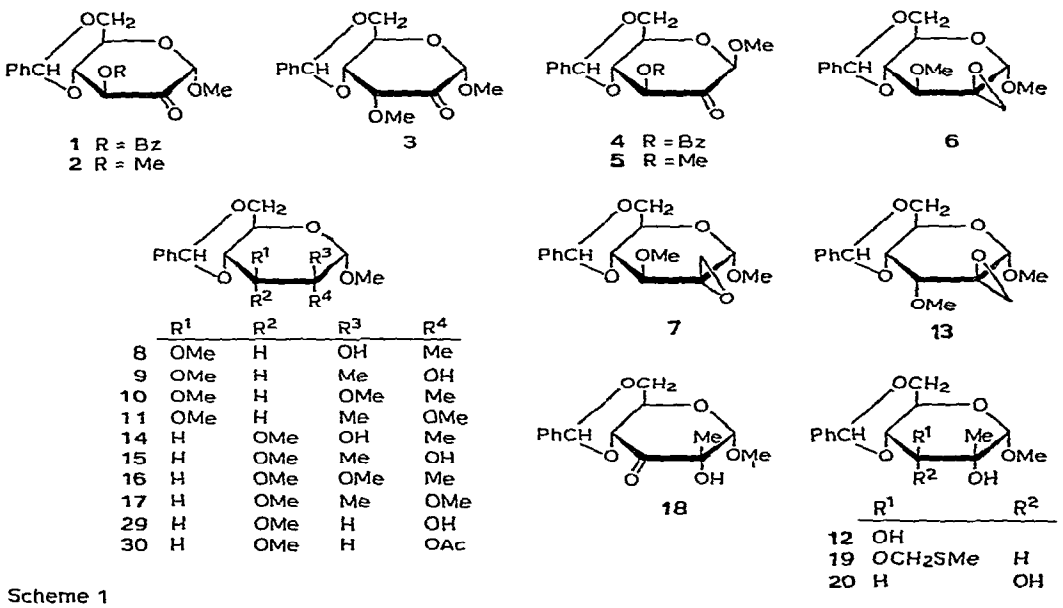
*Branched-chain sugars, Part XIII. For Part XII, see Ref. 4.

dimethyl sulfoxide–trifluoroacetic anhydride. Epimerization at C-3 did not occur during oxidation, but heating **3** in pyridine gave **2** in good yield.

RESULTS

The reaction with diazomethane was usually conducted in a solvent less polar than 1:1:1 benzene–ether–ethanol to suppress the accompanying ring-expansion; the Grignard reaction was performed in benzene–ether at room temperature.

Reaction of **2** with diazomethane gave the corresponding, epimeric spiro epoxides (**6** and **7**) in 63.7 and 31.1% yield, respectively; they were reduced quantitatively with lithium aluminium hydride to give the corresponding 2-*C*-methyl derivatives **8** and **9**. Furthermore, the reaction of **2** with methylmagnesium iodide also gave the epimers **8** and **9** in good yield; these were individually methylated with sodium hydride and methyl iodide to give the corresponding 2-*O*-methyl derivatives (**10** and **11**), respectively. The configuration of **11** (and therefore of **9**) was determined to be D-*gluco* from the fact that the di-*O*-methyl derivative of methyl 4,6-*O*-benzylidene-2-*C*-methyl-α-D-glucopyranoside[1] (**12**) was identical with **11**.



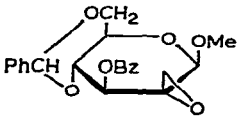
	R^1	R^2	R^3	R^4
8	OMe	H	OH	Me
9	OMe	H	Me	OH
10	OMe	H	OMe	Me
11	OMe	H	Me	OMe
14	H	OMe	OH	Me
15	H	OMe	Me	OH
16	H	OMe	OMe	Me
17	H	OMe	Me	OMe
29	H	OMe	H	OH
30	H	OMe	H	OAc

	R^1	R^2
12	OH	
19	OCH_2SMe	H
20	H	OH

Scheme 1

Reaction of **3** with diazomethane preferentially gave a spiro epoxide (**13**) in 84% yield, and this was reduced quantitatively to give the corresponding 2-*C*-methyl derivative (**14**). Furthermore, the Grignard reaction of methylmagnesium iodide with **3** gave the corresponding, epimeric 2-*C*-methyl derivatives (**14** and **15**) in 92% yield, which were converted into the 2-*O*-methyl derivatives (**16** and **17**), respectively. The configuration of **15** was determined to be D-*allo* by the following conversions. Compound **12** was oxidized with dimethyl sulfoxide–trifluoroacetic anhydride to give the

corresponding glycosid-3-ulose (**18**) and 3-*O*-(methylthio)methyl derivative (**19**) in 42 and 36% yield, respectively. Reduction of **18** with sodium borohydride gave the corresponding D-allopyranoside (**20**) in 88% yield, and subsequent methylation of **20** gave a 2,3-di-*O*-methyl derivative that was identical with **17**. Thus **15** has the *allo* configuration and **14** and **13** have the *altro* configuration.



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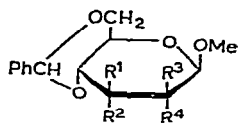
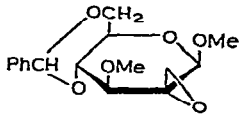


	R^1	R^2	R^3	R^4
22	OH	H	Me	OH
23	OBz	H	Me	OH
24	OBz	H	OH	Me
26	OMe	H	Me	OH
27	OMe	H	Me	OMe
28	OMe	H	OH	Me



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Scheme 2

The configuration of the spiro epoxide (**21**) preferentially obtained from **4** was determined to be D-*gluco* by the rotational change of the corresponding reduced and debenzoylated product (**22**) in cuprammonium solution[11] ($[M]_{436}$—369.0° → $[M]_{436}^{\text{cupra A}}$ 530.7°). Treatment of **4** with methylmagnesium iodide again gave an epimeric mixture of the corresponding 2-*C*-methyl derivatives (**23** and **24**), and the configuration of **23** was determined to be D-*gluco* from the fact that the 3-benzoate of **22** was identical with **23**. Thus **24** has the *manno* configuration.

Reaction of **5** with diazomethane gave the corresponding spiro epoxide (**25**) in good yield, and this was reduced to the 2-*C*-methyl derivative (**26**). The configuration of **26** was determined to be D-*gluco* by the identity of the 2,3-di-*O*-methyl derivative of **22** and 2-*O*-methyl derivative (**27**) of **26**. The Grignard reaction with **5** gave the corresponding, epimeric 2-*C*-methyl derivatives (**26** and **28**) in 77.3 and 17.4% yield, respectively. Thus **28** has the *manno* configuration.

On the other hand, it is known that reduction of alicyclic six-membered ketones by sodium borohydride gives more axial alcohol than that with lithium aluminium hydride[12,13], reflecting the greater effective size of the reagent. In order to compare the stereoselectivities in this reduction of glycosid-2-uloses[5,14], compound **3** was reduced to give the corresponding α-D-allopyranoside (**29**) in 88% yield; this product was characterized as the 2-acetate **30**.

DISCUSSION

The coupling constants ($J_{3,4}$ and $J_{4,5}$) of the glycosid-2-uloses used here [**2** (10.0 and 10.0 Hz), **3** (3.0 and 8.8 Hz), **4** (10.0 and 9.0 Hz), **5** (10.0 Hz and uncertain)] indicate that the pyranosid ring of these compounds is in the $^4C_1$ (D) conformation, flattened slightly by the introduction of the carbonyl group[8]. It is reasonable to suppose that common nucleophiles normally attack a carbonyl group in a pyranoid ring

from the equatorial direction, as established for cyclohexanone derivatives[15]. This behavior was observed in the reaction of methyl 4,6-*O*-benzylidene-α- and -β-D-hexopyranosid-3-uloses with Grignard reagents and with sodium borohydride[4]. However, it has also been reported that the anomeric configuration plays a decisive role in the stereochemical course of the metal-hydride reduction of the 2-carbonyl group of alkyl 4,6-*O*-benzylidene-α- and -β-D-hexopyranosid-2-uloses[6,13,14,16,17], wherein the α anomer mainly undergoes axial attack and the β anomer is attacked equatorially. As shown in Table I, reduction of 3 also gave the product of axial attack exclusively.

TABLE I

YIELDS OF PRODUCTS AND THE DIRECTION OF ATTACK OF NUCLEOPHILES ON THE CARBONYL GROUP IN REACTIONS WITH METHYL 4,6-*O*-BENZYLIDENE-α- AND -β-D-HEXOPYRANOSID-2-ULOSES

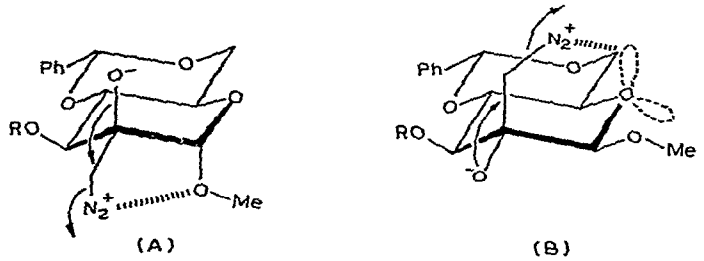
Glycosid-2-ulose	*Yields (%) of products in reactions with CH_2N_2 (upper rows), CH_3MgI (lower rows in parentheses), and $NaBH_4$ (lower rows)*	
	Axial attack	*Equatorial attack*
1		93.4
	77[a] (49.0)	
2	31.1	63.7
	82[b] (49.2)	(44.4)
3		83.5
	88 (35.6)	(56.4)
4	94.4	
	35[c] (45.6)	65[c] (46.3)
5	92 5	
	4[b] (17.4)	82[b] (77.3)

[a–c]Yields are taken from refs. 13, 5, and 14, respectively.

Low stereoselectivities in the Grignard reaction may be due to the ability of magnesium to coordinate with the carbonyl oxygen and also vicinal oxygen atoms at the same time, as deduced from the fact that the stereoselectivities in the Grignard and alkyllithium reactions are sometimes complementary[18].

In contrast, reaction of α anomers with diazomethane gave predominantly the product of equatorial attack, whereas the β anomers suffer axial attack, in complete reversal of the reductions with sodium borohydride. These facts strongly support our previous hypothesis that diazomethane, having a zwitterionic structure, attacks glycosiduloses from the side of an axial alkoxyl group vicinal to the carbonyl group, through operation of an attractive, electrostatic force of the oxygen atom, which also stabilizes the conformation of the diazomethyl cation in the transition state. Thus, the transition state (A) of the α anomer plays a decisive role in determining the stereoselectivity. Although there is no axial oxygen atom in the β anomer, a similar attractive force of a lone pair of electrons on the ring-oxygen atom, as shown in (B), should be considered to explain the exclusive formation of the product of axial

attack. This effect is equivalent to that of the 1-methoxyl oxygen atom of methyl 4,6-*O*-benzylidene-2-*O*-substituted-α-D-*ribo*-hexopyranosid-3-uloses, which controls the stereoselectivity in the same reaction[4].



Scheme 3

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were evaporated under diminished pressure at a bath temperature not exceeding 50°. Optical rotations were measured unless otherwise stated, in chloroform in a 0.2-dm tube with a Carl Zeiss LEP-A1 polarimeter. I.r. spectra were recorded with a Hitachi model EPI-G2 spectrometer. N.m.r. spectra were recorded with a JEOL SP-100 spectrometer in chloroform-*d* containing tetramethylsilane as the internal reference. Chemical shifts and coupling constants are recorded in δ and Hz units, and i.r. frequencies in cm^{-1}.

*Methyl 4,6-O-benzylidene-3-O-methyl-α-D-*ribo*-hexopyranosid-2-ulose* (**3**). — Oxidation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-altropyranoside[10] with dimethyl sulfoxide–trifluoroacetic anhydride under conditions previously reported[7] afforded **3** in 93.5% yield. It was recrystallized from benzene–hexane; m.p. 113–116°, $[\alpha]_D^{22}$ + 69.8° (*c* 1,0); ν_{max}^{KBr} 1730 (C = O); n.m.r. 7.50–7.20 (m, Ph), 5.46 (PhCH), 4.61 (s, H-1), 4.54–4.38 (m, H-5 and 6), 3.99 (d, $J_{3,4}$ 3.0, H-3), 3.72 (q, $J_{4,5}$ 9.0, H-4), 3.68 (t, $J_{5,6}$, = $J_{6,6'}$ = 10.0, H-6'), and 3.47 and 3.40 (2 × OMe).

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.02; H, 6.17.

Crystallization of **3** from methanol–water gave the monohydrate of **3**; m.p. 110–114.5°, $[\alpha]_D^{22}$ + 75.6° (*c* 1.5); ν_{max}^{KBr} 3475 and 3325 (OH).

Anal. Calc. for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.73; H, 6.47.

Epimerization of **3** *to methyl 4,6-O-benzylidene-3-O-methyl-α-D-*arabino*-hexopyranosid-2-ulose* (**2**). — A solution of **3** (2 g) in *N,N*-dimethylformamide (5 mL) and pyridine (0.5 mL) was heated for 12 h at 60–70°, poured into water, and the resulting solution extracted with ether. The extract was evaporated to a solid (72%) that crystallized from ethanol–hexane; m.p. 134–136°, $[\alpha]_D^{22}$ + 39.7° (*c* 0.9) [lit.[6] m.p. 133.5–134.5°, $[\alpha]_D^{22}$ + 42° (*c* 1.0)].

Reaction of glycosid-2-uloses (*2–5*) *with diazomethane.* — To a suspension of **2** (294 mg, 1.0 mmol) in ethanol (30 mL) was added dropwise a solution of diazomethane (2.0 mmol) in ether (10 mL) at 0°. The mixture became homogeneous during the course of the reaction. The mixture was kept for 12 h at room temperature, and then

evaporated to give crystals. Separation of two products by preparative t.l.c. (1:1 ether–hexane) gave methyl 2,2′-anhydro-4,6-*O*-benzylidene-2-*C*-(hydroxymethyl)-3-*O*-methyl-α-D-mannopyranoside (**6**) and -glucopyranoside (**7**) in 63.7 and 31.1% yield, respectively. Compound **6** had m.p. 140–141° (from ethanol-hexane), $[\alpha]_D^{22}$ + 77.9° (*c* 1.0); n.m.r. 7.64–7.20 (m, Ph), 5.56 (PhC*H*), 4.45–3.70 (m, H-3, 4, 5, 6, and 6′), 4.16 (s, H-1), 3.56 and 3.38 (2 × OMe), and 3.14 and 2.74 (ABq, *J* 5.0, epoxy CH_2).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.25; H, 6.56.

Compound **7** had m.p. 168–170° (from ethanol–hexane), $[\alpha]_D^{22}$ + 77.5° (*c* 0.7); n.m.r. 7.64–7.20 (m, Ph) 5.54 (PhC*H*), 4.34 (q, $J_{5,6}$ 4.0, $J_{6,6'}$ 9.6, H-6), 4.24 (s, H-1), 4.20–3.60 (m. H-4, 5, and 6′), 3.50 and 3.44 (2 × OMe), and 3.21 and 2.66 (ABq, *J* 6.0, epoxy CH_2).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.12; H, 6.47.

Similar treatment of **3** (294 mg, 1.0 mmol) in 1:1 benzene–ethanol (30 mL) with diazomethane gave methyl 2,2′-anhydro-4,6-*O*-benzylidene-2-*C*-(hydroxymethyl)-3-*O*-methyl-α-D-altropyranoside (**13**) as a solid (83.5%), which was recrystallized from ethanol–hexane, m.p. 108–109°, $[\alpha]_D^{22}$ + 84.7° (*c* 0.6); n.m.r. 7.50–7.20 (m, Ph), 5.50 (PhC*H*), 4.00 (s, H-1), 3.17 (d, $J_{3,4}$ 3.0, H-3), 3.90 q, $J_{4,5}$ 9.0, H-4), 4.37 (s, H-5), 4.33 (q, $J_{5,6}$ 5.0, H-6), 3.73 (t, $J_{6,6'}$ 11.2, H-6′), 3.48 and 3.36 (2 × OMe), and 2.88 (s, epoxy CH_2).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.15; H, 6.49.

Similar reaction of **4** with diazomethane gave methyl 2,2′-anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-2-*C*-(hydroxymethyl)-β-D-glucopyranoside (**21**) as a syrup that crystallized from ethanol–hexane; yield, 94.4%, m.p. 150–151°, $[\alpha]_D^{22}$ −67.6° (*c* 0.4); n.m.r. 8.10–7.90 and 7.60–7.20 (m, Ph), 5.80 (d, $J_{3,4}$ 9.6, H-3), 5.52 (PhC*H*), 4.79 (s, H-1), 4.60–4.30 (m, H-5), 4.03–3.60 (m, H-4, 6, and 6′), 3.60 (OMe), and 3.30 and 3.15 (ABq, *J* 6.0, epoxy CH_2).

Anal. Calc. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.12; H, 5.53.

Similar reaction of **5** (294 mg, 1.0 mmol) in ethanol (20 mL) with diazomethane gave methyl 2,2′-anhydro-4,6-*O*-benzylidene-2-*C*-(hydroxymethyl)-3-*O*-methyl-β-D-glucopyranoside (**25**) in 92.5% yield. It was recrystallized from ethanol–hexane; m.p. 154–155°, $[\alpha]_D^{22}$ −62.0° (*c* 1.4); n.m.r. 7.60–7.25 (m, Ph), 5.55 (PhC*H*), 4.67 (s, H-1), 4.40 (q, $J_{5,6}$ 4.0, H-6), 3.83 (t, $J_{5,6'} = J_{6,6'}$ 9.0, H-6′), 3.83–3.50 (m, H-4 and 5), 3.54 and 3.52 (2 × OMe), and 3.14 (t, *J* 6.6, epoxy CH_2).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.00; H, 6.93.

Reduction of the spiro epoxides **6**, **7**, **13**, **21**, *and* **25** *with lithium aluminium hydride.* — To a solution of **6** (150 mg, 0.52 mmol) in oxolane (20 mL) was added lithium aluminium hydride (50 mg), and then the mixture was stirred for 1 h at room temperature. The excess of hydride was carefully decomposed with water and the mixture filtered. The filtrate was extracted with chloroform. The extract was washed with water, dried (magnesium sulfate), and evaporated to give colorless syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-methyl-α-D-mannopyranoside (**8**). The syrup was purified by preparative t.l.c. (8:1 benzene–acetone), yield 93%; $[\alpha]_D^{22}$ + 80.2°

(*c* 2.1); ν_{max}^{KBr} 3450 (OH); n.m.r. 7.60–7.32 (m, Ph), 5.56 (PhC*H*), 4.43 (s, H-1), 4.35–3.70 (m, H-4, 5, 6, and 6'), 3.42 (d, $J_{3,4}$ 9.0, H-3), 3.62 and 3.36 (2 × OMe), 2.54 (OH), and 1.29 (Me).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.65; H, 7.09.

Reduction of **7** (150 mg, 0.52 mmol) in oxolane (10 mL) as before gave methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-methyl-α-D-glucopyranoside (**9**) in quantitative yield; m.p. 100–101°, $[\alpha]_D^{22}$ + 95.1° (*c* 1.0); ν_{max}^{KBr} 3500 (OH); n.m.r. 7.60–7.23 (m, Ph), 5.49 (PhC*H*), 4.34 (s, H-1), 4.25 (q, $J_{5,6}$ 2.4, $J_{6,6'}$ 8.0, H-6), 3.90–3.50 (m, H-2, 4, 5, and 6'), 3.52 and 3.37 (2 × OMe), 2.50 (OH), and 1.27 (Me).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.97; H, 7.21.

Similar reduction of **13** (150 mg) in oxolane (5 mL) gave methyl 4,6-*O*-benzylidene-3-*C*-methyl-2-*O*-methyl-α-D-altropyranoside (**14**) in quantitative yield; m.p. 166–168° (from ethanol–hexane), $[\alpha]_D^{22}$ + 68.6° (*c* 1.8); ν_{max}^{KBr} 3575 (OH); n.m.r. 7.60–7.25 (m, Ph), 5.54 (PhC*H*), 4.33 (s, H-1), 4.40–4.00 and 4.00–3.62 (m, H-4, 5, 6, and 6'), 3.62 and 3.44 (2 × OMe), 2.20 (OH), and 1.38 (Me).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.17; H, 7.20.

Similar reduction of **21** (120 mg) in oxolane (5 mL) afforded methyl 4,6-*O*-benzylidene-2-*C*-methyl-β-D-glucopyranoside (**22**) in 94% yield as a syrup; $[\alpha]_D^{22}$ −55.8° (*c* 1.3); ν_{max}^{KBr} 3500 and 3450 (OH); n.m r. 7.60–7.20 (m, Ph), 5.45 (PhC*H*), 4.30 (q, $J_{5,6}$ 4.0, $J_{6,6'}$ 10.0, H-6), 3.92–3.20 (m, H-4, 5, and 6), 3.50 (OMe), 2.73 and 2.25 (s, 2 × OH), 3.50 (OMe), and 1.24 (Me).

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.80: H, 6.80. Found: C, 61.20; H, 7.09.

Similar reduction of **25** (150 mg) in oxolane (5 mL) gave methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-methyl-β-D-glucopyranoside (**26**) in 94% yield; m.p. 113–115° (from ether–hexane), $[\alpha]_D^{22}$ — 53.9° (*c* 0.7); ν_{max}^{KBr} 3500 (OH); n.m.r. 7.60–7.25 (m, Ph), 5.53 (PhC*H*), 4.34 (q, $J_{5,6}$ 4.0, H-6), 4.21 (s, H-1), 3.80 (t, $J_{5,6'}$ $J_{6,6'}$ = 10.0, H-6'), 3.70–3.30 (m, H-3, 4, and 5), 3.64 and 3.56 (2 × OMe), 2.33 (OH), and 1.26 (Me).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.90; H, 7.68.

Reaction of glycosid-2-uloses (**2–5**) *with methylmagnesium iodide.* — To a solution of methylmagnesium iodide in ether (5 mL) and benzene (5 mL), prepared from magnesium turnings (60 mg, 2.47 mmol) and methyl iodide (1 mL), was added a solution of **2** (294 mg, 1 mmol) in benzene (5 mL), and the mixture, after 1.5 h at room temperature, was poured into cold ammonium chloride solution. The resulting solution was extracted with dichloromethane. The extract was washed with water and evaporated to a solid. Separation of two products by preparative t.l.c. (1:1 ether–hexane) gave **8** and its 2-epimer **9** in 44.4 and 49.2% yields, respectively. Both of them were identical with corresponding, authentic samples obtained via the reaction of **2** with diazomethane.

Treatment of **3** with methylmagnesium iodide and separation of two products as before gave **14** and methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-methyl-α-D-allopyranoside (**15**) in 56.4 and 35.6% yield, respectively. Compound **14** was identical with an authentic sample obtained by reaction of **3** with diazomethane.

Compound **15** had m.p. 124–126° (from ether–hexane), $[\alpha]_D^{22}$ + 71.5° (*c* 1.0); ν_{max}^{KBr} 3500 (OH); n.m.r. 7.65–7.25 (m, Ph), 5.51 (PhC*H*), 4.36 (q, $J_{5,6}$ 5.0, H-6), 4.33 (s, H-1), 4.18 (m, H-5), 3.78 (q, $J_{4,5}$ 9.6, H-4), 3.73 (t, $J_{5,6'} = J_{6,6'}$ = 10.0, H-6'), 3.53 (d, $J_{3,4}$ 2.8, H-3), 3.62 and 3.45 (2 × OMe), and 1.37 (Me).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15, Found: C, 62.00; H, 7.16.

Similar reaction of **4** with methylmagnesium iodide and resolution of the two products by preparative t.l.c. (8:1 benzene–acetone) gave methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-*C*-methyl-β-D-mannopyranoside (**23**) and its 2-epimer (**24**) in 45.6 and 46.3% yield, respectively.

Compound **23** had m.p. 163.5°, $[\alpha]_D^{22}$ — 124.1° (*c* 0.9); ν_{max}^{KBr} 3550 and 3400 (OH), 1720 (ester); n.m.r. 8.15–8.00 and 7.66–7.15 (m, Ph), 5.47 (PhC*H*), 5.39 (d, $J_{3,4}$ 9.6, H-3); 4.36 (s, H-1), 4.32 (q, $J_{5,6}$ 3.6, H-6), 4.15 (t, $J_{4,5}$ 9.6, H-4), 3.87 (t, $J_{6,6'} = J_{5,6'}$ 9.6, H-6'), 3.55 (m, H-5), 3.60 (OMe), 2.37 (OH), and 1.27 (Me).

Anal. Calc. for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 66.01; H, 6.07.

Compound **24** had m.p. 162–163° (from benzene–hexane), $[\alpha]_D^{22}$ — 75.1° (*c* 0.8); ν_{max}^{KBr} 3450 (OH), 1730 and 1720 (ester); n.m.r. 8.15–8.00 and 7.60–7.20 (m, Ph), 5.50 (PhC*H*), 5.47 (d, $J_{3,4}$ 9.6, H-3), 4.43 (s, H-1), 4.37 (q, $J_{5,6}$ 4.0, H-6), 3.83 (t, $J_{4,5}$ 9.6, H-4), 3.80 (t, $J_{5,6'} = J_{6,6'}$ = 9.0, H-6'), 3.73 (m, H-5), 3.56 (OMe), 2.02 (OH), and 1.42 (Me).

Anal. Calc. for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 65.98; H, 6.02.

Reaction of **5** and methylmagnesium iodide and separation of the two products as before gave **26** and its 2-epimer, methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-methyl-β-D-mannopyranoside (**28**), in 17.4 and 77.3% yield, respectively.

Compound **28** was a syrup, $[\alpha]_D^{22}$ — 56.8° (*c* 0.8); ν_{max}^{KBr} 3475 (OH); n.m.r. 7.60–7.20 (m, Ph), 5.37 (PhC*H*), 4.34 (q, $J_{5,6}$ 4.8, H-6), 4.18 (s, H-1), 4.02 (t, $J_{3,4} = J_{4,5}$ = 9.2, H-4), 3.86 (t, $J_{5,6'} = J_{6,6'}$ = 10.0, H-6), 3.64 and 3.55 (2 × OMe), 3.37 (m, H-5), 3.12 (d, H-3), 2.30 (OH), and 1.32 (Me).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.34; H, 7.27.

O-*Methylation of* 2-C-*methyl derivatives* (**8**, **9**, **12**, **14**, **15**, **22**, *and* **26**) *with sodium hydride and methyl iodide.* — To a solution of **8** (50 mg, 0.16 mmol) and sodium hydride (10 mg, 0.42 mmol) in *N*,*N*-dimethylformamide (1 mL) was added methyl iodide (0.1 mL) at 0°. The solution was kept for 30 min at room temperature, poured into cold water, and the resulting solution extracted with ether. The extract was evaporated to give syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-2,3-di-*O*-methyl-α-D-mannopyranoside (**10**) in good yield; $[\alpha]_D^{22}$ +84.4° (*c* 0.9); n.m.r. 7.65–7.20 (m, Ph), 5.59 (PhC*H*), 4.50 (s, H-1), 4.26 (q, $J_{5,6}$ 4.0, H-6), 4.13 (m, H-5), 3.88 (t, $J_{3,4} = J_{4,5}$ = 9.0, H-4), 3.80 (d, H-3), 3.50 (t, $J_{5,6} = J_{6,6'}$ = 9.0, H-6'), 3.60, 3.36, and 3.35 (3 × OMe), and 1.33 (Me).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.07; H, 7.49.

Similar methylation of **9** gave syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-2,3-di-*O*-methyl-α-D-glucopyranoside (**11**) in quantitatieve yield; $[\alpha]_D^{22}$ + 72.6° (*c* 1.3); n.m.r. 7.58–7.25 (m, Ph), 5.53 (PhC*H*), 4.51 (s, H-1), 4.28 (q, $J_{5,6}$ 2.8, $J_{6,6'}$ 8.4, H-6), 4.00–3.60 (m, H-4, 5, and 6'), 3.60, 3.42, and 3.37 (3 × OMe), and 1.33 (Me).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.31; H, 7.87.

Similar methylation of methyl 4,6-*O*-benzylidene-2-*C*-methyl-α-D-glucopyranoside (**12**) also gave **11** in good yield.

Similar methylation of **14** gave methyl 4,6-*O*-benzylidene-2-*C*-methyl-2,3-di-*O*-methyl-α-D-altropyranoside (**16**) in 91% yield. It was crystallized from ethanol; m.p. 125–126°, $[\alpha]_D^{22}$ + 44.0° (*c* 0.9); n.m.r. 7.66–7.20 (m, Ph), 5.54 (PhC*H*), 4.37 (s, H-1), 4.37–3.47 (m, H-3, 4, 5, 6, and 6'), 3.58, 3.39, and 3.27 (3 × OMe), and 1.30 (Me).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.68; H, 7.42.

Likewise, methylation of **15** gave methyl 4,6-*O*-benzylidene-2-*C*-methyl-2,3-di-*O*-methyl-α-D-mannopyranoside (**17**) in 88% yield. It was crystallized from ethanol; m.p. 185–187°, $[\alpha]_D^{22}$ + 30.2° (*c* 0.7); n.m.r. 7.60–7.23 (m, Ph), 5.48 (m, PhC*H*), 4.40 (s, H-1), 4.40–4.20 (m, H-5 and 6), 3.87–3.64 (m, H-3, 4, and 6'), 3.60, 3.40, and 3.30 (3 × OMe), and 1.37 (OMe).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: 62.65; H, 7.40.

Methylation of **22** gave syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-2,3-di-*O*-methyl-β-D-glucopyranoside (**27**) in quantitative yield; $[\alpha]_D^{22}$ — 50.2° (*c* 2.9); n.m.r. 7.60–7.20 (m, Ph), 5.53 (PhC*H*), 4.34 (q, $J_{5,6}$ 3.8, H-6), 4.26 (s, H-1), 3.78 (t, $J_{5,6'} = J_{6,6'}$ 10.0, H-6'), 3.70–3.40 (m, H-3, 4, and 5), 3.60, 3,52, and 3.41 (3 × OMe), and 1.26 (Me).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.51; H, 7.75.

Similar methylation of **26** also gave **27** in good yield.

Determination of the configuration of **15**. — Oxidation of **12** (100 mg) with dimethyl sulfoxide–trifluoroacetic anhydride (160 and 315 mg) in dichloromethane under conditions similar to those reported before[7] gave a syrupy mixture of two products that was separated by preparative t.l.c. (8:1 benzene–acetone) to give syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-α-D-*ribo*-hexopyranosid-3-ulose (**18**) and syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-(methylthio)methyl-α-D-glucopyranoside (**19**) in 48 and 36% yields, respectively.

Compound **18** had ν_{max}^{KBr} 3500 (OH), 1740 (C = O); n.m.r. 7.65–7.24 (m, Ph), 5.60 (PhC*H*), 4.78 (s, H-1), 4.65–3.64 (m, H-4, 5, 6, and 6'), 3.44 (OMe), and 1.66 (Me).

Compound **19** showed n.m.r. 7.60–7.23 (m, Ph), 5.53 (PhC*H*), 4.92 (d, $J_{1,2}$ 4.0, H-1), 5.00 (ABq, *J* 16,6, -OCH_2S-), 4.38–3.60 (m, H-4, 5, 6, and 6'), 3.42 (OMe), 2.27 (SMe), and 1.67 (Me).

To a vigorously stirred solution of **18** (30 mg) in methanol (5 mL) was added dropwise a solution of sodium borohydride (10 mg) in methanol (3 mL). After 10 min at room temperature, acetic acid was added to the mixture to decompose the excess of hydride, and the resulting solution was evaporated. An aqueous solution of the residue was extracted with chloroform, and the extract was evaporated to give syrupy methyl 4,6-*O*-benzylidene-2-*C*-methyl-α-D-glucopyranoside (**20**) in 73% yield, which was purified by preparative t.l.c. (8:1 benzene–acetone). The physical constants of **20** were not identical with those of **12**: n.m.r. 7.66–7.20 (m, Ph), 5.57 (PhC*H*), 4.37 (s, H-1), 3.63 (OMe), and 1.33 (Me).

Methylation of **20** as before also gave **17** in good yield.

Reduction of methyl 4,6-O-benzylidene-3-O-methyl-α-D-ribo-hexopyranosid-2-ulose (**3**) *by sodium borohydride.* — Reduction of **3** (100 mg) with sodium borohydride (400 mg) in methanol as before gave methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-allopyranoside (**29**) in quantitative yield. It was crystallized from ethanol–hexane; m.p. 136–138°, $[\alpha]_D^{22}$ + 91.3° (*c* 1.1); ν_{max}^{KBr} 3350 (OH).

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.53; H, 6.92.

Conventional, base-catalyzed acetylation of **29** gave methyl 4,6-*O*-benzylidene-2-*O*-acetyl-3-*O*-methyl-α-D-allopyranoside (**30**) quantitatively; it was crystallized from ethanol–hexane; m.p. 124–125°, $[\alpha]_D^{22}$ + 59.3° (*c* 1.0); ν_{max}^{KBr} 1740 (ester); n.m.r. 7.60–7.26 (m, Ph), 5.53 (PhC*H*), 4.86 (q, H-2), 4.82 (d, $J_{1,2}$ 4.0, H-1), 4.47–4.17 (m, H-5 and 6), 4.00 (t, $J_{2,3} = J_{3,4} = 3.0$, H-3), 3.73 (t, $J_{5,6'} = J_{6,6'} = 10.0$, H-6), 3.67 and 3.47 (2 × OMe), and 2.21 (OAc).

Anal. Calc. for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.34; H, 6.57.

Partial benzoylation of **22** *with benzoic anhydride.* — A solution of **22** (150 mg, 0.51 mmol) and benzoic anhydride (175 mg, 0.77 mmol) in pyridine (2 mL) was stirred for 12 h at room temperature, poured into ice–water, and the resulting solution extracted with chloroform. Conventional processing of the extract gave **23**, identical with product obtained by treatment of **4** with methylmagnesium iodide.

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