Branched-chain Sugars. XII. The Stereoselectivities in the Reaction of Methyl 4,6-*O*-Benzylidene-α- and -β-D-hexopyranosid-3-uloses with Diazomethane[1]

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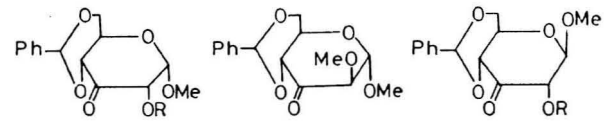
The stereoselectivities in the diazomethane reaction of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose (**2**), its 2-epimer (**3**), β-anomer of **2** and the corresponding 2-*O*-Benzoyl derivative were examined, in comparison with those in the Grignard reaction and sodium borohydride reduction. The complemental stereoselectivity of diazomethane reaction in the case of **2** and **3** indicated that the electrostatic attractive effect in the transition state between diazomethyl cation and the axial methoxyl oxygen at the α-position to carbonyl function in **3** is much stronger than that at β-position which is predominat in the case of **2**. In cases of β-anomers having no axial oxygen, stereoselectivies were preferentially controlled by the usual steric factors.

In previous papers, we examined the stereoselectivities in nucleophilic reactions of methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**)[2] and other uloses,[3,4] and found the complemental stereoselectivity between the Grignard and diazomethane reactions. The abnormality of the latter reaction was deduced to be controlled predominantly by the electrostatic attractive interaction between vicinal or neighboring hydroxyl oxygens and diazomethyl cation in the zwitterionic intermediate.

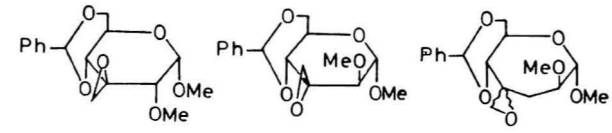
In order to confirm the above hypothesis, the stereoselectivities in the Grignard and diazomethane reactions and in sodium borohydride reduction of 2-*O*-methyl derivative (**2**)[5] of **1**, its 2-epimer (**3**),[6] β-anomer (**4**)[7] of **1** and its 2-*O*-methyl derivative (**5**)[8] were examined in this paper. Compound **5** was obtained by the dimethyl sulfoxide–trifluoroacetic anhydride oxidation[6,9] of methyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-altropyranoside which was synthesized by the preferential ring-opening of the corresponding 2,3-epoxide[10] of D-allo configuration with methanol. Epimerization at C-2 position during the oxidation could not be suppressed in this case.



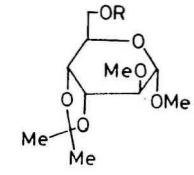
(**1**) R=Bz
(**2**) R=Me

(**3**)

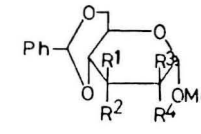
(**4**) R=Bz
(**5**) R=Me



(**6**) (**11**) (**12**)



(**14**) R=H
(**15**) R=Ac



	R^1	R^2	R^3	R^4
(**7**)	OH	Me	H	OMe
(**8**)	Me	OH	H	OMe
(**9**)	Me	OMe	H	OMe
(**10**)	OMe	Me	H	OMe
(**13**)	Me	OH	OMe	H
(**16**)	Me	OAc	H	OMe
(**17**)	Me	OAc	OMe	H
(**18**)	OAc	Me	H	OMe

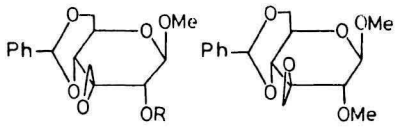
Results

In general, diazomethane reaction was carried out in less polar solvent than benzene–ether–ethanol (1:1:1) to suppress the accompanying ring-expansion, and the Grignard reaction in benzene–ether at room temperature.

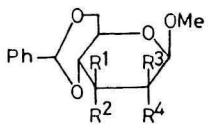
Reaction of **2** with diazomethane gave the corresponding spiro epoxide (**6**) in 73% yield which was reduced with lithium aluminium hydride to give the corresponding 3-*C*-methyl derivative (**7**), quantitatively. Besides, the reaction of **2** with methylmagnesium iodide gave the epimeric 3-*C*-methyl derivative (**8**) of **7** in a good yield which was methylated with sodium hydride and methyl iodide to give 3-*O*-methyl derivative (**9**). The same compound was obtained by *O*-methylation of known methyl 4,6-*O*-benzylidene-3-*C*-methyl-α-D-allopyranoside[3,11] which is the Grignard reaction product of **1**. The 3-*O*-methyl derivative (**10**) of **7** was not identical with **9**. These results indicate that the stereoselectivities in the both reactions of **2** are complemental as was depicted in the case of **1**.[2]

Diazomethane reaction of **3** gave the corresponding spiro epoxide (**11**) and ring-expansion product (**12**) in 41 and 36.9% yields, respectively, by the separation on a TLC. Reduction of **11** gave a 3-*C*-methyl derivative (**13**) which was identical with that obtained by the Grignard reaction of **3**. The configuration of **13** was determined to be D-altro from the following conversions. De-*O*-benzylidenation of **13** with 70% acetic acid and subsequent acetonation gave the corresponding 3,4-*O*-isopropylidene derivative (**14**) which gave the 6-*O*-acetate (**15**) by base-catalyzed acetylation. These results indicate that the tertiary hydroxyl group in **13** was protected by the acetonation, and consequently in *cis*-interrelation to the 4-hydroxyl group.

Chemical shifts of tertiary acetoxyl groups of 3-*O*-acetate of **8** (**16**: δ 2.04) and **13** (**17**: δ 2.00) in the region of axial one (δ 2.07—1.96) supported also the above configurational assignment, but, that of 3-*O*-acetate of **7** (**18**: δ 2.04) was not in agreement with equatorial one (δ 1.93—1.88).[12] Such instances were also reported in the case of nitromethyl-branching derivatives.[13] The position of ring methylene in ring-expanded **12** was determined to be C-3 from the coupling constants ($J_{1,2}$=6.2, $J_{2,3}$=11.0, $J_{2,3'}$=1.8, and $J_{3,3'}$=14.0 Hz) of ring protons.[14]



(**19**) R=Bz (**24**)



	R¹	R²	R³	R⁴
(**20**)	Me	OH	H	OH
(**21**)	Me	OH	H	OBz
(**22**)	OH	Me	H	OBz
(**25**)	Me	OH	H	OMe
(**26**)	Me	OMe	H	OMe
(**27**)	H	OH	H	OMe

The configuration of the spiro epoxide (**19**) predominantly obtained by the diazomethane reaction of **4** was determined to be D-allo by the rotational change of the corresponding reductively cleaved product (**20**) in cupraammonium solution ($[M]_{436}$ −329.2°→ $[M]_{436}^{cupra\ A}$ +77.4°). The Grignard reaction of **4** gave a mixture of epimeric pair of 2-*O*-benzoates (**21** and **22**) and their de-*O*-benzoylated products from which **21**, **22**, and **20** were separated in a pure state on a TLC. The configuration of **21** was determined from the fact that partial benzoylation of **20** gave **21**. The ratio of epimers was measured after de-*O*-benzoylation with a densitometer. Diazomethane reaction of **5** gave the corresponding epimeric spiro epoxides (**23** and **24**) by the separation on a TLC, and the predominant product (**23**) was reduced into the 3-*C*-methyl derivative (**25**). The configuration of **25** was determined to be D-allo from the identity of 2,3-di-*O*-methyl derivative of **20** and 3-*O*-methyl derivative (**26**) of **25**. The Grignard reaction of **5** gave preferentially **25**.

As a standard for the comparison of stereoselectivities, reduction of **2**, **3** and **5** with sodium borohydride in methanol was also carried out. The configuration and the ratio of products were determined with NMR and/or densitomer, after conversion of the products into the corresponding 3-*O*-acetate. In all cases, a product caused by the equatorial attack (from the less-hindered upper side of the pyranose-ring) of the reagent was preferentially obtained, as is known in the cases of cyclohexanone derivatives.[15]

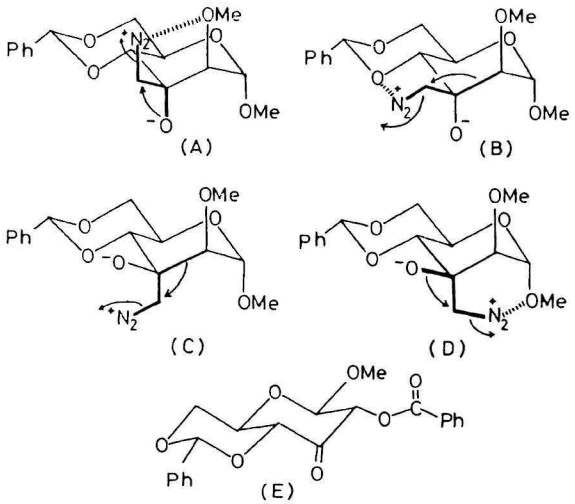
Table 1. Yields of products and the attacking direction of nucleophiles to the pyranose-ring in the reaction with methyl 4,6-*O*-benzylidene-α- and -β-D-hexopyranosid-3-uloses

3-Uloses	Yields (%) of products in CH_2N_2 (upper rows), CH_3MgI (down rows in parentheses), and $NaBH_4$ (down rows) reactions	
	axial attack	equatorial attack
(**1**)	77.3	
		55—90[a] (74.2)
(**2**)	73.0	
		82.0, 94[a] (93.2)
(**3**)		41.0[b]
		77.9 (95.4)
(**4**)		90.2
	45[a] (34.8)	48[a] (52.2)
(**5**)	17.6	76.5
	16.6, 6[a]	75.1, 83[a] (94.2)

a) *Cf.* Y. Kondo, *Carbohydr. Res.*, **30**, 386 (1973). b) A ring-expansion product (**12**) was obtained in 36.9% yield.

Discussion

Coupling constants ($J_{1,2}$ and $J_{4,5}$) of ring protons in starting materials used here [**2** (4.5 Hz and unclear), **3** (0 and 9.0 Hz), **4** (7.5 and 9.5 Hz), and **5** (7.5 and 9.5 Hz)] indicate that the pyranose ring of these compounds is in C1 chair conformation flattened slightly by the introduction of the carbonyl group. Consequently, it is reasonable that nucleophiles preferentially attack the carbonyl group from the equatorial direction, unless any special factors control the stereoselectivity strongly. As shown in Table 1, compound **2** afforded similar results to that of **1** in which the Grignard reaction gave the normal product and diazomethane reaction showed an abnormal stereoselectivity by the electrostatic attractive effect of the oxygen atom in axial C_1-methoxyl group.



In the diazomethane reaction of **3**, three typical transition states (A, B, and C) will be considered for the formation of **11** and **12**. The state (A) in which

the conformation of diazomethylene cation is stabilized by the electrostatic attractive effect of axial C_2-methoxyl oxygen will give smoothly **11**. For the formation of **12** the state (B) in which the conformation of diazomethylene cation is stabilized by C_4-oxygen will be more probable than (C) in which no stabilizing effect can be expected. If diazomethane attacks the carbonyl group of **3** from axial direction as seen in (C), rather stable conformation (D) would afford the 3-epimer of **11**, and actually, a similar transition state should play the essential role in the formation of **6** from **2**. Thus, it will be concluded that **12** was formed *via* (B) and that the complemental stereoselectivity in diazomethane reaction of **2** and **3** is attributed to the more effective electrostatic attractive force of axial oxygen in α-position than β-position to the carbonyl group.

On the other hand, it is known that in reduction of alicyclic six-membered ketones, sodium borohydride produces more axial alcohol than lithium aluminum hydride, reflecting a greater effective size of the reagent.[16] Although there are no remarkable differences in the stereoselectivities of the Grignard reaction and sodium borohydride reduction, the differences in the results of **4** and **5** should be explained by C_2-substituents. However, results in the both reactions of **4** can not compare in the same sense with others, because 2-*O*-benzoyl group is hydrolzyed in reduction and reacts with the Grignard reagent. Nevertheless, it is common that the stereoselectivities in the both reactions of 2-*O*-benzoyl derivatives, **1** and **4**, are lower than those of 2-*O*-methyl derivatives. Higher stereoselectivity in diazomethane reaction of **4** than that of **5** may suggest an attractive effect of carbonyl oxygen of benzoyl group which is placed in the upper region of the pyroanose-ring as shown in (E).

From the results mentioned above, the followings will be concluded. 1) Diazomethane having zwitterionic structure attacks 3-uloses from the side of axial alkoxyl group nearer to the carbonyl group by the electrostatic attractive force of oxygen atom which is also stabilize the conformation of diazomethyl cation in the transition state. Thus, the stereoselectivity in diazomethane reaction of **1** and **2** is complemental to that in usual reactions, whereas, it is the same in the reactions of **3**. 2) When a 3-ulose has no axial substituent, the stereoselectivity in the diazomethane reaction is controlled by the same steric factors as in other reactions.

Experimental

All melting points were uncorrected. The solutions were evaporated under reduced pressure at a bath temperature not exceeding 50 °C. Optical rotations were measured in a 0.2-dm tube with Carl Zeiss LEP-Al polarimeter in chloroform unless otherwise stated. IR spectra were recorded with Hitachi Model EPI-G2 spectrometer. NMR spectra were taken with JEOL SP-100 spectrometer in deuteriochloroform containing TMS as an internal reference. Chemical shifts and coupling constants were recorded in δ and Hz units, and IR frequencies in cm^{-1}.

Methyl 4,6-O-Benzylidene-2-O-methyl-β-D-ribo-hexopyranosid-3-ulose (5). A solution of methyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-allopyranoisde[8] (2 g, 7.6 mmol) and sodium (2 g) in methanol (50 ml) was refluxed for 24 h, poured into water, and then extracted with chloroform. An usual work up of the extract and fractional crystallization of the product from ethanol-hexane and ether-hexane gave the corresponding 2-*O*-methyl-β-D-altropyranoside [mp 122—124 °C; $[\alpha]_D^{22}$ −60.5° (*c* 1.0); Found: C, 59.96; H, 6.91%. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80%; coupling constants ($J_{1,2}$=1.2, $J_{2,3}$=$J_{3,4}$=3.0, $J_{4,5}$=9.0) in the NMR spectrum of the corresponding 3-*O*-acetate supported the structure] and 3-*O*-methyl-β-D-glucopyranoside [mp 168—170 °C; $[\alpha]_D^{22}$ −50.0° (*c* 1.4); lit,[17] mp 172—173 °C, $[\alpha]_D^{14}$ −40.0° (*c* 0.3). Found: C, 60.28; H, 6.77%. Calcd for $C_{15}H_{20}O_6$; C, 60.80; H, 6.80%; coupling constants ($J_{1,2}$=$J_{2,3}$=8.0, $J_{3,4}$=$J_{4,5}$=7.5) in the NMR spectrum of the corresponding 2-*O*-acetate supported the structure] in 45 and 8% yields, respectively.

Oxidation of the above β-D-altropyranoside with dimethyl sulfoxide-trifluoroacetic anhydride under a similar condition reported before[6] afforded **5**, accompanying with the epimerization of 2-*O*-methoxyl group, in 89% yield which was recrystallized from ethanol. Mp 217—219 °C; $[\alpha]_D^{23}$ −110.5° (*c* 0.9) (lit,[8] mp 178—180 °C, $[\alpha]_D^{23}$ −128.2°); IR: 1735 (C=O); NMR: 7.60—7.25 (Ph: m); 5.54 (PhCH); 4.51 (H_1: d, $J_{1,2}$=7.5), 4.49 (H_6: q, $J_{5,6}$=4.5), 4.28 (H_4: q, $J_{4,5}$=9.6, $J_{2,4}$=1.5), 3.89 ($H_{6'}$: t, $J_{5,6'}$=$J_{6,6'}$=9.8), 3.78 (H_2: q), 3.64 (H_5: sex), 3.60 (2×OMe).

Found: C, 61.21; H, 6.18%. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17%.

Reaction of 3-Uloses (2—5) and 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 °C. With proceeding of the reaction, the mixture turned to homogeneous. After keeping the mixture at room temperature for 12 h, the solution was evaporated to give a crystalline methyl 3,3'-anhydro-4,6-*O*-benzylidene-3-*C*-hydroxymethyl-2-*O*-methyl-α-D-glucopyranoside (**6**), which was recrystallized from benzene-hexane. The diazomethane reaction did not proceed in the benzene-ethanol (30 ml, 1:1) in this case. Yield, 167 mg (57%); mp 131—133 °C, $[\alpha]_D^{23}$+76.5° (*c* 0.6), NMR: 7.44—7.20 (Ph: m), 5.45 (PhCH), 4.89 (H_1: d, $J_{1,2}$=4.0), 4.35—4.17 (H_5: m), 3.84 ($H_{6'}$:t, $J_{5,6'}$=$J_{6,6'}$=9.0), 3.84—3.67 (H_4, H_5 and H_6: m), 3.61 (H_2: d), 3.05 (epoxy CH_2: s), 3.49 and 3.44 (2×OMe).

Found: C, 62.10; H, 6.57%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%.

A similar reaction of **3** (294 mg. 1.0 mmol) in benzene-ethanol (30 ml, 1:1) with diazomethane, and sepatartion of two products on a preparative TLC (ether:hexane=1:1) gave methyl 3,3'-anhydro-4,6-*O*-benzylidene-3-*C*-hydroxymethyl-2-*O*-methyl-α-D-altropyranoside (**11**) and a ring-expanded product (**12**) in 41.0% and 36.9% yields, respectively.

11: Mp 141—143 °C (from ether-hexane), $[\alpha]_D^{22}$ +76.1° (*c* 2.1), NMR: 7.55—7.27 (Ph: m), 5.55 (PhCH), 4.76 (H_1: s), 4.44—4.12 (H_4, H_6, and $H_{6'}$: m), 3.86 (H_5: m), 3.18 and 2.75 (epoxy CH_2: ABq, J=4.8), 3.44 (2×OMe), 3.06 (H_2: s).

Found: C, 61.58; H, 7.05%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%.

12: Mp 157—160 °C (from ether-hexane), $[\alpha]_D^{22}$+91.6 °C (*c* 0.5), NMR: 7.55—7.27 (Ph: m), 5.46 (PhCH), 4.48 (H_1: d, $J_{1,2}$=6.2), 4.72 (H_7: q, $J_{6,7}$=4.4), 4.04 (H_6: m), 3.85 (H_5: d, $J_{5,6}$=9.0), 3.67 (H_2: octet), 3.62 ($H_{7'}$: t, $J_{7,7'}$=$J_{6,7'}$=8.8), 3.23 and 2.73 (epoxy CH_2: ABq, J=5.6), 2.34 (H_3: q, $J_{2,3}$=11.0), 1.45 ($H_{3'}$: q, $J_{2,3'}$=1.8, $J_{3,3'}$=14.0), 3.44 and 3.37 (2×OMe).

Found: C, 63.31; H, 6.84%. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%.

Reaction of **4** and diazomethane in a similar manner as above gave methyl 3,3′-anhydro-2-*O*-benzoyl-4,6-*O*-benzylidene-3-*C*-hydroxymethyl-β-D-allopyranoside (**19**) as a sirup in 90.2% yield. $[\alpha]_D^{27}$ −32.6° (*c* 1.9), NMR: 8.13—7.95 and 7.60—7.24 (Ph: m), 5.54 (PhCH), 5.42 (H_1: d, $J_{1,2}$=7.5), 4.83 (H_2: d), 4.43 (H_5: m), 3.58—4.03 (H_4, H_6, and $H_{6'}$: m), 3.10 and 2.72 (epoxy CH_2: ABq, J=4.5), 3.55 (OMe).

Found: C, 65.95; H, 5.46%. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57%.

A similar reaction of **5** (294 mg, 1.0 mmol) in benzene-ethanol (10 ml, 1:1) with diazomethane and the separation of two products in a similar way gave the epimeric pair of spiro epoxides, methyl 3,3′-anhydro-4,6-*O*-benzylidene-3-*C*-hydroxymethyl-2-*O*-methyl-β-D-allopyranoside (**23**) and the corresponding β-D-glucopyranoside (**24**) in 76.5 and 17.6% yields, respectively.

23: Mp 157—158 °C, $[\alpha]_D^{23}$ −63.8° (*c* 1.1), NMR: 7.56—7.23 (Ph: m), 5.51 (PhCH), 4.58 (H_1: d, $J_{1,2}$=7.5), 4.23—4.47 (H_6: m), 3.95—3.60 (H_4, H_5, and $H_{6'}$: m), 3.37 (H_2: d), 3.10 and 3.01 (epoxy CH_2: ABq, J=5.7), 3.59 and 3.55 (2×OMe).

Found: C, 62.53; H, 6.47%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%.

24: Mp 150—151 °C, $[\alpha]_D^{23}$ −74.9° (*c* 1.0), NMR: 7.55—7.20 (Ph: m), 5.46(PhCH), 4.35 (H_6: q, $J_{5,6}$=5.0), 4.34 (H_1: d, $J_{1,2}$=7.6), 3.83 (H_4: d, $J_{4,5}$=9.5), 3.77 ($H_{6'}$: t, $J_{5,6'}$=$J_{6,6'}$=10.4), 3.65—3.35 (H_5: m), 3.36 (H_2: d), 3.06 (epoxy CH_2: s), 3.47 and 3.55 (2×OMe).

Found: C, 62.22; H, 6.51%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%.

*Hydrogenation of Spiro Epoxides (**6**, **11**, **19**, and **23**) with Lithium Aluminium Hydride.* To a solution of **6** (150 mg, 0.52 mmol) in tetrahydrofuran (THF, 20 ml) was added lithium aluminium hydride (LAH, 50 mg), and then the mixture was stirred at room temperature for 1 h. The excess hydride was carefully decomposed with water, and then filtered. The water layer was extracted with chloroform. The combined extract was washed with water, dried with anhydrous magnesium sulfate, and evaporated to give a colorless sirup of methyl 4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-α-D-glucopyranoside (**7**). The sirup was purified with preparative TLC (benzene:acetone=8:1, R_f=0.25). Yield 92%, $[\alpha]_D^{23}$+67.4° (*c* 1.2), NMR: 7.60—7.20 (Ph: m), 5.49 (PhCH), 4.84 (H_1: d, $J_{1,2}$=4.0), 4.28 (H_5: m), 3.80—3.30 (H_2, H_4, H_6, and $H_{6'}$: m), 3.42 and 3.30 (2×OMe), 2.43 (OH: s), 1.46 (Me).

Found: C, 61.87; H, 7.16%. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15%.

A similar reduction of **11** (150 mg, 0.52 mmol) in THF (10 ml) as above gave methyl 4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-α-D-altropyranoside (**13**) in quantitative yield, which was crystallized from ether-hexane. Mp 88—91 °C, $[\alpha]_D^{23}$ +26.6° (*c* 2.1), IR: 3530 (OH), NMR: 7.60—7.20 (Ph: m), 5.58 (PhCH), 4.79 (H_1: broad s), 4.33 (H_6: q), 4.06 (H_5: sex), 3.80 ($H_{6'}$: t, $J_{5,6'}$=$J_{6,6'}$=8.6), 3.67 (H_4: d, $J_{4,5}$ =9.0), 3.15 (H_2: s), 3.49 and 3.46 (2×OMe), 1.38 (Me).

Found: C, 61.99; H, 7.19%. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15%.

A similar hydrogenation of **19** (150 mg) in THF (5 ml) as above gave methyl 4,6-*O*-benzylidene-3-*C*-methyl-β-D-allopyranodise (**20**) in 87% yield. Mp 123—125 °C (from benzene-hexane). $[\alpha]_D^{23}$ −53.2° (*c* 1.2), IR: 3480 (OH), NMR: 7.50—7.16 (Ph: m), 5.47 (PhCH), 4.47 (H_1: d, $J_{1,2}$=8.0), 4.33 (H_6: q, $J_{5,6}$=3.6), 3.67 ($H_{6'}$: t, $J_{5,6'}$=$J_{6,6'}$=10.0), 3.30 (H_4: d, $J_{4,5}$=9.6), 3.20 (H_2: d), 3.50 (OMe), 1.40 (Me).

Found: C, 60.52; H, 6.73%. Calcd for $C_{15}H_{20}O_6$; C, 60.80; H, 6.80%.

A similar hydrogenation of **23** (100 mg) in THF (5 ml) afforded methyl 4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-β-D-allopyranoside (**25**) in 92% yield, which was crystallized from ethanol hexane. Mp 150—151 °C, $[\alpha]_D^{23}$ −79.8° (*c* 1.3), IR: 3525 and 3400 (OH), NMR: 7.50 —7.16(Ph: m), 5.47 (PhCH), 4.47 (H_1: d, $J_{1,2}$=8.0), 4.43 (H_6: q, $J_{5,6}$ =3.6), 3.67 ($H_{6'}$: t, $J_{5,6'}$=10.0), 3.30 (H_4: d, $J_{4,5}$=9.6), 3.20 (H_2: d), 3.50 (OMe), 1.40 (Me).

Found: C, 61.91; H, 7.05%. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15%.

*Reaction of 3-Uloses (**2**—**5**) with Methylmagnesium Iodide.* To a solution of methylmagnesium iodide in ether (5 ml)-benzene (5 ml) prepared from magnesium turnings (60 mg, 2.47 mmol) and methyl iodide (1 ml) was added **2** (294 mg, mmol) in benzene (5 ml), and the reaction mixture was kept at room temperature for 1.5 h, poured into cold ammonium chloride solution. The resulting solution was extracted with dichloromethane. The extract was washed with water and evaporated to give a white powder of methyl 4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-α-D-allopyranoside (**8**) which was crystallized from ethanol-hexane. Yield, 93.2%, mp 140—142° C, $[\alpha]_D^{23}$ +85.0° (*c* 1.5), IR: 3530 (OH), NMR: 7.65—7.27 (Ph: m), 5.55 (PhCH), 4.94 (H_1: d, $J_{1,2}$=3.8), 4.37 (H_6: q, $J_{5,6}$=4.8), 4.10 (H_5: sex), 3.72 ($H_{6'}$:t, $J_{5,6'}$=$J_{6,6'}$=9.8), 3.37 (OH), 3.30 (H_4: d, $J_{4,5}$=9.0), 3.15 (H_2: d), 3.55 and 3.49 (2×OMe), 1.42 (Me).

Found: C, 61.60; H, 7.06%. Calced for $C_{16}H_{22}O_6$: C, 61.92, H, 7.15%.

A similar reaction of **3** and methylmagnesium iodide as above gave **13** in 95.4% yield, which was identical with the authentic sample obtained *via* the diazomethane reaction of **3**.

Reaction of **4** and methyl magnesium iodide in a similar manner as above and separation of three products on a preparative TLC (benzene: acetone=8:1) gave methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*C*-methyl-β-D-allopyranodide (**21**), its 3-epimer (**22**) and de-benzoylated product, **20** in 33, 8, and 19% yields, respectiviely.

21: Mp 180—181 °C (from benzene-hexane), $[\alpha]_D^{23}$ −40.3° (*c* 1.7), IR: 3540 and 3475 (OH), 1724 and 1690 (ester), NMR: 8.15—8.00 and 7.60—7.20 (Ph: m), 5.65(PhCH), 5.02 and 4.86 (H_1 and H_2: each d, $J_{1,2}$=8.0), 4.35 (H_4: d, $J_{4,5}$=8.0), 4.00 (H_5: sex), 4.40 (H_6: q, $J_{5,6}$=4.0), 3.77 ($H_{6'}$: t, $J_{5,6}$=$J_{6,6'}$=10.0), 3.47 (OMe), 2.07 (OH), 1.35 (Me).

Found: C, 65.15; H, 5.93%. Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04%.

22: $[\alpha]_D^{23}$ −37.2° (*c* 1.5), IR: 3500 (OH), 1735 (ester), NMR: 8.20—8.04 and 7.70—7.27 (Ph: m), 5.58 (PhCH), 5.18 (H_2: d, $J_{1,2}$=8.0), 4.57 (H_1: d), 4.39 (H_6: q, $J_{5,6}$=4.2), 3.82 ($H_{6'}$: t, $J_{5,6'}$=$J_{6,6'}$=10.0), 3.82—3.54 (H_4 and H_5: m), 3.49 (OMe), 2.60 (OH: broad s), 1.50 (Me).

20: all phisical constants were identical with the authentic sample which was derived from the reaction of **4** and diazomethane.

Grignard reaction of **5** in a similar way as above gave **25** in 94.2% yield, which was identical with the authentic sample obtained *via* the diazomethane reaction of **5**.

*O-Methylation of 3-C-Methyl Derivatives (**7**, **8**, **20**, and **25**) with Sodium Hydride and Methyl Iodide.* To a solution of **7** (50 mg. 0.16 mmol) and sodium hydride (10 mg, 0.42 mmol) in DMF (1 ml) was added methyl iodide (0.1 ml) at

0 °C. After keeping the mixture at room temperature for 30 min, the solution was poured into cold water, and the water layer was extracted with ether. The extract was evaporated to gave sirupy methyl 4,6-*O*-benzylidene-3-*C*-methyl-2,3-di-*O*-methyl-α-D-glucopyranoside (**10**) in a good yield. $[\alpha]_D^{22}$ +56.4° (*c* 1.7), NMR: 7.60—7.24 (Ph: m), 5.54 (PhCH), 4.82 (H_1: d, $J_{1,2}$=4.0), 4.28 (H_6: m), 3.87—3.60 (H_4, H_5, and $H_{6'}$: m), 3.34 (H_2: d), 3.52, 3.43, and 3.40 (3×OMe), 1.47 (Me).

Found: C, 62.31; H, 7.66%. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46%.

A similar methylation of **8** gave methyl 4,6-*O*-benzylidene-3-*C*-methyl-2,3-di-*O*-methyl-α-D-allopyranoside (**9**) in a quantitative yield which was recrystallized from hexane. Mp 91—92 °C, $[\alpha]_D^{22}$ +95.6° (*c* 2.1), NMR: 7.60—7.20 (Ph: m), 5.41 (PhCH), 4.85 (H_1: d, $J_{1,2}$=4.0), 4.45—4.10 (H_5 and H_6: m), 3.80—3.35 (H_4 and $H_{6'}$: m), 3.09 (H_2: d), 3.45, 3.44 and 3.43 (3×OMe), 1.46 (Me).

Found: C, 63.00; H, 7.43%. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46%.

A similar methylation of methyl 4,6-*O*-benzylidene-3-*C*-methyl-α-D-allopyranoside[2] gave also **9** in a good yield.

Methylation of **20** in a similar manner as above gave sirupy methyl 4,6-*O*-benzylidene-3-*C*-methyl-2,3-di-*O*-methyl-β-D-allopyranoside (**26**) in 89% yield which was crystallized from ether-hexane. Mp 94—95 °C, $[\alpha]_D^{22}$ −45.1° (*c* 1.7), NMR: 7.56—7.27 (Ph: m), 5.39 (PhCH), 4.72 (H_1: d, $J_{1,2}$=8.0), 4.36 (H_6: q, $J_{5,6}$=4.5), 3.90 (H_5: m), 3.68 ($H_{6'}$: t, $J_{5,6'}=J_{6,6'}$=9.8), 3.34 (H_4: d, $J_{4,5}$=9.0), 2.78 (H_2: d), 3.56, 3.52, and 3.47 (3×OMe), 1.49 (Me).

Found: C, 62.82; H, 7.88%. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46%.

Methylation of **25** gave also compound **26** in a good yield.

*Determination of the Configuration of **13**.* To a solution of **13** (150 mg, 0.48 mmol) in 70% aqueous acetic acid was refluxed until the starting material disappeared on TLC (benzene:acetone=8:1). Then the solution was evaporated to give a sirup which was chromatographically homogeneous.

A solution of the sirup and anhydrous copper(II) sulfate (300 mg) in acetone (10 ml) containing one drop of sulfuric acid was stirred for 24 h at room temperature, neutralized with barium carbonate, filtered, and the filtrate was evaporated to give a sirupy methyl 3,4-*O*-isopropyliden-3-*C*-2-*O*-dimethyl-α-D-altropyranoside (**14**) in 73% yield, which was purified on TLC (ether:hexane=1:1). $[\alpha]_D^{22}$ +112.3° (*c* 1.4), IR: 3480 (OH), NMR: 4.37 (H_1: d, $J_{1,2}$=6.0), 4.00—4.30 (H_4, H_5, H_6 and $H_{6'}$: m), 3.30 (H_2: d), 3.60 and 3.46 (2×OMe), 2.15 (OH: broad s), 1.52 and 1.43 (isopropylidene-Me), 1.37 (Me).

Found: C, 54.98: H, 8.35%. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45%.

Base-catalyzed acetylation of **14** gave a sirupy methyl 6-*O*-acetyl-3,4-*O*-isopropylidene-3-*C*,2-*O*-dimethyl-α-D-altropyranoside (**15**) in a quantitative yield. $[\alpha]_D^{23}$ +101.9° (*c* 1.0). IR: 1740 (ester), NMR: 4.35 (H_1: d, $J_{1,2}$=6.0), 4.50—3.87 (H_5, H_6, and $H_{6'}$: m), 3.83 (H_4: d, $J_{4,5}$=9.0), 3.28 (H_2: d), 3.57 and 3.28 (2×OMe), 2.12 (OAc), 1.49 and 1.40 (isopropylidene-Me), 1.35 (Me).

Found: C, 55.33; H, 7.98%. Calcd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95%.

*Acid-catalyzed Acetylation of Tertiary Hydroxyl Gruop in **7**, **8**, and **13**.* A solution of **7** (100 mg) and *p*-toluensulfonic acid (10 mg) in acetic anhydride (3 ml) was stirred at room temperature for 1.5 h, poured into ice-water, and the resulted solution was extracted with chloroform. The extracts were washed with sodium hydrogencarbonate and then water, dried and evaporated to give methyl 3-*O*-acetyl-4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-α-D-glucopyranoside (**18**) which was recrystallized from ethanol-hexane. Yield, 92%; mp 111.5—112.5 °C; $[\alpha]_D^{23}$ +11.9° (*c* 1.4) IR: 1720 (ester), NMR: 7.60—7.25 (Ph: m), 5.53 (PhCH), 4.90 (H_1: d, $J_{1,2}$=4.2), 4.78 (H_4: d, $J_{4,5}$=9.0), 4.62 (H_2: d), 4.45—4.15 and 3.95—3.60 (H_5, H_6 and $H_{6'}$: m), 3.51 and 3.43 (2×OMe), 2.04 (OAc), 1.55 (Me).

Found: C, 59.86; H, 6.69%. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86%.

Acid-catalyzed acetylation of **8** in a similar way as above gave methyl 3-*O*-acetyl-4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-α-D-allopyranoside (**16**) in 94% yield, which was crystallized from ethanol-hexane. Mp 192—194 °C, $[\alpha]_D^{22}$ +39.2° (*c* 0.6), IR: 1738 (ester), NMR: 7.60—7.27 (Ph: m), 5.53 (PhCH), 4.86 (H_1: d, $J_{1,2}$=4.0), 4.33 (H_6: q, $J_{5,6}$=5.0), 4.22 (H_5: m), 3.68 ($H_{6'}$: t, $J_{5,6'}=J_{6,6'}$=9.0), 3.32, (H_4: d, $J_{4,5}$=9.2), 3.14 (H_2: d), 3.56 and 3.46 (2×OMe), 2.04 (OAc), 1.94 (Me).

Found: C, 61.49; H, 6.32%. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86%.

A similar acetylation of **13** as above gave methyl 3-*O*-acetyl-4,6-*O*-benzylidene-3-*C*:2-*O*-dimethyl-α-D-altropyranoside (**17**) in 91% yield, which was crystallized from benzene-hexane. Mp 189—191 °C, $[\alpha]_D^{23}$ +34.9° (*c* 0.7), IR: 1730 (ester), NMR: 7.64—7.28 (Ph: m), 5.55 (PhCH), 4.68 (H_1: d, $J_{1,2}$=1.4) 4.34 (H_2: d), 4.45—4.10 and 3.90—3.60 (H_4, H_5, H_6 and $H_{6'}$: m), 3.52 and 3.38 (2×OMe), 2.00 (OAc), 1.70 (Me).

Found: C, 61.55; H, 6.85%. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86%.

*Partial Benzoylation of **20** with Benzoic Anhydride.* A solution of **20** (150 mg, 0.51 mmol) and benzoic anhydride (175 mg, 0.77 mmol) in pyridine (2 ml) was stirred at room temperature for 12 h, poured into ice-water, and the resulting solution was extracted with chloroform. The usual work up of the extracts gave **21** which was identical with that obtained by the reaction of **4** with methylmagnesium iodide.

*Hydrogenation of 3-Uloses (**2**, **3**, and **5**) with Sodium Borohydride in Mathenol.* To a vigorously stirring solution of **2** (100 mg) in methanol (15 ml) was added dropwise a solution of sodium borohydride (400 mg) in methanol (8 ml). After the reduction was continued for 10 min at room temperature, acetic acid was added to the reaction mixture to decompose the excess hydride, and the resulting solution was evaporated. An aqueous solution of the crude product was extracted with chloroform in a usual manner to give sirupy product. The configuration and the ratio of products were examined with NMR spectrometer and/or densitomether after conversion into the corresponding *O*-acetate by a usual method. In this case, only methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-methyl-α-D-allopyranoside was obtained in 82% yield. Mp 116—117 °C, (from ethanol-hexane), IR: 1738 (ester), $[\alpha]_D^{22}$ +78.8° (*c* 0.7), NMR: 7.60—7.25 (Ph: m), 5.90 (H_3: t, $J_{2,3}=J_{3,4}$=3.0), 4.83 (H_1: d, $J_{1,2}$=4.0), 4.30 (H_5: m, $J_{4,5}$=9.6), 4.16 (H_6: q, $J_{5,6}$=5.0), 3.70 ($H_{6'}$: t, $J_{5,6'}=J_{6,6'}$=9.6), 3.62 (H_4: q, $J_{4,5}$=9.6), 3.47 and 3.45 (2×OMe), 2.17 (OAc).

Found: C, 60.36; H, 6.61%. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55%.

A similar reduction of **3** and subsequent acetylation of the product gave sirupy methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-methyl-α-D-altropyranoside in 77.9% yield. $[\alpha]_D^{22}$ +113.1° (*c* 1.9), NMR: 7.65—7.20 (Ph: m), 5.57 (PhCH), 5.27 (H_3: t, $J_{2,3}=J_{3,4}$=3.2), 4.66 (H_1: s), 3.49 and 3.88 (2×OMe), 2.09 (OAc).

Reduction and acetylation of **5** as above gave epimeric mixture of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-methyl-β-D-glucopyranoside and -allopyranoside in 75.1 and 16.6%

yields, respectively. NMR data of the mixture was the following: major product: 7.60—7.24 (Ph: m), 5.85 (H_3: t, $J_{2,3}=J_{3,4}=3.0$), 5.50 (PhCH), 4.62 (H_1: d, $J_{1,2}=9.0$), 4.37 (H_6: q, $J_{5,6}=3.4$, $J_{6,6'}=8.4$), 4.03—3.46 (H_4, H_5 and $H_{6'}$: m), 3.20 (H_2: q), 3.55 and 3.44 (2×OMe), 2.14 (OAc). Minor product: 5.45 (PhCH), 5.24 (H_3: t, $J_{2,3}=J_{3,4}=9.4$), other protons could not be assigned.

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References

1) Part XI: J. Yoshimura, M. Matsuzawa, and M. Funabashi, *Bull. Chem. Soc. Jpn.*, **51**, 2067 (1978).
2) J. Yoshimura, K. Sato, K. Kobayashi, and C. Shin, *Bull. Chem. Soc. Jpn.*, **46**, 1515 (1973).
3) J. Yoshimura, K. Kobayashi, K. Sato, and M. Funabashi, *Bull. Chem. Soc. Jpn.*, **45**, 1806 (1972).
4) J. Yoshimura, K. Mikami, K. Sato, and C. Shin, *Bull. Chem. Soc. Jpn.*, **49**, 1686 (1976).
5) P. M. Collins, P. Gupta, and R. Lyer, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 1670.
6) J. Yoshimura, K. Sato, and H. Hashimoto, *Chem. Lett.*, **1977**, 1327.
7) P. M. Collins, D. Gardiner, S. Kumar, and W. G. Overend, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2596.
8) Y. Kondo, *Agr. Biol. Chem.*, **39**, 2251 (1975).
9) S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, **41**, 957, 3329 (1976).
10) R. D. Guthrie, A. M. Prior, and S. E. Creasey, *J. Chem. Soc. C*, **1970**, 9761.
11) F. A. Carey and K. O. Hodgson, *Carbohydr. Res.*, **12**, 463 (1970).
12) F. W. Lichtenthaler, *Fortschr. Chem. Forsch.*, **14**, 556 (1970); F. W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, **1976**, 577.
13) J. H. Jordaan, J. J. Nieuwenhuis, and C. J. Lourens, *Carbohydr. Res.*, **51**, 195 (1976).
14) T. D. Inch, G. J. Lewis, R. P. Peel, and N. Williams, *J. Chem. Soc., Chem. Commun.*, **1970**, 1549.
15) E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975).
16) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); M. Milikovic, M. Gligorijevic, and D. Milikovic, *J. Org. Chem.*, **39**, 2118 (1974).
17) Y. Kondo, *Agr. Biol. Chem.*, **39**, 1879 (1975).