Carbohydrate Research, 103 (1982) 221–238
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

STEREOSELECTIVITIES IN THE REACTIONS OF α-D-HEXOPYRANOSID-4-ULOSES WITH DIAZOMETHANE*

KEN-ICHI SATO AND JUJI YOSHIMURA

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227 (Japan)

(Received August 18th, 198.; accepted for publication, October 1st, 1981)

ABSTRACT

The stereoselectivities in the reactions of diazomethane with various α-D-hexopyranosid-4-uloses are compared with those in Grignard reactions. The results support the hypothesis that the stereoselectivity of the diazomethane reaction is mainly controlled by the attractive, electrostatic force between the diazomethyl cation and a neighbouring, axial oxygen or the axial lone-pair electrons of O-5 in the transition state.

INTRODUCTION

We have examined the stereoselectivities of the nucleophilic reactions of various hexopyranosid-2-uloses[2] and -3-uloses[3], and often found complementary stereoselectivities between the Grignard and diazomethane reactions. As a result, it was concluded that the stereoselectivity in diazomethane reactions is mainly controlled by the attractive, electrostatic force between neighboring axial oxygens and the diazomethyl cation in the zwitterionic intermediate[4].

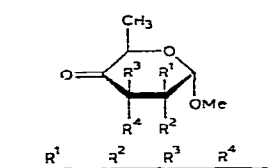
In order to generalise the above hypothesis, the stereoselectivities in the Grignard and diazomethane reactions of methyl 6-deoxy-2,3-di-*O*-methyl-α-D-*xylo*-hexopyranosid-4-ulose (**1**), the corresponding 2,3-di-*O*-benzyl derivative[5] (**2**), the D-*lyxo* (**3**) and D-*ribo* (**4**) diastereomers of **1**, methyl 6-deoxy-2,3-di-*O*-methyl-α-D-*arabino*-hexopyranosid-4-ulose (**5**), the corresponding 3-*O*-benzyl-2-*O*-methyl derivative (**6**), the benzyl 6-deoxy-2,3-*O*-methylene analogue[6] (**7**) of **1**, and methyl 6-deoxy-2,3-*O*-methylene-α-D-*lyxo*-[5] (**8**) and -α-D-*ribo*-hexopyranosid-4-uloses[6] (**9**) have been examined.

RESULTS

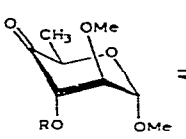
Syntheses of new α-D-hexopyranosid-4-uloses. — Compounds **1**, **3**, **4**, **5**, and **6** were synthesised as follows. The reaction of methyl 4,6-*O*-benzylidene-2,3-di-*O*-

*Branched-chain sugars, XXXI. For part XXX, see ref. 1.

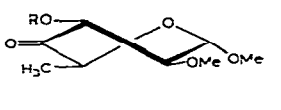
0008-6215/82/0000–0000/S 02.75,



	R^1	R^2	R^3	R^4
1	H	OMe	OMe	H
2	H	OBzl	OBzl	H
3	OMe	H	OMe	H
4	H	OMe	H	OMe

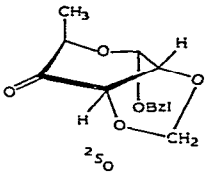


$^4C_1$



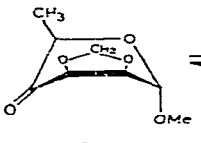
$^0S_2$

5 R = Me
6 R = Bzl



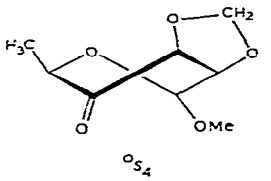
$^2S_0$

7

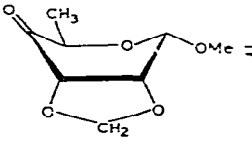


$B_{1,4}$

8

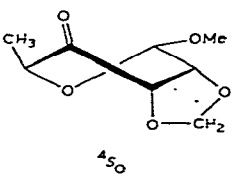


$^0S_4$

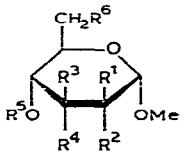


$^1,^4B$

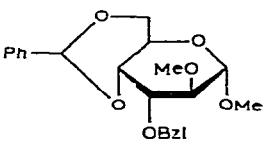
9



$^4S_0$



	R^1	R^2	R^3	R^4	R^5	R^6
10	H	OMe	OMe	H	Bz	Br
11	H	OMe	OMe	H	Bz	H
12	H	OMe	OMe	H	H	H
13	OMe	H	OMe	H	H	OTs
14	OMe	H	OMe	H	H	H
15	OMe	H	H	OMe	Bz	Br
16	OMe	H	H	OMe	Bz	H
17	OMe	H	H	OMe	H	H
19	OMe	H	H	OBzl	H	OTs
20	OMe	H	H	OBzl	H	H



18

methyl-α-D-glucopyranoside[7] with *N*-bromosuccinimide in carbon tetrachloride gave methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (**10**) in 89% yield. Reduction of **10** in dimethyl sulfoxide with sodium borohydride gave the corresponding 6-deoxy derivative **11** in 92% yield. Treatment of **11** with sodium hydroxide in aqueous ethanol gave methyl 6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (**12**, 74%).

Monotosylation of methyl 2,3-di-*O*-methyl-α-D-mannopyranoside[8] gave the corresponding 6-tosylate (**13**) in 86% yield. Reduction of **13** in dimethyl sulfoxide with sodium borohydride gave the corresponding 6-deoxy derivative (**14**, 93%).

TABLE I

^{1}H-N.M.R. PARAMETERS OF THE α-D-HEXOPYRANOSID-4-ULOSES

4-Uloses	*Chemical shifts (δ) and coupling constants (Hz)*					
	H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,5}$)	*H-5* ($J_{5,6}$)	*H-6*	*Others*
1	4.94d (3.4)	3.44dd (10.8)	4.14d	4.21q (6.8)	1.28d	3.58, 3.55 and 3.54 (3 OMe)
3	4.86d (2.0)	3.96dd (3.6)	4.26d	4.20q (7.0)	1.33d	3.53, 3.53 and 3.48 (3 OMe)
4	4.95d (4.5)	4.00dd (3.5)	4.20d	4.46q (7.0)	1.34d	3.55, 3.55 and 3.52 (3 OMe)
5	4.77d (2.5)	3.38dd (8.8)	4.14d	4.13q (7.4)	1.37d	3.56, 3.53 and 3.42 (3 OMe)
6	4.75d (2.6)	3.47dd (9.3)	4.35dd (1.0)	4.15dq (7.0)	1.34d	3.53 and 3.43 (2 OMe) 4.86 and 4.62 (ABq, *J* 11.0, CH_2Ph)

Using the foregoing *N*-bromosuccinimide route, methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-altropyranoside[9] was converted into the corresponding 6-deoxy derivative **17**, *via* **15** and **16**, in 67% overall yield.

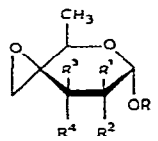
Benzylation of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-altropyranoside[10] in *N*,*N*-dimethylformamide with sodium hydride and benzyl bromide gave the corresponding 3-*O*-benzyl derivative (**18**) quantitatively. Partial hydrolysis of **18** in boiling 70% acetic acid for 6 h followed by monotosylation of the product gave methyl 3-*O*-benzyl-2-*O*-methyl-6-*O*-*p*-tolylsulfonyl-α-D-altropyranoside (**19**, 73%). Reduction of **19** with sodium borohydride in dimethyl sulfoxide gave the corresponding 6-deoxy derivative (**20**, 81%).

Oxidation of **12**, **14**, **17**, and **20**, and methyl 6-deoxy-2,3-di-*O*-methyl-α-D-allopyranoside[11] with dimethyl sulfoxide–trifluoroacetic anhydride[12] gave the 4-uloses **1**, **3**, **5**, **6**, and **4**, respectively, in good yield. ^{1}H-N.m.r. data in Table I indicate that **1**, **3**, and **4** exist in the usual $^4C_1$(D) conformation, flattened slightly by the introduction of the carbonyl group. However, the $J_{2,3}$ values of **5** (8.8 Hz) and **6** (9.3 Hz) imply that these compounds exist in the $^OS_2$ conformation.

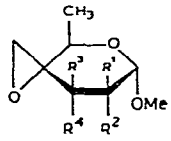
Nucleophilic reactions and structural determination of the products. — In general, the diazomethane and Grignard reactions were carried out at room temperature in ethanol–ether and ether, respectively, until the starting material had disappeared. The configurations of the spiro-epoxides obtained by the diazomethane reaction were mainly determined from the chemical shifts of the *C*-methyl carbons in the ^{13}C-n.m.r. spectra, after reduction to the corresponding 4-*C*-methyl derivatives.

The reaction of **1** with diazomethane gave the spiro-epoxides having D-*galacto* (**21**) and D-*gluco* (**27**) configurations, and a ring-expansion product (**32**), in yields of 21, 51, and 24%, respectively. Likewise, **2** gave analogous products (**22**, **28**, and **33**)

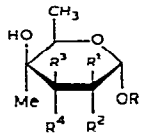
in analogous yields. In contrast, the reactions of **3** and **4** with diazomethane each gave one spiro-epoxide having the D-*manno* (**29**) and D-*gulo* (**23**) configuration in yields of 42 and 87%, respectively. The configuration of **29** and **23** indicates an axial and an equatorial attack of diazomethane, respectively. In the case of **5** in the $^{O}S_{2}$ conformation, the epimeric spiro-epoxides having D-*ido* (**24**) and D-*altro* (**30**) configurations were obtained in yields of 46 and 24%, respectively. A similar reaction of **7** gave the corresponding spiro-epoxide of D-*galacto* configuration (**25**) in 52% yield, together with 21% of the ring-expansion product **34**. The reactions of **8** and **9** each gave one spiro-epoxide (**31** and **26**) having the same configurations as those obtained from the corresponding 2,3-di-*O*-methyl derivatives (**3** and **4**) in yields of 82 and 78%, respectively.



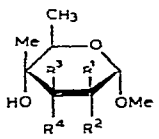
	R	R^1	R^3	R^2	R^4
21	Me	H	OMe	OMe	H
22	Me	H	OBzl	OBzl	H
23	Me	H	H	OMe	OMe
24	Me	OMe	H	H	OMe
25	Bzl	H	OCH_2O		H
26	Me	H	H	OCH_2O	



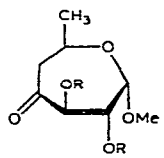
	R^1	R^3	R^2	R^4
27	H	OMe	OMe	H
28	H	OBzl	OBzl	H
29	OMe	OMe	H	H
30	OMe	H	H	OMe
31	OCH_2O		H	H



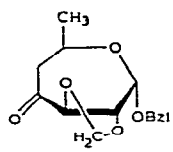
	R	R^1	R^3	R^2	R^4
35	Me	H	OMe	OMe	H
36	Me	H	OBzl	OBzl	H
37	Me	H	H	OMe	OMe
38	Me	OMe	H	H	OMe
39	Bzl	H	OCH_2O		H
40	Me	H	H	OCH_2O	
41	Me	OMe	OMe	H	H
42	Me	OCH_2O		H	H
50	Me	OMe	H	H	OBzl



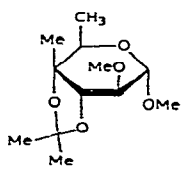
	R^1	R^3	R^2	R^4
43	H	OMe	OMe	H
44	H	OBzl	OBzl	H
45	OMe	OMe	H	H
46	OMe	H	H	OMe
47	OCH_2O		H	H
48	H	H	OMe	OMe
49	H	H	OCH_2O	
51	OMe	H	H	OBzl



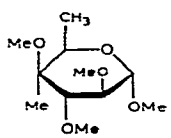
32 R = Me
33 R = Bzl



34



52



53

From the ^{1}H-n.m.r. parameters of the aforementioned spiro-epoxides summarised in Table II, it is evident that **24** ($J_{2,3}$ 7.0 Hz) with the D-*ido* configuration retains the conformation of the parent 4-ulose (**5**), whereas **30** ($J_{2,3}$ 4.0 Hz) with the D-*altro* configuration has the changed $^4C_1$ conformation.

Reduction of the spiro-epoxides **21**–**31** in oxolane with lithium aluminum

TABLE II

^{1}H-N.M.R. PARAMETERS OF 4,4^1-ANHYDRO-4-*C*-HYDROXYMETHYL DERIVATIVES

Compound	*Chemical shifts (δ) and coupling constants (Hz)*						
	H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{1,3}$)	*H-5* ($J_{5,6}$)	*H-6*	*H-4^1,4$^{1'}$* ($J_{A,B}$)	*Others*[a]
21	4.90d (3.8)	3.57dd (9.8)	3.86d	4.24q (6.4)	1.04d	2.95d, 2.65d (4.6)	3.57, 3.57, and 3.47 (3 OMe)
22	4.67d (3.8)	3.77dd (9.8)	4.17d	4.17q (6.6)	1.00d	2.92d, 2.51d (5.0)	3.40 (OMe), 4.87–4.55m (2 ABq, *J* 11.0 and 12.0, 2 CH_2Ph)
23	4.87d (4.0)	3.60dd (3.8)	3.22d	4.54q (6.4)	1.00d	2.86d, 2.84d (5.0)	3.47, 3.47, and 3.44 (3 OMe)
24	4.63d (3.4)	3.25dd (7.0)	3.38d	4.16q (6.4)	1.12d	2.95d, 2.55d (5.0)	3.51, 3.45 and 3.44 (3 OMe)
25	5.39d (3.0)	3.72dd (10.0)	4.27d	4.12q (6.4)	0.98d	2.99d, 2.75d (4.6)	5.17s and 5.03s (OCH_2O) 4.94 and 4.72 (ABq, *J* 12.0, CH_2Ph)
26	4.83d (4.5)	4.38dd (6.0)	3.61d	4.41q (6.8)	1.06d	2.86d, 2.77d (4.0)	5.23d and 4.98d (OCH_2O, *J* 2.0) 3.46 (OMe)
27	4.86d (3.6)	3.29dd (9.8)	3.78d	4.21q (6.6)	1.04d	3.07d, 2.79d (5.4)	3.57, 3.56, and 3.48 (3 OMe)
28	4.61d (3.8)	3.54dd (10.0)	4.15d	4.22q (6.4)	1.01d	3.13d, 2.78d (5.0)	3.41 (OMe), 4.83 and 4.62 (ABq, *J* 12.0, CH_2Ph), 4.69s (CH_2Ph)
29	4.76d (2.0)	3.63dd (3.4)	3.78d	4.14q (7.0)	1.06d	3.06d, 2.89d (5.0)	3.48, 3.44, and 3.43 (3 OMe)
30	4.65bs	— (4.0)	3.18d (0.5)	4.45q (6.4)	1.07d	2.90d, 2.60d (4.4)	3.50, 3.44, and 3.44 (3 OMe)
31	5.10s	4.05d (5.6)	4.25d	4.06q (6.6)	1.13d	2.86d, 2.93d (4.0)	3.44 (OMe), 4.93s (OCH_2O)

[a]Data on phenyl protons are omitted.

hydride gave the corresponding 4-*C*-methyl derivatives (**35–40** and **43–47**) in yields of 85–95%, respectively.

The Grignard reaction of the α-D-hexopyranosid-4-uloses showed complementary stereoselectivities to those of the diazomethane reactions, except for **7**. Thus, the reactions of **1** and **2** with methylmagnesium iodide in ether gave **35** and **36**, respectively, as the main product. Similar reactions of **3** and **4** gave the 4-epimers (**41** and **48**) of **45** and **37** in yields of 85 and 92%, respectively. In the case of **5**, **38** and **46** were obtained in yields of 18 and 77%, respectively. As reported previously[5], the reactions of **7–9** with methylmagnesium iodide in ether gave **39** and the 4-epimers (**42** and **49**) of **47** and **40** in yields of 89, 96, and 95%, respectively.

The ^{1}H-n.m.r. parameters and the ^{13}C-chemical shifts of the *C*-methyl carbons of the 4-*C*-methyl derivatives are summarised in Tables III and IV, respectively. The coupling constants of **38** ($J_{1,2}$ 1.6, $J_{2,3}$ 3.0 Hz), **46** ($J_{1,2}$ 2.0, $J_{2,3}$ 4.2 Hz), **40** ($J_{1,2}$ 5.4, $J_{2,3}$ 5.4 Hz), and **49** ($J_{1,2}$ 5.2, $J_{2,3}$ 5.6 Hz)[5] clearly indicate the conformational change into $^1C_4$ from $^0S_2$ ($J_{1,2}$ 2.0, $J_{2,3}$ 8.8 Hz) and $^4S_0$ ($J_{1,2}$ 4.0, $J_{2,3}$ 8.8 Hz) for the parent 4-uloses (**5** and **9**).

TABLE III

^{1}H-N.M.R. PARAMETERS OF 4-*C*-METHYL DERIVATIVES

4-C-methyl derivative	*Chemical shifts (δ) and coupling constants (Hz)*							
	H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{1,3}$)	*H-5* ($J_{5,6}$)	*H-6*	*CMe*	*OH*	*Others*[a]
35	4.82d (3.8)	3.47dd (9.8)	3.21d	3.69q (6.5)	1.23d	1.16s	2.25bs	3.63s, 3.51s, and 3.43s (3 OMe)
36	4.60d (3.8)	3.86dd (9.5)	3.58d	3.71q (6.5)	1.21d	1.12s	2.25bs	3.38s (OMe)
37	4.82d (4.0)	3.64dd (3.6)	3.38d	4.07q (6.6)	1.13d	1.20s	2.46bs	3.57s, 3.48s, and 3.44s (3 OMe)
38	4.70d (1.6)	3.16dd (3.0)		3.95q (6.6)	1.17d	1.11s		3.50s, 3.50s, and 3.43s (3 OMe)
40	4.74d (5.4)	4.27t (5.4)	3.75d	4.04q (6.6)	1.20d	1.25s	2.35bs	3.40s (OMe), 5.20d and 5.00d (*J* 2.0, OCH_2O)
41	4.79d (1.8)	3.59dd (3.3)	3.18d	3.64q (6.6)	1.22d	1.13s	1.86bs	3.54s, 3.47s, and 3.38s (3 OMe)
43	4.77d (3.8)	3.16dd (10.0)		3.75q (6.6)	1.17d	1.14s	2.16bs	3.64s, 3.49s, and 3.43s (3 OMe)
44	4.55d (3.8)	3.43dd (9.8)	3.73d	3.73q (6.4)	1.11d	1.14s	1.96bs	3.38s (OMe)
45	4.73bs (2.0)	3.59dd (4.0)		3.73q (6.6)	1.20d	1.27s	1.95bs	3.49s, 3.46s, and 3.38s (3 OMe)
46	4.55d (2.0)	(4.2)	3.15d	3.86q (6.6)	1.17d	1.20s	2.88s	3.55s, 3.46s, and 3.40s (3 OMe)
47	4.85d (1.0)	3.95dd (6.2)	4.13d	3.80q (6.6)	1.26d	1.22s	2.81bs	3.43s (OMe), 5.18d and 4.87d (*J* 1.0, OCH_2O)
48	4.74dd (3.0)	3.61–3.43m (2.0)		3.87q (6.6)	1.14d	1.17s	3.04bs	3.61s, 3.49s, and 3.43s (3 OMe)
50	4.68bs (2.0)	3.48–3.30m		4.03q (6.6)	1.15d	1.08s		3.42s and 3.36s (2 OMe)
51	4.57dd (2.0)	3.50–3.35m (1.0)		3.95q (7.0)	1.19d	1.19s	2.81s	3.41s (2 OMe)
52	4.58d (2.0)	(3.2)	3.90d	3.95q (6.6)	1.18d	1.28s	—	3.53s and 3.43s (2 OMe), 1.48s and 1.42s (Ip)
53	4.54d (4.8)	3.11dd (7.8)		3.84q (6.6)	1.21d	1.16s	—	3.56s, 3.53s, 3.43s, and 3.28s (4 OMe)

[a]Data on benzyl protons are omitted.

The ^{13}C-chemical shifts of the methyl branching carbons in **35** and **43** reflect the equatorial and axial orientations as reported[13]. Fairly large deviations observed in the chemical shifts of other axial carbons are attributed to flattened $^4C_1$(D) conformations due to the axial substituents. This deduction was chemically confirmed with **6** as follows. The reaction of **6** with methylmagnesium iodide in ether at −78° gave 94% of the corresponding 4-*C*-methyl-D-*altro* derivative (**51**). This configuration, which is the same as that of **46** from **5**, was proved by the conversion of **51** into methyl 6-deoxy-3,4-*O*-isopropylidene-4-*C*-methyl-2-*O*-methyl-α-D-altropyranoside

TABLE IV

^{13}C-CHEMICAL SHIFTS OF METHYL BRANCHING CARBONS OF 4-*C*-METHYL DERIVATIVES

Chemical shifts (p.p.m.) of 4-C-methyl carbons	
Equatorial	*Axial*
21.9 (**35**)	14.5 (**43**)
19.9 (**41**)	16.1 (**45**)
22.0 (**37**)	17.8 (**48**)
21.4 (**38**)	18.9 (**46**)
22.1 (**39**)[a]	—
21.1 (**42**)[a]	—
21.4 (**40**)	18.4 (**49**)[a]

[a]Data from ref. 5.

(**52**) by successive hydrogenolysis in the presence of palladium-carbon and acetonation with acetone–anhydrous cupric sulfate–sulfuric acid. This fact indicates that the tertiary hydroxyl group in **51** is *cis* to HO-3. In contrast to the Grignard reaction, the reaction of methyl-lithium with **6** at −78° gave the 4-epimer (**50**) of **51** in quantitative yield. Hydrogenolysis of **50** and subsequent *O*-methylation (sodium hydride–methyl iodide) gave methyl 6-deoxy-4-*C*-methyl-2,3,4-tri-*O*-methyl-α-D-idopyranoside (**53**) in a good yield. The same compound was obtained by *O*-methylation of **38**, showing that **46** has the D-*altro* configuration.

The configurations of ring-expansion products (**32–34**) were determined by n.m.r. decoupling experiments involving H-6 and methylene protons.

TABLE V

STEREOSELECTIVITIES IN THE REACTIONS OF α-D-HEXOPYRANOSID-4-ULOSES WITH DIAZOMETHANE AND METHYLMAGNESIUM IODIDE

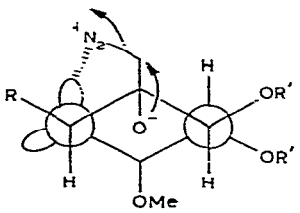
Hexopyranosid-4-ulose	*Yields (%) of products in reaction with CH_2N_2 and MeMgI (in parentheses)*	
	Equatorial attack	*Axial attack*[a]
1	21 (75)	51 (21)
2	15 (74)	45 (19)
3	(85)	42
4	87	(92)
5	46 (18)	24 (77)
7	52 (89)[b]	
8	(96)[b]	82
9	78	(95)[b]

[a]Axial and equatorial attacks refer to the $^4C_1$(D) conformation of individual hexopyranosid-4-uloses. [b]Data from ref. 5.

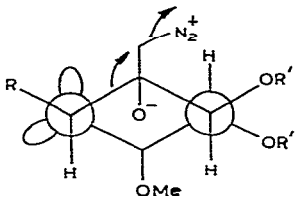
DISCUSSION

The stereoselectivities in the Grignard and diazomethane reactions are summarised in Table V.

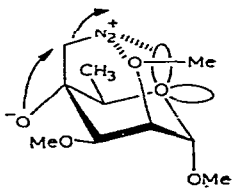
In the diazomethane reaction of **1** and **2**, an attractive, electrostatic force between the axial lone-pair electrons of O-5 and the diazomethyl cation, as shown in **52**, is attributed to the predominant formation of the products (**27** and **28**) of axial attack. However, when the R (Me-5 in **1** and **2**) group sterically hinders the attractive interaction, the diazomethyl group adopts the conformation shown in **53**, and affords the ring-expansion products (**32** and **33**). In fact, the diazomethane reaction of benzyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-D-*xylo*-hexopyranosid-4-ulose, in which R is the bulky Ph_3COCH_2 group, gave similar products of ring expansion and axial attack in yields of 60 and 15%, respectively[14]. For **3** and **4**, the transition states **54** and **55** will predominantly give the products (**29** and **23**) of axial and equatorial attack, respectively. Because the conformation of **5** is easily changed between $^4C_1$ and $^0S_2$, depending on the sp^3 and sp^2 structure of C-4 (*cf.* Results), the transition state will adopt the $^4C_1$



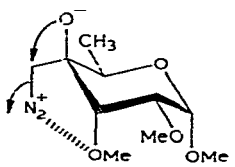
52



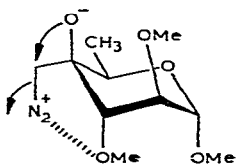
53



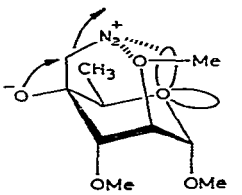
54



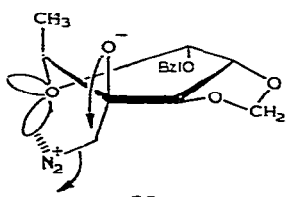
55



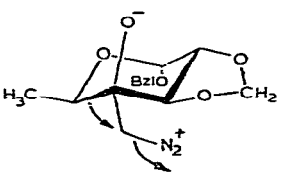
56



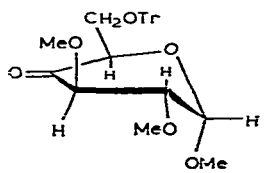
57



58



59



60

conformation. Therefore, the epimeric ratio in the products (**24** and **30**) reflects the predominance of the transition state **56** over **57**. For **7**, the $^{2}S_{0}$ conformation was deduced from the value[15] of $J_{3,5}$ 1.5, in which the strain caused by the 2,3-*O*-methylene ring is released, and consequently the transition state **58** explains the predominant formation of the product of equatorial attack. However, restoration of the conformation **59** before epoxide-ring formation will afford the ring-expansion product (**34**). For **8**, an axial O-3 in the $B_{1,4}$ and $^{O}S_{4}$ conformations, or O-2 in the $^{4}C_{1}$ conformation, commonly controls the stereoselectivity to axial attack, and consequently **31** was formed exclusively. Analogously, the diazomethane reaction of **9** gave only **26**. Thus, our previous hypothesis can be generalised to the α-D-hexopyranosid-4-uloses mentioned here.

The stereoselectivities in the Grignard reaction can be explained as follows. Although the ability of magnesium to co-ordinate with the carbonyl oxygen and also vicinal oxygen atoms can sometimes play the decisive role in the Grignard reaction[16], equatorial attack will be predominant[17] unless hindered by neighbouring axial substituents. Thus, the reaction of **1** and **2** with methylmagnesium iodide gave mainly products (**35** and **36**) of equatorial attack. The axial MeO-2 in **3** enhances equatorial attack, to give **41** exclusively. For **4**, the co-ordination of magnesium to both the carbonyl oxygen and O-3 may cause the conformational change from $^{4}C_{1}$ to $^{O}S_{2}$ where the axial MeO-2 will hinder equatorial attack, to give the product (**48**) of axial attack exclusively. Even if co-ordination does not occur, the axial O-3 in the $^{4}C_{1}$ conformation will prevent equatorial attack. The epimeric ratio of the products in the Grignard reaction of **5** may reflect the comparative magnitudes of the steric hindrances on both sides of the plane of the pyranoid ring in the co-ordination ($^{O}S_{2}$) state. Only in the case of **7** are the stereoselectivities in the Grignard and diazomethane reactions the same, indicating the steric hindrance of Me-5 in the $^{2}S_{0}$ conformation in the former reaction. It is not clear whether the co-ordination of magnesium to **8** and **9** causes the conformational changes from $^{O}S_{4}$ to $^{4}S_{0}$ and from $^{4}S_{0}$ to $^{O}S_{4}$, respectively. However, equatorial attack in such co-ordination states, and also the steric hindrance of axial substituents in other conformations, should commonly give the same results, as shown in Table V.

Differences in the stereochemical course of addition of Grignard reagents and diazomethane to glycosiduloses have been noticed[18–20] and an effect of the neighbouring oxygen has been suggested[21]. The accumulated data[20–22] on the stereoselectivity in these reactions of pyranosid-2-uloses and -3-uloses can now be explained.

The low stereoselectivities in both reactions of 1,2;4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose[23] are attributed to its flexible conformation. Overend *et al.*[24] reported the same stereoselectivity for both reactions of methyl 2,3-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-4-ulose. Although no information on the conformation of the ulose is available, the stereoselectivity of the Grignard reaction can be explained by equatorial attack on the co-ordinated $^{4}C_{1}$ conformation; however, the stereoselectivity of the diazomethane reaction cannot be explained unless the $^{1,4}B$ conformation is involved. Axial attack[25] of the Grignard reagent and diazo-

methane on 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose may be explained as follows. In this rigid-ring system, the axial substituent at C-5 prevents equatorial attack of the Grignard reagent, regardless of the co-ordination and non-co-ordination states. In spite of the presence of an axial O-3, this steric hindrance also occurs in the diazomethane reaction[26], and the axial lone-pair electrons of O-5 will assist axial attack.

Miljkovic *et al.*[27] found that the reaction of 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose with methyl-lithium in ether at −80° gave, stereospecifically, the product of axial attack, whereas methylmagnesium iodide in ether at −80° afforded selectively the product of equatorial attack. They explained the former reaction by hindrance by MeO-1 of equatorial attack in the half-chair conformation **60** which is adopted to avoid the strong electrostatic repulsion arising from coplanarity of the carbonyl and C-3 oxygens. Therefore, the equatorial attack of methyl-lithium on **6** may be explained by the greater steric hindrance of an axial MeO-2 than that of MeO-3 in the $^4C_1$ conformation. More data on this aspect are required.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were evaporated under diminished pressure at a bath temperature not exceeding 45°. Specific rotations were measured for solutions in chloroform with a 0.2-dm tube and a Carl Zeiss LEP-Al polarimeter. I.r. spectra were recorded with a Hitachi Model EPL-G2 spectrometer. ^{1}H-N.m.r. spectra were recorded with a JEOL PS-100 spectrometer for solutions in chloroform-*d* with tetramethylsilane as the internal standard. ^{13}C-N.m.r. data (Table IV) were recorded with a JEOL FX-100 spectrometer at 25.16 MHz for solutions in chloroform-*d*, using 8K data points, with proton-noise decoupling. Column chromatography was performed on silica gel (Wakogel C-200) and preparative t.l.c. was performed on silica gel (Merck, type 60).

Methyl 4-O-benzoyl-6-bromo-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (**10**). — A suspension of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside[7] (5.0 g, 16.1 mmol), *N*-bromosuccinimide (3.4 g, 19.2 mmol), and barium carbonate (0.7 g) in carbon tetrachloride (100 mL) was boiled under reflux for 1.5 h, filtered, and then evaporated to dryness. A solution of the resulting syrup in ether was washed twice with water, dried, filtered, and evaporated, to afford a colorless syrup (5.6 g, 89%), which appeared to be essentially homogeneous (t.l.c. and n.m.r.). A portion of the syrup was purified by preparative t.l.c. with 1:1 ether–hexane, to give **10** as a syrup, $[\alpha]_D^{23}$ +72° (*c* 1.4); n.m.r.: δ 8.20–8.00 and 7.70–7.30 (m, 5 H, Ph), 5.08 (t, 1 H, *J* 9.2 Hz, H-4), 4.94 (d, 1 H, *J* 3.6 Hz, H-1), 4.05 (oct, 1 H, $J_{5,6}$ 3.4, $J_{5,6'}$ 7.4 Hz, H-5), 3.76 (t, 1 H, *J* 9.2 Hz, H-3), 3.55, 3.53, and 3.40 (3 s, 9 H, 3 OMe), 3.40–3.60 (m, 2 H, H-6,6'), and 3.40 (dd, 1 H, H-2).

Anal. Calc. for $C_{16}H_{21}BrO_6$: C, 49.37; H, 5.44; Br, 20.53. Found: C, 49.03; H, 5.40; Br, 20.85.

Methyl 4-O-benzoyl-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (**11**). — To a solution of **10** (3.0 g, 7.7 mmol) in dimethyl sulfoxide (30 mL) was added sodium borohydride (1.5 g, 41 mmol) with stirring, and the mixture was kept at 80° for 3 h, poured into water (150 mL), and extracted with ether. The usual processing of the ether extract gave a colorless syrup which showed essentially one spot in t.l.c. (8:1 benzene–acetone). A portion of the syrup was purified by preparative t.l.c., to give a colorless syrup (2.2 g, 92%), $[\alpha]_D^{23}$ +76° (*c* 1.5); n.m.r.: δ 8.15–8.00 and 7.70–7.30 (m, 5 H, Ph), 4.97 (t, 1 H, *J* 10.0 Hz, H-4), 4.84 (d, 1 H, *J* 4.0 Hz, H-1), 3.91 (oct, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 6.0 Hz, H-5), 3.70 (t, 1 H, *J* 10.0 Hz, H-3), and 3.57, 3.48, and 3.48 (3 s, 9 H, 3 OMe), 3.37 (dd, 1 H, H-2), and 1.23 (d, 3 H, H-6).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.87; H, 7.13.

Methyl 6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (**12**). — A solution of **11** (1.5 g, 4.8 mmol) in ethanol (10 mL) and aqueous sodium hydroxide (2M, 30 mL) was boiled under reflux for 2 h and then extracted with chloroform. The extract was washed with water, dried, and evaporated, to afford a colorless syrup (730 mg, 74%), which was homogeneous by t.l.c. and n.m.r. spectroscopy. A portion of the syrup was purified by preparative t.l.c. (8:1 benzene–acetone), to give **12**, $[\alpha]_D^{23}$ +143° (*c* 1.1); n.m.r.: δ 4.78 (d, 1 H, *J* 3.2 Hz, H-1), 3.70 (oct, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 6.2 Hz, H-5), 3.64, 3.49, and 3.43 (3 s, 9 H, 3 OMe), 3.55–3.40 (t, 1 H, H-3), 3.24 (dd, 1 H, $J_{2,3}$ 9.0 Hz, H-2), 3.14 (t, 1 H, H-4), 2.72 (bs, 1 H, OH), and 1.27 (d, 3 H, H-6).

Anal. Calc. for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.18; H, 8.72.

Methyl 2,3-di-O-methyl-6-O-p-tolylsulfonyl-α-D-mannopyranoside (**13**). — To a solution of methyl 2,3-di-*O*-methyl-α-D-mannopyranoside[8] (5.0 g, 22.5 mmol) in pyridine was added *p*-toluenesulfonyl chloride (5.2 g, 27.0 mmol) at 0° with stirring. After storage at room temperature for 18 h, the solution was poured into ice–water and extracted with chloroform. The usual processing of the extracts gave a colorless syrup which showed one major spot, and a minor, fast-moving substance (ditosylate). The major component (7.3 g, 86%), isolated by chromatography on a column of silica gel with 10:1 benzene–acetone, had $[\alpha]_D^{23}$ +26° (*c* 0.8): n.m.r.: δ 7.77 and 7.29 (2 d, 4 H, *J* 8.4 Hz, Ph), 4.76 (d, 1 H, *J* 1.4 Hz, H-1), 4.50–4.10 (m, 2 H, $J_{5,6}$ 2.0, $J_{5,6'}$ 6.4, $J_{6,6'}$ 11.0 Hz, H-6,6'), 3.77–3.60 (m, 2 H, $J_{4,5}$ 9.0 Hz, H-4,5), 3.57 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 3.45–3.28 (dd, 1 H, $J_{3,4}$ 9.0 Hz, H-3), and 3.41, 3.41, and 3.30 (3 s, 9 H, 3 OMe). Coupling constants were measured by the use of a shift reagent, $Eu(FOD)_3$.

Anal. Calc. for $C_{16}H_{24}O_8S$: C, 51.05; H, 6.43; S, 8.52. Found: C, 50.83; H, 6.33; S, 8.76.

Methyl 6-deoxy-2,3-di-O-methyl-α-D-mannopyranoside (**14**). — To a solution of **13** (5.0 g, 13 mmol) in dimethyl sulfoxide (50 mL) was added sodium borohydride (2.5 g, 68 mmol), and the mixture was heated at 80° for 4 h, poured into water (250 mL), and then extracted with ether. The ethereal extract was processed in the usual way, to give **14** as a colorless syrup (2.55 g, 93%), showing one spot in t.l.c., $[\alpha]_D^{23}$ +26° (*c* 0.5); n.m.r.: δ 4.75 (d, 1 H, *J* 2.0 Hz, H-1), 3.61 (t, 1 H, *J* 2.8 Hz, H-2),

3.50–3.30 (m, 3 H, H-3,4,5), 3.49, 3.47, and 3.37 (3 s, 9 H, 3 OMe), 2.50 (bs, 1 H, OH), and 1.33 (d, 1 H, $J_{5,6}$ 6.0 Hz, H-6).

Anal. Calc. for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.60; H, 8.86%.

Methyl 6-deoxy-2,3-di-O-methyl-α-D-altropyranoside (**17**). — Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-altropyranoside[9] was converted into **17** by the method described for **12**. Oxidative opening of the 4,6-*O*-benzylidene derivative with *N*-bromosuccinimide gave methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-altropyranoside (**15**, 91%). A portion of the syrup, purified by preparative t.l.c. (8:1 benzene–acetone), had $[\alpha]_D^{23}$ +79° (*c* 1.6): n.m.r.: δ 8.20–8.00 and 7.70–7.30 (m, 5 H, Ph), 5.30 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 8.4 Hz, H-4), 4.77 (d, 1 H, *J* 1.4 Hz, H-1), 4.45 (oct, 1 H, $J_{5,6}$ 3.6, $J_{5,6'}$ 7.0 Hz, H-5), 3.90 (t, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 3.60–3.40 (m, 3 H, H-2,6,6'), 3.50, 3.50, and 3.47 (3 s, 9 H, 3 OMe).

Anal. Calc. for $C_{16}H_{21}BrO_6$: C, 49.38; H, 5.44; Br, 20.53. Found: C, 49.15; H, 5.41; Br, 20.74.

Reduction of **15** with sodium borohydride in dimethyl sulfoxide gave methyl 4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methyl-α-D-altropyranoside (**16**, 84%). A portion of the syrup, purified by preparative t.l.c. (8:1 benzene–acetone), had $[\alpha]_D^{23}$ +61° (*c* 1): n.m.r.: δ 8.15–8.05 and 7.60–7.30 (m, 5 H, Ph), 5.17 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 8.0 Hz, H-4), 4.67 (d, 1 H, *J* 2.0 Hz, H-1), 4.27 (oct, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 3.83 (dd, 1 H, $J_{2,3}$ 5.0 Hz, H-3), 3.60–3.40 (dd, 1 H, H-2), 3.53 and 3.46 (2 s, 9 H, 3 OMe), and 1.30 (d, 3 H, H-6).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.88; H, 7.10.

Alkaline hydrolysis of **16** gave **17** (88%), $[\alpha]_D^{23}$ +133° (*c* 1.2): n.m.r.: δ 4.60 (d, 1 H, *J* 1.4 Hz, H-1), 3.84 (oct, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 6.5 Hz, H-5), 3.65–3.35 (m, 3 H, H-2,3,4), 3.13 (bs, 1 H, OH), 3.53, 3.47, and 3.40 (3 s, 9 H, 3 OMe), and 1.27 (d, 3 H, H-6).

Anal. Calc. for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.46; H, 8.81.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-altropyranoside (**18**). — To a solution of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-altropyranoside[10] (7.0 g, 24 mmol) and sodium hydride (1.0 g, 42 mmol) in *N*,*N*-dimethylformamide (50 mL) was added benzyl bromide (5.2 g, 29 mmol) at 0°. The mixture was kept at room temperature for 30 min, poured into cold water, and extracted with ether. The extract was evaporated, to give syrupy **18** in quantitative yield (9.1 g), $[\alpha]_D^{23}$ +37° (*c* 0.6); n.m.r.: δ 7.60–7.20 (m, 5 H, Ph), 5.54 (s, 1 H, PhC*H*), 4.87 and 4.75 (ABq, 2 H, *J* 12.0 Hz, C*H*$_2$Ph), 4.65 (s, 1 H, H-1), 4.45–4.20 (m, 2 H, H-5,6), 4.00–3.80 (m, 2 H, H-3,4), 3.74 (t, 1 H, *J* 10.0 Hz, H-6'), 3.43 and 3.33 (2 s, 6 H, 2 OMe), and 2.87 (d, $J_{2,3}$ 4.4 Hz H-2).

Anal. Calc. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.11; H, 6.72.

Methyl 3-O-benzyl-2-O-methyl-6-O-p-tolylsulfonyl-α-D-altropyranoside (**19**). — Debenzylidenation of **18** with boiling 70% acetic acid for 6 h gave a quantitative yield of methyl 3-*O*-benzyl-2-*O*-methyl-α-D-altropyranoside. To its solution (3.1 g, 10 mmol) in pyridine was added *p*-toluenesulfonyl chloride (1.9 g, 12 mmol) at 0° with stirring. After storage at room temperature for 18 h, the solution was poured

into ice–water and extracted with chloroform. The usual processing of the extracts gave a product that was purified on a column of silica gel (10:1 benzene–acetone), to give **19** (3.3 g, 73%), $[\alpha]_D^{23}$ +63° (*c* 0.9); n.m.r.: δ 7.80 and 7.30 (2 d, 4 H, *J* 8.0 Hz, Ph), 7.38 (s, 5 H, Ph), 4.76 and 4.50 (ABq, 2 H, *J* 11.0 Hz, CH_2Ph), 4.61 (d, 1 H, *J* 1.4 Hz, H-1), 4.44–3.90 (m, 3 H, H-5,6,6'), 3.77 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 3.8 Hz, H-3), 3.68 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.49 (dd, 1 H, H-2), and 3.38 (s, 6 H, 2 OMe).

Anal. Calc. for $C_{22}H_{28}O_8S$: C, 58.39; H, 6.24; S, 7.09. Found: C, 58.03; H, 6.17; S, 7.31.

*Methyl 3-*O*-benzyl-6-deoxy-2-*O*-methyl-α-*D*-altropyranoside* (**20**). — Reduction of **19** with sodium borohydride in dimethyl sulfoxide, as described above, gave **11** (81%) which, when purified on a column of silica gel (3:1 benzene-acetone), had $[\alpha]_D^{23}$ +98° (*c* 0.9): n.m.r.: δ 7.40 (s, 5 H, Ph), 4.76 and 4.54 (ABq, 2 H, *J* 11.0 Hz, CH_2Ph), 4.59 (d, 1 H, *J* 1.4 Hz, H-1), 3.89 (oct, 1 H, $J_{4,5}$ 8.6, $J_{5,6}$ 6.2 Hz, H-5), 3.75 (dd, 1 H, $J_{2,3}$ 3.8, $J_{3,4}$ 4.0 Hz, H-3), 3.50 (m, 1 H, $J_{4,OH}$ 9.6 Hz, H-4), 3.48 (dd, 1 H, H-2), 3.40 (s, 6 H, 2 OMe), 2.38 (d, 1 H, OH), and 1.27 (d, 3 H, H-6).

Anal. Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.69; H, 7.81.

Synthesis of the 4-uloses (**1** *and* **3–6**). — The oxidations were carried out as follows. To a solution of dry dimethyl sulfoxide (4.0 mmol) in distilled, dry dichloromethane (4.0 mL) cooled below −65° was added, dropwise, trifluoroacetic anhydride (3.0 mmol) in dichloromethane (3.0 mL) with stirring for 10 min. After 10 min, a solution of the starting material (2.0 mmol) in dichloromethane (4–10 mL) was added, and the mixture was stirred below −65° for 20 min and then neutralised with triethylamine (~0.8 mL). The rate of addition of trifluoroacetic anhydride, sugar derivative, and triethylamine was controlled to keep the temperature below −65°. The reaction mixture was poured into water and extracted with dichloromethane. The usual processing of the extract gave the corresponding 4-ulose in good yield. Each 4-ulose was purified on a column of silica gel (8:1 benzene–acetone): compound **1**: syrup (93%), $[\alpha]_D^{27}$ +197° (*c* 1.1); **3**: syrup (95%), $[\alpha]_D^{27}$ +98° (*c* 0.8); **4** (91%): m.p. 94–96° (from ether–hexane), $[\alpha]_D^{23}$ +214° (*c* 0.3); **5** (81%): m.p. 66–68° (from ether–hexane), $[\alpha]_D^{27}$ +171° (*c* 0.8).

Anal. Calc. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found for **1**: C, 52.66; H, 7.81; for **3**: C, 53.17; H, 8.03; for **4**: C, 52.54; H, 7.72; for **5**: C, 52.90; H, 7.88.

Compound **6** (91%): m.p. 54–57° (from ether–hexane), $[\alpha]_D^{23}$ +98° (*c* 1.3).

Anal. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.67; H, 7.33.

Reaction of the 4-uloses **1–9** *with diazomethane.* — The diazomethane reaction was generally performed as follows. To a solution of **1** (613 mg, 3.0 mmol) in ethanol (20 mL) was added carefully a solution of diazomethane (~5.0 mmol) in ether at 0°. The mixture was kept at room temperature for 24 h, treated dropwise with acetic acid to remove the excess of diazomethane, and evaporated to give a syrup. Preparative t.l.c. (1:1 ether–hexane) then gave methyl 4,4^1-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-di-*O*-methyl-α-D-glucopyranoside (**27**) and -α-D-galactopyranoside (**21**), and methyl 5,7-dideoxy-2,3-di-*O*-methyl-α-D-*xylo*-heptoseptanosid-4-ulose (**32**) in yields

of 51 (334 mg), 21 (138 mg), and 24% (157 mg), respectively. Compound **27**: syrup, $[\alpha]_D^{23}$ +127° (*c* 0.5); **21**: syrup, $[\alpha]_D^{23}$ +132° (*c* 0.8).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found for **27**: C, 55.26; H, 8.25; for **21**: C, 55.37; H, 8.38.

Compound **32** could not be completely purified, but the n.m.r. and i.r. spectra could be analysed. I.r.: ν_{max}^{NaCl} 1720 cm^{-1} (C=O); n.m.r.: δ 4.79 (d, 1 H, *J* 2.2 Hz, H-1), 4.18 (m, 1 H, H-6), 3.77 (d, 1 H, *J* 9.8 Hz, H-3), 3.53, 3.46, and 3.39 (3 s, 9 H, 3 OMe), 3.52 (dd, 1 H, H-2), 2.74 and 2.40 (dABq, 2 H, $J_{5,6}$ 2.0, $J_{5,6'}$ 10.0, $J_{5,5'}$ 14.0 Hz, H-5,5'), and 1.26 (d, 3 H, $J_{6,7}$ 6.6 Hz, H-7).

Similar reaction of **2** in ethanol with diazomethane, followed by preparative t.l.c. (1:1 ether–hexane), gave methyl 4,4^1-anhydro-2,3-di-*O*-benzyl-6-deoxy-4-*C*-hydroxymethyl-α-D-gluco- (**28**) and -D-galacto-pyranoside (**22**), and methyl 2,3-di-*O*-benzyl-5,7-dideoxy-α-D-*xylo*-heptoseptanosid-4-ulose (**33**), in yields of 45, 15, and 25%, respectively. Compound **28**: syrup, $[\alpha]_D^{23}$ +57° (*c* 1.0); **22**: syrup, $[\alpha]_D^{23}$ +64° (*c* 0.8).

Anal. Calc. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found for **28**: C, 71.26; H, 7.02; for **22**: C, 71.62; H, 7.13.

Compound **33**: syrup, $[\alpha]_D^{23}$ +50° (*c* 0.7); ν_{max}^{NaCl} 1720 cm^{-1} (C=O); n.m.r.: δ 7.30 (s, 10 H, Ph), 4.79 (d, 1 H, *J* 2.0 Hz, H-1), 4.75 and 4.70, 4.65 and 4.58 (2 ABq, 4 H, *J* 11.0 and 12.0 Hz, 2 CH_2Ph), 4.24 (m, 1 H, H-6), 4.08 (d, 1 H, *J* 8.0 Hz, H-3), 3.75 (dd, 1 H, H-2), 3.43 (s, 3 H, OMe), 2.75 and 2.44 (dABq, 2 H, $J_{5,6}$ 2.0, $J_{5,6'}$ 10.0, $J_{5,5'}$ 14.0 Hz, H-5,5'), and 1.26 (d, 3 H, *J* 6.4 Hz, H-7).

Anal. Calc. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.57; H, 7.15.

Similar reaction of **3** and diazomethane, with purification of the main product by t.l.c. (4:1 hexane–ethyl acetate), gave methyl 4,4^1-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-di-*O*-methyl-α-D-mannopyranoside (**29**, 42%) as a syrup, $[\alpha]_D^{23}$ +89.5° (*c* 0.5). By-products were obtained in yields of <15%.

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.76; H, 8.08.

Similar reaction of **4** in ethanol with diazomethane, with purification of the products by preparative t.l.c. (1:1 ether–hexane), gave syrupy methyl 4,4^1-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-di-*O*-methyl-α-D-gulopyranoside (**23**, 87%), $[\alpha]_D^{23}$ +138° (*c* 0.6).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.76; H, 8.08.

In a similar way, **5** gave methyl 4,4^1-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-di-*O*-methyl-α-D-ido- (**24**) and -α-D-altro-pyranoside (**30**) in yields of 46 and 24%, respectively. Compound **24**: syrup, $[\alpha]_D^{23}$ +65° (*c* 0.7); **30**: syrup, $[\alpha]_D^{23}$ +111° (*c* 0.8).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found for **24**: C, 54.75; H, 8.15; for **30**: C, 54.86; H, 8.21.

The reaction of **7** and diazomethane, followed by preparative t.l.c. (1:1 ether–hexane), gave benzyl 4,4^1-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-*O*-methylene-α-D-galactopyranoside (**25**) and benzyl 5,7-dideoxy-2,3-*O*-methylene-α-D-*xylo*-hepto-

septanosid-4-ulose (**34**) in yields of 52 and 21%, respectively. Compound **25**: syrup, $[\alpha]_D^{23}$ +182° (*c* 2.5).

Anal. Calc. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.41; H, 6.47.

Compound **34** could not be completely purified, but the n.m.r. and i.r. spectra could be analysed. I.r.: ν_{max}^{NaCl} 1725 cm^{-1} (C=O); n.m.r.: δ 7.37 (s, 5 H, Ph), 5.29 (d, 1 H, *J* 2.4 Hz, H-1), 5.13 and 5.12 (2 s, 2 H, OCH_2O), 5.10 (d, 1 H, *J* 10.6 Hz, H-3), 4.82 and 4.70 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.58 (sex, 1 H, $J_{5,6} = J_{5',6}$ 6.4 Hz, H-6), 3.75 (dd, 1 H, H-2), 2.50 (d, 2 H, H-5,5'), and 1.19 (d, 3 H, *J* 6.4 Hz, H-7).

In a similar way, **8** gave methyl 4,4[1]-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-*O*-methylene-α-D-mannopyranoside (**31**) as a syrup (82%), $[\alpha]_D^{23}$ +56.5° (*c* 1.4), as the main product.

Anal. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 52.99; H, 6.65.

A similar reaction of **9** in ethanol, with purification of the products by t.l.c., gave methyl 4,4[1]-anhydro-6-deoxy-4-*C*-hydroxymethyl-2,3-*O*-methylene-α-D-gulopyranoside (**26**, 78%), m.p. 79–82° (from ether–hexane), $[\alpha]_D^{23}$ +119° (*c* 0.6).

Anal. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.22; H, 6.81.

Reduction of the spiro-epoxides **21–31** *with lithium aluminum hydride.* — The reduction of spiro-epoxides was generally conducted as follows. To a solution of **21** (150 mg, 0.69 mmol) in oxolane (20 mL) was added lithium aluminum hydride (50 mg), and the mixture was boiled under reflux for 2 h. The excess of hydride was carefully decomposed with water, and the mixture was filtered and then extracted with chloroform. The extract was washed with water, dried, and evaporated, to give colorless, syrupy methyl 6-deoxy-4-*C*-methyl-2,3-di-*O*-methyl-α-D-galactopyranoside (**35**; 142 mg, 94%), which, after purification by preparative t.l.c. (8:1 benzene–acetone), had $[\alpha]_D^{23}$ +126° (*c* 1).

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.35; H, 9.10.

Similar reduction of **22** and **28**, with purification of the products by preparative t.l.c. (10:1 benzene–acetone), gave syrupy methyl 2,3-di-*O*-benzyl-6-deoxy-4-*C*-methyl-α-D-galacto- (**36**) and -α-D-gluco-pyranoside (**44**) in yields of 89 and 88%, respectively. These compounds were identical with those obtained by the reaction of **2** with methylmagnesium iodide[5].

Reduction of **23**, **24**, **27**, **29**, and **30**, with similar purification of the products, gave syrupy methyl 6-deoxy-4-*C*-methyl-2,3-di-*O*-methyl-α-D-gulo- {**37**, $[\alpha]_D^{23}$ +140° (*c* 0.7)}, -α-D-ido- {**38**, $[\alpha]_D^{23}$ +126° (*c* 0.9)}, -α-D-gluco- {**43**, $[\alpha]_D^{23}$ +131° (*c* 1.1)}, -α-D-manno- {**45**, $[\alpha]_D^{23}$ +56° (*c* 0.7)}, and -α-D-altro-pyranoside {**46**, $[\alpha]_D^{23}$ +128° (*c* 1.1)} in yields of 85, 93, 95, 93, and 89%, respectively.

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found for **37**: C, 54.13; H, 9.01; for **38**: C, 55.01; H, 9.30; for **43**: C, 54.96; H, 9.24; for **45**: C, 54.90; H, 9.11; for **46**: C, 54.72; H, 9.27.

Reduction of **25** in oxolane, as described above, gave benzyl 6-deoxy-4-*C*-methyl-2,3-*O*-methylene-α-D-galactopyranoside (**39**, 85%), which was identical with an authentic sample obtained by the reaction of **7** with methylmagnesium iodide[5].

Reduction of **26** and **31** in oxolane with lithium aluminum hydride, with purifi-

cation of the product by preparative t.l.c. (4:1 hexane–ethyl acetate), gave syrupy methyl 6-deoxy-4-*C*-methyl-2,3-*O*-methylene-α-D-gulo- {**40**, $[\alpha]_D^{23}$ +78° (*c* 0.5)} and α-D-manno-pyranoside {**47**, $[\alpha]_D^{23}$ +59.5° (*c* 1.7)} in yields of 92 and 85%, respectively.

Anal. Calc. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found for **40**: C, 53.34; H, 8.07; for **47**: C, 53.22; H, 7.95.

The reaction of the 4-uloses **1**–**5** *with methylmagnesium iodide.* — The Grignard reaction was generally performed as follows. To a solution of methylmagnesium iodide in ether (10 mL), prepared from magnesium turnings (60 mg, 2.5 mmol) and methyl iodide (1.0 mL), was added **1** (204 mg, 1.0 mmol) in ether (10 mL), and the reaction mixture was kept at room temperature for 1.5 h, poured into cold, aqueous ammonium chloride, and extracted with dichloromethane. The extract was washed with water and evaporated, to give syrupy methyl 6-deoxy-4-*C*-methyl-2,3-di-*O*-methyl-α-D-galactopyranoside (**35**) and its 4-epimer (**43**). The yields, after purification by preparative t.l.c. (10:1 benzene–acetone), were 75 (165 mg) and 21% (46 mg), respectively. Both products were identical with those obtained by the reaction of **1** with diazomethane.

Likewise, **3** and **4** gave syrupy methyl 6-deoxy-4-*C*-methyl-2,3-di-*O*-methyl-α-D-talo- {**41**, $[\alpha]_D^{27}$ +49.5° (*c* 0.8)} and -allo-pyranoside {**48**, $[\alpha]_D^{23}$ +126° (*c* 1.1)} in yields of 85 and 92%, respectively.

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found for **41**: C, 54.50; H, 9.11; for **48**: C, 54.96; H, 9.24.

Similar reaction of **5**, followed by preparative t.l.c. (1:1 hexane–ether), gave methyl 6-deoxy-4-*C*-methyl-2,3-di-*O*-methyl-α-D-altro- (**46**) and -ido-pyranoside (**38**) in yields of 77 and 18%, respectively. Both products were identical with those obtained by the reaction of **5** with diazomethane.

*The reaction of methyl 3-*O*-benzyl-6-deoxy-2-*O*-methyl-α-*D*-arabino-hexopyranosid-4-ulose* (**6**) *with methylmagnesium iodide and methyl-lithium at a lower temperature.* — To an ethereal solution (15 mL) of methylmagnesium iodide [from magnesium turnings (120 mg, 5.0 mmol) and methyl iodide (2.0 mL)] at −78° was added an ethereal solution (10 mL) of **6** (560 mg, 2.0 mmol) with stirring. The mixture was stirred for 1.5 h at −78°, aqueous ammonium chloride was added, and the usual processing then gave exclusively methyl 3-*O*-benzyl-6-deoxy-4-*C*-methyl-2-*O*-methyl-α-D-altropyranoside (**51**; 557 mg, 94%), $[\alpha]_D^{23}$ +97.5° (*c* 0.9).

Anal. Calc. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.99; H, 8.23.

To an ethereal solution (15 mL) of **6** (560 mg, 2.0 mmol) at −78° was added ~2M ethereal methyl-lithium (3 mL). The mixture was stirred for 1.5 h at −78°, aqueous ammonium chloride was added, and the usual processing then gave exclusively methyl 3-*O*-benzyl-6-deoxy-4-*C*-methyl-2-*O*-methyl-α-D-idopyranoside (**50**; 568 mg, 96%), as a syrup, $[\alpha]_D^{23}$ +93° (*c* 0.6).

Anal. Calc. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.14; H, 8.31.

Determination of the configuration of **51** *and* **38**. — The catalytic hydrogenation of **51** (300 mg, 1.01 mmol) in ethanol in the presence of palladium–charcoal (10%)

gave the *O*-debenzylated product as a syrup in quantitative yield. A solution of the syrup and anhydrous copper(II) sulfate (500 mg) in acetone (20 mL) containing one drop of conc. sulfuric acid was stirred for 24 h at room temperature, neutralised with barium carbonate, and filtered. The filtrate was evaporated to give syrupy methyl 6-deoxy-3,4-*O*-isopropylidene-4-*C*-methyl-2-*O*-methyl-α-D-altropyranoside (**52**; 165 mg, 66%), which, after purification by preparative t.l.c. (1:1 hexane–ether), had $[\alpha]_D^{27}$ +93° (*c* 0.3). See Table III for n.m.r. data.

Anal. Calc. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.47; H, 8.96.

Similar hydrogenation of **50** (150 mg, 0.51 mmol) gave the *O*-debenzylated product as a syrup in quantitative yield. To a solution of the syrup and sodium hydride (30 mg, 1.26 mmol) in *N*,*N*-dimethylformamide (3 mL) was added methyl iodide (0.3 mL) at 0°. The mixture was stored at room temperature for 30 min, poured into cold water, and extracted with ether. The extract was evaporated, to give syrupy methyl 6-deoxy-4-*C*-methyl-2,3,4-tri-*O*-methyl-α-D-idopyranoside (**53**; 118 mg, quantitative), $[\alpha]_D^{27}$ +72° (*c* 0.7).

Anal. Calc. for $C_{11}H_{22}O_5$: C, 56.39; H, 9.47. Found: C, 56.11; H, 9.38.

From the fact that the *O*-methylation product of **38** was identical with **53**, and the failure and success of acetonation of the reduction product of **50** and **51**, the structures of **51** and **38** were proved.

ACKNOWLEDGMENT

The authors thank Mr. Y. Nakamura for the measurement of ^{13}C-n.m.r. spectra.

REFERENCES

1 J. YOSHIMURA AND M. MATSUZAWA, *Carbohydr. Res.*, 100 (1982) 283–295.
2 J. YOSHIMURA, K. KOBAYASHI, K. SATO, AND M. FUNABASHI, *Bull. Chem. Soc. Jpn.*, 45 (1972) 1806–1812; J. YOSHIMURA, K. MIKAMI, K. SATO, AND C. SHIN, *ibid.*, 49 (1976) 1686–1689.
3 J. YOSHIMURA, K. SATO, K. KOBAYASHI, AND C. SHIN, *Bull. Chem. Soc. Jpn.*, 46 (1973) 1515–1519; K. SATO, J. YOSHIMURA, AND C. SHIN, *ibid.*, 50 (1977) 1191–1194; K. SATO, K. KOGA, H. HASHIMOTO, AND J. YOSHIMURA, *ibid.*, 53 (1980) 2639–2641.
4 K. SATO AND J. YOSHIMURA, *Bull. Chem. Soc. Jpn.*, 51 (1978) 2116–2121; *Carbohydr. Res.*, 73 (1979) 75–84.
5 M. MATSUZAWA, K. SATO, T. YASUMORI, AND J. YOSHIMURA, *Bull. Chem. Soc. Jpn.*, 54 (1981) 3505–3509.
6 M. MATSUZAWA, K. KUBO, H. KODAMA, M. FUNABASHI, AND J. YOSHIMURA, *Bull. Chem. Soc. Jpn.*, 54 (1981) 2169–2173.
7 A. BROWN AND T. C. BRUICE, *J. Am. Chem. Soc.*, 95 (1973) 1593–1601.
8 C. W. BAKER AND R. L. WHISTLER, *Carbohydr. Res.*, 33 (1974) 372–376.
9 M. JIRI, K. VLADISLAV, Z. ALENA, AND J. JIRI, *Collect. Czech. Chem. Commun.*, 37 (1972) 3744–3748.
10 G. A. GROB AND D. A. PRINS, *Helv. Chim. Acta*, 28 (1945) 840–850.
11 J. S. BRIMACOMBE, O. A. CHING, AND M. STACEY, *J. Chem. Soc., C*, (1969) 197–198.
12 J. YOSHIMURA, K. SATO, AND H. HASHIMOTO, *Chem. Lett.*, (1977) 1327–1330.
13 M. MILJKOVIC, M. GLIGORIJEVIC, T. SATOH, D. GLISIN, AND R. G. PITCHER, *J. Org. Chem.*, 39 (1974) 3847–3850; K. SATO, M. MATSUZAWA, K. AJISAKA, AND J. YOSHIMURA, *Bull. Chem. Soc. Jpn.*, 53 (1980) 189–191.

14 K. SATO, K. KUBO, N. HONG, H. KODAMA, AND J. YOSHIMURA, *Bull. Chem. Soc. Jpn.*, 55 (1982) 938–942.
15 H. PAULSEN AND V. SINNWELL, *Chem. Ber.*, 111 (1978) 879–889.
16 D. GUILLERM-DRON, M.-L. CAPAU, AND W. CHODKIEWICZ, *Tetrahedron Lett.*, (1972) 37–40.
17 E. C. ASHBY AND J. T. LAEMMLE, *Chem. Rev.*, 75 (1975) 521–546.
18 J. S. BURTON, W. G. OVEREND, AND N. R. WILLIAMS, *J. Chem. Soc.*, (1965) 3433–3445.
19 J. P. HORWITZ, N. MODY, AND R. GASSER, *J. Org. Chem.*, 35 (1970) 2335–2339.
20 W. G. OVEREND AND N. R. WILLIAMS, *J. Chem. Soc.*, (1965) 3446–3448.
21 B. FLAHERTY, S. NAHAR, W. G. OVEREND, AND N. R. WILLIAMS, *J. Chem. Soc., Perkin Trans. 1*, (1973) 632–638.
22 R. J. FERRIER, W. G. OVEREND, G. A. RAFFERTY, H. M. WALL, AND N. R. WILLIAMS, *J. Chem. Soc., C*, (1968) 1091–1095.
23 I. IZQUIERDO CUBERO AND M. D. PORTAL OLEA, *Carbohydr. Res.*, 89 (1981) 65–72.
24 W. G. OVEREND, A. C. WHITE, AND N. R. WILLIAMS, *Carbohydr. Res.*, 15 (1970) 185–195.
25 D. HORTON AND E. K. JUST, *Carbohydr. Res.*, 18 (1971) 81–94.
26 T. D. INCH, G. J. LEWIS, R. P. PEEL, AND N. WILLIAMS, *Chem. Commun.*, (1970) 1549.
27 M. MILJKOVIC, M. GLIGORIJEVIC, T. SATOH, AND D. MILJKOVIC, *J. Org. Chem.*, 39 (1974) 1379–1384.