Note

Complementary stereoselectivity in the reactions of hexopyranosid-4uloses with methylmagnesium iodide and methyllithium*

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The stereoselectivity of nucleophilic addition to a glycosidulose is extremely important for controlled, stereospecific synthesis of branched-chain sugars. Complementary stereoselectivity in the reactions of 3,4-O-isopropylidenc- β -L-erythropentopyranosid-2-ulose with methylmagnesium iodide² and methyllithium³ was first reported by Williams et al.². Miljković et al.⁴ reported that the reaction of methyllithium with methyl 2,3-di-O-methyl-6-O-triphenylmethyl- α -D-xylohexopyranosid-4-ulose in ether solution at -80° gave stereospecifically the corresponding 4-C-methyl- α -D-glucopyranoside, whereas that of methylmagnesium iodide under similar conditions afforded, again stereospecifically, the corresponding 4-epimer. The stereoselectivity in the Grignard reaction was explained on the basis of equatorial attack of the carbanion on the carbonyl group of the substrate in the ${}^{4}C_{1}$ conformation, which is fixed by chelation of magnesium with the carbonyl oxygen and the adjacent oxygen atoms, as had been suggested in the case of cis- and trans-4-tert-butyl-2-methoxycyclohexanones⁵. The result of the reaction with methyllithium was rationalized on the basis of axial attack of the carbanion on the carbonyl group in a conformation between the ${}^{4}C_{1}$ and a half-chair conformation. The latter arises through dipole repulsion between the almost coplanar C=Ogroup and the adjacent C-O bonds in solvents of low dielectric constant (such as ether). The axial methoxyl group at C-1 hinders equatorial attack because of electrostatic and nonbonding steric repulsions. The remarkable stereoselectivity in the reaction with methyllithium was also confirmed by application to analogous α -Dxylo-hexopyranosid-4-uloses^{6,7}. However, in a previous paper⁸, the authors reported, with methyl 3-O-benzyl-6-deoxy-2-O-methyl- α -D-arabino-hexopyranosid-4-ulose (7b), a complementary stereoselectivity of reverse mode to that aforementioned.

In order to examine the generality of the concepts proposed by Miljković *et al.*, the stereoselectivities in both reactions are compared in this paper by using a

*Branched-chain Sugars, Part XXXIII. For Part XXXII, see ref 1.

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TABLE 1

COMPARISON OF STERFOSELECTIVITIES IN THE REACTION OF METHVELTHIEM AND METHVEMAGNESIUM JODIDI WITH HEXOPYRANOSIDA LOSES IN FIHER

Glycondulose	Reagent	Temperatures	Ratio of products. axial:equatorial attack*, and chemical shifts of C-Me carbon atoms (p.p.m. in parentheses)			Yields (77)
		-			-	
A	MeLi	- 787	(115)	1 7 6		93 Del:
	MeMgl MeMgl	- 78'	(14-5)	01	121-93	96.
2	MeLi	- 78'		01		80
	MeMgI	ambient		0.1	(22-1)	89
3	MeLi	78`		1.0		80
	MeMgI	amhient	(17.8)	1.0		92"
4	MeLi	78-		(1)	(21.4)	46
	McMgI	ambient	(18-4)	1.0		95
5	MeLi	78°	(16-1)	2:3	(19.9)	પા
	McMgl	ambient		0 1		×5*
6	МеГл	- 78°		0.1		94
	McMgI	ambient		()]	(21/2)	96
7a	MeLi	78°		0:1		96
	McMgI	ambient	(18.9)	131	(21.4)	255
	McMgI	78-		1 ()		90
8	MeLi	ambient		1.1.8		93
	MeLi	- 78°	(16, 7)	123	(20.6)	47
	MeMgI	ambient		0 }		034
9	McLi	ambient		1-12		93
	MeLi MaMal	- 78-	(18.5)	1 18	(21.0)	95

"Axial and equatorial attacks are designated based on the ${}^4C_1(0)$ conformation of the individual hexopyranosiduloses ${}^{b^+d}$ Data from refs. 8, 10, and 13, respectively

series of nine different hexopyranosid-uloses.

In addition to several hexopyranosid-4-uloses, namely, methyl 6-deoxy-2.3di-O-methyl- α -D-xylo-hexopyranosid-4-ulose⁸ (1), benzyl 6-deoxy-2.3-Omethylene- α -D-xylo-hexopyranosid-4-ulose^{9,10} (2), the D-*ribo* isomer⁸ (3) of 1 and the corresponding 2.3-O-methylene derivative^{9,10} (4), the D-*lyxo* isomer⁸ (5) of 1 and the corresponding 2.3-O-methylene derivative¹⁰ (6), and D-*arabino* isomer⁸ (7a) of 1, methyl 4.6-O-henzylidene-2-O-methyl- α -D-*rabino*-¹¹ and - α -D-*ribo*hexopyranosid-3-uloses¹² (8 and 9) were used as substrates. The stereoselectivities in the Grignard reaction of 1-9 at room temperature had been examined in previous papers^{8,10,13}. The reaction of these substrates with methyllithium in ether at -78° was performed in the current paper, and the results obtained are summarized in Table I, together with those of the Grignard reaction. Most configurations at the quaternary carbon atom of these products were assigned from the chemical shifts of the *C*-methyl carbon atoms^{8,10,15}, as shown in Table I. For compounds **2**, **3**, and **6**, in which only one isomer was obtained, the product of equatorial attack ob-



tained *via* the reaction of **3** with diazomethane showed⁸ the *C*-methyl carbon signal at 22.0 p.p.m. In addition, the configurations of a few compounds were proved by chemical methods^{8,14}. The stereoselectivity in the reaction of an analogue of **1** with methyllithium⁷ and in the Grignard reaction of **2** have actually been used for synthesis of natural products^{7,16}

The conformations of the hexopyranosiduloses used here are expected to be slightly flattened and flexible, except for compounds 2, 8, and 9, in which the transfused 2,3-O-methylene or 4,6-O-benzylidene ring is expected to maintain a rather rigid conformation. Thus, the ¹H-n.m.r. parameters (in CDCl₃) of 1 ($J_{1,2}$ 3.4, $J_{2,3}$ 10.5 Hz), **2** ($J_{1,2}$ 3.0, $J_{2,3}$ 10.8 Hz), **3** ($J_{1,2}$ 4.5, $J_{2,3}$ 3.5 Hz), **5** ($J_{1,2}$ 2.0, $J_{2,3}$ 3.6 Hz), 8 ($J_{1,2}$ 4.3 Hz), and 9 ($J_{1,2} \simeq 0$ Hz) indicate the ${}^4C_1(D)$ conformation. However, those of **7a** $(J_{1,2}, 2.5, J_{2,3}, 8.8 \text{ Hz})$ indicate a conformational change from the original ${}^{4}C_{1}$ to ${}^{0}S_{2}$ by oxidative introduction of an carbonyl group⁸. The conformation of 4 $(J_{1,2}, 4.0, J_{2,3}, 8.8, J_{3,5}, 0.8 \text{ Hz})$ was considered to be ${}^{0}S_{2}$ by the rationale used¹⁷ to assign the ${}^{0}S_{4}$ conformation to the 2,3-O-isopropylidene analogue ($J_{1,2}$ 3.8, $J_{2,3}$ 9.0, $J_{3,5}$ 1.2 Hz) of 4. It is noteworthy that the reaction products from 4 and 7a are restored into their original distorted $(J_{1,2}, 5.0-5.4, J_{2,3}, 5.4-5.6 \text{ Hz})$ and flattened $(J_{1,2}, 5.0-5.4, J_{2,3}, 5.4-5.6 \text{ Hz})$ 1.6-2.0, $J_{2,3}$ 3.0-4.2 Hz) ${}^{4}C_{1}(D)$ conformations, respectively^{8,10}. The coupling constants of 1 and 7a measured in ether- d_{10} were used in the aforementioned interpretation for the stereoselectivity in the reaction with methyllithium⁴. However, the change of values (1: $J_{1,2}$ 3.4, $J_{2,3}$ 9.9 Hz at 25° and $J_{1,2}$ 3.4, $J_{2,3}$ 10.2 Hz at -70° ; **7a**: $J_{1,2}$ 2.7, $J_{2,3}$ 9.0 Hz at 25° and $J_{1,2}$ 2.2, $J_{2,3}$ 9.4 Hz at -70°) were very small, and the tendency in the changes was contradictory to that expected from the interpretation.

If prior coordination of magnesium to the carbonyl and adjacent oxygen atoms in the Grignard reaction leads to conformational inversion or change of a substrate, the stereoselectivity will expected to be different from that in the reaction with methyllithium. Such an instance is observed in reports on hexopyranosiduloses¹⁸⁻²⁰, even with the rather rigid, bicyclic system of 1,6anhydro-2,3-di-O-(*p*-tolylsulfonyl)- β -D-*ribo*-hexopyranosid-3-ulose⁻¹. Thus, a magnesium-coordinated conformation and the normal conformation of substrates are illustrated on the left and right sides, respectively, of the equilibration formulas.

Exclusive or preponderant equatorial attack in both reactions for compounds 2 and 8 is the most common; reagents approach a six-membered ring in a chair conformation from the sterically favored direction²². Similar results for 9 are rationalized on the basis that steric hindrance of an axial substituent in β disposition is larger than that for the α disposition²². In the case of compound 5, the differing results in the two reactions reflect the extent of the hindrance of the axial methoxyl group at C-2 in slightly different conformations. The results for 6 in non-chair conformations are also explained by the approach of reagents from the less-hindered site, and selective equatorial attack in the reduction of the 2,3-O-tso-propylidene analogue of 6 by sodium borohydride has also been reported²³. Similarly the axial attack in both reactions of 3 may be rationalized.

In the present experiments, the complementary stereoselectivity in the reactions of 4 with methylmagnesium iodide and methyllithium are new results, as are those of 1 and 7a. Among the data for these substrates, the exclusive axial attack in the Grignard reactions of 4 and 7a may only be understood on the basis of approach of the carbanion from the exo direction to the magnesium-coordinated $B_{1,4}$ conformation. However no decisive factor that would control the stereoselectivity in the reaction with methyllithium may be found in the normal conformations of these substrates, except for the quasi-axial bond of C-2 of 4. Although the selective axial attack in the reduction of the 2,3-O-isopropylidene analogue of 4 by sodium borohydride was explained by steric factors in the ${}^{0}S_{4}$ conformation¹⁷, the selectivity in the reaction of 4 with methyllithium is the reverse. It is considered that the factor controlling the stereoselectivity in reaction of these substrates with methyllithium at lower temperature is rather delicate and weak, and appears only when strong steric hindrance is lacking. For example, a factor that would avoid the intersection of C=O and C-O dipoles in the transition state, as illustrated in Scheme 1, is considered as a candidate, but more data are necessary to confirm it.



EXPERIMENTAL

Reaction of hexopyranosiduloses with methyllithium at -78° . — To a solution of a hexopyranosid-ulose (2 mmol) in ether (20 mL) cooled with Dry Ice and acetone was added an excess (10 mmol) of methyllithium in ether (10 mL) with stirring, and then the mixture was kept for 2 h at room temperature, and poured into saturated, aqueous ammonium chloride. Conventional processing of the ethercal solution gave the crude product, for which the epimeric product-ratio was estimated from its ¹H-n.m.r. spectrum. Purification and separation of the products on a column of silica gel with a suitable solvent system, such as a 3:1 hexane-ethyl acetate, gave single products, which were characterized by comparison of their physical properties with those of authentic samples obtained in previous work already cited. The present work was partly supported by a Grant-in-Aid (No. 57430008) for Scientific Research from the Ministry of Education, Science, and Culture, Japan. The authors thank Mr. Y. Nakamura for recording the ¹³C-n.m.r. spectra.

REFERENCES

- 1 J. YOSHIMURA, K. HARA, AND M. YAMAURA, Carbohydr. Res., 101 (1982) 343-347
- 2 J. S. BURTON, W. G. OVEREND, AND N. R. WILLIAMS, J. Chem. Soc. (C), (1965) 3433-3445.
- 3 A. A. J. FEAST, W. G. OVEREND, AND N. R. WILLIAMS, J. Chem. Soc. (C), (1966) 303-306.
- 4 M. MILJKOVIĆ, M. GRIGORIJI-VIĆ, T. SATOH AND D. MILJKOVIĆ, J. Org. Chem., 39 (1974) 1379– 1384
- 5. D. GUILLERN-DRON, M.-L. CAPMAN, AND W. CHODKIFWICZ, Tetrahedron Lett., (1972) 37-40
- 6 S. HANESSIAN AND G. RENCOURT, Can. J. Chem., 55 (1977) 1111-1113.
- 7 (a) J. YOSHIMURA, K. SATO, K. KUBO, AND H. HASHIMOTO, Carbohydr. Res., 99 (1982) C1-C3; (b) K. SATO, K. KUBO, N. HONG, H. KODAMA AND J. YOSHIMURA, Bull Chem. Soc. Jpn., 55 (1982) 938–942
- 8 K. SATO AND J. YOSHIMURA, Carbohydr Res., 103 (1982) 221-238
- 9 M. MATSUZAWA, K. KUBO, H. KODAMA, M. FUNABASHI AND J. YOSHIMURA, Bull Chem. Soc. Jpn., 54 (1981) 2169–2173
- 10 M. MATSUZAWA, K. SATO, T. YASUMORI, AND J. YOSHIMURA, Bull. Chem. Soc. Jpn., 54 (1981) 3505–3509
- 11 P. M. COLLINS, P. GUPTA, AND R. LYER, J. Chem. Soc. Perkin Trans. 1, (1972) 1670-1677
- 12 P. M. COLLINS, D. GARDINER, S. KUMAR, AND W. G. OVEREND, J. Chem. Soc. Perkin Trans. 1, (1972) 2596–2610.
- 13 K. SATO AND J. YOSHIMURA, Bull Chem Soc. Jpn , 51 (1978) 2116-2121
- 14 J. YOSHIMURA, K. SATO, AND M. FUNABASHI, Bull. Chem. Soc. Jpn., 52 (1979) 2630-2634.
- 15 K. SATO, M. MATSUZAWA, K. AJISAKA, AND J. YOSHIMURA, Bull Chem. Soc. Jpn., 53 (1980) 189– 191
- 16 J. YOSHIMURA AND M. MATSUZAWA, Carbohydr. Res., 100 (1982) 283–295, compare ibid., 96 (1981) 7–20, 94 (1981) 173–181
- 17 P. M. COLLINS AND B. R. WHITTON, Carbohydr. Res., 33 (1974) 25-33.
- 18 P. J. GAREGG AND T. NORBERG, Acta Chem. Scand., Ser. B, 29 (1975) 507-512.
- 19 W. G. OVEREND, A. C. WHITE, AND N. R. WILLIAMS, Carbohydr. Res., 15 (1970) 185-195
- 20 I. I. CUBERO AND M. D. PORTAL OLFA, Carbohydr. Res. 89 (1981) 65-72
- 21 M ČERNY, M KOLLMANN, J. PACAK, AND M BUDFSINSKY, Collect Czech Chem Commun. 39 (1974) 2507–2519.
- 22 E. C. ASHBY AND J. T. LAEMMULF, Chem. Rev., 75 (1975) 521-547.
- 23 C. L. STEVENS, R. P. GLINSKY, AND K. G. TAYLOR, J. Org. Chem., 33 (1968) 1586-1592