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Acetal-bond Cleavage of 4,6-O-Alkylidenehexopyranosides by Diisobutylaluminium Hydride and by Lithium Triethylborohydride-$TiCl_4$

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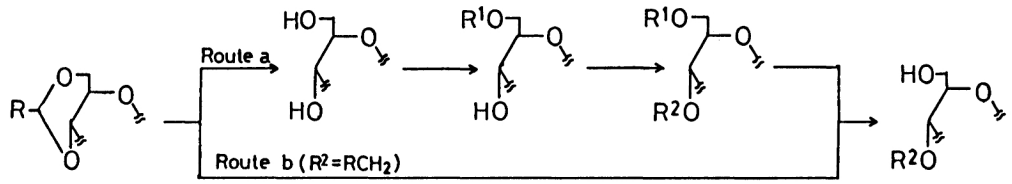
Regioselective acetal-bond cleavage of 4,6-O-benzylidene- and 4,6-O-(4-methoxybenzylidene)-α-D-altropyranosides by DIBAL or $Li(C_2H_5)_3BH$-$TiCl_4$ is described. The sense of regioselectivity could be controlled by suitable choice of the protecting group of hydroxyl function at C-3. Reduction of 4,6-O-alkylideneglucopyranosides by DIBAL is also examined.

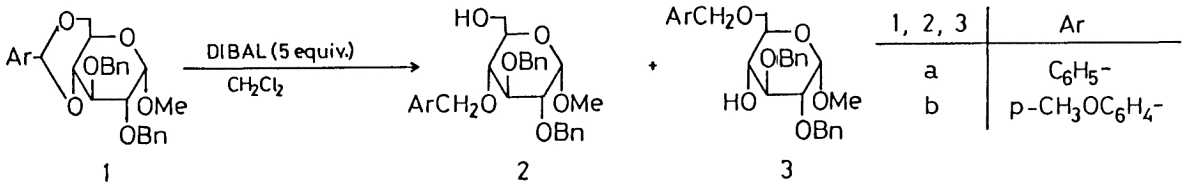
Functionalized 4,6-O-alkylidenehexopyranosides have been widely utilized as starting materials for the synthesis of complex structures, because regio- and stereochemical events occurring in reactions with incoming reagents can be anticipated from the locked conformation of the pyranoside rings.[1] When further modification at the 4- or 6-position of the pyranoside ring is required in the subsequent step, however, removal of the alkylidene group and reprotection of one of the resulted free hydroxyl groups are generally unavoidable. Although selective protection of the primary hydroxyl group of a primary-secondary-diol can be accomplished by the use of a bulky protecting group, a multistage reaction is generally required for protection of the secondary hydroxyl group as depicted in Scheme 1, route a. As an efficient route avoiding lengthy temporary protection and eventual deprotection, reductive cleavage of a carbon-oxygen bond of the acetal moiety has been reported (Scheme 1, route b). In this approach, the position of acetal-bond scission is explained by the difference in steric congestion at the reaction sites, and neighboring participation as well.[2,3]



Scheme 1.

In this paper, we wish to report the reduction of 4,6-O-benzylidene- and 4,6-O-(4-methoxybenzylidene)-acetals of glucopyranosides and altropyranosides by the use of diisobutylaluminium hydride (DIBAL). The reaction course was found to depend on various factors which include the configuration and protecting group of the hydroxyl group at C-3.

The reaction of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (1a) and methyl 2,3-di-O-benzyl-4,6-O-(4-methoxybenzylidene)-α-D-glucopyranoside (1b) with DIBAL gave 4-O-benzyl derivative (2a and 2b) and 6-O-benzyl derivative (3a and 3b) with the former preference (Table 1). The results are consistent with those obtained by the reductive cleavage using $LiAlH_4$-$AlCl_3$.[4]



Scheme 2.

Table 1. Reductive Cleavage of 4,6-O-Alkylideneglucopyranosides by DIBAL

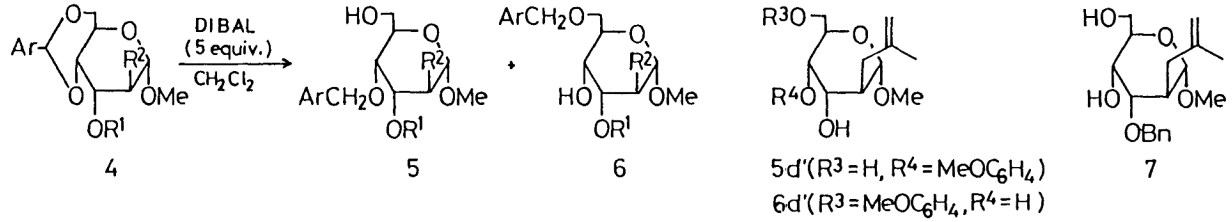
Entry	Suffix	Reactant, 1 Ar	Conditions Temp/°C	Time/h	Product[a] Yield/% 2	3	Ratio 2:3
1			-30	21	88	4[b]	22:1
2	a	C_6H_5	0	6	75	8[c]	9:1
3			40	5.5	57	7	8:1
4			-40	1.5	100		24:1
5	b	p-$CH_3OC_6H_4$	0	1.5	94		7:1
6			40	0.5	97		7:1

a) Ar is same to the reactant. 2a:3a was calculated from isolated yields, while 2b:3b was determined by HPLC analysis. b) 6% of 1a was recovered. c) 2% of 1a was recovered.

A reversal in the sense of the regioselectivity was observed in the reduction of 4,6-O-benzylidene-α-D-altropyranosides, 4a and 4b, by DIBAL as shown in Table 2 (entries 1, 2, 3). Although benzylidene acetal, 4b, exclusively gave 6-O-benzyl ether (6b) (Table 2, entry 3), the corresponding 4-methoxybenzylidene acetal (4c) reacted with DIBAL at -40 °C giving 4-O- and 6-O-(4-methoxybenzyl) derivatives (5c and 6c) in a ratio of 2:3. However, the ratio inverted to 3:1 at 0 °C, and no 6c could be isolated at 40 °C (Table 2, entries 4, 5, 6). Since the C-6 site is apparently less hindered, these results suggest that the regioselectivity would not be determined only by the difference of steric congestions at the reaction sites.[5]

In view of the assumption that acetal-bond cleavage takes place at the site an alminium reagent being coordinated,[2,3,6] the product distribution of regioisomer would be controlled by suitable choice of the protecting group of the hydroxyl group at C-3. Thus, a bulky group would favor the cleavage at the C-6 site, while a group which stabilizes the complexation of the aluminium reagent at the C-4 site would favor the formation of 6-O-protected pyranosides.

In order to attest the effect of the protecting group of hydroxyl function at C-3, the reaction of methyl 3-O-t-butyldimethylsilyl-4,6-O-benzylidene-2-de-



4 5 6 5d'(R^3=H, R^4=$MeOC_6H_4$) 6d'(R^3=$MeOC_6H_4$, R^4=H) 7

Scheme 3 (For Ar, R^1, and R^2, see Table 2).

Table 2. Reductive Cleavage of 4,6-O-Alkylidenealtropyranosides by DIBAL

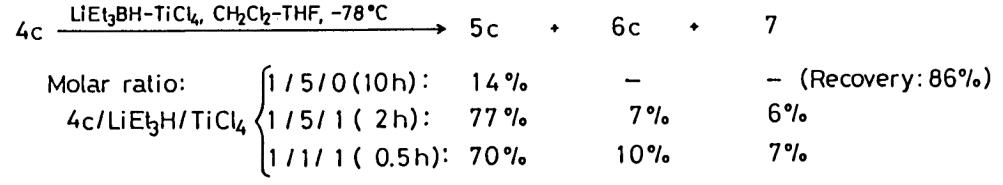
Entry	Suffix	Reactant, 4[a] Ar	R^1	R^2	Conditions Temp °C	Time h	Product[b] Yield/% 5	6	Ratio 5:6
1	a	C_6H_5	Bn	BnO	-30	21	25	55[c]	1:2
2					0	9	22	68[d]	1:3
3	b	C_6H_5	Bn	$CH_2=C(CH_3)CH_2-$	0	3	-	100	
4	c	p-$CH_3OC_6H_4$	Bn	$CH_2=C(CH_3)CH_2-$	-40	5	41	59	2:3
5					0	2	70	27	3:1
6					40	0.5	70[e]	-	
7	d	C_6H_5	TBDMS	$CH_2=C(CH_3)CH_2-$	-30	72	37(7)[f]	-(25)[g]	[2:1][h]
8					0	2	20(16)[f]	-(34)[g]	[1:1][h]
9	e	p-$CH_3OC_6H_4$	MEM	$CH_2=C(CH_3)CH_2-$	-40	5	10	86	1:9
10					0	2	16	70	1:4

a) Bn = Benzyl, TBDMS = t-butyldimethylsilyl, MEM = methoxyethoxymethyl. b) Ar, R^1, and R^2 are same to the corresponding reactant. c) 16% of 4a was recovered. d) 10% of 4a was recovered. e) Compound 7 was obtained in 22% yield. f) ( ): Yield of 5d'. g) ( ): Yield of 6d'. h) Ratio of (5d + 5d'):6d'.

oxy-2-C-(2-methyl-2-propenyl)-α-D-altropyranoside (4d) with DIBAL was attempted (Table 2, entries 7, 8). By comparing the results with that shown in entry 3 (Table 2), bond cleavage at the C-4 site was apparently retarded by the change of 3-O-benzyl group to 3-O-t-butyldimethylsilyl group. The product resulted from acetal-bond scission at the C-4 site was isolated as the desilylated form (6d') rather than expected 6-O-benzyl-3-O-t-butyldimethylsilyl derivative (6d). At present, it is not clear whether the desilylation occurred prior to acetal-bond cleavage.[7] In contrast to 4c, methyl 3-O-methoxyethoxymethyl-4,6-O-(4-methoxybenzylidene)-2-deoxy-2-C-(2-methyl-2-pentenyl)-α-D-altropyranoside (4e) reacted with DIBAL to afford 6-O-(4-methoxybenzyl) derivative (6e) in preference to 4-O-(4-methoxybenzyl) derivative (5e) (Table 2, entries 9, 10). These results would be explained in terms of "crown ether effect".[8]

In the hope of preventing any complexation of DIBAL at the C-4 site,[8] the reaction of 4c with DIBAL (1.1 equiv.) was carried out in the presence of $TiCl_4$ (1.1 equiv.) in CH_2Cl_2 at -78 °C (0.5 h) in which a complex mixture of products was formed rather than expected 5c. On the other hand, 4c reacted smoothly with equimolar amount each of $Li(C_2H_5)_3BH$ (LEBH) and $TiCl_4$ at -78 °C (0.5 h) to give

5c, 6c, and 7 in 70%, 10%, and 7% yields, respectively, while no reaction practically took place without $TiCl_4$ (Scheme 4). Reaction mechanism and actual reducing species formed by combining LEBH with $TiCl_4$ are not clear at present.



Scheme 4.

The procedure described above offers a convenient method for the preparation of protected gluco- and altropyranosides with a free hydroxyl group at the 4- or 6-position.

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References

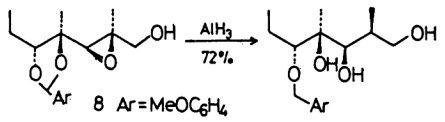
1) For reviews, see for example; S. Hanessian, "Total Synthesis of Natural Products: The 'Chiron' Approach," Pergamon Press, Oxford (1983); T. D. Inch, Tetrahedron, 40, 3161 (1984).

2) Highly regioselective acetal-bond cleavage of 4,6-O-(4-methoxybenzylidene)-hexopyranosides by the use of $Na[B(CN)H_3]$ in the presence of acids has been reported. R. Johansson and B. Samuelsson, J. Chem. Soc., Perkin Trans. 1, 1984, 2371, and refs therein.

3) Takano, et al. have reported reductive cleavage of benzylidene acetals of various 1,2- and 1,3-diols by DIBAL. S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, Chem. Lett., 1983, 1593, and refs therein.

4) S. S. Bhattacharjee and P. A. J. Gorin, Can. J. Chem., 47, 1195 (1969); A. Liptak, I. Jodap, and P. Nanasi, Carbohydr. Res., 44, 1 (1975).

5) Yonemitsu, et al. have reported regioselective acetal-bond cleavage of 8 by the use of AlH_3. Y. Oikawa, T. Nishi, and O. Yonemitsu, J. Chem. Soc., Perkin Trans. 1, 1985, 7.



6) E. L. Eliel, V. G. Badding, and M. N. Rerick, J. Am. Chem. Soc., 84, 2371 (1962); P. A. Bartlett, W. S. Johnson, and J. D. Elliot, ibid., 105, 2088 (1983); V. M. F. Choi, J. D. Elliott, and W. S. Johnson, Tetrahedron Lett., 25, 591 (1984); A. Mori, K. Ishihara, I. Arai, and H. Yamamoto, Tetrahedron, 43, 755 (1987), and refs therein.

7) Joniak, et al. have reported that methyl 4,6-O-(4-methoxybenzylidene)-α-D-glucopyranoside (9) reacted with $LiAlH_4$-$AlCl_3$ to give the corresponding 4-O- and 6-O-(4-methoxybenzyl)-ethers in a ratio of 3:2, while 2,3-di-O-methyl derivative of 9 exclusively afforded 4-O-(4-methoxybenzyl)-ether. D. Joniak, B. Kosikova, and L. Kosakova, Collect. Czech. Chem. Commun., 43, 769 (1978).

8) M. T. Reetz, Angew. Chem., Int. Ed. Engl., 23, 556 (1984).

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