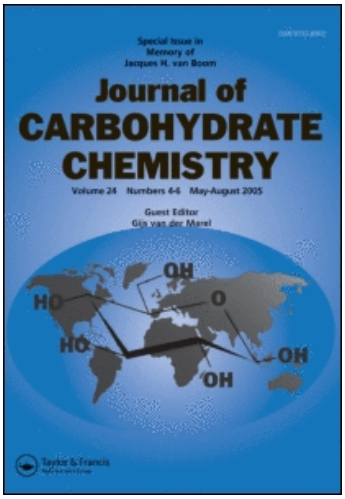

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CHIRAL DEUTERATION AT C-6 OF 1,6-ANHYDROHEXOSE DERIVATIVES

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ABSTRACT

Photobromination and the succeeding deuteration with tri-n-butyltindeuteride were performed on eight 1,6-anhydro-2,3,4-tri-O-benzoylhexopyranoses to give C-6 chirally deuterated hexopyranoses. The stereochemistry of these two reactions are discussed in terms of steric effects of substituents at C-2, C-3 and C-4 of 1,6-anhydrohexopyranoses.

INTRODUCTION

In our previous paper, we have reported facile synthetic methods of (6S)- and (6R)-(6-$^{2}H_{1}$)-D-glucose [1] and galactose[2] and (5S)- and (5R)-(5-$^{2}H_{1}$)-D-ribose.[3] These chirally deuterated sugars are useful for various purposes utilizing ^{1}H- and ^{2}H-NMR spectroscopy and mass spectroscopy; for example in the biosynthetic study of an antibiotic[4], substrate

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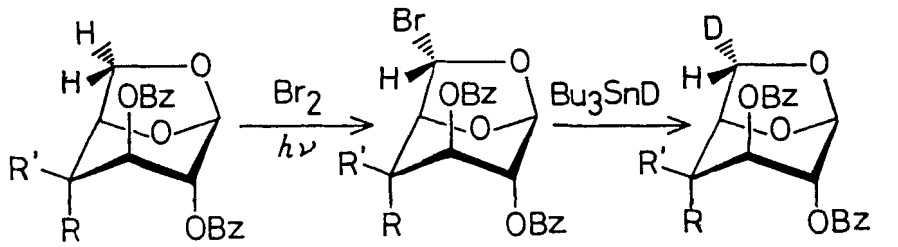


1 R=OBz R'=H 1B1 R=OBz R'=H 1S R=OBz R'=H
2 =H =OBz 2B1 =H =OBz 2S =H =OBz

SCHEME

stereochemistry in the use of galactose oxidase[5], and conformational analysis about C-5 - C-6 single bonds of hexoses.[6,7]

These chirally deuterated hexoses were synthesized from 1,6-anhydro-2,3,4-tri-O-benzoyl-D-gluco 1, and galactopyranose 2, through regio- and stereospecific photobromination[8] followed by stereospecific radical reduction with tri-n-butyltin-deuteride.(SCHEME)[9] However, stereoselectivity of these reactions have not yet been discussed in terms of the configurational changes at C-2, C-3 and C-4 positions. In this paper, we report the application of the mathod to the remaining six aldohexoses and the discussion of the factors of stereoselectivities of the photobromination and the radical reduction.

RESULTS AND DISCUSSION

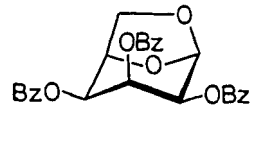
Photobromination of 1,6-anhydro-2,3,4-tri-O-benzoyl-D-talo 3, manno 4[10], ido 5, gulo 6[11], altro 7[12] and allopyranose 8[13] were performed with 1.5 equimolar

TABLE 1.

The Products and their Yields of the Photobromination

compd.	product and yield %	compd.	product and yield %
3	3B1 (87) 3B2 (0)	6	6B1 (77) 6B2 (19)
4	4B1 (92) 4B2 (0)	7	7B1 (70) 7B2 (22)
5	5B1 (87) 5B2 (0)	8	8B1 (68) 8B2 (32)

bromine on irradiation with 300W lamp for 2hr. The products and their yields are listed in TABLE 1. The reactions of 3, 4, and 5, which had two or three β-benzoyloxy groups, proceeded regio- and stereo-specifically and gave only 6 exo-monobromides 3B1, 4B1 and 5B1, respectively, in high yields (87-92%). The reactions of 6, 7 and 8 gave 6 exo-monobromides 6B1, 7B1 and 8B1 as main products (68-77%) and 6,6-di-bromides 6B2, 7B2 and 8B2 as minor products (19-32%), respectively. 6 Endo-monobromide could not be obtained in any case.



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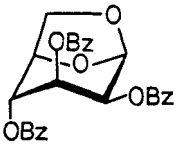

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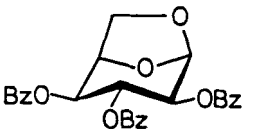

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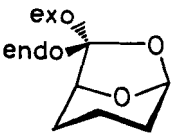

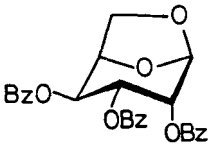

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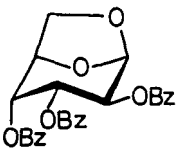

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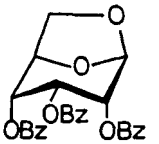

8

suffix	endo	exo
—	H	H
B1	H	Br
B2	Br	Br
S	H	D
R	D	H

The structures of these products were elucidated on the basis of elemental analysis and ^{1}H-NMR spectroscopy (TABLE 3, 4 and 5). 6 Endo-protons of starting materials 1-8 always resonated at lower field than H-6 exo and the range of the values of chemical shifts of them was larger (4.15-4.78 ppm) than that of H-6 exo (3.85-4.04 ppm), since they were more affected by benzoyloxy groups at C-2,3 and 4. The coupling constants $J_{5,6endo}$ were always small (<1 Hz), since the dihedral angles between C-6 - H-6 endo and C-5 - H-5 were near 90°. On the other hand, $J_{5,6exo}$ were moderate (∿5.4 Hz) in all hexoses and "W" long range couplings $J_{4,6exo}$ (<1 Hz) were observed in 2, 3, 5 and 6 which had a proton at 4α. Similar findings had been reported about 1,6-anhydrohexopyranoses and their triacetates.[14, 15] Therefore, the H-6 proS (H-6 exo) and H-6 proR (H-6 endo) can be discriminated in the 1,6-anhydrohexopyranose system.

Although possible conformations of 1,6-anhydrohexoses were $^{1}C_{4}$ and $B_{O,3}$, the preferred conformation of all 1,6-anhydrohexose derivatives described in this paper was $^{1}C_{4}$, since the "W" long range couplings $J_{1,3}$ and $J_{3,5}$ were observed in 1-4, 1B1-4B1 and 1S-4S, which had a proton at 3α, but not in 5-8, 5B1-8B1, 5B2-8B2 and 5S,R-8S,R, which had a proton at 3β.[16]

In the products 1B1-8B1, H-6 endo shifted remarkably to downfield (+2.2-2.4 ppm) and the signals of H-6 exo disappeared. The signals of H-6 endo, H-5 and H-4α were simplified compared with those of the corresponding starting materials due to lack of coupling with H-6 exo. Further, the lack of $J_{5,6endo}$ was observed. These results indicated that the structures of 1B1-8B1 were 6 exo-monobromides.

Both signals of H-6 exo and H-6 endo disappeared

in the spectra of 6B2-8B2 indicating that these compounds were 6,6-dibromides. The H-3 of the three dibromides and H-4 of 7B2 and 8B2 shifted to downfield (∿+0.4 ppm) compared with those of the corresponding monobromides owing to the presence of bromine atom at 6 endo, which was close to these protons.

The shorter reaction time for the photobromination seemed to be favorable to suppress the formation of the dibromide, since the dibromide 6B2 was formed by the photobromination of 6 exo-monobromide 6B1 and after 3hr, the ratio of 6B2 to 6B1 reached to ca. 1:1 judged by TLC ($CHCl_3$). The slow endo-bromination could be ascribable to the steric hindrance of the endo face in the bicyclo[3.2.1]octane system. β-Benzoyloxy group at C-3 was the most important steric factor because the photobromination of 1, which had a β-benzoyloxy group at C-3, gave only 6 exo-monobromide in high yield.[1] The second important steric factor was β-benzoyloxy group at C-4 because the ratio of monobromide to dibromide for the products of 7 was smaller than that for 6.

The reduction of 3B1 and 4B1, which have β-benzoyloxy group at C-3, with tri-n-butyltindeuteride proceeded stereospecifically and gave 6 exo-deuterio-derivatives. On the other hand the reduction of 5B1-8B1, which did not have an β-benzoyloxy group at C-3, proceeded with (6S)-stereoselectivity (84-93%). The stereoselectivity was 84% even for 8B1 which was expected to be the worst because it did not have any β-benzoyloxy groups. The yields and the (6S)-stereoselectivities are listed in TABLE 2. The factors of the stereoselectivity were identical with those described in photobromination.

TABLE 2.

The Yields and the (6S)-Stereoselectivities of the Radical Reduction

compd.	product	yield %	selectivity %
3Bl	3S	74	100
4Bl	4S	90	100
5Bl	5S,R	87	93
6Bl	6S,R	76	91
7Bl	7S,R	69	88
8Bl	8S,R	67	84

The structures of the products of the reduction were elucidated by ^{1}H-NMR spectroscopy (TABLE 3, 4). The aspects of the spectra of 1S-8S,R were identical with those of the corresponding non-deuterated compounds except for the following changes : 1) significant decrease of the peak areas or complete diappearance of the signals of H-6 exo were observed for the products of 5Bl-8Bl and 3Bl and 4Bl, respectively 2) the signals of the protons coupled with H-6 exo were simplified and the signals of H-6 endo and H-5 were slightly broadened by coupling with the deuterium. 3) H-6 endo shifted to upfield (0.020-0.027 ppm) in all hexoses by the isotope effect of the geminal deuterium atom.[17] Although the changes of other chemical shifts were also observed (0.002-0.012 ppm), the reason for the minor changes could not be elucidated by the isotope effect and/or by the measurement conditions.

The (6S)-stereoselectivity was calculated from the ratio of the peak areas of H-6 exo to H-6 endo for

TABLE 3

^{1}H-NMR Cemical Shifts (ppm) of Compounds 1-8, 1S-8S,R and 1B1-8B2.

compd.	H-1	H-2	H-3	H-4	H-5	H-6endo	H-6exo
1	5.745	∿5.075	5.449	∿5.086	4.894	4.388	3.985
1S	5.740	∿5.071	5.447	∿5.086	4.882	4.368	
2	∿5.71	5.255	5.829	∿5.71	4.785	4.643	3.916
2S	∿5.71	5.250	5.824	∿5.75	4.775	4.620	
3	5.723	5.337	6.226	5.608	∿4.77	∿4.78	3.993
3S	5.718	5.335	6.223	5.605	∿4.77	∿4.76	
4	5.735	5.453	5.850	5.284	4.881	4.518	4.043
4S	5.738	5.458	5.859	5.292	4.873	4.493	
5	5.746	5.298	6.098	5.492	4.931	4.408	3.897
5S,R	5.742	5.292	6.092	5.485	4.928	4.385	∿3.9*
6	∿5.7	∿5.7	5.880	∿5.7	4.918	4.337	3.849
6S,R	∿5.7	∿5.7	5.881	∿5.7	4.913	4.314	∿3.85*
7	∿5.75	5.575	∿5.75	∿5.75	4.923	4.194	3.963
7S,R	∿5.75	5.577	∿5.75	∿5.75	4.922	4.167	∿3.95*
8	5.790	∿5.57	5.713	∿5.57	4.970	4.147	3.936
8S,R	5.788	∿5.57	5.713	∿5.57	4.966	4.127	∿3.94*

*The peak areas are 0.07-0.16H.

(continued)

TABLE 3 continued

compd.	H-1	H-2	H-3	H-4	H-5	H-6endo
1B1	6.123	5.050	5.485	5.165	5.138	6.691
2B1	6.096	5.218	5.824	∿5.72	5.055	6.870
3B1	6.069	5.359	6.217	5.610	5.076	6.973
4B1	6.083	5.470	5.861	5.387	5.154	6.819
5B1	6.089	5.311	5.938	5.499	5.178	6.713
6B1	6.070	(5.6 - 5.8)			5.165	6.650
6B2	6.000	5.750	6.254	5.869	5.366	
7B1	6.140	∿5.6	∿5.6	5.882	5.180	6.623
7B2	6.086	5.541	6.021	6.231	5.341	
8B1	6.149	∿5.55	∿5.55	5.721	5.209	6.549
8B2	∿6.1	5.586	5.953	∿6.1	5.374	

The benzoyl protons were observed at 7.2-8.2ppm in all compounds.

TABLE 4

^{1}H-NMR Coupling Constants (Hz) of Compounds 1-8, 1S-8S,R and 1B1-8B2.

compd.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6endo}$*	$J_{5,6exo}$	$J_{6,6}$*	$J_{1,3}$	$J_{3,5}$	$J_{2,4}$	$J_{4,6exo}$*
1,1S	∿1.7	∿1.7	∿1.7	∿1.7	<1	5.13	7.81	∿1.7	∿1.7	1	
2,2S	∿1.7	2.93	5.37	4.39	0.73	4.89	7.56	∿1.2	∿1.2		<1
3,3S	1.71	4.88	4.88	∿4.5	<1	5.37	7.33	∿1	∿1		0.98
4,4S	∿1.71	5.37	∿1.7	∿1.7	0.98	5.62	7.81	∿1.7	∿1.7		
5,5S,R	1.71	8.79	8.79	4.64	<1	5.13	7.81				0.98
6,6S,R	**	4.61	9.52	3.90	<1	4.88	8.06				0.73
7,7S,R	1.46	9.03	**	2.44	0.98	5.37	8.30				
8,8S,R	∿2.2	4.64	4.64	2.44	0.98	5.34	8.30			**	

Accuracy ± 0.3Hz.

* The couplings were not observed in deuterated compounds.

** The coupling constants could not be measured.

(continued)

TABLE 4 continued

compd.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6endo}$	$J_{1,3}$	$J_{3,5}$	$J_{2,4}$
1B1	1.71	∿1.7	∿1.7	∿1.7		∿1.7	∿1.7	∿1
2B1	2.20	∿2	5.37	4.15		∿1.2	∿1.5	
3B1	1.71	4.88	4.88	4.64		∿1.2	∿1.0	
4B1	1.70	5.37	∿1.7	∿1.7		∿1.7	∿1.7	
5B1	1.71	8.30	8.79	4.64				
6B1	2.20	**	**	3.18				
6B2	2.44	4.88	10.50	3.90				
7B1	∿1	**	∿4	2.19				
7B2	1.46	8.79	4.64	2.20				
8B1	1.71	**	4.39	2.44				0.98
8B2	1.71	4.88	4.88	2.20				0.73

TABLE 5. Physical Properties of 1,6-Anhydrohexose Derivatives.

compd.	m.p. C°	$[\alpha]_D^{21}$ ($CHCl_3$)	elemental analysis		
			C	H	Br
3B1	155	-124° (c=0.12)	59.01	3.90	14.77
4B1	173	-190° (c=0.61)	58.60	3.58	14.60
5B1	170	-113° (c=0.14)	58.61	3.89	14.71
6B1	147	+74° (c=0.10)	58.90	3.92	14.47
7B1	-	-288° (c=0.16)	58.61	3.89	14.71
8B1	147	-97° (c=0.19)	58.65	3.80	14.60
		calcd.	58.60	3.82	14.43
6B2	98	+17° (c=0.12)	52.08	3.95	24.16
7B2	131	-272° (c=0.16)	51.48	3.36	25.56
8B2	137	-74° (c=0.13)	51.38	3.17	25.32
		calcd.	51.27	3.16	25.32
3S	178	-52° (c=0.16)	68.38	5.03	
4S	107	-185° (c=0.45)	68.12	4.99	
5S,R	102	-65° (c=0.07)	67.23	5.12	
6S,R	154	+206° (c=0.16)	68.40	4.90	
7S,R	-	-319° (c=0.06)	68.22	5.03	
8S,R	140	-37° (c=0.32)	68.65	4.76	
		calcd.	68.20	4.87	

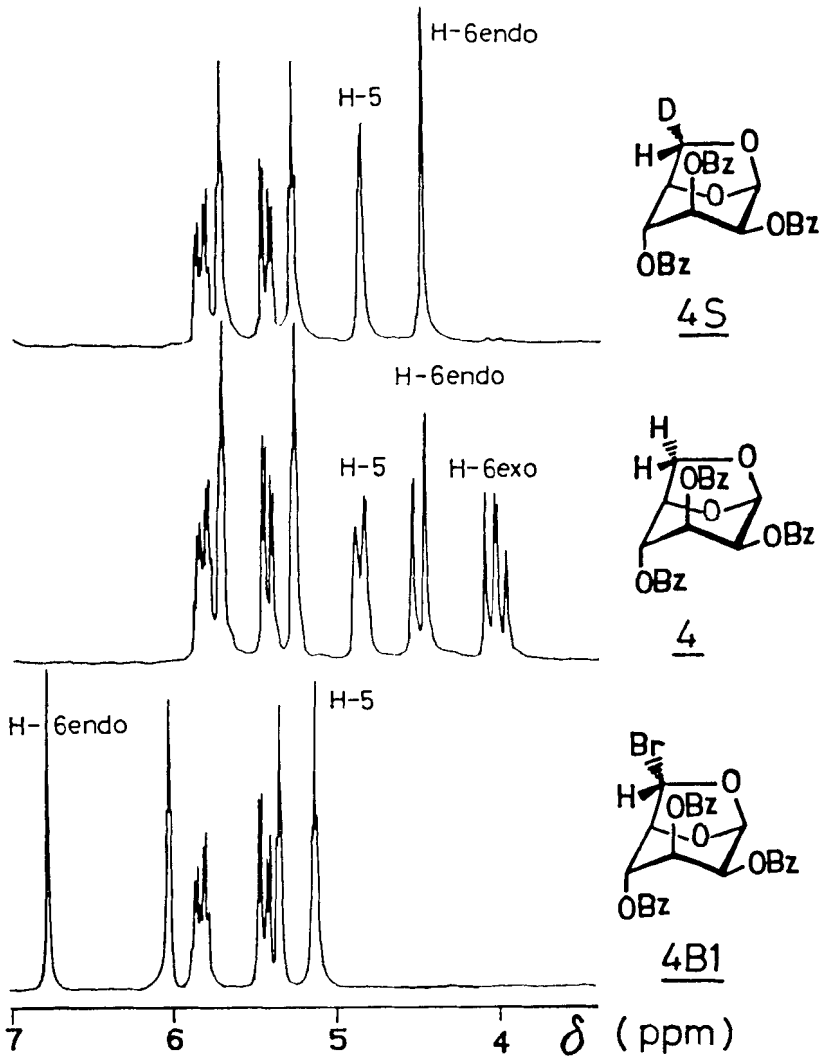

FIG. 1 ^{1}H-NMR spectra of mannose derivatives.

1S-8S,R. The spectra 4 and 4S are shown in FIG. 1 as an example.

The assignments of protons of 1, 1B1 and 1S in our previous paper[1] must be revised[18] as listed in TABLE 3. The revised assignments were based on the

selective proton decoupled ^{13}C-NMR and differential NOE spectra.

Compound 1S-8S may be easily converted to the corresponding free hexoses and inverted to (6R)-deuteriohexoses through S_N2 reaction.[2]

In conclusion, our chiral deuteration method provides the stereospecifically deuterated glucose, galactose and mannose derivatives which are biologically important sugars. Although idose, gulose, altrose and allose derivatives are stereoselectively deuterated, they will be good enough for various purposes and if the stereospecifically deuterated derivatives of these sugars are needed, they can be prepared from 1S by the established methods.[19-22]

The synthesis of stereospecifically deuterated mannooligosaccharides are now in progress in our laboratory to elucidate the preferential rotamers about ω angle.

EXPERIMENTAL

General methods

All melting points were uncorrected. ^{1}H- and ^{13}C-NMR were recorded at 100MHz and 25MHz, respectively, in $CDCl_3$ with tetramethylsilane as internal standard on a JEOL JNM FX-100 spectrometer. Optical rotations were measured on a JASCO DIP-4。 Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 GF_{254}.

1,6-Anhydro-2,3,4-tri-O-benzoyl-D-talopyranose(3).

To a solution of 1,6-anhydrotalopyranose[23] (1.7g) in dry pyridine (50ml) was added benzoyl chloride (10g). After the mixture had been stirred for 12hr at

room temperature, the reaction mixture was added water (50ml) and stirred for 2hr. The mixture was extracted with $CHCl_3$ (25ml×3) and the $CHCl_3$ layer was successively washed with water, sat. $NaHCO_3$ and water and then dried over $MgSO_4$. Evapolation of the solvent gave a syrup, which was crystallized from ether-hexane to give 3 (4.5g 90%); m.p. 178°C, $[\alpha]_D^{21}$ -58° (c=0.1, $CHCl_3$).

1,6-anhydro-2,3,4-tri-O-benzoyl-D-idopyranose(5).

A mixture of D-idose and 1,6-anhydro-D-idose[24] (1.5g) was benzoylated by the method described above and crystallized from ether-hexane to give 5 (3.0g ∿70%); m.p. 102°C, $[\alpha]_D^{21}$ -64° (c=0.1, $CHCl_3$).

Photobromination of 1,6-anhydro-2,3,4-tri-O-benzoyl-D-hexopyranose (3B1-8B1 and 6B2-8B2).

A mixture of 1,6-anhydro-2,3,4-tri-O-benzoyl-D-hexopyranose (500mg) and bromine (250mg) in CCl_4 (30ml) was refluxed over a 300W heat lamp for 2hr. The cooled solution was successively washed with 10% $Na_2S_2O_3$, sat. $NaHCO_3$ and water and dried over $MgSO_4$. Evaporation of the solvent gave a syrup, which was crystallized from ether-hexane for 3B1, 4B1 and 5B1. The syrups of the products of 6, 7 and 8 were chromatographed on silica gel columns with $CHCl_3$-hexane (2:1) as the eluent to give dibromides 6B2-8B2, respectively, and further elution with the same solvent gave monobromides 6B1-8B1. They were crystallized from ether-hexane, except for 7B1.

Deuteration of (6S)-1,6-anhydro-2,3,4-tri-O-benzoyl-6-bromo-D-hexopyranose (3S-8S,R).

A mixture of monobromide (200mg), tri-n-butyltin-deuteride (240mg) and azobisisobutylonitrile (10mg) in toluene (14ml) was refluxed for 2hr. Evaporation of

the solvent gave a syrup, which was crystallized from ether-hexane for 6S,R and 8S,R. The syrups of the products of 3Bl-5Bl and 7Bl were purified through silica gel column chromatography, eluting with $CHCl_3$, and then crystallized from ether-hexane, except for 7S,R.

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REFERENCES

1. H. Ohrui, H. Horiki, H. Kishi and H. Meguro, Agric. Biol. Chem., 47, 1101 (1983)

2. H. Ohrui, Y. Nishida and H. Meguro, Agric. Biol. Chem., 48, 1049 (1984).

3. H. Ohrui, T. Misawa and H. Meguro, Agric. Biol. Chem., 48, 1825 (1984)

4. K. Kakinuma, Y. Ogawa, T. Sasaki, H. Seto and N. Otake, J. Am. Chem. Soc., 103, 5614 (1981).

5. A. Maradufu, G. M. Cree and A. S. Perlin, Can. J. Chem., 49, 3429 (1971).

6. Y. Nishida, H. Ohrui and H. Meguro, Tetrahedron Lett., 25, 1575 (1984).

7. H. Ohrui, Y. Nishida, M. Watanabe, H. Hori and H. Meguro, Tetrahedron Lett., 26, 3251 (1985).

8. R. J. Ferrier and P. C. Tyler, J. Chem. Soc., Perkin Trans., 1, 1528 (1980).

9. H. G. Kuivila, Synthesis, 10, 497 (1970).

10. A. E. Knauf, R. M. Hann and C. S. Hudson, J. Am. Chem. Soc., 63, 1447 (1941)

11. L. C. Stewart and N. K. Richtmyer, J. Am. Chem. Soc., 77, 1021 (1955).

12. I. Johansson and N. K. Richtmyer Carbohydr. Res., 10, 322 (1969).

13. J. S. Brimacombe and L. C. N. Tuker, Carbohydr. Res., 40, 387 (1975).

14. M. Buděšínský, T. Trnka and M. Černý, Collection Czechslovac. Chem. Commun., 44, 1949 (1979)

15. K. Heyns and J. Weyer, Liebig's Ann. Chem., 718, 224 (1968).

16. L. D. Hall and L. Hough, Proc. Chem. Soc., 382 (1962).

17. G. V. D. Tiers, J. Chem. Phys., 29, 963 (1958).

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19. H.Paulsen, W. P. Trautwein, F. Garrido Espinosa and K. Heyns, Chem. Ber., 100, 2822 (1967)

20. W. Meyer zu Reckendorf, Ber., 102, 1071 (1969).

21. N. K. Richtmyer in ; " Methods in Carbohydrate Chemistry", Vol. I ; R. L. Whistler and M. L. Wolfrom, Eds. ; Academic Press, New York, NY, 1962. p. 107.

22. D. C. Baker, D. Horton and C. G. Tindall, Jr. Carbohydr. Res., 24, 192 (1972).

23. D. Horton and J. S. Jewell, Carbohydr. Res., 5, 149 (1967).

24. L. F. Wiggins, J. Chem. Soc., 1590 (1949).