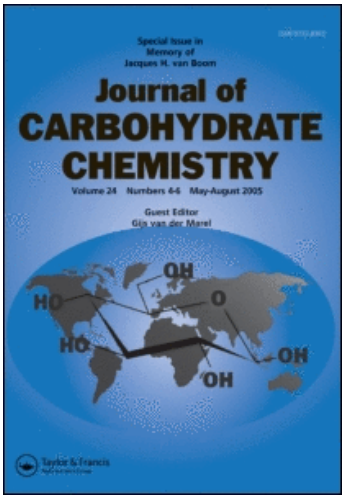

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C-Glycosides V- Synthesis of Aryl 2-Deoxy-α-D-C-Hexopyranosides by Reduction of Aryl 2-Oeoxy-α-D-C-Hex-2-Enopyranosioes

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C-GLYCOSIDES V*- SYNTHESIS OF ARYL 2-DEOXY-α-D-C-HEXOPYRANOSIDES BY REDUCTION OF ARYL 2-DEOXY-α-D-C-HEX-2-ENOPYRANOSIDES.

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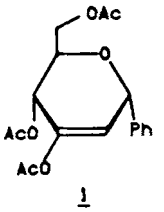
ABSTRACT.

The reduction of two peracetylated aryl 2-deoxy-α-D-C-hex-2-enopyranosides by several reagents is described. The steric course of the reaction is discussed.

INTRODUCTION.

Much research is currently devoted to the synthesis of C-glycosides because many of them are present in natural products of biological importance.[1,2] The ease of preparation and attractive yields obtained for (3,4,6-tri-O-acetyl-2-deoxy-α-D-*erythro*-hex-2-enopyranosyl)benzene 1 and its *threo*- epimer 2 by arylation of glycals[3,4] prompted us to investigate the reduction of these compounds as a route to aryl 2-deoxy-C-glycosides.

*For preceding papers, see refs. 3 and 4.



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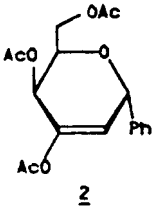
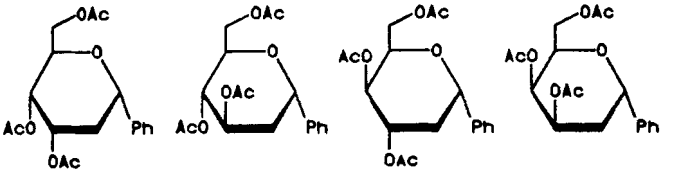


2

In principle, stereoselective reduction of the double bond would allow these compounds to serve as precursors to aryl 2-deoxy-α-D-C-hexopyranosides having *ribo*- 3, *arabino*- 4, *xylo*- 5 and *lyxo*- 6 configurations (scheme 1).

This study describes the reaction of several reducing agents with 1 and 2 as model compounds.

Scheme 1.



3 *ribo* 4 *arabino* 5 *xylo* 6 *lyxo*

RESULTS AND DISCUSSION

First attempts were made to reduce 1 and 2 without cleaving the acetates. Hydrogenation in the presence of heterogenous catalysts did not reduce the enol-ester function in agreement with previous results,[5] although such function has already been reduced under these conditions.[6] The $NaBH_4$-AcOH system which has been successfully employed to reduce an enol-ester function in a keto-nucleoside,[5] was also tried. However, no transformation of the starting material was observed, even after a long reaction time.

Since the reduction of keto-sugar with hydrides is well documented,[7] compounds 1 and 2 were deacetylated (MeONa, MeOH) to generate the 3-keto group. Many spots were detected by TLC indicating epimerization at C-4 of the formed 3-keto-diol and/or

isomerization to 4-keto-diols. Although we demonstrated that the enol-ester function of 1 and 2 reacts selectively with hydroxylamine hydrochloride,[4] its selective hydrolysis to the acetylated 3-keto derivatives was not possible.

Consequently, the reductions with hydrides were carried out directly on the peracetylated compounds. The stereochemical course of the reaction was determined by GLC analysis after acetylation of the crude mixture (see Table I).

Reduction of 1 with potassium borohydride in aqueous methanol at 0 °C in the presence of a catalytic amount of sodium methoxide afforded, after reacetylation, a mixture of 3 (60%) and 4 (40%) in very good yield. These compounds were separated by column chromatography and their configuration was deduced from interpretation of their ^{1}H NMR spectra. The coupling constants of the pyranosyl

Table I. Stereoselectivity of the reduction of 1 and 2.

Entry	Starting compound	Reducing conditions	Ratio of epimers in product.[a]	
			3	4
1	1	KBH_4,MeO^-,MeOH,0°C.	60	40
2	1	$LiAlH_4$,Et_2O,0°C.	45	55
3	1	$LiAlH_4$,THF,0°C.	40	60
4	1	Vitride*,THF,0°C.	68	32
5	1	Vitride*,DME,0°C.	58	42
6	1	Vitride*,THF,0°C.[b]	39	61
7	1	Vitride*,$PhCH_3$,0°C.[b]	35	65
			5	6
8	2	KBH_4,MeO^-,MeOH,0°C.	27	73
9	2	$LiAlH_4$,THF,0°C.	54	46
10	2	Vitride*,THF,0°C.[b]	28	72

a. Calculated by GLC analysis. b. Partly deactivated Vitride.*

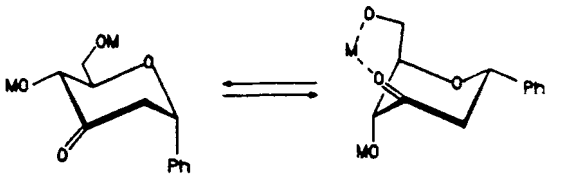
*Trade mark for sodium bis(2-methoxy-ethoxy)aluminium hydride.

ring protons indicated that compound 3, to which the α-D-*ribo*-configuration was assigned, existed in the $^{1}C_{4}$(D) conformation. Significantly, the axial position of H-1 and H-3 was confirmed by large axial-axial coupling constant ($J_{1,2a}$= 9Hz and $J_{2a,3}$= 9,5Hz).

The structure of the other isomer 4 was assigned as the *arabino*-configuration, although only one out of the three coupling constants of H-3 could be measured. Characteristic chemical shifts and spin coupling of the ring protons stand in clear contrast to the values for the *ribo* product 3. From these values it was deduced that the $^{4}C_{1}$(D) conformation, in which only the bulky aromatic ring is axially oriented, is the preferred conformation for compound 4.

When the reduction of 1 was carried out with lithium aluminum hydride the proportions of 3 and 4 were different (Table I, entries 2-6) and the yields were systematically lower, likely due to strong coordination between the polyhydroxylated product and metallic ions.

Under all the conditions employed, only two products, having the C-4 configuration of the starting material were detected, indicating that no epimerization at C-4 ocurred during the reaction; the keto-sugar 1' derived from 1 being quenched by the reducing agent.



1'($^{4}C_{1}$) 1'($^{1}C_{4}$) (eq.1)

Although several factors[8] could influence the steric course of the reduction, the following features could be pointed out. In the case of KBH_4 it is likely that the major product 3 is formed by preferential equatorial attack of hydride to the keto-sugar 1' standing in the $^{4}C_{1}$(D) conformation, this conformation also being preferred for the acetylated derivative of 1'.[9] Such a preference is due to the presence of the bulky phenyl group standing axially β to the keto group to be reduced. The obtained proportions are in good agreement with the results of Murugan[10] and Danishefsky.[11]

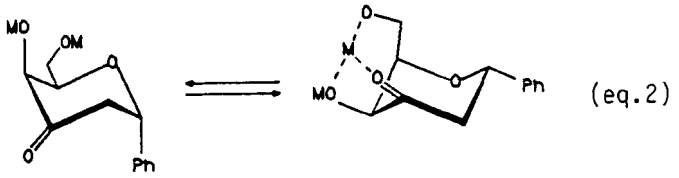
For lithium-aluminum hydride (LAH) the situation is more complex since the formation of alkoxy-aluminium hydride by reduction of the C-6 acetyl group may change the conformation of keto-sugar 1' to $^{1}C_{4}$(D) (eq. 1). That conformational shift is possible because in the studied compounds there is no anomeric effect to strongly direct the steric course of the reaction as in 2-alkoxy-4-pyranones studied by Danishefsky.[11] In this event, an internal delivery of hydride leading to *ribo* configuration could compete with the normally preferred equatorial attack affording the *arabino* one (Table I, entries 2 and 3).

With attenuated aluminum-hydride (Vitride, Table I, entries 4 and 5), the proportions of 3 and 4 were very similar to those obtained with KBH_4, resulting from a preferred equatorial approach of the bulky reagent to the $^{4}C_{1}$(D) conformer.

The change of conformation evoked for LAH was confirmed by complexing compound 1 or resulting keto-diol 1' with hydrolyzed Vitride, making the internal delivery impossible. Reduction of the complex with this reagent (Table I, entries 6 and 7) ocurred by preferential equatorial attack to $^{1}C_{4}$(D) conformation, affording 4 as the major product.

The reduction of 2 with KBH_4 in aqueous methanol afforded a mixture of 5 and 6 (after acetylation) in good yield. Assignement of the structures was possible on the mixture by using 2D 400 MHz NMR spectroscopy (COSY program). Examination of coupling constants of H-1, H-3 and H-4 of the minor product 5 clearly indicated that these protons stand in axial positions; consequently the *xylo*- configuration in $^{1}C_{4}$(D) conformation is assigned to 5. The configuration of the major isomer 6 was deduced to be the *lyxo*- one in the $^{4}C_{1}$(D) conformation. The same trends in selectivity were observed with the different hydrides employed. The preferred conformation of 2' (keto-sugar derived from 2) is probably the $^{4}C_{1}$(D) one as with its acetylated derivative.[9] In this case, the presence of an axial substituant at C-4 reinforced the axial approach of borohydride, affording 73% of *lyxo*- isomer 6 (Table I,entry 8) in agreement with Murugan.[10]

With LAH, the proportions are roughly 1:1 (Table I, entry 9). Since an axial attack of bulky Vitride on $^{4}C_{1}$(D) conformation is not



(eq.2)

2'($^4C_1$) 2'($^1C_4$)

likely, the preferred formation of 6 (72%) with this reagent (Table I, entry 10) could be rationalized by an equatorial attack of this reagent to $^1C_4$ (D) conformation of 2' stabilized by internal coordination (eq.2) by metallic ion as in the case of 1 (*vide supra*).

The moderate stereo-control observed in this study could be attributed to the conformational flexibility of the studied C-glycosides due to the lack of anomeric effect.

EXPERIMENTAL

General methods. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. NMR spectra were recorded at either 250 or 400 MHz with Brucker instruments using tetramethylsilane as internal standard. Elemental analyses were performed at the service de Microanalyse du C.N.R.S. (Gif-s-Yvette). Analytical TLC was performed on Merck aluminium sheets precoated with silica gel 60/PF-254. Gas chromatography (GLC) was carried out with a girdel 75 FD instrument fitted with 0.6m 3 % w/w phenyldiethanolamine succinate (PDEAS) on chromosorb WAW DMCS column (140 °C). Ether-oxydes were distilled from benzophenone-sodium immediately before use.

Reduction with KBH_4 as exemplified by the reduction of (3,4,6-tri-O-acetyl-2-deoxy-α-D-*erythro*-hex-2-enopyranosyl)benzene 1. A solution of 150 mg (0.44 mmol) of 1 in MeOH (5 mL) was cooled in an ice-bath. 0.25 mL of 1.6N MeOK, 81 mg of KBH_4 and 1 mL of water were successively added and the mixture was kept under stirring at 0 °C. After completion of the reaction (1.5 h), 0.7 mL of acetic acid was added. The solvents were carefully evaporated to dryness under reduced pressure and the crude product directly acetylated (pyridine, 3 mL, acetic anhydride, 0.5 mL)

Table II : ^{1}H NMR Data for solutions of 3, 4, 5, 6 in deuteriochloroforme

Chemical Shifts (δ values, ppm/TMS)

Compound	H-1	H-2$_{ax}$	H-2$_{eq}$	H-3	H-4	H-5	H-6	H-6'	OAc	aromat.
3	4.87 dd	2.29 ddd	2.07 m	5.23 ddd	5.11 dd	4.25 ddd	4.52 dd	4.13 dd	2.07 s 1.84 s	7.18-7.34 m
4	5.2 dd	2.14 m	2.77 ddd	5 - 5.16 m		3.7 ddd	4.38 dd	4.09 dd	2.0 s 2.11 s 2.14 s	7.28-7.56 m
5	4.96 dd	2.10≃ m	2.39 m	5.23 m	5.16 dd	4.50 ddd	4.66 dd	4.20 dd	1.94 s 2.09 s 2.11 s	7.27-7.50 m
6	5.25 dd	2.4 m		5.1 ddd	5.23 dd	3.91 ddd	4.33 dd	4.13 dd	2.05 s 2.06 s 2.16 s	7.27-7.50 m

Coupling constants (J values, Hz)

	1,2a	1,2e	2a, 2e	2a, 3	2e, 3	3,4	4,5	5,6	5,6'	6,6'
3	9.	3.5	13	9.5	3.5	3.5	3.5	7	4.0	11.5
4	4.5	3.5	13.5	-	3.5	-	8.5	5.5	3.0	12
5	9.8	3.3	-	-	-	8.9	5.4	8.5	3.4	12.2
6	4.3	4.3	-	7.5	7.5	2.8	2.8	7.6	5.2	11.5

overnight. The TLC of the mixture showed two spots R_F = 0.49 and R_F = 0.41 (pet. ether/ether 1:2). After evaporation of the pyridine, the reaction was taken up in chloroform (10 mL)-water (10 mL) and extracted with chloroform (3x10 mL). The organic layers were washed with water (2x10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the epimeric mixture of 3 and 4 (152 mg, 98 %). GLC analysis showed two peaks corresponding to the *arabino* epimer 4 (1.34 min., 40 %) and to the *ribo* epimer 3 (1.8 min, 60 %).

The compounds were separated by column chromatography (Silica gel Merck 40 ; 0.063-0.2 mm) with a mixture of pet-ether/ether of increasing polarity. The first eluted product proved to be the *arabino*-epimer 4 (53 mg). It crystallized on storage in the refrigerator. After trituration and recrystallization (pet-ether/ether 2:1) : it showed mp 58-59 °C ; TLC R_F = 0.49 (pet-ether/ether 1:2) ; $[\alpha]_D^{20}$ 52.6 (c 1.3, $CHCl_3$).

Anal. Calcd for $C_{18}H_{22}O_7$ (350.37) : C, 61.77 ; H, 6.34. Found : C, 61.80 ; H, 6.56.

The second product (3, 49 mg) failed to crystallize ; R_F = 0.41 (pet.ether/ether 1:2) ; $[\alpha]_D^{20}$ 34.1 (c 1.6, $CHCl_3$).

Anal. Calcd for $C_{18}H_{22}O_7$ (350.37) : C, 61.77 ; H, 6.34. Found : C, 61.97 ; H, 6.65.

The same procedure was applied to 2 (360 mg, 1.03 mmol) affording an epimeric mixture of 5 and 6 (263 mg, 73 %) that failed to be separated by column chromatography.

Typical small-scale procedure for the reduction of 1 with aluminohydrides. 9.5 mg of LAH (0.25 mmol) or 0.3 mL of vitride (3.4 M solution in toluene, 1 mmol) in 6 mL of solvent (THF, ether, DME or toluene) were cooled in an ice-bath. 34.8 mg (0.1 mmol) of 1 in 1 mL of solvent was kept under stirring at 0 °C. In some cases, 1 was previously complexed with hydrolyzed vitride in the following way : 0.15 mL of vitride solution (0.5 mmol) in 6 mL of solvent were cooled in ice-bath and hydrolyzed with 18 10^{-3} mL of water. 34.8 mg (0.1 mmol) of 1 in 1 mL of solvent was added and the mixture was kept under stirring at 0 °C (15 min.). Then 0.3 mL of vitride solution was added and the reaction was carried out at 0 °C. After completion of the reaction, the mixture was hydrolyzed [12] and filtered on celite. The solvents were carefully evaporated to dryness un-

der reduced pressure and the crude mixture was acetylated and worked up as above. After solvent evaporation the mixture of epimers 3 and 4 was obtained (40-70 %) and analyzed by GLC.

The same procedure was applied to compound 2.

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REFERENCES

1. J. C. Buchanan, Progress in the Chemistry of Organic Natural Products, W. Herz, H. Grisebach and G. W. Kirby Eds., Vol. 9, Springer-Verlag, New-York, 243 (1983).

2. V. Hacksell and G. D. Daves Jr., Progress in Medicinal Chemistry, G. P. Ellis and G. B. Wast Eds, Vol. 22, Elsevier, 1 (1985).

3. S. Czernecki and V. Dechavanne, Can. J. Chem., 61, 533 (1983).

4. V. Bellosta and S. Czernecki, Carbohydr. Res., in press.

5. T. Halmos and K. Antonakis, Carbohydr. Res., 68, 61 (1979).

6. O. J. Varela, A. F. Cirelli and R. M. de Lederkremer, Carbohydr. Res., 70, 27 (1979).

7. D. C. Baker, J. Defaye, A. Gadelle and D. Horton, J. Org. Chem., 41, 3834 (1976) and references cited therein.

8. D. C. Wigfield, Tetrahedron, 35, 449 (1979).

9. R. Benhaddou, S. Czernecki and G. Ville, unpublished results.

10. R. Murugan, Can. J. Chem., 58, 1993 (1980).

11. S. Danishefsky and H. E. Langer, J. Org. Chem., 50, 3672 (1985).

12. L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, John Wiley and Sons, New-York, Vol. 1, 584 (1967).