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2,3-UNSATURATED C-GLUCOPYRANOSIDES: A GUIDELINE TO THE ANOMERIC CONFIGURATIONAL ASSIGNMENT

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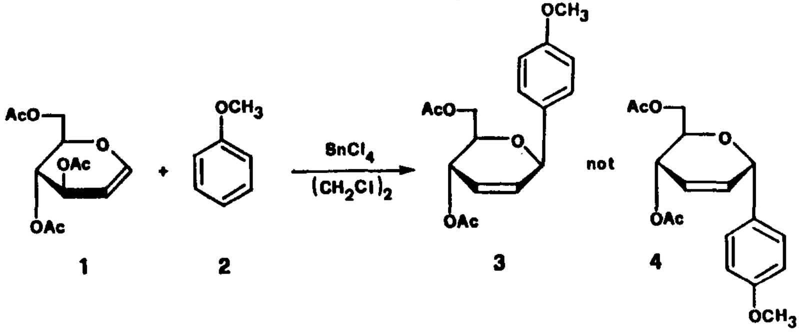
Abstract: Contrary to a previous reporte , the SnCl$_4$-promoted arylation of tri-O-acetyl-D-glucal(1) by means of anisole (2) gives rise to 1'-(4,6-di-O-aceyl-2,3-dideoxy- β -D-erythro-hex-2-enopyranosyl)-4'-methoxybenzene (3) and not α-anomer (4). A guideline to the correct assignment of the anomeric congiguration of 2,3-unsaturated C-glucopyranosides is suggested, which violates the Hudson isorotation rule.

C-Aryl-glycosyl compounds have become a topic of high interest mainly due to the important pharmacological properties displayed by these compounds.[1] Among the synthetic routes to these molecules, the SnCl$_4$-promoted arylation at the anomeric centre of acetylated glycals by means of activated aromatic compounds as discovered by Grynkiewicz and Zamojski[2] is direct and convenient.

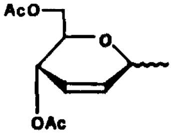
In fact, the reaction of anisole (2) with tri-O-acetyl-D-glucal (1) is highly stereoselective and affords a single glycosidic product, namely 1'-(4,6-di-O-acetyl-2,3-dideoxy-D-erythro-hex-2-enopyranosyl)-4'-methoxybenzene, to which α- anomeric configuration (4) was assigned on the basis of the specific rotation value and ^{1}H NMR analysis.[2]



However, careful inspection of literature data for 2,3-unsaturated C-glucopyranosides[3-7] as well as comparison with our results in similar reactions[8] introduced doubts about the correct assignment of the anomeric configuration of this compound. In particular, the highly positive specific rotation value ($[\alpha]_D$ = +253°) and the ^{1}H NMR coupling constant $J_{4,5}$ =9.0 Hz reported for compound (4) appeared to be inconsistent with the same data for most type-(5) compounds (see Table) whose anomeric configuration was unambiguously determined.

With no exceptions β-anomers (even entries in the Table) show high and positive $[\alpha]_D$ values while α-anomers (odd entries) display less positive or negative values. In the ^1H NMR spectra the vicinal coupling constant between the H-5 and H-4 protons is highly diagnostic α-anomers displaying smaller values ($J_{4,5}$ =3-9 Hz) than those of the corresponding β-counterparts ($J_{4,5}$ = 8.7-10 Hz)

Table. Diagnostic ^1H NMR characteristics and specific rotation values for α- and β-C-glucopyranosides



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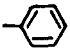
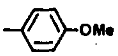
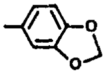
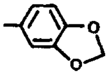
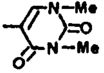
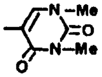
				^1H NMR				NOE	Anomeric Config		
Entry	R	$[\alpha]_D$,deg.	H-2	H-3	H-5	$J_{1,2}$	$J_{4,5}$	H-5 vs H-1	Repd	Actual	Ref
1		+3.3	5.99	6.18	3.86	--	7.5	--	β	α	3
2		+253	5.91	5.82	3.92	1.5	9.2	Yes	α	β	2
3		-24	6.21	6.02	3.91	3.2	7.1	No	α	α	8
4		+187	5.94	5.86	3.95	1.6	8.9	Yes	β	β	8
5		--	6.09	5.93	3.95	1.3	6.5	--	α	α	4
6		--	5.99	5.76	3.88	0.0	9.1	--	β	β	4
7	$-CH_2COPh$	+35.7	6.08	5.86	4.05	2.3	3.5	--	α	α	5
8	$-CH_2COPh$	+111.3	5.99	5.77	3.79	1.1	8.7	--	β	β	5
9	$-CH(CH_3)-CH=CH_2$	--	--	--	--	--	3-4	No	α	α	6
10	$-CH(CH_3)-CH=CH_2$	--	--	--	--	--	9-10	Yes	β	β	6
11	$-CN$	-14.6	5.89	6.03	4.03	2.9	9.0	--	α	α	7
12	$-CN$	+197.5	5.91	6.03	3.83	1.8	8.5	--	β	β	7

Thus, we decided to repeat the same reaction under the reported conditions[9] and isolated a C-glycosidic compound whose physical and spectral data ($[\alpha]_D$, m.p., ^1H NMR) were in agreement with the reported values.

A more detailed ^{1}H NMR investigation strongly supports an equatorial (β) orientation of the aromatic mojety.In particular the 2D-NOESY spectrum (Fig. 1) shows a strong connectivity between H-1 and H-5 (5.16-3.92 ppm), in agreement with the cis orientation observed in the crystal (H-H distance 2.54 A). In addition relevant connectivities are observed between H-1 and the proton in ortho-position in the aromatic ring H-2$'$ (5.16-7.25 ppm), and between H-4 and H-6 (5.41-4.25 ppm).

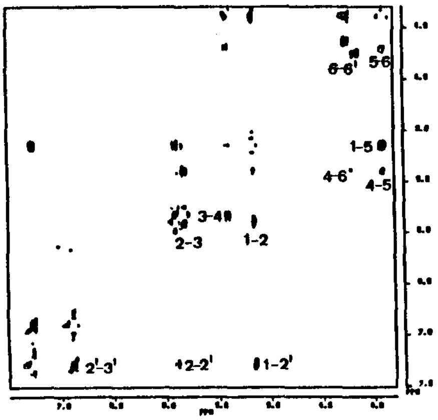


Figure 1. 2D-NOESY spectrum of glycoside 3 in $CDCl_3$, obtained with diagonal suppression (G.Bodenhausen and R.R.Ernst Mol.Phys. 1982, 47, 319).

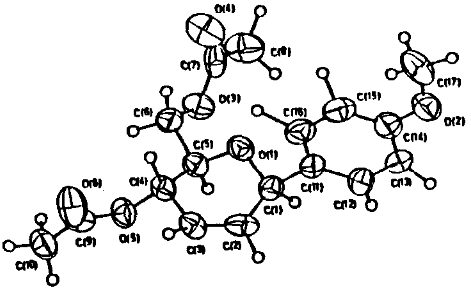


Figure 2. General view of compound 3 showing the labelling scheme used in the crystallographic study. The ellipsoids of thermal motion are 50% envelope.
The molecule is shown in its correct absolute configuration.
The H(1)-H(5) distance is 2.54 Å.

Finally, to corroborate the configurational assignment of glucoside 3, a single crystal X-ray analysis was performed on suitable prismatic crystals grown from n-hexane.[10]

An ORTEP illustration is provided in Figure 2. The enopyranosyl ring shows a half-chair conformation with a two fold axis intersecting the C(5)-O(1) bond [puckering parameters: φ_2 = 141.6(1.6)°, Θ= 128.8(1.4)°].[12]

The arrangement of the phenyl and the acetyl groups with respect to the enopyranosyl ring is defined by the torsional angles O(1)C(1)C(11)C(12) = 47.2(1.4)°; O(1)C(5)C(6)O(3) = 71.6(1.1)°, C(4)C(5)C(6)O(3) = -170.9(9)°; C(9)O(5)C(4)C(5) = -153.0(1.1)°. Some selected distances are: O(1)-C(1) = 1.45(1), O(1)-C(5) = 1.43(1), O(2)-C(14) = 1.39(2), O(2)-C(17) = 1.42(2), O(3)-C(7) =1.35(2), O(4)-C(7) = 1.22(2), O(5)-C(9) = 1.34(2), O(6)-C(9) = 1.20(2), C(2)-C(3) = 1.30(2). The packing of the molecules is entirely due to Van der Waals forces.

In conclusion, the structure of compound 3 (entry 2 of the Table) as well as that in entry 1 have been revised and assigned as β-anomer and α-anomer respectively. A general rule is given which allows easy configurational assignment for 2,3-unsaturated 1-C-glucopyranosides. In the D-series, for a given anomeric pair the more dextrorotatory member having $J_{4,5}$ of 8.7-10 Hz and relevant positive NOE between H-1 and H-5 [13] should be assigned as β-D, whilst the other displaying a $J_{4,5}$ value in the range 3-9 Hz and no NOE between H-1 and H-5 [13] is to be named α-D.[14] Clearly, in this special case the Hudson's rule[15] for the $[\alpha]_D$ -based assignment of the anomeric configuration to α- and β- glycosides is violated.

Reference and Notes

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9. *The experimental conditions were as reported in Ref. 2. However, $SnCl_4$ (0.05 equiv.) was added dropwise as a 0.1M solution in dichloroethane.*
10. *Crystal data: $C_{17}H_{20}O_6$, M = 320.3, orthorhombic, space group $P2_12_12_1$, a = 30.463(4), b = 9.754(2), c = 5.587(1)Å, U = 1660.1Å^3, Z = 4, Dc = 1.28gcm^{-3}, F(000) = 680, Cu-Kα radiation, λ=1.54178Å, μ= 7.7cm^{-1}, crystal size 0.05x0.16x0.32 mm. The intensities of 1505 reflexions were collected to a $2\Theta_{max}$ = 120 , on a computer controlled Siemens AED by the ω-2Θ scan technique. The structure was solved by direct methods using the SHELX86 program[11] and refined to a final R value of 4.9% for 645 reflexions with $I>2\sigma(I)$ (unrefined isotropic hydrogen atoms, $\Delta\rho_{max}$ = 0.11, $\Delta\rho_{min}$ = -0.10). Calculation were carried out on a Gauld 6040 Powernode computer of the Centro di Studio per la Strutturistica Diffrattometrica del C.N.R. (Parma, Italy)*
    The atomic co-ordinantion and bond lengths (with standard deviations) for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompained by the full literature citation for this communication.
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