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Note

Conversion of β-D-C-glucopyranosyl phloroacetophenone to a spiroketal compound

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Abstract

Treatment of β-D-*C*-glucopyranosyl phloroacetophenone in water in the presence of a catalytic amount of *p*-TsOH afforded a spiroketal product. This is the first demonstration of ring conversion in aryl *C*-glycoside. The structure of the product was determined by ^{1}H-^{1}H COSY, HMQC, HMBC, NOESY, and single crystal X-ray analysis of the corresponding acetylated compound.

Keywords: β-D-*C*-Glucopyranosyl phloroacetophenone; Acidic treatment; Tetrahydrospiro{benzofuran-2(3*H*),2′-[2*H*]pyran}

In recent years, the synthesis of aryl *C*-glycosyl compounds [1] and the evaluation of their biological activity [2] has been a subject of considerable interest. The C–C linkage between C-1 of the sugar moiety and the carbon atom of aglycon in an aryl *C*-glycosyl compound is resistant to hydrolysis. As a result, these compounds would be potentially useful as a source of therapeutic agents for clinical use.

It would be of interest to better understand the reactions and interactions which occur in the sugar moiety of *C*-glycosyl compounds under conditions of hydrolysis, even though the pseudoglycosidic linkage is not cleaved during the reaction. In the field of flavonoid chemistry, three types of reactions occur at hydrolytic conditions: (i) the Wessely–Moser rearrangement of the aglycon moiety, but not the sugar; (ii) the expected pyranose–furanose interconversion; and (iii) the acid-catalyzed destruction of the *C*-glycoside [3]. Because of the complexity of these reactions, it is possible that a number of reaction products have not yet been isolated and characterized so far. In addition, it is possible that the use of lower concentrations of acid might well allow the isolation of important reaction products which have not yet been identified. We here report that β-D-*C*-glucopyranosyl phloroacetophenone, on treatment with water and a catalytic amount of *p*-toluenesulfonic acid, gave a novel spiroketal compound in an unexpectedly good yield.

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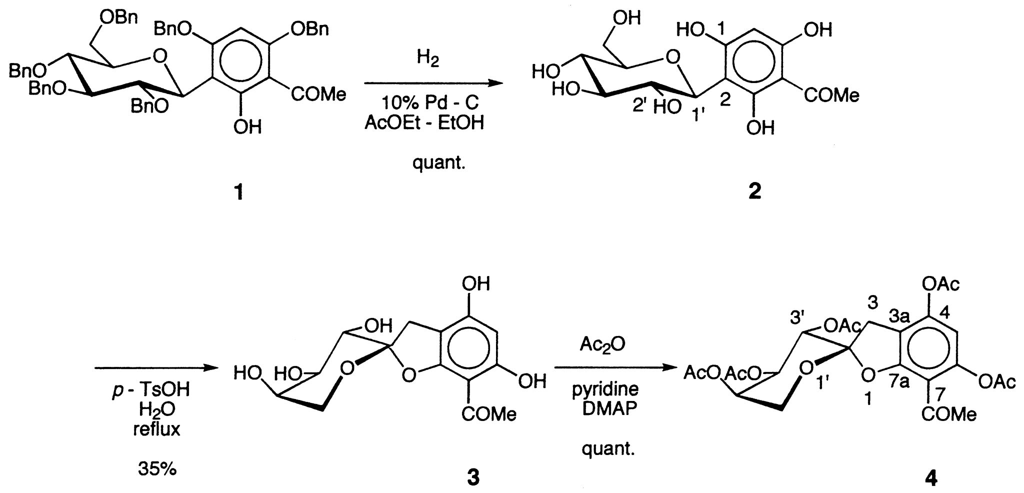

Scheme 1.

We previously described the reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride [4] with 2,4-*O*-benzyl-protected phloroacetophenone in the presence of boron trifluoride diethyl etherate leading to the *C*-glucoside **1** [5]. Hydrogenolytic *O*-debenzylation of **1** with 10% palladium on activated carbon as a catalyst under a hydrogen atmosphere gave the corresponding *O*-unprotected compound **2** [6] in quantitative yield. Compound **2** dissolved in a large quantity of water and was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid. Thin layer chromatography of the reaction (25:35:5:1 Me_2CO–EtOAc–H_2O–AcOH) showed a main product, along with a large amount of other by-products. After column chromatography, the fraction including the main product was isolated and acetylated with acetic anhydride, pyridine, and 4-dimethylaminopyridine (DMAP) to give spiroketal **3** in 35% yield (Scheme 1).

The ^{1}H NMR spectra of **3** showed a signal assignable to a chelated phenolic OH at 13.05 ppm and a signal for a phenolic OH at 10.71 ppm, but H-3′ and H-4′ methine proton signals were overlapped. In addition, C-3′ and C-4′ carbon signals were also overlapped in the ^{13}C NMR spectra. We thus turned our attention to the corresponding acetylated compound **4**. The COSY spectrum of **4** showed the proton–proton coupling network from H-3′ methine to H-6′ geminal methylene, but showed no correlation for the H-3 geminal methylene proton. The presence of a quarternary carbon was observed at 112.3 ppm in the HMQC spectrum of **4**. The HMBC spectrum of 4 showed a correlation between the above-mentioned quarternary carbon and H-3′, H-4′, H-6′a, H-6′b, H-3a, as well as H-3b, and also showed a correlation between the H-3 methylene protons and C-3′. These data confirm that the molecule contains a spiroketal structure. The NOESY spectrum of **4** indicated a correlation between H-3′ and H-3a, between H-4′ and H-6′b, but no correlation between H-3′ and H-3b. The NOESY spectrum also indicated a correlation between H-4′ and the methyl protons of a *C*-acetyl group bonded to the aromatic ring and between H-6′b and the above-mentioned methyl protons, respectively (Fig. 1). The NOESY experiment suggests that C-2 of the original glucopyranosyl moiety of **2** is bonded to a hydroxyl group which is ortho to the *C*-acetyl group and that the pyranose ring of **4** was in the $^1C_4$ conformation. The absolute structure of this spiro compound was confirmed to be as shown in Fig. 1. The compound has a 2*H*-benzofuran closing ring at the hydroxyl group, which is ortho to the *C*-acetyl group. The sugar portion, tri-*O*-acetyl-D-arabinopyranose, exists in the $^1C_4$ conformation. In order to verify the proposed molecular structure, **4** was characterized by a single crystal X-ray structure study[1] (Fig. 2). In all probability, the fundamental skeletal structure of **3** can be presumed to have the same structure as **4**.

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[1] Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

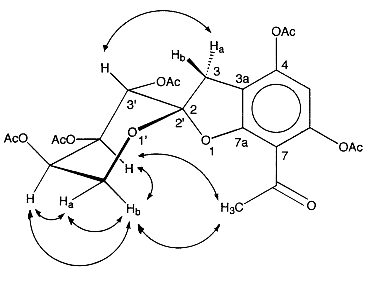

Fig. 1. NOESY correlations of **4**.

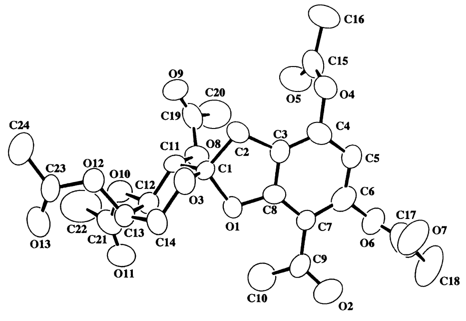

Fig. 2. X-ray structure of **4**.

In conclusion, acidic treatment of β-D-*C*-glucopyranosyl phloroacetophenone in hot water in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded a novel, unique spiroketal product, as an unusual example of a sugar ring conversion. Studies of similar conversions of several other *C*-glycosides are now under investigation.

1. Experimental

General methods.—All nonaqueous reactions were carried out under an atmosphere of dry argon using freshly distilled solvents, unless otherwise noted. All reactions were monitored by thin layer chromatograpy (TLC carried out on 0.25 mm E. Merck Silica Gel 60 F254 plates using either UV light for visualization or an EtOH 5% soln of $FeCl_3$ or an EtOH 5% soln of phosphomolybdic acid with heat as developing agents. Wakogel C-300® (particle size 0.045–0.075 mm) or Wako Polyamide C-200® (particle size 0.075–0.15 mm) was used for column chromatograpy. Melting points are uncorrected. Optical rotations were recorded for solns in $CHCl_3$ or EtOH on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Horiba FF-200 IR spectrometer as KBr pellets. Mass spectra were recorded on a JEOL JMS-AX-505-HA mass spectrometer under FAB ionization conditions using 3-nitrobenzyl alcohol as the matrix. ^1H NMR and ^{13}C NMR spectra were recorded on Varian INOVA 500 instruments using Me_4Si as the internal reference.

4-Acetyl-2-β-D-glucopyranosyl-1,3,5-trihydroxybenzene (**2**).—A soln of **1** (2.414 g) and 10% palladium-on-charcoal (120 mg) in EtOAc (15 mL) and EtOH (40 mL) was stirred at room temperature for 6 h under an atmosphere of H_2. After filtering, the filtrate was concentrated under reduced pressure to give **2** (0.915 g, quant.) as colourless crystals. Recrystallization from EtOH afforded **2** as colourless crystals: mp 167–169 °C; $[\alpha]_D^{22}$ +55.2° (*c* 0.1, EtOH); R_f 0.43 (25:35:5:1 Me_2CO–EtOAc–H_2O–AcOH); IR (KBr): 3361, 2929, 1626, 1510, 1450, 1408, 1365, 1286, 1173, 1082, 1028, 822, 754 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 2.56 (s, 3 H, ArAc), 3.08–3.17 (m, 3 H, H-3′, 4′, 5′), 3.40 (m, 1 H, H-6a), 3.65 (d, 1 H, *J* 11.0 Hz, H-6′b), 3.88 (t, 1 H, *J* 9.5 Hz, H-2′), 4.50 (d, 1 H, *J* 9.8 Hz, H-1′), 4.51 (br. s, 2 H, OH), 4.84 (br. s, 2 H, OH), 5.93 (s, 1 H, ArH), 10.10 (br. s, 1 H, ArOH), 10.99 (br. s, 1 H, ArOH), 13.83 (br. s, 1 H, ArOH); ^{13}C NMR (Me_2SO-d_6): δ 32.4 (ArAc), 61.2 (C-6′), 70.3 (C-4′), 70.5 (C-2′), 73.4 (C-1′), 78.8 (C-3′), 81.2 (C-5′), 94.3 (C-6), 103.8 (C-2, 4), 161.8, 163.7, 164.6 (C-1, 3, 5), 202.5 (ArAc); FAB$^+$MS: *m*/*z* 331 $[M+H]^+$. Anal. Calcd for $C_{14}H_{18}O_9.^3/_2\ H_2O$: C, 47.06; H, 5.92. Found: C, 47.05; H, 5.75.

*(2*S*,3′*S*,4′*R*,5′*R*)-7-Acetyl-3′,4′,5′,6′-tetrahydrospiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-3′,4,4′,5′,6-pentaol* (**3**).—A soln of **2** (120 mg, 0.363 mmol) and *p*-TsOH monohydrate (12 mg, 0.063 mmol, 0.17 equiv) in H_2O (50 mL) was refluxed for 3 d. After cooling, the H_2O was evaporated under reduced pressure and the resulting syrup was column chromatographed on polyamide gel (1:1 MeOH–H_2O) to give crude **3**. Recrystallization from EtOH afforded **3** (40 mg, 35%) as colourless crystals: mp 278–280 °C (dec.); $[\alpha]_D^{22}$ −139° (*c* 0.10, EtOH); R_f 0.58 (25:35:5:1 Me_2CO–EtOAc–H_2O–AcOH); IR (KBr): 3494, 3450, 3273, 3188, 2947, 2929, 1637, 1504, 1446, 1357, 1346, 1306, 1246, 1217, 1205, 1190, 1182, 1138, 1097, 1074, 1063, 1003, 960, 852, 831, 798, 785, 750, 692, 635 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 2.55 (s, 3 H, ArAc), 2.73 (d, 1 H, *J* 15.6 Hz, H-3a), 3.23 (d, 1 H, *J* 15.6 Hz, H-3b), 3.62 (dd, 1 H, *J* 1.7, 12.2 Hz, H-6′a), 3.67–3.71 (m, 1 H, H-3′, 4′), 3.83 (m, 1 H, H-5′), 3.91 (d, 1 H, *J* 12.2 Hz, H-6′b), 4.83 (d, 1 H, *J* 3.2 Hz, OH-5′), 4.89 (d, 1 H, *J* 4.4 Hz, OH-3′ or OH-4′), 5.12 (d, 1 H, *J* 7.1 Hz, OH-4′ or OH-3′), 5.83 (s, 1 H, ArH), 10.71 (br. s, 1 H, ArOH), 13.05 (s, 1 H, ArOH); ^{13}C

NMR (Me_2SO-d_6): δ 31.6 (ArAc), 35.1 (C-3), 66.4 (C-6′), 69.8 (C-5′), 70.9 (C-3′, 4′), 96.3 (C-5), 101.2 (C-7), 103.4 (C-3a), 115.3 (C-2), 160.9 (C-4), 162.0 (C-7a), 164.3 (C-6), 201.4 (ArAc); FAB^-MS: *m*/*z* 311 $[M-H]^-$. Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16. Found: C, 53.82; H, 5.35.

*(2*S*,3′*S*,4′*R*,5′*R*)-3′4,4′,5′,6-Pentakis-acetoxy-7-acetyl-3′,4′,5′,6′-tetrahydrospiro[benzofuran-2(3*H*), 2′-[2*H*]pyran]* (**4**).—Compound **3** (35 mg, 0.11 mmol) was dissolved in Ac_2O (1 mL) and pyridine (200 µL), and DMAP (10 mg) was then added. The mixture was stirred at room temperature for 1 d. The reaction mixture was quenched with 0.1 M HCl and extracted with EtOAc. The extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was chromatographed on a silica gel column (3:2 hexane–EtOAc) to afford **4** (58 mg, quant.) as colourless crystals. Recrystallization from 2-propanol afforded colourless prismatic crystals: mp 182–182.5°; $[\alpha]_D^{22}$ −156° (*c* 0.10, $CHCl_3$); R_f 0.41 (1:1 hexane–EtOAc); IR (KBr): 3072, 2983, 2942, 2897, 2848, 1751, 1691, 1618, 1417, 1371, 1308, 1259, 1244, 1221, 1144, 1072, 1055, 1018, 970, 906, 795 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.01, 2.02, 2.19, 2.27, 2.29 (s, each 3 H, –OAc), 2.61 (s, 3 H, ArAc), 3.11 (d, 1 H, *J* 16.8 Hz, H-3a), 3.15 (d, 1 H, *J* 16.8 Hz, H-3b), 3.90 (dd, 1 H, *J* 1.8, 13.3 Hz, H-6′a), 4.19 (dd, 1 H, *J* 1.3, 13.3 Hz, H-6′b), 5.37 (dd, 1 H, *J* 3.4, 10.7 Hz, H-4′), 5.47 (ddd, 1 H, *J* 1.3, 1.8, 3.4 Hz, H-5′), 5.62 (d, 1 H, *J* 10.7 Hz, H-3′), 6.51 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.8, 21.0 (–OAc×5), 32.0 (ArAc), 36.3 (C-3), 63.6 (C-6′), 68.46 (C-3′), 68.52 (C-5′), 68.7 (C-4′), 110.6 (C-5), 112.3 (C-2), 114.2 (C-7), 116.5 (C-3a), 148.7 (C-4), 149.6 (C-6), 158.6 (C-7a), 167.2, 169.6, 169.9, 170.2, 170.5 (–OAc), 195.3 (ArAc); FAB^+MS: *m*/*z* 523 $[M+H]^+$. Anal. Calcd for $C_{24}H_{26}O_{13}$: C, 55.17; H, 5.02. Found: C, 55.03; H, 5.00.

Crystal structure analysis.—A colourless crystal with dimensions 0.1×0.20×0.30 mm was mounted on a glass fibre. Intensity data for **4** were collected with graphite-monochromated Cu-K_α radiation ($\mu = 7.97\ cm^{-1}$, $\lambda = 1.54178$ Å) on a Rigaku AFC5S diffractorneter at 23 °C corrected for Lorentz polarization effect. Crystal data for **4**: $C_{24}H_{26}O_{13}$, FW = 522.46, monoclinic, space group $P2_1$ (no. 4), $a = 9.326(2)$ Å, $b = 8.846(3)$ Å, $c = 16.371(2)$ Å, $\beta = 102.34(1)°$, $V = 1319.4(5)$ Å^3, $Z = 2$, $D_{calc} = 1.315\ g\,cm^{-3}$. Of the 2468 reflections which were collected, intensity data of 2313 unique reflections were collected in the range $0 \leq h \leq 10$, $0 \leq k \leq 10$, $-18 \leq l \leq 16$. The structure was solved by direct methods using PHASE [7], DIRDIF [8] program system. The atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms were refined by full-matrix least-squares to minimize the functions $\Sigma w(|F_0| - |F_c|)^2$, $w = 4Fo^2/\sigma^2(Fo^2)$, for 1440 observed reflections, $I > 3.00\sigma\ (I)$. The final *R* and *Rw* values were 0.062 and 0.050, respectively.

References

[1] M.H.D. Postema, *Tetrahedron*, 48 (1992) 8545–8599; C. Jaramillo and S. Knapp, *Synthesis*, (1994) 1–20; D.E. Levy and C. Tang, *The Chemistry of* C-*Glycosides*, Elsevier, New York, 1995.

[2] B.K. Catarte, S. Carr, C. DeBrosse, M.E. Hemling, L. Mackenzie, P. Offen, and D.E. Berry, *Tetrahedron*, 47 (1991) 1815–1821; Y. Matsubara and A. Sawabe, *J. Syn. Org. Chem. Jpn.*, 52 (1994) 318–327.

[3] E. Besson and J. Chopin, *Phytochemistry*, 22 (1983) 2051–2056; M.K. Park, J.H. Park, Y.G. Shin, W.Y. Kim, J.H. Lee, and K.H. Kim, *Planta Med.*, 62 (1996) 363–365; B.C.B. Bezuidenhoudt, E.V. Brandt, and D. Ferreira, *Phytochemistry*, 26 (1987) 531–535.

[4] M. Hayashi, S. Hashimoto, and R. Noyori, *Chem Lett.*, (1984) 1747–1750.

[5] T. Kumazawa, K. Ohki, M. Ishida, S. Sato, J. Onodera, and S. Matsuba, *Bull. Chem. Soc. Jpn.*, 68 (1995) 1379–1384.

[6] J. Onodera, M. Takano, Y. Kishi, N. Yokoyama, and R. Ishida, *Chem. Lett.*, (1983) 1487–1488.

[7] J.C. Calbress, PhD thesis, University of Wisconsin-Madison, 1972.

[8] P.T. Beurskens, DIRDIF, Direct methods for difference structures—an automatic procedure for phase extension and refinement of difference structure factors, Technical Report 1984/1, Crystallography Laboratory, Toernooiveld, Nijmegen, The Netherlands.