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Note

The conversion of 3-*C*-β-D-galactopyranosyl phloroacetophenone to a spiroketal derivative

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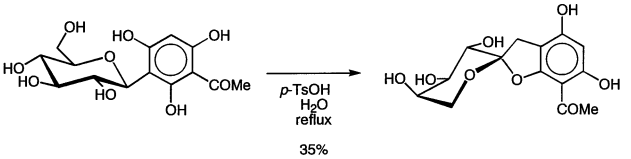
Abstract

Treatment of 3-*C*-β-D-galactopyranosylphloroacetophenone in hot water with a catalytic amount of *p*-toluenesulfonic acid afforded a spiroketal compound as the main product. The chirality of the spiro carbon of the product was R, which is the opposite of the spiroketal obtained by the conversion of 3-*C*-β-D-glucopyranosyl phloroacetophenone under identical conditions. The structure was determined by $^{1}H-^{1}H$ COSY, $^{1}H-^{13}C$ COSY, NOESY and HMBC spectroscopy. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *C*-Glycosylic compound; 3-*C*-β-D-Galactopyranosylphloroacetophenone; Acid treatment; Spiroketal derivative; Tetrahydrospiro{benzofuran-2(3*H*), 2′-[2*H*]pyran}

Studies of the chemistry of aryl *C*-glycosyl derivatives, including their synthesis [1], have been the subject of considerable attention in recent years due to their biological activities [2]. The C–C linkage between C-1 of the sugar moiety and carbon atom of aglycon in an aryl *C*-glycosylic compound is resistant to hydrolysis. However, in an earlier study we showed that a *C*-glucosyl derivative could be converted into a spiroketal compound in surprisingly good yield on treatment with a catalytic amount of *p*-toluenesulfonic acid in hot water, as shown in Scheme 1. Under these conditions, the pseudglycosidic linkage is not cleaved [3]. The structure of the product was determined by single-crystal X-ray analysis of the O-acetylated derivative.



Scheme 1.

Some flavonoids contain aryl *C*-glycosyl moieties as a part of their structure and include the naturally occurring *C*-glycosyl flavonoids [4]. D-Glucose constitutes the sugar moiety in the majority of *C*-glycosyl flavonoids. Compared with the number of *C*-glucosylflavanoids, *C*-glycosylflavanoids that contain D-galactose, D-arabinose, and L-rhamnose moieties are much less extensive, and in second place, as a group [4].

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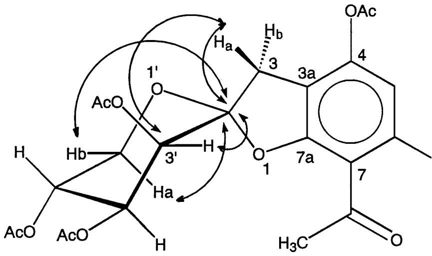


Fig. 1. HMBC correlations of **6** with respect to the spiro carbon.

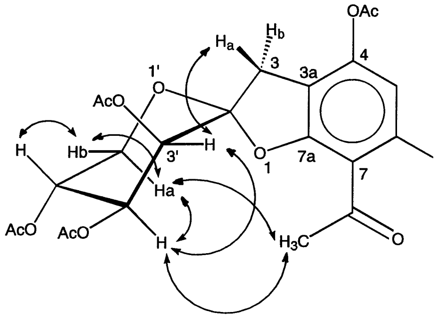
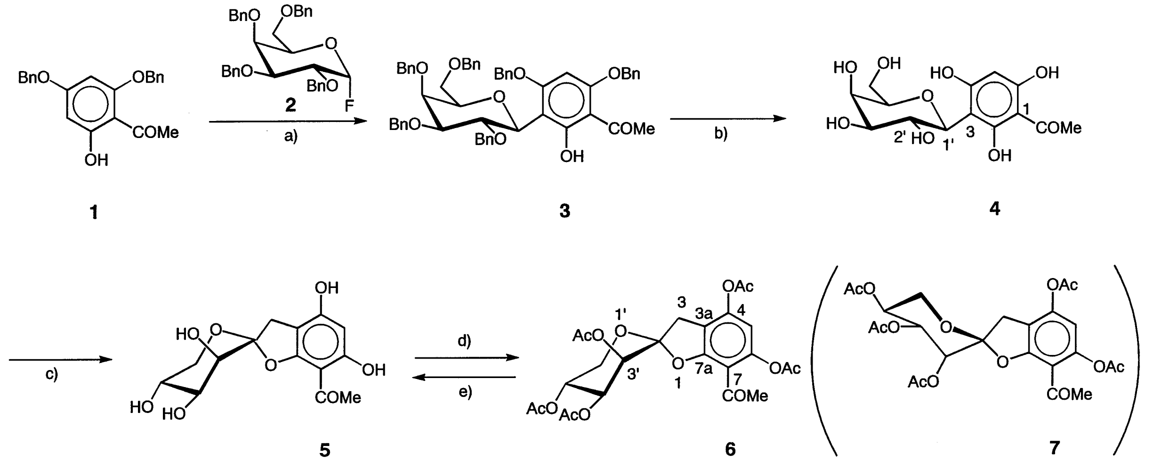


Fig. 2. NOESY correlations of **6**.

In the present study, 3-*C*-β-D-galactopyranosylphloroacetophenone was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid in hot water to afford a spiroketal compound as a main product. The chirality on the spiro carbon of this compound was R, whereas it was S when 3-*C*-β-D-glucosylphloroacetophenone was converted to a spiroketal compound under identical conditions [3] (Scheme 1). 3-*C*-β-D-Galactopyranosylphloroacetophenone was employed as a substance in this reaction, rather than *C*-β-D-galactopyranosylflavone, in order to avoid the Wessely–Moser rearrangement of the aglycon moiety in the flavone during hydrolysis. It would be of interest to better understand the reactions that might occur in the D-galactose moiety of *C*-galactosylflavonoid under hydrolytic conditions.

The protected *C*-galactosylphloroacetophenone **3** was synthesized according to the previously described method [5]. The reaction of 2,4-di-*O*-benzyl phloroacetophenone (**1**) with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl fluoride (**2**) [6] in the presence of boron trifluoride diethyl etherate gave the *C*-galactosyl compound **3**. The structure was confirmed by ^{1}H NMR and ^{1}H–^{1}H COSY spectra at a temperature of 140 °C [5]. The experiments were conducted at elevated temperature because the structural assignment by NMR spectroscopy at ambient temperature was hampered by the slow rotation around the C-1–aglycon bond. Compound **3** was hydogenolyzed with 10% Pd–C as a catalyst under an H_2 atmosphere to afford **4**. Compound **4**, dissolved in a large quantity of water, was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid. Thin-layer chromatography (TLC) of the reaction mixture showed a main product, along with numerous by-products. It was concluded that the main product was not separable from the by-products, and the reaction mixture was therefore acetylated with acetic anhydride, pyridine, and a catalytic amount of 4-dimethylaminopyridine (DMAP). After silica gel column chromatography of the acetylated mixture, pure **6** was obtained by recrystallization from hexane–Et_2O in 30% yield as a major product.

The ^{1}H NMR and ^{1}H–^{1}H COSY spectra of acetylated compound **6** showed a proton–proton coupling network from the H-3′ methine to the H-6′ geminal methylene, but showed no correlation for the singlet peak of the H-3 geminal methylene. The presence of a quarternary carbon was observed at 111.1 ppm in the ^{13}C NMR spectra of **6**. The HMBC spectrum indicated that this carbon signal had a correlation to H-3, H-3′, H-6′a, as well as to the H-6′b signal, and showed a correlation between the H-3 methylene and C-3′, as shown in Fig. 1. It was not possible to determine if either H-3a or H-3b, or both, had a correlation to the carbon signal at 111.1 ppm because H-3 appeared as a singlet (see above). Based on the coupling constants of the ^{1}H NMR spectra of **6**, especially $J_{4',5'}$ 10.3 Hz, and by comparison with the result of the conversion reaction of *C*-glucosylphloroacetophenone under the same conditions [3], the possibility that compound **6** is a spiroketal, in which the chirality on the spiro carbon is R, or a spiroketal compound **7**, in which the chirality is S cannot be excluded. The NOESY spectrum of **6** clearly indicated a correlation between H-4′, H-6′a and the methyl protons of a *C*-acetyl group bonded to the aromatic ring



Scheme 2. Reaction conditions: (a) $BF_3 \cdot Et_2O$, 4 Å MS, CH_2Cl_2, −78 °C→rt, 76%. (b) H_2, 10% Pd–C, EtOAc–EtOH, quant. (c) *p*-TsOH, water, reflux, 30%. (d) Ac_2O, pyridine, DMAP. (e) 28% NaOMe, MeOH, quant.

(Fig. 2). Therefore, it is clear that this spiro compound is the R isomer as shown in Scheme 2.

Deacetylation of **6** using NaOMe in methanol afforded the corresponding **5** in quantitative yield. In the ^{1}H NMR spectra of **5**, the H-3a and H-3b methylene protons both appeared as doublets, even though the ^{1}H NMR spectra of **6** showed that the H-3 methine protons were a singlet. The ^{13}C NMR spectra of **5** showed the presence of a quaternary spiro carbon at 114.4 ppm. The HMBC spectrum of **5** showed a correlation between the spiro carbon and H-3a, H-3′, H-6′a, as well as H-6′b, and also showed a correlation between H-3a and C-3′ (Fig. 3). The NOESY spectrum of **5** indicated a correlation between both H-4′, H-6′a and the methyl protons of a *C*-acetyl group bonded to the aromatic ring.

As a result of the data mentioned above, the absolute structure of the spiro compound **5** was confirmed as that shown in Scheme 2. The compound has a 2*H*-benzofuran ring, which includes the hydroxyl oxygen atom that is ortho to the *C*-acetyl group, as well as a D-lyxosyl moiety, which is in the $^4C_1$ conformation. The chirality of the spiro carbon that connects the two portions of the molecule is R. In order to determine the factors that led to the inversion of the chirality on the spiro carbon, studies of similar conversions of other *C*-glycosylic compounds are presently underway.

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 TLC, which was carried out on 0.25 mm Silica Gel 60 F_{254} plates (E. Merck) using either UV light, a 5% ethanolic soln of ferric chloride or a 5% ethanolic solution of phosphomolybdic acid with heat as developing agents. Wakogel C-300® (particle size 0.045–0.075 mm) was used for column chromatography. Melting points are uncorrected. Optical rotations were recorded using $CHCl_3$ or EtOH as solvents on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Horiba FT-200 IR spectrometer as KBr pellets. Mass spectra were recorded on a JEOL JMS-AX-505-HA mass spectrometer under conditions of fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol as the matrix. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 500 instruments using Me_4Si as the internal reference.

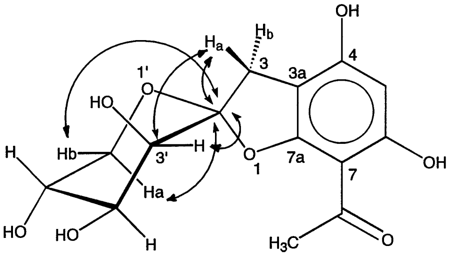


Fig. 3. HMBC correlations of **5** with respect to the spiro carbon.

*4,6-Bis-benzyloxy-2-hydroxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-β-*D*-galactopyranosyl)acetophenone* (**3**).—To a stirred mixture of **1** (11.33 g, 32.5 mmol, 3 equiv), 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl fluoride (**2**) (5.88 g, 10.8 mmol) and powdered 4 Å molecular sieves (5 g) in CH_2Cl_2 at −78 °C, $BF_3 \cdot Et_2O$ (2.93 mL, 23.9 mmol, 2.2 equiv) were added dropwise, and the mixture was then stirred for 1 h. The temperature was allowed to gradually increase to −42 °C, and the stirring was continued for 1 h, then cooled to −20 °C for 1 h, and finally to room temperature (rt) for 1 h. After adding water, the resulting mixture was filtered through a Celite® pad. The filtrate was extracted with $CHCl_3$, the organic layer washed with water and brine, and then dried over anhyd $MgSO_4$. The solvent was evaporated in vacuo, and the resulting syrup was chromatographed on a silica gel column (5:1 hexane–EtOAc) to give **3** (7.17 g, 76%) as a colorless, highly viscous oil: $[\alpha]_D^{25}$ −18° (*c* 0.1, $CHCl_3$); R_f 0.17 (5:1 hexane–EtOAc); IR (KBr): 3107, 3088, 3062, 3030, 3007, 2900, 2868, 1952, 1871, 1813, 1620, 1595, 1497, 1454, 1431, 1389, 1365, 1273, 1223, 1207, 1169, 1109, 1078, 1047, 1028, 1003, 989, 905, 735, 696 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 140 °C): δ 2.48 (s, 3 H, ArAc), 3.55 (dd, 1 H, *J* 6.0, 9.8 Hz, H-6′a), 3.62 (dd, 1 H, *J* 6.1, 9.8 Hz, H-6′b), 3.68–3.71 (m, 2 H, H-3′, 5′), 4.06 (d, 1 H, *J* 2.9 Hz, H-4′), 4.19 (d, 1 H, *J* 11.6 Hz, benzylic CH_2), 4.42 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.46 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.51 (d, 1 H, *J* 11.6 Hz, benzylic CH_2), 4.60 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.66 (t, 1 H, *J* 9.5 Hz, H-2′), 4.69 (d, 1 H, *J* 11.8 Hz, benzylic CH_2), 4.76 (d, 1 H, *J* 11.8 Hz, benzylic CH_2), 4.83 (d, 1 H, *J* 9.8 Hz, H-1′), 4.86 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 5.08 (d, 1 H, *J* 12.7 Hz, benzylic CH_2), 5.12 (d, 1 H, *J* 12.7 Hz, benzylic CH_2), 5.17 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.20 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 6.34 (s, 1 H, ArH), 6.90–7.42 (m, 30 H, ArH), 13.47 (br.s, 1 H, ArOH); FABMS (negative ion): *m*/*z* 869 $[M-H]^-$. Anal. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25. Found: C, 76.92; H, 6.22.

*3-*C*-(β-*D*-Galactopyranosyl)-1,3,5-trihydroxyacetophenone* (**4**).—A solution of **3** (6.81 g, 7.82 mmol) and 10% Pd–C (340 mg) in EtOAc (40 mL) and EtOH (80 mL) was stirred for 1 day at rt under an atmosphere of H_2. After filtration, the filtrate was concentrated under reduced pressure to give **4** (2.62 g, quant) as colorless powder: mp 141–142 °C; $[\alpha]_D^{25}$ +76° (*c* 0.1, MeOH); R_f 0.44 (25:35:5:1 Me_2CO–EtOAc–water–AcOH); IR (KBr): 3348, 2933, 2902, 1626, 1508, 1450, 1406, 1365, 1286, 1171, 1086, 1053, 1030, 883, 824 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 2.57 (s, 3 H, ArAc), 3.35–3.48 (m, 4 H, H-3′, 5′, 6′a, 6′b), 3.74 (d, 1 H, *J* 2.6 Hz, H-4′), 3.89 (t, 1 H, *J* 9.4 Hz, H-2′), 4.56 (d, 1 H, *J* 9.6 Hz, H-1′), 4.58 (br. s, 1 H, –OH), 4.65 (t, 1 H, *J* 5.5 Hz, OH-6′), 4.68 (br. s, 1 H, –OH), 4.76 (d, 1 H, *J* 5.5 Hz, OH-3′), 5.89 (s, 1 H, ArH), 9.72 (br. s, 1 H, ArOH), 11.58 (br.s, 1 H, ArOH), 12.85 (br. s, 1 H, ArOH); ^{13}C NMR (Me_2SO-d_6): δ 32.5 (ArAc), 60.7 (C-6′), 68.5 (C-4′), 69.2 (C-2′), 74.0 (C-1′), 74.8 (C-3′), 79.0 (C-5′), 94.6 (C-5), 103.9 (C-1*), 104.3 (C-3*), 162.4 (C-2**), 163.07 (C-4**), 163.12 (C-6**), 202.6 (ArAc). *, **, Assignments may be interchanged; FABMS (positive ion): *m*/*z* 331 $[M+H]^+$. Anal. Calcd for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 50.93; H, 5.79.

*1-[(2*R*,3′*S*,4′*S*,5′*R*)-3′,4,4′,5′,6-Pentahydroxy-3′,4′,5′,6′-tetrahydrospiro[benzofuran-2(3*H*), 2′-[2*H*]pyran]-7-yl]ethanone* (**5**).—To a stirred solution of **6** (258 mg, 0.494 mmol) in MeOH (10 mL) at 0 °C, a 28 wt% of NaOMe in MeOH (0.67 mL, 3.5 mmol, 7 equiv) was added. After 5 min, the ice was removed and the mixture was then stirred for 30 min at rt. Dowex 50W® was added, and the solution was filtered. The filtrate was concentrated under reduced pressure to give **5** (154 mg, quant) as colorless crystals: mp 260–261 °C (dec.); $[\alpha]_D^{25}$ +62° (*c* 0.10, MeOH); R_f 0.70 (25:35:5:1 Me_2CO–EtOAc–water–AcOH); IR (KBr): 3525, 3365, 3163, 2951, 2891, 2871, 1655, 1608, 1583, 1508, 1439, 1396, 1362, 1306, 1240, 1188, 1167, 1140, 1107, 1090, 1064, 1016, 976, 955, 897, 868, 808 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 2.54 (s, 3 H, ArAc), 2.75 (d, 1 H, *J* 16.3 Hz, H-3b), 3.17 (d, 1 H, *J* 16.3 Hz, H-3a), 3.44 (dd, 1 H, *J* 10.5, 11.0 Hz, H-6′a), 3.64 (dd, 1 H, *J* 3.2, 8.9 Hz, H-4′), 3.66 (dd, 1 H, *J* 5.5, 11.0 Hz, H-6′b), 3.75 (ddd, 1 H, *J* 5.5, 8.9, 10.5 Hz, H-5′), 3.76 (d, 1 H, *J* 3.2 Hz, H-3′), 4.95 (br. s, 2 H, –OH), 5.38 (br. s, 1 H, –OH), 5.87 (s, 1 H, ArH), 10.73 (s, 1 H, ArOH), 13.03 (s, 1 H, ArOH); ^{13}C NMR (Me_2SO-d_6): δ 30.7(ArAc), 35.2 (C-3), 65.0 (C-6′), 65.2 (C-5′), 71.3 (C-3′), 71.4 (C-4′), 95.7 (C-5), 100.9 (C-7), 102.8 (C-3a), 114.4 (C-2), 160.5 (C-4), 160.6 (C-7a), 164.0 (C-6), 200.7 (ArAc); FABMS (positive ion): m/z 313 $[M+H]^+$; FABMS (negative ion): m/z 311 $[M-H]^-$. Anal. Calcd for $C_{14}H_{16}O_8 \cdot 0.5\ H_2O$: C, 52.34; H, 5.33. Found: C, 52.54; H, 5.57.

*1-[(2*R*,3′*S*,4′*S*,5′*R*)-3′,4,4′,5′,6-Pentaacetoxy-3′,4′,5′,6′-tetrahydrospiro[benzofuran-2(3*H*), 2′-[2*H*]pyran]-7-yl]ethanone* (**6**).—A solution of **4** (1.225 g, 3.708 mmol) and *p*-TsOH monohydrate (123 mg, 0.65 mmol, 0.18 equiv) in water (500 mL) was refluxed for 3 days. After cooling, the water was evaporated under reduced pressure and the resulting syrup was acetylated with Ac_2O (50 mL), pyridine (5 mL), and DMAP (100 mg) for 1 day at 25 °C. The reaction mixture was quenched with 0.5 M HCl and extracted with EtOAc. The combined extracts were washed with water and brine, dried over anhyd $MgSO_4$, and then evaporated under reduced pressure. The residual syrup was chromatographed on a silica gel column (2:1 hexane–EtOAc) to afford crude **6**. Recrystallization from hexane–Et_2O afforded pure **6** (589 mg, 30%) as colorless crystals: mp 174 °C; $[\alpha]_D^{25}$ +84° (c 0.10, $CHCl_3$); R_f 0.46 (1:1 hexane–EtOAc); IR (KBr): 2995, 2943, 1772, 1763, 1751, 1689, 1618, 1412, 1371, 1267, 1250, 1219, 1198, 1126, 1090, 1059, 1053, 1038, 984, 908, 876, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3 H, –OAc), 2.08 (s, 3 H, –OAc), 2.22 (s, 3 H, –OAc), 2.28 (s, 3 H, –OAc), 2.29 (s, 3 H, –OAc), 2.63 (s, 3 H, ArAc), 3.05 (s, 2 H, H-3), 3.78 (dd, 1 H, J 10.5, 11.2 Hz, H-6′a), 4.05 (dd, 1 H, J 5.9, 11.2 Hz, H-6′b), 5.33 (ddd, 1 H, J 5.9, 10.3, 10.5 Hz, H-5′), 5.43 (dd, 1 H, J 3.2, 10.3 Hz, H-4′), 5.59 (d, 1 H, J 3.2 Hz, H-3′), 6.57 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ 20.6 (–OAc), 20.7 (–OAc), 20.80 (–OAc), 20.87 (–OAc), 20.91 (–OAc), 32.1 (ArAc), 36.9 (C-3), 61.9 (C-6′), 65.4 (C-5′), 69.2 (C-4′), 70.2 (C-3′), 111.0 (C-5), 111.1 (C-2), 114.6 (C-7), 116.0 (C-3a), 148.9 (C-4), 149.6 (C-6), 158.0 (C-7a), 167.2 (–OAc), 169.5 (–OAc), 169.7 (4′-OAc), 169.8 (3′-OAc), 170.1 (5′-OAc), 195.1 (ArAc); FABMS (positive ion): m/z 523 $[M+H]^+$. Anal. Calcd for $C_{24}H_{26}O_{13}$: C, 55.17; H, 5.02. Found: C, 55.30; H, 5.04.

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