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Note

Conversion of diacetyl-*C*-(β-D-glucopyranosyl)phloroglucinol to spiroketal compounds

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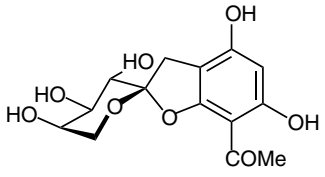
Abstract—Diacetyl-*C*-(β-D-glucopyranosyl)phloroglucinol was converted by refluxing in water to spiro(benzofuran-[2*H*]furan) a new compound, along with spiro(benzofuran-[2*H*]pyran). The stereochemistry of the quaternary carbon of both spiro compounds had an *S*-configuration.

Keywords: Diacetyl-*C*-(β-D-glucopyranosyl)phloroglucinol; Spiro[benzofuran-2(3*H*),2′-[2*H*]pyran]; Spiro[benzofuran-2(3*H*),2′-[2*H*]furan]; Quaternary carbon; Stereochemistry; Pinnatifinoside

We previously reported on the conversion of the *C*-(β-D-glycopyranosyl)phloroacetophenone to spiro derivatives by refluxing in water in the presence of *p*-toluenesulfonic acid (*p*-TsOH); *C*-(β-D-glucopyranosyl)phloroacetophenone and *C*-(β-D-galactopyranosyl)phloroacetophenone to (2*S*,3′*S*,4′*R*,5′*R*)-7-acetyl-spiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-3′,4,4′,5′,6-pentaol (**1**)[1] and (2*R*,3′*S*,4′*S*,5′*R*)-7-acetyl-spiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-3′,4,4′,5′,6-pentaol (**2**),[2] respectively.



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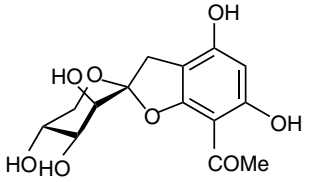

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At the time of our reports, these spiroketal compounds were not known to be naturally occurring.[3] However, in 2001, Zhang and Xu[4] reported on the isolation of four ketohexose furanosides from the leaves of *Crataegus pinnatifida* Bge. var. *major* N.E.Br. (Rosaceae), which is used as a medicinal plant to improve digestion, inhibit the retention of food, promote blood circulation, and resolve blood stasis both in traditional and folk medicine.[5] Pinnatifinosides A and B are flavones (see structures), containing a spiro(benzofuran-furan) ring in which the stereochemistry at C-3′, C-4′, and C-5′ is analogous to that of D-arabinose and the stereochemistry of the spiro-quaternary carbon is *R*. Pinnatifinosides C and D are also flavones that contain a spiro(benzofuran-furan) ring, in which the stereochemistry at C-3′, C-4′, and C-5′ is analogous to that of

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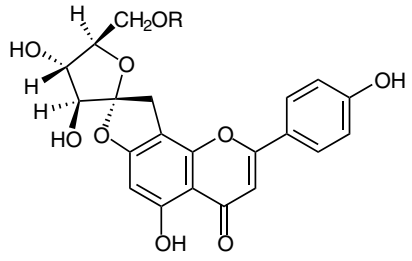
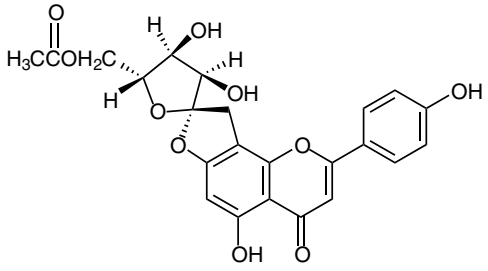
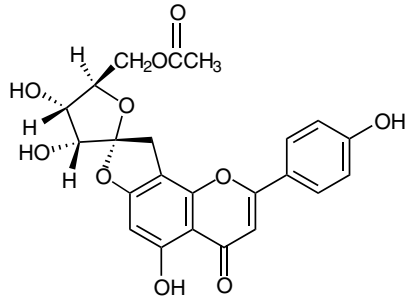
D-ribose, and the stereochemistry of the spiro-quaternary carbons is *R* and *S*, respectively. However, while the naturally occurring spiroketal flavones all contain a spiro(benzofuran-[2*H*]furan) ring, both of the spiroketals synthesized by us also contain a spiro(benzofuran-[2*H*]pyran) ring. The spiroketal skeletons of pinnatifinosides A and B, and C and D could be constructed from *C*-β-D-gluco- and -allopyranoside, respectively, based on the reactions which we developed.



R = H: Pinnatifinoside A
R = acetyl: Pinnatifinoside B

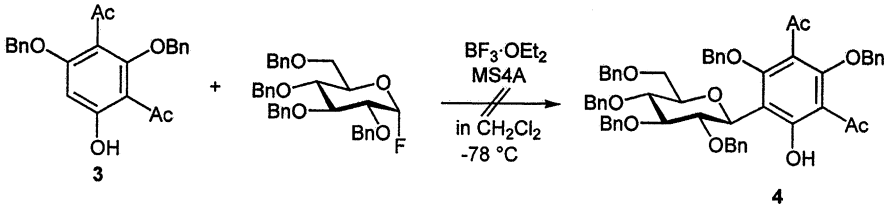


Pinnatifinoside C



Pinnatifinoside D

In an ongoing study of the conversion of *C*-glycopyranosylphloroacetophenone to the spiroketal, we examined the conversion of diacetyl-*C*-(β-D-glucopyranosyl)phloroglucinol (**7**) to the corresponding spiro compound in a similar manner. Compound **7** could not be obtained by the direct $O \rightarrow C$ glycoside rearrangement of diacetylphloroglucinol (**3**) (Scheme 1). However, an $O \rightarrow C$ glycoside rearrangement of the phloroacetophenone,[6–8] followed by acetylation of the hydroxyl group, and *C*-acetylation using $BF_3 \cdot 2AcOH$ and O-deacetylation gave **7** in good yield (Scheme 2). Since the refluxing of **7** in water in the presence of a catalytic amount of *p*-TsOH caused deacetylation, resulting in the formation of *C*-β-D-glucopyranosylphloroacetophenone, **7** was refluxed in water in the absence of any catalyst. The conversion, as expected, proceeded slowly. After refluxing for 1 day, the resulting product was acetylated by treatment with acetic anhydride, pyridine, and a catalytic amount of DMAP, giving two acetates, which were separated and isolated by silica-gel column chromatography (*n*-hexane–EtOAc). A detailed spectroscopic study of both acetates indicated that a new product, spiro(benzofuran-[2*H*]furan) (**9**), was produced along with spiro(benzofuran-[2*H*]pyran) (**8**) in 9.8% and 26.0% yield, respectively. The ^{1}H NMR spectrum of **8** was analogous to that of **1** except for the presence of another *C*-acetyl group. However, that of **9** was different from any spiroketal synthesized thus far. The H-5′ signal at 4.36 ppm (1H, ddd, *J* 4.0, 6.0, and 7.5 Hz) was shifted upfield ($\Delta\delta$ 1.11), and the H-6′a at 4.21 ppm and the H-6′b at 4.43 ppm downfield ($\Delta\delta$ 0.29 and 0.25) compared to that of **8**, respectively. The above findings suggest that **9** does not contain a pyran ring linked between the C-6 oxygen and a quaternary carbon (C-2) of the benzofuran like **8**, which contains a spiro[benzofuran-2(3*H*),2′-[2*H*]furan] ring linked between the C-5 oxygen and a quaternary carbon (C-2). The following data point to the presence of a spiro[benzofuran-3(2*H*),2′-[2*H*]furan] ring;[4,9] the coupling constants for H-3′, -4′, and -5′ ($J_{3,4} = 7.0$, $J_{4,5} = 6.0$ Hz) are not consistent with a pyran ring like **8** ($J_{3,4} = 10.5$, $J_{4,5} = 3.5$ Hz). Further, the difference in chemical shifts between the methylene protons on C-3 of the 2*H*-benzofuran ($\Delta\delta$ 0.136) is apparently larger than those for spiro(benzofuran-[2*H*]pyran) [**1** ($\Delta\delta$ 0.01), **2** ($\Delta\delta$ 0.00), and **8** ($\Delta\delta$ 0.04)]. To determine the stereochemistry of **9** more precisely, nuclear Overhauser and exchange spectroscopy (NOESY) and correlation spectroscopy via long-range coupling spectrum (CO-



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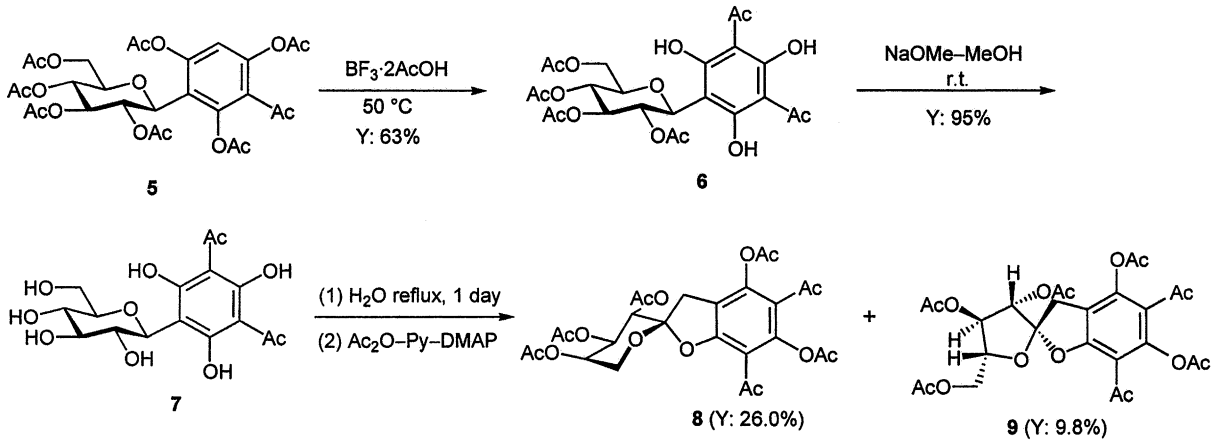
Scheme 1.



Scheme 2.

LOC) experiments were carried out (see Figs. 1 and 2). In the NOESY spectrum, a correlation was found between H-6′a and H-4′, and between H-6′a and one of the two acetyl groups on the benzene ring, as well as between H-3′ and H-3a, respectively. These correlations indicate that the stereochemistry of the quaternary carbon is an *S*-configuration and opposite to that of the natural products, pinnatifinosides A and B. If the quaternary carbon has an *R*-configuration, the above correlation between H-6′a and one of the two acetyl groups, and between H-3′ and H-3a would not exist. Thus, the stereochemistry of the quaternary carbon is of the *S*-configuration. The stereochemistry at C-3, C-4, and C-5 is the same, as that of D-glucose as was found for **8**. In the COLOC correlation of **9**, H-3a and -3b showed a correlation with the quaternary carbon (C-2: 117.4 ppm). Further, H-3b showed a correlation with C-3′ [77.7 p-4 (146.8 ppm), and C-7a (158.3 ppm)]. H-3a also showed a correlation with the C-4 and C-7a. H-3′ showed a correlation with C-4′ (74.7 ppm), H-4′ showed a correlation with C-3′ and C-5′ (79.5 ppm), H-6a showed a correlation with C-5′. From the above structural data, we conclude that the hydrolysis of the di-

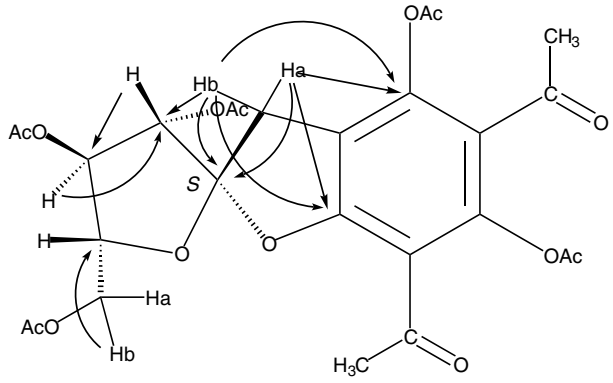


Figure 2. The COLOC correlation of **9**.

acetyl-*C*-(β-D-glucopyranosyl)phloroglucinol produced mainly a spiro[benzofuran-2(3*H*),2′-[2*H*]pyran] and a new spiro[benzofuran-2(3*H*),2′-[2*H*]furan]. Flavones having a spiro[benzofuran(2*H*)furan] skeleton, pinnatifinosides A, B, C, and D might be also formed by the hydrolysis of the corresponding *C*-(β-D-glycopyranosyl)flavones in nature. We are currently attempting the synthesis of pinnatifinoside A using the above approach.

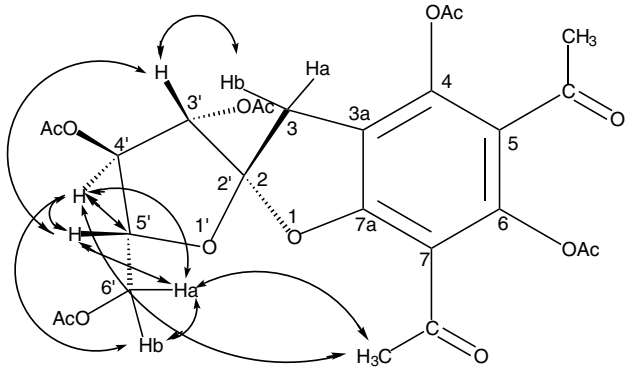


Figure 1. The NOESY correlation of **9**.

1. Experimental

1.1. General

The anhydrous CH_2Cl_2 used in this reaction was prepared in situ by distillation from CaH_2. For separation and purification, flash column chromatography was performed on silica gel (230–400 mesh, Fuji-Silysia Co., Ltd., BW-300). HPLC was performed using an Inertsil ODS-3 column (GL Science; 5 μm, 4.6×250 mm mobile phase, MeOH–water). Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Mass spectral data were obtained by

fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA) or glycerol as a matrix on a JEOL JMS-AX505HA instrument. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Elemental analyses were performed on a Perkin–Elmer PE 2400 II instrument. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as an internal standard.

1.2. 1,3-Diacetyl-2,6-*O*-benzylphloroglucinol (3)

Compound **3** was synthesized via the diacetylation of phloroglucinol, followed by mono-*O*-methoxymethylation, di-*O*-benzylation, and the *O*-demethoxymethylation of phloroglucinol in an overall yield of 40%, as shown in Scheme 3.

Colorless needles (from *n*-hexane–EtOAc): mp 137 °C. IR (KBr) *v* 3444, 2945, 2884, 1699, 1612, 1585, 1367, 1259, 1219, 1190, and 1099 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.49 and 2.60 (each 3H, s, ArAc×2), 4.93 and 5.13 (each 2H, s, benzylic CH_2), 6.36 (1H, s, ArH), 7.34–7.42 (10H, m, ArH), 13.47 (1H, ArOH). FABMS (NBA, *m/z*) 391 $(M+H)^+$. Calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68. Found: C, 73.78; H, 5.75.

1.3. β-*C*-(2′,3′,4′,6′-Tetra-*O*-acetyl-D-glucopyranosyl)-diacetylphloroglucinol (6)

Compound **5** (1.62 g, 2.60 mmol) was stirred at 50 °C for 1 h in 10 mL of boron trifluoride–acetic acid complex (BF_3·2AcOH). The reaction mixture was poured into water, and the solution was extracted with toluene twice. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. After removing the solvent, the residue was recrystallized from EtOH to give **6** (881 mg, 62.8%) as colorless prisms: mp 206–206.5 °C. $[\alpha]_D^{25}$ +18.8 (*c* 0.50, $CHCl_3$). IR (KBr) *v* 3440, 3132, 2927, 1755, 1633, 1365, 1236, and 1045 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.84, 2.02, 2.08, 2.14 (each 3H, s, OAc×4), 2.71 (6H, s, ArAc×2), 3.94 (1H, ddd, *J* 2.4, 3.5, and 10.2 Hz, H-5′), 4.19 (1H, dd, *J* 2.4 and 12.6 Hz, H-6′a), 5.24 (1H, dd, *J* 3.5 and 12.6 Hz, H-6′b), 5.26 (1H, d, *J* 9.4 Hz, H-1′), 5.28 (1H, dd, *J* 9.4 and 10.2 Hz, H-4′), 5.33 (1H, t, *J* 9.4 Hz, H-3′), 5.40 (1H, t, *J* 9.4 Hz, H-2′), 9.25 (1H, s, OH), 16.17 (1H, s, chelated OH). FABMS (NBA, *m/z*) 541 $(M+H)^+$. Calcd for $C_{24}H_{28}O_{14}$: C, 53.33; H, 5.22. Found: C, 53.36; H, 5.04.

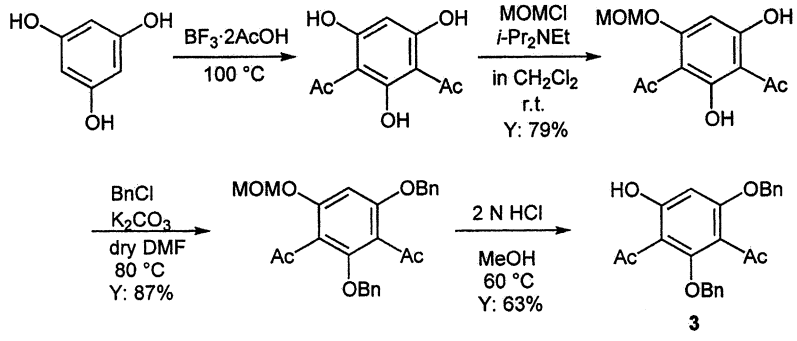
1.4. Diacetyl-*C*-(β-D-glucopyranosyl)phloroglucinol (7)

To a stirred solution of **6** (600 mg, 1.11 mmol) in MeOH (5 mL), 0.5 mL of a 25% NaOMe solution was added, followed by stirring at room temperature for 0.5 h. Dowex 50W (H^+) resin was added to the resulting mixture until the reaction mixture reached neutrality. After filtering, the filtrate was evaporated and recrystallized from EtOH to give **7** (397 mg, 95%) as colorless prisms: mp 150–151 °C. $[\alpha]_D^{25}$ +115 (*c* 0.52, MeOH). IR (KBr) *v* 3430, 2931, 1616, 1365, and 1292 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.62 (6H, s, Ac×2), 3.24–3.40 (5H, m, H-3′, -4′, -5′, -6′a,b), 3.44 (1H, t, *J* 10.0 Hz, H-2′), 4.74 (1H, d, *J* 10.0 Hz, H-1′). FABMS (glycerol, *m/z*) 373 $(M+H)^+$. Calcd for $C_{16}H_{20}O_{10}$·0.25H_2O: C, 50.99; H, 5.48. Found: C, 50.90; H, 5.44.

Compound **7** (550 mg, 1.46 mmol) was refluxed in water (220 mL) for 1 day. After removing the water in vaccuo, the residual syrup was acetylated by stirring with a solution of acetic anhydride (20 mL), pyridine (5 mL), and 4-dimethylaminopyridine (5 mg) at room temperature for 1 day. After the usual workup, the residue was column chromatographed on silica gel (1:1 *n*-hexane–EtOAc) to give **8** (218.6 mg, 26.4%) as colorless prisms and **9** (85.2 mg, 9.8%) as a colorless oil.

1.5. (2*S*,3′*S*,4′*R*,5′*R*)-3′,4,4′,5′,6-Pentakis-acetoxy-5,7-diacetyl-3′,4′,5′,6′-tetrahydrospiro[benzofuran-2(3*H*),2′-[2*H*]pyran] (8)

Colorless prisms: mp 171–172 °C. $[\alpha]_D^{25}$ −144 (*c* 1.025, $CHCl_3$). IR (KBr) *v* 1776, 1747, 1697, 1620, 1371, 1224, and 1184 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.05, 2.07, and 2.11 (each 3H, s, OAc×3), 2.26 and 2.27 (each 3H, s, ArOAc×2), 2.42 and 2.62 (each 3H, s, Ar*Ac*×2), 3.13 and 3.14 (each 1H, d, *J* 17.0 Hz, 3-CH_2), 3.92 (1H, dd, *J* 2.0 and 13.0 Hz, H-6a), 5.47 (1H, dd, *J* 2.0, 3.5, and



Scheme 3.

1.5 Hz, H-5′), 4.18 (1H, dd, *J* 1.5 and 13.0 Hz, H-6b), 5.30 (1H, dd, *J* 3.5 and 10.5 Hz, H-4′), 5.63 (1H, d, *J* 10.5 Hz, H-3′). ^{13}C NMR ($CDCl_3$) δ 20.6 (OAc×2), 20.6, 20.9, 20.9 (OAc×3), 31.4, 31.9 (Ar*Ac*×2), 36.3 (C-3), 63.9 (C-6′), 68.40, 68.46, 68.56 (C-3′, C-4′, C-5′), 112.9 (C-2), 114.4 (C-5*), 117.9 (C-7*), 123.1 (C-3a*), 145.7 (C-4**), 146.8 (C-6**), 158.7, 167.0, 169.0, 169.9, 170.1, 170.4 (OAc×5), 195.2, 197.2 (Ar*Ac*×2). *, **: interchangeable. FABMS (glycerol, *m*/*z*) 565 $(M+H)^+$, 523, 481. Calcd for $C_{26}H_{28}O_{14}$: C, 55.32; H, 5.00. Found: C, 55.44; H, 4.97.

1.6. (2*S*,3′*S*,4′*R*,5′*R*)-3′,4,4′,6,6′-Pentakis-acetoxy-5,7-diacetyl-5′-acetoxymethylspiro[benzofuran-2(3H), 2′-[2*H*]furan] (9)

Colorless amorphous powder. $[\alpha]_D^{25}$ −15.3 (*c* 1.035, $CHCl_3$). IR (KBr) *v* 2925, 1778, 1749, 1697, 1624, 1371, and 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.05, 2.06, and 2.07 (each 3H, s, OAc×3), 2.26 and 2.27 (each 3H, s, ArOAc×2), 2.42 and 2.61 (each 3H, s, Ar*Ac*×2), 3.25 and 3.38 (each 1H, 3-CH_2), 4.21 (1H, dd, *J* 7.5 and 12.0 Hz, H-6a), 4.36 (1H, ddd, *J* 4.0, 6.0, and 7.5 Hz, H-5′), 4.43 (1H, dd, *J* 4.0 and 12.0 Hz, H-6b), 5.44 (1H, dd, *J* 6.0 and 7.0 Hz, H-4′), 5.59 (1H, d, *J* 7.0 Hz, H-3′). ^{13}C NMR ($CDCl_3$) δ 20.7 and 21.0 (ArOAc×2), 31.3 and 31.9 (Ar*Ac*×2), 34.8 (C-3), 64.4 (C-6′), 74.7 (C-4′), 77.7 (C-3′), 79.5 (C-5′), 114.2 (C-2), 116.4 (C-3a), 117.38 (C-7), 117.39 (C-5), 145.5 (C-6), 146.8 (C-4), 158.3 (C-7a), 195.5 and 197.4 (Ar*Ac*×2). FABMS (glycerol *m*/*z*) 565 $(M+H)^+$. Calcd for $C_{26}H_{28}O_{14}$: C, 55.32; H, 5.00. Found: C, 55.06; H, 5.12.

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