Bisabolane-Type Sesquiterpenoids from the Rhizomes of *Glochidion coccineum*

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A novel bisabolane-type sesquiterpenoid lactone, glochicoccin A (**1**), and three new norbisabolane sesquiterpenoids, glochicoccins B–D (**2**–**4**), together with two known norbisabolane sesquiterpenoids, phyllaemblic acid (**5**) and phyllaemblic acid methyl ester (**6**), were isolated from the rhizomes of *Glochidion coccineum*. Their structures were elucidated by different spectroscopic (IR, UV, NMR) and mass-spectrometric (MS) techniques. The structure and relative configuration of **1** was confirmed by single-crystal X-ray diffraction (*Fig. 2*). None of the compounds were found to exhibit cytotoxic or antioxidant activities.

Introduction. – Plants of the genus *Glochidion* (Euphorbiaceae), widely distributed in China, are commonly used as folk medicine in the treatment of influenza, dysentery, impaludism, rheumatoid arthritis, and dyspepsia [1]. Previous studies revealed that the plants of this genus mainly contain lignans and triterpenes [2]. In recent years, some lupane-type triterpenes from *Glochidion* have been found to possess antitumor-promoting and cytotoxic activities [3], and the EtOH extracts were shown to exhibit significant DPPH-radical-scavenging activity [4].

In order to find potentially bioactive secondary metabolites from this genus, we investigated the rhizomes of *Glochidion coccineum* (BUCH.-HAM.) MUELL. ARG., which led to the isolation of a novel bisabolane-type sesquiterpenoid lactone, glochicoccin A (**1**), and three new norbisabolane sesquiterpenoids, glochicoccins B–D, **2**–**4**, together with two known norbisabolane sesquiterpenoids, phyllaemblic acid **5** and phyllaemblic acid methyl ester **6** [5]. This paper deals with the isolation and structure elucidation of the new compounds **1**–**4**, and evaluates the cytotoxic activities and antioxidant properties of **1**–**6**.

Results and Discussion. – 1. *Structure Elucidation*. The molecular formula of compound **1** was $C_{15}H_{22}O_7$, as established by negative HR-ESI-MS (*m*/*z* 313.1283 ($[M-H]^-$, calc. 313.1287)). The ^{1}H-NMR spectrum of **1** (*Table 1*) exhibited one Me group at a secondary C-atom; and the ^{13}C-NMR (DEPT) spectrum (*Table 2*) displayed the signals of 15 C-atoms, including eight oxygenated C-atoms and an ester C-atom, two quaternary C, two CH, and two CH_2, suggesting that **1** was a highly oxygenated sesqui-

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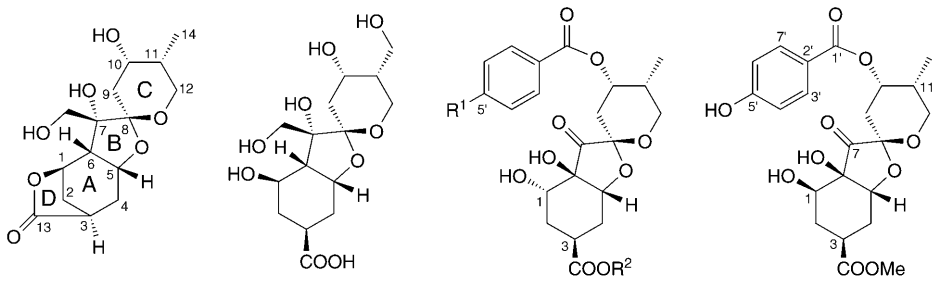

1 phyllaemblic acid B **2** R^1 = OH, R^2 = Me; **4** R^1 = OH, R^2 = H; **5** R^1 = H, R^2 = H; **6** R^1 = H, R^2 = Me; **3**

terpenoid. The ^{13}C-NMR characteristics, including the quaternary hemiacetal-type C-atom at δ(C) 107.9, were similar to those reported for the bisabolane-type sesquiterpenoid phyllaemblic acid B [6].

Comparison of the ^{1}H- and ^{13}C-NMR data of **1** with those of phyllaemblic acid B showed high similarities, except for a Me group replacing one oxygen-bearing CH_2 and an increase in the degree of unsaturation in **1**. This implied that the two compounds had the same structures for rings *A*–*C*, but differed in **1** having an additional ring compared to phyllaemblic acid B. The gross structure of **1** was finally established from its 2D-NMR spectra (HSQC, ^{1}H,^{1}H-COSY, HMBC), as shown in *Fig. 1*. Two partial structures, ring *A* (C(1) to C(6)) and ring *C* (C(9) to C(12)) connected with C(14) could be deduced. HMBC correlations of C(13) with H–C(2), H–C(3), and H–C(4) suggested that the ester C-atom (C(13)) was attached to C(3). The locations of the remaining three C-atoms, an isolated CH_2 (δ(C) 65.3 (C(15)); δ(H) 4.14, 4.20 (2*d*, J = 10.9 Hz each)) and two quaternary C-atoms (δ(C) 83.5 (C(7)), 107.9 C(8)), were also established by HMBC experiments, which showed long-range correlations of H–C(1), H–C(5), H–C(6), and H–C(15) with C(7), of H–C(6), H–C(9), H–C(10), H–C(12), and H–C(15) with C(8), and of H–C(15) with C(6). Thus, the linkage of the two structural fragments could be established *via* C(7) and C(8).

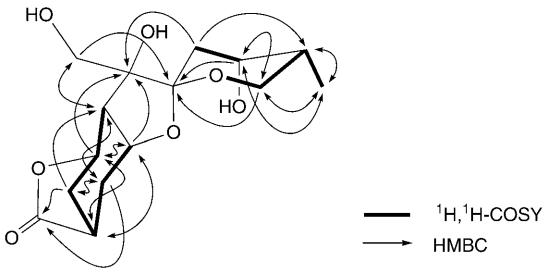

Fig. 1. *Selected 2D-NMR correlations of glochicoccin A* (**1**)

The relative configuration of **1** was ultimately determined by single-crystal X-ray diffraction (*Fig. 2*), which was the same as that in the structurally related compound

phyllaemblic acid B. The crystal structure showed two six-membered rings *A* and *C* adopting 'chair' conformations, and two five-membered rings *B* and *D* in 'envelope' conformations, with a *cis* junction between rings *A* and *B*, and a spirocyclic arrangement with respect to rings *B* and *C*. Rings *A* and *D* are fused such that a CH_2-bridged seven-membered lactone ring results in a 'boat' conformation, H–C(1) and H–C(3) being α-oriented, CH_2(15) being β-oriented. The absolute configuration of **1** was in accord with that proposed for phyllaemblic acid B [6], as deduced by ORD ($[\alpha]_D^{26} = 59.4$ ($c = 1.78$, MeOH)). Thus, the structure of compound **1** corresponds to the 13,1-lactone of '11-dehydroxyphyllaemblic acid B'[1]), and was named *glochicoccin A*.

Table 1. *^{1}H-NMR Data of* **1**–**4**. At 500 MHz; δ in ppm, *J* in Hz. Arbitrary atom numbering.

Position	**1**[a])	**2**[b])	**3**[b])	**4**[c])
H–C(1)	4.40–4.44 (*m*)	3.88 (br. *d*, $J \approx 5$)	3.51 (*dd*, $J = 11.8, 4.2$)	4.03 (br. *s*)
H_α–C(2)	2.91 (*d*, $J = 11.5$)	1.82–1.85 (*m*)	1.79–1.83 (*m*)	1.93–1.97 (*m*)
H_β–C(2)	2.16–2.19 (*m*)	1.63–1.69 (*m*)	1.57–1.61 (*m*)	1.76 (br. *t*, $J = 12.8$)
H–C(3)	2.58 (br. *s*)	2.76 (br. *t*, $J = 12.8$)	2.20 (br. *s*)	2.92 (br. *t*, $J = 12.8$)
H_α–C(4)	2.44–2.48 (*m*)	2.22 (br. *d*, $J = 14.5$)	2.06–2.12 (*m*)	2.31 (*d*, $J = 14.4$)
H_β–C(4)	2.09–2.15 (*m*)	1.76–1.84 (*m*)	1.73–1.76 (*m*)	1.77–1.88 (*m*)
H–C(5)	5.33–5.35 (*m*)	4.22 (br. *s*)	4.28 (br. *s*)	4.30 (br. *s*)
H–C(6)	2.94 (br. *d*, $J = 9.0$)			
H_α–C(9)	2.59–2.61 (*m*)	2.30 (*dd*, $J = 14.7, 3.2$)	2.06–2.10 (*m*)	2.18 (*dd*, $J = 14.8, 3.2$)
H_β–C(9)	2.24 (*dd*, $J = 14.5, 3.0$)	1.90 (*dd*, $J = 14.7, 2.8$)		1.91–1.95 (*m*)
H–C(10)	3.95 (br. *s*)	5.22 (br. *s*)	5.19 (br. *d*, $J = 3.0$)	5.30 (br. *s*)
H–C(11)	1.71 (br. *s*)	2.12–2.15 (*m*)	2.21–2.26 (*m*)	2.13 (br. *s*)
H_α–C(12)	3.82 (*t*, $J = 11.5$)	4.02 (*t*, $J = 11.0$)	4.05 (*t*, $J = 11.5$)	3.92 (*t*, $J = 11.2$)
H_β–C(12)	3.45 (*dd*, $J = 11.5, 4.8$)	3.57 (*dd*, $J = 11.0, 4.5$)	3.59 (*dd*, $J = 11.5, 4.5$)	3.50 (*dd*, $J = 11.2, 4.2$)
Me(14)	0.91 (*d*, $J = 6.8$)	0.89 (*d*, $J = 7.0$)	0.92 (*d*, $J = 6.5$)	0.82 (*d*, $J = 6.8$)
H_α–C(15)	4.14 (*d*, $J = 10.9$)			
H_β–C(15)	4.20 (*d*, $J = 10.9$)			
MeOOC		3.63 (*s*)	3.61 (*s*)	
H–C(3′,7′)		7.99 (*d*, $J = 8.5$)	7.96 (*d*, $J = 8.7$)	8.02 (*d*, $J = 8.4$)
H–C(4′,6′)		6.83 (*d*, $J = 8.5$)	6.80 (*d*, $J = 8.7$)	6.92 (*d*, $J = 8.4$)

[a]) In (D_5)pyridine. [b]) In CD_3OD. [c]) At 400 MHz in (D_6)acetone.

Compound **2** exhibited the $[M-H]^-$ peak at *m*/*z* 449.1437 in the negative HR-ESI mass spectrum, corresponding to the molecular formula $C_{22}H_{26}O_{10}$. The ^{13}C-NMR data of **2** and the HMQC spectrum showed 22 signals due to seven quaternary C-atoms, four CH_2, nine CH, and two Me groups. Detailed analysis of the ^{1}H-NMR data [δ(H) 7.99 (*d*, $J = 8.5$ Hz, 2 H); 6.83 (*d*, $J = 8.5$ Hz, 2 H)] and of the ^{13}C-NMR data (δ(C) 123.0 (C), 133.1 (2 CH), 116.0 (2 CH), 163.4 (C), and 168.1 (C)) indicated a 4-hydroxybenzoyl group. The NMR spectra of **2** and of phyllaemblic acid methyl ester (**6**) [5] were very similar, except that the benzoyl (Bz) unit of **6** was replaced by a 4-hydroxybenzoyl group in **2**.

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[1]) Arbitrary atom numbering. For systematic names, see the *Exper. Part*.

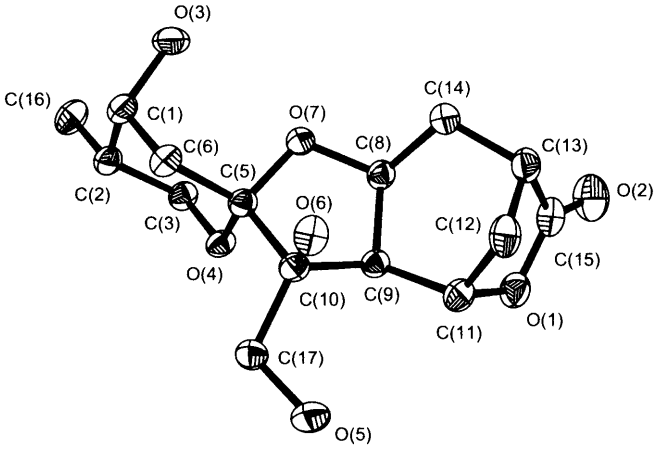

Fig. 2. *X-Ray crystal structure of* **1**. Arbitrary atom numbering, different from that in the chemical formulae.

The relative configuration of **2** was assigned by analysis of NMR coupling constants (*Fig. 3*) and ROESY correlations. A J value of *ca.* 10 Hz for H–C(10) suggested an equatorial orientation, and the axial H-atom of CH_2(12) [δ(H) 3.57 (*dd*, J = 11.0, 4.5 Hz)] revealed an axial configuration for H–C(11). The ROESY spectrum of **2** further revealed that H–C(1), H_β–C(2), H_β–C(4), and H–C(5) were on the β-face of the skeleton. The J value for H–C(1) (br. *d*, $J \approx 5$ Hz), implied equatorial orientations for both H–C(1) and H–C(5), while that of H–C(3) (J = 12.8 Hz) indicated an axial configuration; there were no correlations of neither H_β–C(2) nor of H_β–C(4) to H–C(3). On the basis of these data, a possible 'chair' conformation was, thus, proposed for the fused six-membered ring of **2** in MeOH solution (NMR solvent). Obviously, H–C(1) was β-oriented, and H–C(3) was α-orientated. The absolute configuration of **2** was deduced to correspond to that of phyllaemblic acid methyl ester (**6**), based on the optical rotation in MeOH [5].

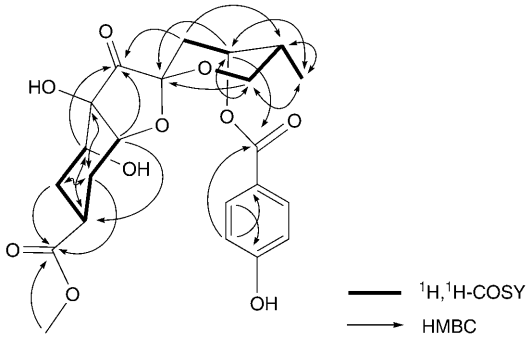

Fig. 3. *Key 2D-NMR correlations for* **2**

Glochicoccin C (**3**) was assigned the same molecular formula, $C_{22}H_{26}O_{10}$, as **2**, by negative HR-ESI-MS (*m/z* 449.1443 ($[M-H]^-$; calc. 449.1447)). There were only small differences between **2** and **3** in the ROESY spectra: the cross-peaks for H_α–C(4)/H–C(1)/H–C(3) and of H_β–C(4)/H–C(5) suggested that H–C(1) and H–C(3) were both in α-position. Consequently, glochicoccin C (**3**) was identified as the 1β-epimer of glochicoccin B (**2**).

Table 2. *^{13}C-NMR Data* of **1**–**4**. At 125 MHz; δ in ppm. Arbitrary atom numbering.

Position	**1**[a])	**2**[b])	**3**[b])	**4**[c])
1	72.3 (*d*)	71.4 (*d*)	68.2 (*d*)	71.2 (*d*)
2	32.4 (*t*)	33.0 (*t*)	32.3 (*t*)	32.6 (*t*)
3	36.6 (*d*)	31.8 (*d*)	34.2 (*d*)	31.0 (*d*)
4	32.8 (*t*)	29.1 (*t*)	28.0 (*t*)	28.4 (*t*)
5	80.3 (*d*)	76.2 (*d*)	77.4 (*d*)	75.6 (*d*)
6	46.2 (*d*)	75.6 (*s*)	77.2 (*s*)	75.0 (*s*)
7	83.5 (*s*)	213.9 (*s*)	210.0 (*s*)	212.8 (*s*)
8	107.9 (*s*)	100.5 (*s*)	99.8 (*s*)	99.7 (*s*)
9	35.8 (*t*)	32.5 (*t*)	34.8 (*t*)	32.1 (*t*)
10	67.9 (*d*)	70.7 (*d*)	70.5 (*d*)	69.4 (*d*)
11	35.1 (*d*)	34.3 (*d*)	37.9 (*d*)	33.4 (*d*)
12	61.8 (*t*)	63.5 (*t*)	63.7 (*t*)	62.6 (*t*)
13	179.9 (*s*)	177.9 (*s*)	176.1 (*s*)	177.7 (*s*)
14	13.4 (*q*)	13.0 (*q*)	13.2 (*q*)	12.8 (*q*)
15	65.3 (*t*)			
1′		168.1 (*s*)	168.1 (*s*)	166.6 (*s*)
2′		123.0 (*s*)	122.2 (*s*)	122.7 (*s*)
3′		133.1 (*d*)	133.1 (*d*)	132.5 (*d*)
4′		116.0 (*d*)	116.3 (*d*)	115.7 (*d*)
5′		163.4 (*s*)	164.5 (*s*)	162.4 (*s*)
6′		116.0 (*d*)	116.3 (*d*)	115.7 (*d*)
7′		133.1 (*d*)	133.1 (*d*)	132.5 (*d*)
*Me*OOC		52.2 (*q*)	52.3 (*q*)	

[a]) In (D_5)pyridine. [b]) In CD_3OD. [c]) At 400 MHz in (D_6)acetone.

Glochicoccin D (**4**) was established to have the molecular formula $C_{21}H_{24}O_{10}$, on the basis of negative HR-ESI-MS (*m/z* 435.1337 ($[M-H]^-$, calc. 435.1291)). Comparison of the NMR data of **4** with those of **2** indicated identical structures, with the exception that the ester group was hydrolyzed in **4**. The chemical shifts of H–C(1), H–C(5), H–C(10), and H–C(11) were in good agreement with those of **2**, suggesting that the two compounds shared the same relative configuration. This was supported by ROESY cross-peaks for H–C(1)/H_β–C(2)/H_β–C(4)/H–C(5), H_α–C(2)/H–C(3)/H_α–C(4), H_α–C(9)/H–C(11)/H_α–C(12)/H–C(10). According to the optical rotation, the absolute configuration of **4** was the same as that of phyllaemblic acid methyl ester (**6**). Glochicoccin D (**4**) was, therefore, concluded to be '5′-hydroxyphyllaemblic acid'[1]).

2. *Biological Assays.* Norbisabolane sesquiterpenoids, with carbon skeletons resulting from the loss of one terminal Me_2C group, are well-known [5–8]. However, the

highly oxygenated bisabolane **1** and the norbisabolanes **2**–**6** were isolated for the first time from the genus *Glochidion*. They were all evaluated for their cytotoxic and antioxidant potentials. However, none of them was found to be active against human lung adenocarcinoma A-549 cells, mice leucocythemia P388 cells, human leucocythemia HL60 cells, or human liver BEL-7402 cancer cells, nor were they active in terms of DPPH-radical scavenging.

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Experimental Part

General. Column chromatography (CC) was performed on silica gel (200–300 mesh; *Qingdao Marine Chemical, Inc.*), silica gel *H* (10–40 μm; *Qingdao*), and *Sephadex LH-20* (40–70 μm; *Amersham Pharmacia*). Zones of prep. TLC plates (1.0–1.5 mm; *Qingdao*) and anal. TLC plates (0.20–0.25 mm; *Qingdao*) were visualized under UV light or by spraying with 10% H_2SO_4 in 95% EtOH, followed by heating. Melting points (m.p.): *XRC-1* apparatus; uncorrected. Optical rotations: *Horiba SEPA-300* or a *Jasco DIP-370* digital polarimeter. UV Spectra: *Shimadzu UV-2401PC* spectrometer, λ_{max} (log ε) in nm. IR Spectra: *Bio-Rad FTS-135* spectrometer, with KBr pellets; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AM-400* or *DRX-500* spectrometer; chemical shifts δ in ppm rel. to Me_4Si, *J* in Hz. MS: *VG Auto-Spec-3000* mass spectrometer; in *m*/*z* (rel. %).

Plant Material. The rhizomes of *G. coccineum* were obtained from Guiyang, Guizhou Province, People's Republic of China, in May 2005. The plant was identified by Prof. *De-Yuan Chen*, Guiyang College of Traditional Chinese Medicine, Guiyang, where a voucher specimen (GTCM No. 050517) was deposited.

Extraction and Isolation. The rhizomes of *G. coccineum* (12 kg) were extracted with 90% EtOH (3×18 l) for 2 h each at reflux. After solvent removal under vacuum, the viscous extract (210 g) was taken up in AcOEt and subjected to CC (SiO_2; petroleum ether/AcOEt 1:0 → 0:1): seven fractions (*Fr. 1–7*) by TLC. *Fr. 5* was repeatedly subjected to CC (1. SiO_2, petroleum ether/Me_2CO 3:2; 2. *Sephadex LH-20*, $CHCl_3$/MeOH 1:1) to afford **1** (38 mg). *Fr. 6* was purified by repeated CC (SiO_2; petroleum ether/Me_2CO 2:3) to afford **6** (32 mg). *Fr. 7* was resubmitted to CC (SiO_2; $CHCl_3$/MeOH 9:1) and further purified by prep. TLC to provide **2** (11 mg), **3** (13 mg), **4** (43 mg), and **5** (19 mg).

Glochicoccin A (=*(2S,3R,3aR,4R,4′S,5′R,7R,8aR)-Octahydro-3,4′-dihydroxy-3-(hydroxymethyl)-5′-methyl-3*H*-spiro[4,7-methanofuro[3,2-c]oxepine-2,2′-pyran]-6(4*H*)-one*; **1**). Colorless crystals (MeOH). M.p. 202–203° (MeOH). $[\alpha]_D^{26} = +59.4$ (*c* = 1.78, MeOH). IR (KBr): 3465, 2938, 1755, 1630, 1462, 1370, 1335, 1280, 1165, 1021, 961, 913, 857. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS (pos.): 651 ($[2M+Na]^+$). FAB-MS (pos.): 315 ($[M+H]^+$). HR-ESI-MS (neg.): 313.1283 ($[M-H]^-$, $C_{15}H_{21}O_7^-$; calc. 313.1287). X-Ray crystal structure: see below.

Glochicoccin B (=*Methyl (2S,3aR,4S,4′S,5′R,6S,7aR)-Decahydro-3a,4-dihydroxy-4′-[(4-hydroxybenzoyl)oxy]-5′-methyl-3-oxo-3*H*-spiro[1-benzofuran-2,2′-pyran]-6-carboxylate*; **2**). Colorless, amorphous solid. $[\alpha]_D^{26} = -9.0$ (*c* = 1.56, MeOH). UV (MeOH): 390 (1.93), 258 (3.76). IR (KBr): 3434, 2933, 1779, 1712, 1609, 1514, 1443, 1347, 1279, 1167, 1098, 1049, 1006, 951, 851, 773. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS (pos.): 473 ($[M+Na]^+$). ESI-MS (neg.): 449 ($[M-H]^-$). HR-ESI-MS (neg.): 449.1437 ($[M-H]^-$, $C_{22}H_{25}O_{10}^-$; calc. 449.1448).

Glochicoccin C (=*Methyl (2S,3aR,4R,4′S,5′R,6S,7aR)-Decahydro-3a,4-dihydroxy-4′-[(4-hydroxybenzoyl)oxy]-5′-methyl-3-oxo-3*H*-spiro[1-benzofuran-2,2′-pyran]-6-carboxylate*; **3**). Colorless, amorphous solid. $[\alpha]_D^{26} = -11.3$ (*c* = 0.47, MeOH). UV (MeOH): 370 (1.90), 258 (3.72). IR (KBr): 3432, 2923, 1777, 1709, 1608, 1514, 1440, 1385, 1354, 1278, 1166, 1045, 1003, 853, 774. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS (neg.): 449 ($[M-H]^-$). HR-ESI-MS (neg.): 449.1443 ($[M-H]^-$, $C_{22}H_{25}O_{10}^-$; calc. 449.1448).

Glochicoccin D (=(2S,3aR,4S,4′S,5′R,6S,7aR)-*Decahydro-3a,4-dihydroxy-4′-[(4-hydroxybenzoyl)-oxy]-5′-methyl-3-oxo-3*H-*spiro[1-benzofuran-2,2′-pyran]-6-carboxylic Acid*; **4**). Colorless, amorphous solid. $[\alpha]_D^{26} = +36.6$ ($c = 0.56$, MeOH). UV (MeOH): 258 (3.79). IR (KBr): 3439, 2930, 1777, 1692, 1608, 1514, 1390, 1351, 1314, 1277, 1169, 1099, 1047, 1006, 951, 851, 773. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS (neg.): 435 ($[M-H]^-$). FAB-MS (neg.): 435 ($[M-H]^-$). HR-ESI-MS (neg.): 435.1337 ($[M-H]^-$, $C_{21}H_{23}O_{10}^-$; calc. 435.1291).

Crystallographic Data for **1**[2]). Formula, $C_{15}H_{22}O_7$, M_r 314.33; monoclinic, space group $P2_1$, $a = 9.303(1)$, $b = 8.443(1)$, $c = 9.895(1)$ Å, $\beta = 71.41(1)^\circ$; $V = 735.7(2)$ Å^3, $Z = 2$, $d = 1.417$ g/cm^3; crystal dimensions, $0.10 \times 0.20 \times 0.60$ mm. The measurements were performed on a *MAC DIP-2030K* diffractometer with a graphite monochromator ($\omega - 2\theta$ scans, $2\theta_{max} = 50.0^\circ$), Mo$K_\alpha$ radiation. The total number of independent and observed reflections was 1376 ($|F|^2 \geq 2\sigma|F|^2$). The crystal structure was solved by direct methods using SHELXS-97 [9], expanded using difference *Fourier* techniques, and refined with NOMCSDP [10] using full-matrix least-squares calculations. Final indices: $R = 0.0485$, $R_w = 0.1342$ ($w = 1/\sigma|F|^2$). H-Atoms were fixed at their calculated positions.

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