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CYCLIC DIARYLHEPTANOIDS FROM RHIZOMES OF *ZINGIBER OFFICINALE**

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Key Word Index—*Zingiber officinale*; Zingiberaceae; ginger; rhizome; cyclic diarylheptanoids.

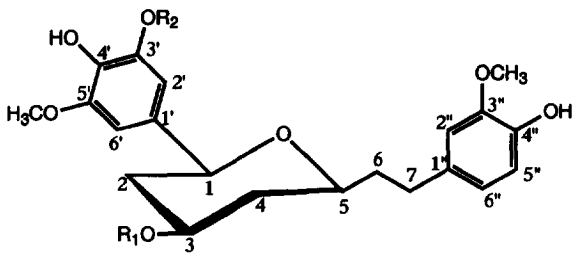
Abstract—Five new diarylheptanoids were isolated from the rhizomes of *Zingiber officinale* and their structures elucidated by spectroscopic and chemical methods. They were oxygenated at C-1, 3 and 5 on the heptane chain and cyclized between C-1 and C-5 through oxygen. Copyright © Elsevier Science Ltd

INTRODUCTION

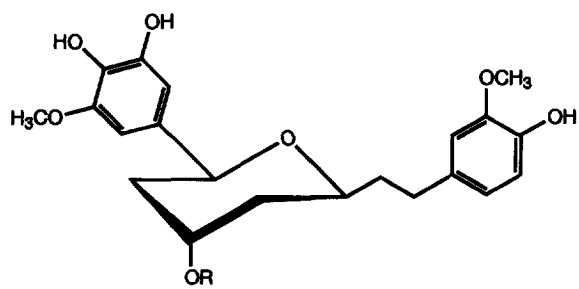
Previously we have reported on the isolation and structural elucidation of gingerol-related compounds [1–3] and diaryl-heptanoids [4, 5] from the dichloromethane extract of the rhizomes of ginger (*Zingiber officinale*). In continuation of our investigations on the chemical constituents in ginger, we have now isolated five new types of cyclic diarylheptanoids (**1–5**). We present here spectroscopic and chemical evidence for the structures of compounds **1–5**.

RESULTS AND DISCUSSION

The dichloromethane extract from the rhizomes of *Zingiber officinale* was purified by a combination of



1: R_1=Ac, R_2=H
3: R_1=R_2=H
5: R_1=H, R_2=CH_3



2: R=Ac
4: R=H

*Part 7 in the series 'Constituents of Zingiberaceae'. For Parts 1–6 see ref. [2].

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Table 1. ^{1}H NMR spectral data of compounds **1**–**5** (400 MHz, δ-values)

H	**1***	**2***	**3**†	**4**†	**5***
1	4.29 *dd* (2, 12)	4.62 *dd* (2, 12)	4.22 *dd* (2, 10)	4.69 *dd* (2, 12)	4.26 *dd* (2, 11)
2ax	1.55 *ddd* (12, 12, 12)	1.78 *ddd* (3, 12, 14)	1.35 *ddd* (10, 10, 12)	1.64 *ddd* (3, 12, 12)	1.50 *ddd* (11, 11, 12)
2eq	2.20 *dddd* (2, 2, 5, 12)	2.01 *dddd* (2, 2, 2, 14)	2.10 *dddd* (2, 2, 4, 12)	1.84 *dddd* (2, 2, 3, 12)	2.19 *dddd* (2, 2, 4, 12)
3	5.0 *dddd* (5, 5, 12, 12)	5.28 *dddd* (3, 3, 3, 3)	3.82 *dddd* (4, 4, 10, 10)	4.22 *dddd* (3, 3, 3, 3)	3.92 *dddd* (4, 4, 11, 11)
4ax	1.41 *ddd* (12, 12, 12)	1.62 *ddd* (3, 12, 14)	1.21 *ddd* (10, 10, 12)	1.50 *ddd* (3, 11, 14)	1.32 *ddd* (11, 11, 12)
4eq	2.02 *m*	1.88 *dddd* (2, 2, 2, 14)	1.94 *dddd* (2, 2, 4, 12)	1.69 *dddd* (2, 2, 3, 14)	2.02 *dddd* (2, 2, 4, 12)
5	3.50 *m*	3.85 *m*	3.41 *dddd* (2, 4, 8, 10)	3.90 *dddd* (2, 4, 9, 11)	3.45 *m*
6a	1.77 *dddd* (4, 7, 9, 14)	1.75 *m*	1.74 *dddd* (4, 8, 9, 14)	1.66 *m*	1.79 *dddd* (4, 7, 9, 14)
6b	1.94 *dddd* (6, 7, 9, 14)	1.92 *m*	1.85 *dddd* (6, 8, 9, 14)	1.78 *dddd* (5, 9, 9, 14)	1.97 *dddd* (6, 8, 9, 14)
7a	2.65 *ddd* (7, 9, 15)	2.69 *ddd* (7, 9, 15)	2.63 *ddd* (8, 9, 14)	2.63 *ddd* (9, 9, 14)	2.69 *ddd* (7, 9, 14)
7b	2.73 *ddd* (6, 9, 15)	2.77 *ddd* (6, 10, 15)	2.70 *ddd* (6, 9, 14)	2.69 *ddd* (5, 9, 14)	2.73 *ddd* (6, 9, 14)
2′	6.63 *d* (2)	6.66 *br s*	6.58 *d* (2)	6.57 *d* (2)	6.62 *s*
6′	6.50 *d* (2)	6.55 *br s*	6.56 *d* (2)	6.54 *d* (2)	6.62 *s*
2″	6.68 *br s*	6.73 *br s*	6.80 *d* (2)	6.80 *d* (2)	6.69 *br s*
5″	6.82 *d* (8)	6.85 *d* (8)	6.71 *d* (8)	6.71 *d* (8)	6.82 *br d* (8)
6″	6.66 *br d* (8)	6.71 *br d* (8)	6.64 *dd* (2, 8)	6.64 *dd* (2, 8)	6.67 *dd* (2, 8)
3′–OMe	—	—	—	—	3.90 *s*
5′–OMe	3.88 *s*	3.92 *s*	3.81 *s*	3.81 *s*	3.90 *s*
3″–OMe	3.83 *s*	3.87 *s*	3.79 *s*	3.77 *s*	3.83 *s*
3–OAc	2.05 *s*	2.14 *s*	—	—	—

*Measured in $CDCl_3$.

†Measured in $(CD_3)_2CO$.

column chromatography on silica gel, Sephadex LH-20 and ODS gel to give five new diaryl-heptanoids (**1–5**).

Compound **1** exhibited an $[M]^+$ peak at *m/z* 432.1803 in the HR-mass spectrum, corresponding to the molecular formula $C_{23}H_{28}O_8$. The IR spectrum showed absorptions at 3428 (a hydroxyl group), 1739 (an ester), and 1614 and 1516 cm^{-1} (an aromatic ring). The ^{13}C NMR spectrum contained the signals of one methyl (δ 21.3), two methoxyls (δ 55.8, 56.1), four methylenes (δ 31.3, 37.0, 37.8, 38.9), three oxygenated methines (δ 70.6, 74.7, 77.0), twelve aromatic and one carbonyl (δ 170.6). In the ^1H NMR spectrum, the *meta*-coupled aromatic protons due to a 1,3,4,5-tetra-substituted benzene ring appeared as two doublets at δ 6.50 ($J = 2$ Hz) and 6.63 ($J = 2$ Hz), together with three typical aromatic protons [δ 6.66 (1H, *br d*, $J =$ 8 Hz), 6.68 (1H, *br s*) and 6.82 (1H, *d*, $J = 8$ Hz)], corresponding to a 1,3,4-trisubstituted phenyl group. The spectrum also contained two arylic methoxy signals at δ 3.83 (3H, *s*) and 3.88 (3H, *s*), and one aliphatic acetyl signal at δ 2.05 (3H, *s*). Three oxygenated methine protons [δ 3.50 (1H, *m*), 4.29 (1H, *dd*, $J = 2$, 12 Hz) and 5.0 (1H, *dddd*, $J = 5$, 5, 12 and 12 Hz)] were observed together with benzylic methylene protons (δ 2.65 and 2.73) and six aliphatic protons (δ 1.3–2.3). Double resonance ^1H NMR measurements allowed assignments of these aliphatic protons as shown in Table 1, which suggested the presence of a six-membered cyclic ether structure, a pyrane skeleton, in the molecule. The signal at δ 4.29 (H-1) was coupled with methylene signals at δ 1.55 and 2.20 (H-2) with coupling constants of 12 Hz and 2 Hz, respectively, indicating the axial orientation of H-1. The signal attributable to H-3 was observed at δ 5.0, which suggested that an acetyl group was attached to C-3. The acetyl group was confirmed to be equatorial, based on the coupling constants of H-3 ($J = 5$, 5, 12 and 12 Hz). Irradiation of H-5 (δ 3.50, *m*) confirmed that H-5 was coupled with the axial proton at H-4 (δ 1.41, *ddd*), with a coupling constant of 12 Hz indicative of the axial orientation of H-5. The W-type H–H long-range coupling displayed between H-2eq (δ 2.20) and H-4eq (δ 2.02) confirmed the chair form of the six-membered ring. C–H COSY and COLOC experiments achieved complete assignments of all protons and carbons (Tables 1 and 2). Long-range ^1H–^{13}C correlations observed in the COLOC spectrum are shown in Fig. 1. The correlation shown on the aromatic rings indicate that one is a 3,4-dihydroxy-5-methoxyphenyl group, the other a 4-hydroxy-3-methoxyphenyl group. The correlation between H-1 and C-1′ or 2′, and H–H long-range coupling between H-1 and H-2′ or 6′ and between H-7 and H-2″ or H-6″, showed that a 3,4-dihydroxy-5-methoxyphenyl group and a 4-hydroxy-3-methoxyphenyl group were attached to C-1 and to C-7, respectively. The presence of a stable fragment ion peak at *m/z* 137 $[CH_2C_6H_3(OH)(OMe)]^+$ supported the attachment of a 4-hydroxy-3-methoxyphenyl group to C-7. Acetylation of **1** with acetic anhydride and pyridine gave **1a**. The IR spectrum of **1a** showed a new absorption band of an arylic acetate (1768 cm^{-1}) with disappearance of the hydroxyl absorption band in the IR spectrum of **1**. An $[M]^+$ peak at *m/z* 558 indicated that three acetyl groups were introduced into the structure of **1**. The ^1H NMR spectrum showed the presence of three aromatic acetates at δ 2.29, 2.30 and 2.31 (each 3H, *s*). Based on the above data, compound **1** was identified as 3-acetoxy-1,5-epoxy-1-(3,4-dihydroxy-5-methoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptane.

Table 2. ^{13}C NMR spectral data of compounds **1–5** (100 MHz, δ-values)

C	1*	2*	3†	4†	5*
1	77.0	74.0	78.2	74.2	77.3
2	38.9	37.3	44.5	41.8	42.8
3	70.6	68.2	68.4	64.8	68.5
4	37.0	35.2	42.1	39.4	40.9
5	74.7	71.9	75.4	71.6	74.9
6	37.8	37.9	39.0	39.3	37.7
7	31.3	31.2	32.0	31.9	31.3
1′	133.8	134.4	135.1	136.0	133.3
2′	106.6	106.5	107.4	107.3	102.9
3′	143.8	143.7	146.0	146.0	146.9
4′	131.7	131.6	133.7	133.5	133.8
5′	146.8	146.8	148.6	148.6	146.9
6′	100.9	100.9	102.1	102.1	102.9
1″	133.8	134.0	134.4	134.6	134.1
2″	111.1	111.1	112.8	112.9	111.0
3″	146.3	146.3	148.1	148.1	146.3
4″	143.6	143.6	145.4	145.4	143.6
5″	114.2	114.1	115.6	115.5	114.1
6″	120.9	120.9	121.5	121.5	121.0
3′–OMe	—	—	—	—	56.3
5′–OMe	56.1	56.2	56.4	56.4	56.3
3″–OMe	55.8	55.8	56.1	56.1	55.8
3–OAc	170.6	170.5	—	—	—
	21.3	21.4	—	—	—

*Measured in $CDCl_3$.
†Measured in $(CD_3)_2CO$.

Compound **2** had the same molecular formula as **1** ($C_{23}H_{28}O_8$, $[M]^+$ *m/z* 432.1803). The spectral data indicated that **2** was an isomer of **1**. Differences between **1** and **2** were observed in the signals corresponding to C-1–C-5 in the NMR spectra. In the ^1H NMR spectrum, the resonance of H-3 appeared at δ 5.28 (*dddd*) with individual coupling constants of 3 Hz, suggesting that H-3 is oriented equatorially, the acetyl group, axially. The ^1H NMR spectrum of **2** showed downfield shifts of H-1 (+0.33 ppm), H-5 (+0.35 ppm) and acetyl methyl protons (+0.09 ppm) relative to those of **1**, consistent with the axial orientation of the acetyl group [6, 7]. In addition, the smaller vicinal coupling constant ($J_{2ax,3eq} = 3$ Hz) in the resonance of H-3 than that of **1** ($J_{2eq,3ax} = 5$ Hz) also supported the axial orientation of the acetyl group [7]. The upfield shifts of C-1 (−3.0 ppm) and 5 (−2.8 ppm) in the ^{13}C NMR spectrum of **2**, caused by the γ-effect, compared with those of **1** confirmed this configuration [8]. Double resonance ^1H NMR and COLOC experi-

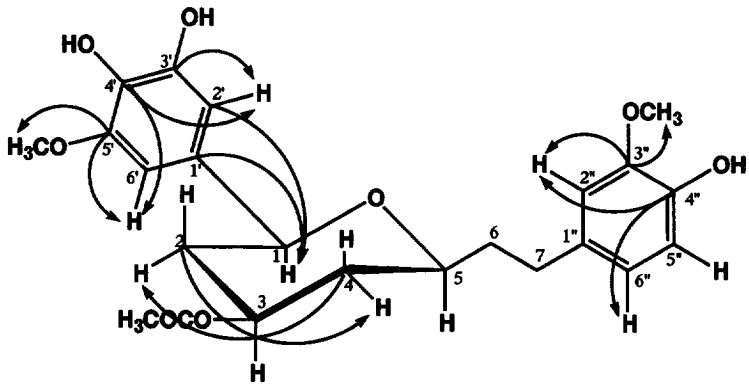

Fig. 1. ^{13}C–^{1}H correlation observed in the COLOC spectrum of compound **1**.

ments allowed the identification of a 3,4-dihydroxy-5-methoxyphenyl group attached to C-1. Acetylation of **2** gave a tetraacetate **2a** ($[M]^+$, *m/z* 558). Its IR spectrum showed phenolic acetate absorption at 1769 cm^{-1}, with the disappearance of the hydroxyl absorption band in **2**. In the ^1H NMR spectrum, the presence of three phenolic acetate groups was supported by three 3H singlets at δ 2.28, 2.30 and 2.31. Consequently, compound **2** is an epimer of **1** at the C-3 position.

Compound **3** showed the exact mass ion at *m/z* 390.1669, in good agreement with the molecular formula of $C_{21}H_{26}O_7$. The spectral data of **3** were similar to those of **1**. The IR spectrum showed absorption bands at 3401 cm^{-1} (hydroxyl groups), and 1614 and 1516 cm^{-1} (aromatic ring). In the ^1H NMR spectrum of **3**, the signal at H-3 was observed at δ 3.82 (*dddd*, $J = 4$, 4, 10 and 10 Hz) in place of δ 5.0 in **1**, which suggested that **3** was a deacetylated product of **1**. This suggestion was supported by the $[M]^+$ of **3** (*m/z* 390) being 42 mu smaller than that of **1** and the lack of a signal due to an acetyl group in the ^1H NMR spectrum; acetylation of **3** gave the same product **1a**. Thus, compound **3** was determined to be 1,5-epoxy-3-hydroxy-1-(3,4-dihydroxy-5-methoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptane.

The HR-mass spectrum of **4** ($[M]^+$ *m/z* 390.1692) suggested that **4** was an epimer of **3**. In the ^1H NMR spectrum, the signal at H-3 was observed at δ 4.22 (*dddd*, $J = 3$, 3, 3 and 3 Hz), indicating the axial orientation of the hydroxyl group at C-3. C–H COSY and COLOC experiments and acetylation of **4** confirmed that **4** was indeed the deacetylated product of **2** and an epimer of **3** at C-3.

Compound **5** showed a $[M]^+$ at *m/z* 404.1786, consistent with the molecular formula $C_{22}H_{28}O_7$. The spectral data of **5** were similar to those of **3**. In the ^1H NMR spectrum, three methoxyl signals were observed at δ 3.83 (3H, *s*) and 3.90 (6H, *s*). A 2H-singlet signal at δ 6.62 was observed instead of the two *meta*-coupled doublets in **3**. These data indicated the presence of a 4-hydroxy-3,5-dimethoxyphenyl moiety in the molecule in place of the 3,4-dihydroxy-5-methoxyphenyl group. The mass fragment ions and the ^{13}C NMR spectrum also supported this structure. The signal of H-3 appeared at δ 3.92 (*dddd*, $J = 4$, 4, 11 and 11 Hz) was consistent with the equatorial orientation of the hydroxyl group. The correlation between H-1 (δ 4.26) and C-1′ (δ 133.3), and between H-2″, 6″ (δ 6.69, 6.82) and C-7 (δ 31.3) in the COLOC spectrum, and the observation of H–H long range-coupling between H-1 and H-2′ and 6′ (δ 6.62), confirmed that a 4-hydroxy-3,5-dimethoxyphenyl group was attached to C-1. Consequently, compound **5** was concluded to be 1,5-epoxy-3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptane.

Though diarylheptanoids have been occasionally reported from the Zingiberaceae [9–10], cyclic dairylheptanoids, such as **1–5**, represent new types of natural products. So far, only one cyclic curcumin has been described recently from *Curcuma longa* [11].

EXPERIMENTAL

^1H and ^{13}C NMR: 400 and 100 MHz, TMS as int. standard. EIMS: direct insertion probe at 70 eV.

Extraction and isolation. Dried ground rhizomes of *Z. officinale* (3 kg) from China were extracted (×4) with CH_2Cl_2 (6 l) at room temp. The CH_2Cl_2 extract (160 g) was subjected to CC on silica gel to give 17 frs eluting with benzene–Me_2CO. Fr. 14 (11.1 g) eluted with benzene–Me_2CO (7:3) was rechromatographed on Sephadex LH-20 (*iso*-PrOH), followed by a combination of CC on silica gel (CH_2Cl_2–MeOH) and ODS (MeOH–H_2O) to give **1–5**.

Compound **1**. Oil (40 mg). UV λ_{max}^{EtOH} nm (log ε): 226.0 (*sh*, 4.32), 280.0 (3.75). $[\alpha]_D^{25}$ −31.2° (EtOH; *c* 1.3). IR ν_{max}^{film} cm^{-1}: 3428 (OH) 1739 (OAc), 1614, 1516 (Ar). EIMS *m/z* (rel. int.): 432 $[M]^+$ (19), 372 (5), 354 (5), 235 (3), 219 (6), 179 (19), 167 (15), 153 (16), 150 (17), 137 (100); HRMS: found: *m/z*: 432.1803 $[M]^+$, $C_{23}H_{28}O_8$ requires: 432.1677. *Acetylation of compound* **1**. A soln of **1** (3.5 mg) in pyridine (0.5 ml) and Ac_2O (0.5 ml) was allowed to stand overnight at room temp. Usual work-up gave **1a** (4.0 mg). IR ν_{max}^{film} cm^{-1}: 1768, 1740 (OAc), 1605, 1510 (Ar). ^1H NMR ($CDCl_3$): δ 1.42 (1H, *ddd*, $J = 12$, 12, 12 Hz, H-4ax), 1.53 (1H, *ddd*, $J = 12$, 12, 12 Hz, H-2ax), 1.84 (1H, *dddd*, $J = 4$, 7, 10, 14 Hz, H-6a),

1.98 (1H, *dddd*, $J = 5, 9, 10, 14$ Hz, H-6b), 2.04 (1H, *m*, H-4eq), 2.05 (3H, *s*, OAc), 2.26 (1H, *m*, H-2eq) 2.29 (3H, *s*, OAc), 2.30 (3H, *s*, OAc), 2.31 (3H, *s*, OAc), 2.71 (1H, *ddd*, $J = 7, 10, 14$ Hz, H-7a), 2.81 (1H, *ddd*, $J = 5, 10, 14$ Hz, H-7b), 3.53 (1H, *m*, H-5), 3.79 (3H, *s*, OMe), 3.85 (3H, *s*, OMe), 4.39 (1H, *br d*, $J = 12$ Hz, H-1), 5.02 (1H, *dddd*, $J = 5, 5, 12, 12$ Hz, H-3), 6.75 (1H, *dd*, $J = 2, 8$ Hz, H-6″), 6.78 (1H, *d*, $J = 2$ Hz, H-2″), 6.81 (1H, *d*, $J = 2$ Hz, H-2′ or 6′), 6.87 (1H, *d*, $J = 2$ Hz, H-2′ or 6′), 6.93 (1H, *d*, $J = 8$ Hz, H-5″). EIMS *m/z* (rel. int.): 558 $[M]^+$(1), 516 (100), 474 (16), 456 (24), 432 (15), 414 (4), 372 (16), 354 (1), 235 (4), 179 (17), 137 (76).

Compound **2**. Oil (10.8 mg). UV λ_{max}^{EtOH} nm (log ε): 226.0 (*sh*, 4.33), 280.0 (3.76). $[\alpha]_D^{25}$ −23.3° (EtOH; *c* 0.49). IR ν_{max}^{film} cm^{-1}: 3436 (OH), 1728 (OAc), 1614, 1514 (Ar). EIMS *m/z* (rel. int.): 432 $[M]^+$ (21), 372 (5), 354 (5), 235 (3), 219 (5), 179 (17), 167 (21), 153 (17), 150 (22), 137 (100); HRMS: found: *m/z*: 432.1803 $[M]^+$, $C_{23}H_{28}O_8$ requires: 432.1677. *Acetylation of compound* **2**. Compound **2** (2.1 mg) was treated in the same manner as described above to give **2a** (2.3 mg). IR ν_{max}^{film} cm^{-1}: 1769, 1735 (OAc), 1605, 1510 (Ar). ^1H NMR ($CDCl_3$): δ 1.59 (1H, *ddd*, $J = 2, 12, 14$ Hz, H-4ax), 1.73 (1H, *ddd*, $J = 2, 12, 14$ Hz, H-2ax), 1.78 (1H, *dddd*, $J = 5, 7, 9, 14$ Hz, H-6a), 1.86 (1H, *dddd*, $J = 2, 2, 2, 14$ Hz, H-4eq), 1.91 (1H, *dddd*, $J = 5, 8, 9, 14$ Hz, H-6b), 2.03 (1H, *dddd*, $J = 2, 2, 2, 14$ Hz, H-2eq), 2.11 (3H, *s*, OAc), 2.28 (3H, *s*, OAc), 2.30 (3H, *s*, OAc), 2.31 (3H, *s*, OAc), 2.70 (1H, *ddd*, $J = 7, 9, 14$ Hz, H-7a), 2.81 (1H, *ddd*, $J = 5, 9, 14$ Hz, H-7b), 3.78 (3H, *s*, OMe), 3.80 (1H, *m*, H-5), 3.86 (3H, *s*, OMe), 4.68 (1H, *dd*, $J = 2, 12$ Hz, H-1), 5.25 (1H, *dddd*, $J = 2$ Hz, H-3), 6.76 (1H, *dd*, $J = 2, 7$ Hz, H-6″), 6.79 (1H, *d*, $J = 2$ Hz, H-2″), 6.80 (1H, *d*, $J = 2$ Hz, H-2′ or 6′), 6.88 (1H, *d*, $J = 2$ Hz, H-2′ or 6′), 6.93 (1H, *d*, $J = 7$ Hz, H-5″). EIMS *m/z* (rel. int.): 558 $[M]^+$(1), 516 (100), 474 (22), 456 (28), 432 (17), 414 (7), 372 (21), 354 (10), 235 (6), 179 (42), 137 (95).

Compound **3**. Amorphous (28 mg). UV λ_{max}^{EtOH} nm (log ε): 226.5 (*sh*, 4.20), 280.0 (3.65). $[\alpha]_D^{25}$ −61.6° (EtOH; *c* 0.98). IR ν_{max}^{film} cm^{-1}: 3401 (OH), 1614, 1516 (Ar). EIMS *m/z* (rel. int.): 390 $[M]^+$ (29), 372 (2), 354 (1), 235 (2), 195 (7), 179 (11), 167 (20), 154 (31), 137 (100); HRMS: found: *m/z*: 390.1669 $[M]^+$, $C_{21}H_{26}O_7$ requires: 390.1676. *Acetylation of compound* **3**. Compound **3** (2.6 mg) was acetylated as described above to give a tetraacetate (3.5 mg). IR, ^1H NMR and MS data were identical in all respects to those of **1a**.

Compound **4**. Oil (22 mg). UV λ_{max}^{EtOH} nm (log ε): 225.5 (*sh*, 4.03), 280.5 (3.51). $[\alpha]_D^{25}$ −41.6° (EtOH; *c* 0.90). *IR* ν_{max}^{film} cm^{-1}: 3401 (OH), 1614, 1515 (Ar). EIMS *m/z* (rel. int.): 390 $[M]^+$ (78), 372 (5), 354 (3), 235 (4), 195 (17), 179 (26), 167 (42), 154 (79), 137 (100); HRMS: found: *m/z*: 390.1692 $[M]^+$, $C_{21}H_{26}O_7$ requires: 390.1676. *Acetylation of compound* **4**. Compound **4** (3.6 mg) was acetylated as described above to give a tetraacetate (5 mg). IR, ^1H NMR and MS data were identical in all respects to those of **2a**.

Compound **5**. Oil (6 mg). UV λ_{max}^{EtOH} nm (log ε): 226.5 (*sh*, 4.09), 280.0 (3.59). $[\alpha]_D^{25}$ −48.6° (EtOH; *c* 0.62). IR ν_{max}^{film} cm^{-1}: 3401 (OH), 1614, 1516 (Ar). EIMS *m/z* (rel. int.): 404 $[M]^+$ (19), 386 (4), 224 (21), 210 (3), 194 (17), 180 (33), 167 (63), 137 (100); HRMS: found: *m/z*: 404.1786 $[M]^+$, $C_{22}H_{28}O_7$ requires: 404.1832.

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