Four Novel Dihydroisocoumarin (= 3,4-Dihydro-1*H*-2-benzopyran-1-one) Glucosides from the Fungus *Cephalosporium sp.* AL031

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Four novel dihydroisocoumarin (= 3,4-dihydro-1*H*-2-benzopyran-1-one) glucosides were isolated from a culture broth of a strain of the fungus *Cephalosporium sp.* AL031. Their structures were elucidated as (2*E*,4*E*)-5-[(3*S*)-5-acetyl-8-(β-D-glucopyranosyloxy)-3,4-dihydro-6-hydroxy-1-oxo-1*H*-2-benzopyran-3-yl]penta-2,4-dienal (**1**), (2*E*,4*E*)-5-[(3*S*)-5-acetyl-8-(β-D-glucopyranosyloxy)-3,4-dihydro-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl]penta-2,4-dienal (**2**), (3*S*)-8-(β-D-glucopyranosyloxy)-3-[(1*E*,3*E*,5*E*)-hepta-1,3,5-trienyl]-3,4-dihydro-6-hydroxy-5-methyl-1*H*-2-benzopyran-1-one (**3**), and (3*S*)-8-[(6-*O*-acetyl-β-D-glucopyranosyl)oxy]-3-[(1*E*,3*E*,5*E*)-hepta-1,3,5-trienyl]-3,4-dihydro-6-methoxy-5-methyl-1*H*-2-benzopyran-1-one (**4**) by spectroscopic methods, including 2D-NMR techniques and chemical methods.

Introduction. – In our ongoing research on biologically active metabolites from fungi, we investigated the secondary metabolites produced by *Cephalosporium sp.* AL031 in culture. The organism is a fungus that was isolated from *Sinarundinaria nitida* grown in the Ailao Mountain, Yunnan, P. R. China. Crude extracts of a culture broth of the fungus showed antibacterial and fungicidal properties [1][2]. In our previous paper, we have reported the isolation of three phenolic acids [3] from the culture broth of the fungus. We describe herein our further study concerning the isolation and structure elucidation of four new dihydroisocoumarin (= 3,4-dihydro-1*H*-2-benzopyran-1-one) glucosides from the AcOEt extract of the culture broth of *Cephalosporium sp.* AL031.

Results and Discussion. – Compound **1** was obtained as yellowish amorphous solid. The molecular formula was assigned as $C_{22}H_{24}O_{11}$ from positive HR-FAB-MS (*m*/*z* 465.1391 ($[M+H]^+$; calc. 465.1395)). It showed UV absorption bands at λ_{max} 220, 268, and 303 nm. The IR spectrum revealed the presence of OH groups (3418 cm^{-1}), a conjugated aldehyde (2817, 2732, and 1672 cm^{-1}), a carbonyl group (1720 cm^{-1}), an unsaturated lactone (1688, 1253, and 1120 cm^{-1}), and C=C bonds and aromatic rings (1629, 1603, 1589, and 1510 cm^{-1}). Acid hydrolysis of **1** yielded D-glucose, identified by paper chromatography. The ^{1}H- and ^{13}C-NMR (*Table 1*), ^{1}H,^{1}H-COSY, HMQC, HMBC, and NOESY experiments and the CD spectra established the structure of **1** as (3*S*,11*E*,13*E*)-5-acetyl-8-(β-D-glucopyranosyloxy)-6-hydroxy-3-(oxopentadienyl)isochroman-1-one[1]) (*Fig.*).

[1]) Arbitrary numbering; for systematic names, see *Exper. Part.*

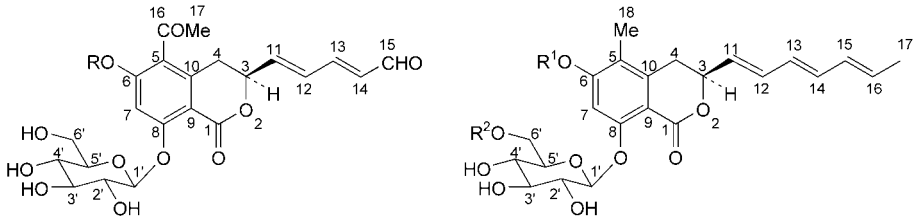

Figure. *Structure of compounds* **1**–**4**

Table 1. *^{1}H- and ^{13}C-NMR Data* (CD_3OD) *of Compounds* **1** *and* **2**[a]). Arbitrary numbering[1]).

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
C(1)		166.3		166.1
H–C(3)	4.71 (*ddd*, *J* = 10.8, 3.7, 6.7)	80.3	4.68 (*ddd*, *J* = 11.0, 3.8, 6.6)	79.9
CH_2(4)	3.17 (*dd*, *J* = 16.0, 3.7),	35.3	3.16 (*dd*, *J* = 15.8, 3.8),	35.1
	2.98 (*dd*, *J* = 16.0, 10.8)		2.95 (*dd*, *J* = 15.8, 11.0)	
C(5)		116.9		117.3
C(6)		156.8		158.0
H–C(7)	7.20 (*s*)	101.3	7.15 (*s*)	101.6
C(8)		164.1		164.4
C(9)		109.2		109.7
C(10)		145.6		145.1
H–C(11)	6.98 (*dd*, *J* = 15.0, 6.7)	140.5	6.95 (*dd*, *J* = 14.7, 6.6)	139.9
H–C(12)	7.75 (*ddd*, *J* = 11.5, 15.0, 3.6)	133.2	7.69 (*ddd*, *J* = 11.2, 14.7, 3.6)	133.8
H–C(13)	7.61 (*t*, *J* = 11.5)	152.1	7.66 (*t*, *J* = 11.2)	152.6
H–C(14)	6.44 (*dd*, *J* = 15.0, 7.0)	134.1	6.38 (*dd*, *J* = 14.7, 7.3)	133.0
H–C(15)	9.60 (*d*, *J* = 7.0)	195.0	9.69 (*d*, *J* = 7.3)	194.8
C(16)		196.2		195.9
Me(17)	1.80 (*s*)	28.7	1.77 (*s*)	28.9
H–C(1′)	4.49 (*d*, *J* = 7.2)	105.4	4.43 (*d*, *J* = 6.9)	105.9
H–C(2′)	3.48 (*dd*, *J* = 9.6, 7.2)	75.2	3.51 (*dd*, *J* = 9.3, 6.9)	75.7
H–C(3′)	3.86 (*t*, *J* = 9.6)	76.8	3.81 (*m*)	77.1
H–C(4′)	3.38 (*t*, *J* = 9.6)	71.4	3.37 (*m*)	70.6
H–C(5′)	3.55 (*m*)	78.6	3.57 (*m*)	78.1
CH_2(6′)	3.72 (*dd*, *J* = 11.2, 5.1),	62.3	3.66 (*dd*, *J* = 11.0, 5.3),	62.8
	3.88 (*dd*, *J* = 11.2, 2.2)		3.71 (*dd*, *J* = 11.0, 2.6)	
OH–C(6)	10.06 (br. *s*)			
MeO–C(6)			3.93 (*s*)	56.0

[a]) Assignments were made by 2D ^{1}H,^{1}H-COSY, HMQC, HMBC, and NOESY experiments; δ in ppm, *J* in Hz.

The ^{1}H-NMR spectrum of **1** exhibited the *AB* portion of a typical *ABX* system characteristic signals of a dihydroisocoumarin lactone at δ(H) 4.71 (*ddd*, *J* = 10.8, 3.7, 6.7 Hz) and 3.17 (*dd*, *J* = 16.0, 3.7 Hz), 2.98 (*dd*, *J* = 16.0, 10.8 Hz) assigned to H–C(3) and H–C(4) (*Table 1*) [4][5]. An aldehyde *d* at δ(H) 9.60 (*J* = 7.0 Hz), four conjugated-olefin protons at δ(H) 6.98 (*dd*, *J* = 15.0, 6.7 Hz), 7.75 (*ddd*, *J* = 11.5, 15.0, 3.6 Hz), 7.61 (*t*, *J* = 11.5 Hz), and 6.44 (*dd*, *J* = 15.0, 7.0 Hz), an aromatic proton at δ(H) 7.20, seven sugar protons at δ(H) 4.49 (*d*, *J* = 7.2 Hz), 3.48 (*dd*, *J* = 9.6, 7.2 Hz), 3.86 (*t*, *J* = 9.6 Hz), 3.38 (*t*, *J* = 9.6 Hz), 3.55 (*m*), 3.72 (*dd*, *J* = 11.2,

5.1 Hz), and 3.88 (*dd*, *J* = 11.2, 2.2 Hz), and a Me *s* at δ(H) 1.80 were also observed. The ^{13}C-NMR signals at δ(C) 105.4, 75.2, 76.8, 71.4, 78.6, and 62.3 and an anomeric proton at δ(H) 4.49 (*d*, *J* = 7.2 Hz) in the ^{1}H-NMR suggested the presence of a β-glucopyranosyl moiety in **1**. Apart from the signals for the β-glucopyranosyl moiety, the ^{13}C-NMR and DEPT spectra further revealed the presence of 16 C-atoms, of which three were C=O groups, four were olefinic, and three were connected to O-atoms. Analysis of coupling constants and the ^{1}H,^{1}H COSY data indicated the presence of a pentadienal side chain. The dihydroisocoumarin skeleton of **1** was confirmed by the HMBC correlations H–C(3)/C(4) and C(10), and CH_2(4)/C(10), C(5), C(3), and C(9)[1]. HMBC Correlations H–C(11)/C(3) and C(4), and OH–C(6)/C(6), C(5), and C(7) located the position of the pentadienal moiety at C(3) and of the OH group at C(6). An Ac group at C(5) was established by the HMBC correlations Me(17)/C(16) and C(5). The anomeric proton H–C(1′) of the glucose moiety showed a correlation to C(8) indicating that the attachment of the glucose unit was at C(8). This was supported by a NOESY experiment, in which H–C(1′) showed a cross-peak with H–C(7). The (*E*)-configurations of the C=C bonds were determined by the coupling constants *J*(H,H) = 15.0 and 15.0 Hz and confirmed by the NOESY cross-peaks H–C(11)/H–C(13), H–C(12)/H–C(14), and H–C(13)/H–C(15). It has been reported [6][7] that the sign of the *Cotton* effect ($n \rightarrow \pi^*$) can be used for establishing the absolute configuration of dihydroisocoumarins. Thus, the (3*S*)-configuration of the pentadienal side chain of **1** was deduced from circular-dichroism (CD) measurements of **1**, which gave rise to a positive *Cotton* effect at 272 nm, and by comparison with those of known related compounds [8–10].

Compound **2** was also obtained as yellowish amorphous solid, and its molecular formula was determined by HR-FAB-MS as $C_{23}H_{26}O_{11}$. Its UV and IR spectra were highly similar to those of **1**. The ^{1}H- and ^{13}C-NMR signals (*Table 1*) of **2** were superimposable to those of **1**, except for an additional MeO group. The HMBC correlation MeO/C(6) indicated the presence of a MeO group at C(6). The CD spectrum of **2** was also similar to that of **1**, implying that **2** possesses the (3*S*) absolute configuration. Hence, compound **2** was identified as (3*S*,11*E*,13*E*)-5-acetyl-8-(β-D-glucopyranosyloxy)-6-methoxy-3-(oxopentadienyl)isochroman-1-one[1]) (*Fig.*).

Compound **3** was obtained as yellowish amorphous solid. The HR-FAB-MS showed a quasi-molecular ion $[M+H]^+$ at *m*/*z* 449.1807, corresponding to the molecular formula $C_{23}H_{28}O_9$. The analysis of its ^{1}H- and ^{13}C-NMR data (*Table 2*) suggested that **3** has a skeleton similar to that of compound **1**, the difference being a heptatrienyl side chain at C(3) of **3** instead of a pentadienal moiety in **1**, and the presence of a Me group in **3** instead of the Ac group in **1**. The spectral data of **3** were consistent with the structure of (3*S*,11*E*,13*E*,15*E*)-8-(β-D-glucopyranosyloxy)-3-heptatrienyl-6-hydroxy-5-methylisochroman-1-one[1]) (*Fig.*).

The Ac signals at δ(C) 196.2 and 28.7 in the ^{13}C-NMR of **1** were replaced by a Me signal at δ(C) 19.8 in the spectrum of **3**. The ^{1}H-NMR spectrum of **3** exhibited heptatrienyl signals at δ(H) 6.68 (*dd*, *J* = 15.0, 6.5 Hz), 6.95 (*ddd*, *J* = 10.0, 15.0, 4.4 Hz), 6.37 (*m*), 6.43 (*m*), 6.17 (*ddd*, *J* = 10.1, 15.1, 1.6 Hz), 5.58 (*dq*, *J* = 15.1, 6.7 Hz), and 1.78 (*d*, *J* = 6.7 Hz). The attachment site of the heptatrienyl group was confirmed by the ^{1}H,^{1}H-COSY cross-peak H–C(3)/H–C(11). The HMBC correlations Me(18)/C(5), C(6), and C(10) indicated that the Me group was linked to C(5) of **3**. The (*E*)-configurations of the three C=C bonds of the heptatrienyl side chain were assigned by the values of the ^{1}H,^{1}H-coupling constants *J* (11,12), *J* (13,14), and *J* (15,16) of 15.0, 15.0, and 15.1 Hz, respectively, which were confirmed by the NOESY cross-peaks H–C(11)/H–C(13), H–C(13)/H–C(15), H–C(14)/H–C(16), and H–C(15)/H–C(17). The absolute (3*S*)-configuration of **3** was established by the similarity of the CD spectra of **3** and **1**.

Compound **4** was also isolated as yellowish amorphous solid. Comparison of its ^{1}H- and ^{13}C-NMR spectra (*Table 2*) with those of **3** revealed that they were very similar, but also indicated the presence of an Ac and a MeO group. This was in accordance with the molecular formula $C_{26}H_{32}O_{10}$ deduced from HR-FAB-MS: The structure of **4** was

Table 2. *^{1}H- and ^{13}C-NMR. Data* (CD_3OD) *of Compounds* **3** *and* **4**[a]). Arbitrary numbering[1]).

	3		**4**	
	δ(H)	δ(C)	δ(H)	δ(C)
C(1)		168.1		168.1
H–C(3)	4.78 (*ddd*, *J* = 10.8, 3.9, 6.5)	80.3	4.73 (*ddd*, *J* = 11.1, 3.6, 6.8)	79.9
CH_2(4)	3.22 (*dd*, *J* = 16.3, 3.6),	35.6	3.19 (*dd*, *J* = 15.9, 3.9),	35.9
	2.96 (*dd*, *J* = 16.3, 11.2)		2.93 (*dd*, *J* = 15.9, 10.7)	
C(5)		117.8		118.1
C(6)		159.2		161.1
H–C(7)	7.18 (*s*)	102.3	7.20 (*s*)	101.9
C(8)		163.9		164.0
C(9)		108.4		109.2
C(10)		140.8		140.3
H–C(11)	6.68 (*dd*, *J* = 15.0, 6.5)	133.9	6.79 (*dd*, *J* = 15.1, 6.8)	133.6
H–C(12)	6.95 (*ddd*, *J* = 10.0, 15.0, 4.4)	128.8	6.99 (*ddd*, *J* = 10.1, 15.1, 4.7)	129.8
H–C(13)	6.37 (*m*)	130.5	6.42 (*m*)	130.3
H–C(14)	6.43 (*m*)	135.5	6.51 (*m*)	137.1
H–C(15)	6.17 (*ddd*, *J* = 10.1, 15.1, 1.6)	131.7	6.27 (*ddd*, *J* = 10.8, 14.7, 1.5)	131.6
H–C(16)	5.58 (*dq*, *J* = 15.1, 6.7)	132.2	5.93 (*dq*, *J* = 14.7, 7.1)	132.9
Me(17)	1.78 (*d*, *J* = 6.7)	18.3	1.83 (*d*, *J* = 7.1)	18.4
Me(18)	2.13 (*s*)	19.8	2.21 (*s*)	20.2
H–C(1′)	4.61 (*d*, *J* = 6.8)	105.0	4.57 (*d*, *J* = 7.0)	105.6
H–C(2′)	3.41–3.58 (*m*)	74.2	3.43–3.60 (*m*)	74.5
H–C(3′)	3.41–3.58 (*m*)	76.9	3.43–3.60 (*m*)	77.3
H–C(4′)	3.41–3.58 (*m*)	70.7	3.43–3.60 (*m*)	71.2
H–C(5′)	3.82 (*m*)	77.9	3.88 (*m*)	75.6
CH_2(6′)	3.91 (*dd*, *J* = 11.0, 5.3)	62.5	3.96 (*dd*, *J* = 11.3, 5.1)	64.9
	4.18 (*dd*, *J* = 11.0, 2.5)		4.21 (*dd*, *J* = 11.0, 2.6)	
OH(6)	10.19 (br. *s*)			
MeO–C(6)			3.90 (*s*)	55.8
AcO–C(6′)			2.30 (*s*)	171.1, 21.3

[a]) Assignments were made by 2D ^{1}H,^{1}H-COSY, HMQC, HMBC, and NOESY experiments; δ in ppm, *J* in Hz.

established as (3*S*,11*E*,13*E*,15*E*)-8-[(6-*O*-acetyl-β-D-glucopyranosyl)oxy]-3-heptatrienyl)-6-methoxy-5-methylisochroman-1-one[1]) (*Fig.*).

In the ^{13}C-NMR spectrum of **4**, a downfield shift of C(6′) and an upfield shift of C(5′) were observed as compared to the similar signals of **3** (see *Table 2*), which revealed that the Ac group was attached at OH–C(6′) of the glucose moiety. A HMBC correlation between the Ac protons and C(6′) confirmed this position. The position of the MeO group of **4** was also assigned by the HMBC correlation MeO/C(5). Compound **4** showed CD curves similar those of **1**–**3**, implying that all four compounds possess the (3*S*) absolute configuration.

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Experimental Part

General. Column chromatography (CC): *Sephadex LH-20* (*Pharmacia*); silica gel. Optical rotation: *Perkin-Elmer 341* polarimeter. UV Spectra: *Shimadzu-UV-240* spectrophotometer; λ_{max} (log ε) in nm. Circular dichroism spectra: *Jasco J-715* specropolarimeter; λ ($\Delta\varepsilon$) in nm. IR Spectra: *Perkin-Elmer 1640*-FTIR spectrometer; in cm^{-1}. NMR Experiments: ^1H, ^{13}C, DEPT, ^1H,^1H-COSY, NOESY, HMQC, and HMBC with a *Bruker DR-500* spectrometer, at 500 (^1H) and 125 MHz (^{13}C); chemical shifts δ in ppm rel. to $SiMe_4$, coupling constants *J* in Hz. HR-FAB-MS: *VG Autospec-3000* mass spectrometer; values in *m*/*z*.

Fungal Material. The fungus *Cephalosporium sp*. AL031 was isolated by us from *Sinarundinaria nitida* grown in the Ailao Mountain, Yunnan, P. R. China. It was identified as a member of Moniliaceae, *Cephalosporium sp*. (strain number AL031), by Professor *Fa-Rong Yang* in the Department of Biology, Yunnan University, and deposited in *Key Laboratory of Industrial Microbial Fermentation Engineering of Yunnan Province*, P. R. China. The fungus was grown in shake culture (200 ml per 500-ml conical flask) on a medium consisting of glucose (20 g), potato (200 g; boiled and filtered), KH_2PO_4 (1 g), $MgSO_4 \cdot 7\,H_2O$ (0.5 g), and vitamin B_1 (10 mg) (per liter of H_2O), and incubated for 4 days at 24°. The culture was harvested for further study.

Extraction and Isolation. The culture (20 l) of *Cephalosporium sp*. AL031 was filtered to separate cell and broth. The culture broth was extracted with AcOEt and the extract evaporated. The crude AcOEt extract was subjected to CC *Sephadex LH-20*, 80% MeOH/H_2O): *Fractions* $A_1 - A_8$. *Fr.* A_3 was repeatedly subjected to CC (*Sephadex LH-20*, MeOH): *Fr.* $B_1 - B_{12}$. *Fr.* B_6 was subjected to CC (silica gel (200–300 mesh), $CHCl_3$/MeOH/H_2O 50:10:1 → 20:10:1): **1** (38 mg) and **2** (36 mg). Separation of *Fr.* B_8 by CC (silica gel (300–400 mesh), $CHCl_3$/MeOH/H_2O 70:10:1) yielded compound **3** (33 mg). Compound **4** (32 mg) was obtained from *Fr.* B_{10} and purified by the procedure reported for **3**.

*(2*E*,4*E*)-5-[(3*S*)-5-Acetyl-8-(β-*D*-glucopyranosyloxy)-3,4-dihydro-6-hydroxy-1-oxo-1*H*-2-benzopyran-3-yl]penta-2,4-dienal* (**1**): Yellowish amorphous solid (38 mg). $[\alpha]_D^{20} = +63$ ($c = 0.1$, MeOH). UV (MeOH): 220 (4.18), 268 (4.36), 303 (3.23). CD: 237 (−1.6), 272 (+3.3). IR (KBr): 3418, 2817, 2732, 1720, 1688, 1672, 1629, 1603, 1589, 1510, 1253, 1120, 1082, 1022, 891. ^1H- and ^{13}C-NMR: *Table 1*. HR-FAB-MS (pos.): 465.1391 ($[M+H]^+$, $C_{22}H_{25}O_{11}^+$; calc. 465.1395).

*(2*E*,4*E*)-5-[(3*S*)-5-Acetyl-8-(β-*D*-glucopyranosyloxy)-3,4-dihydro-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl]penta-2,4-dienal* (**2**): Yellowish amorphous solid (36 mg). $[\alpha]_D^{20} = +68$ ($c = 0.1$, MeOH). UV (MeOH): 222 (4.09), 267 (4.28), 303 (3.31). CD: 237 (−2.1), 271 (+3.6). IR (KBr): 3403, 2813, 2738, 1717, 1682, 1670, 1636, 1601, 1577, 1519, 1259, 1128, 1089, 1013, 890. ^1H- and ^{13}C-NMR: *Table 1*. HR-FAB-MS (pos.): 479.1549 ($[M+H]^+$, $C_{23}H_{27}O_{11}^+$; calc. 479.1552).

*(3*S*)-8-(β-*D*-Glucopyranosyloxy)-3-[(1*E*,3*E*,5*E*)-hepta-1,3,5-trienyl]-3,4-dihydro-6-hydroxy-5-methyl-1*H*-2-benzopyran-1-one* (**3**): Yellowish amorphous solid (33 mg). $[\alpha]_D^{20} = +82$ ($c = 0.1$, MeOH). UV (MeOH): 217 (4.07), 269 (3.88), 252 (3.62), 303 (3.31). CD: 239 (−2.8), 272 (+4.2). IR (KBr): 3390, 1668, 1633, 1600, 1542, 1250, 1123, 1080, 1025, 893. ^1H- and ^{13}C-NMR: *Table 2*. HR-FAB-MS (pos.): 449.1807 ($[M+H]^+$, $C_{23}H_{29}O_9^+$; calc. 449.1810).

*(3*S*)-8-[(6-*O*-Acetyl-β-*D*-glucopyranosyl)oxy]-3-[(1*E*,3*E*,5*E*)-hepta-1,3,5-trienyl]-3,4-dihydro-6-methoxy-5-methyl-1*H*-2-benzopyran-1-one* (**4**): Yellowish amorphous solid (32 mg). $[\alpha]_D^{20} = +96$ ($c = 0.1$, MeOH). UV (MeOH): 219 (4.12), 268 (3.01), 253 (3.57), 306 (3.40). CD: 239 (−3.9), 272 (+4.8). IR (KBr): 3382, 1735, 1670, 1635, 1595, 1549, 1247, 1118, 1089, 1020, 889. ^1H- and ^{13}C-NMR *Table 2*. HR-FAB-MS (pos.): 505.2068 ($[M+H]^+$, $C_{26}H_{33}O_{10}^+$; calc. 505.2072).

Acid Hydrolysis of **1**–**4**. Each compound (10 mg), 1N HCl (10 ml), and MeOH (10 ml) were mixed and refluxed for 4 h. The mixture was extracted with AcOEt. After neutralization of the aq. layer, the soln. was filtered and evaporated. Then the residue was examined by paper chromatography (AcOEt/pyridine/H_2O 12:5:4) and compared with standard D-glucose.

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