Japonicumins A–D: Four New Compounds from *Lycopodium japonicum*

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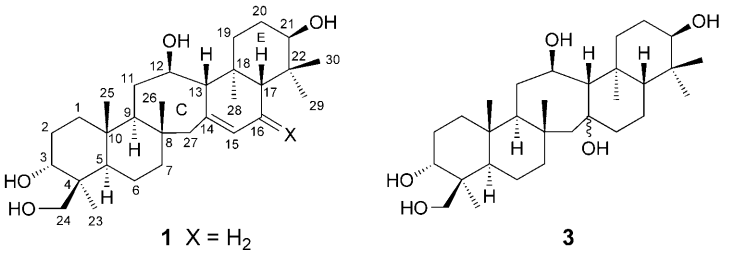
Three new serratane-type triterpenoids, japonicumins A–C (**1**–**3**), as well as a unique, new C_{13} terpenoid, japonicumin D (**4**), were isolated from the dried whole plants of *Lycopodium japonicum*, together with the known compound lycoclavanol (**5**). Their structures were identified by extensive mass-spectrometric and spectroscopic (especially 2D-NMR) experiments. Compounds **1**–**5** exhibited no activity against human-tumor A 549 cells.

Introduction. – The plants of the genus *Lycopodium* are widely used as traditional Chinese herbal medicines for the treatments of arthritic pain, quadriplegia, dysmenorrhea, contusion, and other health problems [1][2]. Previous chemical studies established the occurrence of alkaloids, serratenes, and flavones from this genus, some of them being biologically active [3–11]. Serratenes are an unusual group of naturally occurring, pentacyclic triterpenes with a seven-membered central ring *C*, and they are well-known characteristic constituents of *Lycopodium* plants [5–10]. *Lycopodium japonicum* THUNB., a species of this genus, is widely distributed in the Chinese provinces Guangdong, Guangxi, Yunnan, and Guizhou. It is commonly used as a traditional folk medicine [2], and has been reported to be a source of serratenes [5][11].

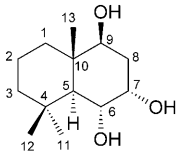
During our search for biologically active secondary metabolites, we analyzed the acetone extract of *J. japonicum* and found four new compounds, japonicumins A–D (**1**–**4**), together with the known serratane-type triterpenoid lycoclavanol (**5**) [12]. In this work, we report their isolation and structure elucidation.

Results and Discussion. – Japonicumin A (**1**) was isolated as a colorless, optically active powder ($[\alpha]_D^{25} = -1.3$ ($c = 0.57$, MeOH)) with the molecular formula $C_{30}H_{50}O_4$, as determined by positive-ion HR-ESI-MS ($[M+Na]^+$ at m/z 497.3605; calc. 497.3606). The IR spectrum of **1** showed absorption bands characteristic of OH (3425) and CH_2 groups (2925 cm^{-1}). The ^{1}H-NMR spectrum (*Table 1*) showed signals for six Me groups at tertiary C-atoms; and the ^{13}C-NMR spectrum (*Table 2*) exhibited signals for 30 C-atoms, including six quaternary ones (one olefinic), eight CH (three oxygenated, one olefinic), ten CH_2 (one oxygenated), and six Me groups. Comparison of the ^{1}H- and ^{13}C-NMR spectroscopic data of **1** with those of the known compound lycoclavanol (**5**) [12], which was also isolated in this study, showed that the two compounds are very similar. The only difference was the replacement of a CH_2(12) signal

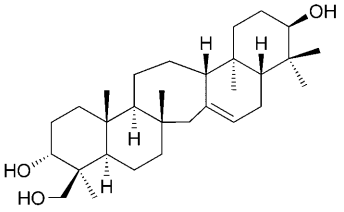


1 X = H_2
2 X = O

3



4



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by an oxygenated CH, as indicated by HMBC correlation from H–C(9) to C(12), and by an ^{1}H,^{1}H-COSY correlation between H–C(12) and both H–C(11) and H–C(13) (*Fig. 1*).

The relative configuration of **1** was derived from the ROESY spectrum. The β-orientation of the 12-OH group was deduced from the correlations of H–C(9)/H–C(12) and H–C(12)/Me(28). The ROESY correlation of H–C(24)/Me(25) suggested that HO–CH_2(24) was β-oriented, that of H–C(3)/H–C(24) established the α-orientation of the 3-OH group, and the 21-OH function was deduced to be in β-position, based on the correlation of H–C(21)/Me(29). These assignments were further supported by a computer-generated 3D structure of **1** made with CHEM 3D Pro (vers. 8.0) using the MM2 force-field for energy minimization (*Fig. 2*). The calculated interatomic H···H distances for the pairs H–C(9)/H–C(12), H–C(24)/Me(25), H–C(3)/H–C(24), and H–C(21)/Me(29) were *ca.* 2.27, 2.40, 2.84, and 2.26 Å, respectively, *i.e.*, below 4 Å. Thus, from the above data, **japonicumin A** (**1**) was established as 3α,12β,21β,24-tetrahydroxyserrat-14-ene[1]).

Japonicumin B (**2**) was isolated as a colorless, optically active powder ($[\alpha]_D^{25} = -8.07$ ($c = 0.55$, MeOH)), with the molecular formula $C_{15}H_{26}O_5$, as derived by HR-ESI-MS ($[M+Na]^+$ at m/z 511.3399; calc. 511.3399). The ^{1}H- and ^{13}C-NMR spectra of **2** (*Tables 1* and *2*, resp.) were very similar to those of **1**, except that the CH_2(16) group was replaced by a C=O function (δ(C) 202.8) in **2**, as revealed by the HMBC correlations between C(16) and the signals for H–C(15), H–C(17), and Me(28), respectively.

The relative configuration of **2** was determined by a ROESY experiment. The ROESY correlations of H–C(9)/H–C(12) and H–C(12)/Me(28) suggested β-orienta-

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[1]) Arbitrary atom numbering for **1**–**4**. The systematic name of the serratane carbon skeleton is (4a*S*,6a*S*,9a*S*,13a*R*,13b*S*,15a*S*,15b*S*)-docosahydro-4,4,6a,10,10,13a,15b-heptamethyl-1*H*-cyclohepta[1,2-*a*:5,4-*a*′]dinaphthalene.

Table 1. *^{1}H-NMR Data of* **1**–**4**. At 400 MHz in $CDCl_3/CD_3OD$; δ in ppm, J in Hz. Arbitrary atom numbering.

	1	**2**	**3**	**4**
H_α–C(1)	1.38–1.42 (*m*)	1.39–1.41 (*m*)	1.50–1.54 (*m*)	1.64–1.68 (*m*)
H_β–C(1)	1.23–1.28 (*m*)	1.26–1.30 (*m*)	1.36–1.42 (*m*)	0.92–0.96 (*m*)
H_α–C(2)	1.51–1.57 (*m*)	1.89–1.93 (*m*)	1.55–1.61 (*m*)	1.48–1.52 (*m*)
H_β–C(2)	1.88–1.94 (*m*)	1.51–1.57 (*m*)	1.85–1.91 (*m*)	1.36–1.42 (*m*)
H_α–C(3)	3.71–3.77 (*m*)	3.70–1.74 (*m*)	3.71–3.77 (*m*)	1.30–1.36 (*m*)
H_β–C(3)				1.16–1.22 (*m*)
H–C(5)	1.29–1.33 (*m*)	1.25–1.31 (*m*)	1.41–1.47 (*m*)	1.31 (*d*, *J* = 11.4)
H_α–C(6)	1.39–1.43 (*m*)	1.50–1.54 (*m*)	1.62–1.68 (*m*)	3.76 (*dd*, *J* = 3.3, 11.4)
H_β–C(6)	1.32–1.38 (*m*)		1.30–1.36 (*m*)	
H_α–C(7)	1.39–1.41 (*m*)	1.39–1.43 (*m*)	1.53–1.57 (*m*)	3.83–3.89 (*m*)
H_β–C(7)	1.18–1.22 (*m*)	1.32–1.36 (*m*)	1.43–1.48 (*m*)	
H_α–C(8)				1.80–1.86 (*m*)
H_β–C(8)				1.63–1.69 (*m*)
H–C(9)	0.68–0.72 (*m*)	0.62–0.68 (*m*)	1.30–1.34 (*m*)	3.43 (*dd*, *J* = 4.5, 12.1)
H_α–C(11)	1.70–1.74 (*m*)	1.89–1.93 (*m*)	1.69–1.73 (*m*)	1.06 (*s*, 3 H)
H_β–C(11)	1.50–1.54 (*m*)	1.58–1.62 (*m*)	1.52–1.58 (*m*)	
H–C(12)	3.68–3.72 (*m*)	3.83–3.89 (*m*)	3.81–3.85 (*m*)	1.18 (*s*, 3 H)
H–C(13)	1.99–2.03 (*m*)	2.50–2.56 (*m*)	1.07 (*d*, *J* = 8.8)	0.84 (*s*, 3 H)
H_α–C(15)	5.28 (*d*, *J* = 5.3)	5.58 (*d*, *J* = 2.9)	1.75–1.81 (*m*)	
H_β–C(15)			1.22–1.28 (*m*)	
H_α–C(16)	1.86–1.92 (*m*, 2 H)		1.42–1.48 (*m*)	
H_β–C(16)			1.39–1.45 (*m*)	
H–C(17)	1.55–1.61 (*m*)	2.51–2.57 (*m*)	2.01 (*d*, *J* = 6.8)	
H_α–C(19)	1.70–1.74 (*m*, 2 H)	1.95–2.01 (*m*, 2 H)	1.88–1.92 (*m*)	
H_β–C(19)			1.58–1.62 (*m*)	
H_α–C(20)	1.52–1.58 (*m*, 2 H)	1.89–1.91 (*m*)	1.90–1.94 (*m*)	
H_β–C(20)		1.58–1.62 (*m*)	1.45–1.51 (*m*)	
H–C(21)	3.36 (overlapped)	3.25 (br. *s*)	3.30 (overlapped)	
Me(23)	0.98 (*s*)	0.97 (*s*)	0.97 (*s*)	
H–C(24)	3.39 (*d*, *J* = 11.3)	3.58 (*d*, *J* = 11.3)	3.38 (*d*, *J* = 11.3)	
	3.61 (*d*, *J* = 11.3)	3.39 (*d*, *J* = 11.3)	3.64 (*d*, *J* = 11.3)	
Me(25)	0.77 (*s*)	0.79 (*s*)	0.78 (*s*)	
Me(26)	0.82 (*s*)	0.92 (*s*)	0.82 (*s*)	
H_α–C(27)	1.55 (*d*, *J* = 11.0)	1.71 (*d*, *J* = 13.0)	1.19 (overlapped)	
H_β–C(27)	2.06 (*d*, *J* = 11.0)	1.55 (*d*, *J* = 13.0)	1.45 (overlapped)	
Me(28)	1.00 (*s*)	1.04 (*s*)	1.16 (*s*)	
Me(29)	0.92 (*s*)	1.15 (*s*)	0.85 (*s*)	
Me(30)	0.91 (*s*)	1.15 (*s*)	0.90 (*s*)	

tion for the 12-OH group. The configurations at the remaining stereogenic centers were fully identical with those derived for compound **1**. Thus, japonicumin B (**2**) was identified as 3α,12β,21β,24-tetrahydroxyserrat-14-en-16-one.

Japonicumin C (**3**) was obtained as a colorless powder (m.p. 199–201°) that was optically active ($[\alpha]_D^{25} = +2.5$ ($c = 0.41$, MeOH)). Its molecular formula was established as $C_{30}H_{52}O_5$ by positive-ion HR-ESI-MS ($[M+Na]^+$ at m/z 515.3700; calc. 515.3712). IR Absorption bands at 3441 and 2933 cm^{-1} indicated OH and CH_2 groups, respec-

Table 2. *^{13}C- NMR Data of* **1**–**4**. At 50 MHz in $CDCl_3/CD_3OD$; δ in ppm. Arbitrary atom numbering.

Position	**1**	**2**	**3**	**4**
1	33.2 (*t*)	33.2 (*t*)	32.0 (*t*)	37.7 (*t*)
2	24.2 (*t*)	25.6 (*t*)	24.3 (*t*)	18.2 (*t*)
3	70.8 (*d*)	70.6 (*d*)	70.1 (*d*)	43.9 (*t*)
4	43.9 (*s*)	43.6 (*s*)	42.5 (*s*)	32.8 (*s*)
5	50.5 (*d*)	50.4 (*d*)	48.7 (*d*)	48.5 (*d*)
6	19.6 (*t*)	19.5 (*t*)	17.4 (*t*)	71.2 (*d*)
7	39.2 (*t*)	40.0 (*t*)	46.2 (*t*)	70.3 (*d*)
8	38.3 (*s*)	39.0 (*s*)	36.4 (*s*)	35.5 (*t*)
9	51.4 (*d*)	52.4 (*d*)	48.7 (*d*)	74.4 (*d*)
10	38.0 (*s*)	38.4 (*s*)	37.2 (*s*)	40.1 (*s*)
11	33.2 (*t*)	33.1 (*t*)	35.5 (*t*)	21.7 (*q*)
12	71.6 (*d*)	71.4 (*d*)	72.6 (*d*)	35.9 (*q*)
13	62.8 (*d*)	63.9 (*d*)	64.7 (*d*)	12.1 (*q*)
14	135.6 (*s*)	160.1 (*s*)	75.1 (*s*)	
15	127.1 (*d*)	130.9 (*d*)	41.5 (*t*)	
16	25.7 (*t*)	202.8 (*s*)	18.7 (*t*)	
17	45.2 (*d*)	59.0 (*d*)	49.1 (*d*)	
18	37.7 (*s*)	43.3 (*s*)	39.5 (*s*)	
19	32.7 (*t*)	30.7 (*t*)	33.4 (*t*)	
20	25.9 (*t*)	25.1 (*t*)	24.8 (*t*)	
21	76.5 (*d*)	76.7 (*d*)	75.1 (*d*)	
22	37.9 (*s*)	37.8 (*s*)	37.2 (*s*)	
23	22.3 (*q*)	22.6 (*q*)	21.0 (*q*)	
24	65.9 (*t*)	65.8 (*t*)	64.7 (*t*)	
25	17.1 (*q*)	17.0 (*q*)	15.9 (*q*)	
26	23.5 (*q*)	23.0 (*q*)	23.1 (*q*)	
27	51.5 (*t*)	50.4 (*t*)	57.1 (*t*)	
28	16.0 (*q*)	16.4 (*q*)	15.9 (*q*)	
29	23.1 (*q*)	28.0 (*q*)	21.6 (*q*)	
30	28.7 (*q*)	22.5 (*q*)	27.9 (*q*)	

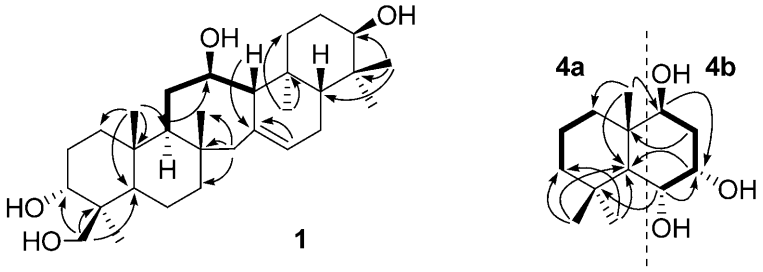

Fig. 1. *Key COSY* (▬) *and HMBC* (→) *correlations for* **1** *and* **4**

tively. The ^{1}H- and ^{13}C-NMR spectra of **3** (*Tables 1* and *2*, resp.) closely resembled those of **1**, except that the two olefinic C-atoms in positions 15 and 14 of **1** were replaced by a CH_2 group (δ(C) 41.5) and an oxygenated quaternary C-atom (δ(C) 75.1), respectively, in **3**. This was confirmed by HMBC correlations from H–C(12) to C(13) and C(14),

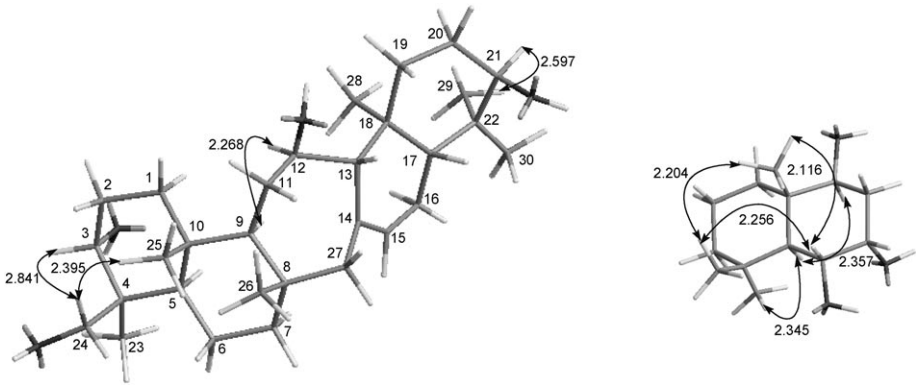

Fig. 2. *Key ROESY correlations and energy-minimized models of* **1** *and* **4** *with selected interatomic distances* (in Å)

from H–C(13) to C(14) and C(15), and from H–C(27) to C(13), C(14), and C(15). The replacement of an OH group at C(14) was evident from the molecular formula.

The configuration of the 14-OH function could theoretically be determined by chemical-transformation methods [13]. However, due to the only minute amounts of material available, this was not possible. Regarding the other stereogenic centers, the ROESY correlation of H–C(12)/Me(28) suggested β-orientation for the 12-OH group, all other configurations of **3** being in complete agreement with those of **1**. Thus, compound **3** was established as 3α,12β,14,21β,24-pentahydroxyserratane.

Japonicumin D (**4**) was obtained as a colorless, optically active powder ($[\alpha]_D^{25} = +33.7$ ($c = 0.35$, MeOH)). Its molecular formula was determined as $C_{13}H_{24}O_3$, based on HR-ESI-MS ($[M+Na]^+$ at m/z 251.1619; calc. 251.1623) and NMR data, with two degrees of unsaturation. The IR absorption at 3424 cm^{-1} indicated the presence of OH groups. The ^{13}C-NMR spectrum of **4** (*Table 2*) displayed the signals of two quaternary C-atoms (δ(C) 40.1, 32.8), four CH (δ(C) 74.4, 71.2, 70.3, 48.5), four CH_2 (δ(C) 43.9, 37.7, 35.5, 18.2), and three Me groups (δ(C) 35.9, 21.7, 12.1). The HMBC spectrum showed correlations of the geminal Me(12) and Me(11) signals at δ(C) 35.9 and 21.7, respectively, with C(3), C(4), and C(5) (δ(C) 43.9, 32.8 and 48.5, resp.). Furthermore, correlations of Me(13) (δ(C) 12.1) with C(1), C(5), and C(10) (δ(C) 37.7, 48.5 and 40.1, resp.) were observed in the HMBC spectrum (*Fig. 1*). In combination with the ^{1}H,^{1}H-COSY correlations of H–C(1)/H–C(2)/H–C(3), fragment **4a** was derived (*Fig. 1*). In addition, the HMBC correlations from H–C(9) (δ(H) 3.43 (*dd*, $J = 4.5, 12.1$ Hz)) to C(8) (δ(C) 70.3) and C(7) (δ(C) 35.5), and from H–C(6) (δ(H) 3.76 (*dd*, $J = 3.3, 11.4$ Hz)) to both C(7) and C(8), along with the ^{1}H,^{1}H-COSY correlations of H–C(6)/H–C(7)/H–C(8)/H–C(9), established fragment **4b**. Furthermore, the strong HMBC correlations from H–C(6) to C(4), and from H–C(13) to C(9) implied that **4a** and **4b** are joined together as shown.

The relative configuration of **4** was determined with the aid of a ROESY spectrum (*Fig. 2*). The ROESY correlations of Me(11)/H–C(5) and H–C(5)/H–C(9) indicated that H–C(5) was α- and 9-OH was β-oriented, respectively. The ROESY correlations of Me(12)/Me(13) and Me(13)/H–C(6) suggested that Me(13) was β- and 6-OH was α-

oriented, respectively. Unfortunately, the ROESY spectrum did not provide sufficient information to elucidate the configuration at C(7). However, if the 7-OH group were β-oriented, one would expect ROESY correlations of H–C(5)/H–C(7) and H–C(7)/H–C(9). These, however, were not detected, not even weak correlations, so, the 7-OH group is most likely α-oriented. From these data, the structure of japonicumin D (**4**) was tentatively established as (1*R**,2*S**,4*S**,4a*S**,8a*S**)-decahydro-4a,8,8-trimethylnaphthalene-1,2,4-triol (systematic name).

Compounds **1**–**5** were tested for their activities towards human-tumor A 549 cells. However, none of these constituents was active in this assay.

Experimental Part

General. Column chromatography (CC) was performed on silica gel (100–200 mesh; *Qingdao Marine Chemical, Inc.*, China) and silica gel *H* (10–40 μm; *Qingdao*); fractions were monitored by TLC, and spots were visualized by spraying with 10% H_2SO_4 in EtOH, followed by heating. UV Spectra: *Shimadzu 210A* double-beam spectrophotometer; λ_{max}(log ε) in nm. Optical rotations: *Horiba SEPA-300* spectropolarimeter IR Spectra: *Bio-Rad FTS-135* spectrophotometer, with KBr discs; in cm^{-1}. 1D- and 2D-NMR Spectra: *Bruker AM-400* and *DRX-500* instruments, resp.; chemical shifts δ in ppm rel. to residual solvent signals, *J* in Hz. ESI-MS and HR-ESI-MS: *VG AutoSpec-3000* spectrometers.

Plant Material. The whole plants of *Lycopodium japonicum* THUNB. were collected in Hekou County, Yunnan Province, China, in 2005, and were authenticated by Prof. *Xiao Cheng*. A voucher specimen was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, P. R. China.

Extraction and Isolation. The air-dried, powdered whole plants of *L. japonica* (2.0 kg) were extracted with acetone (3×15 l) at r.t. After solvent evaporation *in vacuo*, a crude extract (50 g) was obtained, which was directly subjected to column chromatography (CC) on *CHP-20P* gel (*MCI*) eluting with 95% EtOH. The eluate was concentrated in *vacuo*, and the residue (40 g) was repeatedly subjected to CC on silica gel. Further purification on *RP-18* gel yielded **1** (5 mg), **2** (3 mg), **3** (3 mg), **4** (4 mg), and **5** (10 mg).

Japonicumin A (=*3α,12β,21β,24-Tetrahydroxyserrat-14-ene*; **1**). Colorless powder. M.p. 169–171°. UV (MeOH): 207 (0.71). $[\alpha]_D^{25} = -1.3$ ($c = 0.57$, MeOH). IR (KBr): 3424, 2925, 2870, 1626, 1454, 1384, 998. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. HR-ESI-MS (pos.): 497.3605 ($[M+Na]^+$, $C_{30}H_{50}NaO_4^+$; calc. 497.3606).

Japonicumin B (=*3α,12β,21β,24-Tetrahydroxyserrat-14-en-16-one*; **2**). Colorless powder. M.p. 211–212°. UV (MeOH): 203 (0.65). $[\alpha]_D^{25} = -8.07$ ($c = 0.55$, MeOH). IR (KBr): 3441, 2928, 2853, 1667, 1630, 1457, 1385, 1023. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. HR-ESI-MS (pos.): 511.3399 ($[M+Na]^+$, $C_{15}H_{26}NaO_5^+$; calc. 511.3399).

Japonicumin C (=*3α,12β,14,21β,24-Pentahydroxyserratane*; **3**). Colorless powder. M.p. 199–201°. UV (MeOH): 220 (0.06). $[\alpha]_D^{25} = +2.5$ ($c = 0.41$, MeOH). IR (KBr): 3441, 2933, 2871, 1453, 1385, 1028. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. HR-ESI-MS (pos.): 515.3700 ($[M+Na]^+$, $C_{30}H_{52}NaO_5^+$; calc. 515.3712).

Japonicumin D (=*(1*R**,2*S**,4*S**,4a*S**,8a*S**)-Decahydro-4a,8,8-trimethylnaphthalene-1,2,4-triol*; **4**). Colorless powder. M.p. 168–170°. UV (MeOH): 203 (0.23). $[\alpha]_D^{25} + 33.7$ ($c = 0.35$, MeOH). IR (KBr): 3424, 2922, 2853, 1629, 1384, 1064. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. HR-ESI-MS (pos.): 251.1619 ($[M+Na]^+$, $C_{13}H_{24}NaO_3^+$; 251.1623).

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