# New Sesquiterpenoids from *Salvia castanea* DIELS f. *tomentosa*

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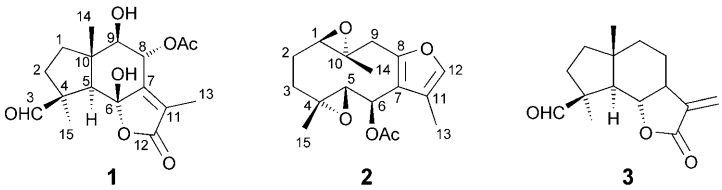
Two new sesquiterpenoids, castanin A (= 4*R**,5*R**,5a*S**,8*S**,8a*R**,8b*R**)-8-formyl-4,5,5a,6,7,8,8a,8b-octahydro-5,8b-dihydroxy-3,5a,8-trimethyl-2-oxo-2*H*-indeno[4,5-*b*]furan-4-yl acetate; **1**) and castanin B (= 1a*S**,6*R**,6a*S**,7a*R**,9a*R**)-1a,2,6,6a,7a,8,9,9a-octahydro-1a,5,7a-trimethylbisoxireno[4,5 : 8,9]cyclodeca[1,2-*b*]furan-6-yl acetate; **2**) were isolated from the aerial parts of *Salvia castanea* DIELS f. *tomentosa*, together with two known compounds, oplophanone and 1*β*,6*α*-dihydroxyeudesm-4(14)-ene. Their structures were elucidated by spectroscopic analyses and, in the case of **2**, also by X-ray crystallography. Castanin A (**1**) represents a novel sesquiterpenoid, with a contracted ring *A*, derived from eudesmanolide. A possible biogenetic pathway is proposed.

**1. Introduction.** – *Salvia* is the largest genus in the family Labiatae, and is widely distributed throughout the world [1]. Many species of this genus are being used as traditional drugs in China [2]. The plants belonging to *Salvia* are known to be rich sources of diterpenoids, especially abietane and clerodane diterpenoids [2–4]. *S. castanea* DIELS f. *tomentosa*, which grows naturally in the southwest of China, has not been chemically investigated before [5]. As a part of our investigations on the chemical constituents of *Salvia* species [6], we isolated two new compounds, castanin A (**1**) and B (**2**)[1])) from the aerial parts of *S. castanea*, together with the two known compounds oplophanone [7] and 1*β*,6*α*-dihydroxyeudesm-4(14)-ene [8].




**2. Results and Discussion.** – Castanin A (**1**) was isolated as a colorless powder. Its molecular formula was determined as $C_{17}H_{22}O_7$ by HR-ESI-MS (*m/z* 361.1255 ([*M* + Na]$^+$, calc. 361.1263)). The IR spectrum of **1** indicated the presence of OH (3407), *α*,*β*-unsaturated *γ*-lactone (1727), and AcO (1763 cm$^{-1}$) functions. The NMR data indicated that **1** contained an AcO group, an *α*,*β*-unsaturated *γ*-lactone, an aldehyde

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

function, three Me, two $CH_2$, and three CH groups (including two oxygenated ones), as well as three quaternary C-atoms (including one dioxygenated one).

Considering the characteristic $^{13}$C-NMR signals at $\delta$(C) 55.4 (*d*) due to C(5), two Me signals at $\delta$(C) 15.7 and 21.0, assignable to Me(14) and Me(15), together with the signals for an $\alpha,\beta$-unsaturated $\gamma$-lactone at $\delta$(C) 154.5 (*s*, C(7)), 129.2 (*s*, C(11)), and 170.8 (*s*, C(12)), compound **1** was initially presumed to be an eudesmanolide [8][10]. However, we then realized that **1** obviously differed from classical eudesmanolide sesquiterpenoids in lacking a methine group (two methines arising from C(4) and C(5) are present in eudesmanolides) and having an additional quaternary C-atom in the high-field region of the $^{13}$C-NMR spectrum. A comparison of the NMR spectroscopic data of **1** with those of saussureal (**3**) suggested that they possessed the same rearranged eudesmanolide skeleton with a contracted ring *A* [9].

Analysis of the $^1$H,$^1$H-COSY spectrum of **1** led to the identification of a $CH_2CH_2$ fragment. All four H-atoms assignable to these two $CH_2$ groups were correlated with C(4) and C(10) in the HMBC spectrum. So, these two $CH_2$ groups were ascribed to C(1) and C(2). The HMBC correlations between the aldehyde H-atom at $\delta$(H) 9.45 (br. *s*, 1 H) and C(4), C(5), and C(15) indicated that the CHO group involved C(3). Ring *C* was found to be present as an $\alpha,\beta$-unsaturated $\gamma$-lactone, as discussed above. The HMBC correlations (*Fig. 1,a*) between the Me group at $\delta$(H) 1.87 (br. *s*, 3 H) and C(7) at $\delta$(C) 154.5 (*s*), C(11) at 129.2 (*s*), and C(12) at 170.8 (*s*) suggested that this Me group corresponded to C(13).

The signals for C(6) at $\delta$(C) 106.0 (*s*), C(8) at 70.3 (*d*), and C(9) at 78.8 (*d*) in ring *B* of **1** all indicated a higher oxidation level compared with saussureal (**3**). The HMBC correlations of the oxygenated methine H-atom at $\delta$(H) 5.78 (*d*, $J$ = 4.2 Hz, 1 H) with C(6) at $\delta$(C) 106.0 (*s*), C(7) at 154.5 (*s*), and C(10) at 49.5 (*s*) indicated that this resonance had to be assigned to H–C(8). The resonance at $\delta$(H) 3.62 (*d*, $J$ = 4.2 Hz, 1 H) was assigned to H–C(8), and, H–C(9) was located from its HMBC correlations with both C(8) and C(14) (*Fig. 1,a*). An OH group at $\delta$(H) 6.24 (*s*, 1 H) was attached at the 6-position, based on its HMBC correlations with C(5) and C(6). The C=O signal of the AcO group at $\delta$(C) 171.1 (*s*) was correlated with H–C(8), which indicated that this group was located at the 8-position.

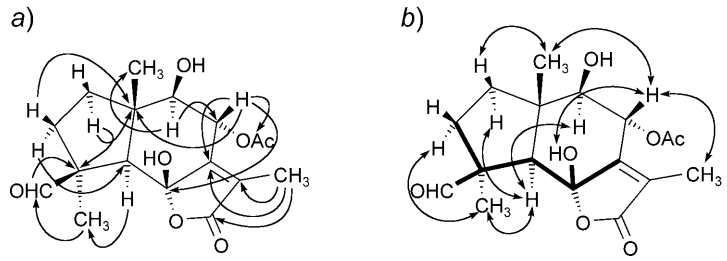


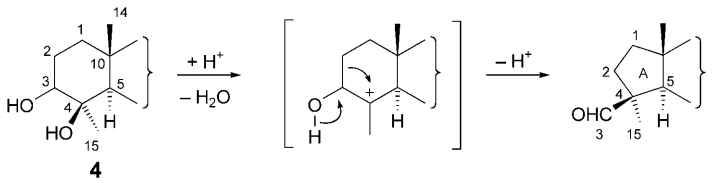

Fig. 1. *Selected* a) *HMBC and* b) *NOE correlations for* **1**

The relative configuration of **1** was established on the basis of a ROESY experiment. ROESY Correlations between H–C(5)/$H_\alpha$–C(1), $H_\beta$–C(1)/Me(14), and $H_\alpha$–C(2)/Me(15) indicated that the angular Me group at C(10) was $\beta$-oriented, while Me(15) and H–C(5) were both $\alpha$-oriented. Furthermore, NOE correlations for

H–C(5)/H–C(9), Me(14)/H–C(8), and H–C(8)/6-OH indicated $\beta$-orientation for both H–C(8) and 6-OH, as well as $\alpha$-orientation for H–C(9) (*Fig. 1,b*). Accordingly, the structure of castanin A (**1**) was established as (4*R**,5*R**,5a*S**,8*S**,8a*R**,8b*R**)-8-formyl-4,5,5a,6,7,8,8a,8b-octahydro-5,8b-dihydroxy-3,5a,8-trimethyl-2-oxo-2*H*-indeno-[4,5-*b*]furan-4-yl acetate. The absolute configuration of this metabolite remains to be determined.

Compound **1** is a novel ring-*A* contracted sesquiterpenoid. To the best of our knowledge, it is only the second example of a sesquiterpenoid with this kind of rearranged *A*/*B* system [9]. From a biogenetic point of view, we propose that the precursor of **1** is an eudesmanolide derivative such as **4**, which could undergo a pinacol-type ring contraction (*Scheme*).

Scheme. *Plausible Biogenetic Pathway Leading to* **1**




Castanin B (**2**) was obtained in the form of colorless crystals from acetone. The molecular formula $C_{17}H_{22}O_5$ was derived by HR-FAB-MS (*m*/*z* 306.1544 ($M^+$, calc. 306.1488)) and $^{13}$C-NMR spectroscopy. The NMR data were in agreement with a 1,10:4,5-diepoxyglechomafuran skeleton, as deduced from the characteristic signals at $\delta$(C) 66.0 (*d*, C(1)), 61.9 (*s*, C(4)), 63.7 (*d*, C(5)), 59.6 (*s*, C(10)), 117.8 (*s*, C(7)), 148.5 (*s*, C(8)), 121.5 (*s*, C(11)), and 137.6 (*d*, C(12)) [10–12]. A detailed comparison of the NMR data of **2** with those of 1$\beta$,10$\alpha$:4$\alpha$,5$\beta$-diepoxy-glechomafuran indicated that they were closely related, except for the appearance of an AcO group in **2** [11]. This AcO group was located at C(6) on the basis of HMBC correlations between H–C(6) at $\delta$(H) 6.48 (br. *s*, 1 H) and C(5) at $\delta$(C) 63.7 (*d*), C(7) at 117.8 (*s*), C(8) at 148.5 (*s*), and the AcO C=O group at $\delta$(C) 169.2 (*s*).

The relative configuration of **2** was established by single-crystal X-ray analysis (*Fig. 2*), which established the $\alpha$-orientation for H–C(1), H–C(5), and H–C(6), and the $\beta$-orientation for Me(14) and Me(15), respectively.

We tried to determined the prevailing conformation of **2** in ($D_6$)acetone solution by means of ROESY experiments. However, the ten-membered ring of **2** was found to be conformationally very flexible. Therefore, the ROESY information alone was insufficient to unambiguously determine the relative configurations at the stereogenic centers. Correlations between Me(14)/$H_\beta$–C(2), Me(14)/$H_\beta$–C(3), and Me(15)/$H_\beta$–C(3) indicated $\beta$-orientation for Me(14) and Me(15), in accord with the X-ray data; and H–C(1) and H–C(5) were found to be $\alpha$-oriented, based on ROESY correlations between H–C(1)/H–C(5) and H–C(1)/$H_\alpha$–C(9). Accordingly, castanin B (**2**) was identified as 1$\beta$,10$\alpha$:4$\alpha$,5$\beta$-diepoxy-6$\beta$-acetoxy-glechomafuran (= (1a*S**,6-*R**,6a*S**,7a*R**,9a*R**)-1a,2,6,6a,7a,8,9,9a-octahydro-1a,5,7a-trimethylbisoxireno[4,5:8,9]-cyclodeca[1,2-*b*]furan-6-yl acetate).

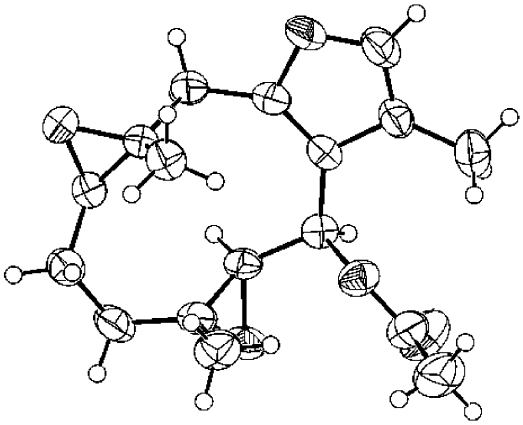


Fig. 2. *X-Ray crystal structure of* **2**

## Experimental Part

*General.* TLC: on silica-gel plates; visualization by spraying with 10% $H_2SO_4$ in EtOH followed by heating. Column chromatography (CC) was performed on silica gel (200–300 mesh, 10–40 µm; *Qingdao Marine Chemical Inc.*), *Lichroprep RP-18* (43–63 µm; *Merck*), and *Sephadex LH-20* (*Pharmacia*). M.p.: *Kofler* apparatus; uncorrected. UV/VIS Spectra: *UV-2401 PC* spectrophotometer; $\lambda_{max}$ (log $\varepsilon$) in nm. Optical rotations: *Horiba SEPA-300* polarimeter. IR Spectra: *Bio-Rad FTS-135* spectrometer, KBr pellets; in $cm^{-1}$. $^1H$- and $^{13}C$-NMR Spectra: *Bruker AM-400* spectrometer (at 400 and 100 MHz, resp.), $\delta$ in ppm, $J$ in Hz. 2D-NMR spectra were recorded on a *Bruker DRX-500* instrument. FAB- and EI-MS: *VG Auto Spec-3000* spectrometer; in $m/z$. ESI- and HR-ESI-MS: *API Qstar Pulsar* instrument.

*Plant Material*. Plants of *Salvia castanea* DIELS f. *tomentosa* were collected in Lijiang, Yunnan province, in July 2000, and were identified by Prof. *Xi-Wen Li*, Kunming institute of Botany, Chinese Academy of Sciences. A voucher specimen (No. 200098) was deposited at the Kunming Institute of Botany, Chinese Academy of Sciences, P. R. China.

*Extraction and Isolation.* The dried and powdered aerial parts (4.1 kg) of *S. castanea* were extracted with acetone for 24 h at r.t. (3 × 10 l). The solvent was removed under vacuum, and the resulting gummy material was subjected to CC (*DM-130* porous resin; MeOH/$H_2O$ 1:1 and 9:1). The residue of the 9:1 fraction was partitioned between $H_2O$ and AcOEt (2 l). The org. extract (56 g dry weight) was subjected to CC ($SiO_2$; petroleum ether/acetone 1:0 → 1:1): Four fractions (Fr.). *Fr. 1* was re-subjected to CC ($SiO_2$; petroleum ether/$CHCl_3$/acetone 80:15:5) to yield **2** (2.6 g) and 1$\beta$,6$\alpha$-dihydroxyeudesm-4(14)-ene (12 mg). *Fr. 2* was purified by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1) to afford **1** (60 mg) and oplophanone (5 mg).

*Castanin A* (= *4*R*,*5*R*,*5a*S*,*8*S*,*8a*R*,*8b*R*)*-8-Formyl-4,5,5a,6,7,8,8a,8b-octahydro-5,8b-dihydroxy-3,5a,8-trimethyl-2-oxo-2*H*-indeno[4,5-*b*]furan-4-yl Acetate*; **1**). Colorless powder. UV (MeOH): 216.2 (3.98). $[\alpha]^{20}_D = +53.0$ ($c = 0.24$, MeOH). IR (KBr): 3407, 2968, 1763, 1727, 1636, 1428, 1254, 1124, 1089, 1053, 946. $^1H$-NMR (400 MHz, ($D_6$)acetone): 1.29–1.31 (*m*, $H_\alpha$–C(1)); 1.51 (br. *s*, Me(14)); 1.53 (br. *s*, Me(15)); 1.73–1.75 (*m*, $H_\beta$–C(1)); 1.77–1.78 (*m*, $H_\alpha$–C(2)); 1.87 (br. *s*, Me(13)); 1.97 (br. *s*, H–C(5)); 2.03 (br. *s*, AcO); 2.08–2.09 (*m*, $H_\beta$–C(2)); 3.62 (*dd*, $J = 7.6$, 4.2, H–C(9)); 4.44 (*d*, $J = 7.6$, 9-OH); 5.78 (*d*, $J = 4.2$, H–C(8)); 6.24 (br. *s*, 6-OH); 9.45 (br. *s*, CHO). $^{13}C$-NMR (100 MHz, ($D_6$)acetone): 8.8 (*q*, C(13)); 15.7 (*q*, C(14)); 21.0 (*q*, C(15)); 21.1 (*q*, *Me*CO); 34.4 (*t*, C(2)); 40.5 (*t*, C(1)); 49.5 (*s*, C(10)); 53.3 (*s*, C(4)); 55.4 (*d*, C(5)); 70.3 (*d*, C(8)); 78.8 (*d*, C(9)); 106.0 (*s*, C(6)); 129.2 (*s*, C(11)); 154.5 (*s*, C(7)); 170.8 (*s*, C(12)); 171.4 (*s*, Me*C*O); 203.9 (*d*, C(3)). EI-MS: 338 (3, $M^+$), 320 (5), 291 (100), 278 (14), 260 (18), 231 (70), 221 (48), 204 (21), 189 (22), 161 (22), 123 (22), 109 (31), 95 (56), 67 (37). HR-ESI-MS: 361.1255 ($[M + Na]^+$, $C_{17}H_{22}O_7Na^+$; calc. 361.1263).

*Castanin B* (**2**). Colorless crystals. M.p. 133.5–135° (acetone). UV ($CHCl_3$): 219.8 (3.83). $[\alpha]^{20}_D = -135.7$ ($c = 0.41$, MeOH). IR (KBr): 2975, 2933, 1743, 1622, 1559, 1432, 1390, 1224, 1110, 1018, 938, 818. $^1H$-NMR (400 MHz, $CDCl_3$): 1.26–1.31 (*m*, $H_\alpha$–C(3)); 1.36 (br. *s*, Me(14)); 1.46–1.48 (*m*, $H_\alpha$–C(2)); 1.47 (br. *s*, Me(15)); 1.90 (br. *s*, Me(13)); 2.03 (br. *s*, 6-AcO); 2.09–2.12 (*m*, $H_\beta$–C(2)); 2.16–2.21 (*m*, $H_\beta$–C(3)); 2.68 (*d*, $J = 16.4$, $H_\alpha$–C(9)); 3.03 (br. *s*, H–C(5)); 3.37 (*dd*, $J = 16.4$, $H_\beta$–C(9)); 2.80 (*d*, $J = 11.1$, H–C(1)); 6.48 (br. *s*, H–C(6)); 7.04 (*s*, H–C(12)). $^{13}C$-NMR (100 MHz, $CDCl_3$): 9.0 (*q*, C(13)); 17.8 (*q*, C(15)); 18.2 (*q*, C(14)); 20.9

(*q*, *Me*CO); 23.1 (*t*, C(2)); 37.6 (*t*, C(3)); 37.7 (*t*, C(9)); 59.6 (*s*, C(10)); 61.9 (*s*, C(4)); 63.7 (*d*, C(5)); 65.0 (*d*, C(6)); 66.0 (*d*, C(1)); 117.8 (*s*, C(7)); 121.5 (*s*, C(11)); 137.6 (*d*, C(12)); 148.5 (*s*, C(8)); 169.2 (*s*, Me*C*O). EI-MS: 306 (38, $M^+$), 291 (3), 247 (6), 203 (42), 175 (46), 165 (58), 159 (49), 147 (37), 137 (60), 124 (100), 123 (64), 95 (27). HR-FAB-MS: 307.1544 ($[M + H]^+$, $C_{17}H_{23}O_5^+$; calc. 307.1546).

*X-Ray Crystal Structure of Compound* **2**. Colorless, transparent needles, 0.10 × 0.30 × 0.50 mm; $C_{17}H_{22}O_5$, $M_r$ 306.36 g/mol; crystal system: orthorhombic, space group *P*2(1); unit-cell dimensions: $a = 10.370$ (1), $b = 8.311$ (1), $c = 10.938$ (1) Å; $V = 812.97$ (9) Å$^3$; $Z = 2$; $D_x = 1.219$ g/cm$^3$. The crystallographic data for **2** have been deposited with the *Cambridge Crystallographic Data Centre* (*CCDC*) as supplementary publication number CCDC-252456. The data can be obtained, free of charge, *via* the internet (http:// www. ccdc.com.ac.uk/ conts/retrieving.html), fax (+ 44-1223-336033), or e-mail (data_request@ccdc.cam.ac.uk).

## REFERENCES


[1] C. Y. Wu, H. W. Li, *Acta Bot. Yunnan.* **1982**, *4*, 97.
[2] X. L. Liu, X. M. Wang, *Zhongguozhongyaozazhi* **1996**, *21*, 73.
[3] J. M. Chang, N. S. Du, *Chin. Tradit. Patent Med.* **1999**, *21*, 480.
[4] H. M. Chang, K. Y. Chui, C. M. Lee, H. L. Sham, H. Wang, *J. Org. Chem.* **1973**, *55*, 3537.
[5] Kunming Institute of Botany, Chinese Academy of Sciences, in 'Flora Yunnannica' Science Press, Beijing, 1977, Vol. 1, p. 672.
[6] G. Xu, L. Y. Peng, X. M. Niu, Q. S. Zhao, R. T. Li, H. D. Sun, *Helv. Chim. Acta* **2004**, *87*, 949.
[7] G. Gonzalez, J. B. Barrera, A. C. Yanes, J. G. Diaz, E. M. Rodriguez, *Phytochemistry* **1989**, *28*, 2520.
[8] W. C. Su, J. M. Fang, *Phytochemistry* **1995**, *39*, 603.
[9] K. K. Talwar, I. P. Singh, P. S. Kalsi, *Phytochemistry* **1992**, *31*, 336.
[10] N. Goren, A. Ulubelen, *Phytochemistry* **1987**, *26*, 2585.
[11] A. G. Gonźalez, T. A. Grillo, A. G. Ravelo, J. G. Luis, M. L. Rodriguez, J. Calle, A. Rivera, *J. Nat. Prod.* **1989**, *52*, 1307.
[12] M. Gavagnin, E. Mollo, F. Castelluccio, A. Crispino, G. Cimino, *J. Nat. Prod.* **2003**, *66*, 1517.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