

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

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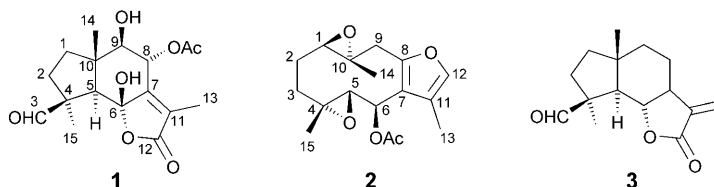
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Two new sesquiterpenoids, castanin A (= 4*R**,5*R**,5*aS**,8*S**,8*aR**,8*bR**)-8-formyl-4,5,5*a*,6,7,8,8*a*,8*b*-octahydro-5,8*b*-dihydroxy-3,5*a*,8-trimethyl-2-oxo-2*H*-indeno[4,5-*b*]furan-4-yl acetate; **1**) and castanin B (= 1*aS**,6*R**,6*aS**,7*aR**,9*aR**)-1*a*,2,6,6*a*,7*a*,8,9,9*a*-octahydro-1*a*,5,7*a*-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 C₁₇H₂₂O₇ 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 CH₂, and three CH groups (including two oxygenated ones), as well as three quaternary C-atoms (including one dioxygenated one).

Considering the characteristic ¹³C-NMR signals at δ (C) 55.4 (*d*) due to C(5), two Me signals at δ (C) 15.7 and 21.0, assignable to Me(14) and Me(15), together with the signals for an α,β -unsaturated γ -lactone at δ (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 ¹³C-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 ¹H,¹H-COSY spectrum of **1** led to the identification of a CH₂CH₂ fragment. All four H-atoms assignable to these two CH₂ groups were correlated with C(4) and C(10) in the HMBC spectrum. So, these two CH₂ groups were ascribed to C(1) and C(2). The HMBC correlations between the aldehyde H-atom at δ (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 α,β -unsaturated γ -lactone, as discussed above. The HMBC correlations (*Fig. 1, a*) between the Me group at δ (H) 1.87 (*br. s*, 3 H) and C(7) at δ (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 δ (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 δ (H) 5.78 (*d*, *J* = 4.2 Hz, 1 H) with C(6) at δ (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 δ (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 δ (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 δ (C) 171.1 (*s*) was correlated with H–C(8), which indicated that this group was located at the 8-position.

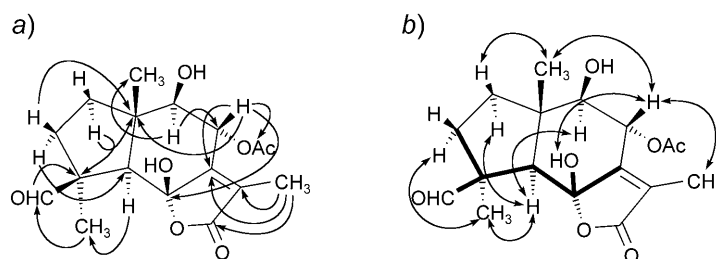


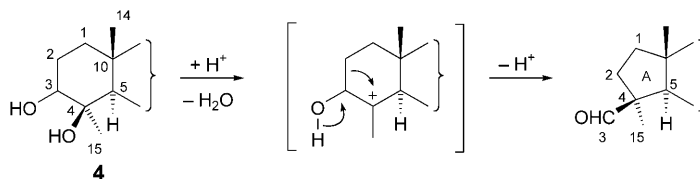
Fig. 1. Selected a) HMBC and b) NOE correlations for **1**

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

H–C(5)/H–C(9), Me(14)/H–C(8), and H–C(8)/6-OH indicated β -orientation for both H–C(8) and 6-OH, as well as α -orientation for H–C(9) (Fig. 1, b). Accordingly, the structure of castanin A (**1**) was established as (4*R**,5*R**,5*aS**,8*S**,8*aR**,8*bR**)-8-formyl-4,5,5*a*,6,7,8,8*a*,8*b*-octahydro-5,8*b*-dihydroxy-3,5*a*,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).

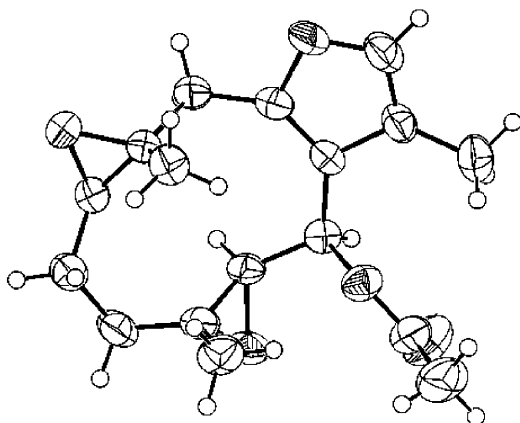
Scheme. Plausible Biogenetic Pathway Leading to **1**



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 β ,10 α :4 α ,5 β -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 α -orientation for H–C(1), H–C(5), and H–C(6), and the β -orientation for Me(14) and Me(15), respectively.

We tried to determine 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 β -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 α -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 β ,10 α :4 α ,5 β -diepoxy-6 β -acetoxy-glechomafuran (= (1*aS**,6-*R**,6*aS**,7*aR**,9*aR**)-1*a*,2,6,6*a*,7*a*,8,9,9*a*-octahydro-1*a*,5,7*a*-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% H₂SO₄ 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; λ_{max} (log ε) in nm. Optical rotations: *Horiba SEPA-300* polarimeter. IR Spectra: *Bio-Rad FTS-135* spectrometer, KBr pellets; in cm⁻¹. ¹H- and ¹³C-NMR Spectra: *Bruker AM-400* spectrometer (at 400 and 100 MHz, resp.), δ 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/H₂O 1:1 and 9:1). The residue of the 9:1 fraction was partitioned between H₂O and AcOEt (2 l). The org. extract (56 g dry weight) was subjected to CC (SiO₂; petroleum ether/acetone 1:0 → 1:1): Four fractions (Fr.). Fr. 1 was re-subjected to CC (SiO₂; petroleum ether/CHCl₃/acetone 80:15:5) to yield **2** (2.6 g) and 1β,6α-dihydroxyeudesm-4(14)-ene (12 mg). Fr. 2 was purified by CC (*Sephadex LH-20*; CHCl₃/MeOH 1:1) to afford **1** (60 mg) and oplophanone (5 mg).

Castanin A (= 4R*,5R*,5aS*,8S*,8aR*,8bR*)-8-Formyl-4,5,5a,6,7,8,8a,8b-octahydro-5,8b-dihydroxy-3,5a,8-trimethyl-2-oxo-2H-indeno[4,5-b]furan-4-yl Acetate; **1**). Colorless powder. UV (MeOH): 216.2 (3.98). [α]_D²⁰ = +53.0 (*c* = 0.24, MeOH). IR (KBr): 3407, 2968, 1763, 1727, 1636, 1428, 1254, 1124, 1089, 1053, 946. ¹H-NMR (400 MHz, (D₆)acetone): 1.29–1.31 (*m*, H_α-C(1)); 1.51 (*br. s*, Me(14)); 1.53 (*br. s*, Me(15)); 1.73–1.75 (*m*, H_β-C(1)); 1.77–1.78 (*m*, H_α-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_β-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). ¹³C-NMR (100 MHz, (D₆)acetone): 8.8 (*q*, C(13)); 15.7 (*q*, C(14)); 21.0 (*q*, C(15)); 21.1 (*q*, MeCO); 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*, MeCO); 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]⁺, C₁₇H₂₂O₇Na⁺; calc. 361.1263).

Castanin B (**2**). Colorless crystals. M.p. 133.5–135° (acetone). UV (CHCl₃): 219.8 (3.83). [α]_D²⁰ = –135.7 (*c* = 0.41, MeOH). IR (KBr): 2975, 2933, 1743, 1622, 1559, 1432, 1390, 1224, 1110, 1018, 938, 818. ¹H-NMR (400 MHz, CDCl₃): 1.26–1.31 (*m*, H_α-C(3)); 1.36 (*br. s*, Me(14)); 1.46–1.48 (*m*, H_α-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_β-C(2)); 2.16–2.21 (*m*, H_β-C(3)); 2.68 (*d*, *J* = 16.4, H_α-C(9)); 3.03 (*br. s*, H-C(5)); 3.37 (*dd*, *J* = 16.4, H_β-C(9)); 2.80 (*d*, *J* = 11.1, H-C(1)); 6.48 (*br. s*, H-C(6)); 7.04 (*s*, H-C(12)). ¹³C-NMR (100 MHz, CDCl₃): 9.0 (*q*, C(13)); 17.8 (*q*, C(15)); 18.2 (*q*, C(14)); 20.9

(*q*, MeCO); 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*, MeCO). 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]*⁺, C₁₇H₂₃O₅⁺; calc. 307.1546).

X-Ray Crystal Structure of Compound 2. Colorless, transparent needles, 0.10 × 0.30 × 0.50 mm; C₁₇H₂₂O₅, *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) Å³; *Z* = 2; *D*_x = 1.219 g/cm³. 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).

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