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Langduin C, a novel dimeric diterpenoid from the roots of *Euphorbia fischeriana*

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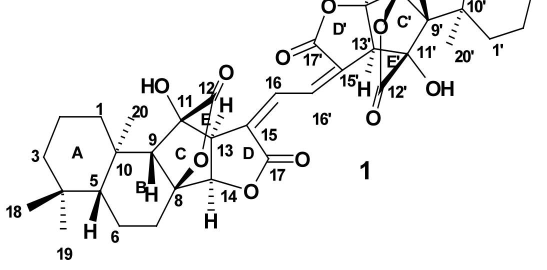
Abstract—Langduin C, a novel dimeric diterpenoid, was isolated from the roots of *Euphorbia fischeriana* and its structure was established by spectral data and single-crystal X-ray diffraction analysis. © 2002 Elsevier Science Ltd. All rights reserved.

Euphorbia fischeriana Steud (Euphorbiaceae) is a perennial herbaceous plant with a milky juice, distributed mainly in North China. Early chemical investigation showed that the plant contains diterpenoids, triterpenoids and steroids including two *ent*-abietane diterpenoids, jolkinolide A and B, which exhibit significant antitumour activities against several tumour lines such as Sarcoma 180 and Ehrlich ascites carcinoma in mice.[1–3] As part of a fundamental study on Chinese medicinal plants, we have re-investigated this plant and reported previously on the isolation of two new tiglane and two new *ent*-abietane diterpenoids along with five known *ent*-abietane diterpenoids, jolkinolides A and B, 17-hydroxyjolkinolides A and B, and *ent*-11β-hydroxyabieta-8(14),13(15)-dien-16,12β-olide, from the plant.[4,5] We have recently found that jolkinolide B induces neuroendocrine differentiation of human prostate LNCaP cancer cell line.[6] Our continuing chemical study on this plant led to the isolation of a novel symmetrical dimeric diterpenoid named langduin C (**1**, 6 mg) from the ether soluble fraction of the ethanol extracts by repeated chromatography over silica gel. This paper reports the isolation and structural elucidation of langduin C (**1**).

Langduin C (**1**)[7] has the molecular formula $C_{40}H_{50}O_{10}$ deduced from HRESIMS spectrum (*m*/*z* 713.3298 $[M+Na]^+$ calcd. for $C_{40}H_{50}O_{10}Na$, 713.3302). Its IR spectrum showed the presence of hydroxyl groups (3440 cm^{-1}), lactone carbonyl groups (1740, 1780 cm^{-1}) and double bonds (1630 cm^{-1}). The ^{13}C NMR and DEPT spectra revealed 20 carbons, a half of the total number of carbons in the molecule, consisting of three tertiary methyls, five methylenes, five methines (one oxygenated and one olefinic) and seven quaternary carbons (one olefinic, two lactone carbonyl, and two oxygenated). The ^1H NMR spectral data showed three methyl singlets (δ 0.88, 0.93, 1.25, each s), one doublet for an oxygenated methine (δ 5.25, d) and one singlet for an olefinic proton (δ 7.39, s). From the above ^1H and ^{13}C NMR data together with consideration of its molecular formula, **1** would appear to be a symmetrical dimeric diterpenoid which contains one tertiary hydroxyl, one trisubstituted double bond and two γ-lactones in each part of the molecule. The HMQC and ^1H–^1H COSY spectra indicated the presence of following fragments: $-CH_2CH_2CH_2$, $-CHCH_2CH_2$ and -CH-CH(O)-. All above features could not be accommodated in a symmetrical dimer derived from any of the usual *ent*-abietane diterpenoids found in *Euphorbia* plants. After



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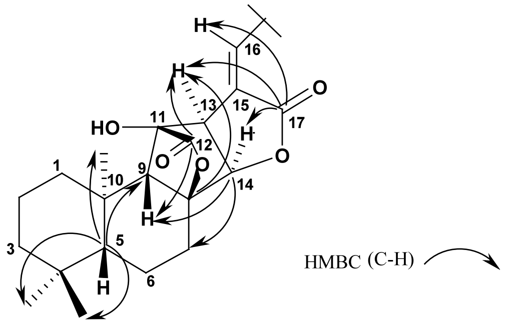

Figure 1. Key HMBC correlations of **1**.

careful investigation of the 2D NMR spectral data, a reasonable structure was proposed for **1**, in which ring C of *ent*-abietane has been reduced from a six- to a five-membered ring, and the C-12 methylene extruded and oxygenated. Assignments of all protons and carbons in **1** can be made by ^1H–^1H COSY, HMQC and HMBC spectra. Important HMBC correlations including C-5 and H-9, H_3-18, H_3-19, H_3-20; C-8 and H-13; C-12 and H-9, H-13; C-14 and H-9, H-7; and C-17 and H-13, H-14, H-16 were observed (Fig. 1), consistent with the proposed structure.

The structure of **1** was finally confirmed and its relative stereochemistry was elucidated by X-ray crystallographic analysis (Fig. 2).[8] NOESY correlations (Fig. 3) of **1** were in agreement with the stereochemistry obtained from the X-ray crystallographic analysis.

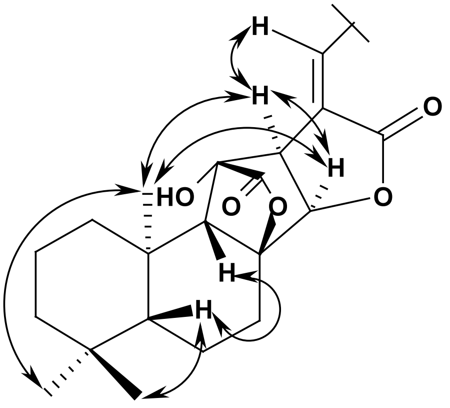

Figure 3. Key NOESY correlations of **1**.

Langduin C (**1**), is a novel symmetrical dimeric diterpenoid with a five-membered ring C instead of the normal six-membered ring C found in the *ent*-abietane skeleton. It is the first example of such a diterpenoid from the *Euphobia* genus. This novel dimer is probably derived from jolkinolide B, a major *ent*-abietane diterpenoids of the plant, by successive oxidative cleavage of ring C and D, rearrangement, lactonization, and dimerization.

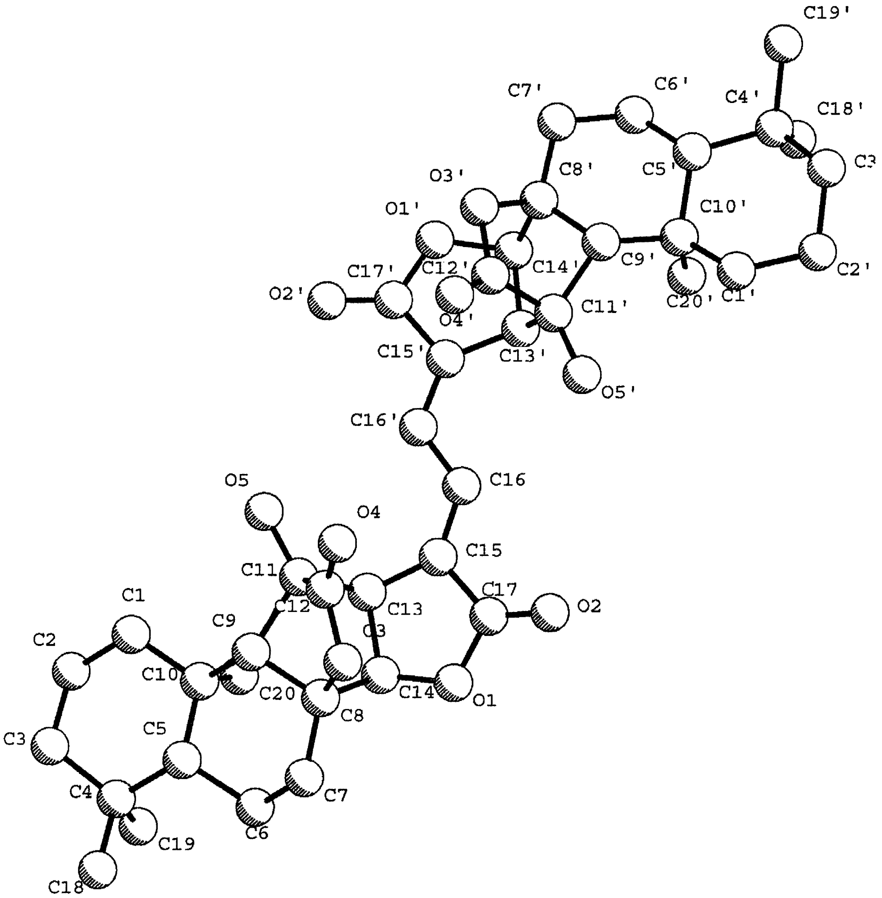

Figure 2. Crystal structure of **1** (hydrogens deleted).

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7. Compound **1**: colourless prisms; mp 195–196°C; HRESIMS m/z 713.3298 $[M+Na]^+$ (calcd for $C_{40}H_{50}O_{10}Na$, 713.3302); IR ν_{max} cm^{-1} (film): 3440 (hydroxy group), 1740, 1780 (lactone carbonyl group), 1630 (double bond); UV ($CHCl_3$): λ_{max} (log ε): 307 (4.24); ^1H NMR (600 MHz, $CDCl_3$, ref. $CHCl_3 = 7.27$ ppm, J/Hz): δ 2.04 (2H, t, $J = 13.2$, 1′α, 1α-H), 1.16 (2H, t, $J = 10.1$, 1′β, 1β-H), 1.60 (2H, m, 2′α, 2α-H), 1.46 (4H, d, $J = 12.1$, 2′β, 2β, 3′α, 3α-H), 1.19 (2H, m, 3′β, 3β-H), 0.99 (2H, d, $J = 11.7$, 5′, 5-H), 1.38 (2H, m, 6′α, 6α-H), 1.90 (2H, d, $J = 14.1$, 6′β, 6β-H), 2.41 (2H, d, $J = 13.9$, 7′α, 7α-H), 1.78 (2H, td, $J = 13.1$, 4.8, 7′β, 7β-H), 2.01 (2H, s, 9′, 9-H), 4.05 (2H, d, $J = 8.6$, 13′, 13-H), 5.25 (2H, d, $J = 8.6$, 14′, 14-H), 7.39 (2H, s, 16′, 16-H), 0.93 (6H, s, 18′, 18-H), 0.88 (6H, s, 19′, 19-H), 1.25 (6H, s, 20′, 20-H); ^{13}C NMR (150 MHz, $CDCl_3$, ref. $CDCl_3 = 76.99$ ppm): δ 40.73 (t, C-1, 1′), 18.01 (t, C-2, 2′), 41.72 (t), 33.04 (s, C-4, 4′), 54.33 (d, C-5, 5′), 18.84 (t, C-6, 6′), 28.41 (t, C-7, 7′), 86.52 (s, C-8, 8′), 69.81 (d, C-9, 9′), 38.12 (s, C-10, 10′), 87.13 (s, C-11, 11′), 176.42 (s, C-12, 12′), 44.52 (d, C-13, 13′), 78.74 (d, C-14, 14′), 133.14 (s, C-15, 15′), 134.51 (d, C-16, 16′), 168.62 (s, C-17, 17′), 33.91 (q, C-18, 18′), 21.54 (q, C-19, 19′), 17.01 (q, C-20, 20′).
8. The crystallographic data for compound **1**: crystal dimension 0.20×0.30×1.00 mm, block colourless crystal, empirical formula $C_{40}H_{50}O_{10}\cdot(C_2H_5OH)_2$, formula weight (not included solvent) 690.83. Crystal system triclinic, space group $P\bar{1}$ (#1), unit cell parameters $a = 6.492(1)$, $b = 9.536(1)$, $c = 18.380(2)$ Å, $\alpha = 77.603(4)$, $\beta = 90.000(5)$, $\gamma = 70.096(5)°$, $V = 1041.63(22)$ Å^3, $Z = 1$, $D_{calcd} = 1.254$ g cm^{-3}, $F(000) = 422$, $\mu = 0.10$ cm^{-1}, $R_f = 0.074$, $R_w = 0.078$ for 2174 reflections. Data were measured at 295 K on a MAC DIP 2030K diffractometer with graphite-monochromated Mo Kα radiation and a 6 kW rotating anode generator.