Seco-Terpenoids and Other Constituents from *Elateriospermum tapos*

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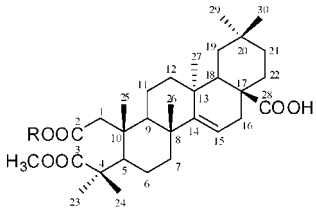
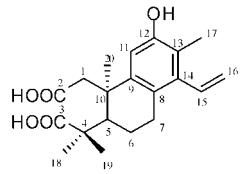
Two new taraxerane triterpenes, 2,3-seco-taraxer-14-ene-2,3,28-trioic acid 2,3-dimethyl ester (**1**) and 2,3-seco-taraxer-14-ene-2,3,28-trioic acid 3-methyl ester (**2**), along with two known triterpenes, hopenol B and aleuritolic acid, and five known flavonoids, putraflavone, kaempferol, sequoiaflavone, amentoflavone, and ginkgetin, were isolated from the leaves of *Elateriospermum tapos*. The stem extract yielded a new cleistanthane diterpene, 2,3-seco-sonderianol (**3**), three known triterpenes, lupeol, lupeol acetate, and 3-acetylaleuritolic acid, and three known diterpenes, yucalexin B-22, yucalexin P-15, and yucalexin P-17. The structures of these compounds were established on the basis of their spectroscopic data. Compound **1** was cytotoxic against NCI-H187 and BC cell lines and also showed *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*.

Elateriospermum tapos Blume (Euphorbiaceae), known in Thailand as "Pra" or "Kra", is a Southeast Asian rainforest tree. Its seeds are poisonous because of their hydrocyanic acid content, but they can be eaten after being cooked or roasted. In Indonesia, the sticky white latex of this plant is used as a wound dressing, and in Sarawak it is applied on the foot as a treatment for cracked sole.[1] A number of triterpenoids, flavonoids, condensed tannins, and cyanogenic glycosides have been identified as constituents of the leaves and stem of this plant.[2,3] We report herein the isolation and structural determination of two new taraxerane triterpenes, 2,3-seco-taraxer-14-ene-2,3,28-trioic acid 2,3-dimethyl ester (**1**) and 2,3-seco-taraxer-14-ene-2,3,28-trioic acid 3-methyl ester (**2**), and one new cleistanthane diterpene, 2,3-seco-sonderianol (*ent*-12-hydroxy-2,3-seco-cleistantha-8,11,13,15-tetraene-2,3-dioic acid, **3**), together with 13 known compounds from the leaves and stem of *E. tapos*.



1 R = CH_3
2 R = H



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Compound **1** was assigned the molecular formula $C_{32}H_{50}O_6$ on the basis of high-resolution ESIMS (observed *m/z* 553.3505 [M + Na]$^+$). The IR spectrum suggested the presence of carboxylic acid (3434 and 1692 cm^{-1}), ester (1729 and 1145 cm^{-1}), and olefinyl (1636 cm^{-1}) moieties. The ^{1}H NMR spectrum showed seven tertiary methyl singlets (δ 0.91, H-30; 0.93, H-27; 0.94, H-29; 0.96, H-26; 1.00, H-25; 1.20, H-23 and H-24) and two carbomethoxy singlets at δ 3.56 and 3.57. An olefinic proton on a trisubstituted double bond appeared as a well-defined doublet of doublets at δ 5.56 (J = 8.0, 3.5 Hz, H-15), suggesting that **1** was a taraxer-14-ene derivative.[4] The ^{13}C NMR spectrum exhibited 32 carbon signals, including those of three carbonyls (δ 172.0, C-2; 179.0, C-28; 179.8, C-3) and a double bond (δ 117.2, C-15; 161.2, C-14). An AB system in the proton spectrum at δ 2.25 (1H, d, J = 18.7 Hz) and 2.35 (1H, d, J = 18.7 Hz) was assigned to the H-1 methylene protons of a 2,3-seco-diacid deriving from a taraxerane triterpene with cleaved A ring. Its NMR data were also compared with those of other 2,3-seco-terpenoids reported from another euphorbiaceous plant, *Excoecaria agallocha*.[5,6] Both acid moieties at C-2 (δ 172.0) and C-3 (δ 179.8) were methylated, as indicated by HMBC cross-peaks between the carbomethoxy singlet at δ 3.57 and C-2, as well as between another carbomethoxy signal at δ 3.56 and C-3. The HMBC spectrum also exhibited correlations of H-1 to C-2, C-5, C-10, and C-25, and both H-23 and H-24 to C-3, C-4, and C-5. Another carboxylic group was determined to be at C-28, on the basis of long-range correlations of this carbonyl carbon at δ 179.0 with H-16, H-18, and H-22. The location of the double bond was confirmed by HMBC correlations of H-15 to C-8 (δ 39.3) and C-13 (δ 37.8) and of both H-16 and H-27 to C-14 (δ 161.2). Therefore, the structure of compound **1** was elucidated as 2,3-seco-taraxer-14-ene-2,3,28-trioic acid 2,3-dimethyl ester.

The molecular formula of compound **2** was determined to be $C_{31}H_{48}O_6$ on the basis of HRESIMS (observed *m/z* 539.3346 [M + Na]$^+$). Its IR spectrum showed nearly identical absorption bands, for carboxylic acid (3433 and 1690 cm^{-1}) and ester moieties (1728 cm^{-1}), to those observed in **1**. The ^{1}H and ^{13}C NMR data of **2** were also very similar to those of **1**. The major difference was the presence of only one carbomethoxy signal at δ 3.52 in the proton spectrum and at δ 178.9 and 51.6 in the carbon spectrum. HMBC correlations of the C-3 carbonyl at δ 178.9 with the carbomethoxy singlet, H-5, H-23, and H-24 established the esterification at this C-3 position. Consequently, the structure of compound **2** was determined as 2,3-seco-taraxer-14-ene-2,3,28-trioic acid 3-methyl ester.

Compound **3** was assigned the molecular formula $C_{20}H_{26}O_5$, according to its [M + Na]$^+$ ion at *m/z* 369.1680 in the HRESIMS. Its IR spectrum exhibited strong carbonyl (1698 cm^{-1}) and O−H stretching (3430 cm^{-1}) bands. The ^{1}H NMR spectrum displayed a phenolic OH singlet at δ 8.87 (1H, 12-OH), as well as a singlet of an aromatic proton located *ortho* to that moiety at δ 6.67 (1H, H-11). Three sets of resonances at δ 6.57 (1H, dd, J = 18.0, 11.4 Hz, H-15), 5.48 (1H, d, J = 11.4 Hz, H-16a), and 5.09 (1H, d, J = 18.0 Hz, H-16b) were characteristic of an AMX terminal vinyl system. Four methyl singlets were observed, including those of an aromatic methyl at δ 2.01 (H-17), a tertiary methyl at δ 1.38 (H-20), and two geminal methyls at δ 1.11 (H-18) and 0.81 (H-19). An AB system at δ 2.56 and 2.33 (each 1H, d, J = 14.6 Hz, H-1a and H-1b), similar to those of the seco-ring A triterpenes **1** and **2**, was also detected. The ^{13}C NMR spectrum, in combination with DEPT experiments, showed the presence of four methyl, four methylene, three methine, and nine quaternary carbons (including two carbonyls). These data indicated that compound **3** was a cleistanthane diterpene very similar to sonderianol, a diterpene isolated from *Croton sonderianus*,[7] with the only difference being

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the C-2/C-3 cleavage of its ring A, producing a 2,3-diacid. HMBC correlations of the methylene H-1 to C-2 carbonyl (δ 171.8) and of H-18 and H-19 methyl protons to C-3 carbonyl (δ 180.6) confirmed the bond fission. The position of the OH group at C-12 was supported by HMBC cross-peaks of the OH proton at δ 8.87 to C-11 (δ 110.1), C-12 (δ 153.1), and C-13 (δ 119.1). The relative stereochemistry of **3** was assumed to be the same as those of sonderianol and other diterpenes isolated from this plant. The structure of **3** was therefore elucidated as *ent*-12-hydroxy-2,3-seco-cleistantha-8,11,13,15-tetraene-2,3-dioic acid and named 2,3-seco-sonderianol.

The hexane extract of the leaves of *E. tapos* also yielded a hopane triterpene, hopenol B,[8] and a taraxerane triterpene, aleuritolic acid,[9] whereas chromatographic separation of the CH_2Cl_2 extract afforded kaempferol[10] and four biflavones: putraflavone,[11] sequoiaflavone,[12] amentoflavone,[12,13] and ginkgetin.[12] Column chromatography (CC) of the hexane extract of its stem gave the triterpenes lupeol, lupeol acetate,[14] and 3-acetylaleuritolic acid.[15] In addition to **3**, the CH_2Cl_2 extract of the stem furnished an *ent*-beyerane diterpene, yucalexin B-22, and two *ent*-pimarane diterpenes, yucalexin P-15 and yucalexin P-17.[16] All of these compounds, with the exception of amentoflavone and lupeol acetate, are reported for the first time from *E. tapos*.

All of the isolated compounds, except kaempferol, were tested for cytotoxicity against three human cancer cell lines: NCI-H187, KB, and BC. Compound **1** was active against NCI-H187 and BC cell lines, with IC_{50} values of 4.65 and 7.08 μg/mL, respectively, while other compounds were inactive at a concentration of 10 μg/mL. Ellipticine, as the positive control, gave IC_{50} values of 0.52, 0.41, and 0.13 μg/mL, respectively, against the three cell lines. The compounds were also assayed for their activity against *M. tuberculosis*, and **1** was shown to exhibit antimycobacterial activity with a MIC of 3.13 μg/mL. The standard drugs isoniazid and kanamycin sulfate exhibited MICs of 0.05 and 1.25 μg/mL, respectively.

Experimental Section

General Experimental Procedures. Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Perkin-Elmer FT IR Spectrum One spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a 500 MHz Varian Unity INOVA or a 300 MHz Bruker Avance DPX-300 NMR spectrometer, using residual solvent as internal standard. HRESIMS spectra were recorded on a Micromass LCT spectrometer. All solvents used for column chromatography were commercial grade and were distilled prior to use. TLC was performed on precoated silica gel 60 F_{254} (Merck), and spots were visualized by spraying with an anisaldehyde/sulfuric acid solution followed by heating.

Plant Material. The leaves and stem of *E. tapos* were collected from Nakorn Si Thammarat Province, Thailand, in March 2004. The plant was identified by one of the authors (R.S.). Voucher specimens (No. RS04031) were deposited at the herbarium of the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand.

Extraction and Isolation. The dried, powdered leaves of *E. tapos* (1.3 kg) were macerated in EtOH (3 × 8 L) at room temperature. Evaporation of the solvent under reduced pressure provided an ethanolic extract, which was further partitioned with hexane (3 × 5 L) and CH_2Cl_2 (3 × 5 L). The hexane fraction (31.8 g) was chromatographed on a silica gel column, eluted with hexane−acetone (1:0 → 0:1), to give nine fractions (L1−L9). Fraction L2 (9.0 g) was separated on a silica gel column, eluted with a hexane−acetone gradient (1:0 → 17:3), to yield hopenol B (93.1 mg). Fraction L4 (4.1 g) was separated by CC, using a hexane−acetone gradient (1:0 → 0:1) as the mobile phase, to give six subfractions (L4a−L4f). Compound **1** (11.3 mg) was obtained as a white powder from subfraction L4d, whereas subfraction L4f, after Sephadex LH20 CC, using CH_2Cl_2−MeOH (2:1) as eluent, afforded aleuritolic acid (12.4 mg). Fraction L6 (1.2 g) was chromatographed, using a gradient of hexane−acetone (9:1 → 0:1), to yield **2** as colorless needles (132.5 mg). The CH_2Cl_2 fraction was subjected to a silica gel column, eluted with a gradient of hexane−acetone (1:0 → 0:1), to give 12 fractions (L10−L21). Putraflavone (93.1 mg) was obtained as a pale yellow solid from fraction L16. Gel filtration chromatography of fractions L15, L17, L18, and L19 on Sephadex LH-20 columns, each one using CH_2Cl_2−MeOH (2:1) as eluent, yielded kaempferol (2.0 mg), sequoiaflavone (10.2 mg), amentoflavone (15.7 mg), and ginkgetin (5.6 mg), respectively.

Powdered stem of the plant (3.8 kg) was extracted successively with hexane, CH_2Cl_2, and MeOH (3 × 5 L) at room temperature; then each solvent was removed under reduced pressure. The hexane extract (19.6 g) was chromatographed on a silica gel column, eluted with a gradient of hexane−acetone (1:0 → 17:3), to yield lupeol (17.0 mg), lupeol acetate (407.8 mg), and 3-acetylaleuritolic acid (37.2 mg). The CH_2Cl_2 extract (19.0 g) was subjected to silica gel CC, eluted with a hexane−acetone gradient (1:0 → 2:3), to afford eight fractions (S1−S8). The same gradient system was used in the purification of fraction S5 on a silica gel column to yield yucalexin P-17 (60.6 mg). Fraction S6 was rechromatographed, eluted with hexane−acetone (7:3), to give yucalexin B-22 (7.9 mg) and a mixture, which, upon purification on a Sephadex LH-20 column with CH_2Cl_2−MeOH (2:1) as eluent, yielded yucalexin P-15 (17.6 mg). Fraction S8 was subjected to a silica gel column, eluted with a gradient of hexane−acetone (3:2 → 0:1), followed by a Sephadex LH-20 column, eluted with CH_2Cl_2−MeOH (1:1), to give **3** as colorless needles (7.0 mg).

2,3-Seco-taraxer-14-ene-2,3,28-trioic acid 2,3-dimethyl ester (1): white powder; mp 232–233 °C; $[\alpha]^{25}_D$ +13.6 (*c* 0.05, MeOH); IR (KBr) ν_{max} 3434 (OH), 2949, 2865, 1729 (C=O), 1692 (C=O), 1636, 1456, 1250, 1209, 1195, 1145, 1015 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 5.56 (1H, dd, J = 8.0, 3.5 Hz, H-15), 3.57 (3H, s, 2-COOC*H*$_3$), 3.56 (3H, s, 3-COOC*H*$_3$), 2.58 (1H, dd, J = 10.5, 9.5 Hz, H-9), 2.41 (1H, m, H-5), 2.40 (1H, m, H-18), 2.39 (1H, m, H-16a), 2.35 (1H, d, J = 18.7 Hz, H-1a), 2.25 (1H, d, J = 18.7 Hz, H-1b), 1.98 (1H, dd, J = 14.5, 3.5 Hz, H-16b), 1.92 (1H, dt, J = 13.0, 3.0 Hz, H-7a), 1.75 (1H, m, H-12a), 1.70 (1H, ddd, J = 14.0, 4.5, 3.0 Hz, H-22a), 1.64 (1H, m, H-6a), 1.63 (1H, m, H-12b), 1.56 (3H, m, H-6b and H-11), 1.47 (1H, td, J = 13.5, 3.0 Hz, H-22b), 1.32 (1H, t, J = 13.5 Hz, H-19a), 1.32 (1H, m, H-7b), 1.20 (6H, s, H-23 and H-24), 1.17 (1H, dd, J = 5.0, 3.5 Hz, H-21a), 1.12 (1H, dd, J = 13.5, 3.5 Hz, H-19b), 1.07 (1H, td, J = 13.5, 3.0 Hz, H-21b), 1.00 (3H, s, H-25), 0.96 (3H, s, H-26), 0.94 (3H, s, H-29), 0.93 (3H, s, H-27), 0.91 (3H, s, H-30); ^{13}C NMR (acetone-d_6, 125 MHz) δ 179.8 (C, C-3), 179.0 (C, C-28), 172.0 (C, C-2), 161.2 (C, C-14), 117.2 (CH, C-15), 51.9 (CH_3, 2-COO*C*H$_3$), 51.4 (C, C-17), 51.0 (CH_3, 3-COO*C*H$_3$), 49.6 (CH, C-5), 46.7 (C, C-4), 43.0 (C, C-10), 42.3 (CH, C-18), 41.5 (CH, C-9), 41.1 (CH_2, C-1), 41.0 (CH_2, C-7), 39.3 (C, C-8), 37.8 (C, C-13), 36.0 (CH_2, C-19), 34.5 (CH_2, C-21), 34.3 (CH_2, C-12), 32.4 (CH_2, C-16), 32.3 (CH_3, C-29), 31.5 (CH_2, C-22), 29.5 (C, C-20), 29.2 (CH_3, C-30), 28.1 (CH_3, C-23), 25.5 (CH_3, C-26), 24.1 (CH_3, C-24), 21.9 (CH_3, C-27), 21.7 (CH_2, C-6), 19.5 (CH_3, C-25), 18.3 (CH_2, C-11); HRESIMS *m*/*z* 553.3509 [M + Na]$^+$ (calcd for $C_{32}H_{50}O_6Na$, 553.3505).

2,3-Seco-taraxer-14-ene-2,3,28-trioic acid 3-methyl ester (2): colorless needles; mp >300 °C; $[\alpha]^{25}_D$ +81.6 (*c* 0.11, MeOH); IR (KBr) ν_{max} 3433 (OH), 2949, 2864, 1728 (C=O), 1690 (C=O), 1465, 1454, 1392, 1297, 1250, 1143 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 5.45 (1H, dd, J = 7.8, 3.3 Hz, H-15), 3.52 (3H, s, 3-COOC*H*$_3$), 2.54 (1H, t, J = 9.8 Hz, H-9), 2.33 (1H, dd, J = 12.3, 1.8 Hz, H-5), 2.25 (1H, m, H-16a), 2.24 (1H, m, H-18), 2.20 (1H, d, J = 19.3 Hz, H-1a), 2.10 (1H, d, J = 19.3 Hz, H-1b), 1.89 (1H, dd, J = 14.5, 3.0 Hz, H-16b), 1.84 (1H, dt, J = 13.0, 3.0 Hz, H-7a), 1.65 (1H, m, H-12a), 1.57 (1H, m, H-22a), 1.55 (1H, m, H-12b), 1.54 (1H, m, H-6a), 1.44 (3H, m, H-6b and H-11), 1.37 (1H, td, J = 13.5, 3.0 Hz, H-22b), 1.21 (1H, t, J = 13.5 Hz, H-19a), 1.21 (1H, m, H-7b), 1.14 (6H, s, H-23 and H-24), 1.11 (1H, t, J = 4.0 Hz, H-21a), 1.04 (1H, dd, J = 13.5, 3.5 Hz, H-19b), 0.94 (1H, td, J = 13.3, 2.8 Hz, H-21b), 0.90 (3H, s, H-29), 0.89 (6H, s, H-25 and H-26), 0.86 (3H, s, H-30), 0.83 (3H, s, H-27); ^{13}C NMR (acetone-d_6, 125 MHz) δ 178.9 (C, C-3), 178.7 (C, C-28), 172.3 (C, C-2), 159.8 (C, C-14), 115.9 (CH, C-15), 51.6 (CH_3, 3-COO*C*H$_3$), 50.1 (C, C-17), 48.0 (CH, C-5), 45.6 (C, C-4), 41.5 (C, C-10), 40.9 (CH, C-18), 40.2 (CH_2, C-1), 39.7 (CH, C-9), 39.7 (CH_2, C-7), 38.0 (C, C-8), 36.6 (C, C-13), 35.0 (CH_2, C-19), 33.5 (CH_2, C-21), 33.2 (CH_2, C-12), 32.0 (CH_3, C-29), 31.3 (CH_2, C-16), 30.4 (CH_2, C-22), 29.0 (C, C-20), 28.8 (CH_3, C-30), 27.2 (CH_3, C-23), 24.9 (CH_3, C-26), 23.7 (CH_3, H-24), 21.3 (CH_3, C-27), 20.6 (CH_2, C-6), 19.0 (CH_3, C-25), 17.2 (CH_2, C-11); HRESIMS *m*/*z* 539.3344 [M + Na]$^+$ (calcd for $C_{31}H_{48}O_6Na$, 539.3349).

2,3-Seco-sonderianol (3): colorless needles; mp 230–233 °C; $[\alpha]^{25}_{D}$ +9.4 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ϵ) 215 (4.17), 292 (3.31) nm; IR (KBr) ν_{max} 3430 (OH), 2984, 1698 (C=O), 1467, 1400, 1313, 1269, 927 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.87 (1H, s, 12-O*H*), 6.67 (1H, s, H-11), 6.57 (1H, dd, J = 18.0, 11.4 Hz, H-15), 5.48 (1H, d, J = 11.4 Hz, H-16a), 5.09 (1H, d, J = 18.0 Hz, H-16b), 2.71 (1H, br s, H-5), 2.56 (1H, d, J = 14.6 Hz, H-1a), 2.49 (2H, m, H-7), 2.33 (1H, d, J = 14.6 Hz, H-1b), 2.01 (3H, s, H-17), 2.01 (1H, m, H-6a), 1.77 (1H, m, H-6b), 1.38 (3H, s, H-20), 1.11 (3H, s, H-18), 0.81 (3H, s, H-19); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 180.6 (C, C-3), 171.8 (C, C-2), 153.1 (C, C-12), 142.3 (C, C-9), 137.7 (C, C-14), 135.7 (CH, C-15), 124.0 (C, C-8), 119.1 (C, C-13), 118.9 (CH_2, C-16), 110.1 (CH, C-11), 49.5 (CH_2, C-1), 44.8 (C, C-4), 42.9 (CH, C-5), 40.7 (C, C-10), 27.8 (CH_3, C-18), 25.8 (CH_2, C-7), 24.3 (CH_3, C-20), 22.6 (CH_3, C-19), 20.8 (CH_2, C-6), 13.2 (CH_3, C-17); HRESIMS *m*/*z* 369.1680 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_5Na$, 369.1678).

Cytotoxicity Assay. Cytotoxicity of the isolated compounds against human small cell lung cancer (NCI-H187), human epidermoid carcinoma (KB), and human breast cancer (BC) cell lines was evaluated using the colorimetric method described by Skehan et al.[17] Ellipticine was used as a positive control.

Antimycobacterial Assay. Antimycobacterial activity was determined against *Mycobacterium tuberculosis* H37Ra using the microplate Alamar Blue assay.[18] Isoniazid and kanamycin sulfate were employed as reference standard drugs.

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