Notes

Dantaxusins C and D, Two Novel Taxoids from *Taxus yunnanensis*

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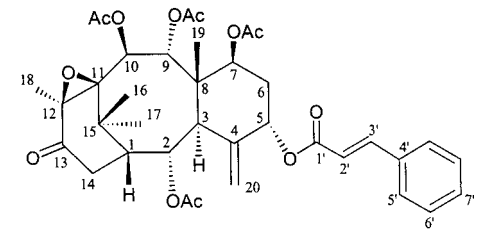
Two new taxane diterpenes, dantaxusin C (**1**) and dantaxusin D (**2**), were isolated from an ethanol extract of the aerial parts of *Taxus yunnanensis* along with 14 known taxoids. All structures were established on the basis of 1D and 2D NMR and HREIMS spectroscopic methods.

Because paclitaxel has shown remarkable antitumor activity, many efforts have been devoted to isolate new taxoids from various *Taxus* species.[1] Structure−activity relationship and synthetic modification studies have been aimed at increasing activity and solubility of new analogues. Recently, several non-paclitaxel-type taxane compounds were reported to also show interesting activities other than cytotoxic activity. In particular, certain non-paclitaxel-type taxoids reduced $CaCl_2$-induced depolymerization of microtubles,[2] and some nonalkaloidal taxoids increased cellular accumulation of vincristine in multidrug-resistant tumor cells.[2,3] In our continuing studies of new antitumor agents from higher plants, we have investigated the taxane diterpene constituents of two species, *T. yunnanensis* Cheng et L. K. Fu and *T. chinensis* (Pilgre) Rehd. var. *mairei* (Taxaceae). Previously, we reported the isolation of taxuchin A, a 11(15→1)*abeo*-taxane-type diterpene, together with 19-acetoxytaxagifine, 5α-cinnamoyloxy-2α,7*β*,-13α-triacetoxy-2(3→20)*abeo*taxa-4(20),11-diene-9,10-dione, and 5α-cinnamoyloxy-9α-hydroxy-10*β*,13α-diacetoxy-taxa-4(20),11-diene and the evaluation of seven isolated taxane diterpenes for cytotoxicity against nine human cell lines, including a *β*-mutant cell line resistant to paclitaxel.[4−6] Subsequently, we also identified two new taxane diterpenes, dantaxusins A and B, together with six known taxoids, taxuspine B, 2-deacetoxytaxinine J, taxuyunnanine C, taxinine B, taxuspine C, and taxinine NN-4.[7] As part of our continuing study on the constituents of *Taxus* species, we report herein on the isolation and structural elucidation of two new taxane diterpenes from *T. yunnanensis* Cheng et L. K. Structural elucidation established the two new taxoids as structures **1** and **2**.



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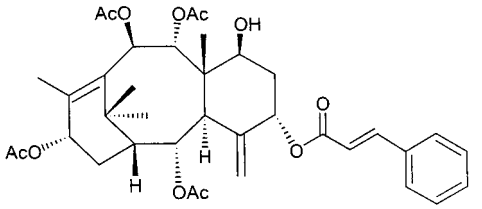

2

The air-dried aerial parts of *T. yunnanensis* were extracted with EtOH to afford a crude extract. After evaporation of the solvent, the crude extract was dissolved in aqueous EtOH and reextracted with *n*-hexane, CH_2Cl_2, and then *n*-BuOH. The CH_2Cl_2 extract was chromatographed on Si gel using benzene−EtOAc−hexane, EtOAc−Et_2O, $CHCl_3$−MeOH−H_2O, and MeOH, successively. Five fractions collected on elution with the mixed solvent of benzene−EtOAc−*n*-hexane were combined and purified with repeated preparative HPLC to give two new taxoids, **1** and **2**.

The IR spectrum of compound **1** showed the presence of ester carbonyl (1740 cm^{-1}), α,*β*-unsaturated carbonyl (1715 cm^{-1}), and ketone (1710 cm^{-1}) groups. Its molecular formula was established as $C_{37}H_{44}O_{12}$ from HREIMS (*m*/*z* 680.2823) and ^1H, ^{13}C, and DEPT spectral data. Its UV spectrum showed an absorption maximum at 274 nm due to a conjugated aromatic ring.

The ^1H NMR spectrum of **1** disclosed the presence of four quaternary methyl groups, four acetyl methyl groups, two olefinic protons, a cinnamoyl group, and five methine groups connected to ester oxygens. The relationships between proton signals in **1** were established by a $^1H-^1H$ COSY spectrum. Detailed analysis of the $^1H-^1H$ COSY spectrum disclosed the following connectivities: H-14/H-1, H-1/H-2, H-2/H-3, H-5/H-6, H-6/H-7, and H-9/H-10. The ^{13}C and DEPT NMR spectral data indicated the presence of a ketone carbonyl group, five ester carbonyl groups, six aromatic ring carbons, four olefinic carbons, four methyl

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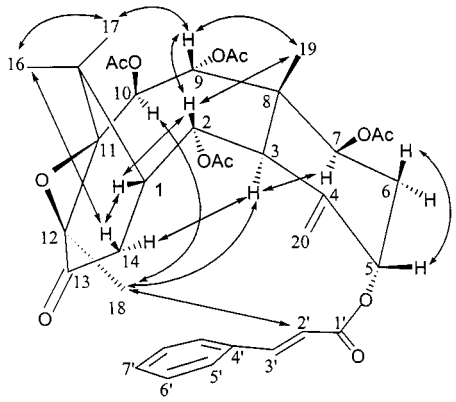

Figure 1. Relative stereochemistry of **1**, deduced from a HOESY experiment (400 MHz).

carbons, two methylene carbons, five methine carbons connected to oxygen atoms, and two quaternary carbons connected to oxygen atoms. The ^{1}H, ^{13}C NMR, and DEPT spectral data suggested that **1** has a normal taxane skeleton, and the ^{1}H−^{1}H COSY and HMBC experiments established the connectivities of these carbons.

The ^{13}C NMR spectrum of **1** showed the presence of two quaternary carbon signals appearing at δ 64.4 (C-11) and 59.3 (C-12) and the absence of the signals due to two olefinic carbons (C-11 and C-12) found in a normal taxane skeleton. The HMBC correlations between the carbon signal at δ 64.4 (C-11) and the proton signals at δ 5.47 (H-10), 0.82 (H-16), and 2.12 (H-18) and the cross-peaks observed between the carbon signal at δ 59.3 (C-12) and the proton signals at δ 5.47 (H-10) and 2.12 (H-18) suggested the position of an epoxide group at C-11 and C-12 in **1**. The molecular formula and the unsaturation number of **1** obtained by HREIMS supported this result.

The HMBC correlations between H-14/C-1, C-2, C-15; H-16/C-1, C-11, C-15; H-17/C-1, C-11, C-15; and H-18/C-11, C-12, C-13 confirmed the partial structure of a cyclohexanone ring (ring A) attached to an epoxide ring at C-11 and C-12. Assignments of the ring B and cyclohexane ring C moieties were supported by the following cross-peaks: H-2/C-1, C-8, C-15; H-3/C-1, C-2, C-8, C-19; H-9/C-7, C-10; H-10/C-9, C-11, C-15; H-6/C-7, C-8; H-5/C-4; H-19/C-3, C-7, C-8, C-9; and H-20/C-3, C-4, C-5.

The positions of the cinnamoyl and acetate esters in **1** were confirmed by long-range correlations with the respective ring protons in the HMBC spectrum. The ester carbonyl carbon signals (OAc-2, 7, 9, 10 at δ 168.8, 169.2, 169.5, 169.6 and C-1′ at δ 165.8) showed long-range correlations with the ring protons (H-2 at δ 5.78, H-7 at δ 5.64, H-9 at δ 6.04, H-10 at δ 5.47, and H-5 at δ 5.52), respectively.

The relative stereochemistry of **1** was determined by analysis of NOE correlations. Correlations between H-16/H-14β, H-14β/H-1, H-1/H-2, H-5/H-6β, H-2/H-19, and H-9/H-17 indicated that H-1, H-2, H-5, and H-9 had β-orientations. The NOE correlations between H-18/H-10, H-18/H-3, H-3/ H-14α, and H-3/H-7 revealed H-18, H-3, H-7, and H-10 had α-orientations. Arrows in Figure 1 show these NOE correlations. From these data, the structure of **1** was established as taxinine B-11,12-oxide and given the trivial name dantaxusin C.

The IR spectrum of compound **2** showed the presence of hydroxyl (3400 cm^{-1}), ester carbonyl (1740 cm^{-1}), and α,β-unsaturated carbonyl (1715 cm^{-1}) groups. Its molecular formula was established as $C_{37}H_{46}O_{11}$ from HREIMS (*m*/*z* 666.3049) and ^{1}H, ^{13}C, and DEPT spectra. Its UV spectrum showed an absorption maximum at 274 nm due to a conjugated aromatic ring.

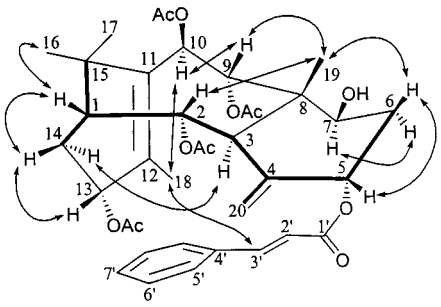

Figure 2. Relative stereochemistry of **2**, deduced from a NOESY experiment (400 MHz).

The ^{1}H NMR spectrum of **2** disclosed the presence of four quaternary methyl groups, four acetyl methyl groups, two olefinic protons, a cinnamoyl group, five methine groups connected to ester oxygens, and a methine proton connected to a hydroxyl group. The ^{1}H, ^{13}C, and DEPT NMR spectral data indicated that **2** has an exocyclic methylene and a normal taxane skeleton.

The relationships between proton signals in **2** were established by ^{1}H−^{1}H COSY examination. The ^{13}C and DEPT NMR spectral data indicated the presence of five ester carbonyls, six aromatic ring carbons, six olefinic carbons, four methyl carbons, two methylene carbons, five methine carbons connected to oxygen atoms, and a methine carbon connected to a hydroxyl group.

In the HMBC spectrum, cross-peaks observed between H-1/C-2, C-11, C-16, C-17; H-17/C-1, C-11, C-15; H-18/C-11, C-12, C-13; and H-14/C-1, C-2, C-13, C-15 confirmed the partial structure of a six-membered A ring moiety. Cross-peaks between H-2/C-1, C-14; H-3/C-2, C-4, C-8, C-19, C-20; H-9/C-10, C-19; H-10/C-9, C-12, C-15; H-19/C-3, C-7, C-8, C-9; and H-20/C-3, C-4, C-5 supported the assignments of the B ring and C ring moieties of **2**. In the HMBC spectrum, cross-peaks appeared between δ 4.40 (H-7) and C-5, C-9 and between δ 5.50 (H-5) and δ 6.10 (H-9) and a methine carbon signal at δ 70.1 (C-7); these data support the position of a hydroxyl group at C-7. The positions of the cinnamoyl and acetate esters in **2** were confirmed by long-range correlations with the respective ring protons in the HMBC spectrum. The ester carbonyl carbon signals (C-1′ at δ 166.5, 2-OAc at δ 169.3, 9-OAc at δ 168.5, 10-OAc at δ 169.3, 13-OAc at δ 171.0) showed long-range correlations with the ring protons (H-2 at δ 5.55, H-5 at δ 5.50, H-9 at δ 6.10, H-10 at δ 6.24, H-13 at δ 5.85), respectively.

The relative stereochemistry of **2** was confirmed by NOE correlations as shown by arrows in Figure 2. From these data, the structure of **2** was established as 5α-cinnamoyloxy-2α,9α,10β,13α-tetraacetoxy-7β-hydroxy-4(20),11-taxadiene and given the trivial name dantaxusin D.

The 14 known compounds (taxinine; 2-deacetoxytaxinine J; 5α-cinnamoyloxy-2α,7β,10β,13α-tetraacetoxy-2(3→20)-*abeo*taxa-4(20),11-diene-9-one; 5α-cinnamoyloxy-9α,10β,-13α-triacetoxytaxa-4(20),11-diene; 5α-cinnamoyloxy-7β-hydroxy-9α,10β,13α-triacetoxytaxa-4(20),11-diene; 2-deacetoxy-7,9-dideacetyltaxinine J; 2,10-diacetyl-5-cinnamoylphototaxinine II; 14β-hydroxy-2α, 5α, 10β-triacetoxytaxa-4(20),11-diene; taxuspine X; yunnaxane; taxinine J; taxinine B; taxezopizine G; and taxezopidine H) were identified by comparing their physical and spectroscopic data with those in the literature.[6,8−21]

Experimental Section

General Experimental Procedures. Melting points were determined on an MRK air-bath type melting point apparatus. Specific rotations were obtained on a JASCO DIP-370 digital polarimeter (L = 0.5 dm). IR and UV spectra were recorded on JASCO IR-810 and Hitachi 320-S spectrophotometers, respectively. ^{1}H and ^{13}C NMR spectra were determined on a JEOL JNM-A400 instrument in $CDCl_3$ using TMS as an internal standard. Mass spectra were recorded on a Hitachi M-80 instrument. Si gel (Merck, type 60, 70−320 mesh) was used for column chromatography. Analytical HPLC was performed on a Tosoh liquid chromatograph equipped with a UV detector at 254 nm and a reversed-phased column (YMC A-303) using a solvent mixture of MeOH−H_2O. Preparative HPLC was carried out on Tosoh or Gilson liquid chromatographs equipped with a reversed-phase column (YMC-Pack, ODS-A) at 254 nm using the same solvents as employed for analytical HPLC.

Plant Material. The plant bark, twigs, and leaves of *Taxus yunnanensis* were collected in August 1993 in Yunnan Province, People's Republic of China, and verified by Prof. Daofeng Chen. The voucher specimen (YNL 19930802) is deposited at Shanghai Medical University, Shanghai, and People's Republic of China.

Extraction and Isolation. The plant bark, twigs, and leaves of *T. yunnanensis* (air-dried material, 7.3 kg) were extracted two times (2 × 20 L) with EtOH. The EtOH solutions were evaporated in vacuo to give two residues (A1; 480 g and A2; 502 g). The residues were dissolved in EtOH and H_2O (3:1) and then extracted with *n*-hexane to give *n*-hexane extracts (42.6 and 53.0 g), respectively. The EtOH−H_2O layers were then extracted with CH_2Cl_2 and *n*-BuOH successively, to give CH_2Cl_2 extracts (111 and 139.6 g), *n*-BuOH extracts (152.0 and 155.8 g), and finally, H_2O-soluble residues (140.0 and 148.4 g), respectively. Si gel column chromatography of each CH_2Cl_2 extract (111 and 139.6 g) eluting with benzene−EtOAc−*n*-hexane (14:5:6, v/v) gave 13 and 12 fractions, with EtOAc−Et_2O (1:1, v/v) gave 9 and 7 fractions, and with $CHCl_3$−MeOH−H_2O (50:14:3, v/v) gave 4 and 9 fractions, respectively. Each fraction was checked by analytical HPLC. Five fractions (A1-Fr 11, 12, 13 and A2-Fr9, 10) collected on elution with the mixed solvent of benzene−EtOAc−*n*-hexane were combined, and the solvent was removed. The resulting residue (4.67 g) was dissolved in MeOH and filtered to remove insoluble materials. The MeOH was removed, and the remaining MeOH-soluble material (3.55 g) was subjected to Sephadex LH-20 column chromatography eluting with MeOH to give three fractions. The second fraction (2.59 g) was subjected to Si gel column chromatography with solvents of increasing polarity (hexanes−EtOAc, 10:0, 9:1, 7:3, 6:4, 5:5, 4:6, 3:7, 1:9 v/v) to give 10 subfractions (sub 1 to 10). Five of these fractions (sub 2−6, 1.28 g) were combined and subjected to preparative HPLC (MeOH−H_2O, 75:25 v/v) to give 15 subfractions. Four subfractions [sub (2-6)-10, 11, 12, and 13] were combined (692 mg) and purified with repeated preparative HPLC (MeOH−H_2O, 75:25 v/v) to provide the new taxane diterpenes **1** (1.3 mg, 0.00013%) and **2** (1.6 mg, 0.00016%) as colorless amorphous powders.

The 14 known compounds taxinine (5.0 mg); 2-deacetoxytaxinine J (4. 2 mg); 5α-cinnamoyloxy-2α,7β,10β,13α-tetraacetoxy-2(3→20)*abeo*taxa-4(20),11-diene-9-one (2.8 mg); 5α-cinnamoyloxy-9α,10β,13α-triacetoxytaxa-4(20),11-diene (3.0 mg); 5α-cinnamoyloxy-7β-hydroxy-9α,10β,13α-triacetoxytaxa-4(20),11-diene (7.7 mg); 2-deacetoxy-7,9-dideacetyltaxinine J (4.1 mg); 2,10-diacetyl-5-cinnamoylphototaxinine II (10.1 mg); 14β-hydroxy-2α,5α,10β-triacetoxytaxa-4(20),11-diene (2.1 mg); taxuspine X (2.1 mg); yunnaxane (16.6 mg); taxinine J (2.6 mg); taxinine B (1.8 mg); taxezopizine G (2.3 mg); and taxezopidine H (0.16 mg) were also isolated as colorless amorphous powders.

Dantaxusin C (1): colorless amorphous powder; mp 122−123 °C; $[\alpha]^{24}_D$ +1.25° (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ϵ) 274 (4.87) nm; IR (KBr) ν_{max} 1740 (ester C=O), 1715 (α,β-unsaturated C=O) cm^{-1}, 1710 (carbonyl group) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (3H, s, H-16), 1.05 (3H, s, H-19), 1.84 (3H, s, H-17), 1.86 (1H, m, H-6β), 2.00 (1H, m, H-1), 2.02 (3H, s, CH_3COO-2), 2.04 (3H, s, CH_3COO-7), 2.05 (3H, s, CH_3COO-10), 2.08 (3H, s, CH_3COO-9), 2.12 (3H, s, H-18), 2.16 (1H, m, H-6α), 2.35 (1H, d, *J* = 20.0, H-14α), 2.70 (1H, dd, *J* = 8.4, 20.0, H-14β), 3.08 (1H, d, *J* = 5.6, H-3), 5.12 (1H, s, H-20b), 5.47 (1H, d, *J* = 11.2, H-10), 5.52 (1H, t, *J* = 4.0 H-5), 5.58 (1H, s, H-20a), 5.64 (1H, dd, *J* = 2.6, 11.2, H-7α), 5.78 (1H, dd, *J* = 1.2, 5.6, H-2β), 6.04 (1H, d, *J* = 11.2, H-9), 6.23 (1H, d, *J* = 16, H-2′), 7.50 (3H, m, H-6′,7′,8′), 7.60 (2H, m, H-5′,9′), 7.70 (1H, d, *J* = 16, H-3′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5 (C-19), 15.6 (C-18), 20.6 (CH_3COO-10), 20.8 (CH_3COO-7), 21.1 (CH_3COO-2), 21.4 (CH_3COO-9), 25.4 (C-17), 29.1 (C-16), 34.6 (C-6), 38.2 (C-14), 38.5 (C-15), 41.9 (C-3), 46.8 (C-8), 51.4 (C-1), 59.3 (C-12), 64.4 (C-11), 68.4 (C-2), 69.1 (C-7), 71.4 (C-10), 75. 6 (C-9), 76.4 (C-5), 116.5 (C-2′), 120.8 (C-20), 128.5 (C-5′,9′), 129.1 (C-6′,8′), 130.8 (C-7′), 134.0 (C-4′), 138.6 (C-4), 165.8 (C-1′), 168.8 (CH_3COO-2), 169.2 (CH_3COO-7), 169.5 (CH_3COO-9), 169.6 (CH_3COO-10), 208.3 (C-13); HREIMS *m*/*z* 680.2823 (calcd for $C_{37}H_{44}O_{12}$, 680.2830).

Dantaxusin D (2): colorless amorphous powder; mp 111−112 °C; $[\alpha]^{24}_D$ +6.88° (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ϵ) 274 (4.16) nm; IR (KBr) ν_{max} 3450 (OH), 1740 (ester C=O), 1715 (α,β-unsaturated C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, s, H-19), 1.15 (3H, s, H-16), 1.44 (1H, m, H-14α), 1.75 (1H, m, H-6β), 1.78 (3H, s, CH_3COO-13), 1.79 (3H, s, H-17), 1.90 (1H, br d, *J* = 8.0 Hz, H-1), 2.04 (3H, s, CH_3COO-2), 2.05 (3H, s, CH_3COO-10), 2.07 (3H, s, CH_3COO-9), 2.15 (1H, m, H-6α), 2.28 (3H, s, H-18), 2.70 (1H, m, H-14β), 3.22 (1H, d, *J* = 5.6, H-3), 4.40 (1H, dd, *J* = 5.2, 11.2, H-7α), 5.06 (1H, s, H-20b), 5.47 (1H, s, H-20a), 5.50 (1H, t, *J* = 3.2 H-5), 5.55 (1H, dd, *J* = 1.2, 5.6, H-2β), 5.85 (1H, d, *J* = 8.8 Hz, H-13), 6.10 (1H, d, *J* = 12, H-9), 6.24 (1H, d, *J* = 12, H-10), 6.65 (1H, d, *J* = 16, H-2′), 7.40 (3H, m, H-6′,7′,8′), 7.55 (2H, m, H-5′,9′), 7.87 (1H, d, *J* = 16, H-3′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.6 (C-19), 15.7 (C-18), 20.7 (CH_3COO-9), 21.0 (CH_3COO-13), 21.4 (CH_3COO-2), 21.5 (CH_3COO-10), 26.9 (C-17), 28.5 (C-14), 31.6 (C-16), 37.1 (C-6), 37.7 (C-15), 42.1 (C-3), 47.9 (C-1), 48.4 (C-8), 70.1 (C-7), 70.4 (C-13), 71.3 (C-2), 72.9 (C-10), 77.2 (C-5), 118.4 (C-2′), 119.6 (C-20), 128.1 (C-5′,9′), 129.1 (C-6′,8′), 130.7 (C-7′), 133.6 (C-11), 134.5 (C-4′), 137.8 (C-12), 145.9 (C-3′), 166.5 (C-1′), 168.5 (CH_3COO-9), 169.3 (CH_3COO-2, CH_3COO-10), 171.0 (CH_3COO-13); HREIMS *m*/*z* 666.3049 (calcd for $C_{37}H_{46}O_{11}$, 666.3038).

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