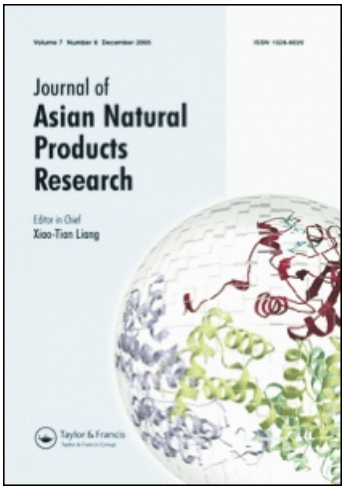

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Two New Taxane Diterpenoids from the Seeds of the Chinese Yew, *Taxus yunnanensis*

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TWO NEW TAXANE DITERPENOIDS FROM THE SEEDS OF THE CHINESE YEW, *TAXUS YUNNANENSIS*

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A new taxoid and a taxinine analogue were isolated from the seeds of the Chinese yew, *Taxus yunnanensis*. The structures were established as 13α-acetoxy-5α-(3′-dimethylamino-3′-phenyl)-propionyloxy-11(15 → 1)-*abeo*taxa-4(20),11-diene-9α,10β-diol and 2α-acetoxy-5α-cinnamoyloxy-9α,10β-dihydroxy-taxa-4(20),11-diene-13-one on the basis of 1D, 2D NMR, and MS spectral analysis.

Keywords: *Taxus yunnanensis*; Taxaceae; Taxoids; 11(15 → 1)-*Abeo*taxane; Seeds

INTRODUCTION

The genus *Taxus* comprises about 10 species in the world, five of them are distributed in China and southeastern Asia. *Taxus yunnanensis*, which was indigenous to China, is an evergreen tall tree or shrub mainly distributed in the wet valley area of Yunnan, Sichuan Provinces, and Tibet Autonomous Region in the south-west of China. Previous studies on taxane diterpenes in the bark, leaves, branches, and root of this plant have resulted in the isolation of more than 40 new taxane diterpenoids [1–22]. In the course of our studies on the yew tree, we have investigated the constitutions of the leaves, bark, and seeds of Chinese yew, *Taxus chinensis* var. *mairei* [23–27]. In view

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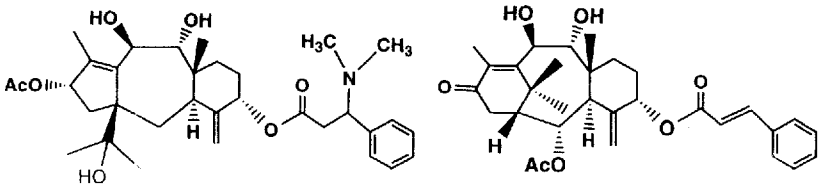

SCHEME 1

of no report on the constitutions of seeds of *T. yunnanensis*, recently we investigated the component of the seeds of this plant, and led to the isolation of two new taxane diterpenoids (Scheme 1). In this communication we describe the isolation and characterization of two compounds.

RESULTS AND DISCUSSION

A methanolic extract of the seeds of *T. yunnanensis* was processed as described in the Materials and Methods section to afford two new taxane diterpenoids (**1** and **2**). Compound **1** was isolated as a colorless gummy substance in a yield of 0.002% on the dry material. EI-MS produced an ion peak at *m/z* 569 ($[M]^+$). The molecular formula of compound **1**, $C_{33}H_{47}O_7N$, was deduced from combined analysis of HR-EI-MS at *m/z* 569.3353 ($[M]^+$) and ^{13}C-NMR spectrum. Intensive absorptions at 3400 and 1730 cm^{-1} in the IR spectrum implied that **1** possesses hydroxyl and ester groups, respectively. The ^{1}H-NMR spectrum of **1**, tabulated in Table I, exhibited the proton signals due to the four methyl groups at δ 0.83, 1.15, 1.29, and 1.92 ppm, which were the characteristic signals of the taxane skeleton. One acetyl group resonated at a relatively lower field (δ 2.15 ppm), which was verified by observation of ^{13}C-NMR signals at δ 171.03 and 20.97 ppm. These signals suggested that **1** had a taxane-type skeleton. The connectivities of the protons at the taxane skeleton of **1** were determined by analysis of the ^{1}H–^{1}H COSY spectrum. Interpretation of ^{1}H-, ^{13}C-NMR and HMBC spectra permitted the positional assignment of functional groups. The ^{1}H-NMR signals at δ 5.07 (1H, br s), 4.67 (1H, br s) and 2.75 (1H, d, $J = 7.70$ Hz) are characteristic of an exocyclic methylene and C-3 ring junction proton in a taxa-4(20),11-diene, respectively [28]. Additionally, four oxygen-bearing one-proton signals appeared at lower field. Of them, the signal at δ 3.97 ppm (1H, d, $J = 9.61$ Hz), which showed cross-peaks with

TABLE I ^{1}H- and ^{13}C-NMR spectral data of **1** in $CDCl_3$

Position	^1H	*J*	^1H–^1H *COSY*	^{13}C
1				62.29
2a	1.88 m		H-3α	28.81
2b	1.28 m		H-2α	
3	2.75 d	7.70	H-2α	40.11
4				147.71
5	5.22 br s		H-6	75.16
6	1.60 m		H-7	27.43
7	1.38 m		H-6	25.03
8				41.26
9	3.97 d	9.61	H-10α	79.39
10	4.40 br d	9.61	H-9β	69.41
11				140.82
12				142.03
13	5.51 t	7.14	H-14, 18-CH_3	80.07
14α	1.13 m		H-14β	44.07
14β	2.36 dd	6.47, 13.24	H-14α, 13β	
15				76.50
16	1.29 s		H-17	29.71
17	1.15 s		H-16	26.59
18	1.92 br s		H-13	11.35
19	0.83 s			17.19
20a	5.07 br s		H-20b	111.46
20b	4.67 br s		H-20a	
13-OAc	2.15 s			20.97, 171.03
1′				170.66
2′	2.88 dd	6.97, 13.74	2″, 3′	39.69
2″	2.66 dd	9.07, 13.74	2′, 3′	
3′	3.77 t	8.30	2′, 2″	67.13
4′				138.57
5′	7.29 m			128.27
6′	7.29 m			128.12
7′	7.29 m			127.67
N–CH_3	2.17 s			42.45

19-CH_3, C-11 in the HMBC spectrum, was attributed to H-9β. The signal at δ 4.40 ppm (1H, br d, $J = 9.61$ Hz), which showed a cross peak with H-9α in the ^{1}H–^{1}H COSY experiment, and showed cross-peaks with C-11 and C-12 in the HMBC spectrum, was assigned to H-10α. Large vicinal coupling indicated a *trans*-oriented configuration of the H-9β and H-10α. The spin system derived from 18-CH_3, H-13β, H-14α, and H-14β was readily interpreted. The signal of three protons as a doublet at δ 1.92 ppm was assigned to 18-CH_3 based on the long-range coupling with H-13β; the triplet at δ 5.51 ppm (1H, t, $J = 7.14$ Hz), was assigned to H-13β; the doublet of doublets at 2.36 ppm and the multiplet at δ 1.13 ppm were assigned to the C-14 methylene protons, H-14β and H-14α, respectively, based on their geminal coupling and coupling to H-13β. The signal at δ 5.22 ppm (1H, br s) was

characteristic signal of H-5β. All of the proton-bearing carbons were assigned by an analysis of the HETCOR spectrum. Four oxygen-containing carbons (C-5, C-9, C-10, and C-13) were correlated with their corresponding proton signals. The H-10α signal showed cross-peaks with the resonances at δ 140.82, 142.03 and 62.29 ppm, which were assigned for C-11, C-12, and C-1, respectively. The C-11 and C-12 carbon signals showed cross-peaks with the H-14β resonance, indicated that both C-11 and C-12 are three bonds apart from H-14β. This means that the A ring was a cyclopentene as in an 11(15 → 1)*abeo*taxane structure [29,30]. The carbon signal at δ 76.50 ppm, assigned to the hydroxyl-bearing C-15, displayed a cross-peak with the C-16 and C-17 methyl resonances at δ 1.29 and 1.15 ppm. The C-1 signal (δ 62.29 ppm), apart from H-10α, also showed three-bond coupling with the H-3α and C-16, C-17 methyl signals. Since no cross-peak was observed between C-16, C-17 (methyl) signals and the C-11 olefinic carbon in the HMBC spectrum further supported the 11(15 → 1)*abeo*taxane skeleton for **1** [31]. The presence of a Winterstein acid [(3′-dimethylamino-3′-phenyl)-propionyloxyl] moiety in **1** was suggested from the signals at δ 2.17 (6H, s), 2.88 (1H, dd, J = 13.74, 6.97 Hz), 2.66 (1H, dd, J = 13.74, 9.07 Hz), 3.77 (1H, t, J = 8.30 Hz), and 7.29 ppm in the ^{1}H-NMR spectrum, and the signals at δ 170.66, 39.69, 67.13, 138.57, 128.27, 128.12, 127.67, and 42.45 ppm in the ^{13}C-NMR spectrum, in good agreement with literature values [32]. Further support was provided by the fragment ions in the EI-MS at *m/z* 192 and 134 (base-peaks), which were the characteristic fragments of Winterstein acid [33–35]. The location of the Winterstein acid moiety was deduced at C-5 from the HMBC spectrum (Fig. 1). The relative stereochemistry of the terpenoid skeleton of **1** was determined from chemical shifts, coupling constants and NOESY experiment. A coupling constant between H-9 and H-10 of J = 9.61 Hz indicated that the B-ring was the chair boat conformation [29]. The NOESY experiment established the

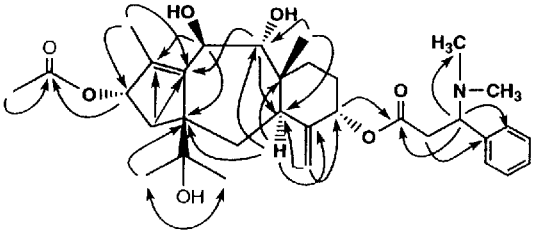

FIGURE 1 Long-range H → C correlations observed by the HMBC spectrum for **1**.

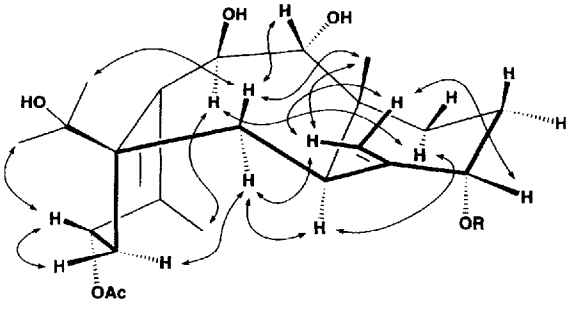

FIGURE 2 Relative stereochemistry of **1**, proposed by NOESY experiment (600 MHz).

relative stereochemistry of **1** at all the position, and the results are shown in Fig. 2. Thus the structure of **1** was determined as 13α-acetoxy-5α-(3′-dimethylamino-3′-phenyl)-propionyloxy-11(15 → 1)-*abeo*taxa-4(20),11-diene-9α, 10β-diol.

Compound **2**, which was isolated as a colorless gummy substance, had a molecular ion peak at *m/z* 522 in its EI-MS (HR-EI-MS, $C_{31}H_{38}O_7$); the base peak was at *m/z* 131 due to the cinnamoyl ion (C_9H_7O), and a peak at *m/z* 374 arose from the loss of cinnamic acid ($C_9H_8O_2$) from M^+. The IR spectrum had bands at 3450 (hydroxy), 3050 (aromatic), 1730 (ester), 1710 (conjugated C=O), 1660, 1620 (benzene), and 1625 (olefinic) cm^{-1}. The UV spectrum had λ_{max} at 279 nm due to the cinnamate ester group. The ^{1}H-NMR spectrum had well-dispersed signals suggestive of a taxane derivative containing one acetate group and one cinnamate group. The fact that 18-CH_3 was a sharp singlet suggested that C-13 did not have a hydrogen attached, but instead bore a ketone function. In accordance with this, H_2-14 displayed a large J_{gem} = 19.78 Hz. By means of the ^{1}H–^{1}H COSY spectrum, the complete connection network was established for H-14α–H-14β–H-1β–H-2β–H-3α–H-20a–H-20b–H-5β H_2-6–H-7α. H-3α and H-5β had allylic coupling with H-20a and H-20b. The lower-field chemical shift of H-2α indicated an acetoxy group located at C-2. A pair of distinguished doublets with a large coupling constant at δ 4.89 and 4.19 ppm were attributed to H-10α and H-9β, respectively, their chemical shifts indicated there are hydroxyl groups attached to C-9 and C-10, i.e. which was 9,10-dideacetyl taxinine. Its ^{1}H-NMR spectrum was closely comparable with that of taxinine with the exception of that H-9β and H-10α were shifted upfield. The cinnamate group was located at C-5α in accordance with what has been observed in the other taxinine derivatives [28,36–38]. Therefore, the

structure of **2** was elucidated as 2α-acetoxy-5α-cinnamoyloxy-9α,10β-dihydroxy-taxa-4(20),11-diene-13-one. Compound **2** can be formed chemically from taxinine [39], but this is the first report as a natural product.

EXPERIMENTAL SECTION

General Experimental Procedures

Optical rotations were recorded on a Horiba SEPA-300 digital polarimeter. UV spectrum was run on a Shimadzu UV-1600 spectro-photometer. IR spectra were obtained on a Jasco IR-810 instrument. MS were measured on a Jeol JMS-700 spectrometer using EI modes. ^{1}H- and ^{13}C-NMR spectra were obtained Varian Unity Inova 600 spectrometers operating at 600 MHz for ^{1}H, 150 MHz for ^{13}C nucleus, in $CDCl_3$ at 20°C, chemical shifts are expressed in parts per million scale relative to that of tetramethylsilane (TMS, $\delta = 0$) as an internal standard, and coupling constants are given in Hertz. ^{1}H-^{13}C HETCOR and HMBC experiments were performed on the same spectrometer, using standard Varian pulse sequences. ^{1}H-^{1}H COSY spectrum was measured on Varian GEMINI 2000/300 spectrometer at 300 MHz. Open column chromatography (CC) was performed using Merck silica gel 60 (100–200 mesh). Thin layer chromatography (TLC) was carried out with the precoated Merck silica gel 60 F_{254} plates. Preparative TLC were performed using the same type of plates as used for TLC but with 0.85 mm (dried for 24 h at room temperature and activated for 4 h at 120°C) thickness, the spots were detected under UV (254 nm) and/or by spraying with 10% sulfuric acid and then heating on a hot plate.

Plant Material

The seeds of *T. yunnanensis* were collected in Congteng county, Yunnan Province, in the south-west of China, in October of 1995. The botanical identification was made by Prof. J.H. Wang, School of Pharmaceutical Science, Hebei Medical University, the People's Republic of China. A voucher specimen has been deposited in our laboratory of Graduate School of Agricultural Science, Tohoku University, Japan.

Extraction and Isolation

Air dried seeds (2.2 kg) were crushed and extracted with hexane three times at room temperature to remove major part of nondesired neutral component.

The residue was extracted three times with methanol (MeOH), the MeOH extracts were condensed to residue (135 g) under reduced pressure. Subsequently this residue was diluted with water and was extracted five times with EtOAc (85 g). The combined EtOAc layer was further extracted with 5% HCl. After neutralization, the aqueous layer was extracted three times with EtOAc. The combined EtOAc extract, upon evaporation, yielded 8.8 g of yellowish syrup, which was subjected to CC, eluted with hexane–ethyl acetate (2 : 1, 1 : 1, 1 : 2, 1 : 4), 12 fractions were obtained, and fraction 3 (900 mg) was further separated by preparative TLC repeatedly with different developing solvent ($CHCl_3$–MeOH, 100 : 4.5; hexane–EtOAc, 1 : 2; hexane–acetone 5 : 3), and finally compound **1** (2.5 mg) and **2** (1 mg) were separated.

13α-Acetoxy-5α-(3′-dimethylamino-3′-phenyl)-propionyloxy-11(15 → 1)-abeotaxa-4(20),11-diene-9α,10β-diol (**1**) Gum, $[\alpha]_D^{24}$ −27 (*c* 0.01, $CHCl_3$). IR (film, $CHCl_3$) ν_{max}: 3400, 2940, 2850, 2850, 2780, 1730, 1650, 1450, 1430, 1365, 1240, 1180, 1020, 750 and 700 cm^{-1}; EI-MS: *m/z* (rel. int.): 569 ($[M]^+$) (19), 509 ($[M-AcOH]^+$) (8), 451 (37), 192 ($[HOCOCH_2CH(Me_2N)Ph]^+$) (76), 134 ($[Me_2N{=}CHPh]^+$) (100), 105 (10), and 43 (9). HR-EI-MS: 569.3353 (calcd. for $C_{33}H_{47}O_7N$, 569.3350), The ^1H- and ^{13}C-NMR spectral data see Table I.

2α-Acetoxy-5α-cinnamoyloxy-9α,10β-dihydroxy-taxa-4(20),11-diene-13-one (**2**) Colorless gum; $[\alpha]_D^{25}$ +132 (*c* 0.01, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 279 (4.3) nm; IR (film, $CHCl_3$) ν_{max}: 3450, 3050, 2925, 1730, 1710, 1660, 1625, 1620, 1440, 1370, 1310, 1240, 1170, 1030, and 750 cm^{-1}; EI-MS *m/z* (rel. int.): 522 (30) ($[M]^+$), 374 (18) ([M-cinnamic acid]$^+$), 131 (100), 103 (98) 91 (100), 77 (65), and 43 (100). HR-EI-MS: *m/z* 522.2621 (calcd. for $C_{31}H_{38}O_7$, 522.2615); ^1H-NMR (ppm, 300 MHz): δ 2.14 (1H, m, H-1), 5.52 (1H, br d, $J = 6.32$ Hz, H-2), 3.36 (1H, d, $J = 6.32$ Hz, H-3), 5.32 (1H, br s, H-5), 1.95 (2H, m, H-6), 1.75 (2H, m, H-7), 4.19 (1H, d, $J = 9.6$ Hz, H-9), 4.89 (1H, br d, $J = 9.6$ Hz, H-10), 2.42 (1H, br d, $J = 19.78$ Hz, H-14α), 2.83 (1H, dd, $J = 19.78$, 7.42 Hz, H-14β), 5.32 (1H, br s, H-20a), 4.84 (1H, br s, H-20b), 6.44 (1H, d, $J = 15.93$ Hz, H-2′), 7.65 (1H, d, $J = 15.93$ Hz, H-3′), 7.76 (2H, d, $J = 6.87$ Hz, H-5′,9′), 7.42 (3H, m, H-6′,7′,8′), 1.22 (3H, s, 16-CH_3), 1.71 (3H, s, 17-CH_3), 2.12 (3H, s, 18-CH_3), 1.10 (3H, s, 19-CH_3), 2.16 (3H, s, CH_3CO–). ^{13}C-NMR (75 MHz, $CDCl_3$): 48.82 (C-1), 69.73 (C-2), 43.17 (C-3), 142.58 (C-4), 78.74 (C-5), 28.44 (C-6), 26.16 (C-7), 44.41 (C-8), 77.76 (C-9), 73.41 (C-10), 155.37 (C-11), 135.86 (C-12), 200.05 (C-13), 36.05 (C-14), 37.54 (C-15), 25.14 (C-16), 37.91 (C-17), 14.06 (C-18), 17.58 (C-19), 118.08 (C-20), 169.87 ($CH_3\underline{C}O$–), 166.53 (C-1′), 21.30($\underline{CH_3}CO$–).

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