Three Novel Bicyclic 3,8-Secotaxane Diterpenoids from the Needles of the Chinese Yew, *Taxus chinensis* var. *mairei*

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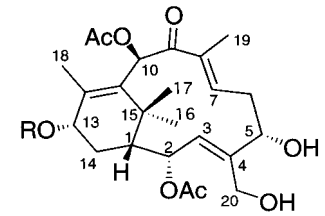
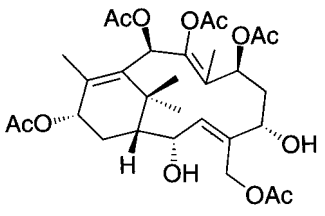
Three novel (**1**−**3**) and five known bicyclic 3,8-secotaxane diterpenoids were isolated from the needles of the Chinese yew, *Taxus chinensis* var. *mairei*. The structures of the new compounds were established, respectively, as (3*E*,7*E*)-2α,10*β*,13α-triacetoxy-5α,20-dihydroxy-3,8-secotaxa-3,7,11-trien-9-one (**1**), (3*E*,7*E*)-2α,10*β*-diacetoxy-5α,13α,20-trihydroxy-3,8-secotaxa-3,7,11-trien-9-one (**2**), and (3*E*,8*E*)-7*β*,9,10*β*,13α,20-pentaacetoxy-3,8-secotaxa-3,8,11-triene-2α,5α-diol (2-deacetyltaxachitriene A) (**3**), on the basis of spectral analysis. The other five bicyclic taxane diterpenoids were determined as canadensene, 5-deacetyltaxachitriene B, taxachitriene B, taxuspine U, and taxuspine X by comparison of their physical properties and spectral data with those previously reported.

The emergence of paclitaxel (TAXOL)[1] as one of the most promising anticancer natural products[2,3] has stimulated worldwide interest in phytochemical studies of *Taxus* species with a view to finding alternative sources of this compound. As a result, over 250 new natural taxane diterpenoids have been isolated in the last two decades.[4−6] In a continuation of our studies on *Taxus* species,[7,8] we have investigated the bark and needles of the Chinese yew, *Taxus chinensis* var. *mairei* (Lemee et Levl) Cheng et L. K. Fu, which is distributed mainly in Jiangxi and Fujian Provinces in the southeast region of the People's Republic of China. Previous studies have led to the isolation of more than 20 new taxanes from this plant.[9−21] Recently, we reexamined the needles of this plant growing in a different area from samples that have been examined by other groups. In a previous communication,[8] we described a 11-(15 → 1)abeotaxane and a bicyclic taxane isolated from the bark and needles of *T. chinensis* var. *mairei*. Here, we report the isolation from this same plant of eight bicyclic taxane diterpenoids, including the structure elucidation of three new compounds (**1**−**3**).



1 R = Ac

2 R = H



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Compound **1** was obtained as a white amorphous powder. The FABMS exhibited pseudomolecular peaks at *m*/*z* 515 [M + Na]$^+$ and 531 [M + K]$^+$, which revealed that its molecular weight was 492. Combined analysis of the FABMS and the ^{13}C NMR data suggested that the molecular formula was $C_{26}H_{36}O_9$, and this was confirmed by HRFABMS. The unsaturation number of **1** was calculated as 9. The IR absorptions at 3450, 1730, and 1680 cm^{-1} implied that **1** possessed hydroxyl, ester, and α,*β*-unsaturated ketone groups. Analysis of the ^{1}H NMR spectrum showed the presence of four tertiary methyl groups (0.86, 1.27, 1.75, and 1.92 ppm), assignable to the C-16, C-17, C-19, and C-18 methyl groups, respectively; three acetyl groups (2.19, 2.02, and 2.15 ppm) at relatively low field; four oxygen-bearing methine groups (5.70 ppm, dd; 4.86 ppm, brs; 6.68 ppm, s; and 5.38 ppm, brd); one oxygen-bearing methylene group (4.53 ppm, 1H, d, J = 12.6 Hz; 3.50 ppm, 1H, dd, J = 12.6, 9.1 Hz); and two trisubstituted olefinic protons (6.23 ppm, 1H, brd, J = 11.3 Hz, 6.40 ppm, 1H, dd, J = 12.2, 1.9 Hz). Four tetrasubstituted olefins (145.46, 139.43, 140.10, and 133.95 ppm), two trisubstituted olefins (120.27 and 134.92 ppm), and an α,*β*-unsaturated ketone (194.75 ppm) were deduced from the ^{13}C NMR spectrum. Since seven out of nine unsaturations were accounted for, only two unsaturation equivalents were left. Thus, the carbon skeleton of **1** was deduced to contain two rings only. The signal at 1.81 ppm (1H, brt) was typical of H-1 in the bicyclic taxanes, which was correlated with H-2, which resonated at 5.70 ppm (1H, dd, J = 5.2, 11.3 Hz) in the ^{1}H−^{1}H COSY spectrum. The downfield chemical shift of H-2 indicated this position was acetylated. This was verified from the HMBC spectrum (Figure 1). The H-3 olefinic proton signal at 6.23 ppm (1H, brd, J = 11.3 Hz) correlated with H-2. H-5 resonated at 4.86 ppm as a broad

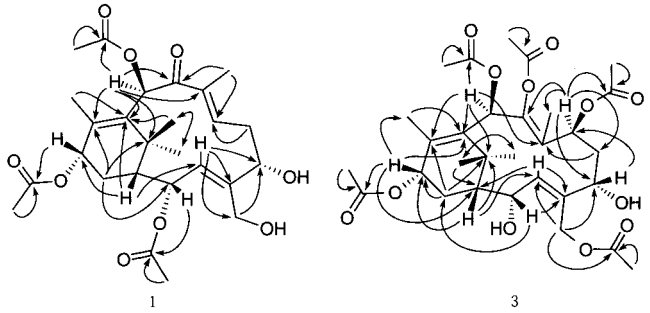

Figure 1. HMBC correlations observed for **1** (500 MHz) and **3** (600 MHz). Most protons are omitted for clarity.

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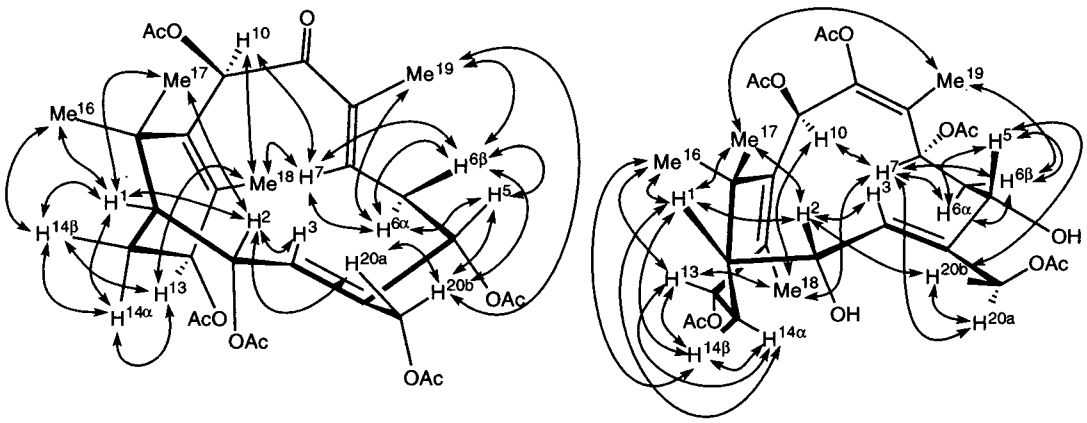

Figure 2. NOEs observed for **1** (ROESY) and **3** (NOESY) (500 MHz).

singlet signal, and its chemical shift indicated that it was a free hydroxyl group. The correlations between signals at both 2.52 ppm (1H, brd, $J = 14.7$ Hz) and 3.01 ppm (1H, ddd, $J = 14.7, 12.2, 4.1$ Hz) with H-5 indicated these two signals were H-6α and H-6*β*, respectively. In turn, these two protons correlated with H-7 resonating at 6.40 ppm (1H, dd, $J = 12.2, 1.9$ Hz). The unusual low field chemical shift of H-7 indicated that it was an olefinic *β*-proton of a ketone. The signal at 6.68 ppm (1H, s), which correlated with an acetyl carbonyl, an α,*β*-unsaturated carbonyl, two olefinic carbons, and an sp^3 carbon in the HMBC spectrum, was attributed to H-10 and an acetyl group attached to C-10. The correlation of the signal at 5.38 ppm (1H, brd, $J = 5.5$ Hz) with H-18 in the $^1H-^1H$ COSY spectrum, and with C-11, C-12, and an acetyl carbonyl carbon in the HMBC spectrum, suggested that there were H-13 and an acetyl group attached to C-13. Combined analysis of the ^{13}C and ^1H NMR spectra revealed that the ketone group should be connected to C-9. Thus, the structure of **1** was proposed as (3*E*,7*E*)-2α,10*β*,13α-triacetoxy-5α,20-dihydroxy-3,8-secotaxa-3,7,11-trien-9-one. The relative stereochemistry and the conformation of **1** were elucidated on the basis of the ROESY NMR spectrum as shown in Figure 2. This compound is the first example of a 7-en-9-one type bicyclic taxane from a natural source; Fang *et al.* have reported the 20-acetyl derivative of **1** as a chemically transformed product from taxachitriene A.[22]

Compound **2** was obtained as a colorless gum. The FABMS gave pseudomolecular ion peaks at *m/z* 451 $[M + H]^+$, 473 $[M + Na]^+$, and 489 $[M + K]^+$, suggesting the molecular formula was 450, which is 42 mass units less than that of **1**. The HRFABMS data obtained were consistent with an empirical formula of $C_{24}H_{34}O_8$. The IR spectrum showed absorptions at 3420, 1725, and 1675 cm^{-1}, so **2** also possessed hydroxyl, ester and α,*β*-unsaturated ketone groups. The ^1H and ^{13}C NMR spectra closely resembled those of **1**, except that H-13 was shifted upfield from 5.38 to 4.25 ppm in the ^1H NMR spectrum and signals for one acetyl group were absent in the ^1H and ^{13}C NMR spectra. The structure of **2** was determined as 13-deacetyl-**1**: (3*E*,7*E*)-2α,10*β*-diacetoxy-5α,13α,20-trihydroxy-3,8-secotaxa-3,7,11-trien-9-one.

Compound **3** was obtained as a white amorphous solid. The molecular formula was determined as $C_{30}H_{42}O_{12}$ (FABMS *m/z* 617 $[M + Na]^+$; HRFABMS *m/z* $C_{30}H_{42}O_{12}$-Na, calcd 617.2571, found 617.2586). The unsaturation number of **3** was calculated as 10. The IR spectrum indicated the presence of hydroxyl (3420 cm^{-1}), ester (1730cm^{-1}), and unsaturated carbons (1660 cm^{-1}) groups. The ^1H NMR spectrum closely resembled that of taxachitriene A[22] with the exception of H-2 being shifted upfield from 5.78 to 4.75 ppm and signals for one acetyl group being absent. Therefore, the structure was proposed as 2-deacetyltaxachitriene A [(3*E*,8*E*)-7*β*,9,10*β*,13α,20-pentaacetoxy-3,8-secotaxa-3,8,11-triene-2α,5α-diol]. The NOESY correlations between H-20a and H-2, H-7, and H-10 confirmed that the two double bonds at C-3 and C-8 had *E*-configurations. The relative stereochemistry and the conformation were also deduced on the basis of the NOESY spectrum, as shown in Figure 2.

The other five bicyclic taxane diterpenoids were determined as canadensene,[22] 5-deacetyltaxachitriene B,[23] taxachitriene B,[24] taxuspine U,[25] and taxuspine X[26] by comparison of their physical properties and spectral data including ^1H NMR, ^{13}C NMR, $^1H-^1H$ COSY, and FABMS with those previously reported.

Bicyclic 3,8-secotaxanes are a recently discovered class of taxanes with 6- and 12-membered rings and are very rare in nature: there are only six such compounds among over 250 natural taxanes.[22−26] Although this kind of skeleton was proposed by Pattenden *et al.*[27,28] as a precursor in taxane biosynthesis as early as 1985, the biosynthesis of taxane diterpenes remains unclear.[29] The early suggestion that taxanes are degraded triterpenoids related to quassinoids[30] has been abandoned, and the current view is that taxanes are diterpenoids biosynthesized from geranylgeranyl diphosphate.[29,31] Clues might come from the isolation of compounds related to the alleged intermediates of the verticillene pathway and from a better knowledge of the structural variation within the natural taxanes. Although the structures of more than 250 taxanes have now been determined, only a few basic structural types exist, and variation is mostly found in the acylation pattern. A bicyclic taxane diterpenoid with a 7-en-9-one structural unit has never been isolated from a *Taxus* species before. Accordingly, the isolation of this kind of compound may shed light on the biosynthesis of taxane diterpenoids and also afford new clues for the total synthesis of paclitaxel and related compounds.

Experimental Section

General Experimental Procedures. Melting points were measured with a MRK micro-melting point apparatus and are uncorrected. Optical rotations were measured on a Horiba SEPA-300 polarimeter. UV spectra were recorded on a Shimadzu UV-1600 spectrophotometer. IR spectra (film) were obtained on a JASCO IR-810 spectrophotometer. ^1H and ^{13}C NMR spectra were run on either a Varian Unity 600 (600 MHz

Table 1. ^{1}H NMR Spectral Data of Compounds **1**−**3** (300 MHz, $CDCl_3$)

	1			**2**			**3**		
proton	δ (ppm)	J (Hz)	^{1}H−^{1}H COSY	δ	J	^{1}H−^{1}H COSY	δ	J	^{1}H−^{1}H COSY
1	1.81 brt	5.2	H-14α, 2	1.81 m		H-14α, 2	1.82 m		H-14α, 2
2	5.70 dd	11.3, 5.2	H-1, 3	5.67 dd	11.3, 5.0	H-1, 3	4.75 dd	11.3, 4.1	H-1, 3
3	6.23 brd	11.3	H-2, 5	6.35 brd	11.3	H-2, 5	6.51 brd	11.3	H-2, 5
5	4.86 brs		H-3, 6α, 6*β*	4.83 brs		H-3, 6α, 6*β*	4.45 brs		H-3, 6α, 6*β*, OH
6α	2.52 brd	14.7	H-5, 6*β*, 7α	2.50 m		H-5, 6*β*, 7α	2.03 m		H-5, 6*β*, 7α
6*β*	3.01 ddd	4.1, 12.2, 14.7	H-5, 6α, 7*β*	2.96 ddd	4.0, 12.2, 14.8	H-5, 6α, 7*β*	2.61 ddd	7.7, 12.2, 3.9	H-5, 6α, 7*β*
7	6.40 dd	12.2, 1.9	H-6α, 6*β*, 19	6.42 dm	12.2	H-6α, 6*β*, 19	5.05 brd	7.7	H-6α, 6*β*
10	6.68 s			6.68 s			6.91 d	1.4	H-19
13	5.38 brd	5.5	H-14*β*, 18	4.25 brd	6.6	H-14*β*, 18	5.32 brd	8.8	H-14*β*, 18
14α	2.34 brd	16.5	H-1, 14*β*	2.45 brd	16.5	H-1, 14*β*	2.28 brd	16.5	H-1, 14*β*
14*β*	2.54 m		H-1, 13, 14α	2.43 m		H-1, 13, 14α	2.47 ddd	16.5, 8.8, 7.1	H-1, 13, 14α
16	0.86 s			0.85 s			1.18 s		
17	1.27 s			1.26 s			1.12 s		
18	1.92 s			2.08 s			1.91 s		
19	1.75 s		H-7	1.75 d	1.1	H-7	1.64 d	1.4	H-10
20a	4.53 d	12.6	H-20b, OH	4.52 d	12.6	H-20b	4.98 d	12.6	H-20b
20b	3.50 dd	12.6, 9.1	H-20a, OH	3.50 m		H-20a	4.01 d	12.6	H-20a
Ac-2	2.02 s			2.05 s			2.11 s		
Ac-10	2.19 s		2.18 s			2.03 s			
Ac-13	2.15 s					2.22 s			
Ac-20						1.97 s			
OH	2.82 brd	9.1	H-20a, 20b	2.82 m			3.91 d	4.1	H-5

Table 2. ^{13}C NMR Spectral Data of Compounds 1−3[a]

carbon	**1**	**2**	**3**	carbon	**1**	**2**	**3**
1	46.92	47.42	47.68	16	34.36	34.74	34.03
2	69.15	67.08	69.10	17	24.69	27.12	24.13
3	120.27	120.90	130.20	18	17.56	18.07	16.85
4	145.46	144.89	133.83	19	11.79	11.83	11.99
5	69.18	69.53	69.10	20	57.37	57.55	59.38
6	33.69	34.30	37.16	Ac-2	21.33[b]	20.99[b]	20.99[b]
7	134.92	136.50	68.05		171.40	171.54	171.54
8	139.43	137.41	122.95	Ac-9			21.27[b]
9	194.75	194.73	144.63				171.12
10	76.16	76.55	67.42	Ac-10	20.92[b]	21.82[b]	21.59[b]
11	140.10	140.38	135.67		169.69	169.73	168.05
12	133.95	134.81	136.15	Ac-13	21.72[b]		21.02[b]
13	70.12	70.40	65.87		170.38		170.63
14	23.83	23.84	24.76	Ac-20			21.27[b]
15	37.15	37.23	35.89				171.12

[a] 126 MHz for **1** and **3**, 75.5 MHz for **2** in chloroform-*d*. [b] Assigment may be interchanged.

for ^{1}H), a Unity 500 (500 MHz for ^{1}H and 126 MHz for ^{13}C), or a Varian 2000/300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) in $CDCl_3$. The spectra were recorded at 300 K with tetramethylsilane as internal standard, and chemical shifts are reported in ppm. Mass spectra were recorded on a JEOL JMS-700 mass spectrometer. Silica gel 60 (Merck 100−200 mesh) was used for column chromatography. Precoated silica gel Kieselgel 60 F_{254} plates (0.2 mm thick) were used for TLC, and the spots were detected by UV illumination and by spraying with 10% H_2SO_4, followed by heating. Merck silica gel 60 F_{254} was used for preparative TLC (0.75 mm or 0.50 mm thick).

Plant Material. The needles of *T. chinensis* var. *mairei* were collected from Jinggangshan (Jinggang mountain near Ziping), Jiangxi Province, People's Republic of China, in August 1995. The plant material was authenticated by Professor R. L. Liu of Zhangzhou Forestry School, where a voucher specimen has been deposited (No. 950823). The material was stored at 0 °C before extraction.

Extraction and Isolation. Air-dried and powdered needles of *T. chinensis* var. *mairei* (7.1 kg) were steeped in MeOH for 1 week at 20 °C. After concentration of the MeOH extract *in vacuo*, the residue was diluted with water and the aqueous solution extracted with EtOAc (3 times). The combined EtOAc extract, upon evaporation, yielded 88 g of dark syrup. Part of this (65 g) was adsorbed to silica gel (80 g, 100−200 mesh), subjected to column chromatography (5 × 50 cm), and eluted with hexane and a gradient of hexane-EtOAc (2:1, 1:1, 1:2, 1:4, and EtOAc) to yield six fractions. Fractions 2 and 3 were repeatedly chromatographed by silica gel column chromatography and preparative TLC and eluted or developed with hexane−acetone, hexane−ethyl acetate, and chloroform−methanol to finally afford **1** (7 mg), **2** (3 mg), and **3** (9 mg), along with five known bicyclic taxoids.

(3*E*,7*E*)-2α,10*β*,13α-Triacetoxy-5α,20-dihydroxy-3,8-seco-taxa-3,7,11-trien-9-one (1): white amorphous powder; mp 77−78 °C; $[\alpha]_D^{25}$ −60° (*c* 0.040, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 202 (4.2), 236 (3.8) nm; IR (neat) ν_{max} 3450 (brs, O−H), 1730 (brs, C=O), 1680 (m, C=C), 1370 (s), 1230 (s), 1020 (m), 755 (s), 670 (w) cm^{-1}; NMR, see Tables 1 and 2; FABMS ($CHCl_3$−glycerol) *m*/*z* 531 ([M + K]$^+$), 515 ([M + Na]$^+$), 493 ([M + H]$^+$), 433 ([M + H − AcOH]$^+$), 373 ([M + M − 2AcOH]$^+$), 313 ([M + M − 3AcOH]$^+$), HRFABMS ($CHCl_3$−glycerol−PEG) *m*/*z* calcd for $C_{24}H_{33}O_7$ ([M + H − AcOH]$^+$) 433.2231, found 433.2224.

(3*E*,7*E*)-2α,10*β*-Diacetoxy-5α,13α,20-trihydroxy-3,8-seco-taxa-3,7,11-trien-9-one (2): colorless gum; $[\alpha]_D^{25}$ −155° (*c* 0.015, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 199 (4.3), 235 (3.8 nm; IR (neat) ν_{max} 3420 (brs, O−H), 1725 (brs, C=O), 1675 (m, C=C), 1370 (s), 1240 (s), 1020 (m), 755 (s), 665 (w) cm^{-1}; NMR, see Tables 1 and 2; FABMS ($CHCl_3$−glycerol) *m*/*z* 489 ([M + K]$^+$), 473 ([M + Na]$^+$), 451 ([M + H]$^+$), 433 ([M + H − H_2O]$^+$), 391 ([M + H − AcOH]$^+$), 373 ([M + H − H_2O − AcOH]$^+$), 335 ([M + H − 2H_2O − AcOH]$^+$), 331 ([M + H − 2AcOH]$^+$) 313 ([M + H − H_2O − 2AcOH]$^+$), 295 ([M + H − 2H_2O − 2AcOH]$^+$); HRFABMS ($CHCl_3$−glycerol−PEG) *m*/*z* calcd for $C_{22}H_{29}O_5$ ([M + H − H_2O − AcOH]$^+$) 373.2013, found 373.2015.

(3*E*,8*E*)-7*β*,9,10*β*,13α,20-Pentaacetoxy-3,8-secotaxa-3,8,-11-triene-2α,5α-diol (2-Deacetyl taxachitriene A) (3): white amorphous solid; mp 82−83 °C; $[\alpha]_D^{25}$ −51° (*c* 0.050, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 201 (4.5) nm; IR (neat) ν_{max} 3420 (brs, O−H), 1730 (brs, C═O), 1660 (m, C═C), 1370 (s), 1230 (s), 1095 (m), 1050 (m), 840 (m), 750 (s), 600 (m) cm^{-1}; NMR, see Tables 1 and 2; FABMS ($CHCl_3$−glycerol) *m*/*z* 617 ($[M + Na]^+$), 577 ($[M + H - H_2O]^+$) 535 ($[M + H - AcOH]^+$), 517 ($[M + H - H_2O - AcOH]^+$) 475 ($[M + H - 2AcOH]^+$), 433, 415 ($[M + H - 3AcOH]^+$), 373, 355 ($[M + H - 4AcOH]^+$), 313, 295 ($[M + H - 5AcOH]^+$); HRFABMS ($CHCl_3$−glycerol−NaCl) *m*/*z* calcd for $C_{30}H_{42}O_{12}Na$ (5 ($[M + Na]^+$) 617.2571, found 617.2586.

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