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TAXANES FROM *TAXUS YUNNANENSIS*

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Key Word Index—*Taxus yunnanensis*; Taxaceae; roots; diterpenoids; taxanes; taxuyunnanine E and F.

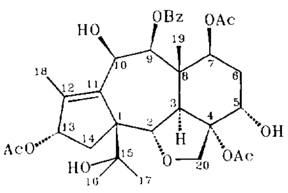
Abstract—Two new taxane diterpenoids as well as a known one, taxayunnansin A, were isolated from the roots of *Taxus yunnanensis*. One of the new compounds was identified as a unique taxane with a 2,20-oxetane ring. Their structures were elucidated by spectroscopic techniques, especially by 2D NMR spectra.

INTRODUCTION

Although taxol, a unique diterpenoid alkaloid, has shown unusual anticancer activity and has been recently approved for treating the sufferers of advanced ovarian cancers [1], its scarcity has limited its widespread use and this has stimulated a search for new sources of taxol. Semi-synthesis from natural taxoids has been successful in producing taxol and related compounds [2]. The total synthesis to taxol has recently been achieved [3], but it has an uncertain future in affording large-scale production of taxol. Cell culture is hoped to provide a new resource for producing taxol or taxol precursors. The search has resulted in the isolation of a large number of new taxoids from *Taxus* plants. Among these new taxoids, a new kind of taxane diterpenoid with an A-5 ring rearranged skeleton has been discovered [4, 5]. As a continuation of our investigation on *T. yunnanensis* [6–8], A-5 ring-rearranged toxoids were also obtained. We now report three such taxanes: taxayunnansin A (**2**) [5] and two new ones, named taxuyunnanine E (**1**) and F (**3**), respectively. These three compounds were isolated from the ethereal extracts of the roots of *T. yunnanensis* as minor constituents. One of them (**1**) proved to have a 2,20-oxetane ring and H-α configuration on C-9, which has never been reported in *Taxus* plants before. The structures of the two novel taxanes were determined by spectroscopic means, including 2D NMR spectra.

RESULTS AND DISCUSSION

Compound **1**, $[\alpha]_D^{26}$ + 3.3° (CHCl$_3$; c 0.6), produced a $[M - 1]^-$ ion at *m/z* 629 in the FAB-mass spectrum. The combination of FAB-mass and ^{13}C NMR spectra (including DEPT technique) suggested a formula $C_{33}H_{42}O_{12}$, which was confirmed by high-resolution FAB-mass spectrum (*m/z* 629.25797 $[M - H]^-$). Compound **1** was shown to have four methyl groups, two methylene groups, one oxymethylene group, one methine group, six oxymethine groups, two quaternary carbons, two oxyquaternary carbons, two olefinic quaternary carbons, three acetyl groups and one benzoyl group in its ^{1}H and ^{13}C NMR spectra (Tables 1 and 2). Based on the comparison of NMR spectra of **1** with those of known taxanes, as well as consideration of the structures of taxanes from the genus *Taxus*, we presumed **1** to have a taxane diterpenoid skeleton. By comparing the ^{1}H and ^{13}C NMR spectra of **1** with those of taxanes from the genus *Taxus*, we could easily assign the only methine group as C-3 [δ_H2.57 (1H, *dd*, J = 7.7 and 1.6 Hz) and δ_C51.1 (*d*)], the only oxymethylene group as C-20 [δ_H4.37 (1H, *dd*, J = 11.5 and 1.8 Hz) and 3.69 (1H, *d*, J = 11.5 Hz) and δ_C 72.8 (*t*)], one quaternary carbon as C-8 (δ_C43.2), the two olefinic quaternary carbons as C-11 (δ_C139.5) and C-12 (δ_C141.7), the four methyls as Me-16 [δ_H1.10 (3H, *s*) and δ_C27.8 (*q*)], Me-17 [δ_H1.50 (3H, *s*) and



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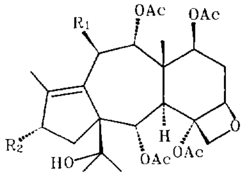

	R_1	R_2
2.	OBz	OH
3.	OH	OAc

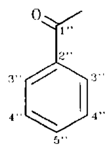

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Table 1. ^{1}H NMR spectral data of compounds **1**–**3** [in $CDCl_3$, 400 MHz, δ in ppm with reference to the signal of $CDCl_3$(δ7.24 ppm)]

H	**1**	**2**	**3**
2	4.93 *d* (7.7)	6.06 *d* (7.8)	5.87 *d* (7.4)
3	2.57 *dd* (7.7, 1.6)	3.09 *d* (7.8)	2.84 *d* (7.4)
5	4.30 *ddd* (11.4, 7.8, 2.6)	4.91 *d* (7.3)	4.91 *dd* (8.2, 1.6)
6α	2.00 *m*	2.48 *dt* (16.1, 8.2)	2.44 *dt* (16.0, 8.2)
6β	1.84 *m*	1.85 *dd* (16.0, 8.7)	1.18 *m*
7	4.82 *dd* (12.6, 3.2)	5.50 *t* (8.3)	5.34 *t* (8.4)
9	5.20 *d* (4.0)	6.10 *d* (10.8)	5.73 *d* (10.3)
10	4.90 *d* (4.0)	6.49 *d* (10.8)	4.53 *t* (10.1)
13	5.62 *br t* (6.9)	4.45 *m*	5.55 *t* (7.2)
14α	2.12 *dd* (14.9, 7.4)	1.59 *dd* (15.1, 7.2)	1.57 *m*
14β	2.28 *dd* (14.9, 7.3)	2.20 *dd* (15.2, 7.5)	2.06 *m*
Me-16	1.10 *s*	1.02 *s*	1.05 *s*
Me-17	1.50 *s*	1.12 *s*	1.12 *s*
Me-18	1.35 *s*	1.97 *s*	1.76 *s*
Me-19	1.52 *s*	1.63 *s*	1.57 *s*
20a	4.37 *dd* (11.5, 1.8)	4.50 AB *d* (7.6)	4.38 AB *d* (7.5)
20b	3.69 *d* (11.5)	4.36 AB *d* (7.6)	4.32 AB *d* (7.5)
H_2-3″	7.96 *dd* (8.0, 1.6)	7.80 *dd* (7.3, 1.2)	
H_2-4″	7.40 *tt* (7.6, 1.6)	7.37 *t* (7.6)	
5″	7.55 *tt* (7.8, 1.6)	7.50 *tt* (7.6, 1.1)	
OH-5	4.40 *d* (2.6)		
OH-10			3.84 *d* (10.0)
OH-15		2.72 *br s*	2.29 *br s*
OAc-Me	2.08 *s*	2.11 *s*	2.06 *s*
	2.05 *s*	2.03 *s* (2-)	2.06 *s*
	1.93 *s*(7-)	1.98 *s*	2.04 *s*
		1.69 *s*(9-)	2.01 *s*
			1.94 *s*

δ_C27.9 (*q*)], Me-18 [δ_H1.35 (3H, *s*) and δ_C12.9 (*q*)] and Me-19 [δ_H1.52 (3H, *s*) and δ_C15.0 (*q*)], respectively. From these NMR signals, we could assign all other proton and carbon NMR signals by using ^{1}H–^{1}H COSY, ^{1}H–^{13}C HETCOR, and COLOC techniques (Tables 3 and 4). The long-range correlation of two quaternary carbons (δ_C65.0 and 76.3) to Me-16 and Me-17 revealed one of them was C-1 and the other was C-15, and the signal of δ_C65.0 was further judged as C-1 owing to its long-range correlation to H-3. Compared with that of normal taxanes, the unusual shift downfield of the C-1 signal and upfield of the C-15 signal in ^{13}C NMR spectrum suggested **1** to have an A-ring rearranged carbon skeleton [4], which was supported by the following. The signal at δ_H5.20 (1H, *d*, $J = 4.0$ Hz) was assigned to H-9 from observation of long-range couplings to C-3 and C-11, from which we established the signal at δ_H4.90 (1H, *d*, $J = 4.0$ Hz) as H-10 owing to the presence of direct coupling to H-9 in the COSY spectrum. H-10 showed three-bond coupling with C-1 in the COLOC spectrum, which thus confirmed **1** to have the rearranged carbon skeleton of taxayunnansin A (**2**).

The ^{13}C NMR and DEPT spectra (Table 2) showed the presence of two methylenes in **1**. HETCOR experiment proved one methylene carbon (δ_C29.9) as attached by the δ_H2.00 (1H, *m*) and 1.84 (1H, *m*) protons, and the other one (δ_C35.6) was attached by the δ_H2.12 (1H, *dd*, $J = 14.9$ and 7.4 Hz) and 2.28 (1H, *dd*, $J = 14.9$ and 7.3 Hz) protons. In addition, the COLOC spectrum revealed three-bond couplings of one methylene proton (δ_H2.00 and 1.84) to C-8 and another methylene proton (δ_H2.12 and 2.28) to C-15, which indicated the former methylene was C-6 and the latter was C-14. Since the dermination of the two methylenes, the six oxymethines in **1** could only be assigned to C-2, C-5, C-7, C-9, C-10 and C-13, respectively. The remaining oxyquaternary carbon (δ_C94.6) on the skeleton of **1** was determined to be C-4 by considering its long-range correlations to H-3, H-20 and H-6. Examining the ^{13}C NMR data between **1** and taxayunnansin A (**2**), we noticed that the ^{13}C NMR data changed strikingly at C-2, C-3, C-4 and C-5 [δ_C79.2 (*d*, C-2), 51.1 (*d*, C-3), 94.6 (*s*, C-4) and 71.7 (*d*, C-5)] in **1**. The 13 ppm upfield shift of C-5 revealed the scission of a 5,20-epoxy group. The observation of three-bond coupling of C-2 and H-20a [δ_H4.37 (*dd*, $J = 11.5$ and 1.8 Hz)] strongly suggested the connection between C-2 and C-20 through an oxygen atom. The severely deshielded ^{13}C NMR shift of C-4 [5] was explained by the hydrogen bond of OH-5 [δ_H4.40 (*d*, $J = 2.6$ Hz)] formed to the oxygen atom which connected to C-4. The same phenomenon has been observed in taxuyunnanine A and related compounds, in which the hydrogen bond of OH-10 to the carbonyl oxygen atom of C-9 led to a 7 ppm downfield shift of C-9 in the ^{13}C NMR spectra [7].

Table 2. ^{13}C NMR spectral data of compounds **1**–**3** [in $CDCl_3$, 100 MHz, δ in ppm from the signal of $CDCl_3$ (δ77.0 ppm)]

C	**1**	**2**	**3**	DEPT
1	65.0	67.7	67.0	C
2	79.2	68.1	68.7	CH
3	51.1	44.1	44.7	CH
4	94.6	79.9	79.4	C
5	71.7	85.0	84.6	CH
6	29.9	34.8	34.7	CH_2
7	70.5	70.4	70.6	CH
8	43.2	43.8	43.3	C
9	75.2	76.6	79.2	CH
10	69.1	69.2	66.1	CH
11	139.5	134.0	139.9	C
12	141.7	151.5	142.8	C
13	81.8	77.0	79.4	CH
14	35.6	39.6	36.5	CH_2
15	76.3	75.5	76.2	C
16	27.8	27.5	27.8	CH_3
17	27.9	25.4	25.5	CH_3
18	12.9	11.8	11.2	CH_3
19	15.0	12.6	12.6	CH_3
20	72.8	74.9	74.5	CH_2
1″	164.8	164.1		C
2″	129.7	129.2		C
3″	129.7	129.5		CH × 2
4″	128.4	128.7		CH × 2
5″	133.3	133.3		CH
OAc-Me	21.9	22.2	21.9	CH_3
	20.9 (7-)	21.5	21.4	CH_3
	20.9	21.3 (2-)	21.4	CH_3
		20.5 (9-)	21.1	CH_3
			21.1	CH_3
OAc-C=O	172.0	171.0	170.7	C
	170.3	170.3 (2-)	170.4	C
	170.1 (7-)	169.8 (9-)	170.4	C
		169.8	169.9	C
			169.0	C

Table 3. 2D ^1H–^1H COSY and NOESY data for compounds **1** and **3** (in $CDCl_3$)

	COSY		NOESY
H	**1**	**3**	**1**
2	H-3	H-3	H-3, 19
3	H-2, 20a	H-2, 20b	H-2
5	H-6	H-6	
H_2-6	H-5, 7		
6α		H-5, 6β, 7	
6β		H-6α, 7	
7	H-6	H-6	H-10
9	H-10	H-10	H-10, 19
10	H-9	H-9, 10-OH	H-7, 9, 18
13	H-14	H-14, 18	
14α	H-13, 14β	H-13, 14β	
14β	H-13, 14α	H-13, 14α	
Me-16	H-17	H-17	
Me-17	H-16	H-16	
Me-18		H-13	
Me-19			
20a	H-3, 20b	H-20b	H-20b
20b	H-20a	H-3, 20a	H-20a
H_2-3″	H-4″		H-17, 19, 4″
H_2-4″	H-3″, 5″		H-3″, 5″
5″	H-4″		H-4″
OH-5			H-6
OH-10		H-10	

Similarly to most taxane compounds, **1** also possessed acyl groups. Its NMR spectra showed the presence of three acetyl and one benzoyl group, which could be assigned by the following considerations. The long-range COLOC spectrum revealed the correlations of the proton signals at δ_H4.82 (1H, *dd*, J = 12.6 and 3.2 Hz, H-7) and 5.20 (1H, *d*, J = 4.0 Hz, H-9) with the carbon signals at δ_C170.1 (*s*, the carbonyl carbon of an acetyl) and 164.8 (*s*, the carbonyl carbon of benzoyl) respectively, indicating that an acetoxy group was attached to C-7 [δ_C70.5 (*d*)] and the benzoxy group to C-9 [δ_C75.2 (*d*)]. An acetoxy substituent was assigned to C-13 [δ_C81.8 (*d*)] owing to the deshielding of H-13 in the ^1H NMR spectrum [δ_H5.62 (1H, *br t*, J = 6.9 Hz)]. The ^1H NMR data of H-10 and H-5 appeared at usual chemical shifts for hydroxylated positions [δ_H4.90 (1H, *d*, J = 4.0 Hz, H-10) and δ_H4.30 (1H, *ddd*, J = 11.4, 7.8 and 2.6 Hz, H-5)]. In the EI-mass spectrum of **1**, the prominent peaks at *m/z* 512 $[M - MeCO_2H - Me_2CO]^+$ (7%), 452 $[M - MeCO_2H \times 2 - Me_2CO]^+$ (83%), 392 $[M - MeCO_2H \times 3 - Me_2CO]^+$ (12%) and 390 $[M - C_6H_5CO_2H - MeCO_2H - Me_2CO]^+$ (11%) confirmed the presence of a $Me_2(OH)$ group in **1**. We could, therefore, conclude that the last acetoxy group was connected to C-4.

The orientation of those secondary oxy groups could be obtained by analysing the ^1H–^1H NOESY spectrum (Table 3). The observation of NOEs between H-2 and Me-19 established the oxy substituents of C-2 as α-orientated. Both H-7 and H-10 were determined to be α owing to the presence of a NOESY correlation between the two protons. H-9 was also assigned to α-configuration owing to its small coupling constant to H-10 (J = 4.0 Hz) and the observation of NOEs between the benzoyl protons and Me-17. The last secondary oxy group at C-13 was judged to be α from comparison of the coupling pattern of H-13 with those similar congeners. Consequently, we established the structure of taxuyunnanine E as **1**.

Compound **3**, $[\alpha]_D^{27}$ − 22.6° ($CHCl_3$; *c* 0.9), had a molecular formular of $C_{30}H_{42}O_{13}$, which was determined by the high-resolution FAB-mass spectrum (609.25131 $[M - 1]^-$). The ^1H and ^{13}C NMR spectra revealed metabolite **3** closely resembled that of taxchinin B [9] except that **3** contained five acetate groups but no other kind of acyloxy groups. ^1H–^1H COSY, ^1H–^{13}C HETCOR and COLOC (Tables 3 and 4) were used to assign proton and carbon signals. The chemical shifts at δ_H5.87 (1H, *d*, J = 7.4 Hz), 5.34 (1H, *t*, J = 8.4 Hz), 5.73 (1H, *d*, J = 10.3 Hz), 4.53 (1H, *t*, J = 10.1 Hz) and 5.55 (1H, *t*, J = 7.2 Hz) were assigned as H-2, H-7, H-9,

Table 4. COLOC data for compounds **1** and **3** (in $CDCl_3$)

C	Correlated proton	
	1 (6/8 Hz)	**3** (8 Hz)
1	H-3,10,14α,16,17	H-16,17
2	H-20a	H-2
3	H-3,9,19,20a	H-19
4	H-3,6α,20	H-20b
5	H-6,5-OH	H-20b
6	5-OH	
7	H-6,7,19	
8	H-3,6,10,19	H-19
9	H-9,10,19	H-3,19
10	H-9	
11	H-9,10,18	H-18
12	H-10,14β,18	H-18
13	H-14α,18	H-18
14	H-14	
15	H-14,16,17	H-16,17
16	H-17	H-16,17
17	H-16	H-16,17
18	H-18	
19	H-19	
20	H-20	H-20
1″	H-9,3″	
2″		
3″	H-3″,4″,5″	
4″	H-4″,5″	
5″	H-3″	
OAc-Me-2		H-2-OAc
OAc-C = O-2		H-2-OAc
OAc-Me-4	H-4-OAc	H-4-OAc
OAc-C = O-4	H-4-OAc	H-4-OAc
OAc-Me-7	H-7-OAc	H-7-OAc
OAc-C = O-7	H-7,7-OAc	H-7-OAc
OAc-Me-9		H-9-OAc
OAc-C = O-9		H-9-OAc
OAc-Me-13	H-13-OAc	H-13-OAc
OAc-C = O-13	H-13-OAc	H-13-OAc

H-10 and H-13, respectively according to the results of 2D ^1H–^1H COSY, ^1H–^{13}C HETCOR and COLOC experiments (Tables 3 and 4). Comparing the ^1H NMR shifts of **3** with those of taxchinin B, the deshielded H-2, H-7, H-9 and H-13 signals established four acetate groups attached to C-2, C-7, C-9 and C-13 respectively, but the usual chemical shift of H-10 indicated no acetate group attached to C-10. Additionally, the stronger ion peak at *m/z* 432 in the EI-mass spectrum of **3**, being produced by the fragment pathway of $[M - MeCO_2H \times 2 - Me_2CO]$, suggested the remaining acetate group attached to C-4 but not to C-15. Thus the structure of taxuyunnanine F is **3**.

Compounds **1**–**3** all belonged to A-5 ring rearranged taxoids, and **1** was the first example having a 2,20-oxetane ring and the H-α configuration on C-9 in the taxane diterpenoid family. The stereo-conformation of **2** [5] was similar to that of usual taxoids, which implied that the A-5 ring rearranged taxoids with a similar taxol 13-side chain would possess similar bioactivity to that of taxol.

EXPERIMENTAL

Prep. HPLC: 10 C_{18} Cosmosil Packed Column, 20 × 250 mm. NMR: Bruker AM-400 Fourier transform spectrometer operating at 400.134 and 100.614 MHz for ^1H and ^{13}C. The samples were made up in $CDCl_3$. All chemical shifts are expressed in ppm with reference to the solvent signals: 7.24 ppm/77.0 ppm for $CDCl_3$.

Plant material. The roots were collected in the suburb of Kunming, Yunnan, China and identified as *Taxus yunnanensis*. A voucher specimen is kept in the Yunnan Academy of Forestry, Kunming, Yunnan, China.

Isolation of taxuyunnanine E and F. Dried, powdered roots (40 kg) of *T. yunnanensis* were extracted with Et_2O (6 × 100 l) at room temp. during 3 weeks to give 650 g crude extract. The ethereal extract was chromatographed on a silical gel column (2 kg), which was eluted with $CHCl_3$–Me_2CO. The $CHCl_3$–Me_2CO (4:1) eluting part (500 mg) was subjected to prep. HPLC (10 C_{18} Cosmosil Packed Column, 20 × 250 mm) eluting with MeOH–H_2O (3:1) to give taxuyunnanine E (**1**, 14.1 mg), F (**3**, 35.6 mg), and taxayunnansin A (**2**, 27.7 mg), respectively.

Taxuyunnanine E (**1**). $C_{33}H_{42}O_{12}$, powders, $[\alpha]_D^{26}$ + 3.3° ($CHCl_3$; *c* 0.6); IRν_{max}^{KBr} cm^{-1}: 3400, 3250, 2960, 2910, 1715, 1595, 1450, 1357, 1320, 1260, 1175, 1105, 1070, 1040, 1015, 945, 828, 810, 755, and 715; EIMS *m/z*: 612 $[M - H_2O]^+$ (10%), 597 $[M - Ac]^+$ (6%), 570 $[M - MeCO_2H]^+$ (4%), 552 $[M - MeCO_2H - H_2O]^+$ (2%), 512 $[M - MeCO_2H - Me_2CO]^+$ (7%), 481 $[M - C_6H_5CHO - Ac]^+$ (4%), 452 $[M - MeCO_2H \times 2 - Me_2CO]^+$ (83%), 434 $[M - MeCO_2H \times 2 - Me_2CO - H_2O]^+$ (15%), 392 $[M - MeCO_2H \times 3 - Me_2CO]^+$ (12%), 390 $[M - C_6H_5CO_2H - MeCO_2H - Me_2CO]^+$ (11%), 373 $[M - MeCO_2H \times 3 - C_6H_5]^+$ (27%), 356 $[M - MeCO_2H \times 3 - Me_2CO - H_2O \times 2]^+$ (13%), 330 $[M - C_6H_5CO_2H - MeCO_2H \times 2 - Me_2CO]^+$ (84%), 313 $[M - C_6H_5CO_2H - MeCO_2H \times 2 - Me_2CO - OH]^+$ (58%), 297 $[M - MeCO_2H \times 3 - Me_2CO - C_6H_5 - H_2O]^+$ (22%), 270 $[M - C_6H_5CO_2H - MeCO_2H \times 3 - Me_2CO]^+$ (41%), 252 $[M - C_6H_5CO_2H - MeCO_2H \times 3 - Me_2CO - H_2O]^+$ (34%), 179 (28%), 148 (53%), 133 (71%), 122 $[C_6H_5CO_2H]^+$ (43%), 105 $[C_6H_5CO]^+$ (64%), 77 $[C_6H_5]^+$ (96%), 60 $[MeCO_2H]^+$ (37%), and 43 $[Ac]^+$ (100%); FAB-MS *m/z*: 629 $[M - 1]^-$ (100%); HRFAB-MS *m/z* 629.25797 (calcd 629.25980 for $C_{33}H_{41}O_{12}$); ^1H and ^{13}C NMR data: see Tables 1 and 2, respectively.

Taxayunnansin A (**2**). $C_{35}H_{44}O_{13}$, powders; IR ν_{max}^{KBr} cm^{-1}: 3530, 2960, 2875, 1725, 1435, 1365, 1260, 1235, 1180, 1085, 1065, 1025, 982, 915, 845, 712, and 602; FAB-MS *m/z*: 711 $[M + K]^+$ (12%), and 695 $[M + Na]^+$ (13%); ^1H and ^{13}C NMR data: see Tables 1 and 2, respectively.

Taxuyunnanine F (**3**). $C_{30}H_{42}O_{13}$, powders, $[\alpha]_D^{27}$ $-22.6°$ ($CHCl_3$, *c* 0.9); IR ν_{max}^{KBr} cm^{-1}: 3400, 2970, 2925, 2880, 1730, 1435, 1369, 1235, 1025, 985, 950, 898, 845, 780, 755, and 605; EIMS *m/z*: 432 $[M - MeCO_2H \times 2 - Me_2CO]^+$ (44%), 372 $[M - MeCO_2H \times 3 - Me_2CO]^+$ (38%), 312 $[M - MeCO_2H \times 4 - Me_2CO]^+$ (21%), 297 (72%), 58 $[Me_2CO]^+$ (59%), and 43 $[Ac]^+$ (100%); FAB-MS *m/z*: 609 $[M - 1]^-$ (100%); HRFAB-MS *m/z* 609.25131 (calcd 609.25472 for $C_{30}H_{41}O_{13}$); ^1H and ^{13}C NMR data: see Tables 1 and 2, respectively.

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