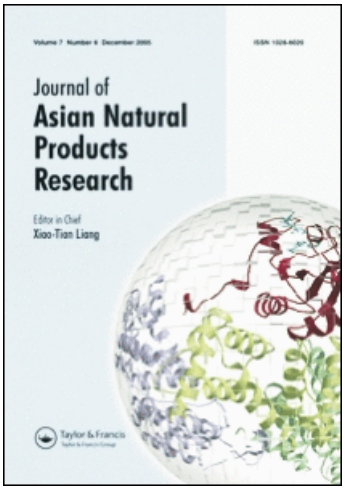

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New taxanes from the seeds of *Taxus mairei*

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New taxanes from the seeds of *Taxus mairei*

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Two new taxoid metabolites were isolated from the methanol extract of the *Taxus mairei* seeds. Their structures were established as 2α-hydroxy-9α,10β,13α-triacetoxy-5α-cinnamoyloxytaxa-11-en-4β,20-epoxide (**1**) and 2′-acetyl taxol (**2**) on the basis of spectral analysis.

Keywords: *Taxus mairei*; Yew; Taxaceae; Taxanes; Taxol analogue; 2′-Acetyl taxol

1. Introduction

Yew trees of genus *Taxus* (Taxaceae) are dioecious and evergreen plants mainly distributed in the northern hemisphere. Since Taxol® (paclitaxel) was isolated from the bark of *Taxus brevifolia* in 1971 [1], more than 300 natural taxanes have been reported from *Taxus* spp. [2–5], but there are still new taxanes awaiting isolation and structural elucidation [6]. The isolation of new taxanes might provide important clues for the biosynthesis of paclitaxel. *Taxus mairei*, a tall tree ubiquitous to the southeast region of China, is the first yew that was chemical studied in China [7–10]. In our continuous search for new taxoids [11–13], we re-examined the seeds of this plant and this resulted in the isolation of two new taxane analogues. In this communication, we report the isolation and structural elucidation of these two new taxane analogues (**1** and **2**) (figure 1).

2. Results and discussion

Compound **1** was isolated as white powder from the methanol extract of *T. mairei* seeds. The molecular formula of **1**, $C_{35}H_{44}O_{10}$, was established from combined analysis of

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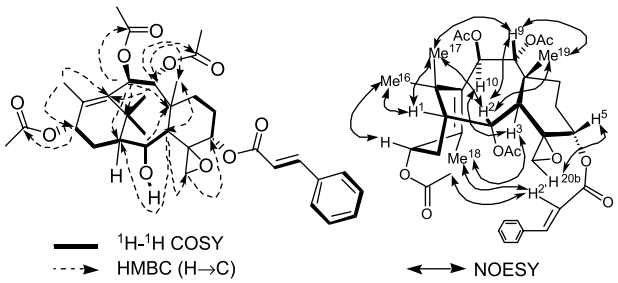

Figure 1. Structures of **1** and **2**.

high-resolution FAB-MS at *m/z* 663.2574 $[M + K]^+$ and ^{13}C NMR spectrum. The ^1H NMR spectrum of **1** (table 1) disclosed well-dispersed signals including three-proton signals due to the four methyl groups at δ_H 1.06, 1.11, 1.65 and 2.34; two signals at δ_H 1.11 and 1.65 were COSY-correlated peaks as geminal methyls. Three acetyl groups were observed at relatively

Table 1. ^1H- and ^{13}C NMR data of **1** (500 MHz for ^1H, 125 MHz for ^{13}C, $CDCl_3$).

Position	*δ (¹H) mult*[a]	*J (Hz)*	*δ (¹³C)*[b]	*HMBC*	*NOESY*[c]
1	1.96 *m*		50.9		2 [s], 14a,, 16 [m], 17 [m]
2	4.07 *br.dd*	10.8, 4.8	72.6		1 [s], 3 [w], 9 [s], 17 [s], 19 [s], 2-OH [w]
2-OH	4.28 *d*	10.8			2 [m], 20a [w]
3	3.08 *d*	4.8	37.8	1, 2, 8, 19, 20	2 [w], 7b [s], 10 [w], 14b [s] 18 [m]
4	–		63.1		
5	4.49 *br.t*	2.5	77.7		6a [m], 6b/7a [m], 20b [s]
6a	1.96 *m*		25.5		
6b	1.85 *m*				
7a	1.85 *m*		26.0		3 [m], 10 [s], 18 [m]
7b	1.79 *m*				
8	–		44.2		
9	5.81 *d*	10.6	76.0	7, 8, 10, 19, CO-9-OAc	2 [s], 17 [s], 19 [w]
10	6.02 *d*	10.6	71.8	9, 11, 12, 15, CO-10-OAc	3 [w], 7b [s], 18 [s]
11	–		134.4		
12	–		136.9		
13	5.85 *br.dd*	9.6, 7.6	70.5	CO-13-OAc	14a, [s] 16, [s] 18 [w]
14a	2.77 *dt*	15.8, 9.6	28.4	2, 12, 13, 15	1 [s], 13 [s], 14b [s], 16 [m]
14b	1.44 *dd*	15.8, 7.6		2, 13	3 [s], 14a [s]
15	–		37.5		
16	1.11 *s*		31.6	1, 11, 15, Me-17	1 [s], 13 [s], 14a [w], 17 [s]
17	1.65 *s*		26.4	1, 11, 15, Me-16	1 [s], 2 [s], 9 [s], 16 [s]
18	2.34 *s*		15.6	11, 12, 13	3 [m], 7b [m], 10 [s], 13 [w], 2′[s], Ph-*o* [w]
19	1.06 *s*		17.8	3, 7, 8, 9	2 [s], 9 [s], 6/7 [s], 20a [m], 20b [m]
20a	3.66 *d*	4.5	53.3	4, 5	2 [w], 19 [m], 20b [s], 2-OH [w]
20b	2.68 *d*	4.5		4, 5	5 [s], 19 [m], 20a [s]
9-OAc	2.07 *s*		20.7	CO-9-OAc	
			170.3		
10-OAc	2.01 *s*		20.9	CO-10-OAc	
			169.7		
13-OAc	1.88 *s*		20.9		
			170.8	CO-13-OAc	
Cinn-1′	–		166.3		
2′	6.76 *d*	15.9	118.0	Ph-*q*	Ph-*o* [w], 18 [m], 13-OAc [m]
3′	7.80 *d*	15.9	146.2	Ph-*o*, 1′	
Ph-*q*			134.1		
Ph-*o*	7.50 *m*		127.9		
Ph-*m*	7.42 *m*		128.9		2 [s], 3 [s], 18 [w], 13-OAc [w]
Ph-*p*	7.42 *m*		130.8		

[a] Mutiplicity: *s*, singlet; *d*, doublet; *dd*, doublet of doublets; *m*, mutiplet. [b] The ^{13}C chemical shifts were extracted from the HMQC experiment (± 0.2 ppm). The values in bold represent quaternary carbons whose chemical shifts were obtained from the HMBC experiment (± 0.2 ppm). [c] NOESY intensities are marked as strong (s), medium (m), or weak (w).

lower field (δ_H 1.88, 2.01 and 2.07) and confirmed by corresponding ^{13}C NMR signals at δ_C 20.9, 170.8, 20.9, 169.7 and δ_C 20.7, 170.3. The proton signals due to the cinnamoyl group were observed at δ_H 7.50 (2H, *m*), 7.42 (3H, *m*) and an AB system centred at δ_H 6.76 (1H, *d*, $J = 15.9$ Hz) and 7.80 (1H, *d*, $J = 15.9$ Hz) indicating the (*E*)-geometry of a *trans*-orientation. This was further confirmed by UV absorption at 278 nm, which we used in the HPLC analysis. The upfield signals appeared as an AB spin system at δ_H 2.68 (1H, d, $J = 4.5$ Hz) and δ_H 3.66 (1H, *d*, $J = 4.5$ Hz) are indicative of a geminal methylene group on the epoxide ring of baccatin I type taxane [3,14], whereas the large chemical shift difference ($\Delta\delta 0.98$) between the geminal oxirane protons is in accordance with a β-oritentation for the epoxide oxygen [17,18]. The connectivities of the protons of **1** were determined by analysis of the ^1H-^1H COSY spectrum. Interpretation of ^1H NMR, ^{13}C NMR and HMBC spectral data permitted the positional assignment of functional groups. The characteristic signal at δ_H 3.08 (1H, *d*, $J = 4.8$ Hz), which correlated with C-1, C-2, C-8, C-19 and C-20 in the HMBC experiment, was attributed to H-3 in a taxane analogue [2,3]. Using H-3 as the starting point, the signals of H-1, H-2, H-14 and H-13 were confirmed from the $^1H-^1H$ COSY spectrum. The chemical shift of H-2 at δ_H 4.07 (1H, *br.dd*, $J = 10.8$, 4.8 Hz) suggested that a free hydroxyl group was located at C-2; this was further confirmed by its correlation with a hydroxyl group at δ_H 4.28 (1H, *d*, $J = 10.8$ Hz), whereas the chemical shift of H-13 at δ_H 5.85 (1H, *dd*, $J = 9.4$, 7.6 Hz) indicated that an acetyl group was attached to C-13. In the HMBC spectrum of **1**, H-14a and H-14b showed long-range correlations with C-2, C-12, C-13 and C-15, and Me-18 exhibited cross-peaks with C-11, C-12 and C-13. The cross-peaks of Me-16 and Me-17 to C-1, C-11 and C-15 indicated that Me-16 and Me-17 were attached at C-15. These correlations suggested the presence of a cyclohexane moiety (ring A) in **1**. The cross-peaks of H-3 to C-1, C-2, C-8, C-19, H-9 to C-8, C-10, C-19, and H-10 to C-9, C-11, C-12 and C-15 implied the presence of an eight-membered ring (ring B). The cross-peaks of H-3 to C-8, C-19, C-20, H-19 to C-3, C-7, C-8 and H-20 to C-4 and C-5 suggested that another cyclohexane moiety (ring C), i.e. compound **1** was a taxane with a 6/8/6-membered-ring skeleton [15]. In the ^1H NMR spectrum of **1**, a pair of isolated AB systems resonating at δ_H 5.81, and 6.02 with a coupling constant ($J = 10.6$ Hz) were attributed to H-9 and H-10, and two acetoxyl groups were attached to C-9 and C-10, respectively. These assignments were further confirmed by HMBC experiment. *Trans*-orientation of H-9 and H-10 was suggested by the large vicinal coupling constant [2,3]. The signal at δ_H 4.49 (1H, *br.t*, $J = 2.5$ Hz) was assigned to H-5 due to $^1H-^1H$ COSY of H-5 and H-6, H-7. The cinnamoyl group was suggested at C-5 by the chemical shift of H-5 and observed NOE correlations between H-2′ and Me-18 and 13-OAc. The unusual high field chemical shift of H-5 due to the magnetic anisotropy of the oxirane ring at C-4 and C-20 further confirmed that the epoxidic oxygen was β-oriented and *cis* to H-5, the shielding effect on H-5 being in good agreement with the observed chemical shift [16,17]. Actually, all naturally occurring 4,20-epoxide taxanes have been formulated as β-epoxides [4,5]. Unnatural occurring 4,20-epoxide taxanes can be formulated as α-epoxide with relatively smaller chemical shift difference between H-20a and H-20b [18]. Thus, the structure of **1** was rigorously characterized as 2α-hydroxy-9α,10β,13α-triacetoxy-5α-cinnamoyloxytaxa-11-en-4β,20-epoxide. This is the fifth 4,20-epoxide taxane with a cinnamoyl group at C-5 reported so far [19,20]. The relative stereochemistry of **1** was elucidated from analysis of the NOESY experiment, chemical shifts and their coupling constants. The coupling constant between H-9 and H-10 ($J = 10$ Hz) and observed NOESY correlations of H-2/H-19, H-2/H-17, H-9/H-19 established a boat-chair conformation for ring B, which is a typical taxane

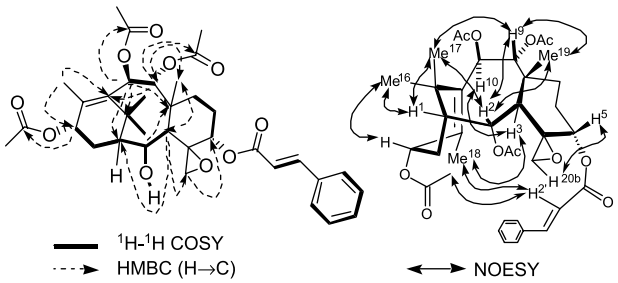

Figure 2. HMBC, ^{1}H–^{1}H COSY (left) and NOESY (right) correlations of **1**.

conformation [2,3]. The β-orientation of H-2 and H-9 were assigned by NOESY correlations of H-2/H-17, H-19/H-2, and H-9/H-19. The α-orientation of H-10 was applied by the observation of NOESY correlations of H-10/H-18 and H-10/H-7b. H-5 adopted an expected β-orientation judging from observed NOE correlation between Me-18 and H-2′ in the NOESY spectrum (figure 2).

Compound **2**, amorphous white powder, exhibited a HR-FAB-MS spectral quasimolecular ion peak at *m/z* 934.3051 $[M + K]^+$, corresponding to the molecular formula of $C_{49}H_{53}NO_{15}$. Complete assignments of ^{1}H- and ^{13}C NMR signals were achieved (table 2) with the help of various NMR techniques such as ^{1}H-^{1}H COSY, HMQC for direct H-C connectivities and HMBC for long-range H–C correlation. The ^{1}H NMR spectrum of **2** showed the characteristic signals of four tertiary methyl groups at δ_H 1.13, 1.23, 1.67 and 1.93 (each 3H, *s*), three acetyl groups at δ_H 2.15, 2.22 and 2.44 (each 3H, *s*), one benzoyl group at δ_H 7.51, 7.60 and 8.13 as well as one oxetane ring at δ_H 4.19 and 4.31 mutually coupled with a coupling constant $J = 8.6$ Hz. In addition, the ^{1}H NMR spectrum of **2** displayed the featured signals of taxol such as H-2 at δ_H 5.68 (1H, *d*, $J = 7.2$ Hz), H-3 at δ_H 3.82 (1H, *d*, $J = 7.2$ Hz), H-5 at δ_H 4.97 (1H, *br.d*, $J = 7.6$ Hz), H-7 at δ_H 4.44 (1H, *dd*, $J = 11.2$, 6.4 Hz), H-10 at δ_H 6.29 (1H, s), and H-13 at δ_H 6.25 (1H, *br.t*, $J = 7.2$ Hz). The presence of a side chain similar to the C-13 side chain of taxol was suggested by the signals at δ_H 5.50 (1H, *d*, $J = 3.2$ Hz, H-2′), 5.94 (1H, *dd*, $J = 9.2$, 3.2 Hz, H-3′), 6.86 (1H, *d*, $J = 9.2$ Hz, H-4′), 7.33–7.42 (5H, m, 3′-Ph), and N-benzoyl signals at δ_H 7.73, 7.41, and 7.49. Comparing the spectral data of **2** with those of taxol revealed that H-2′ of **2** was shifted downfield to δ_H 5.50 and it showed a long-range H–C correlation with one carbonyl carbon at δ_C 169.6, indicating that an acetoxyl group for **2** was instead of the hydroxyl in taxol. This result was in good agreement with the molecular weight of **2**. The configurations at H-2′ and H-3′ were concluded to be 2′*R*, 3′*S* by the proton vicinal coupling constants compared with taxol ($J_{2',3'} = 2.7$ Hz, $J_{3',4'} = 8.9$ Hz) [21]. This conclusion was also verified by lack of an NOE correlation between H-3′ and Me-18 [22]. The relative stereochemistry at C-2, C-7, C-10 and C-13 were established on the basis of chemical shifts, splitting patterns and coupling constants values of corresponding protons as well as by comparing with those of taxol. Taking all these spectral data into account, the structure of **2** was elucidated unequivocally as 2′-acetyl taxol.

3. Experimental

3.1 General experimental procedures

Optical rotation values were recorded on a Jasco DIP-370 digital polarimeter. All the NMR data were obtained at room temperature on a Bruker Avance-500 spectrometer. Positive ion

Table 2. ^{1}H- and ^{13}C NMR data of **2** (500 MHz for ^{1}H, 125 MHz for ^{13}C, $CDCl_3$).

Position	δ (^{1}*H*) *mult*[a]	*J (Hz)*	δ (^{13}*C*)[b]	*HMBC*	*NOESY*[c]
1	–		79.2		
2	5.68 *d*	7.2	74.9	1, 3, 8, 14, CO-OBz	3^{w}, 17^{s}, 19^{s}, $20b^{w}$
3	3.82 *d*	7.2	45.4	1, 2, 8, 19, 20	2^{w}, 7^{s}, 10^{m}, $14a^{s}$, 18^{m}
4	–		81.0		
5	4.97 *br.d*	7.6	84.3		$6a^{s}$
6a	2.56 *ddd*	14.6, 9.4, 6.4	35.4	7, 8	5^{s}, $6b^{s}$, 7^{w}
6b	1.88 *ddd*	14.6, 11.2, 2.1			$6a^{s}$, 19^{m}
7	4.44 *dd*	11.2, 6.4	72.0	9	3^{s}, $6a^{s}$, 10^{s}, 18^{w}
8	–		58.4		
9	–		203.6		
10	6.29 *s*		75.4	9, 11, 12, 15, 171.1	3^{m}, 7^{s}, 18^{s}
11	–		132.6		
12	–		142.8		
13	6.25 *br.t*	~7.2	71.7		$14b^{m}$, 16^{s}
14a	2.36 *dd*	15.5, 9.4	35.5	1, 2, 13	3^{m}, $14b^{s}$
14b	2.17 *m*			1, 12, 13	13^{s}, $14a^{s}$, 16^{w}
15	–		43.2		
16	1.23 *s*		26.7	1, 11, 15, Me-17	13^{s}, 17^{s}
17	1.13 *s*		22.0	1, 11, 15, Me-16	2^{s}, 16^{s}, 19^{m}
18	1.93 *s*		14.6	11, 12, 13	3^{m}, 7^{w}, 10^{s}
19	1.67 *s*		9.5	3, 7, 8, 9	2^{s}, 17^{w}, $20b^{s}$
20a	4.31 *d*	8.6	76.3	3, 4	$20b^{s}$
20b	4.19 *d*	8.6		3, 4, 5	2^{w}, 19^{m}, $20a^{s}$
4-OAc	2.44 *s*		22.6	CO-4-OAc	
			169.5		
10-OAc	2.22 *s*		20.7	CO-10-OAc	
			171.1		
2′-OAc	2.15 *s*		20.4	CO-2′-OAc	
			169.6		
2-OBz					
CO			166.8		
q			126.8		
o	8.13 *d*	7.7	130.1	Bz-*o*, *p*, CO-OBz	Bz-m^{s}, $20a^{w}$
m	7.51 *t*	7.7	128.6		
p	7.60 *t*	7.4	133.5		
1′			167.8		
2′	5.50 *d*	3.2	73.8	3′, 1′, CO-2′ -OAc	$3'^{s}$
3′	5.94 *dd*	9.2, 3.2	52.6	Ph-*q*, Ph-*o*, 166.8, 5′	$2'^{s}$, 4′-NH^{w}
3′-Ph					
q			136.8		$2'^{m}$, $3'^{m}$, $4'^{m}$
o	7.42-7.33		126.4		
m	7.42-7.33		128.7		
p	7.42-7.33		128.3		
4′-NH	6.86 *d*	9.2		166.8	$2'^{w}$, $3'^{w}$, 6′-Ph-o^{w}
5′-CO	–		166.8		
NBz-*q*			131.9		
O	7.73 *d*		126.9	Ph-*o*, *p*	NH-4’^{s}
M	7.41.*m*	7.6	131.9		
p	7.49 *m*		128.7		

[a] Mutiplicity: *s*, singlet; *d*, doublet; *dd*, doublet of doublets; *m*, mutiplet. [b] The ^{13}C chemical shifts were extracted from the HMQC experiment (± 0.2 ppm). The values in bold represent quaternary carbons whose chemical shifts were obtained from the HMBC experiment (± 0.2 ppm). [c] NOESY intensities are marked as strong (s), medium (m), or weak (w).

fast atom bombardment mass spectra (FAB-MS) were obtained with a Vacuum Generators ZAB-HS. Flash chromatography was performed on Silica gel 60 (230–400 mesh EM Science). Thin layer chromatography (TLC) was conducted on Silica Gel 60 F_{254} pre-coated TLC plates (0.25 mm or 0.5 mm, EM Science). The compounds were visualized on TLC plates with 10% sulfuric acid in ethanol and heating on a hot plate. Na_2SO_4 was the drying

agent used in all work-up procedures. Analytical HPLC was performed on a Waters 600 FHU delivery system coupled to a PDA 996 detector. Preparative HPLC were carried out on a Waters Delta Prep 3000 instrument coupled to a UV 486 Tunable Absorbance detector set at 227 nm, 210 nm or 278 nm (Waters). Analytical HPLC was performed with two Whatman partisil 10 ODS-2 analytical columns (4.6 × 250 mm) in series. Preparative HPLC was performed with one partisil 10 ODS-2 MAG-20 preparative column (22 × 500 mm). The products were eluted with a 50 min linear gradient of acetonitrile (25 to 100%) in water at a flow rate of 18 ml min^{-1}.

3.2 Plant material

The seeds of *Taxus mairei* were collected in the autumn of 2000 in Hunan Province, the People's Republic of China. Professor Zhao D. made the botanical confirmation. Several voucher specimens have been deposited in our laboratory.

3.3 Extraction and isolation

Air-dried seeds of *Taxus mairei* (1.4 kg) were ground and extracted with petroleum ether to remove the lipid, and then extracted with methanol five times at room temperature. The combined methanolic extracts were evaporated under reduced pressure. Water (2 L) was added and lipids were further removed by stirring the mixture with petroleum ether. The aqueous phase was then salted and extracted with ethyl acetate. The combined ethyl acetate extracts were dried with anhydrous sodium sulfate, filtered and evaporated, yielding a dark extract (25.5 g). Ethyl acetate extract was absorbed onto 25 g silica gel and packed on a wet column chromatography. Successive elution with petroleum ether, gradient petroleum ether-ethyl acetate and gradient petroleum ether-acetone yielded 114 fractions (Fr_1–Fr_{114}). Fr_{32} to Fr_{38} were combined (1.8 g) according to their TLC behaviour, chromatographed over silica gel and eluted with hexane-acetone to yield 20 fractions (Fr_{32-1} to Fr_{32-20}). The fractions Fr_{32-13} to Fr_{32-18} (219 mg) were combined and applied to preparative HPLC. The material eluted at $t_R = 42.27$ min was concentrated (25 mg) and further purified by a preparative TLC and developed with CH_2Cl_2–$CNCH_3$ (100:20) to yield **1** (1.5 mg, $R_f = 0.52$). Fr_{87} to Fr_{90} were combined (1.0 g) according to their TLC behaviour and chromatographed over silica gel and eluted with hexane–ethyl acetate to provide 18 fractions (Fr_{87-1} to Fr_{87-18}). The fraction Fr_{87-1} was subjected to preparative HPLC to yield **2** (1.0 mg, $t_R = 35.92$ min).

3.3.1 2α-Hydroxy-9α,10β,13α-triacetoxy-5α-cinnamoyloxytaxa-11-en-4β,20-epoxide (1): Amorphous powder; $[\alpha]_D^{22} + 57$ (*c* 0.10, $CHCl_3$). ^{1}H- and ^{13}C NMR, HMBC and NOESY spectral data see table 1; HR-FAB-MS *m/z* 663.2574 $[M + K]^+$ (calculated for $C_{35}H_{44}O_{10}K$, 663.2571).

3.3.2 2′α-Acetyl taxol (2):. Amorphous powder; $[\alpha]_D{}^{22} - 35$ (*c* 0.05, MeOH). ^{1}H- and ^{13}C NMR, HMBC and NOESY spectral data see table 2; HR-FAB-MS *m/z* 934.3051 $[M + K]^+$ (calculated for $C_{49}H_{53}NO_{15}K$, 934.3052).

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