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1-Deoxypaclitaxel and *abeo*-Taxoids from the Seeds of *Taxus mairei*

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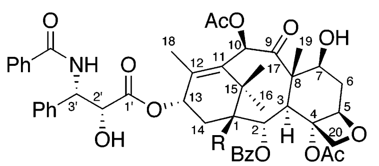
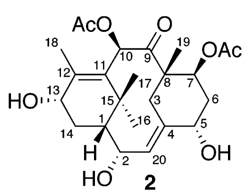
A new paclitaxel derivative and two new 2(3→20)-*abeo*-taxoids were isolated from a methanol extract of the seeds of *Taxus mairei*, and their structures were established as 1-deoxypaclitaxel (**1**), 7*β*,10*β*-diacetoxy-2α,5α,13α-trihydroxy-2(3→20)-*abeo*-taxa-4(20),11-dien-9-one (**2**), and 2α,13α-diacetoxy-10*β*-hydroxy-2(3→20)-*abeo*-taxa-4(20),6,11-triene-5,9-dione (**3**) on the basis of spectroscopic data analysis. Taxane **1** is the first example of a paclitaxel analogue with a C-1*β* hydrogen substituent. Taxane **3** is an 2(3→20)-*abeo*-taxane with a rare C-5 ketone and C-6 double bond.

The extensive utilization of Taxol (paclitaxel)[1] as an anticancer agent has stimulated interest in the analysis of the various *Taxus* species to find alternative sources of paclitaxel or related compounds with improved activity. As a result, about 400 taxane diterpenoids have been isolated and identified.[2−4] The Chinese yew, *Taxus mairei* (Taxaceae), a variety of *Taxus chinensis* (Pilger) Rehd. [*Taxus chinensis* var. *mairei*],[5] is an evergreen tall tree growing in the southeast of mainland China. Previous phytochemical study of this plant has resulted in the isolation of numerous taxane diterpenes.[6] In a continuing search for new taxoids,[7,8] we have isolated three new taxanes (**1**−**3**) including a rare 1-deoxypaclitaxol (**1**) from its seeds. Herein we report the isolation and structural elucidation of these compounds.



paclitaxel R = OH
1 R = H



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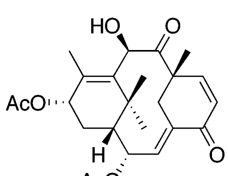

3

Compound **1**, an amorphous white powder, exhibited a HR-FABMS quasimolecular ion peak at *m*/*z* 876.29938, [M + K]$^+$, corresponding to a molecular formula of $C_{47}H_{51}NO_{13}$. Complete assignments of the ^{1}H and ^{13}C NMR signals were determined (Table 1) from the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra (Table S1, Supporting Information). The ^{1}H NMR spectrum of **1** showed the characteristic signals of four tertiary methyl groups at δ_H 1.17, 1.22, 1.66, and 1.80 and two acetyl groups at δ_H 2.22 and 2.38, which were further supported by ^{13}C NMR signals at δ_C 20.8; 171.2 and 22.5; 170.1. Three aromatic protons occurred at δ_H 7.49, 7.60, and 8.09 as well as signals for an oxetane ring at δ_H 4.15 and 4.38, which were mutually coupled with a coupling constant of J = 8.3 Hz. In addition, the ^{1}H NMR spectrum of **1** displayed the diagnostic signals for paclitaxel, such as at δ_{H-3} 3.63 (d, J = 6.9 Hz), δ_{H-5} 4.99 (d, J = 10.2 Hz), δ_{H-7} 4.41 (m), δ_{H-10} 6.24 (s), and δ_{H-13} 6.05 (br, t, J = 8.6 Hz). The only difference was that H-2 appeared as a doublet of doublets at δ_{H-2} 5.65 (dd, J = 6.9, 2.9 Hz) and not as a doublet as in paclitaxel, due to the signal at δ_H 2.14 (1H, m), which correlated with H-14. Thus, this signal was assignable to H-1. In turn, C-1 resonated at δ_{C-1} 45.4 instead of at δ_{C-1} 78.6 in paclitaxel.[9] The presence of a side chain similar to the C-13 side chain of paclitaxel was suggested by the signals at δ_H 4.78 (1H, dd, J = 4.5, 2.4 Hz, H-2′), 5.77 (1H, dd, J = 9.0, 2.4 Hz, H-3′), 6.96 (1H, d, J = 9.0 Hz, NH), 7.33−7.50 (5H, m, Ph), and *N*-benzoyl aromatic signals at δ_H 7.70, 7.41, and 7.49. The molecular weight of **1** was 16 mass units less than that of paclitaxel, which was compatible with the loss of an oxygen atom at C-1. The stereochemistry of the side chain was concluded to be 2′*R*,3′*S* by the ^{1}H NMR vicinal coupling constants compared with the known data for paclitaxel ($J_{2',3'}$ = 2.2 Hz and $J_{3',4'}$ = 9.0 Hz).[10] This conclusion was also verified by lack of an NOE correlation between H-3′ and Me-18.[11] The relative configuration at C-2, C-7, C-10, and C-13 in **1** was established on the basis of chemical shifts, splitting patterns, and coupling constant values of corresponding protons as well as by comparing with analogous data for paclitaxel. Taking all these observation into account, the structure of **1** was elucidated as 1-deoxypaclitaxel.

Compound **2** was obtained as a white amorphous solid. Its molecular composition was established as $C_{24}H_{34}O_8$ on the basis of its HRFABMS data. The ^{1}H NMR spectrum of **2** (Table 2) disclosed characteristic signals for a 2(3→20)-*abeo*-taxane derivative,[2,3,9,12] including the signals for four tertiary methyl groups at δ_H 1.10 (3H, s), 1.19 (3H, s), 1.26 (3H, s), and 2.08 (3H, s), two acetyl groups at δ_H 2.06 (3H, s) and 2.15 (3H, s), and an isolated spin system of doublets at δ 1.89 and 2.55 with a large coupling constant (J = 15.5 Hz). The HMQC spectrum (Table S1, Supporting Infromation) showed one olefinic carbon at δ_C 129.8 bearing one proton (δ_H 5.79, d, J = 9.5 Hz). The connectivities of the protons on the taxane skeleton of **2** were determined by analysis of the ^{1}H−^{1}H COSY spectrum. Interpretation of ^{1}H and ^{13}C NMR and HMBC spectra permitted the positional assignment of all the functional groups. The singlet signal at δ_H 6.32, which showed correlations with C-9, C-11, C-12, and C-15, as well as an acetyl

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Table 1. ^{1}H and ^{13}C NMR Data of **1**−**3** (500 MHz for ^{1}H, 125 MHz for ^{13}C, $CDCl_3$, δ in ppm)

1

position	δ (^{1}H) mult.[a]	J (Hz)	δ (^{13}C)[b]
1	2.14 (m)		45.4
2	5.65 (dd)	6.9, 2.9	72.1
3	3.63 (d)	6.9	43.3
4			81.1
5	4.99 (d)	10.2	84.2
6α	2.56 (m)		35.6
6β	1.88 (m)		
7	4.41 (br.m)		72.0
OH-7	2.41 (br)		
8			**58.9**
9			**204.0**
10	6.24 (s)		75.6
11			**132.9**
12			**140.2**
13	6.05 (t)	8.6	72.1
14α	1.71 (m)		26.6
14β	2.51 (m)		
15			**38.3**
16	1.17 (s)		30.2
17	1.22 (s)		26.0
18	1.80 (s)		14.8
19	1.66 (s)		9.5
20a	4.38 (d)	8.3	76.6
20b	4.15 (d)	8.3	
OAc-4	2.38 (s)		22.5
			170.1
OAc-10	2.22 (s)		20.8
			171.2
OBz-2			
ipso-Ph			**165.0**
o-Ph	8.09 (d)	7.4	129.8
m-Ph	7.49 (o.t)		128.5
p-Ph	7.60 (t)	7.4	133.5
1′			
2′	4.78 (dd)	4.5, 2.4	73.0
OH-2′	3.48 (br d)	4.5	
3′	5.77 (dd)	9.0, 2.4	54.7
Ph-3′	7.50−7.33		128.5
			126.9
NBz-3′			
NH	6.96 (d)	9.0	
C=O			**166.9**
o-Ph	7.70 (d)	7.6	126.9
m-Ph	7.41 (o t)		128.8
p-Ph	7.47 (o t)		131.7

2

position	δ (^{1}H) mult.[a]	J (Hz)	δ (^{13}C)[b]
1	1.65 (br d)	8.3	49.2
2	4.63 (br d)	9.5	67.1
3a	2.55 (d)	15.5	35.7
3b	1.89 (d)	15.5	
4			**134.5**
5	4.58 (br s)		68.4
6ab	2.03 (m)		35.0
7	5.25 (dd)	11.2, 4.5	70.3
8			**52.4**
9			**206.1**
10	6.32 (s)		78.2
11			**128.7**
12			**140.6**
13	4.10 (br d)	9.5	66.7
14α	2.19 (m)		27.7
14β	2.54 (m)		
15			**37.3**
16	1.10 (s)		36.1
17	1.19 (s)		24.4
18	2.08 (s)		19.4
19	1.26 (s)		
20	5.79 (d)	9.5	129.8
OAc-7	2.06 (s)		20.2
			170.3
OAc-10	2.15 (s)		21.1
			169.2

3

position	δ (^{1}H) mult.[a]	J (Hz)	δ (^{13}C)[b]
1	1.74 (dd)	7.9, 2.4	48.3
2	5.72 (dd)	10.5, 2.4	69.5
3α	3.14 (dd)	15.8, 1.6	35.2
3β	2.55 (dd)	15.8, 2.4	
4			**133.8**
5			**189.1**
6	6.27 (d)	10.0	131.4
7			
7	6.53 (dd)	10.0, 1.6	148.7
8			**51.8**
9			**210.5**
10	5.05 (d)	1.3	78.9
OH-10	4.13 (br d)	∼2.0	
11			**133.3**
12			**136.5**
13	5.26 (d)	10.0	67.8
14α	1.97 (d)	16.8	26.7
14β	2.67 (ddd)	16.8, 10.0, 7.9	
15			**37.2**
16	1.17 (o s)		24.5
17	1.16 (o s)		34.3
18	1.51 (o s)		16.9
19	1.51 (o s)		28.4
20	6.40 (dd)	10.5, 2.4	134.6
OAc-2	2.03 (s)		21.1
			170.1
OAc-13	2.17 (s)		21.1
			170.7

[a] Mutiplicity: o, overlapped. [b] The ^{13}C chemical shifts were extracted from the HMQC experiment (±0.2 ppm). The numbers in bold represent quaternary carbons whose chemical shifts were obtained from the HMBC experiment (±0.2 ppm).

carbonyl carbon at δ_C 169.2 in the HMBC spectrum, was assigned to H-10. The signal appearing as a doublet at δ_H 5.79, which correlated with the olefinic carbon at δ_C 129.8 (C-20) in the HMQC spectrum, was assigned to H-20. Using H-20 as a reference, the spin system from H-20 → H-2 → H-1 → H-14β → H-14α → H-13 was readily interpreted. The chemical shifts of H-2 (δ_H 4.63, d, J = 9.5 Hz) and H-13 (δ_H 4.10, d, J = 9.5 Hz) indicated that two hydroxyl groups were positioned at C-2 and C-13. The doublet of doublets signal at δ_H 5.25, which showed a long-range correlation with C-9 in the HMBC experiment, was attributed to H-7. The chemical shift of H-7 suggested that the remaining acetoxyl group was attached to C-7,[9,12] although an expected long-range correlation between H-7 and the carbonyl carbon in the HMBC spectrum was not observed. Using H-7 as a starting point, the spin systems from H-7 to H-6 to H-5 were assigned from the ^{1}H−^{1}H COSY spectrum. The broad singlet resonating at δ_H 4.58 was assigned to H-5 and a free hydroxyl group was located at C-5, as judged from its chemical shift and molecular formula. Thus, the remaining keto carbonyl group had to be located at C-9, as in most 2(3→20)-*abeo*-taxanes.[2,3,9,12] This was verified by the fact that H-3, H-10, and H-19 all showed two- or three-bond correlations with C-9 in the HMBC spectrum. The relative stereochemistry of compound **2** was deduced from the coupling constants and from the ROESY spectrum (Table S1, Supporting Information). The protons at C-2, C-5, C-7, C-10, and C-13 were assigned as β, β, α, α, and β, respectively, having the same configurations as found in most natural taxanes.[2,3] The ROESY spectrum showed NOE correlations between H-2 and H-3a, H_3-17 and between H-20 and H-14β, which indicated that the C-4 double bond is in an *E*-configuration. In addition, the correlations between H-1 and H-2, H-13 and H-14β, H-1 and H-14β, H-1 and CH_3-16, and CH_3-16 and CH_3-17 agreed with the β-configurations assigned for H-2 and H-13. ROESY correlations between H-10 and H-7 and CH_3-18 in **2** implied that H-10 is α-oriented. These findings were consistent with an unusual cage conformation previously reported for taxine B derivatives.[13,14] Taking all these spectroscopic data into account, compound **2** was elucidated as 7β,10β-diacetoxy-2α,5α,13α-trihydroxy-2(3→20)-*abeo*-taxa-4(20),11-dien-9-one.

Compound **3** was obtained as a colorless gummy substance. The HRFABMS revealed a potassium adduct [M + K]$^+$ ion at *m/z*

469.16297, suggesting an empirical formula of $C_{24}H_{30}O_7$. This molecular formula was consistent with data from the ^{1}H and ^{13}C NMR spectra of **3**. The ^{1}H NMR spectrum (Table 3) exhibited three-proton signals due to four tertiary methyl groups at δ_H 1.16, 1.17 (each 3H, s), and 1.51 (6H, s) and two acetyl groups at δ_H 2.03 and 2.17, which were verified by the observation of ^{13}C NMR signals at δ_C 21.1, 170.1 and δ_C 21.1, 170.72. Three oxygenated methines, six olefinic carbons, and two keto carbonyl groups were also observed as downfield resonances, at δ_C 69.5, 78.9, 67.8, 133.8, 131.4, 148.7, 133.3, 136.5, 134.6, 189.1, and 210.5. These signals indicated that **3** has a taxane-type skeleton,[3,4] and the ^{1}H NMR connectivities were determined by analysis of the ^{1}H−^{1}H COSY spectrum (Table S1, Supporting Inforimation). Interpretation of the ^{1}H NMR, ^{13}C NMR, and HMBC spectra permitted the positional assignment of functional groups (Figure S1, Supporting Information). The absence of a C-3 ring junction proton and the presence of a doublet of doublets signals that resonated at δ_H 2.55 and 3.14 with a large coupling constant of $J = 15.5$ Hz are characteristic signals of a 2(3→20)-*abeo*-taxane.[12,13] The signal at δ_H 5.24 (1H, d, $J = 10.0$ Hz), which showed an HMBC correlation with the tetrasubstituted double bond between C-11 and C-12, was assigned to H-13. The chemical shift of H-13 indicated that an acetyl group was located at C-13, which was confirmed by the correlation between H-13 and a carbonyl carbon at δ_C 170.7. Using H-13 as a starting point, the connectivities from C-13 to C-14 to C-1 to C-2 to C-20 were deduced from the ^{1}H−^{1}H COSY spectrum. The chemical shift of H-2 (δ_H 5.72) indicated that an acetyl group was attached at C-2, which was also verified by the HMBC correlation between H-2 and the carbonyl carbon at δ 170.1. The signal at δ_H 5.26, which exhibited a long-range correlation with C-11, C-12, and C-15 and a keto carbonyl group at δ_C 210.5 in the HMBC spectrum, was assigned to H-10. Two olefinic protons at δ_H 6.27 and 6.53, showing HMBC correlations with C-4, C-8, and C-3, C-8, respectively, were assigned to H-6 and H-7. Thus, the remaining α,β-unsaturated keto carbonyl group could be located at C-5. The coupling constant of H-6 and H-7 implied that the double bond is *Z*-oriented. Therefore, the structure of **3** was established as 2α,13α-diacetoxy-10β-hydroxy-2(3→20)-*abeo*-taxa-4(20),6,11-triene-5,9-dione. The relative stereochemistry of **3** was elucidated by a NOESY experiment, and the results are depicted in Figure S1, Supporting Information.

Compound **1** is the first example of a 1-deoxypaclitaxel isolated from a *Taxus* species, although several analogues of this type have been synthesized.[15] It was reported that removal of the C-1 hydroxyl group of paclitaxel is not crucial for its tubulin assembly activity and cytotoxicity.[15] Compounds **2** and **3** are further examples of the rare 2(3→20)-*abeo*-taxanes, with **3** having an unusual α,β-unsaturated keto group at C-5.

Experimental Section

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 FABMS were obtained with a Vacuum Generators ZAB-HS instrument. Flash chromatography was performed on silica gel 60 (230−400 mesh, EM Science). Thin-layer chromatography was conducted on silica gel 60 F_{254} precoated TLC plates (0.25 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 workup procedures. Preparative HPLC was carried out on a Waters Delta Prep 4000 instrument coupled to a Waters 2487 dual λ absorbance detector set at 227 and 210 nm. 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.

Plant Material. The seeds of *Taxus chinesis* var. *mairei* (Taxaceae) were collected in September 2000 in Xinning Country, Hunan Province, the People's Republic of China. Prof. D. Zhao (Hebei Medicinal University) made the botanical confirmation. Several voucher specimens (half bottle of seeds, TM-2000-9-1) have been deposited in the Laboratory of Natural Product Chemistry, School of Pharmaceutical Sciences, Hebei Medicinal University, Hebei Province, the People's Republic of China.

Extraction and Isolation. Air-dried seeds of *T. mairei* were ground (1418 g) and extracted with petroleum ether to remove the lipids 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. The ethyl acetate extract was absorbed onto 25 g of silica gel and packed on a wet column used for chromatography. Successive elution with petroleum ether, a gradient of petroleum ether−ethyl acetate, and a gradient of petroleum ether−acetone yielded 114 fractions (Fr_1−Fr_{114}), These were pooled on the basis of their TLC properties. Fr_{87} to Fr_{90} were combined (1.0 g) and chromatographed over silica gel and eluted with a hexane−ethyl acetate gradient, affording 18 further fractions (Fr_{87-1} to Fr_{87-18}). Fraction Fr_{87-2} was subjected to preparative HPLC to yield **1** (1.1 mg, $t_R = 37.93$ min). Fractions Fr_{91} to Fr_{93} were combined (500 mg) and chromatographed over silica gel and eluted with hexane−ethyl acetate, yielding 23 additional fractions (Fr_{91-1} to Fr_{91-23}). Fraction Fr_{91-7} (23 mg) was applied to preparative HPLC and yielded **2** (1.0 mg, $t_R = 25.87$ min). Fractions Fr_{94} to Fr_{104} were combined (780 mg) and chromatographed over silica gel and eluted with a hexane−ethyl acetate gradient, yielding 14 fractions (Fr_{94-1} to Fr_{94-14}). Fractions Fr_{94-3} to Fr_{94-5} (27 mg) were subjected to preparative HPLC, with the material that eluted at $t_R =$ 21.73 min collected and further purified by preparative TLC (hexane−acetone, 5:6) to yield **3** (2.0 mg, $R_f = 0.43$).

1-Deoxypaclitaxel (1): amorphous power; $[\alpha]^{22}_D$ −57 (*c* 0.05, $CHCl_3$); ^{1}H and ^{13}C NMR data, see Table 1; HRFABMS *m/z* 876.29938 $[M + K]^+$ (calcd for $C_{47}H_{51}NO_{13}K$, 876.29974).

7β,10β-Diacetoxy-2α,5α,13α-trihydroxy-2(3→20)-*abeo*-taxa-4(20),-11-dien-9-one (2): amorphous solid; $[\alpha]^{22}_D$ −89 (*c* 0.05, $CHCl_3$); ^{1}H and ^{13}C NMR data, see Table 1; HRFABMS *m/z* 489.18917 $[M + K]^+$ (calcd for $C_{24}H_{34}O_8K$, 489.18908).

2α,13α-Diacetoxy-10β-hydroxy-2(3→20)-*abeo*-taxa-4(20),6,11-triene-5,9-dione (3): gum; $[\alpha]^{22}_D$ −43 (*c* 0.03, $CHCl_3$); ^{1}H and ^{13}C NMR data, see Table 1; HRFABMS *m/z* 469.16297 $[M + K]^+$ (calcd for $C_{24}H_{30}O_7K$, 469.16285).

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Supporting Information Available: Table of HMBC, NOESY/ROESY NMR data for compounds **1**−**3** and a figure of 2D NMR correlations for **3**. This information is provided free of charge via the Internet at http://www.pubs.acs.org.

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