

A novel 3,8-*seco*-taxane metabolite from the seeds of the Chinese yew, *Taxus mairei*

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Received 25 May 2005; revised 8 July 2005; accepted 11 July 2005

Available online 27 July 2005

This paper is dedicated to Professor Steven V. Ley FRS CBE on the occasion of his 60th birthday

Abstract—The structure of a novel 3,8-*seco*-bicyclic taxanoid metabolite, isolated from the methanol extract of seeds of the Chinese yew, *Taxus mairei*, was established as (11 α H)-3,8-*seco*-taxa-3E,7E,12(18)-triene-2 α ,6 α ,9 β -triol (**1**) on the basis of spectral analysis including ¹H NMR, ¹³C NMR, HMQC, HMBC, NOESY and HR-FABMS.

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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 many taxane-type natural diterpenoids have been found from *Taxus* spp. and some of them exhibit interesting biological activities.² However, very little is known about its production and the many steps involved in assembling its unique structure need to be explored.³ Although more than 300 taxanes diterpenoids have been reported to date,² there are still new taxanes awaiting isolation and structural elucidation. Bicyclic taxanoids, first isolated in 1995,⁴ were considered as the precursor in the biosynthesis of taxanoids, but it still remains unknown.⁵ The isolation of new taxanes might provide important clues in the biosynthesis of paclitaxel, especially for those compounds related to the intermediates of the verticillen pathway. *Taxus mairei*, a tall tree ubiquitous to the southeast region of the People's Republic of China, is the first yew chemically studied in China.⁶ In our continuing search for new taxanoids,⁷ we re-examined the seeds of this plant and resulted in the isolation of a novel less-functionalized bicyclic taxane analogue. In this

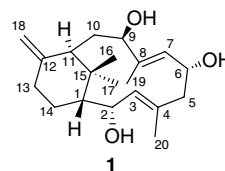


Figure 1. A new taxane isolated from *T. mairei*.

letter, we report the structural elucidation of this new taxane (Fig. 1).

Compound **1** was isolated as white powder from the methanol extract of *T. mairei* seeds. The molecular composition of **1**, C₂₀H₃₂O₃, was established from combined analysis of high-resolution FAB-MS at *m/z* 321 (M+H) and ¹³C NMR spectrum. The ¹H and ¹³C NMR spectral data of **1** was summarized in Table 1. The ¹H NMR spectrum disclosed well-dispersed signals including three-proton signals due to the four methyl groups at δ_H 1.70, 1.66, 0.88 and 0.80, two of the methyl signals at δ_H 0.88 and δ_H 0.80 were COSY-correlated peaks as geminal methyls. These findings together with its *T. mairei* origin suggested that **1** was a taxane derivative. Position of three hydroxy groups and three double bonds were determined by ¹H-¹H-COSY, long-range ¹H-¹H-COSY and HMBC spectra (Fig. 2). Geometry of the double bonds at 3- and 7-positions

Keywords: Taxanes; Bicyclic taxanes; *Taxus mairei*; Isolation.

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Table 1. ^1H and ^{13}C NMR data of taxane **1** (500 MHz for ^1H , 125 MHz for ^{13}C in CDCl_3 , J in Hz)

Position	δ (^1H) mult ^a	J (Hz)	δ (^{13}C) ^b	HMBC	NOESY ^c
1	1.66 (om)		50.7		16, 17
2	4.70 (dd)	11.1, 4.5	68.4	1, 3, 4, 14	17, ^s 20 ^s
3	5.63 (br d)	11.1	130.6	5	5 α , ^s 11, ^s 13 ^s
4	—		133.9		
5 α	2.14 (om)	11.9, 4.2	49.7		3, ^s 5 β , ^s 7 ^w
5 β	2.62 (dd)			3, 4, 6, 20	5 α , ^s 6, ^s 20 ^s
6	4.74 (td)	10.5, 4.6	67.0	5, 8	5 β , ^m 19 ^s
7	4.94 (br d)	9.4	130.1		5 α , 9, ^s 11 ^s
8	—		139.4		
9	4.00 (dd)	11.6, 3.3	77.3	7, 10, 19	7, ^s 10 α , ^m 10 β , 11, ^m 18b ^m
10 α	1.60 (om)		28.1		9, ^m 10 β , ^s 16, ^m 18b ^s
10 β	1.43 (t)	12.7		8, 9, 11, 12, 15	9, ^s 10 α , ^s 16, ^w 17 ^s
11	2.50 (br d)	11.4	42.2		3, ^s 7, ^s 9, ^s 17 ^m
12	—		148.2		
13 $\alpha\beta$	2.30 (om)		35.6	1, 11, 18	3, 18a
14 α	2.06 (om)		20.1		
14 β	1.75 (om)				16
15	—		36.8		
16	0.80 (s)		24.5	1, 11, 15, Me-17	1, ^s 10 α , 10 β , 14 β ^s
17	0.88 (s)		26.9	1, 11, 15, Me-16	1, ^s 2, ^s 10 β , ^s 11, ^m 20 ^s
18a	4.87 (br d)	1.0	105.8	13	13, ^m 18b ^s
18b	4.68 (br d)	1.0		11	9, ^m 10 α , ^s 18a ^s
19	1.66 (d)	1.1	9.8	7, 8, 9	6, ^s 17 ^m
20	1.70 (br s)		16.6	3, 4, 5	2, 5 β , ^s 17

^a Multiplicity: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplet; m, multiplet; br s, broad singlet; br d, broad doublet; o, overlapped.

^b The ^{13}C chemical shifts were extracted from the HMQC experiment (± 0.2 ppm). The numbers in bold character 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).

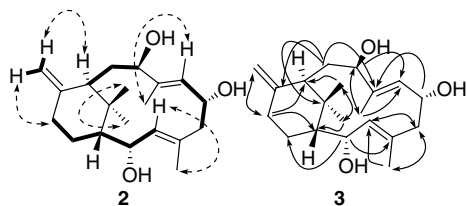


Figure 2. ^1H – ^1H COSY and HMBC correlations. Compound **2**: bold bonds and dashed arrows show ^1H – ^1H COSY and long-range ^1H – ^1H COSY correlations, respectively. Compound **3**: selected HMBC correlations ($\text{H} \rightarrow \text{C}$).

were deduced from NOE correlations: strong NOEs were observed between $\text{H}3$ – $\text{H}5\alpha$, $\text{H}2$ – $\text{H}20$, $\text{H}7$ – $\text{H}9$ and $\text{H}6\beta$ – $\text{H}19$; and not between $\text{H}3$ – $\text{H}20$ and $\text{H}7$ – $\text{H}19$. Configuration of $2\alpha, 6\alpha, 9\beta$ -hydroxy groups and $1\beta, 11\alpha$ -hydrogens were also deduced from the NOEs observed between $\text{H}2$ – $\text{H}17$, $\text{H}2$ – $\text{H}20$, $\text{H}6$ – $\text{H}19$ and $\text{H}3$ – $\text{H}5\alpha$ – $\text{H}7$ – $\text{H}9$ – $\text{H}11$. These observation was consistent with the results of conformational space search calculations.⁸ The most stable conformer is shown in Figure 3 with the observed NOE correlations.

Although more than fifteen 3,8-*seco*-bicyclic taxane diterpenes have been identified to date, **1** is unique and represent the first example of a 3,8-*seco*-bicyclic taxane in which one double bond usually occurring between C11 and C12 shifted to C12 and C18 and usual substituted positions such as C5, C10, C13 and C20 are methylenes and olefinic methyl, while C-6 carbon possess an unusual hydroxy group instead. The finding of this less-substituted bicyclic taxane will shed light on the under-

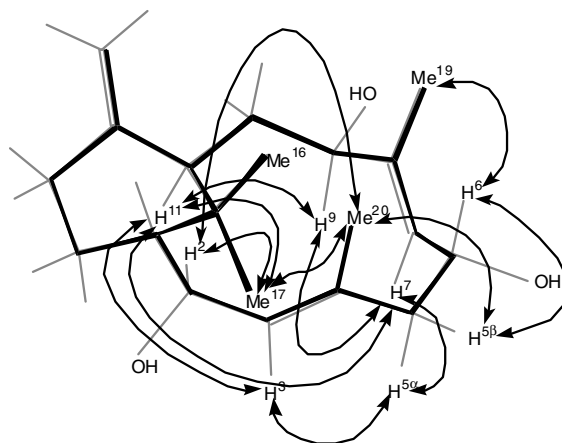


Figure 3. The most stable conformer of **1** deduced from conformational space search calculation, with selected NOESY correlations.

standing of taxane biogenesis. It should be mentioned that recently a 6-hydroxyl diterpene with bicyclic taxane skeleton was also isolated from soft coral *Cespitularia hypotentaculata*.⁹

Acknowledgements

This work was supported partly by the Foundation for Researching New Drugs of People's Republic of China (No: 2003AA2Z3527) and Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry of PR China. We thank Dr.

Takayuki Oritani, emeritus professor of Tohoku University of Japan, for providing extracts for this work.

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