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Canataxpropellane, a novel taxane with a unique polycyclic carbon skeleton (tricyclotaxane) from the needles of *Taxus canadensis*

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Abstract—A novel taxane with an unprecedented 5/5/4/6/6/6-membered hexacyclic skeleton containing [3.3.2]propellane was isolated from the needles of the Canadian yew, *Taxus canadensis*. The structure was established as 2α,10β-diacetoxy-5α,9α,20α-trihydroxy-3α,11α;4α,12α;14α,20-tricyclotaxan-13-one (**1**), which exists as two conformational isomers on the basis of spectroscopic analysis. This compound would be biogenetically derived from a normal 6/8/6-taxane by the intramolecular aldol reaction and [2+2] cycloaddition.

Plants from the genus *Taxus* are a rich source of biologically active diterpenoids belonging to the unique structure class of taxanes.[1,2] Paclitaxel (Taxol®) is one of the most important anti-cancer drugs currently in the market. Extensive phytochemical studies have been carried out to isolate more effective derivatives in the past two decades. As a consequence, more than 500 taxane-type diterpenes have been discovered from various *Taxus* plants to date.[1–11] On the other hand, the biosynthesis of taxanes is still unclear: verticillene is considered to be the most likely intermediate between geranylgeranyl pyrophosphate and taxane diterpenoids.[12] Thus, isolation of taxanes with modified or novel skeleton is of significance. During the course of our search for bioactive taxanes, we have isolated previously a taxane-derived propellane and three di-propellanes from the needles of the Canadian yew, *Taxus canadensis* (Taxaceae).[13,14] Further work on this plant led to the isolation of a novel taxane with a unique 5/5/4/6/6/6-membered ring carbon skeleton and was named canataxpropellane (Fig. 1, **1**).

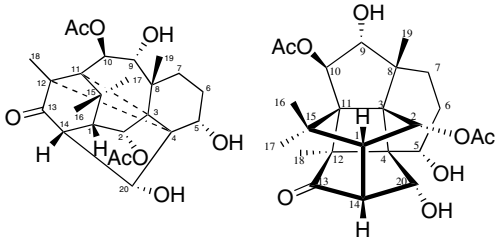

Figure 1. The structure of **1**.

Compound **1** was obtained as a colorless amorphous powder {$[\alpha]_D^{22}$ −39 (*c* 0.10, $CHCl_3$)}. The molecular composition of **1** was established from combined analysis of HR-FABMS at *m*/*z* 449.2188 $[M+H]^+$ (calcd for $C_{24}H_{33}O_8$, 449.2184) and ^{13}C NMR spectrum (Table 1), from which nine indices of hydrogen deficiency were calculated. The ^1H NMR spectrum exhibited four methyl groups at δ_H 1.07, 1.16, 1.31, 1.47 and two acetyl groups at δ_H 2.09 (δ_C 20.9, 169.7), 2.10 (δ_C 21.4, 171.7). These signals together with its plant origin suggested that **1** was a taxane derivative.[15] 1D and 2D NMR data disclosed 24 carbon signals due to one keto carbonyl, five oxymethines, two methines, two methylenes, and

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

Position	Major conformer					Minor comformer				
	δ ^{1}H (Mult)[a]	*J* (Hz)	δ ^{13}C[b]	HMBC	NOESY[c]	δ ^{1}H (Mult)[a]	*J* (Hz)	δ ^{13}C[b]	HMBC	NOESY[c]
1	2.49 (dd)	9.3, 3.3	51.9	2, 3, 13, 15, 16, 20	2,^{s} 16,^{m} 17^{s}	2.56 (dd)	9.0, 3.4	52.0	2, 3, 13, 14, 15, 16	2,^{s} 16,^{m} 17,^{s}
2	5.56 (d)	3.3	76.4	1, 3, 8, 15, **169.7**	1,^{s} 9,^{m} 16,^{s} 19^{s}	5.61 (d)	3.4	75.6	3, **4**, 8, 15, **169.6**	1,^{s} 9,^{m} 16,^{s} 19^{s}
3	—		**53.8**			—		**52.9**		
4	—		**51.5**			—		**48.6**		
5	3.93 (m)		74.8		6,^{s} 7b,^{s} 20^{s}	3.95 (m)		74.8		6a,^{s} 7b,^{s} 20^{s}
6ab	1.83 (m)		28.6	4, 5, 7, 8	5,^{s} 7a,^{s} 7b,^{s} 10,^{s} 18,^{s}	1.90 (o m), 1.81 (o m)		26.2		5,^{s} 7a,^{s} 7b,^{m} 10,^{w} 18^{s}
7a	2.43 (dt)	3.3	29.4	3, 6, 8, 9	6,^{s} 7b,^{s}	2.60 (dt)	3.7	**29.1**	3, 6, 8, 9, 19	6a,^{s} 7b,^{s}
7b	1.11 (o m)				5,^{s} 6,^{s} 7a^{s}	1.13 (o m)				5,^{s} 6a,^{m} 7a^{s}
8	—		**39.5**			—		**38.5**		
9	3.99 (m)	2.8	86.3		2,^{m} 10,^{m} 16,^{s} 19^{s}	3.99 (m)		85.9		2,^{m} 10,^{w} 16,^{s} 19^{s}
9-OH	3.33 (br d)				3.22 (br d)	2.9				
10	5.52 (d)	9.0	82.6	3, 9, 11, 12, 15, 171.7	6,^{s} 9,^{m} 18^{s}	5.43 (d)	9.2	81.5	3, 9, 11, 12, 15, **171.5**	6a,^{w} 9,^{w} 18^{s}
11	—		**57.3**			—		**56.7**		
12	—		**48.6**			—		**48.6**		
13	—		**216.8**			—		**215.3**		
14	2.68 (dd)	9.3, 2.1	52.4	1, 12, 13, 20	20^{s}	2.82 (dd)	9.0, 2.4	50.9	12, 20	20^{s}
15	—		**40.8**			—		**40.9**		
16	1.31 (s)		29.5	1, 11, 15, 17-Me	1,^{m} 2,^{s} 9,^{s} 17^{s}	1.33 (s)		29.6	1, 11, 15, 17-Me	1,^{m} 2,^{s} 9,^{s} 17^{s}
17	1.16 (s)		22.1	1, 11, 15, 16-Me	1,^{s} 16^{s}	1.15 (s)		22.1	1, 11, 15, 16-Me	1,^{s} 16^{s}
18	1.47 (s)		14.0	4, 11, 12, 13	6,^{s} 10^{s}	1.39 (s)		13.5	**4**, 11, 12, 13	6a,^{s} 10^{s}
19	1.07 (s)		27.0	3, 7, 8, 9	2,^{s} 9^{s}	1.08 (s)		**29.0**	3, 7, 8, 9	2,^{s} 9^{s}
20	5.31 (br s)		73.4		5,^{s} 14^{s}	5.29 (br s)		73.3	**4**	5,^{s} 14^{s}
20-OH	2.96 (br s)					2.61 (br s)				
2-OAc	2.09 (s)		20.9	169.7		2.09 (s)		20.9	**169.6**	
			169.7					**169.6**		
10-OAc	2.10 (s)		21.4	171.7		2.11 (s)		21.4	**171.5**	
			171.7					**171.5**		

[a] Multiplicity: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplet; m, mutiplet; 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) and medium (m).

six quaternary carbons. Olefinic carbon was not observed. These observation showed that **1** contained six rings and both the C-11,12, and C-4,20 double bonds were saturated.[1,15] This conclusion was in accordance with the unusual chemical shifts of H_3-18 (δ_H 1.47), H-10 (δ_H 5.52), and C-13 (δ_C 216.8). In addition, the characteristic geminal protons of C-4,20-epoxy or C-5,20-oxetane ring were absented.[15] Compound **1** also lacked a H-3α (δ_H 3.2–3.6, d, $J = \sim 6$ Hz) characteristic to the 6/8/6- and 5/8/6-membered taxanes.[15] A pair of AB doublet ($J = 9.0$ Hz) at δ_H 5.52 and δ_H 3.99 was attributed to H-10 and H-9, respectively.[15] The signal resonated at δ_H 5.56, which correlated to C-1, C-3, C-8, C-15, and a carbonyl carbon at δ_C 169.7 in the HMBC spectrum (Fig. 2), was attributed to H-2, and an acetyl group was attached to C-2. Diagnostic HMBC correlations between H-14 and C-20 as well as between H-1 and C-20 clearly indicated that C-20 connected to C-14 and formed a new six membered ring in **1**. Location of the keto carbonyl group at C-13 was deduced from the correlations of the signal at δ_C 216.8 with H-1, H-14, and H-18. The hydroxy methine signal resonated at δ_H 3.93 was assigned to H-5. Accordingly, the spin system from H-5→H-6→H-7 was easily interpreted in the ^1H–^1H COSY. The cross-peaks of H_3-16 and H_3-17 to C-1, C-11, and C-15 revealed that two methyl groups were connected geminal to C-15, while the ^1H–^{13}C long-range couplings of H_3-19 to C-3, C-7, C-8, and C-9 were indicative of the presence of H_3-19 at C-8. The resonances of H-20 at δ_H 5.31 and C-20 at δ_C 73.4 indicated that the remaining one hydroxyl group was positioned at C-20. The three-bond long-range correlations between H-10 and C-3 as well as between H_3-18 and C-4 indicated that C-3 connected to C-11 and C-4 connected to C-12. The structure of **1** was, therefore, characterized as showed in Figure 1, which we gave a trivial name canataxpropellane according to its originality.

The relative stereochemistry of **1** (Fig. 3) was defined on the basis of the NOESY data, chemical shifts, and their coupling constants. The magnitudes of the vicinal coupling constant ($J = 9.0$ Hz) between H-9 and H-10 indicated that H-9 and H-10 adopted trans-orientations as in other taxanes.[15] The 10α-H orientation was applied by the observation of NOESY correlations of H-10/H_3-18 and H-10/H-6, and the 20α-OH was speculated by that of H-20/H-14 and H-20/H-5. The strong NOESY correlations of H-2/H_3-16, H-2/H_3-19 and H-2/H-1 showed that the 2-acetoxyl group was α-oriented. This

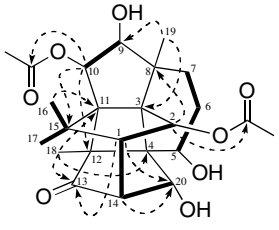


Figure 2. Dashed arrows denoted the selected key HMBC correlations (H→C) of **1**. Bold bones indicated the connectivities deduced by the ^1H–^1H COSY correlations.

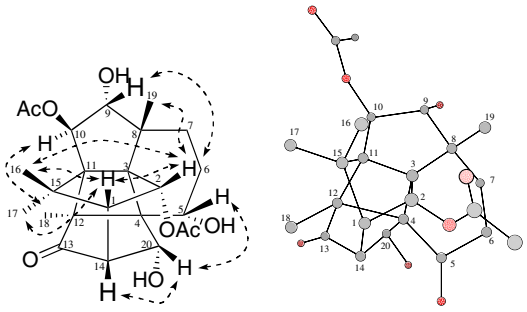
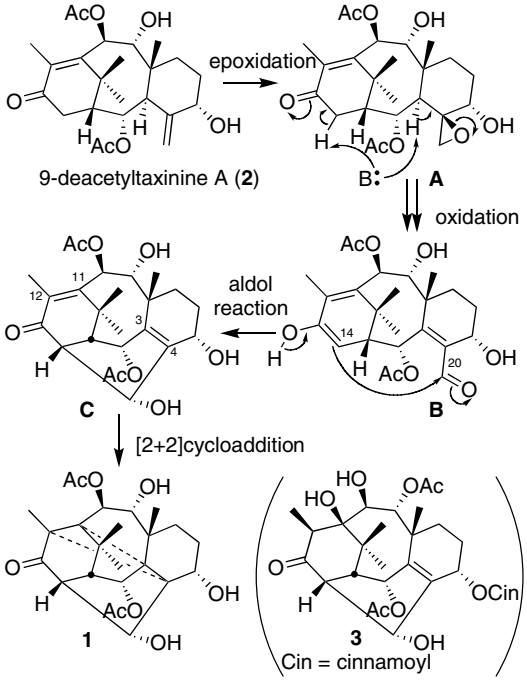


Figure 3. Relative stereochemistry of **1**. The left figure showed selected NOESY correlations by dotted arrows; the right one showed MM2 calculation by minimization and clustering analysis.

substitution pattern is similar to that observed in usual taxane derivatives.

Interestingly, **1** adopted two conformations at ambient temperature. The ^1H NMR was very complex in $CDCl_3$ solution since nearly every signal had a lower intensity double in a ratio of ca. 3:1. Chemical exchange correlations observed between the high and low intensity signals in an NOESY spectrum indicated the presence of conformational isomers and not configurational isomers. The NMR data of minor conformation were assigned after careful interpretation of its 1D and 2D NMR spectra (Table 1). In the minor conformer, H-1, H-10, and H-14 shifted downfield and H_3-18 upfield comparing with the corresponding shifts in the major one. The phenomena of two conformers co-existing in the solution has been previously observed in the 11(15→1) *abeo*taxanes and 3,11-cyclotaxanes.[16]

To the best of our knowledge, compound **1** represents the first example of the novel carbon framework with



Scheme 1. Hypothetical biosynthetic route from 9-deacetyltaxinine A (**2**) to compound **1**.

a rare 5/5/4/6/6/6-membered ring system, which was the most complex core skeleton in the all natural taxanes.[1,6] Proposed hexacyclic structure embodying a unique [3.3.2]propellane ring system (C-2–1–15–11–10–9–8–3–4–12) is entirely consistent with its spectral properties and is chemically and biogenetically reasonable. We propose a plausible biogenetic pathway from 9-deacetyltaxinine A (**2**) to canataxpropellane (**1**) (Scheme 1). It should be emphasized that structure **C** has a 6/8/6/6-tetracyclic skeleton, which shows a cage-like backbone and a similar taxane **3** has been isolated from this plant.[17] The C3–C4, and C11–C12 double bonds were spatially closed and [2+2] cycloaddition could occur to form the cyclobutane ring. The co-existence of the novel type taxane **1** with **3** suggests that the former should be biosynthesized from a tetracyclotaxane-type precursor **C**. The carbon skeleton of **1** was a new addition to the architectural diversity of the taxane family.

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