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Taxezopidine A, a Novel Taxoid from Seeds of Japanese Yew *Taxus cuspidata*

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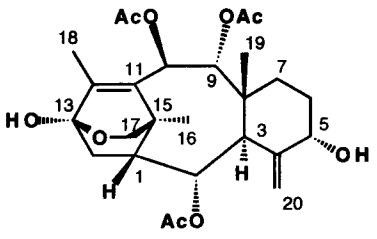
Abstract: A novel taxoid, taxezopidine A (**1**), has been isolated from seeds of Japanese yew *Taxus cuspidata* Sieb. et Zucc. and the structure elucidated on the basis of spectroscopic data. Taxezopidine A (**1**) is the first taxoid with a hemiketal ring at C-11 ~ C-13, C-15, and C-17. © 1997 Elsevier Science Ltd.

In our continuing search for bioactive taxoids, we isolated previously new taxane and related diterpenoids containing various skeletons, taxuspines A ~ H and J ~ Z[1], from stems and leaves of Japanese yew *Taxus cuspidata* Sieb. et Zucc. Further invenstigation on extracts of seeds of this yew led to isolation of a novel taxoid, named taxezopidine A (**1**). In this paper we describe the isolation and structure elucidation of **1**.

The methanolic extract of seeds of the yew collected at Sapporo was partitioned between toluene and water and then the aqueous layer was extracted with chloroform. The chloroform-soluble portion was subjected to a silica gel column followed by reversed-phase column to afford taxezopidine A (**1**, 0.00032%).

Taxezopidine A (**1**)[2] was obtained as a colorless amorphous solid and the molecular formula was established to be $C_{26}H_{36}O_9$ by HRFABMS [*m/z* 493.2428 $(M+H)^+$, Δ -1.0 mmu]. IR absorptions implied that **1** possessed hydroxy (3450 cm^{-1}) and ester (1740 cm^{-1}) groups. Analyses of the ^1H and ^{13}C NMR data and HMQC spectrum of **1** provided three acetyls, one tetrasubstituted olefin, one exomethylene, one ketal carbon, four oxymethines, two methines, one oxymethylene, three methylenes, two quaternary



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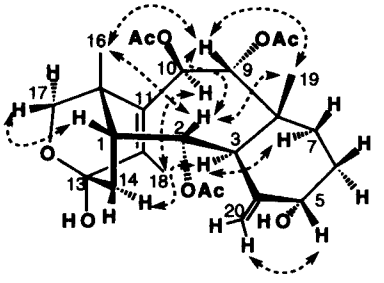

Fig. 1 Relative Stereochemistry of Taxezopidine A (1)
Dotted arrows denote NOESY correlatioin

carbons, and three methyl groups. Connectivities of C-1 to C-3, C-5 to C-7, C-9 to C-10, and C-14 to C-1 were deduced from the ^{1}H-^{1}H COSY spectrum. In the decoupled HMBC (D-HMBC)[3] spectrum, long-range ^{1}H-^{13}C correlations of H-14a, H-17a, and H_3-18 to C-13 (δ 97.50), H-17a to C-1, C-11, and C-15, and H_3-18 to C-11 and C-12 indicated that **1** possessed an oxabicyclo[2.2.2]octene moiety consisting of C-11 ~ C-14, C-1, C-15, C-17, and O-17. HMBC correlations of H_3-18 to C-11, C-12, and C-13 and H_3-16 to C-1, C-11, and C-15 revealed that Me-18 and Me-16 were attached at C-12 and C-15, respectively. HMBC cross-peaks of H-3 to C-8, H-9 to C-8 and C-11, H-10 to C-15, H-1 to C-11 revealed the presence of an eight-membered ring, while the correlations of H-3 to C-4, H-20a to C-3 and C-5, and H-7 to C-3 implied the presence of a cyclohexane moiety with an exomethylene at C-4. Three acetoxy groups were attached at C-2, C-9, and C-10 based on HMBC correlations, while one of two hydroxy groups was connected to C-5 (δ_H 4.22). The remaining hydroxy group was connected to C-13 from comparison of ^{13}C NMR chemical shift of C-13 (δ_C 97.50) with those of hemiketal carbons (δ 96 ~ 98).[4] Thus the structure of taxezopidine A was assigned to be **1**. Relative stereochemistry of **1** was deduced from NOESY data (Fig. 1) and ^{1}H-^{1}H coupling constants. A boat-chair conformation of the eight-membered ring was elucidated from the coupling constant (10.7 Hz) between H-9 and H-10 and NOESY correlations, while a chair conformation of the cyclohexane ring was assigned from NOESY correlations. NOESY correlation between H-1 and H-17a indicated that both protons were quasi-axials and the oxymethylene (C-17) was β-oriented at C-15, while the correlations of H-3 to H-14a and H_3-18 revealed hat **1** has a cage-like backbone conformation.

Taxezopidine A (**1**) is the first taxoid with a hemiketal ring at C-11 ~ C-13, C-15, and C-17 from yew trees. It is noted that **1** has a cage-like backbone conformation similar to usual taxoids consisting 6/8/6-membered ring system, although **1** contains the oxabicyclo[2.2.2]octene moiety.

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