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Structures of Taxane Diterpenoids from the Seeds of Japanese Yew, *Taxus cuspidata*

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Taxacin, a new taxane derivative, and taxagifine were isolated from the seed of *Taxus cuspidata* SIEB. *et* ZUCC. (Taxaceae). The structure and stereochemistry of taxacin were confirmed on the basis of spectral data and X-ray diffraction analysis.

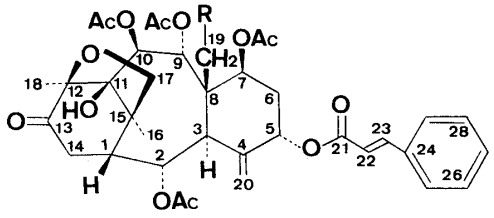
Keywords——*Taxus cuspidata*; Taxaceae; taxagifine; taxacin; taxane derivative; X-ray analysis

Many diterpenoids of the taxane type have been found in the *Taxus* species and some of them show interesting biological activities.[1–6] In the previous paper[7] we reported the isolation and structural characterization of some taxane derivatives as principal constituents of the seeds of *Taxus cuspidata* SIEB. *et* ZUCC. (Japanese yew, Taxaceae). In further studies on the seed of this plant, we have isolated two compounds belonging to the taxane group as minor components and we now report on the structures of these diterpenoids.

Dried seeds of yew were extracted with *n*-hexane and then methanol successively at room temperature. By using silica gel column chromatography and preparative layer chromatography (PLC), two substances, I and II, were isolated from the methanolic extract.

Compound I, isolated as colorless needles, was concluded to be taxagifine[3] (I in Chart 1) based on the infrared (IR), ultraviolet (UV) and proton nuclear magnetic resonance (^{1}H-NMR) spectral and physical data.

Compound II, a new taxane diterpenoid named taxacin, was isolated as colorless prisms. The ^{1}H-NMR spectral properties of II resembled those of compound I except for the disappearance of a methyl signal and appearance of AB pattern signals at δ 4.45 and 5.22. The IR and UV spectra were also similar to those of I. These spectral data indicated that II has a second benzene ring, but the positional relationship between the first, namely cinnamoyl, and the second benzene ring could not be clarified. The structure and stereochemistry of taxacin



I: R=H

II: R=–O–C(=O)– 

Chart 1

TABLE I. Atomic Co-ordinates and Isotropic Thermal Parameters of Non-hydrogen Atoms of II with the Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq} [a)]
C(1)	1.2966 (4)	−0.0326 (3)	1.0702 (2)	3.7 (2)
C(2)	1.2144 (4)	−0.0393 (3)	1.0164 (2)	3.3 (2)
C(3)	1.1238 (4)	−0.1035 (3)	1.0248 (2)	3.1 (2)
C(4)	1.0935 (4)	−0.1504 (3)	0.9639 (2)	3.7 (2)
C(5)	1.0410 (5)	−0.2336 (3)	0.9799 (2)	4.2 (2)
C(6)	0.9425 (4)	−0.2143 (3)	1.0160 (3)	4.3 (2)
C(7)	0.9559 (4)	−0.1523 (3)	1.0717 (2)	3.7 (2)
C(8)	1.0212 (4)	−0.0710 (3)	1.0568 (2)	3.4 (2)
C(9)	1.0476 (4)	−0.0205 (3)	1.1183 (2)	3.3 (2)
C(10)	1.1175 (4)	−0.0680 (3)	1.1657 (2)	3.2 (2)
C(11)	1.2182 (4)	−0.0187 (3)	1.1837 (2)	3.9 (2)
C(12)	1.3024 (5)	−0.0830 (4)	1.2073 (3)	5.3 (3)
C(13)	1.3173 (5)	−0.1517 (4)	1.1574 (3)	5.2 (3)
C(14)	1.3398 (4)	−0.1212 (4)	1.0897 (3)	4.8 (3)
C(15)	1.2778 (4)	0.0250 (4)	1.1283 (2)	4.1 (2)
C(16)	1.2432 (5)	0.1150 (4)	1.1084 (3)	5.2 (3)
C(17)	1.3824 (5)	0.0378 (5)	1.1624 (3)	5.9 (3)
C(18)	1.2913 (6)	−0.1177 (6)	1.2754 (3)	7.2 (4)
C(19)	0.9561 (4)	−0.0138 (3)	1.0128 (3)	4.0 (2)
C(20)	1.0926 (5)	−0.1221 (4)	0.9042 (3)	5.0 (3)
AcC(2)(1)	1.3236 (5)	−0.0151 (4)	0.9256 (2)	4.6 (3)
AcC(2)(2)	1.3909 (5)	−0.0591 (5)	0.8768 (3)	5.8 (3)
C(21)	1.1097 (5)	−0.3648 (3)	1.0231 (3)	4.5 (3)
C(22)	1.1851 (5)	−0.3972 (4)	1.0696 (3)	4.6 (3)
C(23)	1.2022 (4)	−0.4795 (4)	1.0746 (3)	4.5 (2)
C(24)	1.2762 (4)	−0.5226 (4)	1.1173 (3)	4.3 (2)
C(25)	1.3420 (5)	−0.4782 (4)	1.1572 (3)	5.5 (3)
C(26)	1.4135 (6)	−0.5195 (5)	1.1951 (3)	6.6 (4)
C(27)	1.4171 (6)	−0.6092 (5)	1.1915 (3)	6.5 (4)
C(28)	1.3559 (6)	−0.6519 (5)	1.1524 (4)	6.8 (4)
C(29)	1.2833 (6)	−0.6100 (4)	1.1143 (3)	5.8 (3)
AcC(7)(1)	0.8057 (6)	−0.1637 (5)	1.1381 (4)	6.8 (4)
AcC(7)(2)	0.7000 (7)	−0.1282 (6)	1.1505 (4)	8.5 (5)
C(30)	0.9654 (4)	0.1380 (3)	1.0123 (3)	4.4 (2)
C(31)	1.0226 (4)	0.2122 (3)	0.9881 (3)	4.0 (2)
C(32)	0.9870 (5)	0.2932 (3)	1.0033 (3)	4.9 (3)
C(33)	1.0373 (6)	0.3929 (3)	0.9807 (4)	6.0 (3)
C(34)	1.1250 (6)	0.3551 (4)	0.9428 (4)	6.7 (4)
C(35)	1.1598 (6)	0.2745 (4)	0.9275 (4)	6.7 (4)
C(36)	1.1094 (5)	0.2029 (4)	0.9487 (3)	5.4 (3)
AcC(9)(1)	0.9473 (5)	0.0712 (3)	1.1847 (3)	4.9 (3)
AcC(9)(2)	0.8444 (6)	0.0875 (5)	1.2130 (5)	7.9 (4)
AcC(10)(1)	1.0475 (6)	−0.1680 (4)	1.2402 (3)	5.4 (3)
AcC(10)(2)	0.9895 (7)	−0.1729 (5)	1.3012 (4)	7.7 (4)
O(2)	1.2757 (3)	−0.0728 (2)	0.9632 (2)	3.8 (1)
AcO(2)	1.3156 (4)	0.0598 (2)	0.9320 (2)	6.0 (2)
O(5)	1.1127 (3)	−0.2797 (2)	1.0219 (2)	4.9 (2)
Cinnam. O(5)	1.0542 (4)	−0.4060 (2)	0.9896 (2)	6.2 (2)
O(7)	0.8515 (3)	−0.1264 (2)	1.0886 (2)	4.7 (2)
AcO(7)	0.8485 (6)	−0.2182 (5)	1.1686 (4)	12.4 (5)
O(19)	1.0095 (3)	0.0632 (2)	0.9958 (2)	3.9 (2)
Benzo. O(19)	0.8893 (4)	0.1412 (3)	1.0452 (3)	7.2 (3)
O(9)	0.9494 (3)	0.0007 (2)	1.1483 (2)	3.7 (1)
AcO(9)	1.0234 (4)	0.1147 (3)	1.1930 (3)	7.0 (3)
O(10)	1.0634 (3)	−0.0851 (2)	1.2243 (2)	4.0 (2)
AcO(10)	1.0808 (5)	−0.2259 (3)	1.2090 (2)	6.9 (2)
O(11)	1.2014 (3)	0.0392 (2)	1.2343 (2)	5.0 (2)
O(12)	1.3963 (3)	−0.0354 (4)	1.2039 (2)	6.8 (2)
O(13)	1.3209 (5)	−0.2270 (3)	1.1690 (3)	8.4 (3)

a) $B_{eq}=4/3(a^2B_{11}+b^2B_{22}+c^2B_{33})$.

TABLE II. Bond Lengths (Å) of II with Their Standard Deviations in Parentheses

C(1)–C(2)	1.551 (7)	AcC(2)(1)–AcC(2)(2)	1.51 (1)
C(1)–C(14)	1.555 (8)	AcC(2)(1)–O(2)	1.350 (7)
C(1)–C(15)	1.533 (8)	AcC(2)(1)–AcO(2)	1.190 (8)
C(2)–C(3)	1.557 (7)	C(21)–C(22)	1.468 (9)
C(2)–O(2)	1.464 (6)	C(21)–O(5)	1.339 (7)
C(3)–C(4)	1.522 (7)	C(21)–cinnam. O(5)	1.194 (8)
C(3)–C(8)	1.573 (7)	C(22)–C(23)	1.316 (8)
C(4)–C(5)	1.512 (8)	C(23)–C(24)	1.475 (8)
C(4)–C(20)	1.324 (9)	C(24)–C(25)	1.382 (9)
C(5)–C(6)	1.513 (8)	C(24)–C(29)	1.379 (9)
C(5)–O(5)	1.468 (7)	C(25)–C(26)	1.38 (1)
C(6)–C(7)	1.528 (8)	C(26)–C(27)	1.41 (1)
C(7)–C(8)	1.564 (7)	C(27)–C(28)	1.32 (1)
C(7)–O(7)	1.456 (7)	C(28)–C(29)	1.40 (1)
C(8)–C(9)	1.550 (7)	AcC(7)(1)–AcC(7)(2)	1.50 (1)
C(8)–C(19)	1.538 (7)	AcC(7)(1)–O(7)	1.328 (9)
C(9)–C(10)	1.536 (7)	AcC(7)(1)–AcO(7)	1.20 (1)
C(9)–O(9)	1.456 (6)	C(30)–C(31)	1.471 (8)
C(10)–C(11)	1.563 (7)	C(30)–O(19)	1.352 (7)
C(10)–O(10)	1.436 (6)	C(30)–benzo. (19)	1.203 (8)
C(11)–C(12)	1.566 (9)	C(31)–C(32)	1.391 (8)
C(11)–C(15)	1.552 (8)	C(31)–C(36)	1.402 (9)
C(11)–O(11)	1.411 (7)	C(32)–C(33)	1.36 (1)
C(12)–C(13)	1.51 (1)	C(33)–C(34)	1.39 (1)
C(12)–C(18)	1.53 (1)	C(34)–C(35)	1.38 (1)
C(12)–O(12)	1.430 (9)	C(35)–C(36)	1.37 (1)
C(13)–C(14)	1.522 (9)	AcC(9)(1)–AcC(9)(2)	1.48 (1)
C(13)–O(13)	1.210 (9)	AcC(9)(1)–O(9)	1.345 (7)
C(15)–C(16)	1.541 (9)	AcC(9)(1)–AcO(9)	1.212 (8)
C(15)–C(17)	1.544 (9)	AcC(10)(1)–AcC(10)(2)	1.48 (1)
C(17)–O(12)	1.451 (9)	AcC(10)(1)–O(10)	1.361 (8)
C(19)–O(19)	1.438 (6)	AcC(10)(1)–AcO(10)	1.20 (1)

were established by X-ray diffraction analysis of crystals as II, shown in Chart 1. The atomic parameters of nonhydrogen atoms, bond lengths and bond angles are listed in Tables I, II and III respectively. The crystal data are presented in the experimental section.

Only taxacin and taxagifine are known as taxane diterpenoids which have 12β, 17-epoxy and 11β-hydroxyl groups. Taxacin is moreover the first taxane derivative to have a C-19 substituent, namely, the 19-benzoyloxy group.

Recently new diterpenes having a tropone skeleton were isolated from Taiwanese yew.[8] Finding of new diterpenoids such as these new compounds not belonging to the taxane group in Japanese yew is expected as well.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Optical rotations were taken with a JASCO DIP-360 digital polarimeter. Shimadzu IR-430 and Hitachi model 200—20 spectrophotometers were used for the measurements of IR and UV spectra, respectively. Mass spectra (MS) were taken on a JEOL HX-303 mass spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM-FX-60 spectrometer and chemical shifts are given in δ (ppm) with tetramethylsilane as an internal standard (s=singlet, d=doublet, dd=double doublet, m=multiplet).

Isolation——The *n*-hexane (305 g) and methanol (240 g) extracts of seeds (1 kg) of *Taxus cuspidata* SIEB. *et* ZUCC. were obtained as described in the previous paper.[7] The methanolic extract (190 g) was column-chromatographed on silica gel. The fractions eluted with chloroform were rechromatographed on silica gel using *n*-

Table III. Bond Angles (°) of II with Their Standard Deviations in Parentheses

C(2)–C(1)–C(14)	112.1 (4)	C(1)–C(15)–C(17)	107.7 (5)
C(2)–C(1)–C(15)	120.3 (4)	C(11)–C(15)–C(16)	117.5 (5)
C(14)–C(1)–C(15)	112.2 (4)	C(11)–C(15)–C(17)	98.6 (5)
C(1)–C(2)–C(3)	118.6 (4)	C(16)–C(15)–C(17)	105.1 (5)
C(1)–C(2)–O(2)	101.6 (4)	C(15)–C(17)–O(12)	106.3 (6)
C(3)–C(2)–O(2)	105.1 (4)	C(8)–C(19)–O(19)	112.2 (4)
C(2)–C(3)–C(4)	114.5 (4)	AcC(2)(2)–AcC(2)(1)–O(2)	110.5 (5)
C(2)–C(3)–C(8)	118.3 (4)	AcC(2)(2)–AcC(2)(1)–AcO(2)	125.4 (6)
C(4)–C(3)–C(8)	107.1 (4)	O(2)–AcC(2)(1)–AcO(2)	124.0 (6)
C(3)–C(4)–C(5)	110.6 (4)	C(22)–C(21)–O(5)	109.9 (5)
C(3)–C(4)–C(20)	128.8 (5)	C(22)–C(21)–cinnam. O(5)	126.8 (6)
C(5)–C(4)–C(20)	119.7 (5)	O(5)–C(21)–cinnam. O(5)	123.3 (6)
C(4)–C(5)–C(6)	108.4 (5)	C(21)–C(22)–C(23)	120.4 (6)
C(4)–C(5)–O(5)	105.9 (4)	C(22)–C(23)–C(24)	127.5 (6)
C(6)–C(5)–O(5)	109.6 (5)	C(23)–C(24)–C(25)	122.3 (5)
C(5)–C(6)–C(7)	114.3 (5)	C(23)–C(24)–C(29)	118.4 (5)
C(6)–C(7)–C(8)	115.5 (4)	C(25)–C(24)–C(29)	119.3 (6)
C(6)–C(7)–O(7)	104.9 (4)	C(24)–C(25)–C(26)	121.5 (6)
C(8)–C(7)–O(7)	108.8 (4)	C(25)–C(26)–C(27)	117.4 (7)
C(3)–C(8)–C(7)	106.0 (4)	C(26)–C(27)–C(28)	121.4 (7)
C(3)–C(8)–C(9)	109.4 (4)	C(27)–C(28)–C(29)	121.1 (8)
C(3)–C(8)–C(19)	113.6 (4)	C(24)–C(29)–C(28)	119.3 (7)
C(7)–C(8)–C(9)	111.9 (4)	AcC(7)(2)–AcC(7)(1)–O(7)	112.2 (7)
C(7)–C(8)–C(19)	107.6 (4)	AcC(7)(2)–AcC(7)(1)–AcO(7)	126.5 (8)
C(9)–C(8)–C(19)	108.4 (4)	O(7)–AcC(7)(1)–AcO(7)	121.3 (8)
C(8)–C(9)–C(10)	114.5 (4)	C(31)–C(30)–O(19)	112.9 (5)
C(8)–C(9)–O(9)	106.3 (4)	C(31)–C(30)–benzo. O(19)	125.1 (6)
C(10)–C(9)–O(9)	110.4 (4)	O(19)–C(30)–benzo. O(19)	121.9 (6)
C(9)–C(10)–C(11)	114.0 (4)	C(30)–C(31)–C(32)	118.7 (5)
C(9)–C(10)–O(10)	110.6 (4)	C(30)–C(31)–C(36)	121.6 (5)
C(11)–C(10)–O(10)	107.1 (4)	C(32)–C(31)–C(36)	119.7 (5)
C(10)–C(11)–C(12)	109.7 (5)	C(31)–C(32)–C(33)	120.0 (6)
C(10)–C(11)–C(15)	117.0 (4)	C(32)–C(33)–C(34)	121.2 (7)
C(10)–C(11)–O(11)	111.8 (4)	C(33)–C(34)–C(35)	118.5 (8)
C(12)–C(11)–C(15)	100.0 (5)	C(34)–C(35)–C(36)	121.5 (7)
C(12)–C(11)–O(11)	106.8 (5)	C(31)–C(36)–C(35)	119.0 (6)
C(15)–C(11)–O(11)	110.4 (4)	AcC(9)(2)–AcC(9)(1)–O(9)	112.7 (6)
C(11)–C(12)–C(13)	109.5 (5)	AcC(9)(2)–AcC(9)(1)–AcO(9)	125.2 (7)
C(11)–C(12)–C(18)	117.2 (6)	O(9)–AcC(9)(1)–AcO(9)	122.0 (6)
C(11)–C(12)–O(12)	103.9 (5)	AcC(10)(2)–AcC(10)(1)–O(10)	109.7 (6)
C(13)–C(12)–C(18)	113.3 (6)	AcC(10)(2)–AcC(10)(1)–AcO(10)	127.6 (7)
C(13)–C(12)–O(12)	103.3 (5)	O(10)–AcC(10)(1)–AcO(10)	122.7 (7)
C(18)–C(12)–O(12)	108.3 (6)	C(2)–O(2)–AcC(2)(1)	116.7 (4)
C(12)–C(13)–C(14)	116.0 (5)	C(5)–O(5)–C(21)	119.1 (5)
C(12)–C(13)–O(13)	124.5 (6)	C(7)–O(7)–AcC(7)(1)	118.6 (5)
C(14)–C(13)–O(13)	119.2 (6)	C(19)–O(19)–C(30)	117.8 (4)
C(1)–C(14)–C(13)	117.2 (5)	C(9)–O(9)–AcC(9)(1)	116.7 (4)
C(1)–C(15)–C(11)	114.0 (4)	C(10)–O(10)–AcC(10)(1)	117.5 (5)
C(1)–C(15)–C(16)	112.1 (5)	C(12)–O(12)–C(17)	109.8 (6)

hexane–acetone as the eluent. Further purification of the *n*-hexane–acetone fractions (4 : 1) and (19 : 6) by PLC on plates (20 × 20 cm, 0.75 mm thick) coated with Kieselgel PF_{254} (Merck) using *n*-hexane–ethyl acetate (1 : 1) as the solvent gave taxagifine (38 mg) and taxacin (58 mg), respectively.

Taxagifine (I)——Recrystallization from methylene chloride–ethyl acetate gave colorless needles, mp 265—267 °C, 38 mg. $[\alpha]_D^{24}$ −5.4° (c=0.15, $CHCl_3$), MS m/z: 696 (M^+). *Anal.* Calcd for $C_{37}H_{44}O_{13}$: C, 63.78; H, 6.37. Found: C, 63.38; H, 6.28. UV λ_{max}^{EtOH} nm (log ε): 281 (4.35), 223.5 (4.11), 218 (4.17). IR ν_{max}^{KBr} cm^{-1}: 3490, 2940, 1740, 1735, 1721, 1704, 1635, 1370, 1243, 1233, 1214, 1185, 1024, 772. ^{1}H-NMR (in $CDCl_3$) δ: 1.12, 1.22, 1.54 (each 3H, s,

$-CH_3 \times 3$), 1.98, 2.02, 2.12, 2.14 (each 3H, s, $-OCOCH_3 \times 4$), 3.38 (1H, d, $J=9$ Hz, $-C\underline{H}-C=CH_2$), 3.68, 4.14 (each 1H, d, $J=8$ Hz, $-C\underline{H}_2-O- \times 2$), 4.60 (1H, m, $-C=C\underline{H}_2$), 4.92 (1H, d, $J=3$ Hz, $-C\underline{H}-OAc$), 5.22—5.62 (5H, m, $-C\underline{H}-OAc \times 3$, $-C=C\underline{H}_2$, $-C\underline{H}-O$-cinnamoyl), 6.88 (1H, d, $J=16$ Hz, $-C\underline{H}=CH-Ph$), 7.26—7.50 (3H, m, arom. H), 7.58—7.90 (2H, m, arom. H), 7.90 (1H, d, $J=16$ Hz, $-CH=C\underline{H}-Ph$).

Taxacin (II)——Recrystallization from methylene chloride–ethyl acetate furnished colorless prisms, mp 285—287 °C, 58 mg. $[\alpha]_D^{22}-4.8°$ ($c=0.20$, $CHCl_3$), MS m/z: 816 (M^+). *Anal.* Calcd for $C_{44}H_{48}O_{15}$: C, 64.69; H, 5.92. Found: C, 64.22; H, 5.97. UV λ_{max}^{EtOH} nm ($\log\varepsilon$): 281.5 (4.37), 224.5 (4.33), 219 (4.31). IR ν_{max}^{KBr} cm^{-1}: 3440, 2980, 2940, 1762, 1726, 1720, 1706, 1640, 1372, 1252, 1230, 1209, 1179, 1063, 1022, 716. ^{1}H-NMR (in $CDCl_3$) δ: 1.23, 1.29 (each 3H, s, $-CH_3 \times 2$), 2.02, 2.06 (each 3H, s, $-OCOCH_3 \times 2$), 2.17 (6H, s, $-OCOCH_3 \times 2$), 3.53 (1H, d, $J=9$ Hz, $-C\underline{H}-C=CH_2$), 3.61, 4.10 (each 1H, d, $J=8$ Hz, $-C\underline{H}_2-O- \times 2$), 4.45 (1H, d, $J=12$ Hz, $-C\underline{H}_2-OCO-$), 4.83 (1H, m, $-C=C\underline{H}_2$), 5.22 (1H, d, $J=12$ Hz, $-C\underline{H}_2-OCO-$), 5.28—5.72 (5H, m, $-C\underline{H}-OAc \times 3$, $-C=C\underline{H}_2$, $-C\underline{H}-O-$cinnamoyl), 6.13 (1H, dd, $J=2.5$ Hz, 9 Hz, $-C\underline{H}-OAc$), 6.78 (1H, d, $J=16$ Hz, $-C\underline{H}=CH-Ph$), 7.28—8.26 (10H, m, arom. H), 7.95 (1H, d, $J=16$ Hz, $-CH=C\underline{H}-Ph$).

Crystal Data for II——$C_{44}H_{48}O_{15}$, $M_r=816.86$, orthorhombic, space group $P2_12_12_1$, $a=12.955(3)$, $b=15.725(5)$, $c=20.880(6)$ Å, $U=4253(2)$ Å^3, $Z=4$, $D_c=1.276$ g·cm^{-3}, λ(Cu K_α)$=1.5405$ Å. A total of 3449 independent reflections ($\sin\theta/\lambda \leqq 0.588$ Å^{-1}) were collected on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu-K_α radiation with the ω–2θ scan technique, and corrected for the usual Lorentz and polarization effects. The crystal structure was solved by direct and Fourier methods and refined by the block-diagonal least-squares method with anisotropic thermal parameters for C and O and isotropic ones for H. Final R and R_w values are 0.067 and 0.089, respectively.

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