Syntheses of Taxuspine C Derivatives as Functional Inhibitors of P-Glycoprotein, an ATP-Associated Cell-Membrane Transporter

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UV-Irradiation of taxinine and related compounds in acetonitrile induced a smooth transannulation between the *C*-3 and *C*-11 positions without any influence from the *C*-2, *C*-9 and *C*-10 substituents to give tetracyclic taxuspine C derivatives in almost quantitative yields. Photochemical transannular reaction of taxoids possessing a cinnamoyl group in the side-chain was accompanied by an *E,Z*-isomerization of the cinnamoyl moiety. Cellular accumulation of vincristine, a useful drug for cancer chemotherapy, in multidrug-resistant ovarian cancer cells was found to increase most effectively in the case of 5-*O*-benzoylated 5-*O*-decinnamoyltaxuspine C. This indicates that the 5-*O*-benzoylated taxuspine C derivative may be a promising functional inhibitor of P-glycoprotein, which acts as an ATP-associated efflux pump for cancer chemotherapeutic agents.

Key words taxinine; photochemical transannular reaction; taxuspine C; functional inhibitor; P-glycoprotein

P-Glycoprotein,[1] a membrane-spanning protein, plays very important roles as a cell-membrane transporter for a variety of hydrophobic substrates including endogenous steroid hormones and xenobiotics in normal cells.[2] Much attention has been paid to the increased gene-expression of this protein in the course of the chemotherapeutic treatment of advanced solid cancers with hydrophobic antitumour drugs such as Taxol® and Taxotere®.[3] The over-induction of this transport protein results in an emergence of multidrug-resistant cancer cells which display enhanced efflux of these antitumour drugs from the cells.

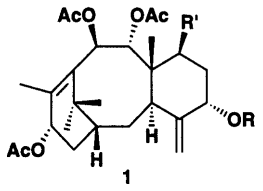
During the search for potent inhibitors of the P-glycoprotein efflux-function to improve cancer chemotherapy,[4] four naturally occurring taxane diterpenoids, *i.e.*, 2′-deacetoxyaustrospicatine (**1a**),[5] 7,2′-dideacetoxyaustrospicatine (**1b**),[6] 2-deacetoxytaxinine J (**1c**)[7] and taxuspine C (**3a**),[5b,8] have been documented to exhibit inhibitory activities comparable to that of verapamil, which is a typical functional inhibitor of the transport protein, as well as azidopine, quinidine and cyclosporin A.[2] Among these taxane diterpenoids, easy preparation of the taxoid **3a** has been previously demonstrated[5b] by the photochemical reaction of taxinine (**2a**) which is a taxane diterpenoid readily available from needles of the Japanese yew.[9] In a preceding paper,[10] we reported convenient methods for regio- and/or chemo-selective *O*-deacylation of taxoid **2a** leading to 9,10-di-*O*-deacetyltaxinine (**2b**), 2-*O*-deacetyltaxinine (**2g**), 2,9,10-tri-*O*-deacetyltaxinine (**2h**) and 5-*O*-decinnamoyltaxinine (taxinine A, **2i**). Our current attention is focused on utilization of these *O*-deacylated taxinines as synthetic intermediates for biologically active taxane diterpenoids.

As a successful synthetic application of the selective *O*-deacylation, we describe herein the preparation of taxuspine C derivatives **3b**—**k**, possessing modified ester moieties at *C*-2, *C*-5, *C*-9 and/or *C*-10, and their inhibitory activities against the ATP-associated efflux of a cancer chemotherapeutic agent by P-glycoprotein.

Results and Discussion

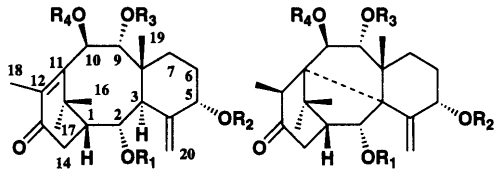
Esterification of the 9,10-di-*O*-deacetylated taxinine **2b** with excess propionic anhydride in pyridine containing 4-dimethylaminopyridine at ambient temperature afforded 9,10-di-*O*-propionated 9,10-di-*O*-deacetyltaxinine (**2c**) in high yield. Employment of benzoyl chloride in place of propionic anhydride in this reaction resulted in the formation of 9,10-di- and 10-mono-*O*-benzoylated 9,10-di-*O*-deacetyltaxinine, (**2d**) and (**2f**), together with a trace of 9-*O*-benzoylated 9,10-di-*O*-deacetyltaxinine (**2e**). In an analogous manner, esterification of 5-*O*-deacylated taxoid (taxinine A, **2i**) with benzoyl chloride led to 5-*O*-benzoylated taxinine A (**2k**).

When a 0.2% solution of taxinine (**2a**) (λ_{max} 278 nm) in dry acetonitrile was irradiated with a high-pressure



1

a: R= $COCH_2CH(NMe_2)Ph$, R'= OAc
b: R= $COCH_2CH(NMe_2)Ph$, R'= H
c: R= COCH=CHPh, R'= OAc



2 3

a: R_1= R_3= R_4= Ac, R_2= COCH=CHPh
b: R_1= Ac, R_2= COCH=CHPh, R_3= R_4= H
c: R_1= Ac, R_2= COCH=CHPh, R_3= R_4= COEt
d: R_1= Ac, R_2= COCH=CHPh, R_3= R_4= Bz
e: R_1= Ac, R_2= COCH=CHPh, R_3= Bz, R_4= H
f: R_1= Ac, R_2= COCH=CHPh, R_3= H, R_4= Bz
g: R_1= H, R_2= COCH=CHPh, R_3= R_4= Ac
h: R_1= R_3= R_4= H, R_2= COCH=CHPh
i: R_1= R_3= R_4= Ac, R_2= H
j: R_1= R_2= R_3= R_4= Ac
k: R_1= R_3= R_4= Ac, R_2= Bz

Chart 1

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mercury arc lamp through a Pyrex filter under argon, the starting substrate **2a** was almost completely consumed after 0.5 h and was converted into the desired taxoid **3a** without detectable formation of other products, though the reaction was accompanied by *E,Z*-isomerization of the cinnamoyl moiety as previously reported.[8] The formation of the *Z*-isomer in this reaction was clearly evidenced by detection of two doublet signals with different coupling constants for the isomeric cinnamoyl groups [δ 7.68 (d, 1H, J=16.1, H-23) and δ 6.39 (d, 1H, J=16.1, H-22) for the *E*-isomer; δ 7.01 (d, 1H, J=12.2, H-23) and δ 5.92 (d, 1H, J=12.2, H-22) for the *Z*-isomer] in the ^{1}H-NMR spectrum of the mixtures which were inseparable by silica gel column chromatography.[11]

Analogous results were obtained in the photochemical reaction of the taxoids **2b—h**, possessing the cinnamoyl moiety at *C*-5, to give the appropriately modified taxuspine C derivatives **3b—h** as stereo isomeric mixtures with a range of *E*/*Z* ratios from 6/4 to 4/6. The structures of the products **3b—h** were assigned on the basis of ^{1}H-NMR spectroscopic data, *i.e.*, disappearance of the doublet signal (δ 3.22—3.55 ppm) with a coupling constant J=*ca.* 6 Hz originating from the *C*-3 proton in the starting compounds **2b—h**, the appearance of two quartet signals (δ 3.49—3.64 ppm for the *E*-isomer; δ 3.30—3.56 ppm for the *Z*-isomer) with a coupling constant J=7.3 Hz assignable to the *C*-12 proton, and two doublet signals (δ 1.22—1.55 ppm for the *E*- and *Z*-isomers) with a coupling constant J=7.3 Hz originating from the *C*-12 methyl group (*cf.* broad singlet signal at δ 2.11—2.43 ppm, for **2b—h**) in the products **3b—h**. Under analogous reaction conditions, the taxoids **2i—k** were consumed more smoothly than in the case of the *C*-5 cinnamoylated taxoids **2a—h**, to give the corresponding taxuspine C derivatives **3i—k** almost quantitatively. For example, complete consumption of taxoid **2i** was observed after only 20 min in this reaction. Thus, photochemical transannulation between the *C*-3 and *C*-11 positions in taxoids **2** to give the corresponding tetracyclic taxuspine C derivatives **3** proceeded without any effect from the *C*-2, *C*-9 and *C*-10 substituents, though the presence of the cinnamoyl group at *C*-5 considerably retarded the reaction. The formation of taxoids **3** in this photochemical reaction can be reasonably explained by virtue of a concerted $\sigma 2s+\pi 2s$ sigmatropic rearrangement between the C_3-H bond and $C_{11}C_{12}$-double bond in the starting compounds **2**.[8,12] The smoothness of the present transannulation apparently can be attributed to the unique cage-conformation of the taxoids **2**.[13]

The cellular accumulation of vincristine, a useful drug for cancer chemotherapy, in multidrug-resistant tumour cells is known to be reduced by increased efflux of this hydrophobic drug from the cells due to the over-induced P-glycoprotein.[14] P-Glycoprotein mediated efflux of this drug has been demonstrated to be effectively inhibited by a variety of compounds including verapamil and taxuspine C (**3a**).[2,4] Therefore, the effects of the taxoids **3b—k** on the cellular accumulation of vincristine in multidrug-resistant human ovarian cancer 2780AD cells were evaluated in comparison with those of verapamil and taxoid **3a**.[15] Results are summarized in Table 1, and are expressed as relative values to that of verapamil.

Table 1. Effects of the Taxoids (**3**) on the Accumulation of Vincristine in Multidrug-Resistant 2780AD Cells

3	R_1	R_2	R_3	R_4	*E*/*Z* Ratio	Vincristine accumulation
a	Ac	Cinnamoyl	Ac	Ac	59/41	108 (*E*-: 96, *Z*-: 100)[a]
b	Ac	Cinnamoyl	H	H	55/45	72
c	Ac	Cinnamoyl	COEt	COEt	55/45	39
d	Ac	Cinnamoyl	Bz	Bz	55/45	43
e	Ac	Cinnamoyl	Bz	H	40/60	38
f	Ac	Cinnamoyl	H	Bz	60/40	41
g	H	Cinnamoyl	Ac	Ac	60/40	33
h	H	Cinnamoyl	H	H	55/45	45
i	Ac	H	Ac	Ac		26
j	Ac	Ac	Ac	Ac		84
k	Ac	Bz	Ac	Ac		125
		Verapamil				100

The amounts of vincristine accumulated in multidrug-resistant human ovarian cancer 2780AD cells were determined in the presence of 1 μg/ml of the taxoids. The values are expressed as the relative amounts of vincristine accumulated in the cells as compared with that of verapamil. *a*) See Ref. 5*b*.

Table 1 shows that (a) *O*-deacylation of the *C*-2, *C*-5, *C*-9 and *C*-10 ester moieties in the taxoids **3** resulted in a drastic reduction of the cellular accumulation of the drug (see, **3b**, **3g—i**) and (b) protection of the *C*-9 and *C*-10 hydroxyl groups with acyl moieties having a short chain-length (*cf.*, **3a**, **3c**) and the introduction of an aromatic substituent to the *C*-5 side-chain are highly effective for binding to the glycoprotein to inhibit the efflux of the antitumor drug from the cancer cells (see, **3a**, **3k**). The present results indicate that the presence of a side chain with appropriate hydrophobicity is a requisite for effective binding to P-glycoprotein. Among the examined taxoids, 5-*O*-benzoylated 5-*O*-decinnamoyltaxuspine C (**3k**) most effectively inhibited the P-glycoprotein function in multidrug-resistant cancer cells. It should be noted that taxoid **3k** has no remarkable cytotoxicity towards normal and cancer cells, indicating that this compound may be regarded as a selective functional inhibitor of P-glycoprotein.

Experimental

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter, using chloroform as a solvent. $[\alpha]_D$-Values are given in units of 10^{-1} deg·cm^2·g^{-1}. Elemental analyses were carried out in the Microanalytical Center of our university. Mass spectra were recorded on a JEOL JMS-SX 102A instrument with a direct inlet system operating at 70 eV. IR spectra were recorded on a Perkin Elmer 1640 IR Fourier transform spectrometer and UV spectra with a Shimadzu-260 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-EX 400 spectrometer using deutero-chloroform as a solvent and tetramethylsilane as the internal standard. The chemical shifts are expressed in δ values (parts per million). Peak multiplicities are denoted by s (singlet), δ (doublet), t (triplet), q (quartet) and m (multiplet) or by a combination of these, *e.g.*, br s (broad singlet) and dd (double doublet), with coupling constants (J) given in Hz. All reactions were conducted under argon. Dry solvents were obtained using standard procedures. Anhydrous magnesium sulfate was used for drying organic solvent extracts. TLC analyses were performed on Silica gel 60 F-254 plates (Merck Art. 5715, 0.25 mm thick) and TLC-scanning was carried out with a Shimadzu CS-9000 dual-wavelength flying-spot scanner. Peak detection on TLC was at 278 nm, which is an absorption maximum of the cinnamoyl moiety. Rotary evaporation was carried out under reduced pressure with the bath temperature below 35 °C unless

otherwise specified. Column chromatographic separation was performed with Merck Silica gel 60 (70—230 mesh).

Materials Taxinine (**2a**) was isolated as prism crystals (mp 265 °C) from needles of the Japanese yew *Taxus cuspidata*.[9,16] According to the procedures described in the preceding paper,[10] 9,10-di-*O*-deacetyltaxinine (**2b**), 2-*O*-deacetyltaxinine (**2g**), 2,9,10-tri-*O*-deacetyltaxinine (**2h**), 5-*O*-decinnamoyltaxinine (taxinine A, **2i**) and 5-*O*-acetylated 5-*O*-decinnamoyltaxinine (taxinine H, **2j**) were prepared.

9,10-Di-*O*-propionylated 9,10-Di-*O*-deacetyltaxinine (2c) To a clear solution of 9,10-di-*O*-deacetyltaxinine (**2b**) (20.0 mg, 0.038 mmol) in pyridine (2.0 ml) containing 4-dimethylaminopyridine (13 mg, 0.106 mmol) was added propionic anhydride (0.025 ml, 0.195 mmol) and the mixture stirred at ambient temperature for 1 d. The reaction mixture was poured into cold water (30 ml) containing 1 N hydrochloric acid (5 ml) with vigorous stirring and extracted with AcOEt (10 ml, 3 times). The combined organic extract was washed with brine, dried and evaporated. The resulting residue was purified by column chromatography, eluting with *n*-hexane–AcOEt (5 : 1) and triturated with *n*-hexane to obtain **2c** (19.2 mg, 79%) as a colorless amorphous powder: mp 218—220 °C (from *n*-hexane–acetone); $[\alpha]_D^{21} = +123.4$ ($c = 1.00$); EI-MS *m/z* (rel. int. %): 634 (M^+, 10), 592 (2), 561 (3), 486 (7), 426 (9), 296 (40), 131 (100); UV λ_{max} (EtOH) nm (ε): 277 (7500); IR (film) cm^{-1}: 1739 (C=O), 1719 (C=O), 1705 (C=O), 1672 (C=O), 1238, 1165; ^{1}H-NMR δ: 7.76 (d, 2H, J=8.3, Ph), 7.67 (d, 1H, J=16.1, H-23), 7.44—7.38 (m, 3H, Ph), 6.44 (d, 1H, J=16.1, H-22), 6.06 (d, 1H, J=10.3, H-10), 5.85 (d, 1H, J=10.3, H-9), 5.56 (br dd, 1H, J=2.0, 6.3, H-2), 5.35 (br s, 2H, H-5, H-20), 4.84 (br s, 1H, H-20), 3.42 (d, 1H, J=6.3, H-3), 2.84 (dd, 1H, J=7.3, 20.0, H-14β), 2.43 (d, 1H, J=20.0, H-14α), 2.40—2.31 (m, 4H, 2 COEt), 2.29 (br s, 3H, H_3-18), 2.23 (dd, 1H, J=2.0, 7.3, H-1), 2.06 (s, 3H, OAc), 2.05—1.65 (m, 4H, H-6, H-7), 1.78 (br s, 3H, H_3-16), 1.16, 1.13 (each t, each 3H, 2 COEt), 1.15 (br s, 3H, H_3-17), 0.92 (br s, 3H, H_3-19); ^{13}C-NMR δ: 199.5, 173.3, 173.1, 169.4, 166.3, 150.8, 145.7, 142.0, 137.9, 134.6, 130.4, 129.1, 129.0, 128.5, 128.4, 117.9, 117.2, 78.2, 75.6, 73.4, 69.7, 48.6, 44.6, 43.2, 37.6, 37.4, 36.1, 28.4, 27.8, 27.6, 27.5, 25.2, 21.4, 17.5, 14.0, 9.2, 9.1; HR EI-MS *m/z*: 634.3146 (Calcd for $C_{37}H_{46}O_9$: 634.3142); *Anal.* Calcd for $C_{37}H_{46}O_9 \cdot 5/6H_2O$: C, 68.39; H, 7.39. Found: C, 68.43; H, 7.26.

Benzoylation of 9,10-Di-*O*-deacetyltaxinine (2b) To a stirred solution of **2b** (113.0 mg, 0.22 mmol) in pyridine (10 ml) containing 4-dimethylaminopyridine (131.8 mg, 1.08 mmol) was added dropwise benzoyl chloride (0.38 ml, 3.27 mmol) at 0 °C and the mixture allowed to warm gradually to ambient temperature and stirred for 22 h. The reaction was quenched by the addition of 1 N hydrochloric acid (10 ml) and the mixture extracted with AcOEt (10 ml, 3 times). The combined organic extract was washed with brine (10 ml), dried and evaporated, and the resulting residue subjected to column chromatography, eluting with $CHCl_3$–AcOEt (50 : 1) to afford 9,10-di-*O*-benzoylated 9,10-di-*O*-deacetyltaxinine (**2d**) (42.4 mg, 26%), 10-*O*-benzoylated 9,10-di-*O*-deacetyltaxinine (**2f**) (92.8 mg, 67%) and 9-*O*-benzoylated 9,10-di-*O*-deacetyltaxinine (**2e**) (7.9 mg, 6%).

9,10-Di-*O*-benzoylated 9,10-Di-*O*-deacetyltaxinine (**2d**): Colorless amorphous powder; mp 72—74 °C (from *n*-hexane–acetone); $[\alpha]_D^{21} = +40.2°$ (c=1.00); EI-MS *m/z* (rel. int. %): 730 (M^+, 1.7), 671 (1), 583 (2), 522 (1), 460 (1), 400 (3), 105 (100); UV λ_{max} (EtOH) nm (ε): 273 (18700), 223 (70000); IR (film) cm^{-1}: 1687 (C=O), 1298; ^{1}H-NMR δ: 7.91 (d, 2H, J=7.4, Ph), 7.86 (d, 2H, J=8.3, Ph), 7.78 (d, 2H, J=6.8, Ph), 7.68 (d, 1H, J=15.6, H-23), 7.5—7.3 (m, 9H, Ph), 6.48 (d, 1H, J=15.6, H-22), 6.39 (d, 1H, J=10.3, H-10), 6.35 (d, 1H, J=10.3, H-9), 5.70 (br dd, 1H, J=2.0, 6.4, H-2), 5.39 (br s, 1H, H-5), 5.37 (br s, 1H, H-20), 4.89 (br s, 1H, H-20), 3.55 (br d, 1H, J=6.4, H-3), 2.87 (dd, 1H, J=6.8, 20.0, H-14β), 2.48 (d, 1H, J=20.0, H-14α), 2.43 (br s, 3H, H_3-18), 2.27 (br dd, 1H, J=2.0, 6.8, H-1), 2.07 (s, 3H, OAc), 2.10—1.70 (m, 4H, H-6, H-7), 1.91 (br s, 3H, H_3-16), 1.12 (br s, 3H, H_3-17), 1.03 (br s, 3H, H_3-19); ^{13}C-NMR δ: 199.5, 169.6, 166.4, 166.1, 165.6, 150.8, 145.9, 142.0, 138.3, 134.6, 133.8, 133.2, 130.4, 130.2, 130.0, 129.8, 129.7, 129.6, 129.4, 129.3, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 117.9, 117.4, 78.3, 76.6, 74.3, 69.8, 48.8, 44.8, 43.4, 37.8, 37.3, 36.2, 28.5, 27.9, 25.4, 21.4, 17.6, 14.2; HR EI-MS *m/z*: 730.3132 (Calcd for $C_{45}H_{46}O_9$: 730.3142); *Anal.* Calcd for $C_{45}H_{46}O_9 \cdot 3/2H_2O$: C, 71.32; H, 6.52. Found: C, 71.63; H, 6.38.

9-*O*-Benzoylated 9,10-Di-*O*-deacetyltaxinine (**2e**): Colorless amorphous powder; mp 128—130 °C (from *n*-hexane–acetone); $[\alpha]_D^{21} = +94.1$ (c=0.17); EI-MS *m/z* (rel. int. %): 626 (M^+, 1), 567 (1), 504 (1), 478 (3), 418 (3), 356 (3), 296 (7), 131 (38), 105 (100); UV λ_{max} (EtOH) nm (ε): 278 (16100); IR (film) cm^{-1}: 1720 (C=O), 1665 (C=O), 1270, 1174; ^{1}H-NMR δ: 8.08 (d, 2H, J=7.8, Ph), 7.76 (d, 2H, J=6.8, Ph), 7.66 (d, 1H, J=16.1, H-23), 7.60 (m, 3H, Ph), 7.42 (m, 3H, Ph), 6.45 (d, 1H, J=16.1, H-22), 6.02 (br d, 1H, J=10.3, H-9), 5.61 (br dd, 1H, J=2.0, 6.4, H-2), 5.34 (br s, 2H, H-5, H-20), 5.17 (br d, 1H, J=10.3, H-10), 4.85 (br s, 1H, H-20), 3.47 (br d, 1H, J=6.4, H-3), 2.87 (dd, 1H, J=6.8, 20.0, H-14β), 2.45 (d, 1H, J=20.0, H-14α), 2.24 (dd, 1H, J=2.0, 6.8, H-1), 2.16 (br s, 3H, H_3-18), 2.06 (s, 3H, OAc), 1.90 (br s, 3H, H_3-16), 2.1—1.70 (m, 4H, H-6, H-7), 1.26 (br s, 3H, H_3-17), 0.98 (br s, 3H, H_3-19); ^{13}C-NMR δ: 199.7, 169.4, 167.2, 166.4, 154.6, 145.7, 142.0, 135.7, 134.6, 133.6, 130.4, 130.1, 129.9, 129.7, 129.4, 129.0, 128.7, 128.6, 128.5, 128.2, 117.9, 117.3, 79.8, 78.3, 72.4, 69.7, 48.8, 44.9, 43.2, 37.9, 37.7, 36.1, 28.5, 27.8, 25.4, 21.4, 17.7, 14.1; HR EI-MS *m/z*: 626.2894 (Calcd for $C_{38}H_{42}O_8$: 626.2880).

10-*O*-Benzoylated 9,10-Di-*O*-deacetyltaxinine (**2f**): Colorless amorphous powder; $[\alpha]_D^{21} = +73.4$ (c=1.00); EI-MS *m/z* (rel. int. %): 626 (M^+, 1.6), 567 (1), 549 (1), 479 (3), 400 (4), 296 (10), 131 (44), 105 (100); UV λ_{max} (EtOH) nm (ε): 273 (15800), 223 (44500); IR (film) cm^{-1}: 1688 (C=O), 1327, 1290; ^{1}H-NMR δ: 8.06 (d, 2H, J=8.3, Ph), 7.76 (d, 2H, J=8.3, Ph), 7.66 (d, 1H, J=15.6, H-23), 7.60—7.36 (m, 6H, Ph), 6.45 (d, 1H, J=15.6, H-22), 6.09 (d, 1H, J=9.8, H-10), 5.55 (br dd, 1H, J=2.0, 5.9, H-2), 5.35 (br s, 1H, H-5), 5.33 (br s, 1H, H-20), 4.89 (br s, 1H, H-20), 4.50 (br dd, 1H, J=3.9, 9.8, H-9), 3.43 (br d, 1H, J=5.9, H-3), 2.83 (dd, 1H, J=6.8, 20.0, H-14β), 2.45 (br d, 1H, J=3.9, 9-OH), 2.44 (d, 1H, J=20.0, H-14α), 2.37 (br s, 3H, H_3-18), 2.15 (dd, 1H, J=2.0, 6.8, H-1), 2.06 (s, 3H, OAc), 2.03—1.60 (m, 4H, H-6, H-7), 1.73 (br s, 3H, H_3-16), 1.15 (br s, 3H, H_3-17), 1.10 (br s, 3H, H_3-19); ^{13}C-NMR δ: 199.5, 171.7 169.7, 166.4, 151.2, 145.6, 142.4, 138.0, 134.6, 133.5, 130.3, 130.2, 129.7, 129.3, 128.9 (2), 128.7 (2), 128.5 (2), 118.0, 116.8, 78.6, 77.2, 76.0, 69.8, 48.9, 45.0, 43.2, 37.8, 37.0, 36.1, 28.5, 26.2, 25.8, 21.4, 17.7, 14.1; HR EI-MS *m/z*: 626.2895 (Calcd for $C_{38}H_{42}O_8$: 626.2880). The Nuclear Overhauser and Exchange Spectroscopy (NOESY) spectrum showed cross peaks for H-10 to H_3-18 and H-3, together with the correlation of H-9 to H-2, H_3-16 and H_3-19.

5-*O*-Benzoylated 5-*O*-Decinnamoyltaxinine (2k) To a stirred solution of taxinine A (**2i**) (10 mg, 0.02 mmol) in pyridine (1 ml) containing 4-dimethylaminopyridine (22 mg, 0.18 mmol) was added benzoyl chloride (0.2 ml, 1.7 mmol) dropwise at 0 °C and the mixture allowed to warm gradually to ambient temperature and stirred for 1 d. The reaction mixture was poured into cold water (10 ml) containing 1 N hydrochloric acid (5 ml) and extracted with $CHCl_3$ (10 ml, 2 times). The combined organic extract was washed with brine (10 ml), dried and evaporated, and the resulting residual oil subjected to column chromatography, eluting with *n*-hexane–toluene–AcOEt (1 : 3 : 1) to afford **2k** (8.5 mg, 70%) and starting material **2i** (2 mg, 20%).

Data for Compound **2k**: Colorless amorphous powder; mp 170—172 °C (from *n*-hexane–acetone); $[\alpha]_D^{22} = +47.2°$ (c=0.25); EI-MS *m/z* (rel. int. %): 580 (M^+, 2.6), 538 (3.6), 521 (2.9), 458 (5), 398 (14), 356 (18), 338 (18), 296 (38), 105 (100); UV λ_{max} (EtOH) nm (ε): 264 (2900), 228 (7100); IR (film) cm^{-1}: 1744 (C=O), 1722 (C=O), 1682 (C=O), 1239; ^{1}H-NMR δ: 7.78 (d, 2H, J=7.3, Ph), 7.60—7.43 (m, 3H, Ph), 5.97 (d, 1H, J=10.3, H-10), 5.92 (d, 1H, J=10.3, H-9), 5.58 (br dd, 1H, J=2.5, 6.8, H-2), 5.42 (br s, 1H, H-20), 5.38 (br t, 1H, H-5), 4.84 (br s, 1H, H-20), 3.27 (br d, 1H, J=6.8, H-3), 2.84 (dd, 1H, J=7.3, 20.0, H-14β), 2.43 (d, 1H, J=20.0, H-14α), 2.23 (dd, 1H, J=2.5, 7.3, H-1), 2.06, 2.05, 2.01, 2.00 (each s, each 3H, H_3-18, 3 OAc), 1.9—1.6 (m, 4H, H-6, H-7), 1.75 (br s, 3H, H_3-16), 1.09 (br s, 3H, H_3-17), 0.94 (br s, 3H, H_3-19); ^{13}C-NMR δ: 199.4, 169.9, 169.6, 169.5, 166.3, 149.4, 141.7, 137.7, 133.6, 133.2, 130.1, 129.7, 128.5 (2), 118.6, 79.5, 75.8, 73.0, 69.8, 48.2, 44.5, 44.2, 37.4, 37.1, 36.4, 28.0, 27.6, 25.2, 21.4, 20.8, 20.7, 17.7, 13.8; HR EI-MS *m/z*: 580.2664 (Calcd for $C_{33}H_{40}O_9$: 580.2672); *Anal.* Calcd for $C_{33}H_{40}O_9 \cdot H_2O$: C, 66.27; H, 7.08. Found: C, 66.10; H, 6.67.

Preparation of Taxuspine C Derivatives 3a—k: General Procedure A solution of the taxinine derivative **2a—k** (10 mg) in dry acetonitrile (5 ml) was irradiated with a 400 W high-pressure mercury arc lamp through a Pyrex filter at ambient temperature under argon for 1 h. After removal of solvent under reduced pressure, the resulting residual oil was triturated with *n*-hexane to obtain the desired taxuspine C derivatives **3a—k**. TLC and ^{1}H-NMR spectroscopic analyses showed complete consumption of starting materials and almost quantitative conversion to the corresponding taxuspine C derivatives **3a—k**, respectively. Taxuspine C derivatives **3a—h** were obtained as inseparable mixtures of *E,Z*-isomers of the cinnamoyl moiety. In this reaction, taxuspine C (**3a**) was obtained as a mixture of the *E*/*Z*-isomers in a 59/41 ratio and structures were confirmed

by comparison with the ^{1}H-NMR spectral data previously reported.[5b,8]

9,10-Di-*O*-deacetyltaxuspine C (**3b**): (*E*/*Z* Ratio: 55/45): EI-MS *m*/*z* (rel. int. %): 522 (M^+, 0.6), 504 (0.5), 480 (0.9), 462 (1.2), 374 (3), 314 (15), 255 (12), 131 (100); ^{1}H-NMR δ: 7.67, 6.96 (each d, 0.55H, 0.45H, J=16.1 or 12.2, H-23), 7.6—7.5 (m, 2H, Ph), 7.43—7.30 (m, 3H, Ph), 6.37, 5.91 (each d, 0.55H, 0.45H, J=16.1 or 12.2, H-22), 6.06, 6.00 (each br d, 0.55H, 0.45H, J=4.9 or 5.4, H-2), 5.80, 5.70 (each br s, 0.55H, 0.45H, H-20), 5.65, 5.57 (each br s, 0.55H, 0.45H, H-20), 5.57, 5.55 (each br s, 0.55H, 0.45H, H-5), 4.32, 4.22 (each d, 0.55H, 0.45H, J=each 9.3, H-9), 4.26, 3.94 (each d, 0.55H, 0.45H, J=each 9.3, H-10), 3.56, 3.35 (each q, 0.55H, 0.45H, J=each 7.3, 12-H), 2.92, 2.54 (each d, 0.55H, 0.45H, J=19.7 or 19.5, H-14α), 2.62—2.40 (m, 1H, H-14β), 2.10 (br d, 1H, J=4.9, H-1), 2.07, 2.04 (each s, 0.55×3H, 0.45×3H, OAc), 2.0—1.1 (m, 4H, H-6, H-7), 1.55, 1.51 (each br s, 0.55×3H, 0.45×3H, H_3-16), 1.54, 1.38 (each d, 0.55×3H, 0.45×3H, J=each 7.3, H_3-18), 1.30, 1.27 (each br s, 0.55×3H, 0.45×3H, H_3-17), 1.24, 1.18 (each br s, 0.55×3H, 0.45×3H, H_3-19); HR EI-MS *m*/*z*: 522.2613 (Calcd for $C_{31}H_{38}O_7$: 522.2618).

9,10-Di-*O*-propionated 9,10-Di-*O*-deacetyltaxuspine C (**3c**): (*E*/*Z* Ratio: 55/45): EI-MS *m*/*z* (rel. int. %): 634 (M^+, 2.5), 592 (1.7), 574 (1.3), 518 (0.9), 486 (5), 296 (37), 131 (100); ^{1}H-NMR δ: 7.66, 7.00 (each d, 0.55H, 0.45H, J=16.1 or 12.2, H-23), 7.63—7.46 (m, 2H, Ph), 7.43—7.28 (m, 3H, Ph), 6.38, 5.90 (each d, 0.55H, 0.45H, J=16.1 or 12.2, H-22), 6.12, 6.10 (each d, 0.55H, 0.45H, J=each 4.9, H-2), 5.83, 5.76 (each s, 0.55H, 0.45H, H-20), 5.74—5.60 (m, 2H, H-9, H-10), 5.69, 5.62 (each s, 0.55H, 0.45H, H-20), 5.65, 5.57 (each t, 0.55H, 0.45H, J=each 9.3, H-5), 3.52, 3.45 (each q, 0.55H, 0.45H, J=each 7.3, H-12), 2.58, 2.56 (each d, 0.55H, 0.45H, J=each 20.5, H-14α), 2.6—2.4 (m, 1H, H-14β), 2.38—2.25 (m, 4H, 2 COEt), 2.25—2.15 (m, 1H, H-1), 2.1—1.1 (m, 4H, H-6, H-7), 2.06, 2.04 (each s, 0.55×3H, 0.45×3H, OAc), 1.69, 1.67 (each br s, 0.55×3H, 0.45×3H, H_3-16), 1.32, 1.30 (each br s, 0.55×3H, 0.45×3H, H_3-19), 1.27, 1.24 (each br d, 0.55×3H, 0.45×3H, J=each 7.3, H_3-18), 1.22, 1.20 (each br s, 0.55×3H, 0.45×3H, H_3-17), 1.12, 1.10 (each t, 0.55×3H, COEt), 1.10, 1.08 (each t, 0.45×3H, COEt); HR EI-MS *m*/*z*: 634.3143 (Calcd for $C_{37}H_{46}O_9$: 634.3142).

9,10-Di-*O*-benzoylated 9,10-Di-*O*-deacetyltaxuspine C (**3d**): (*E*/*Z* Ratio: 55/45): EI-MS *m*/*z* (rel. int. %): 730 (M^+, 0.7), 608 (0.3), 583 (2), 460 (3), 400 (5), 131 (33), 105 (100); ^{1}H-NMR δ: 8.09 (d, 2H, J=7.8, Ph), 7.95 (d, 4H, J=7.3, Ph), 7.73, 7.03 (each d, 0.55H, 0.45H, J=16.1 or 12.2, H-23), 7.65—7.30 (m, 9H, Ph), 6.47, 6.00 (each d, 0.55H, 0.45H, J=16.1 or 12.2, H-22), 6.31—6.05 (m, 3H, H-2, H-9, H-10), 5.90, 5.84 (each s, 0.55H, 0.45H, H-20), 5.74, 5.73 (each s, 0.55H, 0.45H, H-20), 5.70, 5.60 (each t, 0.55H, 0.45H, J=each 8.8, H-5), 3.64, 3.56 (each q, 0.55H, 0.45H, J=each 7.3, H-12), 2.65—2.45 (m, 2H, H-14α, H-14β), 2.26 (m, 1H, H-1), 2.09, 2.07 (each s, 0.55×3H, 0.45×3H, OAc), 2.0—1.1 (m, 4H, H-6, H-7), 1.92, 1.90 (each br s, 0.55×3H, 0.45×3H, H_3-16), 1.44, 1.42 (each br s, 0.55×3H, 0.45×3H, H_3-19), 1.30, 1.27 (each d, 0.55×3H, 0.45×3H, J=each 7.3, H_3-18), 1.27, 1.23 (each s, 0.55×3H, 0.45×3H, H_3-17); HR EI-MS *m*/*z*: 730.3149 (Calcd for $C_{45}H_{46}O_9$: 730.3142).

9-*O*-Benzoylated 9,10-Di-*O*-deacetyltaxuspine C (**3e**): (*E*/*Z* Ratio: 40/60): EI-MS *m*/*z* (rel. int. %): 626 (M^+, 1.6), 567 (0.7), 478 (7), 296 (22), 131 (48), 105 (100); ^{1}H-NMR δ: 8.10—7.95 (m, 4H, Ph), 7.67, 6.97 (each d, 0.4H, 0.6H, J=16.1 or 12.2, H-23), 7.61—7.16 (m, 6H, Ph), 6.37, 5.92 (each d, 0.4H, 0.6H, J=16.1 or 12.2, H-22), 6.15, 6.09 (each d, 0.4H, 0.6H, J=each 6.1, H-2), 5.86, 5.78 (each s, 0.4H, 0.6H, H-20), 5.8-5.6 (m, 1H, H-5), 5.74, 5.68 (each d, 0.4H, 0.6H, J=each 9.3, H-9), 5.67, 5.62 (each s, 0.4H, 0.6H, H-20), 4.53, 4.23 (each d, 0.4H, 0.6H, J=each 9.3, H-10), 3.59, 3.38 (each q, 0.4H, 0.6H, J=each 7.3, H-12), 3.10, 3.00 (each br, 0.4H, 0.6H, OH), 2.56—2.48 (m, 2H, H-14α, H-14β), 2.13—2.00 (m, 1H, H-1), 2.07, 2.04 (each s, 0.4×3H, 0.6×3H, OAc), 2.0—1.1 (m, 4H, H-6, H-7), 1.71, 1.66 (each br s, 0.4×3H, 0.6×3H, H_3-16), 1.56, 1.54 (each br s, 0.4×3H, 0.6×3H, H_3-19), 1.55, 1.39 (each d, 0.4×3H, 0.6×3H, J=each 7.3, H_3-18), 1.28, 1.23 (each br s, 0.4×3H, 0.6×3H, H_3-17); HR EI-MS *m*/*z*: 626.2858 (Calcd for $C_{38}H_{42}O_8$: 626.2880).

10-*O*-Benzoylated 9,10-Di-*O*-deacetyltaxuspine C (**3f**): (*E*/*Z* Ratio: 60/40): EI-MS *m*/*z* (rel. int. %): 626 (M^+, 0.9), 584 (0.3), 567 (0.3), 479 (3), 418 (3), 296 (12), 131 (57), 105 (100); ^{1}H-NMR δ: 8.1—8.0 (m, 4H, Ph), 7.6—7.3 (m, 6H, Ph), 7.68, 6.98 (each d, 0.6H, 0.4H, J=16.1 or 12.7, H-23), 6.41, 5.92 (each d, 0.6H, 0.4H, J=16.1 or 12.7, H-22), 6.13, 6.09 (each d, 0.6H, 0.4H, J=each 6.4, H-2), 5.84, 5.75 (each s, 0.6H, 0.4H, H-20), 5.75—5.60 (m, 1H, H-5), 5.70, 5.63 (each s, 0.6H, 0.4H, H-20), 5.81, 5.69 (each d, 0.6H, 0.4H, J=each 9.8, H-10), 4.55, 4.51 (each d, 0.6H, 0.4H, J=each 9.8, H-9), 3.59, 3.48 (each q, 0.6H, 0.4H, J=each 7.3, H-12), 2.92, 2.85 (each br, 0.4H, 0.6H, OH), 2.65—2.45 (m, 2H, H-14α, H-14β), 2.21—2.16 (m, 1H, H-1), 2.1—1.1 (m, 4H, H-6, H-7), 2.08, 2.05 (each s, 0.6×3H, 0.4×3H, OAc), 1.71, 1.68 (each br s, 0.6×3H, 0.4×3H, H_3-16), 1.32, 1.30 (each s, 0.6×6H, 0.4×6H, H_3-17, H_3-19), 1.29, 1.22 (each d, 0.6×3H, 0.4×3H, J=each 7.3, H_3-18); HR EI-MS *m*/*z*: 626.2880 (Calcd for $C_{38}H_{42}O_8$: 626.2880).

2-*O*-Deacetyltaxuspine C (**3g**): (*E*/*Z* Ratio: 60/40): ^{1}H-NMR δ: 7.66, 6.98 (each d, 0.6H, 0.4H, J=16.1 or 12.7, H-23), 7.62—7.50 (m, 2H, Ph), 7.42—7.32 (m, 3H, Ph), 6.38, 5.90 (each d, 0.6H, 0.4H, J=16.1 or 12.7, H-22), 5.88, 5.77 (each s, 0.6H, 0.4H, H-20), 5.69—5.50 (m, 2H, H-9, H-10), 5.67, 5.62 (each s, 0.6H, 0.4H, H-20), 5.62, 5.54 (each t, 0.6H, 0.4H, J=each 9.3, H-5), 5.14, 5.09 (each d, 0.6H, 0.4H, J=each 4.9, H-2), 3.49, 3.40 (each q, 0.6H, 0.4H, J=each 7.3, H-12), 2.78, 2.75 (each d, 0.6H, 0.4H, J=each 20.5, H-14α), 2.47, 2.46 (each dd, 0.6H, 0.4H, J=each 6.8, 20.5, H-14β), 2.18 (m, 1H, H-1), 2.1—1.1 (m, 4H, H-6, H-7), 2.03, 2.02 (each s, each 3H, 2 OAc), 1.59, 1.57 (each br s, 0.6×3H, 0.4×3H, H_3-16), 1.38, 1.36 (each br s, 0.6×3H, 0.4×3H, H_3-19), 1.26, 1.23 (each d, 0.6×3H, 0.4×3H, J=each 7.3, H_3-18), 1.19, 1.17 (each br s, 0.6×3H, 0.4×3H, H_3-17); HR EI-MS *m*/*z*: 564.2744 (Calcd for $C_{33}H_{40}O_8$: 564.2723).

2,9,10-Tri-*O*-deacetyltaxuspine C (**3h**): (*E*/*Z* Ratio: 55/45): EI-MS *m*/*z* (rel. int. %): 522 (M^+, 0.1), 462 (2.4), 374 (1), 332 (29), 314 (15), 255 (8), 131 (100); ^{1}H-NMR δ: 7.65, 6.95 (each d, 0.55H, 0.45H, J=16.1 or 12.1, H-23), 7.6—7.5 (m, 2H, Ph), 7.42—7.30 (m, 3H, Ph), 6.37, 5.91 (each d, 0.55H, 0.45H, J=16.1 or 12.1, H-22), 5.75, 5.65 (each s, 0.55H, 0.45H, H-20), 5.61, 5.54 (each s, 0.55H, 0.45H, H-20), 5.56 (t, 1H, J=9.3, H-5), 5.02, 4.95 (each d, 0.55H, 0.45H, J=each 5.4, H-2), 4.28, 4.22 (each d, 0.55H, 0.45H, J=9.3, H-10), 4.14, 3.90 (each d, 0.55H, 0.45H, J=each 9.3, H-9), 3.49, 3.30 (each q, 0.55H, 0.45H, J=each 7.3, H-12), 2.79, 2.73 (each d, 0.55H, 0.45H, J=each 20.5, H-14α), 2.58, 2.40 (each dd, 0.55H, 0.45H, J=6.8, 20.5, H-14β), 2.20 (dd, 1H, J=5.4, 6.8, H-1), 1.9—1.1 (m, 4H, H-6, H-7), 1.53, 1.39 (each d, 0.55×3H, 0.45×3H, J=each 7.3, H_3-18), 1.45, 1.42 (each br s, 0.55×3H, 0.45×3H, H_3-16), 1.41, 1.37 (each br s, 0.55×3H, 0.45×3H, H_3-19), 1.22, 1.18 (each br s, 0.55×3H, 0.45×3H, H_3-17).

5-*O*-Decinnamoyltaxuspine C (Taxinine K, **3i**)[17]: Colorless amorphous powder; (lit.[17] mp 167—168 °C); EI-MS *m*/*z* (rel. int. %): 476 (M^+, 17), 458 (8), 416 (28), 398 (22), 356 (67), 314 (58), 296 (100); ^{1}H-NMR δ: 6.06 (d, 1H, J=4.9, H-2), 5.71 (s, 1H, H-20), 5.64 (d, 1H, J=9.8, H-10), 5.61 (d, 1H, J=9.8, H-9), 5.54 (s, 1H, H-20), 4.40 (t, 1H, J=8.8, H-5), 3.78 (q, 1H, J=7.3, H-12), 2.57 (d, 1H, J=20.5, H-14α), 2.45 (dd, 1H, J=6.8, 20.5, H-14β), 2.28 (br s, 1H, OH), 2.10 (dd, 1H, J=4.9, 6.8, H-1), 2.04, 2.02, 2.00 (each s, each 3H, 3 OAc), 2.00 (m, 1H, H-6), 1.8—1.6 (m, 2H, H-6, H-7), 1.64 (br s, 3H, H_3-16), 1.24 (br s, 3H, H_3-19), 1.18 (d, 3H, J=7.3, H_3-18), 1.17 (br s, 3H, H_3-17), 1.06 (m, 1H, H-7); ^{13}C-NMR δ: 216.2, 171.3, 170.2, 170.0, 147.6, 126.1, 82.8, 80.0, 77.5, 75.2, 66.3, 58.0, 52.9, 48.2, 44.9, 42.8, 39.1, 31.6, 29.0, 28.2, 26.9, 26.6, 21.7, 21.4, 21.3, 15.9; HR EI-MS *m*/*z*: 476.2402 (Calcd for $C_{26}H_{36}O_8$: 476.2410). The two signals at δ 4.40 and 3.78 ppm originating from the *C*-5 and *C*-12 protons in the ^{1}H-NMR spectrum closely resembled to those (δ 4.42, 3.79 ppm) of the authentic compounds isolated from the leaves of the Japanese yew *Taxus cuspidata* Sieb. *et* Zucc.[17]

5-*O*-Acetylated 5-*O*-Decinnamoyltaxuspine C (Taxinine L, **3j**)[17]: Colorless amorphous powder; (lit.[17] mp 159—160 °C); $[\alpha]_D^{22} = -15.8$ (c=0.25); EI-MS *m*/*z* (rel. int. %): 518 (M^+, 2.4), 476 (7), 458 (10), 416 (28), 398 (29), 356 (48), 296 (100); IR (film) cm^{-1}: 1741 (C=O), 1229; ^{1}H-NMR δ: 6.09 (br d, 1H, j=5.4, H-2), 5.78 (s, 1H, H-20), 5.67 (d, 1H, J=9.8, H-10), 5.61 (d, 1H, J=9.8, H-9), 5.60 (s, 1H, H-20), 5.52 (t, 1H, J=8.8, H-5), 3.43 (q, 1H, J=7.3, H-12), 2.54 (d, 1H, J=20.0, H-14α), 2.47 (dd, 1H, J=6.8, 20.0, H-14β), 2.16 (dd, 1H, J=5.4, 6.8, H-1), 2.15 (m, 1H, H-6), 2.05, 2.04, 2.02, 2.01 (each s, each 3H, 4 OAc), 1.80—1.65 (m, 2H, H-6, H-7), 1.65 (br s, 3H, H_3-16), 1.28 (br s, 3H, H_3-19), 1.23 (d, 3H, J=7.3, H_3-18), 1.20 (m, 1H, H-7), 1.18 (br s, 3H, H_3-17); ^{13}C-NMR δ: 214.4, 171.0, 170.1, 169.7, 169.5, 142.2, 129.3, 82.3, 79.4, 77.2, 76.7, 65.9, 57.7, 52.3, 47.8, 44.4, 42.6, 38.7, 31.3, 28.7, 26.7, 25.9, 25.5, 21.5, 21.4, 21.1, 21.0, 15.4; HR EI-MS *m*/*z*: 518.2521 (Calcd for $C_{28}H_{38}O_9$: 518.2516). The ^{1}H-NMR spectral data of this product were identical with those of authentic compound isolated from the leaves of the Japanese yew *Taxus cuspidata* Sieb. *et* Zucc.[17]

5-*O*-Benzoylated 5-*O*-Decinnamoyltaxuspine C (**3k**): Colorless amorphous powder; mp 75—77 °C (from *n*-hexane–acetone); $[\alpha]_D^{22} = +17.1$ (c=0.25); EI-MS *m*/*z* (rel. int. %): 580 (M^+, 0.8), 538 (1.6), 520 (1.7), 460 (3), 416 (4), 398 (8), 296 (30), 105 (100); UV λ_{max} (EtOH) nm (ε):

272 (410), 228 (4300); IR (film) cm^{-1}: 1741 (C=O), 1717 (C=O), 1235; ^{1}H-NMR δ: 8.00 (d, 2H, J=7.3, Ph), 7.6—7.4 (m, 3H, Ph), 6.12 (d, 1H, J=5.4, H-2), 5.84 (s, 1H, H-20), 5.75 (t, 1H, J=9.3, H-5), 5.74 (s, 1H, H-20), 5.70 (d, 1H, J=9.8, H-10), 5.64 (d, 1H, J=9.8, H-9), 3.53 (q, 1H, J=7.3, H-12), 2.58 (d, 1H, J=20.5, H-14α), 2.49 (dd, 1H, J=6.8, 20.5, H-14β), 2.25 (m, 1H, H-6), 2.16 (dd, 1H, J=5.4, 6.8, H-1), 2.05, 2.03, 2.03 (each s, each 3H, 3 OAc), 1.83-1.70 (m, 2H, H-6, H-7), 1.69 (br s, 3H, H_3-16), 1.30 (br s, 3H, H_3-19), 1.22 (d, 3H, J=7.3, H_3-18), 1.21 (br s, 3H, H_3-17), 1.20 (m, 1H, H-7); ^{13}C-NMR δ: 214.1, 171.0, 170.0, 169.6, 165.9, 142.1, 133.1, 130.1, 129.8, 129.7 (2), 128.5 (2), 82.3, 79.8, 77.2, 76.6, 66.1, 57.8, 52.3, 47.9, 44.7, 42.7, 39.0, 31.1, 28.8, 26.8, 26.3, 25.7, 21.4, 21.1, 21.0, 16.0; HR EI-MS m/z: 580.2684 (Calcd for $C_{33}H_{40}O_9$: 580.2672).

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References and Notes

1) Juliano R. L., Ling V., *Biochim. Biophys. Acta*, **455**, 152—162 (1976).
2) Bosch I., Croop J., *Biochim. Biophys. Acta*, **1288**, 37—54 (1996) and references cited therein; Stein W. D., *Physiol. Rev.*, **77**, 545—590 (1997); Callaghan P., Berridge G., Ferry D. R., Higgins C. F., *Biochim. Biophys. Acta*, **1328**, 109—124 (1997).
3) Arbuck S. G., Blaylock B. A., "Taxol®, Science and Applications," ed. by Suffness M., CRC Press, Boca Raton, FL, 1995, pp. 379—415; Farina V., "The Chemistry and Pharmacology of Taxol® and Its Derivatives," Pharmacochemistry Library, Vol. 22, ed. by Timmerman H., Elsevier, Amsterdam, 1995.
4) Kobayashi J., Hosoyama H., Wang X.-X., Shigemori H., Koiso Y., Iwasaki S., Sasaki T., Naito M., Tsuruo T., *Bioorg. Med. Chem. Lett.*, **7**, 393—398 (1997) and references cited therein.
5) *a*) From *Austrotaxus spicata*: Ettouati L., Ahond A., Convert O., Laurent D., Poupat C., Potier P., *Bull. Soc. Chim. Fr.*, **1988**, 749—755; *b*) from *Taxus cuspidata*: Kobayashi J., Ogiwara A., Hosoyama H., Shigemori H., Yoshida N., Sasaki T., Li Y., Iwasaki S., Naito M., Tsuruo T., *Tetrahedron*, **50**, 7401—7416 (1994); Zhang Y., Li X., Wu L., *Zhongcaoyao*, **27**, 200—202 (1996); *c*) from *Taxus wallichiana*: Zhang J.-Z., Fang Q.-C., Liang X.-T., He C.-H., *Chin. Chem. Lett.*, **5**, 497—500 (1994); Zhang J.-Z., Fang Q.-C., Liang X.-T., He C.-H., Kong M., He W.-Y., Jin X.-L., *Phytochemistry*, **40**, 881—884 (1995); Chattopadhyay S. K., Kulshrestha M. K., Saha G. C., Sharma R. P., Kumar S., *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **35B**, 508—509 (1996); Banerjee S., Upadhyay N., Kukreja A. K., Ahuja P. S., Kumar S., Saha G. C., Sharma R. P., Chattopadhyay S. K., *Planta Med.*, **62**, 333—335 (1996); *d*) from *Taxus baccata*: Guo Y., Diallo B., Jaziri M., Vanhaelen-Fastre R., Vanhealen M., Ottinger R., *J. Nat. Prod.*, **58**, 1906—1912 (1995); Breeden S. W., Jordan A. M., Lawrence N. J., McGown A. T., *Planta Med.*, **62**, 94—95 (1996); Rojatkar S. R., Sinha B., Sawaikar D. D., Sonawane K. B., Pawar S. S., Panse G. T., Ravindranathan T., Nagasampagi B. A., *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **36B**, 114—117 (1997).
6) *a*) From *Taxus wallichiana*: Ref. 5*c*; *b*) from *Taxus cuspidata*: Kobayashi J., Inubushi A., Hosoyama H., Yoshida, N. Sasaki T., Shigemori H., *Tetrahedron*, **51**, 5971—5978 (1995).
7) *a*) From *Taxus mairei*: Liang J., Min Z., Niwa M., *Huaxue Xuebao*, **46**, 1053—1054 (1988); Yang S.-J., Fang J.-M., Cheng Y.-S., *Phytochemistry*, **43**, 839—842 (1996); Shen Y.-C., Tai H.-R., Hsieh P.-W., Chen C.-Y., *Chin. Pharm. J.* (Taipei), **48**, 207—217 (1996); *b*) from *Austrotaxus spicata*: Ref. 5*a*; *c*) from *Taxus yunnanensis*: Zhang H., Takeda Y., Minami Y., Yoshida K., Matsumoto T., Xiang W., Mu O., Sun H., *Chem. Lett.*, **1994**, 957—960; *d*) from *Taxus cuspidata*: Ref. 5*b*; *e*) from *Taxus wallichiana*: Ref. 5*c*; Chattopadhyay S. K., Saha G. C., Kulshrestha M., Sharma R. P., Kumar S., *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **35B**, 175—177 (1996); Singh B., Gujral R. K., Sood R. P., Duddeck H., *Planta Med.*, **63**, 191—192 (1997); *f*) from *Taxus baccata*: Ref. 5*d*; Rojatkar S. R., Sinha B., Sawaikar D. D., Sonawane K. B., Pause G. T., Ravindranathan T., Nagasampagi B. A., *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **35B**, 752—753 (1996).
8) Kobayashi T., Kurono M., Sato H., Nakanishi K., *J. Am. Chem. Soc.*, **94**, 2863—2865 (1972).
9) Kingston D. G. I., Molinero A. A., Rimoldi J. M., "The Taxane Diterpenoids," Progress in the Chemistry of Organic Natural Products, Vol. 61, ed. by Herz W., Kirby G. W., Moore R. E., Steglich W., Tamm Ch., Springer-Verlag, Wein, 1993.
10) Sako M., Suzuki H., Yamamoto N., Hirota K., Maki Y., *J. Chem. Soc., Perkin 1*, **1998**, 417—421.
11) Kobayashi *et al.* have reported that these isomers are separable by HPLC using Develosil ODS HG-5 column and MeOH/H_2O (80/20) as an eluent.[5b]
12) Photolysis of Taxol®, possessing a fused oxetane ring in the molecule, has been documented to give the corresponding pentacyclic derivative constructed by photochemical transannulation between the *C*-3 and *C*-11 positions in a similar manner to that of taxinine (**2a**) leading to taxuspine C (**3a**). The mechanism for this reaction, however, has been proposed to involve a triplet excitation of the *C*-9 carbonyl group and subsequent oxa-di-π-methane rearrangement, in which the initial steps differ from that of the transannular reaction of the taxoid **2a**. *cf.* Chen S.-H., Farina V., Huang S., Gao Q., Golik J., Doyle T. W., *Tetrahedron*, **50**, 8633—8650 (1994).
13) Morita H., Wei L., Gonda A., Takeda K., Itokawa H., Fukaya H., Shigemori H., Kobayashi J., *Tetrahedron*, **53**, 4621—4626 (1997).
14) Endicott J. A., Ling V., *Ann. Rev. Biochem.*, **58**, 137—171 (1989); Gottesman M. M., Pastan I., *ibid.*, **62**, 385—427 (1993).
15) The 2780AD cells were incubated in a phosphate-buffer solution containing [^{3}H]vincristine and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid with or without the taxoids and verapamil, according to the known method (*cf.*, Tsuruo T., Iida H., Tsukagoshi S., Sakurai Y., *Cancer Res.*, **41**, 1967—1972 (1981)). Radioactivity of the supernatant fluid obtained after centrifugation of the mixture was counted in a liquid scintillation system for the biological evaluation.
16) Yoshizaki F., Madarame M., Takahashi C., Hisamichi S., *Shoyakugaku Zasshi*, **40**, 429—431 (1986); Yashizaki F., Yanagihashi R., Hisamichi S., *ibid.*, **42**, 151—152 (1988).
17) Chiang H.-C., Woods M. C., Nakadaira Y., Nakanishi K., *Chem. Commun.*, **1967**, 1201—1202.