An Efficient Conversion of Taxinine to Taxinine NN-1, an Anticancer Agent and a Modulator of Multidrug-Resistant Tumor Cells

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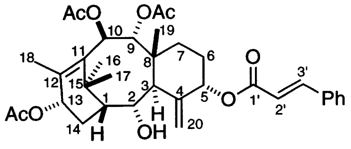
Taxinine NN-1 (**1**), which shows significant activities as a modulator of multidrug-resistant cancer cells and as an anticancer agent in an in vitro assay based on a HCC panel, was synthesized in order to obtain sufficient material for a higher order bioassay from easily available taxinine (**2**). The synthesis was achieved via intermediate **8**, which was derived from **2** by the stepwise protection of a 9,10-dihydroxyl group as acetonide and a 2-hydroxyl group as a MOM protecting group. The temporary elimination of a cinnamoyl group at C-5 of **8** and successive reduction of a C-13 carbonyl group of the resulting **9** gave **10** and the undesired 13-epimer **11**. The latter was recycled to **9** by oxidation with MnO_2. Stepwise acetylation and cinnamoylation at C-13 and C-5 of **10** and successive deprotection of the acetonide protecting group at C-9,10 of the resulting **13** gave diol **14**. Diacetylation of **14** and deprotection of the MOM protecting group at C-2 of the resulting **15** gave **1**. The overall yield of **1** was 45% in 11 steps from **2**.



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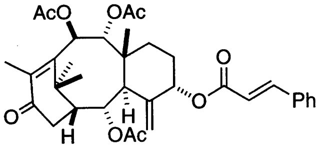

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One of the mechanisms of multidrug resistance (MDR) in cancer chemotherapy is attributed to reduced accumulation of antitumor agents in resistant cells as compared to their drug-sensitive parental cells. Overexpression of a membrane glycoprotein termed P-glycoprotein was widely observed in various multidrug-resistant cell lines. P-Glycoprotein could be a pump molecule that transports antitumor agents outside the cells in a manner analogous to the ATP-driven ion pumps, involving the conformational change of P-glycoprotein induced by ATP hydrolysis.[1] We recently examined the effect of taxinine NN-1 (**1**)[2−4] on the cellular accumulation of vincristine (VCR) in MDR human ovarian cancer 2780AD.[5−9] Taxinine NN-1 (**1**) showed the strongest activity toward VCR accumulation in MDR tumor cells compared with those of previously reported taxoids.[10a−h] The value of VCR accumulation with taxinine NN-1 (**1**) is 670% of control and 323% of verapamil at 1 μg/mL.[5−9,11]

We also examined the effect of **1** as an anticancer agent. The in vitro primary screen, which consists of different human cancer cell lines (HCC) against the compounds tested, gives a characteristic profile or “fingerprint” of cellular response. The profile contains much information that is useful for further research.[12,13] The result of primary screening of taxinine NN-1 (**1**) in vitro based on a panel of 39 kinds of HCC by the Japanese Cancer Chemotherapy Center suggests that **1** possibly belongs to a new mechanistic class and is a new member of anticancer agents.[5,14,15]

Since taxinine NN-1 (**1**) was a very minor compound (0.001% of fresh needles and stems), we decided to examine the efficient synthesis of **1** from taxinine (**2**), a major component of *Taxus cuspidata* (0.1% from fresh needles and stems), for the extensive in vivo assay in animal models.

Results and Discussion

Regio- and stereoselective reduction of the C-13 carbonyl group and regioselective hydrolysis of the acetoxy group at C-2 are necessary for the conversion of **2** to **1**. The hydrolysis of **2** with an aqueous alkali solution in a mixture of MeOH and 1,4-dioxane gave 9,10-diol **3** in 92% yield (Scheme 1). The further hydrolysis of **3** to 2,9,10-triol **4** needed a prolonged reaction time (3.5 h) under these conditions or more drastic conditions, and the yield of **4** became lower than that of **3** (less than 49%). Since this result seemed to suggest that C-2 was the most hindered position of C-2, -9, and -10, we attempted the selective diacetylation at C-9 and C-10 of **4** with 2 equiv of Ac_2O. Unexpectedly, the reaction gave a complex mixture of monoacetates, diacetates, and triacetate **2**. The experimental results may be explained by the neighboring groups' participation and acyl group migration. The attempts to reduce the 13-carbonyl group of taxinine **2** and acetonide **8**, which possess an α-cinnamoyloxy group at C-5, were unsuccessful because of the steric hindrance induced by the α-cinnamoyloxy group. Actually the NOE experiments of taxinine derivatives suggest that the cinnamoyl group connected to the C-5 oxygen is located near the C-13 carbonyl group. So we decided to eliminate the cinnamoyl group temporarily in the course of reduction of the C-13 carbonyl group.

Protection of the 9,10-dihydroxyl groups of **3** as acetonide and successive hydrolysis of the acetoxy group at C-2 in the resulting **5** gave the 2-hydroxy derivative **6** and the

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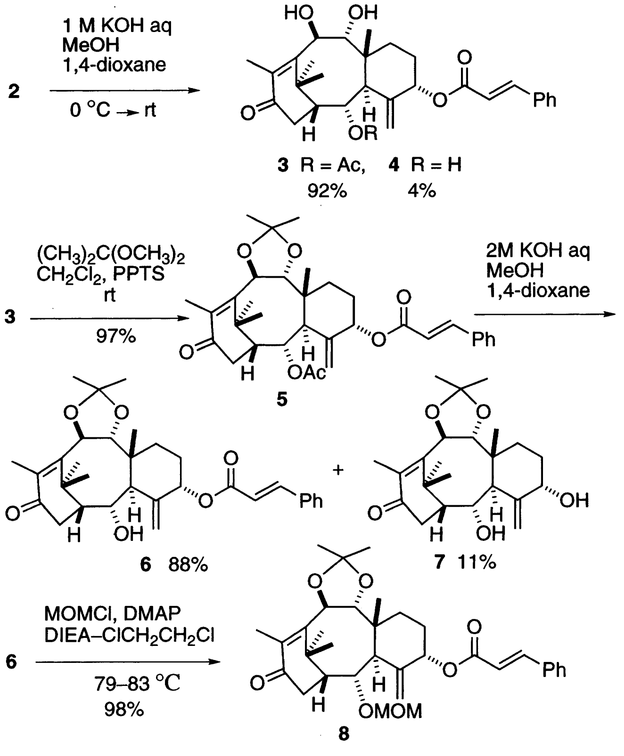
Table 1. Reduction of **9** with $NaBH_4$ under Different Conditions

entry	reagents (equiv)	reaction conditions	yield (%)		
			10	**11**	**9**
1	$NaBH_4$ (32), $CeCl_3$·$7H_2O$ (5), THF/MeOH	0−5 °C, 1.5 h	45	44	8
2	$NaBH_4$ (20), $CeCl_3$·$7H_2O$ (5), 1,4-dioxane/MeOH	22 °C, 11 h	54	22	14
3	$NaBH_4$ (10), $CeCl_3$·$7H_2O$ (4), 1,4-dioxane	22 °C, 20.5 h	52	43	2
4	$NaBH_4$ (10), triethylene glycol, 1,4-dioxane	22 °C, 18 h	54	3	4

Scheme 1

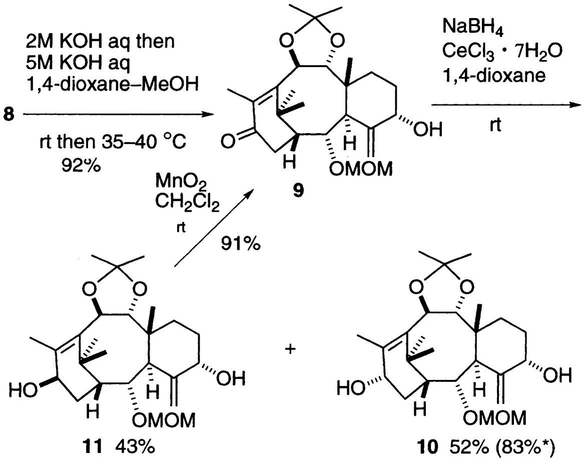


2,5-dihydroxy derivative **7** in 88% and 11% yields, respectively. Further protection of **6** with MOMCl in the presence of DMAP in a mixture of DIEA and dichloroethane gave compound **8** in almost quantitative yield (Scheme 1).

Hydrolysis of **8** with KOH in a mixture of 1,4-dioxane and MeOH gave the 5-hydroxy derivative **9** in 92% yield. After various attempts to reduce **9**, we found that reduction with $NaBH_4$ gave the best results. Since the solubility of **9** in MeOH is low, we tried several solvents in the reduction of **9** with $NaBH_4$, and a portion of the results are shown in Table 1. Reduction of the C-13 carbonyl group of **9** with $NaBH_4$-$CeCl_3$ in 1,4-dioxane gave a mixture of the desired 13α-hydroxy derivative **10** and its 13-epimer **11** in 52% and 43% yields, respectively. Although stereoselectivity in the reduction of **9** is low under these conditions, the total yield of **10** and **11** is the best under the conditions shown in Table 1. The inversion of the stereochemistry of 13*β*-OH of **11** by the Mitsunobu reaction was unsuccessful probably because of the steric hindrance at C-13. Since the regioselective oxidation of 13*β*-OH in 5α,13*β*-diol **11** with active MnO_2 gave **9** in 91% yield,[16] undesired epimer **11** was recycled by oxidation with MnO_2 and successive reduction with $NaBH_4$. The yield of **10** was improved from 52% to 83% by recycling the unwanted product **11** three times (Scheme 2).

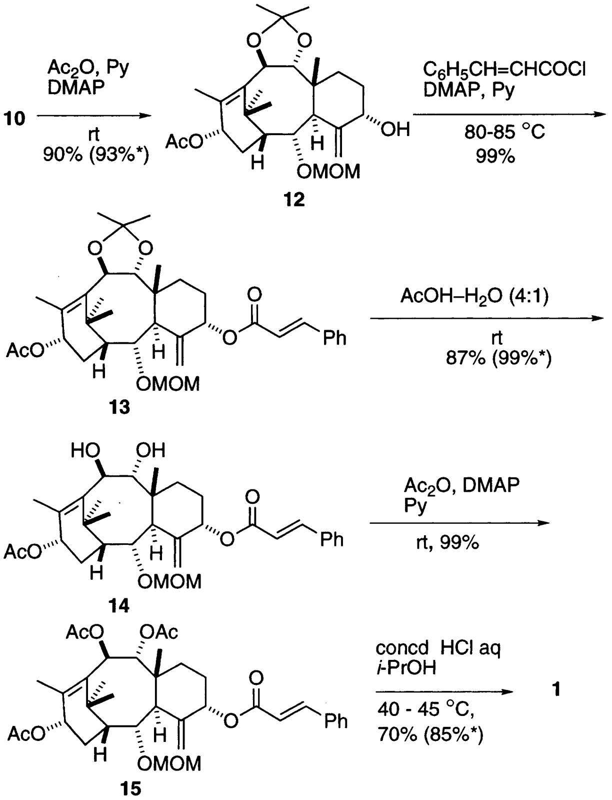
The regioselective acetylation of 13α-OH of **10** was achieved with Ac_2O-DMAP in pyridine at room temperature, which proceed in 93% yield. The cinnamoylation of 5α-OH of the resulting **12** with cinnamoyl chloride-DMAP in pyridine at 80−85 °C gave the desired 13α-acetoy-5α-cinnamoyloxy derivative **13** in almost quantitative yield.

Scheme 2



*The yield in the parenthesis is based on three recyclings of undesired C-13 epimer **11**.

Scheme 3



*The yields in the parentheses are based on recovered starting material.

Deprotection of acetonide **13** with 80% aqueous acetic acid gave 9α,10*β*-diol **14**, and successive acetylation of the resulting **14** gave triacetate **15**. Deprotection of the 2-MOMO group of **15** with concentrated HCl in MeOH at 40−45 °C gave taxinine NN-1 (**1**) in 85% yield (Scheme 3). The physical and spectral data of synthetic **1** are in good agreement with those of natural taxinine NN-1 (**1**) isolated from the needles of the Japanese yew tree (*T. cuspidata*) as one of the minor products.

In conclusion, we have established the practical synthesis of taxinine NN-1 (**1**) from taxinine (**2**), which is the most abundant product of *T. cuspidata*. The overall yield of **1** from **2** was 45% in 11 steps.

Experimental Section

General Experimental Procedures. All melting points are uncorrected. [α]$_D$ values were measured in $CHCl_3$ on a Horiba Sepa-200 polarimeter. UV spectra were measured in MeOH on a Nihonbunko V-550 UV/vis spectrophotometer. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$. The assignments of ^{1}H NMR spectra were determined by H−H COSY experiments. The assignments of ^{13}C NMR spectra were determined by DEPT, HMBC, and HMQC experiments. HREIMS were recorded on a JEOL-HX 110 instrument. Reactions were run under an atmosphere of N_2 or Ar. Dioxane, dichlomehane, 1,2-dichloroethane, diisopropylethylamine, isopropyl alcohol, and pyridine were distilled from CaH_2. MeOH was distilled from $Mg(OMe)_2$, which was prepared from anhydrous MeOH and Mg. Silica gel 70−200 mesh was employed for column chromatography, and silica gel 230−400 mesh for flash column chromatography.

2α-Acetoxy-5α-cinnamoyloxy-9α,10*β*-dihydroxytaxa-4(20),11-dien-13-one (3) and 5α-Cinnamoyloxy-2α,9α,10*β*-trihydroxytaxa-4(20),11-dien-13-one (4). A mixture of taxinine (**2**, 3.00 g, 4.94 mmol), 1,4-dioxane (310 mL), MeOH (310 mL), and a 1 M aqueous solution of KOH (20 mL) was stirred for 2 h at 0 °C and for 1 h at room temperature. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (100 mL), and the mixture was concentrated to a half of the volume under reduced pressure to eliminate MeOH and extracted with $CHCl_3$ (3 × 200 mL). The combined extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (1 × 300 mL), a saturated aqueous solution of NH_4Cl (1 × 300 mL), and a saturated aqueous solution of NaCl (2 × 200 mL), dried (Na_2SO_4), and concentrated to give a crude product (3.90 g) as an amorphous solid, which was purified by flash chromatography on silica gel [117 g, 3.5 cm i.d. column, EtOAc−hexane (4:6)].

The first elution gave **3** (2.33 g, 92%) as colorless microcrystals ($CHCl_3$): mp 265−266 °C; [α]$^{20}_D$ +169.60° (*c* 1.129, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 276 (4.25), 218 (4.00) nm; IR (KBr) ν_{max} 3484, 2960, 1736, 1716, 1670, 1640, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (2H, m, *o*-Ph), 7.65 (1H, d, J = 16.1 Hz, H-3′), 7.42 (2H, m, *m*-Ph), 7.42 (1H, m, *p*-Ph), 6.44 (1H, d, J = 16.1 Hz, H-2′), 5.52 (1H, br dd, J = 6.2, 2.2 Hz, H-2), 5.33 (1H, br dd, J = 2.8, 2.8 Hz, H-5), 5.32 (1H, br s, H-20a), 4.90 (1H, br dd, J = 9.3, 2.2 Hz, H-10), 4.85 (1H, br s, H-20b), 4.19 (1H, br dd, J = 9.3, 3.9 Hz, H-9), 3.37 (1H, br d, J = 6.2 Hz, H-3), 2.84 (1H, dd, J = 19.9, 7.0 Hz, H-14β), 2.69 (1H, br d, J = 3.9 Hz, 9-O*H*), 2.62 (1H, br d, J = 2.2 Hz, 10-O*H*), 2.43 (1H, d, J = 19.9 Hz, H-14α), 2.16 (1H, dd, J = 7.0, 2.2 Hz, H-1), 2.14 (3H, s, H-18), 2.07 (3H, s, 2-OAc), 1.98 (1H, dddd, J = 14.2, 4.6, 2.8, 2.2 Hz, H-6α), 1.82 (1H, br ddd, J = 15.9, 5.0, 2.2 Hz, H-7β), 1.76 (1H, dddd, J = 14.2, 11.2, 5.0, 2.8 Hz, H-6β), 1.71 (3H, s, H-17), 1.50 (1H, ddd, J = 15.9, 11.2, 4.6 Hz, H-7α), 1.23 (3H, s, H-16), 1.11 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.83 (s, C-13), 169.74 (s, 2-OAc), 166.39 (s, C-1′), 155.26 (s, C-11), 145.54 (d, C-3′), 142.45 (s, C-4), 135.74 (s, C-12), 134.55 (s, *q*-Ph), 130.30 (d, *p*-Ph), 128.93 (d, *m*-Ph), 128.43 (d, *o*-Ph), 118.01 (d, C-2′), 116.59 (t, C-20), 78.68 (d, C-5), 77.77 (d, C-9), 73.37 (d, C-10), 69.82 (d, C-2), 48.82 (d, C-1), 44.46 (s, C-8), 43.17 (d, C-3), 37.99 (s, C-15), 37.60 (q, C-16), 36.13 (t, C-14), 28.52 (t, C-6), 26.24 (t, C-7), 25.29 (q, C-17), 21.16 (q, 2-OAc), 17.69 (q, C-19), 14.12 (q, C-18); HREIMS *m/z* 522.2618 (calcd for $C_{31}H_{38}O_7$, 522.2617); *anal.* C 70.96%, H 7.49%, calcd for $C_{31}H_{38}O_7$, C 71.24%, H 7.33%.

The second elution gave **4** (0.12 g, 4%) as colorless microcrystals: mp 295 °C (crystals turned from colorless to brown at 238 °C and finally decomposed at 295 °C); [α]$^{20}_D$ +178.20° (*c* 1.046, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 276 (4.18), 216 (3.98), 206 (3.95) nm; IR (KBr) ν_{max} 3484, 3072, 1700, 1668, 1642, 1342, 1316, 1182 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (2H, m, *o*-Ph), 7.65 (1H, d, J = 16.0 Hz, H-3′), 7.42 (2H, m, *m*-Ph), 7.42 (1H, m, *p*-Ph), 6.41 (1H, d, J = 16.0 Hz, H-2′), 5.43 (1H, s, H-20a), 5.38 (1H, br dd, J = 1.2, 1.2 Hz, H-20b), 5.33 (1H, br dd, J = 2.6, 2.6 Hz, H-5), 4.89 (1H, dd, J = 9.3, 2.7 Hz, H-10), 4.22 (1H, br ddd, J = 8.3, 6.3, 2.2 Hz, H-2), 4.09 (1H, dd, J = 9.3, 4.2 Hz, H-9), 3.23 (1H, d, J = 6.3 Hz, H-3), 2.85 (1H, dd, J = 19.9, 7.0 Hz, H-14β), 2.61 (1H, d, J = 4.2 Hz, 9-O*H*), 2.54 (1H, d, J = 2.7 Hz, 10-O*H*), 2.37 (1H, dd, J = 7.0, 2.2 Hz, H-1), 2.25 (1H, d, J = 19.9 Hz, H-14α), 2.12 (3H, s, H-18), 2.00 (1H, dddd, J = 14.3, 4.0, 2.6, 1.5 Hz, H-6α), 1.93 (1H, d, J = 8.3 Hz, 2-OH), 1.80 (1H, J = 12.9, 4.2, 1.5 Hz, H-7β), 1.74 (1H, dddd, J = 14.3, 12.9, 4.2, 2.6 Hz, H-6β), 1.65 (3H, s, H-17), 1.47 (1H, ddd, J = 12.9, 12.9, 5.0 Hz, H-7α), 1.26 (3H, s, H-16), 1.15 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.11 (s, C-13), 166.43 (s, C-1′), 155.45 (s, C-11), 145.68 (d, C-3′), 144.15 (s, C-4), 135.17 (s, C-12), 134.49 (s, *q*-Ph), 130.35 (d, *p*-Ph), 128.93 (d, *m*-Ph), 128.46 (d, *o*-Ph), 117.85 (d, C-2′), 117.36 (t, C-20), 78.40 (d, C-5), 77.69 (d, C-9), 73.45 (d, C-10), 68.15 (d, C-2), 51.37 (d, C-1), 45.19 (d, C-3), 44.78 (s, C-8), 38.05 (q, C-16), 37.83 (s, C-15), 35.75 (t, C-14), 28.99 (t, C-6), 26.49 (t, C-7), 25.42 (q, C-17), 17.77 (q, C-19), 13.97 (q, C-18); HREIMS *m/z* 480.2506 (calcd for $C_{29}H_{36}O_6$, 480.2512); *anal.* C 72.18%, H 7.65%, calcd for $C_{29}H_{36}O_6$, C 72.47%, H 7.55%.

2α-Acetoxy-5α-cinnamoyloxy-9α,10*β*-(dimethylmethylenedioxy)taxa-4(20),11-dien-13-one (5). To a solution of **3** (2.00 g, 3.83 mmol) and PPTS (191 mg) in CH_2Cl_2 (38 mL) was added 2,2-dimethoxypropane (9.6 mL). The mixture was stirred for 90 min at room temperature and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (50 mL), and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were washed successively with a saturated aqueous solution of NH_4Cl (1 × 30 mL) and a saturated aqueous solution of NaCl (2 × 200 mL), dried (Na_2SO_4), and concentrated to give a crude product (2.20 g) as an amorphous solid, which was purified by flash chromatography on silica gel [110 g, 3.5 cm i.d. column, EtOAc−hexane (4:6)] to give spectroscopically pure **5** (2.07 g, 97%). Compound **5** was obtained as colorless microcrystals ($CHCl_3$): mp 190−192 °C; [α]$^{20}_D$ +188.67° (*c* 0.265, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 277 (4.43), 217 (4.17), 205 (4.15) nm; IR (KBr) ν_{max} 2996, 1736, 1718, 1674, 1642, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (2H, m, *o*-Ph), 7.65 (1H, d, J = 15.9 Hz, H-3′), 7.42 (2H, m, *m*-Ph), 7.42 (1H, m, *p*-Ph), 6.40 (1H, d, J = 15.9 Hz, H-2′), 5.58 (1H, dd, J = 6.2, 2.0 Hz, H-2), 5.35 (1H, br dd, J = 2.7, 2.7 Hz, H-5), 5.33 (1H, s, H-20a), 4.90 (1H, d, J = 9.2 Hz, H-10), 4.80 (1H, br s, H-20b), 4.33 (1H, d, J = 9.2 Hz, H-9), 3.23 (1H, br d, J = 6.2 Hz, H-3), 2.86 (1H, dd, J = 20.0, 7.1 Hz, H-14β), 2.41 (1H, d, J = 20.0 Hz, H-14α), 2.20 (1H, br dd, J = 7.1, 2.0 Hz, H-1), 2.16 (3H, s, H-18), 2.07 (3H, s, 2-OAc), 1.99 (1H, m, H-6β), 1.79 (1H, m, H-6α), 1.79 (1H, m, H-7α), 1.75 (3H, s, H-17), 1.62 (1H, m, H-7β), 1.51 (3H, s, 9,10-acetonide), 1.44 (3H, s, 9,10-acetonide), 1.24 (3H, s, H-16), 1.05 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.17 (s, C-13), 169.64 (s, 2-OAc), 166.24 (s, C-1′), 155.52 (s, C-11), 145.54 (d, C-3′), 141.64 (s, C-4), 138.42 (s, C-12), 134.52 (s, *q*-Ph), 130.33 (d, *p*-Ph), 128.93 (d, *m*-Ph), 128.42 (d, *o*-Ph), 117.94 (d, C-2′), 116.34 (t, C-20), 108.15 (s, 9,10-acetonide), 81.98 (d, C-9), 78.64 (d, C-5), 75.85 (d, C-10), 69.28 (d, C-2), 49.27(d, C-1), 42.02 (d, C-3), 40.81 (s, C-8), 38.35 (s, C-15), 37.63 (q, C-16), 36.11 (t, C-14), 28.52 (t, C-6), 27.12 (q, 9,10-acetonide), 26.80 (q, 9,10-acetonide), 26.57 (t, C-7), 24.23 (q, C-17), 21.43 (q, 2-OAc), 17.31 (q, C-19), 14.33 (q, C-18); HREIMS *m/z* 562.2923 (calcd for $C_{34}H_{42}O_7$, 562.2931); *anal.* C 72.21%, H 7.88%, calcd for $C_{34}H_{42}O_7$, C 72.57%, H 7.52%.

5α-Cinnamoyloxy-9α,10*β*-(dimethylmethylenedioxy)-2α-hydroxytaxa-4(20),11-dien-13-one (6) and 9α,10*β*-(Dimethylmethylenedioxy)-2α,5α-dihydroyloxytaxa-4(20),-11-dien-13-one (7). To a solution of **5** (1.80 g, 3.20 mmol) in a mixture of 1,4-dioxane (200 mL) and MeOH (200 mL) was added a 2 M aqueous solution of KOH (13 mL). The solution was stirred for 1 h at 0 °C and for 3.5 h at room temperature.

The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL), and the mixture was concentrated to a half of the volume under reduced pressure to eliminate MeOH and extracted with $CHCl_3$ (3 × 200 mL). The combined extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (1 × 30 mL) and a saturated aqueous solution of NaCl (2 × 100 mL), dried (Na_2SO_4), and concentrated to give a crude product (2.20 g) as an amorphous solid, which was purified by flash chromatography on silica gel [88 g, 3.5 cm i.d. column, EtOAc−hexane (4:6)] to give spectroscopically pure **6** (1.47 g, 88%) and **7** (0.14 g, 11%). Compound **6** was obtained as colorless microcrystals ($CHCl_3$): mp 105−107 °C; $[\alpha]^{20}_D$ +201.46° (*c* 0.958, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 277 (4.64), 217 (4.41), 205 (4.41) nm; IR (KBr) ν_{max} 3512, 3076, 2992, 1716, 1670, 1642, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (2H, m, *o*-Ph), 7.64 (1H, d, J = 15.9 Hz, H-3′), 7.43 (2H, m, *m*-Ph), 7.43 (1H, m, *p*-Ph), 6.37 (1H, d, J = 15.9 Hz, H-2′), 5.43 (1H, br s, H-20a), 5.37 (1H, br t, J = 1.2 Hz, H-20b), 5.34 (1H, br dd, J = 2.7, 2.7 Hz, H-5), 4.89 (1H, d, J = 9.2 Hz, H-10), 4.26 (1H, ddd, J = 5.9, 5.7, 2.2 Hz, H-2), 4.22 (1H, d, J = 9.2 Hz, H-9), 3.09 (1H, br d, J = 5.9 Hz, H-3), 2.87 (1H, dd, J = 19.8, 7.0 Hz, H-14β), 2.42 (1H, dd, J = 7.0, 2.2 Hz, H-1), 2.22 (1H, d, J = 19.8 Hz, H-14α), 2.14 (3H, s, H-18), 2.01 (1H, m, H-6β), 1.94 (1H, br s, 2-O*H*), 1.79 (1H, m, H-6α), 1.73 (1H, m, H-7α), 1.68 (3H, s, H-17), 1.59 (1H, m, H-7β), 1.50 (3H, s, 9,10-acetonide), 1.44 (3H, s, 9,10-acetonide), 1.26 (3H, s, H-16), 1.08 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.46 (s, C-13), 166.25 (s, C-1′), 155.65 (s, C-11), 145.67 (d, C-3′), 143.34 (s, C-4), 137.93 (s, C-12), 134.48 (s, *q*-Ph), 130.36 (d, *p*-Ph), 128.92 (d, *m*-Ph), 128.44 (d, *o*-Ph), 117.80 (d, C-2′), 117.08 (t, C-20), 108.02 (s, 9,10-acetonide), 81.96 (d, C-9), 78.34 (d, C-5), 75.83 (d, C-10), 68.19 (d, C-2), 51.87 (d, C-1), 44.05 (d, C-3), 41.11 (s, C-8), 38.32 (s, C-15), 38.06 (q, C-16), 35.84 (t, C-14), 28.95 (t, C-6), 27.18 (q, 9,10-acetonide), 26.80 (t, C-7), 26.80 (q, 9,10-acetonide), 24.40 (q, C-17), 17.41 (q, C-19), 14.21 (q, C-18); HREIMS *m/z* 520.2826 (calcd for $C_{32}H_{40}O_6$, 520.2825); *anal.* C 73.52%, H 7.83%, calcd for $C_{32}H_{40}O_6$, C 73.82%, H 7.74%.

Compound **7** was obtained as colorless plates ($CHCl_3$): mp 188−190 °C or colorless microcrystals (MeOH): mp 203−205 °C; $[\alpha]^{20}_D$ +165.55° (*c* 0.331, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 275 (4.27), 204 (4.09) nm; IR (KBr) ν_{max} 3424, 2992, 2940, 1678, 1545, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.24 (1H, br s, H-20a), 5.22 (1H, br t, J = 1.2 Hz, H-20b), 4.29 (1H, d, J = 9.3 Hz, H-10), 4.25 (1H, br s, H-5), 4.25 (1H, br d, J = 6.2 Hz, H-2), 4.19 (1H, d, J = 9.3 Hz, H-9), 3.29 (1H, br d, J = 6.1 Hz, H-3), 2.81 (1H, dd, J = 19.7, 7.1 Hz, H-14β), 2.37 (1H, dd, J = 7.1, 2.4 Hz, H-1), 2.19 (1H, d, J = 19.7 Hz, H-14α), 2.08 (3H, s, H-18), 1.75 (1H, m, H-6α), 1.67 (1H, m, H-6β), 1.67 (3H, s, H-17), 1.63 (1H, m, H-7α), 1.63 (1H, m, H-7β), 1.49 (3H, s, 9,10-acetonide), 1.44 (3H, s, 9,10-acetonide), 1.23 (3H, s, H-16), 1.03 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.49 (s, C-13), 151.86 (s, C-11), 148.57 (s, C-4), 138.44 (s, C-12), 113.83 (t, C-20), 107.84 (s, 9,10-acetonide), 82.02 (d, C-9), 75.81 (d, C-5), 75.68 (d, C-10), 68.42 (d, C-2), 51.70 (d, C-1), 41.93 (d, C-3), 41.39 (s, C-8), 38.33 (s, C-15), 38.03 (q, C-16), 35.96 (t, C-14), 31.35 (t, C-6), 27.19 (q, 9,10-acetonide), 26.81 (q, 9,10-acetonide), 25.82 (t, C-7), 24.45 (q, C-17), 17.27 (q, C-19), 14.19 (q, C-18); HREIMS *m/z* 390.2402 (calcd for $C_{23}H_{34}O_5$, 390.2406); *anal.* C 70.15%, H 8.51%, calcd for $C_{23}H_{34}O_5$, C 70.74%, H 8.78% (calcd for $C_{23}H_{34}O_5 \cdot 1/4H_2O$, C 69.93%, H 8.80%).[17]

5α-Cinnamoyloxy-9α,10β-(dimethylmethylenedioxy)-2α-(methoxymethoxy)taxa-4(20),11-dien-13-one (8). To a solution of **6** (1.00 g, 1.92 mmol) in a mixture of 1,2-dichloroethane (3.9 mL), 4-(dimethylamino)pyridine (DMAP, 23.5 mg), and diisopropylethylamine (DIEA, 3.35 mL) was added chloromethyl methyl ether (MOMCl, 0.73 mL, 9.61 mmol) dropwise. The solution was stirred at 79−83 °C for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL), and the mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL), a saturated aqueous solution of NH_4Cl (5 mL), and a saturated aqueous solution of NaCl (2 × 20 mL), dried (Na_2SO_4), and concentrated to give a crude product (1.13 g) as an amorphous solid, which was purified by flash chromatography on silica gel [40 g, 3.0 cm i.d. column, EtOAc−hexane (4:6)] to give spectroscopically pure **8** (1.06 g, 98%) as colorless microcrystals ($CHCl_3$): mp 110−112 °C; $[\alpha]^{20}_D$ +228.99° (*c* 0.958, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 279 (4.51), 217 (4.29), 204 (4.31) nm; IR ($CHCl_3$) ν_{max} 2992, 2944, 1716, 1672, 1642, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (2H, m, *o*-Ph), 7.62 (1H, d, J = 15.9 Hz, H-3′), 7.41 (2H, m, *m*-Ph), 7.41 (1H, m, *p*-Ph), 6.41 (1H, d, J = 15.9 Hz, H-2′), 5.49 (1H, br t, J = 1.7 Hz, H-20a), 5.33 (1H, br s, H-20b), 5.31 (1H, br dd, J = 3.2, 3.2 Hz, H-5), 4.89 (1H, d, J = 8.8 Hz, H-10), 4.70 (1H, d, J = 6.8 Hz, 2-OMOM), 4.63 (1H, d, J = 6.8 Hz, 2-OMOM), 4.23 (1H, br d, J = 8.8 Hz, H-9), 4.22 (1H, m, H-2), 3.42 (3H, s, 2-OMOM), 3.07 (1H, br d, J = 4.9 Hz, H-3), 2.87 (1H, dd, J = 20.0, 7.0 Hz, H-14β), 2.44 (1H, d, J = 20.0 Hz, H-14α), 2.41 (1H, br d, J = 7.0 Hz, H-1), 2.15 (3H, s, H-18), 1.98 (1H, m, H-6β), 1.80 (1H, m, H-6α), 1.74 (1H, br dd, J = 13.3, 4.0 Hz, H-7α), 1.67 (3H, s, H-17), 1.62 (1H, br dd, J = 13.3, 4.4 Hz, H-7β), 1.50 (3H, s, 9,10-acetonide), 1.44 (3H, s, 9,10-acetonide), 1.25 (3H, s, H-16), 1.10 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.84 (s, C-13), 166.36 (s, C-1′), 152.52 (s, C-11), 145.25 (d, C-3′), 142.10 (s, C-4), 138.51 (s, C-12), 134.62 (s, *q*-Ph), 130.22 (d, *p*-Ph), 128.91 (d, *o*-Ph), 128.40 (d, *m*-Ph), 118.23 (t, C-20), 118.23 (d, C-2′), 108.03 (s, 9,10-acetonide), 95.97 (t, 2-OMOM), 82.34 (d, C-9), 79.42 (d, C-5), 75.96 (d, C-10), 74.61 (d, C-2), 56.56 (q, 2-OMOM), 47.72 (d, C-1), 42.78 (d, C-3), 40.35 (s, C-8), 38.32 (s, C-15), 37.74 (q, C-16), 36.24 (t, C-14), 27.98 (t, C-6), 27.13 (q, 9,10-acetonide), 26.81 (q, 9,10-acetonide), 26.67 (t, C-7), 24.35 (q, C-17), 17.51 (q, C-19), 14.40 (q, C-18); HREIMS *m/z* 564.3082 (calcd for $C_{34}H_{44}O_7$, 564.3087); *anal.* C 72.01%, H 7.88%, calcd for $C_{34}H_{44}O_7$, C 72.31%, H 7.85%.

9α,10β-(Dimethylmethylenedioxy)-5α-hydroxy-2α-(methoxymethoxy)taxa-4(20),11-dien-13-one (9). A mixture of **8** (10.48 g, 18.56 mmol) and 2 M KOH (74 mL) in 1,4-dioxane (300 mL) and MeOH (300 mL) was stirred for 7 h at room temperature. After adding 5 M KOH (15 mL) to the mixture, the solution was stirred at room temperature for 16 h and at 35−40 °C for 6 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (200 mL), and the mixture was concentrated to a half of the volume under reduced pressure to eliminate MeOH and extracted with $CHCl_3$ (3 × 300 mL). The combined extracts were worked up as usual to give a pale yellow solid (7.94 g), which was recrystallized from a mixture of EtOAc and hexane (1:1) to give spectroscopically pure **9** (6.01 g). The mother liquor was purified by column chromatography on silica gel [70 g, 3.5 cm i.d. column, EtOAc−hexane (4:6)] to give spectroscopically pure **9** (1.44 g). The total yield of **9** is 7.45 g (92%). The analytical sample of **9** was obtained as colorless microcrystals (MeOH): mp 184−186 °C; $[\alpha]^{20}_D$ +163.15° (*c* 0.969, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 274 (3.78), 203 (3.71) nm; IR ($CHCl_3$) ν_{max} 3612, 3000, 2944, 1670, 1384, 1218, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.46 (1H, br d, J = 2.0 Hz, H-20a), 5.12 (1H, br d, J = 2.0 Hz, H-20b), 4.92 (1H, d, J = 9.0 Hz, H-10), 4.67 (1H, d, J = 7.1 Hz, 2-OMOM), 4.62 (1H, d, J = 7.1 Hz, 2-OMOM), 4.23 (1H, dd, J = 4.6, 1.7 Hz, H-2), 4.20 (1H, d, J = 9.0 Hz, H-9), 4.14 (1H, br dd, J = 2.5, 2.5 Hz, H-5), 3.41 (3H, s, 2-OMOM), 3.23 (1H, br d, J = 4.6 Hz, H-3), 2.81 (1H, dd, J = 19.8, 7.0 Hz, H-14β), 2.35 (1H, d, J = 19.8 Hz, H-14α), 2.32 (1H, br d, J = 7.1 Hz, H-1), 2.09 (3H, s, H-18), 1.80 (1H, ddd, J = 14.0, 12.0, 3.4 Hz, H-7α), 1.75 (1H, m, H-6β), 1.67 (1H, br d, J = 14.0 Hz, H-7β), 1.64 (3H, s, H-17), 1.61 (1H, m, H-6α), 1.49 (3H, s, 9,10-acetonide), 1.44 (3H, s, 9,10-acetonide), 1.21 (3H, s, H-16), 1.06 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.22 (s, C-13), 151.42 (s, C-11), 147.67 (s, C-4), 138.41 (s, C-12), 115.07 (t, C-20), 107.84 (s, 9,10-acetonide), 95.58 (t, 2-OMOM), 82.40 (d, C-9), 77.26 (d, C-5), 75.87 (d, C-10), 74.79 (d, C-2), 56.41 (q, 2-OMOM), 47.70 (d, C-1), 40.48 (d, C-3), 40.54 (s, C-8), 38.41 (s, C-15), 37.56 (q, C-16), 36.32 (t, C-14), 29.67 (t, C-6), 27.10 (q, 9,10-acetonide), 26.80 (q, 9,10-acetonide), 25.55 (t, C-7), 24.35 (q, C-17), 17.55 (q, C-19), 14.27 (q, C-18); HREIMS *m/z* 434.2668 (calcd for $C_{25}H_{38}O_6$, 434.2668); *anal.* C 69.17%, H 8.98%, calcd for $C_{25}H_{38}O_6$, C 69.09%, H 8.81%.

9α,10β-(Dimethylmethylenedioxy)-2α-(methoxymethoxy)taxa-4(20),11-dien-5α,13α-diol (10) and 9α,10β-(Dimethylmethylenedioxy)-2α-(methoxymethoxy)taxa-4(20),11-dien-5α,13β-diol (11). To a stirred solution of **9** (9.06 g, 20.85 mmol) and $CeCl_3{\cdot}7H_2O$ (38.82 g, 104.19 mmol) in 1,4-dioxane (520 mL) was added $NaBH_4$ (15.77 g, 416.86 mmol) at room temperature. The mixture was stirred at room temperature for 5 h, and the reaction was quenched by adding acetone (50 mL) dropwise. A saturated aqueous solution of NH_4Cl (400 mL) and 2 M HCl (100 mL) were added into the mixture, successively. The mixture was then extracted with $CHCl_3$ (1 × 400, 4 × 100 mL). The combined extracts were worked up as usual to give a crude product as a white solid (10.69 g), which was purified by column chromatography on silica gel [320 g, 5.5 cm i.d. column, EtOAc−hexane (4:6)] to give spectroscopically pure **10** (4.74 g, 52%) and **11** (3.89 g, 43%) as colorless crystals, respectively. Compound **10** was obtained as colorless granular crystals (MeOH): mp 179−181 °C; $[\alpha]^{20}_{D}$ +132.64° (*c* 0.962, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 228 (4.03), 204 (4.04) nm; IR ($CHCl_3$) ν_{max} 3620, 3480, 2996, 2994, 1382, 1212, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.56 (1H, br t, *J* = 1.7 Hz, H-20a), 5.19 (1H, br t, *J* = 1.7 Hz, H-20b), 4.88 (1H, d, *J* = 9.3 Hz, H-10), 4.67 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.59 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.42 (1H, br d, *J* = 9.0 Hz, H-13), 4.25 (1H, br t, *J* = 3.2 Hz, H-5), 4.12 (1H, dd, *J* = 4.4, 3.2 Hz, H-2), 4.05 (1H, d, *J* = 9.3 Hz, H-9), 3.40 (3H, s, 2-OMOM), 3.17 (1H, d, *J* = 4.4 Hz, H-3), 3.12 (1H, br s, 13-O*H*), 2.73 (1H, ddd, *J* = 16.0, 9.0, 9.0 Hz, H-14β), 2.13 (1H, br s, 5-O*H*), 2.11 (3H, br d, *J* = 1.2 Hz, H-18), 1.90 (1H, br d, *J* = 9.0 Hz, H-1), 1.85 (1H, m, H-7α), 1.75 (1H, br d, *J* = 14.4 Hz, H-6β), 1.70 (1H, m, H-7β), 1.61 (1H, br d, *J* = 14.4 Hz, H-6α), 1.60 (1H, br d, *J* = 16.0 Hz, H-14α), 1.53 (3H, s, H-17), 1.45 (3H, s, 9,10-acetonide), 1.42 (3H, s, 9,10-acetonide), 1.06 (3H, s, H-16), 1.01 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.84 (s, C-4), 143.33 (s, C-12), 134.29 (s, C-11), 115.85 (t, C-20), 106.81 (s, 9,10-acetonide), 95.33 (t, 2-OMOM), 82.53 (d, C-9), 77.83 (d, C-5), 75.58 (d, C-2), 75.53 (d, C-10), 68.62 (d, C-13), 56.40 (q, 2-OMOM), 46.46 (d, C-1), 41.20 (d, C-3), 40.61 (s, C-8), 37.45 (s, C-15), 31.29 (t, C-14), 32.90 (q, C-16), 32.22 (t, C-6), 27.22 (q, 9,10-acetonide), 26.93 (q, 9,10-acetonide), 25.68 (t, C-7), 24.80 (q, C-17), 17.68 (q, C-19), 17.31 (q, C-18); HREIMS *m/z* 436.2823 (calcd for $C_{25}H_{40}O_6$, 436.2825); *anal.* C 68.71%, H 9.30%, calcd for $C_{25}H_{40}O_6$, C 68.77%, H 9.24%. Compound **11** was obtained as fine colorless granular crystals (MeOH): mp 152−154 °C; $[\alpha]^{20}_{D}$ +168.09° (*c* 1.000, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 228 (3.78), 204 (3.76) nm; IR ($CHCl_3$) ν_{max} 3624, 3495, 2996, 1228, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (1H, dd, *J* = 3.5, 2.0 Hz, H-20a), 5.14 (1H, br s, H-20b), 4.81 (1H, d, *J* = 9.5 Hz, H-10), 4.64 (1H, dd, *J* = 6.5, 1.0 Hz, 2-OMOM), 4.58 (1H, dd, *J* = 6.5, 1.0 Hz, 2-OMOM), 4.23 (1H, dd, *J* = 9.5, 3.4 Hz, H-13), 4.16 (1H, br t, *J* = 2.5 Hz, H-5), 4.12 (1H, d, *J* = 9.5 Hz, H-9), 4.11 (1H, d, *J* = 4.6 Hz, H-2), 3.38 (3H, d, *J* = 1.0 Hz, 2-OMOM), 2.93 (1H, br d, *J* = 4.6 Hz, H-3), 2.26 (1H, br s, 5-O*H*), 2.20 (1H, br d, *J* = 7.0 Hz, H-1), 2.18 (1H, dd, *J* = 15.0, 9.5 Hz, H-14β), 2.02 (3H, br d, *J* = 1.2 Hz, H-18), 2.01 (1H, ddd, *J* = 15.0, 7.0, 3.4 Hz, H-14α), 1.75 (1H, m, H-7α), 1.70 (1H, m, H-6β), 1.66 (1H, m, H-7β), 1.59 (1H, m, H-6α), 1.52 (3H, s, H-17), 1.45 (3H, s, 9,10-acetonide), 1.41 (3H, s, 9,10-acetonide), 1.37 (3H, s, H-16), 1.11 (1H, br s, 13-O*H*), 1.03 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.89 (s, C-4), 141.30 (s, C-12), 137.97 (s, C-11), 115.18 (t, C-20), 106.94 (s, 9,10-acetonide), 95.77 (t, 2-OMOM), 82.09 (d, C-9), 77.18 (d, C-5), 75.51 (d, C-10), 75.27 (d, C-2), 71.36 (s, C-13), 56.38 (q, 2-OMOM), 56.13 (d, C-1), 41.52 (d, C-3), 40.54 (s, C-8), 37.20 (s, C-15), 36.76 (q, C-16), 30.10 (t, C-6), 30.07 (t, C-7), 30.07 (t, C-14), 27.30 (q, 9,10-acetonide), 26.89 (q, 9,10-acetonide), 25.06 (q, C-17), 19.65 (q, C-19), 17.54 (q, C-18); HREIMS *m/z* 436.2822 (calcd for $C_{25}H_{40}O_6$, 436.2825); *anal.* C 68.50%, H 9.21%, calcd for $C_{25}H_{40}O_6$, C 68.77%, H 9.24%.

Oxidation of 11 with MnO_2. A mixture of **11** (2.73 g, 6.26 mmol) and MnO_2 (6.44 g, 62.62 mmol) in CH_2Cl_2 (63 mL) was stirred for 2 h at room temperature and poured into a saturated aqueous solution of NaCl (160 mL). The reaction mixture was extracted with EtOAc (4 × 50 mL). The combined extracts were worked up as usual to give a crude product (2.73 g), which was purified by flash chromatography on silica gel [109 g, 4.0 cm i.d. column, EtOAc−hexane (3:7)] to give pure **9** (2.48 g, 91%).

13α-Acetoxy-9α,10β-(dimethylmethylenedioxy)-2α-(methoxymethoxy)taxa-4(20),11-diene-5α-ol (12). A mixture of **10** (5.01 g, 11.48 mmol) and Ac_2O (1.19 mL, 12.71 mmol) in pyridine (Py, 77 mL) was stirred in the presence of DMAP (2.81 g, 22.92 mmol) for 1 h at room temperature, and the reaction was quenched by adding 2 M HCl (70 mL) dropwise. The reaction mixture was extracted with EtOAc (4 × 50 mL). The combined extracts were worked up as usual to give a white solid (5.49 g), which was recrystallized from a mixture of EtOAc and hexane (1:1) to give spectroscopically pure **12** (4.33 g). The mother liquor was purified by flash chromatography on silica gel [68 g, 3.0 cm i.d. column, EtOAc−hexane (2:3)] to give additional pure **12** (0.63 g) and recovered **10** (0.17 g). The total yield of **12** is 4.96 g (90%) and recovered **10** is 0.17 g (3%). The analytical sample of **12** was obtained as colorless cubes (MeOH): mp 187−188 °C; $[\alpha]^{20}_{D}$ +120.33° (*c* 0.969, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 221 (4.16), 206 (4.08) nm; IR ($CHCl_3$) ν_{max} 3608, 2996, 2952, 1734, 1232, 1224, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (1H, ddd, *J* = 9.0, 4.9, 1.0 Hz, H-13), 5.56 (1H, br t, *J* = 2.0 Hz, H-20a), 5.23 (1H, br t, *J* = 2.0 Hz, H-20b), 4.89 (1H, d, *J* = 9.3 Hz, H-10), 4.65 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.59 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.21 (1H, br s, H-5), 4.12 (1H, dd, *J* = 3.2, 1.2 Hz, H-2), 4.09 (1H, d, *J* = 9.3 Hz, H-9), 3.39 (3H, s, 2-OMOM), 3.24 (1H, br d, *J* = 3.2 Hz, H-3), 2.69 (1H, ddd, *J* = 15.6, 9.0, 9.0 Hz, H-14β), 2.08 (3H, s, 13-OAc), 1.99 (3H, d, *J* = 1.0 Hz, H-18), 1.98 (1H, br d, *J* = 9.0 Hz, H-1), 1.88 (1H, br dd, *J* = 13.4, 3.7 Hz, H-6β), 1.79 (1H, br d, *J* = 12.7 Hz, H-7α), 1.69 (1H, br s, 5-O*H*), 1.68 (1H, br d, *J* = 13.4 Hz, H-6α), 1.61 (1H, br d, *J* = 12.7 Hz, H-7β), 1.59 (3H, s, H-17), 1.53 (1H, dd, *J* = 15.6, 4.9 Hz, H-14α), 1.45 (3H, s, 9,10-acetonide), 1.42 (3H, s, 9,10-acetonide), 1.11 (3H, s, H-16), 1.05 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.97 (s, 13-OAc), 147.60 (s, C-4), 138.59 (s, C-12), 135.71 (s, C-11), 116.13 (t, C-20), 107.01 (s, 9,10-acetonide), 95.53 (t, 2-OMOM), 82.38 (d, C-9), 77.83 (d, C-5), 76.04 (d, C-2), 75.05 (d, C-10), 70.46 (s, C-13), 56.40 (q, 2-OMOM), 46.68 (d, C-1), 40.93 (d, C-3), 40.63 (s, C-8), 37.67 (s, C-15), 32.68 (q, C-16), 29.50 (t, C-6), 28.83 (t, C-14), 27.24 (q, 9,10-acetonide), 26.91 (q, 9,10-acetonide), 25.45 (t, C-7), 25.02 (q, C-17), 21.02 (q, 13-OAc), 17.82 (q, C-19), 16.49 (q, C-18); HREIMS *m/z* 478.2931 (calcd for $C_{27}H_{42}O_7$, 478.2931); *anal.* C 67.54%, H 9.10%, calcd for $C_{27}H_{42}O_7$, C 67.75%, H 8.85%.

13α-Acetoxy-5α-cinnamoyloxy-9α,10β-(dimethylmethylenedioxy)-2α-(methoxymethoxy) taxa-4(20),11-diene (13). A mixture of **12** (1.42 g, 2.96 mmol), cinnamoyl chloride (3.94 g, 23.67 mmol), and DMAP (3.61 g, 29.58 mmol) in Py (30 mL) was stirred for 16 h at 80−85 °C and cooled to room temperature. The reaction was quenched by adding 2 M HCl (20 mL) dropwise. A saturated aqueous solution of NH_4Cl (50 mL) was added to the reaction mixture, which was extracted with EtOAc (4 × 50 mL). The combined extracts were worked up as usual to give a brown amorphous solid (3.61 g), which was separated by flash chromatography on silica gel [108 g, 4.0 cm i.d. column, EtOAc−hexane (1:4)]. The faster running gave pure **13** (1.73 g). The second running gave a mixture of **12**, **13**, and DMAP. The latter was further purified by column chromatography on silica gel [14.0 g, 2.0 cm i.d., EtOAc−hexane (1:9)] to give pure **13** (0.05 g). The total yield of **13** is 1.78 g (99%). The analytical sample of **13** was obtained as colorless cubes (MeOH): mp 101−103 °C; $[\alpha]^{20}_{D}$ +156.24° (*c* 0.985, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 278 (4.29), 217 (4.29), 205 (4.31) nm; IR ($CHCl_3$) ν_{max} 3000, 2960, 1738, 1710, 1640, 1222, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (1H, d, *J* = 15.9 Hz, H-3′), 7.48 (2H, m, *o*-Ph), 7.40 (2H, m, *m*-Ph), 7.40 (1H, m, *p*-Ph), 6.65 (1H, d, *J* = 15.9 Hz, H-2′), 5.87 (1H, br t, *J* = 9.5 Hz, H-13), 5.80 (1H, br t, *J* = 1.5 Hz, H-20a), 5.48 (1H, br t, *J* = 2.0 Hz, H-5), 5.38 (1H, br t, *J* = 1.5 Hz, H-20b), 4.88 (1H, d, *J* = 9.5 Hz, H-10), 4.65 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.59 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.23 (1H, d, *J* = 9.5 Hz, H-9), 4.16 (1H, dd, *J* = 2.9, 1.2 Hz, H-2), 3.39 (3H, s, 2-OMOM), 3.03 (1H, br d, *J* = 2.9 Hz, H-3), 2.74 (1H, ddd, *J* = 15.0, 9.5, 9.0 Hz, H-14β), 2.20 (3H, d, *J* = 1.5 Hz, H-18), 2.05 (1H, dd, *J* = 9.0, 1.2 Hz, H-1), 1.87 (1H, m, H-6β), 1.83 (1H, m, H-7α), 1.80 (3H, s, 13-OAc), 1.79 (1H, m, H-7β), 1.76 (1H, m, H-6α), 1.65 (3H, s, H-17), 1.47 (3H, s, 9,10-acetonide), 1.42 (3H, s, 9,10-acetonide), 1.38 (1H, br dd, *J* = 15.0, 9.0 Hz, H-14α), 1.20 (3H, s, H-16), 1.12 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.74 (s, 13-OAc), 166.14 (s, C-1′), 145.03 (d, C-3′), 142.69 (s, C-4), 138.16 (s, C-12), 135.18 (s, C-11), 134.62 (s, *q*-Ph), 134.45 (d, *p*-Ph), 129.04 (d, *m*-Ph), 127.89 (d, *o*-Ph), 120.00 (t, C-20), 118.90 (d, C-2′), 107.03 (s, 9,10-acetonide), 95.46 (t, 2-OMOM), 82.39 (d, C-9), 79.57 (d, C-5), 77.00 (d, C-2), 74.80 (d, C-10), 71.04 (s, C-13), 56.34 (q, 2-OMOM), 47.45 (d, C-1), 43.00 (d, C-3), 40.01 (s, C-8), 38.27 (s, C-15), 32.27 (q, C-16), 28.97 (t, C-14), 27.35 (t, C-6), 27.31 (q, 9,10-acetonide), 26.91 (q, 9,10-acetonide), 26.16 (t, C-7), 25.85 (q, C-17), 20.98 (q, 13-OAc), 18.57 (q, C-19), 16.40(q, C-18); HREIMS *m/z* 608.3356 (calcd for $C_{36}H_{48}O_8$, 608.3350); *anal.* C 70.86%, H 7.92%, calcd for $C_{36}H_{48}O_8$, C 71.02%, H 7.95%.

13α-Acetoxy-5α-cinnamoyloxy-2α-(methoxymethoxy)taxa-4(20),11-diene-9α,10β-diol (14). A mixture of **13** (1.75 g, 2.88 mmol) and an 80% aqueous solution of AcOH (AcOH 44 g, H_2O 11 g) was stirred for 8 h at room temperature, diluted with a saturated aqueous solution of NaCl (100 mL), and extracted with EtOAc (5 × 50 mL). The combined extracts were washed with a saturated aqueous solutions of $NaHCO_3$ (2 × 100 mL) and NaCl (2 × 100 mL), dried over Na_2SO_4, filtered, and concentrated to give a pale yellow amorphous solid (1.70 g), which was purified by flash chromatography on silica gel [68 g, 3.0 cm i.d. column, EtOAc−hexane (2:3)] to give pure **14** (1.42 g, 87%) and recovered **13** (0.22 g, 12%). The yield of **14** based on recovered **13** is 99%. The analytical sample of **14** was obtained as colorless amorphous crystals ($CHCl_3$): mp 95−97 °C; $[\alpha]^{20}_D$ +146.27° (*c* 0.992, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 277 (4.65), 217 (4.64), 207 (4.58) nm; IR ($CHCl_3$) ν_{max} 3632, 3572, 2960, 1738, 1710, 1640, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (1H, d, *J* = 15.9 Hz, H-3′), 7.49 (2H, m, *o*-Ph), 7.40 (2H, m, *m*-Ph), 7.40 (1H, m, *p*-Ph), 6.65 (1H, d, *J* = 15.9 Hz, H-2′), 5.85 (1H, ddd, *J* = 10.0, 7.0, 1.5 Hz, H-13), 5.81 (1H, br t, *J* = 2.0 Hz, H-20a), 5.47 (1H, br t, *J* = 2.0 Hz, H-5), 5.38 (1H, br t, *J* = 2.0 Hz, H-20b), 4.80 (1H, dd, *J* = 9.5, 2.7 Hz, H-10), 4.64 (1H, d, *J* = 7.1 Hz, 2-OMOM), 4.59 (1H, d, *J* = 7.1 Hz, 2-OMOM), 4.12 (1H, dd, *J* = 9.5, 3.5 Hz, H-9), 4.08 (1H, br d, *J* = 2.9 Hz, H-2), 3.38 (3H, s, 2-OMOM), 3.16 (1H, m, H-3), 2.71 (1H, ddd, *J* = 15.1, 10.0, 9.0 Hz, H-14β), 2.50 (1H, d, *J* = 3.5 Hz, 9-O*H*), 2.16 (3H, d, *J* = 1.0 Hz, H-18), 2.29 (1H, d, *J* = 2.7 Hz, 10-O*H*), 2.00 (1H, br d, *J* = 9.0 Hz, H-1), 1.90 (1H, m, H-6β), 1.81 (3H, s, 13-OAc), 1.78 (1H, m, H-7β), 1.64 (1H, m, H-7α), 1.61 (3H, s, H-17), 1.51 (1H, dd, *J* = 15.1, 7.0 Hz, H-14α), 1.20 (3H, s, H-16), 1.16 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.91 (s, 13-OAc), 166.23 (s, C-1′), 145.01 (d, C-3′), 143.21 (s, C-4), 137.40 (s, C-12), 134.42 (s, *q*-Ph), 134.34 (s, C-11), 130.43 (d, *p*-Ph), 129.02 (d, *m*-Ph), 127.93 (d, *o*-Ph), 120.09 (t, C-20), 119.00 (d, C-2′), 95.41 (t, 2-OMOM), 79.53 (d, C-5), 78.51 (d, C-2), 77.04 (d, C-9), 71.99 (d, C-10), 70.98 (d, C-13), 56.27 (q, 2-OMOM), 47.13 (d, C-1), 44.19 (d, C-3), 43.57 (s, C-8), 37.97 (s, C-15), 31.96 (q, C-16), 28.87 (t, C-14), 27.90 (t, C-6), 27.01(t, C-7), 26.00 (q, C-17), 21.05 (q, 13-OAc), 18.80 (q, C-19), 15.79 (q, C-18); HREIMS *m/z* 568.3042 (calcd for $C_{33}H_{44}O_8$, 568.3037); *anal.* C 69.39%, H 7.76%, calcd for $C_{33}H_{44}O_8$, C 69.69%, H 7.80%.

9α,10β,13α-Triacetoxy-5α-cinnamoyloxy-2α-(methoxymethoxy)taxa-4(20),11-diene (15). A mixture of **14** (1.15 g, 2.04 mmol), DMAP (0.25 g, 2.04 mmol), and acetic anhydride (3.8 mL, 40.42 mmol) in Py (20.4 mL) was stirred for 2 h at room temperature. The reaction was quenched by addition of 2 M HCl (30 mL). Then, the mixture was poured into a saturated aqueous solution of NH_4Cl (50 mL) and extracted with EtOAc (4 × 50 mL). The combined extracts were worked up as usual to give white crystals (1.458 g), which were purified by flash chromatography on silica gel [30 g, 2.5 cm i.d. column, EtOAc−hexane (3:7)] to give spectroscopically pure **15** (1.32 g, 99%). The analytical sample of **15** was obtained as colorless microcrystals ($CHCl_3$): mp 86−89 °C; $[\alpha]^{20}_D$ +95.73° (*c* 0.985, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 278 (4.42), 217 (4.43), 206 (4.37) nm; IR ($CHCl_3$) v_{max} 2956, 1738, 1710, 1640, 1376, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, d, *J* = 16.1 Hz, H-3′), 7.49 (2H, m, *o*-Ph), 7.40 (2H, m, *m*-Ph), 7.40 (1H, m, *p*-Ph), 6.69 (1H, d, *J* = 16.1 Hz, H-2′), 6.06 (1H, d, *J* = 10.7 Hz, H-10), 5.85 (1H, d, *J* = 10.7 Hz, H-9), 5.83 (1H, ddd, *J* = 10.0, 7.0, 1.0 Hz, H-13), 5.77 (1H, br t, *J* = 1.7 Hz, H-20a), 5.49 (1H, br t, *J* = 1.0 Hz, H-5), 5.41 (1H, br t, *J* = 1.7 Hz, H-20b), 4.66 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.60 (1H, d, *J* = 6.8 Hz, 2-OMOM), 4.14 (1H, dd, *J* = 4.6, 1.5 Hz, H-2), 3.37 (3H, s, 2-OMOM), 3.21 (1H, br d, *J* = 4.6 Hz, H-3), 2.72 (1H, ddd, *J* = 15.1, 10.0, 10.0, H-14β), 2.32 (3H, d, *J* = 1.0 Hz, H-18), 2.08 (1H, br d, *J* = 10.0 Hz, H-1), 2.06 (3H, s, 9-OAc), 2.02 (3H, s, 10-OAc), 1.88 (1H, m, H-6β), 1.85 (1H, m, H-7α), 1.83 (1H, m, H-6α), 1.80 (1H, m, H-7β), 1.80 (3H, s, 13-OAc), 1.69 (3H, s, H-17), 1.50 (1H, dd, *J* = 15.1, 7.0 Hz, H-14α), 1.14 (3H, s, H-16), 1.12 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.75 (s, 13-OAc), 170.25 (s, 10-OAc), 169.83 (s, 9-OAc), 166.21 (s, C-1′), 145.20 (d, C-3′), 142.56 (s, C-4), 137.40 (s, C-12), 134.32 (s, C-11), 134.11 (s, *q*-Ph), 130.48 (d, *p*-Ph), 129.04 (d, *m*-Ph), 127.99 (d, *o*-Ph), 120.53 (t, C-20), 118.91 (d, C-2′), 95.83 (t, 2-OMOM), 79.17 (d, C-5), 77.38 (d, C-2), 76.89 (d, C-9), 72.29 (d, C-10), 70.70 (d, C-13), 56.27 (q, 2-OMOM), 47.02 (d, C-1), 44.15 (d, C-3), 43.74 (s, C-8), 37.63 (s, C-15), 31.70 (q, C-16), 28.73 (t, C-14), 27.84 (t, C-6), 27.27 (t, C-7), 26.87 (q, C-17), 21.02 (q, 10-OAc), 20.98 (q, 9-OAc), 20.79 (q, 13-OAc), 18.29 (q, C-19), 15.61 (q, C-18); HREIMS *m/z* 652.3251 (calcd for $C_{37}H_{48}O_{10}$, 652.3248); anal. C 67.79%, H 7.36%, calcd for $C_{37}H_{48}O_{10}$, C 68.08%, H 7.41%.

9α,10β,13α-Triacetoxy-5α-(cinnamoyloxy)taxa-4(20),11-dien-2α-ol (Taxinine NN-1) (1). Compound **15** (1.01 g, 1.55 mmol) was heated with concentrated HCl (1.3 mL, 15.6 mmol) in *i*-PrOH (15.5 mL) for 5 h at 45−50 °C, cooled, poured into a saturated aqueous solution of $NaHCO_3$ (50 mL), and extracted with $CHCl_3$ (4 × 30 mL). The combined extracts were worked up as usual to give a white amorphous solid (0.99 g), which was purified by flash chromatography on silica gel [50 g, 3.0 cm i.d. column, EtOAc−hexane (3:7)] to give spectroscopically pure taxinine NN-1 (**1**) (0.657 g, 70%) accompanied by recovered **15** (0.19 g, 18%). The yield of **1** based on recovered starting material, **15**, is 85%. An analytical sample of **1** was obtained as colorless microcrystals (EtOAc): mp 107−109 °C; $[\alpha]^{20}_D$ +81.86° (*c* 0.954, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 278 (4.39), 217 (4.40), 206 (4.34); IR ($CHCl_3$) ν_{max} 3612, 2960, 1740, 1712, 1638, 1236 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, d, *J* = 16.1 Hz, H-3′), 7.50 (2H, m, *o*-Ph), 7.40 (2H, m, *m*-Ph), 7.40 (1H, m, *p*-Ph), 6.66 (1H, d, *J* = 10.8 Hz, H-10), 6.65 (1H, d, *J* = 16.1 Hz, H-2′), 5.88 (1H, d, *J* = 10.8 Hz, H-9), 5.84 (1H, br dd, *J* = 9.5, 7.0 Hz, H-13), 5.57 (1H, br s, H-20a), 5.51 (1H, br s, H-20b), 5.45 (1H, br t, *J* = 2.7 Hz, H-5), 4.24 (1H, ddd, *J* = 6.9, 6.3, 2.4 Hz, H-2), 3.22 (1H, br d, *J* = 6.3 Hz, H-3), 2.66 (1H, ddd, *J* = 15.0, 10.7, 9.5 Hz, H-14β), 2.28 (3H, d, *J* = 1.0 Hz, H-18), 2.08 (1H, br d, *J* = 10.7 Hz, H-1), 2.06 (3H, s, 9-OAc), 2.02 (3H, s, 10-OAc), 1.91 (1H, m, H-6β), 1.82 (1H, m, H-7α), 1.78 (1H, m, H-6α), 1.77 (3H, s, 13-OAc), 1.76 (1H, m, H-7β), 1.70 (3H, s, H-17), 1.66 (1H, br d, *J* = 6.9 Hz, 2-O*H*), 1.32 (1H, dd, *J* = 15.0, 7.0 Hz, H-14α), 1.14 (3H, s, H-16), 0.95 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.73 (s, 13-OAc), 170.27 (s, 10-OAc), 169.86 (s, 9-OAc), 166.32 (s, C-1′), 145.52 (d, C-3′), 143.53 (s, C-4), 136.58 (s, C-12), 134.27 (s, *q*-Ph), 133.56 (s, C-11), 130.56 (d, *p*-Ph), 129.03 (d, *m*-Ph), 128.03 (d, *o*-Ph), 119.43 (t, C-20), 118.69 (d, C-2′), 78.54 (d, C-5), 76.70 (d, C-9), 72.38 (d, C-10), 70.52 (d, C-13), 70.32 (d, C-2), 51.23 (d, C-1), 45.63 (d, C-3), 44.42 (s, C-8), 37.33 (s, C-15), 31.73 (q, C-16), 29.18 (t, C-6), 28.35 (t, C-14), 27.55 (t, C-7), 26.89 (q, C-17), 21.02 (q, 10-OAc), 21.01 (q, 9-OAc), 20.83 (q, 13-OAc), 17.92 (q, C-19), 15.32 (q, C-18); HREIMS *m/z* 608.2983 (calcd for $C_{35}H_{44}O_9$, 608.2986); *anal.* C 68.74%, H 7.36%, calcd for $C_{35}H_{44}O_9$, C 69.05%, H 7.29%.

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(11) Modulation of multidrug resistance by taxinine NN-1 (taxezopidine G, **1**) was also reported by Kobayashi et al.[10e] Their values of VCR accumulation with **1** were 419% of control and 147% of verapamil at 1 μg/mL and smaller than the values reported by us probably because of the purity of their sample.

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(14) The primary screen in vitro, which consists of 39 human cancer cell lines, was done by the Screening Committee of New Anticancer Agent by a Grant-in-Aid for Scientific Research on Priority Area "Cancer" from the Ministry of Education, Science, Sports and Culture, Japan. We thank Dr. Yamori and co-workers of this committee for the bioassay of **1**.

(15) Taxinine NN-1 (**1**) shows significant activities as an anticancer reagent in the in vitro primary screening by an HCC panel.[12,13] Effective concentration is high enough and differential growth is recognized. Since the results of COMPARE of **1** are negative, **1** is suggested to be a new type of anticancer agent.

(16) The regioselectivity of this reaction is explained by the stereochemistry of the 13β- and 5α-hydroxyl groups. The analysis of ^{1}H NMR spectrum of **11** showed that the configurations of 13β- and 5α-hydroxyl groups were equatorial (dd, $J = 9.5$ and 3.5 Hz) and axial (br t, $J = 2.5$ Hz), respectively. The $5\alpha(ax)$-hydroxyl group is more hindered than the $13\beta(eq)$-hydroxyl group.

(17) Diol (**7**) probably crystallizes as a hydrate, $C_{23}H_{34}O_5 \cdot 1/4H_2O$.

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