New Taxanes from the Needles of *Taxus canadensis*

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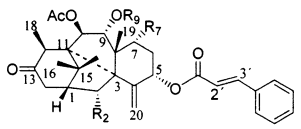
Ten new taxanes were isolated from the methanol extract of the needles of the Canadian yew, *Taxus canadensis*. On the basis of their spectral analysis, their structures were established as 9α-hydroxy-2α,7α,10*β*-triacetoxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one (**1**), 9α,10*β*-diacetoxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one (**2**), 9α,20-dihydroxy-2α,10*β*,13α-triacetoxytaxa-4(5),11(12)-diene (**3**), 2α,9α,10*β*-triacetoxy-20-cinnamoyloxy-11,12-epoxytaxa-4-en-13-one (**4**), 9α-hydroxy-2α,10*β*,13α-triacetoxy-5α-(3′-methylamino-3′-phenyl)-propionyloxytaxa-4(20),11-diene (**5**), 2α,10*β*-diacetoxy-5α,9α-dihydroxytaxa-4(20),11-dien-13-one (**6**), 2α,9α-diacetoxy-5α,10*β*-dihydroxytaxa-4(20),11-dien-13-one (**7**), 5α,9α-dihydroxy-2α,10*β*,13α-triacetoxytaxa-4(20),11-diene (**8**), 5α,10*β*-dihydroxy-2α,9α,13α-triacetoxytaxa-4(20),11-diene (**9**), and 7*β*,11*β*-dihydroxy-2α,9α,10*β*,13-tetraacetoxy-5α-cinnamoyloxytaxa-4(20),12-diene (**10**). Taxane **1** is the first example of a 3,11-cyclotaxane with a 7-*epi*-α-oxygenated group. Taxane **4** is the first taxane with a C-11,12-epoxide ring as well as a C-4(5)-*endo*-double bond. Taxanes with a 12(13) double bond as in **10** instead of the usual 11(12) double bond have been found so far only in the needles, stem, and seeds of the Japanese yew.

We have been studying the composition of the Canadian yew (*Taxus canadensis* Marsh; Taxaceae) since 1992.[1,2] The taxane composition of this low trailing shrub has been shown to differ from other yews.[3−5] Indeed, it is the only yew accumulating 9-dihydro-13-acetylbaccatin III in its needles.[1,2,5] This metabolite, which has been reported in trace amounts in the bark of *Taxus chinensis*,[6] is at least 3−5 five times more abundant than the anticancer drug paclitaxel in the needles of the Canadian yew. We have previously suggested[7−10] that a major conformational change of the core skeleton of a taxane can lead to unusual structure−activity reactivities. Indeed, taxuspine D,[11] which lacks the key elements essential for bioactivity, was found to promote the polymerization of tubulin with a potency corresponding to about half of the activity of paclitaxel.[8] This bioactivity was explained by the major conformational change derived by the C-12/C-13 double bond, enabling the C-5 cinnamoyl group to mimic part of the C-13 side chain of paclitaxel.[8] On the basis of this hypothesis we have also designed and synthesized putative bioactive taxanes.[12] As a continuation of our ongoing program on taxanes, we reinvestigated the needles of the Canadian yew and have identified 10 new metabolites (**1**−**10**) from a methanol extract. The isolation and structural characterization of these components are presented in this paper.



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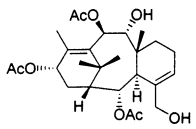
2 R_2=H R_7= H R_9=Ac



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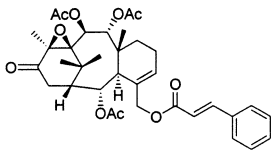

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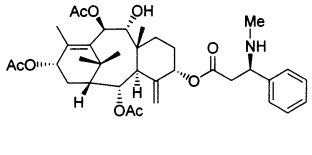

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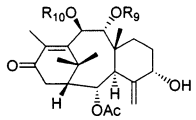
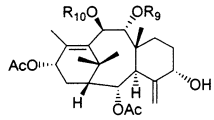
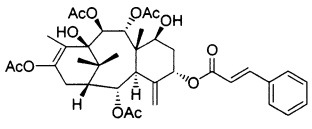


6 R_9=H R_{10}= Ac
7 R_9=Ac R_{10}= H



8 R_9=H R_{10}= Ac
9 R_9=Ac R_{10}= H



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Results and Discussion

Compound **1** was isolated as a colorless gummy substance. HRFABMS at *m*/*z* 661.2415 $(M + K)^+$ revealed the molecular formula of **1** as $C_{35}H_{42}O_{10}$, indicating 15 degrees of double-bond equivalence. Its ^{1}H NMR spectrum, shown in Table 1, indicated the characteristic signals of taxoids. Thus, chemical shifts due to an exomethylene moiety were observed at *δ* 5.70 and 5.84 (each 1H, s). The presence of a cinnamoyl moiety in **1** was revealed by signals at *δ* 6.34 (1H, d, *J* = 16.0 Hz), 7.66 (1H, d, *J* = 16.0 Hz, *trans*-orientation), 7.54 (2H, m), and 7.38 (3H, m) in the ^{1}H NMR spectrum and by fragments at *m*/*z* 131 (C_9H_7O) and 513 $(M + K - cinn)^+$ corresponding to the fission of a cinnamoyl group from the molecular ion in the FABMS. In addition, the presence of three acetyls and one ketone was implied by the resonances at *δ* 2.16, 21.1, 172.4; 2.07, 21.0, 169.1; 1.95, 20.7, 169.6 and *δ* 213.6 in the ^{1}H NMR and ^{13}C NMR spectra. Since 14 out of the 15 unsaturations deduced from the molecular formula were thus accounted for, **1** must contain either an additional double bond or an additional

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Table 1. ^{1}H NMR Spectral Data (δ value) of Compounds **1** and **3**−**5** (500 MHz in $CDCl_3$, J in Hz)[a]

H	1	3	4	5
1	2.15 (m)	1.71 (brd, 8.3)	1.96 (m)	1.83 (m)
2	6.05 (d, 5.5)	5.44 (dd, 3.4, 1.4)	5.86 (brt, 2.2)	5.35 (dd, 6.6, 2.1)
3		3.28 (brt, 2.8)	3.26 (brm, 2.2)	3.12 (d, 6.6)
5	5.71 (t, 9.1)	5.87 (brm)	6.08 (brs)	5.26 (t, 2.4)
6a	2.67 (ddd, 15.3, 10.1,4.3)	2.11 (m)	2.11 (brm)	1.62 (m)
6b	2.01 (dd, 15.3, 8.9)	2.11 (m)		1.62 (m)
7a	5.32 (dd, 4.2, 1.1)	2.12 (m)	1.96 (m)	1.82 (m)
7b		1.21 (m)	1.41 (m)	1.33 (m)
9	4.52 (d, 9.2)	4.33 (d, 10.1)	6.12 (d, 11.2)	4.27 (d, 10.0)
10	5.35 (d, 9.2)	5.68 (d, 10.1)	5.22 (d, 11.2)	5.76 (d, 10.0)
12	3.62 (q, 7.2)			
13		5.61 (ddd, 10.6, 3.0, 1.1)		5.79 (t, 8.3)
14a	2.62 (d, 20.1)	2.73 (m)	2.94 (d, 20.3)	2.48 (dt, 15.0, 9.7)
14b	2.52 (dd, 20.1, 7.2)	1.86 (dd, 15.8, 3.5)	2.78 (dd, 20.3, 8.5)	1.43 (dd, 15.0, 7.8)
16	1.24 (s)	1.00 (s)	0.86 (s)	1.08 (s)
17	1.55 (s)	1.62 (s)	1.91 (s)	1.59 (s)
18	1.33 (d, 7.2)	1.94 (d, 1.1)	1.64 (s)	2.02 (s)
19	1.43 (s)	1.09 (s)	1.02 (s)	1.04 (s)
20a	5.84 (s)	4.31 (d, 13.0)	4.97 (s)	5.28 (s)
20b	5.70 (s)	4.19 (d, 13.0)	4.97 (s)	4.80 (s)
OAc	2.16 (s)	2.10 (s)	2.06 (s)	2.13 (s)
	2.07 (s)	2.09 (s)	2.05 (s)	2.00 (s)
	1.95 (s)	2.01 (s)	2.05 (s)	1.70 (s)
2′	6.34 (d, 16.0)		6.32 (d, 16.1)	2.80 (d, 6.7)
3′	7.66 (d, 16.0)		7.62 (d, 16.1)	3.97 (d, 6.7)
N-Me				2.30 (s)
o	7.54 (m)		7.60 (m)	7.34 (m)
m	7.38 (m)		7.40 (m)	7.34 (m)
p	7.38 (m)		7.40 (m)	7.27 (m)

[a] Mutiplicity: s, singlet; d, doublet; dd, doublet of doublets; q, quartlet; m, mutiplet; brs, broad singlet; brdd, broad doublet of doublets; brt, broad triplet; o, overlapped.

ring. Detailed examination of the ^{1}H NMR spectrum of **1** showed differences from regular taxanes. The signal of H-3α was absent, and one of the methyl groups (Me-18) appeared as a doublet at δ 1.33 (3H, d, J = 7.2 Hz) coupled to a quartet signal at δ 3.62 (1H, q, J = 7.2 Hz, H-12) in the ^{1}H−^{1}H COSY spectrum. The HMBC correlation of H-12 with C-3 suggested that compound **1** is a 3,11-cyclotaxane. The 2D NMR data (^{1}H−^{1}H COSY, HMQC, HMBC) enabled us to assign all functional groups present. Similar to other 3,11-cyclotaxanes,[13−16] C-2, C-7, and C-10 are acetoxylated, C-9 is hydroxylated, there is a carbonyl group at C-13, and a *trans*-cinnamoyl is at C-5. The stereochemistry of **1** was obtained by NOESY correlations. Protons 2 and 9 are β-oriented as expected (H-2 and H-9 correlate with H_3-17 and H_3-19). Me-18 is also β since it correlates with Me-16. Proton-10 is α because of its correlation with H-12 and H-6b. The cinnamate was α-oriented, as shown by the correlations of H-2′ and H-3′ with H-12. The unusual β-orientation of H-7 was indicated by its correlations with Me-19 and H-6a. Thus, the structure of **1** was characterized as 9α-hydroxy-2α,7α,10β-triacetoxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one.

Compound **2** was obtained as a colorless amorphous solid. Its molecular composition, $C_{33}H_{40}O_7$, was established from combined analysis of the high-resolution FABMS at m/z 587.2410 $(M + K)^+$ and its ^{13}C NMR spectrum. The ^{1}H NMR spectrum of **2** exhibited the characteristic signals of a taxane, including the three-proton signals due to the methyl groups at δ 1.19, 1.55, 1.27, and 1.20 and two acetyl groups at δ 2.05 and 2.04; these latter assignments were verified by the observation of ^{13}C NMR signals at δ 21.0 and 170.0 and δ 21.0 and 170.8. The signals for an exocyclic methylene group were observed at δ 5.63 (1H, s) and 5.53 (1H, s) and δ 147.8 and 125.3. A cinnamoyl group was indicated by the proton signals at δ 7.55 (2H, m), 7.37 (3H, m), 6.26 (1H, d, J = 16.0 Hz), and δ 7.66 (1H, d, J = 16.0 Hz, *trans*-oriented). The splitting pattern of Me-18 and H-12 as well as a long-range correlation between H-2 and C-11 implied that **2** is also a C-3,11-cyclotaxane like **1**.[13−16] Protons of an AB system resonating at δ 5.69 and 5.78 with a large coupling constant (J = 9.5 Hz) were attributed to H-9 and H-10, respectively. Their chemical shifts indicated that two acetyl groups were attached to C-9 and C-10. The cinnamoyl group was assigned to C-5; these assignments were verified by the HMBC data. The structure of **2**, therefore, was established as 9α,10β-diacetoxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one.

Compound **3** was isolated as a colorless gum and showed a pseudomolecular ion at m/z 611 $(M + Cs)^+$ in the positive-ion FABMS. High-resolution FABMS analysis revealed the molecular formula of **3** to be $C_{26}H_{38}O_8$. The ^{1}H NMR spectrum of **3** (Table 1) showed characteristic signals due to a taxane skeleton, including four tertiary methyl groups at δ 1.00 (3H, s), 1.62 (3H, s), 1.94 (3H, s), and 1.09 (3H, s) and the methyl groups of three acetyls at δ 2.10 (3H, s), 2.09 (3H, s), and 2.01 (3H, s). Two signals at δ 4.33 (1H) and 5.68 (1H) having a large coupling constant (J = 10.1 Hz) were assigned as H-9 and H-10, with a hydroxy and an acetoxy group assigned to C-9 and C-10, respectively. These assignments were verified by the HMBC correlations of H-9 to C-8 and C-19 and H-10 to C-12, C-15, and a carbonyl carbon. The remaining two acetyl groups were assigned to C-2 and C-13, as deduced from the chemical shifts of the corresponding protons and HMBC experimental results. The presence of another AB system at δ 4.31 and 4.19 with a large coupling constant of J = 13.0 Hz was attributed to the methylene at C-20. The absence of characteristic signals due to an exocyclic methylene group and the presence of two carbon signals in the olefinic region revealed that the C-4 double bond was endocyclic instead of exocyclic, as is usual in most taxoids. Thus, the signal at δ 5.87 was ascribed to H-5. Therefore, the structure of

Table 2. ^{13}C NMR Spectral Data (δ value) of Compounds **1** and **3**−**5** (125 MHz in $CDCl_3$)[a]

C	1	3	4	5
1	48.3	46.0	48.4	48.5
2	76.0	72.3	71.2	72.0
3	**65.4**	43.7	41.6	44.0
4	**141.7**	**139.5**	**132.7**	**142.4**
5	74.0	126.2	134.2	79.2
6	31.0	22.7	22.1	28.3
7	73.5	26.9	27.1	25.6
8	**48.3**	**41.7**	**40.3**	**44.8**
9	83.8	75.7	76.3	75.8
10	84.8	75.8	71.4	75.7
11	**57.9**	**136.0**	**64.9**	**133.7**
12	52.5	**137.3**	**59.8**	**137.0**
13	**213.6**	69.4	**208.0**	69.9
14	38.8	28.7	37.6	28.0
15	**42.6**	**38.2**	**39.1**	**37.8**
16	26.9	32.6	28.7	31.2
17	28.4	25.9	25.2	27.2
18	15.8	15.6	14.9	15.1
19	24.6	18.1	17.8	18.1
20	128.3	66.5	68.9	117.7
OAc	21.1	21.2	21.4	21.3
	172.4	170.1	168.6	170.6
	21.0	21.0	20.5	21.5
	169.1	170.1	169.7	170.0
	20.7	21.5	20.5	20.0
	169.6	169.4	169.0	170.9
1′	**165.4**		**166.3**	**171.6**
2′	117.5		117.4	42.9
3′	145.2		145.2	62.1
N-Me				34.1
Ph′	**134.1**		**134.1**	**141.6**
o	128.2		128.2	126.8
m	129.0		129.0	128.7
p	130.3		130.4	127.8

[a] Chemical shifts were extracted from a HMQC experiment (±0.2 ppm). The numbers in bold emphasize quaternary carbons obtained from the HMBC experiment (±0.2 ppm).

3 was established unambiguously as 9α,20-dihydroxy-2α,10β,13α-triacetoxytaxa-4(5),11(12)-diene. The relative stereochemistry of **3** was derived from NOESY correlations.

Compound **4** was also obtained as a colorless gum. Its molecular composition was $C_{35}H_{42}O_{10}$, as determined from combined analysis of its high-resolution FABMS (*m*/*z* 611.2414, M + K^+) and ^1H and ^{13}C NMR spectral data (Tables 1 and 2). The ^1H NMR spectrum showed characteristic signals due to the taxane skeleton, including well-dispersed signals due to protons connected to oxygenated carbons, four tertiary methyl groups at δ 0.86, 1.91, 1.64, and 1.02, and three acetyl groups at δ 2.05, 2.06, and 2.05, verifying by the observation of ^{13}C NMR signals at δ 21.4, 168.6, 20.5, 169.7 and 20.5 and 169.0. The ^1H NMR signals due to the cinnamoyl group were observed at δ 7.60 (2H, m), 7.40 (3H, m), 6.32 (1H, d, J = 16.1 Hz), and 7.62 (1H, d, J = 16.2 Hz, *trans*-oriented). The connectivities of the protons on the taxane skeleton of **4** were determined by analysis of the $^1H-^1H$ COSY spectrum. Interpretation of ^1H, ^{13}C NMR and HMBC spectra permitted the positional assignment of functional groups. A pair of signals as an AB system at δ 6.12 (1H) and 5.21 (1H) with a large coupling constant (J = 11.2 Hz) was assigned as H-9 and H-10, and two acetoxy groups were attached to C-9 and C-10. This was supported by the observation that H-9 correlated with C-7, C-8, C-10, C-19, and a carbonyl signal at δ 169.7, while H-10 correlated with C-9, C-11, C-12, C-15, and a carbonyl signal at δ 169.0, in the HMBC spectrum. The ^{13}C NMR signal at δ 208.0 suggested the presence of a C-13 ketone moiety. In accordance with this, H_2-14 displayed a large coupling constant (J_{gem} = 20.3 Hz).

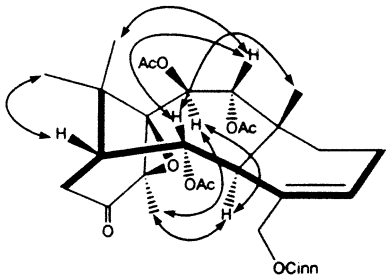

Figure 1. Relative stereochemistry of **4**. The arrows show selected NOEs.

Using H-14 as a starting point, the connectivities from C-14 to C-1 to C-2 to C-3 were deduced from the $^1H-^1H$ COSY spectrum. As in **3**, the absence of the characteristic signals due to the exocyclic methylene group and the presence of two carbon signals in the olefinic region revealed that the C-4 double bond was endocyclic instead of exocyclic. The signal at δ_H 4.97 (s, 2H), which correlated with C-3, C-4, C-5, and the carbonyl carbon of a cinnamoyl group, was attributed to the methylene of H_2-20, and the side chain cinnamoyl was thus assigned to C-20. The downfield chemical shift of C-13 and the upfield chemical shift of Me-18, H-10, and Me-16, as well as the lack of further olefinic carbons in the ^{13}C NMR spectrum, indicated that the endocyclic double bond at C-11,12 was epoxidized (δ 64.9 and 59.8). This conclusion was supported by the HMBC spectrum and the molecular elemental composition. The relative stereochemistry of **4** was established from analysis of NOESY data. The coupling constant between H-9 and H-10 (J = 11.2 Hz) and observed NOESY correlations of H-2/H-9, H-9/H_3-17 established a chair−boat conformation for ring B, which is the typical conformation of natural taxoids. The β-orientations of H-2 and H-9 were assigned by NOESY correlations of H-2/H-1, H-2/H_3-17, H-2/H_3-19, and H-9/H-2, H-9/H_3-17, H-9/H_3-19. In turn, the α-orientation of H-10 was assigned from the NOESY correlations of H-10/H-3 and H-10/H_3-18, and the β-orientation of the epoxide group at C-11 and C-12 from the NOESY correlations of H_3-18/H-3 and H_3-18/H-10. The upfield chemical shift of H_3-16, due to the presence of the C-11,12 epoxide and a γ-effect between the C-16 methyl group and the 11,12-epoxide, also suggested that the epoxide group had a β-orientation (Figure 1). From these data, the structure of **4** was established as 2α,9α,10β-triacetoxy-20-cinnamoyloxy-11,12-epoxytaxa-4-en-13-one.

Compound **5** was separated as a colorless gummy substance. Its molecular composition was determined by high-resolution FABMS as $C_{36}H_{44}NO_9$. The ^1H and ^{13}C NMR spectra (Tables 1 and 2) exhibited signals due to four methyl groups at δ 1.08, 1.59, 2.02, and 1.04, three acetyl groups at δ 2.13, 21.3, and 170.6; 2.00, 21.5, and 170.0; and 1.70, 20.0, and 170.9, and an exocyclic methylene group at δ 5.28 (1H, s), 4.80 (1H, s), 117.7, and 142.4. These signals suggested that **5** has a taxane skeleton.[13−16] The signal at δ 3.12 (1H, d, J = 6.6 Hz) was characteristic of the C-3 ring junction proton in a taxa-4(20),11-diene analogue. In addition, five proton signals attached to oxygenated carbons were detected from NMR data and HMBC correlations. A set of AB spin systems at δ 4.27, which correlated with C-7, C-8, C-19, and δ 5.76, which correlated with C-11, C-12, C-15, and a carbonyl at 170.6, were assigned to H-9 and H-10, respectively. A hydroxyl and an acetyl group were located at C-9 and C-10, which were assigned as *trans* according to the large vicinal coupling constant observed (10 Hz). Using H-3 as a starting point, the spin system derived from H-3 to H-2 to H-1 to

H-14 to H-13 was readily interpreted. The chemical shifts of H-2 (δ 5.35) and H-13 (δ 5.79) implied that acetyl groups were connected to C-2 and C-13. The presence of a nor-Winterstein acid [3′-(*N*-methylamino)-3′-phenylpropanoyl] moiety in **5** was suggested from the signals at δ 2.30 (3H, s, N−CH_3), 2.80 (2H, d, J = 6.7 Hz, H-2′), 3.97 (1H, d, J = 6.7 Hz, H-3′), 7.34 (4H, m, Ph-*o*, *m*), and 7.27 (H, m, Ph-*p*) in the ^{1}H NMR spectrum. Further support was provided by the fragment ions at *m*/*z* 120 and 180 in the FABMS.[17] Appendino et al.[18] reported that removal of one methyl group from the dimethylamino of the Winterstein acid moiety could cause a marked upfield shift (ca. 8 ppm) of the remaining methyl group in the ^{13}C NMR spectrum. The signal of N-Me of **5** resonated at δ 34.1, which is in good agreement with this conclusion. The location of the nor-Winterstein acid side chain was deduced to be at C-5 from the HMBC spectrum. The relative stereochemistry of **5** was determined from chemical shifts, coupling constants, and the NOESY experiment. A coupling constant between H-9 and H-10 of 10.0 Hz indicated that the B-ring was in a chair−boat conformation. The β-orientations of H-2 and H-9 were deduced by NOESY correlations of H-2/H-1, H-2/H_3-17, H-2/H_3-19, and H-9/H-2, H-9/H_3-17, H-9/H_3-19. The α-orientation of H-10 was assigned by the observation of NOESY correlations of H-10/H_3-16 and H-10/H_3-18. The β-orientation of H-5 was indicated by the observation of a NOESY correlation of H-2′/H_3-18, with H-13 being β, as suggested by the observation of a correlation between H-13 and H_3-16. Thus, the structure of **5** was established as 9α-hydroxy-2α,10β,13α-triacetoxy-5α-(3′-methylamino-3′-phenyl)propionyloxytaxa-4(20),11-diene.

HRFABMS analysis of compounds **6** and **7** gave the same molecular formula, $C_{24}H_{34}O_7$. The ^{1}H, ^{13}C, and 2D NMR spectra implied that the structures of **6** and **7** were similar, with each having a six/eight/six-membered ring system with two acetyl groups, two hydroxyl groups, an *exo*-methylene, a carbonyl group, and four tertiary methyl groups. HMBC correlations revealed that **6** and **7** possess a cyclohexane ring (ring A) and a cyclohexane ring (ring C) with an *exo*-methylene group at C-4. Acetyl groups were assigned to C-2 and C-10, hydroxyl groups were assigned to C-5 and C-9, and the carbonyl group was placed at C-13 in **6**, on the basis of chemical shifts and HMBC analysis. In **7**, the two acetyl groups were assigned to C-2 and C-9, and the two hydroxyl groups to C-5 and C-10. Thus, the structures of **6** and **7** were assigned as 2α,10β-diacetoxy-5α,9α-dihydroxytaxa-4(20),11-dien-13-one and 2α,9α-diacetoxy-5α,10β-dihydroxytaxa-4(20),11-dien-13-one, respectively.

The molecular formula of **8** was determined to be $C_{26}H_{38}O_8$ from combined analysis of the HRFABMS and ^{1}H and ^{13}C NMR spectral data. Its ^{1}H NMR spectrum closely resembled that of **6**, except that H-14a appeared as a doublet of doublets of doublets in **8** instead of a doublet of doublets as in **6**, and a signal for H-13 appeared at δ 5.73 (1H, m). This information implied that the ketone group in **6** was replaced by an acetoxy group at C-13 in **8**. This conclusion was supported by the fact that C-11 was shifted upfield in **8** in comparison with **6**. Detailed analysis of the 1D and 2D spectral data of **8** established the structure of **8** as 5α,9α-dihydroxy-2α,10β,13α-triacetoxytaxa-4(20),11-diene.

The molecular formula of **9**, $C_{26}H_{38}O_8$, was established by HRFABMS analysis. Its ^{1}H NMR spectrum closely resembled that of **8** except that H-9α and H-10β resonated at δ 5.67 (1H, d, J = 9.9 Hz) and 4.97 (1H, brd, J = 9.9 Hz) in **9** instead of δ 4.20 (1H, d, J = 9.9 Hz) and 5.86 (1H, d, J = 9.9 Hz), respectively, in **8**. Compound **9** was thus characterized as 5α,10β-dihydroxy-2α,9α,13α-triacetoxytaxa-4(20),11-diene.

Compound **10** was obtained as a colorless amorphous solid and showed a pseudomolecular ion peak at *m*/*z* 721 ($M + K^+$) in its FABMS. The molecular formula was deduced as $C_{37}H_{46}O_{12}$ from the HRFABMS. The ^{1}H and ^{13}C NMR spectra (Table 3) showed characteristic signals of a taxane analogue, including four methyl groups, four acetyl groups, and an exocyclic methylene group. Proton signals due to a *trans*-cinnamoyl group were also observed. The ^{1}H NMR spectrum of **10** also showed five oxygen-bearing methines and one hydroxylated (δ 3.38, 1H, brt, J = ∼9 Hz) and four acylated (δ 5.77, 1H, d, J = 7.2 Hz; 5.28, 1H, brdd, J = 9.7, 6.5 Hz; 4.98, 1H, d, J = 5.0 Hz; 5.46, 1H, d, J = 5.0 Hz) groups. The signal at δ 5.28 was assigned to H-5 and the cinnamoyl group was located at C-5, as deduced from its correlation with C-20 and C-1′ (δ 164.9). The signal at δ 3.38 was assigned to H-7 and a free hydroxy group connected to C-7, as deduced from ^{1}H−^{1}H COSY and HMBC correlations. The signal at δ 5.77 was assigned to H-2 and an acetyl group was attached to C-2 judging by the ^{1}H−^{1}H COSY correlations and the HMBC spectrum. The signals at δ 4.98 and 5.46 were assigned to H-9 and H-10, respectively, and two acetyl groups were connected to C-9 and C-10. These assignments were confirmed by the observation of correlations of H-9 with C-3, C-8, C-11, C-19, and δ 171.3, and of H-10 with C-8, C-12, C-15 and δ 169.9 in the HMBC spectrum. The molecular formula and the lack of any additional protons on oxygenated carbons indicated the remaining hydroxyl and acetoxyl groups must be attached to tetrasubstituted carbons. The ^{13}C NMR data supported this conclusion, since the chemical shift of C-11 at δ 78.0 indicated that a free hydroxyl group was attached to C-11. The chemical shifts of the olefinic carbons (δ 123.8, C-12; δ 144.2, C-13) implied the presence of an enol acetate moiety in ring A (C-13).[19] These conclusions were in good agreement with the observed signals of H-14a and H-14b and with the HMBC correlations. HMBC correlations of CH_3-18 to C-11, C-12, and C-13 suggested that Me-18 was attached to C-12, and correlations of CH_3-16 and CH_3-17 to C-1, C-11, and C-15 implied that both Me-16 and Me-17 were attached to C-15. The cross-peaks of H-2 to C-3, C-8, C-5; H-3 to C-1, C-4, C-5, C-8, C-9; H-10 to C-8, C-11; and H-9 to C-3, C-11 in the HMBC spectrum revealed the presence of an eight-membered ring (ring B) and a cyclohexane moiety (ring C). Thus, the structure of **10** was assigned as 7α,11-dihydroxy-2α,9α,10β,13-tetraacetoxy-5α-cinnamoyloxytaxa-4(20),12-diene, i.e., 7-deacetyltaxuspine D[19] or 7-deacetyl-10-acetyltazopidine K.[20] The relative stereochemistry of **10** was elucidated by a ROESY spectrum. A boatlike conformation of ring B was deduced from ROESY correlations of H-2/H_3-17 and H-2/H_3-19, while a boat conformation of ring C was elucidated from the ROESY correlations of H-2/H-5 and H-5/H_3-19.

Compounds **1**−**10** are new taxanes isolated from the needles of the Canadian yew, *T. canadensis*. Compounds **1** and **2** are 3,11-cyclotaxanes with a six/five/five/six-membered ring system. Taxane **1** is the first example of a 3,11-cyclotaxane with a 7-*epi*-α-hydroxyl group. Compound **3** is the fifth example of a taxane with a C-4(5)-*endo*-double bond instead of the usual 4(20)-*exo*-double bond.[13−16] Some analogues of **3** have been reported in the needles of the Canadian yew,[21,22] the seeds of the Chinese yew, *T. mairei*,[23,24] and the bark extract of the Pacific yew, *T. brevifolia*.[25] In addition, these 4(5),11(12)-taxadienes have been suggested to be biosynthetic precursors to pacli-

Table 3. NMR Spectral Data of Compound **10** in $CDCl_3$ (500 MHz for ^1H, 125 MHz for ^{13}C).

position	δ(H) mult	J (Hz)	δ(C)[a]	HMBC	ROESY[b]
1	1.90 (o.m)		50.2	2, 3, 11, 13, 14, 15, 16	2,[s] 14a,[s] 16,[s] 17[s]
2	5.77 (d)	7.2	68.7	3, 8, 14, AcO-2	1,[s] 3,[w] 5,[w] 9,[w] 17,[s] 19[s]
3	3.51 (d)	7.2	40.2	1, 2, 4, 5, 8, 9, 19, 20	2,[w] 7,[s] 10,[w] 14b,[s] 20b[s]
4			**143.6**		
5	5.28 (brdd)	9.7, 6.5	67.6	4, 20, 1′	2,[m] 6a,[s] 19[s]
6a	2.16 (o.m)		34.8		5,[s] 6b,[s] 19[s]
6b	1.89 (o.m)				6a,[s] 7[s]
7	3.38 (brt)	9.0	68.0		3,[s] 6b,[s] 20b/9,[m] 18[m]
8			**44.0**		
9	4.98 (d)	5.0	75.3	3, 4, 5, 8, 10, 11, 19, AcO-9	19,[s] and see ref 20b
10	5.46 (d)	5.0	77.5	8, 9, 11, 12, 15, AcO-10	3,[w] 18[s]
11			**78.0**		
12			**123.8**		
13			**144.2**		
14a	2.52 (ddq)	18.7, 7.7, 1.9	25.7		1,[s] 14b,[s] 16[s] 1,[w] 3,[s] 20b,[m] 14a[s]
14b	2.37 (d)	18.7			
15			**41.1**		
16	1.17 (s)		31.6	1, 11, 15, 17	1,[s] 14a,[m] 17[s]
17	1.51 (s)		23.8	1, 11, 15, 16	1,[s] 2,[s] 16,[s] 19,[s] Ac(10)[w]
18	1.65 (s)		11.7	11, 12, 13	10,[s] Ac(9),[m] Ac(13)[w]
19	1.43 (s)		13.3	3, 7, 8, 9	2,[s] 5,[s] 6a,[s] 9,[m] 17[s]
20a	5.05 (brs)		109.3	3, 4, 5	20b[s]
20b	4.99 (brs)			4, 5	3,[s] 7,[m] 14b,[s] 20a[s]
OAc-13	2.20 (s)		20.6		
OAc-10	2.15 (s)		168.5		
OAc-9	2.11 (s)		21.0		
OAc-2	2.01 (s)		169.9		
			20.7		
			171.1		
			21.4		
			170.5		
C═O 1′			**164.9**		
═CH 2′	6.46 (d)	16.0	117.7	3′, C1-Ph, 1′	
═CH 3′	7.68 (d)	16.0	144.8	2′, Ph-o, Ph-C_1, 1′	
Ph-3′			**134.1**		
o	7.52 (m)		128.0		
m	7.38 (m)		129.0		
p	7.38 (m)		130.3		

[a] The ^{13}C chemical shifts were extracted from the HMQC experiment (±0.2 ppm). The numbers in bold represent quaternary carbons whose chemical shifts were obtained from the HMBC experiment (±0.2 ppm). [b]ROESY intensities are marked as strong (s), medium (m), and weak (w).

taxel.[26,27] Compound **4** is the first taxane with a C-11,12-epoxide ring as well as a C-4(5)-*endo*-double bond. Previous investigation of this plant resulted in the isolation of two taxanes with an 11,12-epoxide.[22,28] Compound **5** is a nitrogen-containing taxane with a rare nor-Winterstein acid side chain at C-5.[13−16,18] It is isolated in the present study for the first time in the needles of the Canadian yew. Compounds **6**−**9** are new taxinine A analogues. Different taxinine derivatives have been reported in other yew species.[13−16] Taxane **10** (7-deacetyl-taxuspine D) is a new taxane with a rare enol acetate moiety in ring A, like taxuspine D.[19] Taxanes with a 12(13) double bond instead of the usual 11(12) double bond have been found so far only in the needles, stem, and seeds of the Japanese yew.[19,20,29]

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Jasco DIP-370 digital polarimeter. NMR and mass spectrometry measurements were obtained as described previously.[22] Flash chromatography was performed on silica gel 60 (230−400 mesh, EM Science). Thin-layer chromatography was conducted on silica gel 60 F254 precoated TLC plates (0.25 mm, EM Science). The compounds were visualized on TLC plates with 10% sulfuric acid in ethanol and heating on a hot plate. Analytical HPLC was performed on a Waters 600 FHU delivery system coupled to a PDA 996 detector. Preparative and semipreparative HPLC were carried out on a Waters Delta Prep 3000 instrument coupled to a UV 486 Tunable Absorbance detector set at 227 nm (Waters, Montreal, Quebec, Canada). Analytical HPLC was performed with two Whatman Partisil 10 ODS-2 analytical columns (4.6 × 250 mm) in series. Semipreparative HPLC was performed with two Whatman Partisil 10 ODS-2 Mag-9 semipreparative columns (9.4 × 250 mm) in series. Preparative HPLC was performed with one Partisil 10 ODS-2 MAG-20 preparative column (22 × 500 mm). The products were eluted with a 50 min linear gradient of acetonitrile (25 to 100%) in water at a flow rate of 18 mL/min (preparative HPLC) and 3 mL/min (semipreparative HPLC). All the reagents and solvents were of the best available commercial quality and were used without further purification.

Plant Material. *Taxus canadensis* Marsh was collected in September 1997 at St-Jean, Quebec, Canada. Several specimens (under accession voucher number lz97-03) have been deposited in the herbarium of the Montreal Botanical Garden.

Extraction and Isolation. Air-dried needles of *T. canadensis* were ground (4.0 kg), extracted, and treated as described previously[22] to yield 110 g of a dark CH_2Cl_2 extract. A portion of the CH_2Cl_2 extract (50 g) was absorbed onto 110 g of silica gel and subjected to column chromatography (silica gel 230−400 mesh, 1320 g). Successive elution with a CH_2Cl_2−MeOH gradient with increasing amounts of MeOH from 5% to 45% (total 15 L) yielded 45 fractions (Fr_{D-1} to Fr_{D-45}). Fractions Fr_{D-25} to Fr_{D-27} were pooled (0.62 g), absorbed on 1.5 g of silica gel, and subjected to column chromatography (silica gel 230−400 mesh, 56 g, 2.5 × 24 cm). Elution with hexane−acetone (75:40) yielded 10 fractions (Fr_{D-25-1} to $Fr_{D-25-10}$). Fractions Fr_{D-25-3} (160 mg) and Fr_{D-25-4} (220 mg) were combined, absorbed on 1 g of silica gel, and applied to

column chromatography (silica gel 230−400 mesh, 55 g, 2.5 × 23 cm), eluted with hexane−EtOAc (5:3), to yield 15 fractions ($Fr_{D-25-3-1}$ to $Fr_{D-25-3-15}$). Fraction $Fr_{D-25-3-8}$ (40 mg) was further separated by HPLC and afforded **1** (6.4 mg, t_R = 40.75 min). Fraction Fr_{D-3} (75 mg) was applied to preparative TLC (hexane−acetone, 11:3, 3 × 20 × 20 cm, thickness 0.25 mm) and cut into four bands identifiable under a UV lamp. The band at R_f = 0.25 was collected, washed with acetone, filtered, dried, and evaporated in vacuo to yield a residue of 6.5 mg. Further purification was conducted by semipreparative HPLC to yield **2** (1.5 mg, t_R = 54.34 min).

Fraction Fr_{D-33} (700 mg) was absorbed onto 1.5 g of silica gel and subjected to column chromatography (silica gel 230−400 mesh, 57 g, 2.5 × 25 cm). Elution with hexane−acetone (65:40) yielded 12 fractions (Fr_{D-33-1} to $Fr_{D-33-15}$). Fraction Fr_{D-33-7} (105 mg) was subjected to preparative HPLC and yielded **3** (3.9 mg, t_R = 28.98 min). Fraction Fr_{D-6} (35 mg) was purified by preparative HPLC, with the material eluting at t_R = 49.88 min collected, dried (9.5 mg), and further purified by preparative TLC (1 × 20 × 20 cm, 0.25 mm) (solvent, hexane−ethyl acetate 62:46), to yield compound **4** (2.1 mg, R_f = 0.51). Fractions Fr_{D-38} to Fr_{D-41} were combined (24 g) according to their TLC behavior, chromatographed over silica gel (770 g), and eluted with hexane−acetone (3:2, 3000 mL; 1:1, 3000 mL; and 2:3, 3000 mL), to yield 28 fractions (Fr_{D-38-1} to $Fr_{D-38-28}$). Fraction $Fr_{D-38-15}$ (1.8 g) was chromatographed over silica gel (150 g, 4 × 30 cm), eluted with CH_2Cl_2−CH_3CN (8:7, 1000 mL; 8:5, 1000 mL; and 2:1, 1000 mL) to afford 15 fractions ($Fr_{D-38-15-1}$ to $Fr_{D-38-15-15}$). Fraction $Fr_{D-38-15-13}$ (150 mg) was subjected to preparative HPLC. Most of the peaks corresponded to previously isolated metabolites of *T. canadensis*. The HPLC peak at t_R = 87.0 min (15 mg) was selected and further purified by preparative TLC (1 × 20 × 20 cm, thickness 0.25 mm; hexane−acetone, 2:3) to give taxane **5** (2.5 mg, R_f = 0.39). Fractions Fr_{D-36} to Fr_{D-37} were combined (720 mg), absorbed onto 1.4 g of silica gel, subjected to column chromatography (50 g, 2.5 × 23 cm), and eluted with hexane−acetone (3:2), leading to 15 fractions (Fr_{D-36-1} to $Fr_{D-36-15}$). Fraction Fr_{D-36-5} (34 mg) was further purified by preparative HPLC to give **6** (3 mg, t_R = 26.48 min). Fractions Fr_{D-38-9}, $Fr_{D-38-10}$, and $Fr_{D-38-11}$ were combined (1.2 g), absorbed onto 2.5 g of silica gel, and applied to column chromatography (58 g, 2.5 × 26 cm), eluted with CH_2Cl_2−CH_3CN (9:1), giving 17 fractions ($Fr_{D-38-9-1}$ to $Fr_{D-38-9-17}$). Fractions $Fr_{D-38-9-14}$, $Fr_{D-38-9-15}$, and $Fr_{D-38-9-16}$ were combined (36 mg) and subjected to preparative HPLC, affording **9** (7 mg, t_R = 28.05 min). Fraction $Fr_{D-38-9-17}$ (218 mg) was subjected to preparative HPLC, with the material eluted at t_R = 24.45 min collected and concentrated (20 mg) and further purified by preparative TLC (1 × 20 × 20 cm, thickness 0.25 mm), developed with hexane−EtOAc (2:5), yielding **7** (3.2 mg, R_f = 0.59). Fraction Fr_{D-33-6} (124 mg) was applied to preparative HPLC, with the material eluted at t_R = 30.78 min collected, dried (40 mg), and applied to preparative TLC (2 × 20 × 20 cm, 0.25 mm), developed with hexane−EtOAc (5:7), to afford **8** (10 mg, R_f = 0.30). Fraction Fr_{D-31} (280 mg) was subjected to preparative HPLC, with the material eluted at t_R 43.0 min collected, dried (19 mg), and applied to preparative TLC (2 × 20 × 20 cm, 0.25 mm), developed with of hexane−EtOAc (50:60). The band with R_f 0.30 was collected, washed with acetone, and further purified by preparative HPLC to give taxane **10** (8 mg, t_R = 43.00 min).

9α-Hydroxy-2α,7α,10β-triacetoxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one (1): amorphous gum; $[\alpha]^{22}_D$ +32° (*c* 0.05, $CHCl_3$); ^1H and ^{13}C NMR spectral data, see Tables 1 and 2; LRFABMS *m/z* 661, 513, 131; HRFABMS *m/z* 661.2415 $[M + K]^+$ (calcd for $C_{35}H_{42}O_{10}K$, 661.2415).

9α,10β-Diacetoxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one (2): amorphous gum; $[\alpha]^{22}_D$ +28° (*c* 0.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.95 (1H, t, *J* = 6.3 Hz, H-1), 2.57 (1H, dd, *J* = 15.7, 5.5 Hz, H-2a), 2.09 (1H, d, *J* = 15.7 Hz, H-2b), 5.70 (1H, t, *J* = 9.7 Hz, H-5), 2.28 (1H, m, H-6a), 1.82 (1H, m, H-6b), 1.74 (1H, m, H-7a), 0.97 (1H, td, *J* = 14.7, 2.8 Hz, H-7b), 5.60 (1H, d, *J* = 9.5 Hz, H-9), 5.78 (1H, d, *J* = 9.5 Hz, H-10), 3.38 (1H, q, *J* = 7.3 Hz, H-12), 2.66 (1H, dd, *J* = 20.4, 7.1 Hz, H-14a), 2.32 (1H, d, *J* = 20.4 Hz, H-14b), 1.19 (3H, s, Me-16), 1.55 (3H, s, Me-17), 1.27 (3H, s, Me-18), 1.20 (3H, s, Me-19), 5.63 (1H, s, H-20a), 5.53 (1H, s, H-20b), 2.05 (3H, s, CH_3CO-9), 2.04 (3H, s, CH_3CO-10), 6.36 (1H, d, *J* = 16.0 Hz, H-2′), 7.66 (1H, d, *J* = 16.0 Hz, H-3′), 7.55 (2H, m, *o*-Ph), 7.37 (3H, m, *m*, *p*-Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.4 (C-1), 36.2 (C-2), 65.4 (C-3), 147.8 (C-4), 75.3 (C-5), 26.1 (C-6), 31.3 (C-7), 44.3 (C-8), 83.0 (C-9), 80.4 (C-10), 57.8 (C-11), 52.3 (C-12), 215.3 (C-13), 43.8 (C-14), 48.1 (C-15), 26.1 (C-16), 28.4 (C-17), 15.6 (C-18), 26.4 (C-19), 125.3 (C-20), 21.0 (CH_3CO-10), 170.8 (CH_3CO-10), 21.0 (CH_3CO-9), 170.2 (CH_3CO-9), 166 (C-1′), 117.9 (C-2′), 145.2 (C-3′), 134.6 (C-4′) 128.2 (C-5′), 128.8 (C-6′), 130.1 (C-7′); HRFABMS *m/z* 587.2410 $[M + K]^+$ (calcd for $C_{33}H_{40}O_7K$, 587.2411).

9α,20-Dihydroxy-2α,10β,13α-triacetoxytaxa-4(5),11(12)-diene (3): amorphous gum; $[\alpha]^{22}_D$ +39° (*c* 0.2, $CHCl_3$); ^1H and ^{13}C NMR spectral data, see Tables 1 and 2; HRFABMS *m/z* 611.1618 $[M + Cs]^+$ (calcd for $C_{26}H_{38}O_8Cs$, 611.1621).

2α,9α,10β-Triacetoxy-20-cinnamoyloxy-11,12-epoxytaxa-4-en-13-one (4): amorphous gum; $[\alpha]^{22}_D$ +27° (*c* 0.11, $CHCl_3$); ^1H and ^{13}C NMR spectral data, see Tables 1 and 2; HRFABMS *m/z* 611.2414 $[M + K]^+$ (calcd for $C_{35}H_{42}O_{10}K$, 611.2415).

9α-Hydroxy-2α,10β,13α-triacetoxy-5α-(3′-methylamino-3′-phenyl)-propionyloxytaxa-4(20),11-diene (5): amorphous gum; $[\alpha]^{22}_D$ +37° (*c* 0.1, $CHCl_3$); ^1H and ^{13}C NMR spectral data, see Tables 1 and 2; LRFABMS *m/z* 678, 180, 120; HRFABMS *m/z* 678.3042 $[M + K]^+$ (calcd for $C_{36}H_{49}NO_9K$, 678.3044).

2α,10β-Diacetoxy-5α,9α-dihydroxytaxa-4(20),11-dien-13-one (6): amorphous gum; $[\alpha]^{22}_D$ +49° (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.09 (1H, odd, H-1), 5.47 (1H, dd, *J* = 5.9, 1.9 Hz, H-2), 3.56 (1H, d, *J* = 5.9 Hz, H-3), 4.17 (1H, t, *J* = 2.5 Hz, H-5), 1.76 (1H, m, H-6a), 1.62 (1H, m, H-6b), 1.70 (1H, m, H-7), 4.28, (1H, d, *J* = 9.6 Hz, H-9), 5.88 (1H, d, *J* = 9.6 Hz, H-10), 2.75 (1H, dd, *J* = 19.6, 7.1 Hz, H-14a), 2.34 (1H, d, *J* = 19.6 Hz, H-14b), 1.11 (3H, s, Me-16), 1.63 (3H, s, Me-17), 2.21 (3H, s, Me-18), 1.06 (3H, s, Me-19), 5.11 (1H, brs, H-20a), 4.81 (1H, s, H-20b), 2.13 (3H, s, 10-CH_3CO-), 2.06 (3H, s, 2-CH_3CO−); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.7 (C-1), 70.1 (C-2), 40.9 (C-3), 147.5 (C-4), 76.4 (C-5), 30.6 (C-6), 25.2 (C-7), 45.0 (C-8), 75.8 (C-9), 76.6 (C-10), 150.2 (C-11), 138.3 (C-12), 199.7 (C-13), 36.1 (C-14), 37.9 (C-15), 37.0 (C-16), 25.6 (C-17), 14.0 (C-18), 17.5 (C-19), 113.6 (C-20), 21.2 (CH_3CO-10), 170.2 (CH_3CO-10), 21.4 (CH_3CO-2), 169.6 (CH_3CO-2); HRFABMS *m/z* 473.1940 $[M + K]^+$ (calcd for $C_{24}H_{34}O_7K$, 437.1942).

2α,9α-Diacetoxy-5α,10β-dihydroxytaxa-4(20),11-dien-13-one (7): amorphous gum; $[\alpha]^{22}_D$ +34° (*c* 0.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.16 (1H, m, H-1), 5.51 (1H, dd, *J* = 6.1, 1.7 Hz, H-2), 3.58 (1H, d, *J* = 6.1 Hz, H-3), 4.17 (1H, brs, H-5), 1.75 (1H, m, H-6a), 1.58 (1H, m, H-6b), 1.75 (1H, m, H-7a), 1.61 (1H, m, H-7b), 5.72, (1H, d, *J* = 9.9 Hz, H-9), 5.04 (1H, d, *J* = 9.9 Hz, H-10), 2.78 (1H, dd, *J* = 19.7, 7.0 Hz, H-14a), 2.33 (1H, d, *J* = 19.7 Hz, H-14b), 1.21 (3H, s, Me-16), 1.80 (3H, s, Me-17), 2.08 (3H, s, Me-18), 0.88 (3H, s, Me-19), 5.13 (1H, brs, H-20a), 4.78 (1H, s, H-20b), 2.16 (3H, s, CH_3-CO-9), 2.05 (3H, s, CH_3CO-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.7 (C-1), 70.0 (C-2), 41.0 (C-3), 76.1 (C-5), 30.5 (C-6), 26.4 (C-7), 44.5 (C-8), 79.1 (C-9), 71.9 (C-10), 153.3 (C-11), 136.0 (C-12), 199.6 (C-13), 36.2 (C-14), 37.7 (C-15), 37.5 (C-16), 25.3 (C-17), 14.0 (C-18), 17.5 (C-19), 114.0 (C-20), 21.0 (CH_3CO-9), 171.5 (CH_3CO-9), 21.5 (CH_3CO-2), 169.0 (CH_3CO-2); HRFABMS *m/z* 473.1940 $[M + K]^+$ (calcd for $C_{24}H_{34}O_7K$, 437.1942).

5α,9α-Dihydroxy-2α,10β,13α-triacetoxytaxa-4(20),11-diene (8): amorphous gum; $[\alpha]^{22}_D$ +29° (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (1H, m, H-1), 5.38 (1H, dd, *J* = 5.8, 1.7 Hz, H-2), 3.51 (1H, d, *J* = 5.8 Hz, H-3), 4.23 (1H, s, H-5), 1.79 (1H, m, H-6a), 1.61 (1H, m, H-6b), 1.51 (1H, m, H-7), 4.21, (1H, d, *J* = 9.9 Hz, H-9), 5.86 (1H, d, *J* = 9.9 Hz, H-10), 5.73 (1H, m, H-13), 2.63 (1H, ddd, *J* = 15.8, 10.5, 9.1 Hz, H-14a), 1.51 (1H, dd, *J* = 15.8, 5.1 Hz, H-14b), 1.00 (3H, s, Me-16), 1.57 (3H, s, Me-17), 2.14 (3H, s, Me-18), 1.04 (3H, s, Me-19), 5.21 (1H, brs, H-20a), 4.88 (1H, s, H-20b), 2.10 (3H, s, CH_3-CO-13), 2.09 (3H, s, CH_3CO-10), 2.04 (3H, s, CH_3CO-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.6 (C-1), 71.6 (C-2), 41.4 (C-3), 147.1 (C-4), 77.1 (C-5), 30.2 (C-6), 24.9 (C-7), 44.8 (C-8), 76.1 (C-9), 76.0 (C-10), 134.6 (C-11), 137.3 (C-12), 69.6 (C-13), 28.5

(C-14), 37.1 (C-15), 32.0 (C-16), 26.1 (C-17), 17.6 (C-18), 15.6 (C-19), 114.6 (C-20), 21.1 (*CH*$_3$CO-13), 21.1 (*CH*$_3$CO-10), 21.4 (*CH*$_3$CO-2), 170.2 (CH$_3$*CO*-13), 170.2 (CH$_3$*CO*-10), 169.3 (CH$_3$*CO*-2); HRFABMS *m*/*z* 517.2206 [M + K]$^+$ (calcd for $C_{26}H_{38}O_8K$, 517.2203).

5α,10*β*-Dihydroxy-2α,9α,13α-triacetoxytaxa-4(20),11-diene (9): amorphous gum; $[\alpha]^{22}_D$ +43° (*c* 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (1H, m, H-1), 1.10 (3H, s, Me-16), 1.74 (3H, s, Me-17), 1.99 (3H, s, Me-18), 0.85 (3H, s, Me-19), 3.55 (1H, d, J = 6.1 Hz, H-3), 5.43 (1H, dd, J = 6.1, 1.8 Hz, H-2), 4.97 (1H, d, J = 9.9 Hz, H-10), 5.67 (1H, d, J = 9.9 Hz, H-9), 5.77 (1H, m, H-13), 4.85 (1H, s, H-20a), 5.22 (1H, brs, H-20b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.7 (C-1), 71.4 (C-2), 41.3 (C-3), 26.2 (C-7), 41.3 (C-8), 79.7 (C-9), 70.7 (C-10), 137.1 (C-11), 134.4 (C-12), 69.6 (C-13), 37.2 (C-15), 32.2 (C-16), 25.8 (C-17), 15.6 (C-18), 17.4 (C-19), 115.0 (C-20); HRFABMS *m*/*z* 517.2206 [M + K]$^+$ (calcd for $C_{26}H_{38}O_8K$, 517.2203).

7*β*,11 *β*-Dihydroxy-2α,9α,10*β*,13-tetraacetoxy-5α-cinnamoyloxytaxa-4(20),12-diene (10): amorphous gum; $[\alpha]^{22}_D$ +31° (*c* 0.4, $CHCl_3$); ^{1}H and ^{13}C NMR, HMBC, and ROESY spectral data, see Table 3; HRFABMS *m*/*z* 721.2628 [M + K]$^+$ (calcd for $C_{37}H_{46}O_{12}K$, 721.2626).

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Supporting Information Available: HMBC and NOESY data for compounds **1**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Zamir, L. O.; Nedea, M. E.; Bélair, S.; Sauriol, F.; Mamer, O.; Jacqmain, E.; Jean, F. I.; Garneau, F.-X. *Tetrahedron Lett.* **1992**, *33*, 5173−5176.
(2) Zamir, L. O.; Nedea, M. E.; Zhou, Z.-H.; Bélair, S.; Caron, G.; Sauriol, F.; Jacqmain, E.; Jean, F. I.; Garneau, F.-X.; Mamer, O. *Can. J. Chem.* **1995**, *73*, 655−665.
(3) Zamir, L. O.; Zhang, J.; Wu, J. H.; Sauriol, F.; Mamer, O. *J. Nat. Prod.* **1999**, *62*, 1268−1273.
(4) Zhang, J.; Sauriol, F.; Mamer, O.; You, X. L.; Alaoui-Jamali, M. A.; Batist, G.; Zamir, L. O. *J. Nat. Prod.* **2001**, *64*, 450−455, and references therein.
(5) Gunawardana, G. P.; Premachandran, U.; Burres, N. S.; Whittern, D. N.; Henry, R.; Spanton, S.; McAlpine, J. B. *J. Nat. Prod.* **1992**, *55*, 1686−1689.
(6) Zhang, S.; Chen, W. M.; Chen, Y. H. *Yaoxue Xuebao* (*Acta Pharm. Sin.*) **1992**, *27*, 268−272.
(7) Wu, J. H.; Zamir, L. O. *Anti-Cancer Drug Des.* **2000**, *15*, 73−78.
(8) Wu, J. H.; Batist, G.; Zamir, L. O. *Anti-Cancer Drug Des.* **2000**, *15*, 441−446.
(9) Wu, J. H.; Batist, G.; Zamir, L. O. *Anti-Cancer Drug Des.* **2001**, *16*, 129−133.
(10) Zamir, L. O.; Zhang, J.; Kutterer, K.; Sauriol, F.; Mamer, O.; Khiat, A.; Boulanger, Y. *Tetrahedron* **1998**, *54*, 15845−15860.
(11) Kobayashi, J.; Shegemori, H. *Med. Res. Rev.* **2002**, *22*, 305−328.
(12) Nikolakakis, A.; Wu, J. H.; Batist, G.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Bioorg. Med. Chem.* **2002**, *10*, 2387−2395.
(13) Appendino, G. In *The Chemistry and Pharmacology of Taxol and Its Derivatives*; Farina, V., Ed.; Elsevier: Amsterdam, 1995; Vol. 22, pp 55−102.
(14) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C. H., Ed.; Springer-Verlag: New York, 1993; Vol. 61, pp 1−206.
(15) Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1448−1472.
(16) Parmer, V. S.; Jha, A.; Bish, K. S.; Taneja, P.; Sight, S. K.; Kumar, A.; Poonam, J. R.; Olsen, C. E. *Phytochemistry* **1999**, *50*, 1267−1304.
(17) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Yamada, T. *Nat. Prod. Lett.* **1999**, *13*, 179−186.
(18) Appendino, G.; Ozen, H.; Fenoglio, I.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *Phytochemistry* **1993**, *33*, 1521−1525.
(19) Kobayashi, J.; Hosoyama, H.; Shigemori, H.; Koiso, Y.; Iwasaki, S. *Experientia* **1995**, *51*, 592−595.
(20) Shigemori, H.; Sakurai, C.; Hosoyama, H.; Kobayashi, A.; Kajiyama, S.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 2553−2558.
(21) Zhang, J.; Sauriol, F.; Mamer, O.; Zamir, L. O. *J. Nat. Prod.* **2000**, *63*, 929−933.
(22) Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Bioorg. Med. Chem.* **2003**, *11*, 293−303.
(23) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Murakami, R.; Wei, H. Q. *J. Nat. Prod.* **1999**, *62*, 1114−1118.
(24) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Chen, Q. *Nat. Prod. Lett.* **1999**, *13*, 305−312.
(25) Koepp, A. E.; Hezari, M.; Zajicek, J.; Vogel, B. S.; LaFever, R. E.; Lewis, N. G.; Croteau, R. *J. Biol. Chem.* **1995**, *270*, 8686−8690.
(26) Vazquez, A.; Williams, R. *J. Org. Chem.* **2000**, *65*, 7865−7869.
(27) Horiguchi, T.; Rithner, C. D.; Croteau, R.; Williams, R. *J. Org. Chem.* **2002**, *67*, 4901−4903.
(28) Zamir, L. O.; Zhang, J.; Wu, J. H.; Sauriol, F.; Mamer, O. *Tetrahedron* **1999**, *55*, 14323−14340.
(29) Kobayashi, J.; Hosoyama, H.; Katsui, T.; Yoshida, N.; Shigemori, H. *Tetrahedron* **1996**, *52*, 5391−5396.

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