A Yew in Israel, New Taxane Derivatives†

Qing-Wen Shi,‡ Zel Lederman,§ Francoise Sauriol,⊥ Robert S. McCollum,‡ and Lolita O. Zamir*,‡

Human Health Research Center, INRS-Institut Armand-Frappier, Université du Québec, 531 Boulevard des Prairies, Laval, Quebec, Canada H7V 1B7, Jerusalem Botanic Garden, Jerusalem, Israel, and Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

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Five new taxanes, 5α,9α,10*β*,13α-tetraacetoxy-14*β*-*O*-(*β*-D-glucopyranosyl)taxa-4(20),11-diene (**1**), 1*β*,2α,9α,10*β*-tetrahydroxy-5α-cinnamoyoxytaxa-4(20),11-dien-13-one (**2**), 2α,9α,10*β*-trihydroxy-5α-cinnamoyoxytaxa-4(20),11-dien-13-one (**3**), 9α-acetoxy-2α,10*β*-dihydroxy-5α-cinnamoyoxytaxa-4(20),11-dien-13-one (**4**), and 2α,10*β*-diacetoxy-1*β*,9α-dihydroxy-5α-cinnamoyoxy-3,11-cyclotaxa-4(20)-dien-13-one (**5**), have been identified in a *Taxus baccata* yew grown in Israel from seeds imported from the United States. We have also characterized 40 previously known taxanes from this plant material. The structures of the new taxanes (**1**−**5**) were rigorously established with 1D and 2D NMR data and confirmed by high-resolution FAB-mass spectrometry.

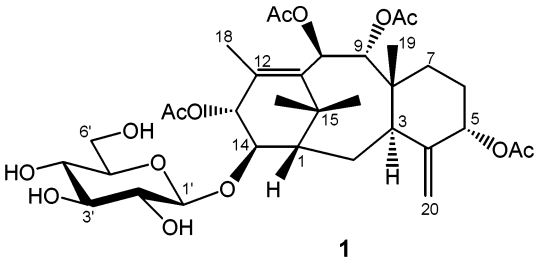
A visit to the Supreme Court in Jerusalem, Israel, led to the surprising discovery of a very elegant small *Taxus* tree (∼2.5 cm diameter and 1 m height). These yews were grown from seeds that were sent from the United States. Mr. Zel Lederman, curator of the Jerusalem Botanic Gardens, enabled us to identify this yew as *Taxus baccata* L. (Taxaceae) and provided us with needles from different Israeli nurseries. In this publication, we will concentrate on the *Taxus baccata* L. needles obtained from the Allon nursery.

This publication is the first report of the chemical structures and stereochemistry of the taxanes composition of an Israeli-grown *T. baccata* L. We discovered five new taxanes, **1**−**5**, in the Israeli *T. baccata*. In addition, 40 known taxanes, **6**−**45**, were characterized including taxol (**33**), 10-deacetyltaxol (**34**), and cephalomannine (**32**) as well as two 5-*epi*-canadensene derivatives (**38**, **39**). The most abundant taxanes were taxine derivatives with a C-1-H or C1-*β*-OH, C-13-keto group and the usual C4(20) double bond with a *trans*-cinnamoyl group.

It is interesting to note that not only the physical properties of the yews but also its taxanes composition can differ very much depending on the season, the location, and temperature.[1] *T. baccata* L. in France is a huge tree with an average height of 30−90 feet and a circumference that can be 20 feet.[2] The secondary metabolites also depend on the species, location, season, and weather. The most abundant metabolite in the European yew (*T. baccata* L.) in France is 10-deacetylbaccatin III.[3] It is present at almost 5−7 times the amount of taxol in the European yew.[4−6] This metabolite is found in trace amounts in the Israeli *T. baccata* L. The amounts of this metabolite in the French yew showed considerable monthly fluctuations.[1]

Results and Discussion

A methanolic extract of the needles of Israeli *T. baccata* L. was processed as described in the Experimental Section to yield compounds **1**−**45** including five new taxanes (**1**−**5**). All the compounds were isolated at low yields (about 1−3 mg from 40 g of dried needles). Taxane **1** was obtained as a colorless amorphous solid. The molecular composition of **1**, $C_{34}H_{50}O_{14}$, was established from the combined analysis of high-resolution FABMS and 2D NMR spectral data. The ^{1}H NMR spectrum of **1**, Table 1, exhibited three-proton signals due to the four tertiary methyl groups at *δ* 1.23, 1.63, 2.04, and 0.73, and four acetyl methyl groups at *δ* 2.17, 2.14, 2.03, and 1.98, which were further confirmed by the observation of the signals at *δ* 21.7, 21.1, 20.4, and 20.6 and the corresponding signals of carbonyl carbons at *δ* 170.1, 171.6, 170.5, and 170.2 in the ^{13}C NMR spectrum.



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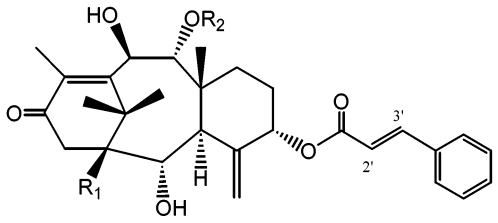
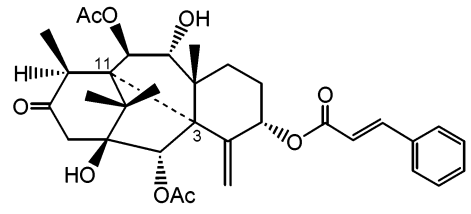


2 R_1 = OH R_2 = H
3 R_1 = H R_2 = H
4 R_1 = H R_2 = Ac



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† Dedicated to the late Dr. Monroe E. Wall and to Dr. Mansukh C. Wani of Research Triangle Institute for their pioneering work on bioactive natural products.

* To whom correspondence should be addressed. Tel: +1 (450) 687-5010, ext. 4260. Fax: +1 (514) 481-2797. E-mail: Lolita.Zamir@inrs-iaf.uquebec.ca.
‡ Université du Québec.
§ Curator, Jerusalem Botanic Garden.
⊥ Queen's University.

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

position	δ (H) mult[a]	J (Hz)	δ (C)[b]	HMBC	NOESY[c]
1	2.00 (br s)		49.5		14,^{s} 17,^{w} 20b,^{s} G1^s (1 overlap 2a)
2a	2.02 (o m)		28.2	8	(down) see 1
2b	1.89 (o m)			8, 15	9,^{s} 17,^{s} 19,^{s} 20b^w
3	2.82 (m)		39.6	1, 2, 8, 19, 20	
4			**149.8**		
5	5.30 (t)	2.1	75.9	3, 4, 20, 170.2	6/7,^{s} 20a^s
6ab	1.74 (o m)		27.6		
7ab	1.74 (o m)		27.6		
8			**43.4**		
9	5.85 (d)	10.6	77.2	7, 8, 10, 11, 19, 170.5	
10	6.02 (d)	10.6	72.4	9, 11, 12, 15, 170.1	6/7,^{m} 18^s
11			**137.4**		
12			**136.4**		
13	6.10 (dq)	6.8, 1.5	76.8	12, 14, 171.6	14,^{w} 16^s
14	3.78 (d)	6.8	83.6	1, 2, 13, 15, **1′**	13,^{w} 1′^{s}
15			**40.0**		
16	1.23 (s)		31.1	1, 11, 15, Me-17	13,^{s} 17^m
17	1.63 (s)		27.5	1, 11, 15, Me-16	2b,^{s} 9,^{s} 16^w
18	2.04 (o s)		14.5	1, 12, 13	10,^{s} 13^w
19	0.73 (s)		17.4	3, 7, 8, 9	2b,^{s} 9,^{s} 6/7,^{w} 20b^w
20a	5.23 (br s)		114.3	3, 4, 5 3, 4, 5	5,^{s} 20b^s
20b	4.98 (d)	1.5			20a^s
5-OAc	1.98 (s)		20.6		
			170.2		
9-OAc	2.03 (s)		20.4		
			170.5		
10-OAc	2.17 (s)		21.7		
			170.1		
13-OAc	2.14 (s)		21.1		
			171.6		
1′	4.37 (d)	7.7	102.8	**14**	3′,^{s} 5′,^{s} 14^s
2′	3.11 (o t)		74.2	1′, 3′	
3′	3.33 (o m)		77.5		
4′	3.32 (o m)		71.3		
5′	3.20 (m)		76.9	1′, 3′, 4′, 6	
6′a	3.77 (o m)		62.9		
6′b	3.64 (o m)			5′	

[a] Mutiplicity: s, singlet; d, doublet; dd, doublet of doublets; q, quartet; m, mutiplet; br s, broad singlet; o, overlapped. [b] ^{13}C chemical shifts were extracted from the HMQC experiment (±0.2 ppm). The numbers in bold character represent quaternary carbons whose chemical shifts were obtained from the HMBC experiment (±0.2 ppm). [c]NOESY intensities are marked as strong (s), medium (m), and weak (w).

These findings suggested that **1** had a taxane-type core skeleton.[7,8] Indeed, the HMBC correlations of H_3-18 to C-11, C-12, and C-13, H_3-16 and H_3-17 to C-1, C-11, and C-15, and H_3-19 to C-3, C-7, C-8, and C-9 revealed that Me-18 was attached to C-12, whereas Me-16 and Me-17 were attached to C-15, and Me-19 was attached to C-8, implying that **1** has a regular 6/8/6 ring system.[7−9] The connectivities of the protons on the skeleton of **1** were determined by analysis of the ^{1}H−^{1}H COSY spectrum. Interpretation of ^{1}H, ^{13}C NMR and HMBC spectra permitted the positional assignment of all the functional groups. The ^{1}H NMR signals at δ 5.23 (1H, br s) and 4.98 (1H, br s) together with the signals at δ 149.8 and 114.3 in the ^{13}C NMR spectrum are characteristic of an *exo*-cyclic methylene in a taxa-4(20),11-diene.[7,8] The signal at δ 2.82, which showed long-range correlations with C-1, C-2, C-8, C-19, and C-20 in the HMBC experiment, was assigned to H-3. Using H-3 as a reference, the connectivities from C-3 to C-2 to C-1 to C-14 to C-13 were deduced from the ^{1}H−^{1}H COSY spectrum. The signal at δ 6.10 (1H, dq, J = 6.8, 1.5 Hz) was attributed to H-13, and the chemical shift indicated that an acetyl group was positioned at C-13. This was further confirmed by the HMBC correlation of H-13 to the carbonyl carbon signal at δ 171.6. The signal at δ 3.78 (1H, d, J = 6.8 Hz) was assigned to H-14; its chemical shift and splitting pattern indicated that a side chain was attached to C-14. Indeed, detailed analysis of the ^{1}H−^{1}H COSY spectrum suggested a glucose unit in taxane **1**. This was further verified by the information observed in the ^{1}H and ^{13}C NMR spectra: an anomeric carbon signal at δ 102.8 as well as five oxygenated carbons between δ 62.9 and 77.4 and six hydrogen signals between δ 3.11 and 4.37. Thus, it was assigned as a glucopyranosyl unit from the chemical shift, multiplicity, and coupling constant values. Analysis of the 2D NMR data (COSY, HMBC) as well as the MS fragment of $[M + K - 180]^+$ also confirmed the presence of the glucopyranosyl group. The coupling constant J = 7.7 Hz of the anomeric proton H-1′ indicated that this moiety was connected to the aglycone via a β-linkage (J = 6−8 Hz). The anomeric proton H-1′ showed a long-range correlation with C-14, and H-14 showed correlation with C-1′ in the HMBC experiment, indicating that the glucose was attached at C-14 of the taxane skeleton. The signal at δ 5.30 (1H, t, J = 2.1 Hz) was assigned to H-5. The chemical shifts of H-5 and C-5 (δ 75.9) suggested that an acetyl group was positioned at C-5.[7−9] This was further confirmed by the HMBC correlations. Similarly, using H-5 as a starting point, the discrete spin system derived from C-5 to C-7 through C-6 was readily interpreted from the analysis of the ^{1}H−^{1}H COSY spectrum. The isolated signals as an AB system at δ 5.85 (1H, d, J = 10.6 Hz) and 6.02 (1H, d, J = 10.6 Hz) were attributed to H-9 and H-10, respectively. The orientations of the substituents on the taxane skeleton were confirmed by the coupling constants in ^{1}H NMR and the correlations in the NOESY experiment (Table 1). The strong NOE correlation of H-14 and H-1 as well as the small coupling constant between H-1 and H-14 suggested that their dihedral angle was about 90°: the C-14 side chain was therefore β-oriented and H-14 was α-oriented. The chemical structure of **1** was therefore established as

5α,9α,10*β*,13α-tetraacetoxy-14*β*-*O*-(*β*-D-glucopyranosyl)-taxa-4(20),11-diene. Taxane **1** is the first reported example of a taxane with a glucose substitution in *T. baccata*. Taxane **1** featured a rare oxidation pattern at both C-13 and C-14 simultaneously.[9]

The elemental formula of compound **2** was found to be $C_{29}H_{36}O_7$ on the basis of HRFABMS analysis of the apparent molecular ion peak at *m/z* 535 $(M + K)^+$. The ^1H NMR spectrum displayed well-dispersed characteristic signals suggestive of a taxane derivative. Four tertiary methyl groups, one cinnamoyl group, one *exo*-cyclene, one α,*β*-unsaturated keto-group, four oxymethines, and five oxygenated carbons were also indicated by the diagnostic signals in the ^1H and ^{13}C NMR spectra. The ^1H, ^{13}C, and 2D NMR data of **2** showed the presence of a 6/8/6-membered ring system.[7,8] Detailed analysis of the $^1H-^1H$ COSY spectrum of **2** revealed the connectivities of C-2 to C-3, C-5 to C-7, and C-9 to C-10. A set of isolated AB systems at *δ* 4.17 and 4.91 with a large coupling constant $J = 9.6$ Hz were assigned to H-9 and H-10, respectively. Another AB system at *δ* 2.71 and 2.64 with a coupling constant $J = 19.2$ Hz was assigned to H-14a and H-14b, respectively. The chemical shifts and splitting patterns of H-14a and H-14b indicated that a ketone and a hydroxyl group were attached to C-13 and C-1, respectively. A pair of coupling systems at *δ* 4.04 and 3.36 with a smaller coupling constant of $J = 6.6$ Hz arose from H-2 and H-3. The chemical shifts of H-2, H-9, and H-10 indicated that only free hydroxyl groups were positioned at C-2, C-9, and C-10. This conclusion was in agreement with the observed ^{13}C NMR data. The signal resonating at *δ* 5.31 (1H, t, $J =$ 2.5 Hz) was assigned to H-5. The chemical shift of H-5 indicated that the remaining cinnamoyl group was connected to C-5. The structure of **2**, therefore, was determined to be 1*β*,2α,9α,10*β*-tetrahydroxy-5α-cinnamoyloxytaxa-4(20),11-dien-13-one. The relative stereochemistry of **2** was established using the information observed from the NOESY experiment, and the results are summarized in the Experimental Section.

The molecular composition of **3** was established as $C_{29}H_{36}O_6$ from combined analysis of high-resolution FABMS at *m/z* 519 $(M + K)^+$ and the ^{13}C NMR spectrum. The molecular weight of **3** was 16 units less than that of **2**, in accord with the loss of one oxygen on C-1. The ^1H NMR spectrum of **3** closely resembled that of **2** except for the splitting pattern of H-14a. In compound **3**, H-14a resonated as a doublet of doublets at *δ* 2.84 (1H, dd, $J = 19.8$, 7.0 Hz) instead of a doublet as in compound **2**. Similarly, H-2 resonated as a doublet of doublets at *δ* 4.21 (1H, dd, $J =$ 6.4, 2.1 Hz) in **3** instead of as a doublet in compound **2**. These observations suggested that a proton on C-1 in compound **3** replaced the hydroxyl group on C-1 in compound **2**. This conclusion was further supported by ^{13}C NMR data: C-1 resonated at *δ* 51.4 in **3** instead of at *δ* 77.9 in compound **2**. Compound **3**, therefore, was characterized as 2α,9α,10*β*-trihydroxy-5α-cinnamoyloxytaxa-4(20),11-dien-13-one. The relative stereochemistry of **3** was established by the NOESY experiment, and the results are summarized in the Experimental Section.

The molecular composition of **4** was calculated as $C_{31}H_{38}O_7$ from combined analysis of high-resolution FABMS at *m/z* 561 $(M + K)^+$ and the ^{13}C NMR spectrum, which was 42 (CH_2CO) mass units more than that of **3**. The ^1H and ^{13}C NMR spectra of **4** closely resembled those of **3** except an additional acetyl group appeared at *δ* 2.16, 20.9, and 171.7, and H-9 shifted downfield to *δ* 5.68 (1H, d, $J = 10.0$ Hz). These observations suggested that an acetyl group was attached to C-9. This conclusion was further verified by the HMBC experiment: the signal at *δ* 5.68 exhibited long-range correlations with C-3, C-7, C-8, C-19, and a carbonyl carbon at *δ* 171.6. The structure of **4**, therefore, was determined to be 9α-acetoxy-2α,10*β*-dihydroxy-5α-cinnamoyloxytaxa-4(20),11-dien-13-one. The relative stereochemistry of **4** was established by the NOESY experiment and coupling constants as indicated in the Experimental Section.

Table 2. ^{13}C NMR Data (*δ*) of **2**−**4** in $CDCl_3$ (125 MHz)

position	**2**	**3**	**4**
C-1	77.9	51.3	51.4
C-2	71.3	68.0	68.0
C-3	46.5	45.0	44.9
C-4	144.2	143.9	143.5
C-5	78.0	78.1	78.0
C-6	28.7	28.9	28.8
C-7	26.1	26.3	27.5
C-8	45.1	44.6	44.5
C-9	77.0	77.6	78.9
C-10	73.2	73.4	71.9
C-11	157.3	155.2	154.7
C-12	136.9	135.0	135.4
C-13	200.1	199.9	199.9
C-14	44.1	35.7	35.6
C-15	42.3	37.6	37.7
C-16	34.1	37.9	37.7
C-17	19.9	25.3	25.5
C-18	13.6	13.9	13.8
C-19	17.3	17.7	17.4
C-20	117.1	117.3	117.6
CH$_3$CO−			20.9
CH$_3$*CO*−			171.7
Cinn-1	166.3	166.1	166.3
2	117.4	117.9	117.6
3	145.5	145.5	145.4
Ph-4	134.3	134.6	134.4
o	128.1	128.4	128.3
m	128.5	128.9	128.7
p	129.9	130.4	130.1

Compound **5** was isolated as a colorless gummy substance. Its quasi-molecular ion at *m/z* 619 $(M + K)^+$ generated by HRFABMS revealed that the molecular formula of **5** was $C_{33}H_{40}O_9$. Fourteen degrees of hydrogen deficiency were determined from the molecular formula and the ^{13}C NMR spectrum. Its ^1H NMR spectrum, Table 3, exhibited the characteristic signals of taxanes. The chemical shift of the characteristic proton resonances due to an *exo*-methylene moiety was observed at *δ* 5.86 and 5.69 (each 1H, s). The presence of a cinnamoyl moiety in **5** was revealed by the signals at *δ* 6.37 (1H, d, $J = 16.0$ Hz), 7.66 (1H, d, $J = 16.0$, *trans*-orientation), 7.56 (2H, m), and 7.38 (3H, m) in the ^1H NMR spectrum. In addition, the presence of two acetyl groups and one unconjugated ketone group was implied by the resonances at *δ* 2.17, 21.3, 172.2; 2.15, 21.3, 172.2, and 212.7 in the ^1H NMR and/or ^{13}C NMR spectra. Since 13 out of 14 unsaturation degrees deduced from the molecular formula were thus accounted for, **5** contains either an additional double bond or a saturated ring. Detailed examination of the ^1H NMR spectrum of **5** revealed some different spectral features compared with regular taxanes: the signal of H-3α, usually appearing at *δ* 3.2−3.6 with a coupling constant in a range of ca. *δ* 5.0−6.0 Hz, disappeared;[7,8] one of the methyl groups gave rise to a doublet, which showed a coupling with a quartet signal at *δ* 3.51 (1H, q, $J = 7.3$ Hz) in the $^1H-^1H$ COSY spectrum. On the basis of analysis of these spectral features and available data, it is clear that **5** was a 3,11-cyclotaxane. Combined analysis of $^1H-^1H$ COSY, HMQC, and HMBC spectra, together with chemical shifts and coupling con-

Table 3. ^{1}H and ^{13}C NMR Data of **5** in $CDCl_3$ (500 MHz for ^{1}H, 125 MHz for ^{13}C)

position	δ (H) mult[a]	J (Hz)	δ (C)[b]	HMBC	NOESY[c]
1			**79.0**		
2	6.08 (br d)	1.8	79.0	3, 8	17,[s] 19[s]
3			**61.4**		
4			**141.4**		
5	5.61 (t)	9.2	76.2	3	6a,[w] 20b[s]
6a	2.17 (o m)		25.9		
6b	1.68 (o m)				
7a	2.06 (o m)		**29.5**		7a[w]
7b	1.11 (o m)				
8			**45.9**		
9	4.43 (d)	9.4	82.7	7, 8, 10	17,[s] 19[m]
10	5.47 (d)	9.6	84.3	8, 9, 11, 12, 172.2	6b,[s] 12,[w] 18[s]
11			**56.2**		
12	3.51 (q)	7.3	51.3		10,[w] 18,[m] 20a[s]
13			**212.7**		
14a	2.88 (d)	20.2 20.2, 1.8	46.3	1, 15 1	14b,[s] 20a[s]
14b	2.41 (br dd)				14a,[s] 16[m]
15			**45.2**		
16	1.10 (s)		23.3	1, 11, 15, Me-17	14b,[m] 17[s]
17	1.49 (s)		22.7	1, 11, 15, Me-16	16,[m] 9,[s] 2[s]
18	1.32 (d)	7.2	15.9	11, 12, 13	10,[m] 12[m]
19	1.27 (s)		26.0	3, 7, 8, 9	2,[s] 7a,[w] 9[m]
20a	5.86 (s)		128.9	3, 5 4, 5	12,[w] 14a,[s] 20b[s]
20b	5.69 (d)	1.8			5,[w] 20a[s]
OAc	2.17 (s)		21.3		
			172.2		
	2.15 (s)			172.2	
			21.3		
			172.2		
Cinn-1′			**165.4**		
2′	6.37 (d)	16.0	117.6	1′, Ph-C1	
3′	7.67 (d)	16.0	145.2		
4′- Ph	7.56 (m)		**134.2**		
o	7.38 (m)		128.0		
m	7.38 (m)		128.7		
p			130.1		

[a] Mutiplicity: s, singlet; d, doublet; dd, doublet of doublets; q, quartet; m, mutiplet; br s, broad singlet; br dd, broad doublet of doublets; o, overlapped. [b] The ^{13}C chemical shifts were extracted from the HMQC experiment (±0.2 ppm). The numbers in bold character represent quaternary carbons whose chemical shifts were obtained from the HMBC experiment (±0.2 ppm). [c] NOESY intensities are marked as strong (s), medium (m), and weak (w).

stants, permitted the assignments of all functional groups on the taxane skeleton. Acetyl groups were located at C-2 and C-10; hydroxyl groups were connected to C-1 and C-9; ketone and cinnamoyl groups were at C-13 and C-5, respectively, as in all the other 3,11-cyclotaxanes.[9] It should be noted that H-2 exhibited a long-range ^{1}H−^{1}H COSY correlation with H-14b (J = 1.8 Hz) in taxane **5**. Thus, **5** was characterized as 2α,10*β*-diacetoxy-1*β*,9α-dihydroxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one. To determine the relative stereochemistry of **5**, a NOESY experiment was performed, and the results are presented in Table 3.

The known compounds **6**−**45** isolated in this work were identified on the basis of spectoscopic analysis and by comparison with reported spectral data. These taxanes are 1*β*,9α-dihydroxy-2α,10*β*-diacetoxy-5α-cinnamoxytaxa-4(20),-11-diene-13-one (**6**),[10] 1*β*,10*β*-dihydroxy-2α,9α-diacetoxy-5α-cinnamoxytaxa-4(20),11-diene-13-one (**7**),[10] 5-cinnamoyl-10-acetyltaxicin II (**8**),[11] 5-*O*-cinnamoyltaxicin I (**9**),[12] 5-cinnamoyl-10-acetyltaxicin I (**10**),[11] taxinine (**11**),[13] 5-cinnamoyltaxicin I triacetate (**12**),[12,13] 9-deacetyltaxinine (**13**),[14] taxinine B (**14**),[15] taxuspine F (**15**),[16] taxusin (**16**),[27,18] taxezopidine D (**17**),[19] triacetyl-5-decinnamoyltaxcine I (1-hydroxyltaxinine A) (**18**),[20] 10*β*-acetoxy-2α,9α-dihydroxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one (**19**),[21] 1-hydroxyltaxuspine C (**20**),[22,23] taxuspine C (**21**),[16] taxinin M (**22**),[24] 5-decinnamoyltaxagifine (**23**),[25] taxagifine (**24**),[26] taxacin (**25**),[27] 5-decinnamoyltaxuspine D (**26**),[27] taxinine 11,12-epoxide (**27**),[14,28] taxuspine V (**28**),[29,30] yunnanxane (**29**),[31] 10-deacetylbaccatin III (**30**),[32] baccatin IV (**31**),[33] cephalomannine (taxol B) (**32**),[34] taxol (**33**),[35] 10-deacetyltaxol (**34**),[36] taxuspine W (**35**),[30,37] 13-deacetyltaxuspine W (**36**),[38] taxuspine B (**37**),[39] 5-*epi*-canadensene (**38**),[40,41] taxachitriene A (**39**),[42] taxine B (**40**),[43] isotaxine B (**41**),[43] taxine II (**42**),[44,45] 2-deacetyltaxine B (**43**),[43] 2-deacetylisotaxine B (**44**),[43] and protonated taxine II (**45**).[44,45] The structures of compounds **6**−**45** are shown in the Supporting Information. Compounds **6**, **7**, **14**, **15**, **17**, **19**−**23**, **25**−**29**, **35**−**39**, and **45** have all been reported for the first time in *T. baccata*. The NMR data of compound **45**, a protonated taxine II, was different from that of taxine II. It should be noted that the two N−CH_3 groups were magnetically nonequivalent in **45**. These differences were caused by the protonated nitrogen forming a salt in **45**. Further support was given by a very deshielded broad signal at δ 12.65 (N−H^+) and downfield shifts of H-2′a, H-2′b, and H-3′ in the ^{1}H NMR spectrum. Compound **45** is the first example of a protonated nitrogen-containing taxane, and its NMR data are reported in the Supporting Information.

The isolation of the new natural products **1**−**5** augments the variety of taxol analogues. Presently more than 300 taxanes are known isolated from a variety of yews. Why are they produced by the *Taxus* species? Are they preventing the attacks of the yew by insects? Many hypotheses have been suggested, but we still do not really know.[46]

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Perkin-Elmer 241 polarmeter. Flash chromatography was performed on silica gel 60 (230−400 mesh EM Science). Thin-layer chromatography was conducted on

silica gel 60 F_{254} precoated TLC plates (0.25 mm or 0.5 mm, EM Science). The compounds were visualized on TLC plates with 10% sulfuric acid in EtOH and heating on a hot plate. Na_2SO_4 was the drying agent used in all workup procedures. 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, 210 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.

All the NMR data were obtained at room temperature on a Bruker Advance-500 spectrometer operating at 500.13 MHz for proton and at 125.77 MHz for carbon-13. The solvents were used as internal references (for $CDCl_3$: 7.25 ppm for proton and 77.0 ppm for carbon-13, and when we used CD_3COCD_3: 2.05 ppm for proton and 29.92 ppm for carbon-13). The various 2D spectra were acquired and processed using standard procedures. For phase-sensitive 2D experiments (NOESY, ROESY, and HSQC), the data were acquired using the TPPI phase mode. The NOESY experiment was obtained using a mixing time of 0.3 s and a relaxation delay of 1.5 s. The intensity of the cross-peaks in the NOESY experiment is designated as strong (s), medium (m), and weak (w). The ROESY (NOE in the rotating frame) experiment was used when NOESY proved to be unsuccessful or weak. Two mixing times were used in the ROESY: 0.3 and 0.5 s. Positive ion fast atom bombardment mass spectra (FABMS) were obtained with a Vacuum Generators ZAB-HS double-focusing instrument using a xenon beam having 8 kV energy at 1 mA equivalent neutral current. Low-resolution mass spectra were obtained in *m*-nitrobenzyl alcohol. FABHRMS was obtained in glycerol at a resolving power of 12 000 or with a Micromass MALDI Q-ToF in α-cyano-4-hydroxycinnamic acid matrix in W-mode with a resolving power of 15 000.

Plant Material. The needles of *T. baccata* (accession voucher number 931790) were obtained from the herbarium of Jerusalem Botanic Garden in Israel by Z.L.

Extraction and Isolation. Air-dried needles of *T. baccata* were ground (40 g) and extracted with 400 mL of MeOH for 1 day at room temperature. The ground plant material was filtered and extracted again with fresh solvent for another three times (each time with 300 mL of solvent) in 3 days. The combined organic extracts were evaporated under reduced pressure. Water (800 mL) was added and lipids were removed by stirring the mixture with hexane (3 × 300 mL). The hexane fraction was condensed into 300 mL and extracted with MeOH three times (each 300 mL). The MeOH extract, after being re-extracted with hexane one time (300 mL), was evaporated under reduced pressure, yielding a dark residue (2 g). The aqueous phase was then salted (NaCl) and extracted with CH_2Cl_2 (4 × 300 mL). The combined CH_2Cl_2 extracts were dried with anhydrous sodium sulfate, filtered, and evaporated, yielding a dark green extract (780 mg).

The hexane extract (2 g) was dissolved in 2 mL of acetone, absorbed onto 5 g of silica gel, and subjected to column chromatography (silica gel 230−400 mesh, 180 g, 33 × 4.2 cm) eluting with a mixture of hexane and acetone (3:2 to 2:3, total 2.5 L). Fifteen fractions were obtained: Fr_{H-1} to Fr_{H-15}). Fr_{H-11} and Fr_{H-12} combined (32 mg) was subjected to preparative HPLC, eluted with a linear gradient of acetonitrile in water from 25% to 100% in 50 min at a flow rate of 18 mL/min. The material eluting at t_R = 22.97 min was **22** (1.8 mg), t_R = 31.33 min was **32** (3.0 mg), and t_R = 32.42 min was **33** (3.0 mg). Fr_{H-9} and Fr_{H-10} combined (43 mg) was subjected to preparative HPLC to yield **5** (1.0 mg, t_R = 32.37 min), **13** (1.3 mg, t_R = 43.30 min), **14** (1.0 mg, t_R = 44.89 min), and **19** (2.0 mg, t_R = 41.64 min). Fr_{H-8} (37 mg) was applied to preparative HPLC to yield **11** (1.5 mg, t_R = 48.00 min) and **25** (2.0 mg, t_R = 41.51 min). Fr_{H-7} (50 mg) was subjected to preparative HPLC to give a mixture of **6** and **7** (1.6 mg, t_R = 37.80 min). Fr_{H-6} (40 mg) was subjected to preparative HPLC to yield **8** (4.0 mg, t_R = 36.29 min), **4** (2.0 mg, t_R = 36.29 min), and **12** (2.0 mg, t_R = 43.50 min). The material eluting at t_R = 56.38 min was further separated by preparative TLC, develped with hexane−EtOAc (35:80), affording **42** (1.0 mg, R_f = 0.20). Fr_{H-5} (47 mg) was subjected to preparative HPLC to give **21** (1.0 mg, t_R = 43.60 min), **27** (0.6 mg, t_R = 46.80min), **29** (0.8 mg, t_R = 40.89 min), and **37** (1.5 mg, t_R = 41.43 min). Fr_{H-3} (20 mg) was applied to preparative HPLC to give **16** (1.0 mg, t_R = 43.10 min). The CH_2Cl_2 fraction (780 mg) was subjected to preparative TLC (18 plates, 20 × 20 cm, 0.5 mm). After developing with hexane−acetone (3:2), they were cut into 12 bands (from top to bottom) under UV light. Band-11 (18 mg) was applied to HPLC to yield **1** (2.0 mg, t_R = 12.95 min). Band-10 (27 mg) was subjected to HPLC; the material eluted at t_R = 43 min was collected, dried, and applied to preparative TLC and developed with hexane−acetone (1:1), yielding **46** (1.0 mg, R_f = 0.5). Band-8 (36 mg) was applied to HPLC to yield **34** (0.0.75 mg, t_R = 22.92 min). Band-7 (38 mg) was applied to HPLC to yield **30** (1.5 mg, t_R = 17.85 min), **2** (2.0 mg, t_R = 29.44 min), and **3** (2.5 mg, t_R = 31.31 min). Band-6 (35 mg) was separated by HPLC, affording **8**, **9** (3.0 mg, t_R = 19.00 min), and **28** (1.5 mg, t_R = 22.49 min). Band-5 (55 mg) was applied to HPLC, affording **17** (2.0 mg, t_R = 13.44 min), **23** (2.0 mg, t_R = 19.30 min), **24** (3.0 mg, t_R = 28.03 min), and **38** (1.0 mg, t_R = 23.98 min). Band-4 (35 mg) was applied to HPLC to yield **26** (1.5 mg, t_R = 30.52 min) and **31** (1.0 mg, t_R = 31.11 min). Band-3 (59 mg) was subjected to HPLC, affording **18** (1.0 mg, t_R = 25.56 min), **15** (3.0 mg, t_R = 29.10 min), **36** (3.0 mg, t_R = 24.77 min), and **39** (1.0 mg, t_R = 30.70 min). The material eluting at t_R = 46 min was collected, dried, and applied to a preparative TLC, developed with hexane−EtOAc (3:8) and redeveloped with 10% EtOH in EtOAc, yielding **40** and **41** (1.5 mg, R_f = 0.5) as well as **44** and **45** (1.8 mg, R_f = 0.4). Band-2 (38 mg) was applied to HPLC to yield **20** (1.5 mg, t_R = 38.60 min).

5α,9α,10*β*,13α-Tetraacetoxy-14*β*-*O*-(*β*-D-glucopyranosyl)-taxa-4(20),11-diene (1): amorphous solid; $[\alpha]^{25}_D$ +7° (*c* 0.30, MeOH); ^{1}H and ^{13}C NMR spectral data, see Table 1; LR-FABMS *m/z* 705 ($M + K^+$); HRFABMS *m/z* 721.2836 $[M + K]^+$ (calcd for $C_{34}H_{50}O_{14}K$, 721.2838).

1*β*,2α,9α,10*β*-Tetrahydroxy-5α-cinnamoyloxytaxa-4(20),-11-dien-13-one (2): amorphous powder; $[\alpha]^{22}_D$ +227° (*c* 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (1H, d, J = 6.6 Hz, H-2), 3.36 (1H, d, J = 6.6 Hz, H-3), 5.31 (1H, br t, J = 2.5 Hz, H-5), 1.98 (1H, m, H-6a), 1.73 (1H, m, H-6b), 1.81 (1H, m, H-7a), 1.43 (1H, m, H-7b), 4.17 (1H, d, J = 9.6 Hz, H-9), 4.91 (1H, d, J = 9.6 Hz, H-10), 2.71 (1H, d, J = 19.2 Hz, H-14a), 2.64 (1H, d, J = 19.2 Hz, H-14b), 1.35 (3H, s, Me-16), 1.60 (3H, s, Me-17), 2.10 (3H, s, Me-18), 1.16 (3H, s, Me-19), 5.45 (1H, br s, H-20a), 5.37 (1H, br s, H-20b), 6.38 (1H, d, J = 15.7 Hz, H-2′), 7.63 (1H, d, J = 15.7 Hz, H-3′), 7.75 (2H, br d, J = 7.5 Hz, Ph-*o*), 7.44 (2H, m, Ph-*m*), 7.41 (1H, m, Ph-*p*); ^{13}C NMR data, see Table 2; HMBC correlations, H/C 2/1, 2/8, 3/1, 3/2, 9/7, 9/8, /9/10, 9/19, 10/9, 10/11, 10/12, 10/15, 14a/1, 14a/2, 14a/13, 16/1, 16/11, 16/15, 16/17, 17/1, 17/11, 17/15, 17/16, 18/11, 18/12, 18/13, 19/3, 19/7, 19/8, 19/9, 20a/3, 20a/4, 20a/5, 2′/1′, 3′/1′, 3′/2′, 3′/5′; NOESY, H/H 2/3, 2/9, 2/17, 2/19, 2/20a, 3/2, 3/7b, 3/14, 3/18, 5/6a, 5/6b, 5/20a, 7b/3, 7b/7a, 7b/10, 7b/18, 9/2, 9/17, 9/19, 10/7b, 10/18, 16/14, 16/17, 18/3, 18/10, 18/2′, 19/2, 19/6b, 19/7a, 19/9, 19/20b, 20a/5, 20a/20b, 20b/20a, 2′/18; HRFABMS *m/z* 535.2098 $[M + K]^+$ (calcd for $C_{29}H_{36}O_7K$, 535.2098).

2α,9α,10*β*-Trihydroxy-5α-cinnamoyloxytaxa-4(20),11-dien-13-one (3): amorphous solid; $[\alpha]^{22}_D$ +98° (*c* 0.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (1H, dd, J = 6.9, 2.1 Hz, H-1), 4.21 (1H, dd, J = 6.4, 2.1 Hz, H-2), 3.23 (1H, d, J = 6.4 Hz, H-3), 5.32 (1H, br s, H-5), 1.99 (1H, m, H-6a), 1.77 (1H,

m, H-6b), 1.78 (1H, m, H-7a), 1.47 (1H, m, H-7b), 4.09 (1H, d, $J = 9.2$ Hz, H-9), 4.87 (1H, d, $J = 9.2$ Hz, H-10), 2.84 (1H, dd, $J = 19.8$, 7.0 Hz, H-14a), 2.24 (1H, d, $J = 19.8$ Hz, H-14b), 1.25 (3H, s, Me-16), 1.64 (3H, s, Me-17), 2.11 (3H, s, Me-18), 1.14 (3H, s, Me-19), 5.42 (1H, br s, H-20a), 5.37 (1H, br s, H-20b), 6.40 (1H, d, $J = 16.0$ Hz, H-2′), 7.64 (1H, d, $J = 16.0$ Hz, H-3′), 7.75 (2H, br d, $J = 7.5$ Hz, Ph-*o*), 7.44 (2H, m, Ph-*m*), 7.39 (1H, m, Ph-*p*); ^{13}C NMR data, see Table 2; HMBC correlations, H/C 3/1, 3/2, 3/8, 3/1/9, 3/20, 9/7, 9/8, /9/10, 9/19, 10/9, 10/11, 10/12, 10/15, 14a/2, 14a/13, 14a/1, 14b/2, 14b/13, 14b/15, 16/1, 16/11, 16/15, 16/17, 17/1, 17/11, 17/15, 17/16, 18/11, 18/12, 18/13, 19/3, 19/7, 19/8, 19/9, 20a/3, 20a/4, 20a/5, 20b/3, 20b/5, 2′/1′, 3′/1′, 3′/2′, 3′/5′; NOESY: H/H 1/2, 1/14a, 1/16, 1/17, 2/1, 2/3, 2/9, 2/17, 2/19, 2/20a, 3/2, 3/5, 3/7b, 3/18, 5/6a, 5/6b, 6a/5, 6a/6b, 6a/7a, 6a/19, 6b/5, 6b/6a,7a/7b, 7a/19, 7b/3, 7b/7a, 7b/10, 7b/18, 9/2, 9/17, 9/19, 10/3, 10/7b, 10/18, 14a/1, 14a/14b, 14a/16, 14b/3, 14b/14a, 16/1,16/14a, 16/17, 17/1, 17/2, 17/9, 17/16, 18/3, 18/10, 18/2′, 19/2, 19/6a, 19/7a, 19/9, 19/20a; HRFABMS *m*/*z* 519.2149 $[M + K]^+$ (calcd for $C_{29}H_{36}O_6K$, 519.2149).

9α-Acetoxy-2α,10β-dihydroxy-5α-cinnamoyloxytaxa-4(20),11-dien-13-one (4): amorphous solid; $[\alpha]^{22}_D$ +113° (*c* 0.41, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (1H, dd, $J = 7.0$, 2.3 Hz, H-1), 4.29 (1H, dd, $J = 6.4$, 2.1 Hz, H-2), 3.25 (1H, d, $J = 6.6$ Hz, H-3), 5.32 (1H, br t, $J = 3.0$ Hz, H-5), 2.01 (1H, m, H-6a), 1.75 (1H, m, H-6b), 1.75 (1H, m, H-7a), 1.65 (1H, m, H-7b), 5.68 (1H, d, $J = 10.0$ Hz, H-9), 5.01 (1H, d, $J = 10.0$ Hz, H-10), 2.86 (1H, dd, $J = 19.8$, 7.0 Hz, H-14a), 2.26 (1H, d, $J = 19.8$ Hz, H-14b), 1.27 (3H, s, Me-16), 175 (3H, s, Me-17), 2.11 (3H, s, Me-18), 0.96 (3H, s, Me-19), 5.43 (1H, br s, H-20a), 5.42 (1H, br s, H-20b), 2.16 (3H, s, CH_3CO-), 6.41 (1H, d, $J = 15.9$ Hz, H-2′), 7.64 (1H, d, $J = 15.9$ Hz, H-3′), 7.75 (2H, br d, $J = 8.0$ Hz, Ph-*o*), 7.44 (2H, m, Ph-*m*), 7.39 (1H, m, Ph-*p*); ^{13}C NMR data, see Table 2; HMBC correlations, H/C 2/1, 2/3, 2/8, 3/1, 3/2, 3/19, 3/20, 9/3, 9/7, 9/8, 9/10, 9/19, 9/171.7, 10/9, 10/11, 10/12, 10/15, 14a/1, 14a/2, 14a/13, 14b/1, 14b/2, 14b/13, 14b/14, 16/1, 16/11, 16/15, 16/17, 17/1, 17/11, 17/15, 17/16, 18/11, 18/12, 18/13; NOESY, H/H 2/1, 2/3, 2/9, 2/17, 2/19 5/6a, 5/6b, 5/20a, 9/2, 9/17, 9/19, 10/7b, 10/18, 19/2, 19/6b, 19/7a, 19/9, 19/20b; HRFABMS *m*/*z* 561.2256 $[M + K]^+$ (calcd for $C_{31}H_{38}O_7K$, 561.2255).

2α,10β-Diacetoxy-1β,9α-dihydroxy-5α-cinnamoyloxy-3,11-cyclotaxa-4(20)-en-13-one (5): gum; $[\alpha]^{22}_D$ +30° (*c* 0.06, $CHCl_3$); ^{1}H and ^{13}C NMR, see Table 3; HRFABMS *m*/*z* 619.2309 $[M + K]^+$ (calcd for $C_{33}H_{40}O_9K$, 619.2309).

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Supporting Information Available: Structures for compounds **6**−**45**; ^{1}H and ^{13}C NMR data for compounds **6**, **7**, **20**, **40**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Hook, I.; Poupat, C.; Ahond, A.; Guénard, D.; Guéritte, F.; Adeline, M.-T.; Wang, X.-P.; Dempsey, D.; Breuillet, S.; Potier, P. *Phytochemistry* **1999**, *52*, 1041−1045.
(2) Hartzell, H., Jr. *The Yew Tree: A Thousand Whispers: Biography of a Species*; Hulogosi: Eugene, OR, 1991; pp 1−319.
(3) Denis, J. N.; Green, A. E.; Guénard, D.; Guéritte-Voegelin, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917−5919.
(4) Senilh, V.; Blechert, S.; Colin, M.; Guénard, D.; Picot, F.; Varenne, P. *J. Nat. Prod.* **1984**, *47*, 131−137.
(5) Gabetta, B.; Orsini, P.; Peterlongo, F.; Appendino, G. *Phytochemistry* **1998**, *47*, 1325−1329.
(6) Gabetta, B.; Bellis, P.; Pace, R.; Appendino, G.; Barboni, L.; Torregiani, E.; Gariboldi, P.; Viterbo, D. *J. Nat. Prod.* **1995**, *58*, 1508−1514.
(7) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, G. M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Moore, R. E., Kirby, G. W., Steglich, W., Tamm, C., Eds.; Springer: Wien, 1993; Vol. 61, pp 1−206.
(8) Appendino, G. In *The Chemistry and Pharmacology of Taxol and Its Derivatives*; Farina, V., Ed.; Amsterdam, 1995; Vol. 22, pp 1−53 and pp 55−101.
(9) Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1448−1472.
(10) Chmurny, G. N.; Paukstelis, J. V.; Alvarado, A. B.; McGuire, M. T.; Snader, K. M.; Muschik, G. M.; Hilton, B. D. *Phytochemistry* **1994**, *34*, 477−483.
(11) Appendino, G.; Gariboldi, P.; Pisetta, A.; Bombardelli, E.; Gabetta, B. *Phytochemistry* **1992**, *31*, 4253−4257.
(12) Baxter, J. N.; Lythgoe, B.; Scrowston, R. M.; Trippett, S. *J. Chem. Soc.* **1962**, 2964−2971.
(13) Chiang, H. C.; Woods, M. C.; Nakadaira, K.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1967**, 1201−1202.
(14) Sakai, J.; Sasaki, H.; Kosugi, K.; Zhang, S.; Hirata, N.; Hirose, K.; Tomida, A.; Tsuruo, T.; Ando, M. *Heterocycles* **2001**, *54*, 999−1009.
(15) Woods, M. C.; Chiang, H. C.; Nakadaira, K.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 522−523.
(16) Kobayashi, J.; Inubushi, A.; Hosoyama, H.; Yoshida, N.; Sasaki, T.; Shigemori, H. *Tetrahedron* **1995**, *51*, 5971−5978.
(17) Della Casa de Marcano, D. P.; Halsall, T. G. *J. Chem. Soc., Chem. Commun.* **1969**, 1282−1283.
(18) Erdtman, H.; Tsuno, K. *Phytochemistry* **1969**, *8*, 931−932.
(19) Wang, X.; Shigemori, H.; Kobayashi, J. *J. Nat. Prod.* **1998**, *61*, 474−479.
(20) Barboni, L.; Gariboldi, P.; Appendino, G.; Enriu, R.; Gabetta, B.; Bombardelli, E. *Liebigs Ann.* **1995**, 345−349.
(21) Shi, Q. W.; Dauriol, F.; Mamer, O.; Zamir, L. *Bioorg. Med. Chem.* **2003**, *11*, 293−303.
(22) Shi, Q. W.; Oritani, T.; Horigucg, T.; Sugiyama, T.; Murakami; Yamada, T. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 924−929.
(23) Kosugi, K.; Sasaki, J.; Zhang, S.; Watanabe, Y.; Sasaki, H.; Suzuki, T.; Hagiwara, H.; Hirata, N.; Hirose, K.; Ando, M.; Tomida, A.; Tsuruo, T. *Phytochemistry* **2000**, *54*, 839−845.
(24) Beutler, J. A.; Chmurny, G. M.; Look, S. A.; Witherup, K. M. *J. Nat. Prod.* **1991**, *54*, 893−897.
(25) Zhang, Z.; Jia, Z.; Zhu, Z.; Cui, Y.; Wang. Q. *Planta Med.* **1990**, *56*, 293−294.
(26) Yoshizaki, F.; Fuduka, M.; Hisamichi, S.; Ishida, T.; In, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2098−2112.
(27) Zamir, L.; Zhang, J.; Wu, J.; Sauriol, F.; Mamer, O. *J. Nat. Prod.* **1999**, *62*, 1268−1273.
(28) Zamir, L.; Zhang, J.; Wu, J.; Sauriol, F.; Mamer, O. *Tetrahedron* **1999**, *55*, 14323−14340.
(29) Zhang, Z.; Jia, Z. *Phytochemistry* **1990**, *29*, 3673−3675.
(30) Hosoyama, H.; Inubushi, A.; Katasui, T.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 13145−13150.
(31) Ma, W.; Stahlhut, R. W.; Adams, T. L.; Park, G. L.; Evans, W. A.; Blumenthal, S. G.; Gomez, G. A.; Nieder, M. H.è Hylands, P. J. *J. Nat. Prod.* **1994**, *57*, 1320−1325.
(32) Chauviere, G.; Guenard, D.; Picot, F.; Senilh, V.; Potier, P. *Acad. Sci. Paris, Ser. II* **1981**, *293*, 501−503.
(33) Della Casa de Marcano, D. P.; Halsall, T. G. *J. Chem. Soc., Chem. Commun.* **1975**, 365−366.
(34) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469−1474.
(35) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.
(36) McLaughlin, J. L.; Miller, R. W.; Powell, R. G., Jr.; Smith, C. R. *J. Nat. Prod.* **1981**, *44*, 312−319.
(37) Rao, K. V.; Reddy, G. C.; Juchum, J. *Phytochemistry* **1996**, *43*, 439−442.
(38) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Phytochemistry* **1999**, *52*, 1559−1563.
(39) Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401−7416.
(40) Zamir, L. O.; Zhou, Z. H.; Caron, G.; Nedea, M. E.; Sauriol, F.; Mamer, O. *J. Chem. Soc., Chem. Commun.* **1995**, 529−530.
(41) Boulanger, Y.; Khiat, A.; Zhou, Z. H.; Caron, G.; Zamir, L. O. *Tetrahedron* **1996**, *52*, 8957−8968.
(42) Fang, W. Fang, Q.; Liang, X.; Lu, Y.; Zheng, Q. *Tetrahedron* **1995**, *51*, 8483−8490.
(43) Louis, H. D. J.; Erik, L. M.; van Rozendaal; Teris, A.; van Beek. *J. Nat Prod.* **1996**, *59*, 117−123.
(44) Yoshizaki, F.; Madarame, M.; Takahashi, C.; Hisamichi, S. *Shoyakugaku Zasshi* **1986**, *40*, 429−432.
(45) Appendino, G.; Tagliapietra, S.; Ozen, H. C.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *J. Nat. Prod.* **1993**, *56*, 514−520.
(46) Horiguchi, T.; Rithner, C. D.; Croteau, R.; Williams, R. M. *Tetrahedron* **2003**, *59*, 267−273.

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