New Bicyclic Taxane Diterpenoids from *Taxus sumatrana*

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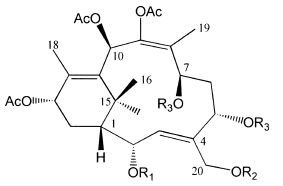
Investigation of an acetone extract of the leaves and twigs of *Taxus sumatrana* has resulted in the isolation of two new bicyclic taxoids, tasumatrols M (1), and N (2) and a new baccatin III derivative, tasumatrol O (3) together with the previous known 7-deacetylcanadensene (4) and 2α,7β,13α-triacetoxy-5α,9α-dihydroxy-2(3→20) abeotaxa-4(20),11-dien-10-one. The structures of these taxanes were established on the basis of spectroscopic analyses, especially 1- and 2D NMR, and chemical derivatization.

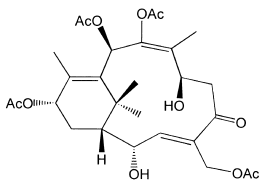
Key words Taxaceae; *Taxus sumatrana*; taxane diterpene

The chemical constituents of *Taxus* have been extensively investigated worldwide as a result of the discovery of paclitaxel with its remarkable anti-cancer activity.[1,2] Although more than 450 taxane diterpenes have been discovered to date, the biogenesis of paclitaxel and taxoids is still unclear. Verticillene is considered to be the most likely intermediate between geranylgeranyl pyrophosphate and the taxane diterpenes.[3—5] In continuation of our research on the taxane diterpenoids of endemic *Taxus* species,[6—14] a phytochemical study of *T. sumatrana* was carried out. A chromatographic fractionation of an acetone extract of the leaves and twigs of the plant has resulted in the isolation of three new taxane diterpenes, named tasumatrols M (**1**), N (**2**) and O (**3**). In addition, two known taxane, 7-deacetylcanadensene (**4**) and 2α,7β,13α-triacetoxy-5α,9α-dihydroxy-2(3→20) abeotaxa-4(20),11-dien-10-one were also isolated. The structures of **1**—**3** were established on the basis of spectroscopic analyses, especially 1- and 2D NMR.

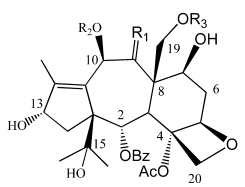
The HR-ESI-MS of **1** revealed a quasi-molecular ion peak at *m/z* 575.2466 $[M+Na]^+$ consistent with the molecular formula $C_{28}H_{40}O_{11}$ and nine degrees of unsaturation. The IR spectrum displayed absorption bands diagnostic of hydroxyl, double bonds and ester groups. Both ^{1}H- and ^{13}C-NMR spectrocopic data (Tables 1, 2) indicated the presence of four *O*-acetyl units at δ_H 2.11, 2.03, 2.16 and 2.20 (each 3H, s) and δ_C 20.3, 20.8, 20.9, 21.2 and δ_C 168.7, 169.7, 170.6, 171.2. The NMR data indicated the existence of a diterpene with two rings and three double bond as verified by six olefinic carbons at δ_C 129.7 (C-3), 134.2 (C-4), 128.2 (C-8), 141.1 (C-9), 136.4 (C-11) and 135.1 (C-12). The four methyl singlets at δ_H 1.18, 1.10, 1.96 and 1.57 (each 3H) and their corresponding carbon signals at δ_C 24.6, 33.9, 16.5 and 11.5 together with six olefinic carbons are characteristic of bicyclic canadensene skeleton.[15,16] The ^{1}H-NMR spectrum revealed one olefinic proton at δ_H 6.17 (H-3) and five oxygenated methines at δ 4.70 (dd, J=10.6, 3.9 Hz, H-2), 4.43 (br s, H-5), 4.33 (d, J=7.8 Hz, H-7), 6.97 (s, H-10), and 5.33 (d, J=9.6 Hz, H-13). The COSY experiment displayed connectivities between H-2/H-3, H-5/H-6/H-7, and H-13/H-14. The relative low field chemical shift of the H-10 indicated its acylation in a bicyclic system that was supported by the HMBC correlations with C-15, C-12, and a carbonyl of *O*-acetyl moiety at C-10. The oxygenated methylene protons at δ 4.90 and 4.04 (each 1H, d, J=12 Hz) were correlated to C-3, C-4 and another carbonyl of *O*-acetyl moiety at C-20. The methyl protons (δ 1.57) at C-19 showed HMBC correlation with C-7, C-8 and C-9 at δ_C 62.6, 128.2 and 141.1. The relative configuration of **1** was determined through comparing ^{1}H-NMR data and the coupling constants with those of 7-deacetylcanadensene (**4**)[17] and from its NOESY spectrum that showed correlations between H-10/H-7; H-1/Me-16; Me-17/H-2 and H-13/Me-16 (Fig. 1). Finally, acetylation of **1** provided compound **5** identical with a product derived from acetylation of **4**. Hence, the structure of **1** was established and named tasumatrol M.



1 R_1 = H, R_2 = Ac, R_3 = H
4 R_1 = Ac, R_2 = R_3 = H
5 R_1 = R_2 = R_3 = Ac



2



3 R_1 = O, R_2 = Ac, R_3 = H
6 R_1 = αOH, βH, R_2 = H, R_3 = Ac

The HR-ESI-MS of **2** revealed the molecular formula $C_{28}H_{38}O_{11}$ (two protons less than **1**), as derived from a quasi-molecular ion at *m/z* 573.2310 ($[M+Na]^+$). The ^{13}C-NMR of **2** (Table 2) displayed four methyls (δ_C 23.4, 34.8, 18.0, 10.6), two quaternary olefinic carbons at δ_C 135.4 (C-11) and 134.8 (C-12), a quaternary carbon at δ_C 36.1 (C-15), oxygenated CH_2 at δ_C 57.8 (C-20) in addition to signals for four acetates and a conjugated ketone (δ_C 199.7). Four oxygenated methines were observed at δ_C 63.6, 67.7, 68.3, and 69.8 and their corresponding protons at δ_H 4.81, 4.91, 7.02 and 5.26 assignable to positions 2, 7, 10 and 13 were indica-

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Table 1. ^{1}H-NMR Data ($CDCl_3$, 300 MHz) of Compounds **1**—**3**[a,b]

Position	**1**	**2**[c]	**3**
1	1.79 m	2.00 m	—
2	4.70 dd (10.6, 3.9)	4.81 d (overlap)	5.91 d (8.1)
3	6.17 d (10.6)	6.81 d (8.4)	3.76 d (8.1)
5	4.43 br s	—	5.07 d (9.0)
		3.15 dd (6.3, 13.2)	2.83 m
6	2.46 m	2.86 dd (6.9, 13.2)	
7	4.33 d (7.8)	4.91 (overlap)	4.50 m
10	6.97 s	7.02 s	6.45 s
13	5.33 d (9.6)	5.26 d (6.9)	4.65 t (2.7)
14	2.46 (overlap)	2.19 m	2.30 m
	—	2.03 m	2.15 m
CH_3-16	1.18 s	1.24 s	1.02 s
CH_3-17	1.10 s	1.15 s	1.09 s
CH_3-18	1.96 s	2.00 s	1.88 s
CH_3-19	1.57 s	1.47 s	4.96 AB q (12)
20	4.90 d (12.6)	5.02 d (10.8)	4.26 d (8.4)
	4.04 d (12.6)	4.95 d (10.8)	4.18 d (8.4)
OAc	2.03 s	2.02 s	2.22 s
OAc	2.11 s	2.07 s	2.25 s
OAc	2.16 s	2.15 s	—
OAc	2.20 s	2.19 s	—
COC_6H_5			
o-	—	—	8.00 d (7.5)
m-	—	—	7.47 t (7.5)
p-	—	—	7.61 t (7.5)

a) Chemical shifts in ppm, *J* values in Hz are in parentheses. *b*) Assignments were made using HMQC and HMBC techniques. *c*) Measured in 500 MHz.

Table 2. ^{13}C-NMR Data ($CDCl_3$, 75 MHz) of Compounds **1**—**4**[a]

Carbon	**1**	**2**[b]	**3**	**4**
1	47.9 d	47.5 d	68.5 s	46.8 d
2	65.9 d	63.6 d	69.0 d	70.8 d
3	129.7 d	146.0 d	44.9 d	121.3 d
4	134.2 s	135.4 s	79.0 d	142.8 s
5	67.7 d	199.7 s	85.2 d	68.0 d
6	38.7 t	46.6 t	38.8 t	39.2 t
7	62.2 d	67.7 d	74.2 d	62.6 d
8	128.2 s	127.0 s	58.1 s	128.4 s
9	141.1 s	139.5 s	205.6 s	141.1 s
10	68.6 d	68.3 d	71.9 d	68.6 d
11	136.4 s	135.4 s	129.6 s	136.6 s
12	135.1 s	134.8 s	151.4 s	135.0 s
13	69.2 d	69.8 d	76.4 d	69.1 d
14	24.3 t	23.1 t	38.9 t	25.6 t
15	35.8 s	36.1 s	75.1 t	36.0 s
CH_3-16	24.6 q	23.4 q	25.0 q	24.5 q
CH_3-17	33.9 q	34.8 q	27.1 q	33.9 q
CH_3-18	16.5 q	18.0 q	11.4 q	16.9 q
CH_3-19	11.5 q	10.6 q	61.7 t	11.6 q
20	59.8 t	57.8 t	74.9 t	57.7 t
OAc	169.7 s	168.5 s	168.7 s	168.8 s
	20.8 q	20.8 q	20.4 q	20.4 q
OAc	168.7 s	170.2 s	170.6 s	169.5 s
	20.3 q	21.0 q	22.0 q	20.9 q
OAc	170.6 s	171.7 s	—	170.7 s
	20.9 q	21.4 q		21.3 q
OAc	171.2 s	170.0 s	—	171.7 s
	21.2 q	20.2 q		21.8 q
COC_6H_5	—	—	165.8 s	—
i-	—	—	133.7 s	—
o-	—	—	129.7 d	—
m-	—	—	128.6 d	—
p-	—	—	133.0 d	—

a) Assignments were made using HMQC and HMBC techniques. *b*) Measured in 125 MHz.

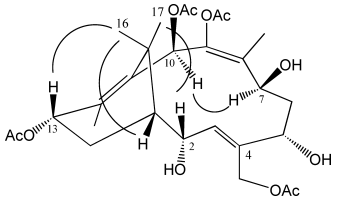

Fig. 1. Key NOESY Correlations of **1**

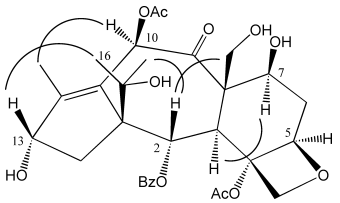

Fig. 2. Key NOESY Correlations of **3**

tive of a 6/12 ring system.[15] Detailed inspection of the ^{1}H- and ^{13}C-NMR spectrocopic data of **1** and **2** (Tables 1, 2) indicated that they are quite similar except for the remarkable downfield shift of a methine signal assigned to H-3 (δ_H 6.81) together with a less profound low field shift of C-3 (δ_C 146.0 instead of δ_C 129.7 in **1**). This was accompanied by missing of H-5 in **2**. The proton at δ_H 4.81 (H-2) exhibited COSY correlations with H-1 and H-3 in addition to correlation of H-6/H-7 and H-13/H-14, together with HMBC correlations of H-3 and H-20 to C-5. On the other hand, the NOESY spectrum of **2** showed cross peaks between H-2/Me-17, Me-16/H-1 and Me-16/H-13 as observed in **1**. The spectroscopic data of **2** indicated the presence of an α,β-unsaturated ketone rather than a hydroxyl group at C-5 in **1**. On the basis of these findings, the structure of **2** was elucidated and named tasumatrol N.

The molecular formula of **3** was determined by HR-ESI-MS at *m*/*z* 625.2260 ($[M+Na]^+$) as $C_{33}H_{42}O_{12}$. The NMR data of **3** (Tables 1, 2) were similar to those of taxumairol Z (**6**) indicating an 11(15→1)-*abeo*-taxane skeleton with two acetates and one benzoyl ester.[11] The presence of a benzoyl ester was evident from signals resonating at δ_C 165.8, 133.7, 129.7, 128.6, and 133.0; and δ_H 8.00 (d, J=7.5 Hz), 7.47 (t, J=7.5 Hz), and 7.61 (t, J=7.5 Hz). This moiety was attached to the position 2 as verified by HMBC correlation between the CH signals at δ_H 5.91 with its benzoyl carbonyl at δ_C 165.8. The two oxygenated geminal protons resonating at δ_H 4.26 and 4.18 (each 1H, d, J=8.4 Hz) attached to the methylene carbon at δ_C 74.9 were assigned to the position 20. This finding together with signal of H-5 at δ_H 5.07 (d, J=9.0 Hz) indicated that **3** contains an oxirane ring.[18,19] The COSY spectrum of **3** revealed the H-3 at rather low field (δ 3.76). In the HMBC spectrum of **3**, cross peaks were observed between H-19 and both C-9 and C-7 suggesting the presence of an hydroxymethylene at C-8. The HMBC of **3** also showed correlations of H-10/C-15 and H-2/C-8, C-3, C-15, C-14. The result of NOESY experiment (Fig. 2), which showed correlations of H-2/Me-16, Me-19 and H-2 agreed with β-orientation of H-2, H-13, Me-16, Me-17, and Me-19, and α-configurations for H-3, H-7, and H-10, respectively. Based on this data, the structure of tasumatrol O was determined as **3**.

Compounds **1** and **2** belong to new taxoids of the 6/12 ring

system, which may be biogenetically derived from verticillene of the C-4(20) double bond.[5,20] Compound **2** is probablly generated by the oxidation of **1** at C-5. Compound **3** represents a new baccatin III derivative, which belongs to 11(15→1)-*abeo*taxane type with a hydroxy at C-19.

Experimental

General Experimental Procedures Optical rotations were recorded on a JASCO DIP-1000 polarimeter. IR spectra were measured on Hitachi T-2001 spectrophotometer. Low-resolution EI-MS and FAB-MS spectra were recorded on a VG Quattro 5022 mass spectrometer. High-resolution ESI-MS spectra were measured on a JEOL HX 110 mass spectrometer. The ^{1}H-, ^{13}C-NMR, COSY, HMQC, HMBC, and NOESY spectra were recorded on a Bruker FT-300 spectrometer or on a Varian Unity INOVA 500 FT-NMR at 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively, using TMS as internal standard. The chemical shifts are given in δ (ppm) and coupling constants in Hz. Silica gel 60, LiChroprep RP-18 (Merck) and Sephadex LH-20 (Amersham Pharmacia Biotech AB, Sweden) were used for column chromatography.

Plant Material The leaves and twigs of seven year old trees of *Taxus sumatrana* (MIQ.) de LAUB. were collected from Kaohsiung county, Taiwan at an altitude of 1000 m in March 2002. This plant was identified by one of the authors (C.-T. Chien). A voucher specimen (TPG 8-7) was kept in the Institute of Marine Resources, National Sun Yat-sen University, Kaohsiung, Taiwan.

Extraction and Isolation Dried leaves and twigs (15.5 kg) were ground and extracted thrice with acetone at room temperature. The combined extracts were filtered and concentrated under vacuum to obtain a crude residue (3.05 kg). The residue was stirred with H_2O and the resulting emulsion was partitioned between EtOAc/H_2O (1 : 1) to produce an EtOAc extract (173 g) and an aqueous layer that was further extracted with *n*-BuOH to furnish the *n*-BuOH extract (142 g). The EtOAc extract was fractionated on Sephadex LH-20 using MeOH into fractions A (60 g) and B (86 g). Fraction A was chromatographed on a NP-silica gel column using *n*-hexane/CH_2Cl_2/MeOH (100 : 100 : 1 to 1 : 1 : 1) to yield 10 fractions A-1 to A-10. Fraction A-6 (1.71 g) was chromatographed on a RP_{18}-silica gel column using a gradient of H_2O/MeOH/CH_3CN (70 : 25 : 5, 60 : 35 : 5, 50 : 45 : 5, 40 : 55 : 5, 30 : 65 : 5, 20 : 75 : 5, each 300 ml) to give 10 fractions. Fraction A-6-4f (252 mg) was chromatographed on a silica gel column using gradient of *n*-hexane/EtOAc to give 6 fractions. Fraction 2 (20 mg) was subjected to a NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (10 : 10 : 1) to afford tasumatrol N (**2**, 2 mg). Separation of fraction 3 (62 mg) by RP-HPLC using H_2O/MeOH/CH_3CN (35 : 65 : 10) yielded tasumatrol O (**3**, 10 mg). Fraction 6 (50 mg) was subjected to NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (10 : 10 : 1) to give tasumatrol M (**1**, 40 mg). Fraction A-6-6f (120 mg) was fractionated by NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (15 : 10 : 1) afforded 7-deacetylcanadensene (**4**, 30 mg)[17] and 2α,7β,13α-triacetoxy-5α,9α-dihydroxy-2(3→20) abeotaxa-4(20),11-dien-10-one (15 mg).[21]

Tasumatrol M (**1**): Colorless powder; $[\alpha]_D^{25}$ +43° (c=0.2, MeOH); IR (CH_2Cl_2) ν_{max} 3416 (O–H st), 2929 (C–H st), 1730 (br s, C=O st of esters), 1435, 1371, 1236 (C–O st of acetate), 1021 (C–O st), 736 (C=C–H) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$) spectral data, see Tables 1 and 2; EI-MS *m*/*z* 372, 312, 215, 199, 187, 173, 145, 135, 133, 121, 105; FAB-MS *m*/*z* 575 $[M+Na]^+$; HR-ESI-MS *m*/*z* 575.2466 $[M+Na]^+$ (Calcd for $C_{28}H_{40}O_{11}Na$, 575.2468).

Acetylation of Compound 1 Compound **1** (10 mg) was acetylated using Ac_2O/py (1 : 1) at room temperature for 16 h. After the usual work up of the reaction product gave **5** (5 mg). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.75 (overlap, H-2), 5.95 (d, J=12.5 Hz, H-3), 5.51 (br s, H-5), 2.59 (m, H-6), 5.79 (d, J=4.5 Hz, H-7), 7.08 (s, H-10), 5.31 (t, J=9.3 Hz, H-13), 2.42 (m, H-14), 1.63, 1.29, 1.25, 1.09 (s, Me-16, -17, -18, -19), 4.94 (d, J=12.9 Hz, H-20), 4.31 (d, J=12.9 Hz, H-20), 1.90, 2.02, 2.05, 2.10, 2.15, 2.21, 2.28 (each $COCH_3$, s); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 46.4 (d, C-1), 68.9 (d, C-2), 125.3 (d, C-3), 132.4 (s, C-4), 70.0 (d, C-5), 34.4 (t, C-6), 66.8 (d, C-7), 124.5 (s, C-8), 143.6 (s, C-9), 68.3 (d, C-10), 136.2 (s, C-11), 135.8 (s, C-12), 69.5 (d, C-13), 26.0 (t, C-14), 36.2 (s, C-15), 25.3 (q, C-16), 34.4 (q, C-17), 16.6 (q, C-18), 12.4 (q, C-19), 59.5 (t, C-20), 168.0, 169.9, 170.5, 170.7, (s, O<u>C</u>OCH$_3$), 20.5, 21.2, 21.4, 21.6 (q, OCOCH$_3$).

Tasumatrol N (**2**): Colorless powder; $[\alpha]_D^{25}$ +14° (c=0.2, MeOH); IR (CH_2Cl_2) ν_{max} 3441 (O–H st), 2926 (C–H st), 1737 (br s, C=O st of esters), 1668 (conjugated C=O st), 1372, 1234 (C–O st of acetate), 1026 (C–O st), 736 (C=C–H) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$) spectral data, see Tables 1 and 2; EI-MS *m*/*z* 550 $[M]^+$, 491, 490 $[M-H_2O]^+$, 431, 371, 311, 259, 217, 187, 173, 149, 121, 105; FAB-MS *m*/*z* 573 $[M+Na]^+$; HR-ESI-MS *m*/*z* 573.2310 $[M+Na]^+$ (Calcd for $C_{28}H_{38}O_{11}Na$, 573.2312).

Tasumatrol O (**3**): Colorless powder; $[\alpha]_D^{25}$ −40° (c=0.2, MeOH); IR (CH_2Cl_2) ν_{max} 3441 (O–H st), 2978 (C–H st), 1724 (C=O st of esters), 1714 (C=O st), 1602 (C=C st of aromatic), 1451, 1372, 1242 (C–O st of acetate), 1026 (C–O st), 736, 715 (C=C–H) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$) spectral data, see Tables 1 and 2; EI-MS *m*/*z* 601, 582, 541, 512, 464, 422, 404, 362, 360, 105, 77; FAB-MS *m*/*z* 625 $[M+Na]^+$; HR-ESI-MS *m*/*z* 625.2260 $[M+Na]^+$ (Calcd for $C_{31}H_{38}O_{12}Na$, 625.2261).

Acetylation of Compound 4 Compound **4** (15 mg) was acetylated using Ac_2O/py (1 : 1) at room temperature for 16 h. After the usual work up of the reaction product gave a compound (10 mg) identical with **5**.

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