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Tetrahedron
Tetrahedron 63 (2007) 115–119

Novel alkaloids, paxdaphnines A and B with unprecedented skeletons from the seeds of *Daphniphyllum paxianum*

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Received 22 August 2006; revised 16 October 2006; accepted 18 October 2006
Available online 2 November 2006

Abstract—Two novel *Daphniphyllum* alkaloids with unprecedented skeletons, namely paxdaphnines A (**1**) and B (**2**), have been isolated from the seeds of *Daphniphyllum paxianum*. Paxdaphnine A (**1**) is a 19-nor-*Daphniphyllum* alkaloid with highly caged skeleton, and paxdaphnine B (**2**) is the first 1,19-bisnor-*Daphniphyllum* alkaloid. The relative structures of **1** and **2** were elucidated by spectral methods, and their unique biosynthetic pathway postulated. The absolute structure of **1** was determined by X-ray diffraction of the iodide derivative (**1a**) of **1**, and the absolute stereochemistry of **2** was proposed by correlation with the biosynthetic pathway for **1**.

1. Introduction

Structurally diversified *Daphniphyllum* alkaloids[1] with unique biosynthetic pathways[2] are still attracting research programs of natural products[3] and synthetic chemistry.[4] Recently, the chemical investigation on *Daphniphyllum* alkaloids conducted in this group has led to the isolation of a number of novel structures with highly complex polycyclic skeletons.[5] *Daphniphyllum paxianum* Rosenth. (Daphniphyllaceae), an evergreen shrub, is native to southern China, and its seeds have been applied traditionally in China for anti-inflammation purposes.[6] Previous studies on its leaves and stems collected from Guangdong and Hainan Provinces of China have resulted in the isolation of several novel structures.[5b,c] In the current research, paxdaphnines A (**1**) and B (**2**) were isolated from the seeds of *D. paxianum* collected from Hainan Island. Paxdaphnine A (**1**) is a 19-nor-*Daphniphyllum* alkaloid with an unprecedented cage-like skeleton, and paxdaphnine B (**2**) is the first 1,19-bisnor-*Daphniphyllum* alkaloid. The absolute structure of **1** was determined by spectroscopic method and X-ray diffraction of the iodide derivative (**1a**, with one H_2O in the crystal) of **1**, and the absolute stereochemistry of **2** was proposed by correlation with the biosynthetic pathway for **1**. Herein, we present the isolation, structural characterization and the plausible biogenetic origin of paxdaphnines A (**1**) and B (**2**).

Keywords: Paxdaphnines A and B; *Daphniphyllum* alkaloids; Absolute stereochemistry; X-ray diffraction; Biosynthetic pathway.
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doi:10.1016/j.tet.2006.10.042

2. Results and discussion

Paxdaphnine A (**1**), a colorless gum with optical rotation of $[\alpha]_D^{20}$ −71, had a molecular formula $C_{22}H_{31}NO_3$ as determined by HR-EIMS at *m/z* 357.2299 $[M]^+$ (calcd 357.2304), further supported by a positive mode of ESI MS at *m/z* 358 $[M+H]^+$. The IR absorption at 1736 cm^{-1} showed the presence of an ester group. The ^1H and ^{13}C NMR spectra revealed the existence of one methyl, eleven methylenes, three methines, six quaternary carbons (including one carbonyl at δ 176.1), and one methoxyl. Except for the ester carbonyl, a heptacyclic ring system was required for the remaining seven degrees of unsaturation.

Two isolated methylenes (CH_2-1 and CH_2-21) were first identified in the ^1H NMR spectrum. Four spin coupling systems **a** (C-18 and C-20), **b** (C-13 to C-17), **c** (C-7, C-6, C-12, and C-11), and **d** (C-3 and C-4) as drawn with bold bonds (Fig. 1) were then revealed by ^1H–^1H COSY. The connectivities of four fragments **a**–**d**, quaternary carbons, heteroatoms, and other functionalities were made by HMBC spectrum (J_{CH}=7.5 Hz). In the HMBC (Fig. 1) spectrum, the linkage of three quaternary carbons C-8, C-9, C-10 was fixed on the basis of the ^2J correlations of H_2-13/C-8, H-15/C-9, H-17β/C-10, and H-11β/C-10 and ^3J correlations of H-16α/C-9, H-16α/C-10, H-17β/C-9, H-11β/C-9, and H-12α/C-10, and these also allowed the linkage of fragments **b** and **c** via C-10. The ^2J correlations of H_2-18/C-2 and H-3a/C-2, and the ^3J correlations of H_3-20/C-2 and H-3b/C-18 enabled us to connect the fragments **a** and **d** to C-2. The ^3J correlation between H-7α and C-2 fixed the C-7 and C-2 to the N-atom, and supported by chemical shifts of C-2

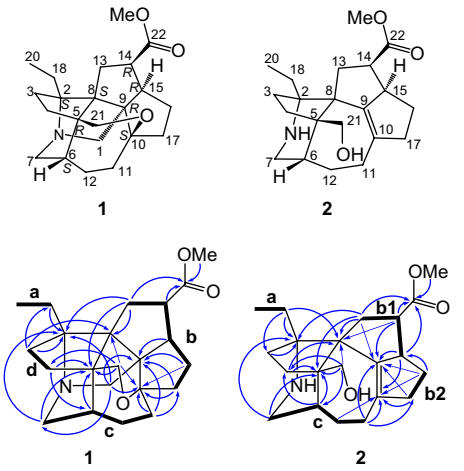


Figure 1. ^{1}H–^{1}H COSY (▬) and key HMBC correlations of **1** and **2**.

and C-7. The ^{2}J correlations of H_2-21/C-5, H_2-4/C-5, and H-6/C-5 attached C-21, C-4, and C-6 to C-5, and supported by the ^{3}J correlations of H-21a/C-4, H_2-4/C-6, and H-7α/C-5. The C-2 and C-5 were attached to the C-8 based on the ground of ^{3}J correlations of H_2-3/C-8, H_2-21/C-8, H_2-13/C-2, and H_2-13/C-5. The ^{2}J correlation between H_2-1 and C-9 implied a connectivity of C-9 and C-1, the latter (C-1) also linked to the nitrogen atom as judged by its chemical shift, and supported by the ^{3}J correlations of H_2-1/C-7 and H-1b/C-2. The ether bond between C-10 and C-21 was established by the strong ^{3}J correlation between H-21a and C-10, and supported by their chemical shifts. The planar structure of **1** was thus constructed.

The relative configuration of **1** was assigned by NOESY spectrum as depicted on a 3D structure (Fig. 2, modeled by CS Chem 3D Pro version 9.0 using MM2 force field calculation for energy minimization). The H-14 showed interactions with H-18a, H-15, and H-13α, indicating that they were co-facial, and was randomly assigned as an α-orientation. In consequence, the CH_2-1 was assigned as an α-orientation by the correlation of H-15/H-1a. The CH_2-21 was thereafter fixed in β-orientation by the correlation of H-21a/H-13β. The H-6 interacting with H-21b was then fixed as β-orientation.

To confirm the relative structure and determine its absolute configuration, **1** was methylated with CH_3I in mild conditions to produce an iodide derivative **1a** (Fig. 3), which gave a qualified crystal (with one H_2O inside) for X-ray study. With the presence of an I-atom in **1a**, the X-ray

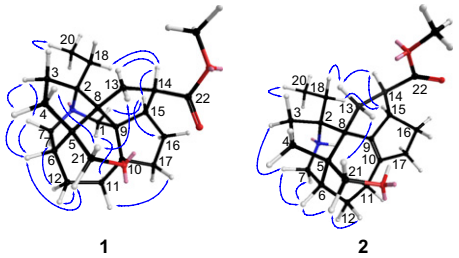


Figure 2. Key NOESY (↔) correlations of **1** and **2**.

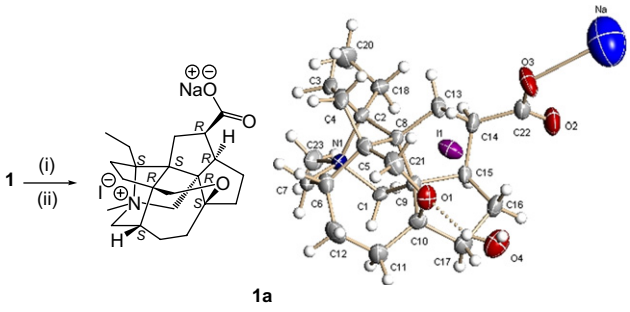


Figure 3. Transformation of **1** to **1a** ((i) MeI in acetone; (ii) Na_2CO_3), and the X-ray structure of **1a** showing the absolute configuration.

diffraction study allowed determination of the absolute configuration (absolute structure parameter, −0.01(3))[7] of **1a** as depicted in Figure 3. With the exception of ester group hydrolysis to a sodium salt, all the chiral centers of **1** were retained in **1a**, and this was verified by its NMR spectral data (Table 1). The absolute structure of paxdaphnine A (**1**) was accordingly determined by correlation with **1a**. Comparing **1** with a known *Daphniphyllum* alkaloid daphnezomine B,[8] whose absolute stereochemistry was determined by X-ray diffraction, the absolute configurations of biogenetically common chiral centers, such as C-5, C-6, and C-8, in both alkaloids are consistent, supporting the absolute structure assigned for **1**.

Paxdaphnine B (**2**), a colorless gum, showed molecular formula $C_{21}H_{31}NO_3$ as determined by HR-EIMS at *m/z* 345.2300 $[M]^+$ (calcd 345.2304), and supported by a positive mode of ESI MS at *m/z* 346 $[M+H]^+$. All 21 carbons were resolved in the ^{13}C NMR spectrum (Table 1, with DEPT) as one methyl, ten methylenes, three methines, six quaternary carbons, and one methoxyl. Twenty-nine protons observed in the ^{1}H NMR (Table 1) were assigned to their binding carbons by HMQC spectral analysis. According to the molecular formula, two missing protons were likely the exchangeable ones (NH and OH, IR absorption at 3425 cm^{-1}). An ester group was identified by the IR absorption at 1732 cm^{-1}, and supported by the ^{13}C NMR signal at δ 177.9. The carbonyl and the double bond claimed two degrees of unsaturation, the remaining five degrees of unsaturation required a pentacyclic ring system in **2**.

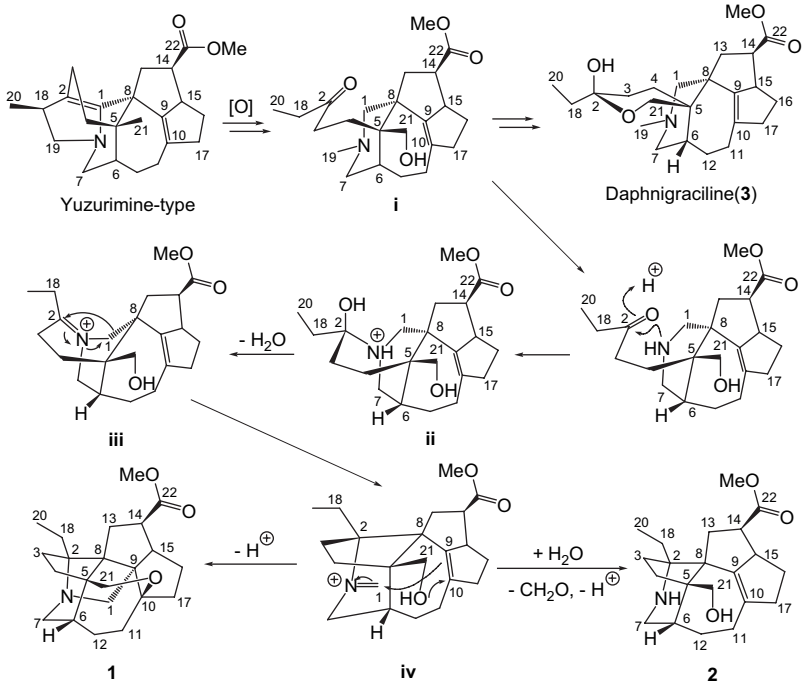
Four structural fragments **a** (C-18 and C-20), **b1** (C-13 to C-15), **b2** (C-16 and C-17), and **c** (C-7, C-6, C-12, and C-11) drawn with bold bonds were established by ^{1}H–^{1}H COSY spectrum (Fig. 1 and Table 1). The CH_2-3 and CH_2-4 proton signals at δ 1.70–1.72 (4H) are overlapped, and it can't be determined whether they are connected by ^{1}H–^{1}H COSY only. A hydroxymethyl was distinguished by the proton signals at δ 3.99 (1H, d, *J*=11.6 Hz) and δ 3.84 (1H, d, *J*=11.6 Hz). The HMBC spectrum (Fig. 1) allowed definition of the planar structure for **2**. In the HMBC, the methoxyl and H-14 showed correlations with C-22 to link the ester carbonyl at C-14; the strong correlations between H_2-16 and C-15 (^{2}J) revealed the connectivity of fragments **b1** and **b2** (the correlations of H_2-16/H-15 were not observed in the ^{1}H–^{1}H COSY due likely to their unfavorable dihedral angle). The linkage of quaternary carbon C-8 and the Δ^9 double bond was made on the basis of the ^{2}J correlations

Table 1. ^{1}H and ^{13}C NMR data of **1**, **1a**, and **2** (in CD_3OD)[a]

	1		1a		2	
	δ_C	δ_H (multi, *J* in hertz)	δ_C	δ_H (multi, *J* in hertz)	δ_C	δ_H (multi, *J* in hertz)
1	68.2	a 3.22 (d, 14.1), b 3.36 (d, 14.1)	76.4	4.07 (d, 13.9), 4.22 (d, 13.9)	—	—
2	79.6		90.9		70.8	
3	31.6	a 2.40 (dt, 8.4, 15.1), b 1.81 (td, 1.2, 11.0)	29.8	2.20 (m), 2.61–2.68 (m)	30.3	1.70 (m[b], 2H)
4	37.9	a 1.59 (m[b]), b 1.68 (m[b])	37.2	1.71–1.78 (m[b], 2H)	35.6	1.71 (m[b], 2H)
5	50.5		50.5		52.2	
6	44.2	1.79 (d, 9.9)	41.6	2.25 (m[b])	40.7	1.93 (t like, 7.1)
7	58.4	α 2.52 (d, 14.9), β 3.75 (dd, 9.9, 14.9)	66.9	3.37 (d, 13.9), 4.12 (dd, 13.9, 10.7)	45.2	α 2.88 (d, 14.6), β 3.18 (ddd, 1.0, 6.6, 14.6)
8	65.4		63.5		60.1	
9	66.8		68.0		145.7	
10	88.0		87.5		138.5	
11	33.4	α 2.10 (m), β 1.92 (ddd, 0.9, 7.5, 13.6)	32.6	2.00–2.10 (m, 2H)	27.2	α 2.41 (m), β 2.17 (m)
12	30.0	α 1.32 (ddd, 2.5, 7.1, 11.8), β 2.20 (m)	29.6	1.52 (m), 2.28 (m[b])	27.9	α 1.52 (m), β 2.19 (m)
13	29.4	α 1.57 (m[b]), β 2.32 (t, 12.9)	31.0	1.70–1.75 (m[b]), 2.45 (t like, 13.3)	37.0	α 2.00 (dd, 9.4, 15.3), β 2.53 (dd, 3.5, 15.3)
14	48.3	3.24 (ddd, 7.1, 8.9, 12.6)	48.5	3.22 (m)	44.5	2.90 (td, 6.1, 9.5)
15	56.5	2.61 (dd, 8.6, 17.4)	56.8	2.85 (m)	58.5	3.40 (m)
16	27.9	α 1.58 (m[b]), β 1.48 (m)	27.9	1.58 (m[b]), 1.70–1.75 (m[b])	30.7	α 1.84 (dt, 6.6, 11.6), β 1.25 (m)
17	43.2	α 1.52 (dd, 7.2, 12.6), β 1.66 (m[b])	43.1	1.55 (m[b]), 1.70–1.75 (m[b])	44.2	α 2.72 (m), β 2.31 (dd, 8.5, 15.0)
18	28.9	a 1.36 (dd, 7.3, 13.2), b 1.65 (m[b])	25.7	2.12 (m), 1.95 (m)	29.4	a 1.10 (dd, 7.3, 13.7), b 1.65 (dd, 7.4, 13.6)
20	10.1	0.97 (t, 7.2, 3H)	11.6	1.23 (t, 7.2, 3H)	9.6	0.90 (t, 7.3, 3H)
21	70.7	a 3.97 (d, 9.6), b 4.14 (d, 9.6)	70.0	4.01 (d, 10.0), 4.26 (d, 10.2)	67.4	a 3.84 (d, 11.6), b 3.99 (d, 11.6)
22	176.1		176.7		177.9	
O*Me*	52.2	3.64 (s, 3H)	—	—	51.9	3.60 (s, 3H)
NMe	—	—	49.4[c]	3.05 (s, 3H)	—	—

[a] Recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C). Compound **1a** was measured in CD_3OD containing a small amount (1/6, v/v) of $CDCl_3$.
[b] Proton signals were overlapped.
[c] Merged in CD_3OD.

of H_2-13/C-8, H-15/C-9, H_2-17/C-10, and H_2-11/C-10 and ^{3}J correlations of H_2-13/C-9, H-14/C-8, H-14/C-9, H-16α/C-9, H-16α/C-10, H_2-17/C-9, H_2-11/C-9, and H_2-12/C-10, which also showed the connectivity of fragments **b2** and **c** via C-10. The ^{2}J correlations of H_2-18/C-2 and H_2-3/C-2 fixed C-18 and C-3 to C-2. The ^{3}J correlation between H-7α and C-2 implied a linkage of C-2 and C-7 via the nitrogen atom, and supported by the chemical shifts of C-2 at δ 70.8 and C-7 at δ 45.2. The ^{2}J correlations of H_2-21/C-5, H_2-4/C-5, and H-6/C-5 and ^{3}J correlations of H_2-21/C-4, H-6/C-4, H-7α/C-5, and H_2-21/C-6 indicated the connections of C-4, C-21, and C-6 to C-5. The quaternary carbons C-2 and C-5 were linked to C-8 based on the ^{3}J correlations of H-18b/C-8, H_2-3/C-8 (or H_2-4/C-8), H_2-21/C-8, H-6/C-8, H_2-13/C-2, and H_2-13/C-5. The planar structure of **2** was thus outlined.



Scheme 1. Biogenetic pathway proposed for **1** and **2**.

The relative configuration of **2** was fixed by NOESY spectrum. The NOESY interactions of H-18a/H-13α and H-18b/H-15 indicated that the ethyl, H-13α, and H-15 were co-facial, and arbitrarily assigned as α-oriented. The H-14 correlating with both H-13α and H-15 was also α-oriented. Furthermore, the correlations of H-13β/H-21a and H-21b/H-6 indicated that H-6 and the hydroxymethyl group at the C-5 were fixed as β-orientation. The relative configuration of **2** assigned above was consistent with the computer-modeled 3D structure, on which NOESY correlations were depicted (Fig. 2). By correlating with paxdaphnine A (**1**) on the basis of biosynthetic reasoning (Scheme 1), the absolute configuration of paxdaphnine B (**2**) was thereby proposed to be the same as **1**.

The origin of **1** and **2** could be biologically traced back to a yuzurimine-type intermediate,[1] the precursor of a co-existing major alkaloid daphnigraciline (**3**) in this plant.[9] The yuzurimine-type intermediate would be oxidized to give a key intermediate (**i**), which would then be transformed to daphnigraciline (**3**) via a nucleophilic attack of 21-OH on C-2. The key intermediate (**i**) would first undergo a demethylation and then a nucleophilic attack of the N-lone-pair of electrons on C-2 to form the intermediate (**ii**), which would be transformed to a Schiff base (**iii**) via dehydration.[10] The intermediate **iii** would be transformed to a more stable and less constrained Schiff base (**iv**) via a 1,3-σ shift.[11] Paxdaphnines A (**1**) and B (**2**) would be finally produced from intermediate **iv** via aza-Prins reaction[12] and Schiff base hydrolysis,[10] respectively.

3. Experimental section

3.1. General experimental procedures

Melting point was recorded on Fisher–Johns melting point apparatus. Optical rotation was determined on a Perkin–Elmer 341 polarimeter. UV and CD spectra were measured on a JASCO J-810 instrument. IR spectra were recorded on a Perkin–Elmer 577 spectrometer. NMR spectra were measured on a Bruker AM-400 spectrometer with TMS as internal standard. EIMS (70 eV) and ESI MS were carried out on a Finnigan MAT 95 mass spectrometer and a Finnigan LCQ^{DECA} instrument, respectively. All solvents used were of analytical grade (Shanghai Chemical Plant). Silica gel (200–300 mesh) was used for column chromatography, and pre-coated silica gel GF_{254} plates (Qingdao Haiyang Chemical Plant) were used for TLC. Amino silica gel (NH-DM 1020, 20–45 μm, Fuji Silysia Chemical Ltd.) and Sephadex LH-20 (Pharmacia Biotech, Sweden) were also used for column chromatography.

3.2. Plant material

Seeds of *D. paxianum* Rosenth. were collected from Hainan Island of PR China in July 2003 and authenticated by Prof. Shi-Man Huang, Department of Biology, Hainan University of PR China. A voucher specimen has been deposited in Shanghai Institute of *Materia Medica*, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (accession number: DPS-HN-2003-4Y).

3.3. Extraction and isolation

The air-dried seeds powder (2.0 kg) was percolated with 95% ethanol, and the extract was dissolved in 1 L acidic water (acidified with 0.5 N H_2SO_4 to pH ≈4) to form a suspension. After removal of non-alkaloid components by ethyl acetate (4×300 mL) partition, the aqueous phase was adjusted with 2 N Na_2CO_3 to pH ≈10 and partitioned with ethyl acetate (4×300 mL) again to obtain the crude alkaloids (8.87 g). The crude alkaloids were subjected to a silica gel column chromatography eluting with $CHCl_3$, and then $CHCl_3$/CH_3OH (60/1 to 10/1) to afford four major fractions 1–4 as monitored by TLC. Fr. 4 was chromatographed on a column of Sephadex LH-20 eluted with EtOH to give a mixture of two alkaloids, which was further separated on a column of amino silica gel eluted with a mixture of cyclohexane/$CHCl_3$ (1/1 to 1/2) to yield paxdaphnines B (**2**) (42 mg, 0.0021%) and A (**1**) (30 mg, 0.0015%) in turn. Fr. 2 was separated on a column of amino silica gel eluted with a mixture of cyclohexane/$CHCl_3$ (1/1) to give a known alkaloid daphnigraciline (**3**) (280 mg, 0.014%).

3.3.1. Paxdaphnine A (1). Colorless gum; $[\alpha]_D^{20}$ −71 (*c* 0.18, CH_3OH); IR (film) ν_{max} 3446 (very weak), 2943, 2875, 1736, 1458, 1435, 1367, 1199, 1028, 1014, 754 cm^{-1}; ^1H and ^{13}C NMR see Table 1; EIMS 70 eV *m/z* (rel int.): 357 $[M]^+$ (100), 342 (14), 329 (44), 314 (30), 300 (22), 288 (15), 270 (24); HR-EIMS *m/z*: 357.2299 (calcd for $[C_{22}H_{31}NO_3]^+$: 357.2304); ESI MS (positive) *m/z*: 358 $[M+H]^+$.

3.3.2. Paxdaphnine B (2). Colorless gum; $[\alpha]_D^{20}$ +23 (*c* 0.12, CH_3OH); IR (KBr) ν_{max} 3425 (moderate), 2931, 2874, 1732, 1639, 1446, 1367, 1190, 1163, 1041, 866 cm^{-1}; ^1H and ^{13}C NMR see Table 1; EIMS 70 eV *m/z* (rel int.): 345 $[M]^+$ (36), 327 (6), 314 (100), 297 (6), 243 (11), 229 (10), 183 (14); HR-EIMS *m/z*: 345.2300 (calcd for $[C_{21}H_{31}NO_3]^+$: 345.2304); ESI MS (positive) *m/z*: 346 $[M+H]^+$.

3.4. Iodide derivative 1a and its X-ray crystallographic analysis

Paxdaphnine A (**1**, 8.0 mg) in 10 mL acetone was reacted with a drop of MeI at rt for 20 h, and then the powder of Na_2CO_3 (50 mg) was added. After filtration, the solvent was removed by evaporation, and the residue was recrystallized in fresh acetone to give **1a** (4.3 mg): colorless plates in acetone; mp 176 °C (decomposed); $[\alpha]_D^{20}$ −31 (*c* 0.13, CH_3OH); IR (KBr) ν_{max} 3531, 3454, 2951, 1726, 1464, 1211, 1009 cm^{-1}; ^1H and ^{13}C NMR see Table 1; ESI MS (positive) *m/z*: 358 $[C_{22}H_{31}NO_3+H]^+$; ESI MS (negative) *m/z*: 484 $[C_{22}H_{31}INO_3]^-$, 127 $[I]^-$.

*X-ray data of **1a***: All measurements were made on a Rigaku AFC7R four circle diffractometer employing graphite monochromated Mo Kα radiation (0.71073 Å) and operating in the ϕ-ω scan mode. Data reduction and empirical absorption corrections (ψ-scans) were performed with the SHELXS-97 package. $C_{22}H_{33}INNaO_4$, M=525.38, monoclinic, dimensions: 0.453×0.317×0.220 mm, space group $P2_1$, Mo Kα, final R indices [$I>2\sigma(I)$], $R1$=0.0392, $wR2$=0.0970, a=9.6885(8), b=10.5910(9), c=11.2061(9) Å, α=90,

β=105.4760(10), γ=90°, V=1108.18(16) Å^3, T=293(2) K, Z=2, d=1.575 g cm^{-3}, reflections collected/unique: 6446/3808 (R_{int}=0.0705), number of observations [$>2\sigma(I)$] 3546, parameters 272. Crystallographic data for **1a** have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 603007).

Acknowledgements

Financial support of the National Natural Science Foundation (No. 20472093), Shanghai Municipal Science Foundation (No. 04XD14019), and the foundation from the Ministry of Science and Technology (No. 2002CB512807) of PR China are gratefully acknowledged. We thank Professor Shi-Man Huang for the collection and identification of the plant material.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.042.

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