Aporphine Alkaloids from the Chinese Tree Neolitsea aurata var. paraciculata

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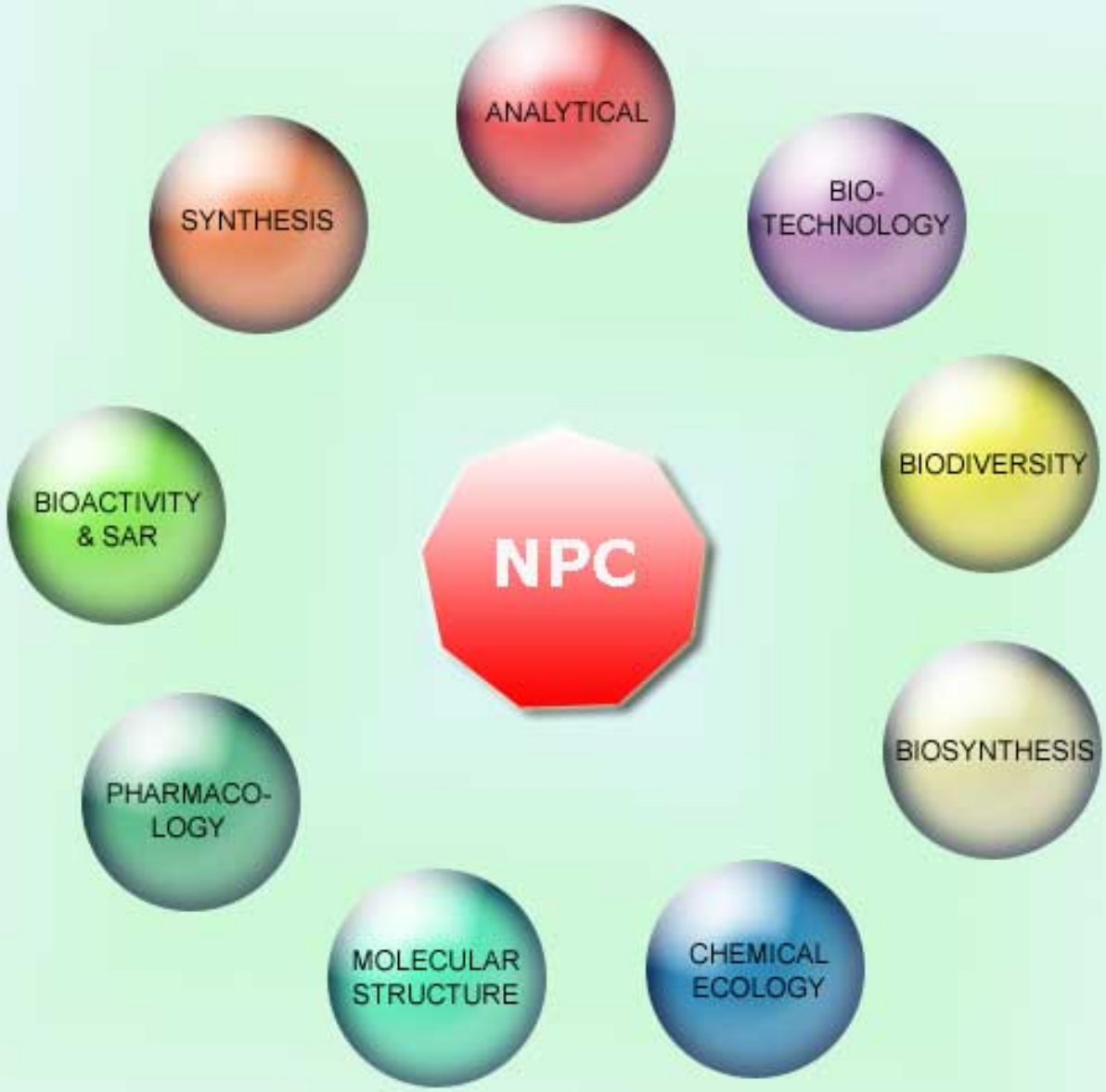

This Issue is Dedicated to
Professor Yoshinori Asakawa
on the Occasion of his 65th Birthday

Volume 2. Issue 3. Pages 223-350. 2007
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
www.naturalproduct.us

NPC Natural Product Communications

2007
Vol. 2
No. 3
255 - 259

Aporphine Alkaloids from the Chinese Tree *Neolitsea aurata* var. *paraciculata*

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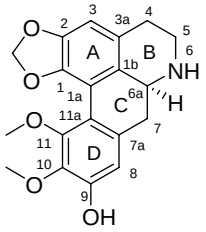
Received: November 2nd, 2006; Accepted: January 2nd, 2007

This paper is dedicated to Professor Yoshinori Asakawa for his 65th birthday.

Three new oxygenated noraporphine alkaloids were isolated from the bark of the Chinese tree *Neolitsea aurata* var. *paraciculata*. The new compounds, (+)-11-methoxynorcassythicine, (+)-11-methoxynorneolitsine, (+)-11-methoxynorboldine, were isolated along with eight known aporphine alkaloids, hernovine, ovigerine, *N*-methylovigerine, 10-*O*-methylhernovine, lindcarpine, *N*,*O*-dimethylhernovine, laurolitsine and nandigerine. Their structures were determined by 1D and 2D NMR spectroscopy. This is the first report of chemical constituents from *N. aurata* var. *paraciculata.*

Keywords: *Neolitsea aurata* var. *paraciculata*, Lauraceae, Aporphine alkaloids, natural products, isolation, structure elucidation, STAT6.

Aporphine alkaloids have previously been reported as constituents of *Neolitsea aurata* [1]. However, chemical investigation of *N. aurata* var. *paraciculata* (Nakai) Y. C. Yang & P. H. Huang (Lauraceae) has not been reported previously. In the present study three new noraporphine alkaloids, (+)-11-methoxynorcassythicine (**1**), (+)-11-methoxy-norneolitsine (**2**), and (+)-11-methoxynorboldine (**3**), were isolated from *N. aurata* var. *paraciculata*, along with eight known aporphine alkaloids, hernovine [2], ovigerine [2], *N*-methylovigerine [3], 10-*O*-methylhernovine [4], lindcarpine [5], *N*,*O*-dimethylhernovine [6], laurolitsine [7] and nandigerine [2]. The compounds studied here were isolated from an extract of *N. aurata* var. *paraciculata* that was active in a bioassay to find inhibitors of STAT6 (Signal Transducer and Activator of Transcription 6) for the treatment of asthma [8]. However, although these compounds were active against STAT6 in this assay, they were also active in the artifact assay and thus were not investigated any further. Aporphine alkaloids are a broad subgroup of benzylisoquinoline compounds, with more than 500 alkaloids isolated [9-10]. Aporphine alkaloids exhibit a wide range of biological properties and two aporphine alkaloids are on the market as pharmaceutical products. These are boldine, an antioxidant and choleretic, and apomorphine, a synthetic dopamine D_1 and D_2 receptor agonist. We report here the isolation and structure elucidation of the new compounds **1-3**.



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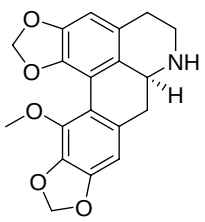

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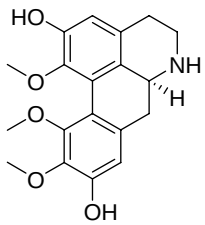

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The bark of *Neolitsea aurata* var. *paraciculata* was collected in Guang Xi Province, China and a MeOH extract was prepared, which was then acidified before passing through a SCX resin. The MeOH/NH_3 (4:1) and CH_2Cl_2 eluents were combined and passed through PAG. The resulting MeOH/H_2O eluent gave an alkaloid extract, which was purified by C18 and DIOL semi-preparative HPLC to yield eight known aporphine alkaloids and three new aporphine alkaloids, **1-3**. The eight known aporphine alkaloids, hernovine, ovigerine, *N*-methylovigerine, 10-*O*-methylhernovine, lindcarpine, *N*,*O*-dimethyl-hernovine, laurolitsine, nandigerine, were identified by comparison of physical and NMR spectroscopic data with previously published data for aporphines [2, 11-12], together with detailed analysis of their own one- and two-dimensional NMR spectra. The new compounds, **1-3**, were all isolated in very low yield, less than 0.0015% of the dry weight of the bark.

Compound **1**, an optically active solid, was found to posses a molecular formula of $C_{19}H_{19}NO_5$, as determined by the HRESIMS (*m/z* 342.13332 $[M+H]^+$). The UV absorption bands at 223, 281, and 304sh, were characteristic of an aporphine chromophore [13]. The ^1H NMR spectrum (Table 1) of **1** contained signals at δ_H 6.77 and 6.63 (both s) in the aromatic region. It also exhibited protons for a methylenedioxy group [δ_H 6.11, 5.96 (both s)] and two 3H singlets (δ_H 3.80, 3.72) characteristic of Ar-OMe groups. The resonances at δ_H 3.07, 2.87, 3.61 and 3.24, were assigned to the Ar-CH_2-CH_2-N spin system of an aporphine and those at δ_H 4.18, 2.87 and 2.65 to the Ar-CH_2-CH-N spin system of an aporphine. The ^{13}C NMR spectrum (Table 1) of **1**, when analyzed with the help of its DEPT spectrum, showed the presence of two methyl, four methylene, three methine and ten quaternary carbons. The location of the methylenedioxy, two methoxyl and one hydroxyl groups on the aporphine unit were established from correlations observed in gHMBC (Table 1) and ROESY spectra. Thus, the attachment of the methylenedioxy group at C-1 and C-2 was assigned from the gHMBC correlations observed between δ_H 6.77 (H-3) and δ_C 142.6 (C-1), 147.5 (C-2) and 24.8 (C-4) and between δ_H 6.11, 5.96 (1-O-CH_2-O-2) and δ_C 142.6 (C-1) and 147.5 (C-2). In natural aporphines, C-1 and C-2 are always substituted by hydroxyl, methoxyl or methylenedioxy groups. A 9,10,11-trioxygenation pattern was deduced from the gHMBC correlation from the aromatic singlet at δ_H 6.63 (H-8) with δ_C 33.6 (C-7).

Table 1: ^1H (600 MHz), ^{13}C (150 MHz), gCOSY and gHMBC NMR data for (+)-11-methoxynorcassythicine (**1**) in DMSO-d_6.

Position	δ_C	δ_H (mult, *J* Hz)	COSY (H no.)	$^{2,3}J_{CH}$ HMBC (C no.)
1a	113.5 s			
1b	122.4 s			
1	142.6 s			
2	147.5 s			
3	106.2 d	6.77 (s)		1b, 1, 2, 4
3a	123.4 s			
4	24.8 t	3.07 (ddd, 18.0, 12.0, 6.0)β	5α, 5β	3a
		2.87 (m)α		
5	40.0 t [a]	3.61 (brdd, 12.0, 6.0)β	5α, 4β	
		3.24 (m)α [c]	5β, 4β	
6		9.53 (m)α		
		8.89 (m)β		
6a	52.0 d	4.18 (m)α	6β, 7α, 7β	
7	33.6 t	2.87 (m)α		
		2.65 (t, 13.5)β	6a	7a, 6a, 1b, 8, 11a
7a	129.7 s			
8	110.9 d	6.63 (s)		7, 10, 11a
9	151.4 s [b]			
10	140.0 s			
11	151.5 s [b]			
11a	113.8 s			
9-OH		9.64 (s)		8, 10
11-OMe	60.3 q	3.80 (s)		
10-OMe	60.0 q	3.72 (s)		10
1-O-CH_2-O-2	100.5 t	6.11 (s)		1, 2
		5.96 (s)		1, 2

[a] Chemical shift obtained from 2D NMR,spectrum. as signal obscured by DMSO peak.
[b] Signals within the same column are interchangeable.
[c] Chemical shift obtained from 2D NMR spectrum, as signal obscured by H_2O peak.

The aromatic proton at δ_H 6.63 (H-8) also showed 3-bond gHMBC correlations to δ_C 113.8 (C-11a) and 140.0 (C-10). The methoxyl at δ_H 3.72 (10-OMe) had a gHMBC correlation with δ_C 140.0 (C-10) and the hydroxyl at δ_H 9.64 (9-OH) had a ROESY correlation with δ_H 6.63 (H-8). The methoxyl at δ_H 3.80 (11-OMe) and the hydroxyl at δ_H 9.64 (9-OH) both showed gHMBC correlations with two aromatic quaternary carbons that were almost coincident (δ_C 151.4, 151.5) and these carbons were assigned to C-9 and C-11. This revealed the substitution pattern of the D-ring as 10,11-dimethoxy-9-hydroxy. The above evidence allowed the structure of **1** to be identified as 10,11-dimethoxy-9-hydroxy-1,2-methylenedioxy-noraporphine and this new compound was given the trivial name 11-methoxy-norcassythicine. Finally, the absolute stereochemistry 6a-*S* was assigned to 11-methoxy-norcassythicine on the basis of the positive value of its optical rotation [13-14].

Table 2: ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data for (+)-11-methoxynorneolitsine (**2**) and (+)-11-methoxynorboldine (**3**) in DMSO-d_6.

Position	**2**		**3**	
	δ_C [a]	δ_H(mult,*J* Hz)	δ_C	δ_H (mult, *J* Hz)
1a	n.o.		n.o.	
1b	122.3 s		121.1 s	
1	142.8 s		144.4 s	
2	147.7 s		150.1 s	
3	106.2 d	6.79 (s)	113.8 d [c]	6.65 (s)
3a	123.0 s		n.o.	
4	24.6 t	3.06 (ddd,18.0, 12.6, 6.0)β	24.2 t	3.03 (ddd, 18.0, 12.6, 6.0)β
		2.88 (brdd, 18.0, 4.2)α		2.85 (brdd, 18.0, 4.5)α
5	40.0 t	3.61 (brdd, 12.0, 6.0)β	40.0 t [d]	3.58 (m)β [b]
		3.24 (m)α [b]		3.24 (m)α [b]
6		9.49 (m)α		9.47 (m)α
		8.89 (m)β		8.74 (m)β
6a	51.7 d	4.19 (m)α	52.2 d	4.07 (m)α
7	33.6 t	2.95 (dd, 14.0, 4.2)α	34.1 t	2.80 (dd, 13.2, 4.2)α
		2.65 (t, 14.0)β		2.59 (t, 13.2)β
7a	128.7 s		129.9 s	
8	102.8 d	6.81 (s)	110.5 d	6.61 (s)
9	148.6 s		150.7 s	
10	136.5 s		140.0 s [e]	
11	140.8 s		152.1 s	
11a	115.3 s		115.6 s	
1-O-CH_2-O-2	100.2 t	6.12 (s)		
		5.97 (s)		
1-OMe			59.7 q	3.49 (s)
2-OH				9.32 (s)
9-O-CH_2-O-10	101.0 t	6.11 (s)		
		5.99 (s)		
9-OH				9.49 (s)
10-OMe			60.1 q	3.74 (s)
11-OMe	58.9 q	3.98 (s)	60.3 q	3.65 (s)

[a] Weak ^{13}C NMR spectrum, most chemical shifts obtained from 2D NMR experiments.
[b] Chemical shift obtained from 2D NMR spectrum, as signal obscured by H_2O peak.
[c] Chemical shift obtained from DEPT experiment.
[d] Chemical shift obtained from 2D NMR spectrum, as signal obscured by DMSO peak.
[e] Chemical shift obtained from 2D NMR experiments.
n.o. = not observed.

Compound **2**, the second noraporphine alkaloid, had the molecular formula $C_{19}H_{17}NO_5$, attributed from its HRESIMS (*m/z* 340.11926 $[M+H]^+$). A comparison of NMR spectroscopic data clearly showed that **2** (Table 2) had the same A-C ring partial structure as **1** (Table 1). Furthermore, the ^{1}H NMR spectroscopic data clearly revealed that ring D of **2** contained a methoxyl group (δ_H 3.98) and a methylenedioxy group [δ_H 5.99, 6.11 (both s)]. Again, a 9,10,11-substitution pattern was inferred by the gHMBC correlation from δ_H 6.81 (H-8) to δ_C 33.6 (C-7). The remaining gHMBC correlations from δ_H 6.81 (H-8) with δ_C 136.5 (C-10), 148.6 (C-9) and 115.3 (C-11a), together with those from the methoxyl (δ_H 3.98) with δ_C 140.8 (C-11), and the methylenedioxy (δ_H 5.99, 6.11) with δ_C 136.5 (C-10) and 148.6 (C-9), clearly revealed the substitution pattern was 11-methoxy-9,10-methylenedioxy. New compound **2**, which had an $[\alpha]_D$ of +51.2°, was thus concluded to be (+)-11-methoxy-1,2:9,10-bis(methylenedioxy)-noraporphine, to which the trivial name (+)-11-methoxynorneolitsine was ascribed.

The HRESIMS (*m/z* 344.15097 $[M+H]^+$) of compound **3** revealed that it had a molecular formula $C_{19}H_{21}NO_5$. The optically active solid had an $[\alpha]_D$ of + 63.7°. By comparing the NMR spectroscopic data for **1** and **3** (Tables 1 and 2, respectively), it was clear that they had the same B-D ring partial structure. Furthermore, the ^{1}H NMR spectroscopic data clearly revealed that ring A of **3** contained a methoxyl group (δ_H 3.49) and a hydroxyl group (δ_H 9.32), compared with a methylenedioxy group in **1** and **2**. A 1,2-substitution pattern was indicated by the gHMBC correlation from δ_H 6.65 (H-3) to δ_C 24.2 (C-4). The ROESY correlation between δ_H 6.65 (H-3) and 9.32 (2-OH), confirmed the substitution pattern of the A-ring was 2-hydroxy-3-methoxy. Compound **3** was given the name (+)-2,9-dihydroxy-1,10,11-trimethoxynoraporphine and the trivial name (+)-11-methoxynorboldine.

Three new noraporphine alkaloids, (+)-11-methoxynorcassythicine (**1**), (+)-11-methoxynor-neolitsine (**2**) and (+)-11-methoxynorboldine (**3**), were identified as minor constituents from *Neolitsea aurata* var. *paraciculata*. All three are C-11 substituted, which is relatively rare among aporphine alkaloids, and had 6a-*S* absolute stereochemistry.

Experimental

General experimental procedures: Water was Millipore Milli-Q PF filtered, while all other solvents used were Omnisolv HPLC grade. Trifluoroacetic acid (TFA) was Fluka spectroscopic grade. Ammonia solution (about 25% NH_3, sp. gr. 0.91) was from Merck. Formic acid 99% was from Ajax Finechem. Betasil C18, 5μm (150 mm x 21.2mm i.d.) and YMC-Pack DIOL-120NP (150 mm x 20 mm i.d.) at flow rates of 10 mL/min were used for semi-preparative HPLC. A Waters 600 pump fitted with a 996 Photodiode Array Detector and 717 plus Autosampler was used for the semi-preparative

separations. SCX (strongly acidic ion exchanger) resin was DOWEX® 50WX8-400A, C18 was 04K-4348 Sepra C18 End-Capped Silica, and PAG (polyamide gel) was Machery Nagel Polyamide CC6 (0.05-0.16 mm). HRESIMS were measured on a Mariner TOF mass spectrometer, equipped with an electrospray ion source (TurboIonSpray). FTIR and UV spectra were recorded on Bruker Tensor 27 FTIR and Agilent 8453 UV/vis spectrophotometers, respectively. Optical rotations ($[\alpha]_D$) were measured on a Jasco P-1020 polarimeter. NMR spectra were recorded at 30°C on Varian Inova 500 and 600 MHz NMR spectrometers. Samples were dissolved in DMSO-d_6 (residual ^{1}H δ 2.50 and ^{13}C δ 39.5 ppm).

Plant material: The bark of *Neolitsea aurata* var. *paraciculata* (Nakai) Y. C. Yang & P. H. Huang (Lauraceae) was collected on the 7th October 1999 from Zi Yuan County in Guang Xi Province, China and a voucher sample (21-OCT-199910:02_04100799C00065) is lodged with the Zi Yuan Medicine Company, China.

Extraction and isolation: The bark (202 g) was ground and extracted with 4L MeOH. The MeOH crude extract was then acidified to about pH = 4 with 1M formic acid and eluted through SCX resin (20 g), and subsequently eluted with 1L MeOH, followed by 1L MeOH/NH_3 (4:1) and finally 1L CH_2Cl_2. The MeOH/NH_3 and CH_2Cl_2 eluents were combined (1.01 g) and eluted through PAG (20 g), eluting with 1.5 L MeOH/H_2O to give 810 mg of alkaloid extract. Next, 405 mg of this alkaloid extract underwent purification by semi-preparative C18 HPLC. The sample was pre-adsorbed onto C18 (1 g) and loaded into a refillable preparative guard column (30 mm x 10 mm i.d.) in line with the semi-preparative C18 HPLC column. The HPLC column was eluted with H_2O/1% TFA to H_2O/1% TFA: CH_3CN/1% TFA (2:3) in 100 min, then to CH_3CN/1% TFA in 20 min and 60 fractions were collected. Three pure compounds, hernovine (18.58 mg, 0.02% dry wt), ovigerine (6.95 mg, 0.007% dry wt) and nandigerine (26.71 mg, 0.03% dry wt), were eluted with retention times of 40, 64 and 50 min, respectively. Fractions 21-23 (10.3 mg), 26-31 (42.3 mg) and 33-40 (37.5 mg) still contained mixtures of alkaloids. Fractions 21-23 were further purified on C18 HPLC using a gradient of H_2O/1% TFA to H_2O/1% TFA: CH_3CN /1% TFA (9:1) in 5 min, then to H_2O/1% TFA: CH_3CN /1% TFA (7:3) in 45 min and finally to CH_3CN/1% TFA in 10 min. Three compounds were purified, (+)-11-methoxynorboldine (**3**) (1.02 mg, 0.001% dry wt), lindcarpine (0.57 mg, 0.0006% dry wt) and laurolitsine (0.71 mg, 0.0007% dry wt), with retention times of 23, 26 and 28 min, respectively. Fractions 26-31 were purified by C18 HPLC using a gradient of H_2O/1% TFA to H_2O/1% TFA: CH_3CN/1% TFA (17:3) in 5 min, then to H_2O/1% TFA: CH_3CN/1% TFA (13:7) in 45 min and finally to CH_3CN/1% TFA in 10 min, yielding three compounds, 10-*O*-methylhernovine (3.17 mg, 0.003% dry wt), *N,O*-dimethylhernovine (0.96 mg, 0.001% dry wt) and (+)-11-methoxynorcassythicine (**1**), with retention times of 24, 27 and 30 min, respectively. A final purification of **1** by DIOL HPLC was achieved using H_2O/1% TFA isocratic elution for 20 min, followed by a gradient to CH_3CN/1% TFA in 10 min. Compound **1** (1.10 mg, 0.0011% dry wt) was eluted with a retention time of 8 min. Fractions 33-40 were purified by C18 HPLC using a gradient of H_2O/1% TFA to H_2O/1% TFA: CH_3CN/1% TFA (3:1) in 5 min, then to H_2O/1% TFA:CH_3CN/1% TFA (11:9) in 45 min and finally to CH_3CN/1% TFA in 10 min. Two compounds were obtained, *N*-methylovigerine (1.03 mg, 0.001% dry wt) and (+)-11-methoxynorneolitsine (**2**) (0.61 mg, 0.0006% dry wt), with retention times of 21 and 25 min, respectively. All compounds were isolated as their trifluoroacetate salts.

(+)-11-Methoxynorcassythicine [(+)-10,11-Dimethoxy-9-hydroxy-1,2methylenedioxynor-aporphine (1)]

Amorphous solid.
$[\alpha]_D^{21}$: +58.9º (*c* 0.050, MeOH).
IR ν_{max} (film) cm^{-1}: 3401, 1679, 1462, 1203.
UV (MeOH) λ_{max} nm (log ε): 223 (4.26), 281 (3.95), 304sh (3.73).
^{1}H NMR: Table 1.
^{13}C NMR: Table 1.
positive-HRESIMS: *m/z* 342.13332 $[C_{19}H_{19}NO_5+H]^+$ (calcd 342.13360).

(+)-11-Methoxynorneolitsine [(+)-11-Methoxy-1,2:9,10-bis(methylenedioxy)noraporphine (2)]

Amorphous solid.
$[\alpha]_D^{21}$: +51.2º (*c* 0.036, MeOH).
IR ν_{max} (film) cm^{-1}: 3435, 1614, 1456, 1205, 1056.
UV (MeOH) λ_{max} nm (log ε): 214sh (4.09), 274 (3.66), 300sh (3.42).
^{1}H NMR: Table 2.
^{13}C NMR: Table 2.

positive-HRESIMS *m/z* 340.11926 $[C_{19}H_{17}NO_5+H]^+$ (calcd 340.11795).

(+)-11-Methoxynorboldine [**2,9-Dihydroxy-1,10,11-trimethoxynoraporphine** (**3**)]

Amorphous solid.
$[\alpha]_D^{21}$: +63.7º (*c* 0.055, MeOH).
IR ν_{max} (film) cm^{-1}: 3391, 1679, 1590, 1469, 1203.
UV (MeOH) λ_{max} nm (log ε): 209sh (4.45), 280 (3.95).
^{1}H NMR: Table 2.
^{13}C NMR: Table 2.
positive-HRESIMS *m/z* 344.15097 $[C_{19}H_{21}NO_5+H]^+$ (calcd 344.14925).

Acknowledgments - We thank AstraZeneca for financial support. We are indebted to Zi Yuan Medicine Company (Manager - Zhong You Wen, Collection Manager - Li Yang, Taxonomist - Prof. Sam Cheung), for the collection and identification of the plant sample. We also thank Mr Paul Baron, for HRESIMS analyses.

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