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QUATERNARY ALKALOIDS FROM *LITSEA CUBEBA* AND *CRYPTOCARYA KONISHII*

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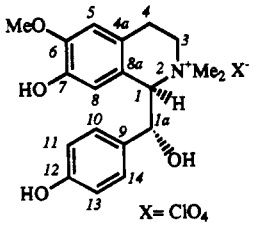
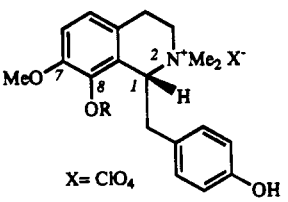
ABSTRACT.—Centrifugal partition chromatography, Sephadex LH-20, and ion-pair reversed-phase lc were applied in the isolation of quaternary alkaloids from two Formosan Lauraceous plants: *Cryptocarya konishii* and *Litsea cubeba*. These efforts led to the isolation of (+)-(1*R*,1a*R*)-1a-hydroxymagnocurarine [**1**] from *C. konishii* and three additional quaternary alkaloids, (−)-oblongine [**3**], (−)-8-*O*-methyloblongine [**4**], and xanthoplanine [**5**], from the stems of *L. cubeba*, along with (−)-magnocurarine [**2**]. Of these compounds, **1** and **4** are new natural products and **3** is the levorotatory optical isomer of the known (+)-oblongine. Structures were elucidated by spectral analyses.

Despite the intensive investigation of the free bases, few quaternary alkaloids have been reported in Lauraceous plants. In a continuation of studies of polar compounds, we report herein the isolation and characterization of quaternary alkaloids from two Formosan Lauraceous plants, *Cryptocarya konishii* Hayata ex Kawakami and *Litsea cubeba* (Lour.) Persoon. The quaternary alkaloids of *L. cubeba* had been previously studied, and only (−)-magnocurarine [**2**] was isolated from the stem (1); while those in *C. konishii* have remained to be investigated.

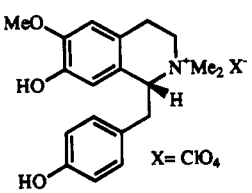
As polar components the quaternary alkaloids are not easily separated by normal phase adsorption chromatography. Good recovery and clean separations are the major challenges in this field. By application of Sephadex LH-20, contrifugal partition chromatography, and dccc, the recovery problem was resolved. In addition, good separation of quaternary alkaloids was achieved by reversed-phase lc using ion-pair solvent sytems. By a combination of these techniques, (+)-(1*R*,1a*R*)-1a-hydroxymagnocurarine [**1**] was isolated from *C. konishii* and three quaternary alkaloids, (−)-oblongine [**3**], (−)-8-*O*-



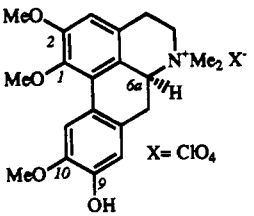
1



3 R=H
4 R=Me



2



5

methyloblongine [**4**], and xanthoplanine [**5**], in addition to **2**, were isolated from the stems of *L. cubeba*.

Compound **1**, isolated as the perchlorate salt, showed in the hreims spectrum $[M-HClO_4]^+$ *m/z* 329.1626, corresponding to a formula of $C_{19}H_{23}NO_4$ (calcd 329.1628). Its ^{1}H-nmr spectrum (in CD_3OD) showed two singlets at δ 6.72 and 6.15 and an AA′BB′ system at δ 6.94 and 6.65 (J_{AB}=8.6 Hz) in the aromatic region, characteristic for 6,7,12-trioxygenated benzyltetrahydroisoquinolines (BZTHISQ) (2). Other significant signals included an MeO singlet at δ 3.80, two *N*-Me signals at δ 2.99 and 3.43, and an AX system at δ 5.15 and 4.52 (J_{AX}=6.2 Hz). The presence of phenolic functions, elucidated from a bathochromic shift in the uv (λ max from 283 nm to 299 nm) under alkaline conditions, and the MeO signal at δ 3.80 would suggest a phenolic function at C-7 (2). The location of the MeO substitution at C-6 was determined by an nOe study which enhanced H-5 (δ 6.72) upon irradiation of the MeO singlet. Hence, **1** is a 7,12-dihydroxy-6-methoxy-BZTHISQ.

With the AX system at δ 5.15 and 4.52, a double resonance experiment showed that the doublet at δ 4.52 collapsed to a singlet upon irradiation of the doublet at δ 5.15, suggesting that these signals are due to H-1 and H-1a. This was confirmed by nOe's (Figure 1). Irradiation of both the N-Me_{ax} singlet (δ 2.99) and H-8 (δ 6.15) enhanced the same doublet at δ 4.52, assigning H-1a at δ 4.52. The signals of H-1 (δ 5.15), H-10 (δ 6.94) and H-14 (δ 6.94) were enhanced by irradiation of the N-Me_{eq} singlet (δ 3.43). These data and chemical model studies pointed out that H-1 is trans to H-1a but cis to 1a-OH. The coupling constant (J=6.2 Hz) of this AX system being close to 7.0 Hz also supported the threo arrangement for the C-1 and C-1a substitution; the erythro arrangement would show a coupling constant close to 4.0 Hz (3). Hence, compound **1** is *threo*-1a-hydroxymagnocurarine.

The stereochemistry at C-1 was elucidated by the cd spectrum. The observed maxima for two positive Cotton effects, near λ 289 and 235 nm, indicated that H-1 is α-oriented (2). These data, taken together with the observed sign of optical rotation, showed compound **1** to be (+)-(1*R*,1a*R*)-1a-hydroxymagnocurarine. To our knowledge, **1** is a novel natural product.

The structure for **1** was also supported by the eims spectrum, which showed the major ions, *m/z* 192, 122, and 58, in accord with fragments **A**, **B** and **C**, respectively. Complete ^{13}C-nmr assignments of **1**, based on nOe's and 2D nmr data, were made (Table 1). The proton-attached carbons were assigned directly from a hetero-COSY spectrum. The signals of the quaternary carbons, C-6 (δ 149.6), C-7 (δ 145.8) and C-8a (δ 122.4), were assigned by a COLOC spectrum (Table 1) from their long range couplings to 6-OMe (δ 3.80) (C-6), H-8 (δ 6.15) (C-6, C-7), and H-5 (δ 6.72) (C-7, C-8a). The signals

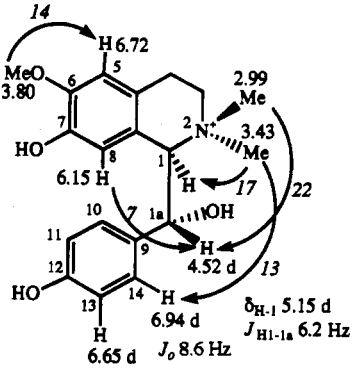
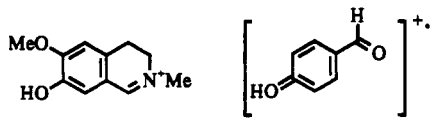


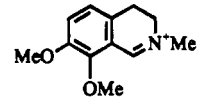
FIGURE 1. ^{1}H-nmr data and nOe's (%) of compound **1** (ClO_4^- salt) in CD_3OD.



m/z 192
A

m/z 122
B

m/z 58
C



m/z 206
D

of the remaining quaternary carbons (C-4a, C-9, and C-12) were assigned from correlation of the corresponding reported data and from the substitution effects (4).

Compound **2**, also isolated as the perchlorate salt, mp 296.5° (MeOH), diplayed in its ^{1}H-nmr spectrum two singlets at δ 6.80 and 5.89 and an AA′BB′ system at δ 6.85 and 6.68 (J_{AB}=8.8 Hz), typical for H-5, H-8, H-10, and H-14, and H-11 and H-13 in a 6,7,12-trioxygenated BZTHISQ. These data and other signals at δ 4.54 (dd, J=3.8, 8.8 Hz, H-1), 3.83 (s, 6-OMe), 3.38 (s, N-Me$_{eq}$) and 3.11 (s, N-Me$_{ax}$) and the levorotatory property identified **2** as (−)-magnocurarine (1).

Compound **3**, an amorphous solid, isolated as the perchlorate salt, $[\alpha]^{24}D$ −11.0° (c=1.0, MeOH), gave in its eims spectrum $[M-HClO_4]^+$ at *m/z* 313. The ir absorption at 3401 cm^{-1} and a bathochromic shift in the uv spectrum (λ 280 nm to 294 nm) under

TABLE 1. ^{13}C nmr Data of Compounds **1**, **3**, **4**, and **6** in CD_3OD (δ in ppm, multiplicity).

Carbon	Compound				2D nmr data of **1**[b]	
	1	**3**	**4**	**6**[a]	δ_C	δ_H
C-1	75.4 d	70.7 d	70.4 d	61.8 d	75.4	5.15 (H-1)
C-1a	77.7 d	37.4 t	38.3 t	39.1 t	77.7	4.52 (H-1a)
2-Me$_{ax}$	53.4 q	51.9 q	52.0 q	—	53.4	2.99 (2-Me$_{ax}$)
2-Me$_{eq}$	55.4 q	54.1 q	54.0 q	43.1 q	55.4	3.43 (2-Me$_{eq}$)
C-3	56.5 t	55.5 t	55.4 t	46.3 t	56.5	3.60 & 4.00 (H-3′s)
C-4	24.1 t	23.9 t	23.8 t	24.8 t	24.1	3.00 (H-4′ s)
C-4a	121.9 s	122.2 s	122.5 s	127.9 s		
C-5	112.0 d	120.0 d	125.1 d	120.1 d	112.0	6.72 (H-5)
C-6	149.6 s	113.4 d	115.5 d	111.2 d	149.6	3.80 (6-OMe), 6.15 (H-8)
C-7	145.8 s	147.8 s	152.5 s	146.6 s	145.8	6.15 (H-8), 6.72 (H-5)
C-8	117.4 d	145.0 s	147.0 s	144.3 s	117.4	6.15 (H-8)
C-8a	122.4 s	120.3 s	126.4 s	126.0 s	122.4	6.72 (H-5)
C-9	132.9 s	129.0 s	127.4 s	133.2 s		
C-10 and C-14	129.4 d	131.4 d	131.3 d	131.3 d	129.4	6.94 (H-10&14)
C-11 and C-13	116.0 d	116.6 d	117.2 d	115.9 d	116.0	6.65 (H-11&13)
C-12	158.2 s	157.8 s	157.9 s	156.4 s		
6-OMe	56.5 q	—	—	—	56.5	3.80 (6-OMe)
7-OMe	—	56.8 q	56.6 q	56.8 q		
8-OMe	—	—	61.1 q	—		

[a]^{13}C nmr data of **6** are from Lee *et al.* (9).

[b]Except for the correlation data of C-6, C-7, and C-8a, which were obtained from COLOC, the δ_C/δ_H correlations were obtained from hetero-COSY (J^1). Hetero-COSY and COLOC (aromatic region) data were recorded in Bruker AM 300 and AC 80, respectively.

alkaline conditions suggested the presence of phenolic functions. Its ^{1}H-nmr spectrum showed an AA′BB′ system at δ 7.05 and 6.68 (J_{AB}=8.5 Hz) and an AB system at δ 6.99 and 6.72 (J_{AB}=8.4 Hz), characteristic for a 7,8,12-trioxygenated BZTHISQ (2). Other assignable signals included a broad doublet at δ 5.03 (J=4.5 Hz, H-1), an MeO singlet at δ 3.86 and two *N*-Me singlets at δ 3.14 and 3.04. The location of the MeO function was assigned to C-7 based on an nOe's, which enhanced the doublet at δ 6.99 (H-6) upon irradiation of the MeO signal. These data and the levorotatory property showed **3** to be (−)-oblongine (5–8).

Compound **4**, an amorphous solid isolated as the perchlorate salt, $[\alpha]^{24}D$ −12.0° (c=1.0, MeOH), gave in its eims spectrum $[M-HClO_4]^+$ *m/z* 327, 14 amu more than **3**. The ^{1}H-nmr spectrum of **4** was very similar to that of **3** except for the presence of an additional MeO singlet at δ 3.82. The mass and ^{1}H-nmr data suggested **4** to be *O*-methyloblongine or its isomer. The two MeO groups were located at C-7 and C-8 as shown by two nOe experiments. Upon irradiation of the C-7 MeO singlet at δ 3.86, a doublet at δ 7.13 (d, J=8.5 Hz, H-6) was enhanced; whereas irradiation of the 8-MeO singlet at δ 3.82 gave no enhanced signals. Further evidence for this structure was supported by the major mass fragment ion **D** (*m/z* 206). These data, along with the levorotatory property, established **4** as (−)-8-*O*-methyloblongine. To our knowledge, this is the first natural occurrence of this compound. Its physical data, except for the optical property, were identical to those reported for the synthetic racemate (6).

The ^{13}C-nmr spectra of compound **3** and **4**, which had not previously been assigned, were assigned by correlation with a model compound, juziphine [**6**], which is the corresponding tertiary base of **3** (9), and with the quaternary effect on ^{13}C nmr deduced from pavine alkaloids (10). These assigned data are listed in Table 1.

Compound **5**, an amorphous solid isolated as the perchlorate salt, $[\alpha]^{26}D$ +66.0° (c=1.0, MeOH), showed in its ^{1}H-nmr spectrum (CD_3OD) two singlets at δ 7.94 (H-11) and 6.84 (H-3 and H-8) for a 1,2,9,10-tetraoxygenated aporphine (2c). These data and other proton signals [δ 3.89 and 3.85 (s, 2- and 10-OMe), 3.68 (s, 1-OMe), 3.39 (s, *N*-Me_{eq}) and 3.06 (s, *N*-Me_{ax})] and the dextrorotatory property showed **5** to be (+)-xanthoplanine (11).

Two species of the *Cryptocarya* genus, i.e., *C. konishii* and *Cryptocarya chinensis*, are found in Taiwan. This study and previous studies reveal that alkaloids in *C. konishii* belong exclusively to the benzylisoquinoline type, while those of *C. chinensis* belong predominately to the pavine type (10,12). Hence, from a chemotaxonomic point of view both plants should not be classified into the same genus. In addition, the quaternary alkaloids, (−)-oblongine [**3**] and (−)-8-*O*-methyloblongine [**4**], were isolated from the family Lauraceae for the first time. This may be of some future value for chemotaxonomy.

EXPERIMENTAL

INSTRUMENTAL.—JASCO DIP-181 Digital Polarimeter; Perkin Elmer 1760-X Infrared FT Spectrometer; Hitachi 150-20 spectrophotometer; JASCO Model J-700 spectropolarimeter; Finnigan Mat 4500 series GC/MS and JEOL JMS-HX 110 spectrometer; Bruker AC-80 and Am-300 spectrometers for ^{1}H nmr and ^{13}C nmr in CD_3OD or Me_2CO-d_6 using solvent peaks as reference standard. 2D Nmr spectra were recorded by using Bruker's standard pulse program. In the hetero-COSY and COLOC experiment, Δ= 1 sec and J=125 Hz and 8 Hz, respectively, the correlation maps consisted of 256×1K data points per spectrum, each composed of 320 transients.

EXTRACTION AND ISOLATION.—The stems of *C. konishii* were collected in May 1988 in Henchung, Pingtung County, Taiwan. A specimen was authenticated by Mr. Fong-Gee Her, Taiwan Forest Research Institute. The stems of *L. cubeba* were collected in January 1991 in Wu-Tai, Pingtung County, Taiwan. A specimen was authenticated by Dr. Ih-Sheng Chen, School of Pharmacy, Kaohsiung Medical College. Both herbarium specimens are deposited at the School of Pharmacy, National Taiwan University. The powdered dry stem bark (0.90 kg) of *C. konishii* was percolated with 95% EtOH (5 liters×3). Concentration of the

EtOH extract afforded a residue (73.47 g) which was partitioned between H_2O (300 ml) and $CHCl_3$ (300 ml×3). The aqueous layer was treated with saturated aqueous $NaClO_4$ to give crude quaternary alkaloids (ClO_4^- salt, 23.16 g). The precipitate dissolved in MeOH was divided equally into three parts, and the solution was passed through a Sephadex LH-20 column (800 ml) eluted with MeOH to give two alkaloidal fractions, A (3.50 g) and B (0.82 g). Repeated Sephadex chromatography of fraction A with MeOH yielded compound **1** (268 mg).

The dried powdered stems (8.50 kg) of *L. cubeba* were extracted with 95% EtOH (35 liters×3). Concentration of the EtOH extract afforded a residue (326.00 g) which after the usual treatment yielded crude total free alkaloids (20.36 g) and crude quaternary alkaloids (Cl^- salt, 6.80 g) (13).

The crude quaternary alkaloids (6.60 g) were fractionated with Sanki cpc (LLN type, 1000E cartridge, flow rate 6 ml/min, 1300 rpm, pressure 28 kg/cm^2, 22°, 15-ml fraction), using the organic and aqueous layers of the solvent system [$CHCl_3$-MeOH-0.5% aqueous HOAc (2:2:1)] as stationary and mobile phases, respectively. This reversed-partition chromatography yielded four fractions, I (2.63 g), II (1.76 g), III (0.60 g), and IV (0.10 g), which were combined after Si gel tlc analysis using the above stationary phase and HOAc (94:6).

Fraction II (1.76 g) was further purified via a Sephadex LH-20 column (300 ml) eluted with MeOH to give (−)-magnocurarine [**2**] (600 mg).

Fraction III (0.60 g) was fractionated with the same Sephadex LH-20 column eluted with MeOH to give fractions A (0.31 g) and B (0.27 g). Fraction A (0.31 g), containing at least four compounds, was separated repeatedly with a Lobar RP-18 (10 mm×240 mm) column eluted with MeOH-0.1 M $HClO_{4(aq)}$ (13:27) to give four fractions, 1–4. After removal of MeOH by rotatory evaporation, the solution of perchloric acid was neutralized with Na_2CO_3, and the neutral solution was then passed through an Amberlite XAD-2 column, eluting with H_2O to remove inorganic salt ($NaClO_4$), and subsequently with MeOH to recover the separated quaternary alkaloids. By such treatment, fraction 1 yielded **2** (27 mg), fraction 3 yielded (−)-oblongine [**3**] (49 mg), and fraction 4 yielded (−)-8-*O*-methyloblongine [**4**] (6.5 mg). Fraction B (0.27 g) was purified via dccc, using the aqueous layer of the solvent system [$CHCl_3$-MeOH-5% aqueous HOAc (2:2:1)] as mobile phase to give (+)-xanthoplanine [**5**] (22 mg), which was converted to the perchlorate precipitate by adding saturated $NaClO_4$ to the aqueous solution of **5**.

(+)-(1R,1aR)-1a-Hydroxymagnocurarine perchlorate [**1**].—Amorphous solid: $[\alpha]^{24.5}D$ +35° (c=0.50, MeOH); mp 142° ir ν max (KBr) 3405 (br s), 2962 (m), 2926 (m), 1614 (m), 1516 (s), 1450 (m), 1370 (w), 1263 (s), 1240 (m), 1114 (m), 1045 (m), 839 (w) cm^{-1}; uv λ max (MeOH) (log ϵ) 283 (3.99), 228 (4.48) nm, λ max (MeOH+KOH) (log ϵ) 299 (4.10), 250 (4.48) nm; cd (MeOH) $[\theta]_{289.4}$ +9960°, $[\theta]_{235.3}$ +41,200°; hreims *m/z* $[M-HClO_4]^+$ 329.1626 (calcd for $C_{19}H_{23}NO_4$, 329.1628); eims *m/z* (rel. int. %) $[M-HClO_4]^+$ 329 (27), [**A**] 192 (69), 177 (24), [**B**] 122 (43), 121 (55), 107 (15), 93 (26), 77 (14), [**C**]$^+$ 58 (100); ^{1}H nmr see Figure 1; ^{13}C nmr see Table 1.

(−)-Magnocurarine perchlorate [**2**].—Prism crystals: mp 296.5° (MeOH); $[\alpha]^{24}D$ −146.0° (c=1.0, MeOH); ir ν max (KBr) 3400 (br m), 1614 (m), 1516 (s), 1448 (m), 1265 (m), 1243 (m), 1224 (m), 1146 (s), 1118 (s), 1087 (s), 834 (m) cm^{-1}; uv λ max (MeOH) (log ϵ) 284 (3.77), 227 (4.25) nm; eims *m/z* (rel. int. %) $[M-HClO_4]^+$ 313 (4), 206 (2), [**B**], 192 (8), 177 (1), [**C**] 58 (100); ^{1}H nmr δ (CD_3OD) 6.85 (d, J=8.8 Hz, H-10, -14), 6.68 (d, J=8.8 Hz, H-11, -13), 6.80 (s, H-5), 5.89 (s, H-8), 4.54 (dd, J=3.8, 8.8 Hz, H-1), 3.83 (s, 6-OMe), 3.38 (s, *N*-Me$_{eq}$), 3.11 (s, *N*-Me$_{ax}$); ^{13}C nmr δ (CD_3OD) 74.33 (d, C-1), 38.44 (t, C-1a), 52.87 (q, 2-Me$_{eq}$), 51.72 (q, 2-Me$_{ax}$), 56.12 (t, C-3), 24.26 (t, C-4), 120.61 (s, C-4a), 112.56 (d, C-5), 149.78 (s, C-6), 146.22 (s, C-7), 116.39 (d, C-8), 123.90 (s, C-8a), 127.15 (s, C-9), 132.09 (d, C-10, -14), 116.57 (d, C-11, -13), 157.83 (s, C-12), 56.51 (q, 6-OMe).

(−)-Oblongine perchlorate [**3**].—Amorphous solid: $[\alpha]^{24}D$ −11.0° (c=1.0, MeOH); mp 109.5°; ir ν max (KBr) 3401 (br s), 1616 (m), 1517 (m), 1504 (m), 1457 (m), 1289 (m), 1250(m), 1147 (m), 1121 (s), 1090 (s), 817 (w) cm^{-1}; uv λ max (MeOH) (log ϵ) 280 (3.71), 227 (4.19) nm, λ max (MeOH+KOH) (log ϵ) 294 (3.80), 246 (4.05) nm; cd (MeOH) $[\theta]_{299}$ +0°, $[\theta]_{287}$ +1240°, $[\theta]_{267}$ +0°, $[\theta]_{238}$ +3460°; eims (30 eV) *m/z* (rel. int. %) $[M-HClO_4]^+$ 313 (3), [**C**] 58 (100); ^{1}H nmr δ (CD_3OD) 7.05 (d, J=8.5 Hz, H-10, -14), 6.99 (d, J=8.4 Hz H-6), 6.72 (d, J=8.4 Hz, H-5), 6.68 (d, J=8.5 Hz, H-11, -13), 5.03 (br d, J=4.5 Hz, H-1), 3.86 (s, 7-OMe), 3.14 (s, *N*-Me$_{eq}$), 3.04 (s, *N*-Me$_{ax}$); ^{13}C nmr see Table 1.

(−)-8-O-Methyloblongine perchlorate [**4**].—Amorphous solid: $[\alpha]^{24}D$ −12.0° (c=1.0 MeOH); mp 102°; ir ν max (KBr) 3431 (br m), 1616 (m), 1518 (m), 1499 (m), 1458 (m), 1286 (m), 1144 (m), 1121 (s), 1090 (s), 818 (w) cm^{-1}; uv λ max (MeOH) (log ϵ) 280 (3.68), 227 (4.18) nm, λ max (MeOH+KOH) (log ϵ) 285 (3.71), 244 (s, 4.06), 228 (s, 4.17) nm; cd (MeOH) $[\theta]_{300}$ +0°, $[\theta]_{288}$ +1940°, $[\theta]_{266}$ +30°, $[\theta]_{240}$ +6690°, $[\theta]_{226}$ −3610°, eims (30 eV) *m/z* (rel. int %) $[M-HClO_4]^+$ 327 (3), [**D**] 206 (10), [**C**]$^+$ 58 (100); ^{1}H nmr δ (CD_3OD) 7.13 (d, J=8.5 Hz, H-6), 6.97 (d, J=8.5 Hz, H-5), 6.92 (d, J=8.5 Hz, H-10, -14), 6.67 (d, J=8.5 Hz, H-11, -13), 5.01 (t, J=5.1 Hz, H-1), 3.86 (s, 7-OMe), 3.82 (s, 8-OMe), 3.20 (s, *N*-Me$_{eq}$), 3.03 (s, *N*-Me$_{ax}$); ^{13}C nmr see Table 1.

Xanthoplanine perchlorate [**5**].—Amorphous solid: $[\alpha]^{26}D$ +65.0° (*c*=1.0, MeOH); mp 144°; ir ν max (KBr) 3400 (br m), 1588 (m), 1517 (m), 1480 (m), 1472 (m), 1464 (m), 1457 (m), 1370 (w), 1280 (m), 1248 (m), 1122 (s), 1104 (s), 1092 (s), 1038 (m), 770 (w) cm^{-1}; uv λ max (MeOH (log ϵ) 304 (4.18), 283 (4.15), 221 (4.56) nm, λ max (MeOH+KOH) (log ϵ) 333 (4.28) nm; ^1H nmr δ (CD_3OD) 7.94 (s, H-11), 6.84 (s, H-3 and H-8), 3.89 (s, 2-OMe), 3.85 (s, 10-OMe), 3.68 (s, 1-OMe), 3.39 (s, *N*-Me_{eq}) and 3.06 (s, *N*-Me_{ax}); δ (Me_2CO-d_6) 7.93 (s, H-11), 6.91 (s, H-3), 6.86 (s, H-8), 4.58 (dd, *J*=3.4, 13.4 Hz, H-6a), 3.88 (s, 2-OMe), 3.83 (s, 10-OMe), 3.70 (s, 1-OMe), 3.58 (s, *N*-Me_{eq}) and 3.20 (s, *N*-Me_{ax}).

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