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Syntheses of (±)-Romucosine and (±)-Cathafiline

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Abstract

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The structures previously assigned to (-)-romucosine and (+)-cathafiline, *N*-(methoxycarbonyl) aporphine alkaloids from *Rollina mucosa* (Annonaceae) and *Cassytha filiformis* (Lauraceae) respectively, have been confirmed by total syntheses of the racemic substances. The key step of the syntheses involved formation of ring C of the aporphines by a radical-initiated cyclisation.

Key words : *N*-(methoxycarbonyl)aporphine alkaloids, (±)-romucosine, (±)-cathafiline, radical-initiated cyclisation

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บทคัดย่อ

สุรชัย นิมจิรวัฒน์
การสังเคราะห์ (±)-Romucosine และ (±)-Cathafiline
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โครงสร้างของ (-)-romucosine และ (+)-cathafiline ซึ่งเป็นอัลคาลอยด์ประเภท *N*-(methoxycarbonyl)aporphine จาก *Rollina mucosa* (Annonaceae) และ *Cassytha filiformis* (Lauraceae) ตามลำดับได้รับการยืนยันว่าถูกต้องโดยการสังเคราะห์ (±)-romucosine และ (±)-cathafiline ขั้นตอนสำคัญของการสังเคราะห์คือ การปิดวงแหวนโดยอาศัยปฏิกิริยาของอนุมูลอิสระ

ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยศิลปากร วิทยาเขตพระราชวังสนามจันทร์ อำเภอเมือง จังหวัดนครปฐม 73000

The *N*-(methoxycarbonyl)aporphine alkaloids form a small subgroup in the family of aporphine alkaloids. Of particular interests are alkaloids in the romucosine series which comprises romucosine (**1a**) (Chen, Chang and Wu, 1996), romucosines A-E (Kuo *et al*., 2001), romucosines F and G (Chang *et al*., 2000), and romucosine H (Chen *et al*., 2001). Romucosines A-E have been evaluated for antiplatelet aggregation induced by thrombin, arachidonic acid, collagen, and platelet-activating factor. It was found that *N*-(methoxycarbonyl)aporphines possess a higher selectivity to arachidonic-induced platelet aggregation than the parent aporphines (Kuo *et al*., 2001).

Cathafiline (**1c**) is another *N*-(methoxycarbonyl)aporphine alkaloid found in *Cassytha filiformis* (Lauraceae) (Wu *et al*., 1997). Due to the minute quantities of these alkaloids found in nature, it is therefore of interest to synthesize these alkaloids for evaluation of their biological activities. We have now completed total syntheses of (±)-romucosine (**1a**) and (±)-cathafiline (**1c**), the details of which are described in this paper.

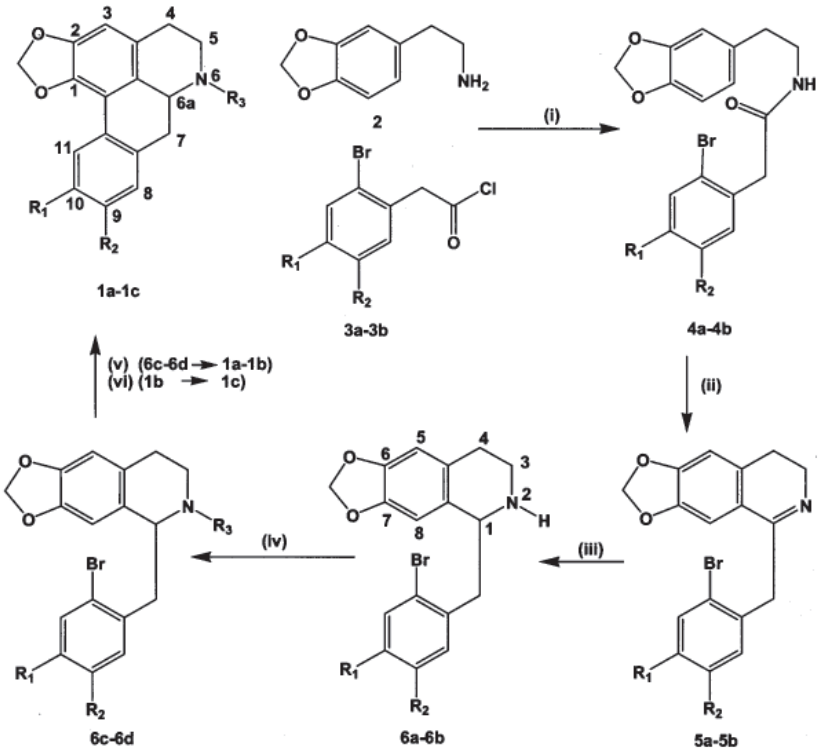
Results and discussion

(±)-Romucosine (1a)

The strategy employed in the present synthesis was based on the construction of ring C of (±)-romucosine (**1a**) by a radical-initiated cyclisation first described by Castedo *et al* (Estevez *et al*., 1994). For this purpose, amide (**4a**) was obtained in good yield on treatment of homopiperonylamine (**2**) with 2-bromophenylacetyl chloride (**3a**). Amide (**4a**) was converted into dihydroisoquinoline (**5a**) by a Bischler-Napieralski reaction. Reduction of (**5a**) with sodium borohydride gave (**6a**) which was treated with methyl chloroformate to give carbamate (**6c**). Carbamate (**6c**) exhibited the phenomenon of hindered rotation around the amide bond as expected of acylated 1-benzyltetrahydroisoquinolines (Nimgirawath and Podoy, 2000). Thus the proton *ortho* to the bromine group in the benzyl substituent gave rise to two distinct doublets at δ 7.52 (J = 8.1 Hz) and δ 7.56 (J = 7.8 Hz) with a total integration of one proton. Each of the aromatic protons on ring A also gave rise to 2 distinct singlets (δ 6.76 and 6.56 for one proton and δ 6.59 and 6.51 for the other). The methylenedioxy protons also appeared as multiplets due to overlap of signals from the two conformers. Most notably, the CH_3 protons of the methoxycarbonyl group gave rise to two distinct singlets at δ 3.18 and 3.58 with a total integration of three protons. Treatment of carbamate (**6c**) with tributyltin hydride and azobis(isobutyronitrile) afforded (±)-romucosine (**1a**) in 27 % yield. The ^{1}H- and ^{13}C-NMR spectra data of the synthetic (±)-romucosine (**1a**) were identical in all respects with those of natural (-)-romucosine (Chen, Chang and Wu, 1996).

(±)-Cathafiline(1c)

The synthesis of (±)-cathafiline (**1c**) was



Synthetic x cheme. Reagents and conditions: (i) 5% $NaHCO_3$, (ii) $POCl_3$, (iii) $NaBH_4$, (iv) $MeOCOCl/(Et)_3N$, (v) $Bw_3SwH/AlBN$, (vi) H_2/10% Pd/C.

	R_1	R_2	R_3
1a	H	H	$COOCH_3$
1b	OCH_3	OCH_2Ph	$COOCH_3$
1c	OCH_3	OH	$COOCH_3$
3a	H	H	
3b	OCH_3	OCH_2Ph	
4a	H	H	
4b	OCH_3	OCH_2Ph	
5a	H	H	
5b	OCH_3	OCH_2Ph	
6a	H	H	H
6b	OCH_3	OCH_2Ph	H
6c	H	H	$COOCH_3$
6d	OCH_3	OCH_2Ph	$COOCH_3$

achieved in the same manner as that employed for (±)-romucosine (**1a**). Thus amine (**2**) and acid chloride (**3b**) gave amide (**4b**) which was converted into dihydroisoquinoline (**5b**). Reduction of **5b** with sodium borohydride gave **6b** which was converted into **6d**. Carbamate (**6d**) also exhibited the phenomenon of hindered rotation around the amide bond as expected of acylated 1-benzyl-tetrahydroisoquinolines (Nimgirawath and Podoy, 2000). Thus, the aromatic protons on rings A and D gave rise to 8 distinct singlets at δ 7.04, 7.00, 6.61, 6.60, 6.58, 6.55, 6.53 and 6.43 with a total

integration of four protons while the CH_3 protons of the methoxycarbonyl group gave rise to two distinct singlets at δ 3.63 and δ 3.36 with a total integration of three protons. Treatment of carbamate (**6d**) with tributyltin hydride and azobis (isobutyronitrile) afforded aporphine (**1b**) in 30% yield. The structure of aporphine (**1b**) was supported by ^{1}H-NMR data in which the two protons of the methylenedioxy group gave rise to two sets of doublets with a coupling constant of 1.2 Hz, characteristic of aporphine alkaloids bearing a methylenedioxy group on positions 1 and 2 (Nimgirawath and Podoy, 2000). In addition, the two protons of the benzyloxy group were found to be non-equivalent. These gave rise to an AB quartet with a coupling constant of 12.3 Hz. In view of the distance of the benzyloxy group from the A/D ring junction, such non-equivalence of these protons is rather unexpected. Finally, the benzyl protecting group was removed by catalytic hydrogenolysis at 45-50 psi to afford (±)-cathafiline (**1c**), the ^{1}H- and ^{13}C-NMR spectral data of which were identical in all respects with those of natural (±)-cathafiline (Wu *et al*., 1997).

Experimental

Melting points were determined on a Stuart MP-2 apparatus and are uncorrected. Ultraviolet spectra were recorded on methanol solutions with a Jasco V-530 UV-VIS spectrophotometer. Infrared spectra were recorded on Nujol mulls with a Perkin-Elmer Spectrum GX FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on (D) chloroform solutions at 300 MHz for ^{1}H and 75 MHz for ^{13}C with a Bruker AVANCE 300 spectrometer. Tetramethylsilane was used as the internal standard. Mass spectra were run on a Hewlett Packard 5989B spectrometer. Elemental microanalyses were performed with a Perkin-Elmer 2400 elemental analyser.

N-[2-(3,4-Methylenedioxyphenyl)ethyl]-2-bromophenylacetamide (4a)

A solution of 2-bromophenylacetic acid (9.1 g, 42.3 mmol) and thionyl chloride (12.7 g, 106.7 mmol) in benzene (50 ml) was refluxed for 1 h and the benzene and excess thionyl chloride were removed under vacuum to give the crude acid chloride (3a). This was dissolved in ethanol-free chloroform (60 ml) and added portionwise to a vigorously stirred mixture of homopiperonylamine (7.0 g, 42.4 mmol) (Nimgirawath and Taylor, 1983), ethanol-free chloroform (100 ml) and 5% sodium hydrogen carbonate (100 ml) under ice cooling. The mixture was stirred at room temperature for 5 h. The chloroform layer was washed with 3 M HCl (2x50 ml), water (100 ml), 5% $NaHCO_3$ (100 ml), water and brine, then dried over anhydrous sodium sulfate. Removal of the solvent gave a pale brown solid which was recrystallized from ethanol to give colourless needles (13.0 g, 84.6%), m.p.129-130ºC (lit. m.p. 128-130ºC). ^{1}H -NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 7.8 Hz, ArH), 7.31-7.27 (2H, m, ArH), 7.19-7.12 (1H, m, ArH), 6.65 (1H, d, *J* = 7.8 Hz, ArH), 6.56 (1H, d, *J* = 1.8 Hg, ArH), 6.48 (1H, dd, *J* = 7.8,1.8 Hz, ArH), 5.92 (2H, s, OCH_2O), 5.43 (1H, br s, NH), 3.67 (2H, s, $ArCH_2CO$), 3.42 (2H, apparent q, *J* = 6.6 Hz, CH_2N), 2.66 (2H, t, *J* = 6.6 Hz, $ArCH_2$). ^{13}C -NMR ($CDCl_3$) δ 169.4, 147.7, 146.1, 134.8, 133.1, 132.3, 131.7, 129.1, 128.0, 125.0, 121.6, 109.0, 108.3, 100.9, 44.1, 40.9, 35.2.

2-(3-Benzyloxy-6-bromo-4-methoxyphenyl)-*N*-(3,4-methylenedioxyphenethyl)acetamide (4b)

Amide (**4b**) was obtained in a similar manner as colourless prisms in 88.0% yield, m.p. 138-140ºC (lit. m.p. 138-140ºC (Kametani and Noguchi, 1969)). ^{1}H-NMR ($CDCl_3$) δ 7.45-7.29 (5H, m, PhH), 7.03 (1H, s, ArH), 6.79 (1H, s, ArH), 6.65 (1H, d, *J* = 7.8 Hz, ArH), 6.52 (1H, d, *J* = 1.5 Hz, ArH), 6.47 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 5.89 (2H, s, OCH_2O), 5.36 (1H, m, NH), 5.08 (2H, s, $PhCH_2$), 3.88 (3H, s, OCH_3), 3.53 (2H, s, $ArCH_2$), 3.38 (2H, apparent q, *J* = 6.6 Hz, CH_2N), 2.62 (2H, t, *J* = 6.7 Hz, $ArCH_2$). ^{13}C-NMR ($CDCl_3$) δ 169.7, 149.7, 147.7, 146.1, 136.3, 132.3, 128.6, 128.1, 127.4, 126.4, 121.6, 116.3, 116.1, 115.4, 109.0, 108.3, 100.9, 71.1, 56.2, 43.6, 40.7, 35.1.

1-(2-Bromobenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (5a)

This compound was obtained in 90% yield by the literature method (Nimgirawath and Taylor, 1983), m.p. 121-123ºC. (lit. m.p. 121-123ºC). ^{1}H-NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 8.1 Hz, ArH), 7.23-7.17 (2H , m, ArH), 7.10-7.04 (1H , m, ArH), 6.90 (1H , s, ArH), 6.65 (1H , s, ArH), 5.92 (2H , s, OCH_2O), 4.10 (2H , s, Ar CH_2C=N), 3.68 (2H , t, *J* = 7.8 Hz, CH_2N), 2.64 (2H, t, *J* = 7.8 Hz, $ArCH_2$). ^{13}C -NMR ($CDCl_3$) δ 164.5, 148.9, 146.4, 137.6, 133.4, 132.8, 130.2, 128.1, 127.5, 124.8, 122.9, 107.9, 106.0, 101.2, 47.3, 42.7, 26.4.

Methyl 1-(2-bromobenzyl)-6,7-methyleledioxy-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (6c)

Sodium borohydride (2.6 g, 68.8 mmol) was added portionwise to a stirred solution of the dihydroisoquinoline (**5a**) (7.0 g, 21.2 mmol), in ethanol (200 ml) and the mixture was stirred at room temperature for 5 h. The solvent was removed under vacuum and the residue shaken with chloroform (160 ml) and water (160 ml). The chloroform layer was washed with brine, then dried. Removal of the solvent gave the tetrahydroisoquinoline (**6a**) as a pale yellow oil (6.6 g, 93.7%) which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ 7.58 (1H, d, *J* = 7.8 Hz, ArH), 7.32-7.24 (2H, m, ArH), 7.18-7.07 (1H , m, ArH), 6.83 (1H ,s, ArH), 6.57 (1H ,s, ArH), 5.90 (2H, s, OCH_2O),4.22 (1H, dd, *J* = 10.5, 2.7 Hz, CHN), 3.38-3.17 (2H, m, CH_2), 3.00-2.85 (2H, m, CH_2), 2.80-2.60 (2H, m, $ArCH_2$). ^{13}C-NMR (CDCl3) δ 145.9, 145.7, 138.7, 133.1, 131.9, 131.7, 128.2, 127.4,124.9, 108.8, 106.5, 100.6, 55.2, 43.0, 39.9, 30.0.

Methyl chloroformate (11.3 g, 119.6 mmol) was added portionwise to a stirred mixture of the tetrahydroisoquinoline (**6a**) (6.6 g, 19.9 mmol) and triethylamine (16.0 g, 158.4 mmol) in chloroform (100 ml) at 0-5ºC. Stirring was continued at room temperature for 3 h. Water (100 ml) and chloroform (100 ml) were added and the chloroform layer was washed with brine, then dried. Removal of the solvent gave a viscous residue (6.9 g) which crystallized from ethanol as pale yellow prisms (5.5 g, 71.4%), m.p. 129-130ºC. *Anal.Calcd* for $C_{19}H_{18}BrNO_4$: C, 56.5; H, 4.5; N, 3.5%. Found: C, 56.6; H, 4.3; N, 3.6%. UV (MeOH) λ_{max}/nm (log ε) 239 (3.87), 291 (3.80). IR(Nujol) ν_{max}/cm^{-1} 1695, 1509, 1485, 1415, 1340, 1320, 1260, 1244, 1216, 1112, 1066, 1041, 1027, 1011, 975, 944, 925, 866, 847, 832, 794, 762, 752, 722. ^{1}H-NMR ($CDCl_3$) δ 7.56 and 7.52 (total 1H, 2 d, J = 8.1, 7.8 Hz, ArH of both conformers), 7.28-7.02 (3H, m, ArH), 6.76 and 6.56 (total 1H, 2 s, ArH of both conformers), 6.59 and 6.51 (total 1H, 2 s, ArH of both conformers), 5.99-5.87 (2H, m, OCH_2O), 5.46-5.32 and 4.34-4.22 (total 1H, 2 m, CHN), 3.58 and 3.17 (total 3H, 2 s, $COOCH_3$ of both conformers), 3.52-2.60 (6H, m, CH_2). ^{13}C-NMR ($CDCl_3$) δ 155.8, 146.5, 146.1, 137.7, 137.6, 132.6, 132.4, 131.6, 131.5, 129.6, 129.5, 128.2, 127.4, 127.3, 127.0, 125.1, 108.6, 108.3, 107.3, 106.8, 100.9, 100.8, 55.0, 54.1, 52.6, 52.1, 42.8, 42.0, 38.7, 37.3, 28.6. EIMS (70 eV) *m*/*z* (rel.int.): 234 (100), 174 (8), 89(19).

1-(3-Benzyloxy-6-bromo-4-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (6b)

Dihydroisoquinoline (**5b**) was obtained in the usual manner as a brown viscous liquid in 84% yield which was used in the next step without further purification.

Tetrahydroisoquinoline (**6b**) was obtained in the usual manner as colourless prisms in 89.4% yield, m.p. 70-72ºC. *Anal. Calcd* for $C_{25}H_{24}BrNO_4$: C, 62.3; H, 5.0; N, 2.9%. Found: C, 62.1; H, 5.2; N, 2.7%. UV (MeOH) λ_{max}/nm (log δ) 226 (4.25), 288 (3.93). IR(Nujol) ν_{max}/cm^{-1} 1599, 1505, 1257, 1214, 1163, 1036, 934, 861, 814. ^{1}H -NMR ($CDCl_3$) δ 7.45-7.27 (5H, m, PhH), 7.07 (1H, s, ArH), 6.77 (1H, s, ArH), 6.74 (1H, s, ArH), 5.89 (2H, s, OCH_2O), 5.12 (2H, AB q, *J* = 12.6 Hz, $PhCH_2$), 4.12 (1H, dd, *J* = 10.2, 3.6 Hz, H1), 3.87 (3H, s, OCH_3), 3.24-3.05 (2H, m, CH_2), 2.86-2.67 (4H, m, 2 CH_2). ^{13}C-NMR ($CDCl_3$) δ 149.1, 147.1, 146.0, 145.8, 136.7, 131.1, 130.1, 128.6, 128.0, 127.3, 117.3, 116.3, 115.3, 108.8, 106.5, 101.7, 71.1, 56.3, 55.4, 42.2, 39.8, 29.6.

Methyl 1-(3-Benzyloxy-6-bromo-4-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline -2-carboxylate (6d)

Carbamate (**6d**) was obtained in the usual manner as pale yellow prisms in 82.7% yield, m.p. 109-110ºC. *Anal.Calcd* for $C_{27}H_{26}$ Br NO_6 : C, 60.0; H, 4.9; N, 2.6%. Found: C, 60.2; H, 4.7; N, 2.8%. UV (MeOH) λ_{max}/nm (log δ) 239.0 (4.08), 289.5 (3.85). IR (Nujol) ν_{max}/cm^{-1} 1687, 1413, 1338, 1315, 1281, 1272, 1253, 1241, 1221, 1208, 1190, 1160, 1138, 1111, 1066, 1041, 1007, 975, 954, 924. ^{1}H-NMR ($CDCl_3$) δ 7.50-7.28 (5H, m, PhH), 7.04 and 7.00 (total 1H, 2 s, ArH of both conformers), 6.61 6.60, 6.58, 6.55, 6.53 and 6.43 (total 3H, 6 s, 3 ArH of both conformers), 5.96 and 5.89 (total 2H, 2 s, OCH_2O of both conformers), 5.36-5.28 and 5.26-5.18 (total 1H, 2 m, H1 of both conformers), 5.10-4.98 (total 2H, m, $PhCH_2$ of both conformers), 4.18-4.08 and 3.83-3.65 (total 1H, 2 m, CH of both conformers), 3.86 and 3.85 (total 3H, 2 s, OCH_3 of both conformers), 3.63 and 3.36 (total 3H, 2 s, $COOCH_3$ of both conformers), 3.35-2.52 (5H, m, CH, 2 CH_2). ^{13}C-NMR ($CDCl_3$) δ 155.9, 155.8, 149.0, 148.9, 147.4, 147.2, 146.5, 146.4, 146.0, 145.9, 136.9, 129.6, 129.5, 129.4, 129.3, 128.6, 128.0, 127.6, 127.3, 127.2, 117.1, 116.7, 115.9, 115.8, 115.7, 115.6, 108.5, 108.3, 107.4, 107.0, 100.9, 100.8, 71.6, 71.3, 56.3, 56.1, 55.1, 54.7, 52.6, 52.3, 42.1, 41.4, 38.8, 37.7, 28.5.

(±)-Romucosine (1a)

A solution of azobis(isobutyronitrile) (1.9 g, 11.6 mmol) and tributyltin hydride (7.2 g, 24.7 mmol) in toluene (100 ml) was added over 3.5 h to a refluxing solution of the carbamate (**6c**) (5.1 g, 13.1 mmol) in toluene (130 ml) under nitrogen. The resulting mixture was then refluxed for 24 h. The solvent was removed under vacuum and the residue was dissolved in acetonitrile (100 ml) and washed with hexane (3x200 ml), then dried. Removal of the solvent under vacuum gave a viscous residue which crystallized from benzene to give (±)-romucosine (**1a**) as colourless prism (1.1 g, 27.0%), m.p. 186-187ºC. *Anal.Calcd* for $C_{19}H_{17}$ N O_4: C, 70.6; H, 5.3; N, 4.3%. Found: C, 70.4, H, 5.5; N, 4.5%. UV (MeOH) λ_{max}/ nm (log ε) 235 (4.29), 273 (4.28), 293 (3.98), 325 (3.59). IR (Nujol) ν_{max}/cm^{-1} 1698, 1409, 1342, 1298, 1271, 1252, 1219, 1205, 1162, 1120, 1072, 1048, 996, 977, 960, 938, 862, 826, 796, 770, 738, 729. ^{1}H-NMR ($CDCl_3$) δ 8.11 (1H, d, *J* = 7.6 Hz, H11), 7.38-7.24 (2H, m, H9 and H10), 6.59 (1H, s, H3), 6.10 and 5.97 (each 1H, 2 d, *J* = 1.5 Hz, OCH_2O), 4.53-4.32 (1H, m, H5α), 3.77 (3H, s, $COOCH_3$), 3.15-2.74 (4H, m, H4α, H7β, H5β and H7α), 2.68-2.56 (1H, m, H4β). ^{13}C -NMR ($CDCl_3$, 75 Hz) β 155.9, 146.8, 143.0, 135.8, 130.7, 128.7, 128.0, 127.8, 127.1, 127.0, 125.6, 117.3, 107.6, 100.9, 52.7, 51.6, 39.1, 34.7, 30.3. EIMS (70 eV) *m*/*z* (rel.int.): 323[M]$^+$(98), 308(38), 292(4), 262(36), 248(31), 236(100), 235(96), 204(29), 178(59), 152 (18), 88(20).

Methyl 9-Benzyloxy-10-methoxy-1,2-methylenedioxynoraporphine-6-carboxylate (1b)

Noraporphine (**1b**) was obtained in the usual manner as pale brown prisms in 30% yield, m.p. 172-173ºC. *Anal.Calcd* for $C_{27}H_{25}N$ O_6: C, 70.6; H, 5.5; N, 3.1%. Found: C, 70.4, H, 5.7; N, 3.2%. UV (MeOH) λ_{max}/nm (log ε) 235.5 (4.40), 283.0 (4.16), 306.5 (4.22), 318.0 (4.15). IR (Nujol) ν_{max}/cm^{-1} 1699, 1604, 1576, 1521, 1408, 1392, 1366, 1339, 1322, 1285, 1265, 1246, 1228, 1205, 1119, 1098, 1076, 1051, 990, 950, 920, 893. ^{1}H-NMR ($CDCl_3$) δ 7.72 (1H, s, H11), 7.50-7.28 (5H, m, PhH), 6.82 (1H, s, ArH), 6.55 (1H, s, ArH), 6.02 (2H, AB q, *J* = 1.2 Hz, OCH_2O), 5.18 (2H, AB q, *J* = 12.3 Hz, $PhCH_2$), 4.87-4.76 (1H, m, H6a), 4.47-4.33 (1H, m, H5α), 3.93 (3H, s, OCH_3), 3.76 (3H, s, $COOCH_3$), 3.05-2.87 (2H, m, H5β and H7α), 2.87-2.70 (2H, m, H7β and H4α), 2.65-2.53 (1H, m, H4β). ^{13}C-NMR ($CDCl_3$) δ 155.8, 148.4, 147.9, 146.7, 142.2, 137.0, 128.7, 128.6, 128.3, 127.9, 127.3, 124.9, 123.7, 117.5, 114.2, 114.0, 111.4, 106.9, 100.8, 71.0, 56.3, 52.7, 52.0, 39.2, 34.2, 30.4.

(±)-Cathafiline (1c)

A solution of the noraporphine (**1b**) (0.8 g, 1.7 mmol) in ethanol (170 ml) was hydrogenolized in the presence of 10% Pd/C (0.4 g) at 45-50 psi for 7 h. The catalyst was filtered off and the solvent

removed under vacuum to give a viscous residue which crystallized from benzene-hexane to give (±)-cathafiline(1c) as pale brown prisms (0.36 g, 56.0%), m.p. 88-90ºC. *Anal.Calcd* for $C_{20}H_{19}NO_6$: C, 65.0; H, 5.2; N, 3.8%. Found: C, 65.2, H, 5.0; N, 3.6%.. UV (MeOH) λ_{max}/nm (log ε) 282 (4.02), 308 (4.10). IR (Nujol) ν_{max}/cm^{-1} 3275, 1695, 1611, 1582, 1519, 1404, 1361, 1330, 1273, 1241, 1223, 1196, 1116, 1098, 1071, 1051, 980, 957, 875, 821. ^{1}H-NMR ($CDCl_3$) δ 7.64 (1H, s, H11), 6.81 (1H, s, H8), 6.51 (1H, s, H3), 6.17 (1H, br s, OH), 6.05 and 5.93 (2H, 2 d, *J* = 1.2 Hz, OCH_2O), 4.80 (1H, m, H6a), 4.39 (1H, m, H5α), 3.90 (3H, s, OCH_3), 3.76 (3H, s, $COOCH_3$), 2.97 (2H, m, H5β and H7α), 2.80 (2H, m, H7β and H4α), 2.57 (1H, m, H4β). ^{13}C -NMR ($CDCl_3$, 75 Hz) β 156.0, 146.6, 145.5, 145.4, 142.0, 129.5, 127.8, 124.8, 122.6, 117.6, 114.8, 110.2, 106.7, 100.7, 56.1, 52.7, 51.9, 39.2, 33.5, 30.3.

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