ORIGINAL ARTICLE

# Syntheses of 3-*O*-Demethylthalicthuberine and *N*-Acetyl-*seco*-*N*-methyllaurotetanine

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## Abstract

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**Syntheses of 3-*O*-Demethylthalicthuberine and**
***N*-Acetyl-seco-*N*-methyllaurotetanine**
**Songklanakarin J. Sci. Technol., 2006, 28(6) : 1217-1226**

**The structures previously assigned to the phenanthrene alkaloids 3-*O*-demethylthalicthuberine and *N*-acetyl-*seco*-*N*-methyllaurotetanine have been confirmed by total syntheses in which the key step involved formation of ring C of the aporphine alkaloids (±)-isodomesticine and *O*-benzyl-*N*-methyllaurotetanine by a radical-initiated cyclization. Opening of ring B of (±)-isodomesticine with methyl chloroformate and subsequent reduction of the *N*-carbomethoxy group afforded 3-*O*-demethylthalicthuberine. Similarly, ring-B opening of *N*-methyllaurotetanine with acetyl bromide followed by hydrolysis afforded *N*-acetyl-*seco*-*N*-methyllaurotetanine.**

**Key words :** alkaloid, aporphine, phenanthrene, synthesis, radical cyclization

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**Received, 7 March 2006 Accepted, 9 April 2006**

## บทคัดย่อ

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**การสังเคราะห์ 3-*O*-Demethylthalicthuberine และ *N*-acetyl-*seco*-*N*-methyllaurotetanine**

**ว. สงขลานครินทร์ วทท. 2549 28(6) : 1217-1226**

**โครงสร้างของ phenanthrene alkaloid 3-*O*-demethylthalicthuberine และ *N*-acetyl-*seco*-*N*-methyllaurotetanine ได้รับการยืนยันความถูกต้องโดยการสังเคราะห์ซึ่งขั้นตอนสำคัญคือการสร้างวงแหวน C ของ aporphine alkaloid (±)-isodomesticine และ *O*-benzyl-*N*-methyllaurotetanine ด้วยปฏิกิริยาของอนุมูลอิสระ การเปิดวงแหวน B ของ (±)-isodomesticine ด้วย methyl chloroformate ตามด้วย reduction ของหมู่ *N*-carbomethoxy ให้ 3-*O*-demethylthalicthuberine ในทำนองเดียวกันการเปิดวงแหวน B ของ *N*-methyllaurotetanine ด้วย acetyl bromide ตามด้วย hydrolysis ให้ *N*-acetyl-*seco*-*N*-methyllaurotetanine**

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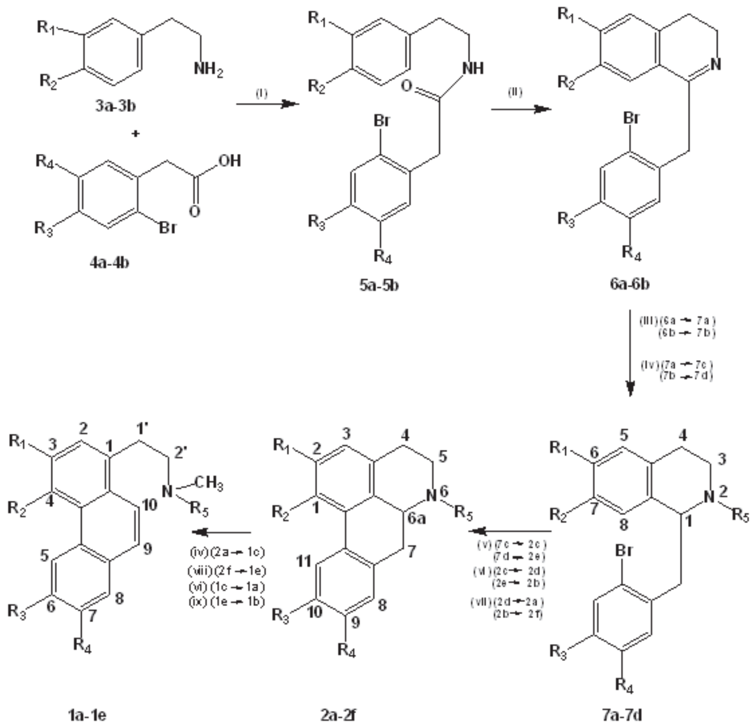
In the isoquinoline family of alkaloids, the phenanthrene alkaloids are a relatively small group whose members number fewer than twenty (Bentley, 1998). 3-*O*-Demethylthalicthuberine (**1a**) is a phenanthrene alkaloid found in *Ocotea insularis* (Lauraceae) (Hasbun and Castro, 1993). *N*-Acetyl-*seco*-*N*-methyllaurotetanine (**1b**), a new alkaloid found in the Malaysian plant *Aromadendron elegans* (Magnoliaceae) (Goh and Jantan, 1992) is unique, since it is the only phenanthrene alkaloid bearing an acetyl group on the nitrogen. In connection with our interest in the ring opening reactions of aporphine alkaloids as a tool for ready access to other alkaloids for biological activity evaluation, we decided to undertake total syntheses of 3-*O*-demethylthalicthuberine (**1a**) and *N*-acetyl-*seco*-*N*-methyllaurotetanine (**1b**) which are reported herein.

## Result and discussion

The strategy employed in the present synthesis was based on the construction of ring C of the aporphine alkaloids (±)-isodomesticine (**2a**) and *O*-benzyl-*N*-methyllaurotetanine (**2b**) by a radical-initiated cyclization first discovered by Castedo *et al.* (Estevez *et al.*, 1994). Opening of ring B of (±)-isodomesticine (**2a**) with methyl chloroformate should give phenanthrene **1c**. Subsequent reduction of the *N*-carbomethoxy group with concurrent loss of the *O*-carbomethoxy group in phenanthrene **1c** should then afford the desired 3-*O*-demethylthalicthuberine (**1a**). On the other hand, ring-B opening of **2b** with acetyl bromide should give the desired target **1b**. For this purpose, condensation of amine **3a** with bromoacetic acid **4a** gave amide **5a** while amine **3b** and acid **4b** afforded amide **5b**. Amides **5a** and **5b** were converted into dihydroisoquinolines **6a** and **6b**, respectively, by a Bischler-Napieralski reaction. Sodium borohydride reduction of **6a** and **6b** gave **7a** and **7b**, respectively. Treatment of **7a** and **7b** with methyl chloroformate gave carbamates **7c** and **7d** which exhibited the phenomenon of hindered rotation around the amide bond as expected for acylated 1-benzyltetrahydroisoquinolines (Nimgirawath and Podoy, 2000). For **7c**, the methoxy protons gave rise to 2 distinct singlets at $\delta$ 3.81 and 3.73 with a total integration of 3 protons while protons of the *N*-carbomethoxy group also gave rise to two distinct singlets at $\delta$ 3.65 and 3.41 with a total integration of three protons. A similar phenomenon was also observed for **7d**. Treatment of **7c** and **7d** with tributyltin hydride and azobis (isobutyronitrile) afforded aporphines **2c** and **2e** in 24% and 30% yield, respectively. The structures of aporphines **2c** and **2e** were supported by $^1$H-NMR data in which H-11 in **2c** gave an unusually low-field signal at $\delta$ 8.00 while H-11 of **2e** gave a singlet at $\delta$ 7.72 as a consequence of deshielding from ring A due to non-planarity of rings A and



**Synthetic scheme.** Reagents and conditions: (i) 140-150ºC (ii) POCl$_3$ (iii) NaBH$_4$ (iv) MeOCOCl/Et$_3$N (v) Bu$_3$SnH/AIBN (vi) LiAlH$_4$ (vii) H$_2$/10% Pd/C (viii) MeCOBr/Et$_3$N (ix) NaOH/EtOH

| | R$_1$ | R$_2$ | R$_3$ | R$_4$ | R$_3$+R$_4$ | R$_5$ |
|---|---|---|---|---|---|---|
| 1a | OH | OCH$_3$ | - | - | OCH$_2$O | CH$_3$ |
| 1b | OCH$_3$ | OCH$_3$ | OCH$_3$ | OH | - | COCH$_3$ |
| 1c | COOCH$_3$ | OCH$_3$ | - | - | OCH$_2$O | COOCH$_3$ |
| 1d | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | COCH$_3$ |
| 1e | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCOCH$_3$ | - | COCH$_3$ |
| 2a | OH | OCH$_3$ | - | - | OCH$_2$O | CH$_3$ |
| 2b | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | CH$_3$ |
| 2c | OCH$_2$Ph | OCH$_3$ | - | - | OCH$_2$O | COOCH$_3$ |
| 2d | OCH$_2$Ph | OCH$_3$ | - | - | OCH$_2$O | CH$_3$ |
| 2e | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | COOCH$_3$ |
| 2f | OCH$_3$ | OCH$_3$ | OCH$_3$ | OH | | CH$_3$ |
| 3a | OCH$_2$Ph | OCH$_3$ | | | | |
| 3b | OCH$_3$ | OCH$_3$ | - | - | - | - |
| 4a | - | - | - | - | OCH$_2$O | - |
| 4b | - | - | OCH$_3$ | OCH$_2$Ph | - | - |
| 5a | OCH$_2$Ph | OCH$_3$ | - | - | OCH$_2$O | - |
| 5b | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | - |
| 6a | OCH$_2$Ph | OCH$_3$ | - | - | OCH$_2$O | - |
| 6b | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | - |
| 7a | OCH$_2$Ph | OCH$_3$ | - | - | OCH$_2$O | H |
| 7b | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | H |
| 7c | OCH$_2$Ph | OCH$_3$ | - | - | OCH$_2$O | COOCH$_3$ |
| 7d | OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_2$Ph | - | COOCH$_3$ |

D. This deshielding of H-11 is characteristic of aporphines bearing a hydrogen at that position. Lithium aluminum hydride reduction of aporphines **2c** and **2e** afforded aporphines **2d** and **2b** in good yields. Hydrogenolysis of **2d** afforded (±)-isodomesticine (**2a**) of which the $^1$H-NMR data were in excellent agreement with those reported for (±)-isodomesticine (**2a**) synthesised by a different route (Hoshino, Ohtani and Umezawa, 1978). Further treatment of (±)-isodomesticine (**2a**) with methyl chloroformate resulted in opening of the ring B to give phenanthrene **1c** in good yield. Finally, lithium aluminum hydride reduction of the *N*-carbomethoxy group in **1c**, with concurrent loss of the carbonate group, afforded 3-*O*-demethylthalicthuberine (**1a**) of which the $^1$H-NMR spectral data were in good agreement with those of natural 3-*O*-demethylthalicthuberine (**1a**) (Hasbun and Castro, 1993). On the other hand, treatment of **2e** with acetyl bromide and triethylamine gave **1d**. Unfortunately, attempts to remove the benzyl protecting group in **1d** by catalytic hydrogenolysis resulted in partial reduction of **1d** to the 9,10-dihydrophenanthrene derivative. Attempts to remove the benzyl protecting group using dilute hydrochloric acid did not lead to a clean product. The benzyl protecting group was successfully removed catalytically from aporphine **2b**, obtained from the lithium aluminum hydride reduction of aporphine **2e**, to afford aporphine **2f**. Treatment of **2f** with acetyl bromide and triethylamine gave phenanthrene **1e** which was further hydrolysed with ethanolic sodium hydroxide to give *N*-acetyl-*seco*-*N*-methyllaurotetanine (**1b**), of which the $^1$H- and $^{13}$C-NMR spectral data were identical in all respects with those of the natural alkaloid) (Goh and Jantan, 1992).

## 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 unless stated otherwise with a Perkin-Elmer Spectrum GX FT-IR spectrophotometer. $^1$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ solutions unless stated otherwise 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 obtained on a Hewlett Packard 5989B spectrometer. Elemental microanalyses were performed with a Perkin-Elmer 2400 elemental analyser.

### 2-(3-Benzyloxy-4-methoxyphenyl)ethylamine (3a)

A solution of 3-benzyloxy-4-methoxy-β-nitrostyrene (48.2 g) in tetrahydrofuran (400 ml) was slowly added to a stirred and cooled solution of lithium aluminum hydride (20 g) in dry tetrahydrofuran (200 ml) and stirring continued for 2 h. Diethyl ether (750 ml) was added, with continued cooling and vigorous stirring, then water (20 ml), 15% sodium hydroxide (20 ml) and water (60 ml) were added in succession. The pale yellow precipitate was filtered off and washed with ether and the combined organic phase was extracted with 25% HCl (6×125 ml). The extract was basified with conc. ammonia to give an oil which was separated and dried. Removal of the solvent under vacuum gave compound **3a** as a yellow gum (36.8 g, 84%). $^1$H-NMR δ/ppm 7.48-7.18 (5H, m, Ph-H), 6.85-6.67 (3H, m, Ar-H), 5.10 (2H, s, $PhCH_2$), 3.81 (3H, s, $OCH_3$), 2.81 (2H, t, $J = 6.9$ Hz, $CH_2N$), 2.58 (2H, t, $J = 6.9$ Hz, $ArCH_2$). $^{13}$C-NMR δ/ppm 148.2, 148.0, 137.2, 132.2, 128.4, 127.7, 127.3, 121.4, 115.1, 112.0, 71.0, 56.0, 43.4, 39.2.

### 2-Bromo-4,5-methylenedioxyphenylacetic acid (4a)

Bromine (72.0 g) was added portionwise to a stirred solution of 3, 4-methylenedioxyphenylacetic acid (69.8 g) in warm acetic acid (500 ml) and stirring was continued for 1 h. The mixture was poured into water (1.5 l) and the precipitate was filtered and was recrystallised from benzene to give compound **4a** as pale brown needles (95.7 g, 95%), m.p.189-190ºC (lit. m.p.189-190ºC (Suguna and Pai, 1976)). $^1$H-NMR δ/ppm 7.02 (1H, s, Ar-H), 6.84 (1H, s, Ar-H), 6.00 (2H, s, $OCH_2O$), 3.62 (2H, s, $CH_2$). $^{13}C$ -NMR δ/ppm 171.6, 147.0, 146.9, 127.4, 114.6, 111.8, 110.9, 101.5, 40.8.

### 2-(2-Bromo-4,5-methylenedioxyphenyl)-*N*-(3-benzyloxy-4-methyoxyphenethyl)acetamide (5a) and 2-(5-Benzyloxy-2-bromo-4-methoxyphenyl) -*N*-(3,4-dimethoxyphenethyl)acetamide (5b)

A mixture of **3a** (24.4 g) and **4a** (24.7 g) was heated at 140-150ºC for 2 h, then dissolved in chloroform (600 ml). The chloroform solution was washed with 5% sodium carbonate (4×200 ml), water (2×200 ml), and 10% HCl (4×200 ml) respectively, then dried. Removal of the solvent under vacuum gave a pale brown solid which was triturated from ethanol to give amide **5a** as white needles (25.6 g, 54%), m.p.178-179ºC (lit. m.p. 181-183ºC (Suguna and Pai, 1976)). $^1H$ -NMR δ/ppm 7.50-7.28 (5H, m, Ph-H), 6.97 (1H, s, Ar-H), 6.77 (1H, d, $J$ = 8.1 Hz, Ar-H), 6.72 (1H, s, Ar-H), 6.67 (1H, d, $J$ = 1.8 Hz, Ar-H), 6.63 (1H, dd, $J$ = 8.1, 1.8 Hz, Ar-H), 5.95 (2H, s, $OCH_2O$), 5.40 (1H, br s, NH), 5.08 (2H, s, $PhCH_2$), 3.86 (3H, s, $OCH_3$), 3.52 (2H, s, $ArCH_2CO$), 3.41 (2H, apparent q, $J$ = 6.6 Hz, $CH_2N$), 2.66 (2H, t, $J$ = 6.6 Hz, $ArCH_2$). $^{13}C$ -NMR δ/ppm 169.5, 148.4, 148.2, 147.9, 147.7, 137.1, 131.0, 128.5, 127.9, 127.5, 127.4, 121.4, 115.3, 114.6, 112.8, 112.0, 110.9, 102.0, 71.0, 56.1, 43.8, 40.6, 34.9.

Amide **5b** was obtained in a similar manner as colourless prisms from ethanol in 60% yield, m.p.136-137ºC (lit. m.p.137-138ºC (Kametani, Ihara and Honda, 1970)). IR (Nujol) $\nu_{max}/cm^{-1}$ 3321, 1643, 1518, 1509, 1268, 1258, 1238, 1212, 1163, 1142, 1075, 1028, 975, 916, 862, 851, 803, 774, 749, 735, 702, 639, 596. $^1H$-NMR δ/ppm 7.45-7.29 (5H, m, Ph-H), 7.01 (1H, s, Ar-H), 6.81 (1H, s, Ar-H), 6.70 (1H, d, $J$ = 8.1 Hz, Ar-H), 6.63 (1H, d, $J$ = 1.8 Hz, Ar-H), 6.56 (1H, dd, $J$ = 8.1 and 1.8 Hz, Ar-H), 5.41 (1H, br s, NH), 5.08 (2H, s, $PhCH_2$), 3.87 (3H, s, $OCH_3$), 3.84 (3H, s, $OCH_3$), 3.83 (3H, s, $OCH_3$), 3.54 (2H, s, $ArCH_2$), 3.43 (2H, apparent q, $J$ = 6.6 Hz, $CH_2N$), 2.67 (2H, t, $J$ = 6.6 Hz, $ArCH_2$). $^{13}C$-NMR δ/ppm 169.8, 149.7, 149.0, 147.7, 136.3, 131.0, 128.6, 128.1, 127.4, 126.4, 120.6, 116.4, 116.1, 115.4, 111.8, 111.2, 71.1, 56.2, 55.9, 55.8, 43.6, 40.7, 35.0.

### 1-(2-Bromo-4,5-methylenedioxybenzyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (6a) and 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (6b)

A solution of amide **5a** (18.6 g) and phosphorus oxychloride (56.1 g) in benzene (300 ml) was refluxed for 2 h. The excess reagent and solvent were removed under vacuum. The resulting brown residue was shaken with chloroform (600 ml) and dilute ammonium hydroxide (500 ml). The chloroform layer was washed with water (4×400 ml), then dried. Removal of the solvent under vacuum gave a pale brown solid which was recrystallised from ethanol to give compound **6a** as pale yellow prisms (16.5 g, 92%), m.p.123-124ºC (lit. m.p.125-127ºC (Suguna and Pai, 1976)). $^1H$ -NMR δ/ppm 7.48-7.30 (5H, m, Ph-H), 7.01 (1H, s, Ar-H), 6.95 (1H, s, Ar-H), 6.76 (1H, s, Ar-H), 6.68 (1H, s, Ar-H), 5.91 (2H, s, $OCH_2O$), 5.15 (2H, s, $PhCH_2$), 4.08 (2H, s, $CH_2C{=}N$), 3.83 (3H, s, $OCH_3$), 3.70 (2H, t, $J$ = 7.5 Hz, $CH_2N$), 2.60 (2H, t, $J$ = 7.5 Hz, $ArCH_2$). $^{13}C$ -NMR δ/ppm 165.1, 150.0, 148.0, 147.6, 147.2, 136.6, 131.4, 130.6, 128.6, 128.0, 127.2, 121.6, 114.4, 112.5, 112.4, 109.6, 109.5, 101.7, 70.8, 56.3, 47.3, 42.4, 25.6.

Dihydroisoquinoline **6b** was obtained as above as pale yellow needles from ethanol in 48% yield, m.p.147-148ºC. Anal. Calcd for $C_{26}H_{26}BrNO_4$ : C, 62.91; H, 5.28; N, 2.82. Found: C, 62.73; H, 5.43; N, 2.74. IR (Nujol) $\nu_{max}/cm^{-1}$ 1622, 1603, 1570, 1508, 1408, 1359, 1330, 1285, 1269, 1252, 1221, 1163, 1142, 1075, 1028, 975, 916, 862, 851, 803, 774, 749, 735, 702, 639, 596. $^1H$-NMR δ/ppm 7.34-7.22 (5H, m, Ph-H), 7.03 (1H, s, Ar-H), 6.89 (1H, s, Ar-H), 6.82 (1H, s, Ar-H), 6.62 (1H, s, Ar-H), 5.01 (2H, s, $PhCH_2$), 4.06 (2H, s, $CH_2C{=}N$), 3.89 (3H, s, $OCH_3$), 3.83 (3H, s, $OCH_3$), 3.80 (3H, s, $OCH_3$), 3.65 (2H, t, $J$ = 7.5 Hz, $CH_2N$), 2.52 (2H, t, $J$ = 7.5 Hz, $ArCH_2$). $^{13}C$-NMR ($CDCl_3$) δ/ppm 165.4, 150.6, 148.9, 147.6, 147.4, 136.6, 131.5, 129.4, 128.4, 127.8, 127.1, 121.3, 115.7, 114.8, 114.6, 110.1, 109.1, 70.9, 56.2, 55.9, 47.3, 42.1, 25.7.

**1-(2-Bromo-4,5-methylenedioxybenzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7a) and 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin (7b)**

Sodium borohydride (1.9 g) was added portionwise to a stirred solution of dihydroisoquinoline **6a** (16.0 g) in ethanol (330 ml) and the mixture was refluxed for 1 h. Chloroform (200 ml) was added and the mixture was washed with water (3×200 ml) and brine (200 ml), then dried. Removal of the solvent under vacuum gave a pale brown solid which was recrystallised from ethanol to give compound **7a** as pale yellow prisms (15.0 g, 93%), m.p.128-129ºC (lit. m.p.130ºC (Suguna and Pai, 1976)). $^1$H -NMR δ/ppm 7.48-7.25 (5H, m, Ph-H), 7.04 (1H, s, Ar-H), 6.78 (1H, s, Ar-H), 6.77 (1H, s, Ar-H), 6.63 (1H, s, Ar-H), 5.95 (2H, s, $OCH_2O$), 5.11 (2H, s, $PhCH_2$), 4.19 (1H, dd, *J* = 10.0, 3.6 Hz, H-1), 3.85 (3H, s, $OCH_3$), 3.28-3.17 (2H, m, $CH_2$), 2.98-2.83 (2H, m, $CH_2$), 2.70-2.66 (2H, m, $CH_2$). $^{13}$C -NMR δ/ppm 147.8, 147.3, 147.1, 146.8, 137.3, 131.8, 131.2, 128.5, 127.8, 127.3, 127.2, 114.9, 114.5, 112.9, 111.3, 110.4, 101.7, 71.1, 56.2, 55.2, 42.9, 40.0, 29.3.

Tetrahydroisoquinoline **7b** was obtained as above as colourless prisms from ethanol in 83% yield, m.p.112-114ºC (lit. m.p.107-108ºC (Kametani, Ihara and Honda, 1970)). IR (Nujol) $\nu_{max}$/cm$^{-1}$ 3286, 1607, 1600, 1506, 1256, 1165, 1110, 1022, 986, 918, 854, 828, 798, 755, 733, 700. $^1$H-NMR δ/ppm 7.45-7.20 (5H, m, Ph-H), 7.08 (1H, s, Ar-H), 6.77 (1H, s, Ar-H), 6.70 (1H, s, Ar-H), 6.58 (1H, s, Ar-H), 5.12 (2H, br s, $PhCH_2$), 4.14 (1H, dd, *J* = 9.75 and 3.60 Hz, H-1), 3.87 (3H, s, $OCH_3$), 3.85 (3H, s, $OCH_3$), 3.82 (3H, s, $OCH_3$), 3.31-3.07 (2H, m, $CH_2$), 2.88-2.76 (2H, m, $CH_2$), 2.74-2.64 (2H, m, $CH_2$). $^{13}$C-NMR δ/ppm 149.0, 147.5, 147.2, 147.1, 136.6, 130.3, 130.1, 128.6, 128.0, 127.3, 127.1, 117.2, 116.2, 115.3, 111.6, 109.5, 71.1, 56.2, 55.9, 55.8, 55.1, 42.3, 40.0, 29.2.

**Methyl 1-(2-bromo-4,5-methylenedioxybenzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (7c) and Methyl 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-6,7-dimethoxy-1, 2,3,4-tetrahydroisoquinoline-2-carboxylate (7d)**

Methyl chloroformate (11.0 g) was added dropwise to a stirred mixture of tetrahydroisoquinoline **7a** (7.5 g) and triethylamine (13.5 g) in chloroform (120 ml) at 0-10ºC. Stirring was continued at room temperature for 3 h. Chloroform (60 ml) was added and the chloroform layer was washed with 10% HCl (6×150 ml) and brine (2× 150 ml), then dried. Removal of the solvent under vacuum gave a pale brown solid which was triturated from ethanol to give the carbamate **7c** as white needles (7.2 g, 85%), m.p.163-164ºC. *Anal. Calcd* for $C_{27}H_{26}BrNO_6$: C, 60.01; H, 4.85; N, 2.59. Found: C, 59.85; H, 4.61; N, 2.73. UV (MeOH) $\lambda_{max}$/nm (log ε): 237sh (4.12), 289 (3.91). IR (Nujol) $\nu_{max}$/ cm$^{-1}$ 1706, 1609, 1504, 1301, 1282, 1261, 1240, 1222, 1192, 1112, 1097, 1032, 1011, 1000, 989, 925, 865, 853, 837, 760, 742, 703. $^1$H -NMR δ/ppm 7.50-7.28 (5H, m, Ph-H), 7.02 and 6.98 (1H, 2 × s, Ar-H of both conformers), 6.93-6.58 (2H, m, Ar-H), 6.55 and 6.45 (1H, 2 × s, Ar-H of both conformers), 5.94 (2H, s, $OCH_2O$), 5.40-5.30 (1H, m, H-1), 5.12 (2H, s, $PhCH_2$), 4.31-4.18 and 3.98-3.86 and (1H, 2 × m, H-3α), 3.81 and 3.73 (3H, 2 × s, $OCH_3$ of both conformers), 3.65 and 3.41 (3H, 2 × s, $COOCH_3$ of both conformers), 3.50-2.56 (5H, m, H-3β and 2 × $CH_2$). $^{13}$C -NMR δ/ppm 156.0, 155.9, 148.1, 148.0, 147.2, 147.1, 147.0, 137.1, 137.0, 130.9, 130.8, 128.8, 128.5, 128.3, 127.9, 127.3, 126.3, 126.2, 115.5, 115.3, 114.1, 114.0, 112.5, 112.4, 111.2, 111.0, 110.6, 101.7, 101.6, 71.1, 71.0, 56.2, 56.0, 54.9, 54.1, 52.6, 52.3, 42.6, 41.9, 38.8, 37.6, 28.0, 27.9. EIMS *m*/*z* (rel.int.): 326 (10), 213 (4), 91 (100).

Carbamate **7d** was obtained as above as colourless prisms from ethanol in 85% yield, m.p. 145-146ºC. *Anal. Calcd* for $C_{28}H_{30}BrNO_6$: C, 60.44;

H, 5.43; N, 2.52. Found: C, 60.14; H, 5.61; N, 2.48. UV (MeOH) $\lambda_{max}$/nm (log $\varepsilon$) 234.5 (4.29), 285.5 (3.93). IR (Nujol) $\nu_{max}$/cm$^{-1}$ 1692, 1608, 1509, 1444, 1347, 1311, 1280, 1261, 1219, 1212, 1166, 1126, 1097, 1022, 980, 860, 850, 836, 802, 768, 759, 736, 701. $^1$H-NMR δ/ppm 7.50-7.30 (5H, m, Ph-H), 7.04 and 6.98 (1H, 2 × s, Ar-H of both conformers), 6.65, 6.60, 6.57, 6.54, 6.49 and 6.29 (3H, 6 × s, 3 × Ar-H of both conformers), 5.37-5.20 (1H, m, H-1 of both conformers), 5.02 (2H, AB q, *J* = 12.3 Hz, PhCH$_2$), 4.25-4.12 (1H, m, H-3α of both conformers), 3.85, 3.84, 3.67 and 3.70 (9H, 4 × s, 3 × OCH$_3$ of both conformers), 3.77 and 3.42 (3H, 2 × s, COOCH$_3$ of both conformers), 3.48-2.53 (5H, m, H-3β and 2 × CH$_2$). $^{13}$C-NMR δ/ppm 155.9, 149.0, 148.9, 147.9, 147.8, 147.4, 147.3, 147.2, 136.8, 129.7, 129.5, 128.6, 128.0, 127.3, 127.2, 126.4, 126.3, 117.1, 116.7, 116.0, 115.8, 115.6, 111.3, 111.0, 110.2, 110.0, 71.5, 71.2. EIMS *m*/*z* (rel.int.): 250 (100), 206 (2), 190 (8), 176 (5), 91 (68).

### Methyl 2-benzyloxy-1-methoxy-9,10-methylenedioxynoraporphine-6-carboxylate (2c) and Methyl 9-Benzyloxy-1,2,10-trimethoxynoraporphine-6-carboxylate (2e)

A solution of azobis(isobutyronitrile) (2.2 g) and tributyltin hydride (15.2 g) in toluene (91 ml) was added in 6 equal portions over 2.5 h to a refluxing solution of carbamate **7c** (8.0 g) in toluene (152 ml). The resulting mixture was then refluxed for 24 h. The solvent was removed under vacuum and the resulting brown residue was shaken with acetonitrile (20 ml) and hexane (50 ml). The white solid was filtered off to give noraporphine **2c** as white needles (1.68 g, 24%), m.p.220-222ºC. *Anal. Calcd* for $C_{27}H_{25}NO_6$ : C, 70.58; H, 5.48 ; N, 3.05. Found: C, 70.42; H, 5.67; N, 3.18. UV (MeOH) $\lambda_{max}$/nm (log $\varepsilon$) 235sh (3.93), 284 (3.94), 309 (4.03), 322 (4.35). IR(Nujol) $\nu_{max}$/cm$^{-1}$ 1699 , 1615, 1588, 1275, 1243, 1226, 1201,1155,1140, 1107, 1059, 1036, 953, 933, 876, 764, 745, 695. $^1$H-NMR δ/ppm 8.00 (1H, s, H-11), 7.50-7.27 (5H, m, Ph-H), 6.75 (1H, s, Ar-H), 6.68 (1H, s, Ar-H), 5.98-5.91 (2H, m, OCH$_2$O), 5.12 (2H, AB q, *J* = 11.9 Hz, PhCH$_2$), 4.69 (1H, dd, *J* = 13.3, 4.3 Hz, H-6a), 4.45-4.30 (1H, m, H-5α), 3.75 (3H, s, OCH$_3$), 3.72 (3H, s, OCH$_3$), 3.02-2.50 (5H, m, H-5β and 2 × CH$_2$). $^{13}$C - NMR δ/ppm 156.0, 151.4, 146.8, 146.7, 145.9, 137.3, 131.3, 129.5, 128.6, 128.0, 127.4, 126.2, 125.4, 113.4, 109.1, 108.7, 101.0, 71.3, 60.1, 52.6, 52.0, 39.1, 35.3, 30.3. EIMS *m*/*z* (rel.int.): 459 [M$^+$] (3), 416 (2), 368 (1), 336 (2), 308 (2), 91 (100).

Noraporphine **2e** was obtained as above as colourless prisms from ethanol in 30% yield, m.p. 155-156ºC. *Anal.Calcd* for $C_{28}H_{29}NO_6$ : C, 70.72; H, 6.15; N, 2.95. Found: C, 70.53; H, 6.40; N, 2.74. UV (MeOH) $\lambda_{max}$/nm (log $\varepsilon$) 237.0 (4.45), 281.0 (4.24), 302.5 (4.22, 317.0 (4.07). IR (Nujol) $\nu_{max}$/cm$^{-1}$ 1710, 1603, 1584, 1514, 1397, 1340, 1271, 1255, 1212, 1195, 1110, 1012, 954, 918, 875, 749, 724, 699. $^1$H-NMR δ/ppm 8.18 (1H, s, H-11), 7.50-7.29 (5H, m, Ph-H), 6.83 (1H, s, Ar-H), 6.63 (1H, s, Ar-H), 5.19 (2H, AB q, *J* = 12.3 Hz, PhCH$_2$), 4.80-4.64 (1H, m, H-6a), 4.50-4.32 (1H, m, H-5α), 3.92 (3H, s, OCH$_3$), 3.90 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 3.66 (3H, s, OCH$_3$), 3.05-2.58 (5H, m, H-5β, H-7α, H-7β, H-4α and H-4β). $^{13}$C-NMR δ/ ppm 155.9, 152.0, 148.1, 147.6, 144.8, 137.1, 129.9, 129.7, 127.7, 125.4, 125.7, 113.5, 112.4, 110.7, 70.9, 60.0, 56.1, 55.9, 52.7, 51.9, 39.0, 34.6, 30.3. EIMS *m*/*z* (rel.int.): 475[M$^+$](66), 384 (100), 281 (18), 250 (22), 91 (100).

### 2-Benzyloxy-1-methoxy-9,10-methylenedioxyaporphine (2d) and 9-Benzyloxy-1,2,10-trimethoxyaporphine (*O*-Benzyl-*N*-methyllaurotetanine) (2b)

A mixture of noraporphine **2c** (4.2 g) and lithium aluminum hydride (4.5 g) in dry tetrahydrofuran (210 ml) was refluxed for 3 h. Water (64 ml) was added dropwise followed by dilute ammonium hydroxide (21 ml). The pale yellow granular residue was filtered off and washed with chloroform. The organic phase was separated and then dried. Removal of the solvent under vacuum gave a pale brown solid which was triturated from ethanol to give aporphine **2d** as yellow needles (3.2 g, 83%), m.p.149-151ºC. *Anal. Calcd* for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37. Found: C, 75.03; H, 5.94; N, 3.53. UV (MeOH) $\lambda_{max}$/nm (log $\varepsilon$) 233sh (4.10), 282 (4.05), 308 (4.14), 317 (4.44). IR (Nujol) $\nu_{max}$/cm$^{-1}$ 1619, 1588, 1260, 1240, 1189, 1128, 1098, 1071, 1048, 1041, 1015, 1001, 935, 915, 875, 843, 811, 797, 751, 697. $^1$H-NMR δ/ppm 7.94 (1H, s, H-11), 7.50-7.28 (5H, m, Ph-H), 6.75 (1H, s, Ar-H), 6.65 (1H, s, Ar-H), 5.95 (2H, AB q, *J* = 1.5 Hz, $OCH_2O$), 5.11 (2H, AB q, *J* = 12.0 Hz, $PhCH_2$), 3.71 (3H, s, $OCH_3$), 3.18-2.92 (4H, m, 2 × $CH_2$), 2.68-2.41 (3H, m, CH, $CH_2$), 2.51 (3H, s, $NCH_3$). $^{13}$C-NMR δ/ppm 151.2, 146.5, 146.3, 145.0, 137.2, 130.8, 128.6, 128.5, 127.9, 127.8, 127.3, 125.6, 112.7, 108.9, 108.3, 100.9, 70.8, 62.5, 60.3, 53.2, 44.0, 35.2, 29.2 EIMS *m*/*z* (rel.int.): 415 [$M^+$] (6), 324 (4), 91 (100).

Aporphine **2b** was obtained as above as pale brown needles from ethanol in 82% yield, m.p. 128-129ºC (lit. m.p.130-132ºC (Hara, Hoshino and Umezawa, 1976)). IR (Nujol) $\nu_{max}$/cm$^{-1}$ 1604, 1597, 1585, 1578, 1514, 1339, 1318, 1252, 1107, 1086, 1002, 856, 838, 827, 744, 723, 699. $^1$H-NMR δ/ppm 8.11 (1H, s, H-11), 7.50-7.29 (5H, m, Ph-H), 6.81 (1H, s, Ar-H), 6.59 (1H, s, Ar-H), 5.20 (2H, AB q, J = 12.6 Hz, $PhCH_2$), 3.90 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$), 3.66 (3H, s, $OCH_3$), 3.21-2.91 (4H, m, 2 × $CH_2$), 2.72-2.45 (3H, m, CH, $CH_2$), 2.54 (3H, s, $NCH_3$). $^{13}$C-NMR δ/ppm 151.9, 148.1, 147.3, 144.3, 137.2, 129.3, 128.9, 128.6, 127.9, 127.3, 126.9, 125.1, 113.3, 112.2, 110.5, 71.0, 62.5, 60.2, 56.1, 55.8, 53.4, 44.0, 34.5, 29.3. EIMS *m*/*z* (rel.int.): 431 ($M^+$] (100), 340 (86), 312 (19), 310 (24), 266 (11), 91 (81).

### (±)-Isodomesticine (2a) and 9-Hydroxy-1, 2,10-trimethoxyaporphine (N-Methyllaurotetanine) (2f)

A solution of aporphine **2d** (2.8 g) in methanol (250 ml) and chloroform (100 ml) was hydrogenolysed in the presence of 10%Pd/C (1.0 g) at 45-50 psi for 3 h. The catalyst was filtered off and the solvent was removed under vacuum. The resulting white residue was shaken with chloroform (80 ml) and 10% ammonium hydroxide (60 ml). The chloroform layer was dried and the solvent was removed under vacuum to give (±)-isodomesticine (**2a**) as a green solid which was recrystallised from ethanol to give pale green prisms (1.94 g, 86%), m.p.179-180ºC (lit. m.p.180-182ºC (Hoshino, Ohtani and Umezawa, 1978)). UV (MeOH) $\lambda_{max}$/nm (log ε) 232sh (4.23), 283 (3.94), 310 (3.99), 319 (3.96). IR(Nujol) $\nu_{max}$/ cm$^{-1}$ 3425, 1620, 1590, 1500, 1242, 1171, 1146, 1126, 1093, 1069, 1038, 1007, 986, 972, 932, 865, 817, 796, 753, 735. $^1$H-NMR δ/ppm 7.83 (1H, s, H-11), 6.76 (1H, s, Ar-H), 6.64 (1H, s, Ar-H), 5.98 (2H, AB q, *J* = 1.3 Hz, $OCH_2O$), 3.58 (3H, s, $OCH_3$), 3.25-2.90 (4H, m, 2 × $CH_2$), 2.66-2.40 (3H, m, CH, $CH_2$), 2.53 (3H, s, $NCH_3$). $^{13}$C -NMR δ/ppm 148.3, 146.9, 146.7, 142.6, 130.9, 129.7, 126.9, 126.0, 125.4, 113.6, 108.5, 107.9, 101.0, 62.6, 60.4, 53.4, 43.8, 35.1, 28.9. EIMS *m*/*z* (rel.int.): 325 ($M^+$](48), 310 (18), 267 (8), 238 (7), 222 (13), 192 (21), 165 (12), 152 (21), 91 (100).

Aporphine **2f** was obtained as above as colourless prisms from ethanol in 79% yield, m.p. 148-149ºC (lit. m.p. 143-144ºC (Hara *et al.*, 1984)). UV (MeOH) $\lambda_{max}$/nm (log ε) 231.5 (4.10), 280.5 (4.02), 302.0 (4.00), 316.0 (3.92).IR (Nujol) $\nu_{max}$/cm$^{-1}$ 3435, 1642, 1590, 1514, 1420, 1322, 1305, 1273, 1252, 1218, 1112, 1081, 1024, 998, 980. $^1$H-NMR δ/ppm 8.05 (1H, s, H-11), 6.73 (1H, s, Ar-H), 6.57 (1H, s, Ar-H), 3.87 (3H, s, $OCH_3$), 3.86 (3H, s, $OCH_3$), 3.64 (3H, s, $OCH_3$), 3.24-2.89 (4H, m, 2 × $CH_2$), 2.72-2.44 (3H, m, CH, $CH_2$), 2.53 (3H, s, $NCH_3$). $^{13}$C-NMR δ/ppm 151.9, 145.5, 145.0, 144.1, 130.0, 128.9, 127.2, 127.1, 123.8, 114.1, 111.2, 110.2, 62.6, 60.1, 55.9, 55.8, 53.3, 43.90, 34.1, 29.1. EIMS *m*/*z* (rel.int.): 340 (100), 326 (37), 298 (19), 267 (16).

### 1-(*N*-carbomethoxy-N-methylamino)ethyl-3-carbomethoxyoxy-4-methoxy-6,7-methylenedioxy-phenanthrene (1c)

Methyl chloroformate (6.3 g) was added dropwise to a stirred mixture of aporphine **2a** (1.7 g) and triethylamine (9.2 g) in chloroform (80 ml) at 0-10ºC and the mixture was refluxed for 2 h. Chloroform (20 ml) was added and the chloroform layer was washed with water (80 ml), 5% sodium carbonate (3×80 ml), 10%HCl (4×80 ml) and water (2×80 ml), then dried. Removal of the solvent gave a red-brown viscous oil which was crystallized from ethanol to give the phenanthrene **1c** as pale brown prisms (0.7 g, 29%), m.p.89-91ºC. *Anal. Calcd* for $C_{23}H_{23}NO_8$: C, 62.58; H, 5.25; N, 3.17.

Found: C, 62.78; H, 5.11; N, 3.05. UV (MeOH) $\lambda_{max}$/nm (log ε): 262 (4.80), 280 (4.32), 313 (3.93). IR (film) $\nu_{max}$/cm$^{-1}$: 2955, 1767, 1702, 1596, 1503, 1467, 1421, 1395, 1367, 1252, 1212, 1132, 1064, 1038, 989, 951, 939, 880, 865, 814, 772. $^1$H-NMR δ/ppm 9.03 (1H, s, H-5), 8.00 and 7.84 (1H, 2 × d, *J* = 8.7 Hz, H-10 of both conformers), 7.68 (1H, d, *J* = 8.7 Hz, H-9), 7.23 (1H, s, Ar-H), 6.11 (2H, s, $OCH_2O$), 3.98 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$), 3.75 and 3.70 (3H, 2 × s, $NCOOCH_3$ of both conformers), 3.65-3.50 (2H, m, H-2'), 3.38-3.18 (2H, m, H-1'), 2.94 and 2.86 (3H, 2 × s, $NCH_3$ of both conformers). $^{13}$C -NMR δ/ppm 156.9, 154.2, 148.4, 148.3, 147.4, 142.0, 132.4, 129.4, 127.5, 125.8, 125.1, 121.7, 120.8, 120.4, 105.9, 105.4, 101.4, 60.7, 55.8, 52.7, 50.8, 49.9, 35.2, 35.0, 32.3, 31.9. EIMS *m*/*z* (rel.int.): 441 (M$^+$] (14), 339 (24), 209 (9), 102 (100).

### 3-*O*-Demethylthalicthuberine (1a)

A mixture of phenanthrene **1c** (0.6 g) and lithium aluminum hydride (0.8 g) in dry tetrahydrofuran (40 ml) was refluxed for 3 h. Water (12 ml) was added dropwise followed by dilute ammonium hydroxide (12 ml). The pale yellow granular residue was filtered off and washed with chloroform. The organic phase was separated then dried. Removal of the solvent under vacuum gave a green solid which was recrystallised from ethanol to give 3-*O*-demethylthalicthuberine (**1a**) as pale green prisms (0.32 g, 72%), m.p.183-185ºC (lit. m.p.182-184ºC (Hasbun and Castro, 1993)). *Anal.Calcd* for $C_{20}H_{21}NO_4$ : C, 70.78; H, 6.24; N, 4.13. Found: C, 70.88; H, 6.10; N, 4.31. UV (MeOH) $\lambda_{max}$/nm (log ε) 260 (4.69), 283 (4.33), 307 (3.97), 319 (2.99). IR(Nujol) $\nu_{max}$/ cm$^{-1}$ 3450, 2576, 1610, 1529, 1497, 1266, 1237, 1214, 1178, 1144, 1101, 1056, 1040, 1000, 956, 936, 879, 868, 852, 840, 807, 792, 778, 721, 626. $^1$H -NMR δ/ ppm 8.88 (1H, s, H-5), 7.78 (1H, d, *J* = 9.0 Hz, H-10), 7.50 (1H, d, *J* = 9.0 Hz, H-9), 7.20 (1H, s, Ar-H), 7.18 (1H, s, Ar-H), 6.11 (2H, s, $OCH_2O$), 3.81 (3H, s, $OCH_3$), 3.28-3.17 (2H, m, H-2'), 2.72-2.62 (2H, m, H-1'), 2.39 (3H, s, $NCH_3$). $^{13}$C-NMR (DMSO-$d_6$) δ/ppm 148.1, 147.4, 146.8, 142.5, 133.5, 129.3, 125.2, 124.9, 124.8, 124.0, 121.0, 118.4, 105.7, 105.0, 101.1, 60.7, 59.4, 45.3, 31.7. EIMS *m*/*z* (rel.int.): 393 [M$^+$](3), 58 (100).

### 1-(*N*-Acetyl-*N*-methylamino) ethyl-3,4,6-trimethoxy-7-hydroxyphenanthrene (*N*-acetyl-*seco*-*N*-methyllaurotetanine) (1b)

Acetyl bromide (0.2 g) was added portionwise to a solution of the aporphine **2f** (1.2 g) and triethylamine (0.7 g) in chloroform (100 ml) and stirring was continued for 3 h. Work-up in the usual manner gave phenanthrene **1e** as a viscous residue (1.3 g, 86%) which was used in the next step without further purification.

The residue (1.3 g) was stirred with a solution of sodium hydroxide (5.8 g) in ethanol (30 ml) for 2 h and the solvent was removed under vacuum to give a brown solid. This was dissolved in water (200 ml) and acidified with 15%HCl to give a yellow solid which was recrystallised from ethanol to give *N*-acetyl-*seco*-*N*-methyllaurotetanine(1b) as pale yellow prisms (1.0 g, 85%), m.p. 209-210ºC (lit. m.p.210-211ºC (Goh and Jantan, 1992)). UV (MeOH) $\lambda_{max}$/nm (log ε) 216.5 (4.15), 264.5 (4.57), 283.0 (4.17), 308.0 (3.84), 319.5 (3.83), 345.0 (3.11), 362.0 (2.94). IR (Nujol) $\nu_{max}$/ cm$^{-1}$ 3360, 1625, 1614, 1593, 1414, 1278, 1236, 1115, 1986, 1017, 980, 862, 722. $^1$H-NMR δ/ppm 9.08 (1H, s, H-5), 7.88 and 7.64 (1H, 2 × d, *J* = 9.0 Hz, H-10 of both conformers), 7.52 (1H, d, *J* = 9.0 Hz, H-9), 7.34 and 7.33 (1H, 2 × s, H-8 of both conformers), 7.18 and 7.04 (1H, 2 × s, H-2 of both conformers), 4.06 and 4.05 (3H, 2 × s, $OCH_3$ of both conformers ), 4.01 (3H, s, $OCH_3$), 3.91 (3 H, s, $OCH_3$), 3.73-3.59 (2H, m, H-2'), 3.38-3.25 (2H, m, H-1'), 3.00 and 2.84 (3H, 2 × s, $NCH_3$ of both conformers), 2.11 and 1.76 (3H, 2 × s, $COCH_3$ of both conformers). $^{13}$C-NMR δ/ppm 171.0, 170.8, 150.3, 146.9, 146.7, 145.8, 145.7, 145.4, 144.9, 132.2, 131.0, 128.7, 128.6, 125.7, 125.4, 125.2, 125.1, 124.8, 123.9, 123.8, 120.7, 119.7, 114.1, 113.8, 111.1, 108.5, 60.1, 60.0, 56.7, 56.5, 55.8, 55.7, 51.8, 49.9, 37.3, 33.7, 32.7, 31.7, 21.9, 20.8. EIMS *m*/*z* (rel.int.): 383 (M$^+$] (87), 210 (100), 279 (10), 263 (22).

## Acknowledgement

The authors are grateful to Mrs Panit Vedkanchana and Mr Witoon Ngow of the Silpakorn University Scientific and Technological Research Equipment Centre for kindly measuring the low resolution mass spectra.

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