



## Indole as a Tool in Synthesis.

### Indolenine Approach to 4,5-Epoxy-10-normorphinans

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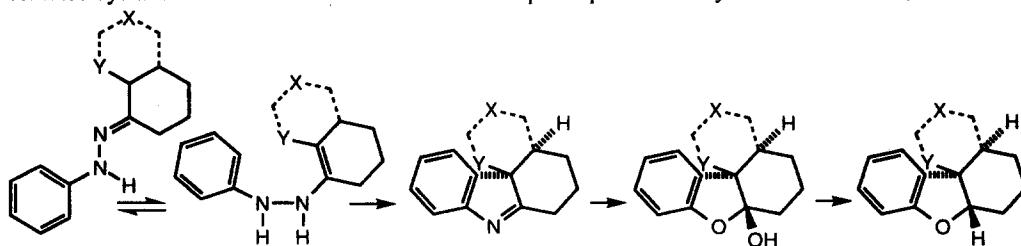
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**Abstract:** The 4,5-epoxy-10-normorphinans **2a** and **2b** featuring the morphine skeleton lacking the B-ring were synthesized using the "nitrous acid deamination" of indolenines as the key step. Thus, indolenines **13** and **15** were prepared by Fischer synthesis from the corresponding bicyclic ketolactams **6** and **12**, respectively, and further transformed into the related hexahydrodibenzofurans. Ketolactam **6** was obtained from 3-nitromethylcyclohexanone using classical chemistry, whereas **12** was built up by fragmentation of a perhydroazepinone, followed by an intramolecular Diels-Alder cyclization. While the process led to the unnatural ring junction (**2b**), the natural configuration (**2a**) was obtained by base catalysed epimerization of 4,5-epoxy-17-methyl-9-oxo-10-nor-14 $\alpha$ -morphinan **21**.

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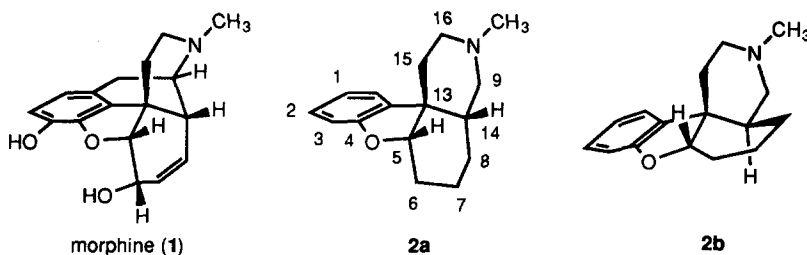
### Introduction

Tautomerism between phenylhydrazones bearing a tertiary carbon atom and the most substituted enehydrazines accounts for the Fischer-indolenine (3*H*-indole) synthesis<sup>1</sup> from the related ketones and thus offers an efficient method for constructing arylated quaternary centers. Combination with nitrous acid deamination<sup>2</sup> then allows replacement of the nitrogen of the indolenine with oxygen, in the form of a 2-hydroxydihydrobenzofuran suitable for further elaboration. For example, the phenylhydrazones of 2-substituted cyclanones are thus transformed in three simple steps into tetrahydrodibenzofurans (Scheme 1).



Scheme 1

This approach could be extended to the phenylhydrazones of bicyclic ketones, and especially of decahydroisoquinoline ( $X = NCH_3$ ,  $Y = CH_2$ ) with the view to preparing the 10-nor analogs **2a,b** of morphine **1** (Scheme 2).<sup>3</sup>



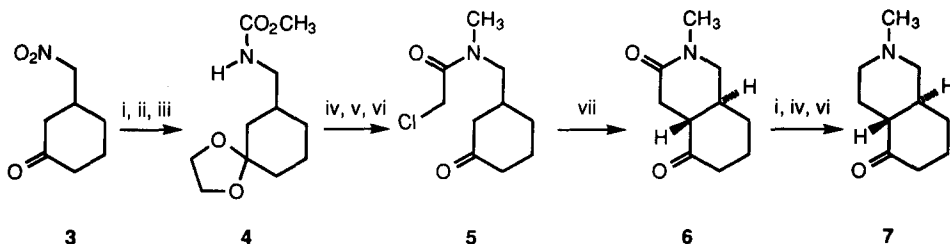
Scheme 2

Such compounds have retained considerable attention in the past years,<sup>4</sup> owing to their potential analgesic properties.<sup>5</sup> However, the indolenine approach will predictably afford the 14-epimer<sup>6</sup> **2b** due to the arylation in the Fischer rearrangement occurring from the less hindered side of the enehydrazine (Scheme 1). This drawback could be circumvented by introduction of a carbonyl function at C-9, thus enabling the C-14 epimerization. We now describe with full experimental details the syntheses of both morphine analogs<sup>7</sup> **2b** and **2a** using these strategies.<sup>8</sup>

## Results and discussion

### Synthesis of the *N*-methyldioxodecahydroisoquinolines **6** and **12a,b**

#### • 2-methyl-3,5-dioxodecahydroisoquinoline **6** (Scheme 3)



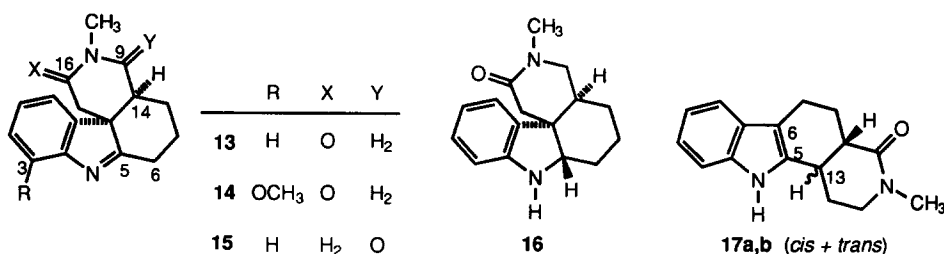
i: *p*-TsOH, ethylene glycol, Dean-Stark; ii: Pd-C,  $H_2$ , EtOH; iii:  $ClCO_2CH_3$ ,  $Et_3N$ ,  $CH_2Cl_2$ , 0.5 h; iv:  $LiAlH_4$ , THF, reflux, 10 h; v:  $ClCH_2COCl$ ,  $Et_3N$ ,  $CH_2Cl_2$ , reflux, 0.5 h; vi: HCl aq., 80°C; vii: *t*-BuOK, toluene, 90°C, 2 h.

Scheme 3

The bicyclic ketolactam **6** was obtained through a conventional synthesis, starting from 3-nitromethylcyclohexanone **3**. The nitro group of **3** was sequentially elaborated to the *N*-methylchloroacetamide **5** via the urethane **4**. Treatment of **5** with potassium *t*-butoxide in toluene at 90°C smoothly gave (86%) the bicyclic ketolactam **6** as the sole product. When the sequence was run without isolation of the intermediates from urethane **4**, ketolactam **6** was prepared in 38% overall yield (calculated from **3**). Proton H-4a in the  $^1H$ -NMR spectrum of **6** appeared as a multiplet at  $\delta$ : 2.13 ppm whose two large coupling constants (ddd,  $J_1 = 4.5$ ,  $J_2 = 10$ ,  $J_3 = 11$  Hz) indicated the *trans* ring junction. The 5-oxodecahydroisoquinoline **7**<sup>9</sup> was further obtained through reduction of **6** with  $LiAlH_4$  after protection of the ketone.



accounted for the predicted *cis* ring junction of the two six-membered rings. Reduction of **13** with  $\text{NaBH}_3\text{CN}$  in acetic acid led to the fully characterized indoline **16** (Scheme 5).

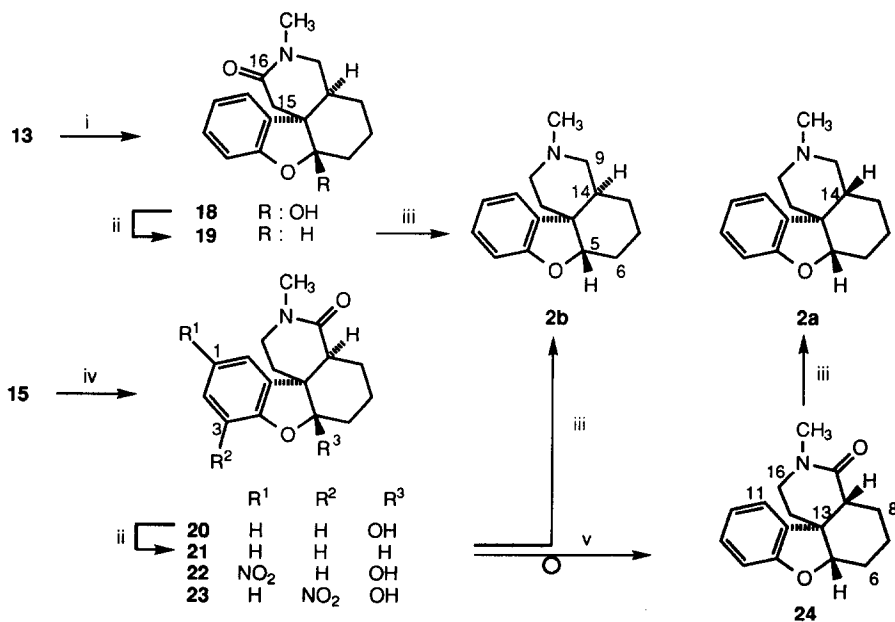


Scheme 5

Indolization of **6** with *o*-methoxyphenylhydrazine led to indolenine **14**, albeit with a disappointing (22 %) yield. The indolenine approach thus seemed to be inappropriate for the synthesis of the analgesic 3-hydroxylated analogs of morphine along this route.

Dependence of the indolenine/indole ratio in the Fischer synthesis on the side of enolization of the hydrazone<sup>17</sup> was once again experienced upon reacting the mixture of ketolactams **12a,b** with phenylhydrazine, which yielded indolenine **15** (27%) and an unseparable mixture of the indoles **17a,b** (40%). Similar treatment of either **12a** or **12b** gave identical results. An improvement was obtained upon heating the mixture of silyl enol ethers **11a,b** with phenylhydrazine and TBAF in acetic acid, providing a better regiochemical outcome (indolenine/indoles = 1.4 : 1), but to the detriment of the overall yield (52%). Despite extensive experimentation, the yield of indolenine **15** could not be increased beyond *ca* 35%.

#### 10-Normorphinans **2b** and **2a** (Scheme 6)



i:  $\text{NaNO}_2$ , HCl aq, rt then HCl aq. (6 M), 60°C, 1 h; ii:  $\text{Et}_3\text{SiH}$ , TFA, rt; iii:  $\text{LiAlH}_4$ , ether, reflux. iv:  $\text{NaNO}_2$ , HCl (4%), 0°C→rt, 12 h, argon; v: toluene,  $\text{NaNH}_2$ , 100°C, 8–12 h then MeOH.

Scheme 6

The 16-oxo indolenine **13** was submitted to careful nitrosation at 0°C, followed by transformation of the diazo compound to hemiketal **18** in 62% yield. Reduction of **18** with triethylsilane in TFA gave lactam **19** (56%). The structure of **19** was confirmed by two-dimensional NMR experiments. The *N*-methyl group and the methylene protons on C-15 gave rise to singlets at  $\delta$ : 3.06 and  $\delta$ : 2.59 ppm, respectively. A one proton doublet of doublet at  $\delta$ : 3.65 ppm was ascribed to the axial H-9, deshielded by the lactam anisotropy. The observed coupling constants of H-9 with H-14 ( $J$ = 4.5 Hz) and H'-9 ( $J$ = 13 Hz) supported the equatorial orientation of H-14 ( $\delta$ : 1.65 ppm) and consequently the *cis* ring junction. The equatorial H'-9 was observed at  $\delta$ : 2.92 ppm with an additional fine splitting ( $J$ = 1 Hz), indicating the C(9)-H - C(14)-H dihedral angle to be about 65°. A one proton triplet with a small coupling ( $J$ = 2 Hz) observed at  $\delta$ : 4.13 ppm was in accordance with H-5 being in the bisector plane of the H-6 vicinal protons. Reduction of lactam **19** was achieved with LiAlH<sub>4</sub> to give quantitatively the ( $\pm$ )-4,5-epoxy-17-methyl-10-nor-14 $\alpha$ -morphinan **2b**.

The 9-oxo indolenine **15** underwent "nitrous acid deamination" at 0°C to give lactol **20** in 75% yield. At higher temperature (80°C) a mixture (67%) of nitro compounds<sup>18</sup> **22** and **23** was obtained, of which the 3-nitro derivative **23** is of interest in view of introducing the C-3 phenol function. Hemiketal **20** was smoothly reduced with triethylsilane in CH<sub>2</sub>Cl<sub>2</sub> in the presence of TFA to give **21** in 95% yield. Identity of the ring junctions in **19** and **21** was confirmed by LiAlH<sub>4</sub> reduction of **21** to **2b**.

Finally, partial epimerization of lactam **21** (NaNH<sub>2</sub>, toluene, reflux, then quenching with MeOH), gave lactam **24** (40%), whose reduction with LiAlH<sub>4</sub> afforded ( $\pm$ )-4,5-epoxy-10-normorphinan **2a**. As compared with that of the *cis* annelated lactam **21**, the <sup>1</sup>H-NMR spectrum of the *trans* annelated **24** revealed some typical differences: the signals of H-11, H-16<sub>ax</sub>, H-8<sub>ax</sub>, and H-6 were moved upfield by 0.2, 0.4, 0.5, and 0.6 ppm, respectively. Single crystal X-ray diffraction analysis<sup>19</sup> of lactam **24** furnished unequivocal evidence for the depicted structure (Figure 1, experimental section).

In conclusion, combination of Fischer indolization and "nitrous acid deamination" of indolenines has been shown a useful strategy for the construction of tetracyclic hexahydrobenzofuranes.

## Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra ( $\nu$ , cm<sup>-1</sup>) were recorded on a BOMEM FTIR apparatus with COSMIC interferometer; UV spectra were recorded on a Varian 634 spectrophotometer; <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were measured on a Bruker AC 300 apparatus at 300 MHz and 75 MHz, respectively. Mass spectra ( $E$  = 70 eV) were obtained on JEOL JMS D-300 and VG Autospec (Fisons) spectrometers; Kieselgel 60 PGF<sub>254</sub> (Merck N° 7749) was used for thin layer chromatography and Kieselgel 60 (Merck N° 9385) for flash chromatography.

"A-type" extraction protocol: after evaporation of the acetic acid, the residue was made alkaline with 10 % Na<sub>2</sub>CO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10-20 ml). The combined organic layers were washed with water (5 ml), dried over MgSO<sub>4</sub>, filtered and evaporated to dryness.

**3-Nitromethylcyclohexan-1-one (3)** : A mixture of 2-cyclohexen-1-one (10.0 g, 0.104 mol), nitromethane (10.0 g, 0.164 mol) and TBAF on silica gel (2 g) in anhydrous THF (400 ml) was heated at 80°C for 1 h. The reaction mixture was poured into water (200 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x100 ml), the organic layers were dried (MgSO<sub>4</sub>), the solvent was evaporated and the residue was distilled under reduced pressure to give **3** (12.1 g, 74%), as a pale yellow oil. Bp 108-110°C / 0.2 Hgmm. IR (neat)  $\nu$  1720, 1560, 1545 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  4.37 (ABX system, 2H, CH<sub>2</sub>NO<sub>2</sub>), 2.64 (m, 1H, H-3), 2.47 (m, 2H), 2.31 (m, 1H), 2.17 (m, 2H), 2.00 (m, 1H), 1.75 (m, 1H), 1.53 (dq,  $J_1$ =2,  $J_2$ =4.5 Hz, 1H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  208.1 (C-1), 80.0 (CH<sub>2</sub>NO<sub>2</sub>), 44.4, 40.7, 37.1 (C-3), 28.1, 24.3. MS  $m/z$  (%) 157 (M<sup>+</sup>, 3), 110 (30), 82 (25), 68 (40), 55 (100). Anal. calc. for C<sub>7</sub>H<sub>11</sub>NO<sub>3</sub>: C 53.49, H 7.05, N 8.91; found: C 53.31, H 7.17, N 8.49.

**Spiro[(3-methoxycarbonylaminomethylcyclohexane)-1,2'-dioxolane] (4)**: A solution of **3** (2.32 g, 14.7 mmol), *p*-TsOH (0.2 g, 0.95 mmol), ethylene glycol (10 ml, 11.13 g, 180 mmol) in benzene (120 ml) was refluxed under a Dean-Stark apparatus for 66 h. It was washed with 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (100 ml), dried (MgSO<sub>4</sub>), filtered, and the solvent evaporated to give spiro[(3-nitromethylcyclohexane)-1,2'-dioxolane] (2.96 g, 99%) as an oil. IR (neat)  $\nu$  1560, 1540, 1105, 1065 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  4.31 (dd, *J*<sub>1</sub>=1.5, *J*<sub>2</sub>=5 Hz, 2H, CH<sub>2</sub>NO<sub>2</sub>), 3.94 (s, 4H, dioxolane), 2.49 (m, 1H, H-3), 1.80-1.45 (m, 7H), 1.33 (t, *J*=7 Hz, 1H), 1.08 (dq, *J*<sub>1</sub>=2, *J*<sub>2</sub>=7 Hz, 1H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  108.7 (C-1), 80.8 (CH<sub>2</sub>NO<sub>2</sub>), 64.3 (CH<sub>2</sub> dioxolane), 38.3, 34.8 (C-3), 34.5, 28.5, 22.1. MS *m/z* (%) 201 (M<sup>+</sup>, 1), 155 (20), 141 (20), 112 (25), 99 (100), 86 (50). Anal. calc. for C<sub>9</sub>H<sub>15</sub>NO<sub>4</sub>: C 53.72, H 7.51, N 6.96; found: C 54.03, H 7.61, N 6.86.

A solution of spiro[(3-nitromethylcyclohexane)-1,2'-dioxolane] (4.02 g, 20.0 mmol) in absolute ethanol (50 ml) was hydrogenated over 5% Pd/C catalyst (200 mg). When H<sub>2</sub> consumption ceased, the catalyst was filtered and the solution evaporated to dryness to give spiro[(3-aminomethylcyclohexane)-1,2'-dioxolane] (3.15 g, 92%), which proved to be pure enough to use in the next step without purification. IR (film)  $\nu$  3220 (br) cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  3.93 (s, 4H, dioxolane), 2.70 (m, 2H, NH<sub>2</sub>), 2.62 (d, *J*=4 Hz, 2H, CH<sub>2</sub>NH<sub>2</sub>), 1.80 (m, 5H), 1.50 (m, 2H), 1.19 (t, *J*=7 Hz, 1H), 0.92 (m, 1H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  108.9 (C-1), 64.2 and 64.1 (CH<sub>2</sub>, dioxolane), 47.0 (CH<sub>2</sub>NH<sub>2</sub>), 36.9, 37.6 (C-3), 34.8, 29.0, 22.6. MS *m/z* (%) 172 ([M+H]<sup>+</sup>, 45), 141 (100), 99 (90).

A solution of spiro[(3-aminomethylcyclohexane)-1,2'-dioxolane] (5.31 g, 30.0 mmol), methyl chloroformate (4.7 ml, 5.75 g, 60.8 mmol) and triethylamine (8.5 ml, 6.17 g, 61.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 ml) was heated under reflux for 30 min. The solution was washed with a 4 % aqueous NH<sub>4</sub>Cl solution (50 ml), dried and filtered through a silica gel (70 g) packed column to afford **4** (6.1 g, 89 %) as pale yellow oil. IR (neat)  $\nu$  3330, 1647, 1564 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  4.70 (m, 1H, NH), 3.93 (s, 4H, dioxolane), 3.64 (s, 3H, OCH<sub>3</sub>), 3.09 (m, 2H, CH<sub>2</sub>-N), 1.80 (m, 5H), 1.50 (m, 2H), 1.20 (t, *J*=7 Hz, 1H), 0.92 (m, 1H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  157.1 (CO), 108.9 (C-1), 64.3 and 64.2 (CH<sub>2</sub>, dioxolane), 52.0 (OCH<sub>3</sub>), 46.6 (CH<sub>2</sub>-N), 40.0, 36.4 (C-3), 34.8, 29.1, 22.7. MS *m/z* (%) 229 (M<sup>+</sup>, 1), 141 (100), 99 (98), 86 (30), 55 (25). Anal. calc. for C<sub>11</sub>H<sub>19</sub>NO<sub>4</sub>: C 57.62, H 8.34, N 6.11; found: C 57.73, H 8.01, N 6.34.

**3-(*N*-Chloroacetyl-*N*-methylaminomethyl)-cyclohexan-1-one (5)**: A solution of **4** (14.4 g, 62.9 mmol) and LiAlH<sub>4</sub> (3.6 g, 94.9 mmol) in anhydrous THF (250 ml) was heated under reflux for 10 h. The excess of hydride was cautiously destroyed with ethyl acetate, then with wet THF. The suspension was filtered off, the filtrate was washed with water, dried (MgSO<sub>4</sub>), filtered and the solvents evaporated. The spiro[(3-methylaminomethylcyclohexane)-1,2'-dioxolane] (11.2 g, 96%) obtained was used without purification in the next step. IR (film)  $\nu$  3320 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  3.92 (s, 4H, CH<sub>2</sub> dioxolane), 3.10 (m, 2H, CH<sub>2</sub>-N), 2.42 (s, 3H, NCH<sub>3</sub>), 1.80 (m, 5H), 1.50 (m, 2H), 1.22 (t, *J*=7 Hz, 1H), 0.94 (m, 1H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  109.1 (C-1), 64.2 and 64.1 (CH<sub>2</sub> dioxolane), 44.1, 39.8, 36.5, 35.5, 35.0, 29.9, 23.0. MS *m/z* (%) 185 (M<sup>+</sup>, 15), 141 (85), 99 (45), 72 (50), 58 (100).

A solution of spiro[(3-methylaminomethylcyclohexane)-1,2'-dioxolane] (3.7 g, 20.0 mmol), chloroacetyl chloride (3.2 ml, 4.54 g, 40.1 mmol) and triethylamine (5.6 ml, 4.06 g, 40.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was heated under reflux for 0.5 h. The solution was washed with 4% aqueous NH<sub>4</sub>Cl (50 ml), dried (MgSO<sub>4</sub>) and filtered through a silica gel (16 g) packed column to give spiro[(3-(*N*-chloroacetyl-*N*-methylaminomethylcyclohexane))-1,2'-dioxolane] (4.05 g, 65%) which slowly crystallized from CH<sub>2</sub>Cl<sub>2</sub>. Mp 78°C (CH<sub>2</sub>Cl<sub>2</sub>). IR (KBr)  $\nu$  3450, 1650, 1445, 1410, 1068 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  4.08 (s, 2H, CH<sub>2</sub>Cl), 3.94 (s, 4H, CH<sub>2</sub> dioxolane), 3.31-3.10 (m, 2H, CH<sub>2</sub>-N), 3.09 and 2.98 (s, 3H, NCH<sub>3</sub>), 2.0 (m, 1H), 1.70-1.20 (m, 7H), 1.10-0.80 (m, 2H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  166.7 (CO), 108.9 and 108.7 (C-1), 64.4 and 64.3 (CH<sub>2</sub> dioxolane), 55.9, 53.4 (2 signals), 50.1, 39.1, 39.0, 34.7 (2 signals), 34.7 and 34.1 (C-3), 29.4 (2 signals), 22.7, 22.6. MS *m/z* (%) 263 and 261 (M<sup>+</sup>, 8), 154 (80), 141 (100), 126 (45), 112 (40), 99 (95). Anal. calc. for C<sub>12</sub>H<sub>20</sub>NO<sub>3</sub>Cl: C 55.06, H 7.70, N 5.35; found: C 55.11, H 7.52, N 4.92.

A solution of spiro[(3-(*N*-chloroacetyl-*N*-methylaminomethylcyclohexane))-1,2'-dioxolane] (4.0 g, 15.1 mmol) in 1.2 M aqueous HCl (100 ml) was heated at 80°C until disappearance of the starting material,

controlled by TLC. It was then extracted with  $\text{CH}_2\text{Cl}_2$  (3x100 ml), washed with 5% aqueous  $\text{NaHCO}_3$ , dried ( $\text{MgSO}_4$ ) and evaporated. The residue (2.8 g) was purified by column chromatography on silica gel (30 g, eluent: hexane) to give **5** (2.08 g, 64%) as a pale yellow oil. IR (neat)  $\nu$  1705, 1650, 1408, 1228, 1116, 790  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  4.09 (s, 2H,  $\text{CH}_2\text{Cl}$ ), 3.39 (m, 2H,  $\text{CH}_2\text{-N}$ ), 3.11 and 2.97 (s, 3H,  $\text{NCH}_3$ ), 2.41-2.11 (m, 7H), 1.86 (m, 1H), 1.67 (m, 1H), 1.45 (m, 1H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  210.3 (CO), 166.8 (NCO), 55.2, 53.1, 45.2 and 45.1, 44.1 (2 signals), 37.9 and 37.2, 36.1 and 34.2, 28.7 and 28.6, 24.8 and 24.7. MS  $m/z$  (%) 220 and 218 ( $[\text{M}+\text{H}]^+$ , 0.5), 181 (4), 140 (5), 122 (30), 120 (100), 110 (95). Anal. calc. for  $\text{C}_{10}\text{H}_{16}\text{NOCl}$ : C 55.17, H 7.41, N 6.43; found: C 55.03, H 6.88, N 6.14.

(*trans*)-3,5-Dioxo-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (**6**) : To a solution of **5** (1.35 g, 6.2 mmol) in dry toluene (50 ml), was added freshly sublimed potassium *t*-butoxide (1.40 g, 12.5 mmol) at  $0^\circ\text{C}$  under argon. The temperature was raised to  $90^\circ\text{C}$  and maintained for 2 h. At the end of the reaction aqueous HCl (1.4 M, 10 ml) and  $\text{CH}_2\text{Cl}_2$  (200 ml) were added; after separation the organic phase was washed with water (50 ml), dried ( $\text{MgSO}_4$ ), and filtered through a silica gel (6 g) packed column to give **3** (0.96 g, 86%) as a white waxy solid. IR (film)  $\nu$  1706, 1638, 1334, 1252  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.34 (dd,  $J_1=4.5$ ,  $J_2=12$  Hz, 1H, H-1), 3.22 (dd,  $J_1=11$ ,  $J_2=12$  Hz, 1H, H'-1), 2.95 (s, 3H,  $\text{NCH}_3$ ), 2.6-2.35 (m, 5H), 2.13 (ddd,  $J_1=4.5$ ,  $J_2=10$ ,  $J_3=11$  Hz, 1H, H-4a), 1.98 (m, 1H, H-8a), 1.82 (m, 2H), 1.52 (m, 1H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  208.6 (CO), 167.0 (NCO), 55.3 (C-1), 48.9 ( $\text{NCH}_3$ ), 41.0, 40.2 (C-4a), 34.3 (C-8a), 31.0, 28.7, 25.7. MS  $m/z$  (%) 181 ( $\text{M}^+$ , 100), 138 (40), 110 (40), 82 (35). Anal. calc. for  $\text{C}_{10}\text{H}_{15}\text{NO}_2$ : C 66.27, H 8.34, N 7.72; found C 66.20, H 8.01, N 7.46.

Otherwise, compound **6** could also be obtained from urethane **4** without purification of the intermediates in 46.9 % overall yield.

*N*-Methyl-*N*-(3-oxohex-1-en-6-yl)-acrylamide (**9**) : To a stirred solution of 1-methyl-1H-hexahydroazepin-4-one<sup>13</sup> (1.52 g, 12.0 mmol) in dry toluene (40 ml) was added a solution of acryloyl chloride (2.72 g, 30.0 mmol) in toluene (10 ml) dropwise over 30 min. After stirring at room temperature for 30 min, Hunig's base (2.32 g, 18.0 mmol) was added and the reaction mixture was heated at  $100^\circ\text{C}$  for 1.5-2.5 h. The mixture was treated with 10 %  $\text{Na}_2\text{CO}_3$  (30 ml), separated and the aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$  (4x30 ml). The organic layers were dried ( $\text{MgSO}_4$ ), filtered, evaporated to dryness and purified by Chromatotron® (eluent:  $\text{CH}_2\text{Cl}_2$ :1->3 % MeOH) to give 0.99 g (46%) of **9**, as pale yellow oil and 0.28 g (18%) of recovered starting material. UV (MeOH) 205, 235 nm. IR (film)  $\nu$  1695, 1685, 1645, 1605  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  6.58 and 6.63 (dd,  $J_1=11$ ,  $J_2=18$  Hz, 1H,  $\text{CH}_2=\text{CHCO}$ ), 6.25-6.40 (m, 2H, olefinic), 6.22 and 6.28 (dd,  $J_1=1$ ,  $J_2=18$  Hz, 1H,  $\text{CH}_2=\text{CHCO}$ ), 5.66 (dd,  $J_1=1.5$ ,  $J_2=11$  Hz, 1H,  $\text{CH}_2=\text{CHCO}$ ), 3.40 and 3.47 (t, 2H,  $\text{CH}_2\text{NCO}$ ), 3.01 and 3.06 (s, 3H,  $\text{NCH}_3$ ), 2.62 (m, 2H,  $\text{CH}_2\text{-CH}_2\text{-CO}$ ), 1.90 (m, 2H,  $\text{CH}_2\text{-CH}_2\text{-CO}$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  201.0 and 199.3 (CO), 166.6 and 166.5 (NCO), 136.5 and 136.3 ( $\text{CH}_2=\text{CHCO}$ ), 128.6 and 128.3 ( $\text{CH}_2=\text{CHCON}$ ), 128.0 and 127.8 ( $\text{CH}_2=\text{CHCO}$ ), 127.9 and 127.5 ( $\text{CH}_2=\text{CHCON}$ ), 49.1 and 47.2 ( $\text{-CH}_2\text{-NCH}_3$ ), 36.7 and 35.7 ( $\text{-CH}_2\text{-CO-CH=CH}_2$ ), 35.4 and 33.9 ( $\text{NCH}_3$ ), 22.5 and 21.3 ( $\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-NCH}_3$ ). MS  $m/z$  (%) 182 ( $[\text{M}+\text{H}]^+$ , 4), 181 ( $\text{M}^+$ , 1), 126 (8), 114 (18), 101 (28). HREIMS calc. for  $\text{C}_{10}\text{H}_{16}\text{NO}_2$   $m/z$  182.1181, found 182.1186.

*N*-Methyl-*N*-(3-*t*-butyldimethylsilyloxyhex-1,3-diene-6-yl)-acrylamide (**10**) : To a solution of freshly sublimed *t*-BuOK (191 mg, 1.72 mmol) in dry THF (10 ml) at  $-78^\circ\text{C}$  was added by syringe a solution of **9** (280 mg, 1.55 mmol) and TBDMSCl (260 mg, 1.72 mmol) in THF (4 ml). After stirring for 10 min the mixture was filtered on a Florisil® column (eluent:  $\text{CH}_2\text{Cl}_2$ :EtOAc 2:1) to give **10**, as an oil (366 mg, 80 %). IR (film)  $\nu$  1650, 1610  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  6.30 and 6.33 (dd,  $J_1=2$ ,  $J_2=17$  Hz, 1H,  $\text{CH}_2=\text{CHCON}$ ), 6.13 and 6.16 (dd,  $J_1=11$ ,  $J_2=18$  Hz,  $\text{CH}_2=\text{CH-C(OSi)=}$ ), 4.98 and 5.03 (dd,  $J_1=2$ ,  $J_2=10.5$  Hz, 1H,  $\text{CH}_2=\text{CHCON}$ ), 4.69 and 4.78 (t,  $J=7.5$  Hz, 1H,  $\text{SiO-C=CH-CH}_2$ ), 3.37 and 3.48 (t,  $J=7.5$  Hz, 2H,  $\text{-CH}_2\text{-CH}_2\text{-N}$ ), 3.01 and 3.05 (s, 3H,  $\text{NCH}_3$ ), 2.41 (dt,  $J_1=J_2=7.5$  Hz, 2H,  $\text{-CH}_2\text{-CH}_2\text{-N}$ ), 0.91 (s, 9H,  $\text{SiC(CH}_3)_3$ ), 0.15 (s, 6H,  $\text{Si(CH}_3)_2$ ).

**2-Methyl-1-oxo-5-*t*-butyldimethylsilyloxy-1,2,3,4,4a,7,8,8a-octahydroisoquinoline** [*cis*(**11a**), *trans*(**11b**)] : Heating a degassed benzene (20 ml) solution of **10** (360 mg, 1.22 mmol) in a sealed tube at 135–140°C for 1.5–3 h, followed by separation by flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>:EtOAc 9:1) led to the less polar *trans* **11b** (57 mg, 16 %) and the more polar *cis* **11a** (244 mg, 68 %), along with some recovered starting material (20 mg, 5 %). **11b** (*trans*) colourless syrup. IR (film)  $\nu$  1695, 1645 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  4.83 (dd,  $J_1=J_2=2.5$  Hz, 1H, -CH=C), 3.31 (m, 2H, -CH<sub>2</sub>-N), 2.92 (s, 3H, NCH<sub>3</sub>), 2.21–2.48 (m, 3H), 2.11 (m, 2H), 1.54 (m, 2H), 1.31 (m, 1H), 0.90 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.15 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>). MS  $m/z$  (%) 295 (M<sup>+</sup>, 22), 281 (14), 238 (36), 224 (41). **11a** (*cis*) colourless syrup. IR (film)  $\nu$  1695, 1650 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  4.90 (t,  $J=3.6$  Hz, 1H, H-6), 3.25 (dd,  $J_1=5$ ,  $J_2=7.7$  Hz, 2H, H<sub>2</sub>-3), 2.93 (s, 3H, NCH<sub>3</sub>), 2.61 (ddd,  $J_1=4$ ,  $J_2=5.5$ ,  $J_3=9.5$  Hz, 1H, H-8a), 2.40 (dt,  $J_1=5$ ,  $J_2=5.5$  Hz, 1H, H-4a), 2.05 (m, 2H, H<sub>2</sub>-7), 1.98 (m, 1H, H'-4), 1.75–1.92 (m, 3H, H<sub>2</sub>-8, H-4), 0.92 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.15 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  172.0 (CO), 150.2 (=C-OSi), 104.4 (C-6), 48.6 (C-3), 41.5 (C-4a), 37.9 (C-8a), 34.9 (NCH<sub>3</sub>), 29.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 24.4 (C-7), 23.7 (C-8), 22.7 (C-4), -4.5 (-OSi(CH<sub>3</sub>)<sub>2</sub>). MS  $m/z$  (%) 295 (M<sup>+</sup>, 45), 280 (22), 238 (42), 211 (83). HREIMS calc. for C<sub>16</sub>H<sub>29</sub>NO<sub>2</sub>Si  $m/z$  295.1966, found 295.1943.

**1,5-Dioxo-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline** [*cis*(**12a**), *trans*(**12b**)] : A mixture of the silylenol ethers (**11a**, **11b**) (110 mg, 0.37 mmol) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was treated with a 10 % solution of TBAF in THF (3 ml) at room temperature for 1 h. After evaporation of the solvent the residue was purified by column chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>:EtOAc 3:1) to give a mixture (61 mg, 92 %) of **12a** (more polar, *cis*) and **12b** (less polar, *trans*) in a 3:1 ratio. **12a** (*cis*) amorphous gum. IR (KBr)  $\nu$  1710, 1625 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  3.43 (ddd,  $J_1=4.5$ ,  $J_2=5.5$ ,  $J_3=11.5$  Hz, 1H, H-3), 3.13 (ddd,  $J_1=5.5$ ,  $J_2=8$ ,  $J_3=11.5$  Hz, 1H, H'-3), 2.84 (s, 3H, NCH<sub>3</sub>), 2.71 (ddd,  $J_1=5$ ,  $J_2=5.5$ ,  $J_3=11.5$  Hz, 1H, H-8a), 2.42–2.25 (m, 4H), 2.15 (m, 1H), 1.85–1.55 (m, 4H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  209.2 (CO), 169.9 (NCO), 47.1 (C-3), 46.5 (C-4a), 43.5 (C-8a), 40.5 (C-6), 34.6 (NCH<sub>3</sub>), 26.0 (C-8), 23.2 (C-7), 22.0 (C-4). MS  $m/z$  (%) 183 ([M+2H]<sup>+</sup>, 8), 182 ([M+H]<sup>+</sup>, 21), 181 (M<sup>+</sup>, 17), 155 (13), 154 (33), 113 (32), 112 (45). HREIMS calc. for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>  $m/z$  181.1103, found 181.1100. **12b** (*trans*) mp 95–97°C (EtOAc, ether). IR (KBr)  $\nu$  1700, 1635 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  3.36 (m, 2H, H<sub>2</sub>-3), 3.01 (s, 3H, NCH<sub>3</sub>), 2.67 (m, 1H, H-8), 2.53 (ddd,  $J_1=3$ ,  $J_2=11$ ,  $J_3=12$  Hz, 1H, H-4a), 2.55–2.36 (m, 2H, H<sub>2</sub>-6), 2.35–2.21 (m, 3H, H-8a, H-4, H-7), 1.78 (m, 1H, H'-4), 1.71 (m, 1H, H'-7), 1.69 (dddd,  $J_1=3.3$ ,  $J_2=12$ ,  $J_3=13$ ,  $J_4=25$  Hz, 1H, H'-8). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  209.2 (CO), 169.9 (NCO), 49.7 (C-4a), 48.3 (C-3), 47.5 (C-8a), 40.6 (C-6), 34.7 (NCH<sub>3</sub>), 26.6 (C-8), 25.6 (C-7), 21.6 (C-4). MS  $m/z$  (%) 183 ([M+2H]<sup>+</sup>, 18), 182 ([M+H]<sup>+</sup>, 100), 181 (M<sup>+</sup>, 11), 154 (19), 153 (14), 139 (27). HREIMS calc. for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>  $m/z$  181.1101, found 181.1102.

**17-Methyl-16-oxo-10-nor-14 $\alpha$ ,5-nitrilomorphinan** (**13**) : A mixture of **6** (0.54 g, 2.98 mmol) and phenylhydrazine (98 %) (4.5 ml, 4.95 g, 4.57 mmol) in acetic acid (10 ml) was heated at 100°C for 2.5 h. The reaction mixture was diluted with water (100 ml), the aqueous phase washed with CHCl<sub>3</sub> (2x30 ml), made alkaline with Na<sub>2</sub>CO<sub>3</sub> and extracted with CHCl<sub>3</sub> (3x50 ml). The combined organic extracts were washed with water (3x30 ml), dried (MgSO<sub>4</sub>) and evaporated to give **13** (0.60 g, 79%), which crystallized in MeOH. Mp 160°C (MeOH). UV (MeOH) 215, 252 nm. IR (KBr)  $\nu$  1648, 1630, 1588 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.62 (d,  $J=7$  Hz, 1H, H-3), 7.38 (m, 1H), 7.19 (m, 2H), 3.96 (dd,  $J_1=5$ ,  $J_2=13.5$  Hz, 1H, H $\alpha$ -9), 3.25 (dd,  $J_1=1$ ,  $J_2=13.5$  Hz, 1H, H $\beta$ -9), 3.11 (s, 3H, NCH<sub>3</sub>), 2.91 (d,  $J=16$  Hz, 1H, H-15), 2.87 (m, 1H, H-6), 2.64 (dt,  $J_1=6$ ,  $J_2=13.5$  Hz, 1H, H'-6), 2.27 (m, 1H, H-7), 2.06 (d,  $J=16$  Hz, 1H, H'-15), 1.96 (m, 1H, H-8), 1.71 (m, 1H, H'-8), 1.58–1.48 (m, 2H, H'-7, H-14a). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  185.3 (C=N), 166.5 (NCO), 154.2 (C-4), 142.9 (C-12), 128.4 (C-2), 125.3 (C-1), 122.3 (C-11), 120.7 (C-3), 56.0 (C-13), 53.0 (C-9), 40.3 (NCH<sub>3</sub>), 34.9 (C-14), 32.8, 28.1, 27.3, 27.0 (C-15, C-8, C-7, C-6). MS  $m/z$  (%) 254 (M<sup>+</sup>, 100), 211 (10), 183 (30), 93 (20). HREIMS calc. for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O  $m/z$  254.1418, found 254.1415.



**3-Methoxy-17-methyl-16-oxo-10-nor-14 $\alpha$ -4,5-nitrilomorphinan (14)** : Under the above mentioned conditions **6** (0.54 g, 2.98 mmol) and 2-methoxyphenylhydrazine (0.62 g, 4.48 mmol) gave **14** (0.20 g, 22%). Mp 145–148°C (MeOH). UV (MeOH) 220 (sh), 245, 270 nm. IR (KBr)  $\nu$  1650, 1590  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.18 (t,  $J=7$  Hz, 1H, H-1), 6.93 (d,  $J=7$  Hz, 1H, H-2), 6.80 (d,  $J=7$  Hz, 1H, H-11), 3.98 (s, 3H,  $\text{OCH}_3$ ), 3.95 (dd,  $J_1=5$ ,  $J_2=13.5$  Hz, 1H,  $\text{H}_{\alpha-9}$ ), 3.25 (d,  $J=13.5$  Hz, 1H,  $\text{H}_{\beta-9}$ ), 3.12 (s, 3H,  $\text{NCH}_3$ ), 2.97 (dd,  $J_1=3.5$ ,  $J_2=13.5$  Hz, 1H, H-6), 2.90 (d,  $J=16$  Hz, 1H, H-15), 2.60 (dt,  $J_1=6$ ,  $J_2=13.5$  Hz, 1H, H'-6), 2.25 (m, 1H, H-7), 2.06 (d,  $J=16$  Hz, 1H, H'-15), 1.96 (dq,  $J_1=3.5$ ,  $J_2=13.5$  Hz, 1H, H-8), 1.70 (m, 1H, H'-8), 1.50 (m, 2H, H'-6, H'-7).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  183.6 (C=N), 166.3 (NCO), 151.4 (C-4), 144.8 (C-3), 142.0 (C-12), 126.5 (C-1), 114.6 (C-11), 110.8 (C-2), 56.3 (C-13), 55.6 ( $\text{OCH}_3$ ), 52.8 (C-9), 40.3 ( $\text{NCH}_3$ ), 34.7 (C-14), 32.6, 28.0, 27.2, 27.0 (C-15, C-8, C-7, C-6). MS  $m/z$  (%) 284 ( $\text{M}^+$ , 100), 283 (80), 255 (30), 204 (20), 199 (70), 170 (30).

**17-Methyl-16-oxo-10-nor-14 $\alpha$ -4,5-iminomorphinan (16)** : To a solution of **13** (0.13 g, 0.51 mmol) in acetic acid (5 ml), was added  $\text{NaBH}_3\text{CN}$  (0.06 g, 0.95 mmol) at room temperature in 15 min. The mixture was stirred for 15 min, quenched with cold water (30 ml), made alkaline ( $\text{Na}_2\text{CO}_3$ ), then extracted with  $\text{CHCl}_3$  (3x30 ml). The organic layers were dried ( $\text{MgSO}_4$ ), filtered, evaporated to dryness and purified by preparative TLC (eluent:  $\text{CHCl}_3$ :MeOH 95:5) to give **16** (0.08 g, 62%). Mp 192–194°C (MeOH). UV (MeOH) 210, 230, 278 nm. IR (KBr)  $\nu$  3345, 1632, 1601  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.08 (m, 2H), 6.74 (m, 2H), 3.80 (m, 1H, NH), 3.73 (dd,  $J_1=4$ ,  $J_2=6$  Hz, 1H, H-5), 3.19 (dd,  $J_1=6$ ,  $J_2=13$  Hz, 1H, H-9), 2.97 (s and m, 5H,  $\text{NCH}_3$ , H'-5, H-15), 2.45 (m, 2H), 2.02–1.71 (m, 4H), 1.29 (dq,  $J_1=3$ ,  $J_2=13$  Hz, 1H), 1.08 (dq,  $J_1=3$ ,  $J_2=13$  Hz, 1H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  169.5 (NCO), 149.4 (C-4), 135.1 (C-12), 127.3 (C-2), 123.4 (C-11), 119.3 (C-1), 110.5 (C-3), 61.5 (C-5), 55.4 (C-9), 41.4 ( $\text{NCH}_3$ ), 38.1 (C-14), 34.3, 32.0, 28.6, 27.8 (C-15, C-8, C-7, C-6). MS  $m/z$  (%) 256 ( $\text{M}^+$ , 100), 170 (10), 145 (15), 135 (30), 130 (30), 113 (35), 98 (10), 93 (20). HREIMS calc. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$   $m/z$  256.1574, found 256.1559. Anal. calc. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$ : C 74.96, H 7.86, N 10.92; found: C 75.10, H 7.70, N 10.59.

**17-Methyl-9-oxo-10-nor-14 $\alpha$ -4,5-nitrilomorphinan (15) and 3-methyl-4-oxo-11H-1,2,3,4,4a,5,6,11b-octahydro-indolo[2,3-f]isoquinoline (17a,b)** : **1. From the bicyclic ketones (12a,b)** : A mixture of **12a,b** (72 mg, 0.40 mmol) and phenylhydrazine (86.4 mg, 0.80 mmol) was stirred at 40°C for 30 min. Glacial acetic acid (0.5 ml) was added and the solution was heated at 100°C for 3 h. The residue, resulting from an "A-type" extraction protocol, was separated by preparative TLC (eluent:  $\text{CH}_2\text{Cl}_2$ :EtOAc 2:1) to give indolenine (**15**) (27 mg, 27 %) and indoles (**17a,b**) (40 mg, 40 %). **15** (indolenine) mp 81–83°C (MeOH, ether). UV (MeOH) 214, 256 nm. IR (KBr)  $\nu$  1630, 1610  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J=7.6$  Hz, 1H, H-3), 7.39 (dt,  $J_1=1.5$ ,  $J_2=7.6$  Hz, 1H, H-2), 7.18 (m, 2H, H-1, H-11), 3.74 (ddd,  $J_1=6$ ,  $J_2=12$ ,  $J_3=13$  Hz, 1H, H-16), 3.51 (ddd,  $J_1=5.5$ ,  $J_2=6$ ,  $J_3=13$  Hz, 1H, H'-16), 3.14 (s, 3H,  $\text{NCH}_3$ ), 2.93 (ddd,  $J_1=2$ ,  $J_2=5$ ,  $J_3=13.5$  Hz, 1H, H-6), 2.63 (m, 1H, H'-6), 2.59 (ddd,  $J_1=5.5$ ,  $J_2=J_3=13$  Hz, 1H, H'-15), 2.23 (m, 3H, H-7, H-8, H-14), 1.85 (dt,  $J_1=4$ ,  $J_2=14$  Hz, 1H, H'-8), 1.52 (dt,  $J_1=4$ ,  $J_2=13$ ,  $J_3=14$  Hz, 1H, H'-7), 1.26 (dd,  $J_1=6$ ,  $J_2=13$  Hz, 1H, H'-15).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  185.9 (C=N), 170.5 (CO), 154.3 (C-4), 142.0 (C-12), 128.6 (C-2), 125.2 (C-1), 122.7 (C-11), 120.8 (C-3), 55.3 (C-13), 48.5 (C-14), 46.7 (C-16), 34.6 ( $\text{NCH}_3$ ), 29.2 (C-6), 27.4 (C-8), 27.3 (C-15), 24.1 (C-7). MS  $m/z$  (%) 254 ( $\text{M}^+$ , 100), 253 (13), 226 (14), 225 (11), 211 (19), 197 (20), 183 (96). HREIMS calc. for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$   $m/z$  254.1417, found 254.1411. **17a,b** (indoles, non separable mixture (1:1) of *cis* and *trans* ring fused products). UV (MeOH) 220, 280, 290 nm. IR (KBr)  $\nu$  3380, 1685  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.32 and 8.21 (s, 1H, indole NH), 7.45–7.07 (m, 4H, aromatic), 3.71 (m, 1H), 3.40–3.15 (m, 2H), 2.95 and 2.81 (s, 3H,  $\text{NCH}_3$ ), 2.90 (m, 1H), 2.72 (m, 1H), 2.31–1.91 (m, 4H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  175.9 and 172.5 (CO), 136.2 and 133.9 (C-4), 132.3 and 136.6 (C-5), 128.9 and 126.6 (C-12), 121.4 and 121.2 (C-1), 118.8 and 118.7 (C-11), 117.9 and 117.8 (C-2), 111.2 (C-6), 110.6 (C-3), 53.9 and 48.0 (C-16), 41.7 and 41.3 (C-14), 34.8 and 29.5 (C-13), 32.0 and 30.7 ( $\text{NCH}_3$ ), 26.3 and 24.8 (C-7), 22.0 (C-8), 19.4 and 17.8 (C-15). MS  $m/z$  (%) 255 ( $[\text{M}+\text{H}]^+$ , 17), 254 ( $\text{M}^+$ , 82), 241 (13), 240 (71), 170 (33), 169 (100). HREIMS calc. for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$   $m/z$  254.1417, found 254.1422.

**2. Starting from silvlenolethers (11a,b)** : To a stirred (room temperature for 15 min) mixture of (11a,b) (93 mg, 0.31 mmol) and TBAF (390 mg, 1.49 mmol) phenylhydrazine (85 mg, 0.78 mmol) was added, the reaction mixture was stirred again at 40°C for 30 min, then acetic acid (4 ml) was added and refluxed for 3 h. The residue resulting from an "A-type" extraction protocol led to **15** (25 mg, 31 %) and **17a,b** (17 mg, 21 %) after preparative TLC (eluent: CH<sub>2</sub>Cl<sub>2</sub>:EtOAc 2:1).

**17-Methyl-5-hydroxy-16-oxo-10-nor-14 $\alpha$ -4,5-epoxymorphinan (18)** : To an ice-cold solution of **13** (0.51 g, 2.0 mmol) in 1.2 M aqueous HCl (30 ml) aqueous NaNO<sub>2</sub> (1 M, 3 ml) was added dropwise. The mixture was stirred for 1 h, treated with 6M aqueous HCl (2 ml) and heated at 60°C for 1 h. After cooling, it was extracted with CHCl<sub>3</sub> (3x30 ml), the organic layers were dried (MgSO<sub>4</sub>), and evaporated to dryness to afford **18** (0.34 g, 62 %), which crystallized from MeOH. Mp 190-192°C (MeOH). UV (MeOH) 210, 273, 280 nm. IR (KBr)  $\nu$  3315, 1630 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.18 (t, J=7 Hz, 1H, H-2), 7.02 (d, J=7 Hz, 1H, H-11), 6.90 (d and t, J=7 Hz, 2H, H-3, H-1), 3.72 (m, 1H, OH), 3.58 (dd, J<sub>1</sub>=4.5, J<sub>2</sub>=13 Hz, 1H, H-9), 3.03 (s, 3H, NCH<sub>3</sub>), 2.94 (dd, J<sub>1</sub>=1, J<sub>2</sub>=13 Hz, 1H, H'-9), 2.70 (AB system, 2H, H<sub>2</sub>-15), 2.34 (m, 1H), 1.85 (m, 3H), 1.50 (m, 5H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  168.4 (NCO), 156.1 (C-4), 135.2 (C-12), 128.6 (C-2), 123.4 (C-11), 121.4 (C-1), 111.5 (C-3), 110.1 (C-5), 51.8 (C-9), 49.9 (C-13), 39.7 (NCH<sub>3</sub>), 34.9 (C-14), 31.3, 31.1, 26.0, 22.0 (C-15, C-8, C-7, C-6). MS *m/z* (%) 273 (M<sup>+</sup>, 45), 245 (80), 244 (65), 202 (100), 181 (25). HREIMS calc. for C<sub>16</sub>H<sub>19</sub>NO<sub>3</sub> *m/z* 273.1364, found 273.1363.

**17-Methyl-16-oxo-10-nor-14 $\alpha$ -4,5-epoxymorphinan (19)** : A solution of **18** (0.55 g, 2.0 mmol) in TFA (2 ml) was stirred with triethylsilane (0.47 g, 4.04 mmol) at room temperature for 10 min. The reaction was quenched with water (50 ml) and extracted with CHCl<sub>3</sub> (3x30 ml). The organic extracts were washed with water, dried (MgSO<sub>4</sub>), evaporated to dryness and purified by preparative TLC (eluent: CHCl<sub>3</sub>:MeOH 95:5) to give **19** (0.29 g, 56%) which crystallized from MeOH. Mp 224-226°C (MeOH). UV (MeOH) 220, 275 nm. IR (KBr)  $\nu$  1645, 1638, 1505, 1499 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.18 (t, J=7 Hz, 1H, H-2), 6.99 (d, J=7 Hz, 1H, H-11), 6.89 (m, 2H, H-3, H-1), 4.13 (t, J=2 Hz, 1H, H-5), 3.65 (dd, J<sub>1</sub>=4.5, J<sub>2</sub>=13 Hz, 1H, H-9), 3.06 (s, 3H, NCH<sub>3</sub>), 2.92 (dd, J<sub>1</sub>=1, J<sub>2</sub>=13 Hz, 1H, H'-9), 2.59 (s, 2H, H<sub>2</sub>-15), 2.28 (m, 1H, H-6), 1.80-1.45 (m, 6H, H<sub>2</sub>-8, H<sub>2</sub>-7, H-14, H'-6). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  167.7 (NCO), 158.4 (C-4), 136.4 (C-12), 128.4 (C-2), 122.7 (C-11), 120.9 (C-1), 110.6 (C-3), 86.5 (C-5), 51.2 (C-9), 45.3 (C-13), 36.5 (NCH<sub>3</sub>), 34.9 (C-14), 33.7, 26.2, 26.1, 21.1 (C-15, C-8, C-7, C-6). MS *m/z* (%) 257 (M<sup>+</sup>, 100), 184 (70), 144 (40), 97 (80). HREIMS calc. for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub> *m/z* 257.1415, found 257.1404. Anal. calc. for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub>: C 74.67, H 7.44, N 5.44; found: C 74.60, H 7.72, N 5.57.

**17-Methyl-10-nor-14 $\alpha$ -4,5-epoxymorphinan (2b)** : LiAlH<sub>4</sub> (0.08 g, 2.1 mmol) was added portionwise to a solution of **19** (0.26 g, 1.0 mmol) in dry ether (100 ml). The reaction mixture was heated under reflux for 3 h. Unreacted LiAlH<sub>4</sub> was destroyed with wet ether, and then with water (50 ml), the ethereal phase was collected, dried (MgSO<sub>4</sub>), and evaporated to dryness to give **2b** (0.23 g, 95%) which crystallized from ether. Mp 66°C (ether). UV (MeOH) 220, 276 nm. IR (KBr)  $\nu$  2770, 1470, 1460 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.42 (d, J=7 Hz, 1H, H-11), 7.11 (t, J=7 Hz, 1H, H-2), 6.82 (m, 2H, H-1, H-3), 4.26 (t, J=2 Hz, 1H, H-5), 2.70 (m, 2H, H<sub>2</sub>-16), 2.57 (dd, J<sub>1</sub>=2, J<sub>2</sub>=11 Hz, 1H, H-9), 2.38 (m, 1H, H'-9), 2.34 (s, 3H, NCH<sub>3</sub>), 2.02 (m, 2H, H-15), 1.70 (m, 7H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  158.7 (C-4), 137.5 (C-12), 127.7 (C-2), 124.2 (C-11), 120.2 (C-1), 110.4 (C-3), 86.6 (C-5), 57.6 (C-16), 53.3 (C-9), 50.5 (C-13), 46.7 (NCH<sub>3</sub>), 38.4 (C-14), 29.6 (C-15), 26.7 (C-8), 26.4 (C-6), 20.0 (C-7). MS *m/z* (%) 243 (M<sup>+</sup>, 100), 200 (10), 186 (15), 71 (60), 70 (80), 58 (30), 57 (35). Anal. calc. for C<sub>16</sub>H<sub>21</sub>NO: C 78.97, H 8.69, N 5.75; found: C 78.67, H 8.96, N 5.93.

**5-Hydroxy-17-methyl-9-oxo-10-nor-14 $\alpha$ -4,5-epoxymorphinan (20)** : To an ice-cold solution of **15** (26 mg, 0.10 mmol) in 4 % aqueous HCl (3 ml) was added a solution (1 M) of NaNO<sub>2</sub> (0.15 ml, 0.15 mmol) dropwise by syringe and the reaction mixture was left at room temperature under argon atmosphere overnight. After extraction with CH<sub>2</sub>Cl<sub>2</sub> (3x5 ml) the residue was purified by preparative TLC (eluent: CH<sub>2</sub>Cl<sub>2</sub>:MeOH 98:2),

crystallized from ether to obtain **20** (21 mg, 77%). Mp 207-210°C (ether). UV (MeOH) 215, 280 nm. IR (KBr)  $\nu$  3240, 1620  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.18 (dt,  $J_1=1.2$ ,  $J_2=8$  Hz, 1H, H-2), 7.05 (dd,  $J_1=1.2$ ,  $J_2=8$  Hz, 1H, H-11), 6.91 (dt,  $J_1=1.2$ ,  $J_2=8$  Hz, 1H, H-1), 6.85 (d,  $J=8$  Hz, 1H, H-3), 4.64 (br, 1H, OH), 3.72 (m, 1H, H-16), 3.58 (m, 1H, H'-16), 3.05 (s, 3H,  $\text{NCH}_3$ ), 2.31-2.18 (m, 4H), 1.91-1.58 (m, 5H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  170.8 (CO), 156.3 (C-4), 134.2 (C-12), 128.8 (C-2), 123.6 (C-11), 121.8 (C-1), 110.9 (C-3), 109.3 (C-5), 49.6 (C-14), 46.7 (C-16), 46.5 (C-13), 34.7 ( $\text{NCH}_3$ ), 32.0 (C-6), 24.3 (C-15), 22.5 (C-8), 20.4 (C-7). MS  $m/z$  (%) 273 ( $\text{M}^+$ , 100), 244 (98), 228 (80), 219 (62), 218 (58). HREIMS calc. for  $\text{C}_{16}\text{H}_{19}\text{NO}_3$   $m/z$  273.1365, found 273.1390.

**17-Methyl-9-oxo-10-nor-14 $\alpha$ -4,5-epoxymorphinan (21)**: A solution of **20** (30 mg, 0.11 mmol), triethylsilane (440 mg, 3.8 mmol) and TFA (900 mg, 7.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml) was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 ml), washed with water (3x5 ml), dried ( $\text{MgSO}_4$ ), evaporated to dryness and purified by preparative TLC (eluent:  $\text{CH}_2\text{Cl}_2$ :MeOH 97:3) to give **21** (27 mg, 95 %), as a colourless solid. UV (MeOH) 210, 225, 280 nm. IR (film)  $\nu$  1640  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.18 (dt,  $J_1=1.2$ ,  $J_2=8$  Hz, 1H, H-2), 7.02 (dd,  $J_1=1.2$ ,  $J_2=8$  Hz, 1H, H-11), 6.91 (t,  $J=8$  Hz, 1H, H-1), 6.84 (d,  $J=8$  Hz, 1H, H-3), 4.45 (dd,  $J_1=4.5$ ,  $J_2=8$  Hz, 1H, H-5), 3.65-3.45 (m, 2H, H-16), 3.05 (s, 3H,  $\text{NCH}_3$ ), 2.52 (dd,  $J_1=4.5$ ,  $J_2=8$  Hz, 1H, H-14), 2.12 (ddd,  $J_1=6.5$ ,  $J_2=7.5$ ,  $J_3=14$  Hz, 1H, H-15), 2.01-1.79 (m, 3H, H-6, H-7, H'-15), 1.76-1.62 (m, 3H, H'-6, H-8), 1.58 (m, 1H, H'-7).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  171.0 (CO), 158.3 (C-4), 134.3 (C-12), 128.7 (C-2), 122.9 (C-11), 120.9 (C-1), 110.4 (C-3), 85.6 (C-5), 46.1 (C-16), 45.7 (C-13), 45.6 (C-14), 34.8 ( $\text{NCH}_3$ ), 28.8 (C-15), 26.1 (C-6), 24.2 (C-8), 18.3 (C-7). MS  $m/z$  (%) 257 ( $\text{M}^+$ , 22), 256 (60), 170 (85). HREIMS calc. for  $\text{C}_{16}\text{H}_{19}\text{NO}_2$   $m/z$  257.1414, found 257.1397.

**17-Methyl-10-nor-14 $\alpha$ -4,5-epoxymorphinan (2b)**: A solution of **21** (18 mg, 0.07 mmol) in ether (30 ml) was refluxed with  $\text{LiAlH}_4$  (8 mg, 0.21 mmol) for 3 h. After destruction of  $\text{LiAlH}_4$  with saturated  $\text{Na}_2\text{SO}_4$  solution the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3x10 ml), the combined organic layers were dried ( $\text{MgSO}_4$ ), filtered off, evaporated to dryness to give **2b** (13 mg, 76 %), identical in all respects with the described compound.<sup>6</sup>

**17-Methyl-9-oxo-10-nor-4,5-epoxymorphinan (24)**:

A solution of **21** (15 mg, 0.058 mmol) in dry toluene (15 ml) was refluxed in the presence of  $\text{NaNH}_2$  (4 mg, 0.10 mmol) under argon overnight. The reaction mixture was quenched with MeOH, evaporated, dissolved in  $\text{CH}_2\text{Cl}_2$  (15 ml), washed with 10 %  $\text{NH}_4\text{Cl}$ , dried ( $\text{MgSO}_4$ ) and evaporated to dryness. The residue was purified by preparative TLC (eluent:  $\text{CH}_2\text{Cl}_2$ : MeOH 97:3) to give **24** (6 mg, 40 %) along with recovered starting material (8 mg, 53 %). Mp 149-151°C (MeOH, ether). UV (MeOH) 215, 225, 280 nm. IR (KBr)  $\nu$  1645  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.18 (m, 1H, H-2), 6.85 (m, 3H, H-1, H-3, H-11), 4.45 (dd,  $J_1=6.5$ ,  $J_2=8$  Hz, 1H, H-5), 3.31-3.15 (m, 2H, H-16), 2.98 (s, 3H,  $\text{NCH}_3$ ), 2.49 (dd,  $J_1=4$ ,  $J_2=12$  Hz, 1H, H-14), 2.06-1.90 (m, 3H, H-6, H-15, H'-15), 1.71-1.55 (m, 1H, H-7), 1.38-1.25 (m, 3H, H'-6, H'-7, H'-8).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  171.6 (CO), 160.0 (C-4), 135.2 (C-12), 128.8 (C-2), 124.3 (C-11), 120.7 (C-1), 111.3 (C-3), 87.9 (C-5), 48.1 (C-13),

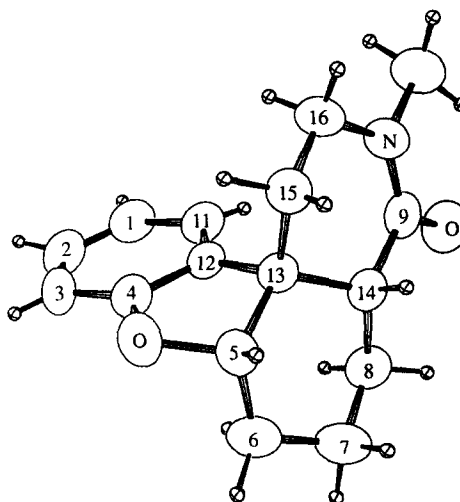


Figure 1. ORTEP drawing of **24**

46.1 (C-16), 44.6 (C-14), 34.5 (C-8), 34.2 (NCH<sub>3</sub>), 28.0 (C-15), 21.3 (C-6), 20.8 (C-7). MS *m/z* (%) 258 ([M+H]<sup>+</sup>, 23), 257 (M<sup>+</sup>, 100), 214 (8), 199 (49), 171 (79). HREIMS calc. for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub> *m/z* 257.1415, found 257.1413.

CRYSTAL DATA of **24**

Formula	C <sub>16</sub> H <sub>19</sub> NO <sub>2</sub>	Max 2 $\theta$ (°)	50°
Mol. Wt.	257.34	Scan	$\omega/2\theta = 1$
Cryst. Syst.	orthorhombic	$t_{\max}$ (for one measure), s	60
Space Group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	Variance of standards	0.2%
a (Å)	7.041(6)	Range of HKL	0.8 ; 0.8 ; 0.31
b	7.252(4)	Reflections measured	1430
c	26.363(7)	Reflections observed ( $I > \sigma(I)$ )	938 (3 $\sigma$ )
$\alpha$ (°)	-	R <sub>int</sub> (from merging equiv refl)	-
$\beta$	-	R(isotropic)	0.095
$\nu$	-	Absorption correction (Difabs),	-
V(Å <sup>-3</sup> )	1346(1)	T <sub>max</sub> , T <sub>min</sub>	
Z	4	R(anisotropic)	0.076
$\rho_{\text{calc}}$ , g·cm <sup>-3</sup>	1.27	Fourier Difference	0.36-0.20
F(000)	552	N(obs)/N(var)	938/230
$\mu$ (MoK $\alpha$ ) cm <sup>-1</sup>	0.78	Final R	0.052
T (°K)	294	R <sub>w</sub>	0.048
		$w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$	
Crystal size (mm)	0.25*0.25*0.40	Sw	0.82
Radiation	Mo K $\alpha$	Max residual e.Å <sup>-3</sup> , $\Delta/\sigma$	0.12, 0.26

**17-Methyl-10-nor-4,5-epoxymorphinan (2a)**: A solution of **24** (15 mg, 0.058 mmol) in dry ether (15 ml) was refluxed with LiAlH<sub>4</sub> (11 mg, 0.29 mmol) for 4 h. After destruction of the excess of LiAlH<sub>4</sub> with saturated Na<sub>2</sub>SO<sub>4</sub>, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 ml), the combined extracts were dried (MgSO<sub>4</sub>), filtered, evaporated to dryness and purified by preparative TLC (eluent: CH<sub>2</sub>Cl<sub>2</sub>: MeOH 95:5) to obtain **2a** (13 mg, 92 %). Mp 61-62°C (hexane-ether). UV (MeOH) 220, 282 nm. IR (KBr)  $\nu$  2830, 1480 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.48 (dd, J<sub>1</sub>=1, J<sub>2</sub>=8 Hz, 1H, H-11), 7.13 (dt, J<sub>1</sub>=1, J<sub>2</sub>=8 Hz, 1H, H-2), 6.82 (dt, J<sub>1</sub>=1, J<sub>2</sub>=8 Hz, 1H, H-1), 6.81 (dd, J<sub>1</sub>=1, J<sub>2</sub>=8 Hz, 1H, H-3), 4.39 (t, J<sub>1</sub>=5 Hz, 1H, H-5), 2.76 (dd, J<sub>1</sub>=4, J<sub>2</sub>=12 Hz, 1H, H-9), 2.71 (dt, J<sub>1</sub>=2, J<sub>2</sub>=12 Hz, 1H, H-16), 2.57 (dd, J<sub>1</sub>=11, J<sub>2</sub>=12 Hz, 1H, H'-9), 2.43 (s, 3H, NCH<sub>3</sub>), 2.38 (m, 1H, H'-16), 2.04 (ddt, J<sub>1</sub>=4, J<sub>2</sub>=11, J<sub>3</sub>=12 Hz, 1H, H-14), 1.93 (m, 1H, H-6), 1.80 (m, 2H, H<sub>2</sub>-15), 1.58-1.41 (m, 4H, H-8, H<sub>2</sub>-7, H'-6), 1.19 (m, 1H, H'-8). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  160.3 (C-4), 132.0 (C-12), 128.1 (C-2), 127.1 (C-11), 119.3 (C-1), 110.7 (C-3), 88.7 (C-5), 57.5 (C-16), 50.8 (C-9), 47.5 (C-13), 46.1 (NCH<sub>3</sub>), 39.4 (C-14), 39.3 (C-15), 29.7 (C-8), 24.5 (C-6), 19.9 (C-7). MS *m/z* (%) 243 (M<sup>+</sup>, 100), 242 (53), 228 (4), 186 (11), 171 (7). HREIMS calc. for C<sub>16</sub>H<sub>21</sub>NO *m/z* 243.1624, found 243.1625.

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19. Crystallographic data were deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, CB2, 1EW, UK.

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