



Indole as a Tool in Synthesis. Indolenine Approach to 4,5-Epoxy-10-normorphinans

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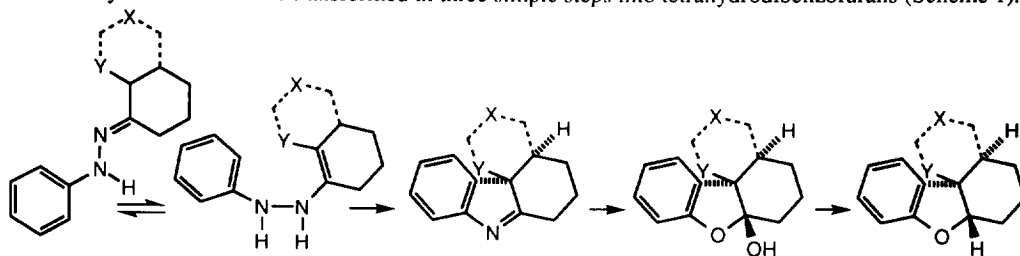
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Abstract: The 4,5-epoxy-10-normorphinans **2a** and **2b** featuring the morphine skeleton lacking the B-ring were synthesized using the "nitrous acid deamination" of indolenines as the key step. Thus, indolenines **13** and **15** were prepared by 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 α -morphinan **21**.

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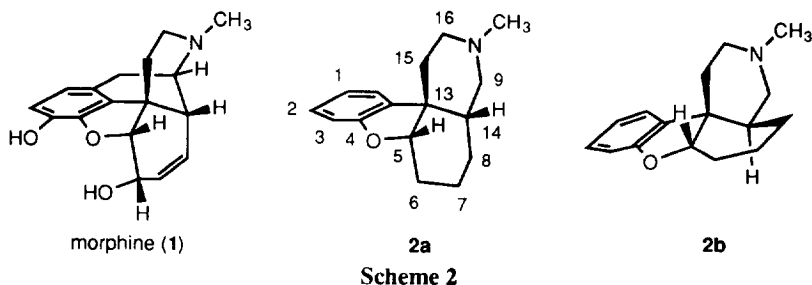
Introduction

Tautomerism between phenylhydrazones bearing a tertiary carbon atom and the most substituted enehydrazines accounts for the Fischer-indolenine (3*H*-indole) synthesis¹ from the related ketones and thus offers an efficient method for constructing arylated quaternary centers. Combination with nitrous acid deamination² 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 ($X = \text{NCH}_3$, $Y = \text{CH}_2$) with the view to preparing the 10-nor analogs of morphine **1** (Scheme 2).³

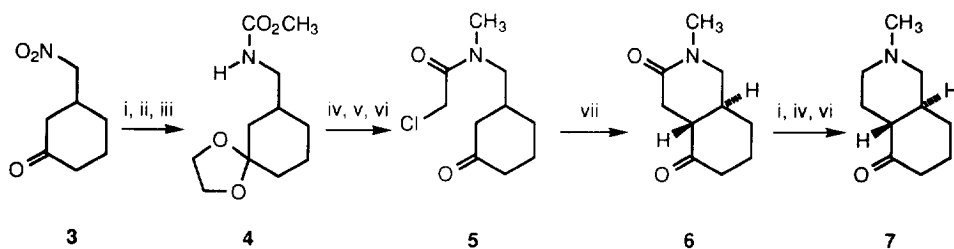


Such compounds have retained considerable attention in the past years,⁴ owing to their potential analgesic properties.⁵ However, the indolenine approach will predictably afford the 14-epimer **2b** due to the arylation in the Fischer rearrangement occurring from the less hindered side of the enehydrazine (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 analogs⁷ **2b** and **2a** using these strategies.⁸

Results and discussion

Synthesis of the *N*-methyl-dioxodecahydroisoquinolines **6** and **12a,b**

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

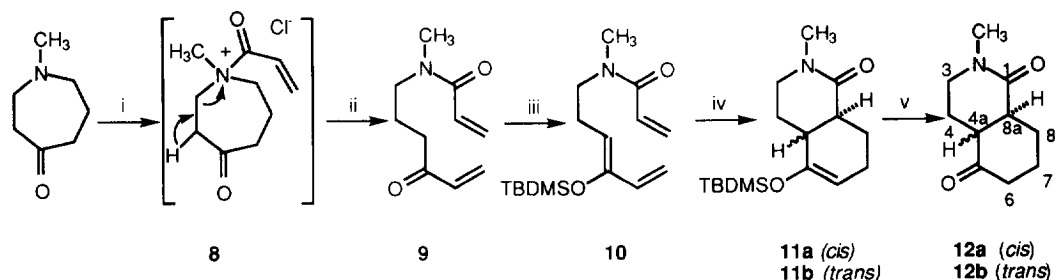


i: *p*-TsOH, ethylene glycol, Dean-Stark; ii: Pd-C, H₂, EtOH; iii: ClCO₂CH₃, Et₃N, CH₂Cl₂, 0.5 h; iv: LiAlH₄, THF, reflux, 10 h; v: ClCH₂COCl, Et₃N, CH₂Cl₂, reflux, 0.5 h; vi: HCl aq., 80°C; vii: *t*-BuOK, toluene, 90°C, 2 h.

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 δ: 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 **7⁹** was further obtained through reduction of **6** with LiAlH₄ after protection of the ketone.

• 2-methyl-1,5-dioxodecahydroisoquinolines **12a,b** (Scheme 4)



i: $\text{CH}_2=\text{CHCOCl}$, toluene, rt; ii: Hunig's base, 100°C , 1.5–2.5 h; iii: *t*-BuOK, TBDMSCl, -78°C , THF; iv: benzene, sealed tube, $135\text{--}140^\circ\text{C}$, 1.5–3 h; v: TBAF, THF, rt.

Scheme 4

Preparation of the bicyclic ketolactam(s) **12** called for an intramolecular Diels-Alder approach,¹⁰ whose efficiency in the synthesis of the decahydroisoquinoline ring system embodied in various natural products has been largely illustrated.¹¹ An expeditious synthesis of the required silyl enol ether **10** via a base induced fragmentation of the *N*-acylammonium salt **8** and its further cyclization were set up¹² for this purpose. Thus, vinylketoacrylamide **9** was obtained in one step from 1-methyl-1*H*-hexahydroazepin-4-one¹³, and further transformed into **10**. Attempts at preparing¹⁴ the apparently unstable trimethylsilyl enol ether failed, but addition of a stoichiometric mixture of **9** and TBDMSCl at -78°C to a THF solution of freshly sublimed potassium *t*-butoxide allowed isolation of **10** in 81% yield. Although **10** appeared to cyclize spontaneously at room temperature, cyclization was more efficiently performed at $130\text{--}140^\circ\text{C}$ (sealed tube), affording a separable mixture of the bicyclic *cis* **11a** and *trans* **11b** lactams (84%, 4:1) along with 5% recovered starting material. Desilylation (TBAF) of the mixture led to the *cis* **12a** and *trans* **12b** ketolactams in a 3:1 ratio. Base treatment (MeOK, MeOH) or prolonged reaction with TBAF only enriched the mixture in *trans* isomer (*cis/trans*=1.1–1.2 : 1), in striking contrast with the results obtained in the 3-oxo series. Energy calculations¹⁵ indeed disclosed very close values of heats of formation for the two epimers: -88.75 kcal/mol for **12a** and -88.64 kcal/mol for **12b**.

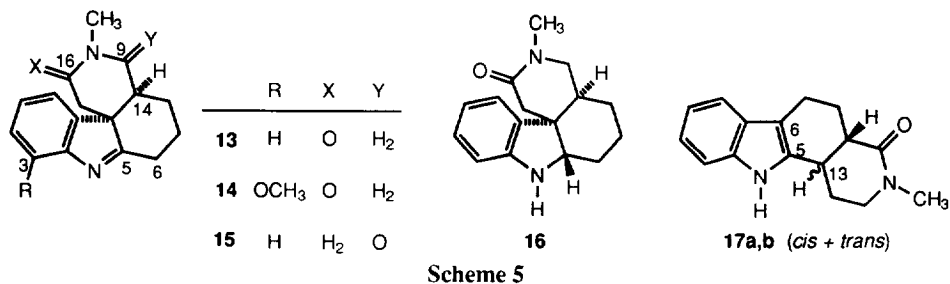
The relative configurations of ketolactams **12a,b** were deduced from their ^1H - and ^{13}C -NMR spectra, with the use of ^1H - ^1H COSY and ^1H - ^{13}C HETCOR experiments. The H-8a angular proton in **12a** displayed a multiplet with one large coupling constant ($J_1=5$, $J_2=5.5$, $J_3=8.5$ Hz), and it was shielded at δ : 2.2 ppm in **12b**. As expected, the H-3_{eq} proton (δ : 3.43 ppm in **12a**), and the H-3_{ax} proton (δ : 3.13 ppm in **12a**) were respectively shielded and deshielded in **12b**, appearing together in the form of a two-proton multiplet at δ : 3.36 ppm.

Fischer synthesis of indolenines 13–15

An initial attempt to carry out the Fischer indol(enin)e synthesis with the phenylhydrazone of aminoketone **7** in the presence of various acids failed, in contrast to Georgian's findings¹⁶ who had used a parent ketoamide (**7**, NAc instead of NCH_3).

Ketolactam **6**, heated with phenylhydrazine in acetic acid, afforded indolenine **13** in 79% yield, while no isomeric indole was detected in the reaction mixture. The structure of **13** was secured by its UV spectrum (maxima at 215 and 252 nm), and by the ^{13}C -NMR signal of the imino carbon atom at δ : 185.3 ppm. With the help of one- and two-dimensional ^1H -NMR experiments, a signal at δ : 3.93 ppm (dd, $J_1=5$, $J_2=13.5$ Hz) was attributed to the *rel*- α axial H-9. The observed coupling constant ($J=5$ Hz) with the angular H-14 proton

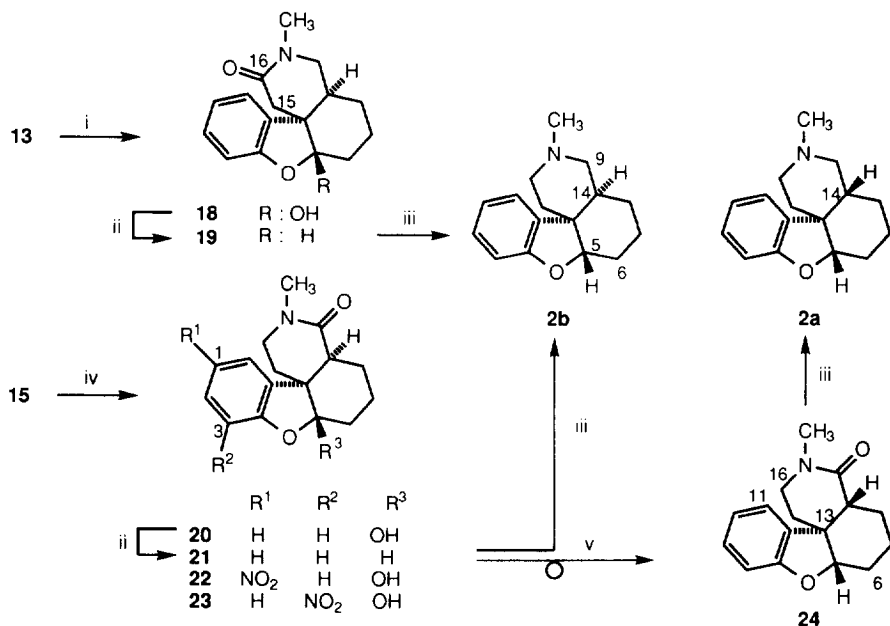
accounted for the predicted *cis* ring junction of the two six-membered rings. Reduction of **13** with NaBH₃CN in acetic acid led to the fully characterized indoline **16** (Scheme 5).



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 hydrazone¹⁷ 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: NaNO₂, HCl aq, rt then HCl aq. (6 M), 60°C, 1 h; ii: Et₃SiH, TFA, rt; iii: LiAlH₄, ether, reflux; iv: NaNO₂, HCl (4%), 0°C → rt, 12 h, argon; v: toluene, NaNH₂, 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 δ : 3.06 and δ : 2.59 ppm, respectively. A one proton doublet of doublet at δ : 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 (δ : 1.65 ppm) and consequently the *cis* ring junction. The equatorial H'-9 was observed at δ : 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 δ : 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 LiAlH₄ to give quantitatively the (\pm)-4,5-epoxy-17-methyl-10-nor-14 α -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 compounds¹⁸ **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 CH₂Cl₂ in the presence of TFA to give **21** in 95% yield. Identity of the ring junctions in **19** and **21** was confirmed by LiAlH₄ reduction of **21** to **2b**.

Finally, partial epimerization of lactam **21** (NaNH₂, toluene, reflux, then quenching with MeOH), gave lactam **24** (40%), whose reduction with LiAlH₄ afforded (\pm)-4,5-epoxy-10-normorphinan **2a**. As compared with that of the *cis* annelated lactam **21**, the ¹H-NMR spectrum of the *trans* annelated **24** revealed some typical differences: the signals of H-11, H-16_{ax}, H-8_{ax}, and H-6 were moved upfield by 0.2, 0.4, 0.5, and 0.6 ppm, respectively. Single crystal X-ray diffraction analysis¹⁹ 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 (ν , cm⁻¹) were recorded on a BOMEM FTIR apparatus with COSMIC interferometer; UV spectra were recorded on a Varian 634 spectrophotometer; ¹H- and ¹³C-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 PGF₂₅₄ (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 % Na₂CO₃, extracted with CH₂Cl₂ (3x10-20 ml). The combined organic layers were washed with water (5 ml), dried over MgSO₄, 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 CH₂Cl₂ (3x100 ml), the organic layers were dried (MgSO₄), 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) ν 1720, 1560, 1545 cm⁻¹. ¹H-NMR (CDCl₃) δ 4.37 (ABX system, 2H, CH₂NO₂), 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). ¹³C-NMR (CDCl₃) δ 208.1 (C-1), 80.0 (CH₂NO₂), 44.4, 40.7, 37.1 (C-3), 28.1, 24.3. MS *m/z* (%) 157 (M⁺, 3), 110 (30), 82 (25), 68 (40), 55 (100). Anal. calc. for C₇H₁₁NO₃: C 53.49, H 7.05, N 8.91; found: C 53.31, H 7.17, N 8.49.

Spiro[(3-methoxycarbonylaminoethyl)cyclohexane]-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 Na₂CO₃ (100 ml), dried (MgSO₄), filtered, and the solvent evaporated to give spiro[(3-nitromethyl)cyclohexane]-1,2'-dioxolane] (2.96 g, 99%) as an oil. IR (neat) ν 1560, 1540, 1105, 1065 cm⁻¹. ¹H-NMR (CDCl₃) δ 4.31 (dd, J₁=1.5, J₂=5 Hz, 2H, CH₂NO₂), 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, J₁=2, J₂=7 Hz, 1H). ¹³C-NMR (CDCl₃) δ 108.7 (C-1), 80.8 (CH₂NO₂), 64.3 (CH₂ dioxolane), 38.3, 34.8 (C-3), 34.5, 28.5, 22.1. MS *m/z* (%) 201 (M⁺, 1), 155 (20), 141 (20), 112 (25), 99 (100), 86 (50). Anal. calc. for C₉H₁₅NO₄: C 53.72, H 7.51, N 6.96; found: C 54.03, H 7.61, N 6.86.

A solution of spiro[(3-nitromethyl)cyclohexane]-1,2'-dioxolane] (4.02 g, 20.0 mmol) in absolute ethanol (50 ml) was hydrogenated over 5% Pd/C catalyst (200 mg). When H₂ consumption ceased, the catalyst was filtered and the solution evaporated to dryness to give spiro[(3-aminomethyl)cyclohexane]-1,2'-dioxolane] (3.15 g, 92%), which proved to be pure enough to use in the next step without purification. IR (film) ν 3220 (br) cm⁻¹. ¹H-NMR (CDCl₃) δ 3.93 (s, 4H, dioxolane), 2.70 (m, 2H, NH₂), 2.62 (d, J=4 Hz, 2H, CH₂NH₂), 1.80 (m, 5H), 1.50 (m, 2H), 1.19 (t, J=7 Hz, 1H), 0.92 (m, 1H). ¹³C-NMR (CDCl₃) δ 108.9 (C-1), 64.2 and 64.1 (CH₂, dioxolane), 47.0 (CH₂NH₂), 36.9, 37.6 (C-3), 34.8, 29.0, 22.6. MS *m/z* (%) 172 ([M+H]⁺, 45), 141 (100), 99 (90).

A solution of spiro[(3-aminomethyl)cyclohexane]-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 CH₂Cl₂ (150 ml) was heated under reflux for 30 min. The solution was washed with a 4 % aqueous NH₄Cl 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) ν 3330, 1647, 1564 cm⁻¹. ¹H-NMR (CDCl₃) δ 4.70 (m, 1H, NH), 3.93 (s, 4H, dioxolane), 3.64 (s, 3H, OCH₃), 3.09 (m, 2H, CH₂-N), 1.80 (m, 5H), 1.50 (m, 2H), 1.20 (t, J=7 Hz, 1H), 0.92 (m, 1H). ¹³C-NMR (CDCl₃) δ 157.1 (CO), 108.9 (C-1), 64.3 and 64.2 (CH₂, dioxolane), 52.0 (OCH₃), 46.6 (CH₂-N), 40.0, 36.4 (C-3), 34.8, 29.1, 22.7. MS *m/z* (%) 229 (M⁺, 1), 141 (100), 99 (98), 86 (30), 55 (25). Anal. calc. for C₁₁H₁₉NO₄: 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 LiAlH₄ (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 (MgSO₄), filtered and the solvents evaporated. The spiro[(3-methylaminomethyl)cyclohexane]-1,2'-dioxolane] (11.2 g, 96%) obtained was used without purification in the next step. IR (film) ν 3320 cm⁻¹. ¹H-NMR (CDCl₃) δ 3.92 (s, 4H, CH₂ dioxolane), 3.10 (m, 2H, CH₂-N), 2.42 (s, 3H, NCH₃), 1.80 (m, 5H), 1.50 (m, 2H), 1.22 (t, J=7 Hz, 1H), 0.94 (m, 1H). ¹³C-NMR (CDCl₃) δ 109.1 (C-1), 64.2 and 64.1 (CH₂ dioxolane), 44.1, 39.8, 36.5, 35.5, 35.0, 29.9, 23.0. MS *m/z* (%) 185 (M⁺, 15), 141 (85), 99 (45), 72 (50), 58 (100).

A solution of spiro[(3-methylaminomethyl)cyclohexane]-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 CH₂Cl₂ (100 ml) was heated under reflux for 0.5 h. The solution was washed with 4% aqueous NH₄Cl (50 ml), dried (MgSO₄) and filtered through a silica gel (16 g) packed column to give spiro[(3-(*N*-chloroacetyl-*N*-methylaminomethyl)cyclohexane)-1,2'-dioxolane] (4.05 g, 65%) which slowly crystallized from CH₂Cl₂. Mp 78°C (CH₂Cl₂). IR (KBr) ν 3450, 1650, 1445, 1410, 1068 cm⁻¹. ¹H-NMR (CDCl₃) δ 4.08 (s, 2H, CH₂Cl), 3.94 (s, 4H, CH₂ dioxolane), 3.31-3.10 (m, 2H, CH₂-N), 3.09 and 2.98 (s, 3H, NCH₃), 2.0 (m, 1H), 1.70-1.20 (m, 7H), 1.10-0.80 (m, 2H). ¹³C-NMR (CDCl₃) δ 166.7 (CO), 108.9 and 108.7 (C-1), 64.4 and 64.3 (CH₂ 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⁺, 8), 154 (80), 141 (100), 126 (45), 112 (40), 99 (95). Anal. calc. for C₁₂H₂₀NO₃Cl: 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*-methylaminomethyl)cyclohexane)-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 CH_2Cl_2 (3x100 ml), washed with 5% aqueous NaHCO_3 , dried (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) ν 1705, 1650, 1408, 1228, 1116, 790 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 4.09 (s, 2H, CH_2Cl), 3.39 (m, 2H, $\text{CH}_2\text{-N}$), 3.11 and 2.97 (s, 3H, NCH_3), 2.41-2.11 (m, 7H), 1.86 (m, 1H), 1.67 (m, 1H), 1.45 (m, 1H). $^{13}\text{C-NMR}$ (CDCl_3) δ 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°C under argon. The temperature was raised to 90°C and maintained for 2 h. At the end of the reaction aqueous HCl (1.4 M, 10 ml) and CH_2Cl_2 (200 ml) were added; after separation the organic phase was washed with water (50 ml), dried (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) ν 1706, 1638, 1334, 1252 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, 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). $^{13}\text{C-NMR}$ (CDCl_3) δ 208.6 (CO), 167.0 (NCO), 55.3 (C-1), 48.9 (NCH_3), 41.0, 40.2 (C-4a), 34.3 (C-8a), 31.0, 28.7, 25.7. MS m/z (%) 181 (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-1*H*-hexahydroazepin-4-one¹³ (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 °C for 1.5-2.5 h. The mixture was treated with 10% Na_2CO_3 (30 ml), separated and the aqueous solution was extracted with CH_2Cl_2 (4x30 ml). The organic layers were dried (MgSO_4), filtered, evaporated to dryness and purified by Chromatotron® (eluent: CH_2Cl_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) ν 1695, 1685, 1645, 1605 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, CH_2NCO), 3.01 and 3.06 (s, 3H, NCH_3), 2.62 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}$), 1.90 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}$). $^{13}\text{C-NMR}$ (CDCl_3) δ 201.0 and 199.3 (CO), 166.6 and 166.5 (NCO), 136.5 and 136.3 ($\text{CH}_2=\text{CH-CO}$), 128.6 and 128.3 ($\text{CH}_2=\text{CH-CON}$), 128.0 and 127.8 ($\text{CH}_2=\text{CH-CO}$), 127.9 and 127.5 ($\text{CH}_2=\text{CH-CON}$), 49.1 and 47.2 ($-\text{CH}_2\text{-NCH}_3$), 36.7 and 35.7 ($-\text{CH}_2\text{-CO-CH}=\text{CH}_2$), 35.4 and 33.9 (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 (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°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: CH_2Cl_2 :EtOAc 2:1) to give **10**, as an oil (366 mg, 80%). IR (film) ν 1650, 1610 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 6.30 and 6.33 (dd, $J_1=2$, $J_2=17$ Hz, 1H, $\text{CH}_2=\text{CH-CON}$), 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, $\text{CH}_2=\text{CH-CON}$), 4.69 and 4.78 (t, $J=7.5$ Hz, 1H, $\text{SiO-C}=\text{CH-CH}_2$), 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, 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: CH₂Cl₂: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) ν 1695, 1645 cm⁻¹. ¹H-NMR (CDCl₃) δ 4.83 (dd, J₁=J₂=2.5 Hz, 1H, -CH=C), 3.31 (m, 2H, -CH₂-N), 2.92 (s, 3H, NCH₃), 2.21-2.48 (m, 3H), 2.11 (m, 2H), 1.54 (m, 2H), 1.31 (m, 1H), 0.90 (s, 9H, SiC(CH₃)₃), 0.15 (s, 6H, Si(CH₃)₂). MS *m/z* (%) 295 (M⁺, 22), 281 (14), 238 (36), 224 (41). **11a** (*cis*) colourless syrup. IR (film) ν 1695, 1650 cm⁻¹. ¹H-NMR (CDCl₃) δ 4.90 (t, J=3.6 Hz, 1H, H-6), 3.25 (dd, J₁=5, J₂=7.7 Hz, 2H, H₂-3), 2.93 (s, 3H, NCH₃), 2.61 (ddd, J₁=4, J₂=5.5, J₃=9.5 Hz, 1H, H-8a), 2.40 (dt, J₁=5, J₂=5.5 Hz, 1H, H-4a), 2.05 (m, 2H, H₂-7), 1.98 (m, 1H, H'-4), 1.75-1.92 (m, 3H, H₂-8, H-4), 0.92 (s, 9H, SiC(CH₃)₃), 0.15 (s, 6H, Si(CH₃)₂). ¹³C-NMR (CDCl₃) δ 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 (NCH₃), 29.6 (-C(CH₃)₃), 25.7 (-C(CH₃)₃), 24.4 (C-7), 23.7 (C-8), 22.7 (C-4), -4.5 (-OSi(CH₃)₂). MS *m/z* (%) 295 (M⁺, 45), 280 (22), 238 (42), 211 (83). HREIMS calc. for C₁₆H₂₉NO₂Si *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 CH₂Cl₂ (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: CH₂Cl₂: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) ν 1710, 1625 cm⁻¹. ¹H-NMR (CDCl₃) δ 3.43 (ddd, J₁=4.5, J₂=5.5, J₃=11.5 Hz, 1H, H-3), 3.13 (ddd, J₁=5.5, J₂=8, J₃=11.5 Hz, 1H, H'-3), 2.84 (s, 3H, NCH₃), 2.71 (ddd, J₁=5, J₂=5.5, J₃=11.5 Hz, 1H, H-8a), 2.42-2.25 (m, 4H), 2.15 (m, 1H), 1.85-1.55 (m, 4H). ¹³C-NMR (CDCl₃) δ 209.2 (CO), 169.9 (NCO), 47.1 (C-3), 46.5 (C-4a), 43.5 (C-8a), 40.5 (C-6), 34.6 (NCH₃), 26.0 (C-8), 23.2 (C-7), 22.0 (C-4). MS *m/z* (%) 183 ([M+2H]⁺, 8), 182 ([M+H]⁺, 21), 181 (M⁺, 17), 155 (13), 154 (33), 113 (32), 112 (45). HREIMS calc. for C₁₀H₁₅NO₂ *m/z* 181.1103, found 181.1100. **12b** (*trans*) mp 95-97°C (EtOAc, ether). IR (KBr) ν 1700, 1635 cm⁻¹. ¹H-NMR (CDCl₃) δ 3.36 (m, 2H, H₂-3), 3.01 (s, 3H, NCH₃), 2.67 (m, 1H, H-8), 2.53 (ddd, J₁=3, J₂=11, J₃=12 Hz, 1H, H-4a), 2.55-2.36 (m, 2H, H₂-6), 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, J₁=3.3, J₂=12, J₃=13, J₄=25 Hz, 1H, H'-8). ¹³C-NMR (CDCl₃) δ 209.2 (CO), 169.9 (NCO), 49.7 (C-4a), 48.3 (C-3), 47.5 (C-8a), 40.6 (C-6), 34.7 (NCH₃), 26.6 (C-8), 25.6 (C-7), 21.6 (C-4). MS *m/z* (%) 183 ([M+2H]⁺, 18), 182 ([M+H]⁺, 100), 181 (M⁺, 11), 154 (19), 153 (14), 139 (27). HREIMS calc. for C₁₀H₁₅NO₂ *m/z* 181.1101, found 181.1102.

17-Methyl-16-oxo-10-nor-14 α -4,5-nitrimorphinan (**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 CHCl₃ (2x30 ml), made alkaline with Na₂CO₃ and extracted with CHCl₃ (3x50 ml). The combined organic extracts were washed with water (3x30 ml), dried (MgSO₄) and evaporated to give **13** (0.60 g, 79%), which crystallized in MeOH. Mp 160°C (MeOH). UV (MeOH) 215, 252 nm. IR (KBr) ν 1648, 1630, 1588 cm⁻¹. ¹H-NMR (CDCl₃) δ 7.62 (d, J=7 Hz, 1H, H-3), 7.38 (m, 1H), 7.19 (m, 2H), 3.96 (dd, J₁=5, J₂=13.5 Hz, 1H, H α -9), 3.25 (dd, J₁=1, J₂=13.5 Hz, 1H, H β -9), 3.11 (s, 3H, NCH₃), 2.91 (d, J=16 Hz, 1H, H-15), 2.87 (m, 1H, H-6), 2.64 (dt, J₁=6, J₂=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). ¹³C-NMR (CDCl₃) δ 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 (NCH₃), 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⁺, 100), 211 (10), 183 (30), 93 (20). HREIMS calc. for C₁₆H₁₈N₂O *m/z* 254.1418, found 254.1415.

3-Methoxy-17-methyl-16-oxo-10-nor-14 α -4,5-nitrimorphinan (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) ν 1650, 1590 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, 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, 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). $^{13}\text{C-NMR}$ (CDCl_3) δ 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 (OCH_3), 52.8 (C-9), 40.3 (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 (M^+ , 100), 283 (80), 255 (30), 204 (20), 199 (70), 170 (30).

17-Methyl-16-oxo-10-nor-14 α -4,5-iminomorphinan (16) : To a solution of **13** (0.13 g, 0.51 mmol) in acetic acid (5 ml), was added NaBH_3CN (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 (Na_2CO_3), then extracted with CHCl_3 (3x30 ml). The organic layers were dried (MgSO_4), filtered, evaporated to dryness and purified by preparative TLC (eluent: 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) ν 3345, 1632, 1601 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, 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). $^{13}\text{C-NMR}$ (CDCl_3) δ 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 (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 (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 α -4,5-nitrimorphinan (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: CH_2Cl_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) ν 1630, 1610 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, 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). $^{13}\text{C-NMR}$ (CDCl_3) δ 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 (NCH_3), 29.2 (C-6), 27.4 (C-8), 27.3 (C-15), 24.1 (C-7). MS m/z (%) 254 (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) ν 3380, 1685 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, NCH_3), 2.90 (m, 1H), 2.72 (m, 1H), 2.31-1.91 (m, 4H). $^{13}\text{C-NMR}$ (CDCl_3 + CD_3OD) δ 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 (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 (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 silylenolethers (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: CH₂Cl₂:EtOAc 2:1).

17-Methyl-5-hydroxy-16-oxo-10-nor-14 α -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 NaNO₂ (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 CHCl₃ (3x30 ml), the organic layers were dried (MgSO₄), 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) ν 3315, 1630 cm⁻¹. ¹H-NMR (CDCl₃) δ 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, J₁=4.5, J₂=13 Hz, 1H, H-9), 3.03 (s, 3H, NCH₃), 2.94 (dd, J₁=1, J₂=13 Hz, 1H, H'-9), 2.70 (AB system, 2H, H₂-15), 2.34 (m, 1H), 1.85 (m, 3H), 1.50 (m, 5H). ¹³C-NMR (CDCl₃) δ 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 (NCH₃), 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⁺, 45), 245 (80), 244 (65), 202 (100), 181 (25). HREIMS calc. for C₁₆H₁₉NO₃ *m/z* 273.1364, found 273.1363.

17-Methyl-16-oxo-10-nor-14 α -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 CHCl₃ (3x30 ml). The organic extracts were washed with water, dried (MgSO₄), evaporated to dryness and purified by preparative TLC (eluent: CHCl₃: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) ν 1645, 1638, 1505, 1499 cm⁻¹. ¹H-NMR (CDCl₃) δ 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, J₁=4.5, J₂=13 Hz, 1H, H-9), 3.06 (s, 3H, NCH₃), 2.92 (dd, J₁=1, J₂=13 Hz, 1H, H'-9), 2.59 (s, 2H, H₂-15), 2.28 (m, 1H, H-6), 1.80-1.45 (m, 6H, H₂-8, H₂-7, H-14, H'-6). ¹³C-NMR (CDCl₃) δ 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 (NCH₃), 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⁺, 100), 184 (70), 144 (40), 97 (80). HREIMS calc. for C₁₆H₁₉NO₂ *m/z* 257.1415, found 257.1404. Anal. calc. for C₁₆H₁₉NO₂: C 74.67, H 7.44, N 5.44; found: C 74.60, H 7.72, N 5.57.

17-Methyl-10-nor-14 α -4,5-epoxymorphinan (2b) : LiAlH₄ (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 LiAlH₄ was destroyed with wet ether, and then with water (50 ml), the ethereal phase was collected, dried (MgSO₄), 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) ν 2770, 1470, 1460 cm⁻¹. ¹H-NMR (CDCl₃) δ 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, H₂-16), 2.57 (dd, J₁=2, J₂=11 Hz, 1H, H-9), 2.38 (m, 1H, H'-9), 2.34 (s, 3H, NCH₃), 2.02 (m, 2H, H-15), 1.70 (m, 7H). ¹³C-NMR (CDCl₃) δ 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 (NCH₃), 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⁺, 100), 200 (10), 186 (15), 71 (60), 70 (80), 58 (30), 57 (35). Anal. calc. for C₁₆H₂₁NO: 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 α -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 NaNO₂ (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 CH₂Cl₂ (3x5 ml) the residue was purified by preparative TLC (eluent: CH₂Cl₂:MeOH 98:2),

crystallized from ether to obtain **20** (21 mg, 77%). Mp 207-210°C (ether). UV (MeOH) 215, 280 nm. IR (KBr) ν 3240, 1620 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, NCH_3), 2.31-2.18 (m, 4H), 1.91-1.58 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3) δ 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 (NCH_3), 32.0 (C-6), 24.3 (C-15), 22.5 (C-8), 20.4 (C-7). MS m/z (%) 273 (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 α -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 CH_2Cl_2 (1 ml) was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 ml), washed with water (3x5 ml), dried (MgSO_4), evaporated to dryness and purified by preparative TLC (eluent: CH_2Cl_2 :MeOH 97:3) to give **21** (27 mg, 95 %), as a colourless solid. UV (MeOH) 210, 225, 280 nm. IR (film) ν 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, 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). $^{13}\text{C-NMR}$ (CDCl_3) δ 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 (NCH_3), 28.8 (C-15), 26.1 (C-6), 24.2 (C-8), 18.3 (C-7). MS m/z (%) 257 (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 α -4,5-epoxymorphinan (2b): A solution of **21** (18 mg, 0.07 mmol) in ether (30 ml) was refluxed with LiAlH_4 (8 mg, 0.21 mmol) for 3 h. After destruction of LiAlH_4 with saturated Na_2SO_4 solution the aqueous layer was extracted with CH_2Cl_2 (3x10 ml), the combined organic layers were dried (MgSO_4), filtered off, evaporated to dryness to give **2b** (13 mg, 76 %), identical in all respects with the described compound.⁶

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 NaNH_2 (4 mg, 0.10 mmol) under argon overnight. The reaction mixture was quenched with MeOH, evaporated, dissolved in CH_2Cl_2 (15 ml), washed with 10 % NH_4Cl , dried (MgSO_4) and evaporated to dryness. The residue was purified by preparative TLC (eluent: CH_2Cl_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) ν 1645 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 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, H₂-16), 2.98 (s, 3H, 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). $^{13}\text{C-NMR}$ (CDCl_3) δ 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),

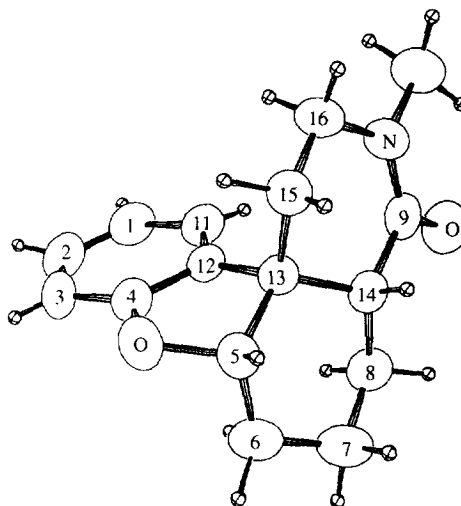


Figure 1. ORTEP drawing of **24**

46.1 (C-16), 44.6 (C-14), 34.5 (C-8), 34.2 (NCH₃), 28.0 (C-15), 21.3 (C-6), 20.8 (C-7). MS *m/z* (%) 258 ([M+H]⁺, 23), 257 (M⁺, 100), 214 (8), 199 (49), 171 (79). HREIMS calc. for C₁₆H₁₉NO₂ *m/z* 257.1415, found 257.1413.

CRYSTAL DATA of **24**

| | | | |
|---|---|--|----------------------|
| Formula | C ₁₆ H ₁₉ NO ₂ | Max 2 θ (°) | 50° |
| Mol. Wt. | 257.34 | Scan | $\omega/2\theta = 1$ |
| Cryst. Syst. | orthorhombic | t_{\max} (for one measure), s | 60 |
| Space Group | P2 ₁ 2 ₁ 2 ₁ | 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> σ (I)) | 938 (3 σ) |
| α (°) | - | R _{int} (from merging equiv refl) | - |
| β | - | R(isotropic) | 0.095 |
| ν | - | Absorption correction (Difabs), | - |
| V(Å ³) | 1346(1) | T _{max} , T _{min} | |
| Z | 4 | R(anisotropic) | 0.076 |
| ρ_{calc} , g·cm ⁻³ | 1.27 | Fourier Difference | 0.36-0.20 |
| F(000) | 552 | N(obs)/N(var) | 938/230 |
| μ (MoK α) cm ⁻¹ | 0.78 | Final R | 0.052 |
| T (°K) | 294 | Rw | 0.048 |
| Crystal size (mm) | 0.25*0.25*0.40 | $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$ | |
| Radiation | Mo K α | Sw | 0.82 |
| | | Max residual e.Å ⁻³ , Δ/σ | 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 LiAlH₄ (11 mg, 0.29 mmol) for 4 h. After destruction of the excess of LiAlH₄ with saturated Na₂SO₄, the aqueous layer was extracted with CH₂Cl₂ (3x10 ml), the combined extracts were dried (MgSO₄), filtered, evaporated to dryness and purified by preparative TLC (eluent: CH₂Cl₂: MeOH 95:5) to obtain **2a** (13 mg, 92 %). Mp 61-62°C (hexane-ether). UV (MeOH) 220, 282 nm. IR (KBr) ν 2830, 1480 cm⁻¹. ¹H-NMR (CDCl₃) δ 7.48 (dd, J₁=1, J₂=8 Hz, 1H, H-11), 7.13 (dt, J₁=1, J₂=8 Hz, 1H, H-2), 6.82 (dt, J₁=1, J₂=8 Hz, 1H, H-1), 6.81 (dd, J₁=1, J₂=8 Hz, 1H, H-3), 4.39 (t, J₁=5 Hz, 1H, H-5), 2.76 (dd, J₁=4, J₂=12 Hz, 1H, H-9), 2.71 (dt, J₁=2, J₂=12 Hz, 1H, H-16), 2.57 (dd, J₁=11, J₂=12 Hz, 1H, H'-9), 2.43 (s, 3H, NCH₃), 2.38 (m, 1H, H'-16), 2.04 (ddt, J₁=4, J₂=11, J₃=12 Hz, 1H, H-14), 1.93 (m, 1H, H-6), 1.80 (m, 2H, H₂-15), 1.58-1.41 (m, 4H, H-8, H₂-7, H'-6), 1.19 (m, 1H, H'-8). ¹³C-NMR (CDCl₃) δ 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 (NCH₃), 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⁺, 100), 242 (53), 228 (4), 186 (11), 171 (7). HREIMS calc. for C₁₆H₂₁NO *m/z* 243.1624, found 243.1625.

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9. Prepared from (6) in 85 % overall yield (Scheme 3.). Selected data of **7** : IR (KBr) ν 1710 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 3.71 (m, 1H), 3.02-2.77 (m, 4H, $-\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2-$), 2.25 (s, 3H, NCH_3), 2.4-1.55 (m, 9H). MS m/z (%) 167 (M^+ , 8), 154 (25), 149 (21).
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18. Mixture (1.6:1) of 1- and 3-nitro compounds (**22**, **23**): UV (MeOH) 215, 277, 290, 315 nm. MS *m/z* (%) 318 (M^+ , 18), 301 (15), 300 (16), 249 (100). Selected NMR data: **22**(1-nitro) 1H -NMR ($CDCl_3$) δ 8.18 (dd, $J_1=2$, $J_2=9$ Hz, 1H, H-2), 7.92 (d, $J=2$ Hz, 1H, H-11), 6.9 (d, $J=9$ Hz, 1H, H-1), 3.05 (s, 3H, NCH_3). **23**(3-nitro) 1H -NMR ($CDCl_3$) δ 7.92 (dd, $J_1=1.5$, $J_2=9$ Hz, 1H, H-2), 7.3 (dd, $J_1=1.5$, $J_2=9$ Hz, 1H, H-11), 6.97 (t, $J=9$ Hz, 1H, H-1), 3.0 (s, 3H, NCH_3).
19. Crystallographic data were deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, CB2, 1EW, UK.

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