# Synthesis of D-norisomorphinans ((±)-[14α]-D-normorphinans)

JOHN P. YARDLEY[1] AND RICHARD W. REES
*Wyeth Laboratories, Inc., P.O. Box 8299, Philadelphia, PA 19101, U.S.A.*

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A synthesis of the D-norisomorphinan ring system is described. Conversion of the initial synthetic target, *trans*-1,3,4,9,10,10a-hexahydro-6-methoxy-9-oxo-4a(2*H*)-phenanthrenecarboxamide (**10***c*) into the D-norisomorphinan (**6***b*) proved possible only after removal of the carboxamide ambident functionality. The successful route proceeds via hypobromous acid addition to *trans*-1,3,4,10a-tetrahydro-6-methoxy-4a(2*H*)-phenanthrenemethanamine (**21**) followed by a facile intramolecular cyclization to the D-norisomorphinan (**23**).

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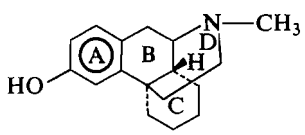
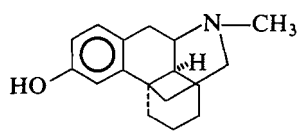
On décrit une synthèse du système cyclique du D-norisomorphinane. On a d'abord obtenu l'hexahydro-1,3,4,9,10,10a méthoxy-6 oxo-9 2*H*-phénanthrène carboxamide-4a *trans* (**10***c*) comme première cible de la synthèse; ce n'est qu'après avoir éliminé la fonction carboxamide ambidente que l'on a pu transformer **10***c* et obtenir le D-norisomorphane (**6***b*). La voie permettant d'effectuer cette réalisation implique une addition d'acide hypobromeux sur la tétrahydro-1,3,4,10a méthoxy-6 2*H*-phénanthrène méthanamine-4a *trans* (**21**) suivie d'une cyclisation intramoléculaire facille en D-norisomorphinane (**23**).
[Traduit par le journal]

## Introduction

(−)3-Hydroxy-*N*-methyl-morphinan (**1**) has clinical utility as an analgesic, while potent analgesic activity has been uncovered in the corresponding B/C-*trans* fused or isomorphinan structure (**2**) (ref. 1). As part of a program to extend the



**1**

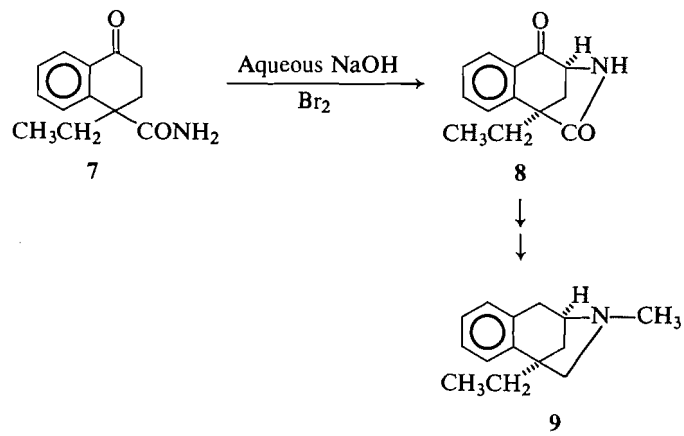


**2**

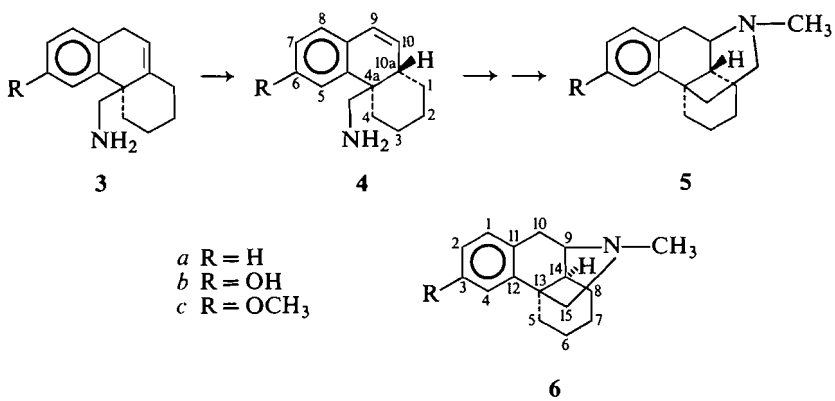
structure–activity relationships to the ring D-nor compounds, synthesis of the D-norisomorphinan ring system was required. Belleau, Conway, and co-workers have already described (2) a synthesis of the ring B/C *cis*-fused, D-normorphinan (**5***a*), which proceeds via 4a-aminomethyl-4a,10a-*cis*-1,2,3,4,10,-10a-hexahydrophenanthrene (**4***a*). Compound **4***a* was obtained by a base catalysed rearrangement of **3***a*; B/C-*trans* fused products were not observed. The synthesis described below passes through a 4a,10a-*trans* counterpart of **4***c* and leads to 3-hydroxy-*N*-methyl-D-norisomorphinan (**6***b*).

## Results and discussion

At the outset it appeared that a viable synthesis of the D-normorphinan or D-norisomorphinan ring system could be modeled on Schenker's approach (3) to 2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (**9**), the key step of which was the cyclization of **7** to **8**. Thus a synthesis of **6** would require construction of the intermediate **10**. The synthesis of **10** is outlined in Scheme 2.



**7** **8** **9**



**3** **4** **5**

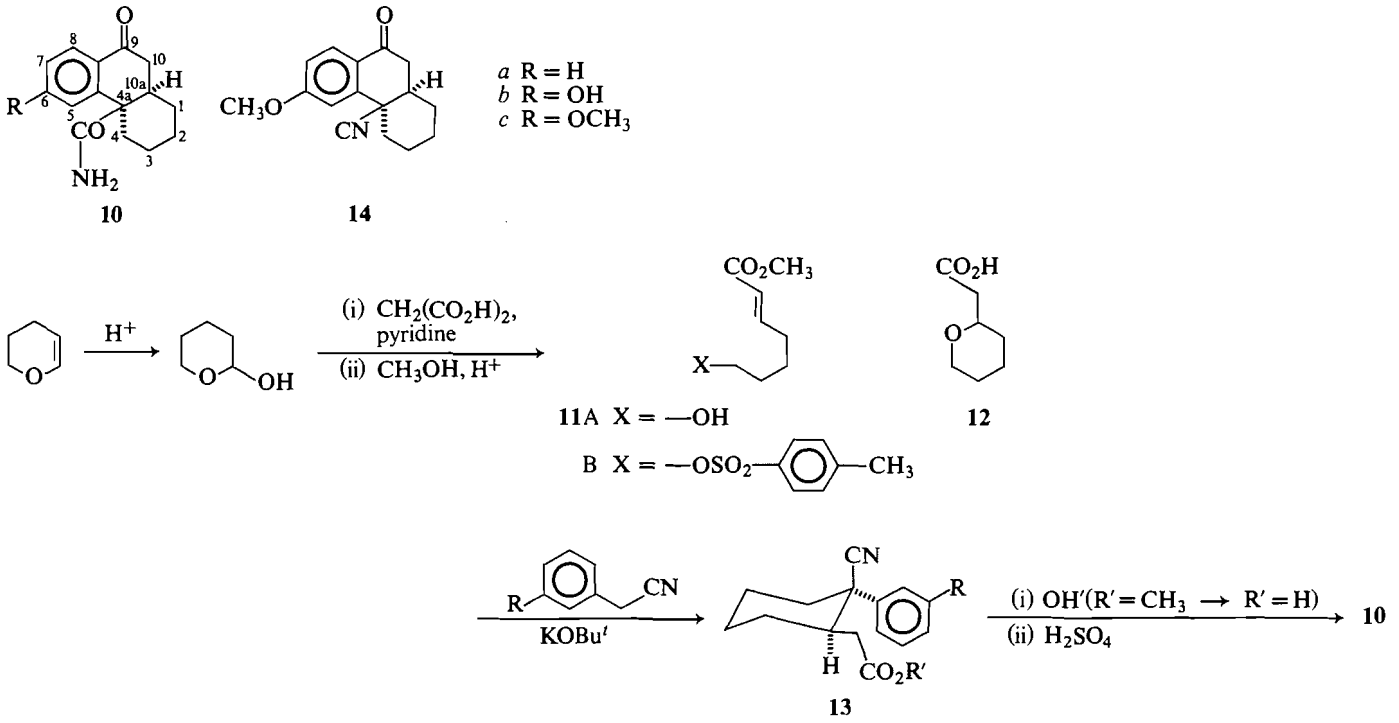
*a* R = H
*b* R = OH
*c* R = $OCH_3$



**6**

SCHEME 1

[1] Author to whom correspondence may be addressed.
[2] Revision received October 19, 1984.




SCHEME 2

Methyl 7-hydroxy-*trans*-2-heptenoate (**11**A) is readily available by Raphael's procedure (4) starting from dihydropyran; in a minor modification, the intermediate 7-hydroxy-*trans*-2-heptenoic acid was not distilled but converted directly to the methyl ester using methanolic hydrogen chloride. In our hands, attempted distillation of the crude acid gave **12** as the predominant product. Cycloaddition was not a major problem in the distillation of **11**A, presumably due to the lower distillation pot temperatures involved. The oily tosylate (**11**B), together with *m*-methoxyphenylacetonitrile, added to a refluxing solution of potassium *tert*-butoxide in *tert*-butanol led, in a combined alkylation – Michael addition step, to **13***c* ($R^1 = CH_3$). **13***c* was not purified but hydrolysed to the acid **13***c* ($R^1 = H$) which in turn was cyclized directly to **10***c*. If the cyclization in sulfuric acid is conducted at 0°C rather than at room temperature, a small yield of the nitrile (**14**) may be isolated in addition to **10***c*, and this argues against participation of glutaric intermediates in the cyclization step. *para*-Activation is not required for cyclization, a virtually identical yield of **10***a* being obtained by a similar sequence from phenylacetonitrile.

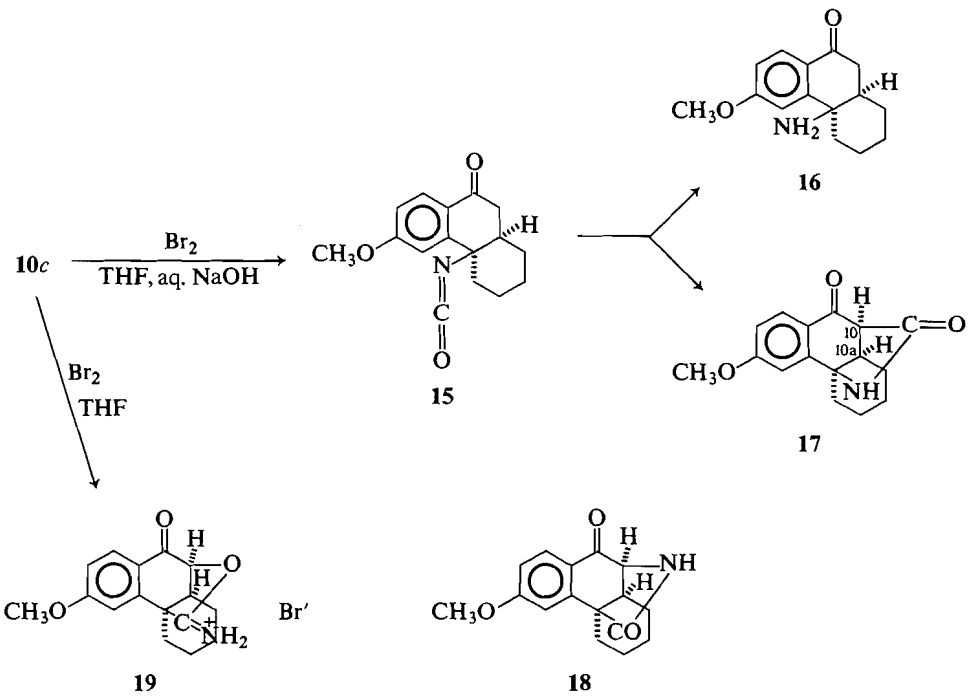
Compound **10***c* showed the appropriate mass ions at 273 ($M^+$) and 229 ($M^+ - CONH_2$), a 1,2,4-trisubstituted benzene $^1$Hmr pattern, and primary amide and aryl ketone ir absorptions at 1690, 1660, 1595, and 1555 $cm^{-1}$. No trace of a second diasteriomer with B/C rings *cis* fused was detected and this deserves comment. Regardless of whether the Michael-addition step, a perpendicular attack on the conjugated system by a *m*-methoxyphenylacetonitrile anion, or nucleophilic displacement of the tosylate occurs first, the final step involves formation of a cyclohexane ring. The preferred transition state will presumably have the bulky *m*-methoxyphenyl and carboxymethyl groups in a low energy *trans* diequatorial relationship leading to **13***c* ($R^1 = CH_3$). Proof of the *trans* stereochemistry follows from the $^1$Hmr of rigid transformation products, *vide infra*, all of which lack visible coupling between the H(9) and H(14) protons for which the Karplus equation predicts (5) a dihedral angle of 100°, in agreement with measurements from Dreiding models. The value for the corresponding B/C *cis*-fused, D-normorphinans $J_{H9H14}$ is 5 Hz, in agreement with the observed dihedral angle $\phi_{H9H14} = 37°$ (2).

*Bromination experiments*

Schenker reports (3) the synthesis of **8** by a heterogeneous reaction of **7** in aqueous sodium hydroxide with bromine. Using the substrate **10***c* no reaction was observed, presumably a consequence of the extreme insolubility of **10***c*. Repetition of the reaction with the addition of tetrahydrofuran, initially added as a cosolvent, rather surprisingly afforded a two-phase system;[3] thin-layer chromatography indicated rapid loss of starting material. The product isolated in essentially quantitative yield was the Hofmann rearrangement product, the isocyanate (**15**), rather than the expected bromoketone (Scheme 3). If the isocyanate is not isolated, but the two-phase reaction mixture stirred overnight at room temperature, the products are the bridged structure (**17**) and a minor component – the amine (**16**). Compound **17** presumably arises via intramolecular attack of the enol form of **15** on the isocyanate moiety, formation of an α-enolate anion from this ketone with sodium hydroxide being unlikely. It is worth noting that **17** had the mass, mass spectral fragmentation pattern, and an ir expected for **18**. The $^1$Hmr of **17** has a sharp one-proton singlet at 3.00 ppm, assigned to the H(10) proton. Lack of coupling with the H(10a) proton was the first evidence that rings B and C were *trans* fused.

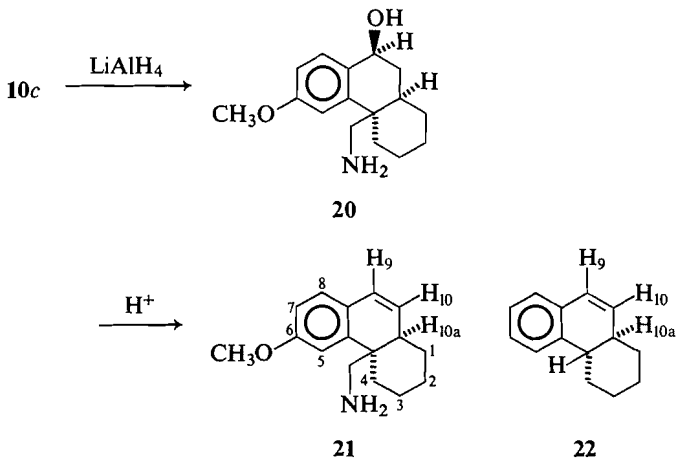
Bromination of **10***c* in anhydrous tetrahydrofuran with no added base afforded **19**. The appropriate mass ion at 271 ($M^+$) was observed and the ir showed typical ammonium bands. Again a peak at 5.39 ppm, assigned to the H(10) proton in the $^1$Hmr was a sharp singlet. The isolation of **17** and **19** rather than

[3] The lowered solubility of tetrahydrofuran in strong alkali proved useful in the synthesis of both **15** and **23**.




SCHEME 3

**18**, while disappointing, suggested that the D-norisomorphinan would be obtainable once the ambident functionality of the amide was removed, e.g., by intramolecular cyclization of the aminomethyl compound **21**.




Conversion of **10*c*** into **21** was achieved in two steps – a prolonged reduction with $LiAlH_4$ to the hydroxyamine (**20**), followed by formation of **21** by an acid-catalysed elimination of the benzylic hydroxyl. Compound **20** was isolated as a sharp-melting crystalline solid. Its isolation as a single isomer upon reduction reflects the lack of steric hindrance to α-face approach by the reducing agent. The quasi-equatorial stereochemical assignment for the ring hydroxyl was inferred from the broad width of the benzylic $^1$Hmr proton signal at 4.8 ppm, reflecting the large diaxial interaction with the 10β proton. In practice, it proved convenient to convert the total crude reaction mixture directly to **21** using *p*-toluenesulfonic acid in benzene. Overall yields of 60% from **10*c*** were obtained.

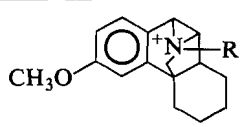
The $^1$Hmr spectrum of **21** deserves comment; the C(10) olefinic proton is observed as the B portion of an ABX system. The Karplus equation (5) predicts a value $J_{H10H10a} \cong 0.1$ Hz for the 4a,10a-*trans* system where the dihedral angle, $\phi_{H10H10a} = 100°$ is found and, indeed, $J_{H10H10a} = 0–1$ Hz is observed in the model system (**22**) reported by Nelson *et al.* (6). In **21** the C(10) proton is observed as a doublet of doublets split by both H(9), $J_{H9H10} = 9$ Hz, and by H(10a), $J_{H10H10a} = 2.2$ Hz, suggesting a small increase in the $\phi_{H10H10a}$ dihedral angle.

A possible explanation may be made using Bucort's principles of conformational transmission, considering rings B and C as a *trans*-fused octalin system (see, for example, references to Bucorts' papers in ref. 7). The *syn* 1,3-diaxial interactions between the large aminomethyl group and the axial hydrogens at C(1) and C(3) are intensified by the ring B unsaturation. In opposition a decrease in steric pressure is obtained by a decrease in the dihedral angle formed by C(4)—C(4a)—C(10a)—C(1) and is not reflected in Dreiding models. The net result of the compromise is an increase in the $\phi_{H10H10a}$ angle.

*Formation of the* D-*norisomorphinan*

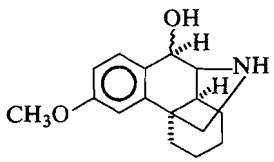
Two concurrent efforts to form the D-norisomorphinan ring system were made. One approach, an attempted synthesis of the azetidium structure[4] (**i**) by assisted solvolysis of an *N*-chloroamine derivative was unsuccessful. Lithium aluminum hydride reduction of **i** might be expected to afford a D-norisomorphinan. The other, a successful method, involved an attempt to prepare a 10α-bromo, 9ε-hydroxybromohydrin from **20** by treatment with *N*-bromoacetamide in aqueous tetrahydrofuran. α-Face attack by the bromonium ion is to be expected on both steric and electronic grounds, since the β-face is swept by the positively charged aminomethyl group. α-Face attack would presumably occur via perpendicular attack on the 9,10-olefin in a pre-boat form and lead to a 10α-bromo-

[4]

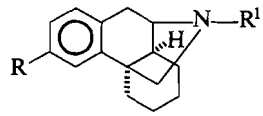



**i**

derivative, since solvent attack is to be expected at the benzylic position. After addition of excess sodium hydroxide the reaction mixture because two-phase and the product isolated after a 45-minute wait proved to be the D-norisomorphinan **23**. Bromohydrin formation is obviously followed by a facile intramolecular alkylation of the amine upon neutralization of the perchloric acid. Conversion of **23** to **24** by vigorous hydrogenolysis confirmed the benzylic location of the hydroxyl function. The benzylic proton of **23** appears in the nmr as a doublet, $J_{9/10} = 4.5$ Hz, a value that is ambiguous with regard to configurational assignment.



**23**



**24** R = $OCH_3$, R' = H
**25** R = $OCH_3$, R' = $CO_2CH_2CH_3$
**6***b* R = OH, R' = $CH_3$
**6***c* R = $OCH_3$, R' = $CH_3$

Completion of the synthesis proved straightforward; **24** was converted to the *N*-methyl compound (**6***c*) via the intermediate urethane **25**. Demethylation of the aromatic methoxyl in **6***c* proceeded smoothly, by brief treatment with hydrogen bromide at 140°C, affording 3-hydroxy-*N*-methyl-D-norisomorphinan **6***b*. Overall the synthetic route is represented by the sequence **10***c* → **20** → **21** → **23** → **24** → **25** → **6***c* → **6***b*.

## Experimental

Melting points (uncorrected) were obtained on a Thomas–Hoover apparatus. The nmr and mass spectra were determined on Jeolco Model C-60HL and Associated Electrical Industries MS-9 spectrometers.

*Methyl 7-hydroxy*-trans-*2-heptenoate,* p-*toluenesulfonate (**11B**)*

Methyl 7-hydroxy-*trans*-2-heptenoate (85 g; 5.4 × $10^{-1}$ mol) in pyridine (450 mL) at 0°C was treated over 2 min with *p*-toluenesulfonyl chloride (123 g; 6.5 × $10^{-1}$ mol) and the mixture allowed to reach room temperature over 6 h. Ice was added and the mixture stirred for a further 45 min. After dilution with water the mixture was extracted with ether (2×) and the extracts washed successively with water, dilute sulfuric acid, water, $NaHCO_3$ solution, and brine and dried over $Na_2SO_4$. After evaporation of the solvent the oily tosylate was used directly; ir: 1730, 1660, 1600, 1360, 1180 $cm^{-1}$.

trans-*1,3,4,9,10,10a-Hexahydro-6-methoxy-9-oxo-4a(2*H*)-phenanthrenecarboxamide (**10**c)*

A mixture of *m*-methoxyphenylacetonitrile (20 g; 1.35 × $10^{-1}$ mol) and **11B** (39.6 g; 1.27 × $10^{-1}$ mol) in *tert*-butanol (550 mL) was added dropwise, during 3 h, to a refluxing solution of potassium *tert*-butoxide (16.4 g; 1.46 × $10^{-1}$ mol) in *tert*-butanol (300 mL). The reaction mixture was refluxed for a further 3 h under nitrogen and then stirred at room temperature overnight. Acetic acid (20 mL) was added and the reaction mixture stripped to a small volume, diluted with water, and extracted with diethyl ether (2×). The ether extracts were washed with water, brine, and evaporated; the residue in methanol (350 mL) was heated under reflux with 20% NaOH solution (100 mL; 5 × $10^{-1}$ mol) during 2.5 h. The reaction mixture was stripped to a small volume, diluted with water, and extracted with ether (rejected). The aqueous solution was acidified strongly with hydrochloric acid and extracted (2×) with ether. The ether extracts were washed with brine, dried ($Na_2SO_4$), and evaporated to a partially crystalline residue (35 g). The total residue was stirred with cold concentrated $H_2SO_4$ (1 L) overnight and poured onto ice. A highly crystalline product (14 g) precipitated and was recrystallized from acetone to yield **10***c* (10 g, 29%), mp 225–228°C; ir: 3350 (s), 3140 (s), 1690 (s), 1660 (s), 1595 (s), 1555 infl. $cm^{-1}$; $^1H$ nmr (DMSO) δ: 3.71 (3H, s, $—OCH_3$), 6.75 (C(7)-H centre of a pair of d, $J_{5/7}$ 2.5 cps, $J_{7/8}$ 8.5 Hz), 6.99 (C(5)-H d, $J_{5/7}$ 2.5 Hz, $J_{5/8}$ 0 Hz), 7.62 (C(8)-H d, $J_{7/8}$ 8.5 Hz), 6.66 (2H, br m, $CONH_2$) ppm; ms *m/e*: 273 ($M^+$), 229 ($M^+ - CONH_2$), 187, 167. *Anal.* calcd. for $C_{16}H_{19}NO_3$: C 70.31, H 7.01, N 5.13; found: C 70.03, 70.54; H 7.04, 7.17; N 5.53, 5.15%.

If the concentrated sulfuric acid cyclization step in the above example is allowed to proceed at 0°C rather than at room temperature, small amounts of a more soluble (methanol), less polar, intermediate carbonitrile may be isolated: *trans*-1,3,4,9,10,10a-hexahydro-6-methoxy-9-oxo-4a(2*H*)-phenanthrenecarbonitrile (**14**), mp 174–177°C; ir: 2220 (very weak), 1685 (s), 1605 (s) $cm^{-1}$. *Anal.* calcd. for $C_{16}H_{17}NO_2$: C 75.21, H 6.71, N 5.49; found: C 75.06, H 6.71, N 5.49%.

*Bromination experiments*

trans-*2,3,4,4a,10,10a-Hexahydro-4a-isocyanato-6-methoxy-9(1*H*)-phenanthrenone (**15**)*

Bromine (144 μL, 0.45 g; 2.8 × $10^{-3}$ mol) was added to a stirred, two-phase solution prepared from **10***c* (600 mg; 2.2 × $10^{-3}$ mol), sodium hydroxide (1 g), water (10 mL), and tetrahydrofuran (10 mL). Thin-layer chromatography indicated complete loss of starting material within 5 min. The reaction mixture was diluted with water and methylene chloride. The methylene chloride extract was washed with water (2×), brine, dried ($Na_2SO_4$), and concentrated to a residue. Crystallization from methylene chloride – hexane afforded **15** (500 mg, 84%), mp 112–113.5°C; ir: 2250 (s) $cm^{-1}$. *Anal.* calcd. for $C_{16}H_{17}NO_3$: C 70.83, H 6.32, N 5.16; found: C 70.60, H 6.45, N 5.04%.

trans-*4a-Amino-2,3,4,4a,10,10a-hexahydro-6-methoxy-9(1*H*)-phenanthrenone (**16**) and (4aα,10α,10aβ)-1,2,3,4,10,10a-hexahydro-6-methoxy-9*H*-4a,10(iminomethano)phenanthrene-9,11-dione (**17**)*

Bromine (720 μL, 2.23 g; 1.4 × $10^{-2}$ mol) was added over 10 min to a stirred two-phase solution prepared from **10***c* (3 g; 1.1 × $10^{-2}$ mol), sodium hydroxide (3 g), water (40 mL), and tetrahydrofuran (45 mL). The reaction mixture was stirred at room temperature overnight, diluted with water, and extracted with methylene chloride. The methylene chloride extract was washed with water (2×), brine, dried ($Na_2SO_4$), and concentrated to a residue. Trituration of the residue with ether afforded a crystalline residue of **17** (1.24 g, 42%) that, after two recrystallizations from methylene chloride – methanol, had mp 239–243°C (dec.).

The ether triturate was evaporated and the residue recrystallized from ether–hexane (charcoal) and then methylene chloride – hexane to afford **16** (360 mg, 13%, mp 101–103°C. Compound **16**: ms *m/e*: 245 ($M^+$), 228, 202, 188. *Anal.* calcd. for $C_{15}H_{19}NO_2$: N 5.71; found: N 5.48, 5.49%. Compound **17**: ms *m/e*: 271 ($M^+$), 243, 228, 214. *Anal.* calcd. for $C_{16}H_{17}NO_3$: C 70.83, H 6.32, N 5.16; found: C 70.50, H 6.32, N 5.33%.

*(4aα,10α,10aβ)-1,2,3,4,10,10a-Hexahydro-12-imino-6-methoxy-9*H*-10,4a-(epoxymethano)phenanthren-9-one (**19**)*

Bromine (0.85 μL, 2.64 g; 1.7 × $10^{-2}$ mol) in tetrahydrofuran (40 mL) was added dropwise to a suspension of **10***c* (4 g; 1.46 × $10^{-2}$ mol) in tetrahydrofuran (40 mL). Complete solution was followed by a voluminous precipitate of **19** (4.3 g, 83%). The analytical sample, mp 216–218°C (dec.), was obtained by rapid recrystallization from methanol–ether; ms *m/e*: 271 ($M^+$). *Anal.* calcd. for $C_{16}H_{17}NO_3 \cdot HBr$: C 54.56, H 5.15, N 3.98, Br 22.69; found: C 54.67, H 5.39, N 3.96, Br 22.06%.

*(4aα,10aβ)-4a-Aminomethyl-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-9-phenanthrenol (**20**)*

Compound **10***c* (30 g) and lithium aluminum hydride (20 g) in tetrahydrofuran (3 L) were refluxed under nitrogen during 2 days. The cooled reaction mixture was treated dropwise with 100 mL, 3% NaOH solution, filtered, and evaporated to a crystalline residue of **20** (28 g)

suitable for further transformation. An analytical sample, mp 149–151°C, was obtained by recrystallization from ethyl ether – hexane; $^1$H nmr ($CDCl_3$–$D_2O$) δ: AB q of aminomethyl protons with $J$ 13.5 Hz at 2.81 and 2.99, 3.84 (3H, s, $OCH_3$), 4.83 (1H center approximate t, C(9)-H) ppm; ms $m/e$: 243 ($M^+ - H_2O$). *Anal.* calcd. for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found: C 73.24, H 8.82, N 5.33%.

trans-*1,3,4,10a-Tetrahydro-6-methoxy-4a(2H)-phenanthrenemethanamine (21)*

Compound **20** (25 g; $8.5 \times 10^{-2}$ mol) and *p*-toluenesulfonic acid monohydrate (18 g; $9.5 \times 10^{-2}$ mol) in benzene (1 L) were heated under reflux using a Dean–Stark head; after 1 h the reaction mixture was stripped to a small volume, diluted with ether, and extracted with water. The aqueous phase together with a crystalline precipitate were washed with ether (rejected), basified strongly with NaOH solution, and extracted with ether (2×). The ether extracts were washed with brine, dried ($Na_2SO_4$), evaporated to a small volume, and filtered through a Woelm alumina column (Grade I, basic 120 g); the product (16 g) eluted with ether and was obtained as a colorless oil; ir: 1610, 1570 cm$^{-1}$; $^1$H nmr ($CDCl_3$) δ: 2.87 (2H, multiplet, $W_{1/2}$ H 5 Hz), 3.79 (3H, s, —$OCH_3$), AB q $J_{9/10}$ 9 Hz, protons centered at 5.48 (C(10)-H) and 6.36 (C(9)-H) further split by C(10a)-H, $J_{10a/10}$ 2.2 Hz, $J_{9/10a}$ 3 Hz ppm.

*(±)-(14α)-3-Methoxy-D-normorphinan-10-ol (23)*

Compound **21** (4.86 g; $2 \times 10^{-2}$ mol) in tetrahydrofuran (150 mL) containing 0.5 *N* $HClO_4$ (80 mL; $4 \times 10^{-2}$ mol) was cooled to 0°C and treated, under nitrogen, with *N*-bromoacetamide (3 g; $2.2 \times 10^{-2}$ mol) added over 1–2 min. Thin-layer chromatography indicated that there was a rapid loss of starting material; after 20 min, excess NaOH solution (20 mL; 50%) and ice were added. The two-phase solution was stirred for 45 min. After dilution with benzene the organic layer was washed with water (2×), brine, dried ($Na_2SO_4$), and evaporated to a residue which readily crystallized on trituration with boiling ether to give the product (4 g; free base form), mp 140–143.5°C. Recrystallization from methanol–ether gave a higher mp form, mp 174–177°C; $^1$H nmr ($CDCl_3$) δ: 2H, AB q, $J$ 10 Hz, aminomethyl protons centered at 2.53 and 3.57; 2H, AB q, $J_{9/10}$ 4.5 Hz, $J_{9/14}$ 0 Hz centered at 3.24 (C(9)-H) and 4.66 (C(10)-H); 3.79 (3 Hs, —$OCH_3$) ppm. *Anal.* calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.4; found: C 73.69, H 8.16, N 5.34%.

Salt (**23**·HCl), mp 244–245°C, crystallized from methanol–ether. *Anal.* calcd. for $C_{16}H_{22}NO_2Cl$: C 64.96, H 7.50, N 4.74, Cl 11.95; found: C 64.60, H 7.47, N 4.69, Cl 11.72%. In a repeat experiment, **21** (14.4 g) was converted into **23**·HCl (8.1 g, 46%), mp 243–245°C, without isolation or purification of the free base.

*(±)-(14α)-3-Methoxy-D-normorphinan (24)*

Compound **23** (5.0 g), acetic acid (80 mL), 70% perchloric acid (2 mL), and 5% Pd on $BaSO_4$ (2.0 g) were stirred at 80°C in an atmosphere of hydrogen overnight (1 mol uptake). After cooling, 30 mL of 10% $K_2CO_3$ solution were added and following filtration the reaction mixture was evaporated, basified with NaOH solution, taken into $CH_2Cl_2$, and washed with brine. After evaporation of the solvent, the residue in ether was dried ($Na_2SO_4$) and treated with isopropanolic hydrogen chloride to give a crystalline precipitate which after trituration with boiling acetone afforded **24**·HCl (4.14 g, 86%), mp 228–231°C (some previous decomposition). The analytical sample, mp 238°C (dec.), was obtained by recrystallization from acetone; ms $m/e$: 243 ($M^+$). *Anal.* calcd. for $C_{16}H_{22}NOCl \cdot \frac{1}{4} H_2O$: C 67.59, H 7.98, N 4.93, Cl 12.47; found: C 67.45, 67.35; H 7.75, 7.84; N 4.82, 4.67; Cl 12.97%.

*(±)-(14α)-3-Methoxy-17-methyl-D-normorphinan (6c)*

Compound **24** (4 g; $1.43 \times 10^{-2}$ mol) in a stirred mixture of methylene chloride (300 mL) and saturated $NaHCO_3$ solution (300 mL) was treated with ethyl chloroformate (1.8 mL; $1.88 \times 10^{-2}$ mol) at room temperature during 30 min. After standing overnight, the organic layer was separated and evaporated. The residue in ether was washed with dilute HCl, brine, dried ($Na_2SO_4$), and evaporated to give the urethane (**25**, 4.2 g). The urethane in ether–tetrahydrofuran (1:1, 400 mL) was heated under reflux with $LiAlH_4$ (2.5 g) during 4 h. After standing overnight the reaction mixture was treated with 12.5 mL 3% NaOH solution, filtered, and evaporated. The residue in ether was filtered through a Woelm alumina column (40 g, Grade I, basic) and eluted with ether. The total eluate was treated with isopropanolic hydrogen chloride and the precipitate, after crystallization from acetone, afforded **6c**·HCl (2.9 g, 70%), mp 238–240°C; $^1$H nmr ($CDCl_3$–$D_2O$) δ: 2.9 (3H, s, N-$CH_3$), 3.88 (3H, s, —$OCH_3$), 3.38 (ca. 2H, d, $J$ = 3 Hz – actually center peaks of AB quartet ($CH_2$—N—$CH_3$)) ppm; ms $m/e$: 257 ($M^+$). *Anal.* calcd. for $C_{17}H_{24}NOCl$: C 69.49, H 8.23, N 4.77, Cl 12.07; found: C 69.30, H 8.29, N 4.64, Cl 12.35%.

*(±)-(14α)-17-Methyl-D-normorphinan-3-ol (6b)*

Compound **6c**·HCl (1.8 g) and 47–49% aqueous hydrogen bromide (30 mL) were heated under reflux during 45 min. The cooled reaction was treated with ice and an excess of concentrated ammonium hydroxide to give a crystalline precipitate of the product (free base form). After aging (1 h) the precipitate (1.6 g) was filtered off. A small portion recrystallized from acetone had mp 223–225°C (dec.). *Anal.* calcd. for $C_{16}H_{21}NO$: C 78.97, H 8.70, N 5.76; found: C 78.93, H 8.91, N 5.73%.

The remainder in acetone was treated with a slight excess of isopropanolic hydrogen chloride and concentrated. The crystalline precipitate was recrystallized from methanol–ether; the product, **6b**·HCl (1.15 g, 66%), had mp 255–258°C (with effervescence); ms $m/e$: 243 ($M^+$). *Anal.* calcd. for $C_{16}H_{22}NOCl$: C 68.68, H 7.93, N 5.01, Cl 12.67; found: C 68.17, H 7.86, N 4.85, Cl 11.97%.

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