Synthesis of a Morphinan from a Benzocyclobutene Derivative. *X*-Ray Structure of 3,3-Ethylenedioxy-1,2,3,4,4a,10aα-hexahydro-6,7-dimethoxyphenanthrene-4aβ-carbonitrile

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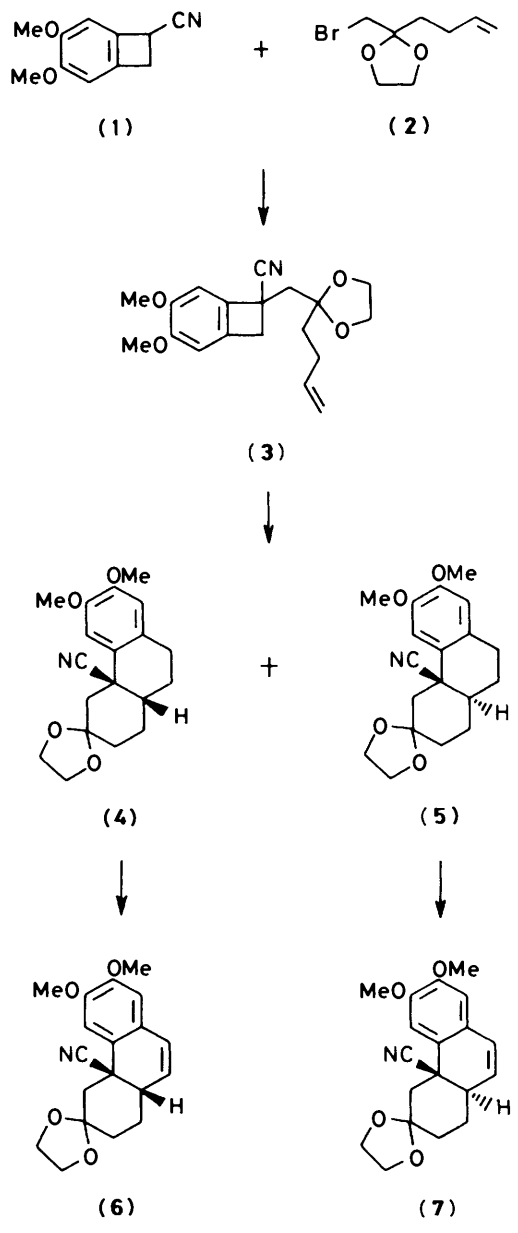
A stereoselective synthesis of a morphinan ring system has been achieved by employing an intramolecular Diels–Alder reaction of a benzocyclobutene derivative (**3**) to provide a tricyclic compound (**4**) having a B/C *cis* ring junction. After manipulation of a cyano group, the resulting amine (**13**) was converted into a morphinan derivative (**16**) by cyclization of an aminylium ion.

During the course of our studies [1] directed towards the synthesis of natural products by employing benzocyclobutene {bicyclo-[4.2.0]octa-1(6),2,4-triene} derivatives [2] as useful synthons, we became interested in developing a method for the stereoselective synthesis of morphinans. With regard to the synthesis of morphinans, a number of papers [3] have been published to date, and many of these syntheses involved the formation of the C(12)–C(13) bond as a key step. We designed an alternative synthesis of morphinans, in which we planned to use a benzocyclobutene derivative as a source of an ABC ring system in morphinans. We note in advance that an intramolecular Diels–Alder thermolytic cycloaddition of a benzocyclobutene derivative, having a cyano group at the 1-position,† always affords a B/C *cis* adduct [4] as the predominant product. This result was an important impetus in our attempts to construct, stereoselectively, a morphinan ring system with a B/C *cis* ring junction, as is observed in morphine itself. If the ABC ring system were constructed as outlined above, we would then have to seek the best way to manipulate a cyano group in order to construct a D-ring. With that prerequisite in mind, we started our synthesis with a preparation of the benzocyclobutene derivatives as follows.

Results and Discussion

Treatment of 3,4-dimethoxybicyclo[4.2.0]octa-1(6),2,4-triene-7-carbonitrile (**1**) [5] with 2-bromomethyl-2-(but-3-enyl)-1,3-dioxolane (**2**) in dimethylformamide (DMF) in the presence of sodium hydride afforded the olefinic benzocyclobutene (**3**) in 72.4% yield. Thermolysis of the benzocyclobutene (**3**) in refluxing xylene for 3 h provided the cyclization products (**4**) and (**5**), in 61 and 29% yield, respectively. Both compounds were deduced to be stereoisomers on the basis of their spectroscopic data. The major product (**4**) was then converted into the olefin (**6**) by treatment with *N*-bromosuccinimide (NBS) and benzoyl peroxide [6] in refluxing carbon tetrachloride for 20 min in 78% yield. In addition, the minor tricyclic compound (**5**) was transformed into the olefin (**7**) by the same treatment in 72% yield. Since the stereochemistry of the minor tricyclic olefin (**7**) was unambiguously confirmed by *X*-ray analysis to have a B/C-*trans* ring juncture as shown in Figure 1, the major compound was assigned to be the B/C-*cis* isomer, whose ring-junction stereochemistry is the same as that in naturally occurring morphine alkaloids (Scheme 1). In this cycloaddition reaction, the observed stereoselectivity leading predominantly to the B/C-

† The 1-position of a 'benzocyclobutene' is the 7-position of a bicyclo-[4.2.0]octane system.



Scheme 1.

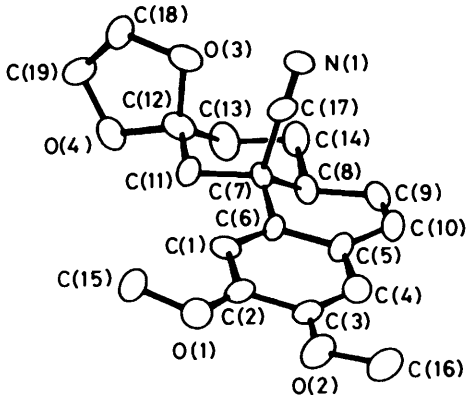


Figure 1. Perspective drawing of compound (7) with the crystallographic numbering system

Table. Atomic positional parameters (× 10^4) with e.s.d.s in parentheses (crystallographic numbering scheme)

Atom	*x*	*y*	*z*
C(1)	4 857(17)	8 030(14)	4 655(10)
C(2)	5 043(18)	8 754(14)	4 178(12)
C(3)	6 683(19)	9 336(14)	4 844(12)
C(4)	7 987(18)	9 225(16)	5 914(12)
C(5)	7 755(17)	8 534(14)	6 376(11)
C(6)	6 157(16)	7 979(14)	5 728(10)
C(7)	6 034(17)	7 119(14)	6 266(11)
C(8)	7 086(18)	7 740(15)	7 331(11)
C(9)	8 873(18)	8 038(16)	7 986(12)
C(10)	9 134(19)	8 445(16)	7 518(12)
C(11)	4 203(18)	6 882(16)	5 587(11)
C(12)	4 146(18)	6 180(15)	6 211(12)
C(13)	5 205(20)	6 800(18)	7 254(11)
C(14)	7 017(18)	6 918(17)	7 900(11)
C(15)	2 358(21)	8 142(19)	2 472(12)
C(16)	8 413(23)	10 362(18)	4 911(16)
C(17)	6 871(18)	5 845(14)	6 494(11)
C(18)	3 091(18)	4 067(17)	5 536(14)
C(19)	1 892(22)	4 839(16)	5 359(16)
N(1)	7 524(15)	4 906(13)	6 652(10)
O(1)	3 861(12)	8 896(11)	3 140(7)
O(2)	6 764(13)	9 954(11)	4 308(8)
O(3)	4 601(13)	4 827(10)	6 358(8)
O(4)	2 416(11)	6 148(10)	5 550(7)

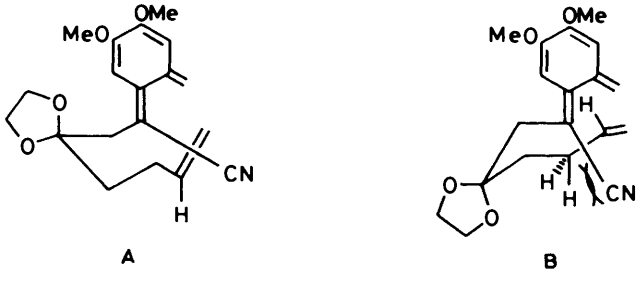


Figure 2.

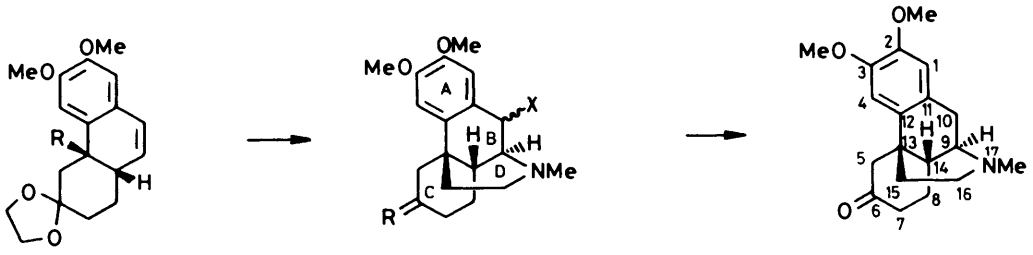
cis ring system was rationalized by assuming that this reaction proceeded *via* the transition state A rather than B in the least sterically hindered manner (Figure 2).

Crystallographic Determination of Compound (7).—Compound (7) was recrystallized from benzene–n-hexane as monoclinic crystals, m.p. 194—195 °C; $C_{19}H_{21}NO_2$, space group $P2_1/c$, with a = 12.951(3), b = 10.279(2), c = 20.871(5) Å, β = 142.21(1)°, Z = 4, D_c = 1.28 g cm^{-3}. Intensity measurements were made with Mo-K_α radiation (λ = 0.7107 Å; graphite monochromater) on a Rigaku AFC-5 FOS diffractometer in the ω—2θ mode within 51°. A total of 835 unique reflections were measured with $F \geq 3\sigma(F)$. The measured reflections were corrected for Lorentz polarization only. Accurate cell parameters were obtained by least-squares techniques from the diffractometer setting for 24 reflections. The structure was solved using MULTAN,[7] and refined by block-diagonal least-squares. Convergence, with anisotropic thermal parameters for all non-hydrogen atoms, was reached at R 0.093 (R_w 0.099) using all the observed reflections. The difference electron density map based on the final atomic parameters showed no maxima greater than 0.22 e Å^{-3}. The atomic positional parameters are given in the Table. Bond lengths, bond angles, and anisotropic thermal parameters are listed in Supplementary Publication No. SUP 56592 (4 pp).*

Elaboration of the 4a-*Side-chain of the Nitrile* (6).—With the required phenanthrene derivative available, we attempted to discover the best way to construct the D ring of the desired morphinan compound. The olefin (6) was first treated with di-isobutylaluminium hydride (DIBAL)[8] in tetrahydrofuran (THF) to afford the aldehyde (8) in 79% yield; treatment of this aldehyde with nitromethane[9] in propan-2-ol in the presence of potassium fluoride and 18-crown-6 at ambient temperature furnished the alcohol (9) as the assumed intermediate *in situ*. Dehydration of the alcohol (9) with acetic anhydride and 4-(*NN*-dimethylamino)pyridine (DMAP)[9] gave the nitro olefin (10) in 97% yield from (8); reduction of the olefin (10) with sodium borohydride in ethanol afforded the nitro compound (11). Thus, the elongation of a methylamine moiety was achieved in moderate yield. Reduction of the nitro compound (11) with lithium aluminium hydride in THF, followed by acylation with methyl chloroformate, provided the urethane (12) in 54% yield from (10). Reduction of the urethane (12) with lithium aluminium hydride in THF afforded the amine (13) in 63% yield (Scheme 2).

Construction of the D *Ring*.—It is well known that *N*-chloroalkylamines with a double bond undergo an intramolecular cyclization reaction[10] to give cyclic amines. We therefore investigated the possibility of using this type of reaction to construct the D ring of a morphinan. *N*-Chloro derivative (14) (as an assumed intermediate) was prepared from the amine (13) by treatement with *N*-chlorosuccinimide (NCS) in methylene dichloride at 0 °C. Decomposition of chloride (14) was first carried out with titanium trichloride as catalyst in acetic acid–water (1:1 v/v) at 0 °C for 1 h to give the cyclized products (15) and (16) as an inseparable mixture. The protected ketone (15), however, was easily converted into the free ketone (16) by acid hydrolysis. Since this reaction is recognized to proceed *via* an aminyl radical rather than an aminylium ion intermediate, the stereochemistry of the product (15) could not be determined from either the (postulated) reaction mechanism or its spectral data. By contrast, treatment of *N*-chloro derivative (14) with silver(I) oxide in methanol brought about cyclization to give the protected morphinanone (17) as the sole cyclized product, probably *via* an aminylium intermediate, in 51% yield. Removal of the methoxy group at the benzylic position of compound (17) was successfully achieved under Birch reduction condition to give the acetal (18), in 58% yield, whose acid hydrolysis furnished the desired morphinanone (19).[11] The structure of the synthetic compound, including its

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, issue 1.



(6) R = CN
(8) R = CHO
(9) R = CH(OH)CH_2NO_2
(10) R = CH=$CHNO_2$
(11) R = $CH_2CH_2NO_2$
(12) R = $CH_2CH_2NHCO_2Me$
(13) R = CH_2CH_2NHMe
(14) R = $CH_2CH_2N(Cl)Me$

(15) X = Cl, R = OCH_2CH_2O
(16) X = Cl, R = O
(17) X = α-OMe, R = OCH_2CH_2O
(18) X = H, R = OCH_2CH_2O

(19)

Scheme 2.

stereochemistry, was confirmed by direct comparison with an authentic specimen.[11]

Thus we have achieved a novel stereoselective construction of a morphinan ring system by using a phenanthrene derivative as an important intermediate, and this synthetic route may well be applicable to other morphinan derivatives, such as C-nor, C-homo, and D-nor compounds.

Experimental

I.r. spectra were run on a Hitachi 260-10 spectrophotometer for samples in $CHCl_3$ solution. ^1H N.m.r. spectra were determined with a JEOL JNM-FX-100 spectrometer for samples in $CDCl_3$ solution, and chemical shifts are expressed in p.p.m. downfield from internal $SiMe_4$. Mass spectra were obtained with a JEOL JMS-D300 spectrometer.

2-Bromomethyl-(2-but-3-enyl)-1,3-dioxolane (**2**).—To a stirred, ice-cooled solution of 2-(but-3-enyl)-2-methyl-1,3-dioxolane[12] (142 mg, 1 mmol) in THF (20 ml) was added pyridinium bromide perbromide (320 mg, 1 mmol). After being stirred for 3 h at the same temperature, the reaction mixture was filtered and the filtrate was taken up in Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, dried (K_2CO_3), and evaporated to give an oil which was purified by column chromatography on silica gel. Elution with benzene gave the title bromide (**2**) (35 mg, 16%) as an oil, $\nu_{max.}$($CHCl_3$) 1 640 cm^{-1}; δ 1.80—2.34 (4 H, m, 2-CH_2CH_2), 3.40 (2 H, s, CH_2Br), 3.92—4.18 (4 H, m, OCH_2CH_2O), 4.88—5.16 (2 H, m, CH=CH_2), and 5.60—6.04 (1 H, m, CH=CH_2); *m/z* 221 (M^+) and 223 ($M^+ + 2$).

7-{[2'-(But-3''-enyl)-1',3'-dioxolan-2'-yl]methyl}-3,4-dimethoxybicyclo[4.2.0]octa-1(6),2,4-triene-7-carbonitrile (**3**).—To a stirred, ice-cooled solution of compound (**1**) (5 g, 26.46 mmol) in DMF (100 ml) was added NaH (952 mg, 39.67 mmol). After the mixture had been stirred for 30 min at 0 °C, a solution of the bromide (**2**) (7.02 g, 31.74 mmol) in DMF (10 ml) was added dropwise to the above solution at 60 °C, and the mixture was further stirred for 1 h at 60 °C. The reaction mixture was poured into ice–water and extracted with Et_2O. The extract was washed with saturated aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with benzene–AcOEt (20:1 v/v) afforded title compound (**3**) (6.3 g, 72%) as an oil, $\nu_{max.}$($CHCl_3$) 2 230 and 1 640 cm^{-1}; δ 1.66–2.32 (4 H, m, 1'' and 2''-CH_2), 2.34 (2 H, s, CH_2), 3.36 and 3.65 (each 1 H, each d, *J* 14 Hz, 8-H_2), 3.86 (6 H, s, 2 × OMe), 3.96—4.28 (4 H, m, OCH_2CH_2O), 4.84—5.12 (2 H, m, CH_2=CH), 5.60—5.96 (1 H, m, CH_2=CH), and 6.69 and 6.83 (each 1 H, each s, 2 × ArH) (Found: M^+, 329.1600. $C_{19}H_{23}NO_4$ requires *M*, 329.1626).

Thermal Reaction of Compound (**3**).—A solution of compound (**3**) (140 mg, 0.43 mmol) in xylenes (80 ml) was heated under reflux for 3 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with benzene–AcOEt (95:5 v/v) gave the phenanthrene (**4**) (85 mg, 61%) as needles, m.p. 146—147 °C. Further elution with the same solvents afforded the isomer (**5**) (41 mg, 29%) as needles, m.p. 185—187 °C. cis-*Compound* (**4**) had $\nu_{max.}$($CHCl_3$) 2 240 cm^{-1}; δ (*inter alia*) 3.84 and 3.89 (each 3 H, each s, 2 × OMe), and 6.55 and 6.89 (each 1 H, each s, 2 × ArH); *m/z* 329 (M^+) (Found: C, 69.25; H, 7.1; N, 4.25%); trans-*compound* (**5**) had $\nu_{max.}$($CHCl_3$) 2 240 cm^{-1}; δ (*inter alia*) 3.85 and 3.87 (each 3 H, each s, 2 × OMe), 3.88—4.28 (4 H, m, OCH_2CH_2O), and 6.59 and 6.78 (each 1 H, each s, 2 × ArH); *m/z* 329 (M^+) (Found: C, 69.25; H, 7.05; N, 4.2. $C_{19}H_{23}NO_4$ requires C, 69.3; H, 7.05; N, 4.25%).

3,3-Ethylenedioxy-1,2,3,4,4a,10aβ-hexahydro-6,7-dimethoxyphenanthrene-4aβ-carbonitrile (**6**).—A mixture of compound (**4**) (213 mg, 0.65 mmol), NBS (115 mg, 0.65 mmol), and a catalytic amount of benzoyl peroxide in CCl_4 (100 ml) was heated under reflux for 20 min. The reaction mixture was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with benzene–AcOEt (20:1 v/v) afforded the *title product* (**6**) as an oil, which was recrystallized from Et_2O to give needles (165 mg, 78%), m.p. 102—104 °C; $\nu_{max.}$($CHCl_3$) 2 250 cm^{-1}; δ (*inter alia*) 2.94—3.12 (1 H, m, 10a-H), 3.89 and 3.94 (each 3 H, each s, 2 × OMe), 5.54 (1 H, dd, *J* 10 and 2 Hz, 10-H), 6.46 (1 H, dd, *J* 10 and 3 Hz, 9-H), and 6.63 and 7.11 (each 1 H, each s, 2 × ArH) (Found: M^+, 327.1470. $C_{19}H_{21}NO_4$ requires *M*, 327.1470).

3,3-Ethylenedioxy-1,2,3,4,4a,10aα-hexahydro-6,7-dimethoxyphenanthrene-4aβ-carbonitrile (**7**).—By the same procedure as described above for the preparation of compound (**6**), compound (**5**) (107 mg, 0.33 mmol) was converted into the title

compound (**7**) (77 mg, 72%) as needles, m.p. 194—195 °C; $\nu_{max.}$($CHCl_3$) 2 240 cm^{-1}; δ (*inter alia*) 3.86 and 3.90 (each 3 H, each s, 2 × OMe), 5.78 (1 H, dd, *J* 10 and 2.0 Hz, 10-H), 6.58 (1 H, dd, *J* 10 and 1.5 Hz, 9-H), and 6.72 and 6.78 (each 1 H, each s, 2 × ArH); *m/z* 327 (M^+) (Found: C, 69.7; H, 6.45; N, 4.1. $C_{19}H_{21}NO_4$ requires C, 69.7; H, 6.45; N, 4.3%).

3,3-*Ethylenedioxy*-1,2,3,4,4a,10aβ-*hexahydro*-6,7-*dimethoxyphenanthrene*-4aβ-*carbaldehyde* (**8**).—To a stirred, ice-cooled solution of nitrile (**6**) (1.61 g, 4.92 mmol) in THF (60 ml) was added a 1.5M solution of DIBAL (3.94 ml, 5.90 mmol) in toluene, and the mixture was stirred for a further 3 h at room temperature. The reaction mixture was then treated with saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave a residue, which was purified by column chromatography on silica gel with benzene–AcOEt (9:1 v/v) as solvent to give the title aldehyde (**8**) (1.28 g, 79%) as an oil, $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1}; δ (*inter alia*) 1.40—1.92 (4 H, m, 2 × CH_2), 2.05 (2 H, s, CH_2), 2.80—2.96 (1 H, m, 10a-H), 3.86 (6 H, s, 2 × OMe), 5.76 (1 H, dd, *J* 10 and 4 Hz, 10-H), 6.38 (1 H, dd, *J* 10 and 2 Hz, 9-H), and 9.68 (1 H, s, CHO) (Found: M^+, 330.1448. $C_{19}H_{22}O_5$ requires *M*, 330.1465).

3,3-*Ethylenedioxy*-1,2,3,4,4a,10aβ-*hexahydro*-6,7-*dimethoxy*-4aβ-(2-*nitrovinyl*)*phenanthrene* (**10**).—A mixture of aldehyde (**8**) (420 mg, 1.27 mmol), KF (74 mg, 1.27 mmol), and a catalytic amount of 18-crown-6 in a mixture of $MeNO_2$ (6 ml) and Pr^iOH (3 ml) was stirred for 24 h at room temperature. The solvents were removed and the residue was extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4), and evaporated. The resulting oil was dissolved in Ac_2O (20 ml) and the solution was stirred for 12 h at 50—60 °C in the presence of a catalytic amount of DMAP. The solvent was removed and the residue was extracted with AcOEt. The extract was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to give the title nitro compound (**10**) (460 mg, 97%) as a yellow oil. This compound was pure enough to use in the next reaction without purification; $\nu_{max.}$($CHCl_3$) 1 640 cm^{-1}; δ (*inter alia*) 3.88 (6 H, s, 2 × OMe), 5.80 (1 H, dd, *J* 10 and 5 Hz, 10-H), 6.36 (1 H, d, *J* 10 Hz, 9-H), 6.62 (1 H, s, ArH), 6.69 (1 H, d, *J* 14 Hz, CH=C*H*NO_2), 6.80 (1 H, s, ArH), and 7.35 (1 H, d, *J* 14 Hz, C*H*=CHNO_2) (Found: M^+, 373.1508. $C_{20}H_{23}NO_6$ requires *M*, 373.1523).

3,3-*Ethylenedioxy*-1,2,3,4,4a,10aβ-*hexahydro*-6,7-*dimethoxy*-4aβ-(2-*nitroethyl*)*phenanthrene* (**11**).—To a stirred, ice-cooled solution of the nitroethene (**10**) (63 mg, 0.17 mmol) in EtOH (3 ml) was added a solution of $NaBH_4$ (19 mg, 0.5 mmol) in EtOH (1 ml). After being stirred for 30 min at 0 °C, the reaction mixture was treated with saturated aqueous NH_4Cl, and extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with benzene–AcOEt (9:1 v/v) gave the reduced product (**11**) (60 mg, 95%) as an oil; δ (*inter alia*) 3.86 and 3.90 (each 3 H, each s, 2 × OMe), 5.78 (1 H, dd, *J* 10 and 5 Hz, 10-H), 6.33 (1 H, d, *J* 10 Hz, 9-H), and 6.61 and 6.87 (each 1 H, each s, 2 × ArH) (Found: M^+, 375.1667. $C_{20}H_{25}NO_6$ requires *M*, 375.1680).

Methyl 2-(3,3-*Ethylenedioxy*-1,2,3,4,4a,10aβ-*hexahydro*-6,7-*dimethoxyphenanthren*-4aβ-*yl*)*ethylcarbamate* (**12**).—To a stirred, ice-cooled solution of nitro compound (**11**) (490 mg, 1.31 mmol) in THF (30 ml) was added $LiAlH_4$ (99 mg, 2.62 mmol) in small portions. After being stirred for 16 h at ambient temperature, the reaction mixture was treated with 15% aqueous NaOH and extracted with Et_2O. The extract was washed with water, dried (Na_2SO_4), and evaporated. The resulting oil was dissolved in THF (30 ml), and the ice-cooled solution was added Et_3N (397 mg, 3.93 mmol) and then $ClCO_2Me$ (248 mg, 2.62 mmol). After being stirred for 2 h at room temperature, the reaction mixture was extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with benzene–AcOEt (1:1 v/v) afforded the *title carbamate* (**12**) (300 mg, 57%) as an oil; $\nu_{max.}$($CHCl_3$) 3 440 and 1 710 cm^{-1}; δ (*inter alia*) 3.60 (3 H, s, CO_2Me), 3.85 and 3.90 (each 3 H, each s, 2 × OMe), 4.48 (1 H, br s, NH), 5.77 (1 H, dd, *J* 10 and 5 Hz, 10-H), 6.30 (1 H, d, *J* 10 Hz, 9-H), 6.57 and 6.94 (each 1 H, each s, 2 × ArH) (Found: M^+, 403.1990. $C_{22}H_{29}NO_6$ requires *M*, 403.1993).

3,3-*Ethylenedioxy*-1,2,3,4,4a,10aβ-*hexahydro*-6,7-*dimethoxy*-4aβ-[2-(N-*methylamino*)*ethyl*]*phenanthrene* (**13**).—To a stirred solution of the carbamate (**12**) (300 mg, 0.74 mmol) in THF (30 ml) was added $LiAlH_4$ (57 mg, 1.49 mmol) and the resulting mixture was stirred for 3 h at 40 °C. The reaction mixture was treated with 15% aqueous NaOH solution and extracted with Et_2O. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was purified by preparative t.l.c. (p.l.c.) with $CHCl_3$–MeOH (5:1 v/v) as solvent to afford the title amine (**13**) (168 mg, 63%) as an oil; $\nu_{max.}$($CHCl_3$) 3 400 cm^{-1}; δ (*inter alia*) 2.20 (3 H, s, NMe), 3.83 and 3.89 (each 3 H, each s, 2 × OMe), 5.73 (1 H, dd, *J* 10 and 5 Hz, 10-H), 6.30 (1 H, d, *J* 10 Hz, 9-H), and 6.53 and 6.86 (each 1 H, each s, 2 × ArH); *m/z* 300 (M^+ − MeNHEt).

10-*Chloro*-2,3-*dimethoxy*-17-*methylmorphinan*-6-*one* (**16**).—To a stirred, ice-cooled solution of the amine (**13**) (120 mg, 0.33 mmol) in CH_2Cl_2 (10 ml) was added NCS (45 mg, 0.33 mmol). After being stirred for 30 min at 0 °C, the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated at low temperature to give the *N*-chloro compound (**14**) as an oil.

To a stirred solution of compound (**14**) in AcOH–water (1:1; 15 ml) at 0 °C was added dropwise an aqueous solution of $TiCl_3$ (5 mg, 0.33 mmol), and the resulting mixture was stirred for 1 h at the same temperature, and was then neutralized with 25% aqueous NaOH and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by p.l.c. with $CHCl_3$–MeOH (9:1 v/v) as solvent to afford a mixture of chloromorphinans (**15**) and (**16**), which was dissolved in acetone (10 ml) and the solution was stirred for 16 h at ambient temperature in the presence of 60% aqueous $HClO_4$ (3 drops). The reaction mixture was neutralized by addition of saturated aqueous $NaHCO_3$, and the organic solvent was removed. The residue was extracted with $CHCl_3$, and the extract was washed with water, dried (Na_2SO_4), and evaporated. The resulting material was purified [p.l.c.; $CHCl_3$–MeOH (9:1 v/v) as solvent] to give the *title morphinanone* (**16**) (40 mg, 34%) as an oil; $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1}; δ (*inter alia*) 2.53 (3 H, s, NMe), 3.82 (6 H, s, 2 × OMe), and 6.74 and 6.86 (each 1 H, each s, 2 × ArH) (Found: M^+, 349.1451. $C_{19}H_{24}ClNO_3$ requires *M*, 349.1445).

6,6-*Ethylenedioxy*-2,3,10α-*trimethoxy*-17-*methylmorphinan* (**17**).—To a stirred, ice-cooled solution of the amine (**13**) (100 mg, 0.28 mmol) in CH_2Cl_2 (10 ml) was added NCS (37 mg, 0.28 mmol). After being stirred for 30 min at 0 °C, the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated at low temperature. The resulting oil was dissolved in MeOH (20 ml) and the solution was stirred in the presence of Ag_2O (59 mg, 0.28 mmol) at 40—50 °C for 16 h. The insoluble materials were filtered off and the filtrate was concentrated to give a residue, which was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and

evaporated. The residue was purified with column chromatography on silica gel with $CHCl_3$–MeOH (20 : 1 v/v) as eluant to give the *title compound* (**17**) (55 mg, 51%) as an oil; δ (*inter alia*) 2.87 (3 H, s, NMe), 3.54 (3 H, s, OMe), 3.79 and 3.83 (each 3 H, each s, 2 × OMe), 4.30 (1 H, s, 10-H), and 6.70 and 6.76 (each 1 H, each s, 2 × ArH) (Found: M^+, 389.2022. $C_{23}H_{31}NO_5$ requires *M*, 389.2022).

6,6-*Ethylenedioxy*-2,3-*dimethoxy*-17-*methylmorphinan* (**18**).—To a stirred solution of compound (**17**) (60 mg, 0.15 mmol) in liq. NH_3 (30 ml) was added sodium metal (28 mg, 1.22 mmol) and the mixture was stirred for a further 5 min at −78 °C, treated with EtOH (1 ml), and then NH_3 was removed by warming. The residue was extracted with CH_2Cl_2, and the extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$–MeOH (9:1 v/v) gave the *title compound* (**18**) (32 mg, 58%) as an oil; δ (*inter alia*) 2.37 (3 H, s, NMe), 3.80 (6 H, s, 2 × OMe), and 6.52 and 6.73 (each 1 H, each s, 2 × ArH) (Found: M^+, 359.2096. $C_{21}H_{29}NO_4$ requires *M*, 359.2096).

2,3-*Dimethoxy*-17-*methylmorphinan*-6-*one* (**19**).—A solution of the protected ketone (**18**) (9 mg, 0.025 mmol) in acetone (10 ml) was stirred for 6 h at ambient temperature in the presence of 60% aqueous $HClO_4$ (3 drops). After removal of the solvent, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by p.l.c. with $CHCl_3$–MeOH (9:1 v/v) as solvent to afford the morphinanone (**19**) (7 mg, 89%) as a yellowish powder, which was identical with an authentic sample in all respects.

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References

1 A part of this work was published as a preliminary communication: T. Kametani, Y. Suzuki, and T. Honda, *Heterocycles*, 1985, **23**, 563; T. Kametani, *Pure Appl. Chem.*, 1979, **51**, 747; T. Kametani and K. Fukumoto, *Mass Spectrosc. Tokyo*, 1981, **29**, 39.
2 For a recent review of intramolecular cycloaddition reaction of *o*-quinodimethane, see W. Oppolzer, *Synthesis*, 1978, 793; *Heterocycles*, 1980, **14**, 1615; T. Kametani and K. Fukumoto, *Kagaku no Ryoiki, Zokan*, 1980, 81; R. L. Funk and K. P. C. Vollhardt, *Chem. Soc. Rev.*, 1980, **9**, 41; T. Kametani and H. Nemoto, *Tetrahedron*, 1981, **37**, 3.
3 H. Holmes and G. Stork, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1952, vol. II, p. 1; G. Stork, *ibid.*, 1960, vol. VI, p. 219; K. W. Bentley, *ibid.*, 1971, vol. XIII, p. 1, and references cited therein; A. B. Shenvi and E. Ciganek, *J. Org. Chem.*, 1984, **49**, 2942; D. A. Evans and C. H. Mitch, *Tetrahedron Lett.*, 1982, **23**, 285; D. A. Evans, C. H. Mitch, R. C. Thomas, D. M. Zimmerman, and R. W. Robey, *J. Am. Chem. Soc.*, 1980, **102**, 5955; W. H. Moos, R. D. Gless, and H. Rapoport, *J. Org. Chem.*, 1983, **48**, 227.
4 T. Kametani, M. Tsubuki, Y. Shiratori, Y. Kato, H. Nemoto, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1977, **42**, 2672.
5 T. Kametani, T. Takahashi, K. Ogasawara, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 1047.
6 T. F. Corbin, R. C. Hahn, and H. Shechter, *Org. Synth.*, 1964, **44**, 30.
7 G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, 1970, **26**, 91.
8 J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Org. Chem.*, 1970, **35**, 186.
9 R. H. Wollenberg and S. J. Miller, *Tetrahedron Lett.*, 1978, 3219.
10 L. Stella, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 337 and references are cited therein.
11 C. Olieman, L. Maat, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, 1980, **99**, 169.
12 C. Fengeas, *Bull. Soc. Chim. Fr.*, 1963, 2579.

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