155. Total Synthesis of (±)-3-Deoxy-7,8-dihydromorphine, (±)-4-Methoxy-*N*-methylmorphinan-6-one and 2,4-Dioxygenated (±)-Congeners[1])

by **Fu-Lian Hsu, Kenner C. Rice** and **Arnold Brossi**[2])

Medicinal Chemistry Section, Laboratory of Chemistry, National Institute of Arthritis, Diabetes, and Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

(26. IV. 82)

Summary

A total synthesis of racemic 3-deoxy-7,8-dihydromorphine ((±)-**2**) and 4-methoxy-*N*-methylmorphinan-6-one ((±)-**3**) is described. The key intermediate was 2,4-dihydroxy-*N*-formylmorphinan-6-one (**11**), obtained from 3,5-dibenzyloxyphenylacetic acid (**4**) in 41.8% overall yield. Bromination of **11**, and treatment with aqueous NaOH-solution afforded, after *N*-deblocking and reductive *N*-methylation with concomitant removal of the aromatic bounded Br-atom, the morphinanone **14**. Elimination of the HO–C(2) group in **14** was accomplished by hydrogenolysis of its *N*-phenyltetrazolyl ether **15**, to give 3-deoxy-6,*O*-didehydro-7,8-dihydromorphine (**16**). Reduction of **16** with *L-Selectride* at low temperature provided (±)-**2** in high yield. The ether **15** directly afforded, under more vigorous reduction conditions, 4-hydroxy-*N*-methylmorphinan-6-one (**17**) and after *O*-methylation of **17**, the methyl ether (±)-**3** was obtained. A (1:1)-mixture of 4-hydroxy-2-methoxy-*N*-methylmorphinan-6-one (**28**) and its 2-hydroxy-4-methoxy isomer **30** were obtained by *Grewe*-cyclization of a mono-methoxylated aromatic precursor similar to that which afforded **11**. The 2,4-dioxygenated *N*-methylmorphinan-6-ones **29**, **31** and **38** were also prepared and characterized.

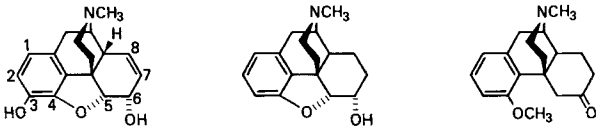
An efficient synthesis of 2,3-dioxygenated morphinan-6-ones by *Grewe et al.* [1] utilized as the key reaction steps a *Birch* reduction of an appropriately substituted 1-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline and the subsequent cyclization of the hexahydrobase to the morphinan with mineral acids. This approach was later followed by *Beyerman et al.* in their clever synthesis of (–)-dihydrothebainone [2] [3], and by *Rice* in his route to compounds of the natural and unnatural series of morphine alkaloids [4] [5]. The same scheme was also utilized by us in our total synthesis

[1]) The morphinanones reported in this paper are racemic entities. Only (±)-**2** and (±)-**3** obtained by total synthesis shall be recorded with a prefix, in order to differentiate them from their (–)-enantiomers **2** and **3** prepared from natural morphine (**1**).

[2]) To whom correspondence should be addressed.

0018-019X/82/5/1576-14$01.00/0

of racemic 3-deoxy-7,8-dihydromorphine (±)-2[1]), reported in a preliminary communication [6], and obtained from natural morphine (**1**) as its (–)-enantiomer **2**[1]) [7]. Our synthesis also provided an entry into the little explored class of 4-oxygenated morphinan-6-ones represented by **17** [6] [8] [9] (s. below) and its methyl ether (±)-**3**. The (–)-enantiomer **3** prepared earlier from morphine derived intermediates showed unusually high antinociception [9] [10].



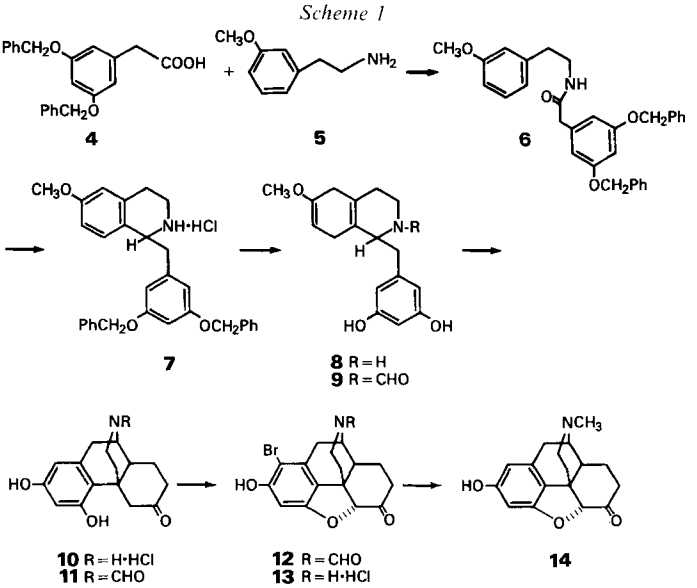
1 **2** **3**

Fig. 1

We now would like to report the experimental details of our total synthesis as illustrated in *Schemes 1* and *2*, supplemented with the chemistry illustrated in *Schemes 3* and *4*, completed after the initial objective had been achieved. The three novel morphinanones **29**, **31** and **38** (s. below) of the 2,4-dioxygenated series also prepared are shown.

The key intermediate **7** was obtained by the reaction of 3,5-dibenzyloxyphenylacetic acid (**4**) [6] (also prepared recently by another group in a lengthy sequence from different starting materials [11]) with 3-methoxyphenethylamine (**5**) and by cyclization of the intermediate amide **6** *(Scheme 1)*. The *Birch* reduction of the tetrahydroderivative **7** to hexahydroderivative **8** and the acid catalyzed cyclization of **8**, or its *N*-formyl derivative **9**, to the morphinanones **10** and **11**, respectively, followed classical procedures. The overall yield of **10** and **11** from 3,5-dihydroxyphenylacetic acid was 40 and 41.8%, respectively, demonstrating the efficiency of this synthesis.

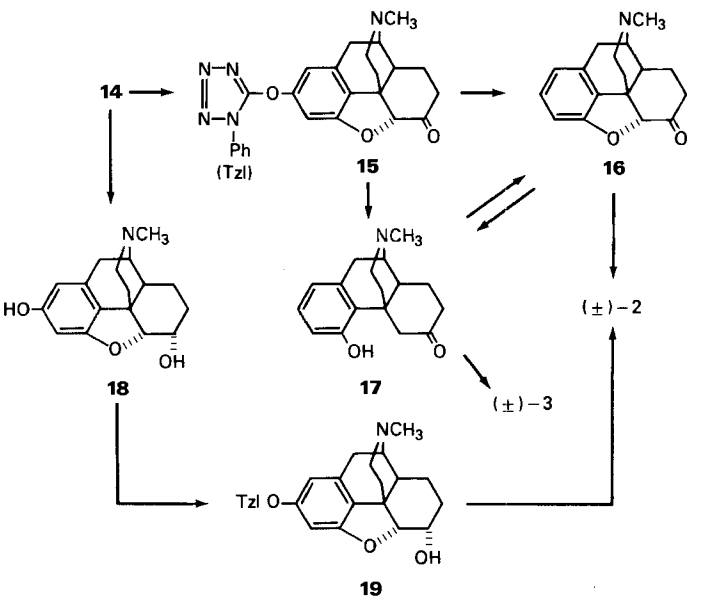
Scheme 1



The formation of the 2-(*N*-phenyltetrazolyl) ether from **11**, required for the reductive 2-deoxygenation, proved unusually difficult and afforded a mixture of *O*- and 5-(*N*-phenyltetrazolyl)-substituted products which were separated and characterized [12]. This difficulty could be circumvented by first closing the oxygen-ether bridge in **11** with the well established bromination-dehydrobromination sequence [13]. Although difficultly soluble, the *N*-formyl compound **11** was successfully brominated in dilute acetic acid at room temperature, directly affording, after treatment with aqueous 10% NaOH-solution, the 1-bromo ketone **12** in 39% yield. This material was found by mass spectral and combustion analysis to be contaminated with 2–5% of its 3,5-dibromo analog. The analytical characterization of all *N*-formylated species obtained during this investigation was complicated by the presence of two rotamers, previously observed in other *N*-formylated isoquinoline systems [14], but this problem disappeared after acid hydrolysis of **12**, affording chemically pure **13**, isolated as its hydrochloride. Concomitant reductive *N*-methylation and hydrogenolysis of the Br-atom [4] of **13**·HCl over Pd/C catalyst was easily accomplished by hydrogenation in 2N CH_3COOH in the presence of CH_3COONa and 37% HCHO-solution, and directly afforded the high melting 4,5-epoxy-morphinanone **14**.

The elimination of the HO–C(2) group in **14** was achieved by catalytic reduction of its *N*-phenyltetrazolyl ether derivative **15**, affording 3-deoxy-6,*O*-didehydro-7,8-dihydromorphine (**16**; *Scheme 2*). The reduction of **16** with *L-Selectride* (lithium tri(*s*-butyl)borohydride) in THF at –70° gave 3-deoxy-7,8-dihydromorphine ((±)-**2**), identical by TLC., ^{1}H-NMR., and mass spectral behaviour with **2** prepared from natural morphine (**1**) [7]. The catalytic reduction of **15** under more vigorous conditions,

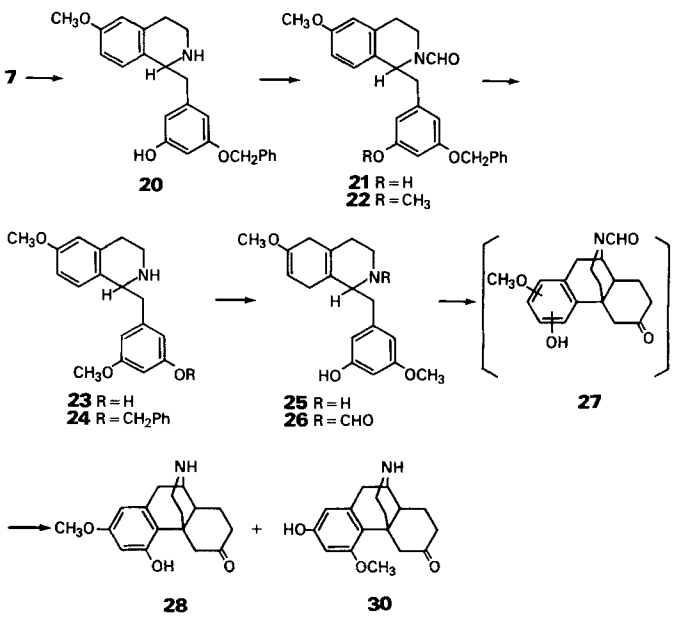
Scheme 2



similar to those applied in the conversion of thebaine to dihydrothebainone [15], afforded the 4-hydroxymorphinan-6-one **17**. *O*-Methylation of **17** gave the methyl ether (±)-**3**, chromatographically and spectrally identical with a sample of the (–)-enantiomer **3** prepared from natural morphine (**1**) [10]. Another route to (±)-**2**, also illustrated in *Scheme 2*, was accomplished by first reducing the ketone **14** with *L-Selectride* at low temperature to the alcohol **18**, formation of its *N*-phenyltetrazolyl ether **19** and catalytic removal of the heterocyclic ether function present in **19**.

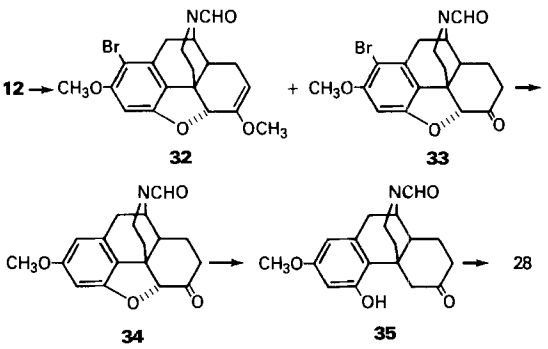
A third route to directly obtain representatives of the 4-methoxy-substituted morphinanones was based on the possibility that the dimethoxy-derivative **26** might cyclize preferentially to a 2-hydroxy-4-methoxy substituted morphinanone. Although it is well established that the formation of the berbine bridge from hydroxy-methoxy-substituted 1-benzyl-tetrahydroisoquinoline with acid afforded mixture of hydroxy-methoxy substituted isomers [16], the course of the acid cyclization of **26** seemed worthy of exploration. The required hexahydro compound **25** was prepared from the tetrahydroisoquinoline **7** by the following classical sequence of reactions *(Scheme 3)*: Partial *O*-debenzylation of **7** with hydrochloric acid (monitored by TLC.) afforded **20**, *N*-formylation of **20** to **21** and *O*-methylation of **21** gave the *N*-formyl-tetrahydroisoquinoline **22**. The acid hydrolysis of **22** yielded a mixture of products from which the *N,O*-deprotected phenol **23** could only be isolated in 50% yield. However, hydrolysis of **22** with 10% NaOH-solution in refluxing methanol, readily afforded the benzyl ether **24** in 97% yield, and provided, after the *Birch* reduction, the crystalline hexahydro compound **25**. The HCl-catalyzed cyclization of the *N*-formyl derivative **26**, prepared from **25** *in situ*, resulted in a (1:1)-mixture of *N*-formylated morphinanones **27**, present as rotamers and thus difficult to analyze.

Scheme 3

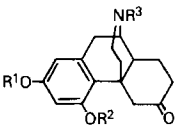


Hydrolysis of the mixture of isomers **27** with methanolic HCl-solution afforded a (1:1)-mixture (by TLC.) of morphinanones **28** and **30**. The slower moving compound crystallized from methanol after standing, and the faster moving isomer was isolated after chromatography as its hydrochloride. The structure assignment of the faster moving compound as 4-hydroxy-2-methoxy-morphinan-6-one (**28**) was made on the basis of the chemical conversion illustrated in *Scheme 4*. *O*-Methylation of the bromo ketone **12** of established aromatic substitution with NaH and dimethyl sulfate in DMF afforded a mixture of the enol ether **32** and its corresponding ketone **33** which were separated by chromatography. Catalytic debromination of **33** yielded **34**, and reductive opening of the ether bridge in **34**, readily accomplished with Zn in boiling ethanol in the presence of ammonium chloride [17], afforded the *N*-formyl-morphinanone **35**. Acid hydrolysis of **35** gave ketone **28**, identical in every respect with the faster moving isomer obtained earlier. It is thus established that the *Grewe* cyclization of 3-hydroxy-5-methoxy-benzyl-substituted tetrahydroisoquinoline did not proceed regioselectively and afforded instead a (1:1)-mixture of the corresponding isomers.

Scheme 4



It is interesting to note that the conversion of **30** into its hydrochloride salt with methanolic HCl-solution resulted in facile formation of its dimethyl ketal hydrochloride, evidenced by the absence of the carbonyl group in its IR. spectrum and the presence of three methoxy groups in its ^{1}H-NMR. spectrum. The unusual biological properties of 4-methoxy-morphinan-6-ones could well be associated with this particular behaviour manifested by the carbonyl group at C(6).



29 $R^1 = R^3 = CH_3$, $R^2 = H$
31 $R^1 = H$, $R^2 = R^3 = CH_3$
36 $R^1 = R^2 = CH_3$, $R^3 = CHO$
37 $R^1 = R^2 = CH_3$, $R^3 = H$
38 $R^1 = R^2 = R^3 = CH_3$

The conversion of morphinanones **28** and **30** into their respective *N*-methyl analogs **29** and **31** was accomplished by reductive *N*-methylation. Moreover, *N*-formyl-dihydroxy-morphinanone **11** was converted into **38** by *O*-methylation (→ **36**), acid hydrolysis (→ **37**), followed by reductive *N*-methylation. Compounds **29**, **31** and **38** were required for biological evaluation.

Experimental Part[3])

General remaks. Physical constants and spectra were determined using the instrumentation indicated. Melting points (m.p.): *Thomas-Hoover* or *Fisher-Johns* apparatus (corrected). IR. Spectra (~[cm^{-1}]): *Beckman IR 4230* spectrophotometer. ^{1}H-NMR. Spectra ([ppm] relative to internal TMS (=O ppm); *s*=singlet, *d*=doublet, *d*×*d*=doublet of doublets, *qa*=quadruplet, *m*=multiplet, *J* [Hz]=apparent coupling constant): *Varian HR 220* or *JOEL LMN-FX 100* spectrometer. Mass spectra (MS.) *[m/z]: Finnigan 1015D* spectrometer with a model 6000 data collection system for chemical ionization (CI.) MS., or *Hitachi Perkin-Elmer RMU-6E* spectrometer (70 eV) for electron ionization (EI.) MS. Thin layer chromatography (TLC.): silica gel GF, *Analtech, Inc.* Column chromatography: alumina *Woelm N*, Act. III, *Woelm Pharma.* or *silica gel 60*, 230–400 mesh ASTM, *EM* reagent.

Synthesis of 3,5-dibenzyloxyphenylacetic acid (**4**). A mixture of 3,5-dihydroxyphenylacetic acid [18] (1 g, 5.9 mmol), benzyl chloride (2.3 g, 18 mmol) and anhy. K_2CO_3 (3.5 g, 25 mmol) in 35 ml of DMF was heated at 70±5° overnight under Ar. The mixture was filtered and the inorganic residue washed with DMF. The filtrate was evaporated under vacuum, and the crude benzylated product was taken into 25 ml of 10% NaOH-solution and refluxed for 2 h. The mixture was cooled to r.t., washed with ether and acidified with 37% HCl-solution. This acidic solution was then extracted with ether, and the combined ether layer was washed with satd. NaCl-solution and dried ($MgSO_4$). Evaporation of the solvent gave a white solid which was recrystallized from benzene/petroleum ether of yield **4** (1.6 g, 77%), m.p. 120–121°. – IR. (KBr): 2400–3200, 1700, 1610, 1460, 1410, 1380, 1330, 1290, 1260, 1230, 1160, 1145, 1055. – ^{1}H-NMR. ($CDCl_3$): 10.05 (br. *s*, 1 H, COOH); 7.25 (*s*, 10 arom. H); 6.47 (*s*, 3 arom. H); 4.93 (*s*, 4 H, 2 PhCH_2O); 3.52 (*s*, 2 H, CH_2COOH). – MS. (EI.): 348 (M^+).

$C_{22}H_{20}4$ (348.40) Calc. C 75.84 H 5.79% Found C 75.57 H 5.83%

Synthesis of N-*(3-methoxyphenethyl)-(3',5'-dibenzyloxyphenyl)acetamide* (**6**). A mixture of **4** (37.0 g, 0.11 mmol) and 3-methoxyphenethylamine (16.0 g, 0.11 mmol) was heated at 185° for 2 h. The crude product was recrystallized from $CHCl_3$/ether to afford white, crystalline **6** (46 g, 89%), m.p. 101–102°. – IR. (KBr): 3260, 1645, 1590, 1550, 1450, 1370, 1340, 1290, 1260, 1150, 1050, 1030. – ^{1}H-NMR. ($CDCl_3$): 7.29 (*s*, 10 H, arom. H); 6.33–7.13 (*m*, 7 arom. H); 5.38 (br. *s*, 1 H, HN); 4.95 (*s*, 4 H, 2 PhCH_2O); 3.68 (*s*, 3 H, CH_3O); 3.42 (*s*, 2 H, Ar'CH_2CON); 3.35 (*t*, *J*=7, 2 H, ArCH_2CH$_2$); 2.63 (*t*, *J*=7, 2 H ArCH$_2$CH_2). – MS. (EI.): 481 (M^+).

$C_{31}H_{31}NO_4$ (481.60) Calc. C 77.31 H 6.49 N 2.91% Found C 77.26 H 6.53 N 2.69%

Synthesis of 1-(3',5'-dibenzyloxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**7**). A solution of **6** (5.0 g, 10.4 mmol) and $POCl_3$ (1.9 g, 12.5 mmol) in 60 ml of CH_3CN was refluxed for 1.5 h under N_2. The low boiling materials were evaporated, and the resulting yellow gum was taken dissolved in a mixture of *i*-PrOH (50 ml) and H_2O (10 ml). The solution was adjusted to pH ~*ca.* 8 with conc. NH_3-solution and THF (60 ml) was added. To this well stirred ice-cold mixture was added $NaBH_4$ (1.0 g, 26.4 mmol) in small portions. After the addition was complete, the mixture was stirred for 1 h. The solvents were evaporated, and the residue was diluted with H_2O and extracted with benzene. The organic layer was washed with sat. NaCl-solution, dried (Na_2SO_4) and evaporated to a gum. This crude free base was treated with methanolic HCl-solution, and after standing for few minutes, crystalline salt separated. Ether was added and the crystals collected and washed with ether. The salt was recrystallized from MeOH/ether to yield **7** (4.6 g, 88%), m.p. 195–196.5°. – IR. (KBr): 1600, 1500, 1450, 1380, 1340, 1300, 1150, 1050. – ^{1}H-NMR. ($CDCl_3$): 9.86, 10.23 (2 br. *s*, 2 H, H_2N^+); 7.23–7.43 (*m*, 10 H, arom. H); 6.45–6.77 (*m*, 6 H, arom. H); 4.94 (*s*, 4 H, 2 PhCH_2O); 3.74 (*s*, 3 H, CH_3O); 2.84–3.52 (*m*, 7 H, H–C(1), 2 H–C(3), 2 H–C(4) and Ar CH_2–C(1)). – MS. (EI.): 162 (M^+ – 304).

$C_{31}H_{31}NO_3 \cdot HCl \cdot H_2O$ (520.07) Calc. C 71.59 H 6.59 N 2.69%
Found „ 71.22 „ 6.18 „ 2.64%

Synthesis of 1-(3',5'-dihydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (**8**). Compound **7** (16.4 g, 32.7 mmol) was converted into its gummy free base for *Birch* reduction. About 500 ml of liq. NH_3 was collected directly from the cylinder in a 1-l-three-necked flask and was then distilled from Na into a 2-l-three-necked flask equipped with a thermometer, dropping funnel and *Dewar* condenser under

---

[3]) Although all materials were dried under high vacuum at 80 or 100° it was often difficult to obtain solvent-free analytical samples.

Ar. After *ca.* 400 ml of liq. NH_3 was collected, Li-wire (5.0 g, 0.72 g-atom) cut into pieces about 2.5 cm long was added so that the temp. did not exceed –60°. To this stirred, blue solution was added dropwise redistilled *t*-BuOH/THF 1:1 (320 ml), followed by addition of the free base of **7** in THF/*t*-BuOH 1:1 (60 ml) so that the temp. was maintained at $-60 \pm 5°$. The reaction was complete within 15 min, and NH_3 was carefully evaporated. Solvents were then evaporated under vacuum at r.t. to give a white cake which was quenched with a solution of 60 g of NH_4Cl in 200 ml of H_2O. The mixture was stirred in an ice-bath, and a light brown top layer formed, which was separated and treated with a small amount of H_2O and evaporated to afford crystalline material. This white solid was collected and washed with H_2O to afford **8** (8.6 g, 92%). Recrystallization from EtOH/H_2O gave an analytical sample, m.p. 199–200° (dec.). – IR. (KBr): 3400, 3280, 1700, 1670, 1600, 1340, 1220, 1150, 1000. – ^{1}H-NMR. (D_6-DMSO): 9.00 (br. *s*, 2 H, 2 HO); 6.04 (*s*, 3 H, arom. H); 4.64 (*s*, 1 H, H–C(7)); 3.44 (*s*, 3 H, CH_3O). – MS. (EI.): 164 (M^+ – 123). – MS. (Cl./NH_3): 288 (MH^+).

$C_{17}H_{21}NO_3 \cdot \frac{1}{4}H_2O$ (291.86) C 70.05 H 7.44 N 4.81% Found C 70.33 H 7.55 N 4.61%

Synthesis of 1-(3',5'-dihydroxybenzyl)-2-formyl-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (**9**). A solution of **8** (12.0 g, 41.7 mmol) in 210 ml of DMF was treated with 510 ml of HCOOEt and refluxed for 30 h. The solvents were evaporated to small volume, and $CHCl_3$ was added. The crystals which formed were collected and washed with $CHCl_3$ to afford **9** (10.8 g, 82%). Recrystallization from DMF/$CHCl_3$ gave an analytical sample, m.p. 213–215°. – IR. (KBr): 3300, 1700, 1650, 1450, 1400, 1220, 1150, 1100, 1000, 840. – ^{1}H-NMR. (D_6-DMSO): 8.97, 9.05 (2 *s*, 2 H, 2 HO); 7.43, 7.90 (2 *s*, 1 H, CHO); 6.00 (*m*, 3 arom. H); 4.70 (*m*, 1 H, H–C(7)); 3.48 (*s*, 3 H, CH_3O). – MS. (Cl./NH_3): 316 (MH^+).

$C_{18}H_{21}NO_4$ (315.37) Calc. C 68.55 H 6.71 N 4.44% Found C 68.80 H 6.62 N 4.39%

Synthesis of 2,4-dihydroxymorphinan-6-one hydrochloride (**10**). A suspension of **8** (1.5 g, 5.2 mmol) in 70 ml of ether was treated with 35 ml of 37% HCl-solution dropwise at ice-bath temp. After the addition was completed, the mixture was refluxed for 7 h, then allowed to stand at r.t. overnight. The solvents were evaporated to a small volume, and the residue was treated with EtOH. The crystals which formed were collected and recrystallized from H_2O/EtOH to afford **10** (1.4 g, 87%), m.p. 287–289° (dec.). – IR. (KBr): 2500–3600, 1700, 1600, 1460, 1425, 1260, 1175, 1145, 1085, 1040, 1010, 850. – ^{1}H-NMR. (D_6-DMSO): 9.36 (br. *s*, 2 H, H_2N^+); 9.23, 9.51 (2 *s*, 2 H, 2 HO); 6.14 (*d*, $J = 2$, 1 arom. H); 6.03 (*d*, $J = 2$, 1 H, arom. H); 4.01 (*d*, $J = 13$, 1 H, H–C(5)). – MS. (Cl./NH_3): 274 (MH^+–HCl).

$C_{16}H_{19}NO_3 \cdot HCl \cdot \frac{1}{3}H_2O$	Calc.	C 60.85	H 6.60	N 4.43%
(315.79)	Found	„ 60.95	„ 6.67	„ 4.37%

Synthesis of 2,4-dihydroxy-N-formylmorphinan-6-one (**11**). The treatment of **9** (1.2 g, 3.8 mmol) in ether with 37% HCl-solution was carried out as described above for the synthesis of **10**. The solid which formed in the aq. layer was filtered, washed with H_2O and recrystallized from DMF/H_2O to yield **11** (1.0 g, 91%), m.p. 316–319° (dec.). – IR. (KBr): 3300, 1705, 1660, 1610, 1510, 1450, 1400, 1340, 1170, 1150, 1040, 1015. – ^{1}H-NMR. (D_6-DMSO): 9.05, 9.33 (2 *s*, 2 H, 2 HO); 7.98, 8.11 (2 *s*, 1 H, CHO); 6.07 (*d*, $J = 2$, 1 H, arom. H); 5.97 (*d*, $J = 2$, 1 H, arom. H); 3.97 (*d*, $J = 13$, 1 H, H–C(5)). – MS. (EI.): 301 (M^+).

$C_{17}H_{19}NO_4$ (301.35) Calc. C 67.76 H 6.35 N 4.65% Found C 67.60 H 6.29 N 5.11%

Synthesis of 1-bromo-4,5-epoxy-N-formyl-2-hydroxymorphinan-6-one (**12**). A mixture of **11** (5.0 g, 16.6 mmol) and 1.6 l of AcOH was heated to solution and cooled rapidly to 20–25°. To this stirred solution was added a solution of Br_2 in AcOH (1M, 41.5 ml; 41.5 mmol) dropwise. The solution was stirred overnight and evaporated under vacuum to afford a gum. The gum was treated with cold 10% NaOH-solution until basic and stirred for 10 min. This solution was acidified with 37% HCl-solution and the resulting precipitate was filtered off and washed with H_2O until the filtrates were neutral. The pale yellow solid was then stirred with CH_3OH, and the undissolved solid was collected by filtration and washed with CH_3OH to yield **12** containing 2–5% of 1,3-dibrominated material (2.5 g, 39%), m.p. > 240° (dec.). This by-product can be removed at the next step during purification. – IR. (KBr): 3420, 1725, 1640, 1610, 1450, 1400, 1345, 1150, 1085, 1035, 960. – ^{1}H-NMR. (D_6-DMSO): 10.2 (*s*, 1 H, HO); 7.98, 8.05 (2 *s*, 1 H, CHO); 6.42 (*s*, 1 H, arom. H); 4.92 (*s*, 1 H, H–C(5)). – MS. (EI.): 377 (M^+), 379 ($M^+ + 2$).

$C_{17}H_{16}BrNO_4 + 2\%\ C_{17}H_{15}Br_2NO_4$	Calc.	C 53.76	H 4.25	N 3.70	Br 21.46%
(379.81)	Found	„ 53.56	„ 4.22	„ 3.74	„ 21.56%

Synthesis of 1-bromo-4,5-epoxy-2-hydroxymorphinan-6-one hydrochloride (**13**). A mixture of **12** (1.7 g, 4.5 mmol), 16.5 ml of 37% HCl-solution and 165 ml of CH_3OH was refluxed for 4 h and concentrated. Crystals gradually formed during the evaporation of solvents to a small volume. The crystals were collected, washed with cold MeOH and recrystallized from MeOH to yield **13** (1.5 g, 86%), m.p. >270° (dec.). – IR. (KBr): 3520, 3440, 1715, 1610, 1470, 1450, 1240, 1225, 1040, 1015, 955. – ^{1}H-NMR. (D_2O): 6.62 (*s*, 1 H, arom. H); 5.14 (*s*, 1 H, H–C(5)). – MS. (EI.): 349 (M^+–HCl), 351 (M^++2–HCl).

$C_{16}H_{16}BrNO_3 \cdot HCl$ (386.67)	Calc.	C 49.70	H 4.43	Cl 18.34	N 3.62%	(Br was calculated as Cl)
	Found	„ 49.52	„ 4.65	„ 18.13	„ 3.33%	

*Synthesis of 4,5-epoxy-2-hydroxy-*N*-methylmorphinan-6-one* (**14**). A mixture of **13** (2.5 g, 6.5 mmol), 37% HCHO-solution (2 ml, 24.7 mmol), AcONa (2.7 g, 33 mmol), and 10% Pd/C (500 mg) in 250 ml of 2N AcOH was hydrogenated at 45 psi overnight at r.t. The catalyst was filtered off and washed with 2N CH_3COOH. The filtrate was adjusted to pH ≈ 8 with conc. aq. NH_3-solution and extracted with $CHCl_3$/*i*-PrOH 3:2. The organic layer was washed with satd. NaCl-solution, dried (Na_2SO_4) and evaporated to give a solid which was recrystallized from CH_3OH to afford **14** (1.5 g, 83%), m.p. 265–268° (dec.). – IR. (KBr): 3440, 1720, 1610, 1480, 1350, 1300, 1130, 1100, 1030, 975. – ^{1}H-NMR. (D_6-DMSO): 9.16 (br. *s*, 1 H, HO); 6.07 (*m*, 2 H, arom. 4); 4.76 (*s*, 1 H, H–C(5)); 2.28 (*s*, 3 H, CH_3N). – MS. (EI.): 285 (M^+).

$C_{17}H_{19}NO_3 \cdot \frac{1}{2}H_2O$ (291.36) Calc. 70.08 H 6.80 N 4.81% Found C 69.73 H 6.95 N 4.89%

A small portion of the free base **14** was converted into hydrochloride salt, m.p. >250° (dec.) (from EtOH).

$C_{17}H_{19}NO_3 \cdot HCl$ (321.80)	Calc.	C 63.45	H 6.26	Cl 11.02	N 4.35%
	Found	„ 63.29	„ 6.16	„ 10.86	„ 4.67%

*Synthesis of 4,5-epoxy-*N*-methyl-2-(1-phenyltetrazol-5-yloxy)morphinan-6-one* (**15**). A mixture of **14** (285 mg, 1 mmol), 5-chloro-1-phenyltetrazole (217 mg, 1.2 mmol), and anh. K_2CO_3 (276 mg, 2.0 mmol) in 10 ml of DMF was heated at 75–80° for 16 h under N_2. The K_2CO_3 was filtered off and washed with DMF. The filtrate was evaporated under high vacuum to give a gum which was taken into $CHCl_3$, washed with 5% NaOH-solution and H_2O, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue which was chromatographed on an alumina column with $CHCl_3$ to give a pale yellow foam. The crude product was recrystallized from 95% ethyl alcohol to yield **15** (380 mg, 88%), m.p. 207–208°. – IR. (KBr): 1720, 1540, 1500, 1470, 1450, 1290, 1130, 1080, 1040, 980. – ^{1}H-NMR. ($CDCl_3$) 7.74–7.79 (*m*, 2 H, arom. H); 7.51–7.60 (*m*, 3 H, arom. H); 6.75, 6.84 (2 *s*, 2 H, arom. H); 4.70 (*s*, 1 H, H–C(5)); 2.41 (*s*, 3 H, CH_3N). – MS. (CI./NH_3): 430 (MH^+).

$C_{24}H_{23}N_5O_3$ (429.46) Calc. C 67.12 H 5.40 N 16.31% Found C 66.76 H 5.60 N 16.17%

*Synthesis of (±)-3-deoxy-6,*O*-didehydro-7,8-dihydromorphine* (= *4,5-epoxy-*N*-methylmorphinan-6-one;* **16**). A mixture of **15** (210 mg, 0.49 mmol), 10% Pd/C (210 mg) and AcOH (50 ml) was hydrogenated at 45 psi at 40° for 36 h. The catalyst was filtered off and washed with HOAc. The filtrate was evaporated, the residue dissolved in $CHCl_3$, washed with 5% NaOH-solution and H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave a solid which was chromatographed on a short alumina column with $CHCl_3$ to give white crystalline material after evaporation of the solvent. Recrystallization from benzene/petroleum ether afforded **16** (91 mg, 69%), m.p. 213–215°. – IR. ($CHCl_3$): 1725, 1630, 1605, 1450, 960. – ^{1}H-NMR. ($CDCl_3$): 7.06 (*d* × *d*, *J*=6 and 6, 1 H, arom. H); 6.76 (*d*, *J*=6, 1 arom. H); 6.69 (*d*, *J*=6, 1 H, arom. H); 4.63 (*s*, 1 H, H–C(5)); 2.43 (*s*, 3 H, CH_3N). – MS. (EI.): 269 (M^+).

$C_{17}H_{19}NO_2$ (269.35) Calc. C 75.81 H 7.11 N 5.20% Found C 75.80 H 7.26 N 5.38%

*Synthesis of 4,5-epoxy-*N*-methylmorphinan-2,6α-diol* (**18**). To a well stirred suspension of **14** (200 mg, 0.7 mmol) in 15 ml of THF at –70° was added a solution of *L-Selectride* (1M in THF, 2.0 ml, 2.0 mmol) dropwise under Ar. The mixture became homogeneous, was stirred for 2 h at –70°, warmed to r.t. and rendered acidic with 10% HCl-solution. Ether was added and the organic layer separated. The acidic solution was washed with ether, adjusted with conc. NH_3-solution to pH ≈ 8 and extracted with $CHCl_3$. The $CHCl_3$-solution was washed with H_2O, dried (Na_2SO_4) and evaporated to give a solid which was recrystallized from MeOH/*i*-Pr_2O to afford **18** (150 mg, 75%), m.p. 245–247° (dec.). – IR. (KBr): 3230, 1600, 1250, 1135, 1080, 1040, 980. – ^{1}H-NMR. (D_6-DMSO): 8.94 (*s*, 1 H, HO); 5.94 (*m*, 2 H, arom. H); 4.38 (*d*, *J*=4, 1 H, H–C(5)); 2.23 (*s*, 3 H, CH_3N). – MS. (CI./NH_3): 288 (MH^+).

$C_{17}H_{21}NO_3 \cdot \frac{1}{4}H_2O$ (291.86) Calc. C 69.95 H 7.43 N 4.80% Found C 70.02 H 7.44 N 4.90%

Synthesis of 4,5-epoxy-N-methyl-2-(1-phenyltetrazol-5-yloxy)morphinan-6α-ol (**19**). A mixture of **18** (50 mg, 0.17 mmol), 5-chloro-1-phenyltetrazole (38 mg, 0.2 mmol), anh. K_2CO_3 (51 mg, 0.36 mmol) and DMF (5 ml) was treated as described above for the synthesis of **15**. The crude product was recrystallized from CH_3OH to afford **19** (47 mg, 63%), m.p. 101–103°. – IR. (KBr): 3420, 1540, 1475, 1130, 1080, 1040. – ^{1}H-NMR. ($CDCl_3$): 7.68–7.75 (*m*, 2 H, arom. H); 7.44–7.50 (*m*, 3 H, arom. H); 6.70 (*d*, *J*=3, 1 H, arom. H); 6.62 (*d*, *J*=3, 1 H, arom. H); 4.58 (*d*, *J*=5, 1 H, H–C(5)); 3.98 (*qa*, *J*=5, 1 H, H–C(6)); 2.34 (*s*, 3 H, CH_3N). – MS. (CI./NH_3): 431 (MH^+).

$C_{24}H_{25}N_5O_3 \cdot H_2O$ (449.52) Calc. C 64.12 H 6.05 N 15.58% Found C 64.33 H 5.67 N 15.57%

Synthesis of (±)-3-deoxy-7,8-dihydromorphine hydrochloride ((±)-2 · HCl). – a) *From* **16**. To a solution of L-Selectride (1M in THF, 0.5 ml, 0.5 ml) at –70° was added a solution of **16** (45 mg, 0.17 mmol) in 4 ml of THF dropwise under Ar. The solution was stirred 1 h at –70°, then warmed to r.t. and quenched with H_2O. Ether and 10% HCl-solution (3 ml) were added to the mixture, and the organic layer was discarded. The acidic aq. solution was washed with ether, then basified with 10% NaOH-solution and extracted with $CHCl_3$. The combined $CHCl_3$-solution was washed with H_2O, dried (Na_2SO_4), and evaporated to afford (±)-**2** as a gum (48 mg, 100%). HPLC. (*Waters Associates C-18 μ-Bondapak*, CH_3OH/1% CH_3COOH-solution in H_2O 1:9, UV. detection at 250 nm) indicated only one isomer (HO_α–C(6)) with a retention time of 3 min; the isomer of **2** with HO_β–C(6) has a retention time of 6 min. The base (±)-**2** was converted into the hydrochloride salt, m.p. 266–268°. – IR. (KBr): 3330, 1600, 1450, 1340, 950. – ^{1}H-NMR. (D_2O): 7.28 (*d* × *d*, *J*=8 and 8, 1 arom. H); 6.90 (*d*, *J*=8, 1 H, arom. H); 6.79 (*d*, *J*=8, 1 H, arom. H); 4.81 (*d*, *J*=5, 1 H, H–C(5)); 4.20 (*qa*, *J*=5, 1 H, H–C(6)); 3.00 (*s*, 3 H, CH_3N). – MS. (EI.): 271 (M^+).

$C_{17}H_{21}NO_2 \cdot HCl$	Calc.	C 66.33	H 7.20	Cl 11.52	N 4.55%
(307.82)	Found	„ 66.01	„ 7.46	„ 11.38	„ 4.70%

The free base (±)-**2** was obtained from its hydrochloride salt and recrystallized from *i*-Pr_2O, m.p. 57–59°.

b) *From* **19**. A mixture of **19** (9 mg, 0.021 mmol), 10% Pd/C (5 mg) and AcOH (3 ml) was hydrogenated at 40° at 45 psi for 16 h. Workup as described above gave a clean, single free base (MS. (EI.): 271 (M^+)) which was converted into the hydrochloride salt (±)-**2** · *HCl* (4.5 mg, 70%), identical to the compound prepared from **16**.

Synthesis of (±)-4-hydroxy-N-methylmorphinan-6-one (**17**). A mixture of **15** (330 mg, 0.77 mmol), 10% Pd/C (400 mg) and AcOH (50 ml) was hydrogenated at 50° for 50 h. The catalyst was filtered off and washed with AcOH. The filtrate was evaporated the residue was dissolved in H_2O, and the solution brought to pH 9 with conc. aq. NH_3-solution. Extraction with $CHCl_3$, drying (Na_2SO_4) and evaporation gave a crude solid which was chromatographed on a short alumina column with $CHCl_3$. The product isolated was recrystallized from benzene to give **17** (140 mg, 68%), m.p. 243–245°. – IR. (KBr): 3300, 1700, 1580, 1455, 1270, 1135, 950. – ^{1}H-NMR. ($CDCl_3$): 6.93 (*d* × *d*, *J*=7 and 7, 1 arom. H); 6.61 (*d*, *J*=7, 1 H, arom. H); 6.58 (*d*, *J*=7, 1 H, arom. H); 4.44 (*d*, *J*=13, 1 H, H–C(5)); 2.42 (*s*, 3 H, CH_3N). – MS. (CI./NH_3): 272 (MH^+).

$C_{17}H_{21}NO_2 \cdot \frac{1}{3}H_2O$ (277.37) Calc. C 73.61 H 7.87 N 5.05% Found C 73.50 H 7.62 N 4.96%

Synthesis of (±)-4-methoxy-N-methylmorphinan-6-one (±)-**3**). A mixture of **17** (70 mg, 0.26 mmol), phenyltrimethylammonium chloride (140 mg, 0.81 mmol), and anh. K_2CO_3 (400 mg) in DMF (5 ml) was heated at 70–75° for 16 h. The mixture was filtered, and the filtrate was evaporated under high vacuum. The residue was taken into $CHCl_3$, washed with 5% NaOH- and satd. NaCl-solution, and dried (Na_2SO_4). Evaporation of the solvent gave a brown crude product which was chromatographed on alumina and recrystallized from benzene/petroleum ether to yield (±)-**3** (45 mg, 61%), m.p. 111–112°. – IR. (KBr): 1705, 1575, 1465, 1250, 1140, 1070. – ^{1}H-NMR. ($CDCl_3$): 7.03 (*t*, *J*=7, 1 H, arom. H); 6.58–6.72 (*m*, 2 H, arom. H); 4.05 (*d* × *d*, *J*=2 and 14, 1 H, H–C(5)); 3.76 (*s*, 3 H, CH_3O); 2.36 (*s*, 3 H, CH_3N). – MS. (EI.): 285 (M^+).

$C_{18}H_{23}NO_2$ (285.39) Calc. C 75.75 H 8.12 N 4.91% Found C 76.01 H 8.29 N 4.86%

Synthesis of 1-(3'-Benzyloxy-5'-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**20**). A mixture of **7** (3.0 g, 6.0 mmol), 37% HCl-solution (90 ml), H_2O (140 ml), and CH_3OH (470 ml) (the final concentration of the HCl-solution was 1.5N) was refluxed for 16 h. The homogeneous solution was evaporated to a small volume, and the white solid which formed was collected and washed with H_2O. This solid was suspended in toluene and evaporated to remove H_2O. The resulting dried solid was then stirred

in $CHCl_3$, and the undissolved solid was filtered off and washed with $CHCl_3$ to give 1.45 g (59%) of the crude product. The filtrate contained starting material which was recycled. The crude product was recrystallized from CH_3OH to afford **20**·*HCl*, m.p. 237–239°. – IR. (KBr): 3250, 1600, 1500, 1450, 1140. – ^{1}H-NMR. (D_6-DMSO): 9.50 (*s*, 1 H, HO); 9.26 (br. *s*, 2 H, H_2N^+); 5.01 (s, 2 H, PhCH_2O); 4.62 (*m*, 1 H, H–C(1)); 3.72 (*s*, 3 H, CH_3O). – MS. (CI./NH_3): 376 (MH^+).

$C_{24}H_{25}NO_3$·HCl	Calc.	C 69.98	H 6.36	Cl 8.61	N 3.40%
(411.93)	Found	„ 70.20	„ 6.39	„ 8.52	„ 3.47%

The free base **20** was obtained from its hydrochloride salt and was crystallized from EtOH, m.p. 129–130°. – IR. (KBr): 3400, 3300, 1600, 1500, 1450, 1370, 1330, 1260, 1160, 1040, 1025, 1000. – ^{1}H-NMR. ($CDCl_3$): 7.32 (*m*, 5 H, arom. H); 6.60–6.78 (*m*, 3 H, arom. H); 6.25 (*m*, 3 H, arom. H); 4.86 (*s*, 2 H, PhCH_2O); 4.18 (*d* × *d*, *J* = 4 and 10, 1 H, H–C(1)); 3.76 (*s*, 3 H, CH_3O). – MS. (EI.): 365 (M^+), 282 (M^+–93), 162 (M^+–213).

$C_{24}H_{25}NO_3$ (375.47) Calc. C 76.77 H 6.71 N 3.73% Found C 76.65 H 6.98 N 3.58%

*Synthesis of 1-(3'-benzyloxy-5'-hydroxybenzyl)-*N*-formyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline* (**21**). A mixture of **20** (3.7 g, 9.85 mmol), HCOOEt (130 ml) and DMF (50 ml) was refluxed for 14 h. Solvents were evaporated, and the resulting yellow oil was treated with $CHCl_3$. The crystals which formed were collected and washed with cold $CHCl_3$ to afford **21** (3.9 g, 92%), m.p. 105–107°. – IR. (KBr): 3200, 1645, 1610, 1590, 1500, 1450, 1150, 1035. – ^{1}H-NMR. (D_6-DMSO): 9.28 (br. *s*, 1 H, HO); 7.98, 8.22 (2 *s*, 1 H, CHO); 4.99 (*s*, 2 H, PhCH_2O); 4.06–4.30 (*m*, 1 H, H–C(1)); 3.72 (*s*, 3 H, CH_3O). – MS. (EI.): 190 (M^+–213). – MS. (CI./NH_3): 404 (MH^+).

$C_{25}H_{25}NO_4 \cdot \frac{1}{3}CHCl_3$ (427.35) Calc. C 70.82 H 5.96 N 3.28% Found C 70.66 H 6.32 N 3.14%

*Synthesis of 1-(3'-benzyloxy-5'-methoxybenzyl)-*N*-formyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline* (**22**). A mixture of **21** (700 mg, 1.64 mmol), dimethyl sulfate (315 mg, 2.5 mmol), 59% NaH-suspension (110 mg, 2.7 mmol) and DMF (15 ml) was heated at 85–90° for 16 h with stirring. The mixture was cooled to r.t. and excess NaH was decomposed with H_2O. Solvents were evaporated under high vacuum, and the resulting oil was partitioned between $CHCl_3$ and 5% NaOH-solution saturated with NaCl. The organic layer was separated, washed with 5% HCl- and satd. NaCl-solution, and dried (Na_2SO_4). Solvent was evaporated and the resulting oil was washed with *i*-Pr_2O. The washings were discarded, and the residue was crystallized from EtOH/*i*-Pr_2O, then recrystallized from 95% ethyl alcohol to give **22** (218 mg, 61%), m.p. 120–121°. – IR. (KBr): 1650, 1610, 1590, 1500, 1450, 1430, 1190, 1150, 1060, 1035. – ^{1}H-NMR. ($CDCl_3$): there were two sets of peaks due to two rotamers; 7.66, 8.05 (2 *s*, 1 H, CHO); 4.94, 5.01 (2 *s*, 2 H, PhCH_2O); 4.36–4.70 (*m*, 1 H, H–C(1)); 3.75, 3.77, 3.80, 3.68 (4 *s*, 6 H, 2 CH_3O). – MS. (CI./NH_3): 418 (MH^+).

$C_{26}H_{27}NO_4$ (417.51) Calc. C 74.80 H 6.52 N 3.35% Found C 74.84 H 6.43 N 3.33%

Synthesis of 1-(3'-hydroxy-5'-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**23**). A suspension of **22** (2.1 g, 5 mmol) in 10% HCl-solution/MeOH 1:1 (180 ml) was refluxed for 16 h. The final homogeneous solution was concentrated, and the remaining aq. solution was washed with ether, adjusted to pH 8, and extracted with $CHCl_3$. The combined $CHCl_3$-phases were washed with satd. NaCl-solution, dried (Na_2SO_4), and evaporated to afford light brown solid. The crude product was washed with CH_3OH, then recrystallized from DMF to yield **23** (530 mg, 35%), m.p. 190–192°. – IR. (KBr): 3400, 3300, 1610, 1590, 1500, 1235, 1190, 1155, 1040. – ^{1}H-NMR. (D_6-DMSO): 9.28 (br. *s*, 1 H, HO); 7.12 (*d*, *J* = 8, 1 H, arom. H); 6.58–6.74 (*m*, 2 H, arom. H); 6.14–6.31 (*m*, 3 H, arom. H); 3.97 (*d* × *d*, *J* = 4 and 10, 1 H, H–C(1)); 3.65, 3.68 (2 *s*, 6 H, 2 CH_3O). – MS. (CI./NH_3): 300 (MH^+).

$C_{18}H_{21}NO_3 \cdot \frac{1}{2}H_2O$ (308.38) Calc. C 70.10 H 7.19 N 4.54% Found C 70.14 H 7.18 N 4.91%

Synthesis of 1-(3'-benzyloxy-5'-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**24**·*HCl*). A mixture of **22** (2.8 g, 6.7 mmol), 10% NaOH-solution (100 ml) and CH_3OH (280 ml) was refluxed for 48 h. Most of the CH_3OH was evaporated, and the remaining aq. solution was extracted with ether. The combined ether solution was washed with satd. NaCl-solution, dried ($MgSO_4$), and evaporated to give a yellow gum which was converted to its hydrochloride. This salt was recrystallized from CH_3OH to give **24**·HCl (2.8 g, 97%), m.p. 189–191°. – IR. (KBr): 1610, 1590, 1500, 1460, 1440, 1345, 1300, 1280, 1245, 1200, 1170, 1150, 1060, 1040, 1030. – ^{1}H-NMR. (D_6-DMSO): 9.20 (br. *s*, 2 H, H_2N^+);

5.04 (*s*, 2 H, PhCH_2O); 4.66 (br. *t*, J=6, 1 H, H–C(1)); 3.70 (*s*, 6 H, 2 CH_3O). – MS. (EI.): 389 (M^+), 387 (M^+–2).

$C_{25}H_{27}NO_3 \cdot HCl$	Calc.	C 70.49	H 6.62	Cl 8.32	N 3.29%
(425.96)	Found	„ 70.37	„ 6.63	„ 8.35	„ 3.36%

Synthesis of 1-(3'-hydroxy-5'-methoxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (**25**). – a) *From* **23**. Li-wire (271 mg, 39 mg at) was cut into about 1 cm pieces and added to 15 ml of liq. NH_3 (redistilled from Na) at –70° under Ar with stirring. Then, *t*-BuOH/THF 1:1 (18 ml) was added dropwise followed by the addition of **23** (420 mg, 1.4 mmol) in a small portion of *t*-BuOH/THF 1:1. The reaction temp. was maintained at –60° during the addition. The reaction was complete within 0.5 h, and 5 ml of MeOH was added. The NH_3 was evaporated gently, then the other organic solvents were evaporated. The white cake was quenched with sat. aq. NH_4Cl-solution (10 ml), and the product that precipitated was collected, washed with H_2O and dried to give **25** (330 mg, 78%). Recrystallization from DMF afforded an analytical sample, m.p. 192–193°. – IR. (KBr): 3440, 3270, 1695, 1668, 1615, 1585, 1470, 1450, 1330, 1220, 1165, 1060, 1005. – ^{1}H-NMR. (D_6-DMSO): 9.22 (*s*, 1 H, HO); 6.10–6.24 (*m*, 3 H, arom. H); 4.65 (*m*, 1 H, H–C(7)); 3.44, 3.64 (2 *s*, 6 H, 2 CH_3O). – MS. (EI.): 301 (M^+), 164 (M^+–137).

$C_{18}H_{23}NO_3 \cdot ¼\ H_2O$ (305.89) Calc. 70.67 H 7.74 N 4.58% Found C 70.89 H 7.94 N 4.43%

b) *From* **24**. *Birch* reduction of **24** (2.7 g, 6.3 mmol) was carried out under conditions identical to those described above to yield **25** (1.8 g, 95%).

Synthesis of (±)-4-hydroxy-2-methoxymorphinan-6-one (**28**) *and (±)-2-hydroxy-4-methoxymorphinan-6-one* (**30**). The base **25** (1.6 g, 5.3 mmol) was refluxed in 105 ml DMF/HCOOEt 30:75 for 24 h. The solvents were evaporated to give **26** as a gum (2.38 g; MS. (CI./NH_3): 330 (MH^+). This crude **26** in 75 ml of ether at ice-bath temp. was treated dropwise with 37% HCl-solution (37 ml). The mixture was refluxed for 16 h, then allowed to stand at 20° for 10 h. The aq. layer was saturated with NaCl, and the ether layer was separated and discarded. The aq. layer was diluted with an equal volume of satd. NaCl-solution and extracted with $CHCl_3$/*i*-PrOH 3:2. The organic layer was washed with satd. NaCl-solution, dried (Na_2SO_4), and evaporated to give a mixture of morphinanones **27** (foam, 2.4 g). In order to facilitate separation, the crude **27** was refluxed in 37% HCl-solution/MeOH 1:10 (88 ml) for 6 h. MeOH was evaporated, and the aq. solution was adjusted to pH 8 with NH_3 and extracted with $CHCl_3$/*i*-PrOH 3:2. The organic layer was washed with satd. NaCl-solution, dried (Na_2SO_4), and evaporated to afford a light brown foam (1.8 g) consisting of two major components in about (1:1)-ratio on TLC. (silica gel. $CHCl_3$/MeOH/conc. NH_3-solution 80:18:2). This crude product was dissolved in CH_3OH and kept at 4° overnight. The crystals which formed showed a major single component (slower moving compound) on TLC, and were recrystallized from DMF to give **30** (630 mg). The mother liquor that contained two compounds was evaporated and chromatographed on a silica gel column with $CHCl_3$/MeOH/conc. NH_3-solution 80:18:2. The faster moving compound was collected and converted to **28**·HCl (625 mg, 37%) which was recrystallized from H_2O, m.p. > 270° (dec.). – IR. (KBr): 3280, 1700, 1610, 1590, 1510, 1430, 1320, 1270, 1190, 1145, 1100, 1040. – ^{1}H-NMR. (D_2O): 6.38 (*d*, J=2, 1 arom. H); 6.29 (*d*, J=2, 1 H, arom. H); 3.69 (*s*, 3 H, CH_3O). – MS. (CI./NH_3): 288 (MH^+).

$C_{17}H_{21}NO_3 \cdot HCl \cdot 0.5\ H_2O$	Calc.	C 61.36	H 6.97	Cl 10.65	N 4.21%
(332.83)	Found	„ 61.68	„ 6.91	„ 10.37	„ 4.14%

Acid hydrolysis of **35** (s. below) in 37% HCl-solution and MeOH gave a product identical to **28** by TLC. and MS.

The slower moving material was collected and combined with the same compound obtained prior to chromatography and recrystallized from DMF to afford **30** (680 mg, 40%), m.p. > 250° (dec.). – IR. (KBr): 3410, 3310, 1715, 1610, 1590, 1460, 1440, 1350, 1215, 1155, 1100, 1070, 1020, 975. – ^{1}H-NMR. (D_6-DMSO): 6.10 (*d*, J=1.5, 1 H, arom. H); 6.07 (*d*, J=1.5, 1 H, arom. H); 3.62 (*s*, 3 H, CH_3O). – MS. (CI./NH_3): 288 (MH^+).

$C_{17}H_{21}NO_3 \cdot 0.2\ H_2O$ (290.96) Calc. C 70.17 H 7.41 N 4.81% Found C 70.22 H 7.22 N 4.97%

A portion of the free base **30** was dissolved in CH_3OH and treated with methanolic HCl-solution to afford the salt which was recrystallized from CH_3OH to give the 6,6-dimethyl acetal of **30**·HCl, m.p. 263–265°. – IR. (KBr): 3330, 1610, 1600, 1590, 1460, 1345, 1300, 1200, 1155, 1100, 1040, 970. – ^{1}H-NMR.

(D_2O): 6.38 (*d*, J=2, 1 H, arom. H); 6.29 (*d*, J=2, 1 H, arom. H); 3.06, 3.17, 3.74 (3 *s*, 9 H, 3 CH_3O). – MS. (CI./NH_3): 334 (M^++1).

$C_{19}H_{27}NO_4 \cdot HCl \cdot ¼\ H_2O$	Calc.	C 61.00	H 7.67	N 3.74%
(374.40)	Found	„ 61.20	„ 7.92	„ 3.64%

Synthesis of (±)-4-hydroxy-2-methoxy-N-methylmorphinan-6-one (**29**). A mixture of **28**·HCl (180 mg, 0.56 mmol), 37% HCHO-solution (0.19 ml, 2.3 mmol), AcONa (230 mg, 2.8 mmol) and 10% Pd/C (35 mg) in 2N CH_3COOH (23 ml) was hydrogenated at 40 psi at r.t. for 16 h. The catalyst was filtered off and washed with 2N CH_3COOH. The filtrate was adjusted to pH 8 with conc. aq. NH_3-solution and extracted with $CHCl_3$. The combined $CHCl_3$-phases were washed with satd. NaCl-solution, dried (Na_2SO_4), and evaporated to give solid **29** (142 mg, 85%). The slightly brown color of the free base was removed by chromatography on an alumina column with $CHCl_3$/MeOH 50:1. This free base was then converted into its hydrochloride and recrystallized from CH_3OH to afford **29**·HCl, m.p. >260° (dec.). – IR. (KBr): 3150, 1705, 1605, 1585, 1430, 1265, 1190, 1150, 1100, 1040. – ^{1}H-NMR. ($CDCl_3$, free base **29**): 6.20 (d, J=2, 1 H, arom. H); 6.15 (*s*, J=2, 1 H, arom. H); 4.18 (*d*, J=14, 1 H, H–C(5)); 3.65 (*s*, 3 H, CH_3O); 2.37 (*s*, 3 H, CH_3N). – MS. (EI.): 301 (M^+–HCl).

$C_{18}H_{23}NO_3 \cdot HCl \cdot 0.5\ CH_3OH$	Calc.	C 62.79	H 7.40	N 3.96	Cl 10.02%
(353.87)	Found	„ 62.76	„ 7.16	„ 4.03	„ 10.24%

Synthesis of 2-hydroxy-4-methoxy-N-methylmorphinan-6-one (**31**). The reductive *N*-methylation of 6,6-dimethyl acetal of **30**·HCl (120 mg, 0.36 mmol) was carried out exactly as described above for the synthesis of **29**. The free base **31** (65 mg, 60%) was recrystallized from MeOH, m.p. 252–254°. – IR. (KBr): 3400, 1710, 1590, 1430, 1340, 1190, 1160, 1070, 970. – ^{1}H-NMR. (D_6-DMSO/$CDCl_3$): 8.72 (br. *s*, 1 H, HO); 6.16 (*s*, 2 H, arom. H); 3.92 (*d*, J=14, 1 H, H–C(5)); 3.70 (*s*, 3 H, CH_3O); 2.34 (*s*, 3 H, CH_3N). – MS. (EI.): 301 (M^+).

$C_{18}H_{23}NO_3$ (301.39) Calc. C 71.73 H 7.69 N 4.65% Found C 71.47 H 7.79 N 4.59%

Synthesis of 1-bromo-4,5-epoxy-N-formyl-2-methoxymorphinan-6-one (**33**). A mixture of **12** (1.8 g, 4.76 mmol), dimethyl sulfate (730 mg, 5.8 mmol), and 59% NaH-suspension (260 mg, 6.4 mmol) in 40 ml of DMF was stirred at r.t. overnight. The mixture was quenched with H_2O (2 ml) and evaporated to give a residue which was taken into $CHCl_3$. The $CHCl_3$-phase was washed with 2N NaOH and satd. NaCl-solution, and dried (Na_2SO_4). Evaporation of the solvent gave a foam which was crystallized from $CHCl_3$/EtOH to yield **33** (1.1 g, 56%), m.p. 237–239°. – IR. (KBr): 1730, 1650, 1470, 1440, 1320, 1190, 1090, 1060, 1030. – ^{1}H-NMR. ($CDCl_3$); 8.00, 8.19, (2 *s*, 1 H, CHO); 6.54 (*s*, 1 H, arom. H); 4.66 (*s*, 1 H, H–C(5)); 3.85 (*s*, 3 H, CH_3O). – MS. (Cl/NH_3); 392 (MH^+), 394 (MH^+ + 2).

$C_{18}H_{18}BrNO_4$ (392.26) Calc. C 55.12 H 4.62 N 3.57% Found C 55.34 H 4.71 N 3.73%

The mother liquor ($CHCl_3$/EtOH solution) of **33** was evaporated and chromatographed on an alumina column with $C_6H_6/CHCl_3$ 1:1 to give a foam which was crystallized from EtOH to afford *1-bromo-4,5-epoxy-N-formyl-2,6-dimethoxy-6,7-didehydromorphinan* **32**; 150 mg, 7%, m.p. 224–228°. – IR. (KBr): 1660, 1460, 1440, 1340, 1315, 1210, 1110, 1090. – ^{1}H-NMR. ($CDCl_3$): 7.98, 8.16 (2 *s*, 1 H, CHO); 6.43 (*s*, 1 H, arom. H); 4.80 (*s*, 1 H, H–C(5)); 4.73 (*d* × *d*, J=1 and 7, 1 H, H–C(7)); 3.82 (*s*, 3 H, CH_3O); 3.49 (*s*, 3 H, CH_3O). – MS. (Cl./NH_3); 406 (MH^+), 408 (MH^+ + 2).

$C_{19}H_{20}BrNO_4 \cdot ¼\ H_2O$	Calc.	C 55.55	H 5.03	N 3.41%
(410.79)	Found	„ 55.50	„ 5.06	„ 3.27%

Synthesis of 4,5-epoxy-N-formyl-2-methoxymorphinan-6-one (**34**). To a suspension of **33** (600 mg, 1.53 mmol) in 2N CH_3COOH (60 ml) were added 10% Pd/C (80 mg) and AcONa (630 mg). The mixture was hydrogenated at 45 psi at r.t. for 16 h. The catalyst was filtered off and the filtrate was basified with 10% NaOH-solution and extracted with $CHCl_3$. The $CHCl_3$ phase was washed with H_2O, dried (Na_2SO_4), and evaporated to afford a white foam (480 mg) which was crystallized from toluene to yield **34** (372 mg, 78%), m.p. 213–214°. – IR. (KBr): 1730, 1665, 1635, 1610, 1430, 1405, 1240, 1140, 1090, 1030, 970, 920. – ^{1}H-NMR. ($CDCl_3$): 8.02, 8.18 (2 *s*, 1 H, CHO); 6.44 (*s*, 1 H, arom. H); 6.27 (*s*, 1 H, arom. H); 4.64 (*s*, 1 H, H–C(5)); 3.74 (*s*, 3 H, CH_3O). – MS. (CI./NH_3): 314 (MH^+).

$C_{18}H_{19}NO_4 \cdot 0.5H_2O$ (322.36) Calc. C 67.06 H 6.25 N 4.34% Found C 67.35 H 6.54 N 4.27%

Synthesis of N-*formyl-4-hydroxy-2-methoxymorphinan-6-one* (**35**). To a refluxing solution of **34** (500 mg, 1.6 mmol) and NH_4Cl (8 g) in 95% ethyl alcohol (100 ml) was added Zn dust (activated by washing with dil. aq. HCl-solution, washing with H_2O and drying; 2.36 g, 36 g.at) during 10 min. The resulting mixture was refluxed for another 2.5 h, filtered and the filtrate evaporated. The residue was partitioned between 2N HCl and $CHCl_3$. The $CHCl_3$ was separated, and the aq. phase was reextracted with $CHCl_3$. The combined $CHCl_3$ phases were washed with satd. NaCl-solution, dried (Na_2SO_4), and evaporated to afford a yellow solid (510 mg). This crude product was recrystallized from CH_3OH to give **35** (320 mg, 64%), m.p. 261–263°. – IR. (KBr): 3200, 1710, 1640, 1420, 1315. – ^{1}H-NMR. (D_6-DMSO): 9.49 (*s*, 1 H, HO); 7.93, 8.08 (2 *s*, 1 H, CHO); 6.15 (*s*, 2 H, arom. H); 4.00 (*d*, *J* = 14, H–C(5)); 3.61 (*s*, 3 H, CH_3O). – MS. (CI./NH_3): 316 (MH^+).

$C_{18}H_{21}NO_4 \cdot 0.25\ H_2O$	Calc.	C 67.58	H 6.78	N 4.37%
(319.87)	Found	„ 67.73	„ 6.86	„ 4.33%

*Synthesis of 2,4-dimethoxy-*N-*formylmorphinan-6-one* (**36**). Compound **11** (1.1 g, 3.65 mmol) was suspended in 1,4-dioxane/DMF 4:1 (45 ml) and treated with phenyltrimethylammonium chloride (3.8 g, 22.2 mmol) and CH_3ONa (2.4 g, 44.4 mmol). The mixture was heated at 80° for 16 h. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2 and washed with 5% NaOH; 5% HCl-, and satd. NaCl-solution, and dried (Na_2SO_4). Evaporation of the solvent gave a brown foam (1.2 g) which was chromatographed on a short alumina column with $CHCl_3$. Evaporation and recrystallization from benzene/hexane afforded **36** (890 mg, 74%); m.p. 172–174°. – IR. (KBr): 1710, 1660, 1600, 1460. – ^{1}H-NMR. ($CDCl_3$): 8.04, 8.18 (2 *s*, 1 H, CHO); 6.32 (*d*, *J* = 2, 1 H, arom. H); 6.22 (*d*, *J* = 2, 1 H, arom. H); 4.21 (*d*, *J* = 13, 1 H, H–C(5)); 3.75, 3.80 (2 *s*, 6 H, 2 CH_3O). – MS. (EI.): 329 (M^+).

$C_{19}H_{23}NO_4$ (329.40) Calc. C 69.28 H 7.04 N 4.25% Found C 69.56 H 6.92 N 4.18%

Synthesis of 2,4-dimethoxymorphinan-6-one hydrochloride (**37** · *HCl*). A mixture of **36** (400 mg, 1.2 mmol), 37% HCl-solution (4.5 ml) and CH_3OH (45 ml) was refluxed for 16 h. Solvents were evaporated, and the residue was crystallized from CH_3OH/ether. The salt was collected and recrystallized from CH_3OH/ether to afford **37** · HCl · CH_3OH (420 mg, 95%), m.p. 175–177°. – IR. (KBr): 1710, 1600, 1460, 1315, 1190, 1150, 1100, 940. – ^{1}H-NMR. (D_2O): 6.50 (*s*, 2 H, arom. H); 3.98 (*d*, *J* = 13, 1 H, H–C(5)); 3.81 (2 *s*, 6 H, 2 CH_3O). – MS. (EI.): 301 (M^+–CH_3OH–HCl).

$C_{18}H_{23}NO_3 \cdot CH_3OH \cdot HCl$	Calc.	C 61.70	H 7.63	Cl 9.58	N 3.79%
(369.88)	Found	„ 61.92	„ 7.43	„ 9.36	„ 3.60%

*Synthesis of 2,4-dimethoxy-*N-*methylmorphinan-6-one* (**38**). A mixture of **37** · HCl · CH_3OH (270 mg, 0.61 mmol), 37% HCHO-solution (0.2 ml, 2.7 mmol), AcONa (330 mg), 10% Pd/C (50 mg), and 2N CH_3COOH (33 ml) was hydrogenated at 40 psi for 16 h. The mixture was filtered, basified with conc. NH_3-solution to pH 8–9 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated to give the crude product. A short alumina column ($CHCl_3$/MeOH 100:1) was used to remove a small amount of impurity, and the product was recrystallized from *i*-Pr_2O to yield **38** (147 mg, 76%), m.p. 124–125°. – IR. (KBr): 1700, 1600, 1200, 1140, 1040. – ^{1}H-NMR. ($CDCl_3$): 6.23 (*s*, 2 H, arom. H); 3.97 (*d* × *d*, *J* = 2 and 14, 1 H, H–C(5)); 3.72, 3.76 (2 *s*, 6 H, 2 CH_3O); 2.38 (*s*, 3 H, CH_3N). – MS. (EI.): 315 (M^+).

$C_{19}H_{25}NO_3$ (315.42) Calc. C 72.35 H 7.99 N 4.44% Found C 72.15 H 7.77 N 4.13%

The hydrochloride of **38** was prepared and recrystallized from CH_3OH/ether; m.p. 255–257° (dec.).

$C_{19}H_{25}NO_3 \cdot 0.5\ CH_3OH \cdot HCl$	Calc.	C 63.66	H 7.67	N 3.80%
(367.90)	Found	„ 63.83	„ 7.71	„ 3.53%

REFERENCES

[1] *R. Grewe, H. Fischer & W. Friedrichsen*, Chem. Ber. *100*, 1 (1967).
[2] *H. C. Beyerman, J. van Berkel, T. S. Lie, L. Maat, J. C. M. Wessels, H. H. Bosman, E. Buurman, E. J. M. Bijsterveld & H. M. J. Sinnige*, Recl. Trav. Chim. Pays-Bas *97*, 127 (1978).
[3] *T. S. Lie, L. Maat & H. C. Beyerman*, Recl. Trav. Chim. Pays-Bas *98*, 419 (1979).
[4] *K. C. Rice*, J. Org. Chem. *45*, 3135 (1980); *idem*, Proc. Prob. Drug. Dep., in press, (1982).

[5] *K. C. Rice*, 183rd ACS National Meeting, Las Vegas, March 28–April 2, 1982, Abstract MEDI-53.
[6] *F.-L. Hsu, K. C. Rice & A. Brossi*, Helv. Chim. Acta *63*, 2042 (1980).
[7] *J. Reden, M. F. Reich, K. C. Rice, A. F. Jacobson, A. Brossi, R. A. Streaty & W. A. Klee*, J. Med. Chem. *22*, 256 (1979).
[8] *F.-L. Hsu, A. E. Jacobson, K. C. Rice & A. Brossi*, Heterocycles *13*, 259 (1979).
[9] *A. Manmade, H. C. Dalzell, J. F. Howes & R. K. Razdan*, J. Med. Chem. *24*, 1437 (1981).
[10] *A. E. Jacobson, F.-L. Hsu, M. D. Rozwadowska, H. Schmidhammer, L. Atwell & A. Brossi*, Helv. Chim. Acta *64*, 1298 (1981).
[11] *P. C. Meltzer, H. C. Dalzell & R. K. Razdan*, J. Chem. Soc., Perkin I *1981*, 2825.
[12] *F.-L. Hsu, K. C. Rice & A. Brossi*, submitted for publication in Heterocycles.
[13] *A. Brossi, F.-L. Hsu, K. C. Rice, M. D. Rozwadowska, H. Schmidhammer, C. D. Hufford, C. C. Chiang & I. L. Karle*, Helv. Chim. Acta *64*, 1672 (1981); *D. D. Weller & H. Rapoport*, J. Med. Chem. *19*, 1171 (1976) and ref. cit. therein.
[14] *P. Buchs, K. C. Rice, A. Brossi, J. V. Silverton & R. Potenzone, jr.*, J. Org. Chem., in press, (1982).
[15] *C. Schöpf*, Justus Liebigs Ann. Chem. *452*, 232 (1927).
[16] *T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka & H. Ishimaru*, J. Chem. Soc. (C) *1968*, 112.
[17] *M. D. Rozwadowska, F.-L. Hsu, A. E. Jacobson, K. C. Rice & A. Brossi*, Can. J. Chem. *58*, 1855 (1980).
[18] *Von W. Teilachker & W. Schmid*, Justus Liebigs Ann. Chem. *570*, 17 (1950).