Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 11.[1] 3-Hydroxycyprodime and Analogues: Opioid Antagonist Profile in Comparison to Cyprodime

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A series of 3-hydroxy-substituted analogues (**3**–**7**) of the μ selective opioid antagonist cyprodime has been synthesized in order to evaluate the role of a hydroxy group at C-3 concerning μ opioid antagonist selectivity. Compounds **3**–**7** were tested in bioassays (electrical stimulated mouse vas deferens preparation and myenteric-plexus longitudinal muscle preparation of the guinea pig ileum) and opioid receptor binding assays. Antagonism of μ receptor-mediated responses induced by the μ selective agonist DAMGO afforded equilibrium dissociation constants in the mouse vas deferens preparation (K_e values) for compounds **3**–**7** which agreed closely with their affinities as determined by opioid receptor binding assays (K_i values). At κ and δ receptors differences were apparent. Although the compounds had high affinity for both κ and δ receptors in opioid receptor binding, they were very poor at antagonizing agonist responses mediated by κ and particularly δ agonists in the mouse vas deferens preparation. None of the compounds tested showed agonist potency in the mouse vas deferens preparation or the myenteric-plexus longitudinal muscle preparation of the guinea pig ileum.

It is well established that opioid receptors can be divided into at least three major receptor types: μ, κ, and δ. The three receptor types have recently been cloned.[2–5] In order to specify the functional correlates of receptor activation by endogenous opioids and to determine the receptor selectivity of new opioid agonists, selective antagonists are being employed. Particularly, nonpeptides are useful pharmacological and biological tools since they are able to enter the central nervous system (CNS) more easily and are less susceptible to degradation than peptides. The prototype antagonists for κ and δ opioid receptors are norbinaltorphimine[6–8] and naltrindole,[9–11] respectively. The nonpeptide, competitive μ opioid antagonist cyprodime (**1**)[12] has become a valuable tool in opioid research.[5,13,14] Recently a new and more efficient synthesis of cyprodime has been reported.[15] Cyprodime has been tritium labeled and has become available for radioligand binding assays especially since it is commercially available.[16]

Removing the 6-keto function in cyprodime produced only a small decrease in μ antagonist potency but was accompanied by an increase in κ and δ antagonist potency, resulting in a much less μ selective compound.[17] An extensive study on cyprodime-related compounds revealed that several changes to the cyprodime molecule (e.g., an additional methoxy group at C-3, different substituents at C-4, a 14-ethoxy group, an *N*-allyl group) yielded compounds with either less μ selectivity or partial agonist activity.[13] Increasing the chain length at C-4 (compound **2**) resulted in higher affinity for μ receptors (ca. 2-fold) but in very little change in either selectivity or intrinsic activity.

In an effort to investigate the role of a hydroxy group at C-3, we have synthesized 3-hydroxycyprodime (**3**) and several 3-hydroxycyprodime analogues (compounds **4**–**7**). The results of this study exhibit the importance of both a 3-hydroxy group and a 14-alkoxy group to μ opioid antagonist potency.

Chemistry

The synthesis of 3-hydroxycyprodime (**3**) started from the oxymorphone derivative **8**[18] (Scheme 1). Reductive cleavage of the 4,5-oxygen bridge was achieved with activated Zn/NH_4Cl in refluxing methanol to give phenol **9**, which was O-methylated with phenyltrimethylammonium chloride in DMF in the presence of potassium carbonate to yield the *O*-methyl ether **10**. N-Demethylation was accomplished with 1-chloroethyl chloroformate,[19] and subsequent cleavage of the carbamate **11** in refluxing methanol afforded *N*-normorphinan **12**. Alkylation with cyclopropylmethyl chloride in DMF in the presence of potassium carbonate gave **13** from which the benzyl protecting group was removed by catalytic hydrogenation over Pd/C catalyst in methanol to yield 3-hydroxycyprodime (**3**).

The 4-*n*-butoxy analogue **4** was prepared from phenol **9** in four steps. 4-O-Alkylation with *n*-butyl iodide in DMF in the presence of potassium carbonate afforded **14**, which was N-demethylated with 1-chloroethyl chloroformate.[19] Treatment of carbamate **15** in refluxing

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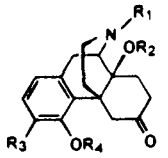
Chart 1



1: R_1=$CH_2CH(CH_2)_2$, R_2=R_4=Me, R_3=H
2: R_1=$CH_2CH(CH_2)_2$, R_2=Me, R_3=H, R_4=n-Bu
3: R_1=$CH_2CH(CH_2)_2$, R_2=R_4=Me, R_3=OH
4: R_1=$CH_2CH(CH_2)_2$, R_2=Me, R_3=OH,R_4=n-Bu
5: R_1=CH_2-CH=CH_2, R_2=R_4=Me, R_3=OH
6: R_1=$CH_2CH(CH_2)_2$, R_2=Et, R_3=OH, R_4=Me
7: R_1=$CH_2CH(CH_2)_2$, R_2=H, R_3=OH, R_4=Me

methanol gave *N*-nor compound **16**, which was alkylated with cyclopropylmethyl chloride to give **17**. Hydrogenolysis of the benzyl ether yielded 4-*n*-butoxy analogue **4**.

The *N*-allyl analogue **5** was prepared from *N*-normorphinan **12** by N-allylation with allyl bromide in DMF in the presence of potassium carbonate and acid hydrolysis of resulting **18** in a mixture of MeOH/concentrated HCl.

The preparation of 14-ethoxy derivative **6** was accomplished by using 3-*O*-benzylmorphone (**19**)[18] as a starting material. Compound **19** was treated in DMF with NaH and further alkylated with 2.2 equiv of diethyl sulfate to afford enol ether **20**. Acid hydrolysis, followed by reductive opening of the 4,5-epoxy bridge of **21** with Zn/NH_4Cl in methanol, yielded phenol **22**. O-Alkylation with phenyltrimethylammonium chloride gave morphinan **23**, which was N-demethylated with 1-chloroethyl chloroformate via carbamate **24**. Refluxing **24** in MeOH afforded the *N*-nor compound **25**, which was N-alkylated with cyclopropylmethyl chloride in DMF. Catalytic hydrogenation of **26** gave the desired 14-ethoxy analogue of 3-hydroxycyprodime (**6**·HBr).

The 14-hydroxy analogue **7** was prepared starting from naltrexone (**27**). Benzylation gave naltrexone benzyl ether (**28**)[20] which was treated with Zn/NH_4Cl in refluxing methanol to yield phenol **29**. O-Methylation with phenyltrimethylammonium chloride followed by hydrogenolysis of benzyl ether **30** afforded 14-hydroxymorphinan **7**.

Results and Discussion

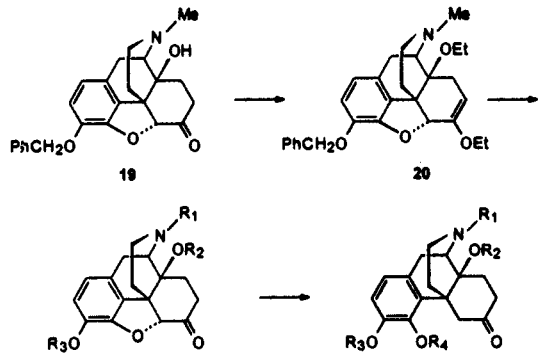
Opioid Receptor Binding. The inhibitory effects of compounds **3**–**7** on the binding of [^{3}H]DAMGO, [^{3}H]-U69593, and [^{3}H]DPDPE to μ, κ, and δ opioid binding sites, respectively, were assessed in homogenates of guinea pig brain in Tris·HCl buffer (50 mM, pH 7.4) for 40 min at 25 °C as described earlier[21] (Table 1). Like cyprodime none of the compounds showed particular selectivity as determined by ligand binding assays. Introduction of a 3-OH group to cyprodime to afford 3-hydroxycyprodime (**3**) greatly enhanced μ affinity but led to a loss of preference for the μ site. The compound with the highest affinity for the μ site (K_i 1.4 nM) was compound **6** which has a 14-OEt group. However this compound also lacked selectivity for the μ receptor site over the κ site (K_i 5.5 nM) but showed some preference for μ and δ sites (K_i 21 nM). Exchange of the 4-OMe group of **3** for the larger *n*-butoxy group in compound **4** did not appear to affect binding properties, nor did replacement of the *N*-cyclopropylmethyl group in **3** by an allyl in **5**. In contrast, replacement of the 14-OMe group of **3** with a 14-OH group to afford compound **7** did markedly alter binding properties, leading to a reduction in affinity at all three binding sites but with a greater reduction at δ (24-fold) than at μ (9-fold) or κ (6-fold) binding sites. Similar μ affinities of compounds **3** (1.95 nM) and **6** (3.08 nM) were obtained when using [^{3}H]CTOP as μ ligand in rat brain membranes.[22]

Bioassays. Compounds **3**–**7** were tested on the electrically stimulated mouse vas deferens preparation (MVD; Table 2) and myenteric-plexus longitudinal muscle preparation of the guinea pig ileum (GPI; Table 3) as described previously.[12,23] In MVD, DAMGO, CI977, and DPDPE were employed as μ, κ, and δ selective agonists, respectively. In GPI, the following agonists were used, CI977, U69593, dynorphin 1–13, ethylketocyclazocine, and tifluadom.

None of the compounds tested showed agonist potency in MVD, but all were effective antagonists in this tissue (Table 2). Antagonism of μ receptor-mediated responses induced by the agonist DAMGO gave equilibrium dissociation constants (K_e values) for compounds **3**–**7** which agreed closely with their affinities as determined by ligand binding assays (Table 1). Indeed comparison of K_i and K_e values afforded a simple relationship with a correlation coefficient of 0.99. At the κ and δ sites however differences were apparent. Thus, although all the compounds tested had high affinity for both κ and δ sites in ligand binding assays (Table 1), they were very poor at antagonizing agonist responses mediated by κ and particularly δ agonists in MVD (Table 2). This was also seen with the parent compound cyprodime and was most marked with **4** which had a δ affinity in binding of 42 nM but was unable to antagonize the δ agonist DPDPE in MVD even at concentrations of **4** of 10 000 nM. Similarly, but less marked, the affinity of compound **4** for the κ site in guinea pig brain was measured by ligand binding as 13 nM but, in MVD, determined as an equilibrium dissociation constant against the κ agonist CI977 was 174 nM. Using compound **3**, and employing both MVD and GPI, the low affinity of this compound at κ receptors was confirmed by determination of the K_e values against a variety of κ agonists (Table 3). The only exception was the antagonism of the agonist action of ethylketocyclazocine in GPI where a K_e value of 3.95 nM was obtained. However ethylketocyclazocine does have agonist actions at μ opioid receptors,[24] and the K_e measured therefore could represent the μ affinity of **3**. Certainly this agrees with the affinity determined at μ receptors in MVD (K_e 5.6 nM) and ligand binding assays (K_i 6.2 nM). In the guinea pig ileum tissue used in these experiments, ethylketocyclazocine did appear to be acting at μ opioid receptors since its action was antagonized by naloxone with a K_e of 2.78 ± 0.56 SEM nM (n = 5) and a Schild slope of unity.

The results thus suggest that the affinities of cyprodime and its analogues **3**–**7** measured in binding assays and by bioassay agree for the μ receptor site but not for the δ and κ receptor sites. A possible explanation is that the compounds are agonists at κ and δ receptors and shift to higher affinity binding in the buffer used (Tris·HCl), which promotes a high-agonist affinity G-protein-coupled state of the receptor, as opposed to a lower affinity state of the receptor which exists under the bioassay conditions.[25,26] However no agonist activity of the compounds was observed in either the MVD or GPI. It is possible that the observed differences are due

Scheme 1



8: R_1=R_2=Me, R_3=CH_2Ph
21: R_1=Me, R_2=Et, R_3=CH_2Ph
27: R_1=$CH_2CH(CH_2)_2$, R_2=R_3=H (naltrexone)
28: R_1=$CH_2CH(CH_2)_2$, R_2=H, R_3=CH_2Ph

9: R_1=R_2=Me, R_3=CH_2Ph, R_4=H
10: R_1=R_2=R_4=Me, R_3=CH_2Ph
11: R_1=$CO_2CHClCH_3$, R_2=R_4=Me, R_3=CH_2Ph
12: R_1=H, R_2=R_4=Me, R_3=CH_2Ph
13: R_1=$CH_2CH(CH_2)_2$, R_2=R_4=Me, R_3=CH_2Ph
3: R_1=$CH_2CH(CH_2)_2$, R_2=R_4=Me, R_3=H
14: R_1=R_2=Me, R_3=CH_2Ph, R_4=n-Bu
15: R_1=$CO_2CHClCH_3$, R_2=Me, R_3=CH_2Ph, R_4=n-Bu
16: R_1=H, R_2=Me, R_3=CH_2Ph, R_4=n-Bu
17: R_1=$CH_2CH(CH_2)_2$, R_2=Me, R_3=CH_2Ph, R_4=n-Bu
4: R_1=$CH_2CH(CH_2)_2$, R_2=Me, R_3=H, R_4=n-Bu
18: R_1=CH_2-CH=CH_2, R_2=R_4=Me, R_3=CH_2Ph
5: R_1=CH_2-CH=CH_2, R_2=R_4=Me, R_3=H
22: R_1=Me, R_2=Et, R_3=CH_2Ph, R_4=H
23: R_1=R_4=Me, R_2=Et, R_3=CH_2Ph
24: R_1=$CO_2CHClCH_3$, R_2=Et, R_3=CH_2Ph, R_4=Me
25: R_1=H, R_2=Et, R_3=CH_2Ph, R_4=Me
26: R_1=$CH_2CH(CH_2)_2$, R_2=Et, R_3=CH_2Ph, R_4=Me
6: R_1=$CH_2CH(CH_2)_2$, R_2=Et, R_3=H, R_4=Me
29: R_1=$CH_2CH(CH_2)_2$, R_2=R_4=H, R_3=CH_2Ph
30: R_1=$CH_2CH(CH_2)_2$, R_2=H, R_3=CH_2Ph, R_4=Me
7: R_1=$CH_2CH(CH_2)_2$, R_2=R_3=H, R_4=Me

Table 1. Opioid Receptor Binding of 3-Hydroxycyprodime and Analogues in Homogenates of Guinea Pig Brain Membranes

	K_i (nM) ± SEM		
compd	[^{3}H]DAMGO (μ)	[^{3}H]U69593 (κ)	[^{3}H]DPDPE (δ)
3	6.15 ± 1.6	4.18 ± 0.6	13.8 ± 3.7
4	10.9 ± 1.9	13.0 ± 1.9	42 ± 4.2
5	7.29 ± 0.55	25.4 ± 3.7	25.6 ± 5.9
6	1.42 ± 0.26	5.46 ± 0.5	21.4 ± 1.6
7	54.4 ± 8.3	23.0 ± 5.2	334 ± 78
cyprodime	23.7 ± 6.3	105 ± 9.7	61.1 ± 12.2

Table 2. Antagonist K_e Values of 3-Hydroxycyprodime and Analogues Determined in the Mouse Vas Deferens Preparation (MVD)

	K_e[a] (nM) ± SEM			selectivity ratio	
compd	DAMGO (μ)	CI977 (κ)	DPDPE (δ)	κ/μ	δ/μ
3	5.62 ± 0.56	368 ± 281	316 ± 84	65	56
4	24.9 ± 3.1	174 ± 37	>10000	7	>400
5	4.60 ± 1.2	4.67 ± 0.13	2272 ± 238	1	494
6	2.92 ± 0.48	233 ± 107	106 ± 9	80	36
7	93.8 ± 16	243 ± 37	8922 ± 110	2.6	95
cyprodime[b]	55.4 ± 4	1551 ± 448	6108 ± 205	28	110
naloxone[b]	1.4 ± 0.1	15.9 ± 6.7	9.6 ± 2.3	12	7

[a] K_e = [antagonist]/DR − 1, where DR is dose ratio (i.e., ratio of equiactive concentrations of the test agonist in the presence and absence of the antagonist). [b] Taken from ref 12.

to differential metabolism of the parent compounds in central tissue and the periphery. This is unlikely since there is no evidence for metabolism of morphinans in isolated tissues or brain homogenates under assay conditions,[27-29] cyprodime and related compounds are

Table 3. Antagonist K_e Values for 3-Hydroxycyprodime (**3**) in the Mouse Vas Deferens Preparation (MVD) and Myenteric-Plexus Longitudinal Muscle Preparation of the Guinea Pig Ileum (GPI) against Various κ Agonists

	K_e[a] (nM) ± SEM	
κ agonist	MVD	GPI
CI977	368 ± 53 (10)	284 ± 50 (7)
U69593	354 ± 90 (6)	97.5 ± 15 (6)
ethylketocyclazocine	910 ± 148 (4)	3.95 ± 1.6 (8)
dynorphine 1−13	450 ± 52 (6)	ND[b]
trifluadom	ND[b]	1009 ± 24 (3)

[a] K_e = [antagonist]/DR− 1, where DR is dose ratio (i.e., ratio of equiactive concentrations of the test agonist in the presence and absence of the antagonist). Number of separate determinations is given in parentheses. [b] ND = not determined.

effective in vivo,[12,18] and displacement curves in binding assays afforded slopes of unity[12] (Table 1) consistent with the presence of a single molecular species.

An alternative suggestion is that the receptors in the brain and the isolated tissues may be different and are distinguishable by this series of compounds. Although cloning studies point to a single receptor type for each of the μ, κ, and δ receptors, there is evidence for differences in both the κ and δ opioid receptor populations. Indeed observations over several years suggest the presence of δ opioid receptor subtypes. This follows from extensive binding studies in central nervous tissue in which μ ligands have been shown to inhibit the binding of δ ligands in both a competitive and noncompetitive manner, leading to a division of δ receptors into δ-complexed (δ cx) and δ noncomplexed (δ ncx) types.[30,31] An alternative division into δ_1 and δ_2 subtypes has been

proposed based on the differential selectivity of δ-mediated effects toward several antagonists,[32] and it has been demonstrated that central tissue contains both δ_1 and δ_2 subtypes.[33,34] The δ cx site may be synonymous with the δ_1 receptor.[35] There is also evidence for differences between the central and peripheral δ opioid receptor populations. Thus the conformationally constrained peptide [D-Ala^2,(2*R*,3*S*)-Δ^EPhe^{4}Leu^5]enkephalin (CP-OH) has high affinity for δ opioid receptors in rat brain homogenates and can modulate the antinociceptive effects of morphine.[36] In contrast it is only weakly active in MVD,[37] supporting recent findings which show no evidence for an interaction of μ and δ sites in this tissue.[38] In addition, the methyl ester CP-OMe has a 33-fold lower affinity for δ receptors in MVD than those in rat brain,[39] and the δ antagonist [^{3}H]naltrindole recognizes multiple δ opioid binding sites in mouse brain but only a single site in mouse vas deferens.[40] This is confirmed by pharmacological studies using antagonists which point to a single receptor site in MVD[41] and work with the δ_1 antagonist 7-benzylidenenaltrexone which is able to discriminate δ opioid receptor subtypes in guinea pig brain but not in the mouse vas deferens, where it is equally potent at inhibiting the actions of a putative δ_1 (DPDPE) and δ_2 (DSLET) ligand.[42] Other pharmacological evidence does however suggests some other form of heterogeneity in this tissue.[43] With the κ receptors there is less direct evidence for differences between central and peripheral receptors, although there are many reports on possible subtypes of this receptor, based mainly on ligand binding assays,[22,44] suggesting up to four subtypes.[45] Differences have also been noted in pharmacological assays between κ receptors in GPI and MVD.[46]

In conclusion introduction of a 3-OH group to cyprodime and analogues markedly enhances affinity at all three receptor types, while a 14-OH group instead of a 14-alkoxy group leads to a reduction in affinity at all three binding sites. The studies confirm the usefulness of the cyprodime group of compounds as opioid receptor antagonists in functional assays and indicate determinants of important structure–activity relationships. Moreover this compound and its analogues may prove useful in defining subtypes of the κ and δ types of opioid receptors.

Experimental Section

Melting points were determined with a Kofler melting point microscope and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR (300 MHz) spectra were performed on a Bruker AM 300 instrument, and chemical shifts are reported as δ values (ppm) relative to TMS. Chemical ionization mass spectra (CI-MS) were obtained from a Finnigan MAT 44S apparatus. Optical rotations (concentration (g/100 mL), solvent) were determined with a Perkin-Elmer 141 polarimeter. Elemental analyses were performed at the Analytical Department of Hoffmann-La Roche & Co., Inc., Basel, Switzerland, and the Institute of Physical Chemistry of the University of Vienna, Vienna, Austria. TLC data were determined with Polygram Sil G/UV$_{254}$ plates (solvent system CH_2Cl_2/MeOH/concentrated NH_4OH, 90:9:1).

3-(Benzyloxy)-4-hydroxy-14-methoxy-*N*-methylmorphinan-6-one (9). Activated zinc powder (12.0 g, 180 mmol) was added in portions to a refluxing mixture of **8**[18] (6.0 g, 12.34 mmol), NH_4Cl (12.0 g, 222 mmol), and MeOH (100 mL) within 5 min. The mixture was stirred under reflux for an additional 30 min, filtered, and washed with MeOH, and the filtrate was evaporated. The oily residue was alkalized with concentrated NH_4OH and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O (2 × 150 mL) and brine (200 mL), dried (Na_2SO_4), and evaporated to yield 7.81 g of a red-brown oil which was crystallized from 8 mL of MeOH to afford 3.11 g (62%) of **9**. An analytical sample was obtained by recrystallization from MeOH: mp 265–268 °C; IR ($CHCl_3$) 3505 (OH), 1705 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–7.31 (m, 5 H, ArH), 6.73 (d, 1 H, ArH, *J* = 8 Hz), 6.55 (d, 1 H, ArH, *J* = 8 Hz), 6.17 (br s, 1 H, OH), 5.00 (s, 2 H, OCH_2), 3.34 (s, 3 H, OCH_3), 2.37 (s, 3 H, NCH_3); CI-MS *m/z* 408 ($M^+ + 1$). Anal. ($C_{25}H_{29}NO_4$·0.5MeOH) C, H, N.

3-(Benzyloxy)-4,14-dimethoxy-*N*-methylmorphinan-6-one (10). A mixture of **9** (3.1 g, 7.61 mmol), K_2CO_3 (4.2 g, 30.4 mmol), and anhydrous DMF (50 mL) was gassed at room temperature with argon for 30 min. Then, phenyltrimethylammonium chloride (4.21 g, 24.5 mmol) was added, and the resulting mixture was stirred at 80 °C (bath temperature) for 2.5 h. The inorganic solid was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The oily residue was dissolved in CH_2Cl_2, washed with H_2O (2 × 100 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated to give 3.03 g of a brownish oil. Purification by flash chromatography (silica gel 70–270 mesh, 300 g; elution with CH_2Cl_2/MeOH/concentrated NH_4OH, 97:3:1) yielded 2.11 g (66%) of **10** as a colorless foam: IR ($CHCl_3$) 1705 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41–7.27 (m, 5 H, ArH), 6.78 (d, 1 H, ArH, *J* = 8 Hz), 6.71 (d, 1 H, ArH, *J* = 8 Hz), 4.99 (s, 2 H, OCH_2), 3.92 (s, 3 H, C-4 OCH_3), 3.33 (s, 3 H, C-14 OCH_3), 2.36 (s, 3 H, NCH_3); CI-MS *m/z* 422 ($M^+ + 1$). Anal. ($C_{26}H_{31}NO_4$·0.2MeOH) C, H, N.

3-(Benzyloxy)-4,14-dimethoxymorphinan-6-one (12). A mixture of **10** (430 mg, 1.02 mmol), $KHCO_3$ (820 mg, 8.2 mmol), 1-chloroethyl chloroformate (0.89 mL, 8.2 mmol), and EtOH-free $ClCH_2CH_2Cl$ (4 mL) was stirred under N_2 at 60–65 °C (bath temperature) for 4.5 h. The inorganic solid was filtered off and washed with CH_2Cl_2. The filtrate was evaporated to give 540 mg of **11** as a reddish glassy solid which was not further characterized and purified. This solid was dissolved in 5 mL of MeOH and refluxed for 1.5 h and the solution evaporated. The oily residue was alkalized with dilute NH_4OH and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (50 mL), dried (Na_2SO_4), and evaporated to afford 340 mg of an oily residue. Purification by column chromatography (silica gel 230–400 mesh, 22 g; elution with CH_2Cl_2/MeOH/concentrated NH_4OH, 90:9:1) gave an oil which was refluxed in a small amount of MeOH to yield 210 mg (51%) of **12** as a slightly brown foam (pure by TLC and spectral analyses): IR ($CHCl_3$) 1707 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.98 (br s, 1 H, NH), 7.34 (m, 5 H, ArH), 6.81 (d, 1 H, ArH, *J* = 8 Hz), 6.73 (d, 1 H, ArH, *J* = 8 Hz), 5.01 (s, 2 H, OCH_2), 3.94 (s, 3 H, C-4 OCH_3), 3.36 (s, 3 H, C-14 OCH_3); CI-MS *m/z* 408 ($M^+ + 1$). Anal. ($C_{25}H_{29}NO_4$·0.7MeOH) C, H, N.

3-(Benzyloxy)-*N*-(cyclopropylmethyl)-4,14-dimethoxymorphinan-6-one (13). A mixture of **12** (160 mg, 0.39 mmol), K_2CO_3 (217 mg, 1.57 mmol), cyclopropylmethyl chloride (40 μL, 0.45 mmol), and anhydrous DMF (5 mL) was stirred under N_2 at 90 °C (bath temperature) for 17 h. The inorganic solid was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The oily residue was dissolved in 20 mL of CH_2Cl_2, washed with H_2O (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated to yield 180 mg of a slightly yellow oil. Purification by column chromatography (silica gel mesh 230–400, 27 g; elution with CH_2Cl_2/MeOH/concentrated NH_4OH, 90:9:1) gave 145 mg (81%) of **13** as a colorless oil (pure by TLC and spectral analyses) which could not be crystallized: IR ($CHCl_3$) 1707 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5 H, ArH), 6.76 (d, 1 H, ArH, *J* = 8 Hz), 6.68 (d, 1 H, ArH, *J* = 8 Hz), 5.01 (s, 2 H, OCH_2), 3.94 (s, 3 H, C-4 OCH_3), 3.46 (s, 3 H, C-14 OCH_3); CI-MS *m/z* 462 ($M^+ + 1$).

***N*-(Cyclopropylmethyl)-3-hydroxy-4,14-dimethoxymorphinan-6-one Hydrobromide (3·HBr).** A mixture of **13** (120 mg, 0.26 mmol), 10% Pd/C catalyst (15 mg), and MeOH (20 mL) was hydrogenated at room temperature and 40 psi for 15 h. The catalyst was filtered off and washed with MeOH, and the filtrate was evaporated to afford 97 mg of a semicrystalline residue, which was converted into the hydrobromide salt in the usual way to yield 78 mg (66%) of **3**·HBr as slightly beige crystals: mp >236 °C dec (acetone); IR ($CHCl_3$) 3450 (OH, $^+$NH), 1702 (CO) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.93 and 7.55 (2 br s, 2 H, $^+$NH, OH), 6.76 (d, 1 H, ArH, *J* = 8 Hz), 6.63 (d, 1 H, ArH, *J* = 8 Hz), 3.82 (s, 3 H, C-4 OCH_3), 3.44 (s, 3 H,

C-14 OCH_3); CI-MS *m/z* 372 ($M^+ + 1$); $[\alpha]^{20}_D = -96.8°$ (c 0.59, MeOH). Anal. ($C_{22}H_{29}NO_4 \cdot HBr \cdot 0.5H_2O$) C, H, N, Br.

4-*n*-Butoxy-3-(benzyloxy)-14-methoxy-*N*-methylmorphinan-6-one (14). A mixture of **9** (279 mg, 0.68 mmol), K_2CO_3 (560 mg, 4.1 mmol), *n*-C_4H_9I (102 μL, 0.89 mmol), and DMF (7 mL) was stirred at room temperature for 30 h. The inorganic material was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The resulting oily residue was dissolved in 30 mL of CH_2Cl_2, washed with H_2O (2 × 50 mL, 1 × 30 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated to give 327 mg of a brown oil. Purification by column chromatography (silica gel 230–400 mesh, 33 g; elution with CH_2Cl_2/MeOH/concentrated NH_4OH, 95:5:1) yielded 273 mg (86%) of **14** as a slightly yellow oil (pure by TLC and spectral analyses) which could not be crystallized: IR ($CHCl_3$) 1702 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H, ArH), 6.77 (d, 1 H, ArH, *J* = 8 Hz), 6.70 (d, 1 H, ArH, *J* = 8 Hz), 4.98 (s, 2 H, OCH_2), 3.32 (s, 3 H, OCH_3), 2.35 (s, 3 H, NCH_3), 0.86 (t, 3 H, CH_3, *J* = 7 Hz); CI-MS *m/z* 464 ($M^+ + 1$).

4-*n*-Butoxy-3-(benzyloxy)-14-methoxymorphinan-6-one (16). A mixture of **14** (307 mg, 0.66 mmol), $KHCO_3$ (530 mg, 5.3 mmol), 1-chloroethyl chloroformate (0.83 mL, 7.6 mmol), and EtOH-free $ClCH_2CH_2Cl$ was stirred under N_2 at 60–65 °C (bath temperature) for 7 h. The inorganic material was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated to give 323 mg of **15** as a red glassy solid which was not further purified and characterized. This solid was dissolved in 10 mL of MeOH and refluxed for 30 min and the solution evaporated. The residue was partitioned between dilute NH_4OH (20 mL) and CH_2Cl_2 (30 mL) and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (50 mL), dried (Na_2SO_4), and evaporated to yield 260 mg of a brownish oil. Purification by column chromatography (silica gel 230–400 mesh, 26 g; elution with CH_2Cl_2/MeOH/concentrated NH_4OH, 97:3:1) afforded 183 mg (62%) of **16** as a slightly yellow oil (pure by TLC and spectral analyses): IR ($CHCl_3$) 1709 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5 H, ArH), 6.77 (d, 1 H, ArH, *J* = 8 Hz), 6.70 (d, 1 H, ArH, *J* = 8 Hz), 4.99 (s, 2 H, OCH_2), 3.37 (s, 3 H, OCH_3), 0.86 (t, 3 H, CH_3, *J* = 7 Hz); CI-MS *m/z* 450 ($M^+ + 1$).

4-*n*-Butoxy-3-(benzyloxy)-*N*-(cyclopropylmethyl)-14-methoxymorphinan-6-one (17). A mixture of **16** (200 mg, 0.44 mmol), K_2CO_3 (245 mg, 1.78 mmol), cyclopropylmethyl chloride (47 μL, 0.52 mmol), and anhydrous DMF (10 mL) was stirred under N_2 at 90 °C (bath temperature) for 16 h. The inorganic material was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The oily residue was dissolved in 40 mL of CH_2Cl_2, washed subsequently with H_2O (2 × 70 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated to afford 275 mg of a slightly yellow oil. Purification by column chromatography (silica gel 230–400 mesh, 28 g; elution with Et_2O/concentrated NH_4OH, 99:1) yielded 179 mg (81%) of **17** as a colorless oil (pure by TLC and spectral data): IR ($CHCl_3$) 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5 H, ArH), 6.77 (d, 1 H, ArH, *J* = 8 Hz), 6.68 (d, 1 H, ArH, *J* = 8 Hz), 4.99 (s, 2 H, OCH_2), 3.37 (s, 3 H, OCH_3), 0.86 (t, 3 H, CH_3, *J* = 7 Hz); CI-MS *m/z* 505 ($M^+ + 1$).

4-*n*-Butoxy-*N*-(cyclopropylmethyl)-3-hydroxy-14-methoxymorphinan-6-one (4). A mixture of **16** (160 mg, 0.32 mmol), 10% Pd/C catalyst (20 mg), and MeOH (35 mL) was hydrogenated at room temperature and 40 psi for 12 h. The catalyst was filtered off and washed with MeOH, and the filtrate was evaporated. The semicrystalline residue (130 mg) was recrystallized from $CHCl_3$/MeOH (3:1) to yield 46 mg (35%) of **4** as colorless crystals: mp 69–71 °C; IR ($CHCl_3$) 3535 (OH), 1707 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.77 (d, 1 H, ArH, *J* = 8 Hz), 6.70 (d, 1 H, ArH, *J* = 8 Hz), 3.37 (s, 3 H, C-14 OCH_3), 0.97 (t, 3 H, CH_3, *J* = 7 Hz); CI-MS *m/z* 414 ($M^+ + 1$); $[\alpha]^{20}_D = -80.8°$ (c 0.48, MeOH). Anal. ($C_{25}H_{35}NO_4 \cdot 0.3CHCl_3$) C, H, N.

***N*-Allyl-3-(benzyloxy)-4,14-dimethoxymorphinan-6-one (18).** A mixture of **12** (205 mg, 0.50 mmol), K_2CO_3 (278 mg, 2.01 mmol), allyl bromide (49 μL, 058 mmol), and anhydrous DMF (3 mL) was stirred under N_2 at 80 °C (bath temperature) for 4 h. The inorganic material was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The residue (310 mg, brown oil) was dissolved in 20 mL of CH_2Cl_2 and washed subsequently with H_2O (2 × 50 mL, 1 × 30 mL) and brine (40 mL). The CH_2Cl_2 phase was dried (Na_2SO_4) and evaporated, and the resulting brownish foam (223 mg) was purified by column chromatography (silica gel 230–400 mesh, 22 g; elution with CH_2Cl_2/MeOH/concentrated NH_4OH, 95:5:1) to afford 189 mg (84%) of **18** as a colorless foam: IR ($CDCl_3$) 1705 (CO) cm^{-1}; δ 7.34 (m, 5 H, ArH), 6.79 (d, 1 H, ArH, *J* = 8 Hz), 6.72 (d, 1 H, ArH, *J* = 8 Hz), 5.81 (m, 1 H, olef H), 5.10 (m, 2 H, olef H), 5.01 (s, 2 H, OCH_2), 3.94 (s, 3 H, C-4 OCH_3), 3.32 (s, 3 H, C-14 OCH_3); CI-MS *m/z* 448 ($M^+ + 1$). Anal. ($C_{28}H_{33}NO_4 \cdot 0.1MeOH$) C, H, N.

***N*-Allyl-3-hydroxy-4,14-dimethoxymorphinan-6-one (5).** A mixture of **18** (132 mg, 0.29 mmol), MeOH (4 mL), and concentrated HCl (2 mL) was refluxed for 18 h and then concentrated in vacuo to about one-half of the original volume. This solution was diluted with H_2O (70 mL), alkalized with concentrated NH_4OH, and extracted with CH_2Cl_2 (1 × 50 mL, 2 × 30 mL). The combined organic layers were washed with brine (2 × 80 mL), dried (Na_2SO_4), and evaporated to give 100 mg of a beige, crystalline residue. Recrystallization from 1 mL of MeOH gave 67 mg (65%) of pure **5**: mp 213–216 °C; IR ($CHCl_3$) 3531 (OH), 1707 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.76 (d, 1 H, ArH, *J* = 8 Hz), 6.71 (d, 1 H, ArH, *J* = 8 Hz), 5.81 (m, 1 H, olef H), 5.36 (br s, 1 H, OH), 5.11 (m, 2 H, olef H), 3.79 (s, 3 H, C-4 OCH_3), 3.32 (s, 3 H, C-14 OCH_3); CI-MS *m/z* 358 ($M^+ + 1$); $[\alpha]^{20}_D = -120.7°$ (c 0.57, CH_2Cl_2). Anal. ($C_{21}H_{27}NO_4 \cdot 0.5MeOH$) C, H, N.

3-(Benzyloxy)-6,7-didehydro-4,5α-epoxy-6,14-diethoxy-*N*-methylmorphinan (20). NaH (1.5 g, 626 mmol; obtained from 2.5 g of a 60% NaH dispersion in oil by washings with petroleum ether) was added to a solution of **19**[18] (2.97 g, 7.59 mmol) in 15 mL of anhydrous DMF under N_2 at 5 °C (bath temperature) while stirring. After 10 min, diethyl sulfate (2.3 mL, 16.67 mmol) was added and the resulting mixture was stirred at 5 °C (bath temperature) for 1.5 h. Excess NaH was destoyed carefully by addition of small pieces of ice, and then the mixture was diluted with H_2O (70 mL) and extracted with CH_2Cl_2 (1 × 150 mL, 2 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL), dried (Na_2SO_4), and evaporated to yield 3.2 g of a slightly brown oil which was crystallized from 3 mL of MeOH to afford 1.94 g (57%) of **20** as colorless crystals. For analysis a small portion was recrystallized from MeOH: mp 59–63 °C; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, ArH), 6.68 (d, 1 H, ArH, *J* = 8.2 Hz), 6.49 (d, 1 H, ArH, *J* = 8.2 Hz), 5.19 (d, 1 H, OCH_2, *J* = 12 Hz), 5.14 (d, 1 H, OCH_2, *J* = 12 Hz), 4.86 (s, 1 H, C-5 H), 4.54 and 4.51 (2 d, 1 H, C-7 H, *J* = 1.9, 1.9 Hz), 2.33 (s, 3 H, NCH_3), 1.28 (t, 3 H, CH_3, *J* = 6.9 Hz), 1.16 (t, 3 H, CH_3, *J* = 6.9 Hz); CI-MS *m/z* 448 ($M^+ + 1$). Anal. ($C_{28}H_{33}NO_4 \cdot 0.7MeOH$) C, H, N.

3-(Benzyloxy)-4,5α-epoxy-14-ethoxy-*N*-methylmorphinan-6-one (21). A solution of **20** (1.9 g, 4.3 mmol) in 40 mL of EtOH and 4 mL of concentrated HCl was refluxed for 80 min and then evaporated. The residue was partitioned between dilute NH_4OH (30 mL) and CH_2Cl_2 (40 mL). The organic phase was washed with H_2O (2 × 30 mL), dried (Na_2SO_4), and evaporated to give 2.1 g of a yellow oil which was crystallized from 1.5 mL of MeOH to yield 1.3 g (72%) of **21** as colorless crystals. A small portion was recrystallized for analysis: mp 123–126 °C; IR (KBr) 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (m, 5 H, ArH), 6.68 (d, 1 H, ArH, *J* = 8.2 Hz), 6.53 (d, 1 H, ArH, *J* = 8.2 Hz), 5.26 (d, 1 H, OCH_2, *J* = 12 Hz), 5.19 (d, 1 H, OCH_2, *J* = 12 Hz), 4.65 (s, 1 H, C-5 H), 2.34 (s, 3 H, NCH_3), 1.26 (t, 3 H, CH_3, *J* = 6.8 Hz); CI-MS *m/z* 420 ($M^+ + 1$). Anal. ($C_{26}H_{29}NO_4$) C, H, N.

3-(Benzyloxy)-14-ethoxy-4-hydroxy-*N*-methylmorphinan-6-one (22). Activated Zn powder (3.94 g, 60.23 mmol) was added in portions to a refluxing mixture of **21** (1.97 g, 3.1 mmol), NH_4Cl (3.94 g, 73.65 mmol), and MeOH (20 mL) within 5 min. The mixture was stirred under reflux for another 30 min and cooled, the inorganic solid was filtered off and washed with MeOH, and the filtrate was evaporated. The residue was alkalized with dilute NH_4OH and extracted with CH_2Cl_2 (3 × 40 mL); the combined organic layers were washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and evaporated. The foamy residue (2.06 g) was crystallized from 1.5 mL of MeOH to yield 1.24 g (63%) of **22** as colorless crystals. An analytical sample

was obtained by recrystallization from MeOH: mp 144–147 °C; IR (KBr) 3300 (OH), 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (m, 5 H, ArH), 6.71 (d, 1 H, ArH, J = 8.3 Hz), 6.53 (d, 1 H, ArH, J = 8.3 Hz), 5.00 (s, 2 H, OCH_2), 2.32 (s, 3 H, NCH_3), 1.27 (t, 3 H, CH_3, J = 6.9 Hz); CI-MS m/z 422 ($M^+ + 1$). Anal. ($C_{26}H_{31}NO_4$) C, H, N.

3-(Benzyloxy)-14-ethoxy-4-methoxy-*N*-methylmorphinan-6-one (23). A mixture of **22** (1.2 g, 2.85 mmol), K_2CO_3 (1.6 g, 11.57 mmol), and anhydrous DMF was gassed at room temperature with N_2 for 30 min. Then, phenyltrimethylammonium chloride (1.64 g, 9.54 mmol) was added, and the resulting mixture was stirred under N_2 at 80 °C (bath temperature) for 3 h. After filtration and washings with CH_2Cl_2, the filtrate was evaporated to give a brown oily residue (1.3 g) which was purified by column chromatography (alumina basic grade II; elution with CH_2Cl_2) to yield 1.07 g (84%) of **23** as a slightly yellow oil (pure by TLC and spectral analysis): ^1H NMR (Me_2SO-d_6) δ 7.38 (m, 5 H, ArH), 6.96 (d, 1 H, ArH, J = 8 Hz), 6.81 (d, 1 H, ArH, J = 8 Hz), 5.03 (s, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 2.22 (s, 3 H, NCH_3), 1.20 (t, 3 H, CH_3, J = 6 Hz); CI-MS m/z 436 ($M^+ + 1$).

3-(Benzyloxy)-14-ethoxy-4-methoxymorphinan-6-one Hydrochloride (25·HCl). A mixture of **23** (1.16 g, 2.66 mmol), $NaHCO_3$ (2.3 g, 27.38 mmol), 1-chloroethyl chloroformate (2.7 mL, 24.74 mmol), and EtOH-free $ClCH_2CH_2Cl$ (12 mL) was stirred at 60–65 °C (bath temperature). The inorganic material was filtered off and washed with $ClCH_2CH_2Cl$, and the filtrate was evaporated to give 1.8 g of **24** as a brownish oil which was not further purified and characterized. This oil was dissolved in 20 mL of MeOH and refluxed for 1 h. Evaporation afforded 1.4 g of a brown oil which was crystallized from 1 mL of MeOH to yield 920 mg (47%) of pure **25**·HCl: mp 155–158 °C; IR (KBr) 3400 ($^+NH_2$), 1719 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.20 and 8.80 (2 br s, $^+NH_2$), 7.37 (m, 5 H, ArH), 6.87 (d, 1 H, ArH, J = 8 Hz), 6.78 (d, 1 H, ArH, J = 8 Hz), 5.02 (s, 2 H, OCH_2), 3.98 (s, 3 H, OCH_3), 1.47 (t, 3 H, CH_3, J = 6 Hz); CI-MS m/z 422 ($M^+ + 1$). Anal. ($C_{26}H_{31}NO_4$·HCl·1MeOH) C, H, N.

3-(Benzyloxy)-*N*-(cyclopropylmethyl)-14-ethoxy-4-methoxymorphinan-6-one (26). A mixture of **25**·HCl (890 mg, 1.94 mmol), K_2CO_3 (1.2 g, 8.68 mmol), cyclopropylmethyl chloride (0.21 mL, 2.29 mmol), and anhydrous DMF (5 mL) was stirred at 90 °C (bath temperature) for 17 h. The inorganic solid was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The crystalline residue (850 mg) was recrystallized from 1 mL of MeOH to afford 607 mg (71%) of pure **26**: mp 154–157 °C; IR (KBr) 1702 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (m, 5 H, ArH), 6.78 (d, 1 H, ArH, J = 8 Hz), 6.69 (d, 1 H, ArH, J = 8 Hz), 5.02 (s, 2 H, OCH_2), 3.95 (s, 3 H, OCH_3), 1.28 (t, 3 H, CH_3, J = 6 Hz); CI-MS m/z 476 ($M^+ + 1$). Anal. ($C_{30}H_{37}NO_4$) H, N; C: calcd, 75.77; found, 75.33.

***N*-(Cyclopropylmethyl)-14-ethoxy-3-hydroxy-4-methoxymorphinan-6-one Hydrobromide (6·HBr).** A mixture of **26** (540 mg, 1.14 mmol), Pd/C catalyst (60 mg), and MeOH (30 mL) was hydrogenated at room temperature at 40 psi for 20 h. The catalyst was filtered off and washed with MeOH, and the filtrate was evaporated. The residue (410 mg, reddish oil) was converted into the HBr salt (**6**·HBr) in the usual way (crystallized from MeOH; 295 mg, 52%). An analytical sample was obtained upon recrystallization from MeOH: mp 241–243 °C dec; IR (KBr) 3500 and 3260 (OH, ^+NH), 1705 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.35 and 8.15 (2 s, OH, ^+NH), 6.83 (d, 1 H, ArH, J = 8 Hz), 6.75 (d, 1 H, ArH, J = 8 Hz), 3.81 (s, 3 H, OCH_3), 1.37 (t, 3 H, CH_3, J = 6 Hz); CI-MS m/z 467 ($M^+ + 1$). Anal. ($C_{23}H_{31}NO_4$·HBr·1MeOH) C, H, N.

3-(Benzyloxy)-*N*-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxymorphinan-6-one (28).[20] A mixture of naltrexone hydrochloride (**27**·HCl; 10 g, 26.5 mmol), K_2CO_3 (10 g, 72.4 mmol), benzyl bromide (3.53 mL, 29.7 mmol), and anhydrous DMF (100 mL) was stirred at room temperature under N_2 for 22 h. The inorganic material was filtered off, washed with CH_2Cl_2, and evaporated. The oily residue was dissolved in 500 mL of 2 N HCl, washed with Et_2O (2 × 200 mL), and alkalized with concentrated NH_4OH. The colorless precipitation was collected, washed subsequently with H_2O and petroleum ether, and dried to yield 10.6 g (93%) of **28** as colorless crystals: mp 104–106 °C (lit.[20] mp 135–136 °c); IR ($CHCl_3$) 3333 (OH), 1722 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, ArH), 6.65 (d, 1 H, ArH, J = 8 Hz), 6.49 (d, 1 H, ArH, J = 8 Hz), 5.20 (d, 1 H, OCH_2, J = 12 Hz), 5.15 (d, 1 H, OCH_2, J = 12 Hz), 4.61 (s, 1 H, C-5 H); CI-MS m/z 432 ($M^+ + 1$). Anal. ($C_{27}H_{29}NO_4$·0.1H_2O) C, H, N.

3-(Benzyloxy)-*N*-(cyclopropylmethyl)-4,14-dihydroxymorphinan-6-one (29). Activated zinc powder (13.34 g, 200.1 mmol) was added to a refluxing mixture of **28** (9.59 g, 22.2 mmol), NH_4Cl (13.34 g, 244.5 mmol), and MeOH (50 mL) within 5 min. After stirring and refluxing for another 40 min, the mixture was cooled to room temperature, the inorganic solid filtered off and washed with MeOH, and the filtrate evaporated. The residue was alkalized with dilute NH_4OH and extracted with CH_2Cl_2/MeOH (3:1) (3 × 100 mL). The combined organic layers were washed subsequently with H_2O (100 mL) and brine (70 mL), dried (Na_2SO_4), and evaporated to yield 9.44 g of a crystalline residue which was recrystallized from MeOH to give pure (7.31 g, 76%) **29**: mp 135–137 °C; IR (KBr) 3400 (OH), 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5 H, ArH), 6.71 (d, 1 H, ArH, J = 8.2 Hz), 6.52 (d, 1 H, ArH, J = 8.2 Hz), 5.00 (s, 2 H, OCH_2); CI-MS m/z 434 ($M^+ + 1$). Anal. ($C_{27}H_{31}NO_4$·0.1MeOH) C, H, N.

3-(Benzyloxy)-*N*-(cyclopropylmethyl)-14-hydroxy-4-methoxymorphinan-6-one Hydrobromide (30·HBr). A mixture of **29** (6 g, 13.84 mmol), K_2CO_3 (5.58 g, 40.5 mmol), phenyltrimethylammonium chloride (4.85 g, 28.1 mmol), and anhydrous DMF (70 mL) was stirred under N_2 at 80 °C (bath temperature) for 4 h. The inorganic solid was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The brownish oily residue was dissolved in 90 mL of CH_2Cl_2, washed subsequently with H_2O (1 × 125 mL, 1 × 75 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated. The oily residue (8 g) was converted into the HBr salt (**30**·HBr) in the usual manner, yield 6.29 g (86%) (MeOH/Et_2O). An analytical sample was obtained by recrystallization of a small amount from MeOH/Et_2O: mp >247 °C dec; IR (KBr) 3200 and 3100 (OH, ^+NH), 1700 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.96 and 6.27 (2 s, 2 H, OH, ^+NH), 7.38 (m, 5 H, ArH), 7.08 (d, 1 H, ArH, J = 8.2 Hz), 6.87 (d, 1 H, ArH, J = 8.2 Hz), 5.09 (d, 1 H, OCH_2, J = 11.6 Hz), 5.04 (d, 1 H, OCH_2, J = 11.6 Hz), 3.83 (s, CH_3O); CI-MS m/z 448 ($M^+ + 1$). Anal. ($C_{28}H_{33}NO_4$·HBr·0.3H_2O) C, H, N, Br.

***N*-(Cyclopropylmethyl)-3,14-dihydroxy-4-methoxymorphinan-6-one Hydrobromide (7·HBr).** A mixture of **30**·HBr (1 g, 1.89 mmol), 10% Pd/C catalyst (100 mg), and MeOH (50 mL) was hydrogenated at room temperature and 30 psi for 16 h. The catalyst was filtered off and washed with MeOH, and the filtrate was evaporated. The resulting colorless foam (940 mg) was crystallized from MeOH/Et_2O to yield 480 mg (58%) of **7**·HBr. Recrystallization from MeOH gave an analytical sample: mp >245 °C dec; IR (KBr) 3350 and 3200 (OH, ^+NH), 1700 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.29, 8.94, and 6.23 (3 s, 3 H, 2 OH, ^+NH), 6.79 (d, 1 H, ArH, J = 8.2 Hz), 6.72 (d, 1 H, ArH, J = 8.2 Hz), 3.90 (s, 3 H, OCH_3); CI-MS m/z 358 ($M^+ + 1$). Anal. ($C_{21}H_{27}NO_4$·HBr·0.9H_2O) C, H, N.

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