402 J. Med. Chem. 2010, 53, 402–418
DOI: 10.1021/jm9013482

Journal of Medicinal Chemistry Article

Synthesis and Opioid Receptor Binding Affinities of 2-Substituted and 3-Aminomorphinans: Ligands for μ, κ, and δ Opioid Receptors

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Received September 10, 2009

The phenolic group of the potent μ and κ opioid morphinan agonist/antagonists cyclorphan and butorphan was replaced by phenylamino and benzylamino groups including compounds with para-substituents in the benzene ring. These compounds are highly potent μ and κ ligands, e.g., *p*-methoxyphenylaminocyclorphan showing a K_i of 0.026 nM at the μ receptor and a K_i of 0.03 nM at the κ receptor. Phenyl carbamates and phenylureas were synthesized and investigated. Selective *o*-formylation of butorphan and levorphanol was achieved. This reaction opened the way to a large set of 2-substituted 3-hydroxymorphinans, including 2-hydroxymethyl-, 2-aminomethyl-, and N-substituted 2-aminomethyl-3-hydroxymorphinans. Bivalent ligands bridged in the 2-position were also synthesized and connected with secondary and tertiary aminomethyl groups, amide bonds, and hydroxymethylene groups, respectively. Although most of the 2-substituted morphinans showed considerably lower affinities compared to their parent compounds, the bivalent ligand approach led to significantly higher affinities compared to the univalent 2-substituted morphinans.

Introduction

Within the group of opioid ligands with a morphinan structure the phenolic group in the 3-position is historically regarded as a requirement for high affinity interactions with a respective H-bond accepting site of the opioid receptor.[1,2] Others have shown that replacing the phenolic group in the opioid antagonist naltrindole[3] and in morphine[4] with alkyl or aryl groups greatly reduces affinity.

Hepatic first-pass metabolism after oral administration by O-glucoronidation of the phenolic group is a common feature of these opioid ligands and determines their pharmacokinetic behavior, bioavailability, and therapeutic application.[5,6] Morphine administered orally, for example, has only approximately one-quarter the bioavailability compared to a parenterally administered dose.[6]

We have previously shown that a 2-aminothiazole moiety can replace the phenolic group bioisosterically yielding compounds showing high potencies.[7] Wentland's group has also shown that the phenolic group in certain opioids (morphine, cyclazocine) can be replaced by primary or secondary amino groups to yield compounds with good affinities.[8,9] Substituting morphine's OH group with NH_2, CH_3NH, phenyl-NH, or benzyl-NH yielded compounds with decreased affinities compared to morphine, with two-digit nanomolar affinities at the μ receptor subtype.[8] Wentland prepared amino derivatives of the potent opioid cyclazocine, which showed subnanomolar affinities for κ and/or μ receptor subtypes.[9] The primary amino derivative of cyclazocine was 5-fold less potent in a rodent antinociception model when administered subcutaneously but equipotent when administered orally. The phenylamine and benzylamine compounds showed subnanomolar affinity at κ and μ receptors, respectively.[9]

There are several findings that show that additional aromatic moieties are tolerated or even beneficial at the 3-position of morphinans. This may be due to the presence of three phenylalanine residues in the μ receptor, information derived from a homology model of the receptor interacting with the antagonist norBNI.[10] We have previously reported carbamate derivatives of levorphanol (**1**), butorphan (**3b**), and cyclorphan (**3a**).[11] Carboxamido analogues of cyclazocine and ethylketocyclazocine bearing a biphenyl unit also showed subnanomolar affinities at both μ and δ receptors.[12] These findings suggest that the introduction of an additional aromatic moiety connected at the 3-position can lead to active compounds without the necessity of the phenolic group.

The highly potent benzyl and especially phenyl carbamates[11] of **3a**/**3b** suggest a promising lead for the development of SPECT ligands (^{123}I for SPECT). The κ receptor has been implicated as a primary target for the development for pharmacotherapies for the treatment of cocaine dependence,[13−15] Thus *p*-iodophenyl carbamates were synthesized and evaluated for their affinity and selectivity profiles. Since primary urea derivatives of the 3-aminomorphinans showed similar high affinities to their parent amino compounds,[16] the phenylureas and *p*-iodophenylureas were also synthesized and evaluated (Figure 1).

High affinity opioid ligands bearing a 3-phenylamino or a 3-benzylamino group were also synthesized and evaluated pharmacologically (Figure 1).

We also report here the synthesis of a series of 2-substituted analogues of **1** and **3b** using a regioselective ortho-formylation method as the key step. The salicylaldehydes obtained by this

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 Published on Web 11/23/2009

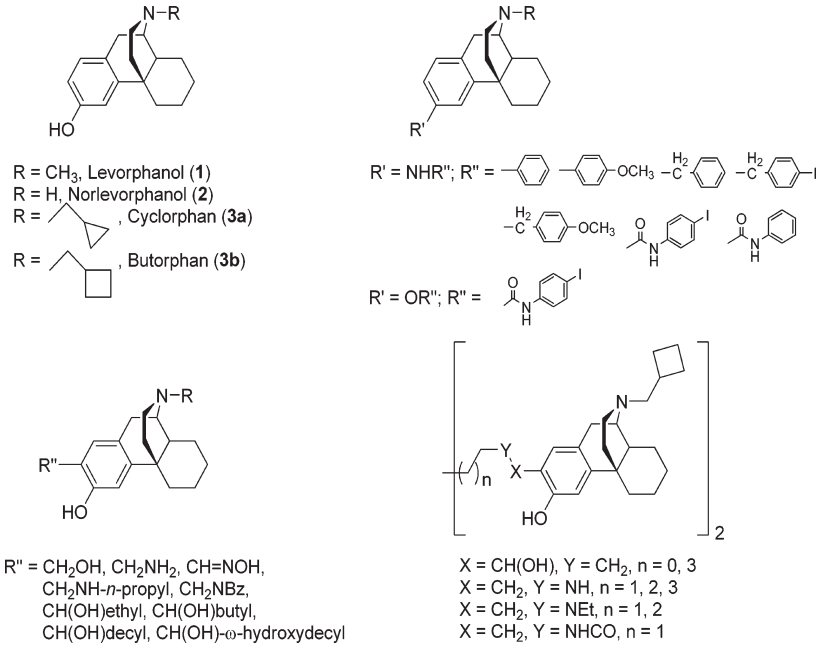


Figure 1. Structures of ligands related to levorphanol (**1**), cyclorphan (**3a**), and butorphan (**3b**).

method provide a structural prototype for the preparation of 2-substituted analogues of **1** and represent a useful starting point for the preparation of bivalent compounds connected at the 2-position, keeping the basic nitrogen and the phenol moiety as important pharmacophoric elements unchanged. We present preliminary information concerning the SAR of such bivalent ligands bridged at the 2-position. Bivalent ligands containing an aminomethyl group in the 2-position could be synthesized with different spacer lengths containing either secondary amino groups (therefore bearing both hydrogen bond accepting and donating properties) or tertiary amino groups (showing only H-bond accepting properties and being sterically more demanding). Furthermore, it was possible to connect two 2-aminomethylbutorphan molecules as diamides lacking any basicity of the N atoms and bivalent ligands without N atoms in the spacer but bearing two hydroxy groups (Figure 1).

Chemistry

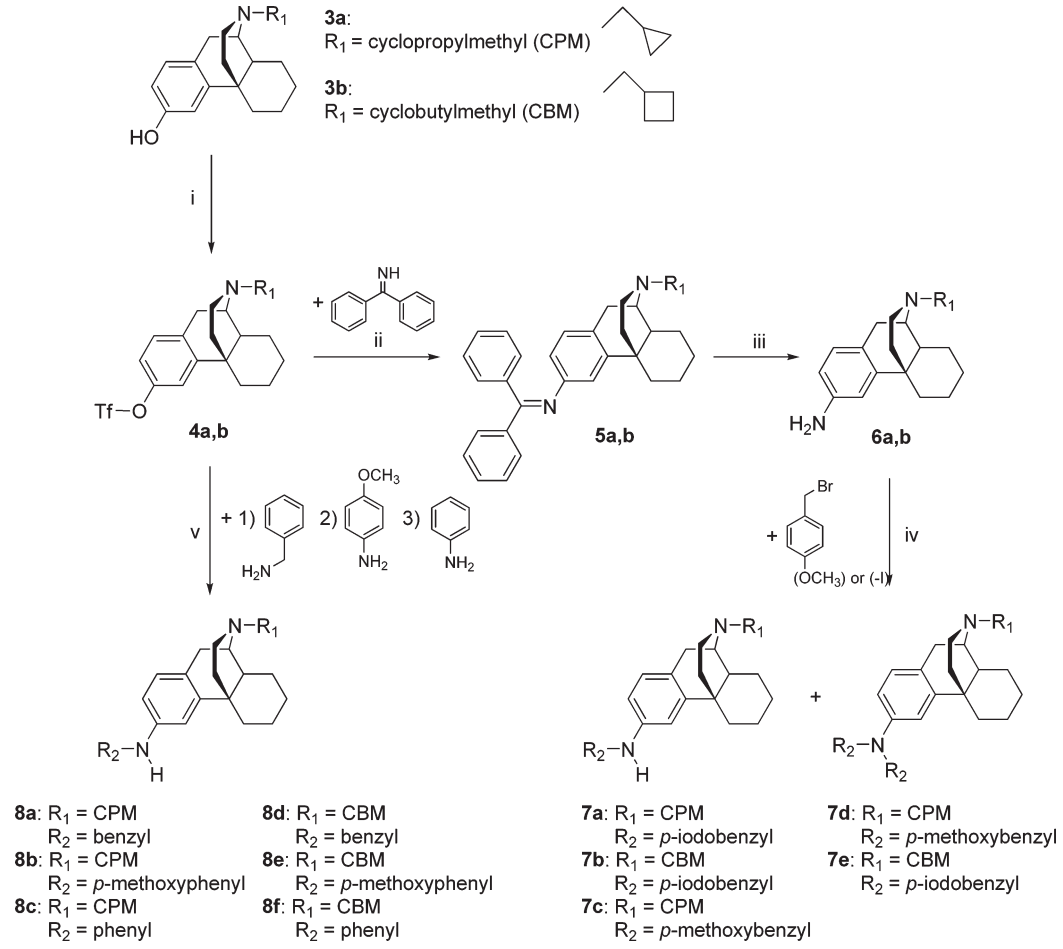
The starting material for the synthesis of all target compounds is the commercially available (−)-3-hydroxy-*N*-methylmorphinan (levorphanol) tartrate, which after conversion to its free base (**1**) could be demethylated to norlevorphanol (**2**) and alkylated with either (bromomethyl)cyclopropane or (bromomethyl)cyclobutane to yield **3a** and **3b**, respectively (Scheme 1).[17] In the presence of pyridine, the triflates (**4a**,**b**) were formed, which could be coupled in a Buchwald−Hartwig reaction,[18] in this case using tris(dibenzylideneacetone)-dipalladium(0) [$Pd_2(dba)_3$] as Pd catalyst, bis(diphenylphosphino)ferrocene (dppf) as ligand, and sodium *tert*-butoxide as a strong base, to yield the benzyl (**8a**,**d**), *p*-methoxyphenyl (**8b**,**e**) and phenyl compounds (**8c**,**f**) directly, albeit in moderately low yields (Scheme 1).[18,19]

For the preparation of the *p*-iodobenzylaminomorphinans (**7a**,**b**) the triflates of **3a** (**4a**) and **3b** (**4b**), respectively, were converted to their 3-aminomorphinans (**6a**,**b**) through Pd catalysis ($Pd(OAc)_2$ and *rac*-BINAP as ligand). Coupling to benzophenone imine in the presence of cesium carbonate resulted in the formation of (diphenylmethylene)morphinan-3-imines (**5a**,**b**). These catalytic conditions enable working in a far less oxygen-sensitive reaction environment. Subsequent cleavage with hydroxylamine hydrochloride leads to the 3-aminomorphinans (**6a**,**b**; Scheme 1).[20,21] Alkylation with 1-(bromomethyl)-4-iodobenzene yielded the *p*-iodobenzylmorphinans (**7a**,**b**) in moderate yield, while some formation of dialkylated product (**7e**) could be observed. In case of the cyclobutylmethyl compound, this dialkylated derivative (**7e**) was isolated. When using 1-(bromomethyl)-4-methoxybenzene to obtain the respective *p*-methoxy compound, the desired product **7c** was obtained in very low yields. The dialkylated product **7d** was formed predominantly, with monoalkylation being the less favored reaction.

For the synthesis of the 4-iodophenyl carbamates, **1**, **3a**, and **3b** were treated with 4-iodophenyl isocyanate, yielding the novel 4-iodophenyl carbamates in 61−80% yield (**9a**−**c**, Scheme 2; the unsubstituted phenyl carbamates have been described previously[11]). For the respective urea compounds, the 3-aminomorphinans **6a**,**b** and the 3-amino derivative of **1**[7a] (**6c**, 17-methylmorphinan-3-amine) were treated with phenyl isocyanate and 4-iodophenyl isocyanate, respectively, to yield the ureas **10a**−**e** in 61−70% yield (Scheme 2; the unsubstituted urea of **3b** was not synthesized because of the comparatively low affinities of compounds).

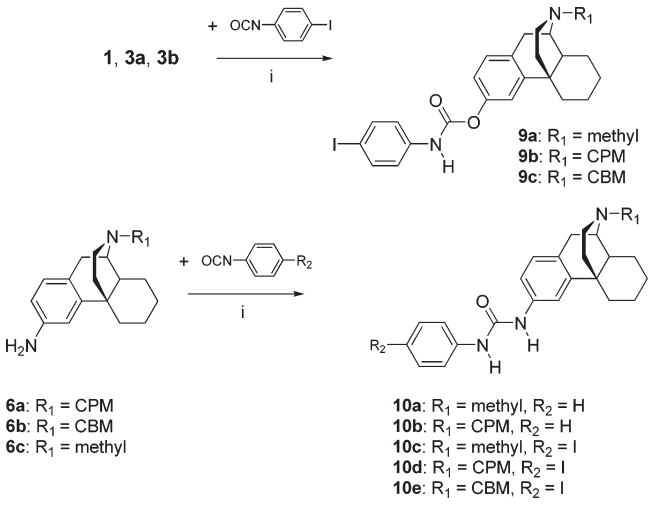
Ortho-formylation of **1** was first carried out as previously described for aporphines using a MeMgBr/HMPA (hexamethylphosphoramide) and paraformaldehyde reaction system.[22] The salicylaldehyde derivative was obtained in 46% yield; however, when the reaction was scaled up under these conditions, it was difficult to remove the HMPA completely from the product. When ortho-formylation of **1** was conducted using $MgCl_2-Et_3N$ base system and paraformaldehyde,[23] ortho-formylation occurred exclusively at the 2-position. By use of these reaction conditions, ortho-formylation of **1** and **3b** yielded aldehydes **11** and **12** (Scheme 3). Further reduction gave the alcohols **13** and **14** (Scheme 3). The salicylaldehyde derivative **11** was also condensed with benzylamine followed by reduction to *N*-benzylsalicylamine **16**

Scheme 1[a]



[a] Reagents and conditions: (i) Tf_2O, pyridine, $CHCl_3$; (ii) (*rac*)-BINAP, $Pd(OAc)_2$, Cs_2CO_3, THF; (iii) NaOAc, $H_2NOH \cdot HCl$; (iv) K_2CO_3, EtOH; (v) $Pd_2(dba)_3$, dppf, sodium *tert*-butoxide, toluene, 80 °C.

Scheme 2[a]



[a] Reagents and conditions: (i) NEt_3, CH_2Cl_2.

(Scheme 3). Compound **16** could also be converted into the fused cyclic compound **17** (Scheme 3).

The aldehyde **12** was also condensed with hydroxylamine to yield its oxime **18**, which could be reduced with hydrogen over Pd/C in acidic medium to give the 2-aminomethylbutorphan **19** (Scheme 4).[24] Compound **12** was condensed with *n*-propylamine followed by reduction to obtain the *N*-*n*-propyl amine **21**. The bivalent ligands **22a**−**c** were prepared by condensation of the aldehyde **12** with diamines, yielding diimines **21a**−**c** followed by reduction with $NaBH_4$ (Scheme 4). The bivalent ligands **24a** and **24b** bearing an additional ethyl group at the amine function were prepared by the reaction of **22a**,**b** with excess acetyl chloride followed by reduction with $LiAlH_4$ (Scheme 4; here only the spacer lengths with 8 and 10 atoms were realized).

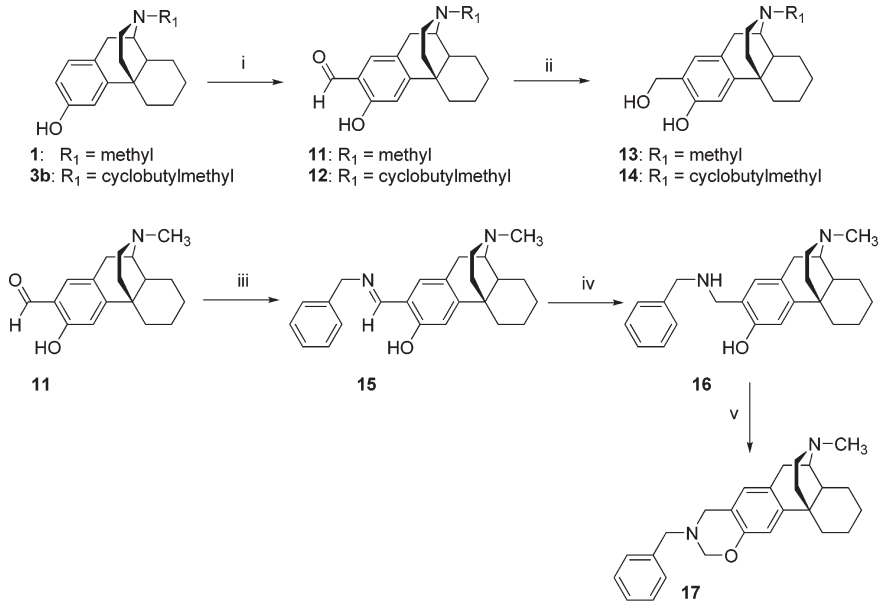
Furthermore, the aldehyde **12** was treated with EtMgBr to obtain **25** (Scheme 5). When the aldehyde **12** was treated with Grignard reagent prepared from 1,4-dibromobutane, the bivalent ligand **26a** and the univalent ligand **27a** were obtained. Similarly, **12** was treated with the Grignard reagent from 1,10-dibromodecane. The bivalent ligand **26b** and the univalent ligands **27b** and **28** were obtained (Scheme 5).

Reacting 2-aminomethylbutorphan **19** with adipic acid yielded a bivalent ligand bridged in position 2 (**29**) without the basic nitrogen atoms in the linking chain.

Results and Discussion

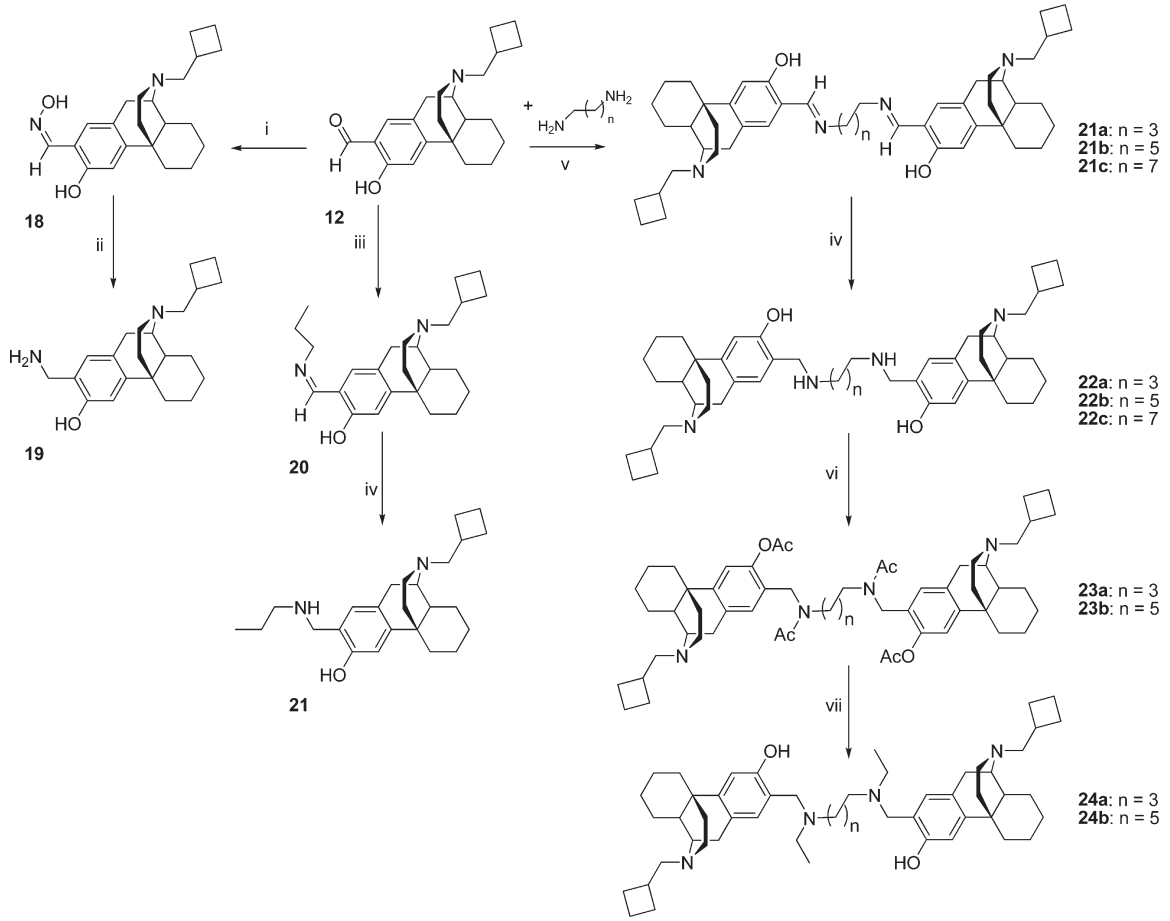
All the novel univalent and bivalent ligands were examined for their affinity and selectivity for μ, κ, and δ opioid receptors with Chinese hamster ovary (CHO) cells stably expressing one of the human opioid receptors. The data are shown in Table 1. It is noted that the lead compounds **3a** and **3b** already represent extremely potent compounds with subnanomolar

Scheme 3[a]



[a] Reagents and conditions: (i) $MgCl_2$ anhydrous, NEt_3, $(HCHO)_n$, THF, reflux; (ii) $NaBH_4$, MeOH; (iii) $BnNH_2$, MeOH; (iv) $NaBH_4$, MeOH; (v) $(HCHO)_n$, MeOH, reflux.

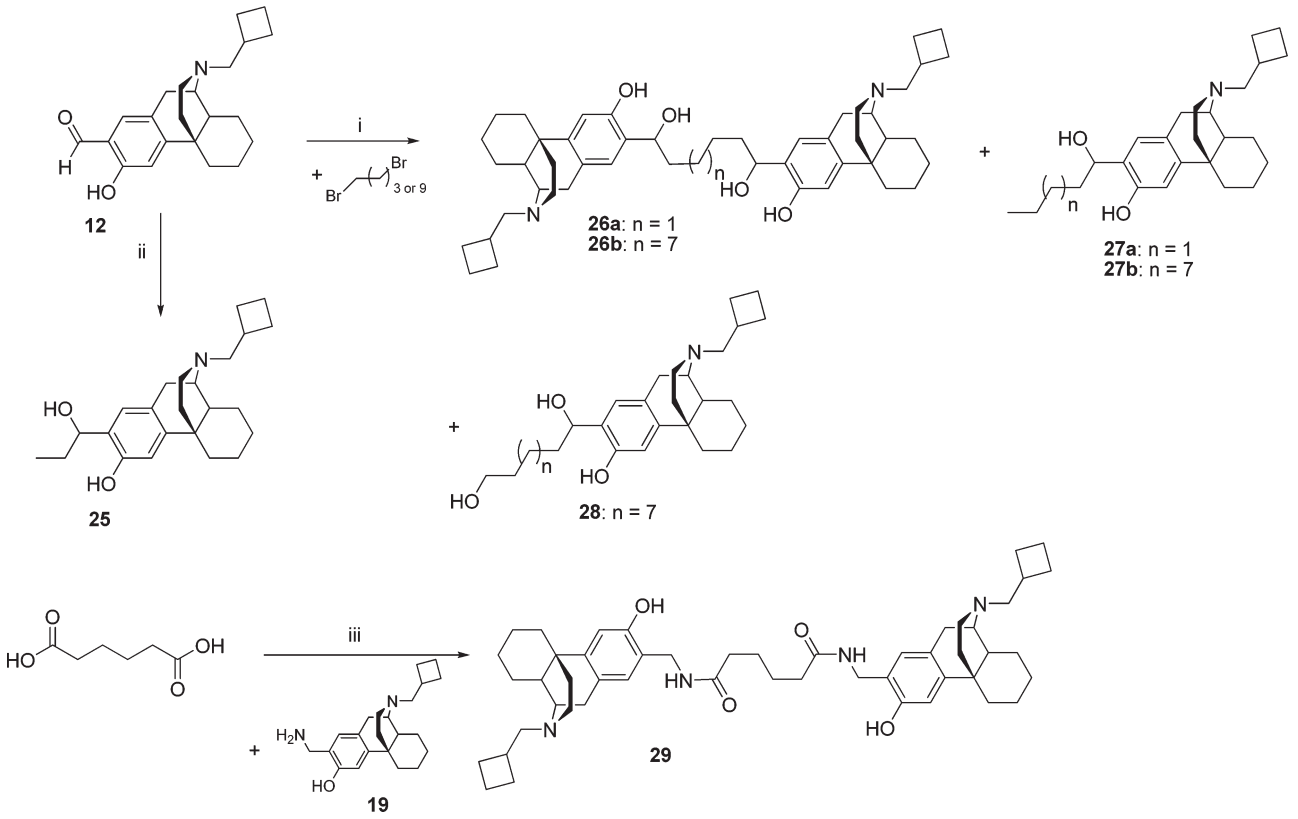
Scheme 4[a]



[a] Reagents and conditions: (i) $H_2NOH \cdot HCl$, MeOH; (ii) H_2, Pd/C, HCl; (iii) *n*-$PrNH_2$, MeOH; (iv) $NaBH_4$, MeOH; (v) 1,4-diaminobutane (or 1,6-diaminohexane or 1,8-diaminooctane), MeOH; (vi) excess acetyl chloride, NEt_3, CH_2Cl_2; (vii) $LiAlH_4$, THF.

affinities at μ and κ receptors. Concerning the 3-aminomorphinans, a number of highly potent compounds could be identified: If the phenol is replaced by a benzylamino group (**8a** and **8d**), a roughly 10-fold decrease in affinity at μ and κ

Scheme 5[a]



[a] Reagents and conditions: (i) 1,4-dibromobutane or 1,10-dibromodecane, Mg, THF; (ii) EtMgBr, THF; (iii) (1) $(COCl)_2$, cat. DMF, NEt_3, CH_2Cl_2; (2) 2-(aminomethyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (**19**), NEt_3, CH_2Cl_2.

receptors is observed and at the δ receptor a 76-fold and 112-fold decrease in affinity are observed. Substitution in para-position (**7c**, $-OCH_3$) does not significantly alter binding affinities, and an iodine atom in para-position (**7a** and **7b**) leads only to a minor decrease in binding affinities.

Since the 3-phenolic group is generally considered as an important pharmacophore in morphinans, it is of interest to note that a benzylamino group can replace the phenolic group to yield compounds with decreased, albeit still high, affinities. In this regard it is also noteworthy that compounds **7d** and **7e**, in which tertiary dibenzylamino groups replace the phenolic group, retain nanomolar affinity. These compounds no longer bear an H-bond donor and are sterically hindered.

The morphinans with phenylamino groups in position 3 are even more potent ligands (**8b**,**c**,**e**,**f**). Although the CBM compound **8f** shows lower affinities than butorphan at μ and κ, the CPM compound **8c** has an affinity of 0.080 nM at μ and 0.047 nM at κ with 70-fold selectivity δ/μ. Substitution with a *p*-methoxy group further increases affinities with 0.61 nM at μ and 0.59 nM at κ for the CBM compound **8e** and 0.026 nM at μ and 0.030 nM at κ for the CPM compound **8b** with 65-fold selectivity δ/μ. Compound **8b** is thus the most potent compound synthesized in this 3-aminomorphinan series, exceeding butorphan and cyclorphan in terms of affinity and selectivity.

For the phenylurea derivates the affinities range from the low nanomolar range (**10b**) to the higher nanomolar range (**10c** and **10e**). For the CPM phenylurea compound **10b**, its *p*-iodo derivate **10d** shows roughly 10-fold decrease in affinity. The carbamates **9a**,**b** show high affinities in the subnanomolar range at μ and κ receptors, again with the CPM compound showing higher affinities. Interestingly, the *p*-iodo-substituted carbamate of **1** (**9a**) shows a remarkable 470-fold selectivity of δ/μ being the most selective compound in the series of compounds described in this study. Compared with the unsubstituted carbamates described previously,[11] the *p*-iodo compounds show lower affinities.

The 2-substituted compounds generally had lower affinities when compared to the highly potent **3b** and **3a**. The 2-hydroxymethyl analogues **13** ($-NCH_3$) and **14** (−N-CBM) show lower affinities at all receptors. The 2-oxime **18** is the most potent compound in the series of 2-substituted compounds synthesized with an affinity of 3.8 nM at the μ receptor and 0.62 nM at the κ receptor. The 2-aminomethyl compound (**19**) and the monobenzylated (**16**) and monopropylated (**21**) derivatives have only submicromolar affinities at κ and μ receptors. Bivalent ligands bridged at secondary amines (**24a**−**c**) are only moderately active, albeit less active than bivalent ligands bridged at the 3-position.[25] When the secondary amine functions in the spacer are ethylated (**24a** with 8 spacer atoms and **24b** with 10 spacer atoms), affinities significantly decrease further. The univalent compounds **25**, **27a**, and **28** show comparatively low affinities. Concerning all compounds with 1-hydroxyalkyl substituents in position 2 (**25**, **26a**,**b**, **27a**,**b**, **28**), the most potent is the 1-hydroxypentyl compound (**27a**) with 17 and 13 nM at μ and κ and the least potent is the 1-hydroxypropyl compound (**25**) with 180 and 72 nM at μ and κ, respectively. Obviously, a longer alkyl chain considerably increases affinities. The respective bivalent compounds **26a**,**b** do not show significantly higher affinities. The only amide-bridged bivalent ligand **29** shows affinities of 36 nM at μ and 30 nM at κ.

Table 1. K_i Values for the Inhibition of μ, δ, and κ Opioid Binding to CHO Membranes

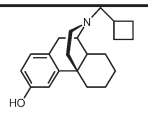
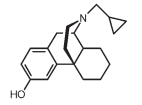
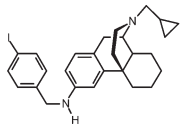
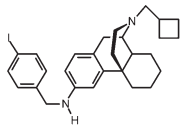
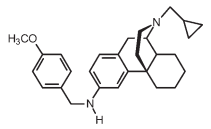
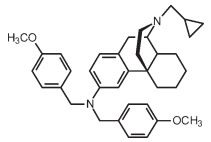
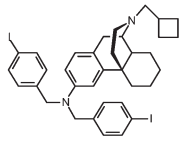
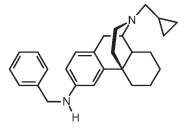
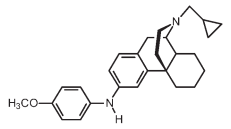
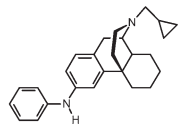
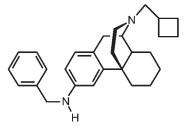
Compound/Structure	K_i (nM) ± SE			Selectivity
	[^{3}H]DAMGO (μ)	[^{3}H]U69,593 (κ)	[^{3}H]Naltrindole (δ)	μ / κ / δ
Butorphan (3b[a]) 	0.23 ± 0.01	0.079 ± 0.003	5.9 ± 0.55	1 / 0.3 / 25
Cyclorphan (3a[a]) 	0.062 ± 0.003	0.034 ± 0.002	1.9 ± 0.072	1 / 0.6 / 31
7a 	0.71 ± 0.074	0.79 ± 0.020	34 ± 3.6	1 / 1.1 / 48
7b 	5.4 ± 0.66	5.8 ± 0.11	190 ± 12	1 / 1.1 / 35
7c 	0.31 ± 0.010	0.51 ± 0.031	20 ± 2.1	1 / 2 / 65
7d 	2.5 ± 0.34	3.9 ± 0.20	120 ± 2.5	1 / 2 / 48
7e 	16 ± 1.6	16 ± 0.42	960 ± 58	1 / 1 / 60
8a 	0.26 ± 0.012	0.34 ± 0.031	29 ± 4.4	1 / 1.4 / 112
8b 	0.026 ± 0.0021	0.030 ± 0.0037	1.7 ± 0.10	1 / 1 / 65
8c 	0.080 ± 0.005	0.047 ± 0.0035	5.4 ± 0.11	1 / 0.5 / 68
8d 	1.7 ± 0.053	2.8 ± 0.33	130 ± 11	1 / 1.6 / 76

Table 1. Continued

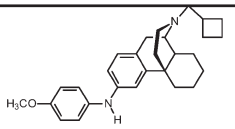
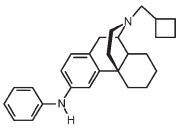
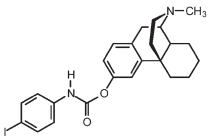
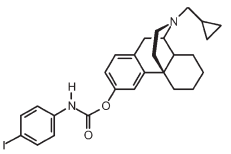
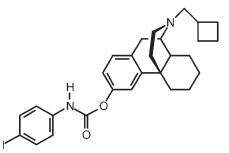
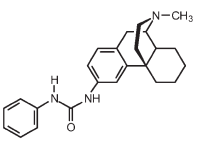
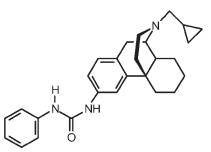
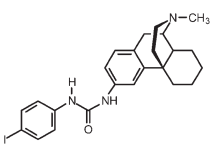
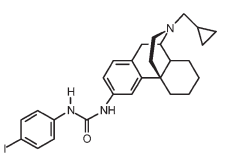
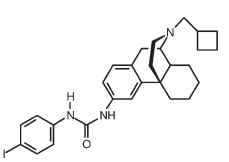
Compound/Structure		K_i (nM) ± SE [^{3}H]DAMGO (μ)	[^{3}H]U69,593 (κ)	[^{3}H]Naltrindole (δ)	Selectivity μ / κ / δ
8e		0.61 ± 0.02	0.59 ± 0.0056	19 ± 1.7	1 / 1 / 3
8f		1.7 ± 0.24	1.5 ± 0.17	39 ± 3.5	1 / 1 / 2
9a		0.34 ± 0.023	5.2 ± 0.034	160 ± 10	1 / 15 / 4
9b		0.58 ± 0.025	0.60 ± 0.014	14.6 ± 0.76	1 / 1 / 24
9c		1.1 ± 0.11	0.99 ± 0.047	67 ± 5.6	1 / 1 / 68
10a		11 ± 1.00	340 ± 19	320 ± 3.2	1 / 31 / 29
10b		3.9 ± 0.28	1.6 ± 0.15	16 ± 1.5	1 / 0.5 / 4
10c		17 ± 1.7	280 ± 8.3	300 ± 6.8	1 / 16 / 18
10d		23 ± 0.97	12 ± 1.0	94 ± 7.1	1 / 0.5 / 4
10e		24 ± 0.97	28 ± 2.2	250 ± 24	1 / 0.5 / 4

Table 1. Continued

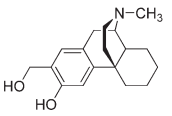
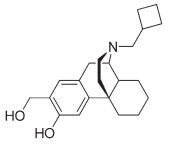
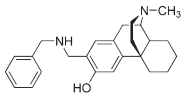
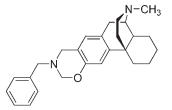
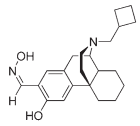
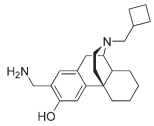
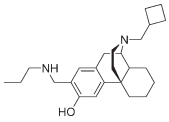
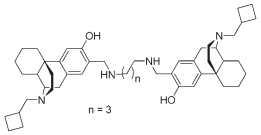
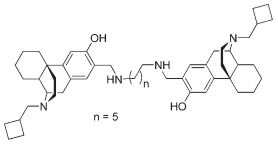
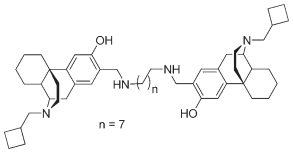
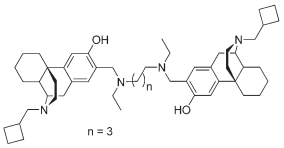
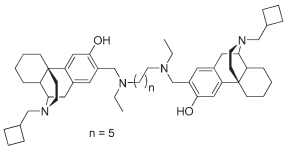
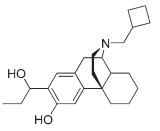
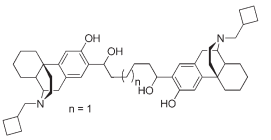
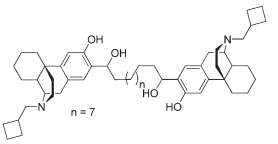
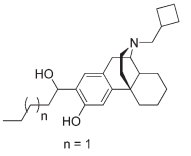
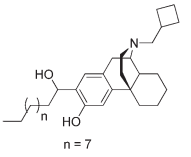
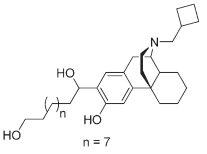
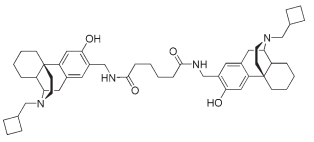
Compound/Structure	K_i (nM) ± SE [^{3}H]DAMGO (μ)	[^{3}H]U69,593 (κ)	[^{3}H]Naltrindole (δ)	Selectivity μ / κ / δ
13 	15 ± 1.5	40 ± 4.2	1400 ± 121	1 / 3 / 93
14 	360 ± 27	86 ± 2.2	>10 μM	1 / 0.25 / >28
16 	190 ± 8.5	380 ± 30	>10 μM	1 / 2 / >50
17 	110 ± 6.2	310 ± 32	>10 μM	1 / 3 / >90
18 	3.8 ± 0.46	0.62 ± 0.058	180 ± 11	1 / 0.16 / 47
19 	290 ± 6.2	140 ± 6.7	>10 μM	1 / 0.5 / >35
21 	330 ± 55	350 ± 20	>10 μM	1 / 1 / >30
22a 	6.8 ± 1.7	4.9 ± 0.33	190 ± 12	1 / 0.7 / 28
22b 	76 ± 14	37 ± 2.3	850 ± 98	1 / 0.5/ 12
22c 	24 ± 1.2	40 ± 1.8	1000 ± 85	1 / 2 / 42
24a 	160 ± 1.9	44 ± 2.4	1100 ± 31	1 / 0.3 / 7

Table 1. Continued

Compound/Structure	K_i (nM) ± SE [^{3}H]DAMGO (μ)	[^{3}H]U69,593 (κ)	[^{3}H]Naltrindole (δ)	Selectivity μ / κ / δ
24b 	64 ± 1.1	54 ± 4.6	710 ± 11	1 / 1 / 13
25 	180 ± 21	72 ± 3.1	>10 μM	1 / 0.3 / > 70
26a 	74 ± 2.3	67 ± 5.6	1,600 ± 110	1 / 1 / 24
26b 	35 ± 2.1	31 ± 4.4	730 ± 100	1 / 1 / 24
27a 	17 ± 0.53	13 ± 1.0	72 ± 2.1	1 /1 / 6
27b 	36 ± 3.0	26 ± 1.6	610 ± 51	1 / 1 / 23
28 	36 ± 3.0	26 ± 1.6	610 ± 51	1 / 1 / 23
29 	36 ± 2.7	30 ± 2.0	630 ± 91	1 / 1 / 21

[a] Reference 7a.

Conclusion

3-Aminobenzyl and 3-aminophenyl derivatives of **3a** and **3b** were synthesized, and it was demonstrated that these pharmacophores could replace the phenolic group to yield high affinity opioid ligands. 3-Phenylureas and carbamates were

synthesized with the 3-phenyl carbamates being nano- and subnanomolar ligands at μ and κ receptors.

Experimental Section

General Synthetic Methods. ^{1}H (and ^{13}C NMR) spectra were recorded at 300 MHz (75 MHz) using $CDCl_3$ as solvent on a Varian Mercury 300 spectrometer. Chemical shifts are given as δ value (ppm) downfield from tetramethylsilane as an internal reference. Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. Elemental analyses, performed by Atlantic Microlabs, Atlanta, GA, were within ±0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2 micrometer Kieselgel 60F-254 silica gel plastic sheets (EM Science, Newark, NJ). Flash chromatography was used for the routine purification of reaction products. Eluent systems are described for the individual compounds.

Synthesis of 17-(Cyclopropylmethyl)morphinan-3-ol (cyclorphan, 3a) and 17-(Cyclobutylmethyl)morphinan-3-ol (butorphan, 3b). 3a and **3b** were prepared as described,[17] and spectral/physical data are in accordance with literature data.[17]

Synthesis of 17-(Cyclopropyl/cyclobutylmethyl)morphinan-3-yl Trifluoromethanesulfonate (Cyclorphan/Butorphan Triflate, 4a,b). To a suspension of 4 mmol of **3a** or **3b**, respectively, in 25 mL of anhydrous chloroform was added 1.26 g (1.32 mL, 16 mmol) of pyridine, and a clear solution was formed. The mixture was put into an ice bath, and under N_2 an amount of 2.26 g (1.35 mL, 8 mmol) of trifluoromethane sulfonic anhydride (triflate anhydride) was added under ice-cooling. The mixture was allowed to reach room temperature, and stirring was continued overnight. TLC control (after microworkup) showed that no **3a/3b** remained. The organic phase was diluted with methylene chloride and washed with brine. The organic phase was dried over anhydrous sodium sulfate and the solvent evaporated. Heating under high vacuum was applied to remove excess pyridine. The residue was purified by column chromatography (EtOAc/NEt_3, 20/1) to yield the product as viscous oils. Spectral data were in accordance with literature data.[26]

17-(Cyclopropylmethyl)morphinan-3-yl Trifluoromethanesulfonate (4a). Colorless oil (47%). ^{13}C NMR ($CDCl_3$): 144.7, 140.0, 134.9, 125.7, 114.6, 114.5, 56.4, 51.7, 41.8, 41.0, 38.1, 34.6, 32.9, 23.1, 22.8, 20.7, 18.3, 5.8 ppm. ^{1}H NMR ($CDCl_3$): 7.17 (d, J = 9 Hz, 1H), 7.13 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 9, 2 Hz, 1H), 3.1 (m, 1H), 2.92 (d, J = 18 Hz, 1H), 2.31−2.88 (m, 4H), 1.81−2.05 (m, 3H), 1.57−1.68 (m, 2H), 1.08−1.42 (m, 7H), 0.86 (m, 1H), 0.51 (m, 2H), 0.10 (m, 2H) ppm.

17-(Cyclobutylmethyl)morphinan-3-yl Trifluoromethanesulfonate (4b). Light-brown viscous oil (76%). ^{13}C NMR ($CDCl_3$): 148.3, 143.6, 138.6, 129.3, 120.9, 118.24, 118.1, 61.4, 55.6, 45.4, 44.6, 41.7, 38.0, 36.4, 34.8. 27.9, 27.7, 26.7, 26.4, 24.5, 21.9, 18.8 ppm. ^{1}H NMR ($CDCl_3$): 7.17 (d, J = 9 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 9, 2.1 Hz, 1H), 3.1 (d, J = 18 Hz, 1H), 2.84 (m, 1H), 1.53−2.63 (m, 18H), 1.04−1.45 (m, 5H) ppm.

Synthesis of 17-(Cyclopropylmethyl/cyclobutylmethyl)morphinan-3-amine (6a,b). The 3-amino derivatives of cyclorphan and butorphan were prepared from the triflates (**4a**,**b**) in two steps as recently described.[7a] Spectral data are in accordance with the literature data.[7a]

17-(Cyclopropylmethyl)morphinan-3-amine (6a). ^{1}H NMR ($CDCl_3$): 6.86 (d, J = 8 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8, 2.4 Hz, 1H), 3.5 (bs, 2H), 3.05 (m, 1H), 2.83 (d, J = 18 Hz, 1H), 2.47−2.57 (m, 2H), 2.23−2.34 (m, 2H), 2.00 (m, 2H), 1.63−1.85 (m, 3H), 1.15−1.43 (m, 7H), 0.86 (m, 1H), 0.50 (m, 2H), 0.11 (m, 2H) ppm.

17-(Cyclobutylmethyl)morphinan-3-amine (6b). ^{1}H NMR ($CDCl_3$): 6.88 (d, J = 8 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 8, 2.4 Hz, 1H), 3.5 (bs, 2H), 2.90 (d, J = 18 Hz, 1H), 2.78 (bs, 1H), 2.40−2.56 (m, 5H), 2.21−2.25 (m, 1H), 1.63−2.15 (m, 10H), 1.12−1.48 (m, 7H) ppm.

General Procedure for the Synthesis of *N*-Benzyl-, *N*-Phenyl-, and *N*-(4-Methoxyphenyl)-17-cyclopropylmethyl/cyclobutylmethyl)morphinan-3-amines (8a−f) by Buchwald−Hartwig Coupling. A three-necked flask was equipped with an N_2 balloon, a septum, and a stopper. Through the neck the flask was charged under a mild N_2 stream with 1.4 mmol (2 equiv to triflate) of aniline (for preparation of **8c**,**f**)/benzylamine (for **8a**,**d**)/4-methoxyaniline (for **8b**,**e**), 81 mg (0.84 mmol, 1.2 equiv to triflate) of sodium *tert*-butoxide, 32 mg (0.035 mmol, 0.05 equiv to triflate) of tris(dibenzylideneacetone)dipalladium(0), and 58 mg (0.105 mmol, 0.15 equiv to triflate) of bis(diphenylphosphino)ferrocene. Nitrogen was flushed for 5 min over the solids. After this time, an amount of 5 mL of toluene, which had been degassed in a Schlenk flask prior to addition, was added via the septum. Under vigorous stirring the mixture was warmed to 80 °C. A solution of 0.7 mmol of cyclorphan triflate (3-trifluoromethyl-(sulfonyl)oxy-*N*-cyclopropylmethylmorphinan, for the preparation of **8a**−**c**) or butorphan triflate (3-trifluoromethyl(sulfonyl)oxy-*N*-cyclobutylmethylmorphinan, for the preparation of **8d**−**f**) in 2 mL of degassed toluene was added dropwise over 1 h. The mixture was heated under vigorous stirring overnight at 80 °C until TLC control (hexane/EtOAc/NEt_3, 10/10/1) showed complete consumption of the triflate. The mixture was filtered over a small pad of silica and the residue washed twice with hexane/EtOAc/NEt_3, 10/10/1 (column eluent system). The solvents were evaporated, and the residue was further dried under high vacuum to remove excess primary amine. The residue was purified by column chromatography first using methylene chloride/methanol, 10/1, followed by hexane/EtOAc/NEt_3, 10/10/1, to yield the respective product.

***N*-Benzyl-17-(cyclopropylmethyl)morphinan-3-amine (8a).** Colorless oil (16%). ^{13}C NMR ($CDCl_3$): 147.0, 141.7, 140.1, 129.0, 128.7, 128.1, 127.6, 127.5, 111.1, 110.2, 60.4, 56.3, 49.2, 46.3, 45.8, 42.4, 38.2, 37.1, 27.3, 27.1, 24.2, 22.7, 9.9, 4.5, 4.0 ppm. ^{1}H NMR ($CDCl_3$): 7.25−7.38 (m, 5 H), 6.91 (d, J = 8 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8, 2.4 Hz, 1H), 4.3 (s, 2H), 3.87 (bs, 1H), 3.05 (m, 1H), 2.84 (d, J = 18 Hz, 1H), 2.46−2.58 (m, 2H), 2.23−2.34 (m, 2H), 2.01 (m, 1H), 1.61−1.85 (m, 3H), 1.17−1.46 (m, 7H), 0.87 (m, 1H), 0.51 (m, 2H), 0.11 (m, 2H) ppm. Anal. ($C_{27}H_{34}N_2 \cdot {}^1/_{10}$EtOAc) C, H, N.

17-(Cyclopropylmethyl)-*N*-(4-methoxyphenyl)morphinan-3-amine (8b). Brown solid (13%). Mp: 60−62 °C. ^{13}C NMR ($CDCl_3$): 154.4, 142.7, 141.5, 136.9, 129.6, 128.38, 120.4, 114.6, 114.3, 113.7, 60.0, 55.8, 55.5, 45.8 45.2, 41.9, 37.7, 36.6, 26.93, 26.6, 23.9, 22.3, 9.4, 4.1, 3.6 ppm. ^{1}H NMR ($CDCl_3$): 7.02 (d, J = 2 Hz, 2H), 6.99 (d, J = 2 Hz, 1H), 6.82−6.98 (m, 3H), 6.75 (dd, J = 8, 2 Hz, 1H), 3.78 (s, 3H), 3.08 (m, 1H), 2.87 (d, J = 18 Hz, 1H), 2.46−2.69 (m, 2H), 2.25−2.34 (m, 2H), 2.04 (m, 1H), 1.62−1.86 (m, 3H), 1.26−1.50 (m, 7H), 0.87 (m, 1H), 0.50 (m, 2H), 0.12 (m, 2H) ppm. Anal. ($C_{27}H_{34}N_2O \cdot {}^1/_{10}$EtOAc) C, H, N.

17-(Cyclopropylmethyl)-*N*-phenylmorphinan-3-amine (8c). White solid (18%). Mp: 63−65 °C. ^{13}C NMR ($CDCl_3$): 144.6, 142.1, 141.1, 131.7, 129.7, 128.8, 120.3, 117.0, 116.8, 116.4, 60.4, 56.2, 46.2, 45.7, 42.4, 38.2, 37.0, 27.3, 27.1, 24.5, 22.7, 9.9, 4.5, 4.0 ppm. ^{1}H NMR ($CDCl_3$): 7.23 (t, J = 15 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 4H), 6.83−6.89 (m, 2H), 5.63 (bs, 1H), 3.1 (m, 1H), 2.89 (d, J = 18 Hz, 1H), 2.46−2.70 (m, 2H), 2.28−2.35 (m, 2H), 2.02 (m, 1H), 1.53−1.88 (m, 3H), 1.26−1.46 (m, 7H), 0.87 (m, 1H), 0.50 (m, 2H), 0.13 (m, 2H) ppm. Anal. ($C_{26}H_{32}N_2 \cdot {}^1/_{10}$EtOAc) C, H, N.

***N*-Benzyl-17-(cyclobutylmethyl)morphinan-3-amine (8d).** Light-yellow oil (9%). ^{13}C NMR ($CDCl_3$): 146.6, 141.3, 139.7, 128.6, 128.3, 127.7, 127.2, 110.8, 109.8, 61.5, 56.1, 48.9, 46.1, 45.3, 41.9, 37.6, 36.7, 35.0, 28.0, 26.9, 26.6, 24.0, 22.3, 18.9 ppm. ^{1}H NMR ($CDCl_3$): 7.23−7.37 (m, 5 H), 6.91 (d, J = 8 Hz, 1 H), 6.53 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8, 2.4 Hz, 1H), 4.3 (s, 2H), 3.85 (bs, 1H), 2.90 (d, J = 18 Hz, 1H), 2.78 (bs, 1H), 2.40−2.58 (m, 5H), 2.21−2.25 (m, 1H), 1.59−2.12 (m, 10H), 1.12−1.44 (m, 7H) ppm. Anal. ($C_{28}H_{36}N_2 \cdot 2HCl \cdot H_2O$) C, H, N.

17-(Cyclobutylmethyl)-*N*-(4-methoxyphenyl)morphinan-3-amine (8e). Brown glassy solid (26%). Mp: 70−74 °C. ^{13}C NMR ($CDCl_3$): 154.5, 142.8, 141.3, 136.8, 128.4, 120.5, 114.6, 114.4, 113.6, 61.3, 56.1, 55.6, 46.0, 44.8, 41.6, 37.5, 36.5, 34.7, 27.9, 26.8, 26.5, 24.2, 22.2, 18.8 ppm. ^{1}H NMR ($CDCl_3$): 6.86−7.03 (m, 3H), 6.82−6.86 (m, 3H), 6.75 (dd, J = 8, 2.4 Hz, 1H), 5.42 (bs, 1H), 3.79 (s, 3H), 2.94 (d, J = 18 Hz, 1H), 2.86 (bs, 1H), 2.42−2.64 (m, 5H), 2.20−2.25 (m, 1H), 1.64−2.13 (m, 10H), 1.12−1.51 (m, 7H) ppm. Anal. ($C_{28}H_{36}N_2O\cdot 0.4$EtOAc) C, H, N.

17-(Cyclobutylmethyl)-*N*-phenylmorphinan-3-amine (8f). Light-yellow solid (14%). Mp: 53−55 °C. ^{13}C NMR ($CDCl_3$): 144.6, 142.1, 141.1, 131.7, 129.7, 128.8, 120.3, 117.0, 116.8, 116.4, 60.4, 56.2, 46.2, 45.7, 42.4, 38.2, 37.0, 27.3, 27.1, 24.5, 22.7, 9.9, 4.5, 4.0 ppm. ^{1}H NMR ($CDCl_3$): 7.23 (t, J = 15 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 4H), 6.83−6.89 (m, 2H), 5.63 (bs, 1H), 3.1 (m, 1H), 2.89 (d, J = 18 Hz, 1H), 2.46−2.70 (m, 2H), 2.28−2.35 (m, 2H), 2.02 (m, 1H), 1.53−1.88 (m, 3H), 1.26−1.46 (m, 7H), 0.87 (m, 1H), 0.50 (m, 2H), 0.13 (m, 2H) ppm. Anal. ($C_{27}H_{34}N_2\cdot {}^1/_{10}$EtOAc) C, H, N.

General Procedure for the Synthesis of 17-(Cyclopropylmethyl/cyclobutylmethyl)-*N*-(4-methoxybenzyl/4-iodobenzyl)morphinan-3-amines (7a−c) and N-Dibenzylated Compounds (7d,e). To a solution of 0.18 mmol of 17-(cyclopropylmethyl)morphinan-3-amine (**6a**) or 17-(cyclopropylmethyl)morphinan-3-amine (**6b**), respectively, in 3 mL of ethanol was added 53 mg (0.18 mmol) of 4-iodobenzyl bromide (to yield compounds **7a**,**b**,**e**) or 4-methoxybenzyl bromide (to yield compounds **7c**,**d**). To the clear solution an amount of 50 mg (0.35 mmol, 2 equiv) of well triturated potassium carbonate was added, and the mixture was vigorously stirred at room temperature overnight. TLC control (EtOAc/NEt_3, 20/1) showed that only small amounts of starting material were left. The solids were filtered off and washed twice with methylene chloride. After evaporation of solvents, the residue was purified by column chromatography using CH_2Cl_2/MeOH, 9/1, and then hexane/EtOAc/NEt_3, 10/10/1.

17-(Cyclopropylmethyl)-*N*-(4-iodobenzyl)morphinan-3-amine (7a). After the first column two spots with very similar R_f values could be observed on TLC, which could be separated into compounds **7a** and **7e** by applying a second column using EtOAc/NEt_3, 9/1, as eluent system. White solid (42%). Mp: 170−173 °C. ^{13}C NMR ($CDCl_3$): 146.4, 141.6, 139.8, 137.8, 129.8, 128.6, 111.0, 110.1, 92.5, 61.8, 56.2, 48.5, 46.2, 45.5, 42.2, 37.8, 37.0, 35.3, 28.2, 28.2, 27.2, 26.9, 24.2, 22.5, 22.4, 19.1 ppm. ^{1}H NMR ($CDCl_3$): 7.63 (d, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 6.88 (d, J = 8 Hz, 1H), 6.46 (d, J = 2 Hz, 1H), 6.41 (dd, J = 8, 2.4 Hz, 1H), 4.22 (s, 2H), 3.86 (bs, 1H), 3.15 (bs, 1H), 2.88 (d, J = 18 Hz, 1H), 2.74 (bs, 1H), 2.38−2.55 (m, 5H), 2.15−2.19 (m, 1H), 1.56−2.07 (m, 10H), 1.07−1.42 (m, 7H) ppm. Anal. ($C_{27}H_{33}IN_2\cdot {}^1/_{10}$EtOAc) C, H, N.

17-(Cyclopropylmethyl)-*N*-(4-iodobenzyl)morphinan-3-amine (7b). White crystals (24%). Mp: 67−69 °C. ^{13}C NMR ($CDCl_3$): 146.6, 141.3, 139.7, 137.8, 129.7, 128.6, 111.1, 110.0, 92.5, 60.0, 56.2, 48.4, 46.2, 45.0, 41.8, 37.8, 36.8, 27.0, 26.8, 24.1, 22.4, 9.3, 4.4, 4.0 ppm. ^{1}H NMR ($CDCl_3$): 7.62 (dd, J = 8, 2 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.88 (d, J = 8 Hz, 1H), 6.50 (d, J = 2 Hz, 1H), 6.43 (dd, J = 8, 2 Hz, 1H), 4.25 (s, 2H), 3.91 (bs, 1H), 3.15 (bs, 1H), 2.51−2.81 (m, 4H), 2.01−2.39 (m, 3H), 1.75−1.90 (m, 2H), 1.63 (m, 1H), 1.11−1.46 (m, 7H), 0.97 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H) ppm. Anal. ($C_{28}H_{35}IN_2$) C, H, N.

17-(Cyclopropylmethyl)-*N*-(4-methoxybenzyl)morphinan-3-amine (7c). After the first column two spots with very similar R_f values could be observed on TLC, which could be separated into compounds **7c** and **7d** by applying a second column using CH_2Cl_2/MeOH, 9/1, as eluent system. White solid (5%). Mp: 38 °C. ^{13}C NMR ($CDCl_3$): 158.5, 148.0, 130.9, 128.1, 128.0, 113.9, 111.47, 110.1, 59.3, 56.2, 55.2, 54.2, 46.1, 40.7, 37.3, 36.2, 26.5, 26.2, 23.7, 21.8, 8.2, 4.2, 4.0 ppm. ^{1}H NMR ($CDCl_3$): 7.17 (dd, J = 8 Hz, 4H), 6.83−6.90 (m, 5H), 6.57−6.63 (m, 2H), 4.50 (s, 4H, 2 × Bn-CH_2), 3.78 (s, 6H, 2 × OCH_3), 3.77 (s, 2H), 3.30 (bs, 1H), 2.61−2.87 (m, 4H), 2.57 (m, 1H), 2.23 (m, 1H), 1.88−2.23 (m, 3H), 1.57 (m, 1H), 1.12−1.43 (m, 7H), 1.05 (m, 1H), 0.59 (m, 2H), 0.24 (m, 2H) ppm. Anal. ($C_{28}H_{36}N_2O\cdot {}^1/_2CH_3OH$) C, H, N.

17-(Cyclopropylmethyl)-*N*,*N*-bis(4-methoxybenzyl)morphinan-3-amine (7d). Brown glassy solid (22%). Mp: 64−66 °C. ^{13}C NMR ($CDCl_3$): 158.8, 146.7, 141.1, 131.6, 129.0, 128.3, 113.9, 110.8, 109.7, 59.8, 56.0, 55.3, 48.2, 46.0, 44.9, 41.7, 37.6, 36.6, 31.4, 26.8, 26.6, 23.8, 22.2, 9.1, 4.1, 3.7 ppm. ^{1}H NMR ($CDCl_3$): 7.29 (d, J = 8 Hz, 2H), 6.82−6.89 (m, 3H), 6.56 (d, J = 2 Hz, 1H), 6.48 (dd, J = 8, 2 Hz, 1H), 4.21 (s, 2H, Bn-CH_2), 3.78 (s, 3H, OCH_3), 3.77 (s, 2H), 3.30 (bs, 1H), 2.49−2.87 (m, 4H), 2.24−2.41 (m, 2H), 2.09 (m, 1H), 1.75−2.13 (m, 2H), 1.64 (m, 1H), 1.12−1.47 (m, 7H), 0.91 (m, 1H), 0.51 (m, 2H), 0.13 (m, 2H) ppm. Anal. ($C_{36}H_{44}N_2O_2\cdot 0.5CH_2Cl_2$) C, H, N.

17-(Cyclobutylmethyl)-*N*,*N*-bis(4-iodobenzyl)morphinan-3-amine (7e). White crystals (12%). Mp: 75−77 °C. ^{13}C NMR (free base, $CDCl_3$): 147.3, 140.7, 138.7, 137.6, 129.0, 128.5, 111.4, 110.3, 92.1, 61.0, 56.2, 54.8, 46.1, 44.6, 41.2, 37.4, 36.5, 28.0, 27.8, 26.7, 26.4, 23.9, 21.9, 18.8 ppm. ^{1}H NMR (free base, $CDCl_3$): 7.60 (d, J = 8 Hz, 4H), 7.11 (d, J = 8 Hz, 4H), 6.88 (d, J = 8 Hz, 1H), 6.51 (dd, J = 8, 2 Hz, 1H), 6.46 (d, J = 2 Hz, 1H), 4.46 (d, J = 6 Hz, 2H), 2.87 (m, 2H), 2.50−2.65 (m, 5H), 1.52−2.05 (m, 11H), 0.88−1.34 (m, 7H) ppm. Anal. ($C_{35}H_{40}I_2N_2$) C, H, N.

General Procedure for the Synthesis of 17-(Methyl/cyclopropylmethyl/cyclobutylmethyl)morphinan-3-yl 4-Iodophenyl Carbamates (9a−c). In an N_2 atmosphere, 0.58 mmol (59 mg, 1.5 equiv) of NEt_3 and 0.39 mmol of 4-iodophenyl isocyanate were added to a suspension of 0.389 mmol of **1**, **3a**, or **3b**, respectively, in 10 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo, and the residue was purified by column chromatography over a short column of silica gel eluting with CH_2Cl_2/MeOH, 100/1. The carbamates were obtained as white solids. The free bases were converted into their hydrochlorides using 1 N HCl in diethyl ether.

17-Methylmorphinan-3-yl 4-Iodophenyl Carbamate (9a). White solid (74%). Mp (free base): 160−162 °C (dec). Mp (HCl salt): 223−225 °C (dec). ^{13}C NMR (base, $CDCl_3$): δ 151.7, 149.0, 141.7, 137.9, 137.3, 134.8, 128.6, 120.6, 118.7, 118.2, 86.7, 57.7, 46.9, 44.6, 42.4, 41.4, 37.1, 36.3, 26.5, 26.3, 23.7, 22.0 ppm. ^{1}H NMR (base, $CDCl_3$): δ 7.60 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 8.4 and 2.4 Hz, 1H), 3.03 (d, J = 18.6 Hz, 1H), 2.89 (m, 1H), 2.67 (dd, J = 18.6 and 5.4 Hz, 1H), 2.51 (dd, J = 12.3 and 2.7 Hz, 1H), 2.42 (s, 3H), 2.30 (d, J = 12.3 Hz, 1H), 2.10 (m, 1H), 1.91−1.73 (m, 2H), 1.61 (m, 1H), 1.50 (m, 1H), 1.43−1.23 (m, 5H), 1.10 (m, 1H) ppm. Anal. ($C_{24}H_{27}IN_2O_2\cdot HCl\cdot 1.5H_2O$) C, H, N.

17-(Cyclopropylmethyl)morphinan-3-yl 4-Iodophenyl Carbamate (9b). White solid (71%). Mp (free base): 189−191 °C (dec). Mp (HCl salt): 238−240 °C (dec). ^{13}C NMR (base, $CDCl_3$): δ 151.7, 148.9, 142.0, 137.9, 137.4, 135.1, 128.5, 120.6, 118.6, 118.2, 86.7, 59.8, 55.6, 45.5, 44.6, 41.5, 37.8, 36.4, 26.6 26.4, 24.1, 22.0, 9.1, 4.0, 3.6 ppm. ^{1}H NMR (base, $CDCl_3$): δ 7.58 (d, J = 8.8 Hz, 2H), 7.37 (br, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.2 and 2.4 Hz, 1H), 3.14 (m, 1H), 2.94 (d, J = 18.6 Hz, 1H), 2.72 (dd, J = 9.3 and 3.0 Hz, 1H), 2.63 (dd, J = 18.6 and 5.7 Hz, 1H), 2.50 (dd, J = 12.6 and 6.3 Hz, 1H), 2.37−2.27 (m, 2H), 2.05−1.70 (m, 3H), 1.63 (d, J = 10.9 Hz, 1H), 1.51 (d, J = 10.9 Hz, 1H), 1.43−1.23 (m, 5H), 1.10 (m, 1H), 0.89 (m, 1H), 0.516 (m, 2H), 0.12 (m, 2 H) ppm. MS (ESI+): m/z 543 $(M + H)^+$. Anal. ($C_{27}H_{31}IN_2O_2\cdot 1HCl$) C, H, N.

17-(Cyclobutylmethyl)morphinan-3-yl 4-Iodophenyl Carbamate (9c). White solid (85%). Mp (HCl salt): 203−205 °C (dec). ^{13}C NMR (base, $CDCl_3$): δ 151.5, 149.8, 139.9, 137.8, 137.4, 131.5, 128.8, 120.7, 119.9, 118.6, 86.8, 59.5, 56.7, 46.2,

41.5, 38.9, 36.6, 35.3, 31.7, 27.7, 27.6, 25.9, 25.6, 24.4, 21.5, 18.6 ppm. ^{1}H NMR (base, $CDCl_3$): δ 7.69 (br, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8.4 and 2.4 Hz, 1H), 3.33 (m, 1H), 2.95 (m, 6H), 2.29 (m 2H), 2,14 (m, 3H), 1.96−1.81 (m, 4H), 1.65−1.32 (m, 6H), 1.25 (m, 2H), 1.02 (m, 1H) ppm. MS (ESI+): m/z 557 $(M + H)^+$. Anal. ($C_{28}H_{33}IN_2O_2 \cdot HCl \cdot H_2O$) C, H, N.

General Procedure for the Synthesis of *N*-[17-(Methyl/cyclopropylmethyl/cyclobutylmethyl)morphinan-3-yl]-*N*′-phenylureas (10a−e). In an N_2 atmosphere, 1.5 equiv of triethylamine and 1.0 equiv of phenyl isocyanate (for preparation of compounds **10a**,**b**) or 4-iodophenyl isocyanate (for preparation of **10c**−**e**) were added to a suspension of 1.0 equiv of the respective 3-aminomorphinan (**6a**−**c**) in 10 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over a short column of silica gel eluting with EtOAc/Et_3N, 50/1. The ureas were obtained in 61−70% yield. The free bases were converted into their hydrochlorides using 1 N HCl in diethyl ether.

***N*-(17-Methylmorphinan-3-yl)-*N*′-phenylurea (10a).** White solid (75%). Mp (HCl salt): 158−160 °C (dec). ^{13}C NMR (base, DMSO-d_6): δ 152.6, 139.9, 139.8, 137.9, 130.7, 128.7, 127.8, 121.6, 118.0, 116.1, 114.7, 57.1, 46.6, 44.3, 42.2, 41.3, 36.5, 35.9, 26.1, 25.9, 23.1, 21.8 ppm. ^{1}H NMR (base, DMSO-d_6): δ 8.64 (s, 1H), 8.61 (s, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.31−7.18 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 2.92 (d, J = 18.6 Hz, 1H), 2.74 (m, 1H), 2.38−2.26 (m, 2H), 2.29 (s, 3H), 2.02−1.94 (m, 2H), 1.75−1.15 (m, 8H), 1.02 (m, 1H), 0.97 (t, J = 7.5 Hz, 1H) ppm. Anal. ($C_{24}H_{29}N_3O \cdot HCl \cdot 1.1H_2O$) C, H, N.

***N*-[17-(Cyclopropylmethyl)morphinan-3-yl]-*N*′-phenylurea (10b).** White solid (73%). Mp (free base): 88−90 °C (dec). Mp (HCl salt): >250 °C (dec). ^{13}C NMR (base, $CDCl_3$): δ 178.8, 153.8, 139.5, 139.2, 138.3, 128.8, 128.2, 122.5, 119.2, 117.9, 116.2, 58.6, 56.0, 45.7, 42.6, 37.0, 35.8, 26.2, 26.0, 24.8, 21.8, 10.3, 7.4, 4.2, 4.1 ppm. ^{1}H NMR (base, $CDCl_3$): δ 8.64 (s, 1H), 8.54 (s, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.32−7.16 (m, 4H), 6.94 (t, J = 7.8 Hz, 2H), 3.40 (s, 1H), 2.91−2.84 (m 2H), 2.74−2.58 (m, 2H), 2.31−1.85 (m, 5H), 1.59−1.02 (m, 9H), 0.57 (m, 2H), 0.22 (m, 2H) ppm. Anal. ($C_{27}H_{33}N_3O \cdot HCl \cdot 1.5H_2O$) C, H, N.

***N*-(4-Iodophenyl)-*N*′-(17-methylmorphinan-3-yl)urea (10c).** White solid (70%). Mp (HCl salt) >250 °C (dec). ^{13}C NMR (base, DMSO-d_6): δ 152.4, 139.8, 139.7, 137.8, 137.2, 130.5, 127.9, 120.3, 116.2, 114.8, 84.3, 57.2, 46.6, 44.0, 42.0, 41.0, 36.4, 35.8, 33.2, 26.5, 25.9, 23.2, 21.8, 14.7 ppm. ^{1}H NMR (base, DMSO-d_6): δ 8.87 (s, 1H), 8.73 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 1.5 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.18 (dd, J = 8.1 and 1.5 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 3.04−2.82 (m, 2H), 2.59−2.25 (m, 3H), 2.05−1.94 (m, 1H), 1.74−1.21 (m, 9H), 1.07−0.95 (m, 2H) ppm. Anal. ($C_{24}H_{28}IN_3O \cdot HCl \cdot 0.4H_2O$) C, H, N.

***N*-[17-(Cyclopropylmethyl)morphinan-3-yl]-*N*′-(4-iodophenyl)-urea (10d).** White solid (75%). Mp (HCl salt): >250 °C (dec). ^{13}C NMR (base, DMSO-d_6): δ 152.4, 140.2, 139.8, 137.6, 137.2, 131.1, 127.8, 120.3, 116.1, 114.9, 84.3, 59.0, 55.1, 45.0, 44.4, 41.4, 37.2, 36.0, 26.3, 26.0, 23.7, 21.8, 9.2, 3.8, 3.4 ppm. ^{1}H NMR (base, DMSO-d_6): δ 8.79 (s, 1H), 8.66 (s, 1H), 7.56 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.16 (dd, J = 8.1 and 1.8 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 2.98 (m, 1H), 2.83 (d, J = 18.3 Hz, 1H), 2.60−2.42 (m, 2H), 2.40−2.20 (m, 2H), 1.96−1.86 (m, 2H), 1.75−0.95 (m, 11H), 0.78 (m,1H), 0.43−0.49 (m, 2H), 0.11−0.04 (m, 2H) ppm. Anal. ($C_{27}H_{32}IN_3O \cdot HCl$) C, H, N.

***N*-[17-(Cyclobutylmethyl)morphinan-3-yl]-*N*′-(4-iodophenyl)-urea (10e).** White solid (86%). Mp (HCl salt): 245−247 °C (dec). ^{13}C NMR (base, DMSO-d_6): δ 152.4, 140.2, 139.8, 137.6, 137.2, 131.2, 127.7, 120.3, 116.1, 114.9, 84.3, 60.6, 55.5, 45.1, 44.5, 41.6, 37.1, 36.0, 33.6, 26.7, 26.6, 26.3, 26.0, 23.9, 21.8, 18.3 ppm. ^{1}H NMR (base, 300 MHz, DMSO-d_6): δ 8.73 (s, 1H), 8.60 (s, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 1.5 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.16 (dd, J = 8.1 and 1.5 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 2.87 (m, 1H), 2.71 (m, 1H), 2.45−2.23 (m, 5H), 1.95−1.14 (m, 17H), 0.99 (m, 1H) ppm. Anal. ($C_{28}H_{34}IN_3O \cdot HCl \cdot H_2O$) C, H, N.

General Procedure for the Formylation of 3-Hydroxymorphinans. Method A (MeMgBr/HMPA System). Under nitrogen at room temperature, MeMgBr (1.0 mL, 3.0 M solution in ether) was added into the suspension of 1.0 mmol of starting material (levorphanol or butorphan) in benzene (25 mL). The resulting mixture was stirred for 30 min. HMPA (3.0 mmol) was added and the clear mixture stirred for 15 min. Paraformaldehyde (300 mg, 10 mmol) was added in one portion. The resulting mixture was heated under reflux for 4 h. The mixture was poured into ice−water and stirred for 15 min. The mixture was extracted with CH_2Cl_2/MeOH, 10:1 (50 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified on silica gel column, eluting with CH_3OH/CH_2Cl_2, 1:50 to 1:20, to obtain the products in 40−50% yield.

Method B ($MgCl_2$/Et_3N System). To a solution (10 mL) of **1** or **3b** (1.0 mmol) in anhydrous THF (distilled freshly from benzophenone ketyl radical), anhydrous magnesium chloride (190 mg, 2.0 mmol, beads, 10 mesh, 99.9% purity, from Aldrich used directly without further drying), and triethylamine (0.28 mL, 2.0 mmol), paraformaldehyde (90 mg, 3.0 mmol) was added. The reaction mixture was heated to reflux under nitrogen atmosphere for 2 days. The reaction was monitored with TLC (CH_3OH/CH_2Cl_2, 1:10). After evaporation of solvent, water (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate and the crude product was purified on silica gel column, eluting with CH_3OH/CH_2Cl_2, 1:50 to 1:20, to obtain the products in 40−75% yield.

2-Formyl-3-hydroxymorphinan (11). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 10.13 (s, br, 1H), 9.84 (s, 1H), 7.30 (s, 1H), 6.92 (s, 1H), 3.06 (d, J = 18.3 Hz, 1H), 2.91 (m, 1H), 2.68 (dd, J = 18.3 and 5.7 Hz, 1H), 2.54−2.33 (m, 2H), 2.43 (s, 3H), 2.05 (m, 1H), 1.93−1.77 (m, 2H), 1.68−1.01 (m, 8H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 195.7, 159.7, 151.8, 132.1, 129.0, 118.9, 113.9, 57.4, 46.8, 44.4, 42.4, 41.4, 38.0, 36.4, 26.8, 26.1, 23.0, 22.0 ppm.

2-Formyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (12). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 10.53 (s, br, 1H), 9.83 (s, 1H), 7.28 (s, 1H), 6.91 (s, 1H), 3.03 (d, J = 18.3 Hz, 1H), 2.88 (m, 1H), 2.68−2.48 (m, 5H), 2.33 (m, 1H), 2.09−1.99 (m, 3H), 1.91−1.63 (m, 7H), 1.54 (m, 1H), 1.45−1.01 (m, 6H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 195.9, 159.7, 152.2, 132.2, 129.3, 118.9, 114.0, 61.2, 55.5, 45.6, 44.2, 41.3, 38.6, 36.5, 34.4, 27.7, 27.0, 26.2, 23.7, 22.1, 18.7 ppm.

General Procedure for the Preparation of 2-Hydroxymethyl-3-hydroxymorphinans. At room temperature, an amount of 2.4 equiv of $NaBH_4$ was added into a solution of the aldehyde **11** derived from **1** or compound **12** derived from **3b** in MeOH (8.0 mL). The mixture was stirred for 1 h at room temperature. Then the mixture was poured into ice−water (50 mL). Then the mixture was stirred for 15 min and evaporated in vacuo to remove MeOH. The residue was extracted with CH_2Cl_2 (50 mL × 4). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified on silica gel column, eluting with CH_3OH/CH_2Cl_2, 1:1 to 10:1, to obtain the products in 90−95% yield. The free base was converted to its HCl salt with 1.0 M HCl in diethyl ether.

2-Hydroxymethyl-3-hydroxymorphinan (13). Mp (HCl salt): >250 °C (dec). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 7.13 (s, br, 1H), 6.76 (s, 1H), 6.69 (s, 1H), 4.76 (ab, J = 13.2 and 5.4 Hz, 2H), 2.87 (d, J = 18.3 Hz, 1H), 2.77 (m, 1H), 2.58 (dd??, J = 18.3 and 5.1 Hz, 1H), 2.33 (s, 3H), 2.25 (m, 1H), 2.05 (m, 1H), 1.78 (m, 1H), 1.68−1.05 (m, 8H) ppm. ^{13}C NMR (base, 75 MHz,

$CDCl_3$): δ 155.1, 140.5, 127.4, 126.6, 123.7, 112.7, 63.7, 57.9, 46.9, 44.0, 42.1, 40.9, 36.6, 36.3, 26.5, 26.3, 23.5, 22.0 ppm. Anal. ($C_{18}H_{25}NO_2 \cdot HCl \cdot H_2O$) C, H, N.

2-Hydroxymethyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (14). Mp (HCl salt): 218−220 °C (dec). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.70 (s, 1H), 4.78 (ab, J = 13.8 Hz, 2H), 2.88 (d, J = 18.0 Hz, 1H), 2.78 (m, 1H), 2.57−2.47 (m, 4H), 2.36 (m, 1H), 2.21 (m, 3H), 2.06−1.98 (m, 3H), 1.91−1.59 (m, 7H), 1.43−1.04 (m, 7H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 154.8, 141.2, 128.2, 126.7, 123.1, 112.7, 64.0, 61.1, 55.6, 45.8, 44.1, 41.1, 37.2, 36.4, 34.5, 28.2, 28.1, 26.8, 26.4, 23.9, 22.1, 18.8 ppm; Anal. ($C_{22}H_{31}NO_2 \cdot HCl \cdot H_2O$) C, H, N.

2-Benzylaminomethyl-3-hydroxymorphinan (16). At room temperature, benzylamine (51 mg, 0.48 mmol) was added into the solution of salicylaldehyde **11** (125 mg, 0.43 mmol) in MeOH (10.0 mL). The mixture was stirred overnight at room temperature. The reaction was monitored by TLC (CH_3OH/CH_2Cl_2, 1:10). After complete consumption of salicylaldehyde and evaporation of solvent, the reaction mixture was directly loaded on silica gel column and eluted with CH_3OH/CH_2Cl_2, 1:10 to 1:1, to obtain the bright-yellow aldimine **15** (80 mg) in 50% yield. To the solution of aldimine **15** (80 mg, 0.21 mmol) in MeOH (8 mL) was added $NaBH_4$ (10 mg, 0.25 mmol), and the mixture was stirred at room temperature overnight. The reaction was monitored by TLC (CH_3OH/CH_2Cl_2, 1:1). After complete consumption of the aldimine, the pH of the mixture was adjusted to 2−3 with 1 N HCl to decompose the excess of $NaBH_4$ and then to 9−10 with saturated $KHCO_3$ aqueous solution. After evaporation of solvent, water was added to the residue and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified on silica gel column, eluting with $CH_3OH/CH_2Cl_2/Et_3N$, 50:50:1, to obtain a colorless oil in 88% yield. The free base was converted to its HCl salt as a white solid with 1 N HCl in diethyl ether.

Aldimine 15. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 13.01 (s, br, 1H), 8.38 (s, 1H), 7.37−7.24 (m, 5H), 7.01 (s, 1H), 6.89 (s, 1H), 4.79 (s, 2H), 2.99 (d, J = 18.3 Hz, 1H), 2.83 (dd, J = 5.1 and 3.3 Hz, 1H), 2.60 (dd, J = 18.3 and 6.0 Hz, 1H), 2.48−2.34 (m, 3H), 2.40 (s, 3H), 2.08 (dt, J = 12.6 and 3.3 Hz, 1H), 1.86−1.62 (m, 3H), 1.53−1.25 (m, 5H), 1.11 (m, 1H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 165.2, 159.1, 146.0, 138.3, 130.1, 128.5, 127.8, 127.6, 127.2, 116.9, 113.3, 63.2, 57.8, 47.1, 45.0, 42.7, 41.8, 37.5, 36.5, 26.9, 26.4, 23.0, 22.2 ppm.

2-Benzylaminomethyl-3-hydroxymorphinan (16). Mp (HCl salt): 188−190 °C. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 7.37−7.25 (m, 5H), 6.74 (s, 1H), 6.70 (s, 1H), 3.95 (s, 2H), 3.83 (s, 2H), 2.90 (d, J = 18.3 Hz, 1H), 2.80 (m, 1H), 2.54 (dd, J = 17.7 and 5.4 Hz, 1H), 2.47−2.30 (m, 2H), 2.39 (s, 3H), 2.09 (dt, J = 12.3 and 3.0 Hz, 1H), 1.82−1.61 (m, 3H), 1.41−1.26 (m, 6H), 1.11 (m, 1H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 156.2, 140.8, 138.4, 128.5, 128.2, 127.7, 127.4, 119.9, 112.7, 58.0, 52.8, 51.6, 47.2, 45.0, 42.6, 41.7, 36.8, 36.5, 26.7, 26.5, 23.2, 22.1 ppm. Anal. ($C_{25}H_{32}N_2O \cdot 2HCl \cdot 1.5H_2O$) C, H, N.

3-Benzyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazinemorphinan (17). Under nitrogen, a mixture of 2-(*N*-benzylaminomethyl)-3-hydroxymorphinan **16** (30 mg, 0.08 mmol) and paraformaldehyde (5 mg, 0.16 mmol) in MeOH (10 mL) was refluxed overnight. After removal of solvent, the residue was loaded on the silica gel column, eluting with $CH_3OH/CH_2Cl_2/Et_3N$, 50:50:1, to obtain a colorless oil (23 mg) in 74% yield. The free base was converted into HCl salt as a white solid with 1 N HCl in diethyl ether. Mp (HCl salt): 208−210 °C. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 7.39−7.26 (m, 5H), 6.70 (s, 1H), 6.65 (s, 1H), 4.83 (s, 2H), 3.93 (s, 4H), 2.93 (d, J = 18.0 Hz, 1H), 2.83 (m, 1H), 2.60−2.30 (m, 3H), 2.41 (s, 3H), 2.14 (dt, J = 12.3 and 3.0 Hz, 1H), 1.85−1.65 (m, 3H), 1.51−1.25 (m, 6H), 1.16 (m, 1H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 152.5, 139.9, 138.2, 129.5, 128.8, 128.6, 128.3, 127.2, 126.3, 117.5, 112.7, 82.1, 58.0, 55.7, 49.5, 47.2, 45.0, 42.6, 41.9, 36.9, 36.5, 26.7, 26.5, 23.3, 22.2 ppm. Anal. ($C_{26}H_{32}N_2O \cdot 2HCl \cdot H_2O$) C, H, N.

17-*N*-(Cyclobutylmethyl)-3-hydroxymorphinan-2-carbaldehyde Oxime (18). To a solution of 2-formyl-3-hydroxy-*N*-cyclobutylmethylmorphinan **12** (434 mg, 1.28 mmol) in methanol (3 mL) were added hydroxylamine hydrochloride (175 mg, 2.56 mmol) and anhydrous sodium acetate (210 mg, 2.56 mmol). Under stirring a clear solution was formed. The solution was stirred overnight at room temperature. The methanol was evaporated under reduced pressure and water (50 mL) added. The water phase was extracted with methylene chloride (50 mL × 3). The combined organic phases were dried over Na_2SO_4, and solvent was evaporated. The crude oxime was column chromatographed using $CH_2Cl_2/MeOH/NEt_3$, 50/50/1, as eluent system to yield 436 mg (96%) of a fluffy white solid. Mp (free base): 214−216 °C; mp (HCl salt, dec): 216−218 °C. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 9.90 (bs, 1H), 8.18 (s, 1H), 6.90 (d, J = 10 Hz, 2H), 2.92−3.02 (m, 2H), 2.51−2.68 (m, 5H), 2.24 (d, J = 12 Hz, 1H), 2.08 (m, 3H), 1.62−1.94 (m, 7H), 1.26−1.54 (m, 6H), 1.12 (m, 1H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 155.8, 151.8, 143.9, 129.2, 128.3, 115.0, 113.1, 61.2, 55.5, 46.0, 44.1, 41.1, 37.8, 36.4, 34.3, 28.2, 28.1, 27.0, 26.4, 23.7, 22.2, 18.8 ppm. Anal. ($C_{22}H_{30}N_2O_2 \cdot HCl \cdot 0.8H_2O$) C, H, N.

2-(Aminomethyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (19). Concentrated HCl (1.0 mL) was added to a solution of 17-(cyclobutylmethyl)-3-hydroxymorphinan-2-carbaldehyde oxime **18** (336 mg, 0.95 mmol) in ethanol (5.0 mL). To this mixture was added 10 wt % palladium on charcoal (40 mg). Under a hydrogen atmosphere (1 atm) the suspension was vigorously stirred until TLC ($CH_2Cl_2/MeOH/NEt_3$, 50/50/1) showed the complete consumption of the oxime (∼36 h). The Pd/C was filtered off through Celite and washed with methanol (30 mL × 3). After removal of the methanol, water (50 mL) was added and the mixture was extracted with methylene chloride (50 mL × 3). The combined organic phases were dried over Na_2SO_4, and solvent was evaporated. The crude product was column-chromatographed using $CH_2Cl_2/MeOH/NEt_3$, 50/50/1, as eluent system to yield 125 mg (39%) of white foam. The foam was repeatedly dissolved in $CH_2Cl_2/MeOH$, 5/1, and solvents were evaporated to remove residual NEt_3. Mp (HCl salt): > 270 °C (dec). ^{1}H (base, 300 MHz, $CDCl_3$): δ 6.67 (d, J = 9 Hz, 2H), 4.03 (bs, 2H), 2.85 (d, J = 18 Hz, 1H), 2.76 (m, 1H), 2.26−2.50 (m, 6H), 1.96−2.26 (m, 3H), 1.58−1.86 (m, 7H), 1.23−1.45 (m, 6H), 1.09 (m, 1H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 156.7, 141.2, 128.3, 127.2, 121.9, 113.3, 61.7, 56.2, 46.2, 45.3, 45.2, 42.0, 37.7, 36.8, 35.1, 28.2, 27.2, 26.8, 24.1, 22.5, 19.1 ppm. Anal. ($C_{22}H_{32}N_2O \cdot 2HCl \cdot H_2O$) C, H, N.

2-(*N*-*n*-Propyl)aminomethyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (21). At room temperature, *n*-propylamine (19 mg, 0.33 mmol) was added into a solution of salicylaldehyde compound **12** derived from **3b** (75 mg, 0.22 mmol) in MeOH (8.0 mL). The mixture was stirred overnight at room temperature. The reaction was monitored with TLC (CH_3OH/CH_2Cl_2, 1:10). After complete consumption of the salicylaldehyde and evaporation of solvent, the reaction mixture was directly loaded to the silica gel column and eluted with CH_3OH/CH_2Cl_2, 1:10 to 1:1, to obtain the bright-yellow aldimine **20** (64 mg) in 77% yield. To the solution of this aldimine (64 mg, 0.168 mmol) in MeOH (10 mL) was added $NaBH_4$ (10 mg, 0.26 mmol), and the mixture was stirred at room temperature overnight. The reaction was monitored with TLC (CH_3OH/CH_2Cl_2, 1:1). After complete consumption of the aldimine, the pH of the mixture was adjusted to 2−3 with 1 N HCl to decompose the excess $NaBH_4$ and then to 9−10 with saturated $KHCO_3$ aqueous solution. After evaporation of the solvent, water (50 mL) was added to the residue and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified on silica gel column, eluting with $CH_3OH/CH_2Cl_2/Et_3N$, 100:100:1, to obtain a colorless oil (60 mg) in 93% yield.

The free base was converted to its HCl salt as a white solid with 1 N HCl in diethyl ether.

Aldimine 20. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 13.23 (s, br, 1H), 8.26 (s, 1H), 6.95 (s, 1H), 6.85 (s, 1H), 3.52 (t, J = 6.9 Hz, 2H), 2.95 (d, J = 17.7 Hz, 1H), 2.83 (m, 1H), 2.62−2.42 (m, 5H), 2.34 (d, J = 11.7 Hz, 1H), 2.08−2.00 (m, 3H), 1.95−1.63 (m, 9H), 1.62 (m, 1H), 1.48−1.28 (m, 5H), 1.09 (m, 1H), 0.95 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 164.0, 159.2, 145.6, 129.7, 127.5, 116.8, 113.2, 61.4, 61.2, 55.8, 45.7, 44.5, 41.5, 37.9, 36.5, 34.6, 27.7, 26.9, 26.4, 24.0, 23.7, 22.1, 18.7, 11.6 ppm.

2-(*N*-*n*-Propyl)aminomethyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (21). Mp (HCl salt): >198−200 °C. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.68 (s, 1H), 3.91 (ab, J = 15.6 and 14.1 Hz, 2H), 2.86 (d, J = 17.7 Hz, 1H), 2.76 (m, 1H), 2.65 (t, J = 6.9 Hz, 2H), 2.56−2.38 (m, 5H), 2.30 (d, J = 9.6 Hz, 1H), 2.06−1.98 (m, 3H), 1.94−1.51 (m, 9H), 1.46 (m, 1H), 1.40−1.25 (m, 5H), 1.11 (m, 1H), 0.94 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 156.3, 140.8, 127.9, 127.0, 120.1, 112.6, 61.4, 55.9, 52.4, 50.6, 45.9, 44.9, 41.7, 37.3, 36.5, 34.9, 27.8, 26.8, 26.5, 23.9, 22.6, 22.2, 18.7, 11.5 ppm. Anal. ($C_{25}H_{38}N_2O\cdot 2HCl\cdot H_2O$) C, H, N.

General Procedure for the Condensation of Aldehyde 12 with Diamine. At room temperature, the appropriate diamine (0.28 mmol) was added into a solution of salicylaldehyde **12** (190 mg, 0.56 mmol) in MeOH (8.0 mL). The mixture was stirred overnight at room temperature. The reaction was monitored with TLC (CH_3OH/CH_2Cl_2, 1:10). After complete consumption of the salicylaldehyde and evaporation of the solvent, the reaction mixture was directly loaded to the silica gel column and eluted with CH_3OH/CH_2Cl_2, 1:10 to 1:1, to obtain the bright-yellow aldimines in 42−62% yield. To the solution of the respective aldimine (0.137 mmol) in MeOH (10 mL) was added $NaBH_4$ (13 mg, 0.32 mmol), and the mixture was stirred at room temperature overnight. The reaction was monitored by TLC (CH_3OH/CH_2Cl_2, 1:1). After complete consumption of the aldimine, the pH of the mixture was adjusted to 2−3 with 1 N HCl to decompose the excess $NaBH_4$ and then to 9−10 with saturated $KHCO_3$ aqueous solution. After evaporation of the solvent, water was added to the residue and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified on silica gel column, eluting with $CH_3OH/CH_2Cl_2/Et_3N$, 50:50:1, to obtain the product as white foam in 81−90% yield. The free base was converted to its HCl salt as a white solid with 1 N HCl in diethyl ether.

Aldimine 21a. Bright-yellow oil (59%). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 13.09 (bs, 2 H), 8.28 (s, 2 H), 6.97 (s, 2H), 6.87 (s, 2H), 3.62 (bs, 4H), 2.95 (d, J = 18 Hz, 2 H), 2.80 (m, 2H), 2.33−2.59 (m, 12 H), 1.29−2.09 (m, 36 H), 1.03−1.26 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 164.5, 159.1, 146.1, 129.9, 128.1, 116.8, 113.3, 61.6, 59.5, 55.8, 45.8, 45.0, 41.9, 38.2, 36.7, 35.0, 28.6, 27.8, 27.1, 26.6, 23.8, 22.3, 18.9 ppm.

Aldimine 21b. Bright-yellow oil (62%). ^{1}H (base, 300 MHz, $CDCl_3$): δ 13.12 (bs, 2 H), 8.25 (s, 2 H), 6.94 (s, 2H), 6.84 (s, 2H), 3.56 (t, J = 7 Hz, 4H), 2.92 (d, J = 18 Hz, 2 H), 2.77 (m, 2H), 2.30−2.57 (m, 12 H), 1.26−2.05 (m, 40 H), 1.04−1.23 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 164.2, 159.2, 146.0, 129.8, 128.0, 116.9, 113.3, 61.6, 59.6, 55.8, 45.8, 45.0, 41.9, 38.1, 36.7, 35.0, 30.8, 27.9, 27.1, 26.9, 26.6, 23.8, 22.3, 18.9 ppm.

Aldimine 21c. Bright-yellow oil (42%). ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 13.25 (s, br, 2H), 8.26 (s, 2H), 6.97 (s, 2H), 6.86 (s, 2H), 3.55 (t, J = 6.9 Hz, 4H), 2.96 (d, J = 18.0 Hz, 2H), 2.84 (m, 2H), 2.63−2.45 (m, 10H), 2.34 (d, J = 11.7 Hz, 2H), 2.08−2.00 (m, 6H), 1.93−1.60 (m, 18H), 1.51 (m, 2H), 1.41−1.25 (m, 18H), 1.10 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 164.0, 159.2, 145.6, 129.7, 127.6, 116.9, 113.261.3, 59.6, 55.8, 45.8, 44.5, 41.6, 37.9, 36.5, 34.6, 30.8, 29.2, 27.8, 27.0, 26.9, 26.4, 23.8, 22.2, 18.7 ppm.

1,4-*N*,*N*-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-methylamino)butane-1,4-diamine (22a). Yield: 81%. Mp: 250−265 °C (dec). Mp (HCl salt): 250−253 °C. ^{1}H NMR (base, 300 MHz, CD_3OD): δ 7.15 (s, 2H), 6.86 (s, 2H), 4.02 (m, 4H), 3.45 (m, 2H), 2.91- 3.22 (m, 14H), 2.79 (qui, J = 7 Hz, 2H), 2.57 (m, 2H), 2.40 (d, J = 14 Hz, 2H), 1.79−2.20 (m, 20H), 1.20−1.65 (m, 14H), 1.02−1.18 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, CD_3OD): δ 156.9, 141.6, 132.0, 126.7, 120.1, 113.0, 60.4, 59.1, 47.9, 43.1, 40.0, 37.7, 36.7, 33.1, 28.4, 28.3, 27.2, 27.1, 26.2, 25.2, 23.0, 19.5 ppm. Anal. ($C_{48}H_{70}N_4O_2\cdot 4HCl\cdot 3.5H_2O$) C, H, N.

1,6-*N*,*N*-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-methylamino)hexane-1,6-diamine (22b). Yield: 85%. Mp: 210−215 °C (dec). Mp (HCl salt): 245−249 °C. ^{1}H NMR (base, 300 MHz, CD_3OD): δ 7.11 (s, 2H), 6.83 (s, 2H), 4.07 (s, 4H), 3.26 (m, 2H), 2.68−3.13 (m, 16H), 2.36−2.41 (m, 4H), 2.12−2.17 (m, 4H), 1.25−2.02 (m, 34 H), 1.04−1.16 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, CD_3OD): δ 157.1, 142.3, 131.6, 127.5, 119.4, 112.0, 61.0, 58.4, 47.4, 44.0, 40.8, 38.0, 37.0, 34.0, 28.6, 28.5, 27.8, 27.5, 27.4, 27.3, 25.0, 23.2, 19.6 ppm. Anal. ($C_{50}H_{74}N_4O_2\cdot$ 4 $HCl\cdot 3.5H_2O$) C, H, N.

1,8-*N*,*N*-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-methylamino)octane-1,8-diamine (22c). Yield: 90%. Mp (free base): 182−184 °C. Mp (HCl salt): >250 °C. ^{1}H NMR (base, 300 MHz, CD_3OD): δ 6.90 (s, 2H), 6.70 (s, 2H), 3.88 (s, 4H), 2.96 (d, J = 18.3 Hz, 2H), 2.89 (m, 2H), 2.73−2.46 (m, 14H), 2.33 (d, J = 11.7 Hz, 2H), 2.12−2.05 (m, 6H), 1.93 (m, 2H), 1.82−1.52 (m, 18H), 1.41−1.25 (m, 18H), 1.12 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, CD_3OD): δ 157.0, 141.9, 130.2, 128.5, 121.5, 112.9, 62.0, 57.3, 50.5, 49.2, 47.2, 45.3, 42.1, 38.3, 37.5, 35.3, 30.2, 29.3, 29.0, 28.8, 27.9, 27.6, 24.8, 23.3, 19.6 ppm. Anal. ($C_{52}H_{78}N_4O_2\cdot 4HCl\cdot 2H_2O$) C, H, N .

General Procedure for the Synthesis of Bivalent Ligands Containing Spacers with Tertiary Amine Groups (24a,b). In a one-neck flask 0.068 mmol of the corresponding secondary diamine (**22a** or **22b**) and 8 equiv (0.55 mmol) of triethylamine were dissolved in CH_2Cl_2 (10 mL). At room temperature, an amount of 8 equiv (43 mg, 0.55 mmol) of acetyl chloride was added dropwise. The solution was stirred overnight under N_2 at room temperature. Additional methylene chloride (50 mL) was added and the organic phase washed with $NaHCO_3$ solution and brine (50 mL). The organic phase was dried over Na_2SO_4, and solvent was evaporated. The crude product was purified by silica gel column chromatography, eluting with $CH_2Cl_2/MeOH/NEt_3$ (50/50/1). Proton NMR showed that both the secondary amine group and the phenolic hydroxy group were acetylated (the latter only partially). Without further characterization the acetylated compound (**23a**,**b**) was dissolved in anhydrous THF (20 mL), and $LiAlH_4$ (30 mg, 0.75 mmol) was added to the solution under nitrogen atmosphere. The mixture was stirred under N_2 at room temperature overnight. Aqueous ammonia solution (50 mL) was added dropwise to decompose excess $LiAlH_4$, and the white suspension was stirred for further 15 min. The aqueous phase was extracted with $CH_2Cl_2/MeOH$, 5/1 (30 mL × 4). The combined organic phases were dried over Na_2SO_4, and solvents were evaporated. The crude product was purified by silica gel column chromatography, eluting with EtOAc/hexane/NEt_3, 10/10/1, to yield a colorless foam that was repeatedly dissolved in CH_2Cl_2/MeOH, 5/1, and solvents were evaporated to remove residual NEt_3.

1,4-*N*,*N*-Diethyl-1,4-*N*,*N*-bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-methylamino)butane-1,4-diamine (24a). Yield: 26 mg (48% over both steps). Colorless solid. Mp: 248−255 °C (HCl salt). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 6.63 (d, J = 6 Hz, 4H), 3.62 (m, 4H), 2.84 (d, J = 18 Hz, 2H), 2.73 (m, 2H), 2.26−2.57 (m, 21H), 2.01 (m, 6H), 1.52−1.97 (m, 21H), 1.11−1.34 (m, 10H), 1.03−1.10 (m, 6H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 156.1, 140.8, 128.1, 127.3, 119.4, 112.3, 61.6, 57.3, 56.0, 52.5, 46.8, 46.0, 45.1, 41.8, 37.5, 36.6, 35.0, 27.9, 27.0, 26.7, 24.3, 24.0, 22.3, 18.9, 11.1 ppm. Anal. ($C_{52}H_{78}N_4O_2\cdot$ 4$HCl\cdot 3H_2O$) C, H, N.

1,6-*N*,*N*-Diethyl-1,6-*N*,*N*-bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-methylamino)hexane-1,6-diamine (24b). Yield: 40 mg (74% over both steps). Colorless solid. Mp: 227−235 °C (HCl salt). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 6.63 (d, J = 6 Hz, 4H), 3.63 (m, 4H), 2.84 (d, J = 18 Hz, 2H), 2.75 (m, 2H), 2.26−2.58 (m, 21H), 2.02 (m, 6H), 1.44−1.90 (m, 21H), 1.24−1.35 (m, 14H), 1.03−1.11 (m, 6H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 156.4, 141.0, 128.2, 127.5, 119.7, 112.5, 61.8, 57.5, 56.3, 53.0, 46.9, 46.3, 45.4, 42.1, 37.7, 36.9, 35.3, 28.2, 27.5, 27.2, 26.9, 26.7, 24.2, 22.6, 19.1, 11.2 ppm. Anal. ($C_{54}H_{82}N_4O_2\cdot 4HCl\cdot 4H_2O$) C, H, N.

(*rac*)-2-(1-Hydroxypropyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (25). Under nitrogen, EtMgBr (2.5 mL, 1.0 M in MeO^{t}Bu) was added slowly by syringe to the solution of 2-formyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan **12** (84 mg, 0.25 mmol) in THF (10 mL) at −78 °C. The mixture was warmed to room temperature slowly and stirred overnight. The reaction was quenched with saturated NH_4Cl, and the pH of the mixture was adjusted to 9−10 with saturated $KHCO_3$ aqueous. The mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography, eluting with CH_3OH/CH_2Cl_2, 1:10, to obtain a white foam (60 mg) in 65% yield. Mp: 113−115 °C. ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.68 (s, 1H), 4.63 (t, J = 2.7 Hz, 1H), 2.91 (m, 1H), 2.83 (m, 1H), 2.55−2.38 (m, 5H), 2.21 (d, J = 12.0 Hz, 1H), 2.10−1.98 (m, 3H), 1.95−1.50 (m, 9H), 1.42 (m, 1H), 1.34−1.06 (m, 6H), 0.98 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 154.2, 140.3, 127.5, 126.0, 125.7, 113.2, 60.9, 55.8, 46.0, 43.8, 40.9, 37.1, 36.3, 34.3, 30.4, 28.1, 28.0, 26.7, 26.3, 24.0, 23.9, 22.1, 18.8, 10.4 ppm. Anal. ($C_{24}H_{35}NO_2\cdot 0.8H_2O$) C, H, N.

(*rac*)-1,6-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)-hexane-1,6-diol (26a) and (*rac*)-2-(1-Hydroxypentyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (27a). Magnesium turnings (175 mg, 7.3 mmol) were weighed into a dry flask containing freshly dried and distilled tetrahydrofuran (10 mL). To the mixture a solution of 1,4-dibromobutane (473 mg, 2.2 mmol) in freshly distilled tetrahydrofuran (5 mL) was added dropwise via syringe. The resulting mixture was heated at reflux for 3 h. The mixture was cooled to room temperature. Under nitrogen atmosphere, this Grignard reagent solution was added dropwise via syringe to a solution of 2-formyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan **12** (250 mg, 0.73 mmol) in anhydrous tetrahydrofuran (20 mL). The resulting mixture was stirred at room temperature overnight. The mixture was cooled to 0 °C, and saturated aqueous ammonium chloride solution (50 mL) was added very slowly. The aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with CH_3OH/CH_2Cl_2, 1:20, obtaining 25 mg of (*rac*)-1,6-bis(*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)hexane-1,6-diol **26a** in 4.6% yield as a white foam and 40 mg of (*rac*)-2-(1-hydroxypentyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan **27a** in 14% yield. The free bases were converted to HCl salts with 1 N HCl in diethyl ether obtaining white solids.

(*rac*)-1,6-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)-hexane-1,6-diol (26a). Mp (HCl salt): >250 °C. ^{1}H NMR (300 MHz, $CDCl_3$, a drop of CD_3OD): δ 6.67 (s, 4H), 4.70 (m, 2H), 2.87 (d, J = 18.0 Hz, 2H), 2.78 (s, 2H), 2.60−2.50 (m, 8H), 2.37 (d, J = 9.0 Hz, 2H), 2.24 (d, J = 9.0 Hz, 2H), 2.04−1.59 (m, 26H), 1.43−1.12 (m, 14H), 1.10 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$, a drop of CD_3OD): δ 153.7, 140.2, 127.9, 126.2, 125.9, 112.9, 74.3, 61.0, 55.4, 45.8, 43.9, 37.3, 37.1, 36.3, 34.4, 28.1, 28.0, 27.9, 26.7, 26.3, 25.6, 23.8, 22.0, 18.7 ppm. Anal. ($C_{48}H_{68}N_2O_4\cdot 2HCl$) C, H, N.

(*rac*)-2-(1-Hydroxypentyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (27a). Mp (HCl salt) 180−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.66 (s, 1H), 4.70 (t, J = 2.7 Hz, 1H), 2.90 (d, J = 5.7 Hz, 1H), 2.77 (m, 1H), 2.52−2.30 (m, 5H), 2.21 (d, J = 12.9 Hz, 1H), 2.10−1.98 (m, 3H), 1.94−1.50 (m, 9H), 1.42−1.03 (m, 11H), 0.92 (t, J = 6.6 Hz, 3H). ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 154.2, 140.1, 127.6, 126.5, 125.8, 113.0, 75.0, 61.0, 55.5, 45.9, 43.9, 40.9, 37.4, 37.0, 36.3, 34.4, 28.2, 28.1, 26.7, 26.3, 23.7, 22.5, 22.0, 18.7, 14.0. Anal. ($C_{26}H_{39}NO_2\cdot HCl\cdot 0.25H_2O$) C, H, N.

(*rac*)-1,12-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)dodecane-1,12-diol (26b), (*rac*)-2-(1-Hydroxydodecyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (27b), and (*rac*)-1-(17-*N*-Cyclobutylmethyl-3-hydroxymorphinan-2-yl)dodecane-1,12-diol (28). The same procedure was followed as described for compounds **26a** and **27a**, using magnesium turnings (144 mg, 6.0 mmol), 1,10-dibromodecane (360 mg, 1.2 mmol), and 2-formyl-3-hydroxy-17-*N*-cyclobutylmethylmorphinan **12** (339 mg, 1.0 mmol). The residue was purified by silica gel column chromatography, eluting with CH_3OH/CH_2Cl_2, 1:10, obtaining the following product: 50 mg of (*rac*)-1,12-bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)dodecane-1,12-diol **26b** in 6.0% yield as a colorless oil, 44 mg of (*rac*)-2-(1-hydroxyundecyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan **27b** in 9.1% yield as a colorless oil, and 16.5 mg of (*rac*)-1-(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)undecane-1,11-diol **28** in 3.3% yield as a white foam. The free bases were converted to HCl salts with 1 N HCl in diethyl ether.

(*rac*)-1,12-Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-yl)-dodecane-1,12-diol (26b). Mp (HCl salt): 235−238 °C. ^{1}H NMR (300 MHz, $CDCl_3$, a drop of CD_3OD): δ 6.72 (s, 2H), 6.69 (s, 2H), 4.71 (t, J = 6.9 Hz, 2H), 2.89 (d, J = 18.0 Hz, 2H), 2.86 (m, 2H), 2.58−2.44 (m, 10H), 2.26 (d, J = 8.1 Hz, 2H), 2.10−2.00 (m, 6H), 1.93−1.61 (m, 18H), 1.47 (m, 4H), 1.40−1.20 (m, 24H), 1.08 (t, J = 12.3 Hz, 2H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$, a drop of CD_3OD): δ 153.6, 139.7, 127.4, 126.4, 125.9, 112.6, 74.0, 60.7, 55.4, 45.8, 43.7, 40.6, 37.2, 36.9, 36.2, 33.9, 29.3, 29.2, 28.0, 27.8, 26.5, 26.2, 25.7, 23.7, 21.9, 18.6 ppm. Anal. ($C_{54}H_{80}N_2O_4\cdot 2HCl\cdot 3H_2O$) C, H, N.

(*rac*)-2-(1-Hydroxyundecyl)-3-hydroxy-17-*N*-cyclobutylmethylmorphinan (27b). Mp (HCl salt): 115−118 °C. ^{1}H NMR (300 MHz, $CDCl_3$, a drop of CD_3OD): δ 6.68 (s, 2H), 4.69 (t, J = 5.7 Hz, 1H), 2.90 (d, J = 17.4 Hz, 1H), 2.86 (m, 1H), 2.59−2.40 (m, 4H), 2.22 (d, J = 11.1 Hz, 1H), 2.10−2.00 (m, 3H), 1.95−1.60 (m, 8H), 1.58−1.40 (m, 3H), 1.39−1.18 (m, 22H), 1.06 (t, J = 12.3 Hz, 1H), 0.87 (t, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$, a drop of CD_3OD): δ 154.1, 139.6, 126.8, 126.5, 125.8, 112.9, 74.6, 60.6, 55.7, 46.0, 43.5, 40.5, 37.4, 37.4, 36.8, 36.1, 33.8, 31.7, 29.5, 29.5, 29.3, 29.2, 28.1, 27.9, 26.5, 26.2, 25.9, 23.7, 22.5, 21.9, 18.6, 14.0 ppm. Anal. ($C_{32}H_{51}NO_2\cdot HCl$) C, H, N.

(*rac*)-1-(17-*N*-Cyclobutylmethyl-3-hydroxymorphinan-2-yl)-undecane-1,11-diol (28). Mp (HCl salt): 143−145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.65 (s, 1H), 4.69 (t, J = 5.4 Hz, 1H), 3.62 (t, J = 6.9 Hz, 2H), 2.87 (d, J = 18.3 Hz, 1H), 2.77 (m, 1H), 2.58−2.30 (m, 5H), 2.21 (d, J = 11.4 Hz, 1H), 2.06−1.94 (m, 3H), 1.90−1.66 (m, 8H), 1.60−1.53 (m, 4H), 1.41−1.07 (m, 20H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 154.0, 140.4, 127.9, 126.1, 125.9, 113.1, 75.0, 62.9, 61.1, 55.5, 45.9, 44.2, 41.1, 37.4, 37.2, 36.3, 34.5, 32.7, 29.5, 29.4, 29.3, 28.1, 28.0, 26.7, 26.4, 25.9, 25.6, 23.9, 22.1, 18.8 ppm. Anal. ($C_{32}H_{51}NO_3\cdot HCl$) C, H, N.

Hexanedioic Acid Bis(17-*N*-cyclobutylmethyl-3-hydroxymorphinan-2-methyl)amide (29). To a suspension of adipic acid (12.0 mg, 0.08 mmol) in anhydrous methylene chloride (1.0 mL) were added 2 drops of DMF, followed by dropwise addition of oxalylchloride (41 mg, 0.03 mL, 0.32 mmol) under N_2 atmosphere. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and excess oxalyl chloride was removed under high vacuum. The residual acid chloride was dissolved in anhydrous methylene chloride (1.0 mL), and a solution of 2-(aminomethyl)-3-hydroxy-17-*N*-(cyclobutylmethyl)morphinan **19** (55 mg, 0.16 mmol) in

methylene chloride (1.0 mL) was added. To the mixture was added triethylamine (65 mg, 0.09 mL, 0.64 mmol). The mixture was stirred at room temperature overnight. Additional methylene chloride (20 mL) was added, and the organic phase was washed with $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, and solvent removed under reduced pressure. The residual oil was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH/NEt_3, 50/50/1, to yield 30 mg (47%) of a white solid. Mp (HCl salt): 240−245 °C (dec). ^{1}H NMR (base, 300 MHz, $CDCl_3$): δ 7.46 (bs, 2H), 6.23−6.84 (m, 4H), 4.16−4.33 (m, 4H), 2.89 (m, 4H), 2.46−2.75 (m, 10H), 2.04−2.24 (m, 12H), 1.40−1.88 (m, 20H), 1.08−1.38 (m, 12H), 1.08 (m, 2H) ppm. ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 175.0, 154.2, 141.6, 130.0, 127.8, 122.3, 113.9, 60.7, 59.1, 56.2, 45.6, 40.1, 37.2, 36.3, 35.3, 33.9, 29.7, 27.8, 26.6, 26.4, 24.8, 24.6, 22.0, 18.8 ppm. Anal. ($C_{50}H_{70}N_4O_4 \cdot 2HCl \cdot 3H_2O$) C, H, N.

To prove unambiguously that only the diamide formed without formation of ester, LC−MS (performed on an Agilent 6210 time-of-flight spectrometer using an ESI source with the LC being performed on an Agilent 1200 series system with an autosampler and the mobile phases A (H_2O with 0.1% formic acid) and B (acetonitrile with 0.1% formic acid)) showed the presence of only one compound, the NMR data of which are in accordance with the diamide structure. MS (TOF ESI−): m/z (% rel intens) = 791 ($[M - 2H]^{2-}$, 100).

Opioid Binding to the Human μ, δ, and κ Opioid Receptors. CHO cells stably transfected with the human κ opioid receptor (hKOR-CHO), δ-opioid receptor (hDOR-CHO), and the μ-opioid receptor (hMOR-CHO) were obtained from Drs. Larry Toll (SRI International, Palo Alto, CA) and George Uhl (NIDA Intramural Program, Bethesda, MD). The cells were grown in 100 mm dishes in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and penicillin/streptomycin (10 000 units/mL) at 37 °C in a 5% CO_2 atmosphere. The affinity and selectivity of the compounds for the multiple opioid receptors were determined by incubating the membranes with radiolabeled ligands and 12 different concentrations of the compounds at 25 °C in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Incubation times of 60 min were used for the μ-selective peptide [^{3}H]DAMGO and the κ-selective ligand [^{3}H]U-69593. A 3 h incubation was used with the δ-selective antagonist [^{3}H]naltrindole.

Acknowledgment. This work was supported in part by NIH Grants R01-DA14251 (J.L.N.) and K05-DA 00360 (J.M.B.) and a research fellowship to M.D. from the "Deutsche Akademie der Naturforscher Leopoldina" (Grant BMBF-LPD 9901/8-147). Levorphanol tartrate was generously donated by Mallinckrodt Inc. We thank Anna Sromek for assistance in the preparation of this manuscript.

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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