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Articles

Synthesis and Opioid Receptor Affinity of a Series of Aralkyl Ethers of 6α- and 6β-Naltrexol

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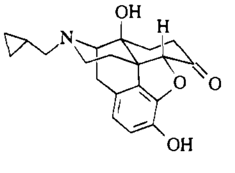
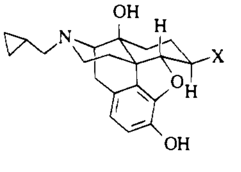
A series of 6-*O*-ethers of 6β- and 6α-naltrexol (**6** and **7**) were prepared to examine the effect of large aralkyl groups on affinity of the ligands for opioid receptors. The affinities of the 6β- and 6α-*O*-ether with benzyl, biphenylmethyl, 1- and 2-naphthylmethyl, and 9-anthracylmethyl groups were determined. Preparation of the ligands was accomplished from suitably 3-*O*-protected derivatives of **6** and **7** by phase transfer catalyzed alkylation using aralkyl halides, followed by deprotection. Both 3-*O*-trityl and -benzyl protecting groups were used. In radioligand displacement assays, compounds from the 6α-*O* ether series had higher affinity than the analogous diastereomers in the 6β-*O* series, with few exceptions. In the 6α-*O* series, the benzyl ether (**29**) and the biphenylmethyl ether (**30**) had the highest affinity, similar to naltrexone. In the 6β-*O* series, the benzyl ether had the highest affinity. The larger aralkyl ethers had slightly less affinity. Large lipophilic 6β-*O*- and 6α-*O*-aralkyl groups are readily accommodated in the drug–receptor interaction.

Naltrexone (**1**), a nearly pure opioid receptor antagonist with high affinity for μ-opioid binding sites, has been modified to prepare many derivatives useful in studying stucture–activity relationships and in characterizing opioid receptors. The 6-position in **1** has been modified to provide many useful compounds.[1] Among these are electrophilic ligands derived from the isomeric 6β- and 6α-naltrexamines, including β-chlornaltrexamine (β-CNA) (**2**), β-funaltrexamine (β-FNA) (**3**),[2] and several other related derivatives.[3] Diastereomeric 6-spiro-α-methylene-γ-lactones (**4** and **5**),[4] related 6α-*O*-tethered ethers, epoxides, and α-methylene-γ-lactones have also generally shown relatively high affinity for μ- and δ-opioid receptors.[5] Because even bulky 6β-*O*-tethered α-methylene-γ-lactones and related agents, including the 6β-glucuronide of morphine,[5,6] have relatively high affinity for μ- and δ-opioid receptors, we have now investigated a series of compounds to examine the effect of additional steric bulk in ethers of both 6β- and 6α-naltrexol (**6** and **7**).

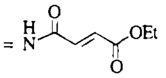


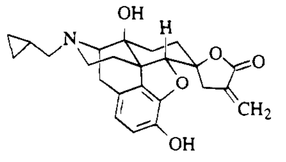
1 naltrexone



2 X = N(CH$_2$CH$_2$Cl)$_2$

3 X =





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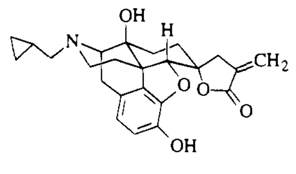

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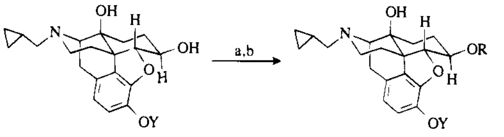
Scheme 1[a]



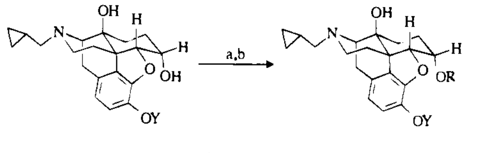
6 Y = H (6β-naltrexol)
8 Y = Tr (CPh$_3$)
21 Y = Bz

9 R = Bz Y = Tr
10 R = 4-CH$_2$-biphenyl Y = Tr
11 R = 1-CH$_2$-naphthyl Y = Tr
12 R = 2-CH$_2$-naphthyl Y = Tr
13 R = 9-CH$_2$-anthracyl Y = Tr
14 $R = CH_2{\cdot}\overset{\overset{O}{\|}}{C}{\cdot}\text{adamantyl}$ Y = Tr
22 $R = CH_2{\cdot}\overset{\overset{O}{\|}}{C}{\cdot}\text{adamantyl}$ Y = Bz

15 R = Bz Y = H
16 R = 4-CH$_2$-biphenyl Y = H
17 R = 1-CH$_2$-naphthyl Y = H
18 R = 2-CH$_2$-naphthyl Y = H
19 R = 9-CH$_2$-anthracyl Y = H
20 $R = CH_2{\cdot}\overset{\overset{O}{\|}}{C}{\cdot}\text{adamantyl}$ Y = H

[a] (a) KOH, *n*-Bu$_4$N$^+$Br$^-$, RX, CH$_2$Cl$_2$; (b) HOAc/H$_2$O for trityl protected derivatives, hydrogenolysis for **22** → **20**.

Scheme 2[a]



7 Y = H (6α-naltrexol)
23 Y = Bz
34 Y = Tr

24 R = Bz Y = Bz
25 R = 4-CH$_2$-biphenyl Y = Bz
26 R = 1-CH$_2$-naphthyl Y = Bz
27 R = 2-CH$_2$-naphthyl Y = Bz
28 R = 9-CH$_2$-anthracyl Y = Bz
35 R = 9-CH$_2$-anthracyl Y = Tr

29 R = Bz Y = H
30 R = 4-CH$_2$-biphenyl Y = H
31 R = 1-CH$_2$-naphthyl Y = H
32 R = 2-CH$_2$-naphthyl Y = H
33 R = 9-CH$_2$-anthracyl Y = H

[a] (a) KOH, *n*-Bu$_4$N$^+$Br$^-$, RX, CH$_2$Cl$_2$; (b) transfer hydrogenation, except HOAc/H$_2$O for **35** → **33**.

In this paper, we report the preparation and opioid receptor affinity for ethers prepared from **6** and **7**, in which the substituents are principally increasingly large aralkyl ethers, ranging from benzyl to 1- and 2-naphthylmethyl and 9-anthracylmethyl substituents. These series were chosen to give substituents of differing size at both the 6α- and 6β-oxygens and were based on relative ease of their preparation. These compounds

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Table 1. Comparison of Opioid Receptor Binding of Aralkyl Ethers of 6β- and 6α-Naltrexol against 0.5 nM [^{3}H]Bremazocine (Total Sites), against 1.0 nM [^{3}H]DAMGO (μ-Sites), against 1.0 nM [^{3}H]DPDPE (δ-Sites), and against 1.0 nM [^{3}H]U-69,593 (κ-Sites) in the Guinea Pig Membrane Preparation

	IC$_{50}$ (nM)^a							
	total sites [^{3}H]bremazocine		μ-sites [^{3}H]DAMGO^b		δ-sites [^{3}H]DPDPE^c		κ-sites [^{3}H]U-69,593^d	
compound	β series	α series	β series	α series	β series	α series	β series	α series
6β-*O*-benzyl ether (**15**)	3.4		2.4		2.9		2.0	
6α-*O*-benzyl ether (**29**)		1.5		0.3		1.4		0.6
6β-*O*-CH$_2$biphenylyl ether (**16**)	28		10		19		12	
6α-*O*-CH$_2$biphenylyl ether (**30**)		3.3		0.7		11		1.5
6β-*O*-1-CH$_2$naphthyl ether (**17**)	11		3.1		5.5		6.1	
6α-*O*-1-CH$_2$naphthyl ether (**31**)		7.3		1.0		6.6		4.4
6β-*O*-2-CH$_2$naphthyl ether (**18**)	5.0		1.7		25		1.5	
6α-*O*-2-CH$_2$naphthyl ether (**32**)		4.7		1.2		20		1.4
6β-*O*-9-CH$_2$anthracyl ether (**19**)	71		16		48		27	
6α-*O*-9-CH$_2$anthracyl ether (**33**)		45		6.6		36		34
6β-*O*-CH$_2$COadamantyl ether (**20**)	13		6.6		30		3.3	
standards								
6β-naltrexol (**6**)	8.3		1.1		32		2.6	
6α-naltrexol (**7**)		6.0		0.5		26		1.8
naltrexone	3.8		0.23		10		0.53	
DPDPE	>1000		>1000		1.8		>1000	
U-69,593	140		1760		5000		2.1	

[a] Averages of duplicate determinations ± 10–15%. [b] [^{3}H]DAMGO or [^{3}H][D-Ala^2,MePhe^4,Gly-ol^5]enkephalin (1 nM). [c] [^{3}H][D-Pen^2,D-Pen^5]enkephalin (1 nM). [d] [^{3}H]U-69,593 or [^{3}H]-(5α,7α,8β)-(−)-*N*-methyl-*N*-(1-pyrrolidinyl-1-oxaspiro[4.5]dec-8-yl)benzeneacetamide (1 nM).

were prepared using phase-transfer etherification conditions starting from 3-*O*-protected derivatives of 6β- and 6α-naltrexol (Schemes 1 and 2).

Chemistry

Because the equatorial 6β-alcohol in **6** is sterically less hindered than the 6α-hydroxyl group in **7**, the 6β-*O*-series was investigated first. These ethers were prepared by phase transfer catalyzed alkylation (aralkyl halide, aqueous KOH, tetrabutylammonium salts, CH$_2$Cl$_2$) of the 3-*O*-trityl-6β-naltrexol (**8**), the trityl group being chosen as the phenolic protecting group because it was both easy to attach and to remove (Scheme 1). Compounds **9**–**13** were prepared in *ca.* 55-90% yield, and removal of 3-*O*-trityl group occurred readily in aqueous acetic acid to afford phenols **15**–**19** (71–98% yield). When we attempted to extend the 6β-*O*-ether series to an adamantyl derivative (**14**) using α-bromomethyl adamantyl ketone as the halide, no product was obtained, perhaps due to the relatively high energy of activation of the alkylation process because of the steric bulk of the nearby trityl substituent at O-3. Alkylation of the corresponding 3-*O*-benzyl ether (**21**), however, afforded a low yield of the desired adamantanacyl ether (**22**). Hydrogenolysis removed the 3-*O*-benzyl group to complete the synthesis of **20**.

Due to the success of the smaller benzyl group as the protecting substituent for preparation of **22**, we sought to use it for preparation of ethers in the sterically more restricted 6α-series *via* benzyl ether **23** (Scheme 2). Attempted removal of the 3-*O*-benzyl substituent from 3-*O*,6α-*O*-dibenzyl ether (**24**) using mild hydrogenolysis conditions (H$_2$, Pd·C) resulted in the removal of both the aromatic and aliphatic benzyl ethers. However, use of 1,4-cyclohexadiene (Pd·C) in transfer hydrogenation conditions,[7] previously used successfully to effect selective hydrogenolysis of aromatic benzyl ethers in the presence of aliphatic benzyl ethers, was quite effective in preparation of phenol **29**.

Preparation of 3-*O*-benzyl derivatives of analogous 4-biphenylylmethyl and 1- and 2-naphthylmethyl analogs (**24**–**26**) occurred in 40–60% yield. However, repeated attempts to effect the transfer hydrogenation process using 1,4-cyclohexadiene failed. Subsequent use of hydrazine hydrate as the hydrogen source, according to the method of Anwer et al.,[8] however, was successful for preparation of these three phenols **30**–**32**.

Preparation of the 6α-*O*-anthracylmethyl analog (**33**) was more difficult. Alkylation of the 3-*O*-benzyl-6α-naltrexol produced very low yields of alkylated products which were obtained as mixtures. One last attempt to prepare **33** via 3-*O*-trityl-6α-naltrexol (**34**), however, afforded a low yield (16%) of the desired 6α-*O*-anthracylmethyl ether **35**, and facile removal of the trityl group was affected with aqueous acetic acid to yield **33**.

Opioid Receptor Binding

The affinities of 6β-*O*-ethers **15**–**20** and 6α-*O*-ethers **29**–**33** at the three opioid receptor sites (μ, δ, and κ) were determined in a crude membrane preparation from the guinea pig brain (Table 1).[9] The radioligand displacement assays were run using [^{3}H]bremazocine (all sites), [^{3}H]DAMGO (μ-sites), [^{3}H]DPDPE (δ-sites), and [^{3}H]U-69,593 (κ-sites).[10–12] Naltrexone (1), 6β- and 6α-naltrexol (**6** and **7**), and standard ligands for the three sites were included in the assays.

In the 6β-*O* ether series (**15**–**20**), the smallest 6β-*O*-benzyl ether (**15**) had the highest affinity, having less affinity than natrexone (1), but similar affinity to the naltrexols. The ethers with large aralkyl groups (**18**, **19** and **20**) had significant affinity, although less than that of **15** by 6–15-fold. Thus large groups extended from the 6β-oxygen atom are accommodated in the drug–receptor interaction.

In the 6α-*O* ethers series (**29**–**33**), the 6α-*O*-benzyl ether (**29**) and the 6α-*O*-(4-biphenyl)methyl ether (**30**) had the highest affinity at μ- and κ-sites. The 6α-*O*-benzyl ether had the highest affinity of the compounds tested, with affinity similar to naltrexone (1) (greater than the naltrexols **6** and **7**), but it was less selective than naltrexone, showing significant affinity for the δ-opioid receptor, approximately equivalent to DPDPE. The linear extended geometry of the biphenyl group in **30** is also readily accommodated in the drug–receptor interaction. Even the ethers with larger aralkyl groups have significant affinity in the radioligand displacement assays.

The ethers in the 6α-*O* series generally showed greater affinity than the analogous diastereomers in the 6β-*O* series, with only a few exceptions. Thus, it seems likely that there are small differences in the geometric requirements of the drug–receptor interactions of the members of the two series.

We conclude that very bulky tethered ethers do not decrease affinity greatly. It seems that the spatial requirements of the receptors accommodate these very significant structural changes at the 6-position in the C-ring, appearing to be sufficiently large to allow large lipophilic 6β-*O*- and 6α-*O*-aralkyl substituents to be present without major loss of affinity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 series FTIR. Absorptions are expressed in frequency units (cm^{-1}). NMR spectra were recorded on the Varian VXR-300 spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on the VG-7070 and the VG-70SEQ mass spectrometers by direct-insertion probe. Optical rotations were measured on a JASCO-DIP-4 digital polarimeter. All reaction procedures were performed under an argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel HLF glass plates. A solvent system of hexane:EtOAc:triethylamine (200:150:4) was used for TLC. Flash column chromatography was performed using a Kontes 19 × 400 nm glass flash column and ~15 cm (21 g) of Merck silica gel 60 (230–400 mesh) which has been conditioned with 100 mL of CH_2Cl_2. Tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) and tetrabutylammonium bromide (TBABr) were the phase transfer catalysts used in the two-phase alkylation reactions.

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β,14-dihydroxymorphinan (8). To a solution of 6β-naltrexol (**6**)[13] (1.50 g, 4.37 mmol), triphenylmethyl chloride (1.59 g, 5.69 mmol), and $TBAHSO_4$ (920 mg, 2.58 mmol) in CH_2Cl_2 (40 mL), was added aqueous KOH (920 mg in 40 mL of H_2O). After the reaction mixture was stirred vigorously overnight at room temperature, the organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, washed with H_2O (15 mL), dried with anhydrous sodium sulfate, and then evaporated to dryness. The resulting oily residue was further purified by flash column chromatography. The silica gel column was conditioned with CH_2Cl_2 (100 mL). The product was then eluted sequentially with CH_2Cl_2 (200 mL), followed by 20:80 EtOAc:CH_2Cl_2 (250 mL), 30:70 EtOAc:CH_2Cl_2 (100 mL), and 50:50 EtOAc:CH_2Cl_2 (200 mL). Evaporation yielded a yellow foam (2.11 g, 83% yield) which was used without further purification: ^1H NMR ($CDCl_3$) δ 0.05–0.12 (m, 2 H, C-19 H, C-20 H), 0.45–0.53 (m, 2 H, C-19 H′, C-20 H′), 0.72-0.85 (m, 1 H, C-18 H), 1.05–1.56 (m, 4 H, C-7 H, C-8 2 H, C-15 H), 1.72–2.11 (m, 3 H, C-7 H, C-15 H, C-16 H), 2.29 (d, *J* = 6.5 Hz, NCH_2 cyclopropyl), 2.38–2.55 (m, 2 H, C-10α H, C-16 H), 2.75–2.80 (m, 1 H, C-6α H), 2.88 (d, *J* = 18.6 Hz, 1 H, C-10β H), 2.98 (d, *J* = 5.8 Hz, 1 H, C-9 H), 4.20 (d, *J* = 5.9 Hz, 1 H, C-5β H), 6.25 (d, *J* = 8.3 H, 1 H, C-1 H), 6.55 (d, *J* = 8.2 H, 1 H, C-2 H), 7.15–7.27 (m, 9 H, trityl C-3, C-4, and C-5 H), 7.39–7.46 (m, 6 H, trityl C-2 and C-6).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-6β-(benzyloxy)-4,5α-epoxy-14-hydroxymorphinan (9). To a solution of **8** (200 mg, 0.342 mmol), TBABr (40 mg, 0.124 mmol), and benzyl bromide (0.163 mL, 1.37 mmol) in CH_2Cl_2 (15 mL) was added aqueous 50% KOH (15 mL) with vigorous stirring. The reaction mixture was slightly yellow. After stirring vigorously overnight, 10 mL each of water and CH_2Cl_2 were added to aid phase separation. The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extractions were dried and evaporated. The product was then purified by flash column chromatography. Elution with CH_2Cl_2 (150 mL), followed by 20:80:EtOAc:CH_2Cl_2 (150 mL) and EtOAc (100 mL), afforded 180 mg of **9** (78% yield): ^1H NMR ($CDCl_3$) δ 2.85 (d, *J* = 18.4 Hz, 1 H, C-10β H), 2.97 (d, *J* = 5.4 Hz, 1 H, C-9 H), 3.13–3.22 (m, 1 H, C-6α H), 4.43 (d, *J* = 6.14 Hz, 1 H, C-5β H), 4.67 and 4.83 (2d, *J* = 12.2 Hz, 2 H, $PhCH_2$), 6.21 (d, *J* = 8.3 Hz, 1 H, C-1 H), 6.47 (d, *J* = 8.25 Hz, 1 H, C-2 H), 7.15–7.52 (m, 20 H, benzyl and trityl aromatic H).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-6β-(4-biphenylylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (10). From trityl ether **8** (200 mg, 0.342 mmol), TBABr (40 mg, 0.124 mmol), 4-(chloromethyl)biphenyl (0.27 mL, 1.37 mmol) in CH_2Cl_2 (15 mL) and aqueous 50% KOH (15 mL) was obtained 200 mg of ether 10 (78% yield) after chromatography: ^1H NMR ($CDCl_3$) δ 2.80–3.02 (m, 2 H, C-9 H, C-10β H), 3.15–3.25 (m, 1 H, C-6 H), 4.44 (d, *J* = 6.2 Hz, 1 H, C-5 H), 4.72 and 4.87 (2d, *J* = 12.2 Hz, 2 H, biphenyl-CH_2), 6.21 (d, *J* = 8.2 Hz, 1 H, C-1 H), 6.46 (d, *J* = 8.2 Hz, 1 H, C-2 H), 7.10–7.60 (m, 24 H, biphenyl and trityl aromatic H).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-6β-(1-naphthylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (11). From trityl ether **8** (100 mg, 0.171 mmol), TBABr (20 mg, 0.062 mmol), and 1-(chloromethyl)naphthalene (120 mg, 0.683 mmol) in CH_2Cl_2 (15 mL) and aqueous 50% KOH (15 mL) was obtained 108 mg of ether 11 (87% yield) after chromatography: ^1H NMR ($CDCl_3$) δ 2.86 (d, *J* = 18.4 Hz, 1 H, C-10β H), 2.98 (d, *J* = 4.8 Hz, 1 H, C-9 H), 3.23–3.35 (m, 1 H, C-6 H), 4.49 (d, *J* = 6.1 Hz, 1 H, C-5β H), 5.02 and 5.32 (2d, *J* = 11.8 Hz, 2 H, Naph-CH_2), 6.24 (d, *J* = 8.2 Hz, 1 H, C-1 H), 6.52 (d, *J* = 8.2 Hz, 1 H, C-2 H), 7.10–7.28 (m, 9 H, trityl C-3, C-4 and C-5 H), 7.38–7.59 (m, 9 H, trityl C-2 and C-6 H, Naph C-3, C-6, C-7 H), 7.61–7.68 (m, 1 H, Naph C-2 H), 7.73–7.88 (m, 2 H, Naph C-4 and C-5 H), 8.07–8.14 (m, 1 H, Naph C-8 H).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-6β-(2-naphthylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (12). From trityl ether **8** (100 mg, 0.171 mmol), TBABr (20 mg, 0.062 mmol), and 2-(bromomethyl)naphthalene (141 mg, 0.683 mmol) in CH_2Cl_2 (15 mL) and aqueous 50% KOH (15 mL) was obtained 116 mg of ether **12** (93% yield) after chromatography: ^1H NMR ($CDCl_3$) δ 2.86 (d, *J* = 18.6 Hz, 1 H, C-10β H), 2.98 (d, *J* = 5.4 Hz, 1 H, C-9 H), 3.20–3.30 (m, 1 H, C-6 H), 4.48 (d, *J* = 6.2 Hz, 1 H, C-5β H), 4.86 and 5.01 (2d, *J* = 12.2 Hz, 2 H, Naph-CH_2) 6.22 (d, *J* = 8.3 Hz, 1 H, C-1 H), 6.50 (d, *J* = 8.2 Hz, 1 H, C-2 H), 7.14–7.30 (m, 9 H, trityl C-3, C-4, and C-5 H), 7.40–7.57 (m, 9 H, Naph C-2 and C-6 H, three Naph C-H), 7.75–7.89 (m, 4 H, Naph C-1, C-4, C-5, and C-7 H).

17-(Cyclopropylmethyl-3-(triphenylmethoxy)-6β-(9-anthracylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (13). From trityl ether **8** (300 mg, 0.512 mmol), TBABr (60 mg, 0.186 mmol), and 9-(chloromethyl)anthracene (464 mg, 2.05 mmol) in CH_2Cl_2 (15 mL) and aqueous 50% KOH (15 mL) was obtained 220 mg of ether **13** (55% yield) after chromatography: ^1H NMR ($CDCl_3$) δ 2.88 (d, *J* = 18.4 Hz, C-10β H), 2.99 (d, *J* = 5.4 Hz, 1 H, C-9 H), 3.46–3.56 (m, 1 H, C-6 H), 4.52 (d, *J* = 6.3 Hz, 1 H, C-5β H), 5.51 and 5.76 (2d, *J* = 10.7 Hz, 2 H, An (anthracyl) CH_2), 6.30 (d, *J* = 8.3 Hz, 1 H, C-1 H), 6.59 (d, *J* = 8.2 Hz, 1 H, C-2 H), 7.09–7.26 (m, 9 H, trityl C-3, C-4, and C-5 H), 7.39–7.57 (m, 10 H, trityl C-2 and C-6 H, An C-2, C-3, C-6, C-7 H), 7.93–8.04 (m, 2 H, An C-1 and C-8 H), 8.40–8.50 (m, 3 H, An C-4, C-5 and C-10 H).

17-(Cyclopropylmethyl)-6β-(benzyloxy)-4,5α-epoxy-3,14-dihydroxymorphinan (15). To a solution of trityl ether **9** (440 mg, 0.652 mmol) was added aqueous 50% acetic acid (25 mL) with vigorous stirring. The reaction mixture was slightly yellow. After stirring vigorously overnight the reaction mixture was evaporated, and 15 mL each of saturated $NaHCO_3$ solution and CH_2Cl_2 were added to dissolve the solid for phase separation. The organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The organic extraction was then back-extracted with water (15 mL). The organic extractions were evaporated to dryness. The product was then purified by flash column chromatography. Elution with CH_2Cl_2 (200 mL), followed by 20:80 EtOAc:CH_2Cl_2 (100 mL), 50:50 EtOAc:CH_2Cl_2 (150 mL), and EtOAc (100 mL) afforded 253 mg of phenol **15** (90% yield): $[\alpha]_D = -139.4°$ (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.09–0.16 (m, 2 H, C-19 H, C-20 H), 0.49–0.59 (m, 2 H, C-19 H′, C-20 H′), 0.78–0.90 (m, 1 H, C-18 H), 1.24–1.87 (m, 4 H, C-7 H, C-8 2 H, C-15 H), 1.90–2.32 (m, 3 H, C-7 H, C-15 H, C-16 H), 2.37 (d, J = 6.6 Hz, 2 H, NCH_2 cyclopropyl), 2.51–2.68 (m, 2 H, C-10α H, C-16 H), 2.95–3.14 (m, 2 H, C-9 H, C-10β H), 3.23–3.33 (m, 1 H, C-6α H), 4.60–4.72 (m, 3 H, C-5β 1 H, $PhCH_2$), 6.52 (d, J = 8.1 Hz, 1 H, C-1 H), 6.68 (d, J = 8.2 Hz, 1 H, C-2 H), 7.21–7.40 (m, 5 H, benayl aromatic H); ^{13}C NMR ($CDCl_3$) δ 3.32 and 3.96 (C-19 and C-20), 9.34 (C-18), 22.63 (C-10), 23.67 (C-7), 29.56 (C-15), 30.44 (C-8), 43.87 (C-16), 47.80 (C-13), 59.09 (C-17), 62.20 (C-9), 70.10 (C-14), 71.02 (C-6), 79.67 ($PhCH_2$), 95.40 (C-5), 116.61 (C-2), 118.67 (C-1), 124.25 (C-11), 127.30, 127.48, 128.08 (5 benzyl aromatic C), 131.53 (C-12), 138.55 (Ph C-1), 139.26 (C-3), 141.94 (C-4); FTIR (neat) 2926, 1500, 1452, 1322, 1238, 1185, 1096, 1035, 915, 736, 698 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{27}H_{32}NO_4$ 434.2331, obsd 434.2303. Anal. ($C_{27}H_{31}NO_4$) C, H, N.

17-(Cyclopropylmethyl)-6β-(4-biphenylylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (16). From ether **10** (520 mg, 0.692 mmol) in 50% AcOH (25 mL) was obtained 256 mg of phenol **16** (72% yield), $[\alpha]_D = -162.8°$ (c = 1.00, CH_2Cl_2), after chromatography: ^1H NMR ($CDCl_3$) δ 0.06–0.17 (m, 2 H, C-19 H, C-20 H), 0.45–0.57 (m, 2 H, C-19 H′, C-20 H′), 0.80–0.92 (m, 1 H, C-18 H), 1.24–1.48 (m, 2 H, C-8 H, C-15 H), 1.58–1.68 (m, 1 H, C-8 H), 1.73–1.85 (m, 1 H, C-7 1 H), 1.91–2.18 (m, 2 H, C-7 H, C-15 H), 2.25–2.35 (m, 1 H, C-16 H), 2.40 (d, J = 6.5 Hz, 2 H, NCH_2 cyclopropyl), 2.54–2.75 (m, 2 H, C-10α H, C-16 H), 2.91–3.03 (m, 1 H, C-9 H), 3.16–3.24 (m, 1 H, C-10β H), 3.26–3.37 (m, 1 H, C-6α H), 4.62–4.71 (m, 3 H, C-5β 1 H, biphenyl-CH_2), 6.51 (d, J = 8.2 Hz, 1 H, C-1 H), 6.71 (d, J = 7.9 Hz, 1 H, C-2 H), 7.25–7.57 (m, 9 H, biphenyl methine H); ^{13}C NMR ($CDCl_3$) δ 3.86 and 4.04 (C-19 and C-20), 8.88 (C-18), 22.75 (C-10), 23.60 (C-7), 29.56 (C-15), 30.10 (C-8), 44.13 (C-16), 47.58 (C-13), 58.98 (C-17), 62.16 (C-9), 70.14 (C-14), 71.67 (C-6), 79.64 (biphenyl-CH_2), 95.14 (C-5), 116.98 (C-2), 118.69 (C-1), 123.47 (C-11), 126.79, 126.83, 126.97, 127.87, 128.50 (biphenyl methine C), 131.31 (C-12), 137.54 (biphenyl C-1), 139.69, 140.07, 140.66 (C-3, biphenyl quaternary C), and 142.04 (C-4); FTIR (neat) 3027, 2924, 1489, 1477, 1150, 1098, 1039, 1007, 985, 899, 785, 699 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{33}H_{36}NO_4$ 510.2644, obsd 510.2624. Anal. ($C_{33}H_{35}NO_4$) C, H, N.

17-(Cyclopropylmethyl)-6β-(1-naphthylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (17). From ether 11 (270 mg, 0.375 mmol) and aqueous 50% acetic acid (15 mL) was obtained 140 mg of phenol **17** (78% yield), $[\alpha]_D = -116.8°$ (c = 1.00, CH_2Cl_2), after chromatography: ^1H NMR ($CDCl_3$) δ 0.07–0.16 (m, 2 H, C-19 H, C-20 H), 0.48–0.57 (m, 2 H, C-19 H′, C-20 H′), 0.75–0.86 (m, 1 H, C-18 H), 1.24–1.48 (m, 2 H, C-8 H, C-15 H), 1.55–1.65 (m, 1 H, C-8 H), 1.78–1.90 (m, 1 H, C-7 1 H), 1.91–2.13 (m, 2 H, C-7 H, C-15 H), 2.15–2.25 (m, 1 H, C-16 H), 2.34 (d, J = 6.5 Hz, 2 H, NCH_2 cyclopropyl), 2.48–2.64 (m, 2 H, C-10α H, C-16 H), 2.91–2.98 (d, J = 18.6 Hz, 1 H, C-10β H), 30.6 (d, J = 4.9 Hz, 1 H, C-7 H), 3.30–3.43 (m, 1 H, C-6 H), 4.65 (d, J = 6.4 Hz, 1 H, C-5 H), 5.04 and 5.12 (2d, J = 12.2 Hz, 2 H, $NaphCH_2$), 6.51 (d, J = 8.3 Hz, 1 H, C-1 H), 6.65 (d, J = 7.8 Hz, 1 H, C-2 H), 7.35–7.58 (m, 4 H, Naph aromatic H), 7.73–7.88 (m, 2 H, Naph C-4 and C-5 H), 8.12–8.18 (m, 1 H, Naph C-8 H); ^{13}C NMR ($CDCl_3$) δ 3.78 and 3.92 (C-19 and C-20), 9.29 (C-18), 22.55 (C-10), 23.64 (C-7), 29.48 (C-15), 30.35 (C-8), 43.78 (C-16), 47.74 (C-13), 58.99 (C-17), 62.11 (C-9), 69.63 (C-14), 70.17 (C-6), 79.74 ($NaphCH_2$), 95.20 (C-5), 116.73 (C-2), 118.59 (C-1), 123.47 (C-11), 124.00, 125.02, 125.44, 125.82, 126.24, 128.19, 128.24 (Naph aromatic methine C), 131.46 (C-12), 133.80, 133.44 (C-Naph C-4a and C-8a), 139.36 (C-3), and 141.93 (C-4); FTIR (neat) 3334, 2926, 1619, 1503, 1454, 1332, 1264, 1237, 1185, 1096, 1035, 835, 799, 776, 735 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{31}H_{34}NO_4$ 484.2488, obsd 484.2480. Anal. ($C_{31}H_{33}NO_4$) C, H, N.

17-(Cyclopropylmethyl)-6β-(2-naphthylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (18). From ether **12** (350 mg, 0.486 mmol) and aqueous 50% acetic acid (15 mL) was obtained 170 mg of phenol **18** (75% yield), $[\alpha]_D = -142.7°$ (c = 1.00, CH_2Cl_2, after chromatography: ^1H NMR ($CDCl_3$) δ 0.07–0.16 (m, 2 H, C-19 H, C-20 H), 0.48–0.58 (m, 2 H, C-19 H′, C-20 H′), 0.80–0.92 (m, 1 H, C-18 H), 1.22–1.32 (m, 1 H, C-8 H), 1.40–1.48 (m, 1 H, C-15 H), 1.55–1.65 (m, 1 H, C-8 H), 1.72–1.84 (m, 1 H, C-7 H), 1.91–2.18 (m, 2 H, C-7 H, C-15 H), 2.21–2.38 (m, 1 H, C-16 H), 2.40 (d, J = 6.6 Hz, 2H, NCH_2 cyclopropyl), 2.53–2.75 (m, 2 H, C-10α H, C-16 H), 2.96 (d, J = 18.4 Hz, 1 H, C-10β H), 3.18 (d, J = 5.5 Hz, 1 H, C-9 H), 3.29–3.40 (m, 1 H, C-6α H), 4.68 (d, J = 6.4, 1 H, C-5β H), 4.75–4.86 (bs, 2 H, $NaphCH_2$), 6.51 (d, J = 8.1 Hz, 1 H, C-1 H), 6.69 (d, J = 8.1 Hz, 1 H, C-2 H), 7.40–7.50 (m, 3 H, Naph methine H), 7.74–7.85 (m, 4 H Naph methine H); ^{13}C NMR ($CDCl_3$) δ 3.86 and 4.04 (C-19 and C-20), 9.00 (C-18), 22.73 (C-10), 23.69 (C-7), 29.59 (C-15), 30.20 (C-8), 44.08 (C-16), 47.67 (C-13), 59.01 (C-17), 62.17 (C-9), 70.12 (C-14), 71.09 (C-6), 79.57 ($NaphCH_2$), 95.35 (C-5), 116.90 (C-2), 118.72 (C-1), 123.73 (C-11), 125.55, 125.65, 125.82, 126.13, 127.45, 127.68, 127.77 (Naph methine C), 131.37 (C-12), 133.03, 132.68 (Naph C-4a and C-8a), 135.94 (Naph C-2), 139.53 (C-3), and 142.00 (C-4); FTIR (neat) 3055, 2947, 1561, 1501, 1458, 1240, 1125, 1096, 982, 915, 735 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{31}H_{34}NO_4$ 484.2488, obsd 484.2462. Anal. ($C_{31}H_{33}NO_4$) C, H, N.

17-(Cyclopropylmethyl)-6β-(9-anthracylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (19). From ether **13** (220 mg, 0.282 mmol) and aqueous 50% acetic acid (15 mL) was obtained 150 mg of **19** (98% yield), $[\alpha]_D = -117.2°$ (c = 1.00, CH_2Cl_2), after chromatography: ^1H NMR ($CDCl_3$) δ 0.05–0.13 (m, 2 H, C-19 H, C-20 H), 0.43–0.53 (m, 2 H, C-19 H′, C-20 H′), 0.70–0.86 (m, 1 H, C-18 H), 1.30–1.50 (m, 2 H, C-8 H, C-15 H), 1.55–1.65 (m-1 H, C-8 H), 1.72–2.12 (m, 3 H, C-7 2 H, C-15 H), 2.12–2.22 (m, 1 H, C-16 H), 2.30 (d, J = 6.4 Hz, 2 H, NCH_2 cyclopropyl), 2.45–2.61 (m, 2 H, C-10α H, C-16 H), 2.96 (d, J = 18.6 Hz, 1 H, C-10β H), 3.05 (d, J = 5.3 Hz, 1 H, C-9 H), 3.43–3.55 (m, 1 H, C-6α H), 4.69 (d, J = 6.35, 1 H, C-5β H), 5.57 (s, 2 H, An-CH_2), 6.51 (d, J = 7.8 Hz, 1 H, C-1 H), 6.67 (d, J = 7.8 Hz, 1 H, C-2 H), 7.35–7.55 (m, 4 H, four An methine H), 7.90–8.01 (m, 2 H, An C-1 and C-8 H), 8.32–8.42 (m, 3 H, three An methine H); ^{13}C NMR ($CDCl_3$) δ 3.78 and 3.91 (C-19 and C-20), 9.41 (C-18), 22.56 (C-10), 24.07 (C-7), 29.61 (C-15), 30.49 (C-8), 43.74 (C-16), 47.90 (C-13), 59.05 (C-17), 62.16 (C-9), 64.07 (C-14), 71.11 (C-6), 80.53 (An-CH_2), 95.60 (C-5), 116.56 (C-2), 118.68 (C-1), 124.27, 125.69, 125.90, 128.08, 128.77, 130.67, 131.25, 131.58 (other aromatic carbons of the anthracene ring and naltrexol), 139.21 (C-3), and 141.92 (C-4); FTIR (neat) 3357, 1622, 1505, 1455, 1264, 1238, 1185, 1157, 1095, 1074, 1035, 733 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{35}H_{36}NO_4$ 534.2644, obsd 534.2623. Anal. ($C_{35}H_{35}NO_4 \cdot 1.75H_2O$) H, N; C: calcd, 74.58; found, 74.06.

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-6β-morphinanyl 2-Adamantyl-2-oxoethyl Ether (20). To a solution of ether **22** (160 mg, 0.263 mmol) in absolute ethanol (10 mL) and H_2O were added 5% palladium on activated carbon catalyst (15 mg) and 2 N HCl (2 drops). The reaction mixture was first flushed with argon and then stirred vigorously under an atmosphere of hydrogen (balloon) at room temperature. After vigorous stirring overnight, the reaction mixture was filtered through Celite. To this mixture were added saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (40 mL). The organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness. The product was then purified by flash column chromatography. Elution with 80:20 CH_2Cl_2:EtOAc (200 mL) followed by 50:50 CH_2Cl_2:EtOAc (200 mL) afforded 110 mg of **20** (81% yield): $[\alpha]_D = -101.8°$ (c = 0.74, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.11–0.17 (m, 2 H, C-19 H, C-20 H), 0.50–0.56 (m, 2 H, C-19 H′, C-20 H′), 0.75–0.90 (m, 1 H, C-18 H), 1.25–1.40 (m, C-8 H), 1.42–1.49 (m, 1 H, C-15 H), 1.57–2.13 (m, 19 H, C-7 2 H, C-8 H, C-15 H, Ad (adamantyl) CH_2 and CH), 2.15–2.30 (m, 1 H, C-16 H), 2.36 (d, J = 6.7 Hz, 2 H, C-17 2 H), 2.51–2.69 (m, 2 H, C-10α H, C-16 H), 3.00 (d, J = 18.2 Hz, 1 H, C-10β H), 3.08 (d, J = 5.4 Hz, 1 H, C-9 H), 3.18–3.28 (m, 1 H, C-6α

H), 4.45 and 4.62 (2d, $J = 17.6$ H, 2 H, AdC(O)CH_2), 4.62 (d, $J = 6.5$ Hz, 1 H, C-5β H), 6.54 (d, $J = 8.0$ Hz, 1 H, C-1 H), 6.70 (d, $J = 8.2$ Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.88 and 4.01 (C-19 and C-20), 9.46 (C-18), 22.64 (C-10), 23.70 (C-7), 27.82 (C-25, C-27, C-30), 29.65 (C-15), 30.43 (C-8), 36.46 (three AdCH_2), 37.99 (three AdCH_2), 43.86 (C-16), 45.19 (Ad quaternary C), 47.89 (C-13), 59.13 (C-17), 62.19 (C-9), 70.12 (C-14), 70.25 (C-6), 80.95 (AdC(O)CH_2), 95.30 (C-5), 116.96 (C-2), 118.80 (C-1), 124.29 (C-11), 131.64 (C-12), 139.52 (C-3), 142.07 (C-4), 211.72 (AdCO); FTIR (neat) 3377, 2905, 2849, 1711, 1641, 1618, 1502, 1453, 1321, 1238, 1186, 1126, 1036, 1004, 917, 854 cm^{-1}; HRFABMS [M + 1]$^+$ calcd for $C_{32}H_{42}NO_5$ 520.3063, obsd 520.3074. Anal. ($C_{32}H_{41}NO_5 \cdot 0.75H_2O$) C, H, N.

17-(Cyclopropylmethyl)-3-(benzyloxy)-4,5α-epoxy-14-hydroxy-6β-morphinanyl 2-Adamantyl-2-oxoethyl Ether (22). A solution of 3-*O*-benzyl-6β-naltrexol (**21**) (315 mg, 0.727 mmol), obtained by the method of Dasher et al.,[5] 1-adamantyl bromomethyl ketone (750 mg, 2.91 mmol), and TBABr (60 mg, 0.186 mmol) in CH_2Cl_2 (15 mL) was cooled to −23 °C in a CCl_4/CO_2 bath. Aqueous 50% KOH (15 mL) was cooled in the same fashion. The aqueous KOH solution was then added to the CH_2Cl_2 solution. After the reaction mixture was stirred vigorously for two days in the dry ice bath, while allowing the ice to melt slowly and the reaction to warm to room temperature, the reaction was stopped and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and washed with H_2O (15 mL) and evaporated to dryness. The product was further purified by flash column chromatography. The product was eluted with CH_2Cl_2 (200 mL) and 15:85 EtOAc:CH_2Cl_2 (600 mL), followed by EtOAc (100 mL). Evaporation yielded 120 mg of **22** (27% yield). Considerable opioid starting material was also recovered: ^{1}H NMR ($CDCl_3$) δ 0.10−0.16 (m, 2 H, C-19 H, C-20 H), 0.48−0.57 (m, 2 H, C-19 H′, C-20 H′), 0.75−0.88 (m, 1 H, C-18 H), 1.23−2.30 [m, 22 H, C-7 CH_2, C-8 CH_2, C-15 CH_2, C-16 H, all adamantyl protons (15 H)], 2.34 (d, $J =$ 6.4 Hz, 2 H, NCH_2 cyclopropyl), 2.52−2.65 (m, 2 H, C-10α H, C-16 H), 3.00 (d, $J = 18.2$ Hz, 1 H, C-10β H), 3.07 (d, $J = 5.1$ Hz, 1 H, C-9 H), 3.21−3.21 (m, 1 H, C-6 H), 4.61−4.70 (m, 3 H, C-5β H, AdC(O)CH_2), 5.10−5.20 (m, 2 H, PhCH_2), 6.55 (d, $J = 8.3$ Hz, 1 H, C-1 H), 6.74 (d, $J = 8.2$ Hz, 1 H, C-2 H), 7.25−7.45 (m, 5 H, benzyl methine H).

17-(Cyclopropylmethyl)-3-(benzyloxy)-4,5α-epoxy-6α,-14-dihydroxymorphinan (23). To a solution of 6α-naltrexol (**7**)[14] (250 mg, 0.729 mmol), $TBAHSO_4$ (100 mg, 0.310 mmol), and benzyl bromide (0.22 mL, 1.9 mmol) in CH_2Cl_2 (25 mL) was added NaOH (200 mg in 25 mL of H_2O). The reaction mixture was stirred for 3.5 h, and the phases were then separated. The organic layer was removed, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were evaporated to dryness, and the product was purified by flash column chromatography. The product was eluted sequentially with 100 mL each of CH_2Cl_2, 10:90 EtOAc:CH_2Cl_2, 50:50 EtOAc:CH_2Cl_2, and EtOAc. Evaporation yielded 300 mg of **23**, as a yellow oil (95% yield): ^{1}H NMR ($CDCl_3$) δ 4.1−4.2 (m, 1 H, C-6β H), 4.63 (d, $J = 6.2$ Hz, 1 H, C-5β H), 5.11 and 5.21 (2d, $J = 12.2$ Hz, 2 H, PhCH_2), 5.21 (d, $J = 12.2$ Hz, 1 H, C-21′ H), 6.54 (d, $J = 8.3$ Hz, 1 H, C-1 H), 6.68 (d, $J = 8.0$ Hz, 1 H, C-2 H), 7.27−7.46 (m, 5 H, benzyl methine H).

17-(Cyclopropylmethyl)-3,6α-bis(benzyloxy)-4,5α-epoxy-14-hydroxymorphinan (24). To a solution of benzyl ether **23** (800 mg, 1.85 mmol), TBABr (160 mg, 0.497 mmol), and benzyl bromide (0.856 mL, 7.4 mmol) in CH_2Cl_2 (15 mL) was added aqueous 50% KOH (15 mL). After stirring vigorously overnight, 15 mL of water was added to aid phase separation. The phases were then separated, and the organic layer was removed. The remaining aqueous fraction was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were then evaporated to dryness, and the product was purified by flash column chromatography. The product was eluted with CH_2Cl_2 (200 mL), followed by 100 mL each of 20:80 EtOAc:CH_2Cl_2, 40:60 EtOAc:CH_2Cl_2, 50:50 EtOAc:CH_2Cl_2, and EtOAc. Evaporation yielded 610 mg of **24** (62% yield): ^{1}H NMR ($CDCl_3$) δ 4.0−4.05 (m, 1 H, C-6β H), 4.60 (d, $J = 12.0$ Hz, 1 H, PhCH), 4.76−4.81 (m, 2 H, C-5β H, PhCH), 5.12 (m, 2 H, Ph CH_2), 6.51 (d, $J = 8.3$ Hz, 1 H, C-1 H), 6.62 (d, $J = 8.0$ Hz, 1 H, C-2 H), 7.27−7.46 (m, 10 H, benzyl methine H).

17-(Cyclopropylmethyl)-3-(benzyloxy)-6α-(4-biphenylylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (25). From benzyl ether **23** (500 mg, 1.15 mmol), TBABr (100 mg, 0.310 mmol), and 4-(chloromethyl)biphenyl (680 mg, 4.6 mmol) in CH_2Cl_2 (15 mL) and aqueous 50% KOH (15 mL) was obtained 297 mg (43% yield) of **25** after chromatography: ^{1}H NMR ($CDCl_3$) δ 4.05−4.11 (m, 1 H, C-6β H), 4.65 (d, $J = 12.0$ Hz, 1H, C-21 H), 4.82 (m, 2 H, C-5β H, C-21 H), 5.15 (m, 2 H, C-21′ CH_2), 6.53 (d, $J = 8.1$ Hz, 1 H, C-1 H), 6.72 (d, $J = 8.2$ Hz, 1 H, C-2 H), 7.25−7.61 (m, 14 H, benzyl methine H and biphenyl methine H).

17-(Cyclopropylmethyl)-6α-(1-naphthylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (26). To a solution benzyl ether **23** (200 mg, 0.46 mmol), TBABr (40 mg, 0.248 mmol), and 1-(chloromethyl)naphthalene (325 mg, 1.84 mmol) in CH_2Cl_2 (15 mL) was added aqueous 50% KOH (15 mL). The reaction mixture was stirred overnight, and 20 mL of water was added to aid in phase separation. The organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were evaporated to dryness, and the product was purified by flash column chromatography, eluting with CH_2Cl_2 (100 mL), followed by 20:80 EtOAc:CH_2Cl_2 (200 mL) and EtOAc (200 mL). Evaporation afforded 150 mg (58% yield) of **26**: ^{1}H NMR ($CDCl_3$) δ 4.08−4.12 (m, 1 H, C-6β H), 4.89 (d, $J = 4.5$ Hz, 1 H, C-5β H), 4.95−5.10 (m, 3 H, PhCH, NaphCH_2), 5.26 (d, $J = 12.3$ Hz, 1 H, PhCH), 6.51 (d, $J = 8.1$ Hz, 1 H, C-1 H), 6.71 (d, $J = 8.2$ Hz, 1 H, C-2 H), 7.23−7.40 (m, 9 H, benzyl methine H, four Naph methine H), 7.70−7.81 (m, 2 H, Naph C-4 and C-5 H), 8.05−8.10 (m, 1 H, Naph C-8 H).

17-(Cyclopropylmethyl)-3-(benzyloxy)-6α-(2-naphthylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (27). From benzyl ether **23** (400 mg, 0.92 mmol), TBABr (80 mg, 0.248 mmol), and 2-(bromomethyl)naphthalene (816 mg, 3.68 mmol) in CH_2Cl_2 (15 mL) and aqueous 50% KOH (15 mL) was obtained 200 mg (38% yield) of **27** after chromatography: ^{1}H NMR ($CDCl_3$) δ, 4.03−4.11 (m, 1 H, C-6β H), 4.72 and 4.90 (2d, $J = 12.0$ Hz, 2 H, NaphCH_2), 4.81 (d, $J = 4.5$ Hz, 1 H, C-5β H), 4.96−5.10 (m, 2 H, PhCH_2), 6.52 (d, $J = 8.1$ Hz, 1 H, C-1 H), 6.71 (d, $J = 8.21$ Hz, 1 H, C-2 H), 7.23−7.45 (m, 8 H, benzyl methine H, Naph C-3, C-6, and C-7 H), 7.62−7.81 (m, 4 H four Naph methine H).

17-(Cyclopropylmethyl)-6α-(9-anthracylmethoxy)-4,5α-epoxy-3-(benzyloxy)-14-hydroxymorphinan (28). To a solution of benzyl after **23** (500 mg, 1.16 mmol), TBABr (100 mg, 0.310 mmol) and 9-(chloromethyl)anthracene (1.05 g, 4.62 mmol) in CH_2Cl_2 (10 mL) was added aqueous 50% KOH (10 mL). After stirring vigorously overnight, 10 mL each of water and CH_2Cl_2 were added to aid phase separation. The phases were then separated, and the organic layer was removed. The remaining aqueous layer was then extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were then washed with water (10 mL) and evaporated to dryness, and the residue was then purified by flash column chromtography. The product was eluted with CH_2Cl_2 (200 mL) followed by 5:95 EtOAc:CH_2Cl_2 (200 mL), and sequentially by 100 mL each of 10:90 EtOAc:CH_2Cl_2, 15:85 EtOAc:CH_2Cl_2, 20:80 EtOAc:CH_2Cl_2, 30:70 EtOAc:CH_2Cl_2, EtOAc, and MeOH. Evaporating yielded 210 mg of product (29% yield): ^{1}H NMR ($CDCl_3$) Assignments were supported by proton decoupling experiments. δ 3.03 (d, $J = 18.3$ Hz, 1 H, C-10β H), 3.10 (d, $J = 5.0$ Hz, 1 H, C-9 H), 4.28−4.36 (m, 1 H, C-6β H), 5.10 (d, $J = 4.2$ Hz, 1 H, C-5β H), 5.16 (s, 2 H, AnCH_2), 5.50 and 5.76 (2d, $J =$ 10.4 Hz, 2 H, PhCH_2), 6.52 (d, $J = 8.1$ Hz, 1 H, C-1 H), 6.75 (d, $J = 8.1$ Hz, 1 H, C-2 H), 7.15−7.50 (m, 9 H, benzyl methine CH, An C-2, C-3, C-6, C-7 H), 7.84−8.03 (m, 2 H, An C-1 and C-8 H), 8.40 (s, 1 H, An C-10 H), 8.40−8.52 (m, 2 H, An C-4 and C-5 H).

17-(Cyclopropylmethyl)-6α-(benzyloxy)-4,5α-epoxy-3,14-dihydroxymorphinan (29). To a solution of benzyl ether **24** (120 mg, 0.229 mmol) in 10 mL of EtOH in a large test tube was added 120 mg of 10% Pd on activated carbon. 1,4-Cyclohexadiene (0.22 mL, 2.29 mmol) was added, and nitrogen was bubbled through the stirred reaction mixture overnight. The mixture was then filtered through Celite, and the filtrate was evaporated to dryness. The product was then purified by flash column chromatography. The product was eluted with CH_2Cl_2 (200 mL) followed by 100 mL each of 10:90 EtOAc:CH_2Cl_2, 20:80 EtOAc:CH_2Cl_2, 30:70 EtOAc:CH_2Cl_2, 40:60 EtOAc:CH_2Cl_2, 50:50 EtOAc:CH_2Cl_2, and EtOAc. Evaporation yielded 90 mg of **29** (74% yield): $[\alpha]_D = -161.7°$ (c = 0.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.05−0.15 (m, 2 H, C-19 H, C-20 H), 0.48−0.58 (m, 2 H, C-19 H′, C-20 H′), 0.79−0.86 (m, 1 H, C-18 H), 1.2−1.70 (m, 4 H, C-7 H, C-8 2 H, C-15 H), 2.12−2.25 (m, 3 H, C-7 H, C-15 H, C-16 H), 2.3−2.4 (m, 2 H, NCH_2 cyclopropyl), 2.52−2.68 (m, 2 H, C-10α H, C-16 H), 2.95−3.10 (m, 2 H, C-9 H, C-10β H), 3.99−4.05 (m, 1 H, C-6β H), 4.59 and 4.68 (2d, J = 12.2, 2 H $PhCH_2$), 4.73 (d, J = 4.2 Hz, 1 H, C-5β H), 6.48 (d, J = 7.8 Hz, 1 H, C-1 H), 6.67 (d, J = 7.9 Hz, 1 H, C-2 H), 7.20−7.30 (m, 5 H, benzyl methine H); ^{13}C NMR ($CDCl_3$) δ 3.74 and 3.94 (C-19 and C-20), 9.39 (C-18), 20.44 (C-10), 22.72 (C-7), 28.53 (C-15), 33.36 (C-8), 43.17 (C-16), 47.48 (C-13), 59.38 (C-17), 62.02 (C-9), 66.93 (C-14), 71.05, 73.99 (C-6, ArCH_2), 89.18 (C-5), 116.99 (C-2), 118.44 (C-1), 124.99 (C-11), 127.26, 127.33, 127.99 (benzyl methine C), 130.60 (C-12), 137.24 (C-3), 138.38 (C-4), and 145.55 (Ph C-1); FTIR (neat) 3355, 2940, 1506, 1458, 1334, 1240, 1116, 1090, 1067, 942, 735, 698 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{27}H_{32}NO_4$ 434.2331, obsd 434.2333. Anal. ($C_{27}H_{31}NO_4\cdot 0.5H_2O$) C, H, N.

17-(Cyclopropylmethyl)-6α-(4-biphenylylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (30). From ether **25** (200 mg, 0.33 mmol), an equal weight of 10% Pd·C, and hydrazine hydrate (0.083 mL, 2.32 mmol) was obtained 100 mg (59% yield) of **30**, $[\alpha]_D = -109.6°$ (c = 1.00, CH_2Cl_2), after chromatography: ^{1}H NMR ($CDCl_3$) δ 0.06-0.17 (m, 2 H, C-19 H, C-20 H), 0.45−0.57 (m, 2 H, C-19 H′, C-20 H′), 0.80−0.92 (m, 1 H, C-18 H), 1.20−1.40 (m, 2 H, C-8 H, C-15 H), 1.48−1.80 (m, 4 H, C-8 H, C-7 2 H, C-15 H), 2.18−2.35 (m, 3 H, NCH_2 cyclopropyl, C-16 H), 2.48−2.65 (m, 2 H, C-10α H, C-16 H), 2.95−3.08 (m, 1 H, C-9 H, C-10β H), 4.01−4.011 (m, 1 H, C-6 H), 4.62−4.80 (m, 3 H, C-5β 1 H, C-21 2 H), 6.49 (d, J = 8.1 Hz, 1 H, C-1 H), 6.71 (d, J = 8.1 Hz, 1 H, C-2 H), 7.29−7.58 (m, 9 H, biphenyl methine H); ^{13}C NMR ($CDCl_3$) δ 3.76 and 3.95 (C-19 and C-20), 9.37 (C-18), 20.40 (C-10), 22.77 (C-7), 28.65 (C-15), 33.41 (C-8), 43.15 (C-16), 47.57 (C-13), 59.42 (C-17), 62.04 (C-9), 69.93 (C-14), 70.82 (C-6), 74.06 (biphenylCH_2), 89.29 (C-5), 117.16 (C-2), 118.47 (C-1), 125.10 (C-11), 126.86, 127.85, 128.50, 127.87, 128.50 (biphenyl methine C), 130.61 (C-12), 137.27, 137.37 (biphenyl C-1, C 3), 140.16, 140.70 (biphenyl quaternary C), and 145.55 (C-4); FTIR (neat) 3381, 2940, 1488, 1459, 1149, 1088, 1034, 979, 942, 887, 761, 698 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{33}H_{36}NO_4$ 510.2644, obsd 510.2666. Anal. ($C_{33}H_{35}NO_4\cdot 0.5H_2O$) C, H, N.

17-(Cyclopropylmethyl)-6α-(1-naphthylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (31). To a solution of ether **26** (350 mg, 0.61 mmol) in 50:50 EtOH:EtOAc (10 mL) stirred at 50 °C was added an equal weight of 10% Pd on activated carbon catalyst. Hydrazine hydrate (0.188 mL, 4.88 mmol) was added, and the reaction mixture was stirred for 1.5 h. The mixture was then filtered through Celite, and the filtrate was evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 washed with water, and dried with anhydrous Na_2SO_4, and the CH_2Cl_2 was removed by evaporation. Elution with CH_2Cl_2 (100 mL), followed by 20:80 EtOAc:CH_2Cl_2 (200 mL) and EtOAc (200 mL), afforded 210 mg (72% yield) of **31**: $[\alpha]_D = -165.8°$ (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.07−0.16 (m, 2 H, C-19 H, C-20 H), 0.48−0.57 (m, 2 H, C-19 H′, C-20 H′), 0.75−0.86 (m, 1 H, C-18 H), 1.17−1.34 (m, 1 H, C-7 H), 1.31−1.80 (m, 4 H, C-7 H, C-8 2 H, C-15 H), 2.11−2.22 (m, 2 H, C-15 H, C-16 H), 2.22−2.38 (m, 21 H, C-17 NCH_2 cyclopropyl), 2.46−2.62 (m, 2 H, C-10α H, C-16 H), 2.98 (d, J = 19.8 Hz, 1 H, C-10β H), 3.03 (d, J = 6.5 Hz, 1 H, C-9 H), 4.08−4.14 (m, 1 H, C-6β H), 4.78 (d, J = 3.15 Hz, 1 H, C-5 β H), 4.98 and 5.10 (2d, J = 12.2 Hz, 2 H, NaphCH_2), 6.46 (d, J = 8.2 Hz, 1 H, C-1 H), 6.67 (d, J = 6.8 Hz, 1 H, C-2 H), 7.32−7.50 (m, 4 H, Naph C-2, C-3, C-6, C-7 H), 7.73−7.82 (m, 2 H, Naph C-4 and C-5 H), 8.04−8.10 (m, 1 H, Naph C-8 H); ^{13}C NMR ($CDCl_3$) δ 3.76, 3.96 (C-19, C-20), 9.33 (C-18), 20.34 (C-10), 22.71 (C-7), 28.66 (C-8), 33.32 (C-15), 43.14 (C-16), 47.53 (C-13), 59.37 (C-17), 61.98 (C-9), 69.35, 69.92 (C-6, C-14), 73.97 (NaphCH_2), 88.98 (C-5), 117.26 (C-2), 118.50 (C-1), 123.85 (C-11), 125.01, 125.42, 125.83, 126.00, 128.14, 128.29, 130.57 (Naph methine C), 131.41 (C-12), 133.42, 133.62 (Naph C-4a and C-8a), 137.36 (C-3), and 145.61 (C-4); FTIR (neat) 3355, 2943, 1614, 1508, 1458, 1375, 1333, 1239, 1165, 1089, 1067, 859, 792, 776, 734 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{31}H_{34}NO_4$ 484.2488, obsd 484.2500. Anal. ($C_{31}H_{33}NO_4\cdot 0.75 H_2O$) C, H, N.

17-(Cyclopropylmethyl)-6α-(2-naphthylmethoxy)-4,5α-epoxy-3,14-dihydroxymorphinan (32). From ether **27** (200 mg, 0.35 mmol), an equal amount of 10% Pd·C catalyst, and hydrazine hydrate (0.1 mL, 2.8 mmol) was obtained 86 mg (51% yield) of **32**, $[\alpha]_D = -169.3°$ (c = 1.01, CH_2Cl_2), after chromatography: ^{1}H NMR ($CDCl_3$) (special assignments were supported by decoupling experiments) δ 0.07−0.16 (m, 2 H, C-19 H, C-20 H), 0.48−0.58 (m, 2 H, C-19 H′, C-20 H′), 0.78−0.86 (m, 1 H, C-18 H), 1.18−1.33 (m, 1 H, C-7 H), 1.40-1.68 (m, 3 H, C-8 2 H, C-15 H), 1.70−1.82 (m, 1 H, C-7 H), 2.11−2.28 (m, 2 H, C-15 H, C-16 H), 2.50−2.63 (m, 2 H, C-10α H, C-16 H), 3.00 (d, J = 18.6 Hz, 1 H, C-10β H), 3.04 (d, J = 6.7 Hz, 1 H, C-9 H), 4.01−4.10 (m, 1 H, C-6 H), 4.70−4.93 (m, 3 H, C-5β H, NaphCH_2), d, J = 8.1 Hz, 1 H, C-1 H), 6.70 (d, J = 8.1 Hz, 1 H, C-2 H), 7.40−7.50 (m, 3 H, Naph C-3, C-6 and C-7 H), 7.70−7.82 (m, 4 H Naph C-1, C-4, C-5 and C-8 H); ^{13}C NMR ($CDCl_3$) δ 3.75, 3.87 (C-19, C-20), 9.31 (C-18), 20.41 (C-10), 22.74 (C-7), 28.61 (C-8), 33.37 (C-15), 43.18 (C-16), 47.54 (C-13), 59.42 (C-17), 62.04 (C-9), 69.91 (C-14), 71.20 (C-6), 74.15 (NaphCH_2), 89.13 (C-5), 117.34 (C-2), 118.58 (C-1), 125.05 (C-11), 125.42, 125.59, 125.90, 126.11, 127.34, 127.58, 127.82 (Naph methine C), 130.63 (C-12), 133.06, 132.76 (Naph C-4a and C-8a), 135.75 (Naph C-2), 137.39 (C-3), and 145.60 (C-4); FTIR (neat) 3358, 3057, 2940, 1504, 1458, 1239, 1149, 1088, 944, 888, 735, 700 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{31}H_{34}NO_4$ 484.2488. Anal. ($C_{31}H_{33}NO_4\cdot 0.5H_2O$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-(9-anthracylmethoxy)-3,14-dihydroxymorphinan (33). To a solution of trityl ether **35** (158 mg, 0.204 mmol) in CH_2Cl_2 was added aqueous 50% acetic acid (20 mL). After stirring vigorously overnight the reaction mixture was evaporated, and 15 mL each of saturated aqueous $NaHCO_3$ and CH_2Cl_2 were added to dissolve the solid for phase separation. The organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were dried with anhydrous Na_2SO_4 and evaporated to dryness. The product was then purified by flash column chromatography. Elution with CH_2Cl_2 (100 mL), followed by 20:80 EtOAc:CH_2Cl_2 (200 mL) and 100 mL each of 50:50 EtOAc:CH_2Cl_2, EtOAc, and MeOH, afforded 90 mg of the product (83% yield): $[\alpha]_D = -147.3°$ (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.09−0.15 (m, 2 H, C-19 H, C-20 H), 0.48−0.56 (m, 2 H, C-19 H′, C-20 H′), 0.78−0.90 (m, 1 H, C-18 H), 1.18−1.30 (m, 1 H, C-7 H), 1.40−1.90 (m, 4 H, C-7 H, C-8 2 H, C-15 H), 2.20−2.28 (m, 2 H, C-15 H, C-16 H), 2.28−2.37 (m 2 H, C-17 NCH_2 cyclopropyl), 2.50−2.67 (m, 2 H, C-10α H, C-16 H), 3.02 (d, J = 18.6 Hz, 1 H, C-10β H), 3.09 (d, J = 6.2 Hz, 1 H, C-9 H), 4.24−4.34 (m, 1 H, C-6α H), 4.96 (d, J = 4.01 Hz, 1 H, C-5β H), 5.52 and 5.63 (2d, J = 10.8 Hz, 2 H, AnCH_2), 6.49 (d, J = 7.9 Hz, 1 H, C-1 H), 6.68 (d, J = 8.1 Hz, 1 H, C-2 H), 7.40−7.49 (m, 2 H, two An methine H), 7.49−7.58 (m, 2 H, two An methine H), 7.94−8.01 (m, 2 H, An C-1 and C-8 H), 8.37−8.45 (m, 3 H, An C-4, C-5 and C-10 H); ^{13}C NMR ($CDCl_3$) δ 3.82, 3.94 (C-19, C-20), 9.36 (C-18), 20.44 (C-10), 22.76 (C-7), 29.17 (C-8), 33.65 (C-15), 43.13 (C-16), 47.80 (C-13), 59.49 (C-17), 62.05 (C-9), 63.14 (C-6), 69.87 (C-14), 74.41 (AnCH_2), 88.98 (C-5), 117.22 (C-2), 118.66 (C-1), 124.16, 124.65, 124.81, 125.32, 125.89, 126.08, 128.21, 128.42, 128.68, 128.85, 130.54, 130.80, 131.25 (C-11, C-12, other arene carbons of the anthracene ring), 137.26 (C-3), and 145.64 (C-4); FTIR (neat) 3357, 3046, 2926, 2841, 1622, 1503, 1458, 1375, 1333, 1242, 1158, 1113, 1086, 942, 886, 790, 733, 701 cm^{-1}; HRFABMS $[M + 1]^+$ calcd for $C_{35}H_{36}NO_4$ 534.2644, obsd 534.2622. Anal. ($C_{35}H_{35}NO_4\cdot H_2O$) C, H, N.

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6α,14-dihydroxymorphinan (34). To a solution of 6α-naltrexol (**7**) (3.50 g, 10.2 mmol), triphenylmethyl chloride (3.7 g, 13.3 mmol), and TBAHSO$_4$ (920 mg, 2.58 mmol) in CH_2Cl_2 (40 mL) was added aqueous KOH (920 mg in 40 mL of H_2O). After the reaction mixture was stirred vigorously overnight at room temperature and the phases were separated, the organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic fractions were evaporated to dryness. The resulting yellow oily residue was further purified by flash column chromatography. The product was eluted sequentially with CH_2Cl_2 (200 mL), 20:80 EtOAc:CH_2Cl_2 (200 mL), and finally with EtOAc (100 mL). Evaporation yielded a yellow foam (4.29 g, 72% yield), which was used witbout further purification: ^{1}H NMR ($CDCl_3$) (spectral assignments were supported by proton decoupling experiments) δ 0.04–0.17 (m, 2 H, C-19 H, C-20 H), 0.45–0.55 (m, 2 H, C-19′ H, C-20′ H), 0.55–0.68 (m, 1 H, C-7 H), 0.74–0.88 (m, 1 H, C-18 H), 1.21–1.38 (m, 2 H, C-8 H, C-15 H), 1.46–1.64 (m, 2 H, C-7 H, C-8 H), 1.72–1.88 (m, exchangeable protons), 2.01–2.18 (m, 2 H, C-15 H, C-16 H), 2.22–2.36 (m, 2 H, C-17 2 H), 2.42–2.60 (m, 2 H, C-10α H, C-16 H), 2.87 (d, J = 18.8 Hz, 1 H, C-10β H), 2.96 (d, J = 6.4 Hz, 1 H, C-9 H), 3.93–4.08 (m, 1 H, C-6α H), 4.38 (d, J = 4.8 Hz, 1 H, C-5β H), 6.22 (d, J = 8.3 Hz, 1 H, C-1 H), 6.50 (d, J = 8.3 Hz, 1 H, C-2 H), 7.12–7.26 (m, 9 H, trityl C-3, C-4, and C-5 H), 7.40–7.50 (m, 6 H, trityl C-2 and C-6 H).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-6α-(9-anthracylmethoxy)-4,5α-epoxy-14-hydroxymorphinan (35). To a solution of trityl ether **34** (1.04 g, 1.78 mmol), TBABr (250 mg, 0.775 mmol), and 9-(chloromethyl)anthracene (1.40 g, 6.17 mmol) in CH_2Cl_2 (10 mL) was added aqueous 50% KOH (10 mL) with vigorous stirring. After the mixture was stirred vigorously overnight, 15 mL each of water and CH_2Cl_2 were added to aid phase separation. The organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were evaporated to dryness, and the product was then purified by flash column chromatography. Elution with 200 mL each of CH_2Cl_2 and 10:90 EtOAc:CH_2Cl_2, followed by 100 mL each of 20:80 EtOAc:CH_2Cl_2, EtOAc, and MeOH, afforded 218 mg of **35** (16% yield): ^{1}H NMR ($CDCl_3$) δ 2.88 (d, J = 18.2 Hz, 1 H, C-10β H), 2.96 (d, J = 5.9 Hz, 1 H, C-9 H), 4.10–4.18 (m, 1 H, C-6α H), 4.77 (d, J = 4.3 Hz, 1 H, C-5β H), 5.61 and 5.7 1 (2d, J = 11.7 Hz, 2 H, AnCH_2), 6.19 (d, J = 8.3 Hz, 1 H, C-1 H), 6.53 (d, J = 8.2 Hz, 1 H, C-2 H), 7.12–7.28 (m, 11 H, trityl C-3, C-4, and C-5 H, two An methine H), 7.30–7.45 (m, 2 H, two An methine H), 7.456–7.55 (m, 6 H, trityl C-2 and C-6 H), 7.92–8.03 (m, 2 H, An C-1 and C-8 H), 8.40–8.50 (m, 3 H, An C-4, C-5, and C-10 H).

Biological Testing. A Brandel Harvestor and FP-100 Whatman GF/B fired filter paper were used for protein filtration. The filter paper in the κ receptor binding assay was pretreated with aqueous 0.1% poly(ethylenimine) to coat the glass fibers.[15] All glassware used in the binding assays was silanized with Prosil-28. Polypropylerne culture tubes and scintillation vials were used in all binding assays.

Opioid Receptor Binding. The binding assay was carried out essentially as described by Lin and Simon,[9] with slight modifications. Hartley-VAF Plus guinea pigs (300–350 g) were killed by decapitation and the brains removed. The brains, less cerebellum, were homogenized in six volumes of 0.05 M Trizma buffer (pH 7.4) with a Virtishear homogenizer at a control setting of 70 for three 5-s intervals. The homogenate was centrifuged at 25000*g* at 4 °C for 20 min. The pellet was resuspended in six volumes of aqueous 0.32 M sucrose and stored at −70 °C until needed. Frozen homogenate was thawed at room temperature and diluted with 0.05 M Trizma buffer (pH 7.4) to give a final dilution ratio of 1:60 (initial brain weight to total solution volume). Radioligands used were [^{3}H]bremazocine (0.5 nM) for total ligand binding, [^{3}H]DAMGO (1.0 nM) for μ-receptor binding, [^{3}H]DPDPE (1.0 nM) for δ-receptor binding, and [^{3}H]U69,593 (1.0 nM) for κ-receptor binding.[10–12] Synthetic ligands were tested in duplicate at nine concentrations between 1.0 and 1000 nM, or between 0.1 and 100 nM. Nonspecific binding was measured in the presence of 10 μM naloxone. The samples were incubated for 60 min at 25 °C. Samples were filtered, rinsed with ice-cold buffer (3 × 2 mL), eluted with 10 mL aliquots of liquid scintillation cocktail, and counted. IC$_{50}$ values were obtained by linear regression analysis of a probit-logit plot.

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