Isothiocyanate-Substituted Benzyl Ether Opioid Receptor Ligands Derived from 6β-Naltrexol

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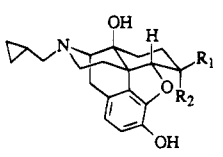
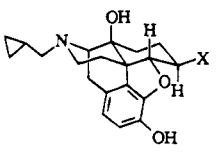
A series of regioisomeric substituted 6-*O*-benzyl ethers of 6β-naltrexol (**12**) in which isothiocyanate groups were attached directly to or one carbon removed from the aromatic ring of the benzyl group were prepared. These agents were prepared to obtain electrophilic opioid ligands potentially useful in the characterization of opioid receptors and drug–receptor interactions. Preparation of these ligands was accomplished from 3-*O*-trityl-6β-naltrexol (**13**) *via* phase transfer-catalyzed alkylation of the regioisomeric *o*-, *m*-, and *p*-nitrobenzyl halides and the *o*-, *m*-, and *p*-cyanobenzyl halides. The intermediates were deprotected and reduced, and formation of the isothiocyanates from the corresponding amines completed the synthesis. The ligands (**6**–**11**) were tested in radioligand displacement assays in guinea pig brain homogenate for opioid receptor binding affinity and irreversibility. All six of the isothiocyanates demonstrated significant affinity in the displacement assays for all three opioid receptors. They also appeared to be irreversibly bound at each of the receptor types. Compound **6**, the *o*-isothiocyanatobenzyl ether analog, had the highest affinity, and it demonstrated significant irreversibility at very low concentration. It appears to be suitable for further investigation.

Naltrexone (**1**), a nearly pure opioid receptor antagonist, has high affinity at opioid receptors. It interacts with all classes of opioid receptors displaying higher affinity for the μ and the κ receptor types than for the δ receptor type by 20–50-fold. Structural modification of naltrexone has shown that C-6 substitution, even with relatively large substituents, affords potent agents. Some examples include 6-desoxy-6-methylenenaltrexone (nalmefene (**2**) and 6β-methyl-6α-naltrexol (**3**), which are potent opioid antagonist,[1] and compounds with even larger substituents attached at the C-6 position, such as β-chlornaltrexamine (β-CNA) (**4**) and β-funaltrexamine (β-FNA) (**5**), which are important electrophilic ligands.[2] The C-6 position has served as the location for a variety of substituents which have led to several derivatives of the 6β- and 6α-amines, including amides as conjugate addition acceptors, thiol reagents, and α-haloacetamides.[3] In addition, several oxygen-containing compounds have also been prepared, including spiro α-methylene-γ-lactones and related 6-tethered ethers which have shown high affinity for μ- and δ-opioid receptors.[4,5]



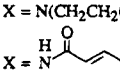


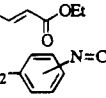
1 R_1–R_2 = O naltrexone

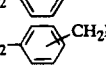
2 R_1–R_2 = CH_2 nalmefene

3 R_1 = CH_3 R_2 = OH

4 X = $N(CH_2CH_2Cl)_2$

5 X = 

6-8 X = OCH_2– 

9-11 X = OCH_2– 

On the basis of the activity of several agents in these series, we have explored a series of 6β-*O*-benzyl ethers in which the isothiocyanate functionality is incorporated to serve as a probe for potential nucleophilic sites at opioid receptors. The isothiocyanate fucntionality has been widely used in the opioid receptor field.[6] Ligands were chosen in which the isothiocyanate is located at the ortho, meta, and para positions of the added benzyl group, both attached directly to the aromatic ring (**6**–**8**) and attached one carbon away from it, as aliphatic isothiocyanates **9**–**11**. The methylene spacer in the aliphatic series would increase slightly the overall size of the attached ligand compared to the aromatic series, and this change might alter the interaction of the agent at opioid receptors. The methylene spacer would also provide additional conformational flexibility for the isothiocyanate-bearing functionality. In addition, a possible difference in chemical reactivity of the aromatic and aliphatic isothiocyanates with a model nucleophile was examined.

Chemistry. The compounds were prepared from 3-*O*-trityl-protected 6β-naltrexol (**13**), obtained by phase transfer catalysis (PTC) 3-*O*-alkylation of 6β-naltrexol (**12**),[7] using tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) as the phase transfer catalyst.[8] The members of the aliphatic isothiocyanate series **9, 10,** and **11** were prepared from phenolic *O*-trityl ether **13** by phase transfer-catalyzed alkylation with regioisomeric cyanobenzyl bromides (Scheme 1). The PTC alkylation of **13** with *p*-cyanobenzyl bromide required use of 4 equiv of the halide and aqueous 40% KOH. Formation of the analogous ortho- and meta-alkylated products (**14** and **15**) required some modification of the PTC conditions (concentration of KOH, benzyl halide concentration and temperature, see Experimental Section). Catalytic reduction of the 3-*O*-trityl-6β-*O*-cyanobenzyl ethers **14**–**16** gave (aminomethyl)benzyl ethers **17**–**19**. Loss of the trityl group occurred in the aqueous acetic acid used as the solvent for the catalytic reduction. Use of aqueous 25% acetic acid (vs 50%) prevented 6β-*O*-debenzylation of **14** and **15** in this process. In contrast to these two regioisomers, no apparent debenzylation

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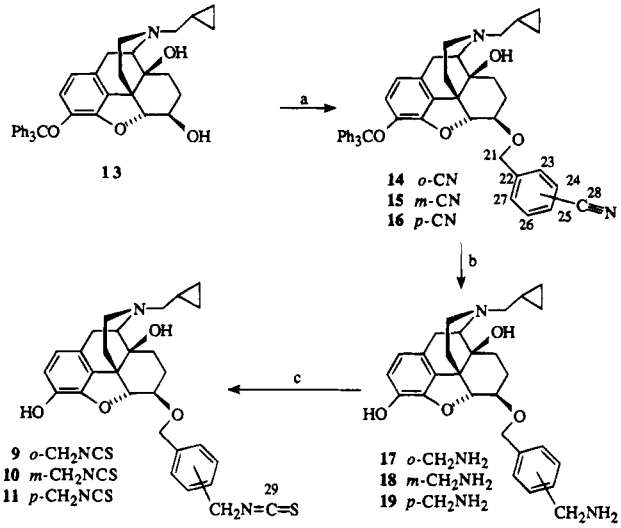
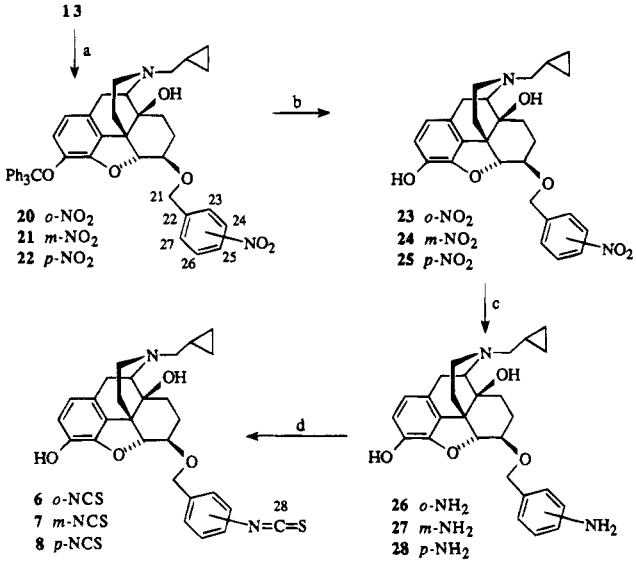
Scheme 1[a]



[a] Reagents: (a) aqueous 50% KOH, CH_2Cl_2, n-$Bu_4N^+Br^-$, regioisomeric cyanobenzyl bromides; (b) H_2 (PtO_2), aqueous 25% KOAc; (c) di-2-pyridyl thiocarbonate or thiophosgene.

Scheme 2[a]

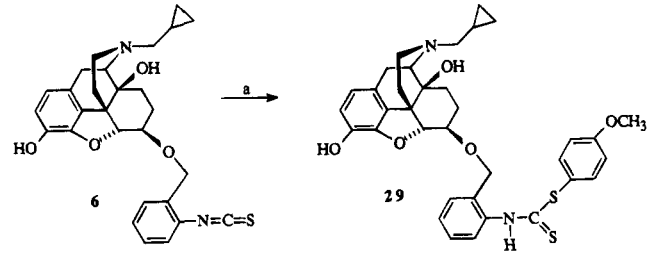


[a] Reagents: (a) aqueous 50% KOH, CH_2Cl_2, n-$Bu_4N^+Br^-$, regioisomeric nitrobenzyl halides; (b) aqueous 50% AcOH, overnight; (c) $FeSO_4 \cdot 7H_2O$, aqueous 50% MeOH; (d) di-2-pyridyl thionocarbonate.

at the 6β-hydroxyl position was observed when 3-*O*-6β-*O*-(*o*-cyanobenzyl) ether **16** was catalytically reduced in aqueous 48% acetic acid in the presence of 1.5% HCl. The *m*- and *p*-(isothiocyanatomethyl)benzyl ethers **10** and **11** were prepared by the reaction of thiophosgene with the corresponding (aminomethyl)benzyl ethers **17** and **18**. Use of thiophosgene on the *o*-(aminomethyl)-benzyl ether **17** was unsuccessful. However, use of di-2-pyridyl thionocarbonate[9] afforded **9**.

The preparation of the aromatic isothiocyanate series **6**–**8** (Scheme 2) proved to be a greater synthetic challenge than preparation of the aliphatic isothiocyanate series **9**–**11**. Initial efforts using the analogous PTC methodology were successful only for preparation of **21** using *m*-nitrobenzyl chloride. Attempts using either *p*-nitrobenzyl bromide or chloride failed. Several alternative methods were examined, including KH

Scheme 3[a]



[a] Reagents: (a) 4-methoxybenzenethiol, triethylamine.

(THF)[10] silver oxide-catalyzed ether formation,[11] use of (*o*-nitrophenyl)diazomethane,[12] and *p*-nitrobenzoylation followed by use of Lawesson's reagent.[13] All were unsuccessful.

The PTC alkylation process was then examined very carefully. In the initial attempts, the reaction mixtures developed a dark purple color consistent with reported decomposition of the nitrobenzyl halides under strongly basic conditions noted by Fukase.[11] Lowering the reaction temperature was attempted to decrease the rate of these competing processes. The alkylation of **13** with *p*-nitrobenzyl bromide was successful (in 13–26% yield) under the PTC conditions by starting the alkylation process at 0 °C, with warming to room temperature. Decreasing the starting temperature to −23 °C improved the yield of this process to about 50%. The alkylation of **13** with the more hindered *o*-nitrobenzyl bromide was also successful starting at a very low temperature. In this series, the trityl protecting group was removed before reduction by treatment of the appropriate 3-*O*-trityl nitrobenzyl ethers **20**–**22** with aqueous 50% acetic acid affording phenols **23**–**25**.

Conversion of the nitro compounds to the corresponding amines was first attempted by catalytic hydrogenation. From the *m*-nitro analog **24**, only low yields of *m*-amino compound **27** were obtained, and significant debenzylation at the 6β-oxygen occurred. However, $SnCl_2$ reduction[14] was successful in the formation of **27** in 80% yield. Unfortunately, $SnCl_2$ reduction of *p*-nitro analog **25** or of *o*-nitro analog **23** was less successful. Subsequently, use of $FeSO_4 \cdot 7H_2O$[15] was successful in reducing the nitro groups to the amines of all three regioisomers in >80% yields, each requiring different optimal reaction times. In the final step, the conversion of each of the regioisomeric aromatic amines **26**–**28** to the corresponding isothiocyanates **6**–**8** was accomplished by reaction of the amine with di-2-pyridyl thionocarbonate.

Reaction Rates with 4-Methoxybenzenethiol. To obtain some insight on the relative reactivity of these isothiocyanates (**6**–**11**), rates of their reaction with 4-methoxybenzenethiol, used as a model thiol nucleophile (Scheme 3), were determined by ^1H NMR.[16] The relative bimolecular rates (starting with approximately equal molar isothiocyanate and thiol) were determined by monitoring changes in the signal of the methoxyl group protons. Second-order reaction kinetics was assumed, and the data were examined on the basis of the simplified equation $1/C - 1/C_o = kt$.[17] The relative rate constants for the regisomeric aliphatic and aromatic isothiocyanate series are given in Table 1. The half-lives of the isothiocyanates under these conditions varied from approximately 35 to 100 min.

Table 1. Relative Rate Constants for the Reaction of Isothiocyanate Ligands with 4-Methoxybenzenethiol

electrophilic ligand	relative rate constant (k)
6β-*o*-isocyanatobenzyl ether **6**	1.3 ($r^2 = 0.99$)[a]
6β-*m*-isothiocyanatobenzyl ether **7**	1.2 ($r^2 = 0.99$)
6β-*p*-isothiocyanatobenzyl ether **8**	1.0 ($r^2 = 0.99$)
6β-*o*-isothiocyanatomethylbenzyl ether **9**	1.4 ($r^2 = 0.94$)
6β-*m*-isothiocyanatobenzyl ether **10**	2.9 ($r^2 = 0.99$)
6β-*p*-isothiocyanatobenzyl ether **11**	2.4 ($r^2 = 1.0$)

[a] Correlation coefficient (r) of reaction rate determined by plotting the reciprocal of unreated thiol vs time.[17]

Only small differences in rates of dithiocarbamate formation were noted, with the rate constants for the meta and para regioisomers of the aliphatic series being about 2.4 times larger than the corresponding regioisomers of the aromatic series. These small differences suggest that any changes in steric constraints between the aliphatic or aromatic isothiocyanates are a small factor in determining the reaction rate with receptor nucleophiles. The structure of the expected dithiocarbamate **29** from the reaction of **6** and 4-methoxybenzenethiol was confirmed by NMR[18] and mass spectrometry.

Receptor Affinity. The affinities of the 6β-*O*-arylisothiocyanates (**6**–**8**) and the 6-*O*-aralkylisothiocyanates (**9**–**11**) at the three opioid receptor sites (μ, δ, and κ) were determined in a crude membrane preparation from guinea pig brain (Table 2). The radioligand displacement assays were determined using [^{3}H]bremazocine (all sites), [^{3}H]DAMGO (μ-sites), [^{3}H]DPDPE (δ-sites), and [^{3}H]U-69,593 (κ-sites).[19–22] Naltrexone (**1**), 6β-naltrexol (**12**), and the 6β-*O*-benzyl ether (**30**),[23] the analagous non-isothiocyanate-substituted ligand, were included as standards in these assays. All of the ligands had relatively high affinity for each of the three receptor types, with IC_{50}s of 20 nM or lower, which was than naltrexone by 4–400-fold. The ligand with greatest affinity was *o*-isothiocyanate **6**, which had affinity approximately equal to naltrexone (**1**) at μ-sites, greater affinity than **1** at δ-sites, and less affinity at κ-sites.

The data obtained from the radioligand displacement assay provide an approximation of the concentrations needed for testing their irreversibility characteristics. In these assays concentrations that reduce specific binding to approximately 25 ± 10% are used. Radioligand binding was determined with standard radioligands before and after washing, and protection by naloxone was examined. The 6β-*O*-benzyl ether (**30**), a structurally analogous reversible ligand, was included as a control. Results of irreversibility assays are provided in Tables 3, 4, and 5 for μ, δ, and κ receptors, respectively.

All of the synthetic isothiocyanate lgiands caused a significant decrease in specific binding at all three receptors (Tables 3–5), compared to closely related 6β-benzyl ether **30**, suggesting that the isothiocyanate moiety of each isomer reacts with an accessible cellular nucleophile or nucleophiles at the receptor sites. *o*-Isothiocyanate **6** displayed concentration-dependent irreversible effects, as indicated by the decrease in radioligand specific binding with increases in the concentration of the electrophilic ligand. At μ-receptors, the *o*-isothiocyanate **6** was effective at reducing radioligand binding at a significantly lower concentration (5 nM) than any of the other test ligands.

When *p*-methyleneisothiocyanate **11** was tested at two different concentrations in the binding assays, it did not show concentration dependence. The maximum inhibition was ~40% at all three receptors, consistent with partial blocking of these receptor sites, as has been seen for other irreversible ligands at μ-receptors[24–27] where only a fraction of the radioligand receptor binding is blocked. This phenomenon has been explained on the basis of differential binding to classes and subclasses of receptors.[24–26]

There was, in general, a lack of complete protection from the electrophile when a large excess of naloxone was added in the presence of the isothiocyanates. Increasing concentrations of test ligand decreased the amount of protection significantly. The isothiocyanate ligand could bind to a nucleophilic site not directly at the opioid binding site in such a way that the receptor was modified so binding of opioids would no longer occur, i.e., have significant nonspecific effects under these conditions. Another possibility is that if the rate of reaction of the isothiocyanate with the receptor nucleophile is very, very rapid compared to the dissociation constant, a low level of protection would be observed. Because concentrations chosen for these experiments inhibit ca. 75–85% of specific binding, nonspecific effects could occur. With increasing ir-

Table 2. IC_{50}s of Synthetic Isothiocyanate Series at Opioid Receptor Types

test ligand	IC_{50}s at opioid receptor types (nM)[a]			
	total [^{3}H]bremazocine	μ [^{3}H]DAMGO[b]	δ [^{3}H]DPDPE[c]	κ [^{3}H]U69,593[d]
	Isothiocyanate Series			
o-NCS (**6**)	8.8	0.8	1.8	8.2
m-NCS (**7**)	27	27	6.5	17
p-NCS (**8**)	22	9.6	35	21
o-CH_2NCS (**9**)	69	20	22	43
m-CH_2NCS (**10**)	24	19	12	6.0
p-CH_2NCS (**11**)	21	11	21	7.4
	Reference Compounds			
naltrexone (**1**)	3.8	0.2	10	0.5
β-naltrexol (**12**)	8.3	1.1	32	2.6
benzyl ether **30**	3.4	2.4	2.9	2.0
DPDPE	>1000	>1000	1.8	>1000
U69,593	139	1760	4970	2.1

[a] Results are calculated from duplicate samples (±19%) at nine concentrations from 1 to 10000 nM of displacing ligand. [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]U69,593 or [^{3}H]-(5α,7α,8β)-(−)-*N*-methyl-*N*-(1-pyrrolidinyl-1-oxaspiro[4.5]dec-8-yl)benzeneacetamide (1 nM).

Table 3. Irreversible Binding of the Synthetic Isothiocyanate Series at the μ-Opioid Receptor

test ligand	concn (nM)[b]	μ receptors ([3H]DAMGO): % of control-specific binding remaining[a] unwashed	washed	protected[c]
o-NCS (**6**)	2.5	47	40	68
	5	7	15	36
m-NCS (**7**)	70	0	20	18
	80	4	14	19
p-NCS (**8**)	35	14	46	48
o-CH_2NCS (**9**)	60	10	40	55
m-CH_2NCS (**10**)	70	17	36	43
p-CH_2NCS (**11**)	30	59	56	67
	50	22	58	60
benzyl ether **30**	10	14[d]	100[d]	104[d]

[a] Results for the synthetic series are the average of triplicate samples (±6%). [b] Test ligand concentrations were chosen to approximate the IC_{65-85} range. [c] Protection experiments were performed in the presence of 1 μM naloxone. [d] Results for benzyl ether **30** are the averages from three separate assays (±10%).

Table 4. Irreversible Binding of the Synthetic Isothiocyanate Series at the δ Opioid Receptor

test ligand	concn (nM)[b]	δ receptors ([3H]DPDPE): % of control-specific binding remaining[a] unwashed	washed	protected[c]
o-NCS (**6**)	6	59	55	72
	10	30	34	47
m-NCS (**7**)	20	34	18	26
	25	28	19	20
p-NCS (**8**)	115	16	28	28
o-CH_2NCS (**9**)	60	12	47	53
m-CH_2NCS (**10**)	40	27	46	52
p-CH_2NCS (**11**)	50	51	56	66
	70	37	57	62
benzyl ether **30**	10	23[d]	93[d]	104[d]

[a] Results for the synthetic series are the average of triplicate samples (±6%). [b] Test ligand concentrations were chosen to approximate the IC_{65-85} range. [c] Protection experiments were performed in the presence of 1 μM naloxone. [d] Results for benzyl ether **30** are the averages from three separate assays (±10%).

Table 5. Irreversible Binding of the Synthetic Isothiocyanate Series at the κ-Opioid Receptor

test ligand	concn (nM)[b]	κ receptors ([3H]U69,593): % control-specific binding remaining[a] unwashed	washed	protected[c]
o-NCS (**6**)	30	36	35	55
	42	13	21	40
m-NCS (**7**)	50	12	25	25
p-NCS (**8**)	90	14	28	27
o-CH_2NCS (**9**)	150	10	35	45
m-CH_2NCS (**10**)	20	56	68	94
	30	22	58	73
p-CH_2NCS (**11**)	20	61	68	95
	40	32	58	64
benzyl ether **30**	10	8[c]	80[c]	94[c]

[a] Results for the synthetic series are the average of triplicate samples (±6%). [b] Test ligand concentrations were chosen to approximate the IC_{65-85} range. [c] Protection experiments were performed in the presence of 1 μM naloxone. [d] Results for benzyl ether **30** are the averages from three separate assays (±10%).

reversible effects (washed and unwashed samples), decreases in naloxone protection are observed. Additional experiments would be necessary to evaluate this possibility. A similar lack of protection has been reported at opioid receptors with other electrophilic ligands.[5,26]

The results obtained from the irreversibility binding assay at δ and κ receptors are given in Tables 4 and 5. At these receptors as well, the synthetic isothiocyanate ligands caused a significant decrease in specific binding of radioligand relative to 6β-benzyl ether **30**, suggesting that the isothiocyanate moiety of each isomer interacts with an accessible reactive nucleophile or nucleophiles at each of the sites, similar to effects at the μ receptor. The high-affinity aromatic *o*-isothiocyanate **6** displayed concentration-dependent irreversibility at these sites, also.

For the non-electrophilic control 6β-benzyl ether **30**, the wash recovery of binding was incomplete in the case of κ receptors, and perhaps at δ receptors. κ Receptor instability, which could account for this observation, has been suggested by Leslie.[21] Alternatively, the lipophilicity of the benzyl ether might lead to wash-resistant binding due to incomplete removal of the ligand from the lipid environment containing the receptor sites. This latter possibility would seem to require significantly different lipid environments of the different receptor types.

Conclusion. The results obtained from the opioid receptor irreversibility binding assays for the synthetic isothiocyanate series suggest that all of the isomers interact with μ, δ, and κ opioid receptors in an irreversible manner. The degree of irreversibility does not correlate with the small differences in relative reactivity of a given specific ligand with the model nucleophile, 4-methoxybenzenethiol. The subtle differences in irreversible binding characteristics of these ligands could result from conformational and geometric differences in alignment of the electrophilic isothiocyanate moiety with cellular nucleophile(s) in the drug receptor interaction(s). However, some caution must be exercised until issues concerning specific vs nonspecific effects are clarified. Clearly, the *o*-isothiocyanate **6** was the electrophilic ligand showing the highest degree of irreversibility at the lowest concentration at all three receptor sites, and thus it is suitable for further study.

General Methods

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded as a liquid film on NaCl plates or as KBr pellets 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. The ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75.5 MHz. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane as an internal standard. Spectral assignments were supported by proton decoupling and APT analysis. Mass spectra were obtained on the VG-7070 and VG-70SEQ mass spectrometers by a direct-insertion probe. Optical rotations were measured on a JASCO DIP-4 digital polarimeter. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel HLF TLC plates (0.25 mm thickness), and compounds were detected using a UV lamp. TLC eluent was 200:150:4 hexane:EtOAc:triethylamine unless otherwise indicated. Merck silica gel 60 (230–400 mesh) was used for preparative flash column chromatography. All reactions were performed under an argon atmosphere and at ambient temperature (20–25 °C) unless otherwise noted. The 0 °C bath was made from ice water, the −23 °C bath was made from a mixture of dry ice and CCl_4, the −56 °C bath was made from a mixture of dry ice and $CHCl_3$, and the −78 °C bath was made from a mixture of dry ice and acetone. Tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) and tetrabutylammonium bromide (TBABr) are catalysts used in the phase transfer catalysis reactions.

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β,14-dihydroxymorphinan (13). To a solution of 17-(cyclopropylmethyl)-4,5α-epoxy-3,6β,14-trihydroxymorphinan (**12**)[7] (1.72 g, 5.0 mmol), triphenylmethyl chloride (1.56 g,

5.5 mmol), and $TBAHSO_4$ (0.855 g, 2.5 mmol) in CH_2Cl_2 (45 mL) was added aqueous 0.34 M KOH (45 mL). After the mixture had been stirred vigorously overnight at room temperature, the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, washed with H_2O (25 mL), dried with sodium sulfate, and the solvent was removed by rotary evaporation. The oily residue was purified by flash column chromatography. After conditioning the silica gel with CH_2Cl_2 (250 mL), the residue was eluted first with 100% CH_2Cl_2 (500 mL) and then 96:4 CH_2Cl_2:triethylamine (500 mL). The product was eluted with the triethylamine solvent front, and evaporation of the solvent afforded **13** as a yellow foam (2.32 g, 80% yield): ^{1}H NMR ($CDCl_3$) δ 7.40–7.52 (m, 6 H, C-23′ 3 H, C-27′ 3 H), 7.08–7.22 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.57 (d, J = 8.3 Hz, 1 H, C-2 H), 6.24 (d, J = 8.3 Hz, 1 H, C-1 H), 4.21 (d, J = 5.5 Hz, 1 H, C-5α H), 2.95 (d, J = 4.9 Hz, 1 H, C-9 H), 2.84 (d, J = 18.4 Hz, 1 H, C-10β H), 2.81–2.98 (m, 1 H, C-6α H), 2.35–2.54 (m, 2 H, C-10α H, C-16 H), 2.25 (d, J = 6.4 Hz, 2 H, C-17 2 H), 1.95–2.11 (m, 1 H, C-15 H), 1.73–1.95 (m, 2 H, C-7 H, C-16 H), 1.44–1.57 (m, 1 H, C-8 H), 1.33–1.44 (m, 1 H, C-7 H), 1.05–1.18 (m, 2 H, C-8 H, C-15 H), 0.67–0.81 (m, 1 H, C-18 H), 0.42–0.50 (m, 2 H, C-19 H, C-20 H), 0.03–0.10 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β-[(4-cyanobenzyl)oxy]-14-hydroxymorphinan (16). To a solution of trityl ether **13** (500 mg, 0.85 mmol), *p*-cyanobenzyl bromide (670 mg, 3.42 mmol), and TBABr (100 mg, 0.31 mmol) in CH_2Cl_2 (15 mL) was added with vigorous stirring aqueous 50% KOH (15 mL). The reaction mixture was colorless. After the reaction mixture was stirred vigorously overnight, additional CH_2Cl_2 (10 mL) and H_2O (10 mL) were added to aid in phase separation. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with H_2O (15 mL) and dried with sodium sulfate. The solvent was removed by rotary evaporation to yield an oily residue which was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL) and 96:4 CH_2Cl_2:triethylamine (200 mL). The product was eluted just after the triethylamine solvent front and evaporation of the solvent afforded **16** as a white foam (450 mg, 75% yield): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 2 H, C-24 H, C-26 H), 7.38–7.49 (m, 8 H, C-23 H, C-27 H, C-23′ 3 H, C-27′ 3 H), 7.14–7.24 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.46 (d, J = 8.2 Hz, 1 H, C-2 H), 6.22 (d, J = 8.2 Hz, 1 H, C-1 H), 4.84 (d, J = 13.7 Hz, 1 H, C-21 H), 4.72 (d, J = 13.7 Hz, 1 H, C-21 H), 4.42 (d, J = 6.1 Hz, 1 H, C-5 H), 3.07–3.19 (m, 1 H, C-6α H), 2.99 (d, J = 5.4 Hz, 1 H, C-9 H), 2.86 (d, J = 18.6 Hz, 1 H, C-10β H), 2.36–2.55 (m, 2 H, C-10α H, C-16 H), 2.29 (d, J = 6.6 Hz, 2 H, C-17 2 H), 1.79–2.12 (m, 3 H, C-7 H, C-15 H, C-16 H), 1.65–1.77 (m, 1 H, C-7 H), 1.47–1.58 (m, 1 H, C-8 H), 1.12–1.27 (m, 1 H, C-8 H), 1.01–1.10 (m, 1 H, C-15 H), 0.72–0.87 (m, 1 H, C-18 H), 0.45–0.55 (m, 2 H, C-19 H, C-20 H), 0.03–0.13 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β-[(3-cyanobenzyl)oxy]-14-hydroxymorphinan (15). Compound **15** was prepared by the phase transfer alkylation method described for preparation of **16**. From trityl ether **13** (500 mg, 0.85 mmol) and *m*-cyanobenzyl bromide (670 mg, 3.42 mmol), **15** was obtained as a brownish-yellow foam (440 mg, 74% yield) after chromatography: ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1 H, C-23 H), 7.61 (d, J = 7.9 Hz, 1 H, C-25 H), 7.53 (d, J = 7.7 Hz, 1 H, C-27 H), 7.40–7.48 (m, 6 H, C-23′ 3 H, C-27′ 3 H), 7.37 (dd, J = 7.7 Hz, 1 H, C-26 H), 7.16–7.25 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.48 (d, J = 8.3 Hz, 1 H, C-2 H), 6.24 (d, J = 8.2 Hz, 1 H, C-1 H), 4.85 (d, J = 12.8 Hz, 1 H, C-21 H), 4.65 (d, J = 12.8 Hz, 1 H, C-21 H), 4.41 (d, J = 6.2 Hz, 1 H, C-5β H), 3.07–3.18 (m, 1 H, C-6α H), 2.99 (d, J = 5.4 Hz, 1 H, C-9 H), 2.87 (d, J = 18.6 Hz, 1 H, C-10β H), 2.38–2.54 (m, 2 H, C-10α H, C-16 H), 2.29 (d, J = 6.6 Hz, 2 H, C-17 2 H), 1.77–2.10 (m, 3 H, C-7 H, C-15 H, C-16 H), 1.63–1.75 (m, 1 H, C-7 H), 1.48–1.58 (m, 1 H, C-8 H), 1.14–1.28 (m, 1 H, C-8 H), 0.98–1.08 (m, 1 H, C-15 H), 0.72–0.87 (m, 1 H, C-18 H), 0.46–0.54 (m, 2 H, C-19 H, C-20 H), 0.05–0.13 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β-[(2-cyanobenzyl)oxy]-14-hydroxymorphinan (14). Compound **14** was prepared by the method described for preparation of **16**. From trityl ether **13** (500 mg, 0.85 mmol) and *o*-cyanobenzyl bromide (670 mg, 3.42 mmol), **14** was obtained as a brown foam (460 mg, 77% yield) after chromatography: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 7.8 Hz, 1 H, C-24), 7.58 (d, J = 7.7 Hz, 1 H, C-27), 7.40–7.53 (m, 7 H, C-23′ 3 H, C-27′ 3 H, C-26 H), 7.21–7.32 (m, 1 H, C-26 H), 7.10–7.20 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.48 (d, J = 8.2 Hz, 1 H, C-2 H), 6.23 (d, J = 8.2 Hz, 1 H, C-1 H), 4.92 (d, J = 12.8 Hz, 1 H, C-21 H), 4.77 (d, J = 12.8 Hz, 1 H, C-21 H), 4.45 (d, J = 6.2 Hz, 1 H, C-5β H), 3.16–3.28 (m, 1 H, C-6α H), 2.99 (d, J = 5.4 Hz, 1 H, C-9 H), 2.86 (d, J = 18.4 Hz, 1 H, C-10β H), 2.38–2.55 (m, 2 H, C-10α H, C-16 H), 2.28 (d, J = 6.4 Hz, 2 H, C-17 2 H), 1.67–2.12 (m, 4 H, C-7 2 H, C-15 H, C-16 H), 1.48–1.58 (m, 1 H, C-8 H), 1.16–1.29 (m, 1 H, C-8 H), 1.01–1.10 (m, 1 H, C-15 H), 0.72–0.85 (m, 1 H, C-18 H), 0.45–0.54 (m, 2 H, C-19 H, C-20 H), 0.05–0.13 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[[4-(aminomethyl)benzyl]oxy]-3,14-dihydroxymorphinan (19). To a solution of the *p*-nitrile **16** (430 mg, 0.61 mmol) in 25% acetic acid (25 mL) was added PtO_2 (25 mg) as catalyst under an atmosphere of argon. After hydrogenation for 39 h at 32 psi, the catalyst was removed by filtration through Celite and the solvent was removed by rotary evaporation. The residue was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL), 96:4 CH_2Cl_2:triethylamine (100 mL), and 96:15:4 CH_2Cl_2:MeOH:triethylamine (200 mL). The product was removed with the last eluent mixture. It was then washed with aqueous saturated $NaHCO_3$, and the solvent was evaporated to yield **19** as a white foam (190 mg, 67% yield): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 7.9 Hz, 2 H, C-24 H, C-26 H), 7.08 (d, J = 8.1 Hz, 2 H, C-23 H, C-27 H), 6.68 (d, J = 8.0 Hz, 1 H, C-2 H), 6.52 (d, J = 8.2 Hz, 1 H, C-1 H), 5.14 (s, broad, NH_2), 4.65 (d, J = 11.7 Hz, 1 H, C-21 H), 4.56 (d, J = 6.5 Hz, 1 H, C-5β H), 4.44 (d, J = 11.7 Hz, C-21 H), 3.78 (s, 2 H, C-28 2 H), 3.28–3.40 (m, 1 H, C-6α H), 3.07 (d, J = 5.4 Hz, 1 H, C-9 H), 2.99 (d, J = 18.2 Hz, 1 H, C-10β H), 2.46–2.65 (m, 2 H, C-10α H, C-16 H), 2.35 (d, J = 6.4 Hz, 2 H, C-17 2 H), 2.03–2.28 (m, 2 H, C-15 H, C-16 H), 1.78–2.03 (m, 2 H, C-7 2 H), 1.52–1.67 (m, 1 H, C-8 H), 1.28–1.49 (m, 2 H, C-8 H, C-15 H), 0.74–0.89 (m, 1 H, C-18 H), 0.45–0.56 (m, 2 H, C-19 H, C-20 H), 0.06–0.16 (m, 2 H, C-19 H′, C-20 H′); FABMS $(M + H)^+$ 463.

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[[3-(aminomethyl)benzyl]oxy]-3,14-dihydroxymorphinan (18). Compound **18** was prepared by catalytic reduction as described for preparation of **19**. From *m*-nitrile **15** (420 mg, 0.60 mmol), the crude product was partially purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL), 96:4 CH_2Cl_2:triethylamine (100 mL), and 100:15:4 CH_2Cl_2:MeOH:triethylamine (200 mL). Impure product was eluted with the last eluent mixture, and evaporation of the solvent afforded a viscous oil. The oil was dissolved in CH_2Cl_2 (25 mL), washed with aqueous saturated $NaHCO_3$ (10 mL), and dried with sodium sulfate, and solvent was removed by rotary evaporation and then purified by flash column chromatography. The column (19 mm diameter) contained silica gel (21 g), which was conditioned with 10:1 EtOAc:MeOH (100 mL), and then the residue was eluted sequentially with 10:1 EtOAc:MeOH (100 mL) and 10:2:1 EtOAc:MeOH:triethylamine (200 mL). The product was eluted with the latter eluent mixture, and evaporation of solvent afforded **18** as a brown foam (200 mg, 72% yield): ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1 H, C-23 H), 7.19 (dd, J = 7.5 Hz, 1 H, C-26 H), 7.03–7.14 (m, 2 H, C-25 H, C-27 H), 6.60 (d, J = 8.1 Hz, 1 H, C-2 H), 6.45 (d, J = 7.9 Hz, 1 H, C-1 H), 5.70 (s, broad, NH_2), 4.80 (d, J = 13.7 Hz, 1 H, C-21 H), 4.58 (d, J = 6.3 Hz, 1 H, C-5β H), 4.51 (d, J = 13.7 Hz, 1 H, C-21 H), 4.02 (d, J = 14.2 Hz, 1 H, C-28 H), 3.89 (d, J = 13.8 Hz, 1 H, C-28 H), 3.14–3.28 (m, 1 H, C-6α H), 3.04 (d, J = 5.5 Hz, 1 H, C-9 H), 2.96 (d, J = 18.2 Hz, 1 H, C-10β H), 2.44–2.63 (m, 2 H, C-10α H, C-16 H), 2.34

(d, J = 6.4 Hz, 2 H, C-17 2 H), 2.15–2.28 (m, 1 H, C-15 H), 2.05–2.15 (m, 1 H, C-16 H), 1.70–1.97 (m, 2 H, C-7 2 H), 1.52–1.60 (m, 1 H, C-8 H), 1.38–1.48 (m, 1 H, C-15 H), 1.20–1.33 (m, 1 H, C-8 H), 0.74–0.88 (m, 1 H, C-18 H), 0.46–0.55 (m, 2 H, C-19 H, C-20 H), 0.07–0.18 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[[2-(aminomethyl)benzyl]oxy]-3,14-dihydroxymorphinan (17). Compound **17** was prepared by catalytic reduction as described for preparation of **19**. From *o*-nitrile **14** (510 mg, 0.73 mmol), the crude reduction product was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL), 96:4 CH_2Cl_2:triethylamine (100 mL), and 85:15:4 CH_2Cl_2:MeOH:triethylamine (200 mL). The product was eluted with the last eluent mixture and evaporation of the solvent afforded **17** as a brown foam (150 mg, 44% yield): ^{1}H NMR ($CDCl_3$) δ 7.28–7.36 (m, 2 H, C-24 H, C-26 H), 7.20–7.28 (m, 2 H, C-25 H, C-27 H), 6.72 (d, J = 8.2 Hz, 1 H, C-2 H), 6.56 (d, J = 8.2 Hz, 1 H, C-1 H), 5.58 (s, broad, NH_2), 4.62 (d, J = 10.3 Hz, 1 H, C-21 H), 4.38 (d, J = 7.3 Hz, 1 H, C-5β H), 4.32 (d, J = 10.2 Hz, C-21 H), 3.67–3.82 (m, 2 H, C-28 2 H), 3.33–3.44 (m, 1 H, C-6α H), 3.08 (d, J = 5.4 Hz, 1 H, C-9 H), 3.02 (d, J = 18.4 Hz, 1 H, C-10β H), 2.51.–2.67 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 6.5 Hz, 2 H, C-17 2 H), 2.05–2.28 (m, 2 H, C-15 H, C-16 H), 1.82–2.03 (m, 2 H, C-7 2 H), 1.55–1.65 (m, 1 H, C-8 H), 1.24–1.52 (m, 2 H, C-8 H, C-15 H), 0.76–0.92 (m, 1 H, C-18 H), 0.47–0.57 (m, 2 H, C-19 H, C-20 H), 0.08–0.18 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[[4-(isothiocyanatomethyl)benzyl]oxy]-3,14-dihydroxymorphinan (11). To a solution of the primary *p*-amine **19** (200 mg, 0.43 mmol) and $NaHCO_3$ (109 mg, 1.30 mmol) in CH_2Cl_2 (1.5 mL) was added thiophosgene dropwise (36 μL, 0.48 mmol) with vigorous stirring. After 15 min, additional CH_2Cl_2 (0.5 mL) was added and then the mixture was stirred an additional 25 min before addition of aqueous 30% ammonia (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with a dilute aqueous solution of $NaHCO_3$ (10 mL) and dried with sodium sulfate, and the solvent was removed by rotary evaporation to yield a viscous oil. This crude product was partially dissolved in CH_2Cl_2 (~5 mL) and filtered, and then the solvent of the filtrate was removed by rotary evaporation, affording **11** as a colorless glass (90 mg, 41% yield): $[\alpha]^{20}_D$ = −107° (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2 H, C-24 H, C-26 H), 7.24 (d, J = 8.1 Hz, 2 H, C-23 H, C-27 H), 6.69 (d, J = 8.0 Hz, 1 H, C-2 H), 6.53 (d, J = 8.2 Hz, 1 H, C-1 H), 4.65, 4.66 (s, s, 4 H, C-21 2 H, C-28 2 H), 4.61 (d, J = 6.4 Hz, 1 H, C-5β H), 3.23–3.34 (m, 1 H, C-6α H), 3.05–3.18 (m, 1 H, C-9 H), 2.99 (d, J = 18.6 Hz, 1 H, C-10β H), 2.50–2.72 (m, 2 H, C-10α H, C-16 H), 2.38 (d, J = 6.0 Hz, 2 H, C-17 2 H), 2.16–2.32 (m, 1 H, C-15 H), 2.00–2.16 (m, 1 H, C-16 H), 1.86–2.00 (m, 1 H, C-7 H), 1.71–1.84 (m, 1 H, C-7 H), 1.56–1.69 (m, 1 H, C-8 H), 1.22–1.46 (m, 2 H, C-8 H, C-15 H), 0.77–0.90 (m, 1 H, C-18 H), 0.47–0.58 (m, 2 H, C-19 H, C-20 H), 0.08–0.18 (m, 2 H, C-19 H′, C-20 H′); ^{13}C NMR ($CDCl_3$) δ 141.90 (C-4), 139.36 (C-3), 138.83 (C-22), 133.08 (C-25), 131.79 (C-29), 131.43 (C-12), 126.60, 127.92 (C-23, C-24, C-26, C-27), 124.00 (C-11), 118.67 (C-1), 116.81 (C-2), 95.18 (C-5), 79.63 (C-6), 70.18, 70.38 (C-14, C-21), 62.11 (C-9), 59.00 (C-17), 48.34 (C-28), 47.71 (C-13), 43.92 (C-16), 30.31 (C-8), 29.43 (C-15), 23.63 (C-7), 22.62 (C-10), 9.22 (C-18), 3.80, 4.01 (C-19, C-20); FTIR (neat) 3500–3100 broad, 3075, 2999, 2926, 2831, 2176, 2095, 1638, 1619, 1502, 1454, 1336, 1239, 1129, 1097, 1036, 981, 914, 854, 802, 736, 634 cm^{-1}; HRFABMS calculated for $C_{29}H_{33}N_2O_4S$ 505.2161, observed 505.2159 (−0.4 ppm). Anal. ($C_{29}H_{32}N_2O_4S$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[[3-(isothiocyanatomethyl)benzyl]oxy]-3,14-dihydroxymorphinan (10). Compound **10** was prepared by a procedure analogous to that described for preparation of **11**. From *m*-amine **18** (126 mg, 0.27 mmol), the crude product **10** was purified by flash column chromatography. After the silica gel (28 g) was conditioned with diethyl ether, the residue was eluted with diethyl ether (100 mL). The solvent was removed by rotary evaporation, affording **10** as a brown glass (30 mg, 22% yield): $[\alpha]^{20}_D$ = −118° (c = 0.754, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.24–7.36 (m, 3 H, C-23 H, C-26 H, C-27 H), 7.13–7.23 (m, 1 H, C-25 H), 6.69 (d, J = 8.0 Hz, 1 H, C-2 H), 6.53 (d, J = 7.9 Hz, 1 H, C-1 H), 4.68 (s, 4 H, C-21 2 H, C-28 2 H), 4.63 (d, J = 6.4 Hz, 1 H, C-5β H), 3.23–3.37 (m, 1 H, C-6α H), 3.09 (d, J = 5.8 Hz, 1 H, C-9 H), 3.00 (d, J = 18.1 Hz, 1 H, C-10β H), 2.50–2.65 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 6.5 Hz, 2 H, C-17 2 H), 2.14–2.30 (m, 1 H, C-15 H), 2.00–2.13 (m, 1 H, C-16 H), 1.86–2.00 (m, 1 H, C-7 H), 1.68–1.82 (m, 1 H, C-7 H), 1.54–1.68 (m, 1 H, C-8 H), 1.22–1.48 (m, 2 H, C-8 H, C-15 H), 0.76–0.90 (m, 1 H, C-18 H), 0.47–0.57 (m, 2 H, C-19 H, C-20 H), 0.09–0.14 (m, 2 H, C-19 H′, C-20 H′); ^{13}C NMR ($CDCl_3$) δ 141.97 (C-4), 139.35, 139.43 (C-3, C-22), 134.08 (C-24), 131.76 (C-29), 131.56 (C-12), 125.66, 125.94, 127.42, 128.76 (C-3, C-25, C-26, C-27), 124.22 (C-11), 118.73 (C-1), 116.83 (C-2), 95.31 (C-5), 79.67 (C-6), 70.20, 70.58 (C-1, C-21), 62.15 (C-9), 59.08 (C-17), 48.50 (C-28), 47.93 (C-13), 43.85 (C-16), 30.51 (C-8), 29.50 (C-15), 23.78 (C-7), 22.62 (C-10), 9.40 (C-18), 3.83, 4.00 (C-19, C-20); FTIR (neat) 3600–3100 broad, 3066, 3006, 2926, 2175, 2096, 1618, 1501, 1452, 1335, 1239, 1152, 1130, 1097, 1076, 1036, 982, 914, 854, 736, 704 cm^{-1}; HRFABMS calculated for $C_{29}H_{33}N_2O_4S$ 505.2161, observed 505.2155. Anal. ($C_{29}H_{32}N_2O_4S$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[[2-(isothiocyanatomethyl)benzyl]oxy]-3,14-dihydroxymorphinan (9). Compound **9** was prepared by a procedure analogous to that described for preparation of **11**. From *o*-amine **17** (90 mg, 0.20 mmol), the oily crude product **9** was chromatographed. After the silica gel was conditioned with CH_2Cl_2 (50 mL), the residue was eluted sequentially with 100% CH_2Cl_2 (50 mL), 80:20 CH_2Cl_2:EtOAc (50 mL), 50:50 EtOAc:CH_2Cl_2 (50 mL), and 100% EtOAc (50 mL). The impure product was further purified by flash column chromatography on a second column (10.5 mm diameter containing silica gel (6 g), which was conditioned with CH_2Cl_2 (25 mL). The product was then eluted sequentially with CH_2Cl_2 (25 mL) and 75:25 CH_2Cl_2:EtOAc (100 mL). The solvent was then removed by rotary evaporation to afford pure **9** as a brown glass (26 mg, 27% yield): $[\alpha]^{20}_D$ −128° (c = 0.78, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.28–7.44 (m, 4 H, C-24 H, C-25 H, C-26 H, and C-27 H), 6.69 (d, J = 8.1 Hz, 1 H, C-2 H), 6.54 (d, J = 8.0 Hz, 1 H, C-1 H), 4.98 (d, J = 16.5 Hz, 1 H, C-21 H), 4.89 (d, J = 16.5 Hz, 1 H, C-21 H), 4.68 (s, 2 H, C-28 2 H), 4.58 (d, J = 6.4 Hz, 1 H, C-5β H), 3.20–3.32 (m, 1 H, C-6α H), 3.05–3.16 (m, 1 H, C-9 H), 3.00 (d, J = 18.6 Hz, 1 H, C-10β H), 2.52.–2.70 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 7.3 Hz, 2 H, C-17 2 H), 2.17–2.30 (m, 1 H, C-15 H), 2.00–2.17 (m, 1 H, C-16 H), 1.85–2.00 (m, 1 H, C-7 H), 1.73–1.85 (m, 1 H, C-7 H), 1.57–1.68 (m, 1 H, C-8 H), 1.24–1.48 (m, 2 H, C-8 H, C-15 H), 0.76–0.92 (m, 1 H, C-18 H), 0.47–0.58 (m, 2 H, C-19 H, C-20 H), 0.08–0.20 (m, 2 H, C-19 H′, C-20 H′); ^{13}C NMR ($CDCl_3$) δ 142.00 (C-4), 139.34 (C-3), 135.42 (C-22), 133.26 (C-23), 131.54 (C-12), 131.33 (C-29), 127.81, 128.25, 128.55, 129.70 (C-24, C-25, C-26, C-27), 124.36 (C-11), 118.84 (C-1), 116.88 (C-2), 95.20 (C-5), 80.31, (C-6), 70.16 (C-21), 69.81 (C-14), 62.23 (C-9), 59.15 (C-17), 47.89 (C-13), 46.47 (C-28), 43.94 (C-16), 30.51 (C-8), 29.60 (C-15), 23.74 (C-7), 22.72 (C-10), 9.42 (C-18), 3.92, 4.06 (C-19, C-20); FTIR (neat) 3600–3100 broad, 3075, 2999, 2826, 2831, 2169, 2097, 1622, 1501, 1454, 1338, 1239, 1186, 1132, 1096, 1074, 1036, 736 cm^{-1}; HRFABMS calculated for $C_{29}H_{33}N_2O_4S$ 505.2161, observed 505.2203. Anal. ($C_{29}H_{32}N_2O_4S$) C, H, N.

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β-[(4-nitrobenzyl)oxy]-14-hydroxymorphinan (22). To a solution of trityl ether **13** (500 mg, 0.86 mmol), 4-nitrobenzyl bromide (739 mg, 3.42 mmol), and TBABr (100 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) at −23 °C was added 50% KOH (10 mL) also at −23 °C with vigorous stirring. The reaction mixture was allowed to warm slowly to room temperature over 10–12 h. After the reaction mixture had been stirred vigorously a total of 39 h, additional CH_2Cl_2 (10 mL) and H_2O (10 mL) were added to aid in phase separation. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The solvent was removed from the combined organic fractions by rotary evaporation to yield a black viscous oil, which was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (150 mL), 80:20 CH_2Cl_2:EtOAc (200

mL), and 50:50 CH_2Cl_2:EtOAc (200 mL). The product was eluted with the second eluent mixture, and evaporation of the solvent afforded **22** as a brown foam (310 mg, 50% yield): ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 8.5 Hz, 2 H, C-24 H, C-26 H), 7.51 (d, J = 8.7 Hz, 2 H, C-23, C-27 H), 7.38–7.48 (m, 6 H, C-23′ 3 H, C-27′ 3 H), 7.15–7.26 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.47 (d, J = 8.2 Hz, 1 H, C-2 H), 6.23 (d, J = 8.3 Hz, 1 H, C-1 H), 4.90 (d, J = 13.7 Hz, 1 H, C-21 H), 4.78 (d, J = 13.8 Hz, 1 H, C-21 H), 4.43 (d, J = 6.3 Hz, 1 H, C-5β H), 3.09–3.20 (m, 1 H, C-6α H), 2.99 (d, J = 5.4 Hz, 1 H, C-9 H), 2.87 (d, J = 18.6 Hz, 1 H, C-10β H), 2.37–2.56 (m, 2 H, C-10α H, C-16 H), 2.29 (d, J = 6.4 Hz, 2 H, C-17 2 H), 1.80–2.12 (m, 3 H, C-7 H, C-15 H, C-16 H), 1.66–1.78 (m, 1 H, C-7 H), 1.48–1.60 (m, 1 H, C-8 H), 1.13–1.28 (m, 1 H, C-8 H), 1.01–1.11 (m, 1 H, C-15 H), 0.72–0.88 (m, 1 H, C-18 H), 0.45–0.55 (m, 2 H, C-19 H, C-20 H), 0.05–0.15 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)-4,5α-epoxy-6β-[(3-nitrobenzyl)oxy]-14-hydroxymorphinan (21). Compound **21** was prepared by a phase transfer alkylation procedure analogous to the preparation of **22**. From trityl ether **13** (500 mg, 0.86 mmol) and *m*-nitrobenzyl chloride (739 mg, 3.42 mmol) was obtained a brown viscous oil which was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL), 75:25 CH_2Cl_2:EtOAc (200 mL), and 50:50 CH_2Cl_2:EtOAc (200 mL). The product was eluted with the second eluent mixture and evaporation of the solvent afforded **21** as a brownish-yellow foam, (510 mg, 83% yield): ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1 H, C-23 H), 8.10 (d, J = 8.2 Hz, 1 H, C-25 H), 7.72 (d, J = 7.3 Hz, 1 H, C-27 H), 7.38–7.50 (m, 7 H, C-26 H, C-23′ 3 H, C-27′ 3 H), 7.15–7.25 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.48 (d, J = 8.2 Hz, 1 H, C-2 H), 6.24 (d, J = 8.2 Hz, 1 H, C-1 H), 4.92 (d, J = 13.0 Hz, 1 H, C-21 H), 4.71 (d, J = 12.8 Hz, 1 H, C-21 H), 4.42 (d, J = 6.1 Hz, 1 H, C-5β H), 3.11–3.22 (m, 1 H, C-6α H), 2.99 (d, J = 5.4 Hz, 1 H, C-9 H), 2.87 (d, J = 18.2 Hz, 1 H, C-10β H), 2.38–2.55 (m, 2 H, C-10α H, C-16 H), 2.29 (d, J = 6.4 Hz, 2 H, C-17 2 H), 1.77–2.12 (m, 3 H, C-7 H, C-15 H, C-16 H), 1.66–1.77 (m, 1 H, C-7 H), 1.49–1.60 (m, 1 H, C-8 H), 1.14–1.28 (m, 1 H, C-8 H), 0.98–1.08 (m, 1 H, C-15 H), 0.72–0.90 (m, 1 H, C-18 H), 0.45–0.56 (m, 2 H, C-19 H, C-20 H), 0.04–0.13 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-3-(triphenylmethoxy)4,5α-epoxy-6β-[(2-nitrobenzyl)oxy]-14-hydroxymorphinan (20). Compound **20** was prepared by a phase transfer alkylation procedure analogous to the preparation of **22**. From trityl ether **13** (500 mg, 0.86 mmol) and *o*-nitrobenzyl bromide (739 mg, 3.42 mmol), a brown viscous oil was obtained which was purified by flash column chromatography. After conditioning the silica gel with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (150 mL), 80:20 CH_2Cl_2:EtOAc (300 mL), and 50:50 CH_2Cl_2:EtOAc (200 mL). The product was eluted with the second eluent mixture, and removal of solvent by rotary evaporation afforded **20** as a yellow foam (390 mg, 63% yield): ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 1 H, C-24 H), 7.98 (d, J = 8.2 Hz, 1 H, C-27 H), 7.52 (dd, J = 7.6, 7.6 Hz, 1 H, C-26 H), 7.39–7.47 (m, 6 H, C-23′ 3 H, C-27′ 3 H), 7.33 (dd, J = 7.8, 7.8 Hz, 1 H, C-25 H), 7.12–7.26 (m, 9 H, C-24′ 3 H, C-25′ 3 H, C-26′ 3 H), 6.47 (d, J = 8.2 Hz, 1 H, C-2 H), 6.22 (d, J = 8.3 Hz, 1 H, C-1 H), 5.09 (d, J = 15.5 Hz, 1 H, C-21 H), 5.01 (d, J = 15.2 Hz, 1 H, C-21 H), 4.45 (d, J = 6.4 Hz, 1 H, C-5β H), 3.10–3.22 (m, 1 H, C-6α H), 2.99 (d, J = 4.9 Hz, 1 H, C-9 H), 2.86 (d, J = 18.6 Hz, 1 H, C-10β H), 2.37–2.55 (m, 2 H, C-10α H, C-16 H), 2.29 (d, J = 6.5 Hz, 2 H, C-17 2 H), 1.72–2.12 (m, 4 H, C-7 2 H, C-15 H, C-16 H), 1.48–1.59 (m, 1 H, C-8 H), 1.14–1.28 (m, 1 H, C-8 H), 1.02–1.11 (m, 1 H, C-15 H), 0.72–0.87 (m, 1 H, C-18 H), 0.44–0.54 (m, 2 H, C-19 H, C-20 H), 0.04–0.12 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(4-nitrobenzyl)oxy]-3,14-dihydroxymorphinan (25). A solution of the trityl-protected *p*-nitro compound **22** (420 mg, 0.57 mmol) in aqueous 50% AcOH (15 mL) was stirred vigorously overnight. The solvent was removed by rotary evaporation, yielding a dark viscous oil which was partitioned between aqueous saturated $NaHCO_3$ (15 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with H_2O (15 mL), and removal of solvent by evaporation yielded a viscous burgundy oil which was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL), 80:20 CH_2Cl_2:EtOAc (100 mL), and 50:50 CH_2Cl_2:EtOAc (200 mL). The product was eluted with the last eluent mixture, and evaporation of the solvent yielded **25** as a dark brown powder (220 mg, 81% yield): mp 182–185 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 2 H, C-24 H, C-26 H), 7.52 (d, J = 8.7 Hz, 2 H, C-23 H, C-27 H), 6.69 (d, J = 8.0 Hz, 1 H, C-2 H), 6.55 (d, J = 8.2 Hz, 1 H, C-1 H), 4.75 (s, 2 H, C-21 2 H), 4.65 (d, J = 6.4 Hz, 1 H, C-5β H), 3.26–3.36 (m, 1 H, C-6α H), 3.10 (d, J = 5.5 Hz, 1 H, C-9 H), 3.01 (d, J = 18.4 Hz, 1 H, C-10β H), 2.52–2.66 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 6.6 Hz, 2 H, C-17 2 H), 2.18–2.32 (m, 1 H, C-15 H), 1.90–2.15 (m, 2 H, C-7 H, C-16 H), 1.74–1.86 (m, 1 H, C-7 H), 1.58–1.68 (m, 1 H, C-8 H), 1.39–1.48 (m, 1 H, C-15 H), 1.24–1.38 (m, 1 H, C-8 H), 0.75–0.90 (m, 1 H, C-18 H), 0.48–0.58 (m, 2 H, C-19 H, C-20 H), 0.08–0.16 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(3-nitrobenzyl)oxy]-3,14-dihydroxymorphinan (24). Compound **24** was prepared by the method described for preparation of **23**. From trityl-protected *m*-nitro compound **21** (340 mg, 0.47 mmol), a brown viscous oil was obtained which was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the residue was eluted sequentially with CH_2Cl_2 (100 mL), 80:20 CH_2Cl_2:EtOAc (100 mL), and 50:50 CH_2Cl_2:EtOAc (200 mL). The product was eluted with the last eluent mixture, and solvent evaporation yielded **24** as a pale yellow powder (190 mg, 84% yield): mp 210–213 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1 H, C-23 H), 8.10 (d, J = 8.2 Hz, 1 H, C-25 H), 7.68 (d, J = 7.6 Hz, 1 H, C-27 H), 7.49 (dd, J = 7.9, 7.9 Hz, 1 H, C-26 H), 6.67 (d, J = 8.1 Hz, 1 H, C-2 H), 6.54 (d, J = 8.2 Hz, 1 H, C-1 H), 4.76 (s, 2 H, C-21 2 H), 4.66 (d, J = 6.4 hz, 1 H, C-5β H), 3.25–3.37 (m, 1 H, C-6α H), 3.09 (d, J = 5.5 Hz, 1 H, C-9 H), 3.01 (d, J = 18.4 Hz, 1 H, C-10β H), 2.50–2.67 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 6.6 Hz, 2 H, C-17 2 H), 2.20–2.33 (m, 1 H, C-15 H), 1.92–2.15 (m, 2 H, C-7 H, C-16 H), 1.76–1.88 (m, 1 H, C-7 H), 1.57–1.68 (m, 1 H, C-8 H), 1.41–1.50 (m, 1 H, C-15 H), 1.25–1.40 (m, 1 H, C-8 H), 0.75–0.92 (m, 1 H, C-17 H), 0.48–0.57 (m, 2 H, C-19 H, C-20 H), 0.07–0.16 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(2-nitrobenzyl)oxy]-3,14-dihydroxymorphinan (23). Compound **23** was prepared by a method described for preparation of **25**. From trityl-protected *o*-nitro compound **20** (290 mg, 0.40 mmol), a viscous oil was obtained which was purified by flash column chromatography. The column (19 mm diameter) contained silica gel (21 g) which was conditioned with CH_2Cl_2 (100 mL), and then the residue was eluted sequentially with 100% CH_2Cl_2 (100 mL), 80:20 CH_2Cl_2:EtOAc (100 mL), 50:50 CH_2Cl_2:EtOAc (200 mL), and 100% EtOAc (100 mL). The product was eluted with the third eluent mixture, and solvent evaporation yielded phenol **23** as a light yellow oil (170 mg, 88%): ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 7.0 Hz, 1 H, C-24 H), 7.79 (d, J = 7.3 Hz, 1 H, C-27 H), 7.60 (dd, J = 7.1, 7.1 Hz, 1 H, C-26 H), 7.40 (dd, J = 7.1, 7.1 Hz, 1 H, C-25 H), 6.70 (d, J = 8.1 Hz, 1 H, C-2 H), 6.54 (d, J = 8.1 Hz, 1 H, C-1 H), 4.98 (d, J = 14.5 Hz, 1 H, C-21 H), 4.91 (d, J = 14.3 Hz, 1 H, C-21 H), 4.56 (d, J = 6.6 Hz, 1 H, C-5β H), 3.25–3.36 (m, 1 H, C-6α H), 3.08 (d, J = 5.4 Hz, 1 H, C-9 H), 3.00 (d, J = 18.2 Hz, 1 H, C-10β H), 2.50–2.66 (m, 2 H, C-10α H, C-16 H), 2.35 (d, J = 6.4 Hz, 2 H, C-17 2 H), 1.98–2.28 (m, 2 H, C-15 H, C-16 H), 1.79–1.98 (m, 2 H, C-7 2 H), 1.57–1.68 (m, 1 H, C-8 H), 1.24–1.47 (m, 2 H, C-8 H, C-15 H), 0.75–0.90 (m, 1 H, C-18 H), 0.47–0.57 (m, 2 H, C-19 H, C-20 H), 0.06–0.15 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(4-aminobenzyl)oxy]-3,14-dihydroxymorphinan (28). A solution of the *p*-nitro compound **25** (140 mg, 0.29 mmol) and $FeSO_4 \cdot 7H_2O$ (692 mg, 2.49 mmol) in aqueous 50% MeOH (20 mL) was heated at reflux using a silicon oil bath (75–80 °C) for 45 min, and then aqueous 30% ammonia (3 mL) was added dropwise over 8 min. The reaction mixture was refluxed an additional 10 min and was dark black. After cooling, the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined

organic fractions were washed with H_2O (15 mL). The solvent was removed by rotary evaporation to yield a gray foam. This foam was dissolved in EtOAc (25 mL) and washed with H_2O (3 × 15 mL). The combined aqueous washes were back-extracted with EtOAc (15 mL), and the solvent was removed from the combined organic fractions by rotary evaporation. The foam was dissolved in EtOAc (25 mL), washed with aqueous saturated $NaHCO_3$ (15 mL), and then dried with sodium sulfate, and removal of solvent by rotary evaporation yielded **28** as a brown resin (115 mg, 88% yield): ^{1}H NMR ($CDCl_3$) δ 7.14 (d, J = 7.9 Hz, 2 H, C-23 H, C-27 H), 6.60–6.7– (m, 3 H, C-2 H, C-24 H, C-26 H), 6.52 (d, J = 8.2 Hz, 1 H, C-1 H), 4.60 (d, J = 6.6 Hz, 1 H, C-21 H), 4.45–4.56 (m, 2 H, C-5β H, C-21 H), 3.21–3.33 (m, 1 H, C-6α H), 3.06 (d, J = 5.4 Hz, 1 H, C-9 H), 2.98 (d, J = 18.2 Hz, 1 H, C-10β H), 2.48–2.66 (m, 2 H, C-10α H, C-16 H), 2.34 (d, J = 6.6 Hz, 2 H, C-17 2 H), 2.16–2.29 (m, 1 H, C-15 H), 2.03–2.15 (m, 1 H, C-16 H), 1.85–2.03 (m, 1 H, C-7 H), 1.71–1.83 (m, 1 H, C-7 H), 1.53–1.64 (m, 1 H, C-8 H), 1.37–1.48 (m, 1 H, C-15 H), 1.23–1.36 (m, 1 H, C-8 H), 0.74–0.92 (m, 1 H, C-18 H), 0.47–0.57 (m, 2 H, C-19 H, C-20 H), 0.06–0.17 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(3-aminobenzyl)oxy]-3,14-dihydroxymorphinan (27). A. Reduction with $SnCl_2$. A solution of the trityl-protected m-nitro compound **21** (180 mg, 0.25 mmol) and $SnCl_2 \cdot 2H_2O$ (279 mg, 1.25 mmol) in EtOAc (5.0 mL) was heated at 70 °C for 45 min and then cooled in an ice bath. After addition of aqueous saturated $NaHCO_3$ (3 mL), followed by aqueous 50% AcOH (20 mL) and aqueous concentrated HCl (0.25 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with H_2O (10 mL) and dried with sodium sulfate, and the solvent was removed by rotary evaporation to yield a viscous oil which was purified by flash column chromatography. The column (19 mm diameter) contained silica gel (17.5 g) which was conditioned with CH_2Cl_2 (100 mL), and then the oil was eluted sequentially with CH_2Cl_2 (100 mL) and 90:10 CH_2Cl_2:MeOH (100 mL). The solvent was removed by rotary evaporation affording **27** as a colorless glass (90 mg, 80% yield).

B. Reduction with $FeSO_4$. A solution of the m-nitro compound **24** (170 mg, 0.36 mmol) and $FeSO_4 \cdot 7H_2O$ (840 mg, 3.02 mmol) in aqueous 50% MeOH (20 mL) was refluxed for 95 min, and then aqueous 30% ammonia (6 mL) was added dropwise over 2 min. The reaction mixture was refluxed an additional 20 min. The reaction mixture was then stirred at room temperature overnight. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic fractions were washed with aqueous saturated $NaHCO_3$ (15 mL), and solvent was removed by rotary evaporation. The oily residue was dissolved in EtOAc (25 mL) and washed with aqueous saturated $NaHCO_3$ (15 mL) and H_2O (2 × 10 mL), and following drying over sodium sulfate, the solvent was removed by rotary evaporation to yield **27** as a yellow foam (130 mg, 82% yield): ^{1}H NMR ($CDCl_3$) δ 7.06 (dd, J = 7.7, 7.7 Hz, 1 H, C-26 H), 7.01 (s, 1 H, C-23 H), 6.55–6.69 (m, 3 H, C-2 H, C-25 H, C-27 H), 6.49 (d, J = 8.1 Hz, 1 H, C-1 H), 4.61–4.72 (m, 2 H, C-5β H, C-21 H), 4.50 (d, J = 13.2 Hz, 1 H, C-21 H), 3.18–3.29 (m, 1 H, C-6α H), 3.06 (d, J = 5.5 Hz, 1 H, C-9 H), 2.97 (d, J = 18.2 Hz, 1 H, C-10β H), 2.46–2.66 (m, 2 H, C-10α H, C-16 H), 2.35 (d, J = 6.4 Hz, 2 H, C-17 2 H), 2.18–2.31 (m, 1 H, C-15 H), 2.03–2.15 (m, 1 H, C-16 H), 1.74–2.03 (m, 2 H, C-7 2 H), 1.53–1.64 (m, 1 H, C-8 H), 1.40–1.49 (m, 1 H, C-15 H), 1.21–1.35 (m, 1 H, C-8 H), 0.74–0.90 (m, 1 H, C-18 H), 0.47–0.55 (m, 2 H, C-19 H, C-20 H), 0.06–0.14 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(2-aminobenzyl)oxy]-3,14-dihydroxymorphinan (26). A solution of the o-nitro compound **23** (80 mg, 0.17 mmol) and $FeSO_4 \cdot 7H_2O$ (395 mg, 1.42 mmol) in aqueous 50% MeOH (20 mL) was refluxed for 30 min, and then aqueous 30% ammonia (3 mL) was added dropwise over 3–5 min. The reaction mixture was refluxed an additional 10 min. The cooled mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were washed with H_2O (25 mL), and the solvent was removed by rotary evaporation to yield **26** as a white foam (60 mg, 80% yield): ^{1}H NMR ($CDCl_3$) δ 7.00–7.15 (m, 2 H, C-25 H, C-27 H), 6.68–6.80 (m, 2 H, C-24 H, C-26 H), 6.66 (d, J = 8.0 Hz, 1 H, C-2 H), 6.51 (d, J = 7.7 Hz, 1 H, C-1 H), 4.74 (d, J = 11.7 Hz, 1 H, C-21 H), 4.47–4.63 (m, 2 H, C-5β H, C-21 H), 3.18–3.33 (m, 1 H, C-6α H), 3.00–3.10 (m, 1 H, C-9 H), 2.98 (d, J = 18.2 Hz, 1 H, C-10β H), 2.45–2.67 (m, 2 H, C-10α H, C-16 H), 2.34 (d, J = 5.4 Hz, 2 H, C-17 2 H), 2.02–2.28 (m, 2 H, C-15 H, C-16 H), 1.73–1.98 (m, 2 H, C-7 2 H), 1.53–1.68 (m, 1 H, C-8 H), 1.20–1.49 (m, 2 H, C-8 H, C-15 H), 0.74–0.95 (m, 1 H, C-18 H), 0.43–0.60 (m, 2 H, C-19 H, C-20 H), 0.04–0.20 (m, 2 H, C-19 H′, C-20 H′).

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(4-isothiocyanatobenzyl)oxy]-3,14-dihydroxymorphinan (8). The a oslution of the aromatic p-amine **28** (80 mg, 0.18 mmol), in CH_2Cl_2 (3.0 mL), a solution of di-2-pyridyl thionocarbonate (42 mg, 0.18 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise with vigorous stirring. After 1 h, the reaction mixture was washed with aqueous saturated $NaHCO_3$ (5 mL) and the solvent was removed by rotary evaporation to yield a viscous oil. The oil was partially purified by flash column chromatography. After the silica gel (6 g) was conditioned with CH_2Cl_2 (25 mL), the oil was eluted sequentially with CH_2Cl_2 (25 mL), 80:20 CH_2Cl_2:EtOAc (150 mL), and EtOAc (50 mL). The solvent was removed by rotary evaporation to afford **8** as a clear brown glass (32 mg, 37% yield): $[\alpha]^{20}_D$ = −181° (c = 0.94, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2 H, C-23 H, C-27 H), 7.17 (d, J = 8.5 Hz, 2 H, C-24 H, C-26 H), 6.69 (d, J = 8.1 Hz, 1 H, C-2 H), 6.55 (d, J = 8.2 Hz, 1 H, C-1 H), 4.65 (s, 2 H, C-21 2 H), 4.58–4.67 (m, 1 H, C-5β H), 3.23–3.34 (m, 1 H, C-6α H), 3.08 (d, J = 5.8 Hz, 1 H, C-9 H), 3.00 (d, J = 18.2 Hz, 1 H, C-10β H), 2.49–2.66 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 6.5 Hz, 2 H, C-17 2 H), 2.17–2.31 (m, 1 H, C-15 H), 2.01–2.15 (m, 1 H, C-16 H), 1.87–2.01 (m, 1 H, C-7 H), 1.72–1.84 (m, 1 H, C-7 H), 1.55–1.65 (m, 1 H, C-8 H), 1.38–1.48 (m, 1 H, C-15 H), 1.24–1.37 (m, 1 H, C-8 H), 0.75–0.92 (m, 1 H, C-18 H), 0.47–0.56 (m, 2 H, C-19 H, C-20 H), 0.07–0.16 (m, 2 H, C-19 H′, C-20 H′); ^{13}C NMR ($CDCl_3$) δ 141.83 (C-4), 139.03 (C-3), 138.06 (C-22), 134.77 (C-28), 131.58 (C-12), 129.96 (C-25), 128.36 (C-23, C-27), 125.42 (C-24, C-26), 124.57 (C-11), 118.75 (C-1), 116.50 (C-2), 95.49 (C-5), 80.00 (C-6), 70.02, 70.20 (C-14, C-21), 62.11 (C-9), 59.07 (C-17), 47.90 (C-13), 43.77 (C-16), 43.77 (C-16), 30.52 (C-8), 29.50 (C-15), 23.73 (C-7), 22.57 (C-10), 9.43 (C-18), 3.78, 3.94 (C-19, C-20); FTIR (neat) 3600–3100 broad, 3077, 2995, 2925, 2831, 2174, 2096, 1636, 1618, 1580, 1503, 1453, 1322, 1238, 1128 1096, 1077, 1035, 930, 854, 800 cm^{-1}; HRFABMS (M + H)$^+$ calculated for $C_{28}H_{31}N_2O_4S$ 491.2004, observed 491.2023. Anal. ($C_{28}H_{30}N_2O_4S$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(3-isothiocyanatobenzyl)oxy]-3,14-dihydroxymorphinan (7). Compound **7** was prepared by the method described for preparation of **8**. From aromatic m-amine **27** (75 mg, 0.17 mmol) in CH_2Cl_2 (3.0 mL), a viscous oil was obtained which was partially purified by flash column chromatography. After the silica gel (8 g) was conditioned with CH_2Cl_2 (50 mL), the column was eluted sequentially with CH_2Cl_2 (50 mL), 75:25 CH_2Cl_2:EtOAc (50 mL), 50:50 CH_2Cl_2:EtOAc, and EtOAc (50 mL). The impure product was then purified by flash column chromatography on a second column (10.5 mm diameter) containing silica gel (6 g) which was conditioned with CH_2Cl_2 (25 mL), and the product was eluted sequentially with CH_2Cl_2 (25 mL) and 75:25 CH_2Cl_2:EtOAc (100 mL). The solvent was removed by rotary evaporation to afford **7** as a clear brown glass (60 mg, 73% yield): $[\alpha]^{20}_D$ = −130° (c = 0.55, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.24–7.31 (m, 3 H, C-23 H, C-26 H, C-27 H), 7.07–7.13 (m, 1 H, C-25 H), 6.69 (d, J = 8.3 Hz, 1 H, C-2 H), 6.55 (d, J = 8.3 Hz, 1 H, C-1 H), 4.65 (s, 2 H, C-21 2 H), 4.62–4.66 (m, 1 H, C-5β H), 3.23–3.34 (m, 1 H, C-6α H), 3.08 (d, J = 5.5 Hz, 1 H, C-9 H), 3.00 (d, J = 18.4 Hz, 1 H, C-10ν H), 2.50–2.67 (m, 2 H, C-10α H, C-16 H), 2.36 (d, J = 6.7 Hz, 2 H, C-17 2 H), 2.15–2.31 (m, 1 H, C-15 H), 1.89–2.15 (m, 2 H, C-7 H, C-16 H), 1.72–1.84 (m, 1 H, C-7 H), 1.55–1.66 (m, 1 H, C-8 H), 1.38–1.49 (m, 1 H, C-15 H), 1.24–1.38 (m, 1 H, C-8 H), 0.75–0.92 (m, 1 H, C-18 H), 0.47–0.56 (m, 2 H, C-19 H, C-20 H), 0.08–0.16 (m, 2 H, C-19 H′, C-20 H′); ^{13}C NMR ($CDCl_3$) δ 141.84 (C-4), 140.60 (C-22), 139.09 (C-3), 134.89 (C-28), 131.58 (C-12), 130.94 (C-24), 129.19 (C-26), 126.20 (C-27), 124.39, 124.51, 124.66 (C-11, C-23, C-25), 118.76 (C-1), 116.60 (C-2),

95.43 (C-5), 79.89 (C-6), 70.05 (C-14, C-21), 62.12 (C-9), 59.08 (C-17), 47.90 (C-13), 43.77 (C-16), 30.53 (C-8), 29.48 (C-15), 23.76 (C-7), 22.58 (C-10), 9.44 (C-18), 3.79, 3.94 (C-19, C-20); FTIR (neat) 3600–3100 broad, 3075, 3000, 2925, 2820, 2112, 1641, 1605, 1584, 1502, 1454, 1322, 1238, 1128, 1098, 1036, 982, 915, 854, 786, 737, 682 cm^{-1}; HRFABMS $(M + H)^+$ calculated for $C_{28}H_{31}N_2O_4S$ 491.2004, observed 491.2002. Anal. ($C_{28}H_{30}N_2O_4S$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-6β-[(2-isothiocyanatobenzyl)oxy]-3,14-dihydroxymorphinan (6). Compound **6** was prepared by the method described for preparation of **8**. From aromatic *o*-amine **28** (120 mg, 0.27 mmol), a viscous oil was obtained which was purified by flash column chromatography. After the silica gel was conditioned with CH_2Cl_2 (100 mL), the oil was eluted sequentially with CH_2Cl_2 (100 mL), 90:10 CH_2Cl_2:EtOAc (100 mL), 80:20 CH_2Cl_2:EtOAc (100 mL), 50:50 CH_2Cl_2:EtOAc (100 mL), and finally with EtOAc (100 mL). The product was eluted with the third eluent mixture. The solvent was then removed by rotary evaporation to afford **6** as a colorless glass (55 mg, 42% yield): $[\alpha]^{20}_D$ = −130° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.47–7.55 (m, 1 H, C-27 H), 7.17–7.30 (m, 3 H, C-24 H, C-25 H, C-26 H), 6.70 (d, *J* = 8.0 Hz, 1 H, C-2 H), 6.55 (d, *J* = 8.0 Hz, 1 H, C-1 H), 4.80 (d, *J* = 12.5 Hz, 1 H, C-21 H), 4.63–4.71 (m, 2 H, C-5β H, C-21 H), 3.30–3.41 (m, 1 H, C-6α H), 3.09 (d, *J* = 5.8 Hz, 1 H, C-9 H), 3.01 (d, *J* = 18.4 Hz, 1 H, C-10β H), 2.52–2.67 (m, 2 H, C-10α H, C-16 H), 2.36 (d, *J* = 6.4 Hz, 2 H, C-17 2 H), 2.17–2.30 (m, 1 H, C-15 H), 1.93–2.15 (m, 2 H, C-7 H, C-16 H), 1.80–1.93 (m, 1 H, C-7 H), 1.57–1.68 (m, 1 H, C-8 H), 1.41–1.50 (m, 1 H, C-15 H), 1.28–1.41 (m, 1 H, C-8 H), 0.75–0.90 (m, 1 H, C-18 H), 0.47–0.58 (m, 2 H, C-19 H, C-20 H), 0.07–0.17 (m, 2 H, C-19 H′, C-20 H′); ^{13}C NMR ($CDCl_3$) δ 141.88 (C-4), 139.15 (C-3), 135.52 (C-28), 135.06 (C-22), 131.49 (C-12), 128.36, 128.91, 129.05 (C-23, C-25, C-27), 127.25 (C-26), 125.95 (C-24), 124.44 (C-11), 118.74 (C-1), 116.54 (C-2), 95.51 (C-5), 80.78 (C-14), 70.08 (C-14), 67.60 (C-21), 62.20 (C-9), 59.11 (C-17), 47.95 (C-13), 43.81 (C-16), 30.57 (C-8), 29.52 (C-15), 23.82 (C-7), 22.60 (C-10), 9.46 (C-18), 3.81, 3.95 (C-19, C-20); FTIR (neat) 3500–3100 broad, 3077, 2925, 2831, 2095, 1618, 1580, 1503, 1453, 1322, 1239, 1128, 1095, 1035, 980, 932, 854, 759 cm^{-1}; HRFABMS $(M + H)^+$ calculated for $C_{28}H_{31}N_2O_4S$ 491.2004, observed 491.2006 (+0.3 ppm). Anal. ($C_{28}H_{30}N_2O_4S$), C, H, N.

Relative Reaction Rates of Isothiocyanate Chemoaffinity Ligands with 4-Methoxybenzenethiol. The relative reaction rates of the regioisomeric aliphatic and aromatic isothiocyanate ligands with a model nucleophile, 4-methoxybenzenethiol, were examined.[16] An aliquot of each electrophilic ligand was dissolved in $CDCl_3$. An initial aliquot (100 μL) of the thiol in CDCl (79 mM) was added to each tube, and the relative amount of thiol present in the reaction mixture was determined by comparing the areas of the signals of the two morphinan aromatic protons attached at C-1 and C-2 to the integrated area of the upfield doublet representing two of the 4-methoxybenzenethiol aromatic protons. Additional thiol solution (79 mM) was added until the ratio of the integrals of the aromatic proton signals was between 0.9 and 1.0. The reaction was then initiated by adding an equal volume of 81 mM triethylamine in $CDCl_3$. At various time points from 10 to 200 min, the relative concentration of unreacted 4-methoxybenzenethiol was calculated based on the integral of the signal for the methyl group of 4-methoxybenzenethiol divided by the sum of methyl group signal integrals observed for the methoxyl group of the thiol and the methoxy group of the newly formed dithiocarbamate adduct. The rate constant (*k*) for each reaction of electrophilic ligand with 4-methoxybenzenethiol was determined by linear regression analysis of the reciprocal relative concentration of unreacted thiol vs time.

Dithiocarbamate 29 Formed from Reaction of 6 and 4-Methoxybenzenethiol. The aromatic proton signal integration ratio of 4-methoxybenzenethiol:**6** was 0.92:1.0 after addition of 200 μL of a 79 mM solution of 4-metoxybenzenethiol in $CDCl_3$. After 2 days, the product was examined by ^1H NMR, FTIR, and mass spectrometry: ^1H NMR ($CDCl_3$) δ 7.48–7.55 (m, 1 H, C-27 H), 7.40 (d, *J* = 8.6 Hz, 2 H, C-2′ H, C-6′ H), 7.20–7.30 (m, 3 H, C-24 H, C-25 H, C-26 H), 6.83 (d, *J* = 8.8 Hz, 2 H, C-3′ H, C-5′ H), 6.69 (d, *J* = 8.0 Hz, 1 H, C-2 H), 6.55 (d, *J* = 8.0 Hz, 1 H, C-1 H), 4.82 (d, *J* = 12.7 Hz, 1 H, C-21 H), 4.62–4.72 (m, 2 H, C-5β H, C-21 H), 3.80, (s, 3 H, OCH_3); FTIR (neat) 3500–3100 broad, 2936, 2097, 1589, 1491, 1454, 1288, 1246, 1171, 1095, 1034, 759 cm^{-1}; HRFABMS calculated for $C_{35}H_{39}N_2O_5S_2$ 631.2300, observed 631.2285 (−2.4 ppm).

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

Radioligand Displacement Assays. The binding assay was carried out essentially as described by Lin and Simon[18] with slight modifications. Hartley-VAF Plus guinea pigs (300–350 g) were killed by decapitation. The brains, less cerebellum, were homogenized in six volumes of 0.05 M Trizma buffer (pH 7.4) with a Virtrishear 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:total solution volume). This corresponded to a final protein concentration of 0.8–1.5 mg protein/mL of homogenate as determined according to the method of Ohnishi and Barr[29] by use of Sigma Diagnostics Micro Protein Determination Kit.

Radioligands used were [^3H]bremazocine (0.5 nM) for total ligand binding, [^3H]DAMGO (1.0 nM) for μ receptor binding, [^3H]DPDPE (1.0 nM) for δ receptor binding, and [^3H]U69,593 (1.0 nM) for κ receptor binding.[20–22] Synthetic ligands were tested in duplicate at nine concentrations between 1.0 and 1000 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), and eluted with 10 mL aliquots of Aquasol, and the radioactivity was counted. Specific binding for each concentration was calculated, and the data were analyzed by probit transformation[30] and linear regression to obtain the IC_{50}.

Irreversibility and Protection Studies. Diluted guinea pig brain homogenate was incubated with each synthetic ligand for 60 min at 25 °C. For protection studies and for recovery samples, the homogenate was preincubated with 1 μM naloxone for 15 min at 37 °C. After incubation, the samples were diluted 3-fold with ice-cold 0.5 M Trizma buffer (pH 7.4) and centrifuged at 10000*g* for 15 min at 4 °C. The membrane preparation was washed by decanting the supernatent, resuspending the pellet in three times the original volume with ice-cold buffer, incubating for 15 min at 37 °C, and then centrifuging again. This wash process was repeated, the supernatent was decanted, and the pellet resuspended in 1.9 mL of ice-cold buffer. A binding assay was performed as described above. The percent of radioligand specific binding remaining was calculated for each sample on the basis of radioligand specific binding values obtained for the recovery samples.

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