Opioid Agonists and Antagonists. 6-Desoxy-6-substituted Lactone, Epoxide, and Glycidate Ester Derivatives of Naltrexone and Oxymorphone

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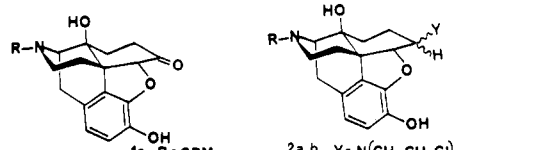
Synthesis and opioid radioreceptor assay data on analogues closely related to 6-desoxy-6-spiro-α-methylene-γ-lactone **5a**, a compound with irreversible activity in this assay, are reported. Saturated lactones (**7a,b**), endocyclic α,β-unsaturated γ-lactones (**8a,b** and **9a**), and 6α,7α-fused α-methylene-γ-lactones (**10a** and **11a**) were prepared. Related 6-desoxy-6-methylene 6β- and 6α-oxides (**12a,b** and **13a**) and glycidate esters **14a,b** and **15a,b** were also prepared with use of naltrexone (**1a**) and oxymorphone (**1b**) as starting material. Compounds in the *N*-cyclopropylmethyl (*N*-CPM) series were more potent than those in the *N*-Me series in displacing [^{3}H]naltrexone in the opioid radioreceptor assay, usually by 2–16-fold in the absence of Na ion. The most potent *N*-CPM analogues were epoxides **12a** and **13a** and glycidate esters **14a** and **15a**, showing IC_{50}'s of 2–6 nM, similar to that of **5a**. Of the *N*-Me analogues, 6β-oxide **12b** was most active, with an IC_{50} of 8 nM in the absence of Na ion. For the *N*-CPM analogues, the Na ion ratios were generally less than 1, with two exceptions. The *N*-Me analogues showed expected larger Na ion effects of 7 or greater. None of the lactone analogues had irreversible effects when preincubated in the rat brain membrane preparation, even at 37 °C for 30 min, i.e., washing restored [^{3}H]naltrexone binding to control levels. These results clearly show that the α-methylene-γ-lactone moiety of **5a** is required for irreversible effects, consistent with it serving as a conjugate addition acceptor of a nucleophilic group from a ligand at or near the receptor. The epoxides and glycidate esters also had no irreversible activity, indicating more electrophilic functional groups are needed and/or these electrophiles are not properly aligned to react with nucleophilic groups at or near the opioid receptor.

Chemoaffinity labels derived from opioid agonist and antagonist molecules have provided an important approach to aid in characterization of opioid drug receptor interactions.[1] Compounds related to naltrexone (**1a**) and oxymorphone (**1b**) with alkylating functionalities at the C-6 position, e.g., the *N,N*-bis(β-chloroethyl) derivatives of 6α- and 6β-naltrexamine and -oxymorphamine (**2a** and **2b**), the fumaramide methyl esters (**3a** and **3b**), the 6α- and 6β-isothiocyanate derivatives (**4a** and **4b**), and other derivatives of these amines have shown interesting characteristics in opioid receptor preparations.[2] Results based on inactivation of opioid receptor binding by sulfhydryl reagents like *N*-ethylmaleimide suggested that alkylation of sulfhydryl groups occurs at or near an opioid binding site.[3] This possibility has been extended with the suggestion that sulfhydryl group(s) may serve as secondary recognition site(s) for certain electrophilic ligands.[4] Results of our recent work[5] on 6-desoxy-6-spiro-α-methylene-γ-lactone derivatives **5a,b** and **6a,b** showing that **5a** had irreversible activity in the opioid radioreceptor assay and that **5b** and diastereomeric α-methylene-γ-lactones **6a** and **6b** had no irreversible activity under the conditions described therein was consistent with this possibility. These results also provided some information concerning the possible location of a receptor nucleophile. Therefore, work on closely related analogues was undertaken.



In this paper, we report the synthesis and opioid radioreceptor assay data for several analogues closely related to **5a** and **5b**. Saturated and endocyclic analogues of these α-methylene-γ-lactones were prepared to obtain more information concerning structural requirements for the irreversible activity observed for **5a** in the opioid radioreceptor assay. These compounds were saturated lactone analogues **7a** and **7b**, the endocyclic α,β-unsaturated γ-lactones **8a**, **8b**, and **9a** and the 6α,7α-fused α-methylene-γ-lactones **10a** and **11a**. Because epoxide **12a** is an intermediate in the synthesis of the lactones, the diastereomeric β- and α-epoxides **12a** and **13a** were prepared and tested. The corresponding 6β-oxide of 6-desoxy-6-methylenenaloxone has been reported to be as a potent antagonist.[6] Closely related epoxides, the (*E*)- and (*Z*)-glycidate esters **14a** and **15a**, were also prepared.

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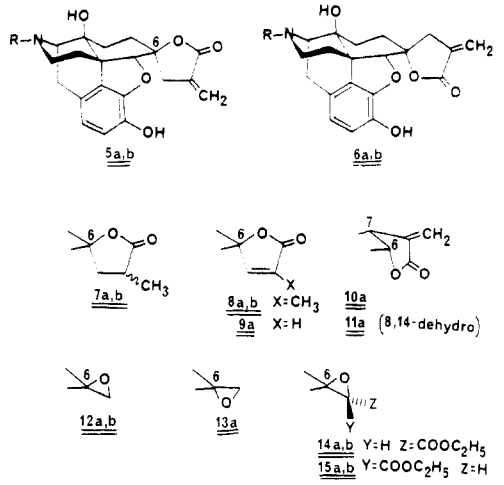

Results and Discussion

Chemistry. Spiro-α-methyl-γ-lactones **7a** and **7b** were prepared from the corresponding THF-protected ketones **16a**[5] and **16b**[5] (Scheme I). Epoxide **17a**, formed from **16a** by reaction with dimethylsulfoxonium methylide, when allowed to react with the dianion of propionic acid provided lactone **7a** directly (as a diastereomeric mixture), with loss of the protecting group in the workup. The corresponding *N*-Me α-methyl-γ-lactone **7b** was prepared from THF-protected oxymorphone (**16b**).

To obtain the related α,β-unsaturated α-methyl-γ-lactone **8a** (Scheme I), lactone **7a** was allowed to react with *tert*-butyldimethylsilyl chloride to give the protected phenol. α-Phenylselenation of the lactone enolate with benzeneselenenyl chloride gave **19a** followed by oxidative elimination with aqueous sodium periodate afforded endocyclic olefin **8a** after deprotection. The *N*-Me analogue **8b** was prepared by a similar series of steps. α,β-Unsaturated lactone **9a** was prepared by reaction of epoxide **17a** with the dianion of (phenylseleno)acetic acid (Scheme II). The intermediate mixture of selenides **20a** gave **9a** upon oxidation with sodium periodate, elimination, and deprotection.

The corresponding 6α,7α-fused α-methylene-γ-lactones **10a** and **11a** were also prepared from **16a** (Scheme III). The anion of **16a**, formed using lithium hexamethyldisilazane, was alkylated with ethyl α-iodoacetate and the resulting protected keto ester **21a** reduced with lithium tri-*sec*-butylborohydride.[7] Acidification of the intermediate hydroxy ester followed by neutralization afforded fused lactone **22a**. Reprotection with *tert*-butyldimethylsilyl chloride afforded the protected phenol, which was hydroxymethylated with gaseous formaldehyde. (Hydroxymethyl)lactone **24a** was converted to the corresponding primary methanesulfonate ester and elimination performed in refluxing pyridine. Deprotection afforded **10a**. By use of an excess of methanesulfonyl chloride, **24a** was converted to **11a** after elimination.

The 6-desoxy-6-methylene 6β- and 6α-epoxides **12a,b** and **13a** were also prepared. 6β-Epoxide **12a** was readily prepared from intermediate **17a** by deprotection. The *N*-Me compound **12b** was also prepared. 6α-Epoxide **13a**, diastereomeric with **12a** at C-6, and closely related glycidate esters **14a,b** and **15a,b** were also prepared (Scheme IV). O^3-(*tert*-Butyldimethylsilyl)naltrexone (**26a**) was acetylated in acetic anhydride at 80 °C and the corresponding ester allowed to react with dimethylsulfonium

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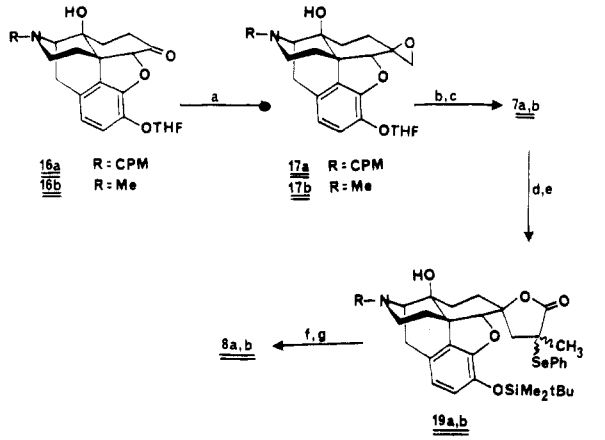
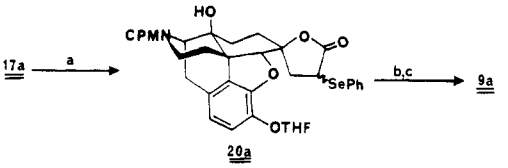
Scheme I[a]



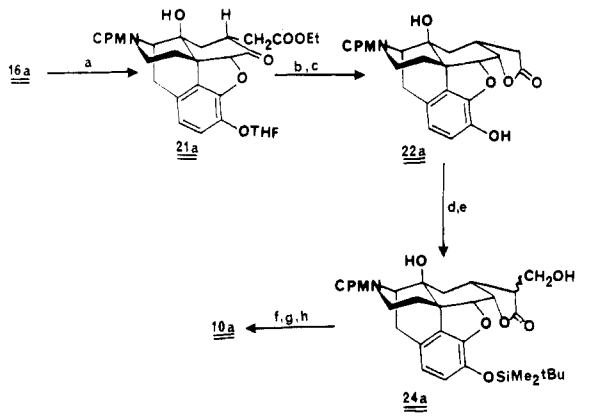
[a] Reagents: a, $(CH_3)_2S(O)CH_2$; b, CH_3CH_2COOH, LiN-*i*-Pr_2; c, H_2O; d, *t*-$BuMe_2SiCl$; e, PhSeCl; f, $NaIO_4$; g, Bu_4NF.

Scheme II[a]



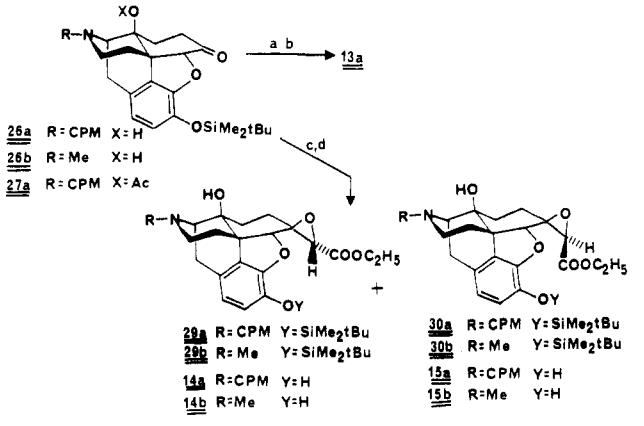
[a] Reagents: a, $PhSeCH_2COOH$, LiN-*i*-Pr_2; b, $NaIO_4$; c, Bu_4NF.

Scheme III[a]



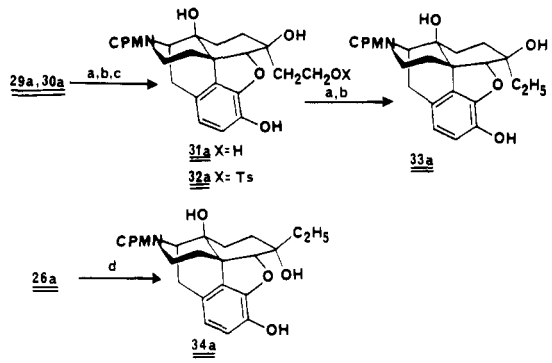
[a] Reagents: a, $LiN(SiMe_3)_2$, ICH_2COOEt; b, LiBH(*sec*-Bu)$_3$; c, H_3O^+; d, *t*-$BuMe_2SiCl$, imidazole; e, LiN-*i*-Pr_2, CH_2O; f, $MeSO_2Cl$; g, pyridine, Δ; h, Bu_4NF.

Scheme IV[a]



[a] Reagents: a, $(CH_3)_2SCH_2$; b, Bu_4NF; c, $LiN(SiMe_3)_2$; d, $BrCH_2COOEt$.

Scheme V[a]



[a] Reagents: a, LAH; b, H_3O^+; c, TsCl; d, EtLi.

methylide, prepared from trimethylsulfonium iodide and *n*-butyllithium. Even with protection of the 14-hydroxyl group to improve the yield in this procedure, a 1:1 mixture of the desired epoxide (**13a**) and naltrexone (**1a**) was isolated, indicating the deprotonation process was competitive with attack of the ylide on the carbonyl group. Separation of **13a** from **1a** was facilitated by the conversion of naltrexone (**1a**) to the corresponding *O*-methyloxime **28a**,[8] affording a 30% yield of the desired 6α-oxide **13a**. The stereochemistry of the addition of dimethylsulfonium methylide and of dimethylsulfoxonium methylide was as expected.[5,6,9]

Glycidate esters related to 6β-epoxides **12a,b** were prepared from **26a,b** by reaction with the lithium salt of ethyl α-bromoacetate (Scheme IV). The mixture of glycidate esters **29a** and **30a** (estimated to be ca. 4:1 *E*/*Z*) was deprotected and careful chromatography afforded the desired (*E*)- and (*Z*)-glycidate esters **14a** and **15a**. The relative stereochemistry (*E* and *Z*) was assigned on the basis of the ^{1}H NMR spectrum in which the signal for the proton on the epoxide ring in the *Z* diastereomers **30a** and **15a** was downfield from the signal of the same proton in the *E* diastereomers **29a** and **14a**. In related epoxides,[9] the signal of the *E* proton was consistently downfield from the signal of the *Z* proton because of deshielding by the aromatic ring. The *N*-Me analogues **14b** and **15b** were prepared from the corresponding oxymorphone derivative **26b**. A mixture of ca. 3:2 *E*/*Z* diastereomers **14b** and **15b** was obtained. The ^{1}H NMR spectra of **14b** and **15b** were similar to the spectra of **14a** and **15a**, respectively.

The stereochemistry of the exocyclic epoxide ring assigned the β-configuration was substantiated by the sequence of chemical reactions in Scheme V. Lithium aluminum hydride reduction of a mixture of **29a** and **30a** afforded diol **31a**. Conversion to the corresponding primary tosylate **32a** was followed by lithium aluminum hydride reduction to give 6α-ethyl-6β-naltrexol (**33a**). Compound **33a** was diastereomeric at C-6 with **34a** prepared by a reaction of **26a** with ethyllithium. The addition of ethyllithium is presumed to occur from the β-face of the molecule, analogous to the addition of methyllithium to similar naltrexone derivatives and other closely related C-6 ketones.[10,11]

The CD spectra of the lactones **7a** and **8a** were compared with those of **5a** and **1a** (naltrexone) (Figure 1). The

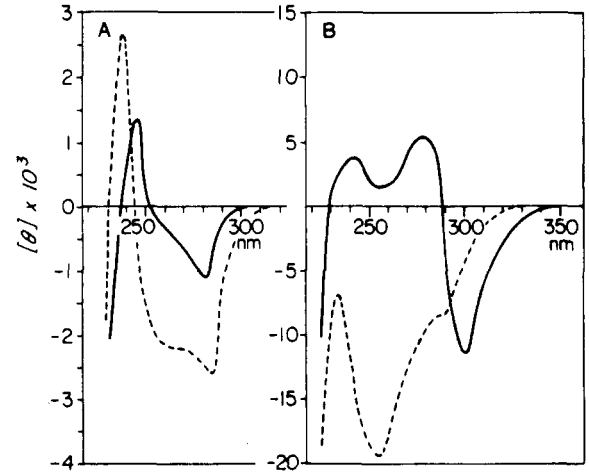


Figure 1. A, CD spectra (MeOH) of **7a** (solid line) and of **5a** (dashed line); B, CD spectra (MeOH) of naltrexone (**1a**) (solid line) and of **8a** (dashed line).

Table I. In Vitro Opioid Receptor Binding Competition against 1 nM [^{3}H]Naltrexone

	IC_{50}, nM		
comp	no NaCl	100 mM NaCl	Na ratio
N-CPM analogues			
5a	5	2	0.4
6a	12.5	15	1.2
7a	10	6	0.6
8a	40	70	1.8
9a	10	10	1.0
10a	10	7	0.7
11a	100	50	0.5
12a	4	2	0.5
13a	5.1	3.4	0.6
14a	2.3	3.5	1.5
15a	6		1.0
N-Me analogues			
5b	35	250	7.0
6b	125	880	7.0
7b	30	500	16.7
8b	200	>1000	>5
12b	8	60	7.5
14b	70	1000	14.2
15b	15	200	13.3

CD spectrum of naltrexone resembles other opioids, showing a positive Cotton effect in the 240–255-nm range assigned to the ^1L_a transition, but differs from the nonketonic opioids morphine and codeine in that a negative Cotton effect is observed in the 300-nm region assigned to the n $\rightarrow$ π^* transition of the ketone carbonyl.[12] A small negative Cotton effect seen at the 280–290-nm region for morphine and codeine, assigned to the ^1L_b transition, was partially obscured by effects of the ketone chromophore.[12] The CD spectrum of saturated lactone **7a** was similar to the spectra of nonketonic opioids, showing a negative Cotton effect in the 280-nm region and a positive Cotton effect in the 240-nm region, although the negative Cotton effect was larger in magnitude. Lactone **5a** showed a similar CD spectrum but with greater intensities. However, lactone **8a** showed a large negative Cotton effect in the 250-nm region which partially obscured the negative Cotton effect at 280 nm and totally obscured the smaller positive one at 240 nm. The observed Cotton effects from the α,β-unsaturated γ-lactone and α-methylene-γ-lactone

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Table II. Irreversible Inhibition of [^{3}H]Naltrexone Binding by **5b**

preincubation conditions	% control[a]			
	-NaCl		+NaCl	
	unwashed	washed	unwashed	washed
control (no ligand)	100	100	100	100
naltrexone (20 nM)	9	97	8	94
5b, 200 nM, 25 °C	35 (n = 3)	79 (n = 3)	43 (n = 3)	63 (n = 3)
5b, 75 nM, 37 °C	66	97		
5b, 500 nM, 37 °C			34	56

[a] Specific binding of [^{3}H]naltrexone is expressed as percent of control.

chromophores have proved to be sensitive to stereochemical environment.[13] In **8a** and **5a**, the electric transition moments of these chromophores are oriented differently because of their inherent geometric differences and their different spatial relationships to the aromatic ring system, a possible interacting chromophore.

Opioid Receptor Binding. Affinity of the compounds for opioid binding sites was determined in the crude rat brain membrane preparation by competition against [^{3}H]naltrexone in the presence and absence of sodium ion. Results are described in Table I. Data from the corresponding spiro-α-methylene-γ-lactones **5a,b** and **6a,b** were also included for comparison. The antagonist analogues (R = CPM) were more potent in displacing [^{3}H]naltrexone than the corresponding agonist analogues (R = Me). Sodium ion ratios were similar to those observed for related compounds, the *N*-Me analogues behaved generally as relatively pure agonists, showing sodium ion ratios of 7 or higher, and the *N*-CPM analogues generally behaved as relatively pure antagonist analogues, showing sodium ion ratios of less than 1. However, as seen in Table I there were two exceptions. Several of the compounds were relatively potent, especially the epoxide analogues **12a** and **13a** and the glycidate esters **14a** and **15a**. All four had IC_{50} values similar to that of **5a**.

To determine whether any of the compounds had irreversible effects on ligand binding in the opioid receptor preparation, concentrations that were approximately 50% inhibitory were incubated for 45 min at 25 °C with rat brain membranes in the absence of sodium ion. The membranes were then washed thoroughly as described in the Experimental Section and bound with [^{3}H]naltrexone to determine the amount of binding capacity inactivated irreversibly. Besides **5a**, which we have previously shown to be irreversible,[5] only the *N*-Me analogue **5b** showed any evidence of irreversible inactivation. This inactivation of opiate binding by **5b** was seen most clearly in the presence of sodium chloride when the compound was incubated at 25 or 37 °C with the membrane preparation (Table II). These experiments were done under different conditions (concentration and/or temperature) than those previously reported, in which no irreversible effects were noted at the IC_{50} in the absence of Na ion at 25 °C for 45 min.[5] None of the other compounds listed produced irreversible effects even after incubation of the test compounds with the membrane preparation at 37 °C for 30 min, i.e., washing restored [^{3}H]naltrexone binding to control levels.

Data from the opioid receptor binding assay clearly indicated that the potential for irreversible activity is extremely sensitive to ligand structure. The lack of irreversible activity of endocyclic α,β-unsaturated lactones **8a** and **9a** demonstrated that the exocyclic α-methylene-γ-lactone is a required functionality for the irreversible activity. The saturated lactone **7a** would not be expected to show irreversible activity unless irreversible binding occurred through acylation of the lactone carbonyl. Only reversible activity was observed. Since epoxides **12a** and **13a** and glycidate esters **14a** and **15a** showed no irreversible activity in the binding assay, we conclude that more reactive electrophiles are needed for irreversible activity, and/or these functional groups are not properly aligned for reaction with a nucleophilic group at or near the receptor.

In summary, the α-methylene-γ-lactone functional group is required for irreversible activity in this series since the endocyclic α,β-unsaturated lactones and the saturated lactones analogues showed only reversible activity. The fact that the fused α-methylene-γ-lactones **10a** and **11a** showed no irreversible effects also demonstrated the extreme sensitivity of ligand–opioid receptor interaction to small structural changes. With the synthesis and testing of other agents, additional information will become available.

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 283 spectrometer. Absorptions are expressed in units of frequency (cm^{-1}). NMR spectra were routinely recorded on a Varian EM-360 spectrometer. Chemical shifts are expressed in parts per million (δ) relative to Me_4Si used as the internal standard and deuteriochloroform was used as solvent. High-resolution NMR spectra were recorded on a Bruker WM-500 MHz spectrometer. CI mass spectra were obtained on a VG-7070 mass spectrometer by direct insertion probe and with use of methane as the reagent gas. Optical rotations were measured on a JASCO-DIP-4 digital polarimeter. Circular dichroism spectra were recorded in methanol on a Jobin Yvon Dichrographe R. J. Mark III instrument. Analytical thin-layer chromatography (TLC) was performed on precoated plates (either Merck EM silica gel 60F-254 or Analtech silica gel HLF, 20 × 20 × 0.25 cm, glass support). Merck silica gel 60 (230–400 mesh) was used for preparative flash column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxypropyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (7a). To a solution of lithium diisopropylamide prepared from 6.54 mL (49.7 mmol) of diisopropylamine and 29.09 mL (46.8 mmol) of a 1.65 M solution of *n*-butyllithium in *n*-hexane with stirring in 130 mL of anhydrous THF at 0 °C over 15 min was added 1.86 mL (23.4 mmol) of propionic acid. The mixture was stirred at 30 °C for 30 min, 2.49 g (5.85 mmol) of **17a**[5] in 40 mL of THF was added, and the mixture was heated to reflux for 20 h under argon. The solvent was evaporated, and the residue was acidified to pH 2 with aqueous 3 N HCl. After stirring for 3 h at room temperature and addition of aqueous sodium carbonate to pH 8.5, the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 3.26 g of the crude lactone. Purification by flash column chromatography on 80 g of silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 2.13 g (89%) of **7a**. The mixture of diastereomers was crystallized from CH_2Cl_2/hexanes: mp 223–228 °C dec; CIMS, m/z (relative intensity) 412 (QM, 100), 394 (QM – H_2O, 15); 500-MHz ^{1}H NMR δ 6.58–6.78 (2 AB systems, J = 8 Hz, 2 H, aromatic), 5.10 (br s, 2 H, OH), 4.82 and 4.80 (2 s, 1 H, C5-H), 1.22 and 1.16 (2 d, J = 7.3 Hz, 1 H, lactone α-CH_3); CD spectrum (**7a**) (MeOH, c 0.5): $[\theta]_{298}$ = 0,

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$[\theta]_{282} = -1110$, $[\theta]_{253} = 0$, $[\theta]_{242} = +1410$, $[\theta]_{237} = 0$; IR (KBr) 1765 cm^{-1} (s, γ-lactone); R_f 0.45 (98:2 EtOAc/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system. Anal. Calcd for $C_{24}H_{29}NO_5$: C, H, N.

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6β,14-dihydroxy-6α-(2-carboxypropyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (18a). A mixture of 2.71 g (6.59 mmol) of **7a**, 1.04 g (6.92 mmol) of *tert*-butyldimethylsilyl chloride, and 1.08 g (15.8 mmol) of imidazole in 6 mL of DMF and 15 mL of CH_2Cl_2 was stirred at room temperature for 2.5 h under argon. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 4.74 g of the crude product. Purification by flash column chromatography on 80 g of silica gel (1:3 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 3.39 g (98%) of **18a** as a solid, which was used without further purification: ^1H NMR δ 6.50–6.87 (AB system, J = 8 Hz, 2 H, aromatic) 4.76 and 4.78 (2 s, 1 H, C5-H), 1.18 and 1.13 (2 s, 3 H, lactone α-CH_3), 0.98 [s, 9 H, $SiC(CH_3)_3$], 0.18 and 0.23 [2 s, 6 H, $Si(CH_3)_2$].

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6β,14-dihydroxy-6α-[2-(phenylseleno)-2-carboxypropyl]-17-(cyclopropylmethyl)morphinan γ-Lactone (19a). To a solution of lithium diisopropylamide prepared from 2.24 mL (15.1 mmol) of diisopropylamine and 8.96 mL (14.8 mmol) of a 1.65 M solution of *n*-butyllithium in *n*-hexane with stirring in 40 mL of anhydrous THF at 0 °C over 15 min and cooled to −78 °C was added 3.38 g (6.43 mmol) of **18a** in 35 mL of THF via cannula. The temperature was brought to −40 °C (acetonitrile/CO_2) for 15 min and returned to −78 °C before 3.08 g (16.1 mmol) of PhSeCl in 7 mL of THF was quickly added. After 6 min, the mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give the crude product. Purification by flash column chromatography on 80 g of silica gel (1:15 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 3.49 g (80%) of **19a** as a mixture of diastereomers: ^1H NMR δ 7.27–7.90 (m, 5 H, SeC_6H_5), 6.45–6.83 (AB system, J = 8 Hz, 2 H, aromatic), 4.80 (br s, 1 H, OH), 4.58 and 4.52 (2 s, C-5H), 1.65 and 1.53 (2 s, 3 H, lactone α-CH_3), 1.02 [s, 9 H, $SiC(CH_3)_3$], 0.22 and 0.26 [2 s, 6H, $Si(CH_3)_2$].

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxypropenyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (8a). To a solution of 3.48 g (5.11 mmol) of 19a in 220 mL of methanol was added 0.49 g (5.9 mmol) of sodium bicarbonate in 8 mL of water and 2.51 g (11.8 mmol) of sodium periodate in 19 mL of water with vigorous stirring. After 1.5 h at room temperature, the solvent was evaporated. The residue was diluted with pH 8.5 buffer and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 3.26 g of the crude product as a foam. Purification by flash column chromatography on 80 g of silica gel (1:1 CH_2Cl_2/hexanes to elute diphenyl diselenide, then with 1:9 with EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 2.31 g (95%) of the O^3-(*tert*-butyldimethylsilyl) ether of **8a**: ^1H NMR δ 6.48–6.77 (AB system, J = 8 Hz, 2 H, aromatic), 5.95 (q, J = 2 Hz, 1 H, lactone β-CH), 5.60 (br s, 1 H, OH), 4.74 (s, 1 H, C5-H), 1.75 (d, J = 2 Hz, 3 H, lactone α-CH_3), 0.96 [s, 9 H, $SiC(CH_3)_3$], 0.15 [s, 6 H, $Si(CH_3)_2$].

To a solution of 2.31 g (4.41 mmol) of the O^3-(*tert*-butyldimethylsilyl) ether of **8a** in 150 mL of THF stirring at room temperature was added 5.29 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran. The mixture was stirred for 1 h at room temperature. The solvent was evaporated and the residue was chromatographed directly on 80 g of flash column silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine) to give 1.77g (98%) of **8a** as a colorless solid. Recrystallization from CH_2Cl_2/hexanes afford 1.53 g (85%) of **8a**: mp 200–200.5 °C; $[\alpha]^{23}_D$ −311.5° (CH_3OH, c 0.5); CIMS (methane), m/z (relative intensity) 410 (QM, 100), 392 (QM − H_2O, 23); ^1H NMR δ 6.42–6.75 (AB system, J = 8 Hz, 2 H, aromatic), 5.90 (q, J = 2 Hz, 1 H, lactone β-H), 4.75 (s, 1 H, C5-H), 1.78 (d, J = 2 H, 3 H, lactone α-CH_3); IR (KBr) 1745 cm^{-1} (s, γ-lactone). CD spectrum (**8a**) (MeOH, c 0.25): $[\theta]_{330} = 0$, $[\theta]_{287} = -8640$, $[\theta]_{253} = -19\,200$, $[\theta]_{235} = -7020$, $[\theta]_{230} = -21\,600$. CD spectrum of **5a** (MeOH, c 0.5): $[\theta]_{310} = 0$, $[\theta]_{284} = -2580$, $[\theta]_{260} = -1720$, $[\theta]_{245} = 0$, $[\theta]_{239} = +2720$, $[\theta]_{231} = 0$. CD spectrum of **1a** (MeOH, c 0.5): $[\theta]_{348} = 0$, $[\theta]_{300} = -11\,800$, $[\theta]_{288} = 0$, $[\theta]_{279} = +5560$, $[\theta]_{255} = +1360$, $[\theta]_{240} = +2500$, $[\theta]_{234} = 0$; R_f 0.47 (98:2 EtOAc/triethylamine). Naltrexone has an R_f value of 0.39 in this solvent system. Compound **8a** has an R_f value of 0.44 in this solvent system. Anal. (**8a**) Calcd for $C_{24}H_{27}NO_5$: C, H, N.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxypropyl)-17-methylmorphinan γ-Lactone (7b). To a solution of lithium diisopropylamide prepared from 8.09 mL (58.1 mmol) of diisopropylamine and 33.2 mL (54.7 mmol) of a 1.65 M solution of *n*-butyllithium in *n*-hexane with stirring in 160 mL of anhydrous THF at 0 °C over 15 min was added 2.16 mL (27.4 mmol) of propionic acid. The mixture was stirred at 30 °C for 30 min, 2.65 g (6.84 mmol) of **17b**[5] in 60 mL of THF was added, and the mixture was heated to reflux for 20 h under argon. The solvent was evaporated, and the residue was acidified to pH 2 with aqueous 3 N HCl. After the mixture was stirred for 3 h at room temperature, the pH was adjusted to 8.5 with aqueous sodium carbonate, and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 3.37 g of the crude lactone. Purification by flash column chromatography on 80 g of silica gel (2:1 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 2.28 g (89%) of **7b**; mp 248–251 °C; ^1H NMR δ 6.43–6.85 (AB system, J = 8 Hz, 2 H, aromatic), 6.10 (br s, 2 H, OH), 4.73 and 4.75 (2 s, 1 H, C5-H), 2.40 (s, 3 H, NCH_3), 1.18 and 1.13 (2 d, J = 7 Hz, 3 H, lactone α-CH_3). Anal. Calcd for $C_{21}H_{25}NO_5$: C, H, N.

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6β,14-dihydroxy-6α-(2-carboxypropyl)-17-methylmorphinan γ-Lactone (18b). A mixture of 2.07 g (5.57 mmol) of **7b**, 0.92 g (6.13 mmol) of *tert*-butyldimethylsilyl chloride, and 0.91 g (13.4 mmol) of imidazole in 6 mL of DMF and 15 mL of CH_2Cl_2 was stirred at room temperature for 2.5 h under argon. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 3.34 g of the crude product. Purification by flash column chromatography on 80 g of silica gel (1:2 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 2.64 g (97%) of **18b** as a solid, which was used without further purification: ^1H NMR δ 6.45–6.80 (AB system, J = 8 Hz, 2 H, aromatic), 5.00 (br s, 1 OH), 4.67 and 4.69 (2 s, 1 H, C5-H), 2.38 (s, 3 H, NCH_3), 1.18 and 1.13 (2 d, J = 7 Hz, 3 H, lactone α-CH_3), 0.99 [s, 9 H, $SiC(CH_3)_3$], 0.15 and 0.18 [2 s, 6 H, $Si(CH_3)_2$)].

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6β,14-dihydroxy-6α-[2-(phenylseleno)-2-carboxypropyl]-17-methylmorphinan γ-Lactone (19b). To a solution of lithium diisopropylamide prepared from 1.94 mL (13.9 mmol) of diisopropylamine and 7.76 mL (12.8 mmol) of a 1.65 M solution of *n*-butyllithium in *n*-hexane with stirring in 40 mL of anhydrous THF at 0 °C over 15 min and cooled to −78 °C was added 2.64 g (5.44 mmol) of **18b** in 35 mL of THF via cannula. The temperature was brought to −40 °C (acetonitrile/CO_2) for 15 min and returned to −78 °C before 2.67 g (13.9 mmol) of PhSeCl in 7 mL of THF was quickly added. After 5 min, the mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give the crude product. Purification by flash column chromatography on 80 g of silica gel (1:4 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 3.31 g (95%) of **19b** as a mixture of diastereomers: ^1H NMR δ 7.25–7.85 (m, 5 H, SeC_6H_5), 6.40–6.77 (AB system, J = 8 Hz, 2 H, aromatic), 4.58 and 4.53 (2 s, 1 H, C5-H), 2.35 (s, 3 H, NCH_3), 1.62 and 1.52 (2 s, 3 H, lactone α-CH_3), 0.98 and 0.93 [2 s, 9 H, $SiC(CH_3)_3$], 0.15 and 0.18 [2 s, 6 H, $Si(CH_3)_2$].

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxypropenyl)-17-methylmorphinan γ-Lactone (8b). To a solution of 3.31 g (5.16 mmol) of **19b** in 210 mL of methanol were added 0.500 g (5.93 mmol) of sodium bicarbonate in 10 mL of water and 2.54 g (11.8 mmol) of sodium periodate in 15 mL of water with vigorous stirring. After 1.5 h at room temperature, the solvent was evaporated. The residue was diluted with pH 8.5 buffer and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 2.77 g of the crude product. Purification by flash column chromatography on 80 g of silica gel (7:3 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 2.09 g (84%) of the O^3-(*tert*-bu-

tyldimethylsilyl) ether of **8b**: ^{1}H NMR δ 6.53–6.83 (AB system, J = 8 Hz, 2 H, aromatic), 5.98 (q, J = 2 H, 1 H, lactone β-H, 4.75 (s, 1 H, C5-H), 4.70 (br s, 1 H, OH), 2.40 (s, 3 H, NCH_3), 1.76 (d, J = 2 Hz, 3 H, lactone α-CH_3), 0.95 [s, 9 H, $SiC(CH_3)_3$], 0.16 [s, 6 H, $Si(CH_3)_2$].

To a stirred solution of 2.09 g (4.31 mmol) of the O^3-(*tert*-butyldimethylsilyl) ether of **8b** in 45 mL of THF was added 5.17 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The mixture was stirred for 1 h at room temperature, and the solvent was evaporated. The residue was chromatographed on 80 g of silica gel (EtOAc + 1% triethylamine eluent) to give 1.56 g (98%) of **8b**: mp 236–236.5 °C; $[\alpha]^{23}_D$, −309.4° (CH_3OH, c 0.5); CIMS (methane), m/z (relative intensity) 370 (QM, 100), 352 (QM − H_2O, 12); ^{1}H NMR δ 6.55–6.90 (AB system, J = 8 Hz, 2 H, aromatic), 5.98 (q, J = 2 Hz, 1 H, lactone vinyl H), 5.60 (br s, 2 H, OH), 4.80 (s, 1 H, C_5-H), 2.40 (s, 3 H, NCH_3), 1.78 (d, J = 2 Hz, 3 H, lactone α-CH_3); IR (KBr) 1745 cm^{-1} (s, γ-lactone); R_f 0.43 (98:2 EtOAc/triethylamine, two elutions). Oxymorphone has an R_f value of 0.26 in this solvent system. Compound **5b** has an R_f value of 0.38 in this solvent system. Anal. Calcd for $C_{21}H_{23}NO_5$: C, H, N.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-[2-(phenylseleno)-2-carboxyethyl]-17-(cyclopropylmethyl)morphinan γ-Lactone (20a). To a solution of lithium diisopropylamide prepared from 0.70 mL (5.00 mmol) of diisopropylamine and 2.73 mL (4.50 mmol) of a 1.65 M solution of *n*-butyllithium in *n*-hexane with stirring in 7 mL of anhydrous THF at 0 °C over 15 min was added 0.45 g (2.09 mmol) of (phenylseleno)acetic acid. The mixture was stirred at 0 °C for 15 min and at 35 °C for 30 min, 426 mg (1.00 mmol) of **17a** in 7 mL of THF was added, and the mixture was heated to 60 °C for 24 h under argon. The solvent was evaporated, and the residue was acidified to pH 2 with aqueous 3 N HCl. After the mixture was stirred for 3 h at room temperature, the pH was adjusted to 8.5 with aqueous sodium carbonate, and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 0.55 g of the crude product. Purification by flash column chromatography on 70 g of silica gel (1:3 EtOAc/CH_2Cl_2 + 1% triethylamine) afforded 97 mg (17%) of **20a** as a solid: ^{1}H NMR δ 7.17–7.87 (m, 5 H, SeC_6H_5), 6.47–6.87 (AB system, J = 8 Hz, 2 H, aromatic), 5.39 (br s, 1 H, OH), 4.74 (s, 1 H, C5-H), 4.40 and 4.56 (2 overlapping d, J = 10 Hz, 1 H, lactone α-H).

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxyethenyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (9a). A mixture of 97 mg (0.18 mmol) of lactone **20a**, 30 mg (0.20 mmol) of *tert*-butyldimethylsilyl chloride, and 27 mg (0.40 mmol) of imidazole in 1 mL of DMF and 2 mL of CH_2Cl_2 was stirred at room temperature for 2.5 h under argon. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 112 mg (93%) of the O^3-(*tert*-butyldimethylsilyl) ether of **20a**: ^{1}H NMR δ 7.23–7.85 (m, 5 H, SeC_6H_5), 6.45–6.83 (AB system, J = 8 Hz, 2 H, aromatic), 4.70 (s, 1 H, C5-H), 4.42 and 4.58 (2 overlapping d, J = 10 Hz, 1 H, lactone α-H), 0.94 [s, 9 H, $SiC(CH_3)_3$], 0.26 and 0.18 [2 s, 6 H, $Si(CH_3)_2$].

To a solution of 112 mg (0.17 mmol) of O^3-(*tert*-butyldimethylsilyl) ether of **20a** in 14 mL of methanol was added 21 mg (0.25 mmol) of sodium bicarbonate in 1 mL of water and 111 mg (0.50 mmol) of sodium periodate in 1 mL of water with vigorous stirring. After 1.5 h at room temperature, the solvent was evaporated. The residue was diluted with pH 8.5 buffer and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to 96 mg of the O^3-silyl ether of **9a**, which was dissolved in 10 mL of THF and treated with 0.22 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF with stirring for 1 h at room temperature. The solvent was evaporated, and the residue was chromatographed directly on 45 g of flash column silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine) to give 53 mg (79%) of **9a** as a solid. Recrystallization from CH_2Cl_2/hexanes afforded 41 mg (60%) of **9**: mp 209–210 °C dec; CIMS (methane), m/z (relative intensity) 396 (QM, 100), 378 (QM − H_2O, 2.2); 500-MHz ^{1}H NMR δ 6.59–6.75 (AB system, J = 8 Hz, 2 H, aromatic), 6.38 (d, J = 6.3 Hz, 1 H, lactone α-H), 5.91 (d, J = 6.3 Hz, 1 H, lactone β-H), 4.87 (s, 1 H, C5-H), 4.70 (br s, 2 H, OH), 0.11–3.15 (m, 18 H); IR (KBr) 1750 cm^{-1} (s, γ-lactone). Anal. Calcd for $C_{23}H_{25}NO_5$: C, H, N.

4,5α-Epoxy-3-(2-tetrahydrofuranyloxy)-14-hydroxy-7α-(carbethoxymethyl)-17-(cyclopropylmethyl)morphinan (21a). To a solution of 4.93 mL (23.4 mmol) of hexamethyldisilazane in 100 mL of anhydrous THF stirring at −78 °C under argon was added 13.3 mL (20.7 mmol) of a 1.56 M solution of *n*-butyllithium in *n*-hexane. The mixture was warmed to −5 °C for 15 min, and after the temperature was returned to −78 °C, 3.70 g (8.99 mmol) of **16a**[5] in 20 mL of THF was added. The mixture was warmed to −5 °C for 5 min, cooled to −78 °C, and 2.55 mL (21.58 mmol) of ethyl α-iodoacetate was added neat. The mixture was stirred at −5 °C for 1 h and at room temperature for 1 h. The solvent was evaporated. The residue was diluted with pH 8.5 buffer and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 5.27 g of the crude product mixture. Purification by chromatography on 150 g of flash column silica gel (1:5 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 1.87 g (42%) of **21a** as a foam: ^{1}H NMR δ 6.37–6.90 (AB and AB′ system, J = 8 Hz, 2 H, aromatic), 5.78–6.07 (m, 1 H, THF 2′-H), 4.90 (br s, 1 H, OH), 4.74 (s, 1 H, C5-H), 3.85–4.27 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.7–4.3 (m, 2 H, THF 5,5′-H), 1.19 (t, J = 7 Hz, 3 H, OCH_2CH_3).

4,5α-Epoxy-3,6α,14-trihydroxy-7α-(carboxymethyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (22a). To a solution of 744 mg (1.50 mmol) of **21a** in 20 mL of anhydrous THF stirring at −78 °C under argon was added 1.65 mL of a 1 M solution of lithium tri-*sec*-butylborohydride in THF. The mixture was stirred for 2 h at −78 °C and quenched with aqueous 3 N HCl. The solvent was evaporated, and the residue was acidified to pH 2 for 14 h. The pH was adjusted to 8.5 with aqueous sodium carbonate, and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 653 mg of the crude product. Purification by chromatography on 70 g of flash column silica gel (1:1 EtOAc/CH_2Cl_2 eluent) afforded 457 mg (80%) of **22a** as a solid. Recrystallization from CH_2Cl_2/hexanes afforded 409 mg (71%) of **22a**: mp 201–201.5 °C; CIMS (methane), m/z (relative intensity) 384 (QM, 100), 366 (QM − H_2O); ^{1}H NMR δ 6.42–6.83 (AB system, J = 8 Hz, 2 H, aromatic), 5.20 (br s, 2 H, OH), 4.76–5.10 (m, 2 H, C5- and C6-H); IR (KBr) 1785 cm^{-1} (s, γ-lactone). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91. Found: C, 68.46, H, N.

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6α,14-dihydroxy-7α-(carboxymethyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (23a). A mixture of 768 mg (2.00 mmol) of **22a**, 332 mg (2.20 mmol) of *tert*-butyldimethylsilyl chloride, and 327 mg (4.80 mmol) of imidazole in 2 mL of dry DMF and 6 mL of CH_2Cl_2 was stirred at room temperature for 2.5 h under argon. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 1.01 g of the crude product. Purification by chromatography on 60 g of flash column silica gel afforded 950 mg (95%) of **23a** as a foam: ^{1}H NMR δ 6.37–6.75 (AB system, J = 8 Hz, 2 H, aromatic), 4.65–5.05 (m, 2 H, C5- and C6-H), 1.02 [s, 9 H, $SiC(CH_3)_3$], 0.22 and 0.18 (2 s, 6 H, $Si(CH_3)_2$].

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6α,14-dihydroxy-7α-(2-carboxy-3-hydroxypropyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (24a). To a solution of lithium diisopropylamide prepared from 0.69 mL (4.97 mmol) of diisopropylamine and 2.81 mL (4.39 mmol) of a 1.56 M solution of *n*-butyllithium in *n*-hexane with stirring in 75 mL of dry THF at 0 °C over 15 min and cooled to −78 °C was added 950 mg (1.91 mmol) of **23a** in 25 mL of THF. The mixture was stirred for 45 min at −78 °C, the temperature was raised to −25 °C (CCl_4/CO_2), and excess formaldehyde (from 450 mg (15 mmol) of paraformaldehyde heated to 190 °C) was bubbled in over 15 min. The mixture was stirred for 30 min longer at −25 °C, diluted with pH 8.5 buffer, and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 1.09 g of crude product. Purification by chromatography on 80 g of flash column silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 913 mg (91%) of

24a as a foam: ^{1}H NMR δ 6.35–6.75 (AB system, J = 8 Hz, 2 H, aromatic), 4.93 (dd, J = 5, 8 Hz, 1 H, C6-H), 4.70 (d, J = 5 Hz, 1 H, C5-H), 3.90 (br s, 2 H, OH), 3.47–3.73 (m, 2 H, CH_2OH), 0.99 [s, 9 H, $SiC(CH_3)_3$], 0.18 and 0.15 (2 s, 6 H, $Si(CH_3)_2$].

4,5α-Epoxy-3,6α,14-trihydroxy-7α-(2-carboxyallyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (10a). To a mixture of 180 mg (0.34 mmol) of **24a** and 0.10 mL (0.71 mmol) of triethylamine in 20 mL of dry CH_2Cl_2 stirring at −25 °C under argon was added 0.76 mL (0.38 mmol) of a 0.5 M solution of methanesulfonyl chloride in CH_2Cl_2 dropwise. After 1 h at −25 °C, 0.2 mL of methanol was added, and the solution was stirred for 15 min before the solvent was evaporated. The residue was chromatographed directly on 10 g of flash column silica gel (1:4 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) to afford 194 mg (95%) of the crude mesylate of **24a** as a solid: ^{1}H NMR δ 6.37–6.73 (AB system, J = 8 Hz, 2 H, aromatic), 4.97 (dd, J = 5, 8 Hz, 1 H, C6-H), 4.70 (d, J = 5 Hz, 1 H, C5-H), 4.20 (m, 2 H, CH_2OMs), 2.95 (s, 2 H, OSO_2CH_3), 0.98 [s, 9 H, $SiC(CH_3)_3$], 0.30 and 0.27 [2 s, 6 H, $Si(CH_3)_2$].

A solution of 775 mg (1.28 mmol) of the crude mesylate of **24a** in 4 mL of pyridine was heated to reflux (bath temperature 150 °C) for 4 h under argon. The solvent was evaporated, the residue was redissolved in 10 mL of THF, and 1.50 mL of a 1 M solution of tetra-*n*-butylammonium fluoride was added with stirring at 0 °C. After the mixture was stirred at 0 °C for 1 h, the solvent was evaporated, and the residue was chromatographed directly on 80 g of flash column silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) to give 462 mg (91%) of **10a**. Recrystallization from CH_2Cl_2/hexanes afforded 431 mg (85%) of **10a**: mp 268 °C dec; $[\alpha]^{23}_D$ −81.2° (CH_3OH, c 0.25; CIMS, m/z (relative intensity) 396 (QM, 100), 378 (QM − H_2O, 3); 500-MHz ^{1}H NMR δ 6.51–6.70 (AB system, J = 8.1 Hz, 2 H, aromatic), 5.89 (d, J = 2.9 Hz, 1 H, α-methylene E-H), 5.03 (dd, J = 5.9, 8.1 Hz, 1 H, C6-H), 4.92 (d, J = 2.9 Hz, 1 H, α-methylene Z-H), 4.90 (br s, 2 H, OH), 4.79 (d, J = 5.7 Hz, 1 H, C5-H); IR (KBr) 1740 cm^{-1} (s, γ-lactone); R_f 0.48 (98:2 ethyl acetate/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system. Anal. Calcd for $C_{23}H_{25}NO_5$: C, H, N.

4,5α-Epoxy-3,6α-dihydroxy-7α-(2-carboxyallyl)-8,14-dehydro-17-(cyclopropylmethyl)morphinan γ-Lactone (11a). To a mixture of 255 mg (0.48 mmol) of **23a** and 0.28 mL (2.00 mmol) of triethylamine in 5 mL of CH_2Cl_2 stirring at 0 °C under argon was added 2.20 mL (1.10 mmol) of a 0.50 M solution of methanesulfonyl chloride. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was chromatographed on 40 g of flash column silica gel (1:9 EtOAc/CH_2Cl_2 + 1% triethylamine eluent), affording 300 mg (92%) of the dimesylate of **24a** as a solid: ^{1}H NMR δ 6.41–6.77 (AB system, J = 8 Hz, 2 H, aromatic), 4.97 (dd, J = 5, 7 Hz, 1 H, C6-H), 4.74 (d, J = 5 Hz, 1 H, C5-H), 4.20 (m, 2 H, CH_2OMs), 3.33 (s, 2 H, C14-OSO_2CH_3), 2.95 (s, 2 H, $CH_2OSO_2CH_3$), 0.96 [s, 9 H, $SiC(CH_3)_3$], 0.18 and 0.15 [2 s, 6 H, $Si(CH_3)_2$].

A solution of 301 mg (0.44 mmol) of the dimesylate of **24a** in 3 mL of pyridine was heated to reflux (bath temperature 150 °C) for 4 h under argon. The solvent was evaporated. The residue was redissolved in 8 mL of THF, and 0.51 mL of a 1 M solution of tetra-*n*-butylammonium fluoride was added with stirring at 0 °C. After the mixture was stirred as 0 °C for 1 h, the solvent was evaporated, and the residue was chromatographed directly on 45 g of flash column silica gel (19:1 ethyl acetate/methanol + 1% triethylamine eluent), affording 129 mg (74%) of **11a**. Recrystallization from CH_2Cl_2/ether/*n*-heptane afforded 116 mg (66%) of **11a** as the hydrate: mp 160–161 °C; CIMS (methane), m/z (relative intensity) 378 (QM); 500-MHz ^{1}H NMR δ 6.51–6.69 (AB system, J = 8.1 Hz, 2 H, aromatic), 6.09 (s, 1 H, α-methylene Z-H), 5.63 (s, 1 H, α-methylene E-H), 5.07 (s, 1 H, C8-H), 4.77–4.81 (m, 2 H, C5- and C6-H), 3.90 (d, J = 5.9 Hz, 1 H, C7-H), 3.64 (d, J = 3.7 Hz, 1 H, C9-H), 3.17 (d, J = 17.7 Hz, 1 H, C10-H); IR (KBr) 1745 cm^{-1} (s, γ-lactone); R_f 0.16 (98:2 EtOAc/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system. Anal. Calcd for $C_{23}H_{23}NO_4 \cdot H_2O$: C, H, N.

4,5α-Epoxy-3,14-dihydroxy-6-methylene-17-(cyclopropylmethyl)morphinan 6β-Oxide (12a). A solution of 851 mg (2.00 mmol) of **17a** in 60 mL of 1:1 HOAc/methanol was heated with stirring to 55 °C for 20 h under argon. The solvent was evaporated, the residue was taken up in aqueous disodium hydrogen phosphate and CH_2Cl_2, and the pH was adjusted to 8.5. The reaction mixture was extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 701 mg of a solid, which was purified by flash column chromatography on 30 g of silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) to afford 608 mg (85%) of **12a**. Recrystallization from CH_2Cl_2/petroleum ether afforded 562 mg (79%) of **12a**: mp 184.5–185 °C; $[\alpha]^{23}_D$ −131.8° (CH_3OH, c 1.0); CIMS (methane), m/e (relative intensity) 356 (QM, 100), 338 (QM − H_2O, 11); 500-MHz ^{1}H NMR δ 6.56–6.72 (AB system, J = 8 Hz, 2 H, aromatic), 2.84 (d, J = 4.9 Hz, 1 H, epoxide Z-H), 2.03 (d, J = 4.9 Hz, 1 H, epoxide E-H); IR (KBr) 3300 (br, OH), 3070 (w), 2990 (m), 2940 (s), 2920 (s), 2800 (m), 1635 (m), 1620 (m), 1495 (m), 1450 (s), 1395 (m), 1370 (m), 1325 (ms), 1290 (m), 1235 (s), 1185 (m), 1145 (ms), 1115 (m), 1050 (w), 1030 (m), 990 (w), 965 (s), 935 (s), 885 (m), 860 (m), 810 (m), 805 (m), 780 (w), 740 (ms), 695 (w), 680 (w), 625 (w), 590 cm^{-1} (w); R_f 0.44 (98:2 EtOAc/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system. Anal. Calcd for $C_{21}H_{25}NO_4$: C, H, N.

4,5α-Epoxy-3,14-dihydroxy-6-methylene-17-methylmorphinan 6β-Oxide (12b). A solution of 798 mg (2.07 mmol) of **17b**[5] in 60 ml in 1:1 HOAc/methanol was heated with stirring to 55 °C for 20 h under argon. The solvent was evaporated, and the residue was taken up to 60 mL of water, and the aqueous solution was washed with 3 × 20 mL of CH_2Cl_2. The aqueous phase was stirred over 60 mL of CH_2Cl_2, and the pH was adusted to 8.5 with aqueous disodium hydrogen phosphate and sodium carbonate. The mixture was extracted with 4 × 60 mL of CH_2Cl_2 washed with brine, and the combined extracts were dried over magnesium sulfate, filtered, and evaporated to give 630 mg of a solid, which was purified by flash column chromatography on 80 g of silica gel (EtOAc + 1% triethylamine eluent) to afford 560 mg (86%) of **12b**. Recrystallization from CH_2Cl_2/hexanes afforded 521 mg (80%) of **12b**: mp 234.5–5-235 °C dec; $[\alpha]^{23}_D$ −117.0° (CH_3OH, c 1.0); EIMS, m/z (relative intensity) 315.1462 (calcd 315.1454, M^+); ^{1}H NMR δ 6.50–6.85 (AB system, J = 8 Hz, 2 H, aromatic), 5.55 (br s, 2 H, OH), 4.70 (s, 1 H, C5-H), (s, 3 H, NCH_3); IR (KBr) 3380 (br, OH), 2940 (s), 2920 (s), 2840 (w), 2800 (w), 1635 (m), 1610 (m), 1500 (m), 1450 (s), 1390 (w), 1370 (m), 1320 (m), 1290 (m), 1265 (w), 1235 (s), 1185 (m), 1155 (m), 1115 (m), 1100 (w), 1060 (w), 1040 (w), 1030 (m), 990 (w), 965 (s), 940 (m), 930 (m), 885 (m) 860 (m), 810 (m), 800 (w), 780 (w), 760 (w), 740 (m), 690 (w), 680 (w), 625 (w), 590 cm^{-1} (w); R_f 0.34 (98% ethyl acetate + 2% triethylamine, two elutions). Oxymorphone (**1b**) has an R_f value 0.26 in this solvent system. Anal. Calcd for $C_{18}H_{21}NO_4$: C, H. N.

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6-oxo-14-hydroxy-17-(cyclopropylmethyl)morphinan (26a). A mixture of 3.42 g (10.0 mmol) of naltrexone (**1a**), 1.58 g (10.5 mmol) of *tert*-butyldimethylsilyl chloride, and 1.50 g (22.0 mmol) of imidazole in 8 mL of dry DMF was stirred at room temperature for 2.5 h under argon. Aqueous sodium carbonate was added and the mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 4.62 g of the crude product as a solid. Recrystallization from *n*-hexane afforded 4.32 g (95%) of **26a**: mp 93–93.5 °C; ^{1}H NMR δ 6.47–6.83 (AB system, J = 8 Hz, 2 H, aromatic), 5.30 (br s, 1 H, OH), 4.58 (s, 1 H, C5-H), 1.02 [s, 9 H, $SiC(CH_3)_3$], 0.25 and 0.22 [2 s, 6 H, $Si(CH_3)_2$].

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6-oxo-14-hydroxy-17-methylmorphinan (26b). A mixture of 2.85 g (9.46 mmol) of oxymorphone (**1b**), 1.50 g (9.93 mmol) of *tert*-butyldimethylsilyl chloride, and 1.42 g (20.8 mmol) of imidazole in 4 mL of DMF and 30 mL of CH_2Cl_2 was stirred at 25 °C for 4 h under argon. The reaction mixture was extracted with CH_2Cl_2, washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to afford 3.80 g (97%) of **26b** as a colorless foam: ^{1}H NMR δ 6.33–6.65 (AB system, J = 8 Hz, 2 H, aromatic), 4.60 (br s, 1 H, OH), 4.53 (s, 1 H, C5-H), 2.38 (s, 3 H, NCH_3), 1.00 [s, 9 H, $SiC(CH_3]$, 0.23 and 0.18 [2 s, 6 H, $Si(nCH_3)_2$].

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-6-oxo-14-acetoxy-17-(cyclopropylmethyl)morphinan (27a). A solution of 2.73 g (6.00 mmol) of **26a** in 30 mL of acetic anhydride was stirred at 80 °C for 1.0 h under argon. The solvent was evaporated to give the product as a solid, which was recrystallized from

n-heptane to afford 2.93 g (98%) of **27a**: mp 129.5–130 °C; 6.42–6.77 (AB system, J = 8 Hz, 2 H, aromatic), 4.60 (s, 1 H, C5-H), 4.43 (d, J = 5 Hz, 1 H, C9-H), 2.18 (s, 3 H, C14-$OOCCH_3$), 0.97 [s, 9 H, $SiC(CH_3)_3$], 0.20 and 0.17 [2 s, 6 H, $Si(CH_3)_2$]; IR (KBr) 1720 (s, C=O).

4,5α-Epoxy-3,14-dihydroxy-6-methylene-17-(cyclopropylmethyl)morphinan 6α-Oxide (13a). To a suspension of 1.56 g (7.63 mmol) of trimethylsulfonium iodide stirring in 30 mL of anhydrous THF was added 4.27 mL (7.04 mmol) of a 1.65 M solution of *n*-butyllithium over 10 min at −5 °C under argon. After stirring for 10 min longer at −5 °C, the mixture was cooled to −78 °C, and 2.92 g (5.87 mmol) of **27a** in 16 mL of THF was added via cannula over 30 min. The mixture was kept at −78 °C for 1.5 h longer, the cooling bath was removed, and stirring was continued at room temperature for 1.5 h. The solvent was evaporated, and the residue and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 2.94 g of the crude oxirane mixed with the starting ketone. The mixture was stirred in 100 mL of methanol containing 1.00 mL (7.20 mmol) of triethylamine at 55 °C for 32 h under argon. The solvent was evaporated, the residue was redissolved in 80 mL of THF, and 7.20 mL of a 1 M solution of tetra-*n*-butylammonium fluoride was added. The mixture was stirred for 1 h at room temperature, the solvent was evaporated, and the residue was chromatographed directly on 80 g of flash column silica gel (1:1 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) to give 1.97 g of a ca. 1:1 mixture of epoxide **13a** and naltrexone (**1a**).

Further purification was facilitated by the conversion of naltrexone to the corresponding 6-*O*-methyloxime (**28a**).[8] To a solution of 418 mg (5.00 mmol) of methoxyamine hydrochloride in 10 mL of methanol was added 0.50 mL of a solution of 10 N sodium hydroxide. The mixture of 1.97 g of naltrexone and its 6-methylene 6α-oxide (**13a**) in 45 mL of methanol was added and the mixture was stirred at 50 °C for 12 h. The solvent was evaporated and the residue was chromatographed directly on 80 g of flash column silica gel (2:3 EtOAc/CH_2Cl_2 + 1% triethylamine eluent). After several chromatographies, 625 mg (30%) of epoxide **13a** was obtained. Recrystallization from CH_2Cl_2/hexanes afforded 519 mg (25%) of **13a**: mp 225–225.5 °C; CIMS (methane), m/z (relative intensity) 356 (QM, 100) 338 (QM − H_2O, 19); 500-MHz ^1H NMR δ 6.55–6.70 (AB system, J = 8 Hz, 2 H, aromatic), 5.20 (br s, 2 H, OH), 4.65 (s, 1 H, C5-H), 2.84 (d, J = 5.5 Hz, 1 H, epoxide *Z*-H), 2.38 (d, J = 5.5 Hz, 1 H, epoxide *E*-H); IR (KBr) 3200 (br, OH), 3040 (w), 2965 (w), 2905 (m), 2800 (w), 1620 (w), 1605 (w), 1490 (m), 1455 (m), 1440 (w), 1360 (w), 1310 (s), 1275 (w) 1250 (w), 1225 (w), 1180 (w), 1140 (w), 1110 (w), 1050 (w), 1025 (w), 985 (w), 940 (ms), 860 (w), 840 (w), 810 (w), 790 (w), 780 (w), 755 (w), 720 (w), 690 (w), 625 cm^{-1} (w); R_f 039 (98:2 ethyl acetate/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system and naltrexone 6-*O*-methyloxime (**28a**) has an R_f value of 0.44 in this solvent system. Anal. Calcd for $C_{21}H_{25}NO_4$: C, H, N.

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-14-hydroxy-6-[(*E*)- and -(*Z*)-carbethoxymethylene]-17-(cyclopropylmethyl)morphinan 6β-Oxide (29a and 30a). To 2.96 mL (14.0 mmol) of hexamethyldisilazane in 20 mL of dry THF was added 7.88 mL (13.0 mmol) of a 1.65 M solution of *n*-butyllithium over 15 min while stirring at −78 °C under argon. The solution was stirred at −5 °C for 15 min, cooled to −78 °C, and 1.44 mL (13.0 mmol) of ethyl bromoacetate in 5 mL of THF was added over 10 min. Stirring was continued at −78 °C for 10 min, and 2.30 g (5.00 mmol) of **26a** in 15 mL of THF was added over 10 min. After the solution was stirred for 20 min longer at −78 °C, the cooling both was removed, and stirring was continued at room temperature for 20 min. The solvent was evaporated and the residue was extracted with CH_2Cl_2. The organic solution was washed with aqueous disodium hydrogen phosphate and brine, dried over magnesium sulfate, filtered, and evaporated to give 3.63 g of the crude product mixture. Purification by flash column chromatography on 80 g of silica gel (1:2 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) afforded 2.67 g of a mixture (~ 4:1 E/Z) of glycidate esters **29a** and **30a** and a small amount of the unreacted ketone **26a**. Most of this mixture was deprotected, but a portion (0.36 g) was converted to 6-ethyl-6α-naltrexol (**33a**) to determine the stereochemistry at C-6.

4,5α-Epoxy-3,14-dihydroxy-6-[(*E*)- and -(*Z*)-carbethoxymethylene]-17-(cyclopropylmethyl)morphinan 6β-Oxide (14a and 15a). To a solution of 2.31 g of the mixture of glycidate esters **29a** and **30a** in 100 mL of THF stirring at 0 °C was added 10 mL of a 1 M solution of tetra-*n*-butylammonium fluoride. The mixture was warmed to room temperature and stirring was continued for 30 min. The solvent was evaporated and the residue chromatographed several times on 80 g of silica gel (1:3 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) to afford 1.04 g (54% from **26a**) of **14a**, the more polar isomer. The solid was recrystallized from CH_2Cl_2/hexanes to afford 909 mg of **14a** in two crops: mp 115.5–116 °C; $[\alpha]^{23}_D$ −173.4° (CH_3OH, c 1.0); CIMS (methane), m/e (relative intensity) 428 (QM, 100), 410 (QM − H_2O, 9); 500-MHz ^1H NMR δ 6.54–6.68 (AB system, J = 8 Hz, 2 H, aromatic), 5.05 (br s, 2 H, OH), 4.74 (s, 1 H, C5-H), 4.23 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 3.59 (s, 1 H, HCO_2Et), 1.28 (t, J = 7.3 Hz, 3 H, OCH_2CH_3); IR (KBr) 1745 cm^{-1} (s, ester); R_f 0.48 (98:2 EtOAc/triethylamine); naltrexone has on R_f value of 0.38 in this solvent system; R_f 0.37 (2:1 EtOAc/methanol); naltrexone has an R_f value of 0.34 in this solvent system; R_f 0.48 (98:2 EtOAc/triethylamine); naltrexone has an R_f value of 0.38 in this solvent system. Anal. Calcd for $C_{24}H_{29}NO_6$: C, H, N.

The minor glycidate ester **15a** was also purified by several flash column chromatographies on 80 g of silica gel eluting with 1:3 EtOAc/CH_2Cl_2 + 1% triethylamine to afford 265 mg (14%) from **15a** as a solid. Recrystallization from dichloromethane/hexanes gave 205 mg of **15a**: mp 93.5–94.0 °C; CIMS (methane), m/z (relative intensity) 428 (QM, 100), 410 (QM − H_2O, 8); 500-MHz ^1H NMR δ 6.57–6.75 (AB system, J = 8 Hz, 2 H, aromatic), 5.20 (br s, 2 H, OH), 4.73 (s, 1 H, C5-H), 4.28–4.40 (2 dq, 2 H, $OOCH_2CH_3$), 3.29 (s, 1 H, $HCCO_2Et$), 1.37 (t, J = 7.0 Hz, 3 H, OCH_2CH_3); IR (KBr) 1740 cm^{-1} (s, C=O); R_f 0.40 (2:1 EtOAc/methanol); R_f 0.51 (98:2 EtOAc/triethylamine). Anal. Calcd for $C_{24}H_{29}NO_6$: C, H. N.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-hydroxyethyl)-17-(cyclopropylmethyl)morphinan (31a). Reduction of Glycidate Esters 29a and 30a. To a slurry of 57 mg (1.50 mmol) of lithium aluminum hydride in 2 mL of dry ether was added 0.36 g of the mixture of glycidate esters **29a** and **30a** in 10 mL of ether dropwise with stirring at 0 °C under argon. The mixture was stirred at 0 °C for 7 h, quenched with wet ether, and extracted with CH_2Cl_2. The organic extracts were dried over magnesium sulfate, filtered, and evaporated to afford 237 mg of **31** as a solid: ^1H NMR δ 6.40–6.77 (AB system, J = 8 Hz, 2 H, aromatic), 4.43 (s, 1 H, C5-H), 3.91 (t, J = 6 Hz, 2 H, CH_2OH).

4,5α-Epoxy-3,6β,14-trihydroxy-6α-[2-(tosyloxy)ethyl]-17-(cyclopropylmethyl)morphinan (32a). Conversion of Diol 31a into Monotosylate 32a. The crude diol (237 mg, 0.47 mmol) was dissolved in 3 mL of CH_2Cl_2 and 0.5 mL of pyridine and cooled to 0 °C under an atmosphere of argon. *p*-Toluenesulfonyl chloride (99 mg, 0.52 mmol) in 1 mL of CH_2Cl_2 was added, and stirring at 0 °C was continued for 1 h. The cold bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue extracted with CH_2Cl_2. The organic extracts were dried over magnesium sulfate, filtered, and evaporated to give 308 mg of a solid, which was reduced directly without further purification.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-ethyl-17-(cyclopropylmethyl)morphinan (33a). Reduction of Monotosylate 32a. To a slurry of 380 mg (10.0 mmol) of lithium aluminum hydride in 4 mL of anhydrous THF was added 308 mg of the crude monotosylate in 10 mL of THF at room temperature under argon. The reaction mixture was stirred at room temperature for 1 h and at reflux for 3 h, cooled to 0 °C, and quenched with EtOAc. The pH was adjusted to 8.5, and the mixture was extracted with CH_2Cl_2. The extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 180 mg of crude **33a**. Purification by flash column chromatography on 40 g of silica gel afforded 64 mg of **33a** as a solid. Purification from CH_2Cl_2/hexanes gave 42 mg of **33a**: mp 220–220.5 °C; 500-MHz ^1H NMR δ 6.51–6.72 (AB system, J = 8 Hz, 2 H, aromatic), 5.20 (br s, 3 H, OH), 4.39 (s, 1 H, C5-H); R_f 0.27 (98:2 ethyl acetate/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system.

4,5α-Epoxy-3,6α,14-trihydroxy-6β-ethyl-17-(cyclopropylmethyl)morphinan (34a). To a slurry of 139 mg (3.00 mmol)

of 30% lithium dispersion in oil + 1% sodium in pentane was added a solution of 0.22 mL (3.00 mmol) of ethyl chloride in 5 mL pentane, and the mixture was heated to reflux for 30 min. The mixture was cooled to −15 °C, and 5 mL of THF was added. After stirring at −15 °C for 10 min, the solution was cooled to −78 °C, and 433 mg (0.95 mmol) of **26a** was added in 7 mL of THF. The mixture was stirred at −78 °C for 4 h and the temperature allowed to come to 23 °C overnight. The mixture was extracted with CH_2Cl_2, washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 494 mg of the crude **34a**. Purification by flash column chromatography on 40 g of silica gel (EtOAc + 1% triethylamine eluent) afforded 276 mg (78%) of **34a**. Recrystallization from dichloromethane/hexanes afforded 213 mg of **34a**: mp 197–198 °C; 500-MHz ^1H NMR δ 6.52–6.66 (AB system, J = 8 Hz, 2 H, aromatic), 5.20 (br s, 3 H, OH), 4.42 (s, 1 H, C5-H); R_f 0.29 (98:2 EtOAc/triethylamine). Naltrexone has an R_f value of 0.38 in this solvent system.

4,5α-Epoxy-3-[(*tert*-butyldimethylsilyl)oxy]-14-hydroxy-6-[(*E*)- and -(*Z*)-carbethoxymethylene]-17-methylmorphinan 6β-Oxide (29b and 30b). To 5.20 mL (24.7 mmol of hexamethyldisilazane in 50 mL of anhydrous THF was added 14.1 mL (22.9 mmol) of a 1.56 M solution of *n*-butyllithium in *n*-hexane with stirring at −78 °C, and 2.54 mL (22.9 mmol) of ethyl bromoacetate was added neat over 5 min. Stirring was continued at −78 °C for 10 min, and 3.80 g (9.14 mmol) of **26b** in 50 mL of THF was added over 15 min. After the mixture was stirred for 20 min longer at −78 °C, the cooling bath was removed, and stirring was continued at room temperature for 20 min. The solvent was evaporated and the residue was chromatographed on 135 g of silica gel (1:4 EtOAc/CH_2Cl_2 + 1% triethylamine eluent) to give 2.39 g of predominantly the major (*E*)-glycidate ester (**29b**) and 1.61 g of predominantly the minor (*Z*)-glycidate ester (**30b**).

4,5α-Epoxy-3,14-dihydroxy-6-[(*E*)- and -(*Z*)-carbethoxymethylene]-17-methylmorphinan 6β-Oxide (14b and 15b). To a solution of 2.39 g (4.76 mmol) of predominantly the (*E*)-glycidate ester **29b** in 45 mL of THF stirring at 0 °C was added 5.71 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The mixture was stirred for 1 h at 0 °C. The solvent was evaporated, and the residue was chromatographed directly on 80 g of flash column silica gel (2:3 EtOAc/CH_2Cl_2 + 1% triethylamine eluent). Similarly, 1.61 g (3.21 mmol) of predominantly (*Z*)-glycidate ester **30b** in 30 mL of THF was treated with 3.85 mL of a 1 M solution of tetra-*n*-butylammonium fluoride for 1 h at 0 °C. After evaporation of the solvent, the residue was chromatographed in the same way as the *E* isomer above, collecting 10-mL fractions, which were analyzed by TLC and separated into >85% *E*-isomer mixture and >85% *Z* isomer. After rechromatography of the >85% pure samples to purify them to >97% purity, the residual mixture of isomers was similarly processed. In this way, 2.23 g (68%) of *E*-isomer **14b** and 0.60 g (17%) of the *Z*-isomer **15b** were obtained. Recrystallization of **14b** from CH_2Cl_2/diethyl ether/hexanes afforded 2.08 g (59%): mp 195.5–196 °C; $[\alpha]^{23}_D$ −135.6° (CH_3OH, *c* 1.0); CIMS (methane), *m/z* (relative intensity) 388 (QM, 100), 370 (QM − H_2O, 24); ^1H NMR δ 6.35–6.70 (AB system, J = 8 Hz, 2 H, aromatic), 5.35 (br s, 2 H, OH), 4.70 (s, 1 H, C5-H), 4.20 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.57 (s, 1 H, $HCCO_2Et$), 2.35 (s, 3 H, NCH_3), 1.24 (t, 3 H, OCH_2CH_3); IR (KBr) 1725 cm^{-1} (s, C=O); R_f 0.55 (98:2 EtOAc/triethylamine, two elutions). Oxymorphone (**1b**) has an R_f value of 0.32 in this solvent system. Anal. Calcd for $C_{21}H_{25}NO_6$: C, H. N.

Recrystallization of **15b** proved to be difficult. As a result, the acetate salt was prepared from 0.60 g (1.55 mmol) of **15b** and 0.11 mL (1.86 mmol) of acetic acid and crystallized from CH_2Cl_2/hexanes: mp 119–120 °C; $[\alpha]^{23}_D$ −102.8° (CH_3OH, *c* 1.0); CIMS (methane), *m/z* (relative intensity) 388 (QM, 97), 370 (QM − H_2O, 23), 61 (HOAc, 100); ^1H NMR δ (free base) 6.42–6.80 (AB system, J = 8 Hz, 2 H, aromatic), 5.15 (br s, 2 H, OH), 4.71 (s, 1 H, C5-H), 4.20 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.27 (s, 1 H, $HCCO_2Et$), 2.35 (s, 3 H, NCH_3), 1.34 (t, J = 7 Hz, OCH_2CH_3); IR (KBr) 1715 cm^{-1} (s, C=O); R_f 0.57 (98:2 EtOAc/triethylamine, two elutions). Oxymorphone (**1b**) had an R_f value of 0.32 in this solvent system. Anal. Calcd for $C_{23}H_{29}NO_8$ (acetate salt): C, H. N.

Opioid Receptor Binding. [^{3}H]Naltrexone (9.8 Ci/mmol) and unlabeled naltrexone were generously supplied by Dr. Richard Hawks of the National Institute of Drug Abuse.

Male Sprague–Dawley rats were decapitated and a crude membrane fraction prepared from the brains (minus the cerebellum) by a method previously described.[14] The membrane preparation (1:6 w/v) was stired in 0.32 M sucrose at −70 °C until needed. For binding assays the thawed membrane preparations were diluted with 9 volumes of 50 mM Tris buffer, pH 7.4, 1 mM potassium EDTA ● 100 mM NaCl.

Specific binding on control and treated samples was assayed on duplicate 2-mL samples as previously described.[15] Samples were incubated with ^{3}H-labeled opioid ● 1 μM unlabeled drug for 45 min at 25 °C and then filtered through GF/B filters. Filters were rinsed twice with 4 mL of buffer, dried, and counted in a toluene-based scintillation cocktail.

Irreversibility of Opioid Receptor Binding. Membrane preparations were incubated with the drug to be tested for 45 min at 25 °C. After incubation, treated membranes were diluted sixfold with 50 mL Tris buffer, pH 7.4, 1 mM potassium EDTA ● 100 mM NaCl and centrifuged for 15 min at 20000*g*. After the supernatant was removed, the pellet was resuspended in 3 times the original volume and incubated at 37 °C for 15 min. Samples were then spun again as above and finally resuspended in the original volume.

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Registry No. **1a**, 16590-41-3; **1b**, 76-41-5; **7a** (isomer 1), 96453-31-5; **7a** (isomer 2), 96453-70-2; **7b** (isomer 1), 96453-36-0; **7b** (isomer 2), 96453-73-5; **8a**, 96453-35-9; **8a** (O^3-(*tert*-butyldimethylsilyl) ether), 96453-34-8; **8b**, 96453-41-7; **8b** (O^3-(*tert*-butyldimethylsilyl) ether), 96453-40-6; **9a**, 96453-43-9; **9a** (O^3-(*tert*-butyldimethylsilyl) ether), 96453-69-9; **10a**, 96453-49-5; **11a**, 96453-50-8; **12a**, 92398-17-9; **12b**, 96553-54-7; **13a**, 96453-55-3; **14a**, 96453-58-6; **14b**, 96453-66-6; **15a**, 96453-59-7; **15b**, 96453-67-7; **16a**, 92398-25-9; **17a**, 96453-32-6; **17b**, 96453-37-1; **18a** (isomer 1), 96453-33-7; **18a** (isomer 2), 96453-71-3; **18b** (isomer 1), 96453-38-2; **18b** (isomer 2), 96453-74-6; **19a** (isomer 1), 96481-05-9; **19a** (isomer 2), 96453-72-4; **19b** (isomer 1), 96453-39-3; **19b** (isomer 2), 96453-75-7; **20a**, 96453-42-8; **20a** (O^3-(*tert*-butyldimethylsilyl) ether), 96453-44-0; **21a**, 96481-27-5; **22a**, 96453-45-1; **23a**, 96453-46-2; **24a**, 96453-47-3; **24a** (mesylate), 96453-48-4; **24a** (dimesylate), 96453-51-9; **26a**, 96453-52-0; **26b**, 96453-53-1; **27a**, 96453-54-2; **27a** (oxirane), 96453-68-8; **28a**, 92078-82-5; **29a**, 96453-56-4; **29b**, 96453-64-4; **30a**, 96453-57-5; **30b**, 96453-65-5; **31a**, 96453-60-0; **32a**, 96453-61-1; **33a**, 96453-62-2; **34a**, 96453-63-3; PhSeCl, 5707-04-0; (phenylselenyl)acetic acid, 17893-46-8; propionic acid, 79-09-4; *tert*-butyldimethylsilyl chloride, 18162-48-6; trimethylsulfonium iodide, 2181-42-2; ethyl bromoacetate, 105-36-2; ethyl iodoacetate, 623-48-3.

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