7-Spirobenzocyclohexyl Derivatives of Naltrexone, Oxymorphone, and Hydromorphone as Selective Opioid Receptor Ligands

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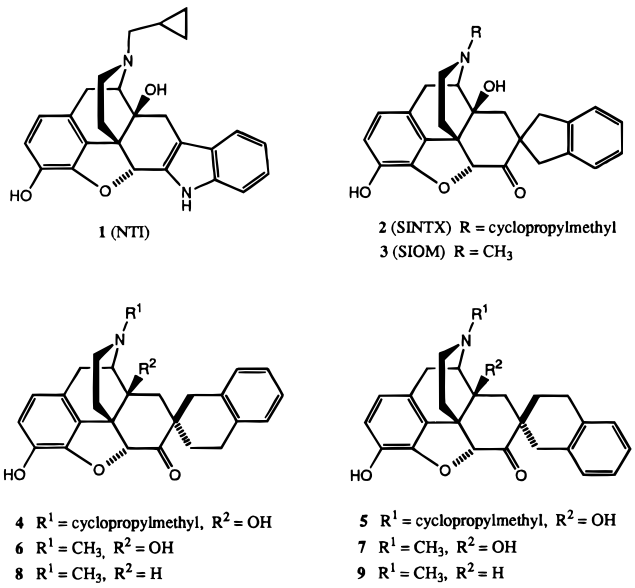
On the basis of previous structure−activity studies of the highly potent and selective δ-opioid receptor antagonist naltrindole (**1**) and the spiroindanyl anologues **2** and **3**, we have synthesized epimeric pairs of spirobenzocyclohexyl derivatives of naltrexone, oxymorphone, and hydromorphone (**4**−**9**). Pharmacologic evaluation in smooth muscle assays has revealed that the oxymorphone derivatives (**6**, **7**) are δ-selective agonists and possess receptor binding profiles that are consistent with their agonist activity. It is proposed that the spirobenzocyclohexyl group of **6** and **7** orients its benzene moiety orthogonally with respect to the C ring of the opiate in a manner similar to that of the spiroindanyl analogue **3**. It is suggested that this orthogonal orientation serves as an "address" to facilitate activation of δ receptors. The finding that the hydromorphone analogues (**8**, **9**) were full μ agonists and exhibited only partial δ agonist activity suggests that the 14-hydroxyl group also contributes to the δ agonist activity. The naltrexone derivatives (**4**, **5**) were μ-selective antagonists and exhibited relatively weak δ antagonist activity. However, the binding data indicated a very high-affinity δ-selective binding profile that was not consistent with the pharmacology. This study illustrates the differential contributions of the δ "address" to agonist and antagonist activity and supports the idea of different recognition sites for interaction of agonist and antagonist ligands with δ-opioid receptors.

Introduction

Naltrindole (**1**) (NTI) is a highly potent and selective non-peptidic δ-opioid receptor antagonist.[1−3] Its high δ-opioid antagonist potency and selectivity have been attributed to the indolic benzene "address" moiety which presumably mimics the Phe[4] residue of enkephalin.[3] In an effort to investigate the conformational role of this moiety in conferring high δ antagonist potency and selectivity of NTI, a variety of related naltrexone and oxymorphone derivatives[4,5] have been examined. Among these, the 7-spiroindanyl derivatives **2** (SINTX) and **3** (SIOM) are especially noteworthy. While the naltrexone derivative **2** is a potent δ-opioid receptor antagonist both *in vitro* and *in vivo*, the *N*-methyl analogue **3** is apparently both an agonist and an antagonist *in vivo* at the δ_1 receptor.[4,5] Here we describe the synthesis and biological activity of a series of 7-spirobenzocyclohexyl derivatives (**4**−**9**) that are structurally related to **2** and **3**. These compounds were of interest because the "address" is oriented differently in the 7α and 7β epimers.

Chart 1



Design Rationale and Chemistry

The design rationale for 7-spirobenzocyclohexane derivatives of naltrexone, oxymorphone, and hydromorphone (compounds **4**−**9**) was based on structure−activity studies of the spiroindanyl series (**2** and **3**), where the aromatic moiety is orthogonal to ring C of the morphinan system. In the present study, we have further investigated the conformational role of the address moiety in conferring opioid receptor selectivity by the synthesis of three pairs of C-7 epimeric compounds that are homologues of **2** and **3**. These compounds were of interest because the C-7 epimeric relationship (**4**, **6**, **8** *vs* **5**, **7**, **9**) affords two different preferred orientations of the "address", as can be seen in Figure 1. Thus, the preferred conformations of the aromatic moiety for the 7α epimers (**5**, **7**, **9**) are similar to those in the indanyl series, whereas the corresponding benzene moiety of the 7β epimers (**4**, **6**, **8**) is above and approximately in the same plane as that for the 7α epimers.

The synthetic route to the target compounds **4**−**9** is outlined in Scheme 1. Lithium aluminum hydride

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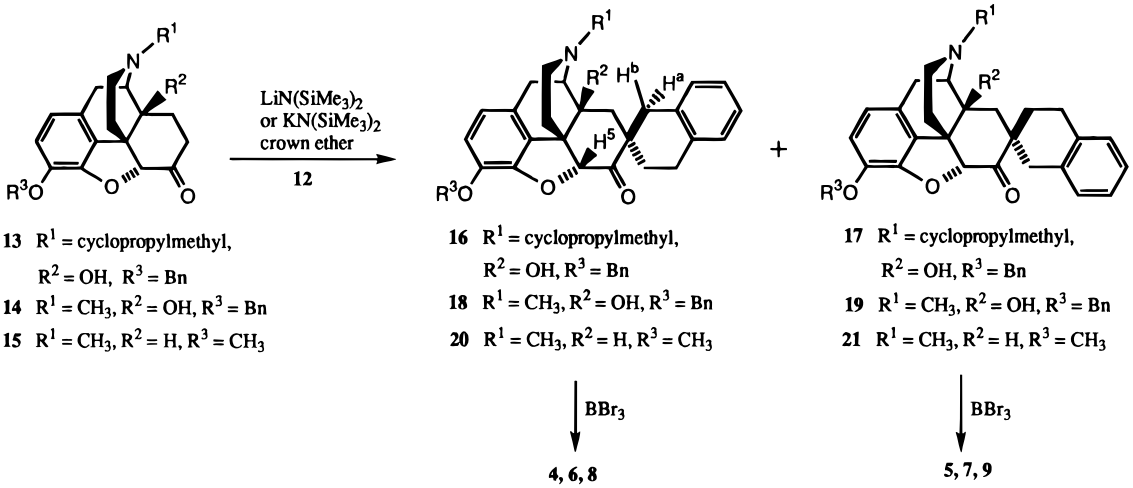
Scheme 1



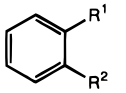
13 R^1 = cyclopropylmethyl, R^2 = OH, R^3 = Bn
14 R^1 = CH_3, R^2 = OH, R^3 = Bn
15 R^1 = CH_3, R^2 = H, R^3 = CH_3

16 R^1 = cyclopropylmethyl, R^2 = OH, R^3 = Bn
18 R^1 = CH_3, R^2 = OH, R^3 = Bn
20 R^1 = CH_3, R^2 = H, R^3 = CH_3

17 R^1 = cyclopropylmethyl, R^2 = OH, R^3 = Bn
19 R^1 = CH_3, R^2 = OH, R^3 = Bn
21 R^1 = CH_3, R^2 = H, R^3 = CH_3

4, 6, 8 **5, 7, 9**

reduction of homophthalic acid (**10**) afforded diol **11**, which was converted to dibromide **12** by treatment with carbon tetrabromide and triphenylphosphine.[6] Naltrexone and oxymorphone were protected as benzyl ethers[4,5] (**13**, **14**) prior to cyclization with the dibromide compound **12**. The key step in this synthetic route was the base-promoted double alkylation by **12** of **13**−**15**, to generate a spiro center at C-7 on the morphinan ring system. Each of the cyclization reactions produced a pair of C-7 epimers (**16**, **17**; **18**, **19**; **20**, **21**), which were carefully separated by column chromatography. Cleavage of benzyl or methyl ether protective groups from intermediates **16**−**21** furnished the target compounds **4**−**9**, respectively.



10 R^1 = CO_2H, R^2 = CH_2CO_2H
11 R^1 = CH_2OH, R^2 = $(CH_2)_2OH$
12 R^1 = CH_2Br, R^2 = $(CH_2)_2Br$

The stereochemistry at the C-7 center of the epimers was determined by NMR spectroscopy. The ^1H NMR spectrum of **16** included a singlet for H-5 at 5.03 ppm and an AB pattern for the CH_2 group (J_{gem} = 16.5 Hz; H_a, 3.86 ppm; H_b, 3.25 ppm) which directly links the spiro C-7 center with the benzene moiety. Similarly, its epimer **17** showed a singlet at 5.00 ppm (H-5) and two doublets (J_{gem} = 15.9 Hz) centered at 3.55 and 3.21 ppm. These peaks are well-separated from one another and from other signals, and therefore they are appropriate for NOE difference studies, in order to assign the configuration of the spiro center (C-7) for compound **16** and its epimer **17**. With compound **16**, irradiation of H-5 gave a positive enhancement (5.1%) for one of the CH_2 protons (H_b). Conversely, irradiation of H_b produced a positive enhancement (6.5%) for H-5. These results indicated that this CH_2 group and H-5 are on the same side of ring C (i.e., the β-face of the morphinan system), and therefore its stereochemistry is as specified in structure **16**. This conclusion was reinforced by the NOE difference spectrum of epimer **17**, which exhibited no enhancement for the CH_2 protons upon irradiation of H-5. Irradiation of this benzylic CH_2 also produced no enhancement of the H-5 signal. Thus, these data suggested that **17** contains an α-oriented CH_2 group which directly links the spiro C-7 center and the benzene ring.

This assignment also is consistent with the modeling studies, which showed that the distance between H-5 and one of the CH_2 protons (H_b) in epimer **16** is 3.47 Å, within the range where the NOE usually is observed. The distance between H-5 and H_a (4.86 Å) is outside this range. In contrast, both of these protons in **17** are too remote (4.75 and 4.77 Å) from H-5 to produce the corresponding NOE enhancements. The C-7 stereochemistry of the other epimeric pairs (**18**, **19**; **20**, **21**) was established in an analogous fashion.

Biological Results

Smooth Muscle Preparations. The opioid activity of **4**−**9** was evaluated on the electrically stimulated guinea pig ileal longitudinal muscle[8] (GPI) and mouse vas deferens[9] (MVD) preparations as reported previously.[10] The antagonists were incubated with the preparations for 15 min before testing with the standard agonists. Morphine, ethylketazocine (EK), and [D-Ala^2,D-Leu^5]enkephalin[11] (DADLE) were employed as μ-, κ-, and δ-selective agonists, respectively. Morphine and EK were used in the GPI, and DADLE was employed in the MVD. Three or more replicate determinations were carried out for each compound. Ligands that were not full agonists were tested at a concentration of 1 μM, and the agonist activity was expressed as percentage of the maximal response. Opioid antagonism is expressed as an IC_{50} ratio, which is the IC_{50} of the agonist in the presence of the test compound (100 nM), divided by the control IC_{50} in the same preparation.

In the MVD, the cyclopropylmethyl epimers (**4**, **5**) were found to be considerably less potent than SINTX (**2**; Table 1) but were approximately equipotent as antagonists of DADLE. Judging from the larger IC_{50} ratios in the GPI, both **4** and **5** may be more potent at μ receptors. The *N*-methyl compounds (**6**−**9**) all behaved as full agonists in the GPI with IC_{50} values > 100 nM. Of these, only **6** and **7** exhibited full agonist activity in the MVD, with potencies similar to that of SIOM (**3**). Interestingly, the potencies of epimers **6** and **7** were not significantly different.

Binding. The opioid receptor affinities of the target compounds were determined on mouse brain membranes employing the procedure of Werling et al.[12] Binding to μ sites was evaluated by competition of the target compounds with [^{3}H][D-Ala^2,MePhe^4,Gly-ol^6]-

Table 1. Opioid Agonist and Antagonist Potencies of 7-Spirobenzocyclohexyl Derivatives of Naltrexone, Oxymorphone, and Hydromorphone

	MVD		GPI		
	antagonism[a] IC_{50} ratio	agonism[b] IC_{50} (nM) or	antagonism[a] IC_{50} ratio		agonism[b] IC_{50} (nM) or
compd	DADLE (δ)	% max resp	M (μ)	EK (κ)	% max resp
2[c]	130 ± 30	−8 ± 6%	24.9 ± 4	1.9 ± 0.5	16 ± 9%
3[d]	*e*	22 ± 9 nM	1.2 ± 0.5	1.0 ± 0.3	55 ± 11%
4	6.8 ± 1.3	4 ± 2%	29.1 ± 6.3	1.9 ± 0.3	2 ± 1%
5	7.4 ± 1.9	3 ± 2%	15.6 ± 4.0	1.7 ± 0.3	16 ± 12%
6	*e*	24 ± 9 nM	*e*	*e*	183 ± 79 nM
7	*e*	28 ± 7 nM	*e*	*e*	629 ± 139 nM
8	4.7 ± 1.4	42 ± 10%	*e*	*e*	130 ± 40 nM
9	3.6 ± 0.9	17 ± 7%	*e*	*e*	107 ± 64 nM

[a] The agonist IC_{50} value in the presence of the test compound divided by the control IC_{50}. [b] Partial agonist activity is expressed as the percent inhibition of contraction at a concentration of 1 μM. Full agonist activity is expressed as an IC_{50} (nM). [c] Data from ref 5. [d] Data from ref 4. [e] Not determined due to full agonist activity.

Table 2. Binding to Mouse Brain Membranes

	K_i (nM)[a]		
compd	[^{3}H]NTI (δ)	[^{3}H]DAMGO (μ)	[^{3}H]U69593 (κ)
2[b]	0.25 ± 0.06	1.5 ± 0.6	>3000
3[c]	2.8 ± 0.4	14 ± 4	>3000
4	0.0019 ± 0.0007	0.38 ± 0.12	>1000
5	0.0041 ± 0.0009	0.72 ± 0.17	147 ± 32
6	4.6 ± 1.3	18 ± 3	>1000
7	9.3 ± 1.1	28 ± 8	>3000
8	8.3 ± 1.7	2.8 ± 0.4	88 ± 30
9	182 ± 39	119 ± 13	>1000

[a] The arithmetic mean of K_i (±SEM) values for $n \geq 3$. The K_i values were calculated from the Cheng−Prusoff equation,[19] $K_i = IC_{50}/(1 + [L]/K_D)$, where IC_{50} is the concentration of competing ligand producing 50% inhibition of the specific binding of radioligand at concentration [L] and having affinity constant K_D. [b] Data from ref 5. [c] Data from ref 4.

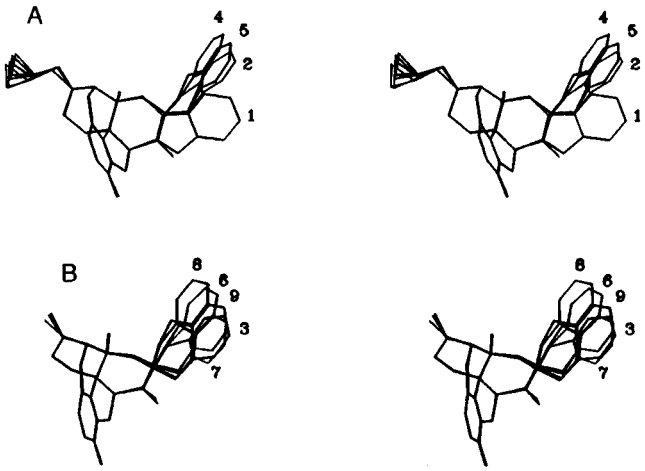


Figure 1. (A) Superposition of epimeric 7-spirobenzocyclohexylnaltrexones (**4**, **5**), SINTX (**2**), and NTI (**1**). (B) Superposition of 7-spirobenzocyclohexyloxymorphone (**6**, **7**) and 7-spirobenzocyclohexylhydromorphone (**8**, **9**) epimers with SIOM (**3**).

enkephalin ([^{3}H]DAMGO),[13] to δ sites with [^{3}H]naltrindole ([^{3}H]NTI),[14] and to κ sites with [^{3}H]-5α,7α,8β-(−)-*N*-methyl-*N*-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl-benzeneacetamide ([^{3}H]U69593).[15] The K_i values of the target compounds **4**−**9** are presented in Table 2.

Although the K_i values of the naltrexone derivatives **4** and **5** indicate that they have extremely high affinity for δ receptors, inspection of the binding curves has revealed that "competition" with [^{3}H]NTI occurred over a 6-decade concentration range, suggesting a noncompetitive binding component. The reason for this discrepancy is not known. Consequently, the K_i values may not reflect true competitive binding affinities for **4** and **5**. The oxymorphone derivatives **6** and **7** have similar binding profiles to the indan homologue **3** in that they have 3−4-fold preference for δ over μ receptors, with virtually no affinity for κ receptors. The hydromorphone epimers (**8**, **9**) have 1.5−3-fold greater affinity for μ over δ receptors. It is noteworthy that the β epimers (**4**, **6**, **8**) have greater affinity for δ receptors than the corresponding α epimers (**5**, **7**, **9**). However, a parallel difference also is observed for μ receptor binding. In this regard, **8** binds with greater affinity to μ and δ receptors by a factor of 20−40 over its epimer **9**.

Discussion

Prior pharmacologic and binding studies of 7-spiroindanyl derivatives of naltrexone and oxymorphone have revealed that an aromatic ring that is orthogonal to ring C of the morphinan system confers a preference for δ-opioid receptors.[4,5] Thus, it has been reported that compounds **2**, **3**, and a number of related spiroindanyl structures exhibit potent δ antagonist or δ agonist activities.[4,5] The naltrexone-derived ligands generally are not as potent or as selective as NTI (**1**), and it appears that an aromatic moiety coplanar to ring C is optimal for δ antagonist activity. However, it was found that an orthogonal "address" attached to oxymorphone favors δ agonist activity.

In the present study, we have investigated epimeric homologues **4**−**9** whose orthogonal aromatic groups are displaced from one another but are approximately in the same plane (Figure 1).

The epimeric oxymorphone derivatives (**6**,**7**) showed some binding selectivity for δ receptors. This was not the case for the hydromorphone analogues (**8**,**9**) which exhibited a preference for μ receptors. This difference in selectivity is related more to differences in the affinity for μ receptors, since the affinity difference for δ receptors was small and differed only by a factor of 2. In any case, the finding that the δ receptor affinities of the spirobenzocyclohexanes **6**−**8** and that of the spiroindan **3** are similar to one another suggests that the position of the orthogonally oriented "address" is not critical for δ agonist activity. It is unclear why **9** binds substantially less avidly than its epimer **8**. However, this appears to be more of a general phenomenon in view of the correspondingly lower affinity of **9** for μ and δ receptors.

The identical agonist potencies of **6** and **7** in the MVD are consistent with the binding data, which show only a minor difference in affinity for δ receptors. These

ligands are substantially less effective as μ agonists in view of the 10−20-fold higher IC_{50} values in the GPI. The nearly identical δ agonist potencies of the oxymorphone derivatives **3**, **6**, and **7** also support the idea that an orthogonal aromatic group is important for full δ agonist activity and that modest displacement of the aromatic group in the orthogonal position does not adversely affect agonist potency. However, the finding that the hydromorphone analogues **8** and **9** are weak δ antagonists and probable μ agonists indicates that the 14-hydroxyl group contributes significantly to the δ agonist activity of **3**, **6**, and **7**. This is consistent with the known potency-enhancing effect of the 14-hydroxyl group.[17]

While **4** and **5** appeared to possess very high affinity for δ receptors, they paradoxically exhibited only feeble antagonism against DADLE in the MVD. In fact, the smooth muscle pharmacological data indicate that both **4** and **5** are most effective as μ antagonists. Since the binding curves of **4** and **5** were shallow and spanned over 6 decades of concentration, these data may be due to a mixed competitive−noncompetitive mechanism. Thus, a significant noncompetitive component could explain the anomalous binding data, which is reminiscent of the apparent noncompetitive interaction of a related ligand, 7-benzospiroindanylnaltrexone,[18] with [^{3}H]NTI. In this regard, it appears that **4** and **5** behave similarly despite the fact that the energetically preferred conformations of the spirobenzocyclohexane moiety in these epimers differ from one another.

Summary and Conclusions

In summary, the present study shows that the δ agonist potency and selectivity resulting from the attachment of an orthogonally oriented spirobenzocyclohexane group to the 7-position of oxymorphone (**6**, **7**) is similar to those reported for the spiroindan derivative SIOM(**3**). These results suggest that the orthogonal orientation of the "address" is important for conferring δ agonist activity to the opiate and that its position within the orthogonal plane is not critical. Also, it appears that the 14-hydroxyl group of the opiate pharmacophore contributes significantly to the δ agonist activity.

On the other hand, identical modification of the 7-position of naltrexone led to weak δ antagonists (**4**, **5**) with selectivity for μ receptors, which is unlike the contribution from the attachment of spiroindanyl group (**2**). This apparent inconsistency is observed with the pharmacological, but not with the binding, data. The apparent differential pharmacologic contribution of the spirobenzocyclohexyl group to agonist and antagonist activities supports the idea of different recognition sites for agonist and antagonist ligands on δ receptors.[5]

Experimental Section

All ^{1}H NMR spectra were recorded on a GE 300 MHz spectrometer in $CDCl_3$, with TMS as reference, and ^{13}C NMR spectra were recorded on a GE 300 MHz spectrometer at 75 MHz in $CDCl_3$ with TMS or $CDCl_3$ as reference, unless otherwise noted. Infrared spectra were recorded on a Nicolet 5DXC FT-IR instrument. Mass spectra were obtained on a VG 7070E-HF instrument. Elemental analyses were performed by M-H-W Laboratories in Phoenix, AZ, and are within ±0.4% of theoretical values. Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. Reactions were generally conducted under inert atmosphere (oxygen-free dry nitrogen or argon) using flame-dried glassware. Column chromatography was carried out on E. Merck silica gel 60 (230−400 mesh), and the eluting solvents are reported as v/v percent mixture, unless otherwise stated. Thin layer chromatography was performed on E. Merck silica gel 60 F-254 0.25 nm plates and visualized with UV light, phosphomolybdic acid, or iodine impregnated on silica gel. Solvents used for reactions were purified by distillation under dry nitrogen atmosphere as follows: dichloromethane, triethylamine, methanol from calcium hydride; diethyl ether, tetrahydrofuran, benzene from sodium/benzophenone; chloroform from P_2O_5. Naltrexone, oxymorphone, and hydrocodone were supplied by Mallinckrodt, St. Louis, MO. All other commercial reagents were purchased from Aldrich Co., Milwaukee, WI, and used without further purification, unless otherwise noted.

2-(2-Hydroxyethyl)-1-(hydroxymethyl)benzene (11). To a stirred solution of homophthalic acid (**10**) (5.13 g, 28.5 mmol) in 150 mL of dry THF was added dropwise a 1.0 M solution of lithium aluminum hydride (90 mL, 90 mmol) over a period of 45 min. After addition was complete, the resulting solution was refluxed for 20 h under a nitrogen atmosphere. Upon cooling to room temperature, the reaction mixture was treated with water (50 mL) added carefully dropwise, followed by the addition of 15% aqueous NaOH (100 mL). This mixture was stirred for 1 h, and 10 g of solid NaCl was added in order to facilitate the subsequent workup. The mixture was then filtered through a pad of cotton wool and washed through with Et_2O. The filtrate was extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on a silica gel column, eluting with EtOAc−hexane (50:50) to furnish 4.01 g (93%) of diol **11** as a colorless oil: TLC R_f 0.20 (EtOAc−hexane, 50:50); ^{1}H NMR ($CDCl_3$) δ 7.33−7.20 (m, 4 H, ArH), 4.61 (s, 2 H, CH_2), 3.86 (t, 2 H, J = 6.0 Hz, CH_2), 3.63 (br, 1 H, OH), 2.95 (t, 2 H, J = 6.0 Hz, CH_2), 2.87 (br, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 138.63, 137.59, 129.66, 129.04, 127.93, 126.23, 62.51, 62.17, 34.70; HRMS (EI) calcd for $C_9H_{12}O_2$ (M^+) 152.0837, found 152.0836.

2-(2-Bromoethyl)-1-(bromomethyl)benzene (12). To a stirred solution of the diol **11** (1.61 g, 10.6 mmol) and carbon tetrabromide (8.96 g, 27.0 mmol) in 50 mL of dry CH_2Cl_2 at 0 °C and under a nitrogen atmosphere was added a solution of triphenylphosphine (6.95 g, 26.5 mmol) in 25 mL of CH_2Cl_2 via syringe. After the addition, the ice bath was removed and the resulting orange solution was stirred at ambient temperature for 18 h. The solvent was evaporated from the reaction mixture, and the resulting residue was treated with Et_2O (100 mL). The mixture was then filtered, and the filter cake was washed with Et_2O (3 × 320 mL). The combined filtrate and washings were concentrated in vacuo, and the residual oil was purified by flash chromatography twice on silica gel (EtOAc−hexane, 10:90 and 3:97) to yield 2.04 g (70%) of dibromide **12** as a colorless oil: TLC R_f 0.84 (EtOAc−hexane, 10:90); ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (m, 4 H, ArH), 4.56 (s, 2 H, CH_2), 3.64 (t, 2 H, J = 7.7 Hz, CH_2), 3.30 (t, 2 H, J = 7.7 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 137.33, 135.39, 130.41, 129.72, 128.83, 127.18, 35.13, 31.69, 31.26; HRMS (EI) calcd for $C_9H_{10}Br_2$ (M^+) 275.9150, found 275.9141.

7α- and 7β-Spirobenzocyclohexyl-3-*O*-benzylnaltrexone (17 and 16). To a stirred solution of 12-crown-4 (3.52 g, 3.24 mL, 20 mmol) in 10 mL of dry THF at room temperature and under a nitrogen atmosphere was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 20 mL, 20 mmol). After 2 min, 3-*O*-benzylnaltrexone (**13**) (2.2 g, 5.1 mmol) was added via syringe as a solution in 15 mL of THF, and the resulting solution was stirred at room temperature for an additional 15 min. A solution of 2-(2-bromoethyl)-1-(bromomethyl)benzene (3.1 g, 11.2 mmol) in 10 mL of THF was introduced via syringe, and the mixture was then heated at reflux for 21 h. After cooling to ambient temperature, the mixture was poured into 150 mL of brine and extracted with ethyl acetate or chloroform (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude cy-

clization products were separated and purified by gravity column chromatography on silica gel, eluting sequentially with 10%, 20%, and 40% EtOAc in hexane, to afford **16** (490 mg, 17.6%) and **17** (120 mg, 4.3%) as white solids.

7*β* Epimer 16: mp 218−219 °C; TLC R_f 0.20 (EtOAc−hexane, 20:80); IR (KBr pellet) 1718.5 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 7.50−7.12 (m, 9 H, ArH), 6.76 (d, 1 H, J = 7.8 Hz, H-2), 6.56 (d, 1 H, J = 7.8 Hz, H-2), 5.44 (br, 1 H, OH), 5.35 (d, 1 H, J = 11.9 Hz, OC*H*HPh), 5.21 (d, 1 H, J = 11.9 Hz, OCH*H*Ph), 5.03 (s, 1 H, H-5), 3.86 (d, 1 H, J = 16.5 Hz, H_a of C(spiro)-CH_aH_b-Ar), 3.25 (d, 1 H, J = 16.5 Hz, H_b of C(spiro)-CH_aH_b-Ar), 3.13 (d, 1 H, J = 5.7 Hz, H-9), 2.79−1.24 (m, 14 H), 0.83 (m, 1 H, H-19), 0.56 (m, 2 H, cyclopropyl), 0.15 (m, 2 H, cyclopropyl); NOE difference expt, irradiation of H-5 gave a positive enhancement (+5.1%) for H_b of C(spiro)-CH_aH_b-Ar, irradiation of H_b gave a positive enhancement (+6.5%) for H-5 and a strong geminal enhancement (+21.5%) for H_a; computer molecular modeling of **16** using Biosym software[7] for energy minimization calculated internuclear distances of 3.47 Å between H-5 and H_b, 4.86 Å between H-5 and H_a; ^{13}C NMR−DEPT ($CDCl_3$) δ CH_2 (73.09, 59.87, 44.29, 43.15, 42.51, 42.45, 42.39, 30.99, 23.48, 4.66, 4.55), CH (129.09, 129.04, 128.54, 128.43, 128.39, 127.30, 127.06, 125.04, 124.67, 120.08, 119.51, 89.89, 62.97, 10.75), quaternary (209.01, 146.96, 142.86, 141.02, 138.25, 131.06, 126.83, 118.05, 70.18, 58.09, 52.74); HRMS (FAB) calcd for $C_{36}H_{38}NO_4$ $(M + H)^+$ 548.2801, found 548.2806.

7α Epimer 17: mp 212−213.5 °C; TLC R_f 0.27 (EtOAc−hexane, 20:80); IR (KBr pellet) 1719.1 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 7.48−7.06 (m, 9 H, ArH), 6.78 (d, 1 H, J = 7.5 Hz, H-1), 6.58 (d, 1 H, J = 7.5 Hz, H-2), 5.38 (d, 1 H, J = 12.4 Hz, OC*H*HPh), 5.19 (d, 1 H, J = 12.4 Hz, OCH*H*Ph), 5.00 (s, 1 H, H-5), 3.55 (d, 1 H, J = 15.9 Hz, H_a of C(spiro)-CH_aH_b-Ar), 3.21 (d, 1 H, J = 15.9 Hz, H_b of C(spiro)-CH_aH_b-Ar), 3.12 (m, 1 H, H-9), 2.70−1.20 (m, 15 H), 0.85 (m, 1 H, H-19), 0.55 (m, 2 H, cyclopropyl), 0.12 (m, 2 H, cyclopropyl); NOE difference expt, irradiation of H-5 gave no enhancement for either H_a or H_b of C(spiro)-CH_aH_b-Ar, irradiation of either H_a or H_b gave no enhancement for H-5; molecular mechanics calculations[7] on an energy-minimized structure of **17** gave internuclear distances of 4.75 Å between H-5 and H_b, 4.77 Å between H-5 and H_a; ^{13}C NMR−DEPT ($CDCl_3$) δ CH_2 (72.38, 59.15, 43.55, 43.52, 42.41, 41.80, 41.67, 30.28, 22.56, 3.90, 3.81), CH (128.31, 128.26, 127.85, 127.81, 127.70, 126.57, 126.33, 124.31, 123.93, 119.35, 118.86, 89.16, 62.18, 9.36), quaternary (208.80, 145.39, 141.83, 140.35, 137.54, 129.90, 125.64, 69.76, 56.41, 51.35); HRMS (FAB) calcd for $C_{36}H_{38}NO_4$ $(M + H)^+$ 548.2801, found 548.2798.

The following compounds **18**−**21** were prepared using the same methodology as described above, except for the differences noted.

7α- and 7*β*-Spirobenzocyclohexyl-3-*O*-benzyloxymorphone (19 and 18). These were prepared from 3-*O*-benzyloxymorphone (**14**) (2.5 g, 6.4 mmol), using potassium bis(trimethylsilyl)amide and 18-crown-6 as base. The two epimers were separated and purified by gravity column chromatography, eluting sequentially with 20%, 40%, and 45% ethyl acetate in hexane and a trace amount of ammonia.

7*β* Epimer 18: yield 680 mg (21%); mp 235−236 °C; TLC R_f 0.18 (EtOAc−hexane, 40:60); IR ($CHCl_3$) 1720.2 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 7.5−7.1 (m, 9 H, ArH), 6.77 (d, 1 H, J = 8.4 Hz, H-1), 6.61 (d, 1 H, J = 8.4 Hz, H-2), 5.40 (d, 1 H, J = 12.0 Hz, OC*H*HPh), 5.24 (d, 1 H, J = 12.0 Hz, OCH*H*Ph), 5.30 (br, 1 H, OH), 5.05 (s, 1 H, H-5), 3.87 (d, 1 H, J = 17.4 Hz, H_a of C(spiro)-CH_aH_b-Ar), 3.24 (d, 1 H, J = 17.4 Hz, H_b of C(spiro)-CH_aH_b-Ar), 3.15 (d, 1 H), 2.84 (d, 1 H, J = 5.4 Hz, H-9), 2.7−2.1 (m, 8 H), 2.44 (s, 3 H, CH_3), 2.04 (d, 1 H, J = 14.1 Hz, 1 H, H-8), 1.84 (d, 1 H, J = 14.1 Hz, H-8), 1.58 (m, 1 H); NOE difference expt, irradiation of H-5 gave a positive enhancement (+5.9%) for H_b of C(spiro)-CH_aH_b-Ar, irradiation of H_b gave a positive enhancement (+6.8%) for H-5 and a strong enhancement (+25.6%) for the geminal proton H_a; molecular modeling calculations[7] for the energy-minimized structure furnished internuclear distances of 3.47 Å between H-5 and H_b, 4.85 Å between H-5 and H_a; ^{13}C NMR−DEPT ($CDCl_3$) δ CH_3 (43.40), CH_2 (73.10, 45.97, 43.29, 43.20, 42.53, 42.33, 31.68, 22.62), CH (129.06, 128.98, 128.57, 128.47, 127.33, 127.12, 127.06, 125.05, 124.69, 120.19, 119.60, 90.10, 65.33), quaternary (209.98, 147.53, 143.95, 142.01, 138.90, 130.66, 126.50, 77.12, 71.05, 58.01, 52.04); HRMS (FAB) calcd for $C_{33}H_{34}NO_4$ $(M + H)^+$ 508.2488, found 508.2492.

7α Epimer 19: yield 140 mg (4.3%); mp 224−225 °C; TLC R_f 0.25 (EtOAc−hexane, 40:60); IR ($CHCl_3$) 1719.8 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 7.6−7.0 (m, 9 H, ArH), 6.74 (d, 1 H, J = 8.1 Hz, H-1), 6.57 (d, 1 H, J = 8.1 Hz, H-2), 5.35 (d, 1 H, J = 12.5 Hz, OC*H*HPh), 5.3 (br, 1 H, OH), 5.20 (d, 1 H, J = 12.5 Hz, OCH*H*Ph), 5.10 (s, 1 H, H-5), 3.56 (d, 1 H, J = 15.9 Hz, H_a of C(spiro)-CH_aH_b-Ar), 3.28 (d, 1 H, J = 15.9 Hz, H_b of C(spiro)-CH_aH_b-Ar), 2.88 (d, 1 H, J = 6.0 Hz, H-9), 2.75−2.25 (m, 9 H), 2.41 (s, 3 H, CH_3), 2.08 (d, 1 H, J = 14.3 Hz, H-8), 1.88 (d, 1 H, J = 14.3 Hz, H-8), 1.62−1.52 (m, 1 H); NOE difference expt, irradiation of H-5 gave no enhancement for either H_a or H_b of C(spiro)-CH_aH_b-Ar, irradiation of either H_a or H_b gave no enhancement for H-5; molecular modeling calculations showed internuclear distances of 4.75 Å between H-5 and H_b, 4.76 Å between H-5 and H_a; ^{13}C NMR−DEPT ($CDCl_3$) δ CH_3 (42.60), CH_2 (73.45, 46.20, 42.48, 42.30, 41.73, 41.53, 30.92, 21.85), CH (128.27, 128.09, 127.78, 127.67, 126.54, 126.30, 126.05, 124.25, 123.89, 119.38, 118.81, 89.06, 64.56), quaternary (208.74, 145.32, 141.82, 141.75, 140.30, 137.47, 129.67, 125.55, 69.89, 56.30, 50.67); HRMS (FAB) calcd for $C_{33}H_{34}NO_4$ $(M + H)^+$ 508.2488, found 508.2485.

7α- and 7*β*-Spirobenzocyclohexylhydrocodone (21 and 20). These were prepared from hydrocodone (**15**) (2.20 g, 7.35 mmol) using a 3-fold molar excess of dibromide **12**. The two C-7 epimers were separated and purified by gravity column chromatography using 1−3% methanol and 1% triethylamine in chloroform as the eluting solvent.

7*β* Epimer 20: yield 461 mg (15%); mp 230−231 °C; TLC R_f 0.26 (3% methanol and 1% triethylamine in $CHCl_3$); IR ($CHCl_3$) 1720.2 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 7.28−7.03 (m, 4 H, ArH), 6.75 (d, 1 H, J = 7.9 Hz, H-2), 6.58 (d, 1 H, J = 7.9 Hz, H-1), 4.83 (s, 1 H, H-5), 3.98 (d, 1 H, J = 17.0 Hz, H_a of C(spiro)-CH_aH_b-Ar), 3.85 (s, 3 H, OMe), 3.66 (d, 1 H, J = 17.0 Hz, H_b of C(spiro)-CH_aH_b-Ar), 3.3−3.2 (m, 2 H), 3.2−2.8 (m, 4 H, CH_2CH_2), 2.64 (m, 1 H, H-16), 2.44 (s, 3 H, NMe), 2.5−1.6 (m, 6 H), 1.43 (t, 1 H, J = 12.9 Hz, H-8a); NOE difference expt, irradiation of H-5 gave a positive enhancement (+5.8%) for H_b, irradiation of H_b gave a positive enhancement (+6.6%) for H-5 and a strong enhancement (+27.4%) for the geminal proton H_a; molecular mechanics calculations[7] on the energy-minimized structure of **20** gave internuclear distances of 3.32 Å between H-5 and H_b, 4.75 Å between H-5 and H_a; ^{13}C NMR−DEPT ($CDCl_3$) δ CH_3 (57.48, 43.49), CH_2 (69.94, 45.51, 45.22, 43.51, 40.02, 37.21, 20.18), CH (129.05, 127.72, 127.30, 126.78, 126.60, 124.09, 123.98, 120.01, 115.06), quaternary (209.02, 145.80, 143.91, 141.46, 139.01, 127.08, 89.56, 59.69, 58.07); HRMS (FAB) calcd for $C_{27}H_{30}NO_3$ $(M + H)^+$ 416.2226, found 416.2230.

7α Epimer 21: yield 159 mg (5.1%); mp 237−238 °C; TLC R_f 0.35 (3% MeOH and 1% of triethylamine in $CHCl_3$); IR ($CHCl_3$) 1720.0 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 7.25−7.08 (m, 4 H, ArH), 6.77 (d, 1 H, J = 7.7 Hz, H-2), 6.60 (d, 1 H, J = 7.7 Hz, H-1), 4.86 (s, 1 H, H-5), 3.89 (s, 3 H, OMe), 3.60 (d, 1 H, J = 16.3 Hz, H_a of C(spiro)-CH_aH_b-Ar), 3.35 (d, 1 H, J = 16.3 Hz, H_b of C(spiro)-CH_aH_b-Ar), 3.3−3.2 (m, 2 H, H-9, H-10), 3.1−2.7 (m, 4 H, CH_2CH_2), 2.64 (m, 1 H, H-16), 2.42 (s, 3 H, NMe), 2.4−1.6 (m, 6 H), 1.40 (t, 1 H, J = 13.1 Hz, H-8a); NOE difference expt, irradiation of H-5 gave no enhancement for either H_a or H_b of C(spiro)-CH_aH_b-Ar, irradiation of either H_a or H_b gave no enhancement for H-5; molecular modeling calculations[7] for distances between H-5 and H_b and between H-5 and H_a were found to be 4.83 and 5.54 Å, respectively; ^{13}C NMR−DEPT ($CDCl_3$) δ CH_3 (56.67, 42.59), CH_2 (70.24, 46.61, 46.30, 42.59, 39.84, 35.03, 19.51), CH (127.15, 126.61, 126.25, 126.18, 126.00, 124.27, 124.18, 119.43, 114.96), quaternary (207.82, 144.95, 142.53, 141.46, 138.41, 128.28, 90.02, 58.66, 56.57); HRMS (FAB) calcd for $C_{27}H_{30}NO_3$ $(M + H)^+$ 416.2226, found 416.2225.

7*β*-Spirobenzocyclohexylnaltrexone (4). To a rapidly stirred solution of the benzyl ether **16** (600 mg, 1.09 mmol) in 30 mL of dry chloroform (freshly distilled over P_2O_5) at room

temperature was added boron tribromide (1.0 M solution in hexanes, 4.4 mL, 4.4 mmol) via syringe. After the addition, stirring of the reaction mixture was continued at room temperature for 2 h. Methanol (10 mL) was added via syringe to quench the reaction, and the resultant white cloudy mixture was stirred for another 10 min. Saturated aqueous sodium bicarbonate solution (20 mL) was added, and the mixture was stirred for an additional 10 min before being extracted with chloroform (3 × 40 mL). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with 2% methanol in chloroform and a trace amount of ammonia, to afford 310 mg (62%) of the desired product **4** as white needles after crystallization from ethyl acetate−chloroform: mp 232−233 °C; TLC R_f 0.37 (5% methanol in chloroform with a trace amount of ammonia); ^{1}H NMR ($CDCl_3$) δ 7.15−7.08 (m, 4 H, ArH), 6.74 (d, 1 H, J = 8.4 Hz, H-1), 6.60 (d, 1 H, J = 8.4 Hz, H-2), 5.8 (br, 1 H, ArOH), 3.85 (d, 1 H, 17.1 Hz, C(spiro)-C*H*H-Ar), 3.22 (d, 1 H, J = 17.1 Hz, C(spiro)-CH*H*-Ar), 3.14 (d, 1 H, J = 5.4 Hz, H-9), 3.06 (d, 1 H, H-10a), 2.65 (m, 1 H, H-16e), 2.54 (dd, 1 H, H-10e), 2.5−2.1 (m, 10 H), 2.00 (d, 1 H, J = 13.5 Hz, H-8), 1.83 (d, 1 H, J = 13.5 Hz, H-8), 1.50 (dd, 1 H, J = 10.8, 1.5 Hz, H-15a), 0.9−0.7 (m, 1 H, H-19), 0.6−0.4 (m, 2 H, H-21, H-20), 0.14 (m, 2 H, H-21, H-20); ^{13}C NMR ($CDCl_3$) δ 210.29, 143.32, 141.83, 140.36, 138.99, 128.94, 126.49, 126.25, 124.21, 123.91, 123.88, 119.64, 118.14, 89.16, 69.84, 62.18, 59.07, 59.23, 56.23, 51.56, 43.53, 42.41, 41.69, 41.61, 30.10, 22.43, 9.31, 3.90, 3.75; HRMS (FAB) calcd for $C_{29}H_{32}NO_4$ $(M + H)^+$ 458.2331, found 458.2327. The base was converted to its hydrochloride salt. Anal. ($C_{29}H_{31}NO_4$·HCl) C, H, N.

7α-Spirobenzocyclohexylnaltrexone (5). Following the methodology as that described for **4,** the benzyl ether **17** (80 mg, 0.146 mmol) furnished 61 mg (91%) of **5**: mp 227−228 °C; TLC R_f 0.24 (2% MeOH and a trace amount of NH_3 in chloroform); ^{1}H NMR ($CDCl_3$) δ 7.13−7.10 (m, 4 H, ArH), 6.71 (d, 1 H, J = 8.0 Hz, H-2), 6.57 (d, 1 H, J = 8.0 Hz, H-1), 5.7 (br, 1 H, ArOH), 3.50 (d, 1 H, J = 15.6 Hz, C(spiro)-C*H*H-Ar), 3.17 (d, 1 H, J = 15.6 Hz, C(spiro)-CH*H*-Ar), 3.10−3.00 (m, 2 H, H-9, H-10), 2.75−2.25 (m, 11 H), 2.04 (d, 1 H, J = 14.0 Hz, H-8), 1.84 (d, 1 H, J = 14.0 Hz, H-8), 1.53 (dd, 1 H, J = 11.0, 1.7 Hz, H-15a), 1.23 (br, 1 H, OH), 0.9−0.7 (m, 1 H, H-19), 0.57−0.51 (m, 2 H, H-21, H-20), 0.12 (m, 2 H, H-21, H-20); ^{13}C NMR ($CDCl_3$) δ 209.85, 145.10, 142.02, 140.44, 139.02, 129.06, 126.53, 126.45, 124.37, 124.01, 123.98, 119.35, 117.97, 89.02, 70.04, 61.97, 59.67, 55.95, 51.09, 43.62, 42.31, 41.88, 41.81, 29.89, 22.53, 9.69, 3.82, 3.69; HRMS (FAB) calcd for $C_{29}H_{32}NO_4$ $(M + H)^+$ 458.2331, found 458.2335. The base was converted to its hydrochloride salt. Anal. ($C_{29}H_{31}NO_4$·HCl) C, H, N.

7β-Spirobenzocyclohexyloxymorphone (6). The benzyl ether **18** (600 mg, 1.18 mmol), treated in the same way as described for **4,** afforded 420 mg (85%) of **6** as a white solid: mp 242−244 °C; TLC R_f 0.29 (5% MeOH and 1% NH_3 in chloroform); ^{1}H NMR (DMSO-d_6) δ 9.22 (br, 1 H, OH), 7.14−7.05 (m, 4 H, ArH), 6.59 (d, 1 H, J = 8.1 Hz, H-1), 6.56 (d, 1 H, J = 8.1 Hz, H-2), 5.22 (br, 1 H, OH), 5.19 (s, 1 H, H-5), 3.68 (d, 1 H, J = 17.2 Hz, C(spiro)-C*H*H-Ar), 3.28 (d, 1 H, J = 17.2 Hz, C(spiro)-CH*H*-Ar), 3.08 (d, 1 H), 2.82 (d, 1 H, J = 5.4 Hz), 2.6−2.1 (m, 6 H), 2.36 (s, 3 H, CH_3), 2.01−1.91 (m, 3 H), 1.76 (d, 1 H, J = 14.1 Hz, H-8), 1.30 (dd, 1 H, J = 11.4, 3.0 Hz); ^{13}C NMR (DMSO-d_6, TMS as reference) δ 209.31, 144.07, 143.11, 141.76, 140.68, 139.42, 129.21, 126.19, 125.96, 124.12, 123.54, 123.15, 118.93, 117.26, 87.92, 69.52, 63.71, 55.32, 50.16, 44.88, 42.17, 42.10, 41.33, 41.24, 29.63, 21.20; HRMS (FAB) calcd for $C_{26}H_{28}NO_4$ $(M + H)^+$ 418.2018, found 418.2022. Anal. ($C_{26}H_{27}NO_4$) C, H, N.

7α-Spirobenzocyclohexyloxymorphone (7). Using the same methodology as described above, benzyl ether **19** (95 mg, 0.19 mmol) afforded 71 mg (90%) of **7:** mp 238−239 °C; TLC R_f 0.32 (5% MeOH and 1% NH_3 in $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 9.4−9.1 (br, 1 H, OH), 7.18−6.96 (m, 4 H, ArH), 5.22 (br, 1 H, OH), 5.16 (s, 1 H, H-5), 3.42 (d, 1 H, J = 16.4 Hz, C(spiro)-C*H*H-Ar), 3.15 (d, 1 H, J = 16.4 Hz, C(spiro)-CH*H*-Ar), 2.84 (d, 1 H, J = 5.6 Hz), 2.76−2.14 (m, 12 H), 2.05−1.82 (m, 3 H), 1.72 (d, 1 H, J = 14.3 Hz, H-8), 1.26 (dd, 1 H, J = 11.6, 3.2 Hz); ^{13}C NMR (DMSO-d_6, TMS as reference) δ 208.94, 146.01, 145.19, 142.71, 141.95, 140.12, 130.05, 127.24, 127.01, 125.21, 124.63, 124.11, 120.00, 117.98, 88.51, 70.08, 65.07, 57.10, 49.83, 45.04, 42.35, 42.28, 41.66, 41.53, 30.12, 21.02; HRMS (FAB) calcd for $C_{26}H_{28}NO_4$ $(M + H)^+$ 418.2018, found 418.2025. Anal. ($C_{26}H_{27}NO_4$) C, H, N.

7β-Spirobenzocyclohexylhydromorphone (8). To a stirred solution of **20** (500 mg, 1.2 mmol) in 30 mL of dichloromethane at 0 °C was added boron tribromide (1.0 M solution in hexanes, 3.61 mL, 3.61 mmol) via syringe under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min and then for 90 min at ambient temperature. Hydrochloric acid (2 N, 24 mL) was added, and the resulting mixture was then refluxed for 1 h. After cooling to room temperature, the reaction mixture was adjusted to pH 8.5 with aqueous sodium bicarbonate solution and then extracted with chloroform (3 × 80 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residual powder was chromatographed on silica gel, eluting with a mixture of 5% methanol and 1% ammonia in chloroform. Crystallization from methanol−chloroform furnished 210 mg (44%) of **8** as light yellow rods: mp 249−250 °C; TLC R_f 0.20 (5% methanol in chloroform); ^{1}H NMR ($CDCl_3$) δ 8.24 (br, 1 H, OH), 7.3−7.0 (m, 4 H, ArH), 6.72 (d, 1 H, J = 8.1 Hz, H-2), 6.60 (d, 1 H, J = 8.1 Hz, H-1), 4.81 (s, 1 H, H-5), 3.94 (d, 1 H, J = 16.9 Hz, C(spiro)-C*H*H-Ar), 3.67 (d, 1 H, J = 16.9 Hz, C(spiro)-CH*H*-Ar), 3.3−3.2 (m, 2 H), 3.2−2.8 (m, 4 H), 2.63 (dd, 1 H, J = 7.5, 1.0 Hz, H-16), 2.42 (s, 3 H, CH_3), 2.5−1.6 (m, 6 H), 1.44 (t, 1 H, J = 13.0 Hz, H-8a); ^{13}C NMR ($CDCl_3$) δ 209.56, 144.82, 142.54, 140.42, 139.47, 127.63, 127.49, 127.30, 127.15, 125.26, 125.13, 120.80, 119.11, 90.71, 78.15, 59.45, 57.34, 47.54, 47.23, 43.11, 40.85, 40.31, 38.72, 37.17, 35.61, 20.66; HRMS (FAB) calcd for $C_{26}H_{28}NO_3$ $(M + H)^+$ 402.2069, found 402.2075. The base was converted to its hydrochloride salt. Anal. ($C_{26}H_{27}NO_3$·HCl) C, H, N.

7α-Spirobenzocyclohexylhydromorphone (9). Following the procedure as described for **8**, methyl ether **21** (110 mg, 0.265 mmol) furnished 44 mg (42%) of **9** as light yellow crystals from methanol−chloroform: mp 242−243 °C; ^{1}H NMR ($CDCl_3$) δ 7.2−7.0 (m, 4 H, ArH), 6.75 (d, 1 H, J = 7.8 Hz, H-2), 6.62 (d, 1 H, J = 7.8 Hz, H-1), 4.84 (s, 1 H, H-5), 3.62 (d, 1 H, J = 16.2 Hz, C(spiro)-C*H*H-Ar), 3.38 (d, 1 H, J = 16.2 Hz, C(spiro)-CH*H*-Ar), 3.30−3.23 (m, 2 H, H-9, H-10), 3.08−2.75 (m, 4 H, CH_2CH_2), 2.65 (m, 1 H, H-16), 2.45 (s, 3 H, CH_3), 2.4−1.6 (m, 7 H), 1.40 (t, 1 H, J = 13.3 Hz, H-8a); ^{13}C NMR ($CDCl_3$) δ 208.82, 145.08, 141.80, 139.68, 138.73, 126.88, 126.75, 126.59, 126.41, 124.52, 124.39, 120.06, 118.37, 89.97, 78.41, 58.71, 56.60, 46.80, 46.49, 42.37, 40.11, 39.57, 37.98, 36.43, 34.87, 19.92; HRMS (FAB) calcd for $C_{26}H_{28}NO_3$ $(M + H)^+$ 402.2069, found 402.2064. The base was converted to its hydrochloride salt. Anal. ($C_{26}H_{27}NO_3$·HCl) C, H, N.

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References

(1) Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. Application of the Message−Address Concept in the Design of Highly Potent and Selective Non-Peptide δ-Opioid Receptor Antagonists. *J. Med. Chem.* **1988**, *31*, 281−282.

(2) Portoghese, P. S.; Sultana, M.; Takemori, A. E. Design of Peptidomimetic δ Opioid Receptor Antagonists Using the Message−Address Concept. *J. Med. Chem.* **1990**, *33*, 1714−1720.

(3) Takemori, A. E.; Portoghese, P. S. Selective Naltrexone-Derived Opioid Receptor Antagonists. *Annu. Rev. Pharmacol. Toxicol.* **1992**, *32*, 239−269.

(4) Portoghese, P. S.; Moe, S. T.; Takemori, A. E. A Selective δ_1 Opioid Receptor Agonist Derived from Oxymorphone. Evidence for Separate Recognition Sites for δ_1 Opioid Receptor Agonists and Antagonists. *J. Med. Chem.* **1993,** *36*, 2572−2574.

(5) Portoghese, P. S.; Sultana, M.; Moe, S. T.; Takemori, A. E. Synthesis of Naltrexone-Derived δ-Opioid Antagonists. Role of Conformation of the δ Address Moiety. *J. Med. Chem.* **1994**, *37*, 579−585.

(6) Lan, A. J. Y.; Heuckeroth, R. O.; Mariano, P. S. Electron-Transfer-Induced Photocyclization Reactions of Arene−Iminium Salt Systems. Effects of Cation Diradical Deprotonation and Desilylation on the Nature and Efficiencies of Reaction Pathways Followed. *J. Am. Chem. Soc.* **1987**, *109*, 2738−2745.
(7) Biosym Technologies, 9685 Scranton Rd., San Diego, CA 92121−2777.
(8) Rang, H. B. Stimulant Actions of Volatile Anaesthetics on Smooth Muscle. *Br. J. Pharmacol.* **1964**, *22*, 356−365.
(9) Lord, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. Endogenous Opioid Peptides Multiple Agonists and Receptors. *Nature (London)* **1977**, *267*, 495−499.
(10) Portoghese, P. S.; Takemori, A. E. TENA, A selective Kappa Opioid Receptor Antagonist. *Life Sci.* **1985**, *36*, 801−805.
(11) Fournie-Zaluski, M.-C.; Gacel, G.; Maigret, B.; Premilat, S.; Roques, B. P. Structural Requirements for Specific Recognition of Mu or Delta Opiate Receptors. *Mol. Pharmacol.* **1981**, *20*, 484−491.
(12) Werling, L. L.; Zarr, G. D.; Brown S. R.; Cox, B. M. Opioid Binding to Rat and Guinea-Pig Neural Membranes in the Presence of Physiologic Cations at 30 °C. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 722−728.
(13) Hand, B. K.; Lane, A. C.; Lord, J. A. H.; Morgan, B. A.; Rance, M. J. Analogues of β-LPH61-64 Possessing Selective Agonist Activity at μ Opiate Receptors. *Eur. J. Pharmacol.* **1981**, *70*, 531−540.
(14) Yamamura, M. S.; Horvath, R.; Toth, G.; Otvos, F.; Malatynska, E.; Knapp, R. J.; Porreca, F.; Hruby, V. J.; Yamamura, H. I. Characterization of [^{3}H]Naltrindole Binding to Delta Opioid Receptors in Rat Brain. *Life Sci.* **1992**, *50*, PL-119− PL-124.
(15) Lahti, R. A.; Mickelson, M. S.; McCall, J. M.; von Voightlander, P. F. [^{3}H]U-69593, a Highly Selective Ligand for the Kappa Opioid Receptor. *Eur. J. Pharmacol.* **1985**, *109*, 281−284.
(16) Abdelhamid, E. E.; Sultana, M.; Portoghese, P. S.; Takemori, A. E. Selective Blockage of Delta Opioid Receptors Prevents the Development of Morphine Tolerance and Dependence in Mice. *J. Pharmacol. Exp. Ther.* **1991**, *258*, 299−303.
(17) Casey, A. F.; Parfitt, R. T. *Opioid Analgesics: Chemistry and Receptors*; Plenum Press: New York, 1986; Chapter 2, pp 54−61.
(18) Ohkawa, S.; DiGiacomo, B.; Larson, D. L.; Takemori, A. E.; Portoghese, P. S. 7-Spiroindanyl Derivatives of Naltrexone and Oxymorphone as Selective Ligands for Delta Opioid Receptors. *J. Med. Chem.* **1997**, *40*, 1720−1725.
(19) Cheng, Y.-C.; Prusoff, W. H. Relationship between the Inhibition Constant (K_i) and the Concentration of Inhibitor which Causes 50 per cent Inhibition (I_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

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