Synthesis of 7-Arylmorphinans. Probing the "Address" Requirements for Selectivity at Opioid δ Receptors

Peng Gao, Dennis L. Larson, and Philip S. Portoghese*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, 308 Harvard Street S.E., Minneapolis, Minnesota 55455

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Through arylation of 6-keto opiates with diaryliodonium iodide, a series of 7-aryl opiates (**3**−**8**) have been prepared in an effort to investigate the effect of conformational mobility of the δ "address" moiety on opioid agonist and antagonist potencies. Evaluation of the ligands in the mouse vas deferens and guinea pig ileum preparations revealed that they were less potent and less selective than the conformationally constrained ligands, naltrindole (**1**, NTI) and 7-(spiroindanyl)oxymorphone (**2**, SIOM), at δ opioid receptors. It is concluded that the coplanarity of the address moiety with the C ring of the morphinan structure enhances δ antagonist potency and selectivity.

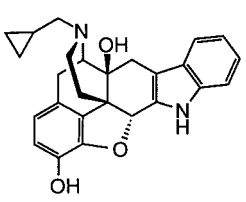
Introduction

At least three major types of opioid receptors (δ, μ, κ) are involved in the modulation of a variety of opioid effects. These receptors have been cloned, and recent studies of mutant and chimeric opioid receptors have provided fresh insight into the molecular basis for recognition of opioid ligands.[1]

The availability of selective antagonists has contributed greatly to opioid receptor classification and to the pharmacologic characterization of a variety of opioid agonists. One approach employed to develop selective nonpeptide opioid ligands has been the application of the message−address concept.[2] In this simple model, the "address" is viewed as a recognition element in the opioid ligand that confers affinity for a specific receptor type, whereas the "message" component is envisaged to be involved in promoting receptor activation.[3] Although the idea of discrete message and address elements has led to the design of selective opioid ligands, it has been useful only in a conceptual context because of the possible overlap in the role of these elements.[4]

The nonpeptide δ-selective opioid receptor antagonist, naltrindole[5] (**1**, NTI), and agonist, spiroindanyloxymorphone[6] (**2**, SIOM), represent examples where this approach was used successfully. Their selectivity has been attributed to the presence of an address element in the form of a benzene moiety attached through a scaffold to the C ring of the morphinan nucleus. This was based on a model that envisages the Phe[4] phenyl group of enkephalin as a key δ address element. The approach also involved the inclusion of conformational constraint using a rigid scaffold attached to an address in an effort to enhance δ opioid receptor selectivity.

In the present study, we have attached a conformationally mobile address moiety to the C-7 position of hydromorphone and naltrexone in order to determine how the potency and selectivity of such ligands (**3**−**8**) compare with those of NTI and SIOM. The results suggest that the conformationally constrained δ address in these ligands may be an important contributor to potency and selectivity.



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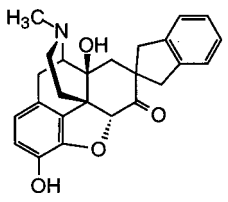

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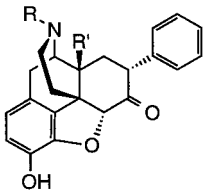
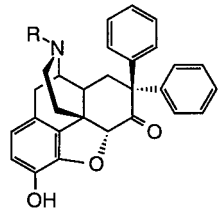
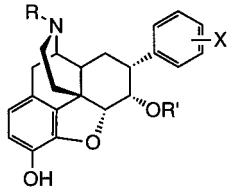


	R	R'
3a	CH_3	H
3b	$CH_2(CH_2)_2$	H
3c	$CH_2(CH_2)_2$	OH



	R
4a	CH_3
4b	$CH_2(CH_2)_2$



	R	R'	X
5a	CH_3	H	H
5b	$CH_2(CH_2)_2$	H	H
6a	CH_3	H	*p*-Br
6b	$CH_2(CH_2)_2$	H	*p*-Br
7a	CH_3	H	*m*-NO_2
7b	$CH_2(CH_2)_2$	H	*m*-NO_2
8a	CH_3	$COCH_3$	H
8b	$CH_2(CH_2)_2$	$COCH_3$	H

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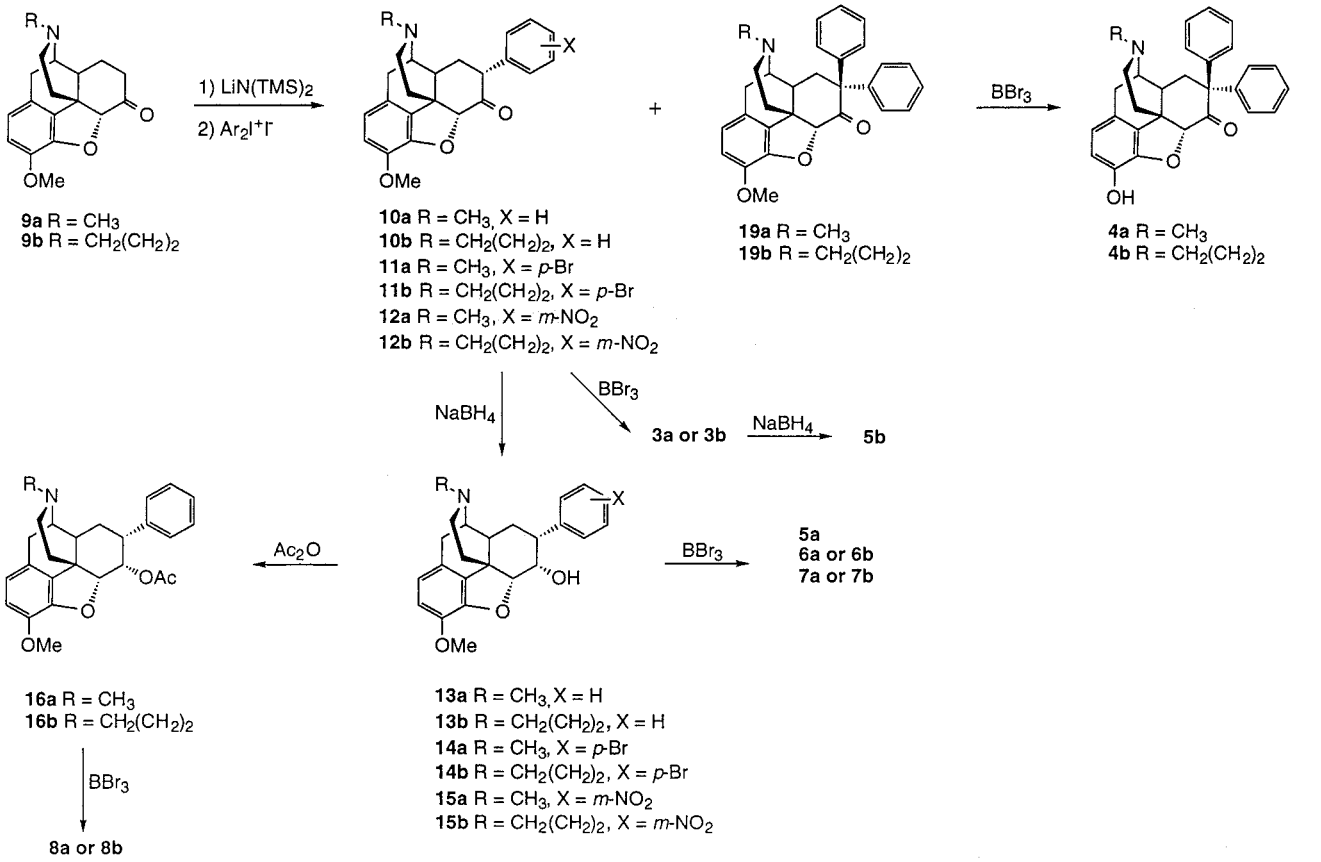
Scheme 1



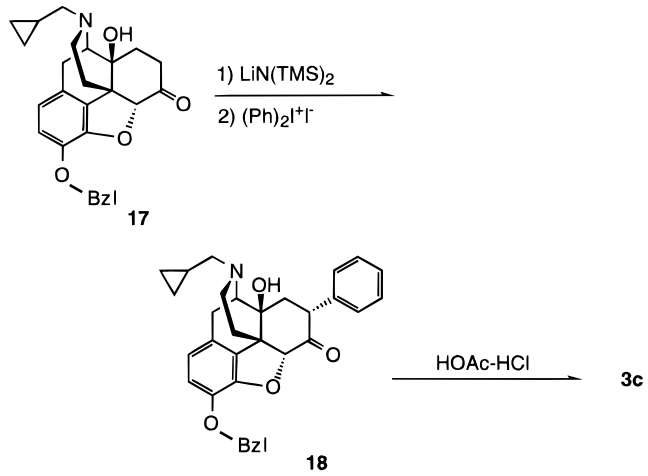
Design Rationale and Chemistry

The benzene moiety (the address) of NTI (**1**) and SIOM (**2**) is conformationally constrained through a pyrrolo or spirocyclopentano "scaffold" that is attached to ring C of the morphinan nucleus. We have investigated the influence of rotational freedom of the address by linking a conformationally mobile phenyl group directly to the C-7 position of hydromorphone and naltrexone. In addition, the 6-keto group was reduced in order to determine its role in selectivity and potency.

The 7-aryl group was incorporated into hydrocodone (**9a**), cyclopropylmethylnorhydrocodone (**9b**), and *O*-benzylnaltrexone (**17**) via a phenylation procedure using diaryliodonium iodide (Schemes 1 and 2).[7] This method provided the desired 7-phenyl intermediates (**10**−**12**, **18**) as major products together with minor amounts of diarylated byproducts (**19a, 19b**). The stereochemistry of the 7-phenyl group was confirmed to be 7α by the positive NOE between the H-5 and H-7 β protons. O-Dealkylation of **10a** and **10b** with BBr_3 provided target compounds **3a** and **3b**, respectively. The naltrexone derivative **3c** was prepared as an analogue of **3b** using a similar procedure (Scheme 2). This involved phenylation of *O*-benzylnaltrexone (**17**) with diphenyliodonium iodide to afford **18**, followed by debenzylation with HCl−HOAc to give **3c**.

Compounds **13**−**15**, which were obtained by the reduction of ketones **10**−**12** with sodium borohydride, were O-demethylated with boron tribromide to afford **5a**, **6a**, **6b**, **7a**, and **7b**. Compound **5b** was prepared through an alternative route by reduction of **3b** with sodium borohydride. The H_6-H_7 coupling constant of

Scheme 2



2.1 Hz indicated that the 6-hydroxy group is cis to the 7-phenyl group. The value of $J_{5,6} = 5.8$ Hz is consistent with the coupling reported in structurally related 6-hydroxy opiates.[8] It appears likely that the C ring is in a chair conformation in view of the stabilizing effect of an equatorial 7-phenyl group.

Alcohols **13a** and **13b** were esterified with acetic anhydride for the preparation of acetate intermediates **16a** and **16b**, respectively. Subsequent treatment of **16a** and **16b** with boron tribromide afforded **8a** and **8b**, respectively. Since H_6-H_7 coupling constant of the alcohols were essentially the same upon acetylation ($J = 2.1$ Hz), the configuration at C-6 and the conformation of the C ring appeared to be unchanged. The 7,7-diphenyl compound **4b** was prepared through the boron

Table 1. Opioid Agonist Activity of 7-Phenyl Opiates in the MVD and GPI

	% max response[a] or IC_{50} (nM)[b]	
compd	MVD	GPI
3a	29.2 ± 2.8% (3)	53.9 ± 2.4% (3)
3b	31.4 ± 9.9% (3)	161 ± 62 nM (3)
3c	30.0 ± 5.1% (3)	−15.1 ± 16.1% (3)[c]
4a	5.4 ± 8.6% (3)	9.7 ± 14.0% (3)
4b	0.0 ± 0.0% (3)	475 ± 121 nM (10)
5a	178 ± 83.1 nM (3)	23.2 ± 2.0% (2)
5b	14.5 ± 6.8% (3)	58.9 ± 4.0 nM (3)
6a	15.2 ± 4.7% (3)	10.0 ± 5.4% (3)
6b	22.4 ± 10.4% (3)	39.2 ± 14.3% (3)
7a	56.1 ± 7.9% (4)	49.3 ± 9.1% (5)
7b	26.8 ± 5.6% (3)	28.3 ± 16.4 nM (3)
8a	34.3 ± 1.8% (3)	24.0 ± 7.9% (3)
8b	21.1 ± 8.6% (3)	118 ± 70.1 nM (6)

[a] Percent of maximal response (±SE) at 1 μM unless otherwise noted. [b] The IC_{50} is the concentration of the agonist required for half-maximal response of the preparation. [c] Negative sign means that the twitch amplitude was enhanced in the present of the test compound.

tribromide O-demethylation of **19b** using a procedure similar to that reported[9] for the corresponding hydrocodone analogue **4a**.

Biological Results

Smooth Muscle Preparation. Hydrochloride salts of the target compounds were tested for opioid agonist and antagonist activity in the electrically stimulated mouse vas deferens[10] (MVD) and the guinea pig ileal longitudinal muscle[11] (GPI) preparations. For determination of antagonist activity, the ligands (100 nM) were incubated with the preparation for 15 min prior to testing with the standard agonists, [D-Ala^2,D-Leu^5]-enkephalin[12] (DADLE), morphine, or ethylketazocine (EK). These agonists are pharmacologically selective for δ, μ, and κ receptors, respectively. DADLE was employed in the MVD; morphine and EK were used in the GPI. When the test compound was found to be weakly active as an agonist, it was incubated with the smooth muscle preparation at a single concentration (1 μM) to determine the maximal agonist response. When a compound was found to be a full agonist, four to six concentrations of the test compound were employed to construct a concentration−response curve which was compared to that of a standard agonist in the same preparation. The opioid antagonist potency was expressed as an IC_{50} ratio, which represents the IC_{50} of the standard agonist in the presence of the tested compound (100 nM) divided by the control IC_{50} of the standard agonist above.

In the GPI, compounds **3b**, **4b**, **5b**, **7b**, and **8b** were found to be full agonists, with IC_{50} values ranging from 28 to 475 nM, and in this regard, compound **7b** was the most active (Table 1). In the MVD, only **5a** possessed full agonist activity (IC_{50} = 178 nM). The remaining compounds displayed either partial agonist activity or, in one case (**3c**), an enhanced electrically stimulated twitch of the GPI.

Evaluation of antagonist activity (Table 2) showed that the *N*-methyl compounds were inactive when tested against DADLE, morphine, or EK. On the other hand, several ligands in the *N*-cyclopropylmethyl series (**3b**, **3c**, **4b**) antagonized DADLE, with the most potent (**4b**) having an IC_{50} ratio of 63. Interestingly, **4b** exhibited full agonist activity in the GPI which probably is μ receptor-mediated in view of its higher affinity for μ (K_e = 0.11 ± 0.15 nM) relative to κ (K_i = 7.58 ± 1.36 nM) receptors. With the notable exception of **3c** (morphine IC_{50} ratio, 17), none of the compounds possessed significant antagonism for morphine or EK in the GPI.

Table 2. Opioid Antagonist Activity of 7-Phenyl Opiates in the MVD and GPI

	IC_{50} ratio		
compd	DADLE[a] (δ)	morphine[b] (μ)	EK[b] (κ)
1 (NTI)[c]	K_e = 0.13 nM[d]	K_e = 29 nM	K_e = 46 nM
3a	0.97 ± 0.2 (3)	1.05 ± 0.17 (3)	0.75 ± 0.2 (3)
3b	17.6 ± 4.6 (3) (K_e = 5.9nM)	*e*	*e*
3c	34.6 ± 8.5 (3) (K_e = 3 nM)	17.3 ± 4.3 (6) (K_e = 6 nM)	3.9 ± 0.9 (7) (K_e = 34 nM)
4a	2.34 ± 0.60 (3)	1.69 ± 0.42 (3)	1.01 ± 0.31 (3)
4b	63.2 ± 11.3 (6) (K_e = 1.6 nM)	*e*	*e*
5a	*e*	1.85 ± 1.1 (2)	1.9 ± 0.5 (2)
5b	3.03 ± 0.72 (5)	*e*	*e*
6a	1.17 ± 0.29 (4)	1.20 ± 0.42 (3)	1.76 ± 0.40 (3)
6b	9.07 ± 1.63 (4)	1.38 ± 0.35 (3)	1.22 ± 0.72 (3)
7a	0.99 ± 0.05 (3)	0.34 ± 0.11 (3)	1.05 ± 0.09 (3)
7b	4.17 ± 0.9 (10)	*e*	*e*
8a	1.02 ± 0.42 (3)	0.90 ± 0.30 (3)	1.08 ± 0.42 (3)
8b	6.38 ± 0.42 (3)	*e*	*e*

[a] Tested in the MVD preparation. [b] Tested in the GPI. [c] Data from ref 5. [d] K_e (nM) = [antagonist]/(IC_{50} ratio − 1). [e] Not tested due to agonist activity.

Table 3. Antagonism by **4b** of the Antinociceptive Effect of Opioid Agonists in Mice

		ED_{50}, nmol/mouse or μmol/kg		
agonist	selectivity	control	treated[a]	ED_{50} ratio[b]
DPDPE[c]	δ_1	8.1 (5.9−11.2)	27.9 (18.1−41.9)	3.5 (2.0−5.9)
DSLET[c]	δ_2	0.7 (0.5−0.9)	2.6 (2.0−3.2)	3.7 (2.6−5.0)
morphine[d]	μ	9.1 (0.4−12.6)	15.7 (9.7−23.3)	1.7 (1.0−3.1)
U50,488[d]	κ	27.5 (4.8−63.2)	22.4 (1.9−44.8)	0.8 (0.1−2.9)

[a] Treated icv with 20 nmol of **4b**. [b] Treated ED_{50} divided by control ED_{50}. [c] Administered icv; ED_{50} values expressed as nmol/mouse. [d] Administered sc; ED_{50} values expressed as μmol/kg.

In Vivo Testing. The most potent antagonist (**4b**) in this series was tested using the tail flick procedure in mice.[13] Administration of **4b** (20 nmol icv) with standard agonists was timed so that the peak effect (45 min) coincided with the center of the observation period. The ED_{50} values of the standard agonists, [D-Pen^2,D-Pen^5]enkephalin (DPDPE; δ_1),[14] [D-Ser^2,Leu^5]enkephalin-Thr^5 (DSLET; δ_2),[15] morphine (μ), and (±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide[16] (U50,488; κ), were then determined and expressed as ED_{50} ratios (treated/control). As indicated in Table 3, **4b** antagonized DPDPE and DSLET equally and to a greater extent than morphine. No antagonism was noted for U50,488. Thus, although **4b** is apparently δ-selective in vivo, it does not distinguish between the putative δ_1 and the δ_2 receptors.[17,18]

Discussion

With NTI (**1**), the aromatic δ address moiety is conformationally constrained due to fusion with ring C of the morphinan structure. This conformational rigidity may be a contributing factor in the approximately 20-fold greater antagonist potency of NTI at δ receptors relative to its analogue, 7-phenylnaltrexone (**3c**). Although the equatorial 7-phenyl group of **3c** (Figure 1)

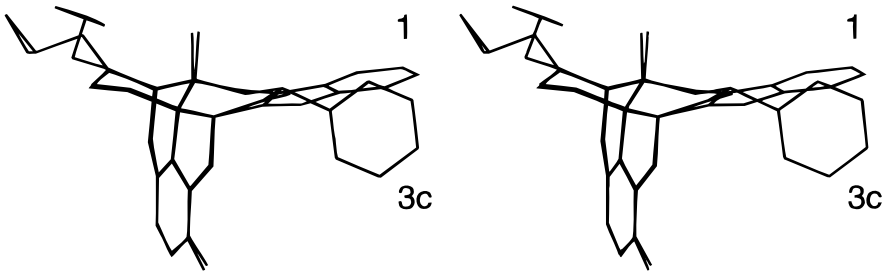


Figure 1. Superposition of the low-energy conformers of NTI **1** and 7-phenylnaltrexone (**3c**).

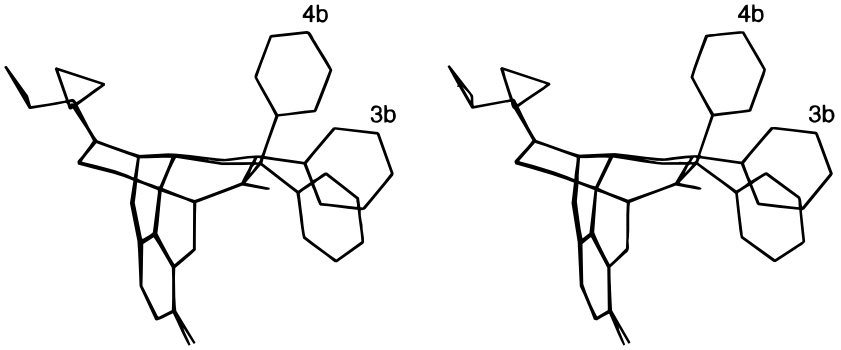


Figure 2. Superposition of the low-energy conformers **3b** and **4b**.

is conformationally mobile, its rotamer population prefers an orthogonal-like population with respect to the plane of ring C of the morphinan structure due to steric hindrance between the phenyl group ortho protons and the vicinal carbonyl and methylene groups. It appears likely that the lack of coplanarity between ring C and the address moiety is the principal reason for the lower δ antagonist potency of **3c**. This is consistent with the significantly lower δ antagonist potency of 7-spiroindanyl and spirobenzocyclohexyl derivatives of naltrexone.[19,20] In these cases the reduced potency was attributed to the fact that the plane of the address moiety is perpendicular rather than coplanar to ring C as in NTI.

The δ antagonist selectivity of 7-phenylnaltrexone (**3c**) is 2 orders of magnitude less than that of NTI due to its lower potency at δ receptors and greater potency at μ and κ receptors. The fact that **3c** more potently antagonizes μ and κ agonists compared to NTI may be explained by the greater conformational mobility of its address. In this regard, it has been reported that the selectivity of NTI is due to increased affinity for δ receptors conferred by its address and to decreased affinity for non-δ receptors as a consequence of steric interactions.[21] Thus, the greater potency of **3c** at μ and κ receptors relative to that of NTI may be due to the possibility that its 7-phenyl group can more easily be accommodated because of its conformational mobility.

In the present study we have found that 7-phenylhydromorphone (**3a**) was inactive as an antagonist or as a full agonist in smooth muscle preparations. These results are in harmony with a related study which revealed that the 14-hydroxyl group is of critical importance for the δ agonist potency of SIOM (**2**).[22] Moreover, the finding that the cyclopropylmethyl analogue **3b** is less potent than its naltrexone analogue **3c** is consistent with the finding that the 14-hydroxyl group contributes to the δ antagonist potency of NTI. It is noteworthy that the 14-hydroxyl group also enhances the opioid antagonist activity of naltrexone.[23] This similarity in the structure−activity relationship suggests that there may be some common structural features at the antagonist recognition site of μ and δ receptors or that some common physicochemical factor conferred by the 14-hydroxy group facilitates access to the recognition sites.

The *gem*-diphenyl compound **4b** was of interest because of its unusual pharmacologic profile in smooth muscle preparations. It was the most potent δ opioid antagonist in the series when tested against DADLE in the MVD (K_e = 1.6 nM), whereas it functioned as a weak, full agonist in the GPI. One possible explanation for the greater antagonist potency relative to its monophenyl analogue **3b** is that the β-phenyl group of **4b** induces its geminal partner to assume a conformation that is more coplanar with ring C. This is illustrated in Figure 2 with superposition of the low-energy conformers of **3b** and **4b**.

The remaining members of the series (**5**−**8**) exhibited only feeble antagonist activity. However, several of the cyclopropyl derivatives (**5b**, **7b**, **8b**) possessed moderate agonist potencies in the GPI, and the *N*-methyl compound **5a** was a full agonist in the MVD. Of these compounds, only **5a** appeared to be a selective δ agonist, as it was found to be inactive in the GPI. This was surprising in view of the finding[22] that the 14-hydroxyl group is critical for the δ agonist activity of SIOM (**2**). Although **3a** is closely strucurally related to **5a**, it is not a full agonist in either of the smooth muscle preparations. There is no obvious explanation as to why substituting an hydroxyl for a ketone group should make such a dramatic difference in activity, aside from the possibility that the 6-hydroxy group may function as a hydrogen bonding donor in altering the mode of interaction with the δ receptor.

In conclusion, the attachment of a phenyl group to the C-7 position of naltrexone to afford **3c** changed antagonist selectivity from μ to δ. This change presumably is due to the aromatic group which functions as a

δ address in a fashion similar to that of NTI (**1**). The substantially lower δ selectivity of **3c** is attributed to the substantially greater conformational mobility and lack of coplanarity of its 7-phenyl group when compared to the rigidly held benzene moiety in NTI.

Some congeners in the series (i.e., **3b**, **4b**) appeared to possess mixed agonist-antagonist activity in vitro. If the agonist component is mediated through μ receptors, they could be leads for the development of analgesics devoid of abuse potential, in view of reports[24−26] that δ antagonists block the tolerance and physical dependence of morphine without antagonizing antinociception.

Experimental Section

Reagents were obtained from Aldrich Chemical Co. unless otherwise noted. Hydrocodone bitartrate and naltrexone hydrochloride were obtained from Mallinckrodt. All the reactions were conducted under nitrogen (N_2) unless specified. Column chromatography was performed with silica gel (200−400 mesh, Aldrich). Thin-layer chromatography was performed on E. Merck silica gel 60 F-254 0.25 nm plates and visualized with UV light or iodine vapor. Centrifugal preparative chromatography was performed on silica gel (EM Science silica gel 60, PF254) layered on glass rotor plates and a Chromatotron apparatus (Harrison Research, model 7924T, Palo Alto, CA). Chromatographic solvent systems are reported as volume/volume ratios. IR spectra were recorded on a Nicolet 5DXC FT-IR instrument. NMR data were collected on a GE Omega 300 MHz or Varian 500 MHz spectrometer at room temperature (18−20 °C). The δ (ppm) scale was in reference to the deuterated solvent, and coupling constants are reported in hertz. Mass spectra were obtained on a Finnigan 4000 or a VG707EHF spectrometer. Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratory (Phoenix, AZ) and are within ±0.4% of theoretical values.

***N*-(Cyclopropylmethyl)-7α-phenylnorhydrocodone (10b).** Hexamethyldisilazane (HMDSA) (0.9 mL, 2.88 mmol) was mixed with THF (25 mL) at −78 °C under nitrogen. A solution of *n*-butyllithium (1.2 mL, 2.88 mmol, 2.5 M in hexane) was added over a 5 min period, and the resulting solution was stirred for another 10 min. *N*-(Cyclopropylmethyl)norhydrocodone (**9b**)[27] (740 mg, 2.18 mmol) in THF (25 mL) was added, and stirring was continued at −78 °C for 30 min. The resulting solution was transferred to a mixture of diphenyliodonium iodide[28] (700 mg, 1.7 mmol) in 55 mL of DMF at −45 °C. The final mixture was stirred at −45 °C for 2 h and then was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (60 mL) and extracted with chloroform (3 × 50 mL). The extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was taken up in a small amount of CH_2Cl_2, applied to a silica gel rotor plate (2 mm layer), and eluted with $CHCl_3$−EtOH−NH_4OH (98:1:1) to afford **10b** (366 mg, 40%): mp 275 °C dec (hydrochloride salt); ^{1}H NMR ($CDCl_3$) δ 7.20−7.24 (m, 3 H, H-Ar), 6.93−6.94 (m, 2 H, H-Ar), 6.71−6.93 (2d, 2H, J = 8.1, H-1and H-2), 4.94 (s, 1 H, H-5), 4.19 (s, 3 H, OCH_3), 3.46−3.94 (m, 2 H, H-7 and H-10), 3.27 (m, 1H, H-10), 2.58 (m, 1 H, H-9), 2.14 (m, 1 H, H-8), 2.00 (m, 1 H, H-14), 0.81 (m, 1 H, H-19), 0.65−0.67 (m, 2 H, H-20 and H-21), 0.40−0.42 (m, 2 H, H′-20 and H′-21); ^{13}C NMR ($CDCl_3$) δ 3.73, 3.94, 8.83, 20.60, 33.16, 34.88, 41.88, 45.26, 47.61, 54.83, 56.62, 56.83, 59.48, 91.96, 115.22, 119.63, 126.95, 128.07, 128.33, 136.69, 142.81, 145.25, 205.49; MS (FAB) *m*/*z* 416 $[M + H]^+$.

7α-(*p*-Bromophenyl)hydrocodone (11a). Using the same procedure as described for **10b** above, hydrocodone (**9a**) (300 mg, 1.0 mmol) was reacted with LiHMDSA [prepared from hexamethyldisilazane (0.42 mL, 2.0 mmol) and *n*-butyllithium (0.60 mL, 1.5 mmol, 2.5 M in hexane)] and 4,4′-dibromophenyliodonium iodide[29] (960 mg, 1.7 mmol) in 40 mL of DMF at −78 °C, followed by centrifugal chromatography using $CHCl_3$−EtOH−NH_4OH (98:1:1), affording **11a** (330 mg, 72%): mp 189−191 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2H, J = 6.6, H-ArBr), 6.86 (d, 2H, J = 6.6, H-ArBr), 6.68−6.78 (2d, 2H, J = 8.1, H-1 and H-2), 4.87 (s, 1H, H-5), 3.93 (s, 3H, O-Me), 3.66−3.70 (m, 1H, H-7α), 3.38 (m, 1H, H-9), 3.07 (d, 1H, J = 18.6, H-10), 1.52−1.66 (q, 1H, J = 12.9, H-8α); MS (FAB) *m*/*z* 454 $[M + H]^+$.

***N*-(Cyclopropylmethyl)-7α-(*p*-bromophenyl)norhydrocodone (11b).** Using the same procedure described above for **10b**, compound **9b**[27] (1.10 g, 3.3 mmol) was reacted with LiHMDSA [prepared from HMDSA (1.35 mL, 6.3 mmol) in THF (10 mL), *n*-butyllithium (2.0 mL, 4.8 mmol, 2.4 M in hexane)] and 4,4′-dibromophenyliodium iodide[29] (2.0 g, 3.54 mmol) in DMF (100 mL). The crude product was purified by column chromatography on silica gel (70 g), eluting with EtOH (2%) in $CHCl_3$ to afford **11b** (0.51 g, 31%): ^{1}H NMR ($CDCl_3$) δ 7.37−7.38 (d, J = 8.4, 2H, H-Ar), 6.85−6.88 (d, J = 8.4, 2H, H-Ar), 6.63−6.75 (2d, J = 8.1, 2H, H-1and H-2), 4.85 (s, 1H, H-5), 3.92 (s, 3H, O-Me), 3.36−3.67 (dd, J = 3.6, 13.5, 1H, H-7), 3.58 (m, 1H, H-9), 2.95 (d, J = 18.0, 1H, H-10), 0.90 (m, 1H, H-19), 0.54−0.57 (m, 2H, H-20 and H-21), 0.15−0.19 (m, 2H, H′-20 and H′-21); MS (FAB) *m*/*z* 494 $[M + H]^+$, 492 $[M - H]^-$.

7α-(*m*-Nitrophenyl)hydrocodone (12a). Following the procedure described for **10b,** compound **9a** (320 mg, 1.06 mmol) was treated with LiHMDSA [from HMDSA (0.42 mL, 2.0 mmol), *n*-butyllithium (0.60 mL, 1.5 mmol, 2.5 M in hexane)] and 3,3′-dinitrophenyliodonium iodide[28,29] (800 mg, 1.6 mmol) in DMF (60 mL), followed by centrifugal chromatography using 3% ethanol in chloroform, to afford 205 mg (45%) of **12a**: mp 221−225 °C; ^{1}H NMR ($CDCl_3$) δ 8.09−8.12 (dd, 1H, J = 2.4, 8.1, H-$ArNO_2$), 7.86−7.87 (m, 1H, H-$ArNO_2$), 7.43−7.48 (dd, 1H, J = 4.5, 8.1, H-$ArNO_2$), 7.32−7.36 (dd, 1H, J = 1.5, 6.6, H-$ArNO_2$), 6.72−6.80 (2d, 2H, J = 6, H-1and H-2), 4.93 (s, 1H, H-5), 3.92 (s, 3H, O-Me), 3.83−3.9 (m, 1H, H-7α), 3.39 (m, 1H, H-9), 3.11 (d, 1H, J = 18.9, H-10), 2.05−2.12 (m, 1H), 1.9−1.94 (m, 1H), 1.62−1.75 (m, H-8); MS (FAB) *m*/*z* 421 $[M + H]^+$.

***N*-(Cyclopropylmethyl)-7α-(*m*-nitrophenyl)norhydrocodone (12b).** Using the procedure of **10b**, compound **9b**[27] (0.98 g, 2.88 mmol) was reacted with LiHMDSA [prepared from HMDSA (1.34 mL, 6.3 mmol), *n*-butyllithium (1.95 mL, 4.7 mmol, 2.4 M in hexane) in THF], and the mixture was added to 3,3′-dinitrophenyliodium iodide[28,29] (1.80 g, 3.6 mmol) in DMF (100 mL). The product was purified through a silica gel column (70 g), eluting with EtOH (3%) in $CHCl_3$ to afford **12b** (220 mg, 17%): ^{1}H NMR ($CDCl_3$) δ 8.07−8.11 (m, 1H, H-$ArNO_2$), 7.87−7.88 (m, 1H, H-$ArNO_2$), 7.41−7.47 (m, 1H, H-$ArNO_2$), 7.32−7.34 (m, 1H, H−$ArNO_2$), 6.66−6.76 (2d, J = 8.4, 2H, H-1 and H-2), 4.89 (s, 1H, H-5), 3.92 (s, 3H, O-Me), 3.78−3.84 (dd, J = 4.2, 13.2, 1H, H-7), 3.55−3.56 (m, 1H, H-9), 2.95−3.01 (d, 1H, H-10), 0.85 (m, 1H, H-19), 0.51−0.57 (m, 2H, H-20 and H-21), 0.13−0.17 (m, 2H, H′-20 and H′-21).

17-(Cyclopropylmethyl)-3-hydroxy-4,5α-epoxy-7α-phenylmorphinan-6-one (3b). To a solution of *N*-(cyclopropylmethyl)-7α-phenylnorhydrocodone (**10b**) (0.64 g, 1.54 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added boron tribromide (6.0 mL, 1 M in CH_2CH_2) over 10 min. The mixture was stirred at 0 °C for 1 h, methanol (12 mL) was added, and the mixture was stirred for another hour. The reaction mixture then was adjusted with saturated aqueous $NaHCO_3$ to pH 8 and extracted with chloroform (4 × 30 mL). The chloroform extract was washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the crude base. This was taken up in a small amount of chloroform and applied to a silica gel rotor plate (2 mm layer) and eluted with 2% ethanol in chloroform to afford pure **3b** base (360 mg, 58%): ^{1}H NMR ($CDCl_3$) δ 7.12−7.23 (m, 3H, H-Ph), 6.94−6.99 (m, 2H, H-Ph), 6.52−6.64 (2d, 2H, J = 7.8, H-1 and H-2), 3.94 (s, 1H, H-5), 3.90−3.96 (dd, 1H, J = 3.6, 14.2, H-7), 3.44−3.50 (m, 1H, H-9), 0.81−0.88 (m, 1H, H-19), 0.42−0.50 (m, 2H, H-20 and H-21), 0.08−0.12 (m, 2H, H′-20 and H′-21); MS (FAB) *m*/*z* 402 $[M + H]^+$. Treatment of the base in methanol with

ethereal HCl gave **3b·HCl**, which was crystallized from MeOH−Et_2O, mp 201−205 °C. Anal. ($C_{23}H_{25}NO_3$·HCl) C, H, N.

17-(Cyclopropylmethyl)-3,6α-dihydroxy-4,5α-epoxy-7α-phenylmorphinan (5b). A mixture of **3b** (260 mg, 0.648 mmol), $NaBH_4$ (450 mg, 11.7 mmol), and EtOH (45 mL) was stirred for 22 h at room temperature. Acetone (20 mL) was added to quench the reaction, and the resulting mixture was stirred for an additional 20 min and filtered. The filtrate was concentrated and mixed with chloroform (2 mL), and the mixture was applied to a silica gel rotor plate (2 mm) and eluted with EtOH (3.8%) in $CHCl_3$ to afford **5b** (167 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 7.10−7.26 (m, 5H, H-Ph), 6.53−6.65 (2d, 2H, J = 8.4, H-1and H-2), 4.57 (d, J = 5.7, 1H, H-5), 4.05−4.07 (dd, 1H, J = 1.5, 5.7, H-6), 3.46−3.47 (m, 1H, H-9), 2.91 (d, 1H, J = 18.3, H-10β), 2.60−2.65 (m, 1H, H-7), 2.31−2.55 (m, 3H, H-10α, H-14, H-17), 1.50−1.74 (m, 1H, H-8α), 1.39−1.44 (m, 1H, H-8β), 1.82−1.94 (m, 1H, H-19), 0.48−0.53 (m, 2H, H-20 and H-21), 0.12−0.13 (m, 2H, H′-20 and H′-21); ^{13}C NMR (CD_3COCD_3) δ 4.80 (s), 4.78 (s), 9.83 (t), 21.50 (s), 23.99 (s), 37.59 (s), 42.65 (q), 44.11 (t), 46.14 (t), 46.73 (s), 57.99 (t), 60.66 (s), 72.61 (t), 91.54 (t), 118.38 (t), 120.12 (t), 125.82 (q), 127.38 (t), 128.95 (t), 128.99 (t), 131.06 (q), 138.60 (q), 143.47 (q), 145.86 (q). Compound **5b** (63 mg, 0.156 mmol) was dissolved in chloroform (2 mL) and treated with ethereal HCl to furnish a solid, which was crystallized from MeOH−Et_2O to afford **5b·HCl** (60 mg, 87%): mp 240 °C dec; MS (FAB) m/z 404 [M + H]$^+$. Anal. ($C_{26}H_{29}NO_3$·HCl) C, H, N, Cl.

Compounds **13a**−**15b** were prepared using the same procedure as described for **5b** above, except for differences noted:

17-Methyl-3-methoxy-4,5α-epoxy-7α-phenylmorphinan-6α-ol (13a). The reaction between 7α-phenylhydrocodone[7] (**10a**) (120 mg, 0.32 mmol) and $NaBH_4$ (200 mg, 5.2 mmol) in EtOH (8 mL) afforded **13a** (106 mg, 87%): mp 84−86 °C; ^{1}H NMR ($CDCl_3$) δ 7.08−7.28 (m, 5H, H-Ph), 6.65−6.74 (2d, J = 8.4, 2H, H-1 and H-2), 4.72 (d, J = 6.0, 1H, H-5), 4.18−4.20 (m, 1H, H-6), 3.85 (s, 3H, O-Me), 3.12−3.15 (m, 1H, H-9), 3.06 (d, J = 18.3, 1H, H-10β), 2.69−2.73 (m, 1H, H-7), 2.44−2.50 (m, 1H, H-10α), 2.43 (m, 3H, N-Me), 2.37−2.43 (m, 1H, H-14), 1.43−1.48 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 20.92 (s), 23.79 (s), 37.55 (s), 43.11 (q), 43.54 (p), 44.94 (t), 46.05 (t), 48.09 (s), 56.89 (p), 60.46 (t), 72.33 (t), 91.40 (t), 113.69 (t), 119.99 (t), 126.84 (q), 128.74 (t), 128.82 (t), 128.83 (t), 131.25 (q), 142.32 (q), 143.66 (q), 146.88 (q).

17-Methyl-3-methoxy-4,5α-epoxy-7α-(*p*-bromophenyl)-morphinan-6α-ol (14a). A mixture of **11a** (440 mg, 0.97 mmol) and $NaBH_4$ (750 mg, 19.5 mmol) in EtOH (35 mL) afforded crude **14a** (445 mg, 99%), which was used directly for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 7.35−7.38 (d, J = 9.0, 2H, H-Ar), 7.04−7.07 (d, J = 9.0, 2H, H-Ar), 6.67−6.75 (2d, J = 7.8, 2H, H-1 and H-2), 4.71 (d, J = 5.7, 1H, H-5), 4.13−4.16 (m, 1H, H-6), 3.85 (s, 3H, O-Me), 3.20 (m, 1H, H-9), 3.07 (d, J = 18.3, 1H, H-10), 2.47 (s, 3H, N-Me); MS (FAB) m/z 456 [M + H]$^+$.

17-(Cyclopropylmethyl)-3-methoxy-4,5α-epoxy-7α-(*p*-bromophenyl)morphinan-6α-ol (14b). Compound **11b** (480 mg, 0.97 mmol) and $NaBH_4$ (750 mg, 19.5 mmol) in EtOH (35 mL) gave **14b** (485 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.34−7.37 (d, J = 8.4, 2H, H-Ar), 7.04−7.07 (d, J = 8.4, 2H, H-Ar), 6.64−6.74 (2d, J = 8.7, 2H, H-1 and H-2), 4.71 (d, J = 5.4, 1H, H-5), 4.14−4.16 (m, 1H, H-6), 3.85 (s, 3H, O-Me), 3.45 (m, 1H, H-9), 2.96 (d, J = 18.3, 1H, H-10), 0.85 (m, 1H, H-19), 0.52−55 (m, 2H, H-20 and H-21), 0.14−0.17 (m, 2H, H′-20 and H′-21); MS (FAB) m/z 496 [M + H]$^+$.

17-Methyl-3-methoxy-4,5α-epoxy-7α-(*m*-nitrophenyl)-morphinan-6α-ol (15a). Compound **12a** (123 mg, 0.29 mmol) treated with $NaBH_4$ (250 mg, 6.5 mmol) in EtOH (15 mL) furnished **15a** (124 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 8.06−8.07 (m, 2H, H-Ar), 7.50−7.54 (m, 1H, H-Ar), 7.40−7.46 (m, 1H, H-Ar), 6.70−6.80 (2d, 2H, J = 9.1, H-1 and H-2), 4.74 (d, J = 5.4, 1H, H-5), 4.20 (m, 1H, H-6), 3.86 (s, 3H, O-Me), 3.30 (m, 1H, H-9), 3.09 (d, 1H, J = 19.7, H-10α), 2.53(s, 3H, N-Me); MS (FAB) m/z 422 [M + H]$^+$, m/z 420 [M − H]$^-$.

17-(Cyclopropylmethyl)-3-methoxy-4,5α-epoxy-7α-(*m*-nitrophenyl)morphinan-6α-ol (15b). A mixture of compound **12b** (220 mg, 0.476 mmol) and $NaBH_4$ (390 mg, 10.1 mmol) in EtOH (40 mL) afforded **15b** (220 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 8.01−8.07 (m, 2H, H-Ar), 7.38−7.54 (m, 2H, H-Ar), 6.65−6.74 (2d, 2H, J = 8.4, H-1 and H-2), 4.72 (d, J = 6.0, 1H, H-5), 4.09−4.19 (m, 1H, H-6), 3.84 (s, 3H, O-Me), 3.42 (m, 1H, H-9), 2.96 (d, 1H, J = 18.3, H-10α), 0.83 (m, 1H, H-19), 0.50−0.52 (m, 2H, H-20 and H-21), 0.10−0.15 (m, 2H, H′-20 and H′-21); MS (FAB) m/z 463 [M + H]$^+$.

The following compounds (**4b**, **5a, 6a**−**8b)** were prepared using compounds described herein as precursors and the same procedure as described for **3b** above, except for differences noted:

17-(Cyclopropylmethyl)-3-hydroxy-4,5α-epoxy-7,7-diphenylmorphinan-6-one (4b). Compound **19b** (210 mg, 0.42 mmol) treated with boron tribromide (1.8 mmol) by this procedure furnished **4b**, 29 mg (14%) after centrifugal chromatography using EtOAc−hexanes (1:3): ^{1}H NMR ($CDCl_3$) δ 7.08−7.46 (m, 8H, H-Ph), 6.63−6.75 (2d, J = 7.8 Hz, 2H, H-1 and H-2), 6.54−6.57 (m, 2H, H-Ph), 4.96 (s, 1H, H-5), 3.63 (m, 1H, H-9), 2.99 (d, J = 18.3 Hz, 1H, H-10); MS (FAB) m/z 478 [M + H]$^+$. The base in $CHCl_3$ was treated with ethereal HCl, and after removal of the solvent, the residual solid was crystallized from i-PrOH−Et_2O to afford the hydrochloride salt, mp 226 °C. Anal. ($C_{32}H_{31}NO_3$·HCl·H_2O) C, H, N.

17-Methyl-4,5α-epoxy-7α-phenylmorphinan-3,6α-diol (5a). Obtained from **13a** (378 mg, 1.0 mmol) in 50% yield, using 9% EtOH in chloroform as the chromatography eluant: ^{1}H NMR (CD_3COCD_3) δ 7.01−7.20 (m, 5H, H-Ph), 6.52−6.70 (2d, 2H, J = 8.1, H-1 and H-2), 4.37 (d, J = 6.0, 1H, H-5), 3.39−3.46 (dd, 1H, J = 6.0, 11.5, H-6), 3.05−3.08 (m, 1H, H-9), 2.96 (d, 1H, J = 18.3, H-10), 2.31 (s, 3H, NMe), 2.24−2.39 (m, 2H, H-14, H-10), 1.20−1.32 (m, 1H, H-8α); ^{13}C NMR (CD_3-$COCD_3$) δ 18.61 (s), 20.64 (s), 24.21 (s), 37.44 (q), 41.87 (p), 42.89 (t), 44.40 (t), 45.89 (t), 47.82 (s), 57.43 (t), 60.29 (t), 71.94 (t), 91.26 (t), 117.47 (t), 118.91 (t), 125.38 (q), 126.36 (t), 128.27 (t), 131.12 (t), 138.93 (q), 144.95 (q), 146.40 (q); MS (FAB) m/z 364 [M + H]$^+$. The base **5a** (158 mg, 0.419 mmol) was dissolved in chloroform (5 mL) and treated with Et_2O−HCl (8 mL) to give a solid, which was crystallized from MeOH−Et_2O to afford **5a·HCl** (165 mg, 95%), mp > 240 °C. Anal. ($C_{23}H_{25}$-NO_3·HCl) C, H, N, Cl.

17-Methyl-4,5α-epoxy-7α-(*p*-bromophenyl)morphinan-3,6α-diol (6a). Obtained from **14a** (445 mg, 0.96 mmol) in 34% yield (145 mg) and using 10% EtOH in chloroform as the chromatography eluant: ^{1}H NMR ($CDCl_3$) δ 7.25−7.28 (d, J = 8.4, 2H, H-Ar), 6.91−6.94 (d, J = 8.4, 2H, H-Ar), 6.49−6.60 (2d, J = 8.7, 2H, H-1 and H-2), 4.51 (d, J = 5.4, 1H, H-5), 3.91−3.93 (m, 1H, H-6), 3.17 (m, 1H, H-9), 2.93 (d, J = 18.3, 1H, H-10), 2.39 (s, 3H, N-Me); MS (FAB) m/z 442 [M + H]$^+$, m/z 440.0 [M − H]$^-$. Compound **6a** (144 mg, 0.325 mmol) was dissolved in $CHCl_3$ (2 mL) and converted to the hydrochloride salt, which was recrystallized from 2-propanol twice to afford **6a·HCl** (94 mg, 60%): mp 255 °C dec; MS (FAB) m/z 442 [M + H]$^+$. Anal. ($C_{23}H_{24}NO_3Br$·HCl·$0.5H_2O$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-7α-(*p*-bromophenyl)morphinan-3,6α-diol (6b). Obtained from **14b** (480 mg, 0.96 mmol) in 52% yield (240 mg) and employing 10% methanol in chloroform as the chromatography eluant: ^{1}H NMR ($CDCl_3$) δ 7.31−7.34 (d, J = 8.4, 2H, H-Ar), 6.97−7.00 (d, J = 8.4, 2H, H-Ar), 6.55−6.70 (2d, J = 8.1, 2H, H-1 and H-2), 4.63 (d, J = 5.4, 1H, H-5), 4.03−4.05 (m, 1H, H-6), 3.65 (m, 1H, H-9), 1.02 (m, 1H, H-19), 0.58−0.60 (m, 2H, H-20 and H-21), 0.23−0.29 (m, 2H, H′-20 and H′-21); MS (FAB) m/z 482 [M + H]$^+$, m/z 480.1 [M − H]$^-$. Compound **6b** (240 mg, 0.50 mmol) was dissolved in $CHCl_3$−MeOH (10:1) and treated with excess ethereal HCl. The solution was left overnight, and the precipitate was recrystallized from i-PrOH−Et_2O twice to afford **6b·HCl** (96 mg, 38%), mp 220 °C dec. Anal. ($C_{26}H_{28}$-NO_3Br·HCl) C, H, N.

17-Methyl-4,5α-epoxy-7α-(*m*-nitrophenyl)morphinan-3,6α-diol (7a). Prepared from **15a** (120 mg, 0.28 mmol) in 78% (98 mg,) and using 10% methanol in chloroform as the

chromatography eluant: ^{1}H NMR ($CDCl_3$) δ 7.99−8.01 (m, 2H, H-Ar), 7.33−7.46 (m, 2H, H-Ar), 6.52−6.61 (2d, J = 8.4, 2H, H-1 and H-2), 4.61 (d, J = 5.4, 1H, H-5), 4.05−4.08 (m, 1H, H-6), 3.16−3.17 (m, 1H, H-9), 2.97 (d, 1H, J = 18.3, H-10β), 2.70−2.74 (m, 1H, H-7), 2.40 (s, 3H, N-Me), 2.32−2.44 (m, 2H, H-14, H-10α), 1.69−1.83 (m, 1H, H-8β), 1.31−1.36 (m, 1H, H-8α); ^{13}C NMR (CD_3COCD_3) δ 20.94 (s), 23.91 (s), 36.94 (s), 41.75 (p), 43.16 (t), 43.63 (q), 45.71 (t), 47.99 (s), 60.35 (t), 71.39 (t), 90.93 (t), 118.47 (t), 120.17 (t), 122.14 (t), 123.92 (t), 129.44 (t), 130.17 (q), 135.28 (t), 138.69 (q), 145.74 (q), 145.87 (q), 148.69 (q); MS (FAB) m/z 409 $[M + H]^+$, 407 $[M - H]^-$. Compound **7a** was dissolved in $CHCl_3$ (2 mL) and treated with ethereal HCl to furnish a light yellow solid that was recrystallized from MeOH−Et_2O to afford **7a·HCl**, mp 228 °C dec. Anal. ($C_{23}H_{24}N_2O_5$·HCl·H_2O) C, H, N, Cl.

17-(Cyclopropylmethyl)-4,5α-epoxy-7α-(*m*-nitrophenyl)-morphinan-3,6α-diol (7b). Prepared from **15b** (220 mg, 0.476 mmol) in 61% (130 mg) yield, using 5% EtOH in $CHCl_3$ as chromatographic eluant: ^{1}H NMR ($CDCl_3$) δ 7.99−8.01 (m, 2H, H-Ar), 7.33−7.46 (m, 2H, H-Ar), 6.52−6.61 (2d, J = 8.4, 2H, H-1 and H-2), 4.61 (d, J = 5.4, 1H, H-5), 4.05−4.08 (m, 1H, H-6), 3.16−3.17 (m, 1H, H-9), 2.97 (d, 1H, J = 18.3, H-10β), 2.70−2.74 (m, 1H, H-7), 2.40 (s, 3H, N-Me), 2.32−2.44 (m, 2H, H-14, H-10α), 1.69−1.83 (m, 1H, H-8β), 1.31−1.36 (m, 1H, H-8α); ^{13}C NMR (CD_3COCD_3) δ 4.79 (s), 21.43 (s), 23.87 (s), 42.12 (q), 45.58 (t), 46.76 (s), 57.96 (t), 59.14 (s), 60.04 (s), 71.30 (t), 90.91 (t), 118.59 (t), 118.67 (t), 120.08 (t), 122.13 (t), 123.94 (t), 129.44 (q), 130.18 (t), 135.32 (q), 138.65 (q), 145.73 (q), 145.96 (q), 148.66 (q); MS (FAB) m/z 449 $[M + H]^+$. The hydrochloride was prepared in $CHCl_3$−MeOH (10:2) and crystallized from i-PrOH−Et_2O; mp 235 °C dec. Anal. ($C_{26}H_{28}N_2O_4$·HCl·1.7H_2O) C, H, N, Cl.

17-Methyl-3-methoxy-4,5α-epoxy-6α-*O*-acetyl-7α-phenylmorphinan (16a). Compound **13a** (400 mg, 1.05 mmol) was mixed with acetic anhydride (5 mL) and glacial acetic acid (10 mL) under N_2. The resulting solution was stirred at 110 °C (oil bath) for 24 h. After removal of solvents under reduced pressure, the residue was taken up in a small volume of chloroform and washed with saturated aqueous $NaHCO_3$. The organic layer was removed under reduced pressure to afford **16a** (380 mg, 99%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.01−7.22 (m, 5H, H−Ph), 6.69−6.77 (2d, J = 8.4, 2H, H-1 and H-2), 5.46−5.50 (m, 1H, H-6), 4.79 (d, J = 2.1, 1H, H-5), 3.83 (s, 3H, O-Me), 3.30 (m, 1H, H-9), 3.12 (d, J = 19, 1H, H-10), 2.76 (s, 3H, N-Me).

17-(Cyclopropylmethyl)-3-methoxy-4,5α-epoxy-6α-*O*-acetyl-7α-phenylmorphinan (16b). By the same procedure employed for preparing **16a**, a solution of **13b** (600 mg, 1.44 mmol) stirred at 110 °C with acetic anhydride (8 mL) and AcOH (16 mL) furnished crude **16b** (570 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.04−7.22 (m, 5H, H-Ph), 6.61−6.70 (2d, J = 8.1, 2H, H-1 and H-2), 5.47−5.50 (dd, J = 2.1, 5.8, 1H, H-6), 4.77 (d, J = 5.8, 1H, H-5), 3.83 (s, 3H, O-Me), 3.50 (m, 1H, H-9), 2.96 (d, J = 18.3, 1H, H-10), 0.90 (m, 1H, H-19), 0.51−0.54 (m, 2H, H-20 and H-21), 0.14−0.15 (m, 2H, H′-20 and H′-21); MS (FAB) m/z 460 $[M + H]^+$.

17-Methyl-4,5α-epoxy-7α-phenylmorphinan-3,6α-diol 6-Acetate (8a). Obtained from **16a** (380 mg, 1.05 mmol) in 52% (189 mg) yield, using 10% EtOH in $CHCl_3$ as eluant in the chromatography step: ^{1}H NMR ($CDCl_3$) δ 7.00−7.25 (m, 5H, H-Ph), 6.59−6.71 (2d, J = 8.2, 2H, H-1 and H-2), 5.39−5.42 (m, 1H, H-6), 4.73 (d, J = 6.2, 1H, H-5), 3.26 (m, 1H, H-9), 3.06 (d, J = 18.6, 1H, H-10), 2.44 (s, 3H, N-Me), 1.51 (s, 3H, H-Ac); MS (FAB) m/z 406 $[M + H]^+$. The base (180 mg, 0.54 mmol) was dissolved in $CHCl_3$ (2 mL) and MeOH (0.2 mL) and treated with ethereal HCl to afford the crude hydrochloride, which was recrystallized twice from MeOH−Et_2O (144 mg, 70%): mp 275 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.08−7.23 (m, 5H, H-Ph), 6.71 (s, 2H, H-1 and H-2), 5.45−5.47 (dd, J = 1.8, 6.2, 1H, H-6), 4.92 (d, J = 6.2, 1H, H-5), 3.85 (m, 1H, H-9), 2.91 (s, 3H, N-Me). Anal. ($C_{25}H_{27}NO_4$·HCl) C, H, N, Cl.

17-(Cyclopropylmethyl)-4,5α-epoxy-7α-phenylmorphinan-3,6α-diol 6-Acetate (8b). Prepared from **16b** (570 mg, 1.43 mmol) in 54% yield following chromatography using 10% EtOH in $CHCl_3$: ^{1}H NMR ($CDCl_3$) δ 7.04−7.22 (m, 5H, H-Ph), 6.61−6.70 (2d, J = 8.1, 2H, H-1 and H-2), 5.47−5.50 (dd, J = 2.1, 5.8, 1H, H-6), 4.77 (d, J = 5.8, 1H, H-5), 3.50 (m, 1H, H-9), 2.96 (d, J = 18.3, 1H, H-10), 0.90 (m, 1H, H-19), 0.51−0.54 (m, 2H, H-20 and H-21), 0.14−0.15 (m, 2H, H′-20 and H′-21); MS (FAB) m/z 386.2 $[M + H]^+$. Treatment of the base with ethereal HCl gave the hydrochloride salt, which was recrystallized twice from i-PrOH−Et_2O (138 mg, 61%): mp 210 °C dec; ^{1}H NMR (CD_3OD) δ 7.08−7.23 (m, 5H, H-Ph), 6.71 (s, 2H, H-1 and H-2), 5.45−5.48 (dd, J = 1.8, 6.2, 1H, H-6), 4.92 (d, J = 6.2, 1H, H-5), 3.85 (m, 1H, H-9), 1.52 (s, 3H, H-Ac); MS (FAB) m/z 446 $[M + H]^+$. Anal. ($C_{28}H_{31}NO_4$·HCl) C, H, N, Cl.

3-*O*-Benzyl-7α-phenylnaltrexone (18). The same procedure employed for **10b** was used to carry out the reaction between 3-*O*-benzylnaltrexone[6] (**17**) (0.84 g, 1.95 mmol), hexamethyldisilazane (1.8 mL, 8.56 mmol), *n*-butyllithium (2.4 *M*, 2.0 mL, 4.8 mmol), and diphenyliodonium iodide (1.4 g, 3.4 mmol) in DMF (80 mL). The crude product was purified by centrifugal chromatography on silica gel, eluting with ethyl acetate−hexane (2:8) to afford compound **18** (85 mg, 8.5%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23−7.47 (m, 10H, H-Ph), 6.53−6.73 (2d, 2H, J = 8, H-1 and H-2), 5.16−5.32 (dd, 2H, J = 12 Hz, CH_2-Ph), 4.70 (s, 1H, H-5), 2.95−3.48 (m, H-10 and H-7), 0.88 (m, 1H, H-19), 0.51−0.60 (m, 2H, H-20 and H-21), 0.14−0.16 (m, 2H, H′-20 and H′-21).

7α-Phenylnaltrexone (3c). A solution of **18** (200 mg, 0.39 mmol) and concentrated HCl (4 mL) in glacial acetic acid (4 mL) was stirred at 85 °C for 1 h. The solvent was evaporated with the aid of ethanol, and the residue was taken up in ethyl acetate (25 mL) and washed with aqueous $KHCO_3$ (5%) and then water. After the ethyl acetate extract was dried over $MgSO_4$, it was evaporated to dryness. The residue (∼160 mg) was applied to a silica gel (1 mm) rotor plate and eluted with ethyl acetate−hexane (2:8) to afford compound **3c** (120 mg, 73%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.20−7.24 (m, 3H, H-Ph), 6.97−7.01 (m, 2H, H-Ph), 6.52−6.70 (2d, 2H, J = 9.4, H-1 and H-2), 4.91 (s, 1H, H-5), 4.40−4.48 (dd, 1H, J = 5.4, 12.6, H-7), 3.26 (d, J = 5.8, H-9), 3.13 (d, 2H, J = 18.4, H-10), 0.895 (m, 1H, H-19), 0.51−0.55 (m, 2H, H-20 and H-21), 0.17−0.19 (m, 2H, H′-20 and H′-21); ^{13}C NMR ($CDCl_3$) δ 3.31, 9.22, 22.26, 28.09, 28.15, 30.63, 39.07, 43.56, 50.07, 51.43, 58.87, 62.11, 90.86, 119.21, 126.54, 127.85, 128.71, 222.00; MS (FAB) m/z 418 $[M + H]^+$. Compound **3c** (100 mg, 0.22 mmol) was treated with ethereal HCl to afford **3c·HCl** (50 mg) after recrystallization three times from i-PrOH−Et_2O. Anal. ($C_{26}H_{27}NO_4$·HCl·2.5H_2O) C, H, N.

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