Pyrrolomorphinans as δ Opioid Receptor Antagonists. The Role of Steric Hindrance in Conferring Selectivity

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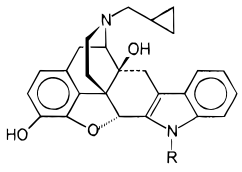
A series of 2′,3′-disubstituted pyrrolomorphinans (**5a**−**i**) were synthesized to determine the role of steric hindrance at μ and κ receptors in promoting δ opioid receptor antagonist selectivity. In smooth muscle preparations, five members of the series (**5a**−**c,e,f**) possessed K_e values in the range 2−15 nM and were δ selective. Since the unsubstituted analogue **4** possessed δ antagonist potency of similar magnitude, but was not δ selective, it is suggested that the 2′,3′-substitution confers δ selectivity by hindering the interaction of the pharmacophore at μ and κ receptors, while not affecting δ receptors.

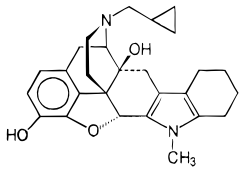
Introduction

The design of the prototypical nonpeptide opioid δ antagonist, naltrindole[1] (**1**, NTI), was based on the attachment of a "δ address" to the opiate pharmacophore to confer selectivity. Structure−activity studies in this series have indicated that two factors contribute to the high affinity and selectivity for δ receptors.[2,3] The indolic benzene moiety is believed to confer selectivity by (1) enhancing affinity for the δ receptor and (2) by decreasing recognition at μ and κ opioid receptors.

The report that the *N*-methyl-NTI analogue **2** is 9-fold more potent than its tetrahydro derivative **3** has demonstrated that an aromatic system or its equivalent plays an important role in the recognition process.[3] Moreover, the fact that pyrrolomorphinan **4** is not a δ selective antagonist and is substantially more potent at μ and κ receptors than either NTI, **2**, or **3** illustrates that the substitution on the pyrrole "spacer" is essential, but need not be aromatic to confer δ antagonist selectivity.[4] Thus, it appears that δ selectivity could be conferred in the absence of an aromatic "address" simply through a mechanism that involves inhibition of binding to μ and κ receptors.



1 (NTI) R = H
2 R = CH_3



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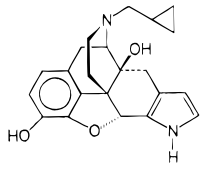

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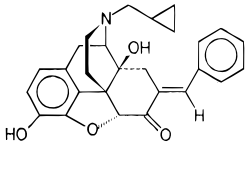

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Because the tetramethylene group attached to the pyrrole "spacer" in **3** appears to confer δ antagonist selectivity by reducing antagonist potency at μ and κ receptors, we have investigated the effect of other substituents attached to the pyrrole moiety in a series of pyrrolomorphinans (**5a**−**i**). Here we describe the results of this study which support the idea that part of the δ selectivity of NTI (**1**) arises from steric hindrance by the indolic benzene moiety at μ and δ receptors.

Chemistry

The rationale for the design of target compounds involved the attachment of alkyl and phenyl substituents to the pyrrole moiety in an effort to hinder recognition at μ and κ receptors. Phenyl substituents were also introduced for the purpose of mimicking the "address" of the δ antagonist, BNTX (**9**).[5]

The target compounds (**5a**−**i**) were synthesized from the condensation of naltrexone with the corresponding amino ketones (**8a**−**i**) under acidic conditions via the Knorr reaction[6] (Scheme 1). Typically, the reaction was conducted in a mixture of benzene/DMF and refluxed in a Dean−Stark apparatus overnight.

The amino ketones (**8a**−**f,h,i**) were derived from the corresponding *N*-benzoyl derivatives of alanine, leucine, and glycine. Ketone **8g** was synthesized from *N*-acetylphenylglycine. Each *N*-acyl amino acid was reacted with the appropriate organolithium or Grignard reagent to afford the acylamino ketone (**7**), which was then converted to the desired ketone **8** by hydrolysis of the amide group in 5 N HCl. The synthesis of the α-amino ketones **8** is similar to that reported by Rapoport.[7]

Biological Results

Smooth Muscle Preparations. Pyrrolomorphinans **5a**−**i** were evaluated for antagonist and agonist activities on the electrically stimulated guinea pig ileum[8] (GPI) and mouse vas deferens[9] preparations (Table 1). The ligands (100 nM) were incubated with the preparations for 15 min prior to testing. The standard agonists, morphine (M), ethylketazocine (EK), and [D-Ala^2,D-Leu^5]enkephalin[10] (DADLE) were employed for testing antagonist potency. They possess pharmacologic selectivity for μ, δ, and κ opioid receptors, respectively. The antagonist potency is expressed as an IC_{50} ratio or as a K_e value. The IC_{50} ratio represents the agonist potency in the presence of the test compound divided by the control IC_{50} in the same preparation. The K_e values were calculated from [antagonist]/[IC_{50} ratio − 1].

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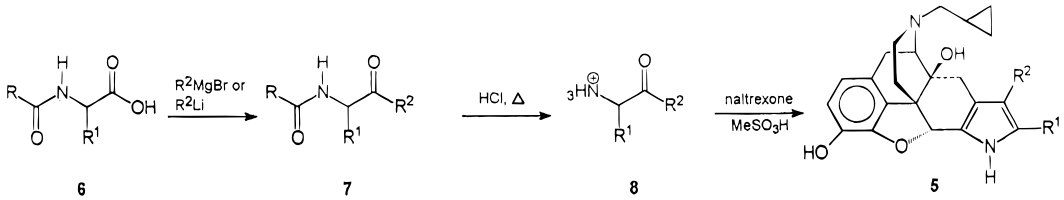
Scheme 1



	R	R^1	R^2
a	C_6H_5CO	CH_3	$(CH_2)_3CH_3$
b	C_6H_5CO	CH_3	$CH_2C_6H_5$
c	C_6H_5CO	CH_3	CH_3
d	C_6H_5CO	CH_3	C_6H_5
e	C_6H_5CO	$CH_2CH(CH_3)_2$	$(CH_2)_3CH_3$
f	C_6H_5CO	$CH_2CH(CH_3)_2$	CH_3
g	CH_3CO	C_6H_5	C_6H_5
h	C_6H_5CO	$CH_2CH(CH_3)_2$	C_6H_5
i	C_6H_5CO	H	C_6H_5

	R^1	R^2
a	CH_3	$(CH_2)_3CH_3$
b	CH_3	$CH_2C_6H_5$
c	CH_3	CH_3
d	CH_3	C_6H_5
e	$CH_2CH(CH_3)_2$	$(CH_2)_3CH_3$
f	$CH_2CH(CH_3)_2$	CH_3
g	C_6H_5	C_6H_5
h	$CH_2CH(CH_3)_2$	C_6H_5
i	H	C_6H_5

Table 1. Antagonist Potencies of Pyrrolomorphinans in the MVD and GPI Preparations

	DADLE (δ)[a]		M (μ)[b]		EK (κ)[b]		IC_{50} selectivity ratio[c]	
compound	IC_{50} ratio	K_e (nM)	IC_{50} ratio	K_e	IC_{50} ratio	K_e	δ/μ	δ/κ
1 (NTI)[d]		0.13		29		46	223[e]	354[e]
2[d]		0.99		11		20	11[e]	20[e]
3[f]		9.2		158		254	17[e]	28[e]
4[g]		3.2		0.65		3.2	0.03[e]	0.17[e]
5a	16.8 ± 3.2 (5)	6.7	2.1 ± 0.3 (4)		0.95 ± 0.36 (4)		8	17
5b	50 ± 12 (6)	2.1	1.3 (2)		1.3 (2)		50	50
5c	7.7 ± 2.2 (9)	14.8	1.5 ± 1.0 (3)		1.4 ± 0.4 (3)		5	7
5d	1.6 ± 0.3 (3)		0.90 ± 0.19 (3)		0.98 ± 0.02 (3)		1.6	1.6
5e	9.8 ± 2.5 (6)	11.4	0.76 (2)		0.99 (2)		10	10
5f	32 ± 8 (3)	3.3	*h*		*h*			
5g	1.4 ± 0.6 (3)		1.2 ± 0.6 (3)		1.1 ± 0.4 (3)		1	1
5h	0.76 ± 0.12 (3)		4.1 ± 0.7 (3)		1.3 (2)		0.2	0.2
5i	1.5 ± 0.4 (3)		2.3 ± 0.7 (5)		2.1 ± 0.8 (5)		0.7	0.7
9[i] (BNTX)		2.9		8.3		100	2.7	18

[a] MVD preparation. [b] Morphine (M) or ethylketozacine (EK) in the GPI preparation. [c] The δ IC_{50} ratio divided by the μ or κ IC_{50} ratio. The IC_{50} ratio in this calculation is designated as 1 when it is not significantly different from 1. [d] Reference 2. [e] K_e selectivity ratio = $K_{e\mu}$ or $K_{e\kappa}$ divided by $K_{e\delta}$. [f] Data from ref 3. [g] Data from ref 4. [h] Full agonist in the GPI, IC_{50} = 380 nM (3), 0.68 × morphine. [i] Data from ref 5.

Table 2. Opioid Receptor Binding of Pyrrolomorphinan Derivatives

	K_i (nM)[a]			K_i selectivity ratio	
compound	δ	μ	κ	μ/δ	κ/δ
1 (NTI)[b]	0.040 ± 0.030	6.1 ± 3.4	355 ± 22	153	8375
5a	12 ± 7	57 ± 4	39 ± 6	4.8	3.3
5b	0.35 ± 0.14	28 ± 3	41 ± 1	80	117
5c	0.41 ± 0.10	39 ± 8	22 ± 2	95	53.7
5i	2.7 ± 1.1	21 ± 7	45 ± 5	7.8	16.7

[a] Values are means ± standard error of the mean of at least three determinations. [b] Data taken from re. 2.

Ligands that were not full agonists were tested at 1 μM, and the agonist activity was expressed as a percent of the maximal response.

Two of the more potent members of the series (**5b,f**) exhibited K_e values in the range 2−3 nM, and others (**5a,c,e**) had values in the vicinity of 7−15 nM. The remainder (**5d,g,h,i**) were virtually inactive as antagonists. Except for **5f**, which was a full agonist in the GPI (0.7 × morphine), the compounds were either partial agonists (GPI or MVD) with not more than 30% maximal effect or they (**5c,d**) induced enhanced contraction (20−30%) in the MVD.

Binding. Opioid receptor binding for compounds **5a−c,1** were carried out using ICR mouse brain membranes and a modification of an established procedure.[11] Binding was determined by competition of the compounds with the selective radioligands: [^{3}H]Naltrindole[12] ([^{3}H]NTI) (δ); [^{3}H][D-Ala^2,Glyol^5]enkephalin[13] ([^{3}H]DAMGO) (μ); and [^{3}H]-(−)-(5α,7α,8β)-*N*-methyl[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzeneacetamide[14] (U69593) (κ).

The K_i values for the binding of target compounds **5b** and **5c** to δ receptors were in the range of 0.3 nM, while the remaining ligands bound with an order of magnitude lower affinity (Table 2). All four compounds were δ selective, with **5b** having the highest selectivity.

Discussion

The results of the present study are in harmony with an earlier report[3] which revealed that the tetrahydroindole **3** is a δ selective opioid antagonist with a potency one-tenth that of its indole analogue **2**. We have found that members of the pyrrolomorphinan series containing only alkyl substituents (**5a−c,e,f**) possessed significantly lower antagonist potency at μ and κ receptors when compared to the unsubstituted analogue **4** (Table 1). Given the fact that the nonselective ligand **4** is as potent as or more potent than the above compounds as

a δ antagonist,[4] it appears that the alkyl substituents in this series confer δ selectivity by reducing the antagonism at non δ opioid receptors without significantly increasing antagonism at δ receptors.

Interestingly, none of the phenyl-substituted members of the series (**5d,g−i**) were active as δ opioid antagonists. This was surprising in view of the structural similarity to the δ antagonist, BNTX (**9**). It can be noted that the phenyl-substituted compounds also are virtually inactive at μ and κ receptors. These data suggest that the pyrrolomorphinans and naltrexone congeners may not interact with δ opioid receptors in the same way.

In contrast to the phenyl congeners, the benzyl-substituted derivative **5b** was the most potent δ antagonist in the pyrrolomorphinan series and in the range of BNTX (**9**). The data suggests that the greater conformational flexibility of a benzyl versus a phenyl group may be responsible for the increased potency and selectivity, and it is consistent with the the idea that the pyrrole moiety and 6-keto group induce different modes of interaction of the morphinan component with δ opioid receptors.

In conclusion, this study supports the idea that the combination of enhanced affinity for δ receptors and steric hindrance at μ and κ receptors conferred by the indolic benzene moiety of NTI (**1**) is responsible for its high potency and selectivity. In this regard, alkyl groups that reduce interaction with μ and κ receptors (i.e., pyrrolomorphinans **5a−c,e,f**) are δ selective, but they have reduced δ antagonist potency and selectivity relative to NTI due to the absence of an appropriately oriented "address" to enhance the binding to δ receptors.

Experimental Section

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 Laboratories, Phoenix, AZ, and are within 0.4% of the theoretical values. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer, and peak positions are expressed in cm^{-1}. NMR spectra were recorded at ambient temperature on GE-300 MHz and Bruker AC-200 MHz, and chemical shifts are reported as δ values (ppm) relative to TMS. Mass spectra were obtained on a VG 7070E-HF instrument. All TLC data were determined with E. Merck Art. 5554 DC-Alufolien Kieselgel 60 F_{254}. Column chromatography was carried out on E. Merck silica gel 60 (230−400 mesh). The eluents used during column chromatography and reverse phase HPLC, $CHCl_3$−MeOH−NH_4OH and MeOH−H_2O−CH_3CN, are denoted by CMA and MWA, respectively. Tetrahydrofuran and benzene were distilled from Na/benzophenone. Dimethylformamide was distilled from calcium hydride. All other solvents and reagents were used without any further purifications unless specified. Benzoylated amino acids were obtained from Aldrich. Naltrexone hydrochloride salt was provided by Mallinckrodt.

(±)-2-*N*-Benzamido-3-heptanone (7a). *N*-Benzoyl-DL-alanine (500 mg, 2.64 mmol) was dissolved in 50 mL of dry THF under N_2 at −78 °C. To this was added *n*-BuLi, 2.5 M in hexane (3.0 equiv, 3.0 mL), and the reaction mixture was stirred at −78 °C for 20 min. The reaction mixture was stirred at room temperature for 2 h. Citric acid 10% was added to quench the reaction, and ethyl acetate (50 mL) was added. The organic layer was washed with water, saturated with $NaHCO_3$, and dried over $MgSO_4$. Upon filtration of $MgSO_4$, the solvent was evaporated under reduced pressure and the crude material was eluted on a column chromatography (silica gel) with ethyl acetate/hexanes (1:5). The desired product was isolated in 52% yield (70 mg, 0.3 mmol) as a white oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.44 (m, 3H), 7.13 (d, 1H, J = 6.00 Hz, NH), 4.80 (m, 1H, CHCO), 2.60 (m, 2H, CH_2CO), 1.66 (m, 2H), 1.47 (d, 3H, J = 7.50 Hz), 1.33 (m, 2H), 0.91 (t, 3H, J = 7.50 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.22, 167.35 134.70, 132.34, 129.24, 127.62, 55.05, 39.66, 26.36, 22.97, 18.58, 14.50; HRMS (FAB) 234 (M + H^+), calcd 234.1494, obsvd 234.1457; IR (neat) 3318, 1721, 1637 cm^{-1}.

(±)-4-Phenyl-2-benzamido-3-butanone (7b). Benzoyl-DL-alanine (1.00 g, 5.2 mmol) was dissolved in 50 mL of dry THF at −78 °C. To this was added in this order, via syringe, *n*-BuLi, 2.5 M in hexane (2.0 equiv 4.2 mL), and BnMgCl, 1.0 M in Et_2O (2.0 equiv, 10.4 mL). The experimental and purification procedures are identical to the ones described for **7a**. The desired material was isolated as a white solid in 64% yield (880 mg, 3.33 mmol): mp 93−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 2H, J = 7.20 Hz, Ph), 7.50−7.10 (m, 8H, Ph), 4.90 (m, 1H, CHCO), 3.87 (m, 2H, CH_2Ph), 1.49 (d, 3H, J = 7.20 Hz); LRMS (FAB) 268 (M + H^+) observed 268.1000.

(±)-2-Benzamido-3-butanone (7c). Benzoyl-DL-alanine (1.00 g, 5.3 mmol) was dissolved in 150 mL of dry THF at −78 °C under N_2. To this was added, via a syringe, 11.1 mL (3.0 equiv) of MeLi, 1.4 M in ether. The reaction mixture was allowed to stir at room temperature overnight. The workup and purification steps were identical to those for **7a**. The desired amino ketone was isolated as a white-yellowish oil in 58% yield (573 mg, 3 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 7.50 Hz, Ph), 7.34 (m, 3H, Ph), 4.70 (m, 1H, CH), 2.19 (s, 3H, Me), 1.37 (d, 3H, J = 7.50 Hz, Me); HRMS(FAB) 192 (M + H^+), calcd 192.1024, obsvd 192.1016.

(±)-2-Benzamidopropiophenone (7d). Benzoyl-DL-alanine (1.00 g, 5.2 mmol) was dissolved in dry THF (100 mL) at −78 °C under N_2. To this was added, via syringe, *n*-BuLi, 2.5 M in hexane (2.0 equiv, 4.1 mL), and PhMgBr, 3.0 M in ether, (2.0 equiv, 3.5 mL). The subsequent experimental conditions have been described for **7a**. The desired product was isolated in 53% yield (697 mg, 2.8 mmol) as a white oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 2H, J = 8.40 Hz, Ph), 7.87 (d, 2H, J = 8.40 Hz, Ph), 7.52 (m, 6H, Ph), 5.76 (m, 1H, CHCO), 1.55 (d, 3H, J = 6.00 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.85, 167.28, 134.76, 134.44, 132.37, 129.64, 129.49, 129.27, 129.07, 127.73, 127.46, 126.28, 51.23, 20.63; HRMS (FAB) 254 (M + H^+), calcd 254.1181, obsvd 254.1161.

L-2-Methyl-4-benzamido-5-nonanone (7e). Benzoyl-L-leucine (614 mg, 2.8 mmol) was dissolved in dry THF (50 mL) under N_2 at −78 °C. *n*-BuLi, 2.5 M in hexane (3.0 equiv, 3.4 mL), was syringed in this mixture, and the temperature was slowly raised to room temperature. The reaction mixture was stirred for 12 h. The workup and purification steps have been described for **7a**. The desired amino ketone was isolated as an oil, in 16% yield (116 mg, 0.4 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, J = 7.50 Hz, Ph), 7.44 (m, 3H, Ph), 6.95 (d, 1H, J = 7.80 Hz), 4.90 (td, 1H, J = 3.60, 18.30 Hz, CH), 2.58 (td, 2H, J = 2.40, 7.20 Hz, CH_2), 1.58 (m, 6H, CH_2's), 1.37 (m, 1H, CH), 1.02 (d, 6H, J = 6.30 Hz, CH_3), 0.94 (t, 3H, J = 6.30 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.87, 167.86, 134.66, 132.32, 129.24, 127.75, 56.97, 40.99, 39.91, 25.73, 25.19, 23.43, 22.36, 22.02, 13.88.

(±)-3-Benzamido-5-methyl-2-hexanone (7f). Benzoyl-DL-leucine (500 mg, 2.1 mmol) was dissolved in dry THF (50 mL) at −78 °C, under N_2. To this was added MeLi (4.0 eq, 6.1 mL), and the reaction mixture was allowed to warm up to room temperature. The experimental conditions have already been described for **7a**. The desired amino ketone was obtained as an oil in 65% yield (320 mg, 1.4 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 1H, J = 7.20 Hz, Ph), 7.43 (m, 4H, J = 7.20 Hz), 4.92 (td, 1H, J = 3.60, 8.70 Hz, CHN), 2.27 (s, 3H), 1.64 (m, 3H), 1.03 (d, 3H, J = 6.00 Hz), 0.91 (d, 3H, J = 6.05 Hz).

(±)-Acetamidophenylacetophenone (7g). Acetyl-DL-phenylglycine (1.00 g, 5.3 mmol) was dissolved in 100 mL of dry THF, under N_2, and the temperature was lowered to −78 °C. To this was added, via a syringe, *n*-BuLi, 2.5 M in hexane (2.0 equiv, 4.1 mL), and PhMgBr, 3.0 M in Et_2O (2.0 equiv, 3.5 mL). The desired product was isolated as a yellow oil in 45% yield (427 mg, 2.12 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 8.70 Hz), 7.50 (m, 8H), 6.59 (d, 1H, J = 7.20 Hz, CHCO), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.50, 169.83, 137.96, 134.89, 134.52, 129.90, 129.87, 129.40, 129.06,

128.88, 128.64, 128.54, 126.68, 126.09, 59.50, 23.99; HRMS (FAB) 254 ($M + H^+$), calcd 254.1181, obsvd 254.1163.

L-2-Methyl-4-*N*-benzoylpentaphenone (7h). Benzoyl-L-leucine (1.68 g, 7.2 mmol) was dissolved in dry THF (100 mL) under N_2 at −78 °C. *n*-BuLi, 2.5 M in hexane, (2.0 equiv, 5.7 mL) was syringed in this mixture, followed by PhMgBr, 3.0 M in ether (2.0 equiv, 4.8 mL), and the temperature was slowly raised to room temperature. The desired amino ketone was obtained as an oil (400 mg, 20%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 7.20 Hz, Ph), 7.86 (d, 1H, J = 7.20 Hz), 7.43 (m, 8H, aromatic), 5.92 (td, 1H, J = 3.60, 8.70 Hz, CHN), 1.58 (m, 3H), 1.13 (d, 3H, J = 6.30 Hz), 0.91 (d, 3H, J = 6.20 Hz); HRMS (FAB) 296 ($M + H^+$), calcd 296.1650, obsvd 296.1639.

Benzamidoacetophenone (7i). Benzoylglycine (1.50 g, 8.4 mmol) was dissolved in dry THF (100 mL) under N_2 at −78 °C. *n*-BuLi, 2.5 M in hexane (2.0 equiv, 6.7 mL), was syringed in this mixture, followed by PhMgBr, 3.0 M in ether (2.0 equiv, 5.6 mL), and the temperature was slowly raised to room temperature. The desired amino ketone was obtained as a solid (450 mg, 23%): mp 115−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 7.20 Hz), 7.86 (d, 1H, J = 7.20 Hz), 7.43 (m, 8H, aromatic), 5.51 (d, 1H, J = 8.70 Hz, CHN); HRMS (FAB) 240 ($M + H^+$), calcd 240.1024, obsvd 240.1019.

(±)-2-Amino-3-heptanone Hydrocloride (8a). Compound **7a** (70 mg, 0.3 mmol) was dissolved in 35 mL of 6 N HCl and 5 mL of MeOH. The solution was refluxed for 9 h. After the aqueous layer was washed with ethyl acetate, water was removed under vacuum from the aqueous fraction acidic extracts to afford **8a** (27 mg, 55%): ^{1}H NMR (300 MHz, methanol-d_4) δ 4.14 (q, 1H, J = 7.20 Hz, CH), 2.60 (m, 2H, $COCH_2$), 1.56 (m, 3H), 1.47 (d, 3H, J = 7.20 Hz), 0.90 (t, 3H, J = 7.50 Hz); ^{13}C NMR (75 MHz, methanol-d_4) δ 206.68, 55.05, 38.15, 25.60, 22.42, 14.97, 13.42; HRMS (FAB) 130 (M^+) calcd 130.1231, obsvd 130.1240.

1-Phenyl-3-amino-2-butanone Hydrochloride (8b). Compound **7b** (140 mg, 0.5 mmol) was dissolved in a mixture of 6 N MeOH:HCl (1:3), refluxed for 5 h, and worked up as described for **8a**. The desired product **8b** was isolated as a solid (61 mg, 62%): ^{1}H NMR (300 MHz, methanol-d_4) δ 7.26 (m, 5H, Ph), 4.26 (q, 1H, J = 6.30 Hz), 3.94 (s, 2H), 1.56 (d, 3H, J = 6.30 Hz); ^{13}C NMR (75 MHz, methanol-d_4) δ 204.57, 134.55, 130.45, 129.86, 127.44, 55.07, 46.07, 15.32; HRMS (FAB) 164 ($M + H^+$) calcd 164.1075, obsvd 164.1072.

(±)-2-Amino-3-butanone Hydrochloride (8c). Compound **7c** (573 mg, 3 mmol) was dissolved in a mixture of 6 N MeOH:HCl (2:3), refluxed for 10 h, and worked up as described for **7a** to afford the desired product **8c**: yield 230 mg (75%); mp 115−117 °C; ^{1}H NMR (300 MHz, methanol-d_4) δ 3.65 (m, 1H, CH), 3.24 (s, 3H, Me), 1.35 (d, 3H, J = 6.35 Hz, Me); LRMS (FAB) 73.3 ($M^+ - Me$).

(±)-2-Aminopropiophenone Hydrochloride (8d). Compound **7d** (697 mg, 2.8 mmol) was dissolved in 6 N HCl (30 mL), refluxed for 2 days, and worked up as described for **7a** to afford **8d**: yield 310 mg (60%); mp 166−170 °C, ^{1}H NMR (300 MHz, methanol-d_4) δ 8.04 (d, 2H, J = 8.70 Hz, Ph), 7.69 (m, 1H, Ph), 7.59 (m, 2H, Ph), 5.15 (bq, 1H, J = 6.90 Hz, CHN), 1.53 (d, 1H, J = 7.20 Hz); ^{13}C NMR (75 MHz, methanol-d_4) δ 196.60, 135.04, 133.47, 129.92, 129.46, 52.133, 17.01; HRMS (FAB) 150 (M^+), calcd 150.0918, obsvd 150.0915.

(±)-2-Methyl-4-amino-5-nonanone Hydrochloride (8e). Compound **7e** (108 mg, 0.4 mmol) was dissolved in 6 N HCl (30 mL), refluxed for 10 h, and worked up as described for **7a** to afford the desired compound **8e** as a gum (40 mg, 50%): ^{1}H NMR (300 MHz, methanol-d_4) δ 3.99 (dd, 1H, J = 3.60, 8.40 Hz, CH), 2.51 (m, 2H, CH_2), 1.55 (m, 6H, CH_2's), 1.28 (m, 1H, CH), 0.98 (t, 6H, J = 6.30 Hz, CH_3), 0.87 (t, 3H, J = 7.20 Hz, CH_3); HRMS (FAB) 172 (M^+), calcd 172.1701, obsvd 172.1699.

(±)-2-Methyl-4-amino-5-hexanone Hydrochloride (8f). Compound **7f** (300 mg, 1.3 mmol) was dissolved in 6 N HCl (20 mL), refluxed for 12 h, and worked up as described for **8a** to afford **8f** (213 mg, 99%) as a plastic solid: ^{1}H NMR (300 MHz, methanol-d_4) δ 3.95 (t, 1H, J = 3.65 Hz), 2.86 (s, 3H, Me), 1.54 (m, 3H), 0.95 (t, 6H, J = 6.45 Hz).

(±)-2-(Aminophenylacetyl)acetophenone Hydrochloride (8g). Compound **7g** (327 mg, 1.3 mmol) was dissolved in 6 N HCl (30 mL), refluxed for 12 h, and worked up as described for **8a** to afford **8g** (180 mg, 56%): mp 210−215 °C; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.96 (d, 2H, J = 8.40 Hz), 7.45 (m, 8H), 6.24 (s, CHCO); HRMS (FAB) 212 (M^+), calcd 212.1075, obsvd 212.1085.

L-2-Methyl-4-aminopentaphenone Hydrochloride (8h). Compound **7h** (400 mg, 1.4 mmol) was dissolved in 6 N HCl (25 mL), refluxed overnight, and worked up as described for **8a** to afford **8h** (78 mg, 26%): mp 190−192 °C (dec at 180 °C); ^{1}H NMR (300 MHz, methanol-d_4) δ 7.43 (m, 5H, Ph), 5.00 (bt, 1H, CHN), 1.55 (m, 3H), 1.10 (d, 6H, J = 6.30 Hz, CH_3); HRMS (FAB) 192 (M^+), calcd 192.1388, obsvd 192.1385.

Aminoacetophenone Hydrochloride (8i). Compound **5i** (210 mg, 0.9 mmol) was dissolved in 6 N MeOH/HCl (1:2), refluxed overnight, and worked up as described for **8a** to afford **8i** (150 mg, 95%): mp >210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−7.50 (m, 10H, Ph), 5.00 (d, 1H, J = 8.70 Hz, CHN).

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′-methyl-3′-butylpyrrolo[6,7:4′,5′]morphinan (5a). Compound **8a** (220 mg, 1.3 mmol) and naltrexone hydrochloride (250.9 mg) were dissolved in 70 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (1.25 equiv, 107 μL). The reaction mixture was equipped with a Dean−Stark apparatus and refluxed for 19 h. Upon cooling, ethyl acetate was added and the organic layer was washed with saturated $NaHCO_3$ (20 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. A TLC plate eluted with CMA (98:2:0.5) showed a single major product, R_f = 0.15. Purification of the crude product was accomplished on a silica gel column using CMA (99:1:0.5), followed by a florisil column eluted with $CHCl_3$. The desired product **5a** was isolated as an oil and was crystallized from chloroform/hexane (123.3 mg, 49%): mp 118−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H, PhOH), 6.62 (d, 1H, J = 8.40 Hz, H_2, $6H_{10}$), 2.71 (m, 2H), 2.53−2.19 (m, 8H), 2.05 (s, 3H, Me-2′), 1.33 (m, 4H, CH_2′s), 0.88 (m, 4H, Me H_{19}), 0.55 (m, 2H, H_{20} H_{21}), 0.16 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.26, 139.54, 131.75, 127.05, 125.94, 120.08, 119.38, 119.12, 118.20, 117.65, 87.49, 74.00, 63.07, 60.19, 48.43, 44.33, 34.18, 32.21, 30.01, 24.75, 23.76, 23.45, 14.70 , 11.94, 10.11, 4.68, 4.52; HRMS (FAB) 435 ($M + H^+$), calcd 435.2647, obsvd 435.2644. Anal. ($C_{27}H_{34}O_3N_2$) C, H, N.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′-methyl-3′-benzylpyrrolo[6,7:4′,5′]morphinan (5b). Compound **8b** (200 mg, 1.1 mmol) and naltrexone hydrochloride (201 mg) were dissolved in 50 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (87 μL) and treated as described for **5a** to afford pyrrole **5b** (75 mg, 20%): mp 125−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H, PhOH), 7.18 (m, 5H, Ph), 6.62 (d, 1H, J = 8.40 Hz, H_2), 6.49 (d, 1H, J = 8.40 Hz, H_1), 5.63 (s, 1H, H_5), 3.64 (s, 2H, CH_2Ph), 3.21 (d, 1H, J = 6.30 Hz, H_9), 3.08 (d, 1H, J = 18.30 Hz, H_{10}), 2.75−2.22 (m, 10H), 2.05 (s, 3H, Me-2′), 1.72 (d, 1H, J = 12.30 Hz, H_{15}), 0.89 (m, 1H, H_{19}), 0.56 (m, 2H, H_{20} H_{21}), 0.11 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.45, 139.43, 128.86, 128.83, 127.99, 120.54, 119.74, 119.32, 117.49, 116.01, 87.17, 73.84, 62.98, 60.14, 48.51, 44.26, 32.21, 30.70, 30.01, 23.70, 12.15, 10.05, 4.68, 4.52; HRMS (FAB) 469 ($M + H^+$), calcd 469.2491, obsvd 469.2496. Anal. ($C_{30}H_{32}N_2O_3$) C, H, N.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′,3′-dimethylpyrrolo[6,7:4′,5′]morphinan (5c). Compound **8c** (300 mg, 2.4 mmol) and naltrexone hydrochloride (458 mg) were dissolved in 100 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (87 μL) and treated as described for **5a** to afford the desired pyrrole **5c** (282 mg, 30%): mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H, PhOH), 6.64 (d, 1H, J = 8.40 Hz, H_2), 6.53 (d, 1H, J = 8.40 Hz, H_1), 5.58 (s, 1H, H_5), 3.29 (d, 1H, J = 6.00 Hz, H_9), 3.11 (d, 1H, J = 18.30 Hz, H_{10}), 2.72 (m, 2H), 2.45−2.28 (m, 10H), 2.04 (s, 3H, Me-2′), 1.79 (s, 3H, Me-3′), 1.28 (m, 1H), 0.85 (m, 1H, H_{19}), 0.56 (m, 2H, H_{20} H_{21}), 0.13 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.39, 139.62, 131.76, 127.04, 125.94, 120.16, 119.38, 119.27, 117.54, 112.68, 87.30, 73.79, 62.99, 60.13, 48.46, 44.37, 32.18, 29.98, 23.76, 11.84, 10.06, 9.32, 4.71, 4.44; HRMS (FAB) 393 ($M + H^+$) calcd 393.2178, obsvd 393.2185. Anal. ($C_{24}H_{28}O_3N_2$) C, H, N.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′-methyl-3′-phenylpyrrolo[6,7:4′,5′]morphi-

nan (5d). Compound **8d** (310 mg, 1.7 mmol) and naltrexone hydrochloride (315 mg) were dissolved in 50 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (135 μL) and treated as detailed for **5a** to afford pyrrole **5d** (93 mg, 13%): mp 164−166 °C (start dec 157 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H, PhOH), 7.29 (m, 2H), 7.17 (m, 3H), 6.68 (d, 1H, J = 7.50 Hz, H_2), 6.57 (d, 1H, J = 7.55 Hz, H_1), 5.72 (s, 1H, H_5), 3.28 (d, 1H, J = 6.30 Hz, H_9), 3.12 (d, 1H, J = 18.30 Hz, H_{10}), 2.79−2.27 (m, 10H), 2.13 (s, 3H, Me-2′), 1.75 (m, 1H), 0.87 (m,1H, H_{19}), 0.54 (m, 2H, H_{21} and H_{20}), 0.13 (m, 2H, H_{21} and H_{20}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.49, 139.68, 136.55, 131.70, 130.05, 128.73, 127.95, 125.95, 121.30, 120.36, 119.58, 118.52, 117.84, 87.04, 74.06, 62.65,60.03, 48.47, 44.43, 32.25, 30.63, 23.72, 12.70, 10.02, 4.85, 4.30; HRMS (FAB) 455 (M + H^+), calcd 455.2334, obsvd 455.2345. Anal. ($C_{29}H_{30}O_3N_2$) C, H, N.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′-isobutyl-3′-butylpyrrolo[6,7:4′,5′]morphinan (5e). Compound **8e** (40 mg, 0.2 mmol) and naltrexone hydrochloride salt (72 mg) were dissolved in 20 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (12 μL) and treated as described for **5a** to afford pyrrole **5e** as an oil (28 mg, 30%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H, PhOH), 6.68 (d, 1H, J = 8.70 Hz, H_2), 6.57 (d, 1H, J = 8.60 Hz, H_1), 5.59 (s, 1H, H_5), 3.28 (d, 1H, J = 5.10 Hz, H_9), 3.12 (d, 1H, J = 19.50 Hz, H_{10}), 2.80−2.69 (m, 2H), 2.51−2.14 (m, 10H), 1.71 (m, 2H), 1.30 (m, 5H, CH CH_2's), 0.87 (m, 10H, 3Me H_{19}), 0.54 (m, 2H, H_{20} H_{21}), 0.14 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.26, 139.42, 131.76, 130.80, 126.12, 120.21, 119.30, 119.15, 118.61, 117.27, 87.70, 73.81, 63.02, 60.13, 48.43, 44.34, 36.04, 34.39, 32.29, 30.08, 29.93, 24.86, 23.73, 23.63, 23.36, 14.68, 10.08, 4.71, 4.46; HRMS (FAB) 477 (M + H^+), calcd 477.3117, obsvd 477.3136. Anal. ($C_{30}H_{40}O_3N_2$).

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′-isobutyl-3′-methylpyrrolo[6,7:4′,5′]morphinan (5f). Compound **8f** (275 mg, 1.7 mmol) and naltrexone hydrochloride (629 mg) were dissolved in 45 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (1.0 equiv, 107 μL) and treated as described for **5a** to afford pyrrole **5f** (210 mg, 30%): mp 114−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H, PhOH), 6.63 (d, 1H, J = 7.50 Hz, H_2), 6.53 (d, 1H, J = 7.50 Hz, H_1), 5.59 (s, 1H, H_5), 3.26 (d, 1H, J = 6.30 Hz, H_9), 3.06 (d, 1H, J = 18.30 Hz, H_{10}), 2.70 (m, 2H), 2.50−2.24 (m, 8H), 1.79 (s, 3H, Me), 1.69 (m, 4H, CH H_{15} CH_2), 0.88 (m, 1H, H_{19}), 0.83 (d, 3H, J = 2.40 Hz, Me), 0.81 (d, 3H, J = 2.40 Hz, Me), 0.53 (m, 2H, H_{20} H_{21}), 0.13 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.24, 139.48, 131.79, 131.06, 126.09, 120.14, 119.35, 119.24, 117.39, 113.03, 87.59, 73.73, 62.90, 60.08, 48.48, 44.37, 36.04, 32.18, 30.05, 29.96, 23.76, 23.29, 23.16, 10.01, 9.51, 4.76, 4.39; HRMS (FAB) 435 (M + H^+), calcd 435.2647, obsvd 435.2652. Anal. ($C_{27}H_{34}O_3N_2 \cdot H_2O$) C, H, N.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′,3′-diphenylpyrrolo[6,7:4′,5′]morphinan (5g). Compound **8g** (180 mg, 0.7 mmol) and naltrexone hydrochloride (137 mg) were dissolved in 40 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (59 μL) and treated as described for **5a** to afford pyrrole **5g** (72 mg, 30%): mp dec 185 °C; ^{1}NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H, PhOH), 7.15 (m, 10H), 6.71 (d, 1H, J = 8.40 Hz, H_2), 6.58 (d, 1H, J = 8.40 Hz, H_1), 5.72 (s, 1H, H_5), 3.27 (d, 1H, J = 6.30 Hz, H_9), 3.10 (d, 1H, J = 18.33 Hz, H_{10}), 2.74−2.26 (m, 10H), 1.75 (d, 1H, J = 10.80 Hz, H_{15}), 0.86 (m, 1H, H_{19}), 0.56 (m, 2H, H_{21} H_{20}), 0.15 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.26, 139.40, 136.17, 133.53, 131.50, 131.47, 130.79, 129.04, 128.78, 127.68, 127.09, 126.49, 126.13, 123.42, 121.06, 120.37, 119.88, 117.64, 87.04, 73.73, 62.53, 60.01, 48.56, 44.44, 32.16, 30.32, 23.65, 9.93, 4.91, 4.26; HRMS (FAB) 517 (M + H^+), calcd 517.2491, obsvd 517.2473. Anal. ($C_{34}H_{32}O_3N_2$).

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′-isobutyl-3′-phenylpyrrolo[6,7:4′,5′]morphinan (5h). Compound **8h** (80 mg, 0.4 mmol) and naltrexone hydrochloride (67 mg) were dissolved in 30 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (29 μL) and treated as described for **5a** to afford pyrrole **5h** (30 mg, 20%): mp 150−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H, PhOH), 7.27 (m, 3H, Ph), 7.17 (m, 2H, Ph), 6.70 (d, 1H, J = 8.40 Hz, H_2), 6.57 (d, 1H, J = 8.40 Hz, H_1), 5.62 (s, 1H, H_5), 3.25 (d, 1H, J = 6.00 Hz, H_9), 3.10 (d, 1H, J = 18.30 Hz, H_{10}), 2.74 (m, 2H), 2.48−2.29 (m, 10H), 1.75 (m, 1H, H_{15}), 0.86 (m, 1H, H_{19}), 0.84 (d, 3H, J = 6.00 Hz, CH_3), 0.80 (d, 3H, J = 6.00 Hz, CH_3), 0.53 (m, 2H, H_{20} H_{21}), 0.12 (m, 2H, H_{20} H_{21}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.28, 136.62, 135.25, 131.68, 131.53, 130.29, 128.57, 126.30, 125.99, 121.19, 121.05, 119.30, 118.59, 117.17, 87.15, 73.68, 62.56, 59.95, 48.51, 44.39, 36.01, 32.19, 30.40, 29.80, 23.60, 23.32, 23.11, 9.93, 4.81, 4.18; HRMS (FAB) 497 (M + H^+), calcd 497.2804, obsvd 497.2786. Anal. ($C_{32}H_{36}O_3N_2$).

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-2′,3′-phenylpyrrolo[6,7:4′,5′]morphinan (5i). Compound **8i** (150 mg, 0.9 mmol) and naltrexone hydrochloride (167 mg) were dissolved in 50 mL of benzene/DMF (1:1) in the presence of methanesulfonic acid (60 μL) and treated as described for **8a** to afford pyrrole **5i** (25 mg, 13%): mp 168−171 °C (155 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (bs, 1H, PhOH), 7.15 (m, 5H, Ph), 6.84 (bs, 1H, $H_{2'}$), 6.65 (d, 1H, J = 8.40 Hz, H_2), 6.58 (d, 1H, J = 8.40 Hz, H_1), 5.66 (s, 1H, H_5), 3.32 (d, 1H, J = 6.00 Hz, H_9), 3.14 (d, 1H, J = 18.30 Hz, H_{10}), 2.70 (m, 4H), 2.38 (m, 5H), 1.75 (d, 1H, J = 10.20 Hz), 0.86 (m, 1H, H_{19}), 0.56 (m, 2H, H_{20} H_{21}), 0.13 (m, 2H, H_{20} H_{21}); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.53, 139.54, 136.49, 131.45, 128.95, 128.10, 126.09, 124.16, 123.99, 119.66, 118.70, 117.77, 86.67, 73.79, 62.63, 60.01, 48.35, 44.42, 32.16, 30.97, 23.71, 9.95, 4.91, 4.26; HRMS (FAB) 441 (M + H^+), calcd 441.2178, obsvd 441.2207. Anal. ($C_{28}H_{28}O_3N_2$).

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