4′-Arylpyrrolomorphinans: Effect of a Pyrrolo-*N*-benzyl Substituent in Enhancing δ-Opioid Antagonist Activity

Sanjay K. Srivastava,[†] Stephen M. Husbands,[‡] Mario D. Aceto,[∥] Carl N. Miller,[§] John R. Traynor,[§] and John W. Lewis*[,†]

School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K., Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, U.K., Department of Pharmacology, University of Michigan, Ann Arbor, Michigan 48109, and Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, Virginia 23298

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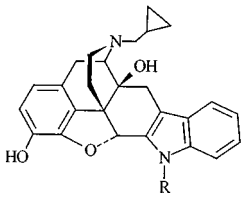
A new method for the preparation of *N*-benzylpyrrolomorphinans has been developed. Thus Michael reaction of the benzylimines of oxycodones and oxymorphones with nitrostyrenes gave a series of 4′-aryl-*N*-benzylpyrrolomorphinans. These were selective δ antagonists of much higher in vitro potency (with **5a** having K_e δ = <1 nM) than their binding affinities predicted. In mice in vivo assays **5a** showed good δ antagonist activity in the antiwrithing analgesic assay and also inhibited δ agonist-induced convulsant activity.

Introduction

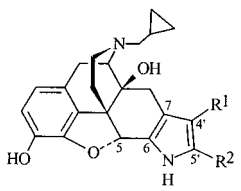
The development of selective antagonists for μ, κ, and δ opioid receptors has allowed both the role of these receptors to be defined and the selectivity of agonists to be determined.[1] The functions in which δ receptors are implicated are quite varied.[1] δ Agonists were first of interest as offering analgesia without the problems associated with the traditional μ agonist analgesics, e.g., morphine.[2,3] But δ agonists also have antidiarrheal effects without affecting gastric mobility[4,5] and are immunostimulants[6−8] and stimulants of respiration.[9] δ Antagonists are immunosuppressants[10] and prevent the development of tolerance and dependence with μ agonists[11] so that opioids with mixed μ agonist, δ antagonist profiles have beeen recognized as having potential as analgesics for the relief of severe pain.[12]

The first non-peptide selective δ opioid antagonist was naltrindole[13] (**1a**, NTI) which was prepared from naltrexone (**3a**) by Fischer indolization. The effect of introducing the indolic group was to increase δ affinity but also to reduce μ and κ affinity. *N*-Benzylnaltrindole (**1b**, BNTI) showed improved δ antagonist selectivity over NTI in smooth muscle preparations primarily as a result of having reduced μ antagonist potency.[14] BNTI had prolonged duration of δ antagonist activity in vivo by icv administration and displayed selectivity for a subtype of δ receptor (δ_2) for which the peptide δ agonist DSLET showed preferential binding.

In a study of the effect of steric hindrance on δ selectivity, Farouz-Grant and Portoghese[15] synthesized pyrrolomorphinans (e.g., **2b**,**c**,**d**) substituted in the 4′- and 5′-positions in low yields by condensation of naltrexone with α-aminoketones under acidic conditions (Knorr reaction). These pyrrolomorphinans displayed high affinity for δ receptors in receptor binding assays and modest (**2d**) or substantial δ selectivity (**2b**, **2c**). In the mouse vas deferens assay, only the 4′-benzyl derivative (**2c**) showed potent δ antagonist activity and significant δ selectivity. The unsubstituted pyrrolomorphinan (**2a**) was a potent opioid antagonist without selectivity.[16]



1
(a) R = H (NTI)
(b) R = $CH_2C_6H_5$ (BNTI)



2
(a) $R^1 = R^2 = H$
(b) $R^1 = R^2 = CH_3$
(c) $R^1 = CH_2C_6H_5$, $R^2 = CH_3$
(d) $R^1 = C_6H_5$, $R^2 = H$

We have recently investigated reactions of the benzylimines of morphinan-6-ones with Michael acceptors including nitro-alkenes.[17] We here report the synthesis and evaluation of a series of *N*-benzyl pyrrolomorphinans (**5**) prepared by these procedures. It was expected that the introduction of the pyrrole *N*-benzyl group, as in BNTI (**1b**), would enhance δ opioid interaction with a lipophilic binding site.

Synthesis

Although the benzylimines of oxycodones and oxymorphones (**3**) could not be easily isolated, when generated in situ, they reacted smoothly with nitrostyrenes to give the required *N*-benzylpyrrolomorphinans in 50−70% yields (Scheme 1).

Results

The new ligands were evaluated in binding assays in human recombinant opioid receptors transfected into Chinese hamster ovary (CHO) cells in which the displaced radioligands were [^{3}H]DAMGO (μ), [^{3}H]Cl-DPDPE (δ), and [^{3}H]U69593 (κ) (Table 1).[18] The 4′-phenylpyrrolomorphinans (**5a**−**f**) displayed modest affinity for δ receptors. The values for the 17-*N*-

* Corresponding author: John W. Lewis, Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, U.K. Tel. U.K. 1225 826 826 ext 3103. Fax: 1225 826 114. E-mail: prxjwl@bath.ac.uk.
[†] University of Bristol.
[‡] University of Bath.
[§] University of Michigan.
[∥] Medical College of Virginia.

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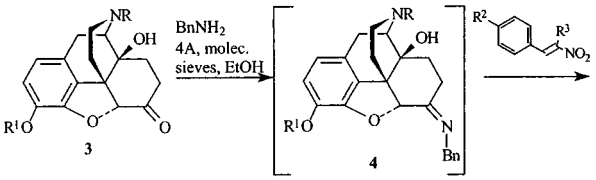
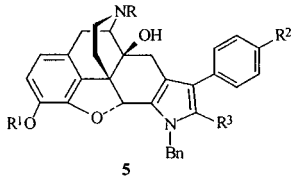
Scheme 1



a: R = CPM, R1 = H
b: R = CH_3, R1 = H
c: R = R1 = CH_3
CPM = $CH_2cC_3H_5$



5

a: R = CPM, R1=R2=R3=H
b: R = CPM, R1=R3=H, R2=CH_3
c: R = CPM, R1=R2=H, R3=CH_3
d: R = Pr, R1=R2=R3=H
e: R=R1=CH_3, R2=R3=H
f: R=CH_3, R1=R2=R3=H

Table 1. Receptor Binding of Pyrrolomorphinans (**5**) to Recombinant Human Opioid Receptors Transfected into CHO Cells

	K_i (nM)				
ligand	μ	δ	κ	μ/δ	κ/δ
5a	16.8 ± 6.2	13.7 ± 0.3	120 ± 9.6	1.2	8.8
5b	77.9 ± 25	23.5 ± 1.4	108 ± 11	3.3	4.6
5c	52.7 ± 19	17.3 ± 0.2	183 ± 16	3.0	10.6
5d	40.1 ± 5.9	21.2 ± 9.8	191 ± 3.9	1.9	9.0
5e	>10000	322 ± 43	>10000	>31	>31
5f	49.5 ± 16	116 ± 52	187 ± 46	0.43	1.6
2d[a,b]	21 ± 7	2.7 ± 1.1[c]	45 ± 5	7.8	16.7
NTI	6.3 ± 2.3	0.2 ± 0.05	10.1 ± 0.65	31	50

[a] Data from ref 15. [b] Using ICR mouse brain membrane. [c] By displacement of [^{3}H]NTI.

Table 2. Antagonist Activities of 4′-Phenylpyrrolomorphinans in [^{35}S]GTPγS Assays in Human Recombinant Receptors in CHO Cells

	K_e (nM)				
ligand	μ	δ	κ	μ/δ	κ/δ
5a	8.09 ± 1.9	0.43 ± 0.09	21.6 ± 1.7	19	50
5b	*a*, *b*	2.37 ± 0.46	61.1 ± 11		26
5c	17.7 ± 2.5	3.68 ± 0.75	306 ± 9	5	83
5d	45.3 ± 4.1	6.4 ± 0.52	210 ± 13	7	33
5f	14.1 ± 1.8	*a*, *c*	1155 ± 184		
NTI	4.26 ± 0.3	0.11 ± 0.005	4.95 ± 0.32	39	45

[a] Partial agonist. [b] EC_{50} = 1360 nM; max effect = 34% of standard (DAMGO). [c] EC_{50} = 55.2 nM; max effect = 41% of standard (Cl-DPDPE).

cyclopropylmethyl (**5a**−**c**) and 17-*N*-propyl (**5d**) derivatives were consistently in the K_i = 10−30 nM range whereas those for 17-*N*-methyl analogues (**5e**, **5f**) were >100nM. Though δ affinity was generally significantly higher than κ affinity and marginally higher than μ, there was no real selectivity of δ opioid receptor binding in this series except for oxycodone derivative **5e**, but it had very low affinity.

The antagonist affinity (K_e) of ligands **5a**−**f** was determined in [^{35}S]GTPγS assays in cloned human opioid receptors transfected into CHO cells.[18,19] K_e values were obtained for the activity of the test compounds in antagonizing the effect of standard agonists for μ (DAMGO), δ (Cl-DPDPE), and κ (U69593) receptors (Table 2). The 17-cyclopropylmethyl derivatives (**5a**−**c**) and the 17-*N*-propyl derivative (**5d**) were all potent δ antagonists; **5a** was the most potent and selective, having K_e δ = 0.43 nM. Introduction of a *p*-methyl group (**5b**) and particularly a 5′-methyl group (**5c**) resulted in some loss of κ and δ antagonist potency and, in the case of **5b**, in the appearance of μ partial agonist activity. The 17-propyl analogue (**5d**) was similar to **5a** but with 15-fold lower δ antagonist potency. All of these δ antagonists showed substantial selectivity in vitro for δ over κ. More limited differentiation between δ and μ antagonist potency was observed. The 17-*N*-methyl analogue (**5f**) showed δ partial agonist activity of modest potency and efficacy. Though it was a very low potency κ antagonist, as a μ antagonist **5f** showed good potency in line with its binding profile in which it had greater affinity for μ than for δ receptors.

Table 3. Effect of Preincubation Time on the Affinity (K_e) of **5a** Evaluated against the δ Agonist DPDPE in the Mouse vas Deferens Preparation[a]

5a (nM)	preincubation time	DPDPE IC_{50}	fold-shift	K_e (nM)
0		2.87 (2.3−3.5)		
3	30 min	2.85 (1.9−4.2)	-	
30	30 min	9.03 (7.5−10.9)	3.14	14.0
0		3.83 (2.7−5.3)		
3	2 h	22.85 (19.7−26.5)	5.97	0.6

[a] IC_{50} values were determined by nonlinear curve fitting (GraphPad Prizm; San Diego, CA) using pooled data from four tissues. IC_{50} values are given with 95% confidence intervals (CI). Significance differences occur if the 95% CIs do not overlap.

The δ antagonist activity of **5a** was also determined in MVD versus DPDPE.[23] When **5a** was preincubated for 30 min with the tissue, a K_e of 14.5 nM was obtained, showing very much lower potency than expected from the δ antagonist potency in the [^{35}S]GTPγS assay. However, with increased incubation time (2 h), **5a** caused a much bigger shift in the concentration effect curve for DPDPE such that the IC_{50} obtained was significantly different when 3 nM **5a** was incubated for 2 h compared to 30 nM **5a** for 30 min. This resulted in a bigger rightward shift and a K_e in line with results from the [^{35}S]GTPγS assay (Table 3).

An investigation of the in vivo δ antagonist activity of **5a** was undertaken in the mouse abdominal stretch assay with *p*-phenylquinone as the nociceptive agent.[22] The test drug was administered subcutaneously 10 min before SNC80[20] (18 mg/kg) as the selective δ agonist. The AD_{50} dose for **5a** was 4.34 (1.55−12.21) mg/kg which compares with the AD_{50} for naltrindole of 1.69 (0.43−7.40) mg/kg. At a dose of 32 mg/kg, SNC8O causes δ mediated convulsions in 6/6 mice.[21] In the presence of 10 and 32 mg/kg **5a**, only $^3/_6$ and $^2/_6$ mice, respectively, showed the convulsive response to SNC80, confirming the in vivo δ antagonist action of **5a**.

Discussion

Comparison of the data for the 4′-phenylpyrrolomorphinan (**5a**) with the equivalent ligand lacking the 1′-*N*-benzyl group (**2d**)[15] shows that in binding to opioid receptors, the effect of the *N*-benzyl group is to reduce δ affinity with no effect on μ affinity and a smaller effect on κ, resulting in lower δ selectivity. However, comparison in opioid receptor functional assays presents a different picture. In the [^{35}S]GTPγS assay, **5a** was a δ selective antagonist about a quarter as potent as NTI, and in MVD, in which **2d** had no δ antagonist activity,[15] **5a** also was a potent δ antagonist. The much greater potency of **5a** over the nonbenzylated parent **2d** in MVD

was unexpected since the potency of BNTI (**1b**) was only half that of NTI (**1a**).[14] It was also surprising that **5a** displayed slow kinetics in MVD, requiring 2 h incubation to achieve high δ antagonist potency. BNTI attained high potency in MVD after only 15 min pretreatment of the tissue. The lead compound of this series (**5a**) was also a good δ antagonist of the selective δ agonist SNC80 in the mouse writhing assay with nearly half the potency of NTI. This in vivo activity was not slow in onset in contrast to the antagonist activity in MVD and to the slow onset of the δ_2-antagonism of BNTI after icv administration.[14]

In summary, a series of pyrrolomorphinans has been synthesized by a procedure that gave much higher yields than those previously reported for this class. The pyrrole *N*-benzyl group had marked effects on the opioid receptor profiles of the new ligands. In particular, the 1′-benzyl-4′-phenyl derivative (**5a**) was a much more potent and selective δ antagonist than its 1′-H parent (**2d**) and had in vivo antagonist activity comparable to NTI.

Experimental Section

Chemistry. Solvents and reagents were purchased from either Aldrich or Lancaster and used as supplied. All TLC data (R_f values) were determined with aluminum sheets coated with silica gel 60 F_{254} (Merck) and eluted with 20% MeOH/DCM. All the compounds were purified by gravity−elution column chromatography using flash silica gel (Fluka; silica gel 60, mesh 220−240). Yields are of purified compounds and were not optimized. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a JEOL JNM -GX FT 300 spectrometer at ambient temperature in CD_3OD, and chemical shifts are reported as δ in ppm relative to tetramethylsilane (TMS). *J* values are reported in hertz. Mass spectra were obtained on a Fission Autospectrometer with electron impact ionization (70 eV). Compounds for pharmacological analysis were converted into their hydrochloride salts by dissolving in methanol and adding methanolic HCl. Melting points (of hydrochloride salts) were determined in capillary tubes with a Reichert hot-stage cap melting point apparatus and are uncorrected. Elemental analyses were obtained from a Carlo Erba EA 1108 analyzer, and the results were within ±0.4 of theoretical values.

1′-Benzyl-17-cyclopropylmethyl-6,7-dedihydro-3,14-dihydroxy-4,5α-epoxy-4′-phenylpyrrolo[2′,3′:6,7]morphinan (5a). Benzylamine (0.18 mL, 1.51 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg) were added to a solution of naltrexone (0.50 g, 1.47 mmol) in dry EtOH (1.5 mL) and refluxed in the presence of molecular sieves (4 Å) under nitrogen for 3 h. *trans*-β-Nitrostyrene (0.22 g, 1.47 mmol) was added, and the resulting solution was further allowed to reflux for 8 h. It was then cooled and filtered. The EtOH was removed under reduced pressure, and the solid obtained was washed with hexane. Purification of the crude product by column chromatography using 1% MeOH/DCM gave **5a** (0.47 g, 60%): R_f 0.70; mp 255 °C; ^{1}H NMR 7.26 (m, 9H, Ph), 7.07 (m, 1H, Ph), 6.81 (s, 1H, H-2′), 6.62 (d, 1H, J = 8.0, H-2), 6.55 (d, 1H, J = 8.0, H-1), 5.41 (s, 1H, H-5), 5.33 (d, 1H, J = 15.7, benzylic proton), 5.21 (d, 1H, J = 15.7, benzylic proton), 3.31 (d, 1H, H-9), 3.11 (d, 1H, J = 18.7, H-10), 2.80 (dd, 1H, J = 6.6, 18.7, H-10), 2.66 (m, 3H), 2.42 (d, 2H, J = 6.6), 2.49 (m, 2H), 1.62 (m, 1H), 0.85 (m, 1H, H-19), 0.50 (m, 2H, H-20, H-21), 0.13 (m, 2H, H-20, H-21); ^{13}C NMR 142.91, 138.77, 128.58, 128.30, 127.38, 127.33, 126.77, 125.38, 122.95, 121.36, 118.79, 85.01, 72.99, 62.19, 59.32, 50.50, 30.90, 30.68, 4.31, 3.75; EI MS *m*/*z* (relative intensity) 530 (M^+, 100%), 91 (90%). Anal. ($C_{35}H_{34}N_2O_3$·2HCl·1.25H_2O) C, H, N.

1′-Benzyl-17-cyclopropylmethyl-6,7-dedihydro-3,14-dihydroxy-4,5α-epoxy-4′-*p*-tolylpyrrolo[2′,3′:6,7]morphinan (5b). Naltrexone (0.50 g, 1.47 mmol), benzylamine (0.15 mL, 1.50 mmol), EtOH (2.0 mL), and *trans*-4-methyl-β-nitrostyrene (0.24 g, 1.47 mmol) were treated as described for **5a** to provide **5b** (0.57 g, 71%): R_f 0.82 (0.5% MeOH/DCM); mp 243 °C; ^{1}H NMR 7.31 (m, 5H, Ph), 7.10 (m, 4H, ArH), 6.80 (s, 1H, H-2′), 6.61 (d, 1H, J = 8.1, H-2), 6.54 (d, 1H, J = 8.1, H-1), 5.41 (s, 1H, H-5), 5.34 (d, 1H, J = 15.6, benzylic proton), 5.23 (d, 1H, J = 15.6, benzylic proton), 3.28 (d, 1H, H-9), 3.14 (d, 1H, J = 18.5, H-10), 2.80 (dd, 1H, J = 6.6, 18.5, H-10), 2.65 (m, 2H), 2.42 (m, 2H), 2.25 (m, 6H), 1.65 (m, 1H), 0.88 (m, 1H, H-19), 0.52 (m, 2H, H-20, H-21), 0.15 (m, 2H, H-20, H-21); ^{13}C NMR 141.77, 139.83, 135.74, 134.46, 129.94, 129.68, 128.53, 128.48, 128.07, 126.37, 126.14, 123.91, 121.72, 119.65, 118.25, 117.46, 85.61, 74.47, 63.57, 60.39, 54.77, 51.44, 44.88, 32.75, 31.87, 23.98, 21.06, 10.17, 4.58, 4.05; EI MS *m*/*z* (relative intensity) 544 (M^+, 100%), 91 (70%). Anal. ($C_{36}H_{36}N_2O_3$·2HCl·0.25H_2O) C, H, N.

1′-Benzyl-17-cyclopropylmethyl-6,7-dedihydro-3,14-dihydroxy-4,5α-epoxy-5′-methyl-4′-phenylpyrrolo[2′,3′:6,7]-morphinan (5c). Naltrexone (0.80 mg, 2.35 mmol), benzylamine (0.24 mL, 2.40 mmol), EtOH (2.0 mL), and *trans*-β-methyl-β-nitrostyrene (0.39 g, 2.35 mmol) were treated as described for **5a** to give **5c** (0.63 g, 49%): R_f 0.89 (0.5% MeOH/DCM); mp 235 °C; ^{1}H NMR 7.28 (m, 5H, Ph), 7.13 (m, 5H, Ph), 6.60 (d, 1H, J = 8.0, H-2), 6.52 (d, 1H, J = 8.0, H-1), 5.47 (s, 1H, H-5), 5.44 (d, 1H, J = 17.0, benzylic proton), 5.26 (d, 1H, J = 17.0, benzylic proton), 3.24 (d, 1H, J = 6.4, H-9), 3.10 (d, 1H, J = 18.5, H-10), 2.72 (m, 2H), 2.50 (d, 2H, J = 11.0), 2.40 (m, 2H), 2.24 (m, 2H), 2.04 (s, 3H, CH_3), 1.64 (m, 1H), 0.87 (m, 1H, H-19), 0.54 (m, 2H, H-20, H-21), 0.14 (m, 2H, H-20, H-21); ^{13}C NMR 140.18, 130.76, 129.67, 129.04, 128.85, 128.06, 127.49, 126.36, 124.52, 119.53, 118.18, 86.06, 74.62, 63.55, 60.35, 48.37, 44.91, 32.75, 31.17, 23.96, 10.72, 10.19, 4.56, 4.05; EI MS *m*/*z* (relative intensity) 544 (M^+, 100%), 91 (70%). Anal. ($C_{36}H_{36}N_2O_3$·2HCl·0.25H_2O) C, H, N.

1′-Benzyl-6,7-dedihydro-3,14-dihydroxy-4,5α-epoxy-17-propyl-4′-phenylpyrrolo[2′,3′:6,7]morphinan (5d). 19,20-Dihydronaloxone (0.92 g, 2.79 mmol), benzylamine (0.34 mL, 2.85 mmol), EtOH (2.0 mL), and *trans*-β-nitrostyrene (0.42 g, 2.79 mmol) were treated as described for **5a** to give **5d** (0.83 g, 58%): R_f 0.94 (0.5% MeOH/DCM); mp 241 °C; ^{1}H NMR 7.26 (m, 9H, Ph), 7.06 (m, 1H, Ph), 6.81 (s, 1H, H-2′), 6.62 (d, 1H, J = 8.2, H-2), 6.55 (d, 1H, J = 8.2, H-1), 5.40 (s, 1H, H-5), 5.34 (d, 1H, J = 15.6, benzylic proton), 5.21 (d, 1H, J = 15.6, benzylic proton), 3.14 (d, 1H, J = 18.6, H-10), 3.05 (d, 1H, J = 6.3, H-9), 2.82 (dd, 1H, J = 6.3, 18.6, H-10), 2.55 (m, 5H), 2.23 (m, 2H), 1.54 (m, 3H), 0.91 (t, 3H, J = 7.3, CH_3); ^{13}C NMR 142.87, 138.82, 128.58, 128.28, 127.37, 127.32, 126.72, 125.37, 124.50, 122.93, 121.35, 118.76, 85.08, 73.02, 62.95, 56.38, 50.50, 30.61, 23.41, 11.73; EI MS *m*/*z* (relative intensity) 518 (M^+,80%), 489 (100%), 91 (90%). Anal. ($C_{34}H_{34}N_2O_3$·2HCl·0.25H_2O) C, H, N.

1′-Benzyl-6,7-dedihydro-4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-4′-phenylpyrrolo[2′,3′:6,7]morphinan (5e). Oxycodone (1.0 g, 3.18 mmol), benzylamine (0.38 mL, 3.20 mmol), EtOH (3. 0 mL), and *trans*-β-nitrostyrene (0.48 g, 3.18 mmol) were treated as described for **5a** to afford **5e** (0.97 g, 61%): R_f 0.64 (0.15% MeOH/DCM); mp 218 °C; ^{1}H NMR 7.28 (m, 9H, Ph), 7.08 (m, 1H, Ph), 6.84 (s, 1H, H-2′), 6.73 (d, 1H, J = 8.3, H-2), 6.65 (d, 1H, J = 8.3, H-1), 5.44 (s, 1H, H-5), 5.26 (bs, 2H, benzylic proton), 3.88 (s, 3H, O-CH_3), 3.25 (d, 1H, J = 18.7, H-10), 2.96 (d, 1H, J = 6.4, H-9), 2.79 (dd, 1H, J = 6.4, 18.7, H-10), 2.65 (m, 2H), 2.47 (d, 1H, J = 7.0), 2.39 (s, 3H, N-CH_3), 2.26 (m, 2H), 1.61 (m, 1H); ^{13}C NMR 145.86, 144.68, 139.86, 137.38, 132.69, 129.69, 129.36, 128.51, 128.46, 128.21, 127.82, 126.39, 126.27, 124.16, 122.14, 119.82, 117.54, 116.03, 85.74, 74.69, 66.14, 57.32, 51.42, 46.38, 43.18, 32.52, 32.00, 23.40; EI MS *m*/*z* (relative intensity) 504 (M^+, 100%), 91 (40%). Anal. ($C_{33}H_{32}N_2O_3$·2HCl) C, H, N.

1′-Benzyl-6,7-dedihydro-4,5α-epoxy-3,14-hydroxy-17-methyl-4′-phenylpyrrolo[2′,3′:6,7]morphinan (5f). Oxymorphone (0.71 g, 2.36 mmol), benzylamine (0.29 mL, 2.4 mmol), EtOH (3.0 mL), and *trans*-β-nitrostyrene (0.35 g, 2.36 mmol) were treated as described for **5a** to give **5f** (0.67 g, 58%): R_f 0.72 (0.5% MeOH/DCM); mp 239 °C; ^{1}H NMR 7.24

(m, 9H, Ph), 7.05 (m, 1H, Ph), 6.78 (s, 1H, H-2′), 6.61 (d, 1H, J = 8.3, H-2), 6.53 (d, 1H, J = 8.3, H-1), 5.38 (s, 1H, H-5), 5.30 (d, 1H, J = 15.6, benzylic proton), 5.25 (d, 1H, J = 15.6, benzylic proton), 3.16 (d, 1H, J = 18.7, H-10), 2.90 (d, 1H, J = 7.0, H-9), 2.74 (m, 1H), 2.64 (m, 2H), 2.42 (m, 1H), 2.32 (s, 3H, N-CH_3), 2.21 (m, 2H), 1.56 (m, 1H); ^{13}C NMR 144.69, 141.20, 139.71, 137.35, 132.28, 129.67, 129.32, 128.55, 128.50, 128.14, 127.42, 126.19, 126.05, 123.96, 122.02, 119.71, 118.28, 117.40, 85.48, 74.64, 66.18, 51.43, 46.41, 43.07, 32.36, 31.91, 23.37; EI MS *m/z* (relative intensity) 490 (M^+, 60%), 91 (100%). Anal. ($C_{32}H_{30}N_2O_3$·2HCl·0.25H_2O) C, H, N.

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