Discovery of an Opioid κ Receptor Selective Pure Antagonist from a Library of N-Substituted 4β-Methyl-5-(3-hydroxyphenyl)morphans

James B. Thomas,[†] Robert N. Atkinson,[†] Nivedita Namdev,[†] Richard B. Rothman,[‡] Kenneth M. Gigstad,[†] Scott E. Fix,[†] S. Wayne Mascarella,[†] Jason P. Burgess,[†] N. Ariane Vinson,[†] Heng Xu,[‡] Christina M. Dersch,[‡] Buddy E. Cantrell,[§] Dennis M. Zimmerman,[§] and F. Ivy Carroll*[,†]

Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709, Clinical Psychopharmacology Section, NIDA Addiction Research Section, P.O. Box 5180, Building C, 4980 Eastern Avenue, Baltimore, Maryland 21224, and Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 4628

Received February 20, 2002

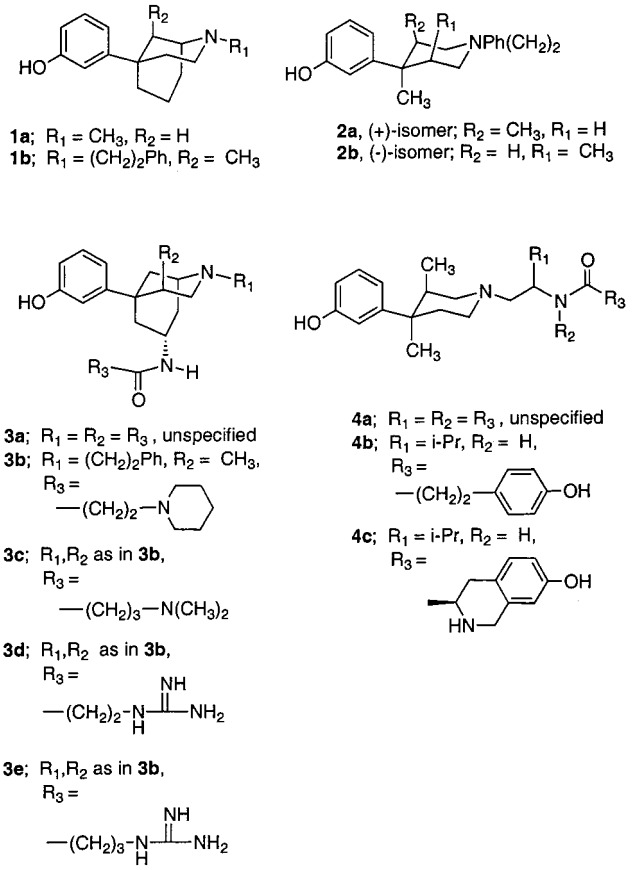
A library of compounds biased toward opioid receptor antagonist activity was prepared by incorporating *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphans as the core scaffold using simultaneous solution phase synthetic methodology. From this library, *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)-7α-[3-(1-piperidinyl)propanamido]morphan [(−)-**3b**] was identified as the first potent and selective κ opioid receptor antagonist from the 5-phenylmorphan class of opioids.

Introduction

Since the discovery of three distinct opioid receptors (μ, δ, and κ), researchers studying the underlying mechanisms of opiate addiction have sought highly potent and receptor subtype selective antagonists.[1] While many agonist structures have been discovered for the opioid receptor system, very few structures displaying potent pure antagonist activity have been identified.[2] The 5-(3-hydroxyphenyl)morphans such as **1a** (Chart 1) are one class of compounds that has produced both agonists and antagonists for the opioid receptors.[3,4] These compounds are structurally similar to the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine class of opioid antagonists (**2a**,**b**) with the exception that they are conformationally rigid as compared to the phenylpiperidines due to the addition of a bridging ring. While potent antagonists based on the 5-(3-hydroxyphenyl)-morphan scaffold remained an elusive goal for many years, we recently demonstrated that *N*-phenethyl-9β-methyl-5-(3-hydroxyphenyl)morphan (**1b**) is a highly potent opioid receptor antagonist that is pharmacologically very similar to *N*-phenethyl-*trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine (**2a**).[5]

In a previous paper, we reported the discovery of **4b** from the library of compounds based on general structure **4a** (Chart 1).[6] Subsequent structure−activity relationships (SAR) based on this screening hit led to the discovery of the highly potent and selective κ opioid antagonist JDTic (**4c**).[7] The discovery that **1b** possessed potent antagonist activity at the μ, δ, and κ opioid receptor similar to that available in the 4-phenylpiperidine series suggested that libraries of compounds (**3a**) where R_3 contained an amino group located at different distances relative to the rigid morphan structure might act as a κ address moiety and thus bias the library for the opioid κ receptor.[6] As illustrated by general structures **3a** and **4a**, the libraries differ by the placement of their diversity elements relative to the core antagonist ligand. Thus, if the *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine substructure, common to both **3a** and **4a**, associates with a similar antagonist domain, then the diversity elements affixed to these scaffolds can occupy different regions of the opioid receptor. The use of this dual scaffold strategy was undertaken to provide a more

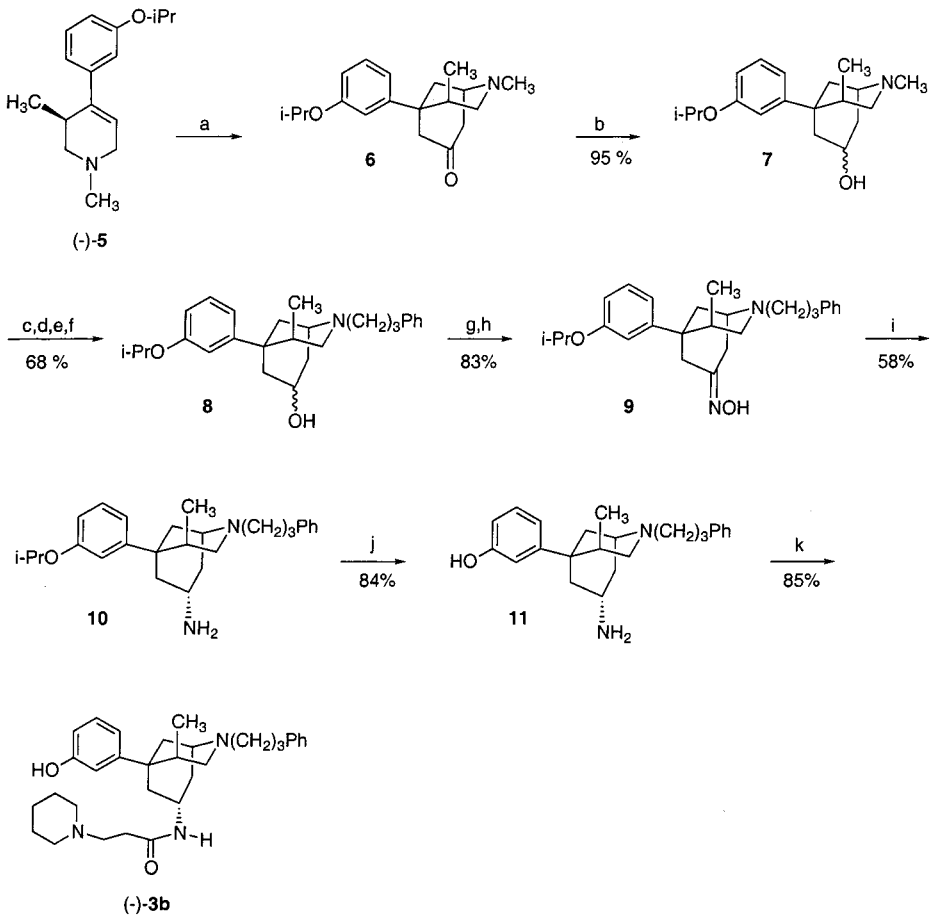
Chart 1



* To whom correspondence should be addressed. Tel: 919 541-6679. Fax: 919 541-8868. E-mail: fic@rti.org.
[†] Research Triangle Institute.
[‡] NIDA Addiction Research Section.
[§] Eli Lilly and Company.

10.1021/jm020084h CCC: $22.00
Published on Web 07/04/2002

Scheme 1[a]



[a] Reagents: (a) *n*-BuLi and then $ClCH_2C(OCH_2OCH_3)CH_2$ and then 1 N HCl, MeOH. (b) $NaBH_4$, EtOH. (c) Benzoyl chloride, pyridine, CH_2Cl_2, catalytic 4-*N*,*N*-dimethylaminopyridine. (d) 1-Chloroethylchloroformate, dichloroethane. (e) LiOH, H_2O, CH_3OH. (f) $NaBH(OAc)_3$, $Ph(CH_2)_2CHO$. (g) $(COCl)_2$, DMSO, Et_3N. (h) $HONH_2$·HCl, EtOH. (i) Na, *i*-PrOH, toluene. (j) 48% HBr, glacial HOAc, reflux. (k) BOP, Et_3N, $C_5H_{10}N(CH_2)_2CO_2H$.

thorough exploration for complimentary binding sites in the vicinity of the opioid antagonist binding domain as compared to that provided by a single scaffold.

In this paper, we report that screening of a library based on general structure **3a** led to the discovery of **3b**, the first 5-(3-hydroxyphenyl)morphan-based compound to display selective antagonist activity for the κ receptor over both the μ and δ opioid receptors (Chart 1). Additional studies with (−)- and (+)-**3b** showed that the (−)-enantiomer [(−)-**3b**] was responsible for the observed pharmacological activity.

Chemistry

The synthesis of (+)- and (−)-**3b** and (−)-**3c**−**e** utilized the same synthetic methods developed for racemic **6**[8] but started with either (+)- or (−)-**5**.[9] To simplify Scheme 1, only the synthesis of (−)-**3b** is illustrated. As previously reported for racemic **5**, treatment of optically pure **5** with *n*-butyllithium followed by addition to a solution of Okahara's reagent followed by concomitant deprotection and acid-catalyzed cyclization gave the 7-oxo derivative **6** as a single diastereomer and in this case a single enantiomer. Conversion of **6** to **8** was accomplished in 65% overall yield without purification of intermediates by reducing the carbonyl group in **6** with sodium borohydride to give **7** followed by protection of the hydroxyl group as the benzoate ester, treatment with 1-chloroethyl chloroformate to remove the *N*-methyl group by carbamate formation, hydrolysis of both the newly formed carbamate and the ester groups using lithium hydroxide in aqueous refluxing methanol, and finally reductive alkylation with hydrocinnamaldehyde and sodium triacetoxyborohydride. Swern oxidation of **8** followed by conversion of the carbonyl to the oxime with hydroxylamine hydrochloride provided the oxime intermediate **9** in 83% yield from **8**. Reduction of **9** using sodium and 2-propanol in refluxing toluene gave **10** in 54% yield.[10] Removal of the isopropyl group in **10** using 48% hydrobromic and glacial acetic acid then provided the 7-amino-derivatized scaffold (**11**) in 84% yield.

Coupling of appropriately substituted carboxylic acid derivatives to **11** provided the desired library of compounds. Briefly, a mixture of the appropriate acid derivative, the phenylmorphan scaffold **11**, and the coupling reagent, benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP, Castro's reagent), were combined in tetrahydrofuran (THF)/triethylamine in parallel using an Argonaut Quest 210. For (−)-**3b**, a 1-piperidinopropionic acid side chain was used to give (−)-**3b** in 85% yield. For those acid derivatives containing a Boc-protected guanidino group, as in **3d**,**e**, a trifluoroacetic acid deprotection step was added.

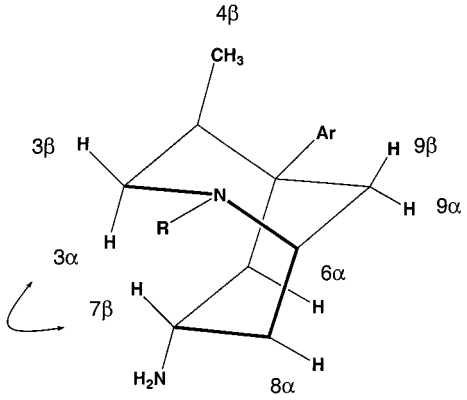


Figure 1. Observation of strong through-space interactions between the 3α and 7*β* protons provided the relative stereochemistry for the 7-amino group in intermediate **11** (R = $(CH_2)_3Ph$).

The relative stereochemical assignment for the 7-amino group in the key intermediate **11** was based on the observation of a strong through-space interaction in the ROESY spectrum between the 3α[11] and 7*β* protons (Figure 1), which places the amino group on the endo face of the ring system. The relative positions of the protons critical to this assertion (3α and 7*β*) were established through a series of steps beginning with a full assignment of all protons and carbons using gradient-enhanced correlation spectroscopy (COSY), HSQC, and HMBC spectra. From this point, the identity of the H3α proton was determined by its COSY interaction with one other proton (H4α) that was readily identified by its COSY interaction with the 4*β*-methyl group. The 7*β* proton was assigned based on its chemical shift and was differentiated from H1 by its large 1,2-diaxial coupling constants with H6α and H8α. The protons on C8 and C6 were in turn readily distinguishable since both C8 protons showed a COSY correlation with H1 while H6α gave a three bond correlation with C4 in the HMBC spectrum. The chemical shift of both C9 protons was located by observation of a COSY correlation between H9α and H1.

The relative stereochemical assignments were then available from the ROESY spectrum, which indicated an exo position for H3*β* due to its strong correlation with the 4*β*-methyl group. The methyl group also showed a strong interaction with H9*β*. Likewise, a mutual correlation between H9α, H6α, and H8α indicates that these protons occupy the endo face on the opposite side of the azabicyclo ring system. Because H3*β* occupies an endo position, H3α must occupy the endo face of the ring system. Given this, the strong interaction observed between H3α and H7*β* implies that the amino group must reside on the endo face along with H6*β* and H8*β*.

Biological

The screening of compound libraries was performed at a single concentration of test compound (100 nM) as previously reported.[6] Compounds showing >70% inhibition of radioligand binding and their close analogues were resynthesized and submitted for determination of their K_i value at each of the opioid receptors. The binding affinities of (+)- and (−)-**3b** as well as (−)-**3c**−**e** and the two optical isomers of **11** were determined using competitive binding assays following previously reported procedures (Table 1).[12] The tissues used in the binding assay included rat brain (*μ* and *δ* receptors) and guinea pig brain (*κ* receptors). Measures of antagonism were obtained by monitoring the test compounds' ability to inhibit stimulation of [^{35}S]GTP-*γ*-S binding produced by the selective agonists, (D-Ala^2, MePhe^4, Glyol^5)enkephalin (DAMGO, *μ* receptor), Phe(p-Cl)^4 cyclo[D-Pen^2, D-Pen^5]-enkephalin (Cl-DPDPE, *δ* receptor), and 5α,7α,8*β*-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69,593, *κ* receptor) in cloned human opioid receptors (Table 2) transfected into Chinese hamster ovary cells.[13,14]

Table 1. Radioligand Binding Data for Test Compounds in *μ*, *δ*, and *κ* Assays Using Opioid Receptor Obtained from Brain Tissues (*μ* and *δ*, Rat; *κ*, Guinea Pig)

	K_i (nM ± SD)				
compd	[^{3}H]DAMGO[a]	[^{3}H]DADLE[b]	[^{3}H]U69,593[c]	*μ*/*κ*	*δ*/*κ*
(+)-**11**	207 ± 24	246 ± 22	893 ± 148	0.23	0.27
(−)-**11**	3.3 ± 0.3	14.7 ± 1.3	122 ± 5.6	0.03	0.1
(−)-**3b**	147 ± 9.8	>3400	4.3 ± 0.7	34	>790
(+)-**3b**	775 ± 55	2184 ± 93	36 ± 5	22	61
(−)-**3c**	57 ± 4.4	1457 ± 113	12 ± 0.65	5	122
(−)-**3d**	5.2 ± 0.3	56.5 ± 3.4	23.3 ± 3	0.2	2
(−)-**3e**	87 ± 6.3	1744 ± 98	13.2 ± 1.7	7	132
nor-BNI, **13**	65.0 ± 5.6	86 ± 7.2	1.09 ± 0.14	60	79

[a] [^{3}H]DAMGO [(D-Ala^2, MePhe^4, Glyol^5)enkephalin]. Tritiated ligand selective for *μ* opioid receptor. [b] [^{3}H]DADLE [(D-Ala^2, D-Leu^5)enkephalin]. Tritiated ligand selective for *δ* opioid receptor. [c] [^{3}H]U69,593 {[^{3}H](5α,7α,8*β*)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzeneacetamide}. Tritiated ligand selective for *κ* opioid receptor.

Table 2. Inhibition of Agonist-Stimulated [^{35}S]GTP-*γ*-S Binding by (−)-**3b** in Cloned Human *μ*, *δ*, and *κ* Opioid Receptors

	K_e (nM ± SD)				
compd	DAMGO[a]	Cl-DPDPE[b]	U69,593[c]	*μ*/*κ*	*δ*/*κ*
(−)-**3b**	41.7 ± 3.74	ND[d]	0.24 ± 0.01	175	
nor-BNI, **13**	19 ± 1.52	4.6 ± 0.39	0.04 ± 0.003	475	115

[a] DAMGO [(D-Ala^2, MePhe^4, Glyol^5)enkephalin]. Agonist selective for *μ* opioid receptor. [b] Cl-DPDPE [Phe(p-Cl)^4 cyclo[D-Pen^2, D-Pen^5]enkephalin]. Agonist selective for *δ* opioid receptor. [c] U69,593 {[^{3}H](5α,7α,8*β*)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]-dec-8-yl]benzeneacetamide}. Agonist selective for *κ* opioid receptor. [d] The K_e for the *δ* receptor was not determined because of the low binding affinity at this site (see Table 1).

Results and Discussion

The initial library screening results showed that few compounds possessed high affinity for the *κ* receptor. Indeed, only **3b** gave greater than 70% inhibition of [^{3}H]-U69,593 binding at a concentration of 100 nM. Overall, the results appeared to be lower than one would expect based on our previous observations with the 5-(3-hydroxyphenyl)morphan antagonists.[5] As opioid receptors are well-known to distinguish between enantiomers, we speculated that part of the lower affinity might arise as a consequence of the addition of a 7-amido substituent to the phenylmorphan nucleus as this would significantly increase the size of such derivatives relative to unsubstituted phenylmorphans. Such increases in size could in turn provide a clearer distinction between optical antipodes. These concerns were validated by obtaining the binding data for the optical isomers of **11** (Table 1), which revealed that (−)-**11** with K_i values of 3.3, 14.7, and 122 nM for the *μ*, *δ*, and *κ*,

respectively, possesses far greater affinity at all opioid receptors relative to (+)-**11** with its K_i values of 207, 247, and 893 nM. These figures indicate a 63-, 17-, and 7-fold preference for the (−)-enantiomer by the μ, δ, and κ receptors.

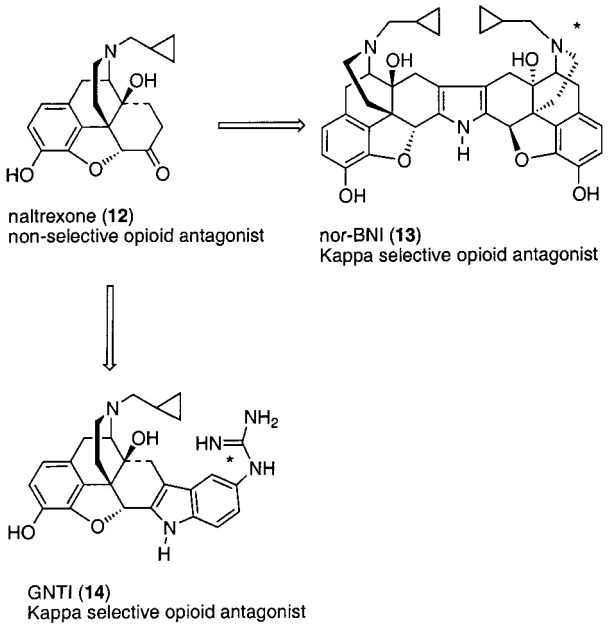
The addition of a 7α-amido-3-(1-piperidinyl)propionyl side chain provided further evidence for a separation of activities between enantiomers. Unlike (−)-**11**, however, (−)-**3b** possessed a high affinity for the opioid κ receptor (K_i value of 4.3 vs 122 nM) and a lower affinity for the μ receptor (K_i value of 147 vs 3.3 nM) and δ receptor (K_i value of >3400 vs 147 nM). Taken together, the comparison of the binding characteristics for compounds (−)-**3b** and (−)-**11** indicates that the 3-(1-piperidinyl)propamido side chain reduces both μ and δ affinity while concomitantly enhancing affinity at the κ receptor. As compared with the standard κ antagonist nor-binaltorphimine (nor-BNI, **13**), compound (−)-**3b** demonstrates roughly one-half of the μ vs κ selectivity (34- vs 60-fold) but a decidedly improved κ vs δ selectivity (>790- vs 79-fold).

Several other library compounds that showed good affinity in screening or were structurally similar to (−)-**3b** were resynthesized in optically pure form using (−)-**11** for direct comparison with compound (−)-**3b**. Compound (−)-**3c**, for example, differs from (−)-**3b** by an additional methylene group in the chain connecting the amino and carbonyl groups as well as possessing a dimethylamino group on the pendant carbon rather than a piperidine ring. In the binding experiments, compound (−)-**3c** showed about 3-fold less affinity for the κ receptor and about 3-fold higher affinity for the μ receptor relative to (−)-**3b**. Neither compound showed appreciable affinity for the δ receptor. Thus, the overall effect of the structural changes in going from **3b** to **3c** is elimination of the modest μ vs κ selectivity displayed by (−)-**3b**.

Compound (−)-**3d** differs from (−)-**3b** by replacement of the piperidine ring for a guanidine group while maintaining the same carbon chain length. This structural difference was found to significantly alter not only the receptor affinity but also the receptor preference of the resulting ligand. As compared to (−)-**3b**, (−)-**3d** favors the μ receptor over the κ receptor with a K_i value of 5.2 vs the 147 nM value found for (−)-**3b** at the μ receptor. This functional group change also provides a dramatic increase in affinity for the δ opioid receptor with a δ K_i value of 56.5 vs >3400 nM for (−)-**3b**. In the κ receptor assay, (−)-**3d** shows diminished affinity relative to (−)-**3b** (23.3 vs 4.3 nM). Altogether, the replacement of piperidine with a guanidino group leads to increases in affinity for both μ and δ opioid receptors and a slight decrease in affinity for the κ receptor.

Compound (−)-**3e** like (−)-**3d** has a guanidino group in its side chain rather than piperidine but differs from (−)-**3d** in the length of its side chain. The addition of a single methylene spacer provides a 2-fold increase in κ affinity (13 vs 23 nM) but losses of receptor affinity in both the μ (87 vs 5.2 nM) and δ receptor assays (1744 vs 56 nM) relative to (−)-**3d**. In this respect, (−)-**3e** behaves more like the tertiary amine-bearing ligand (−)-**3c** rather than the guanidino-bearing ligand (−)-**3d**. As found earlier for (−)-**3c**, however, compound (−)-**3e** is neither very potent nor selective for the κ receptor vs the μ opioid receptor.

Chart 2



Compound (−)-**3b** was also assayed for its antagonist activity by measuring its ability to inhibit agonist-stimulated [^{35}S]GTP-γ-S binding in cloned human opioid receptors (Table 2). In this assay, (−)-**3b** retains the κ receptor as its principle site of action, and its K_e value showed a 18-fold increase relative to its K_i value in the binding assay (0.24 vs 4.3 nM). In the μ receptor assay, (−)-**3b** demonstrated a 5-fold decrease in its K_e value, which together provided a significant increase in its μ vs κ receptor selectivity (175-fold) relative to the binding assay. The K_e value at the δ receptor was not measured due to the very low affinity of (−)-**3b** for the δ opioid receptor. Overall, the data from the functional assay demonstrate that the novel 5-(3-hydroxyphenyl)morphan-based antagonist (−)-**3b** is both potent and selective for the κ opioid receptor.

From a historical perspective, the pharmacological behavior of compound (−)-**3b** parallels previous studies that lead to the discovery of κ opioid selective antagonists. In a broad sense, the addition of pendant amino groups to nonselective opioid receptor antagonist scaffolds to serve as κ selective address units has been demonstrated by Portoghese as illustrated in Chart 2. In this case, the nonselective antagonist naltrexone (**12**) was modified to possess a pendant amine (denoted by an asterisk in the chart) that served to promote affinity and selectivity of the resulting ligand, nor-binaltorphimine (nor-BNI, **13**), for the κ receptor.[15−17] The discovery of the structurally simplified κ antagonist 5′-guanidino-naltrindole (GNTI, **14**) followed the same concept but in this case utilized a guanidine rather than a tertiary amine as the κ address element.[18]

In a more closely related example, we recently demonstrated that addition of a methylene amino group to antagonist **4b** gave a highly potent κ selective antagonist JDTic (**4c**). Taken together with our previous observations of potent but nonselective opioid antagonist activity in **1b**, the discovery of κ selective antagonist activity in (−)-**3b** appears to be consistent with the

concepts of message and address substructures described for previously discovered κ antagonists. In this case, the *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan scaffold could be viewed as the opioid "message" fragment while the 3-(1-piperidinyl) group might be considered as the κ address moiety.[19,20]

However, one aspect of the results demonstrated here is significantly different from the observations made by Portoghese and is worthy of note. This relates to the need for rigid scaffolds in the oxymorphone-based antagonists such as **13** or **14** required to properly align the pendant amine address element with an anionic residue specific to the κ receptor. Such a requirement has been the subject of earlier reports in oxymorphone-based antagonist research.[16,17] Clearly, such rigid scaffolds are absent in both the phenylmorphan-based compound presented herein and the phenylpiperidine-based compound **4c** reported earlier. While the source of these differences has not yet been ascertained, a comparison of the structures of all of the known classes of κ antagonist suggests that the need for a rigid scaffold may be a characteristic particular to the oxymorphones.

Conclusions

This study shows that the addition of a 4β-methyl group to *N*-substituted-5-(3-hydroxyphenyl)morphans results in compounds that show pure opioid antagonist activity. More important, the study shows that the addition of a 7α-3-(1-piperidinyl)propanamido group to the 4β-methyl-5-(3-hydroxyphenyl)morphan structure provides a compound [(−)-**3b**], which possesses potent and selective antagonist activity for the opioid κ receptor. To our knowledge, this is the first demonstration of κ selective antagonist activity in the 5-phenylmorphan series.

Experimental Section

Elemental analyses were obtained by Atlantic Microlabs, Inc. and are within ±0.4% of the calculated values. All optical rotations were determined at the sodium D-line using a Rudolph Research Autopol III polarimeter (1 dm cell). ^{1}H nuclear magnetic resonance (NMR) spectra were determined on a Bruker Avance spectrometer operating at 300 MHz for proton using tetramethylsilane as an internal standard. Silica gel 60 (230−400 mesh) was used for all column chromatography. Mass spectral data was obtained using a Finnegan LCQ electrospray mass spectrometer in positive ion mode at atmospheric pressure. All reactions were followed by thin-layer chromatography (TLC) using Whatman silica gel 60 TLC plates and were visualized by UV, charring using 5% phosphomolybdic acid in ethanol and/or exposure to iodine vapor. All solvents were reagent grade. THF was dried over sodium benzophenone ketyl and distilled prior to use. Methylene chloride was distilled from calcium hydride prior to use.

(−)-(1*R*,4*S*,5*S*)-5-[3-(1-Methylethoxy)phenyl]-2,4-dimethyl-2-azabicyclo[3.3.1]nonan-7-one (6). To a solution of (*S*)-1,2,3,6-tetrahydro-1,3-dimethyl-4-[3-(1-methylethoxy)-phenyl]pyridine (**5**) (1 equiv) dissolved in THF (20 mL/g) and cooled to −10 °C was added *n*-butyllithium (1.6 M in hexanes) slowly until a red color was maintained followed by an addition of 1.1 equiv. This material was stirred for 1 h at −10 °C and then cannulated quickly into a solution of Okahara's reagent (distilled to high purity) in THF (15 mL/g, 1.1 equiv) at −78 °C followed by stirring for 2 h. The temperature should be kept below −30 °C during cannulation. This material was then poured into 2 N HCl and extracted twice with ethyl ether. The aqueous layer was allowed to stand for 15 min followed by addition of 50% NaOH to pH 14 and extraction (3×) with ethyl ether. The ether was then washed (1 N NaOH, H_2O), and the solvent was removed under vacuum. The resulting residue of product and water was dissolved in MeOH (30 mL/g), and nitrogen was bubbled through the solution for 5 min. To this was added concentrated HCl (2 mL/g), and the mixture was allowed to stand at room temperature until the reaction was complete as indicated by TLC [TLC condition: SiO_2; elution with 50% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$; detection: 5% phosphomolybdic acid in ethanol]. To this mixture was added 50% NaOH to adjust the pH to ∼10, and the methanol was removed under aspirator vacuum. The aqueous residue was then extracted several times with 3:1 (methylene chloride:THF). The organic extracts were combined and washed twice with water and once with brine, dried over sodium sulfate, and evaporated to an oil. This material was purified by flash chromatography on silica gel using 15−25% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$ to give **6** in 70% yield from **5**. ^{1}H NMR: 7.24 (t, 1H, J = 7.5 Hz), 6.77 (m, 3H), 4.55 (m, 1H), 3.49 (s, 1H), 2.91 (dd, 2H, J = 17 and 16.5 Hz), 2.60 (m, 2H), 2.35 (m, 5H), 2.05 (m, 3H), 1.35 (m, 6H), 0.78 (d, 3H, J = 6.8 Hz).

(−)-(1*R*,4*S*,5*S*)-5-[3-(1-Methylethoxy)phenyl]-2,4-dimethyl-2-azabicyclo[3.3.1]nonan-7-ol (7). To a solution of **6** (1 equiv) dissolved in absolute ethanol (7 mL/g of **6**) was added solid sodium borohydride (1 equiv) slowly over 10 min. This mixture was allowed to stir at room temperature for 24 h after which time the ethanol was removed under aspirator vacuum and the residue was carefully dissolved in 1.0 N HCl (6 mL/g of **6**). This solution was washed twice with ether (3 mL/g of **6** for each wash), and then, the aqueous solution was made basic with 50% NaOH solution (pH 14), and the ether layers were discarded. This solution was then saturated with sodium chloride and extracted five times with 3:1 methylene chloride:THF (3 mL/g of **6** for each extraction), and the combined organic layers were dried over magnesium sulfate, and the solvent was removed under aspirator vacuum to provide **7** as a yellow oil in 95% yield from **6** as a mixture of 7-hydroxy diastereomers. This material was used in the next step without purification. ^{1}H NMR ($CDCl_3$): δ 0.46−0.48 (d, 3H, J = 6.90 Hz), 1.32−1.34 (d, 6H, J = 6.02 Hz), 1.47−1.58 (m, 2H), 1.87−1.93 (dd, 2H, J = 14.16, 5.09 Hz), 2.27−2.47 (m, 8H), 2.69−2.75 (dd, 1H, J = 11.64, 5.26 Hz), 3.09 (br s, 1H), 4.02−4.05 (t, 1H, J = 4.83 Hz), 4.47−4.59 (septet, 1H, J = 6.07 Hz), 5.30 (br s, 1H), 6.68−6.81 (m, 3H), 7.16−7.62 (m, 1H).

(−)-[(1*R*,4*S*,5*S*,7*R*)-5-[3-(1-Methylethoxy)phenyl]-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-ol (8). To a solution of **7** (1 equiv) in anhydrous methylene chloride (35 mL/g of **15**) at room temperature was added triethylamine (1.1 equiv), a small amount of *N*,*N*-dimethylaminopyridine (0.5 equiv), and benzoyl chloride (2.0 equiv), and the resulting mixture was stirred overnight under a nitrogen atmosphere. Following this, the mixture was washed twice with 10% NaOH, once with water and then dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting oil was not purified but carried directly to the next step. ^{1}H NMR ($CDCl_3$): δ 8.18 (d), 8.02 (d), 7.56 (d), 7.46 (d), 7.20 (t), 6.75−6.69 (m), 5.32−5.28 (m), 4.56−4.52 (quintet), 3.65−3.50 (m), 3.30−3.15 (dd), 3.00 (s), 2.78−2.75 (q), 2.49 (s), 2.44 (s), 2.43−2.25 (m), 2.30 (s), 2.25−1.85 (m), 1.34−1.32 (d), 1.17−1.12 (t), 0.76−0.74 (d).

To a solution of the intermediate oil (1 equiv) in anhydrous 1,2-dichloroethane (20 mL/g of intermediate) at reflux was added 1-chloroethyl chloroformate (1.1 equiv) dropwise. The resulting solution was heated under reflux for 2.5 h and then cooled to room temperature. This mixture was then washed with saturated bicarbonate solution and water, then the organic layer was evaporated, and the resulting oil was dissolved immediately in 1:1 methanol:water. To this was added LiOH (1 g/g of intermediate) and then heated to reflux until the reaction was complete as judged by TLC (∼2 h). After it was cooled to room temperature, the methanol was removed under aspirator vacuum and the remaining aqueous solution was saturated with sodium chloride. This was then extracted

with 3:1 CH_2Cl_2:THF until all of the product was removed, and the combined extracts were washed once with water. Removal of the solvent provided slightly impure material that was not purified but carried directly to the next step. ^{1}H NMR ($CDCl_3$): δ 0.48−0.65 (m, 3H), 1.32−1.34 (d, 6H), 1.54−1.72 (m, 2H), 1.97−2.12 (m, 4H), 2.58−2.64 (m, 1H), 3.45−3.59 (m, 3H), 3.91−4.02 (m, 1H), 4.47−4.68 (m, 1H), 6.68−6.78 (m, 3H), 7.17−7.35 (t, 1H).

To a solution of material from the previous step (1 equiv) in anhydrous 1,2-dichloroethane (40 mL/g of intermediate) was added hydrocinnamaldehyde (freshly opened, 1.2 equiv) and $NaBH(OAc)_3$ (1.2 equiv), and the resulting mixture was stirred for 24 h. After this time, the resulting mixture was washed with 1 N NaOH and the aqueous layer was back-extracted with chloroform. The combined organic layers were dried over sodium sulfate, and the solvent was removed at reduced pressure to give crude **8** as a mixture of diastereomers. This material was purified by flash chromatography on silica gel to give **8** as a yellow oil in 65% yield from **7**. ^{1}H NMR ($CDCl_3$): δ 0.43−0.45 (d, 3H, J = 6.82 Hz), 1.31−1.33 (d, 6H, J = 6.03 Hz), 1.40−1.53 (m, 2H), 1.81−1.88 (m, 4−5 H), 2.27−2.70 (m, 10H), 3.14 (s, 1H), 4.06 (s, 1H), 4.51−4.55 (m, 1H), 6.08 (br s, 1H), 6.68−6.89 (m, 3H), 7.15−7.54 (m, 6H).

(−)-[(1*R*,4*S*,5*S*,7*R*)-5-[3-(1-Methylethoxy)phenyl]-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-one Oxime (9). Dimethyl sulfoxide (6.6 equiv) in dry CH_2Cl_2 (3 mL/g of **8**) was added dropwise over 20 min to a solution of 2 M oxalyl chloride (3 equiv) in CH_2Cl_2 at −78 °C. The reaction mixture was allowed to warm to −20 °C. Maintaining a temperature of −20 °C, **8** (1 equiv) in CH_2Cl_2 (4 mL/g of **8**) was added dropwise over 15 min to the reaction mixture. The reaction was stirred for an additional 30 min and then quenched with the careful addition of triethylamine (8 equiv). The reaction mixture was allowed to warm to room temperature and washed with saturated $NaHCO_3$, the organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [5−10% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in CH_2Cl_2] to afford the 7-oxo derivative of **8** (91%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 6H), 6.77 (m, 3H), 4.54 (sept., 1H, J = 6.1 Hz), 3.47 (br, 1H), 2.83 (m, 2H), 2.68−2.52 (m, 5H), 2.43 (t, 2H, J = 6.9 Hz), 2.09−1.95 (m, 3H), 1.74 (m, 3H), 1.33 (d, 6H, J = 6.0 Hz), 0.79 (d, 3H, J = 6.8 Hz).

The ketone from the previous step (1 equiv) and hydroxylamine hydrochloride (5 equiv) in EtOH (absolute, 17 mL/g of ketone) were heated under reflux for 3 h. The reaction mixture was allowed to cool to room temperature, and the ethanol was removed under reduced pressure. The oil thus obtained was dissolved in 2 M NaOH (17 mL/g of ketone), and the product was extracted with 3:1 CH_2Cl_2:THF (4 × 10 mL/g of ketone). The organic layers were collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The product obtained was purified by flash chromatography [5−10% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in CH_2Cl_2] to afford **9** (90%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 10.09 (br, 1H), 7.26−7.13 (m, 6H), 6.88−6.72 (m, 3H), 4.54 (m, 1H), 3.63 (d, 1H, J = 17 Hz), 3.29 (br, 1H), 2.94−2.85 (m, 2H), 2.69−2.41 (m, 5H), 2.29 (d, 1H, J = 15.9 Hz), 2.04−1.65 (m, 6H), 1.33 (d, 6H, J = 6.0 Hz), 0.76 (d, 3H, J = 6.9 Hz).

(−)-[(1*R*,4*S*,5*S*,7*R*)-5-[3-(1-Methylethoxy)phenyl]-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine (10). Compound **9** (1 equiv) (5.51 g, 13.1 mmol) in a minimum of dry 2-propanol was added dropwise over 1 h to a refluxing mixture of dry toluene (35 mL/g of **9**) and sodium (150 equiv). After complete addition of oxime, two portions of 2-propanol (23 mL/g of **9**) were added dropwise over 30 min. The reaction mixture was heated to reflux until all of the sodium was consumed. The reaction mixture was allowed to cool to 50 °C and then quenched by careful addition of water (135 mL/g of **9**). The toluene layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 90 mL/g of **9**). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The product was purified by flash chromatography [25−50% (80% $CHCl_3$: 18% CH_3OH:2% NH_4OH) in $CHCl_3$] to afford starting material **9** (18% recovered) and **10** (58%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.28−7.15 (m, 6H), 6.76−6.68 (m, 3H), 4.52 (sept., 1H, J = 6.1 Hz), 3.51 (m, 1H), 3.13 (m, 1H), 2.82 (m, 1H), 2.64 (m, 3H), 2.47 (m, 2H), 2.31 (m, 3H), 2.11 (m, 1H), 1.77 (m, 2H), 1.56 (m, 3H), 1.31 (d, 6H, J = 6.0 Hz), 1.15 (m, 1H), 0.94 (m, 1H), 0.73 (d, 3H, J = 6.9 Hz).

(−)-3-[(1*R*,4*S*,5*S*,7*R*)-7-Amino-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol [(−)-11]. A solution of **10** (1 equiv) (2.53 g, 6.23 mmol) in glacial acetic acid (8 mL/g of **10**) and 48% HBr (8 mL/g of **10**) was heated to reflux for 15 h. The reaction mixture was allowed to cool to room temperature, added to ice (40 g/g of **10**), and adjusted to pH 10 with 50% NaOH. The aqueous layer was extracted with 3:1 *n*-butanol:toluene (3 × 40 mL/g of **10**), the organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The product was purified by flash chromatography [50% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in CH_2Cl_2] to afford (−)-**11** (84%) as a yellow oil; $[\alpha]_D^{20}$ −40.8° (c 1.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.27−7.07 (m, 6H), 6.65−6.58 (m, 3H), 4.33 (br, 2H), 3.54 (br, 1H), 2.79 (m, 1H), 2.66−2.53 (m, 3H), 2.46 (t, 2H, J = 7.0 Hz), 2.31 (m, 3H), 2.04 (br, 1H), 1.77 (t, 2H, J = 7.2), 1.53 (m, 1H), 1.14 (m, 1H), 0.98 (m, 1H), 0.70 (d, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 157.5, 151.8, 142.8, 129.7, 128.7, 126.1, 116.7, 113.9, 113.1, 56.3, 54.7, 53.9, 52.1, 47.2, 40.8, 38.1, 33.8, 33.0, 29.4, 19.1. Anal. ($C_{24}H_{32}N_2O$) C, H, N.

(+)-3-[(1*R*,4*S*,5*S*,7*R*)-7-Amino-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol [(+)-11]. This compound was prepared according to the same procedure as described above for (−)-3-[(1*R*,4*S*,5*S*,7*R*)-7-amino-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol [(−)-**11**] with the exception that the synthesis begins with (*R*)-1,2,3,6-tetrahydro-1,3-dimethyl-4-[3-(1-methylethoxy)phenyl]pyridine rather than (*S*)-1,2,3,6-tetrahydro-1,3-dimethyl-4-[3-(1-methylethoxy)phenyl]pyridine. The product was obtained from the phenol deprotection step in 83% yield as a yellow oil; $[\alpha]_D^{20}$ +39° (c 1.0, $CHCl_3$). The NMR spectra were identical to those obtained for (−)-**11**. Anal. ($C_{24}H_{32}N_2O$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxy)phenyl-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(1-piperidinyl)propanamide [(−)-3b]. To a solution of **11** (1 equiv) was added BOP reagent (1.1 equiv), 1-piperidinepropionic acid (2 equiv), and triethylamine (5 equiv) in dry THF (250 mL/g of **11**). The reaction mixture was stirred under N_2 at room temperature for 4 h. The mixture was diluted with Et_2O (20 mL) and washed with saturated $NaHCO_3$, followed by water. The organic layers were collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The product was purified by flash chromatography [33% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$] to afford (−)-**3b** (85%) as an off-white foam. ^{1}H NMR ($CDCl_3$): δ 8.70 (br, 1H), 7.27−7.13 (m, 6H), 6.90−6.67 (m, 3H), 4.64 (m, 1H), 3.22 (br, 1H), 3.05 (m, 1H), 2.80−2.02 (m, 14H), 1.82−1.34 (m, 10H), 1.31−0.97 (m, 4H), 0.72 (d, 3H, J = 6.9 Hz); $[\alpha]_D^{20}$ −50.9° (c 1.42, CH_3OH). Anal. ($C_{32}H_{45}N_3O_2$) C, H, N.

(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxy)phenyl-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(1-piperidinyl)propanamide [(+)-3b]. This compound was prepared in 88% yield according to the method described for (−)-**3b** starting from (+)-3-[(1*S*,4*R*,5*R*,7*S*)-7-amino-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol [(+)-**11**]. The method of purification and ^{1}H NMR ($CDCl_3$) were identical to those found for the antipode; $[\alpha]_D^{20}$ +49.8° (c 0.275, CH_3OH). Anal. ($C_{32}H_{45}N_3O_2$) C, H, N.

(−)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxy)phenyl-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-4-(*N*,*N*-dimethylamino)butanamide [(−)-3c]. This compound was prepared in 89% yield according to the method described for (−)-**3b** starting from (+)-**11** and 4-(dimethylamino)butyric acid hydrochloride**.** The product was obtained as an off-white foam following purification by flash chromatography [33% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$]. ^{1}H NMR ($CDCl_3$): δ 7.28−7.09 (m, 6H), 6.89 (d, 1H, J = 7.0 Hz), 6.64−6.59 (m,

3H), 6.31 (m, 1H), 4.65 (br, 1H), 3.16 (br, 1H), 3.02 (d, 1H, J = 7.8 Hz), 2.69−2.14 (m, 16H), 1.91 (m, 1H), 1.86−1.75 (m, 4H), 1.58 (m 1H), 1.36−0.83 (m, 3H), 0.71 (d, 3H, J = 6.5 Hz); $[\alpha]_D^{20}$ −50.6° (c 0.62, CH_3OH). Anal. ($C_{30}H_{43}N_3O_2$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxy)phenyl-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-guanidinopropanamide [(−)-3d]. A solution on *N*,*N*′-di-Boc-*N*″-trifylguanidine (4.39 g, 11.2 mmol) in dry CH_2Cl_2 was added to a solution of β-alanine (1.00 g, 11.2 mmol) and triethylamine (2.34 mL, 16.8 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 4 h. The organic layer was washed with 1 M $NaHSO_4$, followed by water, the organic layer was collected and dried (Na_2SO_4), and solvent was removed under reduced pressure yielding crude product, which was purified by flash chromatography (1:1:0.004 EtOAc:pentane:AcOH) to afford the Boc-protected guanidino acid (3.58 g, 97%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 10.42 (br, 1H), 8.77 (br, 1H), 3.68 (t, 2H, J = 6.1 Hz), 2.69 (t, 2H, J = 6.1 Hz), 1.49 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 175.9, 162.8, 156.3, 152.9, 83.4, 79.8, 36.2, 34.5, 28.2, 28.0. The acid thus prepared was coupled to (−)-**11** in the manner described for (−)-**3b**. The product from this reaction was not purified but dissolved in CH_2Cl_2 and treated with an equal volume of trifluoroacetic acid at −30 °C. This was stirred for 30 min and allowed to warm to room temperature whereupon the volatiles were removed on a rotary evaporator. The resulting resin was dissolved in methanol and slurried with silica gel, and the solvent was removed under reduced pressure. Purification by flash chromatography using the resulting silica gel on a silica gel column and 33% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$ as the eluent gave (−)-**3d** as an off-white foam (95%). ^{1}H NMR ($CDCl_3$): δ 8.77 (t, 1H, J = 5.7 Hz), 7.28−7.09 (m, 6H), 6.67 (m, 3H), 6.10 (br, 1H), 4.65 (br, 1H), 3.63 (m, 2H), 3.17 (br, 1H), 3.01 (d, 1H, J = 7.8 Hz), 2.69−2.54 (m, 7H), 2.40 (m, 3H), 2.10 (m, 1H), 1.76 (m, 2H), 1.61−1.48 (m, 2H), 1.47 (s, 9H), 1.41 (s, 9H), 1.17−0.85 (m, 3H), 0.71 (d, 3H, J = 6.9 Hz); $[\alpha]_D^{20}$ −26.5° (c 0.17, CH_3OH). Anal. ($C_{28}H_{39}N_5O_2$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxy)phenyl-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-4-guanidinobutanamide [(−)-3e]. A solution on *N*,*N*′-di-Boc-*N*″-trifylguanidine (3.80 g, 9.70 mmol) in dry CH_2Cl_2 was added to a solution of 4-aminobutyric acid (1.00 g, 9.70 mmol) and triethylamine (2.03 mL, 14.55 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 4 h. The organic layer was washed with 1 M $NaHSO_4$, followed by water. The organic layer was collected and dried (Na_2SO_4), and solvent was removed under reduced pressure yielding crude product that was purified by flash chromatography (1:1:0.004 EtOAc:pentane:AcOH) to afford the Boc-protected guanidino acid (2.92 g, 87%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.39 (br, 1H), 3.49 (m, 2H,), 2.45 (t, 2H, J = 7.1 Hz), 1.92 (m, 2H), 1.50 (s, 9H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 177.4, 163.4, 157.1, 153.5, 83.8, 80.1, 40.1, 32.0, 28.5, 28.4, 25.5. The acid thus prepared was coupled to (−)-**11** in the manner described for (−)-**3d** to give (−)-**3e** as an off-white foam (100%) following purification by flash chromatography using 33% (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$. ^{1}H NMR ($CDCl_3$): δ 8.46 (t, 1H, J = 5.6 Hz), 7.33−7.02 (m, 6H), 6.69 (d, 2H, J = 6.6 Hz), 6.63 (d, 1H, J = 6.7 Hz), 5.72 (br, 1H), 4.61 (br, 1H), 3.36 (m, 2H), 3.20 (br, 1H), 3.01 (d, 1H, J = 8.3 Hz), 2.83−2.55 (m, 5H), 2.33 (m, 3H), 2.11 (m, 3H), 1.80 (m, 4H), 1.48 (s, 9H), 1.43 (s, 9H), 1.32−0.83 (m, 5H), 0.70 (d, 3H, J = 6.8 Hz); $[\alpha]_D^{20}$ −24.7° (c 0.45, CH_3OH). Anal. ($C_{29}H_{41}N_5O_2$) C, H, N.

Acknowledgment. This research was supported by the National Institute on Drug Abuse, Grant DA 09045. We thank NIDA (OTDP, Division of Treatment Research and Development) for obtaining the functional assay data provided herein.

References

(1) Zimmerman, D. M.; Leander, J. D. Selective opioid receptor agonists and antagonists: Research tools and potential therapeutic agents. *J. Med. Chem.* **1990**, *33*, 895−902.

(2) Aldrich, J. V. Analgesics. In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1996; Vol. 3.

(3) Rogers, M. E.; May, E. L. Improved synthesis and additional pharmacology of the potent analgetic (−)-5-m-hydroxyphenyl-2-methylmorphan. *J. Med. Chem.* **1974**, *17*, 1328−1330.

(4) Awaya, H.; May, E. L.; Aceto, M. D.; Merz, H.; Rogers, M. E.; Harris, L. S. Racemic and optically active 2,9-dimethyl-5-(*m*-hydroxyphenyl)morphans and pharmacological comparison with the 9-demethyl homologues. *J. Med. Chem.* **1984**, *27*, 536−539.

(5) Thomas, J. B.; Zheng, X.; Mascarella, S. W.; Rothman, R. B.; Dersch, C. M.; Partilla, J. S.; Flippen-Anderson, J. L.; George, C. F.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. N-Substituted 9β-methyl-5-(3-hydroxyphenyl)morphans are opioid receptor pure antagonists. *J. Med. Chem.* **1998**, *41*, 4143−4149.

(6) Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Rothman, R. B.; Mascarella, S. W.; Xu, H.; Partilla, J. S.; Dersch, C. M.; McCullough, K. B.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of an opioid κ receptor subtype-selective N-substituent for (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine. *J. Med. Chem.* **1998**, *41*, 5188−5197.

(7) Thomas, J. B.; Atkinson, R. N.; Rothman, R. B.; Fix, S. E.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of the first *trans*-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine derivative to possess highly potent and selective opioid κ receptor antagonist activity. *J. Med. Chem.* **2001**, *44*, 2687−2690.

(8) Thomas, J. B.; Gigstad, K. M.; Fix, S. E.; Burgess, J. P.; Cooper, J. B.; Mascarella, S. W.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. A stereoselective synthetic approach to *N*-alkyl-4β-methyl-5-phenylmorphans. *Tetrahedron Lett.* **1999**, *40*, 403−406.

(9) Werner, J. A.; Cerbone, L. R.; Frank, S. A.; Ward, J. A.; Labib, P.; Tharp-Taylor, R. W.; Ryan, C. W. Synthesis of *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists: Application of the cis-thermal elimination of carbonates to alkaloid synthesis. *J. Org. Chem.* **1996**, *61*, 587−597.

(10) Bertha, C. M.; Flippen-Anderson, J. L.; Rothman, R. B.; Porreca, F.; Davis, P.; Xu, H.; Becketts, K.; Cha, X.-Y.; Rice, K. C. Probes for narcotic receptor-mediated phenomena. 20. Alteration of opioid receptor subtype selectivity of the 5-(3-hydroxyphenyl)-morphans by application of the message-address concept: Preparation of δ-opioid receptor ligands. *J. Med. Chem.* **1995**, *38*, 1523−1537.

(11) The configuration of the 3- or 4-position substituents is designated as illustrated in Figure 1, i.e., substituents on the same side of the piperidine ring as the propano bridge are designated α/endo.

(12) Thomas, J. B.; Mascarella, S. W.; Rothman, R. B.; Partilla, J. S.; Xu, H.; McCullough, K. B.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Investigation of the N-substituent conformation governing potency and μ receptor subtype-selectivity in (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine opioid antagonists. *J. Med. Chem.* **1998**, *41*, 1980−1990.

(13) Toll, L.; Berzetei-Gurske, I. P.; Polgar, W. E.; Brandt, S. R.; Adapa, I. D.; Rodriguez, L.; White, A.; Kennedy, J. M.; Craymer, K.; Farrington, L.; Auh, J. S. Standard binding and functional assays related to (NIDA) Medications Development Division testing for potential cocaine and narcotic treatment programs. *NIDA Res. Monogr. Ser.* **1998**, *178*, 440−466.

(14) Traynor, J. R.; Nahorski, S. R. Modulation by μ-opioid agonists of guanosine-5′-O-(3-[35S]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848−854.

(15) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Binaltorphimine and nor-binaltorphimine, potent and selective κ-opioid receptor antagonists. *Life Sci.* **1987**, *40*, 1287−1292.

(16) Portoghese, P. S.; Nagase, H.; Takemori, A. E. Only one pharmacophore is required for the κ opioid antagonist selectivity of norbinaltorphimine. *J. Med. Chem.* **1988**, *31*, 1344−1347.

(17) Olmsted, S. L.; Takemori, A. E.; Portoghese, P. S. A remarkable change of opioid receptor selectivity on the attachment of a peptidomimetic κ address element to the δ antagonist, natrindole: 5′-[N^2-alkylamidino)methyl]naltrindole derivatives as a novel class of κ opioid receptor antagonists. *J. Med. Chem.* **1993**, *36*, 179−180.

(18) Jones, R. M.; Hjorth, S. A.; Schwartz, T. W.; Portoghese, P. S. Mutational evidence for a common κ antagonist binding pocket in the wild-type κ and mutant μ[K303E] opioid receptors. *J. Med. Chem.* **1998**, *41*, 4911−4914.

(19) Schwyzer, R. ACTH: A short introductory review. *Ann. N. Y. Acad. Sci.* **1977**, *247*, 3−26.

(20) Portoghese, P. S. An approach to the design of receptor-type-selective non-peptide antagonists of peptidergic receptors: δ opioid antagonists. *J. Med. Chem.* **1991**, *34*, 1757−1762.

JM020084H