Selective Protection and Functionalization of Morphine: Synthesis and Opioid Receptor Binding Properties of 3-Amino-3-desoxymorphine Derivatives[†,1]

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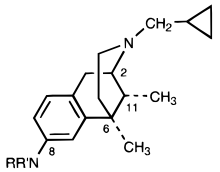
As part of an effort to identify novel opioid receptor interactive agents, we recently prepared a series of 8-(substituted)amino analogues of cyclazocine. We found the chiral 8-phenylamino (NHC_6H_5) cyclazocine derivative to have subnanomolar affinity for κ opioid receptors and a 2-fold lower affinity for μ opioid receptors. To determine if the benefits of (substituted)amino groups could be extended to the morphine core structure, we have made five novel 3-amino-3-desoxymorphine derivatives of general structure **5** where RR′N = H_2N, CH_3NH, $(CH_3)_2N$, C_6H_5NH, and $C_6H_5CH_2NH$. Relative to morphine, these derivatives had 38−273-fold, 11−41-fold, and 10−141-fold lower affinity for μ, δ, and κ opioid receptors, respectively. Target compounds were made via Pd-catalyzed amination of a morphine 3-trifluoromethylsulfonate substrate where the 6-OH group was protected with a *tert*-butyldiphenylsilyl group. To make 6-*tert*-butyldiphenylsilyloxymorphine selectively, a new high-yield method was developed whereby morphine was bis-silylated using normal conditions followed by selective removal of the 3-*tert*-butyldiphenylsilyl group with catalytic tetrabutylammonium fluoride.

Introduction

We recently reported the opioid receptor binding properties of a series of cyclazocine analogues (**1**) where the 8-OH group of cyclazocine (**2**) was replaced with amino groups.[2] Several members of this new series had surprisingly high affinity for μ and κ receptors based on existing SAR knowledge and doctrine.[3,4] For morphine (**3**) and the numerous compounds derived from its structure (e.g., cyclazocine and other benzomorphans), the phenolic OH group was historically thought to be a stringent requirement for binding to opioid receptors serving as a putative H-bond donor to a complementary site on the protein.[3−8] For example, in two recent studies, the 3-OH group of morphine[7] and natrindole[8] was replaced by H, alkyl, acetyl, aryl, and/or heteroaryl groups; all targets had substantially diminished affinity for opioid receptor relative to their 3-OH counterparts. In a recent report, the 3-OH of naltrexone and oxymorphone was replaced by methanesulfonamido, a standard phenolic bioisostere.[9] These replacements abolished opiate activity.

Data from our study corroborate the need for H-bond donation by the 8-substituent, but due to the expanded valence of N (versus O), we found that certain mono-N-substituents (e.g., (−)-(2*R*,6*R*,11*R*)-**4**) enhance binding affinity relative to the 8-NH_2 analogue.[2] We speculate that the N-substituent occupies an accessory binding site on the receptor protein and that affinity is enhanced via specific molecular contacts. Preliminary data support this speculation, and additional SAR and computational data are being collected to confirm our belief.



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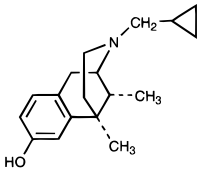

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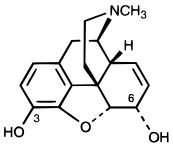

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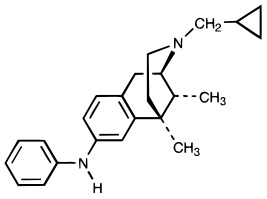

(-)-(2*R*,6*R*,11*R*)-**4**

Prior to publication of our recent paper,[2] opioid receptor binding data for 8-aminobenzomorphans (**1**) have never been reported to our knowledge. Several members of the series, however, date back to the 1970s where we had used this 8-OH → NH_2 conversion to improve the pharmacodynamic properties of cyclazocine (**2**).[10] Cyclazocine was evaluated in humans in the 1960s

[†] This manuscript is dedicated to the memories of Professors Sydney Archer and Arthur G. Schultz.

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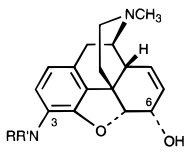
and early 1970s as an analgesic and as a possible treatment for preventing relapse in post-addicts of heroin.[11,12] In humans dosed with the drug, potent analgesia was observed, and following abrupt cyclazocine withdrawal, patients did not display drug-seeking behavior. Further clinical development of cyclazocine was ceased due, in part, to a short duration of analgesic action.[11,12] Cyclazocine is O-glucuronidated in humans which may account for its short duration of action.[10] In an attempt to retard this metabolic inactivation and increase its duration of action, we discovered some years ago that replacement of the 8-OH group of **2** with NH_2 provided the novel racemic compound **1** (R = R′ = H) which had somewhat diminished antinociception potency in mice when delivered by the subcutaneous route but comparable (to **2**) efficacy when delivered orally.[10] For example, in the mouse acetylcholine writhing test, the po/sc ratio of ED_{50} values for cyclazocine was 35, and for **1** (R = R′ = H) this ratio was 4 indicating the 8-OH → NH_2 change accounted for higher oral efficacy. Whether high oral bioavailability due to lower first-pass metabolism, higher gut wall permeability, reduced clearance, or some other factor accounts for the higher (than would be predicted by sc data) oral efficacy of **1** (R = R′ = H) is not known.

Our primary goal for this study was to determine if, as we found in our benzomorphan study, NH_2 is a bioisosteric replacement for the 3-OH of morphine at opioid receptors. In addition, we also wanted to determine if opioid binding was sensitive to the substitution pattern on the 3-amino group. To accomplish this goal we set out to synthesize and evaluate, in opioid binding assays, a small series of morphine analogues of general structure **5** where the 3-OH group of the alkaloid is replaced by amino and (substituted)amino groups. Besides the 3-methanesulfonamido analogues of naltrexone and oxymorphone,[9] the only other 3-amino-3-desoxymorphine derivatives in the literature to our knowledge are several 3-aminodextromorphan analogues.[13] These compounds, however, have the opposite stereochemistry to natural opiates and were studied for other (than opioid receptor binding) pharmacological properties.[13,14] We now report the synthetic methods, μ, δ and κ opioid binding data, and inhibition of adenylyl cyclase activity for these new morphine analogues. We also report comparative opioid receptor binding data for morphine, the (−)-form of cyclazocine, and two optically active 8-aminocyclazocine derivatives.



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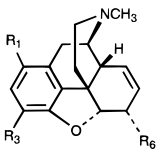

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Chemistry

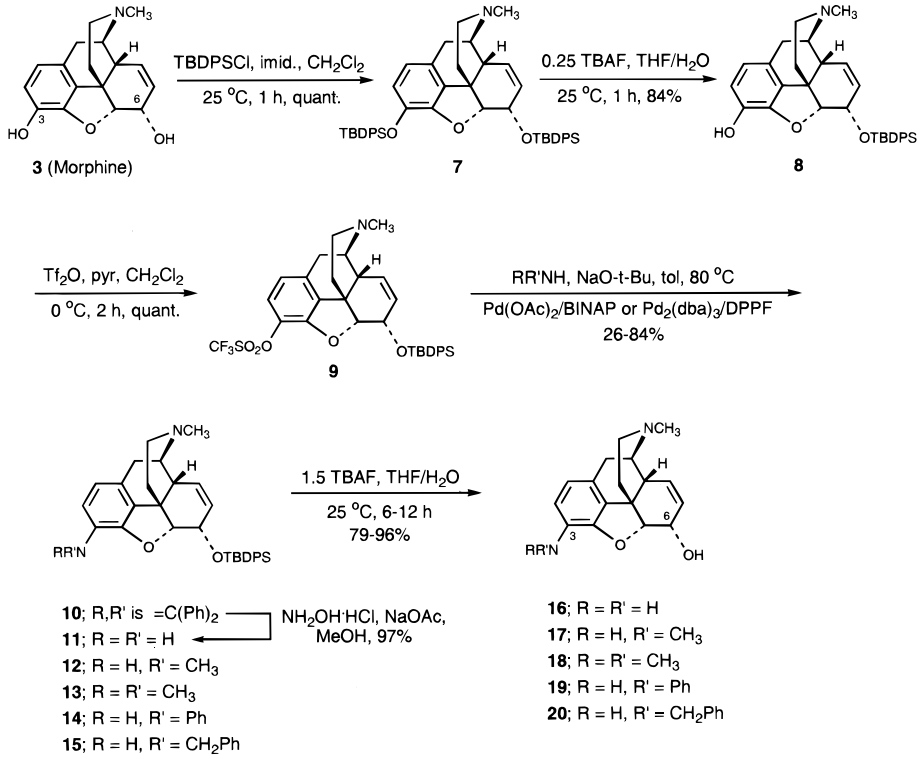
Our approach to make the desired 3-amino-3-desoxymorphine targets **5** centered around our methodology to make the 8-aminocyclazocine analogues, namely the Pd-catalyzed amination of the appropriate aryl triflate.[2,15] This powerful amination procedure pioneered by Buchwald and co-workers[16] and Hartwig and co-workers[17] gave us rapid entry into our initial set of diverse target compounds. For the present study, the requisite morphine 3-triflate (**6**, R_1 = H, R_3 = OSO_2CF_3, R_6 = OH) is a known compound prepared in high yield by treating morphine with triethylamine and *N*-phenyltrifluoromethanesulfonimide.[7,18,19] This compound was subsequently used as substrate for Pd-catalyzed alkyl and (hetero)aryl coupling reactions and as an intermediate to apomorphine derivatives. The naltrexone 3-triflate was also made; it was converted to 3-cyano-3-deoxynaltrexone via a Pd-catalyzed cyanation reaction[20] and to 3-alkyl and (hetero)aryl analogues of naltrindole.[8]

The Pd-catalyzed couplings reported for morphine 3-triflate and naltrexone 3-triflate did not involve strongly basic conditions. Since the use of strong base (NaO*t*-Bu) gave superior results in our Pd-catalyzed aminations of cyclazocine triflate, we felt our needs for the present study would be better served if the morphine 3-triflate substrate had the potentially troublesome 6-OH protected with a group stable to our reaction conditions. Thus, having a triflate substrate amenable to a variety of amine co-reactants and Pd-catalyzed amination conditions would allow us to broaden the scope of our study as guided by a developing SAR.

The 3-triflate (**6**, R_1 = H, R_3 = OSO_2CF_3, R_6 = OAc) of known morphine 6-acetate[21−23] would not be useful due to the likelihood of 6-acetate cleavage by NaO*t*-Bu and/or involvement of the allylic acetate in Pd-mediated π-allyl complex formation. The logical alternative was a 6-silyloxy protecting group. Silylation of morphine with trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride is well-known to give 3,6-disubstituted products.[24,25] Seltzman and co-workers similarly converted 1-iodomorphine (**6**, R_1 = I, R_3 = R_6 = OH) to the corresponding 3,6-bis-*tert*-butyldimethylsilyl ether in 92% yield.[26] They were also able to make each mono-*tert*-butyldimethylsilyl ether; however, they were not formed selectively. For example, when 1-iodomorphine was treated with *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide, the 6-monosilyl ether **6** (R_1 = I, R_3 = OH, R_6 = $OSi(CH_3)_2t$-Bu) was isolated in 8.7% from a mixture of starting material and both mono- and bis-silyl ether derivatives.

We chose an alternate approach to prepare the morphine 6-silyl ether intermediate we needed for subsequent 3-OH triflate formation, namely to make the 3,6-bis-silyl ether followed by selective deprotection of the phenolic (i.e., better leaving group) 3-OH moiety. This standard synthetic tack has been used, for example, in making morphine 6-acetate selectively[21] and to differentiate between the aromatic and aliphatic amines in our early 8-aminobenzomorphan studies.[10] The 6-monoglucuronide of morphine has also been made selectively,[27,28] and in one instance, a selective removal of the 3-glucuronide group from morphine 3,6-diglucuronide was accomplished using an enzyme.[29] We have reduced this stepwise selective protection approach to practice by making the novel morphine 6-*tert*-butyldiphenylsilyl ether **8** in 84% yield from morphine. These results as well as the conversion of **8** to our desired 3-amino-3-desoxymorphine targets **16**−**20** are summarized in Scheme 1.

Scheme 1. Syntheses of 3-Amino-3-desoxymorphine Derivatives

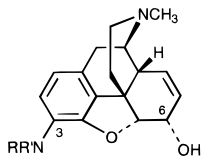


Morphine (**3**) was treated with excess *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole to give morphine 3,6-bis-*tert*-butyldiphenylsilyl ether (**7**) in nearly quantitative yield. Exposure of **7** to 0.25 equiv of tetrabutylammonium fluoride (TBAF, 1 M in THF containing 5% H_2O) for 1 h at 25 °C gave, after purification by flash chromatography, a 84.1% yield of morphine 6-*tert*-butyldiphenylsilyl ether **(8)**. This chromatography was done to provide material for characterization purposes; otherwise the crude product of this reaction, obtained in 97% yield, could be used in the next step without any compromise in yield. While all spectral and combustion data were consistent with the structural assignment of **8** as the mono-6-*tert*-butyldiphenylsilyl ether, we could not prove that the TBDPS group was at the 6-position versus the 3-position. We therefore prepared **8** by an independent route to confirm structure. Morphine 3-acetate[30] was converted to **6** (R_1 = H, R_3 = OAc, R_6 = $OSiPh_2t$-Bu) using TBDPSCl/imidazole. Subsequent base-induced hydrolysis of this ester provided **8** identical in all respects with **8** made via the selective protection approach shown in Scheme 1.

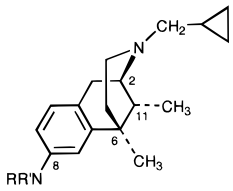
The role of TBAF in this selective deprotection is an interesting one in that much less than 1 equiv of TBAF gave the best results. When 1 full equiv of TBAF (1 M in THF containing 5% H_2O, 15 min, 25 °C) was used, both 3- and 6-TBDPS groups were cleaved. When 0.1 equiv TBAF was used under the same conditions, only the more reactive 3-TBDPS group was cleaved due to the better leaving group properties of the phenolic OH. We found the best yields were obtained when 0.25 equiv of TBAF was used at 25 °C for 15−60 min. The water present in the mixture may play an important role in the catalytic nature of the reaction conditions by, for example, hydrolyzing TBDPSF (from fluoride induced cleavage of 3-TPDPS group from **7**) to TBDPSOH and HF. The HF can then be converted to TBAF (along with the neutral phenol) which can then promote another desilylation of **7** completing one catalytic cycle. Since the nearly quantitative transformation of **7** to **8** filled our needs very well, we did not investigate other methods (e.g., anhydrous TBAF, other silyl groups) of selective deprotection.

Compound **8** was converted to the corresponding 3-triflate derivative **9** in quantitative yield using standard conditions. Triflate **9** was aminated using two known Pd-catalyzed amination methods.[16,17] In one, Pd-$(OAc)_2$ and BINAP were used as catalyst source and Pd ligand, respectively,[16] while the other procedure[17] used $Pd_2(dba)_3$ and DPPF.[31] Both were performed in toluene at 80 °C and 1 equiv of NaO*t*-Bu was required for satisfactory yields. The use of Cs_2CO_3 as base was also reported to give satisfactory results;[32] however, we found like others[15] that NaO*t*-Bu gave much higher yields. As noted by Buchwald,[16] we also observed that NaO*t*-Bu-induced cleavage of the triflate to the corresponding phenol competed with amination. This resulted in somewhat lower yields in those aminations that were relatively slow. Thus, exposure of **9** to methylamine, dimethylamine, aniline, or benzylamine using one of the amination methods described above and in the Experimental Section gave aminated products **12**−**15**, respectively, in yields ranging from 26% to 84%. Treatment of **12**−**15** with 1.5 equiv of TBAF in THF at 25 °C for a much longer period (6−12 h) than used to cleave the 3-TBDPS ether gave the corresponding targets **17**−**20** in 79−96% yields. The primary amino analogue **16** was made by first coupling **9** with Ph_2C=NH following a modification of a known procedure[32] to provide **10** (Scheme 1). Compound **10** was subjected to imine-exchange conditions (hydroxylamine) to provide **11,** and subsequent deprotection gave target **16**. The overall yield for the three steps in converting **9** to **11** was 42%.

Table 1. Opioid Receptor Binding Data for 3-Amino-3-desoxymorphine Derivatives



16-20



4,21,22 [(-)-2*R*,6*R*,11*R*]

			K_i (nM ± SE)[a] versus			receptor selectivity[b]		
compd	R	R′	[^{3}H]DAMGO (μ)	[^{3}H]naltrindole (δ)	[^{3}H]U69,593 (κ)	μ:δ	μ:κ	κ:δ
3 (morphine)			0.88 ± 0.14	140 ± 18	24 ± 2.3	156	27	6
16	H	H	53 ± 3.0	2400 ± 190	740 ± 75	45	14	3
17	H	CH_3	63 ± 15	5700 ± 1100	2800 ± 420	90	44	2
18	CH_3	CH_3	240 ± 16	1600 ± 110	290 ± 8.1	7	1	6
19	H	C_6H_5	59 ± 3.7	1500 ± 100	240 ± 23	25	4	6
20	H	$CH_2C_6H_5$	33 ± 5.1	5500 ± 190	3400 ± 540	167	103	2
21[c]	RR′N = OH		0.10 ± 0.03	0.58 ± 0.06	0.052 ± 0.009	6	0.5	11
22[c]	H	H	1.8 ± 0.12	12 ± 2.3	1.2 ± 0.13	7	0.7	10
4[c]	H	C_6H_5	1.1 ± 0.08	5.2 ± 0.08	0.54 ± 0.01	5	0.5	10

[a] See Experimental Section. [b] Receptor selectivity is expressed as the ratio of the corresponding K_i values. [c] See ref 2.

Results

Opioid receptor binding data for 8-amino-3-desoxymorphine targets **16**−**20** compared to morphine (**3**) are found in Table 1. For further comparison purposes, opioid binding affinities for the active enantiomers of three benzomorphans from our previous study, (−)-cyclazocine (**21**) and the corresponding 8-amino (**22**) and 8-phenylamino (**4**) analogues, are also included. Standard radioligand displacement assays were used to assess the affinity and selectivity of test compounds for μ ([^{3}H]DAMGO), δ ([^{3}H]naltrindole), and κ ([^{3}H]U69,593) opioid receptors in guinea pig membranes (see Experimental Section). For analysis of the binding data, affinity differences of higher than 2-fold are considered significantly different.

The primary amino analogue **16** has good affinity for the μ receptor (K_i = 53 nM), however, affinity was 60-fold lower than that observed with morphine. In the benzomorphan series, the 8-NH_2 analogue **22** also displayed high affinity for μ and was 18-fold less potent than the (−)-cyclazocine (**21**). Morphine is well-known to have much higher affinity for μ than for δ or κ as evidenced by the selectivity data shown in Table 1 where morphine has a μ:δ and μ:κ selectivity ratio of 156 and 27, respectively. Between δ and κ, morphine has higher affinity for κ (κ:δ = 6). Compound **16**, the primary amino derivative, also has substantially less affinity for δ and κ, but the μ:δ, μ:κ, and κ:δ ratios are somewhat lower (2−3-fold) than for morphine suggesting that the NH_2 group accounts for slightly greater relative binding to δ and κ than the prototypic 3-OH. This trend was not evident within the benzomorphan series where the 8-OH and NH_2 derivatives had nearly identical μ:δ, μ:κ, and κ:δ ratios.

When the primary amine of **16** was substituted with one methyl group to give **17**, binding affinity for μ and δ did not change significantly; however, **17** had 4-fold lower affinity for the κ receptor than **16**. When comparing the dimethylamino analogue **18** to either **16** or **17**, affinity for μ decreased 4-fold; for δ receptors, affinity was similar; and for κ, affinity of the dimethylamino compound was slightly improved (3-fold) relative to **16** and significantly improved (10-fold) relative to **17**. For compound **18**, the μ:κ selectivity ratio is 1 suggesting that a dimethylamino group imparts greater κ affinity than for primary amino (μ:κ = 14) or methylamino (μ:κ = 44) analogues. The μ:κ selectivity ratio of 1 for compound **18** is more in line with our benzomorphan studies where we found that the 8-amino and most (monosubstituted)amino or (disubstituted)amino analogues displayed μ:κ selectivity ratios of 0.5−2.

In the benzomorphan study, the 8-PhNH (e.g., **4** in Table 1; K_i = 0.54 nM versus κ) and 8-$PhCH_2NH$ analogues had generally higher affinity for μ, δ, and κ receptors relative to other 8-(monosubstituted)amino derivatives. When these same appendages were introduced into the 3-position of morphine to give **19** and **20**, respectively, affinity for μ and δ was not significantly different from 3-NH_2 or 3-CH_3NH derivatives, **16** and **17**, respectively; for the κ receptor, the affinity of **19** was somewhat greater, while for **20**, affinity was lower. The μ:δ and μ:κ selectivity ratios for the 3-PhNH derivative **19** were close to those of the 3-$(CH_3)_2N$ derivative **18** which were the lowest (i.e., poor selectivity) within the morphine series. This observation contrasts the data for the 8-$PhCH_2NH$ analogue **20** which had the highest μ:δ and μ:κ selectivity ratios (i.e., highest μ selectivity) in the series.

To determine whether these aminomorphine analogues were agonists or antagonists, the compounds were tested to determine if they would inhibit adenylyl cyclase activity in membranes from the human SH-SY5Y neuroblastoma cell line. The compounds were tested at a final concentration of 10 μM and were compared to the μ-selective ligand DAMGO. As shown in Table 2, all of the compounds inhibited cyclic AMP levels, indicating that all the morphine derivatives were agonists. The inhibition by these compounds was lower than was observed with DAMGO. The fact that the compounds have significantly lower affinity than DAMGO, which has affinity in the nanomolar range, would account for the reduced inhibition of cyclic AMP production.

Table 2. Inhibition of Adenylyl Cyclase Activity by 3-Amino-3-desoxymorphine Derivatives

compd	% inhib of cyclic AMP accumulation ± SE[a]
16	26 ± 5.8
17	29 ± 11
18	13 ± 3.8
19	44 ± 3.2
20	17 ± 9
DAMGO	58 ± 4.2

[a] See Experimental Section.

Conclusions

One of the most important questions we wanted answered in this study was if the 3-NH_2 group was an effective bioisosteric replacement for the prototypic 3-OH group of morphine. The answer, in a broad sense, appears to be yes. While it can be argued that the 3-NH_2 analogue **16** has 60-fold lower affinity for μ than morphine, in an absolute sense **16** has significant affinity (K_i = 53 nM) for the receptor. After comparing this result with the corresponding data from our benzomorphan study, the OH → NH_2 replacement is apparently more effective for μ affinity in the cyclazocine core structure than in morphine. There appears to be another difference between the SARs noted in the benzomorphan and morphine series. The difference is in the role of phenyl-containing amino appendages. For benzomorphans, these substitutions are beneficial (compared to 8-NH_2) for μ and κ binding, while in the morphine series, little advantage is seen. Similar to what was observed in the benzomorphan series, dimethylamino substitution (i.e., **18**) results in substantially reduced binding affinity to the μ receptor. All of the aminomorphine analogues were agonists, like morphine. Therefore, the substitution of 3-amino groups for the 3-OH group in morphine did not change the agonistic properties associated with morphinans

From these data, it seems reasonable to conclude that the 3-amino- and 3-(monosubstituted)amino-3-desoxymorphine derivatives interact with the μ opioid receptor in a manner similar to morphine, especially with respect to the putative H-bond donor ability the 3-substituent. Further support for this conclusion stems from the 4-fold lower affinity observed for the 3-dimethylamino analogue **18** for μ. This compound can be an H-bond donor when protonated; however, the low pK_a (<5) for such aromatic amines decreases their likelihood of any significant protonation at the pH (7.5) of the assay. Within this series, the 3-dimethylamino analogue **18** has very close to the highest affinity for κ receptors. This result represents a divergence in κ binding SAR from our benzomorphan study where it was found that the amino, methylamino, phenylamino, and benzylamino analgoues all had higher (up to 60-fold) affinity than the dimethylamino analogue. We have no explanation to account for this divergent SAR.

We will continue to explore this new opportunity in understanding opioid SAR by replacing the phenolic OH groups of other benzomorphan and morphinan derivatives with amino and (substituted)amino groups. Besides their ability to donate the putatively required H-bond, these appendages also hold the prospect of accessory binding of the N-substituent to a complimentary site on the protein. This site is obviously unavailable to the phenolic OH-containing ligands due to the lower valence of oxygen compared to nitrogen.

Experimental Section

Proton NMR and in certain cases ^{13}C NMR [Varian Unity-500 (500 MHz) NMR] data, direct insertion probe (DIP) chemical ionization mass spectra (Shimadzu GC-17A GC−MS mass spectrometer), and infrared spectra (Perkin-Elmer Paragon 1000 FT-IR spectrophotometer) were consistent with the assigned structures. Complete ^1H NMR data are reported for all new compounds. ^1H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants are in hertz (Hz). Carbon, hydrogen, and nitrogen elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ, and were within ±0.4% of theoretical values. Melting points were determined on a Meltemp capillary melting point apparatus and are uncorrected. Optical rotation data were obtained from a Perkin-Elmer 241 polarimeter. Reactions were generally performed under a N_2 atmosphere. For Pd-catalyzed amination reactions, an oven-dried flask equipped with reflux condenser was placed into an N_2 filled glovebox or bag where it was charged with NaO*t*-Bu and either $Pd_2(dba)_3$ and DPPF or $Pd(OAc)_2$ and BINAP. The system was capped with rubber septa and removed from the glovebox/bag where dry toluene (distilled from Na, benzophenone ketyl) was added via syringe. BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] and NaO*t*-Bu were purchased from Sigma-Aldrich, and $Pd_2(dba)_3$ [tris-(dibenzylideneacetone)dipalladium(0)], DPPF [1,1′-bis(diphenylphosphino)ferrocene] and $Pd(OAc)_2$ were purchased from Strem Chemicals, Inc.

7,8-Didehydro-3,6-bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan (7). To a mixture of morphine hydrate (1.0 g, 3.3 mmol), imidazole (1.032 g, 15.2 mmol), and CH_2Cl_2 (20 mL) was added TBDPSCl (2.0 mL, 7.6 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h and diluted with CH_2Cl_2 (50 mL). The resulting mixture was washed with brine (30 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was purified by flash column (silica gel; CH_2Cl_2:MeOH = 20:1) to give 2.5 g (99.5%) of **7** as a oil: ^1H NMR ($CDCl_3$) δ 7.95−7.73 (m, 8H), 7.52−7.32 (m, 12H), 6.35 (d, 1H, J = 8.1 Hz), 6.19 (d, 1H, J = 8.1 Hz), 5.87 (d, 1H, J = 9.8 Hz), 5.20 (dt, 1H, J = 2.7, 9.8 Hz), 4.61 (d, 1H, J = 7.4 Hz), 4.24−4.23 (m, 1H), 3.27 (dd, 1H, J = 2.9, 6.1 Hz), 2.94 (d, 1H, J = 18.8 Hz), 2.52 (dd, 1H, J = 4.2, 11.8 Hz), 2.45−2.44 (m, 1H), 2.41−2.36 (m, 1H), 2.39 (s, 3H), 2.22 (dd, 1H, J = 6.6, 8.8 Hz), 1.82−1.75 (m, 2H), 1.21 (s, 9H), 1.20 (s, 9H). Anal. ($C_{49}H_{55}NO_3Si_2$) C, H, N.

7,8-Didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-ol (8). To a mixture of **7** (2.0 g, 2.62 mmol) and THF (20 mL) was added TBAF (0.656 mL of 1 M in THF containing 5% H_2O, 0.656 mmol) at 25 °C. After stirring at 25 °C for 1 h, water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (50 mL × 3). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was purified by flash column (silica gel; CH_2Cl_2:MeOH = 20:1) to give 1.15 g (84.1%) of **8** as a foam: ^1H NMR ($CDCl_3$) δ 7.76−7.66 (m, 4H), 7.43−7.33 (m, 6H), 6.61 (d, 1H, J = 8.1 Hz), 5.68−5.66 (m, 1H), 5.15−5.13 (m, 1H), 4.41 (d, 1H, J = 5.8), 4.24−4.22 (m, 1H), 3.35 (dd, 1H, J = 3.1, 6.1 Hz), 2.92 (d, 1H, J = 18.8 Hz), 2.54 (dd, 1H, J = 4.4, 12.0 Hz), 2.49 (s, 1H), 2.38 (s, 3H), 2.33 (dt, 1H, J = 3.4, 12.4 Hz), 2.23 (dd, 1H, J = 6.3, 18.8 Hz), 1.78 (dt, 1H, J = 5.1, 12.7 Hz), 1.61 (d, 1H, J = 11.2 Hz); MS m/z 524 (MH^+). Anal. ($C_{33}H_{37}NO_3Si$) C, H, N.

7,8-Didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-ol, 3-(Trifluoromethanesulfonate) (9). To a mixture of **8** (3.95 g, 7.5 mmol), pyridine (2.5 mL, 30 mmol) and CH_2Cl_2 (50 mL) was added triflic anhydride (2.54 mL, 15 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, diluted with CH_2Cl_2 (50 mL), washed with brine (60 mL) and dried (Na_2SO_4). After removal of the solvent on a rotary evaporator and drying in vacuo, compound **9** (foam, 4.75 g, 100%) was characterized by

^{1}H NMR and used without additional purification: ^{1}H NMR ($CDCl_3$) δ 7.82−7.80 (m, 1H), 7.68−7.66 (m, 2H), 7.47−7.34 (m, 6H), 6.92 (d, 1H, J = 8.6 Hz), 6.56 (d, 1H, J = 8.3 Hz), 5.74−5.72 (m, 1H), 5.17 (dt, 1H, J = 2.7, 9.8 Hz), 4.51 (d, 1H, J = 5.9 Hz), 4.18−4.16 (m, 1H), 3.27 (dd, 1H, J = 3.1, 5.8 Hz), 3.02 (d, 1H, J = 19.0 Hz), 2.49 (dd, 1H, J = 3.1, 12.2 Hz), 2.43−2.41 (m, 1H), 2.36 (s, 3H), 2.31−2.24 (m, 2H), 1.74 (dt, 1H, J = 5.1, 12.2 Hz), 1.71−1.70 (m, 1H), 1.11 (s, 9H).

***N*-(Diphenylmethylene)-7,8-didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-amine (10).** A mixture of **9** (300 mg, 0.48 mmol), DPPF (40 mg, 0.07 mmol), $Pd_2(dba)_3$ (22 mg, 0.024 mmol), NaO*t*-Bu (55 mg, 0.57 mmol), $Ph_2C{=}NH$ (96 μL, 0.57 mmol) and toluene (19 mL) was stirred at 80 °C for 8 h. The solvent was removed in vacuo and residue was purified by flash column (silica gel; CH_2Cl_2:MeOH = 10:1) to give 171 mg (51.9%) of **10** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.78−7.75 (m, 4H), 7.67 (dd, 2H, J = 1.2, 8.1 Hz), 7.48−7.22 (m, 14H), 6.36 (d, 1H, J = 7.8 Hz), 6.34 (d, 1H, J = 7.8 Hz), 5.81−5.78 (m, 1H), 5.20−5.17 (m, 1H), 4.19−4.16 (m, 1H), 4.15 (d, 1H, J = 6.2 Hz), 3.22 (dd, 1H, J = 3.4, 6.1 Hz), 2.92 (d, 1H, J = 18.8 Hz), 2.42 (dd, 1H, J = 3.9, 11.9 Hz), 2.39−2.37 (m, 1H), 2.28 (dt, 1H, J = 3.6, 12.6 Hz), 2.20 (dd, 1H, J = 6.1, 18.8 Hz), 1.62 (dt, 1H, J = 5.1, 12.4 Hz), 1.41−1.38 (m, 1H), 1.03 (s, 9H).

7,8-Didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-amine (11). A mixture of **10** (150 mg, 0.22 mmol), $NH_2OH{\cdot}HCl$ (30 mg, 0.43 mmol), NaOAc (92 mg, 1.12 mmol) and MeOH (2 mL) was stirred at 25 °C for 0.5 h and the solvent was removed on a rotary evaporator. The residue was dissolved in 50 mL CH_2Cl_2 and the solution was washed with saturated sodium bicarbonate and dried (Na_2SO_4) and the solvent removed on the rotary evaporator. The residue was purified by flash column (silica gel; CH_2Cl_2:MeOH = 12:1) to give 110 mg (96.5%) of **11** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 2H, J = 7.6 Hz), 7.71 (d, 2H, J = 7.6 Hz), 7.48−7.37 (m, 6H), 6.50 (d, 1H, J = 7.8 Hz), 6.43 (d, 1H, J = 7.8 Hz), 5.77−5.75 (m, 1H), 5.23−5.20 (m, 1H), 4.40 (d, 1H, J = 6.1 Hz), 4.25−4.22 (m, 1H), 3.49 (s, 2H), 3.27 (dd, 1H, J = 6.2, 9.4 Hz), 2.98 (d, 1H, J = 18.3 Hz), 2.51−2.48 (m, 1H), 2.46−2.45 (m, 1H), 2.42−2.37 (m, 1H), 2.40 (s, 3H), 2.26 (dd, 1H, J = 6.2, 8.6 Hz), 1.76 (dt, 1H, J = 4.9, 11.8 Hz), 1.74−1.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 147.3, 135.7, 135.6, 133.9, 133.6, 133.0, 129.6, 129.6, 129.5, 128.0, 127.5, 124.8, 118.5, 115.9, 91.5, 69.0, 58.7, 46.3, 43.2, 42.9, 40.9, 35.5, 26.7, 20.3, 19.2; MS m/z 523 (MH^+).

3-Amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (16). A mixture of **11** (110 mg, 0.21 mmol), TBAF (0.29 mL, 1 M in THF, 0.29 mmol) and THF (4 mL) was stirred at 25 °C for 12 h and the solvent was removed on the rotary evaporator. The residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and the solvent was removed on the rotary evaporator. The residue was purified with flash column (silica gel; CH_2Cl_2:MeOH = 4:1, then CH_2Cl_2:MeOH:NH_4OH = 4 mL:1 mL:4 drops) to give 50 mg (83.3%) of **16**: mp = 193−195 °C; ^{1}H NMR ($CDCl_3$) δ 6.47 (d, 1H, J = 8.0 Hz), 6.45 (d, 1H, J = 8.0 Hz), 5.70−5.68 (m, 1H), 5.30−5.27 (m, 1H), 4.84 (d, 1H, J = 6.3 Hz), 4.15 (dd, 1H, J = 2.4, 6.3 Hz), 4.16−4.14 (m, 1H), 3.6 (s, 3H, broad), 3.33 (dd, 1H, J = 3.1, 5.8 Hz), 2.30 (d, 1H, J = 18.5 Hz), 2.64 (t, 1H, J = 2.4 Hz), 2.58 (dd, 1H, J = 4.2, 12.2 Hz), 2.44−2.39 (m, 1H), 2.27 (dd, 1H, J = 6.3, 18.5 Hz), 2.04 (dt, 1H, J5.1, 12.5 Hz), 1.87−1.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 146.2, 133.0, 129.7, 128.3, 127.2, 125.2, 119.3, 116.2, 91.0, 66.3, 58.7, 46.3, 42.9, 42.8, 40.7, 35.6, 20.2; MS m/z 285 (MH^+); $[\alpha]_D^{24}$ = −130.3° (c = 0.54, $CHCl_3$). Anal. ($C_{17}H_{20}N_2O_2{\cdot}0.25H_2O$) C, H, N.

***N*-Methyl-7,8-didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-amine (12).** A mixture of **9** (500 mg, 0.8 mmol), DPPF (66 mg, 0.12 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), NaO*t*-Bu (92 mg, 0.96 mmol), CH_3NH_2 (0.8 mL, 2 M in THF, 1.6 mmol) and toluene (10 mL) was stirred at 80 °C for 15 h and the solvent was removed on the rotary evaporator. The residue was purified by flash column (silica gel; CH_2Cl_2:MeOH = 12:1) to give 110 mg (25.7%) of **12** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 2H, J = 6.8 Hz), 7.69 (d, 2H, J = 6.8 Hz), 7.33−7.45 (m, 6H), 6.49 (d, 1H, J = 8.0 Hz), 6.43 (d, 1H, J = 8.0 Hz),5.74−5.72 (m, 1H), 5.19−5.17 (m, 1H), 4.36 (d, 1H, J = 5.9 Hz), 4.23−4.21 (m, 1H), 3.30 (dd, 1H, J = 3.2, 6.1 Hz), 2.93 (d, 1H, J = 23.7 Hz), 2.86 (s, 3H), 2.54−2.51 (m, 1H), 2.47−2.45 (m, 1H), 2.45−2.41 (m, 1H), 2.40 (s,3H), 2.28 (dd, 1H, J = 6.1, 23.7 Hz), 1.76 (dt, 1H, J = 4.8, 12.2 Hz), 1.70−1.68 (m, 1H); MS m/z 537 (MH^+).

3-Methylamino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (17). A mixture of **12** (110 mg, 0.2 mmol), TBAF (0.3 mL, 1 M in THF, 0.3 mmol) and THF (3 mL) was stirred at 25 °C for 8 h and the solvent was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). Removal of solvent provided a residue that was purified by flash column (silica gel; CH_2Cl_2:MeOH = 4:1, then CH_2Cl_2:MeOH:NH_4OH = 4 mL:1 mL:2 drops) to give 48 mg (78.5%) of **17** as a foam: ^{1}H NMR ($CDCl_3$) δ 6.55 (d, 1H, J = 7.8 Hz), 6.44 (d, 1H, J = 7.8 Hz), 5.68−5.65 (m, 1H), 5.30−5.27 (m, 1H), 4.83 (d, 1H, J = 7.6 Hz), 4.14 (d, 1H, J = 6.6 Hz), 3.35 (dd, 1H, J = 3.2, 5.9 Hz), 3.02 (d, 1H, J = 18.5 Hz), 2.82 (s, 3H), 2.67−2.66 (m, 1H), 2.59 (dd, 1H, J = 4.1, 12.0 Hz), 2.48−2.42 (m, 1H), 2.44 (s, 3H), 2.30 (dd, 1H, J = 6.4, 18.5 Hz), 2.06 (dt, 1H, J = 5.1, 12.4 Hz), 1.88−1.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 145.6, 133.0, 131.6, 128.6, 128.2, 123.3, 119.4, 111.0, 91.0, 66.3, 58.9, 46.4, 42.9, 42.8, 40.7, 35.7, 30.7, 20.1; MS m/z 299 (MH^+); $[\alpha]_D^{24}$ = −90.0° (c = 0.4, $CHCl_3$). Anal. ($C_{18}H_{22}N_2O_2{\cdot}0.75H_2O$) C, H, N.

***N,N*-Dimethyl-7,8-didehydro-6-[[(1,1-dimethylethyl)-diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-amine (13).** A mixture of **9** (300 mg, 0.48 mmol), $Pd(OAc)_2$ (6 mg, 0.2 mmol), BINAP (17 mg, 0.027 mmol), NaO*t*-Bu (64 mg, 0.67 mmol), dimethylamine (0.335 μL, 2 M in THF, 0.67 mmol) and toluene (5 mL) was stirred at 80 °C under N_2 in sealed tube for 8 h. The solvent was removed on a rotary evaporator and the residue was purified by flash column (silica gel; CH_2Cl_2:MeOH:NH_4OH = 20 mL:1 mL:2 drops) to give 240 mg (91.2%) of **13** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 2H, J = 6.8 Hz), 7.68 (d, 2H, J = 6.8 Hz), 7.47−7.31 (m, 6H), 6.57 (d, 1H, J = 8.0 Hz), 6.51 (d, 1H, J = 8.0 Hz), 5.75−5.72 (m, 1H), 5.18 (dt, 1H, J = 2.7, 9.8 Hz), 4.48 (d, 1H, J = 6.0 Hz), 4.17−4.14 (m, 1H), 3.25 (dd, 1H, J = 2.9, 6.1 Hz), 2.99 (d, 1H, J = 18.8), 2.91 (s, 6H), 2.49−2.46 (m, 1H), 2.42−2.35 (m, 2H), 2.38 (s, 3H), 2.29 (dd, 1H, J = 6.4, 18.6 Hz), 1.79−1.72 (m, 2H); MS m/z 551 (MH^+).

3-Dimethylamino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (18). A mixture of **13** (200 mg, 0.64 mmol), TBAF (0.96 μL, 1 M in THF, 0.96 mmol) and THF (5 mL) was stirred at 25 °C for 6 h. The solvent was removed on a rotary evaporator and the residue was purified by preparative TLC (silica gel; CH_2Cl_2:MeOH = 3:1) to give 90 mg (79.6%) of **18** as a foam: ^{1}H NMR ($CDCl_3$) δ 6.56 (d, 1H, J = 8.3 Hz), 6.54 (d, 1H, J = 8.3 Hz), 5.71−5.68 (m, 1H), 5.29 (dt, 1H, J = 2.7, 8.8 Hz), 4.83 (d, 1H, J = 8.6 Hz), 4.16−4.14 (m, 1H), 3.34 (dd, 1H, J = 3.2, 6.1 Hz), 3.04 (d, 1H, J = 18.5 Hz), 2.80 (s, 6H), 2.66−2.65 (m, 1H), 2.59 (dd, 1H, J = 4.4, 12.2 Hz), 2.44 (s, 3H), 2.43 (dt, 1H, J = 3.7, 12.5 Hz), 2.32 (dd, 1H, J = 6.4, 18.6 Hz), 2.04 (dt, 1H, J = 4.9, 12.4 Hz), 1.89−1.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 148.8, 134.5, 133.2, 129.9, 128.1, 126.3, 119.3, 115.3, 90.4, 66.4, 58.6, 46.3, 42.9, 42.4, 42.0, 40.6, 35.8, 20.3; MS m/z 313 (MH^+); $[\alpha]_D^{24}$ = −100.0° (c = 0.71, $CHCl_3$). Anal. ($C_{19}H_{24}N_2O_2{\cdot}0.75H_2O$) C, H, N.

***N*-Phenyl-7,8-didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-amine (14).** A mixture of **9** (300 mg, 0.48 mmol), Pd_2 $(dba)_3$ (22 mg, 0.024 mmol), DPPF (40 mg, 0.072 mmol), NaO*t*-Bu (55 mg, 0.576 mmol), aniline (82 μL, 0.90 mmol) and toluene (5 mL) was stirred at 80 °C for 5 h. The reaction mixture was passed through a short silica gel plug (eluent CH_2Cl_2:MeOH = 10:1) and the solvent was removed. The residue was purified by flash column (silica gel; CH_2Cl_2:MeOH = 5:0.2) to give 80 mg (62.9%) of **14** as an oil: ^{1}NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 6.9 Hz), 7.76 (d, 2H, J = 6.9 Hz). 7.51−7.40 (m, 5H, 7.30 (t, 2H, J = 7.9 Hz), 7.10 (d, 1H, J = 8.0 Hz), 7.08 (d, 2H, J =

12.4 Hz), 6.92 (t, 1H, J = 7.0 Hz), 6.58 (d, 1H, J = 8.1 Hz), 5.84−5.82 (m, 1H), 5.67 (s, br, 1H, D_2O), 5.30 (dt, 1H, J = 2.4, 9.8 Hz), 4.46 (d, 1H, J = 6.1 Hz), 4.33−4.31 (m, 1H), 3.35 (dd, 1H, J = 3.2, 6.1 Hz), 3.08 (d, 1H, J = 18.5 Hz), 2.58−2.53 (m, 2H), 2.50−2.42 (m, 1H), 2.46 (s, 3H), 2.36 (dd, 1H, J = 6.1, 8.6 Hz), 1.84−1.78 (m, 2H); MS m/z 599 (MH^+).

3-Phenylamino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (19). A mixture of **14** (80 mg, 0.13 mmol), TBAF (0.174 μL, 1 M in THF, 0.174 mmol) and THF (1 mL) was stirred at 25 °C for 3 h and the solvent was removed. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (20 mL) and brine (20 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated using a rotary evaporator to give a residue that was purified by flash chromatography (silica gel; CH_2Cl_2:MeOH:NH_4OH = 5 mL:1 mL:3 drops) to give 40 mg (83.1%) of **19** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.24 (t, 1H, J = 8.0 Hz), 6.94 (d, 1H, J = 8.0 Hz), 6.87−6.84 (m, 2H), 6.59 (d, 1H, J = 8.0 Hz)5.74−5.70 (m, 1H), 5.48 (s, 1H, D_2O), 5.35 (dt, 1h, J = 2.4, 10.0 Hz), 4.87 (d, 1H, J = 6.6 Hz), 4.17−4.16 (m,1H), 3.38 (dd, 1H, J = 3.2, 7.0 Hz), 3.18 (d, 1H, J = 18.8 Hz), 2.69−2.66 (m, 1H), 2.61 (dd, 1H, J = 3.9, 12.2 Hz), 2.46 (s, 3H), 2.45 (dt, 1H, J = 3.6, 8.3 Hz), 2.33 (dd, 1H, J = 6.4, 18.6 Hz), 2.08 (dt, 1H, J = 5.4, 12.7 Hz), 1.90−1.88 (m, 1H).; MS m/z 361 (MH^+); $[\alpha]_D^{24} = -125.0°$ (c = 0.75, $CHCl_3$). Anal. ($C_{23}H_{24}N_2O_2 \cdot 0.75H_2O$).

***N*-Phenylmethylamino-7,8-didehydro-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3-amine (15).** A mixture of **9** (300 mg, 0.48 mmol), BINAP (18 mg, 0.029 mmol), $Pd(OAc)_2$ (6.3 mg, 0.028 mmol), NaO*t*-Bu (63 mg, 0.58 mmol), benzylamine (66 mg, 0.58 mmol) and toluene (6 mL) was stirred at 80 °C for 8 h under N_2. The solvent was removed and the resulting residue was purified by flash chromatography (silica gel; CH_2Cl_2:MeOH = 12:1) to give 245 mg (83.6%) of **15** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 2H, J = 7.9 Hz), 7.68 (d, 2H, J = 7.9 Hz), 7.64−7.22 (m, 11H), 5.75 (d, 1H, J = 8.7 Hz), 5.19 (d, 1H, J = 9.8 Hz), 4.38−4.36 (m, 2H), 4.22−4.20 (m, 1H), 3.89 (s, 1H, D_2O exchange), 3.23 (dd, 1H, J = 3.0, 5.4 Hz), 2.95 (d, 1H, J = 18.6 Hz), 2.46−2.37 (m, 3H), 2.42 (s, 2H), 2.23 (dd, 1H, J = 6.1, 8.3 Hz), 1.77−1.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 146.9, 139.7, 135.6, 133.8, 133.6, 133.0, 130.6, 129.6, 129.6, 128.8, 128.3, 128.1, 127.5, 127.4, 127.4, 126.8, 123.6, 118.5, 111.5, 91.5, 69.0, 58.8, 48.5, 46.3, 43.3, 42.9, 40.9, 35.5, 26.7, 20.1, 19.2.

3-Phenylmethylamino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (20). A mixture of **15** (136 mg, 0.22 mmol), TBAF (0.33 mL, 1 M in THF, 0.33 mmol) and THF (3 mL) was stirred at 25 °C for 8 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (50 mL). The solution was washed with saturated sodium bicarbonate (30 mL), dried (Na_2SO_4) and concentrated to give a residue that was purified by preparative TLC (silica gel; CH_2Cl_2:MeOH:NH_4OH = 5 mL:1 mL:2 drops) to give 80 mg of (96.3%) **20** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.33−7.23 (m, 5H), 6.47 (d, 1H, J = 7.8 Hz), 6.41 (d, 1H, J = 7.8 Hz), 5.64 (m, 1H), 5.25 (dt, 1H, J = 2.6, 10 Hz), 4.75 (d, 1H, J = 6.3 Hz), 4.26 (s, 2H), 4.06 (m, 1H), 3.33 (dd, 1H, J = 3.2, 6.1 Hz), 2.30 (d, 1H, J = 18.8 Hz), 2.64 (t, 1H, J = 2.7 Hz), 2.57 (dd, 1H, J = 3.9, 11.9 Hz), 2.46−2.40 (m, 1H), 2.43 (s, 3H), 2.27 (dd, 1H, J = 6.3, 18.6 Hz), 2.02 (dt, 1H, J = 5.2, 12.5 Hz), 1.83 (dd, 1H, J = 1.7, 12.7 Hz); ^{13}C NMR ($CDCl_3$) δ 145.8, 139.4, 133.0, 130.3, 128.9, 128.4, 128.2, 127.4, 127.0, 123.9, 119.3, 112.2, 91.0, 66.3, 58.8, 48.6, 46.3, 42.9, 42.7, 40.7, 35.5, 20.0; MS m/z 375 (MH^+); $[\alpha]_D^{24} = -72.0°$ (c = 0.90, $CHCl_3$). Anal. ($C_{24}H_{26}N_2O_2 \cdot H_2O$).

Radiolabeled Ligand Binding Assays. Binding assays used to screen compounds are similar to those previously reported.[33] Guinea pig brain membranes, 500 μg of membrane protein, were incubated with 12 different concentrations of the compound in the presence of either 1 nM [^{3}H]U69,593 (κ), 0.25 nM [^{3}H]DAMGO (μ) or 0.2 nM [^{3}H]naltrindole (δ) in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5 at 25 °C. Incubation times of 60 min were used for [^{3}H]U69,593 and [^{3}H]DAMGO. Because of a slower association of [^{3}H]naltrindole with the receptor, a 3-h incubation was used with this radioligand. Samples incubated with [^{3}H]naltrindole also contained 10 μM $MgCl_2$ and 0.5 mM phenylmethanesulfonyl fluoride. Nonspecific binding was measured by inclusion of 10 μM naloxone. The binding was terminated by filtering the samples through Schleicher & Schuell no. 32 glass fiber filters using a Brandel 48-well cell harvester. The filters were subsequently washed three times with 3 mL of cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL Ecoscint A scintillation fluid. For [^{3}H]-naltrindole and [^{3}H]U69,593 binding, the filters were soaked in 0.1% poly(ethylenimine) for at least 60 min before use. IC_{50} values were be calculated by least-squares fit to a logarithm-probit analysis. K_i values of unlabeled compounds were calculated from the equation: $K_i = (IC_{50})/1 + S$ where S = (concentration of radioligand)/(K_d of radioligand).[34] Data are the mean ± SE from at least three experiments performed in triplicate.

Adenylyl Cyclase Assays. Methods for the quantification of cyclic AMP production in SH-SY5Y membranes were measured as described previously.[35] Membranes, 50 μg of proteins in a homogenizing buffer (40 mM HEPES-Na^+, 2 mM EGTA, 0.32 M sucrose, pH 7.4), were incubated for 15 min in a 30 °C water bath with 10 μM either DAMGO, a μ-selective ligand, or the aminomorphine derivatives, and in the presence of 20 mM HEPES, pH 7.4, 30 U creatine phosphokinase, 20 mM phosphocreatine, 1 mM phenanthroline, 60 μM isobutylmethylxanthine, 0.1 mM GTP and 0.1 mM ATP. The reaction was stopped by the addition of 4.5% perchloric acid and neutralized with 30% KHO_3. After centrifugation at 14000*g*, for 4 min, 100 μL of supernatant were used to determine cyclic AMP accumulation, using a [^{3}H]cyclic AMP assay kit (Diagnostic Products Corp., Los Angeles, CA). Results are reported as the mean percent inhibition of basal activity (in the absence of agonist) ± SE. Each experiment was performed in duplicate and each experiment was repeated at least three times.

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