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Synthesis, Binding Affinity, and Functional in Vitro Activity of 3-Benzylaminomorphinan and 3-Benzylaminomorphine Ligands at Opioid Receptors

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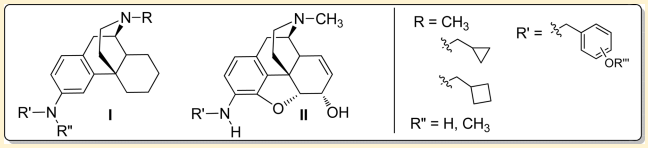
ABSTRACT: A series of 3-benzylamino-3-desoxymorphinan (**I**) and 3-benzylamino-3-desoxymorphine (**II**) derivatives were synthesized and evaluated for their binding affinities, and functional activity data are presented at MOR, KOR, and DOR. Some of these ligands were found to have high binding affinity at MOR and KOR and displayed increased selectivity at MOR over KOR and DOR compared to butorphan or cyclorphan. The most selective compound, 3-(3′-hydroxybenzyl)amino-17-methylmorphinan (**4g**) (24-fold MOR to KOR and 1700-fold MOR to DOR) also showed high binding affinity (0.42 nM to MOR) and was a full agonist in the [^{35}S]GTPγS binding assay. 2-(3′-Hydroxybenzyl)amino-17-cyclopropylmethylmorphinan (**17**) was found to be a KOR-selective ligand (150-fold over MOR and >10000-fold over the DORs). Most 3-benzylaminomorphinan derivatives were partial agonists at MOR and full agonists at KOR in the [^{35}S]GTPγS binding assay.



INTRODUCTION

Morphine is still the drug of choice for treating severe pain caused by trauma.[1] However, morphine has serious side effects, including constipation, respiratory depression, dependence, tolerance, and addiction. Most clinically available opioid analgesics have MOR selective affinity, such as sufentanil,[2] which is 600- to 800-fold more potent than morphine, with 100-fold selectivity for MOR over other opioid receptors.[2b] The most commonly used centrally acting analgesics, hydrocodone[3] and oxycodone,[4] have only about one-tenth the affinity to KOR and DOR as morphine, with good selectivity at MOR.

The free phenolic hydroxyl group in morphine, cyclorphan, and butorphan (Scheme 1) is also a potential site for metabolism, conjugation, and excretion, resulting in low oral bioavailability and short duration of action.[5] Although the phenolic OH group was historically thought to be a requirement for binding to opioid receptors serving as a putative H-bond donor to a complementary site on the protein.[6] Schiller and co-workers[7] reported that replacement of the Tyr residue in TIPP peptides with a Bcp or Dbcp residue resulted in a general increase in DOR binding affinity. We have reported the modification of the phenolic hydroxyl group of cyclorphan and butorphan, such as carbamate,[8] oxazole,[9] urea,[9] and aminothiazole[10] analogues, which maintain high binding affinity. In continuing these studies on the development of effective analgesics and/or treatment for opioid addiction, we focused our interests on the structural modification and pharmacological evaluation of analogues of cyclorphan and butorphan, especially in the development of new MOR selective ligands. Our interest in exploring 3-benzylamino derivatives is twofold: first, replacement of the phenolic hydroxyl group may confer metabolic stability; second, the presence of the 3-amino moiety allows for introduction of a variety of functionalized benzyl groups, which may result in analogues with increased selectivity and affinity for MOR. Here we report the synthesis, binding affinity, and functional activity of 3-benzylamino-3-desoxymorphinans and 3-benzylamino-3-desoxymorphine analogues.

With a combination of affinity labeling experiments using S-activated dihydromorphine derivatives and molecular mechanics, Sagara et al.[11] reported the binding site of the MOR, the hydrogen bonding interaction between the phenolic hydroxyl group of morphine and both the amino group of Lys303 at TM VI and the phenolic hydroxyl group of Tyr148 at TM III. Relatively small ligands, such as morphine, may be able to bind at several different positions in the binding pocket of the receptor. One of the docking models[12] proposed that the phenolic hydroxyl group is placed close to the imidazole group of His297 at TM VI, forming hydrogen bonding interaction. On the basis of these binding models, we speculated that replacement of the OH group with an amino or a substituted amino group would maintain partial hydrogen bonding. Introduction of the aryl group on nitrogen may thus have a π–π interaction with the phenyl group of Tyr148 or imidazole group of His297 which may enhance the binding and increase

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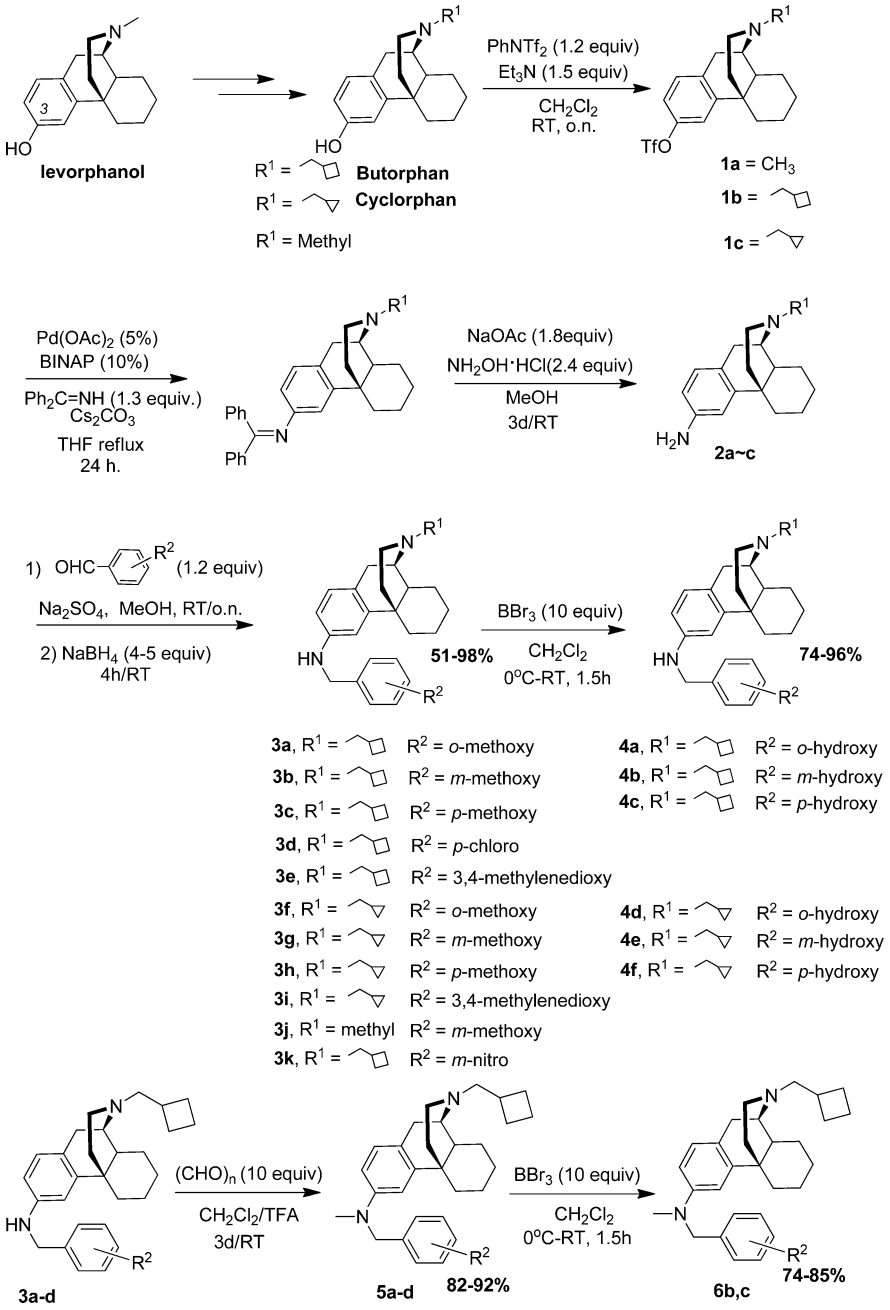
Scheme 1. Synthesis of 3-Benzylaminomorphinan Analogues



the selectivity at the MOR. Wentland et al.[13] had reported the opioid receptor binding properties of a series of cyclazocine analogues where the 8-OH group of cyclazocine was replaced with amino groups. Several members of this new series had surprisingly high affinity for the MOR and KOR. The NH_2 group appears to be an effective bioisosteric replacement for the prototypic 8-OH group in cyclazocine. The replacement of OH with NH_2 in morphine decreased the binding affinity significantly, albeit with better selectivity at the MOR over the other receptors.[14] In our previous report,[15] we also found that replacement OH group of butorphan or cyclorphan (Scheme 1) with NH_2 resulted in a much lower binding affinity. By incorporation of different substituted benzyl groups, ligands with improved binding affinity and selectivity were synthesized. Morphine analogues (**11a**, **11b**, **11c**, **12a**, **12b**, and **12c**) with substituted benzyl groups were generally less active at MOR. Interestingly, **17**, a 2-benzylamino-3-desoxymorphinan, was found to be a highly KOR-selective ligand. Further methylation of the 3-amino nitrogen of these morphinan ligands (i.e., **5a**, **5b**, **5c**, **5d**, **6b**, and **6c**) impaired their binding affinity, which confirmed that the N−H bond participated in hydrogen bonding between the ligand and the receptor.

CHEMISTRY

The synthetic route toward 3-benzylaminomorphinans is described in Scheme 1. Levorphanol tartrate was converted to its free base and then demethylated to afford norlevorphanol.[16] The latter was then alkylated with either (bromomethyl)-cyclobutane or (bromomethyl)cyclopropane to yield butorphan or cyclorphan, respectively.[16] The 3-hydroxy groups were triflated (**1a**, **1b**, **1c**) with *N*-phenyl bistriflimide in the presence of triethylamine, which could then be coupled in a Buchwald−

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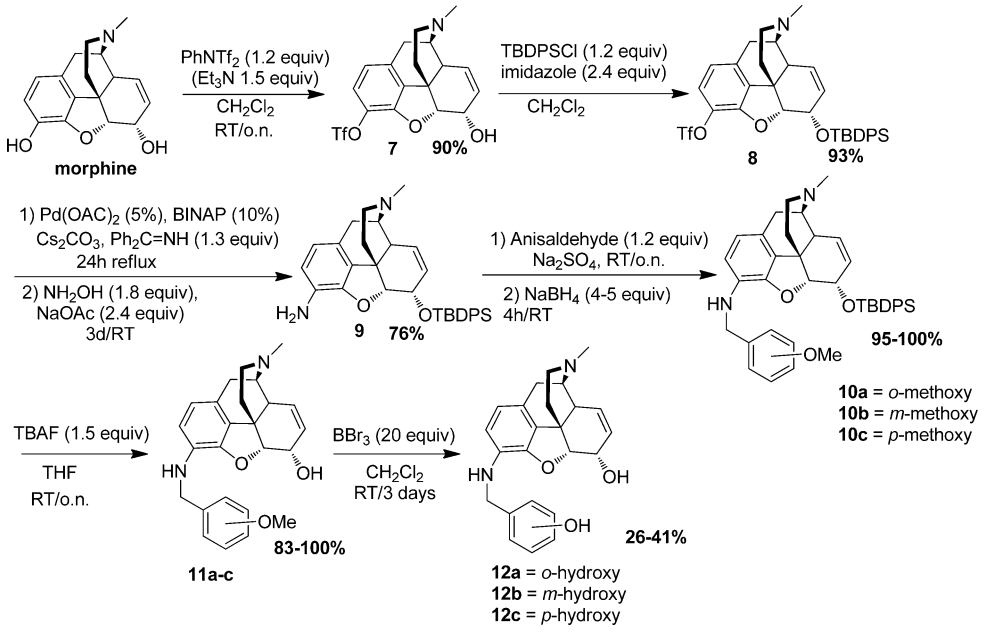
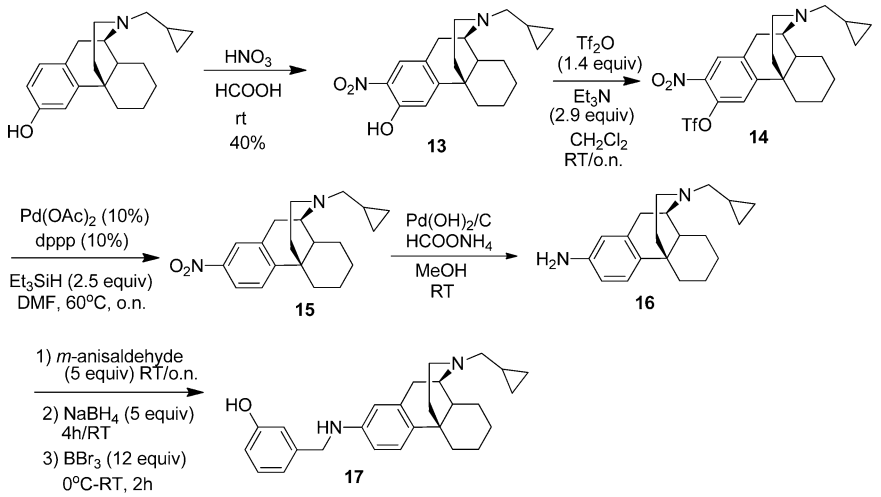
Scheme 2. Synthesis of 3-Benzylamino-3-morphine Analogues



Scheme 3. Synthesis of 2-(3′-Hydroxybenzyl)amino-3-cyclorphan



Hartwig reaction[17] to yield the 3-benzylamino-3-desoxymorphinan directly. For effective preparation of N-substituted 3-aminomorphinans, the triflates were converted to their 3-aminomorphinans (**2a−c**) with benzophenoneimine using catalytic $Pd(OAc)_2$ and rac-BINAP as ligand, followed by hydrolysis and condensation with an aldehyde and reduction of the resultant imine with $NaBH_4$. The resulting amines (**3a−k**) were methylated using paraformaldehyde/$NaBH_4$/TFA.[18] The methoxybenzylaminomorphinans (**3a−c**, **3f−h**) were demethylated with BBr_3 in anhydrous CH_2Cl_2 to yield hydroxybenzylaminomorphinan ligands (**4a−c**, **4d−f**). For the synthesis of morphine analogues (Scheme 2), morphine was treated with 1 equiv of $PhNTf_2$ and Et_3N in dichloromethane to selectively afford morphine-3-triflate **7**.[21] The 6-hydroxy group was protected by TBDPSCl/Et_3N to afford **8**.[14] The triflate was converted to 3-aminomorphine (**9**) by using Pd catalyzed amination with benzophenoneimine, followed by hydrolysis under acidic conditions. The resulting amine (**9**) was condensed with the appropriate benzaldehyde to afford the corresponding imine and reduced with $NaBH_4$ to give 3-benzylaminomorphine derivatives. TBDPS was routinely removed with TBAF to yield the desired ligands (**11a−c**), which after O-demethylation gave **12a−c**. For the preparation of 2-amino-3-desoxymorphinan (**16**), cyclorphan was first nitrated with HNO_3/HCOOH to afford **13**[9] and then triflated to yield 2-nitromorphinan-3-triflate (**14**). The triflate was reduced to 2-nitro-3-desoxymorphinan (**15**) using $Pd(OAc)_2$/dppp/Et_3SiH.[20] Finally, the nitro group was reduced to the amine (**16**) and converted to the corresponding imine with *m*-anisaldehyde and reduced with $NaBH_4$ to give the 2-benzylamino-3-desoxymorphinan (**17**) (Scheme 3).

RESULTS AND DISCUSSION

Target compounds were screened for their affinity and selectivity for MOR, KOR, and DOR with Chinese hamster ovary (CHO) cell membranes stably expressing the human opioid receptors. The data are summarized in Table 1. For comparison purposes, opioid binding affinity data for

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Table 1. K_i for the Inhibition of MOR, KOR, and DOR Opioid Binding to CHO Membranes[a]

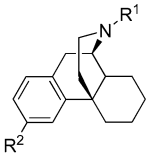
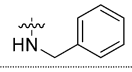
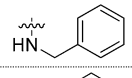
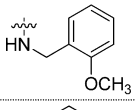
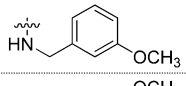
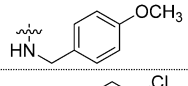
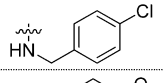
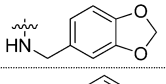
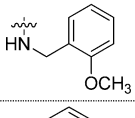
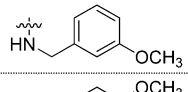
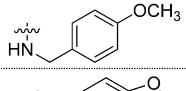
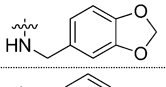
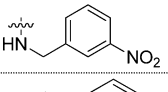
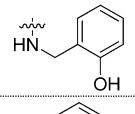
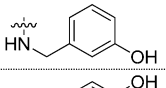
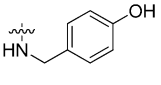
Compound			K_i[a] (nM)			Selectivity
	R^1	R^2	[^{3}H]DAMGO MOR	[^{3}H]U69,593 KOR	[^{3}H]Naltrindole DOR	MOR/KOR/DOR
Levorphanol	CH_3	OH	0.21 ± 0.02	2.3 ± 0.3	4.2 ± 2.3	1/11/20
Butorphan		OH	0.23 ± 0.01	0.079 ± 0.003	5.9 ± 0.6	3/1/75
Cyclorphan		OH	0.062 ±0.003	0.034 ± 0.002	1.9 ± 0.072	2/1/56
2a MCL-181[a]	CH_3	NH_2	7.9 ± 1.0	110 ± 11	1500 ± 770	1 /14 /190
2b MCL-182[a]		NH_2	3.7 ± 0.26	1.8 ± 0.06	180 ± 85	2/1/100
2c MCL-149		NH_2	1.30 ± 0.029	0.18 ± 0.003	150 ± 2	7/1/830
8a MCL-610[b]			0.26 ± 0.012	0.34 ± 0.031	29 ± 4.4	1/1/112
8d MCL-630[b]			1.7 ± 0.053	2.8 ± 0.33	130 ± 11	1/2/76
3a MCL-667			2.7 ± 0.07	2.2 ± 0.37	61 ± 0.41	1/1/28
3b MCL-665			0.69 ± 0.034	3.5 ± 0.45	150 ± 15	1/5/220
3c MCL-662			0.86 ± 0.057	4.5 ± 0.29	260 ± 29	1/5/300
3d MCL-668			1.7 ± 0.23	4.5 ± 0.46	100 ± 11	1/3/59
3e MCL-705			0.34 ± 0.018	1.1 ± 0.11	53 ± 3.7	1/3/160
3f MCL-699			1.2 ± 0.09	1.3 ± 0.096	160 ± 37	1/1/130
3g MCL-700			0.51 ± 0.039	1.5 ± 0.16	110 ± 20	1/3/220
3h MCL-628			0.31 ± 0.010	0.51 ± 0.031	20 ± 2.1	1/2/65
3i MCL-702			0.17 ± 0.013	0.53 ± 0.044	20 ± 3.7	1/3/120
3k MCL-731			0.43 ± 0.046	1.1 ± 0.13	150 ± 8.5	1/3/350
4a MCL-682			1.7 ± 0.41	1.7 ± 0.063	110 ± 32	1/1/65
4b MCL-683			0.32 ± 0.016	1.9 ± 0.088	230 ± 18	1/6/720
4c MCL-706			0.35 ± 0.030	2.3 ± 0.34	120 ± 7.8	1/7/340

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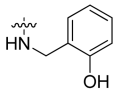
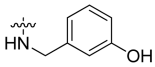
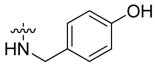
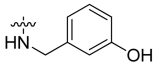
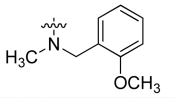
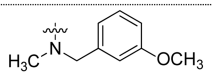
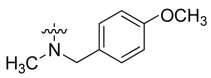
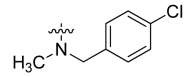
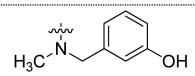
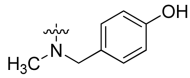
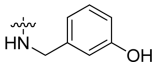
Table 1. continued

Compound	R¹	R²	K_i[a] (nM) [³H]DAMGO MOR	[³H]U69,593 KOR	[³H]Naltrindole DOR	Selectivity MOR/KOR/DOR
4d MCL-713			1.9 ± 0.24	0.26 ± 0.013	30 ± 3.3	10/1/150
4e MCL-701			0.16 ± 0.033	0.36 ± 0.025	41 ± 4.4	1/2/260
4f MCL-703			0.28 ± 0.041	0.27 ± 0.014	13 ± 2.0	1/1/44
4g MCL-725	CH_3		0.42 ± 0.0083	10 ± 0.16	720 ± 64	1/24/1700
5a MCL-681			14 ± 1.2	19 ± 2.4	190 ± 18	1/1/14
5b MCL-666			13 ± 0.92	25 ± 2.1	350 ± 22	1/2/27
5c MCL-663			9.5 ± 0.56	8.5 ± 0.84	290 ± 16	1/1/34
5d MCL-680			26 ± 1.7	27 ± 3.5	730 ± 106	1/1/28
6b MCL-684			17 ± 0.74	23 ± 0.83	170 ± 3.8	1/1/10
6c MCL-664			3.2 ± 0.23	4.1 ± 0.52	530 ± 83	1/1/170
17 MCL-712[c]			150 ± 16	0.99 ± 0.045	46 ± 0.31 inh	150/1/>10000

[a]See ref 19. [b]See ref 15. [c]**17** is *N*-(cyclopropylmethyl)-2-(2-hydroxybenzyl)aminomorphinan.

levorphanol, butorphan, cyclorphan, compounds **8a** and **8d**,[15] morphine, and hydrocodone were also included.

As described in Table 1, we began by investigating butorphan and its derivatives. Butorphan has high affinity to the MOR (0.23 nM), although it is not selective. Addition of a benzyl group to the 3-amino moiety in compound **2b**[19] to yield **8d**[15] (see Table 1 for structures) improved the affinity and selectivity to the MOR. We next investigated the effect of incorporation of different functional groups on the benzyl ring. Introduction of the methoxy group (**3a**–**c** and **3f**–**h**) had a pronounced effect on affinity and selectivity in this series. Thus, while an *o*-methoxybenzyl derivative **3a** had lower affinity and selectivity for MOR compared to butorphan, the *m*-methoxy analogue **3b** restored MOR binding affinity to a subnanomolar level, along with improved selectivity against the DOR. The *p*-methoxy analogue **3c** retained subnanomolar affinity to the MOR with even better selectivity vs the DOR. In contrast, the *p*-chlorobenzyl analogue **3d** had no effect on selectivity and exhibited weaker affinity to the MOR. Next, we investigated the presence of a free phenolic group on the benzyl moiety. Much to our surprise, the *o*-hydroxybenzyl analogue **4a** (K_i = 1.7 nM) possessed MOR binding affinity an order of magnitude lower than butorphan (K_i = 0.23 nM). The *m*- and *p*-hydroxybenzyl analogues **4b** and **4c**, on the other hand, had similar binding and selectivity profiles as their methoxybenzyl derivatives (**3b** and **3c**), as did the methylenedioxybenzyl derivative **3e** and *m*-nitrobenzyl derivative **3k**. The tertiary 3-amino analogues showed a marked loss in affinity and selectivity to the MOR, revealing that the 3-amino group as in **5a**–**c** and **6b**,**c** cannot be fully substituted.

Replacement of the 3-phenolic group in cyclorphan (K_i at MOR of 0.062 nM) for a 3-amino group (**2c**, K_i at MOR of 1.30 nM) resulted in a steep loss in affinity to the MOR. However, introduction of a benzylic group to the nitrogen as in **8a**[15] (K_i at MOR of 0.26 nM) resulted in high affinity to the MOR. In agreement with the methoxybenzylaminobutorphan series (**3a**–**c**), methoxybenzylaminocyclorphan derivatives (**3f**–**h**) also possessed subnanomolar affinity to MOR and similar selectivities against DOR. The *o*-hydroxybenzylamino derivatives **4a** and **4d** exhibited much lower affinity to MOR. The *m*- and *p*- analogues **4e** and **4f**, however, had similar affinities and selectivities as the butorphan derivatives **4b** and **4c**. The methylenedioxy analogue **3e** followed the same trend. The examination of 2-(*m*-hydroxybenzylamino)-3-desoxycy-

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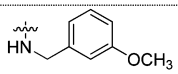
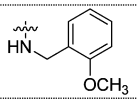
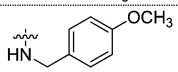
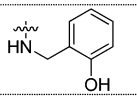
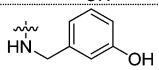
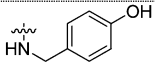
Table 2. K_i for the Inhibition of MOR, KOR, and DOR Opioid Binding to CHO Membranes

Compound	Structure R	K_i[a] (nM) [^{3}H]DAMGO MOR	[^{3}H]U69,593 KOR	[^{3}H]Naltrindole DOR	Selectivity MOR/KOR/DOR
Morphine	OH	0.88 ± 0.14	24 ± 2.3	140 ± 18	1/27/156
Hydrocodone	OCH_3	9.5 ± 0.73	260 ± 9.7	37% inh at 10μM ± 3.7	1/27/>1100
11a MCL-720		8.5 ± 0.79	220 ± 17	22% inh at 10μM ± 0.96	1/16/>1200
11b MCL-718		45 ± 2.2	500 ± 29	33% inh at 10μM ± 2.1	1/11/>220
11c MCL-719		60 ± 0.90	54% inh in 10μM 0.82	12% inh at 10μM ± 0.47	1/>160/>160
12a MCL-721		13 ± 0.53	370 ± 38	27% inh at 10μM ± 1.5	1/28/>770
12b MCL-717		7.0 ± 0.29	910 ± 30	31% inh at 10μM ± 2.8	1/130/>1400
12c MCL-722		44 ± 2.0	560 ± 8.8	19% inh at 10μM ± 1.0	1/13/230

[a]Membranes from Chinese hamster ovary cells, expressing the human MOR, KOR, or DOR, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific radioligands at 25 °C in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Nonspecific binding was determined using 10 μM naloxone. Data are the mean value ± SEM from three experiments, performed in triplicate.

clorphan **17** resulted in a loss of affinity to MOR, although it had high affinity and selectivity to the KOR. Since the hydroxybenzylamino moiety was shown to enhance affinity and selectivity to the MOR for cyclorphan and butorphan, we also examined the analogous derivative of levorphanol. Thus, **4g** was found to possess subnanomolar affinity to MOR (K_i = 0.42 nM), moderate affinity against KOR, and almost 2000-fold lower affinity at DOR.

Because the methoxy- and hydroxybenzylamino substituted morphinan derivatives were found to have high affinity and selectivity to MOR, the corresponding derivatives of morphine were also examined. In contrast to the morphinan derivatives described above, which generally had MOR affinities in the subnanomolar range and improved selectivities to the MOR, the analogous morphine derivatives **11** and **12** suffered a loss of affinity to the MOR. The morphine analogues **12a–c** showed only moderate binding affinity at MOR (K_i of 8.5, 13, 7.4 nM, respectively) (Table 2).

Compounds that exhibited high affinity for the MOR were screened for functional activity at MOR (Table 3) and KOR (Table 4) using the [^{35}S]GTPγS binding assay. Compound **4g**, which contained an *N*-methyl group, was a full agonist at the MOR as shown in Table 3. The 3-benzylaminomorphinans were partial agonists at the MOR. The 3-aminomorphine derivatives (**11a**, **12b**) were full agonists at the MOR, but they were not very potent. While the 3-benzylaminomorphinans were partial agonists at the MOR, they were full agonists at the KOR as shown in Table 4. None of the compounds inhibited U50,488-stimulated [^{35}S]GTPγS binding mediated by the KOR.

CONCLUSION

We have extended the SARs of cyclorphan and butorphan analogues by introducing different substituted benzylamino groups at the 3-position of morphinan. Replacing the *N*-methyl substituent on the morphinan with cyclopropylmethyl or cyclobutylmethyl substituents generally increased the binding affinity at both the MOR and KOR. It was found that benzyl substituents at the 3-amino nitrogen tended to increase the binding affinity and selectivity of the compounds. Further alkylation of 3′-nitrogen reduced the MOR affinity significantly, which suggested that either hydrogen bonding was required or the larger methyl group inhibited binding between the 3-amino group of the compound and the MOR. In general, methoxy-, hydroxyl-, and methylenedioxy-substituted benzylaminomorphinans exhibited the highest bindng affinities to MOR. However, introduction of a free phenolic hydroxyl group may open a potential site for metabolism. The increased selectivity of morphine analogues supported the hypothesis that a methoxybenzylamino or hydroxybenzylamino group at the 3-position of an opioid ligand may interact with another site of the MOR and may be a useful consideration when designing new MOR selective opioid ligands. Functional activity was determined for analogues that exhibited high binding affinity to the MOR and KOR, and it was found that all morphinan derivatives were partial agonists at the MOR and morphine derivatives were full agonists at the MOR although with low

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Table 3. Effect of High Affinity Compounds on [^{35}S]GTPγS Binding Mediated by the μ Opioid Receptor[a]

compd	EC_{50} (nM)	E_{max} (% maximal stimulation over basal)	IC_{50} (nM)	I_{max} (% maximal inhibition)
DAMGO	55 ± 5.0	130 ± 6.1	NI[b]	NI[b]
butorphan	1.6 ± 0.15	50 ± 2.5	20 ± 2.7	50 ± 2.6
cyclorphan	0.80 ± 0.40	40 ± 2.9	1.7 ± 0.40	50 ± 1.2
3b	3.8 ± 0.37	39 ± 4.4	80 ± 16	66 ± 4.3
3c	7.8 ± 0.29	34 ± 2.9	150 ± 20	55 ± 3.0
3e	3.6 ± 0.65	39 ± 3.7	94 ± 17	60 ± 0.84
3g	NA	23 ± 3.1	2.0 ± 0.93	77 ± 2.9
3h	6.8 ± 0.53	30 ± 1.2	10 ± 2.2	67 ± 2.1
3i	NA	18 ± 2.4	0.21 ± 0.065	72 ± 2.8
3k	1.1 ± 0.22	70 ± 8.1	6.8 ± 1.6	49 ± 4.7
4a	38 ± 5.6	49 ± 4.6	810 ± 9.4	32 ± 4.6
4b	NA	30 ± 3.7	4.8 ± 0.48	74 ± 2.7
4c	3.6 ± 0.93	38 ± 4.7	75 ± 13	56 ± 6.6
4d	8.8 ± 1.2	44 ± 2.0	160 ± 5.7	47 ± 1.3
4e	NA	27 ± 0	3.5 ± 0.14	79 ± 8.4
4f	NA	19 ± 1.0	7.6 ± 3.5	80 ± 1.2
4g	6.5 ± 1.5	85 ± 6.1	NI	NI
11a	210 ± 97	81 ± 13	NI	NI
12b	550 ± 53	110 ± 16	NI	NI

[a]Membranes from CHO cells that expressed the human μ opioid receptor were incubated with 12 concentrations of the compound in the presence of 0.08 nM [^{35}S]GTPγS for 60 min at 30 °C. Nonspecific binding was measured by the inclusion of 10 μM GTPγS. For the inhibition experiments, [^{35}S]GTPγS binding was stimulated by the addition of 200 nM DAMGO. Data are the mean ± SEM from three experiments performed in triplicate. [b]NI = no inhibition of DAMGO-stimulated [^{35}S]GTPγS binding.

Table 4. Effect of High Affinity Compounds on [^{35}S]GTPγS Binding Mediated by the κ Opioid Receptor[a]

compd	EC_{50} (nM)	E_{max} (% maximal stimulation over basal)
U50,488[b]	4.2 ± 0.38	140 ± 10
butorphan[b]	1.3 ± 0.4	80 ± 6.8
cyclorphan[b]	0.19 ± 0.4	90 ± 10
3b	39 ± 8.4	120 ± 13
3c	50 ± 2.6	120 ± 7.1
3e	27 ± 2.9	130 ± 12
3g	0.43 ± 0.18	130 ± 14
3h	5.3 ± 0.56	130 ± 3.3
3i	0.077 ± 0.014	120 ± 4.3
3k	0.79 ± 0.11	140 ± 16
4a	47 ± 1.8	130 ± 7.1
4c	38 ± 3.8	130 ± 4.8
4d	2.3 ± 0.28	110 ± 4.9
4e	3.9 ± 0.53	98 ± 1.9
4f	1.8 ± 0.32	100 ± 2.7
4g	230 ± 19	140 ± 9.0
17	27 ± 2.5	160 ± 6.4

[a]Membranes from CHO cells that expressed the human κ opioid receptor were incubated with 12 concentrations of the compound in the presence of 0.08 nM [^{35}S]GTPγS for 60 min at 30 °C. Nonspecific binding was measured by the inclusion of 10 μM GTPγS. Data are the mean ± SEM from three experiments performed in triplicate. None of the compounds produced any inhibition of [^{35}S]GTPγS binding stimulated by 100 nM U50,488. [b]See ref 16.

potency. All compounds proved to be full agonists at the KOR. Our efforts led to the discovery of potent, selective MOR agonists and also led to further insights into their structure–activity relationship. Compounds **4a** and **4g** are promising lead compounds for further evaluation and optimization, and they may be used as chemical and pharmacological tools to elucidate the pharmacodynamic features of opioid receptors. This class of compounds, mixed κ/μ opioids, may have utility in the treatment of cocaine abuse and, with further pharmacological evaluation, may also prove to be useful as analgesics. Notably, **17**, which has the benzylamino group attached to position 2 rather than position 3, was found to be highly selective at the KOR and emerged as a promising lead compound for further design and modification for the development of KOR selective opioid ligands.

EXPERIMENTAL SECTION

General Synthetic Methods. ^{1}H (and ^{13}C NMR) spectra were recorded at 300 MHz (75 MHz) on a Varian Mercury 300 spectrometer. Chemical shifts are given as δ value (ppm) downfield from tetramethylsilane as an internal reference. Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. Elemental analyses, performed by Atlantic Microlabs, Atlanta, GA, were within 0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2 μm Kieselgel 60F-254 silica gel aluminum sheets (EM Science, Newark, NJ). Flash chromatography was used for the routine purification of reaction products. Eluent systems are described for the individual compounds.

Representative Procedure for the Preparation of Morphinans 3a–k and 10a–c. To a solution of *N*-cyclobutylmethyl-3-aminomorphinan **2a** (113 mg, 0.364 mmol) and *p*-anisaldehyde (59 mg, 0.437 mmol) in anhydrous methanol (10 mL) under nitrogen atmosphere was added sodium sulfate (200 g, 1.4 mmol), and the mixture was allowed to stir overnight at room temperature. Next, sodium borohydride (59 mg, 1.54 mmol) was added and the mixture was stirred at room temperature for 4 h. After the reaction was judged complete, the mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (50 mL) and washed sequentially with water and brine. The organic layer was dried over sodium sulfate, then filtered and concentrated, and the residue was purified over silica gel using EtOAc/Et_3N, 200:1, to afford 97 mg of *N*-cyclobutylmethyl-3-(4-methoxybenzyl)aminomorphinan **3c** as a pale yellow oil, 62% yield. The oil was dissolved in a minimal amount of ethyl acetate and treated with excess 1 N ethereal HCl. The resulting solution was then concentrated and the residue was recrystallized from methanol/diethyl ether to afford the corresponding dihydrochloride salt (mp = 180–183 °C).

(−)-17-(Cyclobutylmethyl)-*N*-(2-methoxybenzyl)morphinan-3-amine (3a). Pale yellow oil (339 mg, 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.19 (m, 2H), 6.89 (dd, *J* = 5.8, 11.5, 3H), 6.56 (d, *J* = 2.0, 1H), 6.49 (dd, *J* = 1.8, 8.1, 1H), 4.29 (s, 2H), 4.02 (s, 1H), 3.86 (s, 3H), 2.99–2.78 (m, 2H), 2.73–2.44 (m, *J* = 19.4, 5H), 2.31–1.08 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 146.9, 140.6, 129.2, 128.2, 128.2, 127.4, 125.8, 120.4, 111.3, 110.2, 109.8, 61.0, 56.2, 55.2, 46.1, 44.4, 43.7, 41.2, 37.3, 36.4, 34.2, 27.8, 27.8, 26.7, 26.4, 24.0, 22.1, 18.7; mp = 156–158 °C (HCl salt). Anal. Calcd for $C_{29}H_{38}N_2O{\cdot}2HCl{\cdot}0.8H_2O$: C, 67.25; H, 8.10; N, 5.41. Found: C, 67.37, H, 8.15; N, 5.31.

(−)-17-(Cyclobutylmethyl)-*N*-(3-methoxybenzyl)morphinan-3-amine (3b). Colorless oil (195 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (td, *J* = 2.0, 8.2, 1H), 7.02–6.86 (m, 3H), 6.80 (dd, *J* = 1.7, 8.2, 1H), 6.53 (d, *J* = 2.2, 1H), 6.46 (dd, *J* = 2.4, 8.1, 1H), 4.26 (s, 2H), 3.79 (s, 3H), 2.90 (d, *J* = 17.8, 1H), 2.78 (m, 1H), 2.60–2.37 (m, 5H), 2.23 (d, *J* = 10.8, 1H), 2.15–1.97 (m, 3H), 1.94–1.13 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 146.6, 141.3, 141.0, 129.5, 128.3, 126.5, 119.9, 113.1, 112.6, 110.8, 109.7, 61.2, 56.1, 55.1, 48.8, 46.0, 44.8, 41.6, 37.4, 36.5, 34.5, 27.8, 26.8, 26.5, 23.9, 22.1, 18.8; (HCl salt)

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mp = 151−154 °C. Anal. Calcd for $C_{29}H_{38}N_2O·2HCl·0.8H_2O$: C, 67.25; H, 8.10; N, 5.41. Found: C, 67.19, H, 8.00; N, 5.47.

(−)-17-(Cyclobutylmethyl)-*N*-(4-methoxybenzyl)morphinan-3-amine (3c). Pale yellow oil (276 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.26 (m, 2H), 6.94−6.84 (m, 3H), 6.52 (d, J = 2.4, 1H), 6.46 (dd, J = 2.4, 8.1, 1H), 4.20 (s, 2H), 3.79 (s, 3H), 2.90 (d, J = 18.0, 1H), 2.78 (dd, J = 3.0, 5.3, 1H), 2.59−2.37 (m, 6H), 2.24 (d, J = 10.7, 1H), 2.13 −1.16 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 146.6, 141.2, 131.6, 128.9, 128.2, 127.0, 113.9, 110.7, 109.7, 61.4, 56.0, 55.2, 48.2, 46.0, 45.2, 41.9, 37.5, 36.6, 34.9, 27.89, 27.87, 26.9, 26.6, 23.9, 22.2, 18.8; mp = 180−183 °C (for HCl salt). Anal. Calcd for $C_{29}H_{38}N_2O·2HCl·1.3H_2O$: C, 66.10; H, 8.15; N, 5.32. Found: C, 66.50, H, 8.13; N, 5.05.

(−)-17-(Cyclobutylmethyl)-*N*-(4-chlorobenzyl)morphinan-3-amine (3d). Pale yellow oil (99 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 4H), 6.91 (d, J = 8.1, 1H), 6.49 (s, 1H), 6.44 (d, J = 8.1, 1H), 4.27 (s, 2H), 3.89 (s, 1H), 2.90 (d, J = 18.0, 1H), 2.77 (s, 1H), 2.60−2.36 (m, 5H), 2.20 (d, J = 11.6, 1H), 2.06 (t, J = 10.6, 3H), 1.93−1.07 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 139.5, 137.8, 132.8, 128.69, 128.65, 128.6, 123.5, 11.5, 109.5, 59.6, 56.7, 47.8, 46.4, 42.0, 39.3, 36.6, 35.6, 32.1, 27.85, 27.76, 26.2, 25.8, 24.1, 21.7, 18.6; mp = 160−163 °C (HCl salt). Anal. Calcd for $C_{28}H_{35}N_2Cl·2HCl·0.4H_2O$: C, 65.28; H, 7.40; N, 5.44. Found: C, 65.28, H, 7.46; N, 5.39.

(−)-17-(Cyclobutylmethyl)-*N*-(3,4-methylenedioxybenzyl)-morphinan-3-amine (3e). Yellow oil (42 mg, 51%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (m, J = 8.0, 17.0, 29.7, 4H), 6.51 (d, J = 2.2, 1H), 6.45 (dd, J = 2.3, 8.1, 1H), 5.93 (s, 2H), 4.19 (s, 2H), 2.86 (m, 2H), 2.48 (m, 5H), 1.87 (m, 10H), 1.25 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.8, 146.6, 146.4, 141.2, 133.5, 128.3, 127.0, 120.8, 110.7, 109.8, 108.20, 108.19, 100.9, 61.3, 55.9, 48.6, 45.9, 45.1, 41.8, 37.5, 36.6, 34.8, 27.9, 26.8, 26.6, 23.9, 22.2, 18.8; mp = 165−168 °C (HCl salt). Anal. Calcd for $C_{29}H_{36}N_2O_2·2HCl·0.4H_2O$: C, 65.04; H, 7.53; N, 5.23. Found: C, 64.91, H, 7.33; N, 5.12.

(−)-17-(Cyclopropylmethyl)-*N*-(2-methoxybenzyl)-morphinan-3-amine (3f). Pale yellow oil (118 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 7.2, 1H), 7.23 (t, J = 7.5, 1H), 6.89 (t, J = 9.4, 3H), 6.57 (s, 1H), 6.47 (d, J = 8.1, 1H), 4.29 (s, 2H), 3.85 (s, 3H), 3.07 (s, 1H), 2.83 (d, J = 18.0, 1H), 2.70 (d, J = 9.2, 1H), 2.52−2.48 (m, 2H), 2.31 (m, 2H), 2.05 (m, 1H), 1.81−1.60 (m, 3H), 1.34−1.13 (m, 8H), 0.87 (m, 1H), 0.49 (d, J = 7.6, 2H), 0.11 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 146.8, 141.0, 129.2, 128.2, 128.1, 127.5, 126.6, 120.4, 111.1, 110.2, 109.9, 59.8, 55.7, 55.2, 45.8, 45.2, 43.7, 41.8, 37.6, 36.6, 26.8, 26.6, 23.7, 22.2, 9.3, 4.0, 3.6; mp = 151−153 °C (HCl salt). Anal. Calcd for $C_{28}H_{36}N_2O·2HCl·1.6H_2O$: C, 64.88; H, 8.01; N, 5.40. Found: C, 65.15, H, 7.79; N, 5.14.

(−)-17-(Cyclopropylmethyl)-*N*-(3-methoxybenzyl)-morphinan-3-amine (3g). Pale yellow oil (130 mg, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 6.8, 1H), 6.92 (dd, J = 8.9, 19.9, 3H), 6.80 (d, J = 8.2, 1H), 6.54 (s, 1H), 6.46 (d, J = 8.1, 1H), 4.26 (s, 2H), 3.78 (s, 3H), 3.12 (s, 1H), 2.84 (d, J = 18.1, 1H), 2.75 (d, J = 11.5, 1H), 2.55−2.47 (m, 2H), 2.36 (dd, J = 6.8, 12.2, 1H), 2.25 (d, J = 11.1, 1H), 2.04 (m, 1H), 1.83−1.63 (m, 2H), 1.62 (d, J = 9.7, 1H), 1.29−1.12 (m, 8H), 0.90 (m, 1H), 0.51 (d, J = 7.8, 2H), 0.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 146.6, 141.2, 141.0, 129.5, 128.2, 126.5, 119.8, 113.0, 112.5, 110.7, 109.6, 59.6, 55.8, 55.1, 48.7, 45.8, 44.8, 41.6, 37.5, 36.5, 26.7, 26.5, 23.7, 22.1, 9.0, 4.0, 3.6; mp = 158−160 °C (HCl salt). Anal. Calcd for $C_{28}H_{36}N_2O·2HCl·1.2H_2O$: C, 65.79; H, 7.97; N, 5.48. Found: C, 65.87, H, 7.88; N, 5.50.

(−)-17-(Cyclopropylmethyl)-*N*-(4-methoxybenzyl)-morphinan-3-amine (3h). Pale yellow oil (116 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 7.1, 2H), 6.88 (m, 3H), 6.53 (s, 1H), 6.46 (d, J = 8.2, 1H), 4.20 (s, 2H), 3.79 (s, 3H), 3.14 (s, 1H), 2.81 (t, J = 17.6, 2H), 2.57 (m, 2H), 2.40 (d, J = 6.0, 1H), 2.25 (d, J = 11.1, 1H), 2.05 (m, 1H), 1.84 (m, 2H), 1.60−1.12 (m, 9H), 0.90 (m, 1H), 0.51 (d, J = 6.9, 2H), 0.13 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 146.7, 140.9, 131.5, 128.9, 128.2, 126.3, 113.9, 110.8, 109.6, 59.6, 55.8, 55.2, 48.2, 45.8, 44.7, 41.5, 37.5, 36.5, 26.8, 26.5, 23.8, 22.2, 8.9, 4.0, 3.7; mp = 162−164 °C (HCl salt). Anal. Calcd for $C_{28}H_{36}N_2O·2HCl·H_2O$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.06, H, 7.63; N, 5.52.

(−)-17-(Cyclopropylmethyl)-*N*-(3,4-methylenedihydroxybenzyl)morphinan-3-amine (3i). Pale yellow oil (47 mg, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87−6.75 (m, 3H), 6.53 (d, J = 2.2, 1H), 6.45 (dd, J = 2.3, 8.1, 1H), 5.94 (s, 2H), 4.19 (s, 2H), 3.11 (s, 1H), 2.84 (d, J = 18.2, 1H), 2.74 (d, J = 9.3, 1H), 2.54 (m, 2H), 2.35 (dd, J = 6.6, 12.6, 1H), 2.25 (d, J = 11.4, 1H), 2.07 (m, 1H), 1.78 (m, 2H), 1.62 (d, J = 10.5, 1H), 1.34−1.12 (m, 9H), 0.88 (m, 1H), 0.50 (d, J = 6.8, 2H), 0.12 (d, J = 4.4, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.8, 146.6, 146.5, 141.2, 133.5, 128.3, 126.7, 120.8, 110.8, 109.8, 108.2, 100.9, 59.8, 55.8, 48.6, 45.9, 45.0, 41.7, 37.6, 36.6, 26.8, 26.6, 23.8, 22.2, 9.2, 4.1, 3.7; mp = 166−170 °C (HCl salt). Anal. Calcd for $C_{28}H_{34}N_2O_2·2HCl·1.4H_2O$: C, 63.61; H, 7.40; N, 5.30. Found: C, 63.29, H, 7.13; N, 5.25.

(−)-17-Methyl-*N*-(3′-methoxybenzyl)morphinan-3-amine (3j). White solid (HCl salt, 110 mg, 44%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 7.9 Hz, 1H), 7.07−6.72 (m, 4H), 6.60−6.37 (m, 2H), 4.27 (s, 2H), 3.98−3.61 (m, 4H), 2.94 (d, J = 18.1 Hz, 1H), 2.78 (s, 1H), 2.65−2.07 (m, 8H), 1.85−1.14 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.76, 146.53, 141.29, 141.02, 129.48, 128.28, 126.87, 119.86, 113.06, 112.58, 110.74, 109.72, 58.01, 55.11, 48.76, 47.33, 45.57, 42.75, 42.10, 37.04, 36.66, 26.74, 26.56, 23.22, 22.18.; mp = 146−149 °C (HCl salt). Anal. Calcd for $C_{25}H_{32}N_2O·2HCl·4H_2O$: C, 57.58; H, 8.12; N, 5.37. Found: C, 57.93, H, 7.98; N, 4.87.

(−)-3-(3′-Nitrobenzyl)amino-17-cyclobutylmethylmorphinan (3k). Pale yellow oil (215 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.18 (d, J = 8.1, 1H), 7.71 (d, J = 8.2, 1H), 7.52 (t, J = 8.5, 1H), 6.90 (d, J = 8.2, 1H), 6.51 (s, 1H), 6.45 (d J = 8.5, 1H), 4.40 (s, 2H), 4.18−4.10 (m, 1H), 2.90 (d, J = 18.1, 1H), 2.80−2.71 (m, 1H), 2.60−2.37 (m, 5H), 2.10−1.97 (m, 4H), 1.94−1.13 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 145.7, 142.3, 141.5, 133.4, 129.4, 128.4, 127.8, 122.2, 122.1, 110.8, 109.9, 6q.5, 55.9, 48.0, 45.9, 45.2, 41.9, 37.6, 36.6, 34.9, 27.9, 27.8, 26.8, 26.8, 23.9, 22.1, 18.8; mp = 145−148 °C (HCl salt). Anal. Calcd for $C_{28}H_{35}N_3O_2·2HCl$: C, 64.86; H, 7.19; N, 8.10. Found: C, 65.14, H, 7.28; N, 8.04.

Representative Procedure for the Preparation of Morphinans 4a−f and 6b,c. To a solution of *N*-cyclobutylmethyl-3-(4-methoxybenzyl)aminomorphinan **3c** (149 mg, 0.347 mmol) in anhydrous dichloromethane (3 mL) under nitrogen atmosphere at 0 °C was added slowly dropwise a solution of BBr_3 (3 mL, 1 M in anhydrous dichloromethane). After addition was complete, the resulting solution was allowed to warm to room temperature and stirred for 1.5 h. Next, the solution was diluted with excess diethyl ether and allowed to precipitate at 0 °C. The residue was washed with ethyl acetate, then dissolved in 3 M aqueous HCl (10 mL) and washed with ethyl acetate (10 mL). The aqueous layer was basified with saturated sodium bicarbonate solution and extracted with dichloromethane (2 × 20 mL). The combined dichloromethane extracts were dried over sodium sulfate, then filtered and concentrated. The residue was purified over silica gel using EtOAc/Et_3N (100:1) as eluent to afford 90 mg of *N*-cyclobutylmethyl-3-(4-hydroxybenzyl)-aminomorphinan **4c** as a pale yellow oil, 74% yield. The oil was then dissolved in a minimal amount of EtOAc and treated with excess 1 N ethereal HCl, and then the mixture was concentrated to afford a white solid. The solid was washed with a small amount of EtOAc and ether and dried under reduced pressure to afford 94 mg of the dihydrochloride salt (mp = 165−168 °C).

(−)-17-(Cyclobutylmethyl)-*N*-(2-hydroxybenzyl)morphinan-3-amine (4a). Pale yellow oil, 23 mg (82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, J = 14.2, 21.8, 1H), 6.83−6.62 (m, 4H), 6.48−6.26 (m, 2H), 4.19 (s, 2H), 3.90 (s, 1H), 2.99−2.66 (m, 2H), 2.66−2.40 (m, 4H), 2.39−2.22 (m, 1H), 2.18−0.90 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 147.4, 138.5, 128.7, 128.6, 128.6, 123.7, 123.1, 119.5, 116.1, 113.5, 111.1, 58.7, 57.0, 46.5, 40.7, 38.2, 36.2, 35.0, 30.9, 27.7, 27.6, 25.8, 25.4, 21.5, 18.5; mp = 172−174 °C (HCl salt). Anal. Calcd for $C_{28}H_{36}N_2O·2HCl·1.3H_2O$: C, 61.21; H, 7.63; N, 5.10. Found: C, 60.95; H, 7.35; N, 5.22.

(−)-17-(Cyclobutylmethyl)-*N*-(3-hydroxybenzyl)morphinan-3-amine (4b). Pale yellow foam; 34 mg (96%); ^{1}H NMR (300 MHz,

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$CDCl_3$) δ 8.92 (s, 1H), 7.11 (dd, J = 14.1, 21.8, 1H), 6.85−6.60 (m, 4H), 6.48−6.27 (m, 2H), 4.16 (s, 2H), 3.91 (s, 1H), 2.97−2.69 (m, 2H), 2.69−2.40 (m, 4H), 2.37−2.20 (m, 1H), 2.17−0.92 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 146.9, 141.2, 140.3, 129.6, 128.3, 124.9, 118.2, 114.8, 114.5, 110.5, 109.6, 60.5, 55.9, 48.1, 46.1, 43.4, 40.5, 37.0, 36.1, 33.3, 28.2, 27.9, 26.6, 26.2, 23.7, 22.0, 18.7; mp = 177−180 °C (HCl salt). Anal. Calcd for $C_{28}H_{36}N_2O$·2HCl·0.9H_2O: C, 62.03; H, 7.58; N, 5.17. Found: C, 62.10; H, 7.62; N, 5.08.

(−)-17-(Cyclobutylmethyl)-*N*-(4-hydroxybenzyl)morphinan-3-amine (4c). Pale yellow foam (90 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.3, 2H), 6.91 (d, J = 8.1, 1H), 6.77 (d, J = 8.4, 2H), 6.50 (m, 2H), 4.19 (s, 2H), 2.90 (m, J = 13.7, 2H), 2.55 (m, 5H), 2.14 (m, 4H), 1.72 (m, 7H), 1.26 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 146.9, 140.7, 129.9, 129.1, 128.3, 126.0, 115.9, 110.9, 109.6, 61.1, 55.9, 48.4, 46.0, 44.1, 41.1, 37.3, 36.4, 34.1, 28.1, 26.7, 26.4, 23.8, 22.1, 18.7; mp = 165−168 °C (HCl salt). Anal. Calcd for $C_{28}H_{36}N_2O$·2HCl·1.3H_2O: C, 65.56; H, 7.98; N, 5.46. Found: C, 65.41, H, 7.73; N, 5.50.

(−)-17-(Cyclopropylmethyl)-*N*-(2-hydroxybenzyl)-morphinan-3-amine (4d). Pale yellow foam (68 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, J = 7.4, 14.6, 2H), 6.95 (d, J = 8.1, 1H), 6.87 (dd, J = 2.9, 7.7, 2H), 6.71 (d, J = 2.1, 1H), 6.64 (dd, J = 2.2, 8.1, 1H), 4.39 (s, 2H), 3.19 (s, 1H), 2.87 (d, J = 18.3, 1H), 2.80 (m, 1H), 2.64 (dd, J = 6.6, 19.4, 1H), 2.55 (m, 1H), 2.40 (dd, J = 6.8, 12.5, 1H), 2.22 (d, J = 13.0, 1H), 2.11 (m, 1H), 1.94 (d, J = 12.6, 1H), 1.84 (td, J = 4.3, 12.7, 1H), 1.62 (d, J = 9.3, 1H), 1.19 (m, 8H), 0.52 (m, 2H), 0.16 (q, J = 4.8, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.8, 145.7, 141.1, 128.9, 128.6, 128.4, 123.4, 119.7, 116.4, 113.5, 112.6, 59.6, 55.8, 48.7, 45.8, 44.4, 41.2, 37.5, 36.4, 26.7, 26.4, 23.9, 22.0, 8.8, 4.1, 3.8; mp = 170−173 °C (HCl salt). Anal. Calcd for $C_{27}H_{34}N_2O$·2HCl·1.4H_2O: C, 64.77; H, 7.81; N, 5.59. Found: C, 64.50, H, 7.67; N, 5.46.

(−)-17-(Cyclopropylmethyl)-*N*-(3-hydroxybenzyl)-morphinan-3-amine (4e). Pale yellow oil (65 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 7.9, 1H), 6.81−6.72 (m, 4H), 6.48 (s, 1H), 6.40 (d, J = 8.1, 1H), 4.26 (s, 2H), 3.97 (s, 1H), 3.17 (s, 1H), 2.79 (d, J = 18.3, 1H), 2.61 (m, 1H), 2.41 (m, 2H), 2.25 (m, 2H), 1.97 (m, 2H), 1.67−1.06 (m, 10H), 0.88 (m, 1H), 0.47 (d, J = 7.6, 2H), 0.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 146.8, 141.4, 140.7, 129.6, 128.3, 125.6, 118.0, 114.8, 114.3, 109.8, 109.7, 59.3, 55.5, 47.9, 45.7, 44.0, 41.2, 37.3, 36.3, 26.7, 26.3, 23.5, 22.1, 8.2, 4.1, 4.0; mp = 171−175 °C (HCl salt). Anal. Calcd for $C_{27}H_{34}N_2O$·2HCl·1.1H_2O: C, 65.47; H, 7.77; N, 5.66. Found: C, 65.61, H, 7.67; N, 5.27.

(−)-17-(Cyclopropylmethyl)-*N*-(4-hydroxybenzyl)-morphinan-3-amine (4f). Pale yellow oil (69 mg, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (m, 4H), 6.68 (d, J = 8.0, 1H), 6.47 (s, 1H), 6.43 (d, J = 8.2, 1H), 4.14 (s, 2H), 3.28 (m, 2H), 2.72−2.42 (m, 5H), 2.12−0.91 (m, 14H), 0.53 (d, J = 7.6, 2H), 0.16 (d, J = 4.0, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 146.9, 140.7, 130.0, 129.1, 128.3, 126.0, 115.9, 111.0, 109.7, 59.5, 55.8, 48.4, 45.8, 44.2, 41.1, 37.5, 36.4, 26.8, 26.4, 23.8, 22.1, 8.5,4.2, 3.8; mp = 195 °C (dec) (HCl salt). Anal. Calcd for $C_{27}H_{34}N_2O$·2HCl·1.6H_2O: C, 64.30; H, 7.83; N, 5.55. Found: C, 64.23, H, 7.83; N, 5.28.

(−)-*N*-Methyl-(3′-hydroxybenzyl)morphinan-3-amine (4g). Pale yellow foam (55 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.91−6.67 (m, 4H), 6.49 (d, J = 2.2 Hz, 1H), 6.40 (dd, J = 8.2, 2.3 Hz, 1H), 4.29 (s, 2H), 4.11 (s, 1H), 2.99−2.76 (m, 2H), 2.64 (dd, J = 18.4, 5.8 Hz, 1H), 2.30 (s, 3H), 2.26−1.09 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 147.2, 141.7, 140.7, 130.0, 128.6, 125.4, 118.1, 115.0, 114.4, 110.2, 110.1, 58.5, 48.0, 47.3, 44.3, 42.2, 41.4, 36.9, 36.4, 26.8, 26.5, 23.6, 22.3; mp = 166−169 °C (HCl salt). Anal. Calcd for $C_{24}H_{30}N_2O$·2HCl·3H_2O: C, 58.89; H, 7.83; N, 5.72. Found: C, 59.02, H, 7.93; N, 5.40.

Representative Procedure for the Preparation of Morphinans 5a−d. To a solution of *N*-cyclobutylmethyl-3-(4-methoxybenzyl)aminomorphinan **3c** (210 mg, 0.487 mmol), paraformaldehyde (141 mg, 4.87 mmol), and $NaBH_4$ (93 mg, 2.44 mmol) in anhydrous THF (5 mL) was added TFA dropwise (2.5 mL). The solution was stirred for 3 days at room temperature, then poured into a mixture of excess aqueous NaOH and ice chips and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, then filtered and concentrated to afford 212 mg of *N*-cyclobutylmethyl-3-(4-methoxybenzyl)-3-methylaminomorphinan **5c** as a pale yellow oil, 98% yield. The oil (64 mg) was converted to the dihydrochloride salt as described above to afford 70 mg of a white solid (mp = 146−148 °C).

(−)-17-(Cyclobutylmethyl)-*N*-methyl-*N*-(2-methoxybenzyl)-morphinan-3-amine (5a). Pale yellow oil (102 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.10 (m, 1H), 7.07 (d, J = 7.2, 1H), 6.88−6.76 (m, 3H), 6.50 (dd, J = 3.0, 11.3, 2H), 4.46−4.31 (dd, J = 18, 24, 2H), 3.79 (s, 3H), 2.93 (s, 3H), 2.84 (d, J = 17.8, 1H), 2.71 (s, 1H), 2.43 (m, 5H), 2.15 (d, J = 10.1, 1H), 2.07−1.93 (m, 3H), 1.84−1.49 (m, 7H), 1.35−1.12 (m, 7H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.6, 149.0, 140.1, 128.2, 127.9, 127.9, 126.9, 125.2, 120.3, 111.2, 110.2, 109.5, 61.3, 56.2, 54.7, 52.2, 46.3, 44.9, 41.5, 38.5, 37.6, 36.8, 34.7, 28.2, 28.0, 27.1, 26.8, 23.7, 22.4, 18.7; mp = 133−135 °C (HCl salt). Anal. Calcd for $C_{30}H_{40}N_2O$·2HCl·1.1H_2O: C, 67.05; H, 8.29; N, 5.21. Found: C, 66.79, H, 8.30; N, 5.03.

(−)-17-(Cyclobutylmethyl)-*N*-methyl-*N*-(4-methyloxybenzyl)morphinan-3-amine (5c). Pale yellow oil (212 mg, 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.7, 2H), 6.86 (d, J = 8.2, 1H), 6.78−6.69 (m, 2H), 6.58−6.45 (m, J = 2.5, 8.2, 2H), 4.30 (s, 2H), 3.69 (s, 3H), 2.88−2.75 (m, 4H), 2.69 (dd, J = 3.0, 5.4, 1H), 2.53−2.27 (m, 5H), 2.21−2.08 (m, 1H), 2.05 −0.93 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 148.5, 140.9, 131.3, 128.1, 128,1, 128.0, 126.2, 113.7, 113.7, 110.8, 109.7, 61.5, 56.8, 56.0, 55.2, 46.0, 45.3, 42.0, 38.5, 37.6, 36.7, 35.0, 27.9, 27.8, 26.8, 26.6, 23.8, 22.2, 18.8; mp = 146−148 °C (for HCl salt). Anal. Calcd for $C_{30}H_{40}N_2O$·2HCl·H_2O: C, 67.28; H, 8.28; N, 5.23. Found: C, 67.38, H, 8.23; N, 5.19.

(−)-17-(Cyclobutylmethyl)-*N*-methyl-*N*-(4-chlorobenzyl)-morphinan-3-amine (5d). Pale yellow oil (61 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.14 (m, 2H), 7.13−7.07 (m, 2H), 6.91−6.83 (m, 1H), 6.54−6.46 (m, 2H), 4.33 (s, 2H), 2.88 (s, 3H), 2.84 (d, J = 17.8 Hz, 1H), 2.71 (m, 1H), 2.52−2.31 (m, 5H), 2.11 (d, J = 12.8, 1H), 1.99 (m, 3H), 1.86−1.48 (m, 13H); ^{13}C NMR (75 MHz, CD_3OD) δ 148.7, 140.2, 138.7, 132.4, 128.7, 128.7, 128.5, 128.5, 128.4, 126.0, 111.8, 110.1, 61.3, 56.7, 56.1, 46.2, 44.9, 41.5, 38.7, 37.6, 36.8, 34.7, 28.2, 28.0, 27.0, 26.7, 23.7, 22.3, 18.6; mp = 135−139 °C (HCl salt). Anal. Calcd for $C_{29}H_{37}ClN_2$·2HCl·1.3H_2O: C, 63.86; H, 7.69; N, 5.14. Found: C, 63.69, H, 7.70; N, 5.02.

(−)-17-(Cyclobutylmethyl)-*N*-methyl-*N*-(2-hydroxybenzyl)-morphinan-3-amine (6a). Pale yellow foam (34 mg, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.06 (m, 1H), 7.02−6.94 (m, 2H), 6.92−6.83 (m, 2H), 6.82−6.70 (m, 2H), 4.25 (s, 2H), 2.91 (m, 2H), 2.79−2.46 (m, 5H), 2.73 (s, 3H), 2.26−0.88 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 149.4, 140.4, 128.7, 128.4, 128.3, 122.2, 119.5, 116.6, 116.1, 115.6, 60.5, 59.4, 56.2, 46.0, 43.5, 40.8, 40.5, 37.2, 36.0, 33.5, 27.85, 27.81, 26.4, 26.1, 24.2, 21.8, 18.7; mp = 155−157 °C (HCl salt). Anal. Calcd for $C_{29}H_{38}N_2O$·2HCl·1.4H_2O: C, 66.10; H, 8.15; N, 5.32. Found: C, 65.84, H, 7.89; N, 5.24.

(−)-17-(Cyclobutylmethyl)-*N*-methyl-*N*-(4-hydroxybenzyl)-morphinan-3-amine (6c). Pale yellow oil (107 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.7, 2H), 6.86 (d, J = 8.2, 1H), 6.75 (d, J = 8.7, 2H), 6.53 (dt, J = 2.5, 8.2, 2H), 4.30 (s, 2H), 3.69 (s, 3H), 2.88−2.76 (m, 4H), 2.69 (dd, J = 3.0, 5.3, 1H), 2.43 (m, 4H), 2.33 (dd, J = 3.1, 11.9, 1H), 2.15 (d, J = 11.9, 1H), 1.99 (m, 3H), 1.84−1.48 (m, 7H), 1.35−1.01 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 148.7, 140.2, 129.5, 128.2, 128.2, 128.1, 124.8, 115.9, 115.9, 110.9, 109.7, 60.9, 56.8, 56.0, 46.1, 43.9, 40.9, 38.5, 37.3, 36.3, 33.9, 28.1, 28.0, 26.6, 26.3, 23.7, 22.0, 18.7; mp = 174−178 °C (HCl salt). Anal. Calcd for $C_{29}H_{38}N_2O$·2HCl·0.8H_2O: C, 67.25; H, 8.10; N, 5.41. Found: C, 67.14, H, 8.13; N, 5.39.

Morphine-3-(trifluoromethanesulfonate) (7).[21] Morphine-3-(trifluomethanesulfonate) (7) was prepared according to the literature procedure (4.415 g, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J = 8.4, 1H), 6.65 (d, J = 8.4, 1H), 5.69 (d, J = 9.9, 1H), 5.29 (d, J = 9.7, 1H), 5.02 (d, J = 6.3, 1H), 4.22 (s, 1H), 3.40 (s, 1H), 3.28 (s, 1H), 3.10 (d, J = 19.1, 1H), 2.72 (s, 1H), 2.63 (dd, J = 4.5, 12.2, 1H), 2.44 (s, 3H), 2.33 (m, J = 6.1, 19.0, 2H), 2.12 (td, J = 4.8, 12.5, 1H), 1.88

(d, J = 12.5, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 135.6, 133.6, 133.4, 130.4, 128.2, (124.9, 120.6, 116.4, 112.1, q), 120.8, 120.1, 93.5, 66.4, 58.3, 45.9, 43.2, 42.8, 40.3, 35.1, 20.8.

Morphine-6-(*tert*-butyldiphenylsilyl)oxy-3-(trifluoromethanesulfonate) (8).[14] Morphine-3-(trifluomethanesulfonate) (7) (2.02 g, 4.85 mmol), TBDPSCl (1.60 g, 5.82 mmol), and imidazole (792 mg, 11.6 mmol) were stirred overnight in dichloromethane. Next, ethyl acetate (100 mL) was added to the solution, and it was washed sequentially with water (50 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4. The organic layer was filtered and concentrated under reduced pressure, and the crude product was purified on silica gel (EtOAc/Et_3N, 200:1) to give the title product **8** as a white foam (2.94 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.4, 1.6 Hz, 2H), 7.68 (dd, J = 7.6, 1.3 Hz, 2H), 7.53−7.31 (m, 6H), 6.93 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.74 (d, J = 9.7 Hz, 1H), 5.18 (dt, J = 9.7, 2.6 Hz, 1H), 4.51 (d, J = 5.0 Hz, 1H), 4.18 (dd, J = 5.2, 2.7 Hz, 1H), 3.28 (dd, J = 5.9, 3.0 Hz, 1H), 3.03 (d, J = 19.1 Hz, 1H), 2.52−2.21 (m, 4H), 2.37 (s, 3H), 1.85−1.63 (m, 2H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.8, 135.9, 135.7, 135.3, 133.6, 133.5, 133.3, 130.5, 129.86, 129.76, 128.1, 127.68, 127.66, 121.5, 120.9, 119.1, 116.6, 94.0, 69.2, 58.3, 45.9, 43.9, 43.0, 40.8, 35.4, 26.7, 21.0, 19.2.

3-Amino-6-(*tert*-butyldiphenylsilyl)oxymorphine (9). Under nitrogen atmosphere, morphine-6-(*tert*-butyldiphenylsilyl)oxy-3-(trifluoromethanesulfonate) (**8**) (2.93 g, 4.47 mmol) was dissolved in anhydrous THF (50 mL), and $Pd(OAc)_2$ (50 mg, 0.224 mmol), rac-BINAP (279 mg, 0.448 mmol), and benzophenone imine (1.05 g, 5.81 mmol) were added to the stirring solution. The reaction mixture was refluxed for 24 h under N_2. After the reaction was complete, THF was removed under reduced pressure and the residue was taken up in dichloromethane (200 mL), washed with water, and dried over Na_2SO_4. The organic layer was filtered and concentrated under reduced pressure, and the crude product (orange oil) was used for the next step directly. The residue was dissolved in MeOH (30 mL), and NaOAc (880 mg, 10.7 mmol) and hydroxylamine hydrochloride (560 mg, 8.04 mmol) were added. The resulting reaction mixture was stirred at room temperature for 3 days. After completion, the methanol was removed under reduced pressure and the residue was dissolved in ethyl acetate (200 mL), washed with brine, dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted by EtOAc and EtOAc/Et_3N, 100/1) to afford **9** as a white solid (1.77 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.79 (m, 2H), 7.75−7.66 (m, 2H), 7.42 (m, 6H), 6.47 (dd, J = 22.1, 7.9 Hz, 2H), 5.76 (d, J = 9.7 Hz, 1H), 5.27−5.16 (m, 1H), 4.40 (d, J = 5.9 Hz, 1H), 4.28−4.19 (m, 1H), 3.46 (s, 2H), 3.26 (d, J = 3.0 Hz, 1H), 2.98 (d, J = 18.5 Hz, 1H), 2.57−2.18 (m, 4H), 2.39 (s, 3H), 1.73 (s, 2H), 1.14 (d, J = 8.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.3, 135.8, 135.7, 134.0, 133.7, 133.1, 129.7. 129.6, 128.2, 127.6, 124.9, 118.6, 115.9, 91.6, 69.1, 58.8, 46.4, 43.3, 43.0, 41.0, 35.6, 26.8, 20.4, 19.3.

(−)-3-*N*-(3′-Methoxybenzyl)amino-7,8-didehydro-6-(*tert*-butyldiphenylsilyl)-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (10a). Pale yellow oil (920 mg, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.9, 1.4 Hz, 2H), 7.68 (dd, J = 7.8, 1.5 Hz, 2H), 7.49−7.19 (m, 7H), 6.98 (m, 2H), 6.80 (dd, J = 8.1, 2.5 Hz, 1H), 6.49−6.34 (m, 2H), 5.75 (d, J = 9.8 Hz, 1H), 5.23−5.13 (m, 1H), 4.36 (2, 2H), 4.38−4.36 (m, 1H), 4.24−4.17 (m, 2H), 3.77 (s, 3H), 3.27 (dd, J = 6.0, 3.1 Hz, 1H), 2.96 (d, J = 18.5 Hz, 1H), 2.56−2.16 (m, 4H), 2.38 (s, 3H), 1.74 (t, J = 7.4 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 147.0, 141.6, 135.8, 135.7, 133.9, 133.7, 133.2, 130.7, 129.7, 129.5, 128.9, 128.1, 127.6, 127.5, 123.5, 119.8, 118.7, 112.8, 112.6, 111.7, 91.7, 69.1, 59.0, 55.1, 48.7, 46.4, 43.4, 43.0, 40.9, 35.6, 26.8, 20.4, 19.4.

(−)-3-*N*-(2′-Methoxybenzyl)amino-7,8-didehydro-6-(*tert*-butyldiphenylsilyl)-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (10b). Pale yellow oil (610 mg, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.9, 1.4 Hz, 2H), 7.69 (dd, J = 7.8, 1.5 Hz, 2H), 7.44−7.28 (m, 7H), 7.26−7.17 (m, 1H), 6.95−6.82 (m, 2H), 6.47−6.35 (m, 2H), 5.75 (d, J = 9.8 Hz, 1H), 5.22−5.13 (m, 1H), 4.48−4.33 (m, 3H), 4.20 (d, J = 2.4 Hz, 1H), 3.82 (s, 3H), 3.24 (dd, J = 5.8, 3.0 Hz, 1H), 2.95 (d, J = 18.5 Hz, 1H), 2.52−2.16 (m, 7H), 1.72 (d, J = 4.8 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 147.2, 135.8, 135.7, 134.0, 133.7, 133.1, 130.8, 129.70, 129.67, 128.9, 128.8, 128.3, 127.9, 127.6, 127.5, 123.5, 120.5, 118.6, 112.0, 110.0, 91.7, 69.3, 58.9, 55.2, 46.4, 43.6, 43.5, 43.1, 41.1, 35.7, 26.8, 20.3, 19.3.

(−)-3-*N*-(4′-Methoxybenzyl)amino-7,8-didehydro-6-(*tert*-butyldiphenylsilyl)-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (10c). Pale yellow oil (540 mg, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.73 (m, 2H), 7.70−7.61 (m, 2H), 7.46−7.25 (m, 8H), 6.97−6.80 (m, 2H), 6.44 (s, 2H), 5.74 (d, J = 9.8 Hz, 1H), 5.25−5.06 (m, 1H), 4.36 (dd, J = 6.1, 1.2 Hz, 1H), 4.27 (d, J = 24.0 Hz, 2H), 4.25−4.15 (m, 1H), 3.80 (s, 3H), 3.25 (dd, J = 6.1, 3.2 Hz, 1H), 2.97 (d, J = 18.5 Hz, 1H), 2.50−2.17 (m, 4H), 2.37 (s, 3H), 1.78−1.66 (m, 2H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 147.0, 135.81, 135.75, 134.0, 133.8, 133.1, 131.9, 130.8, 129.7, 129.0, 128.8, 128.2, 127.6, 123.7, 118.6, 113.9, 111.7, 91.7, 69.1, 59.0, 55.2, 48.2, 46.5, 43.4, 43.1, 41.1, 35.7, 26.9, 20.3, 19.4.

Representative Procedure for the Preparation of 11a−c. TBAF (2.1 mL, 1 M in THF) was added to a solution of **10a** (910 mg, 1.42 mmol) in THF (5 mL). The solution was stirred at room temperature overnight. Next, 1 M HCl (30 mL) was added to the solution, which was then washed with ethyl acetate (3 × 20 mL). The aqueous layer was basified with concentrated ammonium hydroxide (28%) and extracted with dichloromethane (3 × 20 mL). The combined organic extract was dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was purified over silica gel (EtOAc/Et_3N, 10:1), and the product was dissolved in ethyl acetate (60 mL), washed with water (4 × 10 mL), brine, and dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the product as a yellow oil. The oil was dissolved in 10 mL of ethyl acetate, and 1 N ethereal HCl (3 mL) was added and the mixture concentrated. The resulting pale yellow solid was washed with minimal ethyl acetate and CH_2Cl_2 to afford 525 mg of pure **11a** as a dihydrochloride 1.6 hydrate, 73% yield (mp = 195 °C, dec)

3-(2′-Methoxybenzyl)amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (11a). Pale yellow solid (419 mg, 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 14.7, 7.7 Hz, 2H), 6.89 (t, J = 7.5 Hz, 2H), 6.46 (s, 2H), 5.62 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 9.7 Hz, 1H), 4.78 (d, J = 6.4 Hz, 1H), 4.29 (dd, J = 18.1, 9.0 Hz, 2H), 4.08 (s, 1H), 3.84 (s, 3H), 3.31 m, 1H), 3.00 (d, J = 18.5 Hz, 1H), 2.62−2.17 (m, 4H), 2.42 (s, 3H), 2.02 (td, J = 12.2, 5.1 Hz, 1H), 1.85 (d, J = 12.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.30, 146.16, 133.06, 130.67, 129.10, 128.98, 128.29, 127.48, 123.91, 120.40, 119.47, 112.75, 110.18, 90.99, 66.34, 58.95, 55.25, 46.50, 44.17, 43.04, 42.86, 40.86, 35.74, 20.25; mp = 194 °C (dec) (HCl salt). Anal. Calcd for $C_{25}H_{28}N_2O_3\cdot 2HCl\cdot H_2O$: C, 60.61; H, 6.51; N, 5.65. Found: C, 60.50, H, 6.49; N, 5.44.

3-(3′-Methoxybenzyl)amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (11b). White solid (525 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.5, 5.3 Hz, 1H), 6.93 (d, J = 12.6 Hz, 2H), 6.81 (d, J = 8.2 Hz, 1H), 6.46 (dd, J = 19.3, 7.9 Hz, 2H), 5.67 (d, J = 9.8 Hz, 1H), 5.29 (d, J = 8.0 Hz, 1H), 4.82 (d, J = 5.9 Hz, 1H), 4.29 (s, 2H), 4.13 (s, 1H), 3.78 (s, 3H), 3.39−3.21 (m, 1H), 3.01 (d, J = 18.6 Hz, 2H), 2.69−2.20 (m, 7H), 2.13−1.93 (m, 1H), 1.86 (d, J = 12.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.76, 145.73, 141.23, 133.03, 130.46, 129.55, 129.07, 128.47, 124.06, 119.78, 119.60, 113.07, 112.58, 112.27, 91.12, 66.41, 58.95, 55.14, 48.75, 46.51, 43.07, 42.95, 40.92, 35.83, 20.26; mp = 195 °C (dec) (HCl salt). Anal. Calcd for $C_{25}H_{28}N_2O_3\cdot 2HCl\cdot 1.6H_2O$: C, 59.31; H, 6.61; N, 5.53. Found: C, 59.37, H, 6.29; N, 5.47.

3-(4′-Methoxybenzyl)amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (11c). Pale yellow solid (380 mg, 100%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.26 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.2 Hz, 2H), 6.71 (d, J = 8.1 Hz, 1H), 5.69 (d, J = 9.3 Hz, 1H), 5.31 (d, J = 10.1 Hz, 1H), 5.10 (d, J = 6.0 Hz, 1H), 4.43 (s, 2H), 4.35 (s, 1H), 4.18 (s, 1H), 3.69 (s, 3H), 3.31 (t, J = 18.5 Hz, 2H), 3.24−3.06 (m, 3H), 3.02−2.78 (m, 1H), 2.92 (s, 3H), 2.44 (t, J = 11.1 Hz, 1H), 2.04 (d, J = 13.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.78, 145.67, 133.06, 131.47, 130.59, 129.02, 128.89, 128.47, 123.96, 119.57, 113.92, 112.10, 91.08, 66.38, 58.96,

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55.24, 48.20, 46.53, 43.10, 42.95, 40.94, 35.85, 20.25; mp = 198 °C (dec) (HCl salt). Anal. Calcd for $C_{25}H_{28}N_2O_3 \cdot 2HCl \cdot H_2O$: C, 60.61; H, 6.51; N, 5.65. Found: C, 60.40, H, 6.64; N, 5.52.

Representative Procedure for the Preparation of 12a–c. To a solution of **11b** (425 mg, 0.89 mmol) in dichloromethane (10 mL) under nitrogen atmosphere was added BBr_3 (1M, 2 mL in dichloromethane) at room temperature. Then the mixture was stirred at room temperature for 3 days. After completion, the reaction was carefully quenched with methanol, and the solvent was removed under reduced pressure. The product was then dissolved in 1 M HCl (30 mL) and washed with CH_2Cl_2 (2×). Then the aqueous layer was basified with concentrated ammonium hydroxide (28%), extracted with CH_2Cl_2 (3×), and the combined organic extracts were dried over Na_2SO_4, then filtered and concentrated. The crude product was purified over silica gel (EtOAc/Et_3N, 10:1, EtOAc/Et_3N/MeOH, 10:1:0.1, EtOAc/Et_3N/MeOH, 10:1:1) to give a purple foam. The foam was dissolved in a minimal amount of dichloromethane and stirred with excess 1 N ethereal HCl. The mixture was concentrated and the resulting white solid was washed with CH_2Cl_2 and dried to afford 125 mg of the pure **12b** as a dihydrochloride 1.6 hydrate, 30% yield (mp = 190 °C, dec).

3-(2′-Hydroxybenzyl)amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (12a). Pale yellow solid (112 mg, 41%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.23 (m, 2H), 7.03 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.82–6.72 (m, 2H), 5.77 (d, J = 9.8 Hz, 1H), 5.38 (d, J = 9.7 Hz, 1H), 5.18 (d, J = 6.2 Hz, 1H), 4.56 (q, J = 12.6 Hz, 2H), 4.44 (s, 1H), 4.26 (s, 1H), 3.49–2.86 (m, 6H), 3.01 (s, 1H), 2.53 (t, J = 11.5 Hz, 1H), 2.10 (d, J = 11.5 Hz, 1H), 0.10 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.68, 153.74, 135.67, 135.16, 133.10, 132.41, 132.01, 126.25, 124.92, 121.57, 120.62, 118.37, 116.84, 116.12, 94.16, 66.97, 61.68, 51.27, 42.91, 41.77, 39.48, 33.69, 22.91; mp = 190 °C (dec) (HCl salt). Anal. Calcd for $C_{24}H_{26}N_2O_3 \cdot 2HCl \cdot 1.6H_2O$: C, 58.56; H, 6.39; N, 5.69. Found: C, 58.46, H, 6.46; N, 5.33.

3-(3′-Hydroxybenzyl)amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (12b). Pale yellow solid (125 mg, 30%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 8.2, 2.9 Hz, 1H), 6.95–6.76 (m, 4H), 5.79 (d, J = 9.9 Hz, 1H), 5.39 (d, J = 10.0 Hz, 1H), 5.19 (d, J = 6.2 Hz, 1H), 4.49 (m, 3H), 4.45 (s, 1H), 4.27 (s, 1H), 3.48–2.87 (m, 7H), 3.01 (s, 3H), 2.53 (t, J = 11.5 Hz, 1H), 2.14 (d, J = 13.9 Hz, 1H), 1.42–1.25 (m, 1H), 0.07 (d, J = 15.3 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.03, 153.76, 135.65, 135.24, 133.36, 132.12, 131.12, 126.28, 124.87, 122.27, 121.74, 118.24, 117.54, 116.81, 94.26, 66.98, 61.70, 55.03, 42.95, 41.78, 39.54, 33.69, 22.93; mp = 190 °C (dec) (HCl salt). Anal. Calcd for $C_{24}H_{26}N_2O_3 \cdot 2HCl \cdot 1.6H_2O$: C, 58.56; H, 6.39; N, 5.69. Found: C, 58.58, H, 6.66; N, 5.75.

3-(4′-Hydroxybenzyl)amino-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-6-ol (12c). Pale yellow solid (71 mg, 26%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.25 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.2 Hz, 1H), 6.79 (m, 3H), 5.78 (d, J = 9.9 Hz, 1H), 5.40 (d, J = 9.8 Hz, 1H), 5.19 (d, J = 6.3 Hz, 1H), 4.48 (s, 3H), 4.27 (s, 1H), 3.50–2.87 (m, 6H), 3.02 (s, 3H), 2.53 (m, 1H), 2.14 (d, J = 12.9 Hz, 1H), 0.10 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.05, 152.90, 134.66, 134.43, 132.19, 131.16, 125.28, 124.14, 121.40, 120.71, 115.63, 115.47, 93.26, 65.96, 60.70, 54.00, 41.93, 40.77, 38.56, 32.69, 21.93; mp = 198 °C (dec) (HCl salt). Anal. Calcd for $C_{24}H_{26}N_2O_3 \cdot 2HCl \cdot 1.6H_2O$: C, 54.57; H, 6.72; N, 5.30. Found: C, 54.76, H, 6.63; N, 5.52.

2-Nitro-3-trifluoromethylsulfonyloxy-*N*-cyclopropylmethylmorphinan (14). 2-Nitro-3-hydroxy-*N*-cyclopropylmethylmorphinan **13**[9] (2.4 g, 6.7 mmol) was dissolved in anhydrous dichloromethane (50 mL) and Et_3N (3.2 mL, 19.3 mmol). The mixture was cooled to 0 °C, and then Tf_2O (1.8 mL, 9.6 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. The solution was diluted with dichloromethane (60 mL), washed sequentially with saturated sodium carbonate solution and brine, and then dried over anhydrous Na_2SO_4. The organic layer was filtered and concentrated under reduced pressure to afford a crude product, which was purified by column chromatography on silica gel (hexanes/EtOAc/Et_3N = 70:30:1) to give 2.8 g of **14** in 88% yield, as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.27 (s, 1H), 3.23–3.12 (m, 1H), 3.05 (d, J = 19.1, 1H), 2.82–2.64 (m, 2H), 2.53–2.42 (m, 1H), 2.38–2.25 (m, 2H), 2.03–0.77 (m, 11H), 0.54 (d, J = 7.9, 2H), 0.12 (d, J = 4.7, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.91, 140.10, 139.91, 138.45, 125.56, 121.31, 59.85, 54.86, 44.98, 44.09, 41.28, 38.94, 36.40, 26.68, 26.09, 24.42, 21.79, 9.24, 4.09, 3.66.

Synthesis of 2-Nitro-*N*-cyclopropylmethylmorphinan (15). Triflate **14** (142 mg, 0.3 mmol), $Pd(OAc)_2$ (7.8 mg, 0.03 mmol), and dppp (12.4 mg, 0.03 mmol) were dissolved in anhydrous DMF (0.8 mL) under nitrogen atmosphere. Next, Et_3SiH (120 μL, 0.75 mmol) was added to the mixture and stirred at 60 °C overnight. The cooled reaction mixture was directly purified over silica gel (hexanes/EtOAc/Et_3N = 70:30:1) to afford 52 mg of **15** as a yellow oil, 53% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.42 (d, J = 8.5, 1H), 3.07 (m, 2H), 2.72 (m, 2H), 2.40 (m, 2H), 1.91 (m, 2H), 1.25 (m, 10H), 0.53 (m, 2H), 0.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.02, 145.67, 139.43, 126.54, 122.51, 121.27, 59.83, 55.22, 45.23, 44.55, 41.44, 38.51, 36.40, 26.78, 26.28, 24.94, 22.07, 9.18, 4.09, 3.68.

Synthesis of 2-Amino-*N*-cyclopropylmethylmorphinan (16). Compound **16** was prepared according to the published procedure.[10a]

Synthesis of 2-Amino-*N*-cyclopropylmethyl-*N*′-*m*-hydroxybenzylmorphinan (17). *m*-Anisaldehyde (99 μL, 0.85 mmol) and anhydrous Na_2SO_4 (10 mg) were added to the solution of **16** (50 mg, 0.17 mmol) in MeOH (2 mL). The resulting mixture was stirred at room temperature overnight. $NaBH_4$ (32.3 mg, 0.8 mmol) was then added and stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and the residue was dissolved in 10 mL of 1 N HCl and washed with ethyl acetate (2 × 10 mL), then basified with ammonium hydroxide until pH ≈ 11 was reached. The aqueous solution was then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified over silica gel (hexane/EtOAc/Et_3N = 40/30/1) to afford **17** as a colorless oil (52 mg, 73%)

To a solution of **17** (52 mg, 0.12) in anhydrous CH_2Cl_2 (2 mL) under nitrogen atmosphere was added BBr_3 (2 mL, 1 M in CH_2Cl_2) at 0 °C. Then the mixture was stirred at room temperature for 2 h. The reaction was carefully quenched with excess MeOH, and the solvent was removed under reduced pressure. The resulting dark oil was dissolved in MeOH (3 mL), refluxed for 15 min. Next, the solvent was removed under reduced pressure, and the product was dissolved in 10 mL of 1 M HCl and washed with ethyl acetate twice. Then the aqueous layer was basified with ammonium hydroxide (28% aqueous solution) and extracted with CH_2Cl_2 (2×). The combined organic extracts were dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The crude product was purified over silica gel (EtOAc/MeOH/Et_3N = 50/1/1) to afford **17**) as a white foam (37 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 1H), 6.88 (d, J = 8.2, 1H), 6.76 (m, 3H), 6.34 (m, 2H), 4.34 (s, 2H), 4.06 (s, 1H), 3.14 (s, 1H), 2.77 (d, J = 18.5, 1H), 2.58 (m, 1H), 2.41 (m, 1H), 2.12 (m, 4H), 1.62 (m, 2H), 1.21 (m, 8H), 0.76 (d, J = 12.8, 1H), 0.53 (m, 2H), 0.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.72, 145.56, 141.60, 137.87, 129.70, 128.80, 126.42, 117.31, 114.70, 113.26, 111.80, 109.73, 59.50, 55.47, 46.95, 45.58, 43.93, 41.54, 36.47, 36.05, 26.64, 26.39, 24.33, 21.95, 8.41, 4.18, 4.13; (HCl salt) mp = 173–175 °C. Anal. Calcd for $C_{20}H_{28}N_3 \cdot 2HCl \cdot 0.7H_2O$: C, 66.44; H, 7.72; N, 5.74. Found: C, 66.43, H, 7.87; N, 5.68

Opioid Binding to the Human κ, δ, and μ Opioid Receptors. Chinese hamster ovary (CHO) cells stably transfected with the human κ opioid receptor (hKOR-CHO) were obtained from Dr. Liu-Yuan Liu-Chen (Temple University, Philadelphia, PA). CHO cells expressing the human δ-opioid receptor (hDOR-CHO) were obtained from Dr. Larry Toll (SRI International, Palo Alto, CA), and the μ-opioid receptor (hMOR-CHO) was obtained from Dr. George Uhl (NIDA Intramural Program, Baltimore, MD). The cells were grown in 100 mm dishes in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and penicillin–streptomycin (10 000 U/mL) at 37 °C in a 5% CO_2 atmosphere. The affinity and selectivity of the compounds for the multiple opioid

receptors were determined by incubating the membranes with radiolabeled ligands and 12 different concentrations of the compounds at 25 °C in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Incubation times of 60 min were used for the κ-selective peptide [^{3}H]DAMGO and the μ-selective ligand [^{3}H]U69,593. A 3 h incubation was used with the δ-selective antagonist [^{3}H]naltrindole.

[^{35}S]GTPγS Binding Studies To Determine the Pharmacological Properties of the Compounds. Membranes from CHO cells stably expressing either the human κ or μ opioid receptor were used in the experiments. Cells were scraped from tissue culture plates and then centrifuged at 1000*g* for 10 min at 4 °C. The cells were resuspended in phosphate-buffered saline, pH 7.4, containing 0.04% EDTA. After centrifugation at 1000*g* for 10 min at 4 °C, the cell pellet was resuspended in membrane buffer, which consisted of 50 mM Tris-HCl, 3 mM $MgCl_2$, and 1 mM EGTA, pH 7.4. The membranes were homogenized with a Dounce homogenizer, followed by centrifugation at 40000*g* for 20 min at 4 °C. The membrane pellet was resuspended in membrane buffer, and those transfected with the centrifugation step were repeated. The membranes were then resuspended in assay buffer, which consisted of 50 mM Tris-HCl, 3 mM $MgCl_2$, 100 mM NaCl, and 0.2 mM EGTA, pH 7.4. The protein concentration was determined by the Bradford assay using bovine serum albumin as the standard. The membranes were frozen at −80 °C until used.

CHO cell membranes expressing either the human κ opioid receptor (15 μg of protein per tube) or μ opioid receptor (7.5 μg of protein per tube) were incubated with 12 different concentrations of the agonist in assay buffer for 60 min at 30 °C in a final volume of 0.5 mL. The reaction mixture contained 3 μM GDP and 80 pmol of [^{35}S]GTPγS. Basal activity was determined in the presence of 3 μM GDP and in the absence of an agonist, and nonspecific binding was determined in the presence of 10 μM unlabeled GTPγS. Then the membranes were filtered onto glass fiber filters by vacuum filtration, followed by three washes with 3 mL of ice-cold 50 mM Tris-HCl, pH 7.5. Samples were counted in 2 mL of ScintiSafe 30% scintillation fluid. Data represent the percent of agonist-stimulation [^{35}S]GTPγS binding over the basal activity, defined as [(specific binding/basal binding) × 100] − 100. All experiments were repeated at least three times and were performed in triplicate. To determine antagonist activity of a compound at the μ opioid receptors, CHO membranes expressing the μ opioid receptor were incubated with the compound in the presence of 200 nM agonist DAMGO. To determine antagonist activity of a compound at the κ opioid receptors, CHO membranes expressing the κ opioid receptor were incubated with the compound in the presence of 100 nM κ agonist U50,488.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

MOR, μ opioid receptor; KOR, κ opioid receptor; DOR, δ opioid receptor; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; TBDPS, *tert*-butyl(diphenyl)silyl; TBAF, tetrabutylammonium fluoride; TM, transmembrane domain; TIPP, H-Tyr-Tic-Phe-Phe-OH; Bcp, 4-[*N*-((4′-phenyl)phenethyl)-carboxamido]phenylalanine; Dbcp, 2′,6,-dinaphthyl-4′-[*N*-((4′-phenyl)phenethyl)carboxamido]phenylalanine

REFERENCES

(1) Mercadante, S.; Villari, P.; Ferrera, P.; Casuccio, A.; Fulfaro, F. Rapid Titration with Intravenous Morphine for Severe Cancer Pain and Immediate Oral Conversion. *Cancer* **2002**, *95*, 203−208.

(2) (a) Colpaert, F. C.; Niemegeers, C. J.; Janssen, P. A.; Van Ree, J. M. Narcotic Cueing Properties of Intraventricularly Administered Sufentanil, Fentanyl, Morphine, and met-Enkephalin. *Eur. J. Pharmacol.* **1978**, *47*, 115−119. (b) Niemegeers, C. J.; Schellekens, K. H.; Van Bever, W. F.; Janssen, P. A. Sufentanil, a Very Potent and Extremely Safe Intravenous Morphine-like Compound in Mice, Rats, and Dogs. *Arzneim. Forsch.* **1976**, *26*, 1551−1556.

(3) Chen, Z. R.; Irvine, R. J.; Somogyi, A. A.; Bochner, F. Mu Receptor Binding of Some Commonly Used Opioids and their Metabolites. *Life Sci.* **1991**, *48*, 2165−2171.

(4) Riley, J.; Eisenberg, E.; Müller-Schwefe, G.; Drewes, A. M.; Arendt-Nielsen, L. Oxycodone: A Review of Its Use in the Management of Pain. *Curr. Med. Res. Opin.* **2008**, *24*, 175−192.

(5) Aldrich, J. V.; Vigil-Cruz, S. C. Narcotic Analgesics. In *Burger's Medicinal Chemistry and Drug Discovery*; Abraham, D., Ed.; John Wiley & Sons: New York, 2003; Vol. *6*, Chapter 7, pp 329−481.

(6) (a) Furst, S.; Hosztafi, S.; Friedmann, T. Structure−Activity Relationships of Synthetic and Semisynthetic Opioid Agonists and Antagonists. *Curr. Med. Chem.* **1995**, *1*, 423−440. (b) Aldrich, J. V. Analgesics. In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1996; Vol. 3, pp 321−441. (c) Mascarella, S. W.; Bai, X.; Williams, W.; Sine, B.; Bowen, W. D.; Carroll, F. I. (+)-*cis*-*N*-(Para-, Meta-, and Ortho-substituted benzyl)-*N*-normetazocines: Synthesis and Binding Affinity at the [^{3}H]-(+)-Pentazocine-Labeled (σ1) Site and Quantitative Structure−Activity Relationship Studies. *J. Med. Chem.* **1995**, *38*, 565−569. (d) Reden, J.; Reich, M. F.; Rice, K. C.; Jacobson, A. E.; Brossi, A. Deoxymorphines: Role of the Phenolic Hydroxyl in the Antinociception and Opiate Receptor Interactions. *J. Med. Chem.* **1979**, *22*, 256−259. (e) Hedberg, M. H.; Johansson, A. M.; Fowler, C. J.; Terenius, L.; Hacksell, U. Palladium-Catalyzed Synthesis of C3-Substituted 3-Deoxymorphines. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2527−2532. (f) Kubota, H.; Rothman, R. B.; Dersch, C.; McCullough, K.; Pinto, J.; Rice, K. C. Synthesis and Biological Activity of 3-Substituted 3-Deoxynaltrindole Derivatives. *Bioorg. Med. Chem. Lett.* **1999**, *8*, 799−804.

(7) Berezowska, I.; Chung, N. N.; Lemieux, C.; Wilkes, B. C.; Schiller, P. W. Agonist vs. Antagonist Behavior of δ Opioid Petides Containing Novel Phenylalanine Analogues in Place of Tyr. *J. Med. Chem.* **2009**, *52*, 6941−6945.

(8) Peng, X.; Knapp, B. I.; Bidlack, J. M.; Neumeyer, J. L. High-Affinity Carbamate Analogues of Morphinan at Opioid Receptors. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 1508−1511.

(9) Peng, X.; Knapp, B. I.; Bidlack, J. M.; Neumeyer, J. L. In-Vitro Investigation of Oxazol and Urea Analogues of Morphinan at Opioid Receptors. *Bioorg. Med. Chem.* **2007**, *15*, 4106−4112.

(10) (a) Zhang, A.; Xiong, W.; Hilbert, J. E.; DeVita, E. K.; Bidlack, J. M.; Neumeyer, J. L. 2-Aminothiazole-Derived Opioids. Bioisosteric Replacement of Phenols. *J. Med. Chem.* **2004**, *47*, 1886−1888. (b) Zhang, A.; Vliet, S. V.; Neumeyer, J. L. Synthesis of aminothiazole derived morphinans. *Tetrahedron Lett.* **2003**, *44*, 6459−6462. (c) Zhang, T.; Yan, Z.; Sromek, A.; Knapp, B. I.; Scrimale, T.; Bidlack, J. M.; Neumeyer, J. L. Aminothiazolomorphinans with Mixed κ and μ Opioid Activity. *J. Med. Chem.* **2011**, *54*, 1903−1913.

(11) Sagara, T.; Egashira, H.; Okamura, M.; Fujii, I.; Shimohigashi, Y.; Kanematsu, K. Ligand Recognition in mu Opioid Receptor: Experimentally Based Modeling of mu Opioid Receptor Binding Sites and Their Testing by Ligand Docking. *Bioorg. Med. Chem.* **1996**, *4*, 2151−2166.

(12) Pogozheva, I. D.; Lomize, A. L.; Mosberg, H. I. Opioid Receptor Three-Dimensional Structures from Distance Geometry Calculations with Hydrogen Bonding Constraints. *Biophys. J.* **1998**, *75*, 612−634.

(13) Wentland, M. P.; Xu, G.; Cioffi, C. L.; Ye, Y.; Duan, W.; Cohen, D. J.; Colasurdo, A. M.; Bidlack, J. M. 8-Aminocyclazocine Analogues:

Synthesis and Structure−Activity Relationships. *Bioorg. Med. Chem. Lett.* **2000**, *9*, 183−187.
(14) Wentland, M. P.; Duan, W.; Cohen, D. J.; Bidlack, J. M. Selective Protection and Functionalization of Morphine: Synthesis and Opioid Receptor Binding Properties of 3-Amino-3-desoxymorphine Derivatives. *J. Med. Chem.* **2000**, *43*, 3558−3565.
(15) Decker, M.; Si, Y. G.; Knapp, B. I.; Bidlack, J. M.; Neumeyer, J. L. Synthesis and Opioid Receptor Binding Affinities of 2-Subtituted and 3-Aminomorphinans: Ligands for μ, κ, and δ Opioid Receptors. *J. Med. Chem.* **2010**, *53*, 402−418.
(16) Neumeyer, J. L.; Bidlack, J. M.; Zong, R.; Bakthavachalam, V.; Gao, P.; Cohen, D. J.; Negus, S. S.; Mello, N. K. Synthesis and Opioid Receptor Affinity of Morphinan and Benzomorphan Derivatives: Mixed κ Agonists and μ Agonists/Antagonists as Potential Pharmacotherapeutics for Cocaine Dependence. *J. Med. Chem.* **2000**, *43*, 114−122.
(17) Wolfe, J. P.; Buchwald, S. L. Palladium-Catalyzed Amination of Aryl Triflates. *J. Org. Chem.* **1997**, *62*, 1264−1267.
(18) Gribble, G. W.; Nutaitis, C. F. Reactions of Sodium Borohydride in Acidic Media: N-Methylation of Amines with Paraformaldehyde/Trifluoroacetic Acid. *Synthesis* **1987**, *1987*, 709−711.
(19) Zhang, A.; Xiong, W.; Bidlack, J. M.; Hilbert, J. E.; Knapp, B. I.; Wentland, M. P.; Neumeyer, J. L. 10-Ketomorphinan and 3-Substituted-3-desoxymorphinan Analogues as Mixed κ and μ Opioid Ligands: Synthesis and Biological Evaluation of Their Binding Affinity at Opioid Receptors. *J. Med. Chem.* **2004**, *47*, 165−174.
(20) Hupp, C. D.; Neumeyer, J. L. Rapid Access to Morphinones: Removal of 4,5-Ether Bridge with Pd-Catalyzed Triflate Reduction. *Tetrahedron Lett.* **2010**, *51*, 2359−2361.
(21) Csutoras, C.; Zhang, A.; Zhang, K.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. Synthesis and Pharmacological Evaluation of *R*(−)-*N*-Alkyl-11-hydroxynoraporphines and Their Esters. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 3553−3559.