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N-Cubylmethyl Substituted Morphinoids as Novel Narcotic Antagonists

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Abstract—*N*-Cubylmethylnormorphine (**1**) and *N*-cubylmethylnoroxymorphone (**2**) have been synthesized and found to be more potent ligands at the μ and κ opioid receptors than morphine and oxymorphone respectively. In the guinea-pig ileum preparation, compounds **1** and **2** were characterized as opioid μ antagonists (Ke = 68 and 16 nM, respectively). Compound **2** also showed effective κ-antagonism (Ke = 22 nM). The narcotic antagonism activity of **1** has been confirmed by in vivo assays.

Introduction

The opioid activity of morphinoids is sensitive to the nature of their nitrogen substituents. Replacement of the *N*-methyl group in morphine and related opioids by substituents rich in π-electron such as allyl, cyclopropylmethyl, or cyclobutylmethyl group resulted in the formation of potent morphine antagonists such as nalorphine,[1] naloxone,[2] naltrexone,[3] and nalbuphine.[4] Naloxone and naltrexone, being practically pure opioid antagonists and devoid of analgesic activity,[5] have been used clinically as narcotic antagonists; while nalorphine and nalbuphine, despite their potent μ-antagonism activity, possess analgesic activity of their own through agonism at the opioid κ receptor.[6] Cubane is a highly strained cage molecule,[7] which occupies an important position in theoretical organic chemistry, but has rarely been incorporated into biologically active molecules.[8] The endocyclic orbitals in cubane are richer in *p* character than the sp^3 hybrid of typical tetracoordinated carbon compounds.[9] This feature makes the cubylmethyl group comparable electronically to the N-substituents present in the above mentioned opioid antagonists and agonist–antagonist analgesics. In order to extend the SAR of narcotic antagonists and to provide additional insights into the role played by the *N*-alkyl substituent in determining the action of morphinoids at the opioid receptors, we describe herein the synthesis and opioid pharmacology of *N*-cubylmethylnormorphine (**1**) and *N*-cubylmethylnoroxymorphone (**2**), which differ from nalorphine and naloxone in having an *N*-cubylmethyl group in the place of an *N*-allyl group.

Results and Discussion

Chemistry

N-Cubylmethylnormorphine (**1**) was synthesized from codeine and cubane-1,4-dicarboxylic acid dimethyl ester[10] as shown in Scheme 1. Codeine was first acetylated, followed by *N*-demethylation via the trichloroethyl carbamate[11] to give 6-acetylnorcodeine (**5**). Compound **5** was then reacted with cubane-

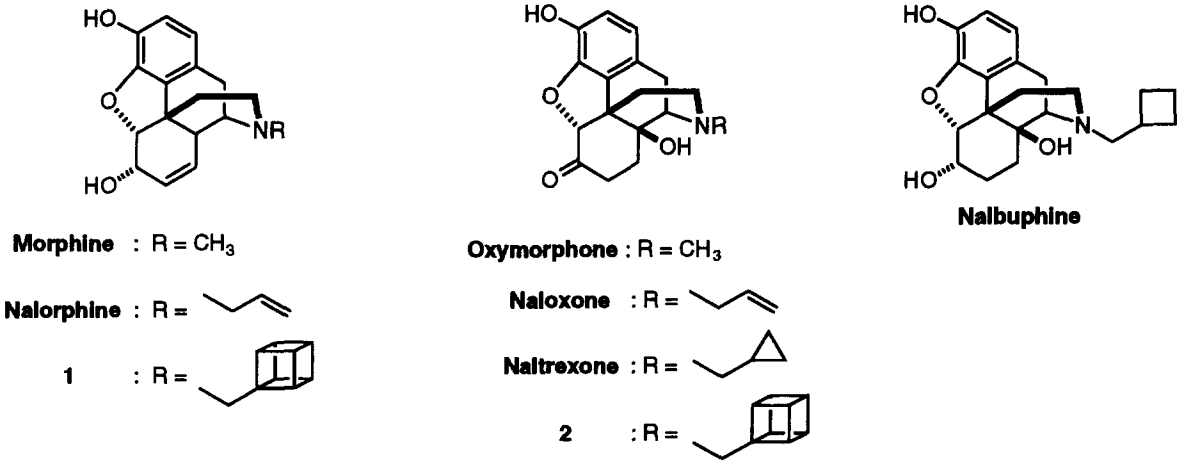


Chart 1.

carbonyl chloride (**6**) derived from cubane-1,4-dicarboxylic acid dimethyl ester via a literature procedure[12] to give amide **7**, which was subjected to ester hydrolysis with aqueous NaOH, followed by reduction with $LiAlH_4$, to provide *N*-cubylmethylnorcodeine (**9**). Target compound **1** was obtained via *O*-demethylation of **9** with boron tribromide–dimethylsulfide complex. *N*-Cubylmethylnoroxymorphone (**2**) was prepared in a similar fashion from oxycodone (Scheme 2). To achieve the desired N-demethylation, oxycodone was first treated with acetic anhydride to give the protected acetate **10**, which was then converted to the trichloroethyl carbamate **11**. Reduction of the carbamate function with zinc to give the desired nor-compound **12** required the prior hydrolysis of the 14-acetate group to avoid the concomitant O to N acyl migration, which would result in the formation of the undesired acetamide of **12**. The 6-keto function in **12** was then protected as an ethylene ketal (**13**), followed by introduction of the cubylmethyl group as described above for the preparation of **1** to give intermediate **15**. Treatment of **15** with boron tribromide–dimethylsulfide complex resulted in simultaneous *O*-demethylation and ketal hydrolysis to provide target compound **2**.

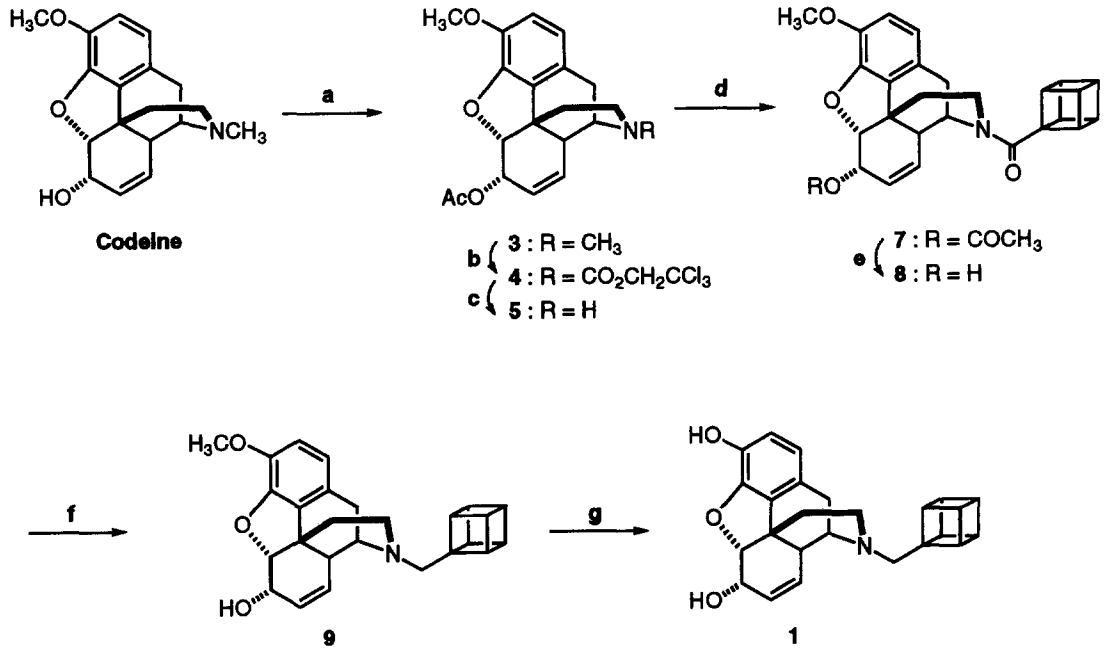
Opioid receptor binding affinity

N-Cubylmethylnormorphine (**1**) demonstrated potent and selective binding towards the μ opioid receptor, while *N*-cubylmethylnoroxymorphone (**2**) showed more potent but less selective binding towards all three opioid receptors. A comparison between compound **1** and morphine revealed that the replacement of the *N*-methyl substituent with a cubylmethyl group resulted in a 2-fold increase in μ-affinity, 17-fold increase in κ-affinity, and 2-fold decrease in δ-affinity, while the same transposition in the oxymorphone series resulted in slight increase in μ-affinity, 37-fold increase in κ-affinity, and 3-fold increase in δ-affinity. The binding affinities of **1** at the three opioid receptors, although less potent, are qualitatively similar to that of its *N*-allyl analogue nalorphine, while the opioid receptor affinities of **2** are significantly less potent and less μ-selective than that of its *N*-allyl analogue naloxone. Consistent with the SAR of morphinoids in general, the codeine analogue **9** showed much reduced binding at all three opioid receptors. (Table 1).

Opioid activity in guinea-pig ileum preparations

The opioid activities of compounds **1** and **2** were further evaluated at μ and κ opioid receptors in guinea-pig ileum (GPI). Both compounds **1** and **2** were characterized as weak partial agonists with a maximum response of 30% at 1 μM. At 100 nM, compound **1** did not show any ability to inhibit the electrically stimulated contraction of the guinea-pig ileum. Nalorphine has been reported to give significant agonist activity in the guinea-pig ileum, with an IC_{50} of 24 nM; while naloxone was almost devoid of agonist activity in this assay.[13] (Table 2).

The opioid antagonist activity of **1** and **2** were tested in the same GPI preparation. Compound **1** was shown to antagonize the action of the typical μ-agonist morphine, although with much reduced potency from its *N*-allyl analogue nalorphine (Ke = 68 versus 4.5 nM). On the other hand, compound **2** demonstrated more effective antagonism against both morphine and the κ-selective agonist U-50488 (Ke = 16 and 22 nM respectively), although with reduced potency and



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine; (b) $ClCO_2CH_2CCl_3$, K_2CO_3 $ClCH_2CH_2Cl$, reflux; (c) Zn 90% HOAc; (d) cubanecarboxylic acid chloride (**6**) Et_3N, CH_2Cl_2 O °C; (e) NaOH, MeOH; (f) $LiAlH_4$ THF; (g) BBr_3-$(CH_3)_2S$, $ClCH_2CH_2Cl$, reflux.

μ-selectivity from its *N*-allyl analogue naloxone (Table 3).

In vivo analgesia and narcotic antagonism activity

When tested in vivo, compound **1** demonstrated moderate narcotic antagonism activity in anti-Straub tail test (AST), although the activity is much weaker than that of either the pure antagonist naloxone or the agonist–antagonist nalorphine. Unlike nalorphine, in mouse phenylquinone writhing (PQW) test, compound **1** failed to show analgesic activity in the dose range tested, indicating its being a relatively pure opioid antagonist (Table 4).

X-ray crystallography

The X-ray structure analysis of *N*-cubylmethyl-normorphine hydrochloride (**1**·HCl) showed the well-established rigid T-shaped 4,5-epoxymorphinan skeleton (Fig. 1). The overall molecular shape of protonated compound **1** in the crystal state is very similar to that of either naloxone [14,15] or naltrexone.[16]

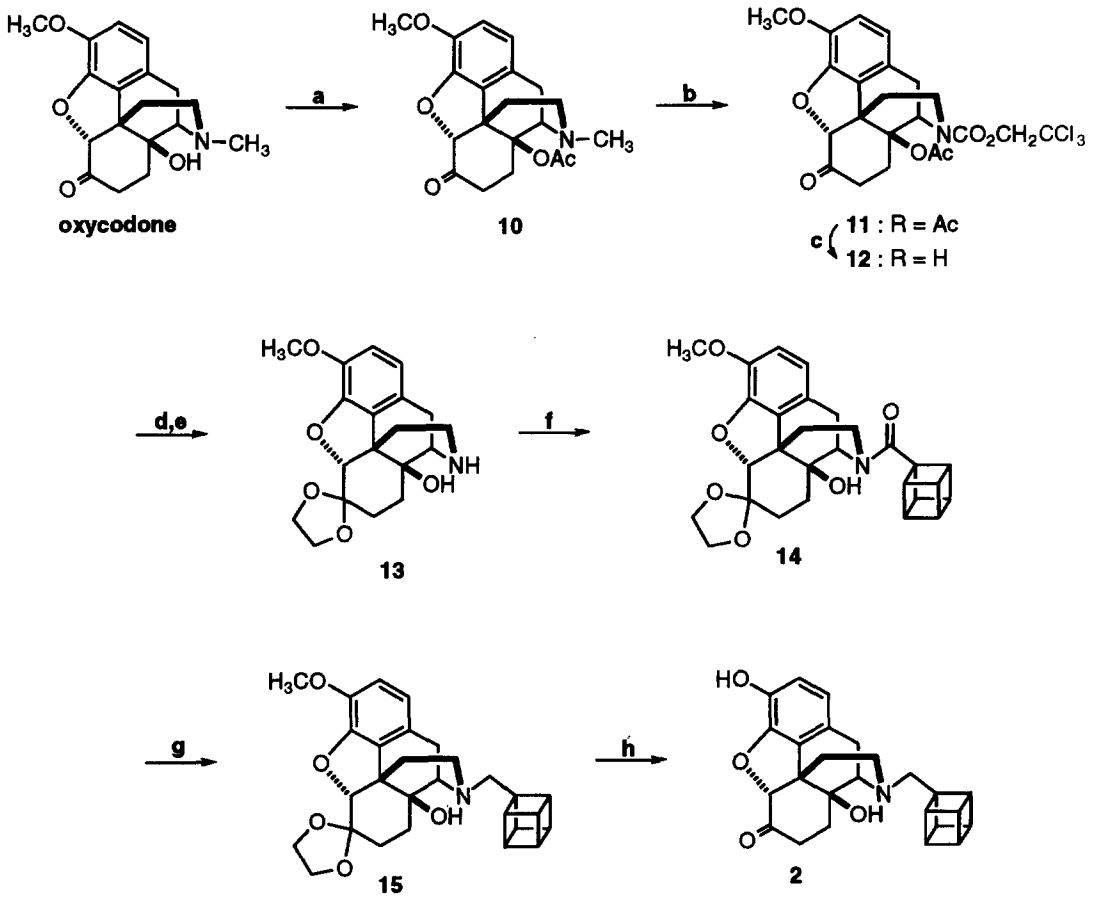
Conclusion

Compounds **1** and **2**, the *N*-cubylmethyl derivatives of morphine and oxymorphone, were found to be more potent than morphine and oxymorphone respectively as binders to the opioid receptors in general. In the guinea-pig ileum preparation, both compounds **1** and **2** were characterized as weak partial agonists. The morphine analogue **1** showed moderate antagonism activity at μ opioid receptor; while the oxymorphone analogue **2** was an effective antagonist at both μ and κ opioid receptors, albeit with reduced potency and μ-selectivity from its *N*-allyl analogue naloxone. The narcotic antagonism activity of compound **1** has been confirmed by in vivo studies. It is conceivable that cubane derivatives **1** and **2** bind to opioid receptors in a similar fashion as their *N*-allyl or *N*-cyclopropylmethyl substituted counterparts such as nalorphine, naloxone and naltrexone; while the observed reduction in potency may be due to unfavorable steric interaction involving the cubane cage.

Experimental Section

Chemistry

Melting points were taken in a capillary tube by using a Yamato MP-21 melting point apparatus and are uncorrected. IR Spectra were determined with a Perkin–Elmer 1760-X FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 or AMX-400 spectrometer. Chemical shifts are expressed in parts per million (d) downfield from



Scheme 2. Reagents and conditions: (a) Ac_2O, 100 °C; (b) $ClCOCH_2CCl_3$, K_2CO_3, $ClCH_2CH_2Cl$, reflux; (c) 6 N HCl; (d) Zn, 90% HOAc; (e) $HOCH_2CH_2OH$, TsOH, toluene, reflux; (f) **6**, Et_3N, CH_2Cl_2, O °C; (g) $LiAlH_4$, THF; (h) BBr_3-$S(CH_3)_2$, $ClCH_2$ CH_2Cl, reflux.

Table 1. Opioid receptor binding affinity (K_i, nM)[a]

Compound	μ	κ	δ
1	17.3±3.5	107±8.8	944±75
2	13.6±1.1	19.5±2.0	44.8±14.1
9	412±17	3340±177	>10,000
Morphine	38±4	1870±83	510±55
Nalorphine	4.5±0.7	31±7	49±7
Oxymorphone	15±1	725±154	145±17
Naloxone	1.1±0.1	12±0.7	16±3

[a]Data represents the mean of three experiments each performed in duplicate.

Table 2. Opioid agonist activity of **1** and **2** in GPI preparation[a]

Compound	IC_{50}, nM	% max response[b]
1	—	30
2	—	30
Morphine	52±4	—
Nalorphine	24.3±1.3[c]	—
U-50488	2.2±0.1	—

[a]Data represents the mean of three experiments each performed in duplicate.
[b]Partial agonist potency at 1 μM.
[c]Adopted from ref. 14.

Table 3. Opioid antagonist activity of **1** and **2** in GPI preparation[a,b]

Compound	μ (morphine)		κ (U-50488)		Ke ratio κ/μ
	IC_{50} ratio[c]	Ke, nM[d]	IC_{50} ratio[c]	Ke, nM[d]	
1	2.5±0.9	68	NT	NT	—
2	7.5±1.1	16	5.6±0.5	22	1.4
Nalorphine	—	4.5[e]	—	—	—
Naloxone	37±2.2	2.8	9.2±1.1	12	4.5

[a]Data represents the mean of three experiment each performed in duplicate.
[b]Concentration of **1** or **2** = 100 nM.
[c]IC_{50} of agonist in the presence of antagonist divided by the control IC_{50} in the same preparation.
[d]K_e = [antagonist]/(IC_{50} ratio − 1).
[e]Adopted from ref. 14. NT = not tested.

Table 4. In vivo analgesia and narcotic antagonism activity[a]

Compound	ED_{50} (mg kg^{-1}, sc)	
	PQW	AST
1	>27	5.1
Morphine	0.98	—
Nalorphine	0.86	0.37
Naloxone	>100	0.020

[a]Data represents the mean of three experiments each performed in duplicate.

tetramethylsilane. Electron impact mass spectra were obtained on a JEOL JMS-D300 mass spectrometer; high resolution mass spectra were obtained with a JEOL JMS-HX110 spectrometer. Elemental analyses were performed with a Perkin–Elmer 240C instrument. Analytical thin layer chromatography was performed on Merck (Art. 5717) silica gel plates and visualized with UV light (254 nm) or upon heating after treatment with 2% phosphomolybdic acid in ethanol. Medium pressure liquid chromatography was performed with Merck 40–63 mm silica gel. Reagent grade THF was distilled from sodium-benzophenone prior to use. Other anhydrous solvents were distilled from CaH_2 and stored over 4-Å molecular sieves until use.

6α-Acetoxy-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (3). A solution of codeine (7.0 g, 23.4 mmol) and Ac_2O (7.2 g, 70.5 mmol) in pyridine (45 mL) was stirred at room temperature for 12 h. The mixture was evaporated. The residue was treated with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and evaporated to afford **3** as a white solid (7.8 g, 98%): mp 131.5–133.5 °C; R_f 0.31 (MeOH:CH_2Cl_2, 1:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (m, 1H), 2.03 (td, J=12.4, 5.1 Hz, 1H), 2.13 (s, 3H), 2.24–2.37 (m, 2H), 2.42 (s, 3H), 2.57 (dd, J=12.1, 4.0 Hz, 1H), 2.74 (m, 1H), 3.01 (d, J=18.6 Hz, 1H), 3.34 (m, 1H), 3.83 (s, 3H), 5.04 (d, J=6.4 Hz, 1H), 5.15 (m, 1H), 5.41 (m, 1H), 5.60 (m, 1H), 6.51 (d, J=8.3 Hz, 1H), 6.63 (d, J=8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.8, 35.3, 40.6, 42.7, 43.0, 46.7, 56.7, 59.1, 68.2, 88.1, 114.0, 119.1, 126.9, 128.4, 129.5, 130.6, 142.1, 146.8, 170.5; IR (KBr) 2920, 2810, 1728, 1501, 1443 cm^{-1}; MS (EI, 70 eV) m/z calcd for $C_{20}H_{23}NO_4^+$: 341.1627, found 341.1626; 341 (M^+, base), 282.

6α-Acetoxy-7,8-didehydro-4,5α-epoxy-3-methoxy-17-[(2,2,2-trichloroethoxy)carbonyl]morphinan (4). A mixture of **3** (5.35 g, 15.6 mmol), K_2CO_3 (5.21 g, 37.7 mmol), and 2,2,2-trichloroethyl chloroformate (6.21 g, 29.3 mmol) in $ClCH_2CH_2Cl$ (100 mL) was refluxed for 2 h. The cooled reaction mixture was washed with 1 N HCl followed by saturated aqueous $NaHCO_3$. The solution was dried ($MgSO_4$), and evaporated to afford crude **4** as a white crystalline solid (8.29 g): R_f 0.76 (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (m, 2H), 2.14 (s, 3H), 2.63–3.08 (m, 4H), 3.84 (s, 3H), 4.12 (m, 1H), 4.71–4.88 (m, 2H), 4.92 (m, 1H), 5.06 (d, J=6.7 Hz, 1H), 5.15 (m, 1H), 5.44 (d, J=10.1 Hz, 1H), 5.67 (m, 1H), 6.55 (d, J=8.2 Hz, 1H), 6.68 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 29.2, 29.5, 34.6, 35.1, 38.1, 38.3, 39.5, 39.7, 43.0, 51.1, 51.3, 56.7, 67.6, 75.2, 87.7, 93.9, 114.5, 119.7, 125.3, 127.8, 127.9, 129.6, 129.8, 142.6, 153.1, 170.5; IR (neat) 2948, 1760, 1728, 1689, 1501 cm^{-1}; MS (EI, 70 eV) m/z calcd for $C_{22}H_{22}NO_6Cl_3^+$: 501.0513, found 501.0507; 501 (M^+), 241 (base).

6α-Acetoxy-7,8-didehydro-4,5α-epoxy-3-methoxymorphinan (5). The crude **4** (8.29 g) was dissolved in 90%

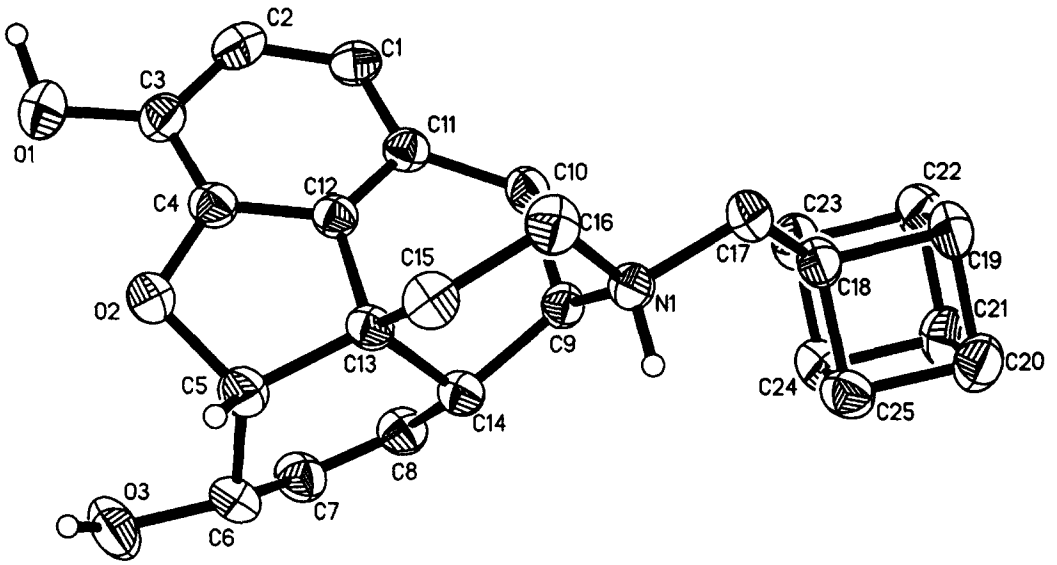


Figure 1. Crystal conformation of *N*-cubylmethylnormorphine hydrochloride (**1**·HCl).

aqueous HOAc, and then Zn powder (2.70 g, 41.3 mmol) was added in portions at room temperature. The mixture was stirred for another 1.5 h, filtered through Celite and evaporated. To the residue was added aqueous Na_2CO_3, and the resultant mixture was extracted with isopropanol:$CHCl_3$ (1:4). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed (MPLC, silica gel; 15–20% MeOH in CH_2Cl_2) to afford **5** (4.11 g, 81% from **3**) as a white solid: mp 120–122 °C; R_f 0.42 (CH_3OH:CH_2Cl_2, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (m, 2H), 2.12 (s, 3H), 2.41 (s, 1H), 2.64 (m, 1H), 2.80–2.91 (m, 4H), 3.64 (m, 1H), 3.82 (s, 3H), 5.01 (d, J=6.3 Hz, 1H), 5.14 (m, 1H), 5.37 (m, 1H), 5.61 (m, 1H), 6.51 (d, J=8.3 Hz, 1H), 6.64 (d, J=8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 31.1, 36.0, 38.6, 41.0, 43.5, 52.2, 56.6, 68.0, 88.5, 114.0, 119.2, 127.0, 128.5, 129.2, 130.6, 142.1, 146.8, 170.5; IR (KBr) 2920, 2835, 1728, 1501, 1438, 1235 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{19}H_{21}NO_4^+$: 327.1471, found 327.1471; 327 (M^+, base); Anal. calcd for ($C_{19}H_{21}NO_4$·HCl: C, 62.72; H, 6.09; N, 3.85; found: C, 62.55; H, 5.85; N, 3.73.

6α-Acetoxy-17-(cubylcarbonyl)-7,8-didehydro-4,5α-epoxy-3-methoxymorphinan (7). To a solution of cubanecarboxylic acid (450 mg, 3.04 mmol) and DMF (3 drops) in CH_2Cl_2 (10 mL) was added oxalyl chloride (2 mL) at room temperature and the resultant mixture was stirred for 1 h. The reaction mixture was then evaporated to dryness and redissolved in CH_2Cl_2 (10 mL). The acid chloride (**6**) solution was added to a stirred solution of **5** (1.44g, 9.45 mmol) and Et_3N (1.3 mL, 9.12 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The stirred mixture was allowed to warm to room temperature, diluted with CH_2Cl_2, washed with 0.1 N HCl and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed (MPLC, silica gel; 4% MeOH in CH_2Cl_2) to afford **7** (1.4 g, 100.0%) as a white solid: mp 192–192.5 °C; R_f 0.34 (ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.97 (m, 2H), 2.12 (s, 3H), 2.53–2.58 (m, 1H), 2.61–2.93 (m, 2H), 3.17–3.28 (m, 1H), 3.83 (s, 3H), 3.96–4.03 (m, 4H), 4.19–4.27 (m, 3H), 5.05 (m, 1H), 5.13 (m, 1H), 5.46 (m, 1H), 5.64–5.71 (m, 1H), 6.53 (m, 1H), 6.67 (d, J=8.2 Hz, 1H), 4.48 and 5.31 (m, 1H), 5.36 and 5.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 29.0, 35.8, 38.8, 39.4, 40.6, 43.4, 44.4, 44.5, 46.6, 47.7, 49.3, 49.5, 53.4, 56.6, 58.1, 58.3, 67.6, 67.8, 87.6, 87.8, 114.36, 114.42, 119.5, 119.7, 125.7, 127.6, 128.4, 129.2, 129.5, 142.4, 142.6, 146.8, 169.8, 170.2, 170.5; IR (KBr) 2974, 1736, 1621, 1504, 1435, 1238 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{28}H_{27}NO_5^+$: 457.1889, found 457.1874; 457 (M^+), 103 (base).

17-(Cubylcarbonyl)-7,8-didehydro-4,5α-epoxy-6-hydroxy-3-methoxymorphinan (8). A mixture of **7** (1.4 g, 3.04 mmol), NaOH (6.2 mmol), and MeOH (70 mL) was stirred for 1 h at room temperature. The mixture was evaporated to dryness, treated with H_2O, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed (MPLC, silica gel; 6% MeOH in CH_2Cl_2) to afford **8** (1.21 g, 96%) as a white solid: R_f 0.46 (CH_3OH:CH_2Cl_2, 3:47); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.97 (m, 2H), 2.45 (m, 1H), 2.63 (d, J=18.7 Hz, 1H), 2.73–2.92 (m, 2H), 3.05 (broad s, 1H), 3.24 (dd, J=8.3, 3.4 Hz, 1H), 3.79 (s, 3H), 3.95–4.01 (m, 4H), 4.13 (broad s, 1H), 4.18–4.24 (m, 3H), 4.85 (d, J=6.6 Hz, 1H), 5.27–5.31 (m, 1H), 5.70–5.78 (m, 1H), 6.54 (m, 1H), 6.66 (m, 1H), 4.47 and 5.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 30.2, 34.8, 35.1, 36.2, 38.4, 39.3, 40.6, 43.6, 43.9, 44.3, 44.4, 46.6, 46.8, 47.4, 49.3, 49.4, 51.7, 56.20, 56.25, 58.0, 58.2, 66.0, 66.1, 90.9, 91.0, 113.3, 113.4, 119.8, 120.0, 125.1, 125.8, 126.2, 127.0, 129.8, 129.9, 134.1, 135.0, 142.4, 142.5, 146.37, 146.42, 169.7, 170.0; IR (KBr) 3402, 2980, 1620, 1504, 1440 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{26}H_{25}NO_4^+$: 415.1784, found 415.1785; 415 (M^+), 103 (base).

17-(Cubylmethyl)-7,8-didehydro-4,5α-epoxy-6-hydroxy-3-methoxymorphinan (9). To a stirred solution of

$LiAlH_4$ (8.84 mmol) in THF (90 mL) was added a solution of **8** (1.17 g, 2.82 mmol) in THF (20 mL). The mixture was further stirred at room temperature for 1 h, then 20% H_2O in THF (3.5 mL) was added. After 15 min, 10 N NaOH (1.2 mL) was added and the mixture was stirred for another 15 min. The resultant suspension was dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed (MPLC, silica gel; 6% MeOH in CH_2Cl_2) to afford **9** (926 mg, 82%) as a white solid: mp 223 °C (dec, HCl salt); R_f 0.62 (CH_3OH:CH_2Cl_2, 1:9); ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (m, 1H), 2.05 (td, J=12.2, 5.4 Hz, 1H), 2.27 (dd, J=18.5, 6.2 Hz, 1H), 2.42 (td, J=12.1, 3.4 Hz, 1H), 2.50 (dd, J=11.6, 4.9 Hz, 1H), 2.66 (m, 1H), 2.73 (d, J=13.3 Hz, 1H), 2.79 (d, J=13.4 Hz, 1H), 3.03 (d, J=18.5 Hz, 1H), 3.21 (m, 1H), 3.82 (s, 3H), 3.85 (m, 3H), 3.91 (m, 3H), 4.01 (m, 1H), 4.15 (s, 1H), 4.86 (d, J=6.5 Hz, 1H), 5.25 (dt, J=9.8, 2.6 Hz, 1H), 5.67 (m, 1H), 6.54 (d, J=8.1 Hz, 1H), 6.63 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 35.9, 40.8, 43.4, 44.6, 45.4, 47.9, 48.5, 56.3, 56.5, 56.9, 57.4, 66.5, 91.5, 112.8, 119.5, 127.4, 128.7, 131.3, 133.2, 142.1, 146.3; IR (neat) 3409, 2970, 1504, 1453 cm^{-1}; MS (EI, 70 eV) m/z calcd for $C_{26}H_{27}NO_3^+$: 401.1991, found 401.1989; 401 (M^+), 298 (base). Anal. calcd for ($C_{26}H_{27}NO_3 \cdot HCl \cdot 0.5H_2O$) C, 69.87; H, 6.54; N. 3.13; found: C, 70.04; H, 6.91; N, 3.10.

17-(Cubylmethyl)-7,8-didehydro-4,5α-epoxy-3,6-dihydroxymorphinan (1). A solution of **1** (319 mg, 0.80 mmol) and BBr_3-$(CH_3)_2S$ (4.0 mmol) in $ClCH_2CH_2Cl$ (50 mL) was brought to reflux for 1.5 h, then cooled to room temperature. The cooled reaction mixture was treated with H_2O (20 mL) and aqueous Na_2CO_3 to pH 8–9 and extracted with isopropanol:$CHCl_3$ (1:4). The extract was dried over $MgSO_4$ and evaporated. The crude product was chromatographed (MPLC, silica gel; 10% MeOH in CH_2Cl_2) to afford **1** (220 mg, 71%) as a white to pale green solid: mp 211 °C (dec, HCl salt); R_f 0.42 (CH_3OH:CH_2Cl_2, 1:9); ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (d, J=11.9 Hz, 1H), 2.08 (td, J=12.3, 4.8 Hz, 1H), 2.27 (dd, J=18.7, 6.3 Hz, 1H), 2.46 (m, 1H), 2.56 (dd, J=11.5, 3.9 Hz, 1H), 2.70 (broad s, 1H), 2.82 (s, 2H), 3.00 (d, J=18.6 Hz, 1H), 3.24 (m, 1H), 3.43 (s, 1H), 3.85–3.90 (m, 6H), 3.99 (m, 1H), 4.16 (d, J=2.8 Hz, 1H), 4.70 (broad s, 1H), 4.80 (d, J=6.2 Hz, 1H), 5.18 (d, J=9.7 Hz, 1H), 5.60 (d, J=9.7 Hz, 1H), 6.43 (d, J=8.1 Hz, 1H), 6.59 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 35.6, 40.7, 43.6, 44.6, 45.5, 47.9, 48.6, 56.5, 56.8, 57.3, 66.7, 91.7, 117.0, 119.9, 126.6, 129.0, 131.1, 132.5, 138.0, 145.5; IR (KBr) 3411, 2972, 1504, 1460 cm^{-1}; FABMS m/z calcd for $C_{25}H_{24}NO_3^-$: 386.1756, found 386.1757; 386 (M^--H); Anal. calcd for $C_{25}H_{25}NO_3 \cdot HCl \cdot H_2O$: C, 67.94; H, 6.39; N, 3.17; found: C, 67.77; H, 6.63; N, 3.30.

14-Acetoxy-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (10). A solution of oxycodone (3.0 g, 9.5 mmol) in acetic anhydride (30 mL) was heated at 100 °C overnight and evaporated under reduced pressure. To the residue was added saturated aqueous $NaHCO_3$, and the resultant mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated to give **10** as a solid: mp 183.5–185.5 °C; R_f 0.55 ($MeOH$:CH_2Cl_2, 1:10); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (dd, J=11.1, 3.4 Hz, 1H), 1.60 (dt, J=14.2, 3.7 Hz, 1H), 2.15 (s, 3H), 2.09–2.22 (m, 2H), 2.30 (s, 3H), 2.39–2.66 (m, 4H), 2.78 (ddd, J=14.3, 5.0, 2.7 Hz, 1H), 3.17 (d, J=18.5 Hz, 1H), 3.87 (s, 3H), 4.16 (d, J=5.5 Hz, 1H), 4.63 (s, 1H), 6.61 (d, J=8.3 Hz, 1H), 6.69 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.3, 27.0, 30.0, 35.6, 42.7, 45.6, 50.5, 56.9, 57.8, 82.5, 90.0, 115.2, 119.5, 125.9, 128.5, 143.0, 145.0, 170.2, 207.2; IR (KBr) 1735, 1720 cm^{-1}; MS (EI, 70 eV) m/z calcd for $C_{20}H_{23}NO_5^+$: 357.1576, found 357.1573; 357 (M^+, base), 314.

14-Acetoxy-4,5α-epoxy-3-methoxy-17-[(2,2,2-trichloroethoxy)carbonyl]morphinan-6-one (11). To a stirred mixture of **10** (2.0 g, 5.7 mmol), K_2CO_3 (2.0 g, 14.3 mmol) and 1,2-dichloroethane (35 mL) was added dropwise trichloroethyl chloroformate (1.6 mL, 11.5 mmol). The reaction mixture was refluxed for 24 h, then cooled and extracted with CH_2Cl_2. The extract was washed successively with 1 N HCl, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and evaporated. The excess trichloroethyl chloroformate was removed via Kügel-rohr distillation under vacuum and crude **11** (3.0 g) was obtained without further purification: mp 197–199 °C; R_f 0.75 (CH_3OH:CH_2Cl_2, 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.65 (m, 2H), 2.09 and 2.13 (s, 3H), 2.27 (dt, J=15.1, 3.2 Hz, 1H), 2.47–2.54 (m, 2H), 2.88–3.18 (m, 4H), 3.88 (s, 3H), 4.07 (td, J=12.9, 5.3 Hz, 1H), 4.64–4.68 (m, 2H), 4.86 (dd, J=12.0, 5.7 Hz, 1H), 5.61–5.65 (m, 1H), 6.65 (m, 1H), 6.74 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.9, 26.2, 28.0, 28.5, 31.7, 32.1, 35.1, 37.4, 37.6, 50.7, 50.8, 51.6, 51.7, 56.77, 56.81, 75.0, 75.1, 80.7, 81.0, 89.6, 95.4, 95.7, 115.69, 115.73, 120.2, 123.6, 123.7, 127.2, 127.3, 143.4, 145.07, 145.12, 153.7, 153.8, 169.4, 169.5, 205.9; IR (KBr) 1730, 1610 cm^{-1}; MS (EI, 70 eV) m/z calcd for $C_{22}H_{22}NO_7Cl_3^+$: 517.0462, found 517.0462; 519, 517, 459, 457.

4,5α-Epoxy-14-hydroxy-3-methoxy-17-[(2,2,2-trichloroethoxy)carbonyl]morphinan-6-one (12). A mixture of crude **11** (3.0 g), concentrated HCl (35 mL), and acetonitrile (30 mL) was heated at 80 °C for 2 days and evaporated. The residue was treated with saturated aqueous $NaHCO_3$ to pH 9.0, and extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated to give **12** (2.4 g, 90.0%): mp 182 °C; R_f 0.19 (CH_3OH:CH_2Cl_2, 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 1.54–1.65 (m, 1H), 1.69 (td, J=14.1, 3.4 Hz, 1H), 1.90 (m, 1H), 2.28 (dt, J=14.5, 2.8 Hz, 1H), 2.51–2.55 (m, 1H), 2.88–3.16 (m, 4H), 3.89 (s, 3H), 4.11–4.13 (m, 1H), 4.51–4.54 (m, 1H), 4.65 (s, 1H), 4.73–4.82 (m, 2H), 6.36 (d, J=8.4 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.6, 30.9, 31.4, 31.9, 35.6, 37.9, 50.3, 56.8, 57.3, 57.8, 70.8, 71.2, 75.3, 76.3, 89.9, 95.5, 115.5, 120.0, 123.4, 128.4, 143.4, 145.1, 155.2, 207.4; IR (KBr) 3542, 1714, 1639, 1614 cm^{-1}; MS (EI, 70 eV) m/z calcd

for $C_{20}H_{20}NO_6Cl_3^+$: 475.0356, found 475.0346; 477, 475, 459, 457.

4,5α-Epoxy-14-hydroxy-3-methoxymorphinan-6-piro-2′-1′,3′-dioxolane (13). To a stirred solution of **12** (584 mg, 1.22 mmol) in 90% acetic acid (60 mL) at room temperature was added in portions activated zinc powder (385 mg, 6.0 mmol). The resultant reaction mixture was further stirred for 24 h, filtered and washed with 90% acetic acid (30 mL) and H_2O (30 mL). The combined filtrate and washings were evaporated, treated with saturated aqueous $NaHCO_3$ to pH 9.0 and extracted with $CHCl_3$:2-propanol, 4:1. The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated to give noroxycodone (200 mg; mp 284–286 °C; R_f 0.26 (CH_3OH:CH_2Cl_2, 1:20); IR (KBr) 3300, 1720 cm^{-1}; MS (EI, 70 eV) *m/z* 301, 216.

A solution of noroxycodone (200 mg, 0.66 mmol), ethylene glycol (0.25 mL, 0.66 mmol) and *p*-toluenesulfonic acid (138 mg, 0.72 mmol) in dry toluene (50 mL) was refulxed with a Dean-Stark trap for 36 h. The cooled reaction mixture was neutralized with saturated aqueous $NaHCO_3$, and evaporated to remove toluene. The residue was treated with saturated aqueous $NaHCO_3$ to pH 9.0 and extracted with $CHCl_3$:2-propanol, 4:1. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give **13** (208 mg, 50% from **12**): mp 298–300 °C; R_f 0.5 (CH_3OH:CH_2Cl_2, 1:6); ^1H NMR (300 MHz, $CDCl_3$) δ 1.40–1.65 (m, 3H), 2.09–2.28 (m, 3H), 2.68–2.70 (m, 2H), 2.91–3.09 (m, 2H), 3.09 (s, 1H), 3.79 (q, J=6.2 Hz, 1H), 3.85 (s, 3H), 3.90 (q, J=6.5 Hz, 1H), 4.02 (q, J=6.4 Hz, 1H), 4.16 (q, J=6.7 Hz, 1H), 4.48 (s, 1H), 6.59 (d, J=8.1 Hz, 1H), 6.73 (d, J=8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.0, 30.9, 32.8, 37.5, 48.4, 56.6, 57.7, 66.0, 66.3, 69.8, 93.5, 108.6, 113.9, 118.2, 125.3, 130.8, 142.4, 146.3; IR (KBr) 3370, 3325 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{19}H_{23}NO_5^+$: 345.1576, found 345.1572; 345 (M^+), 99 (base).

17-(Cubylcarbonyl)-4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-spiro-2′-1′,3′-dioxolane (14). To a solution of cubanecarboxylic acid[12] (58 mg, 0.39 mmol) and 3 drops of DMF in CH_2Cl_2 (4 mL) was added slowly oxalyl chloride (0.37 mL, 4.31 mmol). The mixture was stirred at room temperature for 1 h and evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (2 mL) and cannulated into a stirred solution of **13** (149 mg, 0.43 mmol) and triethylamine (0.33 mL, 2.4 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was warmed to room temperature and evaporated. The residue was chromatographed (MPLC, silica gel; 6% MeOH in CH_2Cl_2) to give **14** (173 mg, 93%) as a white solid: mp 156–158 °C; R_f 0.33 (CH_3OH:CH_2Cl_2, 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 1.41–1.68 (m, 3H), 2.10–2.24 (m, 2H), 2.34 (td, J=12.4, 5.4 Hz, 1H), 2.80–3.12 (m, 3H), 3.27 (s, 1H), 3.77–4.33 (m, 14H), 4.47 and 4.54 (s, 1H), 4.81 and 4.83 (s, 1H), 6.58 and 6.60 (d, J=8.0 Hz, 1H), 6.75 and 6.76 (d, J=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.5, 29.0, 29.4, 31.3, 32.8, 34.8, 38.9, 44.3, 46.5, 46.8, 48.2, 49.3, 49.9, 54.1, 56.5, 58.2, 58.3, 64.9, 66.2, 66.3, 70.2, 70.4, 92.7, 93.2, 108.3, 108.5, 114.1, 114.2, 118.6, 123.5, 124.2, 130.1, 142.6, 146.3, 172.0; IR (KBr) 3400, 1610 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{28}H_{29}NO_6^+$: 475.1995, found 475.1993; 475 (M^+), 99 (base).

17-(Cubylmethyl)-4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-spiro-2′-1′-3′-dioxolane (15). To a stirred solution of **14** (173 mg, 0.36 mmol) in dry THF (10 mL) under nitrogen was added a suspension of $LiAH_4$ (11 mg, 2.9 mmol) in dry THF (15 mL). After being stirred for 1.5 h, the mixture was treated with 25% H_2O in THF (2 mL), followed by 40% NaOH (0.5 mL). The resultant mixture was stirred for 15 min, dried over $MgSO_4$, filtered and the filtrate evaporated to give **15** (154 mg, 92%): mp 196 °C; R_f 0.46 (CH_3OH:CH_2Cl_2, 1:40); ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.53 (m, 4H), 2.21–2.36 (m, 4H), 2.60 (dd, J=18.2, 5.7 Hz, 1H), 2.69–2.70 (m, 3H), 3.11 (d, J=18.2 Hz, 1H), 3.75–3.84 (m, 5H), 3.84 (s, 3H), 3.87–3.92 (m, 3H), 4.00–4.18 (m, 2H), 4.17 (q, J=5.6 Hz, 1H), 4.54 (s, 1H), 6.63 (d, J=8.2 Hz, 1H), 6.76 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 28.9, 29.2, 31.2, 44.57, 44.60, 47.8, 48.1, 48.3, 56.0, 56.6, 57.3, 62.9, 64.9, 66.4, 70.0, 93.8, 108.9, 113.8, 118.1, 124.9, 130.9, 142.2, 146.2; IR (KBr) 3400 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{28}H_{31}NO_5^+$: 461.2202, found 461.2206; 461 (M^+), 358, 99 (base).

17-(Cubylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one (2). To a solution of **15** (43 mg, 0.094 mmol) in 1,2-dichloroethane (6.0 mL) under nitrogen was added a 0.1 M solution of BBr_3-$S(CH_3)_2$ in 1,2-dichloroethane (4.7 mL). The mixture was refluxed for 5 h, then cooled, treated with H_2O, and extracted with $CHCl_3$:2-propanol, 4:1. The organic layer was washed with saturated aqueous $NaHCO_3$, and extracted with 1 N NaOH (10 mL × 2). The aqueous layer was treated with 6 N HCl to pH, 9.0, and then extracted with $CHCl_3$:2-propanol, 4:1. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed (MPLC, silica gel; 0.6% MeOH in CH_2Cl_2) to give **2** (15 mg, 38%) as a solid: mp 216–218 °C (dec. HCl salt); HPLC area%: 98.3% (RP-18, CH_3OH:H_2O:H_3PO_4, 450:550:1, 229 nm); R_f 0.4 (CH_3OH:CH_2Cl_2, 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–1.65 (m, 2H), 1.84 (ddd, J=13.4, 4.9, 3.0 Hz, 1H), 2.22–2.31 (m, 2H), 2.38–2.46 (m, 2H), 2.56 (dd, J=18.4, 6.0 Hz, 1H), 2.74 (s, 2H), 2.79 (d, J=5.9 Hz, 1H), 3.02 (dt, J=14.5, 5.1 Hz, 1H), 3.14 (d, J=18.5 Hz, 1H), 3.85 (m, 3H), 3.93 (m, 3H), 4.03 (m, 1H), 4.64 (s, 1H), 6.59 (d, J=8.2 Hz, 1H), 6.71 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 30.6, 31.4, 36.2, 44.3, 44.6, 48.1, 48.3, 50.8, 56.1, 57.2, 62.6, 70.4, 90.6, 118.1, 120.0, 125.3, 129.0, 138.9, 143.5, 210.1; IR (KBr) 3314, 1729 cm^{-1}; MS (EI, 70 eV) *m/z* calcd for $C_{25}H_{25}NO_4^+$: 403.1783, found 403.1785; 403 (M^+), 115 (base).

Crystallography. Crystals of **1**·HCl were grown from 95% EtOH: $C_{25}H_{25}NO_3$·HCl, FW=428.8, monoclinic,

space group $P2_1$, a=11.424(2), b=19.521(2), c=9.478(2) Å, b=89.95(2)°, Z=4, V=2113.6(4) Å3, Density(calcd)=1.348 g cm^{-3}, m=0.213 mm^{-1}, l=0.71073 Å, F(000)=884. Intensities were collected for a crystal of dimensions 0.58×0.7×0.8 mm on a Siemens R 3 m/v diffractometer. The structure was solved by direct method. All non-hydrogen atoms were refined with anisotropic thermal parameters, where all hydrogen atoms were refined isotropically and included in the structure factor calculation. The final agreement factors were R 0.0584 and Rw 0.0721 for 548 parameters and 8836 observed reflections.

Biological assays

Opioid receptor binding assay. Brain membranes were prepared from male Hartley guinea-pigs, and binding was performed by literature procedures[17] with modification. The following labeled ligands were used: 1.0 nM [^{3}H]DAMGO (μ-binding); 2.0 nM [^{3}H]ethylketocyclazocine with 500 nM DADLE and 500 nM DAMGO (κ-binding); 2.0 nM [^{3}H]DADLE with 100 nM morphiceptin (δ-binding); nonspecific binding was determined with 1 μ DAMGO (μ-binding), 10 μ naloxone and U-50,488 (κ-binding), and 10 μ naloxone and DADLE (δ-binding). Radioactivity was determined by scintillation counting. Protein was determined by the method of Lowry et al.[18] The IC_{50}'s and K_i's were determined with the Mcpherson program,[19] which is a modification of the LIGAND program originally written by Munson and Rodbard.[20]

Stimulated guinea-pig ileum bioassay. This assay was performed by a previously described method.[21]

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