



Pergamon

# Novel Ligands for the Opioid Receptors: Synthesis and Structure–Activity Relationships among 5'-Aryl and 5'-Heteroaryl 17-Cyclopropylmethyl-4,5 $\alpha$ -epoxypyrido[2',3':6,7]morphinans

Subramaniam Ananthan,<sup>a,\*</sup> Naveen K. Khare,<sup>a</sup> Surendra K. Saini,<sup>a</sup> Peg Davis,<sup>b</sup> Christina M. Dersch,<sup>c</sup> Frank Porreca<sup>b</sup> and Richard B. Rothman<sup>c</sup>

<sup>a</sup>Organic Chemistry Department, Southern Research Institute, Birmingham, AL 35255, USA

<sup>b</sup>Department of Pharmacology, The University of Arizona Health Sciences Center, Tucson, AZ 85724, USA

<sup>c</sup>Clinical Psychopharmacology Section, IRP, National Institute on Drug Abuse, Baltimore, MD 21224, USA

Received 14 February 2003; accepted 9 April 2003

**Abstract**—A series of pyridomorphinans possessing an aryl (**10a–s**) or heteroaryl (**11a–h**) substituent at the 5'-position of the pyridine ring of 17-cyclopropylmethyl-4,5 $\alpha$ -epoxypyrido[2',3':6,7]morphinan was synthesized and evaluated for binding and functional activity at the opioid  $\delta$ ,  $\mu$ , and  $\kappa$  receptors. All of these pyridomorphinans bound with higher affinity at the  $\delta$  site than at  $\mu$  or  $\kappa$  sites. The binding data on isomeric compounds revealed that there exists greater bulk tolerance for substituents placed at the *o*-position of the phenyl ring than at *m*- or *p*-positions. Among the ligands examined, the 2-chlorophenyl (**10l**), 2-nitrophenyl (**10n**), 2-pyridyl (**11a**), and 4-quinolinyl (**11g**) compounds bound to the  $\delta$  receptor with subnanomolar affinity. Compound **10c** with the *p*-tolyl substituent displayed the highest  $\mu/\delta$  selectivity (ratio = 42) whereas compound **10l** with the 2-chlorophenyl substituent displayed the highest  $\kappa/\delta$  selectivity (ratio = 23). At 10  $\mu$ M concentration, the in vitro functional activity determined using [<sup>35</sup>S]GTP- $\gamma$ -S binding assays showed that all of the compounds were antagonists devoid of any significant agonist activity at the  $\delta$ ,  $\mu$ , and  $\kappa$  receptors. Antagonist potency determinations of three selected ligands revealed that the *p*-tolyl compound **10c** is a potent  $\delta$  selective antagonist. In the [<sup>35</sup>S]GTP- $\gamma$ -S assays this compound had a functional antagonist  $K_i$  value of 0.2, 4.52, and 7.62 nM at the  $\delta$ ,  $\mu$ , and  $\kappa$  receptors, respectively. In the smooth muscle assays **10c** displayed  $\delta$  antagonist potency with a  $K_e$  value of 0.88 nM. As an antagonist, it was 70-fold more potent at the  $\delta$  receptors in the MVD than at the  $\mu$  receptors in the GPI. The in vitro  $\delta$  antagonist profile of this pyridomorphinan **10c** resembles that of the widely used  $\delta$  selective antagonist ligand naltrindole.

© 2003 Elsevier Ltd. All rights reserved.

## Introduction

In the search for novel ligands for the opioid  $\mu$ ,  $\delta$ , and  $\kappa$  receptors, several compounds derived from naltrexone have gained prominence due to the differential binding profile and varying intrinsic functional activity that they possess.<sup>1–3</sup> A variety of such ligands arising by the fusion of a heteroaromatic system to the C-ring of the morphinan framework present in naltrexone have been explored recently. Some of the heterocyclic systems that have been annulated to the morphinan unit include indole,<sup>4–10</sup> benzofuran,<sup>8,11</sup> pyrazole,<sup>12</sup> pyrrole,<sup>13,14</sup> pyrimidine<sup>12,15,16</sup> and pyridine<sup>16</sup> represented by structures

**1–6** (Chart 1). Among these, the indolomorphinan naltrindole (**2**, NTI) has been used widely as a biochemical and pharmacological tool due to its selective antagonist properties at the opioid  $\delta$  receptors. Studies with  $\delta$  antagonists have indicated that  $\delta$  antagonist ligands may be useful for the treatment of cocaine,<sup>17</sup> methamphetamine<sup>18</sup> and alcohol<sup>19</sup> abuse, and their immunosuppressive effects may lead to useful treatments for preventing rejection in organ transplants.<sup>20</sup> In addition, it has been shown that  $\delta$  antagonists can prevent the development of tolerance and dependence to  $\mu$  agonists such as morphine without affecting  $\mu$  mediated antinociception.<sup>21,22</sup>

In our earlier investigations on C-ring heteroaryl fused morphinans of the type **5** and **6**, we discovered that the pyridine compounds **6**, in general, bind with high

\*Corresponding author. Tel.: +1-205-581-2822; fax: +1-205-581-2726; e-mail: ananthan@sri.org

affinity to the opioid receptors and that the introduction of a phenyl group at the 5'-position on the pyridine ring (**7**) enhances  $\delta$  antagonist potency. The introduction of a chlorine substituent at the *para* position of the phenyl ring gave a compound (**8**) that displayed a mixed  $\delta$  antagonist/ $\mu$  agonist profile of activity.<sup>16</sup> Moreover, our recent studies have revealed that while non-aromatic substituents such as cyano, carbethoxy, nitro, and amino groups at the 5'-position of the pyridomorphinan did not provide any significant improvements in  $\delta$  binding affinity or  $\delta$  antagonist potency, the placement of the heteroaromatic 1-pyrrolyl moiety (**9**) enhanced the  $\delta$  binding affinity,  $\delta$  binding selectivity and  $\delta$  antagonist potency of the parent compound (**6**,  $R=R_1=R_2=H$ ).<sup>23</sup> In view of these findings, it was of interest to explore ligands possessing various aromatic groups at the 5'-position of the pyridomorphinan unit to study their effect on binding and agonist or antagonist intrinsic activity at the opioid  $\delta$ ,  $\mu$ , and  $\kappa$  receptors. In this paper, we describe the synthesis and biological activity of a series of such aryl and heteroaryl analogues **10a–s** and **11a–h** (Chart 2).

## Chemistry

The target compounds **10c,d,n**, and **11a–h** were synthesized from naltrexone (**12**) or its hydrochloride by condensation with appropriate 2-aryl- or 2-heteroarylmalondialdehydes (**13**) and ammonium acetate in refluxing acetic acid as depicted in Scheme 1. The target compounds **10a,b,e,f–j,l,m,p–s** were obtained through a similar pyridine annulation method using 2-aryl-3-

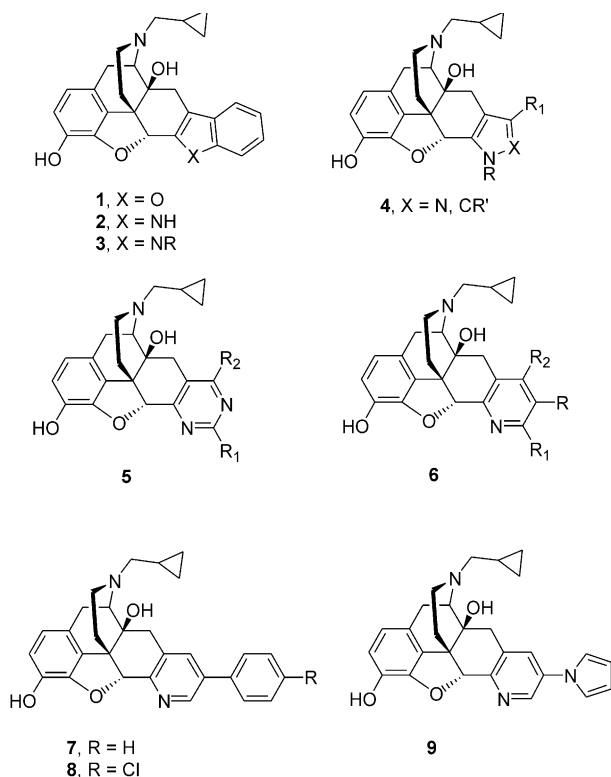
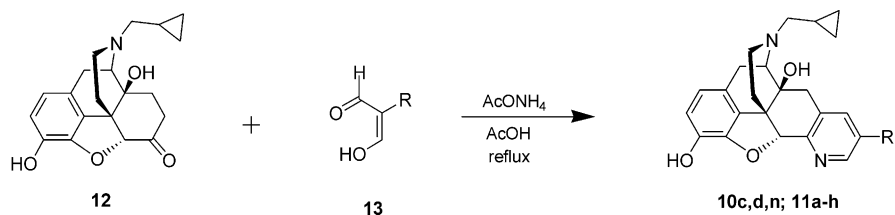


Chart 1.



Scheme 1.

| No  | X                             | Y                             | Z                             |     |
|-----|-------------------------------|-------------------------------|-------------------------------|-----|
| 10a | H                             | H                             | F                             | 11a |
| 10b | H                             | H                             | Br                            | 11b |
| 10c | H                             | H                             | CH <sub>3</sub>               | 11c |
| 10d | H                             | H                             | CH <sub>3</sub> O             | 11d |
| 10e | H                             | H                             | CF <sub>3</sub>               | 11e |
| 10f | H                             | H                             | NO <sub>2</sub>               | 11f |
| 10g | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | 11g |
| 10h | H                             | Cl                            | H                             | 11h |
| 10i | H                             | Br                            | H                             |     |
| 10j | H                             | CF <sub>3</sub>               | H                             |     |
| 10k | H                             | C <sub>6</sub> H <sub>5</sub> | H                             |     |
| 10l | Cl                            | H                             | H                             |     |
| 10m | Br                            | H                             | H                             |     |
| 10n | NO <sub>2</sub>               | H                             | H                             |     |
| 10o | C <sub>6</sub> H <sub>5</sub> | H                             | H                             |     |
| 10p | H                             | Cl                            | Cl                            |     |
| 10q | Cl                            | H                             | Cl                            |     |
| 10r | H                             | CH=CH-CH=CH                   |                               |     |
| 10s | CH=CH-CH=CH                   | H                             |                               |     |

Chart 2.

(dimethylamino)acroleins (**15**) as malondialdehyde equivalents. The dimethylaminoacrolein intermediates were prepared by Vilsmeier-Haack decarboxylative diformylation of arylacetic acids according to the general procedure of Arnold (Scheme 2).<sup>24,25</sup> While the 4-biphenyl compound **10g**, was obtained by the ring synthesis reaction, the 3-biphenyl and 2-biphenyl isomers **10k** and **10o** were obtained from the corresponding bromo compounds **10i** and **10m** by the Suzuki coupling reaction with phenylboronic acid (Scheme 3).<sup>26,27</sup>

## Results and Discussion

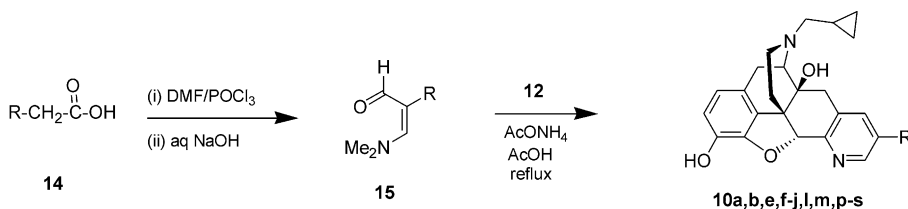
### Opioid receptor binding

The binding affinities of the target compounds for the opioid  $\delta$  and  $\mu$  receptors were determined by inhibition of binding of [<sup>3</sup>H]DADLE<sup>28</sup> and [<sup>3</sup>H]DAMGO<sup>29</sup> to rat brain membranes. The affinities of the compounds for the  $\kappa$  receptors were determined by inhibition of binding of [<sup>3</sup>H]U69,593<sup>30</sup> to guinea pig brain membranes using previously reported procedures.<sup>7,16</sup> The  $\delta$ ,  $\mu$ , and  $\kappa$  opioid receptor binding affinities along with binding selectivity ratios for the target compounds are given in Table 1. The affinity data for compounds **7** and **8** are included in the table for comparison.

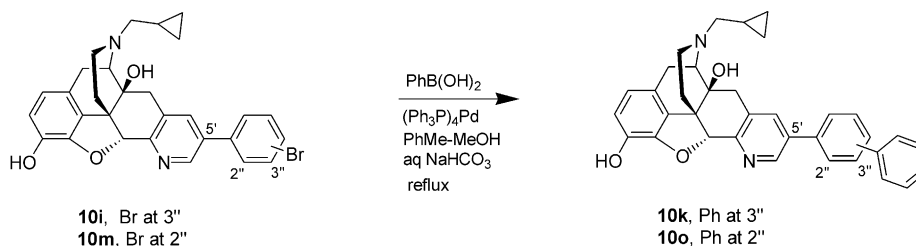
All of the pyridomorphinans examined in the present study bind with high affinity to the opioid  $\delta$  receptor with  $K_i$  values ranging from 0.51–14.0 nM. All of the compounds display higher affinity at the  $\delta$  site in comparison to their affinity at the  $\mu$  and  $\kappa$  sites. Thus the pyridomorphinans are  $\delta$  selective ligands with  $\delta$  over  $\mu$  selectivity ranging from 1.3 to 42 and  $\delta$  over  $\kappa$  selectivity ranging from 1.3 to 23. Among the compounds studied, the *o*-nitrophenyl compound **10n** and the 2-pyridyl analogue **11a** displayed the highest binding affinity at the  $\delta$  site ( $K_i$  = 0.51 nM). Compounds **10a–g** together with **8** represent a series of analogues possessing electron donating, electron withdrawing, and bulky groups at the *p*-position on the exocyclic phenyl ring of the parent compound **7**. The observed rank order of poten-

cies among the unsubstituted and *p*-substituted analogues at the  $\delta$  site is: H > CH<sub>3</sub> > F, Cl > CF<sub>3</sub> > NO<sub>2</sub> > OCH<sub>3</sub> > Br > C<sub>6</sub>H<sub>5</sub>. The fact that all of the *p*-substituted compounds displayed lower affinity than the unsubstituted compound suggests the presence of steric inhibition for binding at the  $\delta$  receptors. Compounds possessing the electron donating methoxy group (**10d**) as well as the electron withdrawing nitro group (**10f**) displayed nearly equal affinity (3.8 and 5.0 nM). The observed order of affinity does not correlate with the lipophilicity substituent constants ( $\pi$  values) for the *p*-substituents. However, there appears to be a rough correlation of decreasing binding affinity of these analogues with increasing molar refractivity, which is a function of molecular size and polarizability of the group.<sup>31</sup> The calculated molar refractivity (CMR) values for these analogues increase in the following order of the *p*-substituent: H (12.88) < F (12.90) < CH<sub>3</sub> (13.30) < Cl (13.37) < CF<sub>3</sub> (13.39) < NO<sub>2</sub> (13.49) < CH<sub>3</sub>O (13.50) < Br (13.60) < C<sub>6</sub>H<sub>5</sub> (15.39).<sup>32</sup>

The *m*-substituted compounds **10h–k** bind with nearly equal affinity to the  $\delta$  receptor and the binding affinities of the chloro- (**10h**), bromo- (**10i**) and trifluoromethyl (**10j**) compounds are similar to those of the *p*-isomers **8**, **10b**, and **10e**, respectively. Interestingly, the *o*-substituted chloro- (**10l**), bromo- (**10m**), nitro- (**10n**) and phenyl- (**10o**) compounds all display higher affinities than their *m*- or *p*-substituted counterparts. Therefore it appears that the  $\delta$  receptor binding site has greater tolerance for substituents at the *o*-position of the 5'-phenyl group than at the *m*- or *p*-position, as illustrated by the affinities of the *o*-, *m*-, and *p*-biphenyl isomers **10o** ( $K_i$  = 2.8 nM), **10k** ( $K_i$  = 4.8 nM) and **10g** ( $K_i$  = 14.0 nM), respectively. Of the two isomeric dichlorophenyl analogues **10p** and **10q**, the 2,4-dichloro isomer **10q** binds with higher affinity ( $K_i$  = 3.5 nM) than the 3,4-dichloro isomer **10p** ( $K_i$  = 7.0 nM). Indeed even among the 1-naphthyl- and 2-naphthyl isomers, it is the 1-naphthyl isomer **10s** that displays higher affinity ( $K_i$  = 3.6 nM) than the 2-naphthyl isomer **10r** ( $K_i$  = 7.1 nM). Differences in steric tolerance at the binding site or subtle differences in the electronic or conformational properties



Scheme 2.



Scheme 3.

**Table 1.** Binding affinities of the pyridomorphinans **10a–s** and **11a–h** in rodent brain membranes

| Compd                     | 5'-Substituent          | $K_i$ (nM) $\pm$ SEM |                 |                 | Selectivity ratio |                 |
|---------------------------|-------------------------|----------------------|-----------------|-----------------|-------------------|-----------------|
|                           |                         | $\delta^a$           | $\mu^b$         | $\kappa^c$      | $\mu/\delta$      | $\kappa/\delta$ |
| <b>10a</b>                | 4-Fluorophenyl          | 2.2 $\pm$ 0.05       | 43.0 $\pm$ 4.0  | 12.0 $\pm$ 1    | 19                | 5.4             |
| <b>10b</b>                | 4-Bromophenyl           | 6.6 $\pm$ 0.9        | 143 $\pm$ 9.0   | 17.0 $\pm$ 1.1  | 21                | 2.5             |
| <b>10c</b>                | 4-Methylphenyl          | 1.2 $\pm$ 0.08       | 51.0 $\pm$ 4.5  | 10.6 $\pm$ 0.6  | 42                | 8.8             |
| <b>10d</b>                | 4-Methoxyphenyl         | 5.0 $\pm$ 0.8        | 29.0 $\pm$ 1.1  | 9.0 $\pm$ 0.3   | 5.8               | 1.8             |
| <b>10e</b>                | 4-Trifluoromethylphenyl | 2.7 $\pm$ 0.11       | 84.0 $\pm$ 14   | 14.0 $\pm$ 1    | 31                | 5.1             |
| <b>10f</b>                | 4-Nitrophenyl           | 3.8 $\pm$ 0.49       | 95.0 $\pm$ 4.6  | 9.3 $\pm$ 1.2   | 25                | 2.4             |
| <b>10g</b>                | 4-Biphenyl              | 14.0 $\pm$ 0.8       | 81.0 $\pm$ 3    | 19.0 $\pm$ 2    | 5.7               | 1.3             |
| <b>10h</b>                | 3-Chlorophenyl          | 3.4 $\pm$ 0.26       | 34.0 $\pm$ 0.9  | 25.0 $\pm$ 1.5  | 10                | 7.3             |
| <b>10i</b>                | 3-Bromophenyl           | 6.3 $\pm$ 0.43       | 34.0 $\pm$ 1.7  | 25.0 $\pm$ 0.8  | 5.4               | 3.9             |
| <b>10j</b>                | 3-Trifluoromethylphenyl | 2.4 $\pm$ 0.20       | 61.0 $\pm$ 7    | 24.0 $\pm$ 1.5  | 25                | 10              |
| <b>10k</b>                | 3-Biphenyl              | 4.8 $\pm$ 0.33       | 30.0 $\pm$ 0.9  | 31.0 $\pm$ 0.7  | 6.2               | 6.4             |
| <b>10l</b>                | 2-Chlorophenyl          | 0.62 $\pm$ 0.07      | 9.5 $\pm$ 0.5   | 14.6 $\pm$ 2    | 15                | 23              |
| <b>10m</b>                | 2-Bromophenyl           | 1.1 $\pm$ 0.11       | 6.3 $\pm$ 0.39  | 16.0 $\pm$ 1    | 5.7               | 14              |
| <b>10n</b>                | 2-Nitrophenyl           | 0.51 $\pm$ 0.04      | 1.9 $\pm$ 0.01  | 2.2 $\pm$ 0.2   | 3.7               | 4.3             |
| <b>10o</b>                | 2-Biphenyl              | 2.8 $\pm$ 0.3        | 3.8 $\pm$ 0.02  | 12.0 $\pm$ 0.5  | 1.3               | 4.2             |
| <b>10p</b>                | 3,4-Dichlorophenyl      | 7.0 $\pm$ 0.4        | 27.0 $\pm$ 0.81 | 13.7 $\pm$ 1.2  | 3.8               | 1.9             |
| <b>10q</b>                | 2,4-Dichlorophenyl      | 3.5 $\pm$ 0.3        | 24.0 $\pm$ 1.2  | 18.0 $\pm$ 1.6  | 6.8               | 5.1             |
| <b>10r</b>                | 2-Naphthyl              | 7.1 $\pm$ 0.6        | 99.0 $\pm$ 6    | 18.0 $\pm$ 1.5  | 13                | 2.5             |
| <b>10s</b>                | 1-Naphthyl              | 3.6 $\pm$ 0.26       | 10.4 $\pm$ 0.67 | 9.4 $\pm$ 0.96  | 2.8               | 2.6             |
| <b>11a</b>                | 2-Pyridyl               | 0.51 $\pm$ 0.04      | 15.0 $\pm$ 1.4  | 2.9 $\pm$ 0.17  | 29                | 5.6             |
| <b>11b</b>                | 4-Pyridyl               | 2.3 $\pm$ 0.08       | 32.0 $\pm$ 2    | 7.9 $\pm$ 0.6   | 13                | 3.4             |
| <b>11c</b>                | 4-Pyrimidinyl           | 2.0 $\pm$ 0.3        | 24.0 $\pm$ 2    | 8.5 $\pm$ 0.4   | 12                | 4.2             |
| <b>11d</b>                | 2-Pyrazinyl             | 2.9 $\pm$ 0.09       | 16.0 $\pm$ 0.7  | 9.7 $\pm$ 1.3   | 5.5               | 3.3             |
| <b>11e</b>                | 2-Benzoxazolyl          | 3.3 $\pm$ 0.28       | 59.0 $\pm$ 5.0  | 6.0 $\pm$ 0.54  | 17                | 1.8             |
| <b>11f</b>                | 2-Quinoliny             | 2.2 $\pm$ 0.08       | 23.5 $\pm$ 1.2  | 9.2 $\pm$ 1.9   | 10                | 4.1             |
| <b>11g</b>                | 4-Quinoliny             | 0.92 $\pm$ 0.06      | 5.5 $\pm$ 0.4   | 3.6 $\pm$ 0.4   | 5.9               | 3.9             |
| <b>11h</b>                | 2-Quinoxaliny           | 2.3 $\pm$ 0.10       | 9.0 $\pm$ 0.7   | 6.3 $\pm$ 0.7   | 3.9               | 2.7             |
| <b>7<sup>d</sup></b>      | Phenyl                  | 0.87 $\pm$ 0.07      | 13.5 $\pm$ 1.0  | 17.6 $\pm$ 1.6  | 16                | 20              |
| <b>8<sup>d</sup></b>      | 4-Chlorophenyl          | 2.2 $\pm$ 0.16       | 51.0 $\pm$ 8.0  | 20.0 $\pm$ 1.04 | 16                | 9.1             |
| <b>2, NTI<sup>d</sup></b> |                         | 0.41 $\pm$ 0.09      | 99.0 $\pm$ 4.6  | 35.8 $\pm$ 4.0  | 241               | 87              |

<sup>a</sup>Displacement of [<sup>3</sup>H]DADLE (1.3–2.0 nM) in rat brain membranes using 100 nM DAMGO to block binding to  $\mu$  sites.<sup>b</sup>Displacement of [<sup>3</sup>H]DAMGO (1.4–3.0 nM) in rat brain membranes.<sup>c</sup>Displacement of [<sup>3</sup>H]U69,593 (1.2–2.2 nM) in guinea pig brain membranes.<sup>d</sup>Data from ref 16.

of the ligands caused by the *o*-substituent may contribute to the observed *ortho* effect. Interestingly, a comparison of the affinity data for the analogues possessing the three substituents Cl, Br, and C<sub>6</sub>H<sub>5</sub> at the *o*-, *m*- and *p*-positions on the phenyl ring reveals that the *o*-substituted isomers bind with higher affinity than the *m*- and *p*-substituted isomers at all three receptor types, the  $\delta$ ,  $\mu$ , and  $\kappa$  sites.

The heteroaryl analogues **11a–h** bind to the  $\delta$  site with affinities in the narrow range of 0.51–3.3 nM. Of the two pyridine isomers, the 2-pyridyl compound **11a** displayed higher affinity than the 4-pyridyl analogue **11b**. Interestingly, among the ligands examined, the 2-pyridyl compound **11a** and the 2-nitrophenyl compound **10f** possessing electron deficient aromatic systems turned out to be the ligands with the highest affinity for the  $\delta$  receptor.

With regard to selectivity in binding among the  $\delta$ ,  $\mu$ , and  $\kappa$  receptors, compounds **10a–c**, **10e**, **10j**, **11a** and **11e** displayed  $\mu/\delta$  selectivity ratios higher than that of the unsubstituted phenyl compound **8**. Among the compounds studied, the *p*-tolyl compound **10c** displayed the highest  $\delta$  over  $\mu$  selectivity (42-fold). This enhanced selectivity of **10c** is primarily due to its relatively diminished affinity at the  $\mu$  site. With the exception of **10l** and

**10m** all of the compounds displayed  $\kappa/\delta$  selectivity ratios of  $\leq 10$ .

### In vitro functional assays

To determine the agonist or antagonist nature of the ligands, all of the target compounds were evaluated in the in vitro [<sup>35</sup>S]GTP- $\gamma$ -S binding assays using guinea pig caudate membranes. The agonist activity was determined by measuring the stimulation of [<sup>35</sup>S]GTP- $\gamma$ -S binding by the compounds in the absence and presence of fixed concentrations of selective antagonists: CTAP to block  $\mu$  receptors, TIPP to block  $\delta$  receptors, and nor-BNI to block  $\kappa$  receptors, as described previously.<sup>33</sup> The antagonist properties of the compounds were determined by measuring the test compound's ability to inhibit stimulation of [<sup>35</sup>S]GTP- $\gamma$ -S binding produced by the selective agonists: SNC-80 for  $\delta$  receptor, DAMGO for  $\mu$  receptor, and U69,593 for  $\kappa$  receptor.<sup>34</sup> The compounds were initially evaluated at a concentration of 10  $\mu$ M. Even at this high concentration none of the compounds displayed any significant agonist activity at the  $\delta$ ,  $\mu$ , or  $\kappa$  receptors. At the same 10  $\mu$ M concentration, all of the compounds displayed antagonist effects at the  $\delta$ ,  $\mu$ , and  $\kappa$  receptors (84–100%). On the basis of the high  $\mu/\delta$  selectivity ratios in the binding assays, compound **10c**, from the 5'-aryl series and com-

**Table 2.** Antagonist activity of **10c**, **11a** and **11e** on agonist stimulated [<sup>35</sup>S]GTP-γ-S binding in guinea pig caudate membranes

| Compd                       | Apparent functional $K_i$ (nM±SD) |                    |                      | $\mu/\delta$ | $\kappa/\delta$ |
|-----------------------------|-----------------------------------|--------------------|----------------------|--------------|-----------------|
|                             | $\delta$                          | $\mu$              | $\kappa$             |              |                 |
|                             | SNC-80 <sup>a</sup>               | DAMGO <sup>b</sup> | U69,593 <sup>c</sup> |              |                 |
| <b>10c</b>                  | 0.20±0.01                         | 4.52±0.36          | 7.62±0.58            | 23           | 38              |
| <b>11a</b>                  | 0.27±0.03                         | 1.59±0.12          | 2.27±0.14            | 5.8          | 8.4             |
| <b>11e</b>                  | 0.62±0.03                         | 5.44±0.57          | 6.32±0.38            | 8.8          | 10              |
| <b>8</b>                    | 0.18±0.01                         | 7.80±0.42          | 11.18±0.44           | 43           | 62              |
| <b>2</b> , <sup>d</sup> NTI | 0.062±0.006                       | 3.21±0.20          | 8.85±0.8             | 52           | 143             |

<sup>a</sup>Apparent functional  $K_i$  (versus 10 μM SNC-80, an agonist selective for  $\delta$  opioid receptor).

<sup>b</sup>Apparent functional  $K_i$  (versus 10 μM DAMGO, an agonist selective for  $\mu$  opioid receptor).

<sup>c</sup>Apparent functional  $K_i$  (versus 10 μM U69,593, an agonist selective for  $\kappa$  opioid receptor).

<sup>d</sup>Data from ref 34 included for comparison.

pounds **11a** and **11e** from the 5'-heteroaryl series were selected as interesting compounds. The antagonist potencies of these compounds were determined at the  $\delta$ ,  $\mu$ , and  $\kappa$  receptors and the results are presented in Table 2. The three compounds examined displayed potent antagonist activity at the  $\delta$  receptors with functional  $K_i$  values <0.62 nM. Among the three compounds, the *p*-tolyl analogue **10c** was the most potent ( $K_i$ =0.2 nM). In this assay **10c** displayed 1/3 the antagonist potency of the standard  $\delta$  antagonist ligand NTI (**2**). The antagonist potencies of these compounds at the  $\mu$  and  $\kappa$  sites were lower than their potencies at the  $\delta$  site.

The functional activity profile of **10c**, **11a** and **11e** were also determined in the electrically stimulated mouse vas deferens (MVD) and guinea pig ileum (GPI) smooth muscle preparations as described previously.<sup>16,35,36</sup> The opioid antagonist and agonist potencies of the target compounds in the MVD and GPI are listed in Table 3. At 1 μM concentration, the selected ligands displayed no or weak agonist activity both in the MVD and the GPI. All three compounds displayed potent antagonist activity in the MVD and the GPI. Their antagonist potencies at the  $\delta$  site in the MVD were greater than their antagonist potencies at the  $\mu$  site in the GPI. While pyridine **11a** and benzoxazole **11e** were moderately potent as  $\delta$  antagonists ( $K_e$  for **11a**=4.8 nM,  $K_e$  for **11e**=4.0 nM), the *p*-tolyl compound **10c** turned out to be the most potent and selective  $\delta$  antagonist ligand ( $K_e$ =0.88 nM, GPI/MVD selectivity ratio = 70).

While the antagonist potency data from GTP-γ-S assays and the smooth muscle assays are qualitatively similar, there are quantitative differences between them. For example, the order of  $\delta$  antagonist potencies for the three compounds in the GTP-γ-S assays (**10c**  $\cong$  **11a** > **11e**) and the MVD smooth muscle assays (**10c** > **11e**  $\cong$  **11a**) are different. Similar differences are discernable between the GTP-γ-S assays for the  $\mu$  receptor and the potencies observed in the GPI. The reasons for these differences between the GTP-γ-S assays and smooth muscle assays are not known but could reflect the differences in the assay systems (brain tissue versus smooth muscles) used in assessing the opioid receptor function.

**Table 3.** Agonist and antagonist potencies of **10c**, **11a** and **11e** in the MVD and GPI smooth muscle preparations

| Compd                       | Agonist activity (%) |                     | Antagonist activity         |                             | Ratio |
|-----------------------------|----------------------|---------------------|-----------------------------|-----------------------------|-------|
|                             | MVD <sup>a</sup>     | GPI <sup>b</sup>    | MVD $K_e$ (nM) <sup>c</sup> | GPI $K_e$ (nM) <sup>d</sup> |       |
| <b>10c</b>                  | 17                   | 0                   | 0.88±0.28                   | 62±19                       | 70    |
| <b>11a</b>                  | 0                    | 0                   | 4.8±0.4                     | 36±7                        | 7     |
| <b>11e</b>                  | 0                    | 19                  | 4.0±0.7                     | 41±6                        | 10    |
| <b>8</b> <sup>e</sup>       | 21                   | 163±22 <sup>f</sup> | 0.91±0.48                   | — <sup>g</sup>              | —     |
| <b>2</b> , NTI <sup>e</sup> | 16                   | 18                  | 0.53±0.18                   | 43±3                        | 81    |

<sup>a</sup>Inhibition of electrically stimulated contraction at a concentration of 1 μM in the MVD.

<sup>b</sup>Inhibition of electrically stimulated contraction at a concentration of 1 μM in the GPI.

<sup>c</sup>Determined using DPDPE as the  $\delta$  selective agonist ligand.

<sup>d</sup>Determined using PL-017 as the  $\mu$  selective agonist ligand.

<sup>e</sup>Data included for comparison.

<sup>f</sup>Agonist IC<sub>50</sub> value in nM.

<sup>g</sup>The agonist effects precluded the determination of antagonist effects.

Among the compounds examined in the present study, the profile of **10c** stands out in that it displayed highest  $\delta$  selectivity in the binding assay, in the GTP-γ-S assay, and in the smooth muscle assay. The  $\delta$  antagonist potency of **10c** in the MVD is similar to that of the chloro analogue **8** and that of NTI (**2**) with antagonist  $K_i$  values in the subnanomolar range (Table 3). Whereas **8** displayed  $\mu$  agonist activity in the GPI, **10c** is devoid of such  $\mu$  agonist action. The profile of **10c** therefore more closely resembles the profile of NTI than that of the mixed  $\delta$  antagonist/ $\mu$  agonist **8**.

## Summary and Conclusions

A series of novel pyridomorphinan ligands possessing various substituted aryl and heteroaryl systems at the 5'-position of the pyridine ring was prepared and evaluated for binding at the opioid  $\delta$ ,  $\mu$ , and  $\kappa$  receptors. All of the pyridomorphinans displayed higher affinity for binding at the  $\delta$  site than at  $\mu$  or  $\kappa$  sites. The observed structure–affinity relationship indicates that sterically bulky groups are tolerated better at the *o*-position of the 5'-phenyl ring than they are at the *m*- or *p*-positions. Functional assays in vitro indicated that all of the ligands possess an antagonist profile of activity at the  $\delta$ ,  $\mu$ , and  $\kappa$  receptors and are devoid of any significant agonist activity. Among the three compounds evaluated for antagonist potencies in vitro in smooth muscle assays, the *p*-tolyl compound **10c** displayed antagonist potency and selectivity nearly equal to that of the standard ligand naltrindole. Further studies are needed to ascertain the potential usefulness of these pyridomorphinans as biochemical and pharmacological tools and as drugs.

## Experimental

### General methods

Melting points were determined in open capillary tubes with a Mel-Temp melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were recorded on a



Nicolet 300NB spectrometer operating at 300.635 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Spectral assignments were supported by proton decoupling. Mass spectra were recorded on a Varian MAT 311A double-focusing mass spectrometer in the fast atom bombardment (FAB) mode or on a Bruker Biotof II in electrospray ionization (ESI) mode. Elemental analyses were performed by Atlantic Microlab, Inc. (Atlanta, GA, USA) or by the Spectroscopic and Analytical Laboratory of Southern Research Institute. Thin layer chromatography (TLC) was performed on Analtech silica gel GF 0.25 mm plates. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Yields are of purified compounds and were not optimized. Naltrexone and naltrexone hydrochloride were obtained from Mallinckrodt. 2-Aryl- and 2-heteroarylmalondialdehydes were purchased from Acros Organics. All other reagents were obtained from Aldrich.

**Procedure A: condensation of naltrexone or naltrexone hydrochloride with 2-aryl- or 2-heteroarylmalondialdehydes**

A solution of naltrexone (0.341 g, 1.0 mmol) or naltrexone hydrochloride (0.378 g, 1.0 mmol), the malondialdehyde (1.2 mmol) and ammonium acetate (0.154 g, 2.0 mmol) in AcOH (10 mL) was heated to reflux in an oil bath at 130–135 °C under an argon atmosphere until TLC analysis of the reaction mixture using EtOAc/cyclohexane/Et<sub>3</sub>N (1:1:0.02) as the solvent system indicated complete disappearance of the ketone (approximately 20 h). The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was treated with water and the pH of the mixture was adjusted to 8 with saturated aqueous NaHCO<sub>3</sub> solution. The solid that separated was collected by filtration and dried. The crude product was chromatographed over a column of silica, using CHCl<sub>3</sub>–MeOH (98:2) or CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH (99:0.5:0.5) as the eluent to obtain the desired product.

**Procedure B: condensation of naltrexone or naltrexone hydrochloride with 2-aryl-3-(dimethylamino)acroleins**

To a solution of naltrexone (1.02 g, 3.0 mmol) or naltrexone hydrochloride (1.13 g, 3.0 mmol) and ammonium acetate (0.925 g, 12.0 mmol) in glacial acetic acid (20 mL) was added the 2-aryl-3-(dimethylamino)acrolein (6.0 mmol) and the mixture was stirred under reflux at 135–140 °C in an oil bath until TLC indicated completion of reaction (approximately 20 h). The solvent was removed under reduced pressure and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The layers were separated, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined extracts were washed with saturated aqueous NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and the solvent was removed under reduced pressure. The crude product thus obtained was purified by chromatography over a column of silica using CHCl<sub>3</sub>–MeOH (98:2) or CHCl<sub>3</sub>–MeOH–

NH<sub>4</sub>OH (99:0.5:0.5) as the eluent to obtain the desired product.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-fluorophenyl)pyrido[2',3':6,7]morphinan (10a).** This compound was obtained from naltrexone hydrochloride and 3-(dimethylamino)-2-(4-fluorophenyl)acrolein<sup>37</sup> by procedure B. Yield 38%, mp 164–166 °C; TLC, *R<sub>f</sub>* 0.3 (CH<sub>2</sub>Cl<sub>2</sub>–MeOH–NH<sub>4</sub>OH, 96.5:3:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.14–0.19 and 0.55–0.60 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.87–0.91 (m, 1H, cyclopropyl CH), 1.81–1.85 (m, 1H, C-15H), 2.35–2.46 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.63–2.81 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.17 (d, 1H, *J* = 18.6 Hz, C-10H), 3.31 (d, 1H, *J* = 6.3 Hz, C-9H), 4.60–5.50 (broad hump, 2H, C-3 OH, C-14 OH), 5.59 (s, 1H, C-5H), 6.58 (d, 1H, *J* = 8.1 Hz, C-2H), 6.69 (d, 1H, *J* = 8.1 Hz, C-1H), 7.09–7.15 (m, 2H, C-3'' H, C-5'' H), 7.40–7.46 (m, 3H, C-4' H, C-2'' H, C-6'' H), 8.65 (d, 1H, *J* = 2.1 Hz, C-6' H); MS *m/z* 471 (MH)<sup>+</sup>. Anal. calcd for C<sub>29</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>3</sub>·0.1H<sub>2</sub>O: C, 73.74; H, 5.80; N, 5.93. Found: C, 73.54; H, 5.68; N, 5.79.

**5'-(4-Bromophenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-pyrido[2',3':6,7]morphinan (10b).** This compound was obtained from naltrexone hydrochloride and 2-(4-bromophenyl)-3-(dimethylamino)acrolein<sup>38</sup> by procedure B. Yield 36%, mp 148–150 °C; TLC, *R<sub>f</sub>* 0.3 (CH<sub>2</sub>Cl<sub>2</sub>–MeOH–NH<sub>4</sub>OH, 95:5:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.14–0.19 and 0.54–0.60 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.87–0.91 (m, 1H, cyclopropyl CH), 1.81–1.84 (m, 1H, C-15H), 2.34–2.49 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.63–2.80 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.17 (d, 1H, *J* = 18.6 Hz, C-10H), 3.30 (d, 1H, *J* = 6.4 Hz, C-9H), 4.60–5.50 (broad hump, 2H, C-3 OH, C-14 OH), 5.58 (s, 1H, C-5H), 6.59 (d, 1H, *J* = 8.1 Hz, C-2H), 6.68 (d, 1H, *J* = 8.1 Hz, C-1H), 7.31–7.35 (m, 2H, C-3'' H, C-5'' H), 7.45 (d, 1H, *J* = 2.1 Hz, C-4' H), 7.54–7.56 (m, 2H, C-2'' H, C-6'' H), 8.65 (d, 1H, *J* = 2.1 Hz, C-6' H); MS *m/z* 531 (MH)<sup>+</sup>. Anal. calcd for C<sub>29</sub>H<sub>27</sub>BrN<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C, 63.39; H, 5.32; N, 5.10. Found: C, 63.31; H, 4.96; N, 5.02.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-methylphenyl)pyrido[2',3':6,7]morphinan (10c).** This compound was obtained from naltrexone hydrochloride and 2-(4-methylphenyl)malondialdehyde by procedure A. Yield 29%, mp 150–152 °C; TLC, *R<sub>f</sub>* 0.6 (CHCl<sub>3</sub>–MeOH, 9:1); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  0.12–0.19 and 0.48–0.54 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.82–0.94 (m, 1H, cyclopropyl CH), 1.56–1.62 (m, 1H, C-15H), 2.14–2.46 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.34 (s, 3H, CH<sub>3</sub>), 2.58–2.74 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.03–3.13 (m, 1H, C-10H), 3.21–3.28 (m, 1H, C-9H), 4.80 (s, 1H, C-14 OH), 5.35 (s, 1H, C-5H), 6.52 (app s, 2H, C-1H, C-2H), 7.29 (app d, 2H, *J* = 8.0 Hz, C-3'' H, C-5'' H), 7.64 (app d, 2H, *J* = 8.0 Hz, C-2'' H, C-6'' H), 7.70 (d, 1H, *J* = 2.2 Hz, C-4' H), 8.76 (d, 1H, *J* = 2.2 Hz, C-6' H), 9.03 (s, 1H, C-3 OH), MS *m/z* 515 (MH)<sup>+</sup>. Anal. calcd for C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>·0.4CHCl<sub>3</sub>: C, 70.99; H, 5.96; N, 5.45. Found: C, 70.72; H, 5.94; N, 5.22.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-methoxyphenyl)pyrido[2',3':6,7]morphinan (10d).** This compound was obtained from naltrexone hydrochloride and 2-(4-methoxyphenyl)malondialdehyde by procedure A. Yield 69%, mp 172–174 °C; TLC,  $R_f$  0.2 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 97:2.5:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.12–0.18 and 0.47–0.53 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.57–1.61 (m, 1H, C-15H), 2.19–2.41 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.60–2.72 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.06–3.12 (m, 1H, C-10H), 3.24–3.26 (m, 1H, C-9H), 3.79 (s, 3H, –OCH<sub>3</sub>), 4.80 (s, 1H, C-14 OH), 5.34 (s, 1H, C-5H), 6.51 (app s, 2H, C-1H, C-2H), 7.02–7.06 (m, 2H, C-3'' H, C-5'' H), 7.61–7.65 (m, 2H, C-2'' H, C-6'' H), 7.68 (d, 1H,  $J$ =2.2 Hz, C-4' H), 8.75 (d, 1H,  $J$ =2.2 Hz, C-6' H), 9.04 (s, 1H, C-3 OH); MS  $m/z$  483 (MH)<sup>+</sup>. Anal. calcd for C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>·0.2H<sub>2</sub>O: C, 74.11; H, 6.30; N, 5.76. Found: C, 74.22; H, 6.32; N, 5.77.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-[4-(trifluoromethyl)phenyl]pyrido[2',3':6,7]morphinan (10e).** This compound was obtained from naltrexone hydrochloride and 3-(dimethylamino)-2-[4-(trifluoromethyl)phenyl]acrolein<sup>38</sup> by procedure B. Yield 27%, mp 158–160 °C; TLC,  $R_f$  0.3 (CH<sub>2</sub>Cl<sub>2</sub>–MeOH–NH<sub>4</sub>OH, 96.5:3:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.15–0.19 and 0.55–0.61 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.85–0.92 (m, 1H, cyclopropyl CH), 1.83–1.86 (m, 1H, C-15H), 2.36–2.51 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.66–2.84 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.18 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.32 (d, 1H,  $J$ =6.3 Hz, C-9H), 5.59 (s, 1H, C-5H), 6.59 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.69 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.52 (d, 1H,  $J$ =2.2 Hz, C-4' H), 7.60 (d, 2H,  $J$ =8.1 Hz, C-3'' H, C-5'' H), 7.69 (d, 2H,  $J$ =8.1 Hz, C-2'' H, C-6'' H), 8.72 (dd, 1H,  $J$ =2.2, 0.6 Hz, C-6' H); MS  $m/z$  521 (MH)<sup>+</sup>. Anal. calcd C<sub>30</sub>H<sub>27</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>·0.3H<sub>2</sub>O: C, 68.51; H, 5.29; N, 5.33. Found: C, 68.29; H, 5.22; N, 5.30.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-nitrophenyl)pyrido[2',3':6,7]morphinan (10f).** This compound was obtained from naltrexone and 3-(dimethylamino)-2-(4-nitrophenyl)acrolein<sup>39</sup> by procedure B. Yield 48%, mp 146–150 °C; TLC,  $R_f$  0.25 (CH<sub>2</sub>Cl<sub>2</sub>–MeOH–NH<sub>4</sub>OH, 97:2.5:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.15–0.20 and 0.55–0.61 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.86–0.91 (m, 1H, cyclopropyl CH), 1.83–1.86 (m, 1H, C-15H), 2.36–2.51 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.67–2.85 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.19 (d, 1H,  $J$ =18.7 Hz, C-10H), 3.33 (d, 1H,  $J$ =6.1 Hz, C-9H), 4.8–5.4 (broad hump, 2H, C-3 OH, C-14 OH), 5.59 (s, 1H, C-5H), 6.60 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.68 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.57 (d, 1H,  $J$ =2.0 Hz, C-4' H), 7.67 (d, 2H,  $J$ =9.0 Hz, C-2'' H, C-6'' H), 8.31 (d, 2H,  $J$ =9.0 Hz, C-3'' H, C-5'' H), 8.77 (d, 1H,  $J$ =2.0 Hz, C-6' H); MS  $m/z$  498 (MH)<sup>+</sup>. Anal. calcd for C<sub>29</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub>·0.5H<sub>2</sub>O: C, 68.76; H, 5.57; N, 8.30. Found: C, 68.88; H, 5.73; N, 8.83.

**5'-(4-Biphenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy pyrido[2',3':6,7]morphinan (10g).** Dimethylformamide (6.45 g, 88.2 mmol) was

added dropwise to phosphorous oxychloride (10.0 g, 65.2 mmole) with efficient stirring while maintaining the temperature of the reaction mixture below 30 °C with external cooling. After the addition was complete, the mixture was stirred for 5 min and then a solution of 4-biphenylacetic acid (5.20 g, 24.5 mmol) in dimethylformamide (15.0 mL) was added dropwise over a period of 5 min. The resulting solution was stirred at 70 °C for 18 h and then poured onto ice. The solution was neutralized by the addition of anhydrous K<sub>2</sub>CO<sub>3</sub> and then made strongly basic by addition of 50% aqueous NaOH maintaining the temperature of the mixture at 50 °C. After the evolution of dimethylamine ceased, the mixture was cooled and the solid obtained was collected by filtration, washed with water and dried to yield 5.71 g (75%) of 2-(4-biphenyl)-3-(dimethylamino)acrolein: mp 154–156 °C; TLC,  $R_f$  0.66 (CHCl<sub>3</sub>–MeOH, 9.5:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.88 [br s, 6H, N(CH<sub>3</sub>)<sub>2</sub>], 6.85 (br s, 1H, =CH–N), 7.21–7.24 (m, 2H, C-2' H, C-6' H), 7.42–7.44 (m, 3H, C-4'' H, C-3'' H, C-5'' H), 7.59–7.61 (m, 4H, C-3' H, C-5' H, C-2'' H, C-6'' H), 9.13 (s, 1H, CHO); MS  $m/z$  252 (MH)<sup>+</sup>. Anal. calcd for C<sub>17</sub>H<sub>17</sub>NO·0.2H<sub>2</sub>O: C, 80.10; H, 6.88; N, 5.49. Found: C, 80.16; H, 6.90; N, 5.74.

The enaminoaldehyde thus obtained was reacted with naltrexone hydrochloride according to the procedure B to obtain the title compound **10g**: Yield 38%, mp 158–160 °C; TLC,  $R_f$  0.3 (CH<sub>2</sub>Cl<sub>2</sub>–MeOH–NH<sub>4</sub>OH, 96.5:3:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.15–0.19 and 0.55–0.61 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.88–0.92 (m, 1H, cyclopropyl CH), 1.83–1.86 (m, 1H, C-15H), 2.36–2.51 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.66–2.85 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.18 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.32 (d, 1H,  $J$ =6.4 Hz, C-9H), 4.80–5.60 (broad hump, 2H, C-3 OH, C-14 OH), 5.61 (s, 1H, C-5H), 6.59 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.69 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.36–7.68 (m, 10H, C-4' H, biphenyl-H), 8.79 (d, 1H,  $J$ =2.2 Hz, C-6' H); MS  $m/z$  529 (MH)<sup>+</sup>. Anal. calcd for C<sub>35</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>: C, 79.52; H, 6.10; N, 5.30. Found: C, 79.73; H, 6.11; N, 5.50.

**5'-(3-Chlorophenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy pyrido[2',3':6,7]morphinan (10h).** This compound was obtained from naltrexone and 2-(3-chlorophenyl)-3-(dimethylamino)acrolein<sup>40</sup> by procedure B. Yield 33%, mp 132–136 °C; TLC,  $R_f$  0.2 (CH<sub>2</sub>Cl<sub>2</sub>–MeOH–NH<sub>4</sub>OH, 97:2.5:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.15–0.20 and 0.55–0.61 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.82–1.86 (m, 1H, C-15H), 2.35–2.48 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.64–2.83 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.17 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.31 (d, 1H,  $J$ =6.4 Hz, C-9H), 5.59 (s, 1H, C-5H), 6.59 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.68 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.34–7.39 (m, 3H, C-4'' H, C-5'' H, C-6'' H), 7.46–7.49 (m, 2H, C-4' H, C-2'' H), 8.67 (d, 1H,  $J$ =2.0 Hz, C-6' H); MS  $m/z$  487 (MH)<sup>+</sup>. Anal. calcd for C<sub>29</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>3</sub>·0.1H<sub>2</sub>O: C, 71.26; H, 5.61; N, 5.73. Found: C, 70.72; H, 5.45; N, 6.01.

**5'-(3-Bromophenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy pyrido[2',3':6,7]morph-**

**inan (10i).** Reaction of 3-bromophenylacetic acid (5.0 g, 23.35 mmol) with Vilsmeier reagent prepared from dimethylformamide (6.12 g, 83.7 mmol) and phosphorous oxychloride (9.97 g, 65.0 mmol) according to the procedure described under **10g** gave 5.11 g (86%) of 2-(3-bromophenyl)-3-(dimethylamino)acrolein: mp 78–80 °C; TLC,  $R_f$  0.6 ( $\text{CHCl}_3$ –MeOH, 9.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.88 [br s, 6H,  $\text{N}(\text{CH}_3)_2$ ], 6.85 (br s, 1H,  $=\text{CH}-\text{N}$ ), 7.11–7.16 (m, 1H, C-4' H), 7.18–7.30 (m, 1H, C-5' H), 7.32–7.34 (m, 1H, C-2' H), 7.36–7.41 (m, 1H, C-6' H), 9.07 (s, 1H, CHO); MS  $m/z$  254 ( $\text{MH}^+$ ). Anal. calcd for  $\text{C}_{11}\text{H}_{12}\text{BrNO}$ : C, 51.99; H, 4.76; N, 5.51. Found: C, 51.98; H, 4.67; N, 5.59.

The above enaminoaldehyde was reacted with naltrexone hydrochloride as described in procedure B to obtain **10i**: Yield 32%, mp 158–160 °C; TLC,  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 96.5:3:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.19 and 0.55–0.61 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.83–1.87 (m, 1H, C-15H), 2.35–2.48 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.64–2.82 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.17 (d, 1H,  $J=18.6$  Hz, C-10H), 3.31 (d, 1H,  $J=6.4$  Hz, C-9H), 5.59 (s, 1H, C-5H), 6.59 (d, 1H,  $J=8.1$  Hz, C-2H), 6.68 (d, 1H,  $J=8.1$  Hz, C-1H), 7.28–7.53 (m, 4H, C-4' H, C-4'' H, C-5'' H, C-6'' H), 7.63–7.64 (m, 1H, C-2'' H), 8.69 (d, 1H,  $J=2.0$  Hz, C-6' H); MS  $m/z$  531 ( $\text{MH}^+$ ). Anal. calcd for  $\text{C}_{29}\text{H}_{27}\text{BrN}_2\text{O}_3 \cdot 0.25\text{H}_2\text{O}$ : C, 64.99; H, 5.17; N, 5.23. Found: C, 64.75; H, 5.08; N, 5.13.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-[3-(trifluoromethyl)phenyl]pyrido[2',3':6,7]morphinan (10j).** This compound was obtained from naltrexone hydrochloride and 3-(dimethylamino)-2-[3-(trifluoromethyl)phenyl]acrolein<sup>37</sup> by procedure B. Yield 22%, mp 146–148 °C; TLC,  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 96.5:3:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.19 and 0.55–0.61 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.88–0.92 (m, 1H, cyclopropyl CH), 1.82–1.86 (m, 1H, C-15H), 2.32–2.51 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.67–2.83 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.18 (d, 1H,  $J=18.6$  Hz, C-10H), 3.32 (d, 1H,  $J=6.3$  Hz, C-9H), 5.59 (s, 1H, C-5H), 6.59 (d, 1H,  $J=8.1$  Hz, C-2H), 6.69 (d, 1H,  $J=8.1$  Hz, C-1H), 7.53–7.73 (m, 5H, C-4' H, C-2'' H, C-4'' H, C-5'' H, C-6'' H), 8.71 (d, 1H,  $J=2.2$  Hz, C-6' H); MS  $m/z$  521 ( $\text{MH}^+$ ). Anal. calcd for  $\text{C}_{30}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_3 \cdot 0.2\text{H}_2\text{O}$ : C, 68.75; H, 5.27; N, 5.34. Found: C, 68.54; H, 5.42; N, 5.15.

**5'-(3-Biphenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-pyrido[2',3':6,7]morphinan (10k).** Under an atmosphere of argon, 0.113 g (0.098 mmol) of tetrakis(triphenylphosphine)palladium was added to a solution of **10i** (1.04 g, 1.96 mmol) in toluene (42 mL) and the mixture was stirred at room temperature for 30 min. A solution of phenylboronic acid (0.359 g, 2.94 mmol) in EtOH (11.6 mL) was then added. The resulting mixture was treated with saturated aqueous  $\text{NaHCO}_3$  (21 mL) and the biphasic reaction mixture was heated under reflux in an oil bath at 120 °C for 16 h. The reaction mixture was allowed to cool to room temperature and poured into saturated aqueous

$\text{NaCl}$  (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (40 mL). The organic extracts were combined, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and the filtrate was concentrated under reduced pressure. The crude product obtained was then purified by flash column chromatography over silica using  $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$  (98.5:1:0.5) as the eluent to obtain 0.7 g (68%) of **10k**: mp 162–164 °C; TLC,  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 96.5:3:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.19 and 0.55–0.61 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.83–1.86 (m, 1H, C-15H), 2.36–2.46 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.65–2.83 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.17 (d, 1H,  $J=18.7$  Hz, C-10H), 3.31 (d, 1H,  $J=6.2$  Hz, C-9H), 5.61 (s, 1H, C-5H), 6.58 (d, 1H,  $J=8.1$  Hz, C-2H), 6.69 (d, 1H,  $J=8.1$  Hz, C-1H), 7.38–7.70 (m, 10H, C-4' H, biphenyl-H), 8.76 (d, 1H,  $J=1.9$  Hz, C-6' H); MS  $m/z$  529 ( $\text{MH}^+$ ). Anal. calcd for  $\text{C}_{35}\text{H}_{32}\text{N}_2\text{O}_3 \cdot 0.1\text{H}_2\text{O}$ : C, 79.25; H, 6.12; N, 5.28. Found: C, 79.00; H, 5.98; N, 5.16.

**5'-(2-Chlorophenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-pyrido[2',3':6,7]morphinan (10l).** This compound was obtained from naltrexone and 2-(2-chlorophenyl)-3-(dimethylamino)acrolein<sup>38</sup> by procedure B. Yield 29%, mp 164–166 °C; TLC,  $R_f$  0.4 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.19 and 0.55–0.60 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.86–0.91 (m, 1H, cyclopropyl CH), 1.83–1.86 (m, 1H, C-15H), 2.36–2.47 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.64–2.84 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.17 (d, 1H,  $J=18.6$  Hz, C-10H), 3.31–3.33 (m, 1H, C-9H), 5.07–5.09 (br s, 2H, C-3 OH, C-14 OH), 5.61 (s, 1H, C-5H), 6.59 (d, 1H,  $J=8.1$  Hz, C-2H), 6.69 (d, 1H,  $J=8.1$  Hz, C-1H), 7.27–7.33 (m, 3H, C-4' H, C-3'' H, C-5'' H), 7.45–7.49 (m, 2H, C-4'' H, C-6'' H), 8.63 (dd, 1H,  $J=2.2, 0.7$  Hz, C-6' H); MS  $m/z$  487 ( $\text{MH}^+$ ). Anal. calcd for  $\text{C}_{29}\text{H}_{27}\text{ClN}_2\text{O}_3$ : C, 71.52; H, 5.59; N, 5.75. Found: C, 71.39; H, 5.71; N, 5.73.

**5'-(2-Bromophenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-pyrido[2',3':6,7]morphinan (10m).** Reaction of 2-bromophenylacetic acid (5.0 g, 23.35 mmol) with Vilsmeier reagent prepared from dimethylformamide (6.12 g, 83.7 mmol) and phosphorous oxychloride (9.97 g, 65.0 mmol) according to the procedure described under **10g** gave an oil after the treatment with aqueous NaOH. The product was extracted with  $\text{CH}_2\text{Cl}_2$ , washed with saturated aqueous NaCl, dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed under reduced pressure to obtain 5.43 g (92%) of 2-(2-bromophenyl)-3-(dimethylamino)acrolein as a viscous oil. TLC,  $R_f$  0.62 ( $\text{CHCl}_3$ –MeOH, 9.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.85 [br s, 6H,  $\text{N}(\text{CH}_3)_2$ ], 6.87 (br s, 1H,  $=\text{CH}-\text{N}$ ), 7.10–7.18 (m, 1H, C-4' H), 7.20–7.27 (m, 1H, C-5' H), 7.28–7.31 (m, 1H, C-3' H), 7.59 (dd, 1H,  $J=7.9, 0.9$  Hz, C-6' H), 9.07 (s, 1H, CHO); MS  $m/z$  254 ( $\text{MH}^+$ ). The crude product thus obtained was used in the next step without further purification.

The enaminoaldehyde obtained as described above was reacted with naltrexone hydrochloride according to procedure B to obtain **10m**: Yield 21%, mp 140–142 °C;



TLC,  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 96.5:3:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.14–0.19 and 0.55–0.60 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.90 (m, 1H, cyclopropyl CH), 1.83–1.86 (m, 1H, C-15H), 2.36–2.51 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.64–2.84 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.17 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.32 (d, 1H,  $J$ =6.4 Hz, C-9H), 4.90–5.50 (broad hump, 2H, C-3 OH, C-14 OH), 5.60 (s, 1H, C-5H), 6.60 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.70 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.20–7.28 (m, 2H, C-3'' H, C-5'' H), 7.34–7.39 (m, 1H, C-4'' H), 7.43 (d, 1H,  $J$ =2.1 Hz, C-4' H), 7.66 (dd, 1H,  $J$ =7.8, 1.0 Hz, C-6'' H), 8.60 (dd, 1H,  $J$ =2.1, 0.7 Hz, C-6' H); MS  $m/z$  531 (MH)<sup>+</sup>. Anal. calcd for  $\text{C}_{29}\text{H}_{27}\text{BrN}_2\text{O}_3\cdot 0.75\text{H}_2\text{O}$ : C, 63.92; H, 5.27; N, 5.14. Found: C, 63.53; H, 5.24; N, 5.27.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-nitrophenyl)pyrido[2',3':6,7]morphinan (10n).** This compound was obtained from naltrexone hydrochloride and 2-(2-nitrophenyl)malondialdehyde by procedure A. Yield 30%, mp 170–172 °C; TLC,  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.14–0.19 and 0.54–0.60 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.86–0.91 (m, 1H, cyclopropyl CH), 1.82–1.87 (m, 1H, C-15H), 2.36–2.50 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.60–2.83 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.14–3.20 (m, 1H, C-10H), 3.20–3.32 (m, 1H, C-9H), 4.96 (br s, 2H, C-3 OH, C-14 OH), 5.59 (s, 1H, C-5H), 6.60 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.70 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.31 (d, 1H,  $J$ =2.2 Hz, C-4' H), 7.37 (dd, 1H,  $J$ =7.6, 1.4 Hz, C-6'' H), 7.54 (dt, 1H,  $J$ =8.0, 7.6, 1.4 Hz, C-4'' H), 7.66 (dt, 1H,  $J$ =7.6, 7.7, 1.4 Hz, C-5'' H), 7.95 (dd, 1H,  $J$ =8.0, 1.4 Hz, C-3'' H), 8.52 (dd, 1H,  $J$ =2.2, 0.5 Hz, C-6' H); MS  $m/z$  498 (MH)<sup>+</sup>. Anal. calcd for  $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_5$ : C, 70.01; H, 5.47; N, 8.45. Found: C, 69.89; H, 5.74; N, 8.27.

**5'-(2-Biphenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-pyrido[2',3':6,7]morphinan (10o).** Compound **10m** (0.27 g, 0.51 mmol) was reacted with phenylboronic acid (0.094 g, 0.77 mmol) in the presence of tetrakis(triphenylphosphine)palladium (0.03 g, 0.026 mmol) in a biphasic medium containing toluene (10.8 mL), EtOH (3 mL) and saturated aqueous  $\text{NaHCO}_3$  (5.4 mL) as described for the preparation of **10k** to obtain 0.098 g (36%) of the title compound **10o**: mp 122–124 °C; TLC,  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 96.5:3:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.13–0.18 and 0.53–0.59 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.85–0.90 (m, 1H, cyclopropyl CH), 1.77–1.80 (m, 1H, C-15H), 2.32–2.74 (m, 8H, C-8  $\text{H}_2$ , C-10H, C-15H, C-16  $\text{H}_2$ , and  $\text{NCH}_2$ -cyclopropyl), 3.14 (d, 1H,  $J$ =18.7 Hz, C-10H), 3.25 (d, 1H,  $J$ =6.2 Hz, C-9H), 4.90 (br s, 2H, C-3 OH, C-14 OH), 5.50 (s, 1H, C-5H), 6.57 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.67 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.09–7.71 (m, 10H, C-4' H', biphenyl-H), 8.23 (d, 1H,  $J$ =2.2 Hz, C-6' H); MS  $m/z$  529 (MH)<sup>+</sup>. Anal. calcd for  $\text{C}_{35}\text{H}_{32}\text{N}_2\text{O}_3\cdot 0.4\text{H}_2\text{O}$ : C, 78.45; H, 6.17; N, 5.23. Found: C, 78.27; H, 6.27; N, 5.12.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(3,4-dichlorophenyl)pyrido[2',3':6,7]morphinan (10p).** This compound was obtained from naltrexone

one and 2-(3,4-dichlorophenyl)-3-(dimethylamino)acrolein<sup>25</sup> by procedure B. Yield 32%, mp 154–158 °C; TLC,  $R_f$  0.2 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.19 and 0.55–0.61 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.82–1.85 (m, 1H, C-15H), 2.35–2.46 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.65–2.83 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.17 (d, 1H,  $J$ =18.7 Hz, C-10H), 3.31 (d, 1H,  $J$ =6.4 Hz, C-9H), 4.6–5.8 (broad hump, 2H, C-3 OH, C-14 OH), 5.59 (s, 1H, C-5H), 6.59 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.67 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.33 (dd, 1H,  $J$ =8.4, 2.2 Hz, C-6'' H), 7.48 (d, 1H,  $J$ =2.1 Hz, C-4' H), 7.51 (d, 1H,  $J$ =8.4 Hz, C-5'' H), 7.58 (d, 1H,  $J$ =2.2 Hz, C-2'' H), 8.69 (d, 1H,  $J$ =2.1 Hz, C-6' H); MS  $m/z$  521 (MH)<sup>+</sup>. Anal. calcd for  $\text{C}_{29}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_3\cdot \text{H}_2\text{O}$ : C, 64.57; H, 5.23; N, 5.19. Found: C, 64.91; H, 4.92; N, 9.07.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2,4-dichlorophenyl)pyrido[2',3':6,7]morphinan (10q).** This compound was obtained from naltrexone and 2-(2,4-dichlorophenyl)-3-(dimethylamino)acrolein<sup>41</sup> by procedure B. Yield 27%, mp 145–148 °C; TLC,  $R_f$  0.2 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.14–0.19 and 0.55–0.60 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.83–1.87 (m, 1H, C-15H), 2.36–2.47 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.63–2.84 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.17 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.32 (d, 1H,  $J$ =6.4 Hz, C-9H), 4.90–5.30 (broad hump, 2H, C-3 OH, C-14 OH), 5.60 (s, 1H, C-5H), 6.59 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.69 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.22 (dd, 1H,  $J$ =8.2, 0.2 Hz, C-6'' H), 7.31 (dd, 1H,  $J$ =8.2, 2.1 Hz, C-5'' H), 7.43 (d, 1H,  $J$ =2.1 Hz, C-4' H), 7.49 (dd, 1H,  $J$ =2.1, 0.2 Hz, C-3'' H), 8.58 (dd, 1H,  $J$ =2.1, 0.6 Hz, C-6' H); MS  $m/z$  521 (MH)<sup>+</sup>. Anal. calcd for  $\text{C}_{29}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_3\cdot 0.5\text{H}_2\text{O}$ : C, 65.67; H, 5.13; N, 5.28. Found: 65.67; H, 4.93; N, 5.53.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-naphthyl)pyrido[2',3':6,7]morphinan (10r).** This compound was obtained from naltrexone and 3-(dimethylamino)-2-(2-naphthyl)acrolein<sup>25</sup> by procedure B. Yield 36%, mp 160–164 °C; TLC,  $R_f$  0.25 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.20 and 0.55–0.61 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.86–0.93 (m, 1H, cyclopropyl CH), 1.84–1.87 (m, 1H, C-15H), 2.36–2.49 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.67–2.87 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.18 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.33 (d, 1H,  $J$ =6.5 Hz, C-9H), 4.80–5.40 (broad hump, 2H, C-3 OH, C-14 OH), 5.63 (s, 1H, C-5H), 6.60 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.69 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.48–7.54 (m, 2H, C-5'' H, C-6'' H), 7.63 (m, 1H, C-10'' H), 7.64 (d, 1H,  $J$ =1.9 Hz, C-4' H), 7.84–7.97 (m, 4H, C-2'' H, C-4'' H, C-7'' H, C-9'' H), 8.87 (d, 1H,  $J$ =1.9 Hz, C-6' H); MS  $m/z$  503 (MH)<sup>+</sup>. Anal. calcd for  $\text{C}_{33}\text{H}_{30}\text{N}_2\text{O}_3$ : C, 78.87; H, 6.02; N, 5.57. Found: C, 78.58; H, 6.09; N, 5.48.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(1-naphthyl)pyrido[2',3':6,7]morphinan (10s).** This compound was obtained from naltrexone

and 3-(dimethylamino)-2-(1-naphthyl)acrolein<sup>42</sup> by procedure B. Yield 24%, mp 150–154 °C; TLC,  $R_f$  0.25 ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.15–0.20 and 0.55–0.61 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.94 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.86–1.89 (m, 1H, C-15H), 2.38–2.48 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.66–2.88 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.19 (d, 1H,  $J$ =18.6 Hz, C-10H), 3.34 (d, 1H,  $J$ =6.5 Hz, C-9H), 4.80–5.40 (broad hump, 2H, C-3 OH, C-14 OH), 5.67 (s, 1H, C-5H), 6.61 (d, 1H,  $J$ =8.1 Hz, C-2H), 6.72 (d, 1H,  $J$ =8.1 Hz, C-1H), 7.36 (dd, 1H,  $J$ =7.1, 1.2 Hz, C-10'' H), 7.41 (m, 4H, C-4' H, C-4'' H, C-5'' H, C-9'' H), 7.81 (dd, 1H,  $J$ =8.2, 0.7 Hz, C-6'' H), 7.87–7.92 (m, 2H, C-3'' H, C-8'' H), 8.68 (d, 1H,  $J$ =1.9 Hz, C-6' H); MS  $m/z$  503 ( $\text{MH}$ )<sup>+</sup>. Anal. calcd for  $\text{C}_{33}\text{H}_{30}\text{N}_2\text{O}_3 \cdot 0.5\text{H}_2\text{O}$ : C, 77.47; H, 6.11; N, 5.48. Found: C, 77.74; H, 6.03; N, 5.59.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-pyridinyl)pyrido[2',3':6,7]morphinan (11a).** This compound was obtained from naltrexone hydrochloride and 2-(2-pyridyl)malondialdehyde by procedure A. Yield 20%, mp 160–163 °C; TLC,  $R_f$  0.55 ( $\text{CHCl}_3$ –MeOH, 9:1);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  0.14–0.8 and 0.46–0.52 (2m, 4H cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.82–0.96 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.57–1.62 (m, 1H, C-15H), 2.18–2.25 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.61–2.74 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.05–3.14 (m, 1H, C-10H), 3.26 (d, 1H,  $J$ =6.2 Hz, C-9H), 4.78 (s, 1H, C-14H), 5.37 (s, 1H, C-5H), 6.52 (app s, 2H, C-1H, C-2H), 7.41 (ddd, 1H,  $J$ =7.4, 4.7, 1.1 Hz, C-5'' H), 7.92 (ddd, 1H,  $J$ =8.0, 7.4, 1.7 Hz, C-4'' H), 8.01 (ddd, 1H,  $J$ =8.0, 1.1, 0.8 Hz, C-3'' H), 8.10 (d, 1H,  $J$ =2.2 Hz, C-4' H), 8.69 (ddd, 1H,  $J$ =4.7, 1.7, 0.8 Hz, C-6'' H), 9.05 (s, 1H, C-3 OH), 9.18 (d, 1H,  $J$ =2.2 Hz, C-6' H), MS  $m/z$  454 ( $\text{MH}$ )<sup>+</sup>. Anal. calcd for  $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$ : C, 72.71; H, 6.10; N, 9.08. Found: C, 72.51; H, 6.13; N, 9.15.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-pyridinyl)pyrido[2',3':6,7]morphinan (11b).** This compound was obtained from naltrexone hydrochloride and 2-(4-pyridyl)malondialdehyde by procedure A. Yield 23%, mp 240–245 °C dec; TLC,  $R_f$  0.47 ( $\text{CHCl}_3$ –MeOH, 9:1);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  0.15–0.18 and 0.45–0.58 (2m, 4H cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.86–0.95 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.56–1.61 (m, 1H, C-15H), 2.19–2.42 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.65–2.72 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.06–3.14 (m, 1H, C-10H), 3.22–3.24 (m, 1H, C-9H), 4.85 (s, 1H, C-14 OH), 5.37 (s, 1H, C-5H), 6.52 (app s, 2H, C-1H, C-2H), 7.76 (dd, 2H,  $J$ =6.2, 1.5 Hz, C-3'' H, C-5'' H), 7.93 (d, 1H,  $J$ =2.0 Hz, C-4' H), 8.67 (dd, 2H,  $J$ =6.2, 1.5 Hz, C-2'' H, C-6'' H), 8.91 (d, 1H,  $J$ =2.0 Hz, C-6' H), 9.06 (s, 1H, C-3 OH), MS  $m/z$  454 ( $\text{MH}$ )<sup>+</sup>. Anal. calcd for  $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_3 \cdot 0.5\text{CHCl}_3$ : C, 66.70; H, 5.40; N, 8.19. Found: C, 67.04; H, 5.62; N, 8.08.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-pyrimidinyl)pyrido[2',3':6,7]morphinan (11c).** This compound was obtained from naltrexone hydrochloride and 2-(4-pyrimidinyl)malondialdehyde

by procedure A. Yield 33%, mp >260 °C dec; TLC,  $R_f$  0.35 ( $\text{CHCl}_3$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{DM}_2\text{SO}-d_6$ )  $\delta$  0.13–0.18 and 0.48–0.53 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.92 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.58–1.63 (m, 1H, C-15H), 2.20–2.41 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.61–2.73 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.07–3.13 (m, 1H, C-10H), 3.26–3.27 (m, 1H, C-9H), 4.83 (s, 1H, C-14 OH), 5.38 (s, 1H, C-5H), 6.52 (app s, 2H, C-1H, C-2H), 8.15 (dd, 1H,  $J$ =5.4, 1.4 Hz, C-5'' H), 8.24 (d, 1H,  $J$ =2.1 Hz, C-4' H), 8.91 (dd, 1H,  $J$ =5.4, 0.3 Hz, C-6'' H), 9.07 (s, 1H, C-3 OH), 9.27 (d, 1H,  $J$ =2.1 Hz, C-6' H), 9.28 (dd, 1H,  $J$ =1.4, 0.3 Hz, C-3'' H); MS  $m/z$  455 ( $\text{MH}$ )<sup>+</sup>. Anal. calcd for  $\text{C}_{27}\text{H}_{26}\text{N}_4\text{O}_3$ : C, 71.35; H, 5.77; N, 12.33. Found: C, 71.03; H, 5.76; N, 12.27.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-pyrazinyl)pyrido[2',3':6,7]morphinan (11d).** This compound was obtained from naltrexone hydrochloride and 2-(2-pyrazinyl)malondialdehyde by procedure A. Yield 24%, mp 178–180 °C; TLC,  $R_f$  0.2 ( $\text{CHCl}_3$ –MeOH– $\text{NH}_4\text{OH}$ , 97:2.5:0.5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.13–0.18 and 0.48–0.53 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.87–0.92 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.59–1.63 (m, 1H, C-15H), 2.17–2.41 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.61–2.72 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.07–3.13 (m, 1H, C-10H), 3.26–3.28 (m, 1H, C-9H), 4.83 (s, 1H, C-14 OH), 5.38 (s, 1H, C-5H), 6.52 (app s, 2H, C-1H, C-2H), 8.17 (d, 1H,  $J$ =2.1 Hz, C-4' H), 8.67 (d, 1H,  $J$ =2.5 Hz, C-3'' H), 8.75 (dd, 1H,  $J$ =2.5, 1.5 Hz, C-4'' H), 9.07 (s, 1H, C-3 OH), 9.21 (d, 1H,  $J$ =2.1 Hz, C-6' H), 9.29 (d, 1H,  $J$ =1.5 Hz, C-6'' H); MS  $m/z$  455 ( $\text{MH}$ )<sup>+</sup>. Anal. calcd for  $\text{C}_{27}\text{H}_{26}\text{N}_4\text{O}_3$ : C, 71.35; H, 5.77; N, 12.33. Found: C, 70.93; H, 5.91; N, 12.22.

**5'-(2-Benzoxazolyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-pyridinyl)pyrido[2',3':6,7]morphinan (11e).** This compound was obtained from naltrexone hydrochloride and 2-(2-benzoxazolyl)malondialdehyde by procedure A. Yield 28%, mp 155–159 °C; TLC,  $R_f$  0.36 (EtOAc);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  0.10–0.21 and 0.44–0.56 (m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.82–0.96 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.58–1.66 (m, 1H, C-15H), 2.14–2.48 (m, 4H, C-15H, C-16H, and  $\text{NCH}_2$ -cyclopropyl), 2.60–2.86 (m, 4H, C-8  $\text{H}_2$ , C-10H, C-16H), 3.07–3.14 (m, 1H, C-10H), 3.18–3.24 (m, 1H, C-9H), 4.86 (s, 1H, C-14 OH), 5.34 (s, 1H, C-5H), 6.54 (app s, 2H, C-1H, C-2H), 7.42–7.51 (m, 2H, C-5'' H, C-6'' H), 7.80–7.88 (m, 2H, C-4'' H, C-7'' H), 8.27 (d, 1H,  $J$ =2.1 Hz, C-4' H), 9.06 (s, 1H, C-3 OH), 9.28 (d, 1H,  $J$ =2.1 Hz, C-6' H), MS  $m/z$  494 ( $\text{MH}$ )<sup>+</sup>. Anal. calcd for  $\text{C}_{30}\text{H}_{27}\text{N}_3\text{O}_4 \cdot 0.5\text{H}_2\text{O}$ : C, 71.70; H, 5.62; N, 8.36. Found: C, 71.38; H, 5.48; N, 8.16.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-quinolinyl)pyrido[2',3':6,7]morphinan (11f).** This compound was obtained from naltrexone hydrochloride and 2-(2-quinolinyl)malondialdehyde by procedure A. Yield 22%, mp 158–160 °C; TLC,  $R_f$  0.57 ( $\text{CHCl}_3$ –MeOH, 9:1);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  0.10–0.20 and 0.45–0.56 (2m, 4H, cyclopropyl  $\text{CH}_2\text{CH}_2$ ), 0.84–0.96 (m, 1H, cyclopropyl  $\text{CH}$ ), 1.56–1.62 (m, 1H, C-

15H), 2.18–2.48 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.60–2.82 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.04–3.18 (m, 1H, C-10H), 3.22–3.24 (m, 1H, C-9H), 4.80 (s, 1H, C-14 OH), 5.48 (s, 1H, C-5H), 6.52 (app s, 2H, C-1H, C-2H), 7.60–7.76 (m, 1H, C-7'' H), 7.72–7.74 (m, 1H, C-6'' H), 8.02 (d, 1H, *J* = 6.8 Hz, C-5'' H), 8.08 (d, 1H, *J* = 8.2 Hz, C-8'' H), 8.17 (d, 1H, *J* = 8.7 Hz, 3'' H), 8.28 (d, 1H, *J* = 2.2 Hz, C-4' H), 8.52 (d, 1H, *J* = 8.7 Hz, C-4'' H), 9.03 (s, 1H, C-3 OH), 9.34 (d, 1H, *J* = 2.2 Hz, C-6' H), MS *m/z* 504 (MH)<sup>+</sup>. Anal. calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>·0.25H<sub>2</sub>O: C, 75.64; H, 5.85; N, 8.27. Found: C, 75.38; H, 5.87; N, 8.16.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(4-quinoliny)pyrido[2',3':6,7]morphinan (11g).** This compound was obtained from naltrexone hydrochloride and 2-(4-quinoliny)malondialdehyde by procedure A. Yield 26%, mp 240–242 °C; TLC, *R<sub>f</sub>* 0.2 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 97.5:2:0.5); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  0.15–0.17 and 0.48–0.53 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.87–0.92 (m, 1H, cyclopropyl CH), 1.61–1.65 (m, 1H, C-15H), 2.22–2.43 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.61–2.72 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.08–3.14 (m, 1H, C-10H), 3.27 (d, 1H, *J* = 6.0 Hz, C-9H), 4.87 (s, 1H, C-14 OH), 5.43 (s, 1H, C-5H), 6.55 (app s, 2H, C-1H, C-2H), 7.52 (d, 1H, *J* = 4.4 Hz, C-2'' H), 7.58–7.64 (m, 1H, C-8'' H), 7.74 (d, 1H, *J* = 2.1 Hz, C-4' H), 7.79–7.84 (m, 2H, C-7'' H, C-9'' H), 8.10–8.14 (m, 1H, C-6'' H), 8.68 (d, 1H, *J* = 2.1 Hz, C-6' H), 8.97 (d, 1H, *J* = 4.4 Hz, C-3'' H), 9.11 (s, 1H, C-3 OH); MS *m/z* 504 (MH)<sup>+</sup>. Anal. calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>·0.1H<sub>2</sub>O: C, 76.05; H, 5.82; N, 8.31. Found: C, 75.84; H, 6.02; N, 8.18.

**17-(Cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 $\alpha$ -epoxy-5'-(2-quinoxaliny)pyrido[2',3':6,7]morphinan (11h).** This compound was obtained from naltrexone hydrochloride and 2-(2-quinoxaliny)malondialdehyde by procedure A. Yield 23%, mp 212–214 °C; TLC, *R<sub>f</sub>* 0.25 (CHCl<sub>3</sub>–MeOH–NH<sub>4</sub>OH, 97.5:2:0.5); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.16–0.21 and 0.55–0.61 (2m, 4H, cyclopropyl CH<sub>2</sub>CH<sub>2</sub>), 0.86–0.93 (m, 1H, cyclopropyl CH), 1.86–1.89 (m, 1H, C-15H), 2.38–2.52 (m, 4H, C-15H, C-16H, and NCH<sub>2</sub>-cyclopropyl), 2.65–2.92 (m, 4H, C-8 H<sub>2</sub>, C-10H, C-16H), 3.17–3.23 (m, 1H, C-10H), 3.34 (d, 1H, *J* = 6.4 Hz, C-9H), 5.68 (s, 1H, C-5H), 6.1–6.6 (broad hump, 2H, C-3 OH, C-14 OH), 6.61 (d, 1H, *J* = 8.1 Hz, C-2H), 6.70 (d, 1H, *J* = 8.1 Hz, C-1H), 7.75–7.83 (m, 2H, C-5'' H, C-6'' H), 8.12–8.18 (m, 2H, C-4'' H, C-7'' H), 8.27 (d, 1H, *J* = 2.1 Hz, C-4' H), 9.44 (s, 1H, C-10'' H), 9.58 (d, 1H, *J* = 2.1 Hz, C-6' H); MS *m/z* 505 (MH)<sup>+</sup>. Anal. calcd for C<sub>31</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>·0.1H<sub>2</sub>O: C, 73.53; H, 5.61; N, 11.06. Found: C, 73.22; H, 5.80; N, 10.98.

### Acknowledgements

This investigation was supported by the National Institute on Drug Abuse, Grant No. DA08883. We thank Dr. James M. Riordan, Mr. Mark D. Richardson, Ms. Joan C. Bearden, and Ms. Jackie W. Truss for analytical and spectral data. We are grateful to Dr. John A. Secrist III and Dr. John A. Montgomery for their

encouragement, valuable comments and suggestions during the course of this work.

### References and Notes

1. Takemori, A. E.; Portoghese, P. S. *Annu. Rev. Pharmacol. Toxicol.* **1992**, *32*, 239.
2. Aldrich, J. V. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1996; Vol. 3, p 321.
3. Schmidhammer, H. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Oxford, A. W., Eds.; Elsevier: New York, 1998; Vol. 35, p 83.
4. Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281.
5. Portoghese, P. S.; Sultana, M.; Takemori, A. E. *J. Med. Chem.* **1990**, *33*, 1714.
6. Korlipara, V. L.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* **1994**, *37*, 1882.
7. Ananthan, S.; Johnson, C. A.; Carter, R. L.; Clayton, S. D.; Rice, K. C.; Xu, H.; Davis, P.; Porreca, F.; Rothman, R. B. *J. Med. Chem.* **1998**, *41*, 2872.
8. Schmidhammer, H.; Schwarz, P.; Wei, Z-Y. *Helv. Chim. Acta* **1998**, *81*, 1215.
9. Coop, A.; Pinto, J.; Wang, L.; McCullough, K.; Rothman, R. B.; Dersch, C.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3435.
10. Jales, A. R.; Husbands, S. M.; Lewis, J. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2259.
11. Portoghese, P. S.; Nagase, H.; MaloneyHuss, K. E.; Lin, C.-E.; Takemori, A. E. *J. Med. Chem.* **1991**, *34*, 1715.
12. Xu, W.; Huang, L.-F.; Bauer, L.; Bhargava, H. N.; Dunn, W. J., III. *Med. Chem. Res.* **1999**, *9*, 389.
13. Farouz-Grant, F.; Portoghese, P. S. *J. Med. Chem.* **1997**, *40*, 1977.
14. Srivastava, S. K.; Husbands, S. M.; Aceto, M. D.; Miller, C. N.; Traynor, J. R.; Lewis, J. W. *J. Med. Chem.* **2002**, *45*, 537.
15. Xu, W.; Huang, L.-F.; Bauer, L.; Bhargava, H. N.; Dunn, W. J., III. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3375.
16. Ananthan, S.; Kezar, H. S., III; Carter, R. L.; Saini, S. K.; Rice, K. C.; Wells, J. L.; Davis, P.; Xu, H.; Dersch, C. M.; Bilsky, E. J.; Porreca, F.; Rothman, R. B. *J. Med. Chem.* **1999**, *42*, 3527.
17. Menkens, K.; Bilsky, E. J.; Wild, K. D.; Portoghese, P. S.; Reid, L. D.; Porreca, F. *Eur. J. Pharmacol.* **1992**, *219*, 345.
18. Suzuki, T.; Mori, T.; Tsuji, M.; Misawa, M.; Nagase, H. *Life Sci.* **1994**, *55*, PL339.
19. June, H. L.; McCane, S. R.; Zink, R. W.; Portoghese, P. S.; Li, T. K.; Froehlich, J. C. *Psychopharmacology (Berlin)* **1999**, *147*, 81.
20. Arakawa, K.; Akami, T.; Okamoto, M.; Akioka, K.; Nakai, I.; Oka, T.; Nagase, H. *Transplant. Proc.* **1993**, *25*, 738.
21. Abdelhamid, E. E.; Sultana, M.; Portoghese, P. S.; Takemori, A. E. *J. Pharmacol. Exp. Ther.* **1991**, *258*, 299.
22. Fundytus, M. E.; Schiller, P. W.; Shapiro, M.; Wel-trowska, G.; Coderre, T. J. *Eur. J. Pharmacol.* **1995**, *286*, 105.
23. Ananthan, S.; Kezar, H. S., III; Saini, S. K.; Khare, N. K.; Davis, P.; Dersch, C. M.; Porreca, F.; Rothman, R. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 529.
24. Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051.
25. Coppola, G. M.; Hardtmann, G. E.; Huegi, B. S. *J. Heterocycl. Chem.* **1974**, *11*, 51.
26. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
27. Carrera, G. M., Jr.; Sheppard, G. S. *Synlett* **1994**, 93.
28. Rothman, R. B.; Bykov, V.; Ofri, D.; Rice, K. C. *Neuropeptides* **1988**, *11*, 13.

29. Rothman, R. B.; Xu, H.; Seggel, M.; Jacobson, A. E.; Rice, K. C.; Brine, G. A.; Carroll, F. I. *Life Sci.* **1991**, *48*, PL111.
30. Rothman, R. B.; Bykov, V.; de Costa, B. R.; Jacobson, A. E.; Rice, K. C.; Brady, L. S. *Peptides* **1990**, *11*, 311.
31. Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.
32. Calculated Molar Refractivity (CMR) values were computed using the BioByte software as implemented in SYBYL molecular modeling software version 6.8; Tripos Inc.: 1699 S. Hanley Rd., St. Louis, MO 63144-2913, USA.
33. Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11934.
34. Partilla, J. S.; Carroll, F. I.; Thomas, J. B.; Rice, K. C.; Zimmerman, D. M.; Rothman, R. B. *Analgesia* **1999**, *4*, 27.
35. Kramer, T. H.; Davis, P.; Hruby, V. J.; Burks, T. F.; Porreca, F. J. *J. Pharmacol. Exp. Ther.* **1993**, *266*, 577.
36. Porreca, F.; LoPresti, D.; Ward, S. J. *Eur. J. Pharmacol.* **1990**, *179*, 129.
37. Church, R.; Trust, R.; Albright, J. D.; Powell, D. W. *J. Org. Chem.* **1995**, *60*, 3750.
38. Stacey, G. J.; Hawkins, A. F.; Pearson, D. P. J.; Sunley, R. L. Eur. Pat. Appl. 67,511, 1982; *Chem. Abstr.* **1983**, *98*, 198028.
39. Gomez-Parra, V.; Carmen Gomez, M. D.; Sanchez, F.; Stefani, V. *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 483.
40. Akashi, K.; Suga, N. Eur. Pat. Appl. 73,456, 1983; *Chem. Abstr.* **1983**, *99*, 88241.
41. Biziere, K.; Chambon, J. P.; Hallot, A. Eur. Pat. Appl. 169,139, 1986; *Chem. Abstr.* **1986**, *105*, 97319.
42. Padmanabhan, S.; Seshadri, S. *Indian. J. Chem., Sect. B* **1985**, *24B*, 1111.