# Catalytic Aerobic Oxidation of nor-Binaltorphimine (nor-BNI) Analogs without 4,5-Epoxy Bridge Affords a More Selective Ligand for κ Opioid Receptor than the Representative κ Antagonist nor-BNI

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**An analog of nor-binaltorphimine (nor-BNI) without the 4,5-epoxy bridge, 17,17′-bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-14β,14′α-dihydroxy-3,3′-dimethoxy-7,7′-bimorphinan (4), which was the precursor of the designed compound 1 as a selective $\kappa_3$ opioid receptor antagonist, was catalytically oxidized with oxygen in the presence of platinum to give the 5′-oxo derivative 3 with some other oxidized products. Morphinan derivatives without the 4,5-epoxy moiety were labile to oxygen, although the corresponding 4,5-epoxymorphinan derivatives resisted aerobic oxidation. One of the oxidized nor-BNI analogs without 4,5-epoxy bridge, compound 18, showed high affinity and selectivity for κ opioid receptor.**

**Key words** aerobic oxidation; morphinan; opioid; κ receptor; platinum catalyst

The opioid receptors are generally classified into three types (μ, δ, and κ), with the receptor types are further subdivided into $\mu_1$, $\mu_2$, $\delta_1$, $\delta_2$, $\kappa_1$, $\kappa_2$, and $\kappa_3$ subtypes.[1—8] Each subtype elicits various pharmacological effects, therefore subtype selective ligands are expected to be not only useful tools for the investigation of pharmacological effects derived from a subtype but also as lead compounds for new medicines. Although there have been several reports on ligands selective for different opioid receptor types,[9,10] only a few examples of non-peptidic ligands selective for the subtypes of opioid receptor have been described: $\delta_1$ selective agonist (−)-TAN-67,[11] $\delta_1$ selective antagonist 7-benzylidenenaltrexone (BNTX),[12] and $\delta_2$ selective antagonist naltriben (NTB).[4]

With respect to the κ receptor, many of the selective agonists were arylacetamide derivatives such as U-50488H, and U-69593,[10] which were selective for the $\kappa_1$ receptor subtype.[13,14] While these $\kappa_1$ selective agonists showed aversive effects, they had analgesic effects without morphine-like side effects such as dependence and constipation.[15—18] Novelly structured TRK-820, whose new drug application for the treatment of severe pruritus in hemodialysis patients has been filed, was a selective κ receptor agonist and produced potent antinociceptive effects.[19] Contrary to the selective $\kappa_1$ receptor agonists, TRK-820 did not induce preference or aversion.[20] Therefore, based on pharmacological findings resulting from comparison experiments between TRK-820 and $\kappa_1$ receptor agonists, TRK-820 was proposed to be a $\kappa_2$ and/or $\kappa_3$ receptor agonist.[20—26] On the other hand, nor-binaltorphimine (nor-BNI) was known as a selective κ antagonist,[9,10,27] and also showed $\kappa_1$ selectivity.[13,28] Selective $\kappa_2$ and $\kappa_3$ receptor antagonists have not yet been described. Therefore, we designed nor-BNI analogs without the 4,5-epoxy bridge (for example, compound **1**) to obtain κ subtype selective antagonists. In the course of our investigation, we made the surprising observation that the nor-BNI analogs lacking the 4,5-epoxy bridge were easily air-oxidized. Nor-BNI, which had the 4,5-epoxy moiety, was known to resist oxidation with air under usual experimental conditions.[27,29—31] Herein we report the catalytic aerobic oxidation of the nor-BNI analogs without the 4,5-epoxy bridge and their pharmacological properties.

## Results and Discussion

To synthesize the nor-BNI analog without the 4,5-epoxy bridge (compound **4**), the reaction of morphinan **2**[32] with hydrazine dihydrochloride was carried out under aerobic conditions (Chart 1). Compound **3** having 5′-keto group was obtained concomitantly with starting compound **2** and other unidentified compounds, but not the objective compound **4**, which was the precursor of the compound **1**. To the best of our knowledge, the detection of oxidized derivatives during the synthesis of nor-BNI has never been reported.[27,29—31] When the reaction of morphinan **2** with hydrazine dihydrochloride was conducted under argon using oxygen-free solvent, compound **4** was obtained concomitantly with starting compound **2**, and compound **3** was not identified (Chart 1). These results suggested that morphinan derivatives would be more readily oxidized than 4,5-epoxy morphinan derivatives, and prompted us to investigate the oxidation of morphinan derivative **4**.

The aerobic oxidation of compound **4** was examined with a platinum catalyst, which was prepared from platinum (IV) oxide under a hydrogen atmosphere[33] under various condi-

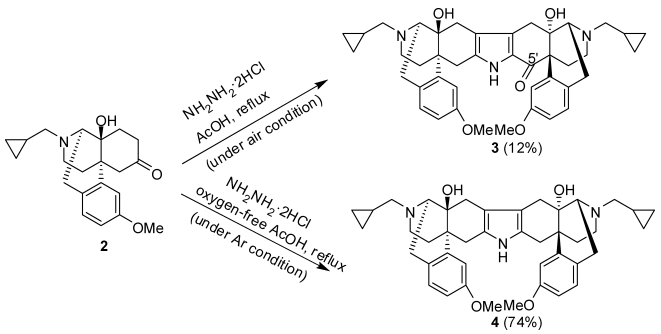


Chart 1. Reaction of Morphinan **2** with Hydrazine Dihydrochloride

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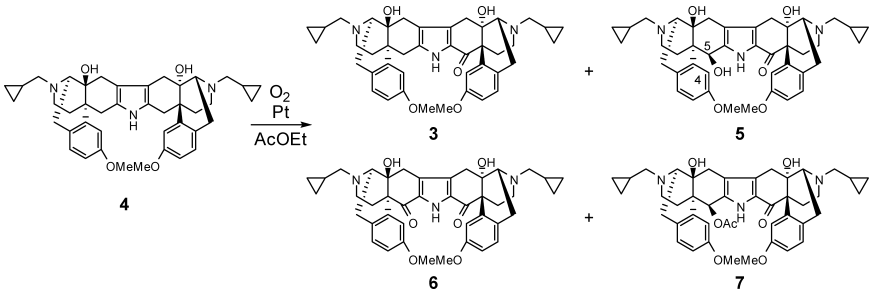
Table 1. The Catalytic Aerobic Oxidation of Compound **4**




| Entry | Pt (eq) | Reaction conditions | | $O_2$ pressure (atm) | Yield (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **3** | **5** | **6** | **7** | **4** |
| 1 | 0.28 | rt | 2 d | 1 | 22 | 23 | 3 | 1 | 1 |
| 2 | 10 | rt | 3 d | 1 | 21 | 12 | 4 | 23 | — |
| 3 | 10 | rt | 1 d | 6 | 34 | 23 | 19 | 8 | Trace |
| 4 | 10 | rt | 1 d | 20 | 37 | 13 | 9 | Trace | Trace |
| 5 | 1 | rt | 2 d | 6 | 28 | 19 | 11 | — | — |
| 6 | 10 | 40 °C | 1 d | 6 | 3 | 12 | 4 | Trace | — |
| 7[a)] | 10 | rt | 3 d | 1 | — | — | — | — | 85[b)] |

*a*) Instead of **4**, nor-BNI dimethyl ether was used as a starting material. *b*) Recovery of nor-BNI dimethyl ether.

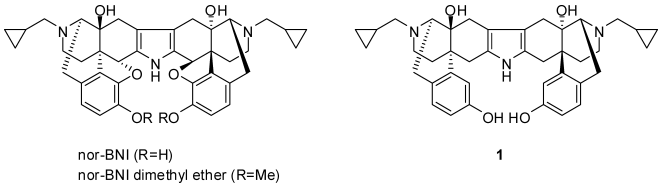



Fig. 1. Structures of nor-BNI and a Designed Compound **1**

tions (Table 1). The catalytic aerobic oxidation of compound **4** afforded 4 products, ketone **3**, ketoalcohol **5**, diketone **6**, and acetoxyketone **7** (Table 1, entry 1). The stereochemistry of the 5-hydroxy group in compound **5** was confirmed to be $\beta$ configuration on the basis of NOE between the 4- and 5-protons. Compound **7** was estimated to have 5$\beta$-acetoxy group from the stereochemistry of compound **5**. Although analogous examples of the oxidation of compound **4** to ketone **3** have been reported,[34,35] the analogous examples of the other products were not known. Increasing amounts of catalyst improved the yield of the oxidized products (entries 2 and 3). The oxygen pressure significantly influenced both the yield and reaction rate, with 6 atm of oxygen providing the best results (entry 3). Heating induced the decomposition of products to decrease the yields (entry 6). Contrary to the compound **4**, the oxidation of nor-BNI dimethyl ether (Fig. 1) gave no products and the only starting material was recovered in 85% (entry 7).

The detailed mechanism of aerobic oxidation catalyzed by platinum was not clear, but 3-hydroperoxyindolenin was known as the intermediate in the oxidation of indole systems.[36] On the basis of this information, two plausible mechanisms for the aerobic oxidation of compound **4** were developed (Chart 2). Path A is in accordance with the report by Leete,[35] which proposes heterolysis of hydroperoxide **8** corresponding to the intermediate in the indole system to give cation **9**. Cation **9** would interact with the methylene hydrogen to yield the non-classical ion **10** which could be converted to compound **3** *via* intermediate **11**. The alternative mechanism, path B, calls for the intramolecular attack by the hydroperoxy group of compound **12**, which is the tautomer of hydroperoxide **8**, upon the enamine moiety to give compound **3** *via* hydroperoxide **13**. Hydroperoxide **14**, which would be prepared from compound **3** *via* path B, may react with compound **3** or **4** to yield ketoalcohol **5**.[37] Platinum might also catalyze the O–O bond cleavage of hydroperoxide **14**. If A is the only reaction pathway, it is difficult to explain

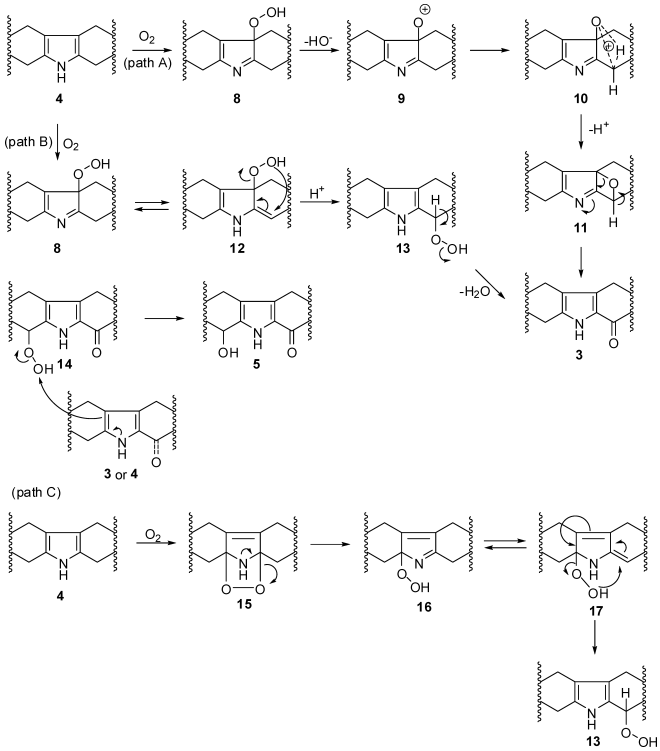



Chart 2. Plausible Mechanism for the Aerobic Oxidation of Compound **4**

the preparation of compound **5**. Taken together, the mechanism of aerobic oxidation of compound **4** could include only the path B or both the paths A and B. According to the investigation of oxidation of 2,3-cycloalkenoindoles with various ring sizes reported by Witkop *et al.*,[34] the ring size affected the structures of the products and in the only case of an 8-membered fused ring, the keto compound comparable to compound **3** was obtained. It is interesting that although compound **4** has a 6-membered fused ring rather than an 8-membered ring, the product was ketone **3**. On the other hand, 2,5-endoperoxide was proposed as the intermediate in the autoxidation of substituted pyrroles.[38] A plausible mechanism based on this information (path C, Chart 2) proposes that the hydroperoxy group of compound **17**, the tautomer of hydroperoxide **16** derived from endoperoxide **15**, would intramolecularly attack the enamine moiety to give compound **13**, which may convert to the products through paths A or B mentioned above.[37] Acetoxyketone **7** seems to be obtained from ketoalcohol **5**, however ketoalcohol **5** has never been converted to acetoxyketone **7** under the experimental conditions. It is not clear how acetoxyketone **7** was obtained.

It is well-known that opioid activities of 4,5-epoxymorphinan-3-ol are more potent than those of 3-methoxy-4,5-epoxymorphinan.[39] Therefore, demethylation of bis-morphinans **3**—**7** was tried. The demethylation of compound **3** with boron tribromide afforded compound **18** in 67% yield (Chart 3). In the case of compounds **4**—**7**, demethylation with boron tribromide or potassium propylthiolate gave complex mixtures, and desired demethylated compounds were not obtained.

The affinity of compound **18** for opioid receptors was assessed by replacement experiment using homogenates of guinea-pig brain ($\kappa$: cerebellum, $\mu$ and $\delta$: forebrain, Table 2). Compound **18** showed higher affinity for $\kappa$ receptor than a representative $\kappa$ antagonist, nor-BNI. Moreover, compound **18** was more selective for $\kappa$ receptors as compared to $\mu$ receptors than was nor-BNI, although **18** was less selective for the $\delta$ receptors. Detailed pharmacological properties of compound **18** including $\kappa$ receptor subtype selectivity are currently under investigation.

## Conclusion

The nor-BNI analog without the 4,5-epoxy bridge was easily oxidized with air in the presence of a platinum catalyst. As opposed to nor-BNI with the 4,5-epoxy bridge intact, which was hardly oxidized with air, the morphinan derivatives without the 4,5-epoxy moiety were labile to air. The aerobic oxidation of morphinan derivatives could proceed by three plausible mechanisms. Some of the oxidation products, **5**—**7**, represent compounds that would arise from the novel type of aerobic oxidation. One of the oxidized nor-BNI analogs, compound **18**, showed higher affinity and selectivity for $\kappa$ receptor than did the selective $\kappa$ antagonist nor-BNI.

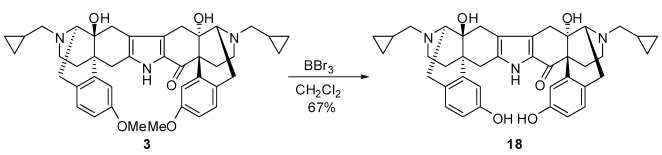



Chart 3. Demethylation of Compound **3**

### Experimental

Melting points were determined on a YAZAWA BY-10 melting point apparatus and were uncorrected. NMR spectra were recorded on a Varian Mercury-300 (300 MHz) or a Varian UNITY INOVA 600 (600 MHz) spectrometer and the chemical shifts were reported as $\delta$ values (ppm) related to chloroform-*d* (7.26 ppm for $^1$H-NMR, 77.16 ppm for $^{13}$C-NMR) or methanol-$d_4$ (3.40 ppm). IR spectra were obtained using a JASCO FT/IR-460 as KBr pellets. MS were obtained on JMS-AX-505HA or JMS-700MA Station instruments by a fast atom bombardment (FAB) ionization method. Elemental analyses were determined with a YANACO MT-5, and results were within 0.4% of the theoretical values. Reaction progress was monitored by TLC on Merck Silica Gel 60 $F_{254}$. All the column chromatographies and preparative TLC were carried out using Kanto Silica Gel 60 and Merck Silica Gel 60 $F_{254}$ PLC plates, respectively.

**17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-14$\beta$,14′$\alpha$-dihydroxy-3,3′-dimethoxy-7,7′-bimorphinan-5′-one (3)** To the acetic acid (1.6 ml) solution of morphinan **2** (104 mg, 0.30 mmol) was added hydrazine dihydrochloride (32 mg, 0.30 mmol) under aerobic conditions and the reaction mixture was refluxed for 21 h. Methanol, sodium bicarbonate solution, and ammonia solution were added to adjust the reaction mixture to pH 9 and the mixture was extracted with chloroform. The organic layer was washed with brine and dried over sodium sulfate. After removing the solvent *in vacuo*, the residue was chromatographed on silica gel to give 12.5 mg (12%) of **3** and 22 mg (21%) of **2** as amorphous substances. IR (KBr) cm$^{-1}$: 3406, 2923, 1617, 1501, 1460, 1239, 1042. $^1$H-NMR ($CDCl_3$, 600 MHz) $\delta$: 0.04—0.14 (4H, m), 0.43—0.53 (4H, m), 0.74—0.87 (2H, m), 1.23 (1H, d, $J$=15.0 Hz), 1.82 (1H, ddd, $J$=2.0, 5.0, 14.0 Hz), 2.04—2.16 (3H, m), 2.20 (1H, d, $J$=16.0 Hz), 2.28 (1H, dt, $J$=5.0, 14.0 Hz), 2.32—2.36 (4H, m), 2.39 (1H, d, $J$=16.0 Hz), 2.50 (1H, d, $J$=16.0 Hz), 2.61 (2H, d, $J$=17.0 Hz), 2.72 (1H, d, $J$=16.0 Hz), 2.81—2.90 (2H, m), 2.93 (1H, d, $J$=17.0 Hz), 3.01 (1H, d, $J$=18.0 Hz), 3.04 (1H, d, $J$=18.0 Hz), 3.07—3.13 (2H, m), 3.17 (1H, d, $J$=17.0 Hz), 3.64 (3H, s), 3.66 (3H, s), 6.61 (1H, dd, $J$=2.5, 8.0 Hz), 6.65 (1H, dd, $J$=2.5, 8.0 Hz), 6.66 (1H, d, $J$=2.5 Hz), 6.67 (1H, d, $J$=2.5 Hz), 6.96 (2H, dd, $J$=2.5, 8.5 Hz), 8.98 (1H, s). (Two protons of tertiary hydroxyl groups were not observed.) $^{13}$C-NMR ($CDCl_3$, 150 MHz) $\delta$: 3.52, 3.79, 3.93, 4.14, 9.36, 24.73, 24.84, 29.44, 29.66, 29.98, 30.24, 37.33, 41.71, 43.86, 43.96, 53.04, 55.08, 55.11, 59.02, 59.50, 59.77, 60.10, 69.81, 74.92, 110.91, 111.35, 111.54, 113.52, 114.38, 125.57, 126.57, 127.53, 127.94, 128.39, 130.21, 134.59, 137.91, 140.87, 158.33, 187.38. FAB-MS $m/z$: 676.3755 (Calcd for $C_{42}H_{50}N_3O_5$: 676.3750).

**17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-14$\beta$,14′$\alpha$-dihydroxy-3,3′-dimethoxy-7,7′-bimorphinan (4)** To the oxygen-free acetic acid (8 ml) solution of morphinan **2** (500 mg, 1.46 mmol) was added hydrazine dihydrochloride (155 mg, 1.46 mmol) under an argon atmosphere and the reaction mixture was refluxed for 70 h. Methanol, sodium bicarbonate solution, and ammonia solution were added to the reaction mixture to adjust the pH to 9 and the mixture was extracted with chloroform. The organic layer was washed with brine and dried over sodium sulfate. After removing the solvent *in vacuo*, the residue was chromatographed on silica gel to give 359 mg (74%) of **4** and 55 mg (11%) of **2** as amorphous substances. IR (KBr) cm$^{-1}$: 3394, 2919, 1611, 1500, 1269, 1238, 1043. $^1$H-NMR ($CDCl_3$, 600 MHz) $\delta$: 0.04—0.12 (4H, m), 0.44—0.53 (4H, m), 0.76—0.91 (2H, m), 1.21 (2H, d, $J$=11.0 Hz), 2.11 (2H, ddd, $J$=2.0, 6.0,

Table 2. Affinity of Compound **18** and nor-BNI for Opioid Receptors

| Compd | $\kappa$ ([$^3$H]U-69593) | | $\mu$ ([$^3$H]DAMGO) | | $\delta$ ([$^3$H]NTI) | | $K_i$ ratio | |
|---|---|---|---|---|---|---|---|---|
| | $IC_{50}$ (nM) | $K_i$ (nM) | $IC_{50}$ (nM) | $K_i$ (nM) | $IC_{50}$ (nM) | $K_i$ (nM) | $\mu/\kappa$ | $\delta/\kappa$ |
| **18** | 0.887 | 0.434 | 49.9 | 20.5 | 10.6 | 5.13 | 47 | 12 |
| nor-BNI | 1.76 | 0.861 | 72.3 | 28.2 | 59.5 | 29.3 | 33 | 34 |

6.5 Hz), 2.12 (2H, d, $J$=11.0 Hz), 2.23 (2H, dt, $J$=6.0, 2.0 Hz), 2.36 (2H, dt, $J$=3.0, 6.5 Hz), 2.36 (4H, dd, $J$=6.0, 9.0 Hz), 2.57 (2H, ddd, $J$=2.0, 3.0, 6.0 Hz), 2.82 (2H, d, $J$=10.0 Hz), 2.88 (2H, dd, $J$=6.5, 18.0 Hz), 3.02 (2H, d, $J$=16.0 Hz), 3.02 (2H, dd, $J$=5.0, 18.0 Hz), 3.06 (2H, dd, $J$=5.0, 6.5 Hz), 3.74 (6H, s), 6.62 (2H, dd, $J$=2.5, 8.5 Hz), 6.77 (2H, d, $J$=2.5 Hz), 6.93 (2H, d, $J$=8.5 Hz), 7.20 (1H, s). (Two protons of tertiary hydroxyl groups were not observed.) $^{13}$C-NMR ($CDCl_3$, 150 MHz) $\delta$: 3.79, 3.81, 9.48, 24.79, 29.56, 29.91, 37.24, 41.93, 44.09, 55.08, 59.47, 60.13, 70.17, 110.65, 111.34, 111.66, 121.65, 128.02, 128.03, 142.12, 158.10. FAB-MS $m/z$: 662.3946 (Calcd for $C_{42}H_{52}N_3O_4$: 662.3958).

**Catalytic Oxidation of Compound 4** The reaction in Table 1, entry 3 was representative. Platinum(IV) oxide (35 mg, 0.15 mmol) was added to the ethyl acetate (2 ml) and the suspension was stirred for 3 h under a hydrogen atmosphere. To the resulting suspension was added compound **4** (10 mg, 0.015 mmol) and stirred for 1 d at rt under oxygen atmosphere (6 atm). The resulting mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by preparative TLC to give 3.5 mg (34%) of **3**, 2.4 mg (23%) of **5**, 2.0 mg (19%) of **6**, and 0.9 mg (8%) of **7** as amorphous substances.

**17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-5$\beta$,14$\beta$,14′$\alpha$-trihydroxy-3,3′-dimethoxy-7,7′-bimorphinan-5′-one (5)** IR (KBr) cm$^{-1}$: 3396, 2924, 1640, 1502, 1465, 1395, 1239, 805. $^1$H-NMR ($CDCl_3$, 600 MHz) $\delta$: 0.05—0.11 (4H, m), 0.45—0.52 (4H, m), 0.74—0.86 (2H, m), 1.22 (1H, d, $J$=16.0 Hz), 1.22 (1H, ddd, $J$=2.0, 3.0, 12.5 Hz), 1.81 (1H, ddd, $J$=2.0, 2.5, 13.5 Hz), 2.09 (1H, dt, $J$=2.5, 12.0 Hz), 2.16 (1H, dt, $J$=3.0, 12.5 Hz), 2.28 (1H, ddd, $J$=4.0, 12.0, 13.5 Hz), 2.33 (2H, dd, $J$=7.0, 13.5 Hz), 2.36 (2H, dd, $J$=7.0, 13.5 Hz), 2.40 (1H, d, $J$=16.0 Hz), 2.54 (1H, d, $J$=16.0 Hz), 2.63 (1H, ddd, $J$=2.0, 4.0, 12.0 Hz), 2.70 (1H, ddd, $J$=2.0, 5.0, 12.5 Hz), 2.76 (1H, d, $J$=16.0 Hz), 2.86 (1H, dd, $J$=6.0, 16.0 Hz), 2.88 (1H, dt, $J$=5.0, 12.5 Hz), 2.91 (1H, dd, $J$=6.0, 16.0 Hz), 3.02 (1H, dd, $J$=2.0, 6.0 Hz), 3.04 (1H, dd, $J$=2.0, 16.0 Hz), 3.07 (1H, dd, $J$=2.0, 16.0 Hz), 3.10 (1H, dd, $J$=2.0, 6.0 Hz), 3.66 (6H, s), 4.22 (1H, s), 5.00 (1H, s), 6.60 (1H, dd, $J$=2.0, 8.0 Hz), 6.61 (1H, dd, $J$=2.0, 8.0 Hz), 6.63 (1H, dd, $J$=2.5, 8.5 Hz), 6.68 (1H, dd, $J$=2.5, 8.5 Hz), 6.93 (1H, d, $J$=8.5 Hz), 6.97 (1H, d, $J$=8.5 Hz), 9.12 (1H, s). (Two protons of tertiary hydroxyl groups were not observed.) $^{13}$C-NMR ($CDCl_3$, 150 MHz) $\delta$: 4.01, 4.24, 9.28, 9.46, 24.72, 25.10, 29.65, 29.84, 30.29, 31.88, 43.49, 43.91, 53.40, 55.17, 58.99, 59.46, 59.71, 60.21, 66.98, 72.73, 74.94, 110.21, 110.40, 111.61, 113.49, 113.70, 126.61, 126.93, 127.08, 128.08, 128.59, 128.92, 136.29, 137.57, 139.88, 158.35, 188.57. FAB-MS $m/z$: 692.3711 (Calcd for $C_{42}H_{50}N_3O_6$: 692.3700).

**17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-14$\beta$,14′$\alpha$-dihydroxy-3,3′-dimethoxy-7,7′-bimorphinan-5,5′-dione (6)** IR (KBr) cm$^{-1}$: 3418, 2926, 1730, 1648, 1502, 1270, 1041. $^1$H-NMR ($CDCl_3$, 600 MHz) $\delta$: 0.10—0.17 (4H, m), 0.51—0.58 (4H, m), 0.84—0.91 (2H, m), 1.87 (2H, ddd, $J$=3.0, 4.0, 13.0 Hz), 2.17 (2H, dt, $J$=4.0, 13.0 Hz), 2.38 (2H, dt, $J$=5.0, 13.0 Hz), 2.45 (2H, dd, $J$=6.0, 12.0 Hz), 2.49 (2H, dd, $J$=6.0, 12.0 Hz), 2.54 (2H, d, $J$=16.0 Hz), 2.81 (2H, ddd, $J$=3.0, 5.0, 13.0 Hz), 2.84 (2H, d, $J$=16.0 Hz), 3.00 (2H, dd, $J$=6.0, 19.0 Hz), 3.12 (2H, dd, $J$=3.0, 19.0 Hz), 3.31 (2H, dd, $J$=3.0, 6.0 Hz), 3.68 (6H, s), 6.51 (2H, d, $J$=2.0 Hz), 6.72 (2H, dd, $J$=2.0, 8.5 Hz), 7.02 (2H, dd, $J$=2.0, 8.5 Hz), 9.74 (1H, s). (Two protons of tertiary hydroxyl groups were not observed.) $^{13}$C-NMR ($CDCl_3$, 150 MHz) $\delta$: 3.80, 4.11, 8.73, 24.85, 29.75, 43.80, 54.03, 55.14, 59.00, 59.64, 74.78, 111.18, 113.97, 126.04, 127.65, 128.50, 130.20, 135.88, 158.52, 176.42. FAB-MS $m/z$: 690.3560 (Calcd for $C_{42}H_{48}N_3O_6$: 690.3543).

**5$\beta$-Acetoxy-17,17′-bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-14$\beta$,14′$\alpha$-dihydroxy-3,3′-dimethoxy-7,7′-bimorphinan-5′-one (7)** IR (KBr) cm$^{-1}$: 3439, 2926, 1719, 1640, 1501, 1240, 1043. $^1$H-NMR ($CDCl_3$, 600 MHz) $\delta$: 0.08—0.17 (4H, m), 0.47—0.58 (4H, m), 0.85—0.95 (2H, m), 1.38 (1H, ddd, $J$=2.0, 4.0, 13.0 Hz), 1.84 (1H, ddd, $J$=2.0, 5.0, 14.0 Hz), 1.94 (3H, s), 2.15 (1H, ddd, $J$=2.0, 5.0, 13.0 Hz), 2.19 (1H, ddd, $J$=2.0, 5.0, 12.5 Hz), 2.38 (1H, d, $J$=16.0 Hz), 2.42 (1H, ddd, $J$=2.0, 12.5, 14.0 Hz), 2.45 (1H, d, $J$=16.0 Hz), 2.49 (1H, d, $J$=16.0 Hz), 2.51—2.62 (4H, m), 2.72 (1H, d, $J$=16.0 Hz), 2.75 (1H, dt, $J$=4.0, 13.0 Hz), 2.90 (1H, dt, $J$=5.0, 12.5 Hz), 2.91 (1H, dt, $J$=4.0, 13.0 Hz), 2.98—3.08 (4H, m), 3.38—3.47 (2H, m), 3.64 (3H, s), 3.69 (3H, s), 6.48 (1H, s), 6.55 (1H, s), 6.65 (1H, d, $J$=9.0 Hz), 6.67 (1H, d, $J$=9.0 Hz), 6.86 (1H, s), 6.95 (1H, d, $J$=9.0 Hz), 6.97 (1H, d, $J$=9.0 Hz), 9.46 (1H, s). (Two protons of tertiary hydroxyl groups were not observed.) $^{13}$C-NMR ($CDCl_3$, 150 MHz) $\delta$: 3.77, 4.00, 4.21, 8.12, 8.15, 21.74, 25.00, 25.64, 29.43, 29.96, 30.15, 30.69, 44.02, 44.38, 52.88, 55.07, 55.16, 58.84, 59.14, 59.57, 60.17, 66.96, 70.11, 74.65, 110.88, 111.83, 112.36, 113.64, 116.24, 125.37, 126.51, 127.16, 128.01, 128.50, 128.92, 131.01, 136.37, 138.51, 158.52, 158.71, 172.57, 187.95. FAB-MS $m/z$: 734.3817 (Calcd for $C_{44}H_{52}N_3O_7$: 734.3805).

**17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-6,6′-imino-3,3′,14$\beta$,14′$\alpha$-tetrahydroxy-7,7′-bimorphinan-5-one (18) Dihydrochloride** To the solution of **3** (61.2 mg, 0.091 mmol) in dichloromethane (2 ml) was added dropwise 1.0 M dichloromethane solution of boron tribromide (0.75 ml, 0.75 mmol) under an argon atmosphere at 0 °C under light shielding conditions and the mixture was stirred for 1.5 h at rt. The reaction mixture was poured into 6% ammonia solution to adjust the pH to 10 and then the mixture was extracted with chloroform. The organic layer was washed with brine and dried over sodium sulfate. After removing the solvent *in vacuo*, the residue was purified by preparative TLC to give 39 mg (67%) of **18** as an amorphous substance. To the acetone solution of **18** was added saturated hydrogen chloride methanol solution at 0 °C. Filtration of the precipitated solid gave 27 mg (66%) compound **18** dihydrochloride as an amorphous substance. mp (dec.) for **18**·2HCl 188—190 °C. IR (for **18**, KBr) cm$^{-1}$: 3342, 2923, 1616, 1460, 1261, 1055. $^1$H-NMR (for **18**, $CD_3OD$, 300 MHz) $\delta$: 0.00—0.08 (4H, m), 0.33—0.46 (4H, m), 0.68—0.81 (2H, m), 1.16 (1H, dd, $J$=3.0, 11.0 Hz), 1.60 (1H, dd, $J$=3.0, 13.0 Hz), 1.96—2.21 (4H, m), 2.10 (1H, d, $J$=17.0 Hz), 2.24—2.36 (5H, m), 2.43 (1H, d, $J$=17.0 Hz), 2.47—2.60 (2H, m), 2.64 (1H, d, $J$=17.0 Hz), 2.73 (1H, d, $J$=17.0 Hz), 2.85 (2H, dt, $J$=2.0, 8.0 Hz), 3.00 (1H, d, $J$=15.0 Hz), 3.06 (1H, d, $J$=9.0 Hz), 3.11 (1H, d, $J$=9.0 Hz), 3.17—3.21 (2H, m), 6.35 (1H, d, $J$=1.0 Hz), 6.43 (2H, dt, $J$=1.0, 4.0 Hz), 6.56 (1H, d, $J$=1.0 Hz), 6.82 (2H, t, $J$=4.0 Hz). FAB-MS (for **18**·2HCl), $m/z$ 648 $(H+H)^+$. *Anal.* Calcd for $C_{40}H_{45}N_3O_5\cdot 2HCl\cdot 2.5H_2O$: C, 62.71; H, 6.82; N, 5.48. Found: C, 62.74; H, 6.84; N, 5.49.

**Membrane Preparations** For membrane preparation, the brain was quickly removed from 4 week male Hartley guinea pigs (Japan SLC) and dissected forebrain and cerebellum, and immediately frozen in liquid nitrogen. These tissues were homogenized using a Potter-Elvejham tissue grinder with a Teflon pestle in 10 volumes/g wet weight of ice-cold 50 mM Tris–HCl buffer (pH 7.4). The homogenate was centrifuged at 12000 ***g*** at 4 °C for 20 min and the pellet was resuspended in 20 volumes/g wet weight of ice-cold Tris buffer. After 1 h of incubation at 4 °C in order to remove endogenous opioid ligands, homogenate was centrifuged at 12000 ***g*** at 4 °C for 20 min. The pellet was resuspended in 20 volumes/g wet weight of ice-cold Tris buffer and centrifuged at 12000 ***g*** at 4 °C for 20 min. The resultant pellet was resuspended in 2 volumes/g wet weight of ice-cold Tris buffer and stored at −80 °C until use.

**Receptor Binding Assay** Binding affinities for $\mu$ and $\delta$ receptors were determined by displacing [$^3$H]DAMGO (specific activity: 1850 GBq/mmol, ARC) and [$^3$H]NTI (specific activity: 2220 GBq/mmol, ARC) from guinea pig forebrain membrane binding sites, and binding affinities for $\kappa$ receptors were measured by displacement of [$^3$H]U-69593 (specific activity: 1541 GBq/mmol, PerkinElmer) from guinea pig cerebellum membrane binding sites. The homogenated membrane fractions (280—500 $\mu$g of protein/assay) were incubated at 25 °C for 2 h in 50 mM Tris–HCl buffer with various concentrations of compounds and 0.5 nM [$^3$H]DAMGO, [$^3$H]NTI or 0.1 nM [$^3$H]U-69593 in a total volume of 500 $\mu$l. Specific bindings were defined as the difference in bindings observed in the absence and presence of 1 $\mu$M non-tritiated ligand in each experiment ($\mu$: DAMGO, $\delta$: NTI, $\kappa$: U-69593). Incubations were terminated by collecting membranes on GF/B filters (Whatman) using a cell harvester (Brandel). The filters were transferred to scintillation vials. Then, 5 ml of Creasol I (Nacalai Tesque) was added to the vials. After 12 h equilibration period, radioactivity in the samples was determined in a liquid scintillation counter (Packard, Liquid Scintillation Analyzer TRI-CARB 1900). Calculated $IC_{50}$ values were converted into $K_i$ values (equilibrium inhibition constants) according to the Cheng & Prusoff equation[40]: $K_i=IC_{50}/(1+L/K_d)$, where $L$ is the concentration of the tritiated ligands. The equilibrium dissociation constants $K_d$ were determined by displacement of the tritiated ligands by the particular non-tritiated ones and were compared to the $K_d$ values resulting from the saturation binding experiments. All reactions were carried out in duplicate.

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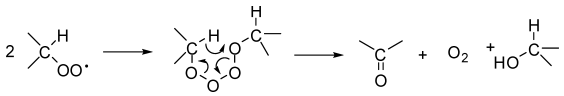
**References and Notes**

1) Fowler C. J., Fraser G. L., *Neurochem. Int.*, **24**, 401—426 (1994).
2) Pasternak G. W., Wood P. J., *Life Sci.*, **38**, 1889—1896 (1986).
3) Tive L. A., Pick C. G., Paul D., Roques B. P., Gacel G. A., Pasternak G. W., *Eur. J. Pharmacol.*, **216**, 249—255 (1992).
4) Sofuoglu M., Portoghese P. S., Takemori A. E., *J. Pharmacol. Exp. Ther.*, **257**, 676—680 (1991).

5) Jiang Q., Takemori A. E., Sultana M., Portoghese P. S., Bowen W. D., Mosberg H. I., Porreca F., *J. Pharmacol. Exp. Ther.*, **257**, 1069—1075 (1991).
6) Fang L., Knapp R. J., Horvath R., Matsunaga T. O., Haaseth R. C., Hruby V. J., Porreca F., Yamamura H. I., *J. Pharmacol. Exp. Ther.*, **268**, 836—846 (1994).
7) Clark J. A., Liu L., Price M., Hersh B., Edelson M., Pasternak G. W., *J. Pharmacol. Exp. Ther.*, **251**, 461—468 (1989).
8) Horan P., De Costa B. R., Rice K. C., Porreca F., *J. Pharmacol. Exp. Ther.*, **257**, 1154—1161 (1991).
9) Gutstein H. B., Akil H., "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 11th ed., ed. by Brunton L. L., Lazo J. S., Parker K. L., McGraw-Hill, New York, 2005, pp. 547—606.
10) Dhawan B. N., Cesselin F., Raghubir R., Reisine T., Bradley P. B., Portoghese P. S., Hamon M., *Pharmacol. Rev.*, **48**, 567—592 (1996).
11) Tseng L. F., Narita M., Mizoguchi H., Kawai K., Mizusuna A., Kamei J., Suzuki T., Nagase H., *J. Pharmacol. Exp. Ther.*, **280**, 600—605 (1997).
12) Portoghese P. S., Sultana M., Nagase H., Takemori A. E., *Eur. J. Pharmacol.*, **218**, 195—196 (1992).
13) Nock B., "The Pharmacology of Opioid Peptides," ed. by Tseng L. F., Harwood Academic Publishers, Singapore, 1995, pp. 29—56.
14) Teberi M., Magnan J., *Eur. J. Pharmacol., Mol. Pharmacol.*, **188**, 379—389 (1990).
15) Millan M. J., *Trends Pharmacol. Sci.*, **11**, 70—76 (1990).
16) Mucha R. F., Herz A., *Psychopharmacology*, **86**, 274—280 (1985).
17) Funada M., Suzuki T., Narita M., Misawa M., Nagase H., *Neuropharmacology*, **32**, 1315—1323 (1993).
18) Shippenberg T. S., Herz A., *NIDA Res. Monogr.*, **75**, 563—566 (1986).
19) Nagase H., Hayakawa J., Kawamura K., Kawai K., Takezawa Y., Matsuura H., Tajima C., Endo T., *Chem. Pharm. Bull.*, **46**, 366—369 (1998).
20) Tsuji M., Takeda H., Matsumiya T., Nagase H., Narita M., Suzuki T., *Life Sci.*, **68**, 1717—1725 (2001).
21) Endoh T., Matsuura H., Tajima A., Izumimoto N., Tajima C., Suzuki T., Saitoh A., Suzuki T., Narita M., Tseng L. F., Nagase H., *Life Sci.*, **65**, 1685—1694 (1999).
22) Endoh T., Tajima A., Kamei J., Suzuki T., Narita M., Tseng L. F., Nagase H., *Eur. J. Pharmacol.*, **387**, 133—140 (2000).
23) Tsuji M., Yamazaki M., Takeda H., Matsumiya T., Nagase H., Tseng L. F., Narita M., Suzuki T., *Eur. J. Pharmacol.*, **394**, 91—95 (2000).
24) Mori T., Takeda H., Matsumiya T., Nagase H., Yamazaki M., Narita M., Suzuki T., *Life Sci.*, **66**, PL353—358 (2000).
25) Endoh T., Tajima A., Izumimoto N., Suzuki T., Saitoh A., Suzuki T., Narita M., Kamei J., Tseng L. F., Mizoguchi H., Nagase H., *Jpn. J. Pharmacol.*, **85**, 282—290 (2001).
26) Mori T., Nomura M., Yoshizawa K., Nagase H., Narita M., Suzuki T., *Life Sci.*, **75**, 2473—2482 (2004).
27) Portoghese P. S., Nagase H., Lipkowsky A. W., Larson D. L., Takemori A. E., *J. Med. Chem.*, **31**, 836—841 (1988).
28) Nock B., Giordano A. L., Cicero T. J., O'Connor L. H., *J. Pharmacol. Exp. Ther.*, **254**, 412—419 (1990).
29) Lipkowsky A. W., Nagase H., Portoghese P. S., *Tetrahedron Lett.*, **27**, 4257—4260 (1986).
30) Schmidhammer H., Smith C. F. C., *Hev. Chim. Acta*, **72**, 675—677 (1989).
31) Schmidhammer H., Ganglbauer E., Mitterdorfer J., Rollinger J. M., Smith C. F. C., *Hev. Chim. Acta*, **73**, 1779—1783 (1990).
32) Casy A. F., Parfitt R. T., "Opioid Analgesics: Chemistry and Receptors," Plenum Press, New York, 1986, pp. 105—151.
33) Guise G. B., Ritchie E., Taylor W. C., *Aust. J. Chem.*, **18**, 1279—1286 (1965).
34) Witkop B., Patrick J. B., Rosenblum M., *J. Am. Chem. Soc.*, **73**, 2641—2647 (1951).
35) Leete E., *J. Am. Chem. Soc.*, **83**, 3645—3647 (1961).
36) Sundberg R. J., "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 282—315.
37) A radical process might also be taken into account. Two molecules of hydroperoxy radicals corresponding to hydroperoxide **14** could produce ketone, alcohol, and oxygen *via* an unstable tetraoxide.



Lowry T. H., Richardson K. S., "Mechanism and Theory in Organic Chemistry," 3rd ed., Harper & Row, Publishers, New York, 1987, pp. 779—782.
38) Gossauer A., Nesvadba P., "Pyrroles: Part One: The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring," ed. by Jones R. A., John Wiley and Sons, Canada, 1990, pp. 499—536.
39) Casy A. F., Parfitt R. T., "Opioid Analgesics: Chemistry and Receptors," Plenum Press, New York, 1986, pp. 9—104.
40) Cheng Y., Prusoff W. H., *Biochem. Pharmacol.*, **22**, 3099—3108 (1973).