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Synthesis of a novel 4,6′-epoxymorphinan derivative and a highly strained novel conjugated ketone

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Abstract—A modification of the 4,5-epoxymorphinan skeleton of naltrexone was carried out to improve the potency and the selectivity of the ligand for an opioid receptor subtype. As one of the modified structures, we newly designed and synthesized a novel 7-membered ring ether derivative, which had an inserted OCH_2 group between the 4- and 6-positions of the morphinan skeleton. The derivative with a 7-membered ring ether, 4,6′-epoxymorphinan, has a more fixed chair form than the 4,5-epoxymorphinan. In addition, we found a new cleavage reaction of the 4,5-epoxy ring in naltrexone, and also obtained a highly strained novel conjugated ketone.

Three types of opioid receptors (μ, δ, κ) are now well established not only by pharmacological studies but also by molecular biological characterizations.[1] Although many highly selective and potent ligands for opioid receptor types are presently available,[2–6] the only selective ligands that target opioid receptor subtypes are TAN-67[7,8] (δ_1), BNTX[9] (δ_1) and NTB[10] (δ_2). Ligands that are specifically directed against the subtypes of opioid receptors (μ_1, μ_2, δ_1, δ_2 and κ_1, κ_2, κ_3) are highly desirable for the investigation of the pharmacological effects attributed to these receptor subtypes. We have been interested in the design of κ and δ receptor subtype (δ_1, δ_2 and κ_1, κ_2, κ_3) selective compounds and have attempted to design and synthesize them using naltrexone **1** with the 4,5-epoxymorphinan skeleton.

However, we had limited success in obtaining subtype selective ligands synthesized from 4,5-epoxymorphinan derivatives. Therefore, we focused on modifying the 4,5-epoxymorphinan skeleton itself. The 4,5-epoxymorphinan structure of naltrexone is believed to influence the intrinsic activity of the opioid receptor and the substituents may help distinguish among the opioid receptor types.[11] The 4,5-epoxymorphinan structure has been considered to contribute to three points of association between the drug molecule and the receptor site, which are an ionic interaction, a π–π interaction and a hydrogen bond.[12,13] We noted that the conformation of the C-ring of naltrexone is flexible and rather half chair form, and attempted to change the flexible chair form into a fixed form in order to obtain ligands selective for the μ opioid receptor subtype.

Herein, we report the conversion of the 4,5-epoxy morphinan structure of naltrexone into 4,6′-epoxymorphinan skeleton **2 (NS13)** (7-membered ring ether), whose C-ring has a fixed chair form (Fig. 1).

In planning the retrosynthetic pathway, we utilized a new epoxy ring cleavage reaction (Scheme 1), which was found by chance in the course of a trial of C-6 side chain extension. Although a similar 4,5-epoxy ring cleavage reaction has been reported,[14] we independently found the new cleavage reaction using the Wittig reaction. In spite of extensive investigation, the double bond of key intermediate **5** could not be selectively reduced

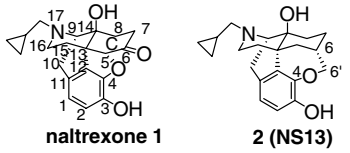

Figure 1. Structures of naltrexone **1** and the novel 4,6′-epoxymorphinan **2**.

Keywords: Opioid; Naltrexone; 4,6′-Epoxymorphinan; Analgesics.
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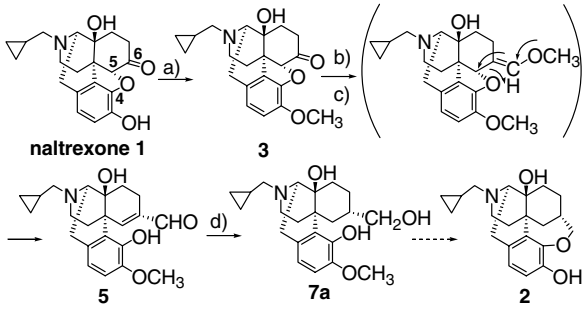
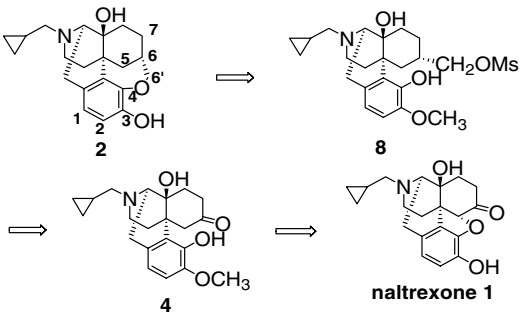


Scheme 1. Reagents and conditions: (a) CH_3I, K_2CO_3, DMF, rt, 90%; (b) $Ph_3P^+C^-HOMe$, Wittig reaction; (c) HCl, rt, 68% (two steps) (d) PtO_2, H_2, CH_3OH, 15%.

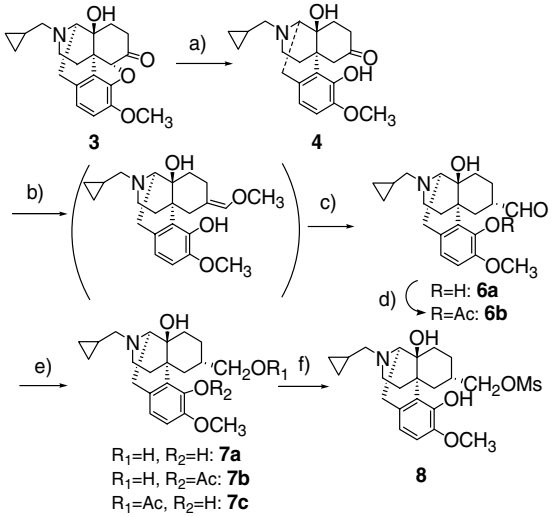
because of steric hindrance around the double bond. The reaction afforded diol **7a** as the main product in low yields concomitantly with some unidentified products.

Therefore, we undertook another retrosynthetic analysis of the objective 7-membered ring ether compound **2** (Scheme 2). In this alternative approach, the 7-membered ring ether **2** would be obtained via compound **8**, which could be derived from compound **4** by the Wittig reaction followed by hydrolysis, reduction and mesylation.

The phenolic hydroxyl group of naltrexone **1** was methylated with CH_3I, and the epoxy ring of the resulting naltrexone methyl ether **3** was reductively cleaved with zinc in acetic acid and hydrochloric acid to give compound **4**.[15] Ketone **4** was converted to aldehyde **6a** (6α:6β = 3:1) by the Wittig reaction[16] with methoxymethyltriphenylphosphonium chloride and sodium hydride in DMSO followed by hydrolysis. To obtain mono mesylate **8**, we first tried a series of reactions as follows: compound **6a** was acetylated with acetic anhydride in pyridine followed by reduction of aldehyde **6b** with $NaBH_4$ in CH_3OH. However the reduction afforded a mixture of two acetates, **7b** and **7c**, which would be obtained by intramolecular transacetylation. The results gave us an insight into the selective functionalization of the primary hydroxyl group over the phenolic hydroxyl. Then we tried the selective mesylation of diol **7a**, which was obtained by the reduction of aldehyde **6a**. As we expected, the mesylation of diol **7a** with methanesulfonyl chloride in pyridine exclusively gave the desired mono mesylate **8** (Scheme 3).



Scheme 2.



Scheme 3. Reagents and conditions: (a) Zn, HCl, CH_3COOH, reflux, 90%; (b) $Ph_3P^+C^-HOMe$, Wittig reaction; (c) HCl, rt, separation from β isomer (19%), 60% (two steps); (d) $(CH_3CO)_2O$, Py; (e) $NaBH_4$, CH_3OH, 0 °C to rt, 80%; (f) CH_3SO_2Cl, Py, 0 °C, quant.

The intramolecular cyclization of mesylate **8** to the objective 7-membered ring ether **9a** was performed under various conditions (Table 1). Using DBU as a base (entry 3) gave the best result. Contrary to our expectation, not only **9a**, but also the highly strained novel conjugated ketone **10**, was obtained under some conditions. Ketone **10** was obtained with loss of its aromaticity. To the best of our knowledge, this reaction is the first example of an intramolecular reaction leading to preparation of a compound like **10** with a highly strained structure, although such intermolecular reactions in low yields have been previously reported.[17–20]

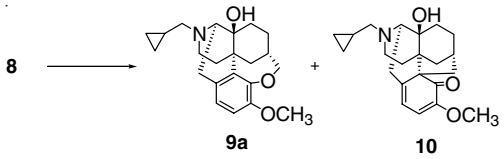
With the desired 4,6′-epoxymorphinan in hand, we tried demethylation of compound **9a** with BBr_3[21] or 1-C_3H_7SK,[22] but obtained only highly polar compounds. We postulated that the opening of a 7-membered ring ether in **2** might lead to highly polar, air sensitive cathechol (Scheme 4).

Therefore, **9b**, obtained by the same procedure shown in Scheme 3 using BnBr instead of CH_3I, was converted to compound **2** by catalytic hydrogenation with Pd (Scheme 5).

The structure of **9a** was determined by NMR and HRMS.[23] In ^1H NMR, peaks of methylene protons of C-6′ were observed at 3.42 ppm, 4.47 ppm, and a peak of a methyne proton of C-6 was observed at 2.52 ppm. In addition, NOE was observed between H-7eq (1.32 ppm) and H-6′ (3.42 ppm), and NOE was also observed between H-6′ (4.47 ppm) and H-6 (2.52 ppm). In HRMS (FAB), a molecular ion peak was observed at 356.2216 $[M+H]^+$, indicating the molecular formula of **9a** as $C_{22}H_{30}NO_3$ $[M+H]^+$ (Fig. 2).

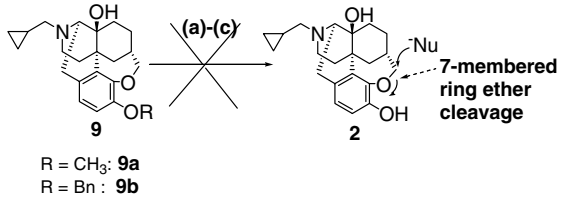
The structure of **2** was also determined by NMR and HRMS. In HMBC (heteronuclear multiple-bond corre-

Table 1. Reaction conditions of the preparation for **9a** and **10**

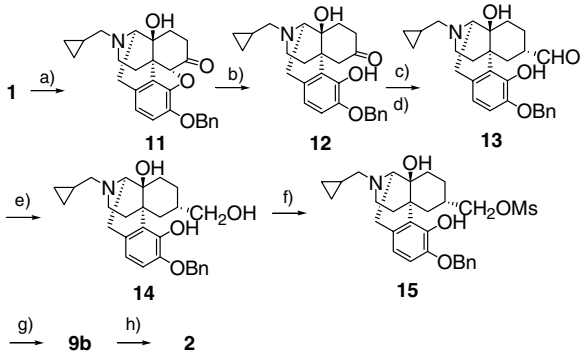


Entry	Condition	**9a** (yield)	**10** (yield)
1	(a) DMF/K_2CO_3, rt, 19 h	60%	26%
2	(b) DMF/KCN, 50 °C, 40 h	53%	21%
3	(c) DBU,[a] rt, 5 h	62%	—[b]
4	(d) DBU, 50 °C, 5 h	51%	—[b]
5	(e) DMF, 100 °C, 40 h	—[b]	—[b]
6	(f) DMF/NaN_3, 50 °C, 16 h	—[b]	—[b]
7	(g) DMF/NaI, 50 °C, 15 h	—[b]	—[b]
8	(h) DMF/NaI, 100 °C, 50 h	—[c]	—[c]

[a] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[b] Not obtained.
[c] Mixtures (not isolated).



Scheme 4. Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0 °C, overnight (b) BBr_3, CH_2Cl_2, 0 °C to rt, 0.5 h; (c) 1-C_3H_7SH, *t*-BuOK, DMF, 150 °C, 7 h.



Scheme 5. Reagents and conditions: (a) BnBr, K_2CO_3, DMF, rt, 96%; (b) Zn, HCl, CH_3COOH, reflux, 55%; (c) $Ph_3P^+C^-HOMe$, Wittig reaction; (d) HCl, rt, separation from β isomer, 17% (two steps); (e) $NaBH_4$, MeOH, 0 °C to rt, 63%; (f) CH_3SO_2Cl, Py, 0 °C, quant; (g) K_2CO_3, DMF, rt, 72%; (h) Pd–C, H_2, MeOH, rt, 80%.

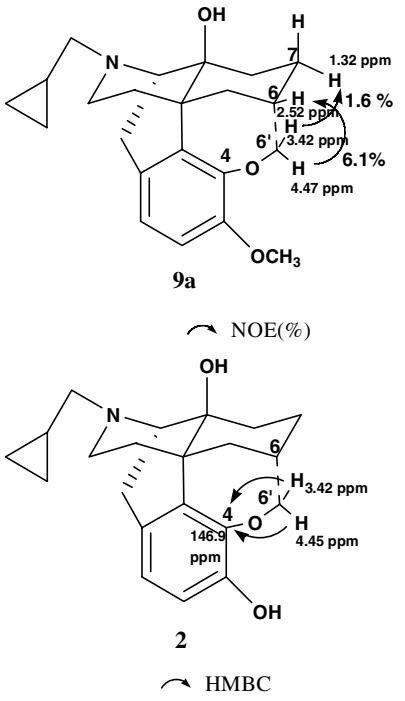


Figure 2. Structures of the novel 4,6′-epoxymorphinans **9a** and **2**.

lation) measurement, a correlation was observed between C-4 (146.9 ppm) and H-6′ (3.42 ppm, 4.45 ppm). In addition, HRMS supported the molecular formula of **2** (Fig. 2). Taken together, these results supported the 7- membered ring ether structures shown in Figure 2.

The structure of **10** was also determined by NMR, IR and HRMS.[24] In ^{1}H NMR, a methyne proton of C-6 was observed at 2.37 ppm and methylene protons of C-6′ at 1.53 ppm, 2.63 ppm. Protons of C-1 and C-2 were observed at 5.80 ppm, 5.86 ppm, (not aromatic region) respectively, while proton peaks of C-1 and C-2 of naltrexone (4,5-epoxymorphinan) were observed at 6.58 ppm, 6.71 ppm (aromatic region). Long range couplings were observed between H-7eq (1.49 ppm) and H-5eq (2.62 ppm) ($J = 1.5$ Hz), and H-6′ax (1.53 ppm) and H-5ax (1.78 ppm) ($J = 1.0$ Hz). In ^{13}C NMR, a peak of a ketone of C-4 was observed at 200.3 ppm, and that of C-12 was observed at 63.5 ppm (Fig. 3). In HMBC measurement, a correlation was observed between a ketone of C-4 and H-6′ (1.53 ppm, 2.63 ppm). In addition, NOE was also observed as

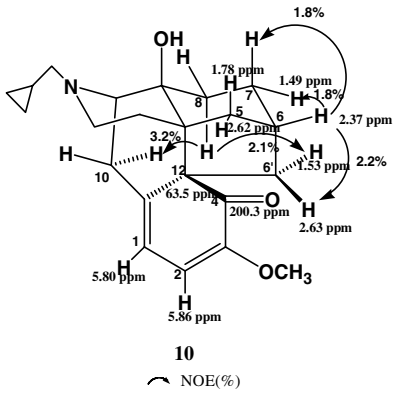


Figure 3. The structure of a highly strained novel conjugated ketone **10**.

shown in Figure 3. The absorption bands derived from the unsaturated ketone at 1674, 1639 cm^{-1} were observed in IR. HRMS also supported the molecular formula of **10**.

Compound **2** showed strong antagonistic activity for DAMGO (μ agonist) more than naltrexone, whose activity may be derived from different μ subtype from naltrexone. Furthermore, 17-methyl-4,6′-epoxymorphinan derivative showed strong agonistic activity for μ receptor. We are also examining the subtype selectivity of these compounds. These pharmacological data will be reported in detail as full paper near future.

In conclusion, we have designed and synthesized a novel 7-membered ring ether derivative **2** in order to obtain more potent ligands selective for opioid receptor subtypes. Conversion of the 4,5-epoxy ring to the 4,6′-epoxy ring resulted in a more rigid morphinan skeleton. A new analgesic could be obtained by synthesizing various derivatives with this skeleton.

Our strategy of 4,5-epoxy ring cleavage, whose example was reported, proceeded under very mild conditions to give novel unsaturated aldehyde **5**. Moreover, a highly strained conjugated ketone **10** with a rigid 5-membered ring was surprisingly obtained in the course of the cyclization of mesylate **8**.

These reactions may give crucial clues to the design and synthesis of new ligands with novel skeletons.

Acknowledgement

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23. *Analytical and spectral data for compound* **9a**. Mp 192–194 °C; IR (KBr) cm^{-1}: 3388; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.08–0.18 (2H, m), 0.46–0.58 (2H, m), 0.87 (1H, m), 1.18 (1H, ddd, $J = 1.0$, 4.0, 13.5 Hz), 1.32 (1H, ddt, $J = 5.0$, 14.0, 1.5 Hz), 1.36 (1H, ddd, $J = 1.5$, 5.5, 13.5 Hz), 1.65 (1H, dt, $J = 5.0$, 13.5 Hz), 1.83 (1H, ddd, $J = 5.0$, 12.0, 13.5 Hz), 2.14 (1H, dd, $J = 5.0$, 13.5 Hz), 2.19 (1H, ddt, $J = 13.5$, 14.0, 5.5 Hz), 2.39 (1H, dt, $J = 12.0$, 4.0 Hz), 2.35–2.58 (5H, m), 2.58 (1H, ddd, $J = 1.0$, 5.0, 12.0 Hz), 2.94 (1H, m), 3.13 (1H, d, $J =$ 18.0 Hz), 3.42 (1H, dd, $J = 6.5$, 12.5 Hz), 3.81 (3H, s), 4.47 (1H, dd, $J = 11.0$, 12.5 Hz), 6.69 (1H, d, $J =$ 8.0 Hz), 6.71 (1H, d, $J = 8.0$ Hz). MS (FAB) $m/z = 356$ $[M+H]^+$. HRMS (FAB) Calcd for $C_{22}H_{30}NO_3[M+H]^+$: 356.2226; found, 356.2216. Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.01; H; 8.14, N; 4.00.

24. *Analytical and spectral data for compound* **10**. Mp 147–150 °C; IR (neat) cm^{-1}: 3397, 1674, 1639; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.03–0.14 (2H, m), 0.44–0.55 (2H, m), 0.80 (1H, m), 1.49 (1H, m), 1.53 (1H, dt, $J = 14.5$, 1.0 Hz), 1.56 (1H, ddd, $J = 4.0$, 6.0, 13.5 Hz), 1.78 (1H, dd, $J = 1.0$, 11.5 Hz), 1.85 (1H, ddt, $J = 6.0$, 13.5, 2.0 Hz), 1.93–2.00 (2H, m), 2.06 (1H, ddt, $J = 7.0$, 13.5, 2.0 Hz), 2.20 (1H, dt, $J = 12.0$, 4.0 Hz), 2.27 (1H, ddd, $J = 1.0$, 6.0 13.0 Hz), 2.31 (1H, ddd, $J = 1.0$, 6.0, 13.0 Hz), 2.37 (1H, m), 2.60 (1H, ddd, $J = 1.5$, 5.5, 12.0 Hz), 2.62 (1H, ddd, $J = 2.0$, 6.0, 11.5 Hz), 2.63 (1H, dd, $J = 8.0$, 14.5 Hz), 2.72 (1H, dt, $J = 19.0$, 1.0 Hz), 2.82 (1H, dd, $J = 1.0$, 5.5 Hz), 2.88 (1H, ddd, $J = 3.0$, 5.5, 19.0 Hz), 3.66 (3H, s), 5.80 (1H, ddd, $J = 1.0$, 3.0, 6.5 Hz), 5.86 (1H, d, $J = 6.5$ Hz). MS (FAB) $m/z = 356$ $[M+H]^+$. HRMS (FAB) Calcd for $C_{22}H_{30}NO_3[M+H]^+$: 356.2226; found, 356.2212. Anal. Calcd for $C_{22}H_{29}NO_3 \cdot 1/3H_2O$: C, 72.77; H, 8.11; N, 3.98. Found: C, 72.91; H; 7.92; N, 3.99.