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Synthesis of a new opioid ligand having the oxabicyclo[3.2.1]octane skeleton using a new rearrangement reaction

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ABSTRACT

An attempt to prepare a trimer having the 1,3,5-trioxazatriquinane skeleton led to discovery of a novel rearrangement reaction that afforded a compound with an oxabicyclo[3.2.1]octane skeleton whose reaction mechanism was proposed. On the basis of this mechanism, we synthesized the rearranged product from a dimethyl acetal intermediate in excellent yield. The compound with an oxabicyclo[3.2.1]octane skeleton showed high affinity for μ and κ but not δ opioid receptor types. The compound expected to be a key intermediate for novel κ selective ligands.

Recent studies have reported that G-protein-coupled receptors (GPCRs) exist as dimers, which may be present as homo- or hetero-dimers/oligomers. Although the occurrence of GPCR dimers/oligomers was predicted from earlier pharmacological and biochemical studies, further evaluations of this phenomenon were impeded by the lack of appropriate reagents.[1,2] One of the useful tools for investigation of GPCR dimers/oligomers would be twin drugs combining two structural components into single molecule. Symmetrical twin drugs can simultaneously fit to the symmetrical binding sites of the protein complex to afford increased activity. Non-symmetrical twin drugs may bind each relevant binding site to give dual action.[1] However, twin drugs can only play one role, by affording either an increase of activity or a dual action. If a rigid triplet drug (trimer drug) was available, the drug could be expected to exert both features of increased activity and dual action. Recently, we have reported a synthetic method for rigid triplet drug **3** with 1,3,5-trioxazatriquinane skeleton baring of three naltrexone units having 4,5-epoxy ring.[3] In the course of the study, we obtained a novel rearrangement compound **10**, not the expected objective trimer **9** with a 1,3,5-trioxazatriquinane skeleton, when morphinan derivative **6** without the 4,5-epoxy ring was used as a starting material. We examined the reaction mechanism and proposed the participation of the 14-hydroxy group to afford the rearrangement compound **10**. Based on this mechanism, the same compound **10** was directly synthesized from dimethyl acetal **6** obtained from morphinan derivative **4** in two steps. Thus obtained compound **10** was demethylated to give phenol **16** which showed strong affinity for μ and κ opioid receptor types. Herein, we report the novel rearrangement reaction, the reaction mechanism, and the pharmacological effect of phenol **16**.

Naltrexone is a μ opioid receptor antagonist and widely used for therapy of drug addiction.[4] We have been interested in design and synthesis of κ, δ, and ε opioid receptor selective ligands from naltrexone and have successfully synthesized many selective ligands, including κ agonist TRK-820,[5] δ agonist TAN-67,[6] and ε agonist TAN-821 (Fig. 1).[7] We also reported many new reactions using naltrexone as a starting material.[8] We have recently reported a synthetic method for a triplet **3** with 4,5-epoxy ring from naltrexone (Scheme 1). This synthetic method could apply for three general

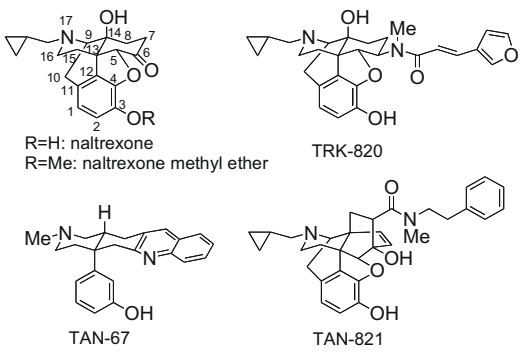

Figure 1. Representative μ, δ, κ, and ε opioid ligands.

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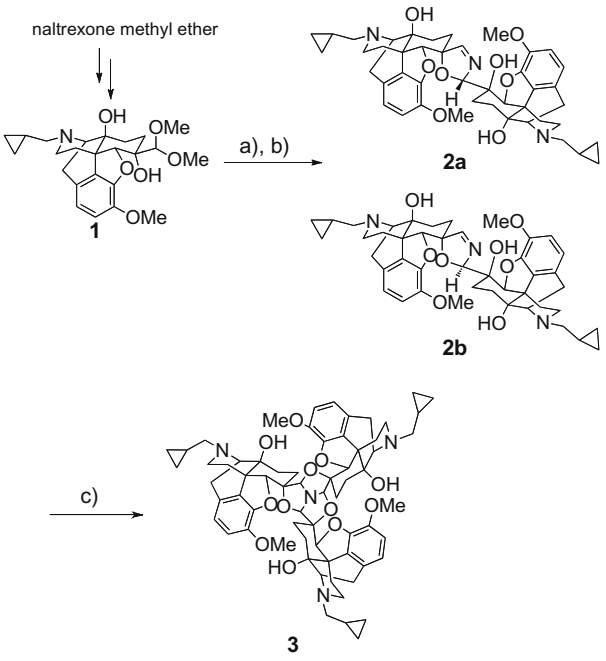
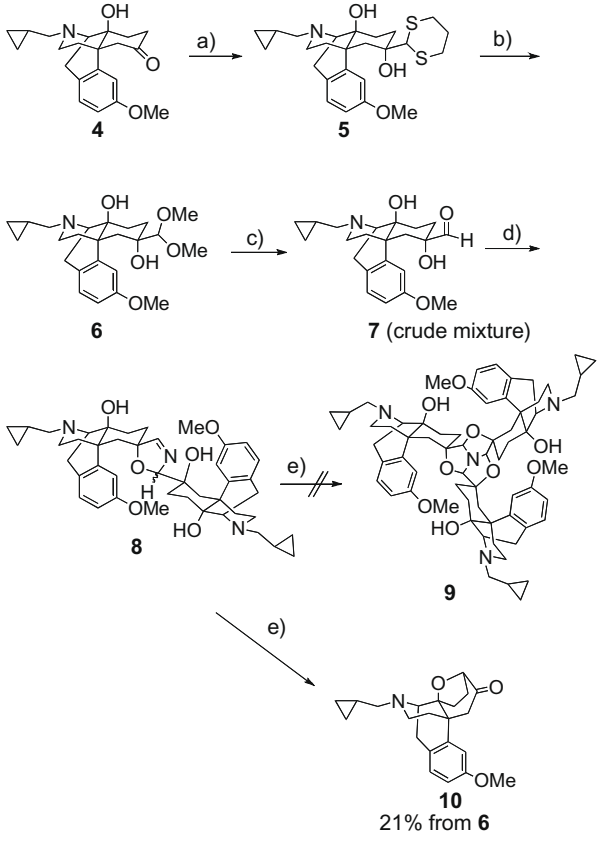


Scheme 1. Reagents and conditions: (a) 2 M HCl, reflux; (b) NH_4Cl, AcONa, MeOH, reflux; (c) CSA, $CHCl_3$, reflux, 79% from **1**.

ketones (*N*-benzyl piperidone, acetophenone, and 4-phenylcyclohexanone).[3] However, when dimethyl acetal **6**, which was synthesized from morphinan derivative **4**[8e,9] in two steps, was subjected



Scheme 2. Reagents and conditions: (a) *n*-BuLi, 1,3-dithiane, DME, −70 °C, 69%; (b) $CuCl_2{\cdot}2H_2O$, CSA, $CH(OMe)_3$, MeOH, 50 °C, 37%; (c) 2 M HCl, reflux; (d) NH_4Cl, AcONa, MeOH, reflux; (e) CSA, $CHCl_3$, reflux.

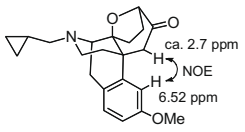
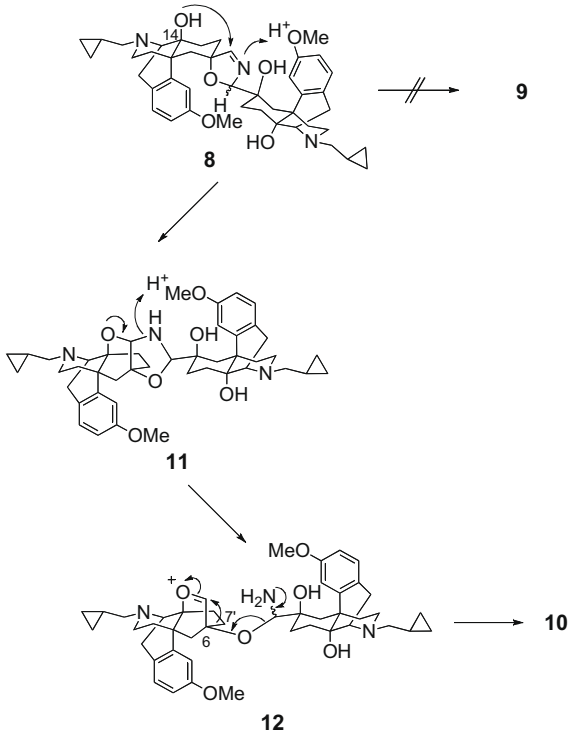


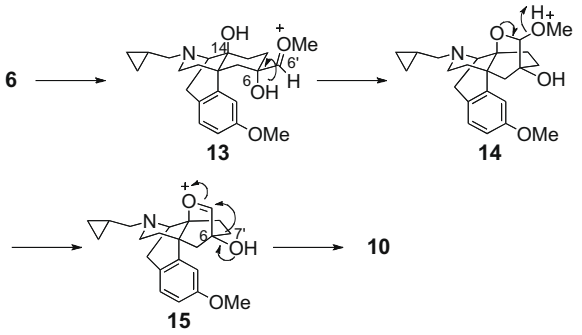
Figure 2. Observed NOE spectra of compound **10**.

to the same reaction conditions as those of naltrexone derivative (4,5-epoxymorphinan), monomer **10**[10] was obtained in 21% yield instead of objective trimer **9** (Scheme 2). The structure of the monomer was identified as novel oxabicyclo[3.2.1]octane derivative **10** by 2D NMR, MS, and IR spectroscopy (Fig. 2). We were interested in the novel structure **10** and examined the reaction mechanism (Scheme 3). As dimer **8**, derived from α-hydroxy aldehyde **7**, would be more flexible than **2** derived from naltrexone methyl ether, the 14-hydroxy group may easily participate in the double bond of the oxazoline ring in **8** to afford cyclic ether **11**. Moreover, oxonium intermediate **12** may also be more flexible than a structure with a 4,5-epoxy ring, and the C6–C7′ σ-bond in **12** may be easily rearranged to the oxonium double bond to afford rearrangement product **10**.

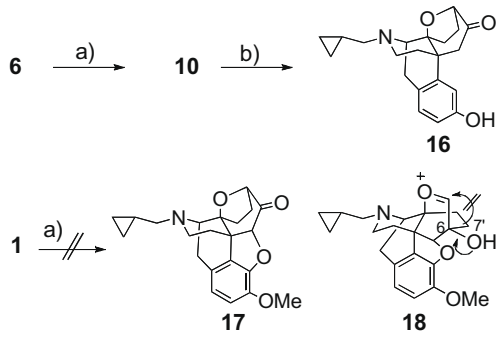
If our hypothesis is correct, oxonium ion **13**, derived from dimethyl acetal **6**, would rearrange more easily than oxazoline **8** to give **10**. Because the bond between the 6-carbon and 6′-oxonium carbon in **13** can rotate freely around the axis, the 14-hydroxy group could easily approach and overlap with the π orbital of the carbonyl carbon in **13** to afford cyclic acetal intermediate **14** which could then rearrange to **10** via oxonium **15** (Scheme 4). Furthermore, as the 3 aforementioned general ketones (*N*-benzyl piperidone, acetophenone, and 4-phenylcyclohexanone) without hydroxyl groups were all converted to the corresponding trimers, the 14-hydroxy group is expected to participate in the rearrangement reaction. On the basis of our hypothesis, dimethyl acetal **6** was treated with *dl*-camphorsulfonic acid (CSA) in toluene under reflux to give the expected compound **10** in 90% yield (Scheme



Scheme 3. Plausible reaction mechanism to give **10** from **8**.



Scheme 4. Plausible mechanism of the rearrangement reaction for preparation of **10** from **6**.



Scheme 5. Reagents and conditions: (a) CSA, toluene, reflux, 90%; (b) BBr_3, CH_2Cl_2, rt, 87%.

5). In contrast, dimethyl acetal **1** with 4,5-epoxy ring was not converted to the corresponding rearrangement product **17**. Existence of the 4,5-epoxy ring in **18** may fix the morphinan skeleton and prevent the 7′-carbon from rearranging to the oxonium carbon.

To evaluate binding affinities of the rearrangement compound for opioid receptors, compound **10** was demethylated with boron tribromide in CH_2Cl_2 to give phenol **16** in 87% yield (Scheme 5). Compound **16** showed strong affinity for μ and κ opioid receptor types, which was comparable to that of naltrexone (Table 1). We previously reported pharmacological data for compound **19** with the oxabicyclo[2.2.1]heptane skeleton with the fixed boat form of the C-ring and its derivative (Fig. 3).[11] At that time, we postulated a boat form for the C-ring in the potent κ agonist TRK-820[5] and we synthesized an amide derivative **19** with the oxabicyclo[2.2.1]heptane skeleton which showed strong κ agonist activity (Fig. 3).[11] This result supported our prediction. Compound **16** also has its C-ring in the fixed boat form, that is, a novel oxabicyclo[3.2.1]octane skeleton. In the comparison with compound **20** which is the fundamental skeleton of **19**, the κ type selectivity

Table 1
Binding affinity of compounds **16**, **20**, and naltrexone for opioid receptors[a]

Compound	K_i (κ)[b] (nM)	K_i (μ)[c] (nM)	K_i (δ)[d] (nM)
16	0.233	0.397	6.84
20	0.102	0.145	3.50
Naltrexone	0.373	0.335	20.7

[a] Binding assay was carried out in duplicate using homogenate of guinea-pig brain (κ: cerebellum, μ and δ: forebrain).
[b] [^{3}H]U-69,593 was used.
[c] [^{3}H]DAMGO was used.
[d] [^{3}H]NTI was used.

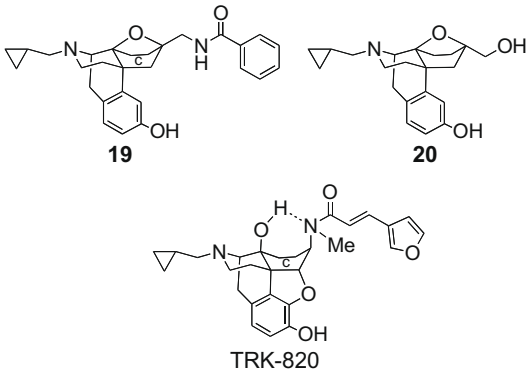


Figure 3. Structures of TRK-820 with C-ring fixed in boat form by intramolecular hydrogen bond and morphinan derivatives having oxabicyclo[2.2.1]heptane skeleton **19** and **20**.

(μ/κ K_i ratio = 1.70) of compound **16** was rather improved over that (μ/κ K_i ratio = 1.42) of **20**, but the affinities of **16** for each opioid receptor type were decreased. We will further modify compound **16** to improve both affinity and κ selectivity by introduction of a C6 side chain similar to that of TRK-820.[5]

In conclusion, we found a rearrangement reaction that gave the novel morphinan derivative **10** having the oxabicyclo[3.2.1]octane skeleton in the course of the study of a trimer with the 1,3,5-trioxazatriquinane skeleton. This rearrangement reaction using dimethyl acetal **6** with the morphinan skeleton lacking the 4,5-epoxy ring proceeded in higher yield (90%). However, the dimethyl acetal derivative **1** having 4,5-epoxy ring was not converted to the same type of rearrangement product. The examination of the reaction mechanism suggested that the existence of the 4,5-epoxy ring may fix the morphinan skeleton and prevent the 7′-carbon from rearranging to the oxonium carbon in **18**. The phenol derivative **16** derived from thus obtained **10** showed strong affinities for μ and κ but not δ opioid receptor types. The resulting **16** is expected to be a key intermediate for novel κ selective compounds with strong analgesic properties without addiction.

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10. *Compound* **10**: IR(KBr) 1730, 1610, 1577, 1502, 1468, 1427 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04–0.17 (m, 2H), 0.43–0.60 (m, 2H), 0.84–1.00 (m, 1H), 1.21 (ddd, J = 1.8, 3.0, 12.9 Hz, 1H), 1.70–1.86 (m, 2H), 1.94–2.11 (m, 2H), 2.19–2.35 (m, 1H), 2.37 (dd, J = 6.9, 12.6 Hz, 1H), 2.44–2.58 (m, 2H), 2.64–2.78 (m, 4H), 3.17 (d, J = 18.0 Hz, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.77 (s, 3H), 4.47 (d, J = 7.5 Hz, 1H), 6.52 (d, J = 2.7 Hz, 1H), 6.73 (dd, J = 2.7, 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.4, 4.2, 9.2, 25.6, 28.0, 31.1, 35.7, 44.6, 45.0, 45.2, 55.2, 57.7, 59.4, 82.58, 82.61, 110.3, 112.0, 123.6, 128.1, 142.3, 158.4, 205.9. HRMS (FAB) calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2069, found: 354.2061.
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