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A NOVEL REARRANGEMENT REACTION OF MORPHINAN TO ARYLMORPHAN SKELETONS AND THE PHARMACOLOGIES OF ARYLMORPHAN DERIVATIVES

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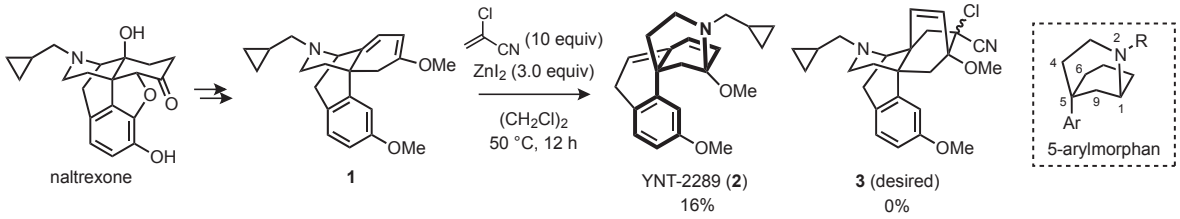
Abstract – A novel rearrangement reaction of the morphinan skeleton by using zinc iodide was developed. The substrate-specific rearrangement afforded two types of novel 5-arylmorphan derivatives, i.e., compounds produced by either a 1,5-shift of the nitrogen bridge or a 1,3-shift of the nitrogen bridge in a starting morphinan derivative. The 5-arylmorphan derivatives showed selective κ opioid receptor activities even though many 5-arylmorphan compounds reported previously have shown selective μ opioid receptor activities. In addition, other related 5-arylmorphan derivatives showed potent dual antagonistic activities toward orexin 1 and 2 receptors.

Since the opioid receptors were clarified to three types (μ, δ, and κ) and drug addiction was recognized to be derived from the μ opioid receptor (MOR), we have been studying δ or κ opioid receptor (DOR or KOR) type-selective ligands to supply drugs that are effective without addiction. Eventually, nalfurafine, the first KOR selective agonist without addiction and aversion, was released to the market as an antipruritic drug for kidney dialysis patients in Japan.[1] Furthermore, the first DOR selective agonist KNT-127 without convulsion and catalepsy was designed and synthesized,[2] and it was recently led to NC-2800 as an antidepressant/antianxiety drug, which is in the preclinical stage. During the course of our

opioid studies, we have focused on distinguishing the structural motifs in the morphinan skeleton with its four sequential asymmetric centers in the commercially available naltrexone, which has been often used as a starting material, and we have investigated the diverse pharmacological effects of a variety of morphinan compounds transformed from naltrexone.[1c,3] In the context of this research, when a morphinan skeleton **1** with a dienol ether moiety derived from naltrexone was treated with 2-chloroacrylonitrile in the presence of zinc iodide,[4] an unexpected novel rearrangement proceeded to yield the 5-arylmorphan derivative YNT-2289 (**2**), but not the objective bicyclo[2.2.2]octane derivative **3** (Scheme 1).



Scheme 1. Reaction of **1** with 2-chloroacrylonitrile

Recently, the synthetically interesting rearrangement reactions of a propellane alkaloid to the corresponding 5-arylmorphan derivative were reported (the reported reactant and product were enantiomeric forms of **1** or **2**), although no pharmacological evaluations were described (Figure 1).[5] Structural similarity between the product and our arylmorphan **2** and the novelty of our rearrangement of morphinan skeleton **1** into arylmorphan skeleton **2** encouraged us to carry out a detailed study of the serendipitous rearrangement. Herein, we describe in detail the novel rearrangement of the morphinan derivatives to 5-arylmorphan derivatives and the pharmacological effects of the resulting products. In addition, we also report that the arylmorphan **2** and its related derivative showed antagonistic activities against both orexin 1 and orexin 2 receptors (OX_1R and OX_2R), which are implicated in regulation of the sleep/wake cycle.[6]

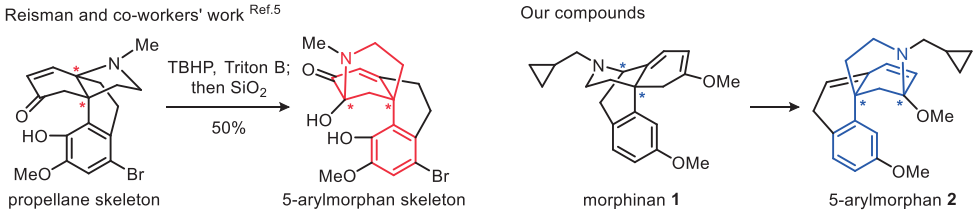
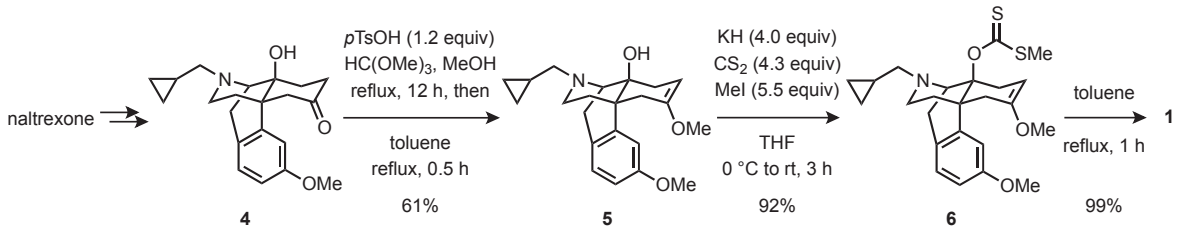


Figure 1. Comparison of the product by the previously reported rearrangement with our compounds

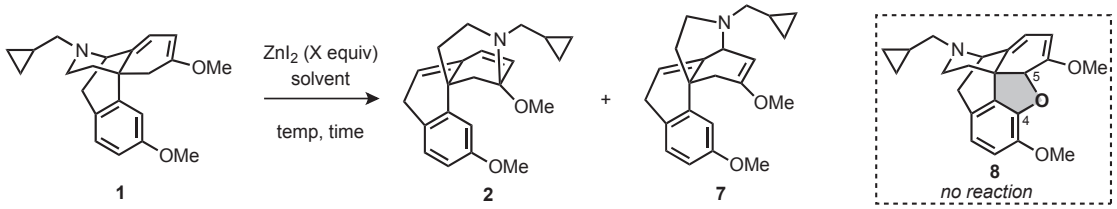
The starting dienol ether **1** was obtained from the known morphinan **4**, which was easily transformed from naltrexone in six steps,[7] by the following process: enolization of the ketone in **4**; formation of xanthate **6** from methyl enol ether **5**; Chugaev elimination of **6** (Scheme 2).



Scheme 2. Synthesis of **1** from naltrexone *via* the known **4**

To investigate the essential reaction conditions, we examined the reaction of **1** without 2-chloroacrylonitrile, because 2-chloroacrylonitrile was not embedded in the structure of the rearrangement product **2** (Table 1). Surprisingly, another novel arylmorphan isomer **7**, which was obtained by 1,3-shift of the nitrogen-bridge in **1**, was mainly produced with the 1,5-shift product **2** under the almost same conditions apart from 2-chloroacrylonitrile (Table 1, entry 1). Changing the solvent (THF) improved the ratio of the yield of **2** (entry 2).[8] Moreover, the reaction under microwave (MW) irradiation increased the total yields of the rearrangement products **2** and **7**, suggesting that the reaction time might have been insufficient to reach equilibrium for experiments shown in entries 1 and 2 (see entry 3). The use of other Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$, and $Yb(OTf)_3$ under the same condition gave complex mixtures. We confirmed that the isolated **7** was gradually converted into another product **2** and the starting morphinan **1** under the same condition. Interestingly, the reaction of the dienol ether **8** having the 4,5-tetrahydrofuran-ring (the 4,5-epoxymorphinan class)[9] did not progress, and **8** was recovered in 94% yield under the same conditions as entry 3. This result suggested that the ring rigidity arising from the 4,5-tetrahydrofuran moiety might prevent the progress of rearrangement.

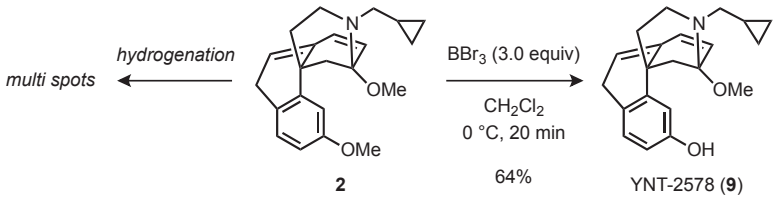
Table 1. Rearrangement of **1** in the presence of zinc iodide



Entry	X/equiv	Solvent	Temp/°C	Time/h	Yields/%	
					2	**7**
1	2.5	$(CH_2Cl)_2$	50	9.0	8	36
2	3.0	THF	60	13	32	43
3	3.0	THF	60 (MW)[a]	9.0	31	65

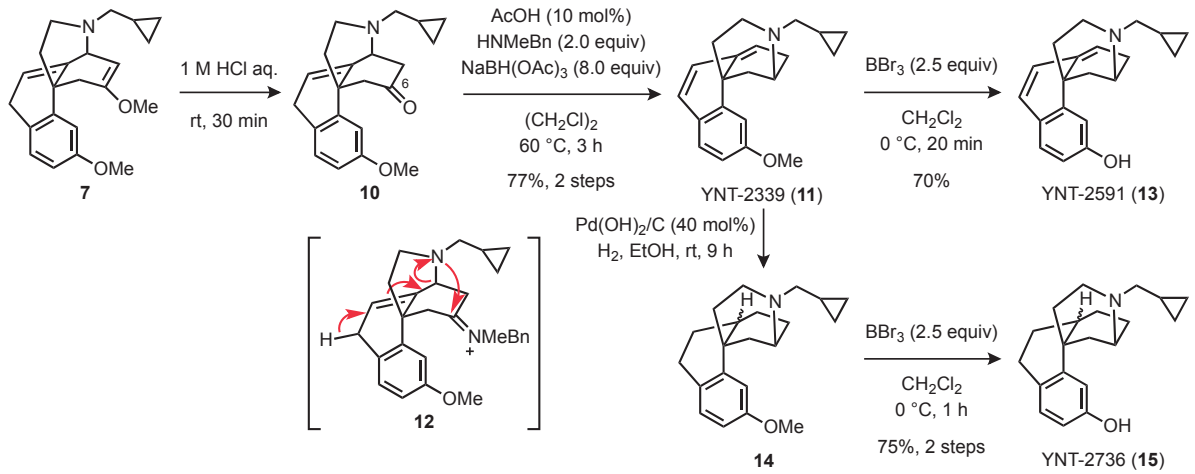
[a] Under microwave (MW) irradiation.

Once the attractive arylmorphan frameworks, especially useful for opioid studies, were obtained, we designed and synthesized a variety of 5-arylmorphan derivatives from **2** or **7** to evaluate their pharmacological effects. First, demethylation of **2** using boron tribromide afforded YNT-2578 (**9**) (Scheme 3). However, hydrogenation of **2** to obtain the corresponding saturated arylmorphan derivative was unsuccessful under all reaction conditions attempted (Pd/C, Pd/Fib, Pd/C(en), $Rh(PPh_3)_3Cl$, Crabtree's catalyst, or PtO_2 under H_2 atmosphere), giving an unidentified complex mixture. These failures were probably due to the unstable moiety of the amino ether at the allylic position in **2**.



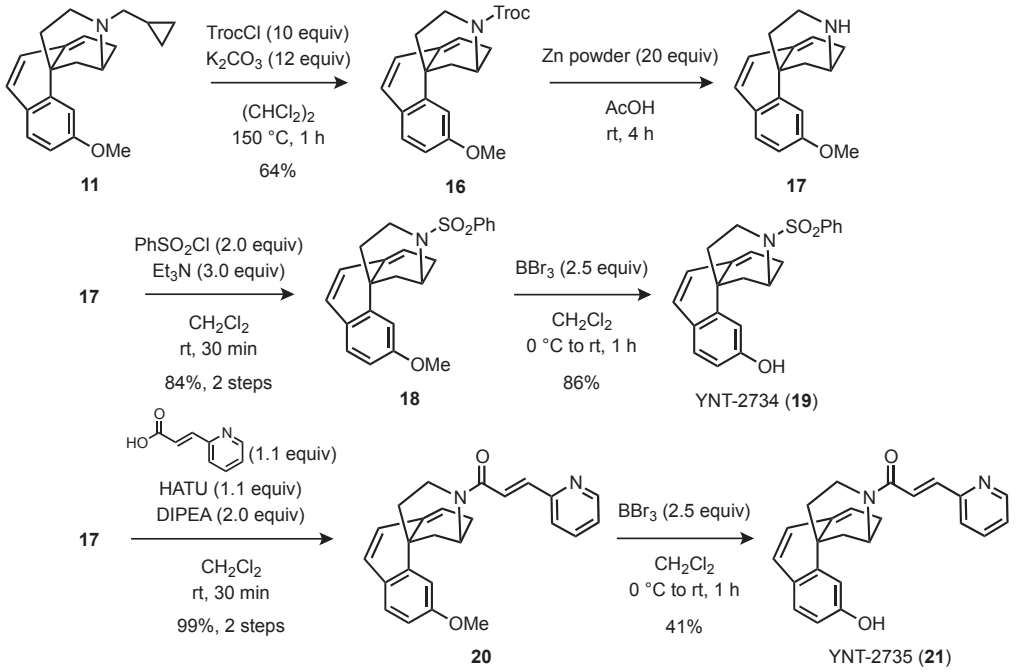
Scheme 3. Transformation from **2** to **9**

The derivatives YNT-2591 (**13**) and YNT-2736 (**15**) were prepared from arylmorphan **7** as shown in Scheme 4. Originally, we attempted to convert the oxygen group into a nitrogen group at the C6 position in ketone **10** derived from **7**. However, interestingly, an unanticipated rearrangement occurred to give YNT-2339 (**11**), which is the same scaffold as **2**, *via* iminium intermediate **12**. Demethylation of **11** using boron tribromide afforded **13**. As hydrogenation of **11** by using 40 mol% of Pearlman's catalyst had succeeded to afford saturated arylmorphan **14** (ca. 5/1 diastereomixture by ^1H NMR), demethylation of **14** was also carried out to obtain **15**.[10]



Scheme 4. Transformation from **7** to **13** and **15**

The derivatives YNT-2734 (**19**) and YNT-2735 (**21**) were prepared from arylmorphan **11** as shown in Scheme 5. After replacement of the cyclopropylmethyl (CPM) group with the 2,2,2-trichloroethyl carbonate (Troc) group, treatment of the obtained **16** with zinc powder afforded the desired secondary amine **17**. Reaction of **17** with benzenesulfonyl chloride and (*E*)-3-(pyridin-2-yl)acrylic acid[11] afforded **18** and **20**, respectively. Demethylation of **18** and **20** afforded **19** and **21**, respectively.



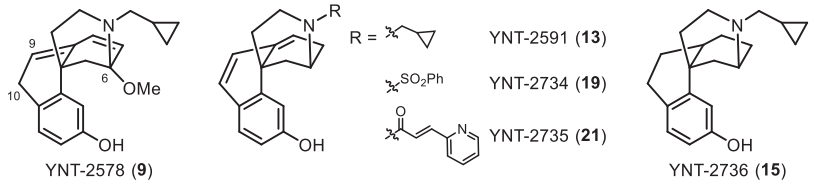
Scheme 5. Transformation from **11** to **19** and **21**

Next, we evaluated the binding affinities and antagonistic activities of the obtained compounds YNT-2578 (**9**),[12] YNT-2591 (**13**),[13] YNT-2736 (**15**),[14] YNT-2734 (**19**),[15] and YNT-2735 (**21**)[16] for the opioid receptors using the opioid receptor binding and the [^{35}S]GTPγS-binding assays.[17] The assays were performed by a previously reported procedure[18a] (Table 2). Interestingly, all arylmorphan derivatives showed affinity for KOR, although most of the known arylmorphan derivatives were reported to be MOR ligands.[19] This observation may be attributed to the presence of the C9–C10 bridge of the morphinan skeleton moiety which could fix the conformation of the phenol ring, unlike many reported 5-arylmorphans. More interestingly, the presence or absence of the methoxy group at the C6 position significantly affected the binding selectivity of the opioid receptors despite the presence of the same functional group (CPM group) on the nitrogen (**9** vs **13** and **15**). With respect to the functional group on the nitrogen, the sulfonamide and amide derivatives **19** and **21** showed weaker binding affinities than **15**. This result suggested that the existence of the basic nitrogen in these novel 5-arylmorphan derivatives as well as the standard morphinan derivatives would be essential for opioid receptor binding.[18] With regard

to the [^{35}S]GTPγS-binding assay, **9** showed the antagonistic activity for the KOR receptors (IC_{50} = 8.18 nM).

Additionally, we evaluated the activities of the synthetically obtained arylmorphan derivatives for orexin receptors,[6] because we have recently reported that morphinan derivatives showed selective antagonistic activities toward OX_1R.[18] As a result, both YNT-2289 (**2**)[20] and YNT-2339 (**11**)[21] showed dual antagonistic activities toward the orexin receptors (**2**: OX_1R, IC_{50} = 4.87 μM; OX_2R, IC_{50} = 3.73 μM/**11**: OX_1R, IC_{50} = 5.48 μM; OX_2R, IC_{50} = 3.46 μM). These results are the first examples in which arylmorphan derivatives showed affinities for orexin receptors.

Table 2. Pharmacological binding properties of the 5-arylmorphan derivatives for opioid receptors



Compounds	K_i (nM)			Selectivity
	μ	δ	κ	μ/κ
9	58.5	978	16.6	3.52
13	552	306	1770	0.31
15[a]	–[b]	–[b]	460	–
19	–[b]	–[b]	705	–
21	–[b]	–[b]	2120	–

[a] The binding assay of **15** was carried out as a 5/1 mixtures of the diastereomers due to the infeasible separation. [b] Not detected.

In conclusion, we have discovered a novel rearrangement reaction of morphinan derivative **1** using zinc iodide to produce 5-arylmorphan derivatives **2** and **7**. On the other hand, the flexibility of the morphinan skeleton was found to be important for this rearrangement, as the reaction of 4,5-epoxymorphinan **8**, which is a more rigid conformation, did not progress under the same conditions. Moreover, we led the rearrangement products into various 5-arylmorphan derivatives. Binding assays of those arylmorphan derivatives toward opioid receptors showed the affinities for KOR. Especially, the compound **9** showed the antagonistic activities for μ and κ receptors (binding selectivity, μ/κ = 3.52). The experimental observation that the basicity of the nitrogen in the 5-arylmorphane derivatives could play an important role in binding opioid receptors indicated the same tendency that the basicity of the nitrogen in morphinan derivatives is essential for affinity for opioid receptors. This conclusion could provide useful information

for medicinal chemists working in the field of opioid receptors. In addition, arylmorphans **2** and **11** showed dual antagonistic activities toward orexin receptors. This first finding encourages us to continue to explore more effective orexin ligands.

ACKNOWLEDGEMENTS

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8. Typical Procedure (Table 1, entry 2): A mixture of **1** (3.16 g, 9.36 mmol) and zinc iodide (8.96 g, 28.1 mmol) in THF (30 mL) was stirred at 60 °C for 13 h. After the addition of sat. $NaHCO_3$ aq. (30 mL) at 0 °C, the mixture was extracted with EtOAc (200 mL, 100 mL), washed with brine, dried

over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by NH-silica gel (CHROMATOREX NH-DM2035, Fuji Silysia Chemical Ltd.) column chromatography (hexane/EtOAc = 12/1 to 5/1) to afford **2** (1.02 g, 32%) as a pale brown oil and **7** (1.35 g, 43%) as a pale brown oil.

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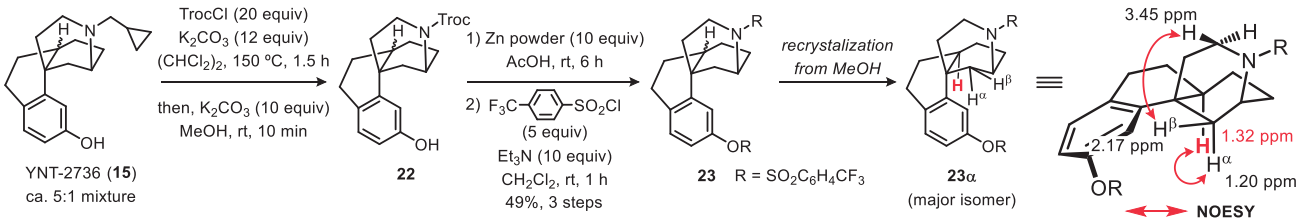
10. We synthesized compound **23** to determine the stereochemistry of the major diastereomer of the compound **15**, as follows. The recrystallization of the ca. 5/1 mixture of **23** (12.3 mg) from refluxing MeOH afforded only the major isomer **23α** (5.0 mg) as a needle-like crystal and the stereochemistry of **23α** was determined by the NOESY experiments. As a result, the stereochemistry of the major isomer of **15** should be the same as that of **23α**.



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12. Compound **9**: Pale yellow oil. IR (neat) 3330, 3007, 2933, 1611, 1292, 1143, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07–0.15 (m, 2H), 0.41–0.48 (m, 1H), 0.52–0.62 (m, 1H), 0.80–0.95 (m, 1H), 1.49–1.67 (m, 3H), 1.85 (dd, *J* = 11.2, 2.8 Hz, 1H), 2.14 (ddd, *J* = 12.4, 12.4, 4.0 Hz, 1H), 2.63 (d, *J* = 11.2 Hz, 1H), 3.17 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.28–3.43 (m, 3H), 3.49 (s, 3H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.99 (dd, *J* = 5.2, 2.8 Hz, 1H), 6.42 (d, *J* = 10.4 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), The OH peak was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.7, 5.9, 9.6, 30.1, 37.8, 39.3, 40.2, 47.9, 48.7, 53.6, 88.0, 111.1, 113.6, 125.66, 125.74, 127.2, 129.0, 132.4, 138.7, 144.7, 155.0; HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}NO_2$: 324.1964, found 324.1957.

13. Compound **13**: Pale yellow oil. IR (neat) 3333, 3006, 2918, 1601, 1470, 1300, 1123, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10–0.20 (m, 2H), 0.49–0.59 (m, 2H), 0.90–1.01 (m, 1H), 1.51–1.62 (m, 2H), 1.78–1.86 (m, 1H), 2.10 (ddd, *J* = 20.4, 4.0, 3.6 Hz, 1H), 2.29 (dd, *J* = 20.4, 4.4 Hz, 1H), 2.36–2.47 (m, 3H), 2.65 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.73 (ddd, *J* = 12.4, 3.2, 3.2 Hz, 1H), 3.49–3.55 (m, 1H), 5.74 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 1H), 6.15 (d, *J* = 9.6 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), The OH peak was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.2, 4.4, 8.3, 23.7, 33.8, 36.8, 37.8, 43.8, 51.7, 59.6, 113.8, 114.8, 124.4, 124.9, 125.0, 126.5, 128.4, 137.9, 144.6, 157.2; HRMS-ESI: *m/z* $[M + H]^+$ calcd for

$C_{20}H_{24}NO$: 294.1858, found 294.1844.

14. Compound **15**: Colorless solid. IR (neat) 3378, 3001, 2922, 1606, 1450, 1253, 1105 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 0.11–0.21 (m, 2H), 0.41–0.52 (m, 2H), 0.87–1.00 (m, 1H), 1.29–1.41 (m, 1H), 1.47–1.85 (m, 6H), 1.90–2.01 (m, 1H), 2.02–2.19 (m, 2H), 2.28 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.46 (dd, *J* = 12.4, 6.0 Hz, 0.17H), 2.55 (dd, *J* = 12.8, 6.0 Hz, 0.83H), 2.65–2.91 (m, 4H), 2.92–3.01 (m, 1H), 3.04–3.09 (m, 0.17H), 3.15–3.25 (m, 0.83H), 7.01–7.11 (m, 2H), 7.37–7.43 (m, 1H), 11.12 (brs, 1H) as a 5:1 mixtures; ^{13}C NMR (100 MHz, pyridine-d_5) δ 3.9, 4.9, 10.1, 26.1, 26.6, 29.5, 30.6, 36.1, 36.2, 40.7, 42.8, 49.7, 53.6, 60.9, 112.7, 114.5, 126.9, 130.7, 148.7, 157.2 as a major isomer; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{28}NO$: 298.2171, found 298.2162.
15. Compound **19**: Colorless solid. IR (KBr) 3389, 2916, 1601, 1569, 1446, 1328, 1156, 1115, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (ddd, *J* = 12.8, 12.8, 4.8 Hz, 1H), 1.65–1.72 (m, 1H), 1.84 (ddd, *J* = 12.4, 2.4, 2.4 Hz, 1H), 1.91 (dd, *J* = 20.8, 4.4 Hz, 1H), 2.36 (dd, *J* = 12.4, 3.6 Hz, 1H), 2.43 (ddd, *J* = 20.8, 5.6, 3.6 Hz, 1H), 3.17 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 3.66–3.73 (m, 1H), 4.48–4.54 (m, 1H), 4.97 (brs, 1H), 5.69 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.92 (d, *J* = 9.6 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.52–7.64 (m, 3H), 7.84–7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 33.8, 36.7, 37.6, 37.7, 48.5, 112.1, 113.5, 124.9, 125.0, 125.9, 126.3, 127.2 (×2), 128.7, 129.4 (×2), 132.7, 136.9, 140.8, 144.0, 155.6; HRMS-ESI *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_3S$: 402.1140, found 402.1137.
16. Compound **21**: Pale yellow oil. IR (neat) 3418, 1650, 1614, 1446, 1298, 1225, 1128, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33–1.50 (m, 1H), 1.52–1.60 (m, 0.7H), 1.81–1.95 (m, 1H), 2.07–2.20 (m, 1.3H), 2.28–2.38 (m, 1H), 2.57–2.73 (m, 1H), 3.09 (ddd, *J* = 13.2, 13.2, 3.6 Hz, 0.3H), 3.39 (ddd, *J* = 13.2, 13.2, 3.6 Hz, 0.7H), 3.79 (dd, *J* = 13.2, 4.0 Hz, 0.7H), 4.45 (dd, *J* = 13.2, 4.0 Hz, 0.3H), 4.63–4.69 (m, 0.3H), 5.28–5.34 (m, 0.7H), 5.81 (dd, *J* = 4.0, 4.0 Hz, 0.3H), 5.84 (dd, *J* = 4.0, 4.0 Hz, 0.7H), 5.93–6.01 (m, 1H), 6.21 (d, *J* = 9.6 Hz, 0.7H), 6.22 (d, *J* = 9.6 Hz, 0.3H), 6.64 (dd, *J* = 8.4, 2.4 Hz, 0.3H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 0.7H), 6.79 (d, *J* = 1.6 Hz, 0.3H), 6.87–6.92 (m, 1.7H), 7.27–7.31 (m, 1H), 7.32–7.36 (m, 0.3H), 7.36–7.40 (m, 0.7H), 7.56 (d, *J* = 14.8 Hz, 0.7H), 7.60–7.66 (m, 1.3H), 7.70–7.77 (m, 1H), 8.58–8.62 (m, 0.7H), 8.62–8.66 (m, 0.3H) as a 7:3 rotamers, The OH peak was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 32.8, 33.4, 34.3, 35.0, 37.0, 37.1, 38.0, 38.57, 38.63, 44.4, 48.8, 112.2, 112.3, 113.5, 113.6, 122.5, 122.7, 124.2, 124.3, 124.6, 124.7, 125.0, 125.1, 125.2, 125.3, 125.5, 125.6 (×2), 126.2, 128.6, 128.7, 137.2, 137.4, 137.5, 137.6, 140.7 (×2), 143.8, 143.9, 149.68, 149.73, 153.3, 153.4, 156.8, 157.3, 165.4, 165.7 as a 7:3 rotamers; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_2$: 371.1760, found 371.1754.
17. Human embryonic kidney (HEK) cells stably expressing human μ, δ, or κ opioid receptors were gifted from Dr. Y. Uezono and Dr. K. Miyano (National Cancer Center Research Institute); these

cell membranes were used for opioid receptor binding assay and GTPγS binding assay. Binding affinity for μ, δ, or κ opioid receptor in test compounds was measured by displacement of [^{3}H]-DAMGO, [^{3}H]-DPDPE, or [^{3}H]-U69,593 (each 2 nM), respectively. Nonspecific binding was measured in the presence of 10 μM unlabeled DAMGO, DPDPE, or U-69,593. Radioactivity in the test samples was determined by a MicroBeta scintillation counter with 96-well microplate (PerkinElmer). In GTPγS binding assay, various concentrations of test compounds were incubated with cell membrane, 30 μM GDP and 0.1 nM [^{35}S]GTPγS in 96-well microplate. In case of IC_{50} calculation (antagonistic activity test), 10^{-6} M U-69,593 (approximately EC_{80}), a standard κ receptor agonist, was added to incubating solution. Nonspecific binding was measured in the presence of 10 μM unlabeled GTPγS. Radioactivity in the test samples was determined by a MicroBeta scintillation counter. The value of each test compounds was calculated as $[(T_1 - T_0)/(T_2 - T_0)] \times 100$, where T_0 is the nonspecific binding, T_1 is the radioligand binding in the presence of various concentrations of test compounds (10^{-5}–10^{-11} M), and T_2 is the radioligand binding in the absence of respective test compounds. For IC_{50} calculation, T_2 is the radioligand binding in the presence of 10^{-6} M U-69,593 without test compounds. Sigmoidal concentration–response curve, K_i and IC_{50} values were calculated by Prism software (version 6.05).

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20. Compound **2**: Pale yellow oil. IR (neat) 2954, 1614, 1498, 1146, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05–0.16 (m, 2H), 0.39–0.50 (m, 1H), 0.50–0.60 (m, 1H), 0.78–0.90 (m, 1H), 1.50–1.61 (m, 2H), 1.66 (ddd, J = 12.4, 12.4, 5.2 Hz, 1H), 1.83 (dd, J = 11.2, 2.8 Hz, 1H), 2.12 (ddd, J = 12.4,

12.4, 4.0 Hz, 1H), 2.59 (d, *J* = 10.8 Hz, 1H), 3.14 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.28–3.35 (m, 1H), 3.37 (d, *J* = 5.6 Hz, 1H), 3.42 (d, *J* = 3.2 Hz, 1H), 3.47 (s, 3H), 3.81 (s, 3H), 5.43 (d, *J* = 9.6 Hz, 1H), 5.99 (dd, *J* = 5.6, 3.2 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.6, 5.7, 9.8, 30.1, 38.1, 39.6, 40.4, 47.9, 48.4, 53.5, 55.5, 87.6, 109.8, 111.0, 125.3, 126.1, 127.6, 128.8, 131.8, 138.8, 144.9, 158.6; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{28}NO_2$: 338.2120, found: 338.2125.

21. Compound **11**: Pale yellow oil. IR (neat) 2912, 1600, 1495, 1308, 1285, 1165, 1099, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07–0.19 (m, 2H), 0.48–0.58 (m, 2H), 0.83–0.94 (m, 1H), 1.62–1.73 (m, 2H), 1.88–1.95 (m, 1H), 2.10 (ddd, *J* = 20.4, 4.8, 3.2 Hz, 1H), 2.28–2.50 (m, 4H), 2.58 (dd, *J* = 12.4, 3.6 Hz, 1H), 2.73 (ddd, *J* = 12.0, 3.2, 3.2 Hz, 1H), 3.46–3.52 (m, 1H), 3.80 (s, 3H), 5.83 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.97 (d , *J* = 9.6 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.9, 4.1, 9.4, 24.0, 35.1, 37.4, 38.7, 44.0, 51.6, 55.4, 60.0, 111.1, 111.2, 124.3, 125.6, 126.2, 127.9, 128.1, 137.7, 145.2, 159.4; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{26}NO$: 308.2014, found 308.2009.