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Novel rearrangement reaction of a 6,14-endoethanomorphinan derivative to a benzomorphan derivative

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ABSTRACT

Treatment of 7α-hydroxymethylendoethenomorphinan derivative with trifluoromethanesulfonic anhydride at rt and subsequent toluene reflux afforded a novel lactone by rearrangement reaction. The skeleton of the lactone is analogous to that of the benzomorphan like pentazocine, which is a useful analgesic. The rearrangement reaction opens the door to a facile synthesis from the 4,5-epoxymorphinans to the benzomorphan derivatives. On the basis of careful examination of the reaction intermediates, a reaction mechanism was proposed.

1. Introduction

Buprenorphine[1] and etorphine[2] (Fig. 1) are potent μ and ε opioid analgesics, and like opiate analgesics in general, they can cause serious respiratory depression. However, these two particular analgesics produce an especially dangerous form of respiratory depression that cannot be reversed by the μ opioid antagonist naloxone. This resistance to naloxone antagonism is generally attributed to the high affinity of these opiates for the μ receptor and to their high lipophilicities.[1]

We have already reported a potent and selective ε agonist TAN-821[3] and antagonist TAN-1014[4] (Fig. 1). TAN-821 produced profound analgesia, which was antagonized by β-endorphin [1–27] (a peptidic ε antagonist) and not β-FNA (μ antagonist), NTI (δ antagonist), nor-BNI (κ antagonist) in in vivo tail-flick and hot-plate tests. However, TAN-821 did not show sufficient selectivity for the ε receptor in vitro and, in fact, has been found to bind to all opioid receptor types (mouse vas deferens assay). Etorphine, buprenorphine, TAN-821, and TAN-1014 share a common 6,14-endoethano- or 6,14-endoethenotetrahydrooripavine skeleton, which has either a 6,14-ethylene or 6,14-vinylene bridge. We hypothesized that the strong affinity of these four compounds for μ opioid receptors may derive in part from the high lipophilicity conferred by this bridge. Therefore, we attempted to modify the endoethenotetrahydrooripavine

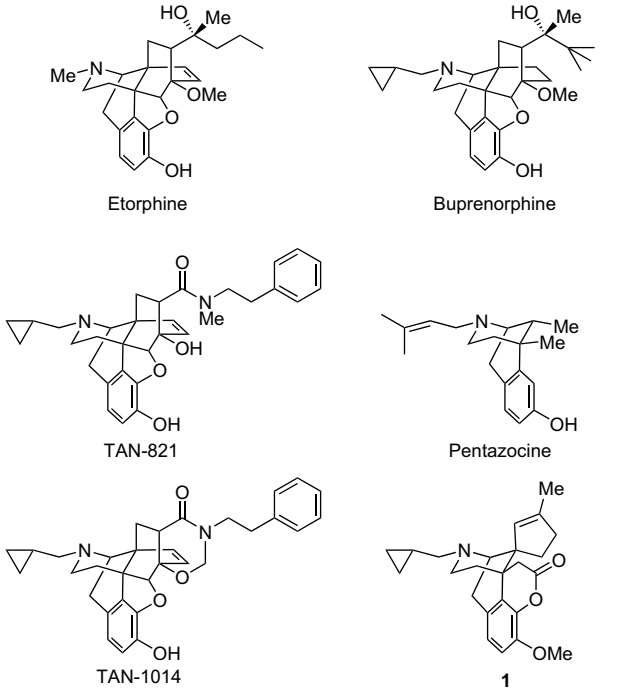

Figure 1. Structures of etorphine, buprenorphine, pentazocine, TAN-821, TAN-1014, and compound **1**.

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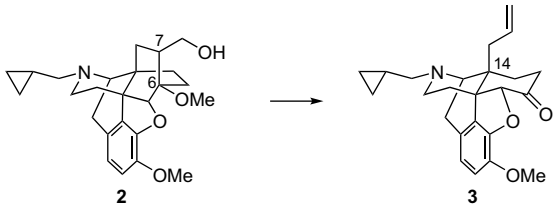


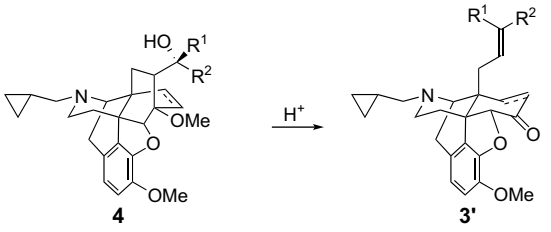
Scheme 1. Synthetic plan of compound **3** from compound **2**.

skeleton to improve the ε selectivity of TAN-821 in vitro. TAN-821 has an ethylene bridge on the C ring. We hypothesized that the substituent above the C ring contributed to the ε receptor selectivity.[3] Based on this hypothesis, we designed naltrexone derivative **3** having a 14-allyl group to which appropriate substituents could be introduced and planned to synthesize **3** from primary alcohol **2** by fragmentation (Scheme 1). In the course of our attempts to convert the alcohol **2** to the 14-allyl derivative **3**, we found a novel rearrangement reaction of compound **2** that afforded benzomorphan derivative **1**, which can be converted to the representative benzomorphan, pentazocine (Fig. 1). We became interested in this novel reaction and have attempted to clarify the reaction mechanism.[5] Herein, we report the novel rearrangement reaction and propose its mechanism.

2. Results and discussion

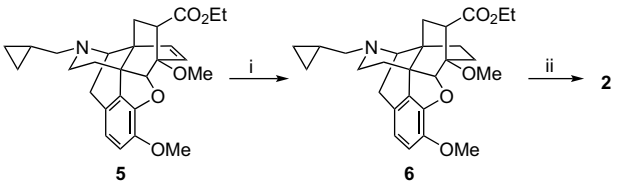
2.1. Synthesis of lactone 1

The endoethano- or endoethenotetrahydrooripavine derivatives **4** with either a tertiary or secondary alcohol moiety were reported to undergo fragmentation under acidic conditions to give 14-

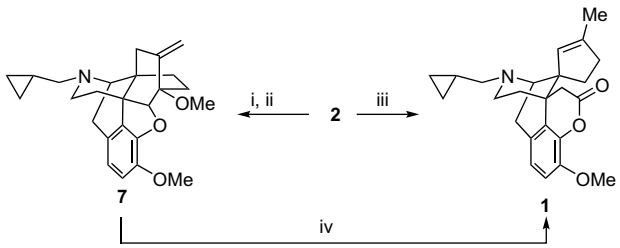


Scheme 2. Fragmentation of compound **4** under acidic conditions.

alkenyl derivative **3′** (Scheme 2).[6,7] We attempted to cleave the C6–C7 bond of alcohol **2** possessing a primary alcohol to afford a naltrexone derivative with a 14-allyl group **3** (Scheme 1). Alcohol **2**, which was synthesized from compound **5**[4] by hydrogenation and subsequent reduction of the ester group (Scheme 3), was treated with trifluoromethanesulfonic anhydride in dichloromethane at rt. After the reaction mixture was washed with saturated sodium bicarbonate solution and concentrated under reduced pressure, the resulting residue was dissolved in toluene and refluxed under argon to give olefin **7**[8] in 91% yield. On the other hand, after the treatment of **2** with trifluoromethanesulfonic anhydride in dichloromethane, the concentrated reaction mixture, without



Scheme 3. Synthesis of compound **2**. Reagents and conditions: (i) H_2 (0.4 MPa), Pd/C, EtOH, 50 °C, 93%; (ii) $LiAlH_4$, THF, 0 °C to rt, 95%.



Scheme 4. Synthesis of the rearranged product **1**. Reagents and conditions: (i) Tf_2O, CH_2Cl_2, rt; (ii) toluene, reflux, 91%; (iii) Tf_2O, CH_2Cl_2, rt, then toluene, reflux, 77%; (iv) TfOH, toluene, reflux, quant.

washing with sodium bicarbonate solution, was refluxed in toluene under argon to afford the unexpected rearrangement product **1** in 77% yield (Scheme 4). The structure of lactone **1** was determined by IR, mass, and NMR spectra (^1H, ^{13}C, COSY, HSQC, and HMBC. See Table 1). Figure 2 shows the HMBC relationships.

Table 1
^1H (400 MHz) and ^{13}C NMR (100 MHz) spectral data ($CDCl_3$) of lactone **1**

	^1H	^{13}C
1	2.67–2.76 (m, 1H), 2.94 (d, *J*=18.3 Hz, 1H)	22.82
2	3.06 (d, *J*=5.7 Hz, 1H)	61.65
4	1.91–2.08 (m, 1H), 2.67–2.76 (m, 1H)	45.47
5	1.33–1.38 (m, 1H), 1.91–2.08 (m, 1H)	32.77
6		55.38
6a		126.0
7		139.9
8		145.4
9	6.79 (d, *J*=8.4 Hz, 1H)	111.3
10	6.85 (d, *J*=8.4 Hz, 1H)	123.0
10a		129.5
11		39.60
12	5.93 (br s, 1H)	127.5
13		142.4
14	2.18–2.37 (m, 2H)	36.87
15	1.58–1.76 (m, 2H)	32.13
16	1.79 (s, 3H)	17.19
17		168.3
18	2.60 (d, *J*=16.5 Hz, 1H), 2.61 (d, *J*=16.5 Hz, 1H)	36.17
19	3.85 (s, 3H)	56.37
1′	2.18–2.37 (m, 2H)	59.55
2′	0.73–0.88 (m, 1H)	9.75
3′	0.01–0.16 (m, 2H)	3.86
	0.42–0.52 (m, 2H)	4.07

We then attempted to clarify the reaction mechanism of this novel rearrangement. When the olefin **7** was treated with trifluoromethanesulfonic acid (2.2 equiv) in toluene under reflux, the objective lactone **1** was obtained in quantitative yield.[9] Next, treatment of the olefin **7** with a weaker acid (DL-camphorsulfonic

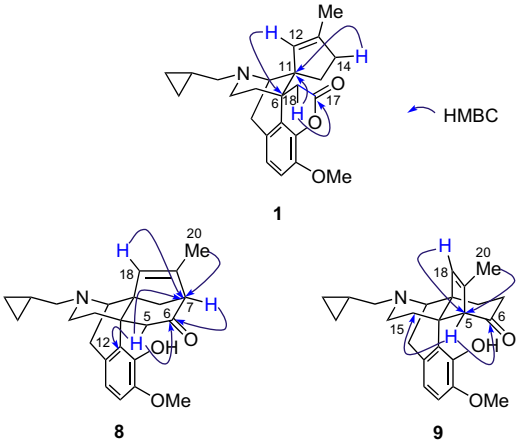
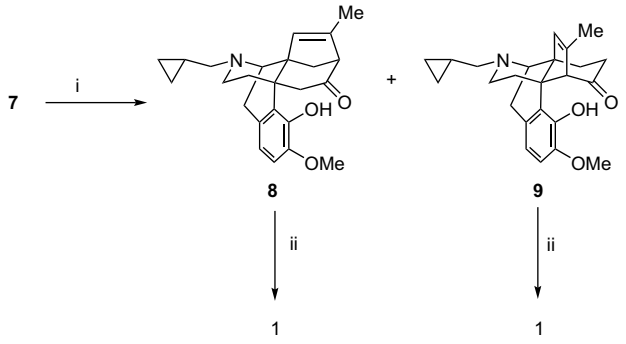


Figure 2. Observed HMBC spectra of compounds **1**, **8**, and **9**.



Scheme 5. Synthesis of the rearranged compound **1** via intermediates **8** and **9**. Reagents and conditions: (i) CSA, toluene, reflux, 34% for **8**, 35% for **9**; (ii) TfOH, toluene, reflux, quant.

acid (CSA)) in toluene under reflux gave ketones **8** and **9** (Scheme 5), whose structures were also determined by IR, mass, and NMR spectra (Tables 2,3, and Fig. 2). Both ketones **8** and **9** were converted into lactone **1** when these compounds were treated with trifluoromethanesulfonic acid in toluene under reflux. Taken together, these outcomes indicate that the three compounds **7**, **8**, and **9** are intermediates toward preparation of lactone **1**.

2.2. Proposed reaction mechanism to lactone 1

On the basis of the structures of the three isolated important intermediates **7**, **8**, and **9**, we proposed a reaction mechanism for preparation of lactone **1** (Scheme 6). In this mechanism, catalytic amounts of water or trifluoromethanesulfonic acid would play an important role. Oxonium **8′** may be obtained by intramolecular aldol reaction of intermediate **10**, which may be derived from olefin **7** by acidic hydration, subsequent fragmentation, and isomerization. Oxonium **8′** may be converted to acetal **11** by intramolecular cyclization to afford lactone **1** by fragmentation and subsequent isomerization. As another possible route, oxonium **8′** may be hydrated to provide carboxylic acid by fragmentation, and then esterification of the resulting carboxylic acid may lead to lactone **1**. However, we believe the former route would proceed predominantly because intramolecular reactions are generally faster than intermolecular reactions. Oxonium **9′** may be prepared from **10′** (regioisomer of **10**) by intramolecular aldol reaction. Both oxoniums **8′** and **9′** would be converted to lactone **1** because of the equilibrium between **8′** and **9′** under the reaction conditions. The equilibrium was confirmed by the observation that treatment of either pure compound **8** or **9** in the presence of CSA under reflux gave mixture of ketones **8** and **9**. Moreover, the distance between the olefin moiety and the carbonyl group in lactone **1** may be so large that the reverse reaction may not occur: the formation of lactone **1** may therefore be irreversible (Fig. 3). As a result, lactone **1** would be obtained in excellent yield regardless of the ratio of **8** and **9** in their equilibrium.

Table 2
^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectral data ($CDCl_3$) of ketone **8**

	^{1}H	^{13}C
1	6.57 (d, *J*=8.1 Hz, 1H)	118.4
2	6.65 (d, *J*=8.1 Hz, 1H)	108.4
3		144.8
4		143.9
5	2.59 (d, *J*=18.0 Hz, 1H), 4.19 (d, *J*=18.0 Hz, 1H)	43.89
6		211.4
7	2.83 (t, *J*=2.1 Hz, 1H)	60.80
8	1.98–2.01 (m, 2H)	43.02
9	3.06 (d, *J*=4.5 Hz, 1H)	57.60
10	2.70 (dd, *J*=4.5, 18.0 Hz, 1H), 2.91 (d, *J*=18.0 Hz, 1H)	24.62
11		131.6
12		127.2
13		52.18
14		41.14
15	1.74–1.96 (m, 2H)	34.51
16	1.74–1.96 (m, 2H)	46.13
18	6.37 (d, *J*=1.8 Hz, 1H)	133.4
19		143.2
20	1.81 (d, *J*=1.5 Hz, 3H)	15.85
21	3.83 (s, 3H)	56.13
1′	2.27 (dd, *J*=6.3, 12.0 Hz, 1H), 2.41 (dd, *J*=6.3, 12.0 Hz, 1H)	59.47
2′	0.77–0.90 (m, 1H)	9.63
3′	0.04–0.15 (m, 2H)	3.63
	0.42–0.52 (m, 2H)	3.83
OH	6.08 (br s, 1H)	

Table 3
^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectral data ($CDCl_3$) of ketone **9**

	^{1}H	^{13}C
1	6.63 (d, *J*=8.7 Hz, 1H)	118.3
2	6.66 (d, *J*=8.7 Hz, 1H)	108.5
3		144.5
4		142.7
5	3.46 (s,1H)	69.30
6		209.1
7	1.83–1.94 (m, 1H), 2.21–2.41 (m, 1H)	34.42
8	1.37–1.55 (m, 1H), 1.83–1.94 (m, 1H)	28.10
9	3.50 (d, *J*=6.3 Hz, 1H)	53.58
10	2.72 (dd, *J*=6.3, 18.6 Hz, 1H), 2.95 (d, *J*=18.6 Hz, 1H)	24.51
11		130.4
12		125.8
13		50.36
14		50.08
15	1.37–1.55 (m, 1H), 2.21–2.41 (m, 1H)	32.32
16	2.03–2.15 (m, 1H), 2.45–2.51 (m, 1H)	44.23
18	5.83 (d, *J*=1.8 Hz, 1H)	133.1
19		140.3
20	1.79 (d, *J*=1.2 Hz, 3H)	16.10
21	3.81 (s, 3H)	55.80
1′	2.16 (dd, *J*=5.1, 12.0 Hz, 1H), 2.57 (dd, *J*=5.1, 12.0 Hz, 1H)	59.93
2′	0.81–0.93 (m, 1H)	9.18
3′	0.06–0.18 (m, 2H)	2.63
	0.44–0.61 (m, 2H)	5.01
OH	5.65 (br s, 1H)	

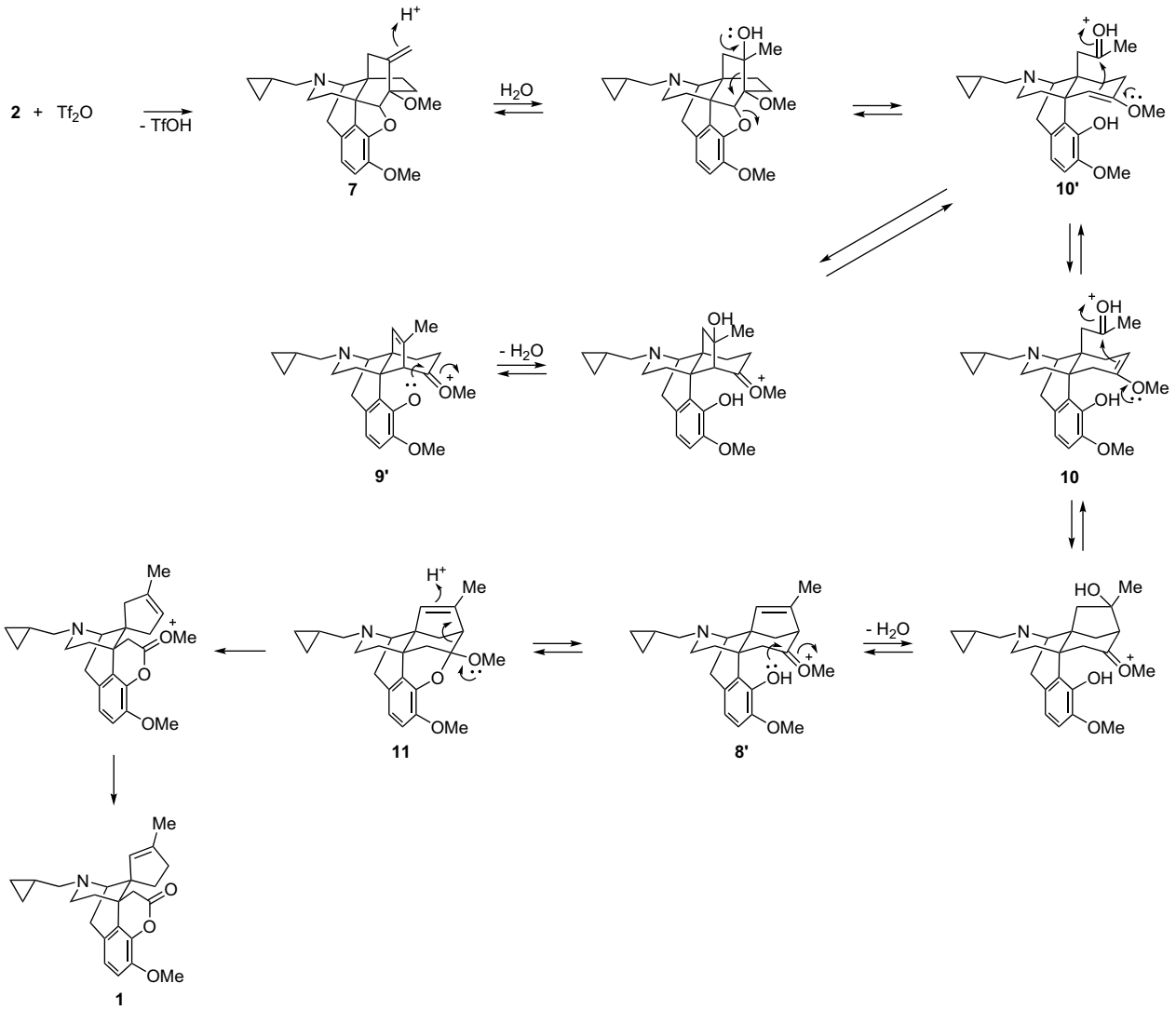
The structure of rearranged product **1** is very similar to that of the benzomorphan like pentazocine,[10] a useful analgesic. Although several papers have already described the total synthesis of pentazocine, most of them were syntheses of a racemic form with several exceptions.[11–15] Lactone **1** was a chiral compound having the desirable absolute configuration because it was derived from the commercially available semi-synthetic opioid (−)-naltrexone via alcohol **2**. Therefore, its conversion from lactone **1** to the pharmacologically active enantiomer (−)-pentazocine would be expected.[16] Presently, we are investigating the conversion of **1** to pentazocine and will give a complete report in the future.

3. Conclusion

We found the novel rearrangement reaction of alcohol **2** to lactone **1** with trifluoromethanesulfonic anhydride in dichloromethane at rt followed by treatment in toluene under reflux. Three important intermediates **7**, **8**, and **9** were isolated and confirmed, indicating that the three compounds could be converted to the identical lactone **1**. A reaction mechanism yielding lactone **1** from the three individual intermediates was proposed. The skeleton of lactone **1** is analogous to that of a benzomorphan such as pentazocine. The rearrangement reaction opens the door to a facile synthesis from 4,5-epoxymorphinans to benzomorphan derivatives. We are presently attempting to synthesize pentazocine from lactone **1**.

4. Experimental section

Melting points were measured on a Yazawa BY-10 melting point apparatus. Infrared (IR) spectra were measured on a JASCO FT/IR-



Scheme 6. Proposed mechanism of the rearrangement reaction to lactone **1**.

460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-300 or Varian UNITY-400 spectrometer operating at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were measured on a JMS-AX505HA or JMS-700 M Station instruments by applying a fast atom bombardment (FAB) ionization method. Elemental analyses were measured by Yanako MT-5 instrument. The progress of the reaction was determined on Merck Silica Gel Art. 5715. Column chromatographies were carried out using Kanto Silica Gel 60N (63–210 μm). Preparative TLC was performed using Merck Silica Gel Art. 5744.

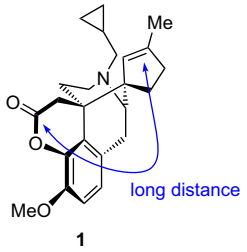


Figure 3. Backside views of lactone **1**.

4.1. Ethyl 17-(cyclopropylmethyl)-4,5α-epoxy-6α,14α-ethano-3,6β-dimethoxymorphinan-7α-carboxylate (6)

To the solution of compound **5** (8.0 g, 17.7 mmol) in EtOH (500 mL) was added 10% Pd/C (790 mg) and stirred at 50 °C for 2 days under H_2 (0.4 MPa). The reaction mixture was filtered through Celite pad and obtained filtrate was concentrated under reduced pressure. Resulting residue was crystallized from MeOH solution to give compound **6** (7.43 g, 93%) as a white prism crystal. Mp 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04–0.14 (m, 2H), 0.42–0.52 (m, 2H), 0.69–0.82 (m, 2H), 1.28 (t, J=7.2 Hz, 3H), 1.42–1.53 (m, 1H), 1.65–1.87 (m, 4H), 2.01 (dt, J=5.7, 12.3 Hz, 1H), 2.23–2.35 (m, 4H), 2.63 (dd, J=4.8, 12.0 Hz, 1H), 2.84–3.06 (m, 4H), 3.44 (s, 3H), 3.87 (s, 3H), 4.09–4.27 (m, 2H), 4.52 (d, J=2.1 Hz, 1H), 6.57 (d, J=8.1 Hz, 1H), 6.70 (d, J=8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.33, 3.96, 9.40, 14.17, 18.97, 22.72, 28.78, 31.20, 35.40, 35.44, 42.80, 43.65, 46.04, 51.23, 56.53, 58.35, 59.73, 60.49, 76.71, 91.60, 113.6, 119.1, 128.6, 132.5, 141.7, 146.8, 173.9. IR (KBr, cm^{-1}): 2937, 1719, 1627, 1601, 1499, 1453, 1209, 1163. MS (FAB) m/z 454 $[M+H]^+$. Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09. Found: C, 71.33; H, 7.88; N, 3.20.

4.2. 17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14α-ethano-3,6β-dimethoxymorphinan-7α-yl methanol (2)

Under Ar, to the suspension of $LiAlH_4$ (2.13 g, 56.2 mmol) in THF (30 mL) was added dropwise the solution of compound **6** (4.64 g, 10.3 mmol) in THF (90 mL) at 0 °C and stirred at rt for 1 h. To the reaction mixture were added dropwise EtOAc and saturated Rochelle salt solution. Obtained reaction mixture was filtered through Celite pad and the filtrate was concentrated under reduced pressure to give compound **2** (4.74 g, quant.) as a brownish amorphous solid. The obtained material was used in the next reaction as a starting material without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04–0.09 (m, 2H), 0.42–0.51 (m, 2H), 0.68–0.85 (m, 3H), 1.00 (ddd, J=6.0, 9.0, 12.0 Hz, 1H), 1.48–1.58 (m, 1H), 1.63–1.75 (m, 3H), 2.01–2.11 (m, 2H), 2.16–2.36 (m, 4H), 2.63 (dd, J=4.8, 12.0 Hz, 1H), 2.85–3.01 (m, 2H), 3.42–3.54 (m, 1H), 3.50 (s, 3H), 3.65 (d, J=10.2 Hz, 1H), 3.86–3.92 (m, 1H), 3.88 (s, 3H), 4.48 (d, J=2.1 Hz, 1H), 6.55 (d, J=8.1 Hz, 1H), 6.70 (d, J=8.1 Hz, 1H). IR (film, cm^{-1}): 3455, 2928, 1629, 1599, 1501, 1450, 1333, 1260, 1093, 755. HRMS (FAB): $[M+H]^+$ Calcd for $C_{25}H_{34}NO_4$: 412.2488. Found: 412.2532.

4.3. 17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14α-ethano-3,6β-dimethoxy-7-methylenemorphinan (7)

Under Ar, to the solution of compound **2** (90 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) was added Tf_2O (64.2 μL, 0.39 mmol) dropwise at 0 °C and stirred at rt for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing solvent under reduced pressure to give yellow oil (113 mg). Under Ar, the solution of the yellow oil (113 mg) in toluene (3 mL) was refluxed for 1.5 h. After concentrating the reaction mixture, $CHCl_3$ and saturated $NaHCO_3$ solution were added and separated. The obtained organic layer was washed with brine and dried over anhydrous Na_2SO_4 followed by removing solvent under reduced pressure. Resulting residue was purified by crystallization from MeOH solution to give compound **7** (78 mg, 91%) as a white prism crystal. Mp: 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06–0.17 (m, 2H), 0.41–0.54 (m, 2H), 0.74–0.92 (m, 2H), 1.12 (ddd, J=6.0, 9.0, 12.0 Hz, 1H), 1.47–1.65 (m, 3H), 1.98 (ddd, J=5.4, 12.0, 12.0 Hz, 1H), 2.17–2.38 (m, 5H), 2.63 (dd, J=5.4, 12.0 Hz, 1H), 3.02 (d, J=19.2 Hz, 1H), 3.04 (d, J=5.4 Hz, 1H), 3.39–3.47 (m, 1H), 3.42 (s, 3H), 3.87 (s, 3H), 4.33 (d, J=1.5 Hz, 1H), 5.08 (d, J=1.8 Hz, 1H), 5.29 (d, J=1.8 Hz, 1H), 6.55 (d, J=8.1 Hz, 1H), 6.70 (d, J=8.1 Hz, 1H). IR (KBr, cm^{-1}): 2927, 2802, 1628, 1599, 1498, 1450, 1325, 1278, 1096. ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.38, 4.06, 9.44, 20.39, 22.61, 29.35, 34.76, 36.28, 37.20, 43.83, 45.63, 51.65, 56.69, 58.28, 59.89, 78.88, 93.17, 110.5, 113.8, 118.9, 128.6, 133.0, 141.8, 145.5, 147.1. IR (KBr, cm^{-1}): 2927, 2802, 1628, 1599, 1498, 1450, 1325, 1278, 1096. MS (FAB) m/z 394 $[M+H]^+$. Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.21; H, 8.00; N, 3.63. Found: C, 76.30; H, 7.94; N, 3.56.

4.4. (11*S*)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-7,6-(2-oxoepoxyethano)-3-benzazocin-11-spiro-1′-(3′-methylcyclopent-2′-ene) (1)

Method A. Under Ar, to the solution of compound **2** (5.62 g, 13.7 mmol) in CH_2Cl_2 was added Tf_2O (4.1 mL, 24.6 mmol) dropwise at 0 °C and stirred at rt for 5 min. After concentrating the reaction mixture, the solution of the obtained residue in toluene (175 mL) was refluxed under Ar for 2.5 h. After concentrating the reaction mixture, $CHCl_3$ and saturated K_2CO_3 solution were added and separated. The obtained organic layer was washed with brine and dried over anhydrous Na_2SO_4 followed by removing solvent under reduced pressure. Resulting residue was purified by silica gel column chromatography ($CHCl_3$ only→5% MeOH/$CHCl_3$) and subsequent recrystallization from MeOH solution to give compound **1** (3.96 g, 77%) as a white prism crystal.

Method B. Under Ar, to the solution of compound **7** (50 mg, 0.13 mmol) in toluene (12 mL) was added TfOH (24.8 μL, 0.28 mmol) and refluxed for 4 h. After concentrating the reaction mixture, $CHCl_3$ and saturated K_2CO_3 solution were added and separated. The obtained organic layer was washed with brine and dried over anhydrous Na_2SO_4 followed by removing solvent under reduced pressure. Resulting residue was purified by preparative TLC (33% MeOH/$CHCl_3$) to give compound **1** (50 mg, quant.) as a white amorphous solid.

Method C. Under Ar, to the solution of compound **8** (12 mg, 0.32 mmol) in toluene (1 mL) was added TfOH (3.1 μL, 0.04 mmol) and refluxed for 2.5 h. The reaction mixture was poured into saturated K_2CO_3 solution and extracted with EtOAc. Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing solvent under reduced pressure to give crude compound **1** (17.6 mg) as a yellow oil. The ^{1}H NMR and IR spectra of the crude **1** matched those of purified **1**.

Method D. Using the method C, compound **9** (30.4 mg, 0.08 mmol) gave crude compound **1** (30.6 mg) as a brownish oil. The ^{1}H NMR and IR spectra of the crude **1** matched those of purified **1**.

Mp: 125–127 °C. $[\alpha]_D^{20}$ −152.44 (c 0.01, $CHCl_3$). ^{1}H and ^{13}C NMR spectra are shown in Table 1. IR (KBr, cm^{-1}): 3517, 2913, 1768, 1618, 1502, 1437, 1284. MS (FAB): m/z 380 $[M+H]^+$. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.91; H, 7.74; N, 3.79. Found: C, 75.96; H, 7.70; N, 3.69.

4.5. 17-(Cyclopropylmethyl)-4-hydroxy-3-methoxy-7β,14β-(1-methyletheno)morphinan-6-one (8) and 17-(cyclopropylmethyl)-4-hydroxy-3-methoxy-5β,14β-(1-methyletheno)morphinan-6-one (9)

Under Ar, the solution of compound **7** (20 mg, 0.05 mmol) and CSA (28 mg, 0.12 mmol) in toluene (2 mL) was refluxed for 15 h. After concentrating the reaction mixture, $CHCl_3$ and saturated K_2CO_3 solution were added and separated. The obtained organic layer was washed with brine and dried over anhydrous Na_2SO_4 followed by removing solvent under reduced pressure. Resulting residue was purified by preparative TLC (1.6% MeOH/saturated NH_4OH–$CHCl_3$) to give compounds **8** (6.6 mg, 34%) as a brownish oil and compound **9** (6.8 mg, 35%) as a brownish oil.

Compound **8**: ^{1}H and ^{13}C NMR spectra are shown in Table 2. IR (neat, cm^{-1}): 3417, 2924, 1705, 1483, 1439, 1280, 1200. HRMS (FAB): $[M+H]^+$ Calcd for $C_{24}H_{30}NO_3$: 380.2226. Found: 380.2217.

Compound **9**: ^{1}H and ^{13}C NMR spectra are shown in Table 3. IR (neat, cm^{-1}): 3418, 2923, 1704, 1484, 1440, 1278, 1200. HRMS (FAB): $[M+H]^+$ Calcd for $C_{24}H_{30}NO_3$: 380.2226. Found: 380.2224.

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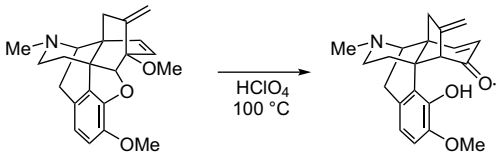

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