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Rearrangement of 4,5α-epoxymorphinan derivatives with carbamoylepoxy rings provide novel oxazatricyclodecane structures

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ABSTRACT

We describe the rearrangement of a carbamoylepoxy 4,5α-epoxymorphinan derivative that provided a novel 4,5α-epoxymorphinan derivative with an oxazatricyclodecane structure via an oxabicyclo[2.2.2] octane intermediate. We proposed the mechanism of the rearrangement reaction based on results observed in different deprotonation conditions. Epimerization occurred during rearrangement under reversible, but not irreversible, deprotonation conditions. The rearrangement product had a novel fundamental structure with moderate affinities for opioid receptors (K_i (μ)=47.7 nM, K_i (δ)=174.6 nM, and K_i (κ)=248.1 nM). Thus, the rearrangement products might have high potency as opioid ligands.

1. Introduction

Due to its strong analgesic effect, morphine has been used for the alleviation of postoperative and cancer pain. However, it also causes severe side effects, including addiction, constipation, and respiratory depression. A landmark investigation[1] demonstrated that the side effects of morphine would be derived only from the μ opioid receptor, but not from the δ and κ opioid receptors. That study encouraged many medicinal chemists to focus on the properties of the δ and κ opioid receptors in an effort to develop an ideal analgesic without morphine-like side effects. Recently, a novel κ selective agonist, nalfurafine hydrochloride (TRK-820)[2] was launched in Japan as an antipruritic for patients undergoing hemodialysis.[2c,d] Many classical κ selective agonists, like U-50,488H[3] and its derivatives (arylacetamide derivatives), were synthesized and developed; however, none of those derivatives were approved as either analgesics or antipruritics due to serious side effects, including psychotomimetic and aversive reactions.[4] On the other hand, nalfurafine did not exhibit either aversive or addictive effects.[5] We previously investigated the basis for the different pharmacological effects of nalfurafine and arylacetamide derivatives in conformational analyses.[6] Based on the analyses and our detailed structure–activity relationship investigation[7] of nalfurafine derivatives, we designed and synthesized some compounds[7,8] that were κ agonists, including KNT-63[8a] (Fig. 1). In the course of investigating the synthesis of KNT-63 derivatives, we found a rearrangement that provided novel morphinan derivatives **1** with an oxazatricyclodecane structure. To the best of our knowledge, although previous studies had described 4,5α-epoxymorphinan derivatives with a bicyclic structure like etorphine, buprenorphine,[9] and KNT-63, no reports described 4,5α-epoxymorphinan derivatives with a tricyclic structure, like **1**. Herein, we report a novel rearrangement that provided **1**, and we discuss the mechanism of the rearrangement.

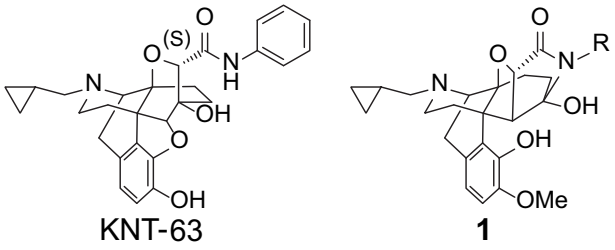

Fig. 1. Structures of KNT-63 and novel morphinan derivatives **1** with an oxazatricyclodecane structure.

2. Results and discussion

2.1. Rearrangement of (*R*)-carbamoylepoxy 4,5α-epoxymorphinan derivatives provide novel oxazatricyclodecane structures

The key reaction in the synthesis of the KNT-63 derivatives was the intramolecular cyclization of the (*R*)-carbamoylepoxy

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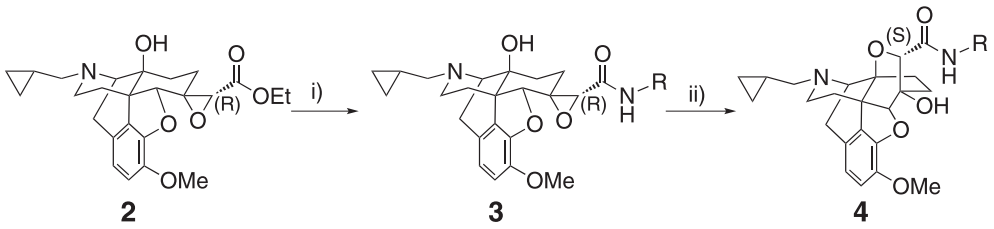
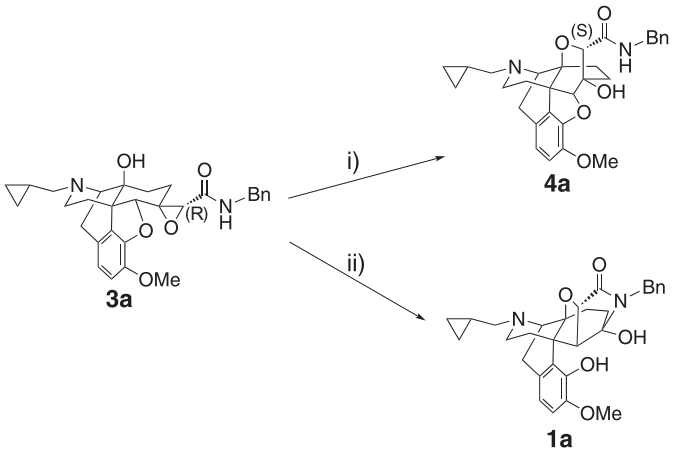
4,5α-epoxymorphinan derivatives **3**, which were obtained by treating (*R*)-ethoxycarbonylepoxy 4,5α-epoxymophinan **2** with lithium amides, prepared in situ by *n*-BuLi and amines, to afford the oxabicyclo[2.2.2]octane derivatives **4** (Scheme 1).[10] When R is a benzyl group, the yield of **4a** was 69% under THF reflux conditions in the presence of NaH (Scheme 2). To improve the yield, we attempted to elevate the reaction temperature by changing the solvent from THF (bp 66 °C) to cyclopentyl methyl ether (CPME, bp 106 °C). Surprisingly, the reaction under the CPME reflux conditions did not give the objective compound **4a**, but a novel oxazatricyclodecane structure **1a** in 81% yield (Scheme 2). The structure of compound **1a**[11] was confirmed in NOESY experiments and X-ray crystallographic analysis[12] (Figs. 2 and 3). To the best of our knowledge, this is the first report of the synthesis of the oxazatricyclodecane derivatives **1**. Therefore, we were interested in the rearrangement reaction and began to investigate it in detail.



Scheme 1. Reagents and conditions: (i) *n*-BuLi, RNH_2, THF, −78 °C; (ii) NaH, THF, reflux.



Scheme 2. Reagents and conditions: (i) NaH, THF, reflux, 69%; (ii) NaH, CPME, reflux, 81%.

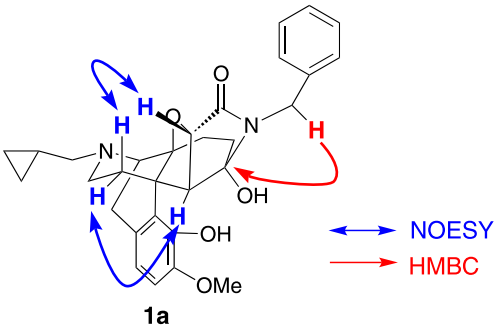


Fig. 2. Observed NOESY and HMBC spectra of compound **1a**.

First, we treated compound **3a** under various reaction conditions. The reaction at 60 °C (bath temperature) with CPME as a solvent in the presence of NaH provided only compound **4a** in 84% yield and compound **3a** was recovered in 11% yield. In the treatment of compound **3a** in the presence of NaH and 15-crown-5 at THF refluxing temperature for 1 h, the starting material **3a** disappeared and compound **4a** and trace amount of the rearrangement product **1a** appeared by a TLC analysis. After refluxing for 6 h, compounds **4a** and **1a** were obtained in 24% and 40% yield, respectively. These results indicated that the reaction temperature was an important factor in facilitating the rearrangement. However, the reaction at 100 °C with DMF as the solvent furnished a complex

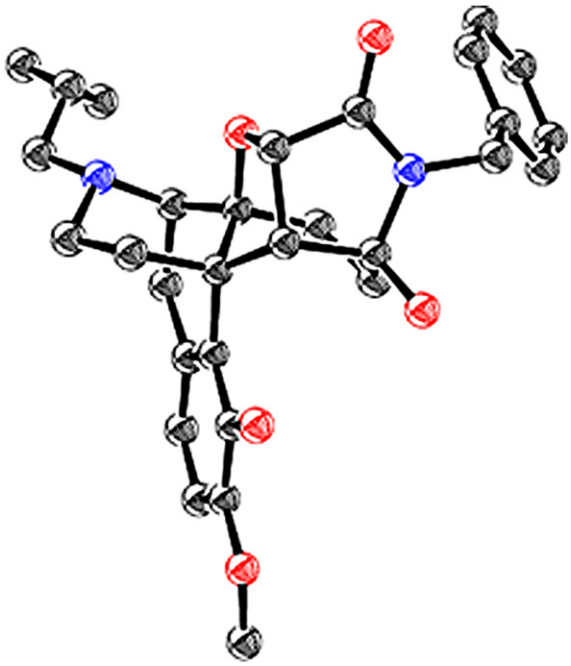


Fig. 3. ORTEP plot of compound **1a**.

mixture. The replacement of NaH and CPME with *t*-BuOK and *t*-BuOH (bp 83 °C), respectively, gave a fruitful result; the rearrangement product **1a** was obtained in 93% yield. It is noteworthy that no **5a** (Fig. 4) was produced in any of these experiments, in spite of the strong basic reaction conditions.

2.2. Rearrangement of (*S*)-carbamoylepoxy 4,5α-epoxymorphinan derivatives

With two optimal reaction conditions (condition A: NaH, CPME reflux; condition B: *t*-BuOK, *t*-BuOH, reflux) for the rearrangement in hand, we examined the reaction of (*S*)-carbamoylepoxy 4,5α-epoxymorphinan **6a**, the epimer of compound **3a**. Astonishingly, each of the two reaction conditions provided different products. Under reaction conditions A, compound **5a** was obtained in 91% yield, whereas the reaction of **6a** afforded compound **1a** in 89% yield under reaction conditions B. The latter was the same product that was obtained from (*R*)-carbamoylepoxy 4,5α-epoxymorphinan **3a**

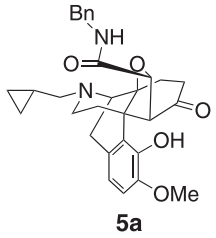
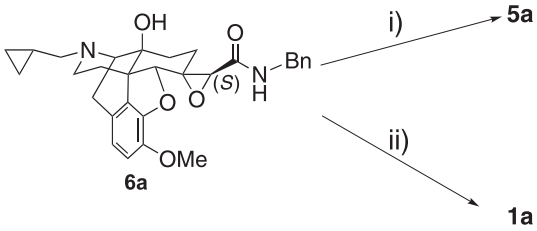


Fig. 4. Structure of compound **5a**.

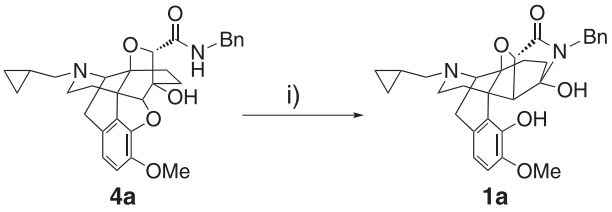
(Scheme 3). These results suggested that an epimerization occurred under reaction conditions B, but not under reaction conditions A.



Scheme 3. Reagents and conditions: (i) NaH, CPME, reflux (conditions A), 91%; (ii) *t*-BuOK, *t*-BuOH, reflux (conditions B), 89%.

2.3. Proposed reaction mechanism of the rearrangement

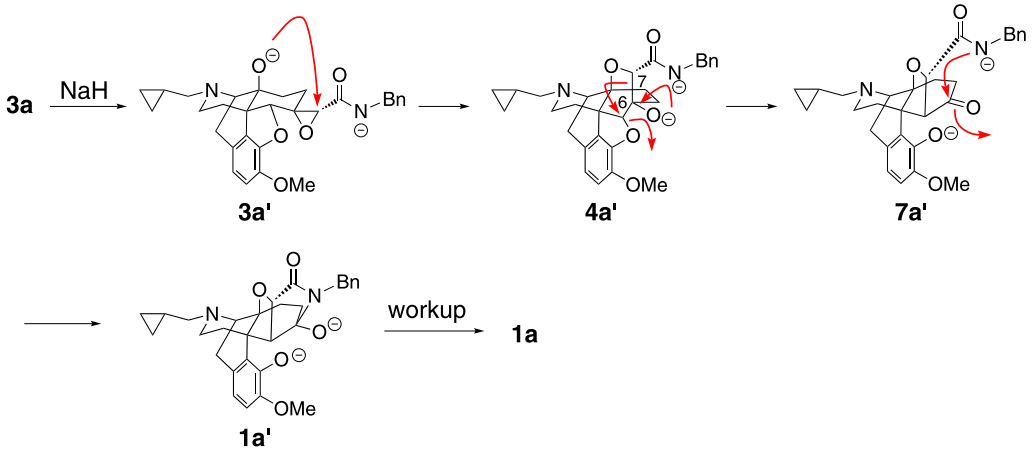
On the basis of the above results, we proposed a reaction mechanism of the rearrangement (Scheme 4). In the case of reaction conditions A, NaH would irreversibly deprotonate two acidic protons (NH and OH) in (*R*)-carbamoylepoxy 4,5α-epoxymorphinan **3a** to provide **3a**′. The resulting alkoxide in **3a**′ would attack the α-carbon of the amide group to afford the intermediate **4a**′. When the reaction temperature was not too high (e.g., a THF refluxing temperature), the reaction would stop at this stage to give the oxabicyclo[2.2.2]octane derivative **4a**. A higher reaction temperature (e.g., a CPME or *t*-BuOH refluxing temperature) would promote the following rearrangement. The alkoxide in **4a**′ would facilitate a 1,2-shift of the C6–C7 bond and, concomitantly, cleave the epoxy bridge to provide the intermediate **7a**′. The amide and ketone moieties in **7a**′ were located sufficiently close to each other that the subsequent cyclization could proceed smoothly to afford the rearrangement product **1a**. The formation of dianion species may prevent further deprotonation of the α-proton of the amide group. Therefore, the epimerization would not be observed, despite the strong basic reaction conditions. On the other hand, the reaction conditions B (reversible deprotonation conditions) would permit the deprotonation of the α-proton of the amide group to enable an epimerization. Eventually, the cyclization (**7a**′→**1a**′) could prompt a convergent production of the rearrangement product **1a**, regardless of the configuration of the amide group in carbamoylepoxy 4,5α-epoxymorphinan **3a** or **6a**. According to this proposed mechanism, **4a**′ was an important intermediate. Indeed, under the rearrangement reaction conditions, the oxabicyclo[2.2.2]octane derivative **4a** gave the rearrangement product **1a** in 57% yield (Scheme 5); this supported the proposed reaction mechanism.



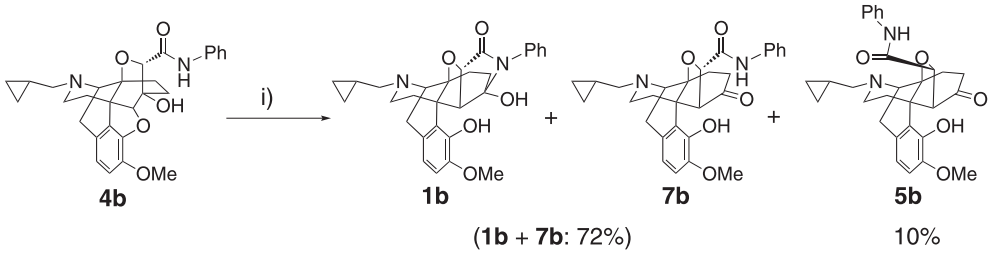
Scheme 5. Reagents and conditions: (i) NaH, CPME, reflux, 57%.

2.4. Rearrangement of an oxabicyclo[2.2.2]octane-*N*-phenylcarboxamide derivative

We next attempted to apply the rearrangement to *N*-phenylamides. Because *N*-phenylcarbamoylepoxy 4,5α-epoxymorphinan **3b** (R=Ph) could not be prepared from (*R*)-ethoxycarbonylepoxy 4,5α-epoxymorphinan **2**, due to the low nucleophilicity of lithium *N*-phenylamide,[8a] we used oxabicyclo[2.2.2]octane-*N*-phenylcarboxamide derivative **4b** as the starting material. Treatment of **4b** under the rearrangement reaction conditions A provided the rearrangement product **5b** and an equilibrium mixture of **1b** and **7b** (Scheme 6). Although an epimerization was not observed in the reaction of *N*-benzylamide **3a** under reaction conditions A, an epimerization was observed in the case of *N*-phenylamide **4b**. The electron-withdrawing property of the phenyl group may increase the acidity of the α-proton of the amide group and also decrease the nucleophilicity of the amide nitrogen. Due to the low nucleophilicity of the amide nitrogen, part of the epimer **7b** could cyclize to achieve equilibrium between **1b** and **7b**. Moreover, when either alkoxide anion or amide anion in **7b** may be transiently protonated, the more acidic α-proton may be simultaneously deprotonated to promote an epimerization. Ultimately, three compounds **1b**, **7b**, and **5b** would be provided.



Scheme 4. Proposed reaction mechanism for the rearrangement (condition A).

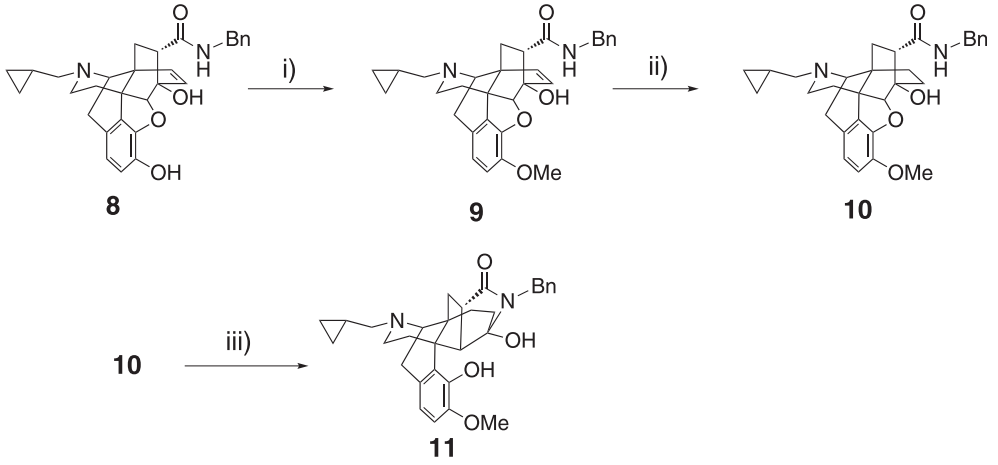


Scheme 6. Reagents and conditions: (i) NaH, CPME, reflux. The ratio of **1b**:**7b** was around 3:1.

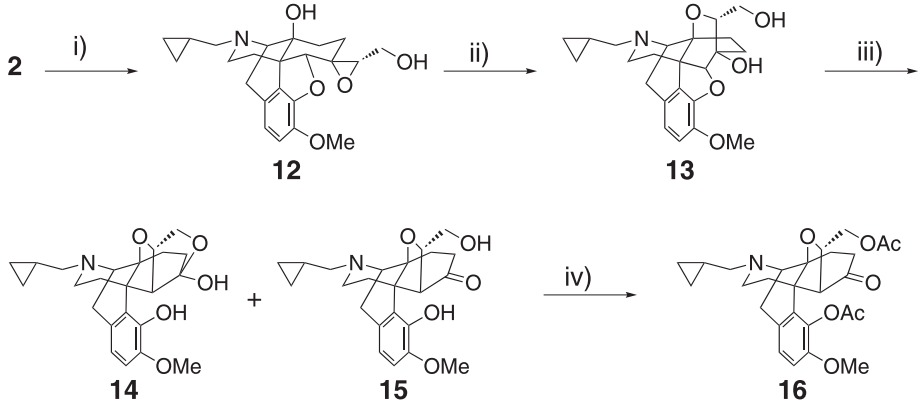
2.5. Rearrangement of the bicyclo[2.2.2]octanecarboxamide derivative

Bicyclo[2.2.2]octanecarboxamide **10** has a well-known structure in the opioid field with a typical endoethanotetrahydrooripavine skeleton, which resembles oxabicyclo[2.2.2]octanecarboxamides **4**. Therefore, we examined the behavior of **10** under rearrangement reaction conditions. Compound **10** was prepared by *O*-methylation of compound **8**[13] and subsequent catalytic hydrogenation. As expected, the treatment of **10** with NaH under CPME reflux conditions (condition A) gave the corresponding rearrangement product **11** in 77% yield (Scheme 7).

which lacked an electron-withdrawing group. We expected to obtain important information on the mechanistic details of the rearrangement (via a 1,2-shift or not) by testing the rearrangement with a compound that lacked an electron-withdrawing group, like compound **13**. Compound **13** was prepared from (*R*)-ethoxycarbonylepoxy 4,5α-epoxymophinan **2** by reduction with $NaBH_4$ and subsequent intramolecular cyclization. The treatment of compound **13** with NaH under CPME reflux conditions (condition A) provided an equilibrium mixture of **14** and **15**; subsequent acetylation of the mixture afforded diacetate **16** in 85% yield (Scheme 8). The preparation of diacetate **16** strongly suggested that the rearrangement of **13** would proceed via a 1,2-shift.



Scheme 7. Reagents and conditions: (i) MeI, K_2CO_3, DMF, rt, 92%; (ii) H_2 (0.5 MPa), Pd/C, MeOH, 50 °C, 90%; (iii) NaH, CPME, reflux, 77%.



Scheme 8. Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 94%; (ii) NaH, DMF, rt, 79%; (iii) NaH, CPME, reflux; (iv) Ac_2O, 60 °C, 85% from **13**.

2.6. Rearrangement of the oxabicyclo[2.2.2]octanylmethanol derivative

After the rearrangements of compounds with electron-withdrawing carboxamide groups, we next investigated the rearrangement of oxabicyclo[2.2.2]octanylmethanol derivative **13**,

3. Conclusion

We found that a rearrangement of carbamoylepoxy 4,5α-epoxymorphinan derivatives **3** provide novel oxazatricyclodecane ones **1** via oxabicyclo[2.2.2]octane intermediates **4**. We observed the same rearrangement in a reaction of a 4,5α-epoxymorphinan

derivative with the bicyclo[2.2.2]octane structure **10**. We proposed the reaction mechanism of the rearrangement based on the different results produced by different deprotonation conditions (irreversible or reversible). An epimerization occurred during the rearrangement under reversible, but not under irreversible, deprotonation conditions. The rearrangement product **1a** had a novel fundamental structure that showed moderate affinities for the opioid receptors (K_i (μ)=47.7 nM, K_i (δ)=174.6 nM, and K_i (κ)=248.1 nM); this indicated that the rearrangement products would be expected to have potency as opioid ligands. We are currently investigating the rearrangement product derivatives as potential opioid ligands.

4. Experimental section

4.1. General

Melting points were measured on a Yanaco MT-5 melting point apparatus. Infrared (IR) spectra were measured on a JASCO FT/IR–460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury–300 (300 MHz) or Varian UNITY-400 (400 MHz) spectrometer. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were measured on a JMS–700 MStation or JMS-T100LP instrument by applying a fast atom bombardment (FAB) or electron spray ionization (ESI) method. The progress of the reaction was determined on Merck Silica Gel Art. 5715. Column chromatographies were carried out using Kanto Silica Gel 60N or Fuji Silysia DM2035 (The surface of the silica gel was modified by amino group). Preparative TLCs were performed using Merck Silica Gel Art. 5744 or Fuji Silysia NH TLC plate.

4.2. (3′*R*,5*R*,6*S*,9*R*,13*S*,14*S*)-*N*-Benzyl-17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxyspiro[morphinane-6,2′-oxirane]-3′-caroxyamide (3a)

Under an Ar atmosphere, to a solution of $BnNH_2$ (4.4 mL, 40 mmol) in THF (100 mL) solution was added 1.65 M *n*-BuLi in hexane solution (24.2 mL, 40 mmol) dropwise at −78 °C and stirred for 15 min. To the reaction mixture was added a solution of compound **2** (4.42 g, 10 mmol) in THF (50 mL) dropwise at the same temperature and stirred for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography (ammonia saturated $CHCl_3$) to give the title compound **3a** (4.97 g, 99%) as a white amorphous material. IR (neat, cm^{-1}): 3407, 1666. ^1H NMR (300 MHz, $CDCl_3$) δ 0.05–0.22 (m, 2H), 0.43–0.62 (m, 2H), 0.83–0.95 (m, 1H), 1.26–1.36 (m, 1H), 1.41–1.66 (m, 3H), 2.12 (dt, *J*=3.6, 12.0 Hz, 1H), 2.20–2.43 (m, 4H), 2.53–2.71 (m, 2H), 3.04 (d, *J*=18.6 Hz, 1H), 3.10 (d, *J*=5.4 Hz, 1H), 3.68 (s, 1H), 3.85 (s, 3H), 4.31–4.46 (m, 2H), 4.75 (s, 1H), 5.15 (br s, 1H), 6.37–6.53 (m, 1H), 6.61 (d, *J*=8.4 Hz, 1H), 6.72 (d, *J*=8.4 Hz, 1H), 7.12–7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.7, 3.9, 9.4, 21.4, 22.6, 28.6, 30.9, 43.0, 44.0, 47.9, 56.8, 57.7, 59.1, 62.3, 63.2, 70.1, 85.5, 114.8, 118.8, 125.2, 127.7, 127.9, 128.7, 130.3, 137.3, 142.0, 145.7, 166.8. HRMS (FAB): $[M+H]^+$ calcd for $C_{30}H_{35}N_2O_5$: 503.2540. Found: 503.2558.

4.3. (5*R*,6*S*,7*S*,9*R*,13*S*,14*S*)-*N*-Benzyl-17-(cyclopropylmethyl)-4,5-epoxy-6,14-ethano-6-hydroxy-3-methoxy-8-oxamorphinan-7-carboxyamide (4a)

Under an Ar atmosphere, to the solution of compound **3a** (400 mg, 0.8 mmol) in THF (20 mL) was added NaH (50% in oil, 400 mg, 8.3 mmol) and refluxed for 3 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with AcOEt. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=100/0 to 100/2) to give the title compound **4a** (277 mg, 69%) as an amorphous material. IR (neat, cm^{-1}): 3408, 1650. ^1H NMR (300 MHz, $CDCl_3$) δ 0.05–0.18 (m, 2H), 0.42–0.64 (m, 2H), 0.79–1.06 (m, 2H), 1.31–1.53 (m, 2H), 1.66–1.91 (m, 2H), 2.12 (dd, *J*=8.1, 12.6 Hz, 1H), 2.18–2.35 (m, 2H), 2.41 (dt, *J*=3.6, 12.6 Hz, 1H), 2.66–2.82 (m, 2H), 3.20 (d, *J*=18.3 Hz, 1H), 3.54 (d, *J*=6.6 Hz, 1H), 3.89 (s, 3H), 4.28 (d, *J*=2.4 Hz, 1H), 4.46 (dd, *J*=5.7, 14.7 Hz, 1H), 4.54 (d, *J*=1.5 Hz, 1H), 4.59 (dd, *J*=6.6, 14.7 Hz, 1H), 5.49 (br s, 1H), 6.53 (d, *J*=8.1 Hz, 1H), 6.72 (d, *J*=8.1 Hz, 1H), 7.23–7.38 (m, 5H), 7.51–7.73 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.9, 4.9, 8.5, 21.0, 24.8, 28.0, 34.1, 35.2, 39.8, 43.6, 46.9, 57.0, 59.6, 70.8, 74.1, 74.9, 93.6, 117.9, 120.3, 126.5, 126.6, 128.6, 128.6, 131.7, 138.2, 138.3, 146.0, 172.1. HRMS (FAB): $[M+H]^+$ calcd for $C_{30}H_{35}N_2O_5$: 503.2540. Found: 503.2557.

4.4. (1*S*,3a*S*,5a*S*,6*R*,11b*R*,11c*R*)-3-Benzyl-14-(cyclopropylmethyl)-3a,11-dihydroxy-10-methoxy-1,3,3a,4,5,6,7,11c-octahydro-2*H*-6,11b-(iminoethano)-1,5a-epoxynaphtho[1,2-*e*]indol-2-one (1a)

Condition A: Under an Ar atmosphere, NaH (60% in oil, 700 mg, 17.5 mmol) was washed with anhydrous hexane and suspended in CPME (30 mL). To the suspension was added a solution of **3a** (4.32 g, 8.6 mmol) in CPME (20 mL) and refluxed for 3 h with stirring. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was crystallized from MeOH solution to give the title compound **1a** (3.51 g, 81%) as a white crystal.

Condition B: Under an Ar atmosphere, to a solution of **3a** (101 mg, 0.20 mmol) in *t*-BuOH (2 mL) was added *t*-BuOK (224 mg, 2.0 mmol) and refluxed for 1 h with stirring. The reaction mixture was poured into 2 M HCl and basified with saturated $NaHCO_3$ aqueous solution, and then extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography (ammonia saturated $CHCl_3$) to give the title compound **1a** (93.2 mg, 93%).

Preparation from compound **4a**: Under an Ar atmosphere, to a suspension of NaH (60% in oil, 1.90 g, 47.5 mmol) in CPME (15 mL) was added a solution of **4a** (1.90 g, 3.8 mmol) in CPME (15 mL) and refluxed for 15 h with stirring. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was crystallized from AcOEt solution to give the title compound **1a** (1.08 g, 57%).

Preparation from compound **6a**: Under an Ar atmosphere, to a solution of **6a** (100.5 mg, 0.2 mmol) in *t*-BuOH (2 mL) was added *t*-BuOK (224 mg, 2.0 mmol) and refluxed for 1 h with stirring. The reaction mixture was poured into 2 M HCl and basified with saturated $NaHCO_3$ aqueous solution, and then extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography (ammonia saturated $CHCl_3$) to give the title compound **1a** (89.4 mg, 89%). IR (KBr, cm^{-1}): 3338, 2933, 1689, 720. ^1H NMR (300 MHz, $CDCl_3$): δ 0.02–0.14 (m, 2H), 0.40–0.58 (m, 2H), 0.87–1.00 (m, 2H), 1.32–1.42 (m, 3H), 1.63 (dd, *J*=7.8, 14.4 Hz, 1H), 1.91 (dt, *J*=4.8, 12.6 Hz, 1H), 2.10 (dt, *J*=3.0, 12.3 Hz, 1H), 2.25 (dd, *J*=7.5, 12.6 Hz, 1H), 2.63 (dt, *J*=3.6, 11.4 Hz, 2H), 2.86 (dd, *J*=6.3,

18.6 Hz, 1H), 3.09 (d, *J*=18.6 Hz, 1H), 3.30 (d, *J*=5.7 Hz, 1H), 3.68 (d, *J*=6.0 Hz, 1H), 3.84 (s, 3H), 4.40 (d, *J*=14.7 Hz, 1H), 4.51 (d, *J*=14.7 Hz, 1H), 4.72 (d, *J*=6.0 Hz, 1H), 6.68 (d, *J*=8.7 Hz, 1H), 6.70 (d, *J*=8.4 Hz, 1H), 7.13–7.30 (m, 3H), 7.41 (d, *J*=6.9 Hz, 2H). (Two protons were not observed.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.0, 4.5, 9.0, 27.3, 30.6, 31.2, 31.9, 42.0, 43.1, 43.5, 54.6, 55.5, 55.9, 59.9, 79.2, 82.2, 91.4, 109.1, 119.5, 126.4, 127.1, 128.2, 128.4, 130.0, 138.6, 140.5, 144.7, 170.4. HRMS (ESI): calcd for $C_{30}H_{35}N_2O_5$ $[M+H]^+$: 503.2546. Found: 503.2530.

4.5. (4*R*,4a*R*,10*R*,10a*S*,12*S*)-*N*-Benzyl-13-(cyclopropylmethyl)-5-hydroxy-6-methoxy-3-oxo-1,2,3,4,9,10-hexahydro-10,4a-(iminoethano)-10a,4-(epoxymethano)phenanthren-12-carboxyamide (5a)

The treatment of **6a** (100.5 mg, 0.2 mmol) under the reaction conditions A gave the title compound **5a** (91.2 mg, 91%) as a colorless oil. IR (film, cm^{-1}): 3360, 2929, 1722, 1673, 1487, 1279, 754. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00–0.07 (m, 2H), 0.36–0.47 (m, 2H), 0.54–0.69 (m, 1H), 1.32 (dd, *J*=2.1, 13.5 Hz, 1H), 1.82 (dt, *J*=5.7, 12.3 Hz, 1H), 1.91–2.06 (m, 3H), 2.15 (dd, *J*=6.6, 12.6 Hz, 1H), 2.30–2.66 (m, 3H), 2.77 (dd, *J*=6.6, 18.3 Hz, 1H), 3.07 (d, *J*=18.3 Hz, 1H), 3.46 (d, *J*=6.3 Hz, 1H), 3.81 (s, 3H), 3.98 (s, 1H), 4.34 (dd, *J*=4.8, 14.4 Hz, 1H), 4.61 (s, 1H), 4.70 (dd, *J*=7.2, 14.7 Hz, 1H), 5.75 (s, 1H), 6.60 (d, *J*=8.1 Hz, 1H), 6.66 (d, *J*=8.4 Hz, 1H), 7.20–7.38 (m, 5H), 7.80–7.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.4, 4.0, 9.3, 27.0, 31.4, 32.2, 33.5, 42.5, 43.2, 45.4, 55.8, 56.0, 59.7, 60.8, 80.2, 84.1, 109.3, 118.1, 124.8, 127.3, 128.0, 128.5, 129.6, 138.0, 142.3, 144.9, 170.9, 207.7. HRMS (ESI): calcd for $C_{30}H_{35}N_2O_5$ $[M+H]^+$: 503.2546. Found: 503.2525.

4.6. (1*S*,3a*S*,5a*S*,6*R*,11b*R*,11c*R*)-14-(Cyclopropylmethyl)-3a,11-dihydroxy-10-methoxy-3-phenyl-1,3,3a,4,5,6,7,11c-octahydro-2*H*-6,11b-(iminoethano)-1,5a-epoxynaphtho[1,2-e]indol-2-one (1b), (4*R*,4a*R*,10*R*,10a*S*,12*S*)-13-(cyclopropylmethyl)-5-hydroxy-6-methoxy-3-oxo-*N*-phenyl-1,2,3,4,9,10-hexahydro-10,-4a-(iminoethano)-10a,4-(epoxymethano)phenanthlen-12-carboxyamide (7b), and (4*R*,4a*R*,10*R*,10a*S*,12*R*)-13-(cyclopropylmethyl)-5-hydroxy-6-methoxy-3-oxo-*N*-phenyl-1,2,3,4,9,10-hexahydro-10,4a-(iminoethano)-10a,4-(epoxymethano)phenanthlen-12-carboxyamide (5b)

The treatment of **4b** (488.6 mg, 1.0 mmol) under the reaction conditions A gave a mixture of **1b** and **7b** (353.7 mg, 72%), and **5b** (50.2 mg, 10%) as colorless oils. A mixture of **1b** and **7b**: IR (film, cm^{-1}): 3378, 2928, 1692, 1488, 1279, 752. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06–0.22 (m, 2H), 0.43–0.67 (m, 2H), 0.84–1.02 (m, 1.75H), 1.42–2.40 (m, 7.25H), 2.58–2.86 (m, 2.25H), 2.95 (dd, *J*=6.6, 18.3 Hz, 0.75H), 3.09–3.19 (m, 1H), 3.50 (d, *J*=5.7 Hz, 0.75H), 3.76 (d, *J*=6.6 Hz, 1H), 3.79 (s, 0.75H), 3.84 (s, 2.25H), 4.08 (d, *J*=5.7 Hz, 0.25H), 4.83 (d, *J*=6.6 Hz, 0.75H), 5.23 (d, *J*=6.0 Hz, 0.25H), 6.63 (d, *J*=8.4 Hz, 0.25H), 6.67 (d, *J*=8.4 Hz, 0.25H), 6.72 (s, 1.5H), 7.08–7.16 (m, 0.25H), 7.24–7.42 (m, 4.25H), 7.55–7.61 (m, 0.5H), 8.73 (s, 0.25H). (1.75 protons were not observed.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.2, 3.6, 4.3, 8.9, 26.8, 27.8, 29.8, 31.1, 31.7, 33.8, 36.4, 43.1, 43.4, 43.5, 54.7, 54.8, 55.8, 56.0, 59.3, 59.8 79.3, 80.7, 82.2, 84.3, 92.6, 109.4, 109.5, 118.2, 119.6, 123.6, 124.6, 126.3, 127.7, 128.4, 128.6, 129.0, 129.4, 129.7, 134.4, 136.9, 140.8, 142.6, 145.0, 162.5, 168.9, 170.3, 206.1. HRMS (ESI): calcd for $C_{29}H_{33}N_2O_5$ $[M+H]^+$: 489.2390. Found: 489.2402. Compound **5b**: IR (film, cm^{-1}): 3320, 2929, 1725, 1685, 1537, 1280, 733. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12–0.28 (m, 2H), 0.50–0.64 (m, 2H), 0.86–1.04 (m, 1H), 1.37–1.49 (m, 1H), 1.87–2.19 (m, 5H), 2.40 (dd, *J*=6.3, 12.6 Hz, 1H), 2.50 (dd, *J*=6.6, 12.9 Hz, 1H), 2.56–2.71 (m, 2H), 2.84 (dd, *J*=6.3, 18.3 Hz, 1H), 3.15 (d, *J*=18.3 Hz, 1H), 3.61 (d, *J*=6.3 Hz, 1H), 3.80 (s, 3H), 4.01 (s, 1H), 4.68 (s, 1H), 5.79 (br s, 1H), 6.63 (d, *J*=8.4 Hz, 1H), 6.66 (d, *J*=8.4 Hz, 1H), 7.07–7.16 (m, 1H), 7.28–7.39 (m, 2H), 7.58–7.69 (m, 2H), 9.45 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.8, 4.1, 9.7, 27.1, 31.7, 32.2, 33.5, 42.8, 45.4, 55.8, 56.4, 60.1, 61.1, 80.2, 84.6, 109.4, 118.2, 119.5, 124.2, 124.7, 128.9, 129.5, 137.6, 142.3, 145.0, 169.3, 207.3. HRMS (ESI): calcd for $C_{29}H_{33}N_2O_5$ $[M+H]^+$: 489.2390. Found: 489.2372.

4.7. (5*R*,6*R*,7*S*,9*R*,13*S*,14*R*)-*N*-Benzyl-17-(cyclopropylmethyl)-4,5-epoxy-6-hydroxy-3-methoxy-6,14-ethenomorpinan-7-carboxamide (9)

Under an Ar atmosphere, to a solution of **8** (402 mg, 0.83 mmol) in DMF (10 mL) were added K_2CO_3 (276 mg, 2.0 mmol) and MeI (61.9 μL, 1.0 mmol) and stirred at rt for 24 h under light shielding conditions. To the reaction mixture was added MeI (20.6 μL, 0.33 mmol) and stirred for 6 h. The reaction mixture was poured into distillated water and extracted with AcOEt. The combined organic layers were washed with distillated water and brine, and then dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography (ammonia saturated $CHCl_3$) to give the title compound **9** (379 mg, 92%) as a white amorphous material. IR (KBr, cm^{-1}): 3376, 2922, 1638, 1499, 749, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06–0.21 (m, 2H), 0.43–0.57 (m, 2H), 0.76–0.90 (m, 1H), 1.65 (dd, *J*=6.0, 12.9 Hz, 1H), 1.83 (dd, *J*=2.4, 13.2 Hz, 1H), 2.00 (dt, *J*=5.7, 12.6 Hz, 1H), 2.27–2.48 (m, 4H), 2.57 (dd, *J*=6.0, 9.6 Hz, 1H), 2.71 (dd, *J*=4.8, 12.0 Hz, 1H), 3.03–3.17 (m, 2H), 3.56 (d, *J*=6.6 Hz, 1H), 3.69–3.88 (m, 1H), 3.81 (s, 3H), 4.33 (d, *J*=1.2 Hz, 1H), 4.43 (d, *J*=5.7 Hz, 1H),5.47 (d, *J*=8.7 Hz, 1H), 5.76 (d, *J*=8.7 Hz, 1H), 6.46–6.56 (m, 2H), 6.62 (d, *J*=8.1 Hz, 1H), 7.19–7.35 (m, 5H). (A proton was not observed.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.4, 4.1, 9.4, 23.2, 30.0, 33.2, 42.9, 43.6, 43.9, 45.7, 47.4, 56.4, 57.1, 59.8, 76.0, 96.8, 112.9, 119.6, 127.3, 127.6, 128.2, 128.6, 129.0, 134.6, 136.4, 138.3, 141.8, 147.9, 172.6. HRMS (ESI): calcd for $C_{31}H_{35}N_2O_4$ $[M+H]^+$: 499.2597. Found: 499.2584.

4.8. (5*R*,6*R*,7*S*,9*R*,13*S*,14*S*)-*N*-Benzyl-17-(cyclopropylmethyl)-4,5-epoxy-6-hydroxy-3-methoxy-6,14-ethanomorpinan-7-carboxamide (10)

To the solution of **9** (99.7 mg, 0.20 mmol) in MeOH (15 mL) was added 10% Pd/C (21.3 mg) and stirred at 50 °C for 24 h under a H_2 atmosphere (0.5 MPa). The reaction mixture was filtered through Celite pad and obtained filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ammonia saturated $CHCl_3$) to give the title compound **10** (89.6 mg, 90%) as a colorless oil. IR (film, cm^{-1}): 3337, 2924, 1632, 1500, 1451, 731. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05–0.14 (m, 2H), 0.42–0.53 (m, 2H), 0.59–0.86 (m, 2H), 1.22–1.37 (m, 2H), 1.63–1.74 (m, 1H), 2.01–2.40 (m, 6H), 2.46–2.69 (m, 3H), 2.87 (ddd, *J*=3.9, 11.4, 13.5 Hz, 1H), 3.00 (d, *J*=18.3 Hz, 1H), 3.11 (d, *J*=6.3 Hz, 1H), 3.88 (s, 3H), 4.25 (d, *J*=2.1 Hz, 1H), 4.49 (d, *J*=5.7 Hz, 2H), 6.53 (br t, *J*=5.7 Hz, 1H), 6.59 (d, *J*=8.1 Hz, 1H), 6.71 (d, *J*=8.1 Hz, 1H), 7.21–7.34 (m, 5H). (A proton was not observed.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.3, 4.1, 9.4, 22.2, 22.8, 28.9, 30.0, 35.0, 35.4, 43.7, 43.8, 45.4, 45.5, 56.4, 58.4, 59.8, 72.5, 95.6, 113.1, 119.5, 127.2, 127.6, 128.5, 128.8, 133.0, 138.5, 141.7, 146.5, 172.5. HRMS (ESI): calcd for $C_{31}H_{37}N_2O_4$ $[M+H]^+$: 501.2753. Found: 501.2757.

4.9. (1*S*,3a*S*,5a*S*,6*R*,11b*S*,11c*S*)-3-Benzyl-14-(cyclopropylmethyl)-3a,11-dihydroxy-10-methoxy-1,3,3a,4,5,6,7,11c-octahydro-2*H*-6,11b-(iminoethano)-1,5a-methanonaphtho[1,2-*e*]indol-2-one (11)

The treatment of **10** (50.1 mg, 0.1 mmol) under the reaction conditions A gave the title compound **11** (38.8 mg, 77%) as a yellow oil. IR (film, cm^{-1}): 3410, 2935, 1667, 1486, 1278, 733. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02–0.18 (m, 2H), 0.37–0.56 (m, 2H), 0.71–1.07 (m, 3H), 1.20–1.64 (m, 4H), 1.73 (dt, *J*=4.8, 12.6 Hz, 1H), 1.88–2.03 (m, 1H), 2.18–2.39 (m, 2H), 2.50–2.67 (m, 1H), 2.92 (d, *J*=2.7 Hz, 2H), 3.08–3.23 (m, 2H), 3.27–3.44 (m, 2H), 3.82 (s, 3H), 4.36

(d, J=15.0 Hz, 1H), 4.51 (d, J=15.0 Hz, 1H), 6.66 (s, 2H), 7.13–7.29 (m, 3H), 7.39 (d, J=6.9 Hz, 2H). (Two protons were not observed.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.7, 9.5, 24.6, 30.5, 30.6, 32.6, 39.0, 42.0, 43.9, 44.2, 44.5, 55.4, 55.9, 56.8, 59.9, 92.5, 108.4, 119.4, 126.9, 128.1, 128.2, 129.0, 130.9, 139.3, 140.3, 144.6, 176.0. HRMS (ESI): calcd for $C_{31}H_{37}N_2O_4$ $[M+H]^+$: 501.2753. Found: 501.2752.

4.10. (3′*R*,5*R*,6*S*,9*R*,13*S*,14*S*)-17-(Cyclopropylmethyl)-4,5-epoxy-3′-hydroxymethyl-3-methoxyspiro[morphinane-6,2′-oxirane]-14-ol (12)

Under an Ar atmosphere, to a solution of **2** (16.4 g, 36.2 mmol) in MeOH (200 mL) was added $NaBH_4$ (6.85 g, 181.2 mmol) at 0 °C and stirred at rt for 1 h. To the reaction mixture was added $NaBH_4$ (2.74 g, 72.5 mmol) and stirred at rt for 2 h. After addition of 50% AcOH aqueous solution, the resulting mixture was poured into saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was crystallized from MeOH solution to give the title compound **12** (13.5 g, 94%) as colorless needles. Mp 140 °C. IR (film, cm^{-1}): 3388. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.10–0.15 (m, 2H), 0.16–0.58 (m, 2H), 0.78–0.90 (m, 1H), 1.52–1.66 (m, 4H), 1.70–1.77 (m, 1H), 2.17–2.26 (m, 2H), 2.30–2.43 (m, 2H), 2.63 (dd, J=18.0, 6.5 Hz, 2H), 3.08 (d, J=19.5 Hz, 1H), 3.13 (d, J=7.5 Hz, 1H), 3.24 (dd, J=8.0, 4.5 Hz, 1H), 3.27–3.29 (m, 1H), 3.54–3.61 (m, 1H), 3.85–3.95 (m, 1H), 3.88 (s, 3H), 4.25 (s, 1H), 5.41 (br s, 1H), 6.60 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 3.7, 4.0, 9.3, 18.6, 22.8, 29.1, 33.1, 43.2, 48.4, 56.8, 59.4, 59.7, 59.8, 60.4, 61.7, 70.5, 91.9, 114.8, 118.7, 125.9, 130.4, 141.9, 146.7. HRMS (FAB) calcd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124. Found: 400.2133.

4.11. (5*R*,6*S*,7*R*,9*R*,13*S*,14*S*)-17-(Cyclopropylmethyl)-6,14-ethano-7-hydroxymethyl-3-methoxy-8-oxamorphinan-6-ol (13)

Under an Ar atmosphere, to a suspension of NaH (60% in oil, 8.52 g, 213 mmol) in DMF (100 mL) was added **12** (12.9 g, 32.3 mmol) at rt and stirred at the same temperature for 22 h. The reaction mixture was poured into distillated water and acidified with 2 M HCl, and then washed with Et_2O. The aqueous layer was basified with 4 M NaOH aqueous solution and extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=100/1 to 30/1) and crystallized from MeOH solution to give the title compound **13** (10.2 g, 79%) as colorless crystals. Mp 211 °C. IR (film, cm^{-1}): 3375. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06–0.15 (m, 2H), 0.43–0.65 (m, 2H), 0.83–0.94 (m, 2H), 1.40–1.51 (m, 1H), 1.57–1.84 (m, 4H), 2.06 (dd, J=8.0, 13.0 Hz, 1H), 2.24–2.44 (m, 3H), 2.66–2.71 (m, 1H), 2.75–2.80 (m, 2H), 3.18 (d, J=18.0 Hz, 1H), 3.53 (d, J=6.5 Hz, 1H), 3.82–4.04 (m, 3H), 3.89 (s, 3H), 4.45 (d, J=2.0 Hz, 1H), 6.57 (d, J=8.0 Hz, 1H), 6.72 (d, J=8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 2.4, 5.2, 8.6, 20.2, 24.5, 28.9, 34.6, 43.8, 46.7, 56.4, 56.7, 59.4, 61.9, 71.9, 73.2, 76.0, 94.6, 114.4, 119.8, 128.1, 132.7, 142.0, 147.4. MS (FAB) m/z 400 $[M+H]^+$. HRMS (FAB) calcd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124. Found: 400.2115.

4.12. ((4*R*,4a*R*,10*R*,10a*S*,12*S*)-5-Acetoxy-13-(cyclopropylmethyl)-6-methoxy-3-oxo-1,2,3,4,9,10-hexahydro-10,4a-(iminoethano)-10a,4-(epoxymethano)phenanthren-12-yl)methyl acetate (16)

The treatment of **13** (799 mg, 2.0 mmol) under the reaction conditions A gave the mixture of compounds **14** and **15** (704 mg). Under an Ar atmosphere, a solution of the obtained mixture (120 mg, 0.3 mmol) in Ac_2O (2 mL) was stirred at 60 °C for 6 h. After concentration of the reaction mixture under reduced pressure, to the residue was added the saturated $NaHCO_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 followed by removing the solvent under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/NH_4OH=100/0/0 to 100/3/0.3) to give the title compound **16** (141 mg, 85%) as an amorphous material. IR (film, cm^{-1}): 2940, 1768, 1743, 1718, 1487, 1216, 1042, 753. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06–0.19 (m, 2H), 0.45–0.63 (m, 2H), 0.84–1.02 (m, 1H), 1.28–1.44 (m, 1H), 1.64–1.81 (m, 1H), 1.91–2.28 (m, 6H), 2.08 (s, 3H), 2.31 (s, 3H), 2.54–2.70 (m, 1H), 2.74 (dd, J=4.8, 12.6 Hz, 1H), 2.91 (dd, J=6.6, 18.6 Hz, 1H), 3.18 (d, J=18.6 Hz, 1H), 3.26 (d, J=5.7 Hz, 1H), 3.76 (s, 3H), 3.84 (d, J=8.4 Hz, 1H), 4.04 (dd, J=7.5, 12.0 Hz, 1H), 4.26 (dd, J=3.6, 12.0 Hz, 1H), 4.82 (m, 1H), 6.82 (d, J=8.4 Hz, 1H), 7.02 (d, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.8, 4.9, 8.9, 20.8, 20.9, 26.7, 30.4, 31.4, 33.7, 43.4, 45.4, 54.0, 55.9, 59.7, 59.8, 64.5, 77.3, 82.0, 111.1, 125.6, 129.5, 132.0, 136.7, 149.5, 168.4, 170.5, 208.4. HRMS (ESI): calcd for $C_{27}H_{34}NO_7$ $[M+H]^+$: 484.2335. Found: 484.2334.

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12. Crystal data for compound **1a**: $C_{30}H_{34}N_2O_5$, MW: 502.61, orthorhombic, $P2_12_12_1$, a=10.8197(3) Å, b=12.3710(4) Å, c=18.2439(7) Å, V=2441.95(13) Å^3, Z=4, D_{calcd}=1.367 g/cm^3. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 816177.
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