DOI: 10.1002/asia.201000458

Total Synthesis of (−)-Morphine

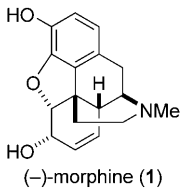
Hifumi Koizumi, Satoshi Yokoshima, and Tohru Fukuyama*[a]

Abstract: We have developed an efficient total synthesis of (−)-morphine in 5% overall yield with the longest linear sequence consisting of 17 steps from 2-cyclohexen-1-one. The cyclohexenol unit was prepared by means of an enzymatic resolution and a Suzuki–Miyaura coupling as key steps. Construction of the morphinan core features an intramolecular aldol reaction and an intramolecular 1,6-addition. Furthermore, mild deprotection conditions to remove the 2,4-dinitrobenzenesulfonyl (DNs) group enabled the facile construction of the morphinan skeleton. We have also established an efficient synthetic route to a cyclohexenol unit containing an *N*-methyl-DNs-amide moiety.

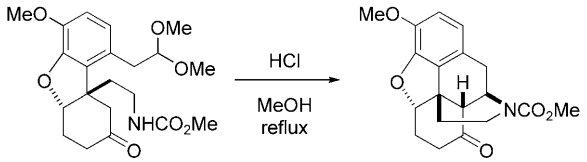
Keywords: alkaloids · cross-coupling · enzyme catalysis · Michael addition · total synthesis

Introduction

Morphine (**1**) is an efficient analgesic that is indispensable in cancer pain management. Whilst access to morphine is restricted by government agencies owing to its addictive nature, the structure of this molecule is quite fascinating from a synthetic point of view. The complicated pentacyclic skeleton, including a quaternary carbon center, has stimulated extensive synthetic efforts. Numerous synthetic studies as well as total syntheses of morphine and related molecules have been reported to date.[1,2] In an effort to develop non-addictive morphine analogues, we initiated our own studies to develop an efficient synthesis of morphine. Our racemic total synthesis, reported in 2006,[1v,z] featured an intramolecular Mannich-type reaction to construct the morphinan skeleton (Scheme 1). Serious drawbacks of this synthetic strategy included a tedious transformation required to install the aminoethyl moiety and an inefficient functionalization of the C ring. Therefore, we have made continued efforts to improve the synthetic route. Herein, we disclose an efficient total synthesis of (−)-morphine.



(−)-morphine (**1**)



2 **3**

Scheme 1. Mannich-type reaction to construct the morphinan skeleton.

Results and Discussion

As illustrated in Scheme 2, our initial synthetic strategy was to perform an intramolecular Mannich-type reaction at the γ position of unsaturated ketone **6**. We envisioned that this approach would furnish enone **4** which could then efficiently be converted into morphine. Unsaturated ketone **6** could be obtained by an intramolecular Heck reaction of **7**,[1s,t,ac,3] which could in turn be accessed from the Mitsunobu reaction of phenol **8** and cyclohexenol **9**.

Our synthesis commenced with a direct α-acetoxylation of 2-cyclohexen-1-one (**10**),[4] followed by iodination of the resulting α-acetoxyketone to furnish iodoketone **11** (Scheme 3). Enzymatic resolution of **11** with lipase AK provided a mixture of the desired (*R*)-alcohol **12** and unreacted acetate **11**.[5] After protection of **12** as the corresponding TBS ether, purification by column chromatography on silica gel afforded **13** in 45% yield and 99% *ee*. Luche reduction of **13** furnished *cis*-alcohol **14** as a single diastereomer.

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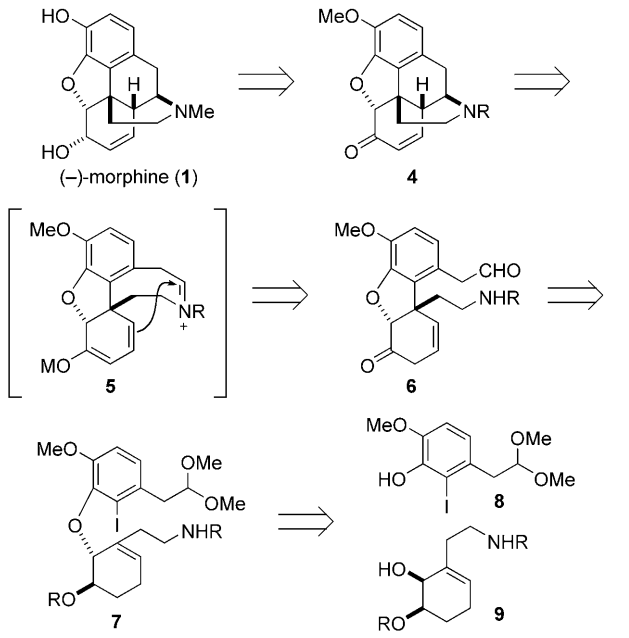
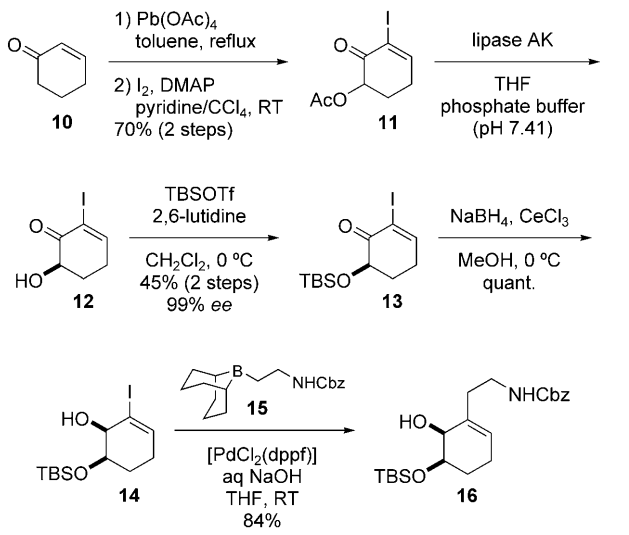
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000458.



Scheme 2. Retrosynthesis.



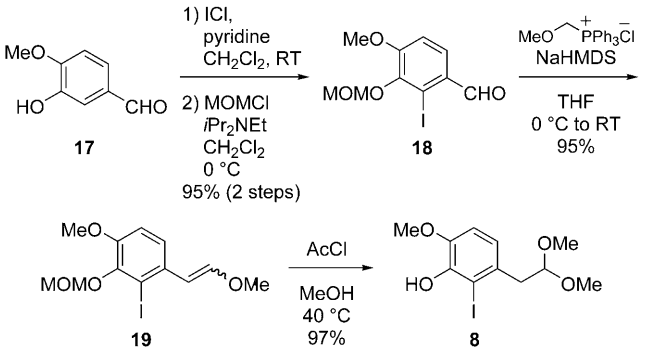
Scheme 3. Preparation of cyclohexenol **16**. DMAP = 4-(dimethylamino)-pyridine, Cbz = benzyloxycarbonyl, THF = tetrahydrofuran, TBS = *tert*-butyldimethylsilyl, dppf = 1,1'-bis(diphenylphosphino)ferrocene.

Suzuki–Miyaura coupling[6] of **14** and boron reagent **15**, prepared from benzyl vinylcarbamate and 9-BBN dimer,[7,8] afforded **16** in good yield.

Abstract in Japanese:

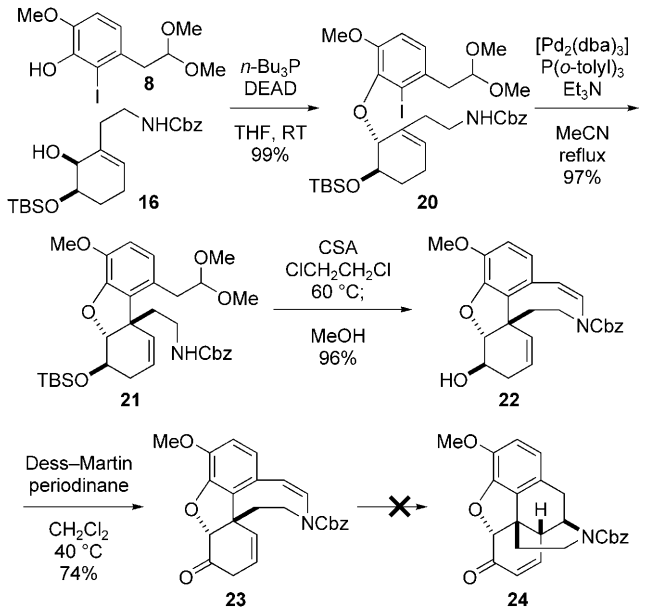
2-シクロヘキセン-1-オンより 17 段階にてモルヒネの全合成を達成した。酵素を用いた光学分割により得た光学活性なシクロヘキセノールユニットと、フェノールユニットとを光延反応により結合した後、分子内ヘック反応、分子内アルドール反応、および分子内 1,6-共役付加反応を経てモルヒナン骨格の構築に成功した。

Phenol **8**, the coupling partner for the key Mitsunobu reaction, was prepared from isovanillin (**17**; Scheme 4). After iodination of **17** according to the known procedure,[9] protection of the hydroxy group with a MOM group and subsequent Wittig olefination gave enol ether **19**. Treatment of **19** with methanolic HCl furnished phenol **8**.



Scheme 4. Preparation of phenol unit **8**. MOM = methoxymethyl, NaHMDS = sodium bis(trimethylsilyl)amide.

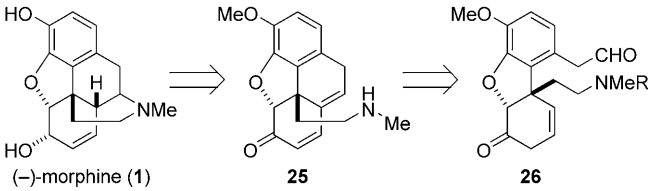
The Mitsunobu reaction[10] (*n*Bu$_3$P, DEAD) of **8** and **16** proceeded uneventfully to give **20** in quantitative yield (Scheme 5).[1j,u] The intramolecular Heck reaction[11] of **20** in refluxing acetonitrile afforded **21** in high yield. Upon treatment with CSA in 1,2-dichloroethane, **21** underwent cyclization to give an eight-membered cyclic enamide, which was isolated after the TBS group was cleaved by addition of methanol to the reaction mixture. Oxidation of the resulting alcohol **22** with Dess–Martin periodinane[12] furnished ketone **23**.



Scheme 5. Attempted Mannich-type reaction. DEAD = diethyl azodicarboxylate, dba = (*E*,*E*)-dibenzylideneacetone, CSA = camphorsulfonic acid.

With the desired substrate in hand, we attempted the crucial Mannich-type reaction. However, treatment of **23** with a variety of acids (HCO_2H, TFA, CSA, $BF_3{\cdot}OEt_2$, TMSOTf, etc) did not lead to the desired compound **24**. In a separate experiment, the corresponding enol acetate was prepared by deprotonation with LHMDS followed by quenching the resulting lithium enolate with acetic anhydride. Once again, the Mannich-type reaction of the enol acetate did not give the desired product. In our previous synthesis, the Mannich-type reaction of **2** proceeded smoothly under acidic conditions (Scheme 1). In our current approach, a slight conformational change in the C-ring, owing to the additional double bond, might have caused a reduction in the overlap of the relevant molecular orbitals. Molecular modeling studies indeed suggested that the diene moiety and the acyl iminium cation in the intermediate were situated orthogonally to one another, thus inhibiting the formation of the desired bond. We attributed the failure of the crucial Mannich-type reaction of **23** to this conformational restriction, and therefore modified our synthetic plan.

As illustrated in Scheme 6, our alternative retrosynthesis is based on the construction of the core morphinan skeleton by means of an intramolecular 1,6-addition reaction of dien-

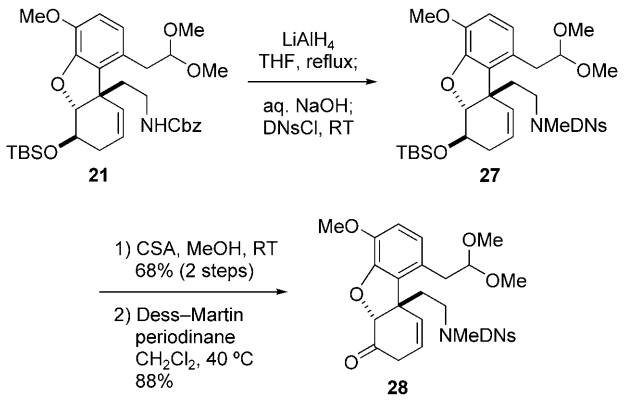


Scheme 6. Alternative retrosynthesis.

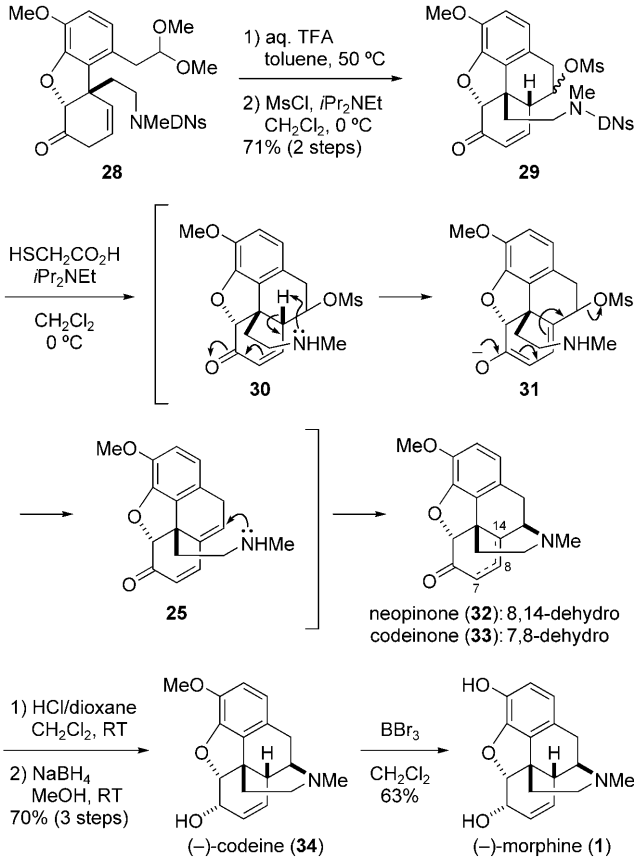
one **25**. Fuchs and co-workers reported that secondary amine **25** underwent a selective 1,6-addition to form the morphinan skeleton. In that synthesis, the 2-(trimethylsilyl)ethyloxycarbonyl (Teoc)-protected form of **25** was prepared from thebaine or by a lengthy, synthetic route, and this key intermediate was elaborated to form morphine.[1g,h] We envisaged that construction of the tetracyclic core in **25** could be efficiently achieved through an intramolecular aldol reaction of **26** at the γ position of the enone.

Our alternative synthesis began with elaboration of the intramolecular Heck reaction product **21** (Scheme 7). Reduction of **21** with lithium aluminum hydride afforded *N*-methylamine, which was protected by a 2,4-dinitrobenzenesulfonyl (DNs) group.[13] Cleavage of the TBS group in **27** followed by oxidation of the resulting alcohol with Dess–Martin periodinane furnished β,γ-unsaturated ketone **28**.[12]

With the requisite substrate in hand, we focused on construction of the morphinan skeleton by the combination of an intramolecular aldol reaction and an ensuing intramolecular 1,6-addition reaction (Scheme 8). Treatment of **28** with aqueous trifluoroacetic acid in toluene resulted in hydrolysis of the acetal and a subsequent intramolecular aldol reaction furnished an epimeric mixture of alcohols, which was sub-



Scheme 7. Preparation of key intermediate **28**. DNsCl = 2,4-dinitrobenzenesulfonyl chloride.



Scheme 8. Completion of the synthesis.

jected to mesylation to provide **29** in good yield.[14] The attempted elimination of the mesyloxy group of **29** with a variety of bases revealed that the epimers showed quite different reactivities. Whilst the β-mesylate smoothly underwent elimination on treatment with iPr_2NEt in dichloromethane at room temperature, the corresponding α-mesylate remained intact under the same conditions. Elimination of the α-mesylate required harsher conditions, leading to substantial decomposition of the product. After extensive investiga-

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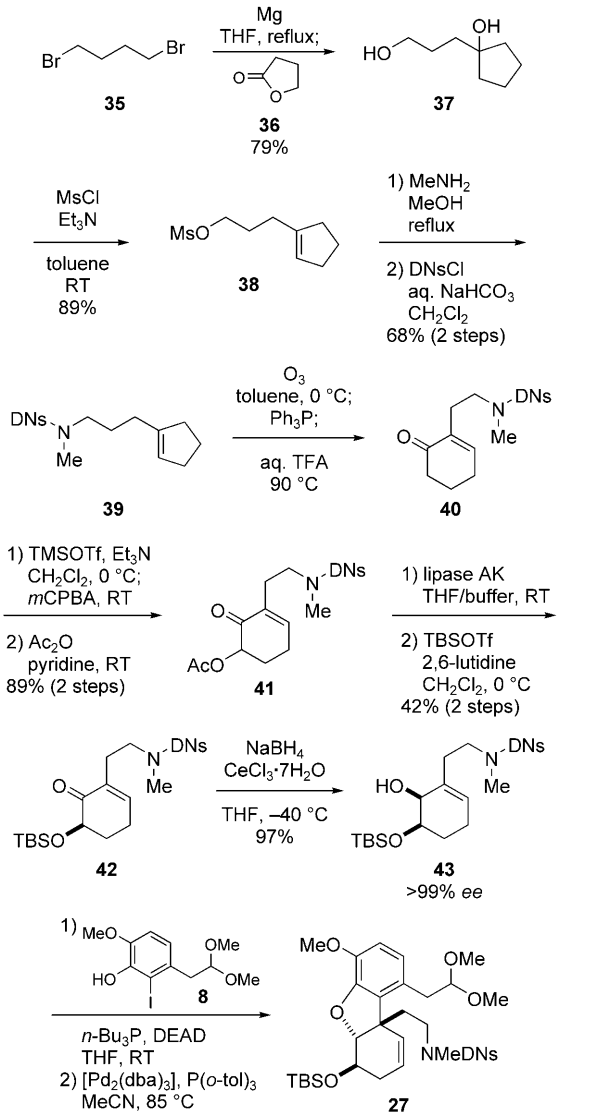
tions, we found that cleavage of the DNs group in **29** effectively caused elimination of both α- and β-mesylates to form the morphinan skeleton. Thus, treatment of **29** with mercaptoacetic acid and iPr$_2$NEt in dichloromethane afforded a mixture of neopinone (**32**) and codeinone (**33**). The facile elimination of the mesylate might be assisted by the deprotected secondary amine.

Several straightforward transformations remained to complete the total synthesis of (−)-morphine. Following the literature procedure,[1h] a mixture of **32** and **33** was converted into pure codeinone (**33**) under acidic conditions, and subsequent reduction of the α,β-unsaturated ketone with sodium borohydride gave (−)-codeine (**34**) in 70% yield over three steps from **29**. Finally, cleavage of the methyl ether with BBr_3 furnished (−)-morphine (**1**).[15]

Whilst our synthesis led to an efficient construction of the morphinan skeleton, the following shortcomings were noted in the elaboration of the lower unit: 1) poisonous lead tetraacetate was used in the first step, 2) a Curtius rearrangement of explosive acryloyl azide had to be performed to prepare boron reagent **15**, and 3) reaction of the substituent on the nitrogen atom required harsh conditions ($LiAlH_4$, reflux). To address these problems, we developed an alternative route in which the *N*-methyl-DNs amide moiety of the lower unit was installed at an early stage of the synthesis (Scheme 9).

The Grignard reagent derived from 1,4-dibromobutane (**35**) was reacted with γ-butyrolactone (**36**) to afford diol **37**.[16] Treatment of **37** with methanesulfonyl chloride in the presence of triethylamine resulted in mesylation of the primary hydroxy group and concomitant elimination of the tertiary hydroxy group to furnish mesylate **38**. Reaction of **38** with methylamine in refluxing methanol followed by treatment with DNsCl provided DNs amide **39**. Ozonolysis of **39** afforded the corresponding ketoaldehyde, which underwent an acid-catalyzed intramolecular aldol condensation to produce α,β-unsaturated ketone **40**. Rubottom oxidation followed by acetylation furnished α-acetoxyketone **41**. Following a similar sequence used for substrate **11**, enzymatic resolution of **41** with lipase AK afforded a hydrolyzed product with >99% *ee*, which was isolated after conversion into its TBS ether **42**. Luche reduction furnished the desired cyclohexenol **43**, which was converted into **27** through a Mitsunobu reaction with **8** and a subsequent intramolecular Heck reaction.



Scheme 9. Alternative synthesis of the lower unit.

Conclusions

We have successfully developed an efficient total synthesis of (−)-morphine in 5% overall yield from 2-cyclohexen-1-one **10**. The longest linear sequence involved 17 steps from **10**. Cyclohexenol unit **16** was prepared by using an enzymatic resolution and a Suzuki–Miyaura coupling as the key steps. Construction of the morphinan core featured an intramolecular aldol reaction and an intramolecular 1,6-addition. Furthermore, mild deprotection conditions of the DNs group in **29** facilitated the construction of the morphinan skeleton. We have also established an efficient synthetic route to cyclohexenol unit **43**, which contained an *N*-methyl-DNs amide moiety. This route features a facile construction of the cyclohexenone moiety by ozonolysis followed by an intramolecular aldol condensation as well as an enzymatic resolution.

Experimental Section

General Remarks: ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were determined on a JEOL-LA400 instrument unless otherwise noted. Chemical shifts of 1H NMR signals are reported in parts per million downfield from tetramethylsilane (δ) as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the center line of a triplet at 77.0 ppm for [D]chloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Trans-

form Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus, either in positive electrospray ionization (ESI) method or in positive direct analysis in real time (DART) ionization mode, using PEG as the internal standard. Melting points (m.p.) were determined on a Yanaco Micro Melting Point Apparatus. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) pre-coated with silica gel 60 F_{254}. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical, 40–100 mesh) unless otherwise noted. Reagents were commercial grades and were used without any purification. Dehydrated tetrahydrofuran, diethyl ether, toluene, and dichloromethane were purchased from Kanto Chemicals Co., Inc., and were purified using a Glass Contour Solvent System. Dehydrated benzene and *N*,*N*-dimethylformamide were purchased from Kanto Chemicals Co., Inc. and stored over activated M.S. 4 Å. Dehydrated methanol, ethanol, and acetonitrile were also purchased from Kanto Chemicals Co., Inc. and stored over activated M.S. 3 Å. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

3-Iodo-2-oxocyclohex-3-enyl acetate (11) To a stirred solution of 2-cyclohexen-1-one (**10**, 9.18 g, 95.5 mmol) in toluene (180 mL) was added $Pb(OAc)_4$ (84.7 g, 191 mmol), and the reaction mixture was refluxed for 4 h. After cooling to room temperature, 1 M HCl was added, and the resulting brown precipitate was removed by filtration. The filtrate was extracted with ethyl acetate, washed with water, dried over sodium sulfate, and filtered. Concentration of the filtrate gave a crude acetate, which was used in the next step without further purification.

To a stirred solution of the above acetate in pyridine (30 mL) and CCl_4 (100 mL) were added DMAP (2.33 g, 19.1 mmol) and I_2 (29.1 g, 115 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with aqueous sodium thiosulfate at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (30% ethyl acetate in *n*-hexane) to afford **11** (18.7 g, 70% for 2 steps) as a yellow oil. IR (film): $\tilde{\nu}$ = 1748, 1703, 1373, 1235, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, J = 6.0, 2.7 Hz, 1H), 5.46 (dd, J = 13.6, 5.4 Hz, 1H), 2.56–2.66 (m, 2H), 2.19–2.34 (m, 2H), 2.18 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2, 169.8, 158.4, 100.3, 72.2, 28.8, 28.3, 20.7 ppm; HRMS (ESI) calcd for $C_8H_9IO_3Na$ $[M+Na]^+$: 302.9494, found 302.9505.

(*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-iodocyclohex-2-enone (13) To a stirred solution of **11** (14.1 g, 50.2 mmol) in THF (100 mL) and phosphate buffer (pH 7.41, 150 mL) was added lipase AK (3.5 g). After stirring at room temperature for 6 h, the solution was extracted with ethyl acetate, washed with brine, dried over sodium sulfate, and filtered. Concentration of the filtrate gave a mixture of alcohol **12** and unreacted acetate **11**. The mixture was dissolved in CH_2Cl_2 (100 mL), to which were added 2,6-lutidine (5.85 mL, 50.2 mmol) and TBSOTf (5.76 mL, 25.1 mmol) at 0 °C. After stirring at 0 °C for 30 min, 1 M HCl was added, and the solution was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified with column chromatography on silica gel (10% ethyl acetate in *n*-hexane) to afford **13** (7.89 g, 45% for 2 steps, 99% *ee*) and acetate **11** (7.17 g, 51%) as a yellow oil. Analytical data of **13**: $[\alpha]_D^{24}$ = +91° (c = 0.50, $CHCl_3$); IR (film): $\tilde{\nu}$ = 2937, 1699, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, J = 4.4, 4.7 Hz, 1H), 4.30 (dd, J = 10.8, 4.8, Hz, 1H), 2.52 (m, 2H), 2.19 (m, 1H), 2.14 (m, 1H), 0.90 (s, 9H), 0.16 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 158.4, 101.6, 73.1, 32.3, 28.5, 25.7, 18.4, −4.6, −5.5 ppm; HRMS (ESI) calcd for $C_{12}H_{21}IO_2SiNa$ $[M+Na]^+$: 375.0253, found 375.0268. The optical purity of **13** was determined by HPLC using the following conditions: eluted with 1% *i*PrOH/hexane at a flow rate of 1.0 mL min^{-1} on Daicel Chemical Ind., Ltd. CHIRALCEL OD-H column (0.46 cm × 25 cm). Retention time: R = 37 min, S = 53 min.

(1*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-iodocyclohex-2-enol (14) To a stirred solution of **13** (7.83 g, 22.2 mmol) and $CeCl_3 \cdot 7H_2O$ (10.8 g, 28.9 mmol) in MeOH (111 mL) was added $NaBH_4$ (1.09 g, 28.9 mmol) in portions at 0 °C. After stirring at 0 °C for 10 min, 1 M HCl was added and the solution was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (10% ethyl acetate in *n*-hexane) to afford **14** (7.76 g, 99%, 99% *ee*) as a yellow oil. $[\alpha]_D^{24}$ = +35° (c = 0.50, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3558, 2952, 1254, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.50 (dd, J = 4.0 Hz, 4.0 Hz, 1H), 4.10 (dd, J = 4.1 Hz, 4.1 Hz, 1H), 3.97 (ddd, J = 4.1 Hz, 7.1 Hz, 7.1 Hz, 1H), 2.76 (d, J = 4.1 Hz, 1H), 2.20 (m, 1H), 2.06 (m, 1H), 1.86 (m, 1H), 1.65 (m, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 98.0, 74.2, 70.3, 27.0, 25.7, 25.3, 18.0, −4.6, −5.0 ppm; HRMS (ESI) calcd for $C_{12}H_{23}IO_2Si$ $[M+Na]^+$: 377.0410, found 377.0398. The optical purity of **14** was determined by HPLC using the following conditions: eluted with 1% *i*PrOH/hexane at flow rate of 1.0 mL min^{-1} on Daicel Chemical Ind., Ltd. CHIRALCEL OD-H column (0.46 cm × 25 cm). Retention time: R = 5 min, S = 6 min.

Benzyl 2-((5*R*,6*S*)-5-(*tert*-butyldimethylsilyloxy)-6-hydroxycyclohex-1-enyl)ethylcarbamate (16) To a solution of benzyl vinylcarbamate (1.40 g, 7.90 mmol) in THF (11 mL), which was degassed by freeze-thawing, was added $(9\text{-BBN})_2$ (964 mg, 3.95 mmol, recrystallized from anhydrous 1,2-dimethoxyethane) at room temperature, and the solution was stirred for 30 min. In another flask **14** (2.00 g, 5.64 mmol) and $[PdCl_2(dppf)]$ (230 mg, 0.28 mmol) were dissolved in THF (11 mL) and 3 M aqueous NaOH (5.6 mL), and the resulting solution was degassed by freeze-thawing. To this solution was added the above solution containing the boron reagent, and the resultant mixture was stirred at room temperature for 1 h. After dilution with Et_2O, the reaction mixture was quenched with H_2O_2, and the mixture was extracted with Et_2O. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (30% ethyl acetate in *n*-hexane) to afford **16** (1.92 g, 84%) as a yellow oil. $[\alpha]_D^{24}$ = +38.1° (c = 1.00, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3336, 2930, 1716, 1521, 1254, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.36 (m, 5H), 5.59 (br, 1H), 5.38 (br, 1H), 5.09 (s, 2H), 3.85 (s, 1H), 3.76 (ddd, J = 7.6, 7.6, 3.7 Hz, 1H), 3.29–3.43 (m, 2H), 2.80 (s, 1H), 2.38–2.43 (m, 1H), 2.12–2.22 (m, 2H), 1.91–2.02 (m, 1H), 1.68–1.81 (m, 1H), 1.52–1.56 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.10 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 136.8, 134.4, 128.5, 128.1, 128.0, 127.9, 71.0, 69.0, 66.5, 39.9, 35.8, 25.8, 25.1, 24.4, 18.1, −4.5, −4.8 ppm; HRMS (ESI) calcd for $C_{22}H_{35}NO_4SiNa$ $[M+Na]^+$: 428.2233, found 428.2253.

Benzyl 2-((5*R*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-6-(3-(2,2-dimethoxyethyl)-2-iodo-6-methoxyphenoxy)cyclohex-1-enyl)ethylcarbamate (20) To a stirred solution of 16 (1.86 g, 4.59 mmol), 8 (1.55 g, 4.59 mmol) and nBu$_3$P (2.29 mL, 9.17 mmol) in THF (15.3 mL) was added DEAD (4.17 mL, 9.17 mmol, 40% in toluene) at 0 °C, and the solution was stirred for 30 min at room temperature. Then the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (20% ethyl acetate in *n*-hexane) to afford 20 (3.30 g, 99%) as a yellow oil. $[\alpha]_D^{24}$ = −47.2° (c = 1.00, $CHCl_3$); IR (film): $\tilde{\nu}$ = 2951, 1723, 1475, 1251, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 5H), 6.99 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.3 Hz 1H), 5.81 (d, J = 3.4 Hz, 1H), 5.08 (s, 2H), 4.90 (br, 1H), 4.58 (s, 1H), 4.54 (t, J = 5.5 Hz, 1H), 4.02 (s, 1H), 3.82 (s, 3H), 3.44–3.49 (m, 1H), 3.34 (s, 6H), 3.21–3.28 (m, 1H), 3.06 (d, J = 5.5 Hz, 2H), 2.24–2.48 (m, 4H), 2.03–2.07 (m, 1H), 1.64–1.68 (m, 1H), 0.75 (s, 9H), −0.13 (s, 3H), −0.18 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 150.1, 146.5, 136.7, 132.9, 130.9, 130.7, 128.5, 128.1, 125.9, 112.1, 104.4, 100.9, 78.6, 67.4, 66.4, 55.6, 54.2, 54.0, 44.3, 39.4, 34.8, 25.8, 25.6, 25.3, 20.7, 18.0, −5.2, −5.2 ppm; HRMS (ESI) calcd for $C_{33}H_{48}INO_7SiNa$ $[M+Na]^+$: 748.2143, found 748.2172.

Benzyl *N*-[2-[(5a*R*,6*R*,9a*S*)-6-(*tert*-butyldimethylsilyloxy)-6,7-dihydro-1-(2,2-dimethoxyethyl)-4-methoxy-9a(5a*H*)-dibenzofuranyl]ethyl]-*N*-methylcarbamate (21) To a stirred solution of 20 (3.30 g, 4.55 mmol), $[Pd_2(dba)_3]$ (416 mg, 0.46 mmol) and P(*o*-tolyl)$_3$ (427 mg, 0.91 mmol) in

MeCN (23 mL) was added Et_3N (1.89 mL, 13.6 mmol) at room temperature and the solution was stirred for 1 h at 85 °C. Then the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (20% ethyl acetate in *n*-hexane) to afford 21 (2.60 g, 96%) as a yellow oil. $[\alpha]_D^{24} = -15.8°$ ($c = 1.00$, $CHCl_3$); IR (film): $\tilde{\nu} = 2930$, 1717, 1507, 1251, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (m, 5H), 6.71 (s, 2H), 5.97 (d, $J = 10.1$ Hz 1H), 5.69 (ddd, $J = 10.1$, 4.0, 4.0 Hz, 1H), 5.05 (s, 2H), 4.76 (br, 1H), 4.56 (t, $J = 5.4$ Hz, 1H), 4.49 (d, $J = 7.1$ Hz, 1H), 3.96 (dd, $J = 12.2$ Hz, 7.1 Hz, 1H), 3.82 (s, 3H), 3.36 (s, 3H), 3.31 (s, 3H), 3.19–3.24 (m, 1H), 2.88–2.91 (m, 1H), 2.89 (d, $J = 5.4$ Hz, 2H), 2.56 (ddd, $J = 16.4$, 4.0, 4.0 Hz, 1H), 2.09 (dd, $J = 16.4$, 7.1 Hz, 1H), 1.98 (t, $J = 7.6$ Hz, 2H), 0.89 (s, 9H), 0.13 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.1$, 146.2, 143.7, 136.6, 132.1, 129.6, 128.5, 128.0, 125.3, 124.5, 122.9, 111.7, 105.2, 89.1, 68.1, 66.5, 55.8, 53.9, 53.1, 51.3, 39.5, 37.4, 35.1, 30.5, 25.8, 18.1, −4.8, −5.3 ppm; HRMS (ESI) calcd for $C_{33}H_{47}NO_7SiNa$ $[M+Na]^+$: 620.3020, found 620.3036.

***N*-[2-[(5a*R*,9a*S*)-6,7-dihydro-1-(2,2-dimethoxyethyl)-4-methoxy-6-oxo-9a-(5a*H*)-dibenzofuranyl]ethyl]-*N*-methyl-2,4-dinitrobenzenesulfonamide (28)** To a stirred solution of 21 (2.60 g, 4.35 mmol) in THF (22 mL) was added $LiAlH_4$ (496 mg, 13.0 mmol) at room temperature and the solution was stirred for 1 h at 70 °C. After dilution with diethyl ether, the reaction mixture was quenched with excess amount of aqueous NaOH. The resulting white precipitate was removed by filtration. To the filtrate was added 2,4-dinitrobenzenesulfonyl chloride (1.16 g, 4.35 mmol), and the solution was stirred for 10 min at room temperature. The mixture was extracted with ethyl acetate, washed with water, dried over sodium sulfate, and filtered. Concentration of the filtrate gave a crude sulfonamide, which was used for the next step without further purification.

To a stirred solution of the crude sulfonamide in methanol (22 mL) was added camphorsulfonic acid (101 mg, 0.44 mmol) at room temperature. After stirring at room temperature for 6 h, aqueous sodium bicarbonate was added, and the solution was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (50% ethyl acetate in *n*-hexane) to afford alcohol **S1** (1.75 g, 68% for 2 steps) as a yellow oil. $[\alpha]_D^{24} = -3.18°$ ($c = 1.00$, $CHCl_3$); IR (film): $\tilde{\nu} = 3490$, 2937, 1554, 1505, 1353, 1275, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.46$ (s, 1H), 8.45 (d, $J = 8.5$ Hz, 1H), 8.07 (d, $J = 8.5$ Hz, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 1H), 6.02 (dd, $J = 10.0$, 1.6 Hz, 1H), 5.83 (ddd, $J = 10.0$, 5.9, 2.3 Hz, 1H), 4.53 (t, $J = 4.5$ Hz, 1H), 4.37 (d, $J = 8.5$ Hz, 1H), 4.37 (s, 3H), 4.37 (1H), 3.37 (s, 3H), 3.35 (m, 1H), 3.31 (s, 3H), 2.97 (m, 1H), 2.91 (s, 3H), 2.86 (d, $J = 4.5$ Hz, 1H), 2.38–2.45 (m, 1H), 2.04–2.16 (m, 2H), 1.93–2.00 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.6$, 148.0, 145.3, 143.8, 137.8, 132.5, 131.6, 128.5, 126.0, 125.7, 125.4, 123.7, 119.7, 111.7, 105.1, 90.1, 67.6, 55.8, 54.2, 53.2, 51.5, 46.3, 37.4, 35.3, 34.9, 29.3 ppm; HRMS (ESI) calcd for $C_{26}H_{31}N_3O_{11}SNa$ $[M+Na]^+$: 616.1577, found 616.1604.

To a stirred solution of alcohol **S1** (800 mg, 1.35 mmol) in CH_2Cl_2 (9 mL) was added Dess–Martin periodinane (800 mg, 1.89 mmol) at room temperature. After stirring at 40 °C for 30 min, aqueous sodium thiosulfate was added, and the solution was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (30% ethyl acetate in *n*-hexane) to afford **28** (702 mg, 88%) as an amorphous solid. $[\alpha]_D^{24} = -24.2°$ ($c = 1.00$, $CHCl_3$); IR (film): $\tilde{\nu} = 2937$, 1736, 1553, 1507, 1353, 1281, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.50$ (dd, $J = 8.5$, 2.0 Hz, 1H), 8.45 (d, $J = 2.0$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 6.04 (dd, $J = 10.1$, 2.1 Hz, 1H), 5.88 (ddd, $J = 10.1$, 3.9, 3.9 Hz, 1H), 4.83 (s, 1H), 4.50 (t, $J = 4.8$ Hz, 1H), 3.88 (s, 3H), 3.37 (s, 3H), 3.34 (m, 1H), 3.32 (s, 3H), 3.08–3.12 (m, 3H), 2.95 (s, 3H), 2.85 (dd, $J = 3.9$, 3.9 Hz, 2H), 2.21–2.27 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.7$, 149.7, 148.0, 146.6, 143.6, 137.6, 132.6, 129.7, 128.8, 126.1, 125.0, 124.5, 124.3, 119.8, 112.6, 105.4, 87.6, 57.4, 56.1, 54.4, 53.5, 46.3, 37.3, 36.6, 35.4, 35.0 ppm; HRMS (ESI) calcd for $C_{26}H_{29}N_3O_{11}SNa$ $[M+Na]^+$: 614.1421, found 614.1440.

***N*-[2-[(3a*R*,9*RS*,9b*S*)-3a,8,9,9a-tetrahydro-9-(methanesulfonyloxy)-5-methoxy-3-oxo-9b-phenanthro[4,5-*bcd*]furanyl]ethyl]-*N*-methyl-2,4-dinitrobenzenesulfonamide (29)** To a stirred solution of 28 (659 mg, 1.11 mmol) in toluene (22 mL) was added 50% aqueous TFA (6 mL) at room temperature. After stirring at 50 °C for 2 h, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2, and to the resulting solution were added *N,N*-diisopropylethylamine (290 μL, 1.67 mmol) and mesyl chloride (103 μL, 1.33 mmol) at 0 °C. After stirring at 0 °C for 10 min, aqueous ammonium chloride was added, and the solution was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (50% ethyl acetate in *n*-hexane) to afford 29 (492 mg, 71%) as a yellow oil. Analytical data of the major isomer of mesylate 29: $[\alpha]_D^{24} = -25.3°$ ($c = 1.00$, $CHCl_3$); IR (film): $\tilde{\nu} = 1681$, 1550, 1510, 1352, 1281, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.48$ (d, $J = 2.0$ Hz, 1H), 8.46 (dd, $J = 8.5$ Hz, 2.0 Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 6.91 (dd, $J = 10.5$ Hz, 4.0 Hz, 1H), 6.77 (d, $J = 8.2$ Hz, 1H), 6.74 (d, $J = 8.2$ Hz, 1H), 6.20 (d, $J = 10.5$ Hz, 1H), 4.86 (s, 1H), 4.71 (dd, $J = 10.3$ Hz, 6.2 Hz, 1H), 3.88 (s, 3H), 3.50 (m, 1H), 3.22 (dd, $J = 6.2$ Hz, 4.0 Hz, 1H), 3.16 (s, 3H), 3.16 (1H), 3.10 (m, 1H), 2.94 (s, 3H), 2.91 (m, 1H), 2.23 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 193.0$, 149.7, 148.1, 146.4, 144.8, 143.8, 137.3, 132.7, 129.2, 127.8, 126.2, 121.6, 121.2, 119.8, 114.9, 86.7, 81.4, 56.7, 46.2, 46.1, 43.9, 38.6, 38.9, 35.3, 32.2 ppm; HRMS (ESI) calcd for $C_{25}H_{25}N_3O_{12}S_2Na$ $[M+Na]^+$: 646.0778, found 646.0756.

(−)-Codeine (34) To a stirred solution of **29** (440 mg, 0.71 mmol) in CH_2Cl_2 (7 mL) was added *N,N*-diisopropylethylamine (369 μL, 2.12 mmol) and mercaptoacetic acid (69 μL, 0.99 mmol) at 0 °C. After stirring at 0 °C for 30 min, aqueous sodium carbonate was added. After stirring for 30 min at room temperature, the solution was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. Concentration of the filtrate gave a 10:1 mixture of neopinone (**32**) and codeinone (**33**).

To a stirred solution of neopinone (**32**) and codeinone (**33**) in $CHCl_3$ (7 mL) was added 4 M HCl in dioxane (2 mL) at room temperature. After stirring at room temperature for 10 h, aqueous NaOH was added. After stirring for 30 min at room temperature, the solution was extracted with 10% EtOH in CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. Concentration of the filtrate gave codeinone (**33**) as a single product.

Codeinone (**33**) was dissolved in methanol (7 mL). To this solution was added $NaBH_4$ (27 mg, 0.71 mmol) in portions at room temperature. After stirring at room temperature for 10 min, water was added, and the solution was thoroughly extracted with 10% EtOH in CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (10% EtOH in CH_2Cl_2) to afford codeine (**34**) (148 mg, 70% from **29**) as an amorphous solid. $[\alpha]_D^{24} = -136°$ ($c = 0.10$, EtOH, lit. $[\alpha]_D^{24} = -137°$); IR (film): $\tilde{\nu} = 3356$, 2929, 1504, 1453, 1277, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.67$ (d, $J = 8.4$ Hz, 1H), 6.58 (d, $J = 8.4$ Hz, 1H), 5.71 (d, $J = 9.8$ Hz, 1H), 5.30 (ddd, $J = 9.8$, 2.6, 2.6 Hz, 1H), 4.90 (d, $J = 6.0$ Hz, 1H), 4.50 (dd, $J = 6.0$, 2.6 Hz, 1H), 3.84 (s, 3H), 3.36 (dd, $J = 6.0$, 3.2 Hz, 1H), 3.05 (d, $J = 18.6$ Hz, 1H), 2.68 (dd, $J = 2.5$, 2.5 Hz, 1H), 2.60 (dd, $J = 12.4$, 4.2 Hz, 1H), 2.45 (s, 3H), 2.39 (dd, $J = 12.4$, 3.6 Hz, 1H), 2.31 (dd, $J = 18.6$, 6.4 Hz, 1H), 2.08 (ddd, $J = 12.5$, 5.0, 5.0 Hz, 1H), 1.88 ppm (dd, $J = 12.5$, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.2$, 142.2, 133.4, 131.0, 128.2, 127.1, 119.6, 112.8, 91.3, 66.4, 58.9, 56.3, 46.5, 43.1, 42.9, 40.7, 35.8, 20.4 ppm; HRMS (ESI) calcd for $C_{18}H_{21}NO_3Na$ $[M+Na]^+$: 322.1410, found 322.1424.

(−)-Morphine (1) To a stirred solution of codeine (**34**, 10 mg, 0.033 mmol) in CH_2Cl_2 (0.3 mL) 1 M boron tribromide (167 μL, 0.167 mmol) was added at room temperature. After stirring at room temperature for 10 min, 28% aqueous ammonia was added and the solution was extracted with 10% ethanol in CH_2Cl_2. The combined organic solution was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the residue was purified with preparative thin layer chromatography (10% EtOH in CH_2Cl_2) to afford **1** (6.0 mg, 63%) as white crystals. $[\alpha]_D^{24} = -132°$ ($c = 0.10$, EtOH, lit. $[\alpha]_D^{24} =$

−132°); mp: 202–206 °C (decomp.); IR (film): $\tilde{\nu}$ = 3379, 2937, 1502, 1461, 1122, 943 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 6.42 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 8.0 Hz, 1H), 5.54 (d, J = 10.1 Hz, 1H), 5.21 (ddd, J = 10.1, 2.8, 2.8 Hz, 1H), 4.69 (d, J = 6.4 Hz, 1H), 4.07 (dd, J = 5.2, 2.8 Hz, 1H), 3.28 (dd, J = 6.4, 3.2 Hz, 1H), 2.93 (d, J = 18.6 Hz, 1H), 2.56 (dd, J = 2.4, 2.4 Hz, 1H), 2.51 (dd, J = 12.4, 4.4 Hz, 1H), 2.40 (dd, J = 12.4, 3.7 Hz, 1H), 2.35 (s, 3H), 2.26 (dd, J = 18.6, 6.6 Hz, 1H), 1.99 (ddd, J = 12.8, 5.0, 5.0 Hz, 1H), 1.74 ppm (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 142.2, 134.1, 131.6, 129.4, 125.7, 120.6, 118.6, 92.5, 67.9, 60.4, 47.6, 44.4, 43.1, 41.5, 36.4, 21.6 ppm; HRMS (ESI) calcd for $C_{17}H_{19}NO_3Na$ [M+Na^+]: 308.1263, found 308.1271.

Acknowledgements

This work was financially supported by Grant-in-Aid (15109001 and 20002004) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. H.K. is a research fellow of the Japan Society for the Promotion of Science (JSPS).

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Received: June 28, 2010
Published online: August 16, 2010

