Organic & Biomolecular Chemistry

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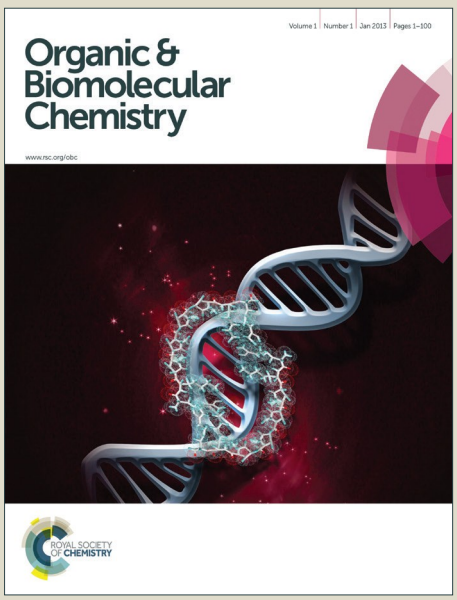

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PAPER

First asymmetric total synthesis of lycoposerramine-R

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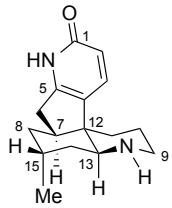
The first asymmetric total synthesis of lycoposerramine-R, a *Lycopodium* alkaloid possessing a novel skeleton, was accomplished by a strategy featuring the stereoselective intramolecular aldol cyclization giving a *cis*–fused 5/6 bicyclic skeleton and a new method for the construction of the pyridone ring *via* the aza-Wittig reaction.

Introduction

The club moss, *Lycopodium*, is a rich source of complex alkaloids, the so-called *Lycopodium* alkaloids,[1] which have a variety of biological activities, such as acetylcholine esterase (AchE) inhibitory activity[2] and neurite outgrowth promotion, and are anticipated to treat Alzheimer's disease, to improve geriatric memory loss and so on. Furthermore, *Lycopodium* alkaloids have complex skeletons and unique structures, and have continued to attract the attention of researchers in the fields of natural product chemistry, synthetic chemistry, and medicinal chemistry.[3]

These several years, we have engaged in the chemical and synthetic researches on *Lycopodium* alkaloids.[4] As one of these studies, we have reported the isolation and structure elucidation of lycoposerramine-R (**1**) from *Lycopodium serratum* in 2009.[4f] Lycoposerramine-R (**1**) is characterized by a novel skeleton consisting of a fused tetracyclic ring system possessing four asymmetric centers, a pyridone ring, and a *cis*-fused 5/6 ring (Fig. 1)

Recently, we have reported the total synthesis of (±)-lycoposerramine-R (**1**) *via* the Diels-Alder reaction, the stereoselective introduction of a methyl group, the regio- and stereoselective reductive amination, and the construction of a pyridone ring.[4a] Although the total synthesis of (±)-**1** was also reported by Bisai and Sarpong,[3s] the asymmetric total synthesis has never been accomplished and the absolute configuration of the natural product has not been clarified thus far. Herein, we report the first asymmetric total synthesis of lycoposerramine-R (**1**) involving such key steps as the intramolecular aldol cyclization to give a *cis*-fused 5/6 bicycle skeleton, and a newly developed procedure for the construction of a pyridone ring *via* the aza-Wittig reaction, which confirmed the absolute configuration of the natural product.

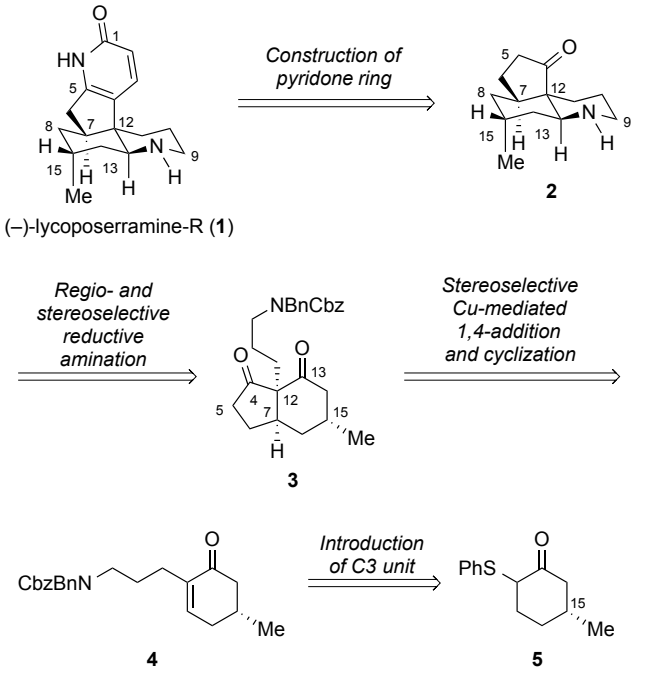


(–)-lycoposerramine-R (**1**)

Fig. 1 Structure of lycoposerramine-R (1).

Results and discussion

The retrosynthetic analysis of (–)-lycoposerramine-R (**1**) is outlined in Scheme 1. We envisioned that the pyridone ring could be constructed at the last stage. Tricyclic key intermediate **2** could be derived from diketone **3** by regio- and



Scheme 1. Retrosynthetic analysis of lycoposerramine-R (**1**).

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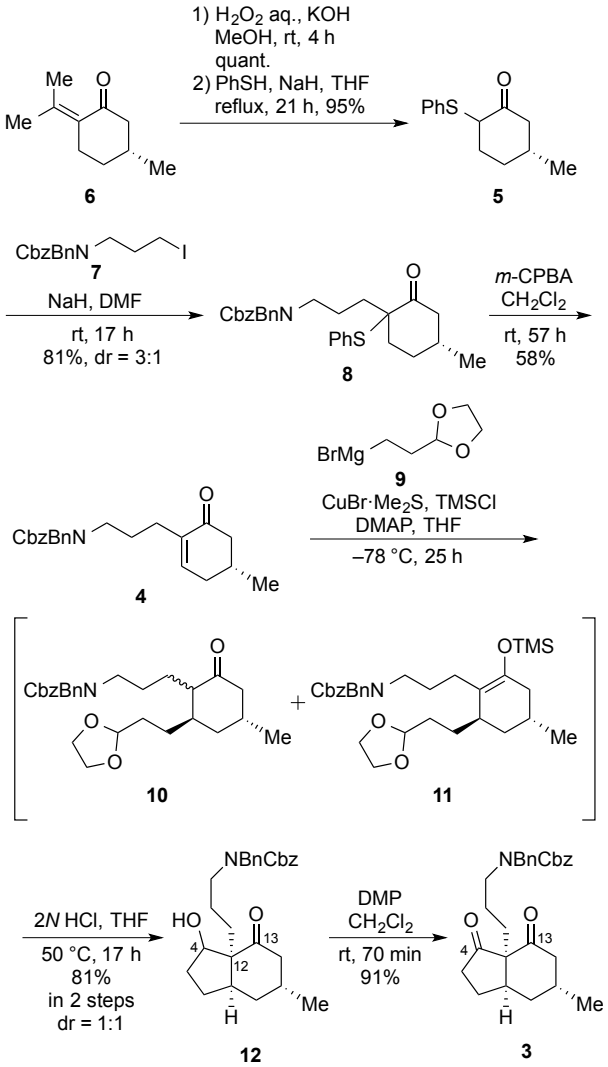
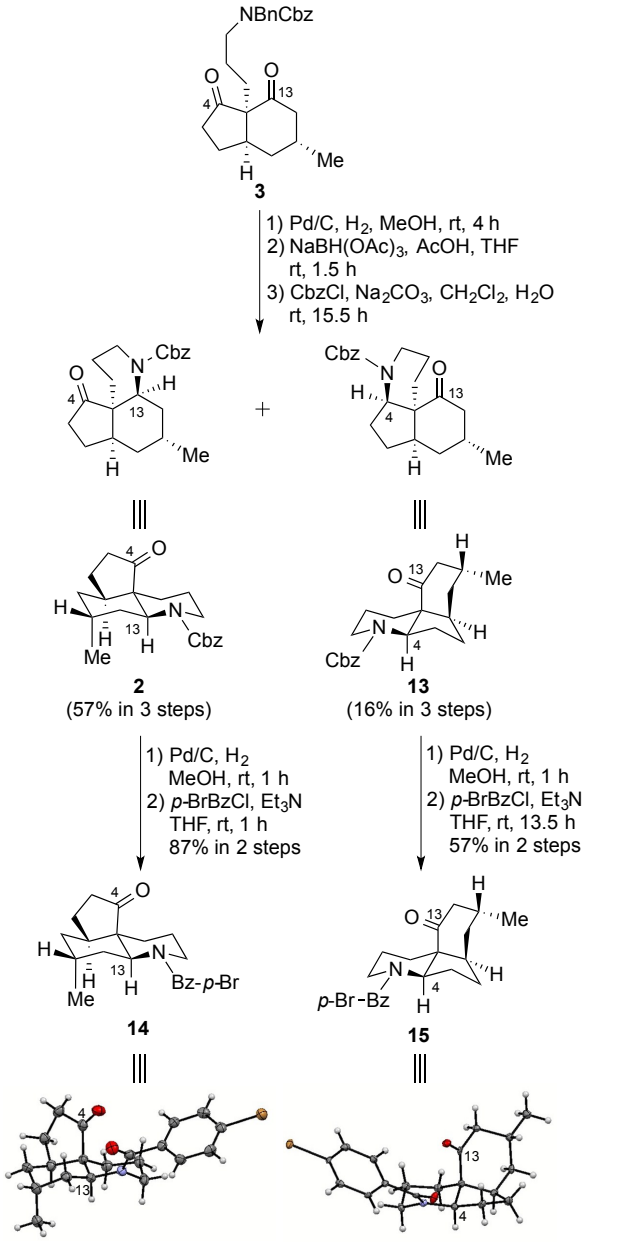
stereoselective reductive amination. Diketone **3** could be obtained from enone **4** *via* a stereoselective copper-mediated conjugated addition and a stereoselective intramolecular aldol cyclization. Enone **4** could be derived from known phenylsulfide **5**[5] *via* the introduction of a C3 unit.

Our project began with the synthesis of diketone **3** (Scheme 2). We initially prepared known phenylsulfide **5**, which was synthesized from commercially available (*R*)-pulegone (**6**) through epoxidation, followed by treatment with sodium thiophenolate in two steps. Alkylation of the enolate of **5**, which was prepared by treatment with sodium hydride, with iodide **7** afforded phenylsulfenyl ketone **8** as a diastereomeric mixture (dr = 3:1) in 81% yield. Oxidation of **8** with *m*-CPBA at –78 °C followed by treatment at room temperature gave enone **4**. Stereoselective installation of a C3 unit at the β position of the α,β-unsaturated carbonyl group in **4** was achieved by the copper-mediated conjugated addition of acetal-containing Grignard reagent **9** to enone **4** to yield a mixture of cyclohexanone **10** and silyl enol ether **11**. Treatment of crude **10** and **11** with aqueous hydrogen chloride at 50 °C gave *cis*-fused 5/6 bicyclic compound **12** in 81% yield (two steps) having the correct configuration of the quaternary stereocenter at C-12 *via* intramolecular aldol cyclization.[6] Oxidation of **12** with Dess-Martin reagent afforded diketone **3** in 91% yield.

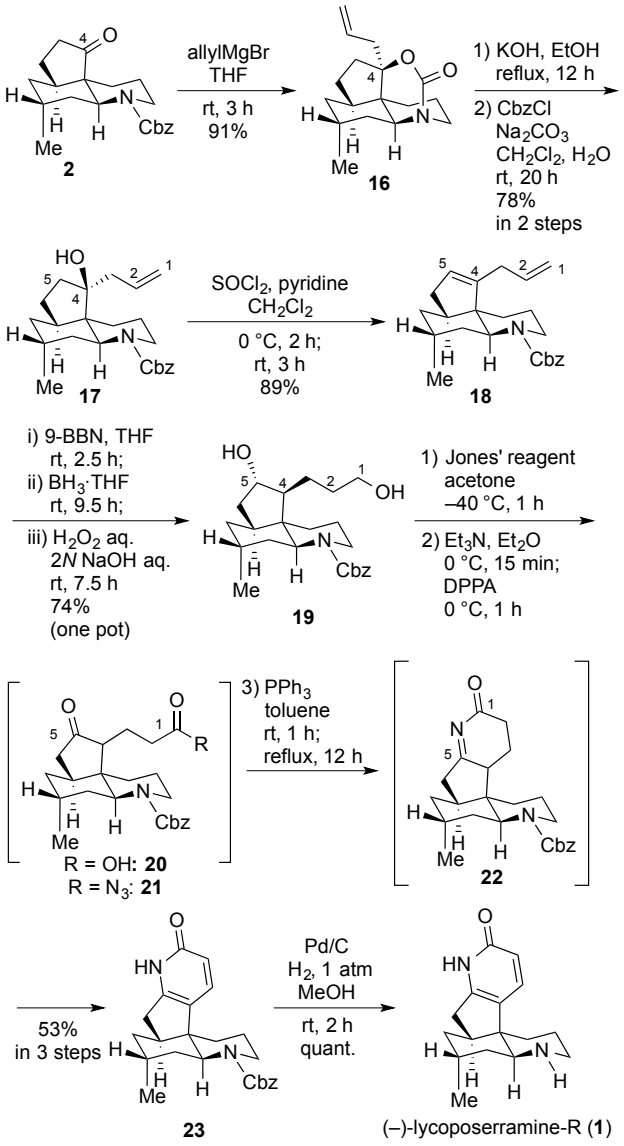


Scheme 2. Synthesis of diketone **3**.

Having succeeded in the synthesis of diketone **3**, we turned our attention to the construction of tricyclic key intermediate **2** (Scheme 3). Reductive amination of diketone **3** followed by Cbz protection afforded desired key intermediate **2**, which was cyclized between the C-13 carbonyl group and nitrogen, and its regioisomer **13**, which was cyclized between the C-4 carbonyl group and nitrogen, in the ratio of 3.6:1.[7] The structures including the stereochemistry of the aminomethine position of **2** and **13** were respectively elucidated by X-ray crystallographic analysis after conversion into *para*-bromobenzamide derivatives **14** and **15**.[8]



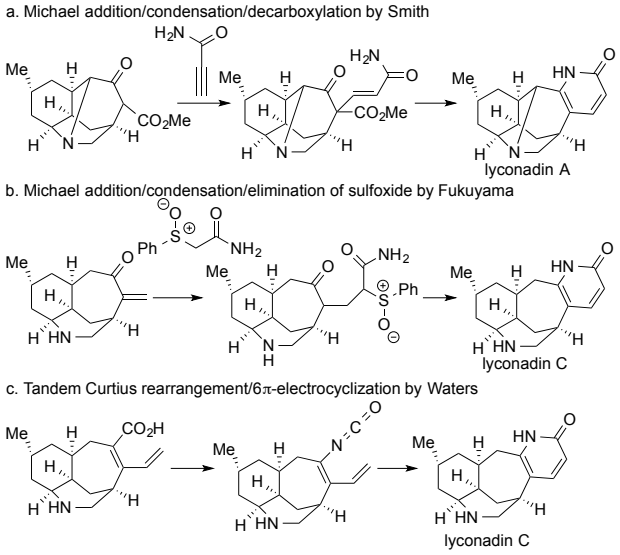
Scheme 3. Synthesis of tricyclic key intermediate **2**.



Scheme 4. Synthesis of (–)-lycoposerramine-R (**1**).

With optically active key intermediate **2** in hand, we next focused on the construction of the pyridone ring. In our previous study[4a] on the racemic synthesis of **1**, **2** was converted into 5-oxocarboxylic acid **20** (Scheme 4), which was then treated with $NH_2OMe·HCl$ to afford pyridone **23**. However, the conversion yield was very low (12% yield in two steps). Previously reported procedures for the construction of the pyridone ring in *Lycopodium* alkaloid syntheses (Scheme 5), namely, (a) Michael addition, condensation, and decarboxylation by Smith,[9] (b) Michael addition, condensation, and elimination of sulfoxide by Fukuyama,[3d] and (c) tandem Curtius rearrangement and 6π-electrocyclization by Waters,[10] were inapplicable to our system. Therefore, we made efforts to improve the reaction conditions for the preparation of 5-oxocarboxylic acid **20** from **2** as well as to develop a new and efficient method for construction of the pyridone ring by utilizing **20** as the intermediate.

We found that in the preparation of **16** from **2** the addition of allyl magnesium bromide two times (each 1.2 equivalents of reagent) improved the conversion yield (85% ⇒ 91%)



Scheme 5. Previous pyridone ring construction strategies in *Lycopodium* alkaloid synthesis.

compared with that in the synthesis of racemic **1**. Further, in dehydration of **17**, slow addition of the reagent ($SOCl_2$) and prolongation of the reaction time increased the yield (65% ⇒ 89%) as well. Further, the yield of the hydroboration-oxidation steps for the preparation of **19** could be greatly increased (from 39% to 74%) by careful addition of the oxidant (see Experimental section). At the final stage, the construction of the pyridone ring was accomplished by the aza-Wittig reaction. Thus, Jones' oxidation of diol **19** followed by the *in situ* formation of acyl azide **21**,[11] treatment with triphenyl phosphine, heating in toluene, and auto-oxidation of resultant dihydropyridone **22** produced pyridone **23** in 53% yield from diol **19** (Scheme 4). Finally, deprotection of the Cbz group in **23** gave (–)-lycoposerramine-R (**1**). Synthetic **1** was identical in all respects with the natural product, including the optical property: synthetic, $[\alpha]^{26}_{D}$ –26.1 (*c* 0.03, $CHCl_3$); natural, $[\alpha]^{25}_{D}$ –23.9 (*c* 0.21, $CHCl_3$). Therefore, the absolute configuration of lycoposerramine-R was established, as shown in formula **1**.

Conclusions

In summary, the first asymmetric total synthesis of lycoposerramine-R (**1**) was achieved in 19 steps and 4.7% overall yield starting from (*R*)-pulegone (**6**). The synthesis involved the stereoselective intramolecular aldol cyclization giving the *cis*-fused 5/6 bicyclic skeleton and a new method for the construction of the pyridone ring *via* the aza-Wittig reaction.

Experimental section

General

Reagents and solvents were purified by standard means or used without further purification. CH_2Cl_2, Et_3N, MeOH, EtOH, pyridine, and toluene were distilled from CaH_2. Acetone and

DMF were distilled after treatment with MS4Å. Anhydrous THF and Et_2O were used as supplied by Kanto Chemical Co., Inc. in the highest purity. IR spectra were recorded on a JASCO FT/IR-230 spectrophotometer. UV spectra were recorded in MeOH on a JASCO V-560 instrument. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM ECP-400, JNM ECP-600, JNM ECS-400, and ECA-600 with $CDCl_3$ as solvent and tetramethylsilane (^1H, 0.00 ppm), $CDCl_3$ (^{13}C, 77.0 ppm) as internal standard. The NMR peak assignments reported herein were confirmed by COSY, HMQC, HMBC, and differential NOE experiments. *J* values are given in Hz. HRESIMS spectra were recorded on a Thermo Fisher Scientific Exactive spectrometer. Optical rotations were measured with a JASCO P-1020 polarimeter. X-ray crystallographic analyses were conducted on a Rigaku R-AXIS RAPID imaging plate diffractometer using a graphite monochromator with Cu-Kα radiation at 93 K. Melting points were measured with a Yanagimoto Micro Melting Point Apparatus 1631A. TLC was performed on precoated silica gel 60 F254 plates (Merck, 0.25 mm thick). Column chromatography was carried out on silica gel 60 [Kanto Chemical Co., Inc., 40-50 μm (for flash column chromatography)] and Chromatorex NH [Fuji Silysia Chemical Ltd., 100-200 mesh (for amino-silica gel column chromatography)]. Medium pressure liquid chromatography (MPLC) was performed using C. I. G. prepacked column CPS-HS-221-05 (Kusano Kagakukikai, SiO_2).

Benzyl benzyl(3-iodopropyl)carbamate (7)

To a solution of 3-amino-1-propanol (26.9 g, 358 mmol) in MeOH (90 mL) at 0 °C were added $HC(OMe)_3$ (39.2 mL, 358 mmol) and benzaldehyde (36.3 mL, 358 mmol). The reaction mixture was warmed to room temperature under argon atmosphere. After stirring at the same temperature for 3.5 h, $NaBH_4$ (14.9 g, 393 mmol) was added at 0 °C. Then, the reaction mixture was stirred for 10 h at room temperature. After quenching the reaction mixture by adding H_2O at 0 °C, the resultant mixture was concentrated under reduced pressure and then diluted with $CHCl_3$. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the next reaction without further purification. To a solution of the crude material in CH_2Cl_2 (358 mL) and H_2O (247 mL) was added K_2CO_3 (59.3 g, 429 mmol) at 0 °C. After the reaction mixture was stirred vigorously at room temperature for 10 min under argon atmosphere, CbzCl (51.0 mL, 358 mmol) was added at 0 °C over 60 min. After stirring at room temperature for 12 h under argon atmosphere, the reaction mixture was diluted with CH_2Cl_2 and H_2O. The organic phase was separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 50:50) to afford *N*-(benzyl)benzyloxycarbonyl 3-amino-1-propanol[12] (104.5 g, 98% in two steps) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ: 7.37-7.20 (10H, overlapped), 5.18 (2H, s), 4.48 (2H, s), 3.55 (2H, q, J = 5.8 Hz), 3.41 (2H, br-s), 3.01 (1H, br-s), 1.67 (2H, quin, J = 5.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, at 55 °C) δ: 157.2, 137.7, 136.6, 128.6, 128.5, 128.1, 127.9, 127.6, 127.4, 67.6, 59.0, 50.6, 43.3, 30.6. IR (ATR) ν_{max} cm^{-1}: 3412, 2947, 1675, 1420, 1232, 1120, 1057. HR-MS (ESI): calcd for $C_{18}H_{21}NO_3Na$ $[M+Na]^+$: 322.1419, found: 322.1392.

To a solution of the above alcohol (21.6 g, 72.2 mmol) in CH_2Cl_2 (722 mL) at 0 °C were added PPh_3 (22.7 g, 86.6 mmol), imidazole (5.90 g, 86.6 mmol), and iodine (22.0 g, 86.6 mmol). After stirring at room temperature for 70 min under argon atmosphere, the reaction mixture was quenched by adding saturated aqueous $NaHCO_3$ solution, and the resultant mixture was diluted with $CHCl_3$. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 15:85) to afford **7** (26.2 g, 89%) as a yellow oil. ^1H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ: 7.32-7.23 (10H, overlapped, PhCH_2OCO- and PhCH_2N-), 5.18 (2H, s, PhCH_2OCO-), 4.51 (2H, s, PhCH_2N-), 3.32 (2H, t, J = 6.8 Hz), 3.07 (2H, br-t, J = 6.8 Hz), 2.03 (2H, br-s). ^{13}C NMR ($CDCl_3$, 100 MHz, at 55 °C) δ: 156.5, 137.7, 136.7, 128.7, 128.5, 128.1, 128.0, 127.7, 127.5, 67.4, 51.2, 47.5, 32.2, 2.3. IR (ATR) ν_{max} cm^{-1}: 3029, 2948, 1692, 1417, 1228, 1097. HR-MS (ESI): calcd for $C_{18}H_{20}NO_3INa$ $[M+Na]^+$: 432.0436, found: 432.0399.

Benzyl benzyl(3-((4*R*)-4-methyl-2-oxo-1-(phenylthio)cyclohexyl)propyl)carbamate (8)

To a solution of **5** (4.38 g, 19.9 mmol) in DMF (60 mL) at –40 °C was added solid NaH (958 mg, 60% in oil, 23.9 mmol) in portions over 20 min with extensive gas evolution. After 3 h, a solution of **7** (24.5 g, 59.9 mmol) in DMF (60 mL) was dropped over 1.5 h at –40 °C. The cooling bath was removed and the reaction mixture was stirred for 17 h at room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl solution and EtOAc. The organic phase was separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 15:85) to afford **8** (8.08 g, 81%, dr = 3:1) as a yellow oil. **Compund 8 (3 : 1 mixture of diastereomers):** ^1H NMR ($CDCl_3$, 600 MHz, at 55 °C, **8-major*** : **8-minor****) δ: 7.31-7.20 (30H, overlapped, PhCH_2OCO- and PhCH_2N- and PhS-), 5.172 (2H, s, PhCH_2OCO-)**, 5.166 (2H, s, PhCH_2OCO-)*, 4.47 (2H, s, PhCH_2N-)*, 4.45 (2H, s, PhCH_2N-)**, 3.23-3.04 (6H, overlapped), 2.26 (2H, m), 2.11 (2H, m), 2.03 (2H, br-s), 1.91 (2H, br-s), 1.79 (2H, br-s), 1.63 (4H, br-s), 1.53-1.42 (6H, overlapped), 1.05 (3H, d, J = 5.5 Hz, H-16)**, 0.92 (3H, d, J = 6.9 Hz, H-16)*. ^{13}C NMR ($CDCl_3$, 150 MHz, at 55 °C) δ: 207.6, 206.9, 156.5, 156.4, 138.1, 138.0, 137.01, 136.99, 136.5, 136.0, 135.4, 130.8, 130.5, 129.3, 129.2, 129.03, 128.96, 128.9, 128.82, 128.77, 128.61, 128.59, 128.5, 128.0, 127.9, 127.7,

127.40, 127.35, 67.3, 61.7, 60.1, 50.8, 46.8, 46.0, 41.2, 37.3, 35.8, 34.6, 33.5, 31.9, 31.8, 31.6, 29.8, 28.0, 27.9, 26.6, 22.4, 22.2, 22.0, 19.7. IR (ATR) ν_{max} cm^{-1}: 3067, 3030, 2950, 2861, 1766, 1694, 1418, 1230, 1212, 1115. HR-MS (ESI): calcd for $C_{31}H_{35}NO_3SNa$ $[M+Na]^+$: 524.2235, found: 524.2203. $[\alpha]^{27}_D$ –26 (*c* 0.98, $CHCl_3$).

Benzyl (*R*)-benzyl(3-(4-methyl-6-oxocyclohex-1-en-1-yl)propyl)carbamate (4)

To a solution of **8** (133 mg, 0.265 mmol) in CH_2Cl_2 (1.7 mL) at –78 °C was added a solution of *m*-CPBA (59.3 mg, 0.265 mmol) in CH_2Cl_2 (1.0 mL) over 10 min. The mixture was warmed to room temperature over 1 h and then stirred for 57 h under argon atmosphere, whereupon the solution became homogeneous. The reaction mixture was diluted with aqueous 10% w/w $NaHSO_3$ solution. The organic phase was separated, and the aqueous phase was extracted five times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 20:80) to afford **4** (59.8 mg, 58%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ: 7.31-7.21 (10H, overlapped, PhCH_2OCO- and PhCH_2N-), 6.57 (1H, br-s, H-7), 5.16 (2H, s, PhCH_2OCO-), 4.49 (2H, s, PhCH_2N-), 3.21 (2H, br-s), 2.44 (1H, br-d, J = 15.0 Hz), 2.32 (1H, br-d, J = 16.5 Hz), 2.12-1.92 (5H, overlapped), 1.63 (2H, br-t, J = 7.2 Hz), 1.01 (3H, d, J = 6.6 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz, at 55 °C) δ: 199.1, 144.3, 138.8, 138.0, 137.7, 137.0, 128.6, 128.53, 128.46, 128.0, 127.9, 127.3, 67.2, 50.4, 46.7, 46.3, 34.4, 31.7, 30.6, 26.7, 21.1. IR (ATR) ν_{max} cm^{-1}: 3030, 2952, 2924, 2871, 1694, 1670, 1454, 1419, 1216, 1119. HR-MS (ESI): calcd for $C_{25}H_{29}NO_3Na$ $[M+Na]^+$: 414.2045, found: 414.2023. $[\alpha]^{28}_D$ –16 (*c* 0.46, $CHCl_3$).

Benzyl benzyl(3-((3a*S*,6*R*,7a*R*)-3-hydroxy-6-methyl-4-oxooctahydro-3a*H*-inden-3a-yl)propyl)carbamate (12)

To a stirred mixture containing 201 mg (8.28 mmol) of fresh magnesium turnings in THF (10 mL) was added a small iodine crystal under argon atmosphere. Then, over a period of 30 min, a solution of 2-(2-bromoethyl)-1,3-dioxolane (824 mg, 4.55 mmol) in THF (10 mL) was added to the mixture, the temperature of which was maintained below 25 °C by using a cooling bath. The resulting Grignard reagent mixture was continuously stirred for 1 h at room temperature before being transferred into a stirred precooled mixture of 4-DMAP (556 mg, 4.55 mmol) and CuBr·Me_2S (430 mg, 2.07 mmol) in THF (30 mL) at –78 °C *via* a cannula. After the resulting reaction mixture was stirred at –78 °C for 1 h, TMSCl (0.58 mL, 4.55 mmol) and a solution of **4** (810 mg, 2.07 mmol) in THF (20 mL) were added dropwise, respectively, at the same temperature. The reaction mixture was stirred at –78 °C for 25 h under argon atmosphere and finally quenched by the addition of saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude **10** and **11** were used in the next reaction without further purification. To a solution of crude **10** and **11** in THF (80 mL) was added 2*N* aqueous HCl (20 mL) at 0 °C. The reaction mixture was stirred for 17 h at 50 °C under argon atmosphere. After cooling to room temperature, the reaction mixture was extracted three times with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 40:60) to afford **12** (752.8 mg, 81% in 2 steps, dr = 1:1) as a brown oil. **Compound 12 (a less polar isomer):** ^{1}H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ: 7.32-7.21 (10H, overlapped, PhCH_2OCO- and PhCH_2N-), 5.16 (2H, br-s, PhCH_2OCO-), 4.51 (1H, br-d, J = 6.2 Hz, H-4), 4.46 (2H, br-s, PhCH_2N-), 3.20 (2H, br-t, J = 7.0 Hz, H-9), 2.28 (1H, m), 2.15 (1H, br-d, J = 9.9 Hz), 2.02-1.94 (2H, overlapped), 1.88 (1H, m), 1.78 (1H, m), 1.67 (1H, br-d, J = 13.2 Hz), 1.54-1.42 (5H, overlapped), 1.35-1.21 (3H, overlapped), 0.97 (3H, d, J = 5.9 Hz, H-16). ^{13}C NMR ($CDCl_3$, 100 MHz, at 55 °C) δ: 214.9, 156.6, 138.0, 136.9, 128.6, 128.5, 128.0, 127.9, 127.7, 127.4, 74.5, 67.3, 62.0, 50.6, 47.8, 47.2, 44.3, 34.1, 33.4, 32.4, 29.6, 29.1, 27.1, 22.2. IR (ATR) ν_{max} cm^{-1}: 3467, 2950, 2925, 2869, 1688, 1685, 1454, 1421, 1231, 1119. HR-MS (ESI): calcd for $C_{28}H_{35}NO_4Na$ $[M+Na]^+$: 472.2464, found: 472.2446. $[\alpha]^{28}_D$ = +47 (*c* 0.75, $CHCl_3$).

Benzyl benzyl(3-((3a*S*,6*R*,7a*R*)-6-methyl-3,4-dioxooctahydro-3a*H*-inden-3a-yl)propyl)carbamate (3)

To a solution of **12** (857.3 mg, 1.91 mmol) in CH_2Cl_2 (9.6 mL) was added a solution of Dess-Martin reagent (1.70 g, 3.81 mmol) in CH_2Cl_2 (9.5 mL) at 0 °C. The reaction mixture was warmed to room temperature under argon atmosphere. After stirring at the same temperature for 70 min, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ solution, and the resultant mixture was diluted with $CHCl_3$. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 30:70) to afford **3** (780.9 mg, 91%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz, at 55 °C) δ: 7.32-7.22 (10H, overlapped, PhCH_2OCO- and PhCH_2N-), 5.17 (2H, s, PhCH_2OCO-), 4.48 (2H, s, PhCH_2N-), 3.23 (2H, br-s, H-9), 2.36-2.32 (2H, overlapped), 2.20 (2H, m), 2.04 (2H, m), 1.87 (1H, br-s), 1.70-1.47 (5H, overlapped), 1.26 (2H, m), 1.00 (3H, d, J = 6.2 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz, at 55 °C) δ: 214.4, 208.4, 156.6, 138.0, 137.0, 128.63, 128.62, 128.5, 128.0, 127.9, 127.4, 67.3, 66.6, 50.4, 47.0, 46.9, 42.3, 35.9, 33.2, 30.2, 29.7, 28.8, 24.0, 21.6. IR (ATR) ν_{max} cm^{-1}: 2952, 1748, 1698, 1508, 1457, 1222. HR-MS (ESI): calcd for $C_{28}H_{33}NO_4Na$ $[M+Na]^+$: 470.2307, found: 470.2327. $[\alpha]^{28}_D$ +49 (*c* 0.18, $CHCl_3$).

Benzyl (4a*R*,7a*S*,9*R*,10a*S*)-9-methyl-5-oxodecahydrocyclopenta[*e*]quinoline-1(2*H*)-carboxylate (2) and benzyl (4a*R*,6a*R*,8*R*)-8-methyl-10-

oxodecahydroindeno[1,7a-*b*]pyridine-4(1*H*)-carboxylate (13)

To a solution of **3** (98.3 mg, 0.220 mmol) in MeOH (2.2 mL) was added 10% Pd/C (23.4 mg, 0.022 mmol) at room temperature under argon atmosphere. Then, the reaction mixture was vigorously stirred for 4 h at room temperature under 1.0 atm pressure of hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure to afford the crude product as a pale yellow oil, which was used in the next reaction without further purification. To a solution of the above product and AcOH (13 μL, 0.220 mmol) in THF (2.2 mL) was added $NaBH(OAc)_3$ (58.6 mg, 0.268 mmol) at 0 °C. After stirring at room temperature for 1.5 h under argon atmosphere, the reaction mixture was quenched by adding 1*N* aqueous NaOH at 0 °C, and the resultant mixture was diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted five times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the next reaction without further purification. To a solution of the crude material in CH_2Cl_2 (2.2 mL) and H_2O (2.2 mL) was added Na_2CO_3 (233.2 mg, 2.20 mmol) at 0 °C. After stirring vigorously at room temperature for 10 min under argon atmosphere, CbzCl (94 μL, 0.660 mmol) was added at 0 °C. After stirring at room temperature for 15.5 h under argon atmosphere, the reaction mixture was diluted with $CHCl_3$ and H_2O. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 17:83) to afford **2** (42.6 mg, 57% in 3 steps) as a pale yellow oil and **13** (12.2 mg, 16% in 3 steps) as a pale yellow oil. **Compound 2:** ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.40-7.26 (5H, overlapped, PhCH$_2$OCO-), 5.24 (1H, d, *J* = 12.6 Hz, PhCH$_2$OCO-), 5.10 (1H, d, *J* = 12.6 Hz, PhCH$_2$OCO-), 4.35 (1H, m, H-9), 3.37 (1H, dd, *J* = 13.5, 3.7 Hz, H-13), 2.74 (1H, ddd, *J* = 13.0, 13.0, 2.6 Hz, H-9), 2.42 (1H, ddd, *J* = 13.5, 13.5, 4.0 Hz), 2.36-2.30 (2H, overlapped), 2.17-2.06 (3H, overlapped), 2.04 (1H, m), 1.94 (1H, m), 1.71 (1H, m), 1.52-1.24 (5H, overlapped), 1.01 (3H, d, *J* = 7.3 Hz, H-16). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 217.5, 155.9, 137.5, 128.3, 127.8, 127.5, 66.5, 58.1, 53.1, 48.5, 40.6, 34.72, 34.68, 34.6, 33.4, 27.8, 23.2, 21.5, 16.6. IR (ATR) ν_{max} cm^{-1}: 1731, 1711, 1683. HR-MS (ESI): calcd for $C_{21}H_{27}NO_3Na$ $[M+Na]^+$ 364.1889; found 364.1871. $[\alpha]^{27}_D$ –28 (*c* 0.110, $CHCl_3$). **Compound 13:** ^{1}H-NMR (600 MHz, $CDCl_3$) *δ*: 7.39-7.26 (5H, overlapped, PhCH$_2$OCO-), 5.20 (1H, d, *J* = 12.7 Hz, PhCH$_2$OCO-), 5.14 (1H, d, *J* = 12.7 Hz, PhCH$_2$OCO-), 4.35 (1H, br-d, *J* = 13.7 Hz), 2.76 (1H, dd, *J* = 12.7, 7.2 Hz), 2.66 (1H, ddd, *J* = 13.1, 13.1, 3.1 Hz), 2.42 (1H, br-s), 2.28 (1H, br-d, *J* = 13.1 Hz), 2.22 (1H, br-s), 2.16 (1H, d, *J* = 13.1 Hz), 2.12 (1H, br-d, *J* = 13.1 Hz), 2.09-2.02 (2H, overlapped), 1.75 (2H, overlapped), 1.60 (1H, ddd, *J* = 14.4, 11.7, 4.8 Hz), 1.52-1.39 (3H, overlapped), 1.35 (1H, ddd, *J* = 13.0, 13.0, 3.8 Hz), 1.00 (3H, d, *J* = 6.2 Hz, H-16). ^{13}C-NMR (150 MHz, $CDCl_3$) *δ*: 213.4, 155.4, 137.3, 128.3, 127.8, 127.6, 66.6, 65.6, 55.0, 48.2, 46.7, 44.8, 34.2, 33.5, 30.0, 27.1, 24.8, 22.2, 21.8. IR (ATR) ν_{max} cm^{-1}: 2948, 2925, 2869, 2847, 1699, 1687, 1497, 1342, 1256, 1109. HR-MS (ESI): calcd for $C_{21}H_{27}NO_3Na$ $[M+Na]^+$ 364.1889; found 364.1880. $[\alpha]^{21}_D$ +116 (*c* 0.38, $CHCl_3$).

(4a*R*,7a*S*,9*R*,10a*S*)-1-(4-Bromobenzoyl)-9-methyldecahydrocyclopenta[*e*]quinolin-5(2*H*)-one (14)

To a solution of **2** (2.0 mg, 5.86 μmol) in MeOH (1.0 mL) was added 10% Pd/C (0.6 mg, 0.586 μmol) at room temperature under argon atmosphere. Then, the reaction mixture was vigorously stirred for 1 h at room temperature under 1.0 atm pressure of hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure to afford the crude product as a pale yellow oil, which was used in the next reaction without further purification. To a solution of the crude material in THF (0.5 mL) were added Et_3N (2 μL, 12.9 μmol) and *p*-bromobenzoyl chloride (1.5 mg, 6.45 μmol) at 0 °C. After stirring at room temperature for 1 h under argon atmosphere, the reaction mixture was diluted with $CHCl_3$ and saturated aqueous $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 50:50) to afford **14** (2.0 mg, 87% in 2 steps) as colorless platelet crystals. Recrystallization of **14** from a mixed solvent of EtOAc/*n*-hexane under ambient temperature gave a suitable crystal for X-ray analysis. ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.50 (2H, d, *J* = 8.8 Hz, BrC$_6$H$_4$CO-), 7.40 (2H, d, *J* = 8.8 Hz, PhCH$_2$OCO-), 3.86 (1H, ddd, *J* = 13.2, 3.3, 3.3 Hz, H-9), 3.60 (1H, dd, *J* = 13.4, 3.5 Hz, H-13), 2.94 (1H, ddd, *J* = 13.5, 13.5, 3.3 Hz, H-9), 2.40-2.32 (3H, overlapped), 2.20-2.09 (4H, overlapped), 2.04 (1H, br-dd, *J* = 12.4, 4.0 Hz), 1.73-1.60 (2H, overlapped), 1.56-1.33 (4H, overlapped), 1.04 (3H, d, *J* = 7.3 Hz, H-16). ^{13}C-NMR (150 MHz, $CDCl_3$) *δ*: 217.8, 170.6, 138.2, 131.4, 128.1, 122.7, 58.9, 53.1, 49.9, 40.8, 34.8, 34.5, 34.0, 32.4, 27.6, 23.3, 21.9, 16.7. IR (ATR) ν_{max} cm^{-1}: 2961, 2929, 2856, 1724, 1644, 1585, 1435, 1365, 1115. HR-MS (ESI): calcd for $C_{20}H_{25}NO_2Br$ $[M+H]^+$ 390.1069; found 390.1064. $[\alpha]^{21}_D$ –44 (*c* 0.54, $CHCl_3$). m.p.: 158.8-159.2 °C (plate).

(4a*R*,6a*R*,8*R*)-4-(4-Bromobenzoyl)-8-methyldecahydroindeno[1,7a-*b*]pyridin-10(1*H*)-one (15)

To a solution of **13** (38.0 mg, 0.112 mmol) in MeOH (1.1 mL) was added 10% Pd/C (11.9 mg, 0.011 mmol) at room temperature under argon atmosphere. Then, the reaction mixture was vigorously stirred for 1 h at room temperature under 1.0 atm pressure of hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure to afford the crude product as a pale yellow oil, which was used in the next reaction without further purification. To a solution of the crude material in THF (1.1 mL) were added Et_3N (35 μL, 0.246 mmol) and *p*-bromobenzoyl chloride (27.0 mg, 0.123 mmol) at

0 °C. After stirring at room temperature for 13.5 h under argon atmosphere, the reaction mixture was diluted with $CHCl_3$ and saturated aqueous $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 50:50) to afford **15** (25.0 mg, 57% in 2 steps) as colorless platelet crystals. Recrystallization of **15** from a mixed solvent of EtOAc/*n*-hexane under ambient temperature gave a suitable crystal for X-ray analysis. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.50 (2H, d, J = 8.8 Hz, PhC$\underline{H_2}$OCO-), 7.43 (2H, br-d, J = 8.1 Hz, PhC$\underline{H_2}$OCO-), 4.08 (1H, br-s), 2.97 (1H, dd, J = 12.4, 7.0 Hz), 2.73 (1H, ddd, J = 13.5, 13.5, 3.6 Hz), 2.34 (1H, br-d, J = 11.0 Hz), 2.25-2.05 (5H, overlapped), 1.77-1.39 (8H, overlapped), 1.01 (3H, d, J = 6.6 Hz, H-16). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 213.8, 170.6, 137.7, 131.2, 129.1, 123.4, 66.2, 55.6, 48.5, 48.2, 44.9, 33.7, 33.2, 30.1, 27.0, 24.9, 22.2, 21.9. IR (ATR) ν_{max} cm^{-1}: 2944, 2909, 2884, 1701, 1638, 1586, 1459, 1439, 1376, 1358, 1260. HR-MS (ESI): calcd for $C_{20}H_{25}NO_2Br$ $[M+H]^+$ 390.1069; found 390.1056. $[\alpha]^{21}_D$ +70 (*c* 0.59, $CHCl_3$). m.p.: 148.0-148.5 °C (plate).

(1*R*,4a*R*,5*S*,7a*S*,9*R*,10a*S*)-5-Allyl-9-methyldecahydro-2*H*-5,1-(epoxymethano)cyclopenta[*e*]quinolin-12-one (16)

To a stirred solution of **2** (141.2 mg, 0.414 mmol) in THF (4.2 mL) was slowly added allylmagnesium bromide (1.0 M in Et_2O, 0.50 mL, 0.50 mmol) at 0 °C under argon atmosphere, and the resultant mixture was stirred at room temperature. After 1 h 45 min, **2** still remained in the reaction mixture. To the reaction mixture was slowly introduced an additional amount of allylmagnesium bromide (1.0 M in Et_2O, 0.50 mL, 0.50 mmol) at 0 °C under argon atmosphere, and the resultant mixture was stirred for an additional 1 h 15 min at room temperature. After adding saturated aqueous NH_4Cl solution at 0 °C, the resultant mixture was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 30:70) to afford **16** (103.6 mg, 91%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 6.05 (1H, dddd, J = 17.2, 9.6, 5.5, 5.5 Hz, H-2), 5.20 (1H, d, J = 9.6 Hz, H-1), 5.12 (1H, d, J = 17.2 Hz, H-1), 3.96 (1H, dd, J = 13.1, 6.9 Hz, H-9), 3.12 (1H, ddd, J = 13.1, 13.1, 4.1 Hz, H-9), 2.94 (1H, dd, J = 13.1, 6.9 Hz, H-13), 2.60 (1H, ddd, J = 14.4, 4.8, 2.0 Hz), 2.28-2.24 (2H, overlapped), 2.03-1.95 (4H, overlapped), 1.93-1.85 (2H, overlapped), 1.77 (1H, m), 1.69 (1H, m), 1.62 (1H, m), 1.48 (1H, dd, J = 13.7, 8.2 Hz), 1.44-1.34 (2H, overlapped), 1.31 (1H, m), 1.01 (3H, d, J = 6.9 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 161.6, 133.2, 118.8, 95.1, 60.9, 54.6, 45.7, 43.4, 40.3, 37.3, 34.12, 34.06, 31.1, 27.2, 24.6, 24.5, 23.0. IR (ATR) ν_{max} cm^{-1}: 2923, 1696, 1508, 1474, 1344, 1245, 1218, 1185, 1062, 1006, 956, 920, 865, 836. HR-MS (ESI): calcd for $C_{16}H_{25}NNa$ $[M–CO_2+Na]^+$: 254.1885, found: 254.1877. $[\alpha]^{24}_D$ +30 (*c* 0.07, $CHCl_3$).

Benzyl (4a*R*,5*S*,7a*S*,9*R*,10a*S*)-5-allyl-5-hydroxy-9-methyldecahydrocyclopenta[*e*]quinoline-1(2*H*)-carboxylate (17)

Compound **16** (50.2 mg, 0.182 mmol) was dissolved in a solution of KOH (102.1 mg, 1.82 mmol) in EtOH (1.8 mL) at 0 °C under argon atmosphere. The reaction mixture was refluxed for 12 h. After the reaction mixture was concentrated, the resultant crude material was dissolved in 10% MeOH/CH_2Cl_2 and H_2O, and then the resultant mixture was extracted five times with 10% MeOH/CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product as a pale yellow oil, which was used in the next reaction without further purification. To a solution of the crude material in CH_2Cl_2 (3.6 mL) and H_2O (1.8 mL) was added Na_2CO_3 (192.9 mg, 1.82 mmol) at 0 °C. After the reaction mixture was stirred vigorously at room temperature for 10 min under argon atmosphere, CbzCl (78 μL, 0.546 mmol) was added at 0 °C, and the reaction mixture was stirred for another 20 h at room temperature. After adding $CHCl_3$ and saturated aqueous $NaHCO_3$ solution, the resultant mixture was extracted three times with $CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 5:95) to give **17** (54.5 mg, 78% in 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.28 (5H, overlapped, $\underline{Ph}CH_2OCO$-), 5.95 (1H, dddd, J = 17.2, 10.3, 7.0, 7.0 Hz, H-2), 5.16 (1H, d, J = 12.4 Hz, PhC$\underline{H_2}$OCO-), 5.13 (1H, d, J = 12.4 Hz, PhC$\underline{H_2}$OCO-), 5.01 (1H, br-dd, J = 10.3, 2,2 Hz, H-1), 4.92 (1H, br-dd, J = 16.8, 2.2 Hz, H-1), 4.29 (1H, dd, J = 13.5, 6.2 Hz, H-9), 4.01 (1H, br-s, -O$\underline{H}$), 3.36 (1H, dd, J = 13.5, 5.1 Hz, H-13), 3.16 (1H, ddd, J = 13.2, 13.2, 6.6 Hz, H-9), 3.04 (1H, ddd, J = 13.2, 13.2, 4.0 Hz), 2.25 (1H, m), 2.20 (2H, d, J = 7.0 Hz), 1.99-1.71 (7H, overlapped), 1.51-1.21 (5H, overlapped), 1.01 (3H, d, J = 7.0 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 156.0, 136.5, 135.9, 128.6, 128.1, 127.9, 116.5, 85.0, 67.0, 61.7, 51.4, 49.9, 47.3, 46.6, 37.9, 37.8, 34.5, 33.2, 27.0, 26.6, 24.3, 19.6. IR (ATR) ν_{max} cm^{-1}: 3421, 2955, 2927, 1675, 1481, 1438, 1385, 1358, 1281, 1239, 1213, 1161, 1120, 1095, 1027, 911. HR-MS (ESI): calcd for $C_{24}H_{33}NO_3Na$ $[M+Na]^+$: 406.2358, found: 406.2341. $[\alpha]^{28}_D$ –64 (*c* 0.29, $CHCl_3$)

Benzyl (4a*S*,7a*R*,9*R*,10a*S*)-5-allyl-9-methyl-3,4,7,7a,8,9,10,10a-octahydrocyclopenta[*e*]quinoline-1(2*H*)-carboxylate (18)

To a stirred solution of **17** (9.9 mg, 0.026 mmol) in CH_2Cl_2 (0.5 mL) were added pyridine (32 μL, 0.387 mmol) and $SOCl_2$ (4.0 μL, 0.052 mmol) at 0 °C under argon atmosphere. After stirring for 2 h at 0 °C and for 3 h at room temperature, the reaction mixture was concentrated. The crude material was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 5:95) to afford **18** (8.4 mg, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.39-7.28 (5H, overlapped, $\underline{Ph}CH_2OCO$-), 5.87 (1H, dddd, J = 17.2, 10.3, 6.9, 6.9 Hz), 5.35 (1H, br-s), 5.12 (1H, d, J = 12.4 Hz, PhC$\underline{H_2}$OCO-), 5.05 (1H, d, J = 12.4 Hz, PhC$\underline{H_2}$OCO-), 4.99 (1H, dd, J = 10.3, 1.4 Hz, H-1), 4.95

(1H, dd, *J* = 17.2, 1.4 Hz, H-1), 4.47 (1H, br-dd, *J* = 13.1, 4.8 Hz, H-9), 3.35 (1H, dd, *J* = 13.7, 3.4 Hz, H-13), 3.04 (1H, br-d, *J* = 17.9 Hz), 2.84 (1H, dd, *J* = 13.1, 13.1, 2.7 Hz, H-9), 2.84 (1H, m), 2.47 (1H, m), 2.26 (1H, ddd, *J* = 13.1, 13.1, 4.8 Hz), 2.06 (1H, m), 2.00-1.93 (3H, overlapped), 1.78 (1H, m), 1.62 (1H, br-d, *J* = 15.8 Hz), 1.56-1.38 (3H, overlapped), 1.23 (1H, m), 0.99 (3H, d, *J* = 6.9 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz) *δ*: 154.6, 147.5, 137.2, 136.7, 128.4, 128.0, 127.8, 125.6, 115.4, 66.5, 59.8, 53.3, 48.6, 44.7, 39.9, 35.6, 35.3, 34.5, 34.1, 27.6, 23.6, 18.1. IR (ATR) ν_{max} cm^{-1}: 2959, 2940, 2917, 1706, 1457, 1437, 1376, 1264, 1236, 1173, 1069, 909. HR-MS (ESI): calcd for $C_{24}H_{32}NO_2$ $[M+H]^+$: 366.2433, found: 366.2416. $[\alpha]^{26}_D$ –28 (*c* 0.10, $CHCl_3$).

Benzyl (4a*S*,5*S*,6*S*,7a*R*,9*R*,10a*S*)-6-hydroxy-5-(3-hydroxypropyl)-9-methyldecahydrocyclopenta[*e*]quinoline-1(2*H*)-carboxylate (19)

To a stirred solution of **18** (9.5 mg, 0.026 mmol) in THF (1.0 mL) was added 9-BBN (0.5 M in THF, 156 µL, 0.078 mmol) at 0 °C under argon atmosphere. After stirring for 2.5 h at room temperature, BH_3·THF (1 M in THF, 156 µL, 0.078 mmol) was added, and then the resultant mixture was stirred for 9.5 h at room temperature. A mixture consisting of 30% aqueous H_2O_2 solution (160 µL, 1.56 mmol) and 2*N* aqueous NaOH solution (0.78 mL, 1.56 mmol) was added dropwise while the reaction temperature maintained 0 °C, and then the resultant mixture was stirred for 7.5 h at room temperature. Saturated aqueous $Na_2S_2O_3$ solution was added to the mixture. After stirring for 40 min at 25 °C, the mixture was extracted five times with 10% MeOH/$CHCl_3$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (MeOH/$CHCl_3$ = 5:95) to afford **19** (7.7 mg, 74% in 3 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.36-7.30 (5H, overlapped, PhCH_2OCO-), 5.07 (2H, s, PhCH_2OCO-), 4.38 (1H, m, H-9), 4.25 (1H, ddd, *J* = 7.4, 7.4, 3.7 Hz, H-5), 3.52 (2H, m, H-1), 3.30 (1H, dd, *J* = 13.7, 4.1 Hz, H-13), 2.81 (1H, ddd, *J* = 13.1, 13.1, 2.8 Hz, H-9), 2.67 (1H, ddd, *J* = 13.7, 13.7, 5.0 Hz), 2.18-2.12 (2H, overlapped), 2.05 (1H, m), 1.92-1.68 (8H, overlapped), 1.51-1.33 (5H, overlapped), 0.99 (3H, d, *J* = 7.2 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz) *δ*: 154.4, 137.1, 128.5, 127.9, 127.8, 80.9, 66.5, 62.8, 61.5, 54.0, 49.4, 48.5, 43.0, 41.7, 39.1, 35.6, 34.1, 32.1, 30.1, 27.8, 22.8, 17.3. IR (ATR) ν_{max} cm^{-1}: 3629, 3428, 2928, 1684, 1457. HR-MS (ESI): calcd for $C_{24}H_{35}NO_4Na$ $[M+Na]^+$: 424.2464, found: 424.2447. $[\alpha]^{26}_D$ –32 (*c* 0.10, $CHCl_3$).

Benzyl (4a*S*,6*R*,7a*R*,12b*S*)-6-methyl-10-oxo-2,3,4a,5,6,7,7a,8,9,10-decahydropyrido[2',3':4,5]cyclopenta[1,2-*e*]quinoline-4(1*H*)-carboxylate (23)

To a stirred solution of **19** (5.0 mg, 0.013 mmol) in acetone (0.3 mL) was added Jones' reagent* at –40 °C until the color (orange) of the reagent persisted under argon atmosphere, and the reaction mixture was stirred for 1 h at the same temperature. After adding *i*-PrOH at –40 °C to destroy excess reagent, the reaction mixture was concentrated. The resultant mixture was extracted five times with 10% MeOH/$CHCl_3$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product as a green solid, which was used in the next reaction without further purification. To a solution of the crude material in Et_2O (1.0 mL) was added Et_3N (3 µL, 0.019 mmol) at 0 °C. After stirring at 0 °C for 15 min under argon atmosphere, diphenylphosphoryl azide (4.0 mL, 0.019 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. After adding Et_2O and saturated aqueous $NaHCO_3$ solution, the resultant mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure at ambient temperature. To a solution of the crude material in toluene (0.5 mL) was added PPh_3 (3.3 mg, 0.013 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and refluxed for 12 h. After adding EtOAc and saturated aqueous $NaHCO_3$ solution, the resultant mixture was extracted five times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (MeOH/$CHCl_3$ = 2:98) to afford **23** (2.6 mg, 53% in 3 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.39-7.25 (6H, overlapped, H-3 and PhCH_2OCO-), 6.15 (1H, d, *J* = 9.1 Hz, H-2), 5.14 (1H, d, *J* = 12.4 Hz, PhCH_2OCO-), 5.07 (1H, d, *J* = 11.8 Hz, PhCH_2OCO-), 4.52 (1H, br-d, *J* = 12.0 Hz, NH), 3.41 (1H, dd, *J* = 13.1, 3.0 Hz, H-9), 3.09 (1H, dd, *J* = 16.9, 6.4 Hz, H-13), 2.88 (1H, m, H-9), 2.33 (1H, d, *J* = 17.0 Hz), 2.26-2.16 (2H, overlapped), 2.05 (1H, br-s), 1.92 (1H, br-d, *J* = 13.7 Hz), 1.77 (1H, m), 1.68-1.54 (2H, overlapped), 1.47-1.35 (3H, overlapped), 1.01 (3H, d, *J* = 6.8 Hz, H-16). ^{13}C NMR ($CDCl_3$, 150 MHz) *δ*: 165.4, 154.9, 150.2, 140.6, 136.9, 128.4, 128.3, 128.1, 122.0, 116.1, 66.7, 59.8, 50.9, 48.7, 42.5, 38.8, 35.5, 34.2, 33.0, 26.9, 22.8, 18.0. IR (ATR) ν_{max} cm^{-1}: 2929, 1715, 1654, 1558, 1456. UV (MeOH) λ_{max} nm: 320.5, 235.0, 203.0. HR-MS (ESI): calcd for $C_{24}H_{29}N_2O_3$ $[M+H]^+$: 393.2178, found: 393.2162. $[\alpha]^{26}_D$ –27 (*c* 0.09, $CHCl_3$). *Preparation of Jones' reagent: To a solution of CrO_3 (399 mg) in H_2O (1.2 mL) were slowly added H_2SO_4 (0.3 mL) and H_2O (0.3 mL) at 0 °C.

(–)-Lycoposerramine-R (1)

To a solution of **23** (1.0 mg, 2.55 µmol) in MeOH (0.5 mL) was added 10% Pd/C (2.7 mg, 2.55 µmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature under 1.0 atm pressure of hydrogen atmosphere. The reaction mixture was concentrated and the crude material was purified by amino-silica gel open column chromatography (MeOH/EtOAc = 5:95) and then by amino-silica gel open column chromatography (MeOH/$CHCl_3$ = 5:95) to afford **1** (0.66 mg, quant.) as a colorless oil. Synthetic **1**, $[\alpha]^{26}_D$ –26.1 (*c* 0.03, $CHCl_3$), was completely identical in all respects (chromatographic behavior and UV, ^{1}H NMR, ^{13}C NMR, optical property, and mass spectra) with the natural compound.

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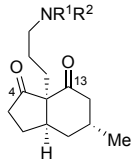
6 In our previous study on racemic synthesis of **1**, the conversion of **24**, the analogue of compound **3**, into tricyclic compound **2** was completely regioselective. However, in case of compound **3** the regioselectivity of the conversion decreased (**2**:**13**=3.6:1), probably due to the difference of reactivity of **3** and **24** towards the hydrogenative debenzylation. Actually, debenzylation of **24** smoothly completed in almost one hour, while that of **3** required four hours. So, we assume that a plausible intermediate **25** would generate by rapid removal of Cbz group in **3**, and the nucleophilicity (or reactivity) of the amino group in **25** towards two carbonyl groups (C-4 and C-13) is slightly different from that of the primary amine in **26**, resulting in the difference of regioselectivity between two compounds **3** and **24**.



R^1=Bn, R^2=Cbz: **3**
R^1=H, R^2=Cbz: **24**
R^1=Bn, R^2=H: **25**
R^1=R^2=H: **26**

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