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FORMAL SYNTHESIS OF GEPHYROTOXIN 287C

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Abstract – The enantioselective formal synthesis of (-)-gephyrotoxin 287C (**1**) has been achieved from octahydroquinolinone **8**. The α, β-unsaturated ester **16**, whose enantiomer was a key intermediate for the total synthesis of (+)-**1**, was synthesized by highly stereoselective Michael-type conjugate addition reaction to **8** and subsequent transformations.

The lipophilic alkaloids, which have been detected in amphibian skin,[1] are rich source for potent blockers of nicotinic acetylcholine receptors.[2] To date, over 800 such alkaloids have been discovered from the skin extracts.[3] The diverse structural feature and potent biological activities of these poison-frog alkaloids have stimulated considerable synthetic efforts. As part of a program directed at studying the synthesis of biologically active alkaloids,[4] we report herein the formal synthesis of (-)-gephyrotoxin 287C (**1**) (**Figure 1**). (-)-Gephyrotoxin 287C (**1**) was isolated from the skin extracts of the Colombian frog *Dendrobates histrionicus* in 1974 by Daly,[5] and then its structure was determined by X-ray analysis in 1977 by the same group.[6] The first enantioselective total synthesis of this alkaloid was reported by Kishi[7] in 1981 as a 1*S*, 3a*S*, 5a*S*, 6*S*, 9a*R* enantiomer same as the natural product. However, the sign of optical rotation of natural product (levorotatory) and synthetic product (dextrorotatory) by Kishi was opposite. This confusion was solved by further two independent enantioselective total syntheses of (-)-[8] and (+)-**1**[9] unambiguously. In 2017, further elegant synthesis of (+)-**1** was reported by Amat[10] as fourth enantioselective total synthesis. Several racemic total syntheses of **1** have also been reported.[11]

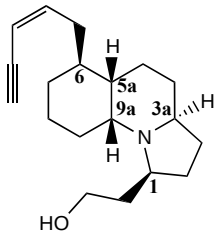
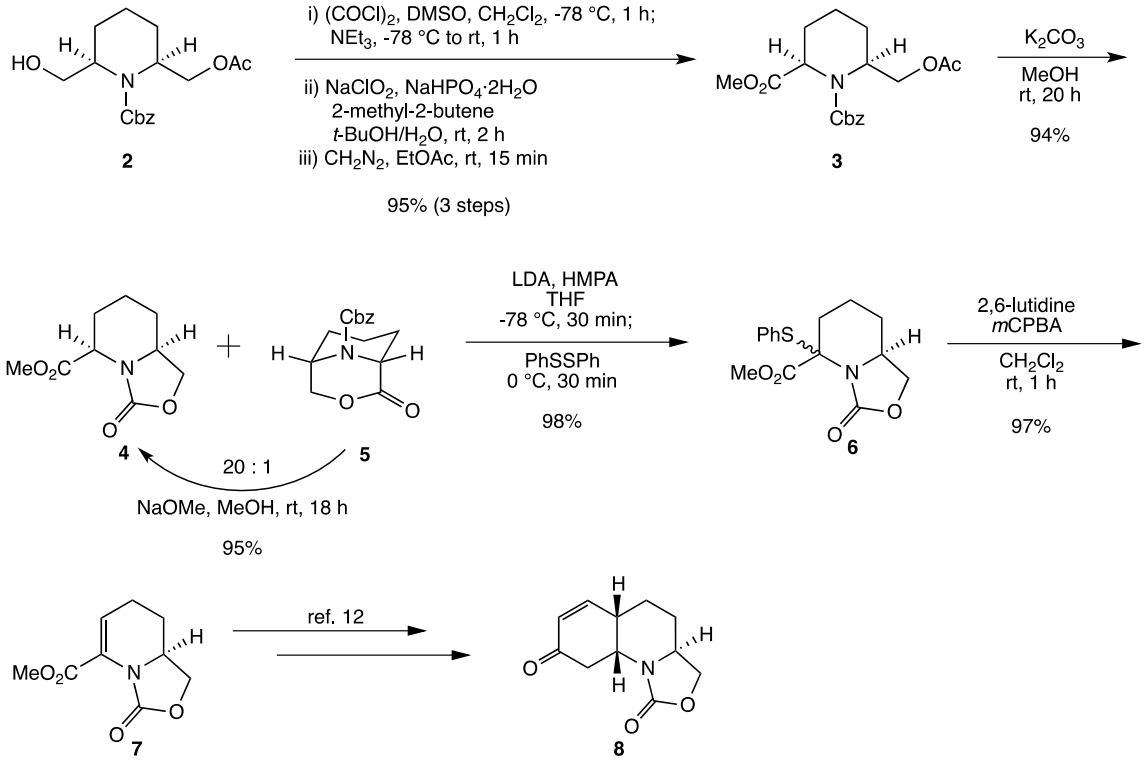


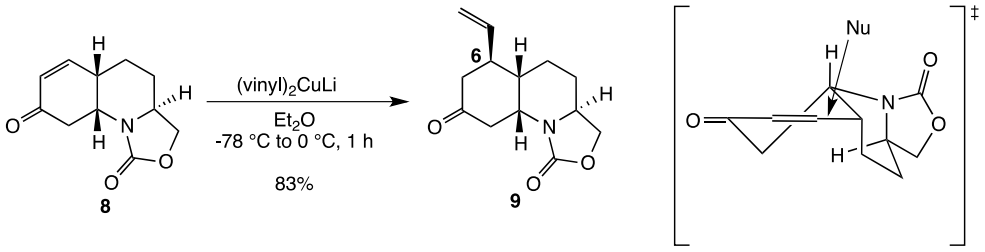
Figure 1. Structure of (-)-gephyrotoxin 287C (**1**)

Previously, we reported the synthesis of octahydroquinolinone **8** *via* the enaminoester **7** in the course of stereodivergent process for the synthesis of decahydroquinolines.[12] In this paper, we achieved the alternative and more efficient synthesis of the key enaminoester **7** in overall yield (81%) compared with previous method (71%),[12,13] and formal synthesis of gephyrotoxin 287C from **8**. The alternative synthesis of **7** began with a known chiral acetate **2**,[14] which was converted to methyl ester **3** using 2-step oxidation followed by esterification by diazomethane in high yield. Deprotection of the acetyl group in **3** resulted in the spontaneous formation of oxazolidinone **4** along with the small amount of bicyclic lactone **5**, which was transformed into **4** by base treatment. The enaminoester **7** was synthesized from **4** *via* phenylthioether **6** using the Matsumura's method.[15] The octahydroquinolinone **8** was constructed from **7** by our former method[12] in 10 steps (**Scheme 1**).



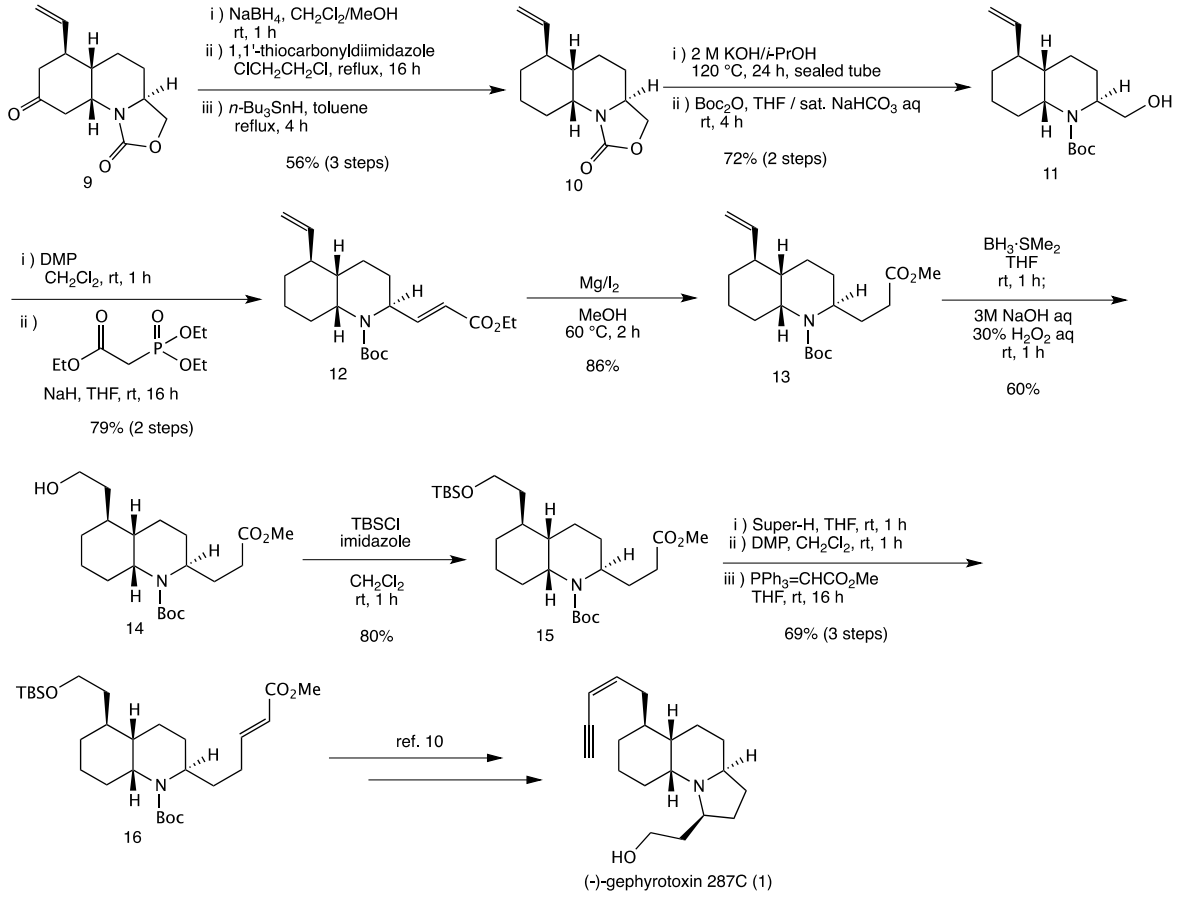
Scheme 1. Synthesis of octahydroquinolinone **8**

The conjugate addition reaction to **8** using lithium divinylcuprate provided the adduct **9** in good yield as a single isomer. The stereochemistry of **9** at the 6-position was easily predicted to be β-configuration by the installation from sterically favored convex face, and the results from the former paper[12] (**Scheme 2**).



Scheme 2. Installation of the vinyl group at the 6-position

Reduction of the ketone moiety in **9** was performed by Barton's method[16] in 3 steps to give the reduction product **10**. Hydrolysis of the oxazolidinone ring in **10** followed by protection of the resulting piperidine by Boc_2O afforded the alcohol **11**. DMP oxidation of **11** and Horner-Wadsworth-Emmons reaction of the resulting aldehyde provided the α, β-unsaturated ester **12**. Selective reduction of the double bond in the α, β-unsaturated ester moiety in **12** was conducted by Mg/MeOH reduction[17] to give rise to saturated ester **13** in 86% yield. Hydroboration-oxidation of the terminal olefin in **13**, and TBS protection of the resulting primary alcohol **14** provided **15**. Finally, reduction of methyl ester in **15** with Super-Hydride followed by oxidation of the resulting alcohol with DMP and then Wittig reaction furnished the homologated α, β-unsaturated ester **16**, which is the key intermediate for the total synthesis of (+)-**1** by Amat[10] (**Scheme 3**).



Scheme 3. Formal synthesis of (-)-gephyrotoxin 287C (**1**)

The ^{1}H- and ^{13}C-NMR spectral data of our synthetic **16** were good accordance with those for the reported values.[10]

In summary, formal synthesis of (-)-**1** has been accomplished from **8**, prepared from **7**, which was synthesized from **2** as an alternative and more efficient route in overall yield compared with previous method as shown in **Scheme 1**. Michael-type conjugate addition reaction to **8** afforded the adduct **9** as a single isomer, and the adduct **9** was transformed into the α, β-unsaturated ester **16**, whose enantiomer was a key intermediate for the total synthesis of (+)-**1** by Amat.[10]

EXPERIMENTAL

All reactions were performed under argon atmosphere. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed with silica gel (0.063-0.2 mm). All yields given refer to as isolated yields. NMR spectra were recorded on a JEOL JNM-A 400 or JEOL JNM-ECX 500 spectrometer in the solvent indicated. Chemical shifts (δ) are given in ppm downfield from TMS and referenced with $CHCl_3$ (7.26 ppm) for ^{1}H, and center line of $CDCl_3$ (77.0 ppm) for ^{13}C as an internal standard. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and coupling constants are given in (*J*) Hz. Infrared spectra were recorded on a SHIMADZU FTIR-8400 spectrometer. MS and HRMS spectra were measured on a JEOL MStation JMS-700.

1-Benzyl 2-methyl (2*R*, 6*S*)-6-Acetoxymethylpiperidine-1,2-dicarboxylate (3)

To a stirred solution of $(COCl)_2$ (1.41 mL, 16.39 mmol) in CH_2Cl_2 (30 mL) was added DMSO (2.33 mL, 32.78 mmol) at -78 °C, and the resulting mixture was stirred at -78 °C for 15 min. To the mixture was added a solution of **2**[14] (3.51g, 10.93 mmol) in CH_2Cl_2 (30 mL) at -78 °C, and the stirring was continued for 1 h. Triethylamine (6.91 mL, 49.16 mmol) was added to the reaction mixture at -78 °C, and the reaction temperature was gradually increased to 0 °C. The reaction mixture was diluted with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (15 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $NaH_2PO_4 \cdot 2H_2O$ (17.04 g, 109.25 mmol), 2-methyl-2-butene (23.22 mL, 218.50 mmol), and the crude aldehyde obtained above in *t*-BuOH (45 mL) was added a solution of $NaClO_2$ (70%, 8.47 g, 65.55 mmol) in H_2O (15 mL), and the resulting suspension was stirred at room temperature for 2 h. The reaction was quenched with satd. $NaHSO_3$ (aq) and 10% HCl (aq) at 0 °C, and the aqueous mixture was extracted with EtOAc (15 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the carboxylic acid obtained above in EtOAc (30 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction mixture was stirred at room temperature for 15 min. The solvent

was evaporated, and the residue was chromatographed on SiO_2 (60 g, acetone/hexane = 1:10) to give **3** (3.63 g, 10.38 mmol, 95% in 3 steps) as pale yellow oil.

IR (neat) : 2953, 1743, 1699, 1456, 1409, 1313, 1229, 1071, 1036 cm^{-1}; ^{1}H-NMR (500 MHz $CDCl_3$) δ: 1.39-1.78 (5H, m), 1.99 (3H, s), 2.27 (1H, m), 3.68 (3H, s), 4.13 (2H, m), 4.47 (1H, m), 4.82-4.90 (1H, m), 5.14-5.22 (2H, m), 7.30-7.34 (5H, m); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 15.72, 20.82, 24.74, 25.88, 48.96, 52.24, 52.94, 63.40, 67.48, 127.78, 127.98, 128.40, 136.38, 156.25, 170.68, 172.80; MS (FAB): *m*/*z* 350 $[M+1]^+$; HRMS (FAB) Calcd for $C_{18}H_{24}NO_6$ 350.1603; Found 350.1605; $[\alpha]_D^{20}$ +20.4 (*c* 2.79, $CHCl_3$).

Methyl (5*R*, 9*S*)-3-Oxohexahydroxazolo[3,4-α]pyridine-5-carboxylate (4) and Benzyl (1*R*, 5*S*)-2-Oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (5)

To a stirred solution of **3** (4.29 g, 12.27 mmol) in MeOH (30 mL) was added K_2CO_3 (5.09 g, 36.80 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (60 g, EtOAc/hexane = 1:1) to give **4** (2.18 g, 10.92 mmol, 89%) as pale yellow oil and **5** (169 mg, 0.61 mmol, 5%) as pale yellow oil.

4: IR (neat) : 2952, 1742, 1767, 1419, 1280, 1254, 1047 cm^{-1}; ^{1}H-NMR (500 MHz $CDCl_3$) δ: 1.29-1.42 (2H, m), 1.68-1.75 (1H, m), 1.81-1.89 (2H, m), 2.17-2.22 (1H, m), 3.76 (3H, s), 3.90 (1H, t, *J* = 8.0 Hz), 4.02-4.08 (1H, m), 4.50 (1H, t, *J* = 8.0 Hz), 4.62 (1H, d, *J* = 6.0 Hz); ^{13}C-NMR (100 MHz $CDCl_3$) δ: 19.55, 26.16, 29.60, 51.90, 52.21, 52.43, 68.92, 157.06, 171.05; MS (FAB): *m*/*z* 200 $[M+1]^+$; HRMS (FAB) Calcd for $C_9H_{14}NO_4$ 200.0923; Found 200.0924; $[\alpha]_D^{20}$ -8.3 (*c* 0.40, $CHCl_3$).

5: IR (neat) : 3648, 2928, 1739, 1734, 1418, 1254, 1047 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.26-1.37 (2H, m), 1.68-1.76 (1H, m), 1.77-1.89 (2H, m), 2.18-2.22 (1H, m), 3.89 (1H, t, *J* = 8.0 Hz), 4.03-4.07 (1H, m), 4.45 (1H, t, *J* = 8.0 Hz), 4.66 (1H, d, *J* = 6.0 Hz), 5.19 (2H, s), 7.34-7.39 (5H, m); ^{13}C-NMR (100 MHz $CDCl_3$) δ: 19.46, 26.19, 29.52, 51.87, 52.29, 67.11, 68.90, 128.09, 128.41, 128.60, 135.25, 157.06, 170.40; MS (FAB): *m*/*z* 276 $[M+1]^+$; HRMS (FAB) Calcd for $C_{15}H_{18}NO_4$ 276.1236; Found 276.1234; $[\alpha]_D^{20}$ -15.7 (*c* 1.20, $CHCl_3$).

Conversion of **5** to **4**:

To a stirred solution of **5** (330 mg, 1.20 mmol) in MeOH (5 mL) was added NaOMe (65 mg, 1.20 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (12 g, EtOAc/hexane = 1:1) to give **4** (228 mg, 1.14 mmol, 95%) as pale yellow oil.

Methyl (8a*S*)-3-Oxo-5-(phenylthio)hexahydro-1*H*-oxazolo[3,4-α]pyridine-5-carboxylate (6)

To a stirred solution of diisopropylamine (1.14 mL, 8.13 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 5.05 mL, 8.13 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. To a stirred solution of **4** (1.08 g, 5.42 mmol) in THF (15 mL) was added a solution of LDA in THF prepared

above at -78 °C, and the reaction mixture was stirred at -78 °C for 5 min. To the reaction mixture was added HMPA (1.41 mL, 8.13 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 25 min. To the reaction mixture was added a solution of $(PhS)_2$ (1.78 g, 8.13 mmol) in THF (10 mL) via cannula at -78 °C, and the temperature was gradually raised to 0 °C. The solvent was evaporated, and the residue was chromatographed on SiO_2 (30 g, EtOAc/hexane = 1:3) to give **6** (1.63 g, 5.30 mmol, 98%) as pale yellow oil as a mixture of diastereomers.

Methyl (*S*)-3-Oxo-3,7,8,8a-tetrahydro-1*H*-oxazolo[3,4-*α*]pyridine-5-carboxylate (7)

To a solution of **6** (4.20 g, 13.68 mmol) in CH_2Cl_2 (50 mL) was added 2,6-lutidine (4.11 mL, 35.29 mmol). *m*CPBA (70%, 8.09 g, 32.83 mmol) was added to the resulting mixture in 4 equal portions once every 15 min at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq) (90 mL), and extracted with CH_2Cl_2 (10 mL × 3). The organic extracts were combined, and washed with 10% HCl (aq) (20 mL). The organic layer was dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g EtOAc/hexane = 1:3) to give **7** (2.62 g, 13.29 mmol, 97%) as a colorless solid. whose spectral data were identical with those for the reported ones.[12]

(3a*S*, 5a*S*, 6*S*, 9a*R*)-6-Vinyloctahydro-1*H*-oxazolo[3,4-α]quinolone-1,8(3*H*)-dione (9)

To a stirred suspension of CuI in Et_2O (3 mL) was added a solution of vinyl lithium at -78 °C, prepared from tetravinyltin (49 μL, 0.27 mmol) and MeLi (1.13 M in Et_2O, 97 μL, 1.07 mmol) in Et_2O (1 mL) at 0 °C for 30 min, and the resulting suspension was warmed to -35 °C for 30 min. The resulting suspension was re-cooled to -78 °C, and a solution of **8**[11] (37 mg, 0.18 mmol) in Et_2O (0.5 mL) was added to the resulting suspension. The reaction mixture was warmed to 0 °C for 1 h, and the reaction was quenched with sat. NH_4Cl (aq) (3 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3), and the organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (5 g, acetone/hexane = 1:5) to give **9**（36 mg, 0.15 mmol, 83%）as pale yellow oil.

IR (neat) : 1747, 1717, 1684, 1418, 1231, 1084, 1028 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.42-1.57 (1H, m), 1.80-1.88 (2H, m), 1.90-2.02 (2H, m), 2.41-2.58 (4H, m), 2.61-2.65 (1H, m), 3.78-3.85 (1H, m), 3.92 (1H, dd, *J* = 8.4, 6.0 Hz), 4.29-4.35 (1H, m), 4.42 (1H, t, *J* = 8.4 Hz), 5.04 (1H, dd, *J* = 17.2, 1.4 Hz), 5.12 (1H, dd, *J* = 10.8, 1.4 Hz), 5.77 (1H, ddd, *J* = 17.2, 10.8, 5.6 Hz); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 24.04, 30.48, 38.12, 39.69, 39.99, 41.55, 47.95, 49.98, 68.09, 116.69, 139.00, 156.154, 207.29; MS (EI): *m*/*z* 235 $[M]^+$; HRMS (EI) Calcd for $C_{13}H_{17}NO_3$ 235.1208; Found 235.1202; $[\alpha]_D^{21}$ -55.9 (*c* 1.00, $CHCl_3$).

(3a*S*, 5a*S*, 6*S*, 9a*R*)-6-Vinyldacahydro-1*H*-oxazolo [3,4-α]quinolin-1-one (10)

To a stirred solution of **9** (220 mg, 0.94 mmol) in CH_2Cl_2 (8 mL) and MeOH (0.8 mL) was added $NaBH_4$ (106 mg, 2.81 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was

quenched with sat. NH_4Cl (aq) (5 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give white solid, which was used directly in the next step.

To a stirred solution of the above solid in 1,2-dichloroethane (8 mL) was added 1,1-thiocarbonyldiimidazole (500 mg, 2.81 mmol) at room temperature. The resulting mixture was refluxed for 16 h. After cooling, the solvent was evaporated to give yellow paste, which was chromatographed on silica gel (8 g, acetone/hexane = 1:7) to give yellow oil, which was used in the next step.

A stirred solution of *n*-Bu_3SnH (0.74 mL, 2.81 mmol) in toluene (7 mL) was heated to reflux for 30 min, and then a solution of above yellow oil in toluene (1.5 mL) was added to the above solution, and the reaction mixture was refluxed for 4 h. After cooling, the solvent was evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, EtOAc/hexane = 1:15) to give **10** (115 mg, 0.52 mmol, 56% in 3 steps) as a colorless oil.

IR (neat) : 2932, 1830, 1749, 1541, 1418, 846, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.29-1.41 (2H, m), 1.45-1.64 (6H, m), 1.72-1.88 (3H, m), 2.28 (1H, br), 3.72-3.78 (1H, m), 3.81 (1H, t, *J* = 7.6 Hz), 3.94-4.00 (1H, m), 4.34 (1H, t, *J* = 7.6 Hz), 5.04 (1H, dm, *J* = 10.0 Hz), 5.05 (1H, dm, *J* = 18.2 Hz), 5.93 (1H, ddd, *J* = 18.2, 10.0, 5.7 Hz); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 20.02, 24.11, 24.23, 24.70, 30.94, 38.66, 42.47, 48.02, 50.43, 68.16, 114.46, 140.86, 156.60; MS (EI): *m*/*z* 221 $[M]^+$; HRMS (EI) Calcd for $C_{13}H_{19}NO_2$ 221.1416; Found 221.1419; $[\alpha]_D^{22}$ -3.9 (*c* 1.00, $CHCl_3$).

_t_-Butyl (2_S_, 4a_S_, 5_S_, 8a_R_)-2-(Hydroxymethyl)-5-vinyloctahydroquinoline-1(_2H_)-carboxylate (11)

A solution of 2M KOH in *i*-PrOH (7 mL) was added to **10** (24 mg, 0.11 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 24 h. After cooling, the solvent was evaporated, and residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (3 mL × 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred solution of the oil obtained above in THF (3 mL) were added satd. $NaHCO_3$ (aq) (3 mL) and Boc_2O (118 mg, 0.54 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 5). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (5 g, EtOAc/hexane = 1:7) to give **11** (23 mg, 0.08 mmol, 72% in 2 steps) as pale yellow oil.

IR (neat) : 3449, 1830, 1670, 1558, 1541, 1456, 1396, 1173, 856, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.44 (9H, s), 1.48-1.82 (10H, m), 1.91-1.96 (1H, m), 2.23 (1H, br), 3.59-3.80 (4H, m), 5.06 (1H, dm, *J* = 10.8 Hz), 5.07 (1H, dm, *J* = 17.5 Hz), 5.94 (1H, ddd, *J* = 17.5, 10.8, 5.7 Hz); ^{13}C-NMR (125 MHz

$CDCl_3$) δ: 20.93, 22.51, 24.72, 25.79, 27.04, 28.52, 37.44, 42.41, 51.97, 54.42, 66.46, 80.04, 114.27, 141.64, 156.40; MS (EI): *m*/*z* 295 $[M]^+$; HRMS (EI) Calcd for $C_{17}H_{29}NO_3$ 295.2147; Found 295.2140; $[\alpha]_D^{23}$ -5.8 (*c* 1.00 , $CHCl_3$).

_t_-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-2-((*E*)-3-Ethoxy-3-oxoprop-1-en-1-yl)-5-vinyloctahydroquinoline-1(2*H*)-carboxylate (12)

To a stirred solution of **11** (23 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (50 mg, 0.12 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd.$Na_2S_2O_3$ (aq) (3 mL), and the aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give an aldehyde as pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 5 mg, 0.130 mmol) in THF (3 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (33 μL, 0.16 mmol) at 0 °C, then the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added the above aldehyde in THF (1 mL) at 0 °C, then the mixture was stirred at room temperature for 16 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (8 g, EtOAc/hexane = 1:7) to give **12** (22 mg, 0.06 mmol, 79% in 2 steps) as pale yellow oil.

IR (neat) : 1830, 1717, 1697, 1653, 1558, 1506, 1456, 1394 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.26 (3H, t, *J* = 7.2 Hz), 1.29-1.33 (1H, m), 1.40 (9H, s), 1.47-1.52 (3H, m), 1.56-1.69 (3H, m), 1.75-1.83 (2H, m), 1.93-2.02 (2H, m), 2.21 (1H, br), 3.98 (1H, br), 4.16 (2H, q, *J* = 7.2 Hz), 4.37 (1H, br), 5.03 (1H, dm, *J* = 17.2 Hz), 5.04 (1H, dm, *J* = 10.8 Hz), 5.76 (1H, dd, *J* = 15.6, 1.6 Hz), 5.95 (1H, ddd, *J* = 17.2, 10.8, 6.0 Hz), 6.96 (1H, dd, *J* = 15.6, 5.4 Hz); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 14.19, 20.40, 20.63, 24.44, 26.66, 28.33, 36.00, 42.15, 50.77, 51.87, 53.37, 60.23, 79.79, 114.38, 119.24, 141.30, 151.24, 155.09, 166.59; MS (EI): *m*/*z* 363 $[M]^+$; HRMS (EI) Calcd for $C_{21}H_{33}NO_4$ 363.2410; Found 363.2412; $[\alpha]_D^{24}$ -46.8 (*c* 1.00, $CHCl_3$).

_t_-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-2-(3-Methoxy-3-oxopropyl)-5-vinyloctahydroquinoline-1(2*H*)-carboxylate (13)

To a stirred suspension of magnesium turnings (362 mg, 14.88 mmol) in MeOH (8 mL) was added iodine (19 mg, 0.07 mmol), and the resulting brown colored mixture was stirred at room temperature for 30 min. as the solution becomes colorless. A solution of **12** (90 mg, 0.25 mmol) in MeOH (1 mL) was added to the resulting suspension, and the reaction mixture was heated to 60 °C for 2 h. After cooling, the MeOH was evaporated and the residue was acidified with 10% HCl (aq) (5 mL). The aqueous mixture was extracted with CH_2Cl_2 (5 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and

evaporated to give pale red oil, which was chromatographed on SiO_2 (8 g, EtOAc/hexane = 1:10) to give **13** (75 mg, 0.21 mmol, 86%) as pale yellow oil.

IR (neat) : 1734, 1697, 1684, 1541, 1506, 1456, 1364, 1173, 856, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.19-1.29 (2H, m), 1.39-1.41 (2H, m), 1.43 (9H, s), 1.45-1.90 (7H, m), 1.91-2.00 (1H, br), 2.10 (1H, br), 2.21 (1H, br), 2.32 (2H, t, *J* = 8.2 Hz), 3.64 (3H, s), 3.73 (1H, br), 3.81-3.86 (1H, m), 5.03 (1H, dm, *J* = 9.8 Hz), 5.04 (1H, dm, *J* = 18.2 Hz), 5.97 (1H, ddd, *J* = 18.2, 9.8, 6.8 Hz); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 19.60, 20.39, 23.46, 24.51, 28.44, 29.10, 30.68, 31.81, 35.56, 42.18, 50.42, 50.67, 51.49, 79.08, 114.20, 141.55, 154.99, 173.88; MS (EI): *m*/*z* 351 $[M]^+$; HRMS (EI) Calcd for $C_{20}H_{33}NO_4$ 351.2410; Found 351.2415; $[\alpha]_D^{24}$ -11.1 (*c* 1.00, $CHCl_3$).

_t_-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-5-(2-Hydroxyethyl)-2-(3-methoxy-3-oxopropyl)octahydroquinoline-1(2*H*)-carboxylate (14)

To a stirred solution of **13** (70 mg, 0.20 mmol) in THF (5 mL) was added $BH_3{\cdot}SMe_2$ (28 μL, 0.30 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. To the reaction mixture were added 10% NaOH (aq) (1 mL) and 30% H_2O_2 (aq) (1 mL) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 5). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (8 g, EtOAc/acetone = 1:7) to give **14** (44 mg, 0.12 mmol, 60%) as pale yellow oil.

IR (neat) : 3734, 1830, 1734, 1697, 1653, 1558, 1456, 1173, 856, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.15-1.28 (2H, m), 1.35-1.52 (12H, m), 1.54-1.86 (9H, m), 1.90-1.99 (2H, m), 2.32 (2H, t, *J* = 8.0 Hz), 3.62-3.68 (6H, m), 3.70-3.76 (1H, m), 3.79-3.84 (1H, m); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 19.92, 20.17, 23.59, 24.06, 28.60, 29.46, 30.87, 31.96, 34.97, 35.32, 35.54, 50.59, 50.72, 51.66, 61.52, 79.30, 155.20, 174.06; MS (EI): *m*/*z* 369 $[M]^+$; HRMS (EI) Calcd for $C_{20}H_{35}NO_5$ 369.2515; Found 369.2524; $[\alpha]_D^{23}$ -10.7 (*c* 1.00, $CHCl_3$).

_t_-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-5-(2-((*t*-Butyldimethylsilyl)oxy)ethyl)-2-(3-methoxy-3-oxopropyl)-octahydroquinoline-1(2*H*)-carboxylate (15)

To a stirred solution of **14** (35 mg, 95 μmol) in CH_2Cl_2 (3 mL) were added imidazole (13 mg, 0.19 mmol) and TBSCl (29 mg, 0.19 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (8 g, acetone/hexane = 1:10) to give **15** (37 mg, 77 μmol, 80%) as pale yellow oil.

IR (neat) : 1747, 1717, 1684, 1558, 1456, 1364, 1175, 1099, 839, 770 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.19-1.43 (4H, m), 1.45 (9H, s), 1.53-1.70 (7H, m), 1.74-1.91 (3H, m), 1.93-2.00 (2H, m), 2.34 (2H, t, *J* = 7.8 Hz), 3.58-3.68 (5H, m), 3.76 (1H, br), 3.80-3.85 (1H, m); ^{13}C-NMR (125 MHz $CDCl_3$) δ: -5.34, 18.31, 19.80, 20.15, 23.47, 24.06, 25.94, 28.50, 29.43, 30.78, 31.91,

34.97, 35.08, 35.40, 50.48, 50.68, 51.53, 61.80, 79.10, 155.08, 173.92; MS (EI): *m*/*z* 483 $[M]^+$; HRMS (EI) Calcd for $C_{26}H_{49}NO_5Si$ 483.3380; Found 483.3377; $[\alpha]_D^{23}$ -2.7 (*c* 1.00 , $CHCl_3$).

_t_-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-5-(2-((_t_-Butyldimethylsilyl)oxy)ethyl)-2-((*E*)-5-methoxy-5-oxopent-3-en-1-yl)octahydroquinoline-1(2*H*)-carboxylate (16)

To a stirred solution of **15** (23 mg, 48 μmol) in THF (3 mL) was added Super-Hydride (0.14 mL, 0.14 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (30 mg, 72 μmmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd.$Na_2S_2O_3$ (aq) (3 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give an aldehyde as pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (3 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (24 mg, 72 μmL) at room temperature, and the resulting mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (5 g, EtOAc/hexane = 1:7) to give **16** (17 mg, 33 μmol, 69% in 3 steps) as pale green oil. The ^{1}H- and ^{13}C-NMR spectra of our synthetic material were good accordance with those for reported values.[10]

IR (neat) : 2930, 1732, 1684, 1653, 1558, 1506, 1456, 1175, 1099, 856 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.18-1.39 (4H, m), 1.45 (9H, s), 1.53-1.97 (12H, m), 2.13-2.38 (2H, m), 3.58-3.67 (2H, m), 3.71 (3H, s), 3.74 (1H, br), 3.81-3.85 (1H, m), 5.83 (1H, d, *J* = 15.6 Hz), 6.96 (1H, dt, *J* = 15.6, 7.0 Hz); ^{13}C-NMR (125 MHz $CDCl_3$) δ: -5.3, 18.3, 19.8, 20.15, 22.88, 24.13, 25.93, 28.55, 29.57, 29.97, 33.66, 35.01, 35.13, 35.39, 50.58, 51.37, 61.78, 79.08, 121.03, 148.97, 155.02, 167.01; MS (EI): *m*/*z* 509 $[M]^+$; HRMS (EI) Calcd for $C_{28}H_{51}NO_5Si$ 509.3537; Found 509.3535; $[\alpha]_D^{23}$ -5.4 (*c* 0.75, $CHCl_3$).

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