An enantioselective formal synthesis of (+)-Gephyrotoxin 287C

Lei Miao, Hong Shu, April R. Noble, Steven P. Fournet, Edwin D. Stevens, and Mark L. Trudell*

Department of Chemistry, University of New Orleans, 2000 Lakeshore Drive, New Orleans, Louisiana 70148 USA
E-mail: mtrudell@uno.edu

Dedicated to Professor James M. Cook on the occasion of his 65th birthday

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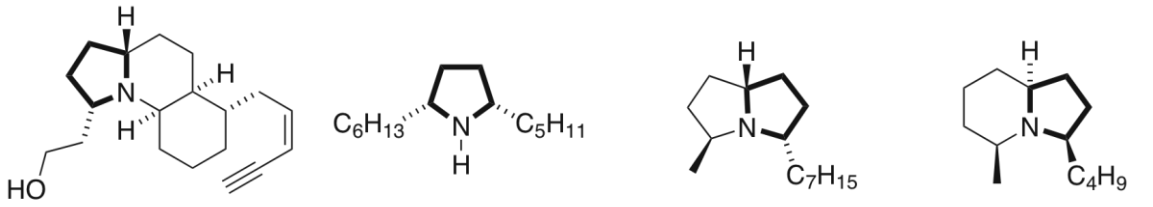
Abstract
The tricyclic skeleton of the gephyrotoxin amphibian alkaloids was synthesized via an enantioselective serial sequence involving nine discrete steps that furnished Kishi's intermediate **5** in 22% overall yield. This efficient and expeditious synthetic approach exploits the inherent stereochemistry of a (1*R*)-2-tropinone derivative for the construction of the core *cis*-2,5-disubstituted pyrrolidine ring system and constitutes a formal synthesis of gephyrotoxin 287C.

Keywords: Amphibian alkaloids, gephyrotoxin, tropane, pyrrolidine

Introduction

Alkaloids isolated from amphibian skin have aroused tremendous academic and pharmaceutical interest due to their structural diversity and biological activity. Over 800 amphibian alkaloids comprising over 20 structural classes have been reviewed through 2005.[1] Gephyrotoxin 287C **1** was first isolated and characterized in 1977 from the skin of tropical frogs *Dendrobates histrionicus*[2] and later revealed to be a weak muscarinic antagonist.[3] Recent studies have indicated that it is also a nontoxic noncompetitive blocker of nicotinic receptors.[4] Despite the unique tricyclic skeleton of the gephyrotoxins, these alkaloids possess a *cis*-2,5-disubstituted pyrrolidine moiety that is a common structural feature among several other classes of amphibian alkaloids. As shown in Figure 1, these alkaloids are represented by the natural products *cis*-pyrrolidine 225H **2**, pyrrolizidine 223H **3**, (+)-monomorine **4**. The paucity of these alkaloids from natural resources has made total synthesis the only practical method to provide sufficient material for intensive structural and biological activity studies. As part of an ongoing study in our laboratory aimed at developing new molecular scaffolds for neurological therapeutic

agents,[5-8] the gephyrotoxin skeleton was an attractive target for synthesis. Herein, we describe the enantioselective construction of the gephyrotoxin tricyclic ring system affording an efficient formal synthesis of (+)-gephyrotoxin **1**.

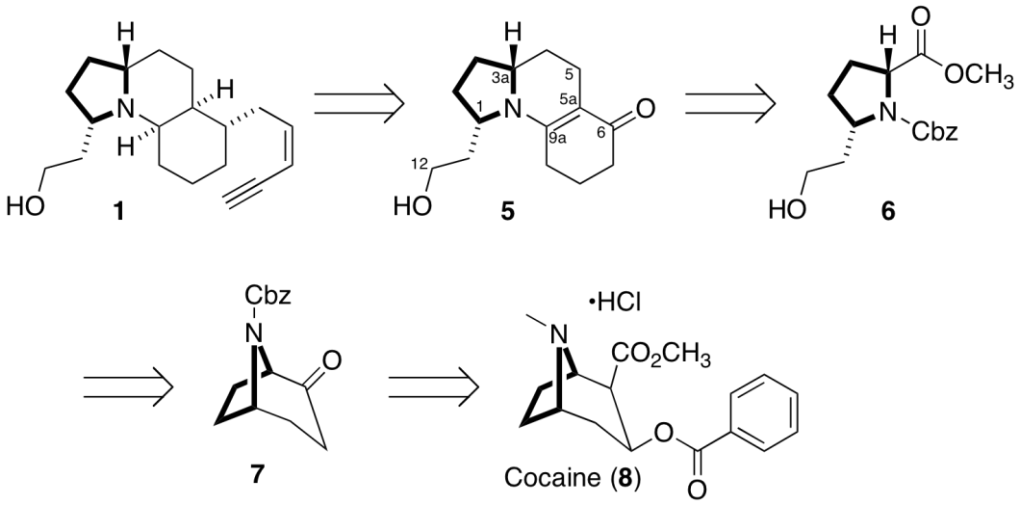


1 **2** **3** **4**

Figure 1. *cis*-2,5-Disubstituted pyrrolidine-based amphibian alkaloids.

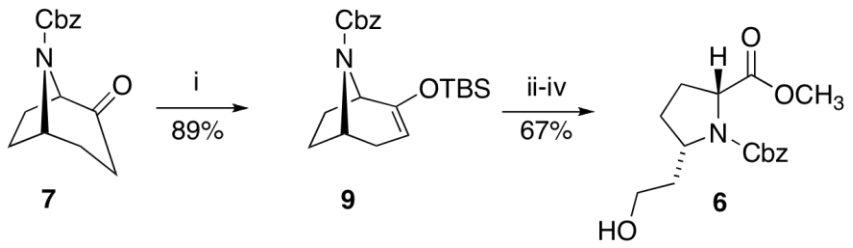
Results and Discussion

As illustrated in Scheme 1, our retrosynthetic analysis focused on the construction of the tricyclic core of the gephyrotoxin skeleton. Previous work in this area identified the tricyclic ketone **5** (Kishi's intermediate) as a key precursor to the natural alkaloid **1**.[9–12] Therefore, our efforts were focused upon the development of an enantioselective method that would give **5** efficiently and in good overall yield. To this end, we envisaged utilization of an enantiopure *cis*-2,5-disubstituted pyrrolidine **6** derived from the (1*R*)-2-tropinone derivative **7**.[7] The ketone **7** is readily available from the degradation of cocaine **8** and can be obtained on a multigram scale in isolated yields ranging from 65–80%.[7,13]



Scheme 1. Retrosynthetic approach.

Ketone **7** was treated with NaH and TBSCl to furnish silyl enol ether **9** (Scheme 2) according to the procedure reported by Rassat and coworkers.[14] The silyl enol ether **9** was stable to chromatography and was obtained in 89% yield. This was a marked improvement over our previously reported approach that was limited by the stability of the corresponding methyl enol ether. The silyl enol ether **9** was then subjected to ozonolysis at –78 °C. Reduction of the intermediate ozonide with $NaBH_4$ and subsequent treatment of the reaction mixture with CH_2N_2 furnished the new *cis*-2,5-disubstituted pyrrolidine building block **6** in 67% yield over three steps. It is noteworthy, that this sequence provided the required stereochemistry at both C1 and C3a of **5**. In addition, by employing $NaBH_4$ for the ozonide reduction, the C12 hydroxyl group was introduced conveniently at an early stage of the synthesis.

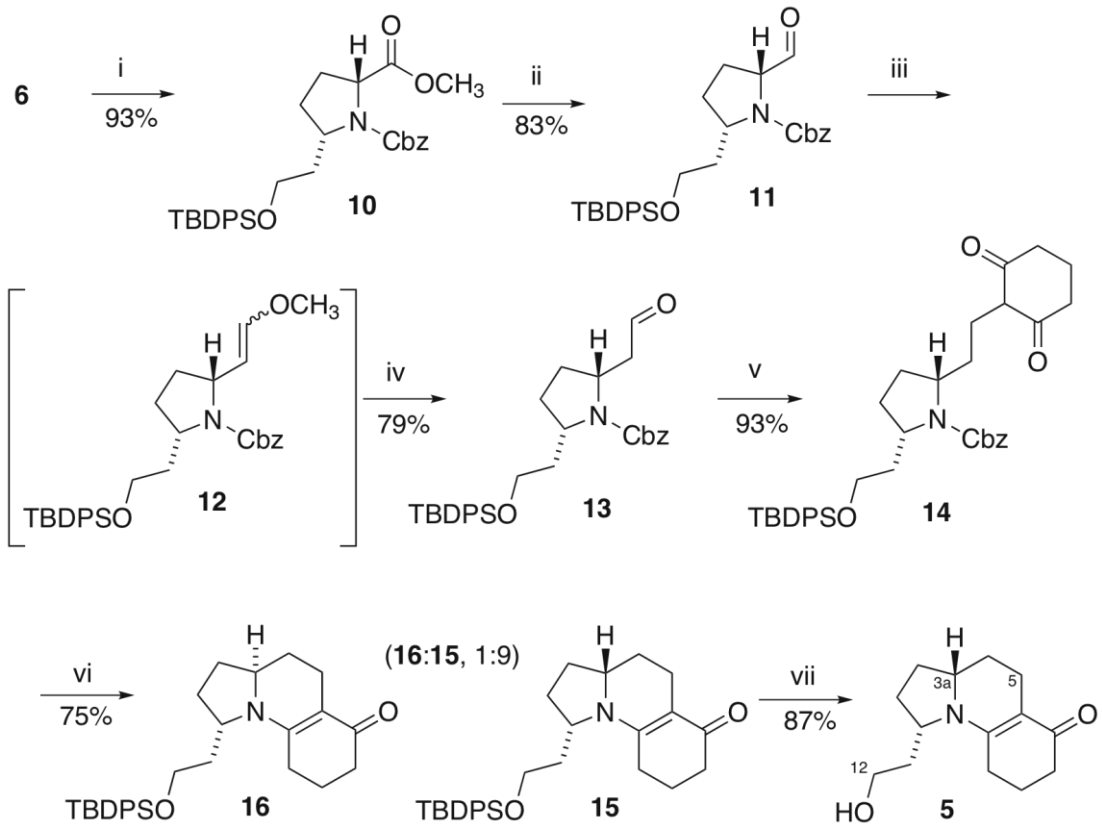


Scheme 2. *Reagents and conditions*: (i) NaH, TBSCl, THF, 0 °C. (ii) O_3, CH_2Cl_2/CH_3OH, –78 °C. (iii) $NaBH_4$, –78 °C. (iv) CH_2N_2, Et_2O, 0 °C.

With the *cis*-2,5-disubstituted pyrrolidine **6** in hand, our attention was directed toward the construction of the remaining rings of tricyclic ketone **5**. To this end, a one-carbon homologation sequence was used to install the C5 atom of the tricyclic system **5**. The alcohol **6** was initially converted into silyl ether **10** using TBDPSCl in 93% yield (Scheme 3). The ester unit of **10** was then reduced using DIBAL-H to furnish the corresponding aldehyde **11** in 83% yield. While there was the potential for epimerization at C3a of **11**, we continued on with the intention of characterizing any diastereoisomers at a later stage in the synthesis. Wittig olefination of **11** using a preformed ylide generated from $(Ph_3PCH_2OCH_3)Cl$ and *t*-BuOK gave the methyl enol ether **12**. Hydrolysis of the enol moiety with $PTSA{\cdot}H_2O$ in acetone furnished the desired aldehyde **13** in 79% yield over the two-step process.

The final stages of the synthesis of **5** were completed by coupling the aldehyde **13** with 1,3-cyclohexanedione using the procedure recently developed by Kishor and Ramachary.[15] This step significantly streamlined the overall synthetic approach by avoiding the tedious multistep functional group manipulations employed in earlier syntheses[9–12] to construct similar dione precursors. This one-step coupling method afforded the dione **14** in 93% yield. Subsequent hydrogenolysis of the diketone **14** catalyzed by 10% Pd/C furnished the tricyclic amine as a mixture of diastereoisomers **15/16** (9:1) in 75% yield via sequential Cbz removal, cyclization/ enamine formation.

The rigid nature of the tricyclic ring system facilitated the structural characterization of **15** and **16**. The two diastereoisomers were readily distinguished by ^{13}C and ^{1}H NMR but were not easily separated by chromatography. Presumably, the minor isomer **16** resulted from epimerization of C3a during either the ozonolysis, the DIBAL-H reduction or the Wittig olefination step.



Scheme 3. *Reagents and conditions*: (i) TBDPSCl, imidazole, DMF, 0 °C. (ii) DIBAL-H, toluene, –78 °C. (iii) $CH_3OCH_2PPh_3Cl$, *t*-BuOK, THF, 0 °C. (iv) PTSA•H_2O, acetone, 0 °C. (v) 1,3-cyclohexanedione, diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, CH_2Cl_2, L-proline, r.t. (vi) H_2 (1 atm), 10% Pd/C, CH_3OH, r.t. (vii) TBAF, THF, r.t.

Nevertheless, the minor diastereoisomer was readily removed after the subsequent step. Removal of the silyl-protecting group by treatment of the mixture **15**/**16** with TBAF gave a separable mixture of diastereoisomers and furnished Kishi's intermediate **5** in 87% yield in enantiopure form. The NMR spectra were consistent with previously reported data,[9–12] and the absolute configuration of **5** was unequivocally established by X-ray crystallography (Figure 2).[16]

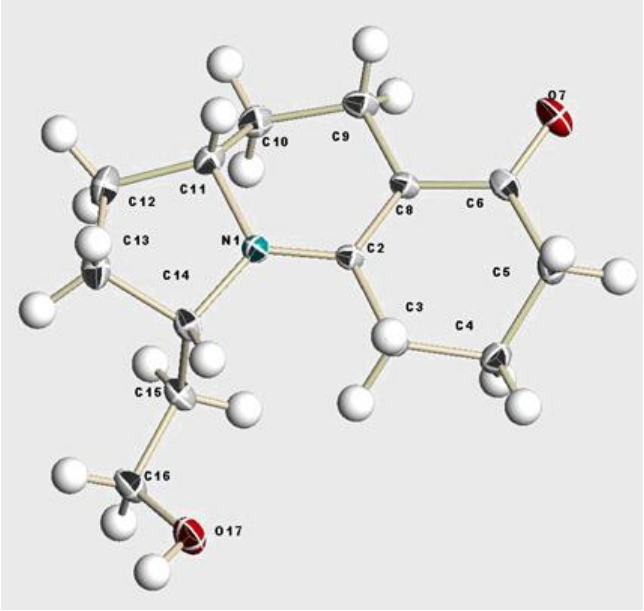


Figure 2. X-ray crystal structure of Kishi's intermediate **5**.

Conclusions

In summary we have developed an enantioselective synthesis of the tricyclic gephyrotoxin skeleton. Kishi's intermediate **5** was obtained in enantiopure form in 22% overall yield via nine discrete steps constituting a formal synthesis of gephyrotoxin 287C. This efficient and expeditious approach exploits the inherent stereochemistry of a (1*R*)-2-tropinone derivative derived from confiscated cocaine for the construction of the core *cis*-2,5-disubstituted pyrrolidine ring system.

Experimental Section

General. All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous dichloromethane was purchased from Mallinckrodt Baker, Inc. Confiscated grade (–)-cocaine hydrochloride was provided by NIDA Drug Supply System, Research Technology Branch, National Institute on Drug Abuse. ^{1}H and ^{13}C NMR were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in $CDCl_3$ from Cambridge Isotope Laboratories, Inc. ^{1}H NMR chemical shifts are reported as δ values relative to TMS, ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Optical rotations were measured on Autopol III polarimeter at the sodium D line (2 mL sample cell). Melting points were measured with an Electrothermal R Mel-Temp apparatus. CHN micro-analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.

(1*R*,5*S*)-8-Benzyloxycarbonyl-2-(*tert*-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene (9). NaH (60 mg, 2.5 mmol) was suspended in dry THF (4 mL) under N_2 at 0 °C. A solution of ketone **7** (130 mg, 0.5 mmol) in dry THF (2 mL) was added dropwise. After stirring for 2 h, TBSCl (1.0 M in THF, 1 mL, 1.0 mmol) was added dropwise at 0 °C. The stirring was continued at 0 °C overnight. Water (5 mL) was added slowly, and the solution was extracted with Et_2O (3 × 10 mL). All organic portions were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexanes/EtOAc, 95:5) to afford **9** (166 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ –43.5 (*c* 1.2, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (m, 6H), 0.90 (s, 9H), 1.58–1.67 (m, 2H), 1.74 (dd, *J* = 16.4, 4.6, 1H), 1.94–2.18 (m, 3H), 2.61–2.79 (m, 0.5H$_{rotamer}$), 4.11–4.49 (m, 2.5H$_{rotamer}$), 5.09–5.19 (m, 2H), 7.28–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.5, –4.1, 18.2, 25.8, 29.4, 30.2, 31.4, 32.4, 33.7, 34.4, 52.5, 57.7, 66.8, 97.3, 128.0, 128.1, 128.6, 137.1, 154.4, 154.8. Anal. calcd. for $C_{21}H_{31}NO_3Si$: C, 67.52; H, 8.36; N, 3.79. Found: C, 67.73; H, 8.58; N, 3.79.

(2*R*,5*S*)-1-Benzyloxycarbonyl-5-(2-hydroxyethyl)-2-methoxycarbonylpyrrolidine (6). TBS enol ether **9** (780 mg, 2.1 mmol) was dissolved in CH_2Cl_2 (50 mL) and CH_3OH (5 mL), and the mixture was cooled to –78 °C. Ozone was then passed through the solution until a slight blue color persisted. Ozone was allowed to continue to pass through the solution for an additional 15 min; then N_2 was passed through the solution for 10 min. At –78 °C, $NaBH_4$ (250 mg, 6.5 mmol) was added to the solution in one portion. After 30 min, another portion $NaBH_4$ (300 mg, 7.9 mmol) was added. The mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residue was treated with 2N HCl (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to afford an oil that was used directly in the next step without further purification.

To a stirred solution of the oil in Et_2O (20 mL) at 0 °C, CH_2N_2 was passed through the solution until a yellow color persisted. N_2 was then passed through the solution for 30 min. The cold bath was removed and any excess solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexanes/EtOAc, 2:3) to afford **6** (430 mg, 67%; 3 steps) as a colorless oil. $[\alpha]_D^{25}$ +52 (*c* 0.6, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61–1.82 (m, 3H), 1.95–2.11 (m, 2H), 2.30–2.37 (m, 1H), 3.60 (s, 3H), 3.64–3.82 (m, 3H), 3.93 (dd, *J* = 9.8, 4.6, 1H), 4.37 (t, *J* = 8.3, 1H), 5.03–5.22 (m, 2H), 7.28–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.2, 30.9, 37.8, 52.4, 55.8, 59.1, 59.9, 67.8, 127.9, 128.3, 128.7, 136.4, 156.1, 173.6. Anal. calcd. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.28; H, 7.00; N, 4.49.

(2*R*,5*S*)-1-Benzyloxycarbonyl-5-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-2-methoxy-carbonyl-pyrrolidine (10). Alcohol **6** (374 mg, 1.22 mmol) and imidazole (166 mg, 2.44 mmol, 2.0 equiv) were dissolved in dry DMF (15 mL) under N_2 at 0 °C. TBDPSCl (402 mg, 0.374 mL, 1.46 mmol, 1.2 equiv) was added dropwise to the mixture. The mixture was allowed to warm to room temperature and stirred overnight. At 0 °C, H_2O (15 mL) was added to the mixture to quench the reaction. The mixture was extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting mixture was purified by

flash column chromatography (SiO_2; hexanes/EtOAc, 85:15) to afford **10** (617 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ +22.1 (*c* 0.73, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, *J* = 11.0, 9H), 1.61–2.02 (m, 4H), 2.15–2.40 (m, 2H), 3.58 (s, 1H), 3.65–3.79 (m, 4H), 4.09–4.16 (m, 1H), 4.31–4.41 (m, 1H), 5.01–5.20 (m, 2H), 7.26–7.44 (m, 11H), 7.63 (t, *J* = 6.4, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.4, 27.0, 28.4, 29.4, 29.9, 30.2, 36.5, 37.2, 52.2, 52.4, 56.5, 57.7, 59.9, 60.2, 61.7, 62.1, 67.0, 67.3, 127.9, 128.1, 128.6, 128.7, 129.8, 134.0, 135.8, 136.9, 155.1, 173.6. Anal. calcd. for $C_{32}H_{39}NO_5Si$: C, 70.43; H, 7.20; N, 2.57. Found: C, 70.64; H, 7.23; N, 2.56.

(2*S*,5*R*)-Benzyloxycarbonyl-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-5-formylpyrrolidine (11). Ester **10** (550 mg, 1.0 mmol) was dissolved in toluene (6 mL) under N_2. The solution was cooled to –78 °C and DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added dropwise over a period of 45 min. The stirring at –78 °C was continued for additional 15 min; then the cold bath was removed. Et_2O (10 mL), H_2O (4 mL) and 15% NaOH (6 mL) were added sequentially. The mixture was extracted with Et_2O (2 × 20 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexanes/EtOAc, 4:1) to afford **11** (431 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ +17.3 (*c* 0.95, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.7, 9H), 1.43–2.45 (m, 6H), 3.59–3.80 (m, 2H), 4.13–4.27 (m, 2H), 5.08–5.22 (m, 2H), 7.26–7.46 (m, 11H), 7.67 (s, 4H), 9.35 (s, $0.5H_{rotamer}$), 9.48 (s, $0.5H_{rotamer}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 24.9, 26.0, 27.1, 29.8, 30.1, 37.3, 37.8, 56.5, 57.7, 61.6, 61.8, 65.9, 66.3, 67.4, 67.6, 127.9, 128.1, 128.3, 128.8, 129.9, 133.9, 135.8, 136.5, 154.7, 155.9, 200.5. Anal. calcd. for $C_{31}H_{37}NO_4Si$: C, 72.20; H, 7.23; N, 2.72. Found: C, 71.88; H, 7.37; N, 2.61.

(2*S*,5*R*)-Benzyloxycarbonyl-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-5-(2-oxoethyl)pyrrolidine (13). $(Ph_3PCH_2OCH_3)Cl$ (1.3 g, 3.6 mmol) was suspended in dry THF (50 mL) under N_2 at 0 °C. *t*-BuOK (1.0 M in THF, 3.4 mL, 3.4 mmol) was added dropwise to the solution. After 10 min, a cooled (0 °C) solution of aldehyde **11** (1.4 g, 2.7 mmol) in dry THF (10 mL) was added dropwise. After the addition was complete, the mixture was stirred for 2 h. H_2O (50 mL) was added to the mixture. The resulting solution was extracted with Et_2O (2 × 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford the vinyl ether **12** as an oil, which was used in the next step without further purification. To a stirred solution of **12** in acetone (50 mL) at 0 °C, PTSA·H_2O (260 mg, 1.4 mmol) was added as one portion. The cold bath was removed after the addition and stirring was continued for an additional 30 min. Most of the solvent was removed under reduced pressure and H_2O (50 mL) was added to the resulting mixture. The resulting solution was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexanes/EtOAc, 4:1) to afford **13** (1.2 g, 79%; 2 steps) as a colorless oil. $[\alpha]_D^{25}$ +2.44 (*c* 1.31, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.39–2.27 (m, 6H), 2.36–2.45 (m, 1H), 2.78–3.11 (m, 1H), 3.69 (s, 2H), 4.04 (s, 1H), 4.22–4.36 (m, 1H), 5.10 (d, *J* = 6.2, 2H), 7.25–7.44 (m, 11H), 7.63 (s, 4H), 9.71 (d, *J* = 52.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 27.1, 27.7, 28.5, 29.7, 30.4, 36.5, 38.4, 48.1, 50.3, 52.9, 54.2, 55.8, 56.4, 61.8, 67.0, 67.1, 127.2, 127.9, 128.1, 128.7, 129.9, 133.9,

135.8, 136.8, 200.9. Anal. calcd. for $C_{32}H_{39}NO_4Si$: C, 72.55; H, 7.42; N, 2.64. Found: C, 72.55; H, 7.39; N, 2.57.

(2*S*,5*S*)-Benzyloxycarbonyl-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-5-(2-(2,6-dioxocyclohexyl)ethyl) pyrrolidine (14). Aldehyde **13** (460 mg, 0.90 mmol) was dissolved in CH_2Cl_2 (2 mL) at room temperature. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (220 mg, 0.90 mmol), 1,3-cyclohexadione (98 mg, 0.90 mmol) and L-proline (20 mg, 0.18 mmol) were sequentially added to the solution. Stirring was continued at room temperature for 1 h. The resulting mixture was subjected to purification by flash column chromatography (SiO_2; hexanes/EtOAc, 1:1) to afford **14** (509 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ +42.1 (*c* 0.4, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.35–1.97 (m, 11H), 2.15–2.54 (m, 6H), 3.60–3.81 (m, 3H), 4.00–4.09 (m, 1H), 5.15 (d, *J* = 2.0, 2H), 7.26–7.45 (m, 11H), 7.60–7.64 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 19.2, 19.4, 21.1, 27.0, 29.7, 30.0, 31.7, 37.0, 37.2, 39.2, 56.9, 58.7, 61.7, 67.8, 114.7, 127.9, 128.2, 128.3, 128.7, 129.9, 133.8, 135.7, 199.4. Anal. calcd. for $C_{38}H_{47}NO_5Si \cdot H_2O$: C, 70.88; H, 7.67; N, 2.18. Found: C, 70.98; H, 7.46; N, 2.18.

(1*S*,3a*S*)-1-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-1,2,3,3a,4,5,8,9-octahydropyrrolo-[1,2-*a*]quinolin-6(7*H*)-one (15). Diketone **14** (470 mg, 0.80 mmol) was dissolved in methanol (100 mL). 10% Pd/C (250 mg) was added to the solution. The mixture was subjected to hydrogenation at 1 atm and room temperature for 24 h. The resulting mixture was filtered through celite 545 (5 g) and rinsed with methanol (2 × 50 mL). All the combined filtrates were concentrated under reduced pressure, and the residue was purified by preparative TLC (SiO_2; EtOAc/CH_3OH, 95:5) to afford **15** (270 mg, 75%) as a yellow oil. $[\alpha]_D^{25}$ +317 (*c* 0.31, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.7, 9H), 1.13–1.28 (m, 1H), 1.38–2.20 (m, 10H), 2.26–2.43 (m, 3H), 2.60–2.75 (m, 2H), 3.20–3.28 (m, 1H), 3.58–3.78 (m, 2H), 4.03 (t, J = 8.6, 1H), 7.37–7.47 (m, 6H), 7.65 (dt, *J* = 8.0, 1.6, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.3, 21.6, 22.1, 27.1, 27.4, 27.6, 27.8, 28.6, 29.1, 29.8, 30.7, 36.3, 36.6, 38.5, 38.9, 55.7, 56.4, 57.3, 59.4, 61.0, 61.4, 107.3, 128.0, 130.1, 133.6, 135.7, 135.8, 158.9, 193.9. Anal. calcd. for $C_{30}H_{39}NO_2Si \cdot 0.5H_2O$: C, 74.64; H, 8.35; N, 2.90. Found: C, 74.51; H, 8.28; N, 2.95. A pure sample of the minor diastereoisomer **16** was not obtained.

(1*S*,3a*S*)-1-(2-Hydroxyethyl)-1,2,3,3a,4,5,8,9-octahydropyrrolo[1,2-*a*]quinolin-6(7*H*)-one (5). Silyl ether **15** (170 mg, 0.37 mmol) was dissolved in THF (5 mL) at room temperature. TBAF (1.0 M in THF, 0.55 mL, 0.55 mmol) was added dropwise to the solution. Stirring was continued for 3 h; then a saturated Na_2CO_3 solution (0.5 mL) was added to the reaction mixture. After 10 min, the mixture was extracted with Et_2O (3 × 10 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, 92:8 CH_2Cl_2/CH_3OH) to afford **5** (75 mg, 87%) as a white solid; mp 178–180 °C (EtOAc/cyclohexane, 1:1) (lit.[10]: mp 176–179 °C). $[\alpha]_D^{25}$ +798 (*c* 0.29, EtOH) {lit.[10]: $[\alpha]_D^{25}$ +538 (*c* 1.40, EtOH)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.29 (m, 1H), 1.49–2.20 (m, 11H), 2.32 (t, *J* = 6.5, 2H), 2.40–2.48 (m, 1H), 2.61–2.68 (m, 2H), 3.23–3.31 (m, 1H), 3.61–3.78 (m, 2H), 4.03 (t, *J* = 8.0, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 21.9, 27.3, 28.4, 29.0, 29.6, 36.3, 38.5, 55.6, 59.3, 60.0, 107.1, 158.9, 193.7.

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16. CCDC 750511 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif