A new route to *trans*-2,6-disubstituted piperidine-related alkaloids using a novel C_2 -symmetric 2,6-diallylpiperidine carboxylic acid methyl ester

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A novel C_2 -symmetric 2,6-diallylpiperidine carboxylic acid methyl ester 1 was prepared by the double asymmetric allylboration of glutaldehyde followed by an aminocyclization and carbamation. On the basis of desymmetrization of 1 using iodocarbamation, one allyl group of 1 was protected and monofunctionalizations of the resulting oxazolidinone 11 were performed. The reaction of the *N*-methoxycarbonyl piperidine 25 employing decarbamation reagent (*n*-PrSLi or TMSI) as a key step gave oxazolidinone 26 or 17 including an intramolecular ring formation, which was transformed in a few steps into (–)-porantheridine (2) and (–)-2-*epi*-porantheridine (3), respectively. In addition, the expedient synthesis of (+)-*epi*-dihydropinidine (4), (2*R*,6*R*)-*trans*-solenopsin A (5), and precoccinelline (6), starting from 11 is described.

Introduction

The abundance of biologically active compounds containing the 2,6-disubstituted piperidine ring has resulted in considerable synthetic efforts to prepare such systems.1 With respect to biologically-active target molecules, an increasing interest in the diastereo- and enantioselective synthesis of piperidines has developed.² The focus of our interest in this field is on the synthetic applications of double or iterative asymmetric reactions to achieve enantiomeric enhancement.3 We recently reported on the asymmetric synthesis of several piperidine-related alkaloids using a novel C_2 -symmetric 2,6-diallylpiperidine (1), prepared by a double asymmetric allylboration of glutaraldehyde followed by aminocyclization as the key steps.⁴ In this paper, we describe the full detail of an expedient synthesis of (-)-porantheridine (2),⁵ a novel tricyclic alkaloid of Poranthera corymbosa, and its 2-epimer (3), (-)-epi-dihydropinidine $(4), ^6$ a constituent of pine and spruce species, and (2R, 6R)-trans-solenopsin A (5),⁷ a constituent of fireant venom, and precoccinelline (6),8 a ladybug defense alkaloid starting from 1 (Fig. 1).

Results and discussion

We began with the synthesis of **1** as a chiral building block. The treatment of glutaraldehyde with *B*-allyldiisopinocamphenylborane, prepared by the reaction of *B*-methoxydiisocamphenylborane $\{(-)-Ipc_2BOMe\}$ and allylmagnesium bromide, followed by oxidation with alkaline H₂O₂ gave the diastereomeric and inseparable mixture of diols **7** in 74% yield.⁹ The diols **7** were successively subjected to ditosylation and aminocyclization with benzylamine to give the diastereomeric isomers of piperidines **8**, which were fortunately separated by chromatography to yield C_2 -



symmetric 2,6-diallylpiperidine **8** and *meso*-**8** in 61 and 14% yields, respectively. This success of the separation can be attributed to both a rigid conformation and close proximity (1,3-relationship) between the two chiral centers of **8** compared with acyclic 1,5-diols 7 (Scheme 1).



The exchange of N-protecting groups from benzyl to carbamate group was examined with methyl chloroformate. First, the use of benzene and toluene as solvents under reflux resulted in the

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recovery of C_2 -8. However, the use of chloroform, a more polar solvent, afforded the title carbamate 1 in 59% yield together with the recovery of C_2 -8 (35%). Finally, methyl carbamate 1 was obtained in 93% yield by a reaction in a sealed tube at 90 °C for 48 h. On the other hand, carbamation using ethyl and benzyl chloroformates in chloroform under the same conditions did not proceed, resulting in the recovery of C_2 -8. No carbamation with chloroformates bulkier than methyl chloroformate would presumably occur due to steric effects (hindrance) of the a,a'-disubstituted allyl groups in the piperidine ring (Scheme 2).



Scheme 2

With the C_2 chiral building block 1 in hand, our synthesis began with the selective monodihydroxylation of the diallyl appendages in 1. Unfortunately, the dihydroxylation of 1 using AD-mix- α was nonselective, resulting in a diasteromeric mixture of monodiols 9 and 10 and inseparable diastereomeric tetraols together with the recovery of the starting material 1 (Scheme 3).¹⁰



We hypothesized that this problem could be overcome by an intramolecular iodocarbamation with one of the two allyl groups, because it is impossible for a second iodocarbamation to occur with the other one. Thus, the intramolecular iodocarbamation of **1** with iodine produced a diastereomeric and inseparable mixture of oxazolidinones **11** in 98% yield. This desymmetrization indicates that one of the two allyl groups was protected (Scheme 4).



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Having the promising piperidine 11, the Sharpless asymmetric dihydroxylation (AD-mix- α) of 11 was conducted to provide the diastereomeric mixtures of diols 12 in 90% yield. Deprotection of the oxazolidine was accomplished by the exposure of 12 to zinc in acetic acid to give the allylpiperidine, of which *N*-protection was achieved by treatment with methyl chloroformate to yield 9 and 10 in 55 and 18% from 11, respectively (Scheme 5).



Treatment of the diol **9** in a three-step sequence (1. cyclic stannoxanation, 2. primary tosylation, 3. epoxidation) afforded the epoxide **13** in 92% yield. Without further purification, epoxide **13** was cleaved with ethylmagnesium bromide in the presence of CuBr–Me₂S to yield the alcohol **14** in 76% yield. *O*-Protection of **14** with MOMCl in the presence of Hünig base gave **15** in 90% yield. Oxidative cleavage of **15** with cat. OsO₄ in combination with NaIO₄ followed by the Horner–Wadsworth–Emmons reaction of the resulting aldehyde with dimethyl 2-oxopropylphosphonate in the presence of NaH afforded the α ,β-unsaturated ketone, which was hydrogenated with cat. Pd(OH)₂ to give the ketone **16** in 84% yield (Scheme 6).



Scheme 6

The decarbamation of **16** with iodotrimethylsilane¹¹ unpredictably led to the production of the oxazolidinone **17** in 50% yield. At this stage, the stereochemistry (C₃ position) of **17** remained undetermined. Acetalization of **17** gave the acetal **18**, the spectral data for which was surprisingly inconsistent with those of Comin's synthetic intermediate of (–)-porantheridine **19**.^{5c} From these results, the formation of **17** can be understood on the basis of an intramolecular cyclization of the proposed reaction intermediate **20** accompanied by an inversion of configuration at the methoxymethyloxy-substituted carbon (Scheme 7).¹²



Therefore, the epimer of 16, *i.e.*, 21 was prepared starting with the diol 10 according to the same procedure as was used for the preparation of 16 (Scheme 8). Deprotection of 21 with TMSI followed by acetalization of the resulting oxazolizinone gave Comin's synthetic intermediate 19, the spectral data of which was in agreement with the reported values.^{5c} Thus, the proposed mechanism was verified.



Next, the *O*-non-protected ketone **25** was synthesized from **14** in a three-step procedure in 79% yield (Scheme 9). In the homologation, the Wittig reagent (1-triphenylphosphranylidene-2propanone) was used in place of the Horner–Wadsworth–Emmons reagent (dimethyl 2-oxopropylphosphonate). The decarbamation of **25** with Corey's reagent *n*-PrSLi¹³ fortunately provided the desired oxazolidinone **24** in 90% yield. An intramolecular attack of a secondary alkoxide anion, generated by *n*-PrSLi, to the carbamate carbonyl had probably occurred. In addition, treatment of **25** with TMSI gave **17** in high yield (97%). Finally, cleavage of the oxazolidinone ring of acetal **18** with 2 M KOH in 2propanol at 120 °C in a sealed tube¹⁴ followed by an intramolecular aminalization of the resulting amine **26** with *p*-TsOH afforded (–)-2-*epi*-porantheridine (**3**) in 25% yield. Thus, **14** was transformed



Scheme 9

to 2 and 3 based on *n*-PrSLi and TMSI-mediated oxzolidinone ring formation of 25, respectively, in a short step.

In addition, we focused on the synthesis of 2,6-trans-dialkylpiperidines such as (+)-epi-dihydropinidine (4), and (2R,6R)-transsolenopsin A (5). OsO₄-Mediated dihydroxylation of 14 followed by an oxidative cleavage of the resulting diol with NaIO₄ provided the aldehyde, which was decarbonylated with (Ph₃P)₃RhCl to afford the methyl-substituted piperidine 27 in 48% yield. Deprotection of oxazolidine occurred upon exposure of 27 to zinc in acetic acid followed by N-protection of the resulting allylpiperidine with Boc₂O to give N-Boc-2-allyl-6-methylpiperidine 28. Transformation of 28 into 4 has been reported previously.¹⁵ The oxidative cleavage of 28 with cat. OsO4 in combination with NaIO4 provided the aldehyde, which was coupled by the Wittig olefination with *n*nonyltriphenylphosphonium bromide in the presence of *n*-BuLi, followed by hydrogenation of the resulting olefin to give the 2,6disubstituted piperidine 29 in 64% yield. N-Deprotection of 29 by treatment with trifluoroacetic acid (TFA) in CH₂Cl₂ provided 5 in 84% yield (Scheme 10).

Next, the transformation of 14 into precoccinelline (6) was pursued. Wacker oxidation of 14 provided the ketone 30 in 86% yield. By a procedure similar to that described for 28, a twostep treatment (deprotection of the oxazolidine and *N*-protection) of 30 gave the allylpiperidine 31 in 81% yield. Treatment of 32 with cat. OsO₄ in combination with NaIO₄ followed by the Wittig reaction of the resulting aldehyde with (triphenylphosphoranylidene)acetaldehyde afforded the α , β -unsaturated aldehyde, which was exposed to hydrogen in the presence of cat. Pd(OH)₂ in ethyl acetate to give the keto aldehyde 32 in 59% yield. *N*-Deprotection of 32 with TFA followed by an intramolecular Mannich-type cyclization with 10-camphorsulfonic acid (CSA) gave the known synthetic intermediate 33 for 6 in 52% yield, which constitutes a formal synthesis of precoccinelline (Scheme 11).



Conclusion

In conclusion, we explored the use of C_2 -symmetric 2,6-diallylpiperidine **1** as a novel chiral building block *via* the double asymmetric allylboration of glutaldehyde followed by aminocyclization and carbamation. The formal asymmetric synthesis of (-)-porantheridine (**2**) and the asymmetric synthesis of (-)-2*epi*-porantheridine (**3**) were demonstrated based on the distinctive desymmetrization of **1** by iodocabamation including the protection of one allyl group and *n*-PrSLi and TMSI-assisted intramolecular oxazolidinone ring formation accompanied by retention and inversion of the configuration at the 2 position of the hydroxypentyl substituent in **25**, respectively. Moreover, the convenient synthesis of (-)-*epi*-dihydropinidine (**4**), (2*R*,6*R*)-*trans*-solenopsin A (**5**), and precoccinelline (**6**), starting from **11** was achieved.

Experimental

General

Melting points are uncorrected. IR spectra were measured with a JASCO A102 and a Perkin Elmer 1600 spectrophotometers. ¹H NMR and ¹³C spectra were recorded on a JEOL FX 270, Varian Gemini-300, and Varian Unity-500. MS and HRMS were taken on a JEOL-JMS D-200 spectrometer using the electron ionization. Elemental analyses were performed by a Perkin Elmer 2400 Elemental Analyzer. Optical rotations were measured with a JASCO-DIP-1000 digital polarimeter. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No 9385) with a medium pressure apparatus. The extracts were dried over Na_2SO_4 unless otherwise specified.

(2S,6S)-1-Benzyl-2,6-bis(2-propenyl)piperidine $(C_2$ -8). 0 M Allylmagnesium bromide (20 mL, 20 mmol) in ether was added to a solution of (-)-Ipc₂BOMe (6.32 g, 20.0 mmol) in ether (25 mL) at -78 °C. After being stirred for 15 min, the reaction was warmed to rt. To the mixture was added a solution of glutaraldehyde (1.0 g, 10 mmol) in ether (5 mL) at $-78 \text{ }^{\circ}\text{C}$. After being stirred for 1 h, the solution was warmed to rt. To the reaction mixture were successively added 3 N NaOH (14.6 mL) and 30% H₂O₂ (6.0 mL) at 0 °C. The mixture was refluxed for 1 h and fractionated with a separatory funnel. The aqueous layer was extracted with ether three times. The combined organic solvents were washed with brine, dried, and evaporated. The residue was purified by flash column chromatography on silica gel (*n*-hexane–ethyl acetate = 2:1) to give the diastereomeric mixture of diols (1.36 g, 74%) as an oil. Et₃N (3.48 mL, 25.0 mmol) and 4-dimethylaminopyridine (305 mg, 2.50 mmol) were successively added to a mixture of the diols (1.15 g, 6.25 mmol) and p-toluenesulfonyl chloride (4.70 g, 25.0 mmol) at 0 °C and the mixture was stirred at room temperature for 2 d. A large amount of ether was added to the mixture. The mixture was filtered through Celite. The filtrate was washed with brine, dried, and evaporated. The residue was purified by chromatography using n-hexane-ethyl acetate (5 : 1) as eluent to yield the ditosylate (2.38 g, 78%) as a yellow oil. A solution of the tosylate in benzylamine (15.3 mL, 0.14 mol) was heated at 75 °C for 2 d. The reaction was diluted with n-pentane (100 mL) at 0 °C and 2 N NaOH (150 mL) was added to the dilute solution. The organic layer was separated and the aqueous layer was extracted with n-pentane (40 mL) four times. The combined organic layers were dried over K₂CO₃ and evaporated. The residue was purified by medium-pressure chromatography using *n*-hexane–ethyl acetate (80:1) as eluent to yield C2-8 (973 mg, 61%) and meso-8 (223 mg, 14%) as oils. C_2 -8: $[a]_D^{26}$ -4.87° (c 1.03, CHCl₃); IR (neat) 2928, 1559, 1447 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.34–1.39 (m, 2 H), 1.57–1.60 (m, 4 H), 2.13–2.24 (m, 4 H), 2.79–2.83 (m, 2 H, H-2, H-6), 3.68, 3.82 (ABq, J = 14.3 Hz, 2 H, $CH_2C_6H_5$), 4.95–5.02 (m, 4 H, $2 \times CH = CH_2$), 5.68–5.81 (m, 2 H, $2 \times -CH = CH_2$), 7.20–7.38 (m, 5 H); 13 C NMR (75 MHz, CDCl₃) δ 20.1, 26.1, 35.7, 51.1, 54.5, 115.7, 126.5, 128.1, 128.5, 137.0, 141.3; anal. calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.73; H, 9.74; N, 5.38.

Methyl (25,6S)-2,6-Bis(2-propenyl)piperidinecarboxylate (1). A solution of C_2 -**5** (297 mg, 1.16 mmol) and methyl chloroformate (0.45 mL, 5.81 mmol) in CHCl₃ (5.2 mL) in a sealed tube was heated at 90 °C for 2 d. The solution was diluted with ether. The resulting mixture was washed with 10% HCl and H₂O and dried. Evaporation left an oil, which was purified with chromatography using *n*-hexane–ethyl acetate (30 : 1) as eluent to yield **1** (242 mg, 93%); $[a]_{D}^{26}$ +6.00° (*c* 1.14, CHCl₃); IR (neat) 2949, 1734, 1700, 1653, 1636, 1559, 1443, 1395 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.59–181 (m, 6 H), 2.1–2.25 (m, 2 H), 2.45–2.53 (m, 2 H), 3.68 (s, 3 H, COOCH₃), 3.81–3.88 (m, 2 H, *H*-2*S*, *H*-6*S*), 5.03–5.08 (m, 4 H), 5.68–5.82 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.6, 23.2, 39.1, 51.7, 52.3, 116.8, 135.9, 156.4; HRMS calcd for C₁₃H₂₁NO₂ (M⁺) 223.1572, found 223.1576.

Methyl (2S,6S)-2-[(2S)-2,3-Dihydroxypropyl]-6-prop-2-enylpiperidinecarboxylate (9) and Methyl (2S,6S)-2-[(2R)-2,3-Dihydroxypropyl]-6-prop-2-enylpiperidinecarboxylate (10) from 1. The olefin 1 (412 mg, 1.84 mmol) was added to a mixture of AD-mix- α (2.58 g) in tert-BuOH (13 mL), and H₂O (13 mL) at 0 °C. After the reaction mixture was stirred for 9 h at the same temperature, sodium sulfite (2.6 g) was added to the mixture. After stirring for 30 min, the mixture was filtered through a Celite pad. The filtrate was extracted with chloroform-2-propanol (5: 1) three times. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed using *n*-hexaneethyl acetate (1 : 1) as eluent to yield 1 (78 mg, 19%), 9 (152 mg, 32%), 10 (51 mg, 11%), and the diastereomeric mixture of tetraols (127 mg, 24%) as oils. 9; $[a]_D^{26} - 27.2^\circ$ (c 0.98, CHCl₃); IR (neat) 3415, 2947, 1673, 1453, 1396 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.68-1.93 (m, 8 H), 2.17-2.28 (m, 1 H), 2.44-2.51 (m, 2 H), 3.40-3.48 (m, 1 H, H-2S or H-6S), 3.61–3.73 (m, 1 H, H-2S or H-6S), 3.71 (s, 3 H), 3.81–3.84 (m, 1 H, –CHOH), 4.00–4.07 (m, 2 H, -CH₂OH), 5.03-5.11 (m, 2 H), 5.67-5.81 (m, 1 H); ¹³C NMR $(75 \text{ MHz}, \text{CDCl}_3) \delta 12.8, 22.8, 24.8, 38.7, 39.7, 49.3, 51.4, 52.5,$ 66.8, 70.3, 116.8, 135.2, 156.7; HRMS calcd for C₁₃H₂₃NO₄ (M⁺) 257.1627, found 257.1616. 10; [a]_D²⁶ +2.34° (c 1.01, CHCl₃); IR (neat) 3418, 2948, 1672, 1452, 1396, 1370, 1112 cm⁻¹; ¹H NMR (300 MHz, CDCl₃)δ 1.40–1.48 (m, 1 H), 1.58–1.70 (m, 4 H), 1.83– 1.98 (m, 1 H), 2.09–2.20 (m, 1 H), 2.39–2.47 (m, 1 H), 3.40–3.50 (m, 2 H), 3.50–3.62 (m, 2 H, H-2S, H-6S), 3.67 (s, 3 H), 3.69–3.70 (m, 1 H, -CHOH), 4.04-4.14 (m, 2 H, -CH₂OH), 4.58 (br s, 1 H), 4.98-5.23 (m, 2 H), 5.60-5.74 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.1, 22.1, 25.7, 38.9, 39.4, 48.3, 51.8, 52.9, 66.5, 68.4, 117.0, 135.4, 158.0; HRMS calcd for C₁₃H₂₃NO₄ (M⁺) 257.1627, found 257.1625.

(4RS,6S,10S)-1-Aza-4-(iodomethyl)-3-oxa-10-prop-2-enylbicyclo[4.4.0]-decan-2-one (11). Iodine (634 mg, 2.50 mmol) was added to a solution of 1 (279 mg, 1.25 mmol) in CH₂Cl₂ (10 mL) at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated Na₂SO₃ and the resulting mixture was extracted with CH₂Cl₂ three times. The extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography using n-hexane-ethyl acetate (3:1) as eluent to yield 11 (412 mg, 98%); IR (neat) 2934, 1685, 1427, 1367, 1269 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.09– 2.52 (m, 10 H), 3.14–3.25 (m, 1 H), 3.31–3.46 (m, 2 H), 4.00–4.08 (m, 0.6 H, H-4), 4.23–4.31 (m, 0.4 H, H-4), 4.58–4.66 (m, 1 H, H-6S), 5.02-5.09 (m, 2 H), 5.68-5.85 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 5.05 (6.13), 19.1 (18.3), 27.3 (27.4), 32.8, 33.2, 33.4, 34.7, 35.1, 35.9, 46.5, 49.2, 50.2, 51.1, 73.2 (73.6), 117.3 (117.3), 135.2, 152.8; HRMS calcd for C₁₂H₁₈NO₂I (M⁺) 335.0382, found 335.0377.

Methyl (2*S*,6*S*)-2-[(2*S*)-2,3-Dihydroxypropyl]-6-prop-2-enylpiperidinecarboxylate (9) and methyl (2*S*,6*S*)-2-[(2*R*)-2,3-Dihydroxypropyl]-6-prop-2-enylpiperidinecarboxylate (10) from 11. The olefin 11 (220 mg, 0.657 mmol) was added to a mixture of AD-mix- α (1.05 g) in *tert*-BuOH (5 mL), and H₂O (5 mL) at 0 °C. After the reaction mixture was stirred for 17 h at the same temperature, sodium sulfite (1.3 g) was added to the mixture. After stirring for 30 min, the mixture was filtered through a Celite pad. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed using ethyl acetate-methanol (10:1) as eluent to yield a diasterometric mixture of the diols 12 (218 mg) as an oil. Zinc (69 mg, 1.06 mmol) was added to a solution of the diols (218 mg, 0.59 mmol) in a mixture of THF (1.7 mL), acetic acid (70 μ L), and H₂O (70 μ L) at 0 °C and the reaction mixture was vigorously stirred at room temperature for 1.5 h. The mixture was filtered through Celite. 1 N NaOH was added to the filtrate. The basic solution was extracted with CHCl₃ three times. The extracts were dried over K₂CO₃ and evaporated. To a solution of the residue in THF (2 mL) and H₂O (2 mL) were added K₂CO₃ (122 mg, 0.88 mmol) and methyl chloroformate (68 µL, 0.88 mmol). The mixture was stirred at room temperature overnight. The mixture was acidified with 20% KHSO4 and extracted with CH₂Cl₂ three times. The extracts were washed with brine, dried and evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (1 : 1) as eluent to yield 9 (93 mg, 55%) and 10 (30 mg, 18%). All spectra of 9 and 10 were in accordance with those of 9 and 10 prepared from 1.

Methyl (2S,6S)-2-[(2R)-2-Hydroxypentyl]-6-prop-2-enylpiperidinecarboxylate (14). n-Bu₂SnO (2.3 mg, 9.41 µmol), triethylamine (78.6 µL, 0.56 mmol) and p-toluenesulfonyl chloride (p-TsCl) (108 mg, 0.56 mmol) were added to a solution of 9 (231 mg, 0.47 mmol) in CH₂Cl₂ (1.5 mL). The mixture was stirred for 1.5 h at room temperature and brine (10 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ three times. The combined organic layers were dried and evaporated. The residue was chromatographed using *n*-hexane–acetone (3:1) as eluent to yield the tosylate. To a solution of the tosylate in methanol (2.0 mL) was added K₂CO₃ (77 mg, 0.56 mmol) at 0 °C. After 1 h of stirring at room temperature and saturated NH₄Cl (5 mL) was added to the mixture. The mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated to yield 13 (125 mg, 92%) as an oil. To a slurry of CuBr-SMe2 (115 mg, 0.56 mmol) in THF (4 mL) was added ethylmagnesium bromide (1 M in THF, 1.12 mL, 1.12 mmol) at -78 °C with stirring. After being stirred for 1 h at -45 °C, a solution of 13 in THF (1 mL) was slowly added. The mixture was gradually warmed to -30 °C, stirred for 1 h, and quenched with saturated NH₄Cl. The mixture was diluted with ether and the phases were separated. The organic layer was washed with brine, dried, and evaporated. The residue was chromatographed using n-hexane-acetone (7 : 1) as eluent to give 14 (76 mg, 76%) as an oil; $[a]_{D}^{26}$ -28.8° (c 1.94, CHCl₃); IR (neat) 3451, 2953, 1674, 1450, 1368, 1115 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, J = 6.9 Hz, 3 H), 1.21–1.89 (m, 12 H), 2.17-2.27 (m, 1 H), 2.45-2.53 (m, 1 H), 3.30 (br s, 1 H), 3.58-3.62 (m, 1 H), 3.71 (s, 3 H), 3.73-3.84 (m, 1 H), 4.00-4.02 (m, 1 H, H-2(2R)), 5.02–5.11 (m, 2 H), 5.68–5.82 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.1, 14.1, 18.8, 23.0, 24.7, 38.7, 40.1, 43.7, 49.7, 51.4, 52.3, 69.7, 116.7, 135.4, 156.6; HRMS calcd for C₁₅H₂₇NO₃ (M⁺) 269.1991, found 270.2000.

(2*S*,6*S*)-Methyl 2-Allyl-6-((*R*)-2-(methoxymethoxy)pentyl)piperidine-1-carboxylate (15). To a solution of 14 (92 mg, 0.34 mmol) in CHCl₃ (3 mL) were successively added *N*,*N*diiopropylethylamine (0.2 mL, 1.12 mmol) and chloromethyl methyl ether (77.8 μ L, 1.03 mmol) at 0 °C and the reaction mixture was refluxed overnight. To the reaction mixture was added 20% KHSO₄ and the mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated. The residue was chromatographed using *n*-hexane–acetone (15 : 1) as eluent to give **15** (96 mg, 90%) as an oil; $[a]_D^{29}$ –16.3° (*c* 0.98, CHCl₃); IR (neat) 2951, 1694, 1448, 1328, 1100 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 7.1 Hz, 3 H), 1.26–1.76 (m, 11 H), 1.85–1.93 (m, 1 H), 2.20–2.30 (m, 1 H), 2.52–2.60 (m, 1 H), 3.39 (s, 3 H), – OCH₂OCH₃, 3.53–3.62 (m, 1 H), 3.68 (s, 3 H), 3.76–3.82 (m, 1 H), 3.99–4.06 (m, 1 H), 4.63 (d, *J* = 7.1 Hz, 1 H, –OCH₂OCH₃), 4.66 (d, *J* = 7.1 Hz, 1 H, –OCH₂OCH₃), 5.01–5.10 (m, 2 H), 5.70–5.84 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 14.2, 15.0, 18.6, 24.1, 24.7, 36.6, 38.2, 38.6, 49.1, 52.0, 52.1, 55.5, 75.0, 95.1, 116.4, 135.8, 156.3; HRMS calcd for C₁₇H₃₁NO₄ (M⁺) 313.2253, found 313.2250.

(2S,6S) - Methyl 2 - ((R) - 2 - (Methoxymethoxy)pentyl) - 6 - (4 oxopentyl)piperidine-1-carboxylate (16). Three drops of an aqueous 4% OsO₄ solution were added to a solution of 15 (96 mg, 0.3 mmol) in dioxane (1.5 mL) and H₂O (1.5 mL) and then the reaction mixture was stirred for 10 min at room temperature. After NaIO₄ (65 mg, 0.30 mmol) was added to mixture, the reaction mixture was stirred for 15 min. Again NaIO₄ (65 mg, 0.30 mmol) was added to the mixture. The reaction was stirred for 1 h, quenched with 10% sodium thiosulfate. The mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated. Dimethyl 2-oxopropylphosphonate (53.4 µL, 0.36 mmol) was added to a suspension of 60% NaH (14.8 mg, 0.36 mmol) in THF (1.5 mL) and the reaction mixture was stirred for 5 min at room temperature. A solution of the above residue was added to the mixture at 0 °C and the reaction was stirred overnight. Saturated NH₄Cl solution was added to the reaction mixture and the mixture was extracted with CH₂Cl₂ three times. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed using n-hexane-acetone (5:1) as eluent to give the unsaturated ketone (91 mg, 85%) as an oil. Pd(OH)₂ (20 mg) was added to a solution of the ketone in ethyl acetate (4.5 mL) and the suspension was stirred under hydrogen for 2 h. The mixture was filtrated through Celite and the filtrate was evaporated. The residue was chromatographed using n-hexane-acetone (5 : 1) as eluent to give the saturated ketone 16 (91 mg, 99%) as an oil; $[a]_{D}^{26}$ -24.0° (c 0.81, CHCl₃); IR (neat) 2949, 1697, 1448, 1369, 1099, 1038 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, J = 7.4 Hz, 3 H, $-CH_3$, 1.23–1.78 (m, 15 H), 1.90–1.99 (m, 1 H), 2.14 (s, 3 H, $-COCH_3$), 2.45–2.49 (m, 2 H), 3.38 (s, 3 H), 3.56 (quint, J =5.8 Hz, 1 H), 3.67 (s. 3 H), 3.74 (br s, 1 H), 3.93–3.96 (m, 1 H), 4.63 $(d, J = 7.1 \text{ Hz}, 1 \text{ H}), 4.66 (d, J = 7.1 \text{ Hz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {}^{13}\text{C} \text{ NMR} (75 \text{ MHz}, 1 \text{ H}); {$ $CDCl_3$) δ 14.2, 15.8, 18.5, 21.1, 25.2, 25.3, 29.8, 33.1, 36.6, 38.1, 43.3, 49.2, 52.9, 52.5, 55.5, 74.9, 95.1, 156.4, 208.5; HRMS calcd for C₁₉H₃₅NO₅ (M⁺) 357.2515, found 357.2513.

(3*S*,4*aS*,8*S*)-Hexahydro-8-(4-oxopentyl)-3-propylpyrido[1,2*c*][1,3]oxazin-1(3*H*)-one (17). Iodotrimethylsilane (61.3 µL, 0.43 mmol) was added to a solution of 16 (35 mg, 0.10 mmol) in CH₃CN (3.5 mL) at 0 °C and the solution was stirred for 2 h. After the reaction was quenched with 10% sodium thiosulfate, the mixture was extracted with CH₂Cl₂ three times. The extracts were dried over K₂CO₃ and evaporated. The residue was chromatographed using CHCl₃ as eluent to give the 17 (14 mg, 50%) as an oil; $[a]_{D}^{2b}$ -57.6° (*c* 0.68, CHCl₃); IR (neat) 2934, 1681, 1431, 1363, 1274 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 6.9 Hz, 3 H), 1.35–1.78 (m, 16 H), 1.85–1.95 (m, 1 H), 2.11 (s, 3 H), 2.38–2.60 (m, 2 H), 3.41–3.48 (m, 1 H), 4.17–4.21 (m, 1 H, *H*-4*aS*), 4.46–4.49 (m, 1 H, *H*-3*S*); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 18.2, 19.2, 20.0, 28.1, 28.7, 29.9, 33.0, 33.1, 36.5, 42.9, 46.8, 50.9, 72.6, 153.7, 208.6; HRMS calcd for C₁₆H₂₈NO₃ (M⁺) 281.1991, found 281.2001.

(3S,4aS,8S)-Hexahydro-8-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)-3-propylpyrido[1,2-c][1,3]oxazin-1(3H)-one (18). A mixture of 17 (82 mg, 0.29 mmol), ethyleneglycol (81.3 μ L, 1.46 mmol), and p-TsOH-H₂O (11 mg) in benzene (5 mL) using a Dean-Stark apparatus was refluxed overnight. Saturated NaHCO3 was added to the mixture. The mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated. The residue was purified by chromatography using CHCl₃ as eluent to yield **18** (87 mg, 92%) as an oil; $[a]_{D}^{26}$ -56.3° (*c* 1.18, CHCl₃); IR (neat) 2936, 2872, 1682, 1433, 1375, 1284, 1229, 1120, 1059 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.94 (t, J = 6.3 Hz, 3 H), 1.30 (s, 3 H, -C-CH₃), 1.25-1.72 (m, 17 H), 1.85-1.96 (m, 1 H), 3.42-3.48 (m, 1 H), 3.92 (s, 4 H. –OCH₂CH₂O–), 4.19 (m, 1 H), 4.50 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 14.1, 18.5, 19.5, 21.0, 24.0, 28.0, 29.8, 33.4, 36.8, 39.2, 47.0, 51.7, 64.8, 72.8, 110.0, 153.8; HRMS calcd for C₁₈H₃₁NO₄ (M⁺) 325.2253, found 325.2246.

(2*S*,6*S*)-Methyl 2-Allyl-6-((*S*)-2-hydroxypentyl)piperidine-1carboxylate (22). According to the same procedure described for preparation of 14, 22 was prepared from 10 in 61% yield. An oil; $[a]_{D}^{28} - 28.8^{\circ}$ (*c* 0.96, CHCl₃); IR (neat) 3452, 2953, 1675, 1450, 1368, 1115 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.90 (t, *J* = 6.9 Hz, 3 H, -CH₃), 1.24–1.93 (m, 12 H), 2.15–2.26 (m, 1 H), 2.49–2.53 (m, 1 H), 3.47–3.49 (m, 1 H), 3.68–3.78 (m, 1 H), 3.72 (s, 3 H), 4.16–4.20 (m, 2 H, -CHOH), 5.02–5.09 (m, 2 H), 5.66–5.80 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.8, 14.5, 189.5, 22.8, 26.3, 38.9, 39.4, 43.7, 48.9, 52.0, 52.9, 67.5, 117.0, 135.8, 158.0; HRMS calcd for C₁₅H₂₇NO₃ (M⁺) 269.1991, found 270.1988.

(2*S*,6*S*) - Methyl 2 - Allyl-6-((*S*) - 2 - (methoxymethoxy)pentyl)piperidine-1-carboxylate (23). According to the same procedure described for preparation of 15, 23 was prepared from 22 in 80% yield. An oil; $[a]_D^{29} - 17.1^\circ$ (*c* 1.02, CHCl₃); IR (neat) 2949, 1698, 1446, 1327, 1100 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 7.1 Hz, 3 H), 1.26–1.93 (m, 12 H), 2.20–2.30 (m, 1 H), 2.50–2.58 (m, 1 H), 3.38 (s, 3 H, –OCH₂OCH₃), 3.53–3.60 (m, 1 H), 3.68 (s, 3 H), 3.73–3.80 (m, 1 H), 3.99 (m, 1 H), 4.62–4.68 (m, 2 H, –OCH₂OCH₃), 5.01–5.10 (m, 2 H), 5.70–5.83 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 14.2, 15.1, 18.2, 24.3, 25.6, 37.1, 38.5, 38.9, 50.1, 52.0, 52.2, 55.5, 76.5, 95.9, 116.4, 135.7, 156.3; HRMS calcd for C₁₇H₃₁NO₄ (M⁺) 313.2253, found 313.2260.

(2*S*,6*S*) - Methyl 2 - ((*S*) - 2 - (Methoxymethoxy)pentyl) - 6 - (4oxopentyl)piperidine-1-carboxylate (21). According to the same procedure described for preparation of 16, 21 was prepared from 23 in 79% yield. An oil; $[a]_D^{26}$ -27.0° (*c* 0.97, CHCl₃); IR (neat) 2949, 1697, 1447, 1368, 1099, 1039 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 7.1 Hz, 3 H), 1.18–1.76 (m, 15 H), 1.88–1.96 (m, 1 H), 2.14 (s, 3 H, -COCH₃), 2.44–2.47 (m, 2 H), 3.38 (s, 3 H), 3.51–3.62 (m, 1 H), 3.66 (s, 3 H), 3.71 (m, 1 H), 3.87 (m, 1 H), 4.63–4.70 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 14.5, 16.0, 18.5, 21.4, 25.5, 26.4, 30.2, 33.4, 37.4, 39.0, 43.6, 50.3, 52.2, 52.8, 55.8, 76.7, 96.1, 156.7, 208.8; HRMS calcd for C₁₉H₃₅NO₅ (M⁺) 357.2515, found 357.2513. (3*R*,4*a*S,8*S*)-Hexahydro-8-(4-oxopentyl)-3-propylpyrido[1,2*c*][1,3]oxazin-1(3*H*)-one (24) from 21. According to the same procedure described for preparation of 17, 24 was prepared from 21 in 48% yield. An oil; $[a]_D^{26}$ +9.67° (*c* 0.73, CHCl₃); IR (neat) 2936, 2870, 1708, 1674, 1433, 1363, 1289, 1129 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, *J* = 6.9 Hz, 3 H), 1.09–1.80 (m, 16 H), 2.04 (dd, *J* = 13.4, 5.5 Hz, 1 H), 2.13 (s, 3 H), 2.42–2.58 (m, 2 H), 3.37–3.47 (m, 1 H), 4.07–4.12 (m, 1 H, *H*-4*aS*), 4.58–4.61 (m, 1 H, *H*-3*R*); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 17.9, 18.2, 19.9, 27.7, 29.1, 30.0, 33.6, 35.8, 36.9, 42.8, 49.1, 49.9, 74.4, 153.9, 208.5; HRMS calcd for C₁₆H₂₈NO₃ (M⁺) 281.1991, found 281.2000.

(3*R*,4*a*S,8*S*)-Hexahydro-8-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (19). According to the same procedure described for preparation of 18, 19 was prepared from 24 in 99% yield. An oil; $[a]_D^{26}$ +10.0° (*c* 0.25, CHCl₃), lit.^{5*c*} [$a]_D^{23}$ +10.3° (*c* 1.96, CHCl₃); IR (neat) 2934, 1682, 1429, 1372, 1286, 1229, 1120, 1059 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, *J* = 6.6 Hz, 3 H), 1.30 (s, 3 H, -CCH₃), 1.07– 1.80 (m, 17 H), 2.02 (dd, *J* = 13.5, 5.2 Hz, 1 H), 3.34–3.43 (m, 1 H), 3.92 (s, 4 H, -OCH₂CH₂O–), 4.04–4.10 (m, 1 H), 4.59 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 17.9, 18.2, 20.7, 23.8, 27.2, 29.8, 33.7, 35.8, 36.9, 38.8, 49.2, 50.4, 64.5, 74.3, 109.7, 153.8; HRMS calcd for C₁₈H₃₁NO₄ (M⁺) 325.2253, found 325.2240.

Methyl (2S,6S) - 2 - [(2R) - 2 - Hydroxypentyl] - 6 - (4 - oxopentyl) piperidinecarboxylate (25). Three drops of 4% OsO₄ solution were added to a solution of 14 (77 mg, 0.29 mmol) in a mixture of dioxane (1.5 mL) and H₂O (1.5 mL) and the solution was stirred at room temperature for 10 min. NaIO₄ (61 mg, 0.29 mmol) was added to the solution, which was stirred for 15 min. NaIO₄ (61 mg, 0.29 mmol) was again added to the mixture. After 1 h, 10% sodium thiosulfate was added, and extracted with CH₂Cl₂ three times. The extracts were dried and the mixture was evaporated to leave the aldehyde. 1-Triphenylphosphranylidene-2-propanone (182 mg, 0.57 mmol) was added to a solution of the aldehyde in CH₂Cl₂ (3 mL). After being refluxed for 15 h, the mixture was evaporated. The residue was diluted with ether and the resulting mixture was filtered through Celite. The filtrated was evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (3 : 1) as eluent to yield the ketone. A suspension of the ketone and $Pd(OH)_2$ (20 mg) in ethyl acetate (4 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified with chromatography using n-hexane-ethyl acetate (3 : 1) as eluent to yield **25** (71 mg, 79%) as an oil; $[a]_{D}^{26}$ -39.2° (c 0.74, CHCl₃); IR (neat) 3445, 2950, 2870, 1677, 1452, 1370, 1190, 1115 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, J = 7.1 Hz, 3 H), 1.25–1.96 (m, 16 H), 2.14 (s, 3 H, -COCH₃), 2.47 (t, J = 5.5 Hz, 2 H), 3.19 (br s, 1 H), 3.58–3.60 (m, 1 H), 3.69 (s, 3 H), 3.76–3.77 (m, 1 H), 3.92–3.96 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 14.1, 18.8, 20.9, 23.9, 25.0, 29.9, 33.2, 40.1, 43.2, 43.4, 49.6, 51.8, 52.3, 69.6, 156.5, 208.4; HRMS calcd for C₁₇H₃₁NO₄ (M⁺) 313.2253, found 313.2249.

(4R,6S,10S)-1-Aza-3-oxa-10-(4-oxopentyl)-4-propylbicyclo-[4.4.0]decan-2-one (24) from 25. *n*-BuLi (1.6 M solution in hexane) (1.58 mL, 2.52 mmol) was added to a solution *n*-PrSH (0.27 mL, 3.03 mmol) in HMPA (1.0 mL) at 0 °C and the mixture was stirred for 30 min. A solution of 22 (79 mg, 0.25 mmol) in THF (2 mL) was added to the mixture at 0 °C and the mixture was stirred at room temperature for 5 d. 28% NH₃ solution was added to the reaction mixture and the mixture was extracted with ether ten times. The extracts were dried over K₂CO₃ and evaporated. The residue was purified by chromatography using CHCl₃ as eluent to yield **24** (63 mg, 90%) as an oil; $[a]_D^{26} + 9.67^\circ$ (*c* 0.74, CHCl₃). All spectra were in accordance with those of **24** prepared from **21**.

(3*S*,4*aS*,8*S*)-Hexahydro-8-(4-oxopentyl)-3-propylpyrido[1,2c][1,3]oxazin-1(3*H*)-one (17) from 25. Iodotrimethylsilane (71 μ L, 0.5 mmol) was added to a solution of 25 (71 mg, 0.23 mmol) in CH₃CN (6 mL) at 0 °C and the solution was stirred for 2 h. After the reaction was quenched with 10% sodium thiosulfate, the mixture was extracted with CH₂Cl₂ three times. The extracts were dried over K₂CO₃ and evaporated. The residue was chromatographed using CHCl₃ as eluent to give 17 (62 mg, 97%) as an oil. All spectra were in accordance with those of 17 prepared from 16.

(*S*)-1-((*2S*,6*S*)-6-(3-(2-Methyl-1,3-dioxolan-2-yl)propyl)piperidin-2-yl)pentan-2-ol (26). A solution of 18 (65 mg, 0.20 mmol) in 2 M KOH of 2-propanol (2.1 mL) was heated in a sealed tube for 3 d at 120 °C. After addition of H₂O to the reaction mixture, the mixture was extracted with CHCl₃ three times. The extracts were dried over K₂CO₃ and evaporated. The residue was purified by chromatography using CHCl₃–MeOH (5 : 1) as eluent to yield **26** (51 mg, 85%) as an oil; $[a]_D^{26}$ +1.22° (*c* 1.31, CHCl₃); IR (neat) 3385, 2932, 2871, 1456, 1375, 1219, 1127, 1061 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.91 (t, *J* = 6.9 Hz, 3 H), 1.20–1.65 (m, 17 H), 1.30 (s, 3 H), 1.77–1.86 (m, 1 H), 2.89–2.90 (m, 2 H), 3.20–3.36 (m, 1 H, *H*-2 or *H*-6), 3.83–3.88 (m, 1 H, –CHOH), 3.92 (s, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 14.5, 19.5, 19.9, 21.2, 24.0, 30.7, 31.7, 33.6, 38.9, 39.4, 39.9, 47.8, 50.9, 64.8, 69.5, 110.1; HRMS calcd for C₁₇H₃₃NO₄ (M⁺) 299.2460, found 299.2449.

(2S,3aS,6aS,9aS) - Decahydro - 9a - methyl - 2 - propyl - 2H - [1,3]oxazino[4,3,2-de]quinolizine $\{(-)-2-epi$ -poranthredine $\}$ (3). A mixture of 26 (51 mg, 0.17 mmol) and p-TsOH-H₂O (39 mg, 0.20 mmol) in benzene (3 mL) was refluxed for 3 h. After addition of saturated NaHCO₃ to the reaction mixture, the mixture was extracted with CHCl3 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was purified by chromatography using ethyl acetate-MeOH (10:1) as eluent to yield **3** (12 mg, 30%) as an oil; $[a]_{D}^{26}$ -42.9° (c 0.36, CHCl₃); IR (neat) 2931, 2867, 1453, 1375, 1254, 1131 cm⁻¹; ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3) \delta 0.93 (t, J = 7.1 \text{ Hz}, 3 \text{ H}, -\text{CH}_2\text{C}H_3), 1.15-$ 1.83 (m, 17 H), 1.49 (s, 3 H, CH₃-9aS), 2.35–2.46 (m, 1 H), 2.96 (t, J = 11.3 Hz, 1 H, H-6aS), 3.74–3.78 (m, 1 H, H-3aS), 4.01–4.07 (m, 1 H, H-2); ¹³C NMR (75 MHz, CDCl₃) δ 14.5, 19.6, 20.2, 20.3, 24.4, 29.0, 30.9, 34.1, 34.4, 40.2, 41.6, 44.5, 50.0, 71.5, 86.1; HRMS calcd for C₁₅H₂₇NO (M⁺) 237.2093, found 237.2102.

(4RS,6S,10S)-1-Aza-4-(iodomethyl)-3-oxa-10-methyl-2-enylbicyclo-[4.4.0]decan-2-one (27). Three drops of 4% OsO₄ solution were added to a solution 14 (89 mg, 0.27 mmol) in a mixture of dioxane (2 mL) and H₂O (2 mL) and the mixture was stirred at room temperature for 10 min. NaIO₄ (57 mg, 0.27 mmol) was added to the mixture, which was stirred for 15 min. NaIO₄ (57 mg, 0.27 mmol) was again added to the mixture, which was stirred for 1 h. The reaction was quenched with 10% sodium thiosulfate, and the resulting mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated. To a solution of the residue in toluene (3 mL) was added RhCl(PPh₃)₃ (270 mg, 0.3 mmol). The reaction mixture was refluxed overnight and filtered through Celite. The filtrate was evaporated. Ethanol was added to the residue and the mixture was filtered through Celite. The filtrate was evaporated to leave an oil, which was purified by chromatography using *n*-hexane–ethyl acetate (3 : 1) as eluent to yield **27** (39 mg, 48%) as a diasteromeric mixture; IR (neat) 2936, 1686, 1428, 1290, 1234, 1136 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.19–1.22 (m, 3 H, –CH₃), 1.38–2.2.38 (m, 8 H), 3.15–3.72 (m, 3H, *H*-6S, – CH₂I), 4.08–4.71 (m, 1 H, *H*-4), ¹³C NMR (75 MHz, CDCl₃) δ 5.34, 6.27, 15.9, 16.4, 18.1, 19.1, 29.7, 29.9, 30,8, 33.1, 33.3, 33.4, 33.6, 35.9, 44.5, 45.1, 46.3, 46.9, 47.8, 48.8, 72.3, 72.5, 73.9, 152.3; HRMS calcd for C₁₀H₁₆NO₂I (M⁺) 309.0226, found 309.0222.

tert-Butyl (2*R*,6*S*)-2-Methyl-6-(2-propenyl)piperidinecarboxylate (28). Zinc (55 mg, 0.842 mmol) was added to a solution of 27 (48 mg, 0.15 mmol) in a mixture of THF (1 mL), acetic acid (40 µL), and H₂O (40 µL) at 0 °C. The reaction mixture was stirred at room temperature for 5 h and filtered through Celite. 2 N NaOH was added to the filtrate. To the basic solution was added Boc₂O (0.16 mL, 0.70 mmol). The mixture was stirred at room temperature overnight. 20% KHSO4 was added to the reaction mixture and the mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated. The residue was purified by chromatography using n-hexane–ethyl acetate (60 : 1) as eluent to yield **28** (28 mg, 80%); $[a]_{D}^{26} - 24.2^{\circ}$ (c 0.23, CHCl₃), lit.¹⁵ $[a]_{D}^{26}$ -24.67° (c 3.1, CHCl₃); IR (neat) 2944, 1689, 1368, 1176 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.22 (d, J = 6.6 Hz, 3 H, CH₃-6S), 1.47 (s, 9 H), 1.53–1.91 (m, 6 H), 2.13–2.24 (m, 1 H), 2.42–2.47 (m, 1 H), 3.83–3.87 (m, 1 H, H-2 or H-6), 3.97 (m, 1 H, H-2 or H-6), 5.00–5.09 (m, 2 H), 5.70–5.82 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.3, 21.2, 22.6, 26.8, 28.8, 39.4, 47.1, 51.2, 79.1, 116.6, 136.3, 155.2; HRMS calcd for C₁₄H₂₅NO₂ (M⁺) 239.1885, found 239.1885.

tert-Butyl (2R,6R)-2-Methyl-6-undecylpiperidinecarboxylate (29). Two drops of 4% OsO₄ solution were added to a solution of 28 (49 mg, 0.21 mmol) in a mixture of dioxane (1.5 mL) and H_2O (1.5 mL) and the reaction was stirred at room temperature for 10 min. NaIO₄ (44 mg, 0.21 mmol) was added to the mixture, which was stirred for 15 min. NaIO₄ (44 mg, 0.21 mmol) was again added to the mixture, which was stirred for 1 h. The reaction was quenched with 10% sodium thiosulfate, and the resulting mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated to leave the aldehyde. n-BuLi (0.19 mL, 0.31 mmol) was added to a mixture of n-nonyltriphenylphosphonium bromide (193 mg, 0.41 mmol) in THF (1.5 mL) at 0 °C and the mixture was stirred at the same temperature for 30 min. A solution of the aldehyde in THF (1 mL) was added to the mixture. After being stirred at room temperature for 5 h, the mixture was quenched with saturated NH₄Cl at 0 °C and extracted with CH2Cl2 three times. The extracts were dried and evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (100 : 1) as eluent to yield olefin (48 mg, 66%). A suspension of the olefin (36 mg, 0.1 mmol) and Pd(OH)₂ (10 mg) in methanol (2 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified with chromatography using *n*-hexane–ethyl acetate (100 : 1) as eluent to yield 29 (35 mg, 97%) as an oil;

 $[a]_{D}^{26} - 26.3^{\circ}$ (*c* 1.58, CHCl₃); IR (neat) 2927, 2855, 1690, 1461, 1369 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.88 (t, *J* = 6.5 Hz, 3 H, -(CH₂)₁₀CH₃), 1.22-126 (m, 23 H), 1.46 (s, 9 H), 1.49-1.85 (m, 6 H), 3.78-3.79 (m, 1 H, *H*-2*R* or *H*-6*R*), 3.91-3.93 (m, 1 H, *H*-2*R* or *H*-6*R*); ¹³C NMR (75 MHz, CDCl₃) δ 13.7, 14.1, 20.8, 22.6, 23.1, 26.8, 27.1, 28.5, 29.3, 29.59, 29.63, 31.8, 34.3, 46.8, 51.6, 78.5, 155.0; HRMS calcd for C₂₂H₄₃NO₂ (M⁺) 353.3294, found 353.3306.

(-)-Solenopsin A (6). Trifluoroacetic acid (1 mL) was added to a solution of **29** (35 mg, 0.10 mmol) in CH₂Cl₂ (1 mL) and the reaction mixture was stirred at room temperature for 2 h. The mixture was evaporated and the residue was diluted with 2 N NaOH. The basic solution was extracted with CH₂Cl₂ three times. The extracts were dried over K₂CO₃ and evaporated. The residue was purified with chromatography using CHCl₃-methanol (5 : 1) as eluent to yield **6** (21 mg, 84%) as an oil; $[a]_{26}^{26} - 1.3^{\circ}$ (*c* 0.94, CH₃OH), lit.^{7c} $[a]_{20}^{20} - 1.3^{\circ}$ (*c* 1.3, CH₃OH); IR (neat) 2924, 2853, 1460 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.88 (t, *J* = 6.5 Hz, 3 H, -(CH₂)₁₀CH₃), 1.07 (d, *J* = 6.5 Hz, 3 H), 1.19–1.64 (m, 26 H), 2.85–2.89 (m, 1 H, *H*-2*R* or *H*-6*R*), 3.03–3.08 (m, 1 H, *H*-2*R* or *H*-6*R*); ¹³C NMR (75 Hz, CDCl₃) δ 14.1, 19.5, 21.2, 22.7, 26.4, 29.3, 29.6, 29.7, 30.7, 31.9, 32.9, 34.0, 45.7, 50.7.

tert-Butyl (2S,6S)-8-(2-Oxopropyl)-2-prop-2-enylpiperidinecarboxylate (31). A suspension of PdCl₂ (4 mg, 23.6 µmol) and CuCl (23 mg, 0.23 mmol) in a solution of DMF and H_2O (7:1) (0.3 mL) was stirred under oxygen atmosphere at room temperature for 1 h. A solution of 14 (79 mg, 0.24 mmol) in DMF and $H_2O(7:1)(0.1 \text{ mL})$ was added to the reaction mixture. After being stirred at room temperature overnight, the mixture was quenched with 20% KHSO₄ and extracted with ether three times. The extracts were successively washed with saturated NaHCO₃ and brine, dried, and evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (3 : 1) as eluent to yield 30 (71 mg, 86%). Zinc (22 mg, 0.337 mmol) was added to a solution of 30 (66 mg, 0.19 mmol) in a mixture of THF (0.5 mL), acetic acid (20 μ L), and H₂O (20 μ L) at 0 °C and the reaction mixture was vigorously stirred at room temperature for 1 h. The mixture was filtered through Celite. 2 N NaOH was added to the filtrate. The basic solution was extracted with CH₂Cl₂ three times. The extracts were dried over K_2CO_3 and evaporated. To a solution of the residue in THF (1 mL) and H₂O (1 mL) were added K₂CO₃ (35 mg, 0.27 mmol) and Boc_2O (79 μ L, 0.34 mmol). The mixture was stirred at room temperature overnight. 20% KHSO₄ was added to the reaction mixture and the mixture was extracted with CH₂Cl₂ three times. The extracts were washed with brine, dried and evaporated. The residue was purified by chromatography using nhexane-ethyl acetate (10:1) as eluent to yield 31 (43 mg, 81%) as an oil; $[a]_{D}^{29}$ +19.4° (c 1.07, CHCl₃); IR (neat) 2942, 1687, 1389, 1253, 1172, 1116 cm⁻¹; ¹H NMR (300 MHz, CDCl₃)δ 1.44 (s, 9 H), 1.61-1.79 (m, 6 H), 2.16 (s, 3 H. -COCH₃), 2.18-2.21 (m, 1 H), 2.24–2.48 (m, 1 H), 2.59 (dd, J = 15.9, 9.1 Hz, 1 H), 2.87–2.94 (m, 1 H), 3.86-3.88 (m, 1 H), 4.17-4.21 (m, 1 H), 4.99-5.08 (m, 2 H), 5.74–5.76 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 14.3, 23.6, 25.4, 28.7, 30.4, 38.7, 47.7, 48.8, 51.9, 79.6, 116.7, 135.8, 155.0, 207.0; HRMS calcd for C₁₆H₂₇NO₃ (M⁺) 281.1991, found 281.1990.

tert-Butyl (2*S*,6*S*)-8-(2-Oxopropyl)-2-(4-oxobutyl)piperidinecarboxylate (32). Two drops of 4% OsO₄ solution were added to a solution of 31 (68 mg, 0.24 mmol) in a mixture of dioxane (1.5 mL) and H₂O (1.5 mL) and the mixture was stirred at room temperature for 10 min. NaIO₄ (52 mg, 0.24 mmol) was added to the mixture, which was stirred for 15 min. NaIO₄ (52 mg, 0.24 mmol) was again added to the mixture. After 1 h, sodium thiosulfate was added, and the mixture was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated to leave the aldehyde. (Triphenylphosphranylidene)acetaldehyde (147 mg, 0.482 mmol) was added to a solution of the aldehyde in toluene (2.5 mL.). After being refluxed for 9 h, the mixture was evaporated. The residue was diluted with ether and the resulting solution was filtered through Celite. The filtrated was evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (5 : 1) as eluent to yield α , β -unsaturated aldehyde (45 mg, 60%). A suspension of the aldehyde (45 mg, 0.15 mmol) and Pd(OH)₂ (10 mg) in ethyl acetate (2 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (5:1) as eluent to yield **32** (44 mg, 98%) as an oil; $[a]_{D}^{28}$ +0.68° (c 0.98, CHCl₃); IR (neat) 2935, 2865, 1717, 1685, 1367, 1252, 1171 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.43 (s, 9 H), 1.48–1.78 (m, 10 H), 2.15 (s, 3 H), 2.40–2.50 (m, 2 H), 2.56-2.64 (m, 1 H), 2.96-3.01 (m, 1 H), 3.88-3.91 (m, 1 H), 4.07 (m, 1 H), 9.75–9.77 (m, 1 H, –CHO); ¹³C NMR (75 MHz, CDCl₃) δ 19.4, 22.3, 25.5, 26.8, 28.7, 30.4, 32.7, 43.8, 47.7, 48.4, 52.5, 79.6, 155.2, 202.5, 206.9; HRMS calcd for C₁₇H₂₉NO₄ (M⁺) 311.2097, found 311.2094.

13-Azatricyclo[7.3.1.0(5,13)]tridecan-3-one (33). Trifluoroacetic acid (1.5 mL) was added to a solution of 32 (62 mg, 0.20 mmol) in CH₂Cl₂ (1.5 mL) and the reaction mixture was stirred at room temperature for 1 h. The mixture was evaporated and the residue was diluted with saturated NaHCO₃. The resulting basic solution was extracted with CH₂Cl₂ three times. The extracts were dried and evaporated. A mixture of the residue and CSA (139 mg, 0.60 mmol) in toluene (9 mL) was refluxed for 2 h. Saturated NaHCO₃ was added to the mixture. The mixture was extracted with CH₂Cl₂ three times. The extracts dried and evaporated. The residue was purified by chromatography using $CHCl_3$ -methanol (30 : 1) as eluent to yield 33 (20 mg, 52%) as a solid; mp. 80-81 °C, lit.8a mp. 81-83 °C; IR (KBr) 2931, 2866, 1708, 1435, 1336, 1253 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.19–2.05 (m, 14 H), 2.79 (t, J = 13.1 Hz, 3 H), 3.24 (br d, J =12.4 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 19.2, 30.1, 34.1, 40.7, 48.4, 58.9, 211.1; HRMS calcd for C₁₂H₁₉NO (M⁺) 193.1467, found 193.1460.

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