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 (2*R*,6*R*)-*trans*-solenopsin A (**5**),[7] a constituent of fire-ant venom, and precoccinelline (**6**),[8] a ladybug defense alkaloid starting from **1** (Fig. 1).

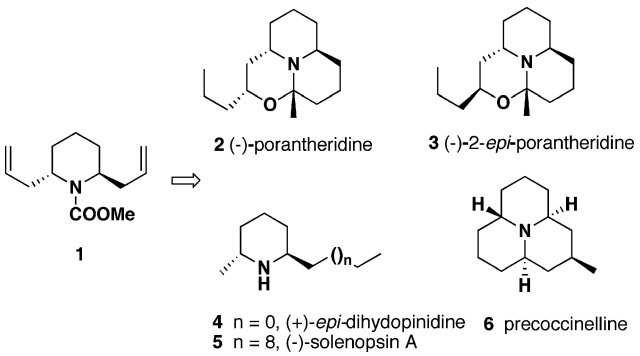
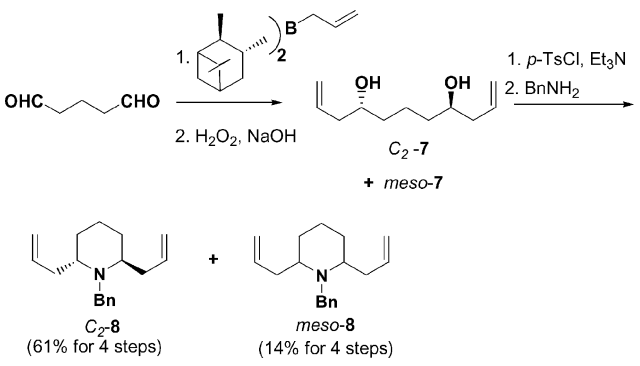


Fig. 1

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$_2$BOMe} and allylmagnesium bromide, followed by oxidation with alkaline H_2O_2 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).



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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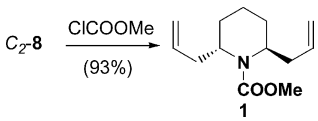
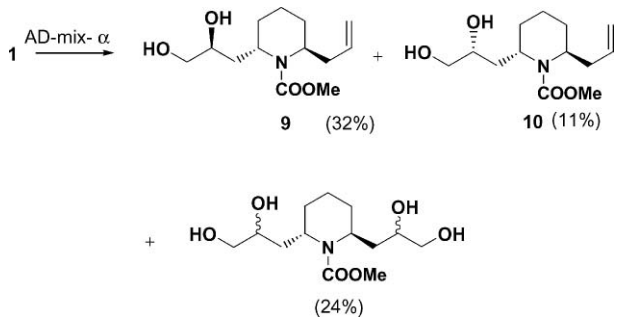
recovery of C_2-**8**. However, the use of chloroform, a more polar solvent, afforded the title carbamate **1** in 59% yield together with the recovery of C_2-**8** (35%). Finally, methyl carbamate **1** was obtained in 93% yield by a reaction in a sealed tube at 90 °C for 48 h. On the other hand, carbamation 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 α,α′-disubstituted allyl groups in the piperidine ring (Scheme 2).



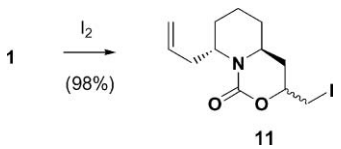
Scheme 2

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]



Scheme 3

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).



Scheme 4

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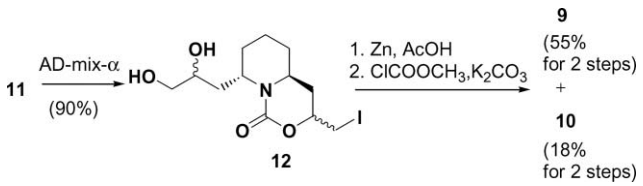
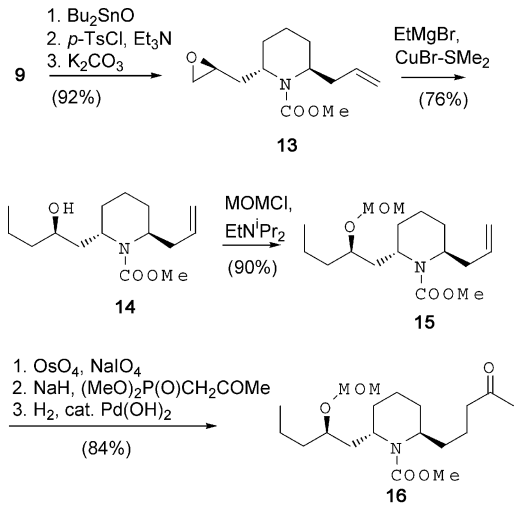
Having the promising piperidine **11**, the Sharpless asymmetric dihydroxylation (AD-mix-α) of **11** was conducted to provide the diastereomeric mixtures of diols **12** in 90% yield. Deprotection of the oxazolidine was accomplished by the exposure of **12** to zinc in acetic acid to give the allylpiperidine, 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).



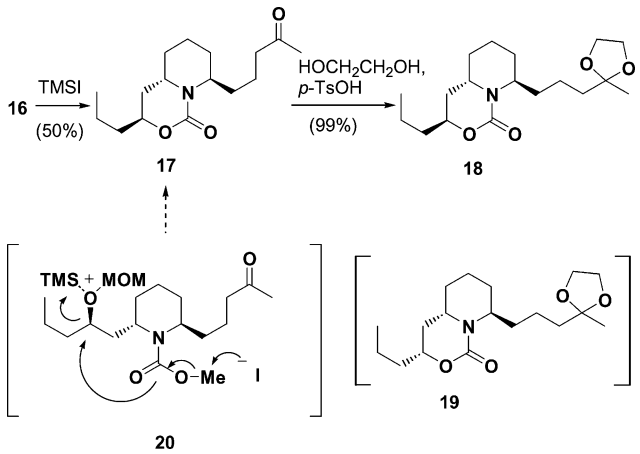
Scheme 5

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–Me_2S 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. OsO_4 in combination with $NaIO_4$ 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).



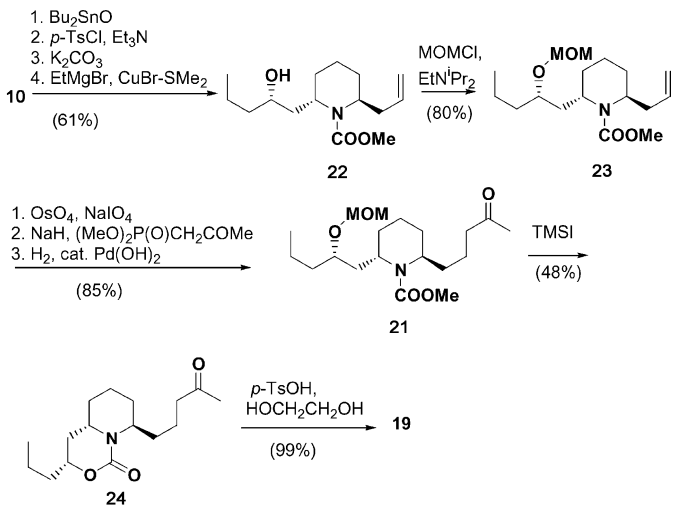
Scheme 6

The decarbamation of **16** with iodotrimethylsilane[11] unpredictably led to the production of the oxazolidinone **17** in 50% yield. At this stage, the stereochemistry (C_3 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]



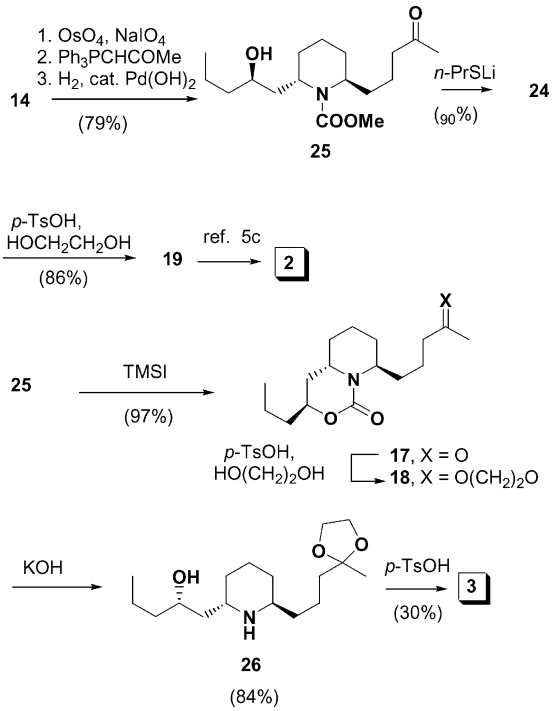
Scheme 7

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.



Scheme 8

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-2-propanone) was used in place of the Horner–Wadsworth–Emmons reagent (dimethyl 2-oxopropylphosphonate). The decarbamation of **25** with Corey's reagent *n*-PrSLi[13] 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 2-propanol at 120 °C in a sealed tube[14] 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

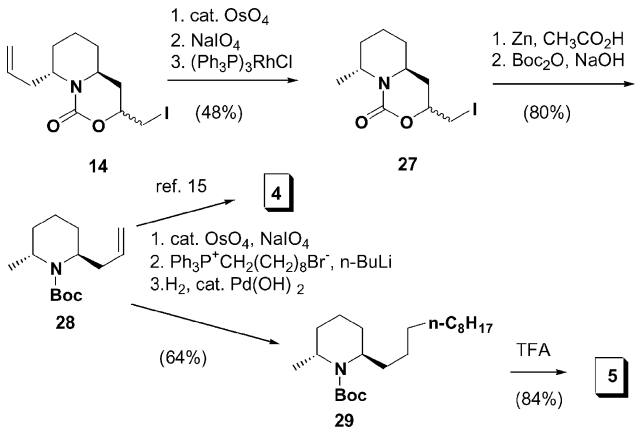


Scheme 9

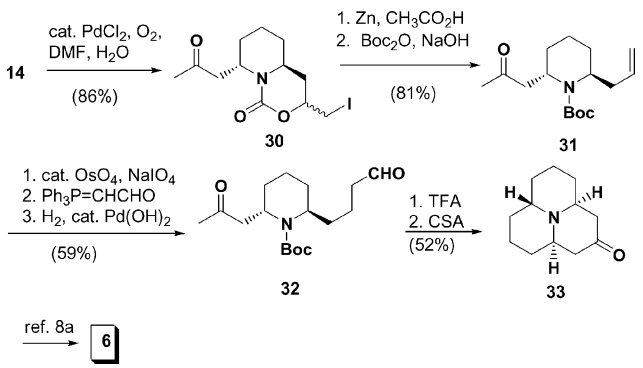
to **2** and **3** based on *n*-PrSLi and TMSI-mediated oxzolidinone ring formation of **25**, respectively, in a short step.

In addition, we focused on the synthesis of 2,6-*trans*-dialkylpiperidines such as (+)-*epi*-dihydropinidine (**4**), and (2*R*,6*R*)-*trans*-solenopsin A (**5**). OsO_4-Mediated dihydroxylation of **14** followed by an oxidative cleavage of the resulting diol with $NaIO_4$ provided the aldehyde, which was decarbonylated with $(Ph_3P)_3RhCl$ 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 Boc_2O 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. OsO_4 in combination with $NaIO_4$ 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 2,6-disubstituted piperidine **29** in 64% yield. *N*-Deprotection of **29** by treatment with trifluoroacetic acid (TFA) in CH_2Cl_2 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 two-step treatment (deprotection of the oxazolidine and *N*-protection) of **30** gave the allylpiperidine **31** in 81% yield. Treatment of **32** with cat. OsO_4 in combination with $NaIO_4$ 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).



Scheme 10



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. ^{1}H NMR and ^{13}C 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.

(2*S*,6*S*)-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 (−)-Ipc$_2$BOMe (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 °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% H_2O_2 (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. Et_3N (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 K_2CO_3 and evaporated. The residue was purified by medium-pressure chromatography using *n*-hexane–ethyl acetate (80 : 1) as eluent to yield C_2-**8** (973 mg, 61%) and *meso*-**8** (223 mg, 14%) as oils. C_2-**8**: $[a]_D^{26}$ −4.87° (*c* 1.03, $CHCl_3$); IR (neat) 2928, 1559, 1447 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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$_6$H$_5$), 4.95–5.02 (m, 4 H, 2 × CH=CH_2), 5.68–5.81 (m, 2 H, 2 × –CH=CH$_2$), 7.20–7.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (2*S*,6*S*)-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 $CHCl_3$ (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 H_2O 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, $CHCl_3$); IR (neat) 2949, 1734, 1700, 1653, 1636, 1559, 1443, 1395 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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, COOCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 23.2, 39.1, 51.7, 52.3, 116.8, 135.9, 156.4; HRMS calcd for $C_{13}H_{21}NO_2$ (M^+) 223.1572, found 223.1576.

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 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 H_2O (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*-hexane–ethyl 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**; $[\alpha]_D^{26}$ −27.2° (*c* 0.98, $CHCl_3$); IR (neat) 3415, 2947, 1673, 1453, 1396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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*-2*S* or *H*-6*S*), 3.61–3.73 (m, 1 H, *H*-2*S* or *H*-6*S*), 3.71 (s, 3 H), 3.81–3.84 (m, 1 H, –C*H*OH), 4.00–4.07 (m, 2 H, –CH_2OH), 5.03–5.11 (m, 2 H), 5.67–5.81 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{13}H_{23}NO_4$ (M^+) 257.1627, found 257.1616. **10**; $[\alpha]_D^{26}$ +2.34° (*c* 1.01, $CHCl_3$); IR (neat) 3418, 2948, 1672, 1452, 1396, 1370, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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*-2*S*, *H*-6*S*), 3.67 (s, 3 H), 3.69–3.70 (m, 1 H, –C*H*OH), 4.04–4.14 (m, 2 H, –CH_2OH), 4.58 (br s, 1 H), 4.98–5.23 (m, 2 H), 5.60–5.74 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{23}NO_4$ (M^+) 257.1627, found 257.1625.

(4*RS*,6*S*,10*S*)-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 CH_2Cl_2 (10 mL) at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated Na_2SO_3 and the resulting mixture was extracted with CH_2Cl_2 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, $CDCl_3$) 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*-6*S*), 5.02–5.09 (m, 2 H), 5.68–5.85 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{18}NO_2I$ (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 H_2O (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 diasteromeric 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 μL), and H_2O (70 μL) 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 $CHCl_3$ three times. The extracts were dried over K_2CO_3 and evaporated. To a solution of the residue in THF (2 mL) and H_2O (2 mL) were added K_2CO_3 (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% $KHSO_4$ and extracted with CH_2Cl_2 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 (2*S*,6*S*)-2-[(2*R*)-2-Hydroxypentyl]-6-prop-2-enylpiperidinecarboxylate (14). *n*-Bu_2SnO (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 CH_2Cl_2 (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 CH_2Cl_2 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 K_2CO_3 (77 mg, 0.56 mmol) at 0 °C. After 1 h of stirring at room temperature and saturated NH_4Cl (5 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 three times. The extracts were dried and evaporated to yield **13** (125 mg, 92%) as an oil. To a slurry of CuBr–SMe_2 (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 NH_4Cl. 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; $[\alpha]_D^{26}$ −28.8° (*c* 1.94, $CHCl_3$); IR (neat) 3451, 2953, 1674, 1450, 1368, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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(2*R*)), 5.02–5.11 (m, 2 H), 5.68–5.82 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{27}NO_3$ (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 $CHCl_3$ (3 mL) were successively added *N*,*N*-diiopropylethylamine (0.2 mL, 1.12 mmol) and chloromethyl methyl ether (77.8 μL, 1.03 mmol) at 0 °C and the reaction mixture was refluxed overnight. To the reaction mixture was

added 20% $KHSO_4$ and the mixture was extracted with CH_2Cl_2 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; $[\alpha]_D^{29}$ −16.3° (*c* 0.98, $CHCl_3$); IR (neat) 2951, 1694, 1448, 1328, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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), –OCH_2OCH_3, 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, –OCH_2OCH_3), 4.66 (d, $J = 7.1$ Hz, 1 H, –OCH_2OCH_3), 5.01–5.10 (m, 2 H), 5.70–5.84 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{31}NO_4$ (M^+) 313.2253, found 313.2250.

(2*S*,6*S*) - Methyl 2 - ((*R*) - 2 - (Methoxymethoxy)pentyl) - 6 - (4 - oxopentyl)piperidine-1-carboxylate (16). Three drops of an aqueous 4% OsO_4 solution were added to a solution of **15** (96 mg, 0.3 mmol) in dioxane (1.5 mL) and H_2O (1.5 mL) and then the reaction mixture was stirred for 10 min at room temperature. After $NaIO_4$ (65 mg, 0.30 mmol) was added to mixture, the reaction mixture was stirred for 15 min. Again $NaIO_4$ (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 CH_2Cl_2 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 NH_4Cl solution was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 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; $[\alpha]_D^{26}$ −24.0° (*c* 0.81, $CHCl_3$); IR (neat) 2949, 1697, 1448, 1369, 1099, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.4$ Hz, 3 H, –C*H*$_3$), 1.23–1.78 (m, 15 H), 1.90–1.99 (m, 1 H), 2.14 (s, 3 H, –COC*H*$_3$), 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, $J = 7.1$ Hz, 1 H), 4.66 (d, $J = 7.1$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{35}NO_5$ (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 CH_3CN (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 CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was chromatographed using $CHCl_3$ as eluent to give the **17** (14 mg, 50%) as an oil; $[\alpha]_D^{26}$ −57.6° (*c* 0.68, $CHCl_3$); IR (neat) 2934, 1681, 1431, 1363, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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*); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{28}NO_3$ (M^+) 281.1991, found 281.2001.

(3*S*,4*aS*,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 (18). A mixture of **17** (82 mg, 0.29 mmol), ethyleneglycol (81.3 μL, 1.46 mmol), and *p*-TsOH–H_2O (11 mg) in benzene (5 mL) using a Dean–Stark apparatus was refluxed overnight. Saturated $NaHCO_3$ was added to the mixture. The mixture was extracted with CH_2Cl_2 three times. The extracts were dried and evaporated. The residue was purified by chromatography using $CHCl_3$ as eluent to yield **18** (87 mg, 92%) as an oil; $[\alpha]_D^{26}$ −56.3° (*c* 1.18, $CHCl_3$); IR (neat) 2936, 2872, 1682, 1433, 1375, 1284, 1229, 1120, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 6.3$ Hz, 3 H), 1.30 (s, 3 H, –C–C*H*$_3$), 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. –O*CH*$_2$*CH*$_2$O–), 4.19 (m, 1 H), 4.50 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{31}NO_4$ (M^+) 325.2253, found 325.2246.

(2*S*,6*S*)-Methyl 2-Allyl-6-((*S*)-2-hydroxypentyl)piperidine-1-carboxylate (22). According to the same procedure described for preparation of **14**, **22** was prepared from **10** in 61% yield. An oil; $[\alpha]_D^{28}$ −28.8° (*c* 0.96, $CHCl_3$); IR (neat) 3452, 2953, 1675, 1450, 1368, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J =$ 6.9 Hz, 3 H, –C*H*$_3$), 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, –C*HOH*), 5.02–5.09 (m, 2 H), 5.66–5.80 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{27}NO_3$ (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; $[\alpha]_D^{29}$ −17.1° (*c* 1.02, $CHCl_3$); IR (neat) 2949, 1698, 1446, 1327, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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, –OCH_2OCH_3), 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, –OCH_2OCH_3), 5.01–5.10 (m, 2 H), 5.70–5.83 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{31}NO_4$ (M^+) 313.2253, found 313.2260.

(2*S*,6*S*) - Methyl 2 - ((*S*) - 2 - (Methoxymethoxy)pentyl) - 6 - (4-oxopentyl)piperidine-1-carboxylate (21). According to the same procedure described for preparation of **16**, **21** was prepared from **23** in 79% yield. An oil; $[\alpha]_D^{26}$ −27.0° (*c* 0.97, $CHCl_3$); IR (neat) 2949, 1697, 1447, 1368, 1099, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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, –COC*H*$_3$), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{35}NO_5$ (M^+) 357.2515, found 357.2513.

(3*R*,4*aS*,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; $[\alpha]_D^{26}$ +9.67° (*c* 0.73, $CHCl_3$); IR (neat) 2936, 2870, 1708, 1674, 1433, 1363, 1289, 1129 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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*); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{28}NO_3$ (M^+) 281.1991, found 281.2000.

(3*R*,4*aS*,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; $[\alpha]_D^{26}$ +10.0° (*c* 0.25, $CHCl_3$), lit.[5c] $[\alpha]_D^{23}$ +10.3° (*c* 1.96, $CHCl_3$); IR (neat) 2934, 1682, 1429, 1372, 1286, 1229, 1120, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, $J = 6.6$ Hz, 3 H), 1.30 (s, 3 H, –CC*H*$_3$), 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, –OC*H*$_2$C*H*$_2$O–), 4.04–4.10 (m, 1 H), 4.59 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{31}NO_4$ (M^+) 325.2253, found 325.2240.

Methyl (2*S*,6*S*)-2-[(2*R*)-2-Hydroxypentyl]-6-(4-oxopentyl) piperidinecarboxylate (25). Three drops of 4% OsO_4 solution were added to a solution of **14** (77 mg, 0.29 mmol) in a mixture of dioxane (1.5 mL) and H_2O (1.5 mL) and the solution was stirred at room temperature for 10 min. $NaIO_4$ (61 mg, 0.29 mmol) was added to the solution, which was stirred for 15 min. $NaIO_4$ (61 mg, 0.29 mmol) was again added to the mixture. After 1 h, 10% sodium thiosulfate was added, and extracted with CH_2Cl_2 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 CH_2Cl_2 (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; $[\alpha]_D^{26}$ −39.2° (*c* 0.74, $CHCl_3$); IR (neat) 3445, 2950, 2870, 1677, 1452, 1370, 1190, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.1$ Hz, 3 H), 1.25–1.96 (m, 16 H), 2.14 (s, 3 H, –COC*H*$_3$), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{31}NO_4$ (M^+) 313.2253, found 313.2249.

(4*R*,6*S*,10*S*)-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% NH_3 solution was added to the reaction mixture and the mixture was extracted with ether ten times. The extracts were dried over K_2CO_3 and evaporated. The residue was purified by chromatography using $CHCl_3$ as eluent to yield **24** (63 mg, 90%) as an oil; $[\alpha]_D^{26}$ +9.67° (*c* 0.74, $CHCl_3$). All spectra were in accordance with those of **24** prepared from **21**.

(3*S*,4*aS*,8*S*)-Hexahydro-8-(4-oxopentyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (17) from 25. Iodotrimethylsilane (71 μL, 0.5 mmol) was added to a solution of **25** (71 mg, 0.23 mmol) in CH_3CN (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 CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was chromatographed using $CHCl_3$ 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-((2*S*,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 H_2O to the reaction mixture, the mixture was extracted with $CHCl_3$ three times. The extracts were dried over K_2CO_3 and evaporated. The residue was purified by chromatography using $CHCl_3$–MeOH (5 : 1) as eluent to yield **26** (51 mg, 85%) as an oil; $[\alpha]_D^{26}$ +1.22° (*c* 1.31, $CHCl_3$); IR (neat) 3385, 2932, 2871, 1456, 1375, 1219, 1127, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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, –C*H*OH), 3.92 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{33}NO_4$ (M^+) 299.2460, found 299.2449.

(2*S*,3*aS*,6*aS*,9*aS*)-Decahydro-9*a*-methyl-2-propyl-2*H*-[1,3]-oxazino[4,3,2-*de*]quinolizine {(−)-2-*epi*-poranthredine} (3). A mixture of **26** (51 mg, 0.17 mmol) and *p*-TsOH–H_2O (39 mg, 0.20 mmol) in benzene (3 mL) was refluxed for 3 h. After addition of saturated $NaHCO_3$ to the reaction mixture, the mixture was extracted with $CHCl_3$ 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; $[\alpha]_D^{26}$ −42.9° (*c* 0.36, $CHCl_3$); IR (neat) 2931, 2867, 1453, 1375, 1254, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.1$ Hz, 3 H, –CH_2C*H*$_3$), 1.15–1.83 (m, 17 H), 1.49 (s, 3 H, C*H*$_3$-9a*S*), 2.35–2.46 (m, 1 H), 2.96 (t, $J = 11.3$ Hz, 1 H, *H*-6a*S*), 3.74–3.78 (m, 1 H, *H*-3a*S*), 4.01–4.07 (m, 1 H, *H*-2); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{27}NO$ (M^+) 237.2093, found 237.2102.

(4*RS*,6*S*,10*S*)-1-Aza-4-(iodomethyl)-3-oxa-10-methyl-2-enyl-bicyclo-[4.4.0]decan-2-one (27). Three drops of 4% OsO_4 solution were added to a solution **14** (89 mg, 0.27 mmol) in a mixture of dioxane (2 mL) and H_2O (2 mL) and the mixture was stirred at room temperature for 10 min. $NaIO_4$ (57 mg, 0.27 mmol) was added to the mixture, which was stirred for 15 min. $NaIO_4$ (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 CH_2Cl_2 three times. The extracts were dried and evaporated. To a solution of the residue

in toluene (3 mL) was added $RhCl(PPh_3)_3$ (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, $CDCl_3$) δ 1.19–1.22 (m, 3 H, –C*H*$_3$), 1.38–2.2.38 (m, 8 H), 3.15–3.72 (m, 3H, *H*-6*S*, –C*H*$_2$I), 4.08–4.71 (m, 1 H, *H*-4), ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{10}H_{16}NO_2I$ (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 H_2O (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 Boc_2O (0.16 mL, 0.70 mmol). The mixture was stirred at room temperature overnight. 20% $KHSO_4$ was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 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%); $[\alpha]_D^{26}$ −24.2° (*c* 0.23, $CHCl_3$), lit.[15] $[\alpha]_D^{26}$ −24.67° (*c* 3.1, $CHCl_3$); IR (neat) 2944, 1689, 1368, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H, C*H*$_3$-6*S*), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{14}H_{25}NO_2$ (M^+) 239.1885, found 239.1885.

***tert*-Butyl (2*R*,6*R*)-2-Methyl-6-undecylpiperidinecarboxylate (29).** Two drops of 4% OsO_4 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. $NaIO_4$ (44 mg, 0.21 mmol) was added to the mixture, which was stirred for 15 min. $NaIO_4$ (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 CH_2Cl_2 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 NH_4Cl at 0 °C and extracted with CH_2Cl_2 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; $[\alpha]_D^{26}$ −26.3° (*c* 1.58, $CHCl_3$); IR (neat) 2927, 2855, 1690, 1461, 1369 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3 H, –$(CH_2)_{10}$C*H*$_3$), 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*); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{22}H_{43}NO_2$ (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 CH_2Cl_2 (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 CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was purified with chromatography using $CHCl_3$–methanol (5 : 1) as eluent to yield **6** (21 mg, 84%) as an oil; $[\alpha]_D^{26}$ −1.3° (*c* 0.94, CH_3OH), lit.[7c] $[\alpha]_D^{20}$ −1.3° (*c* 1.3, CH_3OH); IR (neat) 2924, 2853, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3 H, –$(CH_2)_{10}$C*H*$_3$), 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*); ^{13}C NMR (75 Hz, $CDCl_3$) 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 (2*S*,6*S*)-8-(2-Oxopropyl)-2-prop-2-enylpiperidinecarboxylate (31).** A suspension of $PdCl_2$ (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 mL) was added to the reaction mixture. After being stirred at room temperature overnight, the mixture was quenched with 20% $KHSO_4$ and extracted with ether three times. The extracts were successively washed with saturated $NaHCO_3$ 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 μL), and H_2O (20 μL) 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 CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. To a solution of the residue in THF (1 mL) and H_2O (1 mL) were added K_2CO_3 (35 mg, 0.27 mmol) and Boc_2O (79 μL, 0.34 mmol). The mixture was stirred at room temperature overnight. 20% $KHSO_4$ was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried and evaporated. The residue was purified by chromatography using *n*-hexane–ethyl acetate (10 : 1) as eluent to yield **31** (43 mg, 81%) as an oil; $[\alpha]_D^{29}$ +19.4° (*c* 1.07, $CHCl_3$); IR (neat) 2942, 1687, 1389, 1253, 1172, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 1.61–1.79 (m, 6 H), 2.16 (s, 3 H. –COC*H*$_3$), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{27}NO_3$ (M^+) 281.1991, found 281.1990.

***tert*-Butyl (2*S*,6*S*)-8-(2-Oxopropyl)-2-(4-oxobutyl)piperidinecarboxylate (32).** Two drops of 4% OsO_4 solution were added

to a solution of **31** (68 mg, 0.24 mmol) in a mixture of dioxane (1.5 mL) and H_2O (1.5 mL) and the mixture was stirred at room temperature for 10 min. $NaIO_4$ (52 mg, 0.24 mmol) was added to the mixture, which was stirred for 15 min. $NaIO_4$ (52 mg, 0.24 mmol) was again added to the mixture. After 1 h, sodium thiosulfate was added, and the mixture was extracted with CH_2Cl_2 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; $[\alpha]_D^{28}$ +0.68° (*c* 0.98, $CHCl_3$); IR (neat) 2935, 2865, 1717, 1685, 1367, 1252, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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, –C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{29}NO_4$ (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 CH_2Cl_2 (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 $NaHCO_3$. The resulting basic solution was extracted with CH_2Cl_2 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 $NaHCO_3$ was added to the mixture. The mixture was extracted with CH_2Cl_2 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 30.1, 34.1, 40.7, 48.4, 58.9, 211.1; HRMS calcd for $C_{12}H_{19}NO$ (M^+) 193.1467, found 193.1460.

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