HETEROCYCLES, Vol. 100, No. 1, 2020, pp. 46 - 59. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2019, Accepted, 29th August, 2019, Published online, 24th September, 2019
DOI: 10.3987/COM-19-14123

SYNTHETIC STUDIES ON MARINEOSINS BASED ON A DIRECT COUPLING REACTION OF PYRROLE AND δ-LACTONE

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Abstract – A promising precursor of marineosins A and B, unusual macrocyclic pyrrole and spiroiminal alkaloids isolated from marine microorganism has been synthesized employing a direct coupling of pyrrole and δ-lactone.

INTRODUCTION

In 2008, Fenical *et al*. disclosed the isolation of marineosins A and B, structurally novel *trans*-fused macrocyclic framework, containing a spirocyclic tetrahydropyrans-dihydropyrrole iminal moiety and two pyrroles, from cultures of the marine *Streptomyces* sp. CNQ-617 (Figure 1).[1] The marineosins were found to exhibit significant anticancer activities toward human colon carcinoma (HCT-116) (IC_{50} = 0.5 μM for marineosin A and IC_{50} = 46 μM for marineosin B). Their intriguing molecular architectures and biological activities make marineosins attractive targets for synthesis, and the synthetic studies were reported by Lindsley *et al.*,[2] Snider *et al*.[3] and Shi *et al*.[4] Shi also reported the total synthesis of the proposed structure of marineosin A and its spectroscopic data differed from that reported for the natural product.[5] Furthermore, Reynolds *et al*. reported the elucidation of the biosynthetic pathway for marineosins with the relevant gene cluster. [6] Recently, Harran *et al*. disclosed an eight-step remarkable

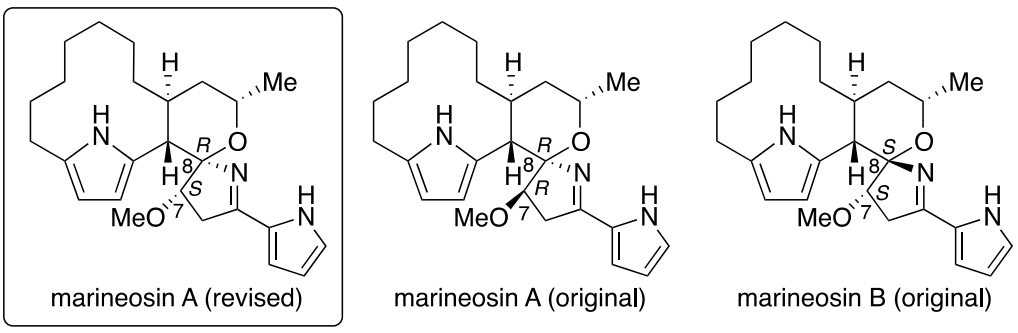
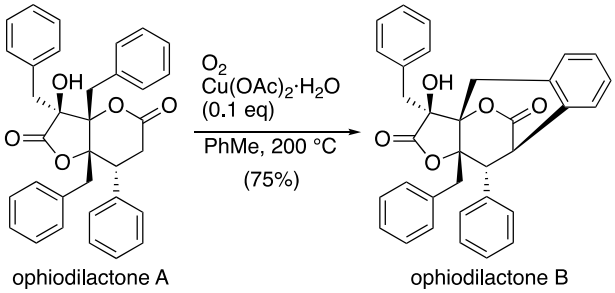


Figure 1. Revised structure of marineosin A and original structures of marineosins A and B

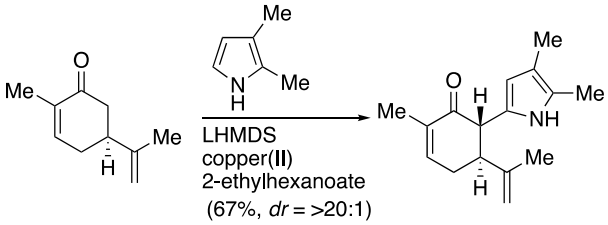
synthesis of marineosin A, together with the stereochemical reassignment of marineosin A from 7*R*,8*R* to 7*S*,8*R*.[7] Herein we report the formation of highly functionalized macrocyclic pyrrole core.

RESULTS AND DISCUSSION

Given the α-pyrrole-lactone structure, one of the most attractive and efficient approaches to marineosins is the direct coupling of a δ-lactone and a pyrrole. In the course of our synthesis of marine natural products, ophiodilactones A and B, we were interested in direct oxidative coupling reactions of C-H and Ar-H bonds. Thus, the intramolecular direct coupling reaction of ophiodilactone A with Cu(II) catalyst under oxygen afforded ophiodilactone B in a good yield (Scheme 1).[8] On the other hand, Baran *et al.* demonstrated the remarkably simple method for the direct coupling of the C-3 carbon of indoles or the C-2 carbon of pyrroles with the α-carbon of carbonyl compounds[9,10] in the presence of Cu(II) (Scheme 2). It was proposed that the coupling proceeds through single-electron transfer of a metal-chelated complex to form a α-keto radical and subsequent nucleophilic attack of indoles or pyrroles to generate a radical anion involving the reduction of Cu(II) to Cu(0).

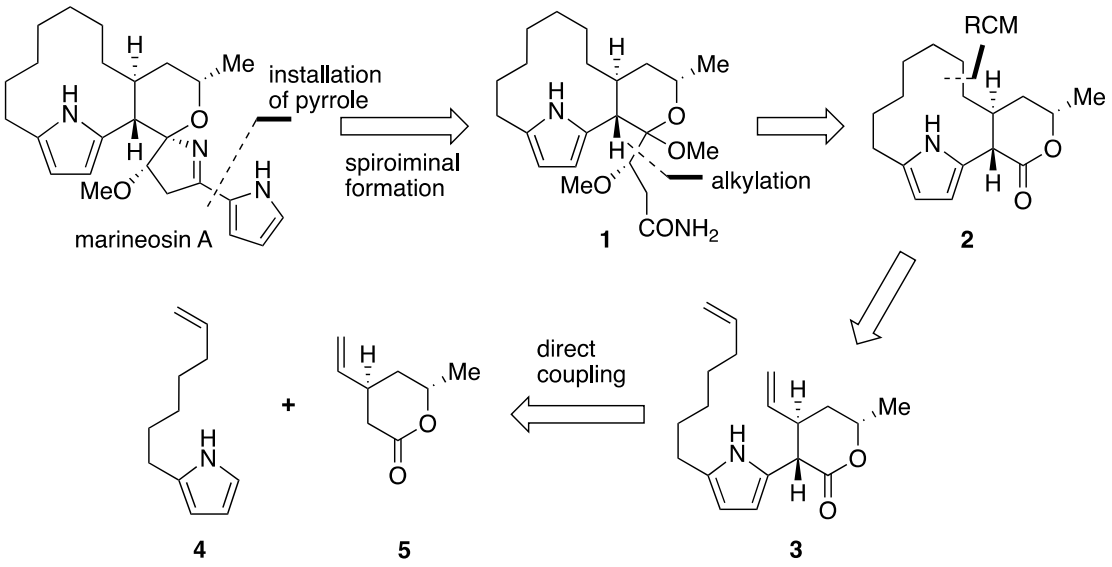


Scheme 1. Synthesis of ophiodilactone B



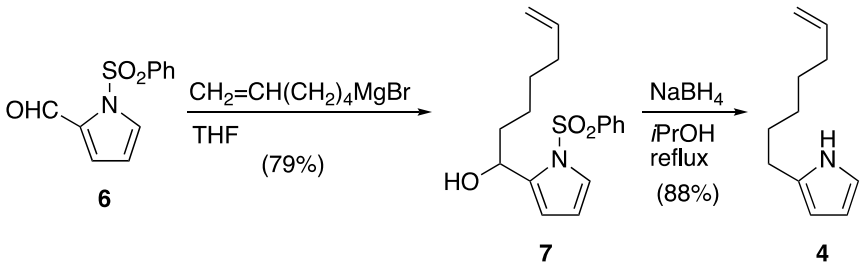
Scheme 2. Baran's direct pyrrole coupling

Taking into account these works, we selected direct pyrrole and δ-lactone coupling for the key step for the synthesis of marineosins. Our synthetic plan makes a disconnection at the spiroiminal to give the methyl acetal **1** (Scheme 3). Methyl acetal **1** was considered to be accessible from tricyclic compound **2** through nucleophilic alkylation. From the retrosynthetic perspective, we envisioned pyrrole-lactone **3** as a precursor of **2** through ring-closing metathesis. We postulated that this precursor **3** could be accessed by a direct coupling of pyrrole **4** with lactone **5**, based on Baran's protocol.[8] This approach is particularly appealing since two functionalized molecules could be unified stereo- and siteselectively without using protecting groups.



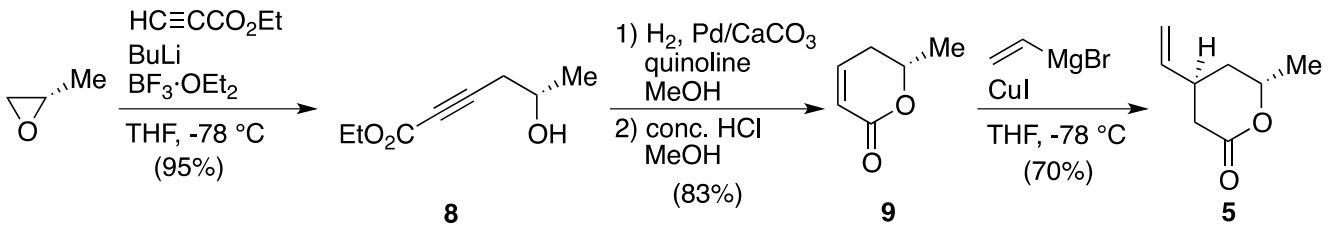
Scheme 3. A retrosynthetic analysis of marineosin A

Pyrrole **4** was obtained from known *N*-benzenesulfonylpyrrole-2-carboxaldehyde **6**[11] shown in Scheme 4. Treatment of aldehyde **6** with 5-hexenylmagnesium bromide gave pyrrole alcohol **7**, which was subjected to $NaBH_4$ reduction under Muchowski's condition to afford 2-(6-heptenyl)pyrrole **4** in a good yield.[12]



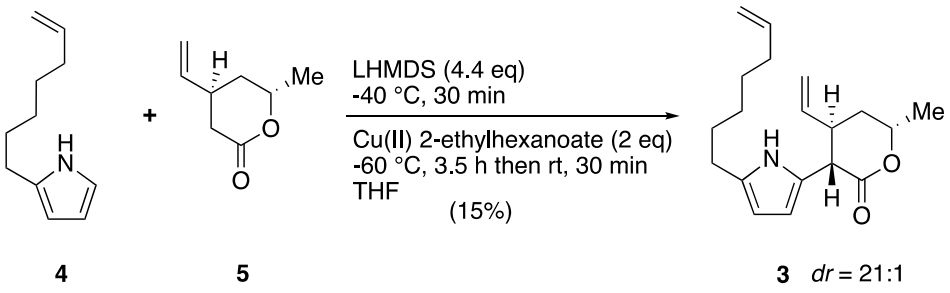
Scheme 4. Preparation of pyrrole compound **4**

On the other hand, the required lactone **5** was synthesized in a stereoselective manner by 1,4-addition of a vinyl group to chiral pyranone **9** based on Ogasawara's protocol[13] (Scheme 5). Thus, the coupling of commercially available (*S*)-propylene oxide with ethyl propiolate afforded compound **8** in 95% yield. Subsequent hydrogenation and lactone formation furnished chiral lactone **9** in 83% yields. The reaction of



Scheme 5. Synthesis of lactone **5**

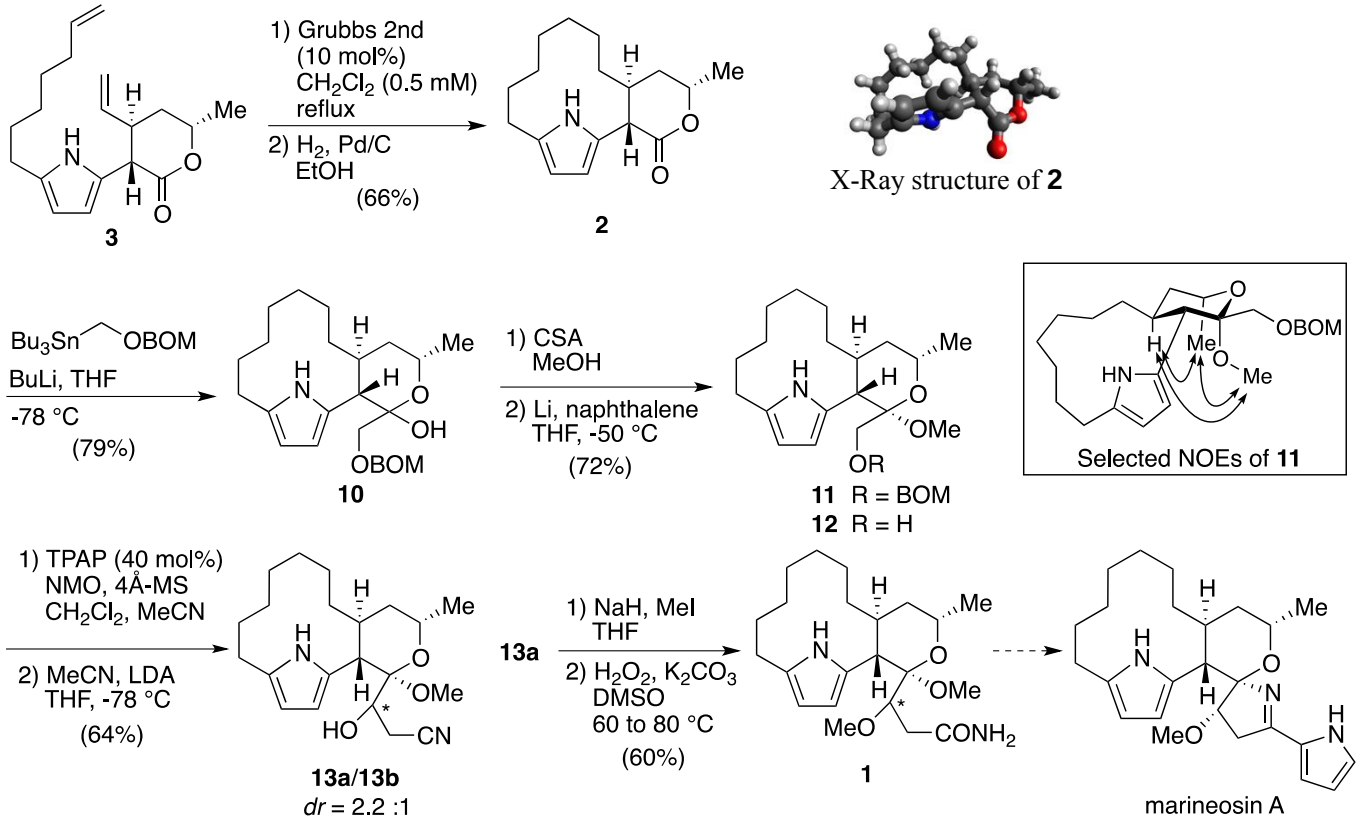
9 with vinylmagnesium bromide and copper iodide furnished stereoselectively lactone **5** in 70% yield. Having **4** and **5** in hand, we explored their direct coupling (Scheme 6). Based on Baran's protocol, the model reaction using simple pyrrole and lactone **5** with base and copper(II) 2-ethylhexanoate was initially investigated; however, the coupled product was not produced at all. After investigation under various conditions, we gratifyingly found that treatment of a mixture of **5** and **4** with LHMDS in the presence of copper(II) 2-ethylhexanoate at -60 °C for 3.5 h and then rt for 30 min furnished the desired product **3** in 15% yield with excellent stereoselectivity together with the recovered **4** in 49% yield and **5** in 49% yield. Although the yield of the product was not satisfying, it is important to note that the synthetic route to **3** avoid any protecting group manipulation.



4 **5** **3** *dr* = 21:1

Scheme 6. Direct coupling of **4** and **5**

Next our efforts focused on the formation of the macrocyclic framework and spirocyclic moiety of marineosins (Scheme 7). Ring-closing metathesis of **3** was found to be promoted cleanly by Grubbs 2nd catalyst in CH_2Cl_2 with high-dilution to deliver macrocyclic compound as a 1:2.2 *E*/*Z*-mixture, which was hydrogenated to afford **2** in 67% yield. The structure of **2** was confirmed by X-ray crystallographic analysis.[14] Installation of a carbon chain to the δ-lactone moiety was accomplished by the addition of the α-alkoxyorganolithium[15] derived from the corresponding α-alkoxystannane to produce compound **10** in 79% yield. When **10** was exposed to acidic methanolysis conditions, methyl acetal **11** was obtained as a single isomer and subsequent removal of the benzyloxymethyl group gave compound **12** in 72% yield. The methyl acetal in **11** was proved to be axial configuration by NOESY. Compound **12** was then converted to nitrile compounds **13a** and **13b** as a 2.2:1 diastereomeric mixture in 64% overall yield via aldehyde by TPAP oxidation followed by addition of lithium acetonitrile. Although we tried to clarify the stereochemistry of the resulting hydroxy group by modified Mosher's method, efforts to assign the absolute configuration was unsuccessful due to no distinct difference between the ^{1}H-NMR spectra of the (*R*)- and (*S*)-MTPA esters of **13a**. Methylation of major product **13a** and subsequent partial hydrolysis of the nitrile group provided lactone **1** in 60% yield.



Scheme 7. Synthesis of macrocyclic compound **1**

In conclusion, we have developed an effective route to macrocyclic compound **1**, a promising precursor of marineosin A and B, which proceeds through direct coupling of the pyrrole and δ-lactone moieties, ring-closing metathesis, and acetonitrile addition. The remaining tasks toward the total synthesis of marineosins are the installation of pyrrole and spiroimination which are currently under investigation.

EXPERIMENTAL

General. Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. Acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane (CH_2Cl_2), pyridine, toluene, and triethylamine (NEt_3) were distilled from CaH_2. Ethyl acetate (AcOEt) was distilled from K_2CO_3. Thin-layer chromatography (TLC) was performed using precoated silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 μm (regular), 40-50 μm (flash)). Optical rotations were recorded on digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ^1H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were measured using $CDCl_3$, or C_6D_6 as solvent, and chemical shifts are reported as δ values in ppm based on

internal $CHCl_3$ (7.26 ppm, ^1H; 77.0 ppm, ^{13}C), C_6D_6 (7.13 ppm, ^1H; 128.6 ppm, ^{13}C). Mass (MS) and high resolution mass (HRMS) spectra were taken in EI, DART or ESI mode.

1-(1-(Phenylsufonyl)-1*H*-pyrrol-2-yl)hept-6-en-1-ol (7). To a mixture of magnesium turnings (2.24 g, 30.7 mmol) in Et_2O (6.0 mL) was added dropwise 6-bromo-1-hexene (0.20 mL, 1.50 mmol) and the mixture was stirred at 34 °C for 30 sec. The mixture was allowed to rt, and a solution of 6-bromo-1-hexene (3.90 mL, 29.2 mmol) in Et_2O (24.0 mL) was added dropwise over 30 min. Thus Grignard reagent (0.83 M in Et_2O) was prepared.

To the solution of compound **6** (1.00 g, 4.25 mmol) in THF (26 mL) was added the above-mentioned Grignard reagent (0.83 M in Et_2O, 14.9 mL, 12.3 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min and then at rt for 30 min. The mixture was neutralized by 2 mol/L HCl and extracted with AcOEt (75 mL × 2). Organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO_2 70 g, hexane–AcOEt, 3:1) gave **7** (1.07 g, 3.36 mmol, 79%); a light red oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.31 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.28-6.26 (m, 2H), 5.76 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 4.97 (d, *J* = 17.2 Hz, 1H), 4.93 (d, *J* = 10.4 Hz, 1H), 4.81 (td, *J* = 7.2, 4.8 Hz, 1H), 2.71 (d, *J* = 4.8 Hz, 1H), 2.00 (q, *J* = 7.2 Hz, 2H), 1.85-1.75 (m, 2H), 1.42-1.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 133.9, 129.5, 126.5, 123.5, 114.4, 112.4, 111.7, 65.2, 34.9, 33.6, 28.5, 25.5; FT-IR (neat) ν 3564, 2930, 1366, 1179, 1089, 726 cm^{-1}; MS (EI) *m/z* 41, 55, 77, 96, 125, 141, 160, 178, 207, 236 (100), 256, 278, 302, 319 (M^+), 341; HRMS (EI) calcd for $C_{17}H_{21}NO_3S$ (M^+) 319.1242, found 319.1250.

2-(Hept-6-enyl)-1*H*-pyrrole (4). To a mixture of $NaBH_4$ (0.98 g, 26.0 mmol) in 2-propanol (50 mL) was added dropwise a solution of **7** (1.65 g, 5.20 mmol) in 2-propanol (37 mL). The mixture was stirred at reflux for 26 h. To the reaction mixture was added water (50 mL) at 0 °C, and the mixture was extracted with AcOEt (80 mL × 2). Organic layers were washed with brine (50 mL) dried, and concentrated. The residue was purified by flash chromatography (SiO_2 50 g, hexane–AcOEt, 15:1) gave **4** (746 mg, 4.57 mmol, 88%); a light red oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (brs, 1H), 6.62 (brs, 1H), 6.12 (dd, *J* = 5.6, 3.0 Hz, 1H), 5.90 (s, 1H), 5.80 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.05 (dd, *J* = 14.0, 6.8 Hz, 2H), 1.61 (dt, *J* = 7.6, 7.6 Hz, 2H), 1.38 (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 132.7, 115.9, 114.3, 108.1, 104.8, 33.6, 29.4, 28.8, 28.6, 27.6; FT-IR (neat) ν 3385, 2928, 2855, 714 cm^{-1}; MS (EI) *m/z* 41, 53, 67, 80 (100), 94, 106, 122, 134, 148, 163 (M^+); HRMS (EI) calcd for $C_{11}H_{17}N$ (M^+) 163.1361, found 163.1373.

Ethyl (*S*)-5-hydroxyhex-2-ynoate (8). To a solution of ethyl propiolate (3.92 g, 40.0 mmol) in THF (100 mL) was added *n*-butyllithium (2.60 M in hexane, 15.4 mL, 40.0 mmol) at -78 °C, and the mixture was stirred for 30 min. To the reaction mixture were added dropwise (*S*)-(-)-propylene oxide (1.16 g, 20.0

mmol) and $BF_3{\cdot}OEt_2$ (5.00 mL, 40.0 mmol) at -78 °C and stirring was continued for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (80 mL) and the mixture was extracted with AcOEt (100 mL × 3). Organic layers were washed with brine (80 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 180 g, hexane–AcOEt, 5:1) gave **8** (2.95 g, 18.9 mmol, 95%); a brown oil; $[\alpha]_D^{23}$ +11.7 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.2 Hz, 2H), 4.06 (sext, *J* = 6.0 Hz, 1H), 2.57-2.46 (m, 2H), 1.89 (brs, 1H), 1.33-1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 86.1, 74.6, 65.5, 61.8, 28.8, 22.3, 13.8; FT-IR (neat) ν 3416, 2979, 2233, 1699, 1238, 1066, 937, 752 cm^{-1}; MS (ESI) *m/z* 179 (100) [$(M+Na)^+$]; HRMS (ESI) calcd for $C_8H_{12}NaO_3$ [$(M+Na)^+$] 179.0684, found 179.0657.

(*S*)-5,6-Dihydro-6-methylpyran-2-one (9). To a solution of **8** (18.6 g, 118.8 mmol) in MeOH (238 mL) were added Lindlar catalyst (285.8 mg, 1.54 wt%) and quinoline (0.85 mL, 7.13 mmol) and the reaction mixture was stirred under H_2 atmosphere at rt for 27 h. The mixture was filtered through Celite and the cake was washed with Et_2O (200 mL × 3) and CH_2Cl_2 (150 mL × 3). The extracts were washed with 15% HCl (150 mL) and saturated aqueous $NaHCO_3$ (150 mL), and brine (150 mL), dried, and concentrated to give the crude alkene (17.6 g).

To a mixture of the crude alkene (17.6 g) in methanol (594 mL) was added dropwise concentrated HCl (100 mL) at 0 °C and the reaction mixture was stirred at rt for 90 min. To the mixture was added saturated aqueous $NaHCO_3$ (50 mL) at 0 °C, and the mixture was extracted with Et_2O (200 mL × 3) and CH_2Cl_2 (150 mL × 3). The extracts were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 350 g, hexane–AcOEt, 3:2) gave **9** (11.1 g, 98.8 mmol, 83%, 2 steps); a yellow oil; $[\alpha]_D^{28}$ +215.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (ddd, *J* = 9.2, 6.0, 2.8 Hz, 1H), 6.03 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.64-4.54 (m, 1H), 2.43-2.27 (m, 2H), 1.45 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 144.9, 121.2, 74.3, 30.9, 20.7; FT-IR (neat) ν 2981, 1726, 1389, 1254, 1114, 1054, 816 cm^{-1}; MS (EI) *m/z* 43, 61, 68 (100), 88, 97, 112 (M^+); HRMS (EI) calcd for $C_6H_8O_2$ (M^+) 112.0524, found 112.0525.

(4*S*,6*S*)-Tetrahydro-6-methyl-4-vinylpyran-2-one (5). To a solution of copper(I) iodide (1.13 g, 5.94 mmol) in THF (150 mL) was added dropwise vinylmagnesium bromide (1.32 M in THF solution, 90.0 mL, 119 mmol) at -78 °C and the mixture was stirred for 15 min. To the mixture was added a solution of **9** (4.44 g, 39.6 mmol) in THF (48 mL), and the reaction mixture was stirred at that temperature for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl (200 mL) and the mixture was extracted with AcOEt (400 mL × 2). Organic layers were washed with H_2O (200 mL), brine (200 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 200 g, hexane–AcOEt, 5:1) gave **5** (3.90 g, 27.8 mmol, 70%); a yellow oil: $[\alpha]_D^{25}$ -43.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.2, 10.8, 6.4 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 4.55 (sext

J = 6.4 Hz, 1H), 2.82-2.74 (m, 1H), 2.61 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.46 (dd, *J* = 17.2, 8.0 Hz, 1H), 1.81 (t, *J* = 6.4 Hz, 2H), 1.38 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.3, 114.8, 73.4, 34.3, 33.7, 32.2, 21.0; FT-IR (neat) ν 2979, 1744, 1380, 1249, 1089, 922 cm^{-1}; MS (EI) *m/z* 43, 54 (100), 68, 81, 98, 112, 125, 140 (M^+); HRMS (EI) calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0837.

(3*S*,4*R*,6*S*)-3-(5-(Hept-6-enyl)-1*H*-pyrrol-2-yl)-tetrahydro-6-methyl-4-vinylpyran-2-one (3). To a solution of HMDS (0.96 mL, 4.5 mmol) in THF (5 mL) was added butyllithium (2.65 M in hexane, 1.66 mL, 4.4 mmol) at -78 °C and the mixture was stirred at 0 °C for 30 min. To this solution of LHMDS was added a solution of pyrrole **4** (489.8 mg, 3.0 mmol) and lactone **5** (140.2 mg, 1.0 mmol) in THF (3.0 mL), and the mixture was stirred at 40 °C for 30 min. To the mixture was added copper(II) 2-ethylhexanoate (700 mg, 2.0 mmol) and the reaction mixture was stirred at -60 °C for 3.5 h. After stirred at rt for 30 min, the reaction was quenched with 5% aqueous ammonia and extracted with AcOEt (10 mL × 3). The extracts were washed with H_2O (10 mL) and brine (10 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 30 g, hexane–AcOEt, 30:1 to 6:1) gave **3** (46.1 mg, 0.153 mmol, 15%; 21:1 diastereomeric mixture based on the ^{1}H NMR spectrum) and recovered **4** (239 mg, 1.46 mmol, 49%) and lactone **5** (68.4 mg, 0.489 mmol, 49%).

3: a brown oil; $[\alpha]_D^{21}$ +22.0 (*c* 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (brs, 0.08H), 8.51 (brs, 0.92H), 5.97-5.76 (m, 4H), 5.17 (d, *J* = 16.0 Hz, 1H), 5.14 (d, *J* = 11.6 Hz, 1H), 4.99 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.93 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.69-4.61 (m, 1H), 3.86 (d, *J* = 4.4 Hz, 0.07H), 3.76 (d, *J* = 5.6 Hz, 0.93H), 3.26-3.20 (m, 0.07H), 3.08 (dt, *J* = 12.0, 5.6 Hz, 0.93H), 2.55 (t, *J* = 8.0 Hz, 2H), 2.11-2.00 (m, 3H), 1.89 (dt, *J* = 10.4, 4.0 Hz, 1H), 1.61 (quint, *J* = 8.0 Hz, 2H) 1.45-1.33 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 139.2, 139.0, 133.5, 124.1, 116.0, 114.3, 106.1, 104.6, 74.0, 42.8, 37.4, 35.4, 33.7, 29.4, 28.8, 28.7, 27.7, 21.3; FT-IR (neat) ν 3359, 2828, 1730, 1600, 1188, 1109, 913, 767 cm^{-1}; MS (EI) *m/z* 43, 58, 76, 104, 120, 147, 176, 203, 218, 232, 260, 272, 301 (M^+); HRMS (EI) calcd for $C_{19}H_{27}NO_2$ (M^+) 301.2042, found 301.2052.

(5-*E* or *Z*)-(3*S*,4a*S*,15a*S*)-3-Methyl-3,4,4a,7,8,9,10,11-octahydro-12,15-epiminocycloundeca[*c*]pyran-1(15a*H*)-one. To the solution of **3** (45.2 mg, 0.15 mmol) in degassed CH_2Cl_2 (150 mL) was added 2nd generation Grubbs catalyst (12.8 mg, 15.0 μmol) and the mixture was stirred under reflux for 1 day. After stirring under air for 4 h, the mixture was concentrated and purified by flash chromatography (SiO_2 5 g, hexane–AcOEt, 3:1 to 1:1) to afford macrocyclic *E*-alkene (9.1 mg, 33.3 μmol, 22%) and *Z*-alkene (20.1 mg, 73.5 μmol, 49%).

***E*-alkene:** a white solid; $[\alpha]_D^{21}$ -47.4 (*c* 0.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (brs, 1H), 6.18 (s, 1H), 5.83 (s, 1H), 5.28-5.15 (m, 2H), 4.67-4.58 (m, 1H), 3.59 (d, *J* = 12.4 Hz, 1H), 2.65 (dt, *J* = 15.2, 5.6 Hz, 1H), 2.57-2.45 (m, 2H), 2.05-1.84 (m, 4H), 1.56-1.26 (m, 7H), 1.08 (quint, *J* = 6.8 Hz, 1H), 0.89-0.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 133.7, 131.9, 130.9, 124.5, 107.4, 107.1, 72.7,

44.6, 43.6, 35.9, 29.5, 26.9, 26.0, 22.6, 21.1; FT-IR (neat) ν 3332, 2927, 1711, 773 cm^{-1}; MS (EI) *m/z* 43, 55, 69, 81, 93, 120, 149, 158, 187, 200, 228, 229, 256, 273 (100, M^+), 293; HRMS (EI) calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1727.

***Z*-alkene:** a yellow solid; $[\alpha]_D^{21}$ +18.9 (*c* 0.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (brs, 0.89H), 7.66 (brs, 0.11H), 5.94-5.81 (m, 1H), 5.76-5.69 (m, 1H), 5.55 (dd, *J* = 15.2, 9.6 Hz, 0.11H), 5.26-5.15 (td, *J* = 10.4, 3.6 Hz, 1H), 5.10 (t, *J* = 10.4 Hz, 0.89H), 4.83-4.63 (m, 1H), 3.93 (d, *J* = 5.2 Hz, 0.11H), 3.62 (d, *J* = 12.4 Hz, 0.89H), 3.31-3.22 (m, 1H), 2.77-2.36 (m, 2H), 2.29-1.92 (m, 3H), 1.80 (dt, *J* = 14.0, 4.8 Hz, 1H), 1.68-0.68 (m, 8H), 0.40 (quint, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 133.5, 132.3, 129.9, 124.3, 109.2, 105.9, 72.9, 44.5, 36.8, 35.3, 31.9, 29.2, 27.5, 27.2, 26.1, 25.7, 21.1, 20.9, 19.4; FT-IR (neat) ν 3361, 2929, 1724, 1209 cm^{-1}; MS (EI) *m/z* 43, 58, 93, 106, 120, 132, 149, 186, 187, 228, 229, 272, 273 (100, M^+), 301, 303; HRMS (EI) calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1727.

(3*S*,4a*S*,15a*S*)-3-Methyl-3,4,4a,5,6,7,8,9,10,11-decahydro-12,15-epiminocycloundeca[*c*]pyran-1(15a*H*)-one (2). To a mixture of *E*-alkene and *Z*-alkene (137 mg, 502 μmol) in EtOH (20 mL) was added palladium/C (54.8 mg, 40 wt%) and the mixture was stirred under atmospheric hydrogen at rt for 22 h. The reaction mixture was filtered through Celite and concentrated. The residue was purified by preparative TLC (hexane–AcOEt, 5:1) to give **2** (127 mg, 461 μmol, 92%); a light yellow solid; Mp 155-156 °C (decomp); $[\alpha]_D^{24}$ -45.6 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, 0.9 mg/0.6 mL $CDCl_3$) δ 7.89 (brs, 1H), 5.94 (t, *J* = 2.8 Hz, 1H), 5.79 (t, *J* = 2.8 Hz, 1H), 4.65-4.58 (m, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 2.64 (ddd, *J* = 14.4, 5.2, 5.2 Hz, 1H), 2.50 (ddd, *J* = 14.4, 9.2, 5.2 Hz, 1H), 2.11-2.00 (m, 2H), 1.69 (ddd, *J* = 13.6, 4.4, 4.4 Hz, 1H), 1.59-1.50 (m, 4H), 1.41 (d, *J* = 6.0 Hz, 3H) 1.31-1.22 (m, 5H), 0.92-0.77 (m, 2H), 0.50-0.40 (m, 1H); ^1H NMR (400 MHz, 13.5 mg/0.6 mL $CDCl_3$) δ 8.54 (brs, 1H), 5.90 (t, *J* = 2.8 Hz, 1H), 5.71 (t, *J* = 2.8 Hz, 1H), 4.64-4.56 (m, 1H), 3.46 (d, *J* = 12.4 Hz, 1H), 2.38-2.22 (m, 3H), 2.15 (ddd, *J* = 14.0, 10.0, 10.0 Hz, 1H), 1.67 (ddd, *J* = 14.0, 4.8, 4.8 Hz, 1H), 1.61-1.04 (m, 12H), 0.88-0.73 (m, 2H), 0.42-0.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 134.4, 124.0, 109.9, 105.0, 73.3, 45.6, 38.2, 33.0, 31.9, 27.9, 27.1, 25.4, 24.6, 24.2, 24.1, 21.0; FT-IR (neat) ν 3353, 2926, 1723, 1209, 758 cm^{-1}; MS (EI) *m/z* 43 (100), 69, 85, 93, 120, 132, 149, 189, 190, 212, 233, 256, 275 (M^+); HRMS (EI) calcd for $C_{17}H_{23}NO_2$ (M^+) 275.1885, found 275.1874.

(3*S*,4*S*,6*S*)-6-Methyl-2-(((benzyloxy)methoxy)methyl)-3,4,5,6-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphan-2-ol (10). To a solution of (benzyloxymethoxymethyl)tributylstannane (1.17 g, 2.66 mmol) in THF (5.0 mL) was added *n*-butyllithium (2.76 M in hexane, 0.964 mL, 2.66 mmol) at -78 °C and mixture was stirred for 5 min. To this mixture was added **2** (122 mg, 443 μmol) in THF (3.9 mL) and the mixture was stirred at -78 °C for 1 h. To the reaction mixture was added saturated aqueous NH_4Cl (10 mL) and extracted with AcOEt (20 mL × 3). The residue was purified by flash chromatography (SiO_2 10 g, hexane–AcOEt, 5:1) to afford **10** (150 mg, 351 μmol, 79%); $[\alpha]_D^{20}$ +11.6 (*c*

0.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (brs, 1H), 7.35-7.26 (m, 5H), 5.80 (t, *J* = 2.8 Hz, 1H), 5.73 (t, *J* = 2.8 Hz, 1H), 4.81-4.76 (m, 2H), 4.65-4.56 (m, 2H), 4.26 (sext, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.61 (brs, 1H), 3.54 (d, *J* =10.0 Hz, 1H), 2.69 (ddd, *J* = 14.8, 4.0, 4.0 Hz, 1H), 2.51 (ddd, *J* = 14.8, 11.2, 4.0 Hz, 1H), 2.37 (d, *J* = 11.6 Hz, 1H), 2.27-2.19 (m, 1H), 1.74-1.61 (m, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.40-1.26 (m, 5H), 1.21-1.08 (m, 2H), 0.93-0.79 (m, 3H), 0.51-0.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 132.7, 128.7, 128.4, 127.9, 127.7, 109.5, 105.0, 97.5, 95.4, 74.6, 69.6, 69.3, 47.0, 38.7, 30.5, 28.4, 27.4, 27.1, 25.4, 24.8, 24.7, 24.6, 22.8; FT-IR (neat) ν 3462, 2925, 1724, 1586, 1456, 1114, 1044, 765, 699, 576 cm^{-1}; MS (ESI) *m/z* 450 (100) [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{26}H_{37}NNaO_4$ [$(M+Na)^+$] 450.2620, found 450.2583.

(2*R*,3*S*,4*S*,6*S*)-2-Methoxy-6-methyl-2-(((benzyloxy)methoxy)methyl)-3,4,5,6-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphane (11). To a solution of **10** (152 mg, 356 μmol) in MeOH (7.1 mL) was added CSA (1.4 mg, 0.0356 mmol), and the mixture was stirred at rt for 15 min. To the mixture was added saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). Organic extracts were washed with brine (5 mL), dried over anhydrous K_2CO_3, and concentrated. The residue was purified by flash chromatography (SiO_2 5 g, hexane–AcOEt, 9:1) to afford **11** (132 mg, 298 μmol, 84%); a brown oil; $[\alpha]_D^{20}$ -3.8 (*c* 0.21, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (brs, 1H), 7.36-7.23 (m, 5H), 5.85 (t, *J* = 2.8 Hz, 1H), 5.72 (t, *J* = 2.8 Hz, 1H), 4.80-4.77 (m, 2H), 4.64-4.57 (m, 2H), 4.31-4.25 (m, 1H), 3.61 (d, *J* = 10.0 Hz, 1H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.32 (s, 3H), 2.82 (d, *J* = 12.4 Hz, 1H), 2.71 (ddd, *J* = 14.8, 4.4, 4.4 Hz, 1H), 2.51 (ddd, *J* = 14.8, 11.2, 4.4 Hz, 1H), 2.17-2.08 (m, 1H), 1.68-1.62 (m, 4H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.39-1.21 (m, 4H), 1.18-1.05 (m, 2H), 0.91-0.73 (m, 3H), 0.54-0.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 132.3, 129.1, 128.3, 128.0, 127.6, 109.5, 105.0, 100.7, 95.2, 69.8, 69.4, 69.3, 49.1, 46.1, 38.5, 30.8, 28.4, 27.3, 26.9, 25.5, 24.8, 24.7, 24.6, 21.6; FT-IR (neat) ν 3467, 2925, 1644, 1454, 1376, 1269, 1115, 1053, 761, 698, 542 cm^{-1}; MS (ESI) *m/z* 432, 450, 464 (100) [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{27}H_{39}NNaO_4$ [$(M+Na)^+$] 464.2777, found 464.2826.

3-Hydroxy-3-((2*R*,2*S*,2*S*,2*S*)-2-methoxy-2-methyl-2,2,2,2-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphan-2-yl)propanenitrile (12). To the mixture of lithium dispersion (30% in oil, 150 mg, 6.42 mmol) in THF (3.7 mL) was added naphthalene (827 mg, 6.42 mmol) and the mixture was stirred at rt for 1 h. The mixture was allowed to cool to -50 °C and a solution of **11** (63.9 mg, 145 μmol) in THF (1.2 mL) was added. After stirring at that temperature for 8.5 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with AcOEt (20 mL × 3). Organic extracts were washed with brine (10 mL) and dried, and concentrated. The residue was purified by flash chromatography (SiO_2 7 g, hexane–AcOEt, 6:1) to afford **12** (40.1 mg, 125 μmol, 86%); a yellow oil: $[\alpha]_D^{20}$ +26.1 (*c* 0.96, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (brs, 1H), 5.90 (t, *J* = 2.8 Hz, 1H), 5.73 (t, *J* = 2.8 Hz, 1H), 4.24-4.17 (m, 1H), 3.59-3.53 (m, 2H), 3.35 (s, 3H), 2.71 (ddd, *J* = 15.2, 4.4, 4.4 Hz,

1H), 2.57 (d, *J* = 12.0 Hz, 1H), 2.50 (ddd, *J* = 15.2, 11.2, 4.4 Hz, 1H), 2.17-2.07 (m, 1H), 1.75-1.63 (m, 3H), 1.59-1.52 (m, 2H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.38-1.23 (m, 4H), 1.18-1.06 (m, 2H), 0.90-0.72 (m, 3H), 0.54-0.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 128.4, 109.4, 105.4, 99.8, 69.5, 65.4, 49.2, 48.1, 38.7, 30.6, 28.3, 27.2, 25.4, 24.8, 24.7, 24.6, 21.5; FT-IR (neat) ν 3466, 2924, 2855, 1453, 1371, 1136, 1056, 765, 491 cm^{-1}; MS (ESI) *m/z* 312, 344 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{19}H_{31}NNaO_3$ [(M+Na)$^+$] 344.2202, found 344.2251.

(2*R*,3*S*,4*S*,6*S*)-2-Methoxy-6-methyl-3,4,5,6-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphane-2-carboaldehyde. To a solution of **12** (62.4 mg, 194 μmol) in CH_2Cl_2 (19.4 mL) and MeCN (2.0 mL) were added 4A-MS (93.6 mg) prepared by heating at 200 °C *in vacuo* and *N*-methylmorpholine *N*-oxide (52.5 mg, 398 μmol) and TPAP (27.3 mg, 77.6 μmol). The reaction mixture was stirred at rt for 2 h, and the mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography (SiO_2 3 g, hexane–AcOEt, 6:1) to afford aldehyde (44.3 mg, 139 μmol, 74%); a colorless oil; $[\alpha]_D^{19}$ +7.8 (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.12 (brs, 1H), 5.76 (t, *J* = 2.8 Hz, 1H), 5.72 (t, *J* = 2.8 Hz, 1H), 4.41-4.34 (m, 1H), 3.38 (s, 3H), 2.76 (ddd, *J* = 14.8, 4.8, 4.8 Hz, 1H), 2.52 (ddd, *J* = 14.8, 11.2, 4.8 Hz, 1H), 2.48 (d, *J* = 12.0 Hz, 1H), 2.20-2.11 (m, 1H), 1.75-1.56 (m, 5H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.38-1.25 (m, 3H), 1.18-1.07 (m, 2H), 0.91-0.75 (m, 3H), 0.54-0.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 133.6, 126.0, 110.0, 105.4, 100.4, 69.8, 51.5, 46.2, 38.3, 30.3, 28.4, 27.2, 27.1, 25.4, 24.8, 24.7, 24.5, 21.2; FT-IR (neat) ν 3468, 2926, 2854, 1745, 1446, 1376, 1133, 1040, 767 cm^{-1}; MS (ESI) *m/z* 260, 288, 342 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{19}H_{29}NNaO_3$ [(M+Na)$^+$] 342.2045, found 342.2023.

3-Hydroxy-3-((2*R*,3*S*,4*S*,6*S*)-2-methoxy-6-methyl-3,4,5,6-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphan-2-yl)propanenitrile (13a and 13b). A mixture of *N,N*-diisopropylamine (114 μL, 812 μmol) in THF (0.7 mL) was added *n*-butyllithium (2.76 M in hexane, 294 μL, 812 μmol) and the mixture was stirred at 0 °C for 15 min. To this LDA solution was added MeCN (49.5 μL, 948 μmol) at -78 °C and stirring was continued for 45 min. To the mixture was added the above-mentioned aldehyde (17.3 mg, 54.2 μmol) in THF (1.5 mL) and the mixture was stirred for 1 h. To the mixture was added saturated aqueous NH_4Cl (5 mL) and extracted with AcOEt (10 mL × 3). Organic extracts were washed with brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography (preparative TLC, hexane–AcOEt, 3:1) to afford **13a** (11.7 mg, 32.4 μmol, 60%) and **13b** (5.2 mg, 14.4 μmol, 27%).

13a: a brown oil; $[\alpha]_D^{19}$ -14.1 (*c* 0.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (brs, 1H), 5.84 (t, *J* = 2.8 Hz, 1H), 5.72 (t, *J* = 2.8 Hz, 1H), 4.29-4.21 (m, 1H), 3.99 (ddd, *J* = 9.6, 4.4, 3.2 Hz, 1H), 3.39 (s, 3H), 2.70-2.57 (m, 3H), 2.55-2.48 (m, 2H), 2.38 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.09-1.99 (m, 1H), 1.72-1.50 (m, 5H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.33-1.26 (m, 3H), 1.20-1.06 (m, 2H), 0.88-0.71 (m, 3H), 0.38-0.29 (m,

1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 127.7, 118.5, 110.3, 105.5, 100.3, 71.7, 69.7, 49.9, 44.5, 38.1, 29.6, 28.4, 27.9, 27.8, 25.7, 24.7, 24.5, 24.3, 21.3, 20.7; FT-IR (neat) ν 3463, 2923, 2854, 2251, 1722, 1452, 1140, 1082, 1023, 769, 546, 415 cm^{-1}; MS (ESI) *m/z* 329, 351, 352, 383 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{21}H_{32}N_2NaO_3$ [(M+Na)$^+$] 383.2311, found 383.2300.

13b: a colorless powder; $[\alpha]_D^{24}$ +7.9 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (brs, 1H), 5.90 (t, *J* = 2.8 Hz, 1H), 5.74 (t, *J* = 2.8 Hz, 1H), 4.23-4.17 (m, 1H), 4.00 (td, *J* = 9.2, 4.0 Hz, 1H), 3.41 (s, 3H), 2.73-2.66 (m, 2H), 2.58 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.50 (ddd, *J* = 14.4, 11.2, 4.0 Hz, 1H), 2.41 (d, *J* = 12.0 Hz, 1H), 2.19 (d, *J* = 9.2 Hz, 1H), 2.15-2.08 (m, 1H), 1.74-1.63 (m, 3H), 1.53-1.47 (m, 3H), 1.53-1.47 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.36-1.08 (m, 6H), 0.94-0.76 (m, 3H), 0.45-0.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 126.4, 118.2, 110.4, 105.9, 99.5, 71.0, 69.5, 49.0, 44.7, 38.4, 29.8, 28.3, 27.8, 27.5, 25.4, 24.7, 24.5, 24.5, 22.5, 21.4; FT-IR (neat) ν 3463, 2927, 2857, 2251, 1725, 1457, 1274, 1137, 1033, 770 cm^{-1}; MS (DART) *m/z* 320, 329, 361 (100) [(M+H)$^+$]; HRMS (DART) calcd for $C_{21}H_{33}N_2O_3$ [(M+H)$^+$] 361.2491, found 361.25127.

3-Methoxy-3-((2*R*,3*S*,4*S*,6*S*)-2-methoxy-6-methyl-3,4,5,6-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphan-2-yl)propanenitrile. To a solution of **13a** (22.2 mg, 61.6 μmol) in THF (3.1 mL) was added sodium hydride (60% in mineral oil, 7.4 mg, 185 μmol) and stirred for 30 min. To this mixture was added MeI (52.4 mg, 370 μmol) and stirring was continued at rt for 2.5 h. To the mixture was added saturatated aqueous NH_4Cl (5 mL) and extracted with AcOEt (10 mL × 3). Organic extracts were washed with brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO_2 1 g, hexane–AcOEt, 8:1) to afford methoxy compound (18.6 mg, 49.7 μmol, 81%); a brown oil; $[\alpha]_D^{19}$-26.6 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (brs, 1H), 5.82 (t, *J* = 2.8 Hz, 1H), 5.70 (t, *J* = 2.8 Hz, 1H), 4.22 (sext, *J* = 6.8 Hz, 1H), 3.59-3.56 (m, 4H), 3.34 (s, 3H), 2.84 (d, *J* = 12.4 Hz, 1H), 2.65 (ddd, *J* = 14.8, 6.0, 4.0 Hz, 1H), 2.51 (ddd, *J* = 14.8, 10.4, 4.0 Hz, 1H), 2.34 (dd, *J* = 17.6, 10.0 Hz, 1H), 2.12 (dd, *J* = 17.6, 2.4 Hz, 1H), 2.02-1.93 (m, 1H), 1.71-1.61 (m, 2H), 1.56-1.44 (m, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.33-1.05 (m, 5H), 0.91-0.69 (m, 3H), 0.32-0.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 128.2, 119.4, 110.3, 105.3, 101.6, 81.5, 68.8, 60.9, 49.0, 42.8, 38.0, 29.7, 28.5, 28.0, 27.9, 25.8, 24.8, 24.5, 24.2, 21.4, 19.7; FT-IR (neat) ν 3466, 3386, 2926, 2248, 1457, 1373, 1268, 1115, 1026, 915, 770, 734 cm^{-1}; MS (ESI) *m/z* 397 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{22}H_{34}N_2NaO_3$ [(M+Na)$^+$] 397.2467, found 397.2451.

3-Methoxy-3-((3*S*,4*S*,6*S*)-2-methoxy-6-methyl-3,4,5,6-tetrahydro-1*H*,2*H*-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphan-2-yl)propanamide (1). To the mixture of methoxy compound (11.8 mg, 31.5 μmol) in DMSO (1.3 mL) were added 30% H_2O_2 (320 μL, 3.15 mmol) and K_2CO_3 (87.1 mg, 630 μmol), and the mixture was stirred at 60 °C for 11.5 h and at 80 °C for 3 h. To this mixture were added 30% H_2O_2 (320 μL, 3.15 mmol) and K_2CO_3 (87.1 mg, 630 μmol), and stirring was continued for 3.5 h. To the

mixture was added H_2O (5 mL), extracted with Et_2O (10 mL × 3). Organic extracts were washed with brine (5 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO_2 0.8 g, hexane–AcOEt, 2:1 to 1:2) to afford **1** (9.2 mg, 23.4 μmol, 74%); $[\alpha]_D^{19}$ -10.5 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (brs, 1H), 5.80 (t, *J* = 2.8 Hz, 1H), 5.68 (t, *J* = 2.8 Hz, 1H), 5.56 (brs, 1H), 5.27 (brs, 1H), 4.22 (sext, *J* = 6.8 Hz, 1H), 3.75 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.49 (s, 3H), 3.34 (s, 3H), 2.84 (d, *J* = 11.6 Hz, 1H), 2.65 (ddd, *J* = 14.8, 6.0, 4.0 Hz, 1H), 2.50 (ddd, *J* = 14.8, 10.8, 4.0 Hz, 1H), 2.10-1.98 (m, 3H), 1.69-1.60 (m, 2H), 1.57-1.41 (m, 3H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.35-1.23 (m, 3H), 1.18-1.04 (m, 2H), 0.89-0.68 (m, 3H), 0.34-0.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 132.5, 129.3, 109.7, 104.9, 102.9, 82.1, 68.5, 60.3, 48.8, 43.3, 38.2, 37.6, 29.7, 28.6, 28.1, 27.9, 25.8, 24.8, 24.6, 24.2, 21.5; FT-IR (neat) ν 3464, 3340, 3199, 2925, 2854, 1674, 1442, 1336, 1113, 1020, 911, 733 cm^{-1}; MS (ESI) *m/z* 242, 301, 329, 351, 383, 385, 413, 415 (100) [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{22}H_{36}N_2NaO_4$ [$(M+Na)^+$] 415.2573, found 415.2622.

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Numbers JP15K07861 (JI), JP18K05126 (JI), JP25253002 (SH) and JP16H05074 (SH). We thank Dr. H. Uekusa in Tokyo Institute of Technology for kind discussion of X-ray analysis.

SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra of new compounds are available.

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