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SYNTHESES OF A PYRROLIDINE ANALOG OF A TETRAHYDRO-FURAN CONTAINING ACETOGENIN, *cis*-SOLAMIN

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Abstract – Practical synthesis of a pyrrolidine analog of a mono-THF acetogenin as a proto-type analog to evaluate the effect of a heteroatom in the mono-THF ring of acetogenins was achieved using Pd(II)-catalyzed diastereo-selective cyclization. Ligand-less $PdCl_2$ catalyzed cyclization yielded the desired pyrrolidine derivative as a single major product having the desired relative configurations. Coupling of the pyrrolidine fragment with a known γ-lactone-containing fragment via a Sonogashira cross-coupling reaction yielded the desired aza-*cis*-solamin analog.

INTRODUCTION

Annonaceous acetogenins are a family of polyketides isolated from *Annonaceae*.[1-3] Structurally, acetogenins contain 35 or 37 carbon atoms and one to three tetrahydrofuran (THF) rings are included at the middle part of the basically linear structure. The terminal carboxylic acid forms a γ-methyl-substituted α, β-unsaturated γ-lactone structure. Most acetogenins show potent cytotoxicity against a variety of tumor cell lines, which is believed to be caused by inhibition of the mitochondrial NADH dehydrogenase complex I.[4] Because of their unique structures, many total syntheses of natural acetogenins, as well as structure-activity relationship (SAR) studies, have been reported.[5,6] Most SAR studies have been focused on the stereo-structure of THF and its neighboring hydroxyl groups, terminal γ-lactone structures, and the

linker structure between THF-ring and the terminal γ-lactone ring. Only a few studies on the THF ring structure itself have been reported, including the replacement of the oxygen-containing five-membered THF ring with tetrahydropyran (THP),[8] a sugar[9] ring, or *trans*-2,5-pyrrolidine.[10] Since the replacement of the oxygen with nitrogen can provide a position of additional substituent, the pyrrolidine analogs would be interesting novel analogs for the SAR studies. Although a pioneer work on pyrrolidine analog of acetogenin has been reported by Shen's group,[10] stereoselectivity of the two hydroxyl groups was not high enough. In this paper, we report synthesis of a *cis*-2,5-pyrrolidine analog of *cis*-solamin, a mono-THF acetogenin (Figure 1), as a proto-type analog to evaluate the effect of the heteroatom in the THF ring of acetogenins on cytotoxicity.

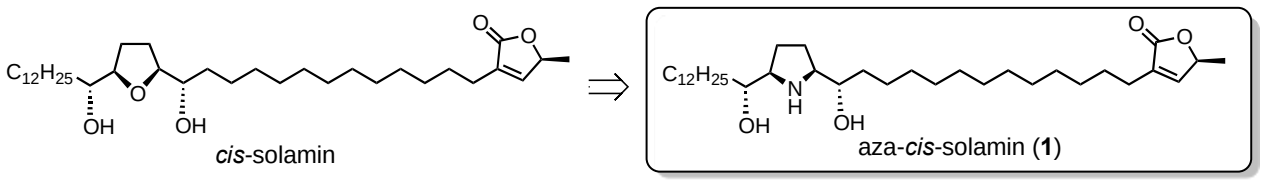
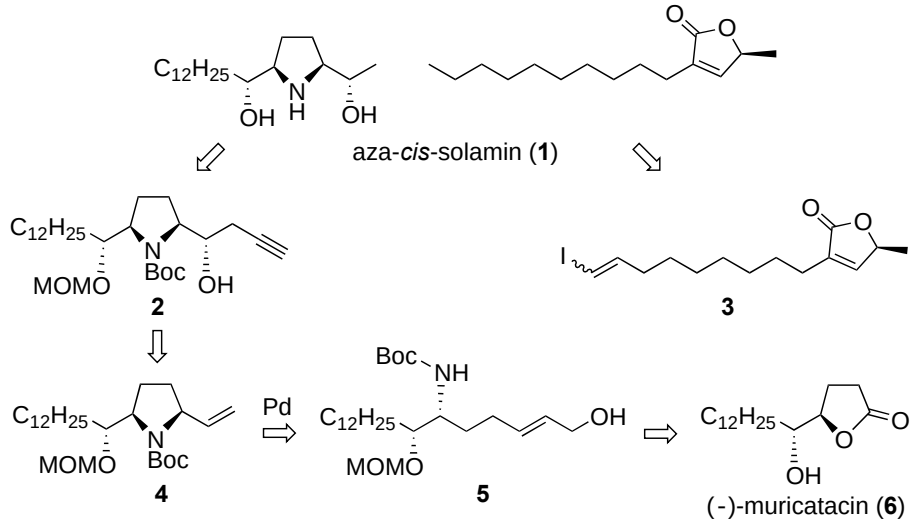


Figure 1

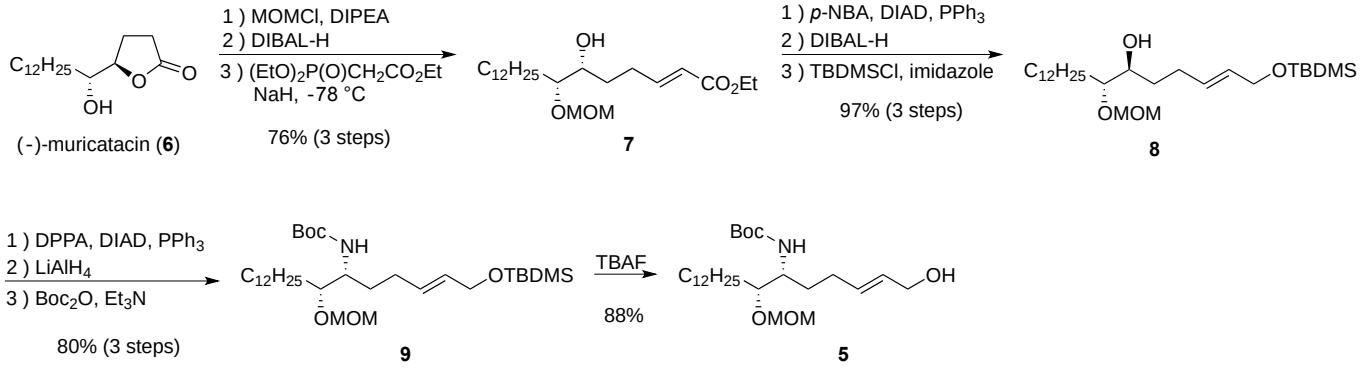
RESULTS AND DISCUSSION

The retro-synthetic route for the aza-*cis*-solamin (**1**) is shown in Scheme 1. The structure of **1** was constructed by Sonogashira cross-coupling reaction of a pyrrolidine fragment **2** with a known compound **3**[11] containing the terminal γ-lactone structure. The key intermediate **4** for the synthesis of **2** was prepared by Pd(II)-catalyzed diastereo-selective cyclization[12,13] of a linear precursor **5**. Precursor **5** was synthesized by the ring-opening reaction of a known compound **6**, (–)-muricatacin,[14,15] followed by the replacement of an oxygen atom with a nitrogen atom via the corresponding azide.



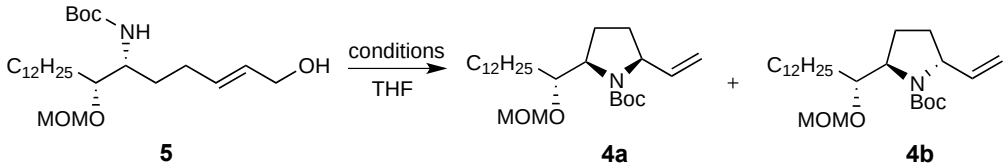
Scheme 1

The linear precursor **5** was synthesized according to the route shown in Scheme 2. According to the published procedure,[16] the hydroxyl group of (–)-muricatacin was protected by the MOM group and the product was reduced with DIBAL-H followed by a Horner-Wadsworth-Emmons reaction to yield the alcohol **7**. The configuration of the hydroxyl group was reversed by a Mitsunobu reaction. The ester of the product was reduced and the resulting primary alcohol was protected as TBDMS ether to give **8**. The secondary hydroxyl group of **8** was then converted to the azide, which was reduced and protected with Boc group to yield **9**. Deprotection of the TBDMS group afforded the desired precursor **5**.



Scheme 2

Next, Pd(II)-catalyzed diastereo-selective cyclization of **5** was examined (Table 1). Although the desired cyclized product was not obtained by $Pd(dba)_2$ or $Cl_2Pd(PPh_3)_2$ catalyzed cyclization or without a catalyst, a ligand-less catalyst, $PdCl_2$, gave the desired cyclized product with an 86% yield. The relative configuration of the product was evaluated by NOE experiments, and the diastereo-excess yield was estimated to be more than 94%. Thus, the desired key intermediate **4a** was obtained as a single diastereomer with a base- and heat-free catalytic reaction.



entry	catalyst (10 mol%)	time (h)	yield (%)
1	-	72	NR
2	$Pd(dba)_2$	72	NR
3	$Cl_2Pd(PPh_3)_2$	72	NR
4	$PdCl_2$	10	86

NR; no reaction

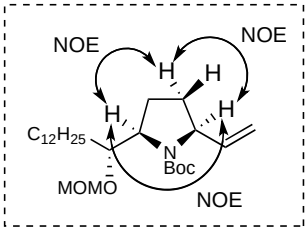
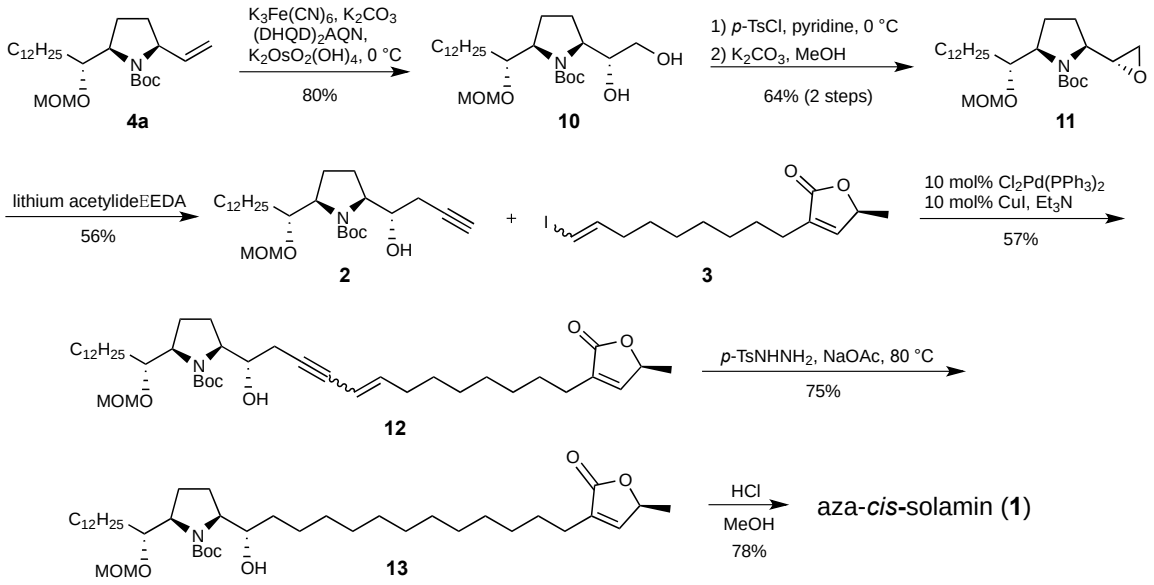


Table 1

Finally, the desired aza-*cis*-solamin (**1**) was synthesized according to the route shown in Scheme 3. Diastereo-selective dihydroxylation of **4a** by Sharpless reaction using $(DHQD)_2AQN$ gave diol **10**, and configuration of the resulting hydroxyl group was confirmed to be >92% de. Diol **10** was converted to epoxide **11**, which was then reacted with lithium acetylide to yield the pyrrolidine-containing fragment **2** without difficulty. Fragment **2** was coupled with a known γ-lactone-containing fragment **3** by a Sonogashira cross-coupling reaction to give an enyne derivative **12**. Careful diimide reduction of **12** with *p*-$TsNHNH_2$ and sodium acetate gave a reduced product **13**. Deprotection of Boc and MOM groups of **13** by methanolic HCl afforded an aza-*cis*-solamin (**1**), the structure of which was confirmed by ^1H and ^{13}C NMRs, as well as high resolution mass analyses. Purity of synthetic **1** was estimated to be more than 95% although trace impurity was observed on the ^1H and ^{13}C NMRs.



Scheme 3

In conclusion, synthesis of a pyrrolidine analog of *cis*-solamin, a mono-THF acetogenin, was first achieved using a ligand-less Pd(II)-catalyst in the key reaction to construct the pyrrolidine structure. Syntheses of related pyrrolidine analogues including *N*-substituted derivatives as well as the stereoisomers and evaluations of the inhibitory activities for mitochondrial NADH dehydrogenase complex I are now underway.

EXPERIMENTAL

General

Melting point was determined with a Yanaco apparatus and was uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on agilent UNITY INOVA 400 NB or Bruker AM-300 spectrometers. Chemical shifts are expressed in ppm relative to tetramethylsilane (0 ppm). The coupling constants are given in Hz. ^{13}C

NMR spectra were recorded on the same spectrometers at 100 or 75 MHz, using the central resonance of $CDCl_3$ (δC 77 ppm) as the internal reference. High-resolution mass spectra (HRMS) were obtained on a Shimadzu GC mate II (EI and CI) or JMS-SX 102A (FAB) mass spectrometers. Optical rotations were determined with a HORIBA SEPA-300 polarimeter.

(2*E*,6*S*,7*R*)-Ethyl 7-methoxymethoxy-6-(4-nitrobenzoyloxy)-nonadec-2-enoate: DIAD (6.9 mL, 35 mmol) was added dropwise to a solution of **7** (3.47 g, 8.66 mmol), *p*-nitrobenzoic acid (1.45 g, 34.6 mmol), and triphenylphosphine (9.09 g, 34.6 mmol) in toluene (50 mL) at 0 ºC. The mixture was stirred for 16 h at room temperature, and then the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford ester (4.62 g, 97%) as a colorless oil. $[\alpha]^{23}_D$ +8.8 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.32-8.28 (m, 2H), 8.22-8.19 (m, 2H), 6.94 (td, *J* = 15.7, 6.0 Hz, 1H), 5.81 (td, *J* = 15.6, 1.6 Hz, 1H), 5.27 (td, *J* = 9.9, 2.9 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.81-3.77 (m, 1H), 3.35 (s, 3H), 2.34-2.29 (m, 2H), 2.01-1.98 (m, 1H), 1.89-1.85 (m, 1H), 1.61-1.51 (m, 3H), 1.38-1.25 (m, 19H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ = 166.3, 164.3, 150.5, 147.4, 135.5, 130.8, 123.6, 122.0, 96.1, 78.0, 76.4, 60.2, 55.9, 31.9, 30.9, 29.64, 29.61, 29.56, 29.5, 29.3, 28.6, 27.8, 25.7, 22.7, 20.4, 14.1; HRMS (FAB) Calcd. For $C_{30}H_{47}NO_8Na$ $[M+Na]^+$: 572.3199. Found: 572.3206.

(2*E*,6*S*,7*R*)-7-Methoxymethoxynonadec-2-ene-1,6-diol: To a solution of above ester (4.62 g, 8.40 mmol) in CH_2Cl_2 (50 mL) was added DIBAL-H (37.0 mL, 37.0 mmol, 1.0 M in hexane) at −78 ºC. After being stirred for 15 min at the same temperature, the reaction was quenched with MeOH (30 mL). The mixture was warmed to room temperature, filtered through a celite and silica gel. Then the filtrate was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1:1) to give diol (3.02 g, quant.) as a colorless oil. $[\alpha]^{23}_D$ −12 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 5.75-5.65 (m, 2H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.10-4.09 (m, 2H), 3.60-3.58 (m, 1H), 3.52 (td, *J* = 8.9, 3.1 Hz, 1H), 3.42 (m, 3H), 2.83, (d, *J* = 7.2 Hz, 1H), 2.35-2.29 (m, 1H), 2.15-2.10 (m, 1H), 1.57-1.50 (m, 3H), 1.49-1.37 (m, 2H), 1.32-1.26 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ = 132.8, 129.4, 97.3, 84.3, 72.3, 63.7, 55.8, 31.9, 30.9, 30.4, 29.63, 29.60, 29.55, 29.3, 28.8, 26.0, 22.7, 14.1; HRMS (CI) Calcd. For $C_{21}H_{43}O_4$ $[M+H]^+$: 359.3161. Found: 359.3154.

(2*E*,6*S*,7*R*)-1-(*tert*-Butyldimethylsilyloxy)-7-methoxymethoxynonadec-2-en-6-ol (8): To a solution of above diol (3.02 g, 8.40 mmol), Et_3N (1.8 mL, 13 mmol), and TBDMSCl (1.39 g, 9.24 mmol) in CH_2Cl_2 (20 mL) was added DMAP (103 mg, 0.840 mmol). The resulting mixture was stirred at room temperature

for 18 h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give **8** (3.97 g, quant.) as a colorless oil. $[\alpha]^{28}_D$ +7.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 5.67-5.64 (m, 1H), 5.61-5.56 (m, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.13 (dd, *J* = 5.2, 1.2 Hz, 2H), 3.59-3.57 (m, 1H), 3.53-3.50 (m, 1H), 3.42 (s, 3H), 2.83 (d, *J* = 6.8 Hz, 1H), 2.30 (m, 1H), 2.11 (m, 1H), 1.53-1.47 (m, 3H), 1.41-1.30 (m, 3H), 1.32-1.26 (m, 18H), 0.84 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz): δ = 130.7, 129.6, 97.3, 84.4, 72.4, 63.9, 55.7, 31.9, 31.0, 30.4, 29.63, 29.61, 29.58, 29.5, 29.3, 28.7, 26.0, 25.9, 22.6, 18.4, 14.1, –5.2; HRMS (EI) Calcd. For $C_{27}H_{56}O_4Si$ $[M]^+$: 472.3948. Found: 472.3954.

(2*E*,6*R*,7*R*)-6-[*N*-(*tert*-Butoxycarbonyl)amino]-1-(*tert*-butyldimethylsilyloxy)-7-methoxymethoxynonadec-2-ene (9): DIAD (6.7 mL, 34 mmol) was added dropwise to a solution of **8** (3.97 g, 8.40 mmol), DPPA (7.3 mL, 34 mmol), and triphenylphosphine (8.92 g, 34.0 mmol) in THF (30 mL) at 0 ºC. The mixture was stirred for 16 h at room temperature, and then the reaction mixture was concentrated. The residue was roughly purified by silica gel column chromatography (hexane/EtOAc = 20:1). To a suspension of $LiAlH_4$ (638 mg, 16.8 mmol) in THF (30 mL), azide, prepared as described above, in THF (10 mL) was added. After being stirred for 1 h, the reaction was quenched with H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by silica gel column chromatography (hexane/EtOAc = 1:1). The residue was dissolved in CH_2Cl_2 then, Et_3N (1.8 mL, 13 mmol) and Boc_2O (2.1 mL, 9.2 mmol) were added. After stirring for 15 h, the reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford **9** (3.84 g, 80%, 3 steps) as a colorless oil. $[\alpha]^{28}_D$ –9.6 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 5.67-5.53 (m, 2H) 4.68 (d, *J* = 6.8 Hz, 1H), 4.66 (m, 1H), 4.59 (d, *J* = 7.2 Hz, 1H), 4.12 (dd, *J* = 5.2, 1.2 Hz, 2H), 3.68-3.66 (m, 1H), 3.52-3.49 (m, 1H), 3.35 (s, 3H), 2.13-2.05 (m, 2H), 1.60-1.54 (m, 2H), 1.49-1.45 (m, 2H), 1.44 (s, 9H), 1.33-1.25 (m, 20H), 0.90 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz): δ = 155.9, 130.5, 129.6, 95.9, 79.0, 78.9, 64.0, 55.9, 52.0, 32.6, 31.9, 31.3, 29.7, 29.64, 29.60, 29.5, 29.3, 28.9, 28.4, 26.0, 25.5, 22.7, 18.4, 14.1, –5.1; HRMS (EI) Calcd. For $C_{32}H_{65}NO_5Si$ $[M]^+$: 571.4632. Found: 571.4628.

(2*E*,6*R*,7*R*)-6-[*N*-(*tert*-Butoxycarbonyl)]-7-methoxymethoxynonadec-2-en-1-ol (5): To a solution of **9** (3.84 g, 6.72 mmol) in THF (20 mL) was added TBAF (13.5 mL, 13.5 mmol, 1.0 M in THF) at 0 ºC.

After stirring for 12 h, the reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to give **5** (2.71 g, 88%) as a colorless oil. $[\alpha]^{28}_D$ –9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 5.73-5.61 (m, 2H), 4.71 (d, *J* = 10.0 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.07 (d, *J* = 4.4 Hz, 2H), 3.72-3.65 (m, 1H), 3.51-3.45 (m, 1H), 3.35 (s, 3H), 2.15-2.10 (m, 2H), 2.00 (brs, 1H), 1.62-1.57 (m, 2H), 1.54-1.45 (m, 2H), 1.44 (s, 9H), 1.39-1.25 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ = 155.9, 132.2, 129.8, 95.9, 79.1, 79.0, 63.6, 55.8, 51.6, 32.2, 31.9, 31.3, 29.7, 29.60, 29.57, 29.4, 29.3, 28.8, 28.4, 25.5, 22.6, 14.1; HRMS (EI) Calcd. For $C_{26}H_{51}NO_5$ $[M]^+$: 457.3767. Found: 457.3763.

(2*R*,5*S*,1'*R*)-*N*-(*tert*-Butoxycarbonyl)-2-(1'-methoxymethoxytridecanyl)-5-vinylpyrrolidine (4a): To a solution of **5** (1.04 g, 2.27 mmol) in THF (15 mL) was added $PdCl_2$ (40.2 mg, 0.227 mmol) at 0 °C under an argon gas atmosphere, and the mixture was stirred at room temperature for 4 h. The reaction mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give **4a** (860 mg, 86 %) as a colorless oil. $[\alpha]^{29}_D$ +16 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz): δ = 5.78 (ddd, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.14 (d, *J* = 16.8 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.26-4.26 (m, 1H), 4.09-4.07 (m, 1H), 3.94-3.90 (m, 1H), 3.38 (s, 3H), 2.05-1.85 (m, 3H), 1.79-1.66 (m, 1H), 1.45 (m, 11H), 1.36-1.25 (m, 20H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ = 155.4, 139.9, 114.5, 96.8, 79.6, 79.1, 61.5, 60.9, 55.7, 31.9, 31.0, 29.67, 29.65, 29.63, 29.61, 29.57, 29.3, 28.4, 26.1, 25.1, 22.7, 14.1; HRMS (EI) Calcd. For $C_{26}H_{49}NO_4$ $[M]^+$: 439.3662. Found: 439.3668.

(2*R*,5*S*,1'*R*,1"*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(1",2"-dihydroxyethyl)-2-(1'-methoxymethoxytridecanyl)pyrrolidine (10): A suspension of $(DHQD)_2AQN$ (16.7 mg, 19.5 μmol), $K_2OsO_2(OH)_4$ (2.9 mg, 7.8 μmol), $K_3[Fe(CN)_6]$ (1.93 g, 5.85 mmol) and K_2CO_3 (809 mg, 5.85 mmol) in *t*-BuOH/H_2O (1:1, 10 mL) was stirred at 0 °C for 15 min. A solution of **4a** (860 mg, 1.95 mmol) in *t*-BuOH (3.0 mL), $MeSO_2NH_2$ (185 mg, 1.95 mmol), and H_2O (3.0 mL) were added to the suspension. The mixture was stirred for 22 h at the same temperature. The reaction was quenched with aqueous Na_2SO_3, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give **10** (713 mg, 80%) as a colorless oil. $[\alpha]^{25}_D$ –9.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, 2:1 amide rotamer): δ = 5.56 (brs, 0.33H), 4.69-4.62 (m, 2H), 4.15-4.09 (m, 1H), 4.06-4.01 (m, 1H), 3.93 (brs, 0.33H), 3.86 (brs, 0.67H), 3.74-3.70 (m, 0.33H), 3.65-3.55 (m, 2H), 3.53-3.47 (m, 0.67H), 3.39 (s, 1H), 3.38 (s, 2H), 3.04 (brs,

0.67H), 2.13-1.73 (m, 5H), 1.53-1.37 (m, 3H), 1.49 (s, 3H), 1.48 (s, 6H), 1.32-1.26 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ = 158.8, 157.2, 96.8, 96.6, 81.3, 81.0, 79.3, 78.8, 78.7, 75.5, 72.1, 64.5, 62.6, 61.5, 61.4, 61.1, 60.8, 55.8, 31.9, 29.7, 29.61, 29.58, 29.54, 29.49, 29.3, 28.28, 28.25, 26.0, 25.7, 22.6, 14.1; HRMS (CI) Calcd. For $C_{26}H_{52}NO_6$ $[M+H]^+$: 474.3795. Found: 474.3787.

(2*R*,5*S*,1'*R*,"*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(1'-methoxymethoxytridecanyl)-5-(oxiran-1"-yl)pyrrolidine (11): To a solution of **10** (713 mg, 1.56 mmol) in pyridine (10 mL) was added *p*-TsCl (327 mg, 1.72 mmol) at 0 °C. The mixture was stirred at the same temperature for 21 h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by silica gel column chromatography (hexane/EtOAc = 3:1). The residue was dissolved in MeOH (10 mL) and K_2CO_3 (2.16 g, 15.6 mmol) was added. After stirring for 10 h, the reaction was diluted with H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by PTLC (hexane/EtOAc = 3:1) to give **11** (455 mg, 64%, 2 steps) as a colorless oil. $[\alpha]^{29}_D$ +11 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 4.74 (d, *J* = 6.8 Hz, 1H), 4.61 (brs, 1H), 4.09-4.06 (m, 1H), 3.95-3.91 (m, 1H), 3.71 (m, 1H), 3.39 (s, 3H), 3.09 (brs, 1H), 2.83 (dd, *J* = 4.8, 4.0 Hz, 1H), 2.71 (brs, 1H), 1.92-1.89 (m, 4H), 1.48 (s, 9H), 1.44-1.38 (m, 4H), 1.32-1.25 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ = 155.4, 96.8, 80.0, 79.0, 60.9, 60.5, 55.8, 53.2, 47.5, 31.9, 29.72, 29.67, 29.65, 29.63, 29.61, 29.3, 28.4, 26.0, 25.3, 22.7, 14.1; HRMS (CI) Calcd. For $C_{26}H_{50}NO_5$ $[M+H]^+$: 456.3689. Found: 456.3683.

(2*R*,5*S*,1'*R*,1"*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(1"-hydroxybut-3"-ynyl)-2-(1'-methoxymethoxytridecanyl)pyrrolidine (2): To a suspension of lithium acetylide, an ethylenediamine complex (348 mg, 3.78 mmol) in DMSO (5.0 mL) was added **11** (172 mg, 0.378 mmol) in DMSO (5.0 mL) at 0 °C. The reaction mixture was stirred for 18 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by PTLC (hexane/EtOAc = 6:1) to give **2** (102 mg, 56%) as a colorless oil. $[\alpha]^{29}_D$ –10 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 4.68 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.33 (brs, 1H), 4.10-4.05 (m, 1H), 3.52 (brs, 1H), 3.40 (s, 3H), 2.43-2.40 (m, 1H), 2.13-2.08 (m, 1H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.92-1.76 (m, 3H), 1.58-1.53 (m, 1H), 1.47 (s, 9H), 1.45-1.39 (m, 2H), 1.34-1.26 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ = 156.5, 96.8, 82.1, 81.0, 80.0, 69.7, 69.4, 63.1, 60.8, 55.9, 32.6, 31.8, 29.8, 29.60, 29.57, 29.52, 29.47, 29.3, 28.4, 27.4, 25.0, 23.6, 22.6, 22.4, 14.0; HRMS (CI) Calcd. For $C_{28}H_{52}NO_5$ $[M+H]^+$: 482.3845. Found: 482.3842.

(8'*EZ*,5*S*,13'*R*,2"*S*,5"*R*,1"'*S*)-3-{13'-[*N*-(*tert*-Butoxycarbonyl)-13'-hydroxy-2"-(1"'-methoxymethoxytridecanyl)pyrrolidin-5"-yl]-tridec-8'-en-10'-ynyl}-5-methyl-2,5-dihydrofuran-2-one (12): To a solution of lactone **3** (30.9 mg, 0.0887 mmol) in Et_3N (1.0 mL) was added $Cl_2Pd(PPh_3)_2$ (1.3 mg, 8.87 μmol) under an argon gas atmosphere. After being stirred for 60 min, a solution of **2** (42.8 mg, 0.0887 mmol) in Et_3N (2.0 mL) and CuI (0.6 mg, 8.87 μmol) were added to the solution. After being stirred for 12 h, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give **12** (35.5 mg, 57%) as a colorless oil. $[\alpha]^{29}_D$ +5.4 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, 5:1 geometrical isomer, major isomer): δ = 6.98 (q, *J* = 1.5 Hz, 1H), 6.09-6.01 (m, 1H), 5.46-5.42 (m, 1H), 5.01-4.97 (m, 1H), 4.69-4.62 (m, 3H), 4.32-4.30 (m, 2H), 4.10-4.04 (m, 3H), 3.51 (m, 1H), 3.39 (s, 3H), 2.50 (m, 1H), 2.33-2.23 (m, 2H), 2.10-2.05 (m, 2H), 1.88-1.75 (m, 2H), 1.63-1.52 (m, 3H), 1.47 (s, 9H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.38-1.25 (m, 30H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ = 173.9, 156.5, 148.9, 143.7, 134.3, 109.7, 96.8, 80.6, 79.9, 77.4, 69.8, 69.5, 60.8, 56.0, 32.9, 31.9, 29.9, 29.65, 29.63, 29.59, 29.5, 29.3, 29.1, 28.7, 28.5, 27.4, 25.1, 22.7, 19.2, 14.1; HRMS (EI) Calcd. For $C_{42}H_{71}NO_7$ $[M]^+$: 701.5230. Found: 701.5228.

(5*S*,13'*R*,2"*S*,5"*R*,1"'*S*)-3-{13'-[*N*-(*tert*-Butoxycarbonyl)-13'-hydroxy-2"-(1"'-methoxymethoxytridecanyl)pyrrolidin-5"-yl]-tridecanyl}-5-methyl-2,5-dihydrofuran-2-one (13): To a solution of **12** (15.5 mg, 0.0221 mmol) in 1,2-diethoxyethane (1.0 mL) was added *p*-$TsHNNH_2$ (288 mg, 1.55 mmol), and the resulting mixture was stirred for 2 h at 80 °C. A solution of AcONa (154 mg, 1.88 mmol) in H_2O (1.0 mL) was added dropwise and stirred at same temperature for 5 h. The reaction was diluted with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by PTLC (hexane/CH_2Cl_2/ether = 6:2:1) to give **13** (11.7 mg, 75%) as a colorless oil. $[\alpha]^{28}_D$ –4.0 (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz): δ = 6.99 (d, *J* = 1.2 Hz, 1H), 5.07 (qd, *J* = 6.8, 1.6 Hz, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.10 (m, 2H), 3.78 (m, 1H), 3.53 (m, 1H), 3.40 (s, 3H), 2.27 (t, *J* = 7.7 Hz, 2H), 2.14-2.04 (m, 2H), 1.83-1.78 (m, 3H), 1.60-1.47 (m, 6H), 1.46 (s, 9H), 1.43-1.25 (m, 38H), 1.41 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ = 173.9, 156.7, 156.6, 148.8, 134.4, 131.9, 96.8, 81.8, 79.7, 70.9, 70.7, 60.9, 56.0, 55.9, 33.7, 31.9, 29.9, 29.8, 29.63, 29.59, 29.54, 29.51, 29.4, 29.34, 29.31, 29.2, 29.0, 28.5, 27.4, 26.3, 25.2, 22.7, 19.2, 14.1; HRMS (CI) Calcd. For $C_{42}H_{78}NO_7$ $[M+H]^+$: 708.5778. Found: 708.5782.

Aza-*cis*-solamin (1): Compound **13** (11.7 mg, 0.0166 mmol) was dissolved in MeOH (1.0 mL) and a few drops of conc. HCl aq. were added. After stirring for 1 h, the reaction was quenched with saturated aqueous of $NaHCO_3$ and the whole was extracted with EtOAc. The organic layer was washed with brine,

dried over Na_2SO_4, filtered, and concentrated and then, the residue was washed with hexane to give **1** (7.3 mg, 78%) as a colorless solid. Mp 82-85 ºC; $[\alpha]^{28}_D$ +7.8 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz): δ = 6.98 (d, *J* = 1.5 Hz, 1H), 5.03-5.96 (m, 1H), 3.58 (m, 1H), 3.27 (m, 2H), 3.12-3.10 (m, 1H), 2.42-2.10 (m, 10H), 1.86-1.68 (m, 4H), 1.57-1.50 (m, 5H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.38-1.26 (m, 34H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ = 173.9, 148.8, 134.3, 73.9, 71.8, 62.8, 35.0, 33.8, 31.9, 29.7, 29.64, 29.61, 29.56, 29.5, 29.33, 29.27, 29.2, 29.1, 28.9, 28.8, 27.4, 26.1, 25.94, 25.85, 25.6, 25.1, 24.4, 22.7, 19.2, 14.1; HRMS (EI) Calcd. For $C_{35}H_{65}NO_4$ $[M]^+$: 563.4914. Found: 563.4920.

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