HETEROCYCLES, Vol. 94, No. 2, 2017, pp. 286 - 296. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 30th November, 2016, Accepted, 13th January, 2017, Published online, 24th January, 2017
DOI: 10.3987/COM-16-13631

SYNTHESIS OF (–)-ISOSOLENOPSIN USING DIASTEREOSELECTIVE AMINOPALLADATION

Yukiko Takemoto,[a] Yasunao Hattori,[b] and Hidefumi Makabe[a]*

[a]Sciences of Functional Foods, Graduate School of Agriculture, Shinshu University, 8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan
[b]Center for Instrumental Analysis, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan
*E-mail: makabeh@shinshu-u.ac.jp

Abstract – Concise synthesis of (–)-isosolenopsin, a piperidine alkaloid isolated from the fire ants (*Solenopsis*) was achieved. 2,6-Disubstituted piperidine ring of (–)-isosolenopsin was constructed using diastereoselective aminopalladation. Chain elongation using Grubbs 2nd catalyst followed by reduction of double bond and deprotection of the Boc group afforded (–)-isosolenopsin.

INTRODUCTION

Among a huge class of biologically active natural compounds, the piperidine alkaloids are most paid attention due to their significant biological activities and unique structures. Many piperidine alkaloids possess a chiral center at C2 and/or C6 position thus stereoselective construction is very important. So far, a large number of synthetic studies on 2,6-disubstituted piperidine have been reported.[1] To construct 2,6-disubstituted piperidine ring in a stereoselective manner, Pd-catalyzed cyclization of amino allylic alcohol (aminopalladation) is powerful tool. For example, stereoselective synthesis of *trans*-2,6-disubstituted piperidine alkaloids (−)-desoxoprosopinine using Pd(0)-catalyzed *N*-alkylation was achieved by Tadano in 1994.[2] In 2000, Hirai reported the synthesis of 1-deoxymannojirimycin using Pd(II)-catalyzed cyclization of amino allylic alcohol to afford 2-substituted piperidine with excellent diastereoselectivity.[3] We also reported the synthesis of (−)-cassine and (+)-azimine using Pd(II)-catalyzed diastereoselective cyclization.[4,5] Isosolenopsin and solenopsin were isolated from the fire ants (*Solenopsis*) and show hemolytic, insecticidal and antibiotic activities (Figure 1).[6] So far, five examples of the synthesis of isosolenopsin have been reported.[7-11] To construct 2,6-disubstituted piperidine ring,

stereoselective aminopalladation is powerful tool.[4,5] In this paper, we wish to report the synthesis of (−)-isosolenopsin using diastereoselective aminopalladation.

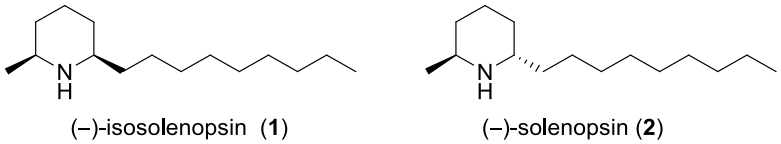
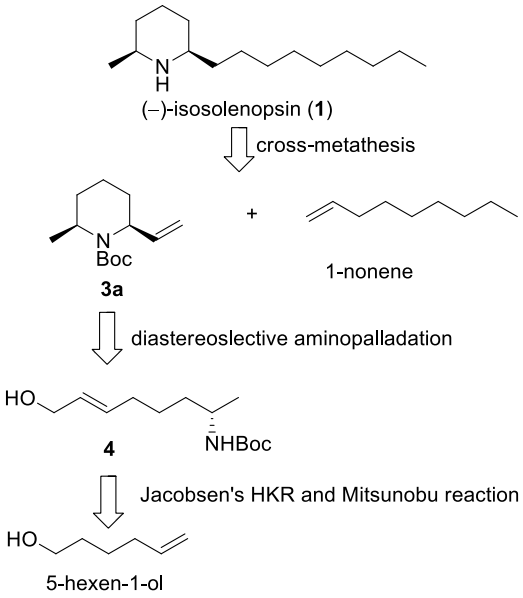


Figure 1. The structures of (−)-isosolenopsin (**1**) and (−)-solenopsin (**2**)

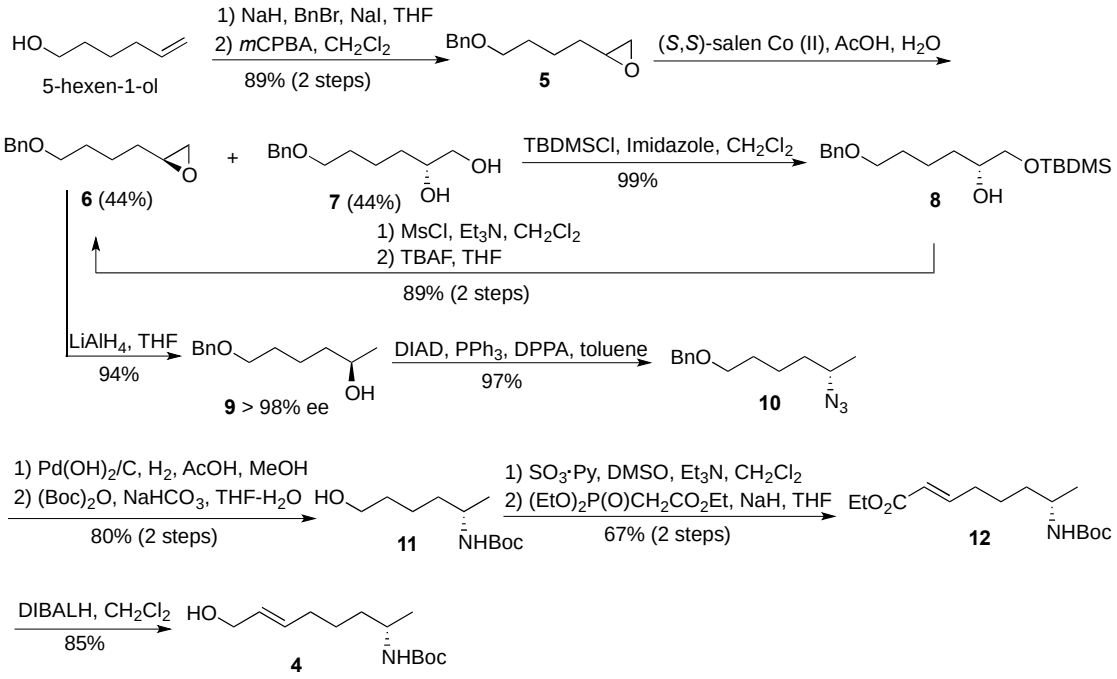
The synthetic strategy is shown in Scheme 1. The side chain would be introduced using cross-metathesis. The piperidine ring **3a** would be constructed using diastereoselective aminopalladation of **4**. Cyclization precursor **4** would be prepared from commercially available 5-hexen-1-ol (Scheme 1).



Scheme 1. Synthetic strategy of (−)-isosolenopsin (**1**)

Scheme 2 shows the preparation of cyclization precursor **4**. Protection of the hydroxy group of 5-hexen-1-ol with BnBr in the presence of NaH and catalytic amount of NaI afforded corresponding benzyl ether. Oxidation of the double bond with *m*CPBA gave racemic epoxide **5**. The Jacobsen's hydrolytic kinetic resolution using (*S*,*S*)-salen Co(II) gave optically active epoxide **6**.[12] The known diol **7**[13] could be converted to **6** after protection of the primary hydroxy group of **7** with TBDMSCl and imidazole followed by mesylation and treatment with TBAF in 89% yield using similar procedure reported by Das and co-workers.[14] Reduction of **6** using $LiAlH_4$ afforded **9**. The enantiomeric excess of **9** was more than 98% ee by ^1H NMR analysis of the corresponding Mosher ester. Mitsunobu reaction of **9** using DPPA and DIAD in the presence of PPh_3 afforded azide **10**.[15] Hydrogenolysis of the benzyl group and reduction of the azido group of **10** with Pearlman's catalyst in the presence of AcOH under hydrogen atmosphere, and subsequent protection of the amino group with *t*-butoxycarbonyl group afforded **11**.

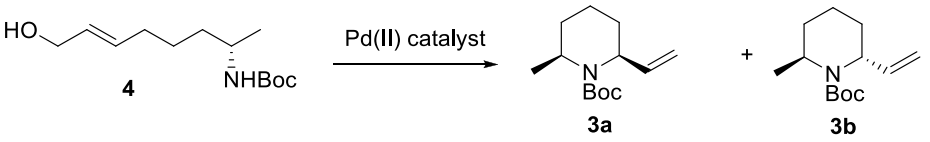
Oxidation of the primary hydroxyl group of **11** with SO_3·pyridine complex and DMSO afforded aldehyde followed by treatment with triethy phosphonoacetate and NaH gave **12** in 67% yield. Reduction of the ester carbonyl group of **12** with DIBALH afforded cyclization precursor **4** (Scheme 2).



Scheme 2. Synthesis of cyclization precursor **4**

With the cyclization precursor in hand, we examined diastereoslective aminopalladation of **4**. As shown in Table 1, $Cl_2Pd(MeCN)_2$ afforded **3a** (*cis*/*trans* > 98 : 2) in moderate yield. Changing the solvent from THF to CH_2Cl_2 to give **3a** in slightly better yield as we reported before.[5] To our surprise, changing the Pd catalyst to $PdCl_2$ gave diastereomeric mixture of **3a** and **3b** as a ratio of 58 : 42 (Table 1).

Table 1. Diastereoselective aminopalladation of **4**.



catalyst	amount of catalyst (mol%)	solvent	time (h)	yield (%)[a]	**3a** : **3b**[a]
$PdCl_2$	10	THF	29	50	58 : 42
$Cl_2Pd(MeCN)_2$	20	THF	29	43	>98 : 2
$Cl_2Pd(MeCN)_2$	20	CH_2Cl_2	6	48	>98 : 2

[a]The yield and ratio of **3a** and **3b** were determined by ^{1}H NMR analysis of crude products using $BrCH_2CH_2Br$ as an internal standard.

Determination of the relative stereochemistry of **3a** was performed by 2D-NOESY experiment. As shown in Figure 2, the NOESY correlation was observed between the methyl proton at C6 position and the internal olefinic proton at C1' position. The correlation between C2 proton and terminal olefinic proton at C2' position was also observed (Figure 2).

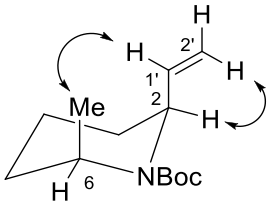


Figure 2. Determination of relative stereochemistry of **3a** using 2D-NOESY correlations

As shown in Figure 3, two kinds of transition state A and B can be considered. The transition A is favorable because of the chelation effect of Pd catalyst between two oxygens of allylic hydroxy group and Boc group. Transition state B would be less favorable because of the steric hindrance between the Boc group and π-allyl Pd complex. When ligand-free Pd catalyst was used, formation of transition state B, which gave 2,6-*trans* piperidine ring, was possible because of lower steric hindrance of Pd catalyst (Figure 3).

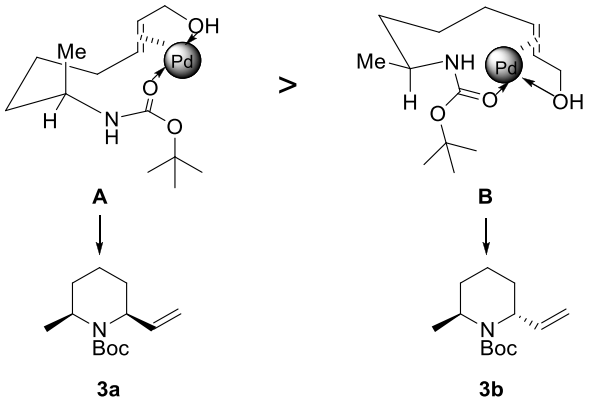


Figure 3. Proposed transition state

The conformation of a model of **3a** and **3b** were obtained using DFT calculations by Spartan'14. As shown in Figure 4, piperidine ring **3b** has severe steric hindrance between the Boc group and vinyl side chain (Figure 4).

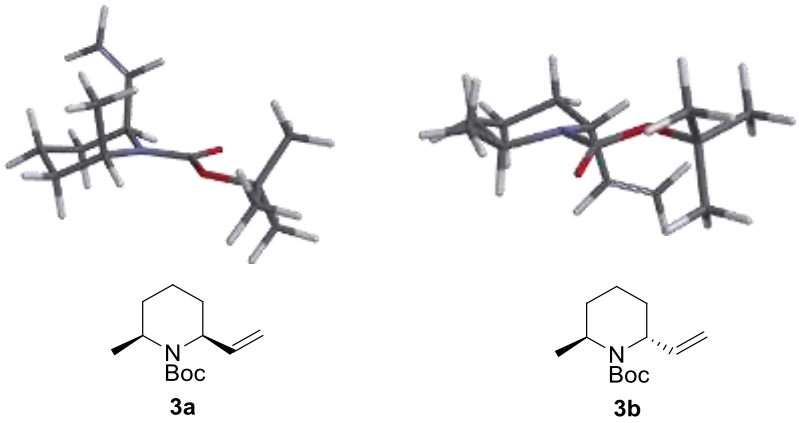
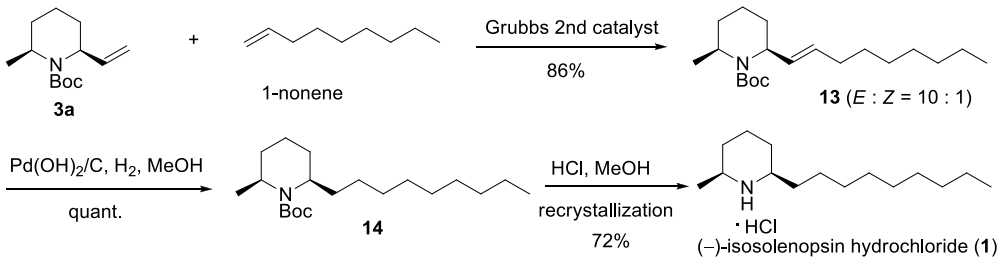


Figure 4. The conformation model **3a** and **3b** were obtained using DFT calculations

Because piperidine ring moiety of **1** was synthesized, we began total synthesis of (–)-isosolenopsin (**1**). Cross-metathesis between **3a** and 1-nonene using second generation Grubbs catalyst afforded chain elongated compound **13** in 86% yield.[16] Saturation of the olefin **13** under hydrogen atmosphere in the presence of Pearlman's catalyst afforded **14**. Finally, deprotection of the Boc group with methanolic HCl and subsequent treatment of 1.0 N HCl in ether gave (–)-isosolenopsin hydrochloride (**1**). The ^{1}H and ^{13}C NMR data of the synthetic (–)-isosolenopsin hydrochloride (**1**) were consistent with those of the reported values (Scheme 3).[6, 11]



Scheme 3. Synthesis of (–)-isosolenopsin (**1**)

CONCLUSION

In conclusion, concise synthesis of (–)-isosolenopsin was achieved using diasereoselective aminopalladation using $Cl_2Pd(MeCN)_2$ as a catalyst. The studies on biological activities of (–)-isosolenopsin (**1**) is now underway.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX 500 FT-NMR spectrometer in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hz. Mass spectra were obtained on JEOL JMS-SX102A

mass spectrometer. IR spectra were recorded with JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

(*S*)-1-(Benzyloxy)-4-(oxyranyl)butane (6). To a solution of (*S*,*S*)-(+)-*N*,*N*`-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) (68 mg, 0.11 mmol) in toluene (0.8 mL) was added AcOH (0.013 mL, 0.11 mmol). After being stirred for 1 h, the solvent was evaporated and **5** (4.6 g, 22 mmol) was added to the mixture. The mixture was cooled to 0 ºC, H_2O (0.22 mL, 12 mmol) was added. After being stirred for 28 h at room temperature, the solvent, AcOH, and H_2O were evaporated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 10 : 1 – 1 : 1) to afford **6** (2.0 g, 44%) as a light yellow oil along with diol **7** (2.2 g, 44%). The data for **6**:, $[\alpha]^{20}_D$ –4.4 (*c* 0.63, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3032, 2935, 2857, 1716, 1653, 1558 1541, 1497, 1455, 1362, 1258, 1098, 1027, 913, 835, 735, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.48-1.60 (4H, m), 1.61-1.70 (2H, m), 2.44 (1H, dd, *J* = 4.8, 2.8 Hz), 2.72 (1H, t, *J* = 4.5 Hz), 2.89 (1H, m), 3.47 (2H, t, *J* = 6.5 Hz), 4.49 (2H, s), 7.24-7.42 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.6, 29.4, 32.2, 46.9, 52.1, 70.0, 72.8, 127.4, 127.5 (C x 2), 128.3 (C x 2), 138.5 ppm; HREIMS $[M]^+$: Found, 206.1310. Calcd for $C_{13}H_{18}O_2$: 206.1307.

(*R*)-6-Benzyloxyhexane-1,2-diol (7). This compound was prepared as described above. $[\alpha]^{20}_D$ +0.400 (*c* 2.42, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3600-3090, 3087, 3063, 3030, 2938, 2863, 1717, 1653, 1496, 1454, 1410, 1363, 111, 1205, 1099, 736, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.39-1.70 (6H, m), 2.97 (1H, brs), 3.06 (1H, brs), 3.35 (1H, t, *J* = 9.0 Hz), 3.46 (2H, t, *J* = 6.3 Hz), 3.54 (1H, d, *J* = 11.0 Hz), 3.62 (1H, m), 4.48 (2H, s), 7.27-7.36 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.1, 29.5, 32.7, 66.5, 70.1, 71.9, 72.8, 127.5, 127.6 (C x 2), 128.3 (C x 2), 138.2 ppm.

(*R*)-6-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hexan-2-ol (8). To a solution of **7** (3.8 g, 17 mmol) in CH_2Cl_2 (30 mL) were added imidazole (1.4 g, 20 mmol). After the mixture was cooled to 0 ºC, TBDMSCl (2.7g, 18 mmol) and catalytic amount of DMAP were added to the mixture. After being stirred for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (50 mL x 2) and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 5 : 1) to afford **8** (5.2 g, 91%) as a colorless oil. $[\alpha]^{20}_D$ –2.4 (*c* 0.56, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3458, 3030, 2929, 2857, 1471, 1462, 11362, 1254, 1100,1029, 1006, 938, 837, 815, 778, 735, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.00 (6H, s), 0.82 (9H, s), 1.34-1.60 (6H, m), 3.31 (1H, dd, *J* = 7.0, 2.5 Hz), 3.41 (2H, t, *J* = 6.5 Hz), 3.55-3.57 (2H, m), 4.43 (2H, s), 7.18-7.27 (5H, m); ^{13}C NMR (125 MHz,

$CDCl_3$) δ: –5.5, –5.4, 18.2, 22.2, 25.8 (C x 3), , 29.7, 32.5, 67.2, 70.2, 71.7, 72.8, 127.4, 127.5 (C x 2), 128.3 (C x 2), 138.5 ppm.

(*S*)-1-(Benzyloxy)-4-(oxyranyl)butane (6) from 8. To a solution of **8** (2.3 g, 6.2 mmol) in CH_2Cl_2 (70 mL) was added Et_3N (9.7 mL, 69 mmol) and MsCl (0.73 mL, 8.3 mmol) at –5 °C. After being stirred for 30 min at this temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved into THF (45 mL) and TBAF (1.0 mol/L solution in THF, 17 mL, 17 mmol) was added to the mixture. After being stirred for 20 min at room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (75 mL x 2) and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 7 : 1) to afford **6** (1.3 g, 89%) as a pale yellow oil. The specific rotation value and spectral data of this compound were completely identical to those of compound **6** prepared as described above.

(*R*)-6-Benzyloxyhexan-2-ol (9). To a suspension of $LiAlH_4$ (3.3 g, 16 mmol) in THF (50 mL) was added **6** (3.0 g, 80 mmol). After being stirred for 1 h, the reaction was quenched with H_2O (4.3 mL, 24 mmol) in THF (40 mL). The reaction mixture was filtered through Celite® and silica gel with EtOAc. The organic solvents were concentrated and the residue was purified with silica gel column chromatography (hexane : EtOAc = 3 : 1) to afford **9** (3.1 g, 94%) as a pale yellow oil. $[\alpha]^{20}_D$ –4.6 (*c* 0.73, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3500-3100, 2935, 2861, 1455, 1365, 1308, 1100, 735, 697 cm^{-1}. ^{1} -NMR (500 MHz, $CDCl_3$) δ: 1.20 (3H, d, *J* = 6.0 Hz), 1.37-1.50 (4H, m), 1.55-1.70 (2H, m), 1.94 (1H, brm), 3.47 (2H, t, *J* = 6.0 Hz), 3.73-3.77 (1H, m), 4.49 (2H, s), 7.25-7.37 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.3, 23.3, 29.5, 38.9, 67.7, 70.1, 72.8, 127.4 (C x 2), 127.5, 128.2 (C x 2), 138.4 ppm. HREIMS $[M]^+$: Found, 208.1460. Calcd. for $C_{13}H_{20}O_2$: 208.1463.

(*S*)-2-Azido-6-benzyloxyhexane (10). To a solution of PPh_3 (2.80 g, 11 mmol) in toluene (80 mL) was added DIAD (2.20 mL, 11 mmol). After being stirred for 5 min, this mixture was added to a solution of **9** (1.1 g, 5.0 mmol) in toluene (90 mL). DPPA (2.5 mL, 11 mmol) was added to the mixture and the mixture was stirred for 19 h. After the reaction had been completed, the solvent was removed *in vacuo* and the resulting material was purified with silica gel column chromatography (hexane : EtOAc = 20 : 1) to afford **10** (1.1 g, 97%) as a pale yellow oil. $[\alpha]^{20}_D$ +19.5 (*c* 0.840, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 2937, 2860, 2360, 2097, 1653, 1455, 1362, 1252, 1102, 736, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (3H,

d, *J* = 6.5 Hz), 1.35-1.55 (4H, m), 1.50-1.66 (2H, m), 3.37-3.42 (1H, m), 3.43 (2H, t, *J* = 6.5 Hz), 4.47 (2H, s), 7.25-7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.2, 22.7, 29.3, 35.8, 57.7, 69.8, 72.7, 127.3, 127.4 (C x 2), 128.2 (C x 2), 138.4 ppm.

(*S*)-5-*tert*-Butoxycarbonylamino)hexan-1-ol (11). To a solution of **10** (1.1 g, 4.6 mmol) in MeOH (40 mL) was added AcOH (40 mL) and $Pd(OH)_2$/C (130 mg) under hydrogen atmosphere. After being stirred for 24 h, the mixture was filtered and the solvent was removed *in vacuo*. The resulting material was dissolved in THF-H_2O (1:1, 50 mL) and $NaHCO_3$ (1.2 g, 14 mmol) and di-*tert*-butyl bicarbonate (1.6 mL, 6.9 mmol) were added to the solution. After being stirred for 34 h, the mixture was extracted with EtOAc (75 mL x 2) and the organic layer was washed with water and dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 10 : 1 – 3 :1) to afford **11** (800 mg, 80% in 2 steps) as a pale yellow oil. $[\alpha]^{19}_D$ +1.4 (*c* 0.78, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3361, 2977, 1741, 1698, 1521, 1457, 1393, 1367, 1281, 1254, 1165, 1091, 857, 795. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (3H, d, *J* = 6.5 Hz), 1.42-1.50 (13H, m), 1.52-1.80 (4H, m), 3.63 (2H, m), 4.33 (1H, brs); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.2, 22.3, 28.4 (C x 3), 28.6, 36.9, 46.3, 66.9, 81.8, 155.3 ppm. HRCIMS $[M+H]^+$: Found, 218.1753. Calcd. for $C_{11}H_{24}NO_3$: 218.1756.

Ethyl (2*E*,7*S*)-7-(*tert*-butoxycarbonylamino)oct-2-enoate (12). To a solution of **11** (1.20 g, 5.7 mmol) in CH_2Cl_2 (28 mL) was added DMSO (4.10 mL, 57 mmol), Et_3N (4.0 mL, 29 mmol), and SO_3 pyridine complex (1.8 g, 11 mmol) at 0 °C. After being stirred for 30 min at room temperature, the reaction was quenched with H_2O. The mixture was extracted with EtOAc (80 mL x 2) and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude aldehyde was used for the next step without further purification. To a suspension of 60% NaH (411 mg, 10 mmol) in THF (18 mL) was added triethyl phosphonoacetate (1.7 mL, 8.6 mmol) at 0 °C. After being stirred for 1 h, the crude aldehyde in THF (10 mL) was added to the mixture and the mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with EtOAc (60 mL x 2). The organic layer was washed with water, brine and dried over $MgSO_4$, filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 10 : 1 – 3 :1) to afford **12** (1.1 g, 67% in 2 steps) as a pale yellow oil. $[\alpha]^{19}_D$ –1.40 (*c* 1.01, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3365, 2977, 2933, 1717, 1653, 1521, 1456, 1366, 1247, 1173, 1042, 681, 668. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (3H, d, *J* = 7.5 Hz), 1.29 (3H, t, *J* = 7.3 Hz), 1.35-1.55 (13H, m), 2.19-2.25 (2H, m), 3.63-3.66 (1H, m), 4.18 (2H, q, *J* = 7.2 Hz), 4.34 (1H, brd, *J* = 5.0 Hz), 5.82 (1H, dt, *J* = 16.0, 1.4 Hz), 6.94 (1H, dt, *J* = 15.5, 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 21.3, 24.5, 28.4 (C x 3), 31.9, 36.8, 46.2, 60.1, 79.1, 121.5, 148.7, 155.3, 166.6 ppm. HRCIMS $[M+H]^+$: Found, 286.2022. Calcd.

for $C_{15}H_{28}NO_4$: 286.2018.

(2*E*,7*S*)-7-(*tert*-Butoxycarbonylamino)oct-2-en-1-ol (4). To a solution of **12** (379 mg, 1.3 mmol) in CH_2Cl_2 (23 mL) was added DIBALH (1.0 mol/L solution in toluene, 4.1 mL, 4.1 mmol) at −78 °C. After being stirred for 1 h at this temperature, the reaction was quenched with water. The mixture was warmed to room temperature and filtered through Celite® and silica gel pad with EtOAc-MeOH (10 :1). The filtrate was concentrated *in vacuo* to give crude material. The residue was purified with silica gel column chromatography (hexane : EtOAc = 10 : 1 – 3 :1) to afford **5** (277mg, 85%) as a pale yellow oil. $[\alpha]^{20}_D$ +1.2 (*c* 0.66, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3334, 2932, 1685, 1523, 1456, 1365, 1250, 1173, 1084. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.10 (3H, d, *J* = 6.5 Hz), 1.39-1.48 (13H, m), 1.72 (1H, brs.), 2.06-2.07 (2H, m), 3.64 (1H, m), 4.09 (2H, d, *J* = 4.5 Hz), 4.35 (1H, brs), 5.66 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.2, 25.6, 28.4 (C x 3), 31.9, 36.7, 46.2, 63.7, 79.0, 129.4, 132.8, 155.4 ppm. HRCIMS $[M+H]^+$: Found, 244.1916. Calcd. for $C_{13}H_{26}NO_3$: 244.1913.

(2*S*,6*S*)-*N*-*tert*-Butoxycarbonyl-2-methyl-6-vinylpiperidine (3a). To a solution of **4** (335 mg, 1.4 mmol) in CH_2Cl_2 (27 mL) was added $Cl_2Pd(MeCN)_2$ (71 mg, 0.27 mmol) at 0 °C. After being stirred for 6 h, the reaction was quenched with water. The mixture was extracted with Et_2O (30 mL x 2). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 20 : 1 – 2 :1) to afford **3** (130 mg, 42%) as a colorless oil. $[\alpha]^{19}_D$ –12.1 (*c* 0.580, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2934, 1689, 1392, 1362, 1178, 1098, 1080. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.14 (3H, d, *J* = 7.0 Hz), 1.42-1.58 (10H, m), 1.60-1.78 (4H, m), 1.85-1.87 (1H, m), 4.32 (1H, m), 4.66 (1H, m), 5.06 (1H, d, *J* = 10.5 Hz), 5.11 (1H, d, *J* = 17.5 Hz), 5.90 (1H, ddd, *J* = 17.5, 11.0, 5.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.3, 20.3, 28.0, 28.4 (C x 3), 30.2, 46.1, 51.5, 79.2, 114.3, 140.4, 155.3 ppm. HREIMS $[M]^+$: Found, 225.1721. Calcd. for $C_{13}H_{23}NO_2$: 225.1729.

(2*S*,6*S*,1'*EZ*)-*N*-*tert*-Butoxycarbonyl-2-methyl-6-(non-1'-enyl)piperidine (13). To a solution of **3** (38 mg, 0.17 mmol) and 1-nonene (160 μL, 0.84 mmol) in CH_2Cl_2 (6.0 mL) was added Grubbs 2nd catalyst (14 mg, 0.02 mmol). After stirring for 1 day under reflux, an additional amount of 1-nonene (160 μL, 0.84 mmol) and Grubbs 2nd catalyst (14 mg, 0.02 mmol) were added. After stirring for 1 day under reflux, the solvent was removed and the residue was purified roughly by silica gel column chromatography (hexane to hexane/EtOAc = 10:1) followed by preparative TLC (hexane : EtOAc = 10 : 1) to give **13** (47 mg, 86%, *E* : *Z* = 10 : 1) as a colorless oil. $[\alpha]^{19}_D$ –10.7 (*c* 0.340, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 2929, 1689,

1363, 1178, 1078, 1077, 796, 712; ^{1}H NMR (500 MHz, $CDCl_3$ for *E*-isomer) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.14 (3H, d, *J* = 7.0 Hz), 1.25-1.40 (10H, m), 1.40-1.85 (6H, m), 1.49 (9H, s), 2.00 (2H, m), 4.30 (1H, m), 4.63 (1H, m), 5.49 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$ for *E*-isomer) δ: 14.1, 14.4, 20.5, 22.7, 28.5 (C x 3), 28.8, 29.1 (C x 2), 29.3, 30.2, 31.9, 32.4, 46.0, 51.0, 79.0, 130.8, 131.6, 155.3 ppm. HREIMS $[M]^+$: Found, 323.2822, Calcd. for $C_{20}H_{37}NO_2$: 323.2824.

(2*S*,6*R*)-2-Methyl-*N*-*tert*-butoxycarbonyl-6-nonylpiperidine (14). $Pd(OH)_2$/C (4.2 mg) was added to a solution of **13** (48.5 mg, 0.15 mmol) in MeOH (15 mL) under hydrogen atmosphere. After being stirred for 12 h, the mixture was filtered and concentrated to afford **14** (48.8 mg, quant.) as a colorless oil. $[\alpha]^{19}_D$ +8.4 (*c* 0.35, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2929, 2856, 2359, 1688, 1559, 1457, 1365, 1177, 1080; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* = 7.0 Hz), 1.15 (3H, d, *J* = 7.0 Hz), 1.20-1.35 (16H, m), 1.35-1.70 (5H, m), 1.49 (9H, s), 4.03 (1H, m), 4.29 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 20.4, 22.7, 27.5, 27.6, 28.4, 28.5 (C x 3), 29.3, 29.6, 29.7 (C x 2), 30.3, 31.9, 35.1, 45.5, 50.3, 78.8, 155.4 ppm; HREIMS $[M]^+$: Found, 325.2984, Calcd. for $C_{20}H_{39}NO_2$: 325.2981.

(–)-Isosolenopsin hydrochloride (1). To a solution of **14** (46.3 mg, 0.14 mmol) in MeOH (5.0 mL) was added a few drops of conc. HCl. After being stirred for 2 days, the solvent was removed *in vacuo* and saturated aqueous $NaHCO_3$ solution was added to the mixture. The mixture was extracted with EtOAc (15 mL x 2). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was crystallized using 1 N HCl solution in Et_2O. Recrystallization from EtOH/EtOAc (1 : 3) afforded **1** (26.2 mg, 72%) as a colorless solids. Mp 167-168 ºC (lit., 172 ºC),[11] $[\alpha]^{20}_D$ –10.0 (*c* 0.700, $CHCl_3$) {(lit., $[\alpha]^{20}_D$ –9.0 (*c* 1.0, $CHCl_3$)}.[11] IR (film) ν_{max} cm^{-1}: 2927, 2855, 2745, 2538, 2359, 2342, 1653, 1588, 1559, 1457, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.20-1.50 (15H, m), 1.58 (3H, d, *J* = 6.5 Hz), 1.61-2.00 (6H, m), 2.17 (1H, m), 2.89 (1H, m), 3.07 (1H, m), 9.08 (1H, brs.), 9.46 (1H, brs.); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 19.5, 22.6, 22.9, 25.7, 27.5, 29.3, 29.4, 29.5, 29.6, 30.8, 31.8, 33.2, 54.6, 58.7; HREIMS $[M]^+$: Found, 225.2454, Calcd. for $C_{15}H_{31}N$: 225.2456.

SUPPORTING INFORMATION

^{1}H, ^{13}C NMR, COSY, and NOESY spectra of **3a**, and ^{1}H and ^{13}C NMR spectra of **1**.

ACKNOWLEDGEMENTS

This work was supported in part by JSPS KAKENHI Grant Number 24580160 to H. M.

REFERENCES

1. H. Makabe, *Studies in Natural Products Chemistry*, Elsevier Science Publishers – Amsterdam, 2014, **42**, 353.
2. K. Takao, E. Nigawara, E. Nishio, I. Takagi, K. Maeda, K. Tadano, and S. Ogawa, *Tetrahedron*, 1994, **50**, 5681.
3. H. Yokoyama, K. Otaya, H. Kobayashi M. Miyazawa, S. Yamaguchi, and Y. Hirai, Y. *Org. Lett.*, 2000, **2**, 2427.
4. H. Makabe, K. K. Looi, and M. Hirota, *Org. Lett.*, 2003, **5**, 27.
5. Y. Kurogome, M. Kogiso, K. K. Looi, Y. Hattori, H. Konno, M. Hirota, and H. Makabe, *Tetrahedron*, 2013, **69**, 8349.
6. S. Leclerq, I. Thirrionet, F. Broeders, D. Daloze, R. Van der Meer, and J. C. Braeckman, *Tetrahedron*, 1994, **50**, 9333.
7. R. S. C. Kumar, E. Sreedhar, G. V. Reddy, K. S. Babu, and J. M. Rao, *Tetrahedron: Asymmetry*, 2009, **20**, 1160.
8. J. C. González-Gómez, M. Medjahdi, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2010, **75**, 6308.
9. M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Heterocycles*, 2012, **88**, 727.
10. R. V. N. S. Murali, and S. Chandrasekhar, *Tetrahedron Lett.*, 2012, **53**, 3467.
11. R. C. Simon, C. S. Fuchs, H. Lechner, F. Zepeck, and W. Kloutil, *Eur. J. Org. Chem.*, 2013, 3397.
12. S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, E. G. Alexandra, M. E. Furrow, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.
13. K. Matsumoto, K. Hashimoto, M. Sakuragi, A. Kusunoki, and M. Nogawa, *Lett. Org. Chem.*, 2011, **8**, 536.
14. S. Bujaranipalli and S. Das, *Tetrahedron: Asymmetry*, 2016, **27**, 254.
15. T. Shioiri, S. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
16. R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413.