A New Stereoselective Entry to Azaspirocyclic Nucleus of Halichlorine and Pinnaic Acids by Radical Translocation/Cyclization Reaction

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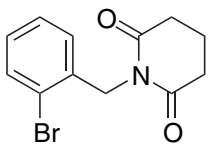
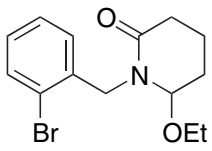
***N*-(*o*-Bromobenzyl)glutarimide** (**8**). A mixture of glutarimide (**7**) (1.0 g, 8.84 mmol) and KOH (545 mg, 9.72 mmol) in DMF (10 mL) was stirred for 30 min at 0 °C, and then, to this was added *o*-bromobenzylbromide (2.3 g, 9.28 mmol) in DMF (2 mL). The resulting mixture was stirred at ambient temperature for 5 h, then poured into water, and extracted with Et_2O three times. The extracts were washed with 2N NaOH aq, saturated NH_4Cl aq, and water, and dried over $MgSO_4$. After concentration, the residue was recrystallized from Et_2O to give the product **8** (2.26 g, 91%) as colorless needles; mp 138-139 ˚C (from Et_2O). IR (neat): ν 1678, 1350, 1171, 734 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.54 (d, 1H, *J* = 8.0 Hz), 7.25 (dd, 1H, *J* = 16.6, 7.6 Hz), 7.08 (dd, 1H, *J* = 16.6, 8.0 Hz), 6.89 (d, 1H, *J* = 7.6 Hz), 5.03 (s, 2H), 2.76 (t, 4H, J = 6.6 Hz), 2.04 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.1, 135.5, 132.8, 128.4, 127.3, 126.7, 123.6, 43.3, 32.9, 17.2. LRMS (*m/z):* 202 (M^+–79). HRMS (*m/z):* calcd for $C_{12}H_{12}NO_2$, 202.0868; found, 202.0850.



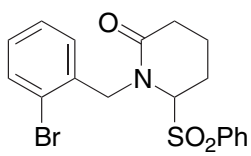
8

***N*-(*o*-Bromobenzyl)-6-ethoxy-2-oxopiperidine**. To a suspension of $NaBH_4$ (1.5 g, 39.9 mmol) and **8** (1.4 g, 5.0 mmol) in EtOH (15 mL) was added two or three drops of 2 N HCl etanol solution every 15 min over 8h at –20 °C. To the resulting mixture was added an ethanolic solution of HCl until the mixture reached pH 3. After being stirred for an additional 1 h at ambient temperature, the



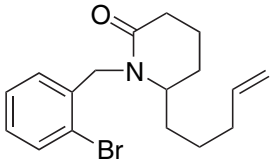
mixture was quenched with water and extracted with $CHCl_3$ three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (3:1 hexane/acetone) to afford *N*-(*o*-Bromobenzyl)-6-ethoxy-2-oxopiperidine (1.04 g, 93%), as colorless oil. IR (neat): ν 1651, 1470, 1076, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, 1H, *J* = 7.8 Hz), 7.28-7.21 (m, 2H), 7.13-7.09 (m, 1H), 5.19 (d, 1H, *J* = 15.8 Hz), 4.47 (s, 1H), 4.40 (d, 1H, *J* = 15.8 Hz), 3.51-3.34 (m, 2H), 2.60-2.37 (m, 2H), 2.12-2.01 (m, 2H), 1.74-1.67 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 170.4, 136.5, 132.6, 129.2, 128.5, 127.5, 123.5, 85.7, 63.6, 47.6, 32.5, 27.2, 16.0, 15.4. LRMS (*m/z*): 311 (M^+). HRMS (*m/z*): calcd for $C_{14}H_{18}{}^{79}BrNO_2$, 311.0521; found, 311.0501.

***N*-(*o*-Bromobenzyl)-6-phenylsulphonyl-2-oxopiperidine** (**9**). A mixture of the above ethoxylactam (950 mg, 3.05 mmol), benzenesulphinic acid (2.5 g, 15.27 mmol), and anhydrous $CaCl_2$ (846 mg, 7.63 mmol) in CH_2Cl_2 was stirred for 3 h. The reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined extracts were washed with saturated $NaHCO_3$, dried over Mg SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (3:1 hexane/acetone) to afford **9** (1.08 g, 87%), as colorless oil. IR (neat): ν 1666, 1306, 1140, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.91 (d, 2H, *J* = 8.0 Hz), 7.75-7.11 (m, 7H), 5.39 (d, 1H, *J* = 15.6 Hz), 4.63 (m,1H), 3.98 (d, 1H, *J* =15.6 Hz), 2.44-2.37 (m, 3H), 2.20-1.99 (m, 2H), 1.78-1.66 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 171.3, 137.4, 135.0, 134.5, 133.1, 131.2, 129.7, 129.6, 129.4, 129.1, 127.5, 123.5, 50.6, 31.1, 23.0, 17.2. LRMS (*m/z*): 265 (M^+–142). HRMS (*m/z*): calcd for $C_{12}H_{12}{}^{79}BrNO_2$, 265.0102; found, 265.0112.



9

***N*-(*o*-Bromobenzyl)-6-pent-4-enylpiperidin-2-one** (**6a**). Pentenylmagnesium bromide (51.6 mmol, 0.2 M in Et_2O), which was prepared from 4-pentenyl-1-bromide (5.1 mL, 51.6 mmol) and Mg (1.25 g, 51.6 mmol) in the usual manner, was added to a solution $ZnCl_2$•Et_2O in CH_2Cl_2 (2.2 M solution; 14.1 mL, 31.0 mmol) and the mixture was stirred at ambient temperature for 30 min. To the mixture was added a solution of **9** (2.58 mmol) in CH_2Cl_2 (8 mL), and the mixture was stirred at room temperature for 2 h. The mixture was quenched with saturated NH_4Cl and extracted with Et_2O three times. The combined extracts were dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel chromatography (2:1 hexane/AcOEt) to afford **6a** (7.50 g, 87%) as colorless oil. IR (neat): ν 1643, 1350, 1026, 748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, 1H, *J* = 8.0 Hz), 7.28-708 (m, 3H), 6.74 (ddt, 1H, *J* = 17.1, 10.3, 6.6 Hz), 5.21 (d, 1H, *J* = 15.9 Hz), 5.00-4.94 (m, 2H), 4.26 (d, 1H, *J* = 15.9 Hz), 3.27-3.24 (m, 1H), 2.51-2.47 (m, 2H), 2.06-1.48 (m, 8H), 1.41-1.25 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 162.7, 137.9, 136.5, 132.7, 128.7, 128.5, 127.5, 115.0, 56.2, 47.9, 44.1, 33.5, 32.0, 31.8, 26.3, 25.3, 17.3. LRMS (*m/z*): 335 (M^+). HRMS (*m/z*): calcd for $C_{17}H_{22}{}^{79}BrNO$, 335.0885; found, 335.0851.

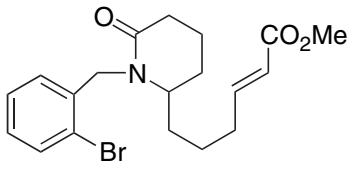


6a

General Procedure of Cross Metathesis

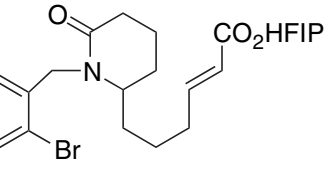
Alkene **6a** (2.99 mmol) and acrylate (or acrolein) (5.97 mmol) were added simultaneously *via* syringe to a stirring solution of Grubbs' catalyst (0.15 mmol) in CH_2Cl_2 (20 ml). The resulting mixture was stirred for 12 h. The solvent was removed, and the residue was purified by chromatography on silica gel (2:1 hexane/EtOAc).

Methyl (*E*)-6-[1-(*o*-Bromobenzyl)]-6-oxopiperidin-2-yl]hex-2-enoate (**6b**). Colorless oil. IR (neat): ν 1715, 1645, 1452, 1177, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, 1H, *J* = 7.8 Hz), 7.28-7.09 (m, 3H), 6.89 (dt, 1H, *J* = 15.6, 7.1 Hz), 5.79 (d, 1H, *J* = 15.6 Hz), 5.21 (d, 1H, *J* = 15.9 Hz), 4.28 (d, 1H, *J* = 15.9 Hz), 3.73 (s, 3H), 3.27-3.24 (m, 1H), 2.51-2.47 (m, 2H), 2.22-2.14 (m, 2H), 1.91-1.33 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 170.3, 166.7, 148.2, 136.5, 132.7, 128.8, 128.6, 127.6, 123.4, 121.5, 56.1, 51.5, 47.8, 32.0, 32.0, 31.9, 26.3, 24.5, 17.4. LRMS (*m/z*): 393 (M^+). HRMS (*m/z*): calcd for $C_{19}H_{24}{}^{79}BrNO_3$, 393.0940; found, 393.0916.



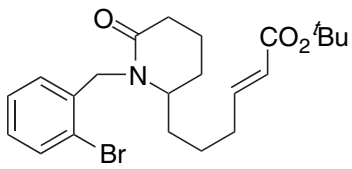
6b

1,1,1,3,3,3-Hexafluoroisopropyl (*E*)-6-[1-(2-Bromobenzyl)-6-oxopiperidin-2-yl]hex-2- enoate (**6c**). Colorless oil. IR (neat): ν 2945, 1755, 1649, 1109 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, 1H, *J* = 7.8 Hz), 7.29-7.09 (m, 3H), 5.91 (d, 1H, *J* = 15.6 Hz), 5.85-5.79 (m, 1H), 5.21 (d, 1H, *J* = 15.9 Hz), 4.30 (d, 1H, *J* = 15.9 Hz), 3.28-3.27 (m, 1H), 2.52-2.48 (m, 2H), 2.29-2.23 (m, 2H), 1.92-1.30 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 170.4, 162.5, 153.5, 136.4, 132.7, 128.9, 128.7, 127.6, 127.6, 123.4, 118.4, 100.5, 66.4, 56.0, 47.7, 32.4, 32.0, 32.0, 26.3, 24.2, 17.4. LRMS *m/z* 529 (M^+). HRMS *m/z* calcd for $C_{21}H_{22}{}^{79}BrF_6NO_3$ (M^+) 529.0687, found 529.0687.



6c

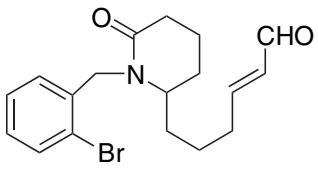
***tert*-Butyl (*E*)-6-[1-(2-Bromobenzyl)-6-oxopiperidin-2-yl]hex-2-enoate** (**6d**). Colorless oil. IR (neat): ν 2939, 1717, 1653, 1159cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, 1H, *J* = 7.8 Hz), 7.28-7.09 (m, 3H), 6.78 (dt, 1H, *J* = 15.6, 6.8 Hz), 5.71 (d, 1H, *J* = 15.6 Hz), 5.22 (dt, 1H, *J* = 15.9 Hz), 4.26 (d, 1H, *J* = 15.9 Hz), 3.28-3.27 (m, 1H), 2.51-2.47 (m, 2H), 2.17-2.11 (m, 1H), 1.92-1.30 (m, 9H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 150.8, 146.6, 136.5, 132.7, 128.9, 128.6, 127.6, 123.6, 123.4, 94.2,



6d

56.0, 47.7, 32.1, 32.0, 31.8, 28.2, 26.3, 24.6, 24.6, 17.4. LRMS *m/z* 378 (M^+_57). HRMS *m/z* calcd for $C_{18}H_{21}BrNO_3$ (M^+_57) 378.0705, found 378.0673.

(*E*)-6-[1-(2-Bromobenzyl)-6-oxopiperidin-2-yl]hex-2-enal (**6e**). Colorless oil. IR (neat): ν 2945, 1680, 1637, 1028, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.48 (d, 1H, *J* = 11.2 Hz), 7.56-7.16 (m, 4H), 6.76 (dt, 1H, *J* = 16.0, 6.4 Hz), 6.07 (dd, 1H, J = 16.0, 7.7 Hz), 5.18 (d, 1H, *J* = 15.6 Hz), 4.31 (d, 1H, *J* = 15.6 Hz), 3.32-3.24 (m, 1H), 2.45-2.43 (m, 2H), 2.34-2.27 (m, 2H), 1.95-1.38 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 193.5, 170.4, 157.0, 136.4, 133.2, 132.7, 128.8, 128.6, 127.6, 123.3, 122.5, 56.1, 47.8, 32.4, 32.0, 26.4, 24.3, 17.4. LRMS *m/z* 363 (M^+). HRMS *m/z* calcd for $C_{18}H_{22}{}^{79}BrNO_2$ (M^+) 363.0834, found 363.0795.

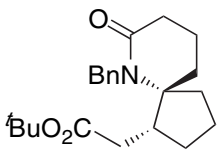


6e

General Procedure for Radical Translocation/Cyclization Reaction

To a stirred solution of **6** (18.3 mmol) in degassed benzene (32 mL) were dropwise added Bu_3SnH (4.9 mL, 18.3 mmol) and AIBN (100 mg, 0.60 mmol) in benzene (90 mL) over 18 h using a syringe pump under reflux. After being stirred under the same temperature for 1 h, the solvent was removed, and the residue was purified by chromatography on silica gel (4:1 hexane/EtOAc).

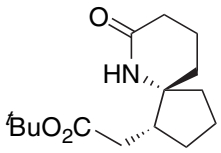
***tert*-Butyl (1*R**,5*S**)-(6-Benzyl-7-oxo-6-azaspiro[4.5]dec-1-yl)acetate** (**5d**). Colorless needles, mp 119 °C (from AcOEt/hexane). IR (neat): ν 2945, 1726, 1641, 1148 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30-7.16 (m, 3H), 7.10 (d, 1H, *J* = 7.8 Hz), 5.36 (d, 1H, *J* = 16.1 Hz), 3.85 (d, 1H, *J* = 16.1 Hz), 2.57-2.55 (m, 2H), 2.38-2.33 (m, 2H), 2.14 (dd, 1H, *J* = 12.0, 15.7 Hz), 2.09-1.30 (m, 11H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.0, 171.4, 138.7, 128.3, 126.4, 125.7,



5d

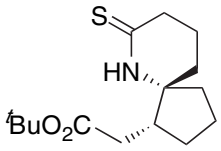
80.7, 69.2, 48.5, 46.7, 39.8, 39.3, 38.9, 34.4, 32.2, 28.2, 23.8, 16.8. LRMS *m/z* 357 (M^+). HRMS *m/z* calcd for $C_{22}H_{31}NO_3$ (M^+) 357.2304, found 357.2335.

***tert*-Butyl (1*R**,5*S**)-(7-Oxo-6-azaspiro[4.5]dec-1-yl)acetate** (**12**). To a solution of **5d** (400 mg, 1.12 mmol) and one portion of HCl in ^{t}BuOH (7 mL) was added $Pd(OH)_2$ (20 wt. % on carbon, 10 mg) at ambient temperature. The mixture was refluxed for 24 h under hydrogen atmosphere. After filtration of the mixture through Celite, the solvent was removed. The residue was purified by chromatography (1:1 hexane/acetone) to give **12** (298 mg, >99 %) as colorless needles (from AcOEt/hexane), mp 88–90 °C. IR (neat): ν 2953, 1726, 1659, 1148 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.68 (s, 1H), 2.39-2.27 (m, 3H), 2.13-2.04 (m, 3H), 1.82-1.62 (m, 9H), 1.44 (s, 9H), 1.46-1.39 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.1, 172.1, 80.5, 64.5, 44.8, 40.9, 36.4, 33.1, 31.4, 29.7, 28.1, 20.8, 18.6. LRMS *m/z* 267 (M^+). HRMS *m/z* calcd for $C_{15}H_{25}NO_3$ (M^+) 267.1834, found 267.1818.

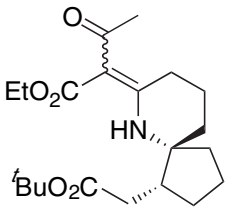


12

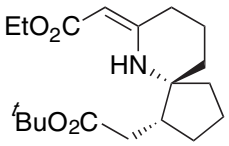
***tert*-Butyl (1*R**,5*S**)-(7-Thioxo-6-azaspiro[4.5]dec-1-yl)acetate** (**13**). A mixture of **12** (100 mg, 0.375 mmol) and Lawesson's reagent (75 mg, 0.187 mmol) in toluene (15 mL) was refluxed for 1 h. After the solvent was evaporated *in vacuo*, the resulting residue was purified by chromatography on silica gel (3:1 hexane/EtOAc) to give **13** (100 mg, 94 %) as pale yellow needles (from AcOEt/hexane), mp 138-141 °C. IR (neat): ν 2939, 1726, 1539, 1148 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.05 (s, 1H), 3.01-2.96 (m, 1H), 2.78-2.73 (m, 1H), 2.40-2.37 (m, 1H), 2.18-2.13 (m, 3H), 1.94-1.89 (m, 1H), 1.80-1.70 (m, 8H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 202.8, 171.6, 81.0, 67.5, 45.5, 40.5, 39.3, 36.2, 32.4, 29.9, 28.1, 21.3, 18.7. LRMS *m/z* 283 (M^+). HRMS *m/z* calcd for $C_{15}H_{25}NO_2S$ (M^+) 283.1606, found 283.1586.



13



Ethyl (1*R,5*S**)-2-(1-*tert*-Butoxycarbonylmethyl-6-azaspiro[4.5]dec-7-ylidene)-3- oxobutyrate**. A solution of **13** (250 mg, 0.883 mmol), ethyl bromoacetoacetate (275 mg, 1.325 mmol), and $NaHCO_3$ (148 mg, 1.766 mmol) in CH_2Cl_2 (7 mL) was stirred for 12 h at ambient temperature. The reaction mixture was diluted with $CHCl_3$ and water. The reaction mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography (1:3 hexane/Et_2O) to give the corresponding keto ester (324 mg, 97 %) as colorless needles (from Et_2O/hexane), mp 78-80 °C. IR (neat): ν 2966, 1730, 1691, 1582, 1148 cm^{-1}. ^1H NMR ($CDCl_3$): δ 13.22 (s, 1H), 4.21 (q, 2H, *J* = 7.3 Hz), 2.78-2.69 (m, 1H), 2.61-2.53 (m, 1H), 2.32-2.26 (m, 1H), 2.26 (s, 3H), 2.14-2.06 (m, 3H), 1.89-1.59 (m, 9H), 1.42 (s, 9H), 1.31 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 172.0, 169.8, 167.7, 101.5, 80.5, 64.0, 60.0, 45.4, .41.1, 36.2, 31.6, 29.8, 29.6, 28.1, 27.9, 20.1, 17.8, 14.4, 14.0. LRMS *m/z* 379 (M^+). HRMS *m/z* calcd for $C_{21}H_{33}NO_5$ (M^+) 379.2359, found 379.2345.

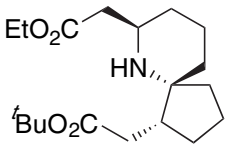


14

Ethyl (1*R,5*S**)-(1-*tert*-Butoxycarbonylmethyl-6-azaspiro[4.5]dec-7-ylidene)acetate** (**14**). A suspension of the above keto ester (400 mg, 1.06 mmol) and NaOEt (108 mg, 1.58 mmol) in EtOH (10 ml) was stirred for 24 h at 40 °C. The reaction mixture was quenched with saturated NH_4Cl, and extracted $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography (1:1 hexane/Et_2O) to give **14** (268 mg, 75 %) as colorless oil.

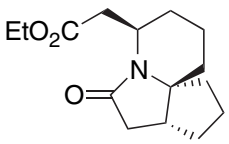
IR (neat): ν 1732, 1607, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.84 (s, 1H), 4.35 (s, 1H), 4.08 (q, 2H, *J* = 7.1 Hz), 2.38-2.28 (m, 3H), 2.18-2.06 (m, 3H), 1.83-1.58 (m, 9H), 1.43 (s, 9H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 172.5, 170.6, 162.2, 80.3, 80.3, 63.1, 58.2, 45.2, 41.1, 36.4, 33.5, 30.0, 29.4, 28.1, 20.9, 18.5, 14.8. LRMS *m/z* 337 (M^+). HRMS *m/z* calcd for $C_{19}H_{31}NO_4$ (M^+) 337.2253, found 337.2229.

Ethyl (1*R,5*S**,7*S**)-(1-*tert*-Butoxycarbonylmethyl-6-azaspiro[4.5]dec-7-yl)acetate** (**4**). A mixture of **14** (250 mg, 0.741 mmol) and PtO_2 (2 mg, 9 μmol) in EtOH (6 mL) was stirred for 12 h at ambient temperature under hydrogen atmosphere. After filtration of mixture through Celite, the solvent was removed. The residue was purified by chromatography (10:1 $CHCl_3$/MeOH) to give **4** (250 mg, >99 %) as colorless oil. IR (neat): ν 2932, 1732, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.12 (q, 2H, *J* = 7.1 Hz), 3.09-3.01 (m, 1H), 2.45-2.24 (m, 3H), 2.13-1.85 (m, 4H), 1.68-1.63 (m, 2H), 1.59-1.29 (m, 8H), 1.44 (s, 9H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.02-0.98, (m, 1H). ^{13}C NMR ($CDCl_3$): δ 173.6, 172.5, 79.8, 62.7, 60.3, 48.3, 46.6, 42.0, 35.5, 34.8, 33.6, 32.7, 29.6, 28.2, 22.4, 21.2, 14.3. LRMS *m/z* 339 (M^+). HRMS *m/z* calcd for $C_{19}H_{33}NO_4$ (M^+) 339.2410, found 339.2409.



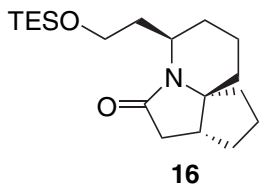
4

Ethyl (3a*R,6*R**,9a*R**)-(5-Oxodecahydro-5a-azacyclopenta[*c*]inden-6-yl)acetate** (**15**). To a solution of **4** (20 mg, 0.059 mmol) in CH_2Cl_2 (0.12 mL) was added trifluoroacetic acid (59 μl, 0.767 mmol) at ambient temperature, and the mixture was stirred for 5 h. Concentration of the mixture gave a crude product of the corresponding calboxylic acid, which was used in the following reaction without further purification. A mixture of the above product (0.059 mmol) and EDCI (17 mg, 0.089 mmol) in CH_2Cl_2 (3 ml) was stirred



15

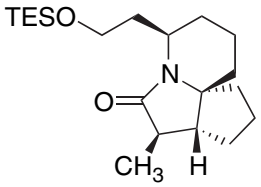
for 12 h at ambient temperature. The mixture was poured onto water, and extracted with $CHCl_3$. The organic layer was washed with brine, then dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (10:1 $CHCl_3$/MeOH) to give **15** (15 mg, 96%) as colorless oil. IR (neat): ν 2939, 1732, 1682, 1177 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.18-4.11 (m, 2H), 3.66-3.56 (m, 2H), 2.64-2.55 (m, 2H), 2.13-1.88 (m, 4H), 1.84-1.35 (m, 10H), 1.26 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 173.2, 171.7, 73.3, 60.2, 51.4, 41.9, 38.5, 37.5, 36.9, 35.1, 33.9, 32.0, 25.1, 22.5, 14.3. LRMS *m/z* 265 (M^+). HRMS *m/z* calcd for $C_{15}H_{23}NO_3$ (M^+) 265.1678, found 265.1690.



16

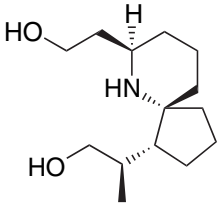
(3a*R,6*R**,9a*R**)-6-[2-(Triethylsilyloxy)ethyl]octahydro-5a-azacyclopenta[*c*]inden-5- one** (**16**). To a solution of ester **15** (42 mg, 0.158 mmol) in THF (1.5 mL) was added a solution of $LiEt_3BH$ (1 M THF solution, 0.63 mL, 0.634 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, and then quenched with water (0.20 ml). To the mixture were added a saturated aqueous $NaHCO_3$ soluton (0.20 mL) and then 30% aqueous H_2O_2 solution (0.40 ml). After being stirred for 1 h, the mixture was extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to give crude product of the corresponding alcohol, which was used in the following reaction without further purification. To a solution of the crude alcohol and DMAP (9.7 mg, 0.079 mmol) in CH_2Cl_2 (2 mL) were added TESCl (40 μL, 0.237 mmol) and NEt_3 (40 μL, 0.284 mmol) at ambient temperature, and the reaction mixture was stirred for 12 h. The reaction mixture was quenched with saturated NH_4Cl, and extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography (1:1 hexane/EtOAc) to give **16** (40 mg, 75 %) as colorless oil. IR (neat): ν 2953, 1688,

1088 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.73 (t, 2H, *J* = 5.1 Hz), 3.42-3.34 (m, 1H), 2.93-2.85 (m, 1H), 2.59 (dd, 1H, *J* = 17.6, 9.6 Hz), 2.16-2.02 (m, 2H), 1.99-1.32 (m, 13H), 0.95 (t, 9H, *J* = 7.8 Hz), 0.59 (q, 6H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 173.5, 73.7, 60.5, 52.3, 42.2, 38.2, 36.8, 35.1, 33.9, 32.2, 31.8, 25.4, 23.1, 6.9, 4.5. LRMS *m/z* 337 (M^+). HRMS *m/z* calcd for $C_{19}H_{35}NO_2Si$ (M^+) 337.2437, found 337.2454.



17

(3a*R,4*R**,6*R**,9a*R**)-4-Methyl-6-[2-(triethylsilyloxy)ethyl]octahydro-5- azacyclopenta[*c*]inden-5-one** (**17**). To a solution of **16** (25 mg, 0.074 mmol) in THF (3 mL) was added 1.0 M LDA solution in THF (0.22 mL, 0.222 mmol) at –78 °C. After the mixture was stirred at _78 °C for 30 min, to the solution wasdropwise added MeI (0.07 mL, 1.12 mmol) at the same temperature. The reaction mixture was stirred at –78°C for additional 1 h. The resulting mixture was quenched with saturated NH_4Cl, and extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, and evaporated. The residue was purified by chromatography (2:1 hexane/EtOAc) to give **17** (22 mg, 85%) as colorless oil. IR (neat): ν 2934, 1682, 1088 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.76-3.71 (m, 2H), 3.41-3.39 (m, 1H), 2.94-2.88 (m, 1H), 2.14 (qd, 1H, *J* = 7.6, 4.5 Hz), 1.98-1.35 (m, 14H), 1.23 (d, 3H, *J* = 7.6 Hz), 0.95 (t, 9H, *J* = 7.8 Hz), 0.58 (q, 6H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 176.2, 71.7, 60.6, 52.5, 51.3, 44.6, 39.2, 35.3, 35.2, 33.5, 31.9, 25.4, 22.9, 18.7, 6.9, 4.5. LRMS *m/z* 351 (M^+). HRMS *m/z* calcd for $C_{20}H_{37}NO_2Si$ (M^+) 351.2594, found 351.5988.



18

(2*S,1'*R**,5'*S**,7'*R**)-2-[7'-(2''-Hydroxyethyl)-6'-azaspiro[4.5]dec-1'-yl]-propan-1-ol (18).** To a solution of borane-ammonia complex (7.8 mg, 0.23 mmol) in THF (1 mL) was added BuLi (1.59 M hexane

solution, 0.93 mL, 0.21 mmol) at 0 °C, and the resulting solution was stirred for 40 min at ambient temperature. To this was added a solution of **17** (4.0 mg, 0.011 mmol) in THF (1 mL) at 0 °C, and warmed to 40 °C. After being stirred for 18 h at 40 °C, the mixture was quenched with water. The resulting mixture was extracted with $CHCl_3$ three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by PTLC (10:1 $CHCl_3$/MeOH) to give **18** (1.6 mg, 59%) as colorless oil. IR (neat): ν 2918, 1456, 1059 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.88-3.75 (m, 2H), 3.34-3.21 (m, 2H), 2.67-2.55 (m, 1H), 2.14-1.19 (m, 19H), 1.08 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 70.5, 59.1, 56.0, 52.8, 38.3, 35.3, 34.2, 32.6, 32.1, 29.7, 26.6, 25.3, 22.5, 18.6. LRMS *m/z* 241 (M^+). HRMS *m/z* calcd for $C_{15}H_{23}NO_3$ (M^+) 241.2042, found 241.3697.