Electronic Supplementary Information for

Versatile Construction of Functionalized Tropane Ring Systems Based on Lactam Activation: Enantioselective Synthesis of (+)-Pervilleine B

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Contents

Experimental

General Methods. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were obtained using electrospray ionization and an ICR analyzer (ESI-MS) for high resolution mass spectra (HRMS). Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/hexane. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

General procedure for the formation of silyl enol ethers (SLXa,b): General procedure 1.

To a cooled (0 ºC) solution of ketone-lactam (0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (5 mL, 0.1 M) was added Et_3N (1.25 mmol, 2.5 equiv) and TBDMSOTf (1.0 mmol, 2.0 equiv) or TMSOTf (1.0 mmol, 2.0 equiv). After being stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. For TBDMS silyl enol ethers, the residue was purified by flash column chromatography (eluent: EtOAc/PE = 1/4 containing 5% Et_3N, *v/v*) to give **SLXa** (terminal) and **SLXb** (internal) as an inseparable mixture; while for TMS silyl enol ethers, the crude product was used in the next step without further purification. The ratio of regioisomers was determined by ^1H NMR.

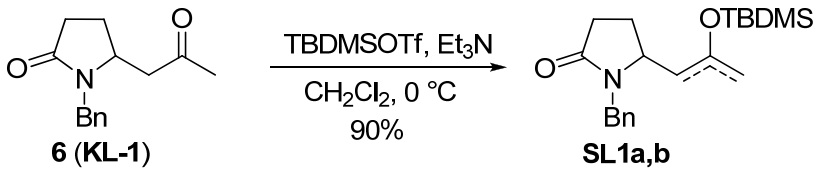
General procedures for the lactam activation-based cyclization: Method A (General procedure 2): To a cooled (−78 ºC) solution of a silyl enol ether (**SLXa,b**) (0.2 mmol) and 2,6-*tert*-butyl-4-methylpyridine (49 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (2.0 mL, 0.1 M) was added dropwise Tf_2O (39 μL, 0.24 mmol) and the resulting mixture was stirred at −78 ºC for 40 min. A solution of $ZnCl_2$ (0.24 mL, 0.24 mmol, 1.0 M in Et_2O) was added dropwise to the resultant mixture. After being stirred at −78 ºC for 1 h, the reaction mixture was allowed to warm to room temperature slowly and was stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (eluent: EtOAc/PE = 1/15) to give the desired product.

General procedures for the lactam activation-based cyclization: Method B (General procedure 3): To a cooled (−78 ºC) suspension of silyl enol ether (**SLXa,b**) (0.2 mmol), 2,6-*tert*-butyl-4-methylpyridine (49 mg, 0.24 mmol) and $ZnBr_2$ (54 mg,

0.24 mmol) in anhydrous CH_2Cl_2 (4.0 mL, 0.05 M) was added dropwise Tf_2O (39 μL, 0.24 mmol) and the mixture was stirred at −78 ºC for 40 min. The reaction mixture was allowed to warm to room temperature slowly and was stirred for 1 h before quenching with saturated $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (eluent: EtOAc/PE = 1/10) to give the desired product.

1-Benzyl-5-(2-(*tert*-butyldimethylsilyloxy)prop-2-en-1-yl))pyrrolidin-2-one (SL1a) and

1-Benzyl-5-(2-(*t*ert-butyldimethylsilyloxy)prop-1-en-1-yl)pyrrolidin-2-one (SL1a)



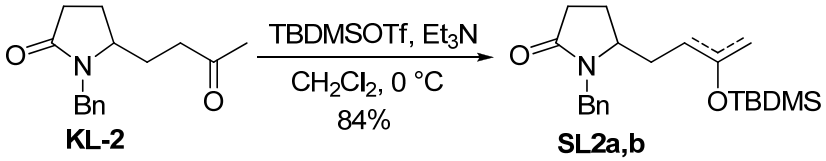
6 (KL-1) **SL1a,b**

Following the **general procedure 1**, reaction of ketone-lactam **6** (**KL-1**) (91 mg, 0.39 mmol) with Et_3N (0.14 mL, 0.98 mmol) and TBDMSOTf (0.18 mL, 0.79 mmol) afforded, after flash column chromatography purification on silica gel (eluent: EtOAc/PE = 1/4 containing 5% Et_3N, *v/v*), silyl enol ether-lactam **SL1a,b** (123 mg, combined yield: 90%) as an inseparable mixture of regioisomers in a ratio of 6.4: 1 (terminal: internal).

Pale yellow oil. IR (film, regioisomeric mixture) ν_{max}: 2954, 2928, 2856, 1692, 1255, 1017, 838, 780, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data read from the regioisomeric mixture) $\delta_{terminal}$ 0.12 (s, 6H), 0.83 (s, 9H), 1.80-1.96 (m, 2H), 2.00-2.10 (m, 1H), 2.35-2.55 (m, 3H), 3.63-3.71 (m, 1H), 4.00 (d, *J*= 15.0 Hz, 1H); 4.06 (br s, 1H), 4.09 (br d, *J*= 0.7 Hz, 1H), 5.01 (d, *J*= 15.0 Hz, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta_{terminal}$ −5.0, −4.8, 17.8, 23.5, 25.5, 29.8, 40.3, 44.2, 54.8, 92.3, 127.4, 128.0, 128.6, 136.6, 155.3, 175.0; HRMS calcd for $C_{20}H_{31}NO_2Si$ $[M+Na^+]$: 368.2016; found: 368.2017.

1-Benzyl-5-(3-(*tert*-butyldimethylsilyloxy)but-3-en-1-yl)pyrrolidin-2-one (SL2a) and

1-Benzyl-5-(3-(*tert*-butyldimethylsilyloxy)but-2-en-1-yl)pyrrolidin-2-one (SL2b)



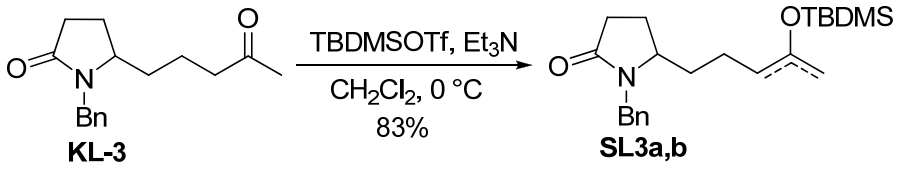
KL-2 **SL2a,b**

Following the **general procedure 1**, reaction of ketone-lactam **KL-2** (94 mg, 0.38 mmol) with Et_3N (0.13 mL, 0.96 mmol) and TBDMSOTf (0.17 mL, 0.77 mmol) afforded, after flash column chromatography purification on silica gel (eluent: EtOAc/PE = 1/4 containing 5% Et_3N, *v/v*), silyl enol ether-lactam **SL2a,b** (115 mg, combined yield: 84%) as an inseparable mixture of regioisomers in a ratio of 1.3: 1 (terminal: internal).

Pale yellow oil. IR (film, regioisomeric mixture) ν_{max}: 2955, 2929, 2857, 1693, 1417, 1255, 1004, 838, 812, 780, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ data read from the regioisomeric mixture) $\delta_{terminal}$ 0.17 (s, 6H), 0.93 (s, 9H), 1.24-1.54 (m, 1H), 1.65-1.74 (m, 1H), 1.80-2.18 (m, 4H), 2.34-2.56 (m, 2H); 3.36-3.50 (m, 1H), 3.96 (d, *J*= 15.2 Hz, 1H), 3.99 (br s, 1H), 4.04 (br s, 1H), 5.01 (d, *J*= 15.2 Hz, 1H), 7.20-7.37 (m, 5H); $\delta_{internal}$ 0.13 (s, 6H), 0.93 (s, 9H), 1.24-1.54 (m, 2H), 1.65-1.74 (m, 1H), 1.75 (s, 3H), 1.80-2.18 (m, 1H), 2.34-2.56 (m, 2H), 3.36-3.50 (m, 1H), 3.96 (d, *J*= 15.2 Hz, 1H), 4.29 (t, *J*= 6.8 Hz, 1H), 5.01 (d, *J*= 15.2 Hz, 1H), 7.20-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$ data read from the regioisomeric mixture) δ –4.8, –4.7, –3.8, 18.0, 18.1, 20.5, 21.5, 22.7, 23.9, 24.0, 25.6, 25.7, 30.2, 31.9, 32.8, 36.3, 44.0, 56.7, 90.2, 106.7, 127.3, 127.4, 127.96, 127.98, 128.5, 128.6, 136.78, 136.84, 147.5, 158.5, 175.0, 175.1; HRMS calcd for $C_{21}H_{33}NO_2Si$ $[M+Na^+]$: 382.2173; found: 382.2178.

1-Benzyl-5-(4-(*tert*-butyldimethylsilyloxy)pent-4-en-1-yl)pyrrolidin-2-one (SL3a) and

1-Benzyl-5-(4-(*tert*-butyldimethylsilyloxy)pent-3-en-1-yl)pyrrolidin-2-one (SL3b)

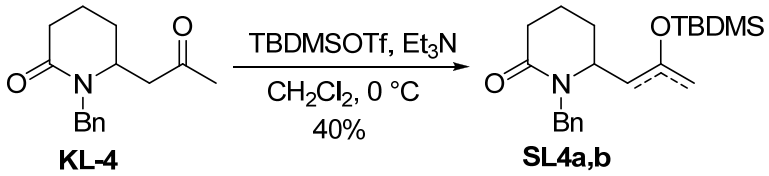


Following the **general procedure 1**, reaction of ketone-lactam **KL-3** (40 mg, 0.15 mmol) with Et_3N (0.06 mL, 0.39 mmol) and TBDMSOTf (0.07 mL, 0.31 mmol) afforded, after flash column chromatography purification on silica gel (eluent: EtOAc/PE = 1/4 containing 5% Et_3N, *v/v*), silyl enol ether-lactam **SL3a,b** (47 mg, combined yield: 81%) as an inseparable mixture of regioisomers in a ratio of 1.4: 1 (terminal: internal).

Pale yellow oil. IR (film, regioisomeric mixture): 2953, 2929, 2857, 1692, 1416, 1255, 1003, 838, 779, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data read from the regioisomeric mixture) $\delta_{terminal}$ 0.16 (s, 3H), 0.17 (s, 3H), 0.93 (s, 9H), 1.29-1.54 (m, 2H), 1.65-1.74 (m, 2H), 1.88-2.16 (m, 4H), 2.35-2.55 (m, 2H); 3.38-3.48 (m, 1H), 3.96 (d, *J*= 15.0 Hz, 1H), 3.99 (br d, *J*= 0.5 Hz, 1H), 4.03 (br d, *J*= 0.7 Hz, 1H), 5.01 (d, *J*= 15.0 Hz, 1H), 7.22-7.36 (m, 5H); $\delta_{internal}$ 0.12 (s, 3H), 0.13 (s, 3H), 0.94 (s, 9H), 1.29-1.54 (m, 2H), 1.65-1.74 (m, 2H), 1.75 (s, 3H), 1.88-2.16 (m, 2H), 2.35-2.55 (m, 2H), 3.38-3.48 (m, 1H), 3.96 (d, *J*= 15.0 Hz, 1H), 4.29 (t, *J*= 7.3 Hz, 1H), 5.00 (d, *J*= 15.0 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, data read from the regioisomeric mixture) δ –4.77, –4.74, –3.9, 18.0, 18.1, 20.5, 21.4, 22.6, 23.8, 24.0, 25.6, 25.7, 30.2, 31.9, 32.8, 36.3, 44.0, 56.7, 90.2, 106.7, 127.29, 127.34, 127.9, 128.0, 128.5, 128.6, 136.77, 136.83, 147.5, 158.5, 175.02, 175.03; HRMS calcd for $C_{22}H_{35}NO_2Si$ [M+Na^+]: 396.2329; found: 396.2327.

1-Benzyl-6-(2-(*tert*-butyldimethylsilyloxy)prop-2-en-1-yl)piperidin-2-one (SL4a) and

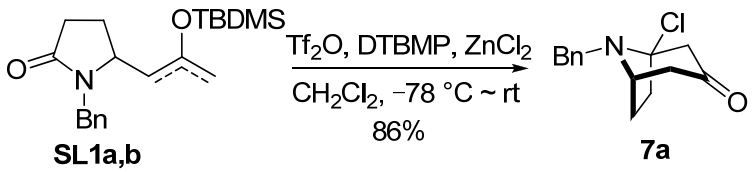
1-Benzyl-6-(2-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl)piperidin-2-one (SL4b)



Following the **general procedure 1**, reaction of ketone-lactam **KL-4** (595 mg, 2.43 mmol) with Et_3N (0.85 mL, 6.08 mmol) and TBDMSOTf (1.12 mL, 4.86 mmol) afforded, after flash column chromatography purification on silica gel (eluent: EtOAc/PE = 1/4 containing 5% Et_3N, *v/v*), silyl enol ether-lactam **SL4a,b** (348 mg, combined yield: 40%) as an inseparable mixture of regioisomers in a ratio of 3.8: 1 (terminal: internal).

Pale yellow oil. IR (film, regioisomeric mixture) ν_{max}: 2954, 2929, 2856, 1676, 1642, 1470, 1451, 1302, 1257, 1023, 836, 811, 780, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data read from the regioisomeric mixture) $\delta_{terminal}$ 0.12 (s, 3H), 0.16 (s, 3H), 0.84 (s, 9H), 1.61-1.81 (m, 2H), 1.83-1.98 (m, 2H), 2.15 (dd, *J*= 10.3, 13.6 Hz, 1H), 2.45-2.56 (m, 3H); 3.57-3.65 (m, 1H), 3.96 (d, *J*= 15.1 Hz, 1H), 4.05-4.08 (m, 2H), 5.38 (d, *J*= 15.1 Hz, 1H), 7.20-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, data read from the regioisomeric mixture) $\delta_{terminal}$ −5.0, −4.8, 16.9, 17.9, 25.5, 25.7, 31.8, 39.7, 47.7, 53.1, 92.1, 127.1, 127.8, 128.5, 137.7, 155.8, 170.2 ; HRMS calcd for $C_{21}H_{33}NO_2Si$ $[M+Na^+]$: 382.2173; found: 382.2176.

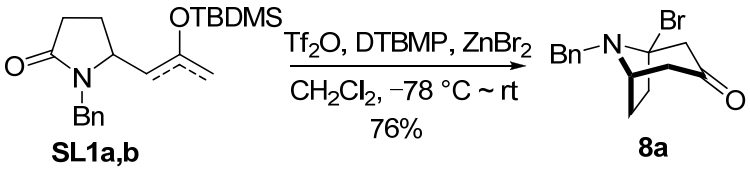
8-Benzyl-1-chloro-8-azabicyclo[3.2.1]octan-3-one (7a)



Following the **general procedure 2**, reaction of the silyl enol ether **SL1a,b** (111 mg, 0.32 mmol) with 2,6-*tert*-butyl-4-methylpyridine (78 mg, 0.38 mmol), Tf_2O (62 μL, 0.38 mmol) and $ZnCl_2$ (0.38 mL, 0.38 mmol, 1 M in Et_2O) afforded cyclization product **7a** (60 mg, yield: 86% from **SL1a**) as a colorless oil after flash column chromatography on silica gel (eluent: EtOAc/PE = 1/15). IR (film) ν_{max}: 3412, 2954, 1716, 1279, 1234, 1186, 1142, 916, 732, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ1.44 (ddd, *J*= 4.8, 9.7, 13.0 Hz, 1H), 2.02-2.15 (m, 2H), 2.21-2.30 (m, 1H), 2.47 (ddt, *J*= 3.3, 4.8, 13.3 Hz, 1H), 2.72 (ddd, *J*= 2.2, 4.5, 16.6 Hz, 1H), 2.83 (dd, *J*= 1.4, 15.9 Hz, 1H), 3.09 (dd, *J*=3.1, 15.9 Hz, 1H), 3.51 (m, 1H), 3.71 (d, *J*= 13.5 Hz, 1H),

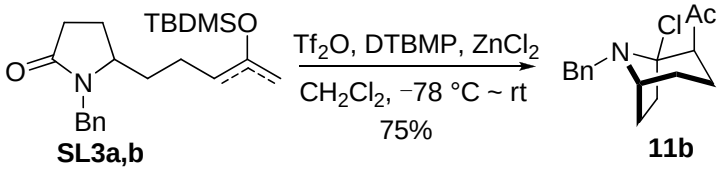
4.42 (d, *J*=13.5 Hz, 1H), 7.25-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 39.9, 41.1, 47.1, 53.1, 54.4, 86.7, 127.4, 128.4, 128.5, 138.2, 205.7; HRMS calcd for $C_{14}H_{16}ClNO$ [M+H$^+$]: 250.0999 and 252.0969; found: 250.1004 and 252.0980.

8-Benzyl-1-bromo-8-azabicyclo[3.2.1]octan-3-one (8a)



Following the **general procedure 3**, reaction of the silyl enol ether **SL1a,b** (73 mg, 0.21 mmol) with 2,6-*tert*-butyl-4-methylpyridine (52 mg, 0.25 mmol), Tf_2O (42 μL, 0.25 mmol) and $ZnBr_2$ (57 mg, 0.25 mmol) afforded cyclization product **8a** (48 mg, yield: 76% from **SL1a**) as a colorless oil after flash column chromatography on silica gel (eluent: EtOAc/PE = 1/15). IR (film) ν_{max}: 2955, 1719, 1454, 1277, 1230, 1209, 1183, 1140, 959, 908, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (ddd, *J*= 4.7, 9.8, 13.0 Hz, 1H), 2.03-2.17 (m, 2H), 2.33-2.45 (m, 1H), 2.65-2.82 (m, 2H), 3.01 (dd, *J*= 1.4, 15.8 Hz, 1H), 3.28 (dd, *J*= 3.0, 15.8 Hz, 1H), 3.46-3.51 (m, 1H), 3.74 (d, *J*= 13.5 Hz, 1H), 4.59 (d, *J*= 13.5 Hz, 1H), 7.25-7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 41.1, 41.2, 47.8, 52.4, 56.6, 81.3, 127.4, 128.4, 128.6, 138.2, 205.4; HRMS calcd for $C_{14}H_{16}BrNO$ [M+H$^+$]: 294.0494 and 296.0473; found: 294.0496 and 296.0476.

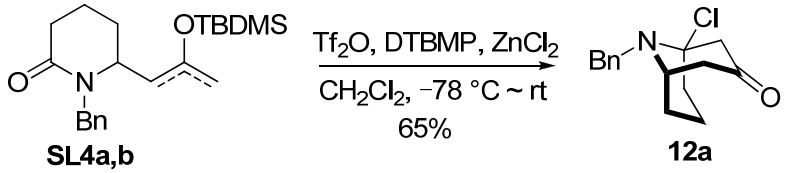
1-(8-Benzyl-1-chloro-8-azabicyclo[3.2.1]octan-2-yl)ethanone (11b)



Following the **general procedure 2**, reaction of the silyl enol ether **SL3a,b** (45 mg, 0.12 mmol) with 2,6-*tert*-butyl-4-methylpyridine (30 mg, 0.15 mmol), Tf_2O (24 μL, 0.15 mmol) and $ZnCl_2$ (0.15 mL, 0.15 mmol, 1 M in Et_2O) afforded cyclization product **11b** (10 mg, yield: 75% from **SL3b**, single isomer) as a colorless oil after

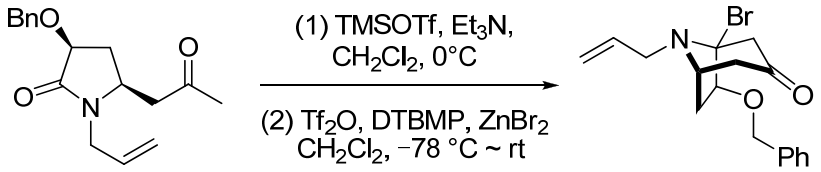
flash column chromatography on silica gel (eluent: EtOAc/PE = 1/15). IR (film) ν_{max}: 2930, 2875, 2854, 1710, 1453, 1359, 1185, 1154, 1110, 1082, 1028, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05-1.14 (m, 1H), 1.46 (ddd, *J*= 4.3, 9.7, 11.7 Hz, 1H), 1.64-1.74 (m, 1H), 1.87-2.08 (m, 3H), 2.15 (ddt, *J*= 0.9, 4.5, 13.2 Hz, 1H), 2.30 (S, 3H), 3.07 (ddd, *J*= 4.5, 9.7, 13.2 Hz, 1H), 3.27 (m, 1H), 3.49 (dd, *J*= 5.0, 11.6 Hz, 1H), 3.87 (d, *J*= 13.5 Hz, 1H), 4.26 (d, *J*= 13.5 Hz, 1H), 7.22-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.9, 25.7, 32.8, 34.5, 46.1, 52.9, 54.7, 89.4, 126.9, 128.3, 128.4, 139.0, 209.5; HRMS calcd for $C_{16}H_{20}ClNO$ [M+H^+]: 278.1312 and 280.1282; found: 278.1310 and 280.1287.

9-Benzyl-1-chloro-9-azabicyclo[3.3.1]nonan-3-one (12a)



Following the **general procedure 2**, reaction of the silyl enol ether **SL4a,b** (72 mg, 0.20 mmol) with 2,6-*tert*-butyl-4-methylpyridine (49 mg, 0.24 mmol), Tf_2O (39 μL, 0.24 mmol) and $ZnCl_2$ (0.24 mL, 0.24 mmol, 1 M in Et_2O), afforded cyclization product **12a** (27 mg, yield: 65% from **SL4a**) as a white solid after flash column chromatography on silica gel (eluent: EtOAc/PE = 1/15). Mp: 91.4-93.4 ºC; IR (film) ν_{max}: 3405, 3026, 2940, 1713, 1494, 1450, 1224, 1125, 916, 728, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36-1.46 (m, 1H), 1.48-1.59 (m, 1H), 1.65-1.75 (m, 1H), 1.92 (ddt, *J*= 4.5, 13.6, 13.6 Hz, 1H), 2.14-2.24 (m, 2H), 2.38 (dddd, *J*= 1.9, 5.3, 13.5, 13.5 Hz, 1H), 2.72 (dd, *J*= 7.1, 16.7 Hz, 1H), 2.99 (dd, *J*= 1.6, 16.2 Hz, 1H), 3.13 (dd, *J*= 1.5, 16.2 Hz, 1H), 3.38-3.45 (m, 1H), 3.99 (d, *J*= 14.0 Hz, 1H), 4.45 (dd, *J*= 14.0 Hz, 1H), 7.25-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 27.7, 41.0, 41.2, 51.4, 52.6, 54.0, 87.9, 127.2, 128.3, 128.4, 139.1, 207.4; HRMS calcd for $C_{15}H_{18}ClNO$ [M+H^+]: 264.1155 and 266.1126; found: 264.1158 and 266.1139.

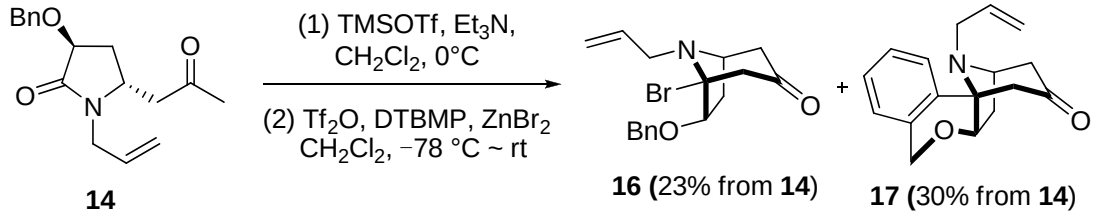
(1*R*,5*S*,7*S*)-8-Allyl-7-(benzyloxy)-1-bromo-8-azabicyclo[3.2.1]octan-3-one (15)



13 **15** (50% from **13**)

Following the **general procedure 1**, reaction of (3*S*,5*S*)-ketone-lactam **13** (123 mg, 0.43 mmol) with Et_3N (0.15 mL, 1.08 mmol) and TMSOTf (0.15 mL, 0.86 mmol) afforded crude silyl enol ether **SL5a,b** (terminal: internal > 20: 1, ^{1}H NMR) which was used in the next step without purification. Following the **general procedure 3**, reaction of the crude silyl enol ether **SL5a,b** with 2,6-*tert*-butyl-4-methylpyridine (97 mg, 0.47 mmol), Tf_2O (78 μL, 0.47 mmol) and $ZnBr_2$ (106 mg, 0.47 mmol) afforded cyclization product (1*R*,5*S*,7*S*)-**15** (74 mg, yield: 50% from (3*S*,5*S*)-**13**) as a colorless oil after flash column chromatography on silica gel (eluent: EtOAc/PE = 1/10). $[\alpha]_D^{20}$ −73.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3409, 3026, 2950, 1723, 1450, 1409, 1347, 1186, 1149, 1101, 896, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (dd, *J*= 3.4, 13.5 Hz, 1H), 2.15 (d, *J*= 17.4 Hz, 1H), 2.46 (dddd, *J*= 2.3, 7.8, 10.4, 13.5 Hz, 1H), 2.62 (ddd, *J*= 1.6, 4.5, 17.4 Hz, 1H), 2.99 (d, *J*= 16.6 Hz, 1H), 3.21 (dd, *J*= 8.6, 13.7 Hz, 1H), 3.29 (d, *J*= 16.6 Hz, 1H), 3.61-3.68 (m, 1H), 3.98 (tdd, *J*= 1.9, 4.0, 13.7 Hz, 1H), 4.51 (dd, *J*= 3.4, 10.4 Hz, 1H), 4.68 (d, *J*= 12.1 Hz, 1H), 4.78 (d, *J*= 12.1 Hz, 1H), 5.21 (td, *J*= 1.4, 10.1 Hz, 1H), 5.26-5.34 (m, 1H), 5.88 (dddd, *J*= 4.0, 8.6, 10.1, 17.2 Hz, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 40.4, 46.7, 49.9, 51.4, 72.4, 84.3, 86.7, 118.0, 127.5, 127.7, 128.4, 134.5, 137.7, 204.3; HRMS calcd for $C_{17}H_{20}BrNO_2$ [M+H$^+$]: 350.0756 and 352.0735; found: 350.0755 and 352.0736.

(1*S*,5*R*,7*S*)-8-Allyl-7-(benzyloxy)-1-bromo-8-azabicyclo[3.2.1]octan-3-one (16)



14 **16** (23% from **14**) **17** (30% from **14**)

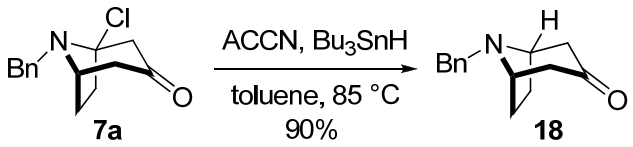
Following the **general procedure 1**, reaction of (3*S*,5*R*)-ketone-lactam **14** (250 mg, 0.87 mmol) with Et_3N (0.30 mL, 2.18 mmol) and TMSOTf (0.32 mL, 1.74 mmol)

afforded crude silyl enol ether **SL6a,b** (terminal: internal > 20: 1, ^{1}H NMR) which was used in the next step without purification. Following the **general procedure 3**, the crude silyl enol ether **SL6a,b** with 2,6-*tert*-butyl-4-methylpyridine (213 mg, 1.04 mmol), Tf_2O (78 μL, 0.47 mmol) and $ZnBr_2$ (392 mg, 1.74 mmol) afforded, after flash column chromatography on silica gel (eluent: EtOAc/PE = 1/10), cyclization product (1*S*,5*R*,7*S*)-**16** (70 mg, yield: 23% from (3*S*,5*R*)-**14**) as a colorless oil and tetracyclic compound **17** (70 mg, yield: 30% from (3*S*,5*R*)-**14**) as a pale yellow solid.

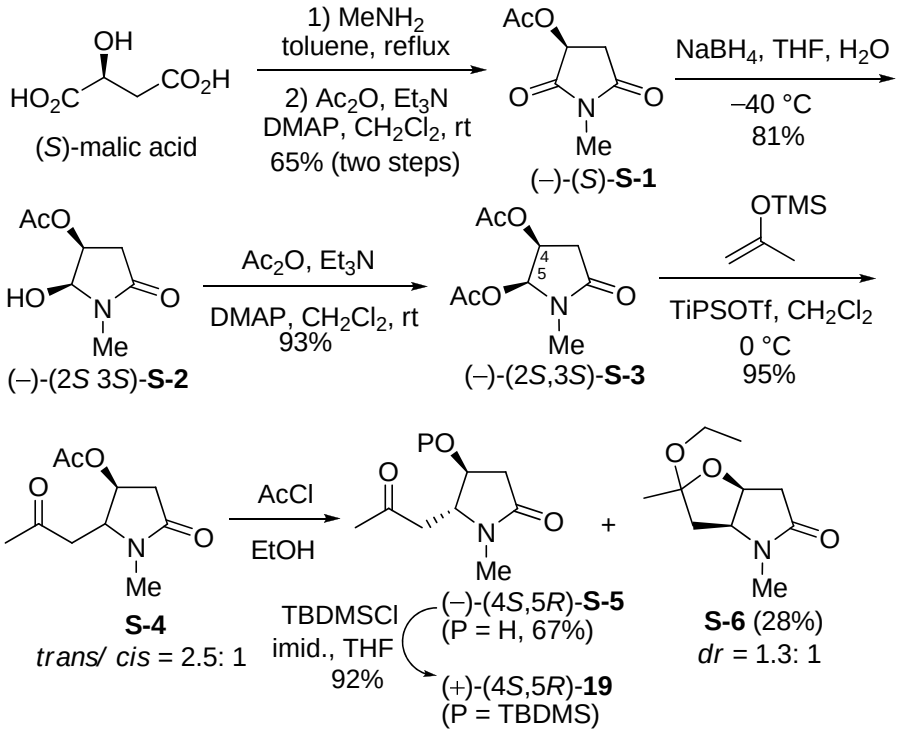
Compound (1*S*,5*R*,7*S*)-**16**: $[\alpha]_D^{20}$ +49.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2916, 2849, 1716, 1453, 1412, 1194, 1150, 1115, 1096, 1013, 929, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (dd, *J*= 7.6, 13.8 Hz, 1H), 1.99-2.07 (m, 1H), 2.12-2.21 (m, 1H), 2.57 (ddd, *J*= 2.2, 4.1, 16.4 Hz, 1H), 2.82 (dd, *J*= 1.3, 16.2 Hz, 1H), 3.19-3.28 (m, 2H), 3.72 (dd, *J*= 3.5, 7.6 Hz, 1H), 3.81 (ddd, *J*= 1.3, 4.3, 7.9 Hz, 1H), 4.03 (tdd, *J*= 1.9, 3.9, 13.4 Hz, 1H), 4.66 (d, *J*= 12.5 Hz, 1H), 4.81 (d, *J*= 12.5 Hz, 1H), 5.16-5.22 (m, 1H), 5.26-5.34 (m, 1H), 5.92-6.06 (m, 1H), 7.24-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.4, 40.6, 47.5, 52.4, 54.4, 72.9, 82.2, 86.1, 117.7, 127.67, 127.70, 128.3, 135.0, 137.7, 205.0; HRMS calcd for $C_{17}H_{20}BrNO_2$ [M+Na$^+$]: 372.0575 and 374.0555; found: 372.0580 and 374.0561.

Compound **17**: Mp: 55-63 ºC; $[\alpha]_D^{20}$ +9.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3073, 2949, 2854, 1717, 1446. 1320, 1099, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (dd, *J*= 7.2, 14.6 Hz, 1H), 2.25-2.37 (m, 3H), 2.66-2.74 (m, 1H), 3.02 (d, *J*= 16.9 Hz, 1H), 3.03-3.13 (m, 2H), 3.78-3.85 (m, 1H), 4.20 (dd, *J*= 3.2, 7.2 Hz, 1H), 4.62 (d, J= 14.7 Hz, 1H), 4.73 (d, *J*= 14.7 Hz, 1H), 5.02-5.09 (m, 1H), 5.10-5.19 (m, 1H), 5.78 (dddd, *J*= 5.2, 7.0, 10.2, 17.1 Hz, 1H), 7.09 (d, *J*= 7.5 Hz, 1H), 7.26 (dt, *J*= 1.2, 7.5 Hz, 1H), 7.33 (t, *J*= 7.5 Hz, 1H), 7.51 (d, *J*= 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0, 48.8, 52.3, 53.7, 56.6, 65.9, 68.1, 83.3, 116.3, 124.6, 127.4, 127.7, 127.9, 133.7, 135.7, 137.3, 209.4; MS (ESI) m/z 270 (M+H$^+$, 100%); HRMS calcd for $C_{17}H_{19}NO_2$ [M+H$^+$]: 270.1449; found: 270.1486.

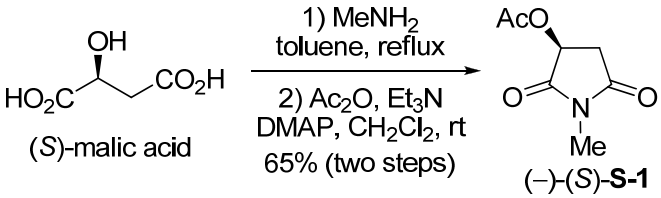
8-Benzyl-8-azabicyclo[3.2.1]octan-3-one (18)



To a solution of 1-chlorotropane derivative **7a** (41 mg, 0.165 mmol) and ACCN 1,1'-azobis(cyclohexanecarbonitrile) (49 mg, 0.200 mmol) in anhydrous toluene (0.8 mL) was added Bu_3SnH (0.09 mL, 0.330 mmol) and the mixture was stirred at 85 ºC for 3 h. After removing the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1/6) to give de-chlorinated product **18** (32 mg, 90%) as a colorless oil. IR (film) ν_{max}: 2953, 2879, 2852, 1714, 1494, 1452, 1347, 1193, 1143, 1072, 1007, 730, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60-1.70 (m, 2H), 2.10-2.18 (m, 2H), 2.19-2.27 (m, 2H), 2.72 (dd, J= 4.3, 16.1 Hz, 2H), 3.48-3.56 (m, 2H), 3.77 (s, 2H), 7.24-7.50 (m, 5H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 27.8, 48.3, 55.2, 58.6, 127.1, 128.35, 128.41, 139.3, 210.4; HRMS calcd for $C_{14}H_{17}NO$ [M+H^+]: 216.1383; found: 216.1379.

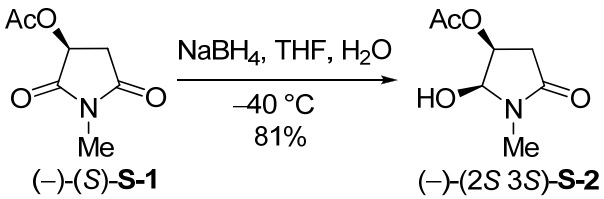


(*S*)-1-Methyl-2,5-dioxopyrrolidin-3-yl acetate (S-1)



To a stirred solution of (*S*)-malic acid (67 g, 500 mmol) in 350 mL of toluene was added 49 mL of 40% aqueous CH_3NH_2. After 0.5 h the mixture was heated to reflux in flask equipped with a Dean-Stark trap and 46 mL of H_2O was collected over a 48 h period. EtOH (150 mL) was added, the mixture was concentrated, and the residue was distilled to give desired imide (50.5 g, 78%). To an ice-bath cooled solution of imide (12.9 g, 100 mmol) in CH_2Cl_2 (200 mL) were added successively DMAP (cat.), Ac_2O (18.8 mL, 200 mmol) and Et_3N (34.9 mL, 250 mmol). After being stirred overnight at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1: 2) to afford compound (*S*)-**S-1** (14.2 g, 83%) as a colorless oil. $[\alpha]_D^{20}$ –20 (*c* 3.4, $CHCl_3$) {lit.[1] $[\alpha]_D^{22}$ –21.0 (*c* 0.43, $CHCl_3$)}; IR (film) ν_{max}: 2953, 1750, 1707, 1438, 1384, 1282, 1224, 1127, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.63 (dd, J = 18.3, 4.6 Hz, 1H), 3.01 (s, 3H), 3.14 (dd, J = 18.3, 8.7 Hz, 1H), 5.43 (dd, J = 8.7, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 24.9, 35.7, 67.4, 169.7, 173.2, 173.5; MS (ESI) *m/z* 194 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_7H_9NO_4$ $[M+Na^+]$: 194.0429; found: 194.0426.

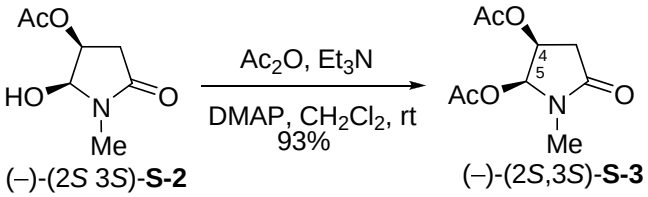
(2*S*,3*S*)-2-Hydroxy-1-methyl-5-oxopyrrolidin-3-yl acetate (S-2)



To a cold solution (–40 °C) of (*S*)-imide **S-1** (2.20 g, 12.87 mmol) in THF (150 mL) was added $NaBH_4$ (0.734 g, 19.30 mmol) in one portion. The resulting mixture was

stirred at –40 °C for 15 min and saturated aqueous $NaHCO_3$ (20 mL) was slowly added. After being stirred for 30 min, the mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure and then EtOAc was added. The solid was filtrated and washed with EtOAc to afford compound (2*S*,3*S*)-**S-2** (1.083 g, 81%) as a white solid. M.p. 115-117 °C (EtOAc); $[\alpha]_D^{20}$ –59 (*c* 0.6, CH_3COCH_3); $[\alpha]_D^{20}$ –22 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3186, 2933, 1727, 1660, 1434, 1384, 1341, 1240, 1092, 1073, 1057 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 2.07 (s, 3H), 2.43 (dd, *J* = 17.1, 6.5 Hz, 1H), 2.57 (dd, *J* = 17.1, 8.0 Hz, 1H), 2.78 (s, 3H), 3.99 (d, *J* = 8.2 Hz, 1H), 5.12 (dd, *J* = 8.2, 5.3 Hz, 1H), 5.16 (ddd, *J* = 8.0, 6.5, 5.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 27.0, 35.1, 68.7, 83.8, 171.2, 171.5; MS (ESI) *m/z* 196 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_7H_{11}NO_4$ [$M+Na^+$]: 196.0586; found: 196.0580.

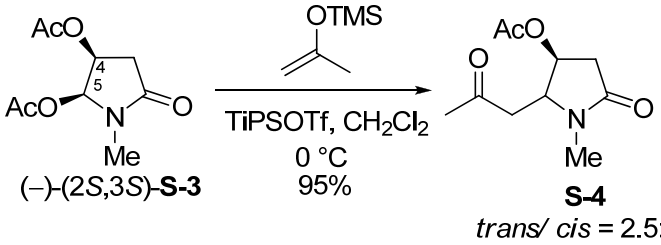
(2*S*,3*S*)-1-Methyl-5-oxopyrrolidine-2,3-diyl diacetate (S-3)



To an ice-bath cooled solution of (2*S*, 3*S*)-**S-2** (2.90 g, 16.76 mmol) in CH_2Cl_2 (50 mL) were added successively DMAP (cat.), Ac_2O (4.7 mL, 50.29 mmol) and Et_3N (7.0 mL, 50.29 mmol). After being stirred overnight at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and water (15 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1: 2) to afford compound (2*S*,3*S*)-**S-3** (3.35 g, 93%) as a colorless oil. $[\alpha]_D^{20}$ –78 (*c* 3.9, $CHCl_3$); IR (film) ν_{max}: 2937, 1750, 1719, 1435, 1380, 1236, 1084, 1003 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 2.03 (s, 3H), 2.07 (s, 3H), 2.49 (dd, *J* = 16.7, 8.3 Hz, 1H), 2.63 (dd, *J* = 16.7, 8.3 Hz, 1H), 2.79 (s, 3H), 5.34 (dt, *J* = 5.4, 8.3 Hz, 1H), 6.25 (d, *J* = 5.4 Hz,

1H); ^{13}C NMR (125 MHz, CD_3CN) δ 20.7, 20.9, 27.9, 34.3, 66.8, 84.3, 170.9, 171.4, 172.2; MS (ESI) *m/z* 238 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_9H_{13}NO_5$ [$M+Na^+$]: 238.0691; found: 238.0688.

(2*R*/*S*,3*S*)-1-Methyl-5-oxo-2-(2-oxopropyl)pyrrolidin-3-yl acetate (S-4)

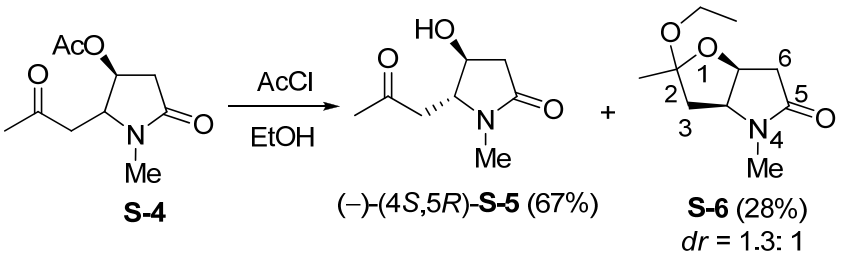


trans/ *cis* = 2.5: 1

To an ice-bath cooled solution of (2*S*, 3*S*)-**S-3** (775 mg, 3.61 mmol) and trimethyl(prop-1-en-2-yloxy)silane (0.9 mL, 5.42 mmol) in anhydrous CH_2Cl_2 (18 mL) was added TIPSOTf[2] (0.097 mL, 0.36 mmol). After being stirred for 1 h at 0 °C, the reaction was stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc to afford compound **S-4** (732 mg, 95%) as an inseparable diastereomeric mixture in a ratio of 2.5: 1 (^{1}H NMR). Colorless oil. IR (film) ν_{max}: 2929, 1734, 1687, 1403, 1372, 1232, 1166, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, two diastereomers, major (M)/minor (m) = 2.5: 1, data read from the spectrum of the diastereomeric mixture) δ_H 1.98 (s, 0.9H, m), 2.02 (s, 2.1H, M), 2.16 (s, 2.1H, M), 2.18 (s, 0.9H, m), 2.29-2.37 (m, 1H, M + m), 2.67-2.85 (m, 6H, M + m), 3.81-3.85 (m, 0.7H, M), 4.18-4.24 (m, 0.3H, m), 4.91-4.96 (m, 0.7H, M), 5.34-5.40 (m, 0.3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_{C(major)}$ 20.9, 27.8, 30.5, 36.5, 44.0, 62.2, 71.6, 170.5, 171.6, 204.9; $\delta_{C(minor)}$ 20.6, 27.5, 30.3, 37.3, 40.9, 57.7, 67.9, 169.6, 171.6, 204.9; MS (ESI) *m/z* 236 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{10}H_{15}NO_4$ [$M+Na^+$]: 236.0899; found: 236.0904.

(4*S*,5*R*)-4-Hydroxy-1-methyl-5-(2-oxopropan-1-yl)pyrrolidin-2-one (S-5)

(2*R*/*S*,3a*S*,6a*S*)-Ethoxy-2,4-dimethyltetrahydro-2*H*-furo[3,2-*b*]pyrrol-5(3*H*)-one (S-6)



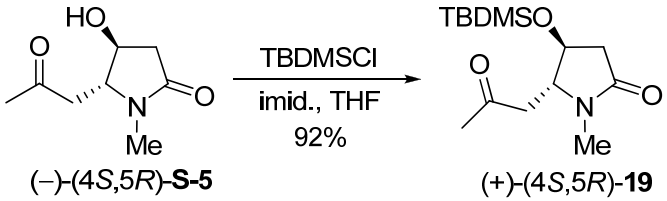
To an ice-bath cooled solution of **S-4** (343 mg, 1.61 mmol) in anhydrous ethanol (6 mL) was added dropwise acetyl chloride (0.28 mL, 4.03 mmol). After being stirred for 1 h at 0 °C, the reaction was stirred overnight at room temperature. The solution was neutralized with solid $NaHCO_3$ until pH = 7, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc to afford compound (4*S*,5*R*)-**S-5** (185 mg, 67%) as a single isomer, and diastereomeric mixture **S-6** (90 mg, 28%) in a ratio of 1.3: 1 (^{1}H NMR), which is only partially separable by flash chromatography.

Compound (4*S*,5*R*)-**S-5**: white solid. M.p. 60-62 °C (EtOAc); $[\alpha]_D^{20}$ −57.8 (*c* 1.9, $CHCl_3$); IR (film) ν_{max}: 3393, 2929, 1711, 1672, 1403, 1365, 1248, 1162, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.38 (dd, *J* = 17.3, 3.7 Hz, 1H), 2.51 (dd, *J* = 18.2, 9.7 Hz, 1H), 2.71 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.77 (s, 3H), 2.98 (dd, *J* = 18.2, 4.0 Hz, 1H), 3.61 (d, *J* = 2.8 Hz, 1H), 3.73 (ddd, *J* = 9.7, 4.0, 2.9 Hz, 1H), 4.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 30.6, 38.8, 45.3, 64.7, 70.2, 172.6, 207.2; MS (ESI) *m/z* 194 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_8H_{13}NO_3$ [$M+Na^+$]: 194.0793; found: 194.0796.

S-6-Major diastereomer: colorless oil. $[\alpha]_D^{20}$ −11.9 (*c* 0.6, $CHCl_3$); IR (film) ν_{max}: 2980, 2929, 1660, 1438, 1400, 1259, 1217, 1150, 1045 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 1.12 (t, *J* = 7.0 Hz, 3H), 1.42 (s, 3H), 1.82 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.28 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.35 (d, *J* = 18.0 Hz, 1H), 2.62 (dd, *J* = 18.0, 7.0 Hz, 1H), 2.73 (s, 3H), 3.43-3.53 (m, 2H), 4.23 (ddd, *J* = 7.8, 6.0, 4.1 Hz, 1H), 4.55-4.58 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 16.0, 22.1, 28.1, 38.1, 44.1, 56.9, 65.8, 75.1, 109.1, 173.7; MS (ESI) *m/z* 222 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{10}H_{17}NO_3$

[M+Na$^+$]: 222.1106; found: 222.1102. **S-6**-Minor diastereomer: colorless oil. $[\alpha]_D^{20}$ +80.9 (*c* 0.4, $CHCl_3$); IR (film) ν_{max}: 2976, 2933, 1680, 1440, 1310, 1256, 1154, 1041 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.40 (s, 3H), 1.80 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.26 (d, *J* = 17.9 Hz, 1H), 2.31 (d, *J* = 14.1 Hz, 1H), 2.57 (dd, *J* = 17.9, 7.7 Hz, 1H), 2.72 (s, 3H), 3.37-3.48 (m, 2H), 4.22 (dd, *J* = 6.7, 6.7 Hz, 1H), 4.74-4.78 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 15.7, 22.4, 28.1, 40.0, 41.6, 57.1, 65.6, 76.8, 109.1, 173.1; MS (ESI) *m/z* 222 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{10}H_{17}NO_3$ [M+Na$^+$]: 222.1106; found: 222.1100.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-methyl-5-(2-oxopropan-1-yl)pyrrolidin-2-one (19)

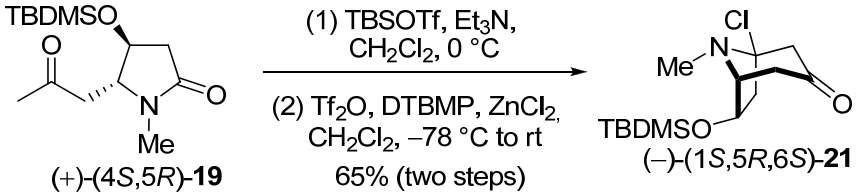


(−)-(4*S*,5*R*)-**S-5** (+)-(4*S*,5*R*)-**19**

To an ice-bath cooled solution of (4*S*,5*R*)-**S-5** (144 mg, 0.84 mmol) and imidazole (172 mg, 2.52 mmol) in anhydrous THF (6 mL) was added a THF solution of TBDMSCl (253 mg, 1.68 mmol). After being stirred for 2 days at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1: 1) to afford compound (4*S*,5*R*)-**19** (220 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ +3.8 (*c* 2.6, $CHCl_3$); IR (film) ν_{max}: 2953, 2929, 2851, 1692, 1396, 1384, 1360, 1256, 1080, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07(s, 6H), 0.87 (s, 9H), 2.20-2.28 (m, 4H), 2.50 (dd, *J* = 17.3, 7.7 Hz, 1H), 2.63 (dd, *J* = 17.0, 6.2 Hz, 1H), 2.73 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.78 (s, 3H), 3.78 (ddd, *J* = 7.7, 5.2, 2.5 Hz, 1H), 4.05 (dt, *J* = 6.2, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.8, 17.9, 25.6, 27.9, 30.6, 40.0, 44.3, 65.2, 70.3, 172.5, 205.4; MS (ESI) *m/z* 308 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{14}H_{27}NO_3Si$

[M+Na$^+$]: 308.1658; found: 308.1652.

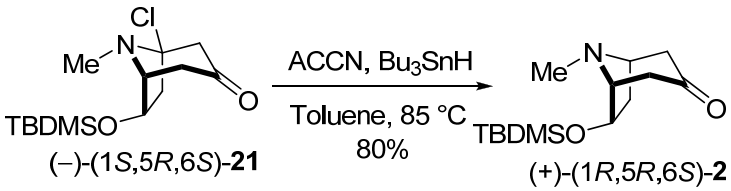
(1*S*, 5*R*, 6*S*)-6-(*Tert*-butyldimethylsilyloxy)-1-chloro-8-methyl-8-azabicyclo[3.2.1] octan-3-one (21)



To a cooled (0 ºC) solution of compound (4*S*,5*R*)-**19** (888 mg, 3.12 mmol) in anhydrous CH_2Cl_2 (16 mL) was added the Et_3N (1.08 mL, 7.8 mmol) and TBSOTf (1.43 mL, 6.24 mmol). After being stirred at 0 ºC for 1 h, the reaction mixture was allowed warmed to room temperature and stirred overnight. Then the mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give an orange residue. The residue was used in the next without purification. The crude product and 2,6-*tert*-butyl-4-methylpyridine (959 mg, 4.68 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) and cooled to −78 ºC, then the Tf_2O (0.62 mL, 3.74 mmol) was added dropwise. After stirring at the same temperature for 40 min, a solution of $ZnCl_2$ (3.2 mL, 3.2 mmol, 1 M in Et_2O) was added dropwise. The reaction mixture was stirred at −78 ºC for 1 h, then the mixture was warmed to room temperature slowly and keep stirring for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a brown oil, which was purified by flash chromatography (eluent: EtOAc/PE = 1/12) to give the desired product (1*S*,5*R*,6*S*)-**21** as a white solid (607 mg, 65% over two steps). M.p. 56-58 °C (EtOAc/PE); $[\alpha]_D^{20}$ –23 (*c* 1.1, $CHCl_3$); IR (film) ν_{max}: 3412, 2952, 2925, 2855, 1711, 1598, 1462, 1384, 1252, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 2.10-2.15 (m, 1H), 2.33-2.38 (m, 1H), 2.58-2.70 (m, 6H), 3.00 (dd, *J* = 15.9, 2.9 Hz, 1H), 3.51 (m, 1H), 3.84 (dd, *J* = 7.4, 3.2 Hz, 1H); ^{13}C NMR (100 MHz,

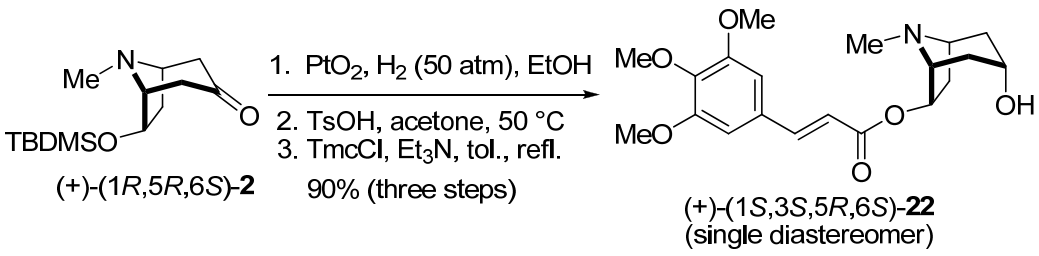
$CDCl_3$) δ –4.8, –4.7, 18.2, 25.8, 30.6, 39.1, 52.3, 52.5, 66.8, 72.4, 85.7, 204.4; HRMS (ESI) calcd for $C_{14}H_{26}ClNO_2Si$ [M+Na^+]: 326.1319 and 328.1290; found: 326.1323 and 328.1290.

(1*R*,5*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-methyl-8-azabicyclo[3.2.1]octan-3-One (2)



To a solution of 1-chlorotropane derivative (1*S*,5*R*,6*S*)-**21** (318 mg, 1.05 mmol) and ACCN (307 mg, 1.26 mmol) in anhydrous toluene (5 mL) was added Bu_3SnH (0.84 mL, 3.15 mmol) and the mixture was stirred at 85 ºC for 5 h. After removing the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1/4) to give (1*R*,5*R*,6*S*)-**2** (221 mg, yield: 80%) as a colorless oil. $[\alpha]_D^{20}$ +24.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2952, 2935, 2856, 1717, 1471, 1463, 1255, 1115, 1079, 869, 838, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 2.01-2.16 (m, 3H), 2.22 (ddd, *J*= 1.9, 1.9 15.9 Hz, 1H), 2.60-2.69 (m, 5H), 3.30-3.35 (m, 1H), 3.56-3.62 (m, 1H), 4.12 (dd, *J*= 3.4, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.82, –4.81, 18.1, 25.8, 38.2, 41.3, 44.4, 46.3, 60.8, 69.5, 77.0, 208.6; HRMS (ESI) calcd for $C_{14}H_{27}NO_2Si$ [M+H^+]: 270.1884; found: 270.1880.

(*E*)-((1*S*,3*S*,5*R*,6*S*)-3-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-6-yl) 3-(3,4,5-trimethoxyphenyl)acrylate (22)

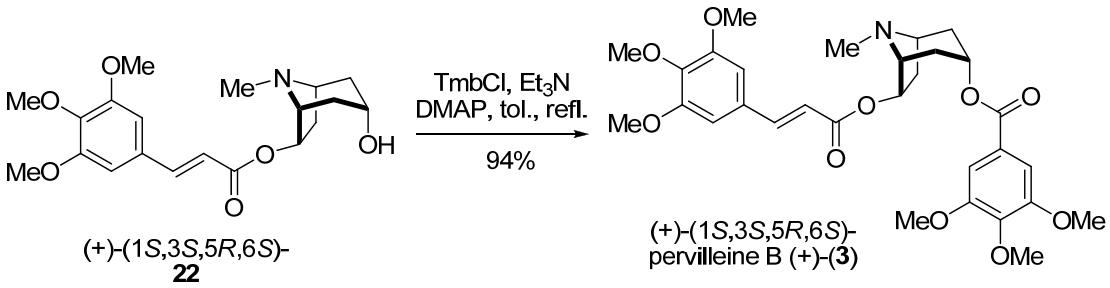


A suspension of (1*R*,5*R*,6*S*)-**2** (8.1 mg, 0.030 mmol) and PtO_2 (4 mg) in EtOH (1 mL) was hydrogenated at room temperature under 50 atm of hydrogen for 30 h. The

mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was dissolved in 1 mL of acetone and to the resulting solution was added *p*-toluenesulfonic acid monohydrate (23 mg, 0.120 mmol). The mixture was stirred at 50 ºC for 2 h. Then saturated aqueous $NaHCO_3$ was added till pH = 8. The solvent was removed under reduced pressure, and the crude product was used in the next step without purification.

To a solution of the crude diol **1** in toluene (1.5 mL) was added Et_3N (0.042 mL, 0.30 mmol) and (*E*)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (TmcCl, 46 mg, 0.18 mmol). The reaction mixture was refluxed overnight. The mixture was cooled down to 0 °C, and quenched with saturated aqueous $NaHCO_3$ (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 40/1) on silica gel to give compound (1*S*,3*S*,5*R*,6*S*)-**22** (11 mg, 90 % over 3 steps) as a white solid. M.p. 50-53 °C (lit.[3] M.p. 48-50 °C); $[\alpha]_D^{20}$ +24.0 (*c* 0.2, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ +29.8 (*c* 1.0, $CHCl_3$)}; IR (film) ν_{max}: 2921, 2843, 1708, 1633, 1584, 1504, 1463, 1415, 1330, 1275, 1220, 1172, 1152, 1127, 1005, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, *J*= 14.7 Hz, 1H), 1.91 (d, *J*= 14.7 Hz, 1H), 2.17-2.40 (m, 3H), 2.65 (s, 3H), 2.87 (dd, *J* = 7.8, 14.0 Hz, 1H), 3.39 (br s, 1H), 3.47-3.53 (m, 1H), 3.87-3.90 (m, 9H), 4.14 (t, *J* = 4.6 Hz, 1H), 5.81 (dd, *J* = 2.8, 7.7 Hz, 1H), 6.34 (d, *J* = 15.9 Hz, 1H), 6.74 (s, 2H), 7.58 (s, *J* = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 35.5, 36.5, 38.8, 56.3, 59.8, 61.1, 64.2, 66.0, 79.4, 105.5, 117.9, 130.1, 140.3, 144.8, 153.6, 167.0; HRMS (ESI) calcd for $C_{20}H_{27}NO_6$ $[M+H^+]$: 378.1911; found: 378.1915.

(+)-(1*S*,3*S*,5*R*,6*S*)-Pervilleine B (3)



(+)-(1*S*,3*S*,5*R*,6*S*)-**22**

(+)-(1*S*,3*S*,5*R*,6*S*)-pervilleine B (+)-(**3**)

To a solution of (1*S*,3*S*,5*R*,6*S*)-**22** (11 mg, 0.027 mmol) and DMAP (2 mg) in toluene (3 mL) was added Et_3N (0.037 mL, 0.27 mmol) and 3,4,5-trimethoxybenzoyl chloride (TmbCl, 18 mg, 0.080 mmol). The reaction mixture was refluxed overnight. After reaction was finished, the mixture was cooled down to 0 °C, and quenched with saturated aqueous $NaHCO_3$ (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 30/1) on silica gel to give (1*S*,3*S*,5*R*,6*S*)-pervilleine B (**3**) (16 mg, 94 %) as a white amorphous solid. M.p. 42-46 °C (lit.[4] M.p. 40-42 °C); $[\alpha]_D^{20}$ +27.0 (*c* 1.0, $CHCl_3$) {lit.[4] $[\alpha]_D^{20}$ –22.5 (*c* 0.25, $CHCl_3$)}; IR (film) ν_{max}: 2921, 2843, 1708, 1633, 1584, 1504, 1463, 1415, 1330, 1275, 1220, 1172, 1152, 1127, 1005, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73 (d, *J*= 15.0 Hz, 1H), 1.93 (d, *J*= 15.0 Hz, 1H), 2.37-2.19 (m, 3H), 2.61 (s, 3H), 2.76 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.33 (br s, 1H), 3.41 (m, 1H), 3.99-3.86 (m, 18H), 5.34 (t, *J* = 4.9 Hz, 1H), 5.77 (dd, *J* = 7.4, 2.8 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.75 (s, 2H), 7.38 (s, 2H), 7.56 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 32.6, 37.3, 38.4, 56.2, 56.3, 59.1, 60.9, 61.0, 64.9, 67.7, 79.0, 105.3, 106.7, 117.6, 125.4, 129.8, 140.2, 142.3, 144.6, 153.1, 153.5, 165.3, 166.5; MS (ESI) *m/z* 572 (M + H^+, 100%). HRMS (ESI) calcd for $C_{30}H_{37}NO_{10}$ [M+H^+]: 572.2490; found: 572.2493.

References:

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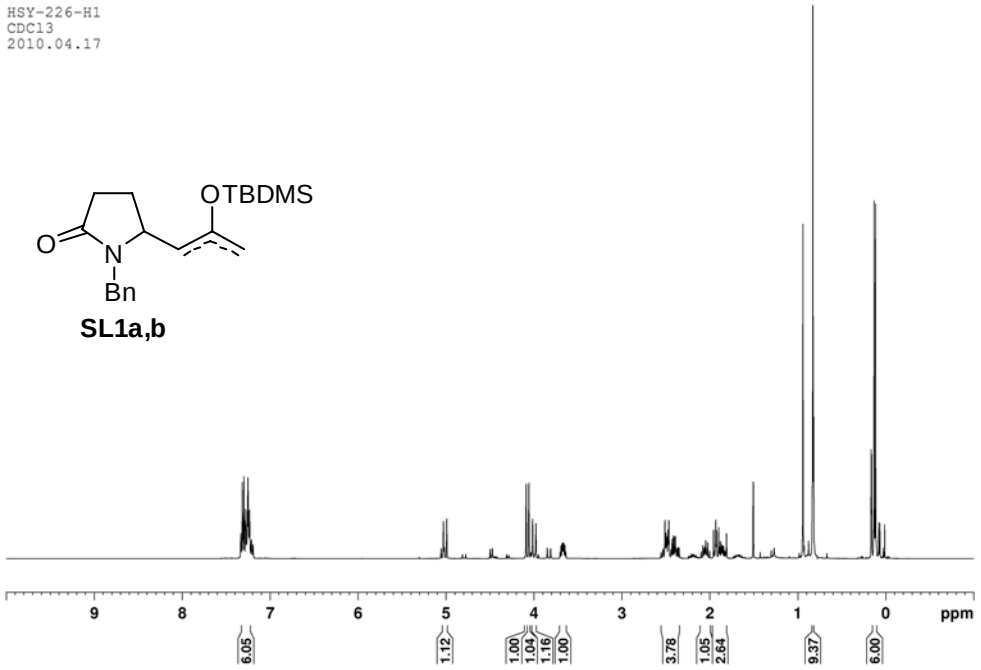
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2010.04.17
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Bn
SL1a,b
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8
7
6
5
4
3
2
1
0
ppm
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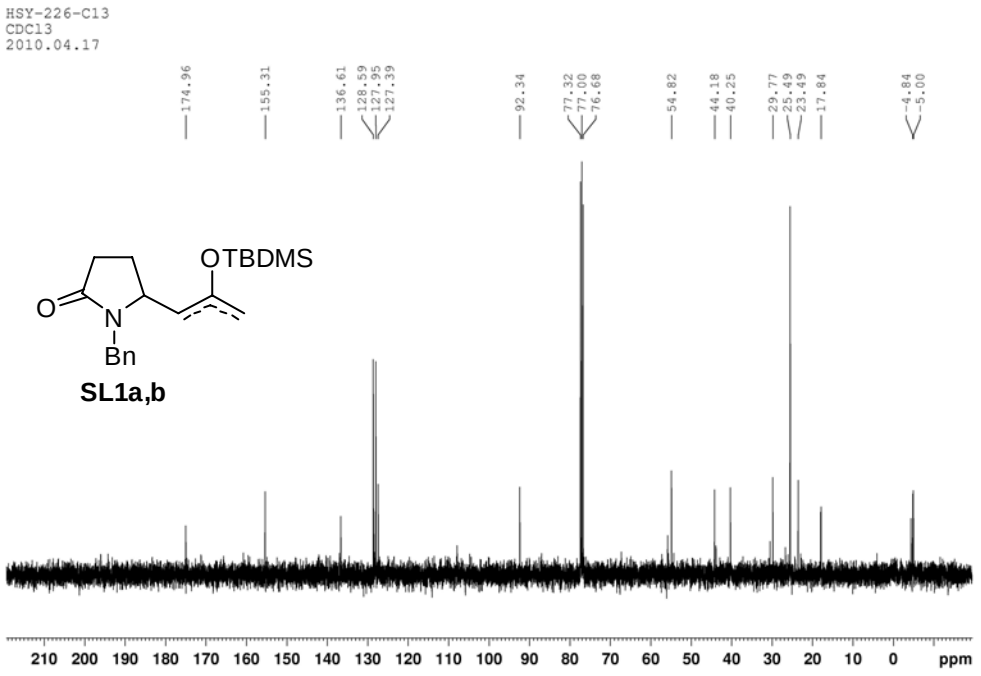
1.00
1.04
1.16
1.00
3.78
1.05
2.64
9.37
6.00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77.00
76.68
54.82
44.18
40.25
29.77
25.49
23.49
17.84
-4.84
-5.00
OTBDMS
O
N
Bn
SL1a,b
210
200
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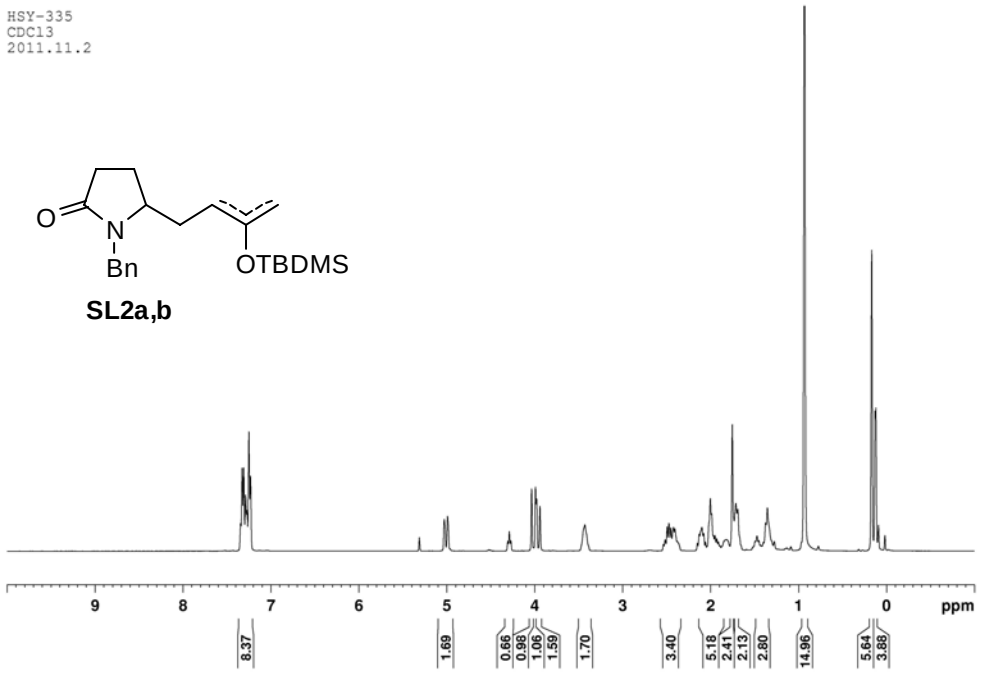
ppm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Bn
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ppm
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14.96
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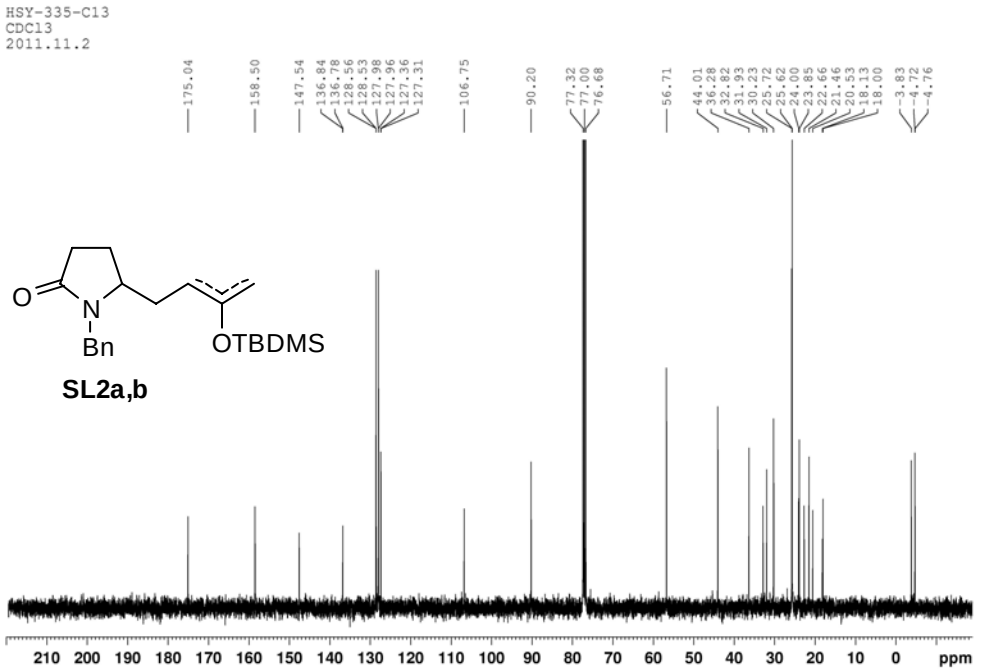
3.88

SL2a,b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77.00
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56.71
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36.28
32.82
31.93
30.23
25.72
25.62
24.00
23.85
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21.46
20.53
18.13
18.00
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O
N
Bn
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200
190
180
170
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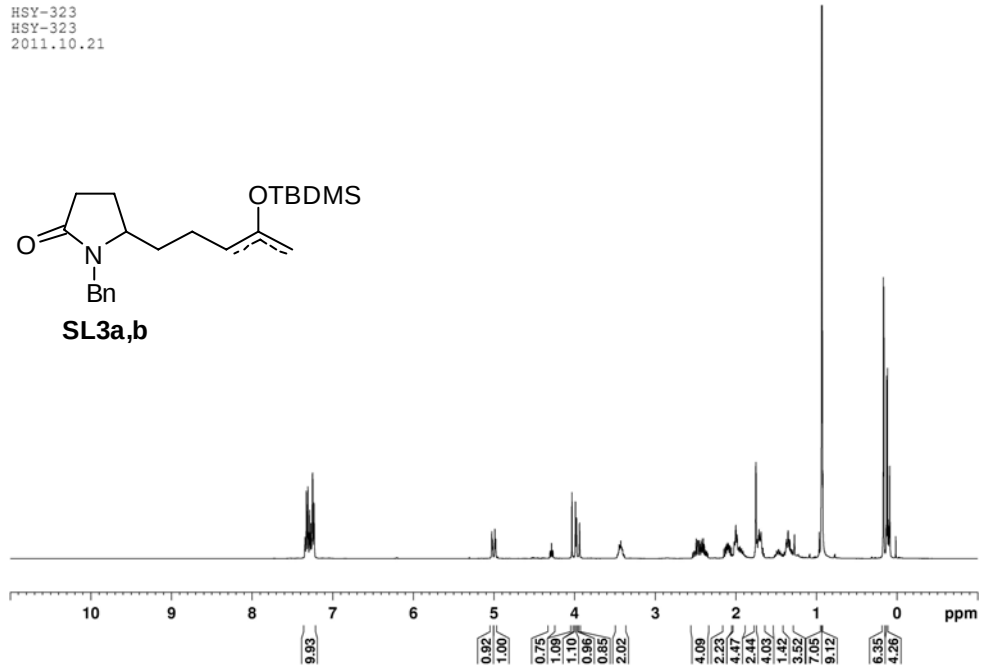
ppm

SL2a,b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2011.10.21
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Bn
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0.75
1.09
1.10
0.96
0.85
2.02
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4.03
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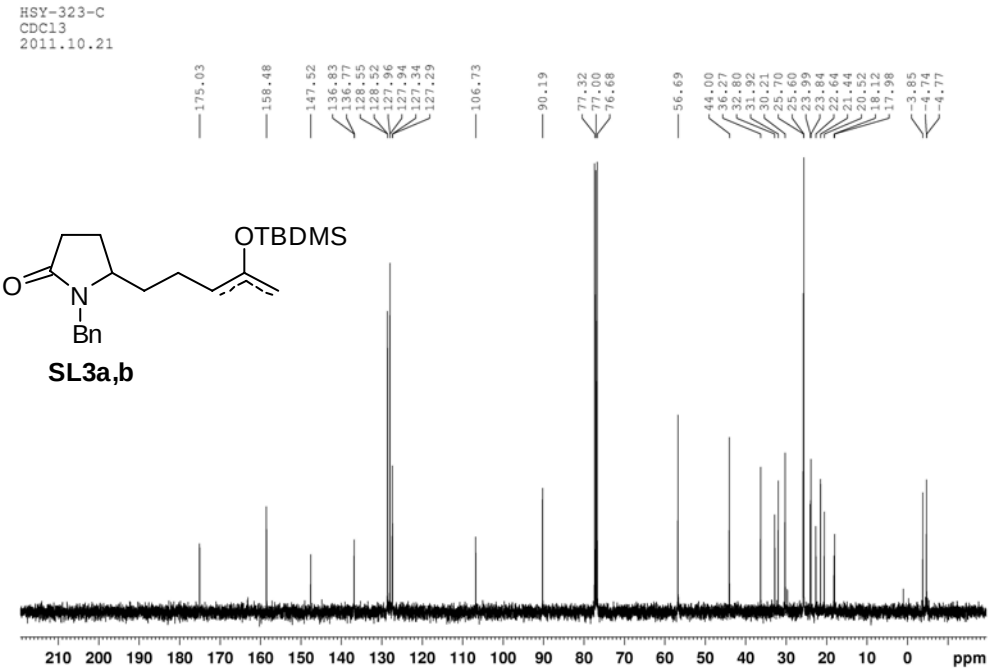
7.05
9.12
6.35
4.26

SL3a,b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23.99
23.84
22.64
21.44
20.52
18.12
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Bn
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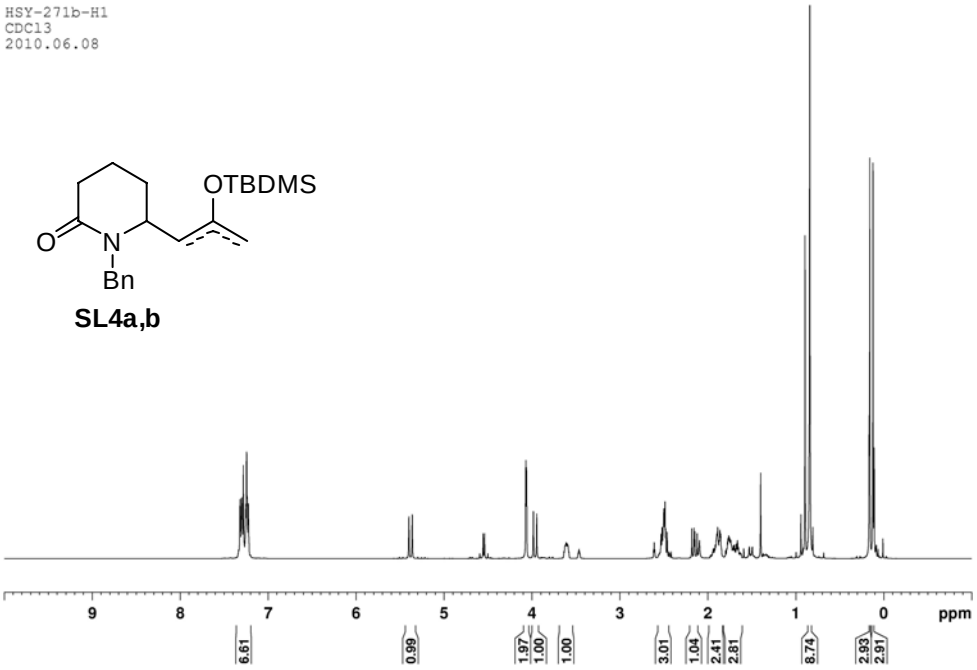
SL3a,b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2010.06.08
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Bn
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ppm
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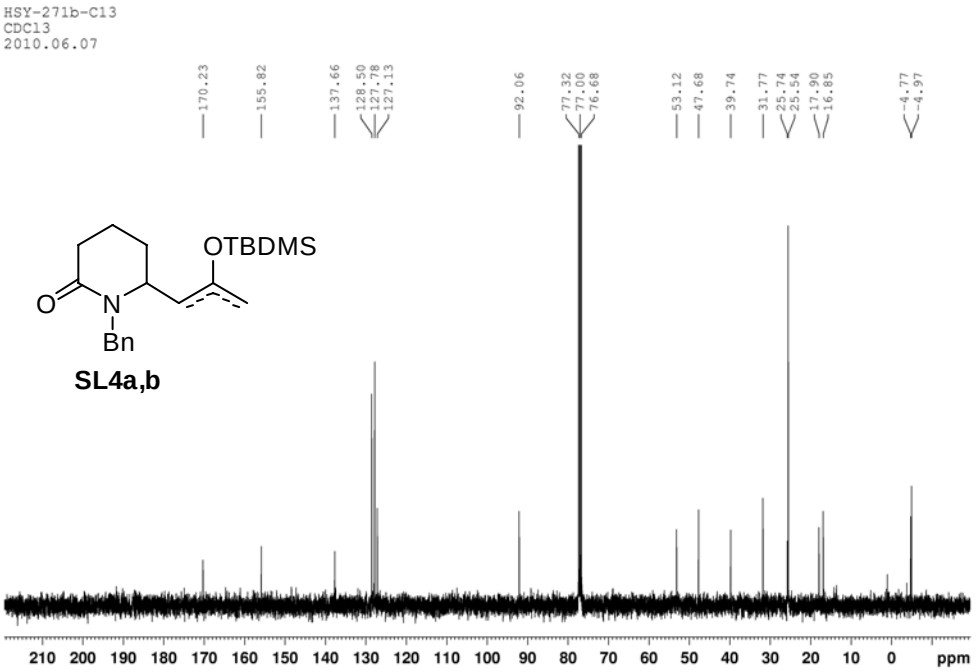
8.74
2.93
2.91

SL4a,b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31.77
25.74
25.54
17.90
16.85
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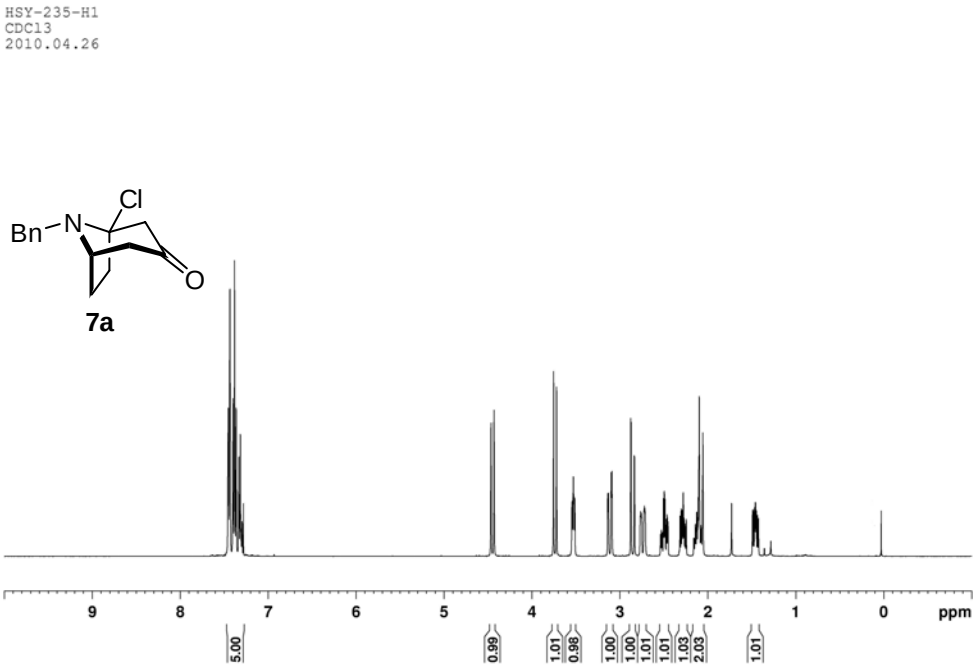
SL4a,b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2010.04.26
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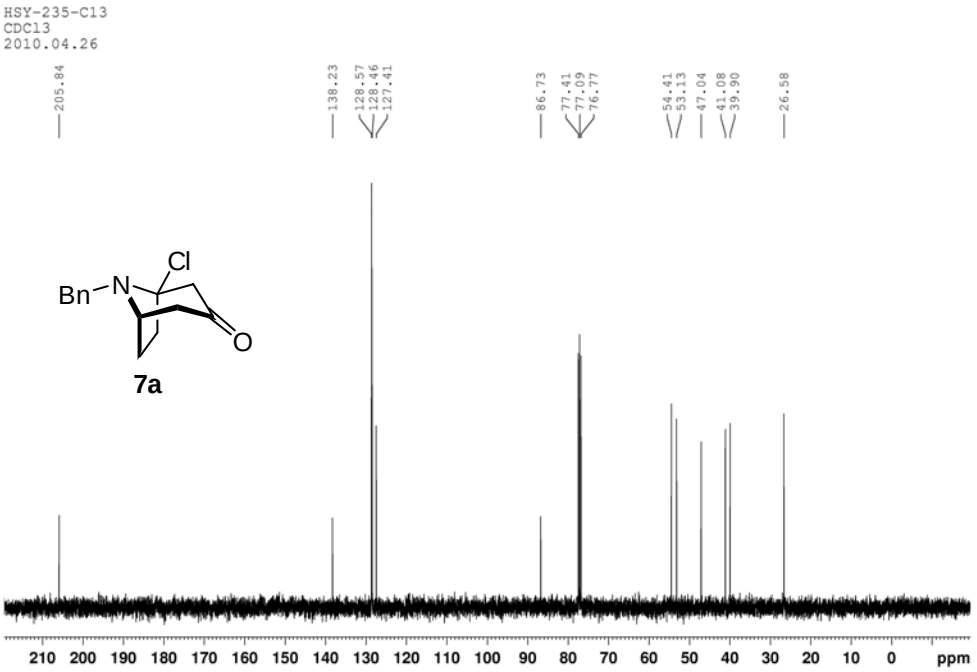
1.01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Bn
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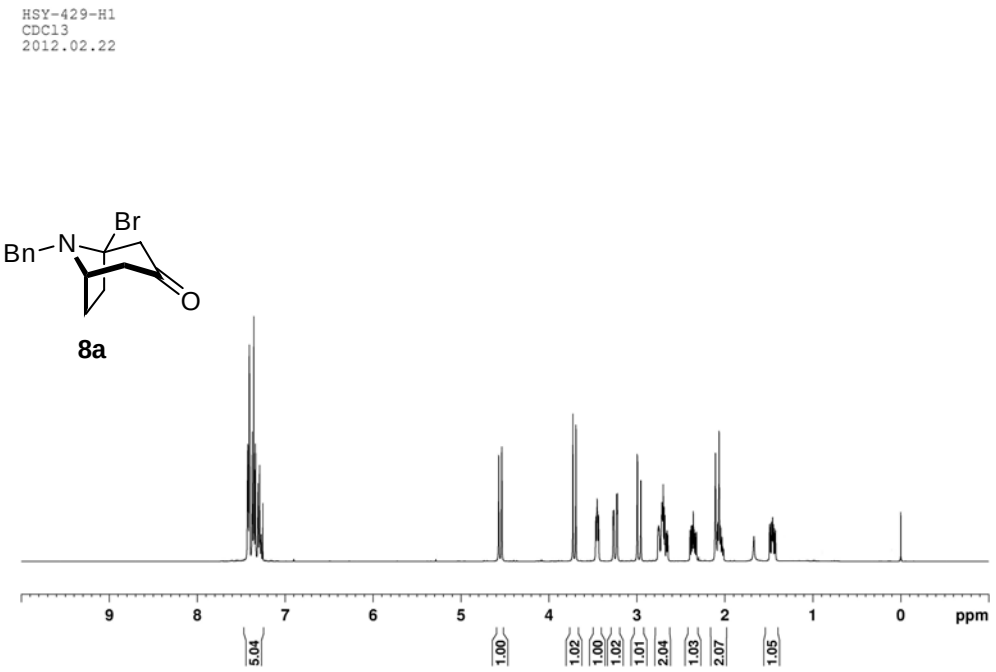
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2012.02.22
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ppm
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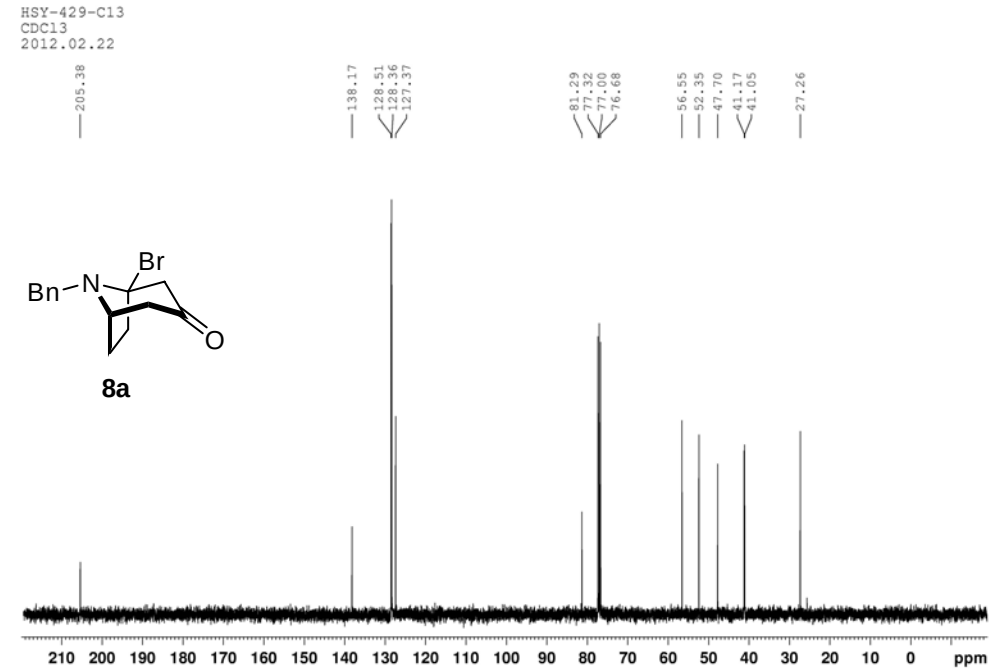
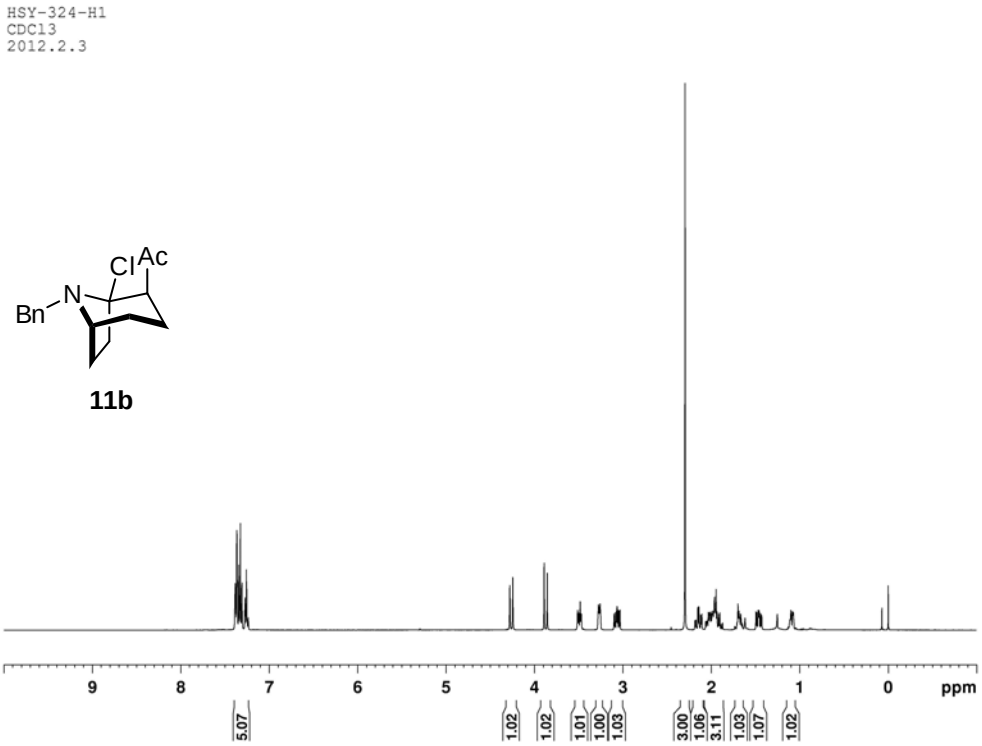
1.01
2.04
1.03
2.07
1.05

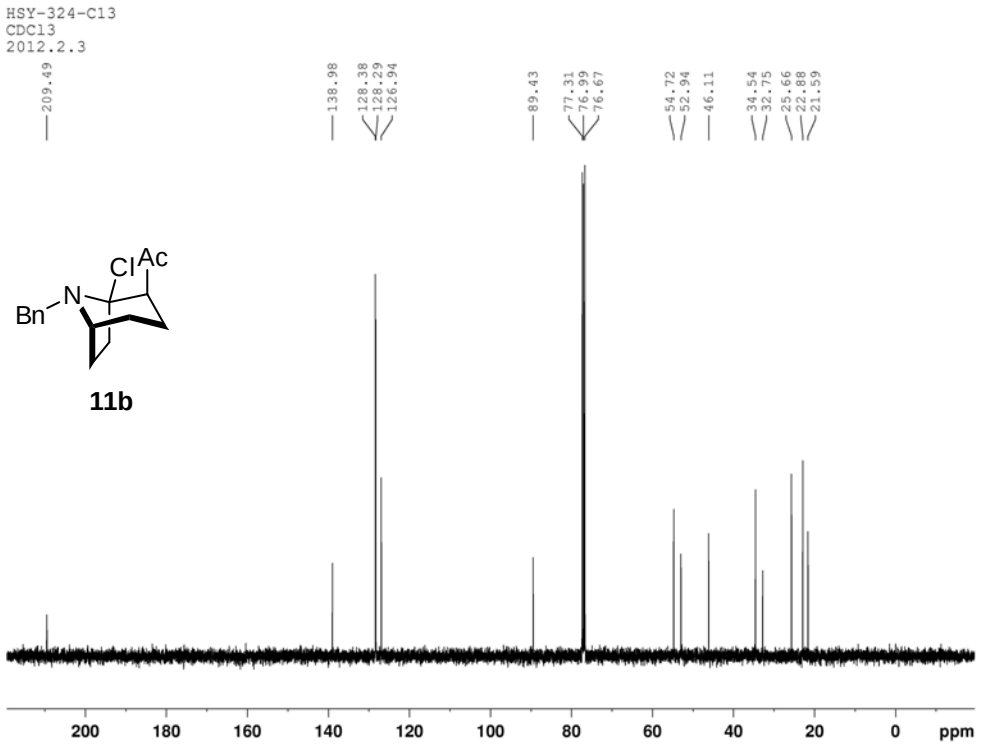
8a


HSY-429-C13
CDCl3
2012.02.22
205.38
138.17
128.51
128.36
127.37
81.29
77.32
77.00
76.68
56.55
52.35
47.70
41.17
41.05
27.26
Br
Bn
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

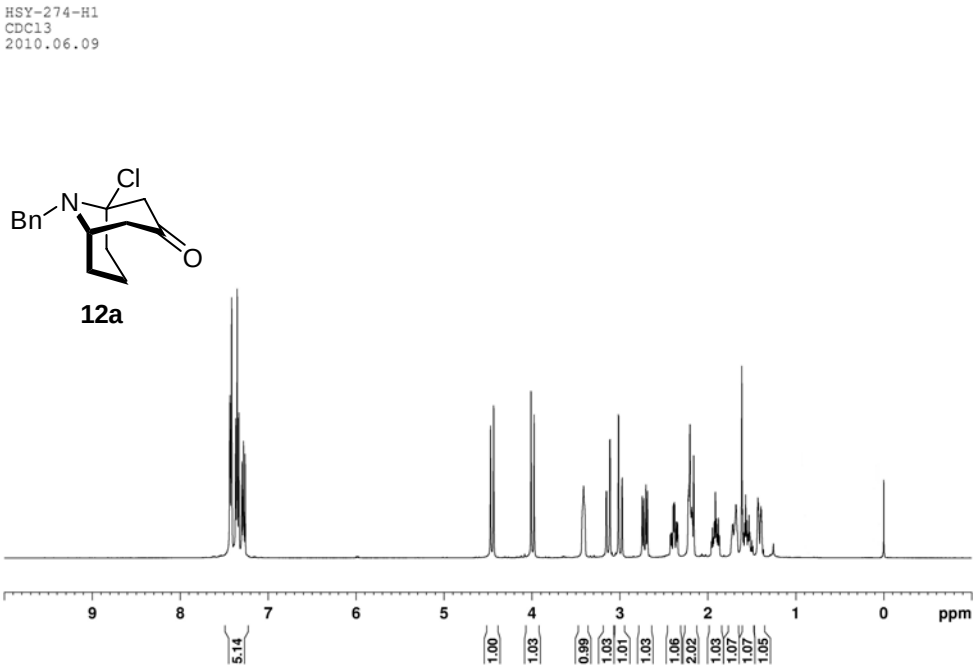
8a

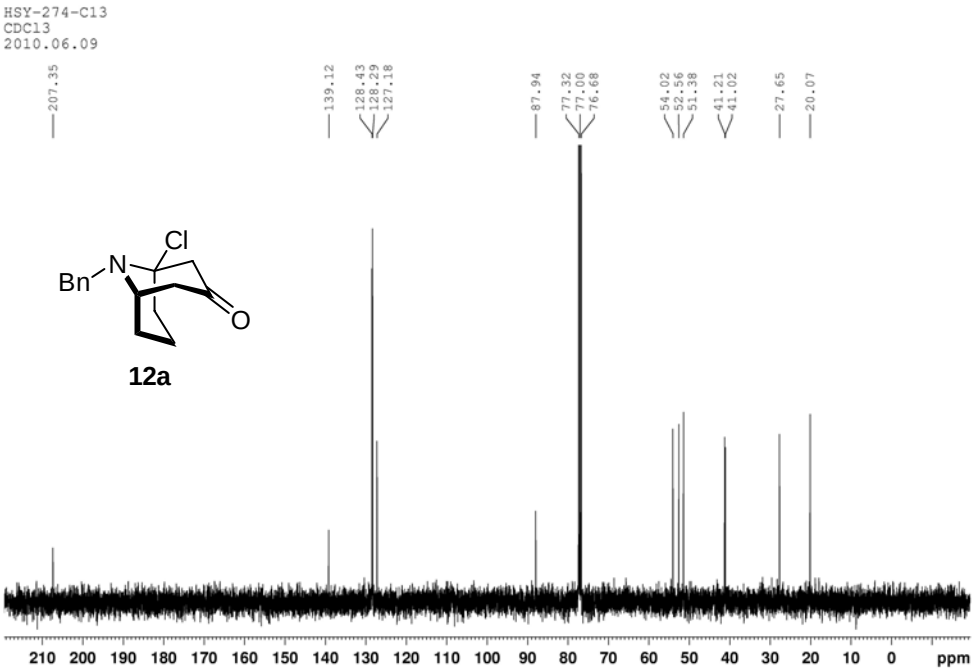

HSY-324-H1
CDCl3
2012.2.3
Cl
Ac
Bn
N
9
8
7
6
5
4
3
2
1
0
ppm
5.07
1.02
1.02
1.01
1.00
1.03
3.00
1.06
3.11
1.03
1.07
1.02

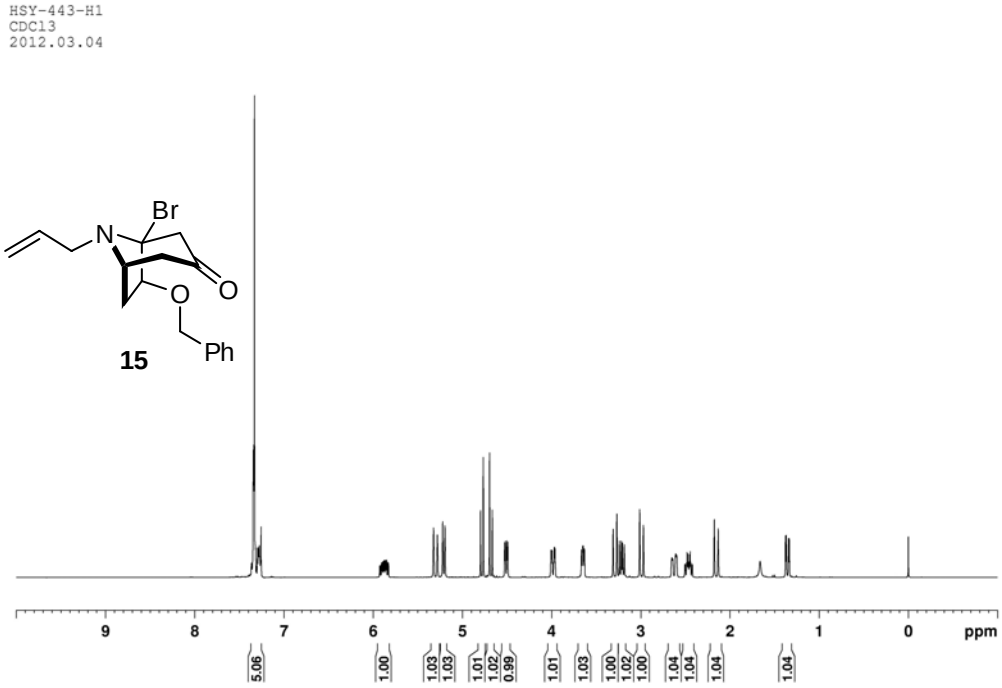
11b

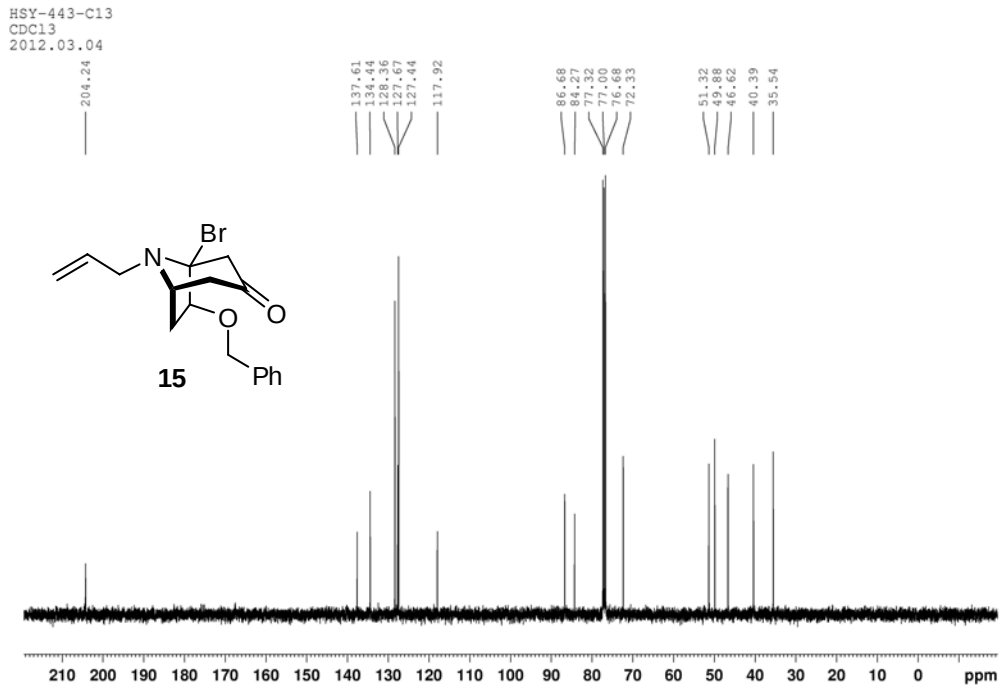

HSY-324-C13
CDCl3
2012.2.3
209.49
138.98
128.38
128.29
126.94
89.43
77.31
76.99
76.67
54.72
52.94
46.11
34.54
32.75
25.66
22.88
21.59
Cl
Ac
Bn
N
200
180
160
140
120
100
80
60
40
20
0
ppm

11b

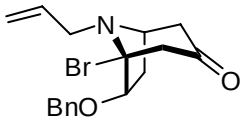

HSY-274-H1
CDCl3
2010.06.09
Cl
N
Bn
O
12a
9
8
7
6
5
4
3
2
1
0
ppm
5.14
1.00
1.03
0.99
1.03
1.01
1.03
1.06
2.02
1.03
1.07
1.07
1.05


HSY-274-C13
CDCl3
2010.06.09
207.35
139.12
128.43
128.29
127.18
87.94
77.32
77.00
76.68
54.02
52.56
51.38
41.21
41.02
27.65
20.07
Cl
N
Bn
O
12a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

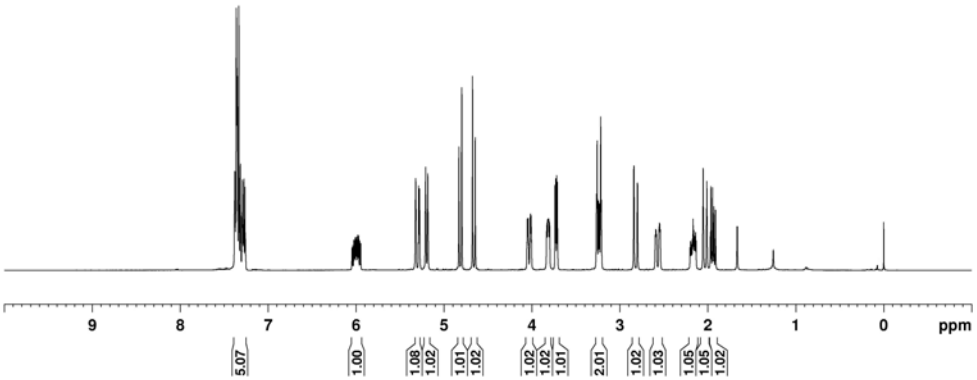

HSY-443-H1
CDCl3
2012.03.04
Br
N
O
O
Ph
15
9
8
7
6
5
4
3
2
1
0
ppm
5.06
1.00
1.03
1.03
1.01
1.02
0.99
1.01
1.03
1.00
1.02
1.00
1.04
1.04
1.04
1.04


HSY-443-C13
CDCl3
2012.03.04
204.24
137.61
134.44
128.36
127.67
127.44
117.92
86.68
84.27
77.32
77.00
76.68
72.33
51.32
49.88
46.62
40.39
35.54
Br
N
O
O
Ph
15
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

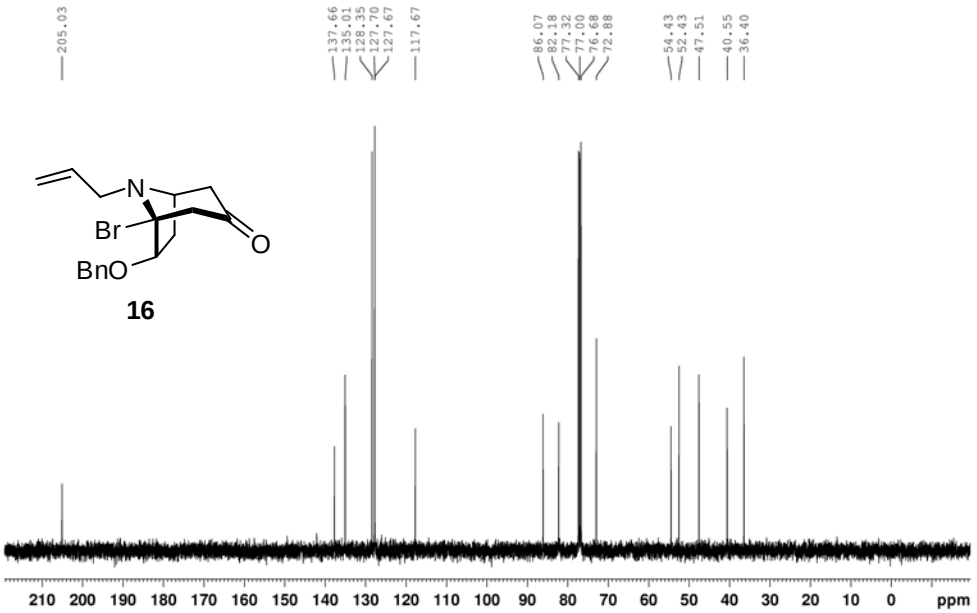
HSY-648-1-H1
CDCl3
2012.12.18



16

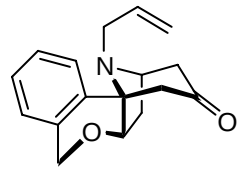


HSY-648-1-C13
CDCl3
2012.12.18

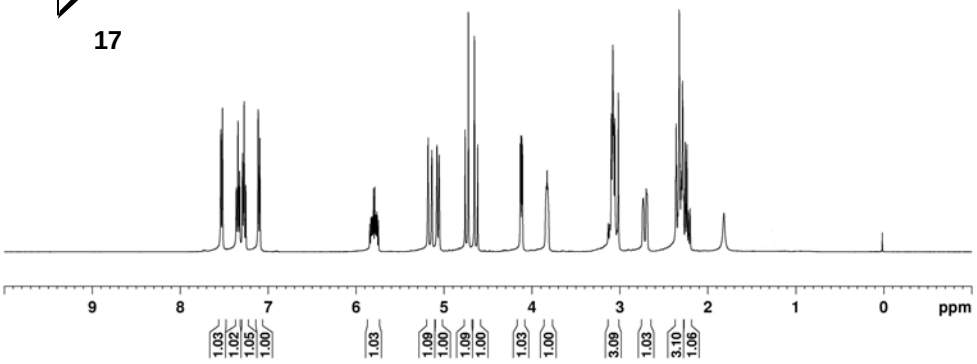


16

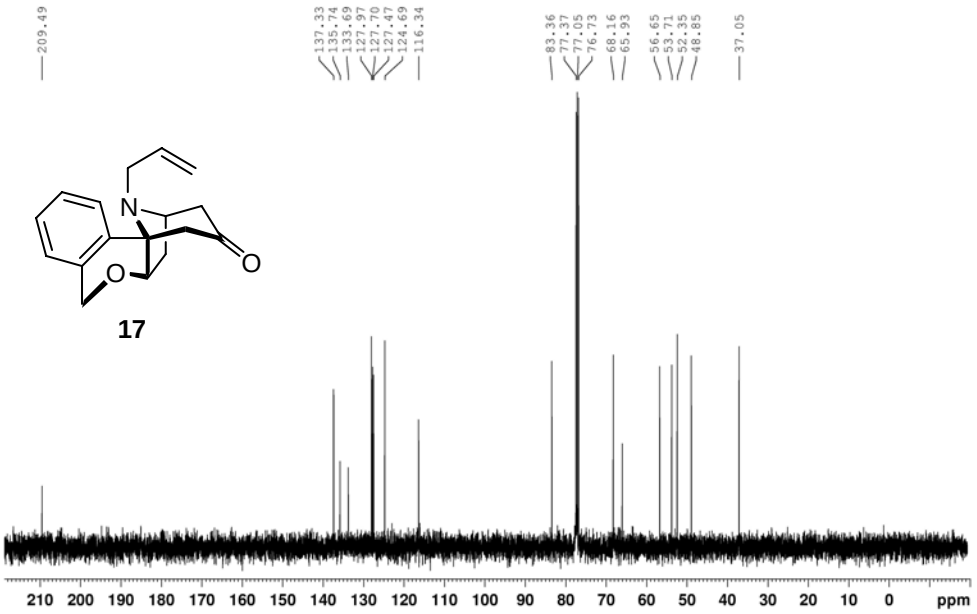
HSY-206A-H1
CDCl3
2010.08.11



17

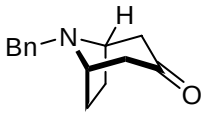


HSY-206A-C13
CDCl3
2010.08.11



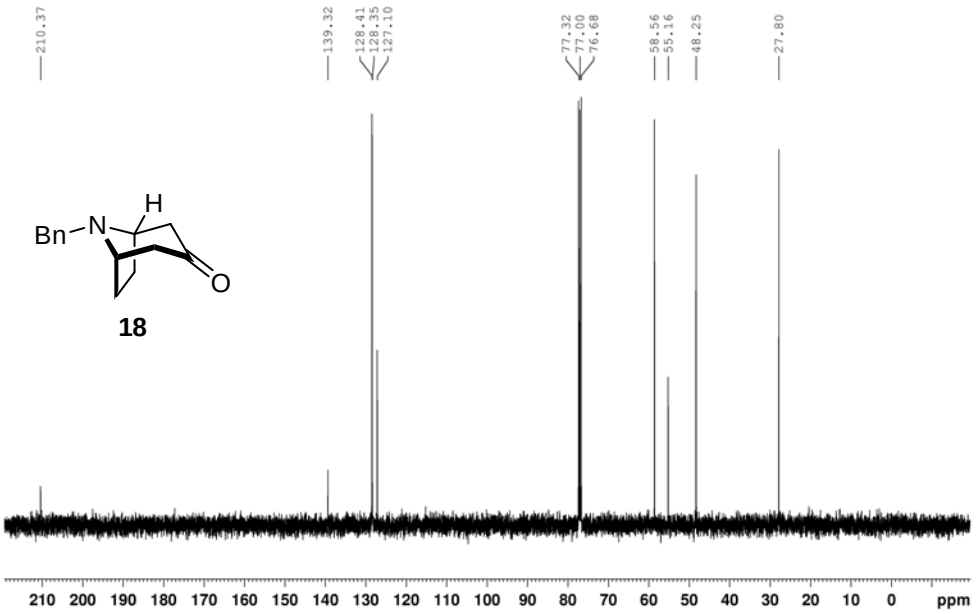
17

HSY-407-3-H1
CDCl3
2011.12.29

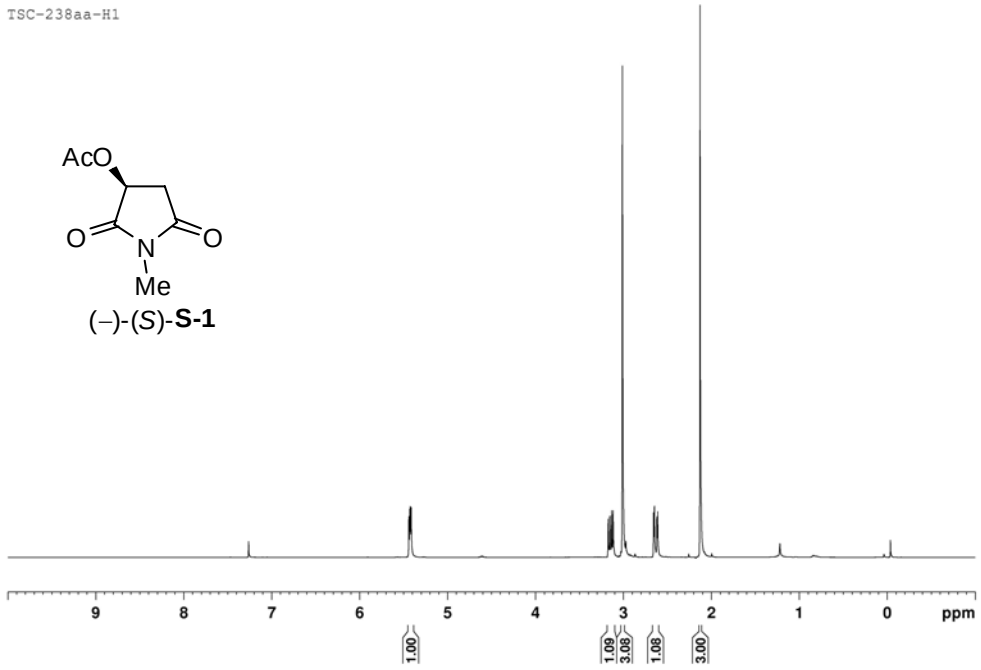


18

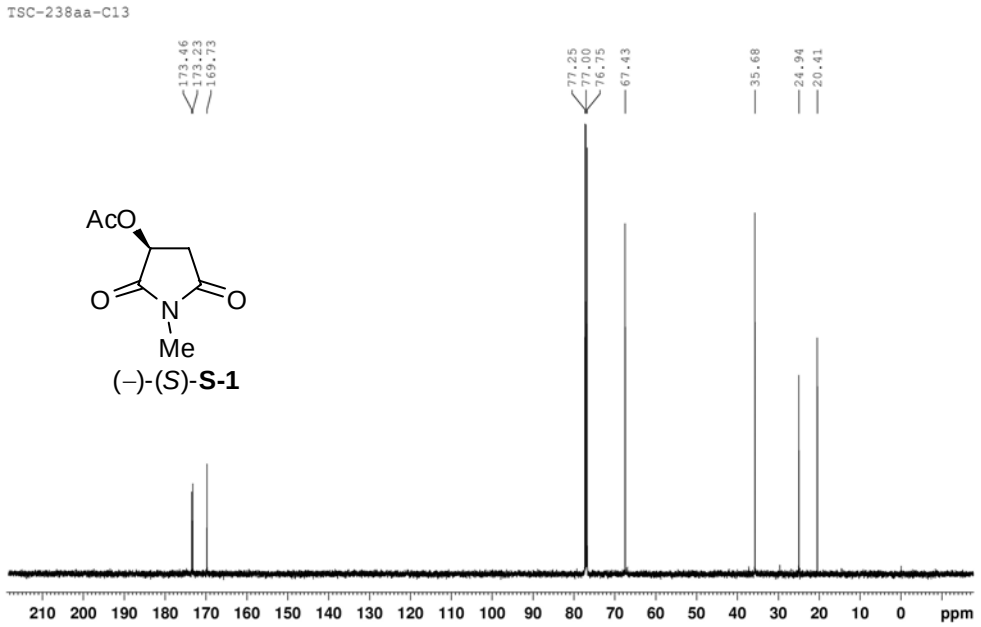
HSY-407-3-C13
CDCl3
2011.12.29



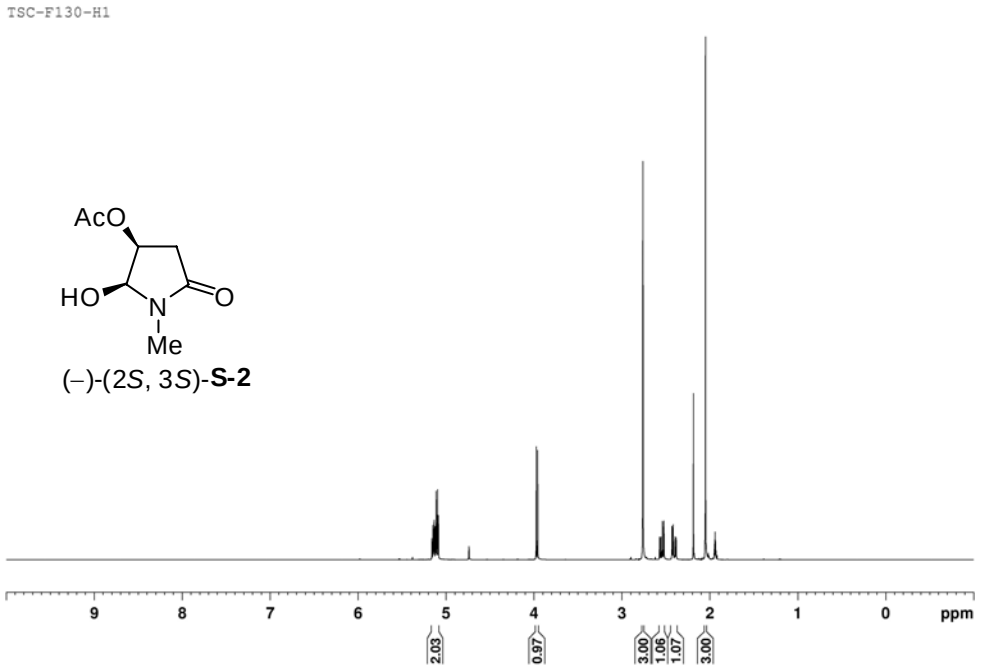
18


TSC-238aa-H1
AcO
O
N
O
Me
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.09
3.08
1.08
3.00

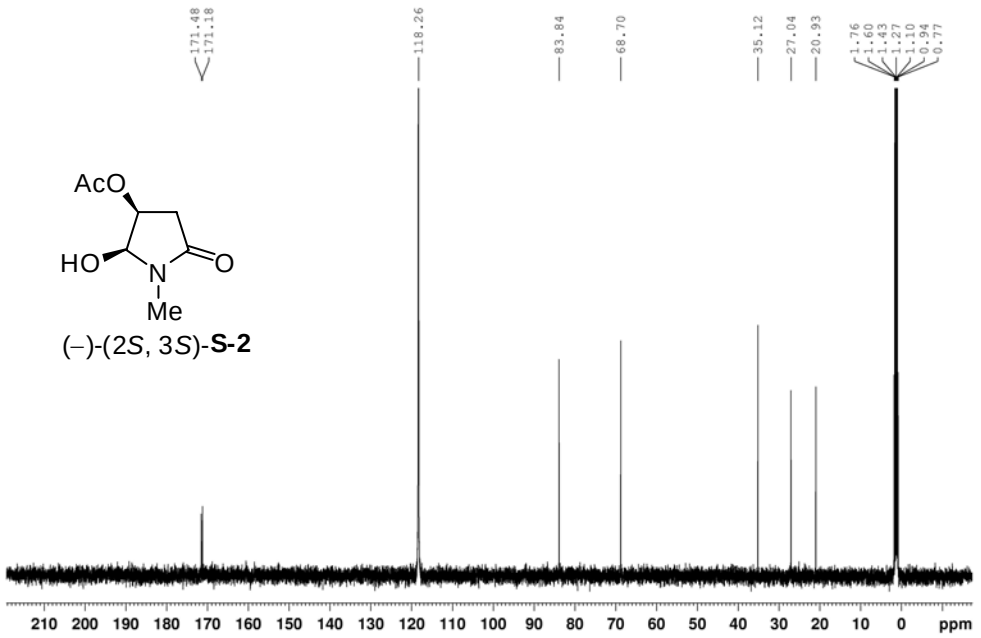
(–)-(*S*)-**S-1**


TSC-238aa-C13
173.46
173.23
169.73
77.25
77.00
76.75
67.43
35.68
24.94
20.41
AcO
O
N
O
Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

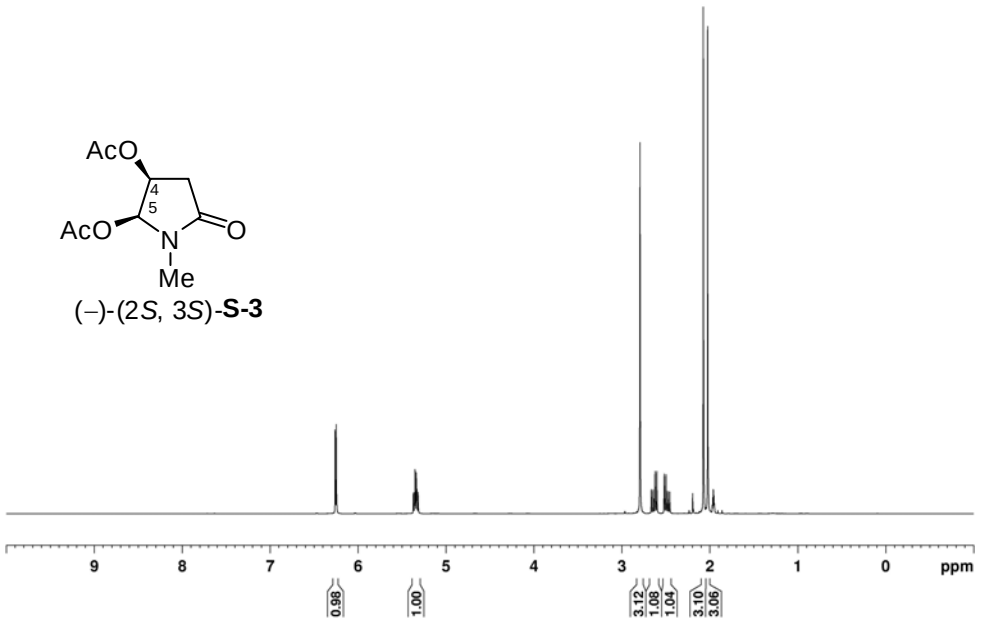
(–)-(*S*)-**S-1**



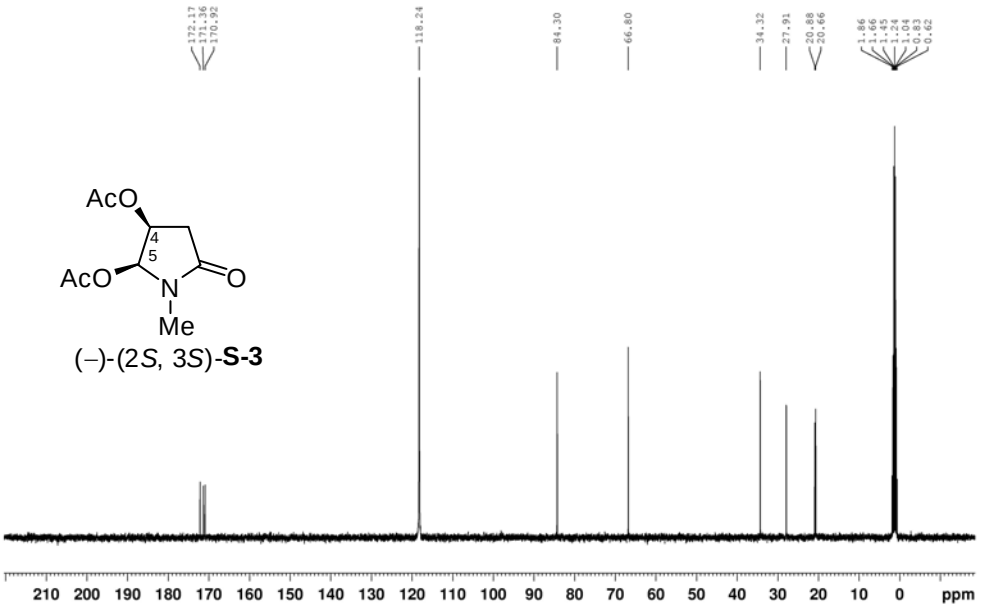
(–)-(2*S*, 3*S*)-**S-2**



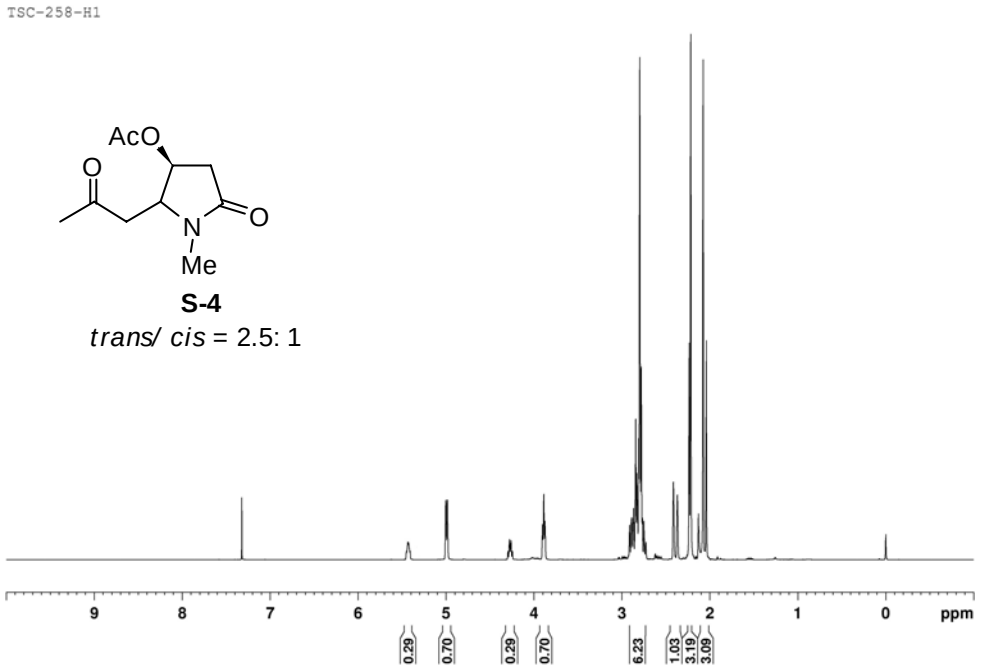
(–)-(2*S*, 3*S*)-**S-2**



(–)-(2*S*, 3*S*)-**S-3**

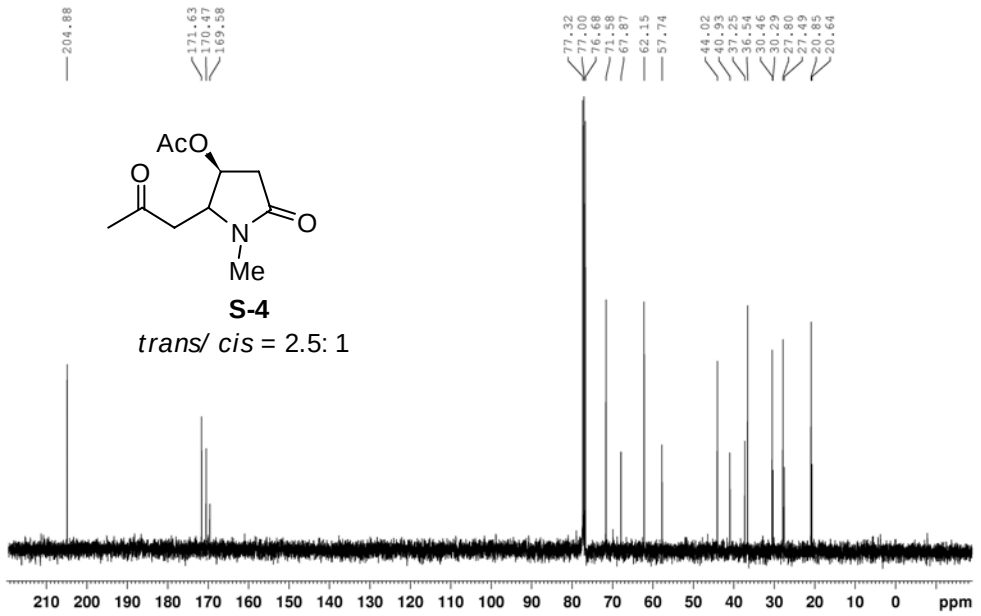


(–)-(2*S*, 3*S*)-**S-3**



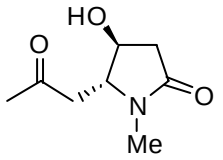
S-4

trans/ *cis* = 2.5: 1

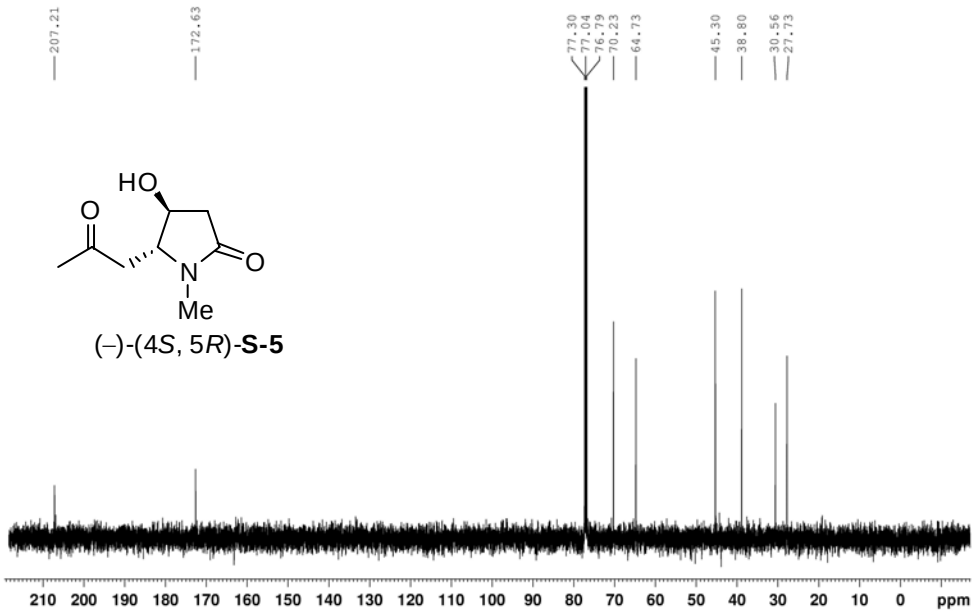


S-4

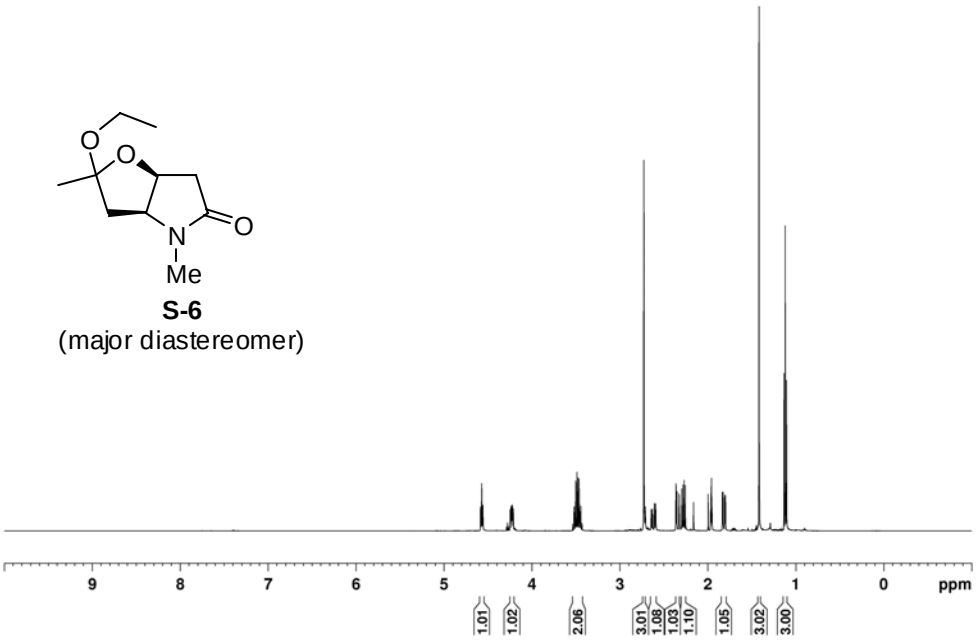
trans/ *cis* = 2.5: 1



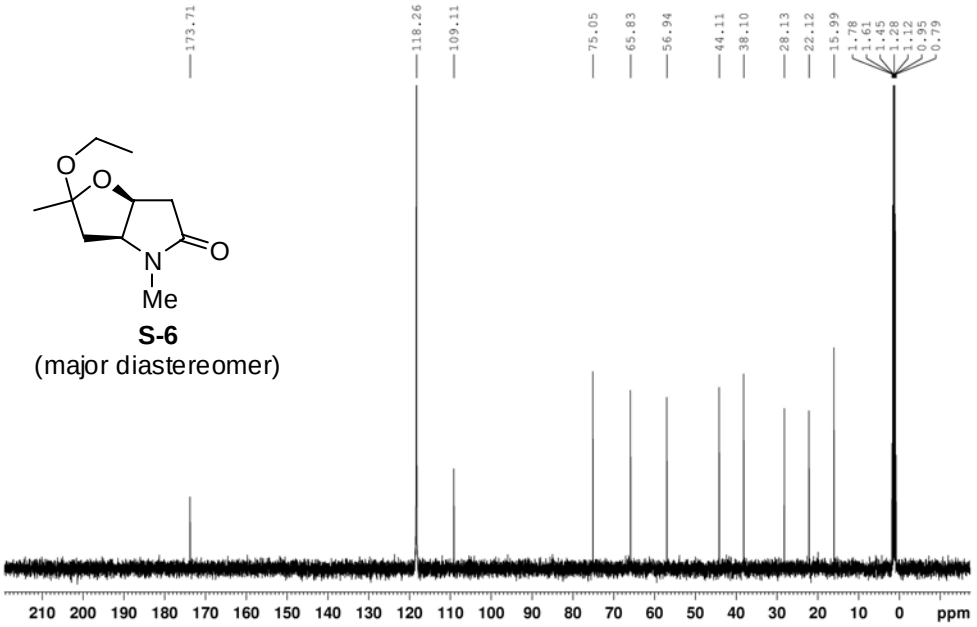
(–)-(4*S*, 5*R*)-**S-5**



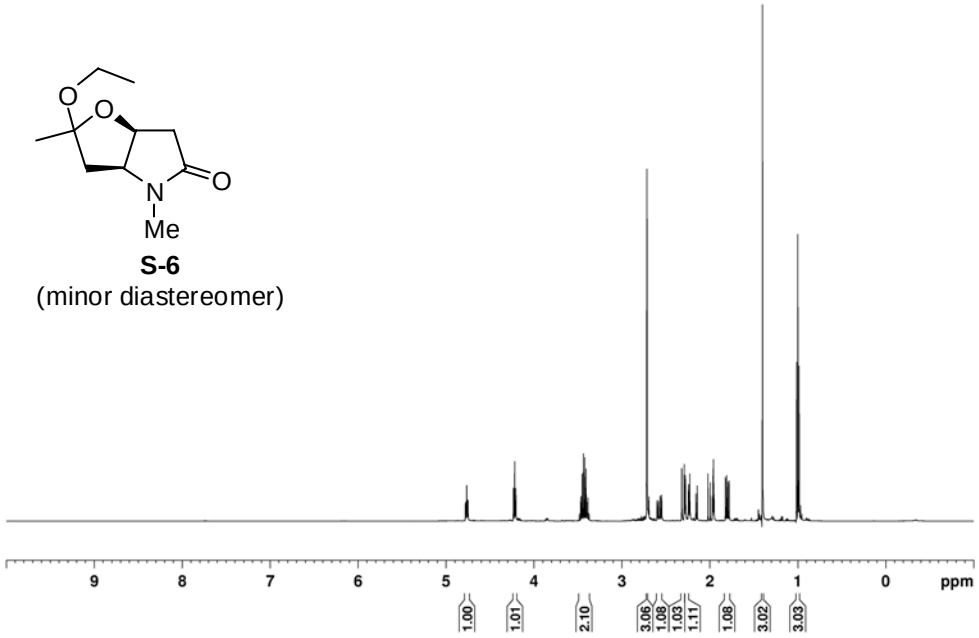
(–)-(4*S*, 5*R*)-**S-5**



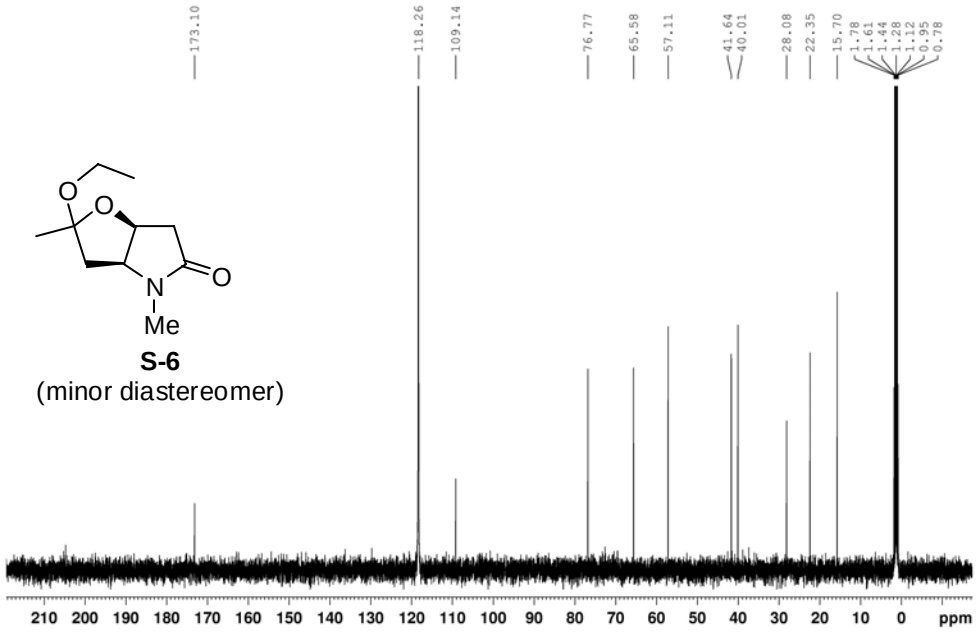
S-6
(major diastereomer)



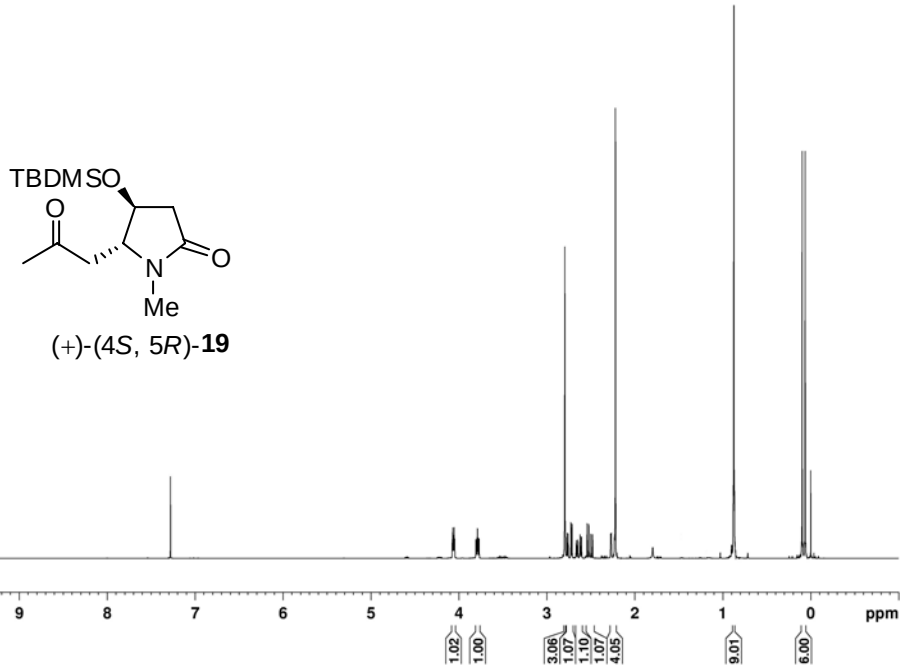
S-6
(major diastereomer)



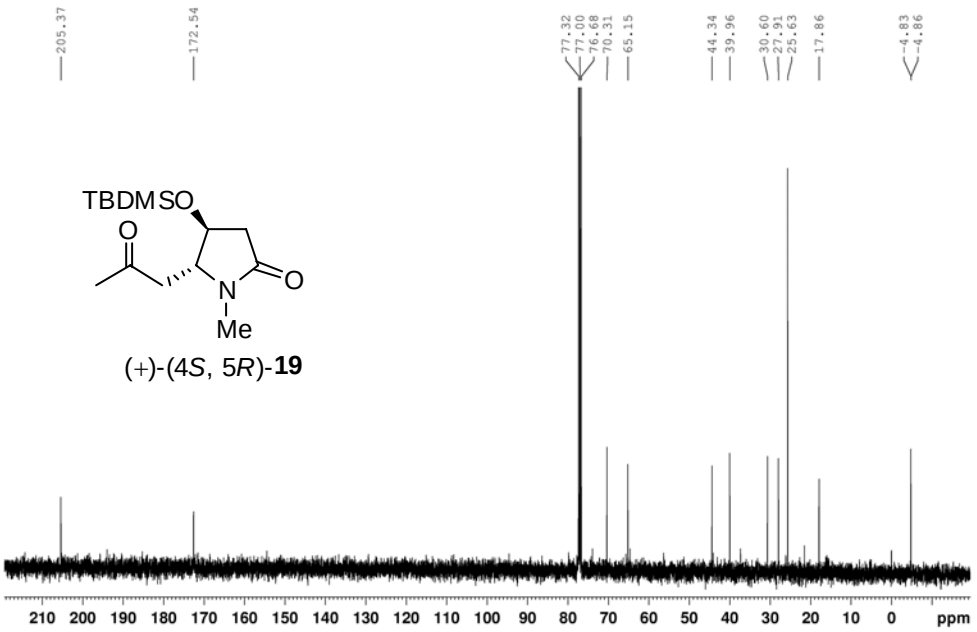
S-6
(minor diastereomer)



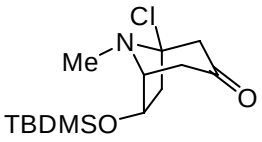
S-6
(minor diastereomer)



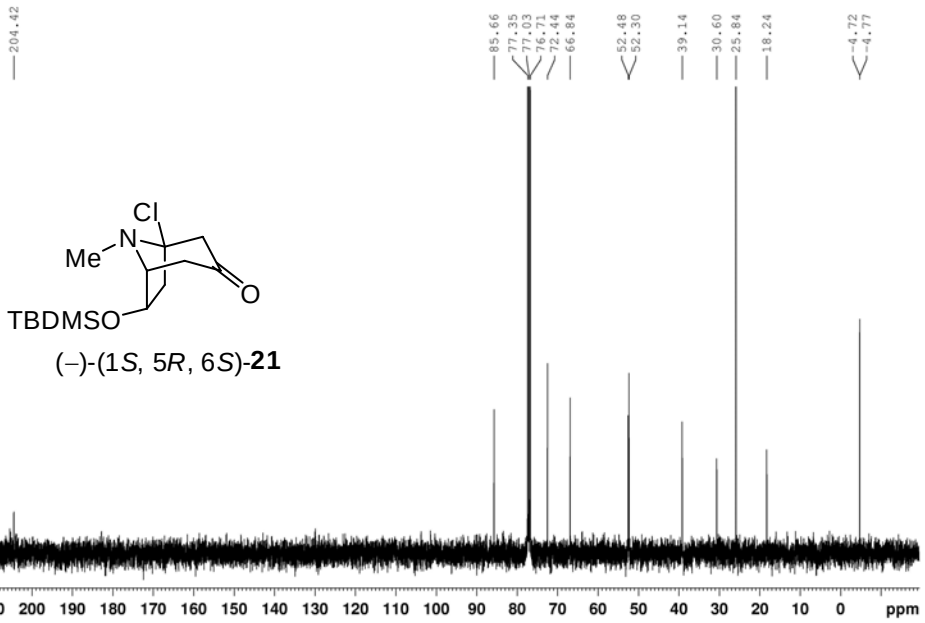
(+)-(4*S*, 5*R*)-**19**



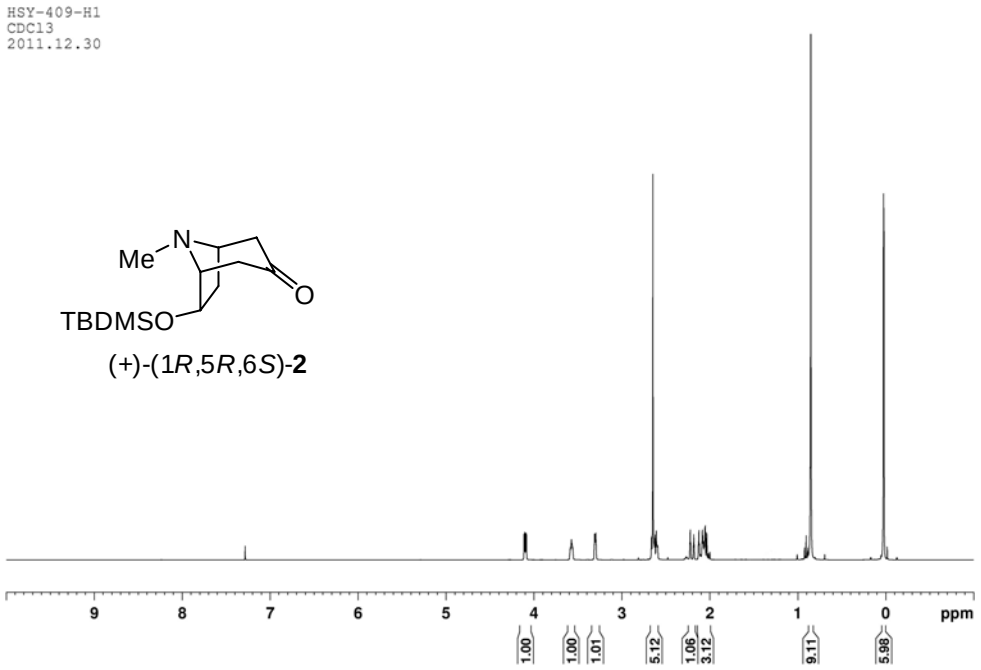
(+)-(4*S*, 5*R*)-**19**



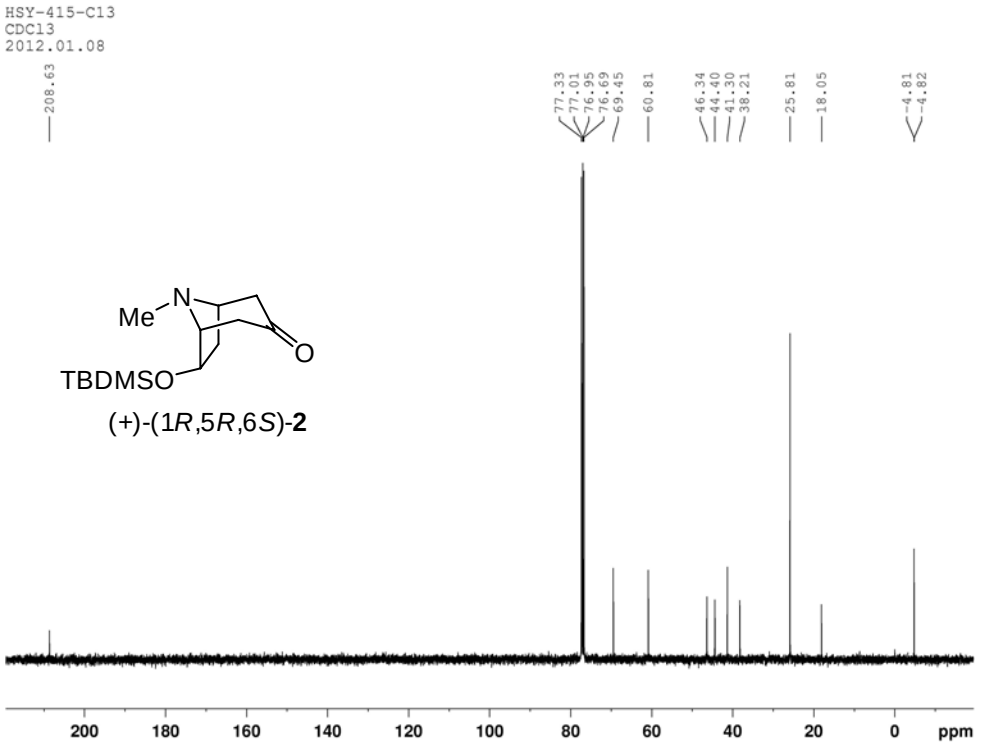
(–)-(1*S*, 5*R*, 6*S*)-**21**



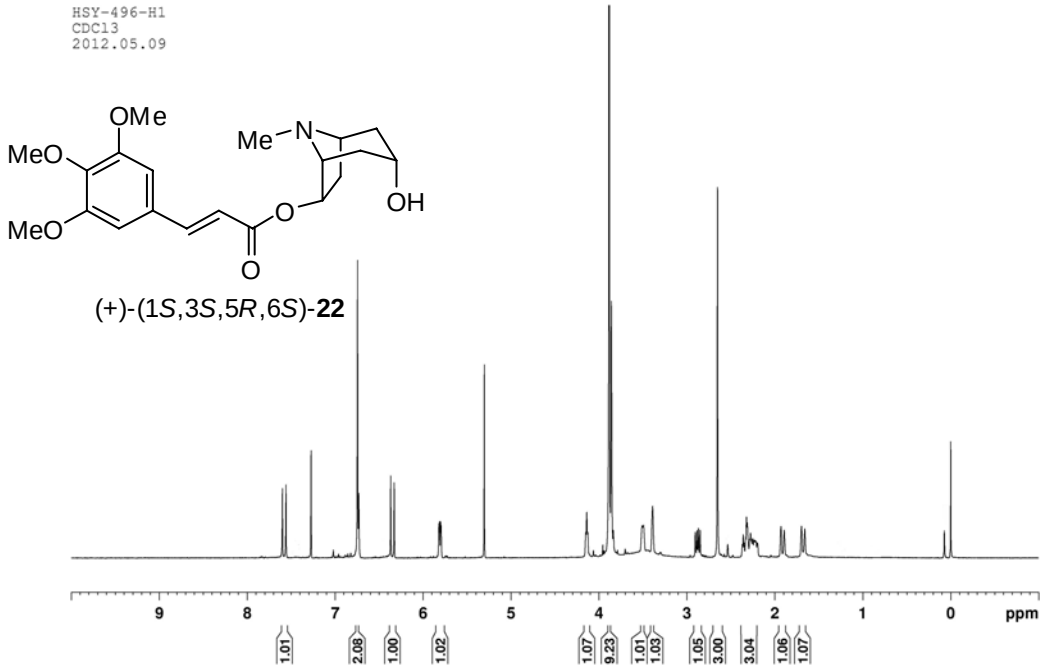
(–)-(1*S*, 5*R*, 6*S*)-**21**



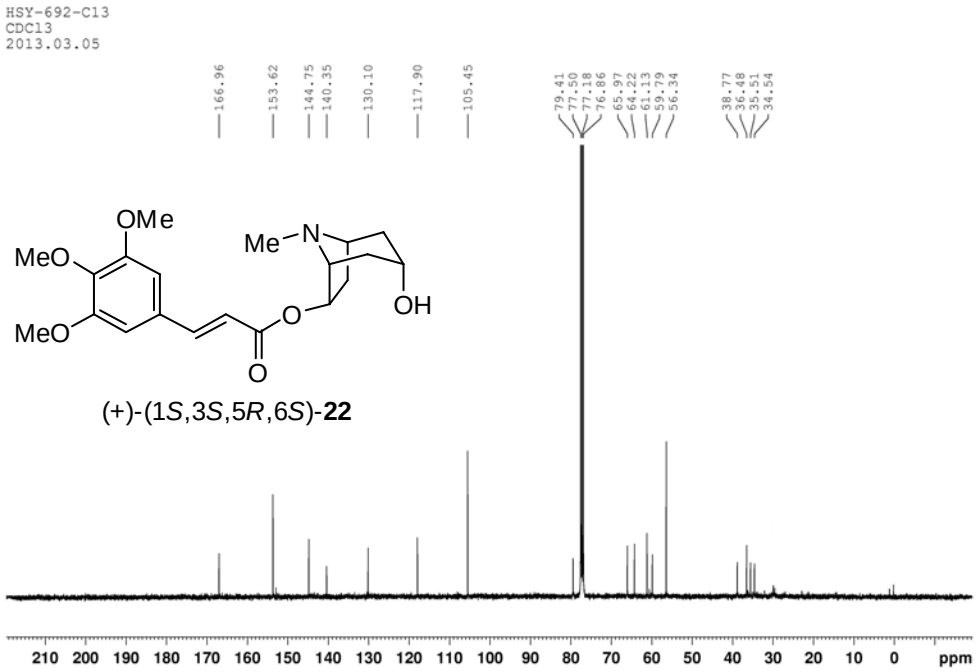
(+)-(1*R*,5*R*,6*S*)-**2**



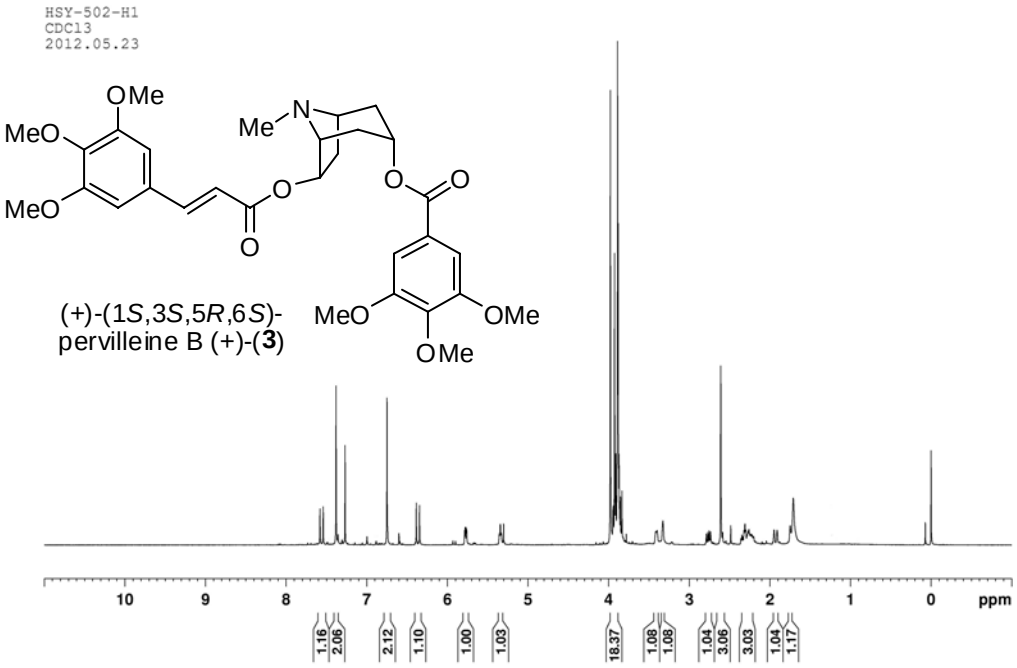
(+)-(1*R*,5*R*,6*S*)-**2**

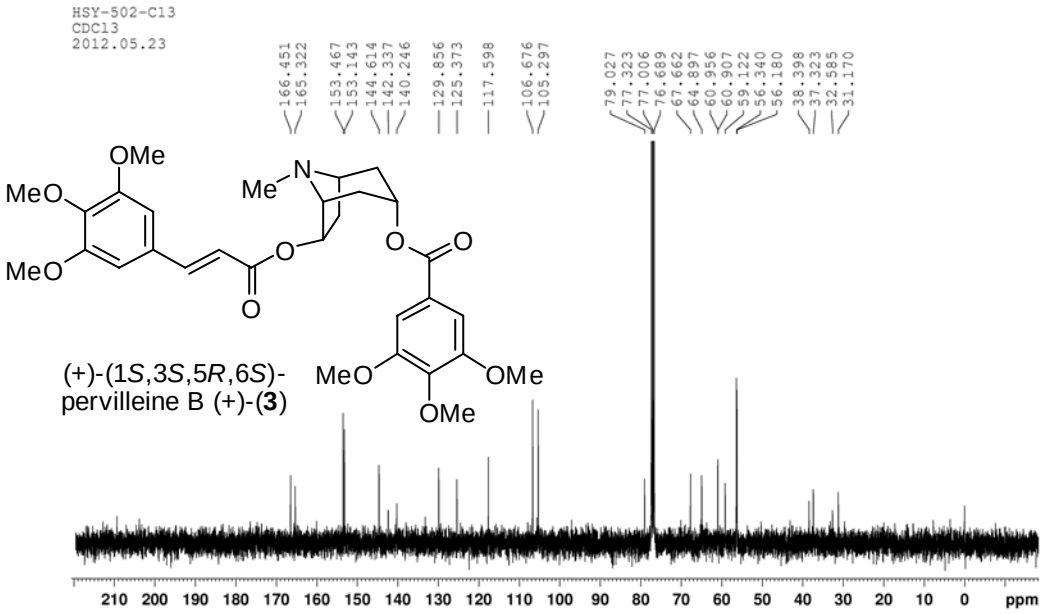


(+)-(1*S*,3*S*,5*R*,6*S*)-**22**



(+)-(1*S*,3*S*,5*R*,6*S*)-**22**


HSY-502-H1
CDCl3
2012.05.23
OMe
MeO
MeO
Me
N
O
O
O
O
O
MeO
OMe
OMe
(+)-(1S,3S,5R,6S)-
pervilleine B (+)-(3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.16
2.06
2.12
1.10
1.00
1.03
18.37
1.08
1.08
1.04
3.06
3.03
1.04
1.17


HSY-502-C13
CDCl3
2012.05.23
166.451
165.322
153.467
153.143
144.614
142.337
140.246
129.856
125.373
117.598
106.676
105.297
79.027
77.323
77.006
76.689
67.662
64.897
60.956
60.907
59.122
56.340
56.180
38.398
37.323
32.585
31.170
OMe
MeO
MeO
Me
N
O
O
O
O
O
MeO
OMe
OMe
(+)-(1S,3S,5R,6S)-
pervilleine B (+)-(3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm