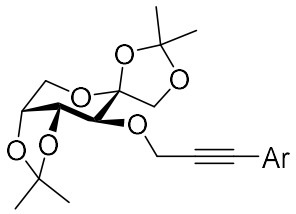
SUPPORTING INFORMATION

EXPERIMENTAL

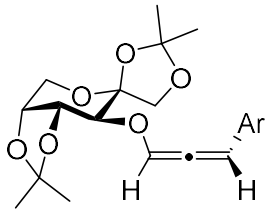
Reactions were generally performed under argon in flame-dried flasks, and the components were added by syringe. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone under argon for all reactions, triethylamine was distilled from potassium hydroxide pellets and stored over potassium hydroxide pellet. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck) or neutral alumina (activity III, Fluka). Unless otherwise stated, yields refer to analytically pure samples. ^{1}H NMR spectra [$CHCl_3$ (δ = 7.26 ppm), TMS (δ = 0.00 ppm) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0 ppm) as internal standard] were recorded with a Jeol Eclipse 500 instrument in solutions as given. Integrals are in accordance with assignments; coupling constants are given in Hz. IR spectra were measured with an FTIR spectrometer Nicolet 5 SXC. HRMS analyses were performed with a MAT CH7A (EI, 80 eV, 3 kV, 30 °C) instrument. Melting points were measured with a Reichert apparatus and are uncorrected. Optical rotations $[\alpha]_D$ were determined with Perkin–Elmer 141 or Perkin–Elmer 241 polarimeters at the temperatures given.

Alkyne **1**[1] and *N*-ethylidene-4-methylbenzenesulfonamide (**5**)[2] were prepared according to literature procedures. All other compounds are commercially available and were used without further purification.

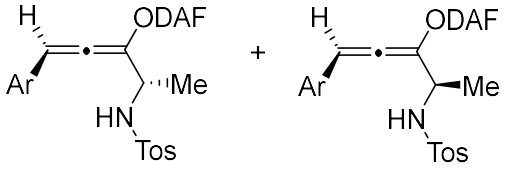


1,2:4,5-Di-*O*-isopropylidene-3-*O*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-*β*-D-fructopyranose (3): To a solution of the 4-iodoanisole (**2**) (3.22 g, 13.8 mmol) and 1,2:4,5-di-*O*-isopropylidene-3-*O*-(prop-2-yn-1-yl)-*β*-D-fructopyranose (**1**) (4.10 g, 13.8 mmol) in Et_3N (55 mL) was added $PdCl_2(PPh_3)_2$ (193 mg, 0.27 mmol), the mixture was stirred for 5 min and CuI (28 mg, 0.15mmol) was added. The mixture was heated at 50 °C for 2 h, it was then allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography (neutral alumina, hexanes/diethyl ether, 1:1) to afford pure **3** (5.07 g, 91%) as colorless oil; $[\alpha]_D^{22}$ = –33.3 (c = 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ auxiliary part 1.38, 1.43, 1.50,

1.61 (4 s, 12H), 3.85 (d, J = 7.7 Hz, 1H), 3.95 (d, J = 8.5 Hz, 1H), 4.02, 4.14 (2 d, J = 13.5 Hz, 1H each), 4.20 (dd, J = 1.9, 5.4 Hz, 1H), 4.33 (d, J = 8.5 Hz, 1H), 4.35 (dd, J = 5.4, 7.6 Hz, 1H); alkyne part 3.81 (s, 3H), 4.69 (m_c, 2H), 6.81–6.86, 7.32–7.36 (2 m, 2H each); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ auxiliary part 26.1, 26.5, 26.9, 28.3, 60.2, 72.0, 74.5, 77.8, 104.5, 109.2, 112.2; alkyne part 55.4, 59.2, 83.5, 86.6, 114.1, 114.6, 133.2, 159.9; IR (KBr) 3075–3040, 2990–2840, 2235 cm^{-1}; HRMS (EI) Calcd. for $C_{22}H_{28}O_7$ (m/z $[M]^+$): 404.18351; Found: 404.18335.

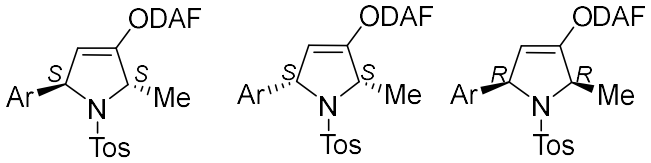


1,2:4,5-Di-*O*-isopropylidene-3-*O*-[3-(4-methoxyphenyl)propa-1,2-dien-1-yl]-*β*-D-fructo-pyranose (*aR*-4): *n*-BuLi (2.5 M in hexanes, 2.34 mL, 5.85 mmol) was added dropwise to a stirred solution of **3** (1.97 g, 4.87 mmol) in dry THF (96 mL) at –50 °C. After 20 min the reaction mixture was cooled to –78 °C and TMEDA (0.88 mL, 5.88 mmol) was added. The mixture was stirred for 1 h and quenched with wet THF. Saturated aqueous $NaHCO_3$ solution (50 mL) was added, the aqueous phase was separated and extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried with $MgSO_4$ and filtered. Removal of the solvents in vacuo gave the crude product which was purified by column chromatography (neutral alumina, hexanes/ethyl acetate, 6:1) to afford pure *aR*-**4** (1.41 g, 72%) as single diastereomer as colorless needles; m. p. 100–102 °C [important note: after column chromatography solvents were removed *in vacuo* at r.t. (<25 °C) to avoid the decomposition of the product which could be stored in the refrigerator at –25 °C for several weeks]; $[\alpha]_D^{22}$ = –444.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ auxiliary part 1.19, 1.28, 1.42, 1.51 (4 s, 12H), 3.90–4.00 (m, 3H), 4.12 (dd, J = 2.7, 13.3 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 4.20 (dd, J = 2.5, 5.6 Hz, 1H), 4.35 (dd, J = 5.6, 7.5 Hz, 1H); allene part 3.80 (s, 3H), 6.73 (d, J = 5.6 Hz, 1H), 6.81–6.86 (m, 2H), 7.11 (d, J = 5.6 Hz, 1H), 7.29–7.33 (m, 2H, Ar); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ auxiliary part 26.0, 26.1, 27.0, 28.0, 60.2, 71.6, 73.7, 75.3, 76.0, 104.2, 112.2; allene part 55.4, 109.3, 114.0, 127.0, 129.1, 159.8, 192.5; IR (KBr) 3075–3040, 2995–2840, 1940; HRMS (EI) Calcd. for $C_{22}H_{28}O_7$ (m/z $[M]^+$), 404.18351; Found: 404.18433.



(d.r. ca.2:1)

(*R,aR* and *S,aR*)-1,2:4,5-Di-*O*-isopropylidene-3-*O*-[1-(toluene-4-sulfonylamido)-1-methyl-4-(4-methoxy-phenyl)-2,3-dien-2-yl]-*β*-D-fructopyranose (6): *n*-BuLi (2.5 M in hexanes, 2.6 mL, 6.50 mmol) was added dropwise at –50 °C to a solution of *aR*-**4** (2.00 g, 4.95 mmol) in dry THF (40 mL). The mixture was stirred for 0.5 h to generate the lithiated intermediate and then a THF solution (25 mL) of *N*-ethylidene-4-methylbenzenesulfonamide (**5**) (1.46 g, 7.40 mmol) was added. The mixture was stirred at –50 °C to –20 °C for 3 h and then quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and warmed up to room temperature. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were dried with $MgSO_4$ and filtered. Removal of the solvents *in vacuo* at room temperature afforded crude **6** as an oil. Immediate flash chromatography (silica gel, hexanes/ethyl acetate, 2:1) furnished semi-purified **6** (1.88 g, *ca.* 60%, ratio of diastereomers ca. 70:30) [note: due to the low stability of compound **6** no efforts were made for further purification and for complete analysis; the semi-purified compound was directly used for the cyclization reaction].

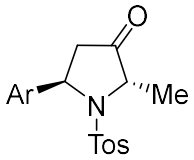


(2*S*,5*S* and 2*S*,5*S*/2*R*,5*R*)-3-*O*-[2,5-Dihydro-5-(4-methoxyphenyl)-2-methyl-1-(tosyl)-1*H*-pyrrol-3-yl]-1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (*trans*-7) and (*cis*-7a/b): To a solution of semi-purified **6** (1.88 g), dissolved in dry acetonitrile (30 mL), were added potassium carbonate (0.86 g, 6.26 mmol) followed by silver nitrate (106 mg, 0.63 mmol). The resulting mixture was stirred in the dark under argon at room temperature for 16 h, then filtered through a pad of celite with ethyl acetate and the filtrate was concentrated *in vacuo* at room temperature. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 2:1) to provide crude **7** (1.29 g, 43% based on allene *aR*-**4**). Separation of the diastereomers by HPLC (hexanes/ethyl acetate 7:3) gave *cis*-**7a/b** (956 mg, 32%, d.r. ca. 2:1) as a yellowish foam and *trans*-**7** (243 mg, 8%) as a colorless solid; m. p. 186–188 °C.

Data of *trans*-**7**: $[\alpha]_D^{22}$ = –104.4 (c = 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ auxiliary 1.35, 1.42, 1.47, 1.50 (4s, 12H), 3.94 (s, 2H), 3.97 (d, *J* = 7.1 Hz, 1H), 4.02 (d, *J* = 13.5 Hz, 1H), 4.14 (dd, *J* = 2.5, 13.3 Hz, 1H), 4.24 (dd, *J* = 2.5, 5.8 Hz, 1H), 4.33 (dd, *J* = 6.0, 6.8 Hz,

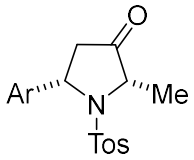
1H); dihydropyrrole part: 1.69 (d, J = 6.2 Hz, 3H), 2.33 (s, 3H), 3.77 (s, 3H), 4.43–4.50 (m, 1H), 4.61–4.65 (m, 1H), 5.51 (dd, J = 2.1, 4.8 Hz, 1H), 6.63, 6.92 (2 d, J = 8.7 Hz, 2H each), 6.98, 7.02 (2 d, J = 8.1 Hz, 2H each) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ auxiliary part 26.0, 26.1, 26.7, 28.1, 60.6, 72.0, 73.7, 76.1, 77.8, 103.7, 109.3, 112.5; dihydropyrrole part 20.7, 21.7, 55.3, 60.4, 67.5, 97.1, 113.5, 126.7, 128.9, 129.6, 131.9, 138.3, 142.1, 156.4, 159.4; IR (KBr) 3100–3000, 3000–2835, 1670, 1610, 1340, 1160 cm^{-1}; HRMS (EI) Calcd. for $C_{31}H_{39}NO_9S$ (*m/z* $[M]^+$): 601.23456; Found: 601.23537.

Data of *cis*-**7a/b** (two diastereomers ca. 1:2): $[\alpha]_D^{22}$ = –53.6 (c = 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ auxiliary part 1.31, 1.32*, 1.39*, 1.40*, 1.42*, 1.47 (6s, 12H), 3.45, 3.76 (2 d, J = 8.8 Hz, 1H each), 3.86–3.92 (m, 1H, 6-H), 3.94–4.02 (m, 1H), 4.06–4.13 (m, 1H), 4.18–4.29 (m, 2H) dihydropyrrole part 1.47 (d, J = 6.5 Hz, 2H)*, 1.55 (d, J = 6.5 Hz, 1 H), 2.37 (s, 1H), 2.38 (s, 2H)*, 3.76, 3.77 (2 s, 3H), 4.29–4.35 (m, 1H), 4.51–4.54 (m, 0.65H)*, 4.56–4.59 (m, 0.35H), 5.37–5.42 (m, 1H), 6.79–6.85, 7.17–7.26, 7.31–7.36 (3 m, 2H, 3H, 1H), 7.57 (d, J = 8.4 Hz, 0.7H), 7.63 (d, J = 8.2 Hz, 1.3H)*; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ auxiliary part 25.8, 26.0*, 26.1, 26.3*, 26.5, 26.9*, 28.0, 28.2*, 60.2, 60.3*, 71.4*, 71.9, 73.7, 73.8, 76.0, 78.0, 78.1, 103.7*, 103.8, 109.1, 109.2, 112.3; dihydropyrrole part 21.0, 21.5, 21.6*, 21.8, 55.3, 60.4, 60.6, 66.8*, 67.0, 95.3, 96.1, 113.7*, 113.9, 127.5, 127.6, 128.4, 128.8, 129.5, 129.6, 134.1, 134.4, 143.2, 143.5, 156.3, 157.2, 159.2, 159.3; * signals assigned to the major diastereomer; IR (KBr) 3095–3000, 3000–2840, 1665, 1610, 1350, 1165 cm^{-1}; HRMS (EI) Calcd. for $C_{31}H_{39}NO_9S$ (*m/z* $[M]^+$): 601.23456; Found: 601.23498.

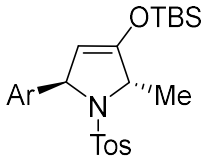


(2*S*,5*S*)-5-(4-Methoxyphenyl)-2-methyl-1-tosylpyrrolidin-3-one (*trans*-8): To a solution of *trans*-**7** (342 mg, 0.57 mmol) in THF (12 mL) was added 6 N aqueous HCl (4.5 mL) and the mixture was stirred under reflux for 1 h. After cooling to room temperature, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution, the aqueous layer was extracted with ethyl acetate (2 x 15 mL), the combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3:1) to provide *trans*-**8** (116 mg, 57%) as colorless solid; $[\alpha]_D^{22}$ = +29.6 (c = 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (d, J = 6.9 Hz, 3H), 2.32 (s, 3H), 2.51 (ddd, J = 0.9, 2.1, 18.0 Hz, 1H), 3.11 (dd, J = 9.4, 18.0 Hz, 1H), 3.77 (s, 3H), 3.74–3.80 (m,

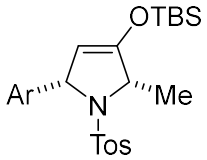
1H), 5.33 (dd, *J* = 2.1, 9.4 Hz, 1H), 6.60–6.67, 6.80–6.90, 6.92–7.05, 7.05–7.12 (4 m, 2H each); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 19.0, 21.4, 44.7, 55.3, 59.7, 59.9, 113.9, 127.1, 128.7, 129.0, 131.6, 136.2, 142.9, 159.6, 211.9; IR (KBr) 3100–3000, 3000–2850, 1760, 1610, 1335, 1160 cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{21}NO_4S$ (*m/z* $[M]^+$): 359.11914; Found: 359.11882.



(4-Methoxyphenyl)-2-methyl-1-tosylpyrrolidin-3-one (*cis*-8): To a solution of *cis*-**7a/7b** (950 mg, 1.58 mmol) in THF (32 mL) was added 6 N aqueous HCl (12 mL) and the mixture was stirred under reflux for 1 h. After cooling to room temperature, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution, the aqueous layer was extracted with ethyl acetate (2 x 15 mL), the combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3:1) to provide *cis*-**8** (426 mg, 75%) as colorless crystals; m. p. 108–110 °C; $[\alpha]_D^{22}$ = –3.2 (c = 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (d, *J* = 7.0 Hz, 3H), 2.41 (s, 3H), 2.56 (ddd, *J* = 0.9, 4.1, 18.2 Hz, 1H), 2.65 (ddd, *J* = 1.1, 9.3, 18.2 Hz, 1H), 3.78 (s, 3H), 3.85–3.98 (m, 1H), 5.16 (dd, *J* = 4.1, 9.3 Hz, 1H), 6.80–6.90, 7.20–7.35, 7.60–7.70 (3 m, 2H 4H, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 19.1, 21.6, 44.2, 55.4, 58.5, 60.2, 114.1, 127.5, 127.9, 130.0, 133.1, 135.3, 144.1, 159.3, 211.5; IR (KBr) 3065–3000, 3000–2845, 1760, 1610, 1345, 1160 cm^{-1}; HRMS (EI) Calcd. for $C_{19}H_{21}NO_4S$ (*m/z* $[M]^+$) 359.11914; Found: 359.11856.

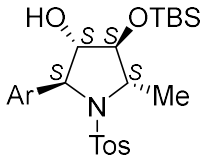


(2*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-(4-methoxyphenyl)-2-methyl-1-tosyl-2,5-dihydro-1*H*-pyrrole (*trans*-9): For the preparation of LDA, *n*-BuLi (2.5 M in hexanes, 180 µL, 0.45 mmol) was dissolved in dry THF (20 mL) at –78 °C and treated with diisopropylamine (63 µL, 0.45 mmol). The mixture was stirred at 0 °C for 0.5 h and then cooled to –78 °C, and *trans*-**8** (108 mg, 0.30 mmol) in dry THF (2 mL) was slowly added. After stirring the mixture for 20 min, *tert*-$BuMe_2SiCl$ (113 mg, 0.75 mmol) and DMPU (72 µL, 0.60 mmol) were added, the resulting solution was stirred for 4 h at –78 °C and then warmed up to room temperature. The solvent was evaporated and the residue dissolved in ethyl acetate, the solution was washed with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3:1) to give *trans*-**9** (96 mg, 68%) as colorless liquid; $[\alpha]_D^{22} = -25.1$ (c = 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15, 0.18 (2 s, 6H), 0.93 (s, 9H), 1.62 (d, *J* = 6.3 Hz, 3H), 2.31 (s, 3H), 3.77 (s, 3H), 4.25–4.40 (m, 1H), 4.52 (m_c, 1H), 5.46 (dd, *J* = 2.1, 4.9 Hz, 1H), 6.58–6.65, 6.91–6.98, 7.01–7.06 (m, 2H, 4H, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ –4.9, –4.7, 18.1, 20.6, 21.4, 25.6, 25.8, 55.3, 60.9, 67.3, 100.8, 113.3, 126.7, 128.7, 129.9, 132.0, 138.4, 141.9, 152.4, 159.4; IR (KBr) 3065–3000, 3000–2860, 1610, 1345, 1160 cm^{-1}; HRMS (EI) Calcd. for $C_{25}H_{35}NO_4SSi$ (*m/z* $[M]^+$): 473.20560; Found: 473.20633.

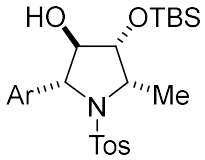


(*tert*-Butyldimethylsiloxy)-5-(4-methoxyphenyl)-2-methyl-1-tosyl-2,5-dihydro-1*H*-pyrrole (*cis*-9): For the preparation of LDA, *n*-BuLi (2.5 M in hexanes, 0.5 mL, 1.25 mmol) was dissolved in dry THF (20 mL) at –78 °C and treated with diisopropylamine (174 µL, 1.23 mmol). The mixture was stirred at 0 °C for 0.5 h and then cooled to –78 °C, and *cis*-**8** (400 mg, 1.11 mmol) in dry THF (5 mL) was slowly added. After stirring for 20 min, *tert*-$BuMe_2SiCl$ (420 mg, 2.77 mmol) and DMPU (270 µL, 2.24 mmol) were added, the resulting solution was stirred for 4 h at –78 °C and then warmed up to room temperature. The solvent was evaporated and the residue dissolved in ethyl acetate, the solution was washed with saturated aqueous

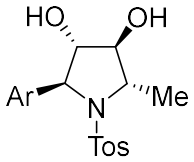
$NaHCO_3$ solution (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate, 3:1) to provide *cis*-**9** (522 mg, 99%) as colorless liquid; $[\alpha]_D^{22}$ = +28.8 (c = 1.02, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07, 0.12 (2 s, 6H), 0.89 (s, 9H), 1.48 (d, *J* = 6.4 Hz, 3H), 2.41 (s, 3H), 3.81 (s, 3H), 4.15–4.30 (m, 1H), 4.49 (m_c, 1H), 5.33 (m_c, 1H), 6.80–6.90, 7.20–7.35, 7.55–7.70 (m, 2H, 4H, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ –5.2, 17.8, 21.1, 21.2, 25.2, 55.1, 60.8, 66.6, 100.4, 113.5, 127.4, 128.3, 129.2, 134.3, 135.5, 142.9, 151.9, 158.9; IR (KBr) 3065–3000, 3000–2840, 1610, 1345, 1165 cm^{-1}; HRMS (EI) Calcd. for $C_{25}H_{35}NO_4SSi$ (*m/z* $[M]^+$): 473.20560; Found: 473.20482.



(all-*S*)-4-(*tert*-Butyldimethylsiloxy)-2-(4-methoxyphenyl)-5-methyl-1-tosylpyrrolidin-3-ol (*trans*-10): To a solution *trans*-**9** (95 mg, 0.20 mmol) in dry THF (2 mL), BH_3-THF (1 M in THF, 0.80 mL, 0.80 mmol) was added at –30 °C. After warm up to room temperature and stirring for 3 h, aqueous 1 N NaOH solution (1.18 mL) and 30% aqueous H_2O_2 (0.44 mL) were added to the reaction mixture at –10 °C. It was then stirred for 16 h at room temperature and saturated aqueous $Na_2S_2O_2$ solution (5 mL) was slowly added. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 2:1) to give *trans*-**10** (99 mg, 99%) as colorless solid; m. p. 155–157 °C; $[\alpha]_D^{22}$ = +8.13 (c = 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02, 0.09 (2 s, 6H), 0.85 (s, 9H), 1.54 (d, *J* = 6.7 Hz, 3H), 2.31 (s, 3H), 2.50 (s_{br}, 1H), 3.72 (s, 3H), 3.85 (s_{br}, 1H), 4.00–4.10 (m, 2H), 4.66 (d, *J* = 2.5 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ –4.8, –4.8, 17.9, 18.9, 21.4, 25.7, 55.3, 66.5, 71.6, 83.1, 86.1, 113.2, 126.9, 128.8, 130.2, 130.5, 139.3, 142.1, 158.9; IR (KBr) 3435, 3070–3000, 3000–2835, 1615, 1325, 1155 cm^{-1}; HRMS (EI) Calcd. for $C_{25}H_{37}NO_5SSi$ (*m/z* $[M]^+$): 491.21619; Found: 491.21555.

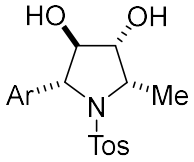


(*t-3,c-4,c-5,r-2*)-4-(*tert*-Butyldimethylsiloxy)-2-(4-methoxy-phenyl)-5-methyl-1-tosyl-pyrrolidin-3-ol (*cis*-10): To a solution of *cis*-**9** (520 mg, 1.10 mmol) in dry THF (11 mL), BH_3-THF (1 M in THF, 4.4 mL, 4.40 mmol) was added at –30 °C. The mixture was allowed to warm up to room temperature. After stirring for 3 h, aqueous 1 N NaOH solution (6.5 mL) and 30% aqueous H_2O_2 (2.4 mL) were added to the reaction mixture at –10 °C. It was then stirred for 16 h at room temperature and saturated aqueous $Na_2S_2O_2$ solution (25 mL) was slowly added. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate, 2:1) to give *cis*-**10** (541 mg, quant.) as colorless solid; m. p. 115–117 °C; $[\alpha]_D^{22}$ = +0.47 (c = 1.08, $CHCl_3$); ^{1}H NMR (500 MHz CD_3OD) δ –0.09, –0.04 (2 s, 6H), 0.77 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H), 2.11 (s_{br}, 1H), 2.40 (s, 3H), 3.76 (s, 3H), 3.56 (t, *J* = 7.1 Hz, 1H), 3.82–3.87 (m, 1H), 3.94 (m_c, 1H), 4.25 (d, *J* = 6.2 Hz, 1H), 6.77–6.83, 7.22–7.28, 7.58–7.64 (3 m, 2H, 4H, 2H); ^{13}C NMR (125.8 MHz, CD_3OD) δ –5.0, –4.8, 17.2, 18.1, 21.6, 25.7, 55.4, 57.8, 67.3, 76.2, 82.2, 113.9, 127.7, 127.9, 129.6, 132.3, 134.9, 143.6, 159.0; IR (KBr) 3475, 3065–3000, 3000–2855, 1615, 1325, 1160 cm^{-1}; HRMS (EI) Calcd. for $C_{25}H_{37}NO_5SSi$ (*m/z* $[M]^+$): 491.21619; Found: 491.21537.



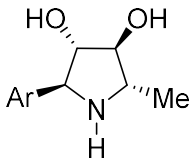
(all-*S*)-2-(4-Methoxyphenyl)-5-methyl-1-tosylpyrrolidine-3,4-diol (*trans*-11): To a solution of *trans*-**10** (83 mg, 0.17 mmol) in dry THF (5 mL), *n*Bu_4NF solution (1 M in THF, 0.51 mL, 0.51 mmol) was added at 0 °C, and the mixture was stirred for 16 h at room temperature. A mixture of ethyl acetate/water (1:1, 5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (silica gel, hexanes/ethyl acetate, 1:4) gave *trans*-**11** (52 mg, 82%) as colorless liquid; $[\alpha]_D^{22}$ = –3.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.7 Hz, 3H), 2.27 (s, 3H), 3.66 (s, 3H), 3.75 (t, *J* = 2.6 Hz, 1H), 3.91–3.94 (m, 1H), 3.96–4.02 (m, 1H), 4.52 (d, *J* = 3.3 Hz, 1H), 4.84 (s, 2H), 6.49–6.55,

6.97–7.05, 7.16-7.21 (3 m, 2H, 4H, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.8, 20.1, 54.4, 65.4, 71.3, 81.9, 85.0, 112.9, 126.8, 128.7, 129.9, 130.8, 139.2, 142.5, 159.2; IR (KBr) 3440, 3050–3000, 3000–2840, 1615, 1335, 1145 cm^{-1}; HRMS (EI) Calcd. for $C_{19}H_{23}NO_5S$ (*m/z* $[M]^+$): 377.12970; Found: 377.12866.



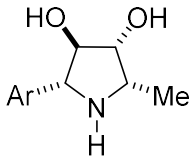
(*t-3,c-4,c-5,r-2*)-2-(4-Methoxyphenyl)-5-methyl-1-tosylpyrrolidine-3,4-diol (*cis*-11): To a solution of *cis*-**10** (535 mg, 1.09 mmol) in dry THF (28 mL), *n*Bu_4NF solution (1 M in THF, 2.2 mL, 2.2 mmol) was added at 0 °C, and the mixture was stirred for 16 h at room temperature. A mixture of ethyl acetate/water (1:1, 5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (silica gel, hexanes/ethyl acetate, 1:4) gave *cis*-**11** (402 mg, 98%) as colorless solid; m. p. 50–52 °C; $[\alpha]_D^{22}$ = +35.0 (c = 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.6 Hz, 3H), 2.36 (s, 3H), 3.55 (t, *J* = 7.9 Hz, 1H), 3.74 (s, 3H), 3.68–3.78 (m, 1H), 3.96 (quint., *J* = 7.2 Hz, 1H), 4.09 (d, *J* = 7.2 Hz, 1He), 6.77, 7.15 (2 d, *J* = 8.4 Hz, 2H each), 7.19, 7.49 (2 d, *J* = 7.9 Hz, 2H each); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.1, 21.6, 55.4, 57.0, 66.6, 74.9, 81.7, 113.9, 127.6, 128.0, 129.7, 131.9, 134.9, 143.8, 159.2; IR (KBr) 3440, 3000–2980, 2980–2840, 1610, 1335, 1160 cm^{-1}; HRMS (EI) Calcd. for $C_{19}H_{23}NO_5S$ (*m/z* $[M]^+$): 377.12970; Found: 377.12868.

Preparation of Sodium Naphthalenide: A solution of sodium naphthalenide [*ca*. 1 M in dimethoxyethane (DME)] was prepared under an argon atmosphere according to a literature procedure[3] by adding naphthalene (1.05 g, 8.20 mmol) and sodium (0.15 g, 6.52 mmol) in dry DME (5 mL) and stirred for 2 h at room temperature. The deeply blue colored solution was used for the detosylation reactions.

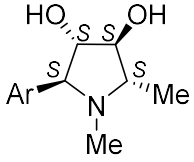


(all-*S*)-2-(4-Methoxyphenyl)-5-methylpyrrolidine-3,4-diol (*trans*-12): To a solution of *trans*-**11** (50 mg, 0.13 mmol) in dry DME (7 mL), sodium naphthalenide (ca. 1 M in DME, 0.70

mL, *ca*. 0.70 mmol) was slowly added at –78 °C and stirred for 1 h. It was then quenched with water (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated. The solid residue was washed with hexanes (3 x 10 mL) to remove the naphthalene and evaporated to furnish *trans*-**12** (21 mg, 71%) as colorless needles; m. p. 140–145 °C (under decomposition); $[\alpha]_D^{22}$ = +18.0 (c = 1.07, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.25 (d, *J* = 6.6 Hz, 3H), 3.20 (dq, *J* = 6.8 Hz, 1H), 3.64 (t, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 3.89–3.98 (m, 2H), 4.91 (s_{br}, 3H), 6.86–6.92, 7.29–7.36 (2 m, 2H each, Ar); ^{13}C NMR (125.8 MHz, CD_3OD) δ 18.1, 54.5, 57.2, 64.8, 83.3, 83.9, 113.7, 128.1, 134.0 159.3; IR (KBr) 3325, 3045–3000, 3000–2835, 1615 cm^{-1}; HRMS (EI) Calcd. for $C_{12}H_{17}NO_3$ (*m/z* $[M]^+$): 223.12085; found: 223.12166.

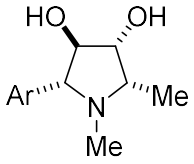


(*t-3,c-4,c-5,r-2*)-2-(4-Methoxyphenyl)-5-methylpyrrolidine-3,4-diol (*cis*-12): To a solution of *cis*-**11** (342 mg, 0.92 mmol) in dry DME (46 mL), sodium naphthalenide (ca. 1 M in DME, 4.5 mL, ca. 4.5 mmol) was slowly added at –78 °C and stirred for 1 h. It was then quenched with water (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated. The solid residue was washed with hexanes (3 x 10 mL) to remove the naphthalene and evaporated to furnish *cis*-**12** (160 mg, 78%) as sticky material; $[\alpha]_D^{22}$ = –13.4 (c = 1.17, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.22 (d, *J* = 6.6 Hz, 3H), 3.21–3.29 (m, 1H), 3.74 (d, *J* = 4.8 Hz, 1H), 3.77 (s, 3H), 3.87 (dd, *J* = 1.3, 3.9 Hz, 1H), 3.97 (dd, *J* = 1.3, 4.7 Hz, 1H), 4.87 (s_{br}, 3H), 6.89, 7.35 (2 d, *J* = 8.7 Hz, 2H each); ^{13}C NMR (125.8 MHz, CD_3OD) δ 12.3, 54.4, 57.2, 70.1, 80.0, 85.7, 113.7, 128.3, 133.0, 159.3; IR (KBr) 3390, 3260, 3070–3000, 3000–2835, 1615; HRMS (EI) Calcd. for $C_{12}H_{17}NO_3$ (*m/z* $[M]^+$): 223.12085; Found 223.12155.



(all-*S*)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol, (+)-Codonopsinine: To a solution of *trans*-**12** (20 mg, 0.090 mmol) in dry THF (6 mL), methyl iodide (80 mg, 0.56 mmol) was added and the mixture was stirred for 16 h at room temperature. It was then

quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane/methanol, 4:1) to give pure (+)-codonopsinine (20 mg, 94%) as colorless solid; m. p. 170–172 °C (Ref. 4: 172.5–173.5 °C); $[\alpha]_D^{22}$ = +5.5 (c = 0.51, MeOH) (Ref. 4: $[\alpha]_D^{20}$ = +12.5 (c = 2.55, MeOH)); ^{1}H NMR (500 MHz, CD_3OD) δ 1.12 (d, *J* = 6.7 Hz, 3H), 1.98 (s, 3H), 3.03–3.13 (m, 1H), 3.56 (d, *J* = 6.2 Hz, 1H), 3.62 (t, *J* = 4.1 Hz, 1H), 3.66 (s, 3H), 3.90 (dd, *J* = 4.1, 6.2 Hz, 1H), 4.78 (s, 2H), 6.78–6.85, 7.18–7.24 (2m, 2H each); ^{13}C NMR (125.8 MHz, CD_3OD) δ 12.2, 33.7, 54.4, 64.3, 73.2, 83.5, 84.8, 113.5, 129.5, 131.9, 159.5; IR (KBr) 3355, 3055–3000, 3000–2835, 1610 cm^{-1}; HRMS (EI) Calcd. for $C_{13}H_{19}NO_3$ (*m/z* $[M]^+$): 237.13649; Found: 237.13722.



(*t-3,c-4,c-5,r-2*)-(2*S*,3*S*,4*S*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol, (5-epi-codonopsinine): To a solution of *cis*-**12** (158 mg, 0.71 mmol) in dry THF (40 mL), methyl iodide (1.14 g, 8.03 mmol) was added and the mixture was stirred for 16 h at room temperature. It was then quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, dichloromethane/methanol, 4:1) to give pure epi-codonopsinine **13** (145 mg, 86%) as sticky material; $[\alpha]_D^{22}$ = –6.6 (c = 1.18, MeOH); ^{1}H NMR (500 MHz, C_6D_5N) δ 1.50 (d, *J* = 6.6 Hz, 3H), 2.33 (s, 3H), 3.05 (quint., *J* = 6.3 Hz, 1H), 3.57–3.62 (m, 1H), 3.65 (s, 3H), 4.57–4.61 (m, 2H), 6.59 (s_{br}, 2H), 6.93–6.99, 7.60–7.66 (2 m, 2H each); ^{13}C NMR (125.8 MHz, CD_3OD) δ 12.5, 38.8, 55.7, 66.1, 79.3, 79.4, 85.6, 114.8, 130.7, 132.2, 160.8; IR (KBr) 3335, 3070–2840, 1615 cm^{-1}; HRMS (EI) Calcd. for $C_{13}H_{19}NO_3$ (*m/z* $[M]^+$): 237.13649; Found: 237.13537.

References

1. A. Hausherr, B. Orschel, S. Scherer, and H.-U. Reissig, *Synthesis* 2001, 1377.

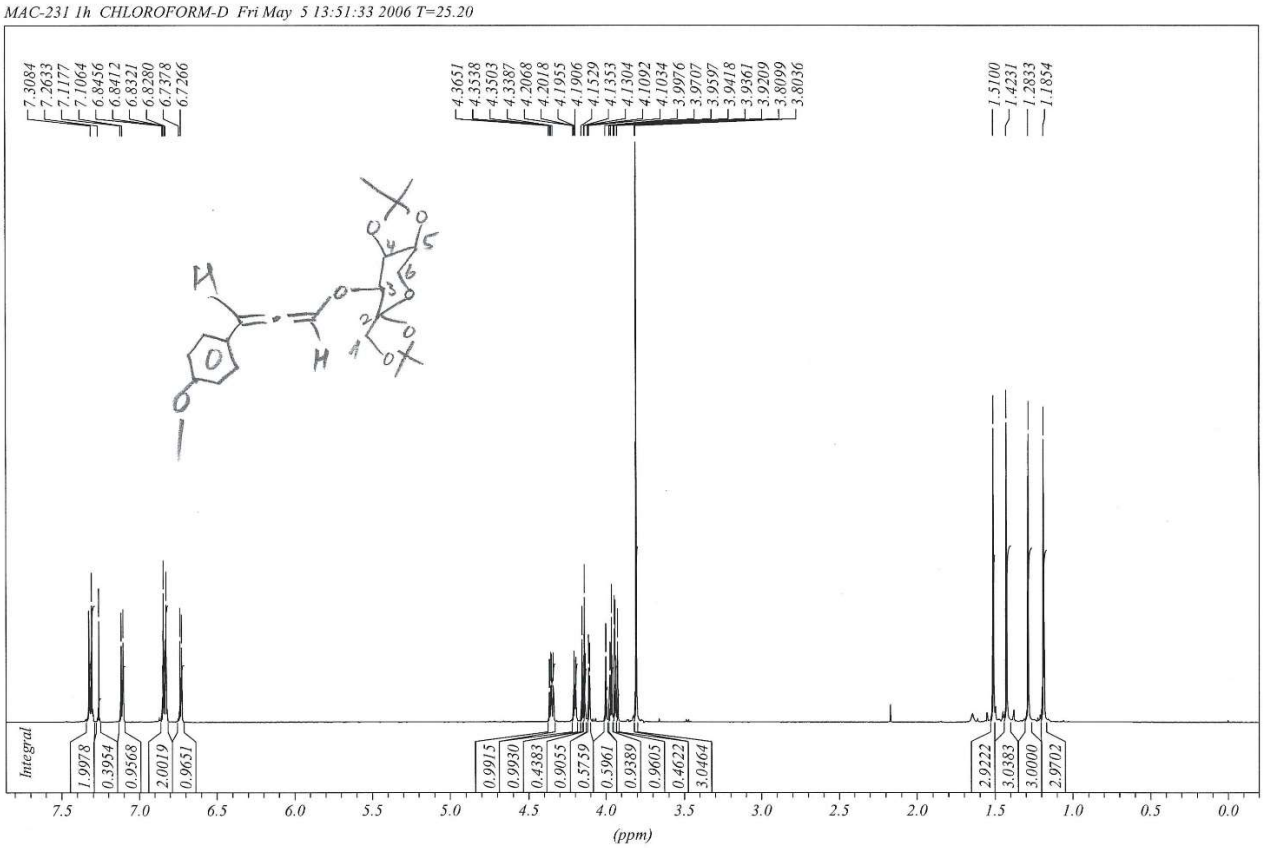
2. F. Chemla, V. Hebbe, and J.-F. Normant, *Synthesis* 2000, 75.

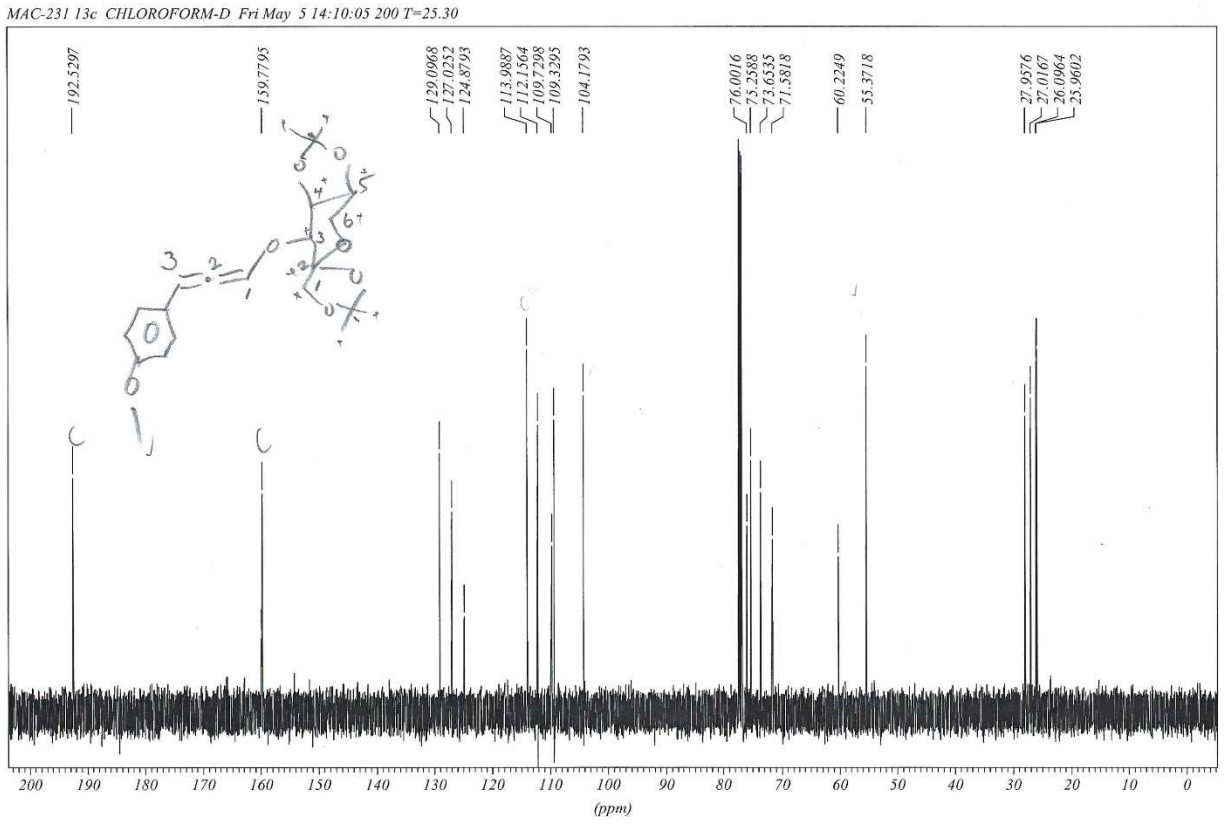
3. C. H. Heathcock, T. A. Blumenkopf, and K. M. Smith, *J. Org. Chem*. **1989**, *54*, 1548.

4. H. Iida, N. Yamazaki, and C. Kibayashi, *J. Org. Chem*. 1987, **52**, 1956.

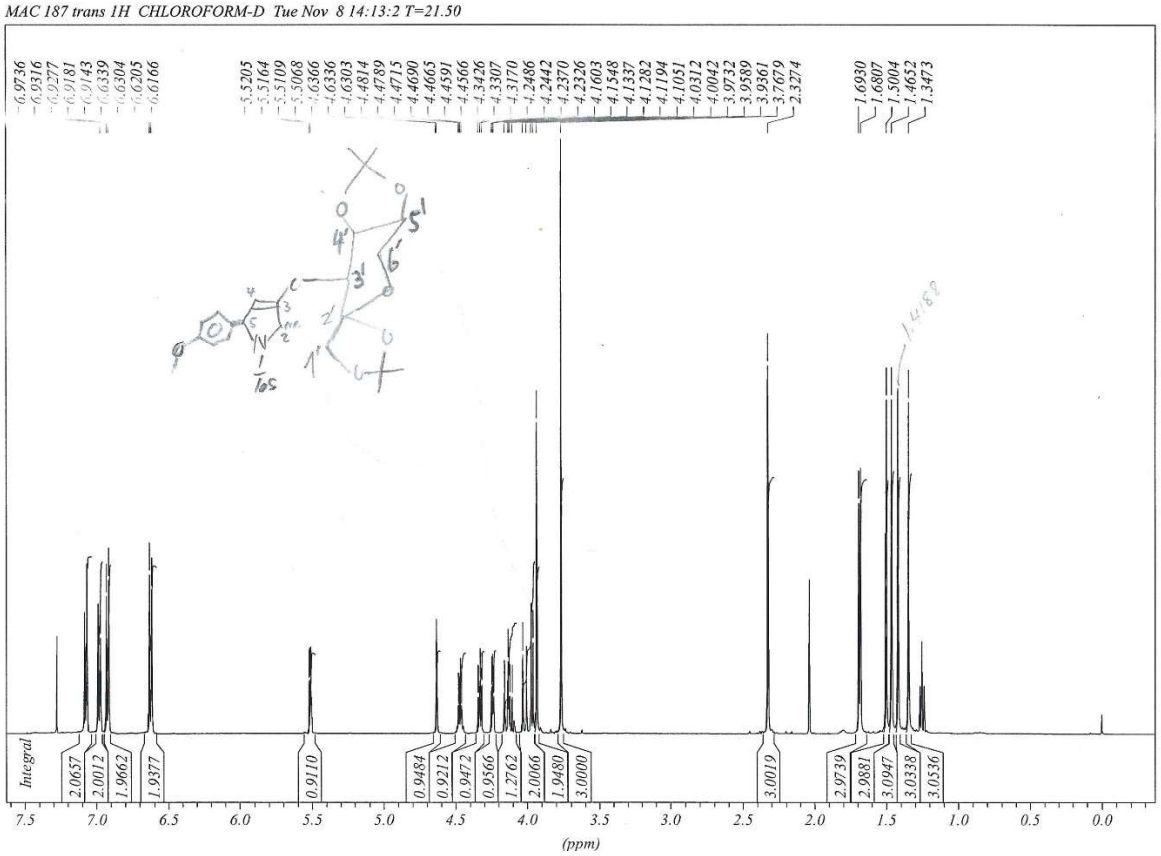
Copies of NMR Spectra of Selected Compounds

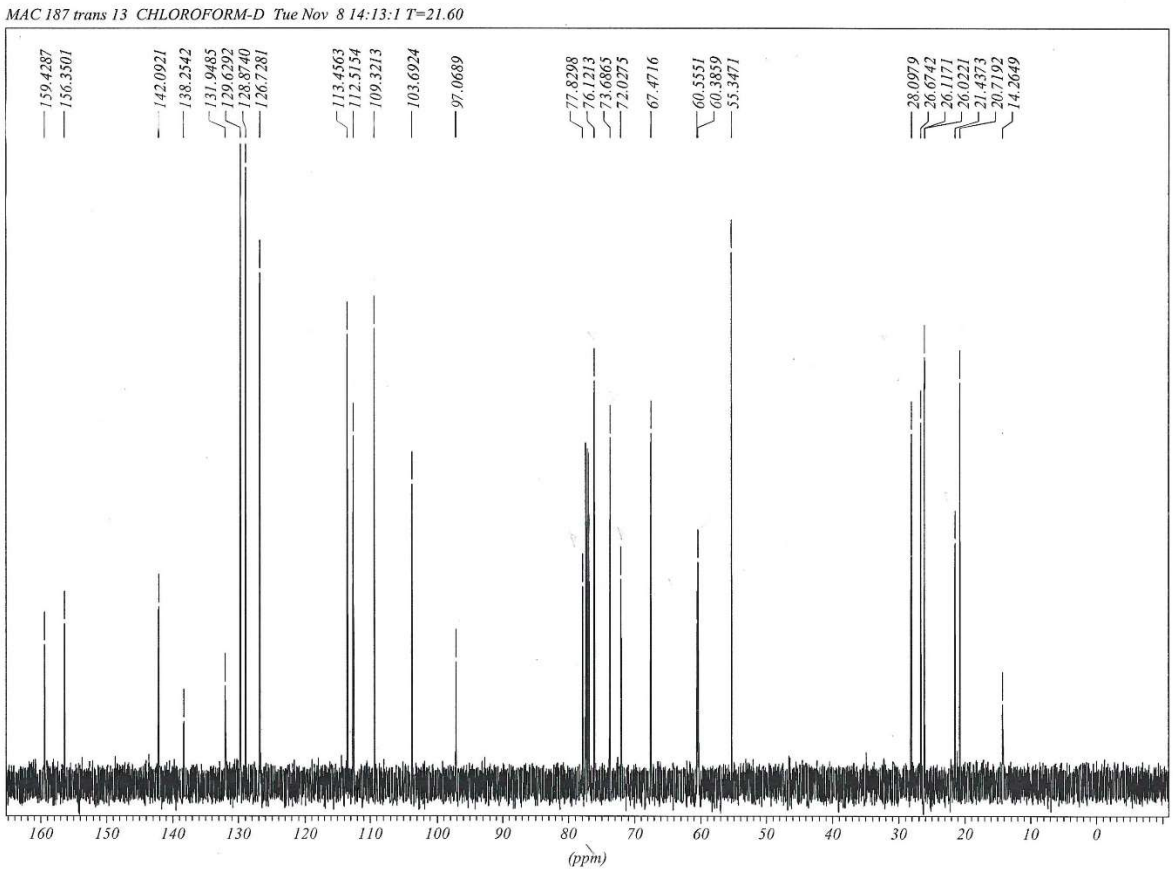
Compound *aR*-**4**



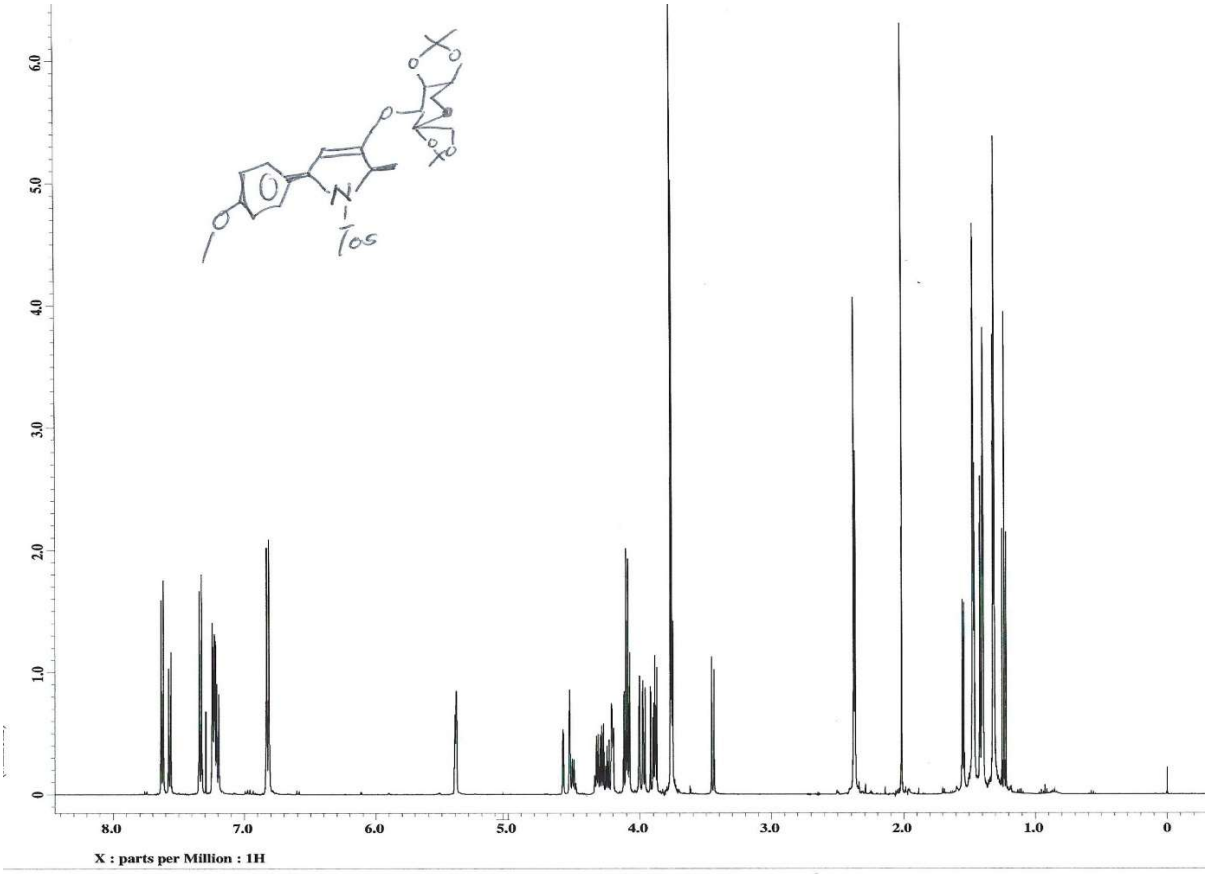


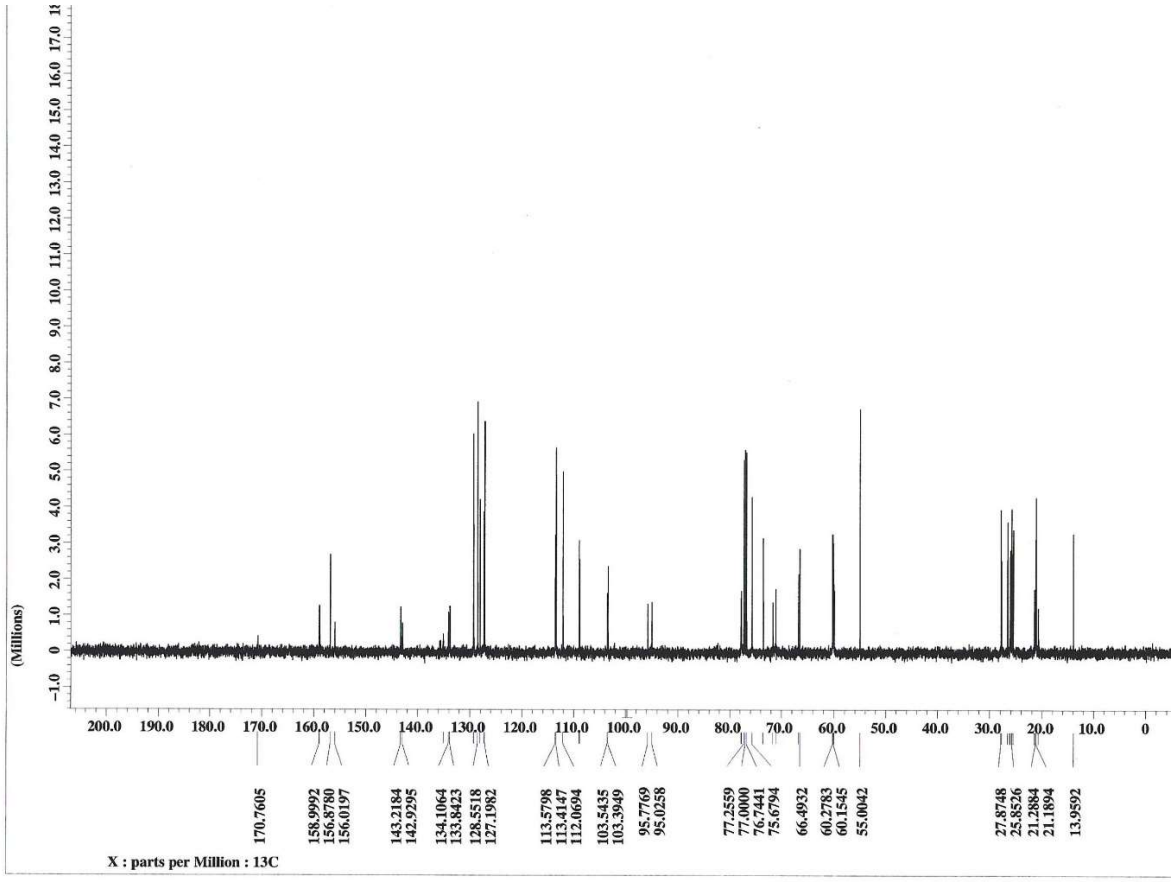
Compound *trans*-**7**



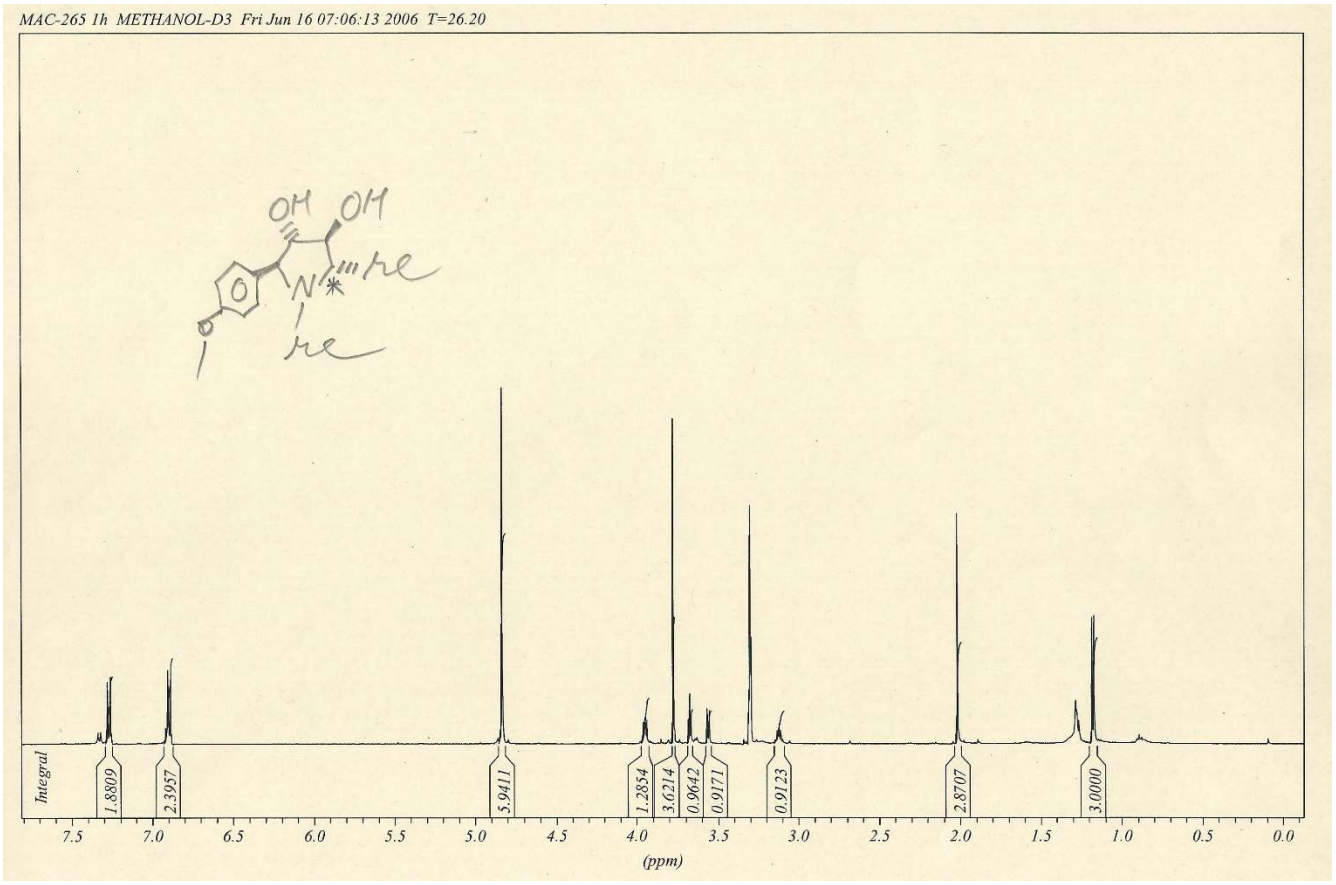


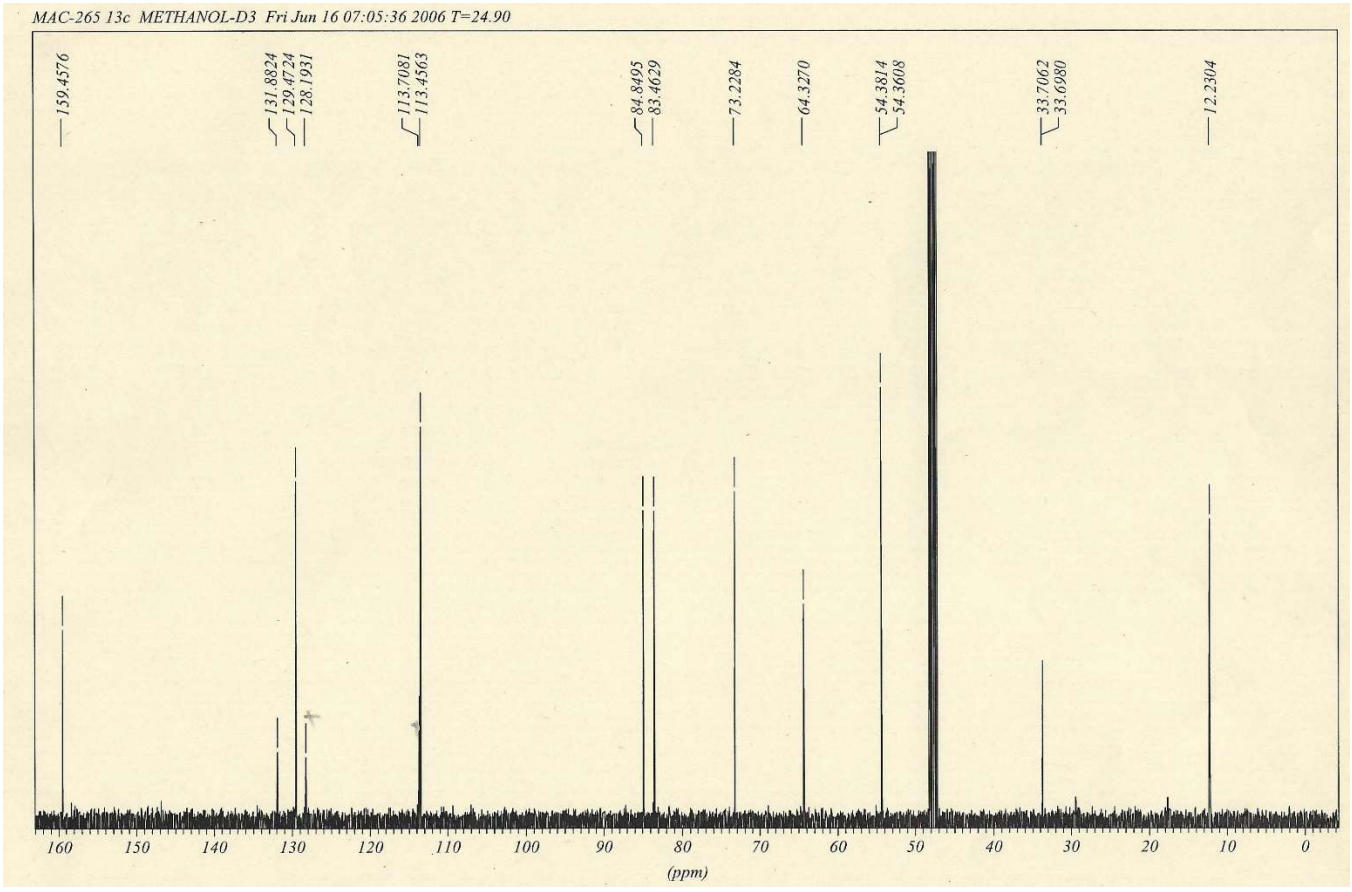
Compounds *cis*-**7a**/**7b**





(+)-Codonopsinine


MAC-265 1h METHANOL-D3 Fri Jun 16 07:06:13 2006 T=26.20
OH
OH
Me
N*
Me
O
Integral
1.8809
2.3957
5.9411
1.2854
3.6214
0.9642
0.9171
0.9123
2.8707
3.0000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


MAC-265 13c METHANOL-D3 Fri Jun 16 07:05:36 2006 T=24.90
159.4576
131.8824
129.4724
128.1931
113.7081
113.4563
84.8495
83.4629
73.2284
64.3270
54.3814
54.3608
33.7062
33.6980
12.2304
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)