Supporting Information

Total Syntheses of (–)-Kopsifoline D and (–)-Deoxoapodine: Divergent Total Synthesis via Late Stage Key Strategic Bond Formation

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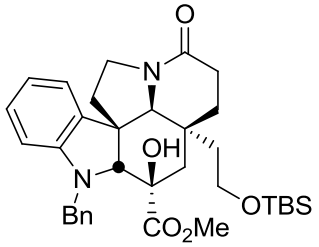
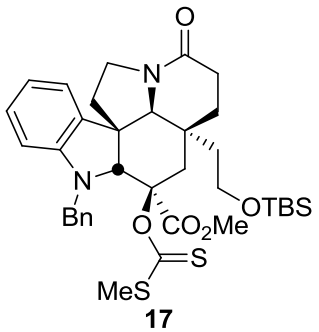


16

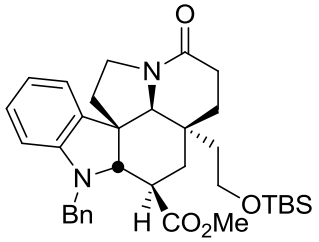
Compound 16. A solution of **15**[3] (953 mg, 1.62 mmol) in *i*-PrOH and acetic acid (16 mL/4 mL) was treated with $NaCNBH_3$ (814 mg, 12.95 mmol, 8 equiv). The mixture was allowed to stir at 25 °C for 16 h before it was cooled to 0 °C and quenched with the addition of saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, gradient elution: 100% EtOAc to 5% MeOH–EtOAc) to provide **16**[7] (841 mg, 88%) as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.28 (m, 3H), 7.12–7.17 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 4.53 (d, *J* = 15.9 Hz, 1H), 3.95 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 1H), 3.53–3.69 (m, 3H), 3.61 (s, 3H), 3.37 (d, *J* = 1.8 Hz, 1H), 3.29 (td, *J* = 11.9, 6.7 Hz, 1H), 2.20–2.35 (m, 2H), 2.04 (ddd, *J* = 13.5, 10.9, 4.9 Hz, 1H), 1.93 (d, *J* = 14.8 Hz, 1H), 1.81–1.90 (m, 2H), 1.78 (dd, *J* = 14.9, 1.9 Hz, 1H), 1.48 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.36 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.25 (dt, *J* = 13.3, 6.4 Hz, 1H), 0.83 (s, 9H), –0.04 (s, 3H), –0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.9, 171.1, 151.7, 137.5, 132.5, 128.9, 128.3, 128.0, 127.4, 122.9, 119.5, 110.7, 76.5, 73.8, 65.9, 59.0, 54.7, 54.5, 52.6, 45.1, 43.0, 41.7, 35.0, 33.9, 32.0, 30.2, 25.8, 18.1, –5.4, –5.5; IR (film) υ_{max} 3233, 2928, 1731, 1633, 1250, 725 cm^{-1}; HRMS (ESI) *m/z* 591.3248 [$(M+H)^+$, $C_{34}H_{46}N_2O_5Si$ requires 591.3249].



17

Compound 17. A cooled (0 °C) solution of **16**[7] (626 mg, 1.06 mmol) and imidazole (62 mg) in THF (20 mL, 0.05 M) was treated with NaH (211 mg, 60% dispersion in mineral oil, 5.30 mmol). The mixture was

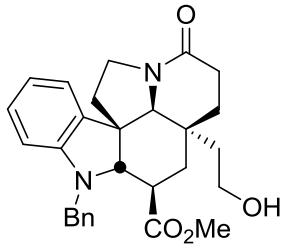
allowed to stir at 25 °C for 30 min before it was cooled to 0 °C followed by the addition of CS_2 (191 μL, 3.18 mmol). The reaction mixture was stirred at 25 °C for 1 h, cooled to 0 °C, and then treated with CH_3I (198 μL, 3.18 mmol). After stirring for 1 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, gradient elution: 70% EtOAc–hexanes to 100% EtOAc) to provide **17**[7] (656 mg, 91%) as a light yellow foam: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23–7.28 (m, 3H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.06–7.11 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 3.93 (d, *J* = 15.6 Hz, 1H), 3.83 (dd, *J* = 12.1, 9.0 Hz, 1H), 3.80 (s, 1H), 3.66 (s, 3H), 3.65 (d, *J* = 2.0 Hz, 1H), 3.60–3.64 (m, 1H), 3.56 (dt, *J* = 11.2, 6.2 Hz, 1H), 3.36 (td, *J* = 11.9, 6.4 Hz, 1H), 2.89 (dd, *J* = 15.5, 2.2 Hz, 1H), 2.51 (s, 3H), 2.17–2.21 (m, 2H), 1.93 (d, *J* = 15.5 Hz, 1H), 1.79–1.91 (m, 2H), 1.51 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.44 (dt, *J* = 14.1, 8.9 Hz, 1H), 1.20–1.28 (m, 1H), 1.11 (dt, *J* = 13.1, 6.2 Hz, 1H), 0.81 (s, 9H), –0.06 (s, 3H), –0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.3, 171.2 169.6, 151.8, 136.9, 132.4, 129.2, 128.4, 127.7, 123.0, 120.4, 112.2, 88.3, 71.7, 65.6, 58.9, 55.5, 54.7, 52.3, 44.6, 42.7, 41.8, 34.3, 31.8, 30.9, 30.6, 25.8, 20.0, 18.1, –5.4, –5.5; IR (film) υ_{max} 2928, 1733, 1650, 1250, 833, 728 cm^{-1}; HRMS (ESI) *m/z* 681.2848 [$(M+H)^+$, $C_{36}H_{48}N_2O_5S_2Si$ requires 681.2847].



18

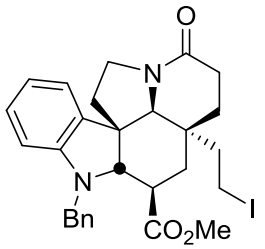
Compound 18. A three neck flask charged with Bu_3SnH (311 μL, 1.16 mmol) and AIBN (9.5 mg, 0.06 mmol) in degassed toluene (24 mL) was heated to reflux. A solution of **17**[7] (197 mg, 0.289 mmol) in toluene (24 mL) was added slowly by syringe pump over 50 min period. The reaction mixture was allowed to stir for additional 10 min at reflux before the resulting mixture was cooled to room temperature. The crude residue was concentrated in vacuo and the residue was purified by flash chromatography (SiO_2, 80% EtOAc–hexanes) to provide **18** (160 mg, 96%) as a light yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21–7.33 (m, 5H), 7.03 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 4.46 (d, *J* = 15.7 Hz, 1H), 4.29 (d, *J* = 15.7 Hz, 1H), 3.93 (s, 1H), 3.62–3.72 (m, 3H), 3.58 (s, 3H), 3.46–3.62 (m, 2H), 2.72 (t, *J* = 11.6 Hz, 1H), 2.44 (dd, *J* = 18.6, 7.2 Hz, 1H),

2.31 (ddd, J = 18.9, 12.2, 7.5 Hz, 1H), 2.06 (dd, J = 13.3, 7.3 Hz, 1H), 1.93 (dd, J = 14.2, 7.3 Hz, 1H), 1.76–1.88 (m, 2H), 1.59 (t, J = 13.6 Hz, 1H), 1.46–1.56 (m, 2H), 1.40 (dt, J = 14.0, 6.7 Hz, 1H), 0.83 (s, 9H), –0.02 (s, 3H), –0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 168.8, 148.5, 138.6, 131.7, 128.5, 128.4, 127.1, 127.0, 122.0, 118.0, 108.0, 65.8, 64.2, 58.6, 54.7, 52.0, 50.3, 42.9, 42.8, 38.2, 36.6, 34.7, 31.2, 27.8, 27.7, 25.9, 18.2, –5.48, –5.52; IR (film) υ_{max} 2928, 2854, 1732, 1640, 1457, 1252, 1092, 669 cm^{-1}; HRMS (ESI) *m/z* 575.3283 [$(M+H)^+$, $C_{34}H_{46}N_2O_4Si$ requires 575.3299].



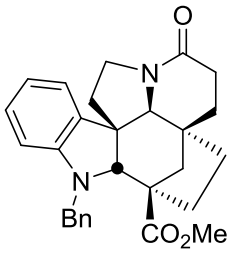
19

Compound 19. A cooled (–78 °C) solution of **18** (625 mg, 1.09 mmol) in THF (15 mL, 0.073 M) was treated with Bu_4NF (3.3 mL, 1.0 M in THF, 3.3 mmol). After stirring for 1 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 5% MeOH–EtOAc) to provide **19** (461 mg, 92%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20–7.31 (m, 5H), 7.02 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.67 (t, J = 7.8 Hz, 1H), 6.35 (d, J = 7.8 Hz, 1H), 4.45 (d, J = 15.6 Hz, 1H), 4.26 (d, J = 15.6 Hz, 1H), 3.92 (s, 1H), 3.64 –3.70 (m, 3H), 3.57 (s, 3H), 3.45–3.60 (m, 2H), 2.72 (t, J = 11.4 Hz, 1H), 2.42 (dd, J = 18.6, 6.6 Hz, 1H), 2.24–2.35 (m, 1H), 2.03 (t, J = 10.8 Hz, 1H), 1.84–1.89 (m, 2H), 1.60 (t, J = 13.8 Hz, 1H), 1.52 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.37–1.46 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 168.8, 148.4, 138.4, 131.6, 128.4, 127.1, 127.0, 121.9, 118.0, 108.0, 65.7, 63.9, 57.9, 54.7, 52.0, 50.2, 42.9, 42.7, 38.2, 36.5, 34.6, 31.1, 27.7, 27.5; IR (film) υ_{max} 3402, 2947, 1731, 1618, 1483, 670 cm^{-1}; HRMS (ESI) *m/z* 461.2426 [$(M+H)^+$, $C_{28}H_{32}N_2O_4$ requires 461.2435].



20

Compound 20. A cooled (–78 °C) solution of **19** (117 mg, 0.254 mmol) in THF (8 mL, 0.032 M) was treated with Et_3N (106 μL, 0.76 mmol) and methanesulfonyl chloride (30 μL, 0.38 mmol). After stirring for 1 h at the same temperature, sodium iodide (381 mg, 2.54 mmol) and acetone (8 mL) were added and the reaction mixture was then warmed to 50 °C. After stirring for 12 h at the same temperature, the resulting mixture was quenched with addition of saturated aqueous $NaHCO_3$ and diluted with H_2O and hexanes (50 mL). The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5% MeOH–EtOAc) to provide **20** (117 mg, 81%) as a white form: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21–7.33 (m, 5H), 7.06 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.73 (t , J = 7.2 Hz, 1H), 6.39 (d, J = 7.8 Hz, 1H), 4.46 (d, J = 15.6 Hz, 1H), 3.89 (s, 1H), 3.66 (d, J = 9.6 Hz, 1H), 3.60 (s, 3H), 3.45–3.62 (m, 2H), 2.99–3.12 (m, 2H), 2.62 (ddd, J = 13.2, 9.6, 3.6 Hz, 1H), 2.48 (dd, J = 18.6, 6.6 Hz, 1H), 2.31 (ddd, J = 19.2, 11.4, 7.8 Hz, 1H), 2.17 (td, J = 13.8, 6.0 Hz, 1H), 2.03 (dd, J = 13.2, 7.2 Hz, 1H), 1.83–1.90 (m, 1H), 1.72–1.83 (m, 2H), 1.49–1.62 (m, 2H), 1.35 (dd, J = 14.4, 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 148.3, 138.3, 131.0, 128.7, 128.5, 127.2, 127.1, 121.4, 118.5, 108.4, 62.7, 54.6, 52.2, 50.3, 42.9, 42.4, 41.3, 37.4, 36.4, 30.3, 27.4, 27.3, –3.2; IR (film) υ_{max} 2945, 2869, 1728, 1629, 1454, 1173, 732, 698 cm^{-1}; HRMS (ESI) *m/z* 571.1456 [$(M+H)^+$, $C_{28}H_{31}IN_2O_3$ requires 571.1452].

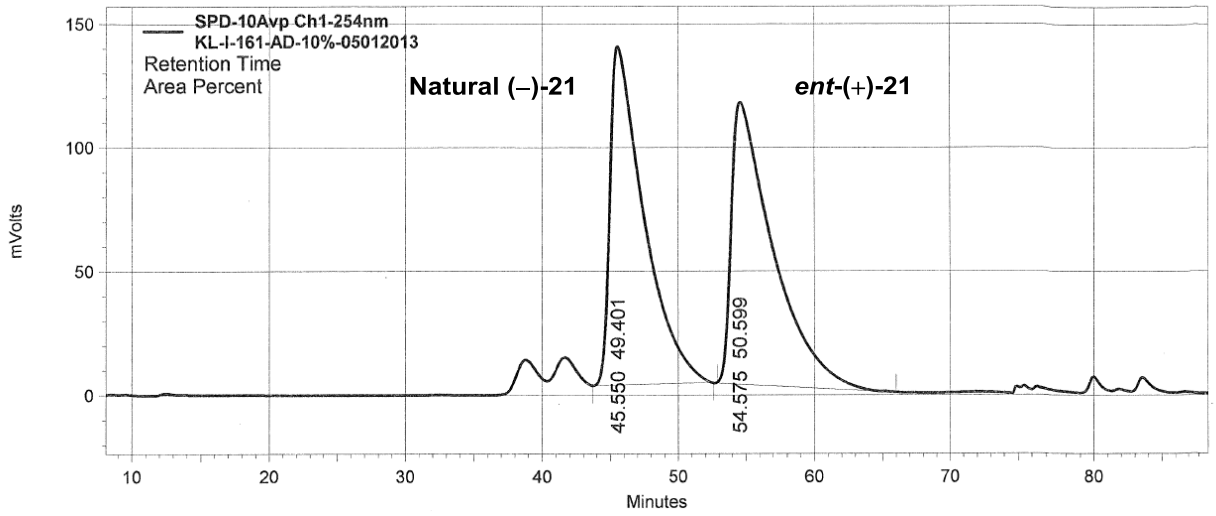


21

Compound 21. A cooled (–78 °C) solution of **20** (18.0 mg, 0.032 mmol) in THF (2.5 mL, 0.013 M) was treated with KO^{t}Bu (95 μL, 1.0 M in THF, 0.095 mmol). The reaction mixture was gradually warmed to

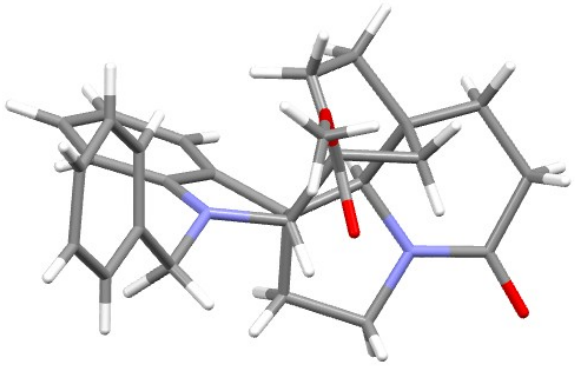
0 °C in a period of 1 h. The resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5% MeOH–EtOAc) to provide **21** (13.3 mg, 95%) as a light yellow oil. The enantiomers of **21** were separated ($\alpha = 1.2$) on a semipreparative ChiralCel AD column (2 × 25 cm, 10% *i*-PrOH–hexanes, 7 mL/min flow rate) providing natural (–)-**21** (t_R: 45.6 min) and *ent*-(+)-**21** (t_R: 54.6 min). For natural enantiomer (–)-**21**: $[\alpha]_D^{25}$ –16.3 (*c* 1.5, $CHCl_3$), unnatural enantiomer (+)-**21**: $[\alpha]_D^{25}$ +16.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17–7.29 (m, 5H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 15.6 Hz, 1H), 4.12 (d, *J* = 15.6 Hz, 1H), 3.61 (dd, *J* = 12.0, 8.4 Hz, 1H), 3.59 (s, 3H), 3.41 (ddd, *J* = 12.0, 7.2, 7.2 Hz, 1H), 2.50 (dd, *J* = 18.6, 8.4 Hz, 1H), 2.33 (dt, *J* = 18.6, 9.6 Hz, 1H), 2.15 (ddd, *J* = 13.2, 13.2, 4.8 Hz, 1H), 1.91 (ddd, *J* = 13.8, 9.6, 9.6 Hz, 1H), 1.72 (d, *J* = 12.0 Hz, 1H), 1.60–1.65 (m, 3H), 1.47–1.55 (m, 2H), 1.38–1.44 (m, 1H), 1.29 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 169.6, 150.7, 138.5, 133.1, 128.6, 128.5, 127.3, 127.1, 121.1, 117.8, 106.9, 70.6, 66.8, 55.9, 54.4, 52.0, 51.4, 43.9, 43.6, 39.5, 38.6, 33.1, 31.7, 29.5, 25.0; IR (film) υ_{max} 2923, 1731, 1635, 1458, 670 cm^{-1}; HRMS (ESI) *m/z* 443.2309 [$(M+H)^+$, $C_{28}H_{30}N_2O_3$ requires 443.2329].

The cyclizations under same reaction conditions of the intermediate mesylate (0%) or corresponding tosylate (32–36%) were not as productive.

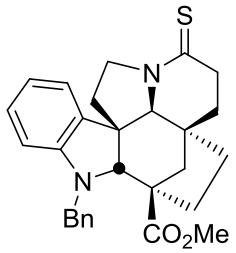


SPD-10Avp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
45.550	23708644	49.40	136828	54.57
54.575	24283313	50.60	113913	45.43
Totals	47991957	100.00	250741	100.00



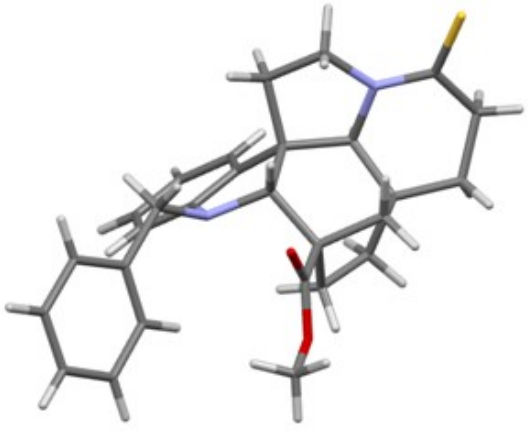
The structure and relative stereochemistry of **21** were confirmed upon X-ray (CCDC 977766) analysis enlisting a white monoclinic crystal obtained from Et_2O.

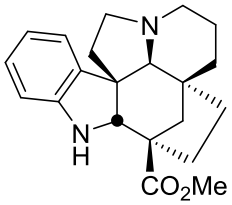


(+)-22

Compound (+)-22. A solution of (–)-**21** (60 mg, 0.14 mmol) in anhydrous toluene (10 mL, 0.014 M) was treated with Lawesson's reagent[S1] (60 mg, 0.15 mmol) at 25 °C. The reaction mixture was heated at 100 °C under Ar for 30 min, cooled to 25 °C and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 30% EtOAc–hexanes) to provide (+)-**22** (55.3 mg, 89%) as a colorless oil: $[\alpha]_D^{25}$ +22.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18–7.31 (m, 5H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 4.63 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H), 4.06 (dt, *J* = 14.4, 5.4 Hz, 1H), 3.90 (s, 1H), 3.85 (s, 1H), 3.60–3.69 (m, 1H), 3.62 (s, 3H), 3.04 (dd, *J* = 9.0, 6.0 Hz, 2H), 2.17 (ddd, *J* = 13.8, 13.8, 5.4 Hz, 1H), 1.91 (dt, *J* = 13.8, 9.0 Hz, 1H), 1.50–1.66 (m, 6H), 1.41–1.49 (m, 1H), 1.34 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.4, 175.5, 150.6, 138.4, 132.5, 129.0, 128.6, 127.5, 127.4, 121.0, 118.1, 107.3, 70.0, 69.4, 56.1, 54.6, 52.1, 51.5, 51.1, 43.8, 39.9, 39.3, 39.0, 33.7, 31.7, 25.2; IR (film) υ_{max} 3349, 2923, 2861, 1723, 1602, 1484, 1241, 730, 669 cm^{-1}; HRMS (ESI) *m/z* 459.2111 [$(M+H)^+$, $C_{28}H_{30}N_2O_2S$ requires 459.2101]. The structure and the absolute configuration of **(+)-22** were unambiguously established with a single crystal X-ray structure determination conducted on a colorless parallelpiped crystal obtained from acetone (CCDC 978175).

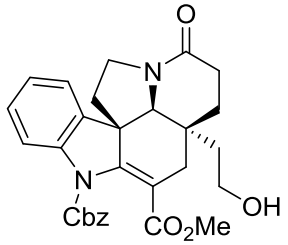
(+)-22 ≡





8, kopsifoline H

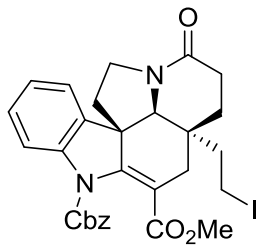
Compound 8. A stirred solution of (+)-**22** (60 mg, 0.13 mmol) in EtOH (3 mL, 0.044 M) was treated with excess Raney 2400 Ni (~ 1 g, pretreated with successive washes with EtOH) at 25 °C. After stirring at 80 °C under H_2 for 30 min, the resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 50% EtOAc–hexanes) to provide kopsifoline H (**8**, 31 mg, 70%) as a white solid: $[\alpha]_D^{25}$ –49 (*c* 0.61, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 4.52 (br s, 1H), 3.80 (s, 1H), 3.71 (s, 3H), 3.11 (t, *J* = 8.4 Hz, 2H), 2.36 (dt, *J* = 11.6, 2.0 Hz, 1H), 2.28–2.34 (m, 1H), 2.19 (ddd, *J* = 12.6, 11.4, 7.8 Hz, 1H), 2.14 (s, 1H), 2.01 (ddd, *J* = 11.4, 11.4, 3.0 Hz, 1H), 1.75 (dd, *J* = 13.2, 7.8 Hz, 1H), 1.56–1.72 (m, 3H), 1.49–1.55 (m, 2H), 1.45 (d, *J* = 12.0 Hz, 1H), 1.42 (ddd, *J* = 13.2, 13.2, 4.8 Hz, 1H), 1.32 (td, *J* = 13.2, 4.8 Hz, 1H), 1.16–1.22 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 149.9, 136.3, 127.7, 121.8, 117.8, 107.4, 76.5, 72.8, 56.9, 54.5, 53.3, 52.0, 45.2, 43.3, 38.4, 35.3, 35.2, 26.3, 23.7; IR (film) υ_{max} 3365, 2922, 1717, 1600, 1459, 1241, 743, 670 cm^{-1}; HRMS (ESI) *m/z* 339.2069 [$(M+H)^+$, $C_{21}H_{26}N_2O_2$ requires 339.2067].



26

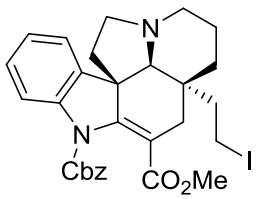
Compound 26. A cooled (0 °C) solution of **25**[7] (134 mg, 0.217 mmol) in THF (10 mL, 0.022 M) was treated with Bu_4NF (652 μL, 1.0 M in THF, 0.652 mmol). After stirring for 1 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 100% EtOAc) to provide **26** (107 mg, 98%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.31–7.41 (m, 5H), 7.29 (t, *J* = 7.9

Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 5.39 (d, J = 12.2 Hz, 1H), 5.18 (d, J = 12.2 Hz, 1H), 4.11 (dd, J = 12.2, 7.5 Hz, 1H), 3.65 (d, J = 1.8 Hz, 1H), 3.57–3.63 (m, 1H), 3.56 (s, 3H), 3.47–3.53 (m, 1H), 3.30 (td, J = 11.8, 6.0 Hz, 1H), 2.50 (dd, J = 15.2, 2.0 Hz, 1H), 2.43 (dt, J = 16.2, 5.4 Hz, 1H), 2.38 (ddd, J = 16.1, 10.3, 5.4 Hz, 1H), 2.24 (d, J = 15.3 Hz, 1H), 2.10 (dt, J = 13.8, 5.6 Hz, 1H), 2.00–2.07 (m, 1H), 1.91 (dd, J = 12.4, 5.7 Hz, 1H), 1.60–1.64 (m, 1H), 1.43 (dt, J = 14.1, 7.0 Hz, 1H), 1.31 (dq, J = 13.5, 6.8, 6.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 167.5, 152.0, 148.7, 136.1, 135.3, 128.6, 128.5, 128.3, 124.5, 121.2, 116.1, 110.9, 68.4, 66.4, 58.4, 54.7, 51.6, 42.4, 39.6, 38.0, 37.9, 31.3, 31.0, 30.3; IR (film) υ_{max} 3389, 2924, 1731, 1649, 670 cm^{-1}; HRMS (ESI) *m/z* 503.2156 [$(M+H)^+$, $C_{29}H_{30}N_2O_6$ requires 503.2177].



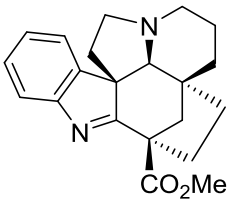
27

Compound 27. A cooled (–78 °C) solution of **26** (52.3 mg, 0.104 mmol) in THF (4 mL, 0.026 M) was treated with Et_3N (44 μL, 0.31 mmol) and methanesulfonyl chloride (12 μL, 0.16 mmol). After stirring for 1 h at the same temperature, sodium iodide (156 mg, 1.04 mmol) and acetone (4 mL) were added and the reaction mixture was then warmed to 50 °C. After stirring for 12 h at the same temperature, the resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with H_2O and hexanes (30 mL). The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, gradient elution: 70% EtOAc–hexanes to 100% EtOAc) to provide **27** (50.9 mg, 80%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 1H), 7.28–7.43 (m, 6H), 7.09–7.16 (m, 2H), 5.39 (d, J = 12.0 Hz, 1H), 5.20 (d, J = 12.0 Hz, 1H), 4.09 (dd, J = 12.0, 7.5 Hz, 1H), 3.58 (s, 3H), 3.49 (s, 1H), 3.32 (ddd, J = 11.5, 11.5, 5.5 Hz, 1H), 3.00 (ddd, J = 13.5, 9.5, 5.0 Hz, 1H), 2.75 (ddd, J = 13.5, 9.5, 5.0 Hz, 1H), 2.50 (d, J = 15.5 Hz, 1H), 2.43 (dt, J = 16.0, 5.0 Hz, 1H), 2.33 (ddd, J = 17.0, 12.0, 5.0 Hz, 1H), 2.12 (d, J = 15.5 Hz, 1H), 1.98–2.07 (m, 2H), 1.90 (dd, J = 12.5, 6.0 Hz, 1H), 1.63–1.79 (m, 2H), 1.48 (ddd, J = 13.0, 13.0, 4.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 167.0, 152.0, 149.2, 140.2, 135.8, 135.1, 128.8, 128.63, 128.55, 128.4, 124.6, 121.3, 116.2, 109.7, 68.6, 66.2, 54.7, 51.7, 42.4, 41.6, 40.5, 39.0, 30.64, 30.59, 30.1, –3.5; IR (film) υ_{max} 2925, 1730, 1664, 1238, 751, 670 cm^{-1}; HRMS (ESI) *m/z* 613.1176 [$(M+H)^+$, $C_{29}H_{29}IN_2O_5$ requires 613.1194].



28

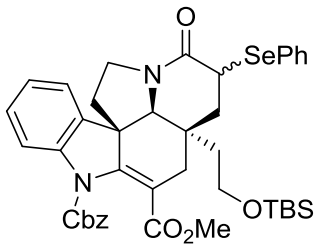
Compound 28. A cooled (0 °C) solution of **27** (23.0 mg, 0.038 mmol) in THF (3 mL, 0.013 M) was treated dropwise with a solution of borane-tetrahydrofuran complex (188 μL, 1.0 M in THF, 0.188 mmol). After stirring for 1.5 h at the same temperature, the resulting mixture was quenched with the addition of H_2O and the solution was treated with 10% aqueous HCl (3 mL). After stirring for 30 min at 0 °C, 1 N aqueous NaOH was then added to the mixture until pH ~13 and the mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 30% EtOAc–hexanes) to provide **28** (17.8 mg, 79%) as a a light yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.28–7.43 (m, 5H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 5.40 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 3.61 (s, 1H), 3.58 (s, 3H), 3.53 (ddd, *J* = 17.5, 12.3, 6.5 Hz, 1H), 3.13–3.25 (m, 2H), 3.07 (ddd, *J* = 12.3, 6.4, 3.6 Hz, 1H), 2.94 (ddd, *J* = 13.2, 9.4, 4.5 Hz, 1H), 2.72 (ddd, *J* = 12.4, 9.4, 5.1 Hz, 1H), 2.57 (d, *J* = 16.4 Hz, 1H), 2.16–2.33 (m, 3H), 2.04–2.16 (m, 2H), 1.73–1.84 (m, 3H), 1.63 (td, *J* = 13.2, 4.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 152.1, 148.3, 139.7, 136.3, 135.3, 128.8, 128.7, 128.6, 128.4, 124.07, 123.0, 116.1, 109.5, 73.5, 68.5, 61.7, 55.5, 52.7, 51.7, 44.9, 39.6, 39.4, 30.9, 25.8, 15.8, –3.6; IR (film) υ_{max} 3370, 2923, 1716, 1458, 1389, 1185, 732, 695 cm^{-1}; HRMS (ESI) *m/z* 599.1385 [(M+H)$^+$, $C_{29}H_{31}IN_2O_4$ requires 599.1401].



30
6,7-dihydrokopsifoline D

Compound 30. A solution of **28** (9.6 mg, 0.016 mmol) in CH_2Cl_2 (4 mL, 0.004 M) was treated dropwise with dimethyl sulfide (198 μL, 1.61 mmol) and boron trifluoride diethyl etherate (198 μL, 2.69 mmol). After stirring for 15 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$, Et_3N (5 drops), and diluted with CH_2Cl_2 (5 mL). The layers were separated, and the aqueous

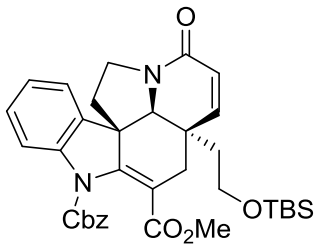
layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 2.5% Et_3N in EtOAc) to afford 6,7-dihydrokopsifoline (**30**, 4.1 mg, 75%) as a light yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.50 (td, *J* = 9.0, 6.6 Hz, 1H), 3.29 (td, *J* = 9.0, 4.8 Hz, 1H), 3.13–3.18 (m, 1H), 2.92 (td, *J* = 12.6, 2.4 Hz, 1H), 2.78 (d, *J* = 1.8 Hz, 1H), 2.74 (dd, *J* = 12.6, 3.0 Hz, 1H), 2.64 (ddd, *J* = 13.8, 9.0, 4.2 Hz, 1H), 2.16–2.24 (m, 1H), 2.04–2.14 (m, 2H), 1.79–1.88 (m, 2H), 1.64 (td, *J* = 14.0, 4.0 Hz, 1H), 1.56 (dd, *J* = 12.6, 2.4 Hz, 1H), 1.40–1.46 (m, 1H), 1.20–1.36 (m, 1H), 0.99 (dt, *J* = 14.4, 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.5, 172.5, 154.3, 147.6, 127.4, 126.0, 121.2, 120.3, 70.9, 63.8, 56.9, 52.5, 50.5, 47.2, 42.2, 42.0, 38.5, 37.1, 35.7, 33.9, 17.9; IR (film) υ_{max} 2923, 1717, 1634, 750, 670 cm^{-1}; HRMS (ESI) *m/z* 337.1916 [$(M+H)^+$, $C_{21}H_{24}N_2O_2$ requires 337.1910].



31

Compound 31. A cooled (–78 °C) solution of **25**[7] (74 mg, 0.12 mmol) in THF (6 mL, 0.020 M) was treated with freshly prepared lithium diisopropylamide (LDA, 0.47 mL, 0.51 M in THF, 0.24 mmol). After stirring for 30 min at the same temperature, phenylselenyl chloride (23 mg, 0.12 mmol) in THF (2 mL) was added dropwise and the mixture was stirred for another 2.5 h at –78 °C. The resulting yellow mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 20–40% EtOAc–hexanes) to provide an isomeric mixture of **31** (β:α = 8:1, 75 mg, 81%) as light yellow oils: **For major β-isomer:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 6.6 Hz, 2H), 7.26–7.40 (m, 9H), 7.12 (d, *J* = 6.0 Hz, 2H), 5.37 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 4.06–4.12 (m, 1H), 4.03 (t, *J* = 5.4 Hz, 1H), 3.93 (s, 1H), 3.54 (s, 3H), 3.32–3.43 (m, 2H), 3.31 (td, *J* = 11.4, 6.6 Hz, 1H), 2.52 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.42 (d, *J* = 15.6 Hz, 1H), 2.22 (d, *J* = 15.6 Hz, 1H), 2.11 (dd, *J* = 15.0, 6.0 Hz, 1H), 1.98–2.03 (m, 1H), 1.88 (ddd, *J* = 12.0, 6.0, 3.0 Hz, 1H), 1.44 (dt, *J* = 14.4, 7.8 Hz, 1H), 1.36 (dt, *J* = 13.2, 6.0 Hz, 1H), 0.80 (s, 9H), –0.07 (s, 3H), –0.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 166.9, 152.0, 149.4, 140.3, 135.6,

135.3, 134.8, 129.2, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 68.4, 65.3, 58.9, 55.1, 51.5, 43.3, 40.0, 39.8, 38.2, 37.9, 37.8, 30.5, 25.9, 18.2, –5.56, –5.59; IR (film) υ_{max} 2926, 1731, 1651, 1459, 1256, 1093, 799, 670 cm^{-1}; HRMS (ESI) *m/z* 773.2511 [$(M+H)^+$, $C_{41}H_{48}N_2O_6SeSi$ requires 773.2519]. **For minor α-isomer:** ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.64 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.31–7.42 (m, 5H), 7.26–7.31 (m, 4H), 7.06–7.13 (m, 2H), 5.37 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 4.19 (dd, *J* = 13.3, 4.7 Hz, 1H), 4.07 (dd, *J* = 11.9, 7.8 Hz, 1H), 3.77 (s, 1H), 3.53 (s, 3H), 3.41 (td, *J* = 12.0, 6.0 Hz, 1H), 3.16–3.27 (m, 2H), 2.46 (dd, *J* = 15.4, 1.9 Hz, 1H), 2.36 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.13 (d, *J* = 15.2 Hz, 1H), 2.02–2.09 (m, 1H), 1.91 (dd, *J* = 12.6, 5.8 Hz, 1H), 1.60–1.66 (m, 1H), 1.27–1.37 (m, 1H), 1.14 (ddd, *J* = 13.4, 7.2, 4.8 Hz, 1H), 0.73 (s, 9H), –0.16 (s, 3H), –0.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 167.0, 152.0, 148.9, 140.3, 136.0, 135.18, 135.15, 129.1, 128.7, 128.6, 128.5, 128.3, 128.0, 124.5, 121.5, 116.1, 110.3, 68.5, 66.0, 59.0, 54.7, 51.5, 43.2, 43.0, 40.3, 39.8, 38.4, 37.9, 33.3, 25.9, 18.2, –5.7.

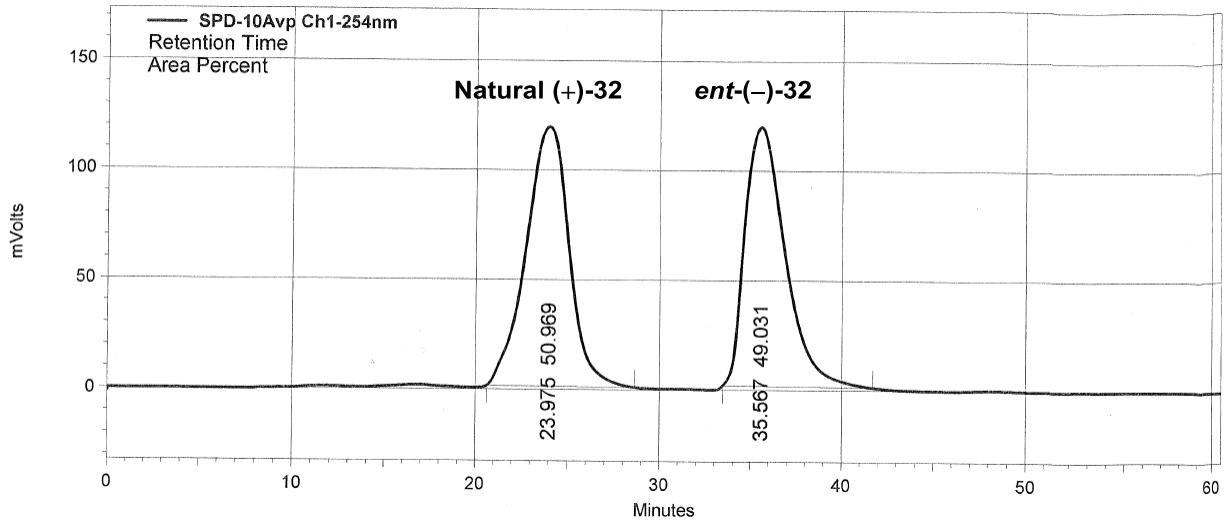


(+)-32

Compound (+)-32. A cooled (–78 °C) solution of a mixture of isomeric phenylselenides **31** (84.5 mg, 0.109 mmol) in CH_2Cl_2 (10 mL, 0.011 M) was treated dropwise a solution of *m*-chloroperoxybenzoic acid (*m*-CPBA, 28.3 mg, 0.164 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL). The reaction mixture was then slowly allowed to warm to 25 °C. After stirring for 1 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$ and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 50% EtOAc–hexanes) to afford **32** (60.5 mg, 90%) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.32–7.44 (m, 5H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 10.2 Hz, 1H), 5.94 (d, *J* = 10.2 Hz, 1H), 5.38 (d, *J* = 12.0 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 4.13–4.23 (m, 2H), 3.56 (s, 3H), 3.42–3.53 (m, 2H), 3.32 (td, *J* = 12.0, 6.0 Hz, 1H), 2.49 (dd, *J* = 15.6, 1.8 Hz, 1H), 2.34 (d, *J* = 15.0 Hz, 1H), 2.09 (ddd, *J* = 12.0, 12.0, 7.8 Hz, 1H), 1.97 (dd, *J* = 12.6, 5.4 Hz, 1H), 1.44 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.31 (dt, *J* = 14.4, 6.0 Hz, 1H), 0.81 (s, 9H), –0.09 (s, 3H), –0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 161.5, 152.0, 150.4, 146.7, 140.2, 135.7, 135.2, 128.6, 128.5, 128.2, 124.5, 122.6, 121.1, 116.0, 110.0, 68.4, 64.4, 59.1, 54.5, 51.6,

42.5, 42.4, 39.7, 36.4, 29.4, 25.8, 18.2, –5.61, –5.66; IR (film) υ_{max} 2926, 1717, 1669, 1458, 1248, 670 cm^{-1}; HRMS (ESI) *m/z* 615.2877 [$(M+H)^+$, $C_{35}H_{42}N_2O_6Si$ requires 615.2885].

The enantiomers of **32** were separated (α = 1.48) on a semipreparative ChiralCel OD column (2 × 25 cm, 20% *i*-PrOH–hexanes, 7 mL/min flow rate) providing natural (+)-**32** (t_R: 24.0 min) and *ent*-(–)-**32** (t_R: 35.6 min). For natural enantiomer (+)-**32**: $[\alpha]_D^{25}$ +6.2 (*c* 1.25, $CHCl_3$); unnatural enantiomer (–)-**32**: $[\alpha]_D^{25}$ –5.7 (*c* 1.25, $CHCl_3$).



SPD-10Avp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
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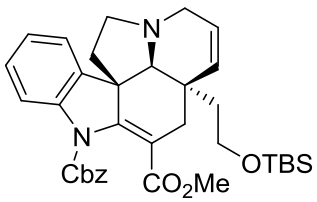
35.567	18262797	49.03	118003	49.97
Totals	37247186	100.00	236164	100.00



(–)-33

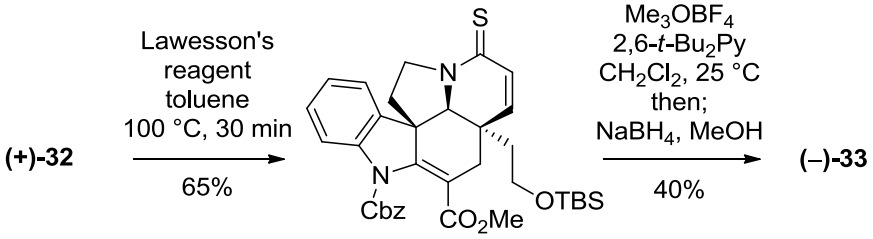
Compound (–)-33. A stirred solution of (+)-**32** (12.6 mg, 0.021 mmol) in CH_2Cl_2 (1 mL, 0.021 M) was treated with 2,6-di-*tert*-butylpyridine (14.7 μL, 0.068 mmol) and trimethyloxonium tetrafluoroborate (9.2 mg, 0.062 mmol) under Ar. After stirring for 12 h at 25 °C, the reaction mixture was cooled to 0 °C, and anhydrous MeOH (2 mL) was added. After 15 min, $NaBH_4$ (7.8 mg, 0.205 mmol) was added, and the mixture was stirred at 0 °C for another 30 min. The resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2 (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 20% EtOAc–hexanes) providing **(–)-33** (6.4 mg, 52%) as a colorless oil: $[\alpha]_D^{25}$ –24.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.29–7.38 (m, 5H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 5.77 (d, *J* = 2.8 Hz, 2H), 5.37 (d, *J* = 12.6 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 3.54 (s, 3H), 3.37–3.49 (m, 3H), 3.06 (d, *J* = 15.6 Hz, 1H), 3.01 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.74 (d, *J* = 15.0 Hz, 1H), 2.66 (s, 1H), 2.47 (ddd, *J* = 12.0, 9.0, 5.4 Hz, 1H), 2.33 (dd, *J* = 15.0, 1.8 Hz, 1H), 2.15 (td, *J* = 12.0, 6.6 Hz, 1H), 1.76 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.21–1.32 (m, 2H), 0.77 (s, 9H), –0.15 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 152.3, 150.5, 140.3, 137.9, 135.7, 133.4, 128.5, 128.2, 128.0, 127.7, 124.8, 123.9, 120.9, 115.7, 111.6, 67.9, 67.8, 59.4, 52.7, 51.40, 51.36, 50.9, 43.0, 40.4, 36.5, 31.8, 25.9, 18.2, –5.5, –5.6; IR (film) υ_{max} 2923, 2853, 1720, 1460, 1254, 1086, 748, 696 cm^{-1}; HRMS (ESI) *m/z* 601.3075 [$(M+H)^+$, $C_{35}H_{44}N_2O_5Si$ requires 601.3092].

Alternative method A:

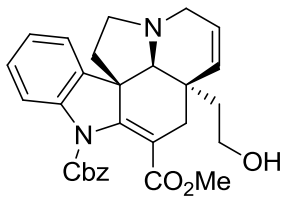
A cooled (–20 °C) solution of **(+)-32** (14.2 mg, 0.023 mmol) in anhydrous THF (1 mL, 0.023 M) was treated dropwise with diisobutylaluminum hydride (Dibal-H, 116 μL, 1.0 M in toluene, 0.116 mmol, 5 equiv). After stirring at the same temperature for 20 min, the reaction mixture was quenched with the addition of MeOH followed by aqueous Rochelle's salt solution and diluted with Et_2O. The resulting mixture was stirred for 5 h at 25 ºC. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The

residue was purified by flash chromatography (SiO_2, 20% EtOAc–hexanes) to provide **(–)-33** (6.7 mg, 48%) as a colorless oil.

Alternative method B:

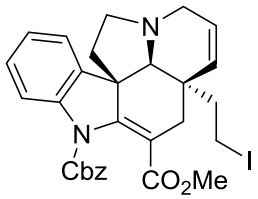


[Formation of thioamide] A solution of **(+)-32** (12.9 mg, 0.021 mmol) in toluene (2 mL, 0.011 M) was treated with Lawesson's reagent[S1] (9.3 mg, 0.023 mmol, 1.1 equiv). The reaction mixture was warmed at 100 °C under Ar for 30 min, cooled to 25 °C and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, 30% EtOAc–hexanes) to afford the thioamide (8.6 mg, 65%) as a light yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 1H), 7.32–7.44 (m, 5H), 7.30 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.43–6.49 (m, 2H), 5.37 (d, J = 12.2 Hz, 1H), 5.18 (d, J = 12.3 Hz, 1H), 4.56 (ddd, J = 13.1, 7.7, 3.1 Hz, 1H), 4.13 (s, 1H), 3.74 (ddd, J = 13.2, 10.2, 6.6 Hz, 1H), 3.55 (s, 3H), 3.48 (dd, J = 7.2, 5.5 Hz, 2H), 2.48 (dd, J = 15.7, 1.8 Hz, 1H), 2.29 (d, J = 15.7 Hz, 1H), 2.24 (ddd, J = 12.9, 10.3, 7.7 Hz, 1H), 2.08 (ddd, J = 12.9, 6.7, 3.1 Hz, 1H), 1.45 (dt, J = 14.4, 7.2 Hz, 1H), 1.33 (dt, J = 14.4, 5.5 Hz, 1H), 0.80 (s, 9H), –0.075 (s, 3H), –0.084 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 166.6, 152.0, 149.8, 140.1, 138.2, 135.2, 135.0, 129.4, 128.8, 128.6, 128.5, 128.2, 124.6, 120.7, 116.1, 110.8, 68.4, 65.4, 59.0, 54.2, 51.7, 49.0, 41.4, 39.3, 36.0, 28.6, 25.8, 18.2, –5.6, –5.7; IR (film) υ_{max} 2925, 1717, 1460, 1234, 1089, 670 cm^{-1}; HRMS (ESI) *m/z* 631.2658 [$(M+H)^+$, $C_{35}H_{42}N_2O_5SSi$ requires 631.2656]. **[Reduction of *S*-methyliminium ion]** A solution of the intermediate thioamide (4.2 mg, 6.66 μmol) in CH_2Cl_2 (0.5 mL, 0.013 M) was treated with 2,6-di-*tert*-butylpyridine (4.8 μL, 21.9 μmol, 3.3 equiv) and trimethyloxonium tetrafluoroborate (3.0 mg, 20.0 μmol, 3.0 equiv) under Ar. After stirring for 12 h at 25 °C, the reaction mixture was cooled to 0 °C, and anhydrous MeOH (2 mL) was added. After 15 min, $NaBH_4$ (2.5 mg, 0.067 mmol, 10 equiv) was added, and the mixture was stirred at 0 °C for another 30 min. The resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2 (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc–hexanes) to provide **(–)-33** (1.6 mg, 40%) as a colorless oil.



(–)-34

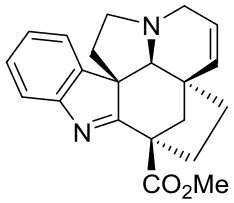
Compound (–)-34. To a cooled (–78 °C) solution of **(–)-33** (24.8 mg, 0.041 mmol) in THF (2 mL, 0.021 M) was treated with Bu_4NF (0.13 mL, 0.124 mmol). After stirring for 1 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 50% EtOAc–hexanes) to provide **(–)-34** (19.7 mg, 98%) as a colorless oil: $[\alpha]_D^{25}$ –28 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.29–7.39 (m, 5H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 5.83 (dd, *J* = 10.2, 4.8 Hz, 1H), 5.72 (dt, *J* = 10.2, 2.4 Hz, 1H), 5.38 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 3.54 (s, 3H), 3.46–3.52 (m, 3H), 3.09 (dt, *J* = 15.6, 1.8 Hz, 1H), 3.02 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.72 (s, 1H), 2.49 (ddd, *J* = 12.0, 8.4, 4.8 Hz, 1H), 2.34 (dd, *J* = 15.0, 1.8 Hz, 1H), 2.16 (td, *J* = 12.0, 6.6 Hz, 1H), 1.77 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.35 (dt, *J* = 13.8, 7.2 Hz, 1H), 1.25–1.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 152.2, 150.1, 140.2, 137.8, 135.6, 132.7, 128.53, 128.22, 128.0, 127.8, 125.6, 123.9, 121.0, 115.8, 111.7, 67.9, 67.7, 58.8, 52.7, 51.5, 51.4, 50.8, 43.0, 40.5, 36.7, 31.9; IR (film) υ_{max} 3391, 2924, 1716, 1458, 670 cm^{-1}; HRMS (ESI) *m/z* 487.2234 [$(M+H)^+$, $C_{29}H_{30}N_2O_5$ requires 487.2227].



(–)-35

Compound (–)-35. A cooled (–78 °C) solution of **(–)-34** (20 mg, 0.041 mmol) in THF (2 mL, 0.021 M) was treated with Et_3N (29 μL, 0.21 mmol) and methanesulfonyl chloride (6.4 μL, 0.082 mmol). After stirring for 1 h at the same temperature, sodium iodide (61.6 mg, 0.411 mmol) and acetone (2 mL) were added and the reaction mixture was then heated at 90 °C (bath temp.). After stirring for 12 h at the same temperature, the resulting mixture was quenched with addition of saturated aqueous $NaHCO_3$ and diluted

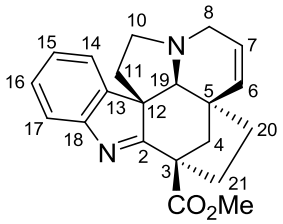
with H_2O and hexanes (10 mL). The layers were separated, and the aqueous layer was extracted with hexanes and washed with saturated aqueous NaCl. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 30% EtOAc–hexanes) to provide **(–)-35** (16.7 mg, 68%) as a colorless oil: $[\alpha]_D^{20}$ –15 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.32–7.39 (m, 5H), 7.24–7.27 (m, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.89 (ddd, *J* = 9.6, 4.8, 1.2 Hz, 1H), 5.61 (dt, *J* = 10.2, 2.4 Hz, 1H), 5.38 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 3.56 (s, 3H), 3.48 (ddd, *J* = 16.2, 4.8, 1.8 Hz, 1H), 3.07 (dt, *J* = 16.2, 1.8 Hz, 1H), 3.01 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.90–2.96 (m, 1H), 2.84–2.90 (m, 1H), 2.72 (d, *J* = 15.0 Hz, 1H), 2.68 (s, 1H), 2.50 (ddd, *J* = 11.4, 8.4, 4.8 Hz, 1H), 2.31 (dd, *J* = 15.0, 1.8 Hz, 1H), 2.15 (td, *J* = 12.0, 7.2 Hz, 1H), 1.77 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.65–1.72 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 152.2, 150.5, 140.2, 137.4, 135.6, 131.4, 128.5, 128.3, 128.1, 128.0, 126.7, 124.1, 120.7, 115.9, 111.1, 68.0, 66.5, 52.8, 51.5, 51.2, 50.8, 43.8, 42.9, 39.4, 31.7, –1.5; IR (film) υ_{max} 2923, 1716, 1458, 1259, 670 cm^{-1}; HRMS (ESI) *m/z* 597.1222 [$(M+H)^+$, $C_{29}H_{29}IN_2O_4$ requires 597.1245].



4, (–)-kopsifoline D

Compound 4. A solution of **(–)-34** (4.5 mg, 7.5 μmol) in CH_2Cl_2 (2 mL, 0.004M) was treated dropwise with dimethyl sulfide (100 μL, 0.81 mmol) and boron trifluoride diethyl etherate (100 μL, 1.36 mmol). After stirring for 12 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$, treated with Et_3N (3 drops), and diluted with EtOAc. After stirring for an additional 12 h at 25 °C, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 2.5% Et_3N in 50% EtOAc–hexanes) to provide (–)-kopsifoline D (**4**, 2.0 mg, 79%) as a light yellow oil identical in all respects with authentic material previously reported[S2]: $[\alpha]_D^{23}$ –69 (*c* 0.08, $CHCl_3$) vs $[\alpha]_D$ –27 (*c* 0.09, $CHCl_3$)[S2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 5.76 (dd, *J* = 10.2, 4.2 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 3.79 (s, 3H), 3.58 (d, *J* = 17.6 Hz, 1H), 3.41 (dd, *J* = 17.7, 4.4 Hz, 1H), 3.35 (q, *J* = 7.8 Hz, 1H), 3.25–3.32 (m, 1H), 2.77 (s, 1H), 2.63 (d, *J* = 11.7 Hz, 1H), 2.56–2.65 (m, 1H), 2.43 (td, *J* = 11.9, 8.2 Hz, 1H), 2.03–2.18 (m, 2H), 1.77 (d, *J* = 12.3 Hz, 1H), 1.69 (t, *J* = 13.1 Hz, 1H), 1.14–1.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.3, 172.4, 154.4,

147.2, 132.5, 127.5, 125.9, 125.3, 121.5, 120.3, 69.1, 62.7, 56.5, 52.6, 50.9, 46.9, 43.4, 42.3, 39.0, 35.0, 34.8; IR (film) υ_{max} 3381, 2920, 1735, 1457, 1239, 801, 670 cm^{-1}; HRMS (ESI) *m/z* 335.1743 $[(M+H)^+$, $C_{21}H_{22}N_2O_2$ requires 335.1754].



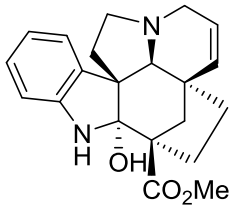
4, kopsifoline D

Table S1. Comparison of ^{1}H NMR data for **4** (Solvent: $CDCl_3$; δ in ppm, *J* in Hz)

carbon #	chemical shifts (δ)	
	Natural *Helv. Chim. Acta* **2004**, *87*, 991–998 (400 MHz)	Synthetic **4** (500 MHz)
4	1.78 (dd, *J* = 13, 2)	1.77 (d, *J* = 12.3 Hz)
	2.63 (br d, *J* = 13)	2.63 (d, *J* = 11.7 Hz)
6	5.64 (dt, *J* = 10, 2)	5.63 (d, *J* = 10.2 Hz)
7	5.77 (ddd, *J* = 10, 4, 2)	5.76 (dd, *J* = 10.2, 4.2 Hz)
8	3.42 (dd, *J* = 17, 4)	3.41 (dd, *J* = 17.7, 4.4 Hz)
	3.59 (br d, *J* = 17)	3.58 (d, *J* = 17.6 Hz)
10	3.31 (m)	3.25–3.32 (m)
	3.36 (td, *J* = 8, 6)	3.35 (q, *J* = 7.8 Hz)
11	2.14 (m)	2.03–2.18 (m)
	2.61 (m)	2.56–2.65 (m)
14	7.48 (br d, *J* = 8)	7.47 (d, *J* = 7.3 Hz)
15	7.30 (td, *J* = 8, 2)	7.29 (t, *J* = 7.6 Hz)
16	7.20 (td, *J* = 8, 2)	7.19 (t, *J* = 7.4 Hz)
17	7.57 (dd, *J* = 8, 2)	7.57 (d, *J* = 7.7 Hz)
19	2.78 (br s)	2.77 (s)
20	1.20 (m)	1.14–1.23 (m)
	1.69 (m)	1.69 (t, *J* = 13.1 Hz)
21	2.13 (dddd, *J* = 12, 9, 3, 2)	2.03–2.18 (m)
	2.43 (td, *J* = 12, 8)	2.43 (td, *J* = 11.9, 8.2 Hz)
MeOOC	3.79 (s)	3.79 (s)

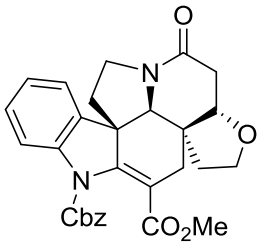
Table S2. Comparison of ^{13}C NMR data for **4** (Solvent: $CDCl_3$; δ in ppm)

carbon #	chemical shifts (δ)	
	Helv. Chim. Acta **2004**, *87*, 991–998 (100 MHz)	Synthetic **4** (150 MHz)
2	187.7	188.3
3	56.5	56.5
4	43.4	43.4
5	42.3	42.3
6	132.5	132.5
7	125.2	125.3
8	46.9	46.9
10	50.9	50.9
11	34.7	34.8
12	63.0	62.7
13	147.0	147.2
14	121.6	121.5
15	125.8	125.9
16	127.5	127.5
17	120.3	120.3
18	154.3	154.4
19	69.1	69.1
20	35.0	35.0
21	39.0	39.0
MeO	52.6	52.6
C=O	172.2	172.4



4a, (–)-kopsifoline D hydrate

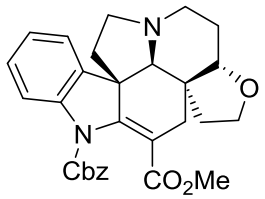
Compound 4a. Upon prolonged storage neat, a sample of kopsifoline D underwent hydration to provide a mixture of kopsifoline D (**4**) and the corresponding carbinol amine (**4a**). This carbinol amine could be also be prepared as detailed below. A solution of **4** (2.0 mg, 5.99 μmol) in THF (1 mL) was treated with H_2O (0.2 mL) at 25 °C. After stirring for 3 h at 25 °C, the resulting solution was diluted with H_2O and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 5% MeOH–CH_2Cl_2) to provide **4a** (2.0 mg, 95%) as a light yellow oil: $[\alpha]_D^{25}$ –27 (*c* 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 5.96 (br s, 1H), 5.74 (ddd, *J* = 10.0, 4.5, 1.6 Hz, 1H), 5.49 (d, *J* = 9.8 Hz, 1H), 3.75 (s, 3H), 3.56 (dd, *J* = 16.1, 4.8 Hz, 1H), 3.27 (t, *J* = 8.1 Hz, 1H), 3.05 (td, *J* = 12.1, 7.7 Hz, 1H), 2.85 (d, *J* = 16.2 Hz, 1H), 2.75 (br s, 1H), 2.50 (s, 1H), 2.41 (dt, *J* = 11.1, 7.3 Hz, 1H), 2.22 (d, *J* = 12.4 Hz, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.78–1.82 (m, 1H), 1.67–1.74 (m, 1H), 1.55 (td, *J* = 12.8, 6.1 Hz, 1H), 1.43 (dd, *J* = 12.7, 6.6 Hz, 1H), 1.20–1.32 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.6, 147.1, 137.9, 132.8, 127.9, 125.5, 122.3, 118.9, 107.5, 96.8, 75.7, 60.1, 55.5, 53.9, 53.1, 52.1, 45.0, 38.3, 35.2, 35.1, 29.6; HRMS (ESI) *m/z* 353.1861 [$(M+H)^+$, $C_{21}H_{24}N_2O_3$ requires 353.1860].



(–)-36

Compound (–)-36. A cooled (–5 °C) solution of (+)-**32** (13.2 mg, 0.021 mmol) in THF (3 mL, 0.007 M) was treated with Bu_4NF (0.11 mL, 1.0 M in THF, 0.107 mmol, 5 equiv). After stirring for 6 h at the same temperature, the resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The

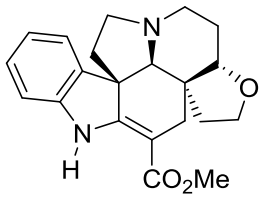
combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 70% EtOAc–hexanes) to provide **(–)-36** (7.5 mg, 70%) as a colorless oil: $[\alpha]_D^{25}$ –23.8 (*c* 1.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.32–7.42 (m, 5H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.39 (d, *J* = 12.2 Hz, 1H), 5.20 (d, *J* = 12.2 Hz, 1H), 3.98 (d, *J* = 1.8 Hz, 1H), 3.92–3.97 (m, 2H), 3.87 (ddd, *J* = 9.3, 7.3, 5.3 Hz, 1H), 3.77 (dt, *J* = 9.2, 7.1 Hz, 1H), 3.58 (s, 3H), 3.45 (ddd, *J* = 11.9, 9.9, 6.5 Hz, 1H), 2.85 (dd, *J* = 15.2, 6.1 Hz, 1H), 2.47–2.60 (m, 2H), 2.34 (d, *J* = 15.2 Hz, 1H), 2.13 (ddd, *J* = 12.8, 10.0, 7.6 Hz, 1H), 1.99 (ddd, *J* = 12.8, 6.5, 3.3 Hz, 1H), 1.65 (ddd, *J* = 12.6, 6.9, 5.3 Hz, 1H), 1.46 (dt, *J* = 13.7, 7.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 167.1, 152.0, 149.4, 140.5, 135.22, 135.15, 128.8, 128.6, 128.5, 128.3, 124.6, 121.1, 116.1, 112.6, 81.1, 68.5, 66.57, 66.53, 54.9, 51.7, 49.5, 43.1, 39.7, 38.1, 36.3, 31.6; IR (film) υ_{max} 2922, 2853, 1723, 1664, 1234, 734, 698 cm^{-1}; HRMS (ESI) *m/z* 501.2021 [$(M+H)^+$, $C_{29}H_{28}N_2O_6$ requires 501.2020].



(–)-37

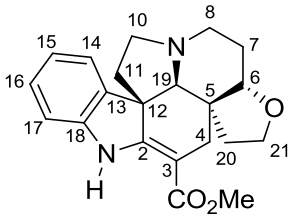
Compound (–)-37. A cooled (0 °C) solution of (–)-**36** (15.0 mg, 0.030 mmol) in THF (3 mL, 0.01 M) was treated dropwise with a solution of borane-tetrahydrofuran complex (0.36 mL, 1.0 M in THF, 0.36 mmol, 12 equiv). After stirring for 1.5 h at the same temperature, the resulting mixture was quenched with the addition of H_2O and the solution was treated with 10% aqueous HCl (3 mL). After stirring for 30 min at 0 °C, 1 N aqueous NaOH was then added to the mixture until pH ~13 and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 30% EtOAc–hexanes) to provide (–)-**37** (10.2 mg, 70%) as a colorless oil: $[\alpha]_D^{25}$ –30 (*c* 0.58, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.30–7.44 (m, 5H), 7.19–7.28 (m, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.40 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 3.87 (s, 1H), 3.84 (t, *J* = 8.8 Hz, 1H), 3.79 (q, *J* = 7.0 Hz, 1H), 3.55–3.65 (m, 2H), 3.57 (s, 3H), 3.47 (dd, *J* = 10.1, 6.6 Hz, 1H), 2.91 (ddd, *J* = 16.3, 10.3, 5.2 Hz, 1H), 2.81 (td, *J* = 13.0, 6.6 Hz, 1H), 2.75 (t, *J* = 12.9 Hz, 1H), 2.57 (d, *J* = 16.6 Hz, 1H), 2.51 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.38 (d, *J* = 16.4 Hz, 1H), 2.23–2.30 (m, 2H), 1.49 (dt, *J* = 12.6, 6.2 Hz, 1H), 1.34–1.44 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 152.2, 150.0, 140.1, 135.4, 134.7, 128.7, 128.5, 128.4, 128.3, 124.9, 122.5, 115.7, 113.2,

81.1, 73.1, 68.4, 65.5, 63.8, 55.4, 54.7, 51.7, 46.8, 41.0, 40.4, 36.0, 25.6; IR (film) υ_{max} 2923, 1716, 1459, 1176, 732, 697 cm^{-1}; HRMS (ESI) *m/z* 487.2235 [$(M+H)^+$, $C_{29}H_{30}N_2O_5$ requires 487.2227].



11, (–)-deoxoapodine

Compound 11. A solution of (–)-**37** (8.6 mg, 0.018 mmol) in CH_2Cl_2 (2 mL, 0.009 M) was treated dropwise with dimethyl sulfide (22 μL, 0.177 mmol) and boron trifluoride diethyl etherate (39 μL, 0.53 mmol). After stirring for 5 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2 (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (SiO_2, 30% EtOAc–hexanes) to afford natural (–)-deoxoapodine (**11**, 5.1 mg, 82%) as a colorless glass identical in all respects with authentic material: $[\alpha]_D^{25}$ –522 (*c* 0.17, $CHCl_3$) vs $[\alpha]_D$ –432 (*c* 0.76, $CHCl_3$)[S3] and $[\alpha]_D$ –593 ($CHCl_3$)[S4]; ^1H NMR (600 MHz, $CDCl_3$) δ 8.90 (br s), 7.24 (d, *J* = 7.4 Hz, 1H), 7.15 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.89 (dt, *J* = 7.4, 0.8 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 3.74–3.83 (m, 1H), 3.66–3.73 (m, 2H), 2.90–2.99 (m, 2H), 2.83 (s, 1H), 2.76 (d, *J* = 14.7 Hz, 1H), 2.70–2.76 (m, 1H), 2.67 (ddd, *J* = 11.1, 8.5, 4.6 Hz, 1H), 2.31 (dd, *J* = 14.6, 1.9 Hz, 1H), 2.03 (ddd, *J* = 11.4, 11.4, 6.3 Hz, 1H), 1.93–2.00 (m, 2H), 1.77 (dd, *J* = 11.5, 4.4 Hz, 1H), 1.45 (ddd, *J* = 12.8, 10.0, 7.4 Hz, 1H), 1.29 (ddd, *J* = 12.9, 8.3, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 167.3, 143.1, 137.9, 127.7, 121.3, 120.7, 109.4, 93.9, 80.0, 68.8, 65.0, 55.1, 51.5, 51.1, 46.6, 46.0, 45.2, 34.9, 27.6, 26.9; IR (film) υ_{max} 3361, 1716, 670 cm^{-1}; HRMS (ESI) *m/z* 353.1855 [$(M+H)^+$, $C_{21}H_{24}N_2O_3$ requires 353.1860].



11, (–)-deoxoapodine

Table S3. Comparison of ^{1}H NMR data for **11** ($CDCl_3$)

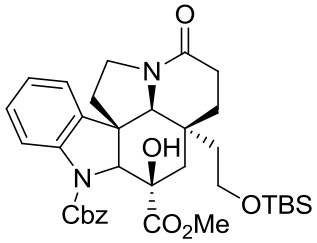
carbon #	chemical shifts (δ)	
	Overman's Synthetic [S5] (500 MHz)	Boger's Synthetic **11** (600 MHz)
Indole NH	8.90 (br s)	8.90 (br s)
ArH	7.24 (d, *J* = 7.3 Hz, 1H)	7.24 (d, *J* = 7.4 Hz, 1H)
ArH	7.15 (dt, *J* = 7.7, 1.1 Hz, 1H)	7.15 (dt, *J* = 7.6, 1.1 Hz, 1H)
ArH	6.89 (dt, *J* = 7.6, 0.9 Hz, 1H)	6.89 (dt, *J* = 7.4, 0.8 Hz, 1H)
ArH	6.81 (d, *J* = 7.7, 1H)	6.81 (d, *J* = 7.7, 1H)
MeOOC	3.78 (s, 3H)	3.78 (s, 3H)
6	3.72–3.81 (m, 1H)	3.74–3.83 (m, 1H)
21	3.65–3.73 (m, 2H)	3.66–3.73 (m, 2H)
8, 10	2.92–2.98 (m, 2H)	2.90–2.99 (m, 2H)
19	2.83 (s, 1H)	2.83 (s, 1H)
4	2.75 (d, *J* = 14.5 Hz, 1H)	2.76 (d, *J* = 14.7 Hz, 1H)
8, 10	2.65–2.77 (m, 2H)	2.70–2.76 (m, 1H)
		2.67 (ddd, *J* = 11.1, 8.5, 4.6 Hz, 1H)
4	2.30 (dd, *J* = 14.6, 1.7 Hz, 1H)	2.31 (dd, *J* = 14.6, 1.9 Hz, 1H)
11	2.03 (ddd, *J* = 11.3, 11.3, 6.3 Hz, 1H)	2.03 (ddd, *J* = 11.4, 11.4, 6.3 Hz, 1H)
7	1.93–2.00 (m, 2H)	1.93–2.00 (m, 2H)
11	1.76 (dd, *J* = 11.5, 4.5 Hz 1H)	1.77 (dd, *J* = 11.5, 4.4 Hz, 1H)
20	1.45 (ddd, *J* = 12.8, 10.0, 7.4 Hz, 1H)	1.45 (ddd, *J* = 12.8, 10.0, 7.4 Hz, 1H)
20	1.29 (ddd, *J* = 12.8, 8.3, 4.6 Hz, 1H)	1.29 (ddd, *J* = 12.9, 8.3, 4.6 Hz, 1H)

Table S4. Comparison of ^{13}C NMR data for **11** ($CDCl_3$)

chemical shifts (δ)	
Overman's Synthetic [S5] (125 MHz)	Boger's Synthetic (150 MHz)
168.8	168.8
167.3	167.3
143.1	143.1
137.9	137.9
127.7	127.7
121.3	121.3
120.7	120.7
109.3	109.4
93.9	93.9
80.0	80.0
68.8	68.8
65.0	65.0
55.1	55.1
51.5	51.5
51.1	51.1
46.6	46.6
46.0	46.0
45.2	45.2
34.9	34.9
27.6	27.6
26.9	26.9

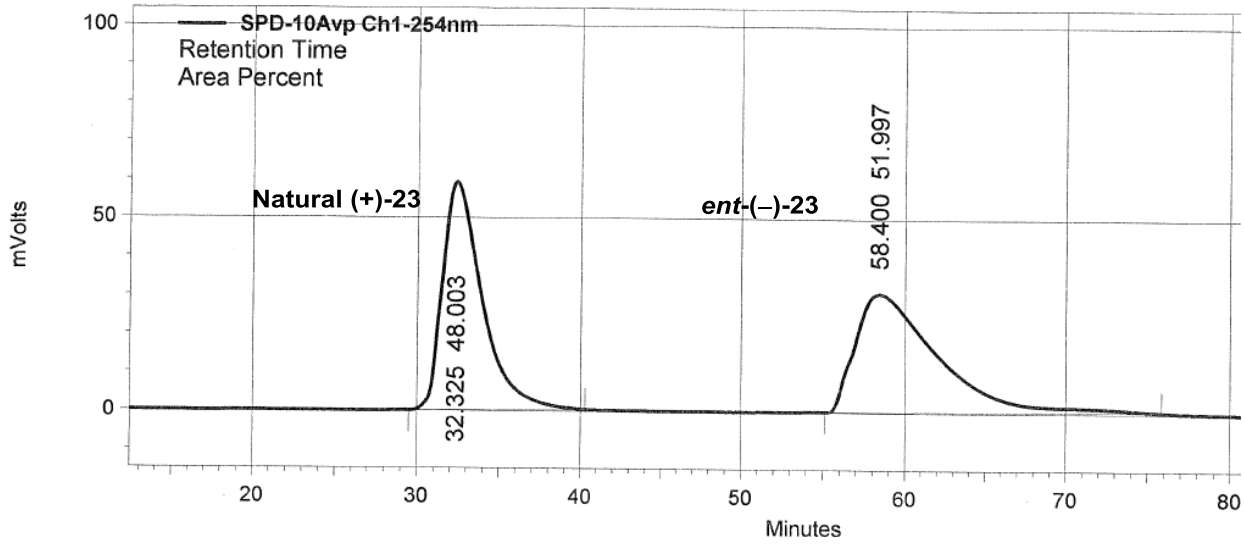
Determination of the absolute configuration of (–)-kopsifoline D (4) and (–)-deoxoapodine (11)

The unambiguous assignment of the absolute configuration of (–)-kopsifoline D (**4**) and (–)-deoxoapodine (**11**) was accomplished with a single crystal X-ray structure determination conducted on the natural enantiomer of the primary alcohol derived from **23**, which was carried forward and correlated with (+)-**32**.

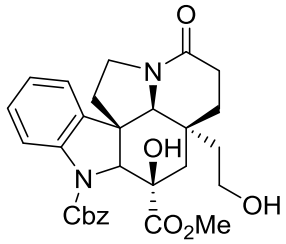


23

The enantiomers of **23** were separated (α = 1.8) on a semipreparative ChiralCel OD column (2 × 25 cm, 20% *i*-PrOH–hexanes, 7 mL/min flow rate) providing natural (+)-**23** (t_R: 32.3 min) and *ent*-(–)-**23** (t_R: 58.4 min). For natural enantiomer (+)-**23**: $[\alpha]_D^{20}$ +32 (*c* 1.0, $CHCl_3$), unnatural enantiomer (–)-**23**: $[\alpha]_D^{20}$ –32 (*c* 1.0, $CHCl_3$).

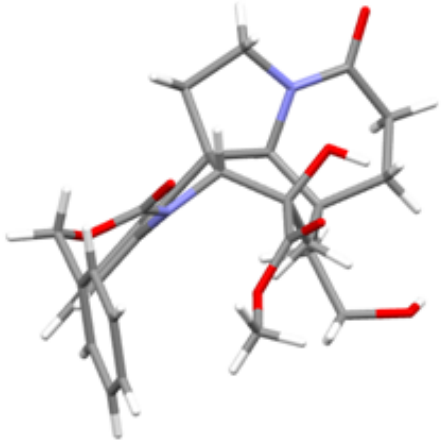


The structure and absolute configuration of natural enantiomer (+)-**23** were unambiguously established in an X-ray crystallographic assignment of the corresponding primary alcohol (CCDC 977767) conducted with white crystals obtained from MeOH.

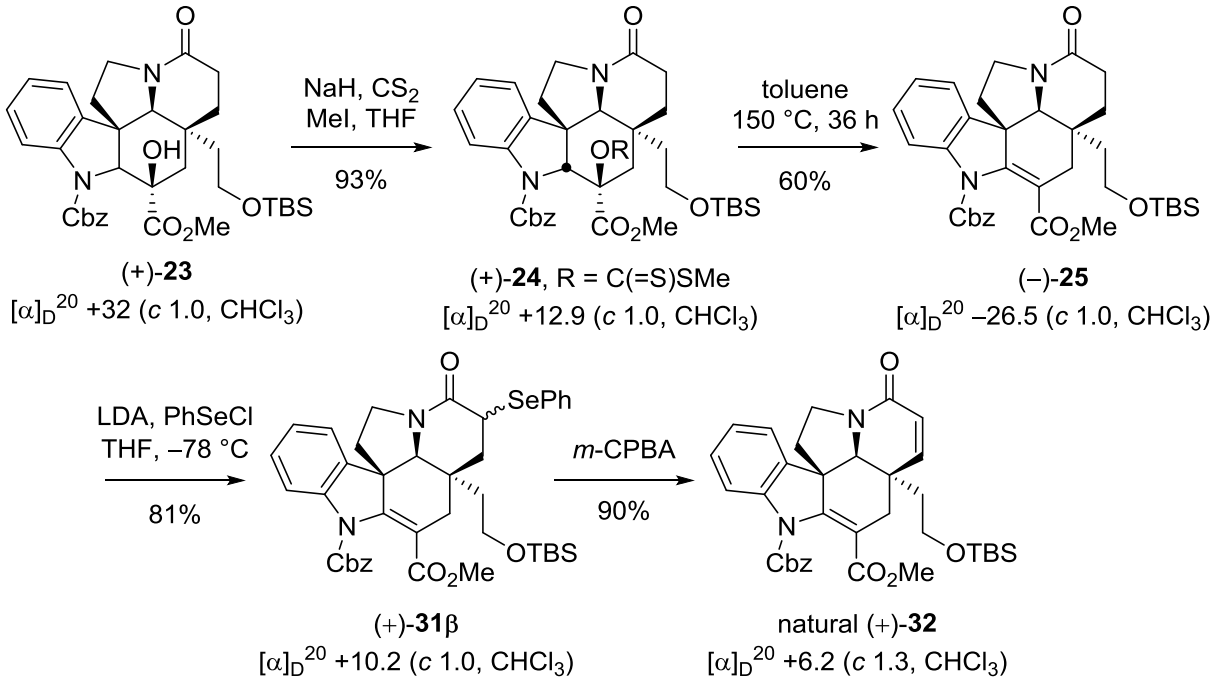


(+)-23-A

≡



Compound (+)-23A. A cooled (0 °C) solution of (+)-**23** (38.0 mg, 0.060 mmol) in THF (5 mL, 0.012 M) was treated with Bu_4NF (0.18 mL, 1.0 M in THF, 0.18 mmol, 3 equiv). After stirring for 2 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 10% MeOH–EtOAc) providing (+)-**23A** (29.0 mg, 93%) as a white solid: $[\alpha]_D^{20}$ +18.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 7.52 (br s, 1H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.36–7.42 (m, 3H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 5.78 (s, 1H), 5.32 (d, *J* = 12.6 Hz, 1H), 5.06 (br s, 1H), 4.34 (br s, 1H), 4.17 (s, 1H), 4.06 (s, 1H), 3.59–3.66 (m, 1H), 3.47 (s, 3H), 3.30–3.44 (m, 1H), 3.22 (td, *J* = 9.8, 5.5 Hz, 1H), 2.96–3.04 (m, 1H), 2.15 (td, *J* = 14.3, 4.1 Hz, 1H), 1.91–2.08 (m, 3H), 1.64–1.71 (m, 1H), 1.57–1.64 (m, 1H), 1.48–1.54 (m, 1H), 1.48 (d, *J* = 15.2 Hz, 1H), 1.35 (d, *J* = 14.7 Hz, 1H), 1.31 (q, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 174.1, 169.5, 153.1, 141.2, 136.1, 133.8, 128.5, 128.4, 128.1, 127.8, 123.9, 123.2, 115.2, 75.1, 69.1, 67.0, 63.6, 56.4, 52.4, 52.1, 51.6, 44.7, 42.6, 33.4, 30.7, 30.6, 24.9, 19.5, 13.6; IR (film) υ_{max} 3336, 2925, 1702, 1630, 1485, 1399, 1261, 748, 697 cm^{-1}; HRMS (ESI) *m/z* 521.2282 $[(M+H)^+$, $C_{29}H_{32}N_2O_7$ requires 521.2282].



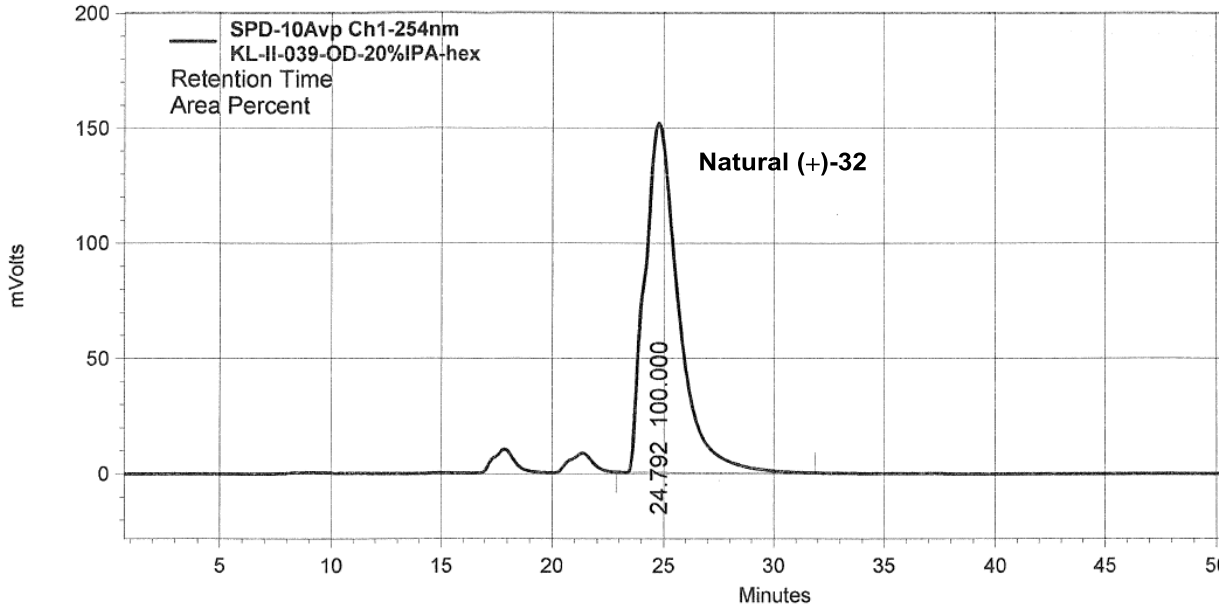
(+)-**23**
$[\alpha]_D^{20}$ +32 (*c* 1.0, $CHCl_3$)

(+)-**24**, R = C(=S)SMe
$[\alpha]_D^{20}$ +12.9 (*c* 1.0, $CHCl_3$)

(–)-**25**
$[\alpha]_D^{20}$ –26.5 (*c* 1.0, $CHCl_3$)

(+)-**31**β
$[\alpha]_D^{20}$ +10.2 (*c* 1.0, $CHCl_3$)

natural (+)-**32**
$[\alpha]_D^{20}$ +6.2 (*c* 1.3, $CHCl_3$)



The X-ray crystallographic assignment of the absolute configuration of the intermediate (+)-**23** in route to (–)-kopsifoline D (**4**) and (–)-deoxoapodine (**11**), and its correlation with (+)-**32** unambiguously confirm the absolute stereochemistry for the natural products. ChiralCel OD column (2 × 25 cm, 20% *i*-PrOH–hexanes, 7 mL/min flow rate) for natural (+)-**32** (t_R: 24.8 min)

References

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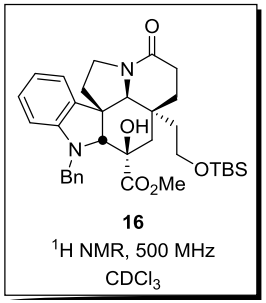
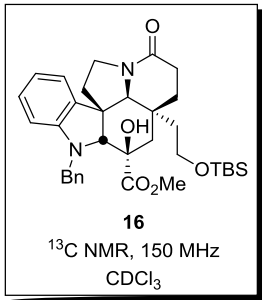


16

^{1}H NMR, 500 MHz

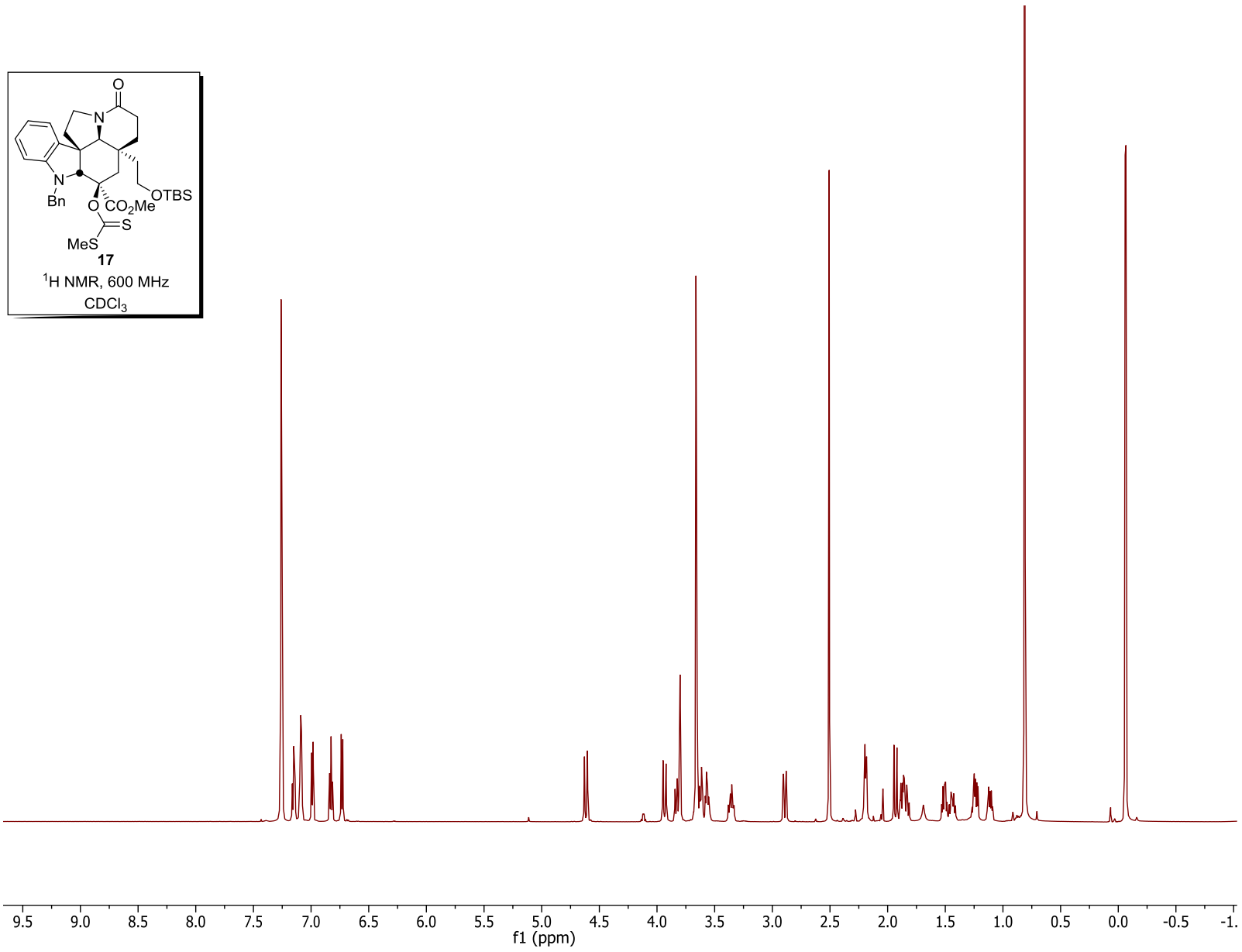
$CDCl_3$

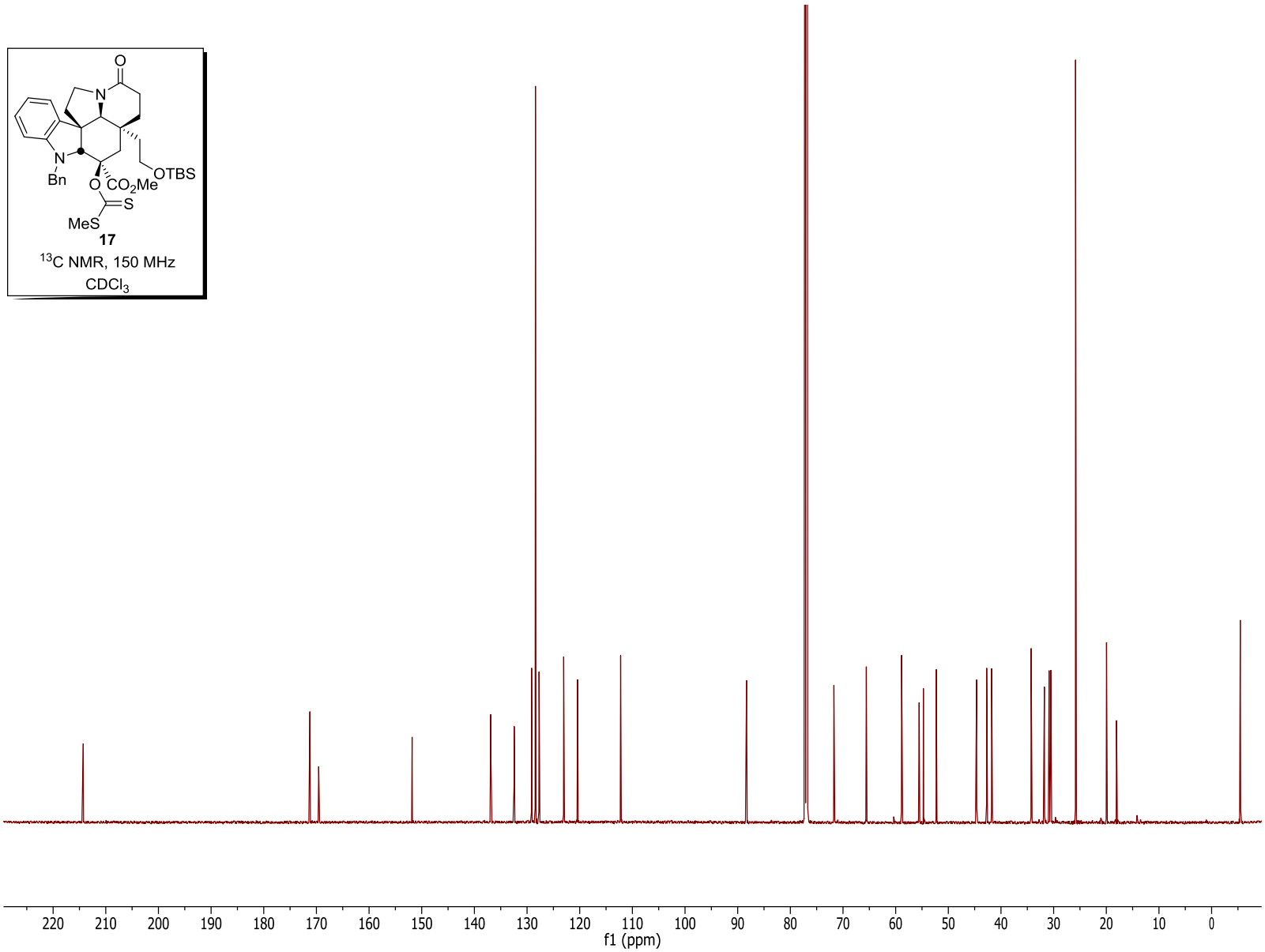


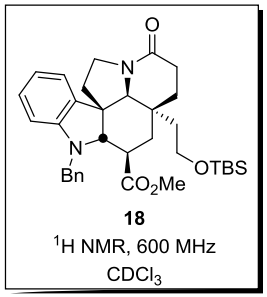
16

^{13}C NMR, 150 MHz

$CDCl_3$


O
N
N
Bn
O
CO2Me
OTBS
S
MeS
17
1H NMR, 600 MHz
CDCl3
9.5
9.0
8.5
8.0
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
-0.5
-1.
f1 (ppm)

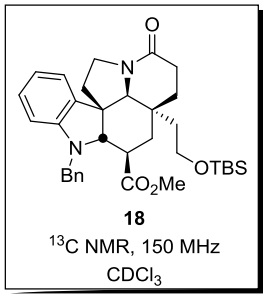

O
N
N
Bn
O
CO2Me
OTBS
O
S
MeS
17
13C NMR, 150 MHz
CDCl3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



18

^{1}H NMR, 600 MHz

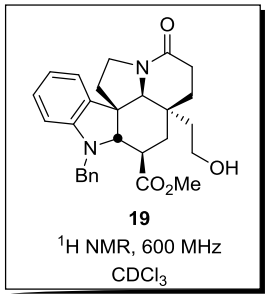
$CDCl_3$



18

^{13}C NMR, 150 MHz

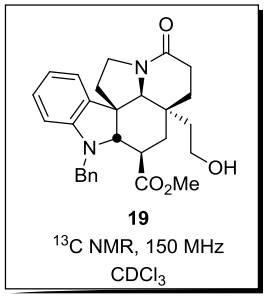
$CDCl_3$



19

^{1}H NMR, 600 MHz

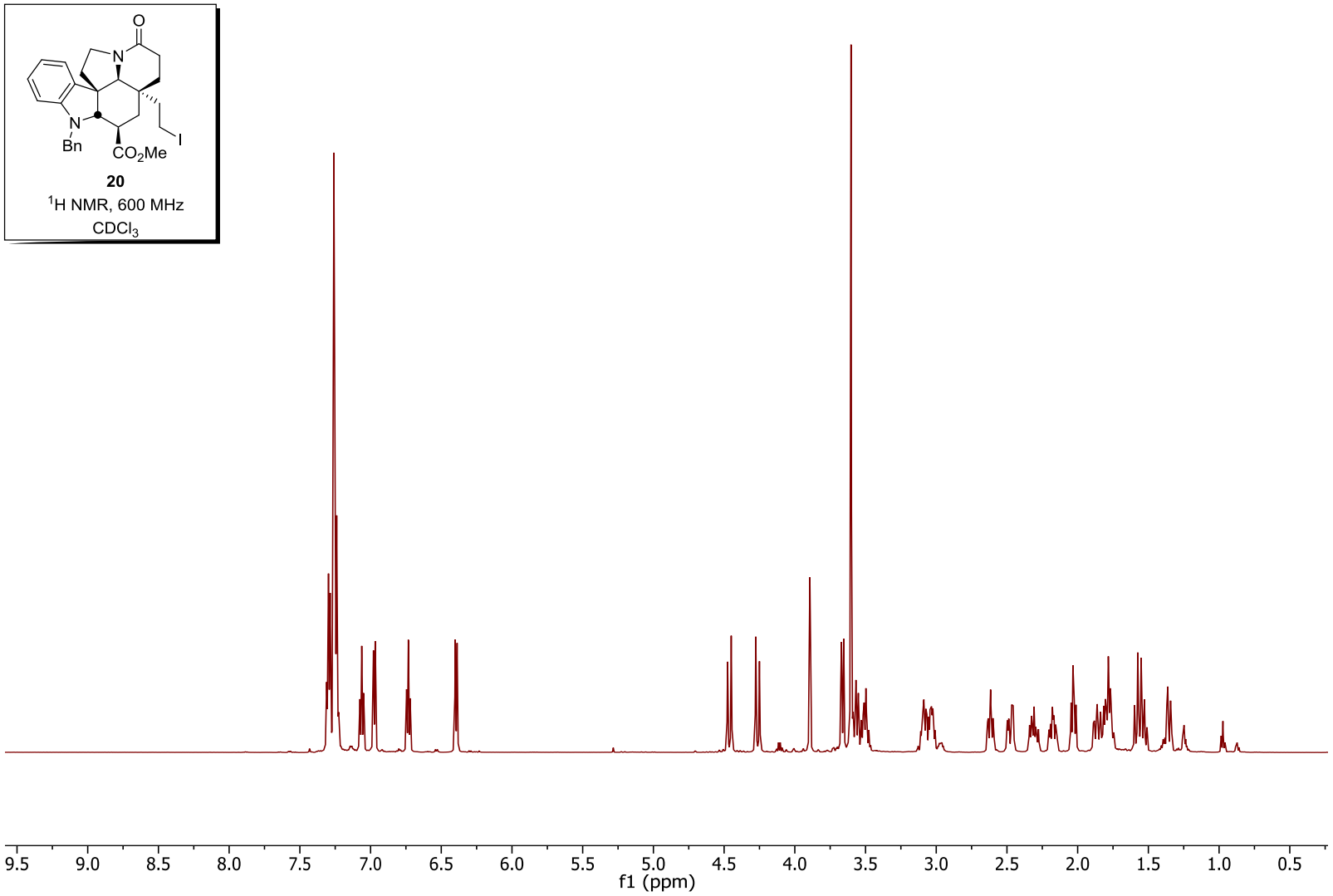
$CDCl_3$

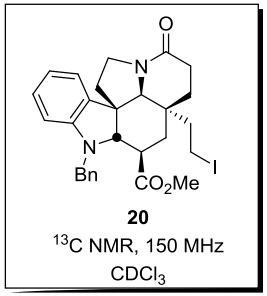


19

^{13}C NMR, 150 MHz

$CDCl_3$

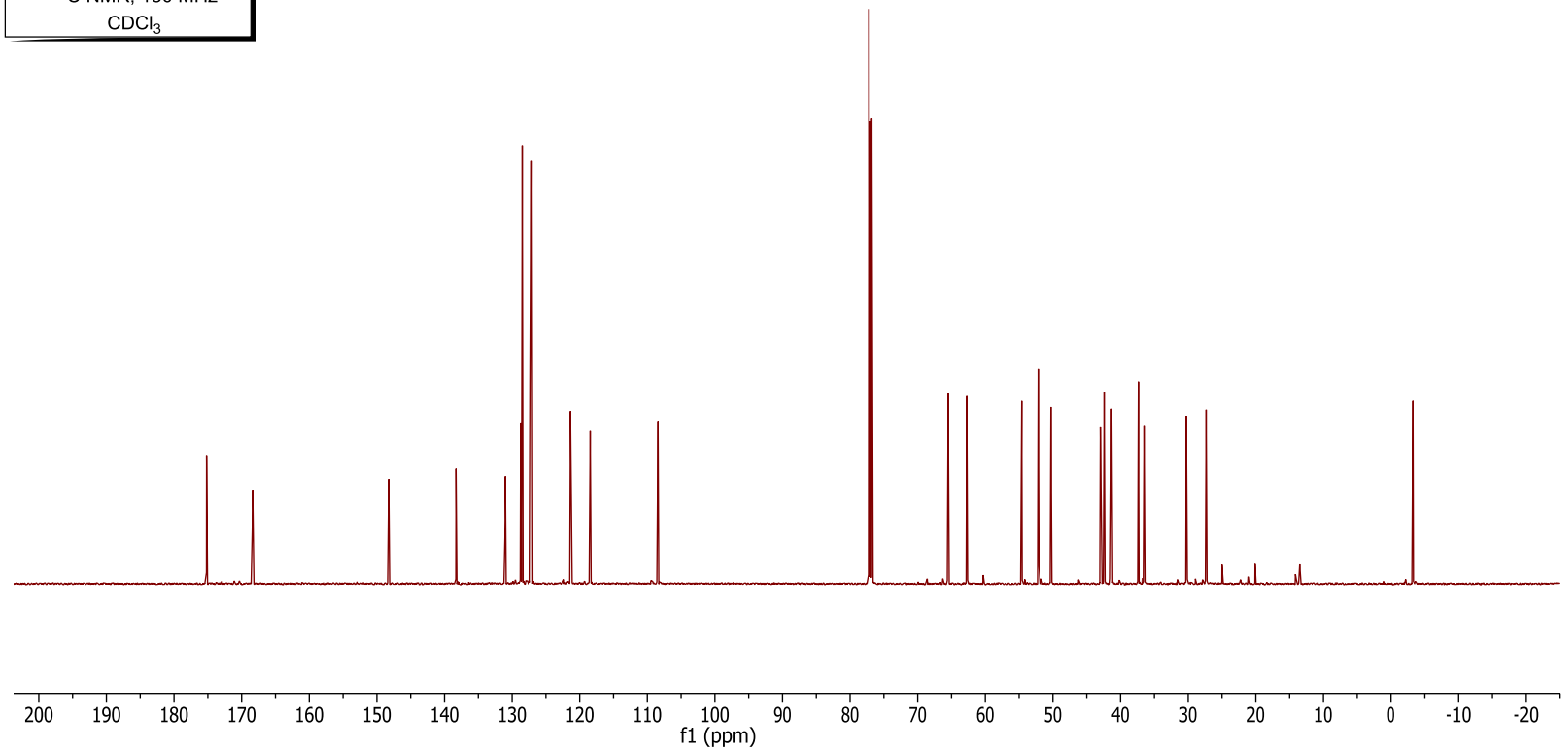

O
N
N
Bn
CO2Me
I
20
1H NMR, 600 MHz
CDCl3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

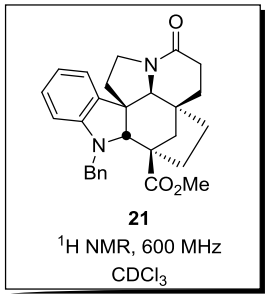


20

^{13}C NMR, 150 MHz

$CDCl_3$

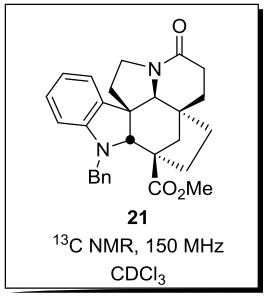




21

^{1}H NMR, 600 MHz

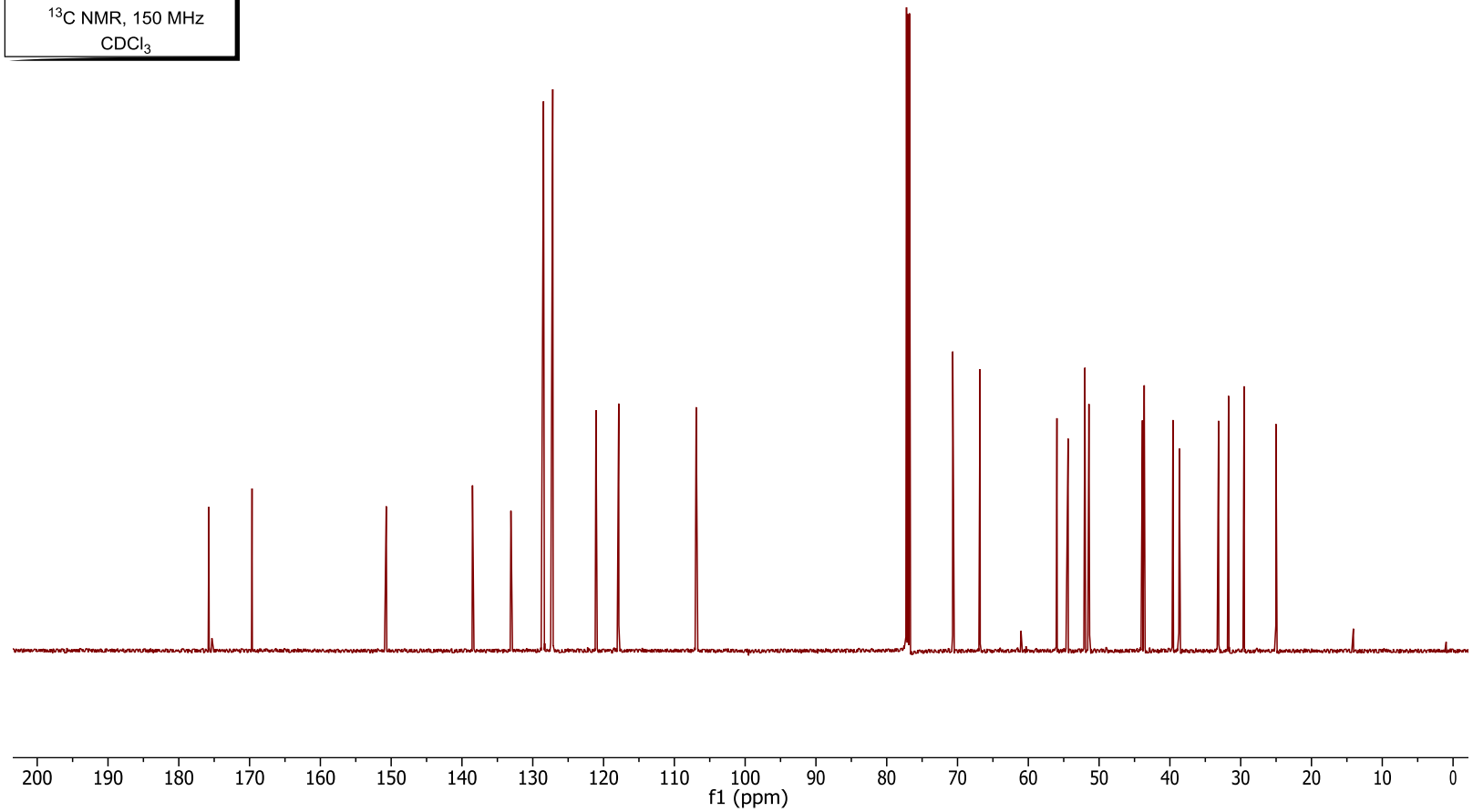
$CDCl_3$

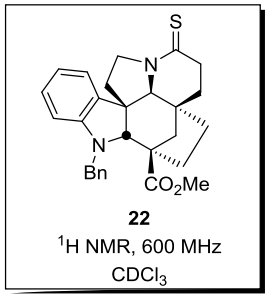


21

^{13}C NMR, 150 MHz

$CDCl_3$

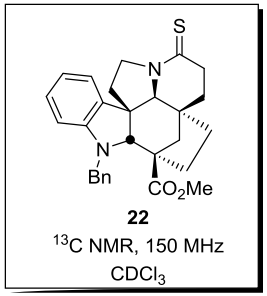




22

^{1}H NMR, 600 MHz

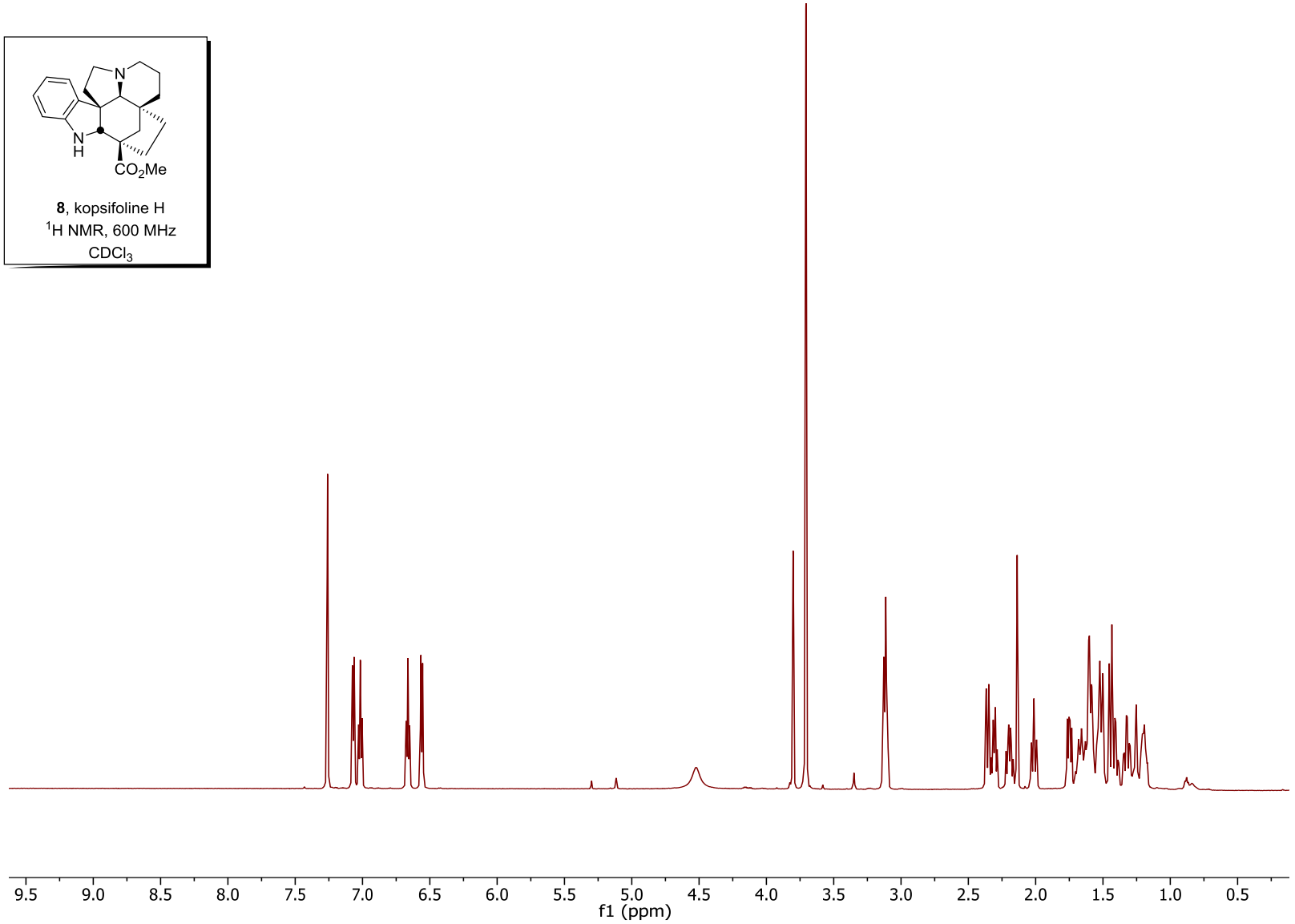
$CDCl_3$

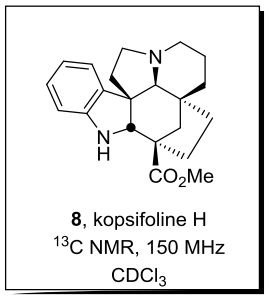


22

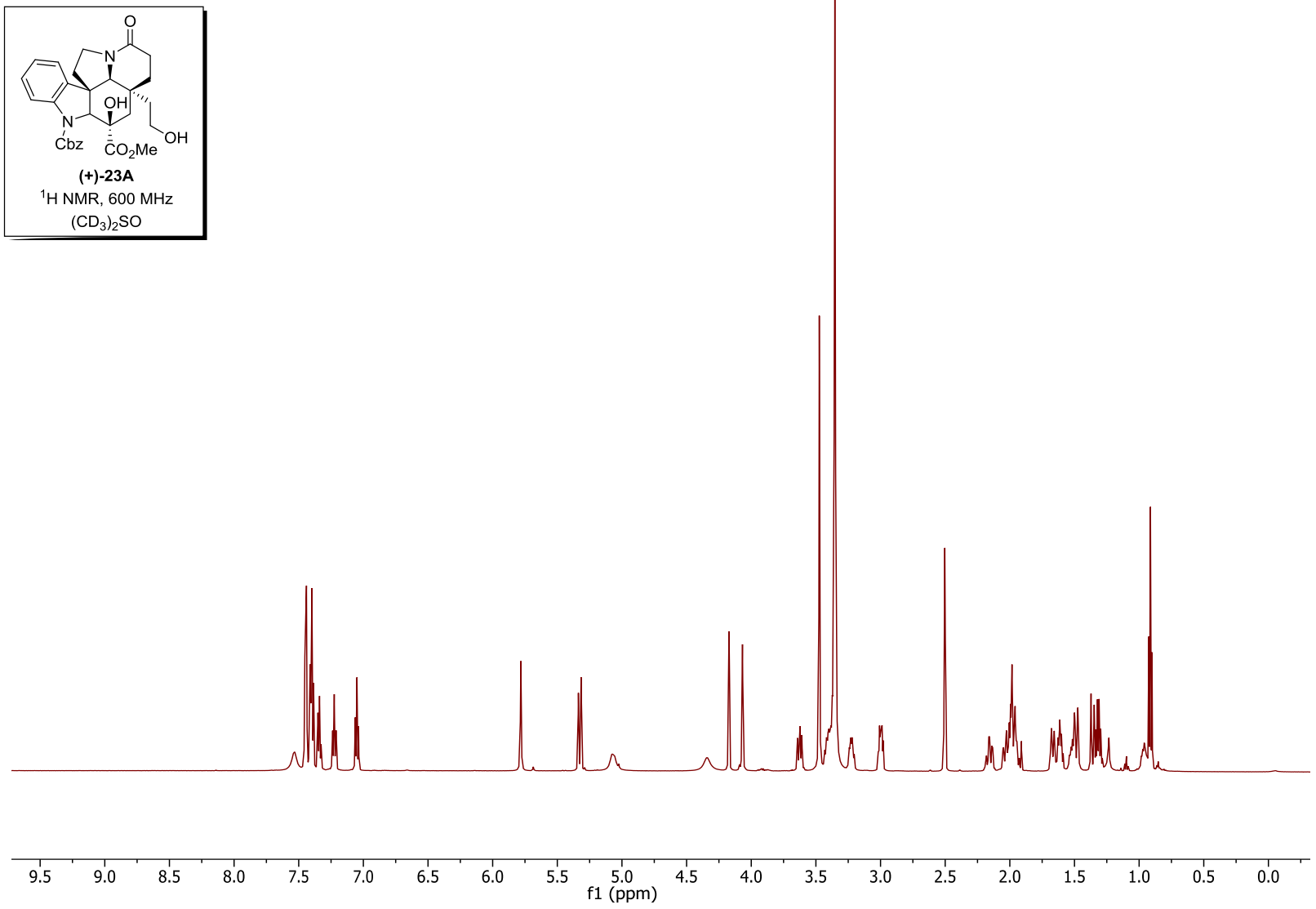
^{13}C NMR, 150 MHz

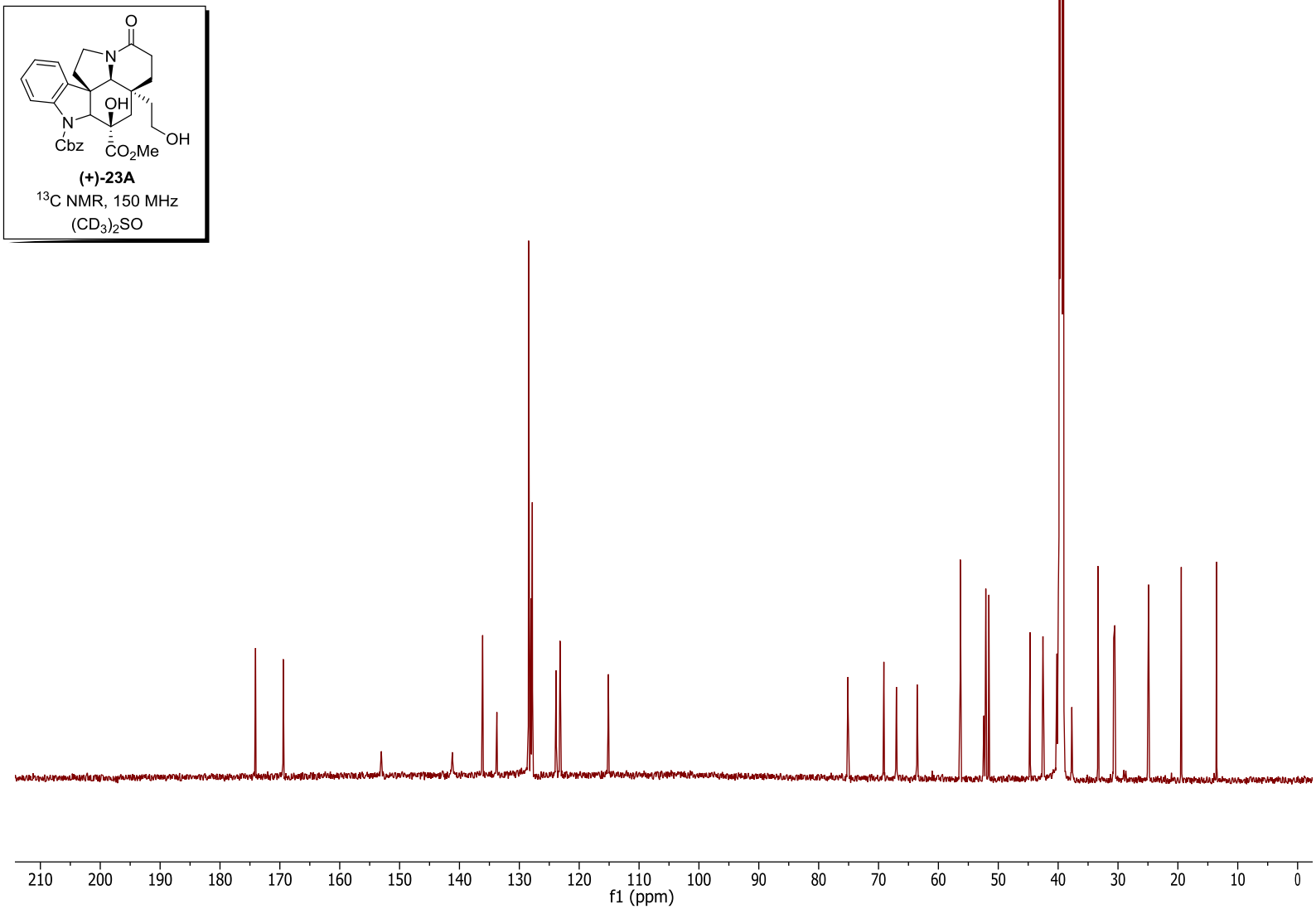
$CDCl_3$

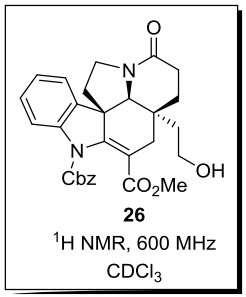

N
N
H
CO2Me
8, kopsifoline H
1H NMR, 600 MHz
CDCl3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



8, kopsifoline H
^{13}C NMR, 150 MHz
$CDCl_3$


O
N
OH
N
Cbz
CO2Me
OH
(+)-23A
1H NMR, 600 MHz
(CD3)2SO
9.5
9.0
8.5
8.0
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
f1 (ppm)

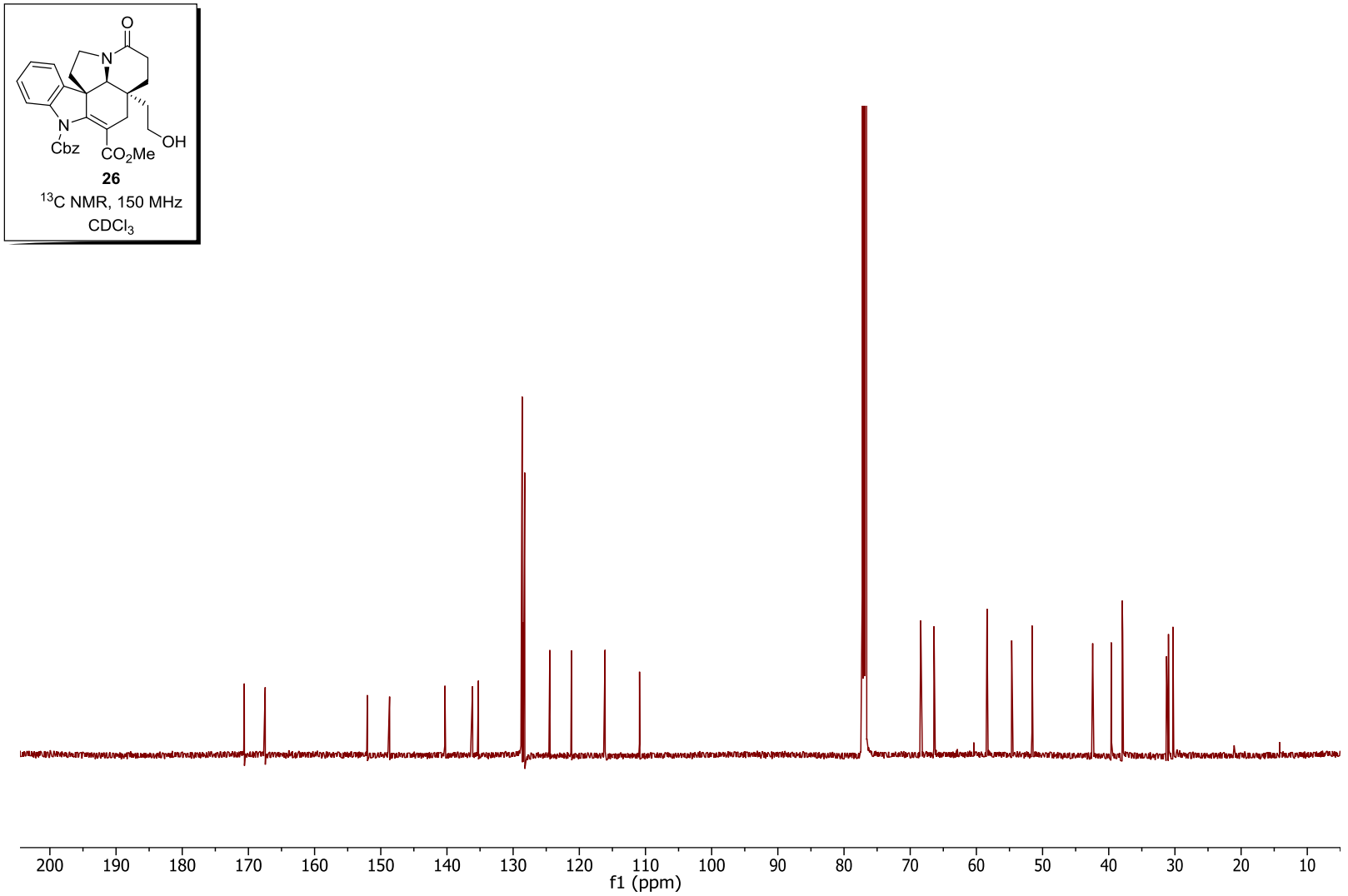

O
N
OH
N
Cbz
CO2Me
OH
(+)-23A
13C NMR, 150 MHz
(CD3)2SO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

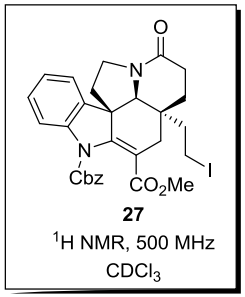


26

^{1}H NMR, 600 MHz

$CDCl_3$

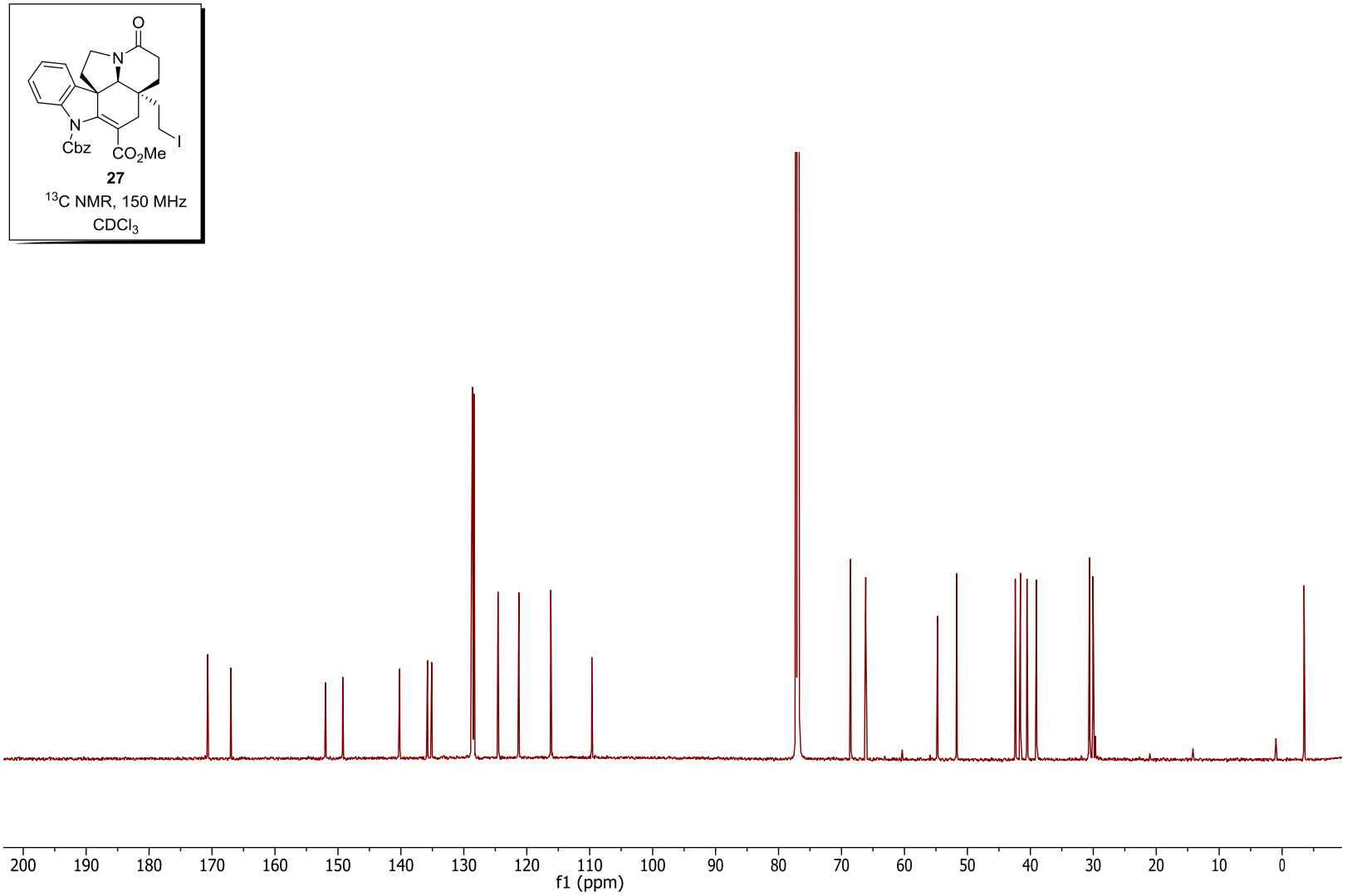

O
N
N
Cbz
CO2Me
OH
26
13C NMR, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

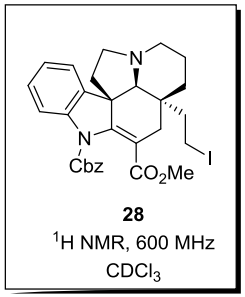


27

^{1}H NMR, 500 MHz

$CDCl_3$

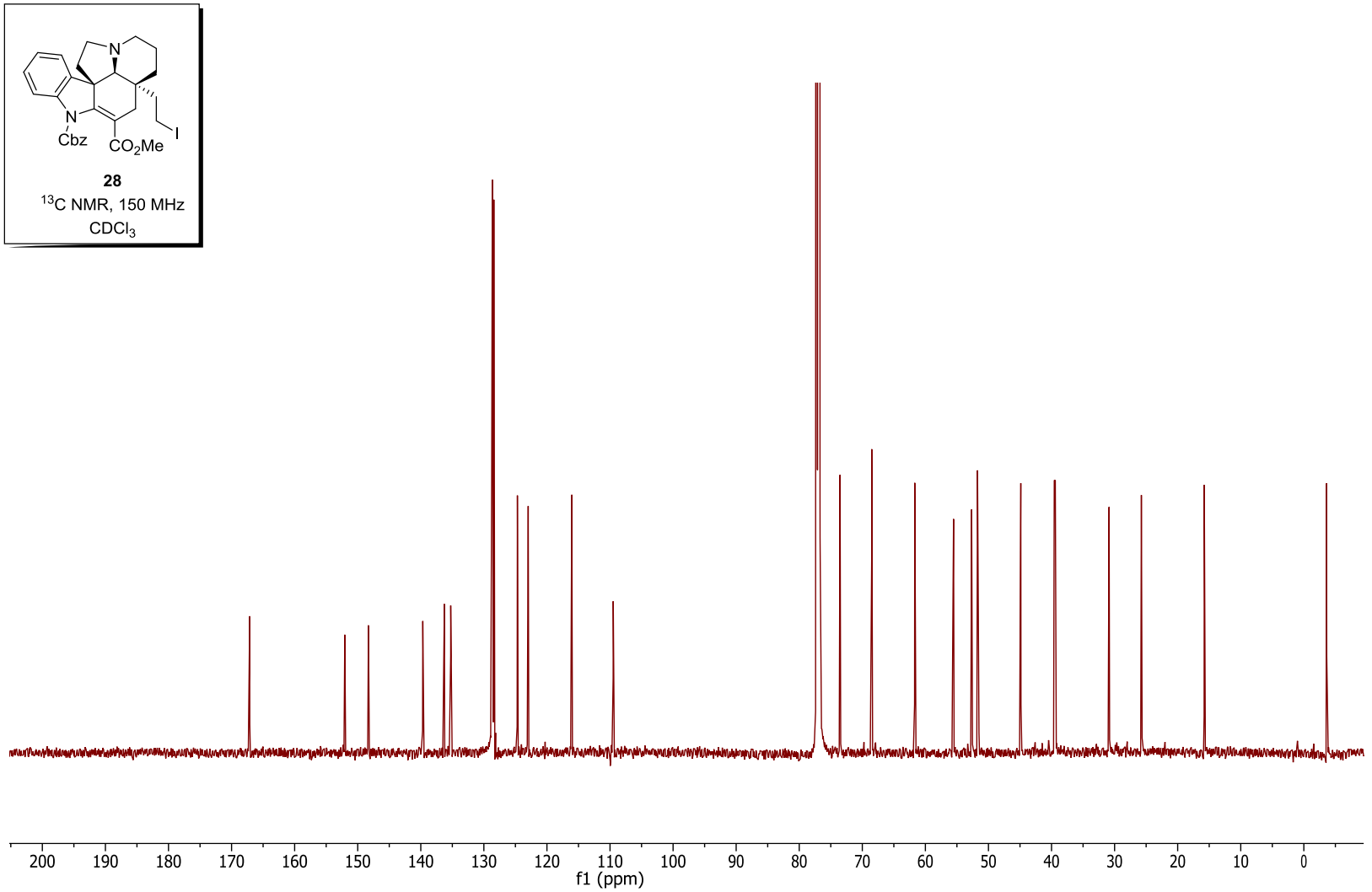

O
N
N
Cbz
CO2Me
I
27
13C NMR, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

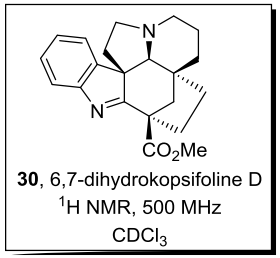


28

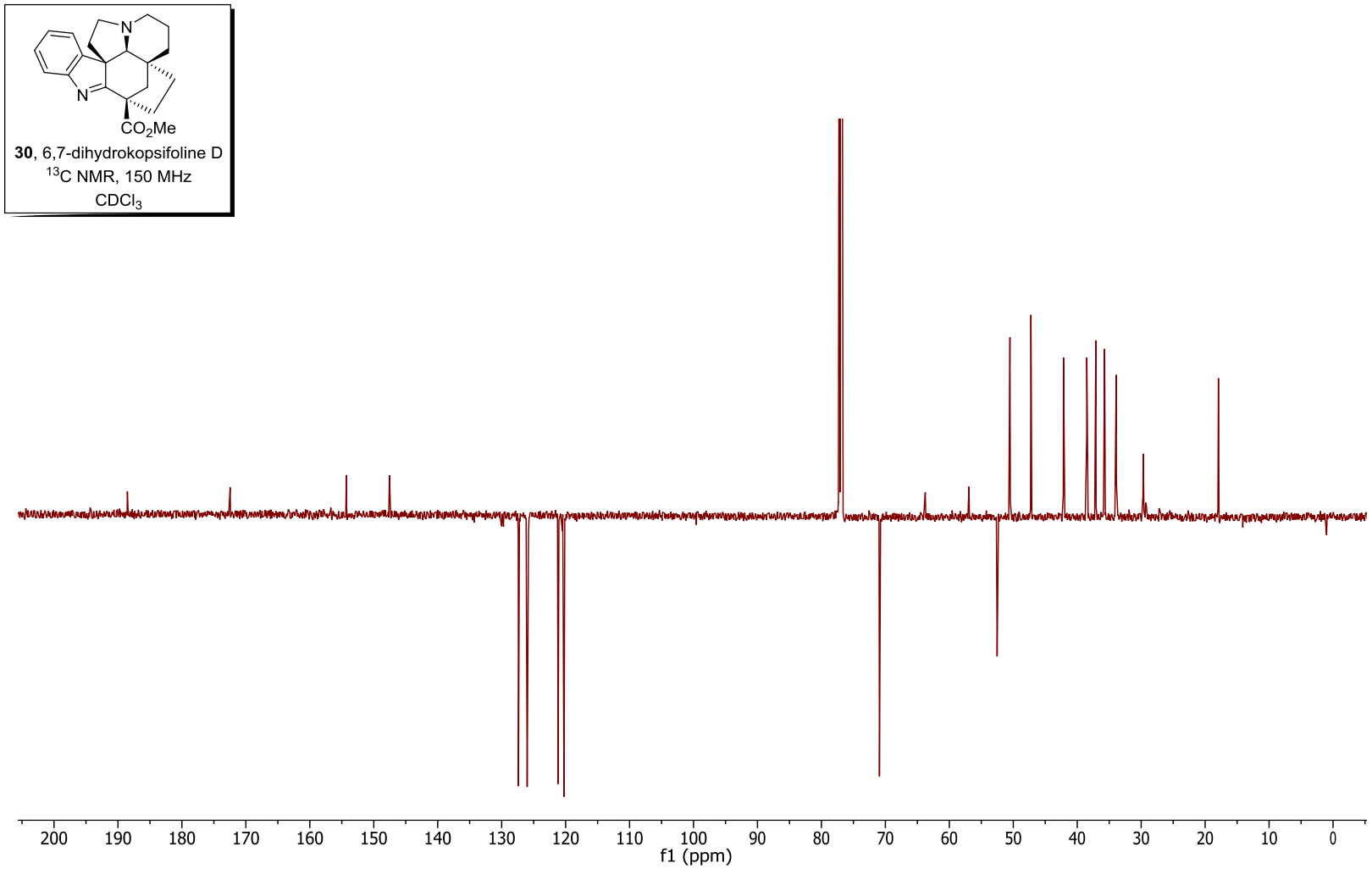
^{1}H NMR, 600 MHz

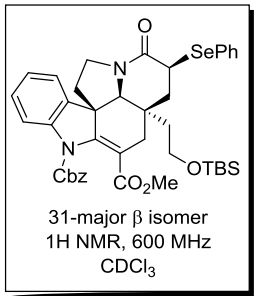
$CDCl_3$


N
N
Cbz
CO2Me
I
28
13C NMR, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

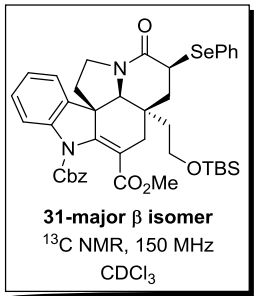


30, 6,7-dihydrokopsifoline D
^{1}H NMR, 500 MHz
$CDCl_3$

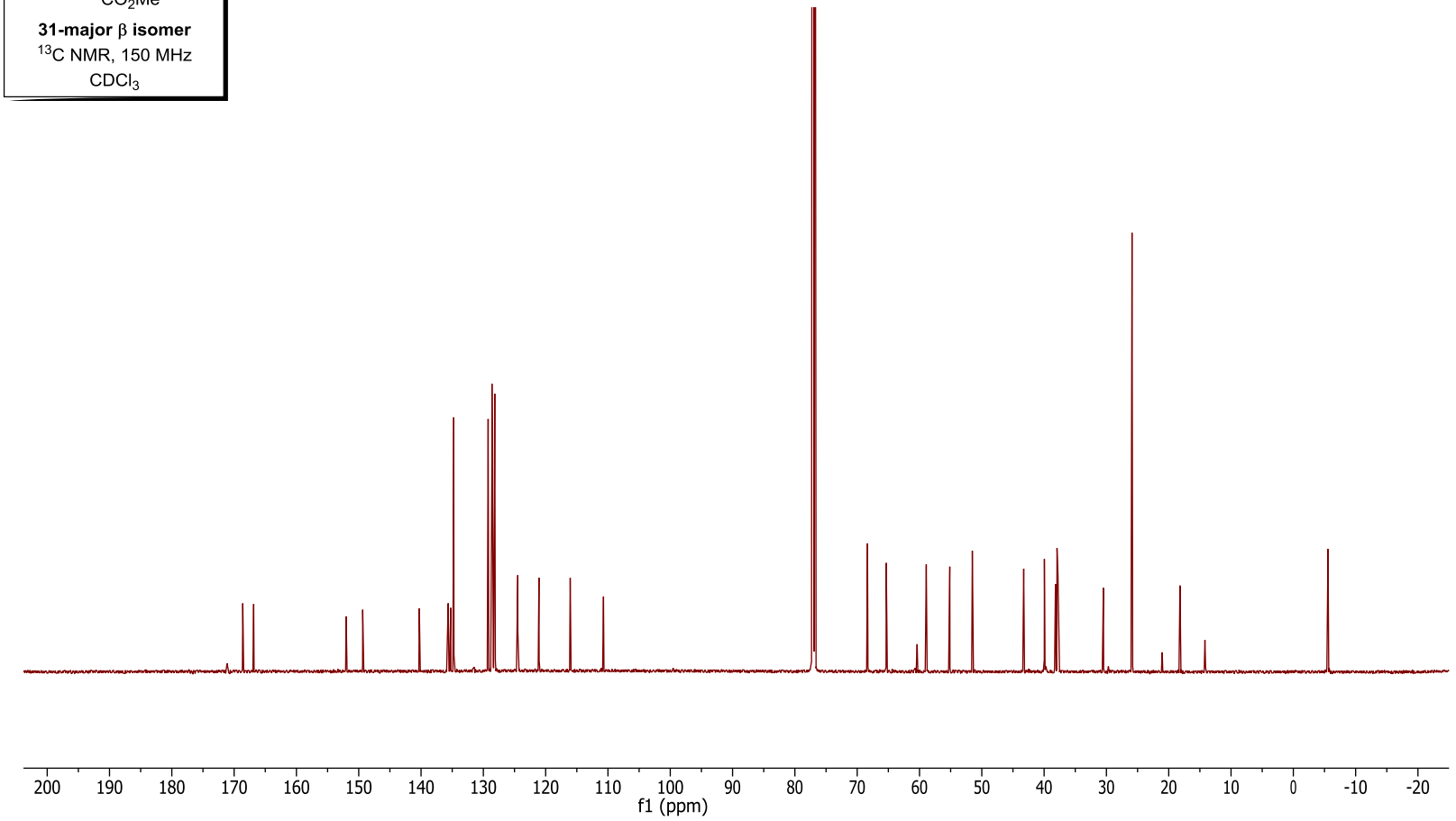

N
N
CO2Me
30, 6,7-dihydrokopsifoline D
13C NMR, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

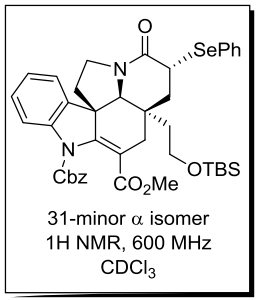


31-major β isomer
1H NMR, 600 MHz
$CDCl_3$

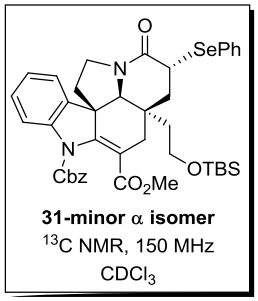


31-major β isomer
^{13}C NMR, 150 MHz
$CDCl_3$

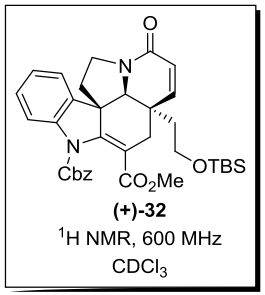




31-minor α isomer
1H NMR, 600 MHz
$CDCl_3$



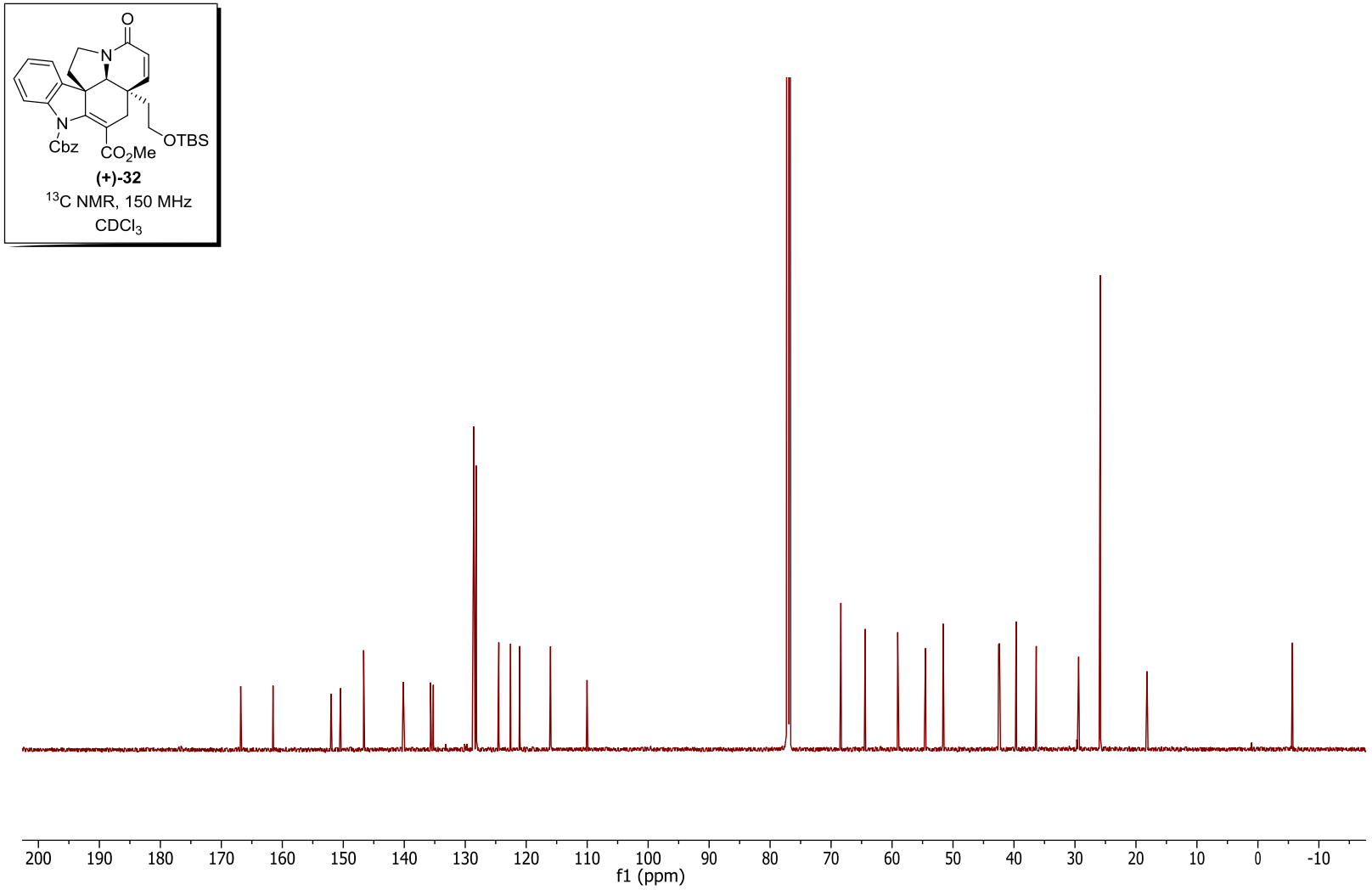
31-minor α isomer
^{13}C NMR, 150 MHz
$CDCl_3$

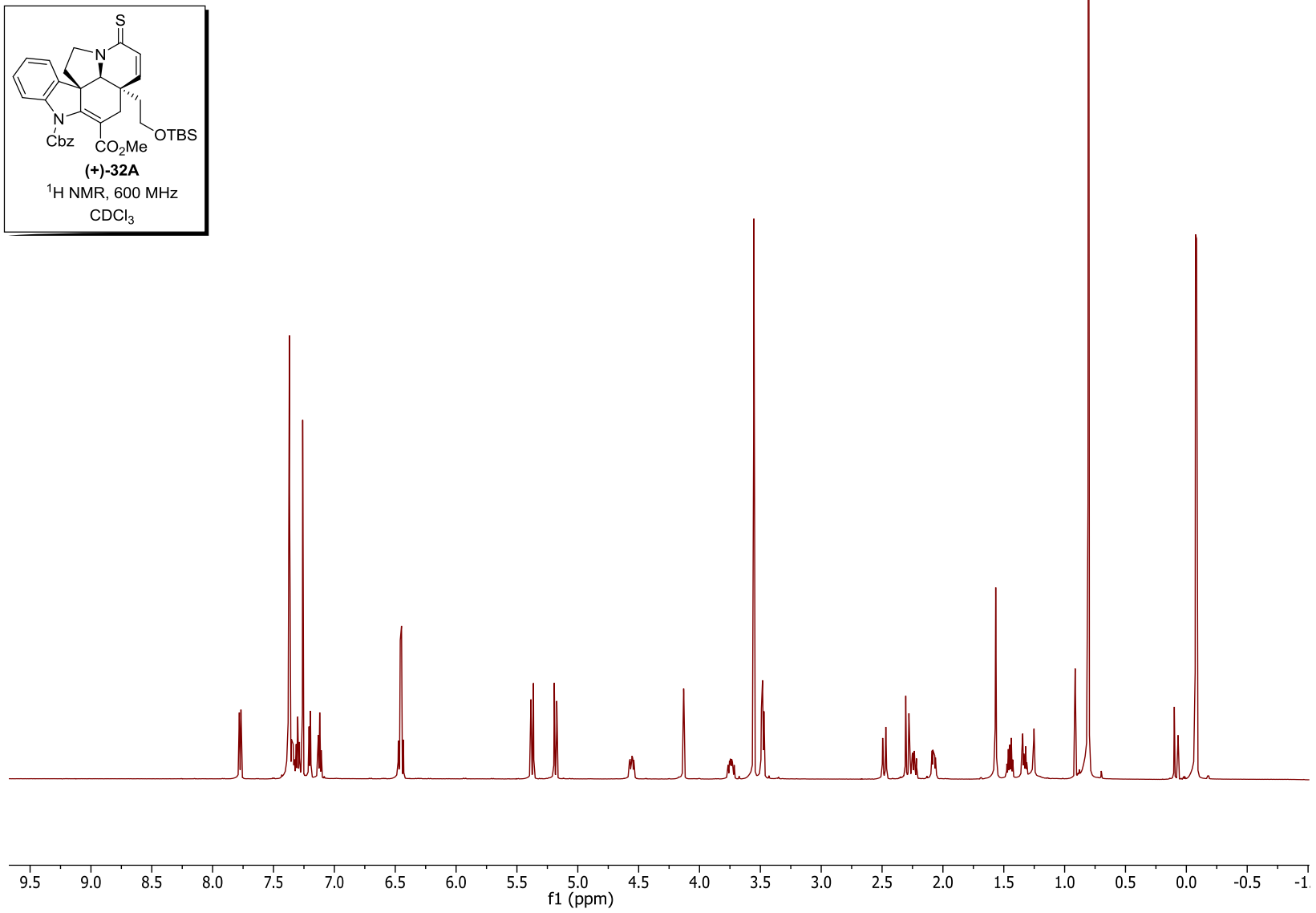


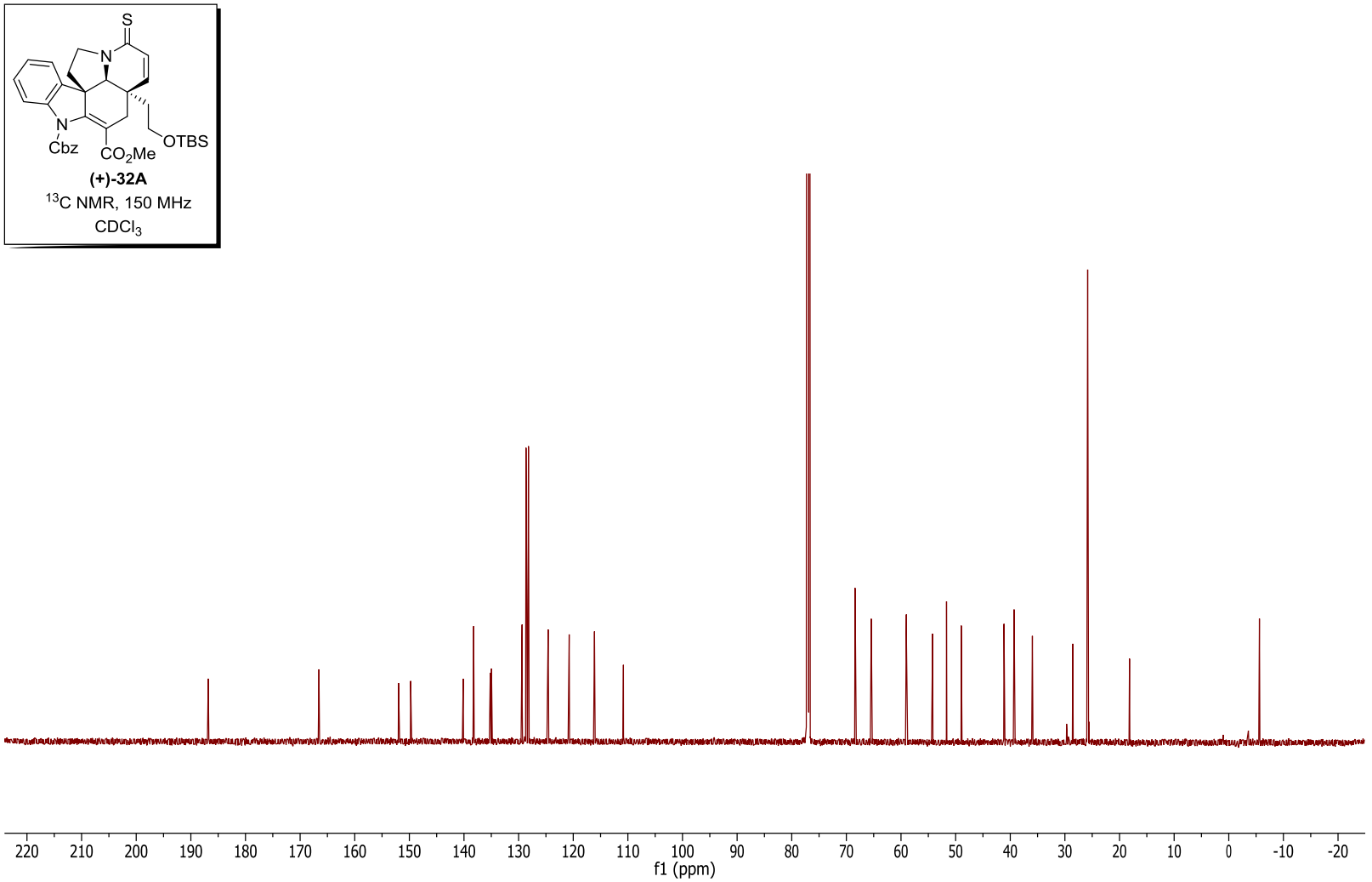
(+)-32

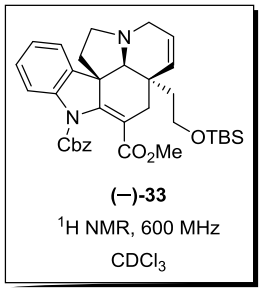
^{1}H NMR, 600 MHz

$CDCl_3$


O
N
N
Cbz
CO2Me
OTBS
(+)-32
13C NMR, 150 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


S
N
N
Cbz
CO2Me
OTBS
(+)-32A
1H NMR, 600 MHz
CDCl3
9.5
9.0
8.5
8.0
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
-0.5
f1 (ppm)

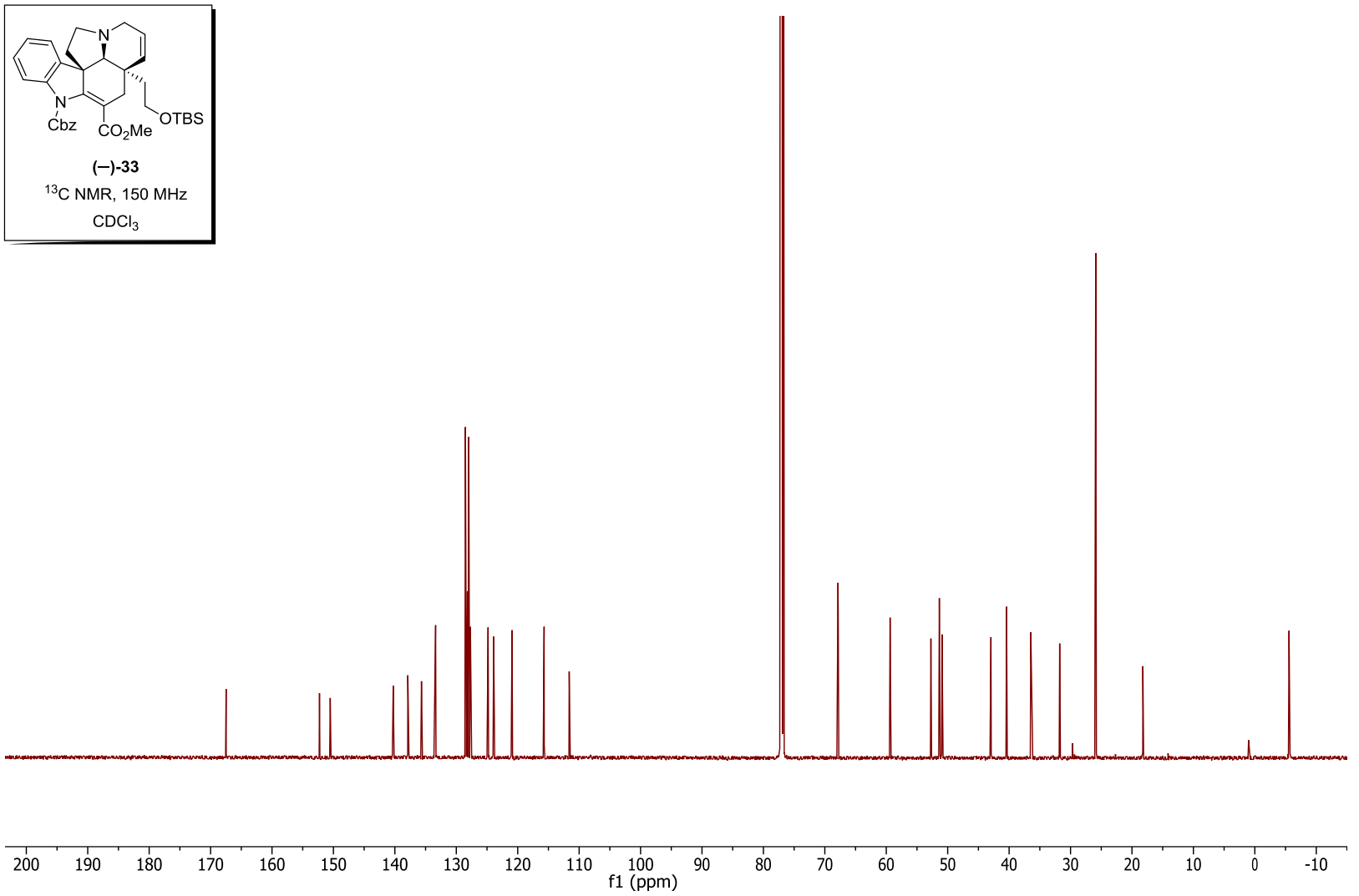

S
N
N
Cbz
CO2Me
OTBS
(+)-32A
13C NMR, 150 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

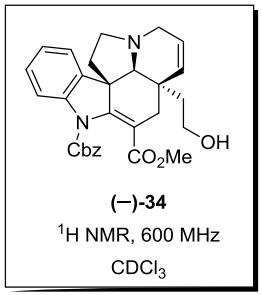


(−)-33

^{1}H NMR, 600 MHz

$CDCl_3$

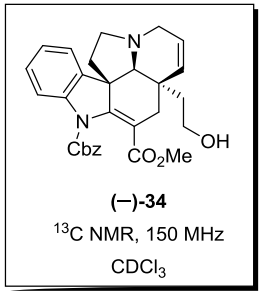

N
N
Cbz
CO2Me
OTBS
(–)-33
13C NMR, 150 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



(−)-34

^{1}H NMR, 600 MHz

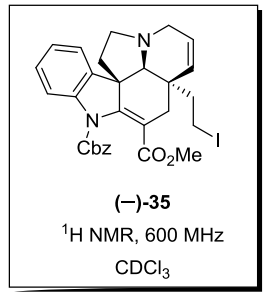
$CDCl_3$



(–)-34

^{13}C NMR, 150 MHz

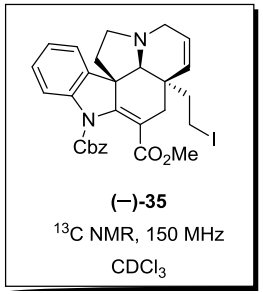
$CDCl_3$



(–)-35

^{1}H NMR, 600 MHz

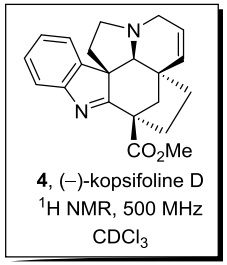
$CDCl_3$



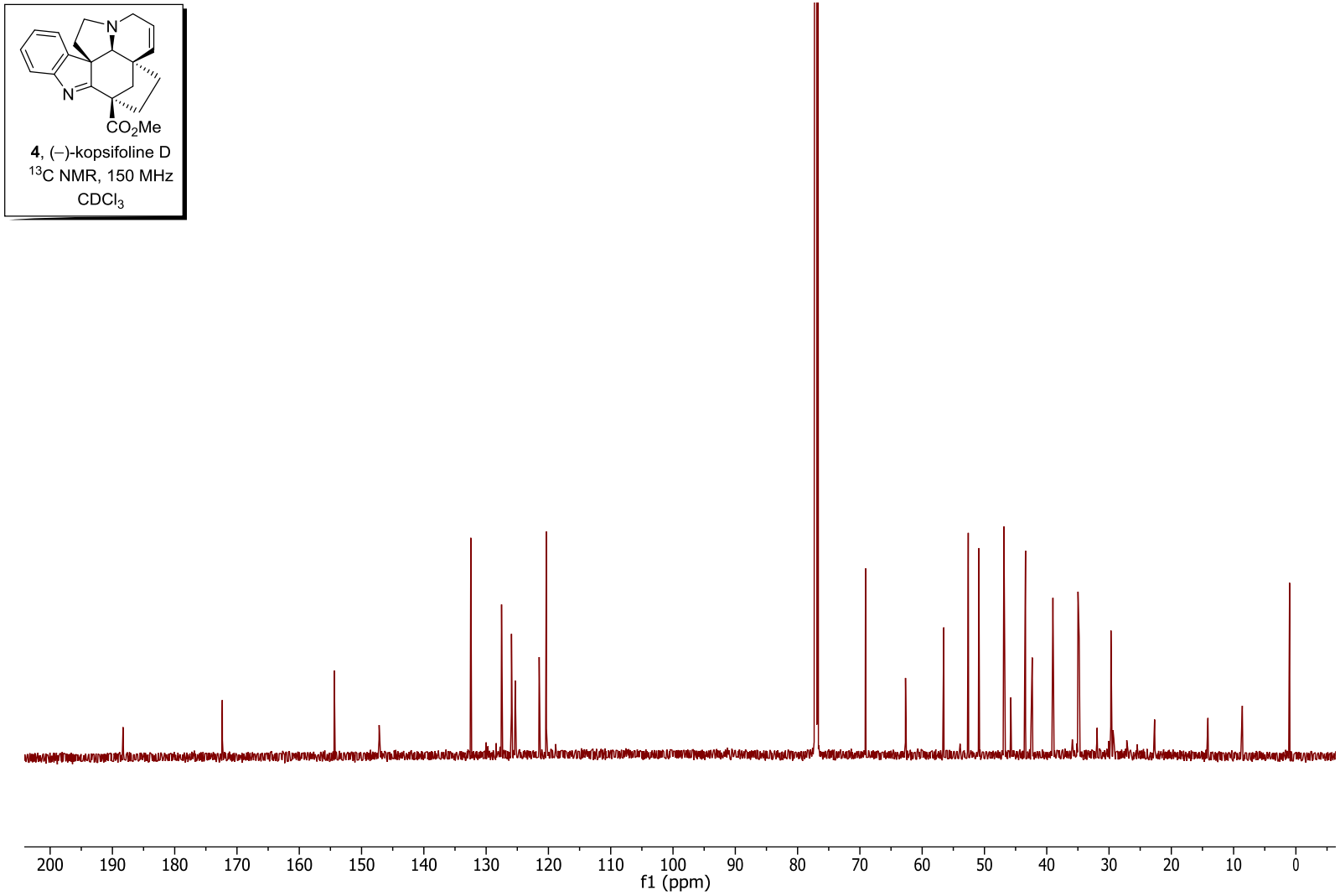
(–)-35

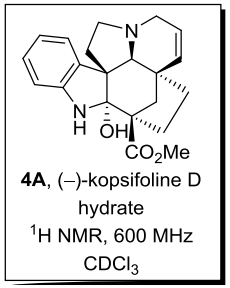
^{13}C NMR, 150 MHz

$CDCl_3$

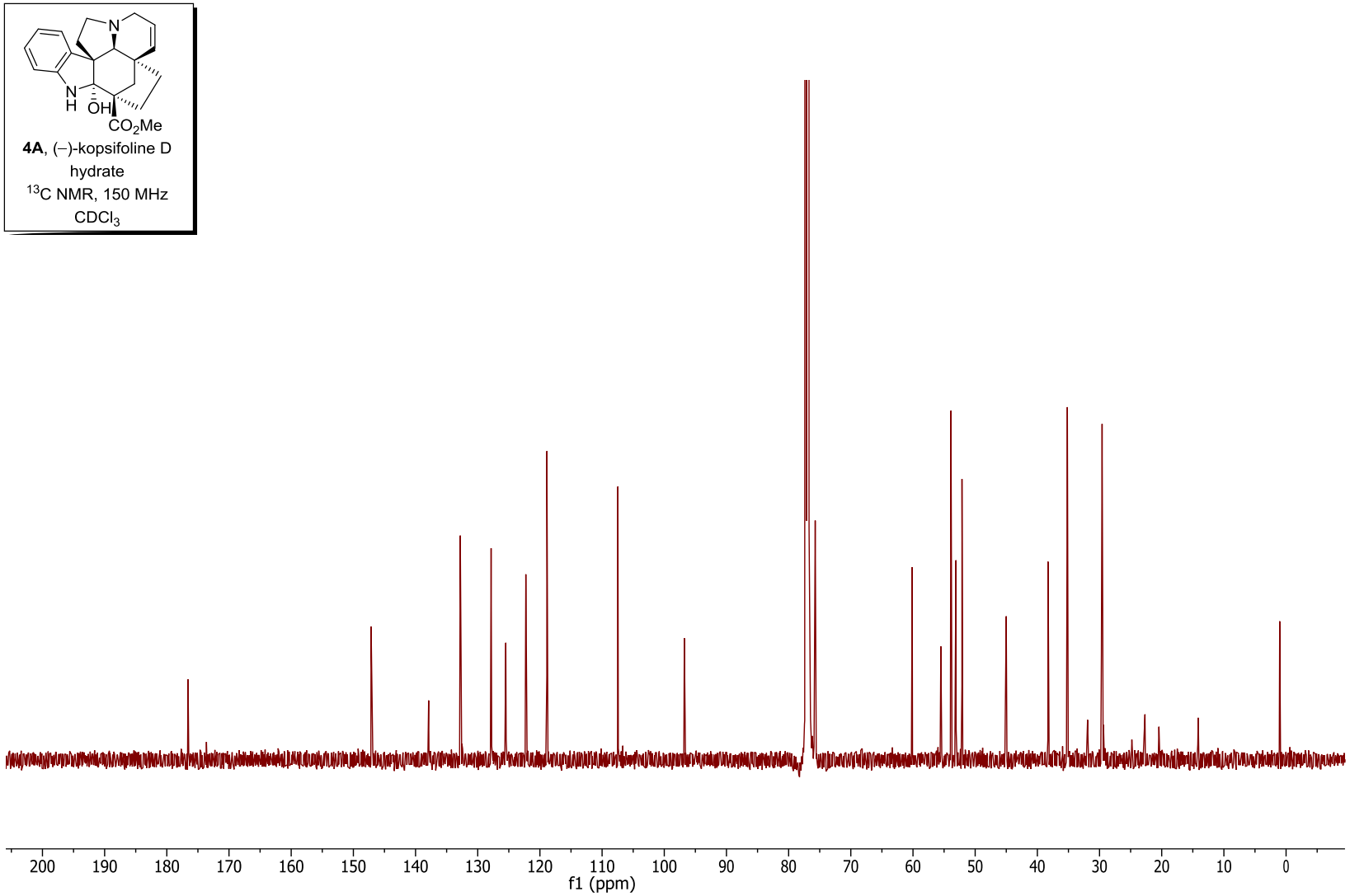


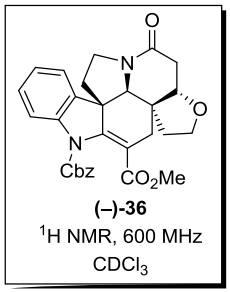
4, (–)-kopsifoline D
^{1}H NMR, 500 MHz
$CDCl_3$


N
N
CO2Me
4, (–)-kopsifoline D
13C NMR, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



4A, (–)-kopsifoline D hydrate
^{1}H NMR, 600 MHz
$CDCl_3$

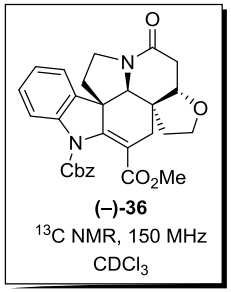

N
N
H
OH
CO2Me
4A, (–)-kopsifoline D
hydrate
13C NMR, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(–)-36

^{1}H NMR, 600 MHz

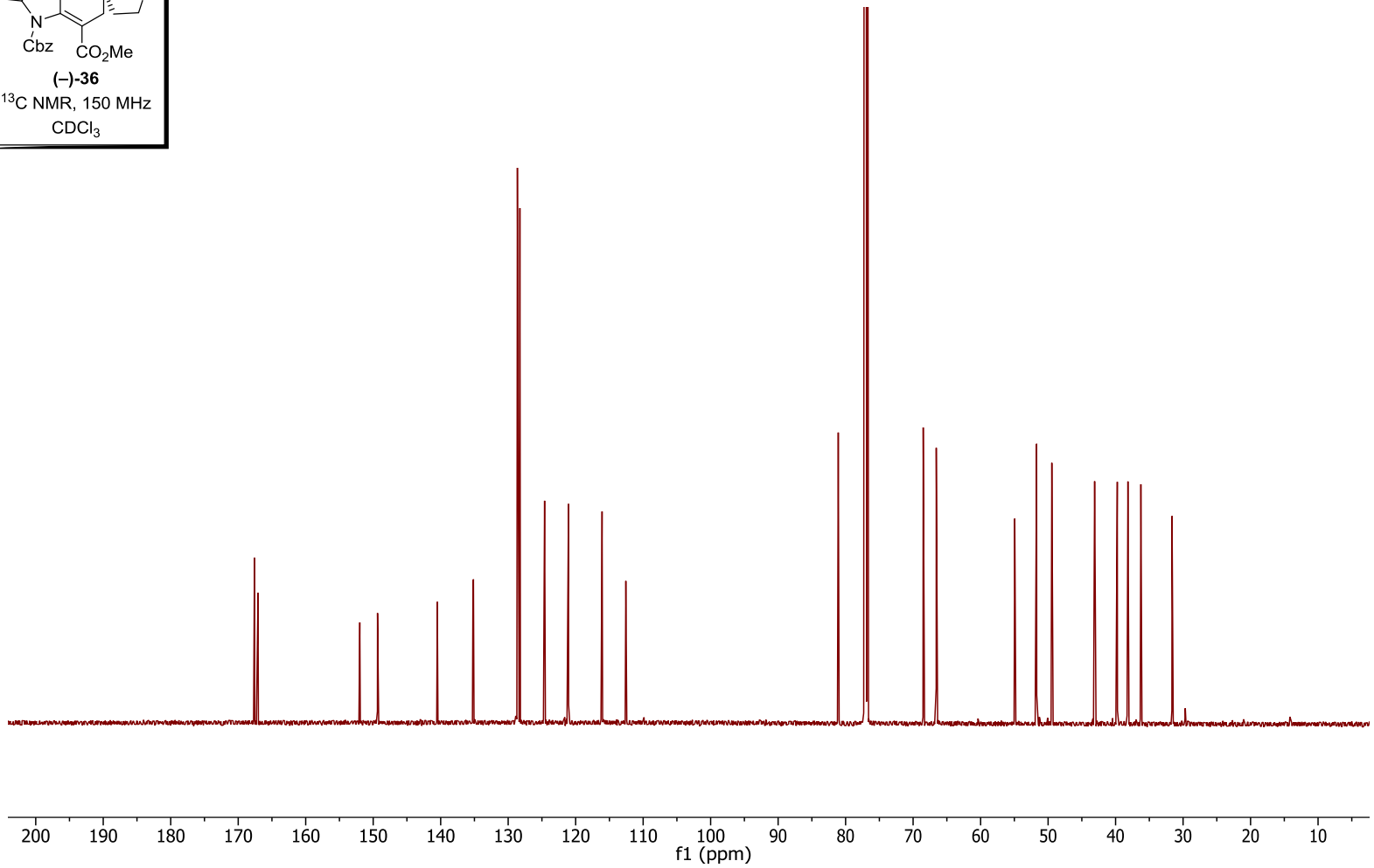
$CDCl_3$

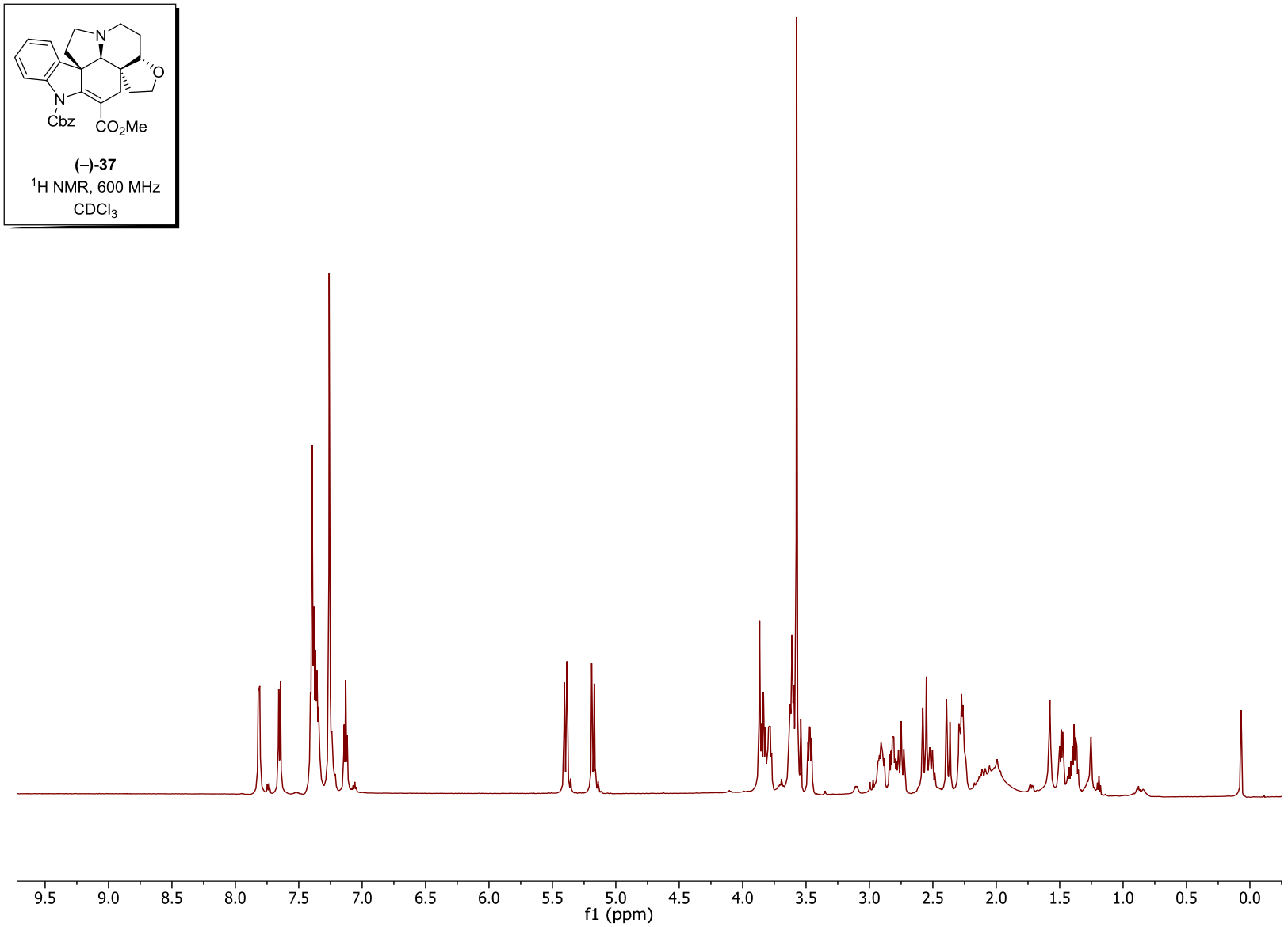


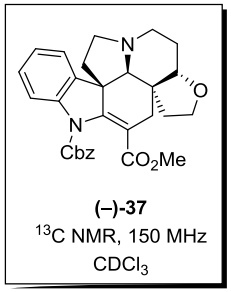
(–)-36

^{13}C NMR, 150 MHz

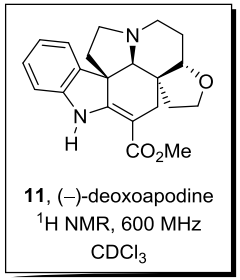
$CDCl_3$



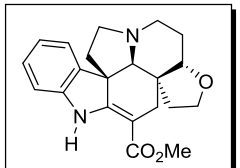

N
O
N
Cbz
CO2Me
(–)-37
1H NMR, 600 MHz
CDCl3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



(–)-37
^{13}C NMR, 150 MHz
$CDCl_3$



11, (–)-deoxoapodine
^{1}H NMR, 600 MHz
$CDCl_3$



11, (–)-deoxoapodine
^{13}C NMR, 150 MHz
$CDCl_3$