Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Asymmetric synthesis of (+)-Vertine and (+)-Lythrine

Laetitia Chausset-Boissarie, Roman Àrvai, Graham R. Cumming, Laure Guénée and

*E. Peter Kündig**

Department of Organic Chemistry University of Geneva, 30, quai Ernest Ansermet,

CH-1211 Geneva, Switzerland.

Supporting Information

1. General information

Chemicals were purchased from Aldrich, Fluka, Acros, Alfa Aesar and used without further purification. Solvents were purified on Al_2O_3 drying columns using a Solvtec© system or by following standard procedures. Reactions and manipulations involving organometallic or moisture sensitive compounds were carried out under dry nitrogen and glassware was heated under vacuum prior use. Analytical thin layer chromatography (TLC) was performed with Merck SIL G/UV_{254} plates visualized with UV light. Flash column chromatography was performed in air with silicagel 60 (Fluka). Analysis with HPLC was performed using Agilent 1100 series chromatograph with JASCO PU-980 pump and Agilent 1100 Series detection system. NMR spectra were recorded on Bruker ARX-500, AMX-400 spectrometers in the solvent indicated. ^{1}H- and ^{13}C-NMR chemical shifts (δ) are quoted in parts per million (ppm) with the residual solvent peak used as an internal standart. Coupling constants *J* are quoted in Hz. Infrared spectra (bands in cm^{-1}) were recorded on a Perkin–Elmer Spectrum 100 spectrophotometer using a diamond ATR Golden Gate accessory. Electron impact (EI) HRMS mass spectra were obtained using a *Finningan MAT 95* spectrometer operating at 70eV. Electrospray ionization (ESI) HRMS analyses were measured on a VG analytical 7070E spectrometer. Melting points were determined on a Büchi 540 and are uncorrected. Optical rotations were measured at 20 °C on a Perkin Elmer 241 polarimeter using a quartz cell (l = 10 cm) with a Na high-pressure lamp (λ = 589).

2. Experimental part

(*R*,*R*)-ammonium salt piperidinethanol (*R*-13)

A solution of (1*R*)-(-)-10-camphorsulfonic acid (31.000 g, 130 mmol), in ethanol (45 mL) was added dropwise to a solution of 2-piperidineethanol (33.000 g, 250 mmol), in ethanol (50 mL) with stirring. The reaction mixture was cooled in a refrigerator overnight and the needle to lath-like crystals (17.700 g) were collected by filtration, washed with ether and dried under vacuum. The first crop crystals were re-dissolved in warm ethanol (20 mL) and cooled in a refrigerator. The formed crystals (12.000 g) were collected and the recrystallization procedure was repeated with warm ethanol (15 mL) to have the lath-like crystal (6.500 g, 12%). Spectral data matches literature values.[1] **m.p.**: 165-167 ˚C. **IR** (neat, cm^{-1}) 3430, 2962, 2859, 1737, 1621, 1225, 1169, 1037. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.01 (3H, s, NH-OH), 4.0-3.95 (1H, m, CHOH), 3.88-3.82 (1H, m, CHOH), 3.54 (1H, d, *J* 12.8 Hz, NCH_2), 3.40-3.32 (2H, m, CH_2SO_3+CHN), 3.09-3.02 (1H, m, CH_2N), 2.73-2.65 (1H, m, alkyl-H), 2.44-2.37 (1H, m, CH_2CO), 2.16-2.37 (3H, m, alkyl-H), 2.00-1.77 (8H, m, alkyl-H), 1.6-1.58 (1H, m, alkyl-H), 1.51-1.44 (1H, m, alkyl-H), 1.16 (3H, s, CH_3), 0.92 (3H, s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 217.1, 59.1, 58.6, 56.4, 48.2, 47.6, 45.4, 43.1, 42.8, 35.6, 29.4, 27.2, 24.8, 22.7, 22.6, 20.1, 20. (*R*,*R*)-**13** $[\alpha]_D^{20}$ = -25.9 (c 1.01, $CHCl_3$). A small amount of salt was converted to (*R*)-benzyl 2-(2-hydroxyethyl)piperidine-1-carboxylate for HPLC determination of ee. HPLC analysis: ee 99%, column: OJ chiral column; UV detector: λ 210 nm; solvent: hexane/*i*-PrOH_gradient 99+1-90+10_1mL/min; retention time 1: 32.9 min (*S*), retention time 2: 39.4 min (*R*).

N-acetyl-L-Leucine-(*S*)-2-Piperidineethanol (*S*-13)[2]

N-acetyl-L-Leucine (16.080 g, 92.88 mmol) was dissolved in MeOH (20 mL), and then the reaction mixture was heated at 35 °C. A solution of piperidineethanol (24.000 g, 185.76 mmol) in THF (100 mL) was added dropwise at 35 °C, additional THF (60 mL) was also added and the reaction mixture was stirred at 55 °C for 30 min. The reaction mixture was cooled down over 2 h to 15 °C and stirred at this temperature for 1 h. The precipitate was filtered and dried under vacuum (23.000 g). The product was purified by 3 recrystallizations to lead a white solid (10.000 g, 36%). A small amount of salt was converted to (*S*)-benzyl 2-(2-hydroxyethyl)piperidine-1-carboxylate for HPLC determination of ee. HPLC analysis: ee 99%, column: OJ chiral column; UV detector: λ 210 nm; solvent: hexane/*i*-PrOH_gradient 99+1-90+10_1mL/min; retention time 1: 32.9 min (*S*), retention time 2: 39.4 min (*R*). **m.p.**: 154-155 °C. **IR** (neat, cm^{-1}): 3242, 2949, 1628, 1560, 1397, 1297, 1057, 747. **^{1}H NMR** (400 MHz, MeOD) δ 4.94 (3H, s, N<u>H</u>), 4.28 (1H, dd, J 4.4, 10.0 Hz, NC<u>H</u>CO_2), 3.76-3.65 (2H, m, C<u>H</u>$_2$OH), 3.35-3.32 (1H, m, NH_2C<u>H</u>$_2$, <u>A</u>BX), 3.22-3.20 (1H, m, NH_2C<u>H</u>), 2.93 (1H, td, 3.2, 14.2 Hz, NH_2C<u>H</u>$_2$, A<u>B</u>X), 1.95 (3H, s, C<u>H</u>$_3$ and 1H, alkyl-<u>H</u>), 1.89-1.47 (10H, m, alkyl-<u>H</u>), 0.92 (6H, d, J 4.8 Hz, C<u>H</u>$_3$CH). **^{13}C NMR** (100 MHz, MeOD) δ 180.5, 172.8, 59.4, 57.0, 55.1, 46.1, 46.3, 43.3, 37.0, 30.1, 26.4, 24.0, 23.7, 23.5, 23.0, 22.2. **$[\alpha]_D^{20}$** = -3.1 (c 1.00, $CHCl_3$).

(*R*)-*tert*-butyl-2-(2-hydroxyethyl)piperidine-1-carboxylate. NEt_3 (7.74 mL, 55.40 mmol) was added at rt to a solution of salt (*R*,*R*)-**13** (6.670 g, 18.50 mmol) and di-*tert*butyldicarbonate (4.430 g, 20.30 mmol) in DCM (30 mL) and the reaction mixture was stirred over night. A saturated NH_4Cl aqueous solution (50 mL) was added then the solution was extracted with DCM (3 × 50 mL); the organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography on silica gel eluting with cyclohexane:EtOAc (3:1) to yield yellow oil (4.080 g, 99%).

(*S*)-desired product was obtained in 80% yield from *N*-acetyl-L-Leucine-(*S*)-2-piperidineethanol (9.800 g, 37.69 mmol) following the same procedure as for the synthesis of (*R*)-product. Spectral data matches literature values.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.40 (1H, s, NC<u>H</u>), 3.92-3.84 (2H, m, NC<u>H</u>+O<u>H</u>), 3.52 (1H, m, C<u>H</u>O), 3.31 (1H, m, C<u>H</u>O), 2.68-2.60 (1H, dt, *J* 2.4, 13.1 Hz, NC<u>H</u>), 1.90 (1H, t, J 12.8 Hz, alkyl-H), 1.7-1.67 (1H, m, alkyl-H), 1.59-1.53 (15H, m, alkyl-H +CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.31, 85.59, 46.0, 44.7, 39.3, 29.0, 28.4, 27.0, 25.3, 19.0. (*R*) **$[\alpha]_D^{20}$** = +38.6 (c 0.9, $CHCl_3$). (*S*) **$[\alpha]_D^{20}$** = -28.3 (c 0.385, $CHCl_3$).

(*R*)-*tert*-butyl-2-(formylmethyl)piperidine-1-carboxylate (*R*-14). A solution of DMSO (1.91 mL, 26.90 mmol) in DCM (12 mL) was added dropwise at -78 °C under N_2 to a solution of $(COCl)_2$ (0.97 mL, 11.30 mmol), in DCM (48 mL). After 10 min of stirring, a solution of (*R*)-*tert*-butyl-2-(2-hydroxyethyl)piperidine-1-carboxylate (2.160 g, 9.43 mmol) in DCM (24 mL) was added. After 20 min, freshly distilled NEt_3 (6.26 mL, 44.80 mmol) was added and the reaction mixture was warmed to rt and stirred during 4 h. Water (20 mL) and HCl 1 N (10 mL) were added. The aqueous layer was extracted with DCM (3 × 75 mL), the organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography on silica gel eluting with cyclohexane:EtOAc (3:1) to yield yellow oil (1.954 g, 91%).

Desired product (*S*)-**14** was obtained in 93% yield from (*S*)-*tert*-butyl-2-(2-hydroxyethyl)piperidine-1-carboxylate (6.700 g, 29.25 mmol) following the same procedure as for the synthesis of (*R*)-**14**. Spectral data matches literature values.[4] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.55 (1H, s, C<u>H</u>O), 4.66 (1H, s, C<u>H</u>N), 3.81 (1H, d, *J* 3.8 Hz, C<u>H</u>$_2$N), 2.63-2.53 (2H, m, C<u>H</u>$_2$CO), 2.39-2.33 (1H, dd, *J* 6.4 Hz, 15.4 Hz, C<u>H</u>$_2$N), 1.54-1.26 (15H, m, C<u>H</u>$_3$ and alkyl-<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.6, 154.4, 136.6, 128.6, 128.1, 127.9, 67.3, 46.2,

44.5, 39.6, 28.7, 25.2, 18.9, 14.2. (*R*)-**14** $[\alpha]_D^{20}$ = +36 (c 1.0, $CHCl_3$). (*S*)-14 $[\alpha]_D^{20}$ = -22.4 (c 0.55, $CHCl_3$).

(*R*)-*tert*-butyl-2-(2-oxopropyl)piperidine-1-carboxylate (*R*-16). To a solution of aldehyde (*R*)-**14** (3.600 g, 15.95 mmol) in THF (150 mL) at -78 °C was added dropwise a solution of MeMgBr (10.57 mL, 31.71 mmol, 3 M in Et_2O). The mixture was allowed to stir at -78 °C for 30 min then warmed to rt and stirred for an aditionnal 4 h. The reaction was quenched with water (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL), the organic layers were dried over Na_2SO_4 and concentrated *in vacuo* leading a yellow oil (3.500 g, 97%). The crude product was pure enough to be engaged in the next step. Dess Martin's reagent (12.900 g, 30.40 mmol) was added to a solution of (*R*)-alcohol (3.500 g, 15.22 mmol), $NaHCO_3$ (6.390 g, 73.16 mmol) in DCM (150 mL). The reaction mixture was stirred at rt for 2 h. A saturated sodium thiosulfate aqueous solution was added until the mixture was clear, the solution was extracted with DCM (3 × 150 mL), the organic layers were combined, washed with brine (3 × 200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography on silica gel eluting with cyclohexane:EtOAc (3:1) to yield yellow oil (3.250 g, 90% over two steps).

Desired product (*S*)-**16** was obtained in 90% yield from (*S*)-**14** (4.400 g, 19.38 mmol) following the same procedure as for the synthesis of (*R*)-**16**. Spectral data matches literature values.[5] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.75 (1H, s, NC<u>H</u>), 4.0 (1H, s, NC<u>H</u>$_2$, <u>A</u>BX), 2.85 (1H, t, *J* 11.3 Hz, NC<u>H</u>$_2$, A<u>B</u>X), 2.69 (2H, dd, *J* 2, 6.8 Hz, C<u>H</u>$_2$CO), 1.6 (6H, C<u>H</u>$_2$, m), 1.48 (9H, C<u>H</u>$_3$, s). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.2, 154.6, 79.5, 47.2, 44.2, 30.1, 28.4, 27.3, 26.8, 25.3, 18.8. (*R*)-**16** $[\alpha]_D^{20}$ = +9.6 (c 2.0, $CHCl_3$). (*S*)-**16** $[\alpha]_D^{20}$ = -8.9 (c 0.615, $CHCl_3$).

(*R*,*E*)-*tert*-butyl-2-(4-(2-iodo-4,5-dimethoxyphenyl)-2-oxobut-3-enyl)piperidine-1-carboxylate (*R*-17). A solution of compound (*R*)-**16** (2.300 g, 9.54 mmol), 6-iodoveratraldehyde (3.190 g, 10.97 mmol) and NaOH 6 M (2.380 mL, 14.30 mmol) in MeOH

(160 mL) was heated at 55 °C during 16 h. The reaction mixture was cooled down and evaporated *in vacuo*. Water was added (50 mL), then the aqueous layer was extracted with DCM (3 × 75 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was then purified by flash column chromatography on silica gel eluting Et_2O:Cyclohexane (6:4) to yield yellow oil (3.610 g, 91 %).

Desired product (*S*)-**17** was obtained in 92% yield from (*S*)-**18** (2.000 g, 8.29 mmol) following the same procedure as for the synthesis of (*R*)-**17**. **IR** (neat): 2934, 1679, 1503, 1592, 1262, 1163, 1058, 903, 723. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* 16.0 Hz, C<u>H</u>), 7.29 (1H, s, Ar<u>H</u>), 7.27 (1H, s, Ar<u>H</u>), 6.56 (1H, d, *J* 16.0 Hz, C<u>H</u>), 4.82 (1H, s, C<u>H</u>), 3.90 (6H, s, C<u>H</u>$_3$ and 1H, C<u>H</u>), 2.93-2.91 (3H, m, alkyl-<u>H</u>), 1.66-1.64 (6H, m, alkyl-<u>H</u>), 1.43 (9H, s, C<u>H</u>$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.4, 155.0, 151.6, 149.8, 146.3, 130.1, 127.4, 122.0, 109.4, 92.4, 78.9, 56.4, 56.2 (2C), 48.2, 41.2, 39.7, 28.6, 25.6, 19.2. **HR-MS** (ESI) for $C_{22}H_{30}INO_5$ $[M+H]^+$: calcd. 515.1169, found 515.1160. (*R*)-**17** $[\alpha]_D^{20}$ = +26.0 (c 0.525, $CHCl_3$). (*S*)-**17** $[\alpha]_D^{20}$ = - 32.4 (c 1, $CHCl_3$).

(4*S*,9a*R*)-hexahydro-4-(2-bromo-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-one (5). To a solution of compound **(*R*)-17** (1.600 g, 3.10 mmol) in DCM (10 mL) was added TFA (12 mL, 134.00 mmol) dropwise at 0 °C. The reaction was then stirred at this temperature for 1 h. The reaction mixture was evaporated *in vacuo* then taken up in THF (24 mL) and cooled to 0 °C. A solution of 1 M NaOH (6 mL) was added dropwise. The reaction mixture was stirred at rt for 4 h then extracted with EtOAc (100 mL); the combined organic layers were washed with brine (3 × 100 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with EtOAc to yield yellow solid (0.930 g, 75%).

Desired product (4*R*,9a*S*)-**5** was obtained in 73% yield from (*S*)-**17** (1.200 g, 2.32 mmol) following the same procedure as for the synthesis of (4*S*,9a*R*)-**17**. **m.p.**: 102-103 °C. **IR**

(neat): 2932, 2841, 1719, 1595, 1495, 1372, 1245, 853. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (1H, s, ArH), 6.87 (1H, s, ArH), 4.53 (1H, dd, *J* 5.0, 8.0 Hz, NCHAr), 3.83 (6H, s, OCH_3), 3.30-3.28 (1H, m, NCHalkyl), 2.92-2.87 (1H, m, Nalkyl-H), 2.78-2.67 (1H, ddd, *J* 1.2, 5.6, 14.0 Hz, COalkyl-H), 2.64-2.58 (1H, dd, *J* 2.5, 14.2 Hz, COalkyl-H), 2.52-2.45 (1H, td, *J* 3.2, 12.0 Hz, Nalkyl-H), 2.37-2.31 (2H, m, COalkyl-H), 1.79-1.75 (1H, m, alkyl-H), 1.64-1.37 (4H, m, alkyl-H), 1.28-1.23 (1H, m, alkyl-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.1, 150.0, 149.0, 135.8, 121.7, 110.8, 88.2, 64.4, 57.2, 56.3, 56.2, 50.0, 47.1 (2C), 28.2, 24.4, 21.5. **HR-MS** (ESI) for $C_{17}H_{23}I_1O_3N$ $[M+H]^+$: calcd. 416.0717, found 416.0694. (4*S*,9a*R*)-**5** :$[\alpha]_D^{20}$ = -11.8 (c 0.32, $CHCl_3$), (96% ee). (4*R*,9a*S*)-**5**: $[\alpha]_D^{20}$ = -25.2 (c 0.39, $CHCl_3$), (98 % ee). HPLC analysis: column: OD chiral column; UV detector: λ 210 nm; solvent: hexane/*i*-PrOH_gradient 99+1-90+10_1mL/min; retention time 1: 22.6 min (4*S*,9a*R*), retention time 2: 25.75 min (4*R*,9a*S*).

(4*S*,9a*S*)-hexahydro-4-(2-bromo-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-one (6). (4*R*,9a*S*)-**5** (0.800 g, 1.92 mmol) was dissolved in MeOH (70 mL) then aqueous solution of NaOH (1 M, 1.92 mL, 1.92 mmol) was added and the mixture was stirred at rt for 72 h. Most of the solvent was removed under reduced pressure; the aqueous layer was extracted with DCM (3 × 75 mL). The combined organic layers were washed with brine (3 × 75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:cyclohexane (1:1) to yield pale yellow foam (0.784 g, 98%). HPLC analysis: ee 96%, column: AD chiral column; UV detector: λ 210 nm; solvent: hexane/*i*-PrOH_iso 99+1-90+10_1mL/min; retention time 1: 23.5 min (4*R*,9a*R*), retention time 2: 26.2 (4*S*,9a*S*). **m.p.** 102-103 °C. **IR (neat)**: 2932, 2841, 2830, 2822, 1719, 1595, 1495, 1372, 1245, 853. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14 (1H, s, ArH), 7.07 (1H, s, ArH), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.60 (1H, dd, *J* 4.0, 11.6 Hz, NCHAr), 2.71 (1H, d, *J* 11.6 Hz, Nalkyl-H), 2.48-2.28 (5H, m, 1H NCHalkyl and 4H

COalkyl-H), 1.75-1.66 (3H, m, alkyl-H), 1.54-1.22 (4H, m, alkyl-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.4, 150.5, 149.0, 136.9, 121.4, 110.5, 87.5, 72.5, 62.0, 56.3 (2C), 52.5, 49.2, 48.8, 34.6, 26.1, 24.4. **HR-MS** (ESI) for $C_{17}H_{23}I_1O_3N$ $[M+H]^+$: calcd. 416.0717, found 416.0694. (4*S*,9a*S*)-**6** $[\alpha]_D^{20}$ = +113.1 (c 0.375, $CHCl_3$), (96% ee).

3-iodo-4-methoxymethyl-benzaldehyde (18). A suspension of 3-iodo-4-hydroxy-benzaldehyde (6.000 g, 24.20 mmol) in DCM (50 mL) was cooled with an ice bath before addition of Hunig's base (6.8 mL, 38.70 mmol); dissolution occurs upon addition of the base. MOMCl (2.4 mL, 31.40 mmol) was added dropwise, and the reaction mixture was stirred for 16 h at rt then quenched with saturated NH_4Cl aqueous solution (50 mL). The aqueous layer was extracted with EtOAc (3 × 75 mL); the combined organic layers were washed with brine (3 × 100 mL) dried over $MgSO_4$ and concentrated in vacuo. The residue was passed through a pad of silica, eluting with EtOAc:pentane (1:4) to yield a yellow solid (6.950 g, 98%). **m.p.**: 65-66 °C. **IR** (neat): 2965, 2832, 1690, 1591, 1488, 1142, 956 828. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.82 (1H, s, CHO), 8.30 (1H, d, *J* 2.0 Hz, ArH), 7.81 (1H, dd, *J* 2.0, 8.6 Hz, ArH), 7.16 (1H, d, *J* 8.6 Hz, ArH), 5.33 (2H, s, OCH_2O), 3.51 (3H, s, CH_2OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ. 189.5, 160.7, 141.1, 132.1, 131.8, 114.0, 94.8, 87.3, 56.8. **HR-MS** (ESI) for $C_9H_{10}IO_3$ $[M+H]^+$: calcd. 292.9669, found 292.9692.

3-(3-Iodo-4-methoxymethoxy-phenyl)-*Z*-acrylic acid methyl ester (20). 18-Crown-6 (1.320 g, 5 mmol) was dissolved under N_2 in THF (20 mL) and the solution was cooled to -78 °C. KHMDS (0.5 M in toluene, 2 mL, 1 mmol) was added *via* septum and the mixture was stirred for 10 min. Bis(2,2,2-trifluoroethyl)(methoxy-carbonylmethyl)phosphinate (0.21 mL, 0.320 g, 1 mmol) was added *via* septum and the reaction mixture was stirred for 10 min. Aldehyde **18** (0.290 g, 1 mmol) was added as a solid and stirring was continued for an additional 45 min. The reaction was quenched with brine and extracted with DCM (3 × 30 mL); the combined organic layers were washed with brine (3 × 100 mL), dried over $MgSO_4$

and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with Et_2O:pentane (1:1) to yield a yellow foam (0.301 g, 89%).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* 2.2 Hz, ArH), 7.62 (1H, dd, *J* 2.2, 8.5 Hz, ArH), 7.00 (1H, d, *J* 8.5 Hz, ArH), 6.73 (1H, d, *J* 12.9 Hz, CHCH), 5.84 (1H, d, *J* 12.9 Hz, CHCH), 5.22 (2H, s, OCH_2), 3.70 (3H, s, OCH_3), 3.46 (3H, s, OCH_3). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.1, 156.3, 141.4, 141.1, 131.5, 129.9, 118.2, 113.4, 94.6, 86.1, 56.3, 51.2**.** **HR-MS** (ESI) for $C_{12}H_{13}O_4I$ $[M+H]^+$: calcd. 347.9859, found 347.9847.

3-[4-Methoxymethoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acrylicacid methyl ester (21). Iodide **20** (1.600 g, 4.59 mmol), bis(pinacolato)diboron (1.280 g, 5.05 mmol), $Pd(OAc)_2$ (0.031 g, 0.0459 mmol) and KOAc (1.350 g, 13.77 mmol, dried by heating at 130 °C under vacum for 16 h) were dissolved under N_2 in degassed DMF (50 mL). The reaction mixture was heated at 90 °C for 1.5 h. Then the reaction mixture was cooled down, quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM (3 × 75 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over Na_2SO_3 and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with EtOAC:pentane:Et_3N (1:1:0.1) to yield yellow oil (0.720 g, 45%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (1H, dd, *J* 2.3, 8.3 Hz, ArH), 7.80 (1H, dd, *J* 2.3 Hz, ArH), 7.02 (1H, d, *J* 8.3 Hz, ArH), 6.89 (1H, d, *J* 12.7 Hz, CHCH), 6.85 (1H, d, *J* 12.7 Hz, CHCH), 5.23 (2H, s, OCH_2), 3.72 (3H, s, OCH_3), 3.51 (3H, s, OCH_3), 1.35 (12H, s, CH_3). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.9, 162.3, 142.9, 139.4, 134.1, 128.1, 117.4, 114.4, 94.7, 83.6, 56.1, 51.2, 24.8**.** **HR-MS** (ESI) for $C_{18}H_{25}O_6B$ $[M+H]^+$: calcd. 348.1744, found 348.1739.

2-trimethylsilylethyl diphenylphosphonoacetate (26).[6] To an ice cold solution of 2-trimethylsilylethanol (6.940 mL, 9.25 mmol), Et_3N (6.780 mL, 48.25 mmol) in dry DCM (18

mL) was added bromoacetylbromide (4.160 mL, 9.25 mmol). The solution was stirred 10 min at 0 °C the reaction mixture was warmed up to rt and stirring was continued for an additional 2.5 h. The resulting solution was filtered through a pad of silica and washed with DCM (100 mL). Concentration *in vacuo* afforded oil (2.220 g, quantitative). The crude product was pure enough to be engaged in the next step. To an iced solution of diphenylphosphite (1.780 mL, 9.25 mmol) in dry DCM was added 2-trimethylsilylethyl bromooacetate **25** (2.220 g, 9.25 mmol), followed by Et_3N (1.820 mL, 13 mmol). After stirring for 15 min at 0 °C, the reaction mixture was warmed up to rt and stirring was continued for an additional 16 h. The reaction mixture was quenched by addition of saturated $NaHCO_3$ aqueous solution (15 mL). The aqueous layer was extracted with DCM (3 × 15mL) the organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified flash column chromatography on silica gel eluting with toluene:acetone (19:1) affording a yellow oil (1.42 g, 40%).**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.45 (4H, m, ArH), 7.07-7.03 (4H, m, ArH), 6.90 (2H, m, ArH), 4.23 (2H, m, OCH_2), 3.08 (2H, d, *J* 2.1 Hz, PCH_2), 0.96-0.92 (2H, m, CH_2Si), 0.05 (9H, s, CH_3Si). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.5 (d, *J* 6.2 Hz), 158.7, 151.3 (d, *J* 8.3 Hz), 130.6, 130.3, 126.1, 121.7 (d, *J* 4.3 Hz), 120.2, 116.6, 64.7, 34.0 (d, *J* 136.3 Hz), 17.9, -1.2. **^{31}P{^{1}H} NMR** (162 MHz, C_6D_6): δ 13.5 (1P, s). **HR-MS** (ESI) for $C_{19}H_{25}NaO_5PSi$ $[M+H]^+$: calcd. 415.1107, found 415.1115.

3-(3-iodo-4-methoxymethoxy-phenyl)-*Z*-acrylic acid 2-trimethylsilylethyl ester (27). 18-Crown-6 (0.670 g, 2.35 mmol) was dissolved under N_2 in THF (20 mL) and the solution was cooled to -78 °C. KHMDS (0.5 M in toluene, 1.03 mL, 0.52 mmol) was added *via* septum and the reaction mixture was stirred for 10 min. Phosphonate **26** (0.200 g, 0.52 mmol) was added *via* septum and the reaction mixture was stirred for 10 min. A solution of aldehyde **18** (0.140 g, 0.47 mmol) in dry THF (5 mL) was cooled to -78 °C and then transferred by cannula. The reaction mixture was warmed up to 0 °C and stirring was continued overnight. The reaction

was quenched with brine and extracted with DCM (3 × 30 mL); the combined organic layers were washed with brine (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with toluene to yield yellow oil (0.160 g, 76%).**^{1}H NMR** (300 MHz, C_6D_6) δ 8.32 (1H, d, *J* 2.2 Hz, ArH), 7.67 (1H, dd, *J* 2.2, 8.6 Hz, ArH), 6.82 (1H, d, *J* 8.6 Hz, ArH), 6.29 (1H, d, *J* 12.8 Hz, CHCH), 5.80 (1H, d, *J* 12.8 Hz, CHCH), 4.72 (2H, s, OCH_2), 4.19 (2H, t, *J* 8.4 Hz, CH_2OCO), 3.04 (3H, s, OCH_3), 0.9 (2H, t, *J* 8.4 Hz, CH_2Si), -0.1 (9H, s, CH_3Si). **^{13}C NMR** (75.5 MHz, C_6D_6) δ 166.5, 157.7, 142.8, 141.8, 133.0, 131.4, 120.0, 114.4, 95.3, 87.2, 63.0, 56.5, 18.1, -1.0. **MS** (ESI): 434 (M+H) (100).

3-[4-Methoxymethoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acrylic acid ethyl -2- trimethylsilylethyl ester (28). Iodide **27** (0.100 g, 0.23 mmol), bis(pinacolato)diboron (0.064 g, 0.25 mmol), $Pd(OAc)_2$ (0.016 g, 0.023 mmol) and KOAc (0.068 g, 0.69 mmol, dried by heating at 130 °C under vacuum for 16 h) were dissolved under N_2 in degassed DMF (2.5 mL). The reaction mixture was heated at 55 °C for 20 h. Then the reaction mixture was cooled down, quenched with saturated $NaHCO_3$ aqueous solution (5 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over Na_2SO_3 and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with Et_2O:pentane (2:1) to yield yellow oil (0.065 g, 65%). **^{1}H NMR** (200 MHz, C_6D_6) δ 8.38 (1H, d, *J* 2.6 Hz, ArH), 8.32 (1H, dd, *J* 2.6, 8.4 Hz, ArH), 7.11 (1H, d, *J* 8.4 Hz, ArH), 6.59 (1H, d, *J* 12.8 Hz, CHCH), 5.87 (1H, d, *J* 12.8 Hz, CHCH), 4.99 (2H, s, OCH_2), 4.3-4.22 (2H, m, CH_2OCO), 3.24 (3H, s, OCH_3), 1.19 (12H, s, CH_3CO), 0.97-0.88 (2H, m, CH_2Si), -0.06 (9H, s, CH_3Si). **^{13}C NMR** (50 MHz, C_6D_6) δ 165.9, 163.4, 142.7, 140.8, 135.1, 128.5, 118.0, 114.3, 94.5, 83.1, 82.5, 61.8, 55.5, 24.7, 17.2, -1.8. **MS** (ESI): 434 (M+H) (100).

4-(methoxymethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (29). A mixture of 3-iodo-4-MOM-benzaldehyde **18** (2.000 g, 6.80 mmol), bis(pinacolato)diboron (2.080 g, 8.20 mmol), $Pd(OAc)_2$ (0.076 g, 0.34 mmol) and KOAc (2.010 g, 20 mmol, dried for 16 h at 130 °C under vacuum) in dry DMF (27 mL) was heated overnight at 60 °C under N_2. Then the reaction mixture was filtered over Celite® and washed with EtOAc (100 mL). The filtrate was evaporated in *vacuo*, the residue was purified by flash column chromatography on silica gel eluting with Et_2O: pentane (1:2) to yield colourless oil (1.460 g, 74%). **IR** (neat): 2977, 1691, 1344, 1141, 915. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.82 (1H, s, CHO), 8.13 (1H, d, *J* 2.2 Hz, ArH), 7.83 (1H, dd, *J* 2.2, 8.6 Hz, ArH), 7.06 (1H, d, *J* 8.6 Hz, ArH), 5.2 (2H, s, OCH_2O), 3.42 (3H, s, OCH_3), 1.28 (12H, s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.1, 166.3, 139.8, 133.7, 130.1, 114.2 (2C), 94.2, 83.9, 56.3, 24.8. **MS** (ESI): 293 (M+H) (100).

(4*S*,9a*R*)-Hexahydro-4-(2-(2'-methoxymethoxy-5'-carboxaldehyphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-one (30). Degassed DME (90 mL) was added under N_2 to a mixture of quinolizidinone **5** (1.170 g, 2.80 mmol), boronate **29** (0.900 g, 3.00 mmol), CsF (1.280 g, 8.40 mmol) and $Pd(PPh_3)_4$ (0.220 g, 0.28 mmol). The reaction mixture was heated at 95 °C for 18 h. The resulting white suspension was filtered through a pad of Celite® and washed with EtOAc (200 mL). After evaporation *in vacuo*, the residue was purified by flash column chromatography on silica gel eluting with EtOAc to yield yellow oil (1.010 g, ~80%, contaminated with triphenylphosphineoxyde). Appears as an 80:20 mixture of rotamers about the biaryl axis (variable with concentration). **IR** (neat): 2931, 1712, 1511, 1244, 987. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.92 (0.8H, s, CHO), 9.89 (0.2H, s, CHO), 7.92 (1H, dd, *J* 2.2, 8.6 Hz, ArH), 7.72 (1H, d, *J* 2.2 Hz, ArH), 7.32 (1H, d, *J* 8.6 Hz, ArH), 6.87 (0.2H, s, ArH), 6.72 (0.8H, s, ArH), 6.63 (0.2H, s, ArH), 6.60 (0.8H, s, ArH), 5.25 (0.2H, d, *J* 7.0 Hz, OCH_2O, AB), 5.18 (0.8H, d, *J* 7.0 Hz, OCH_2O, AB), 5.10 (0.8H, d, *J* 7.0 Hz,

OC$\underline{H}_2$O, A$\underline{B}$), 5.04 (0.2H, d, *J* 7.0 Hz, OC$\underline{H}_2$O, A$\underline{B}$), 4.30 (0.2H, dd, *J* 5.6, 5.7 Hz, NC$\underline{H}$Ar), 4.10 (0.8H, dd, *J* 5.1, 5.3 Hz, NC$\underline{H}$Ar), 3.88 (3H, s, OC$\underline{H}_3$), 3.83 (2.4H, s, OC$\underline{H}_3$), 3.79 (0.6H, s, OC$\underline{H}_3$), 3.39 (0.6H, s, C$\underline{H}_3$OCH$_2$), 3.02 (2.4H, s, C$\underline{H}_3$OCH$_2$), 3.07 (1H, m, NC$\underline{H}$alkyl), 2.81-2.76 (0.8H, dd, *J* 5.3, 14.0 Hz, COalkyl-$\underline{H}$, A$\underline{B}$X), 2.71-2.66 (0.2H, dd, *J* 5.0, 14.0 Hz, COalkyl-$\underline{H}$, A$\underline{B}$X), 2.63-2.52 (2H, m, COalkyl-$\underline{H}$), 2.41-2.38 (1H, d, *J* 12.4 Hz, Nalkyl-$\underline{H}$, A$\underline{B}$X), 2.32-2.26 (1H, m, COalkyl-$\underline{H}$, A$\underline{B}$X), 2.14-2.01 (1H, m, Nalkyl-$\underline{H}$, A$\underline{B}$X), 1.74-1.16 (6H, m, alkyl-$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$): *major isomer* – δ 210.6, 190.1, 159.9, 148.7, 147.9, 133.2, 132.2, 131.9, 130.7, 129.8, 128.6, 114.6, 113.3, 110.3, 95.1, 59.3, 56.8, 56.1, 56.1, 55.7, 50.3 , 47.5, 47.0, 31.0, 23.7, 23.4. **HR-MS** (ESI) for $C_{26}H_{32}NO_6$ $[M+H]^+$: calcd. 454.2224, found 454.2212. (4*S*,9a*R*)-**30** $[\alpha]_D^{20}$ = -25 (c 0.2, $CHCl_3$).

(±)-(*Z*)-2-(trimethylsilyl)ethyl-3-(2'-((2*S*,4*S*,9a*R*)-2-hydroxyoctahydro-1H-quinolizin-4-yl)-4',5'-dimethoxy-6-(methoxymethoxy)biphenyl-3-yl)acrylate (31). 18-Crown-6 (0.840 g, 3.18 mmol) was dissolved under N_2 in THF (17 mL) and the solution was cooled to -78 °C. KHMDS (0.5 M in toluene, 1.4 mL, 0.70 mmol) was added *via* septum and the reaction mixture was stirred for 10 min. Phosphonate **26** (0.270 g, 0.70 mmol) was added *via* septum and the reaction mixture was stirred for 10 min. A solution of aldehyde **30** (0.140 g, 0.47 mmol) in dry THF (5 mL) was cooled to -78 °C and then transferred by cannula. The reaction mixture was warmed up to 0 °C and stirring was continued overnight. The reaction was quenched with brine (20 mL) and extracted with DCM (3 × 30 mL); the combined organic layers were washed with brine (3 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with Et_2O:Et_3N (9.5:0.5) to yield yellow oil (0.250 g, 65%) as a mixture of *Z* and *E* ester in a 1:2 ratio. The product was contaminated with residual 18-Crown-6 but was directed engaged in the next step. **31** (0.10 g, 0.19 mmol) was then dissolved in dry, N_2 saturated THF (10 mL) and solution was cooled down to -78 ºC. L-Selectride (1M, 0.19 mL, 0.19 mmol) was added

via septum and the reaction mixture was stirred for 30 min. The reaction mixture was then quenched at -78 °C by addition of SiO_2. Mixture was concentrated to dryness *in vacuo* and passed to a short pad of silica eluting with $CHCl_3$/MeOH 9/1 affording alcohol in 57% yield (0.057 g, 0.096 mmol) as a mixture of *Z* and *E* isomers. A mixture of two rotamers of eache isomer is observed. Fractional integration are reported below this refers to the minor rotamer. **IR** (neat): 3308, 2940, 2929, 2857, 1668, 1594, 1567, 1504, 1465, 1251, 1116, 1059, 837; **^{1}H NMR** (400 MHz, C_6D_6) δ 12.4 (1H, s), 11.94 (1.7H, s), 8.61 (1H, s), 8.46 (1.7H, s), 8.03-8.01(2.7H, m), 7.97 (0.6H, d, *J* 15.9 Hz), 7.68 (0.4H, d, *J* 8.5 Hz), 7.65 (1.7H, d, *J* 8.5 Hz), 7.37 (1H, dd, *J* 2.0, 8.6 Hz), 7.22-7.19 (5.3 H, m), 7.15-7.12 (5.7H, m), 7.08(1.3H, d, *J* 8.6 Hz), 6.81-6.78 (3.3H, m), 6.71 (1.2H, d, *J* 13 Hz), 6.59-6.56 (3.3H, m), 6.22 (4H, s), 5.92 (1.4 H, d, *J* 12.8 Hz), 5.80 (1.1 H, d, *J* 12.8 Hz), 5.45-5.34 (1.6H, m), 5.02 (2.8H, d, *J* 6.7 Hz), 4.81 (1.2H, d, *J* 6.7 Hz), 4.75-4.73 (1.5H, m), 4.57 (1.2H, d, *J* 6.7 Hz), 4.44-4.37 (4.2H, m), 4.30-4.17 (12.9H, m), 4.11-3.91 (4H, m), 3.44 (4.3 H, s), 3.39 (4H, s), 3.38 (1.4H, s), 3.34-3.25 (2.7H, m), 3.05 (4.1H, s), 3.02 (1.8H, s), 3.0 (5.9H, s), 2.97-2.85 (4.3H, m), 2.70-2.46 (8.1H, m), 2.29-2.08 (3.3H, m), 1.89-1.87 (1.8H, m), 1.67-1.64 (1.4H, m), 1.40-0.79 (27H, m), 0.73-0.56 (4H, m), -0.05 (4.2H, s), -0.09 (11.6H, s), -0.09 (9.7H, s). **^{13}C NMR** (125 MHz, C_6D_6) δ 167.5, 166.9, 166.1, 158.1, 157.2, 156.3, 156.0, 151.4, 150.2, 149.4(2 C), 144.2, 143.9, 143.0, 135.0, 134.0, 133.0, 129.8, 128.7, 128.6, 128.4, 128.2 (2 C), 128.1, 128.0, 127.9, 127.5, 119.8, 118.7, 117.8, 116.2, 114.9, 114.2, 112.0, 95.7, 95.6, 94.4, 77.7, 64.0, 63.6, 63.0, 62.6, 62.4, 57.2, 56.0, 55.9, 55.7, 55.6, 52.1, 51.2, 48.8, 39.3, 30.2, 30.1, 27.2, 27.0, 23.5, 18.7, 17.7, 17.5, 17.4, -1.5, -1.6. **HRMS** (ESI) for $C_{33}H_{48}NO_7Si$ $[M+H]^+$: calcd.: 598.3200, found 598.3212.

(±)-(2*S*,4*S*,9a*R*)-4-(2-iodo-4,5-dimethoxyphenyl)octahydro-1H-quinolizin-2-ol (33) A solution of L-Selectride (1.0 M in THF, 2.88 mL, 2.88 mmol) was added dropwise at -78 °C to a solution of compound **5** (1.000 g, 2.40 mmol) in THF (40 mL). After 1 h the reaction

mixture was quenched by addition of MeOH (50 mL) then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc to yield pale brown foam (0.720 g, 72%). **m.p.**: 85-86 °C. **IR** (neat): 3463, 3025, 2945, 2970, 1506, 1445, 1366, 1217, 854. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (1H, s, ArH), 6.97 (1H, s, ArH), 4.50 (1H, s, CHO), 4.12 (1H, m, NCHAr), 3.84 (6H, s, OCH_3), 3.13 (1H, s, NCHalkyl), 2.71 (1H, d, *J* 12.0 Hz, Nalkyl-H, ABX), 2.41 (1H, m, COalkyl-H), 2.07 (1H, d, J 12.8 Hz, Nalkyl-H, ABX), 1.85-1.23 (10H, m, alkyl-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.0, 148.6, 131.9, 121.7, 111.1, 100.0, 88.1, 64.8, 57.8, 56.3, 56.1 (2C), 51.0, 41.2, 39.6, 30.0, 25.4, 22.8. **MS** (ESI) (M+H) 418 (100).

3-(3-Iodo-4-methoxymethoxy-phenyl)-*Z*-acrylic acid (34). Ester **20** (1.100 g, 3.16 mmol) and LiOH (1 M aq, 6.3 mL) were refluxed in THF (20 mL) for 3 h. After concentrating, the residue was acidified with HCl (1 M aq, 20 mL), extracted with EtOAc (3 × 100 mL). The combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with EtOAc:MeOH (9:1) to yield white oil (0.980 g, 93%).**^{1}H NMR** (300 MHz, C_6D_6) δ 8.05 (1H, d, *J* 2.3 Hz, ArH), 7.59 (1H, dd, *J* 2.3, 8.7 Hz, ArH), 6.74 (1H, d, *J* 8.7 Hz, ArH), 6.20 (1H, d, *J* 12.4 Hz, CHCH), 5.63 (1H, d, *J* 12.4 Hz, CHCH), 4.67 (2H, s, OCH_2), 3.02 (3H, s, OCH_3). **^{13}C NMR** (75 MHz, C_6D_6) δ 171.1, 157.4, 144.2, 142.4, 132.3, 130.2,117.7, 113.8, 85.6, 94.7, 55.9**. HR-MS** (ESI) for $C_{12}H_{13}O_4I$ $[M+H]^+$: calcd. 347.9859, found 347.9847.

(4*S*,9a*R*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-methanolphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-ol (36) A solution of L-Selectride (1.0 M in THF, 6.5 mL, 6.50 mmol) was added dropwise at -78 °C to a solution of compound **30** (1.340 g, 2.95 mmol) in THF (100 mL). After 1 h the reaction mixture was quenched by addition of MeOH (50 mL) then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:MeOH (95:5) to yield pale brown foam

(0.950 g, 72%). Appears as a 60:40 mixture of rotamers about the biaryl axis. **m.p.**: 79-82 °C. **IR** (neat): 3361, 2930, 2853, 1606, 1514, 1494, 1463, 1244, 1205, 1078, 996. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.48 (0.6H, d, *J* 2.0 Hz, ArH), 7.41 (0.6H, br s, ArH), 7.37 (0.4H, d, *J* 1.8 Hz, ArH), 7.31 (0.4H, br s, ArH), 7.27-7.18 (1.4H, m, ArH), 7.12 (0.6H, dd, *J* 2.0, 8.6 Hz, ArH), 6.86 (0.6H, s, ArH), 6.76 (0.4H, s, ArH), 4.97 (0.4H, d, *J* 6.6 Hz, OCH_2O, ABX), 4.92 (0.6H, d, *J* 6.6 Hz, OCH_2O, ABX), 4.83 (0.4H, d, *J* 6.6 Hz, OCH_2O, ABX), 4.78 (0.6H, d, *J* 6.6 Hz, OCH_2O, ABX), 4.66 (0.6H, d, *J* 12.6 Hz, CH_2OH, AB), 4.60-4.52 (2H, m, 1.4H CH_2O and 0.6H CHOH), 4.42-4.37 (0.4H, m, CHOH), 4.34-4.27 (0.4H, m, NCHAr), 4.18-4.12 (0.6H, m, NCHAr), 3.66 (1.8H, s, CH_3), 3.62 (1.2H, s, CH_3), 3.48 (1.8H, s, CH_3), 3.42 (1.2H, s, CH_3), 3.12-3.07 (3.4H, m, 3H CH_3 and 0.4H NCH), 3.06-2.98 (1H, m, alkyl-H), 2.76-2.73 (0.4H, m, alkyl-H), 2.58-2.52 (0.6H, m, alkyl-H), 2.53 (0.6H, m, alkyl-H), 2.13-1.09 (10H, m, alkyl-H). **^{13}C NMR** (100 MHz, C_6D_6) *cannot distinguish isomers, nor see doubling of all carbons as some signals are broad* – Major isomer δ 154.5, 150.1, 148.5, 135.3, 132.5, 131.8, 131.0, 128.3, 127.9, 95.4, 115.6, 115.3, 112.5, 65.5, 64.8, 57.2, 56.1, 56.0, 55.4, 53.4, 51.5, 42.9, 40 (br), 30.9 (br), 26.3, 22.9 (br). **HR-MS** (ESI) for $C_{26}H_{36}NO_6$ $[M+H]^+$: calcd. 458.2537, found 458.2542. (4*S*,9a*R*)-**36** $[\alpha]_D^{20}$ = -31.2 (c 0.2, $CHCl_3$).

(4*S*,9a*R*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-carboxaldehyphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-ol (37). To a solution of the diol **36** (0.780 g, 1.70 mmol) in Et_2O:acetone (6:1, 120:20 mL) was added MnO_2 (4.000 g, 5 wt eq). Starting material was consumed within 20 min. The mixture was filtered through Celite® (washing extensively with EtOAc, 600 mL), and the filtrate was concentrated *in vacuo* to yield brown solid (0.766 g, 98%). Appears as a 60:40 mixture of rotamers about the biaryl axis. **m.p.**: 84-86 °C. **IR** (neat): 3386, 2930, 1692, 1597, 1513, 1245, 1205, 1081, 978. **^{1}H NMR** (400 MHz, C_6D_6) δ 9.74 (0.6H, s, CHO), 9.71 (0.4H, s, CHO), 7.87 (0.6H, d, *J* 2.0 Hz, ArH), 7.82 (0.4H, d, *J* 2.0 Hz, ArH), 7.55 (0.6H, dd, *J* 2.3, 8.6 Hz, ArH), 7.51 (0.4H, dd, *J* 2.3, 8.6 Hz, ArH),

7.29-7.26 (1H, m, ArH), 7.11 (0.6H, d, *J* 8.6 Hz, ArH), 7.06 (0.4H, d, *J* 8.6 Hz, ArH), 6.65 (0.4H, s, ArH), 6.61 (0.6H, s, ArH), 4.90 (0.6H, d, *J* 6.8 Hz, OCH_2O, ABX), 4.78 (0.4H, d, *J* 6.8 Hz, OCH_2O, ABX), 4.73 (0.6H, *J* 6.8 Hz, OCH_2O, ABX), 4.64 (0.4H, d, *J* 6.8 Hz, OCH_2O, ABX), 4.35 (0.4H, dd, *J* 5.5 Hz, CHOH), 4.22-4.17 (1.2H, m, NCHAr and CHOH), 4.04-4.02 (0.4H, m, NCHAr), 3.58 (1.2H, s, CH_3), 3.57 (1.8H, s, CH_3), 3.44 (1.2H, s, CH_3), 3.37 (1.8H, s, CH_3), 3.11-3.04 (0.6H, m, NCH), 2.99 (1.8H, s, CH_3), 3.00 (1.2H, s, CH_3), 2.98-2.89 (1H, m, 0.4H NCH and 0.6H alkyl-H), 2.70-2.67 (0.6H, m, alkyl-H), 2.51 (0.4H, dd, *J* 2.3, 12.4 Hz, alkyl-H, ABX), 2.32-2.26 (0.6H, dd, *J* 2.5, 12.1 Hz, alkyl-H, ABX), 2.23-2.17 (0.6H, m, alkyl-H), 2.11-2.04 (0.6H, m, alkyl-H), 1.99-1.90 (2H, m, alkyl-H), 1.68-1.06 (7.6H, m, alkyl-H). **^{13}C NMR** (100 MHz, C_6D_6) *cannot fully distinguish isomers* – δ Major isomer 190.5, 160.6, 150.2, 149.0, 133.3, 133.2, 131.8, 132.3, 131.5, 130.7, 115.2, 114.7, 112.9, 95.3, 65.6, 56.7, 56.4, 56.4, 55.9, 55.4, 51.6, 42.9, 41.0, 32.0, 25.8, 24.0. **HR-MS** (ESI) for $C_{26}H_{34}NO_6$ $[M+H]^+$: calcd. 456.2380, found 456.2388. (4*S*,9a*R*)-**37** $[\alpha]_D^{20}$ = +4.4 (c 0.5, $CHCl_3$).

(±)-(4*S*,9a*R*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-vinylphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-ol (38). A 1.6M solution of *n*BuLi 1.6M (7.53 mL, 12.0 mmol) in hexane was added dropwise under N_2 to a cooled solution (0 °C) of $[Ph_3PCH_3][Br]$ (4.480 g, 12.5 mmol) in dry THF (11 mL). The mixture was stirred at 0 °C during 30 mn and 30 mn at rt then the reaction mixture was cooled to -78 °C and the aldehyde **37** (1.100 g, 2.4 mmol) was added slowly. The reaction mixture was stirred 16 h until rt. The reaction was quenched with a saturated NH_4Cl aqueous solution (20 mL) then the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:MeOH:NEt_3 (1:0.1:0.05) to yield a yellow solid (0.530 mg, 65%). Appears as a 60:40 mixture of rotamers about the biaryl axis (variable with

concentration). **m.p.**: 100-104 °C. **IR** (neat, cm^{-1}): 3600, 2929, 1631, 1511, 1462, 1242, 987. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (1H, ddd, *J* 2.04, 8.32, 9.34 Hz, ArH), 7.16-7.08 (2H, m, ArH), 6.99 (1H, s, ArH), 6.68-6.59 (1H, s ArH, 1H, dd, *J* 10.8, 17.6 Hz, CHCH$_2$), 5.59 (1H, d, *J* 17.6 Hz, CHCH$_2$), 5.15-5.18 (2H, m, 1H CHCH$_2$, 1H OCH$_2$), 4.98 (H, d, *J* 6.8 Hz, OCH$_2$), 4.28-4.24 (0.7H, m, CHOH), 4.20-4.07 (1.3H, m, 1H ArCHN, 0.3H CHOH), 3.91 (3H, s, OCH$_3$), 3.82 (2.1H, s, OCH$_3$), 3.80 (0.9H, s, OCH$_3$), 3.32 (3H, s, CH$_3$OCH$_2$), 3.08 (0.4H, m, NCH-Alkyl), 2.95 (0.6H, m, NCH-Alkyl), 2.64-2.61 (0.4H, d, *J* 12.8 Hz, CH$_2$N, ABX), 2.47-2.44 (0.6H, d, *J* 12.8 Hz, CH$_2$N, ABX), 2.10-1.16 (11H, m, CH$_2$CO,CH$_2$N alkyl-CH$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 154.8, 148.3, 146.9, 136.2, 131.6, 131.3, 131.2, 131.0, 129.6, 126.8, 114.8, 113.4, 112.7, 111.0, 95.1, 65.3, 56.3, 56.2, 56.2, 56.0, 55.5, 51.0, 41.6, 40.9, 35.8, 25.0, 23.9. **HR-MS** (ESI) for $C_{27}H_{36}NO_5$ $[M+H]^+$: calcd. 454.2598, found 454.2588.

(±)-(4*S*,9a*R*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-vinylphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2yl-acrylate (39). A solution of biaryl **38** (0.669 g, 1.47 mmol), NEt_3 (0.825 mL, 5.90 mmol), acrylic acid (0.172 mL, 2.50 mmol) in DCM (2 mL) was stirred during 5 mn at 0 °C then cannulated to a solution of Mukayama's salt (0.679 mg, 2.65 mmol) in DCM (2mL). The reaction mixture was stirred 1 h at 0 °C and 1 h at rt. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) then the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 20mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:MeOH (1:0.05) to yield a yellow solid (0.56 mg, 84 %). Appears as a 70:30 mixture of rotamers about the biaryl axis (variable with concentration). **m.p.**: 95-98 °C. **IR** (neat, cm^{-1}): 2930, 1716, 1634, 1605, 1497, 1247, 1184, 982, 809. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.42-7.36 (1.7H, m, ArH), 7.26-7.31 (1.3H, m, ArH), 7.17-7.12 (1H, m, ArH), 6.69-6.62 (2H, m 1H ArH, 1H CHCH$_2$), 6.25-

6.19 (1H, m, C<u>H</u>CH$_2$), 6.01-5.90 (1H, dd, *J*.10.4, 17.2 Hz, C<u>H</u>CH$_2$), 5.63-5.55 (1H, dd, *J* 1.2, 17.2 Hz, CHC<u>H</u>$_2$), 5.40-5.29 (2H, m, 1H CHC<u>H</u>$_2$, 1H C<u>H</u>OH), 5.09-5.04 (1H, dd, *J* 1.2 10.4, CHC<u>H</u>$_2$), 6.8 (0.7H, d, *J* 6.8 Hz, OC<u>H</u>$_2$ <u>A</u>BX), 6.72 (0.3H, d, *J* 6.8 Hz, OC<u>H</u>$_2$, <u>A</u>BX), 4.76-4.71 (1H, d, *J* 6.8 Hz OC<u>H</u>$_2$ A<u>B</u>X), 3.4-3.37 (0.3H, m, ArC<u>H</u>N), 3.25-3.23 (0.7H, m, ArC<u>H</u>N), 3.61 (3H, s, C<u>H</u>$_3$O), 3.43 (0.9H, s, OC<u>H</u>$_3$), 3.38 (2.1H, s, OC<u>H</u>$_3$), 3.08 (0.9H, s, OC<u>H</u>$_3$), 3.02 (2.1H, s, OC<u>H</u>$_3$), 2.92-2.89 (1H, m, NC<u>H</u>-alkyl), 2.48-2.36 (1.7H, m, C<u>H</u>$_2$N), 2.09-1.99 (2.3H, m, 0.3H C<u>H</u>$_2$N and 2 alkyl-C<u>H</u>$_2$), 1.73-0.95 (8H, m, alkyl-C<u>H</u>$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 165.6, 154.9, 148.8, 147.3, 136.2, 133.8, 131.4, 130.8, 130.7, 130.5, 129.4, 129.3, 126.8, 115.1, 113.0, 112.6, 110.1, 95.0, 69.0, 56.4, 56.2, 55.9, 55.8, 52.1, 50.6, 38.0, 35.7, 29.0, 25.8, 21.9. **HR-MS** (ESI) for $C_{30}H_{38}NO_6$ $[M+H]^+$: calcd. 508.2689, found 508.2693.

(4*S*,9a*R*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-carboxaldehyphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2yl-acrylate (40). A solution of alcohol **37** (0.700 g, 1.53 mmol), NEt_3 (0.429 mL, 3.07 mmol), 4-DMAP (0.034 g, 0.27 mmol) in DCM (15 mL) was stirred during 15 mn at 0 °C then acryloyl chloride (0.250 mL, 3.07 mmol) was added. The reaction mixture was stirred 1 h at 0 °C and 2 h at rt. The reaction mixture was quenched with a saturated $NaHCO_3$ aqueous solution (20 mL) then the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (3 × 80 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc: MeOH (1:0.05) to yield yellow solid (0.640 g, 84%). Appears as a 70:30 mixture of rotamers about the biaryl axis. **m.p.**: 63-66 °C. **IR** (neat): 2932, 2852, 1716, 1690, 1597, 1244, 1189, 974. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (0.7H, s, C<u>H</u>O), 9.78, (0.3H, s, C<u>H</u>O), 7.83-7.79 (1.0H, m, Ar<u>H</u>), 7.66 (0.7H, d, *J* 2.1 Hz, Ar<u>H</u>), 7.50 (0.3H, d, *J* 2.1, Ar<u>H</u>), 7.31-7.28 (0.3H, d, *J* 8.6 Hz, Ar<u>H</u>), 7.24-7.22 (0.7H, d, *J* 8.6, Ar<u>H</u>), 7.11 (1.0H, s, Ar<u>H</u>), 6.59 (0.3H, s, Ar<u>H</u>), 6.56 (0.7H, s, Ar<u>H</u>), 6.2-6.15 (1.0H, dd,

J.1.2, 17.2 Hz, CHC$\underline{H}_2$, $\underline{A}$BX), 5.98-5.84 (1.0H, dd, *J* 10.4, 17.2 Hz, C$\underline{H}$CH$_2$), 5.77-5.69 (1.0H, dd, *J* 1.2, 10.4 Hz, CHC$\underline{H}_2$, A$\underline{B}$X), 5.23-5.15 (2.0H, m, 1.0H C$\underline{H}$OH and OC$\underline{H}_2$O A$\underline{B}$X), 5.02 (0.3H, d, *J* 6.9 Hz, OC$\underline{H}_2$O, $\underline{A}$BX), 4.95 (0.7H, d, *J* 6.9 Hz, OC$\underline{H}_2$O, $\underline{A}$BX), 4.07 (0.3H, m, ArC$\underline{H}$N), 3.92 (3.0H, s, OC$\underline{H}_3$,and 0.7 H, m, ArC$\underline{H}$N), 3.79 (2.1H, s, OC$\underline{H}_3$), 3.76 (0.9H, s, OC$\underline{H}_3$), 3.36 (0.9H, s, OC$\underline{H}_3$), 3.23 (2.1H, s, OC$\underline{H}_3$), 3.05 (1.0H, m, NC$\underline{H}$alkyl), 2.73-2.6 (1.0H, d, *J* 12.4 Hz, C$\underline{H}_2$N $\underline{A}$BX), 2.33 (1.0H, m, C$\underline{H}_2$N A$\underline{B}$X), 2.0-1.97 (3.0H, m, C$\underline{H}_2$CHO), 1.62-1.47 (3.0H, m, C$\underline{H}_2$CHO, alkyl-$\underline{H}$), 1.24-1.01 (4.0H, m, alkyl-$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 191.1, 165.4, 160.1, 149.2, 147.6, 133.2, 132.2, 131.3, 131.2, 130.7, 130.4, 130.0, 128.8, 114.5, 112.8, 110.1, 94.6, 68.8, 56.5, 56.3, 56.0, 55.9, 52.6, 50.3, 37.5, 35.3, 28.9, 21.9, 20.0. **HR-MS** (ESI) for $C_{29}H_{36}NO_7$ $[M+H]^+$: calcd. 510.2486, found 510.2499. (4*S*,9a*R*)-**40** $[\alpha]_D^{20}$ = -5.6 (c 0.5, $CHCl_3$).

(4*S*,9a*R*)-hexahydro-4-(2-(2'-hydroxy-5'-carboxaldehyphenyl)-4,5-dimethoxy-phenyl)-1H-quinolizin-2yl-acrylate (41). To a stirred solution of compound **40** (0.546 g, 1.07 mmol), in DCM (8 mL) was added TFA (8 mL, 107 mmol) at 0 °C. The reaction mixture was stirred 1 h at 0 °C and 2 h at rt. The reaction mixture was quenched with a saturated $NaHCO_3$aqueous solution (100 mL) then the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (3 × 120 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:MeOH:Et_3N (1:0.1:0.02) to yield yellow solid (0.430 g, 87%). Appears as a 70:30 mixture of rotamers about the biaryl axis. **m.p.**: 102-105 °C. **IR** (neat): 2932, 2851, 1716, 1681, 1582, 1246, 1179, 983. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.78-9.76 (1.0H, s, C$\underline{H}$O), 7.73 (0.7H, dd, *J* 2.0, 8.3 Hz, Ar$\underline{H}$), 7.67 (0.3H, dd, *J* 2.3, 8.3 Hz Ar$\underline{H}$), 7.57 (1.0H, d, *J* 2.0 Hz, Ar$\underline{H}$), 7.28 (0.7H, s, Ar$\underline{H}$), 7.27 (0.3H, s, Ar$\underline{H}$), 7.03 (0.7H, d, *J* 8.3 Hz, Ar$\underline{H}$), 6.88 (0.3H, d, *J* 8.3 Hz, Ar$\underline{H}$), 6.67 (0.3H, s, Ar$\underline{H}$), 6.64 (0.7H, s, Ar$\underline{H}$), 6.40-6.28

(1.0H, d, *J* 17.4 Hz, CHC$\underline{H}_2$, $\underline{A}$BX), 6.14-6.07 (1.0H, dd, *J* 10.3, 17.4 Hz, C$\underline{H}$CH$_2$), 5.87-5.8 (1.0H, dd, *J* 10.3 Hz, CHC$\underline{H}_2$, A$\underline{B}$X), 5.71 (1.0H, m, C$\underline{H}$O), 4.18 (0.3H, m, ArC$\underline{H}$N), 3.98 (2.1H, s, OC$\underline{H}_3$), 3.89 (0.9H, s, OC$\underline{H}_3$ and 0.7H, m, ArC$\underline{H}$N), 3.80 (3.0H, s, OC$\underline{H}_3$), 3.26-3.27 (1H, m, NC$\underline{H}$alkyl), 3.03-3.97 (0.7H, NC$\underline{H}_2$, $\underline{A}$BX), 2.84-2.81 (0.3H, m, NC$\underline{H}_2$, $\underline{A}$BX), 2.53 (0.3H, m, NC$\underline{H}_2$, A$\underline{B}$X), 2.27-2.11 (2.0H, m, C$\underline{H}_2$CHO and 0.7H, C$\underline{H}_2$N, A$\underline{B}$X), 1.99-1.91 (1.7H, m, C$\underline{H}_2$CHO), 1.77-1.37 (6.3H, m, alkyl-C$\underline{H}_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – Major isomer δ 191.1, 165.9, 165.3, 148.6, 148.4, 133.6, 132.6, 132.0, 131.6, 130.9, 128.7, 127.9, 120.1, 114.9, 111.1, 69.5, 56.5, 56.2, 55.4, 49.3, 47.0, 32.2, 29.3, 28.9, 23.9, 18.5. ; 1xC not observed for each isomer. **HR-MS** (ESI) for $C_{27}H_{31}NO_6$ $[M+H]^+$: calcd. 465.2233, found 465.2230. (4*S*,9a*R*)-**41** $\mathbf{[\alpha]_D^{20}}$ = -14.2 (c 0.5, $CHCl_3$).

(4*S*,9a*R*)-hexahydro-4-(2-(2'-tert-butyldimethylsiloxy-5'-carboxaldehyphenyl)-4,5-dimethoxy-phenyl)-1H-quinolizin-2yl-acrylate (42). A solution of coumpond **39** (0.311 g, 0.67 mmol), NEt_3 (0.168 mL, 1.19 mmol), 4-DMAP (0.015 g, 0.13 mmol) in DCM (7 mL) was stirred during 5 mn at 0 °C then TBDMSCl (0.150 g, 1.01 mmol) was added. The reaction mixture was stirred 1 h at 0 °C and 2 h at rt. The reaction mixture was quenched with a saturated NH_4Cl aqueous solution (20 mL) then the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (3 × 70 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:MeOH (1:0.02) to yield yellow solid (0.320 g, 83%). Appears as a 60:40 mixture of rotamers about the biaryl axis. **m.p.**: 85-88 °C. **IR** (neat): 2937, 2855, 1718, 1692, 1595, 1249, 1182, 1047, 834. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (0.6H, s, C$\underline{H}$O), 9.77 (0.4H, s, C$\underline{H}$O), 7.78-7.79 (1.0H, dd, *J* 2.2, 8.3 Hz, Ar$\underline{H}$), 7.69 (0.6H, d, *J* 2.2 Hz, Ar$\underline{H}$), 7.51 (0.4H, d, *J* 2.2 Hz, Ar$\underline{H}$), 7.07 (1.0H, s, Ar$\underline{H}$), 6.96 (0.4H, d, *J* 8.3 Hz, Ar$\underline{H}$), 6.88 (0.6H, d, *J* 8.3 Hz, Ar$\underline{H}$), 6.60 (0.4H, s, Ar$\underline{H}$), 6.57 (0.6H, s, Ar$\underline{H}$), 6.18 (0.4H, dd, *J* 1.5, 17.2 Hz, CHC$\underline{H}_2$), 6.13 (0.6H, dd, *J* 1.5, 17.2 Hz, CHC$\underline{H}_2$), 5.96-5.86 (1.0H, dd, *J* 10.3, 17.2 Hz,

CHCH$_2$), 5.73-5.69 (1.0H, dd, *J* 1.5 10.3, Hz, CHCH$_2$), 5.18-5.15 (1.0H, m, CHO), 4.04-4.01 (0.4H, m, NCHAr), 3.91 (3H, s, OCH$_3$ and 0.6H, m, NCHAr), 3.78 (1.2H, s, OCH$_3$), 3.77 (1.8H, s, OCH$_3$), 3.06-2.95 (1.0H, m, NCH-alkyl), 2.77-2.65 (1.0H, t, *J* 13.4 Hz, NCH$_2$-alkyl, ABX), 2.30-2.24 (1H, q, *J* 13.4 Hz, NCH$_2$-alkyl, ABX), 2.03-1.85 (3.0H, m, CH$_2$CHO), 1.63-1.44 (3.0H, m, 1.0H CH$_2$CHO and 2.0H alkyl-H), 1.16-1.01 (4H, m, alkyl-H), 0.72 (3.6H, s, (CH$_3$)$_3$CSi), 0.64 (5.4H, s, (CH$_3$)$_3$CSi), 0.14 (1.8H, s, CH$_3$Si), 0.04 (3H, s, CH$_3$Si), -0.09 (1.2H, s, CH$_3$Si). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 191.1, 165.4, 159.5, 149.0, 147.3, 134.1, 133.7, 132.9, 130.9, 130.4, 129.9, 129.5, 129.2, 119.8, 113.2, 110.6, 68.6, 56.5, 56.0, 55.8, 52.8, 50.2, 38.8, 35.9, 29.8, 29.1, 25.8, 25.5, 25.4, 22.5, 18.2, -4.2, -4.4. **HR-MS** (ESI) for $C_{33}H_{46}NO_6Si$ $[M+H]^+$: calcd. 580.3088, found 580.3087. (4*S*,9a*R*)-**42** $[\alpha]_D^{20}$ = +2.2 (c 0.5, $CHCl_3$)

(4*S*,9a*R*)-hexahydro-4-(2-(2'-tert-butyldimethylsiloxy-5'-vinylphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2yl-acrylate (43). Into a flame-dried flask and under N_2 was placed a 20% suspension of the Nysted's reagent in THF (0.458 mL, 0.24 mmol) an additional THF was added (0.5 mL). The suspension was cooled to 0 °C and neat titanium tetrachloride (26 μL, 0.24 mmol) was introduced dropwise followed by the addition of a solution of compound **42** (0.115 g, 0.20 mmol) in THF (0.5 mL). The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of 1 M HCl aqueous solution (5 mL) then the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with a saturated NH_4Cl aqueous solution (3 × 20 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc:MeOH (1:0.02) to yield yellow oil (0.070 g, 60%). Appears as a 60:40 mixture of rotamers about the biaryl axis. **IR** (neat): 2928, 2855, 1723, 1603, 1490, 1248, 1034, 905. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26-7.96 (3.0H, m, ArH), 6.82 (0.4H, d, *J* 8.4 Hz, ArH), 6.72 (0.6H, d, *J* 8.4 Hz, ArH), 6.67-6.51 (2.0H, m, 1.0H ArH and 1.0H

C<u>H</u>CH$_2$), 6.2-6.15 (1.0H, d, *J* 17.6 Hz, CHC<u>H</u>$_2$, <u>A</u>BX), 5.98-5.91 (1.0H, m, C<u>H</u>CH$_2$), 5.75-5.67 (1.0H, d, *J* 10.4 Hz, CHC<u>H</u>$_2$, A<u>B</u>X), 5.59-5.5 (1.0H, d, *J* 17.6 Hz, C<u>H</u>CH$_2$, <u>A</u>BX), 5.19 (1.0H, m, C<u>H</u>O), 5.12-5.03 (1.0H, d, *J* 10.4 Hz, CHC<u>H</u>$_2$, A<u>B</u>X), 4.5 (0.6H, m, ArC<u>H</u>N), 3.92 (3.4H, m, 3.0H OC<u>H</u>$_3$ and 0.4H ArC<u>H</u>N), 3.77 (3.0H, s, OC<u>H</u>$_3$), 3.37 (1.0H, m, NC<u>H</u>alkyl), 3.11 (1.0H, m, NC<u>H</u>$_2$alkyl), 2.75-2.71 (1.0H, m, alkyl-<u>H</u>), 2.37-1.39 (10H, m, alkyl-<u>H</u>), 0.72 (3.6H, s, (C<u>H</u>$_3$)$_3$Si), 0.64 (5.4H, s, (CH$_3$)$_3$Si), 0.11 (0.9H, s, C<u>H</u>$_3$Si), 0.08 (0.9H, s, C<u>H</u>$_3$Si), -0.01 (1.8H, s, C<u>H</u>$_3$Si), -0.17 (1.8H, s, CH$_3$Si). **^{13}C NMR** (100 MHz, CDCl$_3$) *cannot fully distinguish isomers* – δ Major isomer 165.3, 153.7, 149.0, 147.4, 136.3, 130.9, 130.7, 130.5, 130.2, 130.0, 129.1, 128.9, 126.6, 119.0, 113.3, 112.2, 110.5, 70.8, 56.0 (2C), 55.8, 52.5, 50.8, 50.2, 38.8, 37.4, 29.2, 26.7, 25.6, 25.5, 22.9, 18.2, -4.1, -4.4. **HR-MS** (ESI) for C$_{34}$H$_{48}$NO$_5$Si [M+H]$^+$: calcd. 578.3296, found 578.3270. (4*S*,9a*R*)-**43** **$[\alpha]_D^{20}$** = +10.0 (c 0.5, CHCl$_3$).

(+)-Vertine (1). Into a flame-dried flask and under N$_2$ was placed compound **1** (0.025 g, 0.04 mmol) and the Hoveyda Grubb's catalyst (0.005 g, 0.008 mmol) then degassed toluene (9 mL) was added. The reaction mixture was heated at 110 °C during 16 h. The reaction mixture was cooled down filtered through Celite® and evaporated *in vacuo*. The residue was passed through a short pad of silica gel, eluting with DCM:MeOH (9:1) to remove most of the impurities. The product was then dissolved in THF (5mL) and TBAF (0.012 g, 0.047 mmol) was added at -30 °C. The reaction mixture was stirred at this temperature for 1 h. The reaction mixture was quenched by addition of a saturated aqueous solution of NH$_4$Cl (3 × 20 mL) then the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on neutral alumina eluting with benzene:MeOH (9:1) to yield pale brown foam (0.007 g, 37%) Spectral data match literature values.**Error! Bookmark not defined.** **^{1}H NMR** (400 MHz, CD$_3$OD) δ 7.08 (1H, dd, *J* 2.3,

8.4 Hz, ArH), 7.02 (1H, s, ArH), 6.98 (1H, s, ArH), 6.94 (1H, d, *J* 2.3 Hz, ArH), 6.85 (1H, d, *J* 8.4 Hz, ArH), 6.72 (1H, d, *J* 12.6 Hz, ArCH), 5.70 (1H, d, *J* 12.6 Hz, CHCH), 5.20 (1H, m, CHO), 4.65 (1H, d, *J* 11.3 Hz, NCHAr), 3.77 (3H, s, OCH_3), 3.74 (3H, s, CH_3O), 3.02-3.01 (1H, m, NCH-alkyl), 2.75 (1H, d, *J* 14.0 Hz, NCH_2, ABX), 2.36-2.29 (1H, td, *J* 3.0, 13.4 Hz, NCH_2, ABX), 2.16-2.04 (2H, m, CH_2CHO), 1.93-1.86 (1H, m, CH_2CHO) 1.65-1.58 (2H, m, 1H for alkyl-H and 1H for CH_2CHO), 1.27-1.05 (2H, m, alkyl-H), 0.98-0.94 (1H, d, *J* 14.4 Hz, CH_2-alkyl), 0.70-0.56 (2H, m, CH_2-alkyl) **^{13}C NMR** (125 HMHz, CD_3OD) δ 170.1, 157.3, 150.9, 148.9, 137.3, 132.6, 131.7, 131.0, 126.6, 126.5, 119.3, 117.4, 115.85, 110.0, 72.7, 59.0, 56.7, 56.3, 51.3, 49.0, 40.5, 35.3, 27.3, 25.1, 20.5 (one quaternary carbon was not detected). **HR-MS** (ESI) for $C_{26}H_{30}NO_5$ $[M+H]^+$: calcd. 436.2118, found 436.2119. **$[\alpha]_D^{20}$** = +65 (c 0.2, $CHCl_3$).

(4*S*,9a*S*)-Hexahydro-4-(2-(2'-methoxymethoxy-5'-carboxaldehyphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-one (44) Desired product **44** was obtained in 84% yield from *trans*-quinolizidinone **6** (0.660 g, 1.59 mmol) following the same procedure as for the synthesis of **30**. Appears as an 70:30 mixture of rotamers about the biaryl axis. **IR** (neat): 2931, 2846, 1712, 1693, 1598, 1493, 1514, 1244, 987. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.90 (0.7H, s, CHO), 9.86 (0.3H, s, CHO), 7.86-7.81 (1.0H, dd, *J* 2.1, 8.6 Hz, ArH), 7.59 (0.7H, d, *J* 2.1 Hz, ArH), 7.57 (0.3H, d, *J* 2.1 Hz, ArH), 7.33 (0.7H, d, *J* 8.6 Hz, ArH), 7.29 (0.3H, d, *J* 8.6 Hz, ArH), 7.24 (0.3H, s, ArH), 7.15 (0.7H, s, ArH), 6.55 (0.7H, s, ArH), 6.53 (0.3H, s, ArH), 5.23 (0.3H, d, *J* 7.1 Hz, OCH_2O, AB), 5.20 (0.7H, d, *J* 6.8 Hz, OCH_2O, AB), 5.12 (0.7H, d, *J* 7.1 Hz, OCH_2O, AB), 5.04 (0.3H, d, *J* 6.8 Hz, OCH_2O, AB), 3.95-3.94 (3H, s, OCH_3), 3.82-3.80 (3H, s, OCH_3), 3.38 (2.1H, s, OCH_3), 3.34 (0.9H, s, OCH_3), 3.08-2.96 (1.3H, m, 1.0H NCHAr and 0.3H NCH_2alkyl, ABX), 2.74-2.72 (0.7H, m, NCH_2alkyl, ABX), 2.63 (0.7H, t, *J* 12.4 Hz, CH_2CO), 2.50-2.01 (4.3H, m, 3.3H CH_2CO and 1.0H NCHalkyl), 1.65-1.36 (6.0H, alkyl-H), 1.74-1.16 (1.0H, m, alkyl-H). **^{13}C NMR** (100 MHz, $CDCl_3$) *major*

isomer – δ 208.3, 191.2, 160.3, 149.7, 147.9, 133.1, 133.0, 132.0, 131.4, 130.5, 129.1, 114.7, 112.7, 119.1, 95.0, 65.6, 62.3, 57.0, 56.4, 56.1, 52.8, 50.1, 48.9, 34.5, 26.1, 24.2. **HR-MS** (ESI) for $C_{26}H_{32}NO_6$ $[M+H]^+$: calcd. 454.2224, found 454.2212. (4*S*,9a*S*)-**44** $[\alpha]_D^{20}$ = -55.0 (c 0.30, $CHCl_3$).

(4*S*,9a*S*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-methanolphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-ol (45). Desired product **45** was obtained in 89 % yield from **44** (0.530 g, 1.16 mmol) following the same procedure as for the synthesis of **37**. Appears as an 60:40 mixture of rotamers about the biaryl axis. **m.p.**: 81-85 °C. **IR** (neat): 3318, 2932, 2846, 1606, 1512, 1493, 1463, 1244, 1205, 1001. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (0.6H, d, *J* 8.7 Hz, ArH), 7.18-7.05 (3.4H, m, ArH), 6.69 (0.6H, s, ArH), 6.59 (0.4H, s, ArH), 5.10 (0.4H, d, *J* 6.4 Hz, OCH_2O, ABX), 5.06 (0.6H, d, *J* 6.8 Hz, OCH_2O, ABX), 5.0 (0.6H, d, *J* 6.8 Hz, OCH_2O, ABX), 4.96 (0.4H, d, *J* 6.4 Hz, OCH_2O, ABX), 4.63-4.58 (1.2H, m, CH_2OH), 4.51 (0.8H, d, *J* 12.2 Hz, CH_2OH), 4.00 (1.0H, s, CHOH), 3.90 (3.0H, s, OCH_3), 3.80 (3.0H, s, CH_3), 3.33 (1.8H, s, CH_3), 3.31 (1.2H, s, CH_3), 3.26-3.23 (1.0H, m, NCHAr), 2.70-2.58 (1.0H, m, NCH_2-alkyl, AB), 2.12 (1.0H, m, NCH), 1.87-1.10 (11.0H, m, alkyl-H). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot distinguish isomers, nor see doubling of all carbons as some signals are broad* – Major isomer δ 154.0, 149.0, 146.8, 134.7, 133.8, 131.5, 130.6, 130.0, 127.9, 115.2, 113.0, 109.7, 94.8, 65.3, 64.9, 58.7, 56.8, 56.3, 56.2, 56.0, 52.9, 42.7, 40.2, 33.8, 26.4, 25.1. **HR-MS** (ESI) for $C_{26}H_{36}NO_6$ $[M+H]^+$: calcd. 458.2464, found 458.2460. (4*S*,9a*S*)- **45** $[\alpha]_D^{20}$ = -55.3 (c 0.32, $CHCl_3$).

(4*S*,9a*S*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-carboxaldehyphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2(6H)-ol (46). Desired product **46** was obtained in 86% yield from **45** (0.450 g, 0.98 mmol) following the same procedure as for the synthesis of **40**. Appears as an 60:40 mixture of rotamers about the biaryl axis. **m.p.**: 87-89 °C. **IR** (neat):

3454, 2999, 2932, 1739, 1598, 1442, 1367, 1215. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (0.6H, s, CHO), 9.88 (0.4H, s, CHO), 7.87 (1.0H, dd, *J* 1.9, 8.5 Hz, ArH), 7.63-7.61 (1.0H, m, ArH), 6.5 (0.4H, d, *J* 8.5 Hz, ArH), 7.24-7.22 (1.2H, m, ArH), 7.13 (0.4H, m, ArH), 6.58-5.7 (1H, s, ArH), 5.25 (0.6H, d, *J* 6.4 Hz, OCH_2O, ABX), 5.21 (0.4H, d, *J* 6.8 Hz, OCH_2O, ABX), 5.08 (1.0H, d, *J* 6.4 Hz, OCH_2O, ABX), 4.03-3.98 (1H, m, OCH), 3.92 (3.0H, s, CH_3), 3.81-3.79 (3.0H, s, CH_3), 3.38 (1.8H, s, CH_3), 3.36 (1.8H, s, CH_3), 3.23-3.14 (1.0H, m, NCHAr), 2.78 (0.4H, d, *J* 9.8 Hz, NCH_2alkyl, AB), 2.58 (0.6H, d, *J* 8.5 Hz, NCH_2alkyl, AB), 2.16-2.10 (1.0H, m, NCH), 1.87-1.12 (11.0H, m, alkyl-CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 191.5, 159.7, 149.3, 147.1, 134.8, 133.4, 132.1, 131.4, 130.7, 129.1, 114.1, 112.5, 109.9, 94.7, 64.9, 59.0, 56.7, 56.4, 56.3, 56.1, 52.6, 43.3, 40.4, 33.9, 26.5, 25.2. **HR-MS** (ESI) for $C_{26}H_{34}NO_6$ $[M+H]^+$: calcd. 456.2380, found 456.2388. (4*S*,9a*S*)- **46 $[\alpha]_D^{20}$** = -30.3 (c 0.52, $CHCl_3$).

(4*S*,9a*S*)-hexahydro-4-(2-(2'-methoxymethoxy-5'-carboxaldehyphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2yl-acrylate (47). Desired product **47** was obtained in 62% yield from **46** (0.380 g, 0.83 mmol) following the same procedure as for the synthesis of **40**. Appears as an 60:40 mixture of rotamers about the biaryl axis. **m.p.**:61-64 °C. **IR** (neat): 2999, 2934, 2845, 1718, 1694, 1512, 1493, 1369, 1243, 1198. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.98 (0.6H, s, CHO), 9.85 (0.4H, s, CHO), 7.90-7.86 (1.0H, dd, *J* 2.1, 8.6 Hz, ArH), 7.65 (0.6H, d, *J* 2.1 Hz, ArH), 7.55 (0.4H, m, ArH), 7.37 (0.4H, d, *J* 8.6 Hz, ArH), 7.30 (0.6H, s, ArH), 7.24 (0.6H, d, *J* 8.6 Hz , ArH), 7.19 (0.4H, s, ArH), 6.62 (1H, s, ArH), 6.16 (0.6H, dd, *J* 1.5, 17.3 Hz, $CHCH_2$, ABX), 6.08-6.04 (0.4H, m, $CHCH_2$, ABX), 5.94 (0.6H, dd, *J* 10.4, 17.3 Hz, $CHCH_2$), 5.84-5.76 (0.4H, m, $CHCH_2$ and 0.6H, $CHCH_2$, ABX), 5.68 (0.4H, dd, *J* 1.5, 10.4 Hz, $CHCH_2$, ABX), 5.27-5.23 (1H, d, *J* 7.0 Hz, OCH_2O ABX), 5.15 (0.4H, d, *J* 7.0 Hz, OCH_2O ABX), 5.08-5.07 (0.6H, m, OCH), 5.01-4.97 (0.4H, m, OCH and 0.6H, d, *J* 7.0 Hz, OCH_2O, ABX), 3.99-3.98 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.47 (1.2H, s, OCH_3), 3.31

(1.8H, s, OC$\underline{H}_3$), 3.13-3.08 (1H, m, ArC$\underline{H}$N), 2.91 (0.4H, m, NC$\underline{H}_2$alkyl, $\underline{A}$BX), 2.79-2.76 (0.6H, m, NC$\underline{H}_2$alkyl, A$\underline{B}$X), 2.13-1.2 (12H, m, alkyl-$\underline{H}$, NC$\underline{H}$ and NC$\underline{H}_2$alkyl). **^{13}C NMR** (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 191.3, 165.4, 160.3, 149.4, 147.4, 135.0, 133.6, 132.0, 131.0, 130.6, 130.4, 129.1, 129.0, 114.5, 112.2, 109.4, 94.5, 68.9, 59.7, 57.5, 56.6, 56.3, 56.1, 52.8, 38.7, 37.3, 33.7, 26.4, 24.9. **HR-MS** (ESI) for $C_{29}H_{36}NO_7$ $[M+H]^+$: calcd. 510.2486, found 510.2499. (4*S*,9a*S*)- **47** $[\alpha]_D^{20}$ = -14.4 (c 0.16, $CHCl_3$).

(4*S*,9a*S*)-hexahydro-4-(2-(2'-hydroxy-5'-carboxaldehyphenyl)-4,5-dimethoxy-phenyl)-1H-quinolizin-2yl-acrylate (48). Desired product **48** was obtained in 93% yield from **47** (0.110 g, 0.22 mmol) following the same procedure as for the synthesis of **41**. Appears as a 99:1 mixture of rotamers about the biaryl axis. **m.p.**: 100-104 °C. **IR** (neat): 2938, 2847, 1719, 1673, 1583, 1346, 1180. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (1H, s, C$\underline{H}$O), 7.74 (1H, dd, *J* 2.1, 8.3 Hz, Ar$\underline{H}$), 7.55 (1H, dd, *J* 2.1, 8.3 Hz Ar$\underline{H}$), 7.0 (1H, d, *J* 8.3 Hz, Ar$\underline{H}$), 6.69 (1H, s, Ar$\underline{H}$), 6.62 (1H, s, Ar$\underline{H}$), 6.41 (1H, dd, *J* 1.1, 17.3 Hz, CHC$\underline{H}_2$, $\underline{A}$BX), 6.14 (1H, dd, *J* 10.4, 17.4 Hz, C$\underline{H}$CH$_2$), 5.85 (1H, dd, *J* 1.1, 10.3 Hz, CHC$\underline{H}_2$, A$\underline{B}$X), 4.91 (1H, m, C$\underline{H}$O), 3.90 (3H, s, OC$\underline{H}_3$), 3.85 (3H, s, OC$\underline{H}_3$), 3.51-3.48 (1H, m, NC$\underline{H}$Ar), 3.07 (1H, d, *J* 10.8 Hz, NC$\underline{H}_2$alkyl, $\underline{A}$BX), 2.61 (1H, t, *J* 11.0 Hz, NC$\underline{H}$), 2.17-2.04 (2H, m, 1H C$\underline{H}_2$CHO and 1H NC$\underline{H}_2$alkyl, A$\underline{B}$X), 1.85-1.47 (8H, m, alkyl-$\underline{H}$), 1.29-1.25 (1H, m, alkyl-$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.0, 165.4, 165.3, 149.0, 147.7, 135.0, 133.0, 131.7, 131.4, 130.9, 128.6, 128.5, 128.0, 121.7, 118.2, 116.0, 67.1, 65.0, 57.2, 56.4, 56.2, 53.2, 35.5, 32.9, 31.7, 24.6, 24.2. **HR-MS** (ESI) for $C_{27}H_{31}NO_6$ $[M+H]^+$: calcd. 465.2233, found 465.2240. (4*S*,9a*S*)-**48** $[\alpha]_D^{20}$ = +89.3 (c 0.15, $CHCl_3$

(4*S*,9a*S*)-hexahydro-4-(2-(2'-*tert*-butyldimethylsiloxy-5'-carboxaldehyphenyl)-4,5-dimethoxy-phenyl)-1H-quinolizin-2yl-acrylate (49). Desired product **49** was obtained in 83% yield from **48** (0.080 g, 0.17 mmol) following the same procedure as for the synthesis of

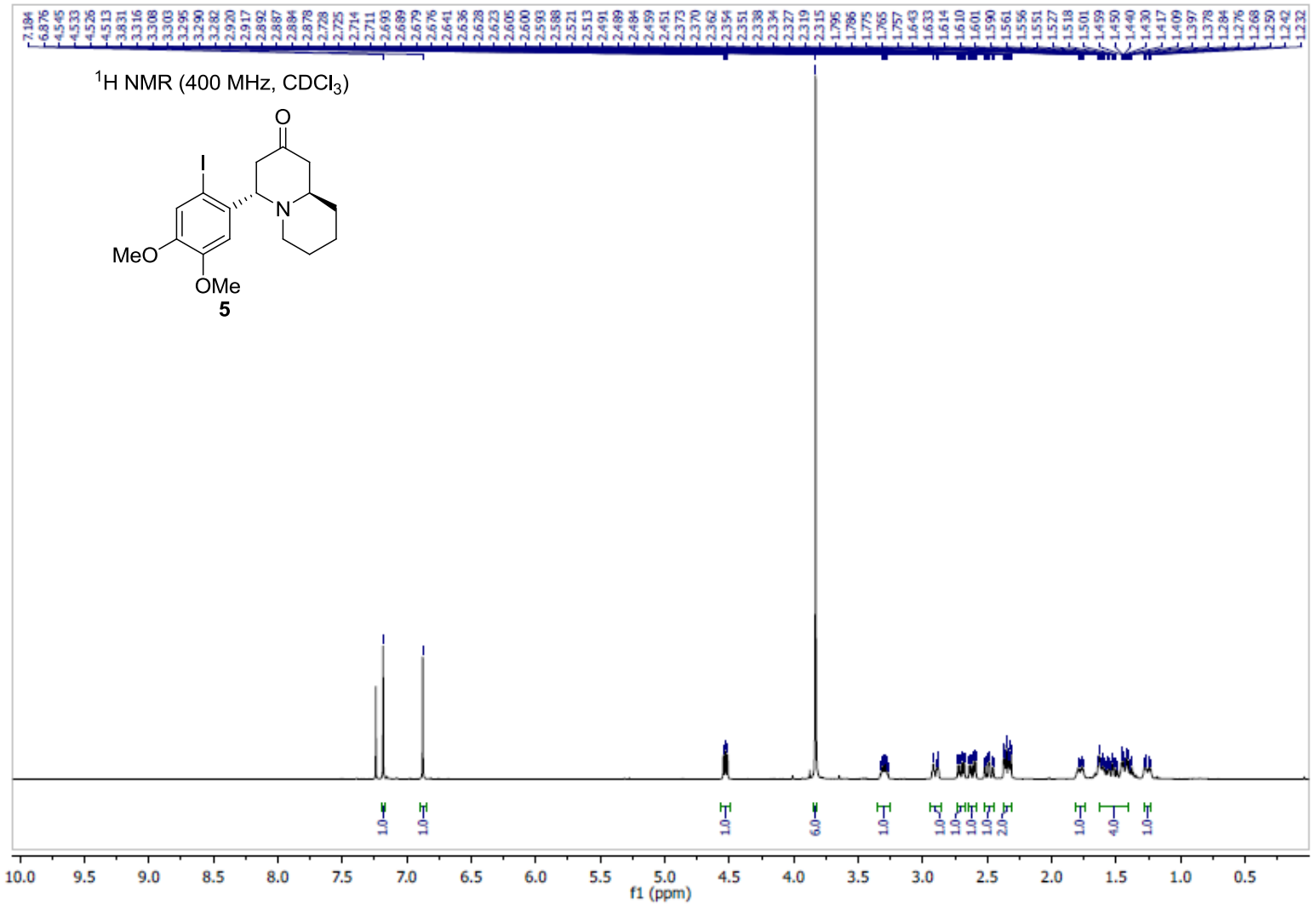
42. Appears as an 60:40 mixture of rotamers about the biaryl axis. **m.p.**: 84-87 °C. **IR** (neat): 2937, 2855, 1718, 1692, 1595, 1249, 1182, 1047, 834. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (0.6H, s, CHO), 9.74 (0.4H, s, CHO), 7.74 (1.0H, dd, *J* 2.2, 8.4 Hz, ArH), 7.60 (0.6H, d, *J* 2.2 Hz, ArH), 7.45 (0.4H, m, ArH), 7.13 (0.4H, s, ArH), 7.11 (0.6H, s, ArH), 6.96 (0.4H, d, *J* 8.4 Hz, ArH), 6.85 (0.6H, d, *J* 8.4 Hz, ArH), 6.56-6.55 (1.0H, s, ArH), 6.05-5.99 (1.0H, dd, *J* 1.6, 17.3 Hz, CHCH_2, AB), 5.86-5.72 (1.0H, dd, *J* 10.4, 17.3 Hz, CHCH_2), 5.67-5.61 (1.0H, dd, *J* 1.6, 10.4 Hz, CHCH_2, AB), 5.01-5.0 (0.6H, m, CHO), 4.96-4.95 (0.4H, m, CHO), 3.90 (3.0H, s, OCH_3), 3.78 (3.0H, s, OCH_3), 3.09 (0.6H, dd, *J* 2.6, 11.7 Hz, NCHAr), 2.99 (0.4H, dd, *J* 2.5, 11.7 Hz, NCHAr), 2.77-2.74 (1.0H, m, NCH_2alkyl, ABX), 2.04 (1.0H, t, *J* 10.2, 11.0 Hz, NCH), 1.94-1.87 (1.0H, m, CH_2CHO, ABX), 1.77-1.14 (10.0H, m, alkyl-H), 0.71 (3.6H, s, (CH_3)$_3$CSi), 0.65 (5.4H, s, (CH_3)$_3$CSi), 0.11 (1.2H, s, CH_3Si), 0.14 (1.2H, s, CH_3Si), 0.05 (1.8H, s, CH_3Si), 0.005 (1.8H, s, CH_3Si). ^{13}C NMR (100 MHz, $CDCl_3$) *cannot fully distinguish isomers* – δ Major isomer 191.2, 165.4, 159.8, 149.4, 147.2, 134.8, 134.3, 132.9, 130.2, 130.0, 129.3, 129.1, 129.1, 119.6, 112.8, 109.6, 68.3, 59.5, 57.5, 56.4, 56.0, 52.9, 38.9, 37.2, 33.8, 26.4, 25.4 (3C), 24.9, 18.2, -4.0, -4.2. **HR-MS** (ESI) for $C_{33}H_{46}NO_6Si$ $[M+H]^+$: calcd. 580.3088, found 580.3087. (4*S*,9a*S*)- **49** $[\alpha]_D^{20}$ = +69.4 (c 0.16, $CHCl_3$).

(4*S*,9a*S*)-hexahydro-4-(2-(2'-tert-butyldimethylsiloxy-5'-vinylphenyl)-4,5-dimethoxyphenyl)-1H-quinolizin-2yl-acrylate (50). Desired product **50** was obtained in 55% yield from **49** (0.057 g, 0.098 mmol) following the same procedure as for the synthesis of**43**. Appears as an 60:40 mixture of rotamers about the biaryl axis. **IR** (neat): 2932, 2853, 1723, 1677, 1589, 1515, 1278, 1183, 918. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (1.0H, s, ArH), 9.23 (1.0H, dd, *J* 2.2, 8.4 Hz, ArH), 7.06 (0.6H, d, *J* 2.2 Hz, ArH), 6.96 (0.4H, d, *J* 2.2 Hz, ArH), 6.83 (0.4H, d, *J* 8.4 Hz, ArH), 6.72 (0.6H, d, *J* 8.4 Hz, ArH), 6.65 (0.6H, dd, *J* 10.9, 17.6 Hz, ArCHCH$_2$), 6.59-6.58 (1.0H, s, ArH), 6.51 (0.4H, dd, *J* 10.9, 17.6 Hz, ArCHCH$_2$), 6.15 (0.6H, d, *J* 17.3 Hz, CHCH_2, ABX), 6.06 (0.4H, d, *J* 17.3 Hz, CHCH_2,

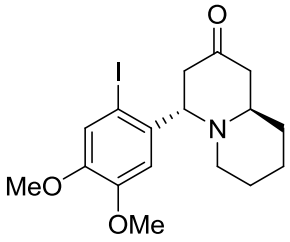
ABX), 5.9 (0.6H, dd, *J* 10.4, 17.3 Hz, CHCH$_2$), 5.81 (0.4H, dd, *J* 10.4, 17.3 Hz, CHCH$_2$), 5.74 (0.6H, d, *J* 10.4 Hz, CHCH$_2$, ABX), 5.64-5.48 (0.4H, d, *J* 10.4 Hz, CHCH$_2$ ABX and 0.6H, d, *J* 10.4 Hz, CHCH$_2$, ABX), 5.5 (0.4H, d, *J* 17.6 Hz, CHCH$_2$, ABX), 5.51 (2.0H, m, 1.0H CHCH$_2$, ABX and 1.0H CHCO), 3.99-3.96 (3.0H, s, OCH$_3$), 3.79-3.76 (3.0H, s, OCH$_3$), 3.6-2.63 (4.0H, m, 1.0H ArCHN and 3.0H alkyl-H), 1.78-1.47 (10.0H, m, alkyl-H), 0.71 (3.6H, s, (CH$_3$)$_3$Si), 0.62 (5.4H, s, (CH$_3$)$_3$Si), 0.10 (1.2H, s, CH$_3$Si), 0.02 (1.2H, s, CH$_3$Si), -0.04 (1.8H, s, CH$_3$Si), -0.17 (1.8H, s, CH$_3$Si). **^{13}C NMR** (100 MHz, CDCl$_3$) *cannot fully distinguish isomers* – δ Major isomer 164.9, 153.8, 149.6, 148.1, 136.2, 132.5, 131.8, 131.2, 130.9, 130.8, 129.3, 128.7, 126.5, 119.9, 113.1, 112.4, 110.4, 67.3, 61.2, 57.2, 56.0, 55.9, 52.4, 48.5, 35.9, 30.6, 25.5 (2C), 25.6, 24.4, 23.8, 18.2, -4.2, -4.4. **HR-MS** (ESI) for $C_{34}H_{48}NO_5Si$ $[M+H]^+$: calcd. 578.3270, found 578.3296. (4*S*,9a*S*)- **50** $[\alpha]_D^{20}$ = +17.3 (c 0.1, CHCl$_3$).

(+)-Lythrine (2). Desired product **2** was obtained in 35% yield from **50** (0.025 g, 0.04 mmol) following the same procedure as for the synthesis of **1**. Spectral data match literature values.**Error! Bookmark not defined.** **^{1}H NMR** (400 MHz, CD$_3$OD) δ 7.18 (1H, dd, *J* 2.2, 8.4 Hz, ArH), 7.11 (1H, d, *J* 2.2 Hz, ArH), 7.04 (1H, s, ArH), 6.98 (1H, d, *J* 8.4 Hz, ArH), 6.92 (1H, s, ArH), 6.77 (1H, d, *J* 12.5 Hz, ArCH), 5.85 (1H, d, *J* 12.5Hz, CHCH), 5.32 (1H, m, CHOH), 3.92 (3H, s, OCH$_3$), 3.86 (3H, s, CH$_3$O), 3.64 (1H, d, *J* 11.2 Hz, NCHAr), 2.65 (1H, d, *J* 11.2 Hz, NCH$_2$, ABX), 2.24 (1H, d, *J* 14.5 Hz, CH$_2$CHO, ABX), 2.05 (1H, t, *J* 16.3 Hz, CH$_2$CHO, ABX), 1.95 (1H, m, CHN), 1.74-1.58 (4H, m, CH$_2$CHO and alkyl-H), 1.46-1.27 (4H, m, alkyl-H), 1.16-1.11 (1H, m, NCH$_2$). **^{13}C NMR** (125 HMHz, CD$_3$OD) δ 168.5, 153.7, 150.2, 148.2, 135.7, 135.0, 131.2, 130.7, 126.5, 126.0, 125.0, 119.6, 116.0, 111.2, 110.9, 71.2, 61.6, 60.5, 56.6, 56.3, 53.0, 39.8, 37.1, 33.1, 26.0, 24.6. **HR-MS** (ESI) for $C_{26}H_{30}NO_5$ $[M+H]^+$: calcd. 436.2119, found 436.2118. $[\alpha]_D^{20}$ = +31 (c 0.15, CHCl$_3$).

3. ^{1}H & ^{13}C Nuclear Magnetic Resonance Spectrum

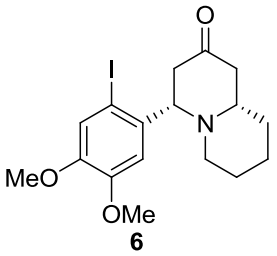


^{13}C NMR (75 MHz, $CDCl_3$)

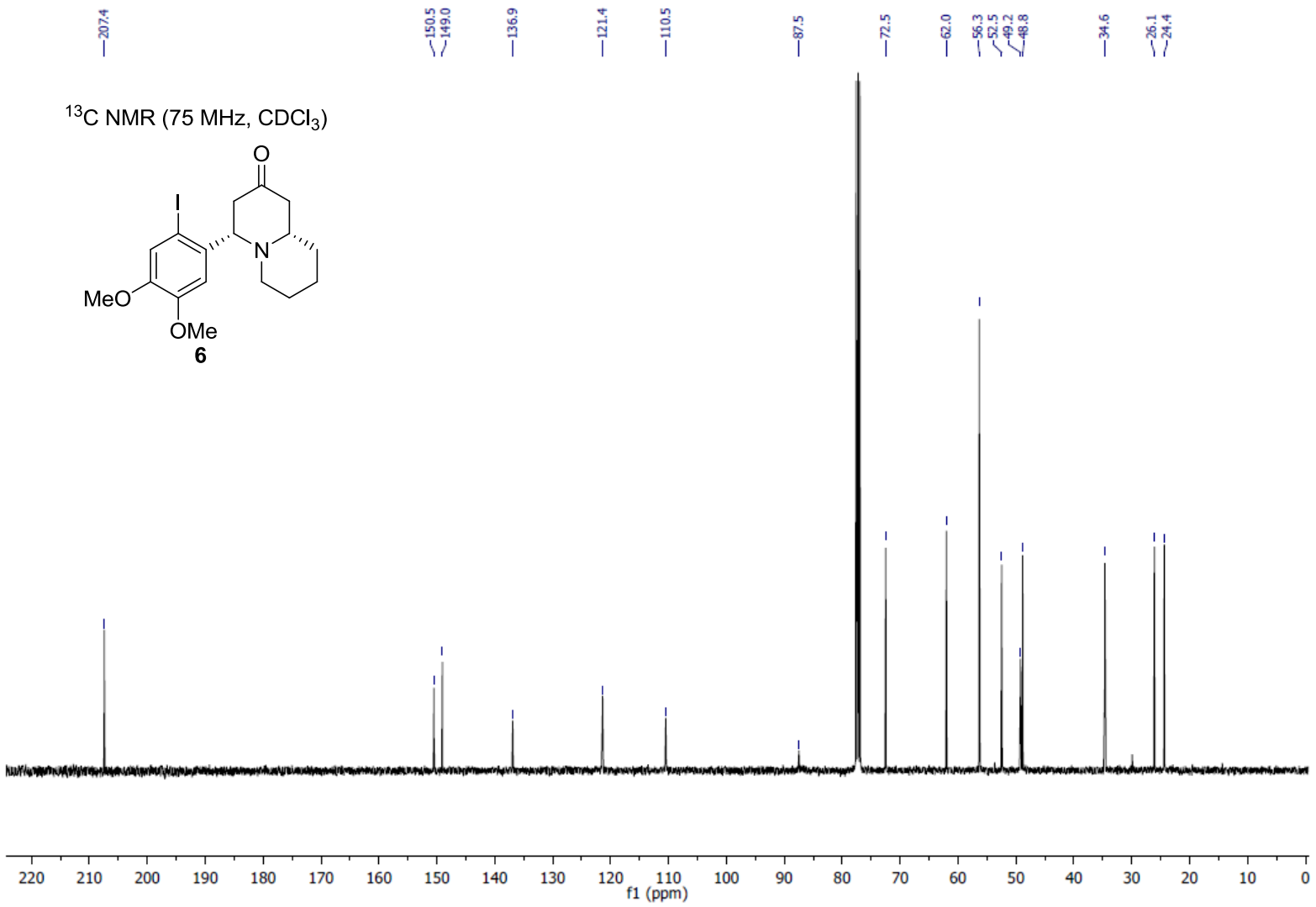


5

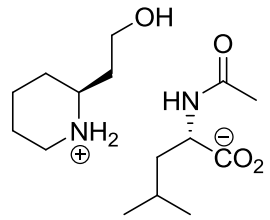
^{1}H NMR (400 MHz, $CDCl_3$)



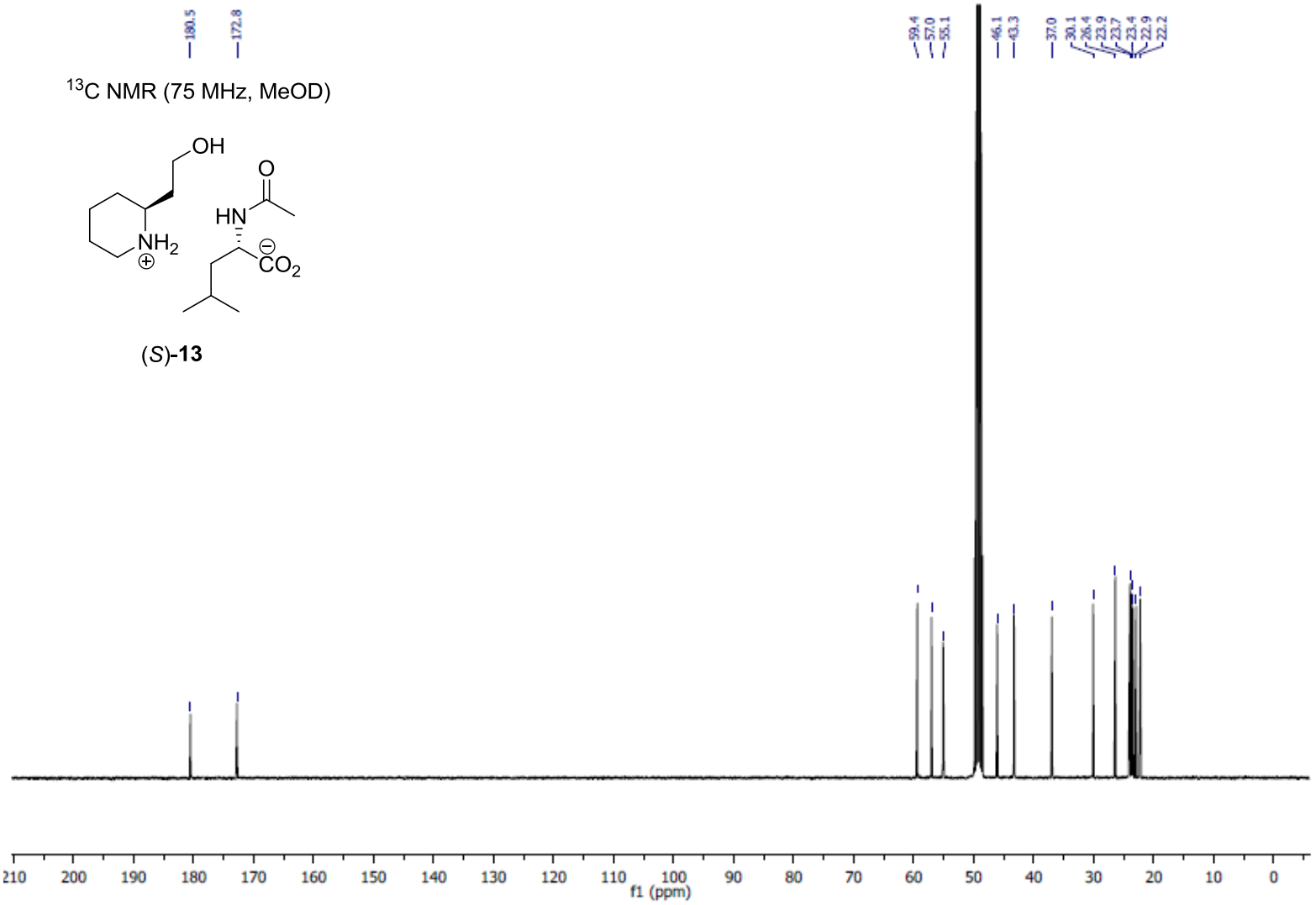
6



^{1}H NMR (400 MHz, MeOD)



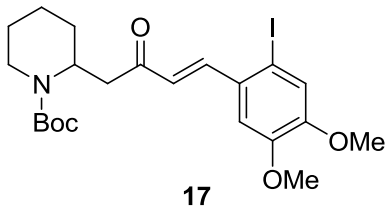
(*S*)-**13**



^{13}C NMR (75 MHz, MeOD)

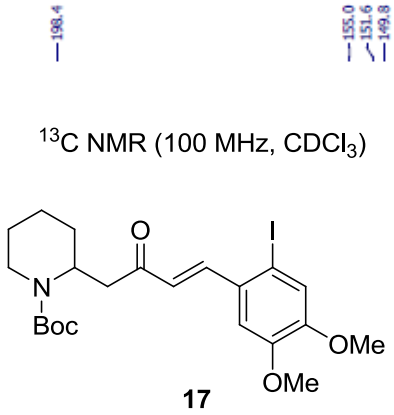
(*S*)-**13**

^{1}H NMR (400 MHz, $CDCl_3$)

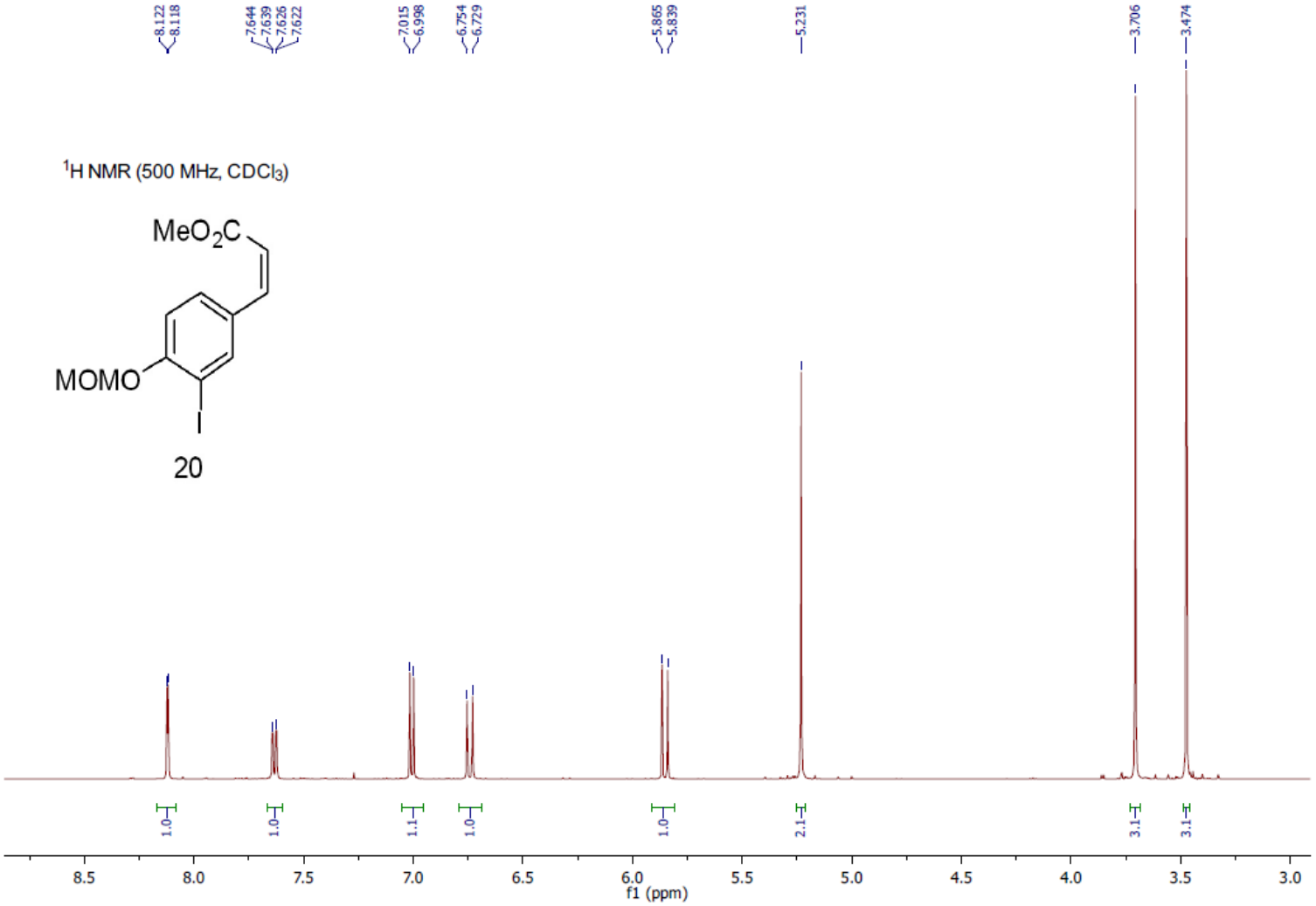


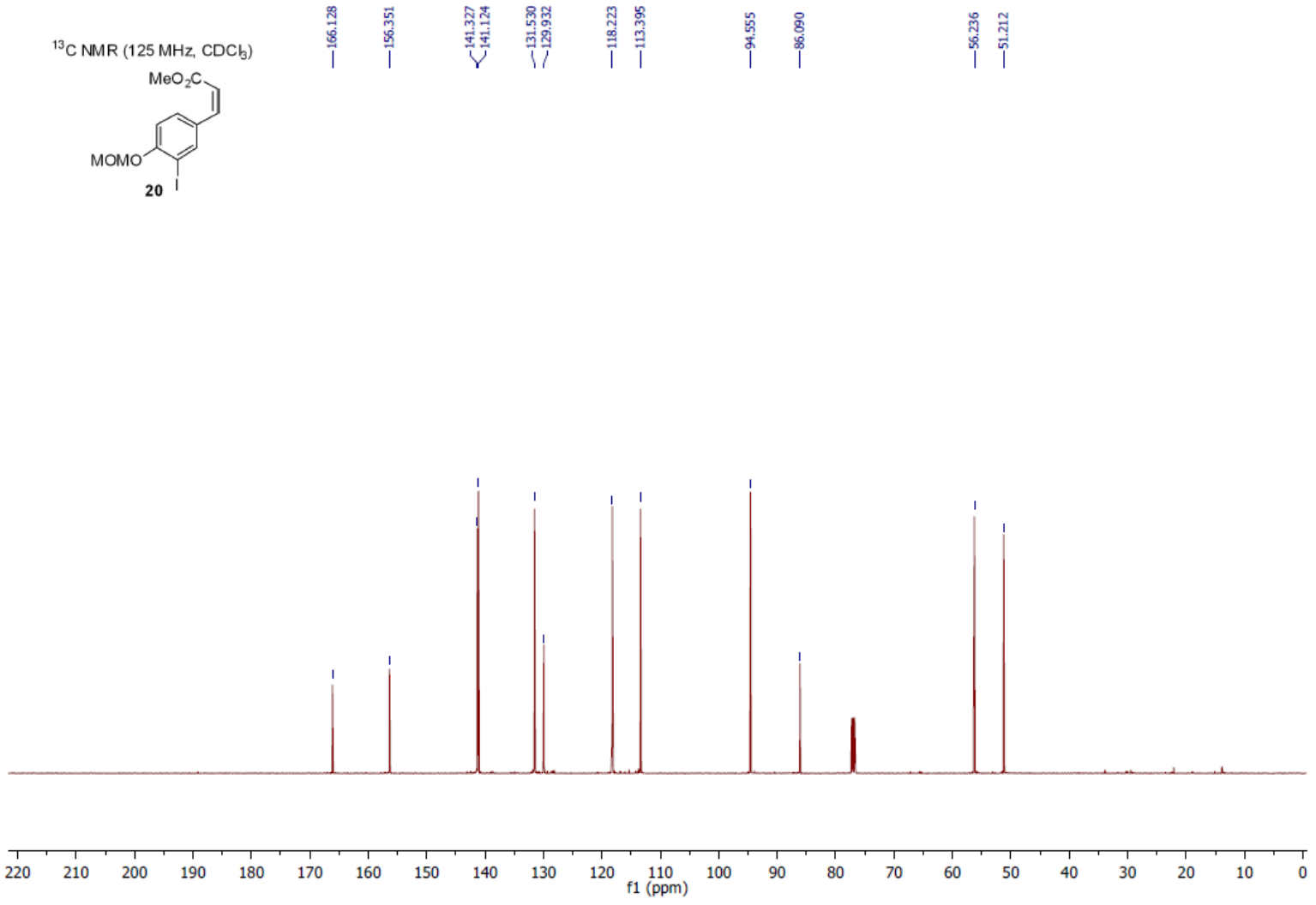
17

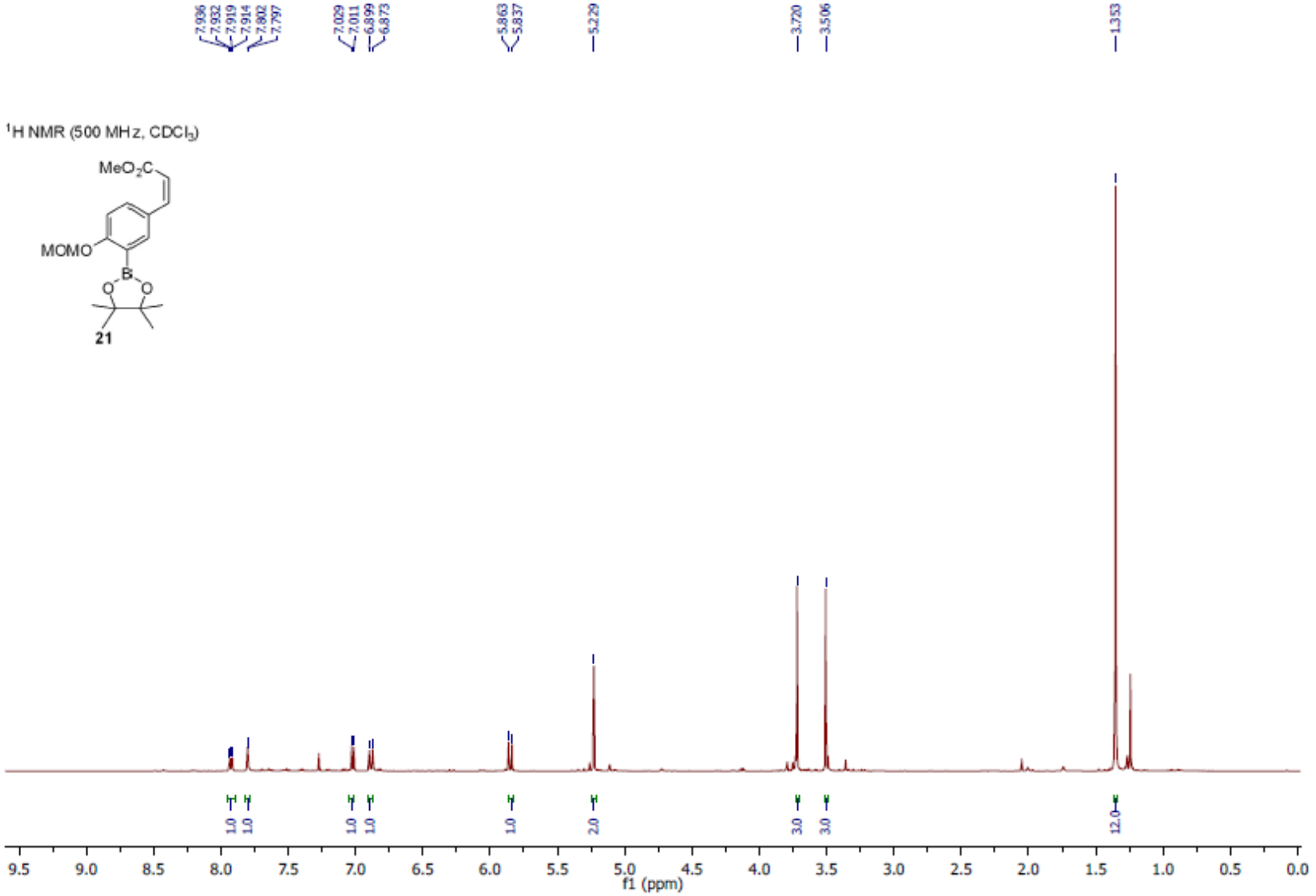
^{13}C NMR (100 MHz, $CDCl_3$)

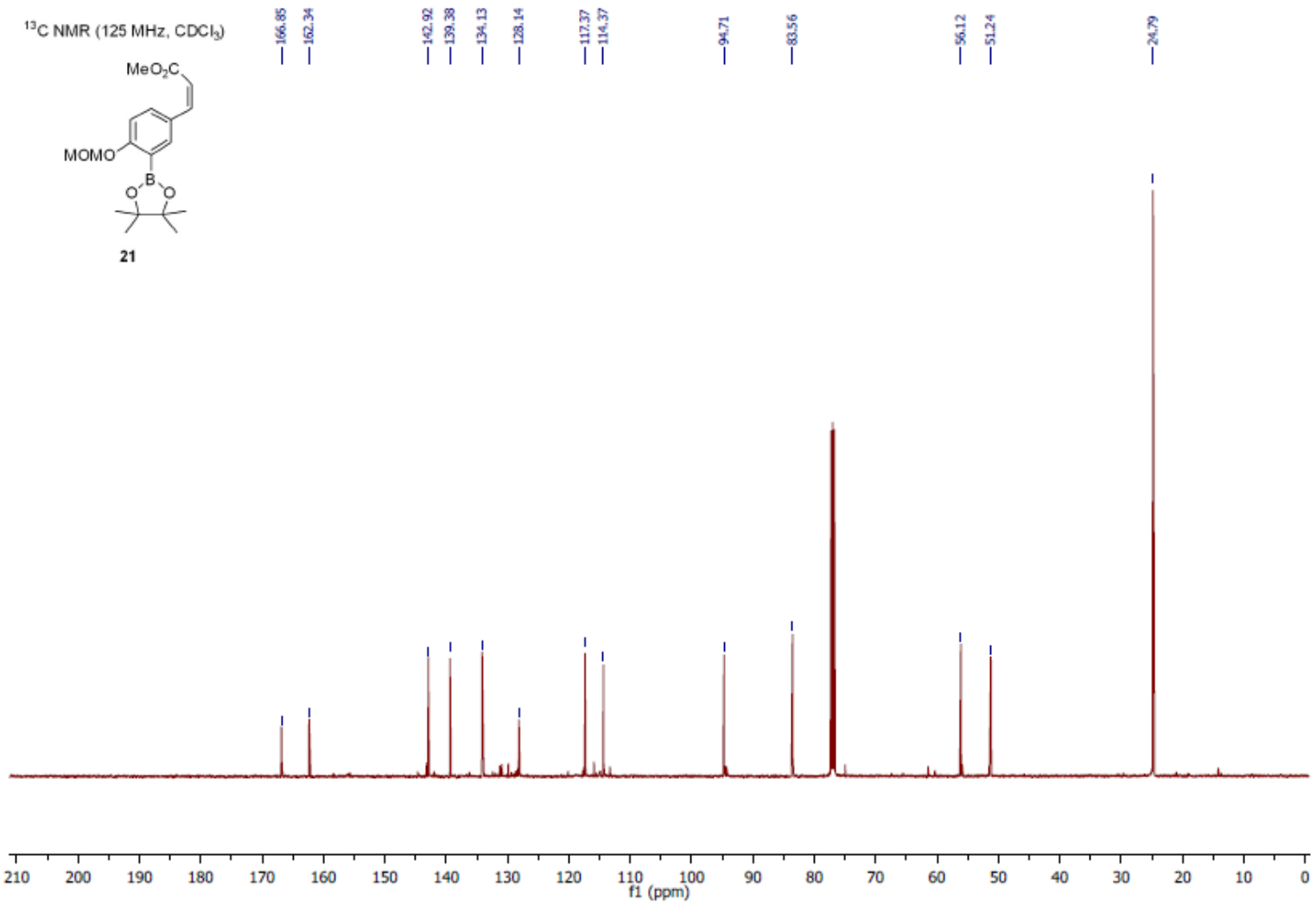


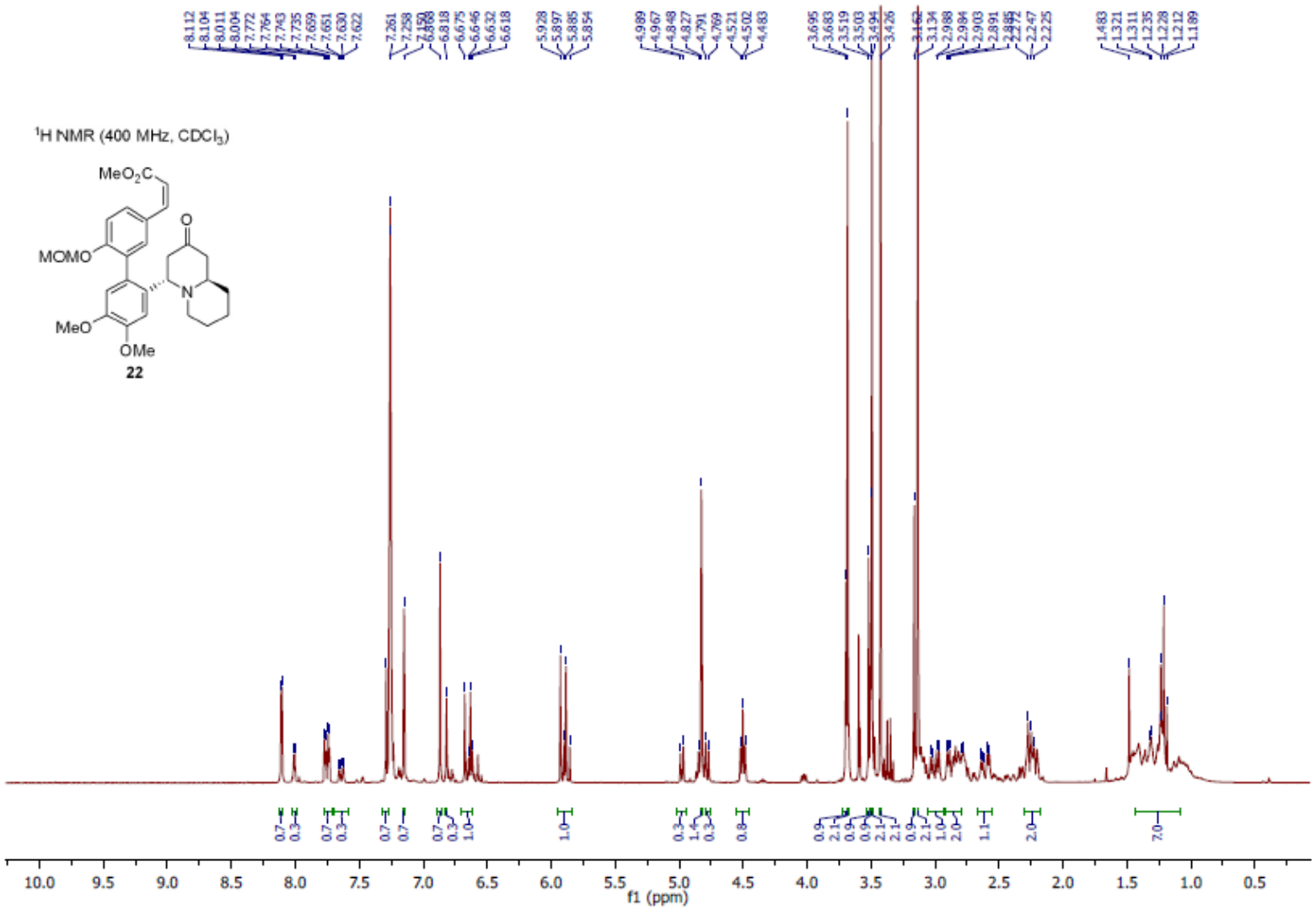
17

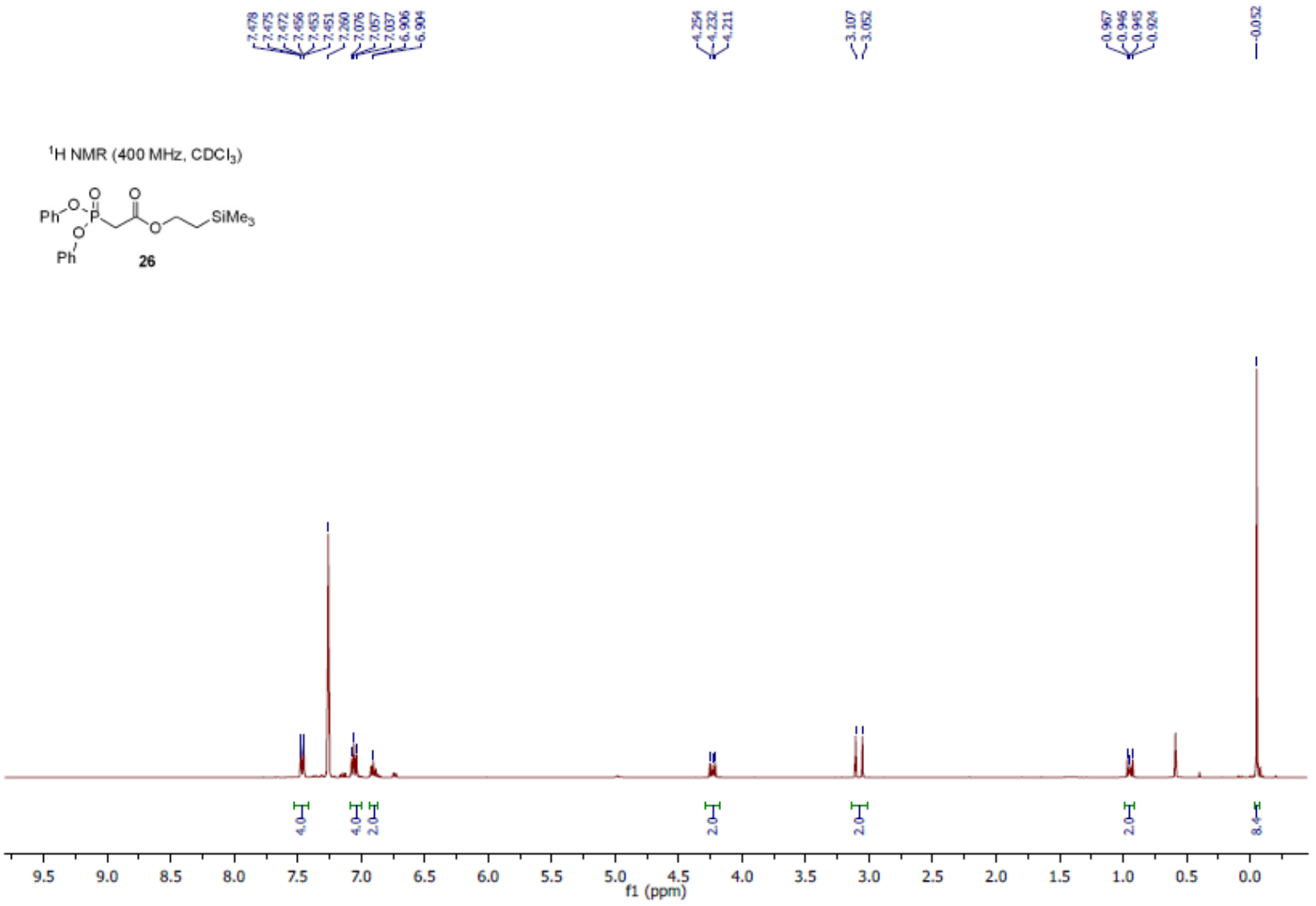


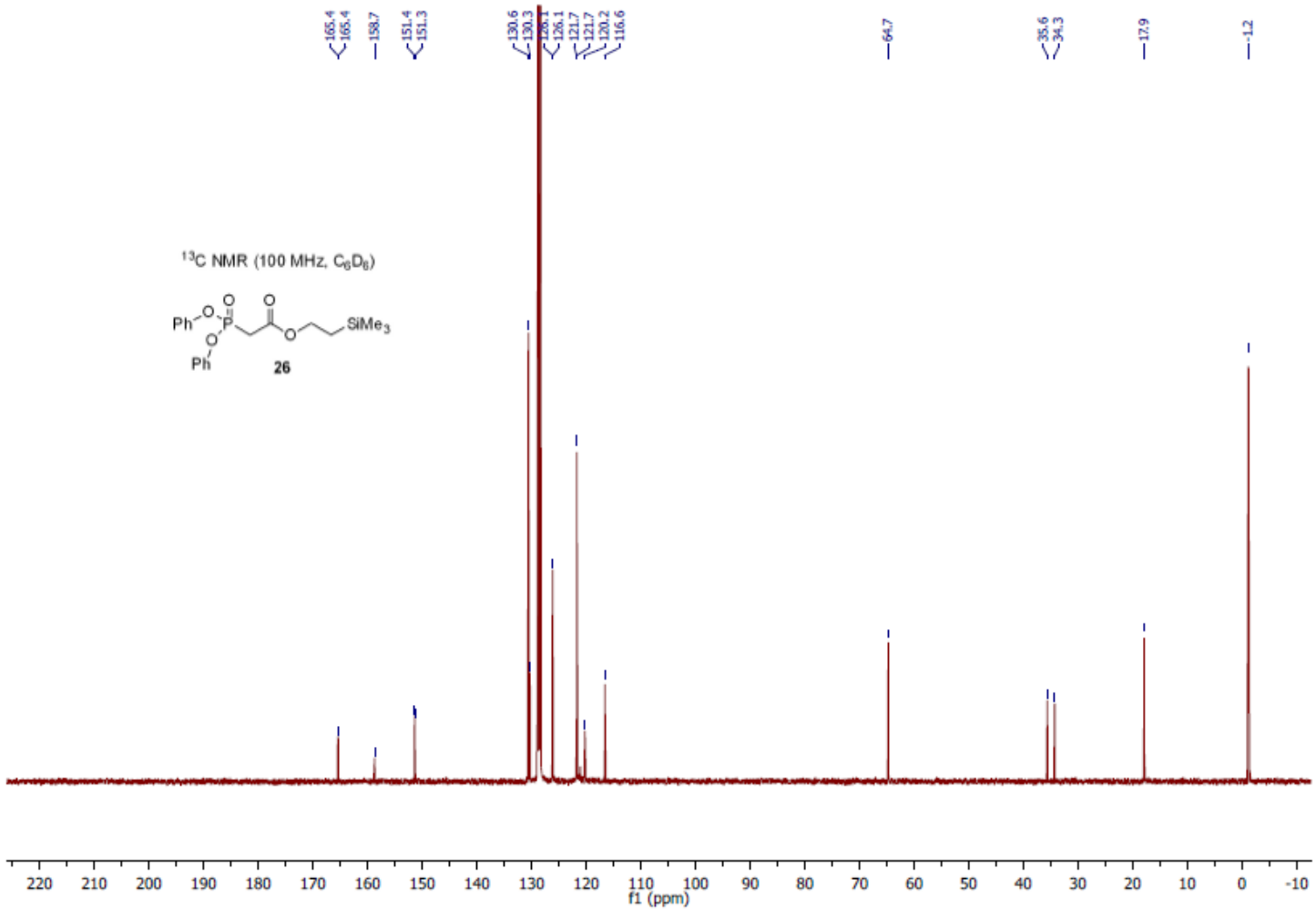


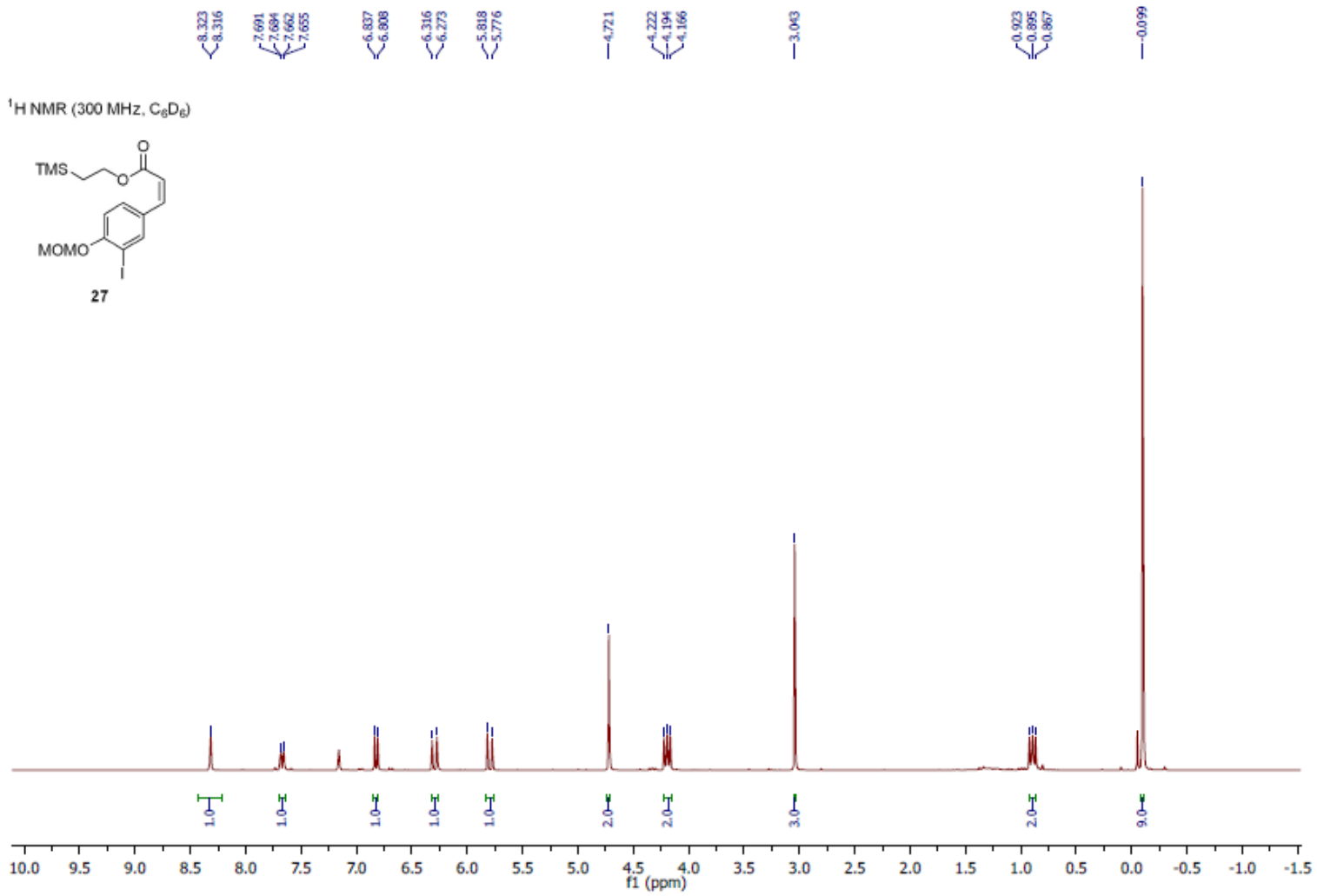


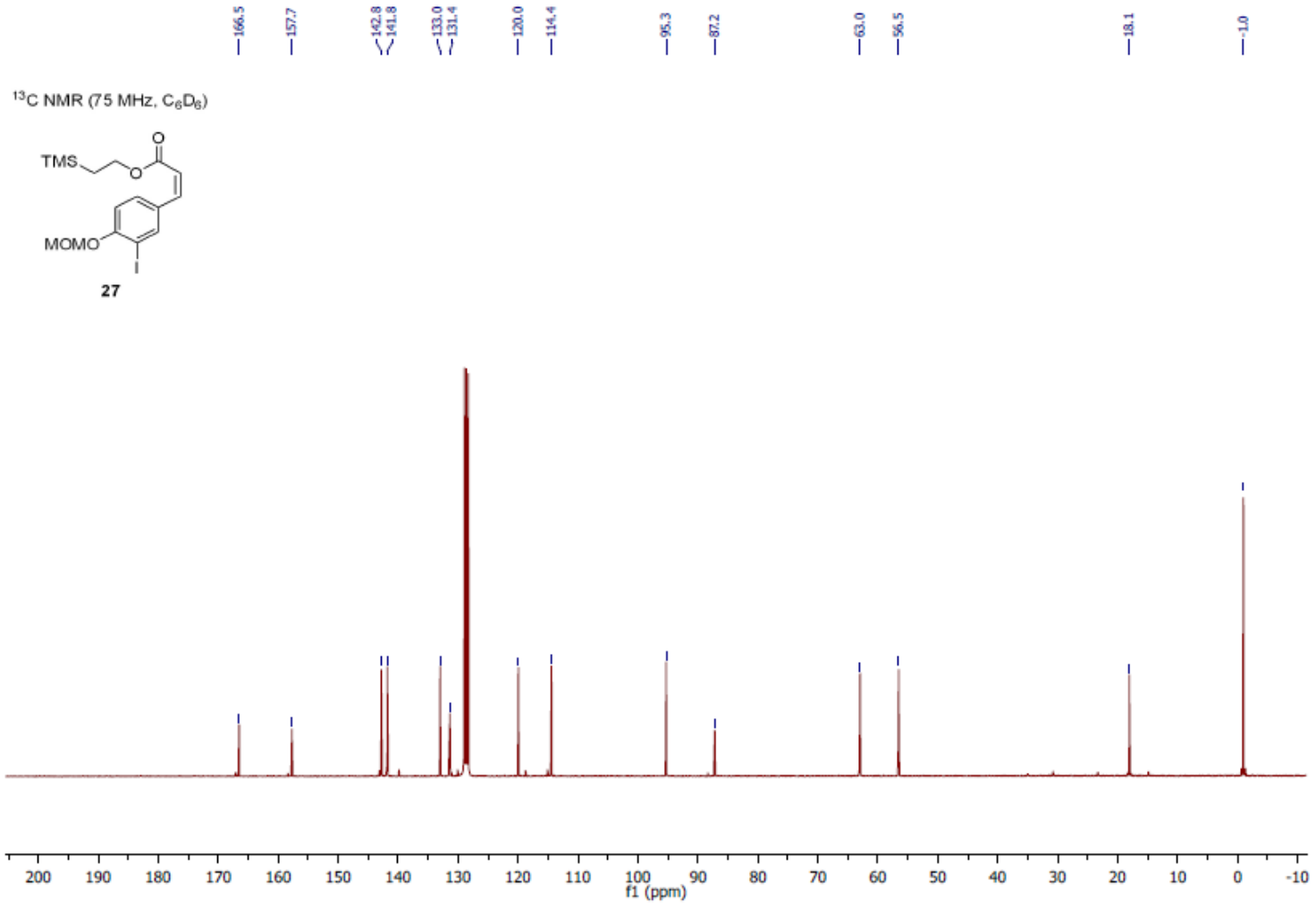


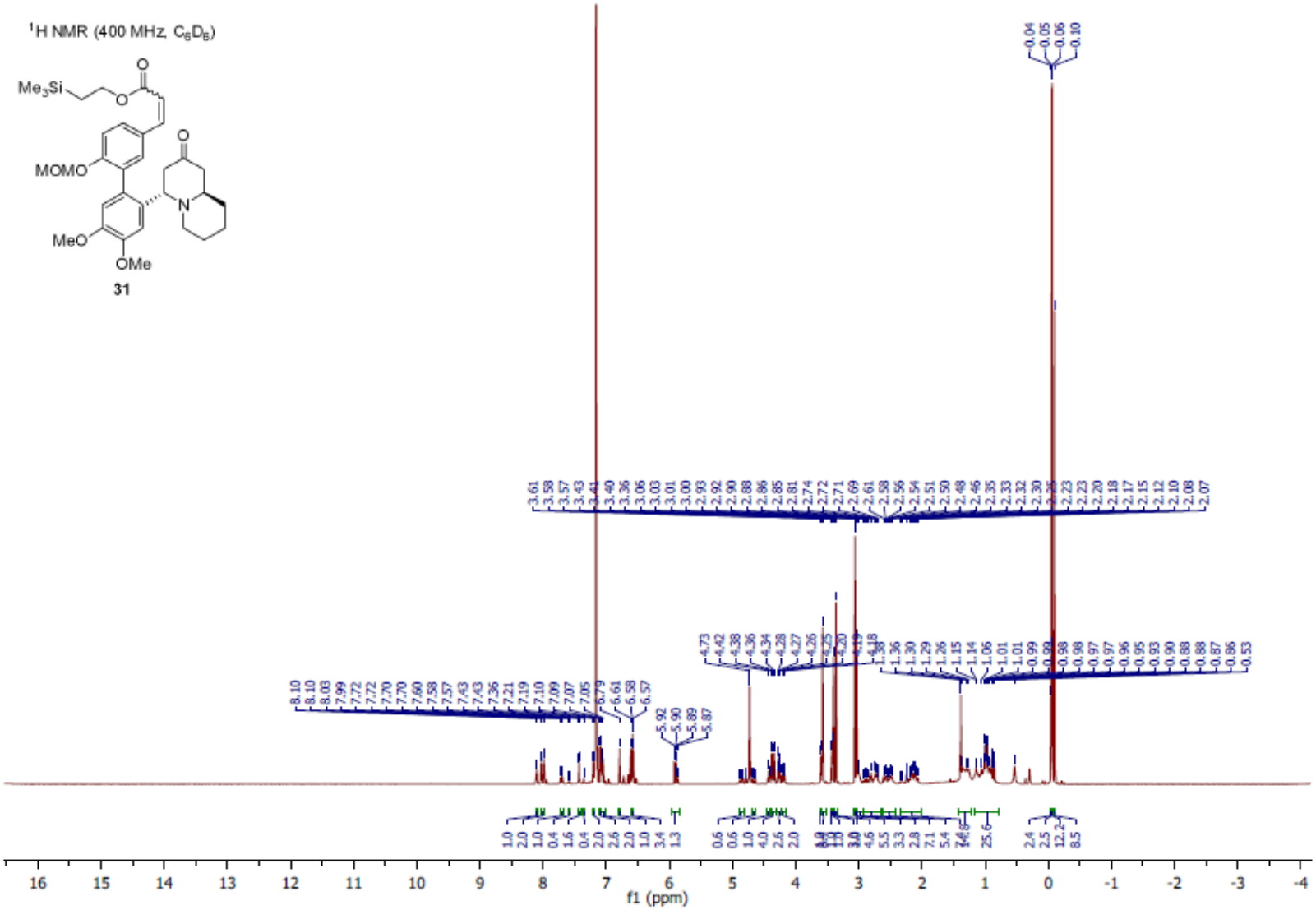


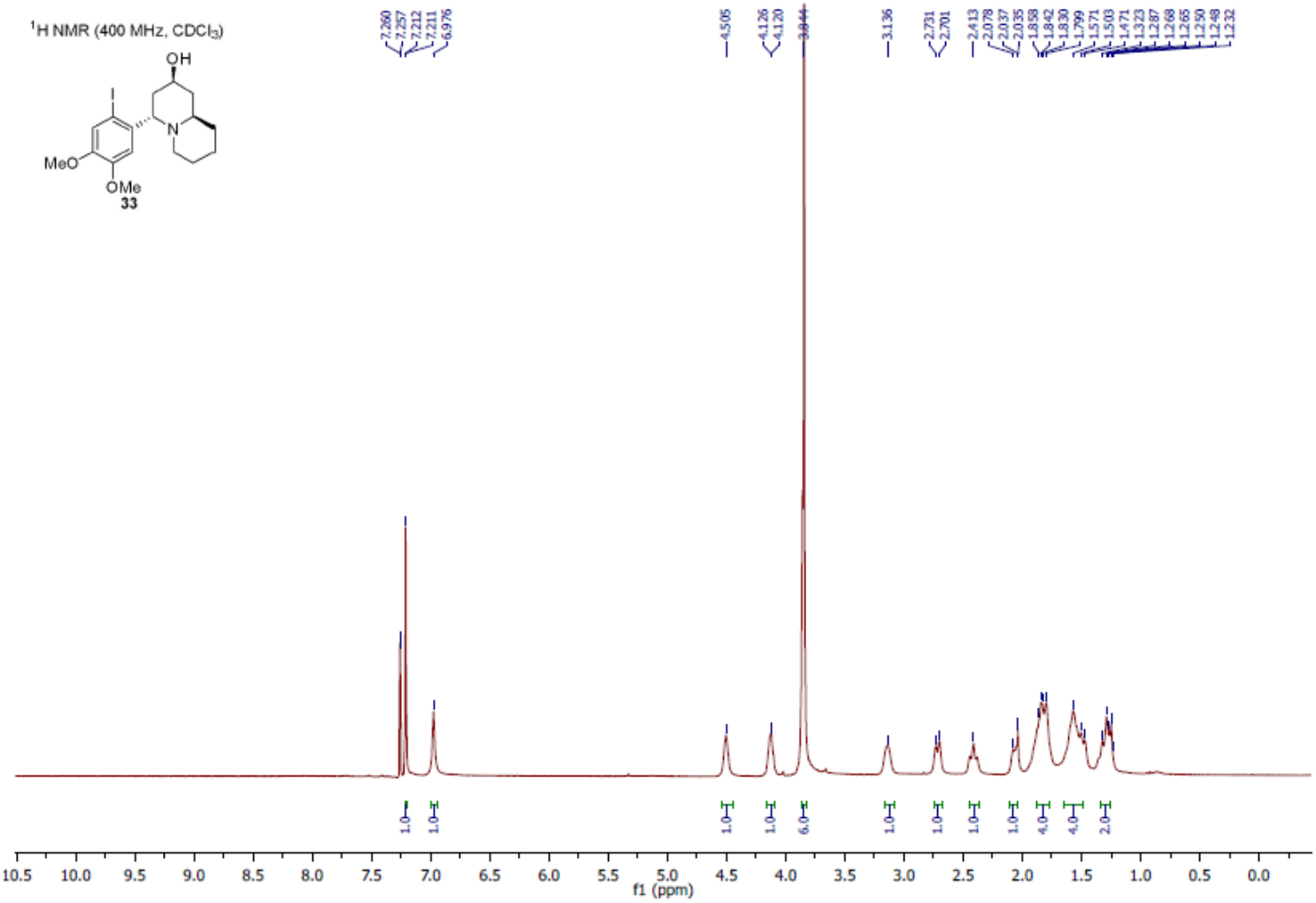


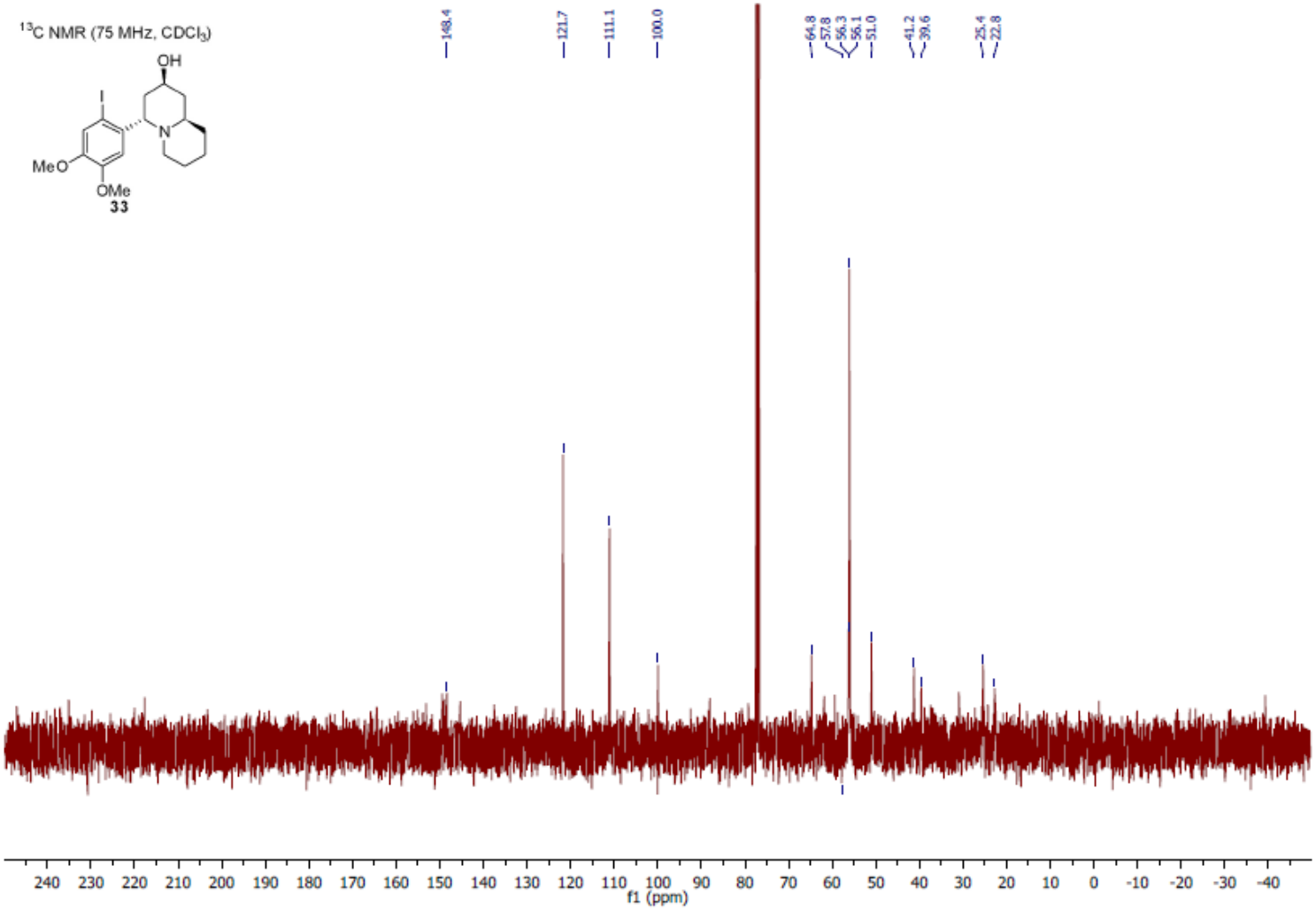


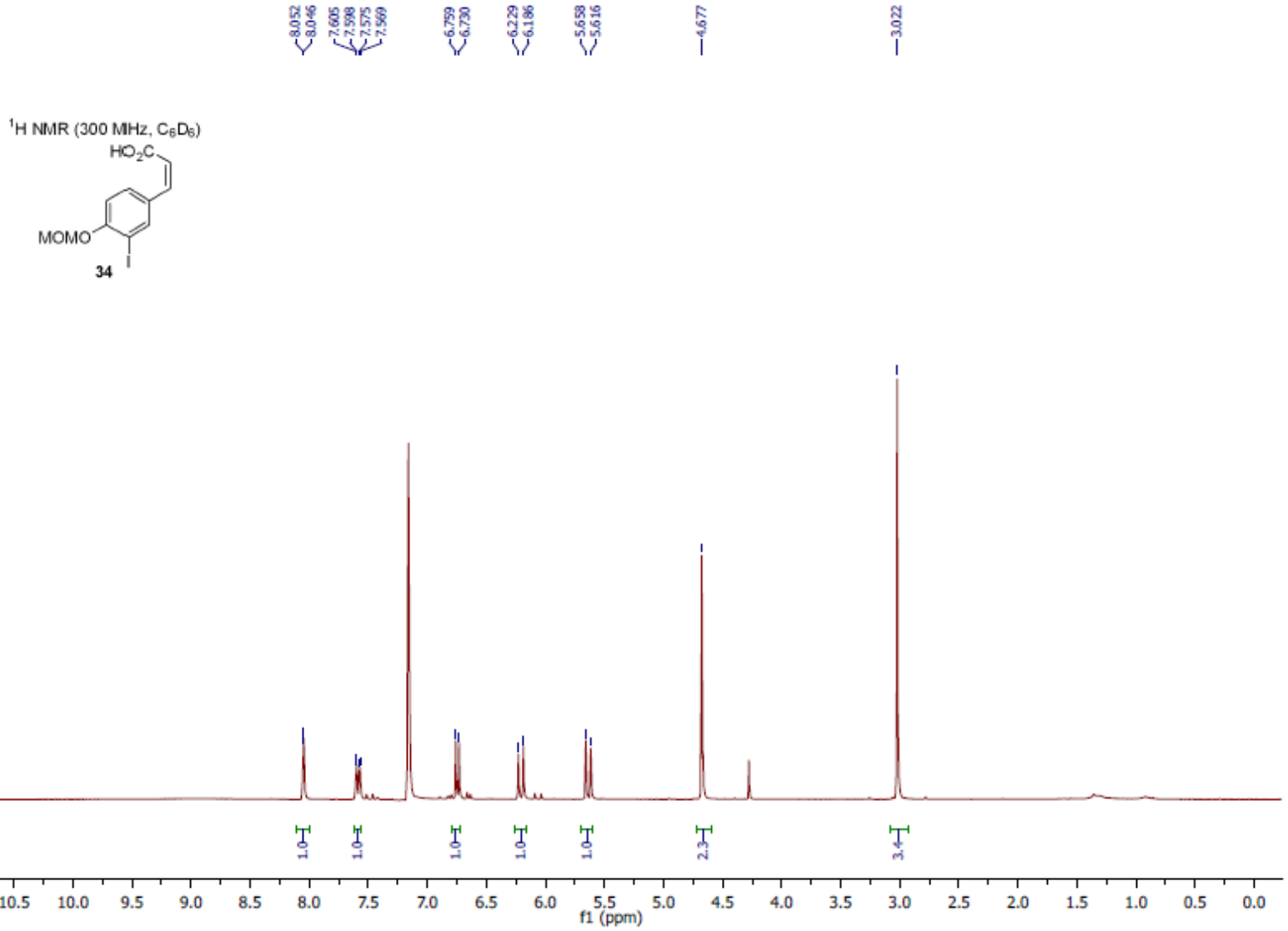




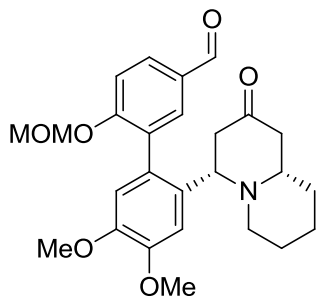






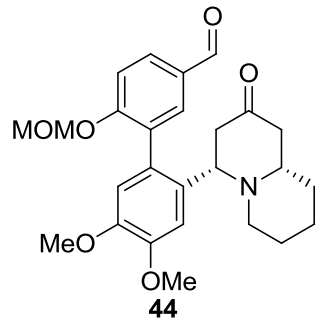


^{1}H NMR (400 MHz, $CDCl_3$)



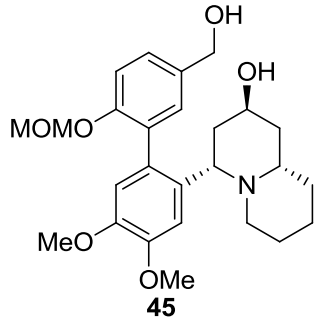
44

^{13}C NMR (75 MHz, $CDCl_3$)



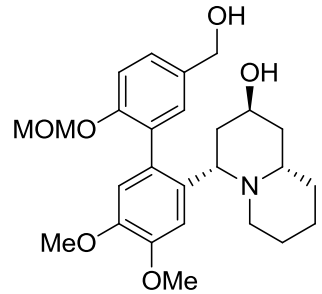
44

^{1}H NMR (400 MHz, $CDCl_3$)



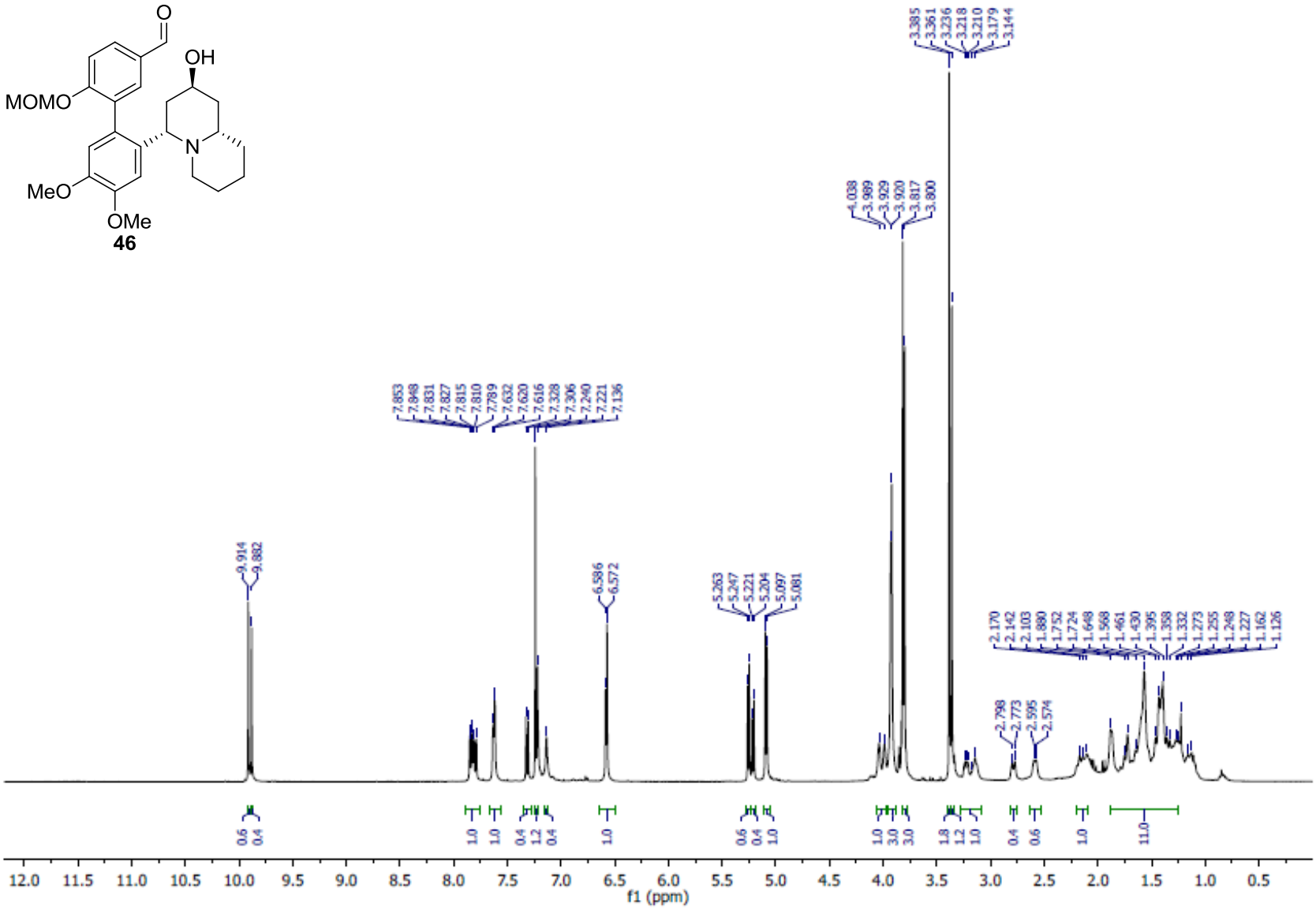
45

^{13}C NMR (75 MHz, $CDCl_3$)

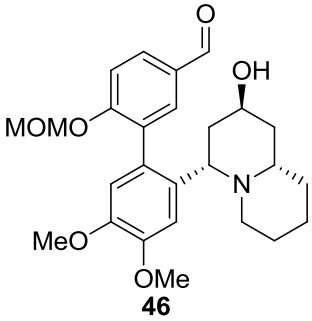


45

^{1}H NMR (400 MHz, $CDCl_3$)

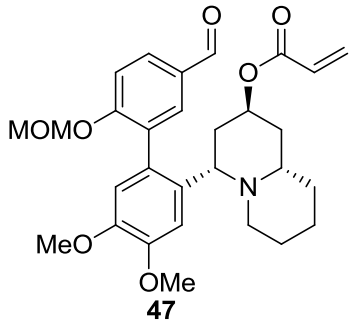


^{13}C NMR (75 MHz, $CDCl_3$)



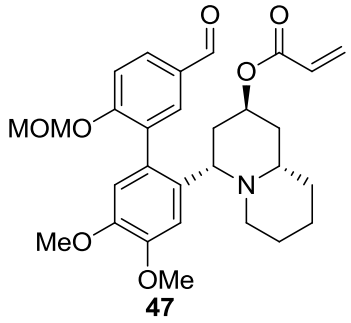
46

^{1}H NMR (400 MHz, $CDCl_3$)



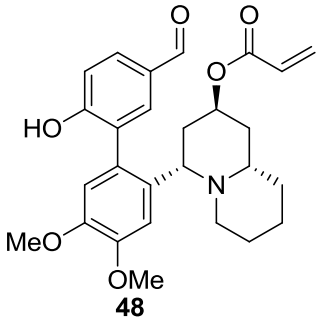
47

^{13}C NMR (75 MHz, $CDCl_3$)



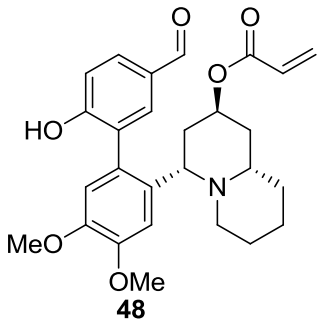
47

^{1}H NMR (400 MHz, $CDCl_3$)



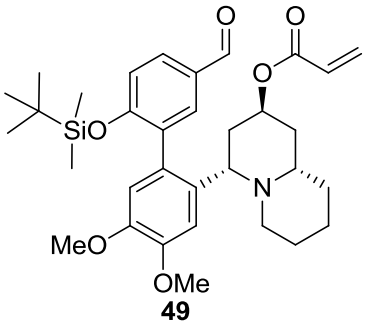
48

^{13}C NMR (75 MHz, $CDCl_3$)

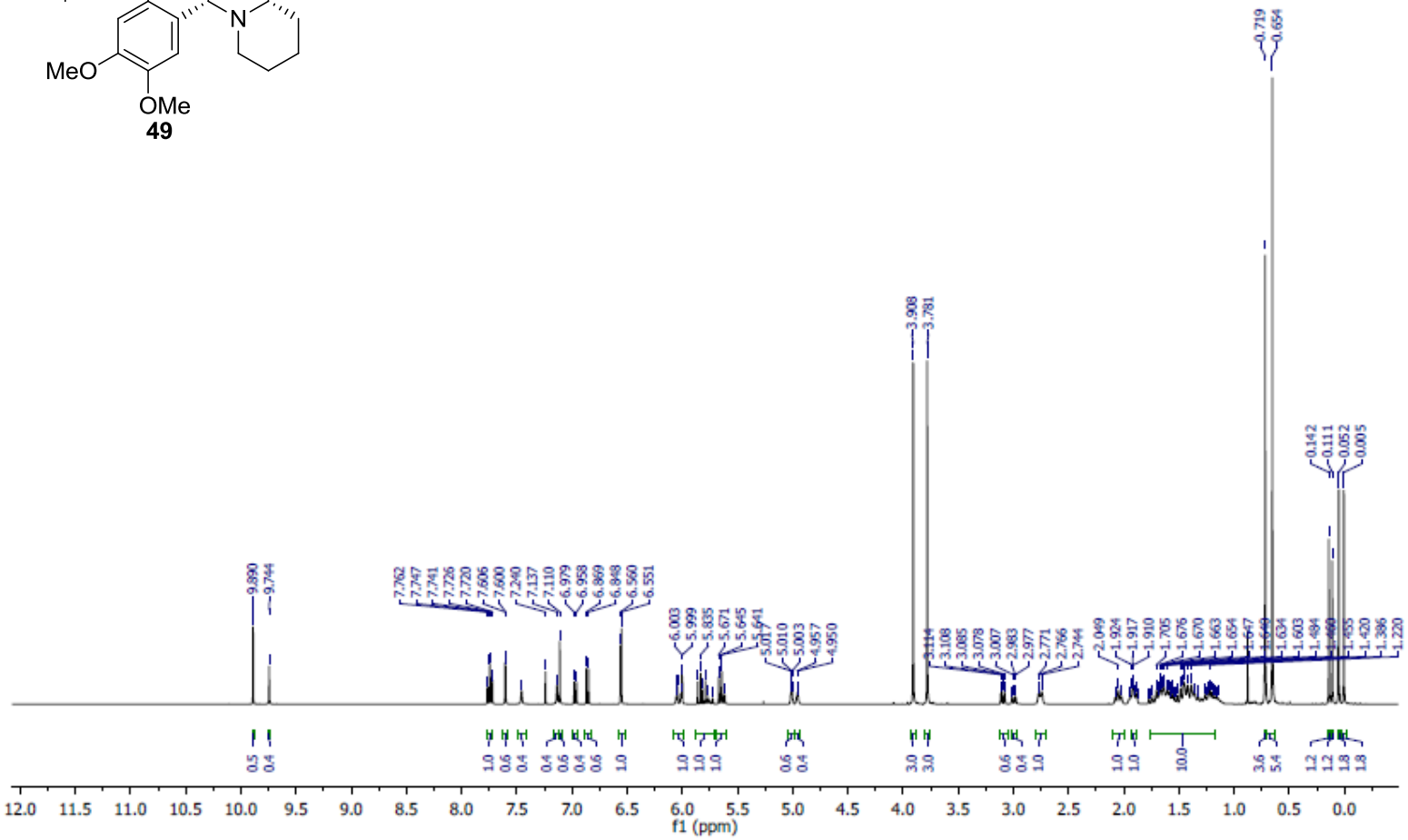


48

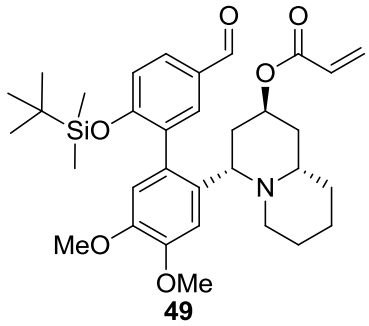
^{1}H NMR (400 MHz, $CDCl_3$)



49

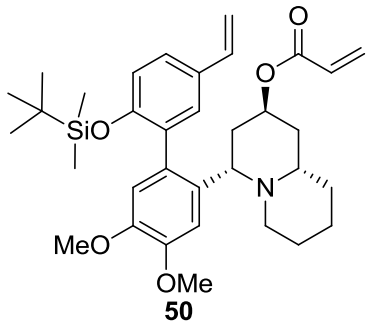


^{13}C NMR (75 MHz, $CDCl_3$)



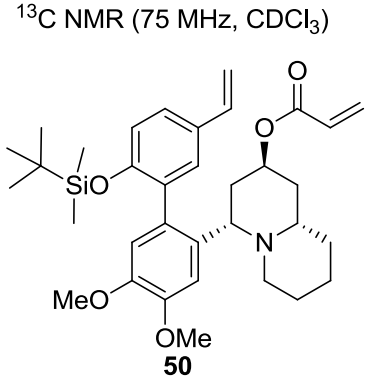
49

^{1}H NMR (400 MHz, $CDCl_3$)



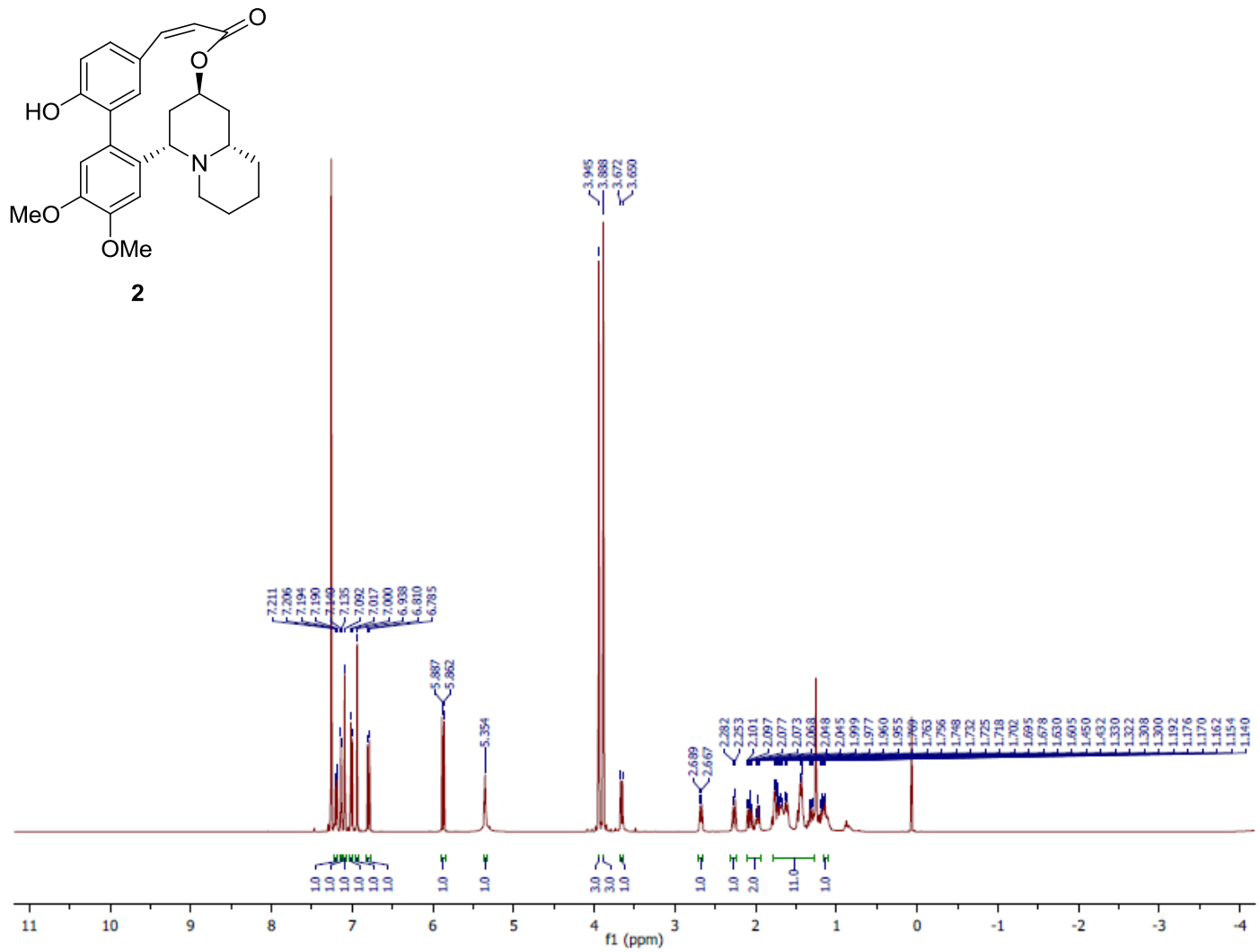
50

^{13}C NMR (75 MHz, $CDCl_3$)

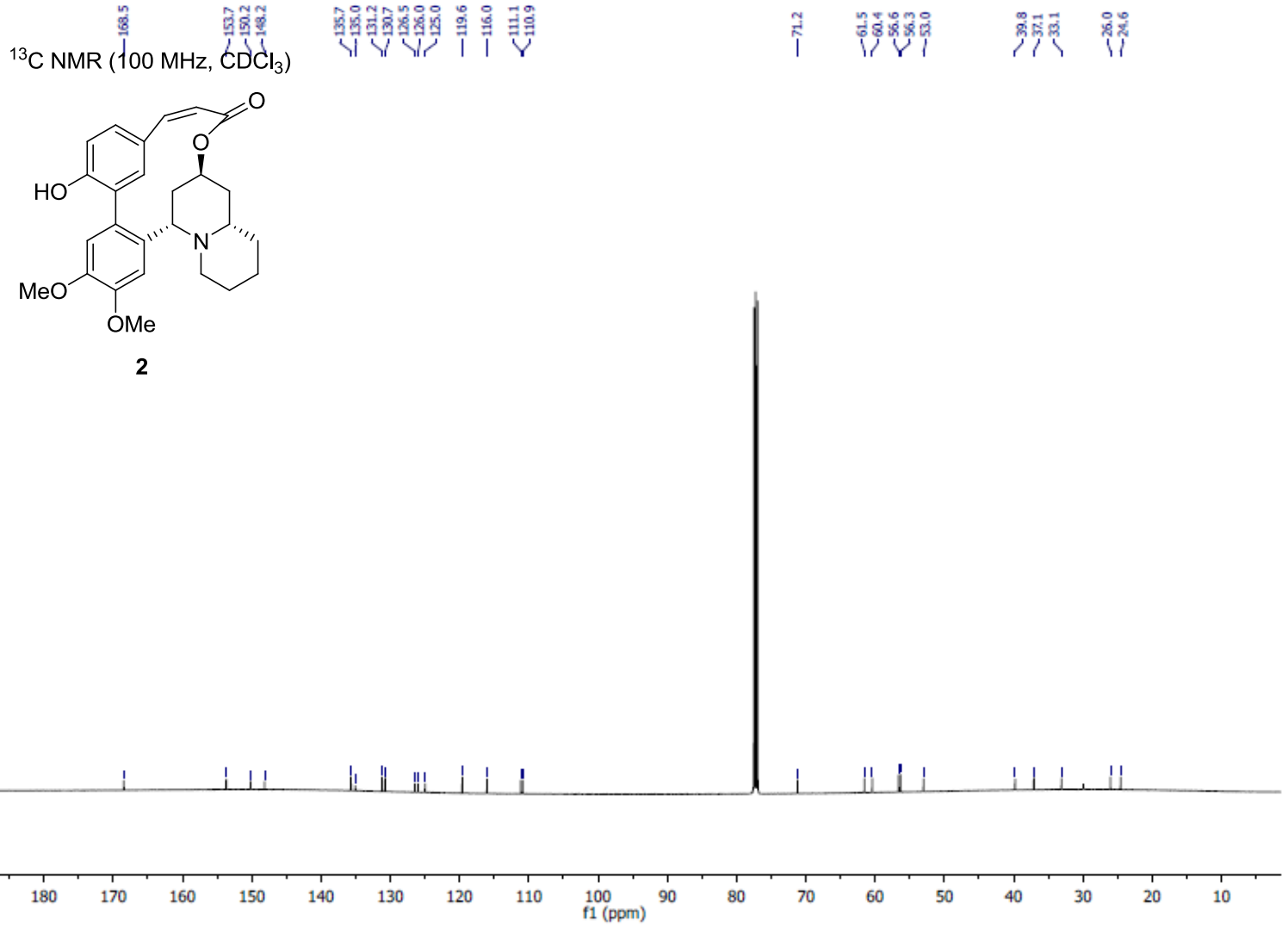


50

^{1}H NMR (500 MHz, $CDCl_3$)



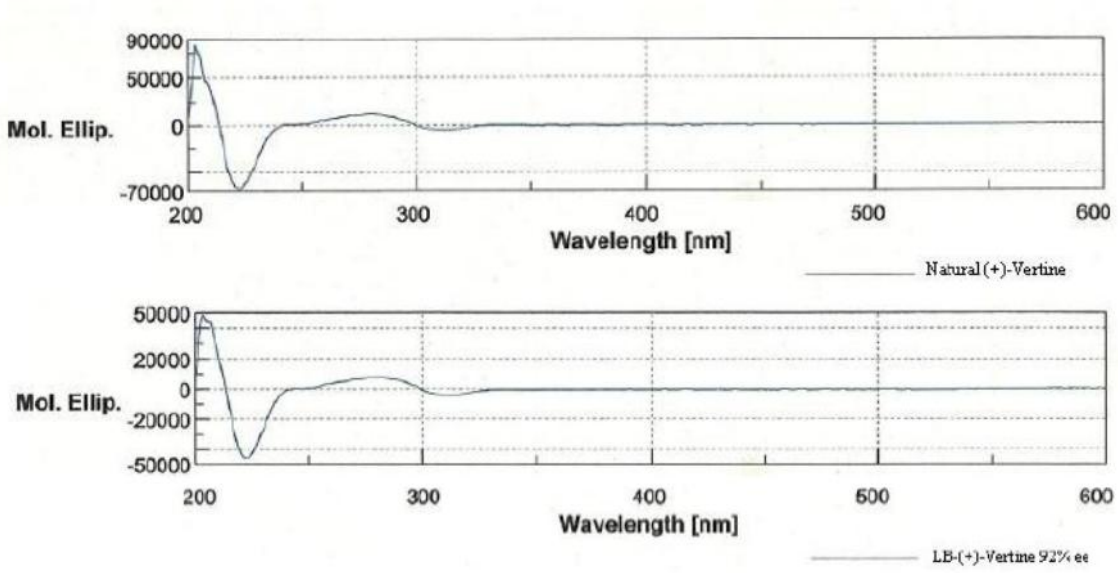
2



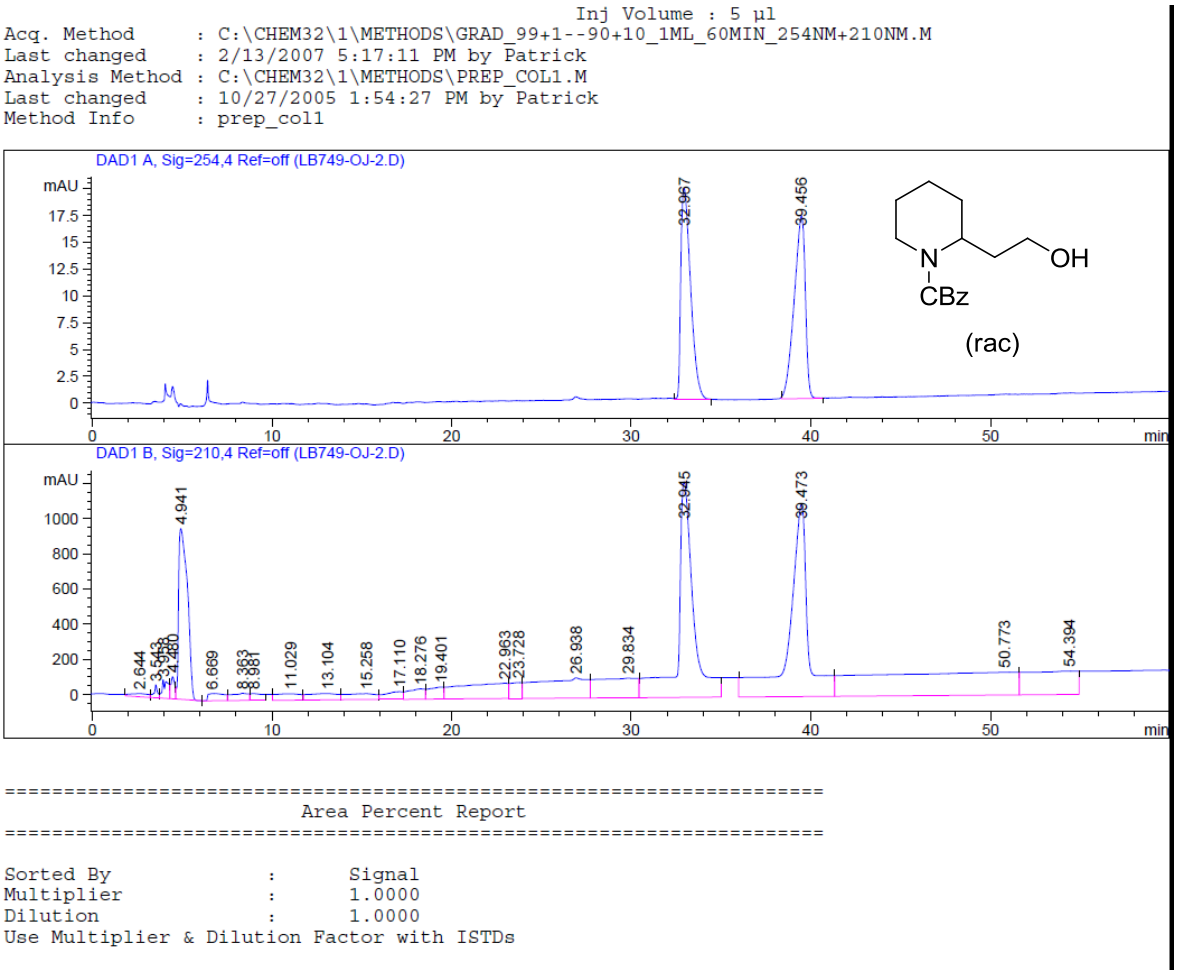
^{13}C NMR (100 MHz, $CDCl_3$)

2

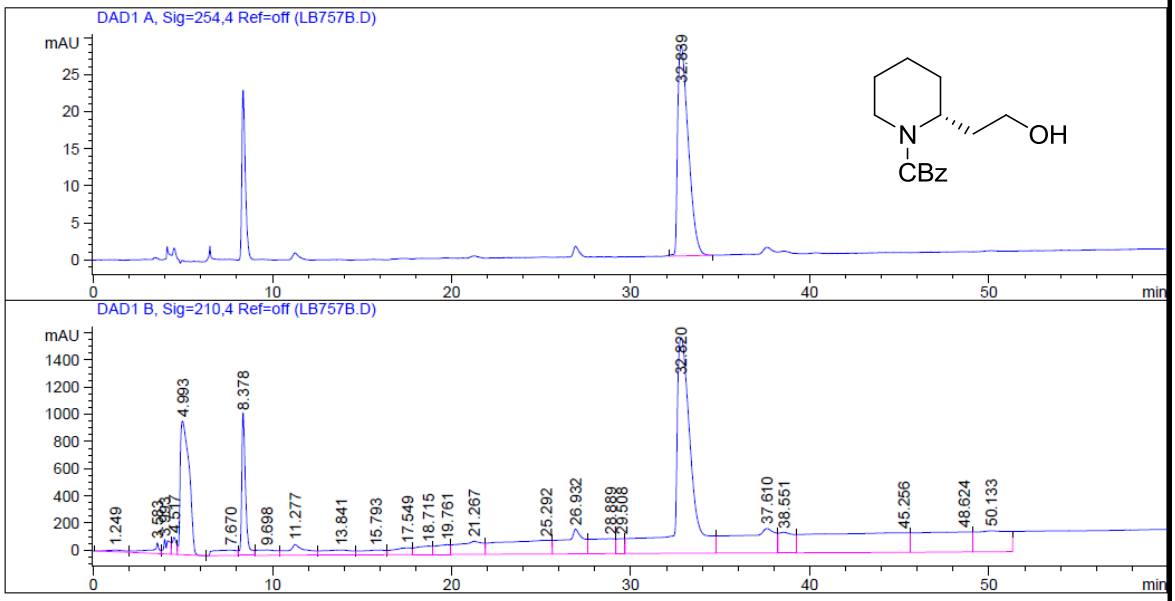
4. UV Spectrum of (+)-vertine



4. HPLC Spectrum

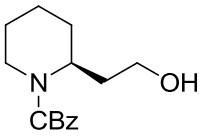


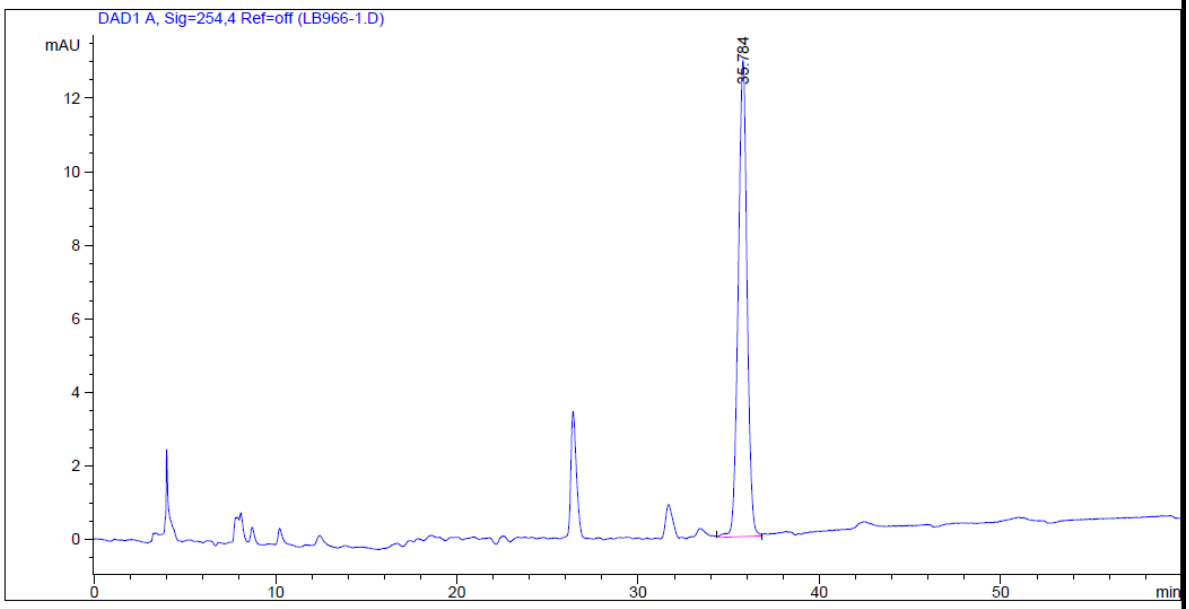
```
======================================================================
Acq. Operator    : Patrick                      Seq. Line :  10
Acq. Instrument  : Instrument 1                  Location : Vial 61
Injection Date   : 10/29/2009 6:11:04 PM            Inj :   1
                                                Inj Volume : 5 µl
Acq. Method      : C:\CHEM32\1\METHODS\GRAD_99+1--90+10_1ML_60MIN_254NM+210NM.M
Last changed     : 2/13/2007 5:17:11 PM by Patrick
Analysis Method  : C:\CHEM32\1\METHODS\PREP_COL1.M
Last changed     : 10/27/2005 1:54:27 PM by Patrick
Method Info      : prep_col1
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

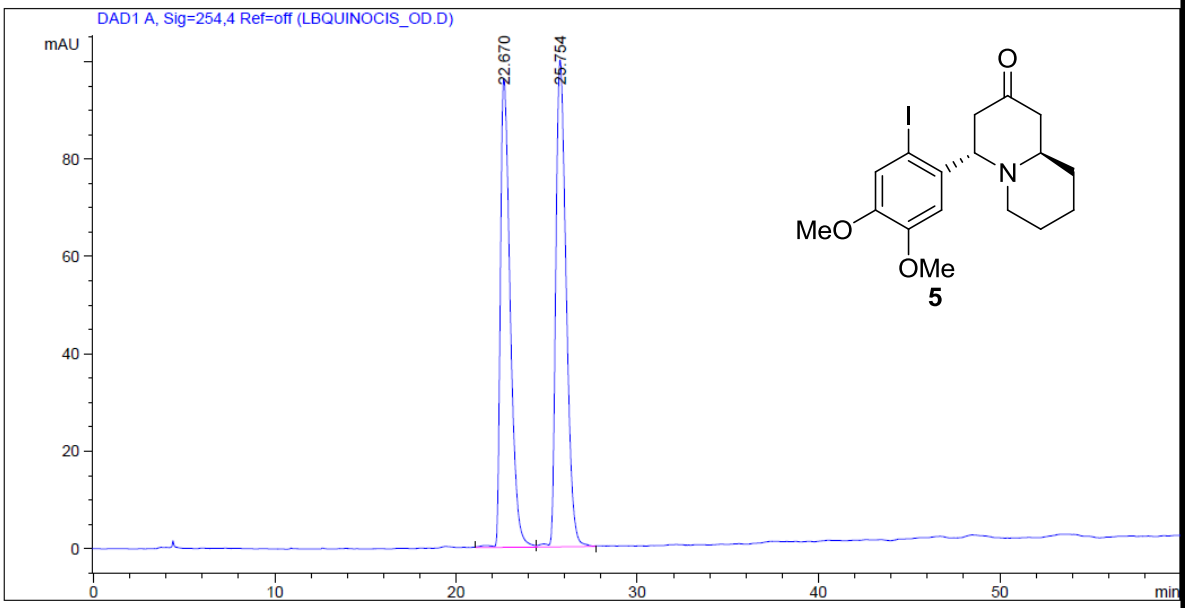
```
======================================================================
Acq. Operator   : Patrick                       Seq. Line :   8
Acq. Instrument : Instrument 1                   Location : Vial 1
Injection Date  : 6/28/2010 4:58:10 PM              Inj :   1
                                                Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\METHODS\GRAD_99+1--90+10_1ML_60MIN_254NM.M
Last changed    : 6/28/2010 5:40:18 PM by Patrick
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\STAB_100+0_50MIN.M
Last changed    : 1/27/2011 5:31:56 PM by Patrick
                  (modified after loading)
Method Info     : Test Agilent
```





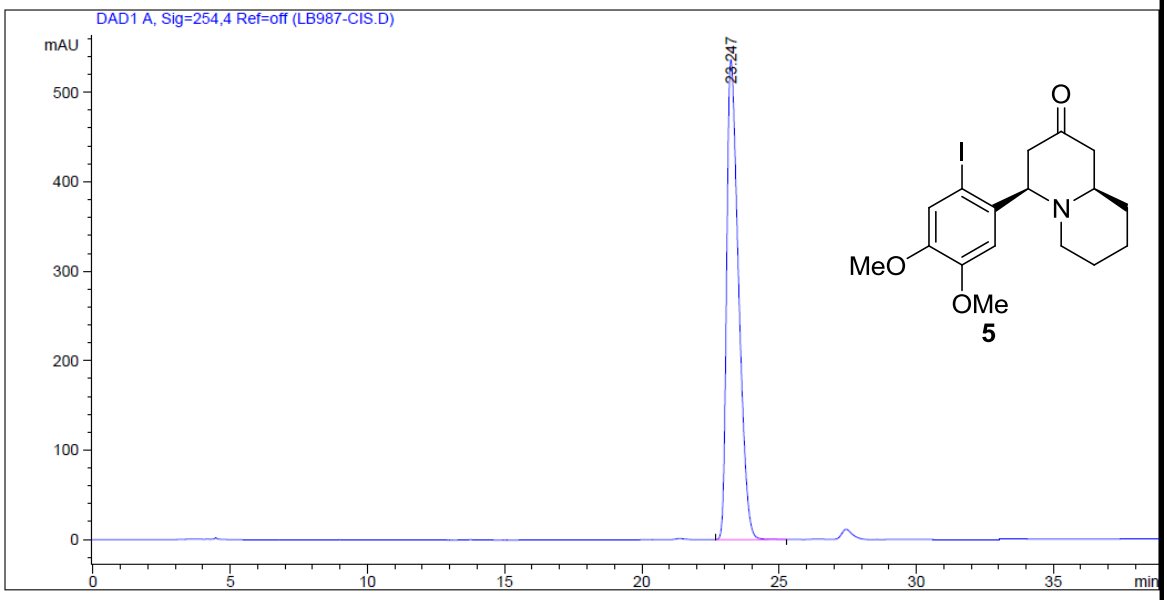

```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  35.784 VV    0.5040  437.20959   12.94684 100.0000

Totals :                   437.20959   12.94684
```

```
==================================================================
Acq. Operator   : Patrick                      Seq. Line :  18
Acq. Instrument : Instrument 1                  Location : Vial 41
Injection Date  : 5/20/2008 8:03:24 PM               Inj :  1
                                               Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\METHODS\GRAD_99+1--90+10_1ML_60MIN_254NM.M
Last changed    : 10/24/2005 11:21:13 AM
Analysis Method : C:\CHEM32\1\METHODS\PREP_COL1.M
Last changed    : 10/27/2005 1:54:27 PM by Patrick
Method Info     : prep_col1
```



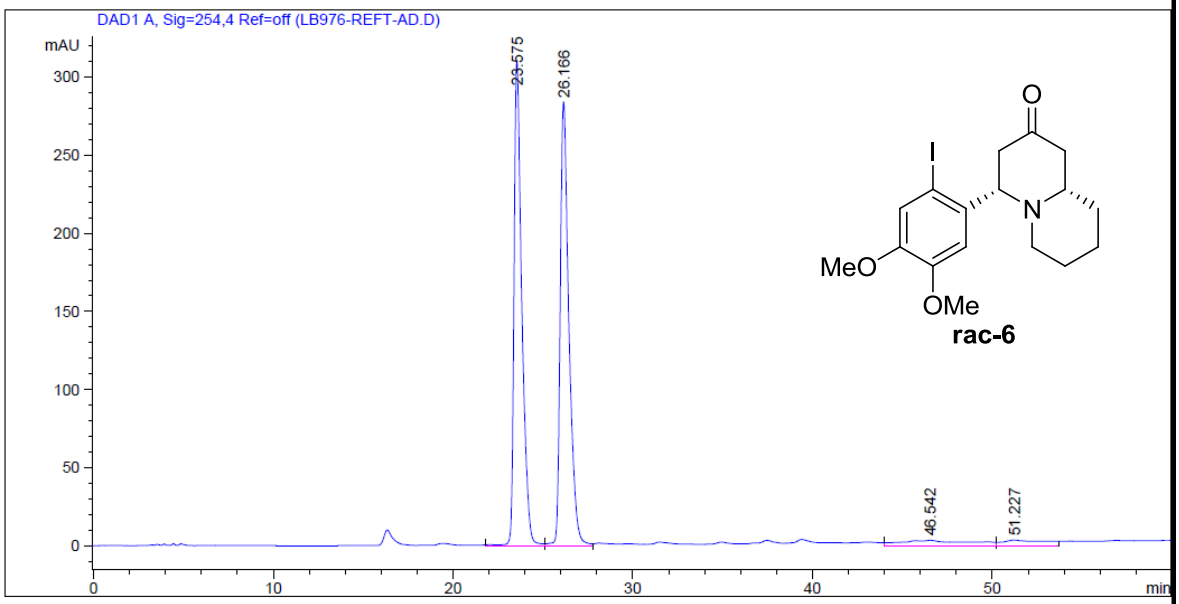

```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  22.670 BV    0.5876 3612.73877   95.02303  47.7469
   2  25.754 VB    0.6253 3953.70117   99.13585  52.2531

Totals :                  7566.43994  194.15888
```

```
Data File C:\CHEM32\1\DATA\LB987-CIS.D
 Sample Name: LB987-Cis

    ========================================================================
    Acq. Operator    : Patrick                      Seq. Line :   3
    Acq. Instrument  : Instrument 1                  Location : Vial 91
    Injection Date   : 7/20/2010 6:25:55 PM               Inj :   1
                                                   Inj Volume : 5 µl
    Acq. Method      : C:\CHEM32\1\METHODS\GRAD_99+1--90+10_1ML_60MIN_254NM.M
    Last changed     : 7/20/2010 7:05:03 PM by Patrick
                       (modified after loading)
    Analysis Method  : C:\CHEM32\1\METHODS\STAB_99+1_30MIN.M
    Last changed     : 1/28/2011 5:07:21 PM by Patrick
                       (modified after loading)
    Method Info      : Test Agilent
```



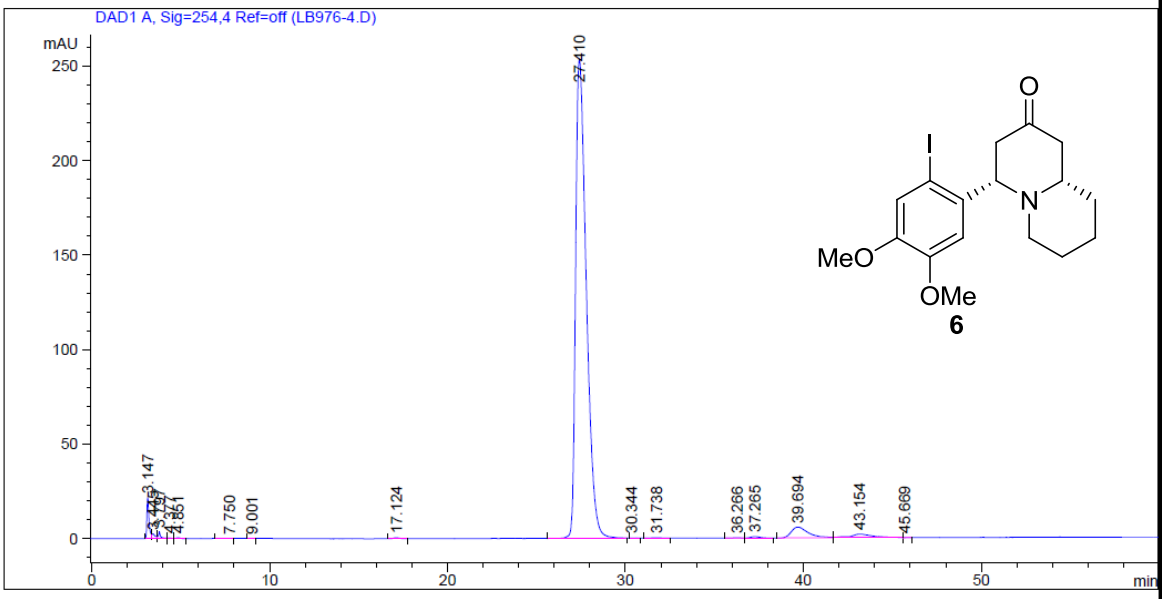

```
    ========================================================================
                            Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]    [mAU*s]     [mAU]      %
    ----|-------|----|-------|----------|----------|--------|
       1  23.247 BB    0.4597 1.61742e4   536.53394 100.0000

    Totals :                  1.61742e4   536.53394


    ========================================================================
                            *** End of Report ***
```

```
=====================================================================
Acq. Operator   : Patrick                      Seq. Line :  15
Acq. Instrument : Instrument 1                  Location : Vial 91
Injection Date  : 7/15/2010 4:49:53 PM               Inj :   1
                                               Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\METHODS\GRAD_99+1--90+10_1ML_60MIN_254NM.M
Last changed    : 10/24/2005 11:21:13 AM
Analysis Method : C:\CHEM32\1\METHODS\STAB_99+1_30MIN.M
Last changed    : 10/25/2005 10:30:50 AM by Patrick
Method Info     : Test Agilent
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.575 BV    0.4729 9375.49902  303.11844  45.9765
   2  26.166 VV    0.5031 9521.61426  284.01517  46.6930
   3  46.542 VV    3.2328  916.01727    3.45983   4.4921
   4  51.227 VB    2.0626  578.81427    3.57935   2.8384

Totals :                  2.03919e4   594.17279


=====================================================================
                        *** End of Report ***
```

```
Data File C:\CHEM32\1\DATA\LB976-4.D
 Sample Name: LB976-4

    ======================================================================
    Acq. Operator    : Patrick                      Seq. Line :  20
    Acq. Instrument  : Instrument 1                  Location : Vial 1
    Injection Date   : 7/10/2010 12:08:25 AM             Inj :   1
                                                   Inj Volume : 5 µl
    Acq. Method      : C:\CHEM32\1\METHODS\GRAD_99+1--90+10_1ML_60MIN_254NM.M
    Last changed     : 10/24/2005 11:21:13 AM
    Analysis Method  : C:\CHEM32\1\METHODS\STAB_100+0_50MIN.M
    Last changed     : 1/27/2011 5:31:56 PM by Patrick
                       (modified after loading)
    Method Info      : Test Agilent
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]    [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   3.147 BV    0.1276  185.96436   21.77985   1.6193
       2   3.445 VV    0.1601   29.00662    2.48559   0.2526
       3   3.797 VV    0.1302   35.87474    3.73114   0.3124
       4   4.377 VV    0.1949    5.97226 4.33133e-1   0.0520
       5   4.851 VB    0.2134    7.20162 5.08097e-1   0.0627
       6   7.750 BV    0.2914    1.84481 7.87110e-2   0.0161
       7   9.001 BV    0.2278    1.20126 6.80915e-2   0.0105
       8  17.124 BB    0.3040   12.08454 5.87553e-1   0.1052
       9  27.410 VB    0.6407 1.05923e4   253.90639  92.2337
      10  30.344 BB    0.3716    5.18030 1.69009e-1   0.0451
      11  31.738 BV    0.5818   14.84405 3.02863e-1   0.1293
      12  36.266 BV    0.3969    6.99716 2.11011e-1   0.0609
      13  37.265 VV    0.5095   26.95295 7.05864e-1   0.2347

Instrument 1 1/27/2011 5:49:10 PM Patrick                    Page   1 of 2
```

5. Crystallographic data.

Cell dimensions and intensities were measured at 200K on a Stoe IPDS diffractometer with graphite-monochromated Mo[$K\alpha$] radiation. (λ = 0.71073 Å). Data were corrected for Lorentz and polarization effects and for absorption. The structures were solved by direct methods (SIR97),[7] all other calculations were performed with ShelX system.[8] **(±)-Lythrine** : moiety formula $C_{26}H_{29}NO_5.CH_4O.H_2O$, *M*r= 485.6, orthorhombic, $P2_12_12_1$, a = 10.5094(6), b = 11.6736(7), c = 20.666(1) Å, V = 2535.3(3) Å^3, Z = 4, μ = 0.091 mm^{-1}, d_x = 1.272 g.cm^{-3}, R_1 = 0.041, ωR_2 = 0.113.

6. References.

1 H. Y. Cheng, D. R. Hou, *Tetrahedron,* 2007, **63**, 3000.

2 F. X. Chen, M. M. Tamarez and J. Xie, PCT Int. Appl. WO 2008/021509, 2008.

3 a) S. Fustero, D. Jimenez, J. Moscardo, S. Catalan and C. del Pozo, *Org. Lett.*, 2007, **9**, 5283; b) D. Passarella, S. Riva, G. Grieco, F. Cavallo, B. Checa, F. Arioli, E. Riva, D. Comi and B. Danieli, *Tetrahedron: Asymmetry*, 2009, **20**, 192.

4 a) M. Angoli, A. Barilli, G. Lesma, D. Passarella, S. Riva, A. Silvani and B. Danieli, *J. Org. Chem.*, 2003, **68**, 9525; b) A. Barilli, F. Belinghieri, D. Passarella, G. Lesma, S. Riva, A. Silvani and B. Danieli, *Tetrahedron: Asymmetry*, 2004, **15**, 2921.

5 a) S. G. Davies, A. M. Fletcher, P. M. Roberts and A. D. Smith, *Tetrahedron,* 2009, **65**, 10192; b) G. L. Cheng, X. Y. Wang, D. Y. Su, H. Liu, F. Liu and Y. F. Hu, *J. Org. Chem.*, 2010, **75**, 1911.

6 K. Ando, *J. Org. Chem.*, 1999, **8**, 8406.

7 A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna; *J. Appl. Cryst*. 1999, 32, 115.

8 G. M. Sheldrick, *Acta Cryst A*, 2008, A64, 112-122.