Electronic Supplementary Material (ESI) for Chemical Communications

Synthesis of the ABH rings of ecteinascidin 597 using a connective Pummerer-type cyclisation

Laura H. S. Smith,[a] Trung Thanh Nguyen,[a] Helen F. Sneddon,[b] David J. Procter*[a]

[a] School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK;

[b] Medicines Research Centre, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK

Contents

General experimental

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents, unless stated otherwise. THF was distilled from sodium and benzophenone, CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2.$ZnCl_2$ was dried in the oven at 120 °C. Microwave reactions were carried out using a Biotage Initiator.

^1H NMR and ^{13}C NMR were recorded using 300, 400 and 500 MHz spectrometers, with chemical shift values reported in ppm relative to residual chloroform (δ_H = 7.27 or δ_C = 77.2) or DMSO (δ_H = 2.50 or δ_C = 39.5) as internal standards. All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained using positive and negative electrospray (ES±) or gas chromatography (GC) methodology. Infra-red spectra were recorded as evaporated films or neat using a FT-IR spectrometer. Column chromatography was carried out using 35 - 70 m, 60A silica gel. Routine TLC analysis was carried out on aluminium

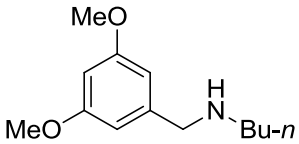
sheets coated with silica gel 60 F254, 0.2 mm thickness. Plates were viewed using a 254 mm ultraviolet lamp and stained using *p*-anisaldehyde or phosphomolybdic acid.

General procedure 1: Swern Oxidation

A solution of oxalyl chloride (0.096 ml/mmol, 1.1 equiv) in CH_2Cl_2 (4 ml/mmol) was cooled to –78 °C. DMSO (0.142 ml/mmol, 2.0 equiv) was added and the solution stirred for 5 minutes. A solution of 2-hydroxyacetamide in CH_2Cl_2 (4 ml/mmol) was added and the reaction stirred for 30 minutes. NEt_3 (0.695 ml/mmol, 5.0 equiv) was added and the solution allowed to warm to room temperature. After 3h the reaction mixture was washed with saturated $NaHCO_3$ solution (3 × 10 ml/mmol) then dried ($MgSO_4$). The crude glyoxamide was used without further purification.

Synthesis of simple 4-sulfanyl tetrahydroisoquinolinones

***n*-Butyl-(3,5-dimethoxy-benzyl)-amine S1**



3,5-Dimethoxybenzaldehyde (1.66 g, 10.0 mmol) was dissolved in dry MeOH (50 ml) under $N_2$and *n*-butylamine (1.30 ml, 11.0 mmol) added. The solution was heated at reflux for 2h then cooled to room temperature and $NaBH_4$ (417 mg, 11.0 mmol) added portionwise. The solution was stirred for 1 h then the solvent evaporated and the residue dissolved in 1 M HCl (100 ml) and extracted with EtOAc (20 ml). The aqueous layer was basified with saturated Na_2CO_3 solution then extracted with EtOAc (3 × 50 ml). The extracts were washed with brine (50 ml) then dried ($MgSO_4$) and evaporated to give **S1** (2.05 g, 94%) as a pale oil which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.51 (2 H, d, *J* = 2.3 Hz, Ar CH), 6.36 (1 H, t, *J* = 2.3 Hz, Ar CH), 3.80 (6 H, s, OCH_3), 3.75 (2 H, s, $ArCH_2N$), 2.63 (3 H, t, *J* = 7.1 Hz, CH_2N), 1.44 - 1.57 (2 H, m, CH_2), 1.28 - 1.43 (2 H, m, CH_2), 0.91 (3 H, t, *J* = 7.2 Hz, CH_3).

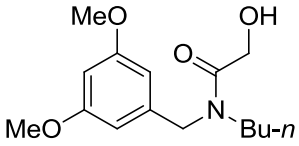
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 160.9 (Ar C-O), 142.9 (Ar C-C), 106.0 (Ar CH), 99.0 (Ar CH), 55.3 (OCH_3), 54.1 ($ArCH_2N$), 49.1 (CH_2N), 32.2 (CH_2), 20.5 (CH_2), 14.0 (CH_3).

MS (ES+) *m/z* 224.1 $[M+H]^+$.

HRMS 224.1646; $C_{13}H_{22}NO_2^+$ requires 224.1645.

IR (thin film) ν_{max} (cm^{-1}) 3322 (NH stretch), 2654 (CH stretch).

_n_-Butyl-_N_-(3,5-dimethoxy-benzyl)-2-hydroxy-acetamide S2



Amine **S1** (223 mg, 1.0 mmol) was placed in an oven-dried microwave vial and 2,2-dimethyl-1,3-dioxolan-4-one[1] (0.235 ml, 2.0 mmol) added. The vial was flushed with N_2 then sealed and heated to 150 °C in the microwave reactor for 1 h. The acetone generated in the reaction was removed *in vacuo* and the residue purified by flash chromatography (50% EtOAc–pet. ether) to give **S2** (191 mg, 68%) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.38 (2 H, s, Ar CH), 6.27 (1 H, s, Ar CH), 4.59 (2 H, s, $ArCH_2N$ of one rotamer), 4.29 (2 H, s, $ArCH_2N$ of one rotamer), 4.24 (2 H, d, *J* = 4.3 Hz CH_2OH of one rotamer), 4.17 (2 H, d, *J* = 4.3 Hz CH_2OH of one rotamer), 3.78 (6 H, s, OCH_3), 3.70 (1 H, t, *J* = 4.3 Hz, OH of one rotamer), 3.65 (1 H, t, *J* = 4.3 Hz, OH of one rotamer), 3.43 (1 H, t, *J* = 7.7 Hz, CH_2N of one rotamer), 3.04 (2 H, t, *J* = 7.7 Hz, CH_2N of one rotamer), 1.48 - 1.58 (2 H, m, CH_2), 1.24 - 1.34 (2 H, m, CH_2), 0.92 (3 H, t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δppm 171.7 (C=O). 161.4 (Ar C-O of one rotamer), 161.1 (Ar C-O of one rotamer), 139.1 (Ar C-C of one rotamer), 138.2 (Ar C-C of one rotamer), 106.0 (Ar CH of one rotamer), 104.3 (Ar CH), 99.2 (Ar CH of one rotamer), 55.4 (OCH_3), 59.9 (CH_2OH), 49.1 ($ArCH_2N$ of one rotamer), 48.6 ($ArCH_2N$ of one rotamer), 46.5 (CH_2N of one rotamer), 44.8 (CH_2N of one rotamer), 29.4 (CH_2), 20.1 (CH_2), 13.7 (CH_3).

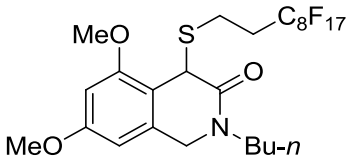
MS (ES+) *m/z* 304 $[M+Na]^+$.

HRMS 304.1522; $C_{15}H_{23}O_4NNa^+$ requires 304.1519.

IR (thin film) ν_{max} (cm^{-1}) 3417 (OH stretch), 2956 (CH stretch), 1645 (C=O stretch).

[1]2,2-Dimethyl-1,3-dioxolan-4-one was purchased from Sigma-Aldrich or prepared according to a literature procedure: Daryaee, F.; Kobarfard, F.; Khalaj, A.; Farnia, P., *Eur. J. Med. Chem.* 2009, **44**, 289.

2-Butyl-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decylsulfanyl)-5,7-dimethoxy-1,4-dihydro-2*H*-isoquinolin-3-one 5



Hydroxyacetamide **S2** (140 mg, 0.5 mmol) was oxidized according to general procedure 1. The crude glyoxamide was dissolved in CH_2Cl_2 (6 ml) and $HSCH_2CH_2C_8F_{17}$ (0.21 ml, 0.75 mmol) and $Sc(OTf)_3$ (49 mg, 0.1 mmol)were added. The solution was stirred at room temperature for 40 h then the reaction mixture was washed with water (10 ml) then brine (10 ml) and dried ($MgSO_4$). Flash chromatography (20% EtOAc–pet. ether) gave **5** (248 mg, 67%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.40 (1 H, d, *J* = 2.3 Hz, Ar C-H), 6.33 (1 H, d, *J* = 2.3 Hz, Ar C-H), 4.81 (1 H, s, ArCHS), 4.77 (1 H, d, *J* = 15.6 Hz, ArC<u>H</u>HN), 4.09 (1 H, d, *J* = 15.6 Hz, ArCH<u>H</u>N), 3.81 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 3.68 (1 H, dt, *J* = 13.6, 7.6 Hz, NC<u>H</u>H), 3.36 (1 H, dt, *J* = 13.6, 7.6 Hz, NC<u>H</u>H), 3.04 - 3.13 (1 H, m, SC<u>H</u>H), 2.82 - 2.91 (1 H, m, SCH<u>H</u>), 2.46 - 2.64 (2 H, m, C<u>H</u>$_2C_8F_{17}$), 1.56 - 1.64 (2 H, m, CH_2), 1.28 - 1.43 (2 H, m, CH_2), 0.95 (3 H, t, *J* = 7.3 Hz, CH_3).

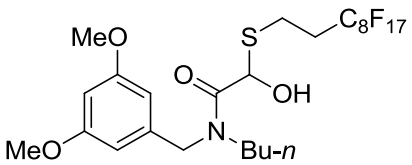
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.7 (C=O), 160.6 (Ar C-O), 157.3 (Ar C-O), 135.4 (Ar <u>C</u>-C), 113.4 (Ar <u>C</u>-C), 101.8 (Ar C-H), 97.5 (Ar C-H), 55.7 (OCH_3), 55.5 (OCH_3), 50.3 ($ArCH_2N$), 47.0 (CH_2N), 41.0 (ArCHS), 31.8 (t, *J* = 21.2 Hz, <u>C</u>$H_2C_8F_{17}$), 29.4 (CH_2), 23.0 (t, *J* = 3.7 Hz, SCH_2), 19.9 (CH_2), 13.8 (CH_3).

MS (ES+) *m/z* 764 $[M+Na]^+$.

HRMS 764.1068; $C_{25}H_{24}F_{17}NO_3SNa^+$ requires 746.1098.

IR (thin film) ν_{max} (cm^{-1}) 2962 (CH stretch), 1653 (C=O).

***rac*-*N*-butyl-*N*-(3,5-dimethoxybenzyl)-2-((3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)thio)-2-hydroxyacetamide S3**

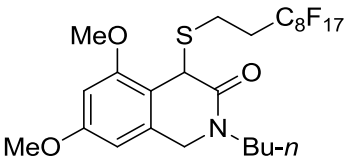


DMSO (147 µl, 2.06 mmol) was added to a solution of $(COCl)_2$ (99 µl, 1.13 mmol) in CH_2Cl_2 (4 ml) at –78 °C. After 15 minutes, a solution of hydroxyacetamide **S2** (290 mg, 1.03 mmol) in CH_2Cl_2 (4 ml) was added and the solution stirred for a further 35 minutes. NEt_3

(695 µl, 5.0 mmol) was added then the reaction mixture allowed to warm to room temperature. $HSCH_2CH_2C_8F_{17}$(354 µl, 1.24 mmol) was added after 3 h and the reaction was allowed to stir for a further 20 minutes then washed with water (10 ml), saturated $NaHCO_3$ solution (2 × 10 ml) and dried ($MgSO_4$) to give crude **S3** which was used without further purification.

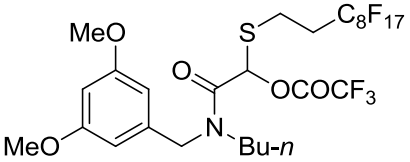
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.27 - 6.42 (6 H, m, Ar CH), 5.49 (1 H, d, *J* = 9.1 Hz, SC<u>H</u>OH of one rotamer), 5.34 (1 H, d, *J* = 8.8 Hz, SC<u>H</u>OH of one rotamer), 4.99 (1 H, d, *J* = 15.1 Hz, ArC<u>H</u>HN of one rotamer), 4.82 (1 H, d, *J* = 17.0 Hz, ArC<u>H</u>HN of one rotamer), 4.65 (1 H, d, *J* = 8.8 Hz, OH of one rotamer), 4.63 (1 H, d, *J* = 9.1 Hz, OH of one rotamer), 4.31 (1 H, d, *J* = 17.0 Hz ArCH<u>H</u>N of one rotamer), 4.21 (1 H, d, *J* = 15.1 Hz ArCH<u>H</u>N of one rotamer), 3.79 (6 H, s, OCH_3 of one rotamer), 3.77 (6 H, s, OCH_3 of one rotamer), 3.44 - 3.55 (1 H, m, NC<u>H</u>H of one rotamer), 2.98 - 3.16 (3 H, m, NCH<u>H</u> of one rotamer and NCH_2), 2.83 - 2.99 (4 H, m, SCH_2), 2.35 - 2.56 (4 H, m, $C\underline{H}_2C_8F_{17}$), 1.58 (4 H, m, CH_2), 1.26 - 1.38 (4 H, m, CH_2), 0.90 - 0.97 (6 H, m, CH_3).

2-Butyl-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decylsulfanyl)-5,7-dimethoxy-1,4-dihydro-2*H*-isoquinolin-3-one 5(from S3)



Hemithioacetal **S3** (0.51 mmol) was dissolved in CH_2Cl_2 (6 ml) and $ZnCl_2$ (70 mg, 0.51 mmol) was added. The solution was stirred for 26 h then washed with saturated $NaHCO_3$ solution (10 ml) and dried ($MgSO_4$). Flash chromatography (20% EtOAc–pet. ether) gave **5** (290 mg, 77%) as a yellow oil.

2-(Butyl(3,5-dimethoxybenzyl)amino)-1-((3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)thio)-2-oxoethyl 2,2,2-trifluoroacetate S4

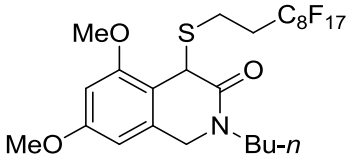


Hemithioacetal **S3** (0.275 mmol) was dissolved in $CDCl_3$ (3.3 ml) and TFAA (57µl, 0.413 mmol) was added. After 3 h the reaction was complete (NMR) and the solution was diluted

with CH_2Cl_2 (5 ml), washed with water (10 ml) then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **S4**.

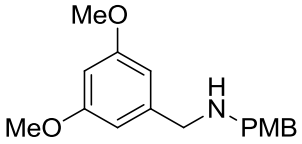
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.44 (1 H, s), 6.44 (1 H, s, Ar CH), 6.41 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.37 (3 H, s, Ar CH), 6.29 (1 H, s, SC<u>H</u>OCOCF$_3$ of one rotamer), 6.14 (1 H, s, SC<u>H</u>OCOCF$_3$ of one rotamer), 4.89 (1 H, d, *J* = 17.3 Hz, ArC<u>H</u>HN of one rotamer), 4.71 (1 H, d, *J* = 15.1 Hz, ArC<u>H</u>HN of one rotamer), 4.44 (1 H, d, *J* = 15.1 Hz, ArCH<u>H</u>N of one rotamer), 4.33 (1 H, d, *J* = 17.3 Hz, ArCH<u>H</u>N of one rotamer), 3.81 (6 H, s, OCH_3 of one rotamer), 3.77 (6 H, s, OCH_3 of one rotamer), 3.42 (1 H, m, ArC<u>H</u>HN of one rotamer), 3.28 - 3.33 (2 H, m), 3.16 - 3.25 (1 H, m ArC<u>H</u>HN of one rotamer), 2.95 - 3.13 (4 H, m), 2.81 - 2.93 (3 H, m), 2.40 - 2.57 (4 H, m C<u>H</u>$_2$C$_8$F$_{17}$), 1.68 (3 H, dt, *J* = 15.6, 7.8 Hz, CH_2 of one rotamer), 1.57 (3 H, dt, *J* = 15.1, 7.7 Hz, CH_2 of one rotamer), 1.33 (4 H, m, CH_2), 0.87 - 0.99 (6 H, m, CH_3).

2-Butyl-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decylsulfanyl)-5,7-dimethoxy-1,4-dihydro-2*H*-isoquinolin-3-one 5(from S4)



S4 (0.275 mmol) was dissolved in CH_2Cl_2 (3.0 ml) and $ZnCl_2$ (7.5 mg, 0.055 mmol) was added. The solution was stirred for 21 h then washed with water (10 ml) and dried ($MgSO_4$). Flash chromatography (20% EtOAc–pet. ether) gave **5** (85 mg, 42%) as a yellow oil.

(3,5-Dimethoxy-benzyl)-(4-methoxy-benzyl)-amine S5



3,5-Dimethoxybenzaldehyde (3.32g, 20 mmol) was dissolved in dry toluene (100 ml) and 4-methoxybenzylamine (3.02 g, 22 mmol) was added. The mixture was heated at reflux under Dean-Stark conditions for 5 h then cooled and the solvent removed *in vacuo*. The residue was dissolved in dry MeOH (100 ml) and $NaBH_4$ (0.834 g, 22 mmol) was added portionwise. The solution was stirred at room temperature overnight then concentrated. The residue was taken up in EtOAc (100 ml) and washed with water (2 ×50 ml) then with brine (50 ml) and dried ($MgSO_4$). Flash chromatography (40% EtOAc–pet. ether) gave **S5** (5.42 g, 94%) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.88 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.52 (2 H, d, *J* = 2.3 Hz, Ar CH), 6.37 (1 H, t, *J* = 2.3 Hz, Ar CH), 3.82 (3 H, s, OCH_3), 3.80 (6 H, s, OCH_3), 3.75 (4 H, s, 2 × CH_2).

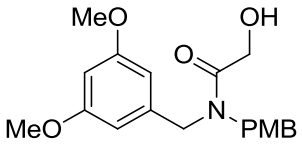
^{13}C NMR (100 MHz, $CDCl_3$) δppm 160.8 (Ar C-O), 158.6 (Ar C-O), 142.9 (Ar C-C), 132.4 (Ar C-C), 129.4 (Ar CH of PMB), 113.8 (Ar CH of PMB), 105.9 (Ar CH), 98.9 (Ar CH), 55.3 (3 × OCH_3), 53.2 (CH_2), 52.5 (CH_2).

MS (ES+) *m/z* 288 $[M+H]^+$.

HRMS 288.1588; $C_{17}H_{22}NO_3^+$ requires 288.1595.

IR (thin film) ν_{max} (cm^{-1}) 3323 (NH stretch), 2937 (CH stretch).

_N_-(3,5-Dimethoxy-benzyl)-2-hydroxy-_N_-(4-methoxy-benzyl)-acetamide S6



Amine **S5** (574 mg, 2.0 mmol) was placed in an oven-dried microwave vial and 2,2-dimethyl-1,3-dioxolan-4-one (0.352 ml, 4.0 mmol) was added. The vial was flushed with N_2 then sealed and heated to 150 °C in the microwave reactor for 1 h. The acetone generated in the reaction was removed *in vacuo* and the residue purified by flash chromatography (50% EtOAc–pet. ether) to give **S6** (494 mg, 74%) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.17 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB of one rotamer), 7.06 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB of one rotamer), 6.90 (4 H, d, *J* = 8.6 Hz, Ar CH of PMB of one rotamer), 6.87 (4 H, d, *J* = 8.8 Hz, Ar CH of PMB of one rotamer), 6.39 (2 H, t, *J* = 2.0 Hz, Ar CH), 6.35 (2 H, d, *J* = 2.3 Hz, Ar CH), 6.24 (2 H, d, *J* = 2.0 Hz, ArCH), 4.59 (2 H, s,$ArCH_2N$ of one rotamer), 4.54 (2 H, s, $ArCH_2N$ of one rotamer), 4.32 (3 H, d, *J* = 4.3 Hz, CH_2O of one rotamer), 4.24 (4 H, d, *J* = 4.3 Hz, CH_2O of one rotamer), 4.21 (2 H, s, CH_2 of PMB of one rotamer), 4.18 (2 H, s, CH_2 of PMB of one rotamer), 3.82 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.78 (6 H, s, OCH_3), 3.72 (1 H, t, *J* = 4.3 Hz, OH of one rotamer), 3.68 (1 H, t, *J* = 4.3 Hz, OH of one rotamer).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.2 (C=O of one rotamer), 172.1 (C=O of one rotamer), 161.4 (Ar C-O), 161.0 (Ar C-O), 159.3 (Ar C-O), 159.2 (Ar C-O), 138.6 (Ar C-C of one rotamer), 137.7 (Ar C-C of one rotamer), 129.9 (Ar CH of PMB of one rotamer), 128.3 (Ar C-C of one rotamer), 128.0 (Ar CH of PMB of one rotamer), 126.8 (Ar C-C of one rotamer), 114.4 (Ar CH of PMB of one rotamer), 114.0 (Ar CH of PMB of one rotamer),

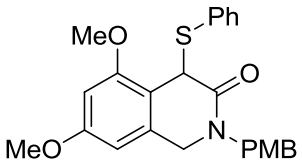
106.2 (2 × Ar C-H of one rotamer), 104.5 (2 × Ar C-H of one rotamer), 99.3 (Ar C-H of one rotamer), 99.3 (Ar C-H of one rotamer), 60.0 (CH_2OH of one rotamer), 60.0 (CH_2OH of one rotamer), 55.3 (OCH_3), 55.2 (OCH_3), 55.2 (OCH_3), 48.3 (CH_2N), 47.9 (CH_2N of one rotamer), 47.4 (CH_2N of one rotamer).

MS (ES+) *m/z* 368.1 $[M+Na]^+$.

HRMS 368.1458; $C_{19}H_{23}NO_5Na^+$ requires 368.1469.

IR (thin film) ν_{max} (cm^{-1}) 3426 (OH stretch), 2936 (CH stretch), 1651 (C=O stretch).

5,7-Dimethoxy-2-(4-methoxybenzyl)-4-(phenylthio)-1,2-dihydroisoquinolin-3(4*H*)-one S7



Hydroxyamide **S6** (166 mg, 0.5 mmol) was oxidized according to general procedure 1. The crude glyoxamide was dissolved in CH_2Cl_2 (6 ml) and thiophenol (77 µl, 0.75 mmol) and $Sc(OTf)_3$ (49 mg, 0.1 mmol) were added. The reaction mixture was stirred at room temperature for 30 h then diluted with CH_2Cl_2 (5 ml) washed with water (10 ml) then brine (10 ml) and dried ($MgSO_4$). Flash chromatography (33% EtOAc–pet. ether) gave **S8** (168 mg, 78%) as a yellow gum.

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.25 - 7.35 (3 H, m, Ar CH), 7.14 - 7.20 (4 H, m, Ar CH), 6.85 (2 H, d, *J* = 8.5 Hz, Ar CH of PMB), 6.38 (1 H, d, *J* = 1.9 Hz, Ar CH), 6.07 (1 H, d, *J* = 1.6 Hz, Ar CH), 5.09 (1 H, s, ArCHS), 4.62 (1 H, d, *J* = 14.5 Hz, ArCHHN), 4.48 (1 H, d, *J* = 14.5 Hz, ArCHHN), 3.81 - 3.86 (5 H, m, CH_2 and OCH_3), 3.80 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3)

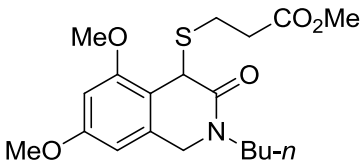
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.4 (C=O), 159.9 (Ar C-O), 158.6 (Ar C-O), 156.9 (Ar C-O), 135.0 (Ar C-H), 134.5 (Ar C-C), 131.7 (Ar C-C), 129.2 (Ar C-H), 128.2 (Ar C-C), 128.1 (Ar C-H), 128.0 (s), 113.5 (Ar C-C), 113.3 (Ar C-C), 100.3 (Ar C-H), 97.1 (Ar C-H), 55.3 (OCH_3), 55.0 (OCH_3), 54.9 (OCH_3), 49.2 (CH_2), 49.1 (CH_2), 45.1 (ArCHS).

MS (ES+) *m/z* 458 $[M+Na]^+$.

HRMS 458.1390; $C_{25}H_{25}O_4NNaS^+$ requires 458.1397.

IR (thin film) ν_{max} (cm^{-1}) 2928 (C-H), 1651 (C=O), 1610

3-(2-Butyl-5,7-dimethoxy-3-oxo-1,2,3,4-tetrahydro-isoquinolin-4-ylsulfanyl)-propionic acid methyl ester S8



Hydroxyamide **S2** (143 mmol, 0.5 mmol) was oxidized according to general procedure 1. The crude glyoxamide was dissolved in CH_2Cl_2 (6 ml) and methyl 3-mercaptopropanoate (81 µl, 0.75 mmol) and $Sc(OTf)_3$ (49 mg, 0.1 mmol) were added. The solution was stirred at room temperature for 40 h then washed with water (2 ×10 ml) then brine (10 ml) and dried ($MgSO_4$). Flash chromatography (30%EtOAc–pet. ether) gave **S8** (150 mg, 79%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm6.34 (1 H, d, *J* =1.9 Hz, Ar C-H), 6.27 (1 H, d, *J* = 1.7 Hz, Ar C-H), 4.75 (1 H, s, ArCHS), 4.75 (2 H, d, *J* = 15.4 Hz, ArC<u>H</u>HN), 4.03 (1 H, d, *J* = 15.6 Hz, ArCH<u>H</u>N), 3.80 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.65 (3 H, s, CO_2CH_3), 3.56 - 3.68 (1 H, m, NC<u>H</u>H), 3.31 (1 H, dt, *J* = 13.7, 7.0 Hz, NC<u>H</u>H), 3.02 - 3.15 (1 H, m, SC<u>H</u>H), 2.80 - 2.94 (1 H, m, SCH<u>H</u>), 2.70 - 2.79 (2 H, m, C<u>H</u>$_2$$CO_2$Me), 1.48 - 1.62 (2 H, m, CH_2), 1.24 - 1.39 (2 H, m, CH_2), 0.90 (3 H, t, *J* = 7.2 Hz, CH_3).

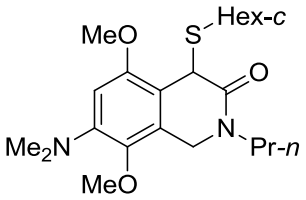
^{13}C NMR (75 MHz, $CDCl_3$) δppm 172.4 (C=O), 168.1 (C=O), 160.4 (Ar C-O), 157.2 (Ar C-O), 135.3 (Ar <u>C</u>-C), 113.7 (Ar <u>C</u>-C), 101.7 (Ar C-H), 97.5 (Ar C-H), 55.7 (OCH_3), 55.4 (OCH_3), 51.6 (CO_2<u>C</u>H_3), 50.2 ($ArCH_2N$), 46.9 (NCH_2), 40.7 (ArCHS), 34.4 (<u>C</u>H_2CO_2Me), 29.4 (CH_2), 27.2 (SCH_2), 23.9 (CH_2), 19.9 (CH_2), 13.9 (CH_3).

MS (ES+) *m/z* 404.2 $[M+Na]^+$.

HRMS 404.197, $C_{19}H_{27}NO_5NaS^+$ requires 404.1502.

IR (thin film) ν_{max} (cm^{-1}) 2954 (C-H stretch), 1734 (ester C=O stretch), 1653 (amide C=O stretch).

4-(Cyclohexylthio)-7-(dimethylamino)-5,8-dimethoxy-2-propyl-1,2-dihydroisoquinolin-3(4*H*)-one S9



N-(3-(dimethylamino)-2,5-dimethoxybenzyl)-2-hydroxy-*N*-propylacetamide (0.20 g, 0.64 mmol) was oxidized according to general procedure 1. An aliquot of the crude glyoxamide (0.22 mmol) was dissolved in anhydrous $CHCl_3$ (3.5 ml) and cyclohexanethiol (40 µl, 0.32 mmol) and $ZnCl_2$ (44.0 mg, 0.32 mmol) were added. The reaction was heated at reflux for 16 h then diluted with $CHCl_3$ (5 ml), washed with water (5 ml) and brine (5 ml) and dried ($MgSO_4$). Flash chromatography (15% EtOAc–*n*-hexane with 1% NEt_3) gave **S10** (51.0 mg, 58%) as a pale oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.37 (1H, s, Ar CH), 4.87 (1H, s, CHS), 4.57 (1H, d, J = 16.1 Hz, C<u>H</u>HN), 4.44 (1H, d, J = 16.1 Hz, CH<u>H</u>N), 3.84 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.59 - 3.64 (1H, m, NC<u>H</u>H), 3.32 - 3.39 (1H, m, NCH<u>H</u>), 3.09 - 3.15 (1H, m, SC<u>H</u>$(CH_2)_2$), 2.83 (6H, s, $N(CH_3)_2$), 2.31 - 2.33 (1H, m, C<u>H</u>H), 1.90 - 1.92 (1H, m, CH<u>H</u>), 1.23 - 1.8 (10H, m, 4 × CH_2 of *c*-hexyl ring and C<u>H</u>$_2$$CH_3$), 0.95 (3H, t, J = 7.3 Hz, CH_3).

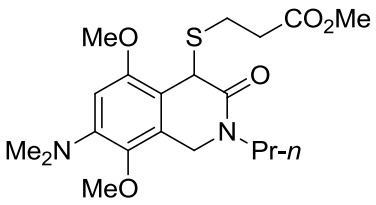
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.9 (C=O), 152 (Ar C-O), 145.0 (Ar C-O), 140.8 (Ar C-N), 128.0 (Ar C-C), 114.5 (Ar C-C), 100.7 (Ar CH), 58.7 (OCH_3), 56.0 (OCH_3), 48.8 (NCH_2), 45.1 (CH_2N), 43.8 (S<u>C</u>H$(CH_2)_2$), 42.2 ($N(CH_3)_2$), 39.6 (CHS), 33.6 (CH_2), 32.9 (CH_2), 25.9 (CH_2), 20.6 (CH_2), 11.1 (CH_3).

MS (ES+) *m/z* 429 $[M+Na]^+$.

HRMS 429.2181; $C_{22}H_{34}N_2O_3NaS^+$ requires 429.2182.

IR (thin film) ν_{max} (cm^{-1}) 2928, 2851, 1645 (C=O), 1605.

Methyl 3-(7-(dimethylamino)-5,8-dimethoxy-3-oxo-2-propyl-1,2,3,4-tetrahydro-isoquinolin-4-ylthio)propanoateS12



N-(3-(dimethylamino)-2, 5-dimethoxybenzyl)-2-hydroxy-*N*-propylacetamide (0.20 g, 0.64 mmol) was oxidized according to general procedure 1. An aliquot of the crude glyoxamide (70mg, 0.22 mmol) was dissolved in anhydrous $CHCl_3$ (3.5 ml) and methyl 3-mercaptopropanoate (40 µml, 0.32 mmol) and $ZnCl_2$ (44.0 mg, 0.32 mmol) were added. The reaction was heated at reflux for 16 h then diluted with $CHCl_3$ (5 ml) and washed with water (5 ml) then brine (5 ml) and dried ($MgSO_4$). Flash chromatography (20% EtOAc–*n*-hexane with 1% NEt_3) gave **S12** (60 mg, 63%) as a pale oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.36 (1H, s, Ar CH), 4.78 (1H, s, CHS), 4.54 (1H, d, J = 16.1 Hz, CHHN), 4.44 (1H, d, J = 16.1 Hz, CHHN), 3.83 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.59 - 3.66 (1H, m, NCHH), 3.31 - 3.36 (1H, m, NCHH), 3.09 - 3.15 (1H, m, SCHH), 2.88 - 2.94 (1H, m, SCHH), 2.82 (6H, s, $N(CH_3)_2$), 2.74 - 2.81 (2H, m, CH_2C=O), 1.62 - 1.70 (2H, m, CH_2), 0.94 (3H, t, J = 7.6 Hz, CH_3).

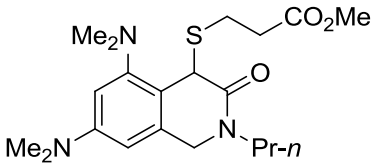
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 172.4 (C=O), 168.1 (C=O), 152.2 (Ar C-O), 145.3 (Ar C-O), 140.6 (Ar C-N), 127.8 (Ar C-C), 113.4 (Ar C-C), 100.5 (Ar CH), 58.6 (OCH_3), 55.9 (OCH_3), 51.6 (OCH_3), 48.8 (NCH_2), 45.1 (NCH_2), 42.1 ($N(CH_3)_2$), 40.9 (ArCHS), 34.4 (CH_2CO_2Me), 27.2 (SCH_2), 20.6 (CH_2), 11.1 (CH_3).

MS (ES+) m/z 433 $[M+Na]^+$.

HRMS 433.1779; $C_{20}H_{30}N_2O_5NaS^+$ requires 433.1768.

IR (thin film) ν_{max} (cm^{-1}) 2939, 1736 (C=O), 1646 (C=O).

Methyl 3-(5,7-bis(dimethylamino)-3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-ylthio)propanoate S11



SO_3·pyridine complex (76.0 mg, 0.48 mmol) was dissolved in anhydrous CH_2Cl_2 (2.0 ml) at -8 to -5 °C. DMSO (46.0 µl, 0.64 mmol) was added and the mixture stirred for 15 min then NEt_3 (0.34 ml, 2.40 mmol) was added, followed by a solution of *N*-(3,5-bis(dimethylamino)benzyl)-2-hydroxy-*N*-propylacetamide (47.0 mg, 0.16 mmol) in CH_2Cl_2 (0.5 ml) and the reaction was stirred for 5 h. The reaction mixture was washed with saturated $NaHCO_3$solution (3 ml) and dried ($MgSO_4$). The crude glyoxamide was dissolved in anhydrous $CHCl_3$ (3.5 ml) and methyl 3-mercaptopropanoate (29.0 µl, 0.24 mmol) and $ZnCl_2$ (33.0 mg, 0.24 mmol) were added. The reaction was heated at reflux for 20 h then diluted with $CHCl_3$ (5 ml), washed with water (5 ml) then brine (5 ml) and dried ($MgSO_4$). Flash chromatography (30% EtOAc–*n*-hexane with 0.5% NEt_3) gave **S11** (26 mg, 41%) as a pale oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.37 (1H, br. s., Ar CH), 6.24 (1H, br. s., Ar CH), 4.89 (1H, s, CHS), 4.88 (1H, d, J = 14.8 Hz, CHHN), 3.97 (1H, d, J = 14.8 Hz, CHHN), 3.68 (3H, s, OCH_3), 3.64-3.69 (1H, m, SCHH), 3.21-3.27 (1H, m, SCHH), 3.09-3.14 (1H, m,

NCHHCH$_2$), 2.95 (6H, s, N(CH$_3$)$_2$), 2.88-2.95 (1H, m, NCHHCH$_2$), 2.77-2.83 (2H, m, SCH$_2$CH$_2$), 2.77 (6H, s, N(CH$_3$)$_2$), 1.60-1.67 (2H, m, CH$_2$), 0.95 (3H, t, *J* = 7.6 Hz, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$) δ ppm 172.5 (C=O), 168.8 (C=O), 153.3 (Ar C-N), 150.6 (Ar C-N), 136.1 (Ar C-C), 115.2 (Ar C-C), 104.5 (Ar CH), 103.2 (Ar CH), 51.6 (OCH$_3$), 51.0 (CH$_2$N), 48.6 (SCH$_2$), 45.2 (N(CH$_3$)$_2$), 43.4 (CHS), 40.4 (N(CH$_3$)$_2$), 34.3 (SCH$_2$CH$_2$), 27.1 (NCH$_2$CH$_2$), 20.8 (CH$_2$CH$_3$), 11.2 (CH$_3$).

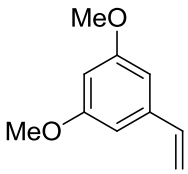
MS (ES+) *m/z* 411 [M+H]$^+$, 433 [M+Na]$^+$.

HRMS 433.1779; $C_{20}H_{30}N_2O_5NaS^+$ requires 433.1768.

IR (thin film) ν_{max} (cm^{-1}) 2936, 1734 (C=O), 1645 (C=O), 1603, 1504.

Synthesis of model ABH ring systems

1, 3-Dimethoxy-5-vinyl-benzene 6[2]



Methyltriphenylphosphonium bromide (15.5 g, 43.2 mmol) was suspended in dry THF (67 ml) under N$_2$ and KO*t*-Bu (5.7 g, 50.4 mmol) added and the mixture stirred at room temperature for 30 minutes then cooled to –78 °C. A solution of 3, 5-dimethoxybenzaldehyde (6.0 g, 36.1 mmol) in dry THF (33 ml) was added dropwise and the reaction mixture allowed to warm to room temperature. The reaction was quenched with MeOH (10 ml) and the solvent evaporated. The crude material was filtered through a short silica column (6% Et$_2$O–pet. ether) to give **6** (5.90 g, 99%) as a colourless oil.

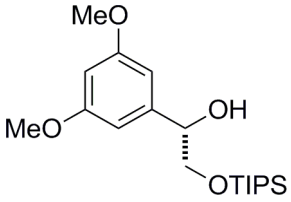
^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 6.66 (1 H, dd, *J* = 17.4, 10.8 Hz, ArCH=CH$_2$), 6.58 (2 H, d, *J* = 2.3 Hz, Ar CH), 6.40 (1 H, t, *J* = 2.3 Hz, Ar CH), 5.74 (1 H, d, *J* = 17.4 Hz, ArCH=CHH), 5.26 (1 H, d, *J* = 10.8 Hz, ArCH=CHH), 3.82 (6 H, s, OCH$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ ppm 160.5 (Ar C-O), 139.3 (Ar C-C), 136.5 (ArCH=CH$_2$), 114.0 (CH$_2$), 103.9 (Ar C-H), 99.7(Ar C-H), 55.0 (OCH$_3$).

NMR data was consistent with literature values.[2]

[2] Roberts, J. C., Pincock, J. A. *J. Org. Chem.* 2006, **71**, 1480.

(*S*)-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethanol S12



AD-mix-α (27.7 g) was dissolved in water (100 ml) and *t*-BuOH (100 ml) and the solution cooled to 0°C. Styrene **6** (3.28 g, 20 mmol) was added and the solution stirred for 16 h. Saturated Na_2SO_3 solution (50 ml) was added and the mixture stirred for a further 30 minutes. The layers were separated and the aqueous phase extracted with EtOAc (2 × 150 ml). The organic layers were combined and washed with water (100 ml) then brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude diol was dissolved in CH_2Cl_2 (150 ml) under N_2 then imidazole (3.41 g, 50 mmol) and TIPSCl (4.27 ml, 20 mmol) were added. The solution was stirred for 18 h at room temperature then washed with saturated NH_4Cl solution and dried ($MgSO_4$). Flash chromatography (5-10%EtOAc–pet. ether) gave **S12** (6.135 g, 86% over two steps) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.55 (2 H, d, *J* = 2.4 Hz, Ar CH), 6.40 (1 H, t, *J* = 2.4 Hz, Ar CH), 4.73 (1 H, dd, *J* = 8.9, 3.4 Hz, ArC<u>H</u>OH), 3.85 (1 H, dd, *J* = 10.0, 3.4 Hz, C<u>H</u>HOSi), 3.81 (6 H, s, OCH_3), 3.61 (1 H, dd, *J* = 10.0, 8.9 Hz, CH<u>H</u>OSi), 3.09 (1 H, br. s., OH), 1.05 - 1.11 (21 H, m, SiCH and SiCH(C<u>H</u>$_3$)$_2$)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 160.8 (Ar C-O), 142.7 (Ar <u>C</u>-C), 104.1(Ar C-H), 99.7 (Ar C-H), 74.5 (Ar<u>C</u>HOH), 69.2 (CH_2OSi), 55.3 (OCH_3), 17.9 (SiCH(<u>C</u>H$_3$)$_2$), 11.9 (SiCH).

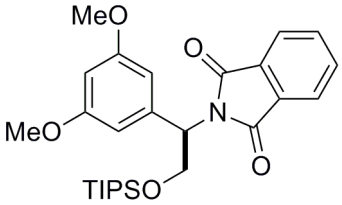
MS (ES+) *m/z* 377 $[M+Na]^+$.

HRMS 377.2118, $C_{19}H_{34}O_4NaSi^+$ requires 377.2119.

IR (thin film) ν_{max} (cm^{-1}) 3460 (br., OH), 2642, 2866, 1598.

$[\alpha]_D^{34}$ = –1.2° (c = 3.18, EtOH).

(*R*)-2-(1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)isoindoline-1,3-dione S13



Alcohol **S12** (5.11 g, 14.4 mmol) was dissolved in THF (85 ml) and phthalimide (2.97 g, 20.2 mmol), DIAD (3.98 ml, 20.2mmol) and PPh_3 (5.30 g, 20.2mmol) were added. The solution

was stirred at room temperature for 90 h then concentrated *in vacuo*. The residue was dissolved in Et_2O (100 ml) then hexane (50 ml) was added. The mixture was triturated then filtered through a plug of silica and the precipitate was washed with 40% Et_2O–*n*-hexane. The filtrate was concentrated *in vacuo* and purified by flash chromatography (10-15%Et_2O–pet. ether) to give **S13** (4.34 g, 62%) as a colourless solid, melting point (Et_2O) 62-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 (2 H, dd, *J* = 5.4, 3.0 Hz, phthalimide Ar CH), 7.70 (2 H, dd, *J* = 5.4, 3.0 Hz, phthalimide Ar CH), 6.71 (2 H, d, *J* = 2.4 Hz, 2 ×Ar CH), 6.39 (1 H, t, *J* = 2.4 Hz, Ar CH), 5.41 (1 H, dd, *J* = 10.2, 5.7 Hz, ArCHN), 4.78 (1 H, t, *J* = 10.4 Hz, C<u>H</u>HOSi), 4.20 (1 H, dd, *J* = 10.0, 5.7 Hz, CH<u>H</u>OSi), 3.78 (6 H, s, OCH_3), 0.92 - 1.00 (21 H, m, SiCH and SiCH($C\underline{H}_3$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.6 (C=O), 160.8 (Ar C-O), 139.3 (Ar <u>C</u>-C), 133.9 (phthalimide Ar CH), 131.9 (phthalimide Ar C-C), 123.1 (phthalimide Ar CH), 106.3 (Ar CH), 99.9 (Ar CH), 66.8 (ArCHN), 57.4 (CH_2OSi), 55.3 (OCH_3), 17.8 (CH($\underline{C}H_3$)$_2$), 11.8 (SiCH).

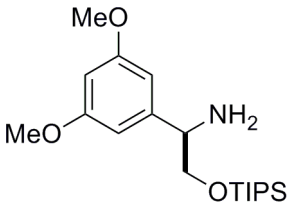
MS (ES+) *m/z* 506 $[M+Na]^+$.

HRMS 506.2330; $C_{27}H_{37}O_5NNaSi^+$ requires 506.2333.

IR (thin film) ν_{max} (cm^{-1}) 3470, 2943, 2865, 1774 (C=O), 1712, 1598.

$[\alpha]_D^{30}$ = +15.5° (c = 1.17, EtOH).

(*R*)-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethanamine 7



Phthalimide **S13** (4.34 g, 8.98 mmol) was dissolved in EtOH (60 ml) and hydrazine (62% aq. solution, 1.8 ml, 35 mmol) was added. The solution was heated under reflux for 2 h then cooled, diluted with Et_2O (150 ml) and filtered through celite. The precipitate was washed with Et_2O (200 ml) and the combined filtrate was concentrated *in vacuo* to give **7** (3.15 g, 99%) as a pale oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.57 (2 H, d, *J* = 2.4 Hz, Ar CH), 6.37 (1 H, t, *J* = 2.4 Hz, Ar CH), 4.06 (1 H, dd, *J* = 8.8, 3.8 Hz, ArCHN), 3.83 (1 H, dd, *J* = 9.1, 5.3 Hz, C<u>H</u>HO), 3.80 (6 H, s, OCH_3), 3.59 (1 H, dd, *J* = 9.6, 8.8 Hz, CH<u>H</u>O), 1.02 - 1.18 (21 H, m, SiCH and CH($C\underline{H}_3$)$_2$)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 160.7 (Ar C-O), 145.2 (Ar C-C), 104.9 (Ar C-H), 99.2 (Ar C-H), 69.7 (CH_2O), 58.1 (NCH), 55.3 (OCH_3), 18.0 ($CH(CH_3)_2$), 11.9 (SiCH).

MS (ES+) *m/z* 354 $[M+H]^+$.

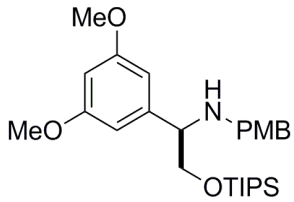
HRMS 354.2472; $C_{19}H_{36}O_3NSi^+$ requires 354.2459.

IR (thin film) ν_{max} (cm^{-1}) 3386, 2941, 2865, 1597 (C=O).

$[\alpha]_D^{34}$ = –6.0 ° (c = 0.69, EtOH)

Enantiomeric excess was measured as 84% using chiral HPLC (ChiralPak AD column, 90:10 hexane–isopropanol).

(*R*)-1-(3,5-Dimethoxyphenyl)-*N*-(4-methoxybenzyl)-2-((triisopropylsilyl)oxy) ethanamine S14



Amine **7** (3.02 g, 8.56 mmol) was dissolved in dry MeOH (15 ml) under N_2, 4-methoxybenzaldehyde (1.14 ml, 9.41 mmol) was added and the solution heated under reflux for 2 h. The solution was cooled to room temperature and $NaBH_4$ (356 mg, 9.41 mmol) was added portionwise and the solution stirred for 75 min. The reaction was quenched with water (50 ml) then extracted with EtOAc (3 × 50 ml). The extracts were washed with brine (20 ml) and dried ($MgSO_4$). Flash chromatography (10% EtOAc–pet. ether) gave **S14** (3.88 g, 96%) as a pale oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.20 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.86 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.61 (2 H, d, *J* = 2.4 Hz, Ar CH), 6.39 (1 H, t, *J* = 2.4 Hz, Ar CH), 3.81 (6 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.74 - 3.80 (2 H, m, CH_2O), 3.72 (1 H, d, *J* = 13.0 Hz, CHH of PMB), 3.64 (1 H, t, *J* = 9.5 Hz, CHN), 3.51 (1 H, d, *J* = 13.0 Hz, CHH of PMB), 1.00 - 1.11 (21 H, m, SiCH and $SiCH(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 160.5 (C-O), 158.2 (C-O), 143.3 (C-C), 132.7 (C-C), 128.9 (C-H of PMB), 113.5 (C-H of PMB), 105.4 (Ar C-H), 99.1 (Ar C-H), 68.4 (ArCHN), 64.3 (CH_2OSi), 55.1 (OCH_3), 55.0 (OCH_3), 50.5 (CH_2 of PMB), 17.7 ($SiCH(CH_3)_2$), 11.6 ($SiCH(CH_3)_2$).

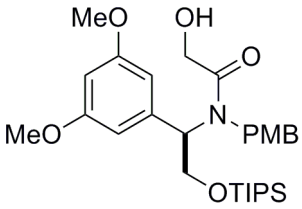
MS (ES+) *m/z* 474 $[M+H]^+$.

HRMS 474.3045; $C_{27}H_{44}O_4NSi^+$ requires 474.3034.

IR (thin film) ν_{max} (cm^{-1}) 2940, 2864, 1609, 1596.

$[\alpha]_D^{34}$ = –45.6° (c = 1.05, EtOH).

(*R*)-*N*-(1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)-2-hydroxy-*N*-(4-methoxybenzyl)acetamide 8



Amine **S14** (1.73 g, 3.7 mmol) was dissolved in CH_2Cl_2 (7.4 ml) and $AcOCH_2COCl$ (0.44 ml, 4.07 mmol) and NEt_3 (0.57 ml, 4.07 mmol) were added. The solution was stirred for 15 h then diluted with CH_2Cl_2(20 ml) and washed with saturated $NaHCO_3$ solution (2 × 20 ml) then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (24 ml), MeOH (4 ml) and water (6 ml) and $LiOH·H_2O$ (311 mg, 7.4 mmol) was added. The solution was stirred for 26 h then the volatiles evaporated and the aqueous layer diluted with water (50 ml), extracted with EtOAc (3 × 50 ml) and dried ($MgSO_4$). Flash chromatography (30%EtOAc–pet. ether) gave **8** (1.75 g, 89%) as a pale oil.

^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) δ ppm 7.06 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.79 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.48 (2 H, d, *J* = 2.2 Hz, Ar CH), 6.40 (1 H, t, *J* = 2.2 Hz, Ar CH), 5.13 (1 H, t, *J* = 6.3 Hz, ArCHN), 4.52 (1 H, d, *J* = 16.2 Hz, C<u>H</u>H of PMB), 4.33 (1 H, d, *J* = 16.2 Hz, CH<u>H</u> of PMB), 4.16 - 4.25 (2 H, m, CH_2OSi), 4.12 (2 H, d, *J* = 6.8 Hz, CH_2OH), 3.73 (3 H, s, OCH_3), 3.71 (6 H, s, OCH_3), 0.97 - 1.09 (21 H, m, SiCH and $CH(C\underline{H}_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 173.3 (C=O), 173.2 (C=O), 161.0 (Ar C-O), 160.6 (Ar C-O), 158.9 (Ar C-O), 158.5 (Ar C-O), 139.6 (Ar <u>C</u>-C), 138.2 (Ar <u>C</u>-C), 130.4 (Ar <u>C</u>-C), 129.1 (Ar CH of PMB), 128.5 (Ar <u>C</u>-C), 127.8 (Ar CH of PMB), 114.0 (Ar CH of PMB), 113.5 (Ar CH of PMB), 106.5 (Ar CH), 105.9 (Ar CH), 99.5 (Ar CH), 99.5 (Ar CH), 62.7 (CH_2O), 62.5 (CH_2O), 61.0 (ArCHN), 60.8 (ArCHN), 60.7 (CH_2O), 60.4 (CH_2O), 55.3 (OCH_3), 55.2 (OCH_3), 55.2 (OCH_3), 47.2 (CH_2 of PMB), 45.9 (CH_2 of PMB), 17.9 ($CH(\underline{C}H_3)_2$), 11.8 (SiCH), 11.7 (SiCH).

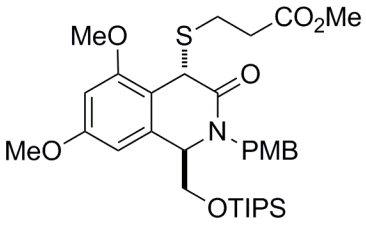
MS (ES+) *m/z* 554 $[M+Na]^+$.

HRMS 554.2904; $C_{29}H_{45}O_6NNaS^+$ requires 554.2908.

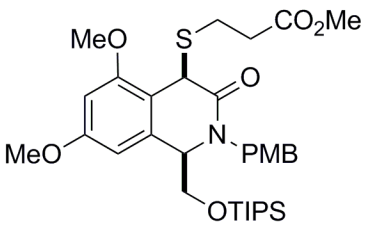
IR (thin film) ν_{max} (cm^{-1}) 3431 (br., OH), 2943, 2865, 1650 (amide C=O stretch), 1610.

$[\alpha]_D^{30}$ = –11.5° (c = 0.72, EtOH).

Methyl 3-(((1*R*,4S)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilyl) oxy) methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate 9a and methyl 3-(((1*R*,4*R*)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilyl)oxy) methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate 9b



9a



9b

Hydroxyamide **8** (274 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (1.4 ml) and DMSO (1.4 ml) at 0 °C and NEt_3 (0.36 ml, 2.60 mmol) and SO_3•py (325 mg, 2.1 mmol) were added. The solution was stirred for 2 h then methyl 3-mercaptopropanoate (84 µl, 0.78 mmol) was added. After 15 minutes, the solution was diluted with Et_2O (10 ml) and washed with 1 M HCl (10 ml), saturated $NaHCO_3$ solution (10 ml) then brine (10 ml) and dried ($MgSO_4$). The crude hemithioacetal was dissolved in CH_2Cl_2 (6 ml) and $ZnCl_2$ (141 mg, 1.04 mmol) was added. The solution was stirred at room temperature for 22 h then diluted with CH_2Cl_2 (10 ml) and washed with water (10 ml) then brine (10 ml) and dried ($MgSO_4$). Flash chromatography (30% EtOAc–pet. ether) gave a 1:1 mixture of **9a** and **9b** (267 mg, 81%) as pale gums.

MS (ES+) *m/z* 654 $[M+Na]^+$.

HRMS 654.2891; $C_{33}H_{49}O_7NNaSSi^+$ requires 654.2891.

For **9a** ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.30 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.85 - 6.90 (2 H, d, *J* =8.8 Hz, Ar CH of PMB), 6.36 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.22 (1 H, d, *J* = 2.0 Hz, Ar CH), 5.62 (1 H, d, *J* = 15.4 Hz, C<u>H</u>H of PMB), 4.57 (1 H, s, ArCHS), 4.49 (1 H, br. s, ArC<u>H</u>N), 4.15 (1 H, dd, *J* = 3.3, 10.3 Hz, C<u>H</u>HOSi), 3.99 (1 H, d, *J* = 15.4 Hz, CH<u>H</u> of PMB), 3.85 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.75 - 3.79 (1 H, m, CH<u>H</u>OSi), 3.73 (3 H, s, OCH_3), 3.68 (3 H, s, CO_2CH_3), 3.29 (1 H, dt, *J* = 7.6, 13.6 Hz, SC<u>H</u>H), 2.95 (1 H, dt, *J* = 7.6, 13.6 Hz, SCH<u>H</u>), 2.73 (2 H, t, *J* = 7.6 Hz, C<u>H</u>$_2$$CO_2$Me), 0.82 - 0.94 (21 H, m, SiCH and SiCH(C<u>H</u>$_3$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.6 (C=O), 170.7 (C=O), 160.1 (Ar C-O), 158.8 (Ar C-O), 157.3 (Ar C-O), 134.3 (Ar C-C), 129.1 (Ar CH of PMB), 129.1 (Ar <u>C</u>-C) 114.7 (Ar C-C), 114.1 (Ar CH of PMB), 101.0 (Ar C-H), 98.0 (Ar C-H), 64.5 (CH_2OSi), 60.2 (Ar<u>C</u>HN),

55.7 (OCH_3), 55.3 (OCH_3), 55.2 (OCH_3), 51.6 ($CO_2\underline{C}H_3$), 45.9 (CH_2 of PMB), 41.1 (ArCHS), 34.3 ($\underline{C}H_2CO_2CH_3$), 28.2 ($S\underline{C}H_2$), 17.7 ($SiCH(\underline{C}H_3)_2$), 11.8 ($Si\underline{C}H(CH_3)_2$).

IR (thin film) ν_{max} (cm^{-1})2925, 2865, 1739 (ester C=O), 1651 (amide C=O).

$[\alpha]_D^{30}$ = –129.3° (c = 2.61, EtOH).

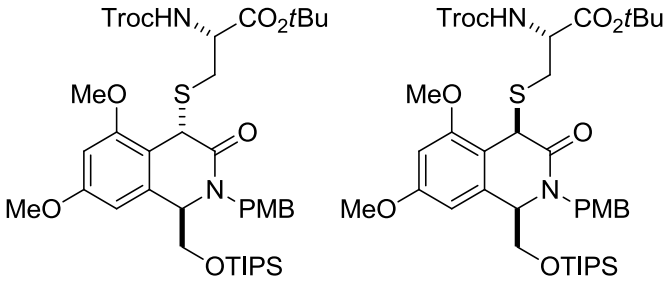
For **9b** ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.14 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.80 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.37 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.23 (1 H, d, *J* = 2.3 Hz, Ar CH), 5.43 (1 H, d, *J* = 15.0 Hz, C$\underline{H}$H of PMB), 4.72 (1 H, s, ArCHS), 4.40 (1 H, dd, *J* = 7.7, 5.8 Hz, ArCHN), 4.39 (1 H, d, *J* = 15.1 Hz, CH$\underline{H}$ of PMB), 4.27 (1 H, dd, *J* = 7.7, 9.9 Hz, C$\underline{H}$HOSi), 3.91 (1 H, dd, *J* = 5.8, 9.9 Hz, CH$\underline{H}$OSi), 3.86 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.38 (1 H, dt, *J* = 6.7, 13.9 Hz, SC$\underline{H}$H), 3.00 - 3.13 (1 H, m, SCH$\underline{H}$), 2.85 - 2.92 (2 H, m, CH_2CO_2Me), 1.01 - 1.10 (21 H, m, $Si[C\underline{H}(C\underline{H}_3)_2]_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.5 (C=O), 169.1 (C=O), 160.0 (Ar C-O), 158.8 (Ar C-O), 157.2 (Ar C-O), 136.1 (Ar C-C), 129.4 (Ar C-C), 129.1 (PMB CH), 113.9 (PMB CH), 113.5 (Ar C-C), 102.9 (Ar C-H), 98.0 (Ar C-H), 68.8 (CH_2OSi), 62.6 (ArCHN), 55.7 (OCH_3), 55.3 (OCH_3), 55.2 (OCH_3), 51.7($CO_2\underline{C}H_3$), 49.1 (CH_2 of PMB), 39.8 (ArCHS), 34.4 ($\underline{C}H_2CO_2Me$), 28.5 (SCH_2), 18.0 ($SiCH(\underline{C}H_3)_2$), 11.7($Si\underline{C}H(CH_3)_2$).

IR (thin film) ν_{max} (cm^{-1}) 2926, 2865, 1740 (ester C=O), 1648 (amide C=O).

$[\alpha]_D^{30}$ = +32.5° (c = 2.14, EtOH).

(*R*)-*tert*-Butyl 3-(((1*R*,4*S*)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilyl)oxy) methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 10a and (*R*)-*tert*-butyl 3-(((1*R*,4*R*)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilyl)oxy) methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 10b



10a **10b**

Hydroxyamide **8** (141 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (0.7 ml) and DMSO (0.7 ml) at 0 °C and NEt_3 (0.18 ml, 1.32 mmol) and SO_3•py (126 mg, 0.79 mmol) were added. The solution was stirred for 2 h then a solution of (*R*)-*tert*-butyl 3-mercapto-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate (280 mg, 0.79 mmol) in CH_2Cl_2 (2 ml) was added. After 30 minutes, the solution was diluted with Et_2O (10 ml) and washed with 1 M HCl (10 ml), saturated $NaHCO_3$ solution (10 ml) then brine (10 ml) and dried ($MgSO_4$). The crude hemithioacetal was dissolved in CH_2Cl_2 (3 ml) and $ZnCl_2$ (54 mg, 0.397 mmol) was added. The solution was stirred for 23 h then diluted with CH_2Cl_2 (10 ml) and washed with water (10 ml) then brine (10 ml) and dried ($MgSO_4$). Flash chromatography (30% EtOAc–pet. ether) gave a 1:1 mixture of **10a** and **10b** (130 mg, 57%) as pale gums.

MS (ES+) *m/z* 865 $[M+Na]^+$.

HRMS 863.2709; $C_{39}H_{58}N_2O_9SSiCl_3^+$ requires 863.2693.

For **21a** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.96 (1 H, d, *J* = 9.1 Hz, NH), 6.88 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.41 (1 H, d, *J* = 2.0 Hz, Ar CH), 6.18 (1 H, d, *J* = 2.0 Hz, Ar CH), 5.63 (1 H, d, *J* = 15.3 Hz, C<u>H</u>H of PMB), 4.85 (1 H, d, *J* = 11.9 Hz, OC<u>H</u>HCCl$_3$), 4.66 (2 H, d, *J* = 11.9 Hz, OCH<u>H</u>CCl$_3$), 4.63 - 4.68 (1 H, m, C<u>H</u>NHTroc), 4.59 (1 H, s, ArCHS), 4.43 (1 H, br. s., ArCHN), 4.13 (1 H, dd, *J* = 10.2, 2.6 Hz, ArC<u>H</u>HO), 4.00 (3 H, s, OCH_3) 3.94 (1 H, d, *J* = 15.3 Hz, CH<u>H</u> of PMB), 3.86 (1 H, dd, *J* = 14.7, 4.0 Hz, C<u>H</u>HS), 3.80 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.68 (1 H, d, *J* = 10.2 Hz, CH<u>H</u>O), 3.32 (1 H, dd, *J* = 14.7, 4.4 Hz, CH<u>H</u>S), 1.44 (9 H, s, C(CH$_3$)$_3$), 0.82 - 0.94 (21 H, m, Si[C<u>H</u>(C<u>H</u>$_3$)$_2$]$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 171.5 (C=O), 169.5 (C=O), 160.3 (Ar C-O), 158.9 (Ar C-O), 157.6 (Ar C-O), 154.6 (carbamate C=O), 134.2 (Ar <u>C</u>-C), 129.2 (Ar CH of PMB), 128.8 (Ar <u>C</u>-C), 114.1 (Ar CH of PMB), 113.9 (Ar <u>C</u>-C), 101.2 (Ar CH), 98.1 (Ar CH), 95.5 (CCl_3), 82.2 (O<u>C</u>(CH$_3$)$_3$), 74.7 (O<u>C</u>H$_2$CCl$_3$), 64.9 (CH_2OSi), 60.4 (ArCHN), 55.9 (<u>C</u>HNHTroc), 55.4 (OCH_3), 55.3 (OCH_3), 55.2 (OCH_3), 45.8 (CH_2 of PMB), 42.3 (ArCHS), 35.7 (CH_2S), 27.9 (C(<u>C</u>H$_3$)$_3$), 17.7 (s), 17.6 (CH(CH$_3$)$_2$), 11.7 (SiCH).

IR (thin film) ν_{max} (cm^{-1}) 3350, 2941, 2865, 1738, 1651, 1612.

$[\alpha]_D^{30}$ = –96.7° (c = 1.04, EtOH).

For **21b** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.57 (1 H, d, *J* = 8.2 Hz, NH), 7.15 (2 H, d, *J* = 8.5 Hz, Ar CH of PMB), 6.80 (2 H, d, *J* = 8.5 Hz, Ar CH of PMB), 6.39 (1 H, d, *J* = 1.9 Hz, Ar CH), 6.23 (1 H, d, *J* = 2.2 Hz, Ar CH), 5.42 (1 H, d, *J* = 14.8 Hz, C<u>H</u>H of PMB), 4.86 (1

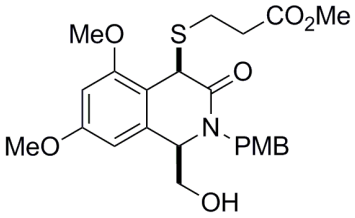
H, s, ArCHS), 4.86 (2 H, d, *J* = 12.0 Hz, OCHHCCl$_3$), 4.73 (1 H, d, *J* = 12.0 Hz, OCHHCCl$_3$), 4.67 (1 H, m, CHNHTroc), 4.42 (1 H, d, *J* = 14.8 Hz, CHH of PMB), 4.38 (1 H, t, *J* = 6.6 Hz, ArCHN), 4.12 (1 H, dd, *J* = 9.8, 7.6 Hz, CHHO), 3.87 (3 H, s, OCH$_3$), 3.83 - 3.86 (1 H, m, CHHO), 3.77 (3 H, s, OCH$_3$), 3.75 (3 H, s, OCH$_3$), 3.56 (1 H, dd, *J* = 14.5, 6.0Hz, SCHH), 3.31 (1 H, dd, *J* = 14.5, 4.1 Hz, SCHH), 1.50 (9 H, s, C(CH$_3$)$_3$), 1.00 - 1.08 (21 H, m, Si(CH(CH$_3$)$_2$)$_3$).

^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 169.4 (C=O), 169.1 (C=O), 160.0 (Ar C-O), 158.8 (Ar C-O), 157.3 (Ar C-O), 154.7 (carbamate C=O), 135.7 (Ar C-C), 129.2 (Ar CH of PMB), 129.1 (Ar C-C), 113.9 (Ar CH of PMB), 113.8 (Ar C-C), 102.9 (Ar C-H), 98.0 (Ar C-H), 95.7 (CCl$_3$), 82.3 (OC(CH)$_3$), 74.5 (OCH$_2$CCl$_3$), 69.1 (CH$_2$OSi), 62.4 (ArCHN), 55.9 (CHNHTroc), 55.7 (OCH$_3$), 55.3 (OCH$_3$), 55.2 (OCH$_3$), 49.2 (CH$_2$ of PMB), 40.9 (CHS), 36.3 (CH$_2$S), 28.0 (C(CH$_3$)$_3$), 17.9 (CH(CH$_3$)$_2$), 11.7 (SiCH).

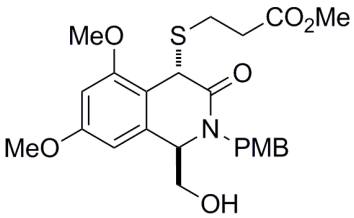
IR (thin film) ν_{max} (cm^{-1}) 3215, 2942, 2865, 1737, 1637, 1611.

$[\alpha]_D^{30}$ = +8.8° (c = 1.06, EtOH).

Methyl 3-(((1*R*,4*R*)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate S15a and methyl 3-(((1*R*,4S)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate S15b



S15a



S15b

Silyl ether **9** (1.3:1 dr, 183 mg, 0.3 mmol) was dissolved in CH$_2$Cl$_2$ (1.5 ml) and TBAF (1 M solution in THF, 0.6 mmol, 0.6 ml) was added. The solution was stirred for 6.5 h then quenched with saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$ (2 ×20 ml). The extracts were combined, dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (60% EtOAc–pet. ether) gave **S15a** and **S15b** (108 mg, 78%, 1:2 dr) as a pale gum.

For **S15a** ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.17 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB), 6.81 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB), 6.39 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.21 (1 H, d, *J* = 2.3 Hz, Ar CH), 5.35 (1 H, d, *J* = 14.9 Hz, CHH of PMB), 4.74 (1 H, s, ArCHS), 4.40 (1 H, t, *J* = 6.2 Hz, ArCHN), 4.31 (1 H, d, *J* = 14.9 Hz, CHH of PMB), 4.08 (1 H, dd, *J* = 11.3, 6.3 Hz,

CHHOH), 3.93 (1 H, dd, *J* = 11.3, 6.1 Hz, CHHOH), 3.87 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.71 (3 H, s, OCH_3), 3.34 (1 H, dt, *J* = 13.9, 7.1 Hz, SCHH), 3.13 (1 H, dt, *J* = 13.9, 7.1 Hz, SCHH), 2.86 (2 H, t, *J* = 7.1 Hz, $CH_2CO_2CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.7 (C=O), 169.2 (C=O), 160.4 (Ar C-O), 158.9 (Ar C-O), 157.6 (Ar C-O), 135.7 (Ar C-C), 129.2 (Ar CH of PMB), 129.0 (Ar C-C), 114.1 (Ar CH of PMB), 113.4 (Ar C-C), 102.4 (Ar CH), 98.1 (Ar CH), 66.3 (CH_2OH), 62.4 (CHN), 55.8 (OCH_3), 55.5 (OCH_3), 55.3 (OCH_3), 51.8 (OCH_3), 48.8 (CH_2 of PMB), 39.9 (CHS), 34.4 ($CH_2CO_2CH_3$), 28.9 (CH_2S).

MS (ES+) *m/z* 476 $[M+H]^+$, 498 $[M+Na]^+$.

HRMS 476.1728 $C_{24}H_{30}NO_7S^+$ requires 476.1737.

IR (thin film) ν_{max} (cm^{-1}) 3400 (br., OH), 2951, 1737 (ester C=O), 1612 (amide C=O).

$[\alpha]_D^{32}$ = –222.7° (c = 0.90, EtOH).

For **S15b** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31 (2 H, d, *J* = 8.7 Hz, Ar CH of PMB), 6.89 (2 H, d, *J* = 8.7 Hz, Ar CH of PMB), 6.41 (1 H, d, *J* = 2.4 Hz, Ar CH), 6.30 (1 H, d, *J* = 2.4 Hz, Ar CH), 5.55 (1 H, d, *J* = 15.4 Hz, CHH of PMB), 4.71 (1 H, s, ArCHS), 4.58 (1 H, s, ArCHN), 4.25 (1 H, d, *J* = 15.4 Hz, CHH of PMB), 4.18 (1 H, m, *J* = 4.5 Hz, CHHOH), 3.92 (1 H, dd, *J* = 12.7, 3.4 Hz, CHHOH), 3.88 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 3.70 (3 H, s, OCH_3), 3.28 (1 H, dt, *J* = 13.8, 6.8 Hz, SCHH), 2.97 (1 H, dt, *J* = 13.8, 7.5 Hz, SCHH), 2.78 (2 H, m, CH_2CO_2Me), 1.79 (1 H, t, OH).

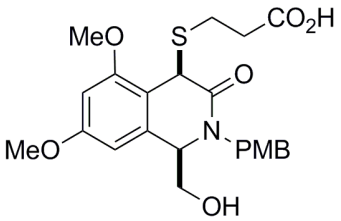
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.5 (C=O), 170.5 (C=O), 160.6 (Ar C-O), 158.9 (Ar C-O), 157.6 (Ar C-O), 133.6 (Ar C-C), 129.1 (Ar CH of PMB), 128.7 (Ar C-C), 114.4 (Ar CH of PMB), 114.3 (Ar C-C), 101.0 (Ar C-H), 98.0 (Ar C-H), 59.2 (ArCHN), 55.8 (OCH_3), 55.3 (OCH_3), 51.7 (OCH_3), 45.9 (CH_2 of PMB), 40.5 (CHS), 34.3 ($CH_2CO_2CH_3$), 28.0 (CH_2S).

MS (ES+) *m/z* 498 $[M+Na]^+$.

HRMS 498.1560; $C_{24}H_{29}O_7NNaS^+$ requires 498.1557.

$[\alpha]_D^{30}$ = +30.6° (c = 0.57, EtOH).

3-(((1*R*,4*R*)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoic acid 11



S15 (108 mg, 0.23 mmol, 1:2 dr) was dissolved in THF (1.4 ml) and water (0.4 ml) and $LiOH{\cdot}H_2O$ (19 mg, 0.46 mmol) was added. The solution was stirred at room temperature for18h then acidified with 1 M HCl (5 ml) and extracted with EtOAc (2 × 10 ml).The extracts were washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (10% MeOH−CH_2Cl_2) gave **11** (87 mg, 82%) as a pale solid, melting point (CH_2Cl_2) 70-73 °C.

Recrystallisation from EtOH gave crystals for single crystal X-ray diffraction analysis (see page 89 for structure).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.14 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.79 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB), 6.37 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.20 (1 H, d, *J* = 2.3 Hz, Ar CH), 5.39 (1 H, d, *J* = 15.0 Hz, C<u>H</u>H of PMB), 4.75 (1 H, s, ArCHS), 4.41 (1 H, apparent t, *J* = 6.2 Hz, ArCHN), 4.29 (1 H, d, *J* = 15.0 Hz, CH<u>H</u> of PMB), 4.10 (1 H, dd, *J* = 6.7, 11.5 Hz, C<u>H</u>HOH), 3.90 (1 H, dd, *J* = 5.7, 11.5 Hz, CH<u>H</u>OH), 3.84 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.31 (1 H, dt, *J* = 6.8, 13.9 Hz, SC<u>H</u>H), 3.11 (1 H, dt, *J* = 7.1, 13.9 Hz, SCH<u>H</u>), 2.78 - 2.98 (2 H, m, C<u>H</u>$_2$$CO_2H$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 175.8 (CO_2H), 170.0 (C=O), 160.3 (Ar C-O), 158.9 (Ar C-O), 157.4 (Ar C-O), 135.4 (Ar <u>C</u>-C), 129.2 (PMB CH), 128.6 (Ar <u>C</u>-C), 114.0 (PMB CH), 113.3 (Ar <u>C</u>-C), 102.3 (Ar CH), 98.0 (Ar CH), 66.5 (CH_2OH), 62.3 (ArCHN), 55.71 (OCH_3), 55.41 (OCH_3), 55.21 (OCH_3), 49.1 (CH_2 of PMB), 40.0 (ArCHS), 34.4 (<u>C</u>H_2CO_2H), 28.7 (CH_2S).

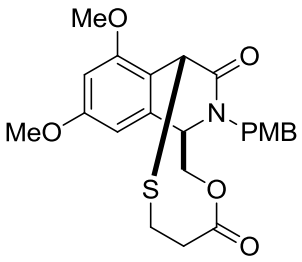
MS (ES+) *m/z* 484 $[M+Na]^+$.

HRMS 484.1393, $C_{23}H_{27}O_7NSNa^+$ requires 484.1400.

IR (thin film) ν_{max} (cm^{-1}) 3400 (br.), 2938 (CH stretch), 1705 (acid C=O), 1634 (amide C=O).

$[\alpha]_D^{30}$ = +14.2° (c = 0.90, EtOH).

(1*R*,8*R*)-10,12-Dimethoxy-13-(4-methoxybenzyl)-3,4,7,8-tetrahydro-8,1-(epiminomethano)benzo[*g*][1,5]oxathiecine-5,14(1*H*)-dione 13



A solution of hydroxyacid **11** (46 mg, 0.10 mmol) in CH_2Cl_2 (22 ml) was added *via* pressure-equalising dropping funnel over 2.5 h to a solution of MNBA (41.3 mg, 0.12 mmol) and DMAP (29 mg, 0.24 mmol) in CH_2Cl_2 (36 ml) at room temperature. The solution was stirred for a further 3.5h then concentrated *in vacuo* and the residue taken up in CH_2Cl_2 (10 ml), washed with saturated $NaHCO_3$ solution (10 ml) then brine (10 ml) and dried ($MgSO_4$). Flash chromatography (15% EtOAc–CH_2Cl_2) gave **13** (29 mg, 65%) as a pale solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.84 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB), 6.42 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.20 (1 H, d, *J* = 2.3 Hz, Ar CH), 5.60 (1 H, d, *J* = 15.2 Hz, C<u>H</u>H of PMB), 5.00 (1 H, s, ArCHS), 4.89 (1 H, dd, *J* = 11.4, 1.8 Hz, C<u>H</u>HO), 4.43 (1 H, br. s, ArCHN), 4.28 (1 H, dd, *J* = 11.4, 1.6 Hz, CH<u>H</u>O), 3.98 (1 H, d, *J* = 15.2 Hz, CH<u>H</u> of PMB), 3.87 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 2.91 (1 H, m, C<u>H</u>HS), 2.42 - 2.63 (3 H, m, CH<u>H</u>S and C<u>H</u>$_2$$CO_2$R).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.7 (C=O), 168.6 (C=O), 160.9 (Ar C-O), 159.4 (Ar C-O), 158.2 (Ar C-O), 134.6 (Ar <u>C</u>-C), 129.8 (Ar CH of PMB), 128.4 (Ar <u>C</u>-C), 114.5 (Ar CH of PMB), 102.0 (Ar CH), 98.2 (Ar CH), 63.4 (CH_2O), 59.9 (ArCHN), 56.1 (OCH_3), 55.7 (OCH_3), 55.6 (OCH_3), 47.2 (CH_2 of PMB), 41.3 (ArCHS), 38.8 (<u>C</u>H_2CO_2R), 26.5 (CH_2S).

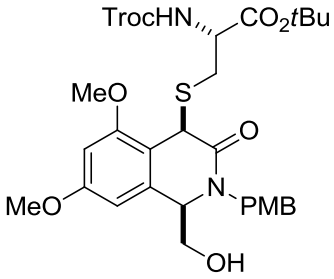
MS (ES+) *m/z* 466 $[M+Na]^+$.

HRMS 466.1292; $C_{23}H_{25}O_6NNaS^+$ requires 466.1295.

IR (thin film) ν_{max} (cm^{-1}) 2394, 1742 (ester C=O), 1640 (amide C=O).

$[\alpha]_D^{34}$ = +54.3° (c = 1.44, $CHCl_3$).

(*R*)-*tert*-Butyl 3-(((1*R*,4*R*)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate S16



Silyl ether **10** (190 mg, 0.23 mmol, 1:1 dr) was dissolved in MeCN (2.3 ml) at 0 °C and 60% aqueous HF (0.23 ml) was added. The solution was stirred for 30 minutes then allowed to warm to room temperature and stirred for a further 90 minutes. The solution was neutralized by dropwise addition of saturated $NaHCO_3$ solution then extracted with EtOAc (3 × 15 ml). The extracts were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (40% EtOAc−pet. ether) gave **S16** (99 mg, 64%, single diastereoisomer) as a pale gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 (1 H, d, *J* = 8.6 Hz, NH), 7.16 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB), 6.81 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.40 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.19 (1 H, d, *J* = 2.3 Hz, Ar CH), 5.46 (1 H, d, *J* = 14.9 Hz, C<u>H</u>H of PMB), 4.88 (1 H, s, ArCHS), 4.79 (1 H, d, *J* = 12.1 Hz, OC<u>H</u>HCCl$_3$), 4.77 (1 H, d, *J* = 12.1 Hz, OCH<u>H</u>CCl$_3$), 4.70 (1 H, ddd, *J* = 8.4, 6.2, 4.3 Hz, C<u>H</u>NHTroc), 4.41 (1 H, m, CHN), 4.38 (1 H, d, *J* = 14.9 Hz, CH<u>H</u> of PMB), 4.09 (1 H, m, C<u>H</u>HOH), 3.87 (3 H, s, OCH$_3$), 3.83 (1 H, m, CH<u>H</u>OH), 3.76 (3 H, s, OCH$_3$), 3.76 (3 H, s, OCH$_3$), 3.43 (2 H, m,CH$_2$S), 2.75 (1 H, m, OH), 1.49 (9 H, s, C(C<u>H</u>$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 169.4 (C=O), 169.1 (C=O), 160.18 (Ar C-O), 158.6 (Ar C-O), 157.3 (Ar C-O), 154.6 (carbamate C=O), 135.2 (Ar <u>C</u>-C), 128.9 (Ar C-H of PMB), 128.5 (Ar <u>C</u>-C), 113.7 (Ar C-H of PMB), 112.9 (Ar <u>C</u>-C), 101.9 (Ar C-H), 97.7 (Ar C-H), 95.2 (CCl_3), 82.3 (O<u>C</u>(CH$_3$)$_3$), 74.3 (O<u>C</u>H$_2$CCl$_3$), 66.3 (CH_2OH), 61.8 (ArCHN), 55.5 (OCH$_3$), 55.3 (OCH$_3$), 55.1 (OCH$_3$), 54.9 (<u>C</u>HNHTroc), 48.8 (CH_2 of PMB), 40.9 (ArCHS), 36.1 (CH_2S), 27.7 (C(<u>C</u>H$_3$)$_3$).

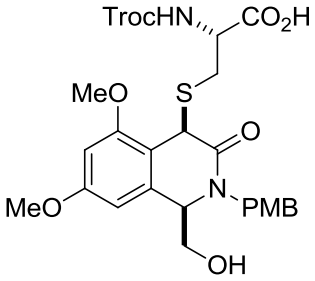
MS (ES+) *m/z* 707 $[M+H]^+$, 729 $[M+Na]^+$.

HRMS 707.1356; $C_{30}H_{38}N_2O_9SCl_3^+$ requires 707.1359.

IR (thin film) ν_{max} (cm^{-1}) 3400-3300 (br., OH), 2935 (CH stretch), 1737 (ester C=O), 1732 (amide C=O), 1612 (carbamate C=O).

$[\alpha]_D^{30}$ = –13.6° (c = 0.76, EtOH).

(*R*)-3-(((1*R*, 4*R*)-1-(Hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1, 2, 3, 4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoic acid 12



Ester **S16** (35 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (1.3 ml) and TFA (0.44 mmol) was added. The solution was stirred at room temperature for 2 h then evaporated and the residue dried *in vacuo* to give crude **12** as a yellow gum which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.33 (1 H, d, *J* = 8.8 Hz, NH), 7.15 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.80 (2 H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.36 (1 H, d, *J* = 1.9 Hz, Ar CH), 6.17 (1 H, d, *J* = 1.9 Hz, Ar CH), 5.54 (1 H, d, *J* = 14.8 Hz, C<u>H</u>H of PMB), 4.93 (1 H, s, ArCHS), 4.85 (1 H, d, *J* = 12.0 Hz, OC<u>H</u>HCCl$_3$), 4.75 - 4.81 (1 H, m, C<u>H</u>NHTroc), 4.68 (1 H, d, *J* = 12.0 Hz, OCH<u>H</u>CCl$_3$), 4.46 (1 H, dd, *J* = 7.6, 4.5 Hz, ArCHN), 4.33 (1 H, d, *J* = 14.8 Hz, CH<u>H</u> of PMB), 4.11 (1 H, dd, *J* = 11.9, 7.6 Hz, C<u>H</u>HO), 3.86 (1 H, dd, *J* = 11.9, 4.5 Hz, CH<u>H</u>O), 3.83 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.55 (1 H, dd, *J* = 15.1, 2.8 Hz, C<u>H</u>HS), 3.34 (1 H, dd, *J* = 15.1, 6.9 Hz, CH<u>H</u>S)

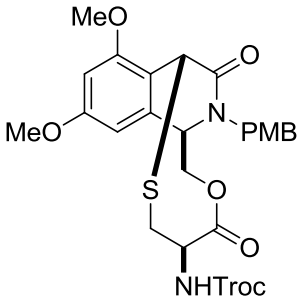
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 172.2 (C=O), 171.1 (C=O), 160.6 (Ar C-O), 159.1 (Ar C-O), 157.6 (Ar C-O), 155.2 (carbamate C=O), 135.0 (Ar <u>C</u>-C), 129.4 (Ar CH of PMB), 128.0 (Ar <u>C</u>-C), 113.9 (Ar CH of PMB), 113.1 (Ar <u>C</u>-C), 102.1 (Ar CH), 98.1 (Ar CH), 95.4 (CCl_3), 74.7 (O<u>C</u>H$_2$CCl$_3$), 66.8 (CH_2O), 62.2 (ArCHN), 55.8 (OCH_3), 55.4 (OCH_3), 55.3 (<u>C</u>HNHTroc), 55.2 (OCH_3), 49.7 (CH_2 of PMB), 41.9 (ArCHS), 37.3 (CH_2S).

MS (ES+) *m/z* 673 $[M+Na]^+$.

HRMS 673.0549; $C_{26}H_{29}N_2O_9SCl_3Na^+$ requires 673.0552.

IR (thin film) ν_{max} (cm^{-1}) 3400-3300 (br., OH), 2932, 1731, 1612.

2,2,2-Trichloroethyl ((1*R*,4*R*,8*R*)-10,12-dimethoxy-13-(4-methoxybenzyl)-5,14-dioxo-1,3,4,5,7,8-hexahydro-8,1-(epiminomethano)benzo[*g*][1,5]oxathiecin-4-yl)carbamate 14



Hydroxyacid **12** (0.05 mmol) was dissolved in CH_2Cl_2 (11 ml) and added *via* syringe pump over 5.5 h to a solution of MNBA (21 mg, 0.06 mmol) and DMAP (14.6 mg, 0.12 mmol) in CH_2Cl_2 (17 ml). After the addition was complete the reaction was stirred for a further 19 h then concentrated and the residue taken up in CH_2Cl_2 (10 ml) and washed with saturated $NaHCO_3$ solution (10 ml) then brine (10 ml) and dried ($MgSO_4$) before concentration *in vacuo*. Flash chromatography (10% EtOAc–CH_2Cl_2) gave **14** (18 mg, 57% for 2 steps) as a pale foam.

^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) δ ppm 7.24 (1 H, d, *J* = 8.0 Hz, NH), 7.19 (2 H, d, *J* = 8.5 Hz, Ar CH of PMB), 6.87 (2 H, d, *J* = 8.8 Hz, Ar CH of PMB), 6.58 (1 H, d, *J* = 2.3 Hz, Ar CH), 6.56 (1 H, d, *J* = 2.3 Hz, Ar CH), 5.23 (1 H, dd, *J* = 11.8, 2.0 Hz, CHHO), 5.21 (1 H, d, *J* = 15.1 Hz, CHH of PMB), 4.81 (1 H, s, ArCHS), 4.77 (2 H, s, OCH_2CCl_3), 4.67 (1 H, br. s, ArCHN), 4.22 (1 H, td, *J* = 7.2, 3.0 Hz, CHNHTroc), 4.16 (1 H, dd, *J* = 11.8, 1.8 Hz, CHHO), 4.03 (1 H, d, *J* = 15.1 Hz, CHH of PMB), 3.86 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 3.04 (1 H, dd, *J* = 15.8, 7.0 Hz, CHHS), 2.68 (1 H, dd, *J* = 15.8, 2.9 Hz, CHHS).

^{13}C NMR (101 MHz, DMSO-d_6, 120 °C) δ ppm 168.3 (C=O), 165.9 (C=O), 160.0 (Ar C-O), 158.3 (Ar C-O), 157.2 (Ar C-O), 152.9 (carbamate C=O), 134.2 (Ar C-C), 128.5 (Ar C-H of PMB), 128.3 (Ar C-C), 113.7 (Ar CH of PMB), 113.2 (Ar C-C), 102.4 (Ar C-H), 98.0 (Ar C-H), 95.4 (CCl_3), 73.6 (OCH_2CCl_3), 64.3 (CH_2O), 59.0 (ArCHN), 55.5 (OCH_3), 55.4 (CHNHTroc), 54.9 (OCH_3), 54.6 (OCH_3), 46.0 (CH_2 of PMB), 30.6 (CH_2S).

MS (ES+) *m/z* 655 $[M+Na]^+$.

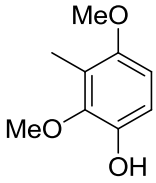
HRMS 633.0598; $C_{26}H_{28}N_2O_8SCl_3^+$ requires 633.0627.

IR (thin film) ν_{max} (cm^{-1}) 3410, 1737, 1643, 1611.

$[\alpha]_D^{34}$ = +76.8° (c = 1.25, EtOH).

Synthesis of the protected ABH ring system

2,4-Dimethoxy-3-methylphenol 16[3]



AcCl (2.15 ml, 30.0 mmol) was added to a 1 M solution of $TiCl_4$ in CH_2Cl_2 (30 ml, 30 mmol) at - 10 °C. The temperature was maintained below 0 °C and a solution of 1,3-dimethoxy-2-methylbenzene **15** (2.28 g, 15.0 mmol) in CH_2Cl_2 (7.0 ml) was added over 10 minutes with vigorous stirring. The reaction was stirred at 0 °C for 30 minutes then poured into cooled 1 M HCl (70 ml) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 ml). The organic extracts were combined and washed with 1 M HCl (2 × 100 ml), saturated $NaHCO_3$solution (100 ml) then brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 ml) then $KHCO_3$ (2.59 g, 30.8 mmol) was added and the mixture cooled to 0 °C. A solution of MCPBA 70% (7.59 g, 30.8 mmol) in CH_2Cl_2 (50 ml) was added over 30 min then the reaction was stirred at room temperature for 17 h. An aqueous solution of 10% Na_2CO_3 (80 ml) and saturated Na_2SO_3 (20 ml) were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were combined and washed with 10% aqueous Na_2CO_3 (2 × 150 ml), then water (200 ml) and brine (200 ml) then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in MeOH (155 ml) and a solution of K_2CO_3 (21.5 g, 154 mmol) in water (77.5 ml) was added. The reaction was stirred at room temperature for 16 h then the solvent was evaporated. The residue was dissolved in water (100 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The extracts were combined and dried ($MgSO_4$) then concentrated *in vacuo* to give **16** (1.95 g, 77%) as yellow oil.

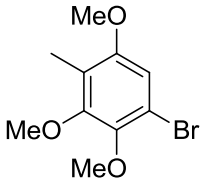
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.76 (1H, d, *J* = 8.9 Hz, Ar CH), 6.55 (1H, d, *J* = 8.9 Hz, Ar CH), 5.26 (1H, br. s, OH), 3.79 (6H, s, OCH_3), 2.18 (3H, s, $ArCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.9 (Ar C-O), 145.9 (Ar C-O), 142.9 (Ar C-O), 119.9 (Ar C-C), 111.6 (Ar CH), 106.7 (Ar CH), 60.9 (OCH_3), 56.1 (OCH_3), 9.3 ($ArCH_3$).

NMR data was consistent with literature values.[3]

[3]Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Synthesis*,2002, 557.

1-Bromo-2,3,5-trimethoxy-4-methylbenzene S17[4]



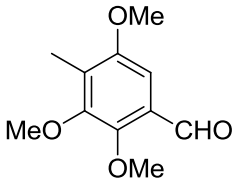
Phenol **16** (1.77 g, 10.5 mmol) was dissolved in anhydrous CH_2Cl_2 (20 ml) and K_2CO_3 (2.32 g, 16.8 mmol) was added. The mixture was cooled to –78 °C and a solution of Br_2 (0.60 ml, 11.6 mmol) in anhydrous CH_2Cl_2 (5 ml) was added over 2 h. The reaction mixture was added to a 10% aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 100 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 70 ml). The organic phases were combined and washed with 10% aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (2 × 150 ml) then brine (100 ml) and dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in anhydrous DMF (29 ml) and K_2CO_3 (2.90 g, 21.0 mmol) and Me_2SO_4 (2.05 ml, 21.6 mmol) was added. The reaction was stirred at room temperature for 17 h. Further Me_2SO_4 (1.03 ml, 10.8 mmol) was added and the reaction was stirred at room temperature for a further 16 h. The reaction mixture was diluted with water (200 ml) and extracted with EtOAc (3 × 100 ml). The extracts were combined and washed with brine (200 ml) then dried ($MgSO_4$). Flash chromatography (10% Et_2O–pet. ether) gave **17** (1.66 g, 61%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.77 (1H, s, Ar CH), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.08 (3H, s, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 152.6 (Ar C-O), 154.6 (Ar C-O), 144.6 (Ar C-O), 120.6 (Ar C-C), 113.6 (Ar C-C), 109.7 (Ar CH), 60.8 (OCH_3), 60.6 (OCH_3), 55.9 (OCH_3), 8.9 ($ArCH_3$).

NMR data was consistent with literature values.[4]

2,3,5-Trimethoxy-4-methylbenzaldehyde S18[5]



[4] (a) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.*, 2002, **4**, 43. (b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.*2007, **130**, 269.

[5] (a) White, J. D.; Smits, H. *Org. Lett.*2005, **7**, 235. (b) Kitahara, Y.; Nakahara, S.; Numata, R.; Kubo, A. *Chem. Pharm. Bull.*1985, **33**, 2122.

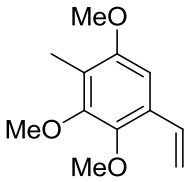
Bromide **S17** (2.08 g, 7.97 mmol) was dissolved in anhydrous THF (130 ml) and the solution was cooled to –78 °C. *n*-BuLi (2.2 M in hexanes, 9.0 ml, 19.9 mmol) was added slowly. The reaction was stirred at -78 °C for 15 minutes then DMF (6.48 ml, 83.7 mmol) was added. The reaction was allowed to warm to –10 °C then saturated NH_4Cl solution (5 ml) was added. The reaction was stirred at room temperature for 20 minutes. H_2O (50 ml) was added and the phases separated. The aqueous phase was extracted with EtOAc (3 × 50 ml) then the extracts were combined, washed with brine (200 ml) then dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (10% Et_2O–*n*-hexane) gave **S18** (1.00 g, 60%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.33 (1H, s, CHO), 7.02 (1H, s, Ar CH), 3.94 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.19 (3H, s, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 189.4 (C=O), 154.5 (Ar C-O), 152.0 (Ar C-O), 151.3 (Ar C-O), 129.7 (Ar C-C), 127.0 (Ar C-C), 102.2 (Ar CH), 62.5 (OCH_3), 60.4 (OCH_3), 55.8 (OCH_3), 9.7 (CH_3).

NMR data was consistent with literature values.[5]

1,3,4-Trimethoxy-2-methyl-5-vinylbenzene 17



Methyltriphenylphosphonium bromide (4.29 g, 12.0 mmol) was suspended in anhydrous THF (40 ml) under $N_2$and KO*t*-Bu (1.57 g, 14.0 mmol) added and the mixture was stirred at room temperature for 30 minutes then cooled to –78 °C. A solution of aldehyde **S18** (2.10 g, 10.0 mmol) in THF (12 ml) was added dropwise then the reaction mixture was allowed to warm to room temperature. The reaction was quenched with MeOH (20 ml) and the solvent evaporated. The crude material was filtered through a short silica column (5% EtOAc–pet. ether) to give **17** (2.00 g, 9.62 mmol, 96%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02 (1H, dd, *J* = 17.9, 11.1 Hz, $ArCH=CH_2$), 6.74 (1H, s, Ar CH), 5.72 (1H, dd, *J* = 17.9, 1.3 Hz, CHH), 5.28 (1H, dd, *J* = 11.1, 1.3 Hz, CHH), 3.84 (6H, s, 2 × OCH_3), 3.80 (3H, s, OCH_3), 2.14 (3H, s, $ArCH_3$).

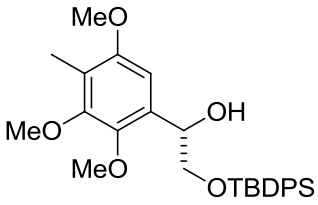
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.2 (Ar C-O), 152.1 (Ar C-O), 144.9 (Ar C-O), 131.2 (Ar CH), 128.5 (Ar C-C), 120.9 (Ar C-C), 113.9 (CH_2), 101.9 ($ArCH=CH_2$), 61.1 (OCH_3), 60.5 (OCH_3), 55.7 (OCH_3), 9.0 (CH_3).

MS (ES+) *m/z* 208 $[M]^+$, 209 $[M+H]^+$, 231 $[M+Na]^+$.

HRMS 209.1167; $C_{12}H_{17}O_3^+$ requires 209.1173.

IR (thin film) ν_{max} (cm^{-1}) 2933, 1601, 1572, 1480, 1463.

(*S*)-2-((*tert*-Butyldiphenylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanol S19



AD–mix–α (4.44 g) was dissolved in water (15 ml) and *t*-BuOH (10 ml) and the solution cooled to 0 °C. Styrene **S18** (0.67 g, 3.22 mmol) in *t*-BuOH (5 ml) was added and the solution stirred for 17 h. Saturated Na_2SO_3 solution (9 ml) was added and the reaction mixture was stirred for 30 minutes. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 ml). The organic layers were combined and washed with brine (50 ml) then dried ($MgSO_4$). The crude product was dissolved in CH_2Cl_2 (23 ml) and imidazole (0.44 g, 6.44 mmol) and TBDPSCl (0.84 ml, 3.22 mmol) were added and the reaction was stirred at room temperature for 2 h. Water (20 ml) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 ml) then the organic phases were combined and dried ($MgSO_4$). Flash chromatography (2.5% EtOAc–pet. ether) gave **S19** (1.46 g, 3.03 mmol, 94% over 2 steps) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62-7.69 (4H, m, Ar CH of TBDPS), 7.35-7.46 (6H, m, Ar CH of TBDPS), 6.73 (1H, s, Ar CH), 5.10-5.14 (1H, m, ArC<u>H</u>OH), 3.89 (1H, dd, *J* = 10.1, 3.8 Hz, C<u>H</u>HO), 3.78 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.66 (1H, dd, *J* = 10.1, 2.0 Hz, CH<u>H</u>O), 3.64 (3H, s, OCH_3), 3.18 (1H, d, *J* = 3.3 Hz, OH), 2.11 (3H, s, $ArCH_3$), 1.10 (9H, s, $C(C\underline{H}_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.1 (Ar C-O), 151.4 (Ar C-O), 144.1 (Ar C-O), 135.6 (Ar CH of TBDPS), 133.2 (Ar C-Si), 130.5 (Ar <u>C</u>-C), 129.7 (Ar CH of TBDPS), 127.7 (Ar CH of TBDPS), 120.0 (Ar <u>C</u>-C), 103.7 (Ar CH), 69.8 (ArCHOH), 68.6 (CH_2O), 60.6 (OCH_3), 60.1 (OCH_3), 55.7 (OCH_3), 26.9 ($C(\underline{C}H_3)_3$), 19.3 ($Si\underline{C}(CH_3)_3$), 8.8 ($ArCH_3$).

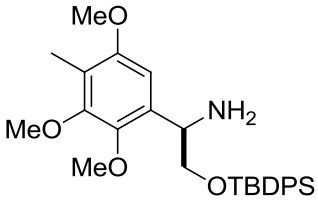
MS (ES+) *m/z* 503 $[M+Na]^+$.

HRMS 503.2223; $C_{28}H_{36}O_5SiNa^+$ requires 503.2225.

IR (thin film) ν_{max} (cm^{-1}) 2930, 2856, 1483, 1462.

$[\alpha]_D^{24}$= –2.5° (c = 1.4, $CHCl_3$).

(*R*)-2-((*tert*-Butyldiphenylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanamine 18



Alcohol **S19** (0.57 g, 1.19 mmol) and PPh_3 (0.78 g, 2.98 mmol) were dissolved in anhydrous THF (8 ml) and cooled to 0 °C. DIAD (0.59 ml, 2.98 mmol) was added dropwise, followed by DPPA (0.64 ml, 2.98 mmol) and the reaction mixture was stirred at 0 °C for 6 h then concentrated *in vacuo*. Flash chromatography (1% EtOAc–pet. ether) gave the azide intermediate which was dissolved in THF (8 ml) then PPh_3 (0.94 g, 3.57 mmol) and H_2O (0.21 ml, 11.9 mmol) were added. The reaction was heated at 60 °C for 3 h then concentrated *in vacuo*. Flash chromatography (30% EtOAc–pet. ether) gave **18** (0.30 g, 0.63 mmol, 53% over 2 steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.63 - 7.69 (4H, m, Ar CH of TBDPS), 7.34 - 7.43 (6H, m, Ar CH of TBDPS), 6.73 (1H, s, Ar CH), 4.49 (1H, dd, *J* = 7.9, 4.1 Hz, CHN), 3.83 (1H, dd, *J* = 9.8, 4.1 Hz, OC<u>H</u>H), 3.77 (6H, s, OCH_3), 3.62 - 3.66 (4H, m, OCH<u>H</u>, OCH_3), 2.11 (3H, s, $ArCH_3$), 1.08 (9H, s, $C(CH_3)_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 154.0 (Ar C-O), 151.2 (Ar C-O), 144.6 (Ar C-O), 135.6 (Ar CH of TBDPS), 133.5 (Ar C-Si), 132.8 (Ar C-C), 129.6 (Ar CH of TBDPS), 127.6 (Ar CH of TBDPS), 119.5 (Ar C-C), 104.1 (Ar CH), 69.2 (CH_2O), 60.8 (OCH_3), 60.1 (OCH_3), 55.8 (OCH_3), 51.5 (ArCHN), 26.9 ($C(\underline{C}H_3)_3$), 19.3 ($Si\underline{C}(CH_3)_3$), 8.8 ($ArCH_3$).

MS (ES+) *m/z* 480 $[M+H]^+$.

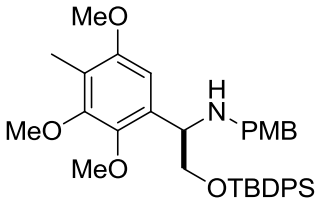
HRMS 480.2568; $C_{28}H_{38}NO_4Si^+$ requires 480.2565.

IR (thin film) ν_{max} (cm^{-1}) 2996, 2931, 1639, 1608, 1586, 1511, 1482.

$[\alpha]_D^{24}$= + 0.4° (c = 3.5, $CHCl_3$).

Enantiomeric excess was measured as 95% using chiral HPLC (ChiralPak AD column, 98:2 hexane–isopropanol).

(*R*)-2-((*tert*-Butyldiphenylsilyl)oxy)-*N*-(4-methoxybenzyl)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanamine S20



Amine **18** (0.24 g, 0.50 mmol) was dissolved in MeOH (10 ml) and 4-methoxybenzaldehyde (0.08 ml, 0.6 mmol) was added. The reaction was heated at reflux for 4 h then cooled to 0 °C. $NaBH_4$ (0.06 g, 1.50 mmol) was added quickly and the reaction was allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was concentrated *in vacuo* then taken up in water (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The organic extracts were combined and dried ($MgSO_4$). Flash chromatography (20% EtOAc–pet. ether with 1% NEt_3) gave **S20** (0.30 g, 0.50 mmol, 100%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.61-7.64 (4H, m, Ar CH of TBDPS), 7.33 - 7.44 (6H, m, Ar CH of TBDPS), 7.25 (2H, d, *J* = 8.5 Hz, Ar CH of PMB), 6.86 - 6.88 (3H, m, Ar CH), 4.31 (1H, dd, *J* = 8.8, 4.1 Hz, ArCHN), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.77-3.80 (1H, m, C<u>H</u>HO), 3.76 (3H, s, OCH_3), 3.71 (1H, d, *J* = 12.9 Hz, C<u>H</u>H of PMB), 3.62-3.66 (1H, m, OCH<u>H</u>), 3.57 (1H, d, *J* = 12.9 Hz, C<u>H</u>H of PMB), 3.53 (3H, s, OCH_3), 2.11 (3H, s, CH_3), 1.05 (9H, s, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.5 (Ar C-O), 154,2 (Ar C-O), 151.6 (Ar C-O), 145.5 (Ar C-O), 135.6 (Ar CH), 135.5 (Ar CH of TBDPS), 133.4 (Ar C-Si), 133.0 (Ar <u>C</u>-C), 130.7 (Ar <u>C</u>-C), 129.3 (Ar CH of TBDPS), 127.6 (Ar CH of TBDPS), 119.4 (Ar <u>C</u>-C), 113.8 (Ar CH of PMB), 104.3 (Ar CH), 68.0 (CH_2O), 60.6 (OCH_3), 60.1 (OCH_3), 57.3 (ArCHN), 55.8 (OCH_3), 55.3 (OCH_3), 51. 0 (CH_2 of PMB), 26.8 ($C(\underline{C}H_3)_3$), 19.2 ($Si\underline{C}(CH_3)_3$), 8.8 ($ArCH_3$).

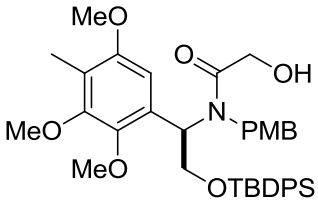
MS (ES+) *m/z* 600 $[M+H]^+$.

HRMS 600.3141; $C_{36}H_{46}NO_5Si^+$ requires 600.3140.

IR (thin film) ν_{max} (cm^{-1}) 2931, 2856, 1638, 1610, 1510, 1461.

$[\alpha]_D^{24}$= –5.5° (c = 1.2, $CHCl_3$).

(*R*)-*N*-(2-((*tert*-Butyldiphenylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethyl)-2-hydroxy-*N*-(4-methoxybenzyl)acetamide S21



Amine **S20** (300 mg, 0.50 mmol) was dissolved in CH_2Cl_2 (8 ml) and $AcOCH_2COCl$ (70µl, 0.60 mmol) was added and the reaction mixture was cooled to 0°C and NEt_3 (80µl, 0.60 mmol) was added. The reaction allowed to warm to room temperature and stirred for 5 h. The reaction mixture was concentrated *in vacuo* then the residue was dissolved in MeOH (10 ml) and a solution of K_2CO_3 (0.69 g, 5.00 mmol) in H_2O (5 ml) was added. The reaction was stirred at room temperature for 17 h then concentrated *in vacuo*. The residue was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The organic phases were combined and washed with brine (50 ml), dried ($MgSO_4$) and concentrated to give **S21** (300 mg, 92%) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 - 7.62 (4H, m, Ar CH of TBDPS), 7.33 - 7.48 (6H, m, Ar CH of TBDPS), 6.97 (2H, d, *J* = 8.6 Hz, Ar CH of PMB of one rotamer), 6.92 (2H, d, *J* = 8.6 Hz, Ar CH of PMB of one rotamer), 6.71 (2H, d, *J* = 8.6 Hz, Ar CH of PMB of one rotamer), 6.70 (1H, s, Ar CH of one rotamer), 6.66 (2H, d, *J* = 8.6 Hz, Ar CH of PMB of one rotamer), 6.22 (1H, s, Ar CH of one rotamer), 5.87 - 5.90 (1H, m, ArCHN of one rotamer), 5.02 (1H, dd, *J* = 8.7, 5.4 Hz, ArCHN of one rotamer), 3.83 - 4.59 (6H, m, CH_2OH, CH_2OSi and CH_2 of PMB), 3.64 - 3.75 (12H, m, OCH_3), 2.09 (3H, s, $ArCH_3$), 1.02 (9H, s, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.4 (C=O of one rotamer), 172.8 (C=O of one rotamer), 158.8 (Ar C-O of one rotamer), 158.4 (Ar C-O of one rotamer), 153.9 (Ar C-O), 151.8 (Ar C-O), 145.9 (Ar C-O of one rotamer), 145.8 (Ar C-O of one rotamer), 135.6 (Ar CH of TBDPS of one rotamer), 135.4 (Ar CH of TBDPS of one rotamer), 132.6 (Ar C-Si), 130.4 (Ar CH of TBDPS of one rotamer), 130.0 (Ar CH of TBDPS of one rotamer), 129.7 (Ar CH of PMB of one rotamer), 129.0 (Ar CH of PMB of one rotamer), 127.9 (Ar CH of TBDPS of one rotamer), 127.7 (Ar CH of one rotamer of TBDPS), 127.5 (Ar C-C of one rotamer), 125.8 (Ar C-C of one rotamer), 121.9 (Ar C-C of one rotamer), 121.1 (Ar C-C of one rotamer), 114.0 (Ar CH of PMB of one rotamer), 113.4 (Ar CH of PMB of one rotamer), 106.1 (Ar CH of one rotamer), 104.8 (Ar CH of one rotamer), 62.9 (CH_2OH), 60.7 (OCH_2), 61.2 (OCH_3), 60.0 (OCH_3 of one rotamer), 59.9 (OCH_3 of one rotamer), 56.0 (OCH_3), 55.8

(CHN of one rotamer), 55.3 (OCH_3 of one rotamer), 55.2 (OCH_3 of one rotamer), 54.8 (CHN of one rotamer), 47.3 (NCH_2 of one rotamer), 45.2 (NCH_2 of one rotamer), 26.7 ($C(\underline{C}H_3)_3$), 19.0 ($\underline{C}(CH_3)_3$), 8.8 ($ArCH_3$).

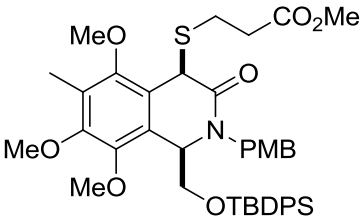
MS (ES+) *m/z* 658 $[M+H]^+$, 680 $[M+Na]^+$.

HRMS 658.3193; $C_{38}H_{48}NO_7Si^+$ requires 658.3195.

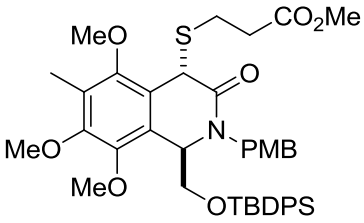
IR (thin film) ν_{max} (cm^{-1}) 3432, 3071, 2932, 2857, 1642, 1610, 1586, 1511, 1485.

$[\alpha]_D^{24}$= –7.8° (c = 3.5, $CHCl_3$).

Methyl 3-(((1*R*,4*R*)-1-(((*tert*-butyldiphenylsilyl)oxy) methyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate 19a and methyl 3-(((1*R*,4*S*)-1-(((*tert*-butyldiphenylsilyl)oxy) methyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate 19b



19a



19b

SO_3•py (220 mg, 1.38 mmol) was dissolved in DMSO (0.22 ml, 2.75 mmol) and CH_2Cl_2 (5 ml) at 0 °C. After 15 minutes, NEt_3 (0.77 ml, 5.50 mmol) and a solution of hydroxyamide **S21** (183 mg, 0.28 mmol) in CH_2Cl_2 (0.5 ml) were added. The reaction was allowed to warm to room temperature and stirred for 16 h then quenched with $NaHCO_3$ solution (15 ml) and extracted with CH_2Cl_2 (3 × 15 ml). The organic phases were combined and washed with 1 M HCl (40 ml) then $NaHCO_3$ solution (40 ml) and dried ($MgSO_4$). The crude product was dried under high vacuum at 35 °C for 4-5 h. The crude glyoxamide **3** (P = Me) was then dissolved in anhydrous CH_2Cl_2 (5 ml), methyl 3-mercaptopropanoate (0.017 ml, 0.14 mmol) was added and the reaction was stirred at room temperature for 17 h then concentrated *in vacuo*. The residue was dissolved in anhydrous $CHCl_3$ (3 ml), $Sc(OTf)_3$ (34 mg, 0.07 mmol) was added and the reaction was heated at reflux for 16 h, then $NaHCO_3$ solution (10 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 10 ml). The organic phases were combined and dried ($MgSO_4$). Flash chromatography (20-60% EtOAc–pet. ether) gave a 1:1 mixture of **19a** and **19b** (151 mg, 0.20 mmol, 71%) as a pale oil.

For **19a** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.20 - 7.73 (10H, m, Ar CH of TBDPS), 7.13 (2H, d, *J* = 7.7 Hz, Ar CH of PMB), 6.85 (2H, d, *J* = 7.7 Hz, Ar CH of PMB), 5.54 (1H, d, *J*

= 14.8 Hz, CHH of PMB), 4.69 (1H, br. s, ArCHN), 4.57 (1H, s, ArCHS), 3.94 (1H, dd, *J* = 10.4, 2.5 Hz, CHHO), 3.86 (1H, d, *J* = 14.8 Hz, CHH of PMB), 3.79 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.42 - 3.44 (1H, m, CHHO), 3.20 - 3.26 (1H, m, SCHH), 2.93 -2.99 (1H, m, SCHH), 2.59 - 2.69 (2H, m, CH_2CO_2Me), 2.27 (3H, s, $ArCH_3$), 0.94 (9H, s, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.5 (C=O), 170.8 (C=O), 158.9 (Ar C-O), 152.0 (Ar C-O), 151.0 (Ar C-O), 144.3 (Ar C-O), 135.6 (Ar C-C), 135.3 (Ar CH of TBDPS), 133.0 (Ar C-Si), 132.5 (Ar C-C), 129.9 (Ar C-C), 129.5 (Ar CH of TBDPS), 128.9 (Ar C-C), 127.8 (Ar CH of TBDPS), 127.4 (Ar CH of PMB), 125.5 (Ar C-C), 123.9 (Ar C-C), 123.1 (Ar C-C), 114.0 (Ar CH of PMB), 63.3 (CH_2O), 61.2 (OCH_3), 60.0 (2 × OCH_3), 57.3 (ArCHN), 55.2 (OCH_3), 51.6 (OCH_3), 46.6 (CH_2 of PMB), 42.3 (ArCHS), 34.2 (CH_2CO_2Me), 28.2 (CH_2S), 26.5 ($C(CH_3)_3$), 19.0 ($SiC(CH_3)_3$), 9.8 (CH_3).

MS (ES+) *m/z* 758 $[M+H]^+$, 780 $[M+Na]^+$.

HRMS 758.3177; $C_{42}H_{52}NO_8SiS^+$ requires 758.3178.

IR (thin film) ν_{max} (cm^{-1}) 2997, 1738, 1651, 1513, 1465, 1428.

$[\alpha]_D^{24}$= –15.9° (c = 0.64, $CHCl_3$).

For **19b** ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.69 - 7.73 (4H, m, Ar CH of TBDPS), 7.38 - 7.40 (6H, m, Ar CH of TBDPS), 7.16 (2H, d, *J* = 8.5 Hz, Ar CH of PMB), 6.80 (2H, d, *J* = 8.5 Hz, Ar CH of PMB), 5.68 (1H, d, *J* = 14.5 Hz, CHH of PMB), 4.91 (1H, dd, *J* = 9.6, 3.3 Hz, ArCHN), 4.74 (1H, s, ArCHS), 4.62 (1H, d, *J* = 14.5 Hz, CHH of PMB), 4.42 - 4.46 (1H, dd, *J* = 10.1, 9.6 Hz, CHHO), 3.81 (3H, s, OCH_3), 3.79 (1H, dd, *J* = 10.1, 3.3 Hz, CHHO), 3.76 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.38 - 3.41 (1H, m, SCHH), 3.06 - 3.12 (1H, m, SCHH), 2.85 - 2.88 (2H, m, CH_2CO_2Me), 2.14 (3H, s, $ArCH_3$), 1.13 (9H, s, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.4 (C=O), 168.8 (C=O), 158.8 (Ar C-O), 151.7 (Ar C-O), 151.1 (Ar C-O), 144.9 (Ar C-O), 135.6 (Ar CH of TBDPS), 133.2 (Ar C-Si), 132.9 (Ar C-C), 129.7 (Ar CH of TBDPS), 129.6 (Ar C-C), 129.5 (Ar CH of PMB), 127.7 (Ar CH of TBDPS), 125.9 (Ar C-C), 125.3 (Ar C-C), 122.0 (Ar C-C), 114.0 (Ar C-C), 113.9 (Ar CH of PMB), 69.1 (CH_2O), 61.5 (OCH_3), 60.0 (2 × OCH_3), 57.0 (ArCHN), 55.2 (OCH_3), 51.7 (OCH_3), 49.7 (CH_2 of PMB), 40.3 (ArCHS), 34.3 (CH_2CO_2Me), 28.5 (SCH_2), 26.9 ($C(CH_3)_3$), 19.2 ($SiC(CH_3)_3$), 9.7 (CH_3).

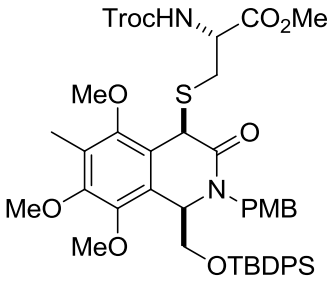
MS (ES+) *m/z* 758 $[M+H]^+$, 780 $[M+Na]^+$.

HRMS 758.3193; $C_{42}H_{52}NO_8SiS^+$ requires 758.3178.

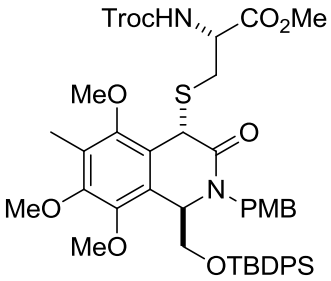
IR (thin film) ν_{max} (cm^{-1}) 2934, 1739, 1649, 1512, 1463.

$[\alpha]_D^{24}$= –2.6° (c = 0.66, $CHCl_3$).

(*R*)-Methyl 3-(((1*R*,4*R*)-1-(((*tert*-butyldiphenylsilyl)oxy) methyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 20a and (*R*)-methyl 3-(((1*R*,4*S*)-1-(((tert-butyldiphenylsilyl)oxy) methyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 20b



20a



20b

SO_3•py (289 mg, 1.82 mmol) was dissolved in DMSO (0.29 ml, 3.71 mmol) and CH_2Cl_2 (7 ml) at 0 °C. After 15 minutes, NEt_3 (1.02 ml, 7.33 mmol) and a solution of hydroxyamide **S21** (236 mg, 0.36 mmol) in CH_2Cl_2 (4 ml) were added and the reaction allowed to warm to room temperature and stirred for 16 h. $NaHCO_3$ solution (15 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 15 ml). The organic extracts were combined and washed with 1 M HCl (30 ml), $NaHCO_3$ solution (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude glyoxamide **3** (P = Me) was dried under high vacuum at 35 °C for 4-5 h then dissolved in CH_2Cl_2 (10 ml) and (*R*)-methyl 3-mercapto-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate (222 mg, 0.72 mmol) was added. The reaction was stirred at room temperature for 16 h then $Sc(OTf)_3$ (180 mg, 0.36 mmol) was added and the reaction was heated at reflux for 17 h. $NaHCO_3$ solution (10 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 10 ml). The organic phases were combined and dried ($MgSO_4$). Flash chromatography (20-60% EtOAc–pet. ether) gave a 1:1 mixture of **20a** and **20b** (284mg, 0.30 mmol, 84%) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.72 (20 H, m, 10 × Ar CH), 7.15 - 7.20 (4H, m, 2 × Ar CH), 6.80 - 6.86 (4H, m, 2 × Ar CH), 5.70 (1H, d, *J* = 14.6 Hz, C<u>H</u>H of PMB of one diastereoisomer), 5.30 - 5. 39 (2H, m, C<u>H</u>HO of one diastereoisomer, and C<u>H</u>H of PMB of

one diastereoisomer), 4.89 - 4.92 (2H, m, ArCHS of one diastereoisomer and ArCHN of one diastereoisomer), 4.75 - 4.84 (6H, m, CH_2CCl_3 and CHNH of both diastereoisomers), 4.59 - 4.63 (2H, m, CHH of PMB of one diastereoisomer and ArCHS of one diastereoisomer), 4.37 (1H, d, *J* = 14.6 Hz, CHH of PMB of one diastereoisomer), 4.29 (1H, dd, *J* = 10.3, 10.3 Hz, OCHH of one diastereoisomer), 3.70 - 3.84 (27H, m, 4 × OCH_3, CHHO of both diastereoisomers and ArCHN of one diastereoisomer), 3.52 - 3.62 (2H, m, SCHH), 3.43 (3H, s, OCH_3 of one diastereoisomer), 3.40 (3H, s, OCH_3 of one diastereoisomer), 3.19 - 3.25 (2H, m, SCHH), 2.24 (3H, s, $ArCH_3$ of one diastereoisomer), 2.14 (3H, s, $ArCH_3$ of one diastereoisomer), 1.12 (9H, s, $C(CH_3)_3$ of one diastereoisomer), 0.99 (9H, s, $C(CH_3)_3$ of one diastereoisomer).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.4 (C=O), 170.9 (C=O), 168.8 (C=O), 159.0 (Ar C-O of one diastereoisomer), 158.9 (Ar C-O of one diastereoisomer), 154.7 (Ar C-O of one diastereoisomer), 152.7 (Ar C-O of one diastereoisomer), 151.4 (Ar C-O of one diastereoisomer), 150.7 (Ar C-O of one diastereoisomer), 144.9 (Ar C-O of one diastereoisomer), 144.2 (Ar C-O of one diastereoisomer), 133.0 (Ar C-Si of one diastereoisomer), 132.8 (Ar C-Si of one diastereoisomer), 132.6 (Ar C of one diastereoisomer), 132.4 (Ar C of one diastereoisomer), 129.9 (2 × Ar CH of one diastereoisomer), 129.8 (2 × Ar CH of one diastereoisomer), 129.5 (2 × Ar CH of one diastereoisomer), 129.4 (2 × Ar CH of one diastereoisomer), 129.2 (Ar C of one diastereoisomer), 128.5 (Ar C of one diastereoisomer), 127.8 (Ar CH of TBDPS of one diastereoisomer), 127.7 (Ar CH of TBDPS of one diastereoisomer), 126.7 (Ar C of one diastereoisomer), 126.0 (Ar C of one diastereoisomer), 124.9 (Ar C of one diastereoisomer), 124.1 (Ar C-C of one diastereoisomer), 123.1 (Ar C-C of one diastereoisomer), 121.7 (Ar C-C of one diastereoisomer), 114.0 (Ar CH of PMB of one diastereoisomer), 113.9 (Ar CH of PMB of one diastereoisomer), 95.5 (CCl_3 of both diastereoisomers), 74.7 (CH_2CCl_3 of one diastereoisomer), 74.6 (CH_2CCl_3 of one diastereoisomer), 69.2 (CH_2OSi of one diastereoisomer), 65.8 (CHNHTroc of one diastereoisomer), 65.5 (CH_2OSi of one diastereoisomer), 61.4 (OCH_3), 60.8 (OCH_3), 60.0 (OCH_3), 56.8 (OCH_3), 56.0 (ArCHN of one diastereoisomer), 55.7 (ArCHN of one diastereoisomer), 55.2 (OCH_3), 52.7 (CHNHTroc), 49.1 (CH_2 of PMB of one diastereoisomer), 48.8 (CH_2 of PMB of one diastereoisomer), 40.8 (ArCHS of both diastereoisomers), 35.1 (CH_2S of both diastereoisomers), 26.9 ($C(CH_3)_3$ of one diastereoisomer), 26.8 ($C(CH_3)_3$ of one

diastereoisomer), 19.2 ($\underline{C}(CH_3)_3$ of one diastereoisomer), 19.0 ($\underline{C}(CH_3)_3$ of one diastereoisomer), 9.8 ($ArCH_3$ of one diastereoisomer), 9.4 ($ArCH_3$ of one diastereoisomer).

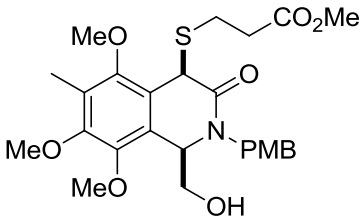
MS (ES+) *m/z* 947 $[M+]^+$.

HRMS 947.2366; $C_{45}H_{54}N_2O_{10}SSiCl_3^+$ requires 947.2329.

IR (thin film) ν_{max} (cm^{-1}) 2933, 1738, 1640, 1511, 1460, 1427, 1408.

$[\alpha]_D^{24}$= –1.6° (c = 0.3, $CHCl_3$).

Methyl 3-(((1*R*,4*R*)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate S22



Silyl ether **19** (1:1 dr, 40 mg, 52.8 μmol) was dissolved in MeCN (0.5 ml), pyridine (0.2 ml) was added and the mixture was cooled to 0 °C then 60% aqueous HF (0.05 ml) was added. The reaction was stirred at 0 °C for 2 hours then allowed to warm to room temperature over 15 hours. Aqueous 1 M HCl (10 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 10 ml). The organic phase was washed with aqueous 1 M HCl (20 ml) then dried ($MgSO_4$). Flash chromatography (45% EtOAc–petrol. ether) gave recovered starting material (10 mg, 25%) and **S22** (22 mg, 31 μmol, 71% based on recovered starting material).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 (2H, d, *J* = 8.7 Hz, Ar CH of PMB), 6.82 (2H, d, *J* = 8.7 Hz, Ar CH of PMB), 5.43 (1H, d, *J* = 14.9 Hz, C$\underline{H}$H of PMB), 4.79 (1H, s, ArCHS), 4.75 (1H, dd, *J* = 7.1, 5.0 Hz, ArCHN), 4.35 (1H, d, *J* = 14.9 Hz, CH$\underline{H}$ of PMB), 4.16 - 4.20 (1H, m, C$\underline{H}$HOH), 3.89 - 3.93 (1H, m, CH$\underline{H}$OH), 3.86 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.30 - 3.40 (1H, m, SC$\underline{H}$H), 3.16 - 3.23 (1H, m, SCH$\underline{H}$), 2.82 - 2.93 (2H, m, C$\underline{H}_2CO_2$Me), 2.19 (3H, s, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.5 (C=O), 168.8 (C=O), 158.9 (Ar C-O), 152.1 (Ar C-O), 151.4 (Ar C-O), 144.8 (Ar C-O), 129.4 (Ar CH of PMB), 129.0 (Ar $\underline{C}$-C), 126.0 (Ar $\underline{C}$-C), 125.7 (Ar $\underline{C}$-C), 121.6 (Ar $\underline{C}$-C), 114.0 (Ar CH of PMB), 66.1 (CH_2OH), 61.6 (OCH_3), 60.1 (2 × OCH_3), 57.4 (ArCHN), 55.2 (OCH_3), 51.8 (OCH_3), 49.1 (CH_2 of PMB), 40.6 (ArCHS), 34.3 ($\underline{C}H_2CO_2$Me), 28.6 (CH_2S), 9.8 ($ArCH_3$).

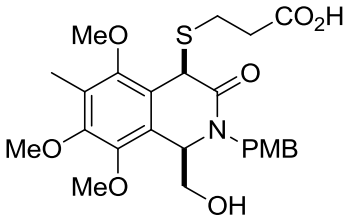
MS (ES+) *m/z* 542 $[M+Na]^+$.

HRMS 520.2004; $C_{26}H_{34}NO_8S^+$ requires 520.2000.

IR (thin film) ν_{max} (cm^{-1}) 2937, 1736, 1641, 1612, 1511, 1460.

$[\alpha]_D^{24}$= +3.2° (c = 1.2, $CHCl_3$).

3-(((*1R,4R*)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoic acid 21



Ester **S22** (80 mg, 0.15 mmol) was dissolved in MeOH (5.6 ml) and a solution of K_2CO_3 (0.39 g, 2.80 mmol) in H_2O (2.8 ml) was added and the reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* then the residue was dissolved in H_2O (5 ml), acidified to pH 5.5 with 1 M HCl then extracted with CH_2Cl_2 (3 × 10 ml). The organic phases were combined, dried ($MgSO_4$) and concentrated to give **21** (55 mg, 0.11 mmol, 73%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 (2H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.81 (2H, d, *J* = 8.6 Hz, Ar CH of PMB), 5.46 (1H, d, *J* = 14.6 Hz, C<u>H</u>H of PMB), 4.82 (1H, s, ArCHS), 4.76 (1H, dd, *J* = 7.3, 4.8 Hz, ArCHN), 4.35 (1H, d, *J* = 14.6 Hz, CH<u>H</u> of PMB), 4.16 - 4.21 (1H, m, C<u>H</u>HOH), 3.88 - 3.93 (1H, m, CH<u>H</u>OH), 3.87 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.56 (3H, s, OCH_3), 3.32 - 3.39 (1H, m, SC<u>H</u>H), 3.17 -3.24 (1H, m, SCH<u>H</u>), 2.94 - 3.01 (1H, m, C<u>H</u>HCO_2Me), 2.81 - 2.88 (1H, m, CH<u>H</u>CO_2Me), 2.19 (3H, s, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.4 (C=O), 169.6 (C=O), 159.0 (Ar C-O), 152.0 (Ar C-O), 151.4 (Ar C-O), 144.8 (Ar C-O), 129.5 (Ar CH of PMB), 128.7 (Ar <u>C</u>-C), 126.1 (Ar <u>C</u>-C), 125.4 (Ar <u>C</u>-C), 121.7 (Ar <u>C</u>-C), 114.0 (Ar CH of PMB), 66.1 (CH_2OH), 61.5 (OCH_3), 60.2 (2 × OCH_3), 57.3 (ArCHN), 55.2 (OCH_3), 49.4 (CH_2 of PMB), 40.6 (ArCHS), 34.4 (<u>C</u>H_2CO_2H), 28.8 (SCH_2), 9.8 ($ArCH_3$).

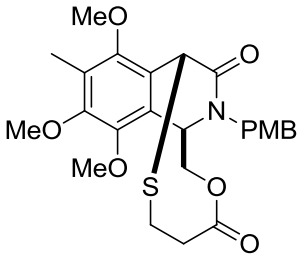
MS (ES–) *m/z* 504 $[M-H]^-$.

HRMS 504.1705, $C_{25}H_{30}NO_8S^-$ requires: 504.1697

IR (thin film) ν_{max} (cm^{-1}) 2904, 1724, 1613, 1512, 1465.

$[\alpha]_D^{24}$= –3.7° (c = 1.1, $CHCl_3$)

(1*R*,8*R*)-9,10,12-trimethoxy-13-(4-methoxybenzyl)-11-methyl-3,4,7,8-tetrahydro-8,1-(epiminomethano)benzo[g][1,5]oxathiecine-5,14(1*H*)-dione 23



A solution of **21** (50 mg, 0.099 mmol) in CH_2Cl_2 (10 ml) was added using a syringe pump over 12 h to a solution of MNBA (41 mg, 0.12 mmol) and DMAP (27 mg, 0.22 mmol) in CH_2Cl_2 (10 ml) at room temperature. The solution was stirred for a further 3h then $NaHCO_3$ solution (20 ml) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 ml) then the organic layers were combined and dried ($MgSO_4$). Flash chromatography (40% EtOAc–pet. ether) gave **23** (34.7 mg, 0.071 mmol, 72%) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 (2H, d, *J* = 8.7 Hz, Ar CH of PMB), 6.85 (2H, d, *J* = 8.7 Hz, Ar CH of PMB), 5.55 (1H, d, *J* = 15.4 Hz, C<u>H</u>H of PMB), 5.01 (1H, s, ArCHS), 4.84 (1H, dd, *J* = 11.3, 2.0 Hz, C<u>H</u>HO), 4.68 (1H, br. s, ArCHN), 4.34 (1H, dd, *J* = 11.3, 1.3 Hz, CH<u>H</u>O), 4.01 (1H, d, *J* = 15.4 Hz, CH<u>H</u> of PMB), 3.81 (OCH_3), 3.80 (OCH_3), 3.78 (OCH_3), 3.69 (OCH_3), 2.97 -3.02 (1H, m, SCH<u>H</u>), 2.64 - 2.71 (1H, m, SC<u>H</u>H), 2.47 - 2.60 (2H, m, CH_2CO_2Me), 2.22 (3H, s, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.5 (2 × C=O), 159.1 (Ar C-O), 152.2 (Ar C-O), 151.2 (Ar C-O), 144.6 (Ar C-O), 129.5 (Ar CH of PMB), 128.3 (2 ×Ar <u>C</u>-C), 126.1 (Ar <u>C</u>-C), 123.7 (Ar <u>C</u>-C), 114.1 (Ar CH of PMB), 61.9 (OCH_2), 61.0 (OCH_3), 60.1 (OCH_3), 60.0 (OCH_3), 55.2 (OCH_3), 55.1 (ArCHN), 47.1 (CH_2 of PMB), 41.2 (CHS), 38.4 (SCH_2), 26.8 (<u>C</u>H_2CO_2Me), 10.0 ($ArCH_3$).

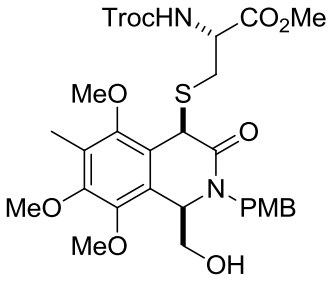
MS (ES+) *m/z* 488 $[M+H]^+$, 510 $[M+Na]^+$.

HRMS 488.1759, $C_{25}H_{30}NO_7S^+$requires 488.1738.

IR (thin film) ν_{max} (cm^{-1}) 2937, 1743, 1645, 1512, 1460.

$[\alpha]_D^{24}$= +14.2° (c = 3.2, $CHCl_3$).

(*R*)-Methyl 3-(((1*R*,4*R*)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate S23



Silyl ether **20** (65 mg, 68 μmol) was dissolved in MeCN (0.7 ml), pyridine (0.4 ml) was added and the mixture was cooled to 0 °C then aqueous 60% HF (0.1 ml) was added and the reaction was stirred then allowed to warm to room temperature gradually and stirred for a further 15 hours. 1 M HCl (15 ml) was added and extracted by CH_2Cl_2 (3 × 15 ml). The organic phases were washed with aqueous 1 M HCl (30 ml) then dried ($MgSO_4$) and evaporated to give crude product. Flash chromatography (45% EtOAc–petrol. ether) gave recovered starting material (12 mg, 18%) and **S23** (31.5 mg, 44 μmol, 65%, 79% based on recovered stating material).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20 (2H, d, *J* = 8.6 Hz, Ar CH of PMB), 6.95 (1H, d, *J* = 8.8 Hz, NH), 6.81 (2H, d, *J* = 8.6 Hz, Ar CH of PMB), 5.57 (1H, d, *J* = 14.8 Hz, C<u>H</u>H of PMB), 4.90 - 4.96 (2H, m, CHS and C<u>H</u>NHTroc), 4.76 - 4.78 (3H, m, CH_2CCl_3 and ArCHN), 4.40 (1H, d, *J* = 14.8 Hz, CH<u>H</u> of PMB), 4.10 - 4.16 (1H, m, C<u>H</u>HO), 3.76 - 3.85 (13H, m, 4 × OCH_3 and CH<u>H</u>O), 3.54 - 3.58 (4H, m, SC<u>H</u>H and OCH_3), 3.34 - 3.40 (1H, m, SCH<u>H</u>), 2.19 (3H, s, Ar CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.2 (C=O), 169.4 (C=O), 158.9 (carbamate C=O), 155.1 (Ar C-O), 152.3 (Ar C-O), 151.7 (Ar C-O), 144.8 (Ar C-O), 129.6 (Ar CH of PMB), 128.9 (Ar <u>C</u>-C), 126.1 (Ar <u>C</u>-C), 125.4 (Ar <u>C</u>-C), 121.1 (Ar <u>C</u>-C), 114.0 (Ar CH of PMB), 95.3 (CCl_3), 74.7 (O<u>C</u>H_2CCl_3), 66.0 (OCH_2), 61.6 (OCH_3), 60.2 (OCH_3), 60.1 (OCH_3), 57.2 (ArCHN), 55.2 (OCH_3), 54.9 (CHNHTroc), 52.8 (OCH_3), 49.5 (CH_2 of PMB), 42.1 (ArCHS), 36.7 (SCH_2), 9.9 ($ArCH_3$).

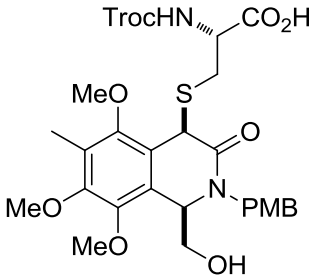
MS (ES+) *m/z* 731 $[M+Na]^+$.

HRMS 709.1183; $C_{29}H_{36}N_2O_{10}SCl_3^+$ requires 709.1151.

IR (thin film) ν_{max} (cm^{-1}) 3307, 2951, 1736, 1630, 1511, 1463, 1408.

$[\alpha]_D^{24}$= –2.6° (c = 2.7, $CHCl_3$).

(*R*)-3-(((1*R*,4*R*)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoic acid 22



Ester **S23** (26 mg, 0.037 mmol) was dissolved in MeOH (1 ml) and a solution of K_2CO_3 (10 mg, 0.073 mmol) in H_2O (0.5 ml) was added and the reaction was stirred at room temperature for 4 h. The residue was diluted with H_2O (2 ml) and acidified to pH 5.5 with 1 M HCl then extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were combined and dried ($MgSO_4$). Flash chromatography (50% EtOAc–*n*-hexane with 0.5% TFA) gave **22** (14.5 mg, 0.021 mmol, 56%) as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 (2H, d, *J* = 8.3 Hz, Ar CH of PMB), 7.06 (1H, d, *J* = 7.8 Hz, NH of one rotamer), 6.80 (2H, d, *J* = 8.3 Hz, Ar CH of PMB), 6.37 (1H, d, *J* = 7.8 Hz, NH of one rotamer), 5.60 (1H, d, *J* = 14.8 Hz, C<u>H</u>H of PMB of one rotamer), 5.50 (1H, d, *J* = 14.8 Hz, C<u>H</u>H of PMB of one rotamer), 4.97 (1H, s, ArCHS), 4.69 - 4.86 (4H, m, C<u>H</u>$_2$CCl$_3$, ArCHN and C<u>H</u>NHTroc), 4.40 (1H, d, *J* = 14.8 Hz, CH<u>H</u> of PMB of one rotamer), 4.32 (1H, d, *J* = 14.8 Hz, CH<u>H</u> of PMB of one rotamer), 4.07 - 4.22 (1H, m, C<u>H</u>HO), 3.74 - 3.86 (10H, m, OCH_3 and CH<u>H</u>O), 3.63 (1H, dd, *J* = 14.9, 2.5 Hz, C<u>H</u>HS), 3.54 (3H, s, OCH_3), 3.31 (1H, dd, *J* = 14.9, 7.8 Hz, CH<u>H</u>S), 2.17 (3H, s, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.7 (C=O), 159.0 (2 × C=O), 155.3 (Ar C-O), 152.2 (Ar C-O), 151.7 (Ar C-O), 144.7 (Ar C-O), 129.7 (Ar CH of PMB of one rotamer), 129.5 (Ar CH of PMB of one rotamer), 128.2 (Ar <u>C</u>-C), 126.2 (Ar <u>C</u>-C), 124.9 (Ar <u>C</u>-C), 121.1 (Ar <u>C</u>-C), 114.1 (Ar CH of PMB of other rotamer), 114.0 (Ar CH of PMB of one rotamer), 95.2 (CCl_3), 74.8 (<u>C</u>H$_2$CCl$_3$), 65.9 (CH_2O), 61.5 (OCH_3), 60.2 (OCH_3), 60.1 (OCH_3), 57.3 (CHNHTroc), 55.2 (ArCHN and OCH_3), 50.1 (CH_2 of PMB), 42.6 (ArCHS), 37.6 (CH_2S), 9.6 ($ArCH_3$).

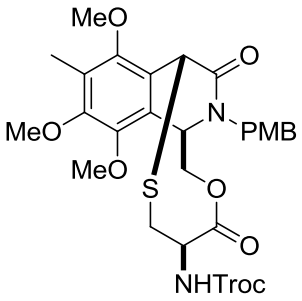
MS (ES+) *m/z* 695 $[M+H]^+$, 717 $[M+Na]^+$.

HRMS 717.0819; $C_{28}H_{33}N_2O_{10}SNa^+$ requires 717.0814.

IR (thin film) ν_{max} (cm^{-1}) 2927, 1728, 1629, 1512, 1465.

$[\alpha]_D^{24}$= –8.9° (c = 1.2, $CHCl_3$).

2,2,2-Trichloroethyl ((1*R*,4*R*,8*R*)-9,10,12-trimethoxy-13-(4-methoxybenzyl)-11-methyl-5,14-dioxo-1,3,4,5,7,8-hexahydro-8,1-(epiminomethano)benzo[g][1,5]oxathiecin-4-yl)carbamate 2



A solution of hydroxyacid **22** (12 mg, 17.2 μmol) in CH_2Cl_2 (7 ml) was added *via* syringe pump over 12 h at room temperature to MNBA (7.7 mg, 22.4 μmol) and DMAP (5.0 mg, 41.3 μmol) in anhydrous CH_2Cl_2 (5 ml) then the reaction was stirred for a further 3 h. $NaHCO_3$ solution (10 ml) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 ml) then the organic layers were combined and dried ($MgSO_4$). Flash chromatography (40% EtOAc–pet. ether) gave **2** (7.8 mg, 11.5 μmol, 67%) as a white foam.

^{1}H NMR (400 MHz, DMSO–d_6, 110 °C) δ ppm 7.01 (1H, br. s, NH), 6.79 (2H, d, *J* = 8.7 Hz, Ar CH of PMB), 6.45 (2H, d, *J* = 8.7 Hz, Ar CH of PMB), 4.77 - 4.82 (2H, m, C<u>H</u>H of PMB and OC<u>H</u>H), 4.48 (1H, s, ArCHS), 4.35 - 4.39 (3H, m, C<u>H</u>$_2$CCl$_3$ and ArCHN), 3.79 (1H, ddd, *J* = 7.6, 3.0, 3.0 Hz, C<u>H</u>NHTroc), 3.64 - 3.67 (2H, m, CH<u>H</u> of PMB and OCH<u>H</u>), 3.37 (6H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.68 (1H, dd, *J* = 15.8, 7.6 Hz, SC<u>H</u>H), 2.35 (1H, dd, *J* = 15.8, 3.0 Hz, SCH<u>H</u>), 1.76 (3H, s, ArCH_3).

^{13}C NMR (100 MHz, DMSO–d_6, 110 °C) δ ppm 168.6 (2 × C=O), 165.5 (C=O), 158.4 (Ar C-O), 151.5 (Ar C-O), 150.5 (Ar C-O), 143.7 (Ar C-O), 128.7 (Ar CH of PMB), 128.2 (Ar <u>C</u>-C), 124.8 (Ar <u>C</u>-C), 123.3 (Ar <u>C</u>-C), 113.8 (Ar CH of PMB), 95.5 (Ar <u>C</u>-C), 78.5 (<u>C</u>Cl$_3$), 73.6 (<u>C</u>H$_2$CCl$_3$), 62.8 (CH_2O), 60.2 (OCH_3), 59.5 (OCH_3), 59.4 (OCH_3), 55.5 (CHNHTroc), 54.7 (OCH_3), 54.6 (ArCHN), 46.0 (CH_2 of PMB), 39.9 (ArCHS), 31.2 (CH_2S), 9.1 (ArCH_3).

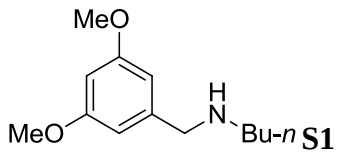
MS (ES+) *m/z* 677 $[M+H]^+$, 699 $[M+Na]^+$.

HRMS 677.0883; $C_{28}H_{32}N_2O_9SCl_3^+$ requires 677.0889.

IR (thin film) ν_{max} (cm^{-1}) 2944, 1739, 1645, 1521, 1463.

$[\alpha]_D^{24}$= +12.4° (c = 1.0, $CHCl_3$).

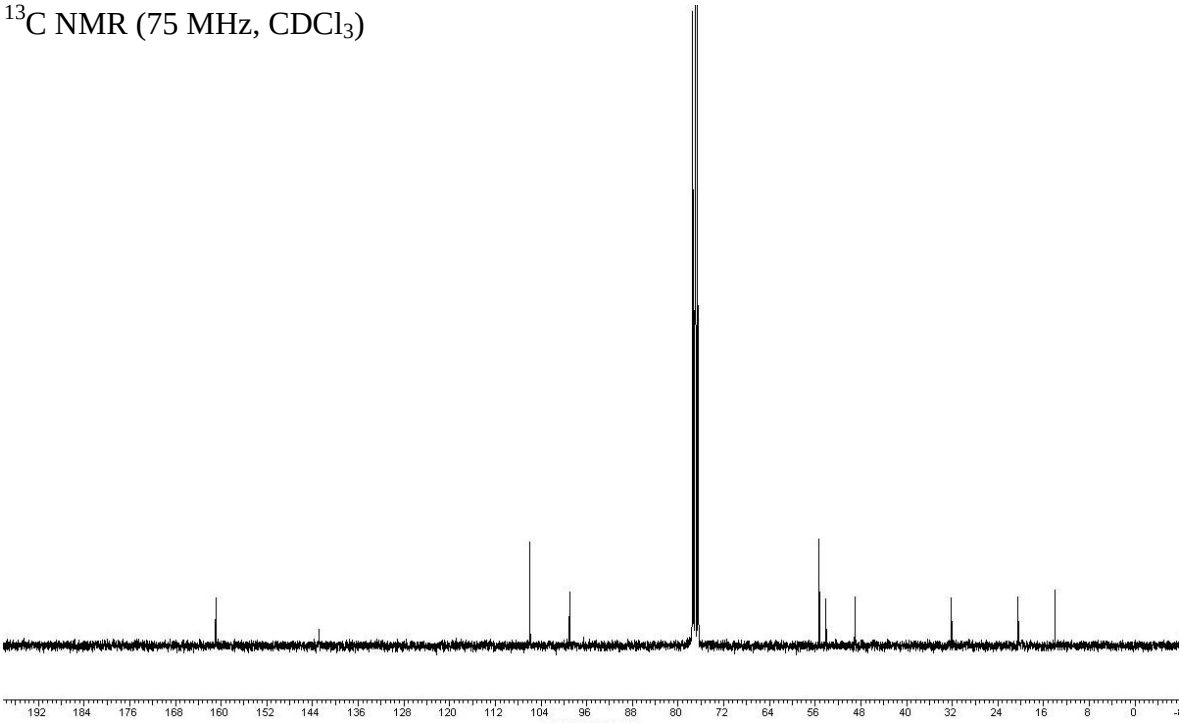
NMR Spectra of New Compounds

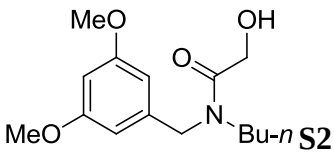


S1

^{1}H NMR (300 MHz, $CDCl_3$)

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

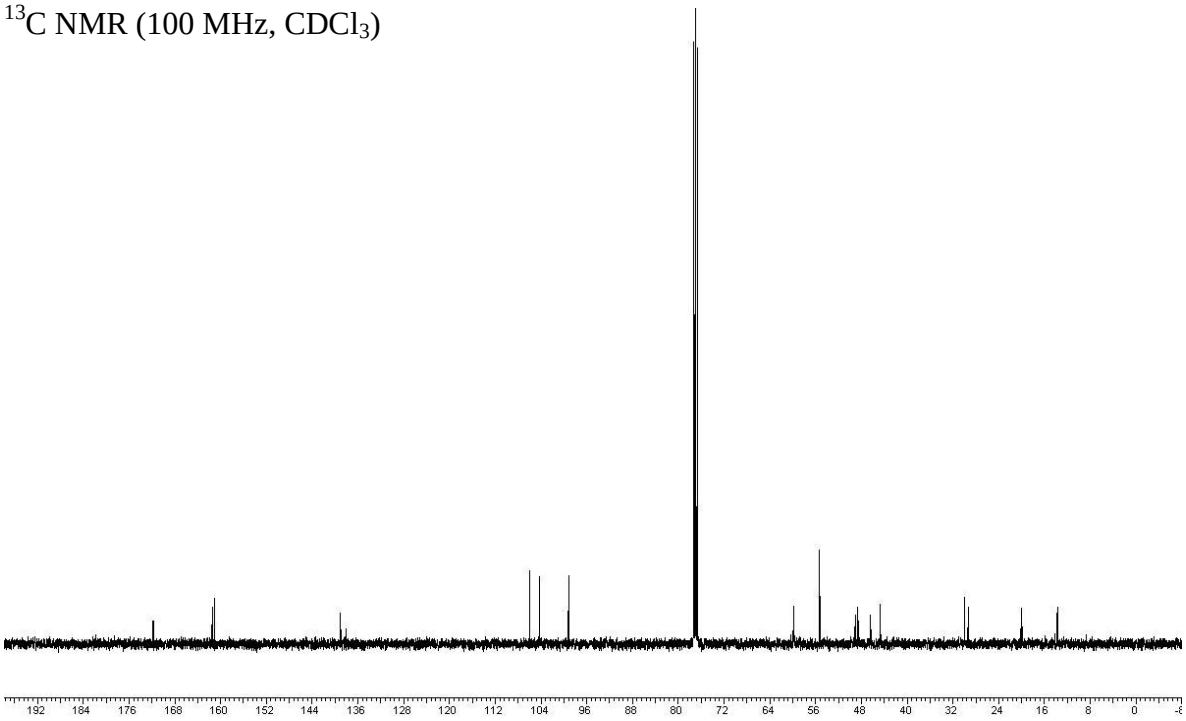


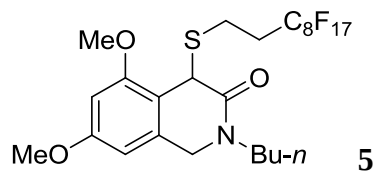


S2

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

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

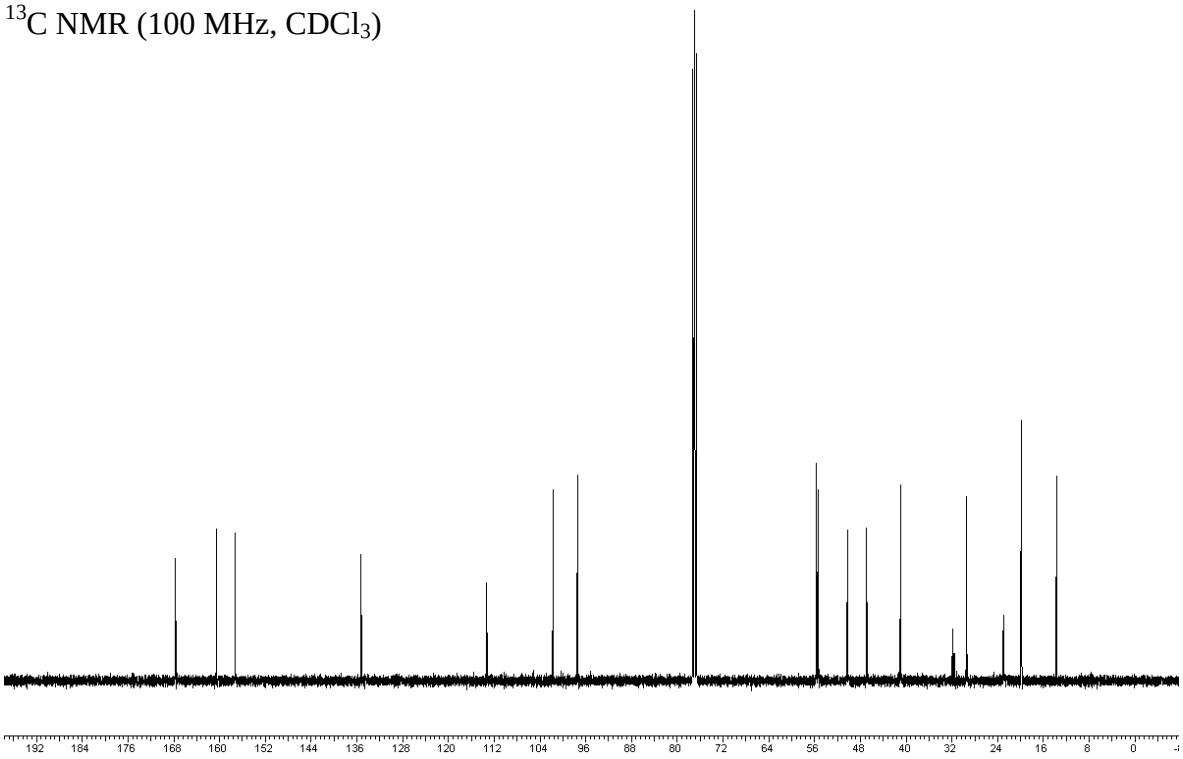


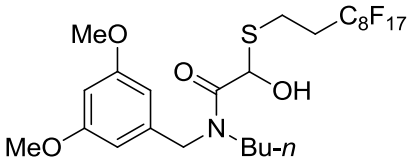


5

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

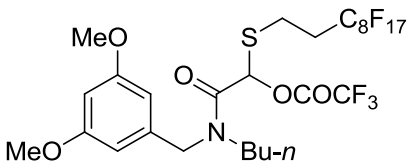
^{13}C NMR (100 MHz, $CDCl_3$)





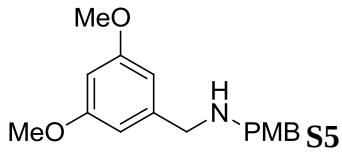
S3

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



S4

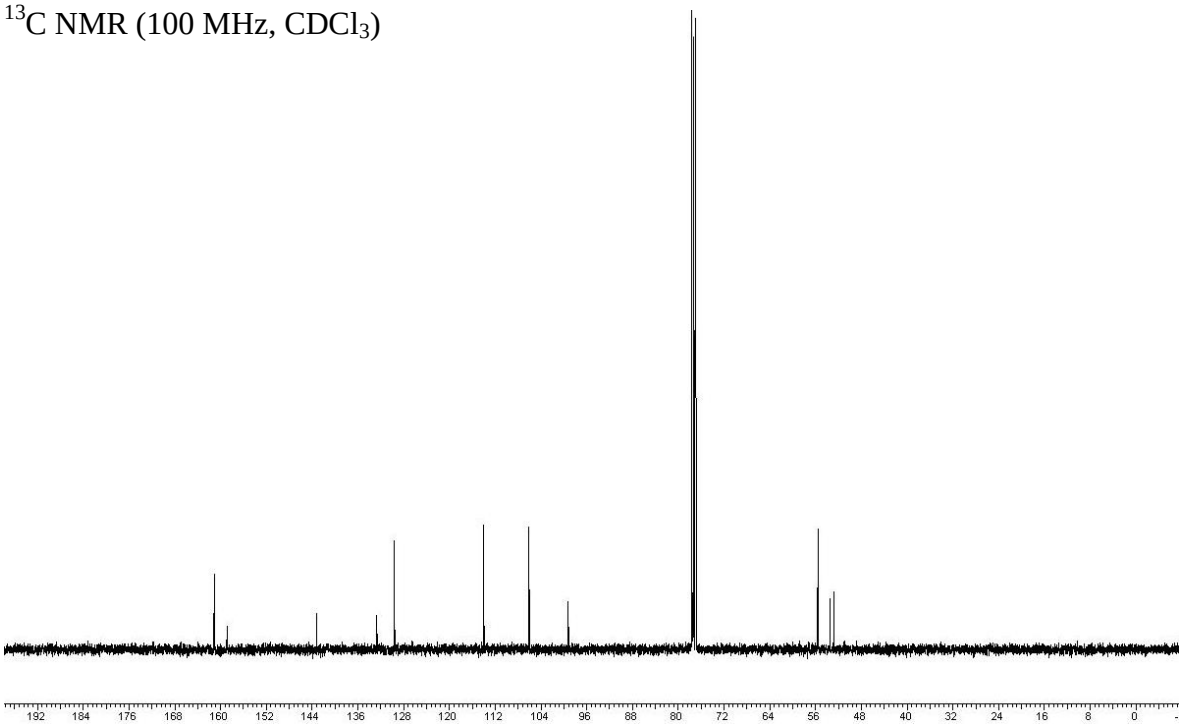
^{1}H NMR (400 MHz, $CDCl_3$)

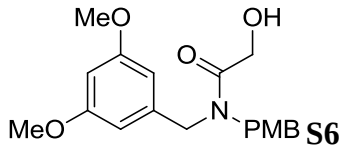


S5

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

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

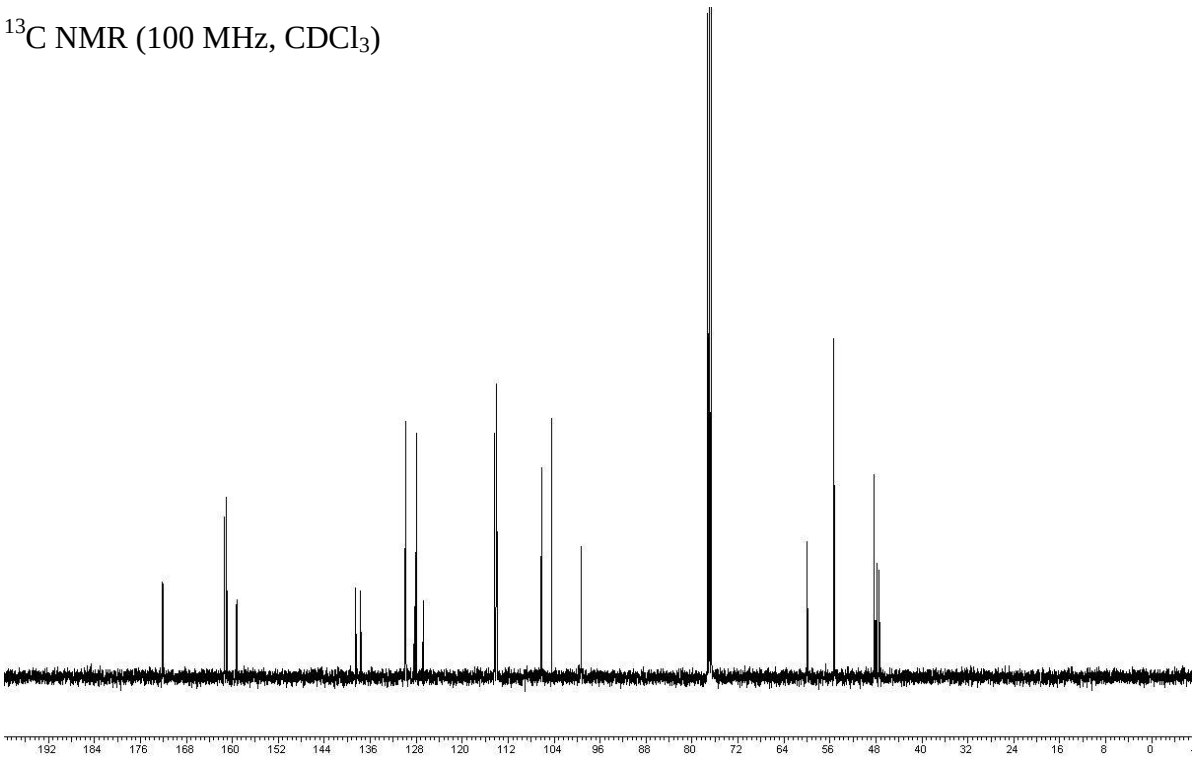


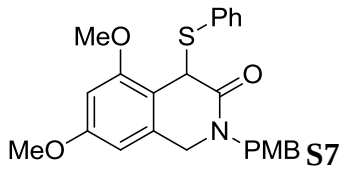


S6

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

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

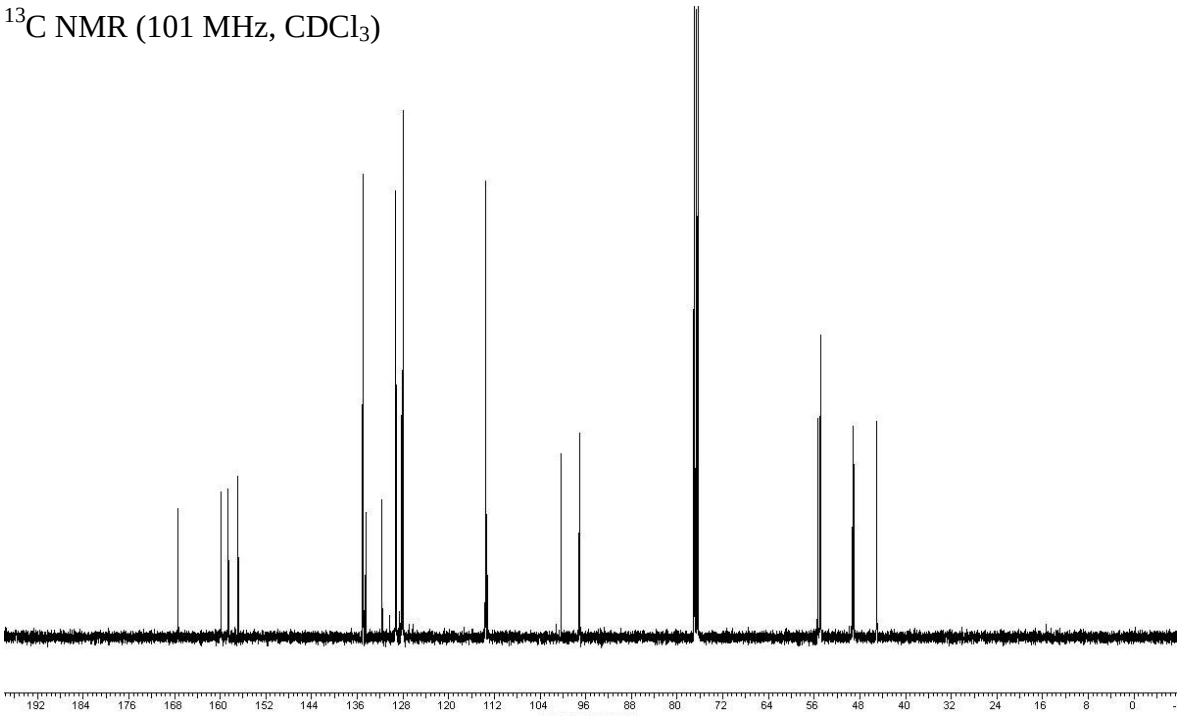


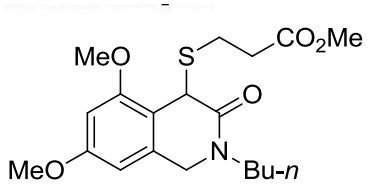


S7

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

^{13}C NMR (101 MHz, $CDCl_3$)

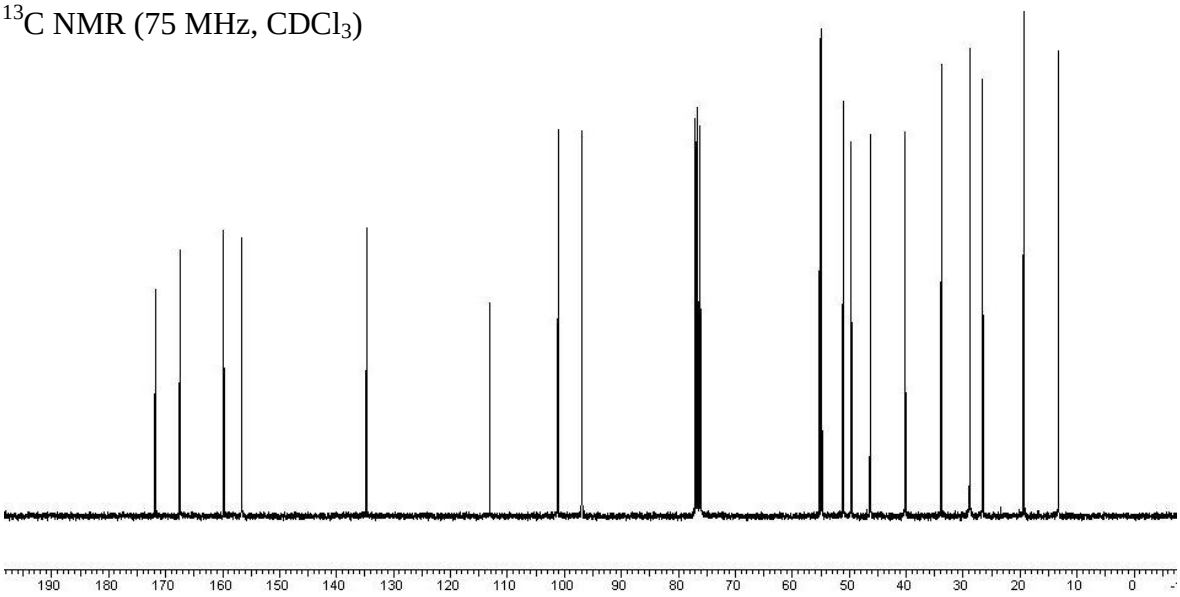


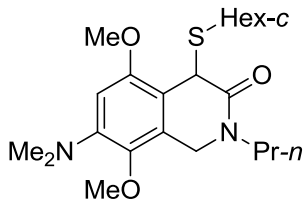


S8

^{1}H NMR (300 MHz, $CDCl_3$)

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

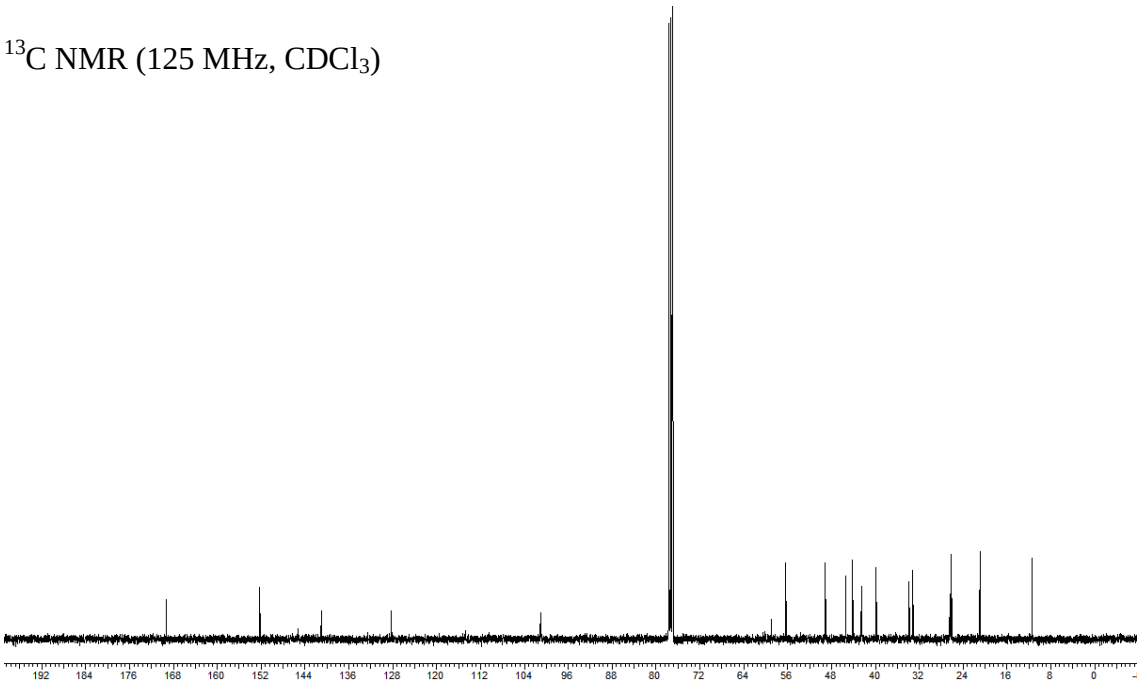


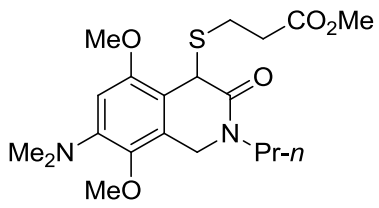


S9

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

^{13}C NMR (125 MHz, $CDCl_3$)

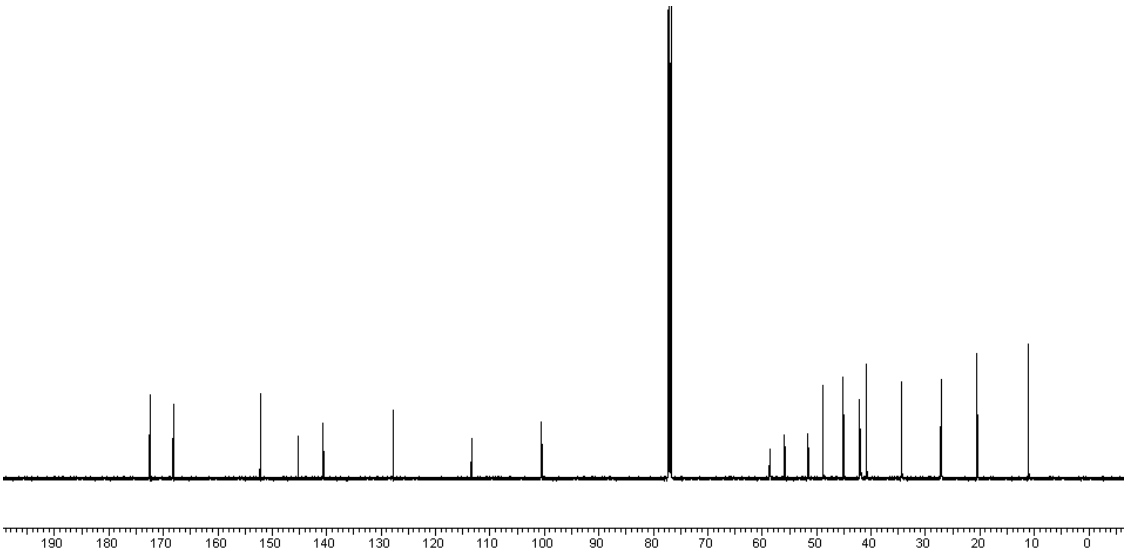


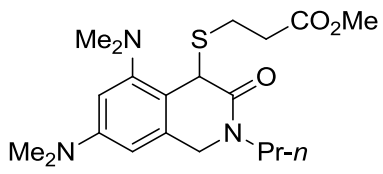


S11

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

^{13}C NMR (125 MHz, $CDCl_3$)

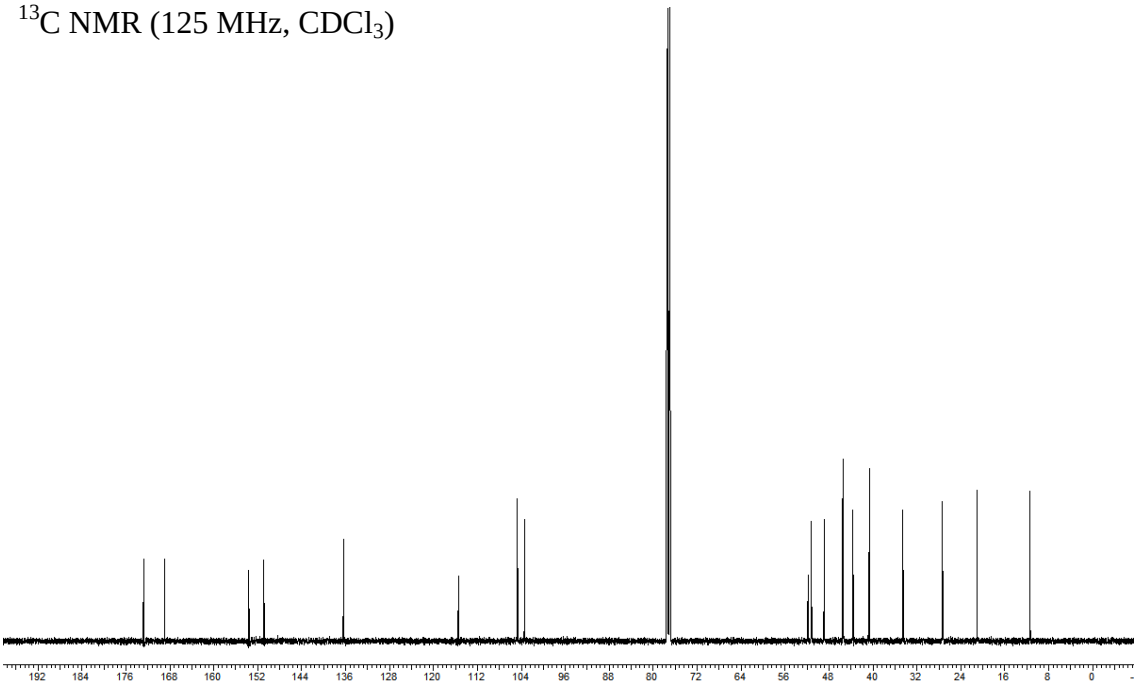


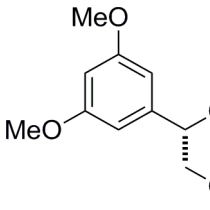


S11

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

^{13}C NMR (125 MHz, $CDCl_3$)

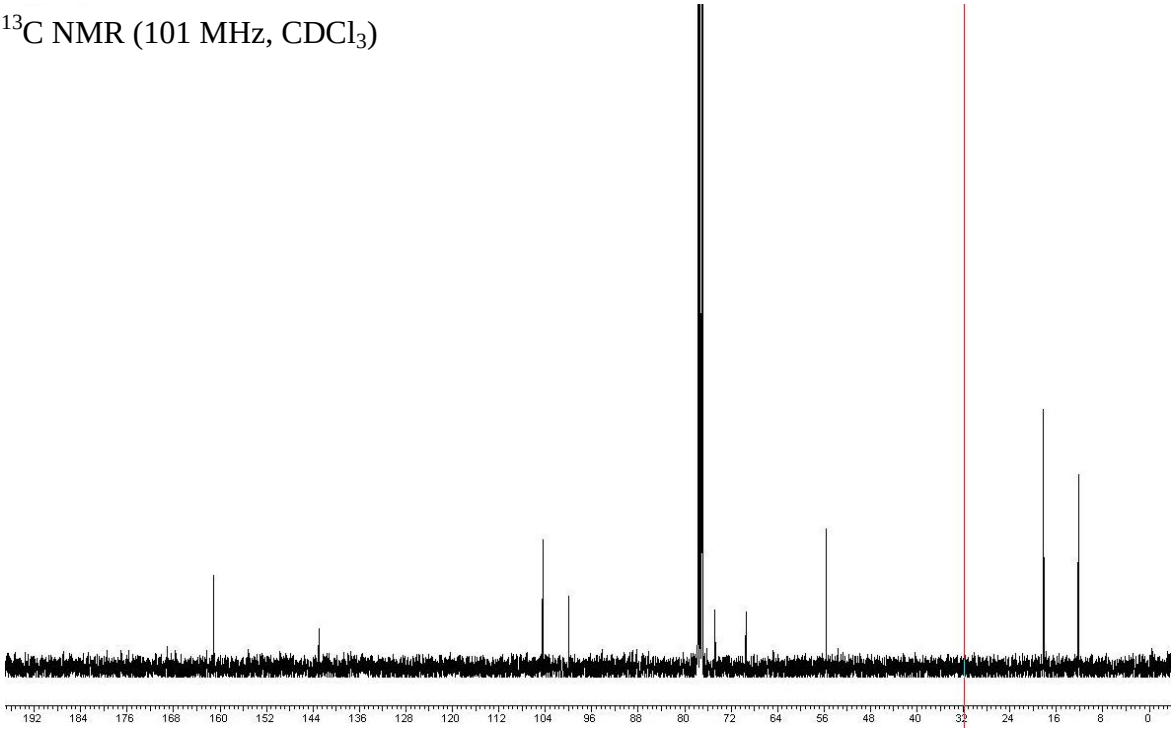


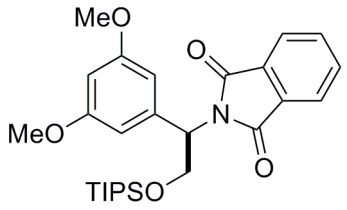


S12

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

^{13}C NMR (101 MHz, $CDCl_3$)

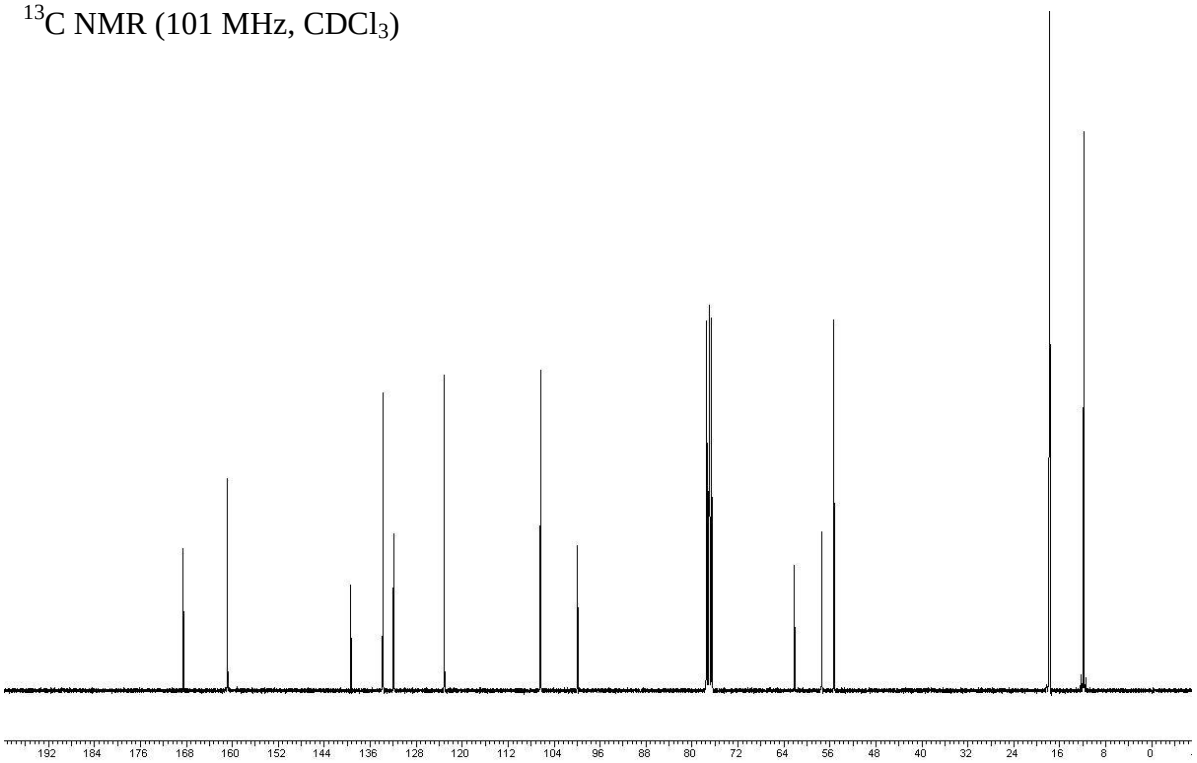


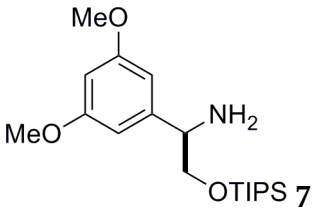


S13

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

^{13}C NMR (101 MHz, $CDCl_3$)

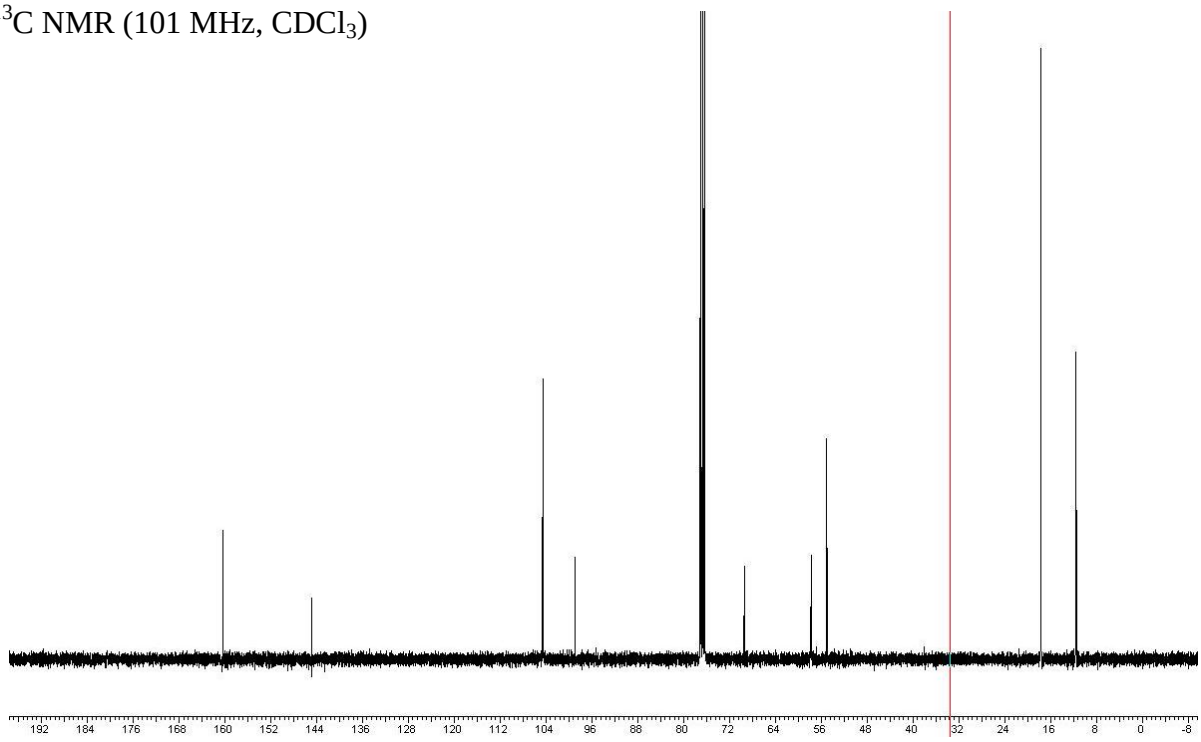


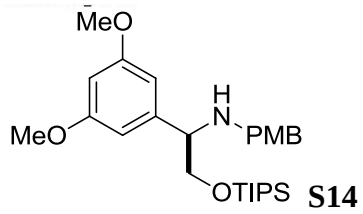


7

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

^{13}C NMR (101 MHz, $CDCl_3$)

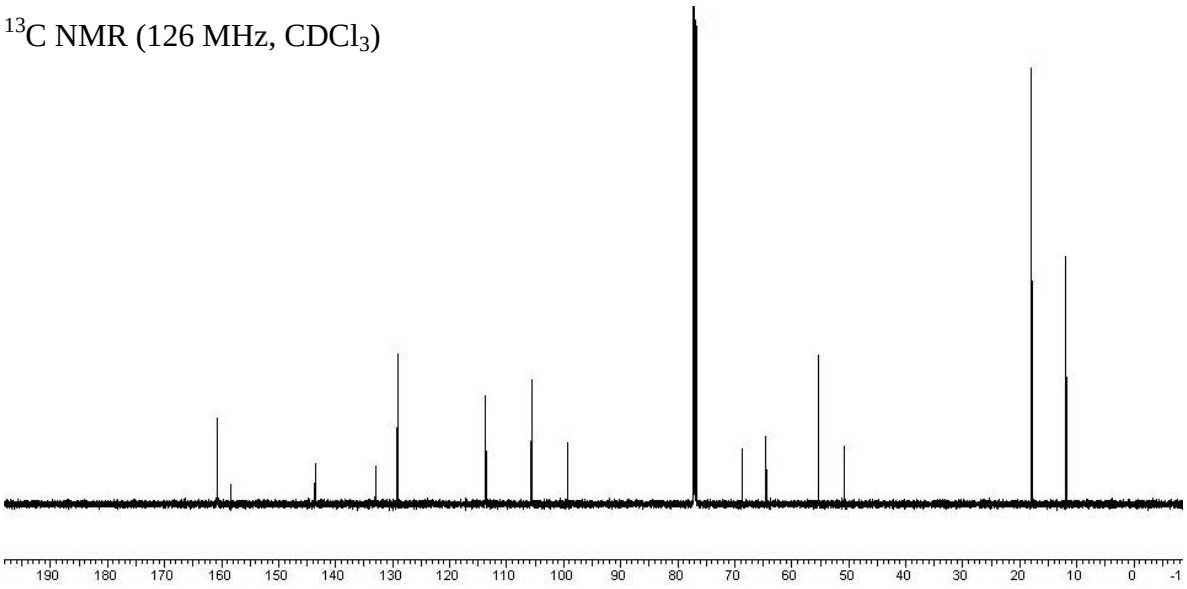


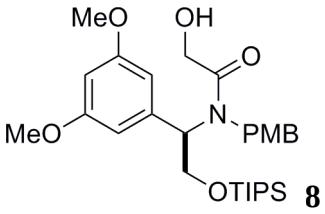


S14

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

^{13}C NMR (126 MHz, $CDCl_3$)

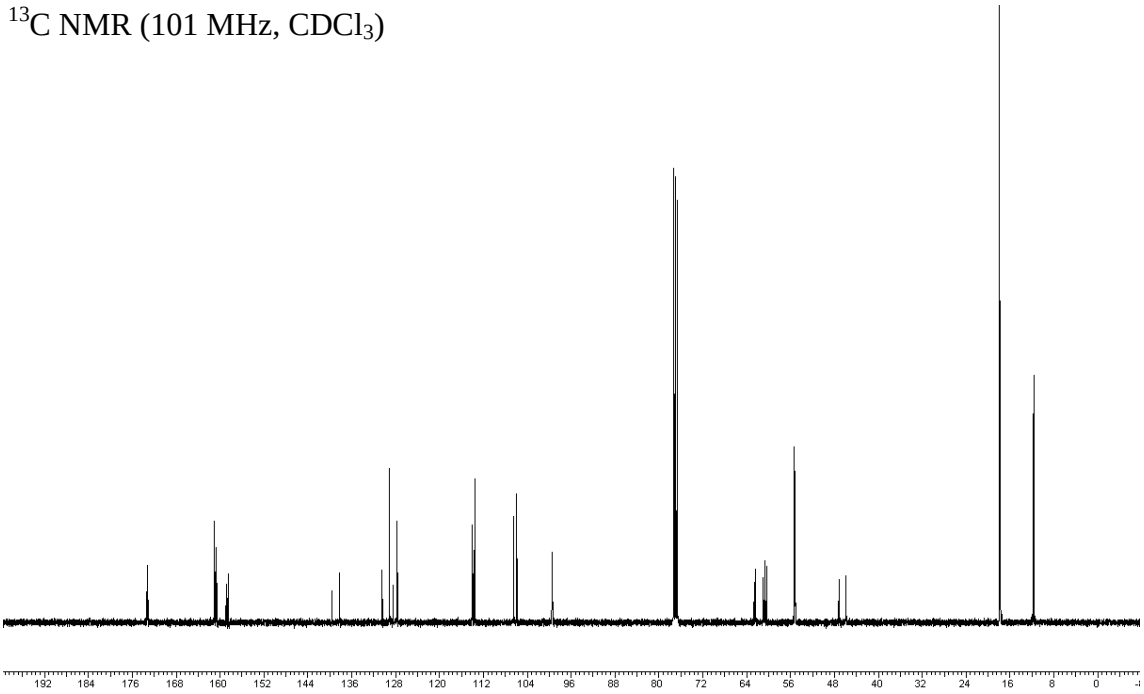


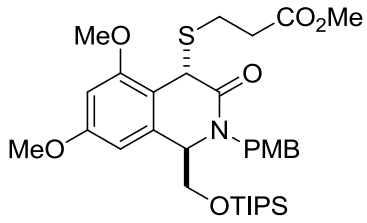


8

^{1}H NMR (400 MHz, DMSO-d6, 120 °C)

^{13}C NMR (101 MHz, $CDCl_3$)

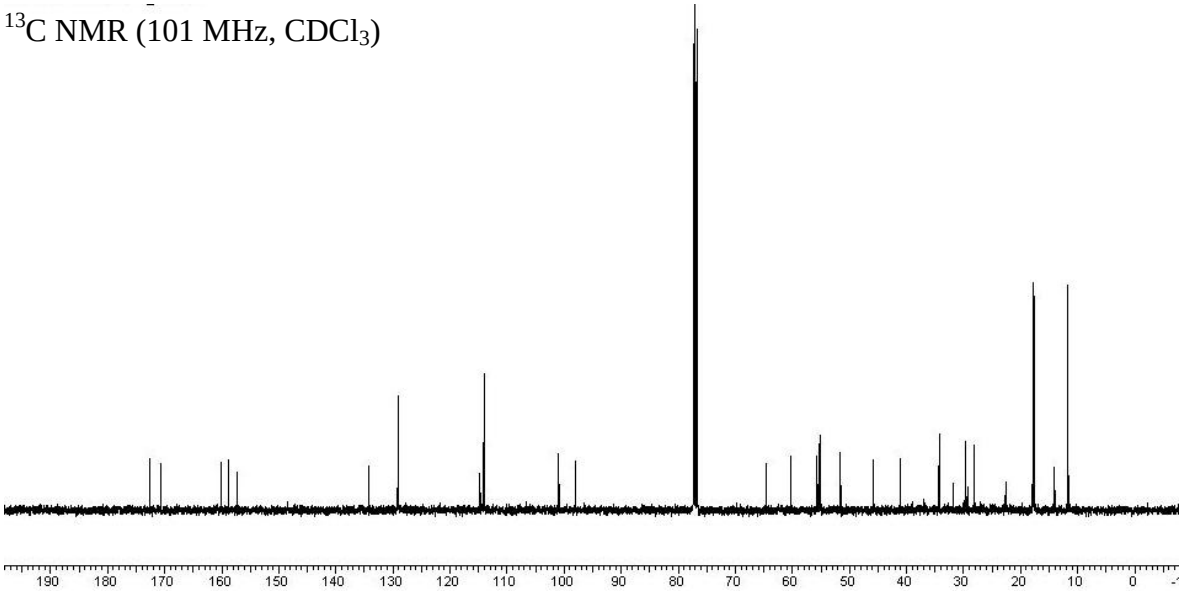


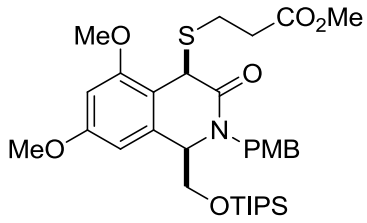


9a

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

^{13}C NMR (101 MHz, $CDCl_3$)

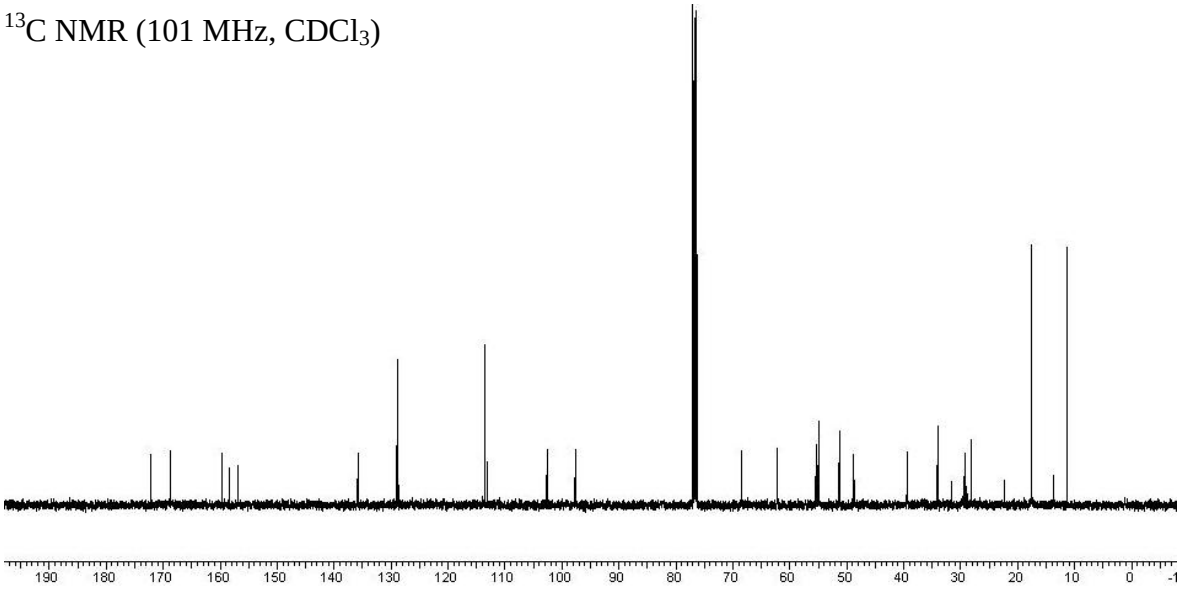


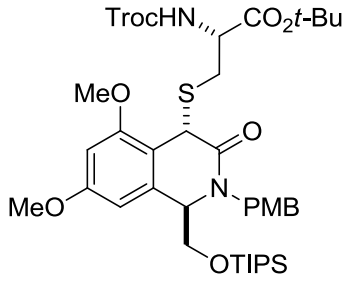


9b

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

^{13}C NMR (101 MHz, $CDCl_3$)

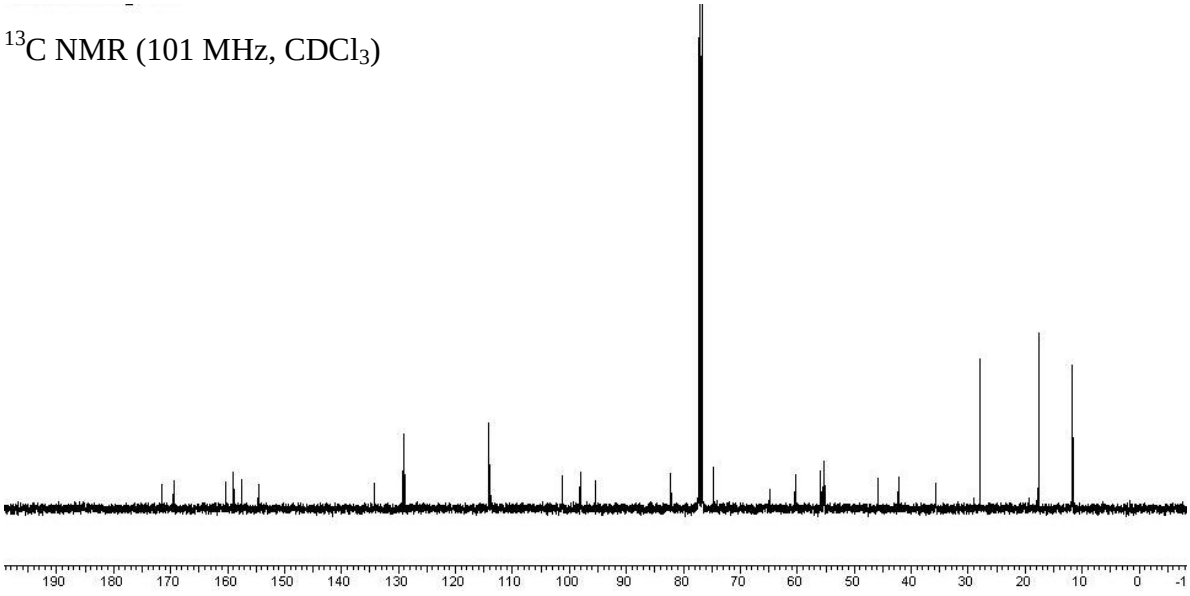


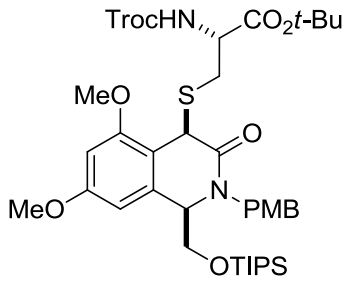


10a

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

^{13}C NMR (101 MHz, $CDCl_3$)

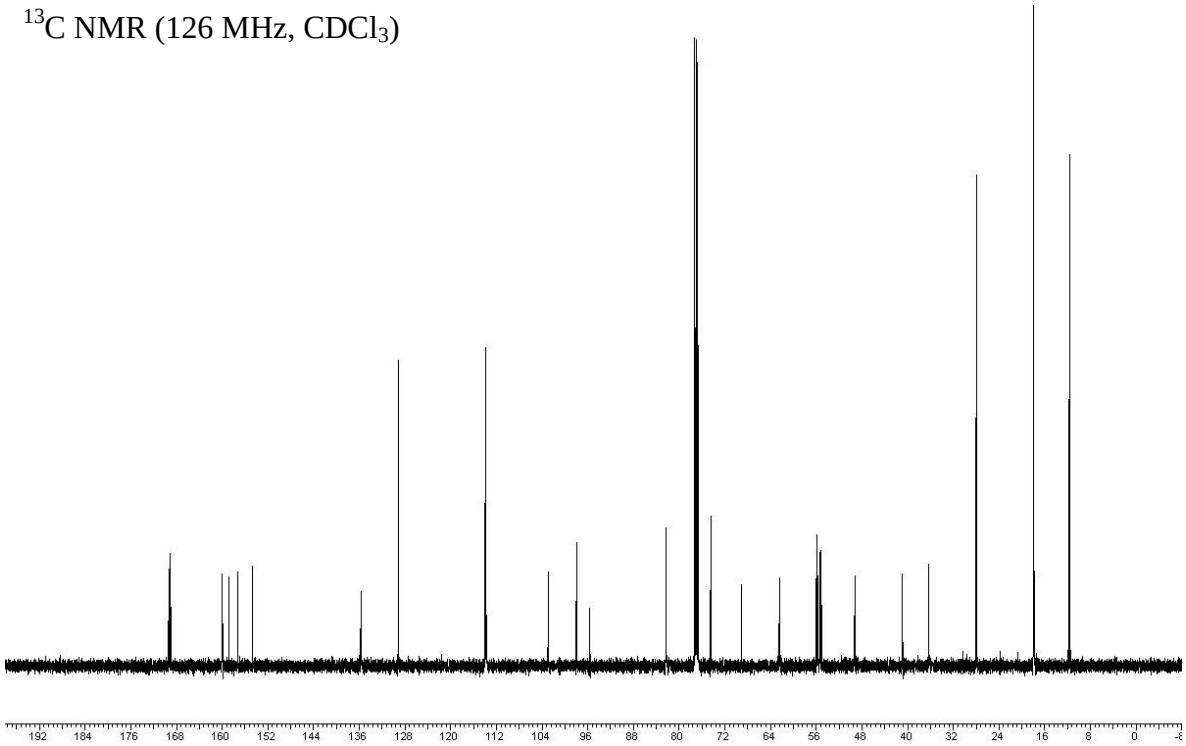


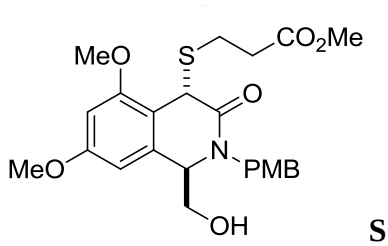


10b

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

^{13}C NMR (126 MHz, $CDCl_3$)

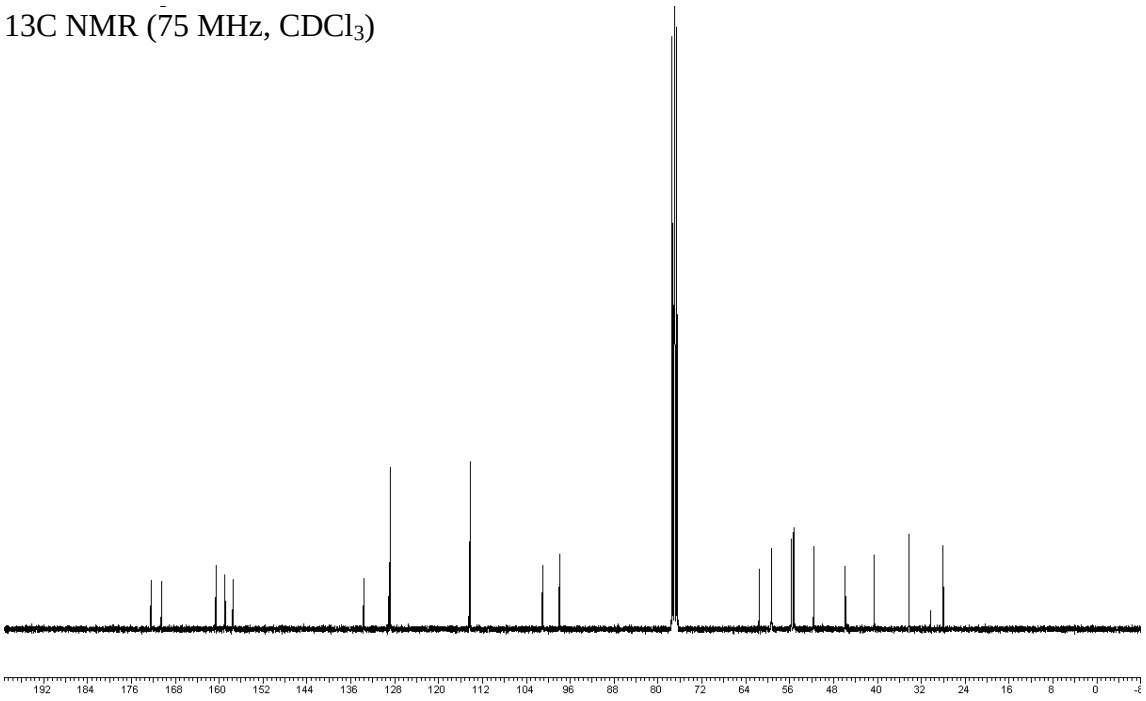


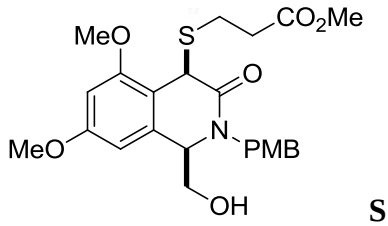


S15a

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

13C NMR (75 MHz, $CDCl_3$)

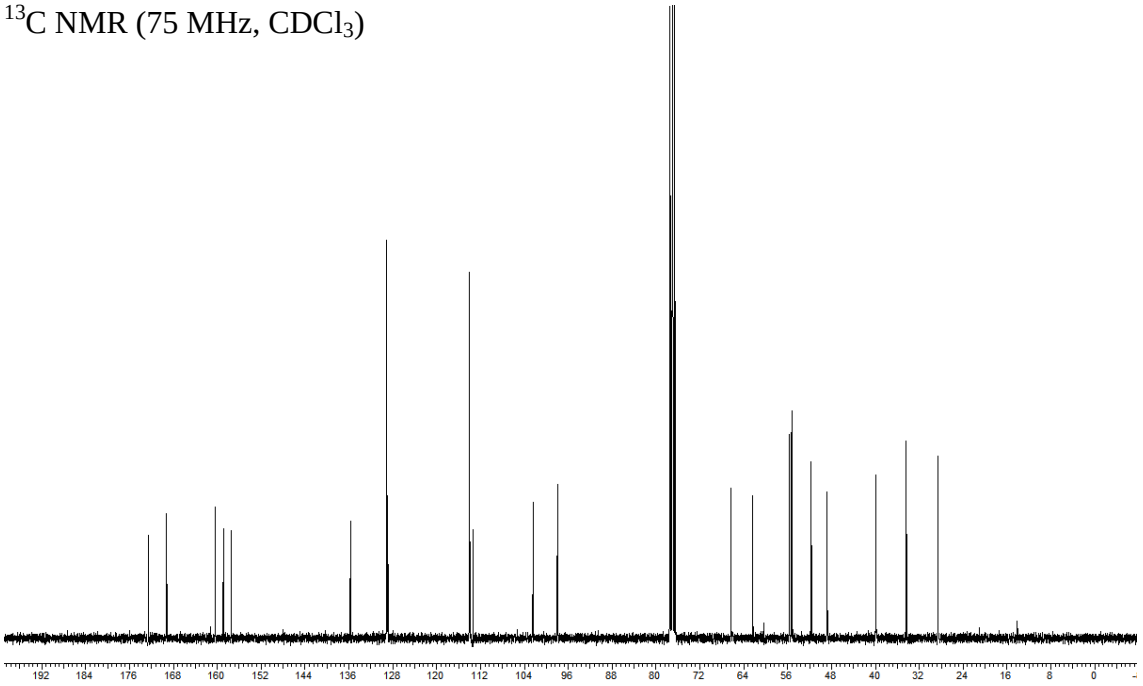


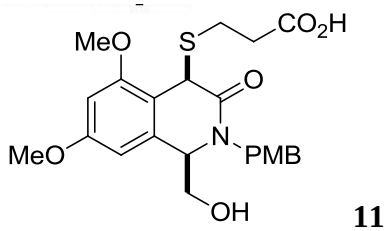


S15b

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

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

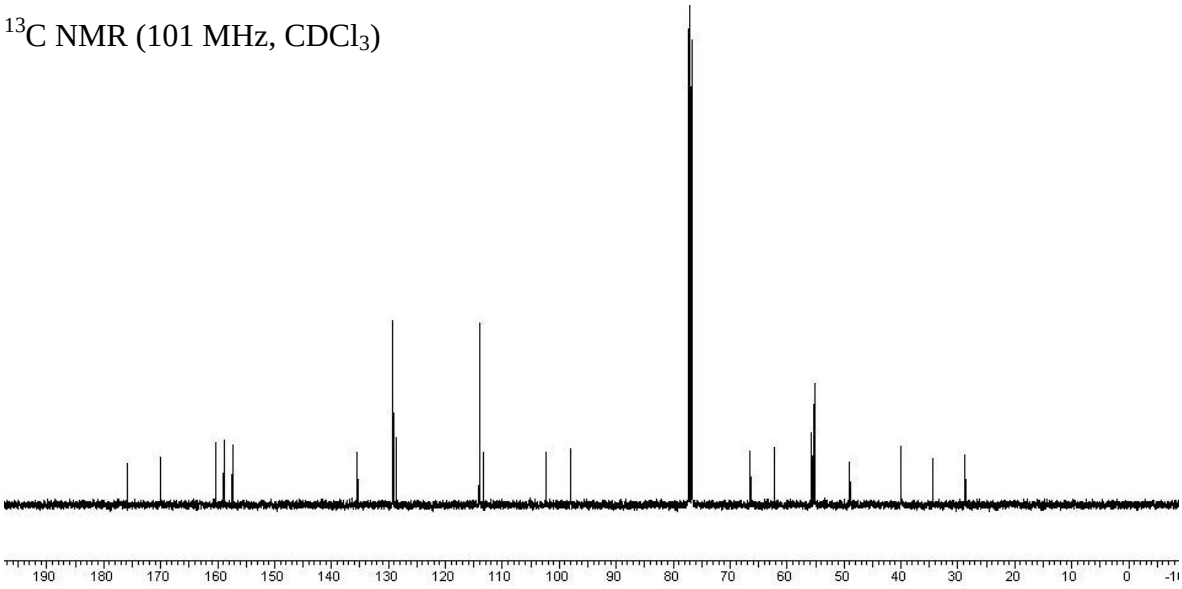


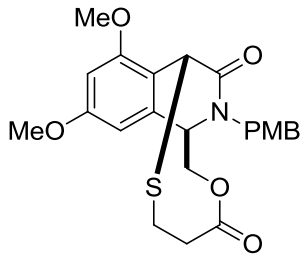


11

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

^{13}C NMR (101 MHz, $CDCl_3$)

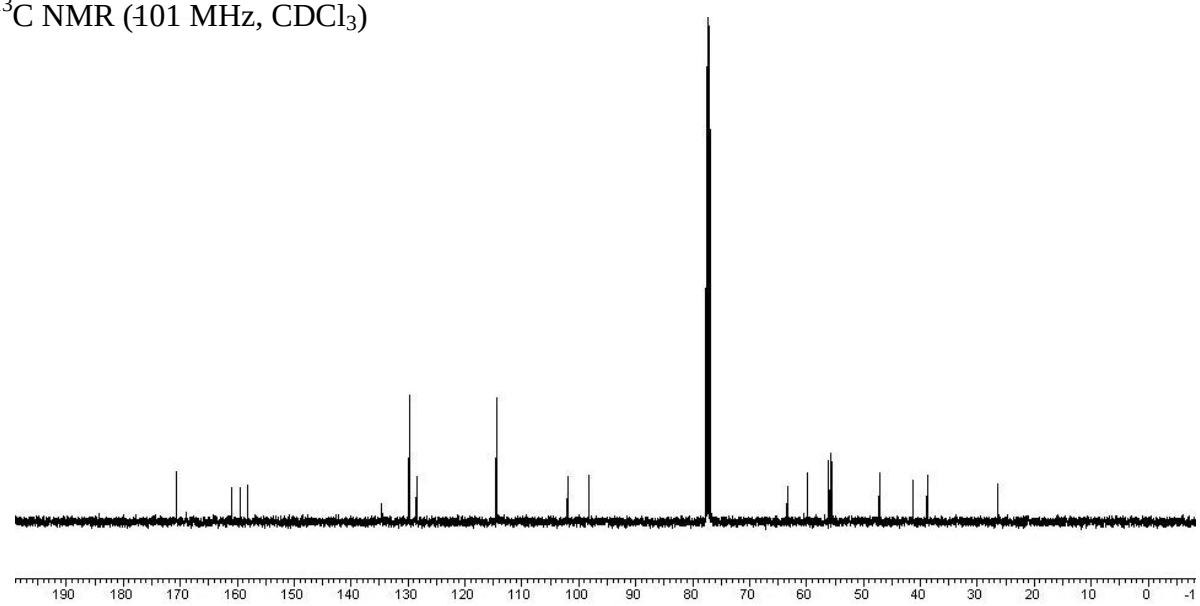


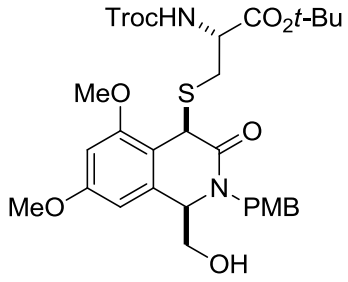


13

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

^{13}C NMR (101 MHz, $CDCl_3$)

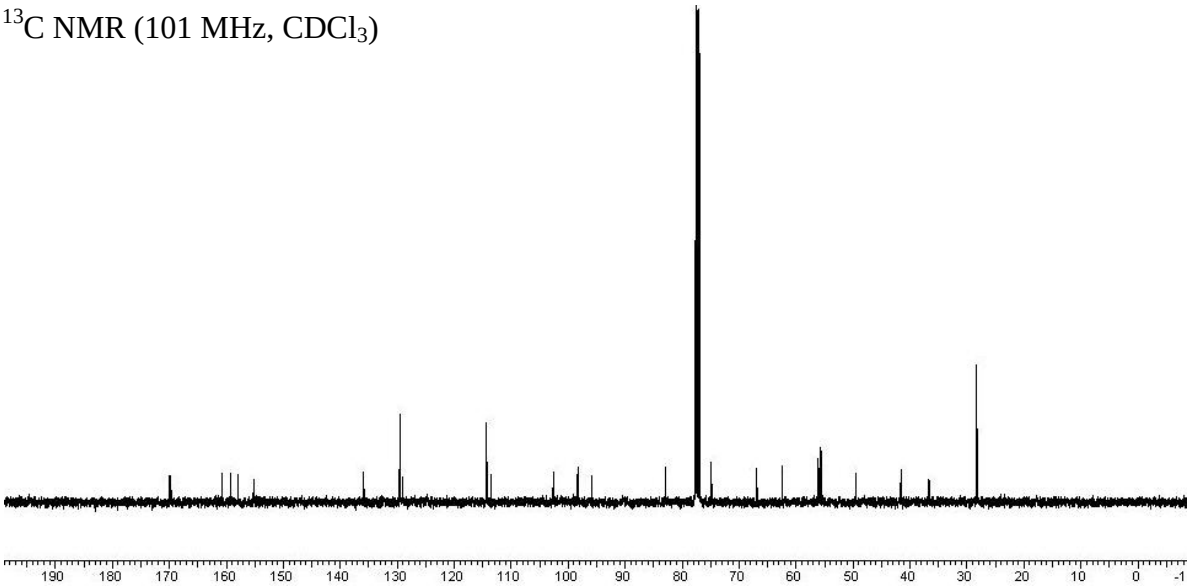


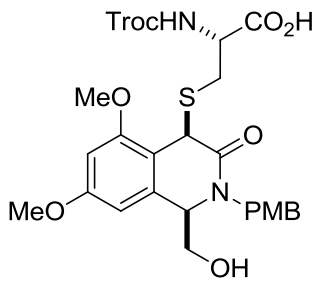


S16

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

^{13}C NMR (101 MHz, $CDCl_3$)

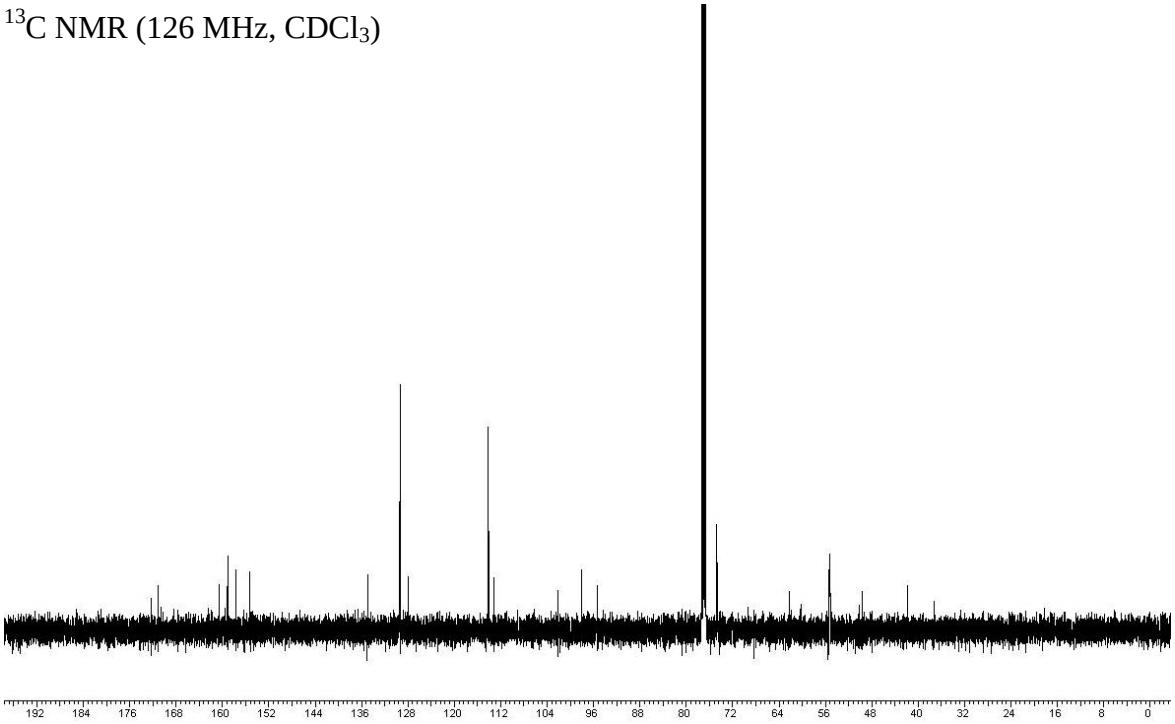


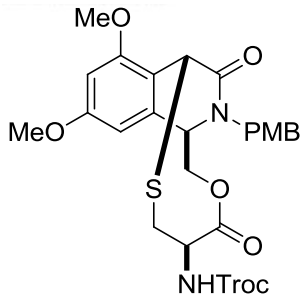


12

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

^{13}C NMR (126 MHz, $CDCl_3$)

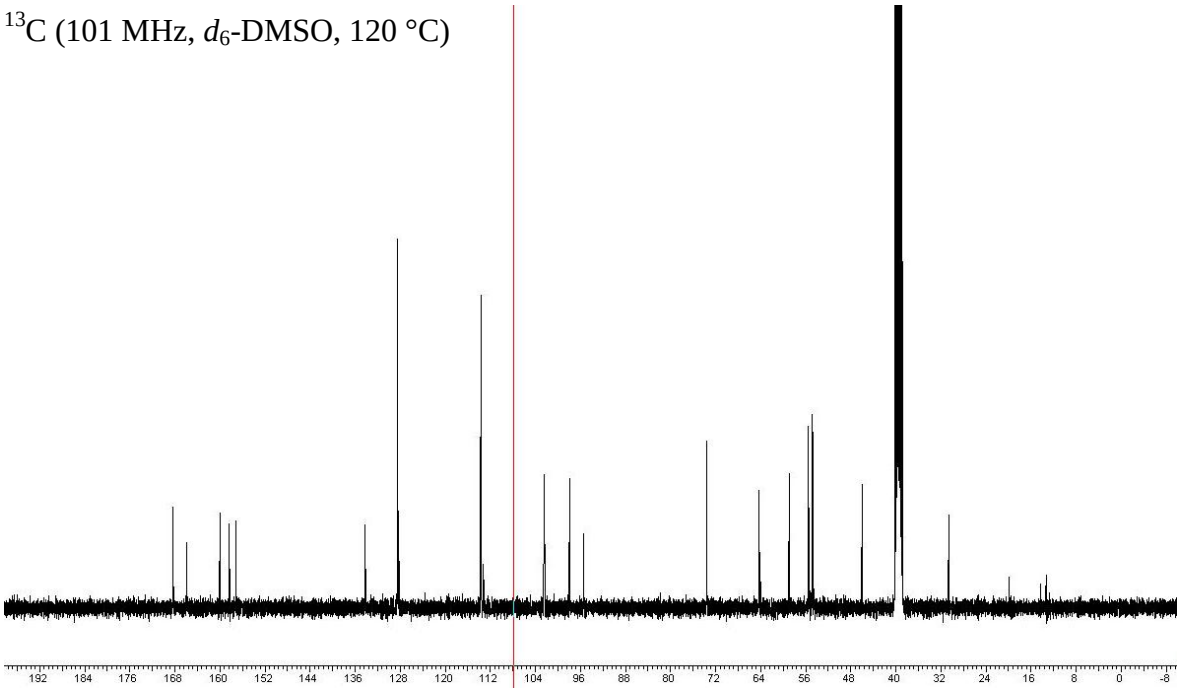


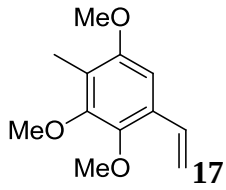


14

^{1}H (400 MHz, d_6-DMSO, 120 °C)

^{13}C (101 MHz, d_6-DMSO, 120 °C)

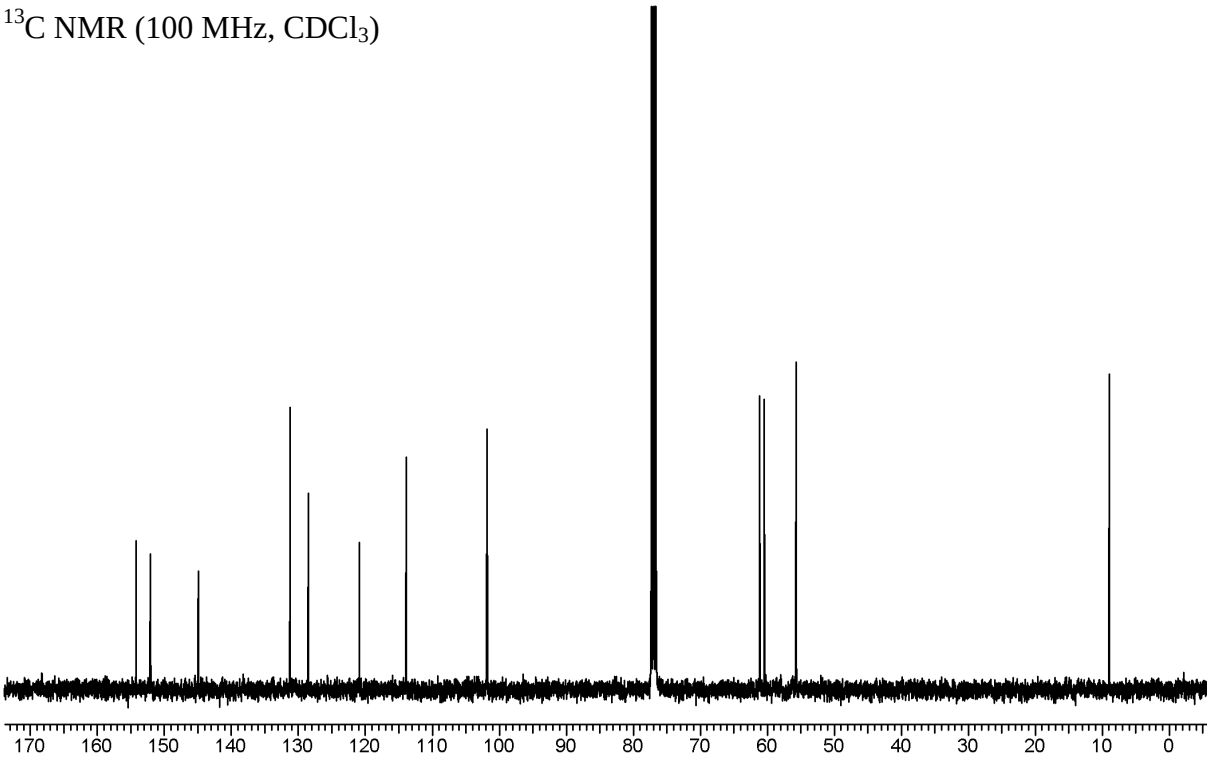


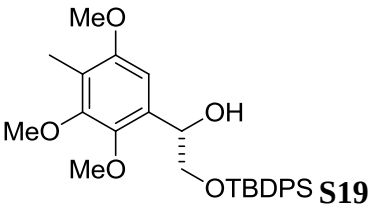


17

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

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

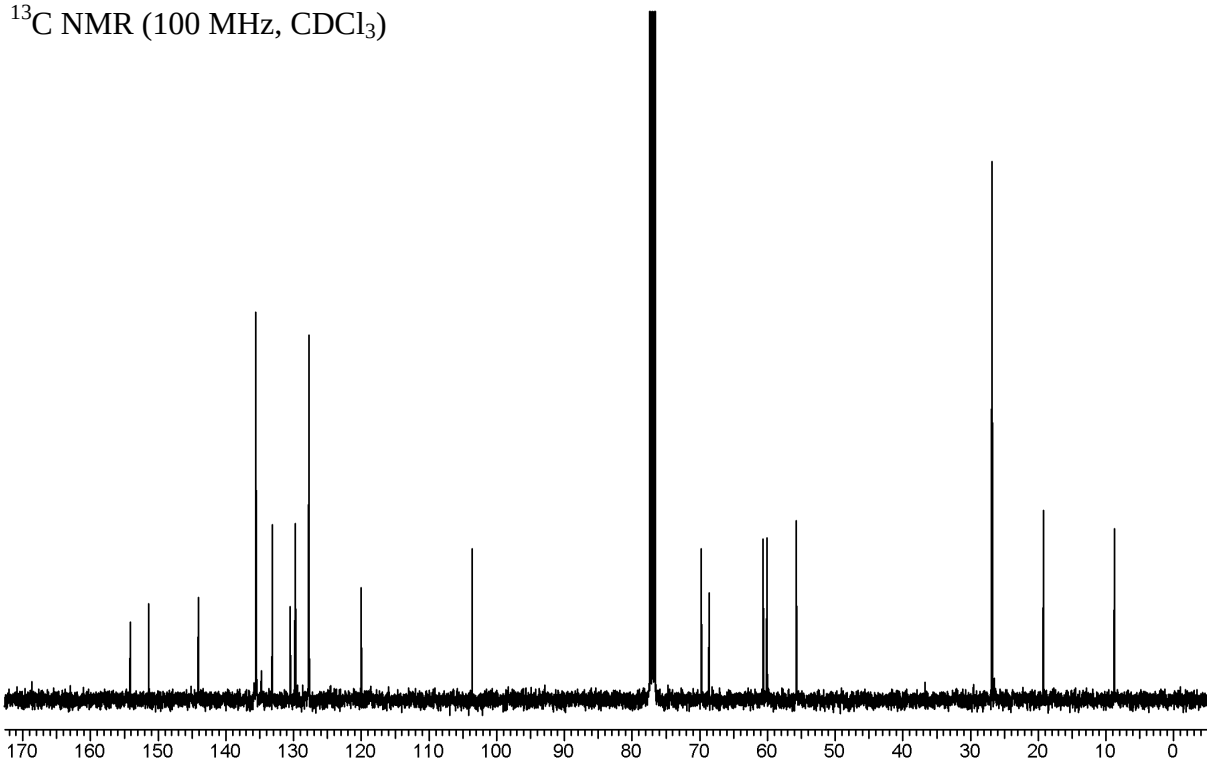


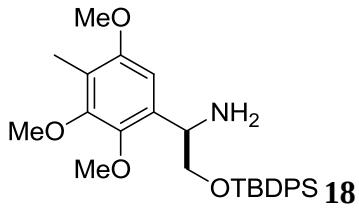


S19

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

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

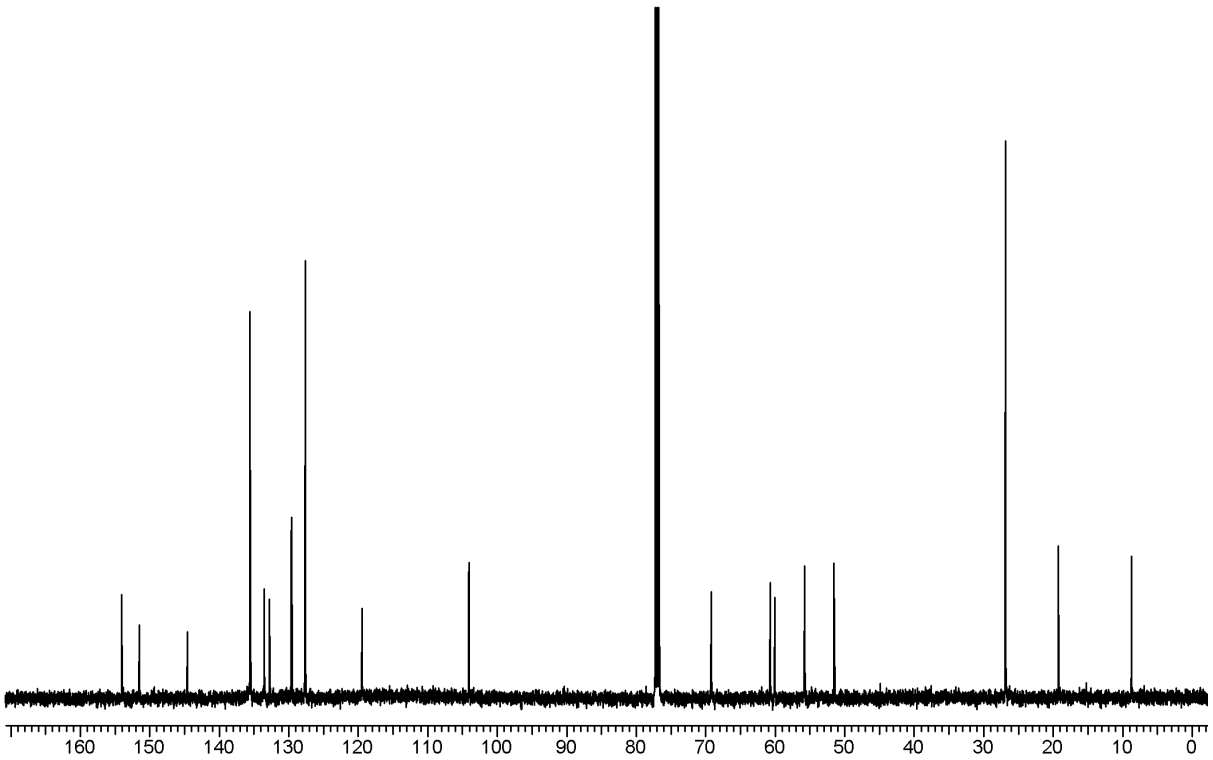


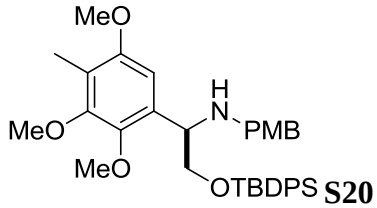


18

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

^{13}C NMR (125 MHz, $CDCl_3$)

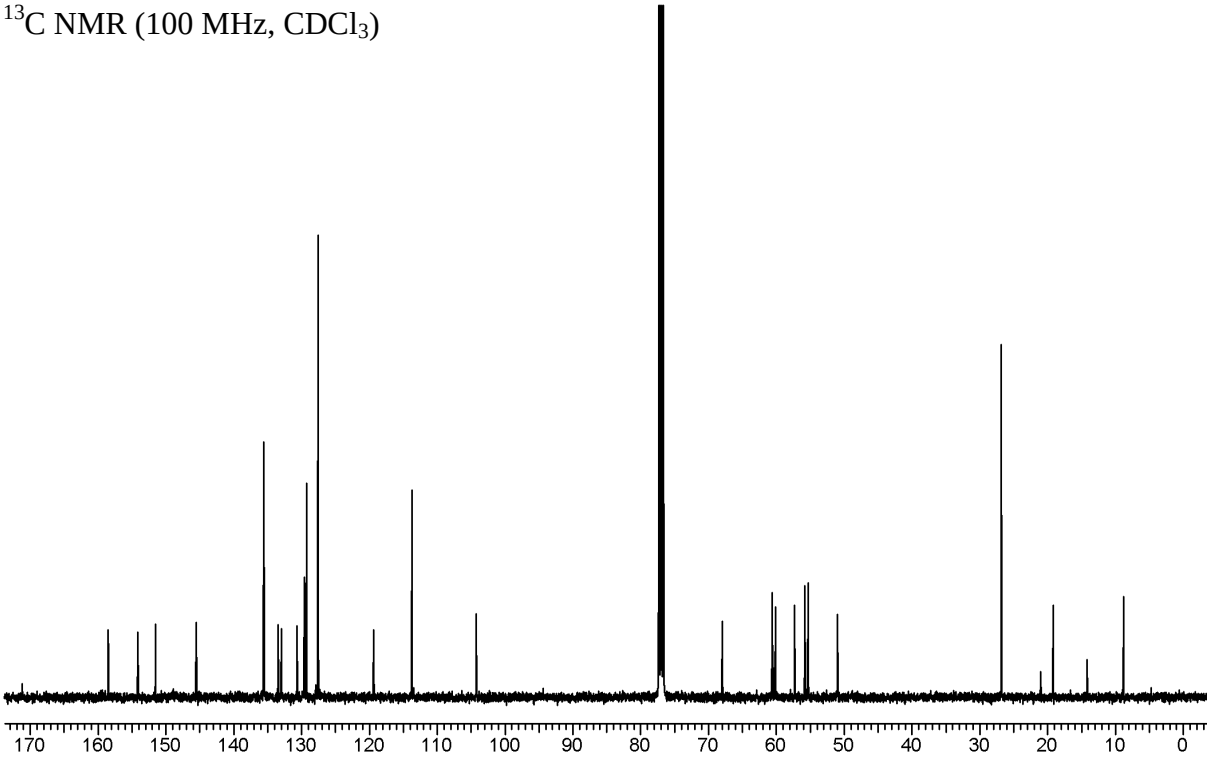


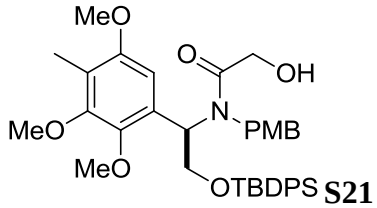


S20

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

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

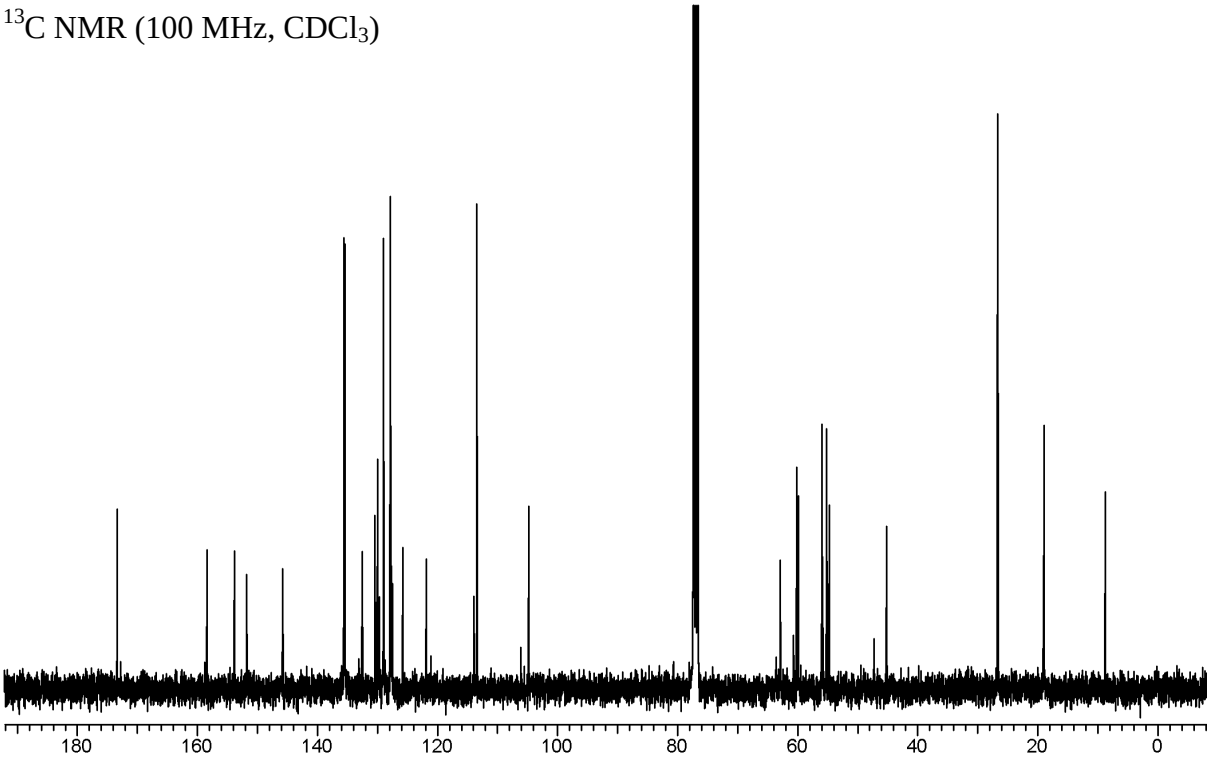


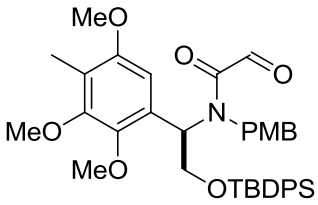


S21

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

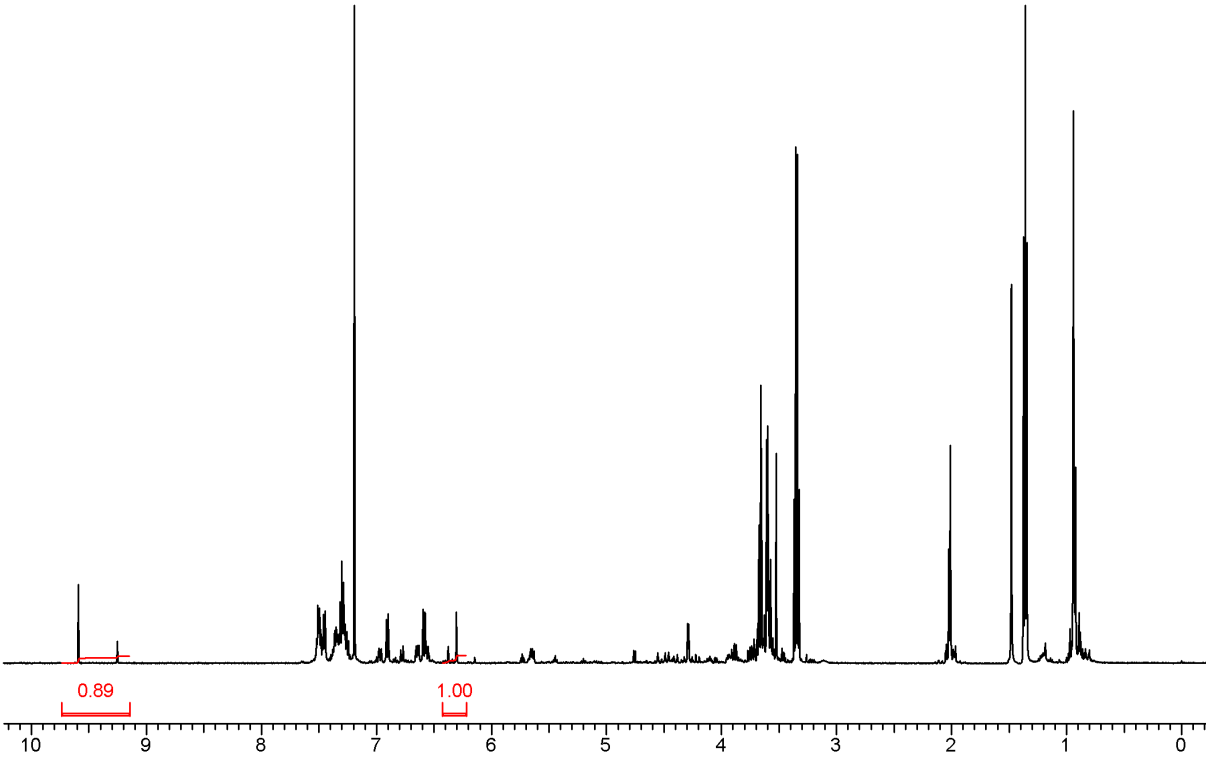
^{13}C NMR (100 MHz, $CDCl_3$)

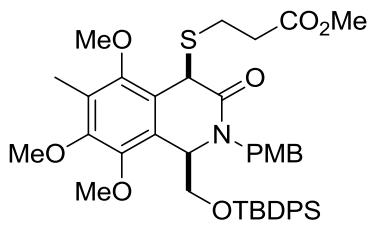




3 (P = Me)

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

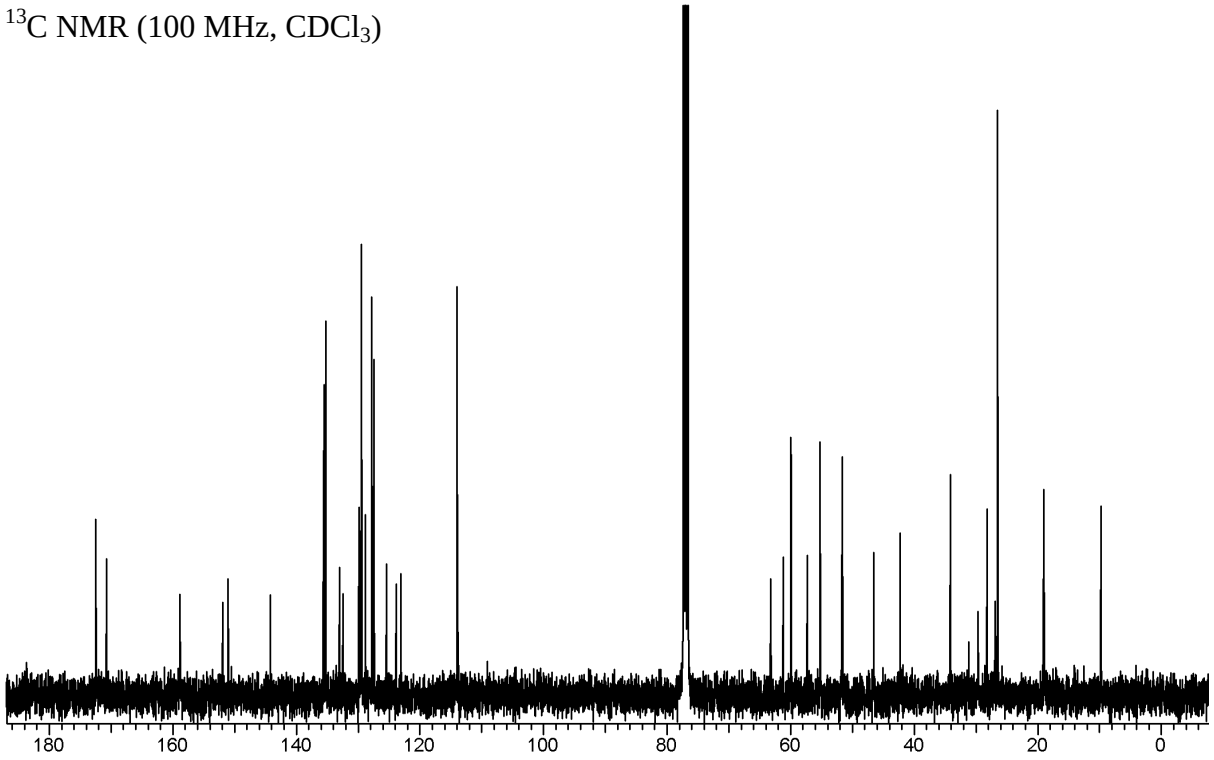


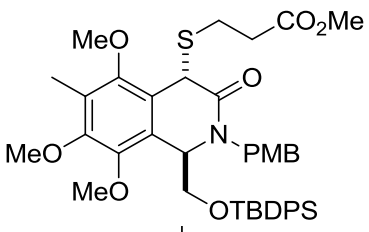


19a

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

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

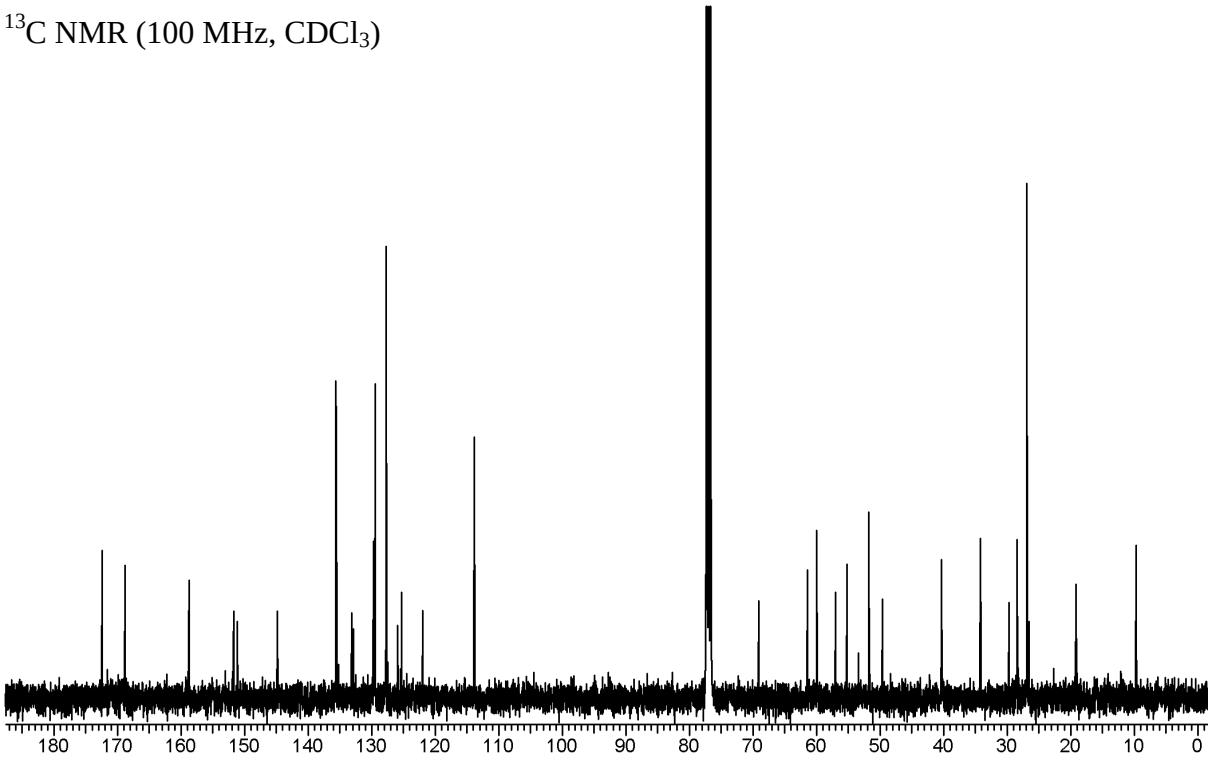


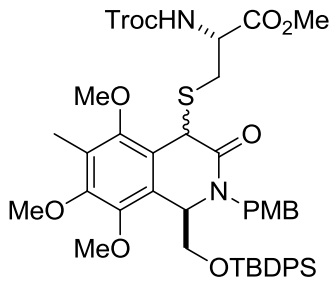


19b

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

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

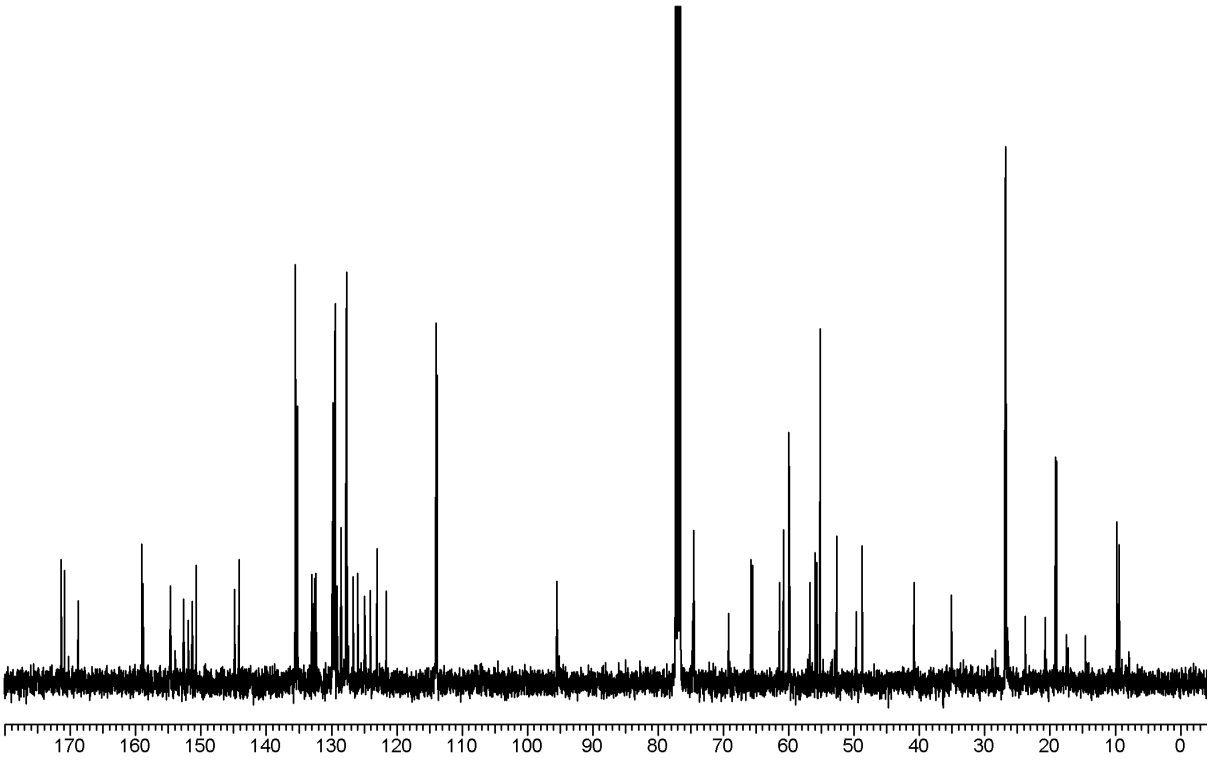


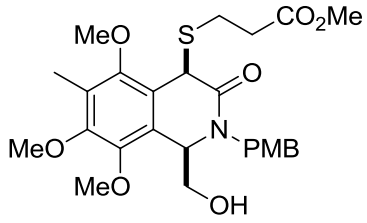


20a and **20b**

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

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

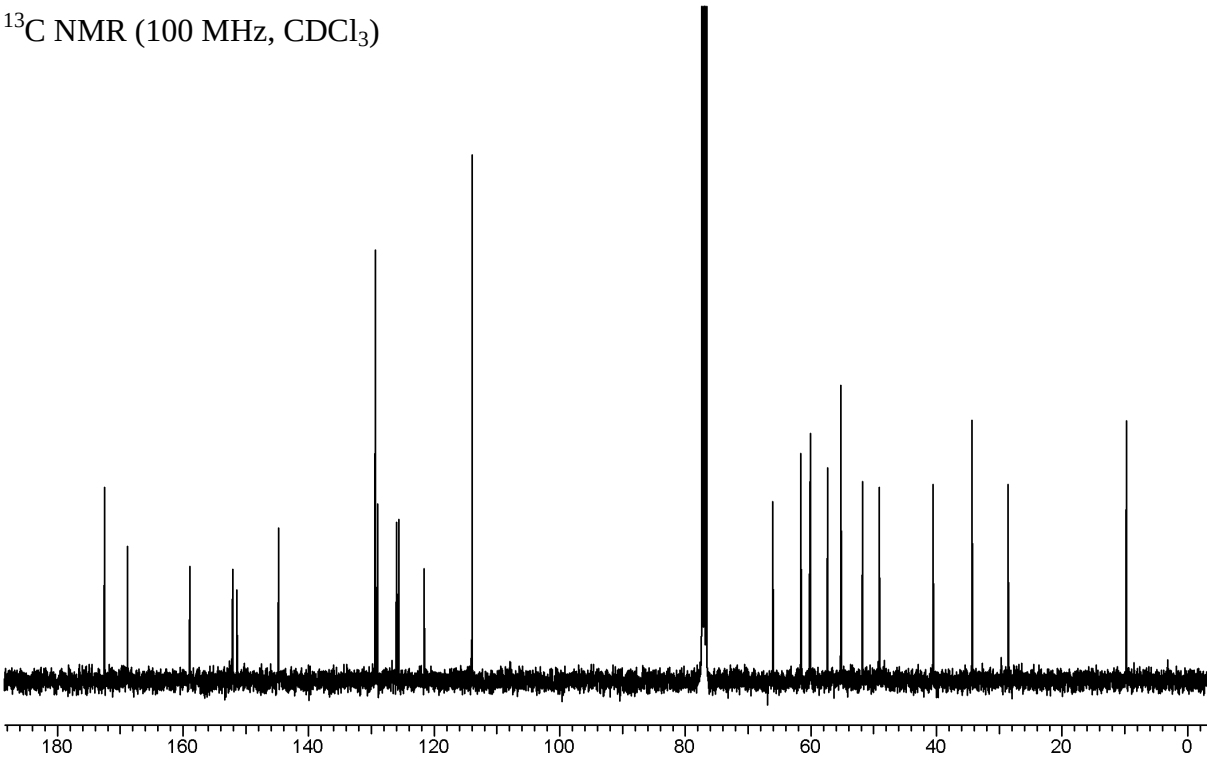


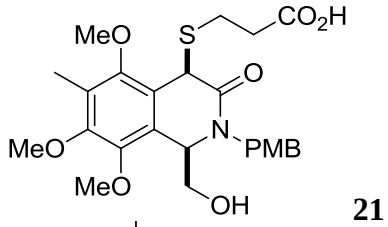


S22

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

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

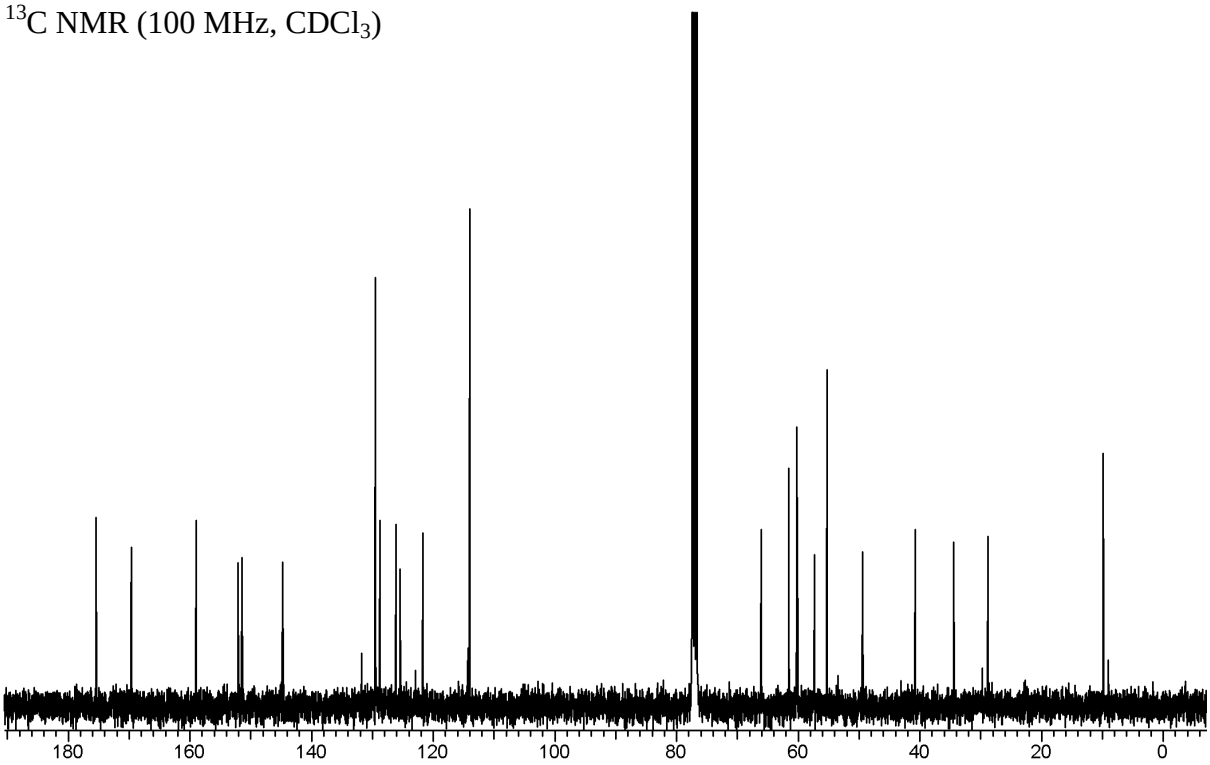


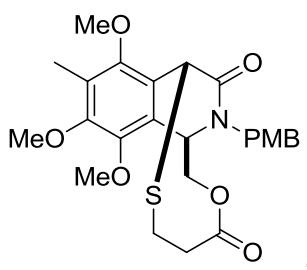


21

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

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

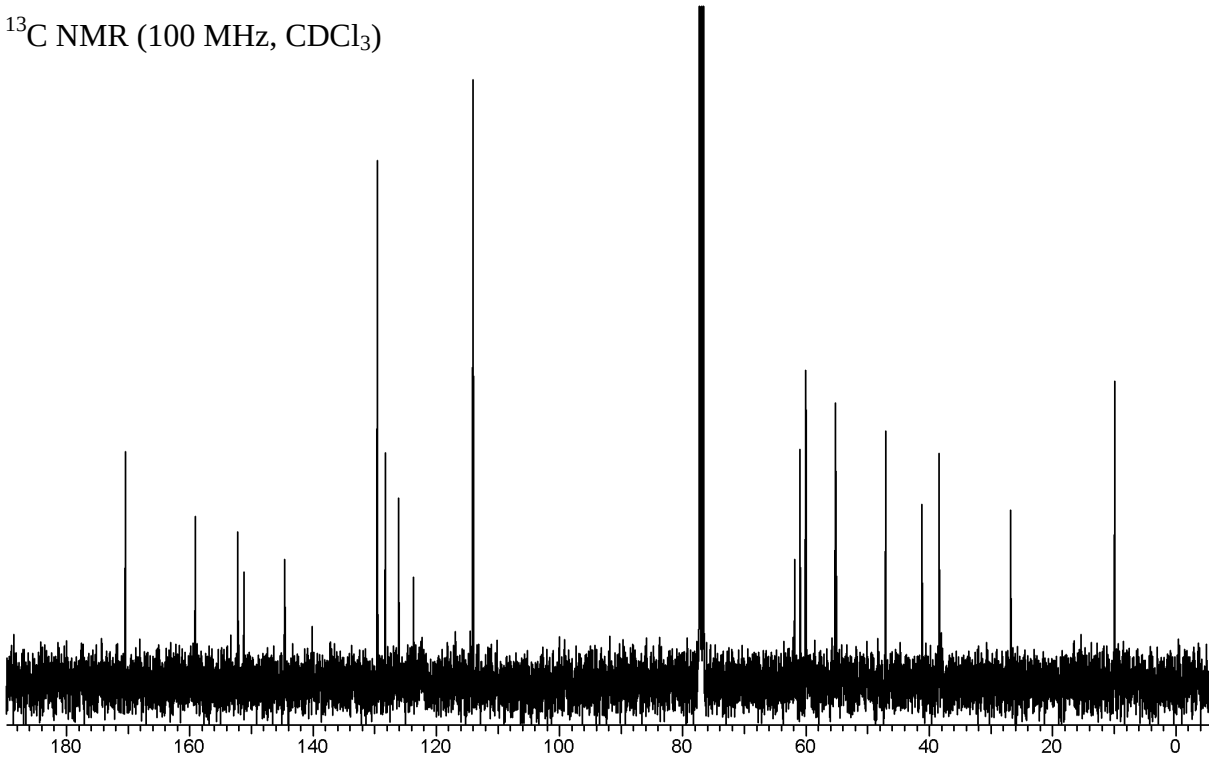


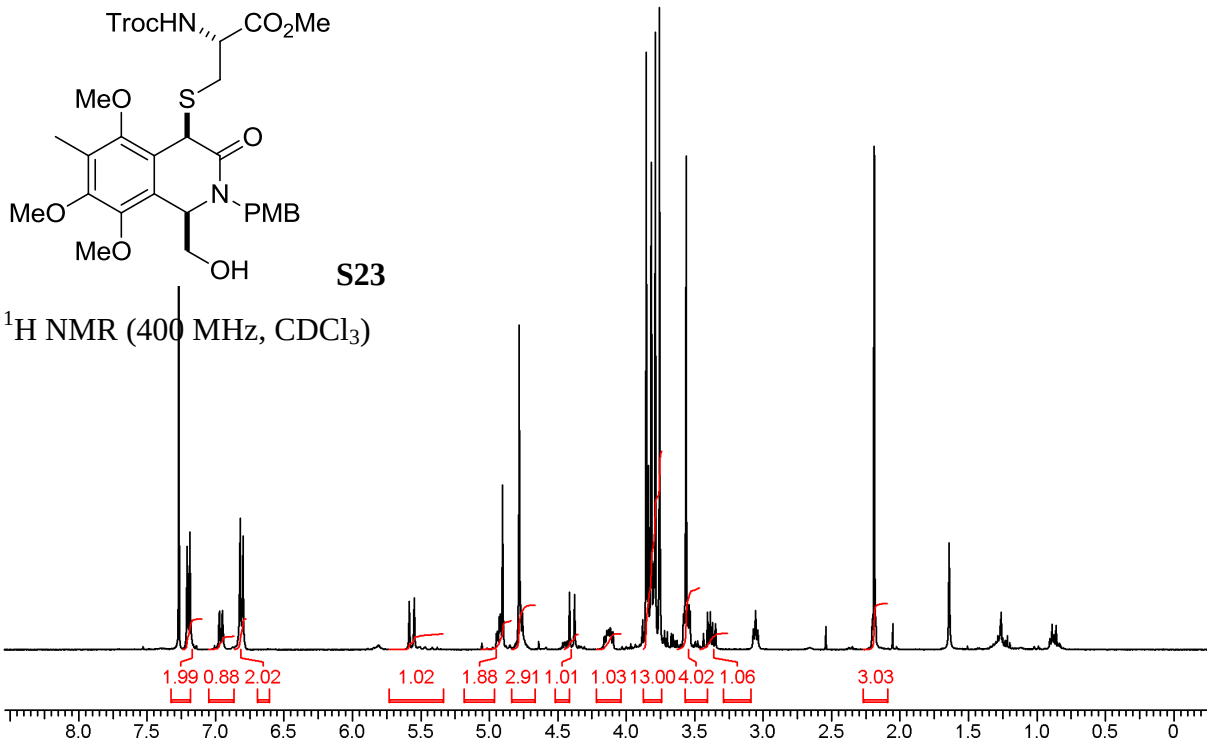


23

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

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

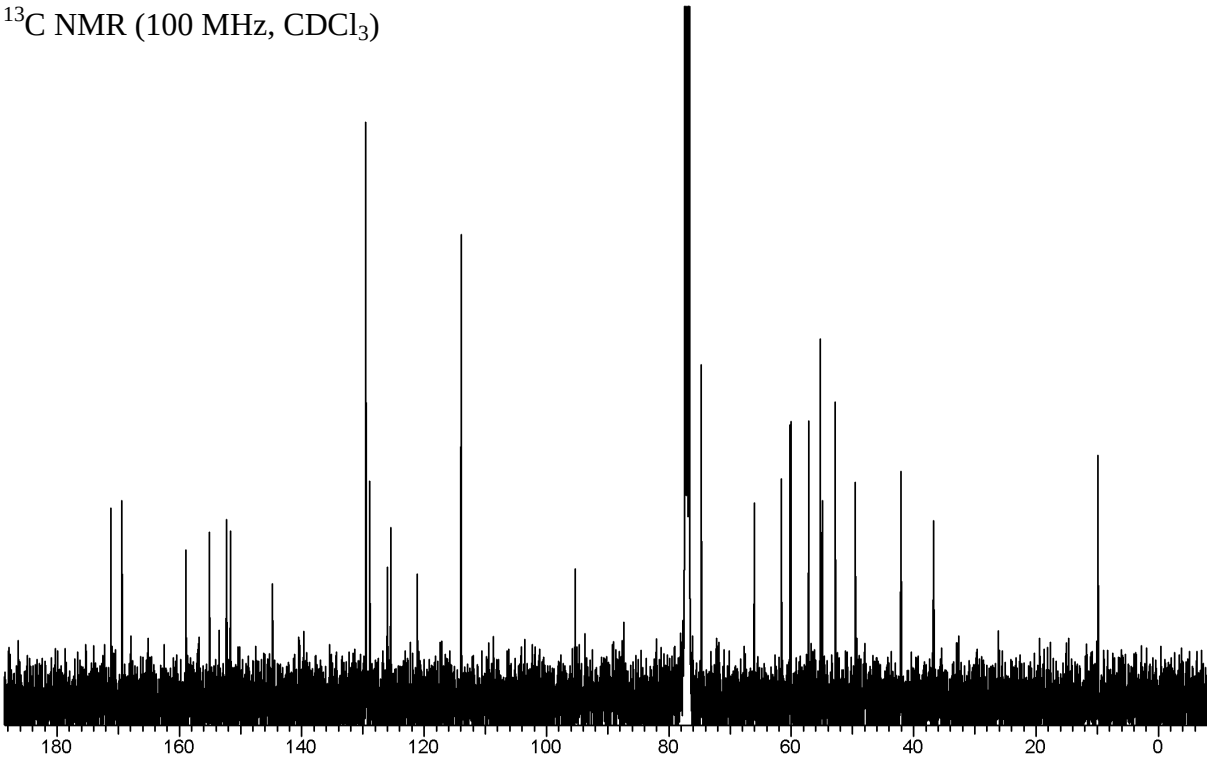


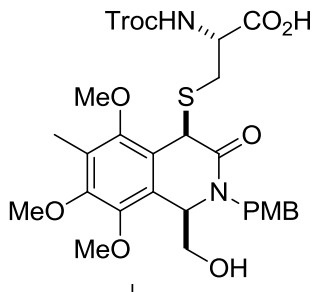


S23

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

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

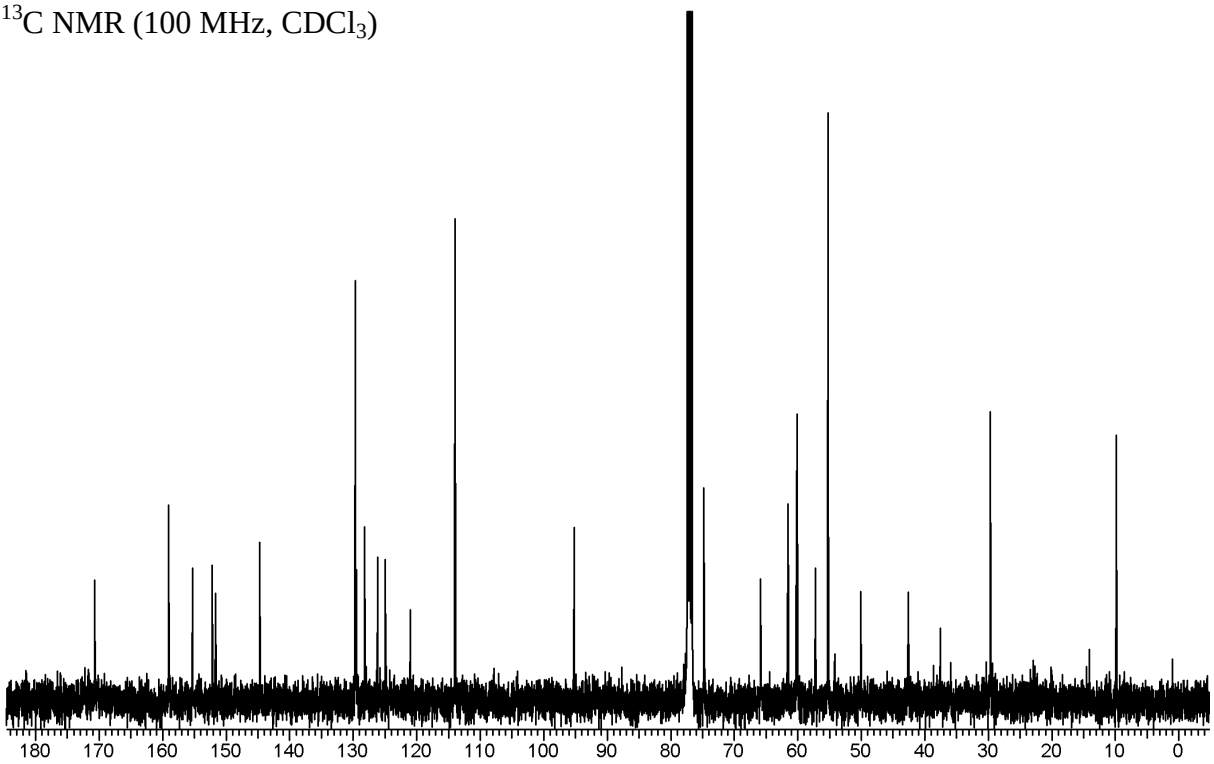


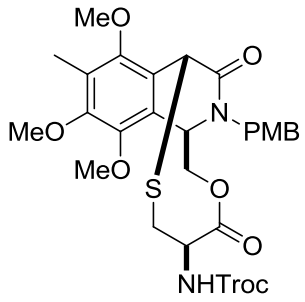


22

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

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

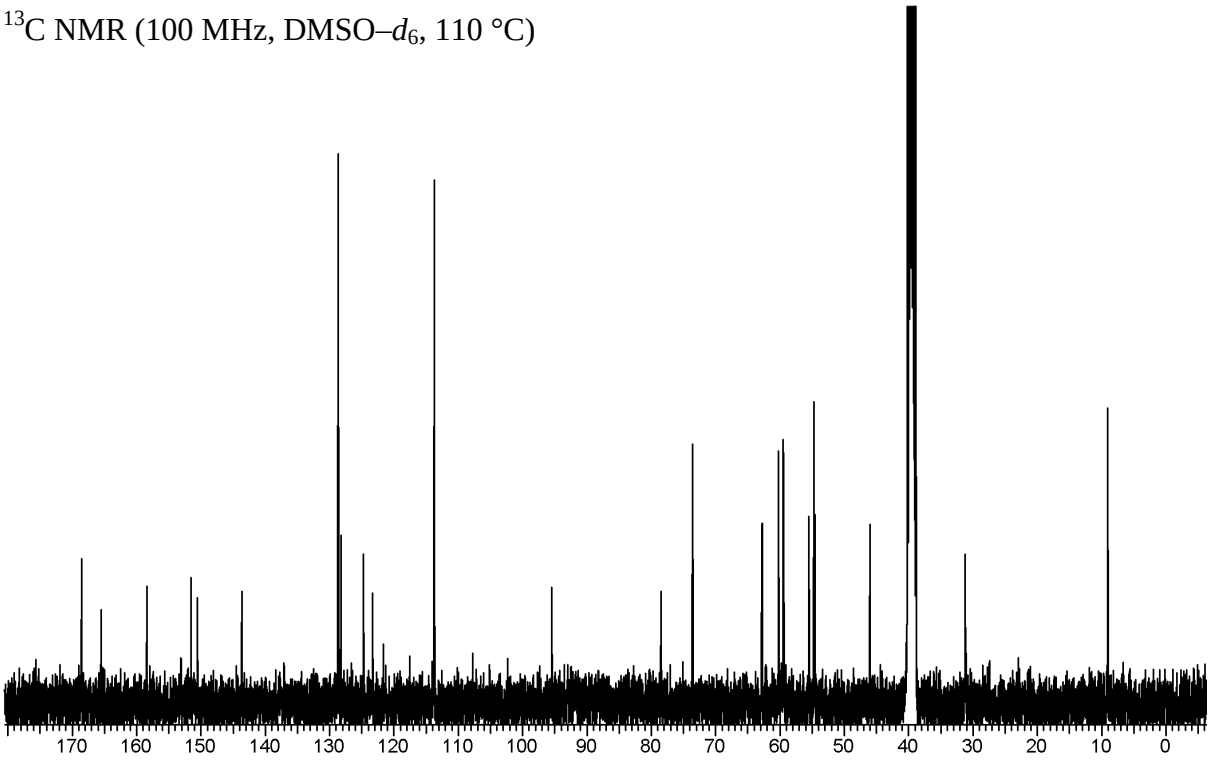




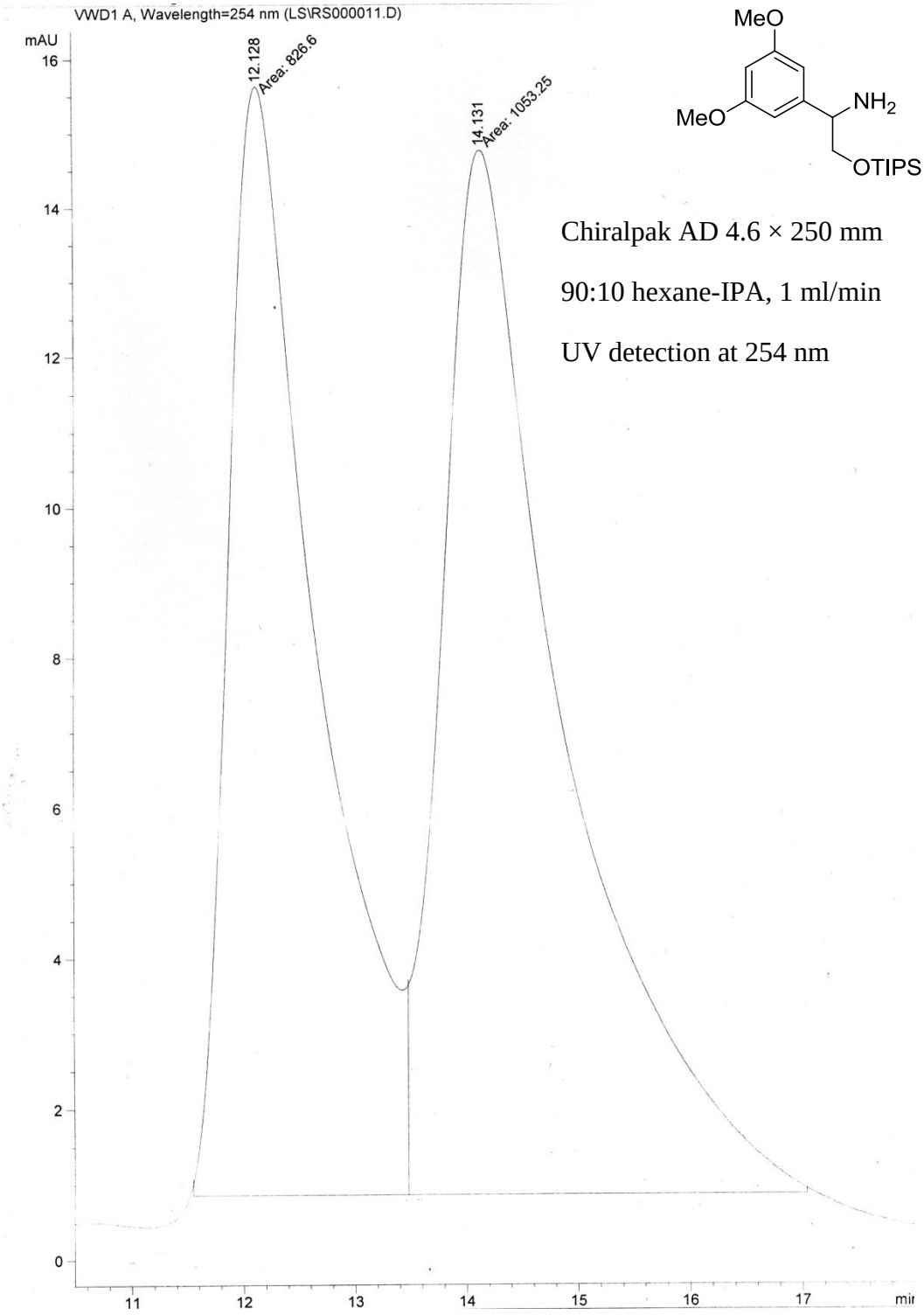
2

^{1}H NMR (400 MHz, DMSO–d_6, 110 °C)

^{13}C NMR (100 MHz, DMSO–d_6, 110 °C)



Chiral HPLC Chromatograms

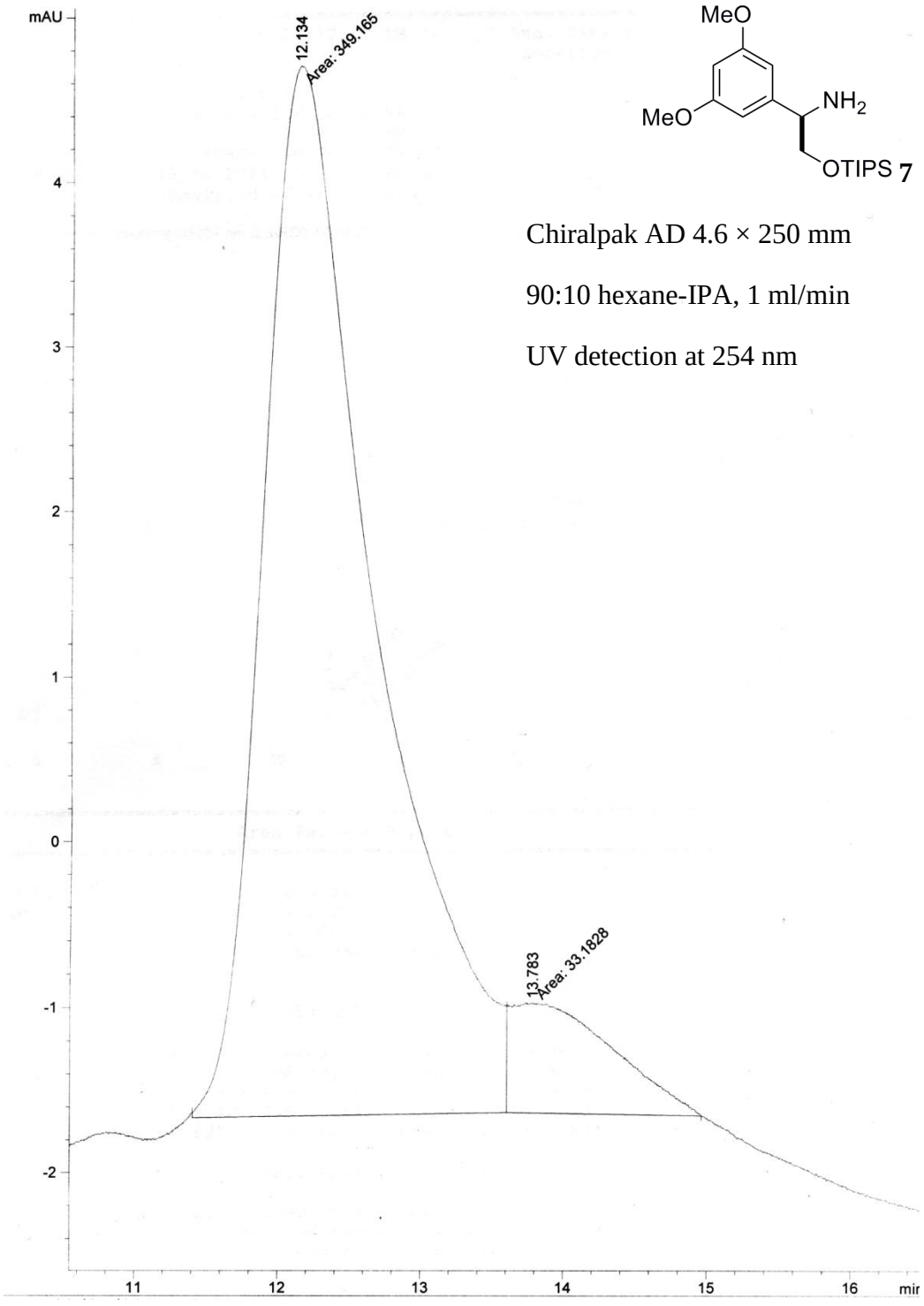


***Rac*-7**

Chiralpak AD 4.6 × 250 mm

90:10 hexane-IPA, 1 ml/min

UV detection at 254 nm

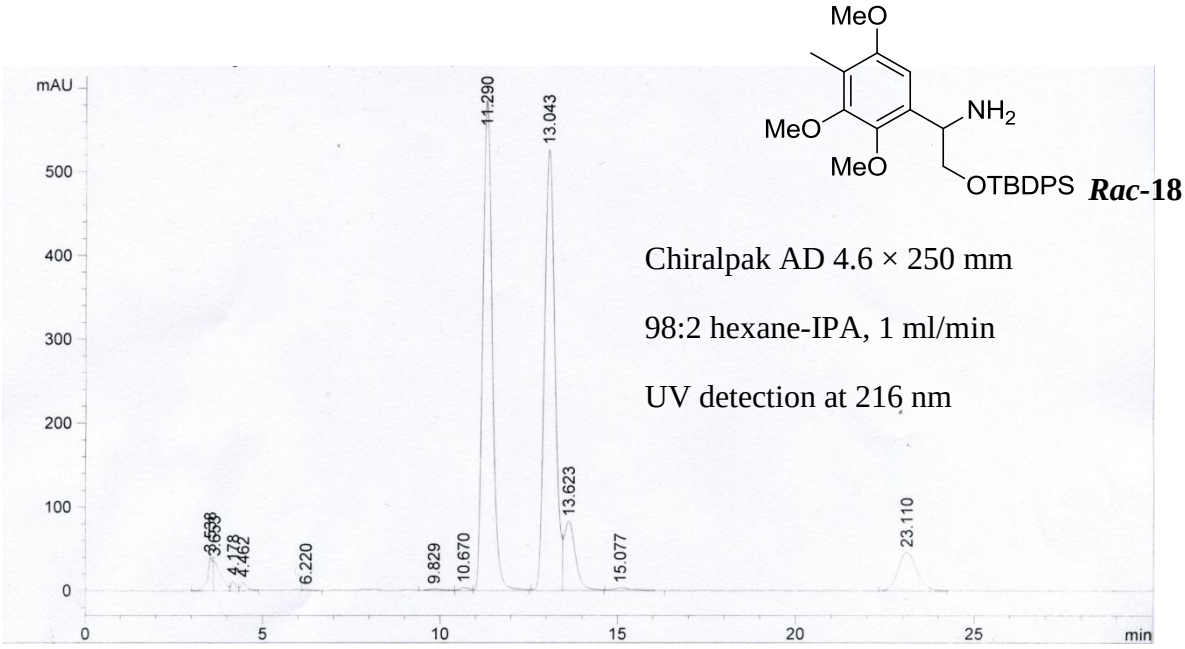


7

Chiralpak AD 4.6 × 250 mm

90:10 hexane-IPA, 1 ml/min

UV detection at 254 nm

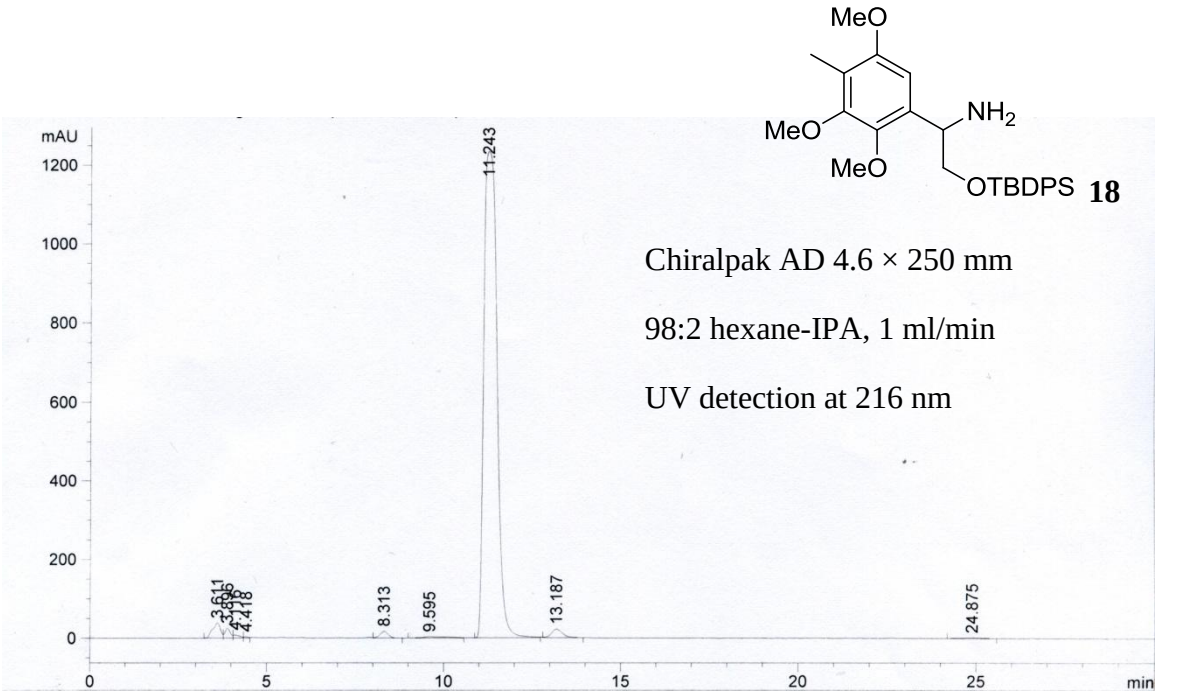


***Rac*-18**

Chiralpak AD 4.6 × 250 mm

98:2 hexane-IPA, 1 ml/min

UV detection at 216 nm



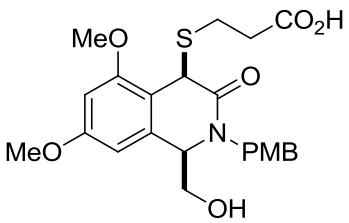
18

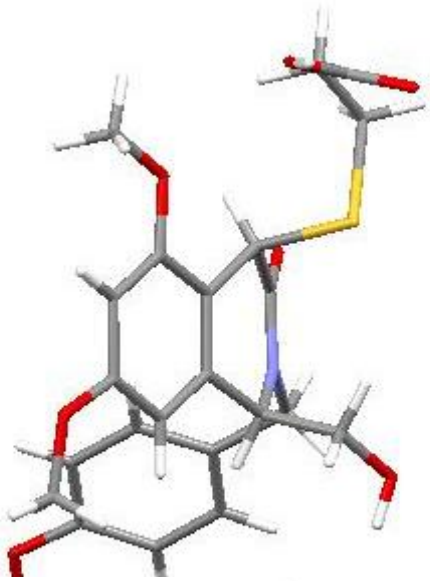
Chiralpak AD 4.6 × 250 mm

98:2 hexane-IPA, 1 ml/min

UV detection at 216 nm

X-Ray Crystal Structure of 11





$C_{23}H_{27}NO_7S$; M = 461.52

CCDC 808088

Crystal system: monoclinic

Space group: P2 1

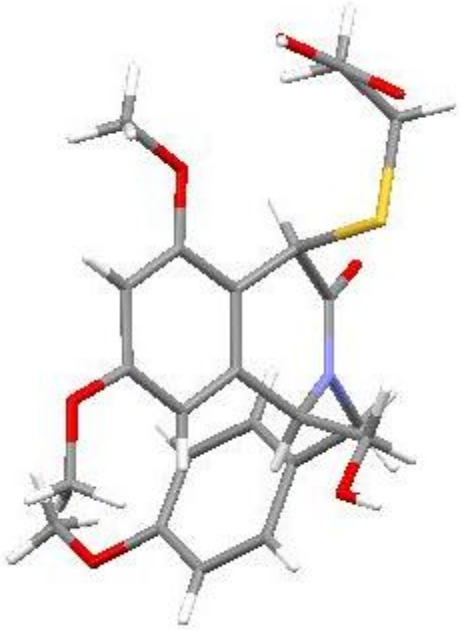
Unit cell dimensions:

a = 9.535(17) Å, b = 21.700(4) Å, c = 11.136(2) Å

α = 90 °, β = 103.28(3) °, γ = 90 °

Volume = 2237.4(7) $Å^3$

Z = 4



Reflections collected: 17909

Unique reflections: 8994

R_{int} = 0.0196

R1 (all data) = 0.0345

Temperature = 100 K

Diffractometer: Bruker Smart Apex CCD

Solution and refinement software: SHELXS 97; SHELXL 97

The structure was solved by the direct methods. All non-H atoms were refined anisotropically. H atoms bonded to C were included in calculated positions. Those bonded to O were found by difference Fourier techniques and refined isotropically. The absolute configuration was determined by refining the Flack parameter.[6]

[6] Burla M. C., Caliandro R., Camalli M., Carrozzini B., Cascarano G. L., De Caro L., Giacovazzo C., Polidori G. and Spagna R. *J. Appl. Cryst*., 2005, **38**, 381.
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