Supporting Information for:

Catalytic Enantioselective Allylic Amination of Olefins for the Synthesis of *ent*-Sitagliptin

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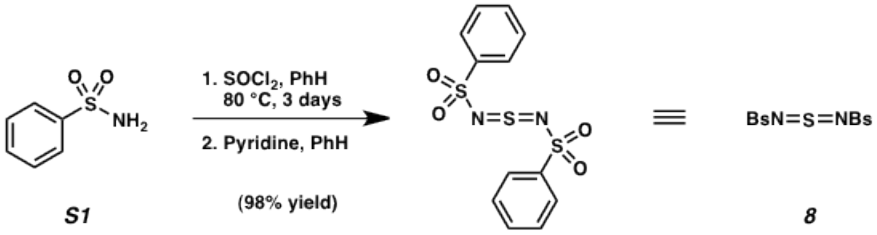
Materials and Methods

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring unless otherwise indicated. Commercially obtained reagents were used as received. All bisoxazoline and bisoxazolinyl-pyridine ligands **10a-h** were purchased from Sigma-Aldrich. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032 - 0.063 mm) purchased from SiliCycle was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400 or 500 spectrometers. Data for ^{1}H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.50 ppm) as an internal standard and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported relative to chloroform as an internal standard (77.23 ppm) and are reported in terms of chemical shift (δ ppm). Optical rotations were measured on a JAS DIP-360 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. Chiral HPLC analyses were performed on an Agilent 1200 Series system. HRMS data were obtained at The Scripps Center for Mass Spectrometry.

Synthesis of Benzenesulfonyl Sulfurdiimide 8



S1 *8*

Our procedure was modified from a method reported in the literature for the synthesis of similar arylsulfonyl sufurdiimides[1]: A solution of benzenesulfonamide **S1** (50 g, 0.318 mol) and $SOCl_2$ (80 mL, 1.1 mol) in benzene (30 mL) was refluxed at 80 °C for 3 days (over the course of the reaction, the mixture became a clear solution). When the starting material was consumed by ^1H NMR analysis of an aliquot, the mixture was concentrated under vacuum to remove benzene and excess $SOCl_2$. Trace amounts of $SOCl_2$ were removed by redissolving the residue in toluene (50 mL), concentrating under reduced pressure, and storing under vacuum at 50 °C for 6 h. The residue was then treated with benzene (70 mL) and heated slightly to ensure all material dissolved in the solvent. Once the solution was cooled to 23 °C, pyridine (0.5 mL) was added, and the mixture was stirred. After 12 h, stirring was ceased, and a yellow precipitate crystallized slowly from the solution. The precipitate was separated by vacuum filtration and stored under vacuum at 50 °C for 8 h. Benzensulfonyl sulfurdiimide **8** was obtained as a yellow solid (53.5 g, 98% yield). *Since benzenesulfonyl sulfurdiimide **8** is sensitive to water, we store it in a dessicator inside a sealed flask that has been purged with N_2. Optimal results for the enantioselective allylic amination were obtained when benzenesulfonyl sulfurdiimide **8** was broken into a fine powder immediately before use.*

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 135.0, 129.6, 128.3. IR (thin film): 3348, 3255, 1557, 1332, 1159 cm^{-1}.

*Although we continue to synthesize benzensulfonyl sulfurdiimide **8** in our lab, Sigma-Aldrich has commercialized this reagent based on conversations with our group about its synthetic utility (Catalog # L511390, $25/gram).*

Synthesis of Unactivated Olefins

Olefin **2b** was purchased from Sigma-Aldrich, and olefin **2c** was purchased from GFS Chemicals.

2b *2c*

Olefins **2d** and **2e**, and trifluorophenyl butene **7** were prepared by reacting the corresponding benzyl bromides with allylmagnesium chloride according to the procedure of Molander[2]:

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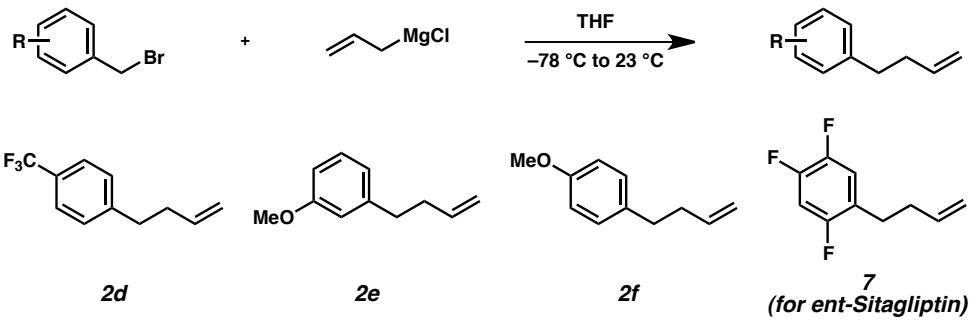
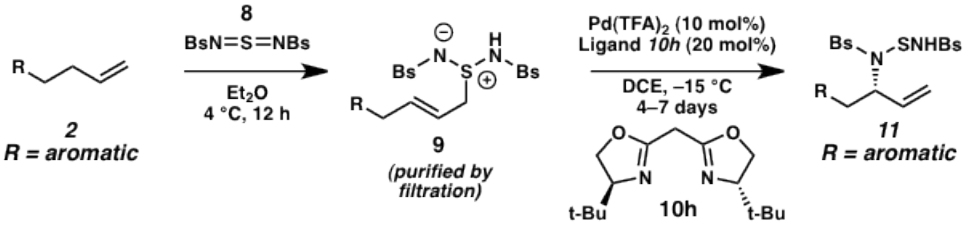
[1] Smyth, T. P.; O'Donnell, M. E.; O'Connor, M. J.; St. Ledger, J. O. *J. Org. Chem.* **1998**, *63*, 7600.

[2] Molander, G. A.;Sandrock, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 15792.

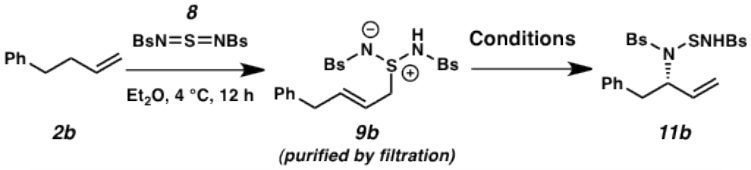


General Procedure for the Catalytic Enantioselective Allylic Amination



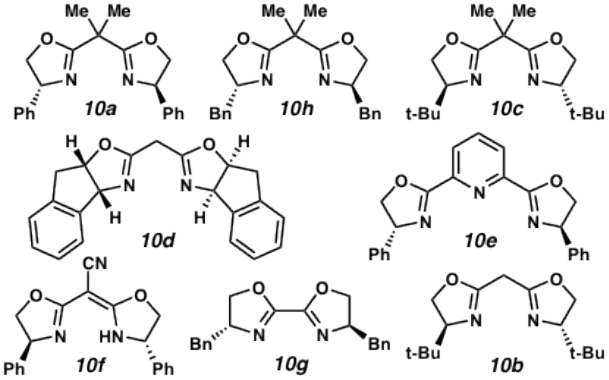
A solution of benzenesulfonyl sulfurdiimide **8** (685 mg, 2 mmol) in Et_2O (4 mL, 0.5 M) was cooled to 0 °C and treated with the terminal olefin **2** (6–10 mmol, 3–5 equiv). The reaction was stirred at 4 °C for 12 h. The ene adduct **9**, which formed a white precipitate, was purified at room temperature by vacuum filtration, washed with Et_2O (20–40 mL), and dried under vacuum. The ene adduct **9** was then suspended in DCE (1,2-dichloroethane, 5 mL) and cooled to –20 °C. The solution was treated with the palladium-ligand complex in DCE (10 mL), which was made by premixing $Pd(TFA)_2$ (10 mol%) and ligand **10b** (20 mol%) in DCE (10 mL) and stirring for 30 min at 50 °C. The reaction was warmed to –15 °C and stirred for 4-7 days.

Optimization of the Catalytic Enantioselective Allylic Amination (Table S1)



2b *9b* (purified by filtration) *11b*

Entry	Metal Catalyst (10 mol%)	Ligand (12 mol%)	Solvent (0.13M)	Temp (°C)	Time (d)	Yield[a]	ee (%)
1	–	–	CH_2Cl_2	4	0.5	< 5	–
2	$Pd(TFA)_2$	10a	MeOH	4	2	91	4
3	$Pd(OAc)_2$	10a	CH_2Cl_2	4	0.5	71	19
4	$Pd(OAc)_2$	10h	CH_2Cl_2	4	0.5	60	0
5	$Pd(OAc)_2$	10c	CH_2Cl_2	4	0.5	73	33
6	$Pd(OAc)_2$	10d	CH_2Cl_2	4	0.5	60	0
7	$Pd(OAc)_2$	10e	CH_2Cl_2	4	0.5	7	10
8	$Pd(OAc)_2$	10f	CH_2Cl_2	4	0.5	47	0
9	$Pd(OAc)_2$	10g	CH_2Cl_2	4	0.5	60	0
10	$Pd(OAc)_2$	10b	CH_2Cl_2	4	0.5	75	79
11	$Pd_2(dba)_3$	10b	CH_2Cl_2	4	2	60	0
12	$PdCl_2(CH_3CN)_2$	10b	CH_2Cl_2	4	2	63	6
13	$Pd(acac)_2$	10b	CH_2Cl_2	4	2	73	0
14	$Pd(TFA)_2$	10b	CH_2Cl_2	4	2	80	85
15	$Pd(TFA)_2$	10b	CH_3CN	4	2	75	6
16	$Pd(TFA)_2$	10b	$MeNO_2$	4	2	80	32
17	$Pd(TFA)_2$	10b	THF	4	2	82	49
18	$Pd(TFA)_2$	10b	DMF	4	2	99	58
19	$Pd(TFA)_2$	10b	Et_2O	4	2	70	79
20	$Pd(TFA)_2$	10b	PhMe	4	3	90	79
21	$Pd(TFA)_2$	10b	Dioxane	4	0.5	75	85
22	$Pd(TFA)_2$	10b	$PhCF_3$	4	3	85	90
23	$Pd(TFA)_2$	10b	MeOH	4	2	91	90
24	$Pd(TFA)_2$	10b	DCE	4	2	94	91
25	$Pd(TFA)_2$	10b[b]	DCE	–15	7	94	93



Characterization Data for Ene Adducts 9

*Ene adducts **9** undergo facile [2,3]-rearrangement at ambient temperature. Therefore, we assayed the identity and purity of these compounds by rapid NMR spectral analysis. The allylic amination products **11** were then fully characterized after [2,3]-rearrangement (vide infra).*

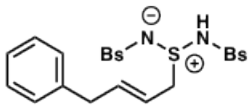


Table 2, entry 1: Following the general procedure for ene adduct formation (in Et_2O at 4 °C for 12 h), purification by vacuum filtration (washing with Et_2O) afforded the product as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.79 (d, *J* = 8.0 Hz, 4H), 7.55 (t, *J* = 7.0 Hz, 2H), 7.44 (dd, *J* = 8.0 Hz, *J* = 7.0 Hz, 4H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.06 (dt, *J* = 15.0 Hz, *J* = 7.0 Hz, 1H), 5.37 (dt, *J* = 15.0 Hz, *J* = 8.0 Hz, 1H), 4.14 (d, *J* = 8.0 Hz, 2H), 3.31 (d, *J* = 7.0 Hz, 2H).

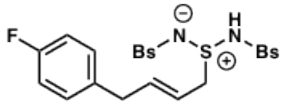


Table 2, entry 2: Following the general procedure for ene adduct formation (in Et_2O at 4 °C for 12 h), purification by vacuum filtration (washing with Et_2O) afforded the product as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.78 (d, *J* = 7.5 Hz, 4H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 4H), 7.07-6.96 (m, 4H), 6.05 (dt, *J* = 15.5 Hz, *J* = 7.0 Hz, 1H), 5.37 (dt, *J* = 15.5 Hz, *J* = 8.0 Hz, 1H), 4.14 (d, *J* = 8.0 Hz, 2H), 3.29 (d, *J* = 7.0 Hz, 2H).

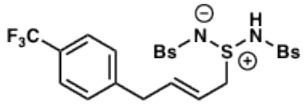


Table 2, entry 3: Following the general procedure for ene adduct formation (in Et_2O at 4 °C for 12 h), purification by vacuum filtration (washing with Et_2O) afforded the product as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.70 (d, *J* = 8.0 Hz, 4H), 7.50 (t, *J* = 7.0 Hz, 2H), 7.38 (dd, *J* = 8.0 Hz, , *J* = 7.0 Hz, 4H), 7.10 (s, 4H), 6.04 (dt, *J* = 16.0 Hz, *J* = 7.5 Hz, 1H), 5.40 (dt, *J* = 17.0 Hz, *J* = 7.0 Hz, 1H), 4.18 (d, *J* = 7.5 Hz, 2H), 3.31 (d, *J* = 7.0 Hz, 2H).

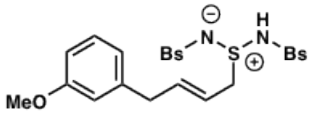


Table 2, entry 4: Following the general procedure for ene adduct formation (in Et_2O at 4 °C for 12 h), purification by vacuum filtration (washing with Et_2O) afforded the product as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.70 (d, *J* = 8.0 Hz, 4H), 7.54 (t, *J* = 7.0 Hz, 2H), 7.44 (dd, *J* = 8.0 Hz, , *J* = 7.0 Hz, 4H), 7.00(d, *J* = 8.5 Hz), 6.72 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 6.62 (s, 1H), 6.04 (dt, *J* = 15.0 Hz, *J* = 6.5 Hz, 1H), 5.40 (dt, *J* = 15.0 Hz, *J* = 6.0 Hz, 1H), 4.16 (d, *J* = 6.5 Hz, 2H), 3.28 (d, *J* = 6.0 Hz, 2H).

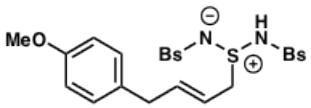


Table 2, entry 5: Following the general procedure for ene adduct formation (in Et_2O at 4 °C for 12 h), purification by vacuum filtration (washing with Et_2O) afforded the product as a white solid : ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.92 (d, *J* = 8.0 Hz, 4H), 7.81 (t, *J* = 7.0 Hz, 2H), 7.44 (dd, *J* = 8.0 Hz, , *J* = 7.0 Hz, 4H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.01-5.98 (m, 1H), 5.30-5.28 (m, 1H), 4.06 (d, *J* = 7.5 Hz, 2H), 3.78 (s, 3H), 3.18 (d, *J* = 7.0 Hz, 2H).

Characterization Data for Allylic Amination Products 11

At ambient temperature, most of the allylic amination products ***11*** *yielded ^{1}H NMR spectra with a mixture of rotamers. Therefore, we performed the majority of these ^{1}H NMR experiments at 50 °C to simplify the analysis of the spectra.*

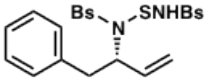


Table 2, entry 1: Following the general procedure for catalytic enantioselective allylic amination (in DCE at –15 °C for 7 d), purification by flash chromatography (20:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded the product (887 mg, 94 % yield for two steps) as a clear oil. The enantiomeric excess of the product was determined to be 93% by comparison to a sample of the racemate (see HPLC trace below). $[\alpha]^{23}_D$ = +93.0° (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C), δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 4H), 7.37 (m, 2H), 7.18-7.10 (m, 6H), 6.95 (s, 1H), 6.10 (bs, 1H), 5.07 (m, 2H), 4.80 (m, 1H), 3.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C), δ 140.9, 139.6, 137.8, 133.4, 133.3, 129.6, 129.4, 129.1, 128.6, 127.9, 127.3, 126.7, 118.9, 68.2, 39.9. IR (thin film): 3234, 1447, 1352, 1165, 1088, 806 cm^{-1}. HRMS (ESI) calcd for $[C_{22}H_{22}N_2O_4S_3Na]^+$ ([M+Na]$^+$): 497.0634, found 497.0645.

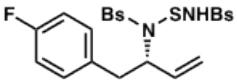


Table 2, entry 2: Following the general procedure for catalytic enantioselective allylic amination (in DCE at –15 °C for 5 d), purification by flash chromatography (20:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded the product (910 mg, 89 % yield for two steps) as a clear oil. The enantiomeric excess of the product was determined to be 90% by comparison to a sample of the racemate (see HPLC trace below). $[\alpha]^{23}_D$ = +61.7° (c = 2.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C), δ 7.93 (d, *J* = 7.5 Hz, 2H), 7.69 (bs, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 4H), 7.39-7.35 (m, 3H), 7.08 (m, 2H), 6.86 (m, 2H), 6.10 (bs, 1H), 5.08 (m, 2H), 4.74 (m, 1H), 3.25-3.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C), δ 161.8 (*J* = 243 Hz), 140.8, 139.5, 133.4, 133.3, 130.9 (*J* = 8.0 Hz), 129.4, 129.1, 127.8, 127.2, 118.9, 115.3 (*J* = 21 Hz), 68.3, 39.1. IR (thin film): 3237, 1602, 1509, 1448, 1352, 116 cm^{-1}. HRMS (ESI) calcd for $[C_{22}H_{22}FN_2O_4S_3]^+$ ([M+H]$^+$): 493.0720, found 493.0718.

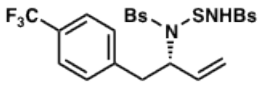


Table 2, entry 3: Following the general procedure for catalytic enantioselective allylic amination (in DCE at –15 °C for 5 d), purification by flash chromatography (20:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded the product (860 mg, 79 % yield for two steps) as a clear oil. The enantiomeric excess of the product was determined to be 90% by comparison to a sample of the racemate (see HPLC trace below). $[\alpha]^{23}_{D}$ = +57.2° (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 50 ^{o}C), δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.73 (bs, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 4H), 7.39 (m, 2H), 7.13 (m, 3H), 7.05 (m, 2H), 6.10 (bs, 1H), 5.08 (m, 2H), 4.74 (m, 1H), 3.29-3.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 ^{o}C) δ 183.27, 148.27, 140.91, 139.57, 136.56, 133.56, 133.52, 130.91, 129.48, 129.18, 127.90, 127.28, 122.05, 120.94, 119.49, 119.23, 77.55, 77.23, 76.91, 68.31, 39.16. IR (thin film): 3238, 1509, 1354, 1262, 1166, 1088 cm^{-1}. HRMS (ESI) calcd for $[C_{22}H_{22}FN_2O_4S_3]^+$ ($[M+H]^+$): 493.0720, found 493.0718.

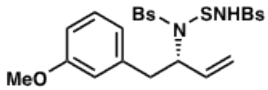


Table 2, entry 4: Following the general procedure for catalytic enantioselective allylic amination (in DCE at –15 °C for 4 d), purification by flash chromatography (20:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded the product (840 mg, 83 % yield for two steps) as a clear oil. The enantiomeric excess of the product was determined to be 95% by comparison to a sample of the racemate (see HPLC trace below). $[\alpha]^{23}_{D}$ = +84.4° (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 50 ^{o}C), δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.73-7.68 (m, 3H), 7.53 (t, *J* = 7.0 Hz, 4H), 7.39 (m, 2H), 7.12 (m, 1H), 6.97 (s, 1H), 6.12 (bs, 1H), 5.10 (m, 2H), 4.82 (m, 1H), 3.76 (s, 3H), 3.26-3.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 ^{o}C), δ 140.9, 139.3, 133.5, 133.3, 129.6, 129.4, 129.1, 127.9, 127.3, 121.9, 118.8, 115.2, 112.5, 28.2, 55.4, 39.9. IR (thin film): 3233, 1585, 1447, 1351, 1165, 1088 cm^{-1}. HRMS (ESI) calcd for $[C_{23}H_{25}N_2O_5S_3]^+$ ($[M+H]^+$): 505.0920, found 505.0920.

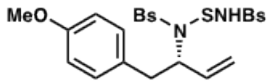
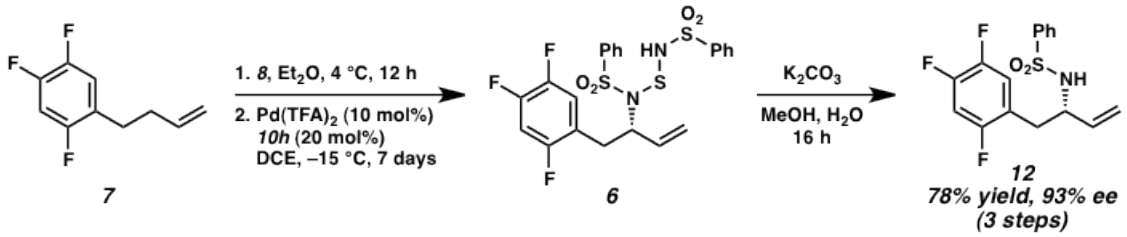


Table 2, entry 5: Following the general procedure for catalytic enantioselective allylic amination (in DCE at –15 °C for 4 d), purification by flash chromatography (20:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded the product (42 mg, 72% yield for two steps) as a clear oil. The enantiomeric excess of the product was determined to be 80% by comparison to a sample of the racemate (see HPLC trace below). $[\alpha]^{23}_{D}$ = 60.2 ° (c = 0.8, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 50 ^{o}C), δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.62-7.59 (m, 2H), 7.53 (t, *J* = 7.0 Hz, 4H), 7.37 (m, 2H), 7.01-6.99 (m, 2H), 6.73-6.71 (m, 2H), 6.23-5.876 (br, 1H), 5.10-5.06 (m, 2H), 4.78-4.70 (m, 1H), 3.79 (s, 3H), 3.22-3.00 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 ^{o}C), δ 140.4, 133.3, 133.0, 130.2, 129.2, 128.8, 127.6, 127.0 118.4, 113.7, 68.0, 55.2, 55.1. IR (thin film): 3235, 1612, 1513, 1353, 1166, 1088 cm^{-1}. LRMS (ESI) calcd for $[C_{23}H_{25}N_2O_5S_3]^+$ ($[M+H]^+$): 505.1, found 505.1.

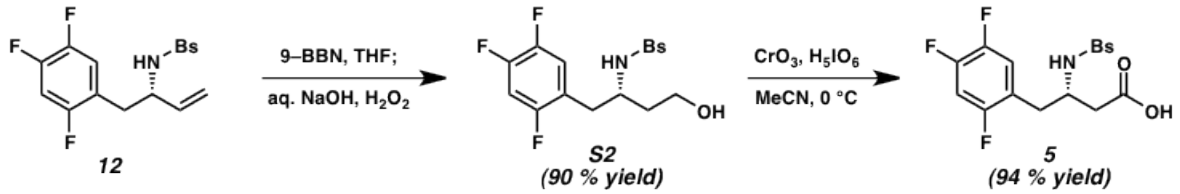
Synthesis of *ent*-Sitagliptin (1)



Sulfonamide 12: A solution of benzenesulfonyl sulfurdiimide **8** (890 mg, 2.6 mmol) in Et_2O (4 mL, 0.5 M) was cooled to 0 °C and treated with trifluorophenyl butene **7** (4.5g, 24 mmol, 9 equiv). The reaction was stirred at 4 °C for 12 h. The ene adduct, which formed a white precipitate, was purified at room temperature by vacuum filtration, washed with Et_2O (20–40 mL), and dried under vacuum. *The filtrate was subjected to flash chromatography to recover most of the unreacted trifluorophenyl butene 7 (3.7 g).* The ene adduct was then suspended in DCE (10 mL) and cooled to –20 °C. The solution was treated with the palladium-ligand complex in DCE (20 mL), which was made by premixing $Pd(TFA)_2$ (10 mol%) and ligand **10h** (20 mol%) in DCE (20 mL) and stirring for 30 min at 50 °C. The reaction was stirred at –15 °C for 7 days. The reaction mixture was concentrated under reduced pressure to yield rearrangement product **6**: $[\alpha]^{23}_D$ = +10.9° (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C), d 7.91 (d, *J* = 7.0 Hz, 2H), 7.76 (bs, 2H), 7.63-7.52 (m, 4H), 7.45-7.42 (m, 2H), 6.82-6.75 (m, 3H), 6.09 (bs, 1H), 5.10 (d, *J* = 9.5 Hz, 2H), 4.73-4.73 (m, 1H), 3.20 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.5, 133.6, 129.5, 129.2, 128.1, 127.8, 127.3, 119.4, 105.8, 105.6, 105.5, 105.3, 66.5, 33.1. IR (thin film): 3234, 1631, 1519, 1448, 1335, 1166 cm^{-1}. HRMS (ESI) calcd for $[C_{22}H_{20}F_3N_2O_4S_3]^+$ ($[M+H]^+$): 529.0532, found 529.0529.

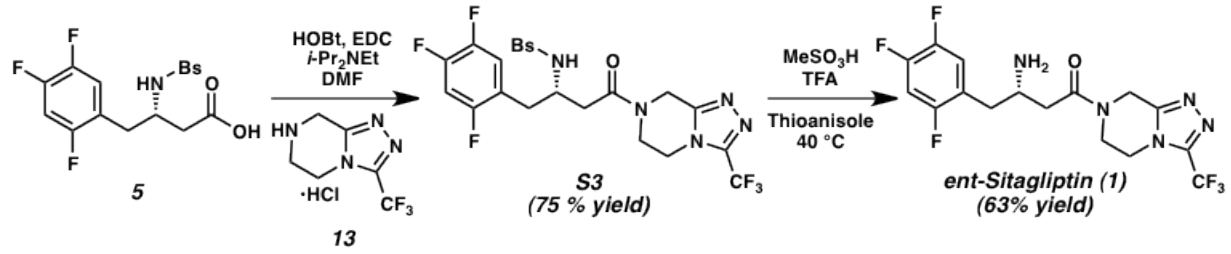
Unpurified rearrangement product **6** was resuspended in MeOH (6 mL) and H_2O (9 mL), and the resulting solution was treated with K_2CO_3 (13 mmol, 5 equiv). After stirring for 14 h at 23 °C, the reaction mixture was poured into a mixture of H_2O (20 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography provided sulfonamide **12 (**690 mg, 78% yield for two steps) as a clear oil: $[\alpha]^{23}_D$ = -15.0° (c = 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 6.89-6.83 (m, 1H), 6.77-6.71 (m, 1H), 5.69 (ddd, *J* = 16.8 Hz, *J* = 10.4 Hz, *J* = 6.4Hz, 1H), 5.07 (d, *J* = 16.8 Hz, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.89 (d, *J* = 8.4 Hz, 1H), 4.00 (m, 1H), 2.75 (m, 2H). ^{13}CNMR (100MHz, $CDCl_3$), 157.4-145.4(m), 140.6, 136.8, 132.7, 129.1, 127.0, 120.4-120.3(m), 119.4-119.1(m), 116.9, 105.8-105.3(m). IR (thin film): 3292, 1519, 1422, 1319, 1154, 1094 cm^{-1}. HRMS (ESI) calcd for $[C_{16}H_{15}F_3NO_2S]^+$ ($[M+H]^+$): 342.0770, found 342.0771.

The enantiomeric excess of the product was determined to be 93% by analysis of the [2,3]-rearrangement product **6** prior to treatment with aqueous K_2CO_3 in MeOH (see HPLC trace for **6** below).



β-Amino Acid 5: A solution of sulfonamide **12** (620 mg, 1.8 mmol) in THF (8 mL) was treated with 9-BBN (7.2 mL, 3.6 mmol, 0.5 M in THF, 2 equiv). After stirring for 1 h at 23 °C, the reaction mixture was cooled to 0 °C and quenched with aqueous NaOH (3 N, 3 mL) and 30% aqueous H_2O_2 (3 mL). After 20 min the excess peroxide was reduced with Na_2SO_3, and the reaction mixture was extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography provided alcohol **S2** (570 mg, 90% yield) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 8.0 Hz, *J* = 7.6 Hz, 2H), 6.80-6.74 (m, 1H), 6.69-6.62 (m, 1H), 3.90 (m, 1H), 3.67 (m, 2H), 2.67 (d, *J* = 7.2 Hz, 2H), 1.89-1.81 (m, 1H), 1.55 -1.43 (m, 1H).

To a solution of H_5IO_6 (800 mg, 3.5 mmol) and CrO_3 (20 mg, 0.2 mmol) in wet CH_3CN (8 mL) was slowly added a solution of **S2** (550 mg, 1.5 mmol) in wet CH_3CN (10 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with aqueous Na_2HPO_4 (0.46 g in 6 mL of H_2O). Excess oxidant was reduced by $NaHSO_3$ (240 mg in 5 mL of H_2O). The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography provided acid **5** (540 mg, 94% yield) as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6), δ 12.30 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.58-7.51 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.27-7.12 (m, 2H), 3.68-3.646 (m, 1H), 2.74-2.69 (m, 1H), 2.55-2.51 (m, 1H), 2.38 (d, *J* = 8.4 Hz, 2H).

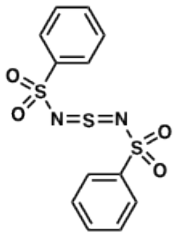


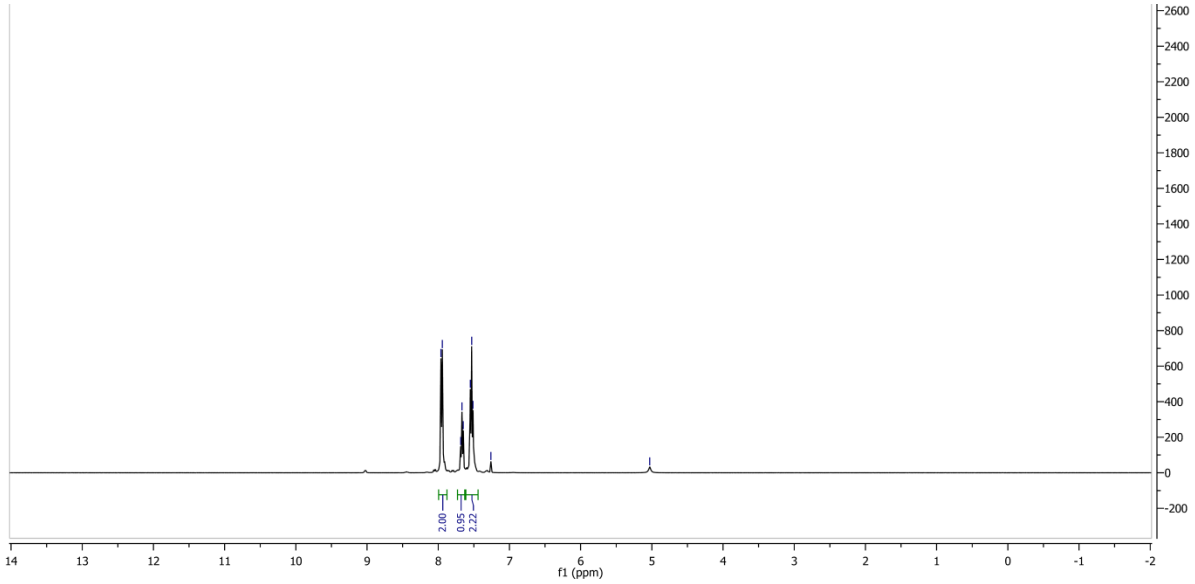
***ent*-Sitagliptin (1)**: A solution of **5** (500 mg, 1.4 mmol), **13** (320 mg, 1.05 equiv), HOBt (215 mg, 1.2 equiv), and EDC (305 mg, 1.2 equiv) in DMF (5 mL) was treated with *i*-Pr_2NEt (0.7 mL, 3.0 equiv). After stirring at 23 °C for 2 d, the reaction was diluted with ethyl acetate (50 mL) and washed sequentially with aqueous HCl (1 N, 10 mL) and aqueous NaOH (1 N, 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography provided amide **S3** (550mg, 75% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.61–7.29 (m, 4H), 6.87-6.47 (m, 2H), 5.37-4.87 (m, 2H), 4.51-3.75 (m, 4H), 3.68-3.646 (m, 1H), 2.98-2.65 (m, 4H).

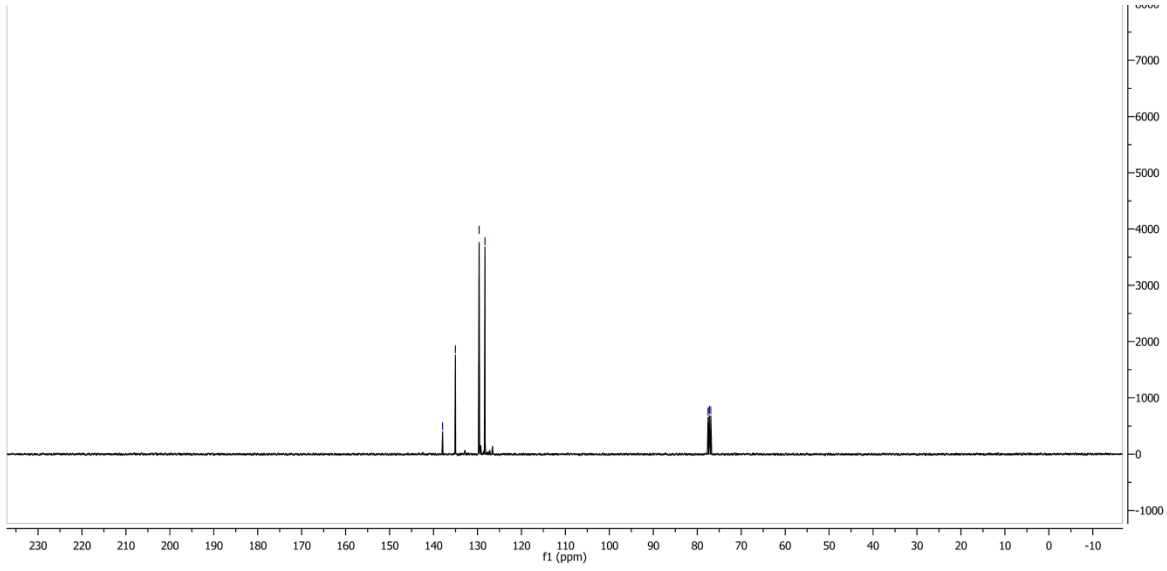
Amide **S3** (130 mg, 0.24 mmol) was treated with $MeSO_3H$ (40 μL), CF_3COOH (1.8 mL), and PhSMe (0.2 mL). After stirring for 12 h at 40 °C, the reaction mixture was concentrated under reduced pressure to remove volatile compounds. The remaining residue was diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by

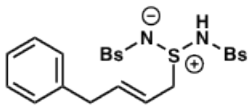
flash chromatography provided the free base of *ent*-Sitagliptin (**1**) (60 mg, 63% yield) as a clear oil: $[\alpha]^{23}_{D}$ = +20.9° (c = 1.7, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3Cl), 7.10–7.05 (m, 1H), 6.94-6.89 (m, 1H), 5.29-4.89 (m, 2H), 4.23-3.92 (m, 4H), 3.57 (s, 1H), 2.81-2.77 (m, 1H), 2.70-2.66 (m, 1H), 2.57-2.44 (m, 2H), 1.98 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 157.3, 157.2, 154.9, 154.8, 150.3, 150.2, 149.9, 149.6, 149.5, 147.5, 147.3, 145.4, 145.4, 145.3, 143.6, 143.4, 121.7, 121.5, 119.0, 119.0, 118.9, 118.83, 105.80, 105.6, 105.5, 105.3, 76.7, 48.5, 43.5, 43.2, 42.3, 41.5, 40.1, 40.0, 39.1, 37.9, 36.2, 29.8, 29.6. IR (thin film): 3372, 2829, 1652, 1519, 1424, 1150 cm^{-1}. HRMS (ESI) calcd for $[C_{16}H_{16}F_6N_5O]^+$ ($[M+H]^+$): 408.1253, found 408.1255.

NMR Spectra





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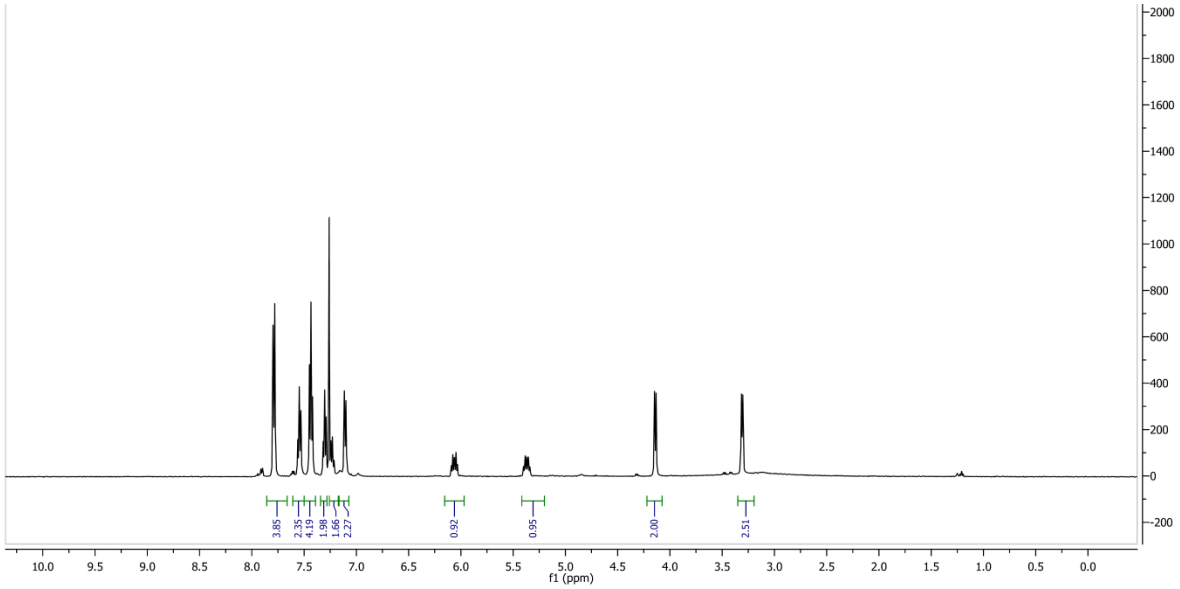
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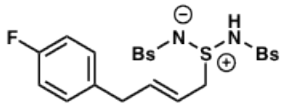
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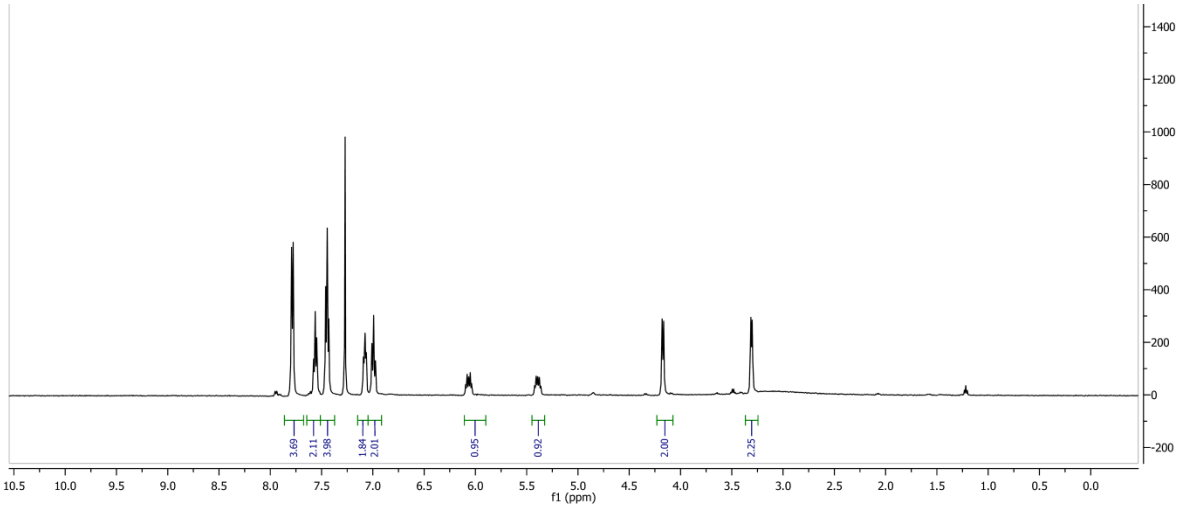
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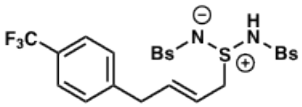
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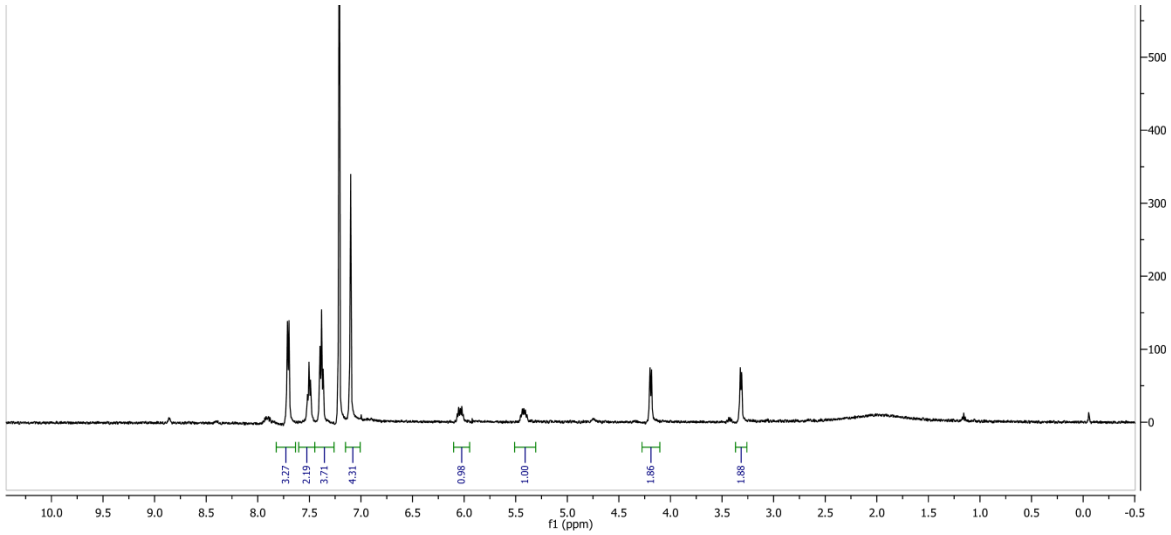
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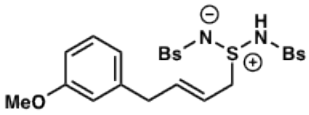
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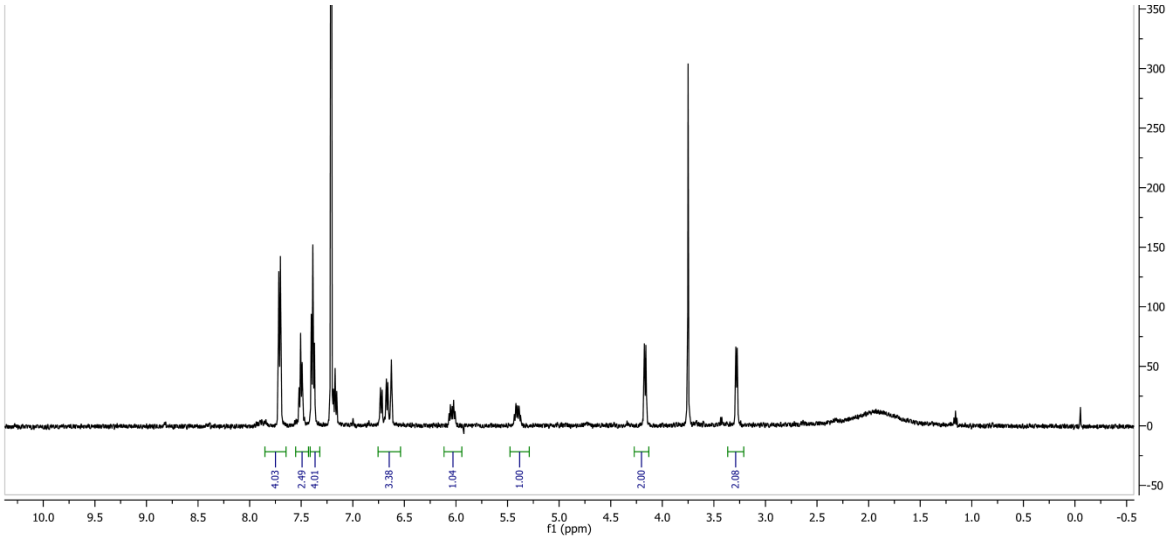
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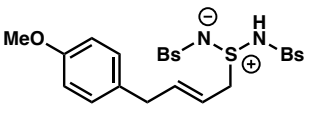
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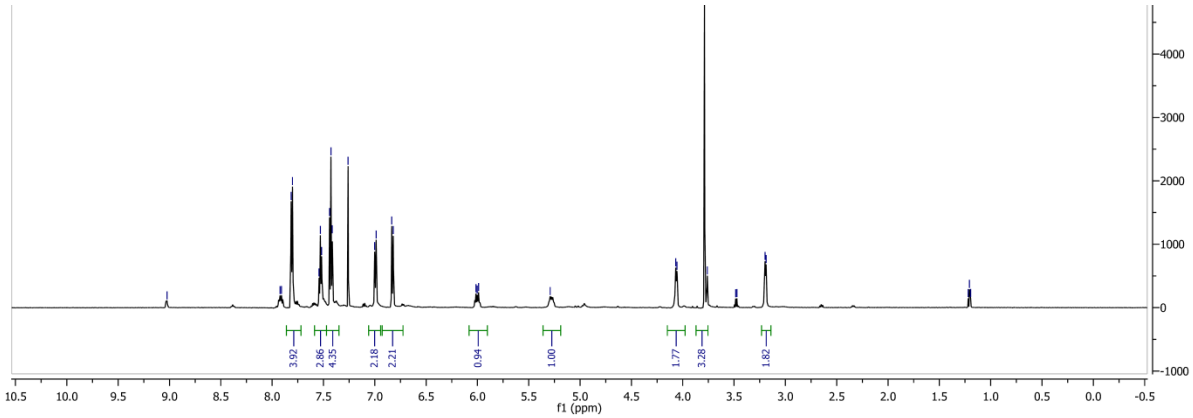
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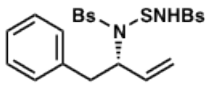
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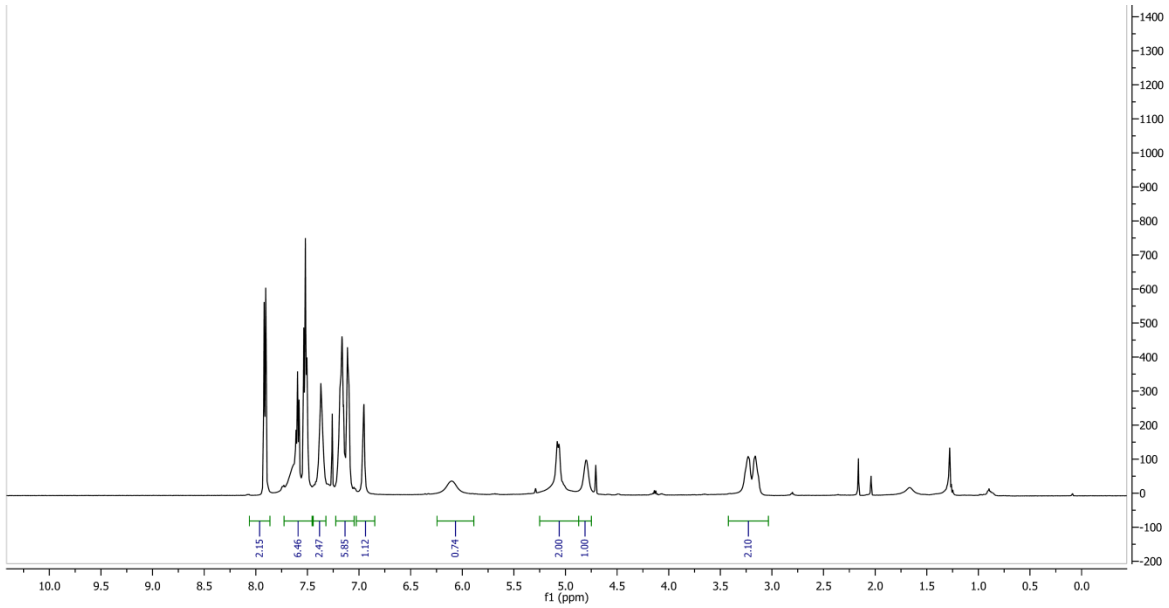
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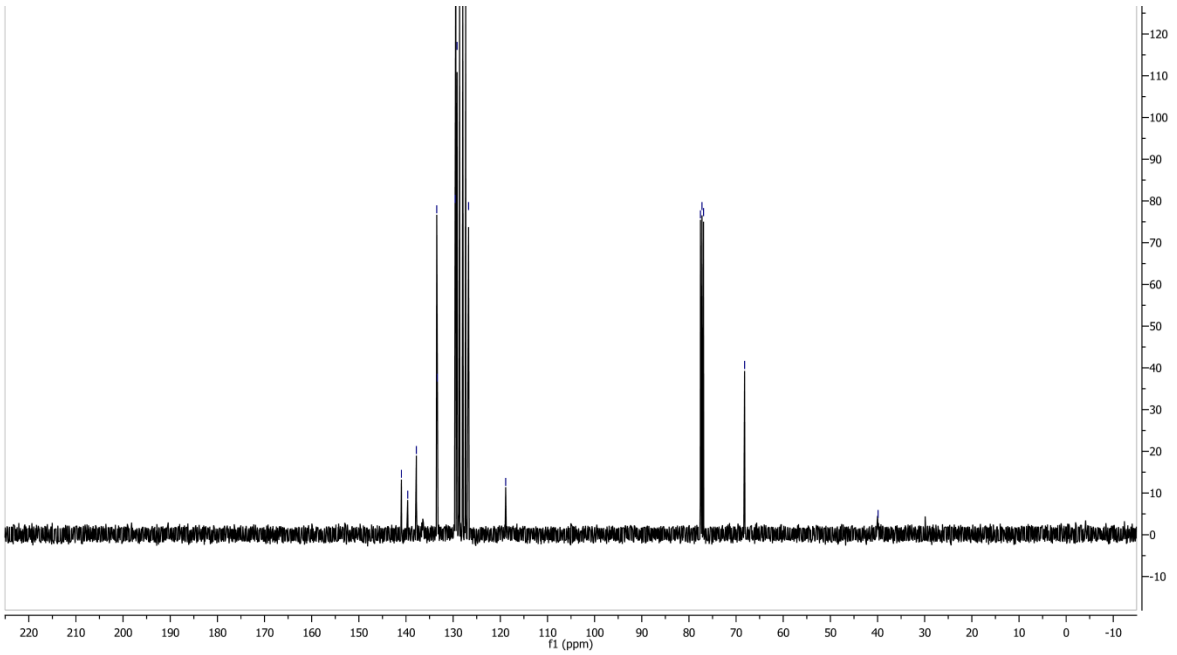
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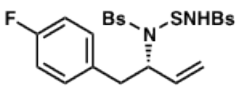
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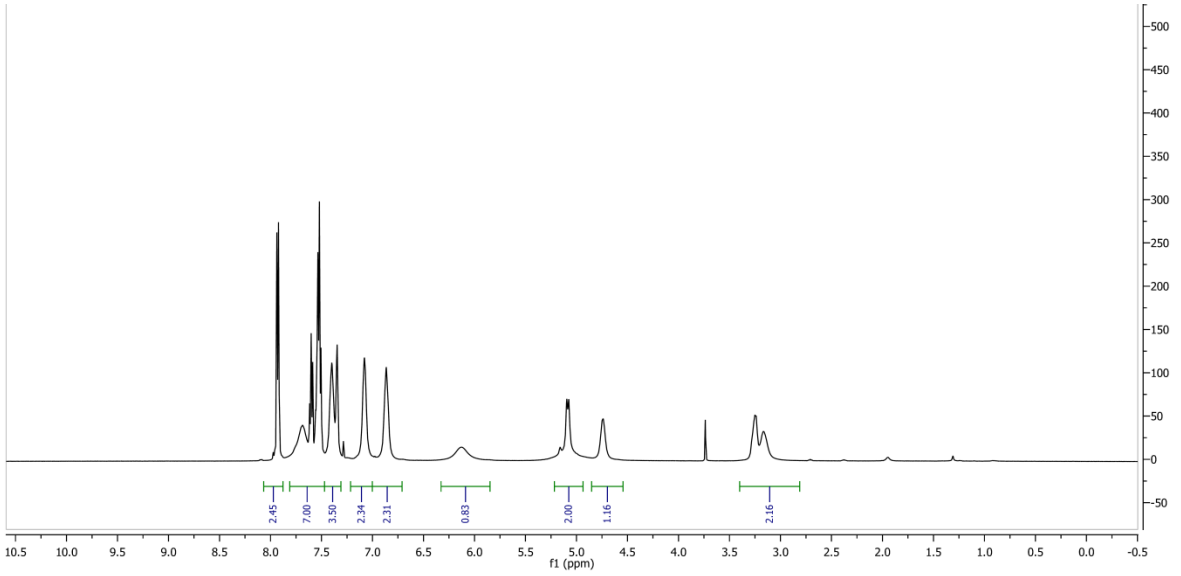
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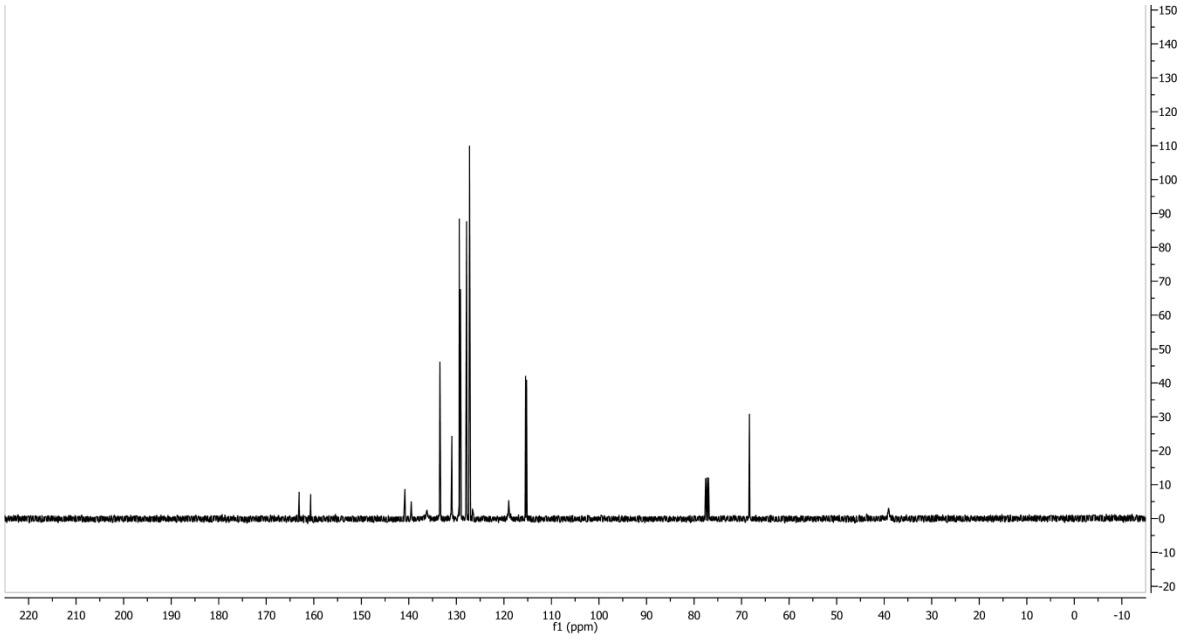
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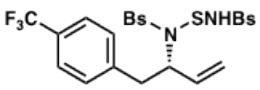
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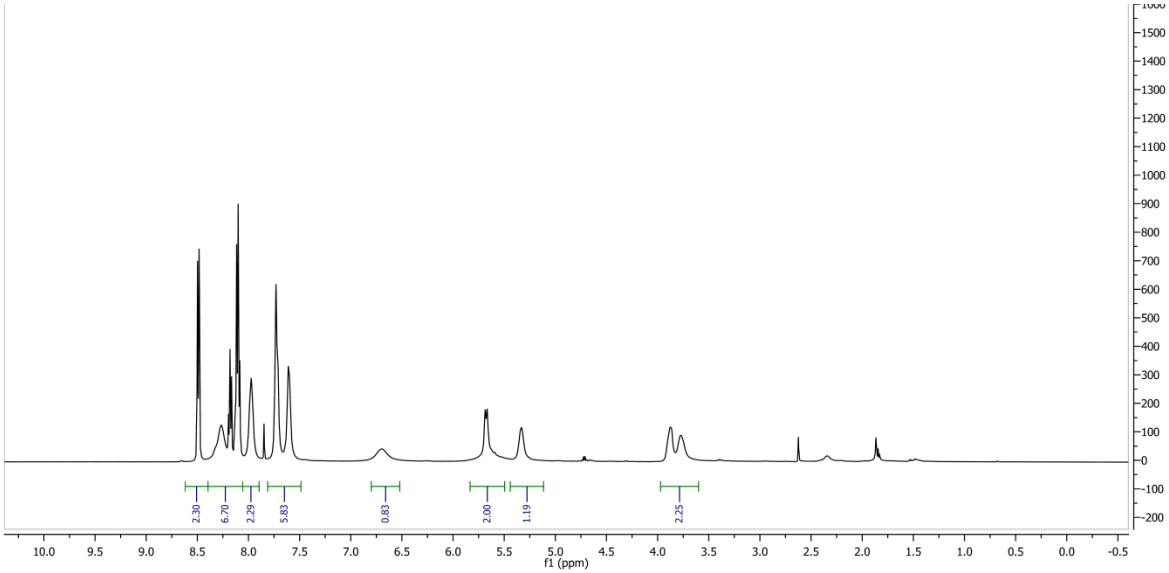
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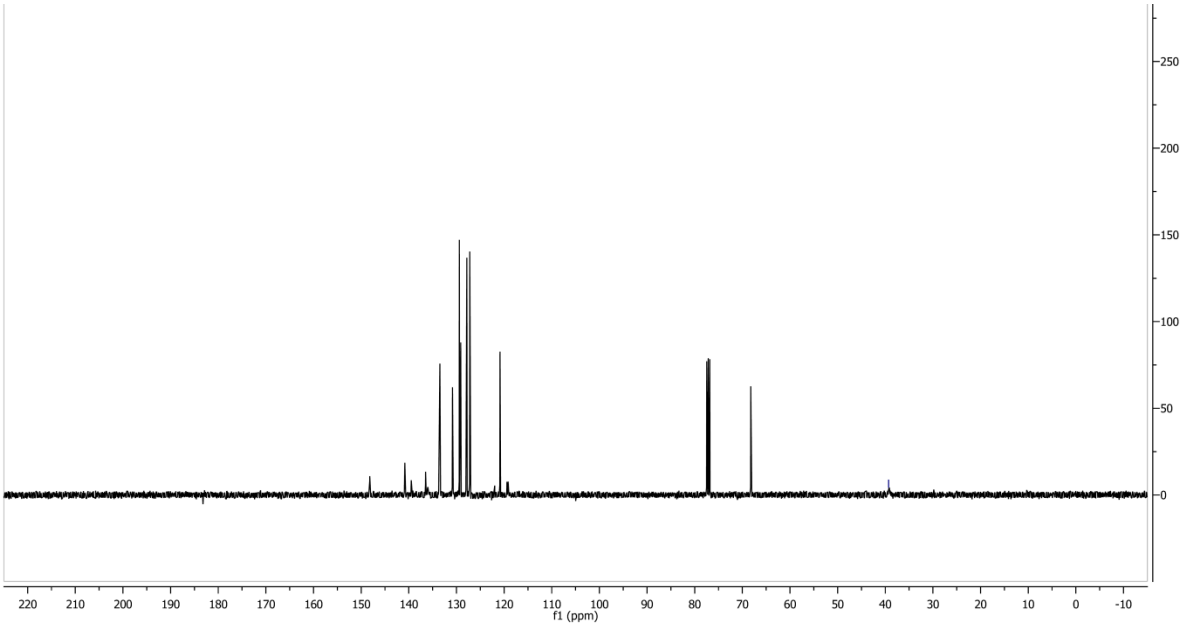
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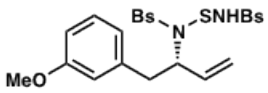
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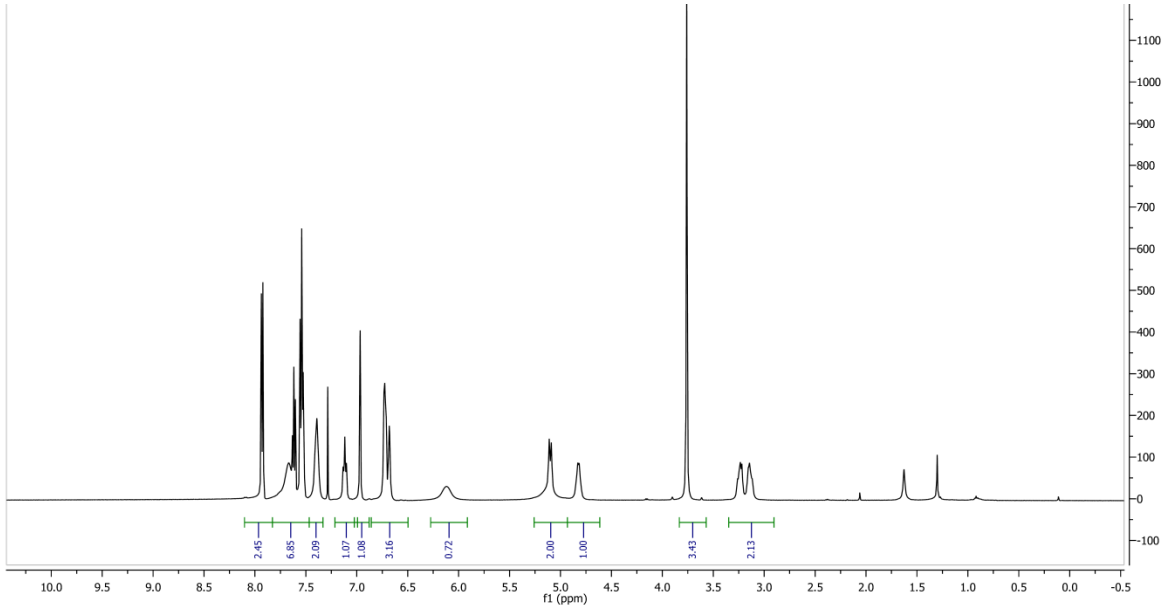
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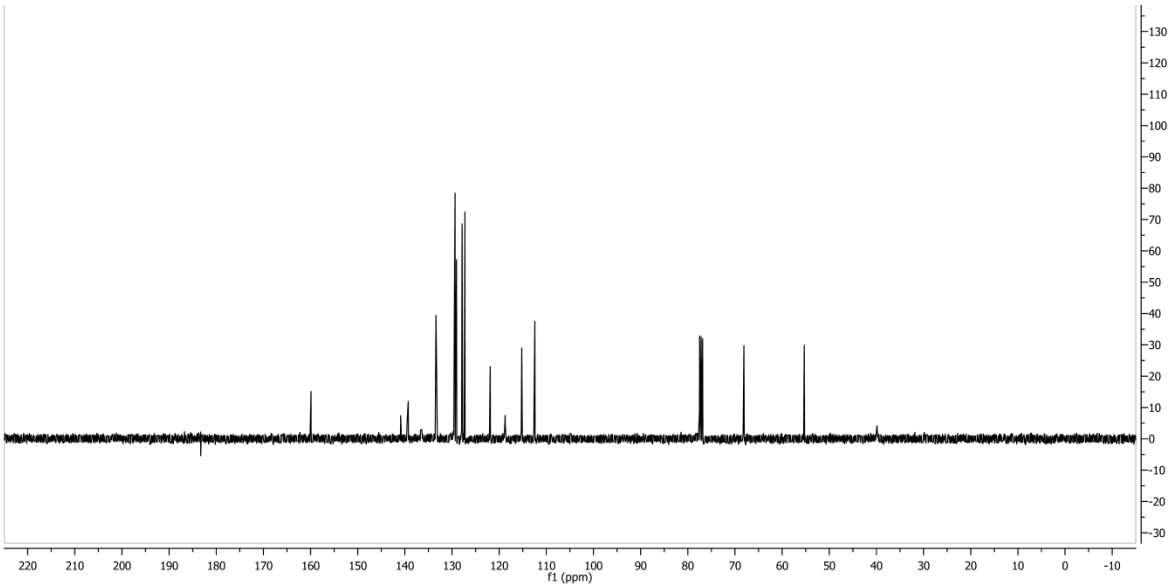
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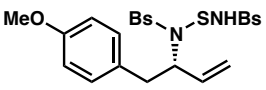
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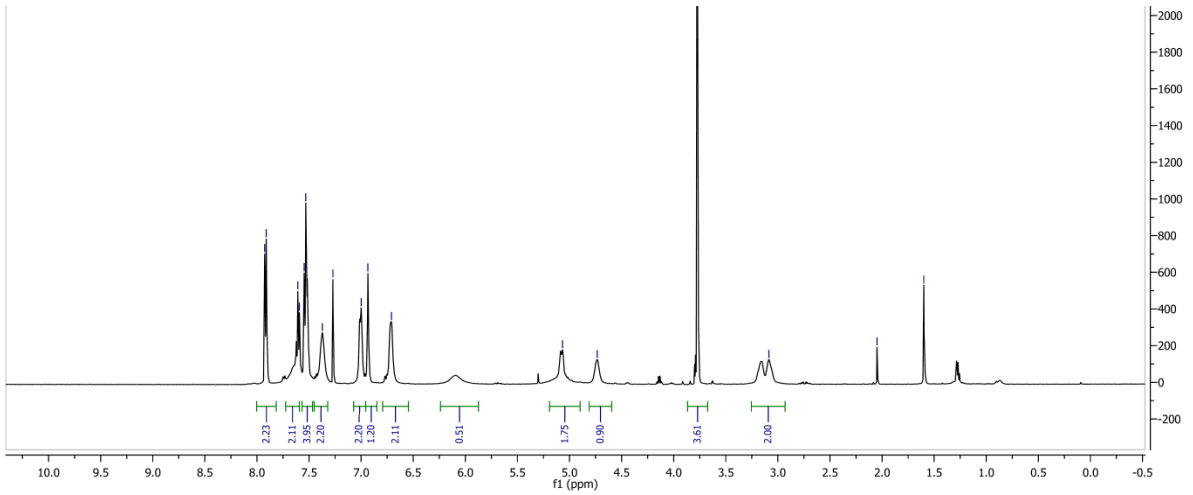
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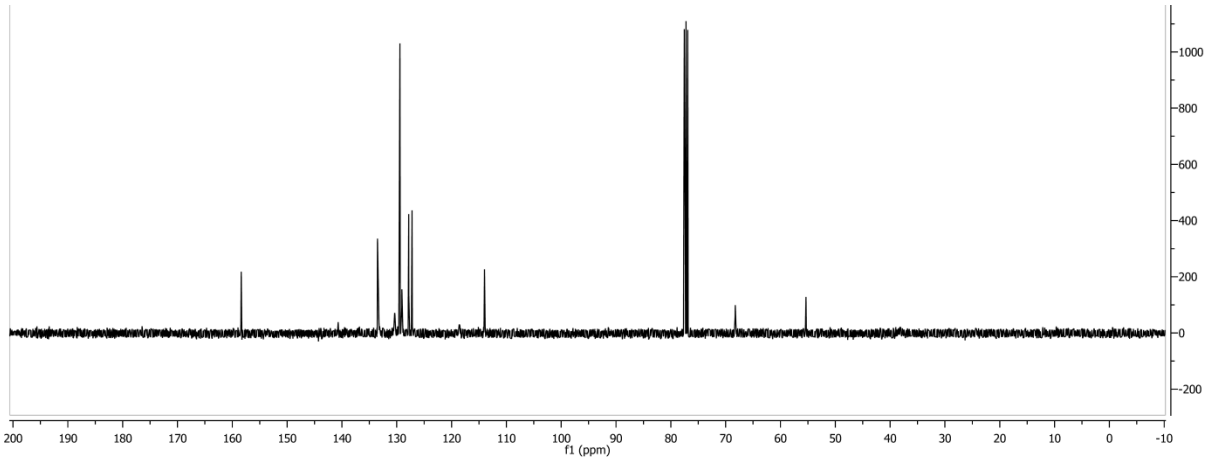
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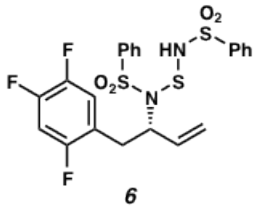
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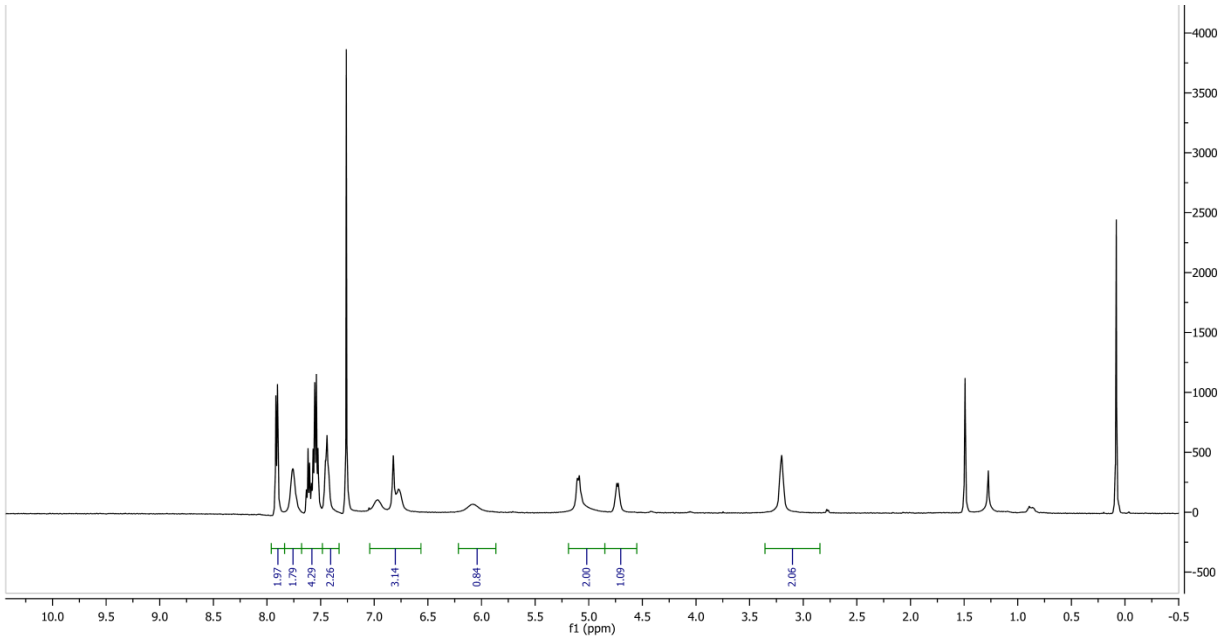
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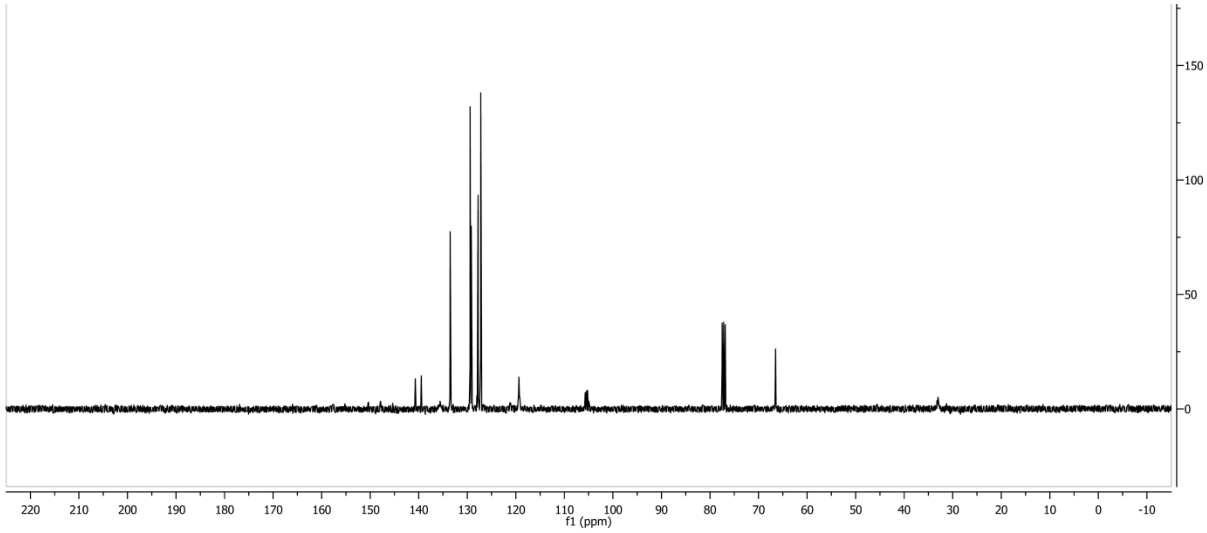
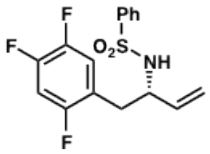
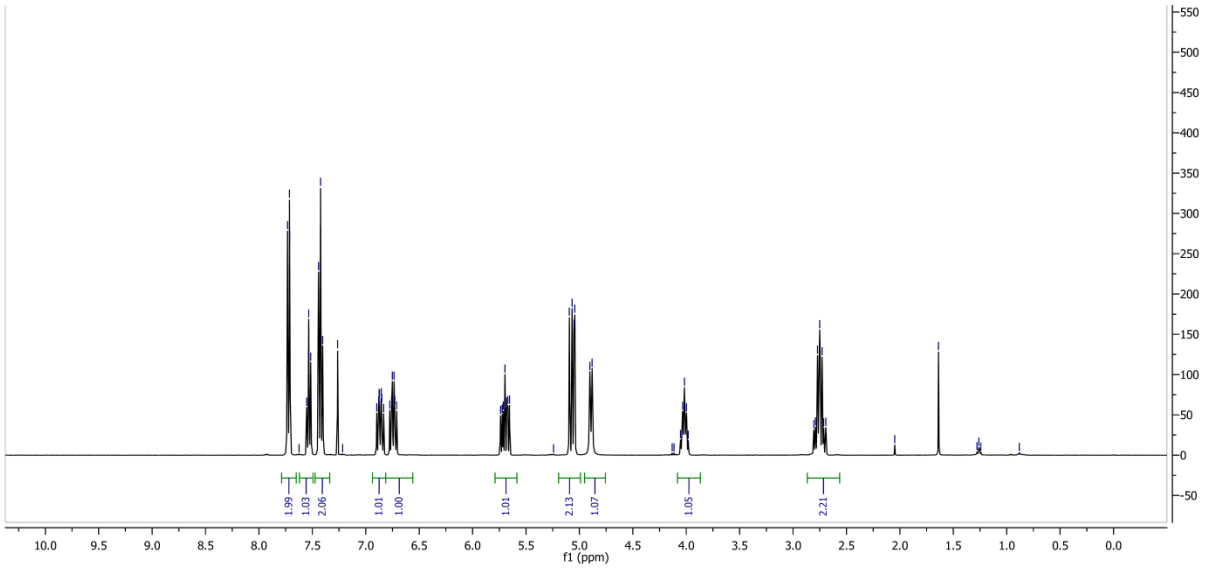
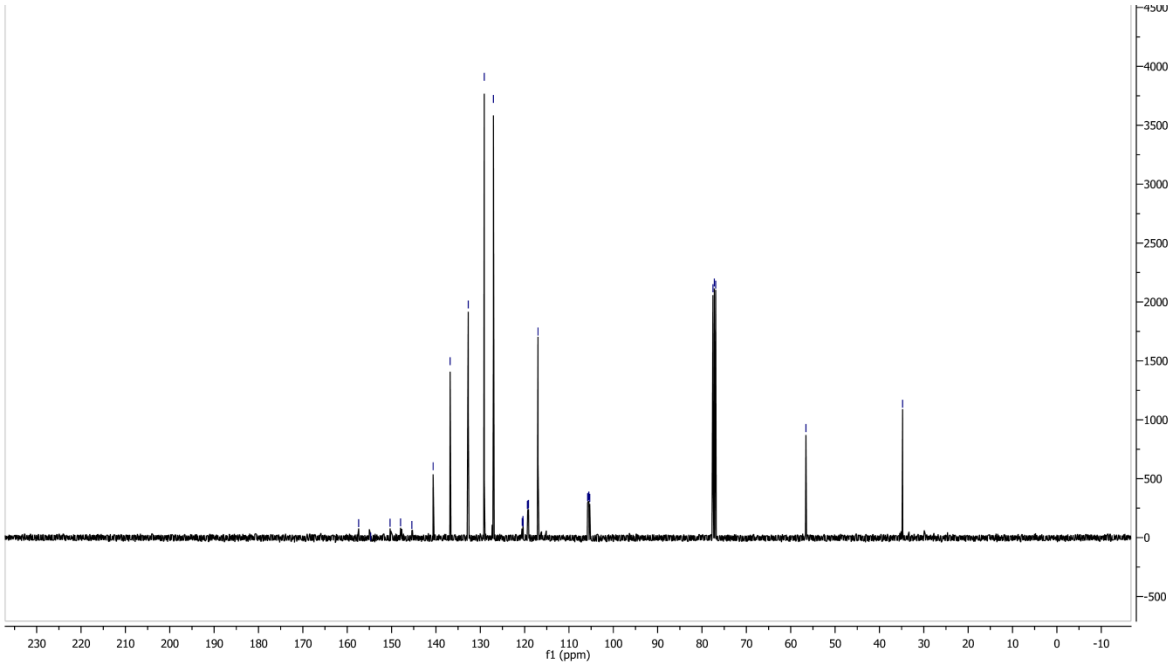
0.5
0.0
-0.5
f1 (ppm)

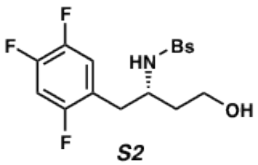

150
100
50
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


F
Ph
F
O2S
NH
F

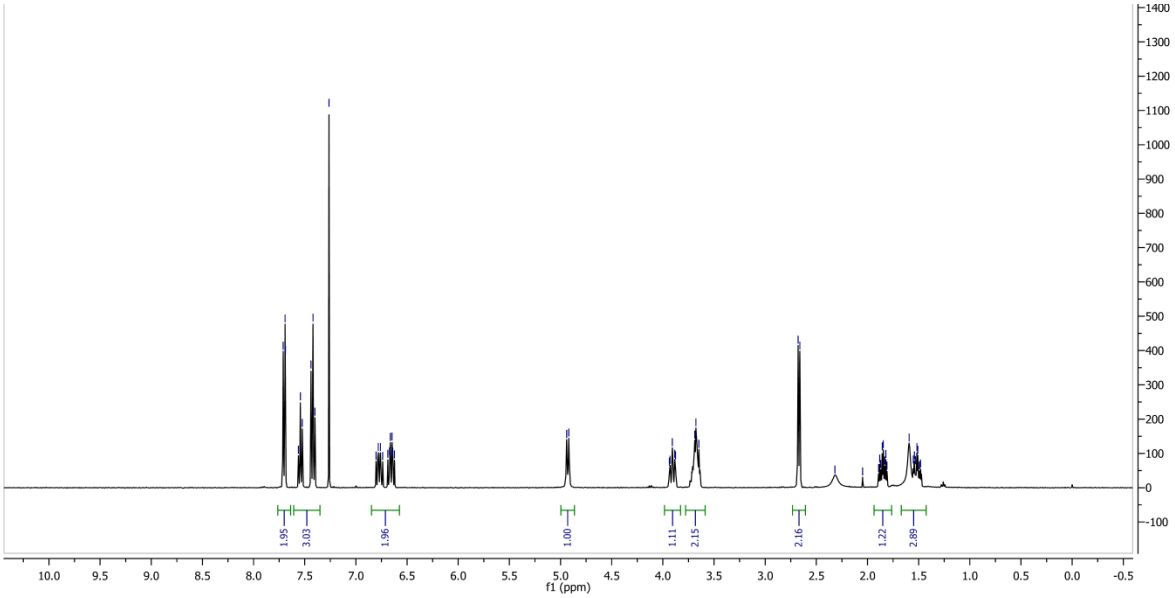
12

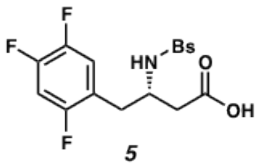

1.99
1.03
2.06
1.01
1.00
1.01
2.13
1.07
1.05
2.21
f1 (ppm)


f1 (ppm)

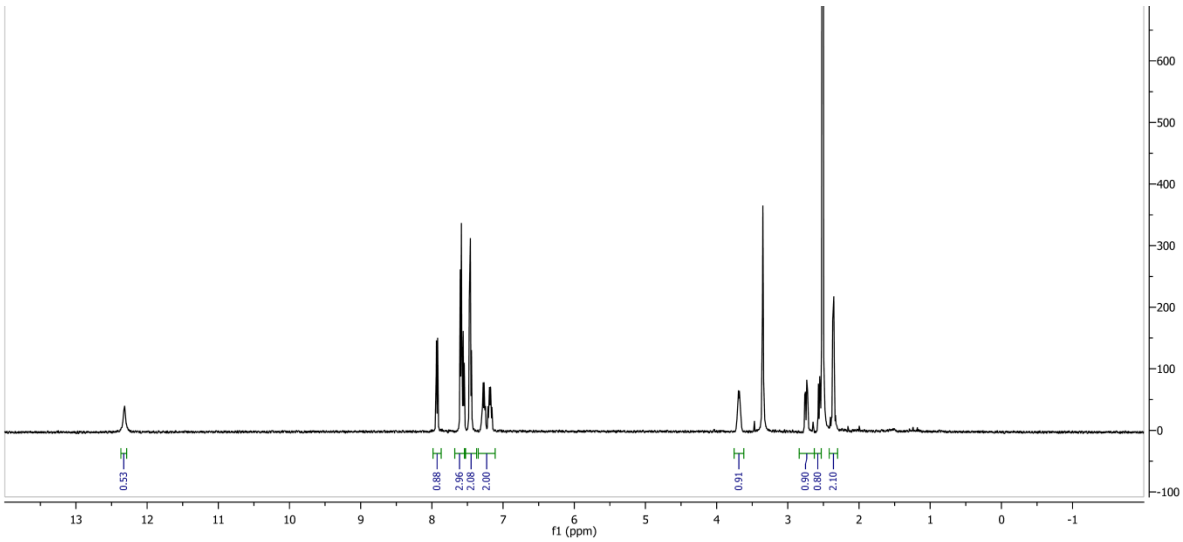

F
F
HN
Bs
OH
F

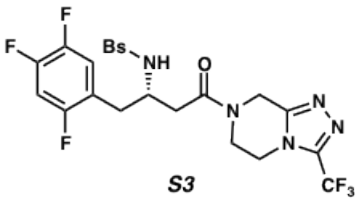
S2


1.95
3.03
1.96
1.00
1.11
2.15
2.16
1.22
2.89
f1 (ppm)

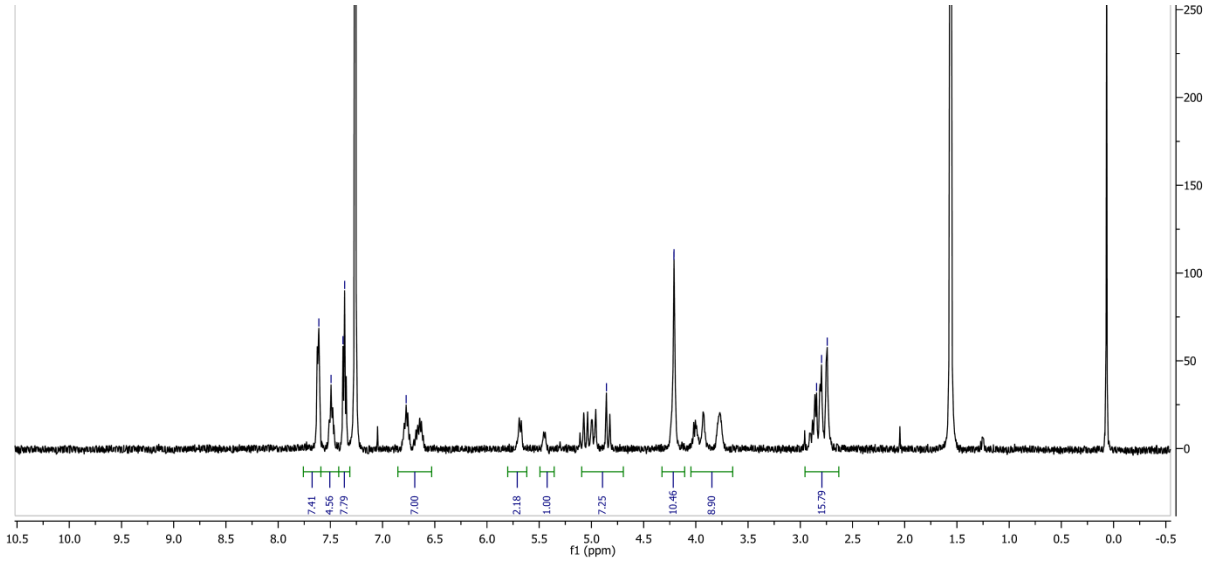

F
F
HN
Bs
O
OH
F

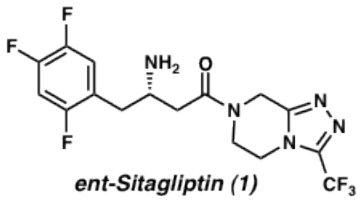
5


0.53
0.88
2.96
2.08
2.00
0.91
0.90
0.80
2.10
f1 (ppm)

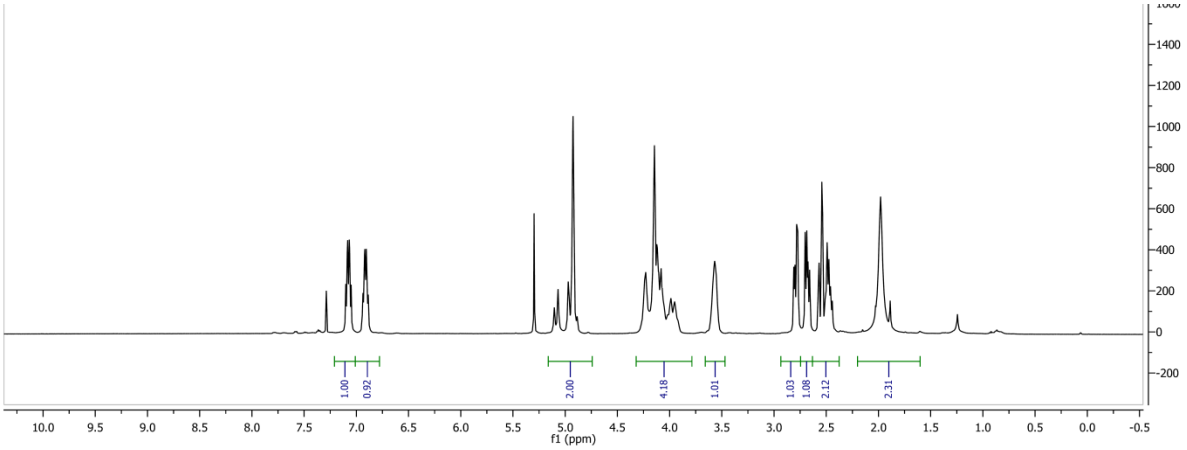

F
F
Bs
NH
O
N
N
N
N
F
CF3

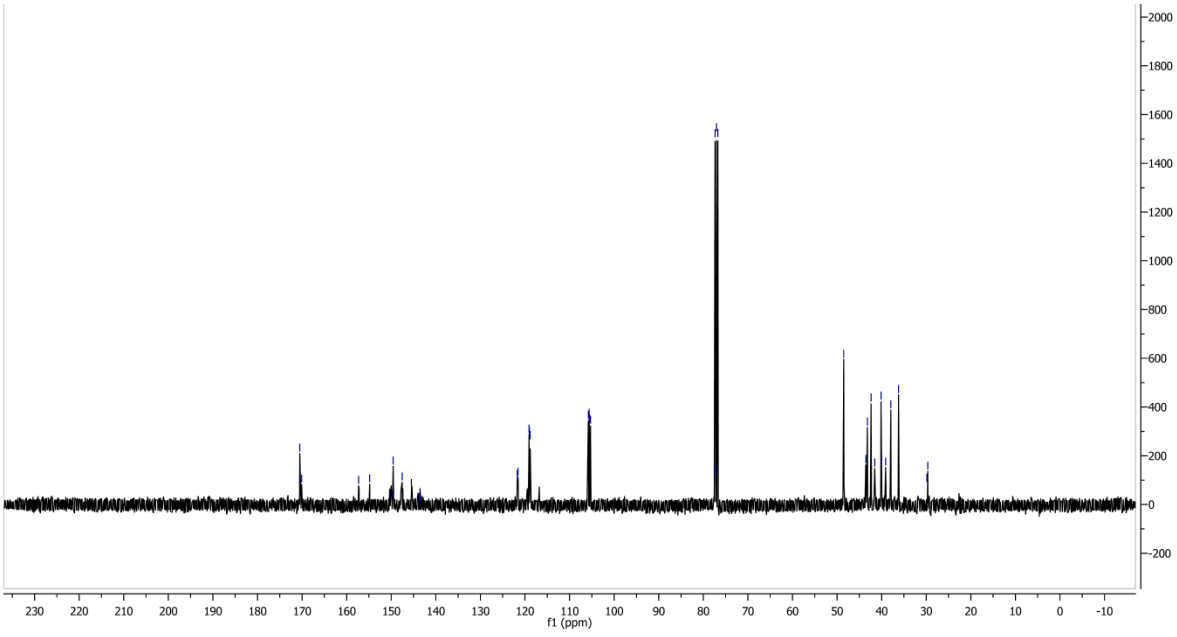
S3


7.41
4.56
7.79
7.00
2.18
1.00
7.25
10.46
8.90
15.79
f1 (ppm)

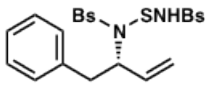


ent-Sitagliptin (1)

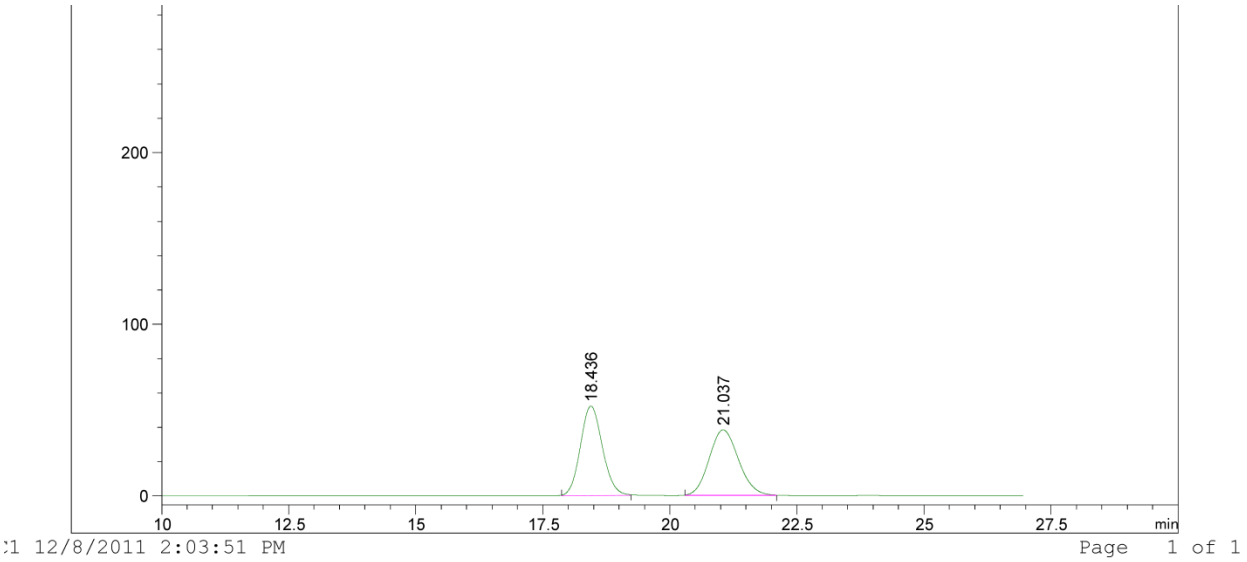


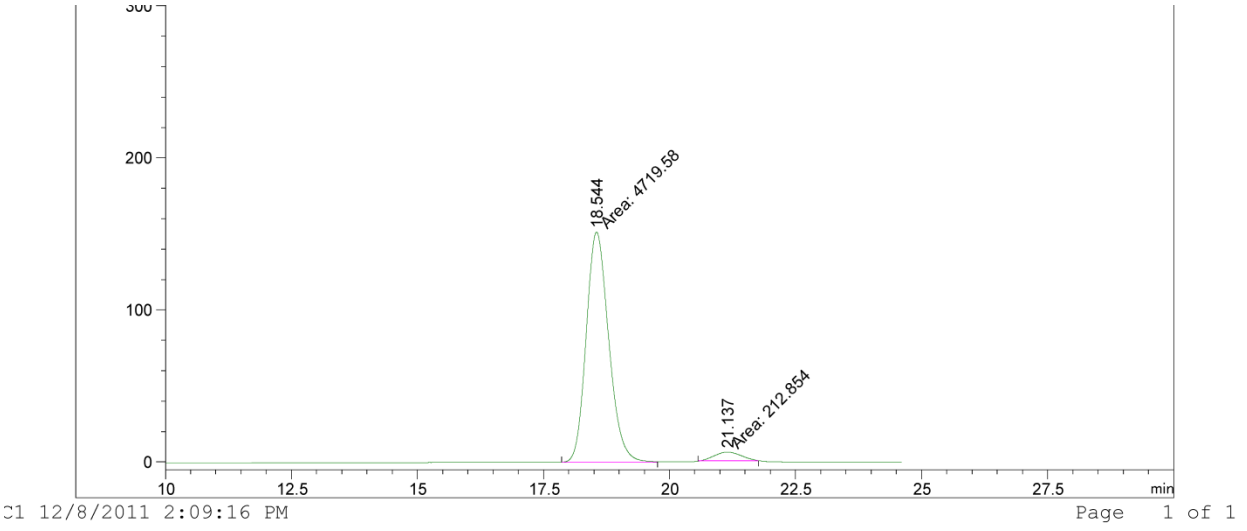


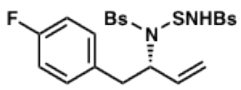
HPLC Traces of Products



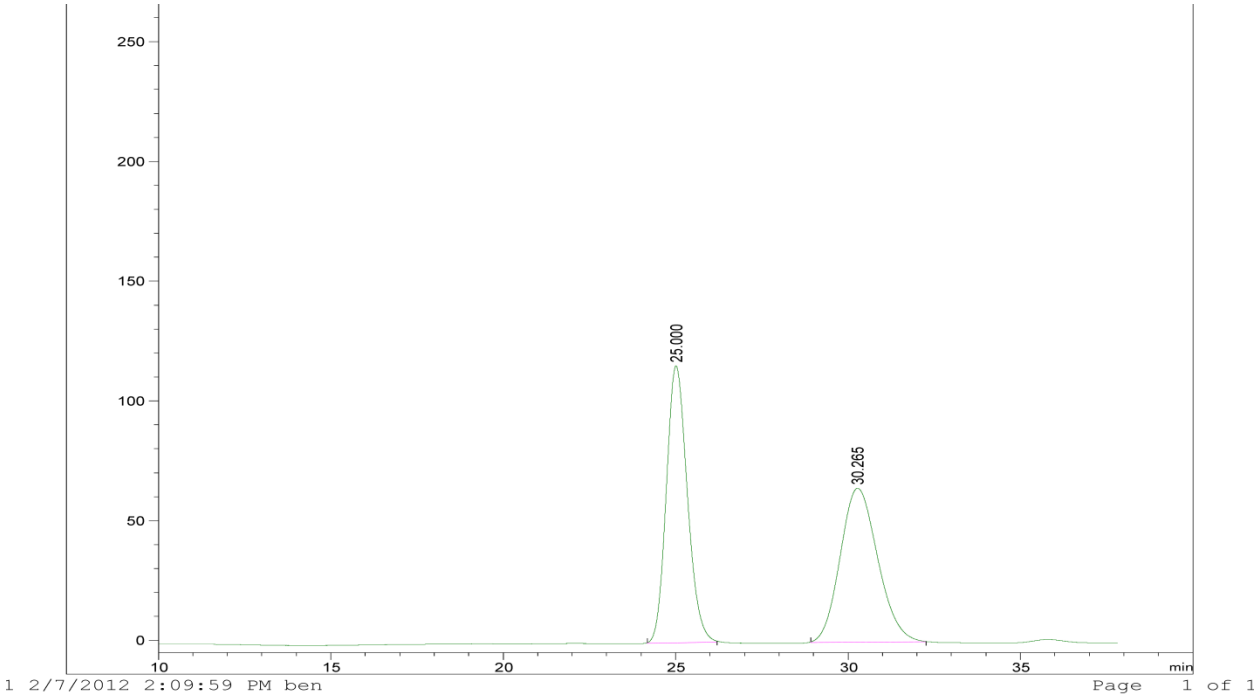
AD-H 80/20 Hx/*i*PrOH, 0.8 mL/min, 230 nm, 93%ee.

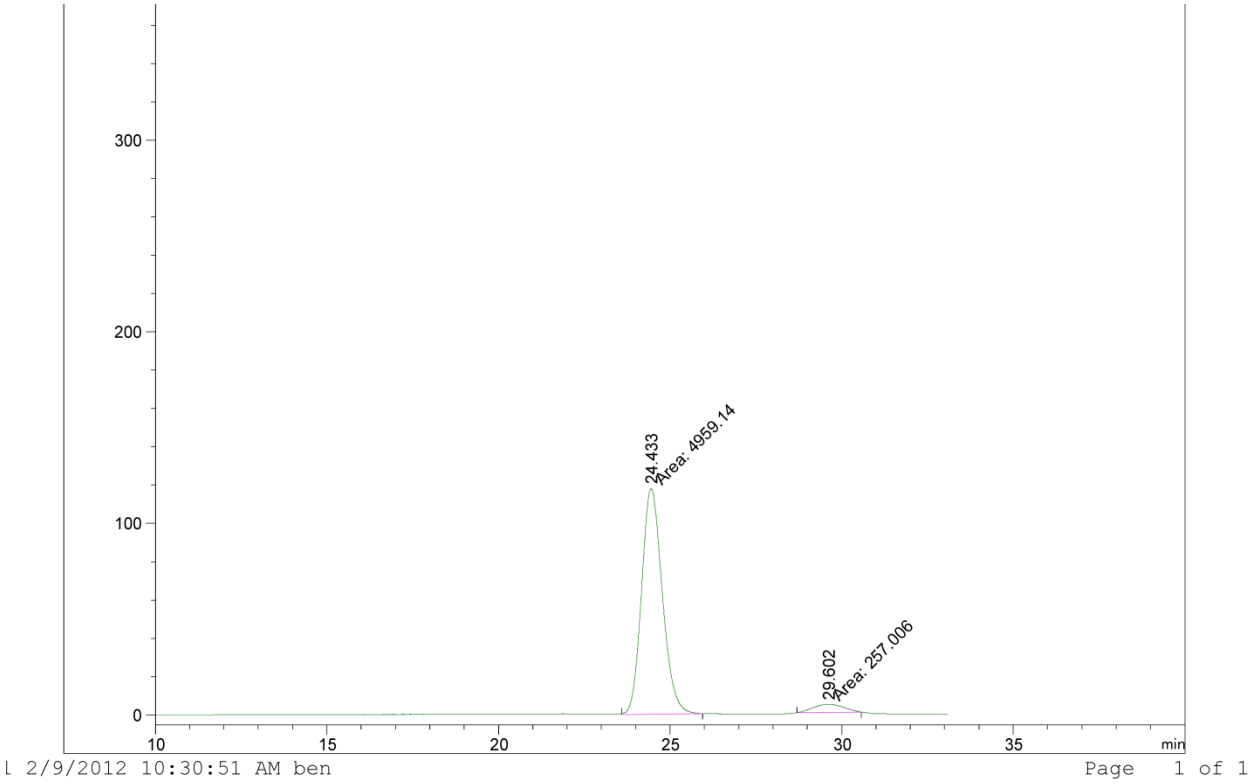


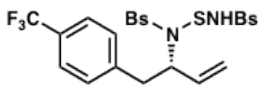




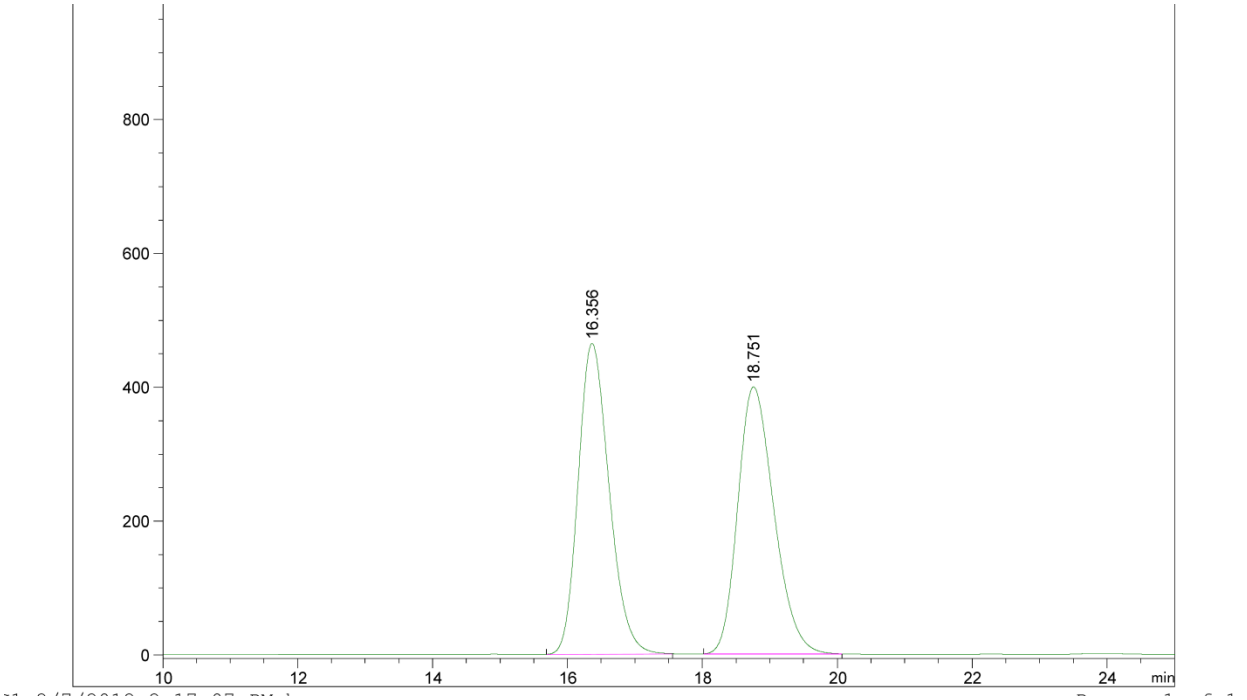
AD-H 80/20 Hx/*i*PrOH, 0.8 mL/min, 230 nm, 90%ee.

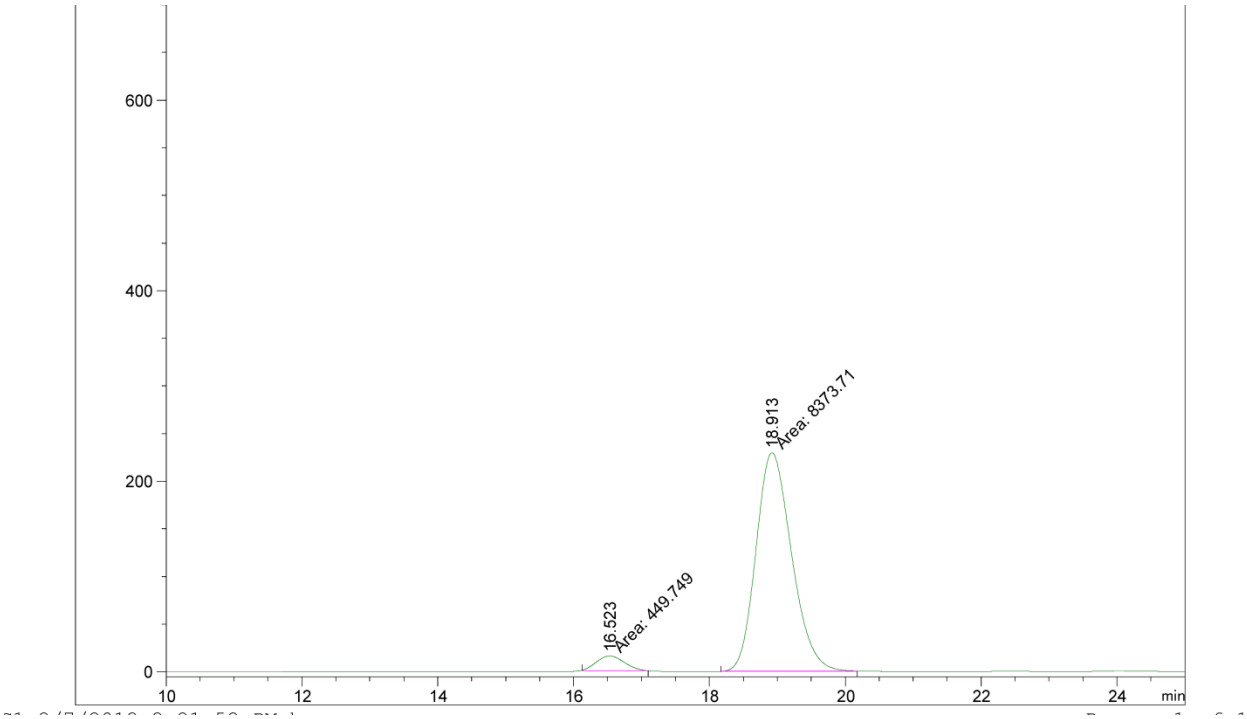


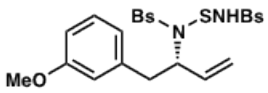




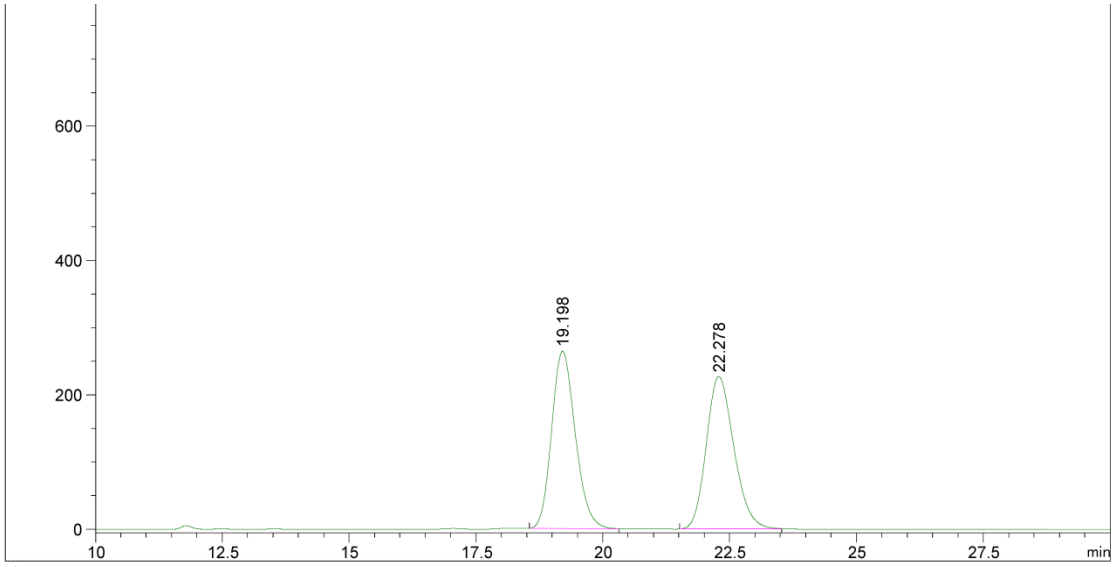
AD-H 80/20 Hx/*i*PrOH, 0.85 mL/min, 230 nm, 90%ee.



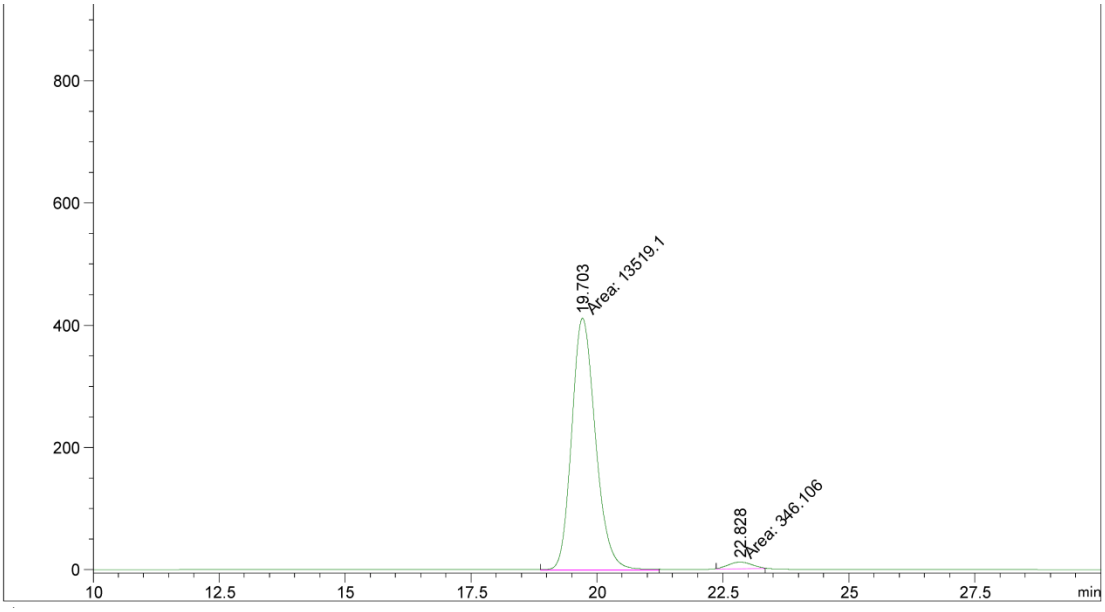




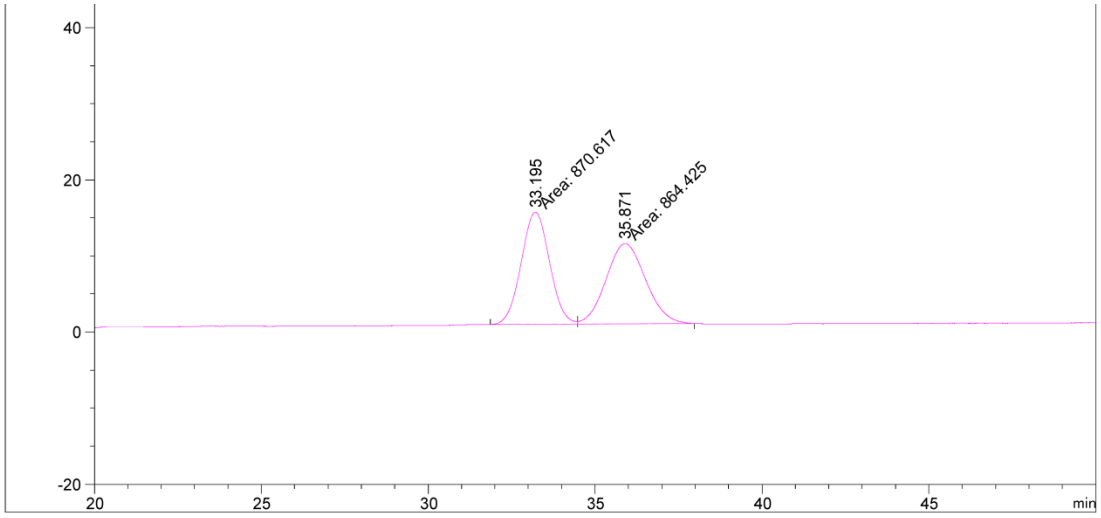
AD-H 80/20 Hx/*i*PrOH, 0.85 mL/min, 230 nm, 95%ee.

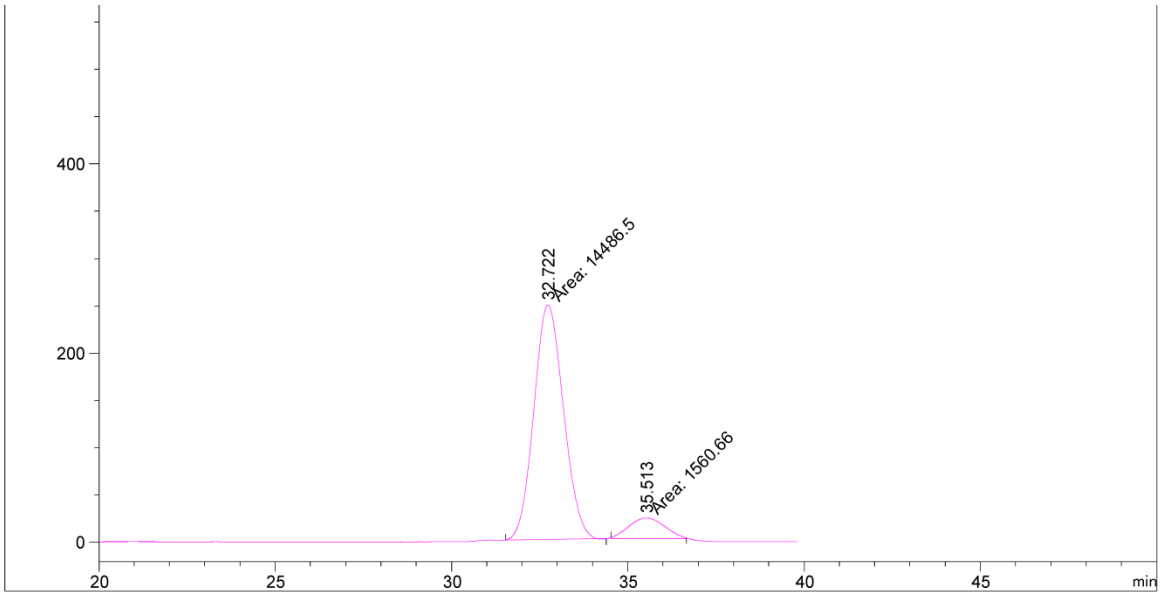


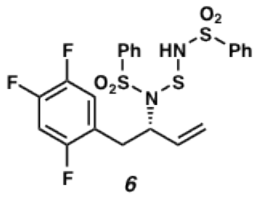
:1 2/7/2012 2:19:29 PM ben Page 1 of 1



AD-H 80/20 0.8 mL/min, 230 nm, 81% ee.







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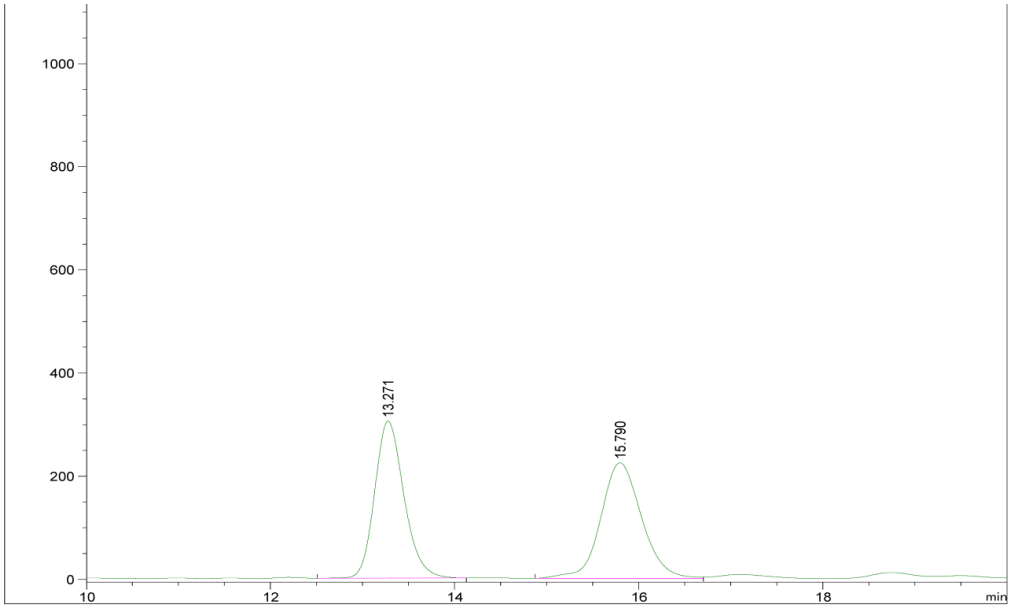
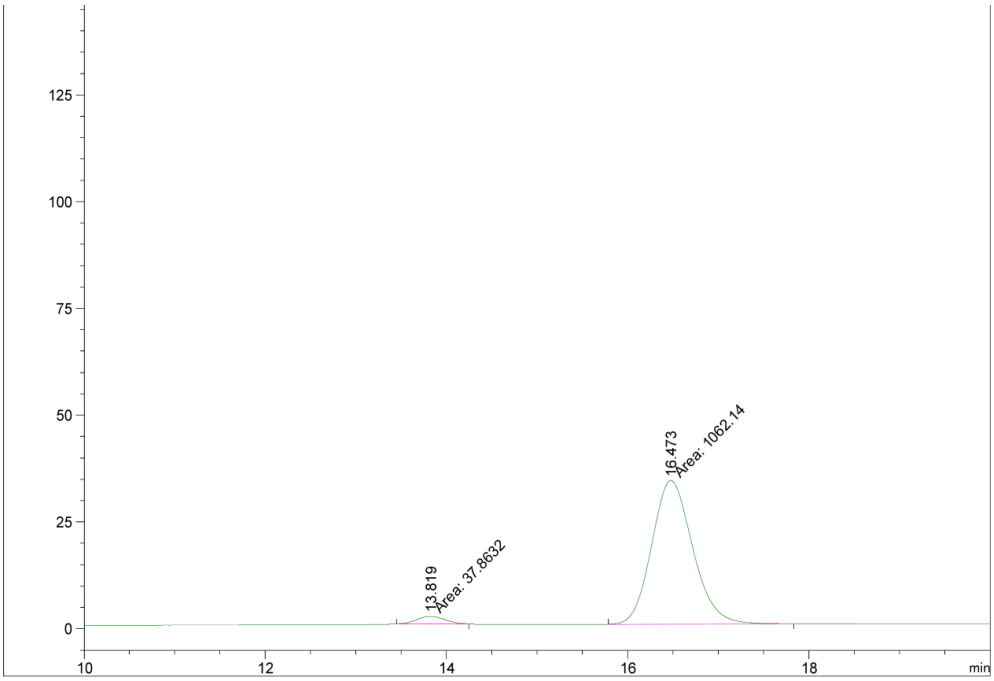
AD-H 80/20 Hx/*i*PrOH, 0.85 mL/min, 230 nm, 93%ee.





Structural Analysis of FDA Drugs (DrugBank)

The structures of more than 1400 FDA-approved small molecule drugs were downloaded from DrugBank (http://www.drugbank.ca/) and analyzed manually for the presence of nitrogen atoms.