Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Supporting Material

Functional Analysis of an Aspartate-Based Epoxidation Catalyst with Amide-to-Alkene Peptidomimetic Catalyst Analogues

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Table of Contents

1. Materials and General Procedures

Column chromatography was performed with 60 Å 40–63 μm silia–P flash silica gel. **Solvents** for reactions (acetonitrile, DMF, DCM, ether, THF, and toluene) were dried using a solvent purification system. Other solvents were used as received. **Bases** (triethylamine, Hünig's base) were dried by distillation from calcium hydride. **Chemicals** were purchased and used as received unless noted otherwise. **High Vacuum** pump was measured to pull 0.25 mmHg. **Spectra** were measured in $CDCl_3$ at ambient temperature unless otherwise noted.

^{1}H NMR spectra were recorded on either a Bruker 500 MHz or a Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane with the solvent as a reference ($CDCl_3$ = 7.26 ppm, DMSO-d_6 = 2.49, D_2O = 4.80). The following is an example data point: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sext = sextet, sept = spetet, oct = octet, m = multiplet, br = broad, and combinations thereof], coupling constants [Hz], integration). **^{13}C NMR** spectra were recorded on a Bruker 500 MHz (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane with the solvent as a reference ($CDCl_3$ = 77.0 ppm, DMSO-d_6 = 39.5). **^{1}H–^{1}H NOESY** spectra were recorded at approximately 0.05 M. Solvent was degassed by the freeze-pump-thaw protocol that follows. Under a nitrogen atmosphere, solvent was frozen in a liquid nitrogen bath (-196 ºC) and maintained under high vacuum (5 min). The flask was sealed, transferred to an ambient temperature water bath, and allowed to melt (evolving gas). The process was repeated three times, and the degassed solvent was used immediately. **IR** spectra were recorded on a Nicolet 6700 FT–IR spectrometer, using a thin film from solution evaporation on a salt plate. Spectra are partially reported (υ_{max}, cm^{-1}). **$[\alpha]_D$** Optical rotations were measured on a Perkin Elmer 341 polarimeter at 20 ºC with 589 nm radiation. Sample concentrations (c) are reported in $cg \cdot mL^{-1}$. **HRMS** (high resolution mass spectrometry) was performed at either the University of Illinois at Urbana–Champaign or at The Keck Center at Yale Medical School. Unless otherwise noted, data were obtained by positive mode electrospray ionization. **TLC** was performed on 60 Å F_{254} precoated silica gel plates. Samples were visualized by either ultraviolet irradiation, potassium permanganate staining, or cerium ammonium molybdenate staining. **Chiral GC** analysis was performed on a Hewlett Packard 6890 GC system. **Chiral HPLC** was performed on either a Hewlett Packard 1100 series or a Agilent Technologies 1200 series liquid chromatography system.

List of Abbreviations

DCC = dicyclohexylcarbodiimide
DCM = dichloromethane
DEAD = diethyl azodicarboxylate
DMAP = *N*,*N*-dimethyl-4-aminopyridine
DMF = dimethylformamide
DMSO = dimethylsulfoxide
THF = tetrahydrofurane

2. Standard Experimental Procedures

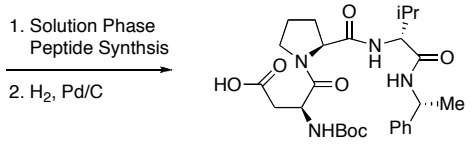
Solution Phase Peptide Synthesis Into a flask was added the Boc-protected peptide (1.0 equiv). The flask was capped with a septum and flushed with nitrogen. Hydrogen chloride (4.0 M in dioxane, 3–5 mL) was added, the nitrogen line and vent needle were removed, and the mixture was stirred (30 min). Volatiles were removed under a stream of nitrogen (3 h) and under high vacuum (1 h). To the crude product were added DCM (0.1–0.2 M), triethylamine (1.2 equiv), the Boc protected coupling partner (1.0 equiv), HOBt hydrate (1.1 equiv), and EDC hydrochloride (1.1 equiv). The mixture was stirred (12 h), diluted with DCM, washed with sodium bicarbonate (saturated aqueous), brine (50% aqueous), and citric acid (10% aqueous), and dried with sodium sulfate. Volatiles were removed under reduced pressure to yield the crude product.

Benzyl Ester Hydrogenolysis To a reaction vessel were added the starting benzyl ester and methanol (0.2 M). To another flask was added 10% palladium on carbon catalyst (125 mg/mmol ester). The palladium flask was capped with a septum and flushed with nitrogen. Methanol (equal to previous volume) was added by syringe, the flask was uncapped, and the slurry was transferred to the ester solution. The mixture was capped and flushed with nitrogen (5 min). A hydrogen-filled balloon was attached, the flask was flushed briefly with hydrogen, and the reaction was stirred at room temperature under the balloon's pressure (3 h). The balloon was removed, the flask was flushed with nitrogen, the mixture was filtered through Celite, and volatiles were removed under reduced pressure. Due to cleanliness of the reaction, the crude product was usually not purified further.

Catalytic Epoxidation A DCM stock solution of the catalyst was added to a small vial and dried in a nitrogen stream, with a hexane azeotrope, and under high vacuum (yielding a white powder). To the vial was added aqueous hydrogen peroxide and a stock solution of DMAP, DCC, substrate (approximately 0.1 mmol), and toluene. The mixture was capped, mixed vigorously (for the indicated time, producing white precipitate), diluted with ether (6 mL), filtered through cotton, washed with sodium thiosulfate (5% aqueous, 6 mL) and sodium bicarbonate (saturated, 6 mL), dried with sodium sulfate, and filtered through cotton again. Volatiles were removed under reduced pressure to give crude product. The crude material was dissolved in $CDCl_3$ (approximately 1 mL), and dioxane (1/8 equiv) was added as an internal NMR standard. Conversion and mass recovery were measured by ^1H NMR. Approximately 2 drops of the $CDCl_3$ solution was put in a GC vial insert and dried in a stream of nitrogen. The sample was either dissolved in (9:1) hexane:2-propanol and analyzed by chiral HPLC or dissolved in ether and analyzed by chiral GC.

3. Experimental Procedures

3.1 Synthesis of Peptide 5



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Synthesis of Peptide 5 The standard solution phase peptide synthesis was followed using (*R*)-methylbenzylamine (772 μL, 6.00 mmol, 1.2 equiv), DCM (25 mL, 0.2 M), Boc-D-Val-OH (1.09 g, 5.00 mmol, 1.0 equiv), HOBt hydrate (841 mg, 5.50 mmol, 1.1 equiv), and EDC hydrochloride (1.06 g, 5.50 mmol, 1.1 equiv). Crude Boc-D-Val-(*R*)NMeBn (1.64 g, quantitative) was used directly for the next step.

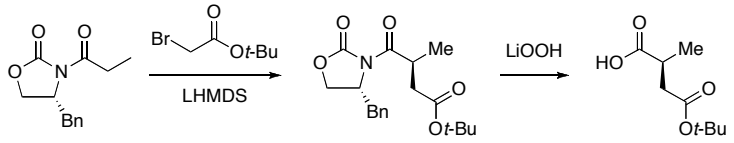
The standard solution phase peptide synthesis was followed using crude Boc-D-Val-(*R*)NMeBn (5.00 mmol, 1.0 equiv), hydrogen chloride (4.0 M in dioxane, 6 mL), DCM (25 mL, 0.2 M), triethylamine (830 μL, 6.00 mmol, 1.2 equiv), Boc-Pro-OH (1.07 g, 5.00 mmol, 1.0 equiv), HOBt hydrate (841 mg, 5.50 mmol, 1.1 equiv), and EDC hydrochloride (1.06 g, 5.50 mmol, 1.1 equiv). One third of the crude Boc-Pro-D-Val-(*R*)NMeBn (2.13 g, quantitative) was used directly for the next step.

The standard solution phase peptide synthesis was followed using crude Boc-Pro-D-Val-(*R*)NMeBn (1.67 mmol, 1.0 equiv), hydrogen chloride (4.0 M in dioxane, 5 mL), DCM (17 mL, 0.1 M), triethylamine (227 μL, 2.00 mmol, 1.2 equiv), Boc-Asp(OBn)-OH (539 mg, 1.67 mmol, 1.0 equiv), HOBt hydrate (153 mg, 1.84 mmol, 1.1 equiv), and EDC hydrochloride (353 mg, 1.84 mmol, 1.1 equiv). The crude product was purified via column chromatography (70 mL silica gel, [17:4 to 3:1] toluene/acetone), yielding Boc-Asp(OBn)-Pro-D-Val-(*R*)NMeBn (764 mg, 1.22 mmol), which was used for the next step. **TLC** (3:1) toluene/acetone, $R_f = 0.36$.

The standard benzyl ester hydrogenolysis was followed using Boc-Asp(OBn)-Pro-D-Val-(*R*)NMeBn (764 mg, 1.22 mmol, 1.0 equiv), methanol (12 mL, 0.1 M), and palladium on carbon catalyst (10%, 154 mg), yielding the desired product (578 mg, 1.09 mmol, 65% yield overall). ^{1}H NMR signals were assigned by ^{1}H-^{1}H COSY.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.15 (m, 6H, Ph, Val-NH), 6.72 (d, J = 7.9 Hz, 1H, NHBn), 5.10 (d, J = 9.9 Hz, 1H, NHBoc), 5.02 (quint, J = 7.4 Hz, 1H, CHBn), 4.79 (td, J_t = 9.5 Hz, J_d = 5.5 Hz, 1H, Asp-α), 4.60 (t, J = 6.0 Hz, 1H, Pro-α), 3.95 (t, J = 8.6 Hz, 1H, Val-α), 3.78–3.69 (m, 2H, Pro-δ), 2.77 (dd, J_1 = 16.2 Hz, J_2 = 10.0 Hz, 1H, Asp-β), 2.63 (dd, J_1 = 15.4 Hz, J_2 = 5.2 Hz, 1H, Asp-β), 2.29–2.22 (m, 1H, Pro-β), 2.02–1.80 (m, 4H, Pro-β, Pro-γ, Val-β), 1.39 (d, J = 6.9 Hz, 3H, MeBn), 1.36 (s, 9H, Boc), 0.80 (d, J = 6.7 Hz, 3H, Val-γ), 0.75 (d, J = 6.7 Hz, 3H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 172.5, 171.7, 171.4, 171.3, 154.9, 142.8, 128.6, 127.3, 126.2, 80.3, 60.5, 59.7, 49.0, 48.6, 47.6, 37.8, 29.8, 28.5, 28.3, 24.5, 21.6, 19.4, 18.4; **IR** (film, cm^{-1}) 3301, 2970, 1716, 1638; $[\alpha]_D$ = -49.0° (c = 2.0, $CHCl_3$); **HRMS** Calculated for $[C_{27}H_{40}N_4O_7H]^+$, requires m/z = 533.2975, found m/z = 533.2954 (ESI); **TLC** (20:10:2) ethyl acetate/hexane/acetic acid, $R_f = 0.35$.

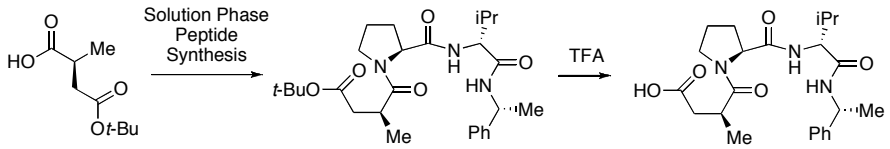
3.2 Synthesis of Peptide 8



8a **8b**

Synthesis of Acid 8b[1] Into a flame-dried flask were added (*R*)-(-)-4-benzyl-3-propionyl-2-oxazolidinone (599 mg, 2.40 mmol, 1.0 equiv) and THF (5 mL, 0.5 M). The flask was capped with a septum, maintained under a nitrogen atmosphere, and cooled in a dry ice/acetone bath (-78 °C). Sodium bis(trimethylsilyl)amide (1.0 M in THF, 4.0 mL, 4.0 mmol, 1.7 equiv) was added to the solution, and the mixture was stirred (1.5 h). *tert*-Butyl bromoacetate (1.77 mL, 12.0 mmol, 5.0 equiv) was added to the mixture, which was stirred (3 h), quenched with ammonium chloride (saturated aqueous, 3 mL), warmed to ambient temperature, concentrated under reduced pressure, diluted with ammonium chloride (50% saturated, 50 mL), extracted with ethyl acetate (50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude product was purified via column chromatography (60 mL silica gel, [5:1] hexane/ethyl acetate), yielding a mixture of diastereomers (10:1). The mixture was dissolved in boiling ether (10 mL), diluted with hexane (10 mL), and allowed to crystallize overnight. Needle crystals of pure alkylated imide **8a** (255 mg, 0.735 mmol, 31% yield) were obtained and washed with hexanes. $[\alpha]_D$ = -48.9° (*c* = 1.0, DCM); previously reported[1] value for enantiomer = +49.6° (*c* = 1.0, DCM); **TLC** (5:1) hexane/ethyl acetate, R_f = 0.25.

Into a flask were added imide **8a** (437 mg, 1.26 mmol, 1.0 equiv) and THF (18 mL, 0.07 M). The flask was cooled in an ice bath (0 °C). Lithium hydroxide monohydrate (106 mg, 2.52 mmol, 2.0 equiv) was dissolved in water (6.3 mL, 0.2 M). To the oxazolidinone solution were added hydrogen peroxide (30% aqueous, 573 μL, 5.04 mmol, 4.0 equiv) and the hydroxide solution. The mixture was stirred (2 h), quenched with sodium sulfite (saturated aqueous, 15 mL) and sodium bicarbonate (saturated aqueous, 10 mL), stirred (15 min), concentrated under reduced pressure, diluted with water (30 mL), washed with DCM (3 x 30 mL), acidified with hydrochloric acid (1 M, to pH 1), extracted with ethyl acetate (4 x 30 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure to yield pure product (228 mg, 1.21 mmol, 96% yield, 30% yield overall). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.94–2.84 (m, 1H), 2.63 (dd, J_1 = 16.4 Hz, J_2 = 8.2 Hz, 1H), 2.36 (dd, J_1 = 16.4 Hz, J_2 = 5.9 Hz, 1H), 1.43 (s, 9H), 1.23 (d, J = 7.2 Hz, 3H). Product analysis is consistent with published data.[2]



8b **8c** **8**

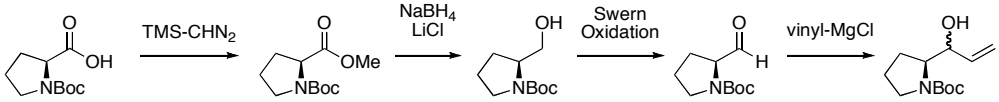
[1] Procedure and compound data from: D. A. Evans, D. L. Wu, J. M. Wiener, J. S. Johnson, D. H. B. Ripin, J. S. Tedrow, *J. Org. Chem.* **1999**, *64*, 6411–6417.
[2] S. G. Davies, D. J. Dixon, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2635–2643.

Synthesis of Peptide 8 The standard solution phase peptide synthesis was followed using Boc-Pro-D-Val-(*R*)NMeBn (750 mg, 1.80 mmol, 1.5 equiv), hydrogen chloride (4.0 M in dioxane, 4 mL), DCM (12 mL, 0.1 M), triethylamine (285 μL, 2.06 mmol, 1.7 equiv), acid **8b** (228 mg, 1.21 mmol, 1.0 equiv), HOBt hydrate (223 mg, 1.46 mmol, 1.2 equiv), and EDC hydrochloride (280 mg, 1.46 mmol, 1.2 equiv). The crude product was purified via column chromatography (60 mL silica gel, [3:1] toluene/acetone), yielding *tert*-butyl ester **8c** (429 mg, 0.881 mmol, 49% yield), which was used for the next step.

Into a flask were added *tert*-butyl ester **8c** (429 mg, 0.881 mmol) and DCM (6 mL, 0.1 M). The flask was capped with a septum and flushed with nitrogen. The gas line was removed, and TFA (3 mL) was added by syringe. The mixture was stirred (2.5 h) with occasional venting of pressure. Volatiles were removed under reduced pressure (toluene then hexane azeotrope), and the crude product was purified via column chromatography (40 mL silica gel, [16:14:2 then 13:17:2] hexane/ethyl acetate/acetic acid), yielding the desired product (342 mg, 0.793 mmol, 90% yield, 44% yield overall). At low concentration the product shows a single conformation by ^{1}H NMR, however, at higher concentration (~50 mg·mL^{-1}), a minor conformation (approximately 4:1) also exists. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY and comparison to similar peptides. An X-ray structure was obtained from crystals grown in DCM.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, J = 8.1 Hz, 1H, NHVal), 7.35–7.25 (m, 5H, Ph), 6.78 (d, J = 6.7 Hz, 1H, NHBn), 5.10 (quint, J = 7.2 Hz, 1H, CHBn), 4.69 (d, J = 6.6 Hz, 1H, Pro-α), 4.04 (t, J = 8.4 Hz, 1H, Val-α), 3.77 (td, J_t = 8.7 Hz, J_d = 2.1 Hz, 1H, Pro-δ), 3.49–3.43 (m, 1H, Pro-δ), 3.05 (qdd, J_q = 6.9 Hz, J_d = 11.3 Hz, J_d = 4.1 Hz, 1H, Asp-α), 2.81 (dd, J_1 = 16.3 Hz, J_2 = 11.3 Hz, 1H, Asp-β), 2.40 (dd, J_1 = 16.2 Hz, J_2 = 4.1 Hz, 1H, Asp-β), 2.43–2.38 (m, 1H, Pro-β/γ), 2.08 (oct, J = 7.1 Hz, 1H, Val-β), 2.00–1.83 (m, 3H, Pro-β/γ), 1.47 (d, J = 6.9 Hz, 3H, MeBn), 1.15 (d, J = 6.9 Hz, 3H, MeAsp), 0.89 (d, J = 6.7 Hz, 3H, Val-γ), 0.84 (d, J = 6.7 Hz, 3H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.1, 173.2, 171.5, 171.4, 142.7, 128.6, 127.4, 126.2, 60.0, 59.9, 49.1, 47.2, 39.0, 34.8, 30.2, 27.9, 24.4, 21.5, 19.5, 18.5, 16.6; **IR** (film, cm^{-1}) 3293, 2972, 2931, 2874, 1635, 1538, 1209, 754; $[\alpha]_D$ = -25.8° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{23}H_{33}N_3O_5H]^+$, requires m/z = 432.2498, found m/z = 432.2505 (ESI); **TLC** (15:15:2) hexane/ethyl acetate/acetic acid, R_f = 0.15.

3.3 Synthesis of Alkene Isostere 9



10a **10b** **10c** **10d**

Synthesis of Alcohol 10d[3,4] Into a flask were added Boc-Pro-OH (10.8 g, 50.0 mmol, 1.0 equiv), methanol (50 mL, 1.0 M), and benzene (150 mL, 0.3 M). The solution was maintained under a nitrogen atmosphere and cooled in an ice bath (0 °C). (Trimethylsilyl)diazomethane (2.0 M in ether, 25.0 mL, 50.0 mmol, 1.0 equiv) was added dropwise, producing gas evolution. Additional (trimethylsilyl)diazomethane (approximately 6 mL) was added until the solution remained pale yellow. The mixture was returned to ambient temperature (10 min), and volatiles were removed under reduced pressure. The crude mixture was dissolved in ether (70 mL), washed with citric acid (10% aqueous, 2 x 30 mL), brine (15 mL), and sodium bicarbonate (saturated aqueous, 30 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and a fraction of crude methyl ester **10a** was used for the next step.

Into a flask were added one fifth of crude ester **10a** (10.0 mmol, 1.0 equiv), THF (12 mL, 0.8 M), lithium chloride (820 mg, 19.3 mmol, 1.9 equiv), and sodium borohydride (729 mg, 19.3 mmol, 1.9 equiv). The flask was capped with a rubber septum and maintained under a nitrogen atmosphere. The suspension was stirred in an ice bath (0 °C), and ethanol (24 mL, 0.4 M) was added dropwise by addition funnel (over 5 min). The mixture was stirred (40 min), allowed to warm to ambient temperature, and stirred (additional 16 h). Citric acid (10% aqueous, 12 mL, to pH 7) was added, and volatiles were carefully removed under reduced pressure. The mixture was diluted with water (50 mL) and additional citric acid (10% aqueous, 3 mL, to pH 5), extracted with DCM (4 x 30 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and a fraction of crude alcohol **10b** was used for the next step.

Into a flame-dried flask were added DCM (18 mL, 0.3 M) and oxalyl chloride (654 μL, 7.52 mmol, 1.5 equiv). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in a dry ice/acetone bath (-78 °C). DMSO (1.07 mL, 15.1 mmol, 3.0 equiv) was added by syringe, producing gas evolution. The mixture was stirred (15 min). Half the crude alcohol (5.00 mmol, 1.0 equiv) was dissolved in DCM (6 mL, 0.8 M) and added by syringe. The mixture was stirred (15 min), and triethylamine (2.80 mL, 20.0 mmol, 4.0 equiv) was added. The mixture was stirred (5 min), transferred to an ice bath (0 °C), stirred (additional 1 h), quenched with sodium bicarbonate (saturated aqueous, 100 mL), extracted with ether (130 mL), and dried with

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[3] a) Borohydride procedure from: S. Mori, T. Ohno, H. Harada, T. Aoyama, T. Shioiri, *Teteahedron* **1991**, *47*, 5051–5070. b) Swern procedure from: T. Inoue, K. Ito, T. Tozaka, S. Hatakeyama, N. Tanaka, K. T. Nakamura, T. Yoshimoto, *Arch. Biochem. Biophys.* **2003**, *416*, 147–154.

[4] Grignard addition, mesylation, allylic alkylation, and compound data from: T. Ibuka, T. Taga, H. Habashita, K. Nakai, H. Tamamura, N. Fujii, *J. Org. Chem.* **1993**, *58*, 1207–1214.

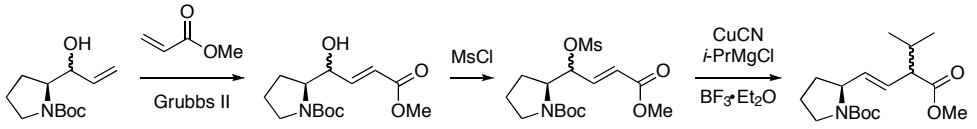
sodium sulfate. Volatiles were removed, and crude aldehyde **10c** was used for the next step.

Crude aldehyde **10c** (5.00 mmol, 1.0 equiv) was placed in a flask, which was capped with a rubber septum and flushed with nitrogen. THF (25 mL, 0.2 M) was added. The solution was cooled in a dry ice/acetonitrile bath (-40 °C), and vinylmagnesium chloride (1.6 M in THF, 6.30 mL, 10.0 mmol, 4.0 equiv) was added. The solution was stirred (5 min), transferred to an ice bath (0 °C), stirred (additional 30 min), quenched with citric acid (10% aqueous, 60 mL), concentrated under reduced pressure, extracted with ethyl acetate (100 mL), washed with sodium bicarbonate (saturated aqueous, 60 mL) and brine (60 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (130 mL silica gel, [12:1 then 8:1] chloroform/ethyl acetate), yielding pure and diastereomerically mixed fractions of the desired product (636 mg combined, 2.80 mmol, 56% yield overall, d.r. = [0.8:1] desired/undesired). It was found most convenient to collect both diastereomers and separate them after additional transformations.

Desired diastereomer (***S,S***, upper spot by TLC): **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.80 (ddd, J_1 = 17.1 Hz, J_2 = 10.7 Hz, J_3 = 6.7 Hz, 1H), 5.30 (d, J = 17.1 Hz, 1H), 5.17 (d, J = 10.7 Hz, 1H), 3.98–3.92 (m, 1H), 3.85–3.80 (m, 1H), 3.50–3.42 (m, 1H), 3.34–3.28 (m, 1H), 1.92–1.65 (m, 4H), 1.47 (s, 9H); **TLC** (10:1) chloroform/ethyl acetate, R_f = 0.31.

Undesired diastereomer (***S,R***, lower spot by TLC): **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.74 (ddd, J_1 = 16.8 Hz, J_2 = 10.5 Hz, J_3 = 6.1 Hz, 1H), 5.24 (d, J = 17.1 Hz, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.14–4.08 (m, 1H), 4.04–3.97 (m, 1H), 3.46–3.40 (m, 1H), 3.18–3.12 (m, 1H), 2.04–1.95 (m, 1H), 1.85–1.76 (m, 1H), 1.70–1.60 (m, 2H), 1.40 (s, 9H); **TLC** (10:1) chloroform/ethyl acetate, R_f = 0.25.

Product analysis is consistent with published data.[4]



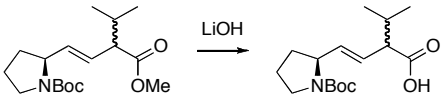
10d **10e** **10f** **10**

Synthesis of Ester 10[4] Methyl acrylate was purified by distillation (80–81 °C). Into a flask were added allyl alcohol **10d** (mixture of diastereomers, 2.10 g, 9.25 mmol, 1.0 equiv), DCM (25 mL, 0.4 M), methyl acrylate (4.16 mL, 46.3 mmol, 5.0 equiv), and Grubbs's second generation metathesis catalyst (196 mg, 0.231 mmol, 2.5 mol %). The flask was fit with a reflux condenser and warmed in an oil bath (40 °C, 18 h). Additional acrylate and catalyst (equal amounts to previous) were added, and the reaction was continued (additional 17 h). Volatiles were removed under reduced pressure, and the crude mixture was passed through a short silica gel plug (125 mL silica gel, [5:1] chloroform/ethyl acetate), yielding crude γ-hydroxyester **10e** (1.67 g, 5.86 mmol, 63% yield), which was used for the next step. **TLC** (5:1) chloroform/ethyl acetate, R_f = 0.22.

Into a flask were added crude hydroxyester **10e** (5.86 mmol, 1.0 equiv), chloroform (10 mL, 0.6 M), and pyridine (9.5 mL, 117 mmol, 20 equiv). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 °C). Methanesulfonyl chloride (6.70 mL, 59.0 mmol, 10 equiv) was added by

syringe. The mixture was stirred (50 min), quenched with water (100 mL), warmed to ambient temperature, extracted with ether (100 mL), washed with citric acid (10% aqueous, 50 mL), brine (50 mL), and sodium bicarbonate (saturated aqueous, 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude mixture was passed through a short silica gel plug (120 mL silica gel, [3:1 then 1:1] hexane/ethyl acetate), yielding crude mesylate **10f** (1.54 g, 4.24 mmol, 72% yield), which was used for the next step. **TLC** (1:1) hexane/ethyl acetate, $R_f = 0.37$.

Into a flame-dried flask (250 mL) were added dry copper (I) cyanide (1.14 g, 12.7 mmol, 3.0 equiv) and THF (65 mL, 0.07 M). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in a dry ice/acetone bath (-78 °C). Isopropylmagnesium chloride (2.0 M THF, 6.36 mL, 12.7 mmol, 3.0 equiv) was added to the suspension. The mixture was transferred to an ice bath (0 °C), stirred (15 min), and returned to the dry ice/acetone bath. Borontrifluoride etherate (1.60 mL, 12.7 mmol, 3.0 equiv) was added to the deep maroon solution, and the mixture was stirred (5 min). Crude mesylate **10f** was placed in a flask, flushed with nitrogen, dissolved in THF (30 mL), and added to the reaction mixture dropwise (over 20 min). The mixture was stirred (additional 30 min), quenched with a mixture of ammonium hydroxide and saturated ammonium chloride (1:1, 30 mL), returned to ambient temperature, diluted with water (50 mL), extracted with ether (3 x 80 mL), washed with brine (100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, yielding nearly pure desired product (1.23 g, 3.95 mmol, 93% yield). The two diastereomers were not readily distinguished by ^{1}H NMR or TLC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.45–5.39 (m, 2H), 4.25–4.17 (m, 1H), 3.63 (s, 3H), 3.40–3.30 (m, 2H), 2.63 (t, J = 8.7 Hz, 1H), 2.00–1.88 (m, 2H), 1.86–1.76 (m, 2H), 1.69–1.61 (m, 1H), 1.39 (s, 9H), 0.89–0.82 (m, 6H); **TLC** (1:1) hexane/ethyl acetate, R_f = 0.64. Product analysis is consistent with published data.[4]



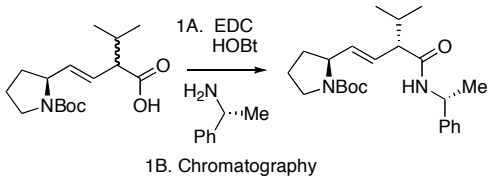
10 **9a**

Synthesis of Acid 9a[5] Into a flask were added methyl ester **10** (1.20 g, 3.86 mmol, 1.0 equiv), dioxane (19 mL, 0.2 M), and lithium hydroxide (2.0 M aqueous, 19.0 mL, 38.0 mmol, 10 equiv). The mixture was stirred (14 h), cooled in an ice bath (0 °C), and neutralized with hydrochloric acid (6 M aqueous, approximately 6 mL, to pH 7). The mixture was concentrated under reduced pressure, further acidified with hydrochloric acid (to pH 1), diluted with water (50 mL), extracted with ethyl acetate (2 x 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure to yield the desired product (quantitative), a fraction of which was used directly for the next step. The two diastereomers were not readily distinguished by ^{1}H NMR or TLC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.48–5.42 (m, 2H), 4.35–4.19 (m, 1H), 3.42–3.28 (m, 2H), 2.67–2.62 (m, 1H), 2.04–1.92 (m, 2H), 1.85–1.75 (m, 2H), 1.70–1.63 (m, 1H), 1.40 (s, 9H), 0.95–0.85 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 179.6, 179.5, 154.7,

[5] Hydrolysis procedure from: H. Yang, X. C. Sheng, E. M. Harrington, K. Ackerman, A. M. Garcia, M. D. Lewis, *J. Org. Chem.* **1999**, *64*, 242–251.

134.9, 134.7, 126.1, 79.3, 58.1, 56.6, 46.1, 32.2, 30.1, 28.4, 22.7, 20.7, 19.5; **IR** (film, cm^{-1}) 3089, 2966, 2868, 1732, 1695, 1650, 1417, 1393, 1168; $[\alpha]_D$ = -27.6° (*c* = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{16}H_{27}NO_4H]^+$, requires *m*/*z* = 298.2018, found *m*/*z* = 298.2029 (ESI); **TLC** (10:10:1) hexane/ethyl acetate/acetic acid, R_f = 0.55.

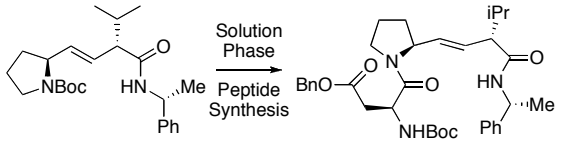


9a **9b**

Synthesis of Amide 9b Into a flask were added half of crude acid **9a** (573 mg, 1.93 mmol, 1.0 equiv), DCM (10 mL, 0.2 M), (*R*)-(+)-α-methylbenzylamine (299 μL, 2.32 mmol, 1.2 equiv), HOBt hydrochloride (325 mg, 2.12 mmol, 1.1 equiv), and EDC hydrochloride (407 mg, 2.12 mmol, 1.1 equiv). The mixture was stirred (17 h), diluted with DCM (50 mL), washed with sodium bicarbonate (saturated aqueous, 40 mL), brine (40 mL), and citric acid (10% aqueous, 40 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (250 mL silica gel, [11:1 then 7:1] toluene/acetone). The two diastereomers were readily separated, yielding pure desired diastereomer (325 mg, 42% yield) plus undesired diastereomer and mixed fractions (367 mg, 48% yield, 90% yield overall from methyl ester **10**). By NMR, at room temperature each isomer showed two rotational states, whose signals coalesce at 100 ºC in DMSO-d_6. The desired diastereomer was identified first by carrying diasteromerically enriched material to this point and identifying the major product and later by X-ray crystallography. X-Ray quality crystals were grown from a dilute hexane solution at ambient temperature.

Desired diastereomer (***S*,*S*,*R***, upper spot by TLC): **^{1}H NMR** (DMSO-d_6, 100 °C, 500 MHz) δ 7.68 (s, 1H), 7.33–7.24 (m, 4H), 7.21–7.16 (m, 1H), 5.52–5.43 (m, 2H), 4.94 (quint, *J* = 7.4 Hz, 1H), 4.21 (dd, J_1 = 7.0 Hz, J_2 = 3.2 Hz, 1H), 3.34–3.23 (m, 2H), 2.58 (t, *J* = 7.4 Hz, 1H), 2.04–1.93 (m, 1H), 1.91–1.82 (m, 1H), 1.80–1.72 (m, 2H), 1.67–1.59 (m, 1H), 1.32 (s, 9H), 1.36 (d, *J* = 7.0 Hz, 3H), 0.82–0.76 (m, 6H); **^{13}C NMR** (DMSO-d_6, 100 °C, 125 MHz) δ 171.3, 153.0, 144.2, 132.5, 127.5, 127.3, 125.7, 125.4, 77.4, 57.3, 56.1, 47.2, 45.3, 31.2, 29.4, 27.6, 22.0, 21.2, 19.8, 19.0; **IR** (film, cm^{-1}) 3306, 2870, 2931, 2872, 1694, 1641, 1538, 1396, 1170, 700; $[\alpha]_D$ = +7.2° (*c* = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{24}H_{36}N_2O_3H]^+$, requires *m*/*z* = 401.2804, found *m*/*z* = 401.2816 (ESI); **TLC** (10:1) toluene/acetone, R_f = 0.27.

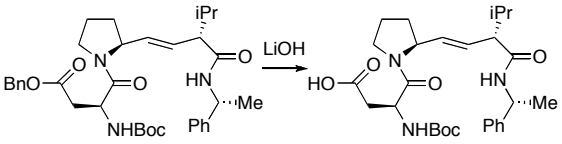
Undesired diastereomer (***S*,*R*,*R***, lower spot by TLC): **^{1}H NMR** (DMSO-d_6, 100 °C, 500 MHz) δ 7.65 (d, *J* = 7.3 Hz, 1H), 7.32–7.25 (m, 4H), 7.21–7.16 (m, 1H), 5.51–5.42 (m, 2H), 4.95 (quint, *J* = 7.4 Hz, 1H), 4.22–4.17 (m, 1H), 3.34–3.24 (m, 2H), 2.60 (t, *J* = 8.2 Hz, 1H), 2.00–1.88 (m, 2H), 1.80–1.72 (m, 2H), 1.62–1.57 (m, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H), 0.89 (d, *J* = 6.3, 3H), 0.87 (d, *J* = 6.8, 3H); **^{13}C NMR** (DMSO-d_6, 100 °C, 125 MHz) δ 171.2, 152.9, 144.0, 132.3, 127.8, 127.3, 125.7, 125.3, 77.4, 57.2, 56.1, 46.9, 45.3, 31.0, 29.3, 27.6, 22.1, 21.3, 19.8, 19.1; **IR** (film, cm^{-1}) 3303, 2971, 2929, 2872, 1694, 1641, 1539, 1393, 1169, 699; $[\alpha]_D$ = -44.0° (*c* = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{24}H_{36}N_2O_3H]^+$, requires *m*/*z* = 401.2804, found *m*/*z* = 401.2818 (ESI); **TLC** (10:1) toluene/acetone, R_f = 0.19.



9b **9c**

Synthesis of Ester 9c The standard solution phase peptide synthesis was followed using amide **9b** (270 mg, 0.675 mmol, 1.0 equiv), hydrogen chloride (4.0 M in dioxane, 2 mL), DCM (5 mL, 0.1 M), triethylamine (140 μL, 1.00 mmol, 1.5 equiv), Boc-Asp(OBn)-OH (317 mg, 0.981 mmol, 1.5 equiv), EDC hydrochloride (248 mg, 1.30 mmol, 1.9 equiv), and HOBt hydrate (202 mg, 1.32 mmol, 1.9 equiv). The crude material was purified via column chromatography (40 mL silica gel, [1:1] hexane/ethyl acetate), yielding the desired product (234 mg, 2.80 mmol, 57% yield). By NMR, at room temperature the product showed two rotational states (approximately 2.5:1), whose signals coalesce at 100 ºC in DMSO-d_6.

^{1}H NMR (DMSO-d_6, 100 °C, 500 MHz) δ 7.53 (d, J = 8.2 Hz, 1H), 7.36–7.25 (m, 9H), 7.20–7.15 (m, 1H), 6.58–6.44 (brs, 1H), 5.49 (s, 2H), 5.10 (s, 2H), 4.94 (quint, J = 7.3 Hz, 1H), 4.67 (q, J = 7.2 Hz, 1H), 4.52–4.47 (m, 1H), 3.65–3.40 (m, 2H), 2.76 (dd, J_1 = 15.8 Hz, J_2 = 6.2 Hz, 1H), 2.63–2.55 (m, 2H), 1.98–1.75 (m, 4H), 1.73–1.65 (m, 1H), 1.38 (s, 9H), 1.36 (d, J = 7.0 Hz, 3H), 0.80–0.77 (m, 6H); **^{13}C NMR** (DMSO-d_6, 100 °C, 125 MHz) δ 171.1, 169.2, 167.9, 144.1, 135.4, 131.6, 127.7, 127.4, 127.2, 127.1, 125.7, 125.4, 78.5, 77.9, 65.1, 57.2, 55.9, 48.8, 47.2, 45.3, 29.2, 27.6, 21.2, 19.9, 18.9; **IR** (film, cm^{-1}) 3313, 2972, 2930, 2869, 1734, 1713, 1642, 1168, 754; **$[\alpha]_D$** = +9.9° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{35}H_{47}N_3O_6H]^+$, requires m/z = 606.3543, found m/z = 606.3546 (ESI); **TLC** (3:2) ethyl acetate/hexane, R_f = 0.30.



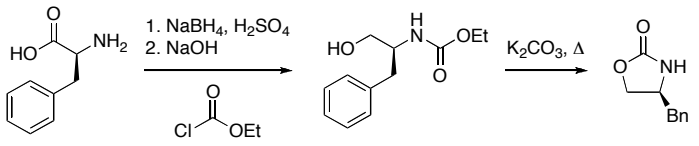
9c **9**

Synthesis of Alkene Isoster 9 Into a flask were added benzyl ester **9c** (195 mg, 0.322 mmol, 1 equiv), dioxane (8.4 mL, 0.04 M), water (4.2 mL, 0.08 M), and a solution of lithium hydroxide (2.0 M aqueous, 0.644 mmol, 322 μL, 2.0 equiv). The mixture was stirred (17 h), diluted with water (50 mL) and sodium carbonate (10% aqueous, 1 mL, to pH 9), washed with ether (2 x 50 mL), acidified with hydrochloric acid (1 M aqueous, approximately 2 mL, to pH 1), extracted with ethyl acetate (3 x 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (40 mL silica gel, [15:15:2] hexane/ethyl acetate/acetic acid) and azeotrope (5 x benzene), yielded the desired product (152 mg, 0.295 mmol, 92% yield). By NMR, at ambient temperature the product shows two rotational states (3.5:1), whose signals coalesce at 100 ºC in DMSO-d_6. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY and comparison to previous compounds.

^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz, major signals) δ 7.40–7.14 (m, 5H, Bn), 6.31 (quint, J = 8.1 Hz, BnHN), 5.63–5.53 (m, 1H, Val-vinyl), 5.34 (dd, J_1 = 15.6 Hz, J_2 = 6.8

Hz, 1H, Pro-vinyl), 5.24 (d, J = 10.9 Hz, 1H, BocNH), 5.17 (quint, J = 7.4 Hz, 1H, BnCH), 4.80–4.70 (m, 1H, Asp-α), 4.60–4.55 (m, 1H, Pro-α), 3.77–3.60 (m, 2H, Pro-δ), 2.63 (dd, J_1 = 15.6 Hz, J_2 = 8.2 Hz, 1H, Asp-β), 2.54 (dd, J_1 = 10.2 Hz, J_2 = 7.2 Hz, 1H, Val-α), 2.47 (dd, J_1 = 15.3 Hz, J_2 = 5.2 Hz, 1H, Asp-β), 2.19 (d, J = 7.8 Hz, 1H, Val-β), 2.08–1.98 (m, 1H, Pro-β), 1.95–1.88 (m, 2H, Pro-γ), 1.78–1.70 (m, 1H, Pro-β), 1.50 (d, J = 7.0 Hz, 3H, MeBn), 1.44 (s, 9H, Boc), 0.88–0.80 (m, 6H, Val-γ); **^{1}H NMR** (DMSO-d_6, 100 °C, 500 MHz) δ 7.55 (d, J = 8.1 Hz, 1H, BnNH), 7.32–7.26 (m, 4H, Bn), 7.20–7.16 (m, 1H, Bn), 6.48–6.25 (brs, 1H, BocHN), 5.50 (s, 2H, vinyl), 4.94 (quint, J = 7.4 Hz, 1H, BnCH), 4.59 (q, J = 6.6 Hz, 1H, Asp-α), 4.55–4.50 (brs, 1H, Pro-α), 3.65–3.40 (m, 2H, Pro-δ), 2.61 (dd, J_1 = 16.1 Hz, J_2 = 6.2 Hz, 1H, Asp-β), 2.58–2.55 (m, 1H, Val-α), 2.45 (dd, J_1 = 16.0 Hz, J_2 = 7.0 Hz, 1H, Asp-β), 2.00–1.80 (m, 4H, Pro-β, Val-β, Pro-γ), 1.74–1.65 (m, 1H, Pro-γ), 1.39 (s, 9H, Boc), 1.37 (d, J = 7.0 Hz, 3H, Me), 0.81–0.77 (m, 6H, Val-γ); **^{13}C NMR** (DMSO-d_6, 100 °C, 125 MHz) δ 171.2, 170.6, 168.4, 154.2, 144.2, 131.7, 127.6, 127.4, 125.7, 127.4, 77.9, 57.0, 56.0, 48.9, 47.2, 45.3, 36.7, 29.2, 27.6, 21.3, 19.9, 19.0; **IR** (film, cm^{-1}) 3309, 2968, 2931, 2870, 1712, 1635, 1526, 1448, 1168, 753; **$[\alpha]_D$** = -6.2° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{28}H_{41}N_3O_6H]^+$, requires m/z = 516.3074, found m/z = 516.3083 (ESI); **TLC** (15:15:2) hexane/ethyl acetate/acetic acid, R_f = 0.21.

3.4 Synthesis of Fluoroalkene Isostere 11



Synthesis of Oxazolidinone 12b[6] Into a flask (1 L) were added sodium borohydride (20.0 g, 530 mmol, 2.6 equiv), THF (200 mL, 1.0 M), and L-phenylalanine (33.0 g, 200 mmol, 1.0 equiv). The mixture was cooled in an ice bath (0 °C). With cooling in an ice bath, sulfuric acid (concentrated, 13.2 mL, 250 mmol, 1.25 equiv) was ***carefully*** mixed with ether (to 40 mL total volume), and added dropwise (over 40 min) via an addition funnel to the phenylalanine solution, producing gas evolution. The heterogeneous mixture was stirred (30 min), warmed to ambient temperature, stirred (additional 14 h), concentrated under reduced pressure (to approximately half the volume), cooled in an ice bath (0 °C), and ***carefully*** diluted with sodium hydroxide (40.0 g in 200 mL water, 5 M, 1.00 mol, 5.0 equiv) dropwise via an addition funnel. This process was exothermic and caused gas evolution (possibly solvent boiling). The mixture was heated to distill volatiles (<100 °C) and maintained at reflux (3 h). The resulting biphasic mixture was used for the next step.

The biphasic mixture was cooled in an ice bath (0 °C) and diluted with sodium bicarbonate (84 g) and water (150 mL). Ethyl chloroformate (21.0 mL, 271 mmol, 1.36 equiv) was added dropwise via addition funnel. The mixture was warmed to ambient temperature (1.5 h), extracted with ethyl acetate (200 + 100 mL), washed with sodium chloride (50% saturated, 2 x 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and crude hydroxycarbamate **12a** was used for the next step.

Potassium carbonate (140 mg, 1.00 mmol, 0.005 equiv) was added to crude hydroxycarbamate **12a**. The mixture was maintained at 45–50 mBar in an automatically controlled rotary evaporator and heated to 125–130 ºC with an oil bath. Remaining ethyl acetate distilled within the first ten minutes. The mixture stopped bubbling as it continued to warm but began bubbling again after about fifteen minutes. The bubbling subsided after approximately 1.5 h, indicating completion of the reaction, and the mixture was cooled. The resulting thick yellow oil (30.7 g, 173 mmol, 87% yield) was used for the next step. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36–7.15 (m, 5H), 5.80–5.50 (brs, 1H), 4.44 (t, J = 8.2 Hz, 1H), 4.18–4.05 (m, 2H), 2.89–2.85 (m, 2H). Compound analysis is consistent with published data.[7]

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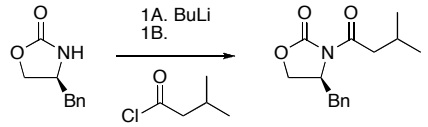
[6] a) Procedures from: Y. Wu, X. Shen, *Tetrahedron: Asymmetry* **2000**, *11*, 4359–4363. b) Reduction procedure from: A. Abiko, S. Masamune, *Tetrahedron Lett.* **1992**, *33*, 5517–5518.

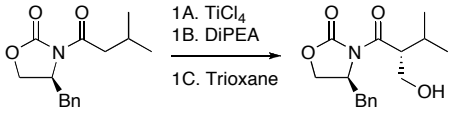
[7] A. Correa, J.–N. Denis, A. E. Greene, *Synth. Comm.* **1991**, *21*, 1–9.



12b **12c**

Synthesis of Imide 12c[8] Into a flame-dried flask were added crude oxazolidinone **12b** (32.9 g, 186 mmol, 1.0 equiv), THF (375 mL, 0.5 M), and triphenylmethane (an indicator, 50 mg, 0.20 mmol, 0.001 equiv). An oven-dried addition funnel was attached, and the system was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in a dry ice/acetone bath (-78 °C). *n*-Butyllithium (2.5 M in hexanes, 75.0 mL, 186 mmol, 1.0 equiv) was added dropwise (over 35 min). Additional butyllithium solution (approximately 25 mL) was added until the solution changed from yellow to orange (a discernable but not sharp color change). Isovaleryl chloride (34.3 mL, 279 mL, 1.5 equiv) was added (in one portion). The mixture was stirred (10 min), allowed to warm to ambient temperature (1 h), returned to the ice bath, quenched with sodium bicarbonate (saturated aqueous, 200 mL), stirred (30 min, giving pH 8), concentrated under reduced pressure, diluted with water (200 mL) and sodium carbonate (10% aqueous, 50 mL), extracted with ethyl acetate (200 + 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure. Attempts to crystallize the product at this point resulted in an oil contaminating the crystals. The crude material was purified via short column chromatography (800 mL silica gel, 3 cm high x 18 cm wide, [2:1] hexanes/ether), yielding an oil, which was mostly desired product. This material was dissolved in ether (70 mL) and hexane (700 mL) and allowed to crystallize (-20 °C, 12 h). White crystals of the desired product (31.2 g, 120 mmol, 64% yield) were isolated by vacuum filtration, washed with cold hexanes, and dried under high vacuum.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.32 (m, 2H), 7.30–7.26 (m, 1H), 7.23–7.20 (m, 2H), 4.72–4.65 (m, 1H), 4.21–4.14 (m, 2H), 3.31 (dd, J_1 = 14.0 Hz, J_2 = 3.0 Hz, 1H), 2.89 (dd, J_1 = 17.7 Hz, J_2 = 6.7 Hz, 1H), 2.82–2.73 (m, 2H), 2.22 (sept, J = 6.4 Hz, 1H), 1.04–1.00 (m, 6H); $[\alpha]_D$ = +49.2º (c = 1.0, $CHCl_3$); previously reported = +55.8º (c = 1.0, $CHCl_3$).[8] Compound analysis is consistent with published data.[8]



12c **12**

Synthesis of Hydroxyimide 12[9,10] Titanium tetrachloride was purified by distillation under argon (137 ºC). Pure material was collected directly into a flask with a stopcock adaptor, capped, sealed, and used immediately. Over time the joints became tightly sealed, presumably by TiO_2 buildup. It was found that using impure titanium

[8] D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, *Tetrahedron* **1988**, *44*, 5525–5540.

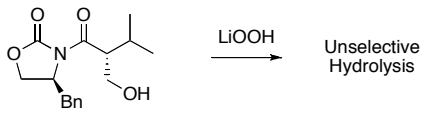
[9] Aldol procedure from: D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bildeaux, *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

[10] Aldol procedure and compound data from: J. M. Takacs, M. R. Jaber, A. S. Vellekoop, *J. Org. Chem.* **1998**, *63*, 2742–2748.

tetrachloride or imide **12c** resulted in significantly reduced yields and diastereoselectivity.

Into a flask were added imide **12c** (24.1 g, 92.3 mmol, 1.0 equiv) and DCM (462 mL, 0.2 M). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ºC). Titanium tetrachloride (10.1 mL, 92.4 mmol, 1.0 equiv) was added dropwise (over 10 min). At this point the solution solidified. More DCM was added and the suspension was stirred vigorously (additional 10 min). Hünig's base (17.7 mL, 101.6 mmol, 1.1 equiv) was added dropwise (over 15 min), producing a deep reddish purple mixture, which was stirred (additional 45 min). Trioxane (9.99 g, 111 mmol, 1.2 equiv) was dried in a desiccator, dissolved in DCM (10 mL), and added by syringe. An additional equivalent of titanium tetrachloride was added dropwise. The mixture was stirred (2.5 h), quenched with ammonium chloride (saturated aqueous, 200 mL), and diluted with water (150 mL). The organic layer was isolated, and the aqueous layer was further extracted with DCM (100 mL). The combined organic layers were washed with sodium bicarbonate (50% saturated aqueous, 200 mL) and ammonium chloride (50% saturated aqueous, 100 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure. The crude material was purified via short column chromatography (silica gel, 2.5 cm high, [2:1] ether/DCM), yielding a pale yellow solid. This material was mixed with boiling ether (380 mL) and allowed to crystallize (-20 ºC, 12 h). White crystals of the desired product (19.9 g, 68.4 mmol, 74% yield) were isolated by vacuum filtration, washed with cold ether, and dried under high vacuum. Only a single isomer was detectable by NMR.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.24 (m, 5H), 4.76–4.69 (m, 1H), 4.24–4.17 (m, 2H), 3.96–3.85 (m, 3H), 3.32 (dd, J_1 = 13.5 Hz, J_2 = 3.5 Hz, 1H), 2.83 (dd, J_1 = 13.5 Hz, J_2 = 9.4 Hz, 1H), 2.13 (oct, J = 7.2 Hz, 1H), 2.06–2.02 (m, 1H), 1.02–0.96 (m, 6H). Compound analysis is consistent with published data.[11]

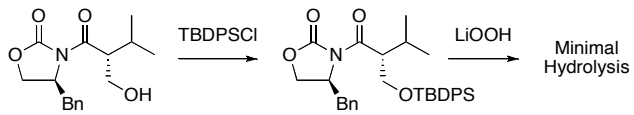


12

Unselective Hydrolysis of Imide 12 Into a flask were added imide **12** (127 mg, 0.436 mmol, 1.0 equiv) and THF (1.5 mL, 0.3 M). The mixture was cooled in an ice bath (0 ºC), and to it were added hydrogen peroxide (30% aqueous = 8.8 M, 248 μL, 2.18 mmol, 5.0 equiv) and lithium hydroxide (1.0 M aqueous, 872 μL, 0.872 mmol, 2.0 equiv). The mixture was warmed to ambient temperature, stirred (1 h), quenched with sodium sulfite (saturated aqueous, 2 mL) and ammonium chloride (saturated aqueous, 1 mL), diluted with water (5 mL), acidified with hydrochloric acid (1.0 M, to pH 1), extracted with ethyl acetate (20 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude mixture was analyzed by ^{1}H NMR, which showed nonspecific conversion (75% hydrolysis product, 25% byproduct). The byproduct is consistent with a

[11] a) Uncharacterized compound: R. J. Watson, D. Batty, A. D. Baxter, D. R. Hannah, D. A. Owen, J. G. Montana, *Tetrahedron Lett.* **2002**, *43*, 683–685. b) Characterized enantiomer: D. L. Boger, J. Hong, *J. Am. Chem. Soc.* **2001**, *123*, 8515–8519.

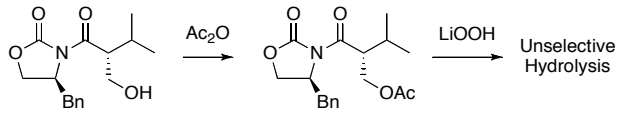
published observation that with sterically hindered oxazolidinone imides, hydrolytic opening of the oxazolidinone ring competes with the desired hydrolytic cleavage.[10]



12 **13a**

Failed Hydrolysis of TBDPS Ether 13a Into a flame-dried flask were added imide **12** (108 mg, 0.371 mmol, 1.0 equiv), DCM (3,7 mL, 0.1 M), and imidazole (30 mg, 0.45 mmol, 1.2 equiv). The flask was capped with a rubber septum and maintained under a nitrogen atmosphere. *tert*-Butyldimethylsilyl chloride (105 μL, 0.408 mmol, 1.1 equiv) was added by syringe. The mixture was stirred (2 h, producing precipitate), quenched with water (20 mL), diluted with brine (20 mL), extracted with DCM (30 mL), and dried with sodium sulfate. Volatiles were removed, and crude silyl ether **13a** was used to test the hydrolysis step. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.73–7.67 (m, 5H), 7.45–7.20 (m, 10H), 4.76–4.70 (m, 1H), 4.18–4.08 (m, 4H), 3.87–3.84 (m, 1H), 3.43 (dd, J_1 = 13.2 Hz, J_2 = 3.5 Hz, 1H), 2.54 (dd, J_1 = 13.2 Hz, J_2 = 10.4 Hz, 1H), 1.96 (oct, J = 7.0 Hz, 1H), 1.03 (s, 9H), 0.91 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); **TLC** (1:1) hexane/ether, R_f = 0.67.

Into a flask were added half of crude imide **13a** (0.186 mmol, 1.0 equiv), THF (1.5 mL, 0.1 M), and water (100 μL, 1.9 M). The mixture was cooled in an ice bath (0 °C), and to it was added hydrogen peroxide (30% aqueous = 8.8 M, 106 μL, 0.930 mmol, 5.0 equiv) and lithium hydroxide (1.0 M aqueous, 372 μL, 0.372 mmol, 2.1 equiv). The mixture was warmed to ambient temperature, stirred (13 h), quenched with sodium sulfite (saturated aqueous, 1 mL), diluted with water (5 mL), acidified with hydrochloric acid (1.0 M aqueous, to pH 1), extracted with ethyl acetate (20 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude mixture was analyzed by ^{1}H NMR, which showed minimal conversion (>90% starting material).

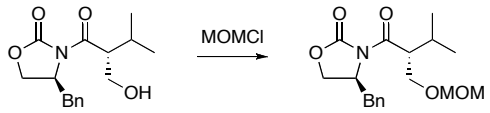


12 **13b**

Unselective Hydrolysis of Acetate 13b Into a flask were added imide **12** (22 mg, 0.076 mmol, 1.0 equiv), DCM (760 μL, 0.1 M), DMAP (2 mg, 0.02 mmol, 0.2 equiv), pyridine (18 μL, 0.23 mmol, 3.0 equiv), and acetic anhydride (14 μL, 0.15 mmol, 2.0 equiv). The mixture was stirred (3 h), diluted with DCM (20 mL), washed with sodium bicarbonate (saturated aqueous, 20 mL) and citric acid (10% aqueous, 20 mL), and dried with sodium sulfate. Volatiles were removed, and crude acetate **13b** was used to test the hydrolysis step. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.38–7.25 (m, 5H), 4.78–4.72 (m, 1H), 4.47 (dd, J_1 = 11.9 Hz, J_2 = 5.0 Hz, 1H), 4.38 (t, J = 10.0 Hz, 1H), 4.24–1.19 (m, 2H), 4.10–4.05 (m, 1H), 3.29 (dd, J_1 = 13.5 Hz, J_2 = 3.0 Hz, 1H), 2.83 (dd, J_1 = 13.5 Hz, J_2 = 9.3 Hz, 1H), 2.10 (oct, J = 6.8 Hz, 1H), 1.03 (t, J = 6.8 Hz, 3H); **TLC** (1:1) hexane/ether, R_f = 0.37.

Into a flask were added crude acetate **13b** (0.076 mmol, 1.0 equiv), THF (760 μL, 1.0 M), and water (200 μL, 0.4 M). The mixture was cooled in an ice bath (0 °C), and to it were added hydrogen peroxide (30% aqueous = 8.8 M, 69 μL, 0.61 mmol, 8.0 equiv)

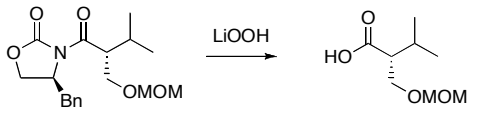
and lithium hydroxide (1.0 M aqueous, 152 μL, 0.152 mmol, 2.0 equiv). The mixture was warmed to ambient temperature, stirred (1 h), quenched with sodium sulfite (saturated aqueous, 1 mL) and ammonium chloride (saturated aqueous, 1 mL), diluted with water (20 mL), acidified with hydrochloric acid (1.0 M, to pH 1), extracted with ethyl acetate (20 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude mixture was analyzed by ^{1}H NMR, which showed incomplete and nonspecific conversion (50% recovered starting material, 40% hydrolysis product, and 10% byproduct).



12 **13c**

Synthesis of MOM Ester 13c[12] Into a flask were added hydroxyimide **12** (11.6 g, 39.9 mmol, 1 equiv), DCM (40 mL, 1.0 M), and Hünig's base (20.8 mL, 120 mmol, 3.0 equiv). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ºC). Chloromethyl methy ether (8.18 mL, 108 mmol, 2.7 equiv) was added by syringe. The mixture was stirred (2.5 h), diluted with DCM (200 mL), washed with ammonium chloride (50% saturated, 200 mL) and sodium bicarbonate (50% saturated, 200 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure to give pure desired product (quantitative), which was used directly for the next step.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.24 (m, 5H), 4.78–4.72 (m, 1H), 4.61 (dd, J_1 = 10.5 Hz, J_2 = 6.6 Hz, 2H), 4.20–4.10 (m, 3H), 3.93 (t, J = 9.4 Hz, 1H), 3.76 (dd, J_1 = 9.2 Hz, J_2 = 4.2 Hz, 1H), 3.35 (s, 3H), 3.26 (dd, J_1 = 13.5 Hz, J_2 = 3.3 Hz, 1H), 2.81 (dd, J_1 = 13.5 Hz, J_2 = 9.2 Hz, 1H), 2.03 (oct, J = 6.9 Hz, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.9, 153.2, 135.4, 129.5, 128.9, 127.3, 96.5, 67.2, 65.5, 55.3, 49.0, 37.7, 28.7, 20.9, 19.4; **IR** (film, cm^{-1}) 2960, 2927, 2874, 1778, 1696, 1387, 1215, 1048; **$[\alpha]_D$** = +29.8° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{18}H_{25}NO_5Na]^+$, requires m/z = 358.1625, found m/z = 358.1617 (ESI); **TLC** (3:1) hexane/ethyl acetate, R_f = 0.19.



13c **13d**

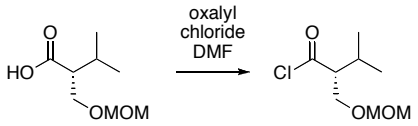
Synthesis of Acid 13d[13] Into a flask was added crude imide **13c** (39.9 mmol), THF (166 mL, 0.24 M), and water (29 mL, 0.73 M). The homogeneous solution was cooled in an ice bath (0 °C). Hydrogen peroxide (30% aqueous = 8.8 M, 28.5 mL, 250 mmol, 6.25 equiv) and lithium hydroxide (1.0 M, 100 mL, 100 mmol, 2.5 equiv) were combined, mixed, and added to the imide solution. The mixture was stirred (1.5 h), allowed to warm

[12] MOM etherification from: T. B. Durham, N. Blanchard, B. M. Savall, N. A. Powell, W. R. Roush, *J. Am. Chem. Soc.* **2004**, *126*, 9307–9317.

[13] Hydrolysis from: A. B. Smith III, K. P. Minbiole, P. R. Verhoest, M. Schelhaas, *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953.

to ambient temperature (over another 1.5 h), returned to the ice bath, quenched with sodium sulfite (saturated aqueous, 100 mL, giving pH 8 solution), washed with DCM (2 x 100 mL, during the first wash the organic layer was the top one, these organic phases contain recovered chiral auxiliary suitable for reuse), acidified with hydrochloric acid (6 M aqueous, 18 mL, to pH 1), extracted with ethyl acetate (3 x 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure to yield pure product (6.70 g, 38.1 mmol, 95% yield from alcohol), a fraction of which was used directly for the next step. Enantiopurity of this compound was assessed by coupling it to each enantiomer of methylbenzylamine. Each product showed a pure diastereomer by ^{1}H NMR.

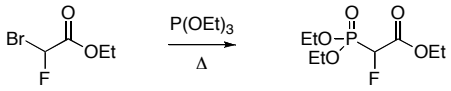
^{1}H NMR ($CDCl_3$, 500 MHz) δ 12.0–11.0 (brs, 1H), 4.59 (s, 2H), 3.76 (t, J = 9.2 Hz, 1H), 3.65 (dd, J_1 = 9.2 Hz, J_2 = 4.7 Hz, 1H), 3.32 (s, 3H), 2.52–2.45 (m, 1H), 1.96 (oct, J = 6.8 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 180.0, 96.5, 67.0, 55.2, 52.7, 28.1, 20.4, 20.3; **IR** (film, cm^{-1}) 2963, 2934, 2877, 1742, 1710, 1109, 1043; **$[\alpha]_D$** = -2.5º (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_8H_{16}O_4Na]^+$, requires m/z = 199.0941, found m/z = 199.0936 (ESI); **TLC** (15:5:1) hexane/ethyl acetate/acetic acid, R_f = 0.20.



13d **13**

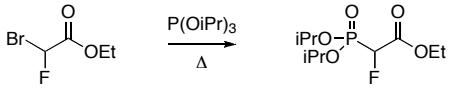
Synthesis of Acid Chloride 13[14] Although this reaction is generally done in hexane, acid **13d** is insoluble in that solvent, and ether was found to be a capable substitute. Also, although MOM groups are acid labile, no deprotection of this group was observed under these conditions. Crude acid **13d** (91% of material, 36.2 mmol, 1.0 equiv) was added into a flame-dried flask and briefly dried under high vacuum. The flask was capped with a rubber septum, maintained under nitrogen, and cooled in an ice bath (0 ºC). To the flask was added ether (74 mL, 0.5 M) and DMF (8.17 mL, 104 mmol, 2.9 equiv). Oxalyl chloride (8.14 mL, 92.9 mmol, 2.6 equiv) was added ***dropwise*** (over 10 min), producing vigorous gas evolution and gooey precipitate. The thick mixture was warmed to ambient temperature, stirred (10 min), diluted with hexane (HPLC grade, 140 mL), mixed, allowed to settle without stirring (another 10 min), decanted into a flame-dried flask, and chased with additional hexane (40 mL). Volatiles were removed under reduced pressure, and the crude material (29 mmol product measured with an internal NMR standard with DMF as the only contaminant, 80% yield from alcohol **12**) was used directly for the next step. The goo remaining in the original flask was found to contain no isopropyl-containing material. The product was only partially characterized due to its reactivity. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.62 (s, 2H), 3.84 (t, J = 9.8 Hz, 1H), 3.73 (dd, J_1 = 9.9 Hz, J_2 = 4.3 Hz, 1H), 3.37 (s, 3H), 2.92–2.83 (m, 1H), 2.13 (oct, J = 6.8 Hz, 1H), 1.05 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H).

[14] Acid chloride formation modified from: D. E. Ward, C. K. Rhee, *Tetrahedron Lett.* **1991**, *32*, 7165–7166.



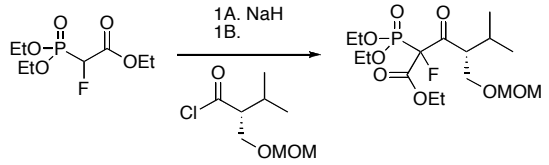
14

Synthesis of α-Fluorophosphonate 14[15] Into a flask were added ethyl bromofluoroacetate (25.0 g, 135 mmol, 1.0 equiv) and triethyl phosphite (58.0 mL, 337 mmol, 2.5 equiv). A reflux condenser was attached and capped with a rubber septum, and the system was maintained under a nitrogen atmosphere. The mixture was heated to 130 ºC (oil bath, 21 h) and cooled to approximately 50 ºC. Volatiles were removed by distillation (0.25 mmHg, up to 105 ºC). The remaining pale yellow oil was pure desired product (25.1 g, 104 mmol, 77% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.20 (dd, J_1 = 47.0 Hz, J_2 = 12.5 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 4.30–4.20 (m, 4H), 1.39–1.32 (m, 9H); **TLC** (3:2) hexane/ethyl acetate, R_f = 0.16. Compound analysis is consistent with published data.[15]



14a

Synthesis of α-Fluorophosphonate 14a[16] Into a flask were added ethyl bromofluoroacetate (3.00 g, 16.2 mmol, 1.0 equiv) and triisopropyl phosphite (5.07 g, 24.3 mmol, 1.5 equiv). A reflux condenser was attached and capped with a rubber septum, and the system was maintained under a nitrogen atmosphere. The mixture was heated to 145 ºC (oil bath, 4 h) and cooled to approximately 50 ºC. The crude mixture was purified by distillation (0.25 mmHg, 117–120 ºC) to give pure desired product (1.00 g, 3.70 mmol, 23% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.14 (dd, J_1 = 48.4 Hz, J_2 = 13.8 Hz, 1H), 4.86–4.67 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 1.38–1.30 (m, 15H); **BP** 117–120 ºC, 0.25 mmHg. Compound analysis is consistent with published data.[16]



14 **13** **15**

Synthesis of Fluorophosphonate 15[17] Into a flame-dried flask was added sodium hydride (1.40 g, 58.3 mmol, 2.0 equiv). The flask was capped with a rubber septum and maintained under a nitrogen atmosphere. THF (70 mL, 0.4 M) was added by syringe, producing a colorless suspension. Phosphonate ester **14** (14.3 mL = 16.9 g, 69.7 mmol,

[15] Arbuzov procedure and compound data from: M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537.

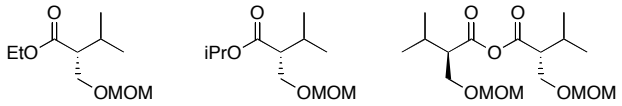
[16] Arbuzov procedure and compound data from: A. Thenappan, D. J. Burton, *J. Org. Chem.* **1990**, *55*, 2311–2317.

[17] Example coupling constants from and acylation and reduction procedures modified from: a) S. Sano, Y. Kuroda, K. Saito, Y. Ose, Y. Nagao, *Tetrahedron* **2006**, 11881–11890. b) S. Sano, K. Saito, Y. Nago, *Tetrahedron Lett.* **2003**, 3987–3990.

2.4 equiv) was added ***dropwise*** (over 30 min) and stirred (30 min), producing gas evolution and giving a clear red solution. Into a second flask were added crude acid chloride **13** (29 mmol, 1 equiv) and THF (30 mL, 1.0 M). This flask was capped with a rubber septum and maintained under a nitrogen atmosphere. Both flasks were cooled in an acetonitrile/dry ice bath (-40 ºC). The phosphonate solution was transferred via cannula into the acid chloride solution. The mixture was stirred (1 h), quenched with ammonium chloride (saturated, 200 mL), warmed to ambient temperature, diluted with water (200 mL), extracted with ethyl acetate (400 + 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was passed through a short silica column (200 mL silica gel, [2:1] hexane/ether to remove non-polar contaminants then [3:2] ethyl acetate/hexane to recover product mixed with remaining phosphonate ester **14**). Two diastereomers were produced (approximately 29 mmol total, approximately 5:1), which were separated on an analytical scale. The combined impure product was stored at -20 ºC and used for the next step.

Major diastereomer (top spot by TLC): **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.47 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.40–4.23 (m, 6H), 3.73–3.64 (m, 2H), 3.30–3.24 (m, 1H), 3.96 (s, 3H), 2.11 (oct, J = 6.9 Hz, 1H), 1.38 (t, J = 7.5 Hz, 3H), 1.36 (t, J = 7.35 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 201.3 (d, J = 25.0 Hz), 161.3 (d, J = 23.3 Hz), 99.1 (dd, J_1 = 209.8 Hz, J_2 = 162.3 Hz), 96.3, 66.4, 64.9 (d, J = 6.3 Hz), 64.8 (d, J = 6.5 Hz), 62.9, 55.2, 52.8, 27.6, 21.3, 19.2, 16.3 (d, J = 6.1 Hz), 16.2 (d, J = 6.5 Hz), 13.8; **IR** (film, cm^{-1}) 2974, 2934, 2884, 1761, 1728, 1279, 1250, 1053, 1021; **$[\alpha]_D$** = +26.4° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{16}H_{30}FO_8PH]^+$, requires m/z = 401.1736, found m/z = 401.1735 (ESI); **TLC** (3:2) hexane/ethyl acetate, R_f = 0.27.

Minor diastereomer (bottom spot by TLC): **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.55–4.51 (m, 2H), 4.38–4.23 (m, 6H), 3.82 (t, J = 9.5 Hz, 1H), 3.62 (dd, J_1 = 9.6 Hz, J_2 = 4.4 Hz), 3.35–3.29 (m, 1H), 3.31 (s, 3H), 2.11 (oct J = 6.8 Hz, 1H), 1.40–1.30 (m, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); **TLC** (3:2) hexane/ethyl acetate, R_f = 0.21



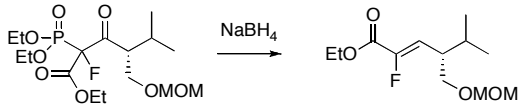
15a **15b** **15c**

If *n*-butyllithium was used instead of sodium hydride, a significant amount of ethyl ester **15a** was obtained. If phosphonate ethyl ester **14** was replaced with phosphonate isopropyl ester **14a**, isopropyl ester **15b** was observed instead. Furthermore, using *n*-butyllithium led to a significant amount of anhydride **15c**.

Ethyl ester **15a**: **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.60 (s, 2H), 4.22–4.13 (m, 2H), 3.77 (t, J = 9.7 Hz, 1H), 3.65 (dd, J_1 = 9.5 Hz, J_2 = 4.7 Hz), 3.34 (s, 3H), 2.50–2.45 (m, 1H), 1.94 (oct J = 6.9 Hz, 1H), 1.27 (t, J = 9.0 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); **LRMS** Calculated for $[C_{10}H_{20}O_4Na]^+$, requires m/z = 227, found m/z = 227 (ESI); **TLC** (3:2) ethyl acetate/hexane, R_f = 0.89.

Isopropyl ester **15b**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.58 (s, 2H), 4.15 (t, J = 7.1 Hz, 1H), 3.75 (t, J = 9.6 Hz, 1H), 3.62 (dd, J_1 = 9.5 Hz, J_2 = 4.7 Hz, 1H), 3.32 (s, 3H), 2.48–2.42 (m, 1H), 1.91 (oct, J = 7.1 Hz, 1H), 1.25 (t, J = 7.1 Hz, 6H), 0.94 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); **TLC** (3:2) hexane/ethyl acetate, R_f = 0.78.

Anhydride **15c**: **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.59 (s, 4H), 3.79 (t, J = 9.5 Hz, 2H), 3.67 (dd, J_1 = 9.7 Hz, J_2 = 4.6 Hz, 2H), 3.34 (s, 6H), 2.59–2.53 (m, 2H), 2.03 (oct J = 6.9 Hz, 2H), 1.03 (d, J = 6.8 Hz, 6H), 1.00 (d, J = 6.8 Hz, 6H); **LRMS** Calculated for $[C_{16}H_{30}O_7Na]^+$, requires m/z = 357, found m/z = 357 (ESI); **TLC** (3:2) ethyl acetate/hexanes, R_f = 0.87.

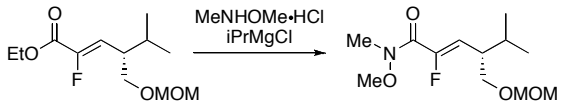


15 **16**

Synthesis of Enoate 16[17] Into a flask were added a semi-pure diastereomeric mixture of phosphonate **15** (29 mmol, 1.0 equiv) and ethanol (HPLC grade, 95 mL, 0.3 M). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in a acetonitrile/dry ice bath (-40 ºC). Into another flask was added ***powdered*** sodium borohydride (5.10 g, 134 mmol, 4.6 equiv) and ethanol (250 mL, 0.1 M). The suspension was mixed in an ultrasonic water bath (2 min, dissolving most of the solid and evolving some gas), capped with a rubber septum, maintained under a nitrogen atmosphere, cooled in the bath (10 min), and quickly poured into the phosphonate solution. The mixture was stirred (2.5 h), quenched with ammonium chloride (saturated aqueous, 350 mL), diluted with water (350 mL), extracted with ethyl acetate (400 + 200 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via a short silica plug (250 mL silica gel, [4:1] hexanes/ether), yielding the desired product (4.95 g, 20.0 mmol, 69% yield from acid chloride **13**). A minor olefin diastereomer (>20:1) could not be separated by TLC. Running the reaction at -78 ºC led to incomplete reaction, and running it at 0 ºC led to decreased selectivity. The major isomer of the phosphonate ester gives better olefin selectivity than the minor isomer. Olefin geometry was assigned by $^3J_{H,F}$ coupling[17] and by X-ray crystallography of a later compound.

Major isomer (***Z***): **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.04 (dd, J_1 = 33.2 Hz, J_2 = 10.7 Hz, 1H), 4.56 (brs, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.58–3.49 (m, 2H), 3.31 (s, 3H), 2.74–2.68 (m, 1H), 1.83 (oct J = 6.7 Hz, 1H), 1.30 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 160.7 (d, J = 35.8 Hz), 148.8 (d, J = 256.8 Hz), 120.6 (d, J = 11.2 Hz), 96.5, 68.5 (d, J = 1.9 Hz), 61.5, 55.2, 42.0, 28.8 (d, J = 1.8 Hz), 20.7, 19.2, 14.1; **IR** (film, cm^{-1}) 2961, 2933, 2876, 1740, 1679, 1312, 1230, 1039; **$[\alpha]_D$** = +23.6º (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{12}H_{21}FO_8Na]^+$, requires m/z = 271.1316, found m/z = 271.1314 (ESI); **TLC** (4:1) hexane/ether, R_f = 0.38.

Minor isomer (***E***, isolated as an enriched but impure mixture): **^{1}H NMR** ($CDCl_3$, 500 MHz, partially reported) δ 5.85 (dd, J_1 = 22.5 Hz, J_2 = 11.1 Hz, 1H), 3.32–3.25 (m, 1H), other signals were indistinguishable from the major isomer; **TLC** (4:1) hexane/ether, R_f = 0.38, indistinguishable from major isomer.



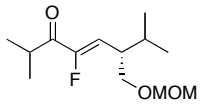
16 **18a**

Synthesis of Weinreb Amide 18a[18] *N*,*O*-Dimethylhydroxyamine was finely ground and dried in a desiccator over phosphorous pentaoxide overnight. Isopropylmagnesium chloride was analyzed by titration as follows.[19] Into a flame-dried flask were added 1,10-phenylanthroline (9 mg), *sec*-butyl alcohol (100 μL, 1.09 mmol), and ether (4 mL, 0.3 M). The Grignard reagent was added dropwise by syringe until the light pink mixture suddenly became a deep violet color.

Into a flame-dried flask were added ester **16** (4.43 g, 17.9 mmol, 1.0 equiv), *N*,*O*-dimethylhydroxyamine (2.62 g, 26.9 mmol, 1.5 equiv), and THF (36 mL, 0.5 M), giving a suspension. The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ˚C). Isopropylmagnesium chloride (1.36 M in THF, 39.5 mL, 53.7 mmol, 3.0 equiv) was added dropwise (over 30 min). The mixture was stirred (additional 45 min), quenched with ammonium chloride (saturated, 200 mL), diluted with water (200 mL), extracted with ethyl acetate (200 + 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (600 mL silica gel, [3:1] hexanes/ether to remove non-polar contaminants, then [2:1] ether/hexane to elute product), yielding the desired product (3.70 g, 14.1 mmol, 79% yield) as a pale yellow oil and a single diastereomer. ^{1}H NMR peaks were assigned by comparison to previous spectra.

Major isomer (***Z***): **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.81 (dd, J_1 = 35.2 Hz, J_2 = 10.6 Hz, 1H, vinyl), 4.60 (s, 2H, O-CH_2-O), 3.74 (s, 3H, NOMe), 3.60–3.52 (m, 2H, CH_2-OMOM), 3.35 (s, 3H, COMe), 3.24 (s, 3H, NMe), 2.78–2.71 (m, 1H, allyl-CH), 1.88 (oct J = 6.7 Hz, 1H, iPr-CH), 0.97 (d, J = 6.7 Hz, 3H, iPr-Me), 0.91 (d, J = 6.8 Hz, 3H, iPr-Me); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 162.4 (d, J = 36.3 Hz), 151.5 (d, J = 256.4 Hz), 117.9 (d, J = 11.3 Hz), 96.4, 68.5, 61.6, 55.1, 41.6, 33.7, 28.7, 20.6, 18.8; **IR** (film, cm^{-1}) 2960, 2932, 2875, 2819, 1650, 1384, 1109, 1041; **$[\alpha]_D$** = +26.4º (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{12}H_{22}FNO_4Na]^+$, requires m/z = 286.1422, found m/z = 286.1421 (ESI); **TLC** (1:1) hexane/ether, R_f = 0.28.

Minor isomer (***E***, isolated as an enriched but impure mixture): **^{1}H NMR** ($CDCl_3$, 400 MHz, partially reported) δ 5.48 (dd, J_1 = 22.8 Hz, J_2 = 11.3 Hz, 1H), other signals were indistinguishable from the major isomer; **TLC** (1:1) hexane/ether, R_f = 0.32



18b

When excess Grignard reagent was used, a significant amount of isopropyl ketone **18b** was recovered. Isolated as an enriched but impure mixture: **^{1}H NMR** ($CDCl_3$, 400 MHz, partially reported) δ 5.98 (dd, J_1 = 34.8 Hz, J_2 = 10.6 Hz, 1H), 3.06 (dsept, J_{sept} = 6.9 Hz, J_d = 1.8 Hz, 1H), 1.11 (d, J = 6.9 Hz, 6H), other signals were indistinguishable from the major product; **TLC** (3:1) hexane/ether, R_f = 0.43.

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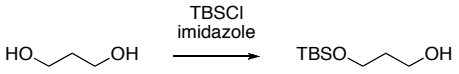
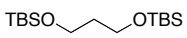
[18] Amination procedure from: W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2007**, *129*, 498–499.

[19] Titration procedure from: S. C. Watson, J. F. Eastman, *J. Organomet. Chem.* **1967**, *9*, 165–168.



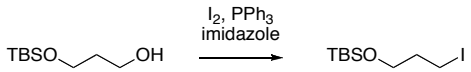
17a

Synthesis of TBS Ether 17a[20] 1,3-Propanediol was distilled (0.25 mmHg, 88–89 ºC). Into a flame-dried flask were added imidazole (4.90 g, 72.0 mmol, 1.2 equiv), DMF (120 mL, 0.5 M), and 1,3-propanediol (43.4 mL, 600 mmol, 10.0 equiv). The flask was fitted with an addition funnel, capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ºC). *tert*-Butyldimethylsilyl chloride (9.04 g, 60.0 mmol, 1.0 equiv) was dissolved in DMF (120 mL, 0.5 M) and added dropwise (over 1 h) to the mixture, which was then allowed to gradually warm to ambient temperature (over 11 h). The mixture was diluted with water (200 mL, somewhat exothermic) and brine (100 mL), returned to ambient temperature, extracted with ether (200 + 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via short column chromatography (250 mL silica gel, [20:1] hexanes/ethyl acetate to remove non-polar contaminants, then [3:1] hexanes/ethyl acetate to elute product), yielding the desired product (9.1 g, 47.9 mmol, 80% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.78–3.85 (m, 4H), 2.53 (t, J = 6.0 Hz, 1H), 1.77 (pent, J = 5.6 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); **TLC** (4:1) hexane/ethyl acetate, R_f = 0.19. Compound analysis is consistent with published data.[21]



17b

Only a small amount of diether **17b** was formed.



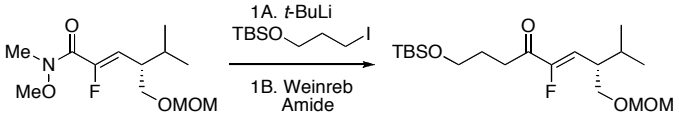
17a **17**

Synthesis of Iodide 17[21] Into a flame-dried flask were added DCM (91 mL, 0.2 M), alcohol **17a** (3.48 g, 18.3 mmol, 1.0 equiv), imidazole (1.37 g, 20.1 mmol, 1.1 equiv), triphenylphosphine (5.42 g, 20.1 mmol, 1.1 equiv), and iodine (5.12 g, 20.1 mmol, 1.1 equiv). The flask was covered with aluminum foil, capped with a rubber septum, and maintained under a nitrogen atmosphere. The flask warmed slightly. The mixture was stirred (2.5 h), producing an orange suspension. White precipitate was removed by vacuum filtration. The filtrate was concentrated (producing red–brown precipitate), diluted with ethyl acetate (20 mL) and hexane (60 mL, causing additional precipitate), and again passed through a vacuum filter. The filtrate was concentrated, giving a fine white suspension. Volatiles were removed under reduced pressure, and the crude material was purified via short column chromatography (40 mL silica gel, [8:1] hexanes/ethyl acetate), yielding the pure product (4.69 g, 15.6 mmol, 85% yield) as a colorless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.66 (t, J = 6.7 Hz, 2H), 3.27 (t, J = 7.6

[20] TBS Ether formation from: G. Zhu, E.–I. Negishi, *Org. Lett.* **2007**, 2771–2774.

[21] Compound data from and iodination procedure modified from: A. B. Smith III, R. J. Fox, J. A. Vanecko, *Org. Lett.* **2005**, *7*, 3099–3102.

Hz, 2H), 1.98 (pent, J = 6.6 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H); **TLC** (8:1) hexane/ether, R_f = 0.90. Compound analysis is consistent with published data.[22]



18a **17** **18**

Synthesis of Enone 18[23] *tert*-Butyllithium (1.7 M in pentane) was transferred via canula from the original sure-seal bottle into an oven-dried storage flask with a Teflon screw-seal top, which was flushed with argon and stored at -20 °C. For use, the reagent was warmed to ambient temperature, maintained under an argon atmosphere, and transferred into a syringe with positive pressure. Pulling the solution into syringes caused significant solvent evaporation. Syringes were quenched with (5:1) hexane/*sec*-butyl alcohol. *tert*-Butyllithium was analyzed by titration as follows.[24] Into a flame-dried flask were added 1,10-phenylanthroline (18 mg), *sec*-butanol (50 μL, 0.55 mmol), and ether (2 mL, 0.3 M). The organolithium reagent was added dropwise by syringe until the yellow mixture suddenly became deep red.

Into a flame-dried flask was added iodide **17** (4.13 g, 13.8 mmol, 2.75 equiv). The flask was dried under high vacuum, capped with a rubber septum, flushed with argon (10 min), and maintained under an argon atmosphere. Ether (70 mL, 0.07 M) was added, and the mixture was cooled in a dry ice/acetone bath (-78 °C). To the solution was added *tert*-butyllithium (1.21 M in pentane, 16.8 mL, 20.3 mmol, 4.0 equiv) dropwise (over 10 min). The mixture was stirred (5 min), warmed to ambient temperature (30 min, causing precipitate), and returned to the cold bath. Into a separate flame-dried flask were added amide **18a** (1.88 g, 5.00 mmol, 1.0 equiv) and ether (15 mL). This flask was capped with a rubber septum, flushed with argon (10 min), maintained under an argon atmosphere, and cooled in the bath. The amide solution was transferred by cannula into the lithium solution. The mixture was stirred (1 h), quenched with ammonium chloride (saturated aqueous, 100 mL), warmed to ambient temperature, diluted with water (100 mL), extracted with ether (150 + 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material (approximately 60% clean conversion) was purified via column chromatography (250 mL silica gel, [5:1] hexanes/ether to elute product then [1:1] hexanes/ether to recover starting material), yielding the pure product (1.11 g, 2.59 mmol, 59% yield) and recovered starting material (400 mg, 1.52 mmol, 30% yield).

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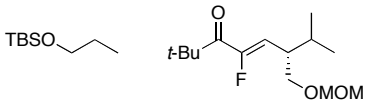
[22] X. Gu, M. Sun, B. Gugiu, S. Hazen, J. W. Crabb, R. G. Salomon, *J. Org. Chem.* **2003**, *68*, 3749–3761.

[23] Lithium-halogen exchange procedure from: a) W. F. Bailey, E. R. Punzalan, *J. Org. Chem.* **1990**, *55*, 5404–5406. b) E.–I. Negishi, D. R. Swanson, C. J. Rousset, *J. Org. Chem.* **1990**, *55*, 5406–5409. Addition to Weinreb amide procedure from: c) W.–H. Jung, C. Harrison, Y. Shin, J.–H. Fournier, R. Balachandran, B. S. Raccor, R. P. Sikorsku, A. Vogt, D. P. Curran, B. W. Day, *J. Med. Chem.* **2007**, *50*, 2951–2966. d) S. P. Fearnley, R. L. Funk, R. J. Gregg, *Tetrahedron* **2000**, *56*, 10275–10281.

[24] Titration procedure from: S. C. Watson, J. F. Eastman, *J. Organomet. Chem.* **1967**, *9*, 165–168.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.99 (dd, J_1 = 34.5 Hz, J_2 = 10.6 Hz, 1H), 4.60 (s, 2H), 3.64 (t, J = 6.1 Hz, 2H), 3.60–3.52 (m, 2H), 3.33 (s, 3H), 2.74–2.67 (m, 3H), 1.92–1.80 (m, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.89–0.83 (m, 12H), 0.03 (s, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 193.9 (d, J = 31.8 Hz), 155.9 (d, J = 262.9 Hz), 118.7 (d, J = 12.1 Hz), 96.5, 68.6, 62.0, 55.3, 41.9, 34.3, 29.0, 26.6, 25.9, 20.7, 19.3, 18.3, -5.4; **IR** (film, cm^{-1}) 2956, 2927, 2823, 2858, 1700, 1655, 1111, 1046, 838; **$[\alpha]_D$** = +17.3° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{19}H_{37}FO_4SiH]^+$, requires m/z = 377.2918, found m/z = 377.2514 (ESI); **TLC** (5:1) hexane/ether, R_f = 0.28.

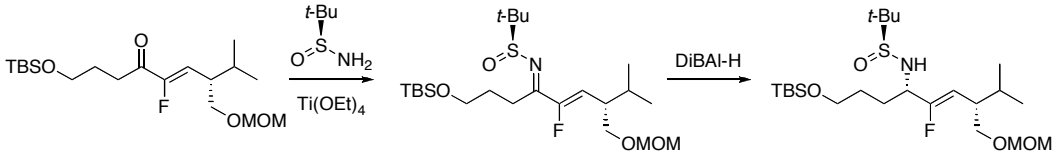


18b **18c**

The major byproduct was dehalogenated alkyliodide **18b**. Isolated as an enriched but impure compound: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.56 (t, J = 8.3 Hz, 2H), 1.53 (pent, J = 8.1 Hz, 2H), 0.90–0.85 (m, 12H), 0.05 (s, 6H); **TLC** (5:1) hexane/ether, R_f = 0.94. Analysis is consistent with published data.[25]

If the iodide solution was not warmed to ambient temperature after *tert*-butyllithium addition, a significant amount of *tert*-butylketone **18c** was recovered. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.98 (dd, J_1 = 35.0 Hz, J_2 = 10.7 Hz, 1H), 4.58 (s, 2H), 3.60–3.50 (m, 2H), 3.34 (s, 3H), 3.73–3.65 (m, 1H), 1.86 (oct, J = 6.7 Hz, 2H), 1.23 (s, 9H), 0.94 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); **TLC** (8:1) hexane/ether, R_f = 0.27.

If oxygen was not rigorously excluded, the reaction produced minimal desired product and a significant amount of silyl alcohol **17a**.



18 **20a** **20b**

Synthesis of Sulfinamide 20b[26] Into a dry flask were added ketone **18** (1.35 g, 3.59 mmol, 1.0 equiv), (*S*)-2-methyl-2-propanesulfinamide (1.74 g, 14.4 mmol, 4.0 equiv), and THF (36 mL, 0.1 M). The flask was fitted with a reflux condenser, capped with a rubber septum, and maintained under a nitrogen atmosphere. Titanium (IV) ethoxide (2.98 g, 14.4 mmol, 4.0 equiv) was added by syringe. The mixture was heated to reflux (3 h, giving a yellow solution), and cooled to ambient temperature. The solution of crude sulfinimine **20a** (full conversion by NMR) was used directly for the next step.

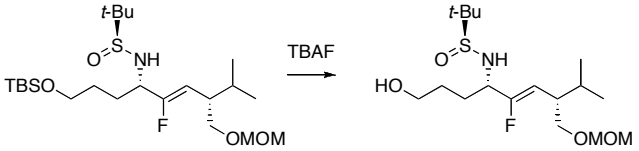
The reflux condenser was exchanged for an addition funnel, the system was flushed with nitrogen, and the mixture was cooled in a dry ice/acetone bath (-78 °C). Diisobutylaluminum hydride (1.0 M in THF, 18.0 mL, 18.0 mmol, 5.0 equiv) was added dropwise (over 30 min), causing the solution to become dark brown. The mixture was stirred (additional 2.5 h). Since analysis by NMR showed incomplete reaction, additional

[25] H. A. Brune, D. Schulte, *Chem. Ber.* **1967**, *100*, 3438–3449.

[26] Reductive amination procedure from: G. Dutheuil, S. Couve–Bonnaire, X. Pannecoucke, *Angew. Chem. Int. Ed.* **2007**, *46*, 1290–1292.

diisobutylaluminum hydride (1.0 M in THF, 7.20 mL, 7.20 mmol, 2.0 equiv) was added dropwise (over 5 min). The mixture was stirred (additional 30 min), quenched with ammonium chloride (saturated aqueous, 50 mL), warmed to ambient temperature, and diluted with water (50 mL) and ethyl acetate (50 mL, giving a heterogeneous mixture containing large black chunks). This mixture was mixed with potassium sodium tartrate (25 g), stirred vigorously (3 h, giving a milky white aqueous layer and a clear organic layer), further diluted with water (100 mL), extracted with ethyl acetate (100 + 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and an aliquot (approximately 200 mg) of the crude material was purified via column chromatography (40 mL silica gel, [1:1] hexanes/ethyl acetate), yielding the pure product. The crude product showed only one diastereomer by ^{1}H NMR and was used for the next step. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY and comparison to previous spectra.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.76 (dd, J_1 = 37.3 Hz, J_2 = 10.3 Hz, 1H, vinyl), 4.59 (s, 2H, O-CH_2-O), 3.77 (dq, J_d = 20.0 Hz, J_q = 7.2 Hz, 1H, N-CH), 3.61 (t, J = 6.2 Hz, 2H, TBSO-CH_2), 3.50 (d, J = 6.1 Hz, 2H, CH_2-OMOM), 3.37 (d, J = 9.5 Hz, 1H, NH), 3.34 (s, 3H, OMe), 2.67–2.60 (m, 1H, allyl-CH), 1.85 (oct, J = 6.6 Hz, 1H, iPr), 1.77–1.72 (m, 2H, CH_2-C-N), 1.60–1.53 (m, 2H, C-CH_2-C), 1.19 (s, 9H, S-*t*-Bu), 0.91 (d, J = 6.8 Hz, 3H, iPr-Me), 0.87 (s, 9H, Si-*t*-Bu), 0.85 (d, J = 6.8 Hz, 3H, iPr-Me), 0.03 (s, 6H, Si-Me); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 158.9 (d, J = 258.2 Hz), 107.2 (d, J = 13.7 Hz), 96.5, 68.9, 62.4, 57.3 (d, J = 28.6 Hz), 56.1, 55.2, 40.7, 29.7, 28.8, 28.2, 25.8, 22.5, 20.9, 18.4, 18.2, -5.4; **IR** (film, cm^{-1}) 3220, 2958, 2929, 2860, 1111, 1046, 837; **$[\alpha]_D$** = +45.9° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{23}H_{48}FNO_4SSiNa]^+$, requires m/z = 504.2950, found m/z = 504.2933 (ESI); **TLC** (1:1) hexane/ethyl acetate, R_f = 0.25.



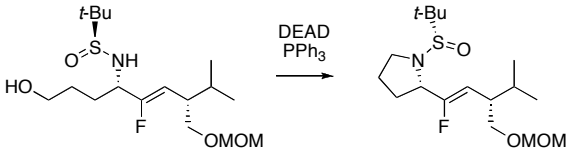
20b **20**

Synthesis of Alcohol 20[27] Into a flask were added crude TBS ether **20b** (3.59 mmol, 1.0 equiv) and THF (36 mL, 0.1 M). The flask was capped with a rubber septum and maintained under a nitrogen atmosphere. Tetrabutylammonium fluoride (1.0 M in THF, a bright pink solution, 7.20 mL, 7.20 mmol, 2.0 equiv) was added by syringe. The mixture was stirred (40 min, gradually becoming pink), quenched with ammonium chloride (saturated aqueous, 50 mL), diluted with water (50 mL) and brine (50 mL), extracted with ethyl acetate (100 + 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (150 mL silica gel, [3:2] toluene/acetone), yielding pure (1.00 g) and slightly impure (260 mg) fractions of the desired product (1.26 g overall, 3.43 mmol, 95% yield from ketone **18**). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (dd, J_1 = 37.4 Hz, J_2 = 10.4 Hz, 1H, vinyl), 4.60 (s, 2H, O-CH_2-O), 3.83 (dq, J_d = 18.1 Hz, J_q = 7.2 Hz, 1H, N-CH), 3.70–3.65 (m,

[27] TBS deprotection procedure from: Y.–J. Kim, P. Wang, M. Navarro–Villalobos, B. D. Rohde, J. Derryberry, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 11906–11915.

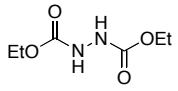
2H, HO-CH_2), 3.58 (d, J = 7.6 Hz, 1H, NH), 3.54–3.50 (m, 2H, CH_2-OMOM), 3.35 (s, 3H, OMe), 2.68–2.60 (m, 1H, allyl-CH), 1.91–1.55 (m, 6H, iPr, CH_2-C-N, C-CH_2-C, OH), 1.21 (s, 9H, *t*-Bu), 0.93 (d, J = 6.8 Hz, 3H, iPr-Me), 0.87 (d, J = 6.8 Hz, 3H, iPr-Me); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 158.8 (d, J = 258.2 Hz), 107.3 (d, J = 13.6 Hz), 96.4, 68.9, 61.8, 57.0 (d, J = 28.8 Hz), 56.1, 55.1, 40.7, 29.6, 28.7, 28.3, 22.4, 20.8, 18.5; **IR** (film, cm^{-1}) 3391, 3236, 2954, 2925, 2872, 1046; **$[\alpha]_D$** = +65.3° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_7H_{34}FNO_4SH]^+$, requires m/z = 368.2265, found m/z = 368.2250 (ESI); **TLC** (3:2) toluene/acetone, R_f = 0.27.



20 **21**

Synthesis of Pyrrolidine 21[28] Into a flame-dried flask were added alcohol **20** (1.00 g, 2.72 mmol, 1.0 equiv) and triphenylphosphine (855 mg, 3.26 mmol, 1.2 equiv). The flask was capped with a rubber septum, flushed with nitrogen, and maintained under a nitrogen atmosphere. To the flask were added THF (27 mL, 0.1 M) and diethyl azodicarboxylate (506 μL, 3.26 mmol, 1.2 equiv). The mixture was stirred (2 h), diluted with water (100 mL) and brine (100 mL), extracted with ethyl acetate (100 + 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (150 mL silica gel, [2:1] hexane/ethyl acetate), yielding slightly contaminated desired product (783 mg, 2.24 mmol, 80% yield). ^{1}H NMR signals were assigned by ^{1}H COSY.

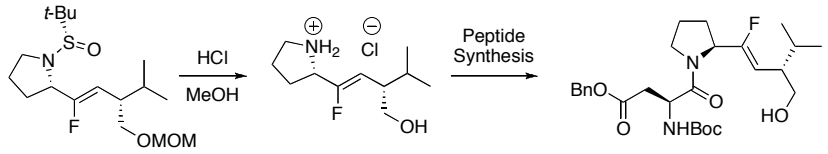
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.66 (dd, J_1 = 37.3 Hz, J_2 = 10.4 Hz, 1H, vinyl), 4.59 (s, 2H, O-CH_2-O), 4.47–4.42 (m, 1H, Pro-α), 3.50–3.36 (m, 4H, CH_2-OMOM, Pro-δ), 3.35 (s, 3H, OMe), 2.68–2.60 (m, 1H, Val-α), 1.91–1.80 (m, 5H, Val-β, Pro-β, Pro-γ), 1.19 (s, 9H, *t*-Bu), 0.91 (d, J = 6.8 Hz, 3H, Val-γ), 0.84 (d, J = 6.8 Hz, 3H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 160.2 (d, J = 257.5 Hz), 105.6 (d, J = 13.9 Hz), 96.4, 69.3, 57.5, 55.1, 55.3 (d, J = 33.4 Hz), 54.1, 40.6 (d, J = 2.2 Hz), 31.2, 28.5, 24.3, 22.8, 20.8, 18.4; **IR** (film, cm^{-1}) 2959, 2926, 2873, 1112, 1075, 1042; **$[\alpha]_D$** = -32.8° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{17}H_{32}FNO_3SH]^+$, requires m/z = 350.2160, found m/z = 350.2152 (ESI); **TLC** (3:2) hexane/ethyl acetate, R_f = 0.31.



21a

The desired product was slightly contaminated by DEAD byproduct **21a**. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.45–6.35 (brs, 2H), 4.22 (q, J = 7.1 Hz, 4H), 1.28 (d, J = 7.1 Hz, 6H); **TLC** (3:2) hexane/ethyl acetate, R_f = 0.27.

[28] Cyclization procedure from: T. P. Tang, J. A. Ellman, *J. Org. Chem.* **2002**, *67*, 7819–7832.

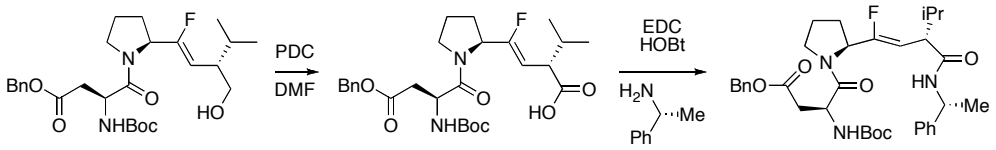


21 **22a** **22**

Synthesis of Amide 22 Protected fluoroolefin **21** (783 mg, 2.19 mmol, 1.0 equiv) was placed in a dry flask, which was capped with a rubber septum and maintained under an argon atmosphere. Methanol (7 mL, 0.3 M) was added into the flask, and the mixture was cooled in an ice bath (0 °C). Hydrochloric acid (4.0 M in dioxane, 7 mL, 28 mmol, 13 equiv) was added to the flask by syringe. The mixture was warmed to ambient temperature and stirred (1.5 h). Volatiles were removed under reduced pressure, and the mixture was maintained under high vacuum (1 h). A fraction of crude aminoalcohol hydrochloride **22a** was used for the next step. X-ray quality crystals were grown from methanol/ethyl acetate with slow solvent evaporation.

Into a flask were added crude amine hydrochloride **22a** (53% of the material, 1.16 mmol, 1.0 equiv), HOBt hydrate (185 mg, 1.21 mmol, 1.05 equiv), EDC hydrochloride (216 mg, 1.21 mmol, 1.05 equiv), Boc-Asp(OBn)-OH (391 mg, 1.21 mmol, 1.05 equiv), DCM (12 mL, 0.1 M), and triethylamine (168 μL, 1.21 mmol, 1.05 equiv). The mixture was stirred (14 h), diluted with DCM (80 mL), washed with sodium bicarbonate (saturated aqueous, 50 mL), brine (50% aqueous, 50 mL), and citric acid (10% aqueous, 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (60 mL silica gel, [1:1] hexane/ethyl acetate), yielding the desired product (overall 429 mg, 0.848 mmol, 70% yield). Early fractions (326 mg) were slightly contaminated by DEAD byproduct **21a**, and late fractions (103 mg) were slightly contaminated with a minor isomer (approximately 20:1). Fractions free of isomeric contaminants were used for the next step. NMR spectra show two rotational isomers (approximately 1.2:1 in $CDCl_3$), whose signals coalesce at 100 ºC in DMSO-d_6. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ 7.37–7.27 (m, 5H, Bn), 5.48 (d, J = 9.0 Hz, 0.5H, NHBoc), 5.38 (d, J = 9.0 Hz, 0.5H, NHBoc), 5.13–5.00 (m, 2.5H, Bn, Asp-α), 4.87–4.78 (m, 1H, Asp-α, vinyl), 4.66–5.48 (m, 1.5H, vinyl, Pro-α), 3.80–3.50 (m, 3H, Pro-δ, CH_2OH), 3.39–3.28 (m, 1H, CH_2OH), 2.84–2.59 (m, 2H, Asp-β), 2.52–2.30 (m, 2H, Val-α), 2.12–1.75 (m, 4H, Pro-β, Pro-γ), 1.69 (oct, J = 6.9 Hz, 0.5H, Val-β), 1.57 (oct, J = 6.9 Hz, 0.5H, Val-β), 1.43–1.38 (m, 9H, Boc), 0.92–0.78 (m, 6H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 170.1, 169.9, 169.6, 158.5 (d, J = 259.6 Hz), 158.1 (d, J = 257.9 Hz), 155.2, 155.0, 135.6, 135.4, 128.5, 128.4, 128.3, 128.2, 128.1, 109.4 (d, J = 13.9 Hz), 107.8 (d, J = 13.7 Hz), 80.4, 79.9, 66.9, 66.7, 64.2, 63.9, 58.5 (d, J = 30.2 Hz), 58.1 (d, J = 28.5 Hz), 49.1, 48.6, 44.4, 44.1, 39.3, 37.5, 31.5, 28.9, 28.8, 28.7, 28.2, 24.4, 22.4, 20.7, 20.6, 19.8, 19.7; **IR** (film, cm^{-1}) 3425, 3311, 2956, 2927, 2871, 1729, 1709, 1639, 1443, 1293, 1167; **$[\alpha]_D$** = -22.5° (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{27}H_{39}FN_2O_6H]^+$, requires m/z = 507.2865, found m/z = 507.2850 (ESI); **TLC** (2:1) ethyl acetate/hexane, R_f = 0.41.



22 **11a** **11b**

Synthesis of Amide 11a[29] Pyridinium dichromate was purified by recrystallization as follows. Into a beaker were added pyridinium dichromate (9.0 g) and water (15 mL). Particulate material was removed by gravity filtration, the filtrate was combined with acetone (60 mL), and the mixture was allowed to crystallize (2 h, -20 °C). Orange crystals (4.3 g) were isolated by vacuum filtration, washed with acetone, and dried under high vacuum.

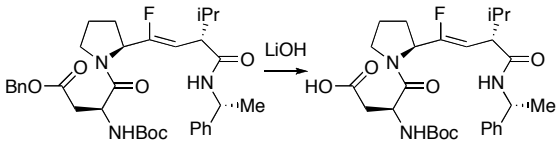
Into a flask were added alcohol **22** (326 mg, 0.644 mmol, 1.0 equiv), DMF (3 mL, 0.2 M), and pyridinium dichromate (1.70 g, 4.51 mmol, 7.0 equiv). The deep red solution was stirred (6 h, becoming a brown suspension), poured into cold water (40 mL), diluted with brine (30 mL), and extracted with ether (2 x 50 mL). The aqueous layer was acidified with HCl (1 M, to pH 1) and further extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, and volatiles were removed under reduced pressure. The resulting mixture was mixed with brine (20 mL) and citric acid (10% aqueous, 40 mL), extracted with ether (40 + 20 mL), and dried with sodium sulfate. Crude acid **11a** (approximately 90% yield by NMR, contaminated with solvent) was used directly for the next step.

Into a flask were added crude acid **11a** (0.644 mmol, 1.0 equiv), HOBt hydrate (104 mg, 0.676 mmol, 1.05 equiv), EDC hydrochloride (130 mg, 0.676 mmol, 1.05 equiv), (*R*)-(+)-methylbenzylamine (83 μL, 0.68 mmol, 1.05 equiv), and DCM (7 mL, 0.1 M). The mixture was stirred (11 h), diluted with DCM (40 mL), washed with sodium bicarbonate (saturated aqueous, 40 mL), brine (50% aqueous, 40 mL), and citric acid (10% aqueous, 40 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (60 mL silica gel, [15:7] hexane/ethyl acetate), yielding the desired product (176 mg, 0.283 mmol, 42% yield overall). Middle fractions (69 mg) were slightly contaminated by the DEAD byproduct. Early and late fractions (107 mg) were slightly contaminated with minor isomers. Fractions free of isomeric contaminants were used for the next step. NMR spectra show two rotational isomers (approximately 9:1 in $CDCl_3$), whose signals coalesce at 100 ºC in DMSO-d_6. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C, major signals) δ 7.40–7.10 (m, 10H, Bn, MeBn), 6.79 (d, J = 8.1 Hz, 1H, NHMeBn), 5.17–5.05 (m, 4H, CHMeBn, BocNH, Bn), 4.93 (dd, J_1 = 35.9 Hz, J_2 = 10.5 Hz, 1H, vinyl), 4.76–4.70 (m, 1H, Asp-α), 4.52 (ddd, J_1 = 21.6 Hz, J_2 = 7.7 Hz, J_3 = 4.8 Hz, 1H, Pro-α), 3.75–3.58 (m, 2H, Pro-δ), 3.17 (dd, J_1 = 10.5 Hz, J_2 = 4.9 Hz, 1H, Val-α), 2.50 (dd, J_1 = 16.0 Hz, J_2 = 6.2 Hz, 1H, Asp-β), 2.41 (oct, J = 5.4 Hz, 1H, Val-β), 2.24 (dd, J_1 = 16.0 Hz, J_2 = 6.9 Hz, 1H, Asp-β), 2.10–1.90 (m, 4H, Pro-β, Pro-γ), 1.49 (d, J = 7.0 Hz, 3H, MeBn), 1.43 (s, 9H, Boc), 0.87 (d, J = 6.9 Hz, 3H, Val-γ), 0.84 (d, J = 6.8 Hz, 3H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz, 25 °C, major signals) δ 171.3, 170.1, 169.9, 159.2 (d, J = 257.6 Hz), 154.9, 143.7, 135.4, 128.5, 128.3, 128.3, 128.2, 126.9, 126.2, 103.1 (d, J = 18.8 Hz), 80.0, 66.7, 58.6 (d, J = 36.5

[29] Oxidation procedure from: E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, 399–402.

Hz), 49.1, 48.4, 47.7, 47.3, 37.2, 28.8, 28.2, 24.4, 21.4, 20.8, 17.7; **IR** (film, cm^{-1}) 3312, 2970, 2933, 2872, 1739, 1711,1650, 1520, 1447, 1170; $[\alpha]_D$ = +10.4° (*c* = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{35}H_{46}FN_3O_6H]^+$, requires *m*/*z* = 624.3443, found *m*/*z* = 624.3425 (ESI); **TLC** (1:1) ethyl acetate/hexane, R_f = 0.31.

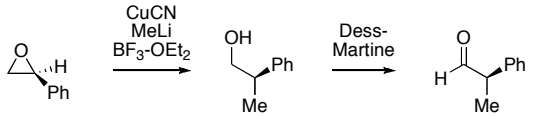


11b **11**

Synthesis of Fluoroalkene Isostere 11 Into a flask were added benzyl ester **11b** (69 mg, 0.11 mmol, 1.0 equiv), dioxane (2.0 mL, 0.05 M), water (1.0 mL, 0.1 M), and lithium hydroxide (1.0 M aqueous, 220 μL, 0.220 mmol, 2.0 equiv). The solution was stirred (16 h), diluted with water (40 mL) and sodium carbonate (10% aqueous, 1 mL, producing pH 10), washed with ether (2 x 40 mL), acidified with hydrochloric acid (1.0 M, to pH 1), extracted with ethyl acetate (3 x 40 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (60 mL silica gel, [1:1] hexane/ethyl acetate, to remove contaminants, then [60:40:3] hexane/ethyl acetate/acetic acid, then [50:50:3] hexane/ethyl acetate/acetic acid to elute product) and azeotrope (3 x toluene, 3 x ethyl acetate, 3 x hexane) to yield pure desired product (52 mg, 0.98 mmol, 89% yield). NMR spectra show two rotational isomers (approximately 10:1 in $CDCl_3$), whose signals coalesce at 100 ºC in DMSO-d_6. ^{1}H NMR chemical shifts vary with concentration (although the isomer ratio remains constant). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C, 0.1 M) δ 9.50–9.00 (brs, 1H, COOH), 7.35–7.20 (m, 5H, Bn), 6.51 (d, *J* = 7.2 Hz, 0.9H, NHBn), 6.43 (d, *J* = 7.2 Hz, 0.1H, NHBn), 5.51 (d, *J* = 8.9 Hz, 0.1H, NHBoc), 5.23 (d, *J* = 8.9 Hz, 0.9H, NHBoc), 5.13 (pent, *J* = 7.5 Hz, 1H, CHBn), 5.02 (dd, J_1 = 36.3 Hz, J_2 = 9.9 Hz, 0.1H, vinyl), 4.87 (dd, J_1 = 36.8 Hz, J_2 = 10.2 Hz, 0.9H, vinyl), 4.90–4.87 (m, 0.1H, Asp-α), 4.79–4.73 (m, 0.9H, Asp-α), 4.73–4.67 (m, 0.1H, Pro-α), 4.63–4.55 (m, 0.9H, Pro-α), 3.80–3.70 (m, 1.8H, Pro-δ), 3.57–3.53 (m, 0.2H, Pro-δ), 3.04 (dd, J_1 = 10.0 Hz, J_2 = 6.5 Hz, 0.9H, Val-α), 2.95–2.88 (m, 0.1H, Val-α), 2.76–2.64 (m, 0.2H, Asp-β), 2.59 (dd, J_1 = 15.5 Hz, J_2 = 7.7 Hz, 0.9H, Asp-β), 2.38 (dd, J_1 = 15.7 Hz, J_2 = 5.7 Hz, 0.9H, Asp-β), 2.22 (oct, *J* = 7.1 Hz, 0.9H, Val-β), 2.10–1.85 (m, 4.1H, Val-β, Pro-β, Pro-γ), 1.45 (d, *J* = 6.9 Hz, 3H, MeBn), 1.43 (s, 8.1H, Boc), 1.37 (s, 0.9H, Boc), 0.84 (d, *J* = 6.8 Hz, 3H, Val-γ), 0.83 (d, *J* = 6.7 Hz, 3H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz, 25 °C, major signals) δ 173.0, 172.3, 170.3, 158.6 (d, *J* = 260.0 Hz), 154.1, 143.4, 128.5, 127.2, 126.2, 103.0 (d, *J* = 12.5 Hz), 80.2, 58.1 (d, *J* = 32.0 Hz), 49.0, 48.7, 48.6, 47.3, 37.4, 29.7, 28.7, 28.3, 24.2, 21.5, 20.8, 18.4; **IR** (film, cm^{-1}) 3305, 2974, 2929, 2872, 1712, 1642, 1168, 760; $[\alpha]_D$ = -14.9° (*c* = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{28}H_{40}FN_3O_6H]^+$, requires *m*/*z* = 534.2974, found *m*/*z* = 534.2973 (ESI); **TLC** (60:40:3) hexane/ethyl acetate/acetic acid, R_f = 0.38.

3.5 Synthesis of Alkene Isostere 24



24a **24b**

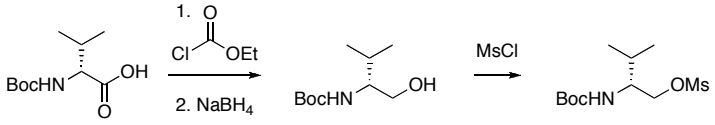
Synthesis of Aldehyde 24b[30] Into a flame-dried flask were added copper (I) cyanide (2.24 g, 25.0 mmol, 1.5 equiv) and THF (30 mL, 0.6 M). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in a methanol/ice bath (-20 ºC). Methyllithium (1.6 M in ether, 15.6 mL, 25.0 mmol, 1.5 equiv) was added to the suspension, yielding a colorless solution, which was stirred (30 min) and transferred into an ethyl acetate/dry ice bath (-84 ºC). Boron trifluoride etherate (3.14 mL, 25.0 mmol, 1.5 equiv) was added. The mixture was stirred (5 min). Into another flame-dried flask were added (*S*)-styrene oxide (1.90 mL, 16.7 mmol, 1.0 equiv) and THF (10 mL, 1.7 M). This solution was cooled in the ethyl acetate/dry ice bath and transferred via cannula into the cupprate solution. The mixture was stirred (20 min, producing yellow precipitate), quenched with an aqueous buffer (20 mL saturated ammonium chloride and 20 mL concentrated ammonium hydroxide), warmed to ambient temperature, stirred (1 h), filtered, concentrated under reduced pressure, extracted with ether (3 x 30 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude product was purified via column chromatography (150 mL silica gel, [10:1 to 3:1] hexanes/ethyl acetate), yielding pure alcohol **24a** (1.30 g, 9.56 mmol, 57% yield), which was used directly for the next step. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32–7.20 (m, 5H), 3.71 (t, J = 6.5 Hz, 2H), 2.90 (sext, J = 6.9 Hz, 1H), 1.29 (d, J = 7.0 Hz, 3H); **TLC** (2:1) hexane/ethyl acetate, R_f = 0.42. Compound analysis is consistent with published data.[31]

Into a flask were added alcohol **24a** (1.30 g, 9.56 mmol, 1.0 equiv), DCM (40 mL, 0.2 M), and Dess–Martin periodinane (4.80 g, 11.4 mmol, 1.2 equiv). The mixture was stirred (20 min), quenched with an aqueous buffer (2.5 g sodium phosphate monobasic, 3.5 g sodium phosphate dibasic, and 25 mL water), stirred vigorously (10 min, producing significant precipitate), and mixed with celite (25 mL). Solids were removed by gravity filtration. The filtrate was washed with sodium bicarbonate (saturated aqueous, 2 x 50 mL) and brine (50% aqueous, 50 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure to give a yellow solid, which was mixed with (2:1) hexane/ethyl acetate (50 mL). Solids were removed by vacuum filtration. The filtrate was concentrated under reduced pressure, and the crude material was purified via column chromatography (120 mL silica gel, [9:1] hexane/ethyl acetate), yielding the desired product (576 mg, 4.30 mmol, 45% yield, 26% yield overall). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.69 (d, J = 1.4 Hz, 1H), 7.41–7.19 (m, 5H), 3.64 (dq, J_d = 1.3 Hz, J_q = 6.9 Hz,

[30] Both procedures from: C. Botuha, M. Haddad, M. Larchevêque, *Tetrahedron: Asymmetry* **1998**, *9*, 1929–1931.

[31] A. Solladié–Cavallo, A. G. Csaky, I. Gantz, J. Suffert, *J. Org. Chem.* **1994**, *59*, 5343–5346.

1H), 1.45 (d, J = 7.0 Hz, 3H); **TLC** (9:1) hexane/ethyl acetate, R_f = 0.40. Compound analysis is consistent with published data.[32]

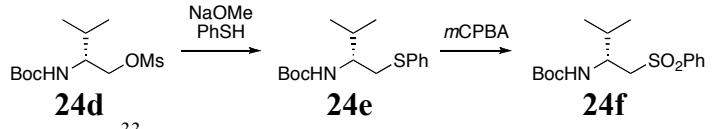


24c **24d**

Synthesis of Mesylate 24d[33] Into a flask were added Boc-D-Val-OH (6.52 g, 30.0 mmol, 1.0 equiv), THF (40 mL, 0.8 M) and triethylamine (5.19 mL, 37.5 mmol, 1.25 equiv). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ºC). Ethyl chloroformate (2.87 mL, 30.0 mmol, 1.0 equiv) was added dropwise (over 10 min), forming white precipitate. The mixture was stirred (additional 20 min). Solid was removed by filtration, and the cake was washed with THF (15 mL). The combined filtrate was used directly for the next step.

Into a flask were added sodium borohydride (2.83 g, 75.0 mmol, 2.5 equiv) and water (40 mL, 0.8 M). The flask was capped with a septum, vented with a wide needle, and cooled in an ice bath (0 ºC). To this mixture was added dropwise (over 20 min) by cannula the filtrate from the previous step. *A significant amount of gas evolved.* The mixture was stirred (2 h), warmed to ambient temperature, concentrated under reduced pressure, diluted with ammonium chloride (saturated aqueous, 15 mL), extracted with ether (100 + 2 x 50 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure to yield alcohol **24c**, which was used directly for the next step.

Into a flask were added crude alcohol **24c** (30.0 mmol) and DCM (200 mL, 0.2 M). The flask was capped with a septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ºC). Triethylamine (12.5 mL, 90.0 mmol, 3.0 equiv) was added to the mixture. Methanesulfonyl chloride (5.60 mL, 72.0 mmol, 2.4 equiv) was added to the mixture dropwise (over 10 min). The mixture was stirred (20 min), washed with sodium bicarbonate (saturated aqueous, 100 mL), brine (50% aqueous, 100 mL), and citric acid (10% aqueous, 100 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by recrystallization (25 mL ethyl acetate and 100 mL hexane, -20 ºC, two crops), yielding pure desired product (5.72 g, 20.4 mmol, 68% yield), which was used directly for the next step. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.61 (d, J = 9.1 Hz, 1H), 4.27 (d, J = 4.3 Hz, 2H), 3.70–3.60 (m, 1H), 3.03 (s, 3H), 1.86 (oct, J = 6.9 Hz, 1H), 1.45 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H).



24d **24e** **24f**

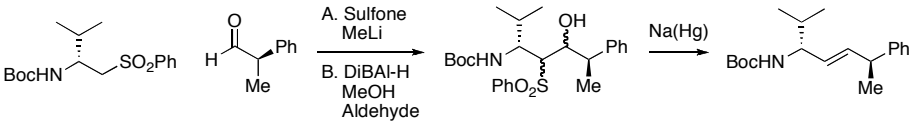
Synthesis of Sulfone 24f[33] Sodium metal (1.50 g, 65.1 mmol, 3.2 equiv) was washed with hexane, dried on a paper towel, cut into small pieces (approximately 3 x 3 x 1 mm) and dropped into a flask containing methanol (13 mL, 1.6 M). Gas evolved slowly and

[32] E. J. Corey, F. J. Hannon, N. W. Boaz, *Tetrahedron* **1989**, *45*, 545–555.

[33] Procedures and enantiomer compound data from: A. Spaltenstein, P. A. Carpino, F. Miyake, P. B. Hopkins, *J. Org. Chem.* **1987**, *52*, 3759–3766.

the sodium dissolved slowly (over 2 h), during which time the flask was occasionally flushed with nitrogen gas and returned to ambient temperature with an ice bath. Once a homogeneous solution was obtained, to it were added THF (50 mL, 0.4 M) and benzenethiol (6.92 mL, 67.3 mmol, 3.3 equiv). The mixture was stirred (30 min, slightly exothermic). Mesylate **24d** (5.72 g, 20.4 mmol, 1.0 equiv) was added, and the mixture was heated to 50 ºC (oil bath, 30 min). Precipitate formed. The mixture was concentrated under reduced pressure, diluted with sodium hydroxide (1.0 M, 100 mL), extracted with DCM (2 x 100 mL), washed with sodium hydroxide (0.3 M, 150 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, yielding crude phenylsulfide **24e** as a yellow solid, half of which was used for the next step.

Into a flask were added half of crude phenylsulfide **24e** (10.2 mmol, 1.0 equiv), DCM (80 mL, 0.1 M), and sodium phosphate dibasic (4.60 g, 32.6 mmol, 3.2 equiv). The mixture was cooled in an ice bath (0 ºC), and *meta*-chloroperbenzoic acid (77% solid, 7.14 g, 32.6 mmol, 3.2 equiv) was added portionwise (over 3 min). The ice bath was removed. The mixture was stirred (1.5 h), cooled in an ice bath, quenched with sodium thiosulfate (10 g in 100 mL water), and diluted with DCM (50 mL). Solids were removed by vacuum filtration. The organic phase was washed with sodium carbonate (10% aqueous, 100 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure. The crude material was dissolved in hot ethyl acetate (7 mL), diluted with hexane (15 mL), and allowed to crystallize (ambient temperature). The desired product was isolated by vacuum filtration as a fluffy white solid (2.21 g, 6.76 mmol, 66% yield overall). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.94–7.91 (m, 2H), 7.68–7.64 (m, 1H), 7.59–7.54 (m, 2H), 4.76–4.70 (brs, 1H), 3.83–3.74 (brs, 1H), 3.38–3.20 (m, 2H), 2.08–1.97 (m, 1H), 1.42 (s, 9H), 0.83 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). Compound analysis is consistent with reported data.[33]



24f **24b** **24g** **24h**

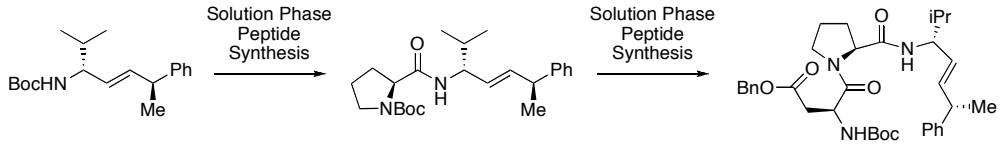
Synthesis of Alkene 24h[33,34] Into a flame-dried flask were added sulfone **24f** (1.18 g, 3.60 mmol, 1.0 equiv) and THF (54 mL, 0.07 M). The flask was capped with a septum, maintained under a nitrogen atmosphere, and cooled in a dry ice/acetone bath (-78 ºC). Methyllithium (1.6 M in ether, 4.97 mL, 7.92 mmol, 2.2 equiv) was added. The mixture was stirred (25 min). Another flame-dried flask was capped with a septum, maintained under a nitrogen atmosphere, and cooled in the bath. To this flask were added diisobutylaluminum hydride (1.0 M in THF, 4.68 mL, 4.68 mmol, 1.3 equiv) and methanol (191 μL, 4.68 mmol, 1.3 equiv). The mixture was stirred (5 min), allowed to warm to ambient temperature (10 min), and cooled again. Aldehyde **24b** (576 mg, 4.30 mmol, 1.2 equiv) was added to the aluminum solution, and the resulting solution was immediately transferred via cannula into the sulfone solution. The mixture was stirred (30 min), quenched with ammonium chloride (saturated aqueous, 8 mL), warmed to

[34] For reductive sulfone removal procedure: a) Q. Wang, N. A. Sasaki, *J. Org. Chem.* **2004**, *69*, 4767–4773. b) L. Ermolenko, N. A. Sasaki, P. Potier, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2465–2473.

ambient temperature, concentrated under reduced pressure, diluted with ether (70 mL) and water (90 mL), mixed with potassium sodium tartrate (6 g), and stirred vigorously (2 h). The organic layer was removed, and the aqueous layer was further extracted with ether (80 mL). The combined organic phases were dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (125 mL silica gel, [6:1 to 5:1] hexane/ethyl acetate), yielding a mixture of two diastereomers of β-hydroxysulfone **24g** (731 mg, 1.59 mmol, 44% yield), which was used directly for the next step. **TLC** (2:1) hexane/ethyl acetate, R_f = 0.42 and 0.45.

Into a flask were added β-hydroxysulfone **24g** (731 mg, 1.59 mmol, 1.0 equiv), methanol (16 mL, 0.1 M), and sodium phosphate dibasic (2.26 g, 15.9 mmol, 10 equiv). The flask was fitted with a funnel bearing a gas inlet, maintained under continuous argon flow, and cooled in an ice bath (0 ºC). To the mixture was added sodium mercury amalgam (5%, 10 g, 21.7 mmol, 13.7 equiv). Gas evolved. The flask was capped with a septum and maintained under an argon atmosphere. The mixture was stirred (2 h), decanted through a cotton plug, quenched with saturated ammonium chloride (10 mL), concentrated under reduced pressure, diluted with ethyl acetate (60 mL), washed with brine (50%, 2 x 40 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (70 mL silica gel, [10:1] hexane/ethyl acetate), yielding the desired product (282 mg, 0.931 mmol, 58% yield, 26% overall). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY. Olefin geometry was determined from ^{1}H–^{1}H coupling constants.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.26 (m, 2H, Ph), 7.21–7.16 (m, 3H, Ph), 5.75 (dd, J_1 = 15.9 Hz, J_2 = 6.5 Hz, 1H, vinylMePh), 5.34 (dd, J_1 = 15.5 Hz, J_2 = 5.9 Hz, 1H, vinylBoc), 4.52–4.44 (brs, 1H, NHBoc), 4.02–3.95 (brs, 1H, CHBoc), 3.47 (quint, J = 6.2 Hz, 1H, CHMePh), 1.81–1.71 (m, 1H, iPr), 1.43 (s, 9H, Boc), 1.35 (d, J = 7.0 Hz, 3H, Me), 0.89–0.86 (m, 6H, iPr); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 155.4, 154.7, 136.0, 128.3, 127.8, 127.2, 126.0, 78.9, 57.3, 41.8, 32.5, 28.3, 21.3, 18.6, 18.2; **IR** (film, cm^{-1}) 3344, 2964, 2928, 2871, 1697, 1492, 1362, 1171; **$[\alpha]_D$** = +6.0^o (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{19}H_{29}NO_2H]^+$, requires m/z = 304.2277, found m/z = 304.2284 (ESI); **TLC** (5:1) hexane/ethyl acetate, R_f = 0.63.

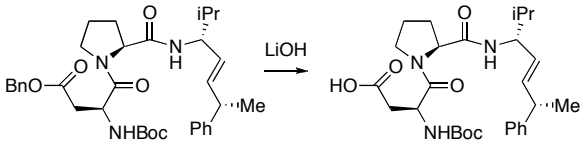


24h **24i** **24j**

Synthesis of Ester 24j The standard solution phase peptide synthesis was followed using alkene **24h** (141 mg, 0.465 mmol, 1.0 equiv), hydrogen chloride (4.0 M in dioxane, 3 mL), DCM (4 mL, 0.1 M), triethylamine (77 μL, 0.56 mmol, 1.2 equiv), Boc-Pro-OH (120 mg, 0.558 mmol, 1.2 equiv), HOBt hydrate (92 mg, 0.61 mmol, 1.3 equiv), and EDC hydrochloride (116 mg, 0.605 mmol, 1.3 equiv). Crude alkene **24i** (209 mg, quantitative) was used directly for the next step.

The standard solution phase peptide synthesis was followed using alkene **24i** (0.465 mmol, 1.0 equiv), hydrogen chloride (4.0 M in dioxane, 3 mL), DCM (4 mL, 0.1 M), triethylamine (77 μL, 0.56 mmol, 1.2 equiv), Boc-Asp(OBn)-OH (180 mg, 0.558 mmol, 1.2 equiv), HOBt hydrate (92 mg, 0.61 mmol, 1.3 equiv), and EDC hydrochloride

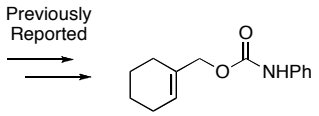
(116 mg, 0.605 mmol, 1.3 equiv). The crude product was dissolved in ethyl acetate (20 mL), washed with sodium carbonate (10% aqueous), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude product was purified via column chromatography (80 mL silica gel, [3:2 to 4:3] hexanes/ethyl acetate), yielding the desired product (172 mg, 0.284 mmol, 61% yield), which was used directly for the next step. **TLC** (3:2) ethyl acetate/hexane, $R_f = 0.49$.



Synthesis of Alkene Isostere 24 Into a flask were added ester **24j** (172 mg, 0.284 mmol, 1 equiv), dioxane (7.1 mL, 0.04 M), water (3.6 mL, 0.08 M), and lithium hydroxide (2 M aqueous, 0.570 mL, 1.14 mmol, 4.0 equiv). The mixture was stirred (16 h), concentrated under reduced pressure, diluted with water (50 mL), washed with ether (2 x 50 mL), acidified with hydrochloric acid (1 M, to pH 1), extracted with ethyl acetate (3 x 30 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (40 mL silica gel, [18:12:2] hexanes/ethyl acetate/acetic acid), yielding the desired product (131 mg, 0.254 mmol, 89% yield). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

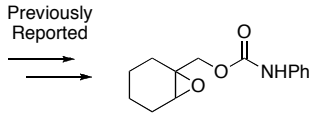
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26–7.18 (m, 5H, Ph), 6.87 (d, J = 8.9 Hz, 1H, NHVal), 5.73 (dd, J_1 = 15.4 Hz, J_2 = 6.6 Hz, 1H, vinyl-Bn), 5.52 (d, J = 9.2 Hz, 1H, BocNH), 5.36 (dd, J_1 = 15.5 Hz, J_2 = 7.1 Hz, 1H, Val-vinyl), 4.81 (td, J_t = 9.0 Hz, J_d = 4.7 Hz, 1H, Asp-α), 4.54 (dd, J_1 = 8.2 Hz, J_2 = 2.3 Hz, 1H, Pro-α), 4.13 (q, J = 7.9 Hz, 1H, Val-α), 3.85–3.65 (m, 2H, Pro-δ), 3.42 (quint, J = 6.8 Hz, 1H, CHBn), 2.85 (dd, J_1 = 16.7 Hz, J_2 = 9.6 Hz, 1H, Asp-β), 2.61 (dd, J_1 = 16.6 Hz, J_2 = 4.0 Hz, 1H, Asp-β), 2.24–2.17 (m, 1H, Pro-β/γ), 2.04–1.88 (m, 3H, Pro-β, Pro-γ), 1.72 (oct, J = 6.8 Hz, 1H, Val-β), 1.42 (s, 9H, Boc), 1.31 (d, J = 7.0 Hz, 3H, Me), 0.80 (d, J = 6.7 Hz, 6H, Val-γ); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 173.0, 171.2, 170.5, 155.1, 145.7, 137.0, 128.3, 127.2, 127.2, 126.0, 80.4, 60.7, 57.0, 48.2, 47.6, 41.8, 37.5, 32.2, 28.9, 28.2, 24.3, 21.3, 18.9, 18.6; **IR** (film, cm^{-1}) 3340, 2967, 2930, 2874, 1716, 1643, 1534, 1453, 1165, 757; $[\alpha]_D = -94.7^o$ (c = 1.0, $CHCl_3$); **HRMS** Calculated for $[C_{28}H_{41}N_3O_6H]^+$, requires m/z = 516.3074, found m/z = 516.3071 (ESI); **TLC** (18:12:2) hexane/ethyl acetate/acetic acid, $R_f = 0.27$.

3.6 Catalytic Epoxidation



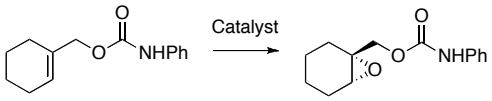
3

Alkene **3** was synthesized as reported by us.[35] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.34 (m, 2H), 7.30–7.23 (m, 2H), 7.06–7.00 (m, 1H), 6.72 (s, 1H), 5.77 (s, 1H), 4.52 (s, 2H), 2.06–1.97 (m, 4H), 1.67–1.60 (m, 2H), 1.60–1.53 (m, 2H).



4

Racemic epoxide **4** was prepared as reported by us.[35] **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.34 (d, J = 7.9 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 7.04 (t, J = 7.9 Hz, 1H), 6.88 (s, 1H), 4.30 (d, J = 11.8 Hz, 1H), 4.02 (d, J = 11.8 Hz, 1H), 3.14 (d, J = 3.5 Hz, 1H), 1.97–1.90 (m, 2H), 1.86–1.75 (m, 2H), 1.49–1.38 (m, 2H), 1.33–1.20 (m, 2H); **Chiral HPLC** (Chiralpak AD column, [95:5] hexane/2-propanol, flow = 1.0 mL·min^{-1}, monitor at 210 nm) product elutes at 14.7 and 16.3 min on one column and 19.1 and 21.2 min on another; (Chiralpak AD column, [97:3] hexane/2-propanol, flow = 1.0 mL·min^{-1}, monitor at 210 nm) product elutes at 21.6 and 24.0 min.



3 **4**

Three reactions, one with peptide **5** (20 mg, 0.037 mmol, 0.25 equiv), one with alkene isostere **9** (19 mg, 0.037 mmol, 0.25 equiv), and one with alkene isostere **24** (19 mg, 0.037 mmol, 0.25 equiv) were done according to the general procedure using catalyst, hydrogen peroxide (30% aqueous, 104 μL, 0.913 mmol, 6.25 equiv), and a stock solution of alkene **3** (34 mg, 0.15 mmol, 1.0 equiv), DMAP (4.5 mg, 0.037 mmol, 0.25 equiv), DCC (105 mg, 0.511 mmol, 3.5 equiv), and toluene (365 μL, 0.4 M) for 12 h.

A separate reaction was done with fluoroalkene isostere **11** (7 mg, 0.013 mmol, 0.25 equiv) according to the general procedure using catalyst, alkene **3** (12 mg, 0.053 mmol, 1.0 equiv), DCC (37 mg, 0.18 mmol, 3.5 equiv), hydrogen peroxide (30% aqueous, 38 μL, 0.33 mmol, 6.25 equiv), and a stock solution of DMAP (1.6 mg, 0.013 mmol, 0.25 equiv), and toluene (135 μL, 0.4 M) for 12 h.

A separate reaction was done with peptide analogue **8** (16 mg, 0.037 mmol, 0.25 equiv) according to the general procedure using catalyst, hydrogen peroxide (30% aqueous, 104 μL, 0.913 mmol, 6.25 equiv), and a stock solution of alkene **3** (34 mg, 0.15 mmol, 1.0 equiv), DMAP (4.5 mg, 0.037 mmol, 0.25 equiv), DCC (105 mg, 0.511 mmol, 3.5 equiv), and toluene (365 μL, 0.4 M) for 12 h.

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[35] G. Peris, C. E. Jakobsche, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 8710–8711.

Reaction efficiency and selectivity were determined by ^{1}H NMR and chiral HPLC respectively and are summarized below. Absolute stereochemistry of the major product was assigned as reported by us.[35]

Catalyst	Mass Recovery	Conversion	ee (er)
Peptide **5***	80%	63%	81% (9.5:1)
Peptide Analogue **8**	81%	26%	88% (15.4 : 1)
Fluoroalkene Isostere **11** **	90%	>98%	52% (3.2:1)
Alkene Isostere **9**	67%	>98%	16% (1.4:1)
Alkene Isostere **24**	67%	>98%	16% (1.4:1)

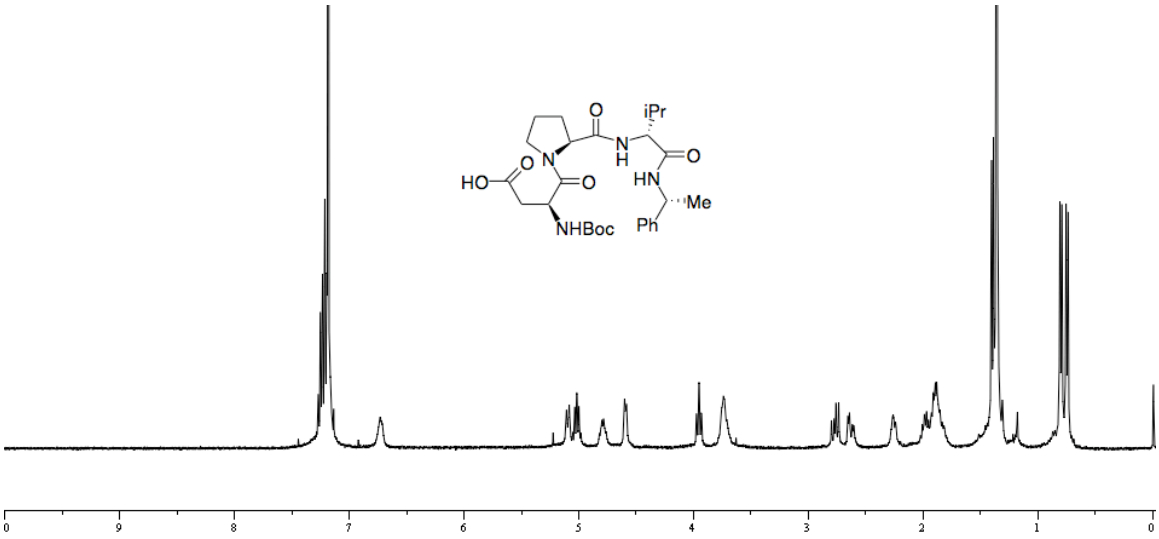
*Average of four reactions

**Average of two reactions

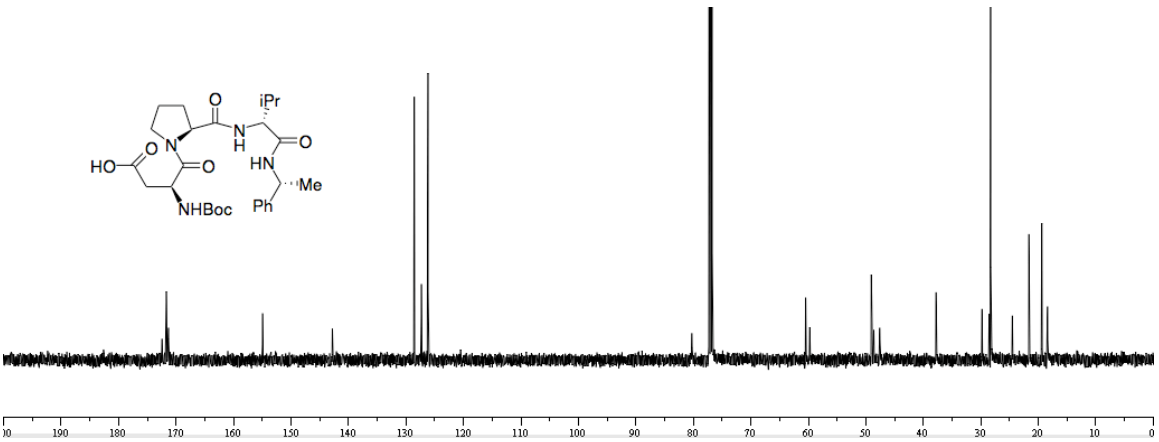
4. Spectra

4.1 Spectra from the Synthesis of Peptide 5

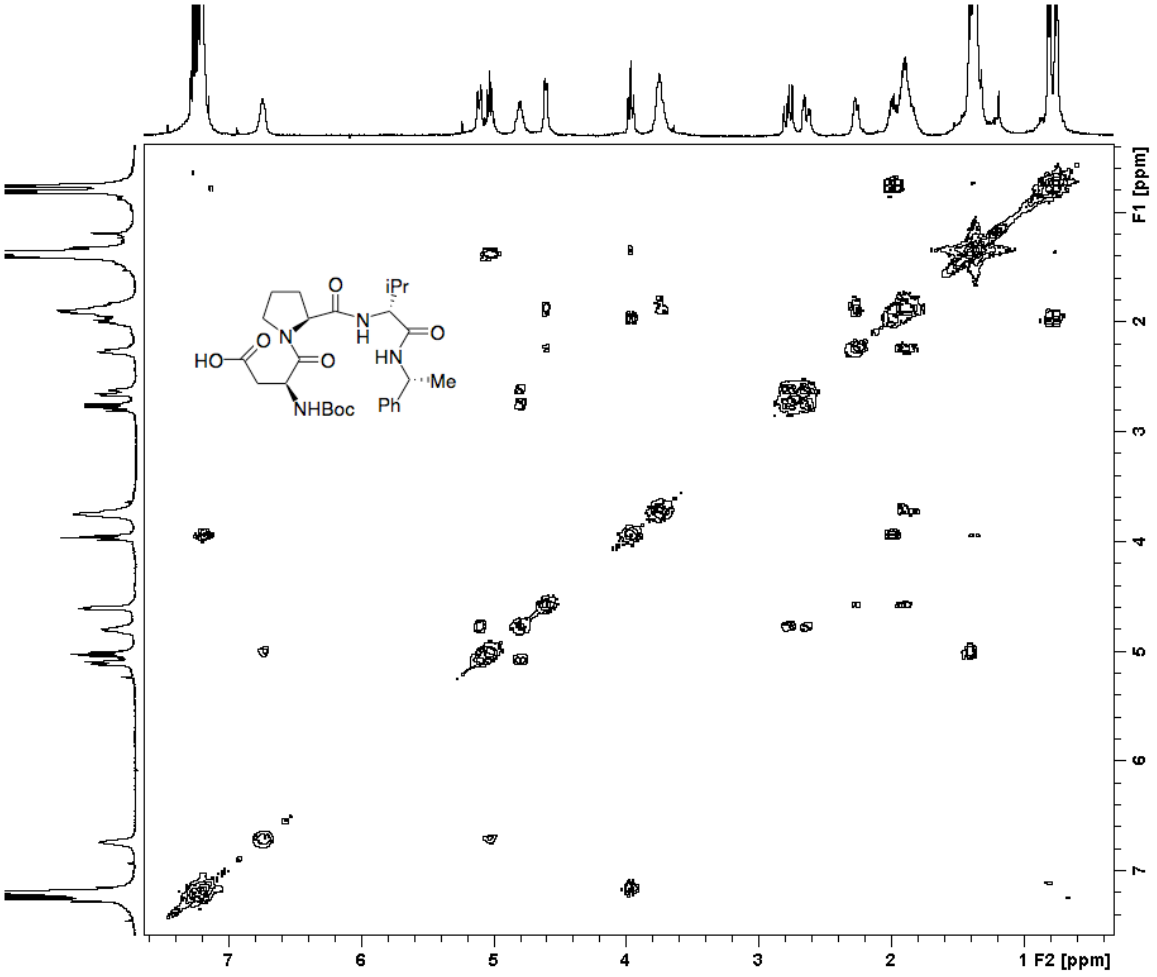
^{1}H NMR Spectrum of 5



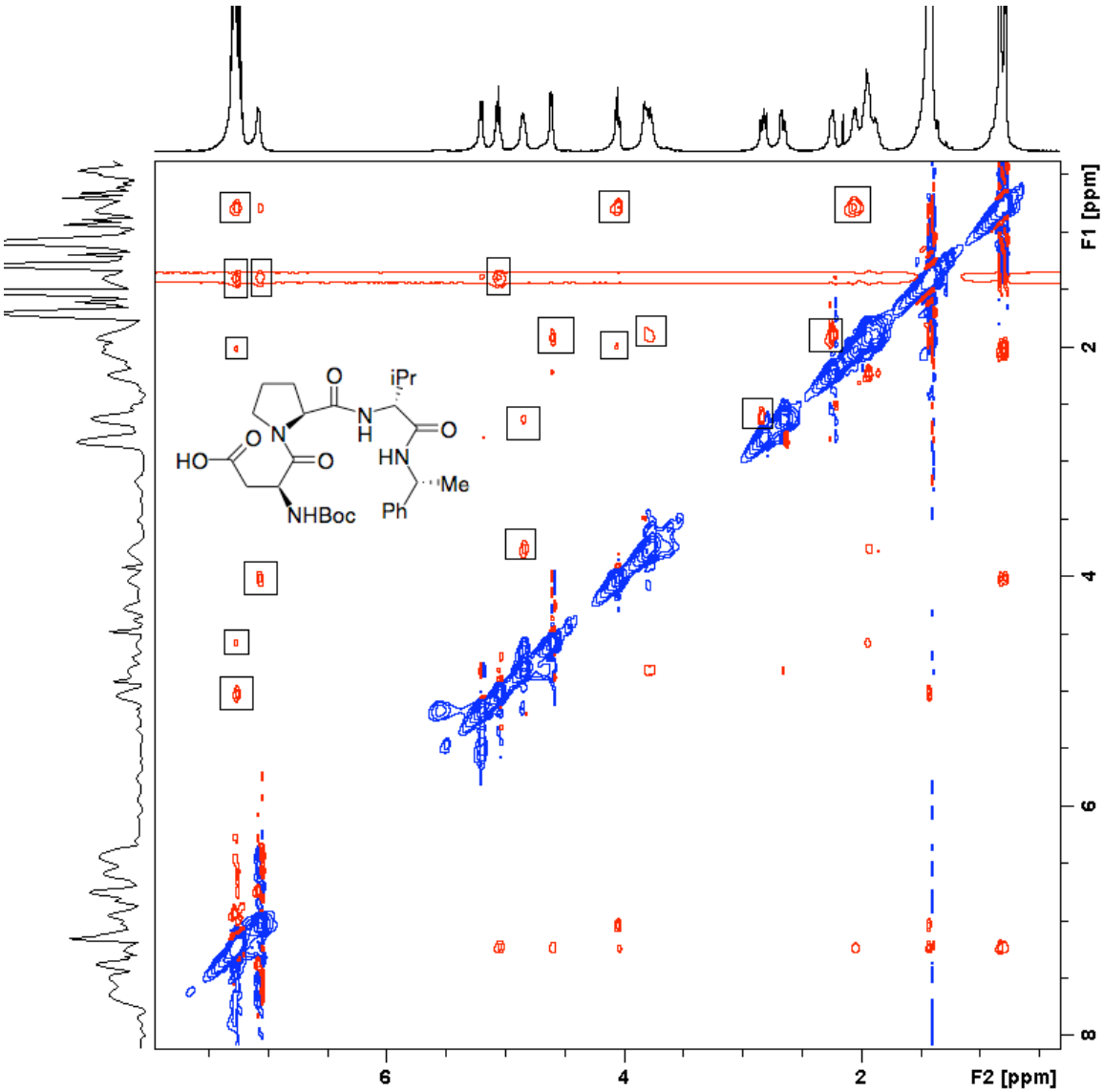
^{13}C NMR Spectrum of 5



$^{1}H–^{1}H$ COSY Spectrum of 5



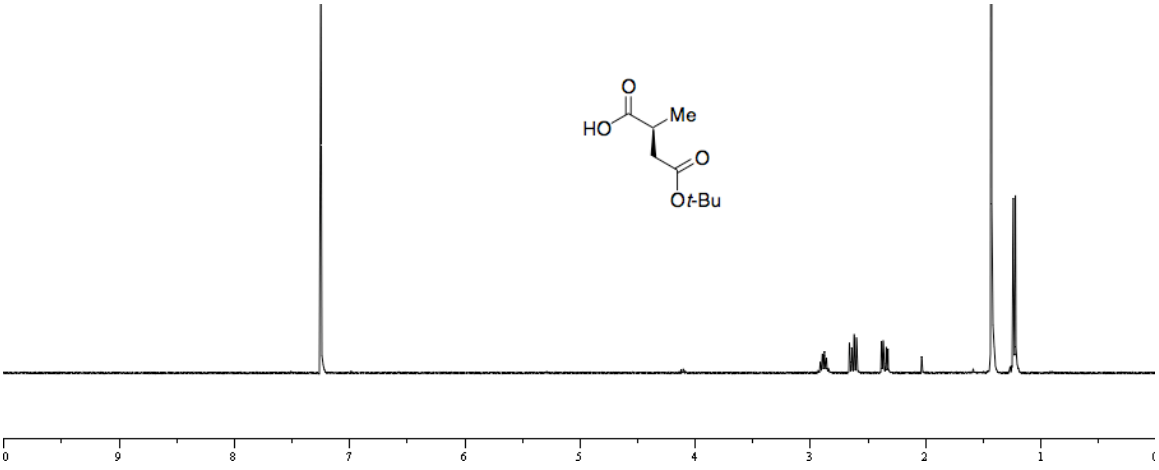
^{1}H–^{1}H NOESY Spectrum of 5



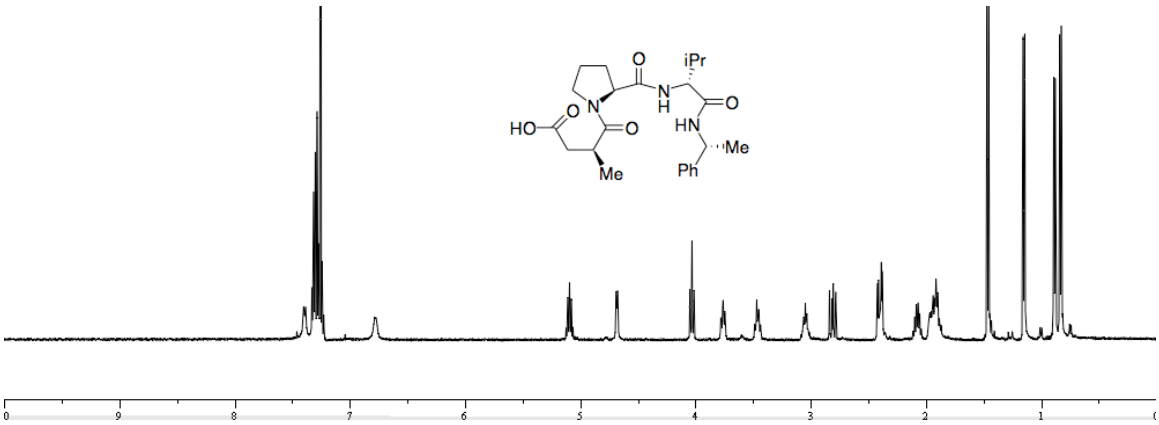
This spectrum was not symmetrized, Legitimate signals are enclosed in rectangles.

4.2 Spectra from the Synthesis of Peptide 8

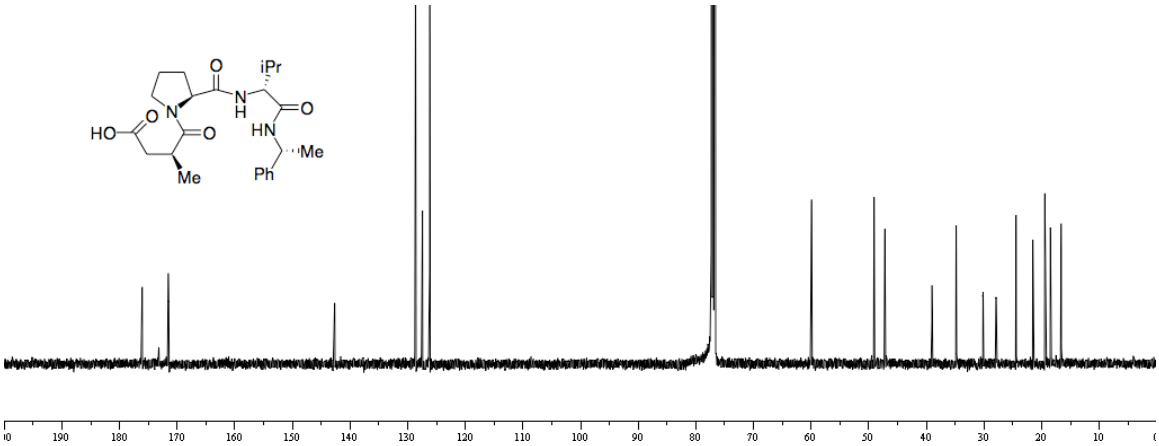
^{1}H NMR Spectrum of 8b



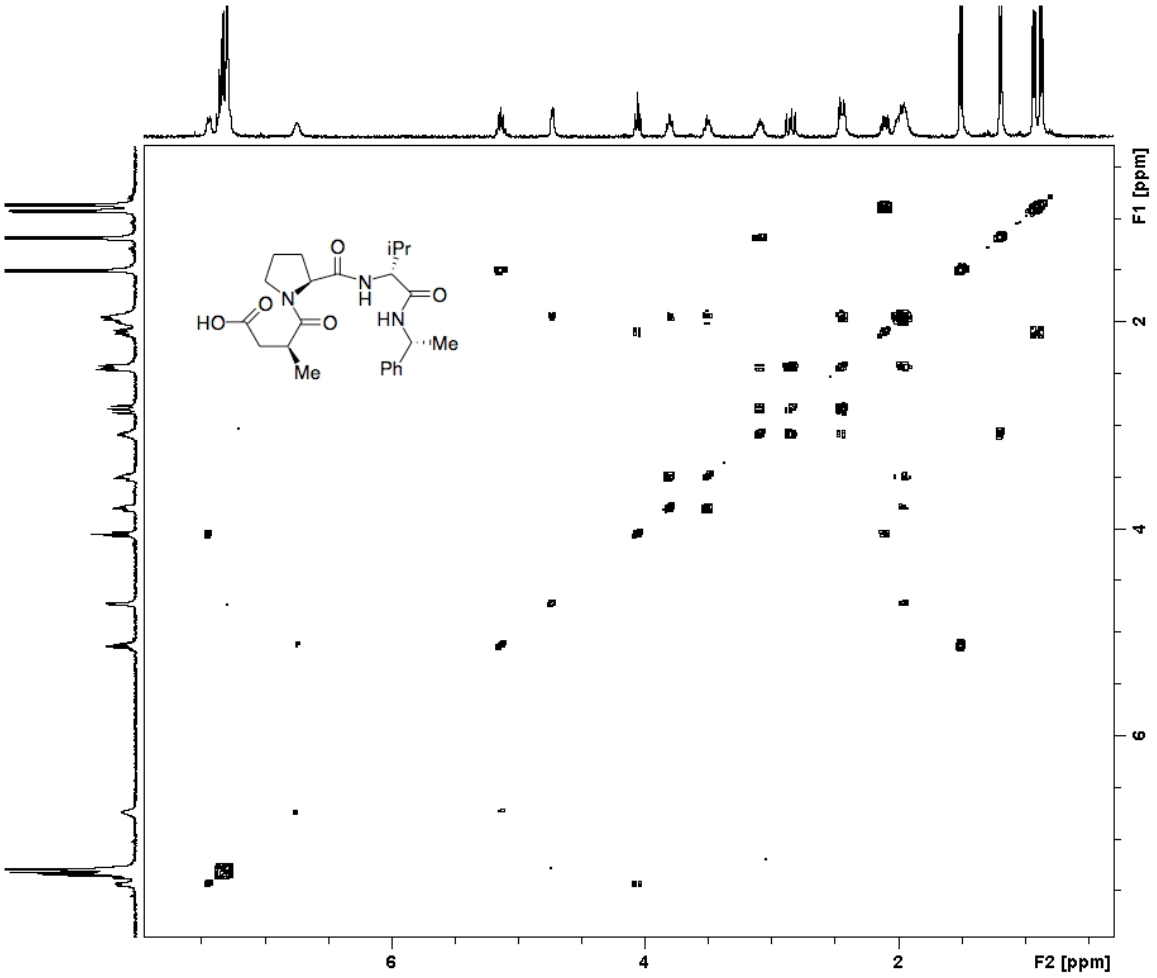
^{1}H NMR Spectrum of 8



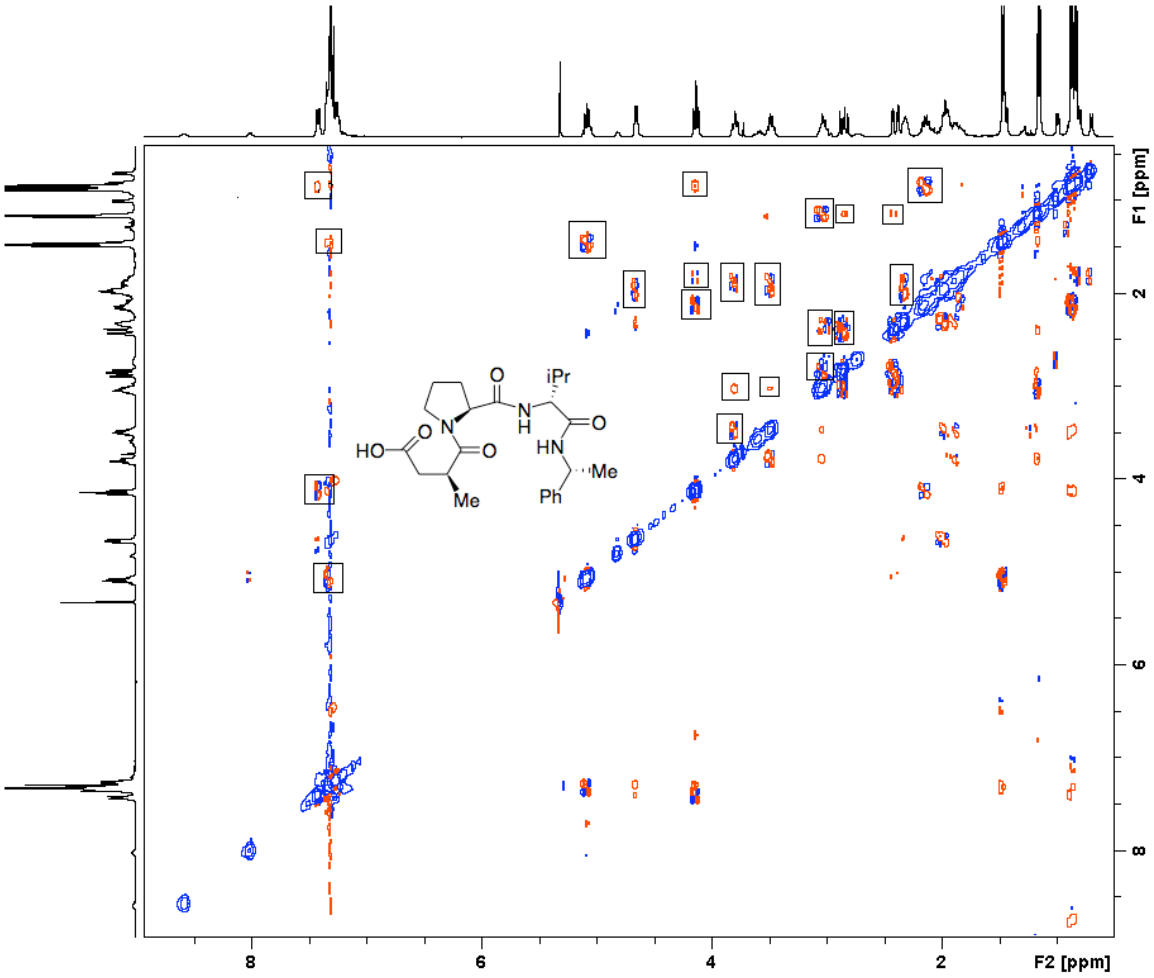
^{13}C NMR Spectrum of 8



$^{1}H–^{1}H$ COSY Spectrum of 8



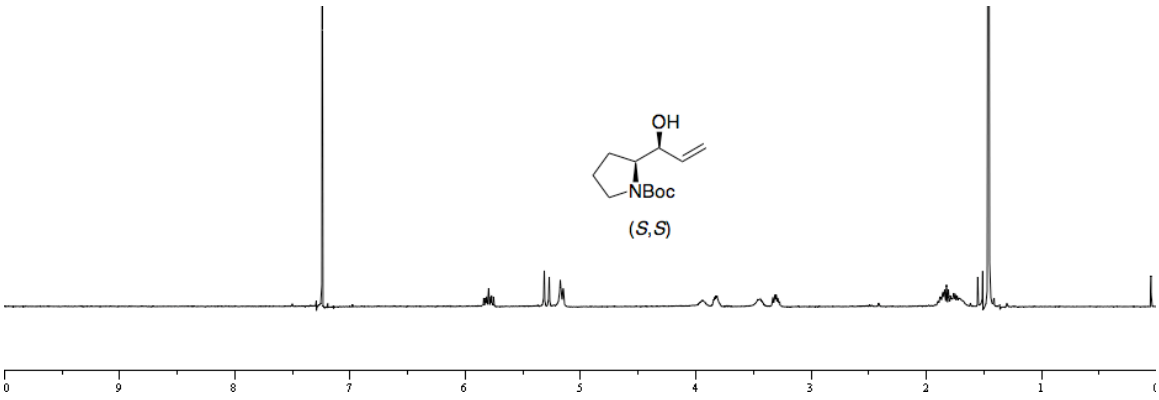
^{1}H–^{1}H NOESY Spectrum of 8



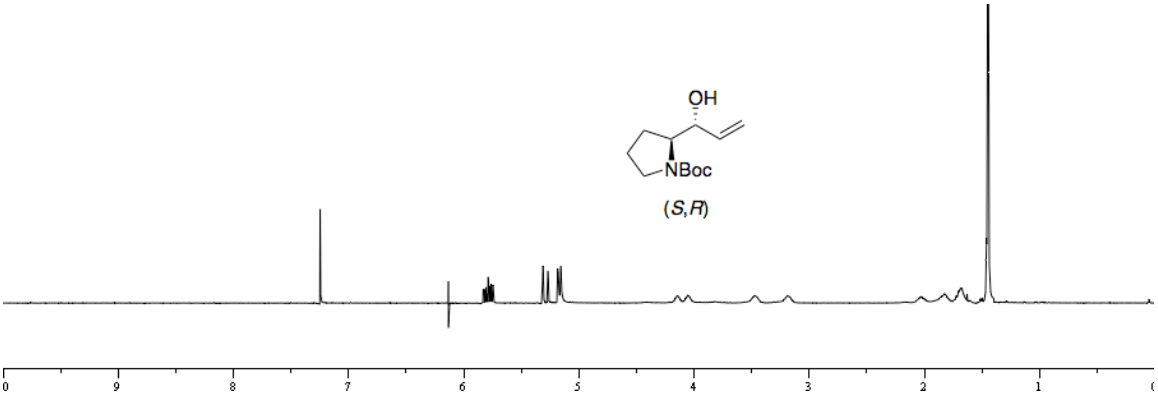
This spectrum was not symmetrized, Legitimate signals are enclosed in rectangles.

4.3 Spectra from the Synthesis of Alkene Isostere 9

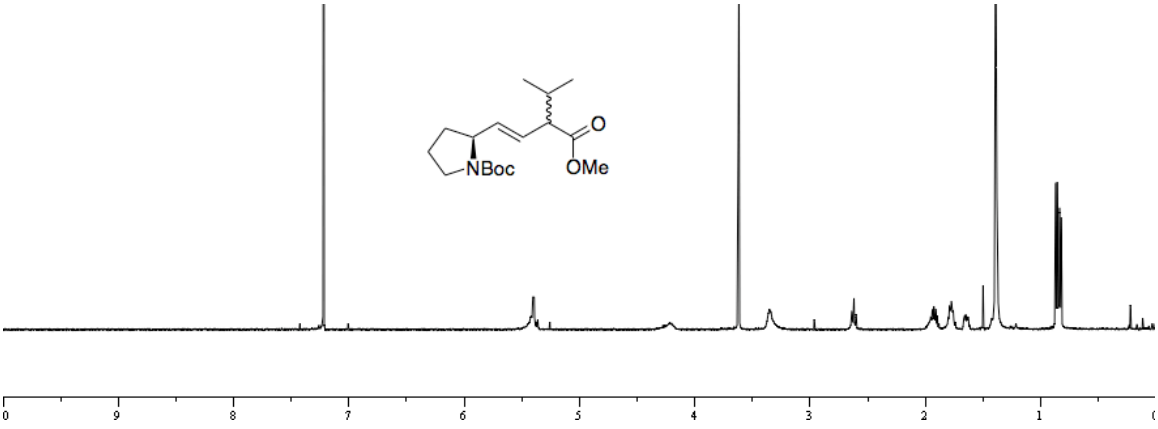
^{1}H NMR Spectrum of 10d



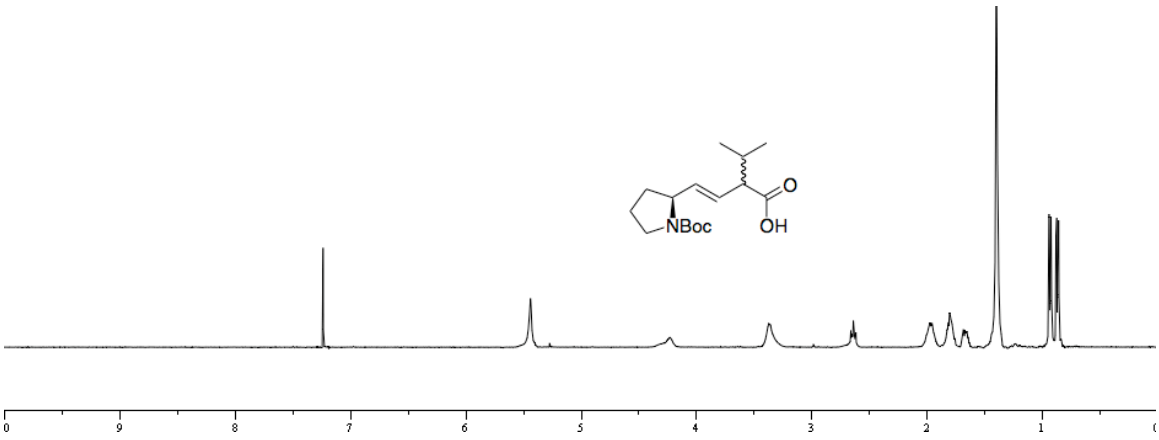
^{1}H NMR Spectrum of 10d



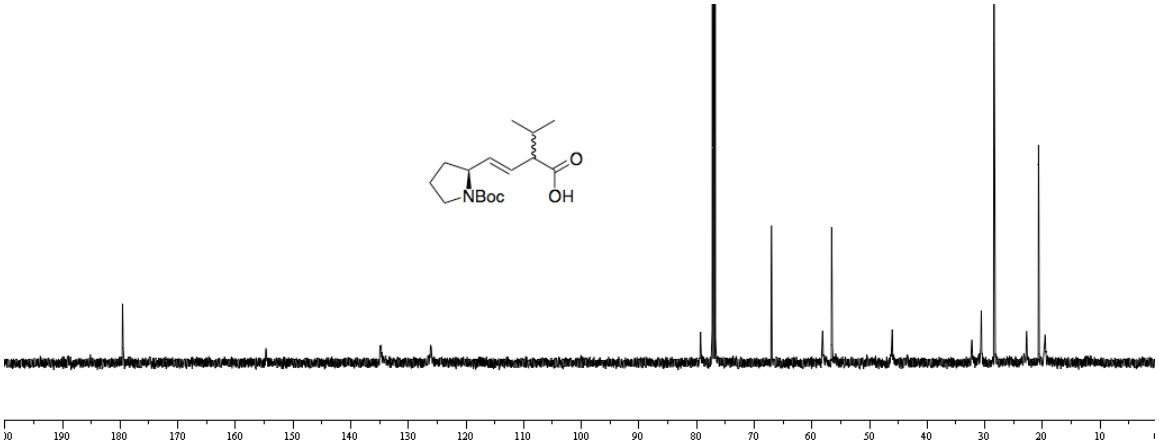
^{1}H NMR Spectrum of 10



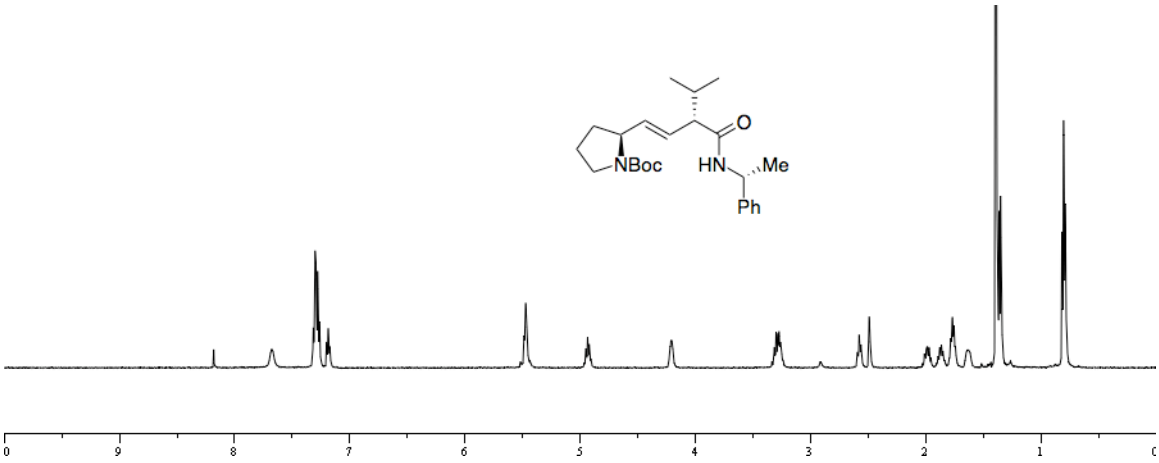
^{1}H NMR Spectrum of 9a



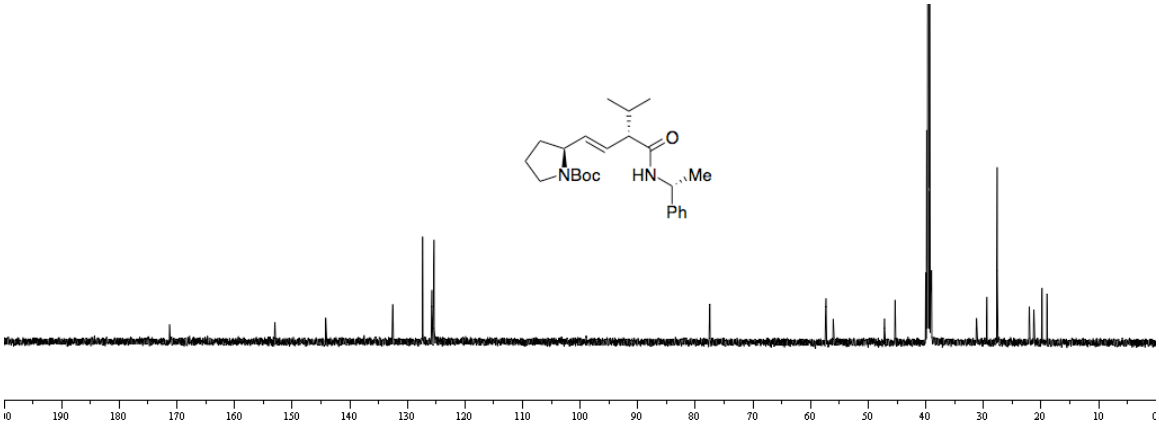
^{13}C NMR Spectrum of 9a



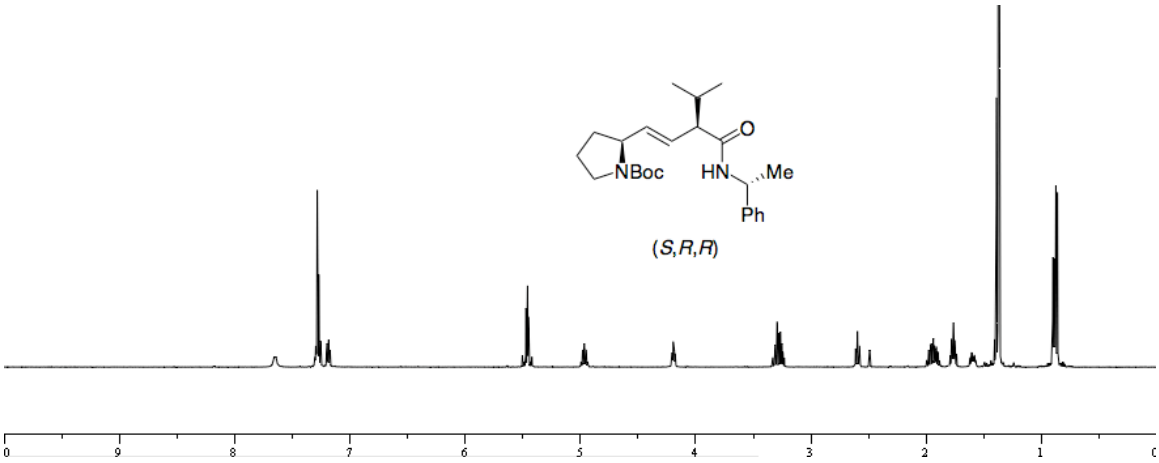
^{1}H NMR Spectrum of 9b (DMSO-d_6, 100 °C)



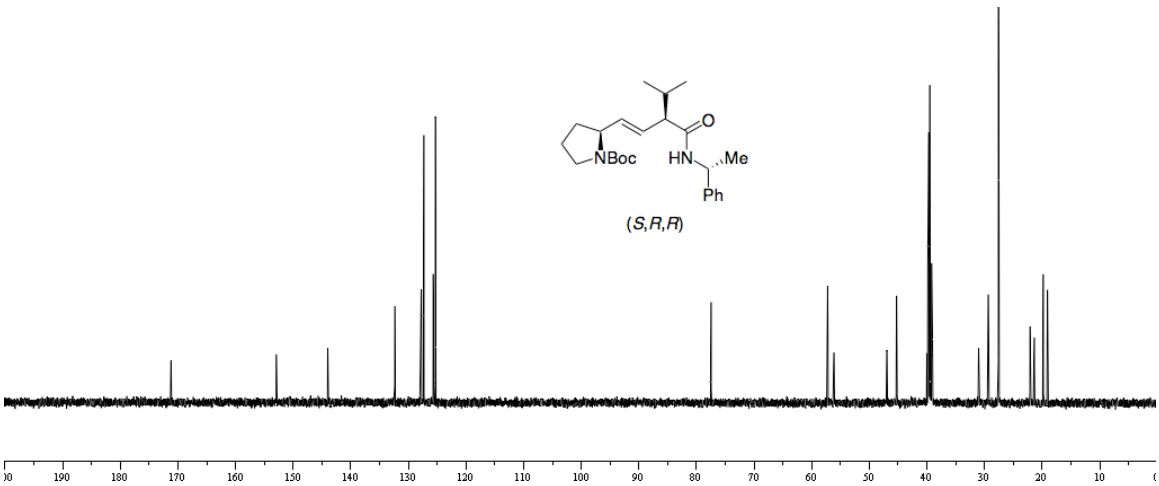
^{13}C NMR Spectrum of 9b (DMSO-d_6, 100 °C)



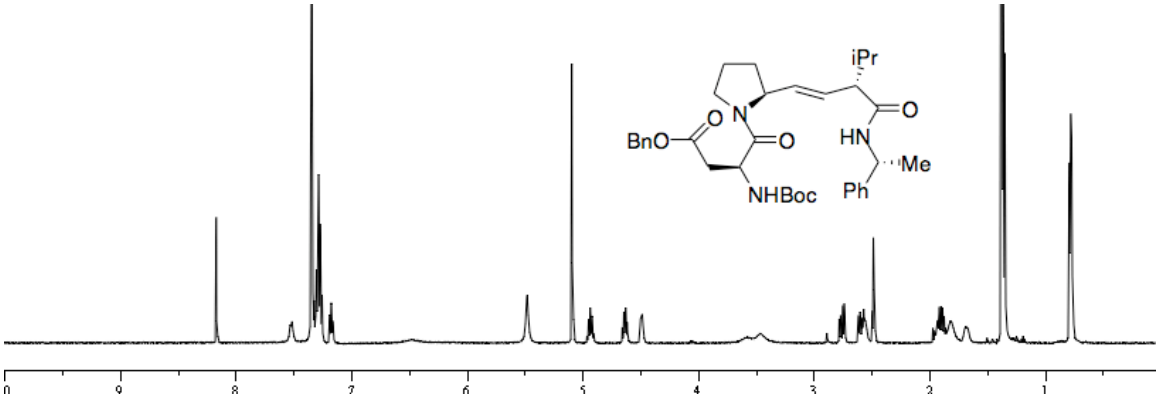
^{1}H NMR Spectrum of 9b (DMSO-d_6, 100 °C)



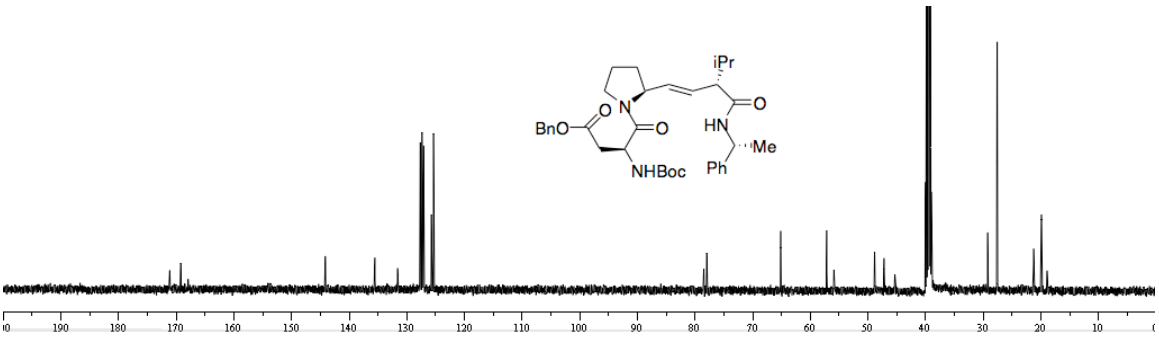
^{13}C NMR Spectrum of 9b (DMSO-d_6, 100 °C)



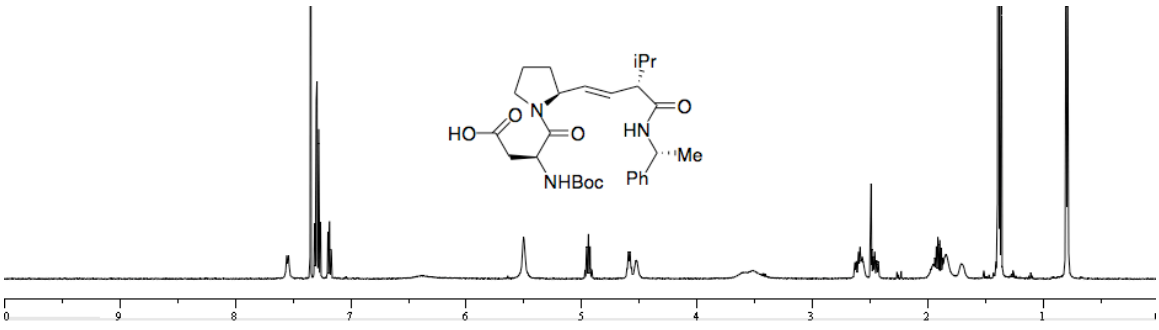
^{1}H NMR Spectrum of 9c (DMSO-d_6, 100 °C)



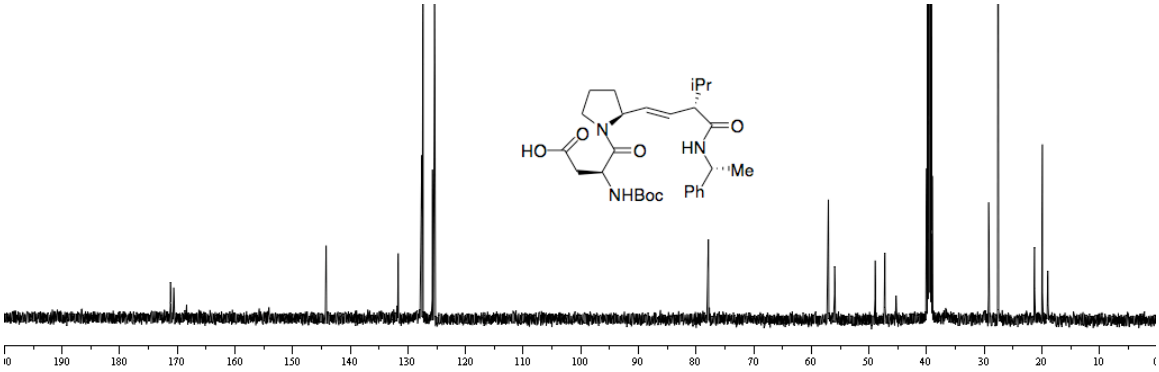
^{13}C NMR Spectrum of 9c (DMSO-d_6, 100 °C)



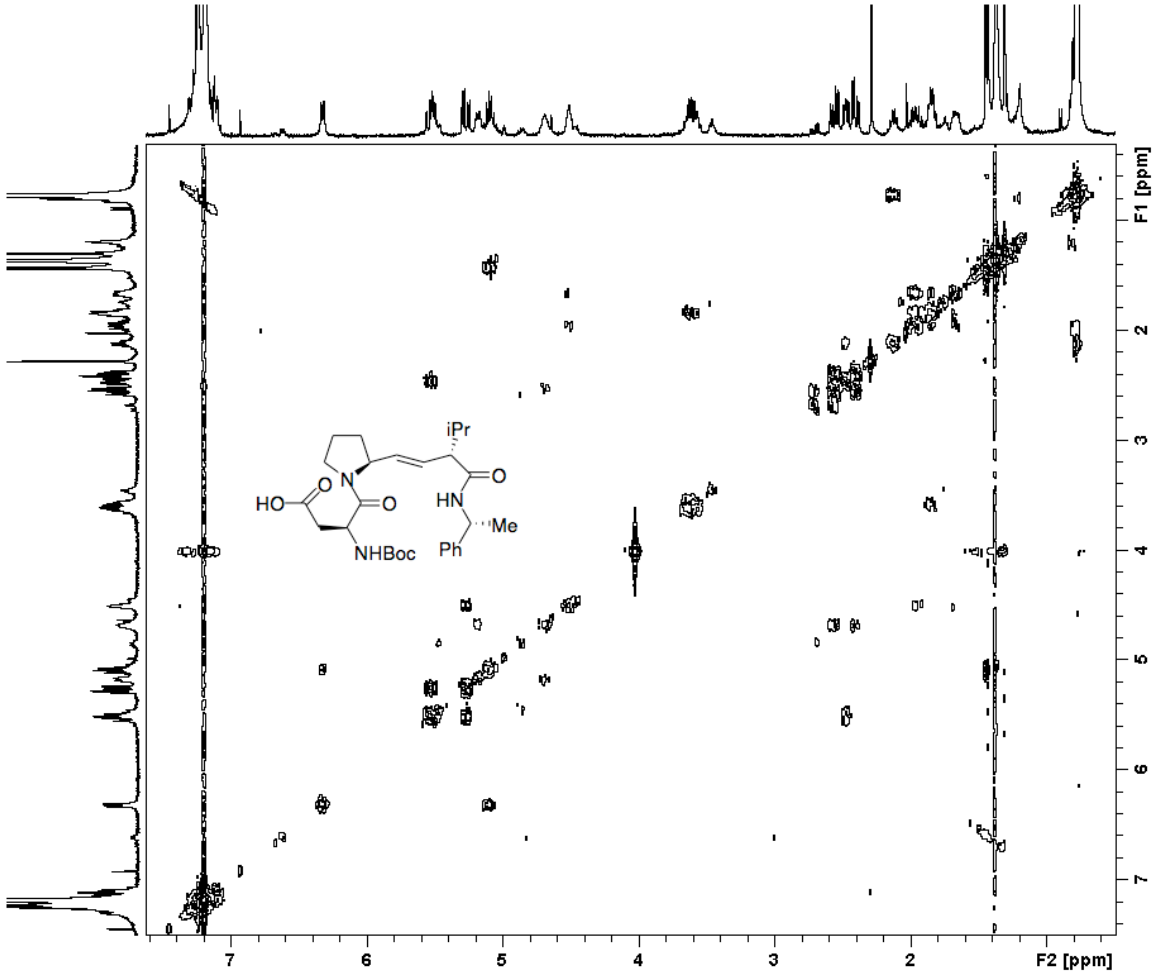
^{1}H NMR Spectrum of 9 (DMSO-d_6, 100 °C)



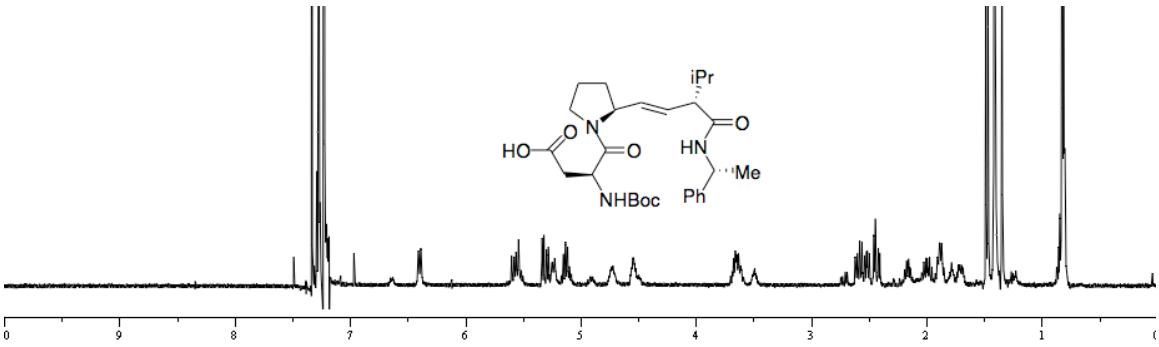
^{13}C NMR Spectrum of 9 (DMSO-d_6, 100 °C)



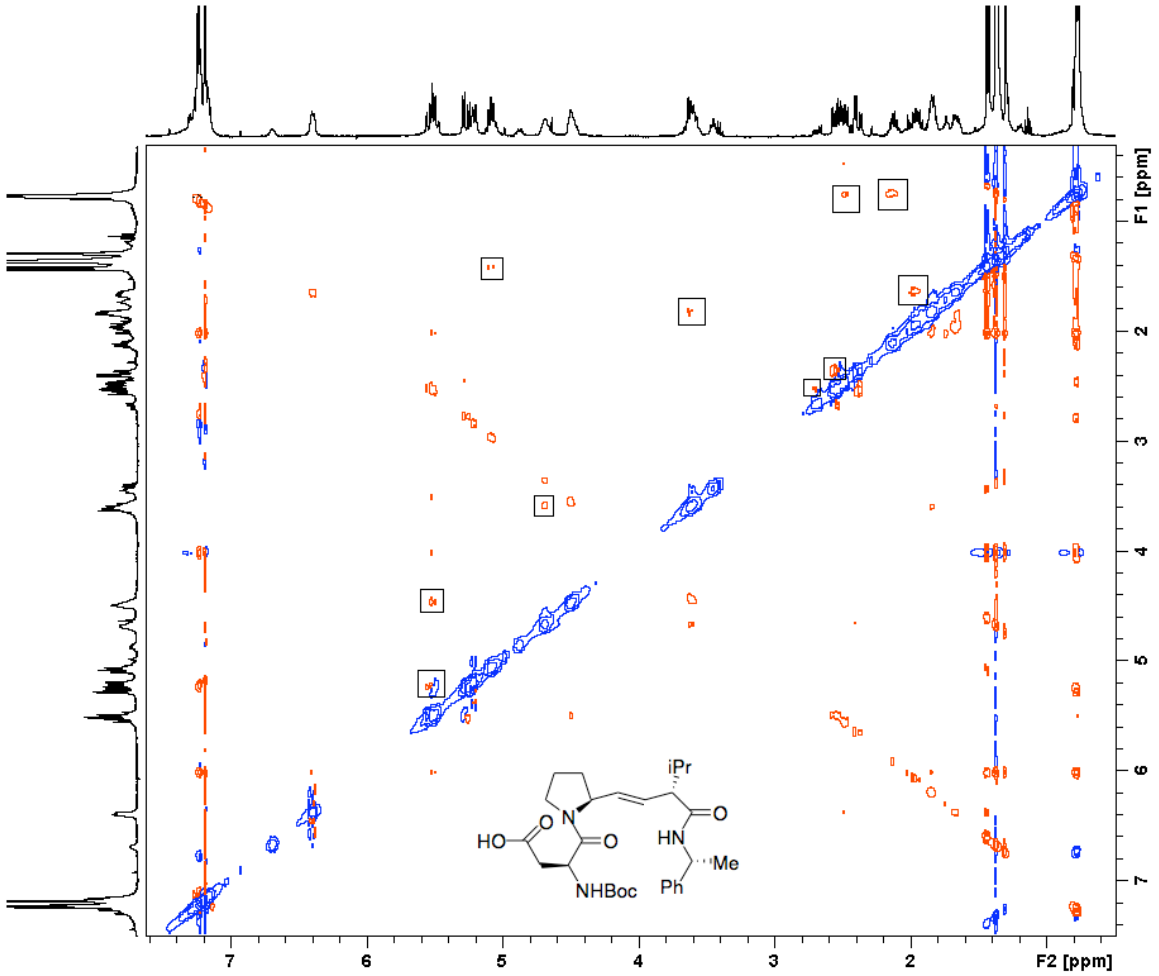
^{1}H–^{1}H COSY Spectrum of 9



^{1}H NMR Spectrum of 9



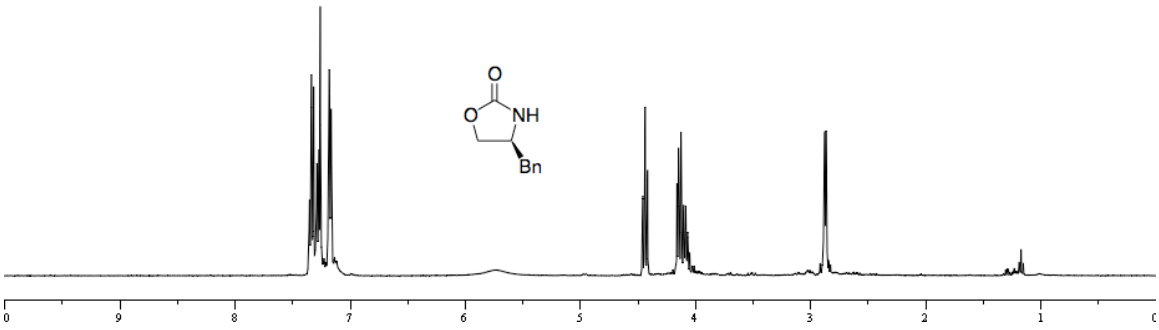
^{1}H–^{1}H NOESY Spectrum of 9



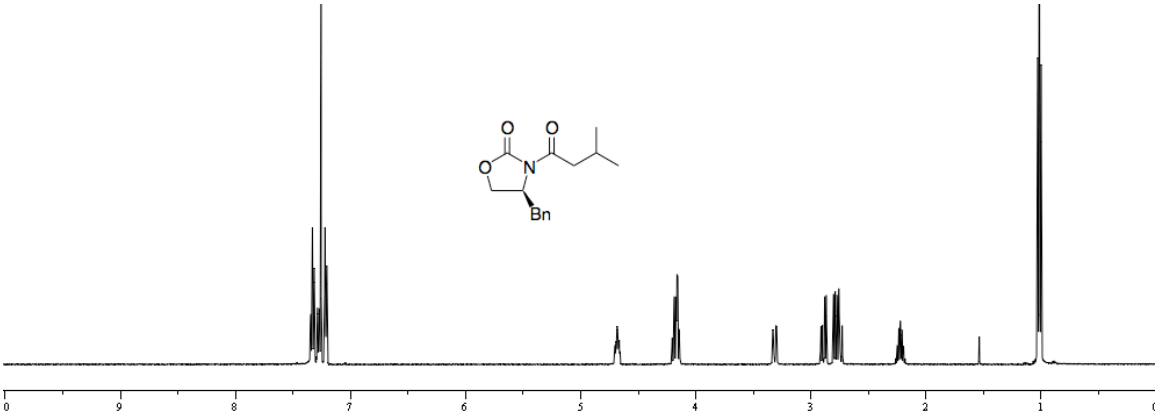
This spectrum was not symmetrized, Legitimate signals are enclosed in rectangles.

4.4 Spectra from the Synthesis of Fluoroalkene Isostere 11

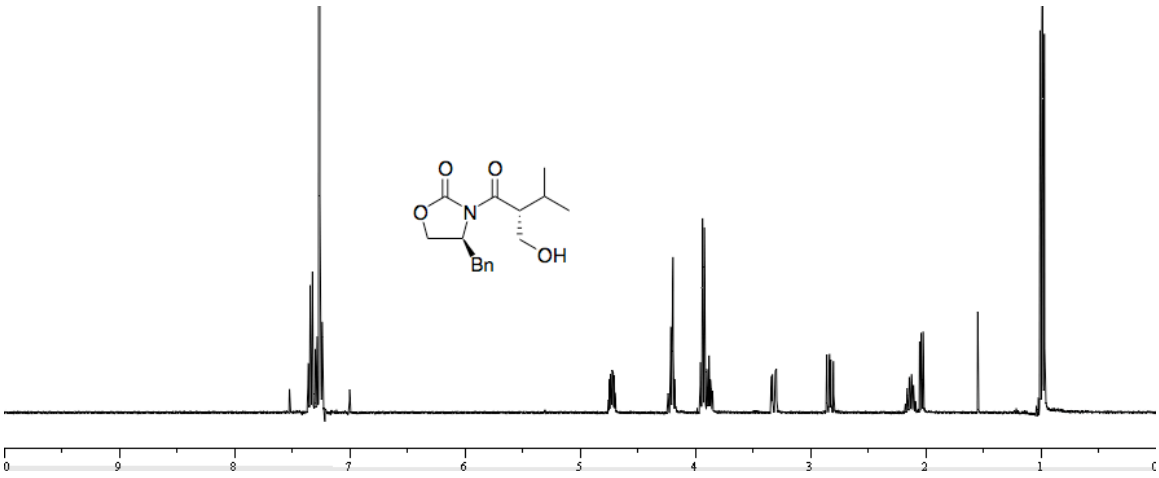
^{1}H NMR Spectrum of 12b



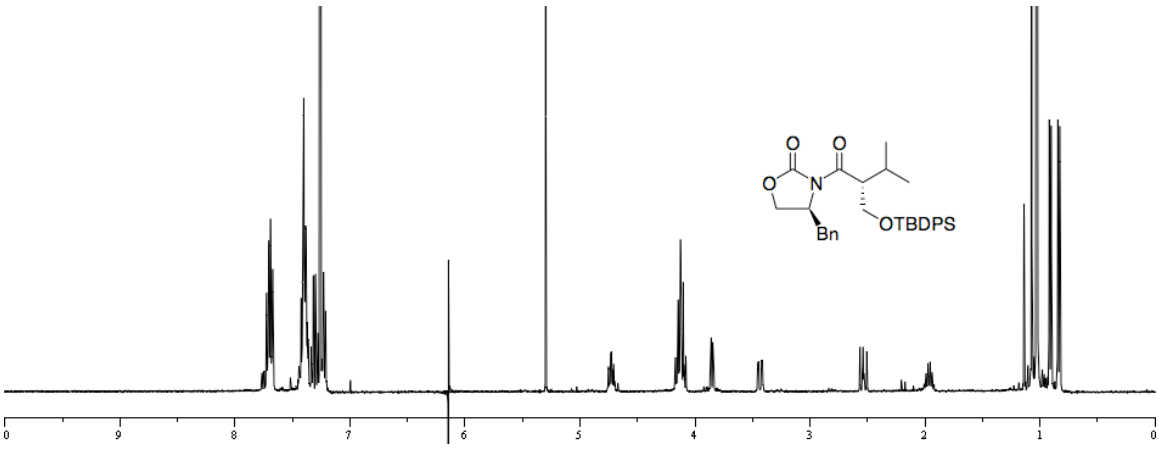
^{1}H NMR Spectrum of 12c



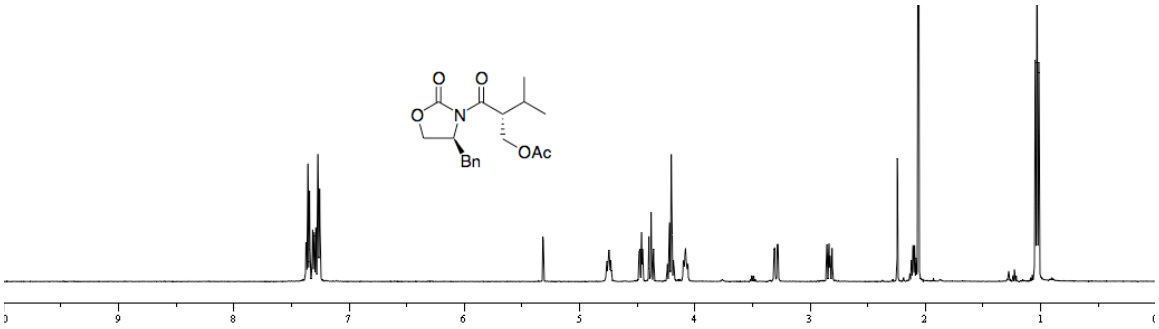
^{1}H NMR Spectrum of 12



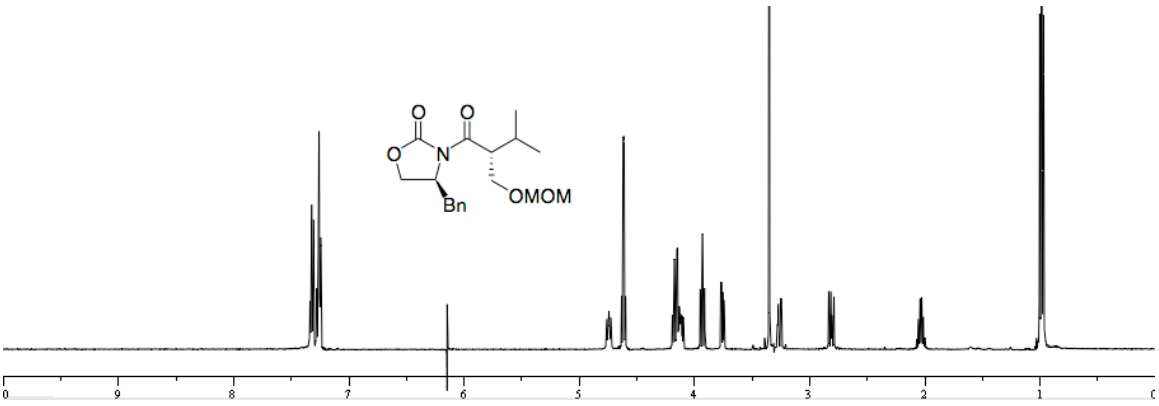
^{1}H NMR Spectrum of 13a



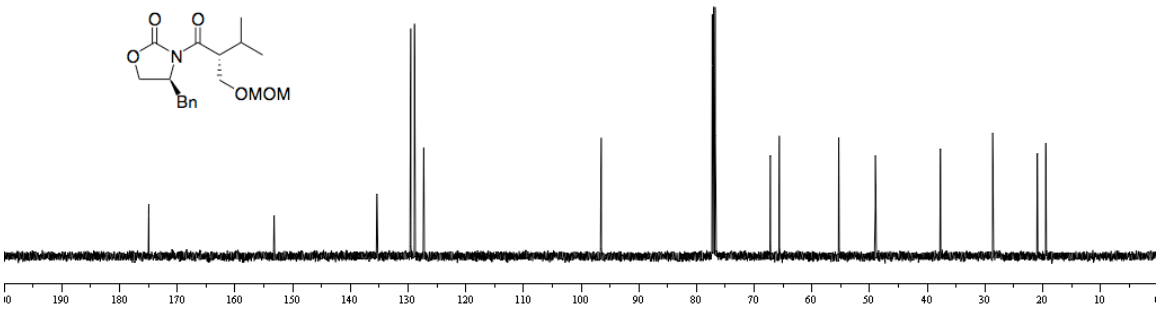
^{1}H NMR Spectrum of 13b



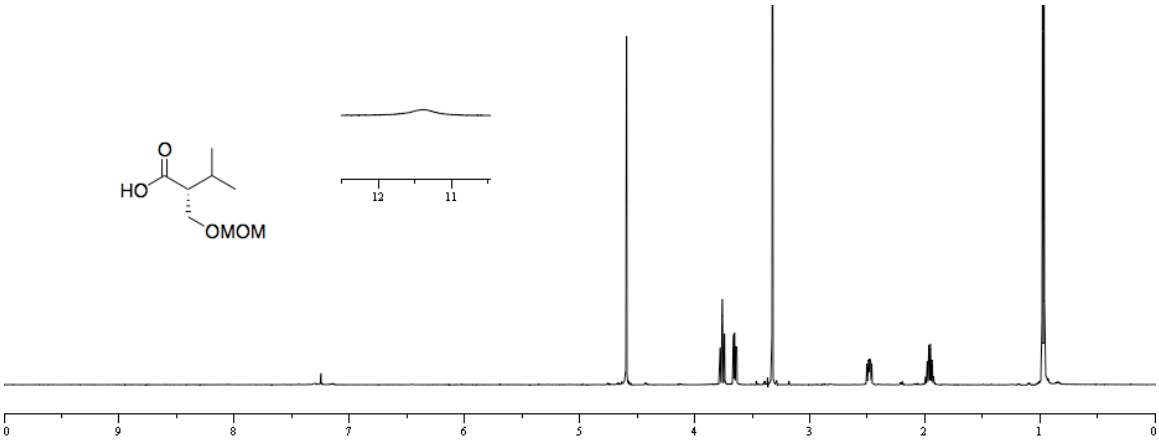
^{1}H NMR Spectrum of 13c



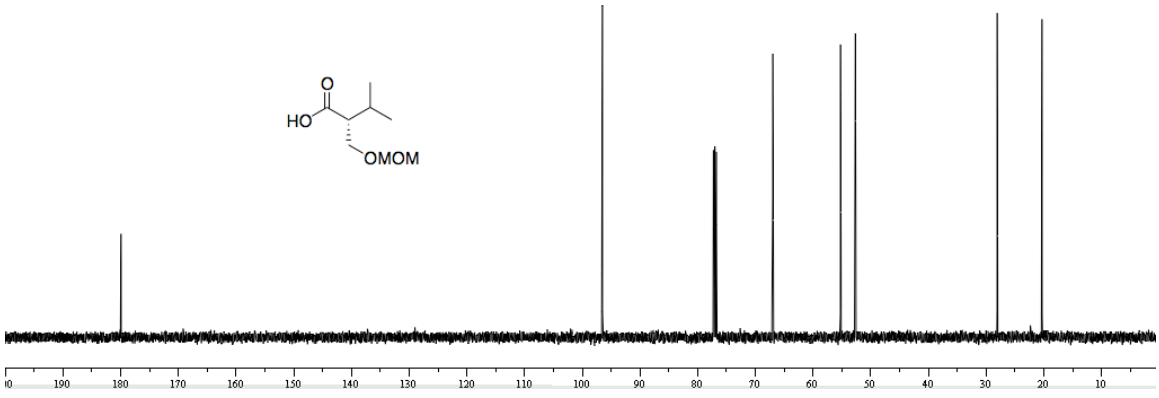
^{13}C NMR Spectrum of 13c



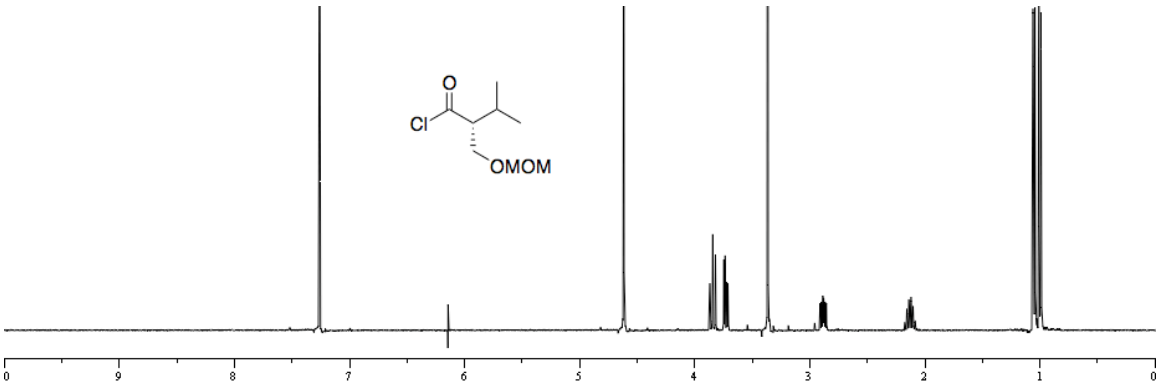
^{1}H NMR Spectrum of 13d



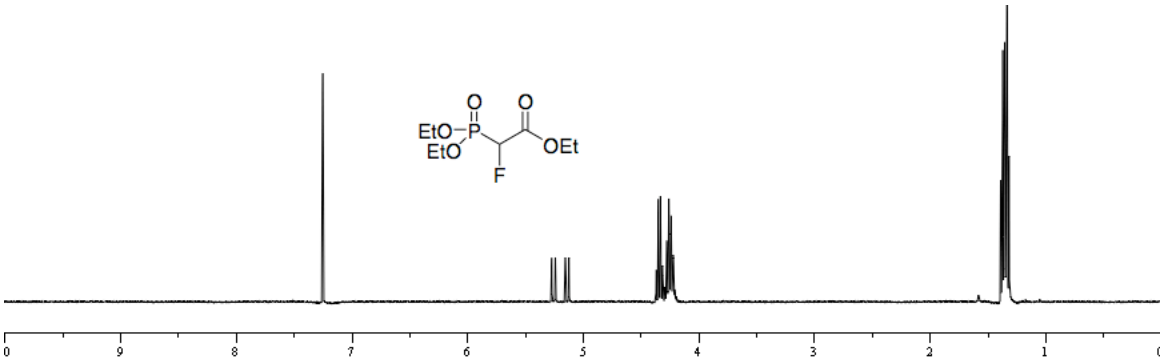
^{13}C NMR Spectrum of 13d



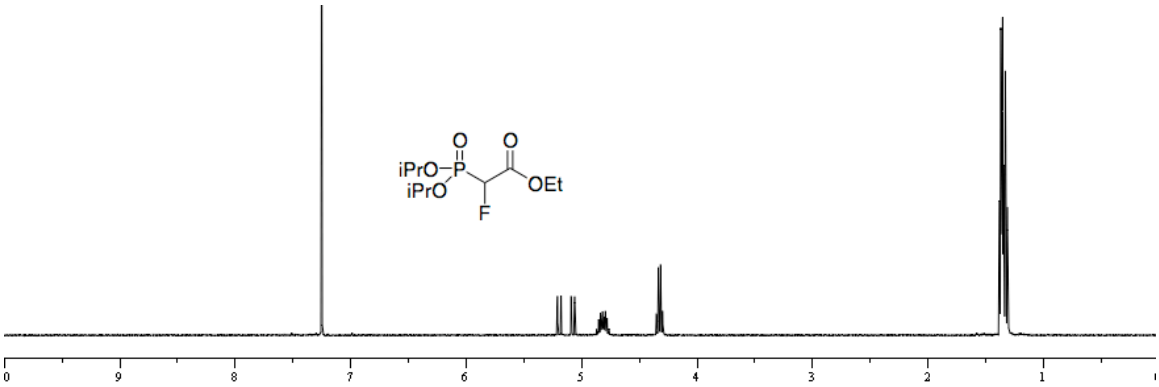
^{1}H NMR Spectrum of 13



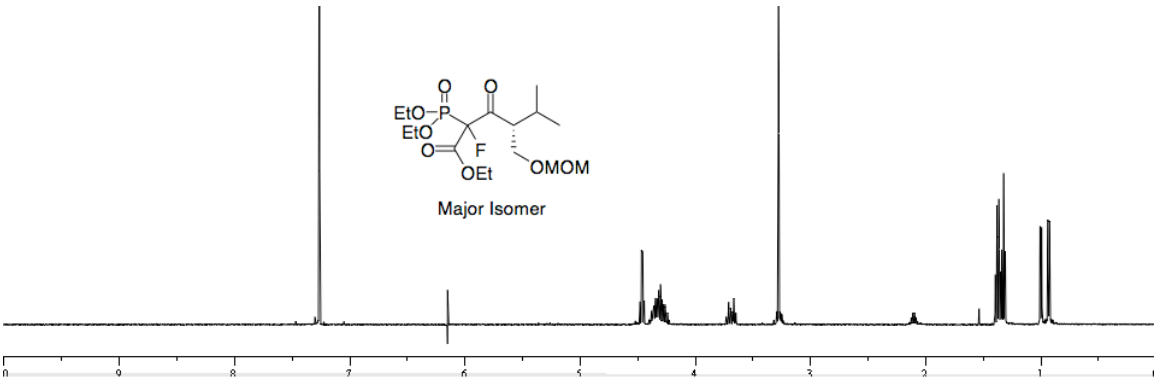
^{1}H NMR Spectrum of 14



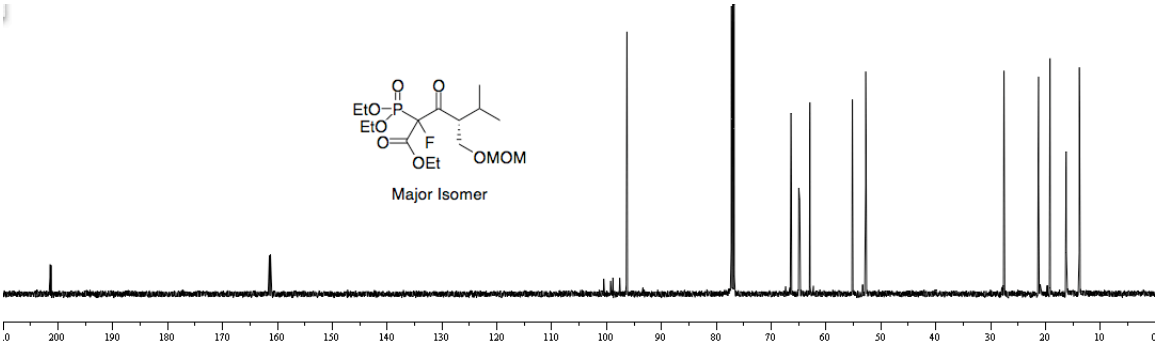
^{1}H NMR Spectrum of 14a



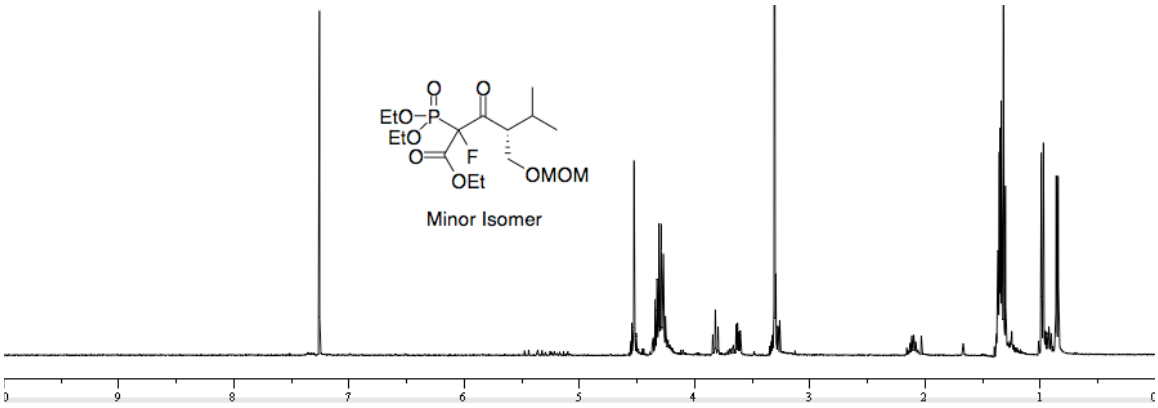
^{1}H NMR Spectrum of 15



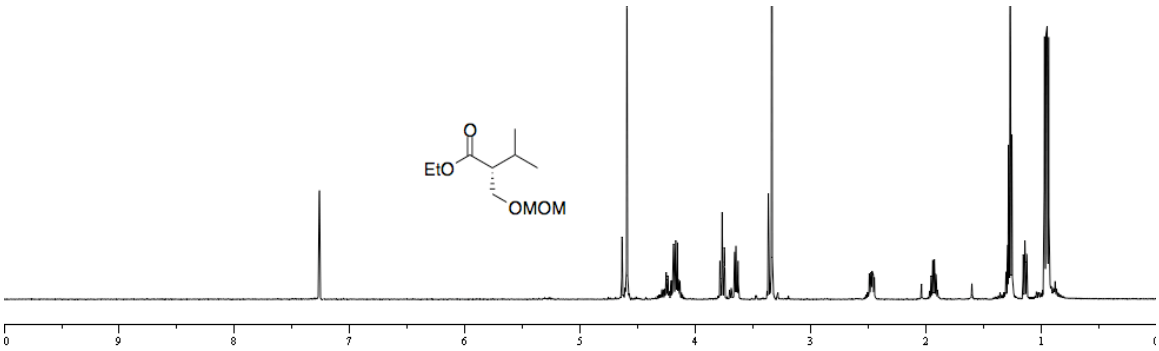
^{13}C NMR Spectrum of 15



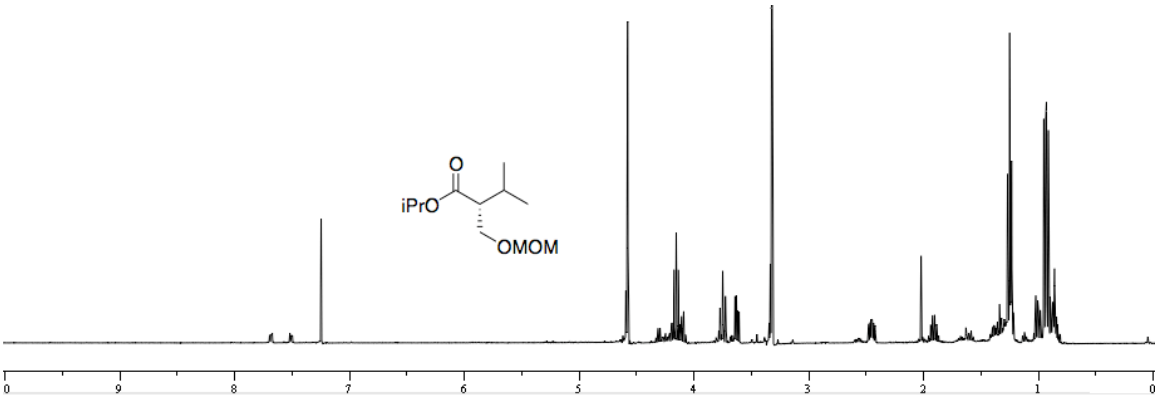
^{1}H NMR Spectrum of 15



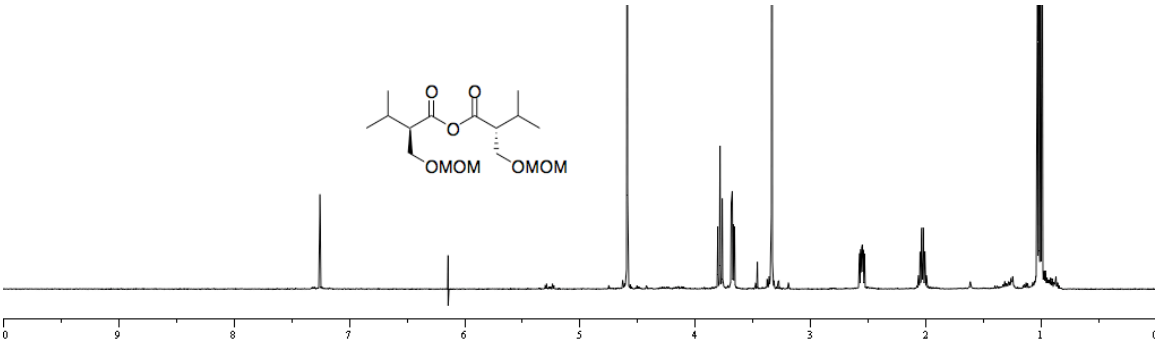
^{1}H NMR Spectrum of 15a



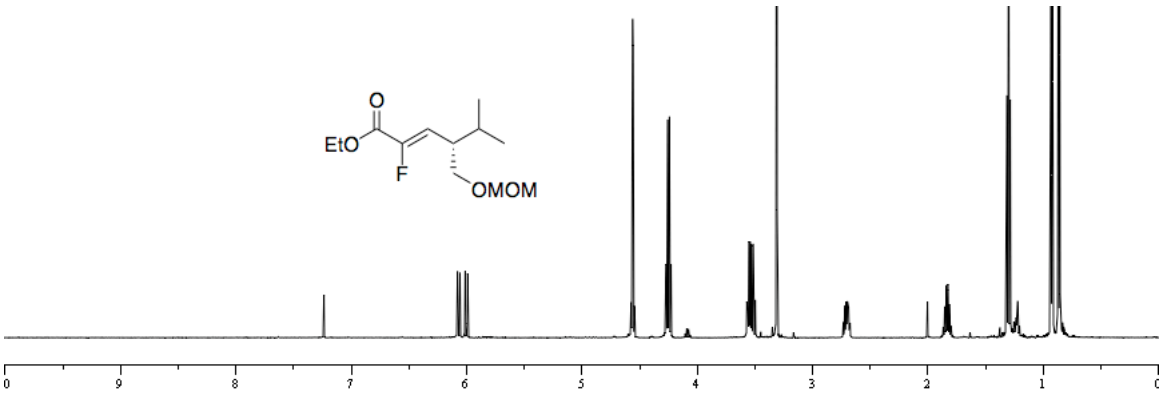
^{1}H NMR Spectrum of 15b



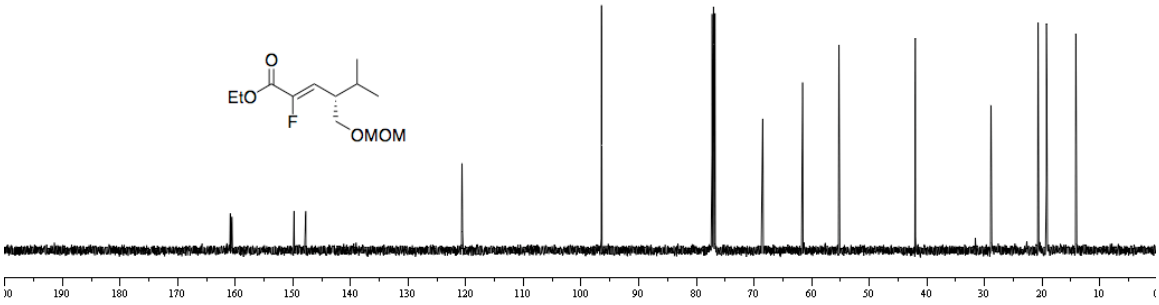
^{1}H NMR Spectrum of 15c



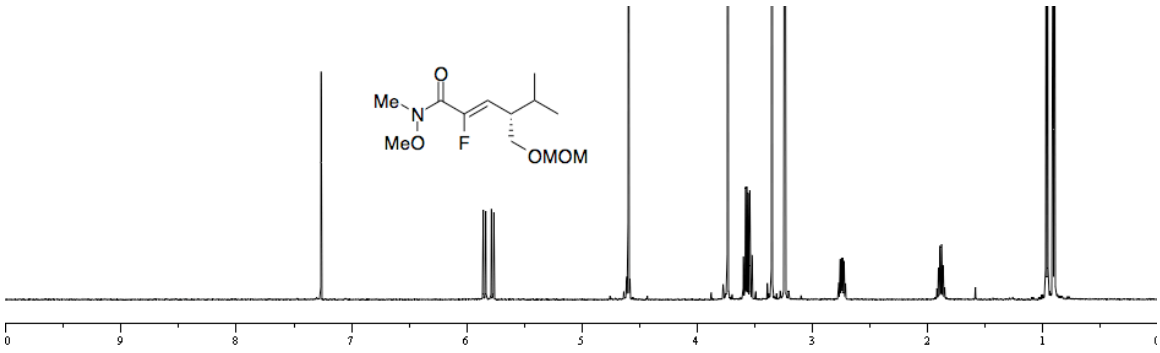
^{1}H NMR Spectrum of 16



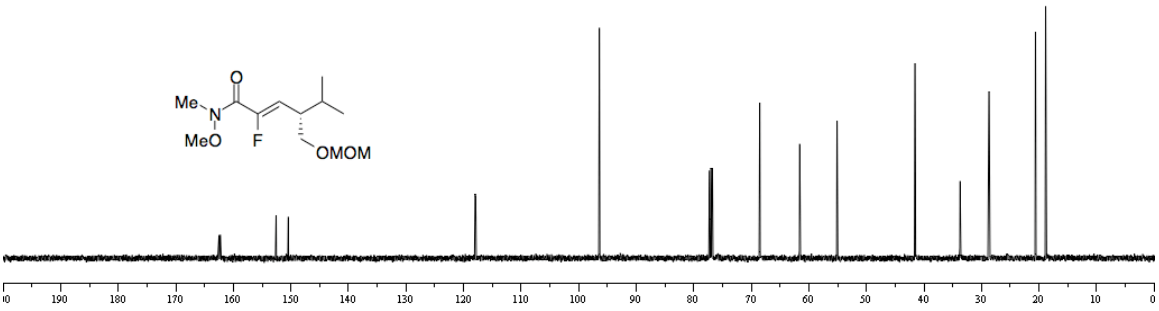
^{13}C NMR Spectrum of 16



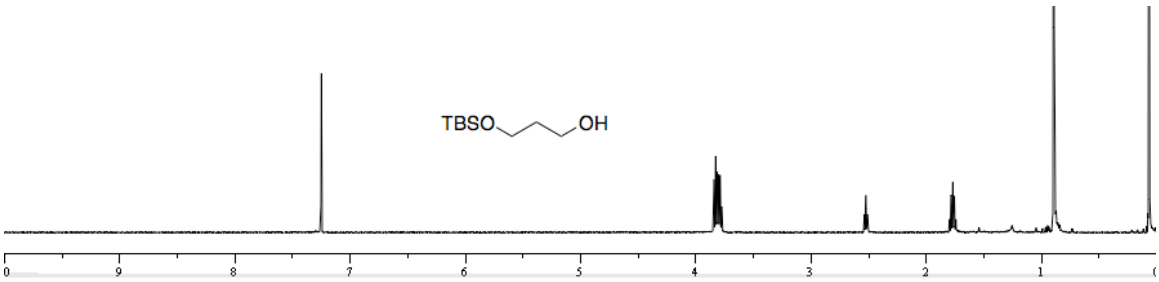
^{1}H NMR Spectrum of 18a



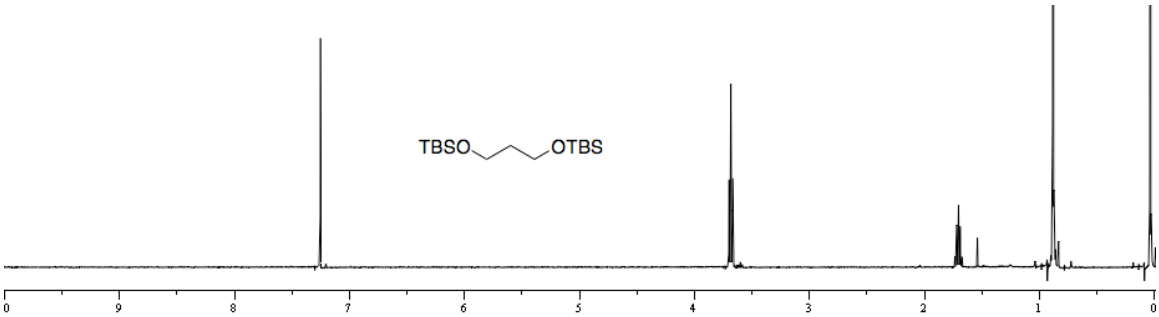
^{13}C NMR Spectrum of 18a



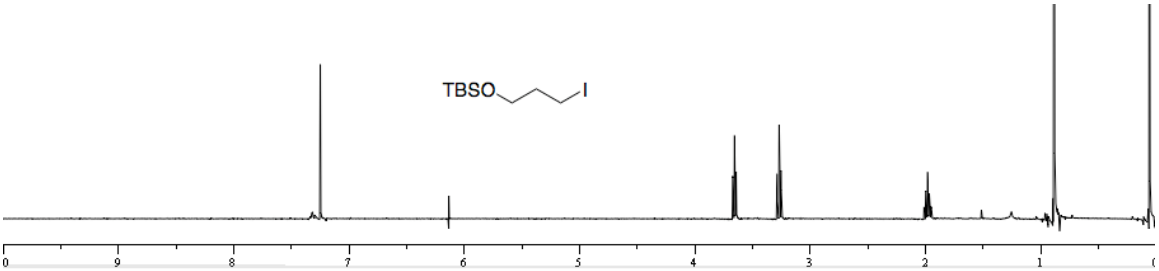
^{1}H NMR Spectrum of 17a



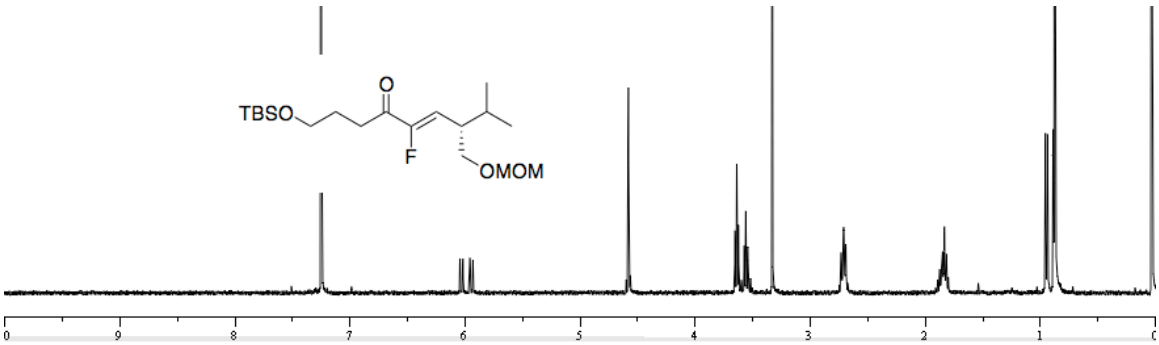
^{1}H NMR Spectrum of 17b



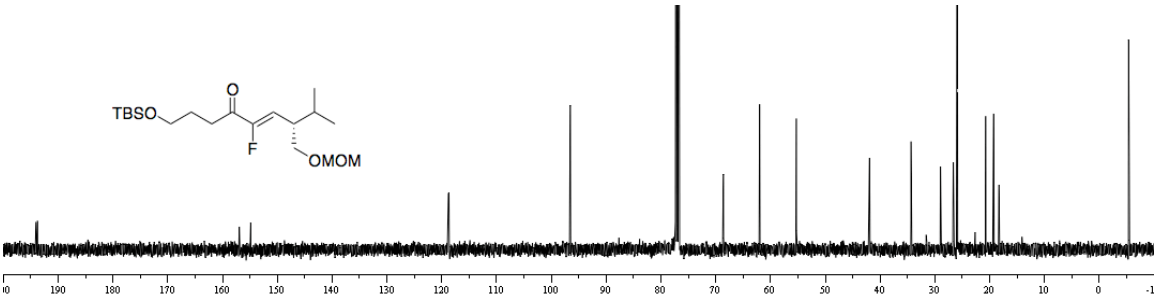
^{1}H NMR Spectrum of 17



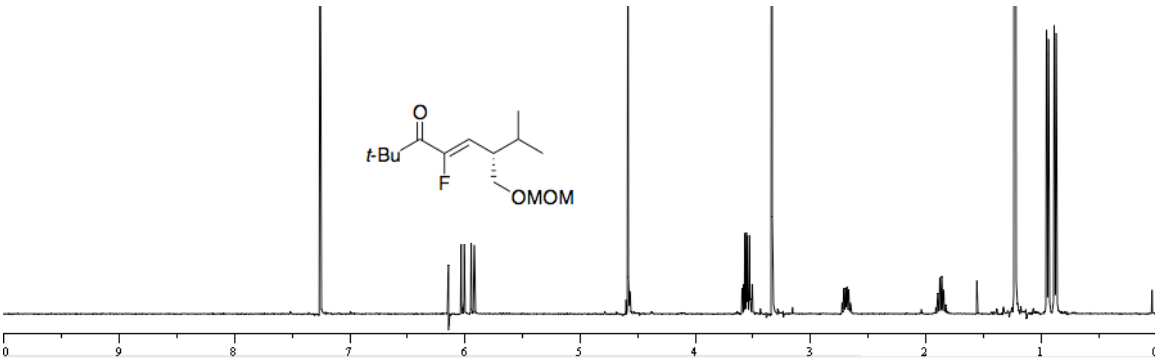
^{1}H NMR Spectrum of 18



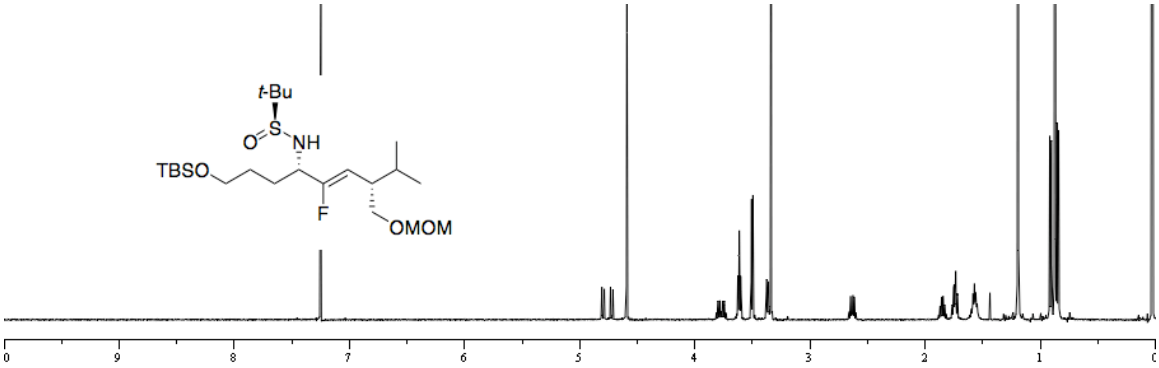
^{13}C NMR Spectrum of 18



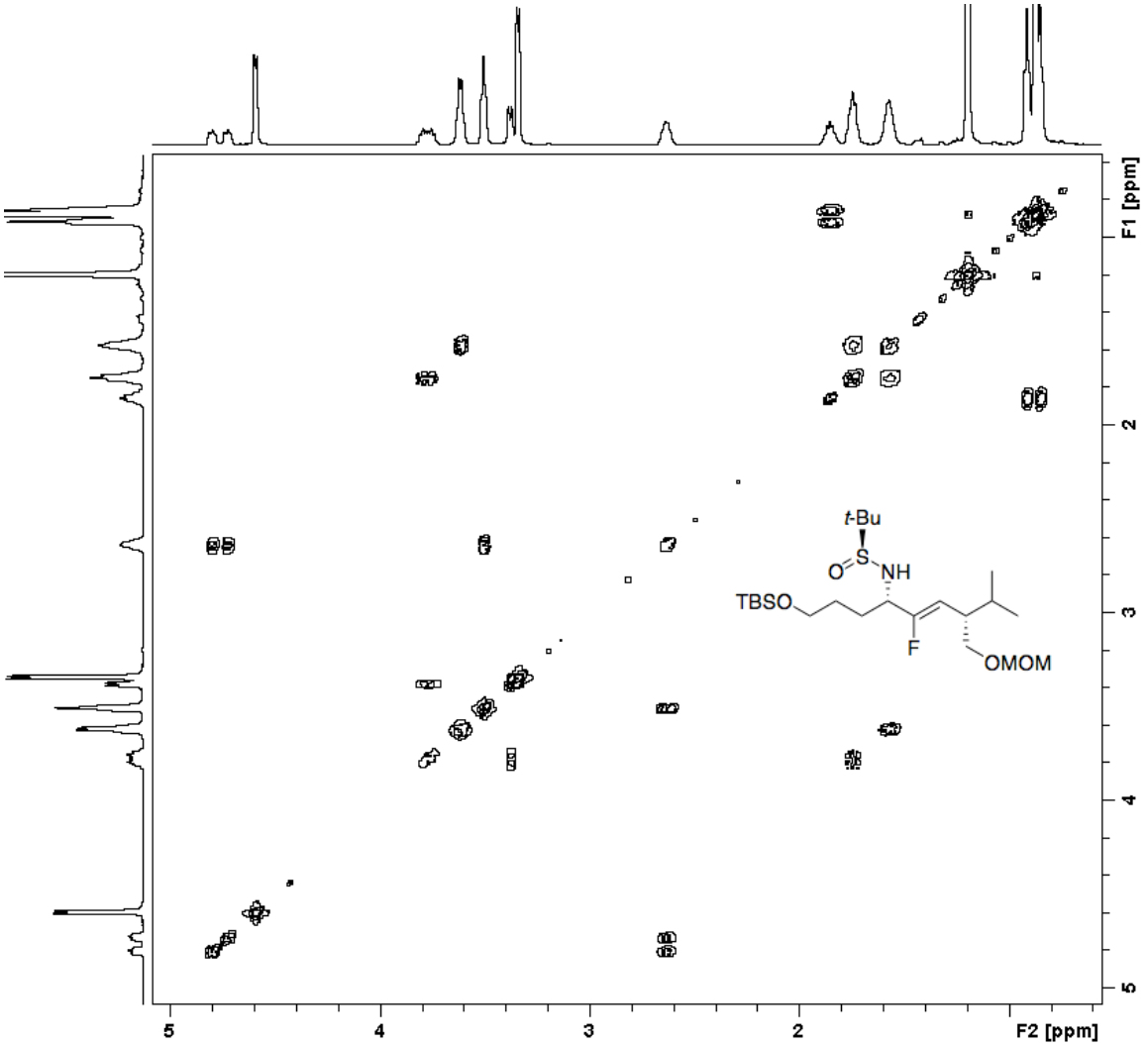
^{1}H NMR Spectrum of 18c



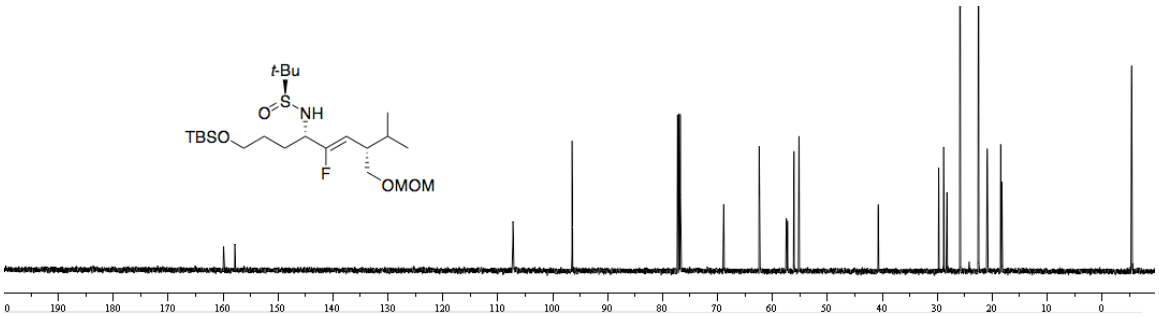
^{1}H NMR Spectrum of 20b



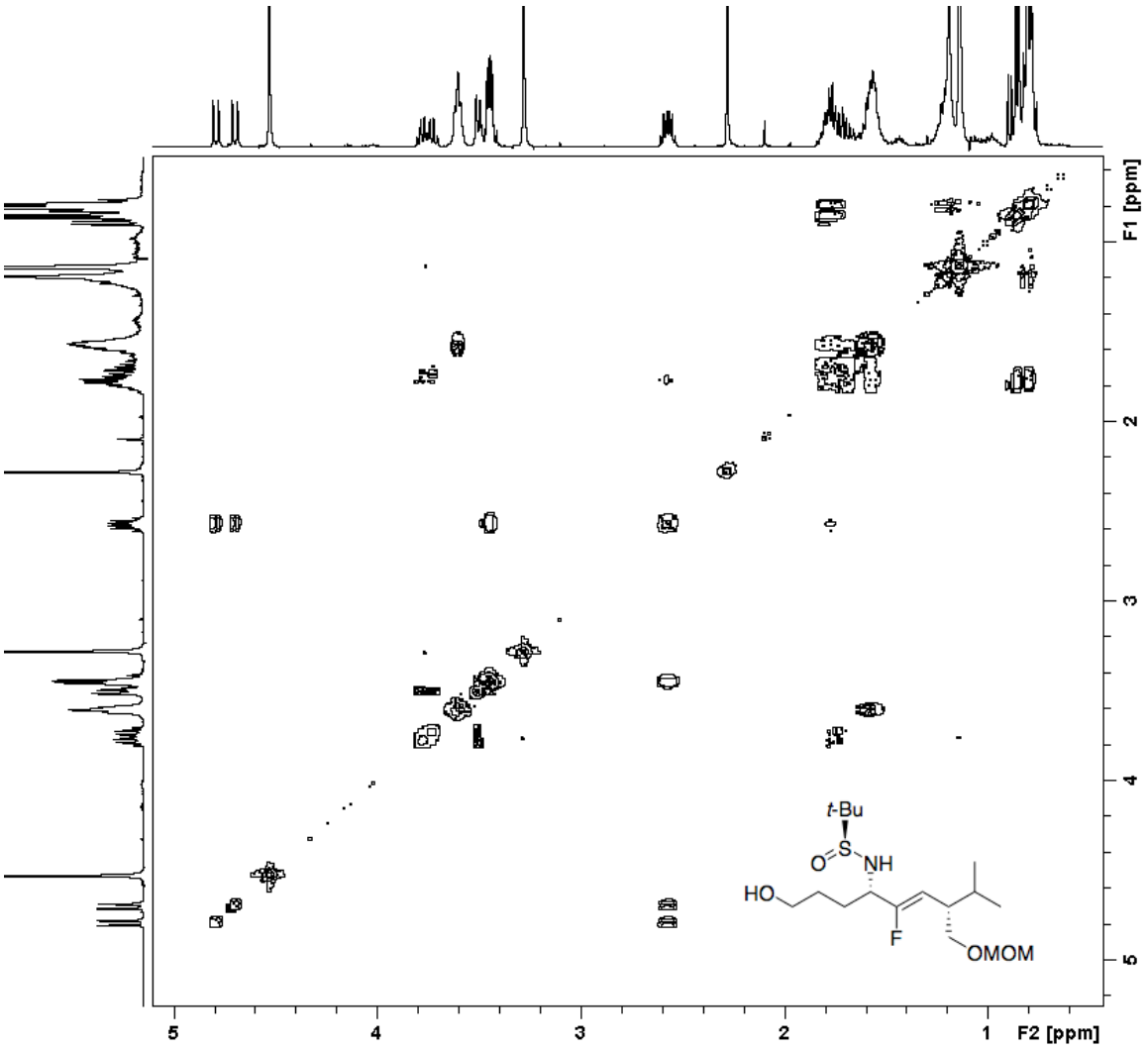
^{1}H–^{1}H COSY Spectrum of 20b



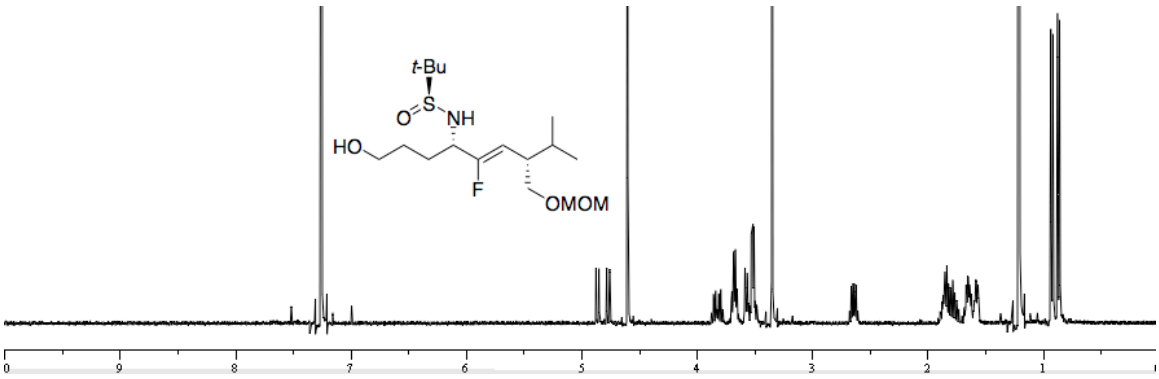
^{13}C NMR Spectrum of 20b



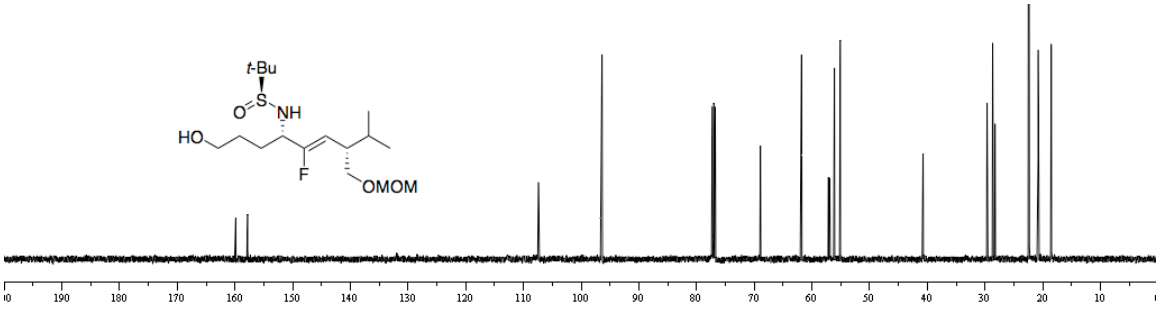
^{1}H–^{1}H COSY Spectrum of 20



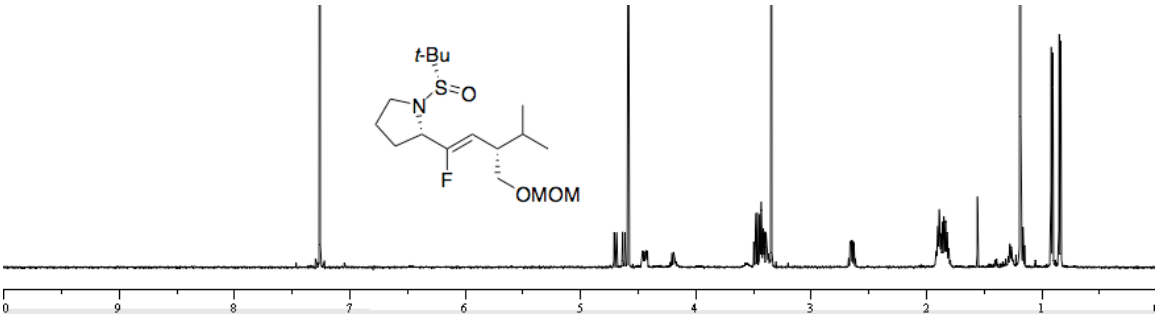
^{1}H NMR Spectrum of 20



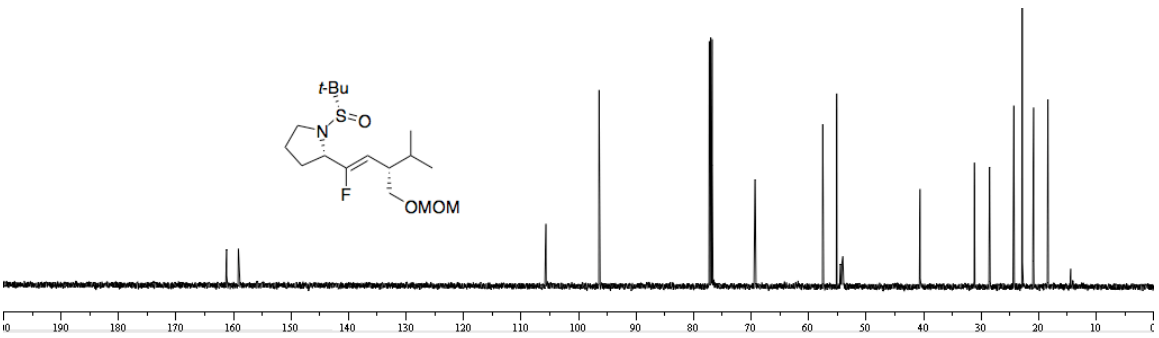
^{13}C NMR Spectrum of 20



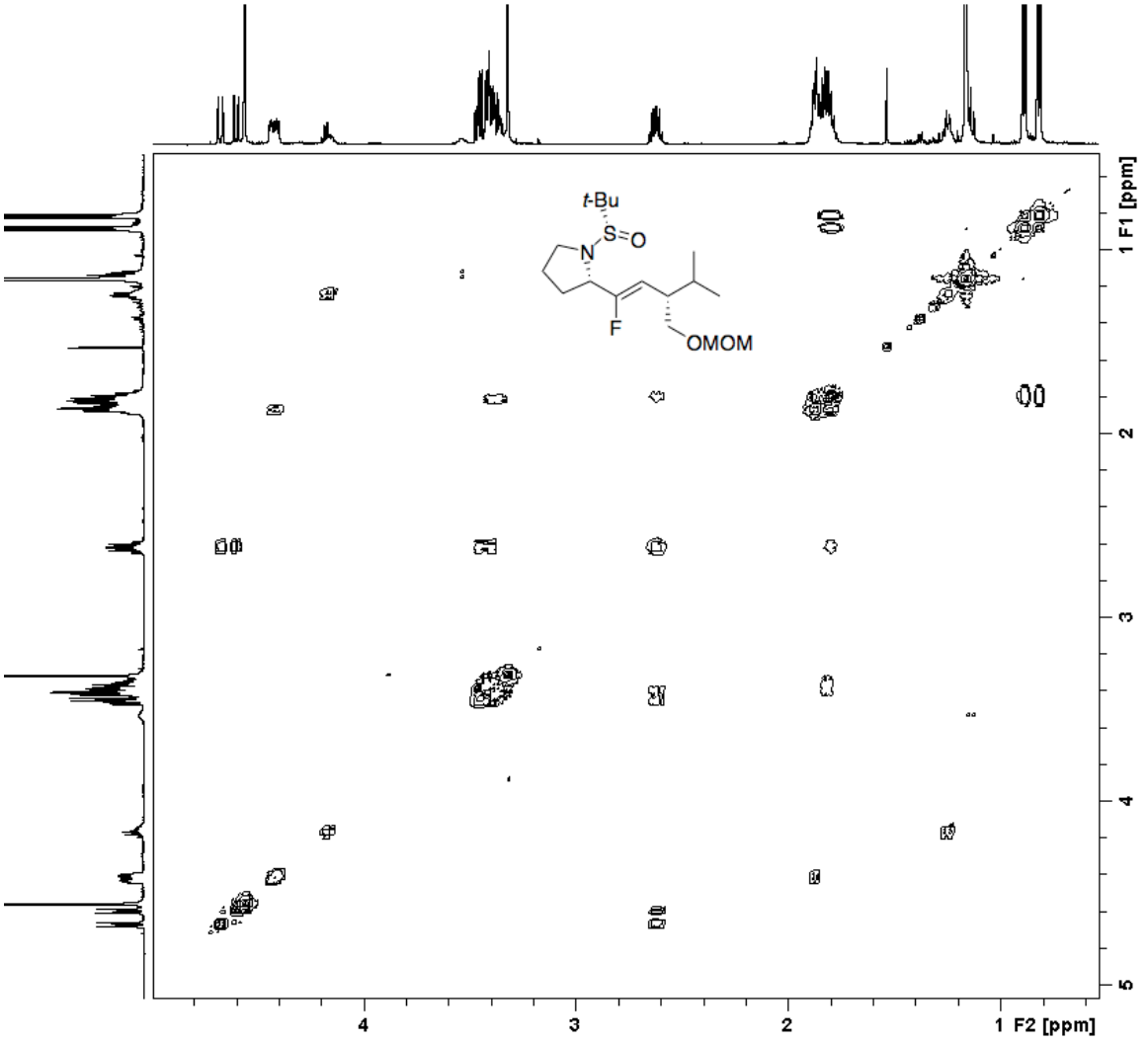
^{1}H NMR Spectrum of 21



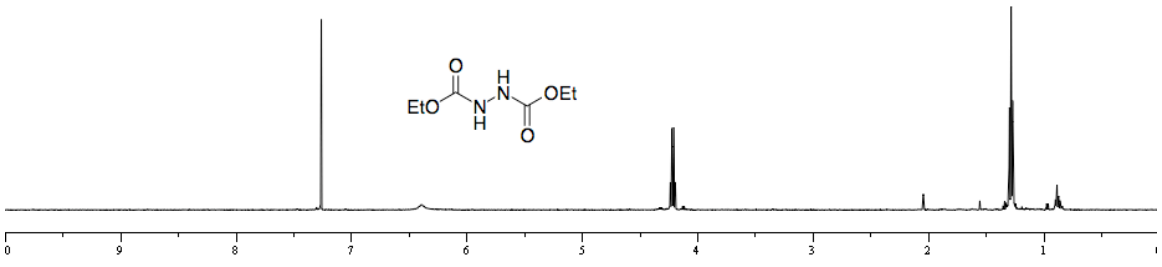
^{13}C NMR Spectrum of 21



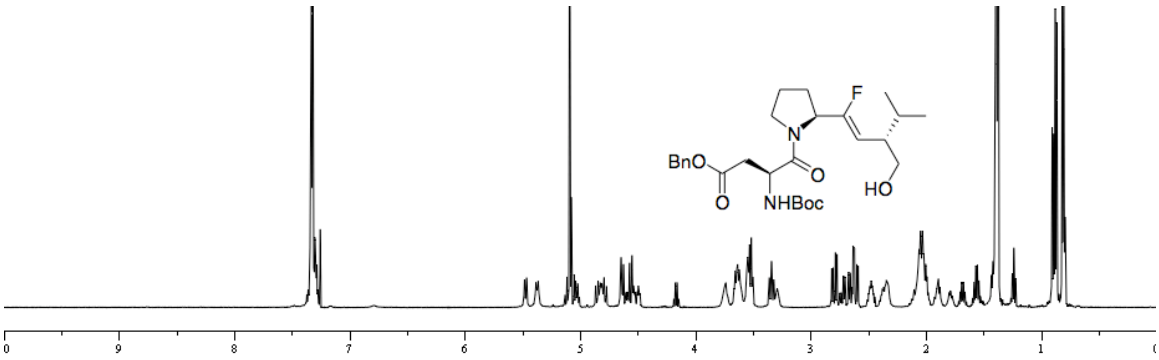
^{1}H–^{1}H COSY Spectrum of 21



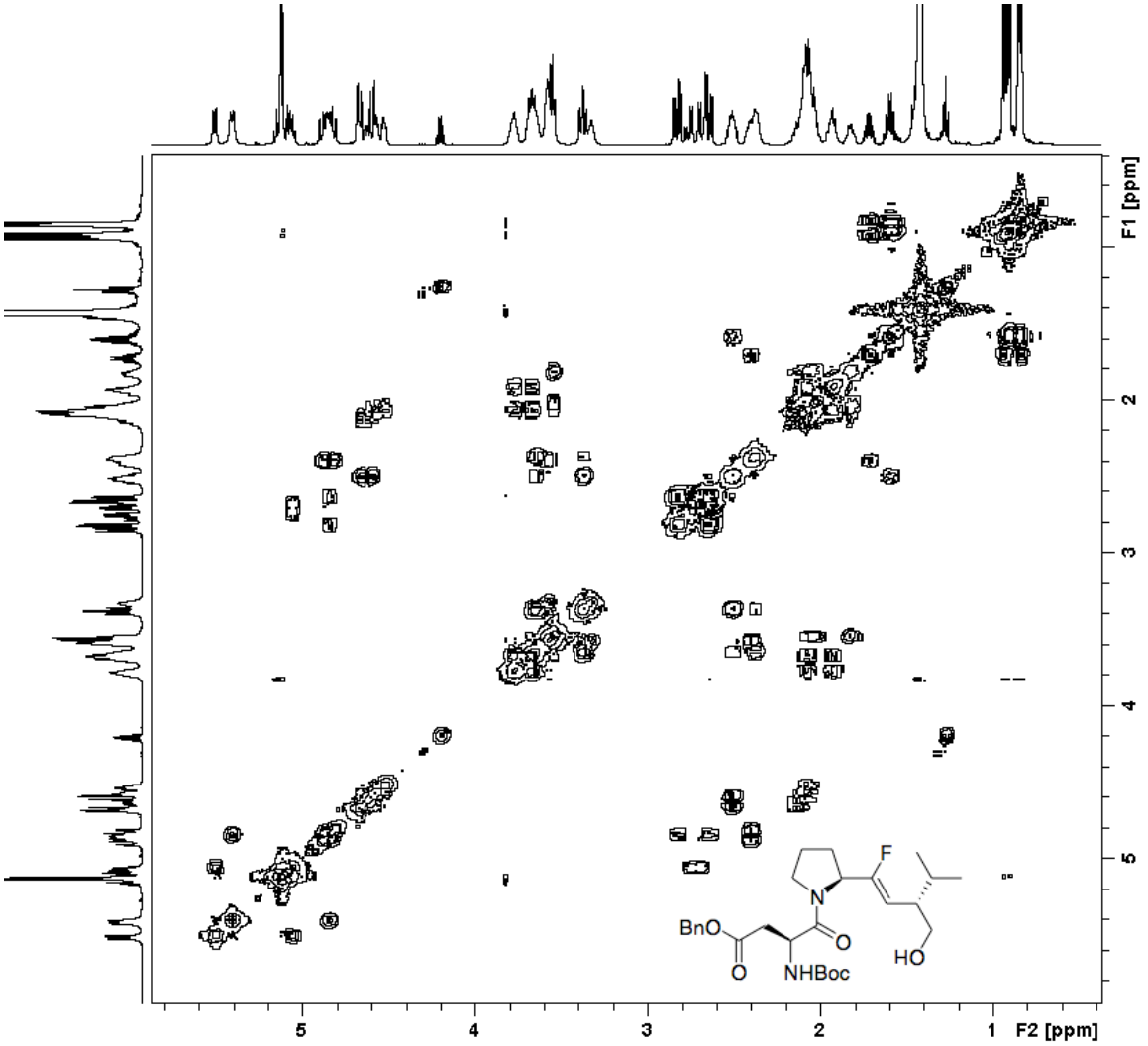
^{1}H NMR Spectrum of 21a



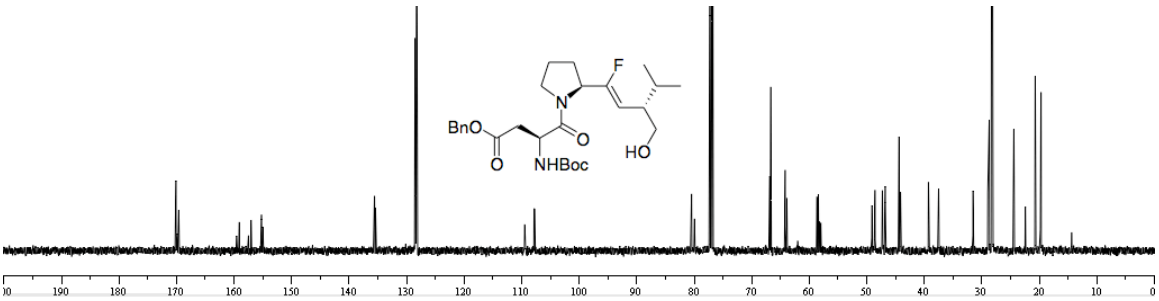
^{1}H NMR Spectrum of 22



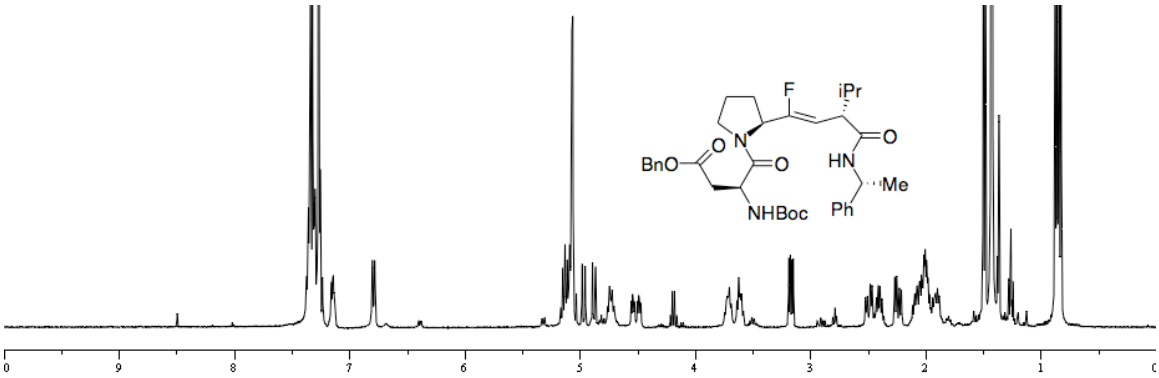
^{1}H–^{1}H COSY Spectrum of 22



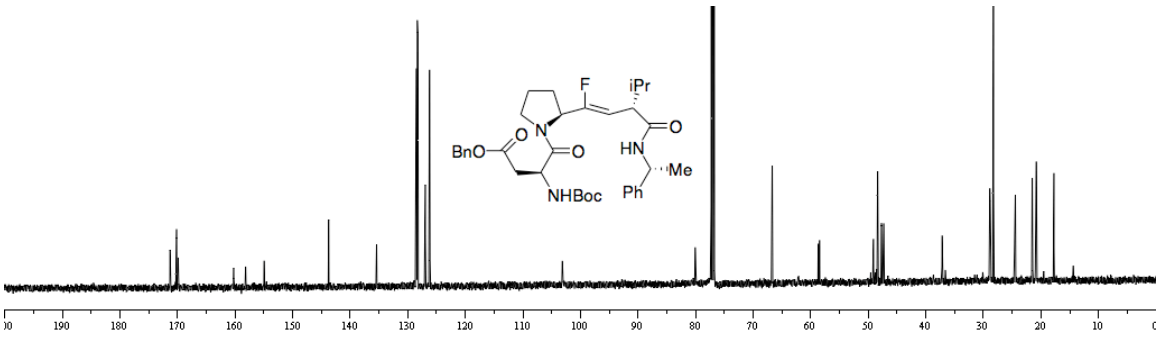
^{13}C NMR Spectrum of 22



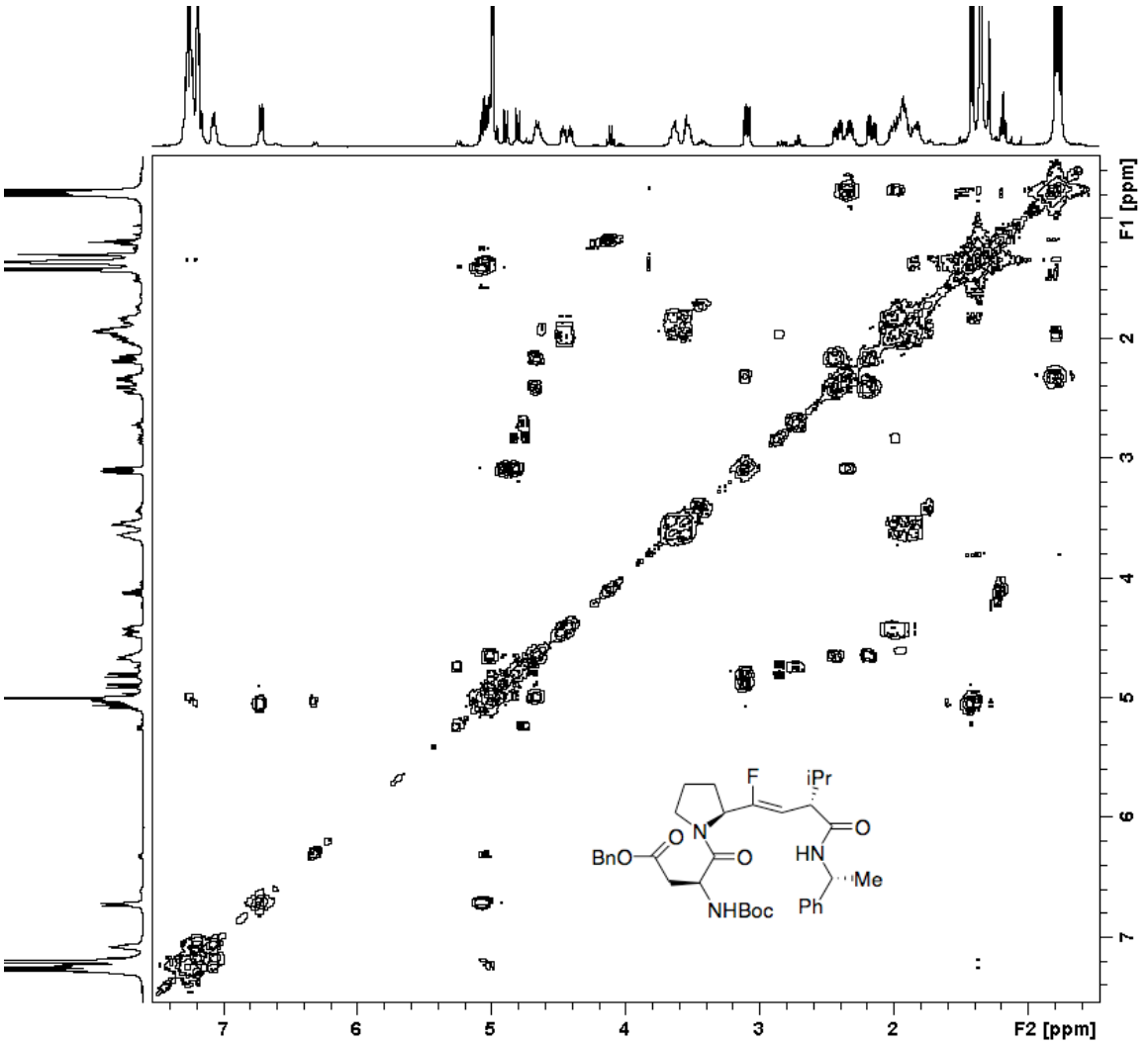
^{1}H NMR Spectrum of 11b



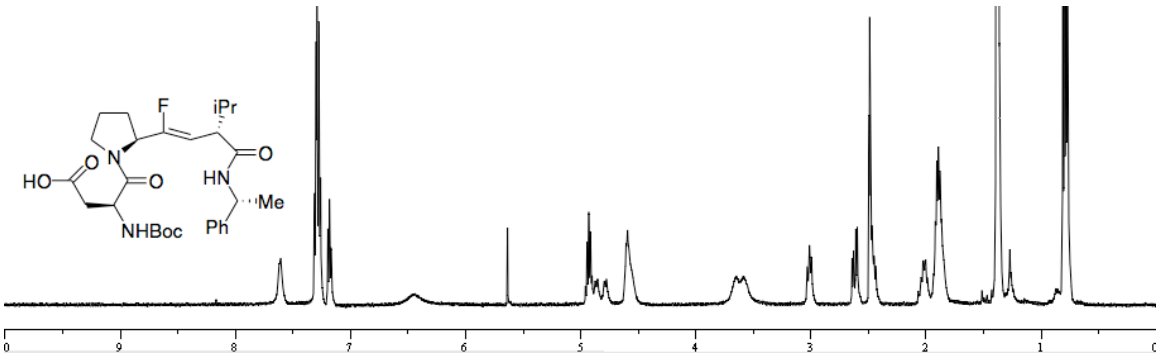
^{13}C NMR Spectrum of 11b



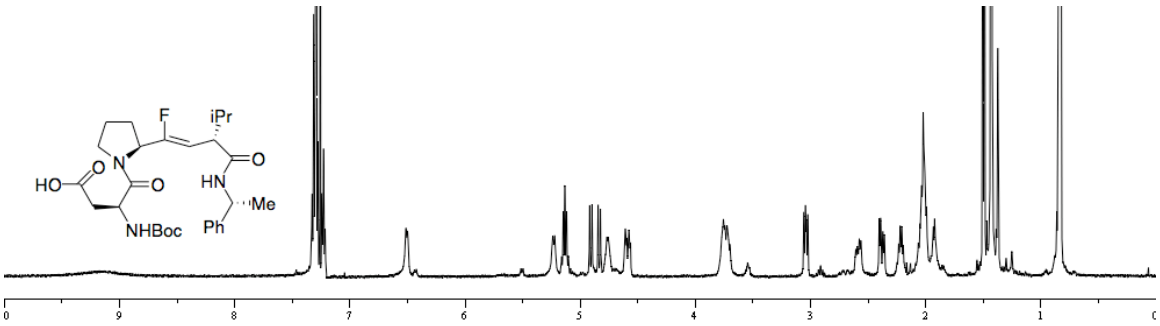
^{1}H–^{1}H COSY Spectrum of 11b



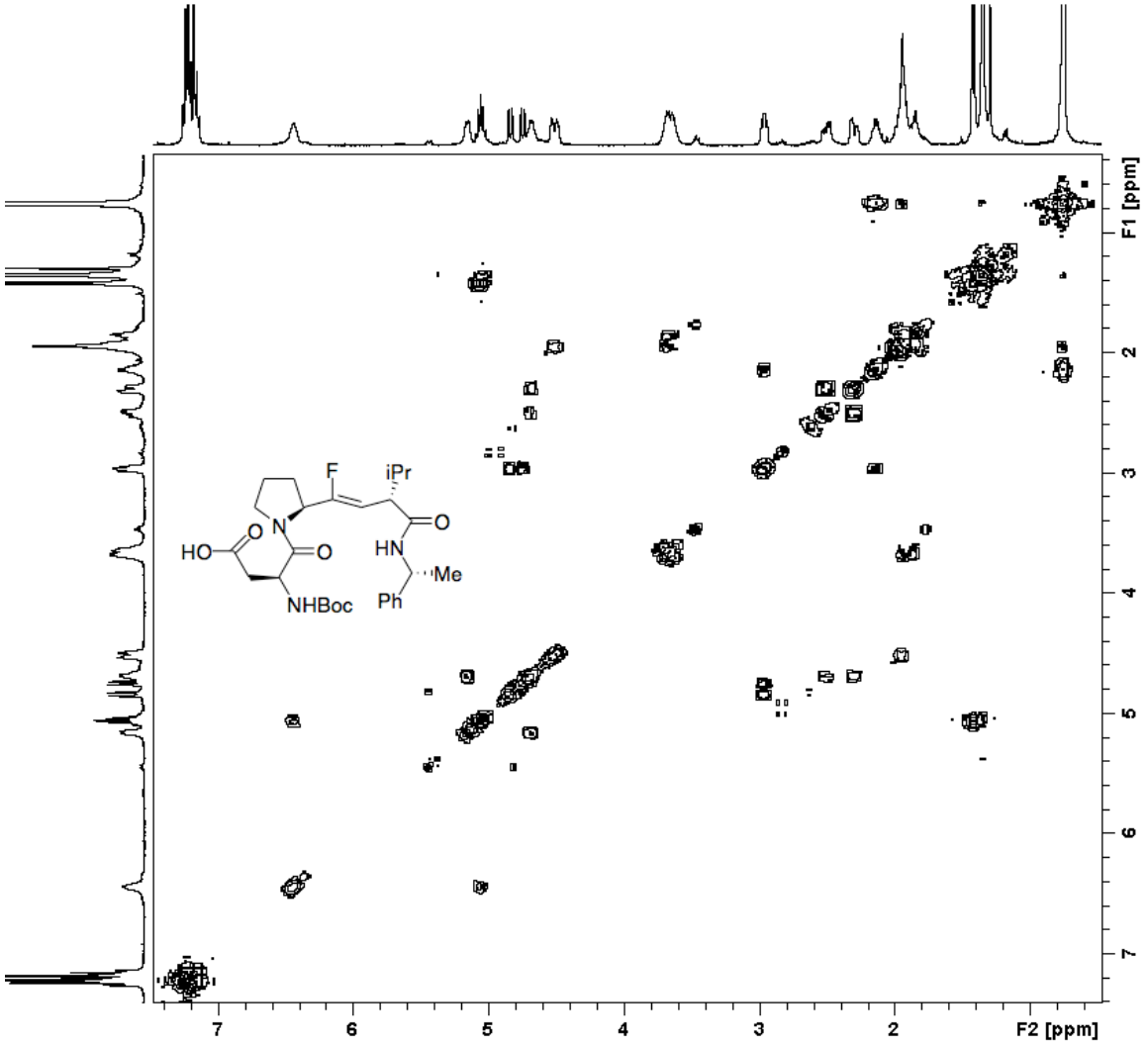
^{1}H NMR Spectrum of 11 (DMSO-d_6, 100 °C)



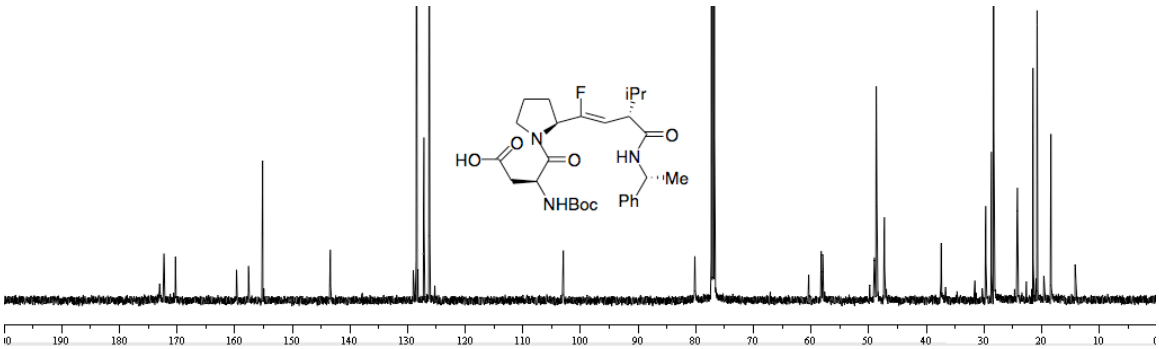
^{1}H NMR Spectrum of 11



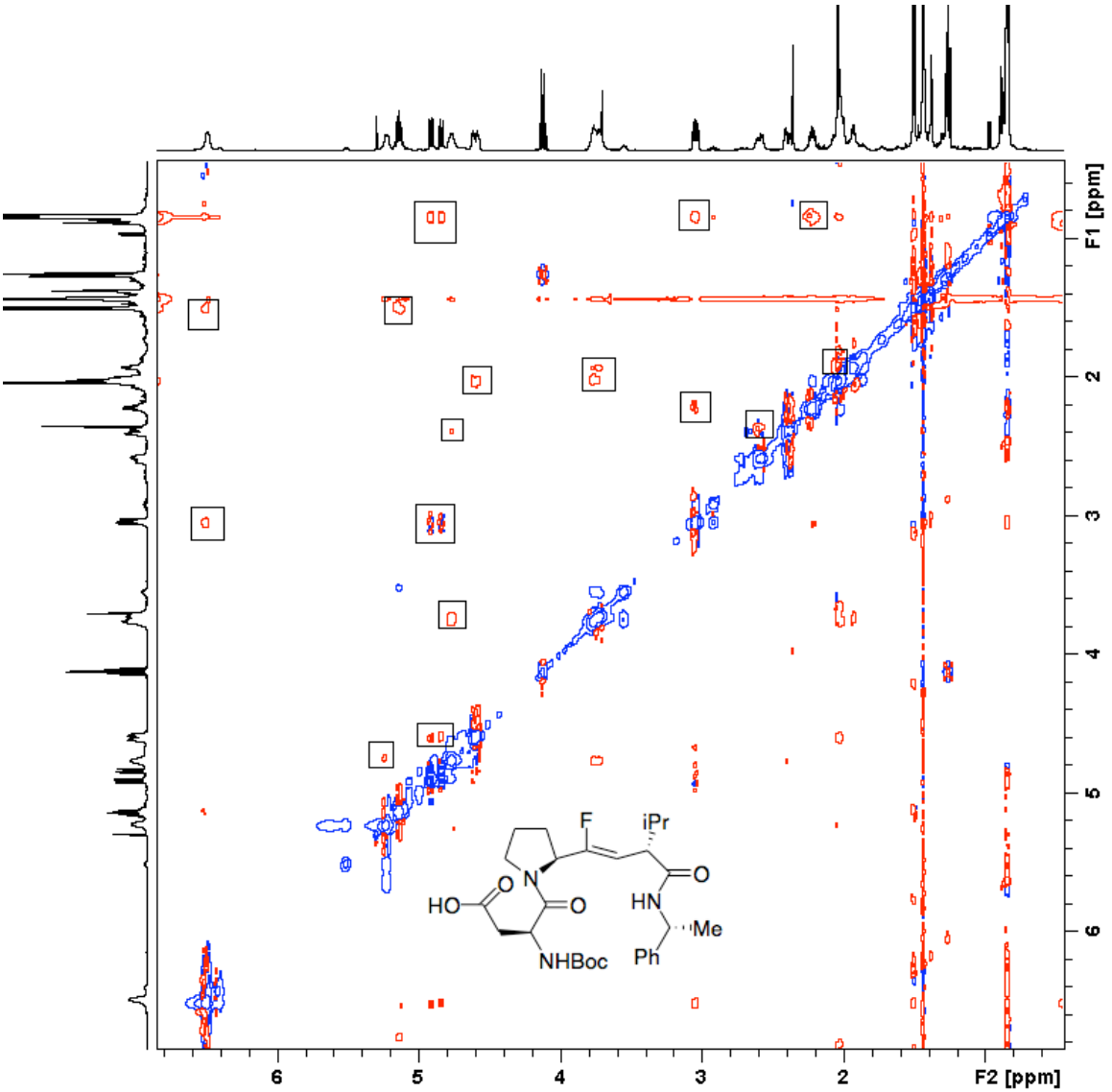
^{1}H–^{1}H COSY Spectrum of 11



^{13}C NMR Spectrum of 11



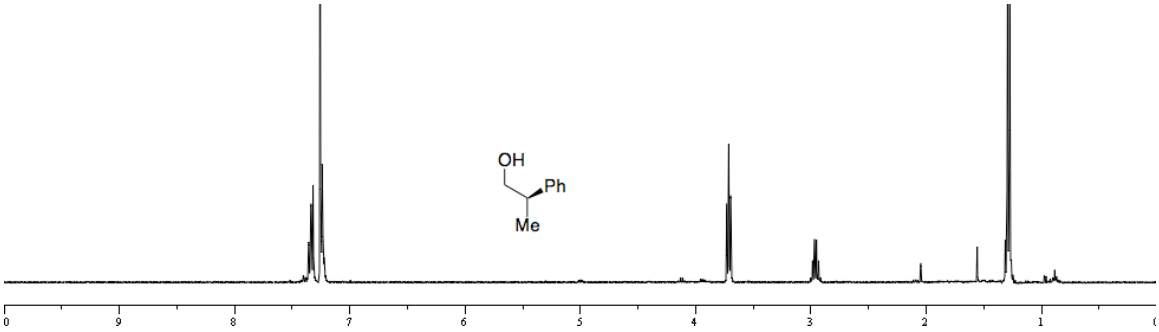
^{1}H–^{1}H NOESY Spectrum of 11



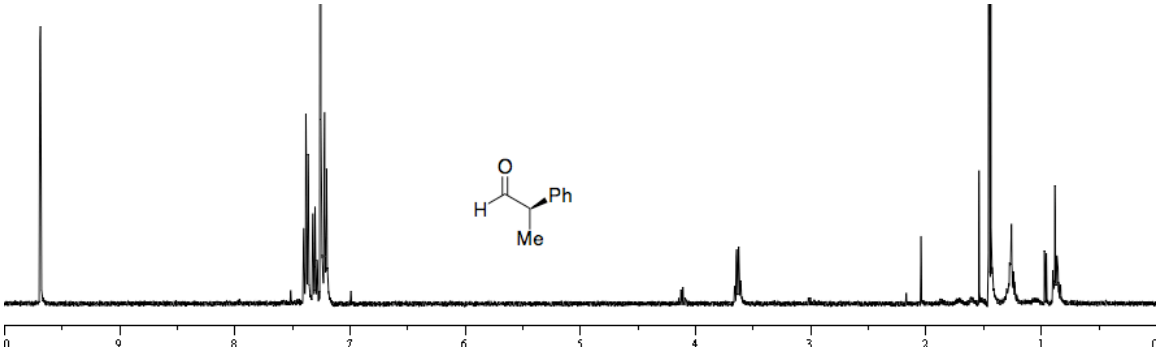
This spectrum was not symmetrized, Legitimate signals are enclosed in rectangles.

4.5 Spectra from the Synthesis of Alkene Isostere 24

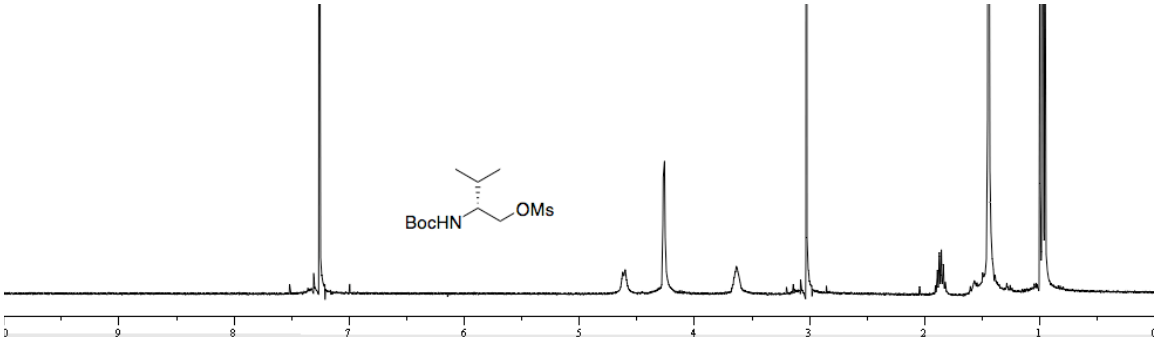
^{1}H NMR Spectrum of 24a



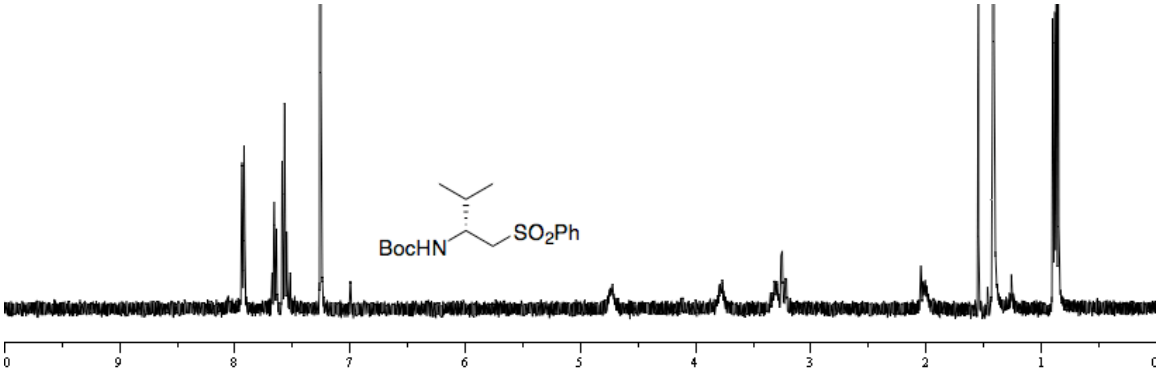
^{1}H NMR Spectrum of 24b



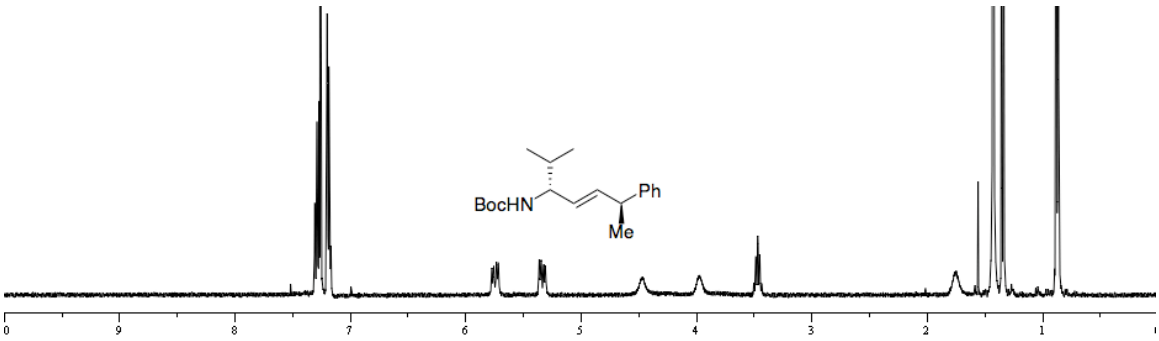
^{1}H NMR Spectrum of 24d



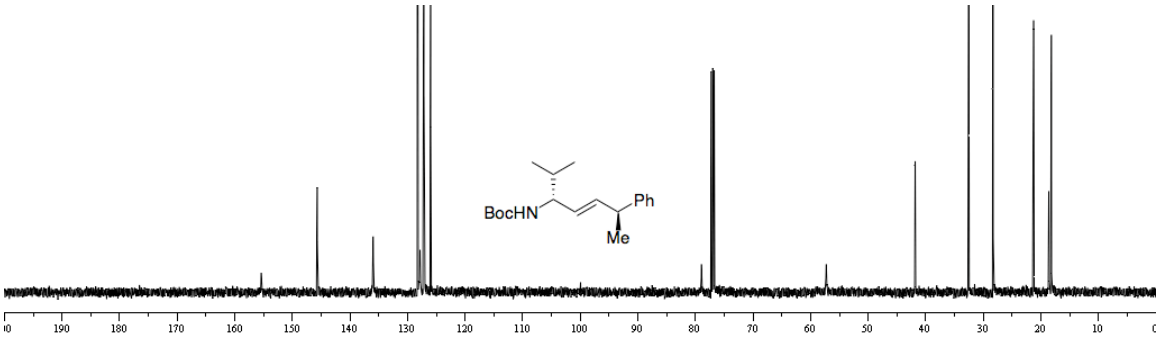
^{1}H NMR Spectrum of 24f



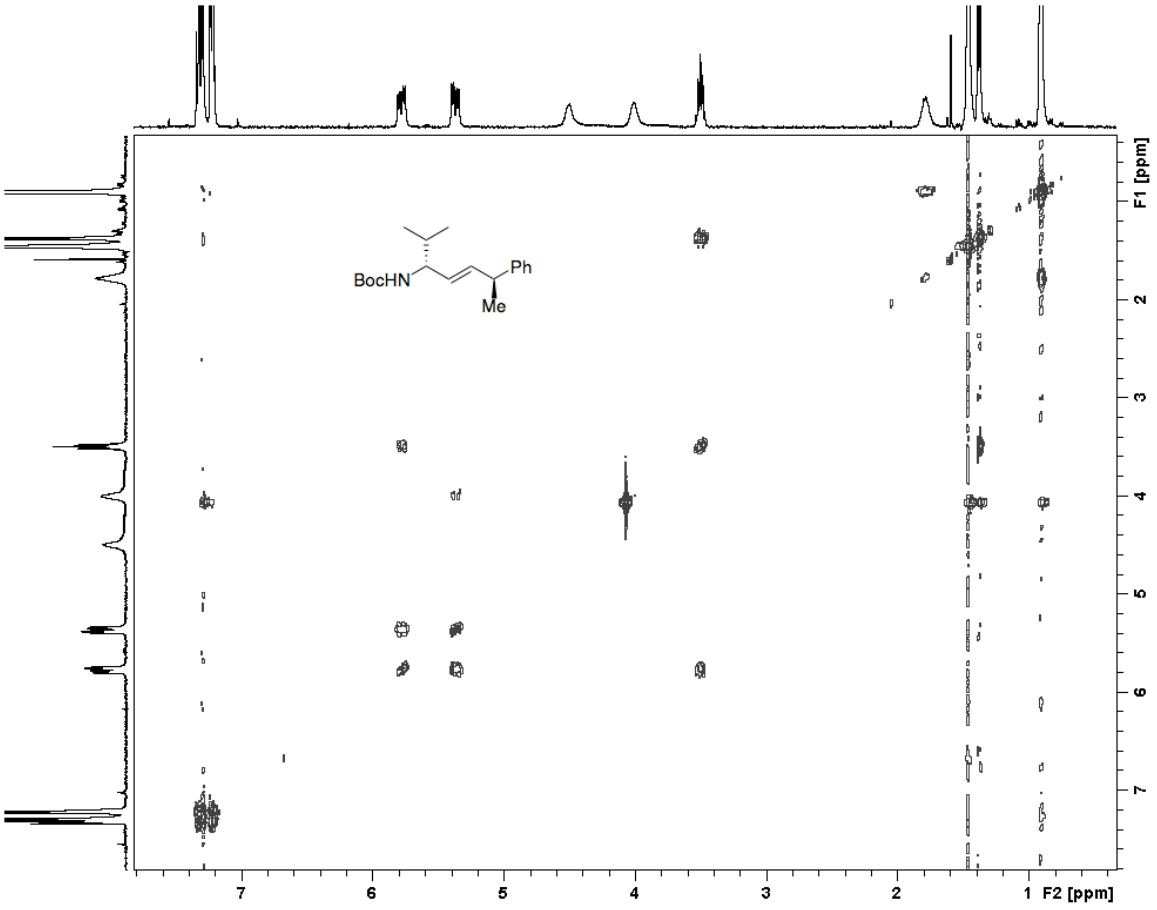
^{1}H NMR Spectrum of 24h



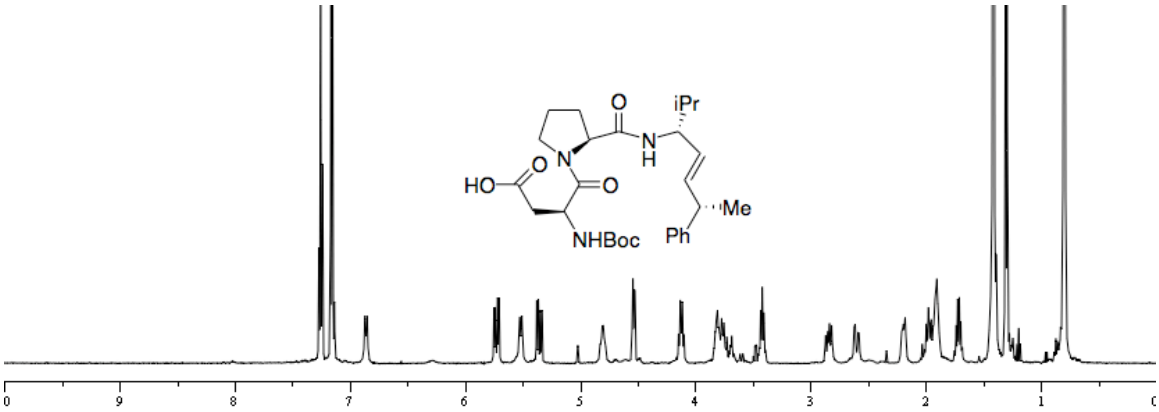
^{13}C NMR Spectrum of 24h



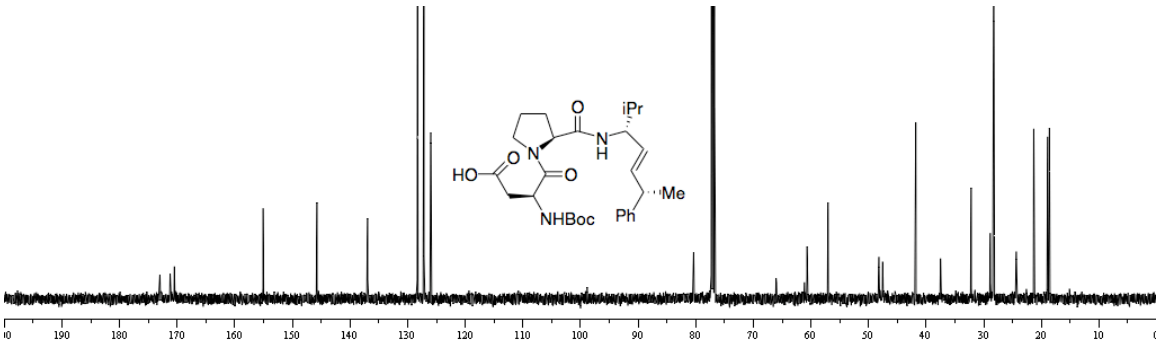
^{1}H–^{1}H COSY Spectrum of 24h



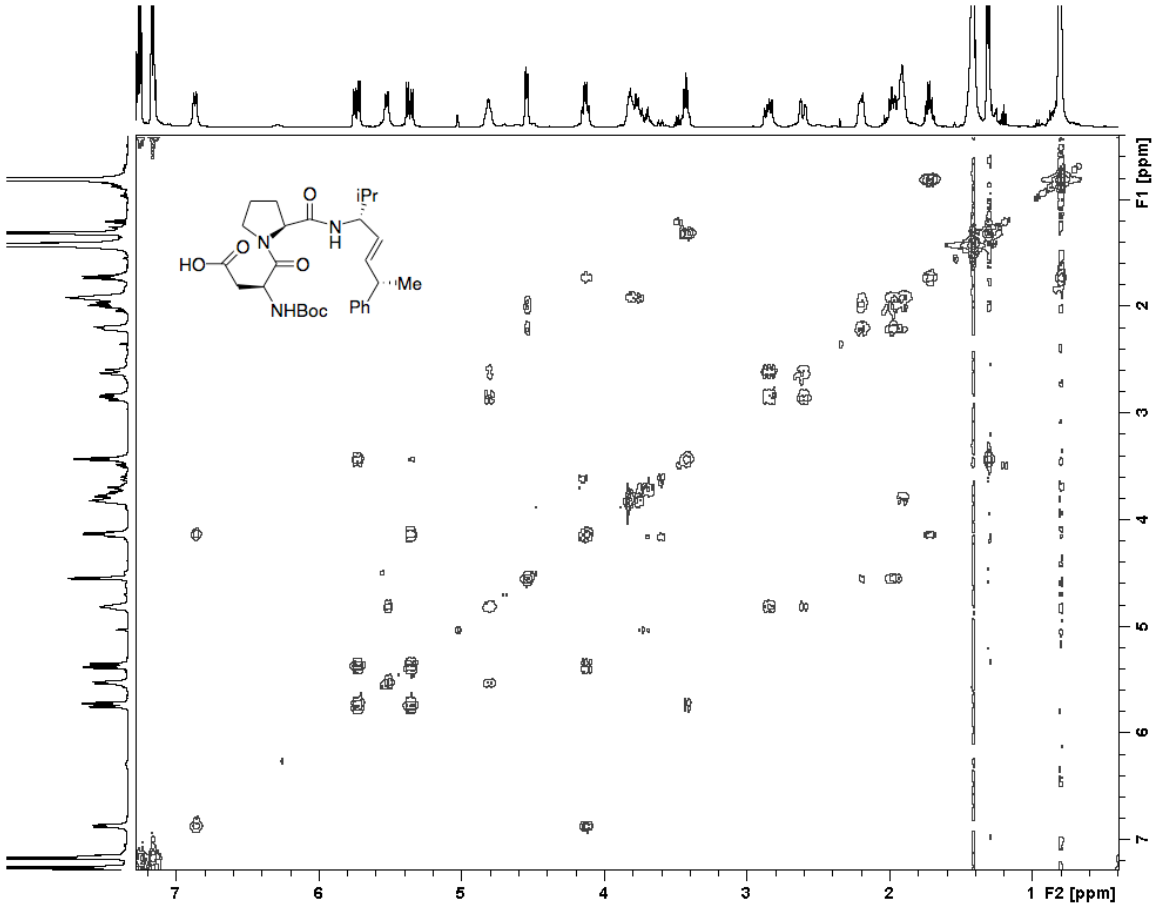
^{1}H NMR Spectrum of 24



^{13}C NMR Spectrum of 24

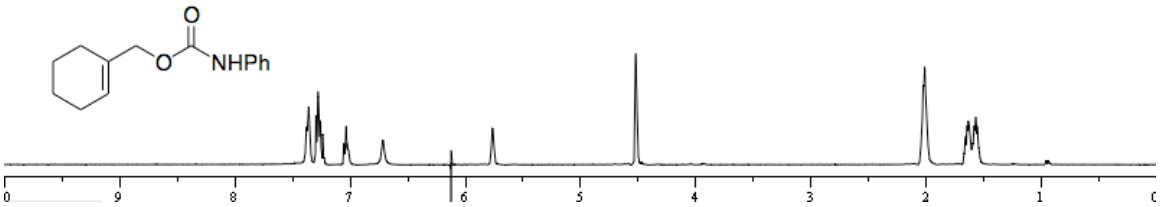


^{1}H–^{1}H COSY Spectrum of 24



4.6 Spectra from Epoxidation Reactions

^{1}H NMR Spectrum of 3



^{1}H NMR Spectrum of 4