A Peptide-Embedded Trifluoromethyl Ketone Catalyst for Enantioselective Epoxidation

Supporting Information

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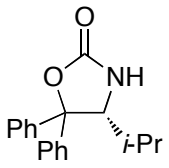
I. General Procedures

Proton NMR spectra were recorded on 500 MHz, 400 MHz, or 300 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) relative to residual $CHCl_3$ (δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of doublets of doublets of doublets (dddd), doublet of doublets of triplets (ddt), doublet of triplets (dt), doublet of triplets of triplets (dtt), doublet of quartets (dq), doublet of quartets of doublets (dqd), triplet (t), quartet (q), quartet of doublets (qd), quintet (p), quintet of doublets (pd), sextet (h), multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on 500 MHz (125 MHz), 400 MHz (100 MHz), or 300 MHz (75 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). Fluorine NMR spectra were recorded on a 400 MHz (376 MHz) spectrometer without proton decoupling. Fluorine chemical shifts are reported in ppm relative to $FCCl_3$ (δ 0.00 ppm) and were calibrated automatically by the spectrometer using the solvent deuterium lock signal. Unless otherwise noted, all NMR spectra were acquired at ambient temperature. Infrared spectra (thin film) were recorded on a FT-IR, νmax (cm^{-1}) and are partially reported. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and staining with potassium permanganate ($KMnO_4$) or ceric ammonium molybdate (CAM). Flash column chromatography was performed using Flash Silica Gel (32-63 micron). The gradient of the eluent (∇) is given as % polar solvent / column volume (CV). Optical rotations were recorded at the sodium D line (1.0 dm path length). Mass spectrometry data were collected using liquid chromatography-mass spectrometry (LCMS) or direct analysis in real time (DART). Ultra high performance LCMS was performed on a UPLC/MS instrument equipped with a reverse-phase C_{18} column (1.7 μm particle size, 2.1 x 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Analytical normal phase HPLC was performed at a column temperature of 25

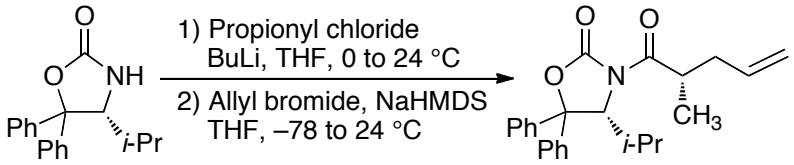
°C on a chromatograph equipped with a photodiode array detector (210 nm or 230 nm). Solvents were purified using a solvent purification system. All other chemicals were purchased commercially and used as received unless otherwise indicated. Reactions that required atmosphere and moisture control were carried out in a nitrogen atmosphere employing flame-dried glassware.

II. Synthesis of Trifluoromethyl Monomer (9)



4

(*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (4). This was prepared according to the procedure reported by Seebach and coworkers.[1]

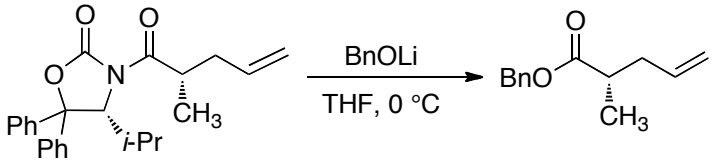


4 **5**

(*R*)-4-isopropyl-3-((*S*)-2-methylpent-4-enoyl)-5,5-diphenyloxazolidin-2-one (5). In a flame-dried flask under N_2, **4** (20.0 g, 71.0 mmol, 1.00 equiv) was suspended in anhydrous THF (300 mL, 0.25 M), then cooled in a bath of ice and water to ~0 °C. Butyllithium (30 mL, 2.5 M in hexanes, 1.1 equiv) was added to the vigorously stirring suspension, which subsequently became homogeneous. Freshly distilled propionyl chloride (7.4 mL, 85 mmol, 1.2 equiv) was added in one portion and the reaction was allowed to warm slowly to 24 °C over a period of 12 h, after which the reaction was quenched by the addition of saturated aq. NH_4Cl. The THF was removed *in vacuo*, then the product was extracted with Et_2O (100 mL, then 2 x 50 mL). The combined organic layers were washed with 1 N HCl (2 x 50 mL), 1 M aq. NaOH (2 x 50 mL), and brine (100 mL). The organic phase was dried over $MgSO_4$ and filtered, then concentrated *in vacuo*. The resulting white solid was dissolved in anhydrous THF (100 mL, 0.71 M) under N_2, then cooled to in a dry ice/acetone bath to –78 °C. A solution of NaHMDS (31 mL, 3.0 M in THF, 1.3 equiv) was added and

the reaction was held at –78 °C for 30 min. Freshly distilled allyl bromide (9.2 mL, 107 mmol, 1.5 equiv) was added and the reaction was allowed to warm slowly to 24 °C over a period of 19 h. Saturated aq. NH_4Cl (100 mL) was added and the THF was removed *in vacuo*. The product was extracted with Et_2O (100 mL, then 2 x 50 mL) and the combined organic layers were washed with 1 N aq. HCl (2 x 50 mL), 1 M aq. NaOH (2 x 50 mL), and brine (100 mL). The organic phase was dried over $MgSO_4$ and filtered, then concentrated *in vacuo*. The crude product was dissolved in a refluxing mixture of 10% Et_2O/pentane (475 mL), which was then filtered and slowly cooled to –20 °C. The product crystallized as colorless needles, which were filtered and washed with pentane and H_2O. The filtrate was concentrated *in vacuo*, then recrystallized as before from 10% Et_2O/pentane (100 mL). Both crops of crystals were combined (19.4 g, 72% yield).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2H), 7.40 (dd, *J* = 7.5, 2.7 Hz, 2H), 7.37–7.23 (m, 6H), 5.80 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.38 (t, *J* = 3.0 Hz, 1H), 5.14–4.98 (m, 2H), 3.73 (h, *J* = 6.9 Hz, 1H), 2.54 (dtt, *J* = 13.7, 6.7, 1.4 Hz, 1H), 2.16 (dtt, *J* = 13.9, 6.9, 1.3 Hz, 1H), 2.03–1.88 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H). This spectrum was matched to the literature.[2] The diastereomeric ratio (d.r.) was estimated by comparing the ^{1}H NMR signal at 0.76 ppm to the corresponding signal at 0.72 ppm. Ratios ranged from 100:0 to 98:2, depending on the extent of recrystallization. These results were in accord with those reported by Seebach.[2]

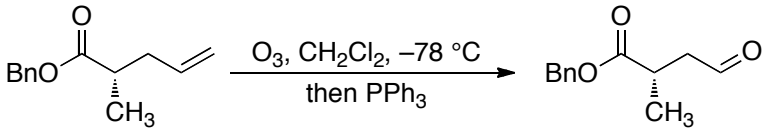


5 **6**

(*S*)-benzyl 2-methylpent-4-enoate (6). Oxazolidinone **5** (19.0 g, 51.0 mmol, 1.0 equiv) was dissolved in anhydrous THF (100 mL, 0.5 M) under N_2, then cooled to 0 °C in a water/ice bath. Lithium benzyloxide was generated by treating benzyl alcohol (10.5 mL, 103 mmol, 2.0 equiv) in THF (51 mL) with butyllithium (31 mL, 2.5 M in hexanes, 1.5 equiv) at –40 to –30 °C. This was added to the main reaction mixture *via* cannula over 5 min. The reaction was held at 0 °C for 80 min, then quenched by the addition of saturated aq. NH_4Cl (100 mL). The THF was removed *in vacuo*, then the residue was diluted with Et_2O (100 mL)

and filtered. The aqueous phase of the filtrate was washed with Et_2O (2 x 50 mL), then the combined organic layers were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The crude product was purified by fractional distillation through a Vigreaux column at 6 torr pressure. The first fraction (b.p. 56 °C) contained mostly benzyl alcohol and was discarded. The second fraction (b.p. 90 °C) afforded the product as a colorless liquid (7.6 g, 72% yield)

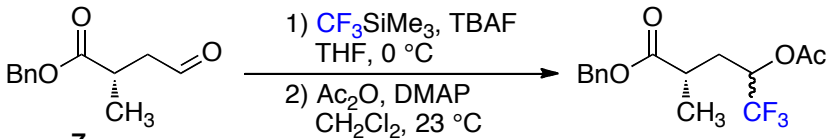
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 5.74 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.12 (s, 2H), 5.09–4.98 (m, 2H), 2.59 (h, *J* = 7.0 Hz, 1H), 2.44 (dtt, *J* = 13.9, 6.9, 1.3 Hz, 1H), 2.21 (dtt, *J* = 14.2, 7.1, 1.3 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H). This spectrum was in agreement with the literature.[3]



6 **7**

(*S*)-benzyl 2-methyl-4-oxobutanoate (7). Alkene **6** (7.6 g, 37 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (75 mL, 0.5 M) and cooled to –78 °C in a dry ice/acetone bath. Ozone was bubbled through the reaction mixture until a persistent blue color appeared. The reaction mixture was sparged with N_2 until it became colorless, after which PPh_3 (14.6 g, 55.8 mmol, 1.5 equiv) was added and the reaction was warmed to 24 °C. The volume of the reaction was reduced *in vacuo*, then the residue was loaded onto a flash column (CV = 200 mL of silica) and eluted with 15% Et_2O/pentane to afford the product as a pale yellow oil (7.6 g, 98% yield).

R_f: 0.22 (20% EtOAc/hexanes). **$[\alpha]_D^{23}$** +24 (c 1.1, $CHCl_3$). **MS:** (DART) *m/z* calculated for $C_{12}H_{14}O_3$ $[M]^+$ 206.1, observed 206.1. **IR:** (neat, cm^{-1}) 1721, 1456, 1386, 1258, 1222, 1169, 1133, 1079, 969, 909, 733, 696. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.0 Hz, 1H), 7.42–7.27 (m, 5H), 5.13 (s, 2H), 3.04 (pd, *J* = 7.2, 5.8 Hz, 1H), 2.92 (ddd, *J* = 18.0, 7.7, 0.8 Hz, 1H), 2.55 (ddd, *J* = 18.0, 5.7, 0.9 Hz, 1H), 1.25 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR:** (125 MHz, $CDCl_3$) δ 200.0, 174.9, 135.9, 128.5, 128.2, 128.0, 66.5, 46.8, 33.6, 17.0.



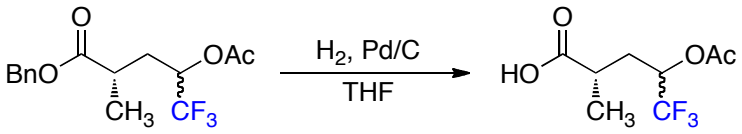
7 **8**

(2*S*)-benzyl 4-acetoxy-5,5,5-trifluoro-2-methylpentanoate (8). In a flame-dried flask under N_2, aldehyde **7** (5.6 g, 27 mmol, 1.0 equiv) was dissolved in anhydrous THF (135 mL, 0.2 M), then cooled to 0 °C in an ice/water bath. Trimethyl(trifluoromethyl)silane (6.1 mL, 41 mmol, 1.5 equiv) was added, followed by TBAF (2.7 mL, 1 M in THF, 0.10 equiv). After 1 h at 0 °C, 1 N aq. HCl was added and the heterogeneous reaction mixture was stirred vigorously. After 19 h, the THF was removed *in vacuo* and the product was extracted with EtOAc (3 x 90 mL). The combined organic layers were washed with H_2O (180 mL) and brine (180 mL), dried over Na_2SO_4, filtered, then concentrated *in vacuo*.

The crude alcohol and 4-(dimethylamino)pyridine (330 mg, 2.7 mmol, 0.10 equiv) were dissolved in anhydrous CH_2Cl_2 (135 mL, 0.2 M), then cooled to 0 °C in an ice/water bath. Acetic anhydride (2.8 mL, 30 mmol, 1.1 equiv) was added and the reaction was warmed to 23 °C. After 80 min, the reaction was partitioned between 1 N aq. HCl (100 mL) and EtOAc (400 mL). The volume was reduced *in vacuo* to 250 mL, then the layers were separated. The organic phase was washed with 1 N aq. HCl (50 mL), 1 M aq. NaOH (90 mL), and brine (180 mL). Finally, the organic portion was dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude product was purified by flash chromatography (CV = 450 mL of silica, 5%–15% EtOAc/hexane, ∇ = 2% EtOAc/CV). The recovered product contained a small amount of benzyl acetate, which was removed by heating to 70 °C under 30 mtorr of pressure for 1 h. The product was obtained as a colorless oil (5.6 g, 65% yield). The diastereomeric ratio (d.r.) was determined by comparing the integrations of the signals in the ^{19}F NMR spectrum. The reaction gave a d.r. of 1.5:1.0, which became 1.9:1.0 after purification.

R_f: 0.40 (20% EtOAc/Hexanes). **LCMS:** (ESI) *m/z* calculated for $C_{15}H_{17}F_3NaO_4$ $[M+Na]^+$ 341.10, observed 340.97. **IR:** (neat, cm^{-1}) 1759, 1733, 1282, 1210, 1173, 1145, 1105, 1082, 1050, 1021, 750, 696. Major diastereomer: **^1H NMR:** (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.48–5.37 (m, 1H), 5.22–5.06 (m, 2H), 2.61 (dqd, *J* = 10.9, 7.2, 3.9 Hz, 1H), 2.20 (ddd, *J* = 13.6, 10.3, 3.0 Hz, 1H), 2.07 (s, 3H), 1.91–1.83 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR:** (125 MHz, $CDCl_3$) δ 174.8, 169.2, 135.8, 128.7, 128.4,

128.3, 123.7 (q, *J* = 281.0 Hz), 67.8 (q, *J* = 32.3 Hz), 66.7, 35.1, 31.3, 20.3, 17.8. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -77.50 (d, *J* = 5.7 Hz). Minor diastereomer: **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.44–7.29 (m, 5H), 5.48–5.38 (m, 1H), 5.18–5.10 (m, 2H), 2.54 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.27 (ddd, *J* = 14.6, 10.7, 6.0 Hz, 1H), 2.08 (s, 3H), 1.92–1.81 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR:** (125 MHz, $CDCl_3$) δ 175.0, 169.4, 135.8, 128.7, 128.4, 128.3, 123.7 (q, *J* = 281.0 Hz), 67.6 (q, *J* = 32.5 Hz), 66.7, 35.6, 31.1, 20.4, 16.9. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -77.42 (d, *J* = 6.6 Hz).

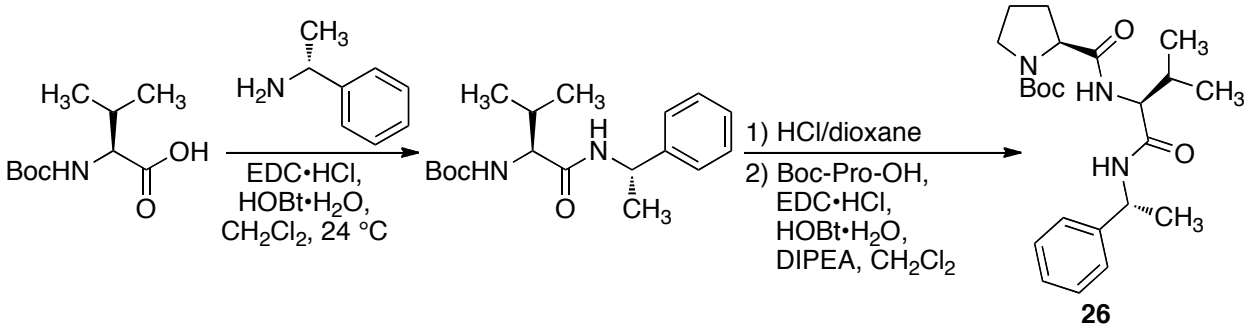


8 **9**

(2*S*)-4-acetoxy-5,5,5-trifluoro-2-methylpentanoic acid (9). Benzyl ester **8** (4.6 g, 14 mmol, 1.0 equiv) was dissolved in THF (72 mL, 0.2 M). Pd/C (1.8 g, 10% w/w) was added and the suspension was stirred vigorously at 23 °C. The headspace of the reaction vessel was flushed with a H_2 balloon for 1 min, after which the reaction was put under static H_2 pressure. After 3 h, the reaction was pushed through Celite with EtOAc (4 x 70 mL), then concentrated *in vacuo*. The product was obtained as a colorless liquid (3.2 g, 98% yield). The d.r. of the product was identical to the d.r. of the starting material.

R_f: 0.46 (10% CH_3OH/CH_2Cl_2). **LCMS:** (ESI) *m/z* calculated for $C_8H_9F_3O_3$ $[M-H_2O]^+$ 210.05, observed 210.03. **IR:** (neat, cm^{-1}) 1750, 1707, 1375, 1282, 1209, 1177, 1150, 1104, 1082, 1049, 1022, 954, 923, 896, 698. Major diastereomer: **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 11.97 (s, 1H), 5.50–5.31 (m, 1H), 2.57 (dqd, *J* = 10.8, 7.2, 3.8 Hz, 1H), 2.16 (ddd, *J* = 13.5, 10.3, 3.0 Hz, 1H), 2.10 (s, 3H), 1.92–1.77 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR:** (125 MHz, $CDCl_3$) δ 181.7, 169.5, 123.7 (q, *J* = 280.6 Hz), 67.9 (q, *J* = 32.4 Hz), 35.0, 31.1, 20.3, 17.7. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -77.47 (d, *J* = 6.4 Hz). Minor diastereomer: **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 11.97 (s, 1H), 5.50–5.31 (m, 1H), 2.48 (h, *J* = 7.1 Hz, 1H), 2.23 (ddd, *J* = 14.6, 10.8, 6.3 Hz, 1H), 2.10 (s, 3H), 1.92–1.77 (m, 1H), 1.24 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR:** (125 MHz, $CDCl_3$) δ 182.0, 169.6, 123.7 (q, *J* = 280.8 Hz), 67.7 (q, *J* = 32.6 Hz), 35.6, 31.1, 20.3, 16.7. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -77.44 (d, *J* = 6.8 Hz).

III. Synthesis of Peptide Catalyst (14)



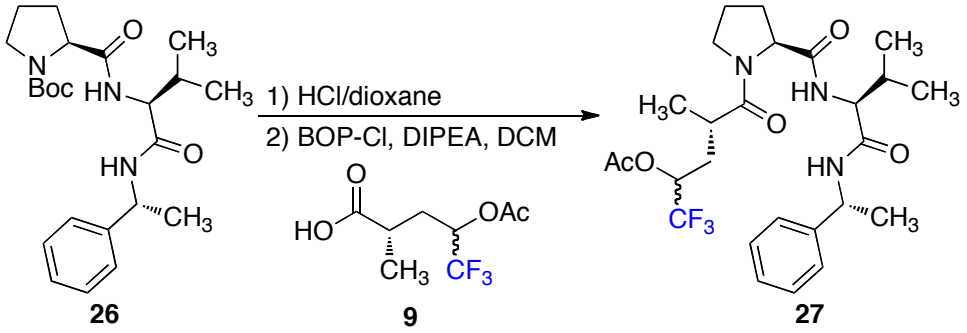
26

Boc-Pro-Val-(*R*)-Mba (26). Boc-Val-OH (533 mg, 2.46 mmol, 1.00 equiv), EDC•HCl (518 mg, 2.70 mmol, 1.10 equiv), and HOBt•H_2O (414 mg, 2.70 mmol, 1.10 equiv) were suspended in anhydrous CH_2Cl_2 (12 mL, 0.25 M) at 24 °C. (*R*)-α-methylbenzylamine (328 μL, 2.60 mmol, 1.05 equiv) was added and the reaction mixture was stirred vigorously at 24 °C. After 15.5 h, the reaction was diluted with EtOAc (150 mL) and washed with aq. citric acid (10% w/w, 50 mL), saturated aq. $NaHCO_3$ (50 mL), and brine (50 mL). The organic portion was dried over $MgSO_4$ and filtered, then concentrated *in vacuo*. The resulting solid was used as obtained (crude mass 708 mg).

The resulting solid was dissolved in 4.0 M HCl/dioxane (2.2 mL, 8.8 mmol, 4.0 equiv). After 2 h at 23 °C, the mixture was concentrated *in vacuo*. The residue and Boc-Pro-OH (521 mg, 2.42 mmol, 1.1 equiv) were dissolved in CH_2Cl_2 (11 mL, 0.20 M). HOBt•H_2O (371 mg, 2.42 mmol, 1.10 equiv), EDC•HCl (464 mg, 2.42 mmol, 1.10 equiv), then diisopropylethylamine (422 μL, 2.42 mmol, 1.10 equiv) were added and the resulting suspension was stirred at 23 °C. After 16 h, the reaction mixture was partitioned between EtOAc (130 mL) and aq. citric acid (10% w/w, 40 mL). The layers were separated and the organic layer was washed with H_2O (40 mL), saturated aq. $NaHCO_3$ (40 mL), and brine (40 mL). The organic portion was dried over Na_2SO_4 and filtered, then concentrated *in vacuo*. The crude product was purified by flash chromatography (CV = 75 mL of silica, 50–65% EtOAc/hexanes, ∇ = 2.5% EtOAc/CV).

R_f: 0.40 (70% EtOAc/hexanes). **LCMS:** (ESI) *m/z* calculated for $C_{23}H_{36}N_3O_4$ $[M+H]^+$ 418.27, observed 418.14. **IR:** (neat, cm^{-1}) 3280, 2970, 2873, 1698, 1640, 1543, 1450, 1391, 1365, 1237, 1162, 1120, 1090, 924, 761, 736, 699. **^{1}H NMR:** (300 MHz, 50 °C, $CDCl_3$) δ 7.48–7.15 (m, 5H), 6.79 (s, 2H), 5.11 (p, *J* = 7.0 Hz, 1H), 4.38–4.07 (m, 2H), 3.52–3.32 (m, 2H), 2.46–1.96 (m, 3H), 1.94–1.78 (m, 2H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.38 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR:** (75 MHz, 50 °C,

$CDCl_3$) δ 172.4, 170.0, 155.8, 143.5, 128.6, 127.2 126.4, 80.9, 61.0, 58.8, 49.0, 47.4, 30.09, 28.4, 24.6, 21.9, 19.6, 17.5.

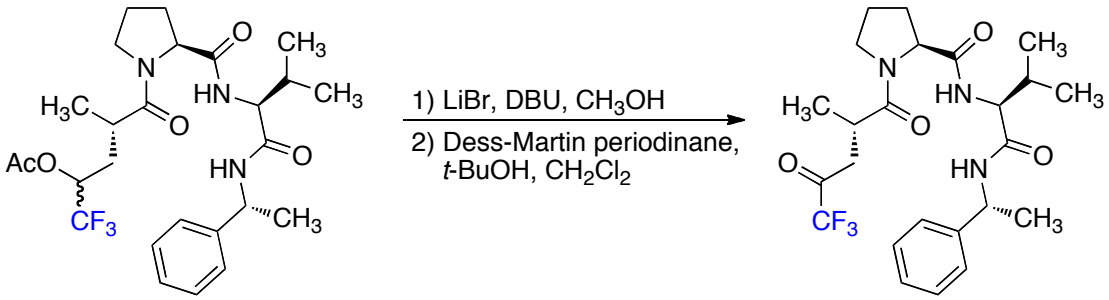


Peptide 27. Boc-Pro-Val-(*R*)-Mba (662mg, 1.58 mmol, 1.00 equiv) was suspended in 4.0 M HCl/dioxane (1.6 mL, 6.4 mmol, 4.0 equiv) and stirred to homogeneity at 23 °C. After 1 h, the reaction mixture was concentrated *in vacuo* giving H-Pro-Val-(*R*)-Mba•HCl as a white solid. This was dissolved under N_2 in anhydrous CH_2Cl_2 (9.0 mL, 0.18 M) and diisopropylethylamine (1.65 mL, 9.48 mmol, 6.00 equiv).

In a flame-dried flask under N_2, **9** (397 mg, 1.74 mmol, 1.1 equiv) was dissolved in anhydrous CH_2Cl_2 (4.0 mL), then cooled to 0 °C in a water/ice bath. BOP-Cl (443 mg, 1.74 mmol, 1.1 equiv) was added and the resulting suspension was stirred at 0 °C. After 2 h, the solution of H-Pro-Val-(*R*)-Mba•HCl prepared in the previous step was added *via* cannula. The source vessel was rinsed with additional CH_2Cl_2 (1.0 mL), which was also added. The reaction was warmed to 23 °C. After 18h, the reaction was partitioned between EtOAc (100 mL) and 1 N aq. HCl (20 mL). The layers were separated and the aqueous layer was washed with additional EtOAc (2 x 25 mL). The combined portions of EtOAc were washed with 1 N aq. HCl (20 mL), 1 M aq. NaOH (2 x 20 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered, then concentrated *in vacuo*. Flash chromatography (CV = 65 mL of silica, 1% MeOH/CH_2Cl_2 (120 mL), then 2.5% MeOH/CH_2Cl_2 (150 mL)) afforded the product as a white solid (740 mg, 89% yield). The d.r. of the product was identical to the d.r. of the starting material.

R_f: 0.52 (10% CH_3OH/CH_2Cl_2). **LCMS:** (ESI) Calculated for $C_{26}H_{37}F_3N_3O_5$ $[M+H]^+$ 528.27, observed 528.22. **IR:** (neat, cm^{-1}) 3297, 2971, 2240, 1755, 1642, 1541, 1432, 1375, 1354, 1280, 1215, 1181, 1149, 1081, 1049, 909, 868, 727, 698. Major diastereomer: **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H),

7.18 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 5.22 (dtt, *J* = 12.9, 6.5, 3.2 Hz, 1H), 5.03 (p, *J* = 7.1 Hz, 1H), 4.48 (dd, *J* = 8.2, 3.8 Hz, 1H), 4.15 (dd, *J* = 8.1, 6.8 Hz, 1H), 3.54–3.40 (m, 2H), 2.62–2.50 (m, 1H), 2.36 (ddd, *J* = 13.9, 11.3, 2.2 Hz, 1H), 2.29–2.22 (m, 1H), 2.19 (s, 3H), 2.15–1.93 (m, 4H), 1.64 (ddd, *J* = 14.4, 11.2, 3.3 Hz, 1H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 174.7, 171.9, 170.5, 170.4, 143.7, 128.5, 126.9, 126.1, 123.4 (q, *J* = 280.0 Hz), 69.5 (q, *J* = 32.6 Hz), 61.6, 60.2, 49.0, 47.4, 34.2, 29.6, 29.4, 24.9, 22.2, 20.8, 19.5, 18.1, 18.0. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -77.35 (d, *J* = 6.6 Hz). Minor diastereomer: **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 7.01 (d, *J* = 6.6 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 5.42–5.33 (m, 1H), 5.09 (p, *J* = 7.1 Hz, 1H), 4.49 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.18 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.60–3.54 (m, 2H), 2.62–2.50 (m, 1H), 2.29–2.22 (m, 1H), 2.13 (s, 3H), 2.10–1.88 (m, 5H), 1.84 (ddd, *J* = 14.4, 9.4, 3.2 Hz, 1H), 1.47 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 175.0, 171.4, 170.0, 169.5, 143.3, 128.6, 127.3, 126.2, 123.7 (q, *J* = 280.9 Hz), 67.6 (q, *J* = 32.4 Hz), 60.3, 59.0, 48.9, 33.4, 31.7, 30.1, 28.1, 25.2, 21.9, 20.5, 19.5, 17.7, 16.1. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -77.22 (d, *J* = 6.6 Hz).



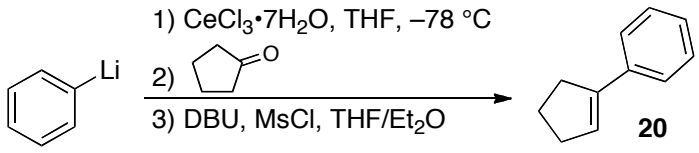
27 **14**

Tfk-Pro-Val-(*R*)-Mba (14). Peptide **27** (854 mg, 1.62 mmol, 1.00 equiv) and LiBr (703 mg, 8.09 mmol, 5.00 equiv) were dissolved in methanol (8.1 mL, 0.20 M). DBU (124 μL, 0.809 mmol, 0.500 equiv) was added and the reaction was held at 24 °C for 15 min, then diluted with 1 N aq. HCl (10 mL). The methanol was removed *in vacuo*, then the product was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting solid was used in the next step without further purification.

In a flame-dried flask under N_2, Dess-Martin periodinane (893 mg, 2.10 mmol, 1.32 equiv) was suspended in anhydrous CH_2Cl_2 (11 mL, 0.20 M). Freshly distilled *tert*-butanol (201 μL, 2.10 mmol, 1.32 equiv) was added and the suspension was stirred vigorously at 24 °C. The solid from the previous step was dissolved in anhydrous CH_2Cl_2 (8.1 mL). After 15 min, this solution was transferred to the main reaction mixture *via* cannula. The source vessel was rinsed with additional CH_2Cl_2, which was also added. The reaction was held at 24 °C for 14 h, then treated with a solution of $Na_2S_2O_3$ (2.38 g, 15.1 mmol, 9.41 equiv) and $NaHCO_3$ (1.73 g, 20.5 mmol, 12.8 equiv) in H_2O (21 mL). The cloudy mixture was stirred vigorously until it became transparent (~20 min), after which the product was extracted with EtOAc (100 mL, then 2 x 25 mL). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and filtered, then concentrated *in vacuo*. The crude product was purified by flash chromatography (CV = 70 mL of silica, 70–90% EtOAc/hexanes, ∇ = 2.5% EtOAc/CV). The product was obtained as a 1:4 mixture of the ketone and its hydrate (659 mg, 82% yield). The activity of the catalyst for epoxidation was not affected by the ratio of ketone to hydrate, but for characterization purposes, the catalyst was equilibrated to the ketone (96% w/w) by dissolving it in $CDCl_3$ and stirring it in the presence of 4 Å molecular sieves for 18 h.

R_f: 0.19 (70% EtOAc/hexanes). **LCMS:** (ESI) *m/z* calculated for $C_{24}H_{33}F_3N_3O_4$ $[M+H]^+$ 484.24, observed 484.18. **IR:** (neat, cm^{-1}) 3279, 2970, 1764, 1643, 1550, 1437, 1208, 1150, 699. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.37–7.17 (m, 5H), 6.71 (t, *J* = 9.4 Hz, 2H), 5.04 (p, *J* = 7.1 Hz, 1H), 4.50 (dd, *J* = 7.6, 3.2 Hz, 1H), 4.25 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.87 (ddd, *J* = 10.3, 6.7, 3.8 Hz, 1H), 3.64–3.49 (m, 1H), 3.13–2.95 (m, 2H), 2.73 (d, *J* = 16.5 Hz, 1H), 2.40–2.22 (m, 2H), 2.19–1.96 (m, 3H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR:** (125 MHz, $CDCl_3$) δ 192.4 (q, *J* = 36.1 Hz), 174.8, 171.3, 170.1, 143.5, 128.5, 127.2, 126.5, 115.2 (q, *J* = 291.4 Hz), 61.4, 59.3, 49.1, 47.8, 40.9, 33.0, 29.3, 29.2, 24.9, 22.0, 19.6, 17.5, 17.0. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -78.89.

IV. Synthesis of Substrates

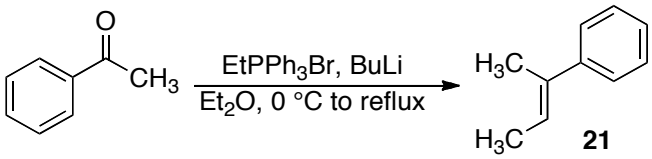


20

1-Phenylcyclopent-1-ene (20). Prepared according to the procedure of Tallineau *et al.*[4] A flame-dried 2-neck flask was charged with $CeCl_3$•$7H_2O$ (10.8 g, 29.0 mmol, 1.30 equiv). The vessel was evacuated, then immersed in an oil bath at 145 °C. After 2 h, the vessel was equilibrated to 22 °C. Anhydrous THF was added and the vigorously stirring suspension was cooled to –78 °C in a dry ice/ acetone bath. Phenyllithium (12.5 mL, 2.0 M in Et_2O, 1.1 equiv) was added dropwise and the reaction was held at –78 °C for 90 min. A separate flame-dried flask under N_2 was charged with freshly distilled cyclopentanone (2.0 mL, 23 mmol, 1.0 equiv) and anhydrous THF (200 mL, 0.115 M). This solution was added to the main reaction mixture by cannula. The reaction was held at –78 °C for 90 min, then removed from the cold bath and allowed to equilibrate to 22 °C. Saturated aq. NH_4Cl (50 mL) was added and the heterogeneous mixture was vigorously stirred at 22 °C. After 100 min, the reaction mixture was partitioned between Et_2O (100 mL) and H_2O (200 mL). The layers were separated and the aqueous layer was washed with additional Et_2O (2 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The nonpolar contaminants were removed by passing the crude alcohol through a plug of silica, eluting with 10–30% Et_2O/pentane.

The crude alcohol was dissolved in 2:1 Et_2O/THF (150 mL) under N_2. DBU (10 mL, 69 mmol, 3.0 equiv) was added, followed by methanesulfonyl chloride (5.3 mL, 69 mmol, 3.0 equiv). After 10 h, 1 N aq. HCl was added and the mixture was vigorously stirred. After 2 h, the layers were separated and the aqueous layer was washed with Et_2O (100 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography in isocratic pentane afforded the product as a colorless oil (1.161 g, 35% yield).

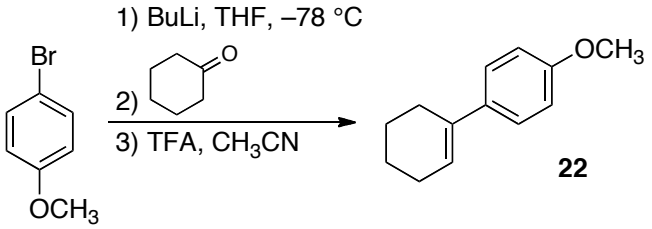
R_f: 0.76, pentane. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.47–7.43 (m, 1H), 7.34–7.29 (m, 1H), 7.24–7.20 (m, 1H), 6.20 (p, *J* = 2.3 Hz, 1H), 2.76–2.68 (m, 2H), 2.59–2.49 (m, 2H), 2.03 (p, *J* = 7.5 Hz, 2H). This spectrum was in agreement with the literature.[5]



21

(*E*)-2-Phenylbut-2-ene (21). Ethyltriphenylphosphonium bromide (5.8 g, 16 mmol, 1.0 equiv) was suspended in anhydrous Et_2O (64 mL, 0.25 M) in a flame-dried flask under N_2. The suspension was vigorously stirred at 22 °C as butyllithium (6.9 mL, 2.5 M in hexanes, 1.1 equiv) was added dropwise. The reaction was held at 22 °C for 7 h, then cooled to 0 °C. In a separate flame-dried flask, freshly distilled acetophenone (2.0 mL, 17 mmol, 1.1 equiv) was dissolved in anhydrous Et_2O (17 mL). This solution was added to the main reaction mixture *via* cannula, after which the reaction was heated to reflux. After 15 h, the reaction was equilibrated to 22 °C, then filtered. The filtrate was diluted with pentane, then washed with H_2O (100 mL), and brine (50 mL). The organic portion was dried over $MgSO_4$ and filtered, then concentrated *in vacuo*. Flash chromatography in isocratic pentane afforded the product as a colorless oil (1.140 g, 54% yield, *E/Z* 2.6:1.0).

Major isomer: **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.43–7.28 (m, 4H), 7.25–7.18 (m, 1H), 5.93–5.83 (m, 1H), 2.04 (s, 3H), 1.83–1.79 (m, 3H). Minor isomer: **^{1}H NMR:** δ 7.43–7.28 (m, 4H), 7.25–7.18 (m, 1H), 5.63–5.53 (m, 1H), 2.04 (s, 3H), 1.65–1.57 (m, 3H). This spectrum was in agreement with the literature.[6]



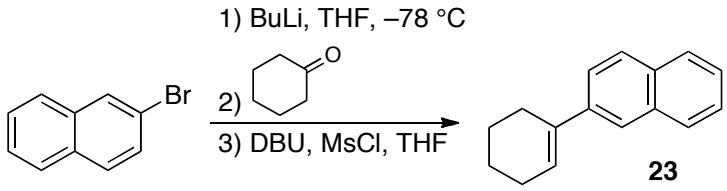
22

1-(4-Methoxyphenyl)cyclohex-1-ene (22). A flame-dried flask under inert atmosphere was charged with 1-bromo-4-methoxybenzene (1.25 mL, 10.0 mmol, 1.00 equiv) and anhydrous THF (21 mL, 0.48 M), then cooled to –78 ºC in a dry ice/acetone bath. Butyllithium (4.0 mL, 2.5 M in hexanes, 1.0 equiv) was added dropwise and the reaction was held at –78 ºC. After 90 minutes, a solution of cyclohexanone (1.0 mL, 10 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added *via* cannula over 2 min. After an additional 20 min, the reaction was equilibrated to 24 ºC, then quenched with saturated aqueous NH_4Cl (30 mL). The product was extracted with EtOAc (3 x 30 mL) and the combined organic

layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude alcohol was purified by flash chromatography (CV = 50 mL of silica, 20–35% EtOAc/hexanes, ∇ = 2.5% EtOAc/CV).

The pure alcohol was then dissolved in CH_3CN (25 mL, 0.40 M). Trifluoroacetic acid (0.23 mL, 3.0 mmol, 0.30 equiv) was added and the mixture was stirred at 24 ºC. After 17 hours, the reaction was diluted with H_2O (50 mL) and the product was extracted with hexanes (4 x 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, then concentrated *in vacuo*. The crude product was purified by flash chromatography (CV = 70 mL of silica, 20% Et_2O/pentane) to afford the title compound as a white solid (1.391 g, 74% yield).

R_f: 0.38, 2% Et_2O/pentane. **^{1}H NMR**: (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H), 6.88–6.81 (m, 2H), 6.07–5.96 (m, 1H), 3.80 (s, 3H), 2.47–2.29 (m, 2H), 2.29–2.11 (m, 2H), 1.86–1.71 (m, 2H), 1.71–1.59 (m, 2H). This spectrum was in agreement with the literature.[4]



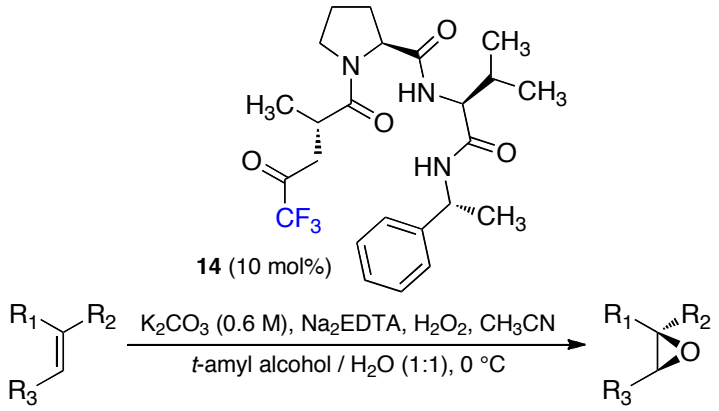
23

1-(2-Naphthyl)cyclohex-1-ene (23). A flame-dried flask was charged with 2-bromonaphthalene (2.17 g, 10.5 mmol, 1.05 equiv), then evacuated and back-filled with nitrogen thrice. Anhydrous THF was added, then the reaction mixture was cooled to –78 ºC in a dry ice/acetone bath. Butyllithium (4.2 mL, 2.5 M in hexanes) was added dropwise and the reaction was held at –78 ºC. After 90 minutes, a solution of cyclohexanone (1.0 mL, 10 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added by cannula over 4 minutes. After 2.5 h, the reaction was equilibrated to 24 ºC, then quenched with saturated aqueous NH_4Cl (20 mL). The product was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude alcohol was purified by flash chromatography (CV = 70 mL of silica, 5–20% EtOAc/hexanes, ∇ = 2.5% EtOAc/CV).

The pure alcohol was dissolved in anhydrous THF (25 mL, 0.50 M), then cooled to –30 ºC. DBU (4.5 mL, 30 mmol, 3.0 equiv) was added dropwise, followed by methanesulfonyl chloride (2.3 mL, 30 mmol, 3.0 equiv). The reaction was diluted with additional THF (25 mL), then stirred as it was allowed to equilibrate to 24 ºC. After 10 h, the reaction was treated with 1 N aq. HCl (30 mL), then stirred for 1 h. The product was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The crude product was purified by flash chromatography (CV = 70 mL of silica, 2% Et_2O/pentane) to afford the title compound as a white solid (592 mg, 58% yield).

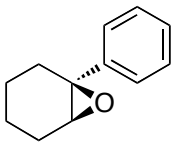
R_f: 0.62, 2% Et_2O/pentane. **^{1}H NMR**: (500 MHz, $CDCl_3$) δ 7.86–7.73 (m, 4H), 7.60 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.49–7.37 (m, 2H), 6.34–6.25 (m, 1H), 2.63–2.45 (m, 2H), 2.34–2.22 (m, 2H), 1.92–1.78 (m, 2H), 1.76–1.66 (m, 2H). This spectrum was in agreement with the literature.[7]

V. Epoxidation Procedures and Product Data



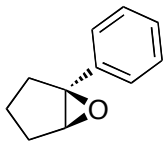
Epoxidation of volatile substrates (Table 2, entries 1–3 and 6–7). An aqueous buffer solution containing K_2CO_3 (0.6 M) and Na_2EDTA (4 x 10^{-4} M) was prepared. The substrate (100 mg) and peptide **14** (10 mol%) were dissolved in a 1:1 mixture of 2-methylbutan-2-ol and buffer solution such that the substrate was 0.165 M with respect to the total volume. Anhydrous CH_3CN (8.0 equiv) was added and the heterogeneous mixture was stirred vigorously as it was cooled to 0 ºC in a cryostatically controlled 2-propanol bath. Aqueous H_2O_2 (30% w/w, 8.0 equiv) was added in one portion and the reaction was stirred at 0 ºC. When the reaction was complete by TLC (typically 6 hours), the reaction was diluted with H_2O (5 mL) and the product was extracted with hexanes (4 x 5 mL). The combined organic layers were

washed with 1 M $Na_2S_2O_3$ (2 x 2 mL), then dried over Na_2SO_4 and filtered. The volume was partially reduced *in vacuo* at 0 ºC, then the residue was loaded onto a flash column (CV = 50 mL of silica) and eluted with pentane (125 mL), then 5% Et_2O/pentane (250 mL). The product was concentrated *in vacuo* at 0 ºC. *(For 2-methyl-2-phenyloxirane (Table 2, entry 7), the column was buffered with 1% Et_3N to prevent rearrangement to the aldehyde.)*



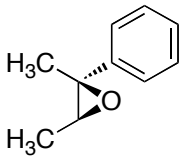
11

(1*S*,6*S*)-1-phenyl-7-oxabicyclo[4.1.0]heptane (11).[8] $[\alpha]_D^{23}$ –57 (c 0.46, $CHCl_3$). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.1 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.29–7.23 (m, 1H), 3.08 (d, *J* = 3.8 Hz, 1H), 2.29 (ddd, *J* = 14.3, 8.6, 5.3 Hz, 1H), 2.13 (dt, *J* = 15.0, 5.4 Hz, 1H), 2.07–1.93 (m, 2H), 1.68–1.53 (m, 2H), 1.53–1.43 (m, 1H), 1.39–1.26 (m, 1H). **HPLC** (Chiralcel OJ-H, 90:10 hexanes/2-propanol, 0.5 mL/min, monitor at 210 nm): 11.7 min (90.6%) and 13.0 min (9.4%), 81% *ee*.



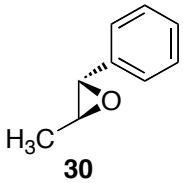
28

(1*S*,5*S*)-1-phenyl-6-oxabicyclo[3.1.0]hexane (28).[9] $[\alpha]_D^{23}$ –49 (c 0.63, $CHCl_3$). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 2H), 7.37–7.32 (m, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 3.56 (s, 1H), 2.28–2.08 (m, 3H), 1.85–1.54 (m, 3H). **HPLC** (Chiralpak IC, 98:2 hexanes/2-propanol, 0.5 mL/min, monitor at 210 nm): 16.4 min (88.3%) and 18.5 min (11.7%), 77% *ee*.



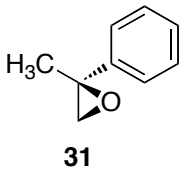
29

(2*S*,3*S*)-2,3-dimethyl-2-phenyloxirane (29).[10] **^{1}H NMR:** (500 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4H), 7.30–7.23 (m, 1H), 2.95 (q, *J* = 5.4 Hz, 1H), 1.66 (s, 3H), 1.43 (d, *J* = 5.4 Hz, 3H). **HPLC** (Chiralcel AS-H, isocratic hexanes, 0.5 mL/min, monitor at 210 nm): 17.8 min (13.1%) and 20.8 min (86.9%), 74% *ee*.



30

(2*S*,3*S*)-2-methyl-3-phenyloxirane (30).[10] **$[\alpha]_D^{23}$** –23 (c 0.61, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 5H), 3.58 (d, *J* = 2.2 Hz, 1H), 3.04 (qd, *J* = 5.1, 2.1 Hz, 1H), 1.46 (d, *J* = 5.1 Hz, 3H). **HPLC** (Chiralcel AD-H, 99:1 hexanes/2-propanol, 1.0 mL/min, monitor at 210 nm): 10.1 min (28.8%) and 13.8 min (71.2%), 42% *ee*.

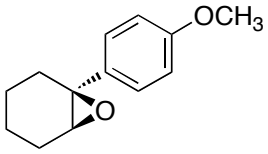


31

(*S*)-2-methyl-2-phenyloxirane (31).[10] **$[\alpha]_D^{23}$** +5.4 (c 0.89, $CHCl_3$). **^{1}HNMR:** (500 MHz, $CDCl_3$) δ 7.40–7.31 (m, 4H), 7.31–7.26 (m, 1H), 2.98 (d, *J* = 5.4 Hz, 1H), 2.81 (d, *J* = 5.4 Hz, 1H), 1.73 (d, *J* = 0.6 Hz, 3H). **HPLC** (Chiralcel OD-H, 95:5 hexanes/2-propanol, 0.3 mL/min, monitor at 210 nm): 14.8 min (30.4%) and 16.4 min (69.6%), 39% *ee*.

Epoxidation of 1-(4-methoxyphenyl)cyclohex-1-ene (Table 2, entry 4). The substrate (100 mg) and peptide **14** (10 mol%) were dissolved in a 1:1 mixture of 2-methylbutan-2-ol and buffer solution (*vide supra*) such that the substrate was 0.085 M with respect to the total volume. Anhydrous CH_3CN

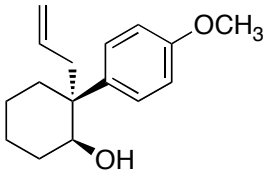
(8.0 equiv) was added and the heterogeneous mixture was stirred vigorously as it was cooled to 0 ºC in a cryostatically controlled 2-propanol bath. Aqueous H_2O_2 (30% w/w, 8.0 equiv) was added in one portion and the reaction was stirred at 0 ºC. After 11 h, the reaction was diluted with H_2O (5 mL) and the product was extracted with hexanes (4 x 5 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 x 2 mL), then dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude product was purified by flash chromatography (CV = 50 mL of silica) and eluted with 10% EtOAc/hexanes that was buffered with 1% Et_3N.



32

(1*S*,6*S*)-1-(4-methoxyphenyl)-7-oxabicyclo[4.1.0]heptane (32).[8] $[\alpha]_D^{23}$ –50 (c 1.8, $CHCl_3$). **^{1}HNMR:** (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H), 6.91–6.81 (m, 2H), 3.80 (s, 3H), 3.07 (t, *J* = 2.1 Hz, 2H), 2.24 (ddd, *J* = 14.3, 8.7, 5.4 Hz, 1H), 2.11 (dt, *J* = 14.8, 5.2 Hz, 1H), 2.04–1.91 (m, 2H), 1.69–1.38 (m, 3H), 1.38–1.21 (m, 1H).

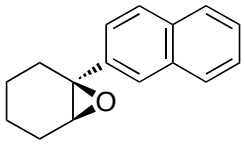
For enantioselectivity analysis, the epoxide was opened stereospecifically with allylmagnesium chloride according to the method reported by Taber and coworkers.[11]



33

(1*S*,2*R*)-2-allyl-2-(4-methoxyphenyl)cyclohexanol (33).[11] **^{1}HNMR:** (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H), 6.92–6.88 (m, 2H), 5.25 (dddd, *J* = 17.0, 10.1, 8.5, 5.7 Hz, 1H), 4.99–4.84 (m, 2H), 4.04–3.97 (m, 1H), 3.81 (s, 3H), 2.61 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.32 (ddd, *J* = 13.7, 5.8, 1.5 Hz, 1H), 2.04–1.94 (m, 1H), 1.93–1.78 (m, 2H), 1.78–1.44 (m, 5H), 1.33 (t, *J* = 1.8 Hz, 1H). **HPLC**: (Chiralcel OD-H, 99:1 hexanes/2-propanol, 1.0 mL/min, monitor at 230 nm): 12.8 min (10.3%) and 13.8 min (89.7%), 79% *ee*.

Epoxidation of 1-(2-naphthyl)cyclohex-1-ene (Table 2, entry 5). Same as for 1-(4-methoxyphenyl)cyclohex-1-ene except that the flash chromatography was conducted with 2.5% Et_2O/pentane (125 mL), then 5% Et_2O/pentane (250 mL).



34

(1S,6S)-1-(naphthalen-2-yl)-7-oxabicyclo[4.1.0]heptane (34).[12] $[\alpha]_D^{23}$ –60 (c 0.31, $CHCl_3$). **^{1}HNMR:** (400 MHz, Chloroform-d) δ 7.88–7.76 (m, 4H), 7.53–7.41 (m, 3H), 3.17 (dt, *J* = 3.5, 1.1 Hz, 1H), 2.41 (ddd, *J* = 14.9, 8.5, 5.3 Hz, 1H), 2.27–2.14 (m, 1H), 2.13–1.94 (m, 2H), 1.75–1.46 (m, 3H), 1.46–1.29 (m, 1H). **HPLC** (Chiralcel OJ-H, 98:2 hexanes/2-propanol, 1.0 mL/min, monitor at 230 nm): 15.4 min (8.9%) and 17.3 min (91.1%), 82% *ee*.

VI. References

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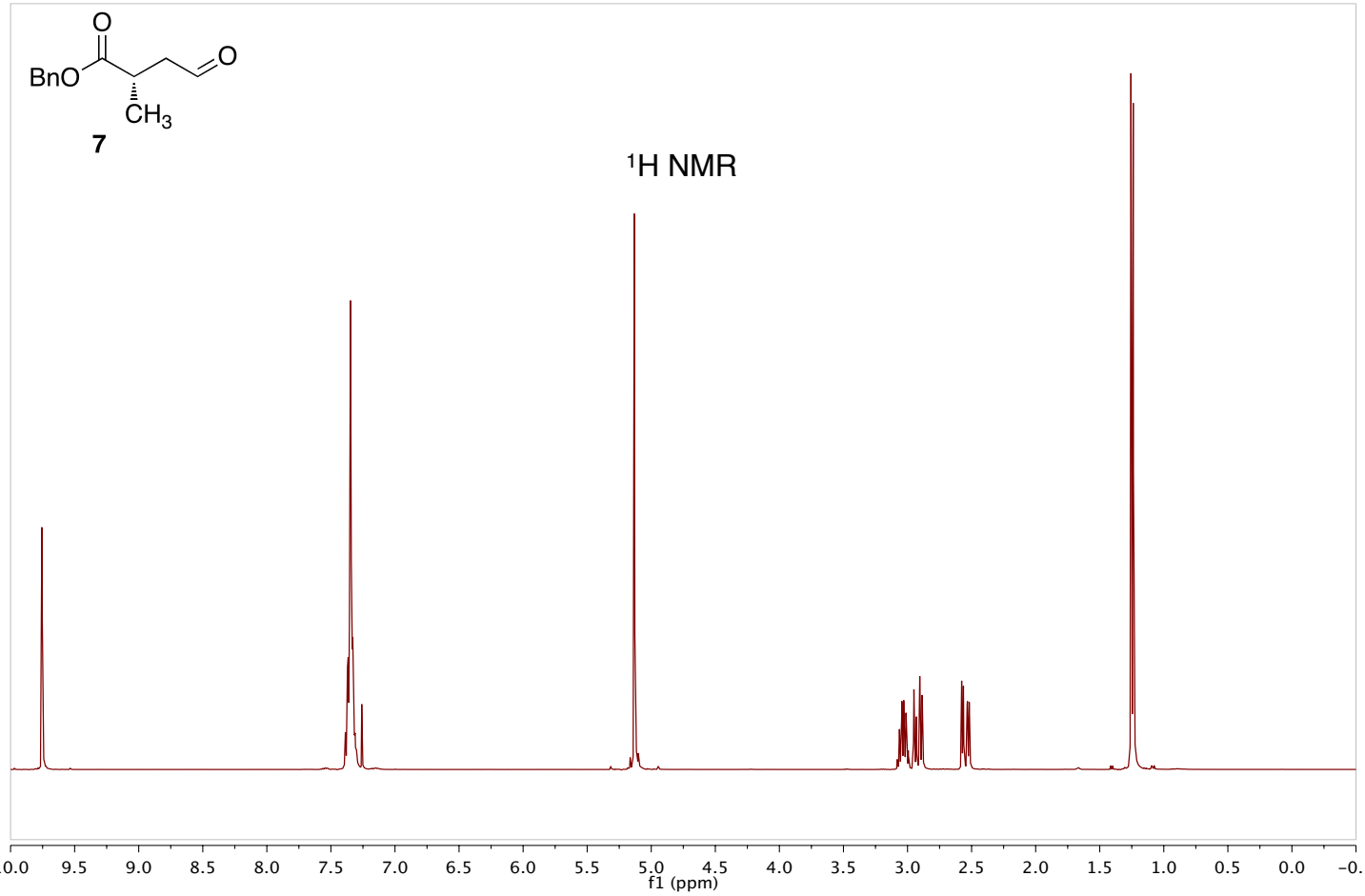
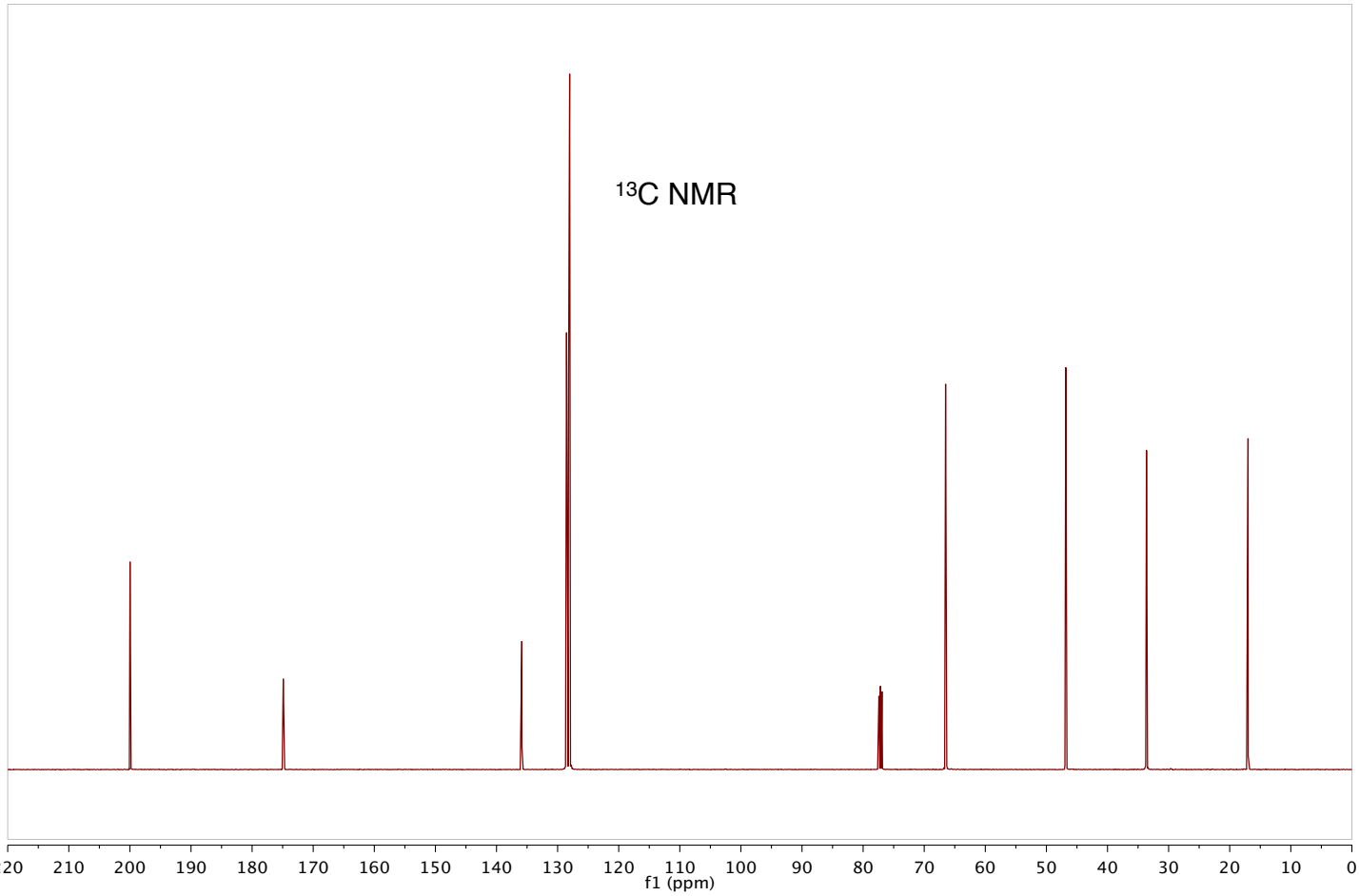
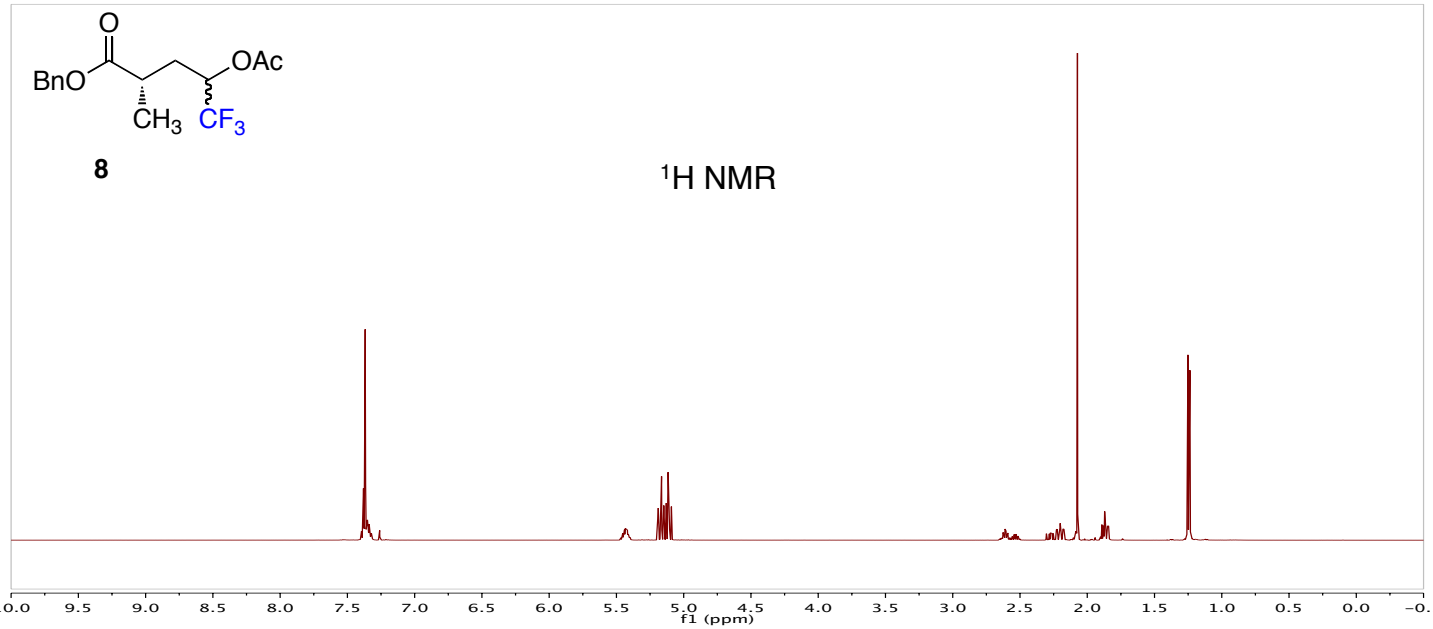

O
BnO
O
CH3
7
1H NMR
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


13C NMR
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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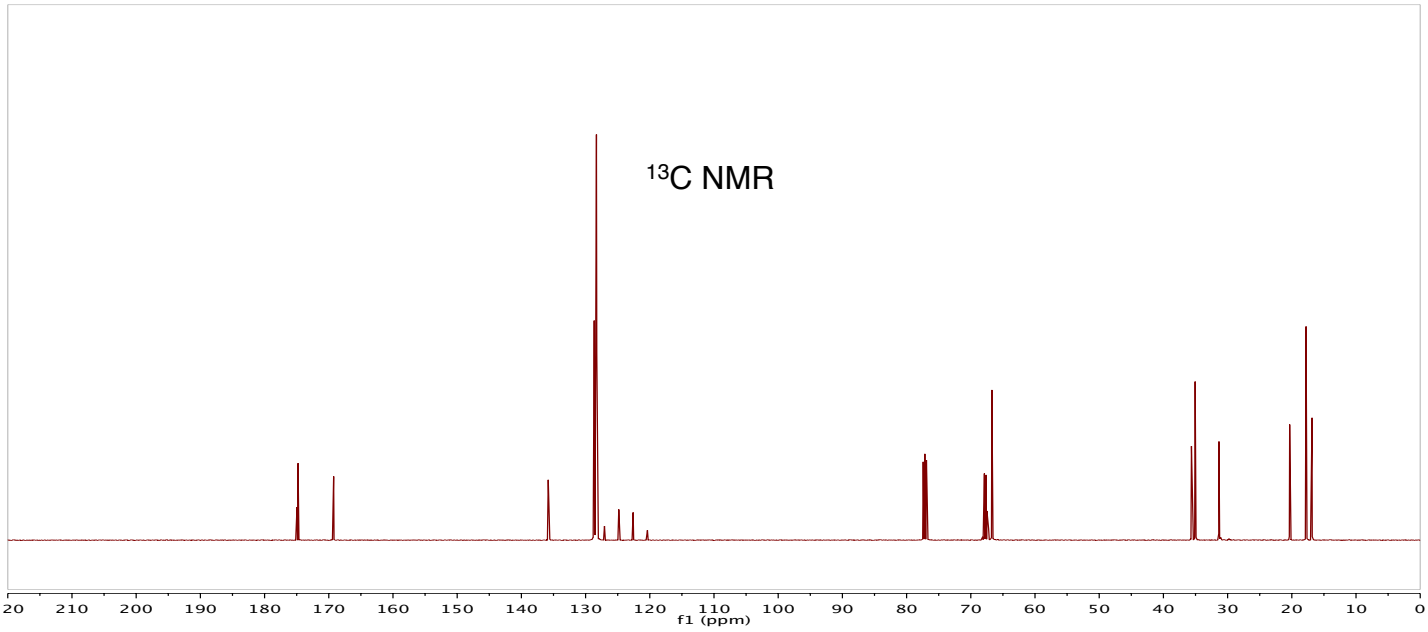
BnO
OAc
CH3
CF3
8
1H NMR
f1 (ppm)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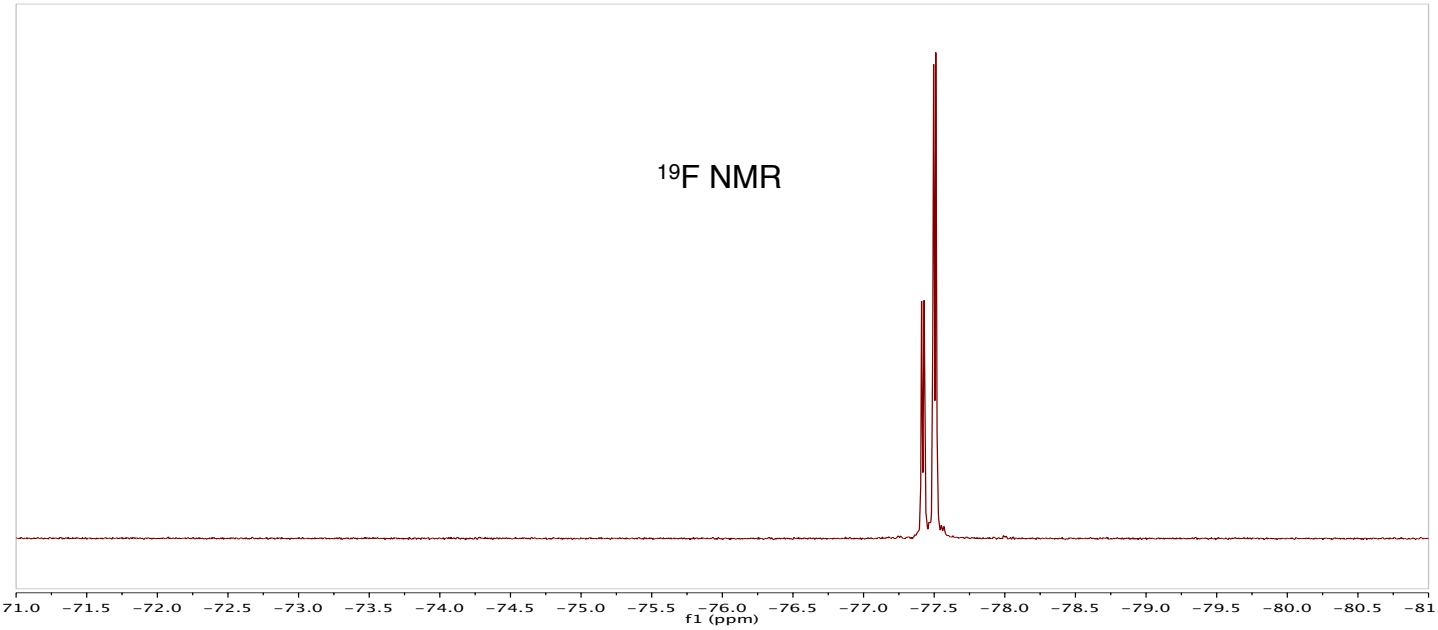
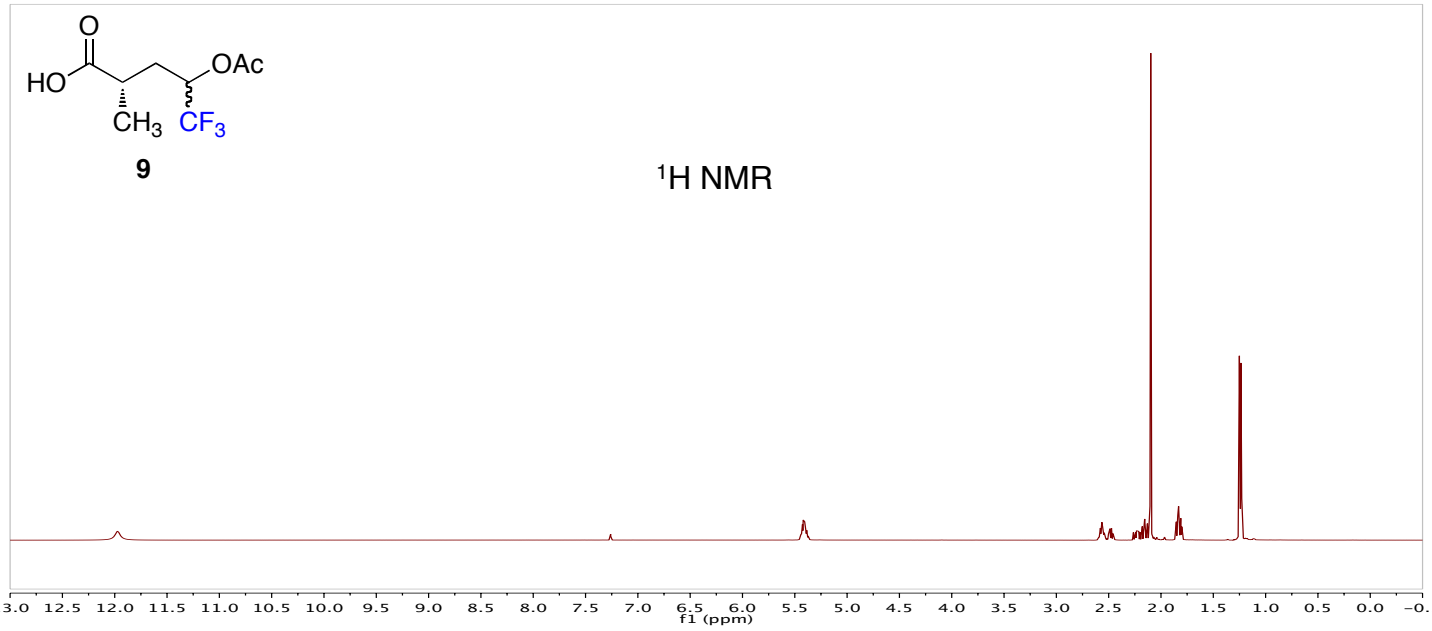
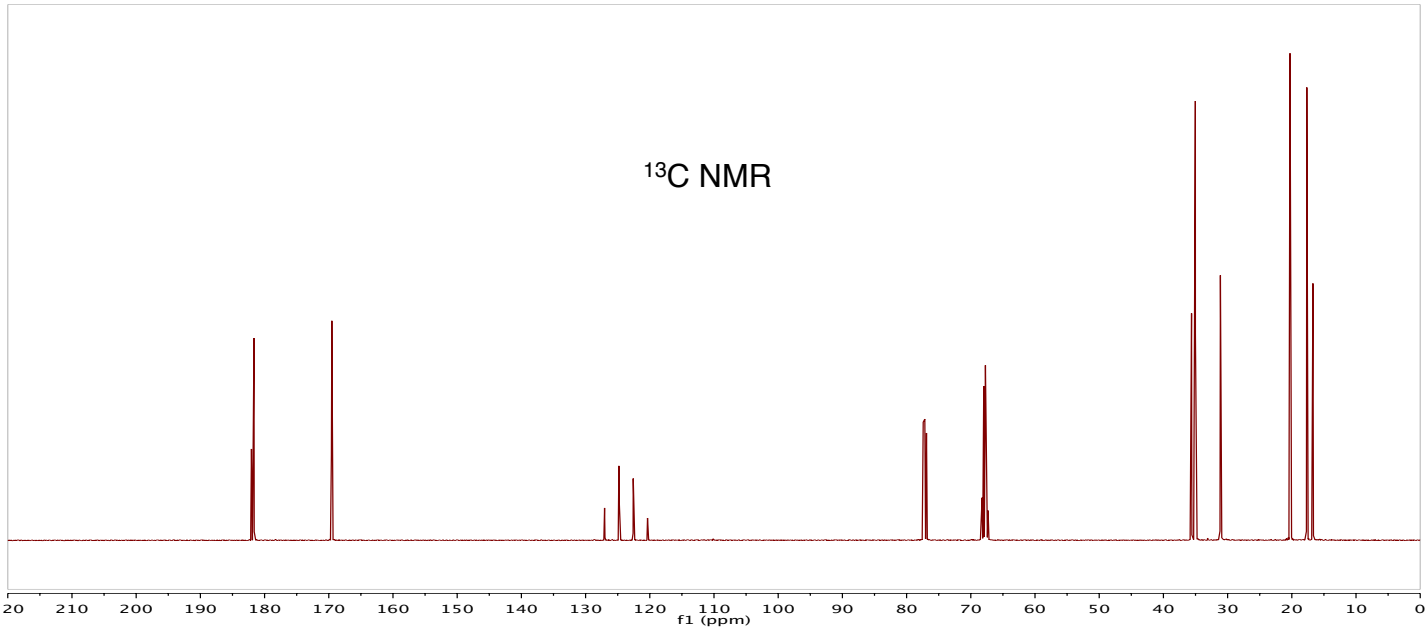
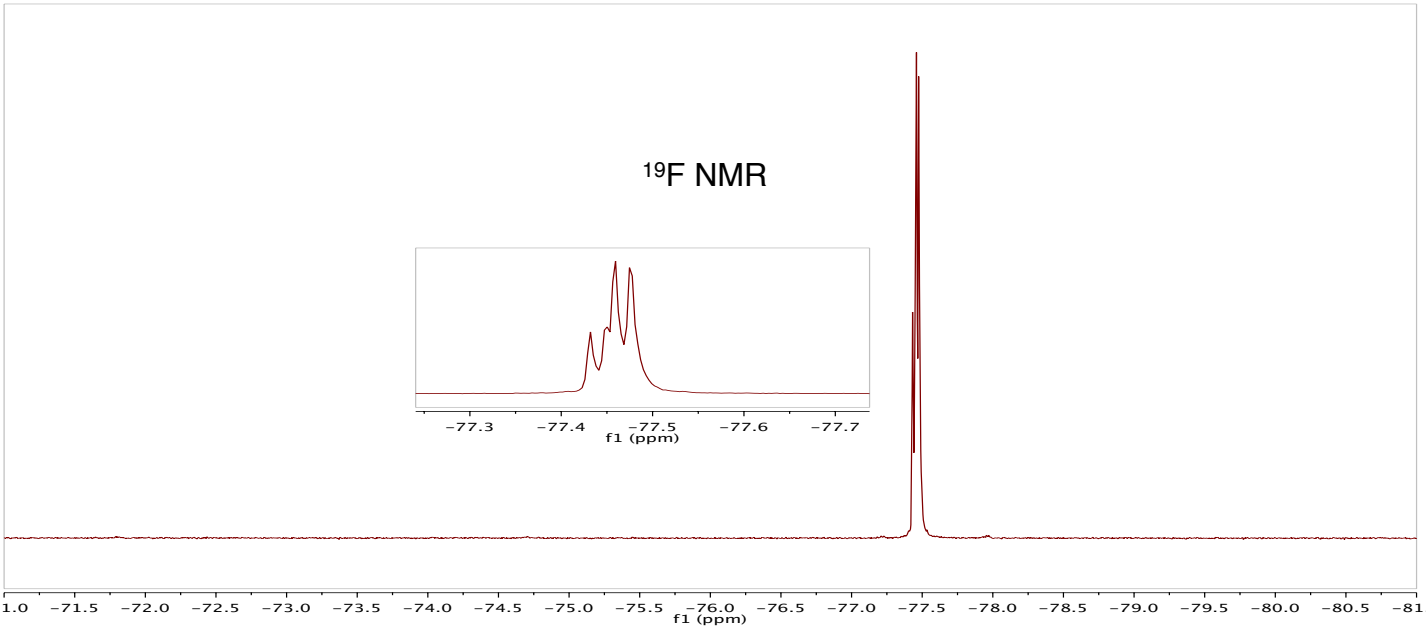
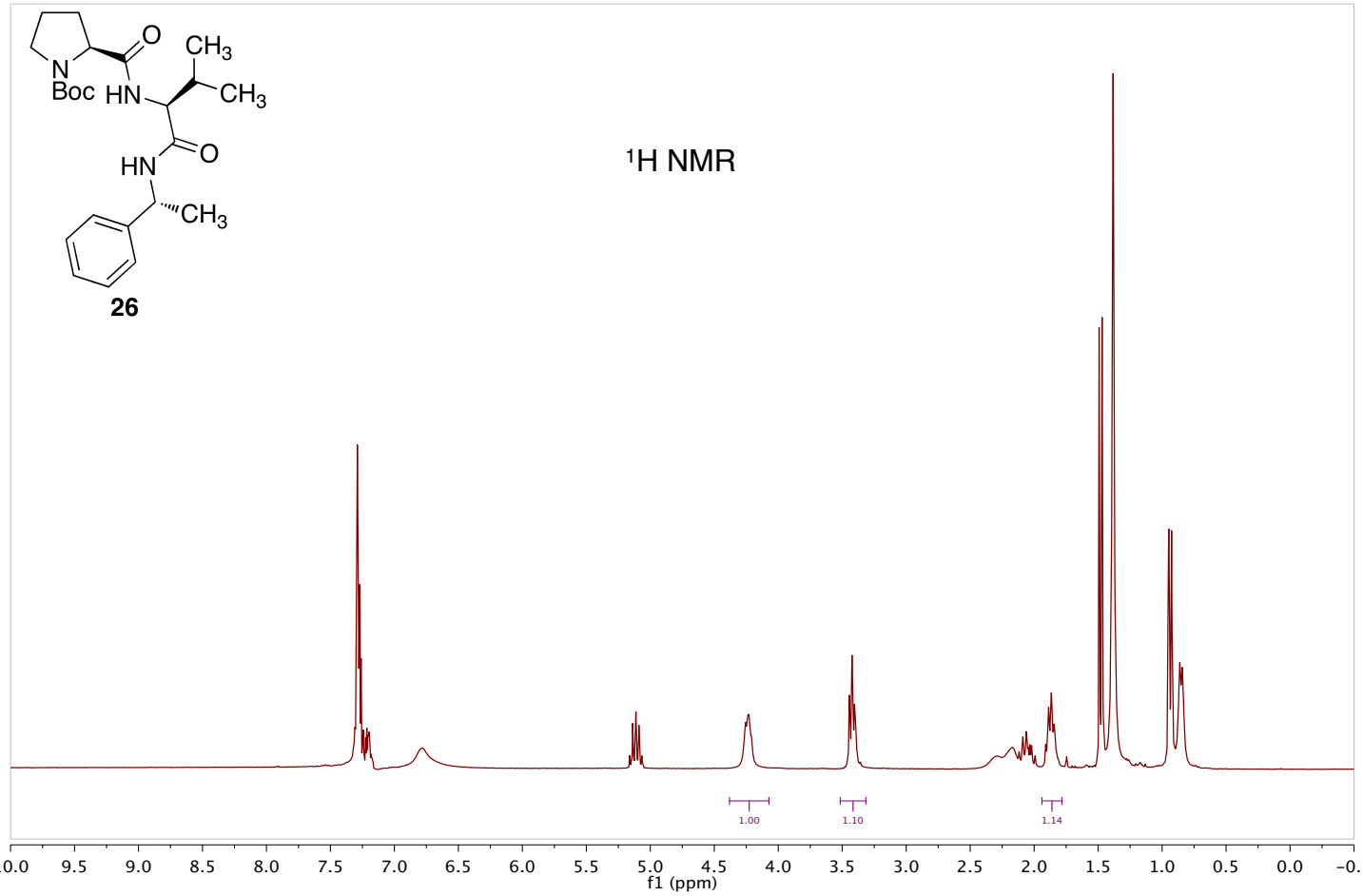
f1 (ppm)

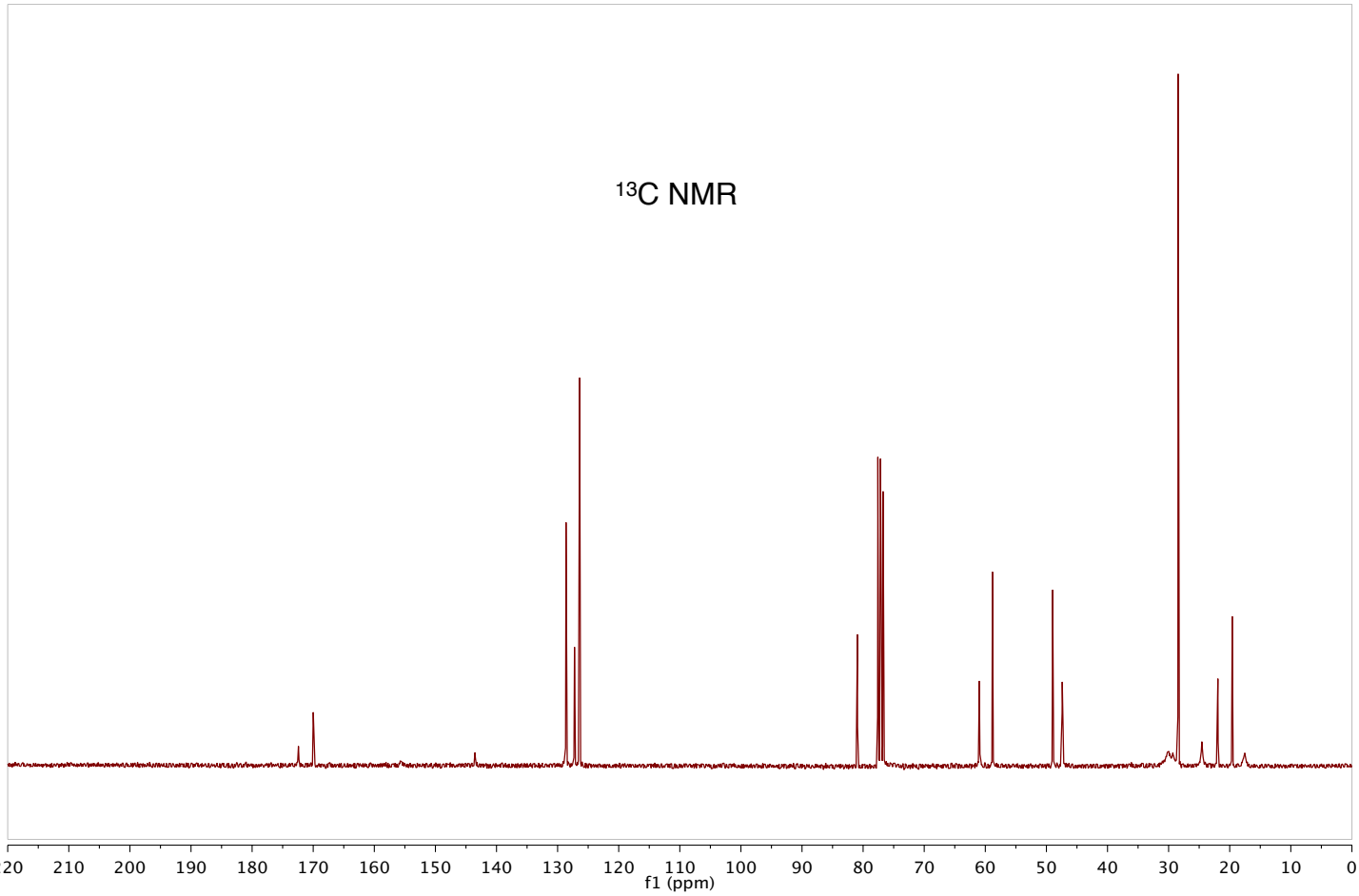

19F NMR
f1 (ppm)


O
HO
OAc
CH3
CF3
9
1H NMR
f1 (ppm)


13C NMR
f1 (ppm)


19F NMR
f1 (ppm)


O
CH3
N
Boc HN
CH3
O
HN
CH3
26
1H NMR
1.00
1.10
1.14
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


13C NMR
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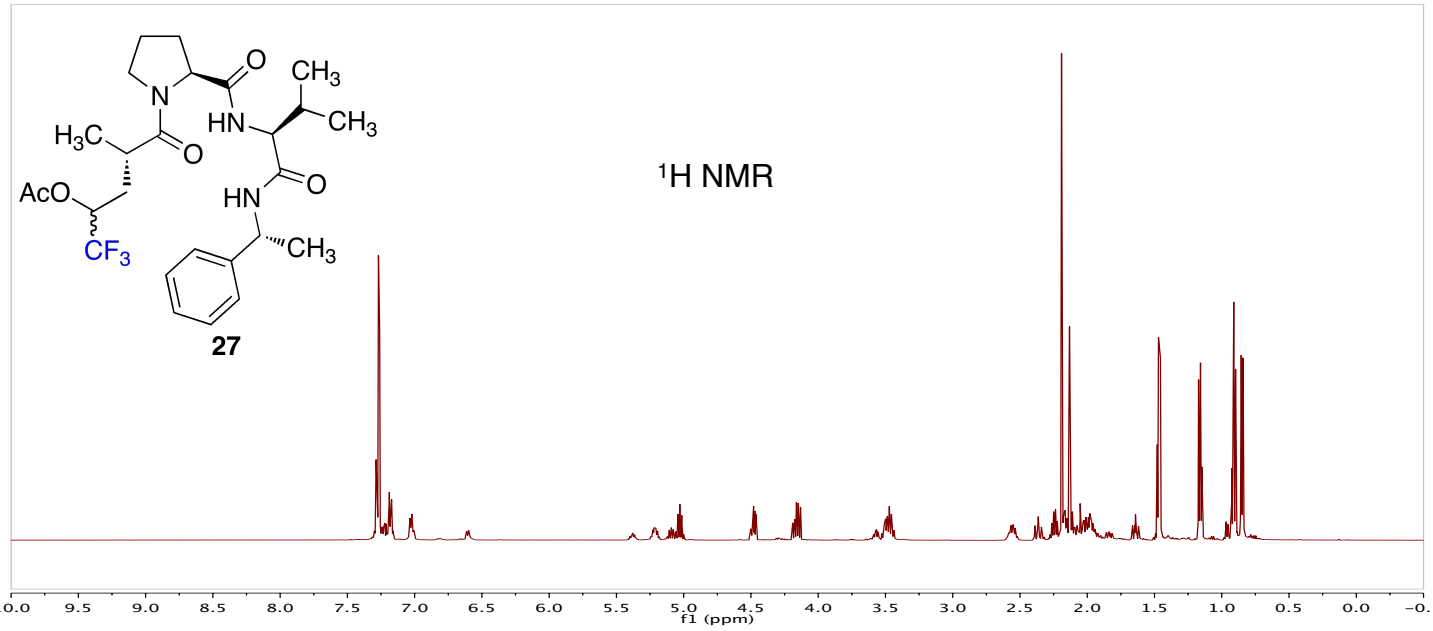
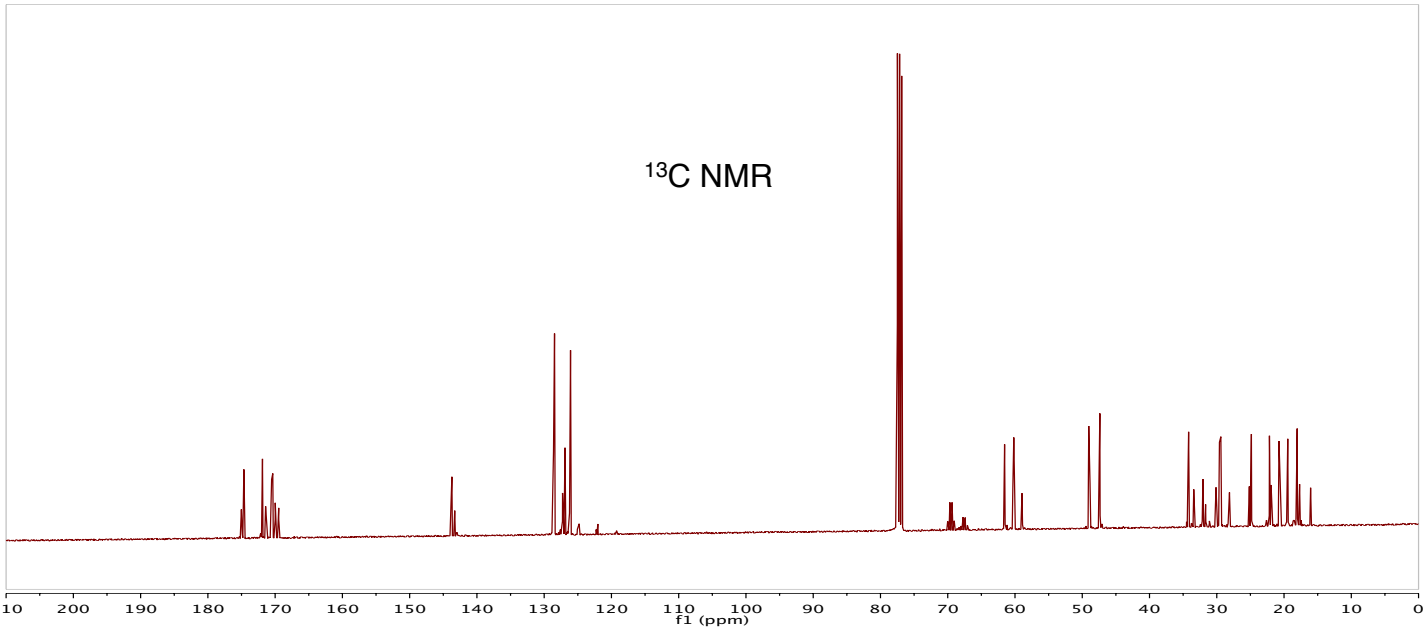
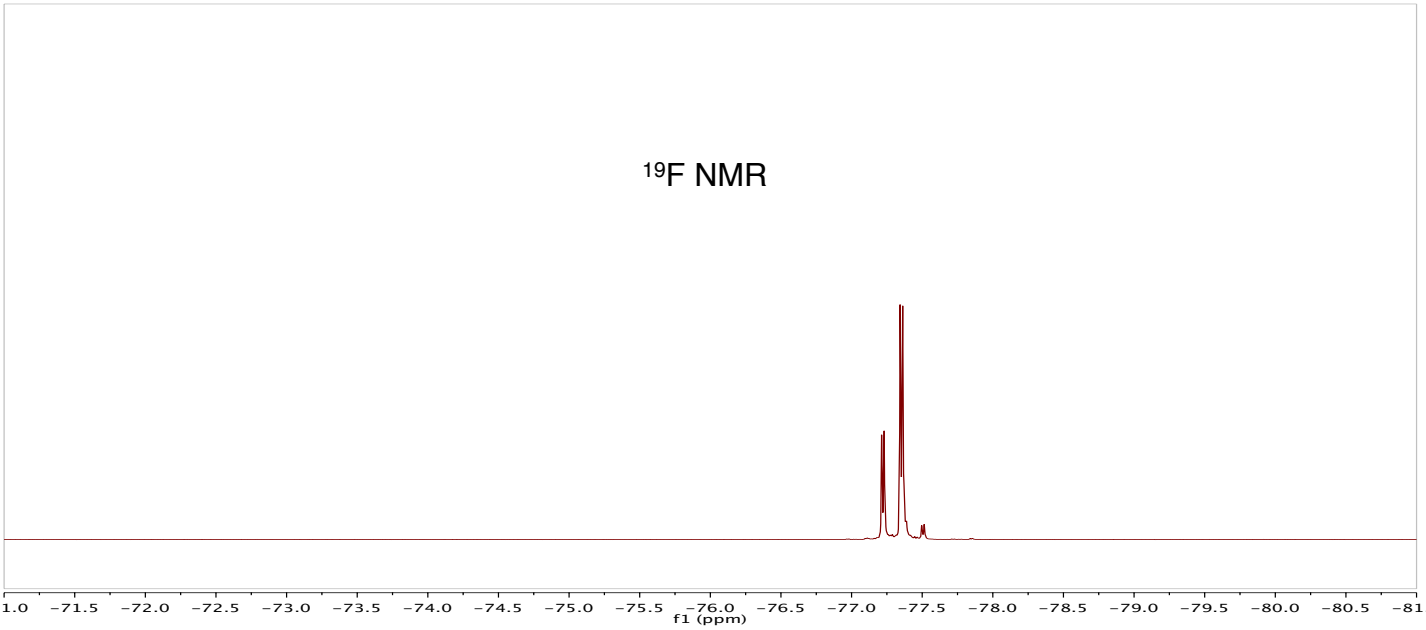
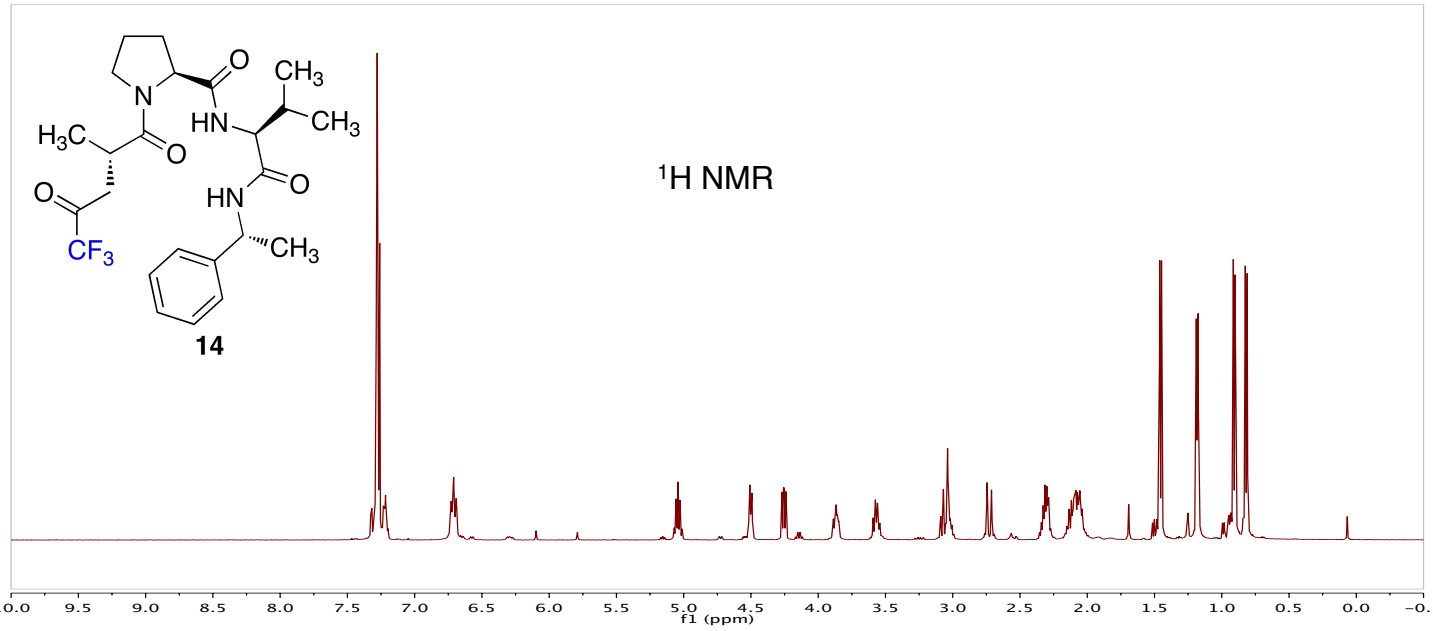
f1 (ppm)



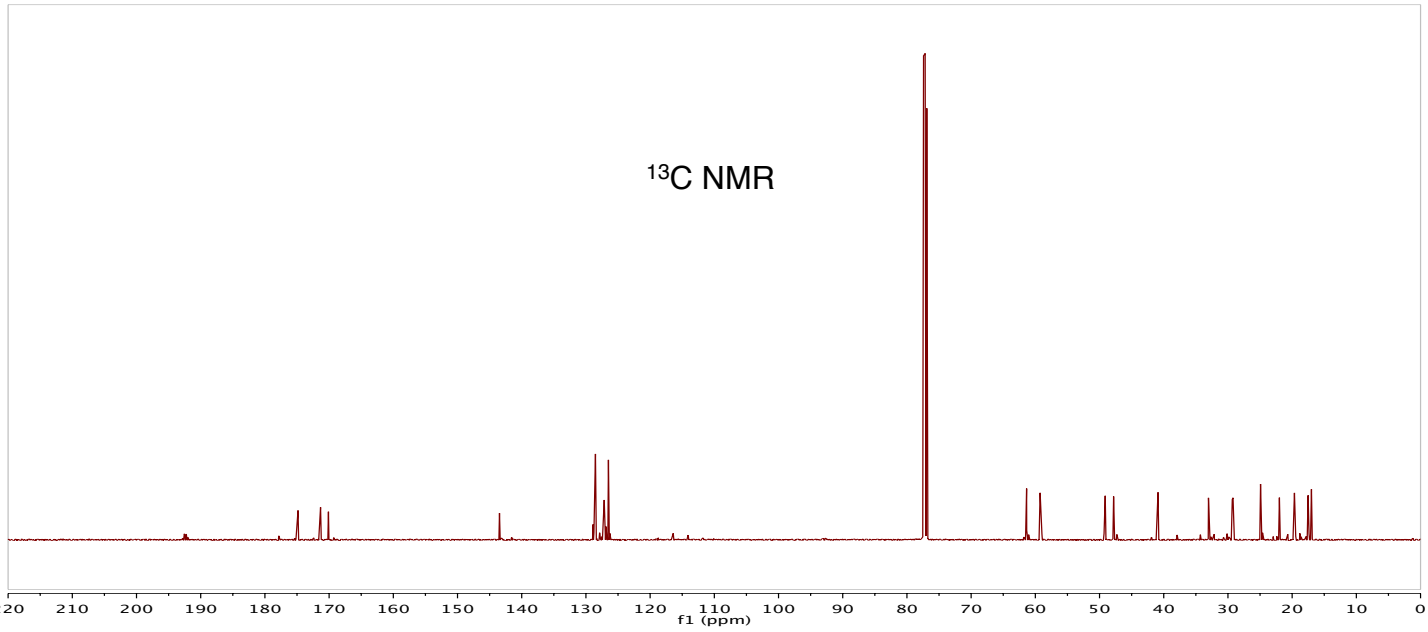
27

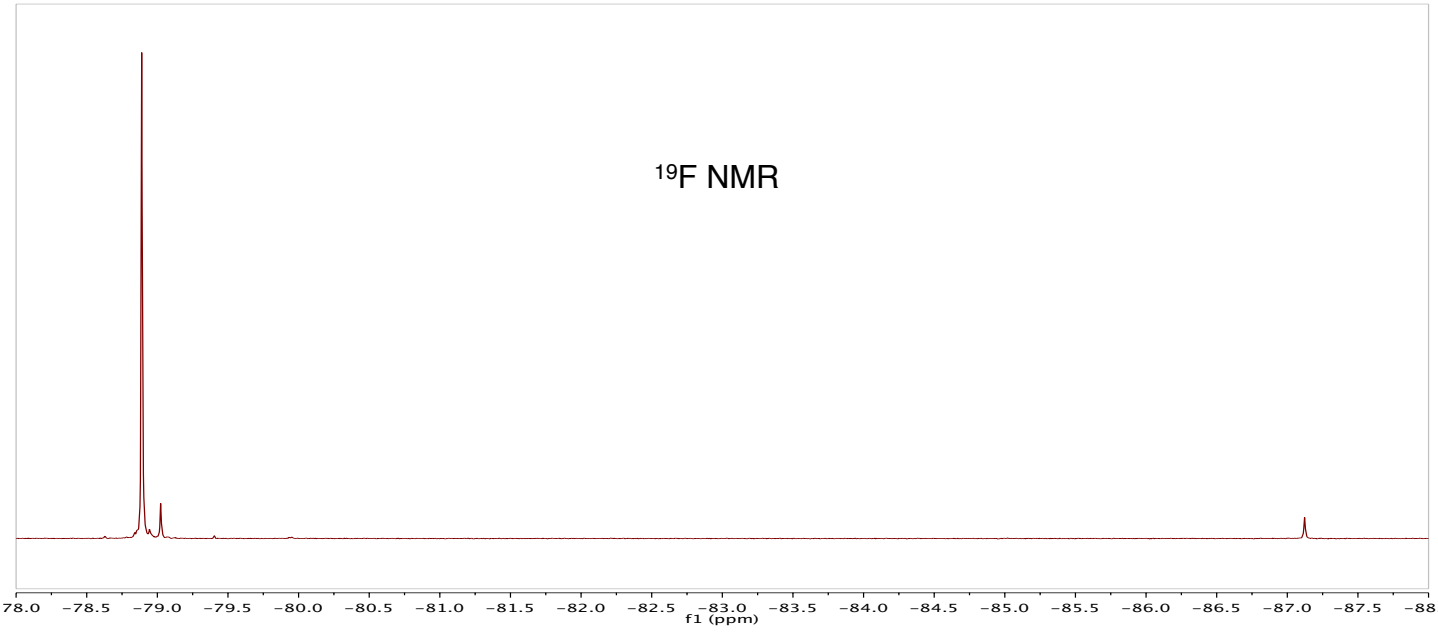


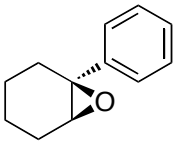




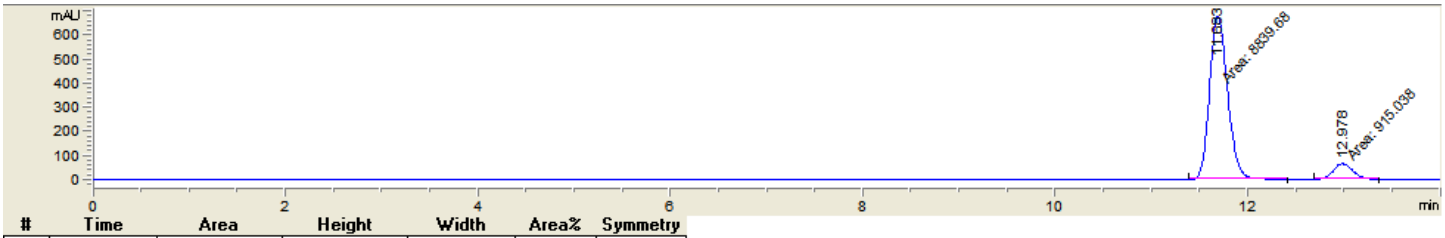
14







Chiralcel OJ-H, 90:10 hexanes/2-propanol, 0.5 mL/min, monitor at 210 nm



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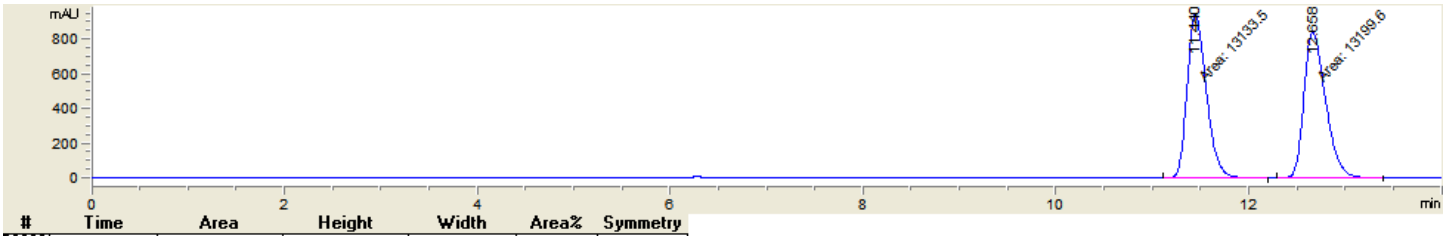
Racemate:



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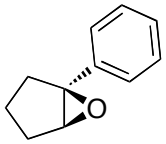
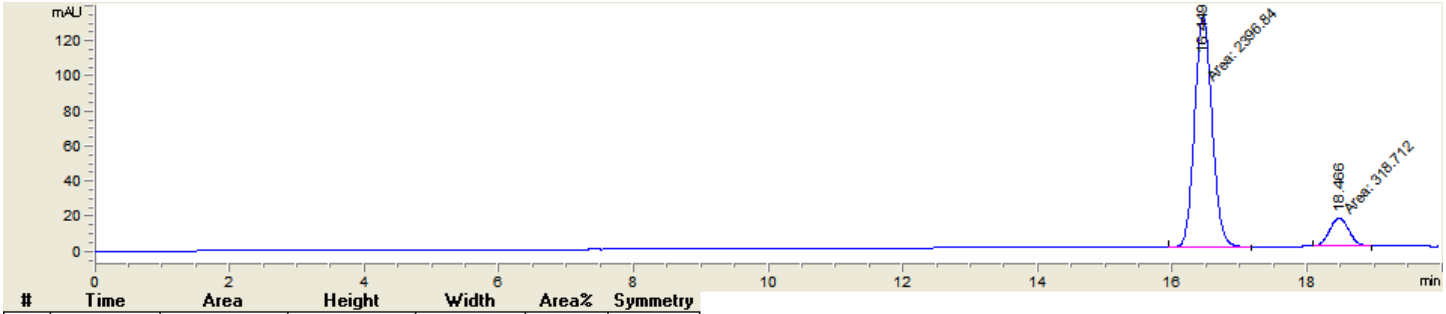


Chiralpak IC, 98:2 hexanes/2-propanol, 0.5 mL/min, monitor at 210 nm



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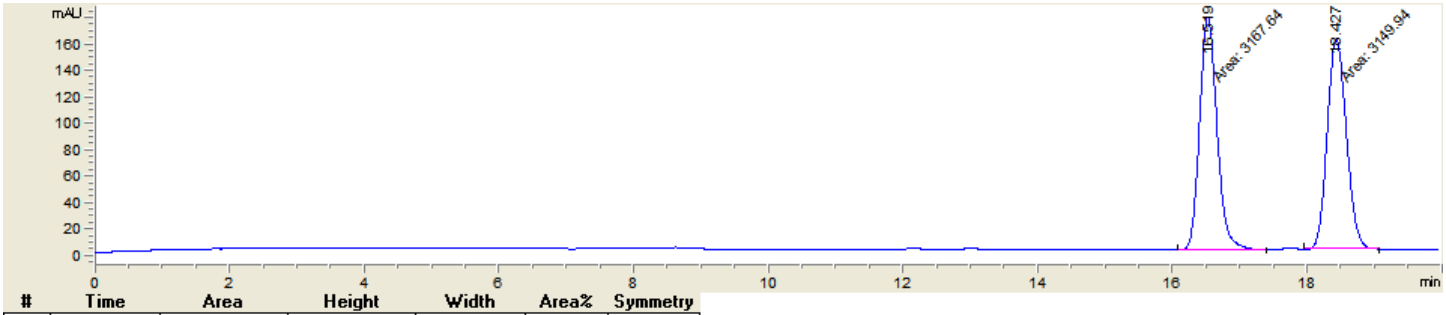
Racemate:



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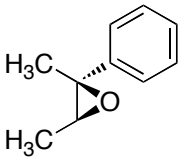
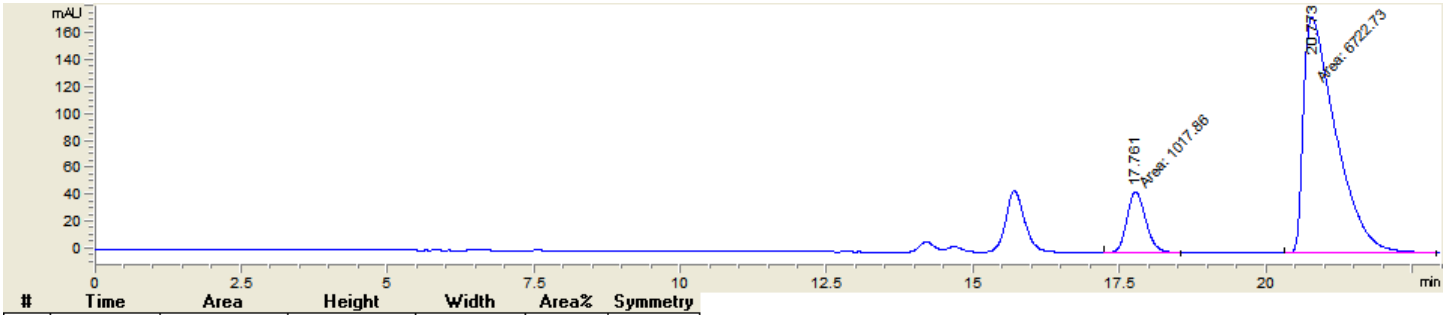


Chiralcel AS-H, isocratic hexanes, 0.5 mL/min, monitor at 210 nm



#	Time	Area	Height	Width	Area%	Symmetry
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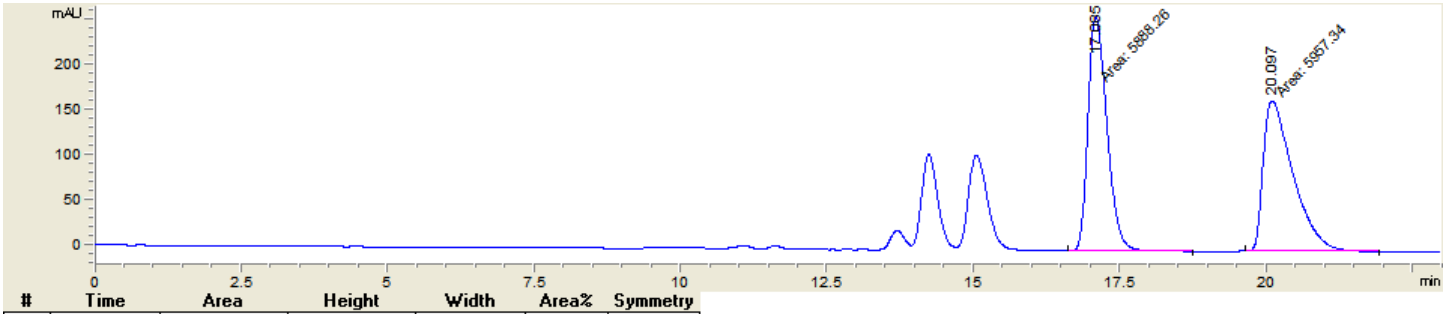
Racemate:



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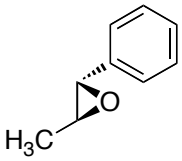
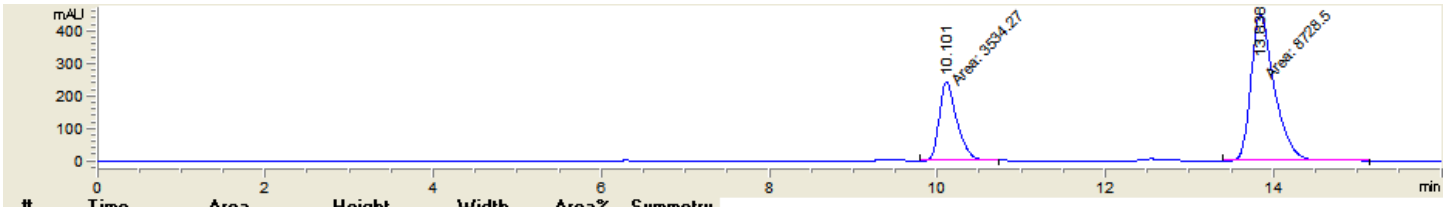


Chiralcel AD-H, 99:1 hexanes/2-propanol, 1.0 mL/min, monitor at 210 nm



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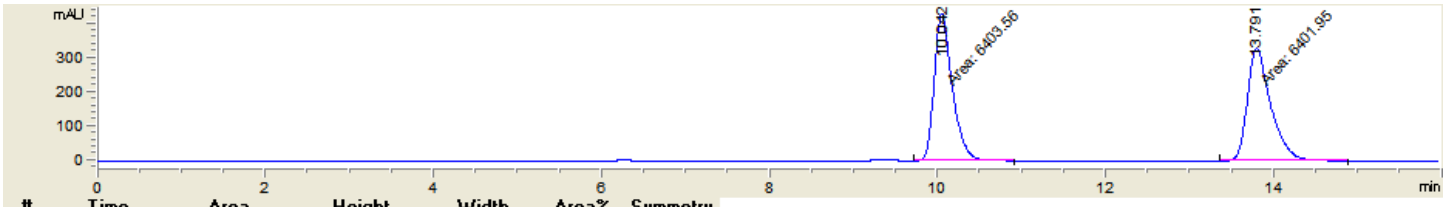
Racemate:



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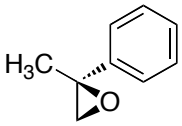
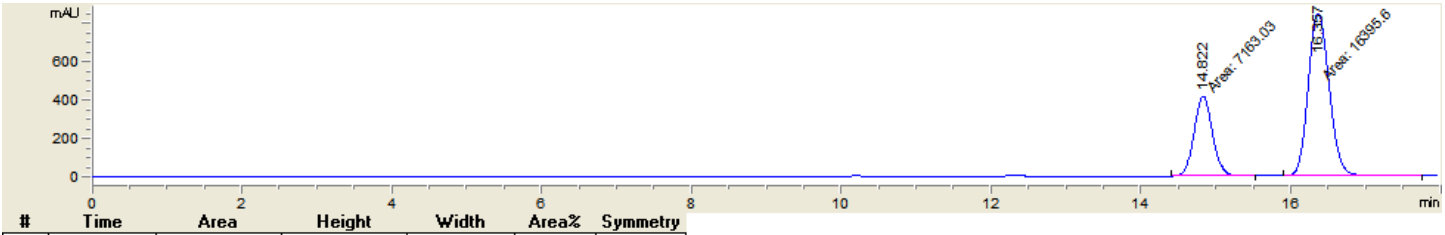


Chiralcel OD-H, 95:5 hexanes/2-propanol, 0.3 mL/min, monitor at 210 nm



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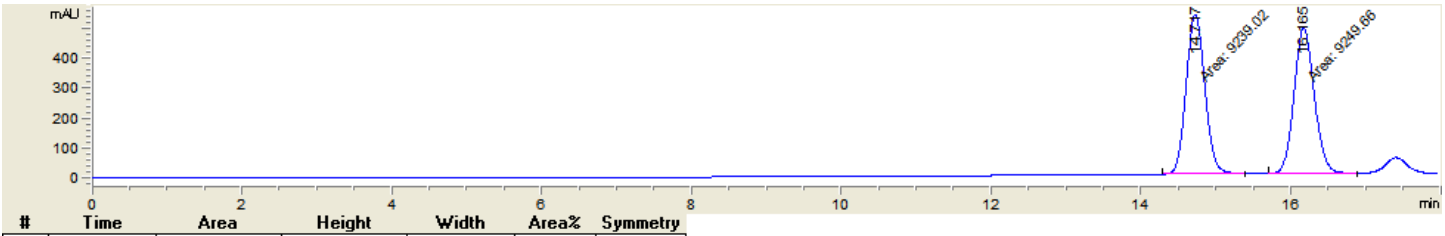
Racemate:



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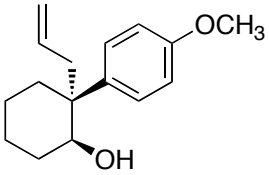
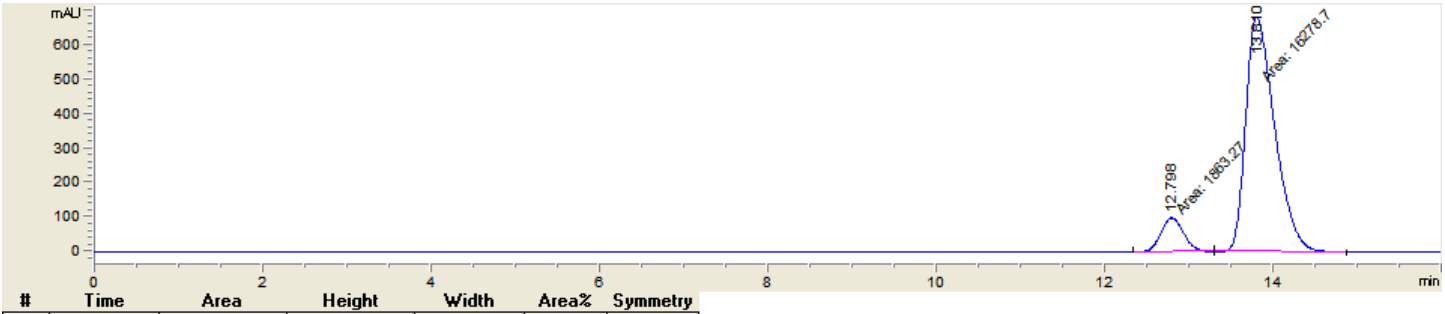
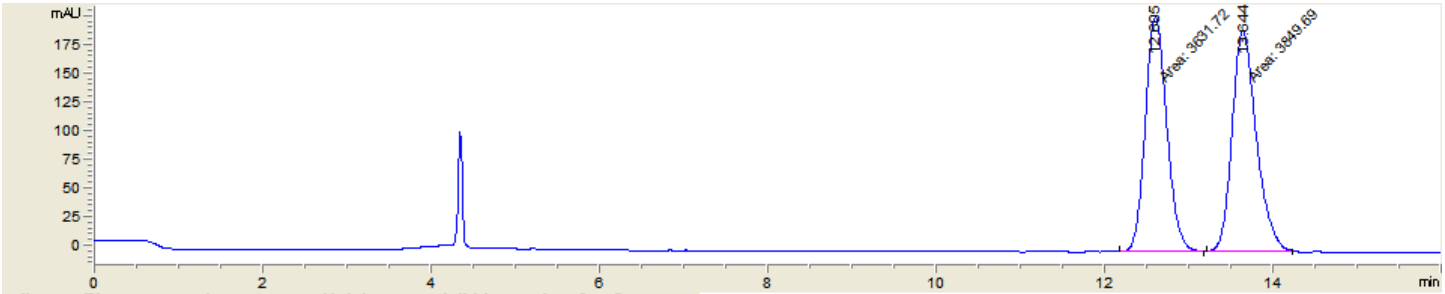


Chiralcel OD-H, 99:1 hexanes/2-propanol, 1.0 mL/min, monitor at 230 nm

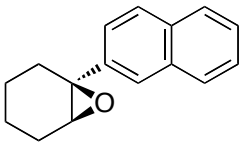


#	Time	Area	Height	Width	Area%	Symmetry
1	12.798	1863.3	98.6	0.3149	10.270	0.876
2	13.81	16278.7	680.9	0.3985	89.730	0.593

Racemate:



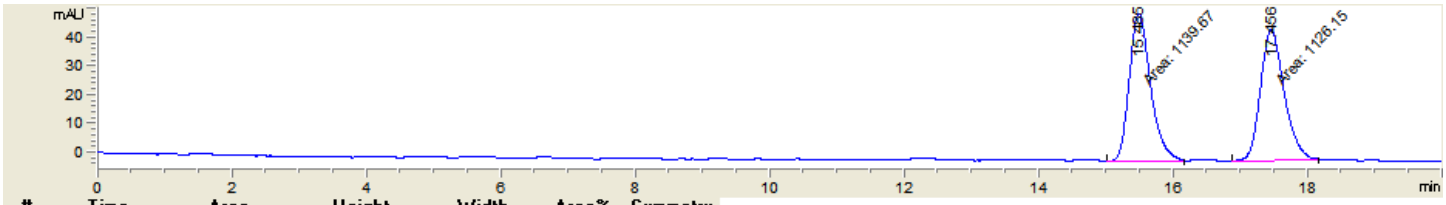
#	Time	Area	Height	Width	Area%	Symmetry
1	12.605	3631.7	204.4	0.2961	48.543	0.868
2	13.644	3849.7	192	0.3342	51.457	0.766



Chiralcel OJ-H, 98:2 hexanes/2-propanol, 1.0 mL/min, monitor at 230 nm

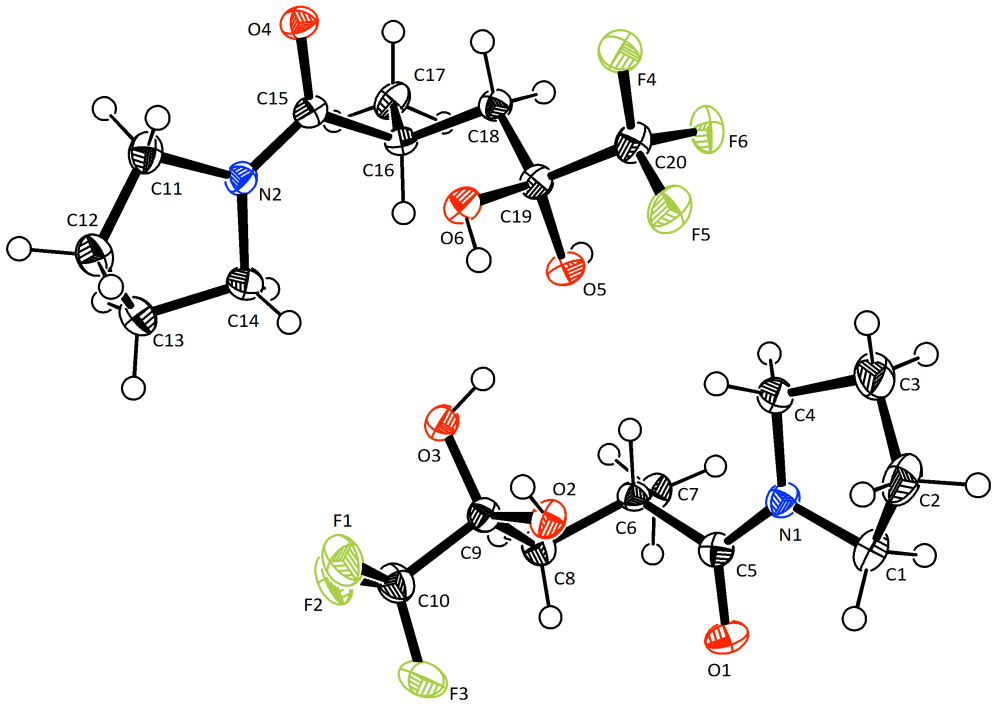
#	Time	Area	Height	Width	Area%	Symmetry
1	15.39	440.4	18.7	0.3924	8.928	0.712
2	17.31	4491.7	186.9	0.4005	91.072	0.768

Racemate:



#	Time	Area	Height	Width	Area%	Symmetry
1	15.485	1139.7	51.5	0.369	50.299	0.755
2	17.456	1126.1	45.5	0.4121	49.701	0.785

IX. X-ray Crystal Structure of Tfk-Pyrrolidine Hydrate (18·H_2O)



A. Crystal Data

Empirical Formula	$C_{10}H_{16}NO_3F_3$	
Formula Weight	255.24	
Crystal Color, Habit	colorless, block	
Crystal Dimensions	0.26 X 0.20 X 0.16 mm	
Crystal System	monoclinic	
Lattice Type	Primitive	
Indexing Images	8 images @ 5.0 seconds	
Detector Position	50.00 mm	
Lattice Parameters	a = 9.28387(17) Å	α = 90°
	b = 10.75170(19) Å	β = 94.002(7)°
	c = 11.9589(8) Å	γ = 90°
	V = 1190.79(9) $Å^3$	
Space Group	$P2_1$ (#4)	
Z value	4	
D_{calc}	1.424 g/cm^3	
F_{000}	536.00	
μ(CuKα)	11.739 cm^{-1}	

B. Intensity Measurements

Diffractometer	Rigaku Saturn944+ CCD
Radiation	CuKα (λ = 1.54187 Å)
Detector Aperture	94 mm x 94 mm
Data Images	1473 images
Exposure Rate (detector angle = 42°)	3.0 sec./°

Exposure Rate (detector angle = 90°)	5.0 sec./°
Detector Position	50.00 mm
$2\theta_{max}$	127.4°
No. of Reflections Measured	Total: 11044 Unique: 3296 (R_{int} = 0.0288) Friedel pairs: 1293
Corrections	Lorentz-polarization, Absorption (trans. factors: 0.692 - 0.829)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\ \sigma^2\ (Fo^2) + (0.0133 \cdot P)^2 + 0.3107 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	127.4°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3296
No. Variables	313
Reflection/Parameter Ratio	10.53
Residuals: R1 (I>2.00σ(I))	0.0228
Residuals: R (All reflections)	0.0231
Residuals: wR2 (All reflections)	0.0539
Goodness of Fit Indicator	1.034
Max Shift/Error in Final Cycle	0.000
Flack parameter	0.07(8)
Hooft parameter	0.06(4)
Maximum peak in Final Diff. Map	0.13 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.12 $e^-/Å^3$

D. Experimental Details

The crystal sample was mounted in a Hampton Research loop with immersion oil. All measurements were made on a Rigaku Saturn944+ CCD diffractometer with filtered Cu-Kα radiation at a temperature of -180°C. The structure was solved by direct methods[a] and expanded using Fourier techniques.[b] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The absolute structure was deduced based on Flack parameter, 0.07(8), using 1293 pairs.[c] The Hooft[d] absolute structure parameter y = 0.06(4) was calculated using PLATON,[e] and is in agreement with the assigned absolute configuration.

The final cycle of full-matrix least-squares refinement[f] on F^2 was based on 3296 observed reflections and 313 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

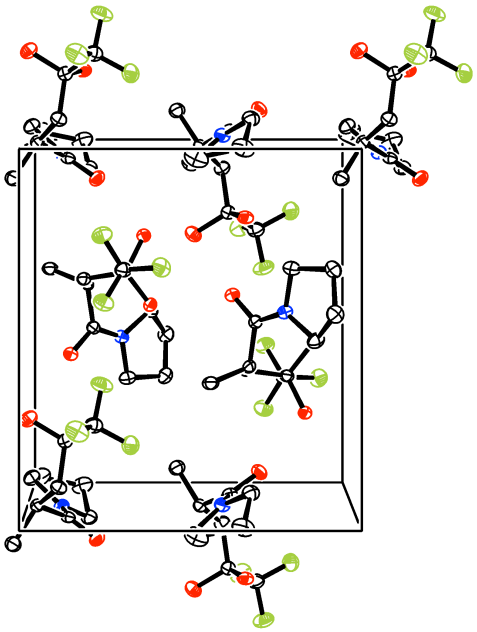
$$R1 = \Sigma\ ||Fo| - |Fc||\ /\ \Sigma\ |Fo| = 0.0228$$

$$wR2 = [\ \Sigma\ (\ w\ (Fo^2 - Fc^2)^2\ )/\ \Sigma\ w(Fo^2)^2]^{1/2} = 0.0539$$

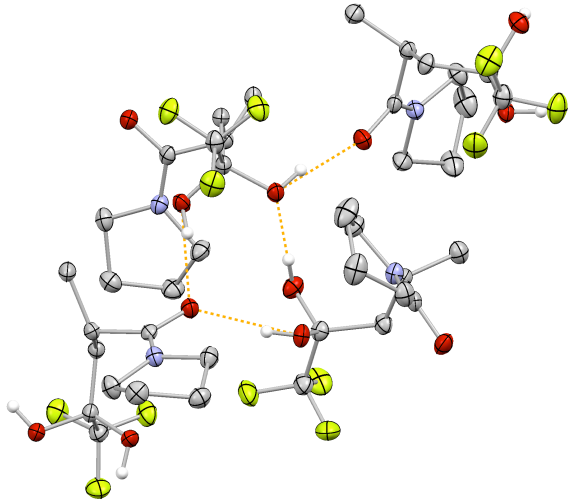
The standard deviation of an observation of unit weight[g] was 1.03. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.13 and -0.12 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[h] Anomalous dispersion effects were included in Fcalc[i]; the values for Δf' and Δf'' were those of Creagh and McAuley.[j] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[k] All calculations were performed using the CrystalStructure[l] crystallographic software package except for refinement, which was performed using SHELXL-97.[a]

E. Additional Images



View of packing along a (H atoms omitted)



View of H-bond network (C-H hydrogens omitted)

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}^{m}
F(1)	0.26426(10)	0.73533(12)	0.64302(7)	3.00(2)
F(2)	0.10617(9)	0.66633(11)	0.75140(8)	3.15(2)
F(3)	0.24154(11)	0.82175(11)	0.80305(8)	3.01(2)
F(4)	0.84195(9)	0.24315(11)	0.58646(7)	2.494(18)
F(5)	0.83799(10)	0.41411(10)	0.67977(8)	2.658(20)
F(6)	0.82315(9)	0.23810(11)	0.76492(7)	2.550(19)
O(1)	0.52905(11)	0.71420(11)	1.09615(8)	2.20(2)
O(2)	0.49073(10)	0.67243(11)	0.79667(8)	1.825(20)
O(3)	0.33247(11)	0.51255(12)	0.74219(9)	2.07(2)
O(4)	0.40596(11)	0.13027(11)	0.41087(8)	1.82(2)
O(5)	0.56672(11)	0.35933(11)	0.75045(8)	1.722(20)
O(6)	0.57537(11)	0.37938(11)	0.56103(8)	1.775(20)
N(1)	0.70347(13)	0.59777(14)	1.02892(10)	1.76(2)
N(2)	0.25462(13)	0.28527(13)	0.44633(10)	1.66(2)
C(1)	0.81873(16)	0.68100(19)	1.07611(12)	2.15(3)
C(2)	0.94139(18)	0.6556(2)	1.00104(15)	2.93(4)
C(3)	0.92394(17)	0.5179(2)	0.97450(16)	3.17(4)
C(4)	0.76050(16)	0.50131(18)	0.95613(13)	2.10(3)
C(5)	0.56431(16)	0.62274(16)	1.04098(11)	1.66(3)
C(6)	0.45015(15)	0.53284(16)	0.99290(12)	1.57(3)
C(7)	0.39190(17)	0.46145(18)	1.09112(13)	2.10(3)
C(8)	0.32719(15)	0.60309(17)	0.92778(12)	1.78(3)
C(9)	0.35329(15)	0.62211(16)	0.80431(12)	1.65(3)
C(10)	0.24100(16)	0.71146(18)	0.74989(13)	2.20(3)
C(11)	0.21344(16)	0.30420(18)	0.32586(12)	2.01(3)
C(12)	0.12477(17)	0.42329(18)	0.32339(13)	2.17(3)
C(13)	0.06066(17)	0.42582(19)	0.43747(14)	2.22(3)
C(14)	0.18180(17)	0.37487(18)	0.51679(13)	2.11(3)
C(15)	0.35014(14)	0.19954(15)	0.48004(11)	1.46(3)
C(16)	0.38687(14)	0.18147(16)	0.60539(11)	1.46(3)
C(17)	0.31384(17)	0.06263(17)	0.64351(13)	1.98(3)
C(18)	0.55182(15)	0.17561(16)	0.63047(11)	1.56(3)
C(19)	0.61438(15)	0.30446(16)	0.65232(12)	1.58(3)
C(20)	0.78056(16)	0.30038(17)	0.66998(12)	1.99(3)

Table 2. Atomic coordinates and B_{iso} of hydrogen atoms

atom	x	y	z	B_{iso}
H(1A)	0.8470	0.6598	1.1552	2.59
H(1B)	0.7882	0.7692	1.0716	2.59
H(2A)	0.9312	0.7065	0.9319	3.51
H(2B)	1.0364	0.6729	1.0408	3.51
H(2)	0.5142	0.6670	0.7303	2.19
H(3A)	0.9639	0.4662	1.0377	3.80
H(3B)	0.9726	0.4957	0.9062	3.80
H(3)	0.4088	0.4703	0.7471	2.49
H(4A)	0.7272	0.5151	0.8766	2.52
H(4B)	0.7307	0.4172	0.9790	2.52
H(5A)	0.5476	0.3033	0.7961	2.07
H(6)	0.4950	0.4730	0.9416	1.88
H(6A)	0.5907	0.4542	0.5783	2.13
H(7A)	0.4725	0.4236	1.1363	2.52
H(7B)	0.3257	0.3962	1.0621	2.52
H(7C)	0.3402	0.5189	1.1378	2.52
H(8A)	0.2362	0.5562	0.9331	2.13
H(8B)	0.3151	0.6853	0.9632	2.13
H(11A)	0.1553	0.2335	0.2947	2.42
H(11B)	0.2999	0.3139	0.2827	2.42
H(12A)	0.0477	0.4212	0.2619	2.61
H(12B)	0.1866	0.4969	0.3136	2.61
H(13A)	0.0348	0.5116	0.4584	2.67
H(13B)	-0.0264	0.3726	0.4375	2.67
H(14A)	0.2486	0.4419	0.5439	2.53
H(14B)	0.1429	0.3331	0.5820	2.53
H(16)	0.3483	0.2538	0.6465	1.75
H(17A)	0.3547	-0.0095	0.6068	2.38
H(17B)	0.2099	0.0672	0.6231	2.38
H(17C)	0.3302	0.0541	0.7250	2.38
H(18A)	0.5745	0.1223	0.6969	1.87
H(18B)	0.5968	0.1377	0.5660	1.87

Table 3. Bond lengths (Å)

atom	atom	distance
F(1)	C(10)	1.3358(18)
F(3)	C(10)	1.345(2)
F(5)	C(20)	1.336(2)
O(1)	C(5)	1.2408(20)
O(3)	C(9)	1.399(2)
O(5)	C(19)	1.4119(18)
N(1)	C(1)	1.476(2)
N(1)	C(5)	1.3372(19)
N(2)	C(14)	1.475(2)
C(1)	C(2)	1.523(2)
C(3)	C(4)	1.528(2)
C(6)	C(7)	1.533(2)
C(8)	C(9)	1.527(2)
C(11)	C(12)	1.521(3)
C(13)	C(14)	1.522(2)
C(16)	C(17)	1.531(2)
C(18)	C(19)	1.518(2)

atom	atom	distance
F(2)	C(10)	1.3438(18)
F(4)	C(20)	1.3344(18)
F(6)	C(20)	1.3532(18)
O(2)	C(9)	1.3948(18)
O(4)	C(15)	1.2519(18)
O(6)	C(19)	1.3844(18)
N(1)	C(4)	1.476(2)
N(2)	C(11)	1.4786(19)
N(2)	C(15)	1.3224(19)
C(2)	C(3)	1.521(3)
C(5)	C(6)	1.518(2)
C(6)	C(8)	1.535(2)
C(9)	C(10)	1.529(2)
C(12)	C(13)	1.526(2)
C(15)	C(16)	1.5264(18)
C(16)	C(18)	1.5411(19)
C(19)	C(20)	1.543(2)

Table 4. Anisotropic displacement parameters[n]

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F(1)	0.0412(5)	0.0493(7)	0.0235(4)	0.0107(5)	0.0014(4)	0.0107(5)
F(2)	0.0210(5)	0.0544(8)	0.0436(6)	0.0064(5)	-0.0010(4)	0.0096(5)
F(3)	0.0482(6)	0.0295(7)	0.0369(5)	0.0148(5)	0.0057(4)	0.0024(5)
F(4)	0.0232(4)	0.0420(7)	0.0305(5)	-0.0010(4)	0.0088(3)	-0.0053(5)
F(5)	0.0281(5)	0.0350(7)	0.0380(5)	-0.0127(4)	0.0032(4)	-0.0042(5)
F(6)	0.0265(4)	0.0421(7)	0.0273(5)	0.0012(4)	-0.0050(4)	0.0045(5)
O(1)	0.0341(6)	0.0251(8)	0.0256(5)	-0.0023(5)	0.0095(4)	-0.0065(5)
O(2)	0.0222(5)	0.0301(7)	0.0175(5)	-0.0028(5)	0.0048(4)	-0.0019(5)
O(3)	0.0231(5)	0.0291(7)	0.0261(6)	-0.0001(5)	-0.0013(4)	-0.0064(5)
O(4)	0.0275(5)	0.0226(7)	0.0194(5)	0.0014(5)	0.0047(4)	-0.0011(5)
O(5)	0.0274(5)	0.0200(7)	0.0186(5)	-0.0027(5)	0.0055(4)	-0.0002(5)
O(6)	0.0306(6)	0.0181(7)	0.0187(5)	-0.0035(5)	0.0007(4)	0.0014(5)
N(1)	0.0219(6)	0.0255(9)	0.0197(6)	-0.0021(6)	0.0023(5)	-0.0022(6)
N(2)	0.0198(6)	0.0246(9)	0.0185(6)	0.0002(6)	0.0012(5)	-0.0022(5)
C(1)	0.0278(8)	0.0313(11)	0.0222(8)	-0.0089(8)	-0.0016(6)	-0.0019(7)
C(2)	0.0257(8)	0.0527(14)	0.0329(9)	-0.0127(8)	0.0029(7)	-0.0098(9)
C(3)	0.0231(8)	0.0587(15)	0.0388(10)	0.0048(9)	0.0036(7)	-0.0118(10)
C(4)	0.0232(7)	0.0301(11)	0.0264(8)	0.0028(7)	0.0014(6)	-0.0044(7)
C(5)	0.0256(8)	0.0238(10)	0.0141(7)	0.0001(7)	0.0047(6)	0.0022(7)
C(6)	0.0217(7)	0.0199(10)	0.0183(7)	0.0021(6)	0.0035(5)	-0.0008(7)
C(7)	0.0285(8)	0.0278(11)	0.0231(8)	-0.0051(7)	0.0006(6)	0.0012(7)
C(8)	0.0187(7)	0.0273(10)	0.0221(7)	0.0006(7)	0.0053(6)	0.0026(7)
C(9)	0.0184(7)	0.0231(10)	0.0213(7)	-0.0010(6)	0.0024(6)	-0.0006(7)
C(10)	0.0260(8)	0.0333(12)	0.0246(8)	0.0055(7)	0.0041(6)	0.0018(7)
C(11)	0.0250(7)	0.0321(11)	0.0193(7)	-0.0015(7)	0.0002(6)	0.0022(7)
C(12)	0.0262(8)	0.0269(11)	0.0291(8)	0.0003(7)	-0.0005(6)	0.0047(7)
C(13)	0.0223(7)	0.0301(11)	0.0320(8)	0.0045(7)	0.0010(6)	0.0017(8)
C(14)	0.0236(7)	0.0309(11)	0.0259(8)	0.0066(7)	0.0028(6)	-0.0046(7)
C(15)	0.0176(7)	0.0193(10)	0.0190(7)	-0.0043(6)	0.0047(5)	-0.0012(7)
C(16)	0.0205(7)	0.0177(9)	0.0177(7)	0.0003(6)	0.0039(5)	-0.0021(6)
C(17)	0.0293(8)	0.0286(11)	0.0179(7)	-0.0069(7)	0.0045(6)	-0.0015(7)
C(18)	0.0217(7)	0.0208(9)	0.0169(7)	0.0009(7)	0.0031(5)	0.0002(7)
C(19)	0.0222(7)	0.0223(10)	0.0157(7)	-0.0010(7)	0.0033(5)	0.0009(6)
C(20)	0.0248(8)	0.0289(11)	0.0218(8)	-0.0052(7)	0.0020(6)	-0.0004(7)

[a] "A short history of SHELX". Sheldrick, G.M. *Acta Cryst.* **2008**, A64, 112-122.

[b] DIRDIF99: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1999). The DIRDIF-99 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

[c] Flack, H. D. *Acta Cryst.* **1983**, A39, 876-881.

[d] Hooft, R.W.W., Straver, L.H., Spek, A.L. *J. Appl. Cryst.*, **2008**, 41, 96-103.

[e] (a) A.L.Spek (2010) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands (b) A.L.Spek, *Acta Cryst.* **2009**, D65, 148-155.

[f] Least Squares function minimized: (SHELXL97) $\Sigma w(Fo^2-Fc^2)^2$ where w = Least Squares weights.

[g] Standard deviation of an observation of unit weight: $[\Sigma w(Fo^2-Fc^2)^2/(No-Nv)]^{1/2}$
where: No = number of observations, Nv = number of variables

[h] Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

[i] Ibers, J. A. & Hamilton, W. C.; *Acta Cryst*. **1964,** 17, 781.

[j] Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

[k] Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

[l] CrystalStructure 3.8: Crystal Structure Analysis Package, Rigaku and Rigaku Americas (2000-2007). 9009 New Trails Dr. The Woodlands TX 77381 USA.

[m] $B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

[n] The general temperature factor expression: $\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$