Experimental Lineage and Functional Analysis of a Remotely Directed Peptide Epoxidation Catalyst

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Supporting Information

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General information

NMR spectra were acquired at ambient temperature. The concentration of the peptide NMR samples was 20 mM with respect to peptide, unless otherwise specified. Spectra were processed using MestReNova 8.1 using default phasing and baseline correction features. ^{1}H NMR spectra are calibrated to an internal TMS standard (0.00 ppm) or residual solvent peak (7.26 ppm in $CDCl_3$). ^{13}C NMR spectra were completely proton decoupled and are calibrated to $CHCl_3$ (77.16 ppm). NMR spectral data are reported as chemical shift (multiplicity, coupling constants, integration). Multiplets were reported from the "multiplet analysis" feature of MestreNova with some manual adjustment. Multiplicity is reported as follows: singlet (s), doublet (d), doublet of doubles (dd), triplet (t), quartet (q), and multiplet (m), *etc*.

Gas chromatography (GC) was performed on an instrument with two HP-5 columns (50 m, 0.320 mm diameter, 0.25 μm film thickness) and flame ionization detectors using He as a carrier gas. Site-selectivity ratios for the monoepoxides of farnesol are reported as the area of the indicated peak to the sum of the areas of all the monoepoxide products. For method detail and characterization of farnesol oxidation products, see the Supplementary Information of Lichtor, P. A.; Miller, S. J. *Nature Chem*. **2012**, *4*, 990-995. Details pertaining to other GC methods are included where relevant.

Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F_{254} pre-coated plates (0.25 mm thickness) and visualized using irradiation by a UV lamp and/or staining with I_2/silica, and/or cerium ammonium molybdate (CAM). Flash column chromatography was perfomed using Silica Gel 60 Å (32-63 micron).

Peptide sequencing and high-resolution liquid chromatography-mass spectrometry (HRMS) was performed on a Waters XEVO instrument equipped with ESI, a QToF mass spectrometer, and a photodiode array detector.

Reverse phase chromatography was performed with a Biotage instrument.

On-bead library synthesis and screening

Study of split-and-pool libraries

Split-and-pool libraries were synthesized and screened as described previously.[1] Briefly described, the peptide libraries were synthesized on Polystyrene A NH_2 macrobeads (500-560 μm) using double deprotections and double couplings to Fmoc-protected amino acids (except when coupling to the N-terminal Boc-Asp(OFm)-OH). Before synthesizing peptide libraries, the resin was first coupled to Fmoc-Met-OH and then to three Fmoc-Ahx-OH (Ahx = 6-aminohexanoic acid) residues.

Study of parallel synthesis library

Peptides sequences that were evaluated in Table 1 were synthesized on A RAM macrobeads (500-560 μm), which were first coupled to a single Fmoc-Ahx-OH residue (3 equiv; 3 equiv HOBt, 3 equiv HBTU; 6 equiv iPr_2EtN; DMF).

Peptide sequences were then attached to the resin by first deprotecting with two ~20 min treatments with 20% (v/v) piperidine in DMF and then using single couplings in DMF with Fmoc-protected amino acids (4 equiv), HBTU (4 equiv), HOBt•H_2O (4 equiv), and iPr_2EtN (8 equiv). Upon addition of the coupling reagents, the resin mixture was sealed and generally mixed for 3-6 h on a rotary mixer, and then drained, washing with a combination of DMF, DCM, and/or CH_3OH. Following the final coupling to Boc-Asp(OFm)-OH, the resin was then treated with two ~20 min treatments with 20% (v/v) piperidine in DMF, and then washed with copious DMF, DCM, and/or CH_3OH.

[1] Lichtor, P. A.; Miller, S. J. *Nature Chem*. **2012**, *4*, 990-995.

Some of the on-bead synthesized peptides were checked by treating a single bead with 100% TFA for 30 min and then concentrating the resulting mixture under N_2. The resulting cleaved material was analyzed by LC/MS/MS and confirmed to contain expected peptide/fragment masses.

To 400 μL glass reaction vials containing a single bead was added 0.5 μL of an aqueous solution of H_2O_2 (2 M, 1 equiv). Immediately following the H_2O_2 addition, 5.05 μL of a DCM solution containing farnesol (1 μmol, 1 equiv), DIC (0.3 μmol, 0.3 equiv), HOBt•H_2O (0.1 μmol, 0.1 equiv), and DMAP (0.1 μmol, 0.1 equiv) was then added to start the reaction. The vials were sealed and allowed to stand for 12 h before quenching with 20 μL of a saturated aqueous solution of Na_2SO_3, vortexing with additional 220 μL hexanes, and analyzing by GC.

Testing, synthesis, and characterization of truncated peptides

General procedure for screening truncated catalyst analogs

Peptide (0.1 equiv) was added into a tared screw cap test tube with DCM. The solvent was concentrated, the tube was weighed, and the peptide mass was determined. Farnesol (1.0 equiv) was weighed into the tube and then a stir bar was added. A solution of HOBt•H_2O (0.1 equiv) and DMAP (0.1 equiv) in $CHCl_3$ (to bring reaction to 0.2 M with respect to farnesol; solvent passed through basic alumina) was then added, washing down the sides of the tube, followed by H_2O_2 (1.5 equiv, 30% w/w aqueous solution). The tube was placed in an ice bath and chilled. DIC (1.1 equiv) was added and the tube was immediately placed in an iPrOH bath maintained at –20 ºC by cryostat. The reaction was stirred for 48 h before quenching with saturated aqueous Na_2SO_3, warming to room temperature, and then mixing vigorously with additional saturated aqueous $NaHCO_3$ and hexanes. After the layers

separated, an aliquot of the organic layer was removed, diluted with hexanes and EtOAc and analyzed by GC.

General protocols for truncated peptide synthesis

Solution peptide synthesis. To peptide acid (1 equiv) was added amine coupling partner (1.0-1.1 equiv), EDC•HCl (1.1 equiv), HOBt•H_2O (1.1 equiv), and DCM (to 0.1 M in peptide acid). iPr_2EtN or Et_3N (1.2 equiv) was also added if the amine coupling partner was the hydrochloride salt. The resulting solution was allowed to stir until the reaction was deemed complete as determined by LCMS, usually 3-48 h. The reaction solution was diluted with additional DCM and then washed with aqueous 0.5 M citric acid, half-saturated brine, and saturated aqueous $NaHCO_3$. The combined organics were dried over Na_2SO_4, filtered, and concentrated.

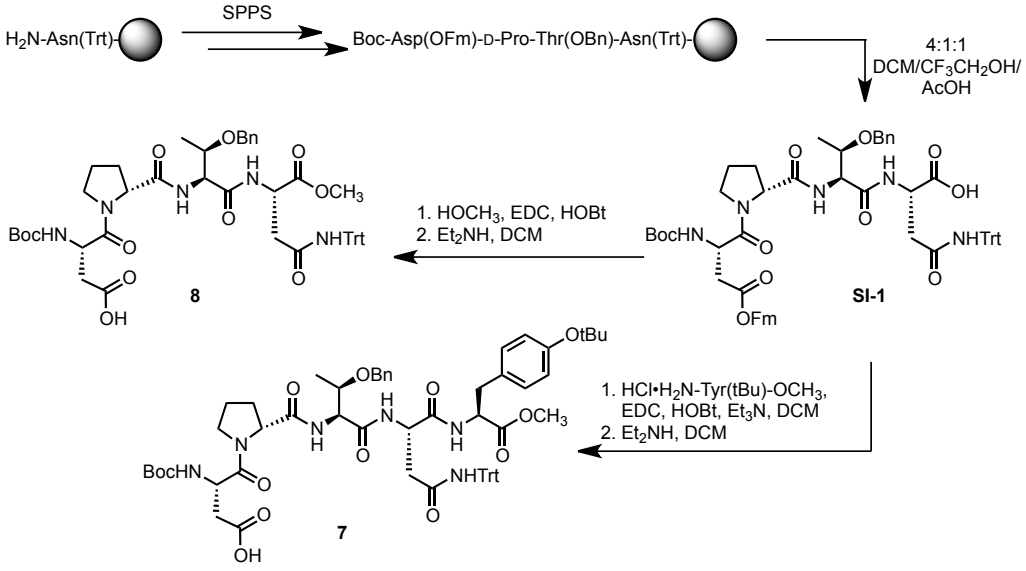
Solid phase peptide coupling protocol. To pre-swollen resin was added Fmoc-protected amino acid (3 equiv), HBTU (3 equiv), HOBt•H_2O (3 equiv) with DMF, followed by iPr_2EtN (6 equiv). The resin mixture was sealed and mixed for 3-6 h on a rotary mixer and then drained, washing with a combination of DMF, DCM, and/or CH_3OH. If required for the next coupling, the Fmoc-protecting group was removed with two treatments of 20% piperidine in DMF (v/v) for 20 min each.

Standard Fm-ester deprotection. To protected peptide was added 1:1 (v/v) solution of Et_2NH and DCM. The resulting solution was swirled occasionally over the course of 30-60 min before concentrating via rotary evaporator. The resulting material was dissolved in DCM and then concentrated further. Typically, the crude material was loaded on a silica gel column as a solution in DCM, where it was eluted with a gradient of 1% CH_3OH to 4% CH_3OH in 1% AcOH/DCM.

Hydrogenolysis Protocol. To a flask containing peptide and stir bar was added a slurry of 10% (wt.) Pd/C in CH_3OH (~0.1 M). The flask was sealed with a septum and the reaction atmosphere was flushed

first with N_2, and then H_2. The reaction was allowed to stir under pressure of a balloon filled with H_2. Once the reaction was deemed complete as determined by LCMS, the reaction atmosphere was flushed with N_2. The crude reaction mixture was then filtered through celite and concentrated.

Synthesis and characterization of truncated peptides



SI Figure 1. Synthesis of peptides **7** and **8**.

Synthesis of peptide **7** and **8** began from common intermediate **SI-1** (SI Figure 1), which was synthesized starting with 2-chlorotrityl resin, preloaded with Asn(Trt), and then coupling the appropriate amino acid monomers (Fmoc-Thr(Bn)-OH, Fmoc-DPro-OH, and then Boc-Asp(OFm)-OH) using the Solid Phase Peptide Coupling protocol. Resin was cleaved with a 4:1:1 mixture of DCM: 2,2,2-trifluoroethanol: acetic acid, treating for 30-60 min before draining. The resulting solution, along with washes, was concentrated a couple of times with additional toluene.

Intermediate **SI-1** was coupled to HCl•H_2N-Tyr(tBu)-OCH_3 (1.1 equiv) using the Solution Peptide Synthesis protocol with additional Et_3N. After work-up, the crude material was deprotected using the

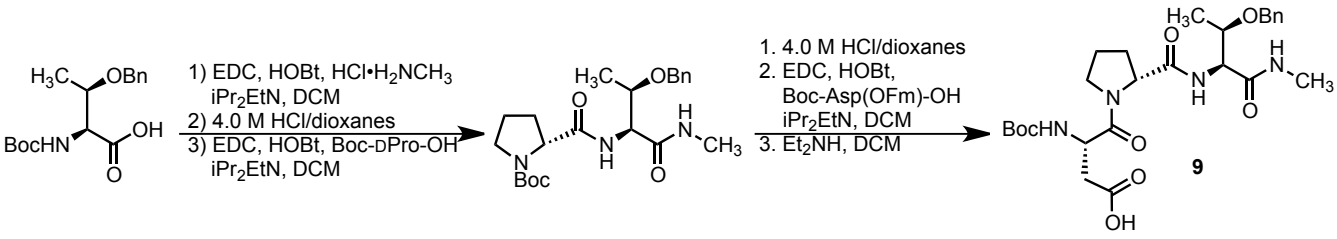
Standard Fm-ester Deprotection protocol, and upon concentration, was purified with a silica gel column eluted with a gradient of 1% to 4% CH_3OH in 1% AcOH/DCM (as described in the standard protocol). A portion of this material was further purified by reverse phase chromatography using a Biotage C18 column eluting with a gradient of 40% CH_3OH to 100% CH_3OH in water with 0.1% formic acid.

Peptide **7**: white solid. **TLC**: 4% CH_3OH, 1% AcOH in DCM (R_f =0.38). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.52 (s, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.10 (m, 20H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 9.2 Hz, 1H), 6.22 (d, *J* = 10.3 Hz, 1H), 4.89 – 4.82 (m, 1H), 4.81 – 4.73 (m, 1H), 4.63 – 4.55 (m, 1H), 4.49, 4.41 (ABq, J_{AB} = 11.4 Hz, 2H), 4.47 – 4.42 (m, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 3.98 (t, *J* = 7.4 Hz, 1H), 3.71 – 3.50 (m, 5H), 3.12 (dd, *J* = 15.1, 9.6 Hz, 1H), 3.02 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.96 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.74 – 2.65 (m, 1H), 2.63 – 2.54 (m, 2H), 2.17 – 1.97 (m, 3H), 1.90 – 1.79 (m, 1H), 1.43 (s, 9H), 1.31 (s, 10H), 1.17 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.5, 172.4, 171.6, 171.1, 170.7, 170.1, 169.1, 155.5, 154.4, 144.8, 137.9, 130.9, 130.0, 129.0, 128.6, 128.2, 128.0, 127.9, 127.0, 124.3, 80.4, 78.4, 73.8, 72.4, 70.7, 61.5, 57.9, 54.6, 52.3, 50.3, 49.6, 47.9, 37.6, 37.1, 36.7, 29.0, 28.9, 28.4, 25.9, 17.3. **IR** (film in/from DCM, cm^{-1}): 3311, 2977, 1672, 1632, 1505, 1447, 1366, 1236, 1208, 1161, 1091, 1048, 1026. **HRMS**: calculated mass for $[C_{62}H_{74}N_6O_{13}+H]^+$: 1111.5387, ESI+ found 1111.5427.

Peptide **8**: white solid. Intermediate **SI-1** was coupled to methanol using the Solution Peptide Synthesis protocol, except instead of performing the reaction in DCM, it was performed in 0.2 M methanol. After work-up, the crude reaction mixture was purified by flash silica gel chromatography with a gradient of 0% to 30% acetone in toluene (**TLC**: 25% acetone in toluene, R_f = 0.45, visualized by UV, I_2, and CAM). The resulting material was deprotected using the Standard Fm-ester Deprotection protocol, and upon concentration, was purified with a silica gel column eluted with a gradient of 1% to

4% CH_3OH in 1% AcOH/DCM (as described in the protocol). A portion of this material was further purified by reverse phase chromatography using a Biotage C18 column eluting with a gradient of 40% CH_3OH to 100% CH_3OH in water with 0.1% formic acid.

Peptide **8**: white solid. **TLC**: 4% CH_3OH, 1% AcOH, DCM (R_f =0.32). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.35 (d, *J* = 6.9 Hz, 1H), 7.33 (d, *J* = 4.3 Hz, 4H), 7.36 – 7.18 (m, 20H), 7.16 (s, 1H), 6.65 (d, *J* = 9.2 Hz, 1H), 6.26 (d, *J* = 10.4 Hz, 1H), 4.67 (dt, *J* = 10.5, 4.0 Hz, 1H), 4.53 (apparent d, *J* = 11.3 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.37 – 4.27 (m, 2H), 4.12 (t, *J* = 7.8 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.65 – 3.53 (m, 4H), 3.38 (dd, *J* = 14.8, 10.1 Hz, 1H), 2.75 (dd, *J* = 14.8, 3.7 Hz, 1H), 2.61 (dd, *J* = 16.8, 3.5 Hz, 1H), 2.39 (dd, *J* = 16.7, 4.4 Hz, 1H), 2.22 – 2.00 (m, 3H), 1.91 – 1.79 (m, 1H), 1.47 (s, 9H), 1.15 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.0, 172.5, 171.9, 171.3, 170.9, 170.2, 155.4, 144.2, 138.1, 128.9, 128.6, 128.1, 128.1, 128.0, 127.2, 80.3, 73.2, 72.1, 71.2, 62.3, 57.6, 52.5, 50.7, 49.9, 48.0, 38.8, 35.4, 29.0, 28.5, 26.2, 18.1. **IR** (film in/from DCM, cm^{-1}): 3322, 2978, 1669, 1632, 1493, 1447, 1367, 1285, 1265, 1231, 1208, 1162, 1080, 1047, 1026. **HRMS**: calculated mass for $[C_{49}H_{57}N_5O_{11}+H]^+$: 892.4127, ESI+ found 892.4189.



SI Figure 2. Synthesis of peptide **9**.

The standard Solution Peptide Coupling protocol was followed using Boc-Thr(Bn)-OH and CH_3NH_2•HCl, with iPr_2EtN (SI Figure 2). After 16 h, the reaction was worked up and then concentrated

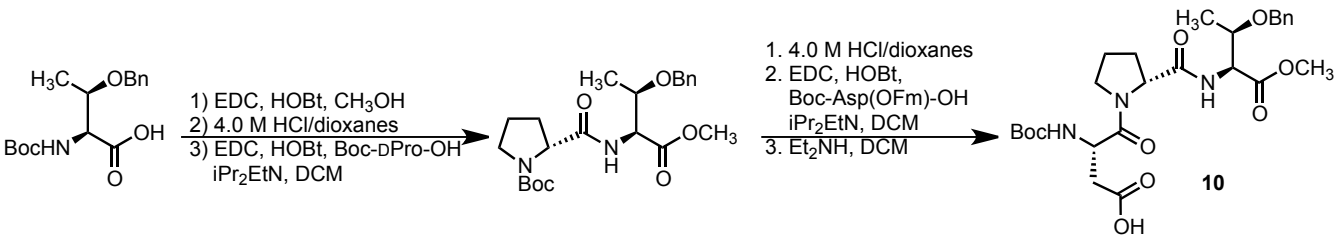
to ultimately yield a white powder. The *N*-terminus of Boc-Thr(Bn)-$NHCH_3$ was deprotected by treating with 4.0 M HCl/dioxanes for ~1.5 h before concentrating the resulting solution under a stream of N_2. The resulting yellow oil was dissolved in DCM and concentrated further. The material was then coupled to Boc-DPro-OH using the standard Solution Peptide Synthesis protocol with iPr_2EtN. After running for ~21 h, the reaction was worked up and concentrated to yield a whitish foam.

The resulting material was deprotected using 4.0 M HCl/dioxanes as before for ~2 h. Following HCl removal and concentration, DCM was added and the peptide was coupled to Boc-Asp(OFm)-OH using the standard Solution Peptide Coupling protocol with iPr_2EtN, running the reaction for ~32 h. Following work-up, the resulting yellowish thick oil was purified by flash column chromatography with a silica gel column packed in 10% acetone in toluene. The material was eluted with a gradient of 10% to 30% acetone in toluene (**TLC**: 20% acetone in toluene, R_f = ~0.15, visualized by UV).

The tripeptide solid was subjected to the Standard Fm-ester Deprotection protocol. After a silica gel column, as the protocol describes, the resulting material was further purified on a C18 reverse phase column with a gradient of 40% MeOH in 0.1% (v/v) aqueous formic acid to 100% MeOH. Desired fractions were concentrated.

Peptide **9**: white solid. **TLC**: 4% CH_3OH, 1% AcOH, DCM (R_f =0.23). NMR chemical shift assignments made by ^1H-^1H gCOSY spectrum. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 6H, Ar-*H*'s and N*H*CH_3), 7.15 (d, *J* = 8.6 Hz, 1H, N*H*-Thr), 5.55 (d, *J* = 9.3 Hz, 1H, N*H*Boc), 4.85 – 4.77 (m, 1H, α-Asp), 4.54, 4.51 (ABq, J_{AB} = 11.6 Hz, 2H, -OCH_2Ph), 4.46 – 4.35 (m, 2H, α/β-Thr), 4.31 (t, *J* = 6.8 Hz, 1H, α-DPro), 3.78 – 3.63 (m, 2H, δ-DPro), 2.85 – 2.76 (m, 4H, -NHCH_3 and β-Asp), 2.69 (dd, *J* = 16.0, 4.4 Hz, 1H, β-Asp), 2.21 – 2.03 (m, 3H, β/ɣ-DPro), 1.99 – 1.88 (m, 1H, ɣ-DPro), 1.44 (s, 9H, Boc), 1.15 (d, *J* = 6.3 Hz, 3H, ɣ-Thr). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.0, 172.5, 170.5, 170.1, 155.3, 137.9, 128.6, 128.1, 128.0, 80.6, 74.2, 72.3, 61.4, 57.6, 49.3, 47.8, 36.8, 29.0, 28.4, 26.7, 25.6,

17.1. **IR** (film in/from DCM, cm^{-1}): 3284, 3094, 2978, 2878, 1708, 1688, 1630, 1572, 1517, 1452, 1420, 1391, 1366, 1293, 1246, 1206, 1159, 1101, 1048, 1002. **HRMS**: calculated mass for $[C_{26}H_{38}N_4O_8+H]^+$: 535.2762, ESI+ found 535.2778.



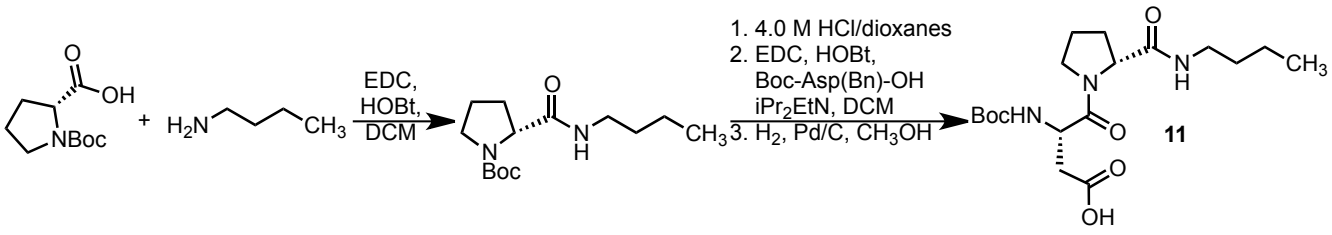
SI Figure 3. Synthesis of peptide **10**.

The standard Solution Peptide Coupling protocol was followed using Boc-Thr(Bn)-OH and CH_3OH, which was used as a solvent instead of DCM (SI Figure 3). After 21 h, the crude reaction was concentrated using a rotary evaporator. The resulting material was dissolved in DCM and then worked up as described in the standard protocol. The *N*-terminus of Boc-Thr(Bn)-OCH_3 was deprotected by treating with 4.0 M HCl/dioxanes for ~50 min before concentrating the resulting solution under a stream of N_2. The resulting yellow oil was dissolved in DCM and concentrated further by rotary evaporation. The material was then coupled to Boc-DPro-OH using the standard Solution Peptide Coupling protocol with iPr_2EtN. After running for ~14 h, the reaction was worked up and concentrated.

The resulting off-white solid was deprotected using 4.0 M HCl/dioxanes as before, though for ~1.2 h. Following HCl removal and concentration, the resulting yellowish solid was dissolved in DCM and then coupled to Boc-Asp(OFm)-OH using the standard Solution Peptide Synthesis protocol with iPr_2EtN, running the reaction for ~20 h. Following work-up, the resulting white solid was purified by flash column chromatography with a silica gel column packed in toluene. The material was eluted with a gradient of 0% to 17% acetone in toluene to yield, upon concentration, a clear, colorless oil, which

turned to a solid upon standing under vacuum (**TLC**: 20% acetone in toluene (R_f =0.45)). The tripeptide solid was subjected to the Standard Fm-ester Deprotection protocol. After a silica gel column, as the protocol describes, the resulting yellow oil was further purified on a C18 reverse phase column with a gradient of 40% MeOH in 0.1% (v/v) aqueous formic acid to 100% MeOH. Desired fractions were concentrated.

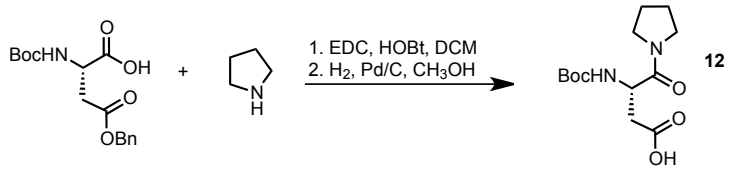
Peptide **10**: Clear, colorless, oily looking solid. **TLC**: 4% CH_3OH, 1% AcOH in DCM (R_f =0.23), visualized with CAM. Material was determined to contain a mixture of conformational isomers using a TOCSY experiment. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 9.5 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.32 – 7.23 (m, 3H), 5.72 (d, *J* = 9.2 Hz, 1H), 4.84 (td, *J* = 8.9, 4.2 Hz, 1H), 4.79 – 4.67 (m, 1H), 4.66 – 4.53 (m, 2H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.09 (qd, *J* = 6.3, 2.3 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.62 (s, 3H), 2.93 (dd, *J* = 16.4, 8.4 Hz, 1H), 2.75 (dd, *J* = 16.3, 4.1 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.18 – 2.06 (m, 1H), 2.06 – 1.93 (m, 2H), 1.43 (s, 9H), 1.21 (d, *J* = 6.3 Hz, 3H). Minor conformer peaks were also observed: 7.00 (d, *J* = 9.3 Hz), 5.42 (d, *J* = 9.4 Hz), 5.01 (bs), 4.22 – 4.14 (m), 3.64 (s), 2.28 – 2.20 (m). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.5, 171.6, 171.2, 170.9, 155.4, 137.9, 128.5, 127.9, 127.9, 80.5, 73.9, 70.7, 60.1, 56.8, 52.4, 49.3, 47.2, 37.0, 28.4, 27.3, 25.0, 16.3. **IR** (film in/from DCM, cm^{-1}): 3307, 2978, 1710, 1685, 1640, 1518, 1437, 1367, 1268, 1249, 1207, 1159, 1084, 1048, 1026, 1000. **HRMS**: calculated mass for $[C_{26}H_{37}N_3O_9+H]^+$: 536.2603, ESI+ found 536.2643.



SI Figure 4. Synthesis of peptide **11**.

Boc-DPro-OH was coupled to *n*-butyl amine using the Solution Peptide Synthesis Protocol (SI Figure 4). Following work-up, the Boc group was removed by treatment with a 4.0 M solution of HCl in dioxanes. After 30 min, the solution was concentrated, dissolved in DCM, and then concentrated again. To the resulting crude oil was added coupling reagents, iPr_2EtN, and Boc-Asp(Bn)-OH, following the Solution Peptide Synthesis Protocol. After work-up, the material was dissolved in CH_3OH and purified using a Biotage C18 column with a gradient of 20% to 100% CH_3CN in water. Desired fractions were concentrated and the resulting material was deprotected following the Standard Hydrogenolysis Protocol. Finally, the resulting material was purified on a Biotage C18 column running a gradient of 20% to 100% CH_3CN in water with 0.1% formic acid. Desired fractions were collected and concentrated.

Peptide **11**: white solid. Compound exists as a putative mixture of conformational isomers. **TLC**: 4% CH_3OH, 1% AcOH in DCM (R_f =0.18), visualized with I_2/silica. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.96 – 6.85 (m, 1H), 5.65 – 5.53 (m, 1H), 4.65 (apparent q, *J* = 6.9 Hz, 1H), 4.53 (d, *J* = 5.4 Hz, 1H), 3.90 – 3.81 (m, 1H), 3.70 (q, *J* = 7.9 Hz, 1H), 3.23 (dt, *J* = 13.2, 8.0 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.85 (dd, *J* = 16.4, 7.3 Hz, 1H), 2.69 (dd, *J* = 16.4, 5.8 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.08 – 1.92 (m, 3H), 1.53 – 1.36 (m, 11H), 1.30 (q, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). Minor conformer peaks also observed at 5.49 (d, *J* = 9.8 Hz), 4.73 – 4.69 (m), 3.59 (d, *J* = 8.3 Hz), 2.18 – 2.08 (m). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.0, 171.2, 171.0, 155.8, 80.8, 61.0, 49.4, 47.7, 39.8, 39.5, 36.4, 31.6, 28.9, 28.4, 24.7, 20.2, 13.9. **IR** (film in/from DCM, cm^{-1}): 3341, 2965, 2935, 2875, 1713, 1691, 1547, 1506, 1418, 1408, 1393, 1365, 1348, 1327, 1269, 1255, 1181, 1158, 1077, 1046, 1015. **HRMS**: calculated mass for $[C_{18}H_{31}N_3O_6+H]^+$: 386.2286, ESI+ found 386.2314.



SI Figure 5. Synthesis of peptide **12**.

The Solution Peptide Synthesis protocol was used to couple Boc-Asp(Bn)-OH to pyrrolidine (SI Figure 5). Following work-up, the resulting oil was purified by flash silica gel chromatography, eluting with a gradient of 15% to 60% EtOAc in hexanes. Desired fractions were concentrated to yield a clear, colorless oil (**TLC**: 60% EtOAc in hexanes (R_f =0.40)). Much of the resulting material was deprotected using the Standard Hydrogenolysis Protocol, reacting for ~6.5 h. Material was further purified by elution through a Biotage C18 column with a gradient of 20% to 100% CH_3OH in aqueous 0.1% formic acid.

Peptide **12**: white solid. **TLC**: 4% CH_3OH, 1% AcOH in DCM (R_f =0.23), visualized with I_2/silica. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.64 (d, *J* = 9.3 Hz, 1H), 4.87 – 4.77 (m, 1H), 3.72 – 3.57 (m, 2H), 3.47 (td, *J* = 6.9, 1.6 Hz, 2H), 2.82 (dd, *J* = 15.9, 6.6 Hz, 1H), 2.71 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.93 – 1.81 (m, 2H), 1.44 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.1, 169.9, 155.4, 80.5, 49.0, 47.0, 46.6, 37.8, 28.5, 26.2, 24.3. **IR** (film in/from DCM, cm^{-1}): 3308, 2977, 1706, 1609, 1515, 1454, 1392, 1367, 1342, 1250, 1160, 1046, 1023, 1001. **HRMS**: calculated mass for $[C_{13}H_{22}N_2O_5+H]^+$: 287.1601, ESI+ found 287.1596.

NMR experiments and modeling of peptide 1

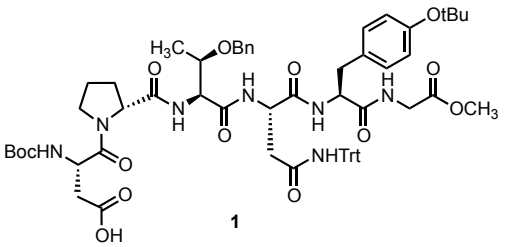
NMR experiments

NMR spectra were acquired on a Varian Inova 500 MHz spectrometer running VnmrJ 2.2D with pulse sequences provided by Varian. A combination of 1D ^{1}H NMR with 2D gCOSY, TOCSY, and ROESY experiments (provided by Varian) were used to assign proton chemical shifts. T1 relaxation times were measured by performing an inversion-recovery experiment (INVREC, provided by Varian), acquiring ^{1}H NMR spectra with different relaxation delay times (d1) ranging from (0.0625 s to 30 s). The intensity (M_z) of each peak was measured as a function of time (t) and fit to Equation 1 using Prism Graphing Software. Measurements are shown in SI Table 1. All reported NMR data were collected on 20 mM samples of peptide in $CDCl_3$.

$$M_z = M_{01} + 2M_{02}e^{-t/T1} \quad (1)$$

SI Table 1. T1 relaxation values determined for protons within peptide **1**.

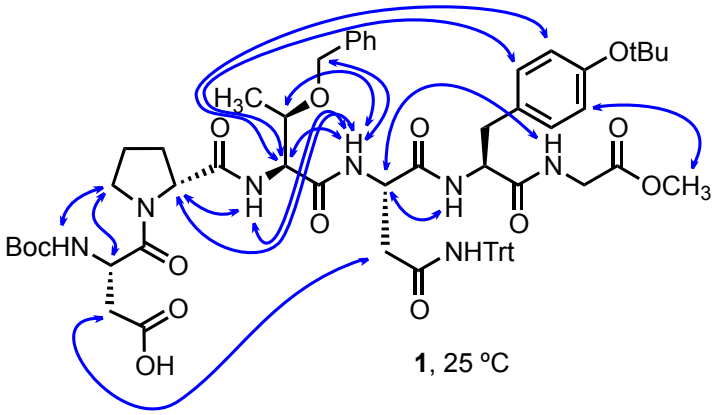
Entry	Signal	T1 (s)	Entry	Signal	T1 (s)
1	Boc(tBu)	0.395	18	Aryl peaks	0.854
2	NH-Asp	0.576	19	NH-Asn(Trt)	0.392
3	α-Asp	0.496	20	α-Asn(Trt)	0.590
4	β-Asp	0.337	21	β-Asn(Trt)	0.279
5	β-Asp	0.310	22	β-Asn(Trt)	0.285
6	α-DPro	0.406	23	δ-Asn(Trt)	0.319
7	β/ɣ-DPro	0.441	24	NH-Tyr	0.434
8	β-DPro	0.419	25	α-Tyr(tBu)	0.713
9	ɣ-DPro	0.408	26	β-Tyr(tBu)	0.337
10	δ-DPro	0.341	27	β-Tyr(tBu)	0.341
11	δ-DPro	0.440	28	δ-Tyr(tBu)	0.885
12	NH-Thr(Bn)	0.350	29	ε-Tyr(tBu)	1.068
13	α-Thr(Bn)	0.798	30	Tyr(tBu)	0.796
14	β-Thr(Bn)	0.669	31	NH-Gly	0.593
15	ɣ-Thr(Bn)	0.396	32	α-Gly	0.510
16	δ-Thr(Bn)	0.556	33	α-Gly	0.494
17	δ-Thr(Bn)	0.550	34	OCH_3	0.884



1

ROESY data was acquired with a 200 ms mixing time; spectral width of 5102.4 Hz in both F1 and F2; 765 points in t2 and 512 points in t1; 128 scans; relaxation delay (d1) of 3.06 s (three times the highest T1 relaxation of 1.07 s less acquisition time of 0.15 s); and at 25 ºC. Data were processed using MestReNova version 8.1.1-11591 using zerofilling to bring the spectral size to 1024, 1024; automatic phasing with manual adjustments; apodization with a Gaussian function; and automatic baseline correction with a polynomial fit.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) δ 7.61 – 7.53 (m, 2H, N*H*-Asn and Asn(N*H*)), 7.31 – 7.14 (m, 20H, Trt and Bn aryl peaks), 7.14 – 7.09 (m, 1H, N*H*-Gly), 7.07 (d, J = 8.4 Hz, 2H, δ-Tyr), 6.95 (d, J = 8.2 Hz, 1H, N*H*-Tyr), 6.89 (d, J = 8.4 Hz, 1H, ε-Tyr), 6.69 (d, J = 9.1 Hz, 1H, N*H*-Thr), 6.35 (d, J = 10.4 Hz, 1H, N*H*-Asp), 4.80 (dt, J = 10.2, 5.6 Hz, 1H, α-Asp), 4.67 (ddd, J = 11.2, 8.2, 5.3 Hz, 1H, α-Asn), 4.59 – 4.52 (m, 1H, α-Tyr), 4.49, 4.38 (ABq, J_{AB} = 11.4 Hz, 2H, Thr(CH_2Ph), 4.49 – 4.43 (m, 1H, β-Thr), 4.33 – 4.27 (m, 1H, α-Thr), 4.12 (t, J = 7.3 Hz, 1H, α-DPro), 3.77 (dd, J = 17.6, 6.8 Hz, 1H, α-Gly), 3.73 – 3.61 (m, 2H, δ-DPro, individual protons assigned in F2 of TOCSY spectrum to be 3.69 and 3.64), 3.58 (s, 3H, OCH_3), 3.42 (dd, J = 15.9, 11.2 Hz, 1H, β-Asn), 3.29 (dd, J = 14.2, 6.1 Hz, 1H, β-Tyr), 2.99 (dd, J = 14.2, 5.6 Hz, 1H, β-Tyr), 2.84 (dd, J = 17.6, 4.9 Hz, 1H, α-Gly), 2.77 (dd, J = 16.5, 6.1 Hz, 1H, β-Asp), 2.57 (dd, J = 16.4, 4.0 Hz, 1H, β-Asp), 2.47 (dd, J = 15.8, 5.3 Hz, 1H, β-Asn), 2.23 – 2.11 (m, 2H, β/γ-DPro), 2.11 – 1.98 (m, 1H, β-DPro), 1.95 – 1.82 (m, 1H, γ-DPro), 1.47 (s, 9H, Boc-tBu), 1.32 (s, 9H, Tyr(tBu)), 1.19 (d, J = 6.3 Hz, 3H, γ-Thr).



SI Figure 6. Unabridged ROESY correlation map of peptide **1** in $CDCl_3$ at 25 ºC. The crosspeaks assigned to both N*H*-Asn and Asn(N*H*) were difficult to resolve; thus, ROESY assignment of crosspeaks were made by analogy to the those observed with peptide **7**.

Modeling of peptide **1**.[2] Distances between protons diagramed in SI Figure 6 were estimated by manually integrating the peak volumes (generally the average of both peaks across the diagonal) and fitting to Equation 2, where r_{ij} (the distance between H_i and H_j) is a function of a reference distance (r_{ref}), the reference crosspeak volume (v_{ref}), and the crosspeak volume between H_i and H_j (v_{ij}).

$$r_{ij} = r_{ref} \sqrt[6]{v_{ref} / v_{ij}} \quad (2)$$

Three different sets of crosspeaks and distance restraints were considered for internal distance calibration. While two sets of methylene peaks assigned to α-Gly and β-Asn are resolved well enough for clear integration, the relative volumes of these sets differ substantially (v_{Asn}/v_{Gly} = 1.8) and we were not comfortable referencing to these distances alone if possible. We established that only a limited number of conformations were accessible given the ROESY data of the α-Asp and δ-DPro and the stereochemical configuration of the *N*-terminal Boc-Asp. These data led us to estimate the approximate distances between the α-Asp and δ-DPro protons that satisfied the possible conformations. We

[2] The basic approach and equations employed are described in: (a) Wüthrich, K. *NMR of Proteins and Nucleic Acids* John Wiley & Sons, Inc.: New York, 1986. (b) Cavanagh, J.; Fairbrother, W. J.; Palmer, A. G., III; Rance, M.; Skelton, N. J. *Protein NMR Spectroscopy: Principles and Practice*, 2nd ed., Inc.: Burlington, 2007.

reasoned that the distance between Hα-Asp and Hδ2-DPro were in the vicinity of 2.2 or 2.3 Å (defined as Ref1 and Ref2, respectively), which were also in line with those determined from another similar peptide structure that we had observed,[3] and we used these values in our calculations.[4] Importantly, these two reference values provided some agreement with the distances derived from the α-Gly and β-Asn crosspeaks. Specifically, the reference distance between methylene protons would be 1.8 Å. With Ref1, the calculated distances of α-Gly and β-Asn are 1.9 and 1.7 Å; and with Ref2 these calculated distances round to 2.0 and 1.8 Å, respectively.

The distance estimates were then assigned to bins, which were used as restraints (SI Table 2). The bins were defined according to the ROESY crosspeak intensity such that the strongest peaks were assigned to the narrowest range of distances as follows: very strong (1.8 to 2.5 Å), strong (1.8 to 3.0 Å), medium (1.8 to 3.5 Å), and weak (1.8 to 4.5 Å). In the case of some H-H correlations, while crosspeaks were observed, the corresponding distances were not calculated due to inconclusive integrations (*i.e.*, there was overlap with neighboring peaks or excessive noise). In such cases, the peaks were assigned to the largest bin (1.8 to 4.5 Å).

The distance restraints were then input into the Crystallography & NMR System (CNS)[5] modeling program, version 1.21. The amino acid monomer topology/parameter files were built manually (except Gly) using the distances and angles from existing crystal structures in combination with the provided

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[3] Blank, J. T.; Miller, S. J. *Biopolymers* **2006**, *84*, 38-47. See Cambridge Structural Databank, entry WEDBUD.

[4] The calculated distance was derived from integration of the crosspeak where Hδ2-DPro could be resolved from Hδ1-DPro in F2.

[5] (a) Brunger, A. T.; Adams, P. D.; Clore, G. M.; Delano, W. L.; Gros, P. Grosse-Kunstleve, R. W.; Jiang, J.-S.; Kuszewski, J.; Nilges, N.; Pannu, N. S.; Read, R. J.; Rice, L. M.; Simonson, T.; Warren, G. L. *Acta Cryst*. **1998**, *D54*, 905-921. (b) Brunger, A. T. *Nature Protocols* **2007**, *2*, 2728-2733.

amino acid topology/parameter files, where appropriate.[6] For each reference, 1000 structures were generated during the annealing, ten of which were accepted for further analysis.

[6] Some of the amino acid monomer topology/parameter files were built with Dr. Michael Giuliano and Nadia Abascal.

SI Table 2. Calculated distances between protons within peptide **1**, and the associated bin, derived from ROESY crosspeaks with different reference distances.

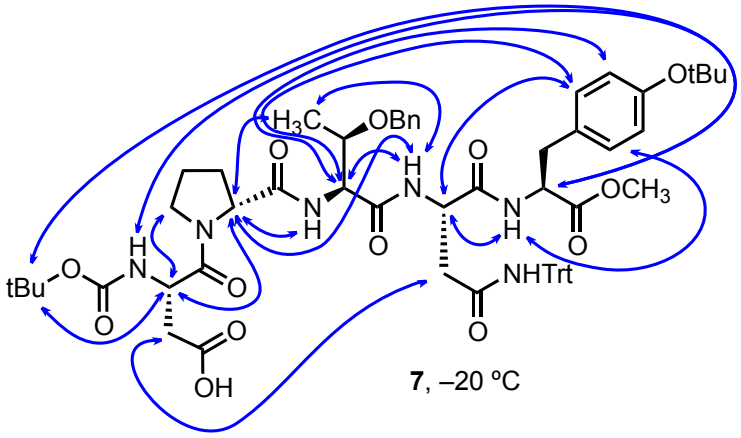
Entry	Peak 1	Peak 2	Ref1 distance (Å)	Ref1 bin	Ref2 distance (Å)	Ref2 bin
1	NH-Asp	Hδ1-DPro	3.5	weak	3.7	weak
2	NH-Asp	Hδ2-DPro	3.5	weak	3.7	weak
3	Hα-Asp	Hδ1-DPro	2.5	very strong	2.6	strong
4	Hα-Asp	Hδ2-DPro	2.2	very strong	2.3	very strong
5	Hβ-Asp	Hβ-Asn(Trt)	3.0	strong	3.1	medium
6	Hα-DPro	NH-Thr(Bn)	2.1	very strong	2.2	very strong
7	Hα-DPro	NH-Asn(Trt)	3.6	weak	3.7	weak
8	NH-Thr(Bn)	NH-Asn(Trt)	2.6	strong	2.7	strong
9	Hα-Thr(Bn)	NH-Asn(Trt)	3.0	strong	3.1	medium
10	Hα-Thr(Bn)	Hδ-Tyr(tBu)	3.7	weak	3.9	weak
11	Hα-Thr(Bn)	Hε-Tyr(tBu)	3.6	weak	3.7	weak
12	Hβ-Thr(Bn)	NH-Asn(Trt)	ND	weak	ND	weak
13	Hδ-Thr(Bn)	NH-Asn(Trt)	ND	weak	ND	weak
14	Hα-Asn	NH-Tyr(tBu)	2.2	very strong	2.5	very strong
15	Hα-Asn(Trt)	NH-Gly	ND	weak	ND	weak
16	Hε-Tyr(tBu)	$COOCH_3$	ND	weak	ND	weak

NMR experiments with peptide 7

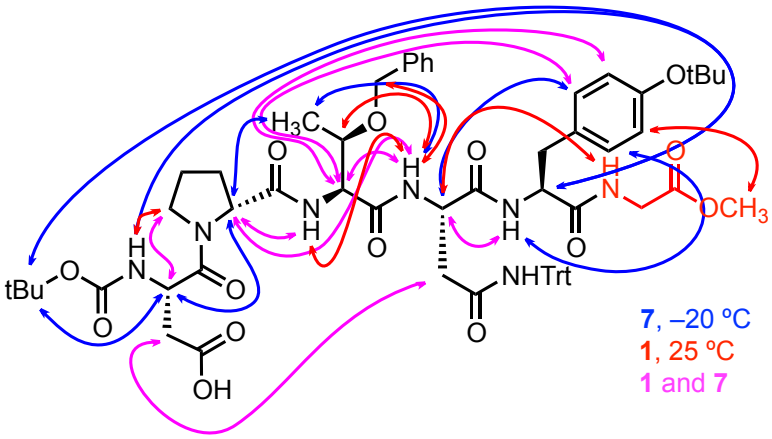
NMR spectra were acquired on a Varian Inova 500 MHz spectrometer running VnmrJ 2.2D with pulse sequences provided by Varian. Peak assignments for peptide **7** acquired at –20 ºC were based upon 2D gCOSY, TOCSY, and ROESY data.

ROESY data was acquired with a 200 ms mixing time; spectral width of 5102.4 Hz in both F1 and F2; 765 points in t2 and 512 points in t1; 32 scans; relaxation delay (d1) of 3.328 s and at –20 ºC. Data were processed using MestReNova version 8.1.1-11591 using zerofilling to bring the spectral size to 1024, 1024; automatic phasing with manual adjustments; apodization with a Gaussian function; and automatic baseline correction with a polynomial fit.

^{1}H NMR (500 MHz, $CDCl_3$, –20 ºC): δ 7.74 (d, *J* = 8.0 Hz, 1H, N*H*-Asn), 7.70 (s, 1H, Asn(N*H*Trt)), 7.56 (d, *J* = 7.3 Hz, 1H, N*H*-Tyr), 7.41 – 7.19 (m, 20H, Trt and Bn aryl peaks), 7.18 – 7.03 (m, 1H, N*H*-Thr), 6.98 (d, *J* = 8.4 Hz, 2H, *δ*-Tyr), 6.90 (d, *J* = 8.4 Hz, 1H, *ε*-Tyr), 6.67 (d, *J* = 8.2 Hz, 1H, N*H*-Asp), 4.93 – 4.84 (m, 1H, *α*-Asn), 4.81 (ddd, *J* = 10.9, 7.1, 4.0 Hz, 1H, *α*-Asp), 4.57 (apparent q, *J* = 6.7 Hz, 1H, *α*-Tyr), 4.51 – 4.38 (m, 3H, *β*-Thr and benzylic CH_2), 4.35 (d, *J* = 9.6 Hz, 1H, *α*-Thr), 4.03 (t, *J* = 7.5 Hz, 1H, *α*-DPro), 3.72 – 3.51 (m, 5H, *δ*-DPro and OCH_3, one *δ*-DPro proton is resolved/assigned in F2 of TOCSY spectrum to be 3.65), 3.19 (dd, *J* = 15.6, 10.1 Hz, 1H, *β*-Asn), 3.04 – 2.88 (m, 2H, *β*-Tyr), 2.77 (dd, *J* = 16.6, 7.4 Hz, 1H, *β*-Asp), 2.66 – 2.48 (m, 2H, *β*-Asp and *β*-Asn, assigned in F2 of TOCSY spectrum to be 2.59 and 2.56, respectively), 2.17 – 2.07 (m, 2H, *β*/*γ*-DPro), 2.05 – 1.94 (m, 1H, *β*-DPro), 1.89 – 1.74 (m, 1H, *γ*-DPro), 1.44 (s, 9H, Boc-tBu), 1.31 (s, 9H, Tyr(tBu)), 1.18 (d, *J* = 6.3 Hz, 3H, *γ*-Thr).



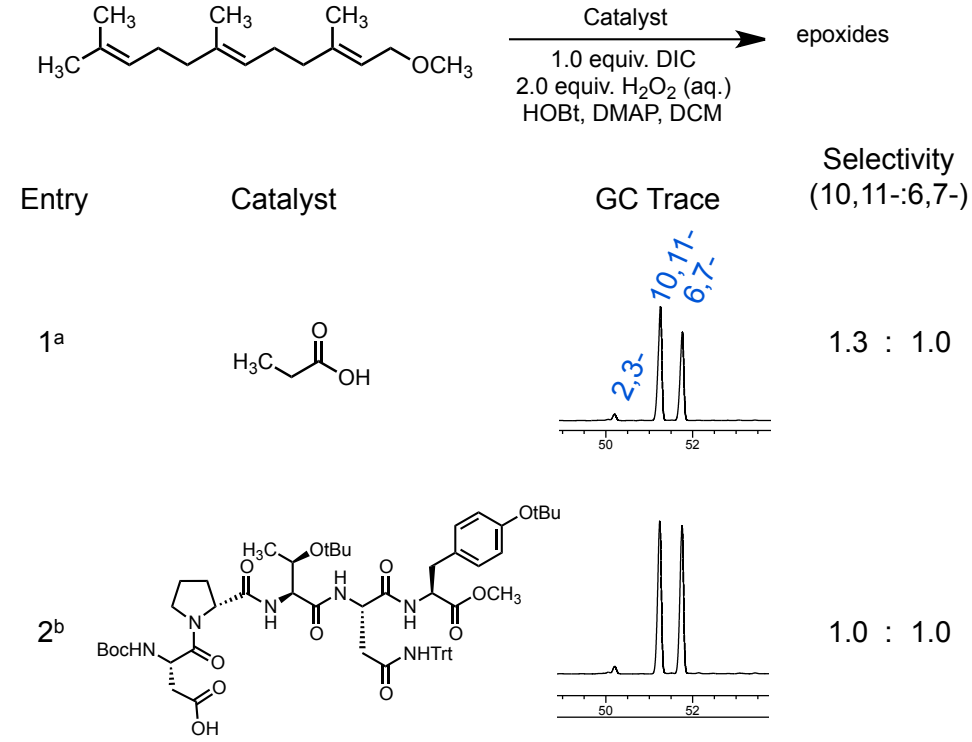
SI Figure 7. Unabridged ROESY correlation map of peptide **7** in $CDCl_3$ at –20 ºC.



SI Figure 8. Composite map of ROESY correlations found in peptide **7** at –20 ºC (blue), **1** at 25 ºC. (red), and those shared by both **1** and **7** (purple).

Experiments with farnesyl methyl ether[7] (13)

Preliminary experiments



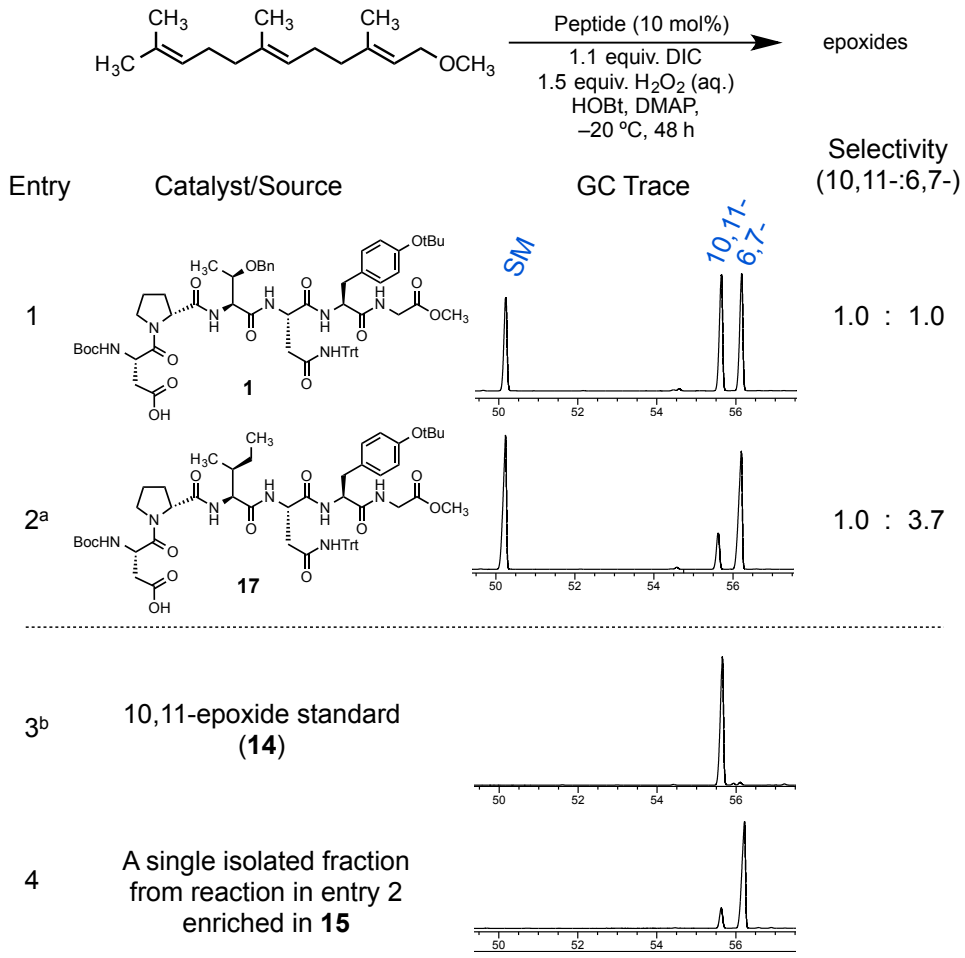
SI Figure 9. Comparison of selectivity derived from acid catalysts with farnesyl methyl ether and one theoretical equivalent of oxidant (controlled by DIC stoichiometry) as determined by GC (acquisition method is the same as for farnesol). [a]Performed with 0.3 equiv propionic acid, run for approximately 2 h at room temperature. [b]Performed at 4 ºC with 0.1 equiv peptide, run for 5 h.

Peptide **17** was prepared analogously to peptide **1**. Fmoc-Ile-OH was used in the solid-phase peptide synthesis to be present in the *i*+2 position. Following the Fm-ester deprotection and purification by silica gel chromatography (see the Standard Fm-ester deprotection protocol, SI-5), peptide **17** was used without further purification and used in most reaction studies. This batch of material was found to

[7] Schwartz, M. A.; Dunn, T. J. *J. Am. Chem. Soc.* **1972**, *94*, 4205-4211.

contain an impurity and was further purified by reversed phase chromatography for characterization (H NMR spectrum included). When tested with **13** and **18**, this further purified batch of **17** did not indicate any appreciable change in performance, as determined by GC of the crude reactions.

Peptide **17**: white solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.10 – 7.73 (m, 2H), 7.31 – 7.11 (m, 16H), 6.97 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.3 Hz, 2H), 6.55 (bs, 1H), 5.91 (bs, 1H), 4.92 – 4.84 (m, 1H), 4.51 (apparent t, J = 9.8 Hz, 1H), 4.36 (bs, 1H), 4.22 (dd, J = 9.0, 3.7 Hz, 1H), 4.06 (apparent t, J = 7.2 Hz, 1H), 3.70 – 3.57 (m, 6H), 3.52 (apparent t, J = 8.8 Hz, 1H), 3.43 – 3.26 (m, 1H), 3.10 (dd, J = 14.0, 6.4 Hz, 1H), 3.05 – 2.94 (m, 2H), 2.66 (dd, J = 16.8, 3.9 Hz, 1H), 2.33 (d, J = 14.1 Hz, 1H), 2.07 – 1.74 (m, 4H), 1.52 – 1.44 (m, 10H), 1.31 (s, 9H), 1.07 (bs, 1H), 0.83 – 0.78 (m, 4H), 0.75 (d, J = 6.8 Hz, 3H). A TOCSY spectrum was used to assist the assignment of proton integer values given the peak broadening.



SI Figure 10. Comparison of selectivity derived from acid catalysts with farnesyl methyl ether as determined by GC (acquisition method is the same as for farnesol). a. Performed in DCM b. Prepared from selective bromohydration,[8] followed by epoxide-forming ring closer with K_2CO_3 in CH_3OH.[9] GC retention times differ from those shown in SI Figure 9 on account of a newer column being installed and used for these experiments.

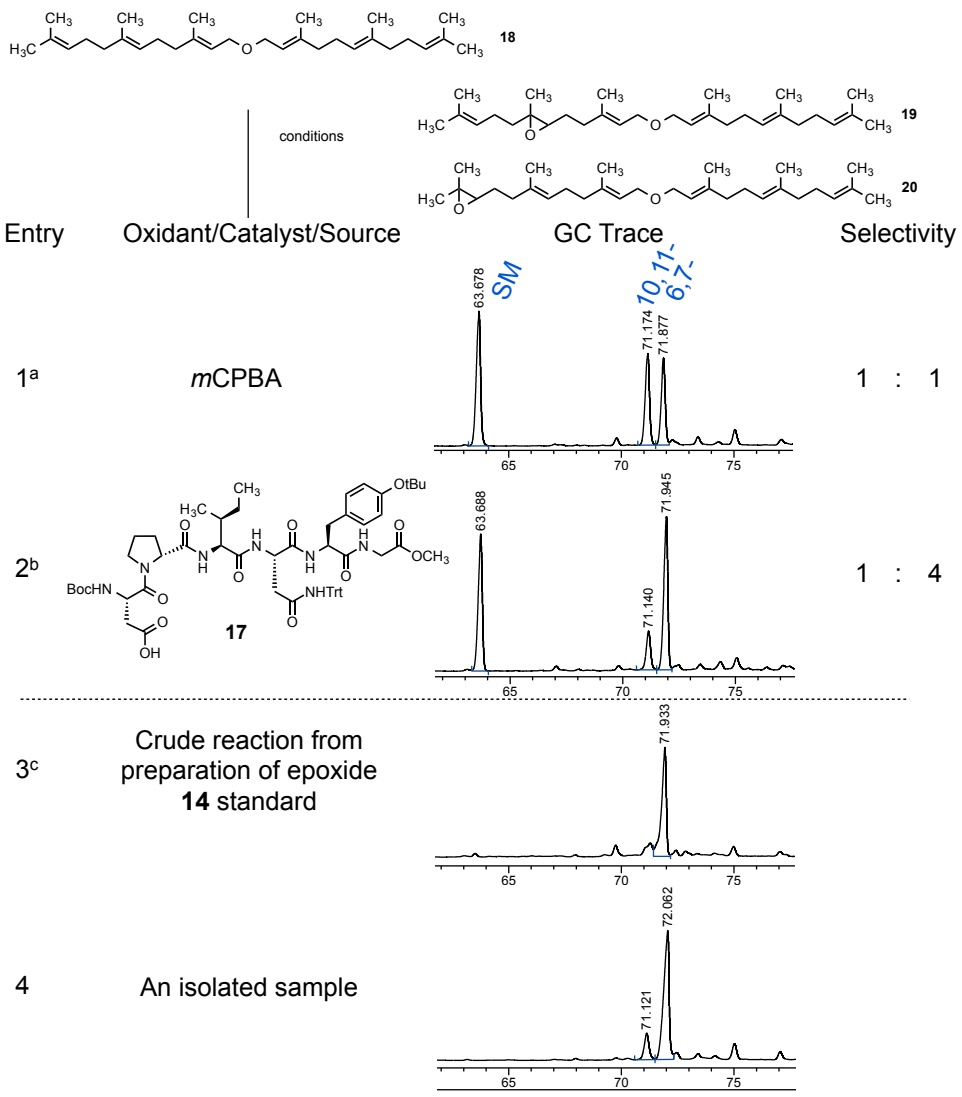
Reactions of farnesyl methyl ether (**13**) and peptide **17** were performed as described for the screening of truncated catalyst analogs (see SI-4), except DCM was used as a reaction solvent. Following work-up and GC analysis, the remaining organics, along with two additional hexanes extracts of the aqueous material, were combined, concentrated. The resulting material was loaded onto a silica gel column, eluting with a gradient of 0% to 30% Et_2O in hexanes.

[8] van Tamelen, E. E.; Sharpless, K. B. *Tetrahedron Lett.* **1967**, *8*, 2655-2659.
[9] Ceruti, M.; Balliano, G.; Viola, F.; Cattel, L.; Gerst, N.; Schuber, F. *Eur. J. Med. Chem.* **1987**, *22*, 199-208.

Epoxide **15**: (major product, isolated as an enriched mixture with epoxide **14**): **TLC**: 30% Et_2O in hexanes (R_f =0.43), visualized with I_2/silica. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.39 (tdt, *J* = 6.8, 2.8, 1.3 Hz, 1H), 5.07 (ddp, *J* = 8.6, 5.8, 1.5 Hz, 1H), 3.95 – 3.91 (m, 2H), 3.33 (s, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.24 – 2.01 (m, 4H), 1.73 – 1.57 (m, 12H), 1.41 (ddd, *J* = 13.6, 9.5, 7.1 Hz, 1H), 1.25 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 139.6, 132.0, 123.8, 121.3, 69.0, 63.4, 61.0, 58.1, 38.9, 36.3, 27.2, 25.9, 24.0, 17.8, 16.6, 16.6.

Epoxide **14** (minor product of isolated mixture with epoxide **15**, partially reported): **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.34 (tdt, *J* = 6.7, 2.6, 1.3 Hz, 1H), 5.18 – 5.13 (m, 1H), 3.32 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H).

Experiments with difarnesyl ether (18)



SI Figure 11. Comparison of selectivity derived from oxidants/catalysts with difarnesyl ether[10] as determined by GC (275 ºC injector and detector; 1.5 mL/min He flow through column; 60 ºC initial oven temp, ramp at 10 ºC/min to 200 ºC, hold for 1 min, ramp at 1 ºC/min to 260 ºC with 3 min hold at 237 ºC and 2 min hold at 238 ºC; final hold at 260 ºC for 3 min; 84 min total). Selectivities are reported as the ratio of area of **19** to that of the next most intense peak, presumed to be **20**. [a]*m*CPBA (1 equiv), $NaHPO_4$ (2 equiv), DCM, H_2O, room temp, 4 h; [b]**17** (0.1 equiv), HOBt (0.1 equiv), DMAP (0.1 equiv), 1.5 equiv DIC, 2.0 equiv H_2O_2, DCM, –20 ºC, 48 h; [c]Crude GC of reaction preparing 6,7-epoxydifarnesyl ether standard: 6,7-epoxyfarnesol (90%),[11] NaH, and farnesyl bromide.

[10] Prashad, M.; Kathawala, F. G.; Scallen, T. *J. Med. Chem.* **1993**, *36*, 1501-1504.
[11] Lichtor, P. A.; Miller, S. J. *Nature Chem.* **2012**, *4*, 990-995.

Reactions of difarnesyl ether (**18**) and peptide **17** were performed as described for the screening of truncated catalyst analogs (see SI-4), except DCM was used as a reaction solvent and either 1.1 or 1.5 equiv DIC (higher equiv results in slightly higher conversion of starting material) with 2.0 equiv H_2O_2 were used. Following work-up and GC analysis, the remaining organics, along with two additional hexanes extracts of the aqueous material, were combined, concentrated. The resulting material was loaded onto a silica gel column, eluting with a gradient of 0% to 30% Et_2O in hexanes. The monoepoxide products were found to be somewhat unstable to silica gel, as was evident from a two-dimensional TLC of a crude reaction run with *m*CPBA, where products were allowed to stand for 25 min on the TLC plate following the first elution, and then separated in the perpendicular direction. Additionally, trace amounts of unidentified products were sometimes isolated along with mixtures of **19** and **20**. The ratio of epoxide products following isolation was >3:1 (**19**:**20**), as determined by NMR. Furthermore, we note that the estimation of the crude ratios by both NMR and GC is similar to that observed in the isolated material by NMR (~3:1; See page S-51).

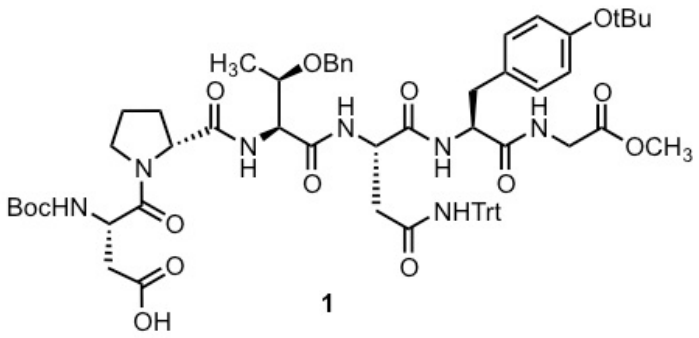
We note further that epoxide ratios from the crude reactions with **18** are challenging to ascertain. As in previous reactions, the site selectivity was estimated by comparing the GC spectra of the crude reactions and measuring the ratio of the most intense peak areas eluting at the retention time characteristic of the monoepoxides. We confirmed the GC assignment of the major product (**19**) by synthesizing it independently (SI Figure 11, entry 3). We presume that the other major peak in the GC to be **20** based upon its analogy to GC spectra/studies with **13** in addition to the observation that epoxide **19** is isolated as a minor product along with **20**. We note, however, that reinjection of the isolated mixture of **19** and **20** results in the slightly different epoxide ratio (SI Figure 11, entry 4) and the appearance of other neighboring peaks that seem to have increased intensity relative to the main products (compared to the crude reaction), the cause of which may be the instability of products under

the high temperature conditions of this GC assay. Nonetheless, the GC trace of the crude reactions is illustrative of the comparative selectivities observed with peptide-based catalysts **1** and **17**, and mCPBA (entry 1) and **17** (entry 2); moreover, the selectivity estimated from these traces is corroborated by the ^{1}H NMR of the crude reactions where we estimate a ratio of what attribute to all "6,7-" and "10,11-" epoxides (that is, integrating over the di- and potentially higher epoxidized products as well; see page S-53). Furthermore, we note that the estimation of the crude ratios by both NMR and GC is similar to that observed in the isolated material by NMR (~3:1).

Epoxide **19**: (major product, isolated as an enriched mixture with epoxide **20**): **TLC**: 20% Et_2O in hexanes (R_f =0.45), visualized with I_2/silica. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.41 (tdd, J = 6.8, 2.8, 1.4 Hz, 1H), 5.37 (tdd, J = 6.8, 2.6, 1.3 Hz, 1H), 5.15 – 5.04 (m, 3H), 3.98 (d, J = 6.7 Hz, 4H), 2.70 (t, J = 6.2 Hz, 1H), 2.24 – 1.94 (m, 12H), 1.76 – 1.58 (m, 24H), 1.41 (ddd, J = 13.6, 9.3, 7.2 Hz, 1H), 1.25 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 140.3, 139.2, 135.4, 132.0, 131.4, 124.5, 124.1, 123.9, 121.8, 121.1, 66.7, 66.5, 63.4, 60.9, 39.9, 39.8, 38.9, 36.3, 27.3, 26.9, 26.5, 25.8, 24.0, 17.8, 17.8, 16.7, 16.7, 16.6, 16.1. **MS**: calculated mass for $[C_{30}H_{50}O_2+H]^+$: 443.388, ESI+ found 443.389; $[C_{30}H_{50}O_2+NH_4]^+$: 460.415, ESI+ found 460.414; $[C_{30}H_{50}O_2+Na]^+$: 465.370, ESI+ found 465.374.

Epoxide **20** (minor product of isolated mixture with epoxide **19**, partially reported): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.19 – 5.14 (m, 1H), 1.30 (s, 3H), 1.25 (s, 3H).

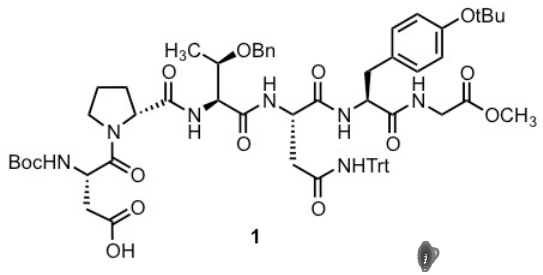
NMR spectra follow beginning on page S-29.


OtBu
H3C
OBn
O
H
N
O
N
H
O
N
H
O
OCH3
BocHN
O
NHTrt
O
O
OH

1

25 ºC

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
f1 (ppm)

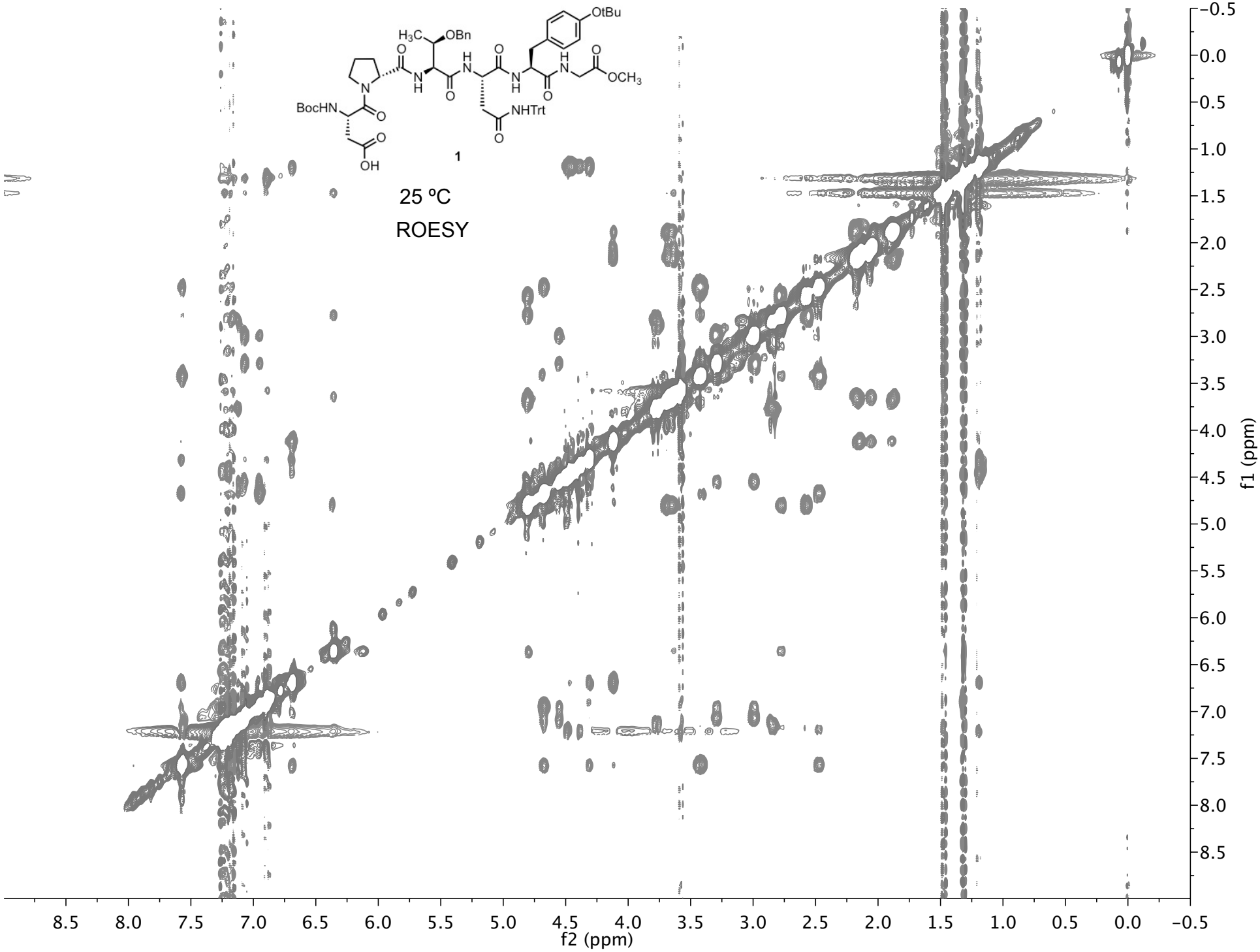


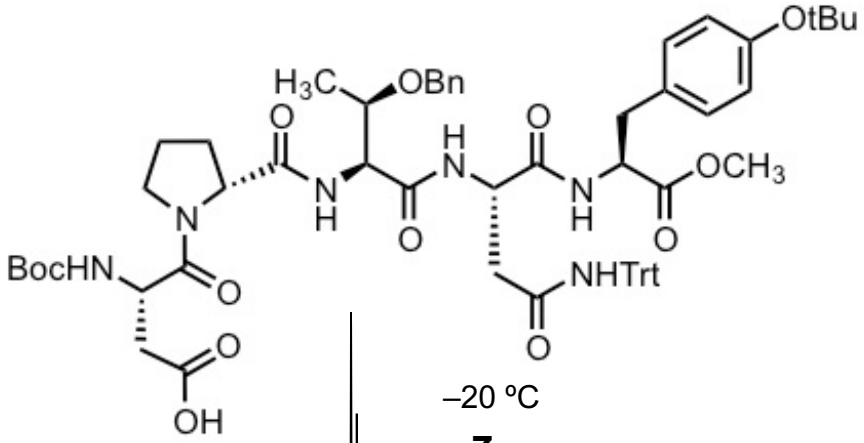
25 ºC

zTOCSY

f2 (ppm)

f1 (ppm)


OtBu
H3C
OBn
OCH3
BocHN
NHTrt
OH
1
25 ºC
ROESY
f1 (ppm)
f2 (ppm)


OtBu
H3C
OBn
OCH3
BocHN
NHTrt
OH

–20 ºC

7

8.5
8.0
7.5
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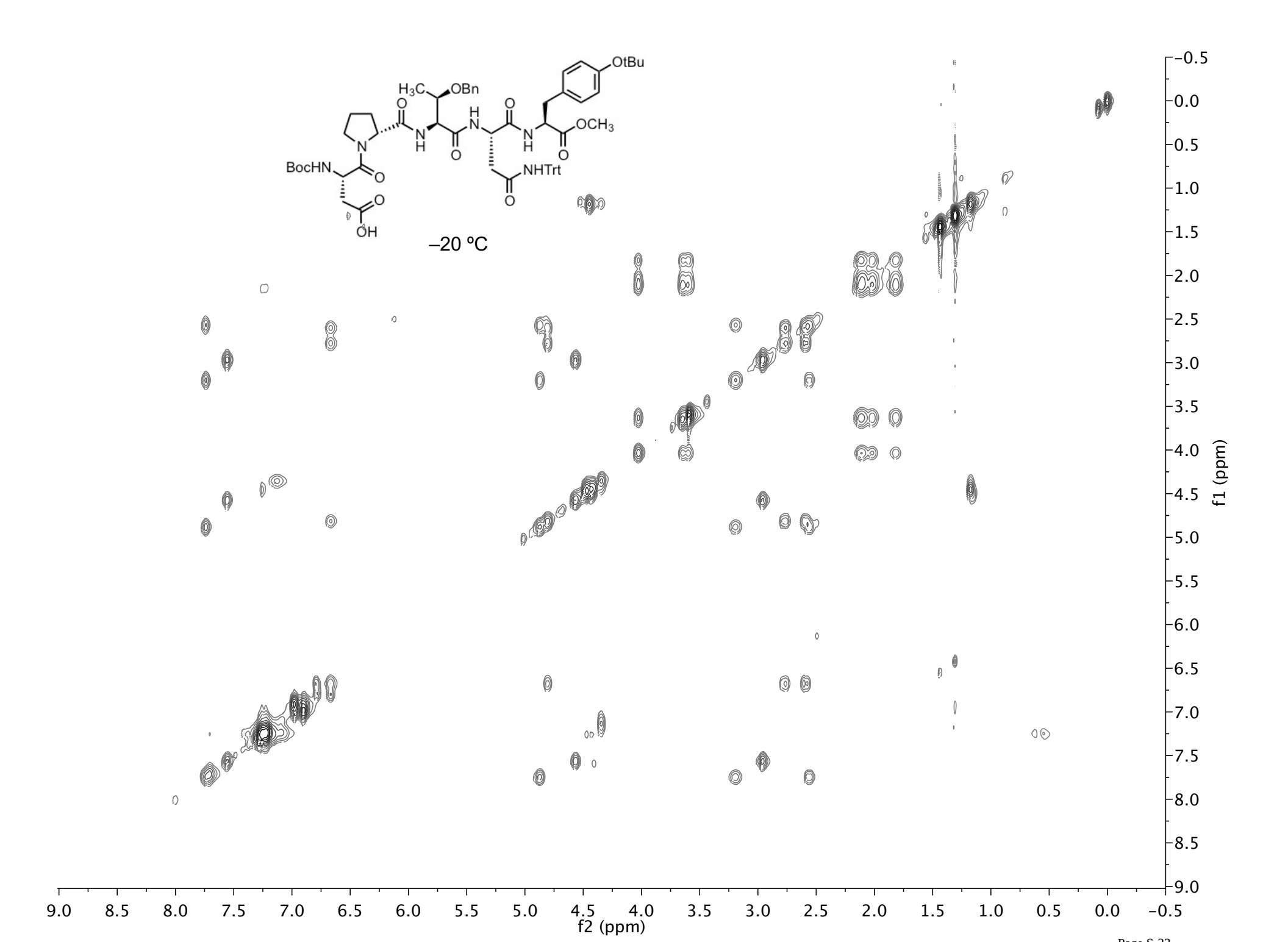
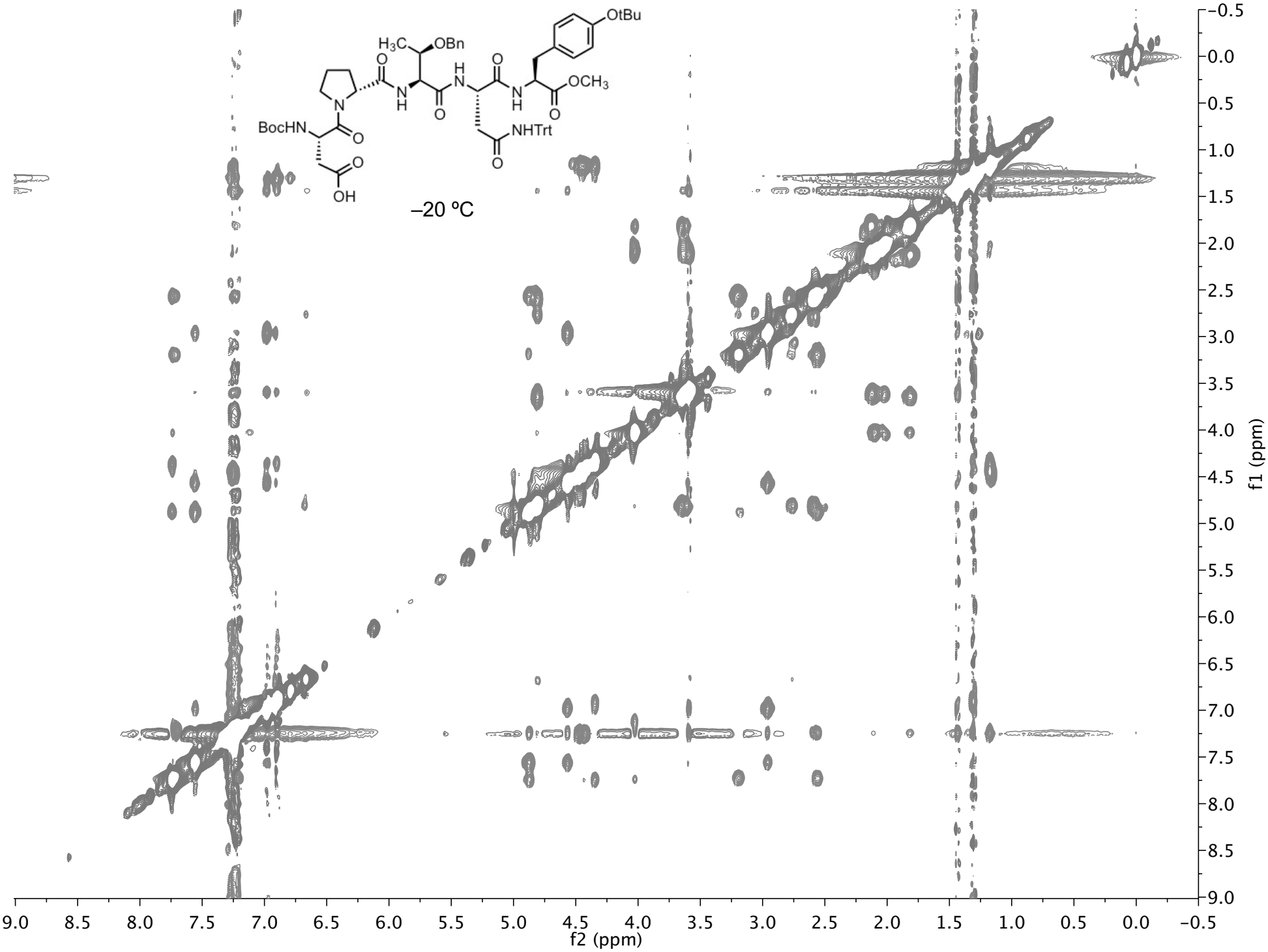
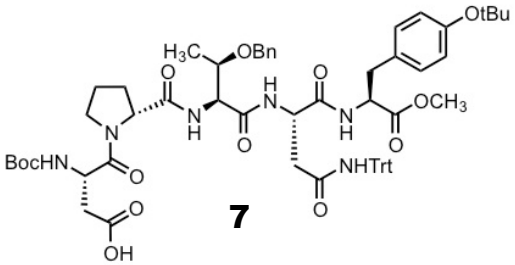
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OtBu
H3C
OBn
OCH3
BocHN
NHTrt
OH
–20 °C
f1 (ppm)
f2 (ppm)


OtBu
H3C
OBn
OCH3
BocHN
NHTrt
OH
–20 °C
f2 (ppm)
f1 (ppm)


OtBu
H3C
OBn
OCH3
BocHN
NHTrt
OH

7

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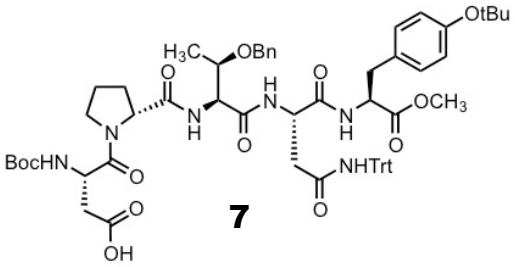
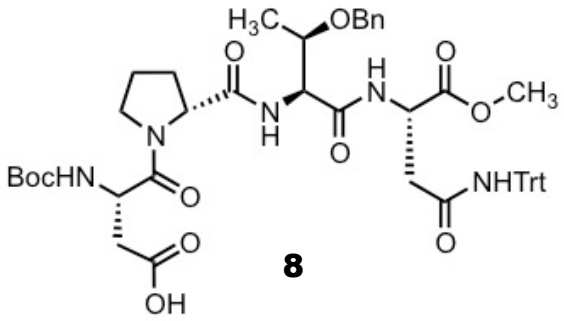
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


OtBu
H3C
OBn
OCH3
BocHN
NHTrt
OH

7

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


H3C
OBn
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H
N
O
O
CH3
N
N
H
O
BocHN
O
NHTrt
O
O
OH

8

.0.0
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
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0.5
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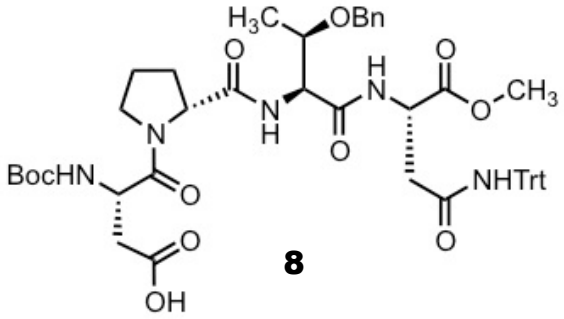
-0.5
f1 (ppm)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OBn
O
H
N
O
O
CH3
N
H
N
O
O
BocHN
O
NHTrt
O
O
OH

8

210
200
190
180
170
160
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120
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100
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80
70
60
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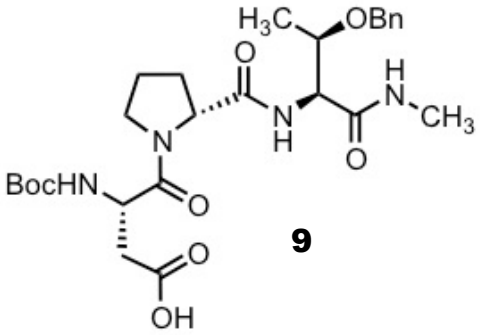
40
30
20
10
0
-10
f1 (ppm)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CH3
N
H
O
N
BocHN
O
O
OH

9

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9.0
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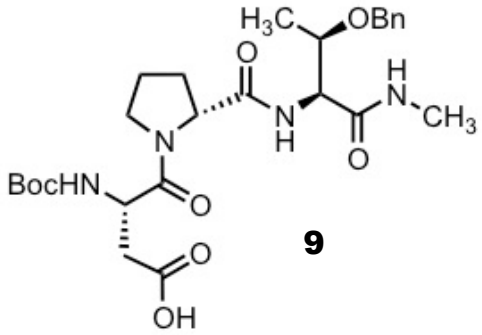
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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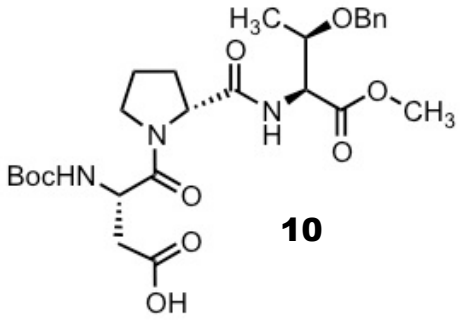
OBn
O
H
N
CH3
N
H
O
N
BocHN
O
O
OH

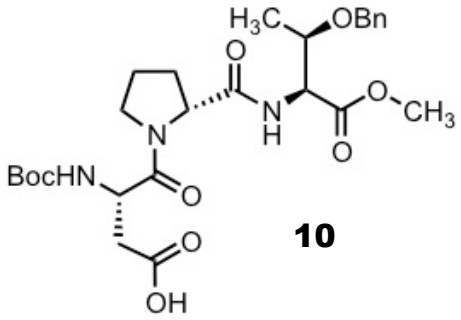
9

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


H3C
OBn
O
N
H
O
O
CH3
N
BocHN
O
O
OH

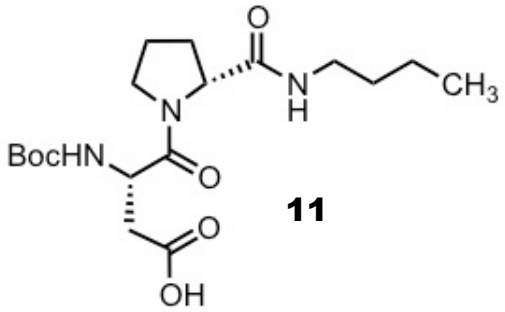
10

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
f1 (ppm)


H3C
OBn
O
N
H
O
O
CH3
N
BocHN
O
O
OH

10

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


O
N
H
CH3
N
BocHN
O
O
OH

11

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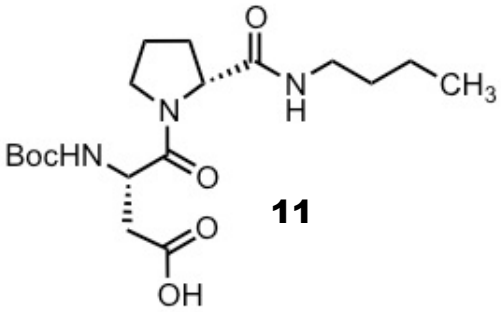
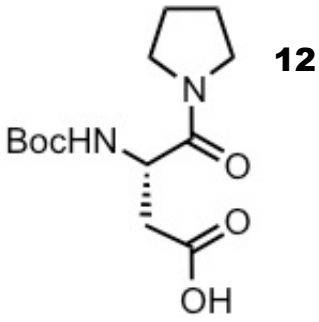
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


O
N
H
CH3
N
BocHN
O
O
OH

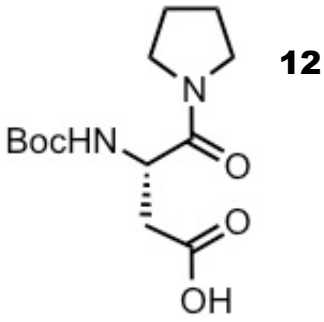
11

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


BocHN
N
O
O
OH

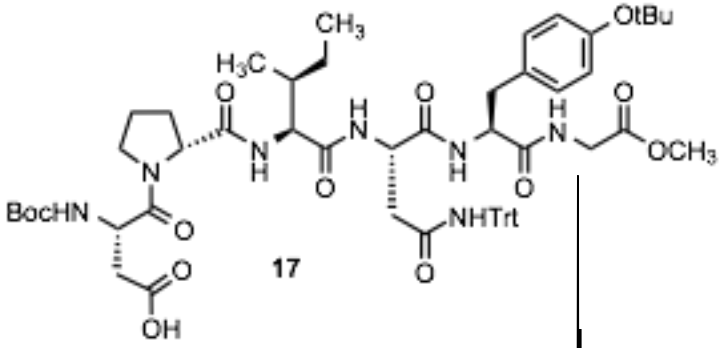
12

.0.0
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)

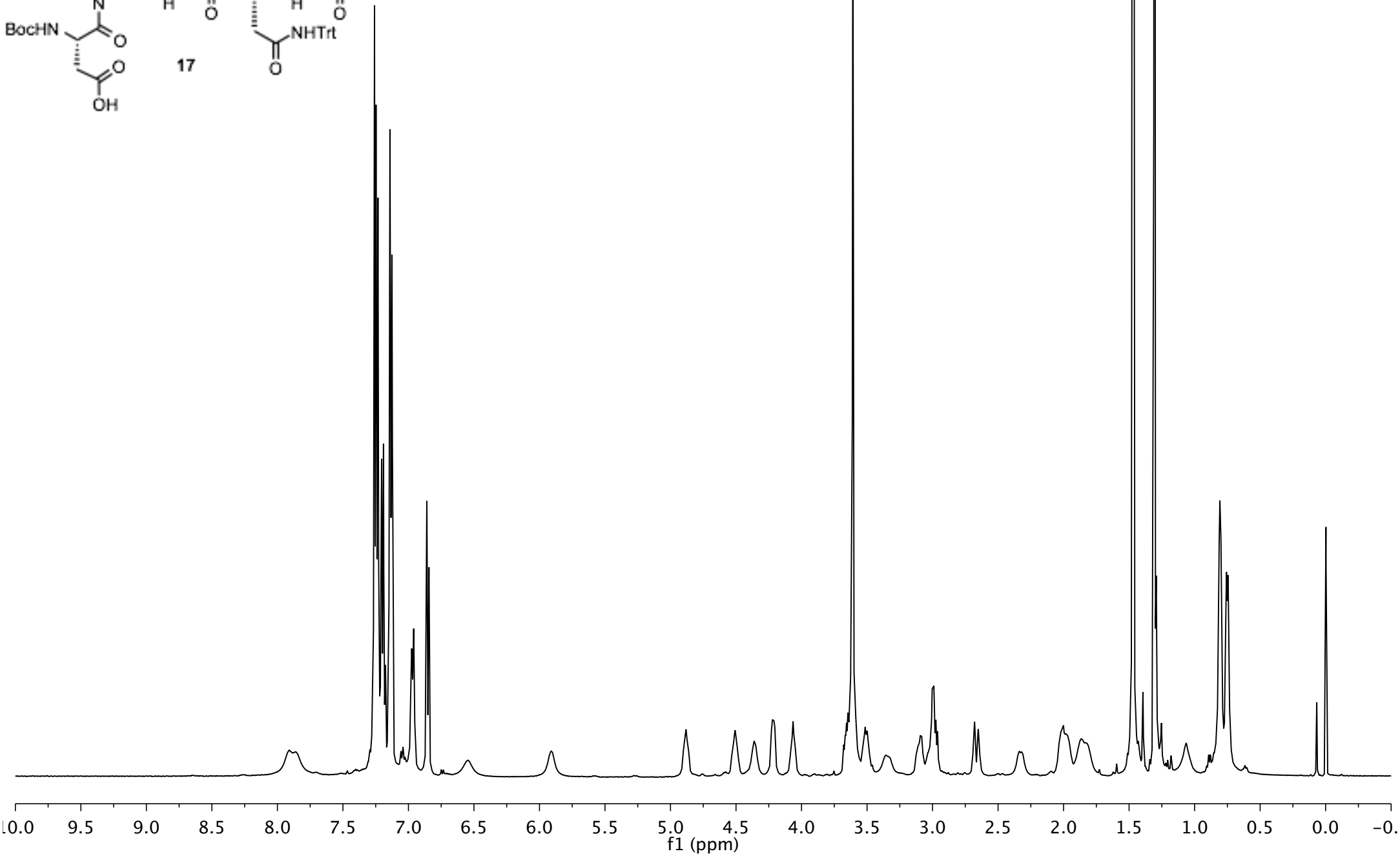

N
BocHN
O
O
OH

12

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


CH3
H3C
OtBu
BocHN
NHTrt
OCH3
OH

17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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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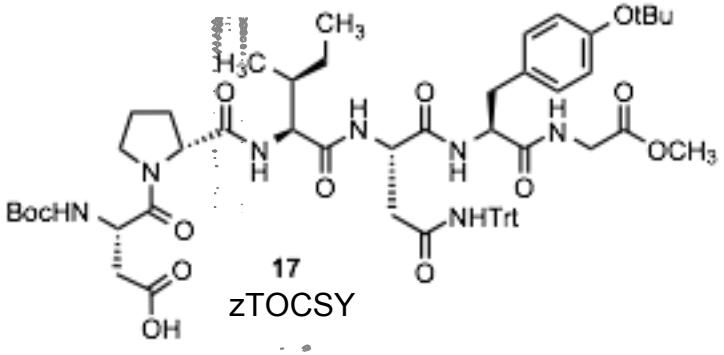
−0.5
f1 (ppm)



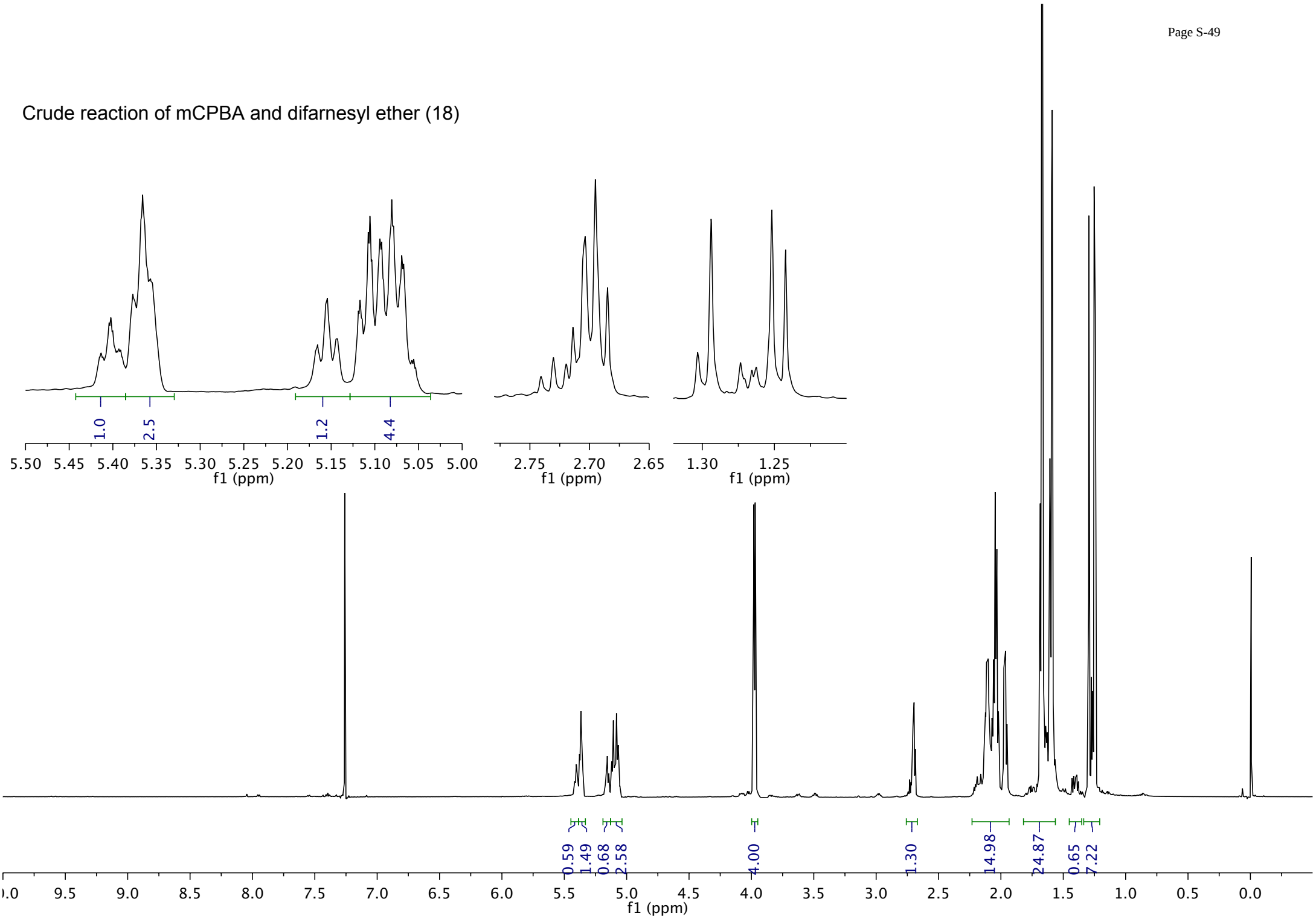
17

zTOCSY

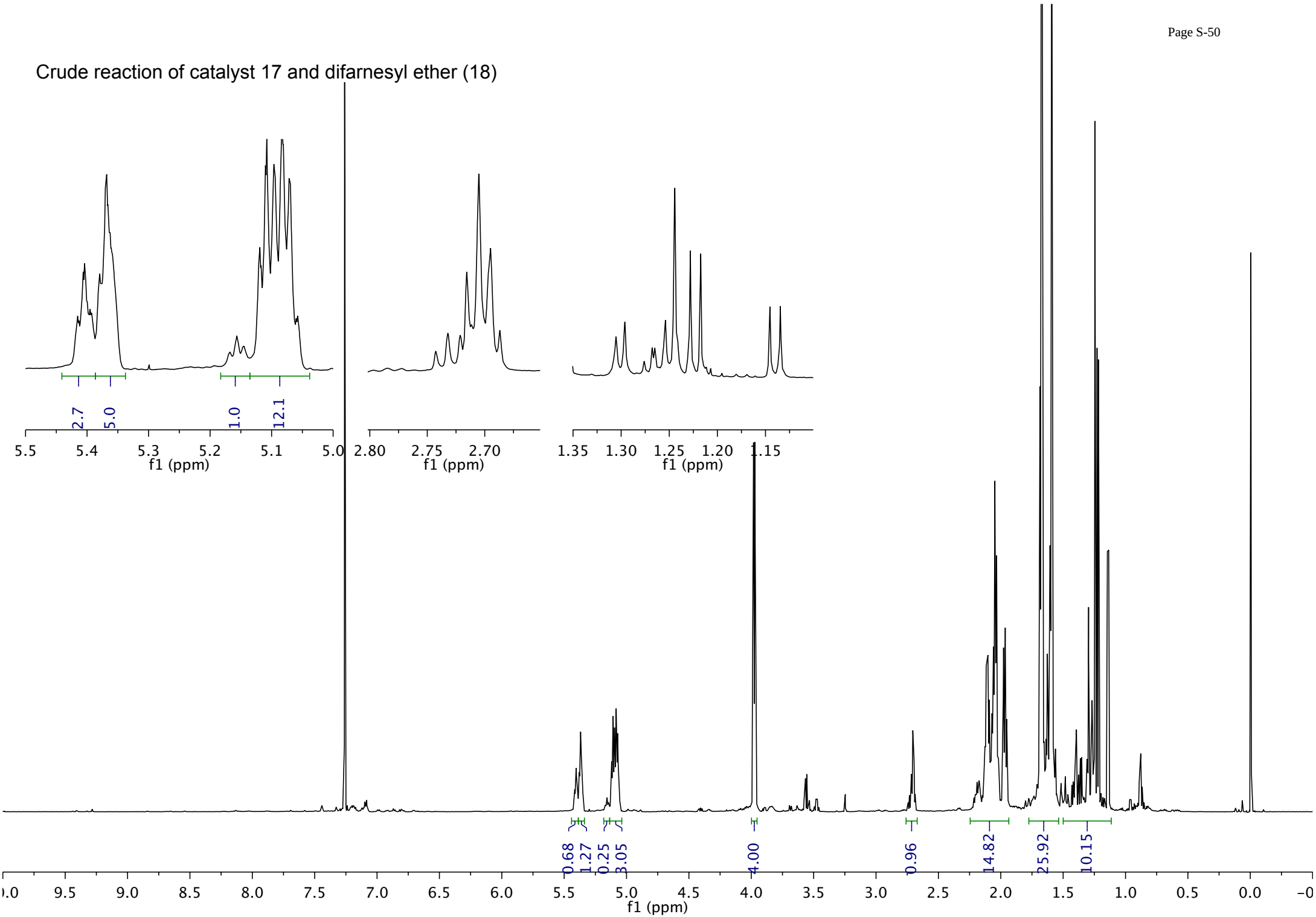
f2 (ppm)

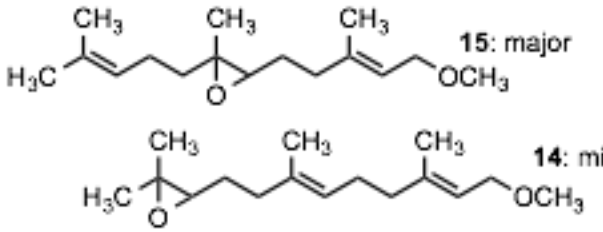
f1 (ppm)

Crude reaction of mCPBA and difarnesyl ether (18)

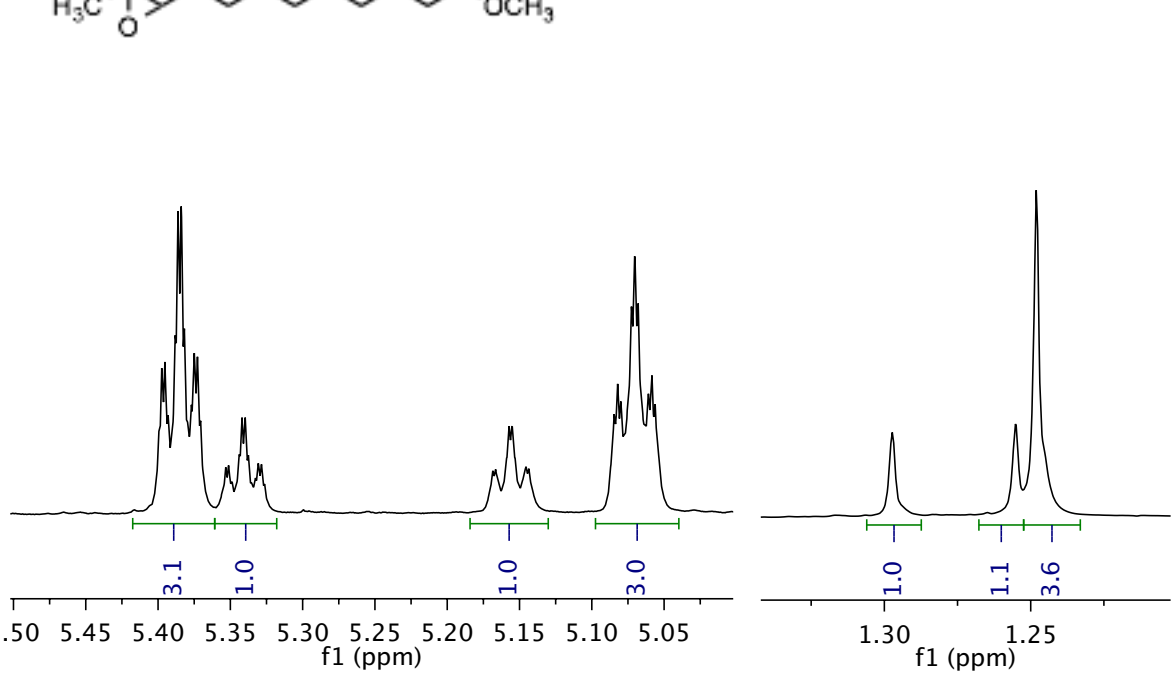


Crude reaction of catalyst 17 and difarnesyl ether (18)

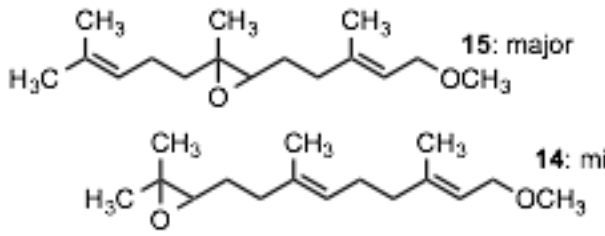



CH3
CH3
CH3
15: major
H3C
OCH3
O

CH3
CH3
CH3
14: minor
H3C
OCH3
O

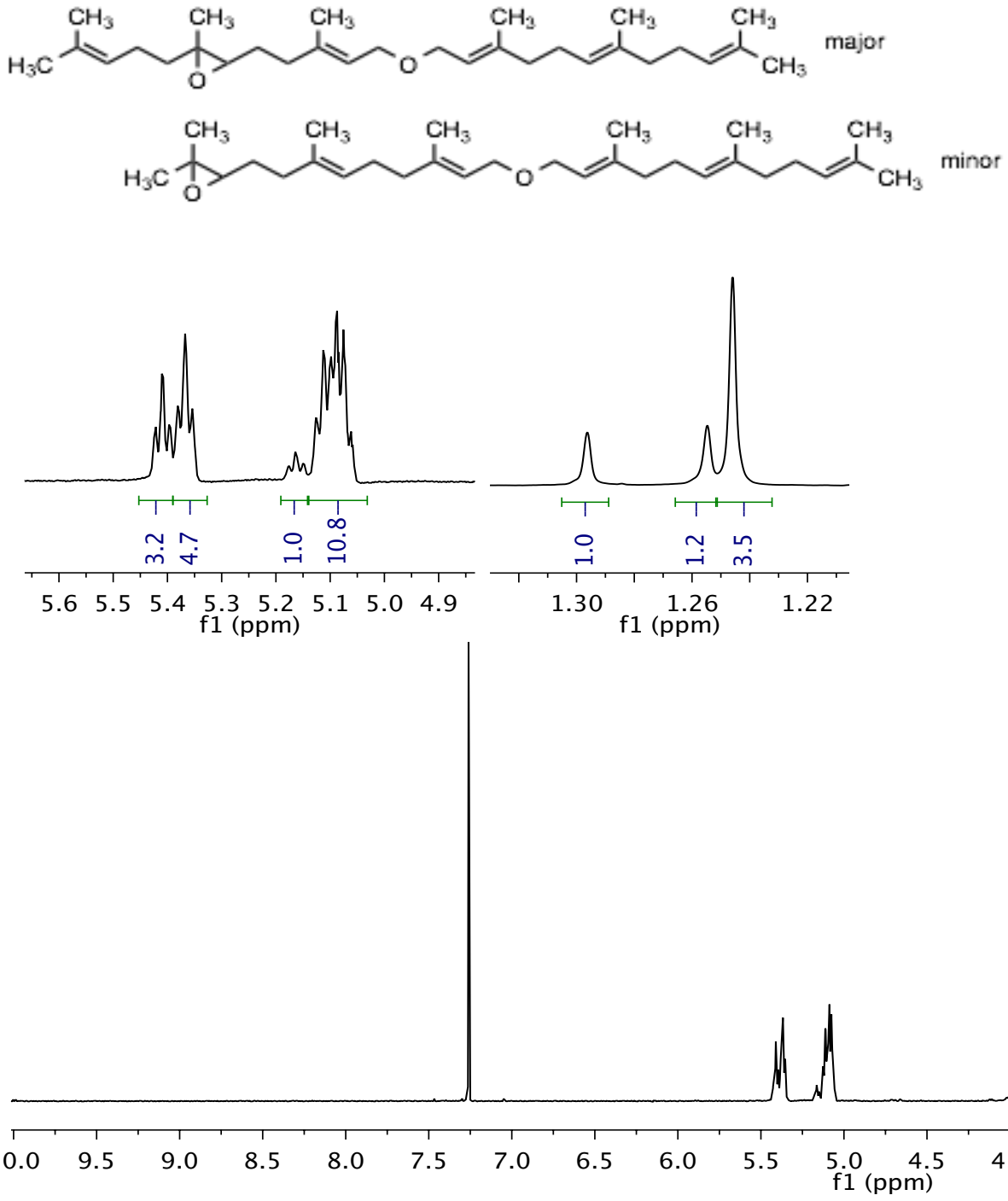

3.1
1.0
1.0
3.0
5.50 5.45 5.40 5.35 5.30 5.25 5.20 5.15 5.10 5.05
f1 (ppm)
1.0
1.1
3.6
1.30 1.25
f1 (ppm)

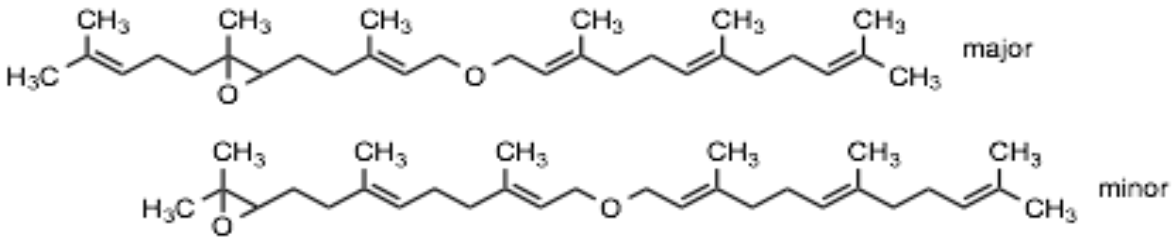
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



15: major

14: minor


major
minor
3.2
4.7
1.0
10.8
1.0
1.2
3.5
f1 (ppm)
f1 (ppm)
f1 (ppm)


major
minor

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