Combinatorial evolution of site- and enantioselective catalysts for polyene epoxidation

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Supplementary Information

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General Information.

Proton NMR spectra were recorded on a 500 MHz or a 400 MHz spectrometer and carbon NMR spectra were recorded on a 126 MHz or a 101 MHz, spectrometer, all at ambient temperature. All NMR chemical shifts are referenced in ppm relative to residual solvent or internal tetramethylsilane according to Gottlieb *et al*.[1] Solvent reference ppm in ^{1}H-NMR and ^{13}C-NMR for $CDCl_3$ are 7.26 ppm and 77.16 ppm, respectively. Carbon NMR spectra were completely proton decoupled. NMR spectral data are reported as chemical shift (multiplicity, coupling constants, integration). Multiplicity is reported as follows: singlet (s), doublet (d), doublet of doubles (dd), doublet of doublet of doublets (ddd), triplet (t), quartet (q), pentet (p), and multiplet (m). Multiplet analysis was performed using MestReNova version 7.0.3-8830 from Mestrelab Research S.L.

Unless otherwise specified, reported yields represent isolated yields. Compounds described in the literature are characterized by comparing ^{1}H-NMR.

Gas chromatography (GC) was performed on an instrument with two parallel HP-5 columns (30 m, 0.320 mm diameter, 0.25 μm film thickness) and flame ionization detectors using He as a carrier gas. While both columns were used in peptide library screening, unless otherwise specified, all data presented in this document are from the same column/detector. Products were not calibrated by internal standard unless otherwise specified. Site-selectivity ratios for monoepoxides are reported as the area of the indicated peak to the sum of the areas of all the epoxide products. Due the sensitivity of site-selective reactions to starting material conversion, the uncalibrated starting material "conversion" is sometimes reported and used to qualitatively compare reactions to each other. This relative conversion is calculated as the integrated area of the monoepoxide products divided by the sum of the areas of the starting material and monoepoxide products.

Attenuated total reflectance-infrared (ATR-IR) spectra were obtained on a FT-IR spectrometer; υ_{max} (cm^{-1}) are partially reported.

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, cerium ammonium molybdate (CAM), ninhydrin, or $KMnO_4$ solutions. Preperative thin-layer chromatography was generally performed using 1000 μm thick plates with silica gel GF (Uniplate) and a UV 254 indicator. Flash column chromatography was perfomed using Silica Gel 60 Å (32-63 micron).

Optical rotations were recorded on a polarimeter at the sodium D line (1.0 dm path length) at 20 ºC.

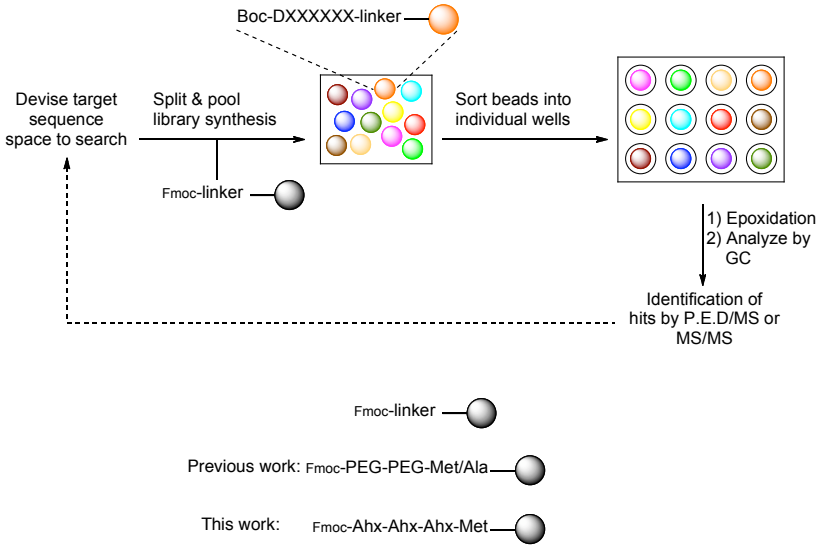
Routine mass spectrometry was performed using ultra high performace liquid chromatography-mass spectrometry using an instrument equipped with a reverse-phase C_{18} column (1.7 μm particle size, 2.1 x 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI), a SQ mass spectrometer, and a photodiode array detector. 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. Analysis was run on a Waters Acquity UPLC® BEH C_8 (1.7 μm, 2.1 x 100 mm) column.

Chiral analytical HPLC was performed using a column at ambient temperature on an instrument with a diode array detector (210 nm, 230 nm, and/or 254 nm). All methods described in this document use either a Chiralcel OJ-H or Chiralpak IC column (4.6 mm internal diameter, 250 mm length, 5 μm particle size).

Many reaction solvents were purified using a Seca Solvent Purification System by GlassContour. All other chemicals were purchased commercially and used as received, unless otherwise indicated.

General Assay Design.

In this study, we followed many of the protocols that we outlined previously[2], but made a few improvements. Following the initial screening (see below), we adopted a linker tethering the peptides to resin from a PEG-based linker to a linker constructed from three aminohexanoic acid monomers (Supplementary Fig. S1). We constructed the linker to the resin such that instead of using a mixture of methionine and alanine at the position adjacent to the resin, we used only methionine. Second, for peptide sequencing, we opted to use LC/MS/MS experiments to circumvent the more time-intensive degradation protocol.

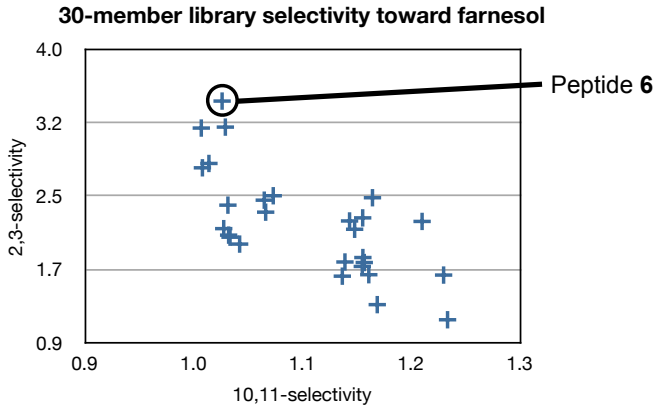


Supplementary Figure S1. Schematic of peptide screening.

Initial Screening.

On-bead peptides used for initial screening were derived from a few libraries from both parallel synthesis (peptides with known sequences) and split-and-pool synthesis (peptides with unknown sequences requiring identification post-screening). The general design of the initial split-and-pool libraries screened was described previously.[2] Specifically, we used unbiased libraries with both three

and five variable positions adjacent to the *N*-terminal aspartic acid; however, peptides from these libraries were identified post-screening using protocols outlined below (*i.e.*, LC/MS/MS: *vida infra*). Several peptides were also screened from a library of 30 peptides that were synthesized directly on 500-560 μm polystyrene A NH_2 resin (0.85 mmol/g loading; Rapp Polymere) using an automated peptide synthesizer. Couplings were performed in DMF using HBTU (5 equiv.), Fmoc-protected amino acid monomers (5 equiv.), and *i*-Pr_2EtN (6-10 equiv.) for 3 h. Deprotections were performed for 20 min using 20% piperidine in DMF (v/v). The peptide synthesizer was used to couple the first four residues to resin. The *N*-terminal Boc-Asp(OFm)-OH residue was coupled to each set of beads manually, first with two 20 min deprotection cycles as before and then with two couplings with amino acid monomer (4 equiv.), HBTU (4 equiv.), HOBt•H_2O (4 equiv.), and *i*-Pr_2EtN (8 equiv.) in DMF for about 3 h per coupling cycle. The aspartyl side chain was subjected to deprotection conditions with four 10 min treatments with 20% piperidine in DMF (v/v), followed by exhaustive washing with DCM and MeOH. The resin was dried under a stream of N_2. Data from the screen of the 30-member library using the screening protocol below are shown in Supplementary Fig. S2.



Supplementary Figure S2. Data from screen of parallel synthesis library. Each point represents a different resin-bound peptide and is normalized to the 6,7-selectivity. For example, in this study peptide **6** affords selectivity of 1.0:1.0:3.5 (**5**:**4**:**3**), but is plotted as (1.0, 3.5). Three of the 30 beads from this

small library did not produce sufficient product to be analyzed appropriately and are omitted from this figure.

Synthesis and Screening of Peptides from Split-and-Pool Libraries.

Peptide coupling procedure for libraries. Polystyrene macrobeads (Polystyrene A NH_2, 500-560 μm, 0.85 mmol/g loading, Rapp Polymere, Batch No. 122.816) were swelled in DMF for 20 minutes and then coupled twice for about 3 hours each to an amino acid coupling partner using Fmoc-protected amino acid monomers (4 equiv.), HBTU (equiv.), HOBt•H_2O (4 equiv.), and *i*-Pr_2EtN (8 equiv.). After coupling, the resin was washed several times with DMF and DCM. Deprotections commenced with two 20-minute treatments of 20% piperidine in DMF, and were followed by exhaustive washing with DMF and DCM.

All beads were first coupled to Fmoc-Met-OH (PerSeptive Biosystems). Next, the resin was coupled to three Fmoc-Ahx-OH (6-aminohexanoic acid, NovaBiochem). The beads were then split into the appropriate number of tubes for coupling according to the library design. After a round of double couplings, all of the beads were then combined and deprotected together in one reaction vessel. After washing exhaustively, the beads were then split again into the number of separate reaction vessels corresponding to library design and the split-and-pool process was performed additional times as indicated. The final coupling was performed with Boc-Asp(OFm)-OH (AAPPTEC). The Asp-side chain was deprotected by treatment with 20% piperidine/DMF four times for 10 minutes each. Finally, beads were washed exhaustively with DMF, DCM, and MeOH; then dried under N_2.

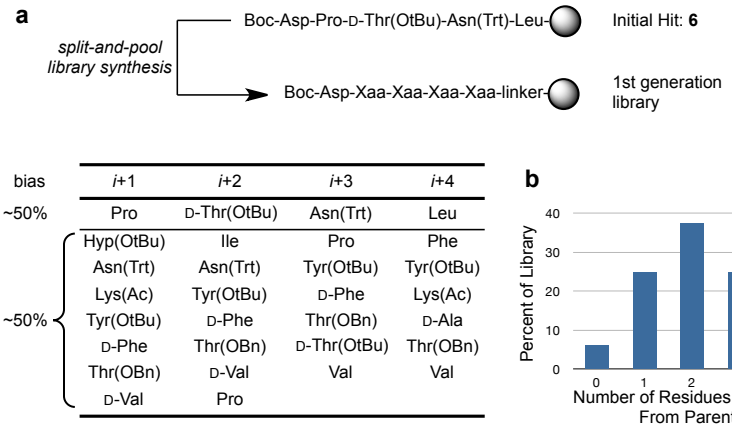
Synthesis of directed libraries. Libraries biased towards a parent sequence were generally split such that half of the linker-functionalized resin was coupled to the amino acid monomer present in the parent

sequence; the other half of resin was divided amongst other residues (indicated in the library design tables shown below in Supplementary Figures S3-S6).[3]

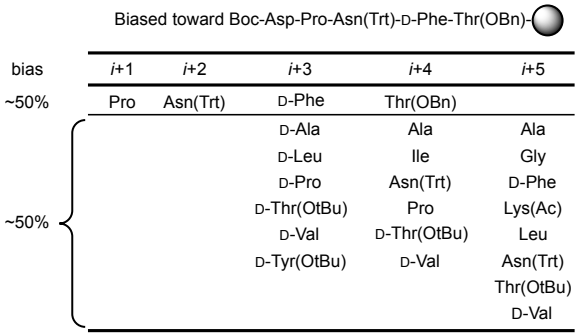
Screening protocols. We used two types of reaction vessels in this study. In earlier screens leading to the identification of hit peptides **6** and **7**, we used plastic 200 μL PCR tubes, but in all subsequent studies we used 400 μL sealable tubes with screw caps.

Beads were transferred individually to either 200 μL PCR tubes or 400 μL sealed tubes, and inspected for uniformity of size. An aqueous solution of H_2O_2 (0.5 μL, 2 M, 1 equiv.) was added to each tube followed by 5.05 μL of a DCM solution containing farnesol (**1**: 1 μmol, 1 equiv.), DIC (0.3 μmol, 0.3 equiv.), and HOBt•H_2O (0.1 μmol, 0.1 equiv.), DMAP (0.1 μmol, 0.1 equiv.), bringing the total reaction concentration of **1** to ~0.2 M. The tubes were then sealed and, if using PCR tubes, centrifuged, and allowed to stand for either 5-6 or 12 h. We found that the libries with longer peptides gave better results with longer reaction times using the sealed glass tubes.

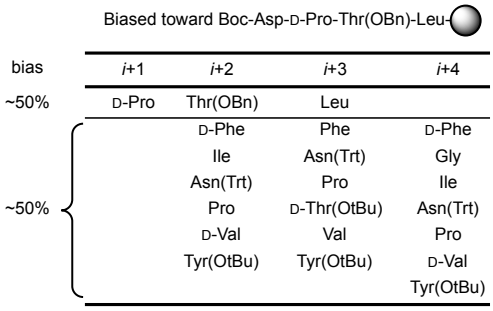
Work-up with plastic tubes (used earlier in screening): reactions were quenched with ~3 drops of sat. aq. Na_2SO_3, ~185 μL HPLC grade hexanes were added, and the tubes were vortexed and centrifuged. The top layer of the biphasic mixture was carefully moved to a GC vial with insert and then analyzed by GC. *Work-up with glass tubes:* reactions were quenched with 20 μL sat. aq. Na_2SO_3, 220 μL of hexane was added, and the samples were vortexed and analyzed by GC (sampling from the organic layer).



Supplementary Figure S3. Reproduced from Fig. 2 in manuscript. **a,** Design of first directed library. **b,** Histogram of theoretical library composition.



Supplementary Figure S4. Residues used in second library biased toward 2,3-selective peptide (**7**).



Supplementary Figure S5. Residues used in library toward 6,7-selective peptide (**11**).

Biased toward

Boc-Asp-D-Pro-Thr(OBn)-Asn(Trt)-Tyr(OtBu)-●

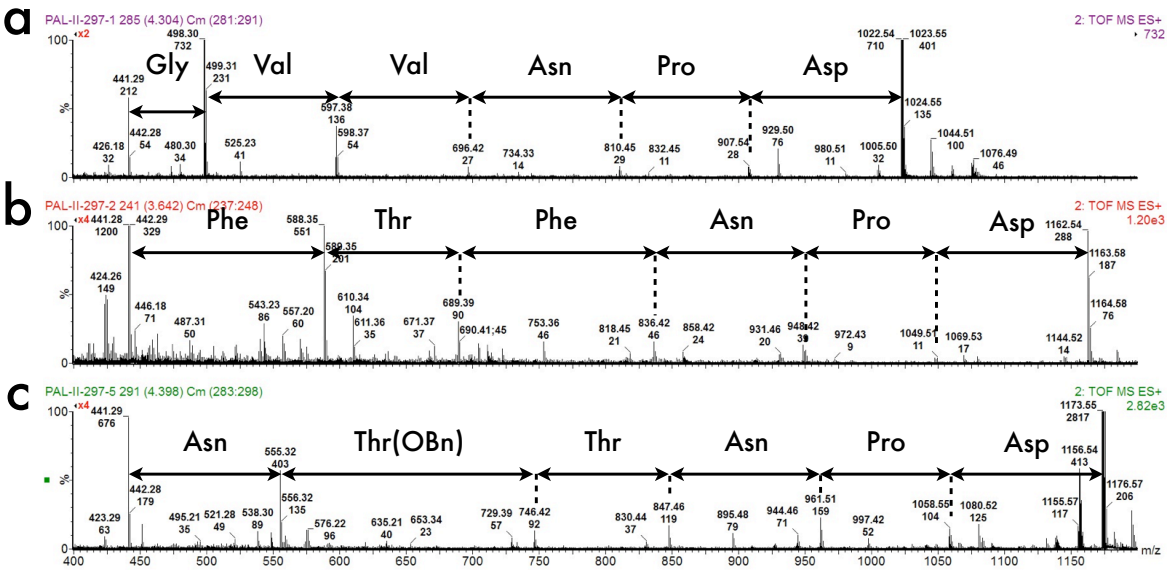
bias	*i*+2	*i*+3	*i*+4	*i*+5
~50%	Thr(OBn)	Asn(Trt)	Tyr(OtBu)	
~50%		Phe	Phe	D-Phe
		Thr(OtBu)	Thr(OBn)	Gly
		Leu	Pro	Ile
		Pro	D-Thr(OtBu)	Asn(Trt)
		D-Val	Asn(Trt)	Pro
		Tyr(OtBu)	Leu	Thr(OtBu)
		Ala	D-Val	D-Val
				Tyr(OtBu)

Supplementary Figure S6. Residues used in library biased toward 6,7-selective peptide (**12a**).

Peptide Sequencing Protocol.

Post-reaction, individual beads were removed from the reaction medium and placed in a fritted tube. Each bead was generally washed with H_2O (3x) and then MeOH (3x), which was repeated twice, and then removed to a clean 200 μL PCR tube to dry. Beads were treated with a few drops of 20 mg/mL CNBr in 70% TFA (aq.) overnight in the dark for at least 12 h. After drying the beads under vacuum, the resulting white solid was dissolved in 10 μL of a 33% H_2O in MeCN solution. 8 μL of the peptide solution was diluted in 92-100 μL of 33% H_2O in MeCN and analyzed by LC/MS/MS.

Prior to screening, a few beads from most libraries were sequenced to validate the library composition (sample validation is shown in Supplementary Fig. S7).



Supplementary Figure S7. Mass spectrum (MS^E program) of three beads from the second library directed towards 2,3-epoxidation (stereochemistry omitted; see Supplementary Fig. S4 for library composition). Prior to cleaving from resin, the sequences of the peptides were **a**, Boc-Asp-Pro-Asn(Trt)-D-Val-D-Val-Gly-linker/resin **b**, Boc-Asp-Pro-Asn(Trt)-D-Phe-D-Thr(OtBu)-D-Phe-linker/resin and, **c**, Boc-Asp-Pro-Asn(Trt)-D-Thr(OtBu)-Thr(OBn)-Asn(Trt)-linker/resin.

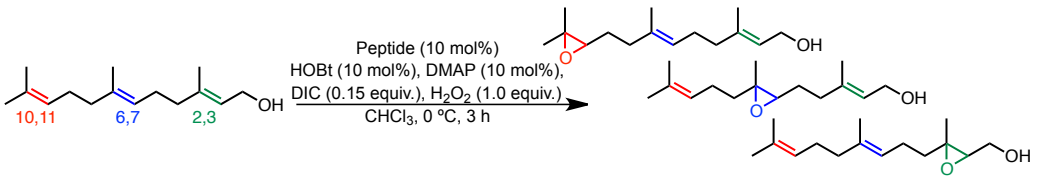
Validation Studies of On-bead Peptides and Optimization of 12.

On-bead peptide resynthesis. Polystyrene A NH_2 macrobeads (500-560 μm) were functionalized with Fmoc-protected amino acid monomers using peptide coupling protocols described above for synthesis of split-and-pool libraries with one exception: peptides (except **2a**) were synthesized with two 2 h couplings of monomers; however, the terminal aspartic acid residue was coupled with two 3 h couplings.

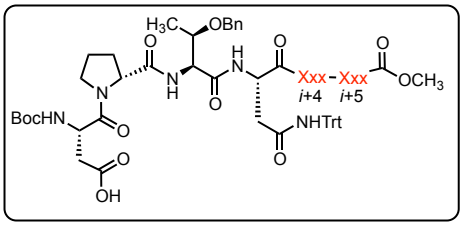
Evaluation as on-bead catalyst. Once synthesized, individual beads were sorted into glass tubes and evaluated following the same screening protocol detailed above for the split-and-pool libraries. Beads of entries 1-5 in Manuscript Table 1 were evaluated separately from entries 6 and 7.

Evaluation of solution phase catalysts. Peptides found in the second generation of 6,7-directed catalysts (Supplementary Fig. S6) were not resynthesized on-bead. Instead they were direcly validated in solution-phase studies. Results from some of these peptides are shown in Supplementary Table S1. Data from of these peptides (entries 1-9) were not substantially better than those found for **12b**. Given that an *i*+5 Gly appears in two of the peptides found from this library (entries 6 and 9), we investigated peptides **12c** and **12d**.

Supplementary Table S1. Comparison of resynthesized hit peptides found from screening of second 6,7-selective directed library (Supplementary Fig. S6) and catalyst **12d**.



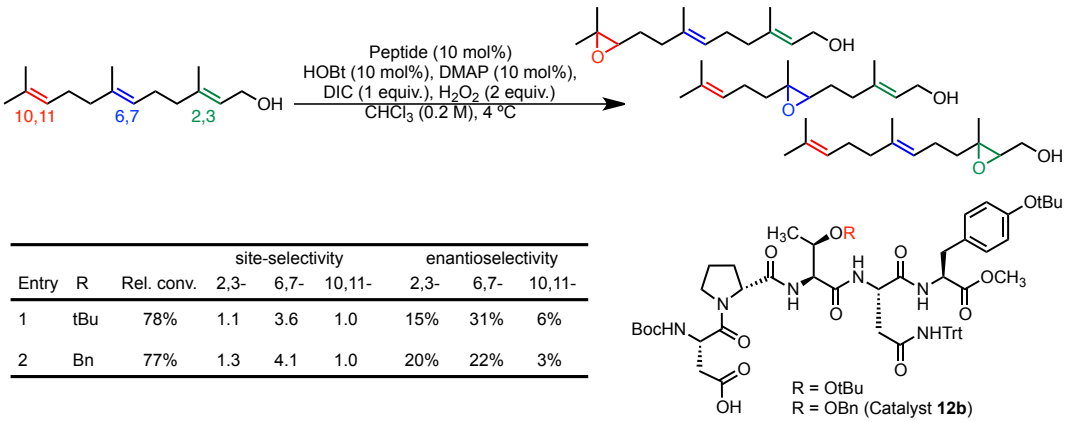
Entry	*i*+4	*i*+5	approx. conv.	2,3-	6,7-	10,11-
1	Asn(Trt)	DPhe	17%	1.1	2.0	1.0
2	Thr(OBn)	Pro	24%	1.5	3.2	1.0
3	Thr(OBn)	DVal	21%	1.0	3.3	1.0
4	Thr(OBn)	Thr(OtBu)	22%	1.5	3.3	1.0
5	Thr(OBn)	DPhe	24%	1.0	3.5	1.1
6	Thr(OBn)	Gly	21%	1.0	3.7	1.1
7	Tyr(OtBu)	DVal	22%	1.2	3.4	1.0
8	Tyr(OtBu)	D-Phe	22%	1.0	3.7	1.1
9	Phe	Gly	22%	1.0	3.5	1.1
10	Tyr(OtBu)	Gly	21%	1.0	4.1	1.2



Found in library screen

12d: Hypothesis-driven optimization

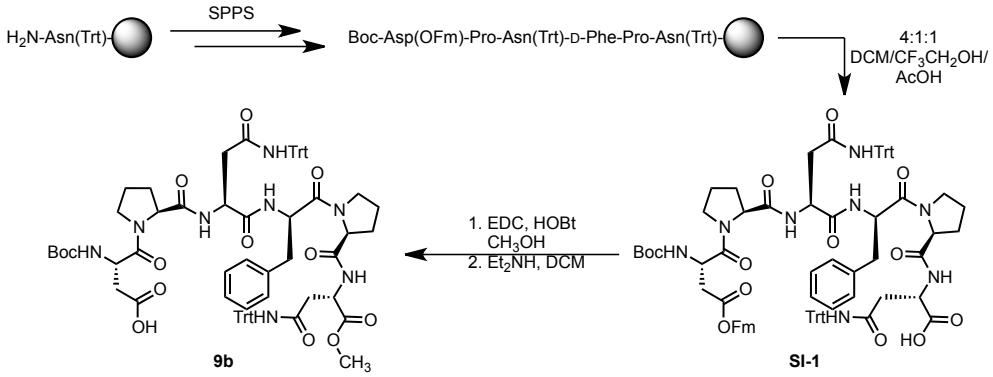
Supplementary Table S2. Comparison of site-selectivity and enatioselectivity of catalyst **12b** with a variant.



			site-selectivity			enantioselectivity		
Entry	R	Rel. conv.	2,3-	6,7-	10,11-	2,3-	6,7-	10,11-
1	tBu	78%	1.1	3.6	1.0	15%	31%	6%
2	Bn	77%	1.3	4.1	1.0	20%	22%	3%

Synthesis of Hit Peptides 9b and 12d.

*Synthesis of Peptide **9b**:*



Synthesis of precursor peptide **SI-1** was accomplished by coupling the appropriate amino acid monomers (Fmoc-Pro-OH, Fmoc-D-Phe-OH, Fmoc-Asn(Trt)-OH, Fmoc-Pro-OH, and then Boc-Asp(OFm)-OH) to 2-chlorotrityl functionalized polystyrene resin (2.573 g resin, 2.187 mmol, 0.85 meq/g loading, 1% DVB, Chem-Impex International Inc.) preloaded with Fmoc-Asn(Trt)-OH. Couplings were carried out in DMF by treating deprotected resin-bound peptide with 3 equiv. amino acid monomer, 3 equiv. HOBt•H_2O, 3 equiv. HBTU, and 6 equiv. $^{i}Pr_2EtN$. Couplings generally proceeded for 3 to 5 h. Deprotections were achieved with 20% (v/v) piperidine in DMF for

approximately 20 min. The resin was split into two roughly equal portions before coupling the final amino acid monomer, Boc-Asp(OFm)-OH.

Following the coupling of Boc-Asp(OFm)-OH, the peptide was cleaved from the resin with 4:1:1 DCM/AcOH/2,2,2-trifluoroethanol (v/v/v) for about 30 min. The liquid was collected into a flask along with several washes of additional cleavage solution and DCM. Toluene was added to the crude reaction mixture and was concentrated. The material was redissolved in DCM and toluene and concentrated, repeating a couple of times. The crude material was loaded onto a silica gel column (~80-90 mL silica) packed with 1% MeOH/1% AcOH in DCM. **SI-1** was purified by flash column chromatography eluting with a gradient of 1% MeOH to 4% MeOH in 1% AcOH/DCM. Fractions were collected, diluted with toluene and then concentrated *in vacuo* to afford approximately 600 mg of an off-white solid per batch. **TLC**: 3% MeOH, 1% AcOH in DCM (R_f = 0.1 to 0.3 streak), visualized by UV lamp, I_2/silica, and CAM.

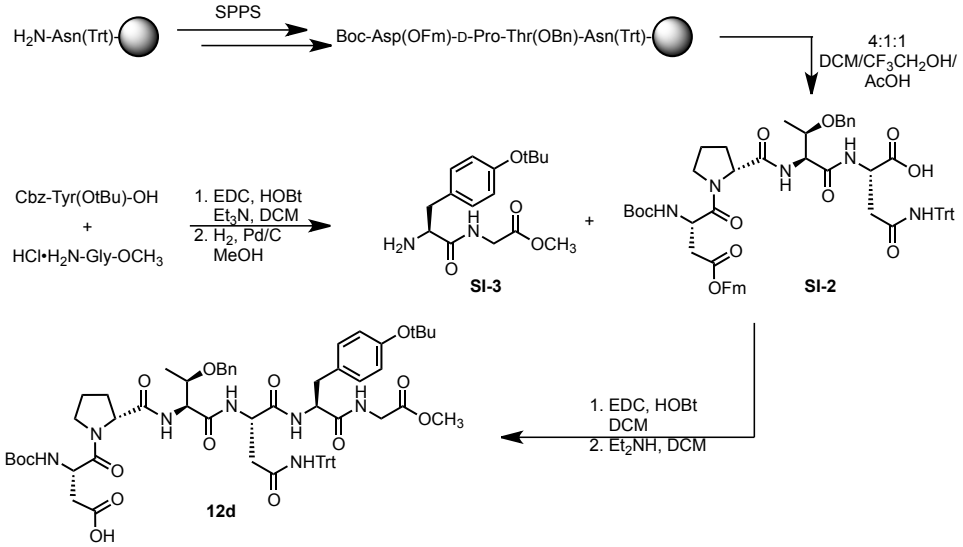
Peptide **SI-1** (~600 mg, ~0.41 mmol) was esterified by treatment with EDC•HCl (157 mg, 0.82 mmol, 2 equiv.) and HOBt•H_2O (125 mg, 0.82 mmol, 2 equiv.) in MeOH (5 mL). After 5-11 h of stirring, the crude reaction was concentrated, diluted with DCM and then washed with 0.5 M citric acid, saturated aqueous $NaHCO_3$, and then half-saturated brine. The organics were dried over Na_2SO_4, filtered and then concentrated.

The off-white solid was dissolved in 10 to 20 mL of Et_2HN/DCM (1:1 v/v) and allowed to stand, swirling occasionally. After about 30 min, the reaction was diluted with DCM, concentrated, and then diluted/concentrated a couple more times. The crude solid was loaded onto a silica gel column (~90 mL silica) packed in DCM with 1% MeOH and 1% AcOH. Peptide **9b** was purified by flash column chromatography eluting with a gradient of 1% MeOH to 5% MeOH in 1% AcOH/DCM. Fractions were collected and concentrated. To remove residual AcOH, the material was diluted with toluene and then

concentrated a couple of times. Concentration *in vacuo* furnished an off-white solid in a total of 905 mg (0.695 mmol) from the two batches, 32% overall yield.

TLC: 5% MeOH, 1% AcOH in DCM (R_f = 0.45). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 12.56 (bs, 1H), 7.53 (s, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.36 (s, 1H), 7.32-7.03 (m, 38H), 6.99 (d, *J* = 8.4 Hz, 1H), 5.39 (d, *J* = 9.1 Hz, 1H), 4.93-4.74 (m, 2H), 4.52 (dd, *J* = 7.1, 7.0 Hz, 1H), 4.41 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.35 (dd, *J* = 6.9, 3.2 Hz, 1H), 4.31-4.17 (m, 1H), 3.82-3.72 (m, 1H), 3.68-3.57 (m, 1H), 3.51 (s, 3H), 3.36-3.25 (m, 1H), 3.20-3.05 (m, 2H), 2.98-2.79 (m, 3H), 2.73-2.61 (m, 2H), 2.55 (dd, *J* = 15.8, 9.5 Hz, 1H), 2.32-2.14 (m, 2H), 2.04-1.80 (m, 4H), 1.72-1.57 (m, 2H), 1.38 (s, 9H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 173.6, 173.4, 172.4, 171.9, 171.3, 170.3, 168.5, 168.4, 155.0, 144.8, 144.6, 135.6, 129.4, 128.8, 128.8, 128.7, 127.9, 127.9, 127.7, 127.5, 127.0, 126.7, 80.4, 70.8, 70.5, 62.0, 60.9, 54.8, 52.3, 50.3, 49.9, 49.2, 47.8, 46.8, 38.7, 38.1, 37.3, 36.5, 29.5, 29.0, 28.3, 25.0, 23.8. **IR** (film, cm^{-1}): 3323, 1637, 1515, 1493, 1447, 1368, 1247, 1165, 1027, 1003. **HRMS**: calculated mass $[C_{75}H_{80}N_8O_{13}+H]^+$: 1301.592; ESI+ found 1301.593. **$[\alpha]_D$** = –82.0° (c = 1.0 g/100 mL $CDCl_3$).

*Synthesis of Peptide **12d**:*



*Sythesis of **SI-2**:* Synthesis of precursor peptide **SI-2** was accomplished by coupling the appropriate amino acid monomers (Fmoc-Thr(OBn)-OH, Fmoc-D-Pro-OH, and then Boc-Asp(OFm)-OH) to 2-chlorotrityl functionalized polystyrene resin (1.712 g resin, 0.924 mmol, 0.54 meq/g loading, 1% DVB, Chem-Impex International Inc.) preloaded with H_2N-Asn(Trt)-OH. Couplings were carried out in DMF by treating deprotected resin-bound peptide with 3 equiv. amino acid monomer, 3 equiv. HOBt•H_2O, 3 equiv. HBTU, and 6 equiv. $^{i}Pr_2EtN$. Couplings generally proceeded for about 5 h each. Deprotections were achieved with 20% (v/v) piperidine in DMF for approximately 20-30 min.

Following the coupling of Boc-Asp(OFm)-OH, the peptide was cleaved from the resin with 4:1:1 DCM/AcOH/2,2,2-trifluoroethanol (v/v/v) for about 30 min. The liquid was collected into a flask along with several washes of additional cleavage solution and DCM. Toluene was added to the crude reaction mixture and was concentrated. The material was redissolved in DCM and toluene and concentrated, repeating a couple of times. The crude material was loaded onto a silica gel column packed with 1% MeOH/1% AcOH in DCM. **SI-2** was purified by flash column chromatography eluting with a gradient of 1% MeOH to 4% MeOH in 1% AcOH/DCM. Fractions were collected, diluted with toluene and then concentrated *in vacuo* to afford approximately 930 mg of an off-white solid. **TLC**: 3% MeOH, 1% AcOH in DCM (R_f = 0.20), visualized by UV lamp, I_2/silica, and CAM (blue).

*Synthesis of **SI-3**:* To a round-bottom flask was added Cbz-Tyr(OtBu)-OH (1.106 g, 2.0 mmol, 1 equiv.), HCl•H_2N-Gly-OMe (251 mg, 2.0 mmol, 1 equiv.), EDC•HCl (422 mg, 2.2 mmol, 1.1 equiv.), HOBt•H_2O (337 mg, 2.2. mmol, 1.1 equiv.), Et_3N (243 mg, 335 μL, 2.4 mmol, 1.2 equiv.), and DCM (~20 mL). After about 8 h of stirring at room temperature, the reaction was diluted with DCM, washed with 0.5 M citric acid, half-saturated brine, and then saturated aqueous $NaHCO_3$. The organics were dried over Na_2SO_4, filtered, and then concentrated *in vacuo* to yield 780 mg (1.76 mmol, 88 % yield) of a viscous, colorless oil. The resulting dipeptide was dissolved in MeOH and added via syringe to a flask

that contained a stir bar and Pd/C (220 mg, 10% Pd w/w) under a N_2 atmosphere. Additional MeOH washes were added (17 mL MeOH total) and the flask was then purged of N_2 and then allowed to stir under an atmosphere of H_2. After a total of 4.75 h of stirring under H_2, the flask was flushed with N_2 and the reaction slurry was filtered through a thick pad of celite. The MeOH was removed by rotary evaporation and then DCM was added and concentrated.

Peptide **SI-2** (809 mg, 0.77 mmol) was added to the flask containing concentrated dipeptide **SI-3** along with EDC•HCl (163 mg, 0.85 mmol, 2 equiv.), HOBt•H_2O (153 mg, 0.85 mmol, 1.1 equiv.) in DCM (~8 mL). After ~12 h, another 0.25 equiv of EDC and HOBt were added. After a total time of ~18.6 h, reaction was diluted with DCM, washed with 0.5 M citric acid, half-saturated brine, and then saturated aqueous $NaHCO_3$. The solution was dried over Na_2SO_4, filtered, and then concentrated down to a yellow oil, which solidified upon standing.

The solid was dissolved in 20 mL of Et_2HN/DCM (1:1 v/v) and stirred. After about 40 min, the reaction was diluted with DCM, concentrated, and then diluted/concentrated a couple more times. The crude solid was loaded onto a silica gel column packed in DCM with 1% MeOH and 1% AcOH. Peptide **12d** was purified by flash column chromatography eluting with a gradient of 1% MeOH to 4% MeOH in 1% AcOH/DCM. A set of fractions deemed to be clean by TLC were collected and concentrated. A second set of fractions containing an impurity were collected, concentrated, and purified further by flash silica gel column chromatography (see note below). To remove residual AcOH, both portions of material were diluted with toluene and then concentrated a couple of times. A total of 610 mg (0.52 mmol) **12d** was obtained in an overall 57% yield.

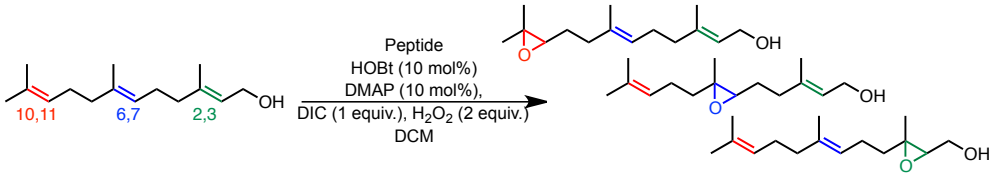
Note: the major impurity present in the chromatographed peptide was likely *N*-acetylated **SI-3** resulting from incomplete removal of acetic acid prior to the coupling of **SI-3** with **SI-2**. The presence of this impurity appeared to have little appreciable effect on reaction selectivity as it was used in the

synthesis of **4** (trial 3) and **15** (trials 1 and 2). The material containing the impurity was further purified by reverse phase chromatography using a 60g Biotage C_{18}-column with a gradient of 40% MeOH in acidic H_2O with 0.1% formic acid to 100% MeOH. The material was then concentrated *in vacuo*.

TLC: 4% MeOH, 1% AcOH in DCM (R_f = 0.30). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 1H), 7.46 (s, 1H), 7.32-7.13 (m, 20H), 7.13-7.03 (m, 3H), 6.92-6.86 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.29 (d, *J* = 10.5 Hz, 1H), 4.81 (ddd, *J* = 10.5, 6.5, 4.3 Hz, 1H), 4.69 (ddd, = 11.3, 8.5, 5.5, 1H), 4.55 (bs, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.44 (qd, *J* = 6.3, 1.8 Hz (resolution of peaks is not complete; J inferred from interior of q), 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.32 (dd, *J* = 9.0, 1.7 Hz, 1H), 4.14 (t, *J* = 7.3 Hz, 1H), 3.74 (dd, *J* = 17.6, 6.9 Hz, 1H), 3.71-3.59 (m, 2H), 3.55 (s, 3H), 3.42 (dd, *J* = 15.9, 11.4 Hz, 1H), 3.35 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.94 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.85 (dd, *J* = 16.6, 6.5 Hz, 1H), 2.80-2.68 (m, 1H), 2.57 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.43 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.24-1.98 (m, 3H), 1.87 (dp, *J* = 11.7, 7.9 Hz, 1H), 1.47 (s, 9H), 1.32 (s, 9H), 1.20 (d, *J* = 6.4 Hz, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 173.9, 172.7, 171.6, 170.6, 170.4, 170.2, 170.0, 169.8, 155.6, 154.4, 144.2, 137.8, 130.6, 130.4, 128.7, 128.5, 128.0, 128.0, 127.9, 127.1, 124.3, 80.5, 78.3, 77.4, 74.0, 72.1, 70.6, 61.3, 58.2, 54.0, 51.9, 50.0, 49.3, 47.8, 41.1, 36.9, 35.3, 29.0, 29.0, 28.5, 25.8, 17.2. **IR** (film, cm^{-1}): 3306, 2976, 1671, 1633, 1505, 1447, 1366, 1285, 1236, 1205, 1161, 1090, 1026. **HRMS**: calculated mass $[C_{64}H_{77}N_7O_{14}+H]^+$: 1168.561; ESI+ found 1168.536. **$[\alpha]_D$** = –63.7° (c = 1.0 g/100 mL $CHCl_3$).

Condition Optimization of Allylic Epoxidation.

Supplementary Table S3. Studies of peptide **8b** and **9b** under different conditions. GC detection limits were not established.



Entry	Acid	cat. loading (mol%)	temp.	time (h)	"conv."	10,11	6,7	2,3	ee
1	**8b**	10	r.t.	3.1	87%	1.0	1.3	115	79%
2	**8b**	10	4 °C	3.9	97%	1.0	2.0	603	82%
3	**9b**	10	r.t.	3.0	90%	1.0	1.3	126	85%
4	**9b**	10	4 °C	3.0	93%	1.0	1.7	328	87%
5	**9b**	5	r.t.	5.0	87%	1.0	1.3	93	84%
6	**9b**	5	4 °C	7.1	80%	1.0	1.1	108	85%

Substrate Studies with Peptide 9b.

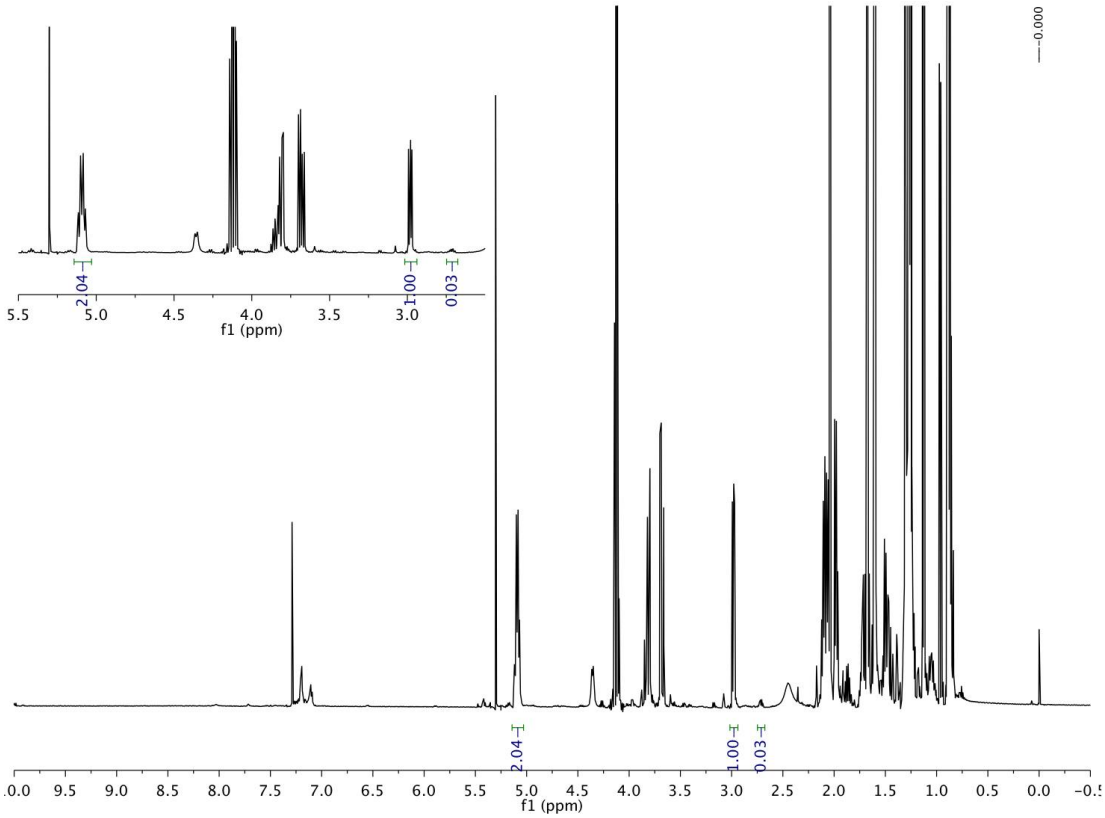
Experimental conditions are described for an individual run. Any deviations from the general Epoxidation Procedures are indicated.

Epoxidation Procedure A: allylic epoxidation with peptide 9b.

To a test tube with stir bar and Teflon-lined screw cap was added peptide **9b** (0.1 equiv); allylic alcohol (1.0 equiv.); a freshly prepared/sonicated solution containing HOBt•H_2O (0.1 equiv.) and DMAP (0.1 equiv.) in DCM (to a concentration of 0.2 M of substrate); and 30% aqueous H_2O_2 (2.0 equiv.). The test tube was placed in ice (if running reaction below room temperature) and allowed to chill before adding DIC (1.0 equiv.). The reaction tube was then sealed with a screw-cap under ambient conditions without exclusion of air and brought to a cold room (4 °C) where the reaction was stirred vigorously. After 7 h following addition of DIC, the reaction was quenched with a saturated aqueous solution of Na_2SO_3 and stirred for a few moments, sitting in ice, before allowing to warm to room

temperature. Saturated aqueous $NaHCO_3$ and hexane or EtOAc were added, the mixture was vortexed, allowed to settle, and then the organic layer was removed, followed by two to three additional hexane or EtOAc extracts, peformed similarly. If site-selectivity was to be determined, an aliquot of the combined organics was removed, diluted with additional hexanes and analyzed by GC. The organics were concentrated *in vacuo* or under a stream of N_2, and then purified by flash silica gel column chromatography.

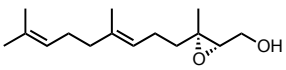
Derivatization Protocol for enantioselectivity assay by HPLC. An aliquot of the crude reaction mixture or purified alcohol was concentrated into a tared vial. DMAP (approximately 2.5 equiv.), 100 μL DCM, and benzoyl chloride (approximately 2.0 equiv.) were added and allowed to stand. Reactions were left for anywhere between a few minutes to a few hours before quenching with saturated aqueous $NaHCO_3$ and then vortexing. A portion of hexanes was added, vortexed, and the organics were concentrated. A smaller volume of hexanes was added, vortexed in the reaction vial, and the organic crude was loaded on a prepTLC plate and eluted in an Et_2O/hexanes mixture. Spots were isolated from the plate, sonicated in EtOAc, filtered, and then concentrated to dryness under a stream of N_2. The isolated derivatized products were dissolved in HPLC grade hexanes and analyzed by HPLC.



Supplementary Figure S8. ^{1}H-NMR (500 MHz) of crude reaction mixture of peptide **9b** and farnesol. Highlighed integration shows ratio of epoxide protons: the major peak (integrated to 1.00) includes all farnesol derivatives oxidized at the 2,3-position and the minor peak (integrated to 0.03) includes all derivatives oxidized in other positions (*i.e.*, the 6,7-/10,11-monoepoxides and any overoxidized products).

Experimental Procedures for Compounds in Table 2:

Synthesis of 2,3-epoxyfarnesol (**3**):



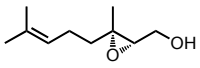
Epoxidation Procedure A was followed with farnesol (111 mg, 125.4 μL, 0.50 mmol, 1 equiv., Aldrich), peptide **9b** (65 mg, 0.050 mmol), HOBt•H_2O (7.7 mg, 0.050 mmol, 0.1 equiv.), DMAP (6.1 mg, 0.050 mmol, 0.1 equiv.) and DCM (2.5 mL). Note that for this scale of reaction, DMAP and

HOBt•H_2O were added as solids directly to the reaction flask rather than preparing a solution as described in the general Epoxidation Procedure A, whereas the protocol was followed as written in the other trial. The reaction was run with DIC (63 mg, 78.3 μL, 0.50 mmol, 1 equiv.) and 30% aq. H_2O_2 (103 μL, 1.0 mmol, 2.0 equiv.). The crude reaction mixture was extracted with a mixture of hexanes and EtOAc (trial 1 was extracted with hexanes). A ^{1}H-NMR of the crude reaction from trial 2 is shown in Supplementary Fig. S8. Epoxide **3** was isolated by flash column chromatography on a silica gel column (~60 mL silica) with a gradient of 10% Et_2O to 55% Et_2O in hexanes. Fractions were collected, concentrated, filtered, and then concentrated *in vacuo* to yield 88.7 mg, 0.372 mmol of a clear, colorless oil. Average yield of 81% (trial 1 from 0.100 mmol farnesol: 87%; trial 2 from 0.500 mmol farnesol: 74%).

TLC: 50% Et_2O in hexanes (R_f = 0.30), visualized with I_2/silica and CAM stain. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.17-5.00 (m, 2H), 3.83 (ddd, *J* = 11.8, 7.3, 4.3 Hz, 1H), 3.69 (ddd, *J* = 11.7, 6.6, 4.6 Hz, 1H), 2.98 (dd, *J* = 6.7, 4.3 Hz, 1H), 2.15-1.92 (m, 6H), 1.75-1.64 (m, 4H), 1.63-1.53 (m, 7H), 1.48 (ddd, *J* = 13.7, 9.1, 7.5 Hz, 1H), 1.31 (s, 3H). Data are consistent with ^{1}H-NMR spectra in the literature[4].

A small portion of **3** was derivatized according to the Derivatization Protocol to make the corresponding benzoate ester to assess enantiopurity by HPLC analysis. **TLC**: 10% Et_2O in hexanes (R_f = 0.40), visualized by UV lamp. **^{1}H-NMR** (400 MHz, $CDCl_3$, tabulated from spectrum of racemic standard): δ 8.11-8.04 (m, 2H), 7.61-7.53 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.16-5.00 (m, 2H), 4.57 (dd, *J* = 12.1, 4.3 Hz, 1H), 4.30 (dd, *J* = 12.1, 6.8 Hz, 1H), 3.15 (dd, *J* = 6.8, 4.3 Hz, 1H), 2.22-1.90 (m, 6H), 1.73 (ddd, *J* = 13.5, 8.6, 6.7 Hz, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.58 (s, 3H), 1.51 (ddd, *J* = 13.7, 9.2, 7.1 Hz, 1H), 1.38 (s, 3H). **HPLC**: average 86% ee (trial 1: 86% ee; trial 2: 87% ee). Stereochemistry is assigned based on a comparison to HPLC trace of derivatized **3** produced from Sharpless asymmetric epoxidation with D-DIPT[5] and by optical rotation[6].

Synthesis of 2,3-epoxygeraniol:



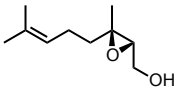
Epoxidation Procedure A was followed with geraniol (28.0 mg, 31.5 μL, 0.181 mmol, 1 equiv., Alfa Aesar) and peptide **9b** (23.6 mg, 0.0181 mmol) in a solution of HOBt•H_2O (2.8 mg, 0.0181 mmol, 0.1 equiv.) and DMAP (2.2 mg, 0.0181 mmol, 0.1 equiv.) in DCM (910 μL). The reaction was run with DIC (22.9 mg, 28.4 μL, 0.181 mmol, 1 equiv.) and 30% aq. H_2O_2 (37.4 μL, 0.363 mmol, 2.0 equiv.). 2,3-Epoxygeraniol was isolated by flash column chromatography on a silica gel column (~40 mL silica) with a gradient of 10% Et_2O to 60% Et_2O in pentane. Fractions were collected, filtered and concentrated *in vacuo* to yield 25.9 mg (0.152 mmol) of a clear, colorless oil. Average yield of 80% (trial 1 from 0.100 mmol geraniol: 76%; trial 2 from 0.181 mmol geraniol: 84%).

TLC: 50% Et_2O in hexanes (R_f = 0.20). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 5.11-5.05 (m, 1H), 3.83 (ddd, *J* = 11.7, 7.1, 4.3 Hz, 1H), 3.68 (ddd, *J* = 11.7, 6.7, 4.0 Hz, 1H), 2.97 (dd, *J* = 6.7, 4.3 Hz, 1H), 2.14-2.02 (m, 2H), 1.78-1.62 (m, 5H), 1.61 (s, 3H), 1.47 (ddd, *J* = 13.8, 9.1, 7.4 Hz, 1H), 1.30 (s, 3H). **$[\alpha]_D$** = –3.2° (c = 1.5 g/100 mL $CDCl_3$). Stereochemistry is assigned by comparison of the sign of optical rotation to a reported literature value for this compound[7].

A portion of the epoxide product was derivatized using the Derivatization Protocol to make 2,3-geranyl benzoate. **TLC**: 10% Et_2O in hexanes (R_f = 0.40). **^{1}H-NMR** (400 MHz, $CDCl_3$, tabulated from a spectrum of a racemic standard): δ 8.12-8.03 (m, 2H), 7.61-7.53 (m, 1H), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H), 5.09 (dddd, *J* = 8.7, 7.0, 2.9, 1.5 Hz, 1H), 4.57 (dd, *J* = 12.1, 4.3 Hz, 1H), 4.30 (dd, *J* = 12.1, 6.7 Hz,

1H), 3.14 (dd, *J* = 6.7, 4.3 Hz, 1H), 2.19-2.01 (m, 2H), 1.79-1.63 (m, 4H), 1.61 (s, 3H), 1.51 (ddd, *J* = 13.6, 9.2, 7.2 Hz, 1H), 1.38 (s, 3H). **HPLC**: average 87% ee (trial 1: 86% ee; trial 2: 87% ee).

Synthesis of 2,3-epoxynerol:



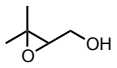
Epoxidation Procedure A was followed with nerol (26.7 mg, 30.3 μL, 0.173 mmol, 1 equiv., Alfa Aesar) and peptide **9b** (23.6 mg, 0.0173 mmol) in a solution of HOBt•H_2O (2.6 mg, 0.0173 mmol, 0.1 equiv.)/DMAP (2.1 mg, 0.0173 mmol, 0.1 equiv.) in DCM (865 μL). The reaction was run with DIC (21.8 mg, 27.1 μL, 0.173 mmol, 1 equiv.) and 30% aq. H_2O_2 (35.6 μL, 0.346 mmol, 2.0 equiv.). The crude reaction mixture was extracted with EtOAc (trial 1 was extracted with hexanes) and then 2,3-epoxynerol was isolated by flash column chromatography on a silica gel column (~30-40 mL silica) with a gradient of 10% Et_2O to 60% Et_2O in pentane. Fractions were collected, filtered and concentrated *in vacuo* to yield 26.5 mg, 0.156 mmol of a clear, colorless oil. Average yield of 79% (trial 1 from 0.100 mmol nerol: 68%; trial 2 from 0.173 mmol nerol: 90%).

TLC: 50% Et_2O in hexanes (R_f = 0.25). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 5.09 (m, 1H), 3.81 (ddd, *J* = 11.6, 6.6, 4.3 Hz, 1H), 3.66 (ddd, *J* = 11.7, 6.9, 3.4 Hz, 1H), 2.96 (dd, *J* = 6.9, 4.4 Hz, 1H), 2.20-2.00 (m, 2H), 1.90-1.82 (m, 1H), 1.72-1.63 (m, 5H), 1.61 (s, 3H), 1.48 (ddd, *J* = 13.8, 9.8, 7.0 Hz, 1H), 1.34 (s, 3H). **$[\alpha]_D$** = –13.8° (c = 0.83 g/100 mL $CHCl_3$). Stereochemistry is assigned based on the sign of optical rotation compared to the literature[8].

A small portion of 2,3-epoxynerol was derivatized according to the Derivatization Protocol to make the corresponding benzoate ester to assess enantiopurity by HPLC analysis. **TLC**: 20% Et_2O in hexanes (R_f = 0.55), visualized by UV lamp. **^{1}H-NMR** (500 MHz, $CDCl_3$, tablulated from spectrum of racemic

standard): δ 8.11-8.03 (m, 2H), 7.62-7.53 (m, 1H), 7.49-7.41 (m, 2H), 5.12 (m, 1H), 4.59 (dd, *J* = 12.1, 4.2 Hz, 1H), 4.27 (dd, *J* = 12.1, 7.0 Hz, 1H), 3.13 (dd, *J* = 7.0, 4.2 Hz, 1H), 2.24-2.07 (m, 2H), 1.76-1.66 (m, 4H), 1.62 (s, 3H), 1.59-1.48 (m, 1H), 1.38 (s, 3H). **HPLC**: average 93% ee (trial 1: 92% ee; trial 2: 94% ee).

Synthesis of 2,3-epoxyprenol:



Epoxidation Procedure A was followed with prenol (8.6 mg, 10.0 μL, 0.100 mmol, 1 equiv., Aldrich) and peptide **9b** (13.0 mg, 0.0100 mmol) in a solution of HOBt•H_2O (1.5 mg, 0.0100 mmol, 0.1 equiv.)/DMAP (1.2 mg, 0.0100 mmol, 0.1 equiv.) in DCM (500 μL). The reaction was run with DIC (12.6 mg, 15.7 μL, 0.100 mmol, 1 equiv.) and 30% aq. H_2O_2 (20.6 μL, 0.200 mmol, 2.0 equiv.). After 7 h, the reaction was quenched and extracted with EtOAc. A solution containing 0.10 mmol menthol (internal standard) was added to the combined extracts and mixed. An aliquot was removed, diluted with EtOAc, and then analyzed by GC to determine the reaction yield. Average yield of 75% (trial 1 from 0.100 mmol prenol: 78%; trial 2 from 0.100 mmol prenol: 73%).

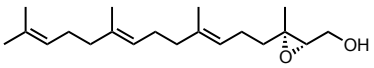
TLC: 100% Et_2O (R_f = 0.50). **^{1}H-NMR** (500 MHz, $CDCl_3$, tabulated from spectrum of racemic standard): δ 3.84 (ddd, *J* = 11.7, 7.2, 4.3 Hz, 1H), 3.69 (ddd, *J* = 11.7, 6.6, 4.4 Hz, 1H), 2.98 (dd, *J* = 6.7, 4.4 Hz, 1H), 1.67 (bs, 1H), 1.35 (s, 3H), 1.32 (s, 3H).

Although the product was not isolated, a portion of the crude reaction mixture was removed to a vial and concentrated under a stream of N_2. The Derivatization Protocol was used on the crude material to afford the benzoate ester. **TLC**: 10% Et_2O in hexanes (R_f = 0.20). **^{1}H-NMR** (400 MHz, $CDCl_3$, tabulated from spectrum of racemic standard): δ 8.11-8.04 (m, 2H), 7.61-7.53 (m, 1H), 7.49-7.41 (m,

2H), 4.59 (ddd, *J* = 12.2, 4.3, 1.1 Hz, 1H), 4.28 (ddd, *J* = 12.1, 6.6, 1.1 Hz, 1H), 3.14 (dd, *J* = 6.8, 4.3 Hz, 1H), 1.39 (s, 6H). **HPLC**: average 92% ee (trial 1: 92% ee; trial 2: 92% ee).

Experimental Procedure for the Synthesis of Compound 14 in Figure 3:

Synthesis of 2,3-epoxygeranylgeraniol (**14**):



Epoxidation Procedure A was followed with geranylgeraniol (**13**: 31.8 mg, 0.109 mmol, 1 equiv., Sigma) and peptide **9b** (14.2 mg, 0.0109 mmol) in a solution of HOBt•H_2O (1.7 mg, 0.0109 mmol, 0.1 equiv.)/DMAP (1.3 mg, 0.0109 mmol, 0.1 equiv.) in DCM (550 μL). The reaction was run with DIC (13.8 mg, 17.1 μL, 0.109 mmol, 1 equiv.) and 30% aq. H_2O_2 (22.6 μL, 0.219 mmol, 2.0 equiv.). **14** was isolated by flash column chromatography on a silica gel column (~35 mL silica) with a gradient of 10% Et_2O to 60% Et_2O in hexanes. Fractions were collected, filtered and concentrated *in vacuo* to yield a clear colorless oil in an average of 85% yield (trial 1 from 0.100 mmol geranylgeraniol: 83%; trial 2 from 0.109 mmol geranylgeraniol: 86%).

TLC: 50% Et_2O in hexanes (R_f = 0.25), best visualized by I_2/silica. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 5.09 (m, 3H), 3.82 (ddd, J = 11.7, 7.3, 4.2 Hz, 1H), 3.68 (ddd, J = 11.7, 6.7, 4.5 Hz, 1H), 2.97 (dd, J = 6.8, 4.2 Hz, 1H), 2.14-2.01 (m, 6H), 2.01-1.93 (m, 4H), 1.87 (bs, 1H), 1.74-1.64 (m, 4H), 1.62-1.56 (m, 9H), 1.47 (ddd, J = 13.7, 9.2, 7.4 Hz, 1H), 1.30 (s, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 136.0, 135.2, 131.4, 124.5, 124.2, 123.3, 63.1, 61.6, 61.3, 39.9, 39.8, 38.7, 26.9, 26.7, 25.8, 23.7, 17.8, 16.9, 16.1. **IR** (film, cm^{-1}): 3420, 2965, 2921, 2855, 1449, 1383, and 1033. **HRMS**: calculated mass $[C_{20}H_{34}O_2+H]^+$: 307.264; ESI+ found 307.265. **$[\alpha]_D$** = –1.4° (c = 1.0 g/100 mL $CHCl_3$).

A small portion of **14** was derivatized according to the Derivatization Protocol to make the corresponding benzoate ester to assess enantiopurity by HPLC analysis. **TLC**: 20% Et_2O in hexanes (R_f

= 0.60), visualized by UV lamp. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.11-8.04 (m, 2H), 7.61-7.54 (m, 1H), 7.49-7.42 (m, 2H), 5.14-5.05 (m, 3H), 4.57 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.30 (dd, *J* = 12.1, 6.8 Hz, 1H), 3.15 (dd, *J* = 6.8, 4.3 Hz, 1H), 2.18-1.92 (m, 10H), 1.73 (ddd, *J* = 13.8, 8.9, 6.4 Hz, 1H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.54-1.48 (m, 1H), 1.38 (s, 3H). **HPLC**: average 86% ee (trial 1: 87% ee; trial 2: 86% ee). Stereochemistry is assigned based on analogy to other compounds presented herein.

Substrate Studies with Peptide 12d.

Experimental conditions are described for an individual run. Any deviations from the general Epoxidation Procedures are indicated.

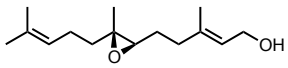
Epoxidation Procedure B: epoxidation of 6,7-olefins with peptide 12d.

To a test tube with stir bar and Teflon-lined screw cap was added peptide **12d** (0.1 equiv); substrate (1.0 equiv.); about two thirds of a freshly prepared/sonicated solution containing HOBt•H_2O (0.1 equiv.) and DMAP (0.1 equiv.) in $CHCl_3$ (the $CHCl_3$ was passed through basic alumina prior to mixing with DMAP/HOBt); and 30% aqueous H_2O_2 (1.5 equiv.). The test tube was placed in ice and allowed to chill before adding DIC (1.0 equiv.) followed by the remaining $CHCl_3$ solution (to a concentration of 0.2 M of substrate), rinsing down the sides of the reaction tube. The reaction tube was then sealed with a screw-cap under ambient conditions without exclusion of air and placed in an ^{i}PrOH bath maintained at –12 ºC to –18 ºC by cryostat. The reaction was then stirred vigorously. 25–48 h following addition of DIC, the reaction was quenched with a saturated aqueous solution of Na_2SO_3 and stirred for a few moments, still at low temperature, before allowing to warm to room temperature. Saturated aqueous $NaHCO_3$ and EtOAc were then added and the mixture was vortexed, allowed to settle, and then the organic layer was removed, along with three additional EtOAc extracts, peformed similarly. An aliquot

of the combined organics was removed, diluted with additional EtOAc and analyzed by GC. The organics were concentrated *in vacuo* and then purified by flash column chromatography.

Experimental Procedures for Compounds 4 and 15 in Table 2:

Synthesis of 6,7-epoxyfarnesol (**4**):



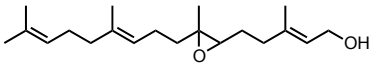
Epoxidation Procedure B was followed with farnesol (30.5 mg, 34.3 μL, 0.137 mmol, 1 equiv., Aldrich), peptide **12d** (16.0 mg, 0.0137 mmol), HOBt•H_2O (2.1 mg, 0.0137 mmol, 0.1 equiv.), DMAP (1.7 mg, 0.0137 mmol, 0.1 equiv.) and $CHCl_3$ (684 μL). The reaction was run with DIC (19.0 mg, 23.6 μL, 0.151 mmol, 1.1 equiv.) and 30% aq. H_2O_2 (21.2 μL, 0.205 mmol, 1.5 equiv.). After 25 h (trial 1 and trial 2; trial 3 was run for 48 h), the reaction was quenched and worked up. Epoxide **4** was isolated by flash column chromatography on a silica gel column (~50 mL silica) with a gradient of 10% Et_2O to 60% Et_2O in hexanes. Fractions were collected, concentrated, filtered and then concentrated *in vacuo* to yield 13.6 mg (0.0571) mmol of a clear, colorless oil. Average yield of 43% (trial 1 from 0.137 mmol farnesol: 42%; trial 2 from 0.129 mmol farnesol: 44%; trial 3 from 0.125 mmol farnesol, 44%).

TLC: 2:1 Et_2O to hexanes (R_f = 0.25). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 5.45 (t, *J* = 6.9 Hz, 1H), 5.07 (t, *J* = 7.1 Hz, 1H), 4.16 (d, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.27-1.97 (m, 4H), 1.77-1.55 (m, 12H), 1.46-1.37 (m, 1H), 1.25 (s, 4H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 138.9, 132.1, 124.0, 123.8, 63.4, 60.9, 59.5, 38.9, 36.3, 27.2, 25.8, 24.0, 17.8, 16.7, 16.4. **IR** (film, cm^{-1}): 3423, 2964, 2920, 2855, 1670, 1450, 1384, 1111, 1073, 1002. **MS**: calculated mass $[C_{15}H_{26}O_2+H]^+$: 261.183; ESI+ found 261.186. **$[\alpha]_D$** = +4.1° (c = 1.0 g/100 mL $CHCl_3$).

A small portion of **4** was derivatized according to the Derivatization Protocol to make the corresponding benzoate ester to assess enantiopurity by HPLC analysis. The derivatized products are

isolated as a mixture of 6,7- and 10,11-epoxyfarnesyl benzoates. **TLC**: 20% Et_2O in hexanes (R_f = 0.40), visualized by UV lamp. **HPLC**: average 10% ee (trial 1: 9.9% ee; trial 2: 9.6% ee). Stereochemistry is assigned based on a comparison to HPLC trace of derivatized **4** and **5** produced from asymmetric epoxidation with the Shi ketone[9].

Synthesis of 6,7-epoxygeranylgeraniol (**15**):



Epoxidation Procedure B was followed with geranylgeraniol (32.1 mg, 0.111 mmol, 1 equiv., Sigma) and peptide **12d** (12.9 mg, 0.0111 mmol, 0.1 equiv.) in a solution of HOBt•H_2O (1.7 mg, 0.0111 mmol, 0.1 equiv.)/DMAP (1.4 mg, 0.0111 mmol, 0.1 equiv.) in $CHCl_3$ (550 μL). The reaction was run with DIC (15.3 mg, 19.0 μL, 0.121 mmol, 1.2 equiv.) and 30% aq. H_2O_2 (17.1 μL, 0.166 mmol, 1.5 equiv.). After 65 h (trial 1 was run for 25 h), **15** was isolated by flash column chromatography on a silica gel column (~50 mL silica) with a gradient of 10% Et_2O to 60% Et_2O in hexanes. Fractions were collected for purity (mixed fractions were discarded), filtered and concentrated *in vacuo* to yield a clear colorless oil in an average of 42% yield (trial 1 from 0.101 mmol geranylgeraniol: 42%; trial 2 from 0.111 mmol geranylgeraniol: 42%; trial 3 from 0.112 mmol geranylgeraniol: 41%).

TLC: 2:1 Et_2O to hexanes (R_f = 0.30), best visualized by I_2/silica. Note that, under these conditions, the 6,7-epoxide is the last of the monoepoxides to elute. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 5.48-5.43 (m, 1H), 5.12-5.05 (m, 2H), 4.16 (d, *J* = 6.8 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.25-1.93 (m, 8H), 1.73-1.54 (m, 15H), 1.47-1.37 (m, 1H), 1.28-1.16 (m, 4H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 139.0, 135.7, 131.6, 124.4, 124.0, 123.6, 63.4, 61.0, 59.5, 39.8, 39.0, 36.4, 27.2, 26.8, 25.9, 23.9, 17.8, 16.7, 16.4, 16.1. **IR** (film, cm^{-1}): 3418, 2963, 2920, 2855, 1670, 1448, 1383, 1108, 1071, 1002. **HRMS**: calculated mass $[C_{20}H_{34}O_2+Na]^+$: 329.246; ESI+ found 329.248. **$[\alpha]_D$** = +5.0° (c = 1.0 g/100 mL $CHCl_3$). The structure

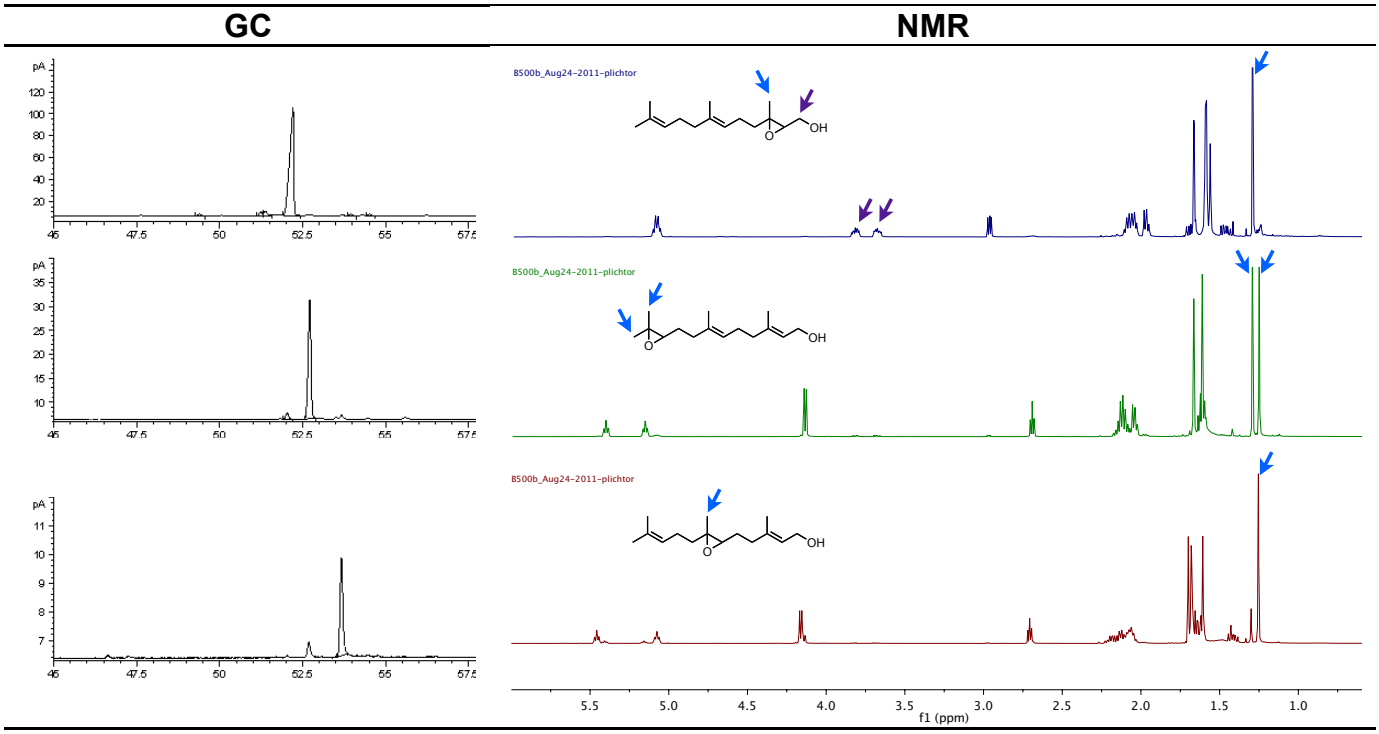
of this product was further validated by degradation analysis, which is discussed in the GC analysis section below.

GC Methods, Spectra, and Assignments.

GC analysis of farnesol oxidation products.

GC method information for farnesol oxidation products: 250 ºC inlet, 280 ºC detector, flow 1.5 mL/min, oven temperature program: 60 ºC for 2 min; 2 ºC/min ramp to 180 ºC; 10 ºC/min ramp to 230 ºC; hold at 230 ºC for 4 min.

The identity of relevant peaks within the GC spectrum of the farnesol oxides was confirmed by synthesis. Standards (shown in Supplementary Figure S9) were isolated by flash silica gel column chromatography from a reaction of *m*CPBA with farnesol.



Supplementary Figure S9. Validation of GC assay for monoepoxyfarnesol isomers showing GC spectra (relevant spectral width shown) of monoepoxide standards beside their corresponding NMR spectra

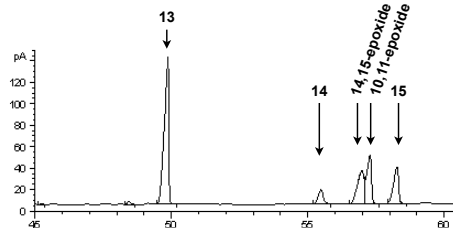
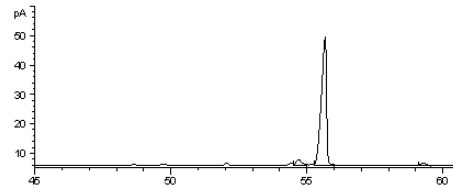
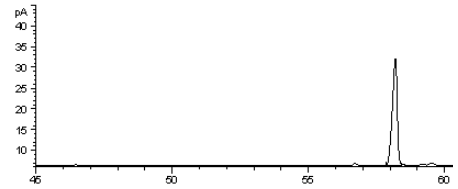
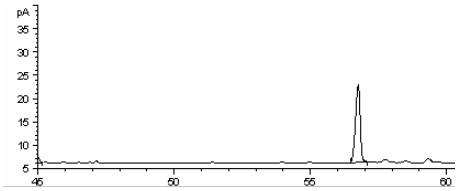
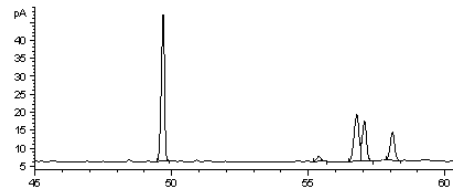
highlighting some signature peaks of each product. Approximate GC retention times for compounds 52.2 min (**3**: 2,3-epoxyfarnesol), 52.7 min (**5**: 10,11-epoxyfarnesol), and 53.7 min (**4**: 6,7-epoxyfarnesol).

GC analysis of geranylgeraniol oxidation products.

GC method information for geranylgeraniol oxidation products: 250 ºC inlet, 280 ºC detector, flow 1.5 mL/min, oven temperature program: 100 ºC for 2 min; 2 ºC/min ramp to 188 ºC, hold for 10 min; 1 ºC/min ramp to 192 ºC; 10 ºC/min ramp to 260 ºC; hold at 230 ºC for 4 min.

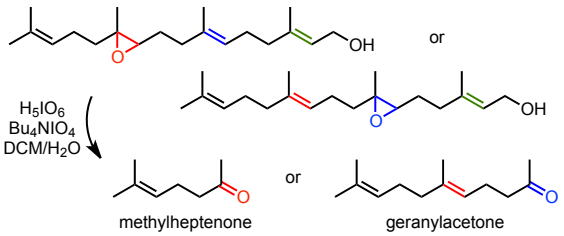
Peak assignment in GC spectrum of geranylgeraniol oxidation products relied on preparation of three of the four mono-epoxygeranylgeraniol standards (Supplementary Table S3). Four peaks appear in the relevant spectral width when geranylgeraniol is treated with 1 equiv. *m*CPBA (entry 1). An authentic standard of **14** (2,3-epoxygeranylgeraniol) was confirmed by NMR using standards prepared using both $VO(acac)_2$ (entry 2) and the chemistry presented herein (also see crude reaction trace in manuscript Fig. 3). Epoxide **15** (6,7-epoxygeranylgeraniol) was isolated and injected using the same GC method (Table 3, entry 3). The identity of **15** was confirmed by degradation analysis (*vida infra*). Identification of the 14,15-epoxygeranylgeraniol peak was confirmed by a previously reported synthesis[10] using the method of van Tamelan and Sharpless[11] (entry 4). Owing to the lack of separation and possibility of slight retention time changes, the crude sample from entry 1 was spiked with that of entry 4, the result of which further confirms the assignment shown in entry 1. The remaining 10,11-epoxide is thus tentatively assigned by elimination.

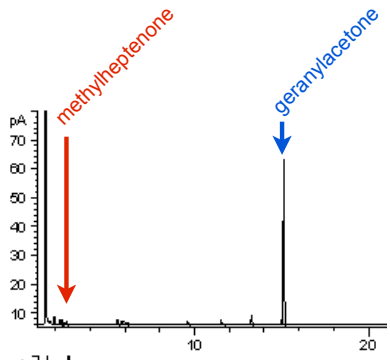
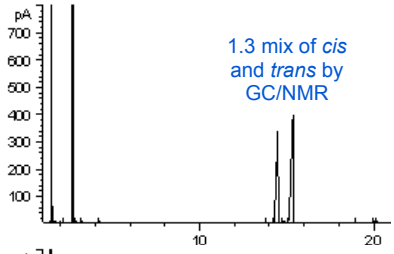
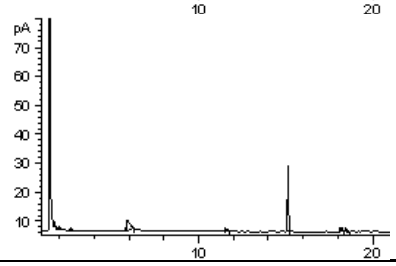
Supplementary Table S3. Study of geranylgeraniol oxidation products from *m*CPBA compared with monoepoxide standards.

entry	GC spectrum	produduct description
1		Mixture of products from epoxidation of **13** with *m*CPBA
2		Isolated **14** from epoxidation of **13** with $VO(acac)_2$ and $^{t}BuOOH$
3		Epoxide **15**
4		14,15-epoxygeranylgeraniol
5		Product mixture from treatment of **13** with *m*CPBA spiked with 14,15-epoxide

The product formed from epoxidation of **13** with peptide **12d** was assigned by degradation analysis using the protocol outlined by Gnanadesikan and Corey[12] whereby the isolated epoxide was hydrolyzed and oxidatively cleaved. The crude reaction mixture was then analyzed by GC (Supplementary Table S4, entry 1). The crude reaction mixture was compared to a one-to-one mixture of commercially available methylheptenone and geranylacetone (entry 2). The purchased geranylacetone standard was mixture of olefin isomers and the *trans*-isomer was thus confirmed by degradation of **3** (entry 3).

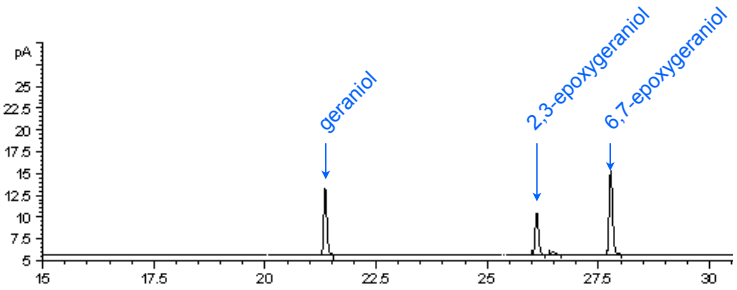
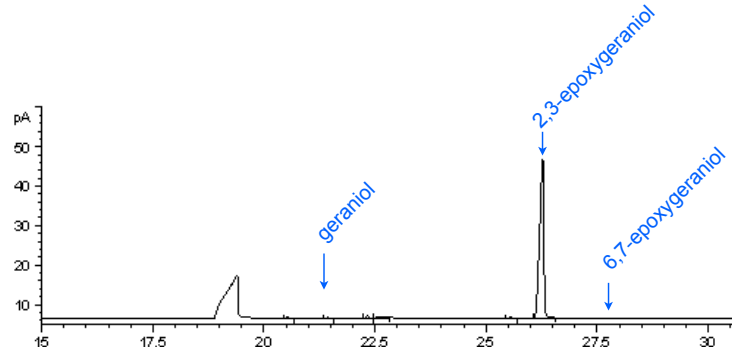
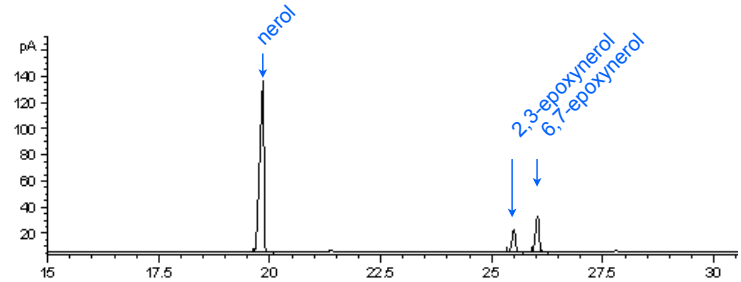
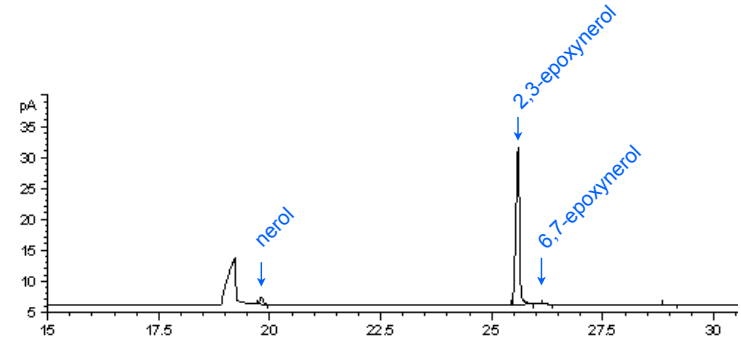
Supplementary Table S4. Study of geranylgeraniol oxidation products from *m*CPBA compared with monoepoxide standards.



entry	GC spectrum	sample description
1		degradation of **15**
2		1:1 mixture of purchased methylheptenone and geranylacetone
3		degradation of **3**

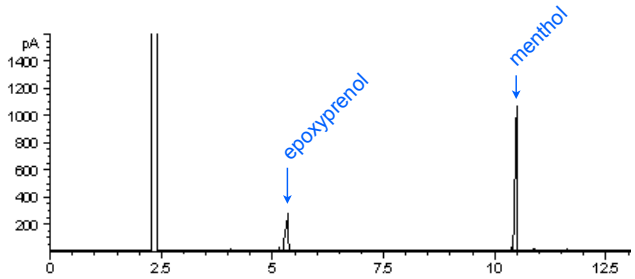
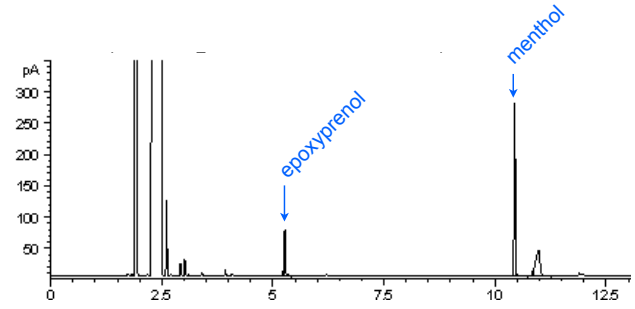
GC analysis of geraniol and nerol oxidation products.

GC method information for geraniol and nerol oxidation products: 250 ºC inlet, 280 ºC detector, flow 1.5 mL/min, oven temperature program: 60 ºC for 2 min; 2 ºC/min ramp to 120 ºC, 10 ºC/min ramp to 230 ºC; hold at 230 ºC for 4 min.

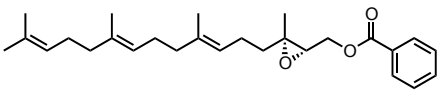
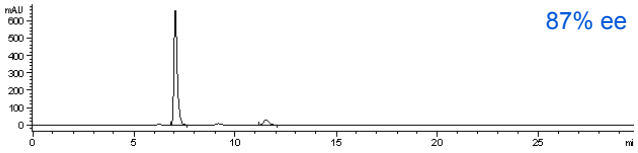
Method of preparation	GC Spectrum
Geraniol with *m*CPBA (1 equiv.)	
Geraniol under Epoxidation Protocol A with peptide **9b** (trial 2)	
Nerol with *m*CPBA (0.25 equiv.)	
Nerol under Epoxidation Protocol A with peptide **9b** (trial 2)	

GC analysis of prenol oxidation reactions.

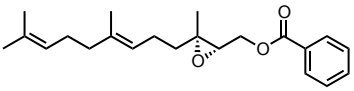
GC method information for geraniol and nerol oxidation products: 250 ºC inlet, 280 ºC detector, flow 1.5 mL/min, oven temperature program: 40 ºC for 2 min; 10 ºC/min ramp to 180 ºC; hold at 180 ºC for 4 min.

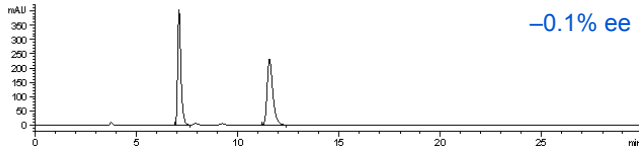
Sample	GC Spectrum
1 to 1 (mmol) epoxyprenol to menthol calibration standard. Relative peak area is 0.374 epoxyprenol/menthol standard	
Crude reaction of prenol under Epoxidation Protocol A with peptide **9b** (trial 2). Sample was spiked with 1 equiv. menthol standard. Relative peak area is 0.290 epoxyprenol/menthol standard. Estimated GC yield is thus 78%.	

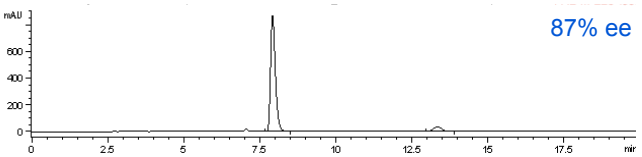
HPLC Methods and Spectra.

Compound	HPLC Spectra
	

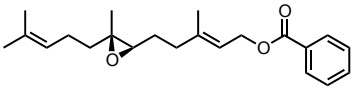
OJ-H, 1% ^{i}PrOH in hexanes at 1.0 mL/min, 20 ºC

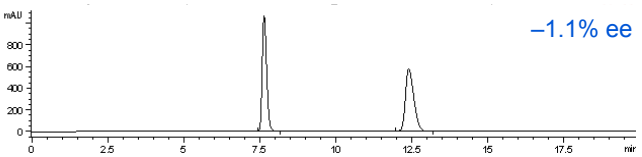


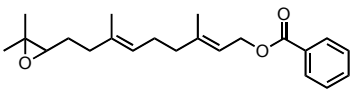


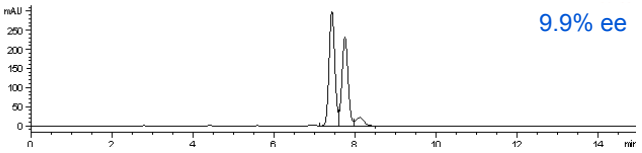


OJ-H, 1% ^{i}PrOH in hexanes at 1.0 mL/min, 20 ºC

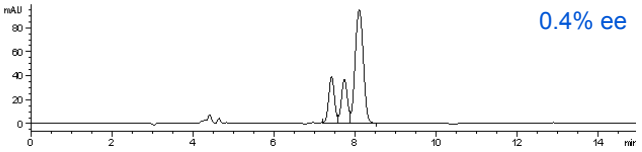


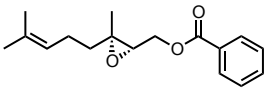


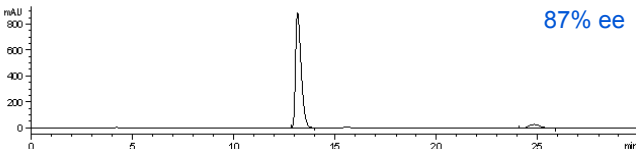




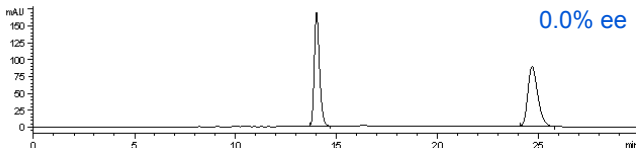
IC, 2% ^{i}PrOH, 1% EtOH in hexanes at 1.2 mL/min, 13 ºC

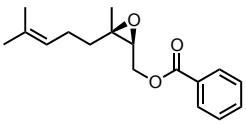


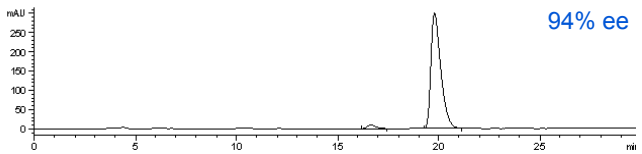




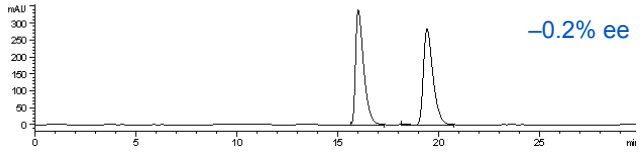
OJ-H, 1% ^{i}PrOH in hexanes at 1.0 mL/min, 20 ºC

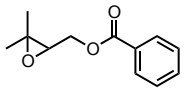




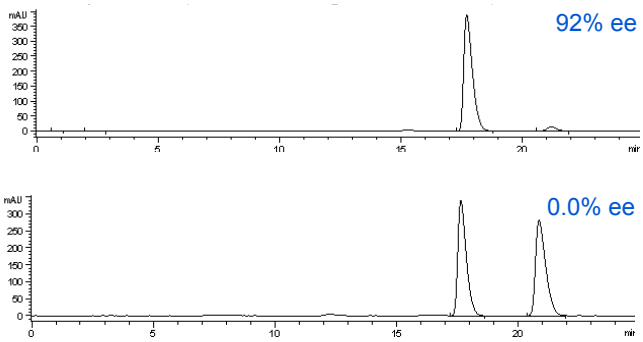


OJ-H, 1% ^{i}PrOH in hexanes at 1.0 mL/min, 20 ºC





OJ-H, 3% ^{i}PrOH in hexanes at 1.0 mL/min, 20 ºC



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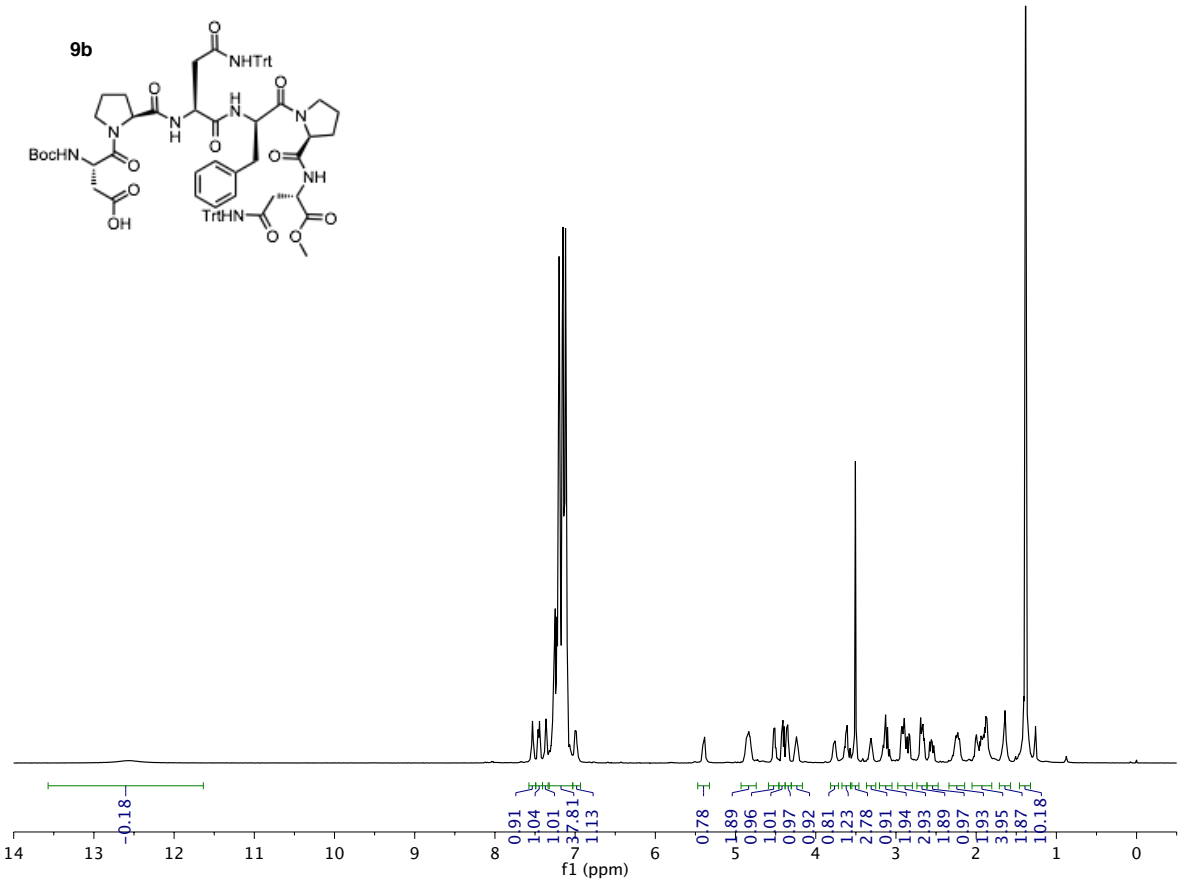
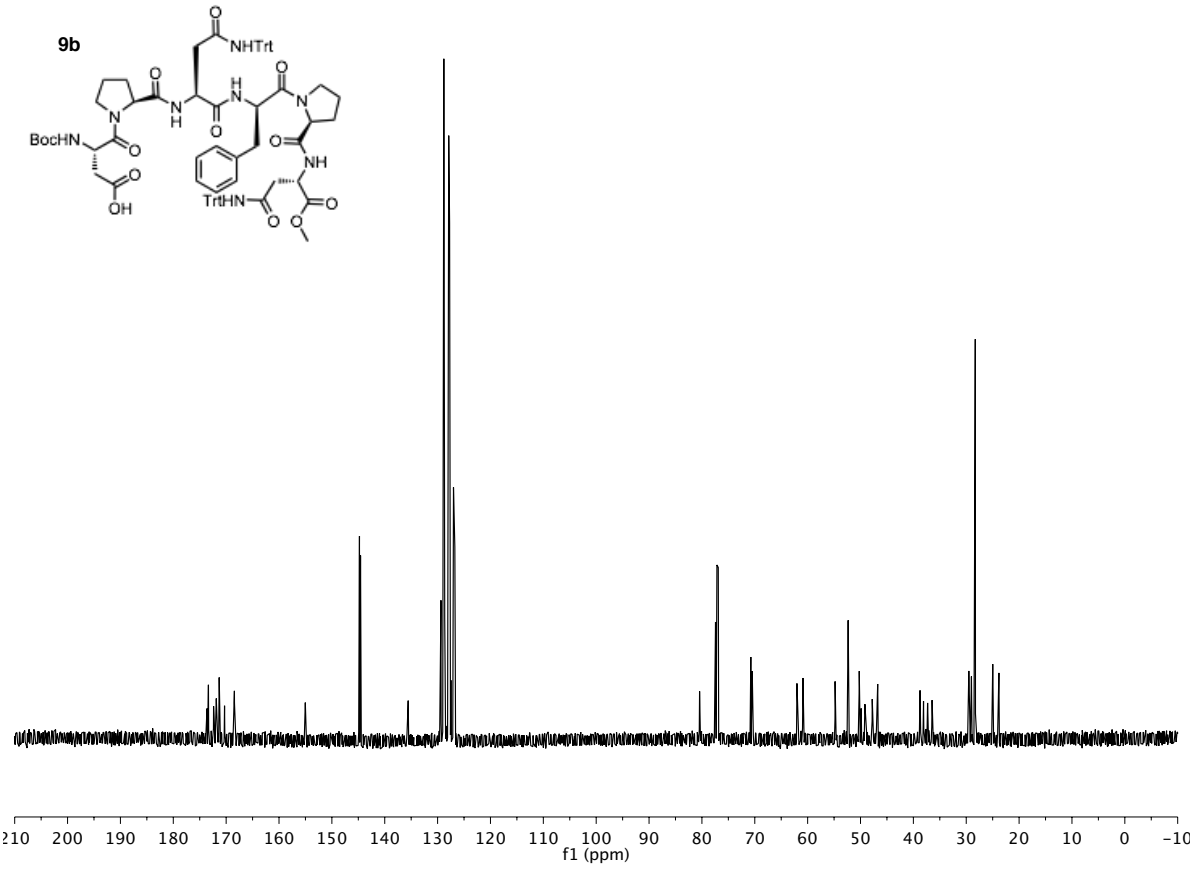
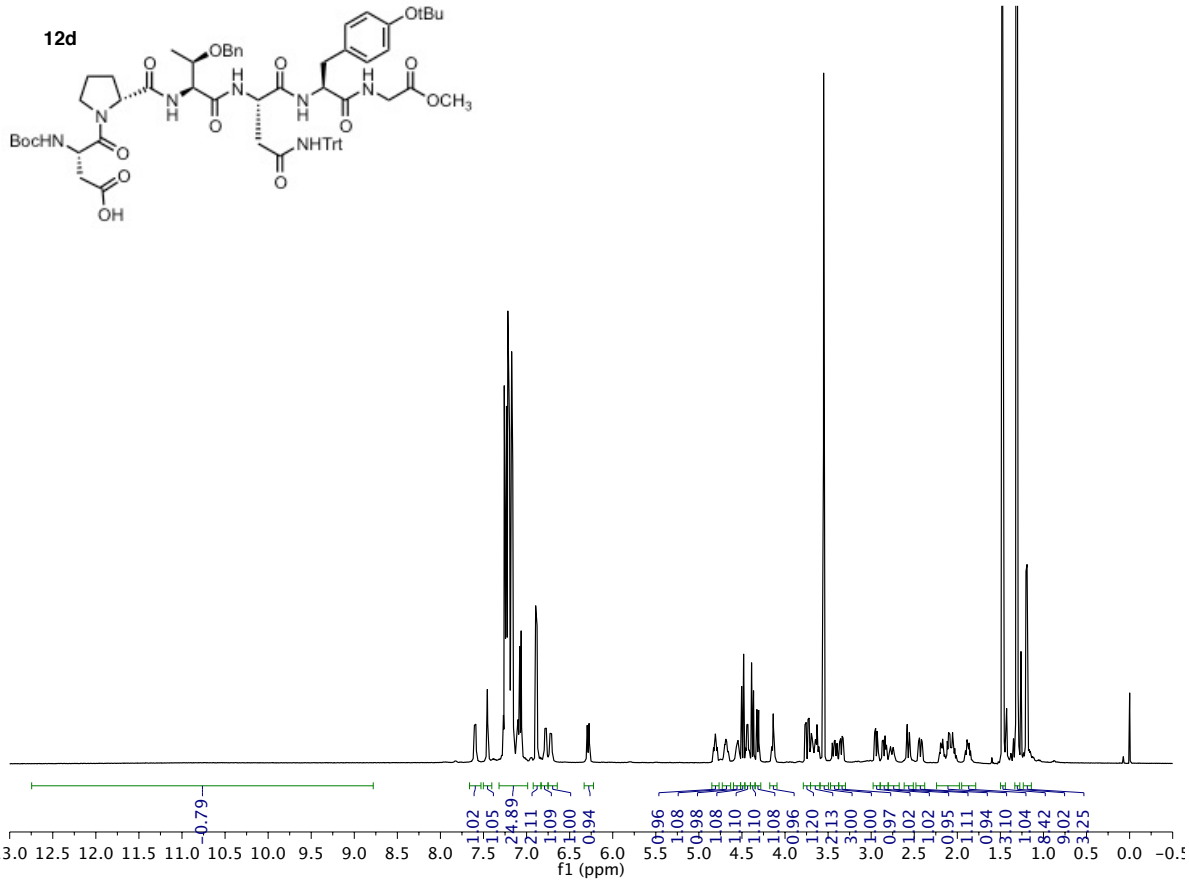
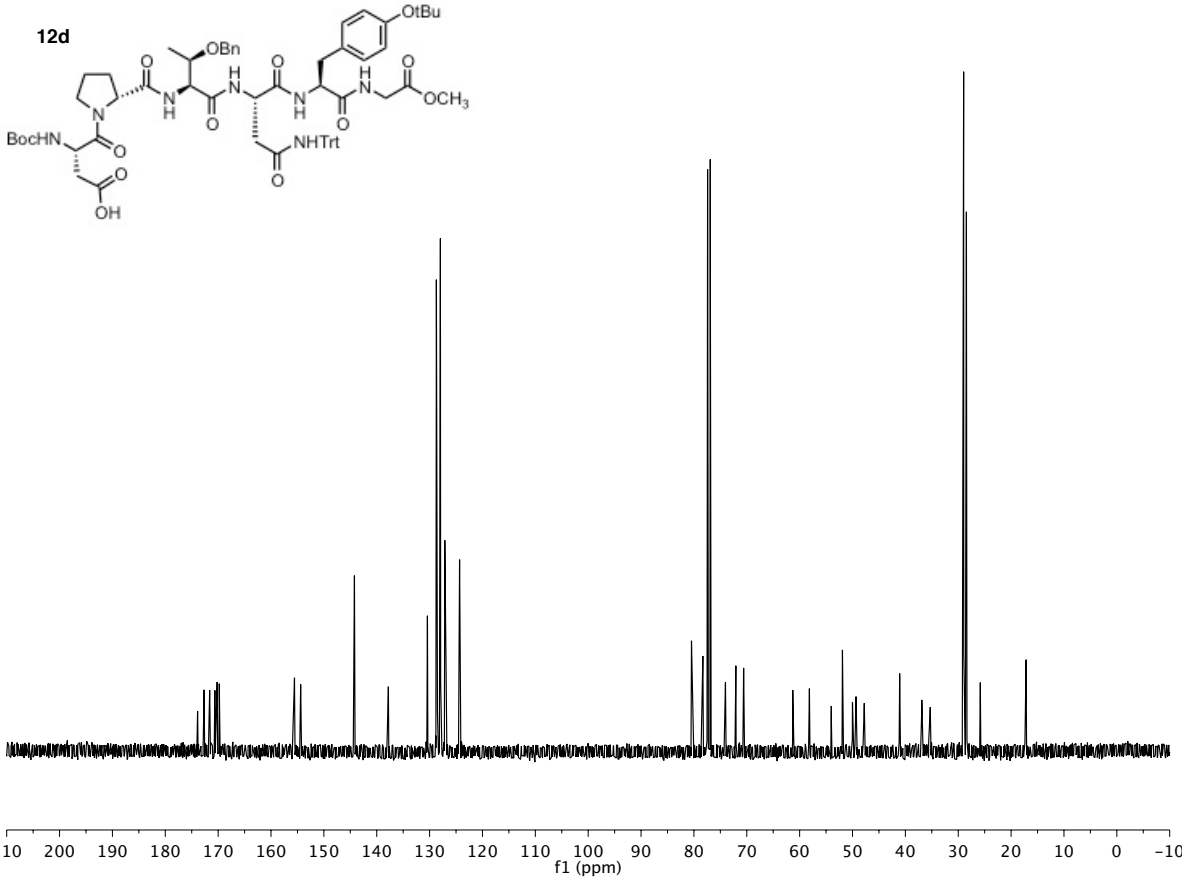
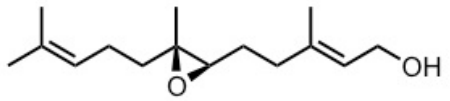
NMR Spectra of Selected Compounds Follows.


9b
NHTrt
BocHN
OH
TrtHN
NH
0.18
0.91
1.04
1.01
37.81
1.13
0.78
1.89
0.96
1.01
0.97
0.92
0.81
1.23
2.78
0.91
1.94
2.93
1.89
0.97
1.93
3.95
1.87
10.18
f1 (ppm)

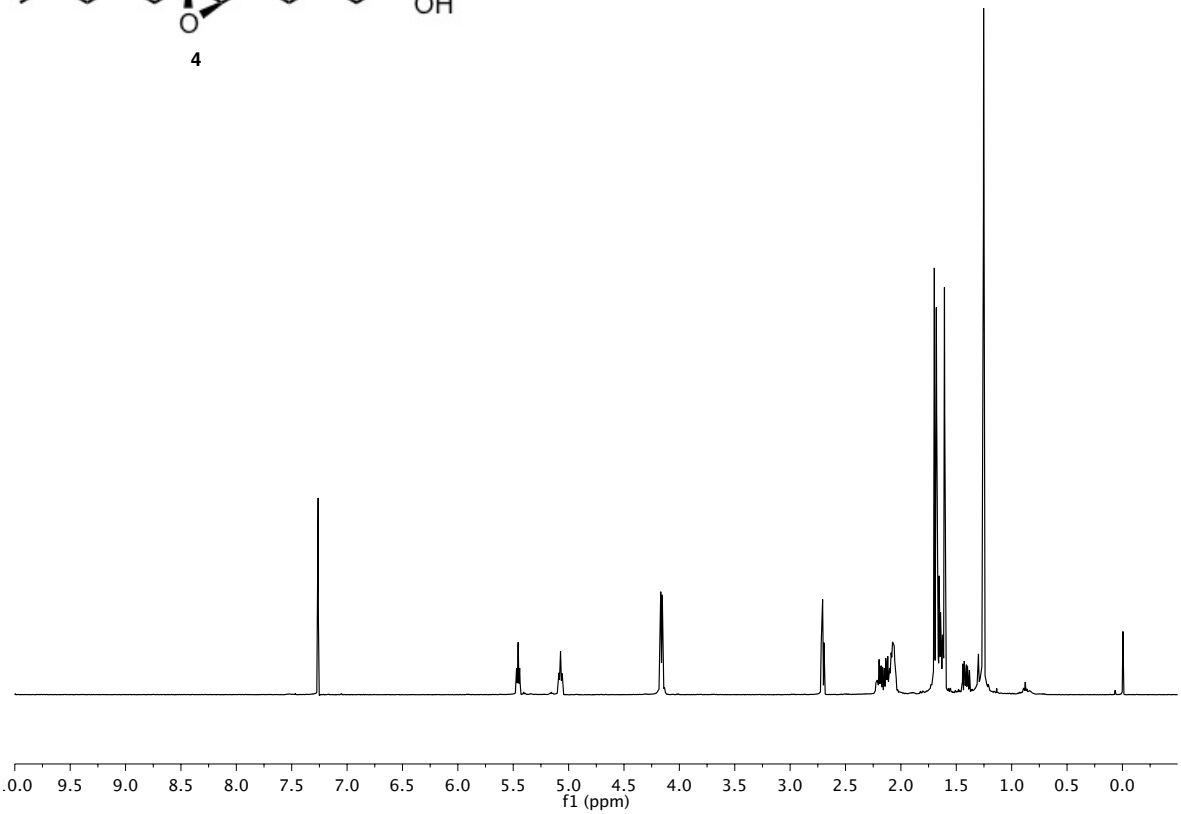

9b
NHTrt
BocHN
OH
TrtHN
NH
f1 (ppm)


12d
OtBu
OBn
OCH3
BocHN
NHTrt
OH
0.79
1.02
1.05
24.89
2.11
1.09
1.00
0.94
0.96
1.08
0.98
1.08
1.10
1.10
1.08
0.96
1.20
2.13
3.00
1.00
0.97
1.02
1.02
0.95
1.11
0.94
3.10
1.04
8.42
9.02
3.25
f1 (ppm)


12d
OtBu
OBn
OCH3
BocHN
NHTrt
OH
f1 (ppm)


OH
O

4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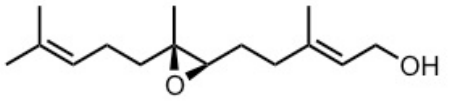
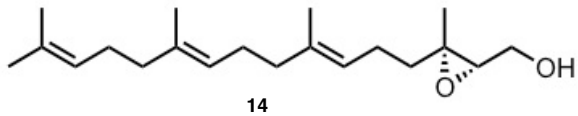
f1 (ppm)

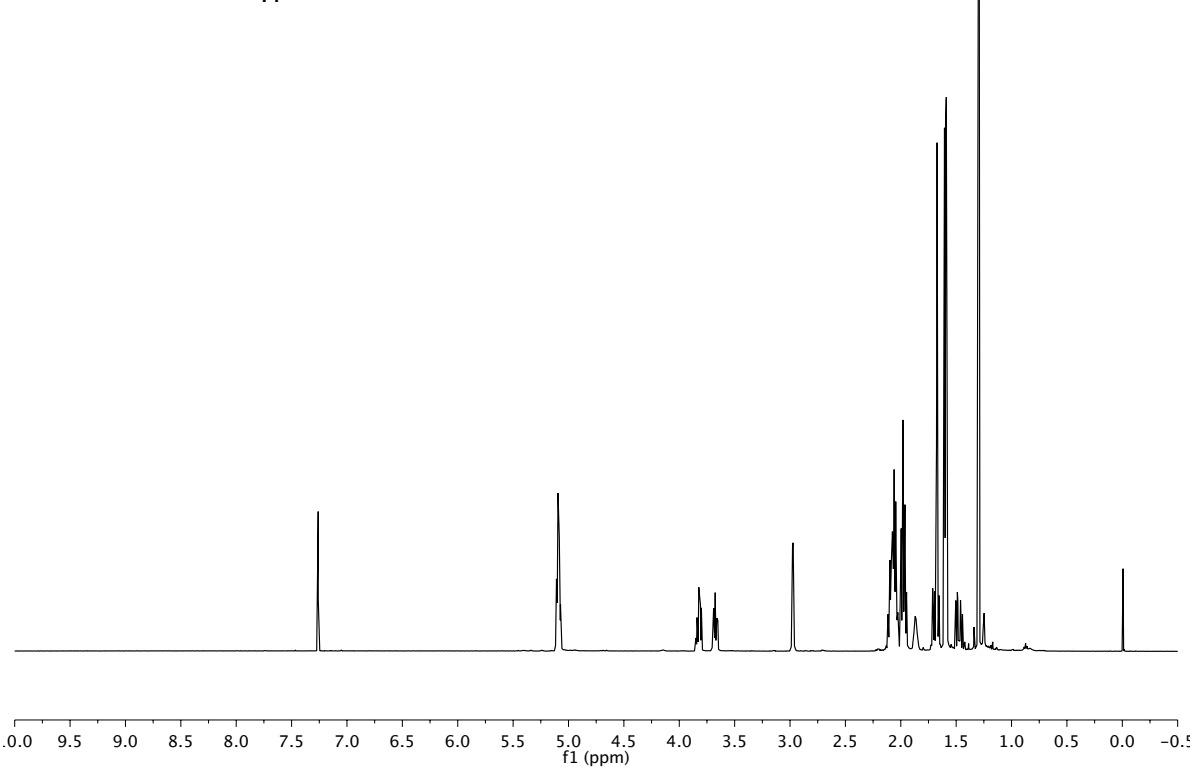

OH
O

4

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)


OH
O

14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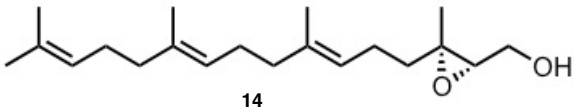
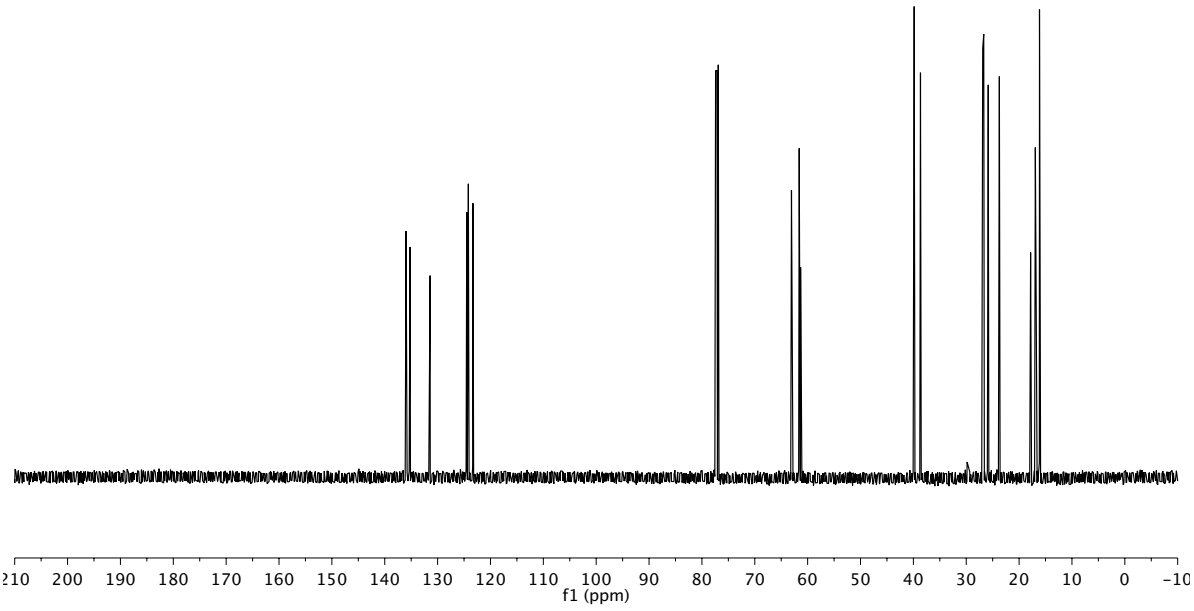
f1 (ppm)


OH
O

14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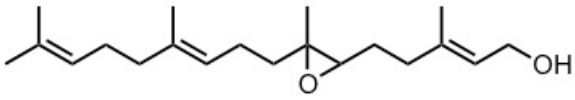
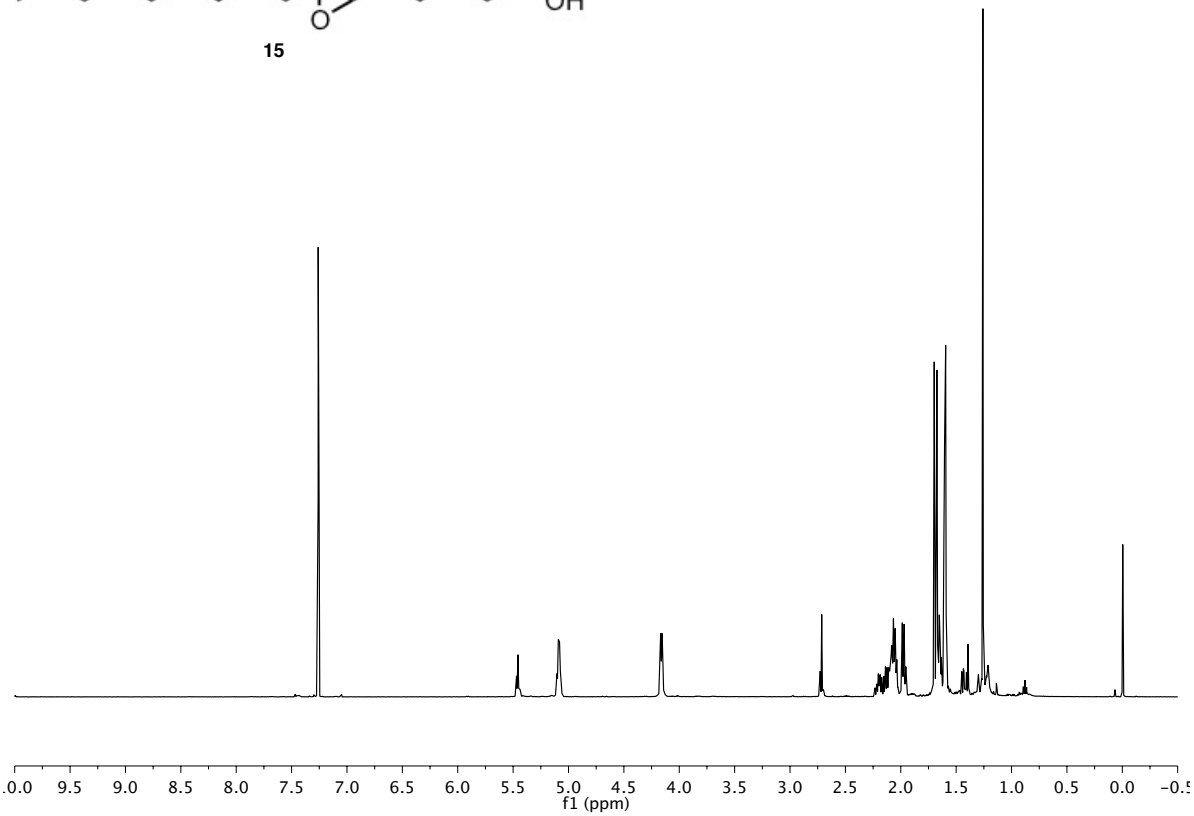
f1 (ppm)


OH
O

15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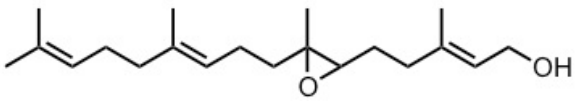
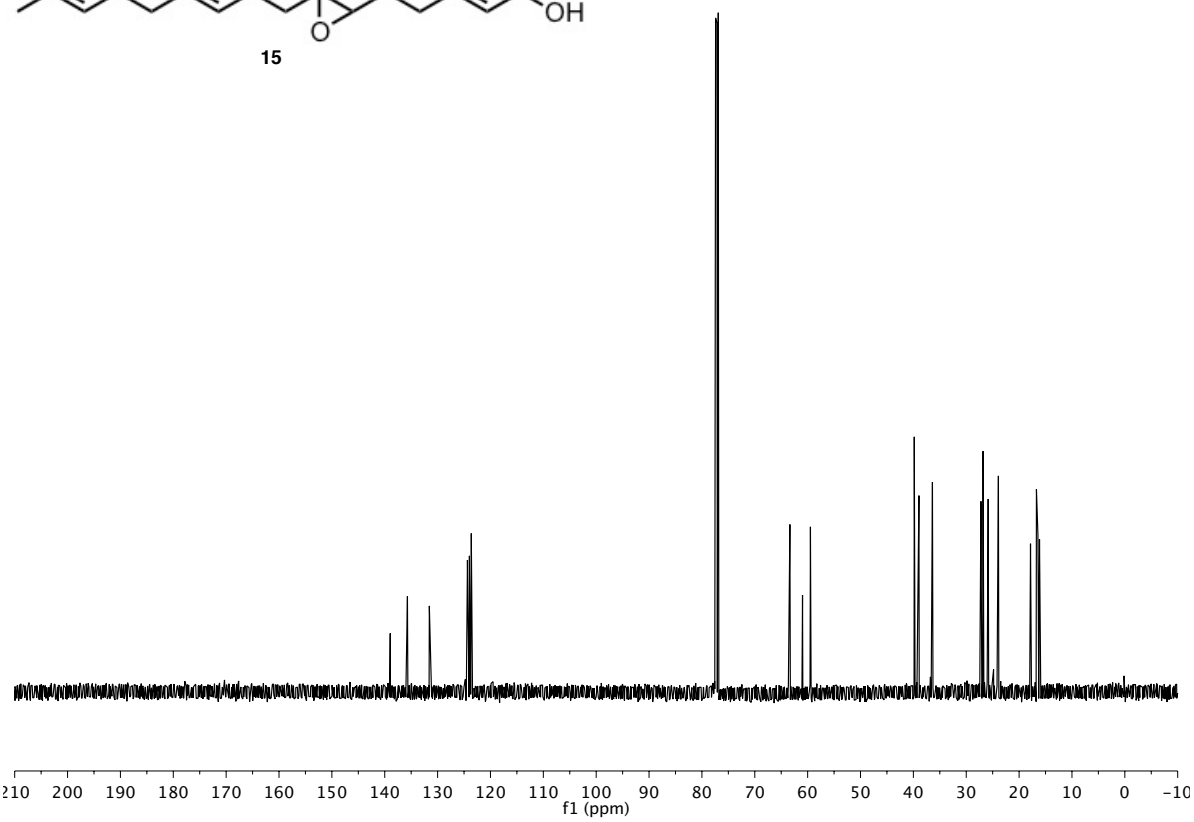
f1 (ppm)


OH
O

15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f1 (ppm)