SUPPLEMENTARY INFORMATION

Aspartyl Oxidation Catalysts that Dial In Functional Group Selectivity, along with Regio- and Stereoselectivity

Joshua S. Alford, Nadia C. Abascal, Christopher R. Shugrue, Sean M. Colvin, David K. Romney, Scott J. Miller

Department of Chemistry, Yale University, 225 Prospect Street, New Haven, CT 06520

Index

1. Synthetic procedures

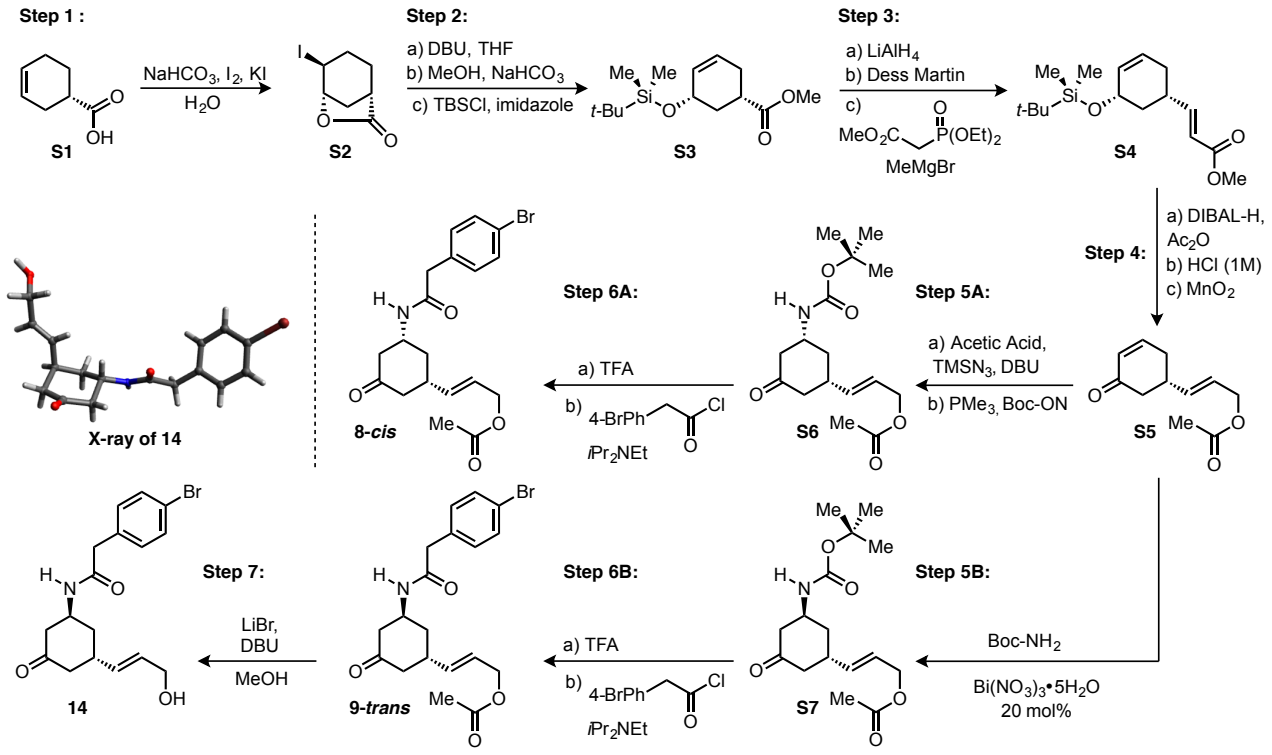
General information: Proton NMR spectra were recorded on Agilent 600 or 400 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane and calibrated using the residual solvent resonance ($CDCl_3$, δ 7.26 ppm; CD_3OD, δ 3.31 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of doublets of triplets (ddt), doublet of triplets (dt), doublet of triplets of doublets of doublets (dtdd), triplet of doublets (td), triplet of doublets of doublets (tdd), triplet of doublets of triplets (tdt), triplet of triplets (tt), triplet of quartets (tq), quartet (q), quartet of doublets (qd), quartet of triplets (qt), pentet (p), pentet of doublets (pd), septet (sept), multiplet (m)], coupling constants [Hz], integration, specific proton assignment). Carbon NMR spectra were recorded on 600 MHz (150 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm relative to tetramethylsilane and calibrated using the respective solvent resonances ($CDCl_3$, δ 77.16 ppm; CD_3OD, δ 49.0 ppm). Unless otherwise noted, all NMR spectra were acquired at ambient temperature. Infrared spectra were recorded on a Nicolet 6700 FT-IR, ν_{max} (cm^{-1}) and are partially reported in accordance with convention. Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness) and were visualized by irradiation with UV light (254 nm) and staining with $KMnO_4$. TLC R_f values are reported. Normal phase flash chromatography was performed using Silicycle silica gel (particle size 32-63 μm). Reversed phase chromatography used C-18 silica and was performed on a Biotage Isolera One purification system. The gradient of the eluent (∇) is given as % strong solvent/column volume (CV). Optical rotation was recorded on a Perkin Elmer Polarimeter 341 at the D line (1.0 dm path length). Normal phase HPLC was performed on an Agilent 1100 series chromatograph equipped with a photodiode array detector (210, 220, 230, and 254 nm). Chiral separations used a Chiralpack IA, IB, IC, or Chiralcel AD-H column (5 μm particle size, 4.5 x 250 mm). Column temperatures were unregulated. Low resolution mass spectrometry (MS) was performed with UPLC-MS on a Waters Acquity UPLC® BEH C8 (1.7 μm, 2.1 x 100 mm) column on a Waters XEVO instrument equipped with ESI, a QToF mass spectrometer, and a photodiode array detector. High resolution mass spectrometry (HRMS) used electrospray ionization (ESI) and was conducted by the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign as an external validation.

All reaction solvents were purified using a Seca Solvent Purification System by Glass Contour, with the exception of chloroform, which was purchased from JT Baker and passed through basic alumina immediately prior to use. Di-*iso*-propylamine was distilled from calcium hydride and was stored under nitrogen. All chemicals were purchased commercially and used as received unless otherwise noted. The chiral building blocks (*S*)-3-cyclohexene carboxylic acid **S1** (product code C11079) and (*R*)-3-cyclohexene carboxylic acid *ent*-**S1** (product code C11080) were purchased from Synthonix and used as received.

1.1 Synthesis of the substrates

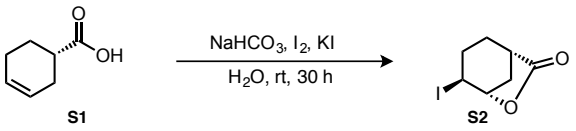
Overview: The synthesis of the 3-amidocyclohexanones started from the (*S,S*)-lactone **S2**, which is easily accessible from commercially available 3-cyclohexene-1-carboxylic acid *via* an iodolactonization process (Step 1).[1] Dehydroiodination of **S2** furnished the unsaturated lactone, which was then subjected to methanolysis and the resulting hydroxyl group was protected with TBSCl (74% yield for **S3**; Step 2). This was followed by a reduction/oxidation sequence of the ester **S3** and the resulting intermediate aldehyde was subjected to a highly (*E*)-selective Horner-Wadsworth-Emmons olefination promoted by methylmagnesium bromide to afford the α,β-unsaturated ester **S4** (>30:1 *E*:*Z*; 58% yield for **S4**; Step 3).[2] A chemoselective reduction of the ester moiety by DIBAL–H and acetylation of the crude allylic alcohol, followed by deprotection of the allylic OTBS and mild oxidation furnished the desired enone product **S5** in a straightforward manner (55% yield; Step 4). Only 3 purifications were needed by this point in the synthesis.

At this juncture, we pursue both diastereomers of the 3,5-disubstituted cyclohexanones. To access the *cis* isomer, we chose the small, reactive, trimethylsilyl azide as the amine source. Thus, subjection of the enone **S5** to an amine-catalyzed 1,4-addition of TMS-azide[3] with the *in situ* reduction of the azido intermediate under Staudinger conditions (PMe_3, Boc-ON, THF, rt) furnished the desired *N*-Boc product in 28% yield (Step 5A).[4] Treatment with trifluoroacetic acid then selectively removed the *N*-Boc group, and the intermediate amine salt was acetylated with 4-bromophenyl acetyl chloride providing the desired *cis* 3-amidocyclohexanone **8**-*cis* (Step 6A). On the other hand, using a $Bi(NO_3)_3$-catalyzed *aza*-Michael addition of *tert*-butyl carbamate selectively furnished the *trans N*-Boc-protected product in good yield with high diastereoselectivity (Step 5B). Treatment with trifluoroacetic acid selectively removed the *N*-Boc group, and then the intermediate amine salt was acetylated with 4-bromophenyl acetyl chloride to provide the desired *trans* 3-amidocyclohexanone **9**-*trans* (Step 6B). The same synthetic route was employed to access the enantiomers of **8**-*cis* and **9**-*trans* starting from (*R*)-3-cyclohexene carboxylic acid *ent*-**S1.**



Supplementary Scheme S1: The telescoped synthetic route employed to access both diastereomers and the corresponding enantiomers of the proposed substrates **8**-*cis* and **9**-*trans*.

Step 1: Synthesis of the iodolactone S2

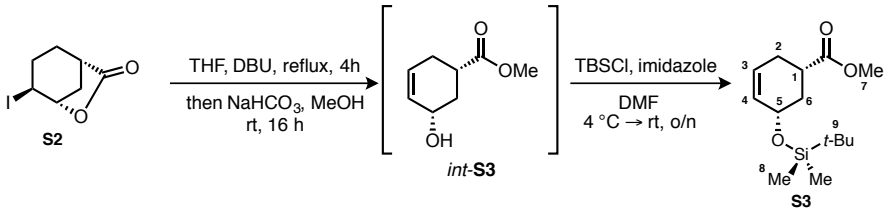


S1 S2

The (*S*)-3-cyclohexene carboxylic acid **S1** (20.0 g, 158 mmol, 1.0 equiv) was added in one portion to a solution of sodium bicarbonate (39.9 g, 475 mmol, 3.0 equiv) in water (400 mL), and the mixture was stirred at room temperature until it became homogenous (~1 h; 2 L *E*-flask). The flask was then protected from light using aluminum foil and charged with a solution of potassium iodide (157.3 g, 948 mmol, 6.0 equiv) in 400 mL of water. Upon completion of the addition, the stirring was increased and iodine (42.1 g, 166 mmol, 1.05) was added portion wise over 30 minutes. The reaction mixture was stirred for 30 h. After the allotted time had expired and a visible yellow precipitate had formed, the reaction mixture was diluted with chloroform (~500 mL) with stirring. The biphasic mixture was transferred to a 2 L separatory funnel and the layers were separated (flashlight used behind the funnel for layer separation visualization). The aqueous layer was re-extracted with chloroform (2 x 100 mL). The organic layers were combined and washed sequentially with 10% aqueous $Na_2S_2O_3$ (2 x 150 mL), and saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered through a plug of silica (40 mL) and the filtrate was concentrated under reduced pressure (12 mbar). The off-white solid was then recrystallized from boiling ethanol (120 mL) to afford the lactone **S2** as a free-flowing white solid (39.8 g, 99% yield). ^{1}H and ^{13}C NMR spectroscopic data for lactone **S2** obtained in this way were in agreement with those published.[5] **TLC:** R_f = 0.31 (hexane/EtOAc = 4:1; UV (254 nm)); **Optical:** $[\alpha]_D^{20.0}$ = -39.3 (*c* = 1.60, $CHCl_3$, >99:1 e.r.).

The corresponding enantiomer *ent*-**S2** (37.2 g, 93% yield) was synthesized in a similar fashion starting from (*R*)-3-cyclohexene carboxylic acid *ent*-**S1** (20.0 g, 158 mmol, 1.0 equiv). **Optical:** $[\alpha]_D^{20.0}$ = +36.7 (*c* = 1.24, $CHCl_3$, >99:1 e.r.).

Step 2: Synthesis of the allylic silyl ether S3



1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (36.1 g, 237 mmol, 1.7 equiv) was added in a single portion to a solution of the lactone **S2** (39.8 g, 143 mmol, 1 equiv) in tetrahydrofuran (204 mL) at 21 °C. The reaction flask was fitted with a reflux condenser and the headspace was purged with nitrogen. The suspension was stirred under nitrogen at reflux for 4 h, at which time a white precipitate was observed indicating the completion of the reaction. The product mixture was diluted with diethyl ether (100 mL) and filtered through a glass Buchner funnel with a medium frit. The filter cake was washed with diethyl ether (2 x 50 mL). The filtrates were combined and transferred to a separatory funnel containing saturated aqueous ammonium chloride (200 mL). The layers were separated and the aqueous layer was re-extracted with diethyl ether (2 x 75 mL). The organic layers were combined and the combined layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered through a plug of silica and the filtrate was concentrated under reduced pressure (180 mbar) (Caution: the intermediate product can be stripped away under strong vacuum) to afford the intermediate cyclohexene lactone as a colorless oil (18.2 g with traces of THF). The residue obtained was used directly in the following step. ^{1}H and ^{13}C NMR spectroscopic data for cyclohexene carboxylate obtained in this way were in agreement with those published.[5]

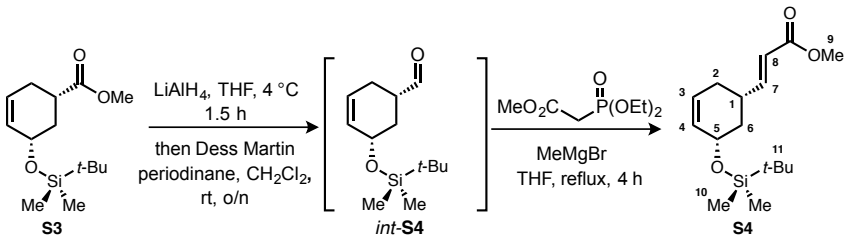
Sodium bicarbonate (16.2 g, 193 mmol, 1.5 equiv) was added to a solution of the crude cyclohexene carboxylate obtained in the preceding step (nominally 16.0 g, 129 mmol, 1 equiv) in freshly distilled methanol (60 mL) at 21 °C. The reaction flask was fitted with a rubber septum and the septum was penetrated with a needle. A balloon of nitrogen was fixed to the vessel and the suspension was stirred for 4 h, at which time complete methanolysis of the lactone was observed (*via* TLC; R_f = 0.51 for the allylic alcohol, 0.60 for the lactone, 57% ethyl acetate/hexanes; $KMnO_4$ stain). The product mixture was concentrated under reduced pressure (13 mbar) to afford a white semi-solid. The product mixture was diluted sequentially with water (80 mL) and ethyl acetate (200 mL) and the diluted product mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 100 mL). The organic layers were combined and dried over magnesium sulfate. The dried solution was filtered through a plug of silica (40 mL) and the filtrate was concentrated under reduced pressure (12 mbar) to afford the allylic alcohol as a colorless oil (18.7 g). The residue obtained was used directly in the following step. ^{1}H and ^{13}C NMR spectroscopic data for the allylic alcohol *int*-**S3** obtained in this way were in agreement with those published.[6] **TLC:** R_f = 0.10 (hexane/EtOAc = 4:1; stained with $KMnO_4$)

Imidazole (13.2 g, 194 mmol, 1.6 equiv) was added in a single portion to a stirred solution of allylic alcohol obtained in the preceding step (nominally 18.7 g, 121 mmol, 1.0 equiv) in dry dimethylforamide (100 mL) at 21 °C. The solution was then cooled to 4 °C using an ice bath for 15 minutes. *tert*-Butyldimethylsilyl chloride (TBSCl) (23.3 g, 155 mmol, 1.28 equiv) was added in three portions spaced 5 minutes apart. The reaction mixture was warmed over 2 h to 21 °C, and was stirred an additional 16 h at 21 °C. The product solution was diluted with saturated aqueous ammonium chloride (150 mL) and transferred to a separatory funnel containing diethyl ether (200 mL). The layers were separated, and the aqueous layer was re-extracted with additional diethyl ether (2 x 100 mL). The organic layers were combined and dried over magnesium sulfate. The dried solution was filtered through a plug of silica and the filtrate was concentrated under reduced pressure (12 mbar). The residue obtained was purified by flash-column chromatography (eluting with 3% ethyl acetate-hexanes) to afford the allylic silyl ether **S3** as a colorless oil (28.6 g, 74% yield for the sequence). *Note:* product hydrolyzes to the free –OH upon standing in chloroform for an extended time (~10 days).

*Characterization data for **S3**:* **TLC:** R_f = 0.56 (hexane/EtOAc = 4:1; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 5.74 – 5.65 (m, 1H, H_3), 5.63 – 5.55 (m, 1H, H_4), 4.39 – 4.29 (m, 1H, H_5), 3.69 (s, 3H, H_7), 2.63 (dtd, *J* = 12.8, 8.1, 2.6 Hz, 1H, H_1), 2.29 – 2.17 (m, 3H, $H_{2,6}$), 1.70 – 1.58 (m, 1H, H_6), 0.89 (s, 9H, H_9), 0.08 (d, *J* = 4.2 Hz, 6H, H_8); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 175.2 (C), 132.1 (CH), 126.4 (CH), 67.9 (CH), 51.9 (CH_3), 38.8 (CH), 35.0 (CH_2), 27.6 (CH2), 26.0 (CH_3), 18.3 (C), -4.4 (CH_3), -4.6 (CH_3); **IR** (FT-ATR, cm^{-1}): 2954, 2929, 2856, 1737, 1472, 1389, 1249, 1199, 1169, 1086, 1059, 1007, 833, 773; **HRMS** (EI-) (*m/z*) for $[M-H]^-$ $C_{14}H_{25}O_3Si$ requires 269.1573, observed 269.1576; **Optical:** $[\alpha]_D^{20.0}$ = -17.2 (*c* = 1.05, $CHCl_3$).

The corresponding enantiomer *ent*-**S3** (31.5 g, 79% yield) was synthesized in a similar fashion starting from lactone *ent*-**S2** (37.2 g, 158 mmol, 1.0 equiv). **Optical:** $[\alpha]_D^{20.0}$ = +16.7 (*c* = 1.13, $CHCl_3$).

Step 3: Synthesis of the acrylate S4



Lithium aluminum hydride (2.53 g, 66.6 mmol, 1.5 equiv) was added in a single portion under nitrogen to a round bottom flask equipped with a magnetic stir bar. The reaction vessel was fitted with an addition funnel capped with a septum and the septum was penetrated with a needle. A balloon of nitrogen was fixed to the vessel and the headspace purged with nitrogen. Tetrahydrofuran was added to the vessel and the suspension was cooled to 4 °C using an ice bath for 15 minutes. The allylic silyl ether **S3** (12.0 g, 44.3 mmol, 1.0 equiv) as a solution in tetrahydrofuran (20 mL) was added to the addition funnel using a syringe and then to the lithium aluminum hydride solution drop-wise over 20 minutes. After the addition was complete, the reaction continued to stir at 4 °C for 1.5 h. The cold product mixture was quenched by the slow addition of solid sodium sulfate•$10H_2O$ (added until bubbling ceased) followed by anhydrous magnesium sulfate. The resulting white suspension was filtered through a pad of Celite (40 mL). The filter cake was washed with diethyl ether (2 x 100 mL). The filtrates were collected and combined, and the combined filtrates were concentrated under reduced pressure (12 mbar). **TLC:** R_f = 0.26 (hexane/EtOAc = 4:1; stained with $KMnO_4$) The resulting colorless residue was dissolved in dichloromethane (150 mL) and cooled to 4 °C using an ice bath. 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (DMP) (20.7 g, 48.7 mmol, 1.1 equiv) was added in three portions spaced 5 minutes apart to the reaction vessel followed by water (0.8 mL, 44.3 mmol, 1.0 equiv). The resulting white suspension was stirred for 2 h. The white product mixture was filtered through a glass Buchner filtering funnel with a coarse frit. The filter cake was washed with dichloromethane (2 x 100 mL). The combined filtrates were transferred to a separatory funnel containing saturated aqueous sodium bicarbonate (300 mL). The layers were separated, and the aqueous layer was re-extracted with additional dichloromethane (2 x 50 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered through a plug of silica and the filtrate was concentrated under reduced pressure (12 mbar). The residue obtained was purified by elution over a short pad of silica gel (50 mL, eluting with 83% pentane-diethyl ether). The filtrate was collected and concentrated. The residue obtained (6.8 g; 64% yield) was used directly in the following step without further purification. An analytically-pure sample of the aldehyde *int*-**S4** was obtained by flash-column chromatography (eluting with 5% ethyl acetate-hexanes): **TLC:** R_f = 0.48 (hexane/EtOAc = 4:1; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 9.68 (d, *J* = 1.2 Hz, 1H), 5.78 – 5.70 (m, 1H), 5.70 – 5.60 (m, 1H), 4.31 (dq, *J* = 4.8, 2.3 Hz, 1H), 2.55 (tt, *J* = 9.6, 3.9 Hz, 1H), 2.37 – 2.28 (m, 1H), 2.23 – 2.08 (m, 2H), 1.73 (ddd, *J* = 12.8, 10.0, 7.4 Hz, 1H), 0.88 (s, 9H), 0.07 (d, *J* = 3.1 Hz, 6H); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 202.9, 131.5, 126.6, 66.3, 45.2, 32.4, 25.9, 24.0, 18.3, -4.4, -4.5; **IR** (FT-ATR, cm^{-1}): 3032, 2954, 2929, 2857, 1728, 1472, 1388, 1252, 1088, 1058, 1022, 875, 835, 775; **MS** (ESI) (*m/z*) for $[M+H]^+$ $C_{13}H_{25}O_2Si$ requires 241.16, observed 241.13.

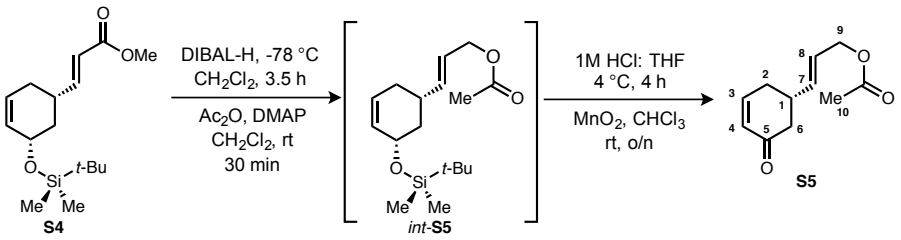
Adapting the protocol of Claridge *et al.*,[2] a solution of methyl magnesium bromide (3.0 M in ether, 7.9 mL, 23.8 mmol, 1.0 equiv) was added drop-wise over 10 minutes to a solution of methyl 2-(diethoxyphosphoryl)acetate (5.0 g, 23.8 mmol, 1.0 equiv) in tetrahydrofuran (79 mL) at 4 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 h at 4 °C. A solution of the aldehyde (6.0 g, 25.0 mmol, 1.05 equiv) in tetrahydrofuran (12 mL) was then added dropwise *via* syringe. The resulting mixture was stirred for 15 minutes at 4 °C, then the ice bath was removed and the reaction flask was fitted with a reflux condenser and the headspace was purged with nitrogen again. The reaction mixture was stirred under nitrogen at reflux for 4 h. The product mixture was then cooled over 30 minutes to 21 °C. The cooled product mixture was diluted with saturated aqueous ammonium chloride (50 mL) and

transferred to a separatory funnel containing diethyl ether (100 mL). The layers were separated, and the aqueous layer was re-extracted with additional diethyl ether (2 x 50 mL). The organic layers were combined and dried over magnesium sulfate. The dried solution was filtered through a plug of silica and the filtrate was concentrated under reduced pressure (12 mbar). The residue obtained was purified by flash-column chromatography (eluting with 0-20% ethyl acetate-hexanes; ∇ = 2% ethyl acetate/CV; 5CV for product) to afford the acrylate **S4** as a colorless oil (6.8 g; >30:1 *E*:*Z*).

*Characterization data for **S4**:* **TLC:** R_f = 0.53 (hexane/EtOAc = 4:1; UV active (254 nm), stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 6.94 (dd, *J* = 15.7, 7.0 Hz, 1H, H_7), 5.82 (dd, *J* = 15.8, 1.3 Hz, 1H, H_8), 5.70 (ddt, *J* = 9.0, 4.4, 1.9 Hz, 1H, H_3), 5.62 (d, *J* = 10.2 Hz, 1H, H_4), 4.42 – 4.30 (m, 1H, H_5), 3.73 (s, 3H, H_9), 2.50 (tt, *J* = 12.0, 5.8 Hz, 1H, H_1), 2.15 – 2.07 (m, 1H, H_2), 2.01 (dd, *J* = 12.5, 5.8 Hz, 1H, H_6), 1.92 (ddq, *J* = 16.7, 10.5, 2.8 Hz, 1H, H_2), 1.49 – 1.39 (m, 1H, H_6), 0.89 (s, 9H, H_{11}), 0.07 (d, *J* = 5.5 Hz, 6H, H_{10}); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 167.3 (C), 152.4 (CH), 132.3 (CH), 126.6 (CH), 119.6 (CH), 67.9 (CH), 51.6 (CH_3), 37.7 (CH_2), 36.1 (CH), 30.3 (CH_2), 26.0 (CH_3), -4.4 (CH_3), -4.5 (CH_3); **IR** (FT-ATR, cm^{-1}): 2951, 2929, 2858, 1726, 1658, 1472, 1435, 1276, 1252, 1101, 1076, 833; **HRMS** (EI+) (*m/z*) for [M^+] $C_{16}H_{27}O_3Si$ requires 295.1730, observed 295.1723; **Optical:** $[\alpha]_D^{20.0}$ = +6.1 (*c* = 1.08, $CHCl_3$).

The corresponding enantiomer *ent*-**S4** (6.9 g) was synthesized in a similar fashion starting from acrylate *ent*-**S3**. **Optical:** $[\alpha]_D^{20.0}$ = -5.4 (*c* = 1.34, $CHCl_3$).

Step 4: Synthesis of enone S5



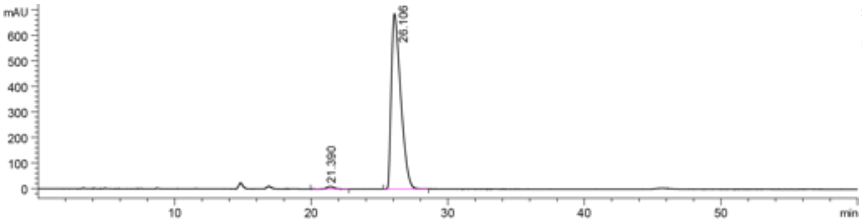
A solution of diisobutylaluminum hydride (1.0 M in THF, 52 mL, 52.3 mmol, 2.5 equiv) was added slowly (down the side of the reaction vessel over 20 minutes) to a solution of acrylate **S4** (6.2 g, 20.9 mmol, 1.0 equiv) in dichloromethane (121 mL) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2.5 h at -78 °C. The cold product mixture was quenched with methanol (5 mL). The product mixture was warmed over 30 minutes to 21 °C with stirring, at which time it was further diluted sequentially with dichloromethane (100 mL) and Rochelle's salt solution (100 mL). The biphasic solution was vigorously stirred for 12 h. The product mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was re-extracted with additional dichloromethane (2 x 50 mL). The organic layers were combined and dried over magnesium sulfate. The dried solution was filtered through a sintered glass funnel and the filtrate was concentrated under reduced pressure (12 mbar). The crude residue was dissolved in fresh dichloromethane (75 mL) and then acetic anhydride (3.20 g, 31.4 mmol, 1.5 equiv) and 4-dimethylaminopyridine (DMAP) (3.06 g, 25.1 mmol, 1.2 equiv) were added sequentially. The reaction mixture was stirred for 30 minutes at 21 °C. The product solution was diluted with saturated aqueous ammonium chloride (150 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional dichloromethane (2 x 75 mL). The organic layers were combined and dried over magnesium sulfate. The dried solution was filtered through a plug of silica and the filtrate was concentrated under reduced pressure (12 mbar). An analytically-pure sample of the allylic acetate *int*-**S5** was obtained by flash-column chromatography (eluting with 5% ethyl acetate-hexanes). **TLC:** R_f = 0.56 (hexane/EtOAc = 4:1; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 5.74 (dd, *J* = 15.5, 6.9 Hz, 1H), 5.69 (ddt, *J* = 9.2, 4.4, 2.0 Hz, 1H), 5.62 – 5.53 (m, 2H), 4.52 (d, *J* = 6.4 Hz, 2H), 4.35 (dddt, *J* = 7.6, 5.6, 3.6, 1.9 Hz, 1H), 2.36 (qd, *J* = 8.9, 8.3, 3.8 Hz, 1H), 2.07 – 2.03 (m, 4H), 2.00 – 1.96 (m, 1H), 1.88 – 1.82 (m, 1H), 1.42 – 1.36 (m, 1H), 0.90 (s, 9H), 0.08 (d, *J* = 5.3 Hz, 6H); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 171.0, 140.0, 132.2, 127.8, 122.6, 68.4, 65.3, 38.6, 36.2, 31.2, 26.1, 21.2, 18.4, -4.4, -4.5; **IR** (FT-ATR, cm^{-1}): 3030, 2954, 2929, 2857, 1742, 1472, 1388, 1362, 1230, 1075, 836, 775; **MS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{31}O_3Si$ requires 311.20, observed 333.26;

Hydrochloric acid (1 M, 50 mL, 50 mmol) was added to a solution of the crude allylic acetate (6.2 g, 20.0 mmol, 1 equiv) obtained in the preceding sequence in tetrahydrofuran (50 mL) at 4 °C. The reaction mixture was stirred vigorously for 4 h at 4 °C, at which time complete hydrolysis of the TBS ether was observed (*via* TLC; R_f = 0.90 for the silyl ether, 0.36 for the allylic alcohol, 50% ethyl acetate/hexanes; $KMnO_4$ stain). The cooled product mixture was slowly diluted with saturated aqueous sodium bicarbonate (added until bubbling ceased) and then further diluted with ethyl acetate (150 mL). The resulting transparent mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 50 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered through a plug of silica and the filtrate was concentrated under reduced pressure (12 mbar). The crude residue was dissolved in chloroform (150 mL) and manganese dioxide (17.4 g, 200 mmol, 10.0 equiv) was added. The resulting suspension was stirred for 16 hours at 21 °C. The product mixture was filtered through a bed of celite (40 mL) and the filter cake was washed with chloroform (3 x 25 mL). The filtrates were combined and concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate-hexanes) to afford the enone **S5** as a colorless oil (3.5 g, 86% yield).

*Characterization data for **S5**:* **TLC:** R_f = 0.58 (hexane/EtOAc = 7:3; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 6.95 (ddd, *J* = 10.1, 5.4, 2.7 Hz, 1H, H_3), 6.07 – 5.99 (m, 1H, H_4), 5.74 (dd, *J* = 15.6, 6.6 Hz, 1H, H_7), 5.61 (dt, *J* = 15.5, 6.1 Hz, 1H, H_8), 4.51 (d, *J* = 6.2 Hz, 2H, H_{10}), 2.82 (tq, *J* = 10.7, 4.8 Hz, 1H, H_1), 2.54 (dd, *J* = 16.2, 4.1 Hz, 1H, H_6), 2.48 (dt, *J* = 18.7, 5.2 Hz, 1H, H_2), 2.29 (dd, *J* = 16.3, 12.3 Hz, 1H, H_6), 2.23 (ddt, *J* = 18.6, 9.9, 2.7 Hz, 1H, H_2), 2.05 (s, 3H, H_{11}); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 198.7 (C), 170.8 (C), 149.1 (CH), 136.9 (CH), 130.0 (CH), 124.4 (CH), 64.7 (CH_2), 43.5 (CH_2), 37.7 (CH), 31.7 (CH_2), 21.1 (CH_3); **IR** (FT-ATR, cm^{-1}): 3032, 2945, 2884, 1733, 1677, 1386, 1366, 1224, 1025, 969, 880, 736 cm^{-1}; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{11}H_{15}NO_3$ requires 195.1021, observed 195.1013; **Optical:** $[\alpha]_D^{20.0}$ = +46.9 (*c* = 1.03, $CHCl_3$, 99:1 er). **HPLC** (Chiralcel AD-H column, 10% EtOH/hexanes eluent, 5 μL injection, 1 mL/min, regulated at 21 °C, 230 nm): major enantiomer t_R = 26.1 min, minor enantiomer t_R = 21.4 min for **S5**.

The corresponding enantiomer *ent*-**S5** (10.1 g) was synthesized in a similar fashion starting from enone *ent*-**S4**. **Optical:** $[\alpha]_D^{20.0}$ = -47.8 (*c* = 1.05, $CHCl_3$, 99:1 er); **HPLC** (Chiralcel AD-H column, 10% EtOH/hexanes eluent, 5 μL injection, 1 mL/min, regulated at 21 °C, 230 nm): major enantiomer t_R = 21.0 min, minor enantiomer t_R = 26.6 min for *ent*-**S5**.

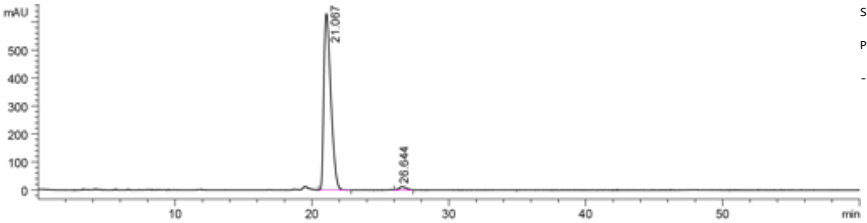
a)



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.390	BB	0.5815	340.08948	9.23902	1.0231
2	26.106	BB	0.7435	3.29026e4	686.11133	98.9769

b)

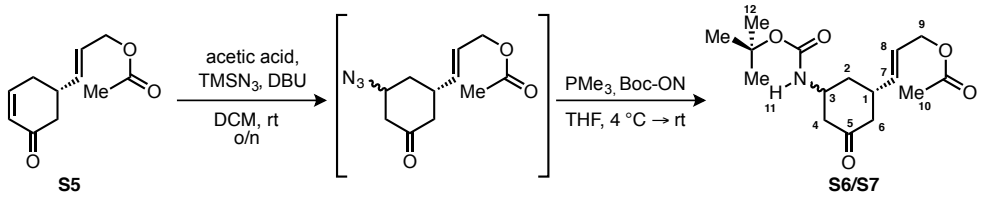


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.067	VB	0.5532	2.25026e4	629.27472	98.0245
2	26.644	MF	0.6452	453.49170	11.71458	1.9755

Supplementary Figure S1: Representative HPLC traces with raw data; a) **S5**, b) ***ent*-S5**.

Step 5A: Synthesis of the *cis*-*N*-Boc cyclohexanone S6

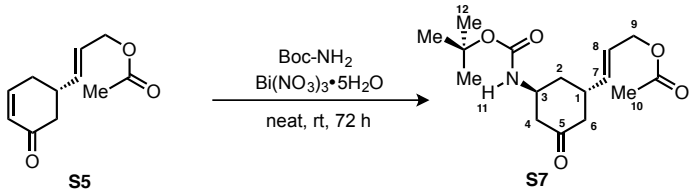


Adatping the protocol of Guerin *et al.*,[3] glacial acetic acid (0.47 mL, 8.4 mmol, 3.5 equiv) was added to a solution of azidotrimethylsilane (934 mg, 8.4 mmol, 3.5 equiv) in dichloromethane (10 mL) at 21 °C under a nitrogen atmosphere. The reaction was stirred for 20 minutes and then enone **S5** (450 mg, 2.32 mmol, 1.0 equiv) and DBU (141 mg, 0.93 mmol, 0.4 equiv) were added *via* syringe separately. The reaction mixture was aged for 6 h with stirring, at which time the reaction was quenched by passage through a silica plug, eluting with 50% ethyl acetate/hexanes. A light yellow liquid was obtained after concentration *in vacuo*, which was taken forward without further purification. **TLC:** R_f = 0.65 (hexane/EtOAc = 7:3; stained with $KMnO_4$)

Adapting the protocol of Ariza *et al.*,[4] 2-(boc)-oxyimino)-2-phenylacetonitrile (Boc-ON, 857 mg, 3.48 mmol, 1.5 equiv) was added to a solution of the crude azide obtained in the preceding step in dry tetrahydrofuran (15 mL; Note: Boc-ON readily decomposes over a period of a few months. It should be triturated with 90% aqueous MeOH, filtered, dried, then recrystallized from *warm* MeOH). The reaction flask was fitted with a rubber septum and the septum was penetrated with a needle. A balloon of nitrogen was fixed to the vessel and the solution was cooled to -18 °C with stirring. A solution of trimethylphosphine (1.0 in THF, 2.45 mL, 2.44 mmol, 1.05 equiv) was added slowly (Note: the reaction is exothermic and evolves nitrogen gas). After the addition, the cooling bath was removed and the reaction mixture was warmed over 30 minutes to 21 °C with stirring, and continued to age for 4 h. The product mixture was slowly diluted with saturated aqueous ammonium chloride (20 mL) and then further diluted with ethyl acetate (50 mL). The resulting mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 15 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (20 mL), and dried over sodium sulfate. The dried solution was filtered and concentrated under reduced pressure (12 mbar) to afford a mixture of **S6/S7** (1:1). The residue obtained was subjected to flash-column chromatography (first eluting with 10% ethyl acetate-hexanes for 1 CV, which was then strengthened to 50% ethyl acetate over 10 CV; 50g, 100 mL/min). The fractions containing the *cis* product (TLC analysis, $KMnO_4$ stain) were collected and concentrated to afford **S6** as a colorless oil (201 mg with ~90% purity, contaminated with **S5**; 28% yield; Note: the compound is not UV active).

*Characterization data for **S6**:* **TLC:** R_f = 0.49 (hexane/EtOAc = 7:3; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 5.69 (dd, *J* = 15.5, 6.2 Hz, 1H, H_7), 5.59 (dt, *J* = 15.9, 6.2 Hz, 1H, H_8), 4.60 – 4.49 (m, 3H, $H_{9,11}$), 3.81-3.77 (m, 1H, H_3), 2.71 (d, *J* = 15.7 Hz, 1H, H_4), 2.49 – 2.38 (m, 2H, $H_{1,6}$), 2.31 – 2.23 (m, 1H, H_2), 2.17 (t, *J* = 13.2 Hz, 1H, H_4), 2.10 (t, *J* = 14.5 Hz, 1H, H_6), 2.06 (s, 3H, H_{10}), 1.47 – 1.35 (m, 10H, $H_{2,12}$); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 207.0 (C), 170.9 (C), 154.8 (C), 137.0 (CH), 124.0 (CH), 80.0 (C), 64.7 (CH_2), 48.7 (broad, CH), 47.8 (broad, CH_2), 46.2 (CH_2), 38.4 (CH_2), 37.0 (CH), 28.5 (CH_3), 21.1 (CH_3); **IR** (FT-ATR, cm^{-1}): 3348, 2976, 2938, 1735, 1708, 1519, 1365, 1227, 1164, 1015, 969; **HRMS** (ES+ w/ NaCl) (*m/z*) for $[M+Na]^+$ $C_{16}H_{25}NNaO_5$ requires 334.1630, observed 334.1630; (ESI) (*m/z*) for $[M+H]^+$ $C_{16}H_{26}NO_5$ requires 312.1811, observed 312.1817; **Optical** $[\alpha]_D^{20.0}$ = -21.5 (*c* = 1.03, $CHCl_3$).

Step 5B: Synthesis of the *trans-N*-Boc cyclohexanone S7

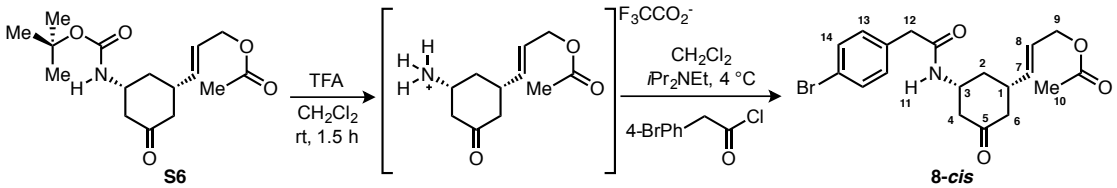


Adapting the protocol of Srivastava *et al.*,[7] bismuth(III) nitrate pentahydrate (485 mg, 1.0 mmol, 0.2 equiv) (Note: ground to a fine powder prior to use) was added neat to a reaction vessel containing the enone **S5** (1.00 g, 5.1 mmol, 1.0 equiv) and *tert*-butyl carbamate (668 mg, 5.7 mmol, 1.1 equiv) at 21 °C. The resulting semi-solid mixture was stirred for 72 hours at 21 °C. The product mixture was diluted with ethyl acetate (10 mL) and filtered through a plug of silica (20 mL). The plug was washed with ethyl acetate (3 x 40 mL). The filtrates were combined and concentrated. The residue was purified by flash-column chromatography (eluting with 0- 50% ethyl acetate/hexanes; ∇ = 3.33% ethyl acetate/CV; 15 CV for product). The colorless oil **S7** eventually solidifies upon standing (1.01 g, 63% yield, 50:1 dr).

*Characterization data for **S7**:* **TLC:** R_f = 0.44 (hexane/EtOAc = 7:3; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 5.72 (dd, *J* = 15.6, 6.1 Hz, 1H, H_7), 5.64 – 5.55 (m, 1H, H_8), 4.54-4.51 (m, 3H, $H_{9,11}$), 4.21 (br s, 1H, H_3), 2.75 (br s, 1H, H_1), 2.62 (dd, *J* = 14.3, 5.0 Hz, 1H, H_3), 2.46 (dd, *J* = 14.0, 4.7 Hz, 1H, H_6), 2.36 (dd, *J* = 14.3, 5.1 Hz, 1H, H_3), 2.30 (dd, *J* = 13.8, 10.1 Hz, 1H, H_6), 2.11 – 2.01 (m, 4H, $H_{2,10}$), 1.88 – 1.77 (m, 1H, H_2), 1.43 (s, 9H, H_{12}); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 208.7 (C), 170.9 (C), 154.9 (C), 136.8 (CH), 124.6 (CH), 80.0 (C), 64.7 (CH_2), 47.9 (CH), 47.0 (CH_2), 46.3 (CH_2), 36.0 (CH), 35.7 (CH_2), 28.5 (CH_3), 21.12 (CH_3); **IR** (FT-ATR, cm^{-1}): 3340, 2976, 2936, 1737, 1707, 1518, 1365,1226, 1166, 1028, 970; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{16}H_{26}NO_5$ requires 312.1811, observed 312.1817; **Optical** $[\alpha]_D^{20.0}$ = -24.6 (*c* = 1.05, $CHCl_3$).

The corresponding enantiomer *ent*-**S7** (2.51 g, 52% yield) was synthesized in a similar fashion starting from enone *ent*-**S5** (3.0 g, 15.4 mmol, 1.0 equiv). **Optical** $[\alpha]_D^{20.0}$ = +20.9 (*c* = 0.75, $CHCl_3$).

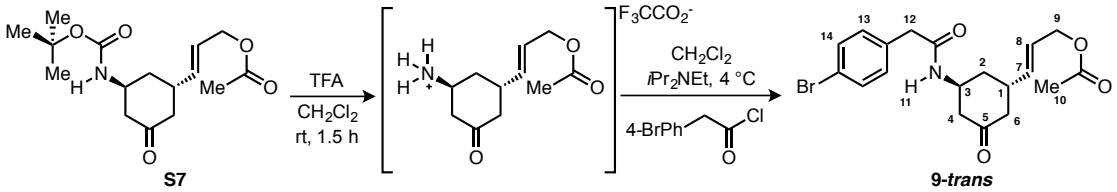
Step 6A: Synthesis of the *cis*-*N*-arylacetamide cyclohexanone 8-*cis*



Trifluoroacetic acid (3.5 mL) was added to a solution of *cis*-*N*-Boc cyclohexanone **S6** (141 mg, 0.45 mmol, 1 equiv) in dichloromethane (3.5 mL) at 21 °C. The reaction flask was fitted with a rubber septum and the septum was penetrated with a needle. An external line ending in a solution of saturated aqueous sodium bicarbonate was fitted to the needle. The reaction mixture was stirred for 1.5 hours at 21 °C at which point gas evolution in the external flask containing the saturated aqueous sodium bicarbonate solution ceased indicating the complete deprotection of the *N*-Boc group. The product mixture was concentrated, and excess trifluoroacetic acid was removed by azetropic distillation with toluene/dichloromethane (1:1; 3 x 10 mL) to afford the intermediate amine ion. (Note: Attempted purification of the amine ion resulted in isolation of a complex mixture of unidentified decomposition products. Accordingly, the unpurified residue was used directly in the acetylation step). The amine ion was dissolved in 20 mL of dichloromethane and cooled to 4 °C using an ice bath. To this solution, 4-bromophenylacetyl chloride (146 mg, 0.68 mmol, 1.5 equiv) and *N,N*-diisopropylethylamine (116 mg, 0.90 mmol, 2.0 equiv) were added in sequence. The resulting mixture was stirred for 4 hours at 21 °C. The product mixture was slowly diluted with saturated aqueous ammonium chloride (20 mL) and then further diluted with ethyl acetate (50 mL). The resulting mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 15 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (20 mL), and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue obtained was subjected to flash-column chromatography (first eluting with 33% ethyl acetate-hexanes for 2 CV, then 100% ethyl acetate). The fractions containing the product (TLC analysis) were collected and concentrated. The residue obtained was further purified directly by chromatography on C-18 silica (30 g). The compound was eluted with 20% acetonitrile/water (4 CV), which was then strengthened to 55% acetonitrile/water over 8 CV, then held constant for 6 CV (the product elutes at 50% acetonitrile/water) to afford the *cis*-*N*-arylacetamide cyclohexanone **8-*cis*** as a white solid (131 mg, 71% yield).

*Characterization data for **8**:* **TLC:** R_f = 0.13 (hexane/EtOAc = 7:3; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.49 (d, *J* = 8.1 Hz, 2H, H_{14}), 7.13 (d, *J* = 8.1 Hz, 2H, H_{13}), 5.66 (dd, *J* = 15.6, 6.1 Hz, 1H, H_7), 5.58 (dt, *J* = 15.5, 6.1 Hz, 1H, H_8), 5.31 (d, *J* = 8.0 Hz, 1H, H_{11}), 4.50 (d, *J* = 6.0 Hz, 2H, H_9), 4.13 (dtt, *J* = 16.4, 8.4, 4.4 Hz, 1H, H_3), 3.50 (s, 2H, H_{12}), 2.65 (dd, *J* = 13.8, 4.6 Hz, 1H, H_4), 2.51 – 2.38 (m, 2H, $H_{1,6}$), 2.19 (d, *J* = 12.8 Hz, 1H, H_2), 2.15 – 2.02 (m, 5H, $H_{4,6,10}$), 1.36 (q, *J* = 12.0 Hz, 1H, H_2); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 206.4 (C), 170.9 (C), 169.6 (C), 136.7 (CH), 133.6 (C), 132.4 (CH), 131.1 (CH), 124.3 (CH), 121.7 (C), 64.7 (CH_2), 47.6 (CH), 47.2 (CH_2), 46.2 (CH), 43.2 (CH_2), 37.7 (CH2), 37.0 (CH), 21.1 (CH_3); **IR** (FT-ATR, cm^{-1}): 3289, 3051, 2938, 1741, 1702, 1643, 1536, 1488, 1242, 1071, 968; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{23}BrNO_4$ requires 408.0810, observed 408.0818; **Optical** $[\alpha]_D^{20.0}$ = -9.5 (*c* = 0.58, $CHCl_3$).

Step 6B: Synthesis of the *trans*-*N*-arylacetamide cyclohexanone 9-*trans*

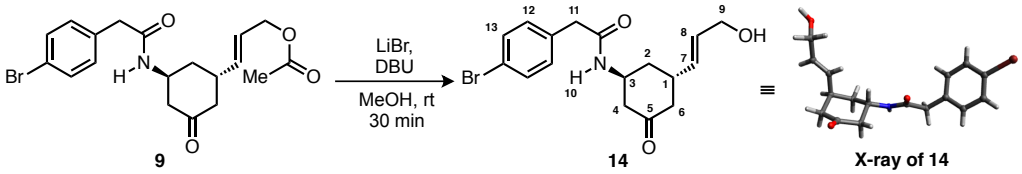


Trifluoroacetic acid (10 mL) was added to a solution of *trans*-*N*-Boc cyclohexanone **S7** (1.21 g, 3.89 mmol, 1 equiv) in dichloromethane (10 mL) at 21 °C. The reaction flask was fitted with a rubber septum and the septum was penetrated with a needle. An external line ending in a solution of saturated aqueous sodium bicarbonate was fitted to the needle. The reaction mixture was stirred for 1.5 hours at 21 °C at which point gas evolution in the external flask containing the saturated aqueous sodium bicarbonate solution ceased indicating the complete deprotection of the *N*-Boc group. The product mixture was concentrated, and excess trifluoroacetic acid was removed by azetropic distillation with toluene/dichloromethane (1:1; 3 x 10 mL) to afford the intermediate amine ion (Note: Attempted purification of the amine ion resulted in isolation of a complex mixture of unidentified decomposition products. Accordingly, the unpurified residue was used directly in the acetylation step). The amine ion was dissolved in 39 mL of dichloromethane and cooled to 4 °C using an ice bath. To this solution, 4-bromophenylacetyl chloride (1.25 g, 5.8 mmol, 1.5 equiv) and *N,N*-diisopropylethylamine (1.35 mL, 7.8 mmol, 2.0 equiv) were added in sequence. The resulting mixture was stirred for 2 hours at 21 °C. The product mixture was slowly diluted with saturated aqueous ammonium chloride (75 mL) and then further diluted with ethyl acetate (100 mL). The resulting mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 25 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (75 mL), and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue obtained was subjected to flash-column chromatography (first eluting with 33% ethyl acetate-hexanes for 2 CV, then 100% ethyl acetate). The fractions containing the product (TLC analysis) were collected and concentrated. The residue obtained was further purified directly by chromatography on C-18 silica (60 g). The compound was eluted with 20% acetonitrile/water (4 CV), which was then strengthened to 55% acetonitrile/water over 8 CV, then held constant for 6 CV (the product elutes at 50% acetonitrile/water) to afford the *trans*-*N*-arylacetamide cyclohexanone **9-*trans*** as a white solid (492 mg, 31% yield).

*Characterization data for **9**:* **TLC:** R_f = 0.13 (hexane/EtOAc = 7:3; stained with $KMnO_4$); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.46 (d, *J* = 8.2 Hz, 2H, H_{14}), 7.11 (d, *J* = 8.1 Hz, 2H, H_{13}), 5.68 (dd, *J* = 15.6, 6.1 Hz, 1H, H_7), 5.60 (d, *J* = 7.4 Hz, 1H, H_{11}), 5.54 (dtd, *J* = 15.5, 6.1, 1.2 Hz, 1H, H_8), 4.50 (d, *J* = 6.1 Hz, 2H, H_9), 4.47-4.44 (m, 1H, H_1), 3.46 (s, 2H, H_{12}), 2.64-2.56 (m, 2H, $H_{1,4}$), 2.41 (dd, *J* = 14.0, 4.7 Hz, 1H, H_6), 2.33 – 2.26 (m, 2H, $H_{4,6}$), 2.07-2.02 (m, 4H, $H_{2,10}$), 1.79 (ddd, *J* = 13.7, 10.1, 3.5 Hz, 1H, H_2); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 208.6 (C), 170.8 (C), 169.9 (C), 136.4 (CH), 133.7 (C), 132.2 (CH), 131.0 (CH), 124.7 (CH), 121.6 (C), 64.6 (CH_2), 47.0 (CH), 46.4 (CH_2), 46.3 (CH_2), 43.1 (CH_2), 36.2 (CH), 35.0 (CH_2), 21.1 (CH_3); **IR** (FT-ATR, cm^{-1}): 3298, 3050, 2940, 1734, 1712, 1643, 1537, 1487, 1226, 1071, 1026, 1012, 968; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{23}BrNO_4$ requires 408.0810, observed 408.0813; **Optical** $[\alpha]_D^{20.0}$ = -17.8 (*c* = 1.01, $CHCl_3$, 99:1 er).

The corresponding enantiomer *ent*-**9** (551 mg, 35% yield) was synthesized in a similar fashion starting from *trans*-*N*-Boc cyclohexanone *ent*-**S7** (1.21 g, 3.89 mmol, 1.0 equiv). **Optical** $[\alpha]_D^{20.0}$ = +19.6 (*c* = 1.04, $CHCl_3$, 98:2 er).

Step 7: Synthesis of the *trans*-*N*-arylacetamide cyclohexanone 14



The *trans*-*N*-arylacetamide cyclohexanone **9** (558 mg, 1.37 mmol, 1 equiv) was added to a pre-made cocktail (13.6 mL) containing LiBr (13.6 mmol, 10 equiv) and DBU (1.36 mmol, 1 equiv) in methanol. The resulting mixture was stirred at 21 °C for 30 minutes. The product mixture was then diluted with saturated aqueous ammonium chloride (20 mL) and then further diluted with ethyl acetate (60 mL). The resulting mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (60 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue obtained was further purified directly by chromatography on C-18 silica (60 g). The compound was eluted with 20% acetonitrile/water (4 CV), which was then strengthened to 55% acetonitrile over 8 CV, then held constant for 6 CV (the product elutes at 45% acetonitrile/water) to afford the *trans*-*N*-arylacetamide cyclohexanone **14** as a white solid (476 mg, 95% yield).

Characterization data: **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.47 (d, *J* = 8.2 Hz, 2H, H_{13}), 7.11 (d, *J* = 8.1 Hz, 2H, H_{12}), 5.66 – 5.58 (m, 2H, $H_{7,8}$), 5.57 – 5.50 (m, 1H, H_{10}), 4.46 (h, *J* = 5.7 Hz, 1H, H_3), 4.10 (br s, 2H, H_9), 3.46 (s, 2H, H_{11}), 2.64 – 2.54 (m, 2H, $H_{1,4}$), 2.42 (dd, *J* = 14.0, 4.8 Hz, 1H, H_6), 2.35 – 2.25 (m, 2H, $H_{4,6}$), 2.03 – 1.96 (m, 1H, H_2), 1.80 (ddd, *J* = 13.5, 9.6, 3.5 Hz, 1H, H_2), 1.66 – 1.60 (m, 1H, OH); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 208.6 (C), 169.7 (C), 133.5 (C), 133.0 (CH), 132.0 (CH), 130.8 (CH), 129.7 (CH), 121.4 (C), 63.1 (CH_2), 46.8 (CH), 46.4 (CH_2), 46.3 (CH_2), 43.0 (CH_2), 36.0 (CH), 35.2 (CH_2); **IR** (FT-ATR, cm^{-1}): 3388, 3287, 2950, 2905, 1700, 1641, 1531, 1487, 1088, 1024, 968; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_3$ requires 366.0705, observed 366.0705; **Optical** $[\alpha]_D^{20.0}$ = -26.8 (*c* = 1.02, $CHCl_3$, 99:1 er).

The corresponding enantiomer *ent*-**14** (454 mg, 92% yield) was synthesized in a similar fashion starting from *trans*-*N*-arylacetamide cyclohexanone *ent*-**9** (551 mg, 1.35 mmol, 1.0 equiv). **Optical** $[\alpha]_D^{20.0}$ = +22.5 (*c* = 1.0, $CHCl_3$, 98:2 er).

1.2 Synthesis of peptide catalysts

General information: The peptide synthesis was conducted using the Fmoc protecting group strategy, starting with 2-Cl-Trt resin that was preloaded with H-amino acid. The swelling of the resin was accomplished by suspending the resin in DMF for 30 minutes, then filtering and washing with additional DMF prior to the first coupling. A "wash cycle" consisted of suspending the resin in CH_2Cl_2 for 1 minute, then filtering, and then preforming the same series of events with DMF. The amino acid residues and coupling reagents were purchased from commercial suppliers and used as received. Yields are not optimized. Once synthesized, peptides **1**, ***ent*-1**, **2** and ***ent*-2** were stored at 21 °C in a dry box containing Drierite.

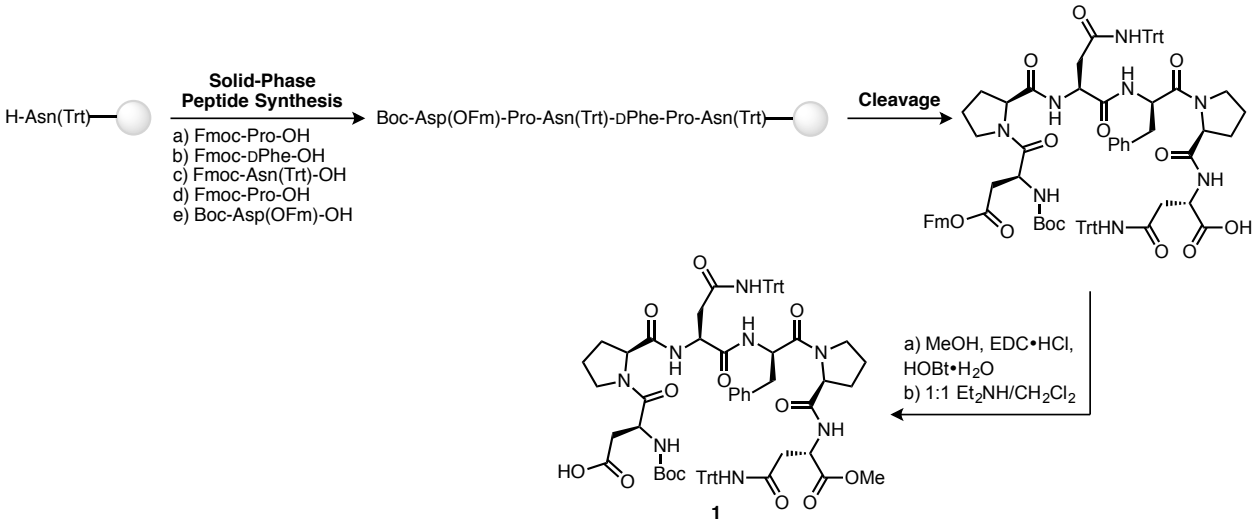
Peptide 1 and *ent*-1 coupling cocktail: The amino acid (3 equiv), *N,N,N′,N′*,tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU; 3 equiv), and 1-hydoxybenzotriazole hydrate (HOBt•H_2O; 3 equiv) were suspended in *N,N*-dimethylformamide (DMF; 17 mL). *N,N*-Diisoproylethylamine (5 equiv) was added and the mixture was agitated to homogeneity using a vortex stirrer. After 5 minutes, the mixture was added to the reaction vessel containing the resin, which was then gently agitated at 21 °C.

Peptide 2 and *ent*-2 coupling cocktail: The amino acid (3 equiv), *N,N,N′,N′*-tetramethyl-*O*-(6-chloro-1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HCTU; 3 equiv), and 6-chloro-1-hydroxybenzotriazole (Cl-HOBt; 3 equiv) were suspended in *N*-methylpyrrolidinone (NMP; 17 mL). *N*-Methylmorpholine (NMM; 5 equiv) was added and the mixture was agitated to homogeneity using a vortex stirrer. After 5 minutes, the mixture was added to the reaction vessel containing the resin, which was then gently agitated at 21 °C.

Deprotection of the Fmoc group: The resin was suspended in 20% (v/v) piperdine/DMF (17 mL), then gently agitated at 21 °C. After 20 minutes, the resin was filtered, and then subjected to five wash cycles.

Peptide cleavage: The resin was suspended in 4:1:1 dichloromethane/trifluoroethanol/acetic acid, then gently agitated for 1 minute, vented, then agitated at 21 °C. After 30 minutes, the product mixture was filtered into a flask. The resulting resin was washed thrice as follows: the resin was suspended in dichloromethane for 1 minute, after which the resin was filtered into the same flask as the cleavage solution. The combined filtrate was concentrated under reduced pressure, which was used without further purification.

Amino acid coupling for peptide 1 (Based on the method of Lichtor *et al.*[8]):



Peptide Coupling A: To a reaction vessel containing H-Asn(Trt)-2-Cl-Trt-resin (1.39 g, 0.75 mmol, 0.52 meq/g, 1.0 equiv) was added the first peptide coupling cocktail: Fmoc-Pro-OH (760 mg, 2.3 mmol, 3.0 equiv), HBTU (854 mg, 2.3 mmol, 3.0 equiv), HOBt•H_2O (345 mg, 2.3 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude dipeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling B: To a reaction vessel containing H-Pro-Asn(Trt)-2-Cl-Trt-resin (0.75 mmol, 1.0 equiv) was added the second peptide coupling cocktail: Fmoc-DPhe-OH (872 mg, 2.3 mmol, 3.0 equiv), HBTU (854 mg, 2.3 mmol, 3.0 equiv), HOBt•H_2O (345 mg, 2.3 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude tripeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling C: To a reaction vessel containing H-DPhe-Pro-Asn(Trt)-2-Cl-Trt-resin (0.75 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Fmoc-Asn(Trt)-OH (1344 mg, 2.3 mmol, 3.0 equiv), HBTU (854 mg, 2.3 mmol, 3.0 equiv), HOBt•H_2O (345 mg, 2.3 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

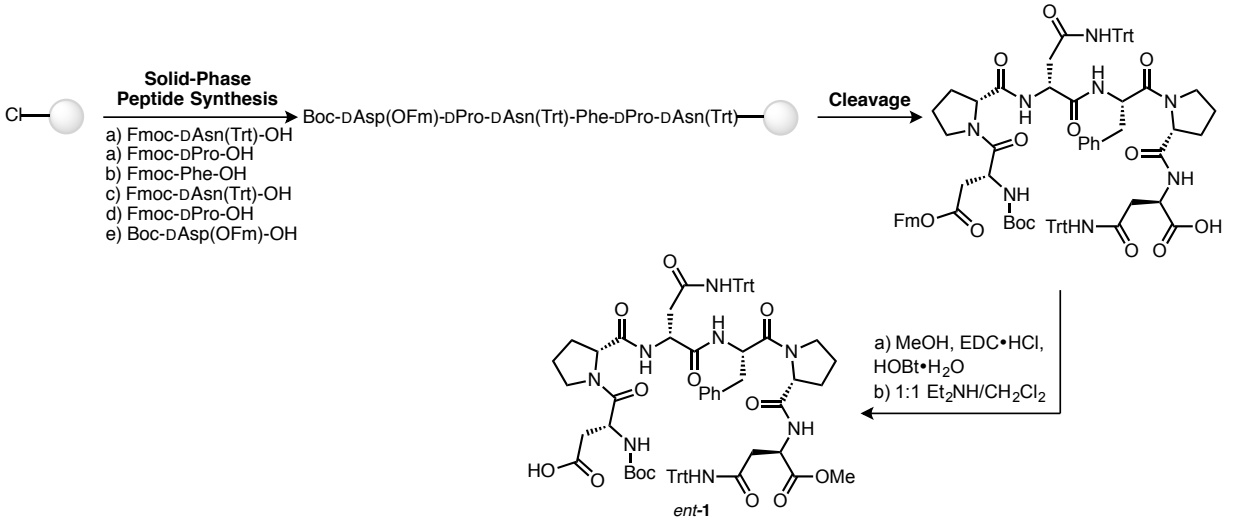
Peptide Coupling D: To a reaction vessel containing H-Asn(Trt)-DPhe-Pro-Asn(Trt)-2-Cl-Trt-resin (0.75 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Fmoc-Pro-OH (760 mg, 2.3 mmol, 3.0 equiv), HBTU (854 mg, 2.3 mmol, 3.0 equiv), HOBt•H_2O (345 mg, 2.3 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling E: To a reaction vessel containing H-Pro-Asn(Trt)-DPhe-Pro-Asn(Trt)-2-Cl-Trt-resin (0.75 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Boc-Asp(OFm)-OH (927 mg, 2.3 mmol, 3.0 equiv), HBTU (854 mg, 2.3 mmol, 3.0 equiv), HOBt•H_2O (345 mg, 2.3 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*). Cleavage of the crude peptide was accomplished in the same manner as described in Peptide cleavage (*vide supra*). The crude peptide was loaded onto a silica gel column packed with 98:1:1 CH_2Cl_2/MeOH/AcOH and eluted with this gradient increasing to 95:4:1 CH_2Cl_2/MeOH/AcOH after 3 CV. The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar).

C-terminal coupling and Fm deprotection: To a reaction vessel containing the crude peptide in methanol (3.8 mL), was added EDC•Hall (158 mg, 0.83 mmol, 1.1 equiv) and HOBt•H_2O (126 mg, 0.83 mmol, 1.1 equiv) at 21 °C. After 10 h, the reaction mixture was concentrated under reduced pressure (12 mbar), diluted with dichloromethane and then washed with 0.5 M citric acid, saturated aqueous sodium bicarbonate, and then half-saturated brine. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure (12 mbar). The resulting residue was dissolved in a mixture of 1:1 Et_2NH/CH_2Cl_2 (10 mL) at 21 °C. After 30 minutes, the reaction mixture was concentrated under reduced pressure (12 mbar). The crude peptide was loaded onto a silica gel column packed with 98:1:1 CH_2Cl_2/MeOH/AcOH and eluted with this gradient increasing to 95:4:1 CH_2Cl_2/MeOH/AcOH after 3 CV. The fractions containing the peptide were collected, pooled, and concentrated

under reduced pressure (12 Mbar). The title compound was obtained as a white solid (501 mg, 51% overall yield). **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{75}H_{81}N_8O_{13}$ requires 1301.5923, observed 1301.5924; **Optical:** $[\alpha]_D^{20.0}$ = -101.5 (*c* = 1.04, $CHCl_3$). The characterization data is consistent with the literature.[8] Purity determined by ^1H NMR analysis was >96%.

Amino acid coupling for peptide *ent*-1 (Based on the method of Lichtor *et al.*[8]):



Synthesis of the Resin: To a reaction vessel containing pre-swelled 2-chlorotrityl resin (1840 mg, 1.5 equiv), Fmoc-DAsn(Trt)-OH (585 mg, 0.98 mmol, 1.0 equiv) in DMF (17 mL) and *N,N*-diisoproylethylamine (850 mL, 4.91 mmol, 5.0 equiv) was added. The resulting yellow solution was agitated at 21 °C for 3 hours, and then methanol (4 mL) was added into the reaction vessel. The solution was agitated for 5 minutes, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the loaded amino acid was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling A: To a reaction vessel containing H-DAsn(Trt)-2-Cl-Trt-resin (0.98 mmol, 1.0 equiv) was added the first peptide coupling cocktail: Fmoc-DPro-OH (987 mg, 2.9 mmol, 3.0 equiv), HBTU (1.10 g, 2.9 mmol, 3.0 equiv), HOBt•H_2O (448 mg, 2.9 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (1.02 mL, 5.9 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude dipeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling B: To a reaction vessel containing H-DPro-DAsn(Trt)-2-Cl-Trt-resin (0.98 mmol, 1.0 equiv) was added the second peptide coupling cocktail: Fmoc-Phe-OH (1.13 g, 2.9 mmol, 3.0 equiv), HBTU (1.10 g, 2.9 mmol, 3.0 equiv), HOBt•H_2O (448 mg, 2.9 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (1.02 mL, 5.9 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude tripeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling C: To a reaction vessel containing H-Phe-DPro-DAsn(Trt)-2-Cl-Trt-resin (0.98 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Fmoc-DAsn(Trt)-OH (1.75 g, 2.9 mmol, 3.0 equiv), HBTU (1.10 g, 2.9 mmol, 3.0 equiv), HOBt•H_2O (448 mg, 2.9 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (1.02 mL, 5.9 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after

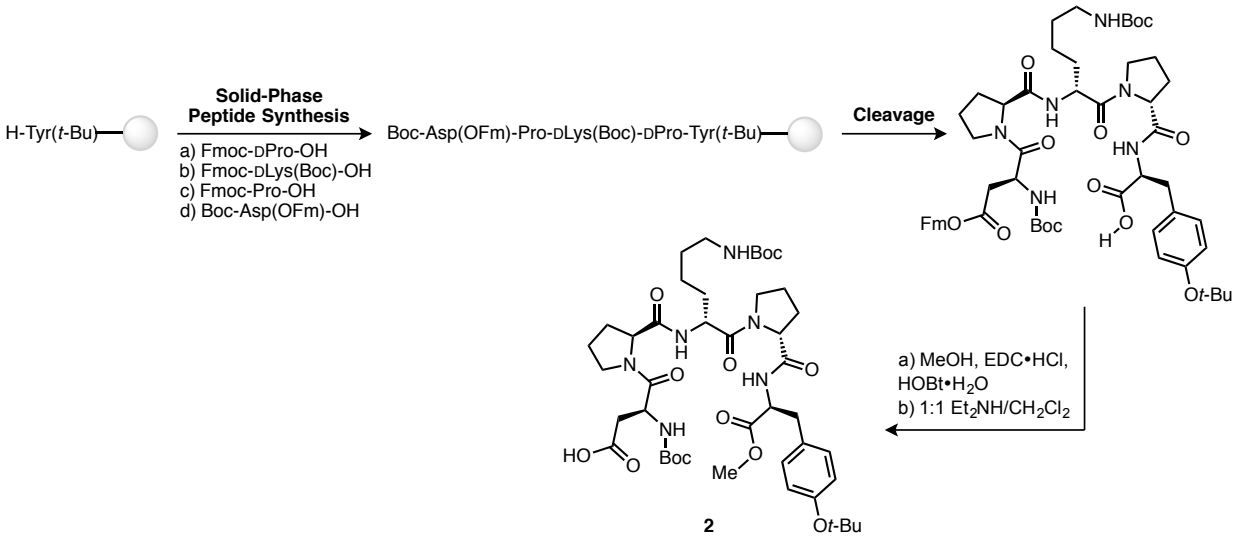
which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling D: To a reaction vessel containing H-DAsn(Trt)-Phe-DPro-DAsn(Trt)-2-Cl-Trt-resin (0.98 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Fmoc-DPro-OH (987 mg, 2.9 mmol, 3.0 equiv), HBTU (1.10 g, 2.9 mmol, 3.0 equiv), HOBt•H_2O (448 mg, 2.9 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (1.02 mL, 5.9 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling E: To a reaction vessel containing H-DPro-DAsn(Trt)-Phe-DPro-DAsn(Trt)-2-Cl-Trt-resin (0.98 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Boc-DAsp(OFm)-OH (1.20 g, 2.9 mmol, 3.0 equiv), HBTU (1.10 g, 2.9 mmol, 3.0 equiv), HOBt•H_2O (448 mg, 2.9 mmol, 3.0 equiv), *N*,*N*-diisopropylethylamine (1.02 mL, 5.9 mmol, 6.0 equiv), *N,N*-dimethylformamide (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*). Cleavage of the crude peptide was accomplished in the same manner as described in Peptide cleavage (*vide supra*). The crude peptide was loaded onto a silica gel column packed with 98:1:1 CH_2Cl_2/MeOH/AcOH and eluted with this gradient increasing to 95:4:1 CH_2Cl_2/MeOH/AcOH after 3 CV. The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar).

C-terminal coupling and Fm deprotection: To a reaction vessel containing the crude peptide in methanol (5.0 mL), was added EDC•HCl (206 mg, 1.07 mmol, 1.1 equiv) and HOBt•H_2O (164mg, 1.07 mmol, 1.1 equiv) at 21 °C. After 10 h, the reaction mixture was concentrated under reduced pressure (12 mbar), diluted with dichloromethane and then washed with 0.5 M citric acid, saturated aqueous sodium bicarbonate, and then half-saturated brine. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure (12 mbar). The resulting residue was dissolved in a mixture of 1:1 Et_2NH/CH_2Cl_2 (10 mL) at 21 °C. After 30 minutes, the reaction mixture was concentrated under reduced pressure (12 mbar). The crude peptide was loaded onto a silica gel column packed with 98:1:1 CH_2Cl_2/MeOH/AcOH and eluted with this gradient increasing to 95:4:1 CH_2Cl_2/MeOH/AcOH after 3 CV. The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar). The title compound was obtained as a white solid (551 mg, 43% overall yield). **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{75}H_{81}N_8O_{13}$ requires 1301.5923, observed 1301.5924; **Optical:** $[\alpha]_D^{20.0}$ = +99.3 (*c* = 1.03, $CHCl_3$). NMR characterization data is consistent with peptide **1**. Purity determined by ^1H NMR analysis was >96%.

Amino acid coupling for peptide 2 (Based on the method of Romney *et al.*):



Peptide Coupling A: To a reaction vessel containing H-Tyr(*t*-Bu)-2-Cl-Trt-resin (1.03 g, 0.687 mmol, 1.0 equiv) was added the first peptide coupling cocktail: Fmoc-DPro-OH (695 mg, 2.1 mmol, 3.0 equiv), HCTU (852 mg, 2.1 mmol, 3.0 equiv), Cl-HOBt (349 mg, 2.1 mmol, 3.0 equiv), NMM (0.45 mL, 4.1 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude dipeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling B: To a reaction vessel containing H-DPro-Tyr(*t*-Bu)-2-Cl-Trt-resin (0.687 mmol, 1.0 equiv) was added the second peptide coupling cocktail: Fmoc-DLys(Boc)-OH (965 mg, 2.1 mmol, 3.0 equiv), HCTU (852 mg, 2.1 mmol, 3.0 equiv), Cl-HOBt (349 mg, 2.1 mmol, 3.0 equiv), NMM (0.45 mL, 4.1 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude tripeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

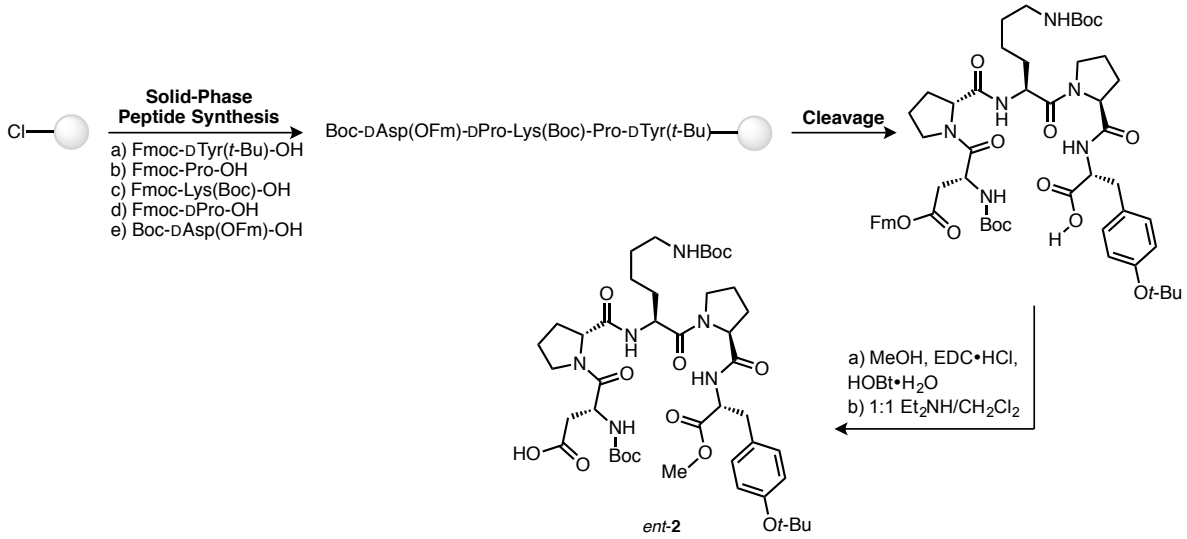
Peptide Coupling C: To a reaction vessel containing H-DLys(Boc)-DPro-Tyr(*t*-Bu)-2-Cl-Trt-resin (0.687 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Fmoc-Pro-OH (695 mg, 2.1 mmol, 3.0 equiv), HCTU (852 mg, 2.1 mmol, 3.0 equiv), Cl-HOBt (349 mg, 2.1 mmol, 3.0 equiv), NMM (0.45 mL, 4.1 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 4 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling D: To a reaction vessel containing H-Pro-DLys(Boc)-DPro-Tyr(*t*-Bu)-2-Cl-Trt-resin (0.687 mmol, 1.0 equiv) was added the fourth peptide coupling cocktail: Boc-Asp(OFm)-OH (848 mg, 2.1 mmol, 3.0 equiv), HCTU (852 mg, 2.1 mmol, 3.0 equiv), Cl-HOBt (349 mg, 2.1 mmol, 3.0 equiv), NMM (0.45 mL, 4.1 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Cleavage of the crude peptide was accomplished in the same manner as described in Peptide cleavage (*vide supra*).

C-terminal coupling and Fm deprotection (Based on the method of Romney *et al.*): To a reaction vessel containing the crude peptide in methanol (5.7 mL), was added EDC•HCl (145 mg, 0.76 mmol, 1.1 equiv) and HOBt•H_2O (116 mg, 0.76 mmol, 1.1 equiv) at 21 °C. After 10 h, the reaction mixture was concentrated under reduced pressure (12

mbar) and purified directly by chromatography on C-18 silica (60 g). The peptide was eluted with 5% acetonitrile/water (2 CV), which was then strengthened to 100% acetonitrile over 10 CV, then held constant for 2 CV (the peptide elutes last and has a characteristic absorbance at 265 nm). The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar). The resulting residue was dissolved in a mixture of 1:1 Et_2NH/CH_2Cl_2 (7 mL) at 21 °C. After 30 minutes, the reaction mixture was concentrated under reduced pressure (12 mbar). The crude mixture was dissolved in dichloromethane and passed through a plug of silica gel. The byproduct from the deprotection eluted through the plug first with 2 CV of 95:5:0.5 CH_2Cl_2/MeOH/AcOH. Then, the peptide was eluted through the plug with 5 CV of 90:10:1 CH_2Cl_2/MeOH/AcOH. The peptide was obtained as the free acid, which was purified by chromatography with C-18 silica (60g, same gradient as above) providing a white solid (441 mg, 72% overall yield). **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{44}H_{69}N_6O_{13}$ requires 889.4923, observed 889.4934; **Optical:** $[\alpha]_D^{20.0}$ = -14.4 (*c* = 1.04, $CHCl_3$). The characterization data is consistent with the literature.[9] Purity determined by ^{1}H NMR analysis was >96%.

Amino acid coupling for peptide *ent*-2 (Based on the method of Romney *et al.*):



Synthesis of the Resin: To a reaction vessel containing pre-swelled 2-chlorotrityl resin (1840 mg, 1.3 equiv), Fmoc-DTyr(*t*-Bu)-OH (520 mg, 1.13 mmol, 1.0 equiv) in DMF (17 mL) and *N,N*-diisoproylethylamine (980 mL, 5.65 mmol, 5.0 equiv) was added. The resulting yellow solution was agitated at 21 °C for 3 hours, then methanol (4 mL) was added into the reaction vessel. The solution was agitated for 5 minutes, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the loaded amino acid was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling B: To a reaction vessel containing H-DTyr(*t*-Bu)-2-Cl-Trt-resin (1.13 mmol, 1.0 equiv) was added the first peptide coupling cocktail: Fmoc-Pro-OH (1145 mg, 3.4 mmol, 3.0 equiv), HCTU (1404 mg, 3.4 mmol, 3.0 equiv), Cl-HOBt (576 mg, 3.4 mmol, 3.0 equiv), NMM (0.75 mL, 6.8 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude dipeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling C: To a reaction vessel containing H-Pro-DTyr(*t*-Bu)-2-Cl-Trt-resin (1.13 mmol, 1.0 equiv) was added the second peptide coupling cocktail: Fmoc-Lys(Boc)-OH (1591 mg, 3.4 mmol, 3.0 equiv), HCTU (1404 mg, 3.4 mmol, 3.0 equiv), Cl-HOBt (576 mg, 3.4 mmol, 3.0 equiv), NMM (0.75 mL, 6.8 mmol, 6.0 equiv), NMP (17

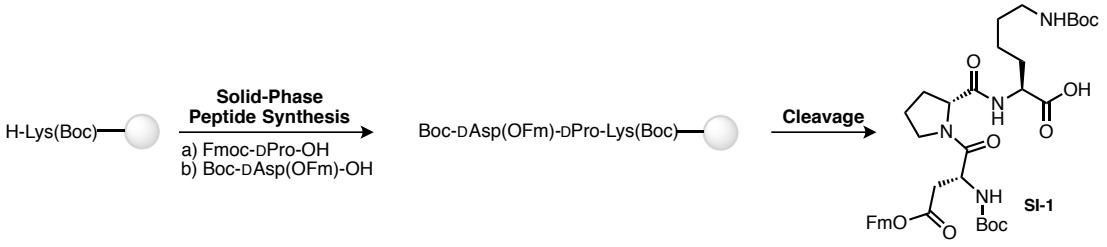
mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude tripeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling D: To a reaction vessel containing H-Lys(Boc)-Pro-DTyr(*t*-Bu)-2-Cl-Trt-resin (1.13 mmol, 1.0 equiv) was added the third peptide coupling cocktail: Fmoc-DPro-OH (1145 mg, 3.4 mmol, 3.0 equiv), HCTU (1404 mg, 3.4 mmol, 3.0 equiv), Cl-HOBt (576 mg, 3.4 mmol, 3.0 equiv), NMM (0.75 mL, 6.8 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 4 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Deprotection of the crude peptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

Peptide Coupling E: To a reaction vessel containing H-DPro-Lys(Boc)-Pro-DTyr(*t*-Bu)-2-Cl-Trt-resin (1.13 mmol, 1.0 equiv) was added the fourth peptide coupling cocktail: Boc-DAsp(OFm)-OH (1397 mg, 3.4 mmol, 3.0 equiv), HCTU (1404 mg, 3.4 mmol, 3.0 equiv), Cl-HOBt (576 mg, 3.4 mmol, 3.0 equiv), NMM (0.75 mL, 6.8 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Cleavage of the crude peptide was accomplished in the same manner as described in Peptide cleavage (*vide supra*).

C-terminal coupling and Fm deprotection: To a reaction vessel containing the crude peptide in methanol (5.7 mL), was added EDC•HCl (239 mg, 1.24 mmol, 1.1 equiv) and HOBt•H_2O (191 mg, 1.24 mmol, 1.1 equiv) at 21 °C. After 10 h, the reaction mixture was concentrated under reduced pressure (12 mbar) and purified directly by chromatography on C-18 silica (60 g). The peptide was eluted with 5% acetonitrile/water (2 CV), which was then strengthened to 100% acetonitrile over 10 CV, then held constant for 2 CV (the peptide elutes last and has a characteristic absorbance at 265 nm). The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar). The resulting residue was dissolved in a mixture of 1:1 Et_2NH/CH_2Cl_2 (12 mL) at 21 °C. After 30 minutes, the reaction mixture was concentrated under reduced pressure (12 mbar). The crude mixture was dissolved in dichloromethane and passed through a plug of silica gel. The byproduct from the deprotection eluted through the plug first with 2 CV of 95:5:0.5 CH_2Cl_2/MeOH/AcOH. Then, the peptide was eluted through the plug with 5 CV of 90:10:1 CH_2Cl_2/MeOH/AcOH. The peptide was obtained as the free acid, which was purified by chromatography with C-18 silica (60g, same gradient as above) providing a white solid (481 mg, 48% overall yield). **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{44}H_{69}N_6O_{13}$ requires 889.4923, observed 889.4904; **Optical:** $[\alpha]_D^{20.0}$ = +13.1 (*c* = 1.0, $CHCl_3$). The NMR characterization data is consistent with peptide **2**. Purity determined by ^1H NMR analysis was >96%.

Amino acid coupling for peptide SI-1 (Based on the method of Romney *et al.*):

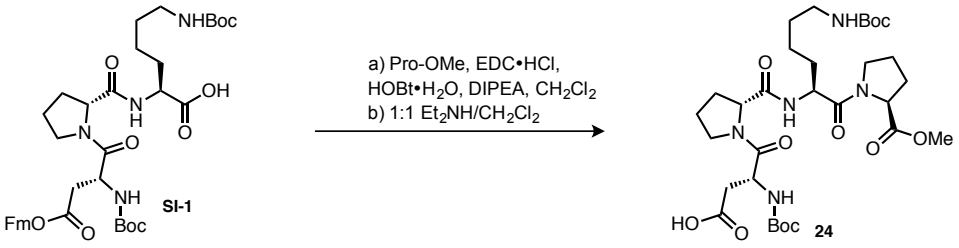


Peptide Coupling A: To a reaction vessel containing H-Lys(Boc)-2-Cl-Trt-resin (1.69 g, 1.01 mmol, 1.0 equiv) was added the first peptide coupling cocktail: Fmoc-DPro-OH (1026 mg, 3.0 mmol, 3.0 equiv), HCTU (1258 mg, 3.0 mmol, 3.0 equiv), Cl-HOBt (516 mg, 3.0 mmol, 3.0 equiv), NMM (0.67 mL, 6.1 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 3 hours, after which the solution was filtered and the resin

was subjected to five wash cycles. Deprotection of the crude dipeptide was accomplished in the same manner as described in Deprotection of the Fmoc group (*vide supra*).

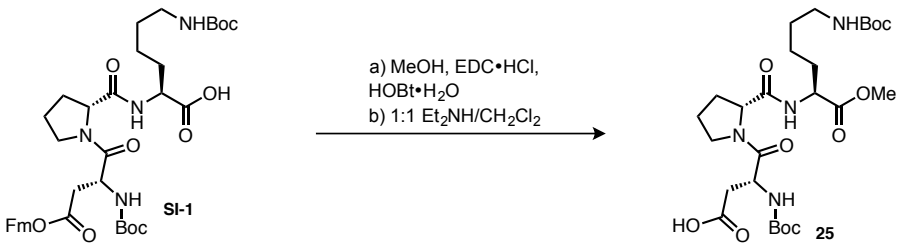
Peptide Coupling B: To a reaction vessel containing H-D-Pro-Lys(Boc)-2-Cl-Trt-resin (1.01 mmol, 1.0 equiv) was added the second peptide coupling cocktail: Fmoc-D-Asp(OFm)-OH (834 mg, 2.0 mmol, 2.0 equiv), HCTU (838 mg, 2.0 mmol, 2.0 equiv), Cl-HOBt (344 mg, 2.0 mmol, 2.0 equiv), NMM (0.67 mL, 6.1 mmol, 6.0 equiv), NMP (17 mL). The resulting yellow solution was agitated at 21 °C for 16 hours, after which the solution was filtered and the resin was subjected to five wash cycles. Cleavage of the crude peptide was accomplished in the same manner as described in Peptide cleavage (*vide supra*). **LC-MS** (ESI) (*m/z*) for $[M+Na]^+$ $C_{39}H_{52}N_4O_{10}Na$ requires 759.36, observed 759.71. The peptide was used directly without further purification in the subsequent couplings.

Amino acid coupling for peptide 24:



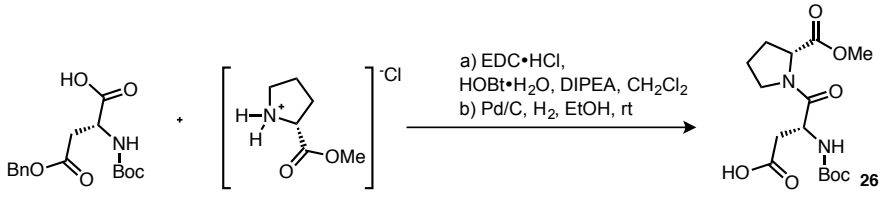
C-terminal coupling and Fm deprotection: To a reaction vessel containing the crude peptide **SI-1** (65 mg, 0.088 mmol, 1.0 equiv) was added EDC•HCl (19 mg, 0.097 mmol, 1.1 equiv), HOBt•H_2O (15 mg, 0.97 mmol, 1.1 equiv), Pro-OMe•HCl (18 mg, 0.11 mmol, 1.2 equiv) in dicholoromethane (1 mL) followed by *N,N'*-diisopropylethylamine (25 mg, 0.19 mmol, 2.2 equiv) at 21 °C. After 10 h, the reaction mixture was diluted with ethyl acetate and then washed with 0.5 M citric acid, saturated aqueous sodium bicarbonate, and then half-saturated brine. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure (12 mbar) and purified directly by chromatography on C-18 silica (30 g). The peptide was eluted with 5% acetonitrile/water (2 CV), which was then strengthened to 100% acetonitrile over 10 CV, then held constant for 2 CV (the peptide elutes last and has a characteristic absorbance at 265 nm). The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar). The resulting residue was dissolved in a mixture of 1:1 Et_2NH/CH_2Cl_2 (12 mL) at 21 °C. After 30 minutes, the reaction mixture was concentrated under reduced pressure (12 mbar). The crude mixture was dissolved in dichloromethane and passed through a plug of silica gel. The byproduct from the deprotection eluted through the plug first with 2 CV of 95:5:0.5 CH_2Cl_2/MeOH/AcOH. Then, the peptide was eluted through the plug with 5 CV of 90:10:1 CH_2Cl_2/MeOH/AcOH. The peptide was obtained as the free acid, which was purified by chromatography with C-18 silica (30g, same gradient as above) providing a white solid (31 mg, 53% overall yield). **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{31}H_{52}N_5O_{11}$ requires 670.3659, observed 670.3663; **Optical:** $[\alpha]_D^{20.0} = +30.1$ (c = 1.0, $CHCl_3$).

Amino acid coupling for peptide 25:



C-terminal coupling and Fm deprotection: To a reaction vessel containing the crude peptide (465 mg, 0.63 mmol, 1.0 equiv) in methanol (3.5 mL), was added EDC•HCl (133 mg, 0.69 mmol, 1.1 equiv) and HOBt•H_2O (106 mg, 0.69 mmol, 1.1 equiv) at 21 °C. After 10 h, the reaction mixture was concentrated under reduced pressure (12 mbar) and purified directly by chromatography on C-18 silica (60 g). The peptide was eluted with 5% acetonitrile/water (2 CV), which was then strengthened to 100% acetonitrile over 10 CV, then held constant for 2 CV (the peptide elutes last and has a characteristic absorbance at 265 nm). The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar). The resulting residue was dissolved in a mixture of 1:1 Et_2NH/CH_2Cl_2 (12 mL) at 21 °C. After 30 minutes, the reaction mixture was concentrated under reduced pressure (12 mbar). The crude mixture was dissolved in dichloromethane and passed through a plug of silica gel. The byproduct from the deprotection eluted through the plug first with 2 CV of 95:5:0.5 CH_2Cl_2/MeOH/AcOH. Then, the peptide was eluted through the plug with 5 CV of 90:10:1 CH_2Cl_2/MeOH/AcOH. The peptide was obtained as the free acid, which was purified by chromatography with C-18 silica (60g, same gradient as above) providing a white solid (201 mg, 58% overall yield). **HRMS** (ESI) (*m/z*) for $[M+Na]^+$ $C_{26}H_{44}N_4O_{10}Na$ requires 595.2949, observed 595.2955; **Optical:** $[\alpha]_D^{20.0}$ = +98.6 (*c* = 1.0, $CHCl_3$).

Amino acid coupling for peptide 26:

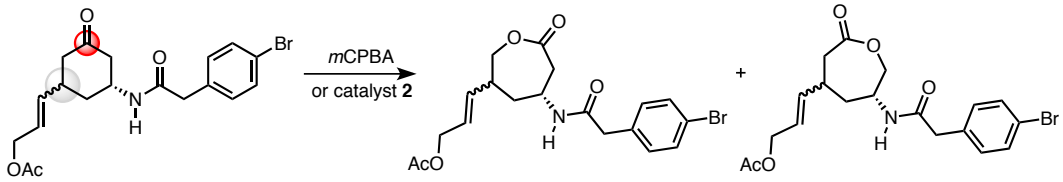


To a reaction vessel containing Boc-DAsp(OBn)-OH (350 mg, 1.08 mmol, 1.0 equiv) was added EDC•HCl (249 mg, 1.3 mmol, 1.2 equiv), HOBt•H_2O (198 mg, 1.3 mmol, 1.2 equiv), DPro-OMe•HCl (197 mg, 1.2 mmol, 1.1 equiv) in dicholoromethane (5.4 mL, 0.2 M) followed by *N,N'*-diisopropylethylamine (308 mg, 2.38 mmol, 2.2 equiv) at 21 °C. After 16 h, the reaction mixture was diluted with ethyl acetate (30 mL) and then washed with 10% citric acid (15 mL), saturated aqueous sodium bicarbonate (15 mL), and then half-saturated brine (15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure (12 mbar) and purified directly by chromatography on C-18 silica (120 g). The peptide was eluted with 5% acetonitrile/water (2 CV), which was then strengthened to 100% acetonitrile over 10 CV, then held constant for 2 CV (the peptide elutes second to last). The fractions containing peptide were collected, pooled, and concentrated under reduced pressure (12 mbar). LC-MS (ESI) (*m/z*) for $[M+Na]^+$ $C_{22}H_{30}N_2O_7Na$ requires 457.20, observed 457.36. The resulting residue was dissolved in ethanol (9.2 mL) and added to a flask containing Pd/C (10 wt%; 5 mg) under an argon atmosphere at 21 °C. The flask was evacuated and back-filled with hydrogen. After 18 hours, the flask was evacuated again and back-filled with argon. The product mixture was then filtered through a pad of celite, washing with ethyl acetate, and concentrated under reduced pressure (12 mbar). The peptide was obtained as the free acid providing an off-white solid (280 mg, 75% overall yield). **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{24}N_2O_7Na$ requires 367.1481, observed 367.1476; **Optical:** $[\alpha]_D^{20.0}$ = +84.4 (*c* = 1.0, $CHCl_3$).

1.3 Baeyer-Villiger oxidations of the substrates 8 and *ent*-9

General information: In order to obtain accurate information about the reaction mixture, the reactions were subjected to NMR and HPLC analysis with as little purification as possible (generally, filtration through a silica plug). However, the oxidation products were purified by preparative, reversed phase HPLC (eluting with H_2O and CH_3CN) and characterized by HPLC, NMR, and HRMS in order to ascertain their identity.

General procedure A for reaction parameter identification: A reaction vial equipped with a stir bar was charged with substrate **8** or *ent*-**9** (10.2 mg, 0.025 mmol, 1.0 equiv). To this vial, catalyst (2.2 mg, 0.0025 mmol, 0.1 equiv in 150 μL of chloroform) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv in 100 μL of chloroform) were added and the total volume was diluted to the desired concentration with respect to the substrate. The mixture was gently agitated until substrate was fully dissolved, then was transferred to a cold room (4 °C) and stirred for 1 hour. To this vial, aqueous H_2O_2 was added followed by *N,N'*-diisopropylcarbodiimide (DIC, 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion, and then the reaction mixture was vigorously stirred at 4 °C for 18-26 hours. After the allotted time had passed, the reaction media was pushed through a silica column (1 cm in a Pasteur pipette) topped with a plug of sodium sulfite, eluting with ethyl acetate (CV = 10), which was then concentrated under reduced pressure at ambient temperature. The residue was dissolved in $CDCl_3$ and analyzed by NMR and HPLC.

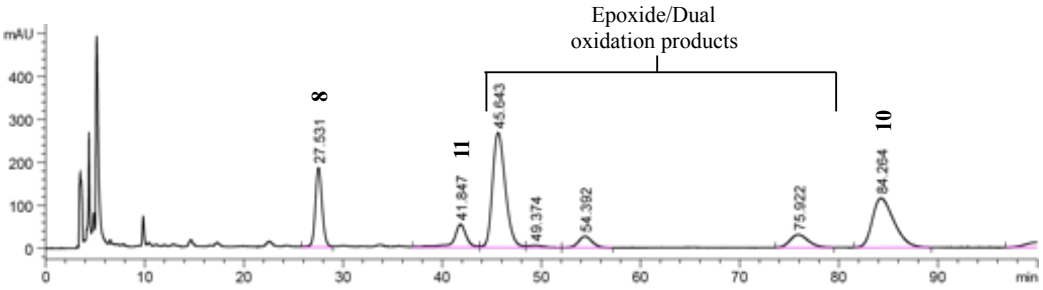


15% w/w H_2O_2 (4.41 M): Aqueous H_2O_2 (22.5 mL, 30% w/w, 9.79 M) was diluted with deionized water to a total volume of 50 mL.

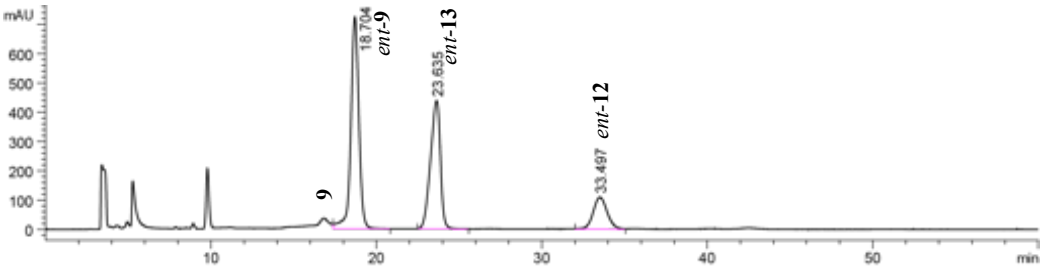
3% w/w H_2O_2 (0.88 M): Aqueous H_2O_2 (9.0 mL, 30% w/w, 9.79 M) was diluted with deionized water to a total volume of 100 mL.

HPLC method: Chiralpak IC column, 20% ethanol/hexanes, 1.0 mL/min, monitor at 230 nm.

a)



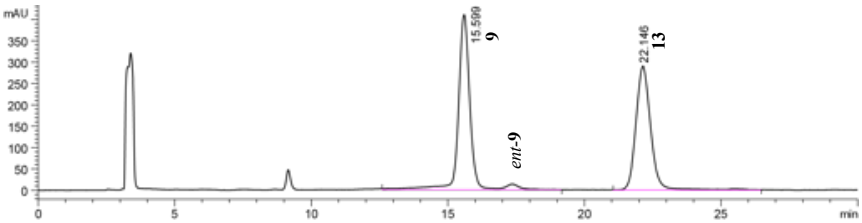
b)



Supplementary Figure S2: Representative crude HPLC traces for Baeyer-Villiger oxidations of **8** (a) and *ent*-**9** (b).

Data analysis: The relative conversion was approximated as (I_L) /$(I_S + I_L)$ where I_L is the integrations of both lactone products and I_S is the integration of the starting material. Differences in response factors for the different products and the starting material were not incorporated into this analysis. The use of different wavelengths (*i.e.* 210, 220, 230, and 254 nm) and their corresponding integrations were used as a check for internal consistency of the data.

Molar absorptivity study: An equimolar solution (0.01M, $CHCl_3$) was prepared containing: substrate **9** (0.05 M, 50 μL), and lactone **13** (0.05 M, 50 μL; prepared by reaction with *ent*-**2**). These compounds are the major components of reaction media being analyzed. This solution was mixed thoroughly using a vortex stirrer and immediately injected (5 μL) for HPLC analysis. The raw data is presented below.

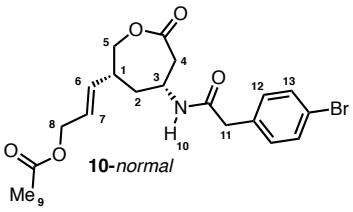


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

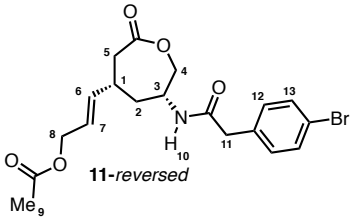
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.599	MM	0.5073	1.24967e4	410.54642	53.3247
2	22.146	MM	0.6283	1.09384e4	290.14139	46.6753

Supplementary Figure S3: Representative HPLC trace for the molar absorptivity study for compounds **9** and **13**.

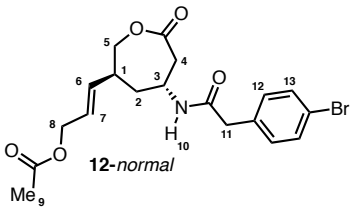
Characterization of oxidized products: Compounds **10-13** were isolated by reverse-phase HPLC (H_2O/MeCN with 0.1% formic acid) and characterized by 1D and 2D NMR (^1H, ^{13}C, gCOSY, HSQC, HMBC) techniques, HRMS, and FT-IR. In our hands, compound **11** was particularly challenging to isolate in its pure form and is characterized as a mixture with compound **10**.



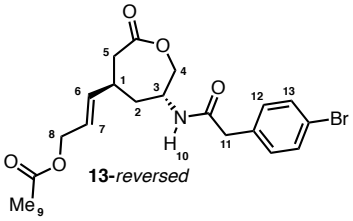
Spectral data for compound **10:** **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.49 (d, *J* = 8.2 Hz, 2H, H_{13}), 7.13 (d, *J* = 8.1 Hz, 2H, H_{12}), 5.71 – 5.64 (m, 1H, H_7), 5.61 (dd, *J* = 15.7, 6.7 Hz, 1H, H_6), 5.51 (d, *J* = 7.6 Hz, 1H, H_{10}), 4.49 (d, *J* = 5.8 Hz, 2H, H_8), 4.20 (d, *J* = 12.8 Hz, 1H, H_5), 4.17 – 4.12 (m, 1H, H_3), 4.10 (dd, *J* = 12.8, 8.1 Hz, 1H, H_5), 3.50 (s, 2H, H_{11}), 2.91 (dd, *J* = 13.9, 10.1 Hz, 1H, H_4), 2.79 (d, *J* = 13.6 Hz, 1H, H_4), 2.69 – 2.57 (m, 1H, H_1), 2.15 (dt, *J* = 14.0, 4.0 Hz, 1H, H_2), 2.06 (s, 3H, H_9), 1.68 – 1.59 (m, 1H, H_2); **^{13}C NMR** (151 MHz, chloroform) δ 171.4 (C), 170.9 (C), 169.6 (C), 133.5 (C), 133.0 (CH), 132.3 (CH), 131.2 (CH), 131.1 (CH), 126.5 (CH), 121.7 (C), 71.3 (CH_2), 64.5 (CH_2), 44.8 (CH), 43.1 (CH_2), 40.7 (CH_2), 40.3 (CH_2), 39.9 (CH), 21.1 (CH_3); **IR** (FT-ATR, cm^{-1}): 3293, 2999, 2943, 1739, 1724, 1638, 1486, 1437, 1274, 1230, 1069, 1047, 801; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{23}BrNO_5$ requires 424.0760, observed 424.0761.



Spectral data for compound **11** (Isolated as a minor component with compound **10**): **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.49 (d, *J* = 8.2 Hz, 2H, H_{13}), 7.13 (d, *J* = 8.1 Hz, 2H, H_{12}), 5.71 – 5.61 (m, 2H, $H_{6,7}$), 5.54 (d, *J* = 7.6 Hz, 1H, H_{10}), 4.49 (d, *J* = 5.8 Hz, 2H, H_8), 4.23 (d, *J* = 10.4 Hz, 1H, H_4), 4.18 – 4.12 (m, 1H, $H_{4,5}$), 3.50 (s, 2H, H_{11}), 2.79-2.75 (m, 1H, H_5), 2.69 (dd, *J* = 14.1, 9.2 Hz, 1H, H_5), 2.69 – 2.57 (m, 1H, H_1), 2.06-2.01 (m, 4H, $H_{2,9}$), 1.68 – 1.59 (m, 1H, H_2); **^{13}C NMR** (151 MHz, chloroform) δ 172.9 (C), 170.9 (C), 169.9 (C), 136.6 (C), 133.5 (CH), 133.0 (CH), 132.2 (CH), 131.1 (CH), 125.0 (CH), 121.7 (C), 70.3 (CH_2), 64.5 (CH_2), 48.6 (CH), 43.0 (CH_2), 39.5 (CH_2), 38.9 (CH_2), 34.7 (CH), 21.1 (CH_3).



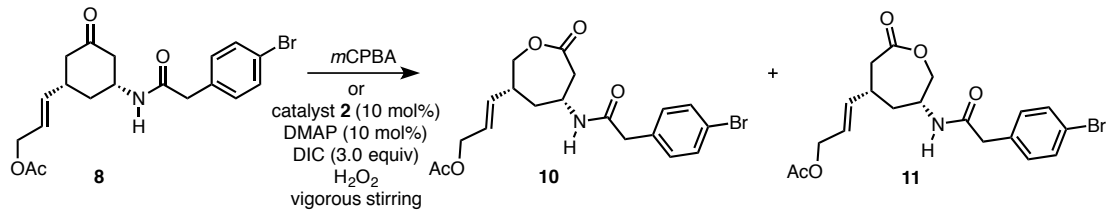
Spectral data for compound *ent*-**12**: **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.48 (d, *J* = 8.1 Hz, 2H, H_{13}), 7.13 (d, *J* = 8.1 Hz, 2H, H_{12}), 5.67 (dt, *J* = 15.8, 5.5 Hz, 1H, H_7), 5.62 (dd, *J* = 15.8, 6.2 Hz, 1H, H_6), 5.49 (d, *J* = 7.8 Hz, 1H, H_{10}), 4.52 (d, *J* = 5.5 Hz, 2H, H_8), 4.47 – 4.40 (m, 1H, H_3), 4.18 (d, *J* = 12.8 Hz, 1H, H_5), 4.08 (dd, *J* = 12.8, 8.9 Hz, 1H, H_5), 3.50 (s, 2H, H_{11}), 2.95 (dd, *J* = 14.0, 7.2 Hz, 1H, H_4), 2.88 (dd, *J* = 13.9, 2.1 Hz, 1H, H_4), 2.47 (q, *J* = 9.6, 7.8 Hz, 1H, H_1), 2.12 (dt, *J* = 14.0, 4.3 Hz, 1H, H_2), 2.07 (s, 3H, H_9), 1.75 (ddd, *J* = 14.5, 10.8, 3.8 Hz, 1H, H_2); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 171.9 (C), 170.8 (C), 170.0 (C) , 133.4 (CH), 132.4 (CH), 132.3 (CH), 131.1 (CH), 126.8 (CH), 121.7 (CH), 71.6 (CH_2), 64.4 (CH_2), 43.1 (CH_2), 42.6 (CH), 38.78 (CH_2), 38.60 (CH_2), 37.7 (CH), 21.09 (CH_3); **IR** (FT-ATR, cm^{-1}): 3310, 2943, 1735, 1650, 1536, 1487, 1232, 1171, 1050, 1012, 969; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{23}BrNO_5$ requires 424.0760, observed 424.0749;



Spectral data for compound *ent*-**13**: **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.45 (d, *J* = 10.8 Hz, 2H, H_{13}), 7.14 (d, *J* = 9.5 Hz, 2H, H_{12}), 6.43 (d, *J* = 8.4 Hz, 1H, H_{10}), 5.66 (dd, *J* = 15.6, 6.5 Hz, 1H, H_6), 5.63 – 5.55 (m, 1H, H_7), 4.51 (d, *J* = 5.8 Hz, 2H, H_8), 4.43 – 4.36 (m, 1H, H_3), 4.30 (d, *J* = 12.9 Hz, 1H, H_4), 4.27 – 4.18 (m, 1H, H_4), 3.49 (s, 2H, H_{11}), 2.75 – 2.58 (m, 2H, H_5), 2.56 – 2.43 (m, 1H, H_1), 2.13 (d, *J* = 14.4 Hz, 1H, H_2), 2.07 (s, 3H, H_9), 1.70 – 1.58 (m, 1H, H_2); **^{13}C**

NMR (151 MHz, chloroform-*d*) δ 173.6 (C), 170.8 (C), 170.2 (C), 136.7 (CH), 133.8 (C), 132.0 (CH), 130.9 (CH), 124.8 (CH), 121.4 (C), 69.7 (CH_2), 64.4 (CH_2), 46.3 (CH), 42.8 (CH_2), 39.7 (CH_2), 39.5 (CH_2), 32.4 (CH), 21.1 (CH3); **IR** (FT-ATR, cm^{-1}): 3309, 2939, 1729, 1650, 1533, 1487, 1362, 1226, 1173, 1070, 1029, 966, 909, 802, 726; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{23}BrNO_5$ requires 424.0760, observed 424.0765;

Supplementary Table S1: Reaction screening and HPLC analysis of *cis* substrate 8:

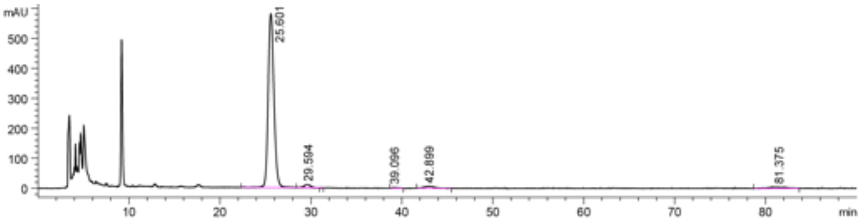


Entry	Reaction conditions in $CHCl_3$	Temp (°C)	*t* (h)	Conv (%)‡	Product Ratio:‡ Lactone (**10:11**)
1	**8** (0.05 M), *m*CPBA only (1 equiv)	4	4	5	7.0:1
2	**8** (0.1 M), *m*CPBA only (1 equiv)	21	18	72	4.3:1
3	**8** (0.1 M), H_2O_2 (30 wt%; 2 equiv)	4	70	4	--
4	**8** (0.1 M), H_2O_2 (30 wt%; 2 equiv)	21	70	4	--

‡Determined by uncalibrated HPLC integrations; see molar absorptivity study.

In-Depth description of Supplementary Table S1 entries and representative HPLC traces:

Entry 1: A reaction vial (1 mL) with a stir bar was charged with substrate (10.2 mg, 0.025 mmol). *m*-Chloroperoxybenzoic acid (6.3 mg, 70% w/w, 0.025 mmol, 1.0 equiv) was added as a solution in chloroform (total 500 μL; 0.05 M w.r.t. **8**) in an ice bath. The mixture was gently agitated with magnetic stirring and then transferred to a cold room (4 °C). After 4 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$ and analyzed by chiral HPLC.



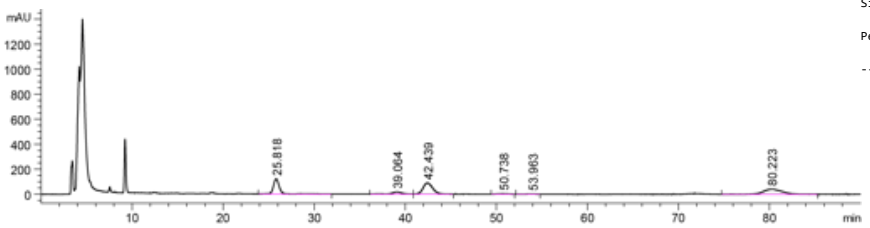
Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.601	VV R	0.6845	2.56923e4	580.33344	93.1975
2	29.594	VV E	0.7560	531.82050	10.55181	1.9291
3	39.096	BB	0.6406	102.73342	2.16911	0.3727
4	42.899	BB	1.0536	525.85449	6.35323	1.9075
5	81.375	MM	2.7571	714.88098	4.32150	2.5932

Supplementary Figure S4: Representative crude HPLC trace for Entry 1, Supplementary Table S1 with raw data.

Entry 2: A reaction vial (1 mL) with a stir bar was charged with substrate (10.2 mg, 0.025 mmol). *m*-Chloroperoxybenzoic acid (6.3 mg, 70% w/w, 0.025 mmol, 1.0 equiv) was added as a solution in chloroform (total 250 μL; 0.1 M w.r.t. **8**). The mixture was gently agitated with magnetic stirring. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were

separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$ and analyzed by chiral HPLC.

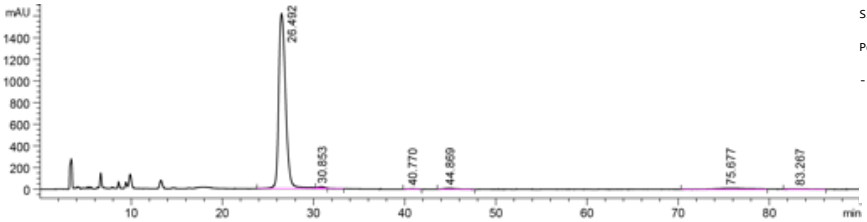


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.818	BV R	0.6572	5509.26172	120.37523	27.6136
2	39.064	VV R	0.9903	1374.76416	17.51872	6.8906
3	42.439	VV R	1.1659	6579.88086	89.90244	32.9797
4	50.738	BB	0.9996	337.59039	4.17407	1.6921
5	53.963	BV	0.9303	173.35286	2.29214	0.8689
6	80.223	VV R	1.7449	5976.44043	41.08868	29.9552

Supplementary Figure S5: Representative crude HPLC trace for Entry 2, Supplementary Table S1 with raw data.

Entry 3: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 30% H_2O_2 (5.1 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 μL, total 0.1 M w.r.t. substrate), 4 °C, 70 h, magnetic stirring.

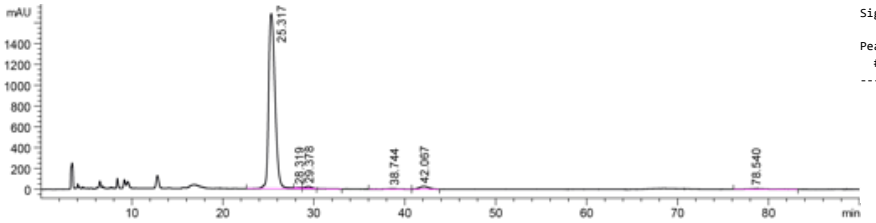


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.492	BV R	0.8207	8.60101e4	1615.14832	94.3283
2	30.853	VB E	0.6648	486.49069	11.42425	0.5335
3	40.770	BV	0.8085	184.84120	3.02676	0.2027
4	44.869	BB	1.2446	881.31091	9.69450	0.9665
5	75.677	VV R	3.3739	2938.80225	10.35868	3.2230
6	83.267	VV	2.0444	680.06165	3.94257	0.7458

Supplementary Figure S6: Representative crude HPLC trace for Entry 3, Supplementary Table S1 with raw data.

Entry 4: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 30% H_2O_2 (5.1 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 μL, total 0.1 M w.r.t. substrate), 21 °C, 70 h, magnetic stirring.

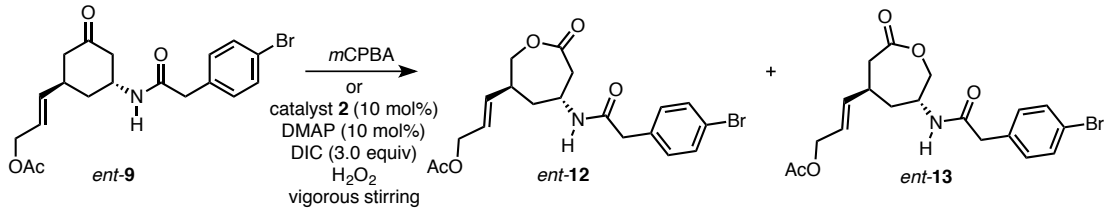


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.317	BV R	0.7723	8.35753e4	1680.29480	95.4089
2	28.319	VV E	0.5312	105.04793	2.71639	0.1199
3	29.378	VB E	0.7359	792.86047	17.00536	0.9051
4	38.744	BV	1.1524	442.02731	5.28177	0.5046
5	42.067	VB	1.0307	1943.74377	26.78244	2.2190
6	78.540	BB	1.7441	737.96844	5.24946	0.8425

Supplementary Figure S7: Representative crude HPLC trace for Entry 4, Supplementary Table S1 with raw data.

Supplementary Table S2: Reaction screening and HPLC analysis of substrate *ent*-9

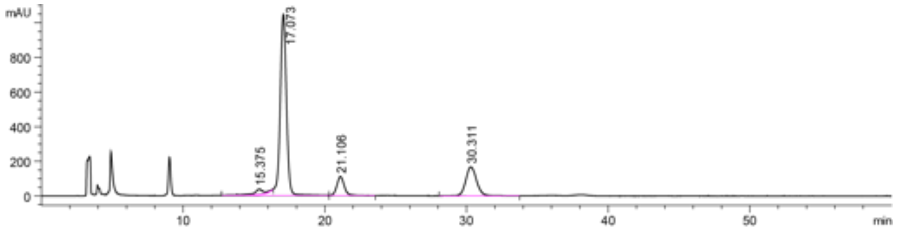


Entry	Reaction conditions in $CHCl_3$	Temp (°C)	*t* (h)	Relative Conv (%)	Product Ratio: Lactone (*ent*-**12**:**13**)
1	*m*CPBA only (1 equiv)	4	4	37	2.3:1
2	*m*CPBA only (1 equiv)	21	18	90	2.2:1
3	*ent*-**9** (0.1 M), H_2O_2 (30 wt%; 2 equiv)	4	24	89	1:>100
4	*ent*-**9** (0.1 M), H_2O_2 (15 wt%; 2 equiv)	4	24	91	1:>100
5	*ent*-**9** (0.1 M), H_2O_2 (3 wt%; 2 equiv)	4	24	80	1:>100
6	*ent*-**9** (0.05 M), H_2O_2 (30 wt%; 2 equiv)	4	24	83	1:>100
7	*ent*-**9** (0.05 M), H_2O_2 (15 wt%; 2 equiv)	4	24	87	1:>100
8	*ent*-**9** (0.05 M), H_2O_2 (3 wt%; 2 equiv)	4	24	69	1:>100
9	*ent*-**9** (0.1 M), H_2O_2 (15 wt%; 2 equiv), 2.5 mol% catalyst **2**	4	70	73	1:90

‡Determined by uncalibrated HPLC integrations; see molar absorptivity study.

In-Depth description of Supplementary Table S2 entries and representative HPLC traces:

Entry 1: A reaction vial (1 mL) with a stir bar was charged with substrate *ent*-**9** (10.2 mg, 0.025 mmol). *m*-Chloroperoxybenzoic acid (6.3 mg, 70% w/w, 0.025 mmol, 1.0 equiv) was added as a solution in chloroform (total 500 μL; 0.05 M w.r.t. *ent*-**9**) in an ice bath. The mixture was gently agitated with magnetic stirring and then transferred to a cold room (4 °C). After 4 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$ and analyzed by chiral HPLC.



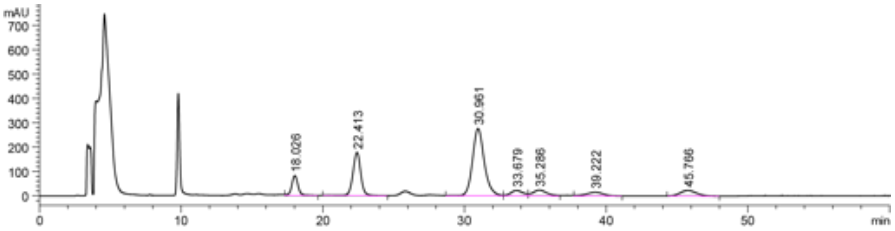
Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.375	BV E	0.7327	1666.38708	31.31913	3.4739
2	17.073	VV R	0.4911	3.32940e4	1046.83533	69.4083
3	21.106	VB	0.5669	4035.66431	109.26853	8.4132
4	30.311	BB	0.8351	8972.30664	166.92892	18.7046

Supplementary Figure S8: Representative crude HPLC trace for Entry 1, Supplementary Table S2 with raw data.

Entry 2: A reaction vial (1 mL) with a stir bar was charged with substrate *ent*-**9** (10.2 mg, 0.025 mmol). *m*-Chloroperoxybenzoic acid (6.3 mg, 70% w/w, 0.025 mmol, 1.0 equiv) was added as a solution in chloroform (total 250 μL; 0.1 M w.r.t. *ent*-**9**). The mixture was gently agitated with magnetic stirring. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the

filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$ and analyzed by chiral HPLC.

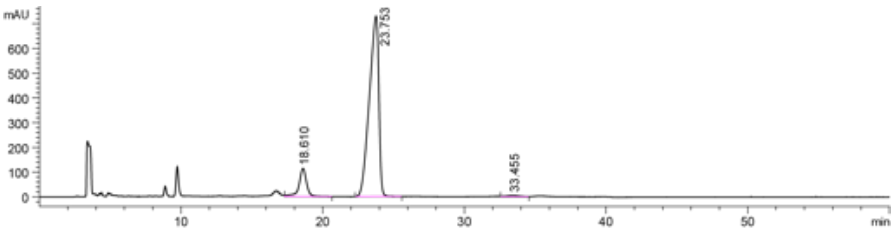


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.026	VB	0.4814	2590.48364	81.80746	8.2100
2	22.413	BB	0.5996	6919.41846	177.17372	21.9297
3	30.961	VV	0.8833	1.59889e4	276.21436	50.6737
4	33.679	VV	0.9135	1332.84790	22.03946	4.2242
5	35.286	VV	1.0344	1630.29236	23.94412	5.1669
6	39.222	VB	1.2141	1259.54871	15.46697	3.9919
7	45.766	BB	1.2450	1831.21716	23.09611	5.8037

Supplementary Figure S9: Representative crude HPLC trace for Entry 2, Supplementary Table S2 with raw data.

Entry 3: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 30% H_2O_2 (5.1 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 μL, total 0.1 M w.r.t. substrate), 4 °C, 24 h, magnetic stirring.

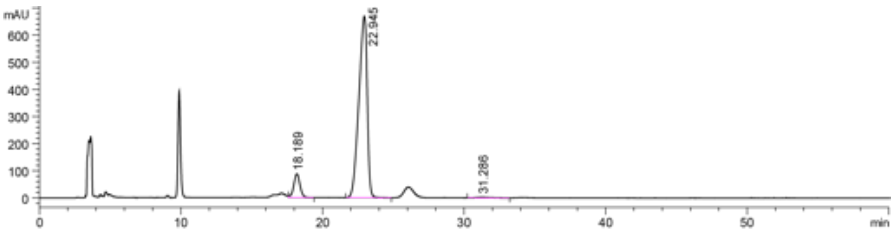


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.610	VB	0.5604	4217.64307	113.80375	10.8945
2	23.753	BB	0.7286	3.39810e4	727.99060	87.7754
3	33.455	FM	1.0772	298.61594	4.62023	0.7713

Supplementary Figure S10: Representative crude HPLC trace for Entry 3, Supplementary Table S2 with raw data.

Entry 4: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 15% H_2O_2 (11.3 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 μL, total 0.1 M w.r.t. substrate), 4 °C, 24 h, magnetic stirring.

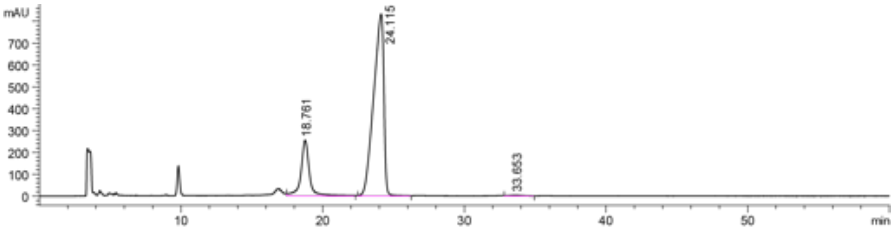


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.189	VB	0.4663	2666.61328	87.79984	8.8175
2	22.945	BB	0.6460	2.74133e4	669.03528	90.6459
3	31.286	BV	0.8623	162.27986	2.44511	0.5366

Supplementary Figure S11: Representative crude HPLC trace for Entry 4, Supplementary Table S2 with raw data.

Entry 5: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 μL, total 0.1 M w.r.t. substrate), 4 °C, 24 h, magnetic stirring.

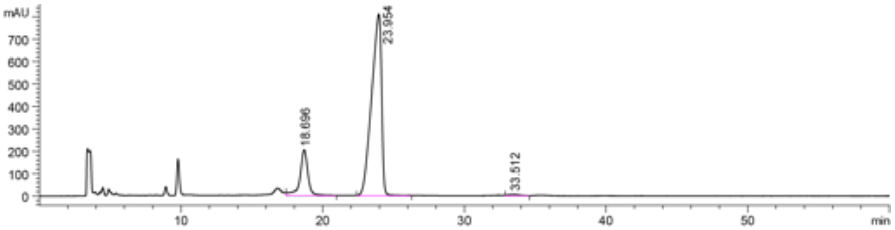


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.761	VB	0.6041	1.05608e4	254.51973	20.0911
2	24.115	BV	0.7859	4.17668e4	831.74512	79.4583
3	33.653	FM	1.1236	236.85699	3.51347	0.4506

Supplementary Figure S12: Representative crude HPLC trace for Entry 5, Supplementary Table S2 with raw data.

Entry 6: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 30% H_2O_2 (5.1 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (500 μL, total 0.05 M w.r.t. substrate), 4 °C, 24 h, magnetic stirring.

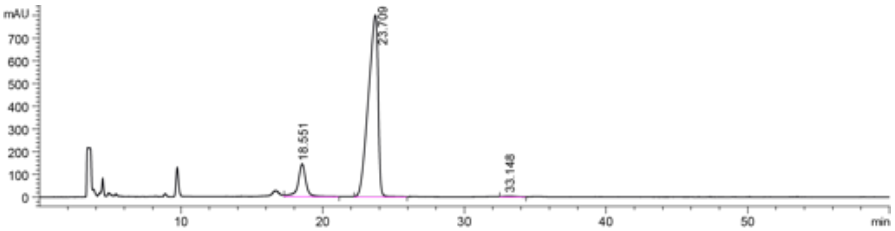


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.696	VB	0.5736	7967.99512	204.92619	16.5044
2	23.954	BB	0.7782	3.96001e4	810.21393	82.0254
3	33.512	FM	1.0016	353.01999	5.87411	0.7312

Supplementary Figure S13: Representative crude HPLC trace for Entry 6, Supplementary Table S2 with raw data.

Entry 7: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 15% H_2O_2 (11.3 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (500 μL, total 0.05 M w.r.t. substrate), 4 °C, 24 h, magnetic stirring.

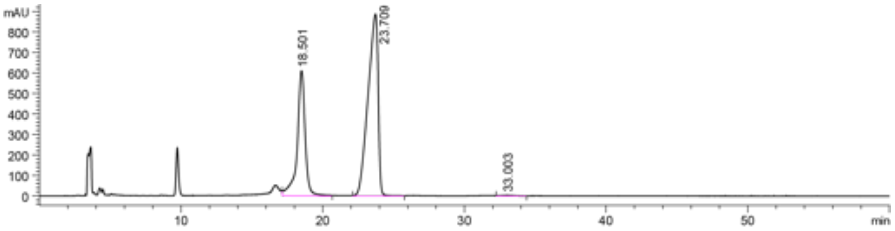


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.551	VB	0.5809	5698.35107	144.24710	12.8231
2	23.709	BV	0.7488	3.82567e4	801.58551	86.0896
3	33.148	FM	1.0299	237.53006	3.84375	0.5345

Supplementary Figure S14: Representative crude HPLC trace for Entry 7, Supplementary Table S2 with raw data.

Entry 8: General procedure **A**; peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (500 μL, total 0.05 M w.r.t. substrate), 4 °C, 24 h, magnetic stirring.

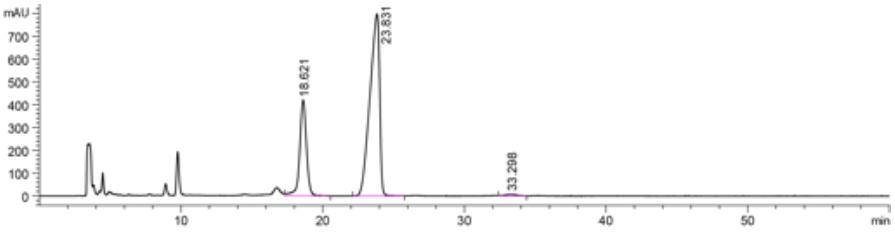


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.501	MF	0.6485	2.37761e4	611.07916	34.9224
2	23.709	BV	0.7880	4.41083e4	887.17853	64.7866
3	33.003	FM	0.9946	198.10385	3.31981	0.2910

Supplementary Figure S15: Representative crude HPLC trace for Entry 8, Supplementary Table S2 with raw data.

Entry 9: General procedure **A**; peptide **2** (0.56 mg, 0.000625 mmol, 0.025 equiv), 4-dimethylaminopyridine (0.16 mg, 0.00125 mmol, 0.05 equiv), 15% H_2O_2 (11.3 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 μL, total 0.1 M w.r.t. substrate), 4 °C, 70 h, magnetic stirring.



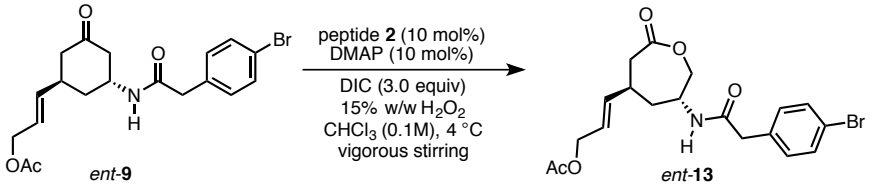
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.621	VB	0.5084	1.39492e4	418.95233	26.6197
2	23.831	MM	0.7943	3.80279e4	797.95612	72.5701
3	33.298	FM	1.0178	424.54456	6.95181	0.8102

Supplementary Figure S16: Representative crude HPLC trace for Entry 9, Supplementary Table S2 with raw data.

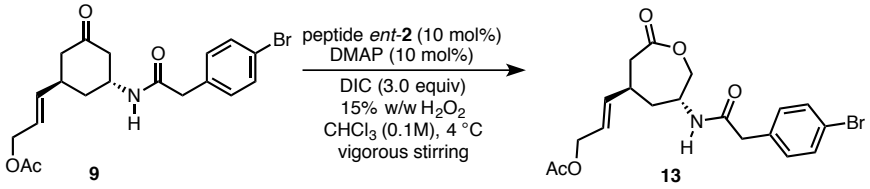
Baeyer-Villiger oxidation of substrate 9 and *ent*-9 on 0.25 mmol scale:

General notes about purification: Purification of these compounds was difficult due to the starting material, lactones, peptide catalyst, and *N-N*-diisopropylurea having similar elution rates on silica. For isolation of these products, the crude product mixture was purified by reversed phase chromatography using a C18 column.



A reaction vial equipped with a stir bar was charged with substrate *ent*-**9** (102 mg, 0.25 mmol, 1.0 equiv). To this vial, catalyst **2** (22 mg, 0.025 mmol, 0.1 equiv in 1.5 mL of chloroform) and 4-dimethylaminopyridine (3.1 mg, 0.025 mmol, 0.1 equiv in 1.0 mL of chloroform) were added. The mixture was gently agitated until substrate was fully dissolved, after which was transferred to a cold room and stirred for 1 hour. To this vial, aqueous H_2O_2 (15% w/w; 0.051 mL, 0.50 mmol, 2.0 equiv) was added followed by *N,N'*-diisopropylcarbodiimide (0.116 mL, 0.75 mmol, 3.0 equiv) in one portion, and then the reaction mixture was vigorously stirred at 4 °C for 24 hours. After the allotted time had expired, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (15 mL). The product solution was further diluted with saturated aqueous ammonium chloride (12 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 75 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified using a C18 column (30 g column) with 10-40% acetonitrile/water (∇ = 2.3% acetonitrile/CV; 50

mL/min; monitor at 210 nm). The lactone product elutes at 40% acetonitrile/water to afford the *ent*-**13** as a colorless oil (93 mg) in 88% yield. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = +9.1 (*c* = 1.0). See above section for characterization data.



A reaction vial equipped with a stir bar was charged with substrate **9** (102 mg, 0.25 mmol, 1.0 equiv). To this vial, catalyst *ent*-**2** (22 mg, 0.025 mmol, 0.1 equiv in 1.5 mL of chloroform) and 4-dimethylaminopyridine (3.1 mg, 0.025 mmol, 0.1 equiv in 1.0 mL of chloroform) were added. The mixture was gently agitated until substrate was fully dissolved, after which was transferred to a cold room and stirred for 1 hour. To this vial, aqueous H_2O_2 (15% w/w; 0.051 mL, 0.50 mmol, 2.0 equiv) was added followed by *N,N'*-diisopropylcarbodiimide (0.116 mL, 0.75 mmol, 3.0 equiv) in one portion, and then the reaction mixture was vigorously stirred at 4 °C for 24 hours. After the allotted time had expired, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (15 mL). The product solution was further diluted with saturated aqueous ammonium chloride (12 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 75 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified using a C18 column (30 g column) with 10-40% acetonitrile/water (∇ = 2.3% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The lactone product elutes at 40% acetonitrile/water to afford the **13** as a colorless oil (90 mg) in 86% yield. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = -9.3 (*c* = 1.0). See above section for characterization data.

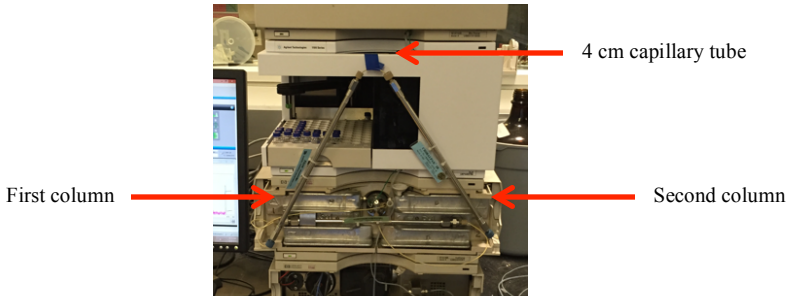
1.4 Chemoselectivity studies with substrates 14 and *ent*-14

General information: In order to obtain accurate information about compound ratios, the reactions were subjected to HPLC analysis with as little purification as possible (generally, quenching with saturated aqueous sodium sulfite (1 mL), extraction using ethyl acetate (~4 mL) and washing with saturated aqueous sodium bicarbonate (~3 mL)). However, the oxidation products were purified by preparative, reverse-phase HPLC (eluting with H_2O and CH_3CN) and characterized by HPLC, NMR, and HRMS in order to ascertain their identity (see below for their preparation). Due to the numerous products being formed in the screening reactions, in our hands, the most reliable means of calculating conversion and product ratios was by chiral HPLC analysis (see molar absorptivity study below). NMR analysis resulted in overlapping signals for the starting material, peptide catalyst, *N,N'*-diisopropylcarbodiimide, reaction by-products (*i.e. N,N*-di-*iso*-propylurea), and the products (400-600 MHz instruments employed), and was also hampered by poor solubility of the crude reaction mixture in $CDCl_3$.

General procedure B for chemoselectivity evaluation with substrate *ent*-14/peptide 2 combinations: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol). Catalyst (0.0025 mmol) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol) were added as solutions in chloroform (total 250 μL; 0.1 M w.r.t. *ent*-**14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (30% w/w) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol) in one portion. The reaction mixture was vigorously stirred at 4 °C. After the noted time had expired, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CHCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC. Each variation was run in duplicate with the same batch of reagents. It is important that the chloroform used in this reaction be ethanol-free.

3% w/w H_2O_2 (0.88 M): Aqueous H_2O_2 (9.0 mL, 30% w/w, 9.79 M) was diluted with deionized water to a total volume of 100 mL.

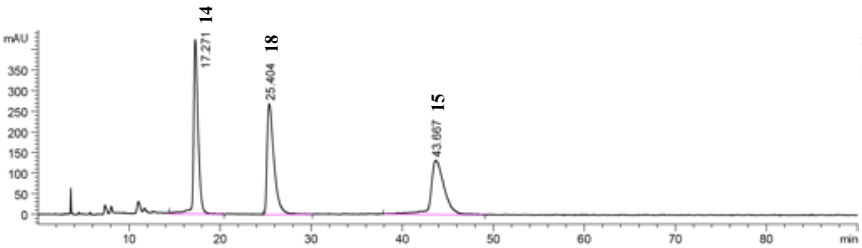
HPLC method: Four HPLC methods were employed to analyze the reaction mixtures with substrates **14** and *ent*-**14**. For each substrate, the HPLC method is listed in the corresponding section with a representative trace identifying the peaks. For methods that required two Chiralpak columns, the column listed first is connected to the column listed second in a sequential fashion using a 4 cm connecting tube (the setup can be seen in the photo in **Supplementary Figure S17**). Flow is initially against gravity.



Supplementary Figure S17: Chiralpak HPLC columns run in series. Column on the left (first) is connected to the column on the right (second).

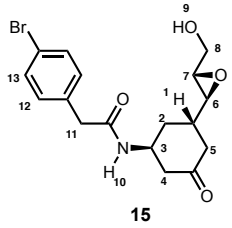
Data analysis: The relative conversion was approximated as $(I_L + I_E + I_D) /(I_X + I_L + I_E + I_D)$ where I_L is the integrations of both lactone products, I_E is the integrations of both epoxide products, I_D is the integrations of the four possible dual oxidation products, and I_X is the integration of the starting material. Differences in response factors for the different products and the starting material were not incorporated into this analysis. The use of different wavelengths (*i.e.* 210, 220, 230, and 254 nm) and their corresponding integrations were used as a check for internal consistency of the data.

Molar absorptivity study: An equimolar solution ($CHCl_3$:*i*PrOH 7:3) was prepared containing: substrate **14** (0.025 M, 100 μL), epoxide **15** (0.025 M, 100 μL), and lactone **18** (0.025 M, 100 μL). These compounds are the major components of reaction media being analyzed in the chemoselectivity studies. This solution was mixed thoroughly using a vortex stirrer and immediately injected (5 μL) for HPLC analysis. The product distribution was found to be 1.10 (**14**) : 1.00 (**15**) : 1.07 (**18**), the raw data is presented below (**Figure S18**).

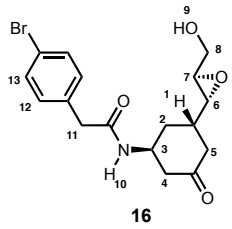


Supplementary Figure S18: Representative HPLC trace for molar absorptivity study for compounds **14**, **15**, and **18**.

Characterization of oxidized products: Compounds **15-22** were isolated by reverse-phase HPLC (H_2O/MeCN with 0.1% formic acid; see below section for specifics) and characterized by 1D and 2D NMR (^1H, ^{13}C, gCOSY, HSQC, HMBC) techniques, HRMS, FT-IR, and X-ray (for compound **15**). In our hands, compound **22** was particularly challenging to isolate in its pure form and is characterized as a mixture with compound **21**.

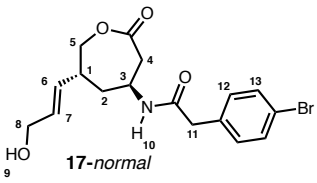


Compound 15: Isolated as a white solid. **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.46 (d, *J* = 8.1 Hz, 2H, H_{13}), 7.11 (d, *J* = 8.1 Hz, 2H, H_{12}), 5.67 (d, *J* = 7.1 Hz, 1H, H_{10}), 4.54 (h, *J* = 5.3 Hz, 1H, H_3), 3.88 (ddd, *J* = 12.7, 5.3, 2.6 Hz, 1H, H_8), 3.64 (ddd, *J* = 12.5, 7.5, 3.9 Hz, 1H, H_8), 3.45 (s, 2H, H_{11}), 2.94 (dd, *J* = 5.1, 2.2 Hz, 1H, H_6), 2.93 – 2.90 (m, 1H, H_7), 2.63 (dd, *J* = 14.6, 5.2 Hz, 1H, H_4), 2.38 (dd, *J* = 14.2, 4.7 Hz, 1H, H_5), 2.32 – 2.20 (m, 2H, $H_{4,5}$), 2.09 – 1.95 (m, 3H, $H_{1,2,9}$), 1.88 (ddd, *J* = 13.3, 10.0, 3.5 Hz, 1H, H_2); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 208.2 (C), 170.1 (C), 133.7 (C), 132.2 (CH), 131.0 (CH), 121.6 (C), 61.3 (CH_2), 58.1 (CH), 56.5 (CH), 47.1 (CH), 46.3 (CH_2), 43.1 (CH_2), 42.8 (CH_2), 35.1 (CH), 32.7 (CH_2); **IR** (FT-ATR, cm^{-1}): 3300, 3072, 2923, 2855, 1711, 1647, 1541, 1488, 1238, 1072, 1013, 898, 804; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_4$ requires 382.0654, observed 382.0639; **X-ray**: Crystals suitable for X-ray analysis were grown by vapor diffusion from ethyl acetate (first heated to boiling, then slowly cooled to 21 °C) with pentane as the antisolvent. Crystal growth took approx. 4 days.

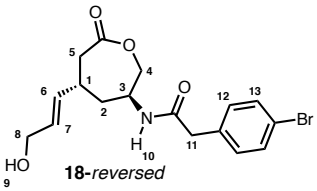


Compound 16: Isolated as a colorless oil. **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.47 (d, *J* = 8.0 Hz, 2H, H_{13}), 7.10 (d, *J* = 8.2 Hz, 2H, H_{12}), 5.44 (d, *J* = 7.2 Hz, 1H, H_{10}), 4.52 (dq, *J* = 10.6, 5.2 Hz, 1H, H_3), 3.89 (dd, *J* = 12.7, 2.6 Hz, 1H, H_8), 3.66 (dd, *J* = 12.7, 3.9 Hz, 1H, H_8), 3.46 (s, 2H, H_{11}), 3.01 – 2.97 (m, 1H, H_7), 2.93 (dd, *J* = 5.9, 2.2 Hz, 1H, H_6), 2.63 (dd, *J* = 14.3, 5.1 Hz, 1H, H_4), 2.40 (dd, *J* = 14.2, 4.9 Hz, 1H, H_5), 2.37 – 2.27 (m, 2H, $H_{4,5}$), 2.09 –

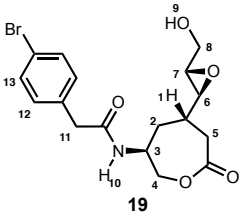
2.03 (m, 1H, H_2), 1.99 – 1.75 (m, 3H, $H_{1,2,9}$); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 208.1 (C), 170.0 (C), 133.6 (C), 132.2 (CH), 131.0 (CH), 121.6 (C), 61.3 (CH_2), 57.8 (CH), 57.2 (CH), 47.1 (CH), 46.4 (CH_2), 43.5 (CH_2), 43.1 (CH_2), 35.6 (CH), 31.7 (CH_2); **IR** (FT-ATR, cm^{-1}): 3300, 3064, 2927, 1709, 1648, 1541, 1487 1229, 1071, 1012, 973, 908; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_4$ requires 382.0654, observed 382.0649.



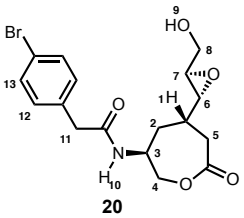
Compound 17: Isolated as a colorless oil. **^{1}H NMR** (600 MHz, methanol-d_4) δ 7.45 (d, *J* = 8.3 Hz, 2H, H_{13}), 7.20 (d, *J* = 8.1 Hz, 2H, H_{12}), 5.81 (dt, *J* = 16.3, 5.7 Hz, 1H, H_7), 5.67 (dd, *J* = 15.7, 7.0 Hz, 1H, H_6), 4.34 – 4.22 (m, 3H, $H_{3,5}$), 4.05 (d, *J* = 5.3 Hz, 2H, H_8), 3.54 – 3.44 (m, 2H, H_{11}), 3.02 (dd, *J* = 13.9, 7.9 Hz, 1H, H_4), 2.96 (d, *J* = 15.2 Hz, 1H, H_4), 2.88 (p, *J* = 7.1 Hz, 1H, H_1), 2.00 – 1.93 (m, 2H, H_2); **^{13}C NMR** (151 MHz, methanol-d_4) δ 175.1 (C), 173.1 (C), 136.2 (C), 132.7 (CH), 132.5 (CH), 132.1 (CH), 130.5 (CH), 121.6 (C), 72.9 (CH_2), 63.3 (CH_2), 44.2 (CH), 42.6 (CH_2), 39.6 (CH_2), 39.5 (CH_2), 38.9 (CH); **IR** (FT-ATR, cm^{-1}): 3302, 3045, 2935, 1725, 1650, 1539, 1488, 1291, 1265, 1171, 1070, 1058, 1012, 973, 803; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_4$ requires 382.0654, observed 382.0652.



Compound 18: Isolated as a colorless oil. **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.08 (d, *J* = 7.8 Hz, 1H), 5.66 (dt, *J* = 15.5, 4.9 Hz, 1H), 5.61 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.37 (dq, *J* = 8.9, 4.6 Hz, 1H), 4.31 (d, *J* = 12.8 Hz, 1H), 4.23 (dd, *J* = 12.8, 5.1 Hz, 1H), 4.12 (d, *J* = 4.8 Hz, 2H), 3.51 (s, 2H), 2.73 – 2.61 (m, 2H), 2.51 – 2.41 (m, 1H), 2.12 (dt, *J* = 14.3, 4.2 Hz, 1H), 1.66 (ddd, *J* = 14.6, 11.0, 3.9 Hz, 1H); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 173.50, 170.11, 133.68, 133.24, 132.17, 130.95, 129.90, 121.57, 69.60, 63.11, 46.44, 42.99, 39.83, 39.57, 32.59; **IR** (FT-ATR, cm^{-1}): 3311, 2968, 2925, 1726, 1651, 1540, 1488, 1290, 1274, 1070, 1012, 803; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_4$ requires 382.0654, observed 382.0649.

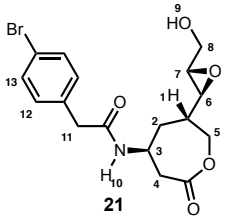


Compound 19: Isolated as a colorless oil. **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.46 (d, *J* = 8.1 Hz, 2H, H_{13}), 7.14 (d, *J* = 8.0 Hz, 2H, H_{12}), 6.38 (d, *J* = 7.9 Hz, 1H, H_{10}), 4.42 (dq, *J* = 8.0, 4.1 Hz, 1H, H_3), 4.34 (d, *J* = 12.9 Hz, 1H, H_4), 4.25 (dd, *J* = 12.9, 4.6 Hz, 1H, H_4), 3.90 (ddd, *J* = 12.7, 4.8, 2.3 Hz, 1H, H_8), 3.63 (ddd, *J* = 12.4, 7.1, 4.0 Hz, 1H, H_8), 3.49 (s, 2H, H_{11}), 2.94 (dt, *J* = 4.3, 2.5 Hz, 1H, H_7), 2.84 (dd, *J* = 6.3, 2.0 Hz, 1H, H_6), 2.78 (d, *J* = 13.8 Hz, 1H, H_5), 2.61 (dd, *J* = 13.9, 10.7 Hz, 1H, H_5), 2.15 – 2.09 (m, 1H, H_2), 1.96 (t, *J* = 6.3 Hz, 1H, H_9), 1.78 – 1.67 (m, 2H, $H_{1,2}$); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 173.3 (C), 170.3 (C), 133.8 (C), 132.1 (CH), 130.9 (CH), 121.5 (C), 69.7 (CH_2), 61.2 (CH_2), 58.3 (2 x CH), 46.2 (CH), 42.8 (CH_2), 36.6 (CH_2), 36.3 (CH_2), 32.4 (CH); **IR** (FT-ATR, cm^{-1}): 3325, 3084, 2982, 2930, 2870, 1729, 1647, 1544, 1488, 1251, 1178, 1071, 1013, 804; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_5$ requires 398.0603, observed 398.0612.

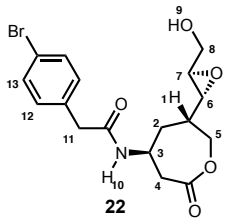


Compound 20: Isolated as a colorless oil. **^{1}H NMR** (600 MHz, chloroform-*d*) δ 7.47 (d, *J* = 8.3 Hz, 2H, H_{13}), 7.14 (d, *J* = 8.3 Hz, 2H, H_{12}), 5.86 (d, *J* = 7.4 Hz, 1H, H_{10}), 4.42 (dq, *J* = 8.1, 4.2 Hz, 1H, H_3), 4.32 (d, *J* = 12.9 Hz, 1H, H_4), 4.26 (dd, *J* = 12.9, 4.8 Hz, 1H, H_4), 3.90 (d, *J* = 12.7 Hz, 1H, H_8), 3.69 (dq, *J* = 12.1, 3.6 Hz, 1H, H_8), 3.50 (s, 2H, H_{11}), 3.02 – 2.96 (m, 1H, H_7), 2.92 (dd, *J* = 6.2, 2.1 Hz, 1H, H_6), 2.69 (d, *J* = 13.8 Hz, 1H, H_5), 2.60 (dd, *J* = 13.9, 10.9 Hz, 1H, H_5), 2.24 (d, *J* = 13.7 Hz, 1H, H_2), 1.76 – 1.62 (m, 2H, $H_{1,2}$), 1.62 – 1.58 (m, 1H, H_9); **^{13}C NMR** (151 MHz, chloroform-*d*) δ 172.7 (C), 169.9 (C), 133.3

(C), 132.1 (CH), 130.8 (CH), 121.5 (C), 69.4 (CH_2), 60.8 (CH_2), 57.8 (CH), 57.0 (CH), 46.1 (CH), 42.8 (CH_2), 36.3 (CH_2), 35.9 (CH_2), 31.8 (CH); **IR** (FT-ATR, cm^{-1}): 3327, 2921, 2856, 1727, 1650, 1538, 1488, 1440, 1293, 1275, 1228, 1175, 1070, 1059, 1013, 909, 729; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_5$ requires 398.0603, observed 398.0587.

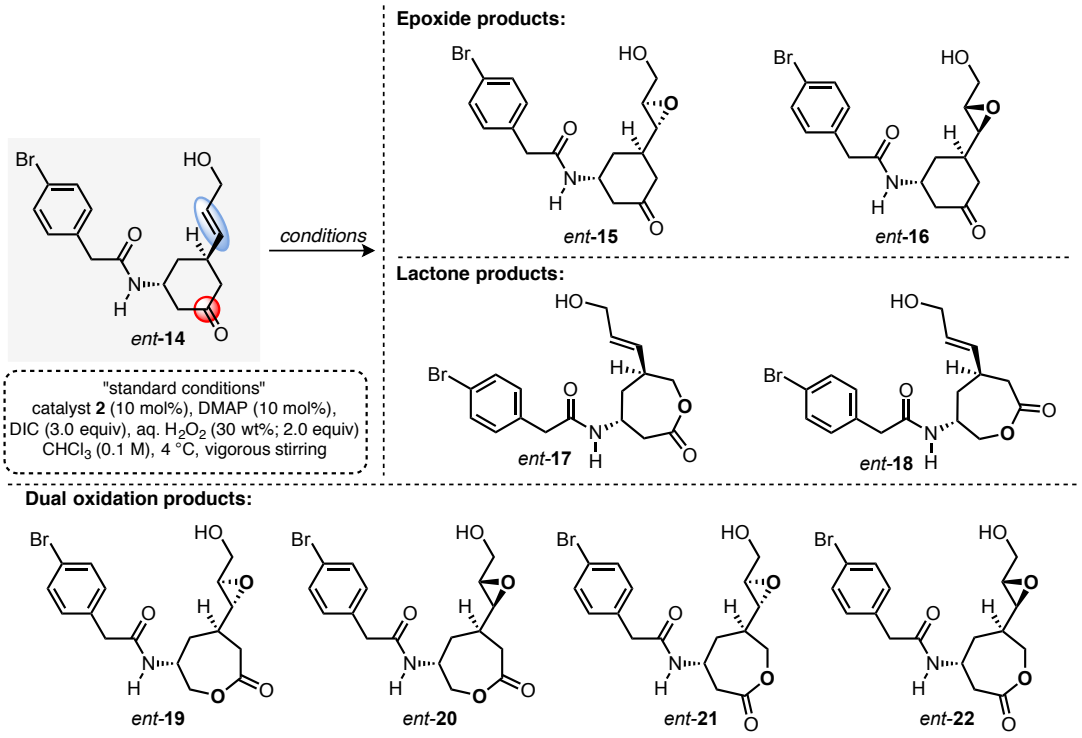


Compound 21: Isolated as a colorless oil. **^{1}H NMR** (600 MHz, methanol-d_4) δ 7.45 (d, J = 8.2 Hz, 2H, H_{13}), 7.19 (d, J = 8.1 Hz, 2H, H_{12}), 4.41 – 4.36 (m, 2H, H_5), 4.32 – 4.27 (m, 1H, H_3), 3.74 (dd, J = 12.6, 3.2 Hz, 1H, H_8), 3.55 (dd, J = 12.6, 5.0 Hz, 1H, H_8), 3.53 – 3.45 (m, 2H, H_{11}), 3.07 – 2.99 (m, 3H, $H_{4,7}$), 2.82 (dd, J = 7.5, 2.0 Hz, 1H, H_6), 2.02 – 1.91 (m, 3H, $H_{1,2}$); **^{13}C NMR** (151 MHz, methanol-d_4) δ 175.0 (C), 173.2 (C), 136.1 (C), 132.5 (CH), 132.1 (CH), 121.6 (C), 70.8 (CH_2), 62.7 (CH_2), 59.7 (CH), 56.6 (CH), 44.4 (CH), 42.5 (CH_2), 39.4 (CH), 39.2 (CH_2), 36.1 (CH_2); **IR** (FT-ATR, cm^{-1}): 3356, 2928, 2871, 1729, 1642, 1593, 1488, 1437, 1221, 1086, 1071, 1012, 804; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_5$ requires 398.0603, observed 398.063.



Compound 22: Isolated as a colorless oil (contaminated with **21** (7:3)). **^{1}H NMR (**600 MHz, methanol-d_4) δ 7.45 (d, J = 8.0 Hz, 2H, H_{13}), 7.19 (d, J = 8.3 Hz, 2H, H_{12}), 4.41 – 4.28 (m, 3H, $H_{3,5}$), 3.75 (dd, J = 12.6, 3.1 Hz, 1H, H_8), 3.56 – 3.44 (m, 3H, $H_{8,11}$), 3.08 – 3.00 (m, 2H, $H_{4,7}$), 2.97 (dd, J = 13.9, 2.2 Hz, 1H, H_4), 2.90 (dd, J = 6.2, 2.1 Hz, 1H, H_6), 2.20 (tt, J = 10.0, 4.9 Hz, 1H, H_1), 2.01 – 1.94 (m, 2H, H_2); **^{13}C NMR** (151 MHz, methanol-d_4) δ 173.5 (C), 171.6 (C), 134.7 (C), 131.1 (CH), 130.7 (CH), 120.2 (CH), 69.1 (CH_2), 61.3 (CH_2), 56.7 (CH), 55.6 (CH), 42.8 (CH), 41.1 (CH_2), 37.9 (CH_2), 36.6 (CH), 34.9 (CH_2); **IR** (FT-ATR, cm^{-1}): 3305, 3051, 2980, 2931, 1728, 1649, 1540, 1488, 1245, 1174, 1069, 1044, 1012, 803; **HRMS** (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{21}BrNO_5$ requires 398.0603, observed 398.0615.

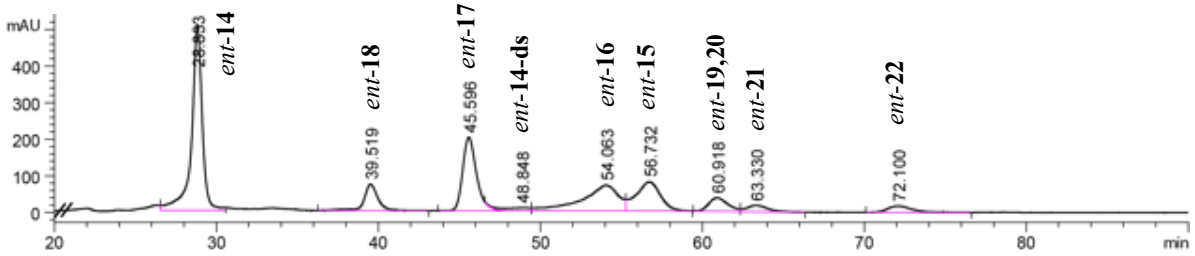
Supplementary Table S3: Screening and HPLC analysis of the chemoselectivity studies



Entry	Change from listed reaction conditions	*t* (h)	Conv (%)‡	Product Ratio (*ent*):‡ Epoxide **15+16**	Lactone (**18:17**)	Dual **19-22**
1	*m*CPBA only (1 equiv)	18	65	1.0	0.8 (1:2.8)	0.4
2	none	18	49	1.0	0.7 (27:1)	0.3
3	*ent*-**14** (0.1 M), H_2O_2 (3 wt%; 2 equiv)	18	68	1.0	4.3 (>50:1)	1.6
4	*ent*-**12** (0.05 M), $CHCl_3/H_2O$ (4:1), H_2O_2 (30 wt%; 2 equiv)	18	34	1.0	5.2 (>50:1)	0.3
5	*ent*-**12** (0.05 M), H_2O_2 (3 wt%; 2 equiv)	18	50	1.0	4.3 (>50:1)	0.5
6	*ent*-**12** (0.033 M), H_2O_2 (3 wt%; 2 equiv)	19	43	1.0	4.5 (>50:1)	0.5
7	*ent*-**12** (0.033 M), H_2O_2 (3 wt%; 2 equiv), DIC (1.5 equiv @ 0h, 6h)	18	49	1.0	5.1 (>50:1)	0.7
8	*ent*-**12** (0.033 M), H_2O_2 (3 wt%; 2 equiv), DIC (1 equiv @ 0h, 4h, 8h)	18	57	1.0	6.9 (>50:1)	1.0
9	*ent*-**12** (0.033 M), H_2O_2 (3 wt%; 2 equiv), DIC added over 10 h	18	45	1.0	6.9 (>50:1)	0.7
10	*ent*-**12** (0.033 M), H_2O_2 (3 wt%; 2.5 equiv), DIC added over 10 h	18	52	1.0	7.1 (>50:1)	0.9
11	Same as entry 8, **2** (20 mol%), DMAP (20 mol%), rotamix @ 30 rpm	18	77	1.0	11.2 (>50:1)	3.2
12	Same as entry 8, rotamix @ 30 rpm	18	53	1.0	8.8 (>50:1)	1.2
13	Same as entry 12, **2** (15 mol%), DMAP (15 mol%)	26	60	1.0	5.2 (>50:1)	1.1
14	Same as entry 8, H_2O_2 (3 wt%; 2.5 equiv), rotamix @ 30 rpm	28	60	1.0	5.7 (>50:1)	1.1
15	Same as entry 3, DIC (1 equiv @ 0h, 23h, 46h), 2.5 mol% **2**	70	27	1.0	3.1 (>50:1)	0.2

‡Determined by uncalibrated HPLC integrations; see molar absorptivity study.

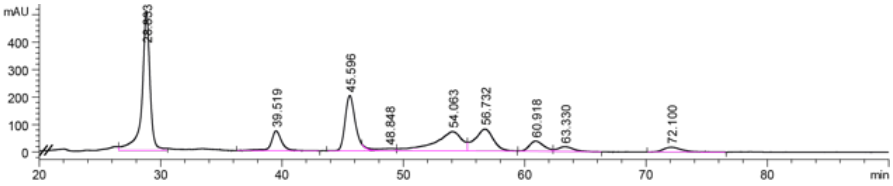
HPLC method for *ent*-14: Chiralpak IB into Chiralpak IC column, 18% ethanol/hexanes, 0.8 mL/min, 90 minutes, monitor at 230 nm.



Supplementary Figure S19: Representative crude HPLC trace for oxidation of *ent*-**14**.

In-Depth description of Supplementary Table 3 entries and representative HPLC traces:

Entry 1: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol). *m*-Chloroperoxybenzoic acid (6.3 mg, 70% w/w, 0.025 mmol, 1.0 equiv) was added as a solution in chloroform (total 500 µL; 0.05 M w.r.t. *ent*-**14**). The mixture was gently agitated and transferred to a cold room (4 °C). After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CHCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

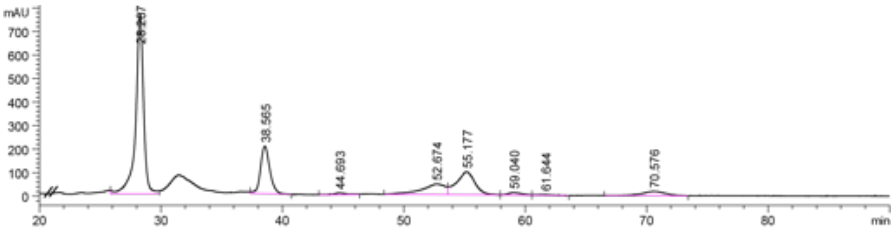


Signal 3: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.833	MF	0.7686	2.34329e4	508.11948	35.2762
2	39.519	BB	0.8945	4352.31689	72.27913	6.5520
3	45.596	BV R	0.9134	1.19981e4	200.72012	18.0621
4	48.848	VV E	1.4898	1015.69189	8.35791	1.5290
5	54.063	VV	2.0820	1.08817e4	70.13954	16.3815
6	56.732	VB	1.5390	8337.19238	79.27071	12.5509
7	60.918	BV	1.2421	2962.60425	36.84612	4.4599
8	63.330	VB	1.3711	1556.32166	17.27433	2.3429
9	72.100	BV R	1.5545	1890.10571	17.41148	2.8454

Supplementary Figure S20: Representative crude HPLC trace for Entry 1, Supplementary Table S3 with raw data.

Entry 2: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 30% H_2O_2 (9.7 µL, 0.095 mmol, 3.8 equiv), *N,N'*-diisopropylcarbodiimide (11.6 µL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (250 µL, 0.1 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

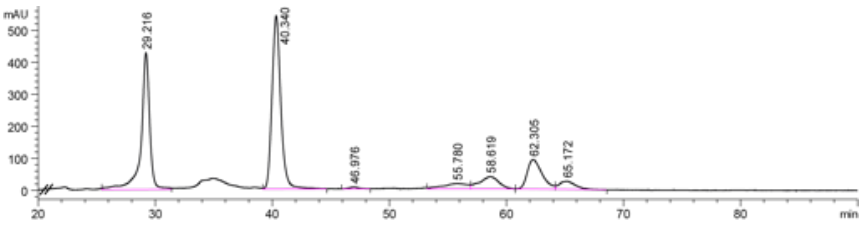


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.287	MM	0.7579	3.47534e4	764.22321	52.8732
2	38.565	FM	0.8855	1.07433e4	202.20868	16.3447
3	44.693	BV	1.0182	516.30682	6.95408	0.7855
4	52.674	BV	1.6932	6060.66162	44.04978	9.2206
5	55.177	VB	1.4827	1.01044e4	97.36593	15.3726
6	59.040	BV	0.9638	771.37885	10.56552	1.1736
7	61.644	VB	1.1925	272.14914	2.85411	0.4140
8	70.576	BB	1.6473	2508.04565	18.38823	3.8157

Supplementary Figure S21: Representative crude HPLC trace for Entry 2, Supplementary Table S3 with raw data.

Entry 3: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 µL, 0.095 mmol, 3.8 equiv), *N,N'*-diisopropylcarbodiimide (11.6 µL, 0.075 mmol, 3.0 equiv), chloroform (250 µL, 0.1 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

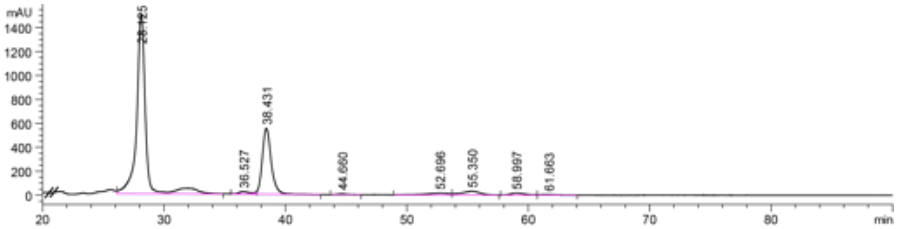


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.216	FM	0.8569	2.19846e4	427.62454	32.3975
2	40.340	VB	0.8023	2.83225e4	541.39130	41.7373
3	46.976	BB	0.7348	318.06488	5.73699	0.4687
4	55.780	FM	2.4297	2394.22412	16.42303	3.5282
5	58.619	VB	1.5852	4333.63232	38.26860	6.3862
6	62.305	BV	1.3860	8020.97803	91.91933	11.8201
7	65.172	VB	1.2306	2485.00024	25.55132	3.6620

Supplementary Figure S22: Representative crude HPLC trace for Entry 3 Supplementary Table S3 with raw data.

Entry 4: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 30% H_2O_2 (5.1 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), water (100 μL), chloroform (400 μL, total 0.05 M including water w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

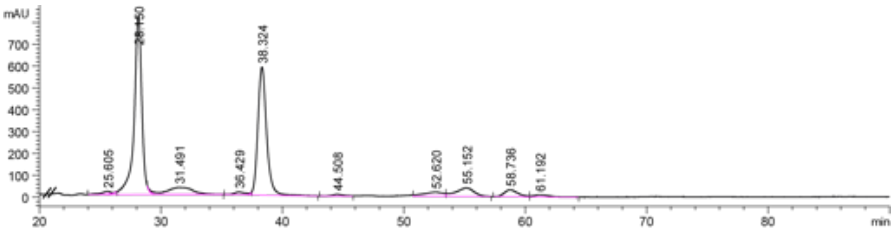


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.125	FM	0.8626	7.77870e4	1503.03418	67.4514
2	36.527	BV E	0.8646	1198.93079	20.08010	1.0396
3	38.431	VB R	0.7885	2.85263e4	550.56482	24.7360
4	44.660	BV	0.8822	452.54330	7.56235	0.3924
5	52.696	BV	1.6264	2139.31787	16.39432	1.8551
6	55.350	VB	1.4305	3380.11060	32.04876	2.9310
7	58.997	BV	1.1680	1386.17029	16.98651	1.2020
8	61.663	VB	1.0567	452.67941	5.36321	0.3925

Supplementary Figure S23: Representative crude HPLC trace for Entry 4 Supplementary Table S3 with raw data.

Entry 5: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (500 μL, total 0.05 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

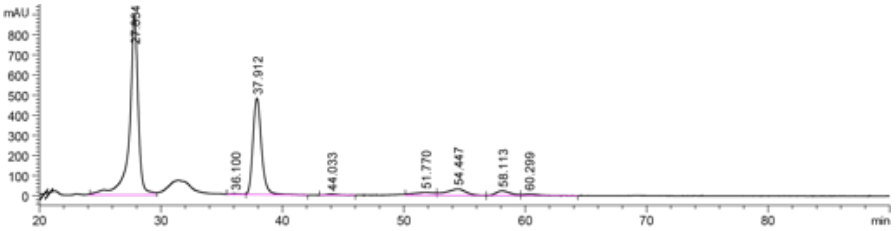


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.605	BV E	0.8476	760.11798	12.74930	0.9167
2	28.150	VV R	0.6574	3.67307e4	821.94757	44.2952
3	31.491	VB E	1.9085	5059.74512	33.00613	6.1018
4	36.429	BV E	0.8699	746.66766	11.86963	0.9004
5	38.324	VV R	0.7685	2.93801e4	586.44958	35.4307
6	44.508	BV	0.8207	494.91510	8.05694	0.5968
7	52.620	FM	1.8949	2246.30054	19.75749	2.7089
8	55.152	VB	1.4497	4225.35010	39.95737	5.0955
9	58.736	BV	1.1341	2458.92017	31.52275	2.9653
10	61.192	VB	1.1035	819.73450	9.64555	0.9886

Supplementary Figure S24: Representative crude HPLC trace for Entry 5, Supplementary Table S3 with raw data.

Entry 6: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added in one portion), chloroform (750 μL, total 0.033 M w.r.t. substrate), 4 °C, 19 h, magnetic stirring.



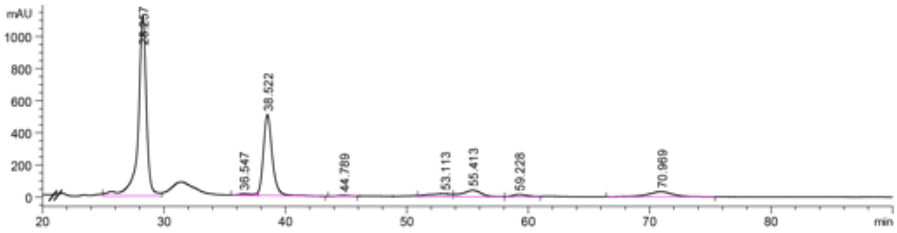
Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.834	MM	0.8390	4.52519e4	898.91974	58.6119
2	36.100	BV E	0.5960	119.64025	2.70486	0.1550
3	37.912	VB R	0.7500	2.35309e4	478.23804	30.4780
4	44.033	BV R	0.8825	315.11234	4.97831	0.4081
5	51.770	FM	1.9278	1765.16968	15.26081	2.2863
6	54.447	VB	1.5799	3600.69580	31.92350	4.6637
7	58.113	BV	1.1448	1896.88403	23.42261	2.4569
8	60.299	VV R	1.1997	725.78119	7.56214	0.9401

Supplementary Figure S25: Representative crude HPLC trace for Entry 6, Supplementary Table S3 with raw data.

Entry 7: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075

mmol, 3.0 equiv total; 1.5 equiv @ 0h, 6h), chloroform (750 µL, total 0.033 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

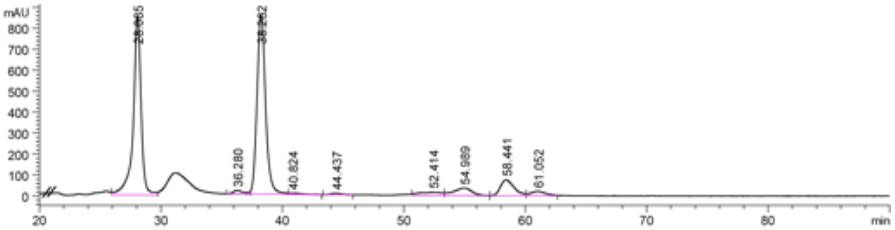


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.257	MM	0.7899	5.33542e4	1125.80566	57.8411
2	36.547	BV E	0.9586	654.26141	9.18991	0.7093
3	38.522	VB R	0.7725	2.56986e4	502.58493	27.8598
4	44.789	BV	0.8898	336.26059	5.26035	0.3645
5	53.113	FM	2.1986	2221.95117	16.84399	2.4088
6	55.413	VB	1.4764	4132.27148	40.02744	4.4798
7	59.228	BV	1.2318	1152.33118	14.12521	1.2492
8	70.969	BB	1.7999	4692.77686	32.13078	5.0874

Supplementary Figure S26: Representative crude HPLC trace for Entry 7, Supplementary Table S3 with raw data.

Entry 8: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 µL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 µL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 4h, 8h), chloroform (750 µL, total 0.033 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

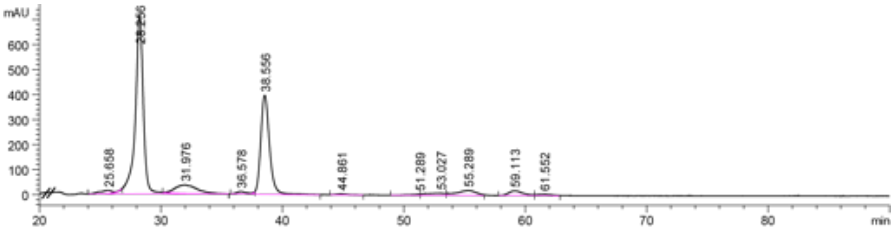


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.085	MM	0.7531	3.85154e4	852.36444	40.2387
2	36.280	BV E	0.8458	937.41718	16.52579	0.9794
3	38.262	VV R	0.7568	4.21713e4	858.96002	44.0583
4	40.824	VB E	1.2076	256.60059	2.58168	0.2681
5	44.437	BB	0.9047	426.79733	7.22966	0.4459
6	52.414	FM	2.1587	1977.11340	15.26451	2.0656
7	54.989	VB	1.4893	3743.16211	35.40981	3.9107
8	58.441	BV	1.1630	5854.36865	75.30711	6.1163
9	61.052	MF	1.4622	1835.00769	20.91657	1.9171

Supplementary Figure S27: Representative crude HPLC trace for Entry 8, Supplementary Table S3 with raw data.

Entry 9: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 µL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 µL, 0.075 mmol, 3.0 equiv; added as solution in 750 µL chloroform over 10 h), chloroform (starting 500 µL, end 750 µL total 0.033 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

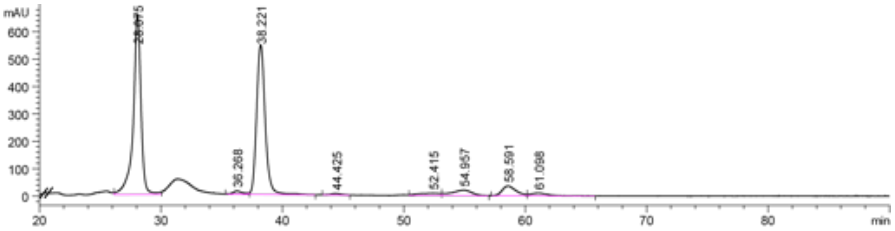


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.658	BV E	1.0261	945.34509	12.97377	1.4463
2	28.256	VV R	0.6860	3.39097e4	719.35883	51.8807
3	31.976	VB E	1.5805	4411.64404	34.85963	6.7497
4	36.578	BV E	0.8311	564.00128	9.92273	0.8629
5	38.556	VB R	0.7710	1.99127e4	395.76221	30.4658
6	44.861	BB	0.8297	243.43242	3.95695	0.3724
7	51.289	MF	0.8663	227.49586	4.37670	0.3481
8	53.027	FM	1.7788	939.37451	8.80159	1.4372
9	55.289	MF	1.8510	2206.54321	19.86782	3.3759
10	59.113	BV	1.2445	1538.62903	18.76682	2.3541

Supplementary Figure S28: Representative crude HPLC trace for Entry 9, Supplementary Table S3 with raw data.

Entry 10: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (70 µL, 0.063 mmol, 2.5 equiv), *N,N'*-diisopropylcarbodiimide (11.6 µL, 0.075 mmol, 3.0 equiv; added as solution in 750 µL chloroform over 10 h), chloroform (starting 500 µL, end 750 µL total 0.033 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

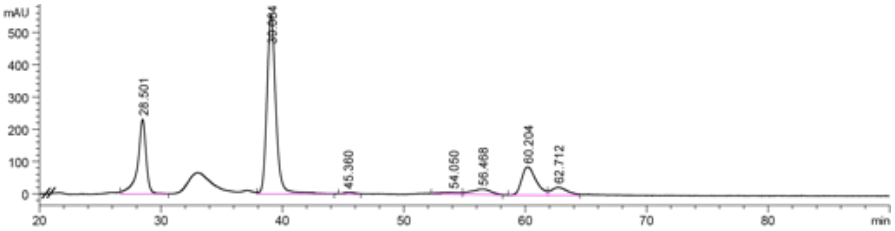


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.076	VV R	0.6398	2.88799e4	658.33386	39.6810
2	36.275	MF	0.8054	558.35944	11.55400	0.7672
3	38.220	FM	0.8225	2.69584e4	546.26398	37.0409
4	44.405	BB	0.8610	351.61151	5.25222	0.4831
5	52.377	BV	1.7352	1255.52625	8.76483	1.7251
6	54.957	VB	1.6613	2326.91382	20.48318	3.1972
7	58.591	BV	1.1870	2822.22656	35.36709	3.8777
8	61.098	VB	1.2918	989.88879	10.20385	1.3601

Supplementary Figure S29: Representative crude HPLC trace for Entry 10, Supplementary Table S3 with raw data.

Entry 11: General procedure **B**, peptide **2** (4.4 mg, 0.005 mmol, 0.2 equiv), 4-dimethylaminopyridine (0.62 mg, 0.005 mmol, 0.2 equiv), 3% H_2O_2 (70 μL, 0.063 mmol, 2.5 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; added as solution in 750 μL chloroform over 10 h), chloroform (starting 500 μL, end 750 μL total 0.033 M w.r.t. substrate), 4 °C, 18 h, magnetic stirring.

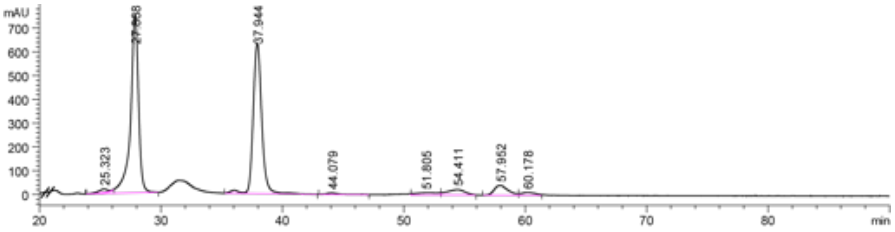


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.501	FM	0.8030	1.11546e4	231.50941	21.5421
2	39.084	VB	0.7751	2.81972e4	556.57458	54.4554
3	45.360	FM	1.0551	321.71771	5.08215	0.6213
4	54.050	MF	1.9237	676.36798	5.86001	1.3062
5	56.468	FM	1.9165	1975.10779	17.17658	3.8144
6	60.204	BV	1.2147	7196.28809	86.84894	13.8977
7	62.712	MF	1.5213	2259.08862	24.74945	4.3628

Supplementary Figure S30: Representative crude HPLC trace for Entry 11, Supplementary Table S3 with raw data.

Entry 12: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 4h, 8h), chloroform (750 μL, total 0.033 M w.r.t. substrate), 4 °C, 18 h, rotamix @ 30 rpm.

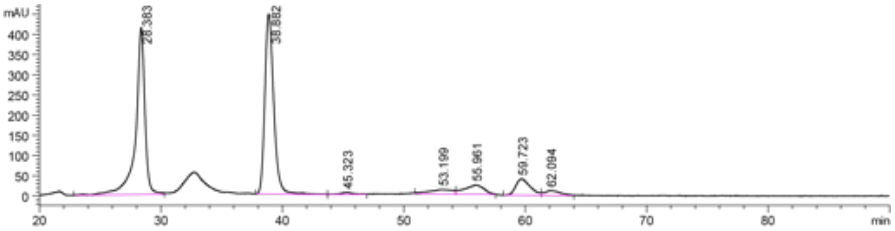


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.323	BV E	0.7714	824.99121	15.14809	1.0963
2	27.868	VB R	0.6747	3.46884e4	751.26740	46.0961
3	37.944	VB R	0.7442	3.14630e4	632.54639	41.8099
4	44.079	BB	0.9230	451.84760	6.31303	0.6004
5	51.805	MF	2.1356	1271.85925	9.92565	1.6901
6	54.411	FM	1.6973	2302.91992	22.61341	3.0603
7	57.952	BV	1.1786	3251.32959	41.11324	4.3206
8	60.178	MF	1.3454	998.02661	12.36302	1.3262

Supplementary Figure S31: Representative crude HPLC trace for Entry 12, Supplementary Table S3 with raw data.

Entry 13: General procedure **B**, peptide **2** (3.3 mg, 0.00375 mmol, 0.15 equiv), 4-dimethylaminopyridine (0.47 mg, 0.00375 mmol, 0.15 equiv), 3% H_2O_2 (56 μL, 0.050 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 4h, 8h), chloroform (750 μL, total 0.033 M w.r.t. substrate), 4 °C, 26 h, rotamix @ 30 rpm.

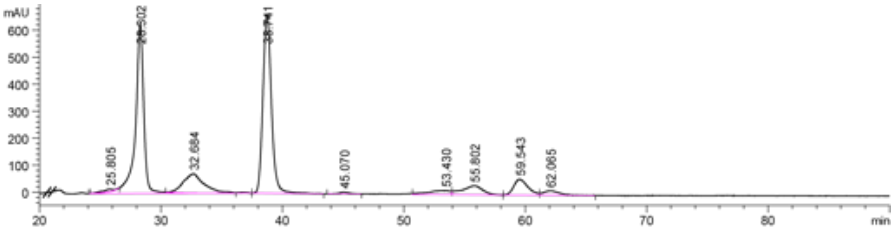


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.383	MF	0.8851	2.20006e4	414.26477	41.0172
2	38.882	BV R	0.7868	2.26926e4	445.11234	42.3073
3	45.323	BV	0.9157	320.23599	4.69524	0.5970
4	53.199	MF	2.3694	1627.37891	11.44709	3.0340
5	55.961	FM	1.8481	2606.89917	23.50947	4.8602
6	59.723	BV	1.2287	3310.32910	40.36644	6.1717
7	62.094	MF	1.5096	1079.54822	11.91861	2.0127

Supplementary Figure S32: Representative crude HPLC trace for Entry 13, Supplementary Table S3 with raw data.

Entry 14: General procedure **B**, peptide **2** (2.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (0.31 mg, 0.0025 mmol, 0.1 equiv), 3% H_2O_2 (70 μL, 0.063 mmol, 2.5 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 4h, 8h), chloroform (750 μL, total 0.033 M w.r.t. substrate), 4 °C, 28 h, rotamix @ 30 rpm.

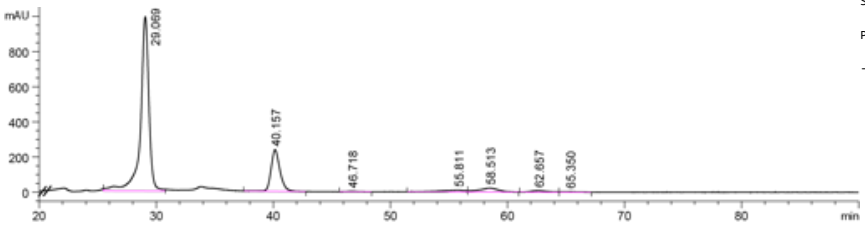


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.805	BV E	0.8723	563.57422	8.73971	0.6612
2	28.302	VV R	0.7080	3.09933e4	628.53546	36.3643
3	32.684	VV E	1.5599	8675.37793	71.88896	10.1788
4	38.741	BV R	0.7635	3.25373e4	664.23804	38.1758
5	45.070	BV	0.8562	427.95950	6.85640	0.5021
6	53.430	FM	2.1311	1924.39783	15.05027	2.2579
7	55.802	VB	1.5288	3908.56128	33.50861	4.5859
8	59.543	BV	1.2088	4669.36719	58.65446	5.4785
9	62.065	VB	1.3837	1530.31348	15.83224	1.7955

Supplementary Figure S33: Representative crude HPLC trace for Entry 14, Supplementary Table S3 with raw data.

Entry 15: General procedure **B**; peptide **2** (0.56 mg, 0.000625 mmol, 0.025 equiv), 4-dimethylaminopyridine (0.16 mg, 0.00125 mmol, 0.05 equiv), 3% H_2O_2 (56 μL, 0.05 mmol, 2.0 equiv), *N,N'*-diisopropylcarbodiimide (11.6 μL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 23h, 46h), chloroform (250 μL, total 0.1 M w.r.t. substrate), 4 °C, 76 h, rotamix @ 30 rpm.

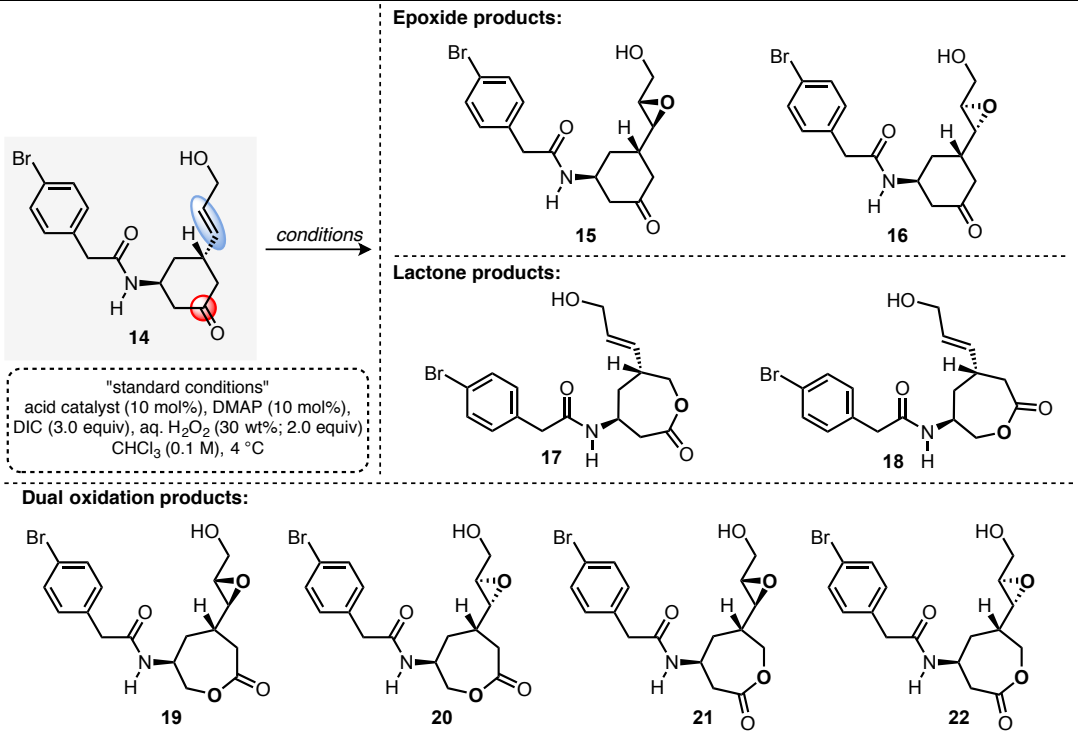


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.069	FM	0.8430	5.01654e4	991.85541	73.9618
2	40.157	VB R	0.8056	1.24551e4	236.80142	18.3633
3	46.718	BB	1.0180	219.06110	3.09393	0.3230
4	55.811	BV	1.8020	1484.48901	10.15166	2.1887
5	58.513	VB	1.6361	2542.30127	21.74396	3.7483
6	62.657	BV	1.2145	718.00891	7.54303	1.0586
7	65.350	VB	1.0860	241.75203	2.69653	0.3564

Supplementary Figure S34: Representative crude HPLC trace for Entry 15, Supplementary Table S3 with raw data.

Supplementary Table S4: Oxidations of substrate 14



Entry	Change from listed reaction conditions	*t* (h)	Conv (%)‡	Product Ratio:‡ Epoxide (**15:16**)	Lactone (**17:18**)	Dual **19-22**
1	*m*CPBA only (1 equiv)	18	65	2.4	1.8 (2.8:1)	1.0
2	octanoic acid (10 mol%)	20	4	1.2	1.0	n.d
3	Boc-Asp(OH)-OMe (20 mol%), DMAP (20 mol%)	20	27	4.9 (1:1)	1.0 (1.2:1)	n.d
4	**14** (0.05 M), catalyst *ent*-**1**, H_2O_2 (30 wt%; 2 equiv)	18	64	>100 (1:4.8)	1.0	1.0
5	**14** (0.05 M), catalyst **1**, H_2O_2 (30 wt%; 2 equiv)	18	99	>100(>99:1)	1.0	1.0
6	**14** (0.05 M), catalyst **2**, H_2O_2 (30 wt%; 2 equiv)	19	32	6.0	1.0 (6.1:1)	n.d
7	**14** (0.033 M), catalyst *ent*-**2**, H_2O_2 (3 wt%; 2 equiv)	24	53	1.0	12.5 (1:72)	1.9
	Truncation Study results:					
8	**14** (0.033 M), catalyst **24**, H_2O_2 (3 wt%; 2 equiv)	24	37	1.3 (2.9:1)	1.0 (1:14.1)	0.3
9	**14** (0.033 M), catalyst **25**, H_2O_2 (3 wt%; 2 equiv)	24	20	3.3 (1.6:1)	1.0 (1.1:1)	n.d.
10	**14** (0.033 M), catalyst **26**, H_2O_2 (3 wt%; 2 equiv)	24	17	3.1 (1.5:1)	1.0 (1.2:1)	n.d.

‡Determined by uncalibrated HPLC integrations; see molar absorptivity study; n.d. = not detected

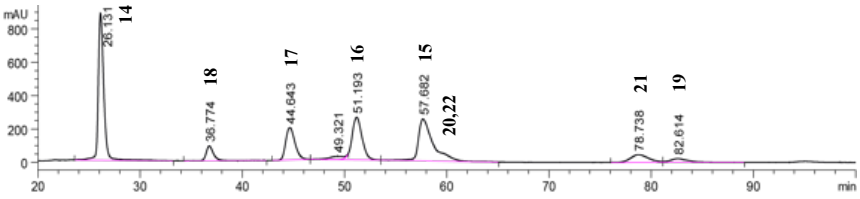
HPLC methods for substrate 14: Chiralpak IA into Chiralpak IC column, 22% ethanol/hexanes, 0.8 ml/min, monitor at 230 nm (entries 1-2,5-7, Table S4); Chiralpak IA column, 15% ethanol/hexanes, 1.0 mL/min (entries 1-7, Table S4); Chiralpak IC column, 14% ethanol/hexanes, 1.0 mL/min (entries 4-5, Table S4).

In-Depth description of Supplementary Table S4 entries and representative HPLC traces:

Entry 1: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol). *m*-Chloroperoxybenzoic acid (6.3 mg, 70% w/w, 0.025 mmol, 1.0 equiv) was added as a solution in chloroform (total 500 μL; 0.05 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4

mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

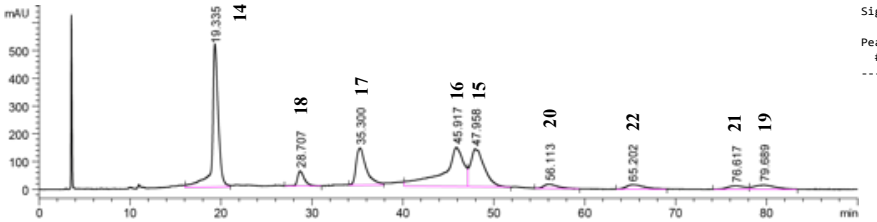
a)



Signal 3: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.407	BB	0.2394	32.61805	1.98849	0.0316
2	26.131	VV R	0.5680	3.32852e4	881.14105	32.2429
3	36.774	VV R	0.7760	4626.35645	88.77077	4.4815
4	44.643	BB	0.9997	1.22409e4	194.10918	11.8576
5	49.321	BV E	1.3039	1872.85339	18.83775	1.8142
6	51.193	VB R	1.0535	1.76086e4	255.03148	17.0572
7	57.682	VV R	1.4240	2.49766e4	251.20097	24.1945
8	78.738	BV	1.8082	5710.04150	45.74850	5.5312
9	82.614	VV R	1.8189	2879.29932	22.17408	2.7891

b)

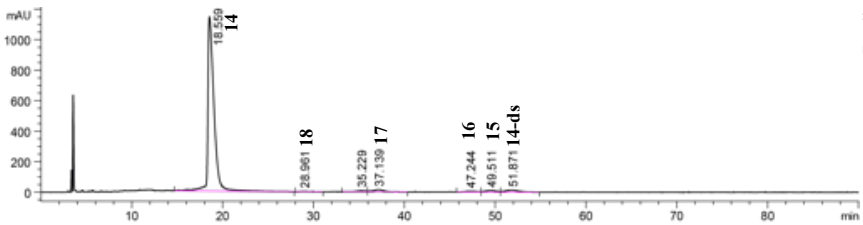


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.335	MF	0.7788	2.41173e4	516.15179	29.5005
2	28.707	BB	0.7917	2785.71851	53.48169	3.4075
3	35.300	MM	1.2986	1.04024e4	133.50774	12.7243
4	45.917	FM	2.6179	2.21888e4	141.26277	27.1416
5	47.958	VB	1.3724	1.43703e4	135.59454	17.5779
6	56.113	MF	1.7873	1666.14722	15.53667	2.0381
7	65.202	MF	2.2918	2164.31274	15.73960	2.6474
8	76.617	BV	1.5831	1583.71545	12.49150	1.9372
9	79.689	MF	2.6807	2473.33203	15.37713	3.0254

Supplementary Figure S35: Representative crude HPLC traces for Entry 1, Supplementary Table S4 with raw data; a) Chiralpak IA/IC, b) Chiralpak IA

Entry 2: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Octanoic acid (3.2 mg, 0.0025 mmol, 0.1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 250 μL; 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 20 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar) at which time crude HPLC analysis was performed.

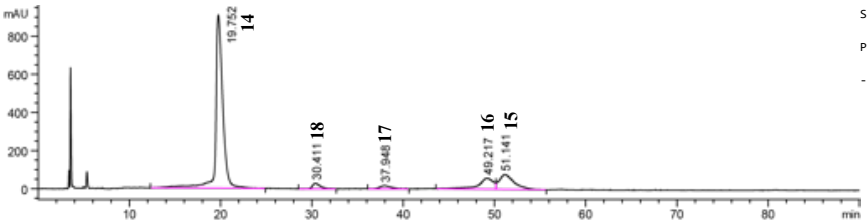


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.559	VV R	0.7150	5.35735e4	1138.51062	92.0119
2	28.961	BB	0.8586	189.82468	2.93500	0.3260
3	35.229	BV	1.0229	540.50818	7.04648	0.9283
4	37.139	VB	1.2437	1287.29834	14.38957	2.2109
5	47.244	BV	1.0123	471.52533	5.61159	0.8098
6	49.511	VV	1.1110	842.42505	9.83849	1.4469
7	51.871	VB	1.3171	1319.43127	12.77340	2.2661

Supplementary Figure S36: Representative crude HPLC traces for Entry 2, Supplementary Table S4 with raw data; Chiralpak IA.

Entry 3: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst **2** (1.2 mg, 0.005 mmol, 0.2 equiv) and 4-dimethylaminopyridine (DMAP; 0.62 mg, 0.005 mmol, 0.2 equiv) were added as solutions in chloroform (total 250 μL; 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 20 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.



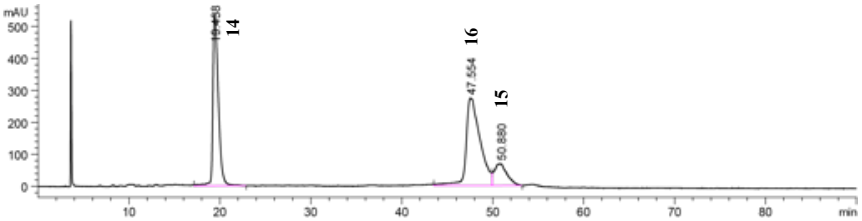
Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.752	VB R	0.8030	4.90154e4	908.33734	72.2676
2	30.411	BV	0.8785	1761.95129	28.93030	2.5978
3	37.948	BB	1.1656	1412.13757	16.78441	2.0820
4	49.217	VV R	1.5567	6703.96533	57.99247	9.8842
5	51.141	VB	1.5901	8931.39746	77.63820	13.1683

Supplementary Figure S37: Representative crude HPLC traces for Entry 3, Supplementary Table S4 with raw data; Chiralpak IA.

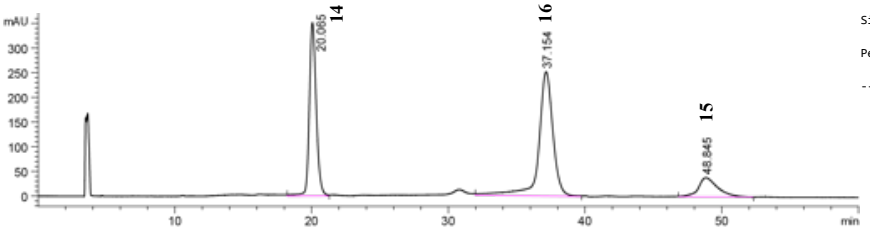
Entry 4: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst *ent*-**1** (3.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv), and HOBt•H_2O (0.34 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 500 μL; 0.05 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar) at which time crude HPLC analysis was performed. Due to incompatibility of the peptide catalyst (streaking) for the given HPLC conditions, a crude purification was performed to remove the peptide. This purification used a C18 column (12 g column) with 10-40% acetonitrile/water (∇ = 3.5% acetonitrile/CV; 25 mL/min). Fractions at CV=10-14 were pooled and concentrated under reduced pressure.

a)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.438	FM	0.6935	2.24045e4	538.43176	35.9597
2	47.554	FM	1.7864	2.92996e4	273.35425	52.7323
3	50.880	VB	1.2283	6592.11670	67.44664	11.3080

b)



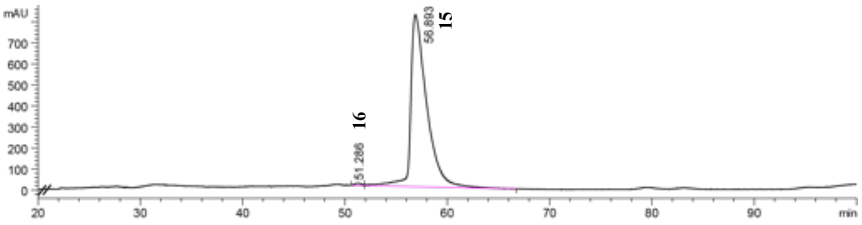
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.065	BV	0.5463	1.23467e4	351.07364	35.9379
2	37.154	VB	1.0840	1.82196e4	251.84694	53.0323
3	48.845	BB	1.4064	3789.36182	38.97001	11.0298

Supplementary Figure S38: Representative crude HPLC traces for Entry 4, Supplementary Table S4 with raw data: a) Chiralpak IA, b) Chiralpak IC.

Entry 5: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst **1** (3.2 mg, 0.0025 mmol, 0.1 equiv), 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv), and HOBt•H_2O (0.34 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 500 μL; 0.05 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar) at which time crude HPLC analysis was performed. Due to incompatibility of the peptide catalyst (streaking) for the given HPLC conditions, a careful crude purification was performed to remove the peptide. This purification used a C18 column (12 g column) with 10-40% acetonitrile/water (∇ = 3.5% acetonitrile/CV; 25 mL/min). Fractions at CV=10-14 were pooled and concentrated under reduced pressure.

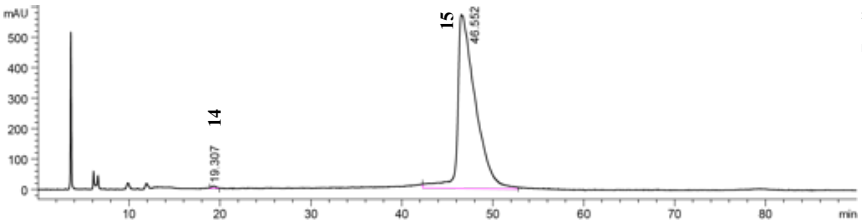
a)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.286	MF	0.8701	539.87225	10.34138	0.6002
2	56.893	FM	1.8219	8.94130e4	817.96704	99.3998

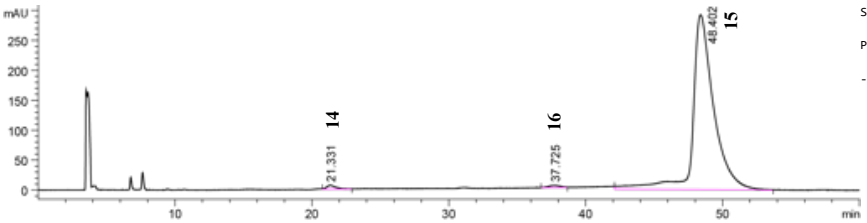
b)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.307	MM	0.5833	272.73975	7.79352	0.3494
2	46.552	FM	2.2722	7.77841e4	570.55261	99.6506

c)



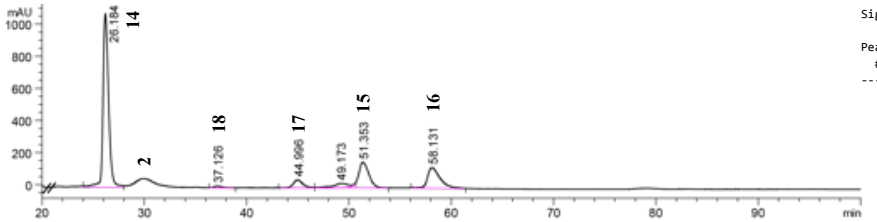
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.331	FM	0.7818	314.22153	6.69853	0.9907
2	37.725	MM	0.9640	197.78865	3.41943	0.6236
3	48.402	MM	1.7782	3.12061e4	292.49399	98.3857

Supplementary Figure S39: Representative crude HPLC traces for Entry 5, Supplementary Table S4 with raw data; a) Chiralpak IA/IC, b) Chiralpak IA, c) Chiralpak IC.

Entry 6: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst **2** (2.2 mg, 0.0025 mmol, 0.1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 500 μL; 0.05 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

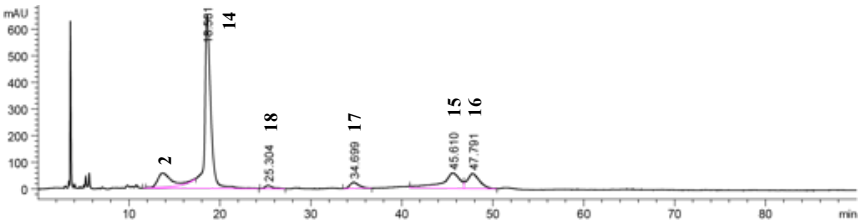
a)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.867	BB	0.3267	36.41815	1.84194	0.0519
2	26.184	FM	0.6352	4.12363e4	1082.00134	58.7254
3	37.126	BB	0.7894	549.62634	9.81318	0.7827
4	44.996	BV	0.9417	3143.13623	49.43920	4.4762
5	49.173	VV E	1.3116	2867.66626	27.34277	4.0839
6	51.353	VB R	1.0738	1.12507e4	158.94516	16.0224
7	58.131	MF	1.4426	1.11350e4	128.64154	15.8576

b)



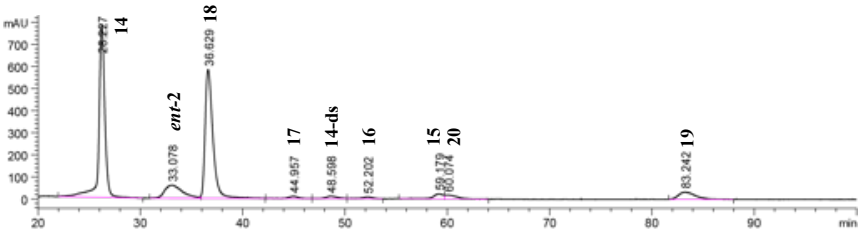
Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.571	MF	0.8145	3.18536e4	651.78363	62.9506
2	25.304	MM	0.6561	421.80209	10.71461	0.8336
3	34.699	MM	1.4789	2253.18433	25.39293	4.4529
4	45.610	MF	2.8847	1.04757e4	60.52513	20.7025
5	47.791	FM	1.5881	5596.67383	58.73719	11.0604

Supplementary Figure S40: Representative crude HPLC traces for Entry 6, Supplementary Table S4 with raw data; a) Chiralpak IA/IC, b) Chiralpak IA.

Entry 7: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 0.1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 750 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 24 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

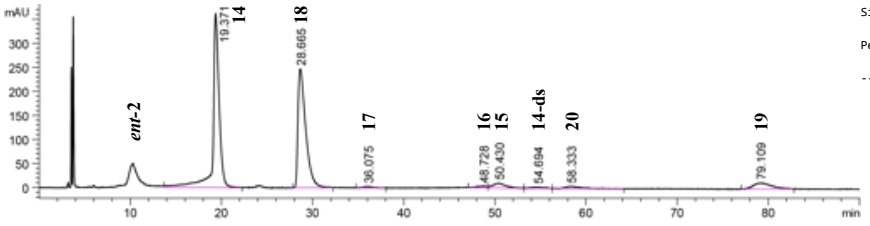
a)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.227	BB	0.6130	3.19730e4	782.04077	40.5229
2	33.078	BV E	1.8029	7161.79736	59.21925	9.0769
3	36.629	VB R	0.8008	3.08204e4	582.98737	39.0620
4	44.957	VV R	0.9339	661.26599	9.96859	0.8381
5	48.598	VV	1.0234	837.06818	10.90625	1.0609
6	52.202	VB	1.0068	622.23425	8.04110	0.7886
7	59.179	MF	1.2132	1643.14392	22.57229	2.0825
8	60.074	FM	1.3693	1411.17200	17.17582	1.7885
9	83.242	BB	1.5501	3771.10205	32.97820	4.7795

b)

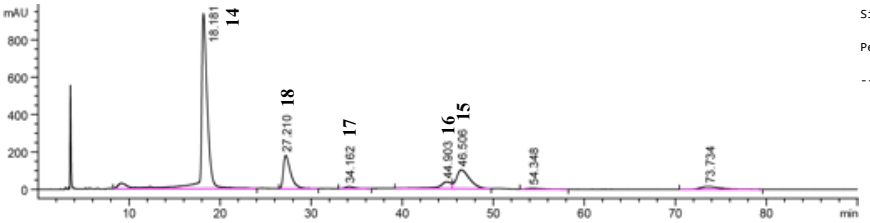


Signal 1: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.371	MM	0.6995	1.51546e4	361.07358	44.9806
2	28.665	VB	0.8821	1.46471e4	247.60657	43.4744
3	36.075	BB	0.9540	202.58025	2.78048	0.6013
4	48.728	BV	0.9474	257.90836	3.31615	0.7655
5	50.430	VB	1.1532	932.64490	9.84474	2.7682
6	54.694	BV	1.2241	247.53181	2.59677	0.7347
7	58.333	VB	1.4234	497.91290	4.24825	1.4779
8	79.109	BB	1.7260	1751.08447	12.35141	5.1974

Supplementary Figure S41: Representative crude HPLC traces for Entry 7, Supplementary Table S4 with raw data; a) Chiralpak IA/IC, b) Chiralpak IA.

Entry 8: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst **24** (1.7 mg, 0.0025 mmol, 0.1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 750 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 24 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

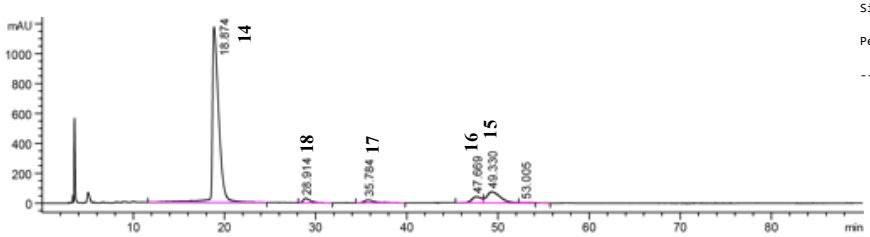


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.181	VV R	0.6737	4.54207e4	933.53101	63.0243
2	27.210	BB	0.8442	9780.53906	177.13461	13.5712
3	34.162	BB	0.9634	692.85431	9.86478	0.9614
4	44.903	BV	1.2905	3202.69995	35.57003	4.4440
5	46.506	VB	1.3892	9964.81152	99.76971	13.8269
6	54.348	BB	1.3687	614.94824	5.39960	0.8533
7	73.734	BB	1.8828	2392.00537	15.54852	3.3191

Supplementary Figure S42: Representative crude HPLC traces for Entry 8, Supplementary Table S4 with raw data; Chiralpak IA.

Entry 9: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst **25** (1.4 mg, 0.0025 mmol, 0.1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 750 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 24 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

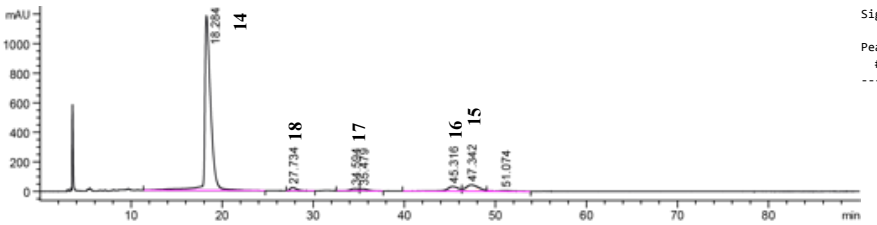


Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.874	VV R	0.7359	5.79956e4	1172.94812	80.0540
2	28.914	BB	0.8491	1669.76208	28.93958	2.3048
3	35.784	BV R	1.2246	1627.39258	19.12818	2.2464
4	47.669	BV	1.0645	2976.70728	40.54757	4.1089
5	49.330	VV R	1.4411	8038.24658	74.59953	11.0955
6	53.005	VB E	0.8850	137.94675	1.99928	0.1904

Supplementary Figure S43: Representative crude HPLC traces for Entry 9, Supplementary Table S4 with raw data; Chiralpak IA.

Entry 10: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst **26** (1.2 mg, 0.0025 mmol, 0.1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 0.1 equiv) were added as solutions in chloroform (total 750 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 24 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.284	VB R	0.6629	5.44311e4	1179.59546	83.8023
2	27.734	BB	0.7902	1190.76733	22.04503	1.8333
3	34.594	BV	0.9082	923.91046	14.72122	1.4225
4	35.479	VB	0.8586	823.07440	13.00061	1.2672
5	45.316	BV	1.3434	2778.16431	30.48007	4.2773
6	47.342	VV R	1.4973	4340.45166	42.72171	6.6826
7	51.074	VB E	1.2687	464.30533	4.46669	0.7148

Supplementary Figure S44: Representative crude HPLC traces for Entry 10, Supplementary Table S4 with raw data; Chiralpak IA.

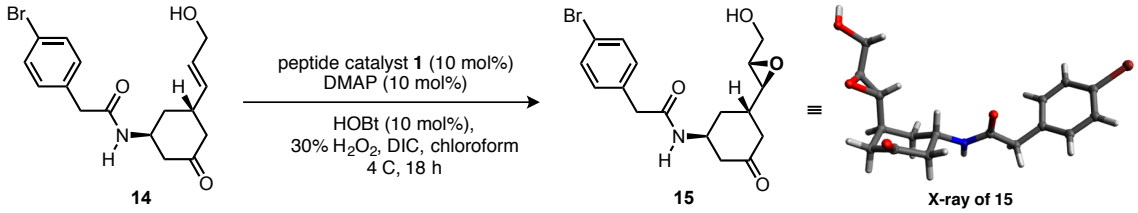
Oxidations of substrate 14 on 0.27 mmol scale or larger:

General notes about purification: Purification of these compounds was difficult due to the starting material, lactones, epoxides, peptide catalysts, dual-oxidation products, and *N*-*N*-diisopropylurea having similar elution rates on silica. For isolation of these products, the crude product mixture was purified by reverse phase chromatography as described below:

1. The first purification used a C18 column with 10-50% acetonitrile/water (∇ = 2.5% acetonitrile/CV). The epoxides and dual-oxidation products appeared at 36% acetonitrile/water, and the lactone and starting material appeared 38-40% acetonitrile.

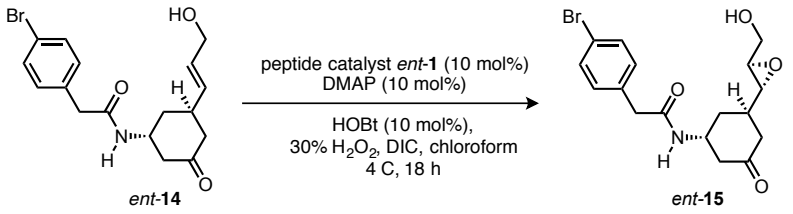
2. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 25% MeCN/H_2O to 45% MeCN/H_2O over 35 minutes at a flow rate of 20 mL/min. Epoxide and dual oxidation products appeared at 14-17 minutes and lactones at 20 minutes (monitored at 210/230 nm)

*Synthesis of Compound **15**:*



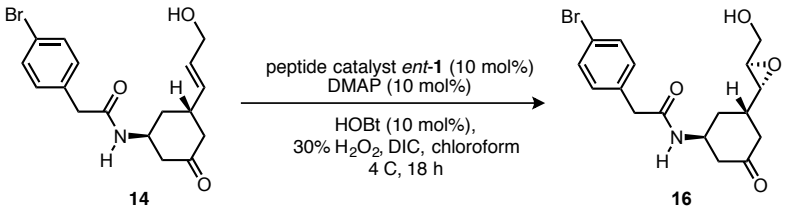
A reaction vial equipped with a stir bar was charged with substrate **14** (100 mg, 0.273 mmol), catalyst **1** (35 mg, 0.027 mmol, 0.1 equiv), 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.027 mmol), and HOBt•H_2O (3.7 mg, 0.027 mmol, 0.1 equiv). The solids were suspended in chloroform (2.73 mL, 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After stirring for 1 h, aqueous H_2O_2 (30% w/w, 56 μL, 0.55 mmol, 2.0 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 114 μL, 0.74 mmol, 2.7 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (15 mL). The product solution was further diluted with saturated aqueous ammonium chloride (12 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 35 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified using a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 25 mL/min; monitor at 210 nm). The epoxide product elutes at 36% acetonitrile/water to afford the **15** as a colorless oil (86 mg) in 83% yield. No further purification was needed. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = - 15.1 (*c* = 1.02, $CHCl_3$, >99:1 er). See the above section for characterization data.

*Synthesis of Compound ent-**15**:*



A reaction vial equipped with a stir bar was charged with substrate *ent*-**14** (100 mg, 0.273 mmol), catalyst *ent*-**1** (35 mg, 0.027 mmol, 0.1 equiv), 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.027 mmol), and HOBt•H_2O (3.7 mg, 0.027 mmol, 0.1 equiv). The solids were suspended in chloroform (2.73 mL, 0.1 M w.r.t. *ent*-**14**). The mixture was gently agitated and transferred to a cold room (4 °C). After stirring for 1 h, aqueous H_2O_2 (30% w/w, 56 μL, 0.55 mmol, 2.0 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 114 μL, 0.74 mmol, 2.7 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (15 mL). The product solution was further diluted with saturated aqueous ammonium chloride (12 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 35 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified using a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 25 mL/min; monitor at 210 nm). The epoxide product elutes at 36% acetonitrile/water to afford the *ent*-**15** as a colorless oil (83 mg) in 80% yield. No further purification was needed. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = + 14.4 (*c* = 0.5, $CHCl_3$, >99:1 er). See above section for characterization data.

*Synthesis of Compound **16**:*

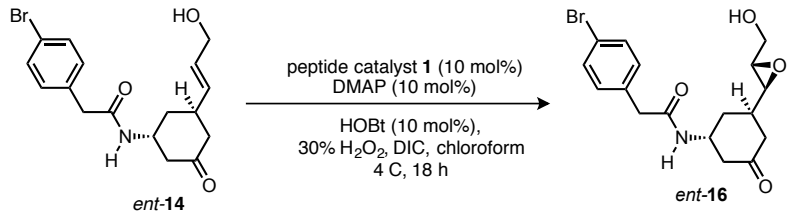


A reaction vial equipped with a stir bar was charged with substrate **14** (100 mg, 0.273 mmol), catalyst *ent*-**1** (35 mg, 0.027 mmol, 0.1 equiv), 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.027 mmol), and HOBt•H_2O (3.7 mg, 0.027 mmol, 0.1 equiv). The solids were suspended in chloroform (2.73 mL, 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After stirring for 1 h, aqueous H_2O_2 (30% w/w, 56 μL, 0.55 mmol, 2.0 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 114 μL, 0.74 mmol, 2.7 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (15 mL). The product solution was further diluted with saturated aqueous ammonium chloride (12 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 35 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified as described below (6.2:1 dr):

1. The first purification used a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The epoxides appeared at 36% acetonitrile/water. These fractions were pooled and concentrated under reduced pressure (12 mbar).

2. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 20% MeCN/H_2O to 31% MeCN/H_2O over 38 minutes at a flow rate of 20 mL/min. The epoxide products appeared at 27.5-29 minutes (monitored at 210/230 nm). The later fractions contained a predominately the depicted diastereomer **16**. Yield was not calculated for this reaction. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = - 4.3(*c* = 3.7, $CHCl_3$). See above section for characterization data.

*Synthesis of Compound ent-**16**:*

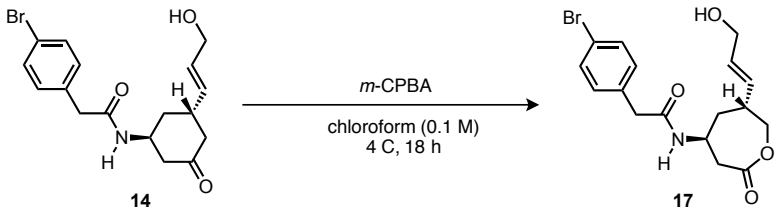


A reaction vial equipped with a stir bar was charged with substrate *ent*-**14**(100 mg, 0.273 mmol), catalyst **1** (35 mg, 0.027 mmol, 0.1 equiv), 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.027 mmol), and HOBt•H_2O (3.7 mg, 0.027 mmol, 0.1 equiv). The solids were suspended in chloroform (2.73 mL, 0.1 M w.r.t. *ent*-**14**). The mixture was gently agitated and transferred to a cold room (4 °C). After stirring for 1 h, aqueous H_2O_2 (30% w/w, 56 μL, 0.55 mmol, 2.0 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 114 μL, 0.74 mmol, 2.7 equiv) in one portion. The reaction mixture was vigorously stirred at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (15 mL). The product solution was further diluted with saturated aqueous ammonium chloride (12 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 35 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified as described below (6.2:1 dr):

1. The first purification used a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The epoxides appeared at 36% acetonitrile/water. These fractions were pooled and concentrated under reduced pressure (12 mbar).

2. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 20% MeCN/H_2O to 31% MeCN/H_2O over 38 minutes at a flow rate of 20 mL/min. The epoxide products appeared at 27.5-29 minutes (monitored at 210/230 nm). The later fractions contained a predominately the depicted diastereomer *ent*-**15**. Yield was not calculated for this reaction. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = + 4.0 (*c* = 1.3, $CHCl_3$). See above section for characterization data.

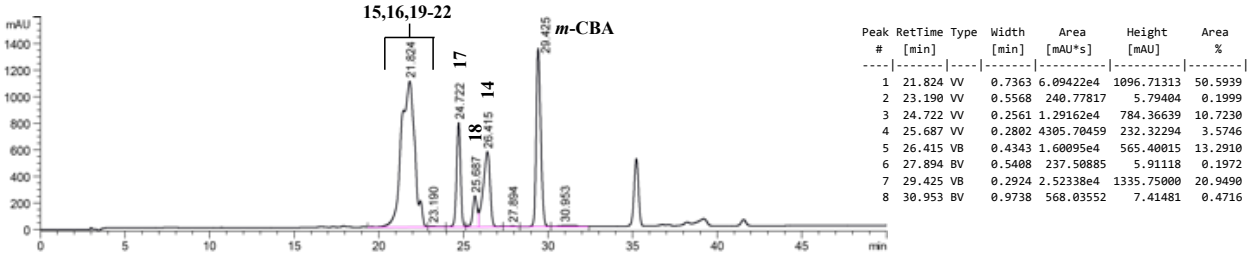
*Synthesis of Compound **17**:*



A reaction vial equipped with a stir bar was charged with substrate **14** (161 mg, 0.44 mmol). *m*-Chloroperoxybenzoic acid (108 mg, 70% w/w, 0.44 mmol, 1.0 equiv) was added as a solution in chloroform (total 4.4 mL; 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (30 mL). The product solution was further diluted with saturated aqueous sodium bicarbonate (20 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 35 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified as described below:

1. The first purification used a C18 column (CV = 30 g) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The lactone appeared at 38% acetonitrile/water with the starting material. These fractions were pooled and concentrated under reduced pressure (12 mbar).

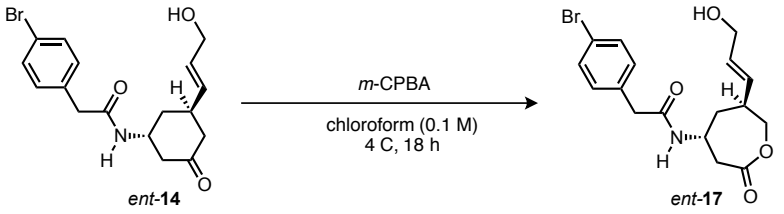
2. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 27% MeCN/H_2O to 31% MeCN/H_2O over 38 minutes at a flow rate of 20 mL/min. The lactone product **17** appeared at 24.0 minutes (monitored at 210/230 nm), before lactone **18** and substrate **14**. Yield was not calculated for this reaction. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = -27.7 (*c* = 1.0, CH_3OH) See above section for characterization data.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.824	VV	0.7363	6.09422e4	1096.71313	50.5939
2	23.190	VV	0.5568	240.77817	5.79404	0.1999
3	24.722	VV	0.2561	1.29162e4	784.36639	10.7230
4	25.687	VV	0.2802	4305.70459	232.32294	3.5746
5	26.415	VB	0.4343	1.60095e4	565.40015	13.2910
6	27.894	BV	0.5408	237.50885	5.91118	0.1972
7	29.425	VB	0.2924	2.52338e4	1335.75000	20.9490
8	30.953	BV	0.9738	568.03552	7.41481	0.4716

Supplementary Figures S45: Reverse phase HPLC trace of crude reaction indicating lactone **17**.

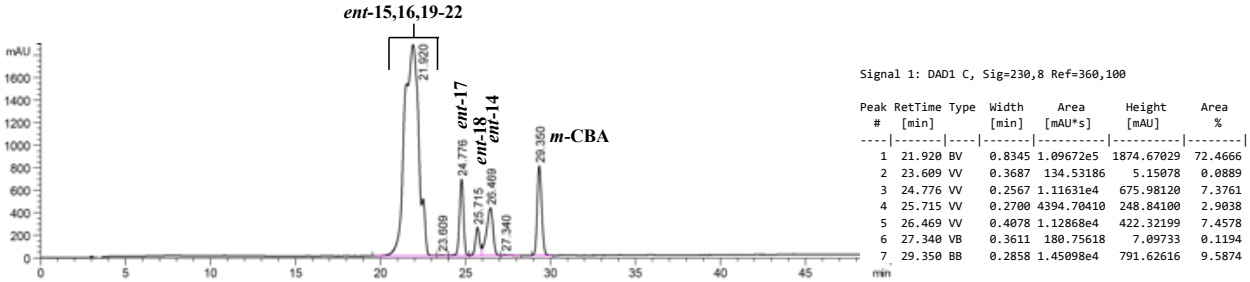
*Synthesis of Compound ent-**17**:*



A reaction vial equipped with a stir bar was charged with substrate *ent*-**14** (100 mg, 0.44 mmol). *m*-Chloroperoxybenzoic acid (123 mg, 70% w/w, 0.50 mmol, 1.1 equiv) was added as a solution in chloroform (total 4.4 mL; 0.1 M w.r.t. *ent*-**14**). The mixture was gently agitated and transferred to a cold room (4 °C). After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (2 mL) and diluted with ethyl acetate (30 mL). The product solution was further diluted with saturated aqueous sodium bicarbonate (20 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 35 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified as described below:

1. The first purification used a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The lactone appeared at 38% acetonitrile/water with the starting material. These fractions were pooled and concentrated under reduced pressure (12 mbar).

2. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 27% MeCN/H_2O to 31% MeCN/H_2O over 38 minutes at a flow rate of 20 mL/min. The lactone product *ent*-**17** appeared at 24.0 minutes (monitored at 210/230 nm), before lactone *ent*-**18** and substrate *ent*-**14**. Yield was not calculated for this reaction. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = +27.1 (*c* = 0.8, CH_3OH) See above section for characterization data.

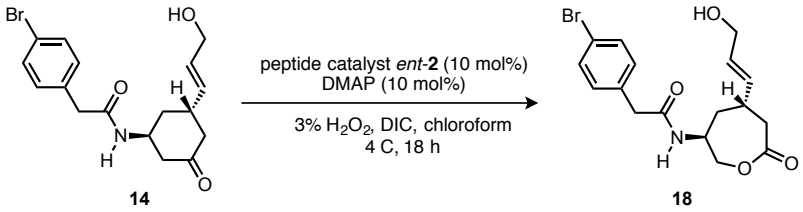


Signal 1: DAD1 C, Sig=230,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.920	BV	0.8345	1.09672e5	1874.67029	72.4666
2	23.609	VV	0.3687	134.53186	5.15078	0.0889
3	24.776	VV	0.2567	1.11631e4	675.98120	7.3761
4	25.715	VV	0.2700	4394.70410	248.84100	2.9038
5	26.469	VV	0.4078	1.12868e4	422.32199	7.4578
6	27.340	VB	0.3611	180.75618	7.09733	0.1194
7	29.350	BB	0.2858	1.45098e4	791.62616	9.5874

Supplementary Figures S46: Reverse phase HPLC trace of crude reaction indicating lactone *ent*-**17**.

*Synthesis of Compound **18**:*



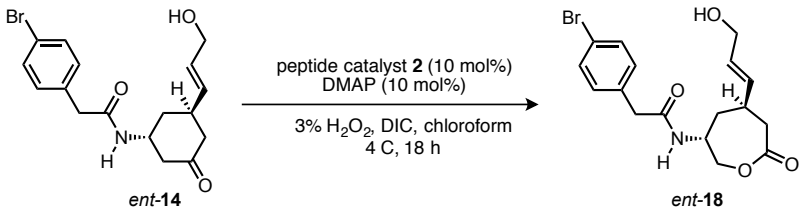
A reaction vial with a stir bar was charged with substrate (100 mg, 0.273 mmol, 1 equiv). Catalyst (24 mg, 0.027 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.027 mmol, 1 equiv) were added as solutions in chloroform (total 8.2 mL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 620 mL, 0.55 mmol, 2 equiv) was pipetted into the reaction vessel followed by DIC (114 μL, 0.74 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (3 mL) and extracted with ethyl acetate (30 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (15 mL) was added. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 30 mL). The organic

layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified as described below (65% by analytical HPLC, 230 nm):

3. The first purification used a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The lactone appeared at 38% acetonitrile/water with the starting material. These fractions were pooled and concentrated under reduced pressure (12 mbar).

4. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 27% MeCN/H_2O to 31% MeCN/H_2O over 38 minutes at a flow rate of 20 mL/min. The lactone product **18** appeared at 24.5-26.5 minutes (monitored at 210/230 nm). The earlier fractions contained the lactone **18**, while the latter contained the starting material. Yield was not calculated for this reaction. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = -14.1 (*c* = 0.58, $CHCl_3$) See above section for characterization data.

*Synthesis of Compound ent-**18**:*



A reaction vial with a stir bar was charged with substrate (100 mg, 0.273 mmol, 1 equiv). Catalyst (24 mg, 0.027 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.027 mmol, 1 equiv) were added as solutions in chloroform (total 8.2 mL; 0.033 M w.r.t. *ent*-**14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 620 mL, 0.55 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 114 μL, 0.74 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 18 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (3 mL) and extracted with ethyl acetate (30 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (15 mL) was added. The layers were separated, and the aqueous layer was re-extracted with additional ethyl acetate (2 x 30 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure (12 mbar). The residue was purified as described below (61% by analytical HPLC, 230 nm):

1. The first purification used a C18 column (30 g column) with 10-50% acetonitrile/water (∇ = 2.7% acetonitrile/CV; 50 mL/min; monitor at 210 nm). The lactone appeared at 38% acetonitrile/water with the starting material. These fractions were pooled and concentrated under reduced pressure (12 mbar).

2. The mixed fractions were subjected to reverse-phase prep HPLC using a Waters SymmetryPrep C8 7 um column (19 x 300 mm) with a gradient of 27% MeCN/H_2O to 31% MeCN/H_2O over 38 minutes at a flow rate of 20 mL/min. The lactone product *ent*-**18** appeared at 24.5-26.5 minutes (monitored at 210/230 nm). The earlier fractions contained the lactone *ent*-**18**, while the latter contained the starting material. Yield was not calculated for this reaction. For optical rotation, a sample with >99:1 er was used: $[\alpha]_D^{20.0}$ = +14.0 (*c* = 0.5, $CHCl_3$). See above section for characterization data.

Water study: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 1 equiv) were added as solutions in chloroform (total 250 μL; 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, DI H_2O (15 μL increments, see Table **S5**) and aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) were pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 24 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

Table S5: Summary of reactions with increasing water content.

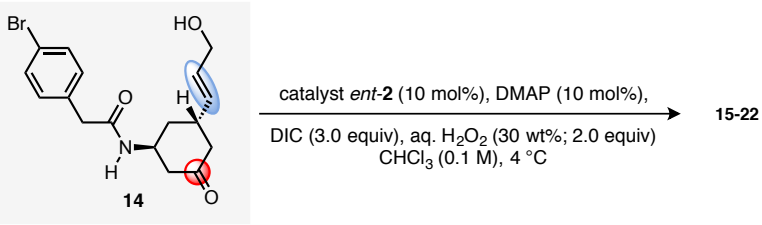
Water (amount in μL)	Water (equivalents)	Water [M]	% Conversion	Chemoselectivity (Lactone:Epoxide)
15	33.3	1.67	73.9	2.1
30	66.6	0.83	71.8	2.6
45	99.9	0.56	67.8	2.7
60	133.2	0.42	61.9	3.2
75	166.5	0.33	58.9	3.4
90	199.8	0.28	57.3	3.7
105	233.1	0.24	55.9	3.8
120	266.4	0.21	50.6	4.2

Alcohol study as a substitute for water:

General comments: We decided to investigate other protic solvents as a substitute for water, mainly various alcohols. The raw data is presented below. A key difference, as compared to water, was the miscibility of the alcohol solvents in chloroform, which had a drastic outcome. Futhermore, a significant amount of esterification of the catalyst was observed in these studies.

Procedure: A reaction vial (1 mL) with a stir bar was charged with substrate (9.2 mg, 0.025 mmol, 1 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 1 equiv) were added as solutions in chloroform (total 250 μL; 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, the indicated alcohol (50 μL, see Table **S6**) and aqueous H_2O_2 (30% w/w, 5.1 μL, 0.05 mmol, 2 equiv) were pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv) in one portion. The reaction mixture was rotated (30 rpm) at 4 °C. After 24 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC.

Table S6: Summary of reactions with various alcohols.



							Product Ratio:‡		
Entry	Alcohol	Quantity	Mmol	Equiv.	*t* (h)	Conv (%)‡	Epoxide (**15**+**16**)	Lactone (**17**:**18**)	Dual **19-22**
1	**MeOH**	50 μL	1.23	49.4	24	32	1.8	1.0 (1:6.5)	0.2
2	**EtOH**	50 μL	0.86	34.2	24	38	1.7	1.0 (1:10.7)	0.2
3	***i*PrOH**	50 μL	0.65	26.2	24	46	1.8	1.0 (1:17.9)	0.3
4	**AmylOH**	50 μL	0.46	18.4	24	57	1.6	1.0 (1:18.3)	0.4

‡Determined by uncalibrated HPLC integrations; see molar absorptivity study; n.d. = not detected

Competition of epoxide 15 in the chemoselectivity studies:

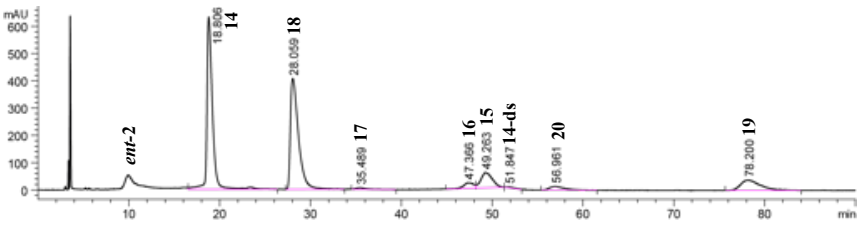
General comments: During the course of the studies, it became apparent that higher concentrations of the epoxide products **15-16** led to diminished conversions and selectivity. It is possible that the epoxide is competing with the amido-directing group, presumably sequestering the peptide catalyst **2** (and *ent*-**2**) in a non-productive manner. To test this hypothesis, epoxide product **15** (20 mol%) was doped into the reaction media in both a high dilution, low conversion reaction and in a high concentration, high conversion reaction. The raw data is presented below:

High dilution, low conversion:
Control reaction: A reaction vial (1 mL) with a stir bar was charged with substrate **14** (9.2 mg, 0.025 mmol, 1 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 1 equiv) were added as solutions in chloroform (total 700 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL in 100 μL chloroform, 0.075 mmol, 3.0 equiv, 8.33 μL/hr) via a syringe pump. The reaction mixture was vigorously stirred at 4 °C. After 13 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC: Chiralpak IA column, 15% ethanol/hexanes, 1.0 mL/min.

Epoxide doped reaction: A reaction vial (1 mL) with a stir bar was charged with substrate **14** (9.2 mg, 0.025 mmol, 1 equiv) and epoxide **15** (1.9 mg, 0.005 mmol, 0.2 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 1 equiv) were added as solutions in chloroform (total 700 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL in 100 μL chloroform, 0.075 mmol, 3.0 equiv, 8.33 μL/hr) via a syringe

pump. The reaction mixture was vigorously stirred at 4 °C. After 13 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC: Chiralpak IA column, 15% ethanol/hexanes, 1.0 mL/min.

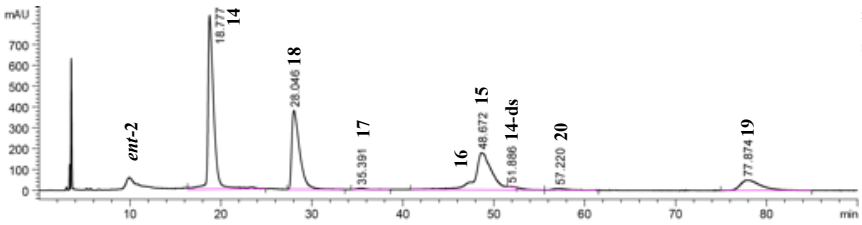
a)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.806	VV R	0.6237	2.73793e4	633.05493	40.8975
2	28.059	BB	0.9212	2.51381e4	406.64835	37.5498
3	35.489	BB	1.0275	419.28549	5.25140	0.6263
4	47.366	BV	1.0025	1576.20642	20.65078	2.3544
5	49.263	VB	1.1620	4906.63623	56.67733	7.3292
6	51.847	BB	0.8045	170.23004	2.74105	0.2543
7	56.961	BB	1.4441	1569.20667	13.18888	2.3440
8	78.200	BB	1.8730	5787.13574	37.99433	8.6445

b)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.777	VV R	0.6451	3.69391e4	830.06140	39.6564
2	28.046	BB	0.9246	2.30640e4	379.75262	24.7607
3	35.391	BB	0.9835	390.85083	5.38021	0.4196
4	48.672	BV R	1.8600	2.39853e4	177.10927	25.7497
5	51.886	VB E	0.5098	93.43184	2.44509	0.1003
6	57.220	BB	1.4581	862.13171	7.42800	0.9256
7	77.874	BB	1.9464	7813.11523	49.69101	8.3879

Supplementary Figures S47: HPLC traces of crude reaction; a) control reaction, b) doped reaction.

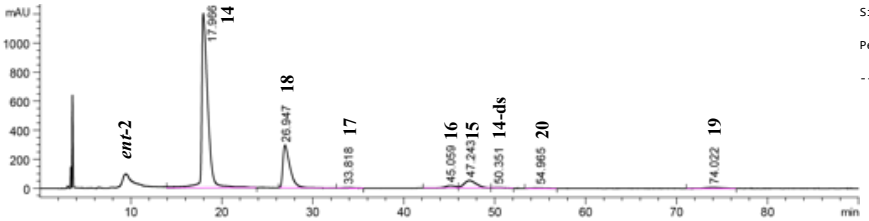
High concentration, high conversion:

Control reaction: A reaction vial (1 mL) with a stir bar was charged with substrate **14** (9.2 mg, 0.025 mmol, 1 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 1 equiv) were added as solutions in chloroform (total 250 μL; 0.1 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 4h, 8h). The reaction mixture was rotated (30 rpm) at 4 °C. After 20 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC: Chiralpak IA column, 15% ethanol/hexanes, 1.0 mL/min.

Epoxide doped reaction: A reaction vial (1 mL) with a stir bar was charged with substrate **14** (9.2 mg, 0.025 mmol, 1 equiv) and epoxide **15** (1.9 mg, 0.005 mmol, 0.2 equiv). Catalyst *ent*-**2** (2.2 mg, 0.0025 mmol, 1 equiv) and 4-dimethylaminopyridine (DMAP; 0.31 mg, 0.0025 mmol, 1 equiv) were added as solutions in chloroform (total 700 μL; 0.033 M w.r.t. **14**). The mixture was gently agitated and transferred to a cold room (4 °C). After standing for 1 h, aqueous H_2O_2 (3% w/w, 56 μL, 0.05 mmol, 2 equiv) was pipetted into the reaction vessel followed by *N,N'*-diisopropylcarbodiimide (DIC; 11.6 μL, 0.075 mmol, 3.0 equiv; 1.0 equiv @ 0h, 4h, 8h). The reaction mixture was

rotated (30 rpm) at 4 °C. After 20 h, the reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL) and extracted with ethyl acetate (4 mL). To this biphasic mixture, saturated aqueous sodium bicarbonate (3 mL) was added and the mixture was vortexed. The layers were separated and the organic was washed again with saturated aqueous sodium bicarbonate (3 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a plug of cotton and the filtrate was concentrated under reduced pressure (12 mbar). The residue was dissolved in 1 mL of $CDCl_3$:*i*PrOH (7:3) and analyzed by chiral HPLC: Chiralpak IA column, 15% ethanol/hexanes, 1.0 mL/min.

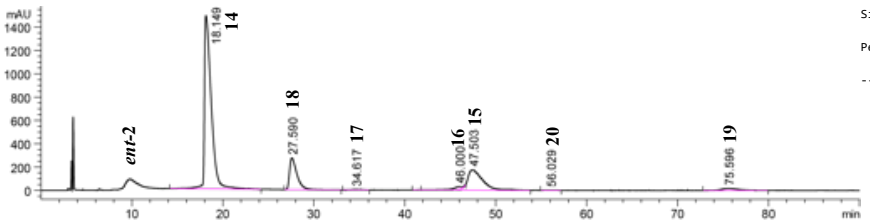
a)



Signal 1: MWD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.966	VB	0.7156	5.61870e4	1197.17114	70.1091
2	26.947	BV R	0.7995	1.60296e4	292.44260	20.0014
3	33.818	VB E	1.0202	317.31958	3.97121	0.3959
4	45.059	BV	1.0706	1261.69141	15.35527	1.5743
5	47.243	VB	1.3567	4708.54492	51.02026	5.8752
6	50.351	BB	0.9993	213.66325	2.73545	0.2666
7	54.965	BV	1.4338	365.77637	3.11537	0.4564
8	74.022	VV R	1.6400	1058.65808	7.83693	1.3210

b)

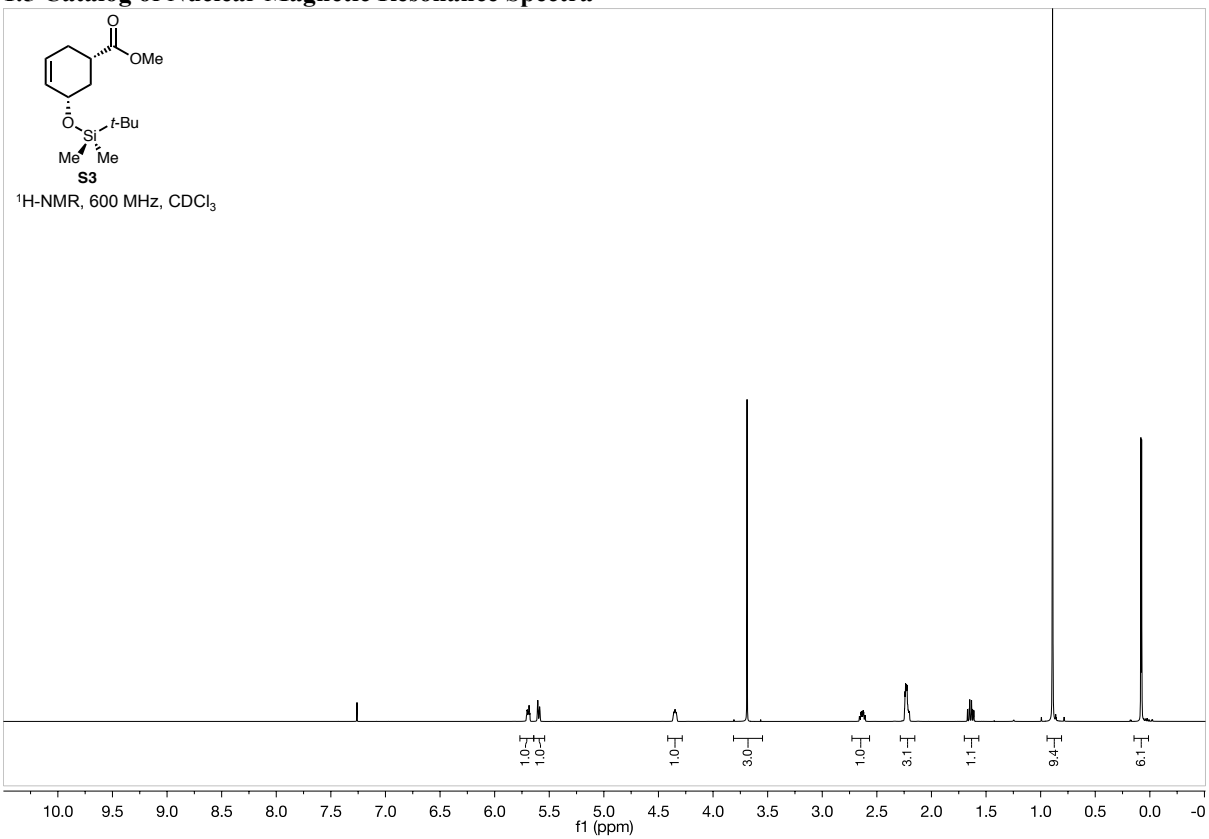


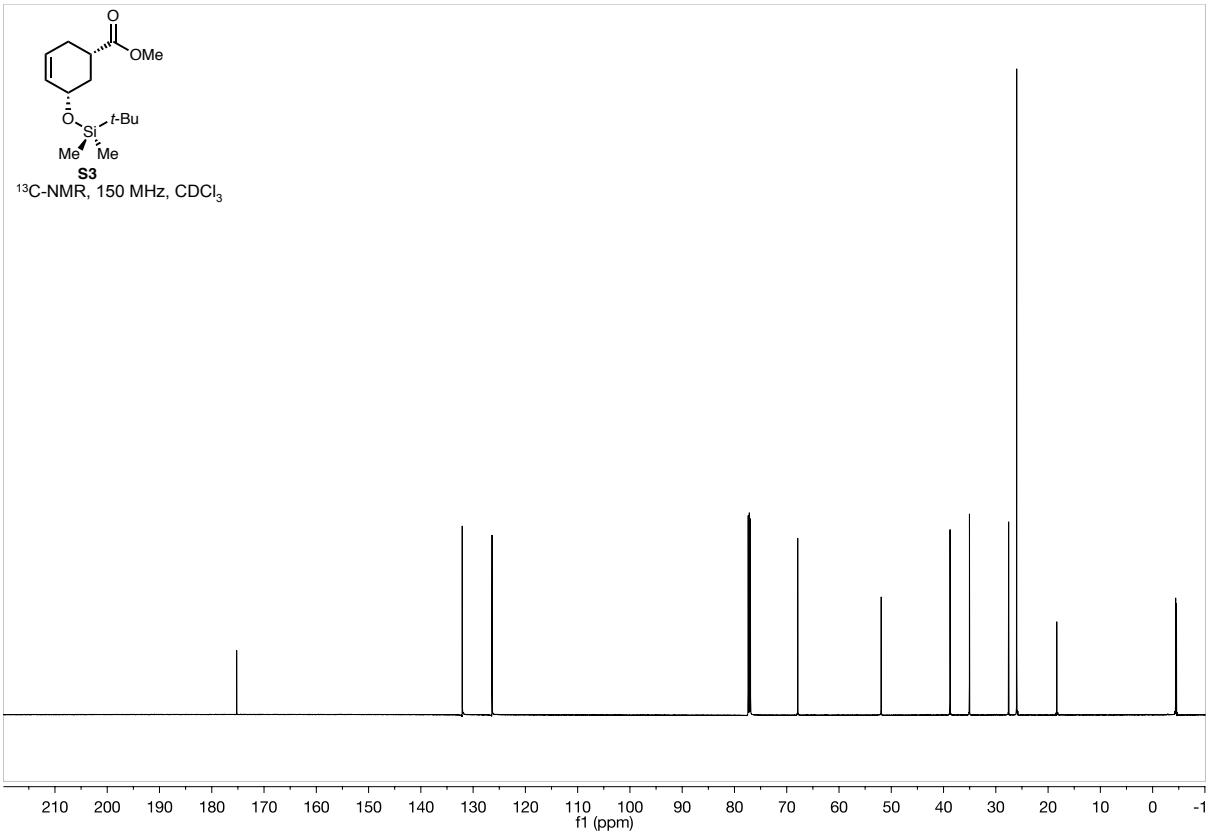
Signal 1: MWD1 D, Sig=230,4 Ref=360,100

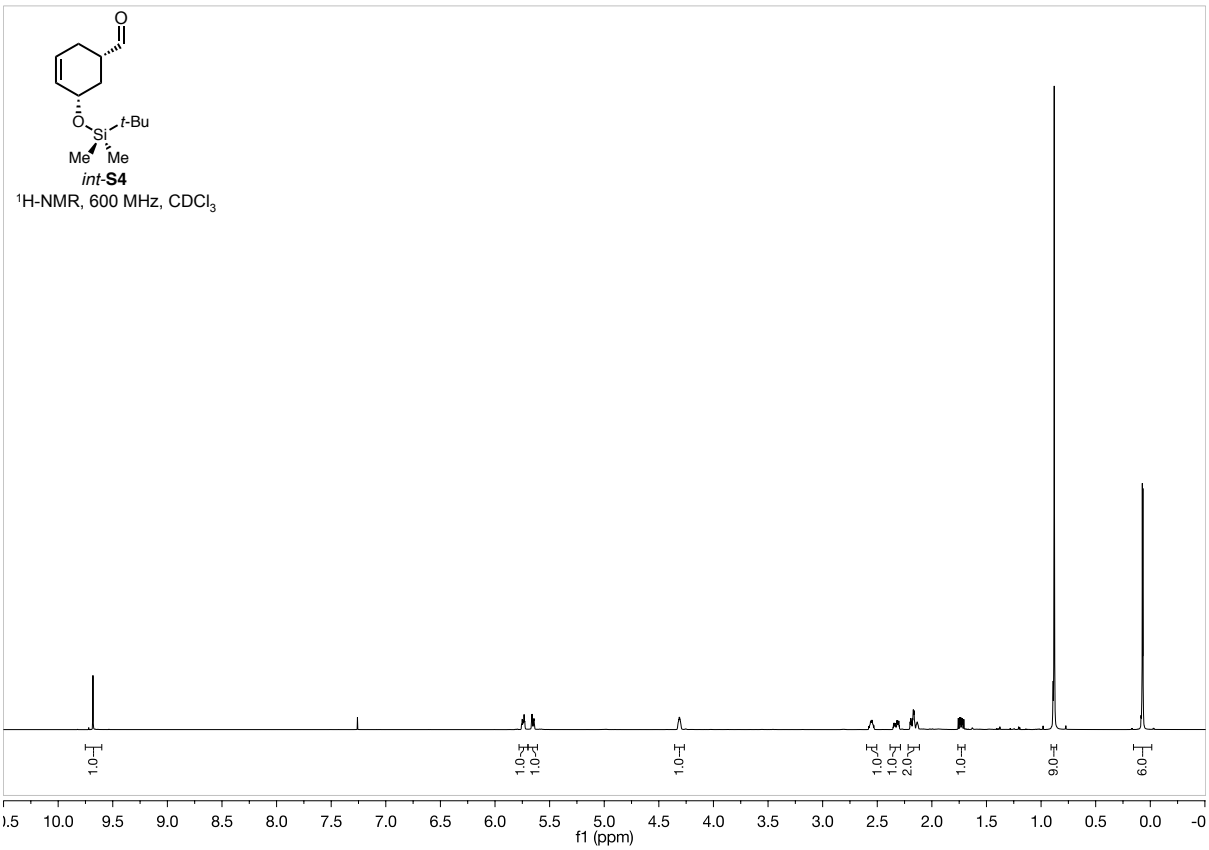
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.149	VV R	0.7863	7.78345e4	1483.26697	65.6802
2	27.590	BB	0.8685	1.54185e4	272.33075	13.0108
3	34.617	BV	0.9768	331.58023	4.78275	0.2798
4	46.000	VV E	1.1751	2057.71411	23.46449	1.7364
5	47.503	VB R	1.6078	2.02358e4	172.59964	17.0759
6	56.029	BV	1.0476	195.08275	2.24090	0.1646
7	75.596	BB	1.7375	2432.06641	17.28587	2.0523

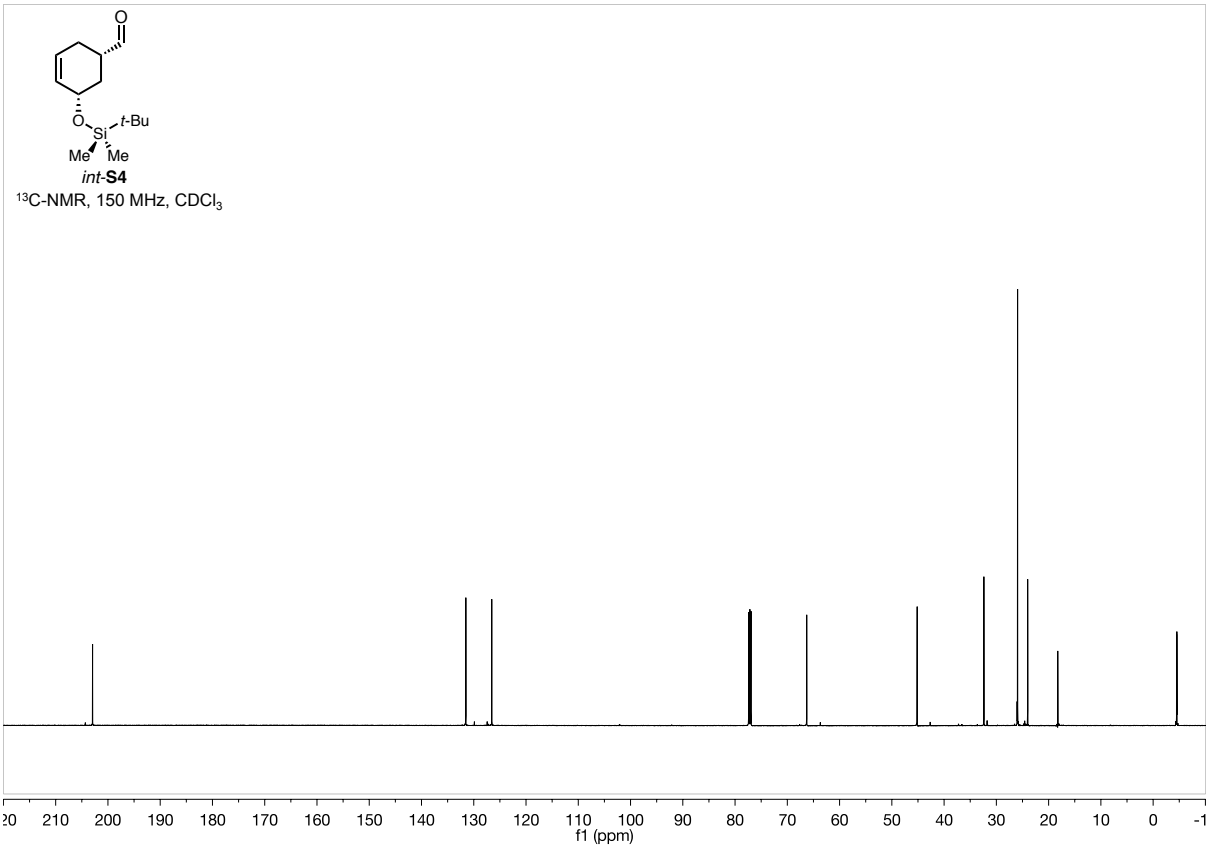
Supplementary Figures S48: HPLC traces of crude reaction; a) control reaction, b) doped reaction.

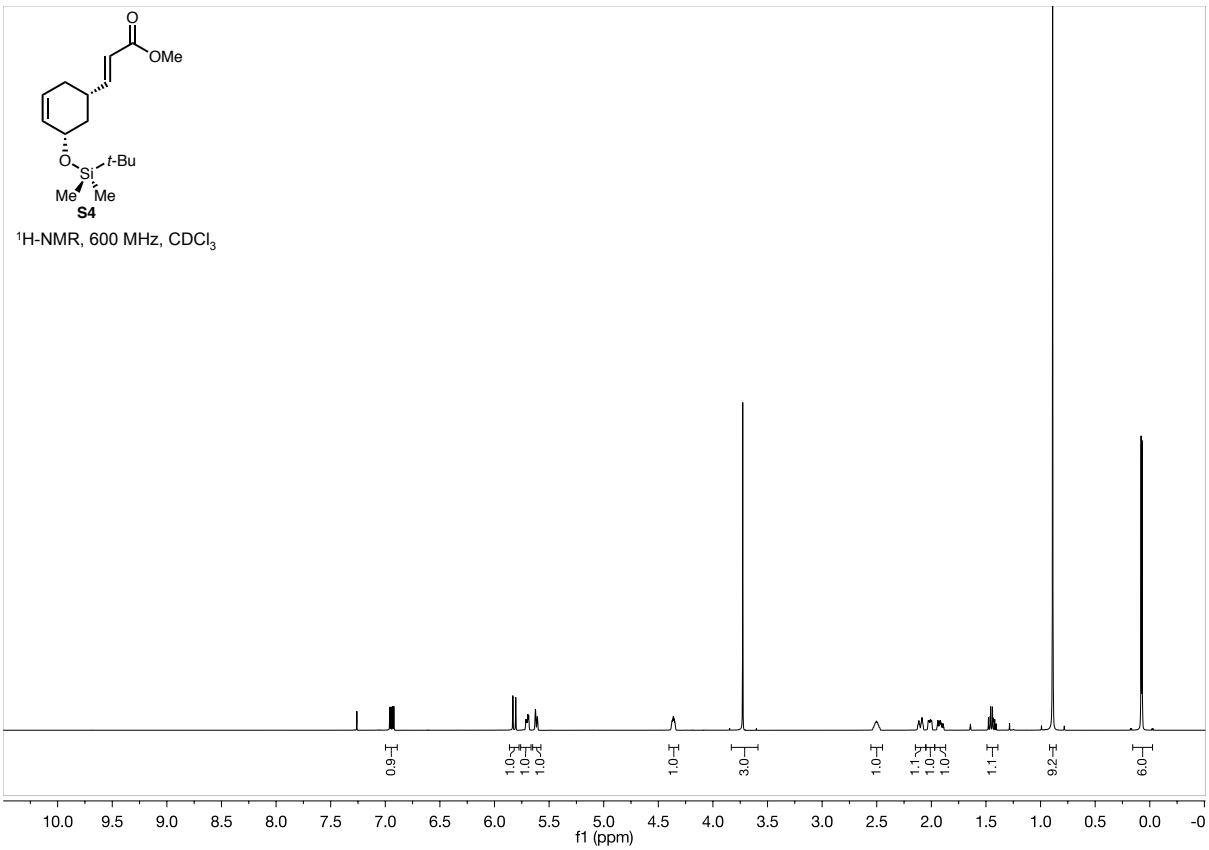
1.5 Catalog of Nuclear Magnetic Resonance Spectra



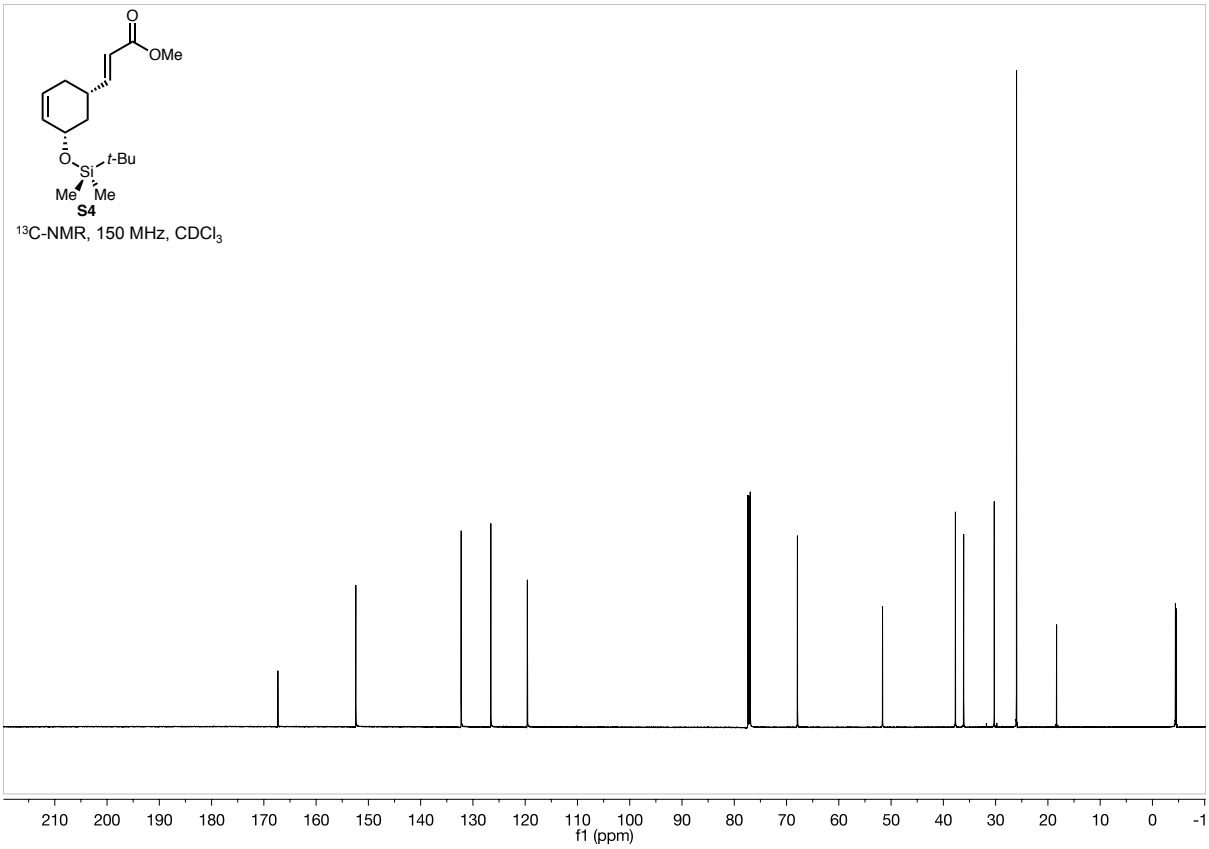



O
O
Si
t-Bu
Me
Me
int-S4
1H-NMR, 600 MHz, CDCl3
1.0
1.0
1.0
1.0
1.0
2.0
1.0
9.0
6.0
f1 (ppm)

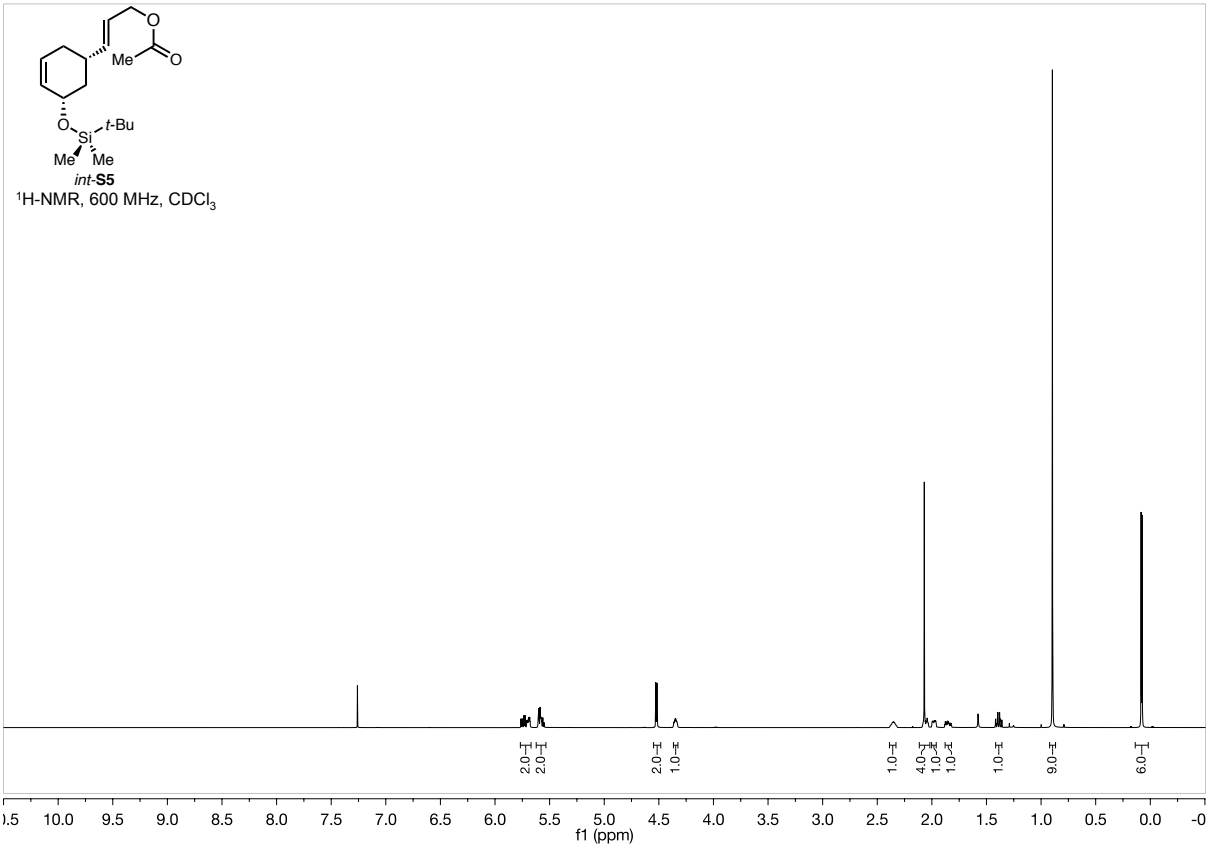

O
O
Si
t-Bu
Me
Me
int-S4
13C-NMR, 150 MHz, CDCl3
f1 (ppm)

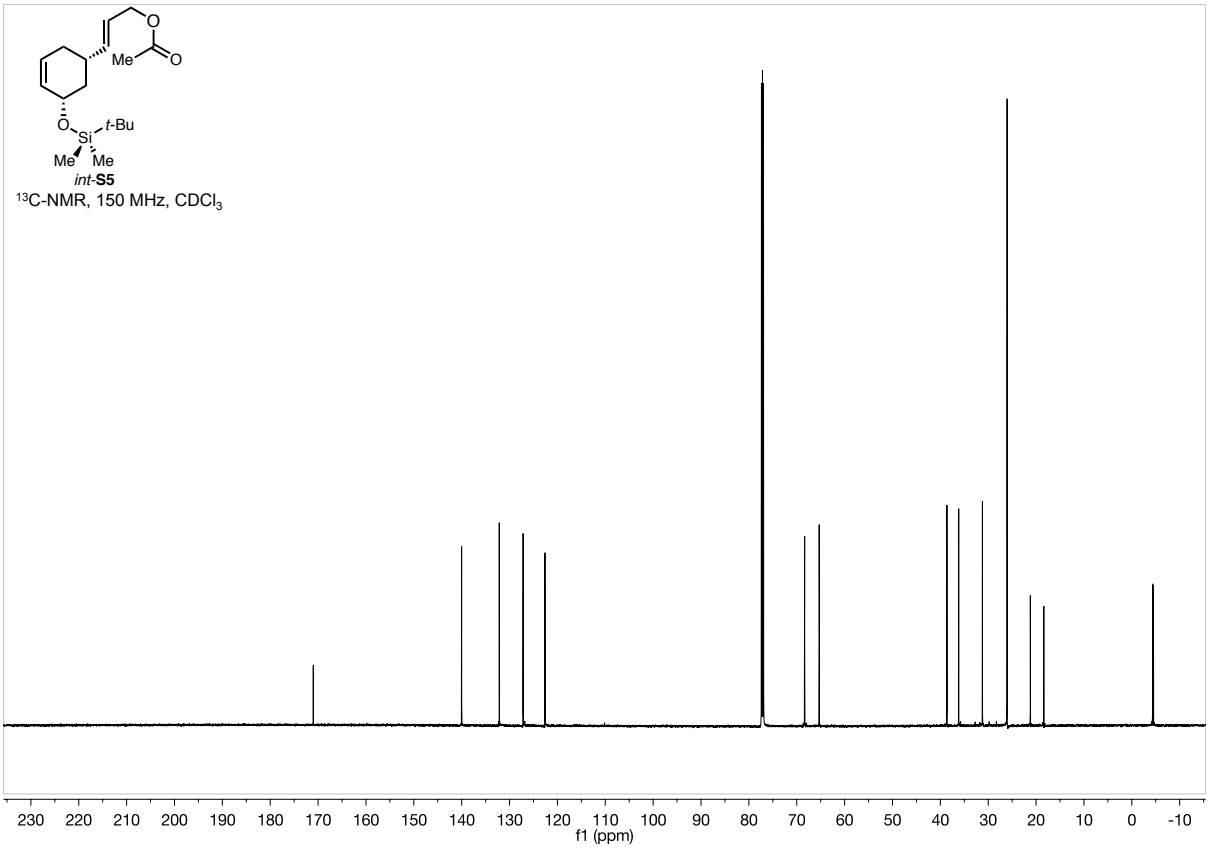


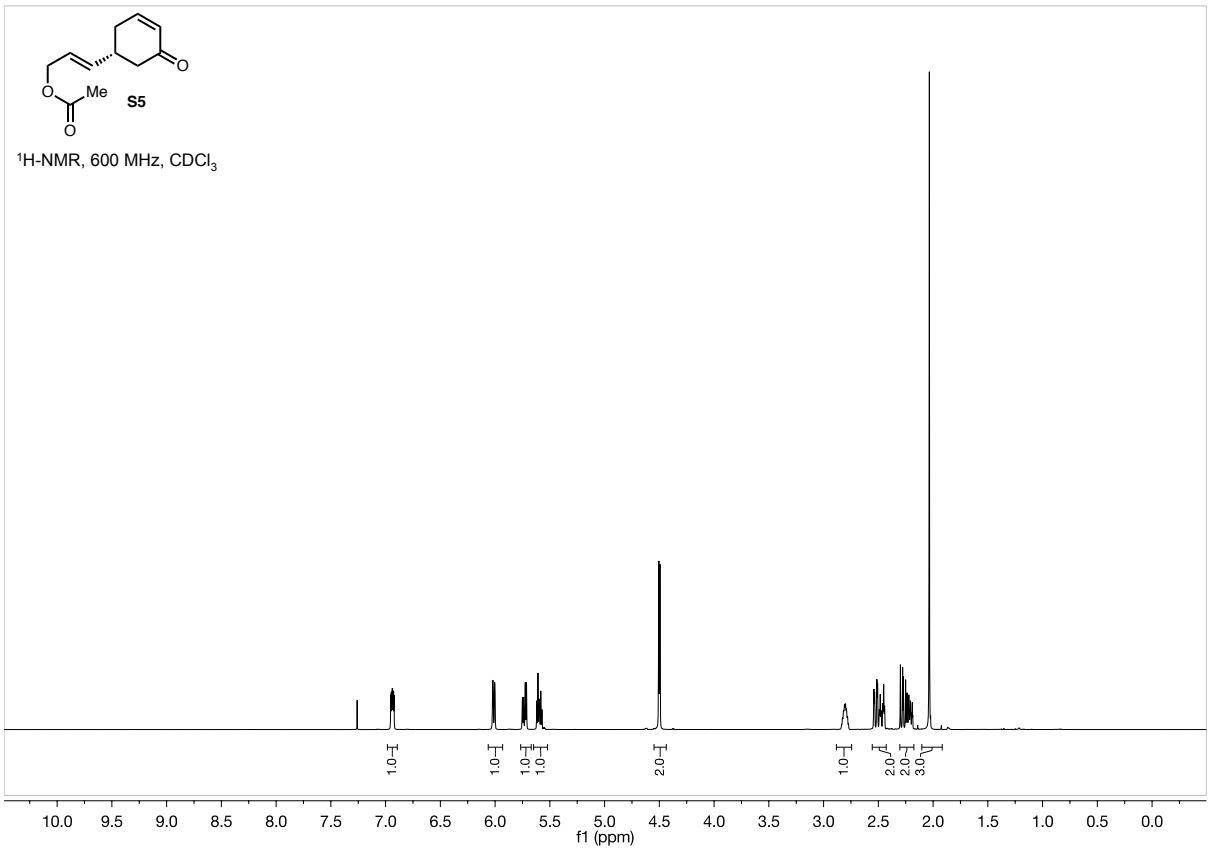
^{1}H-NMR, 600 MHz, $CDCl_3$

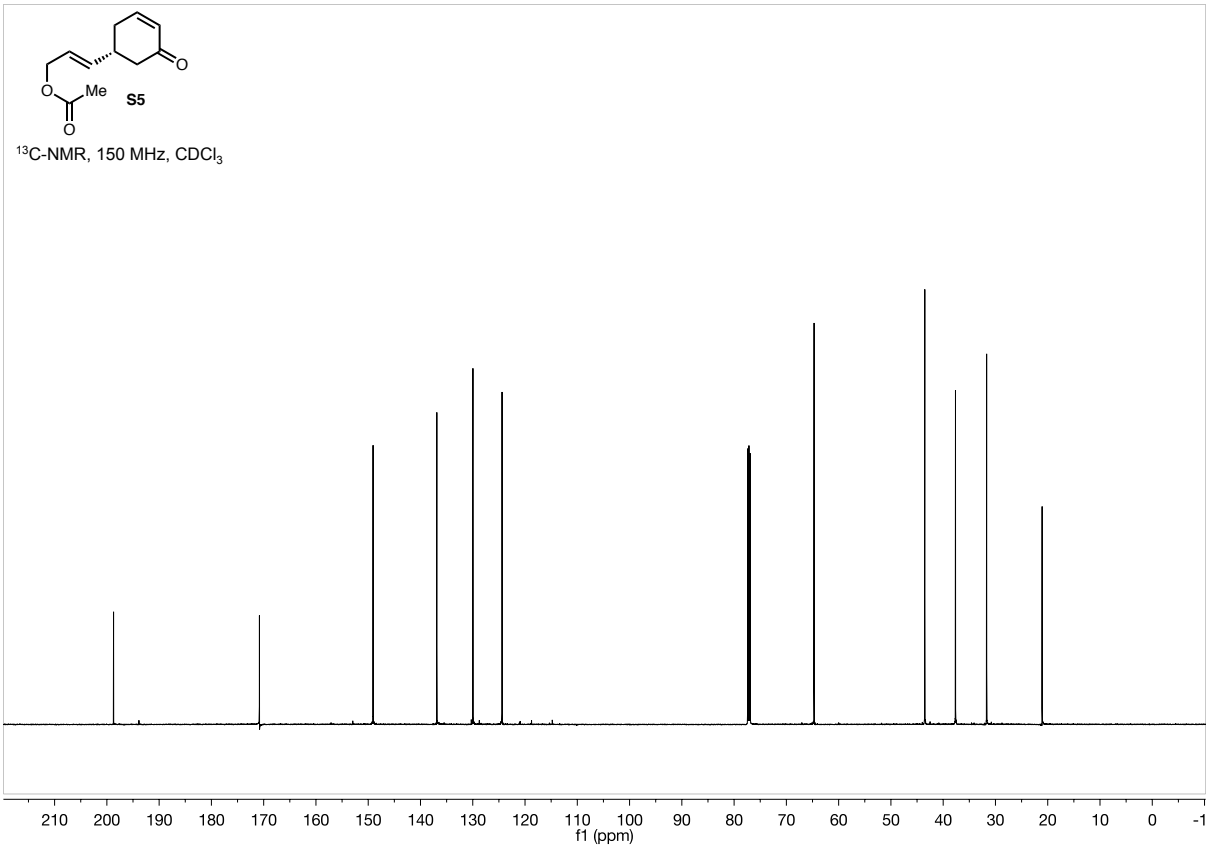


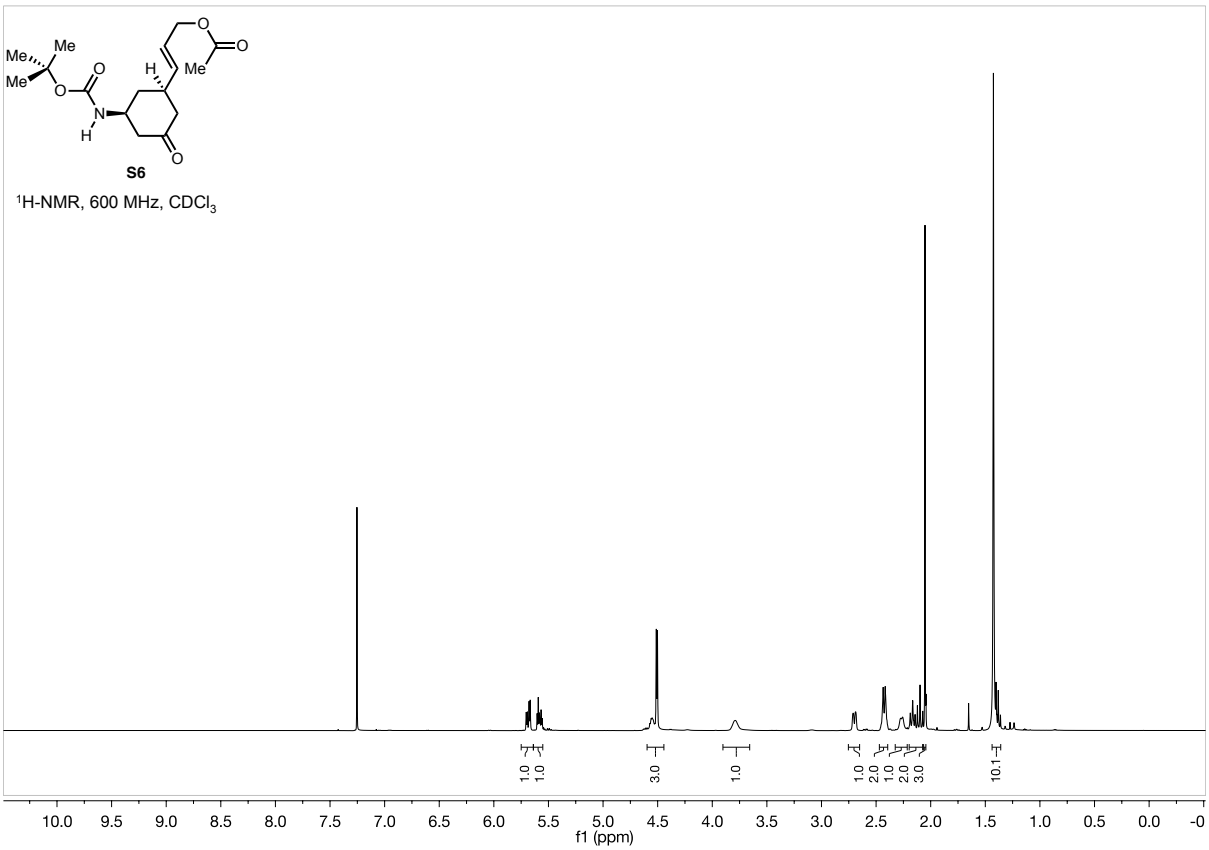
^{13}C-NMR, 150 MHz, $CDCl_3$

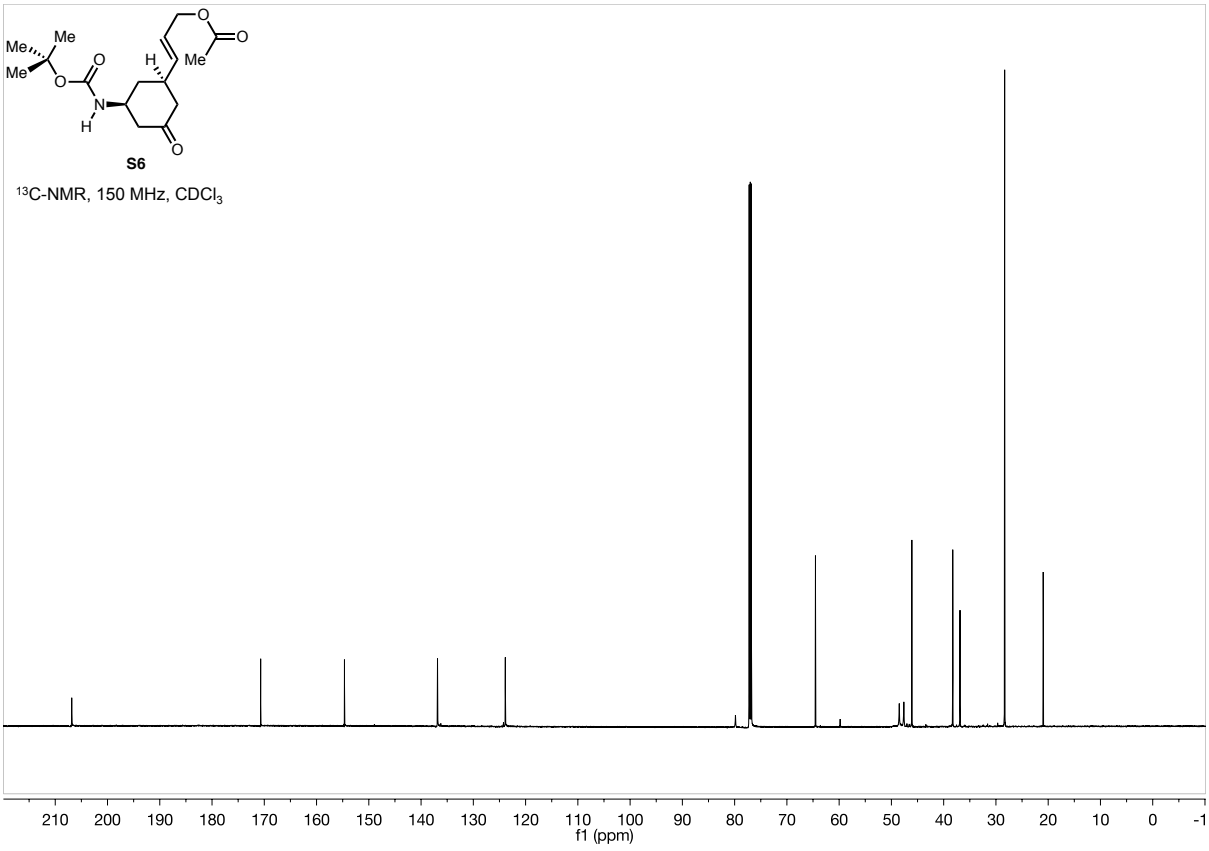

Me
O
O
O
Si
t-Bu
Me
Me
int-S5
1H-NMR, 600 MHz, CDCl3
2.0
2.0
2.0
1.0
1.0
4.0
1.0
1.0
9.0
6.0
f1 (ppm)

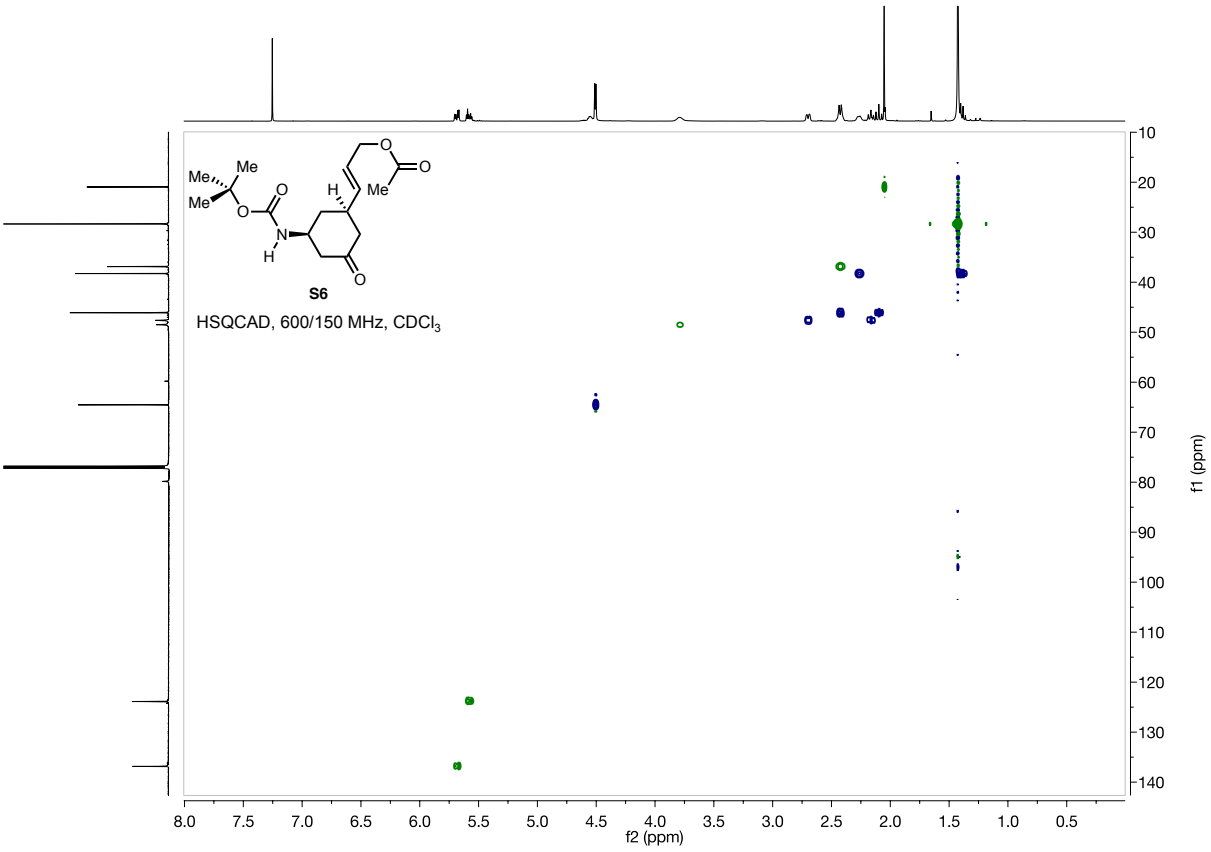

Me
O
O
O
Si
t-Bu
Me
Me
int-S5
13C-NMR, 150 MHz, CDCl3
f1 (ppm)

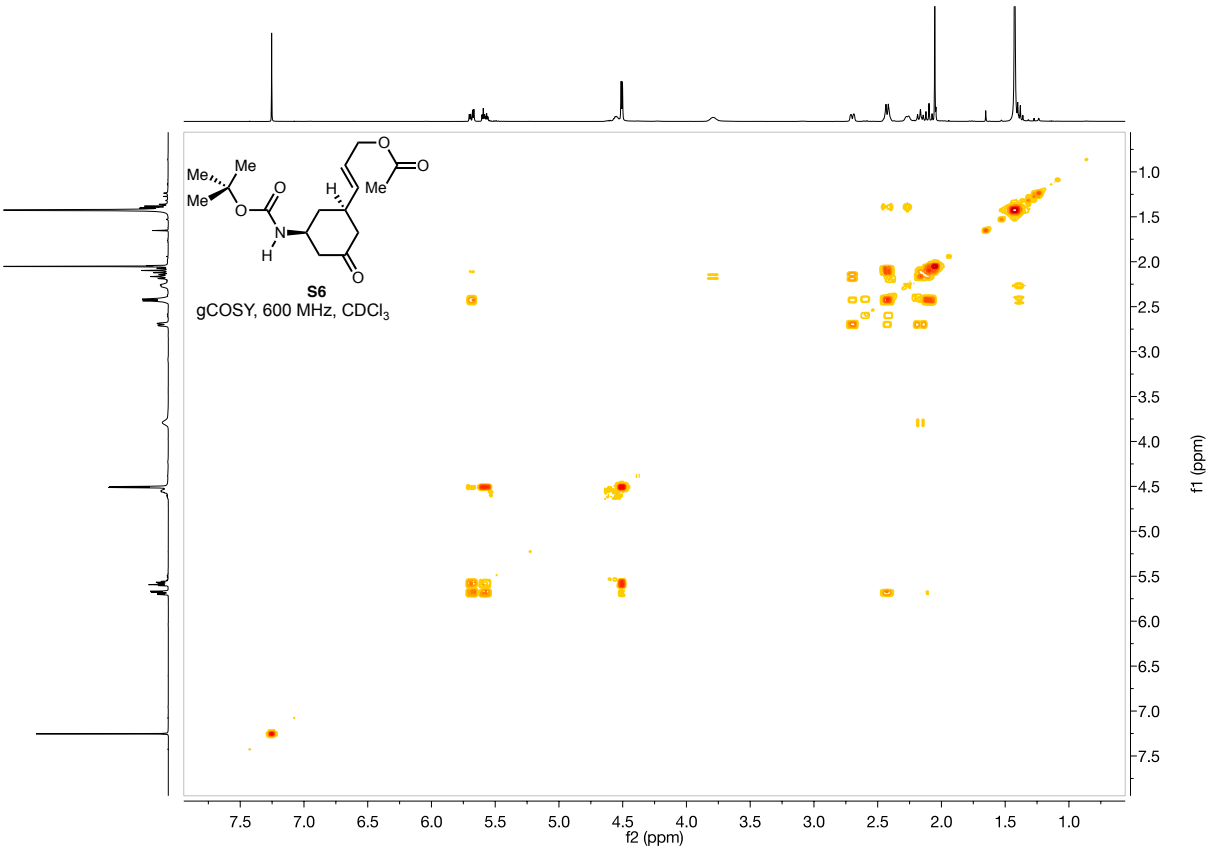

S5
^{1}H-NMR, 600 MHz, $CDCl_3$
1.0
1.0
1.0
1.0
2.0
1.0
2.0
2.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

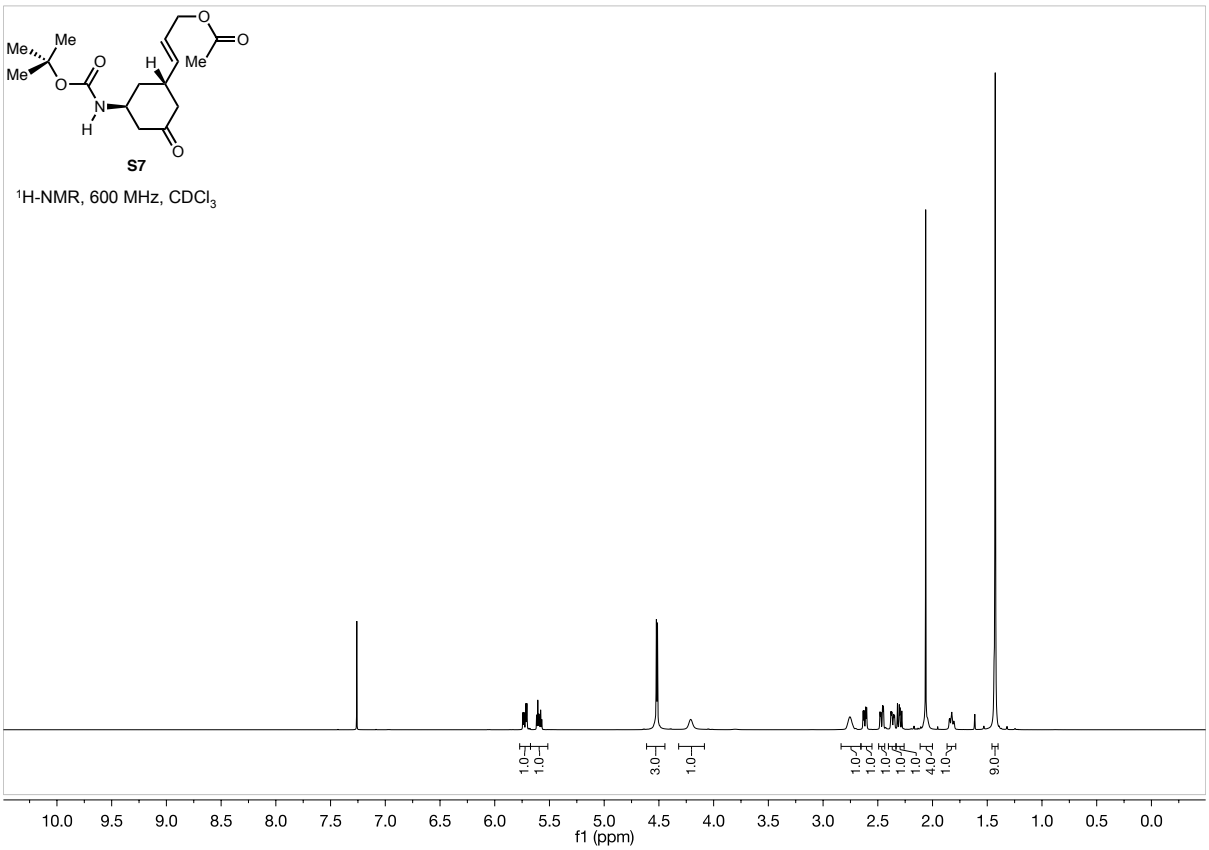

S5
^{13}C-NMR, 150 MHz, $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

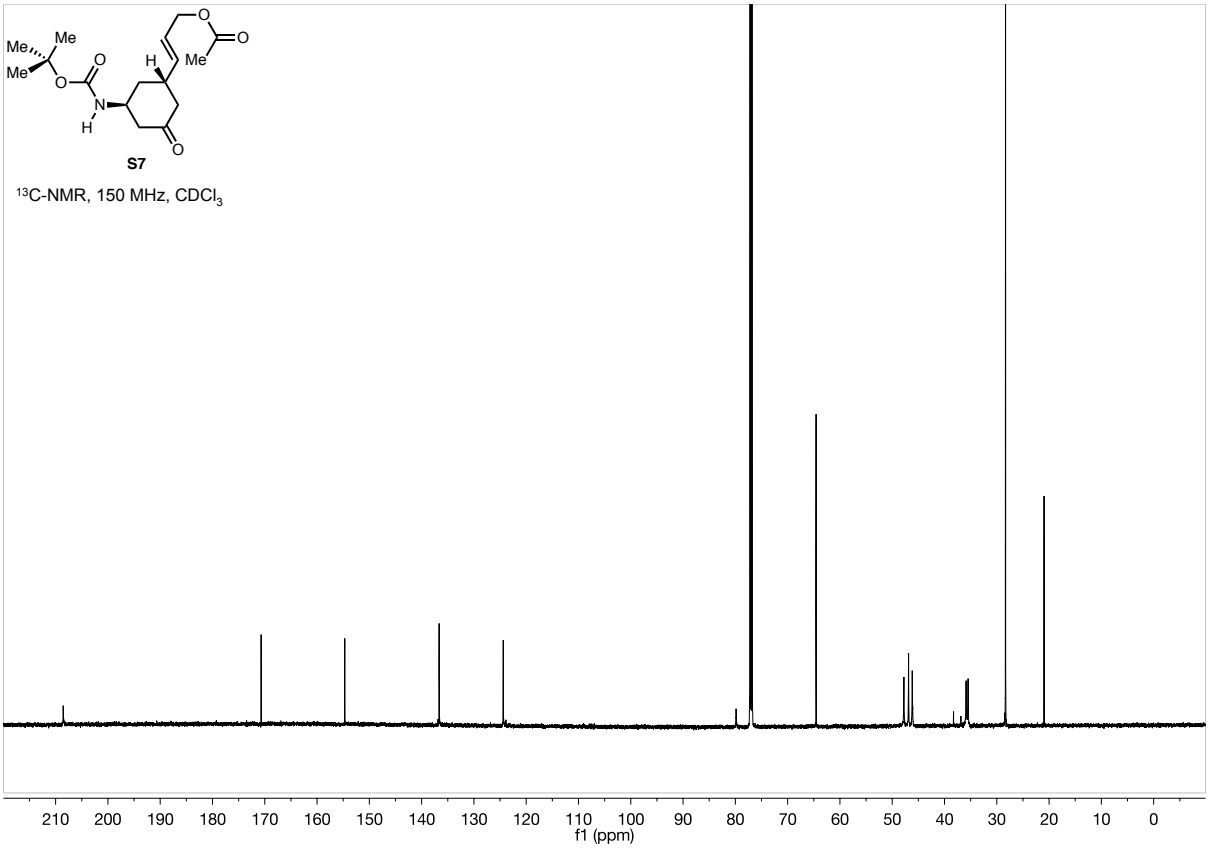

S6
^{1}H-NMR, 600 MHz, $CDCl_3$
1.0
1.0
3.0
1.0
1.0
2.0
1.0
2.0
3.0
10.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

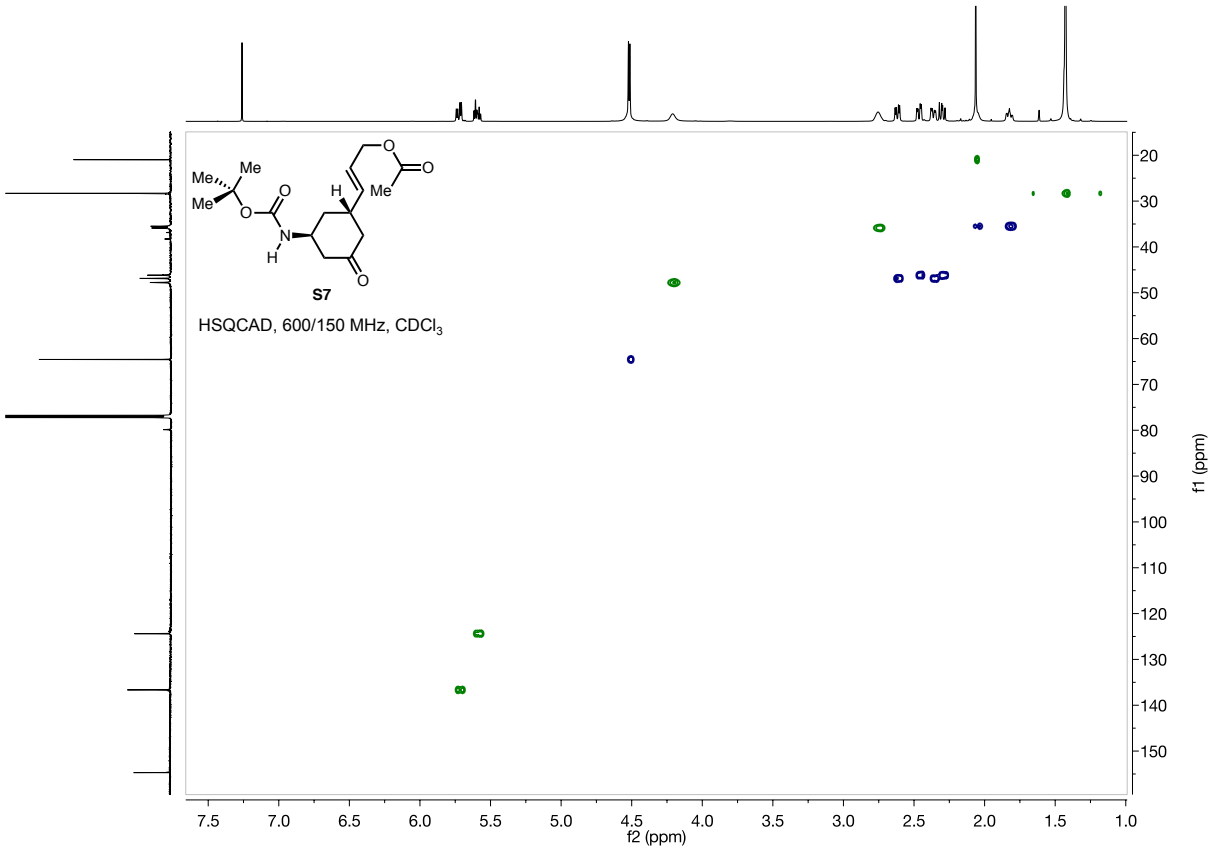

S6
^{13}C-NMR, 150 MHz, $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

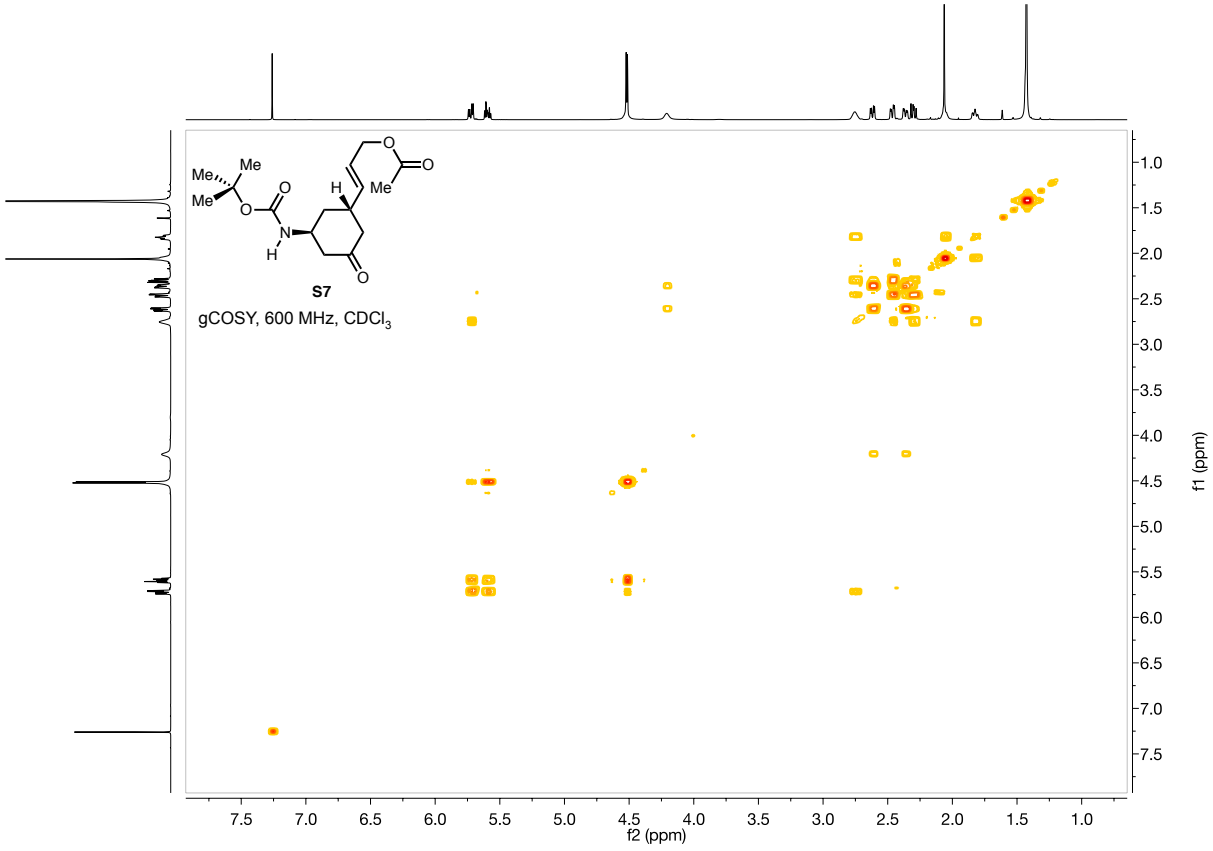

S6
HSQCAD, 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

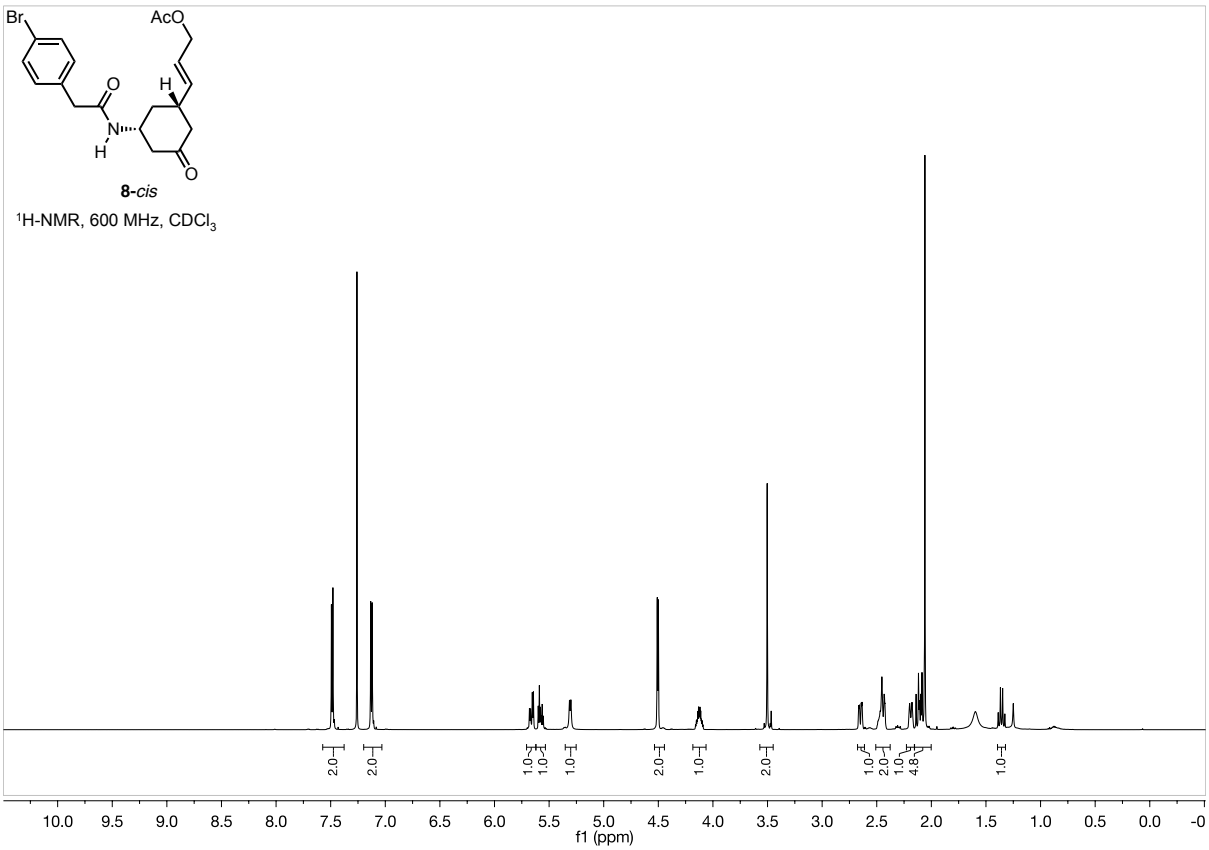

S6
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

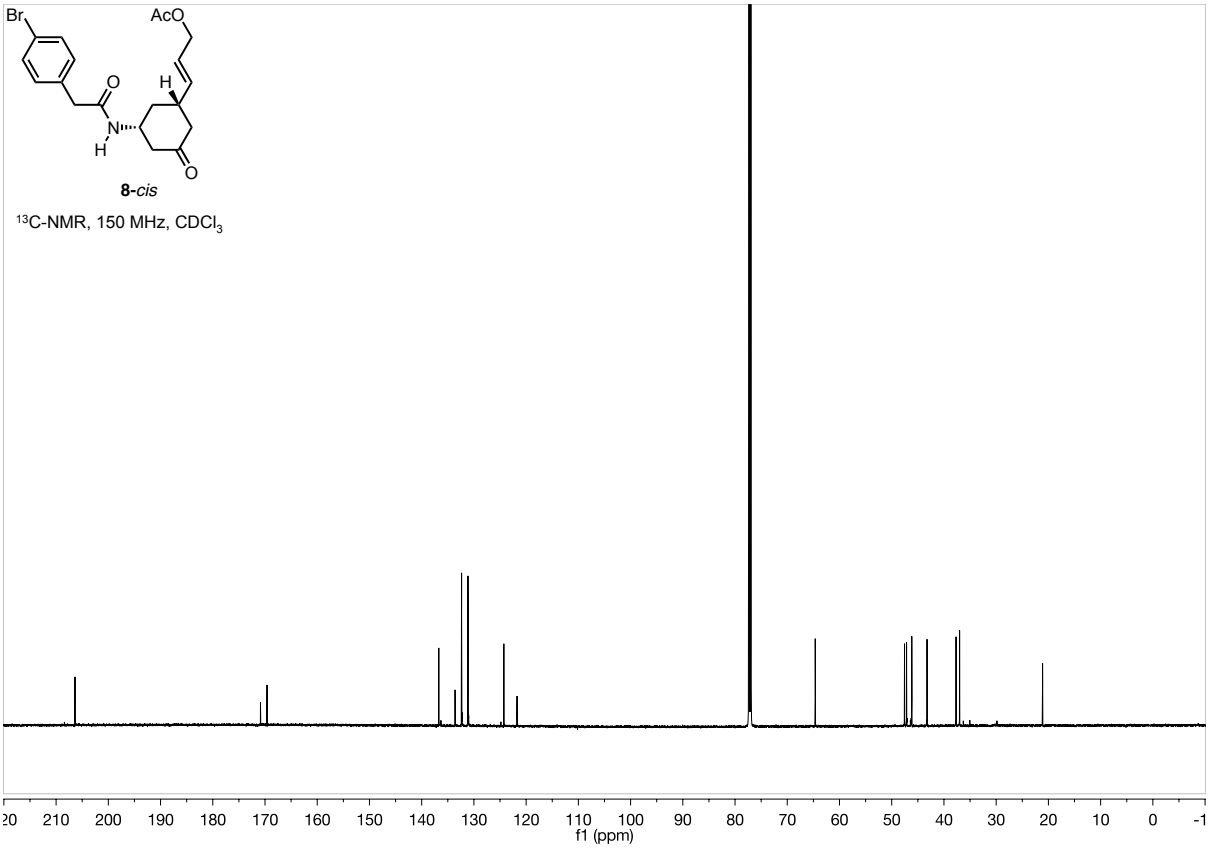

S7
1H-NMR, 600 MHz, CDCl3
1.0
1.0
3.0
1.0
1.0
1.0
1.0
1.0
4.0
1.0
9.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

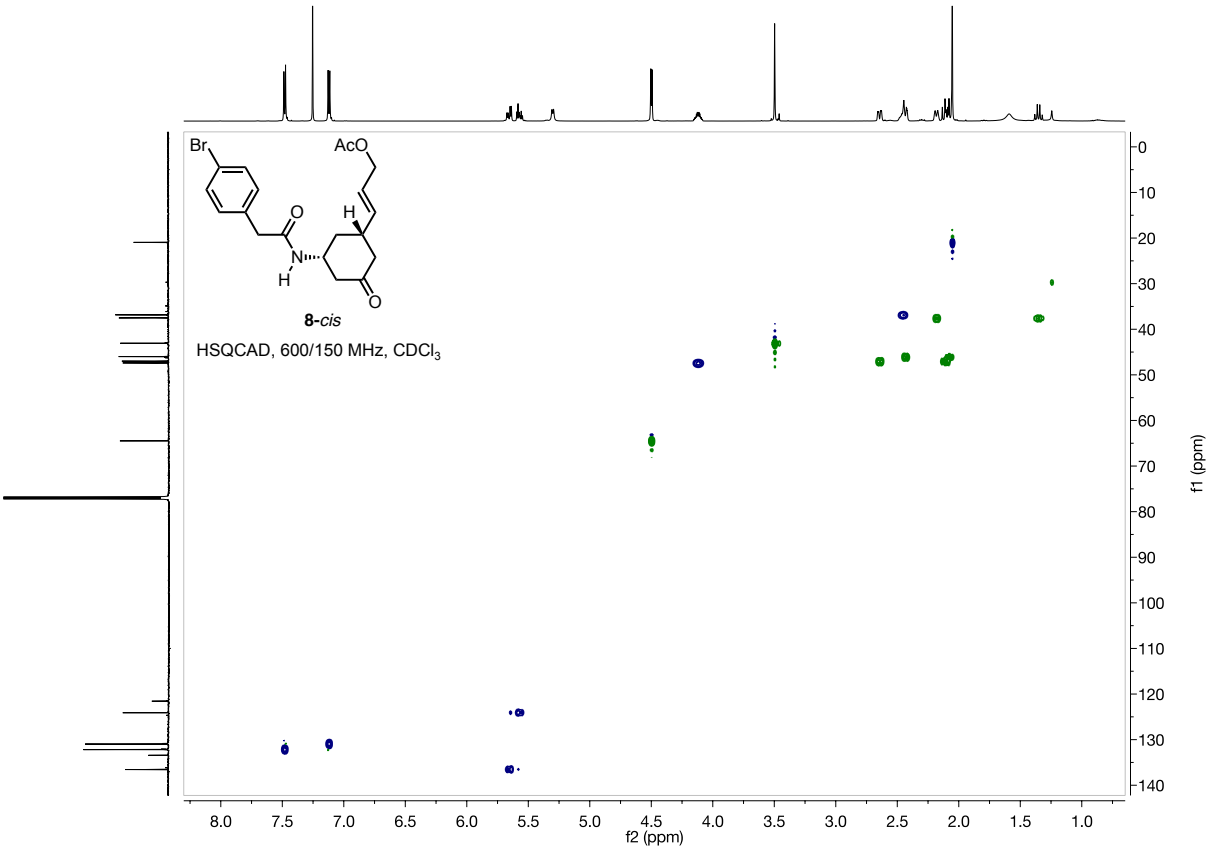

S7
13C-NMR, 150 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

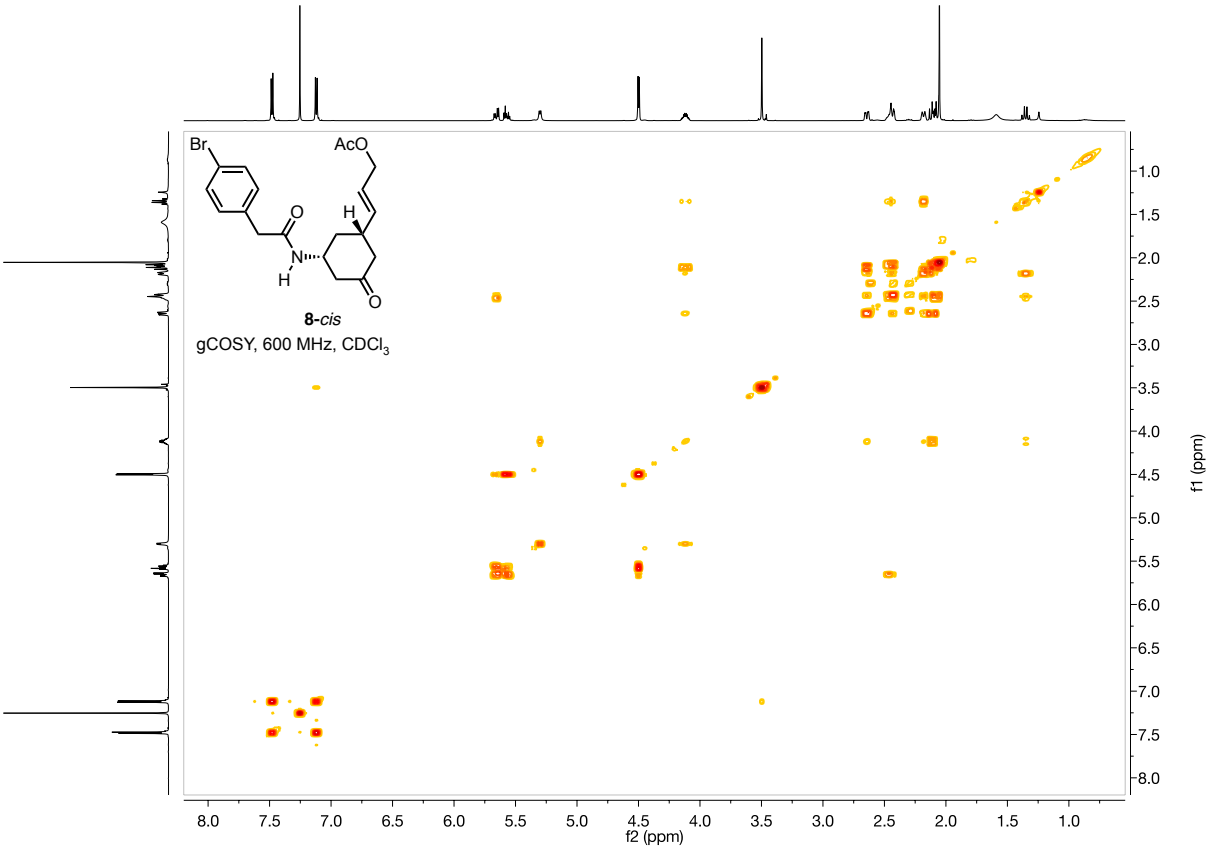

S7
HSQCAD, 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

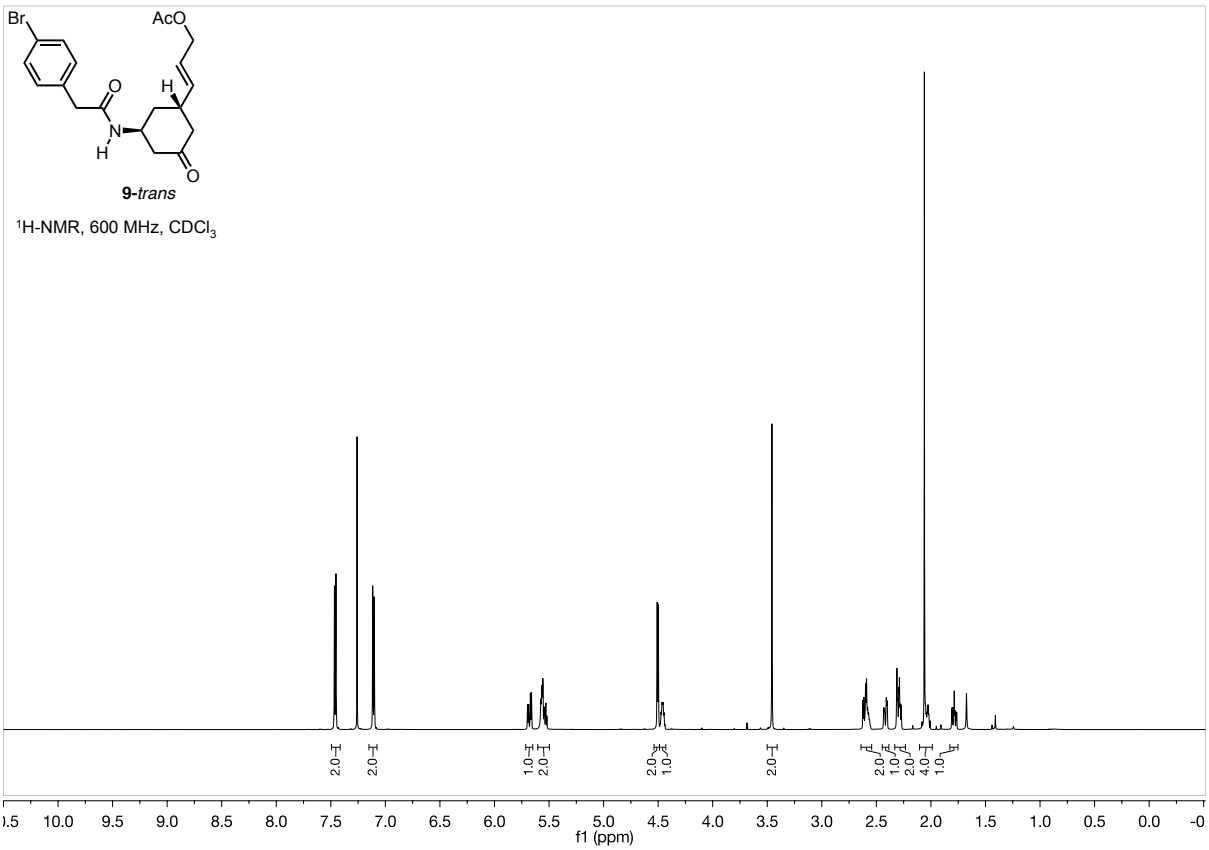

S7
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

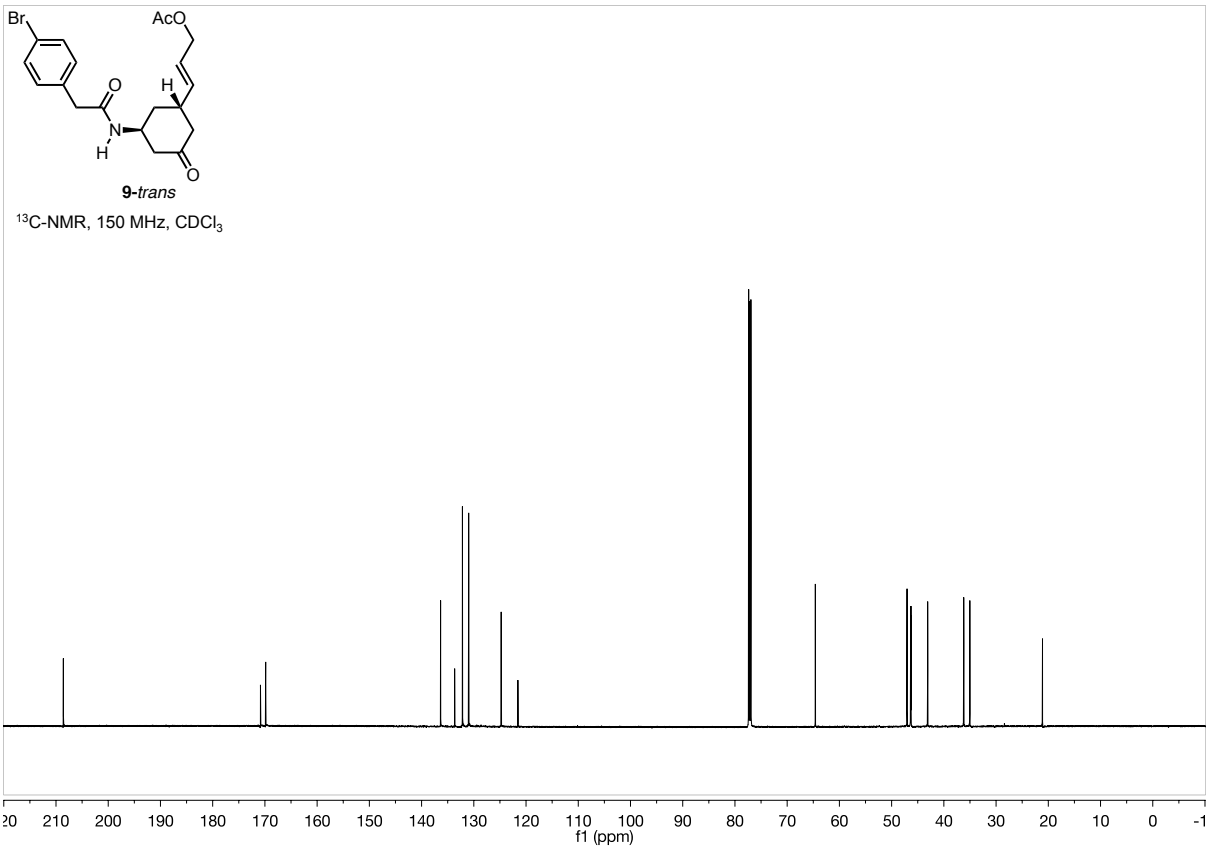

Br
AcO
O
H
N
H
O
8-*cis*
^{1}H-NMR, 600 MHz, $CDCl_3$
2.0
2.0
1.0
1.0
1.0
2.0
1.0
2.0
1.0
2.0
1.0
4.8
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

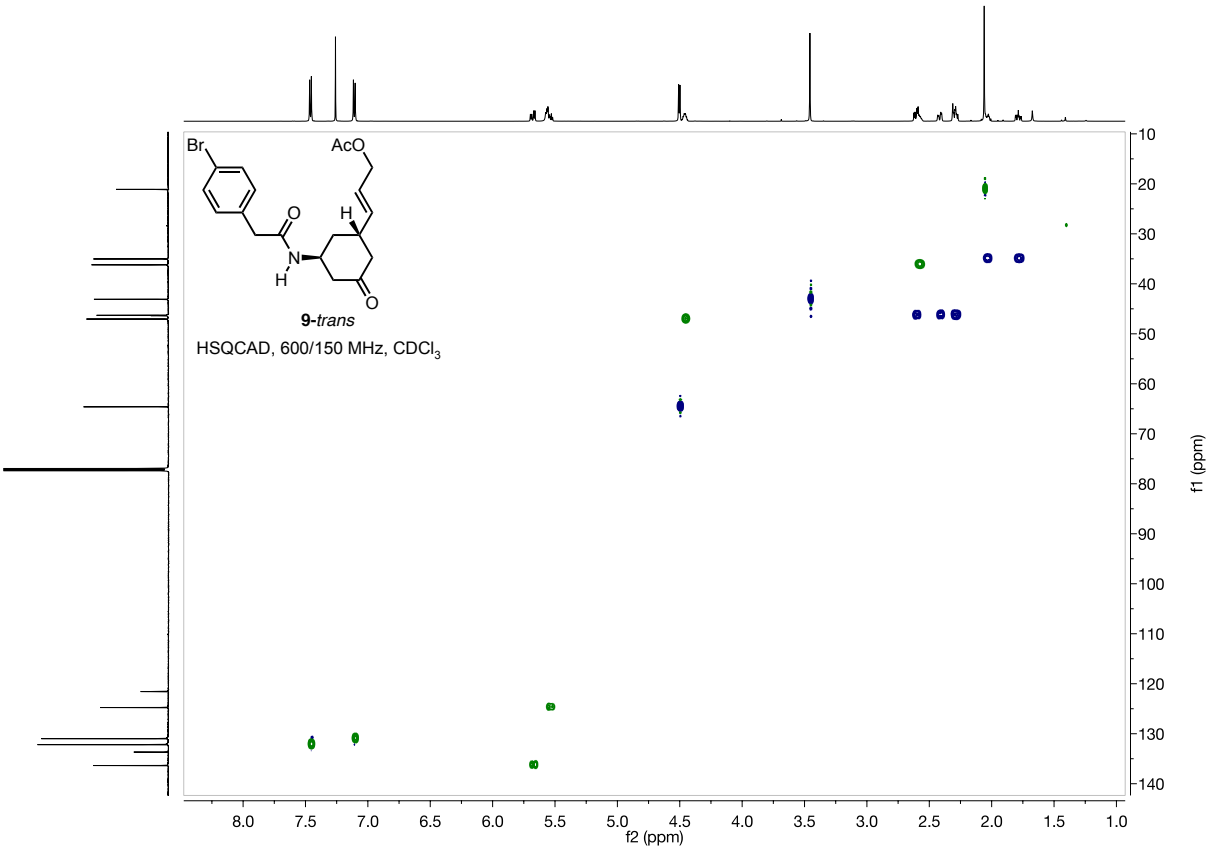

Br
AcO
O
H
N
H
O
8-*cis*
^{13}C-NMR, 150 MHz, $CDCl_3$
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

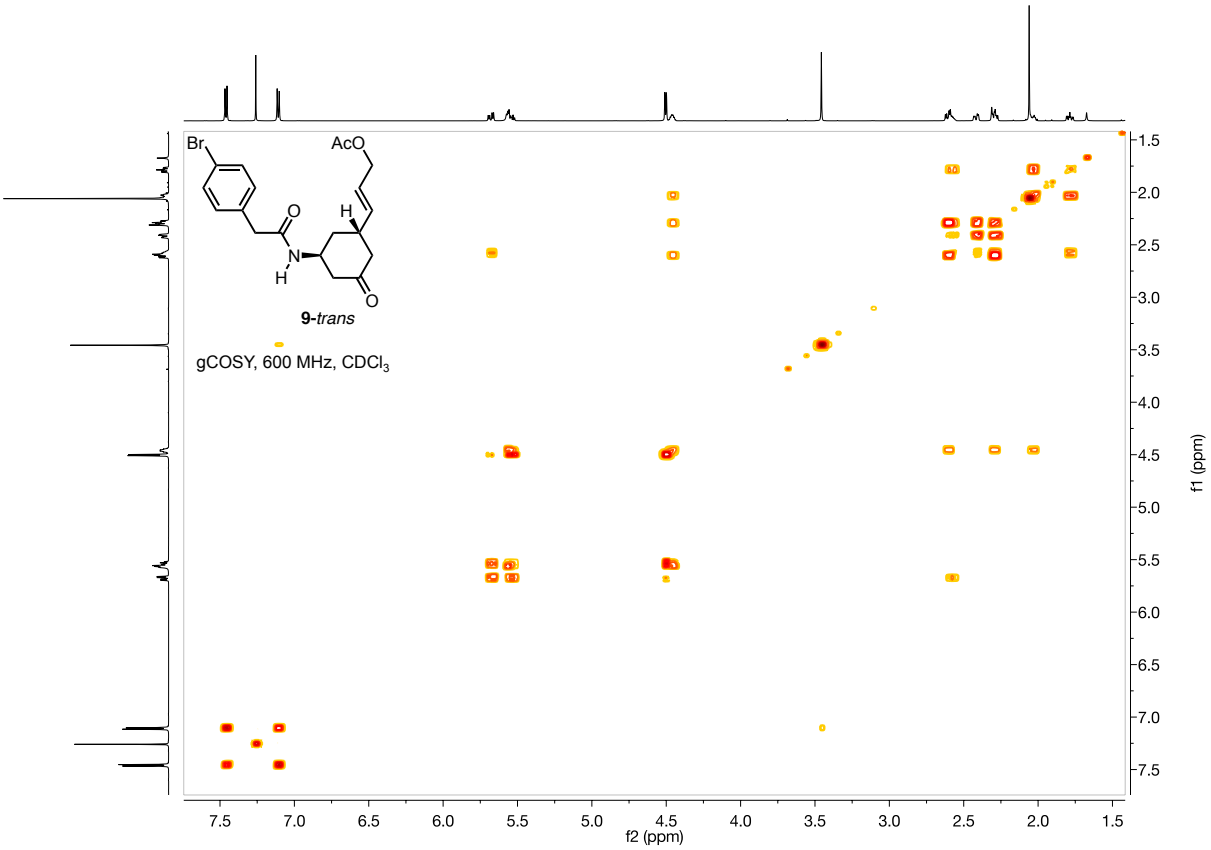

Br
AcO
O
H
N
H
O
8-cis
HSQCAD, 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

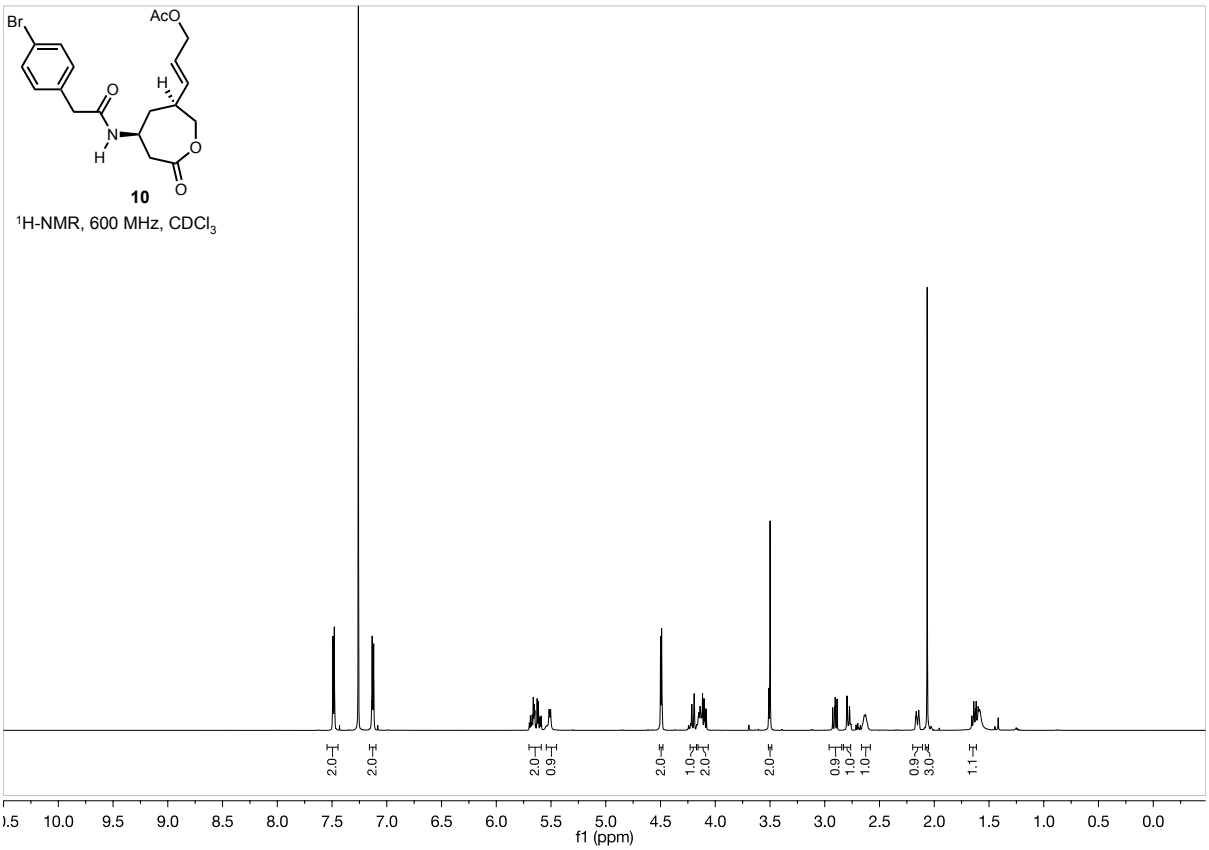

Br
AcO
O
H
N
H
O
8-cis
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

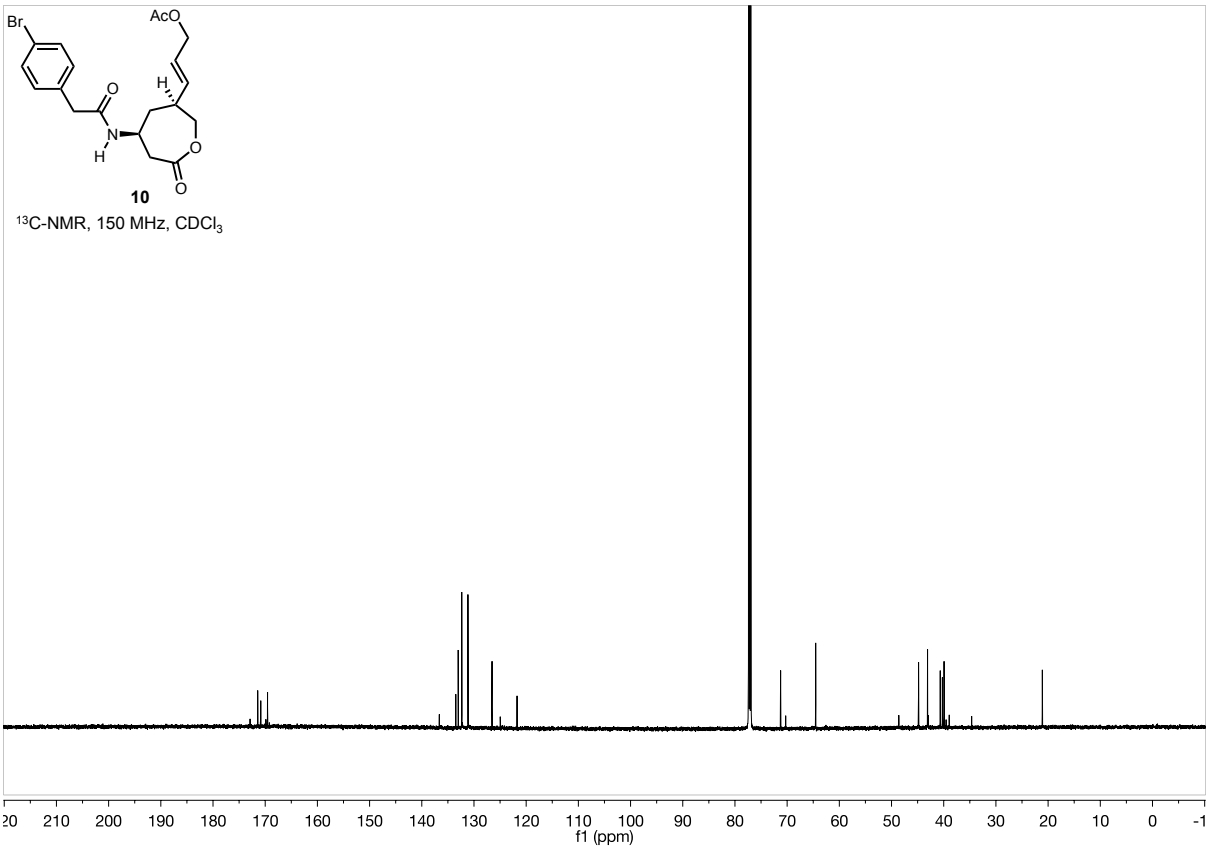

Br
AcO
O
H
N
H
O
9-trans
1H-NMR, 600 MHz, CDCl3
2.0
2.0
1.0
2.0
2.0
1.0
2.0
2.0
1.0
2.0
4.0
1.0
f1 (ppm)

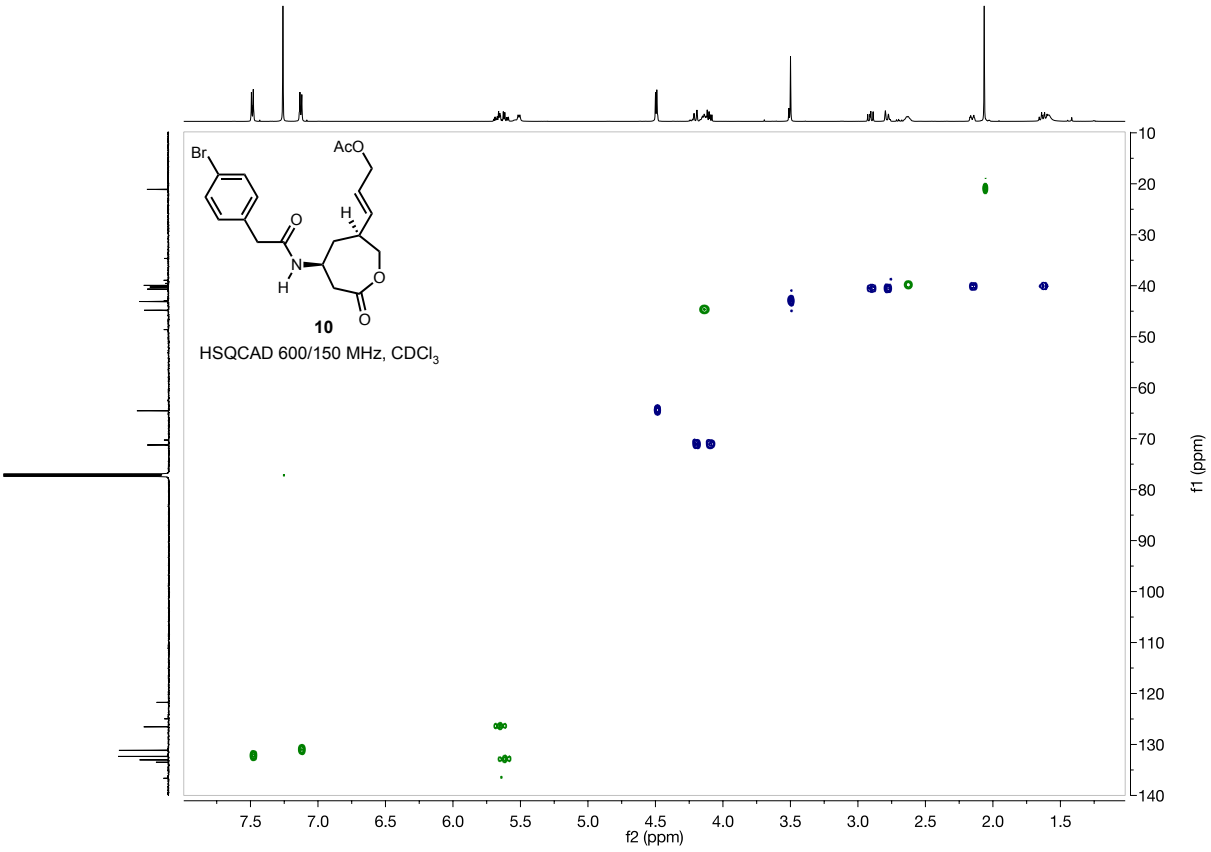

Br
AcO
O
H
N
H
O
9-trans
13C-NMR, 150 MHz, CDCl3
f1 (ppm)

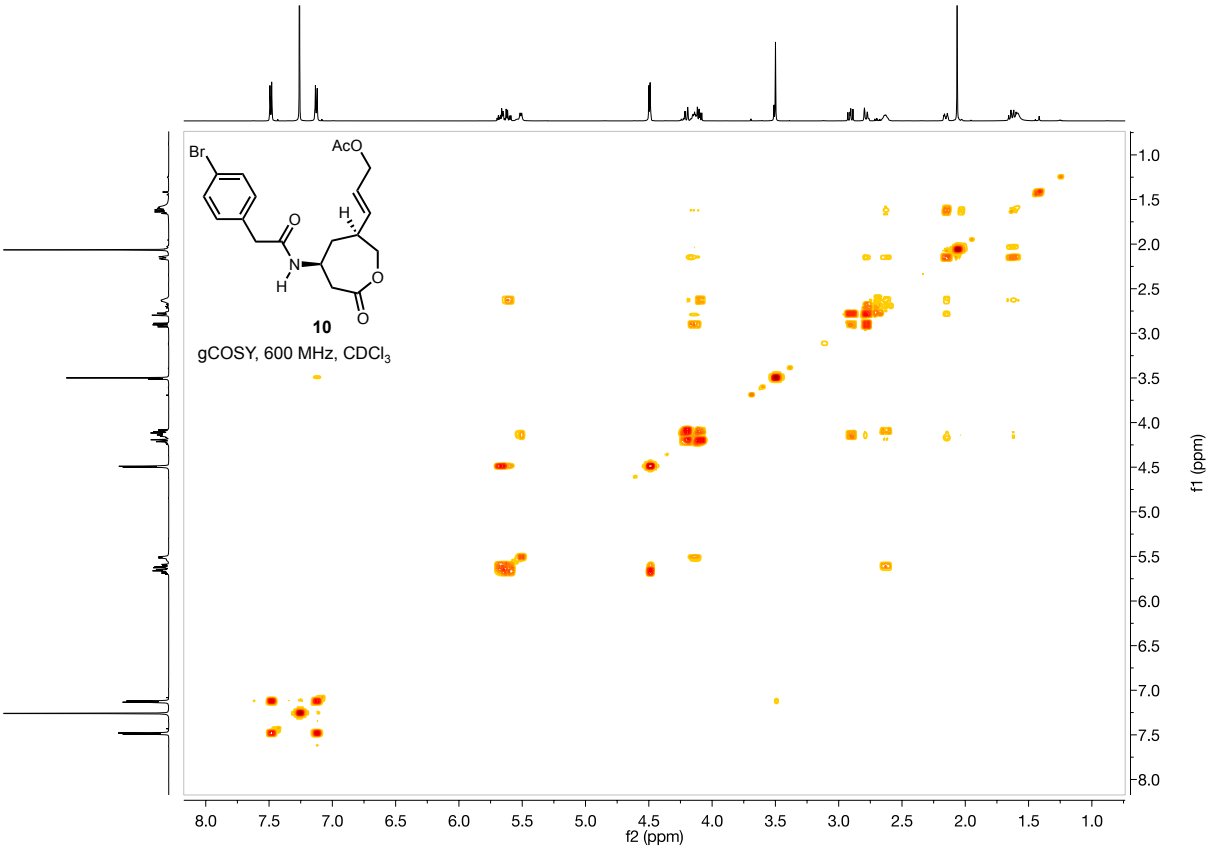

Br
AcO
O
H
N
H
O
9-trans
HSQCAD, 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

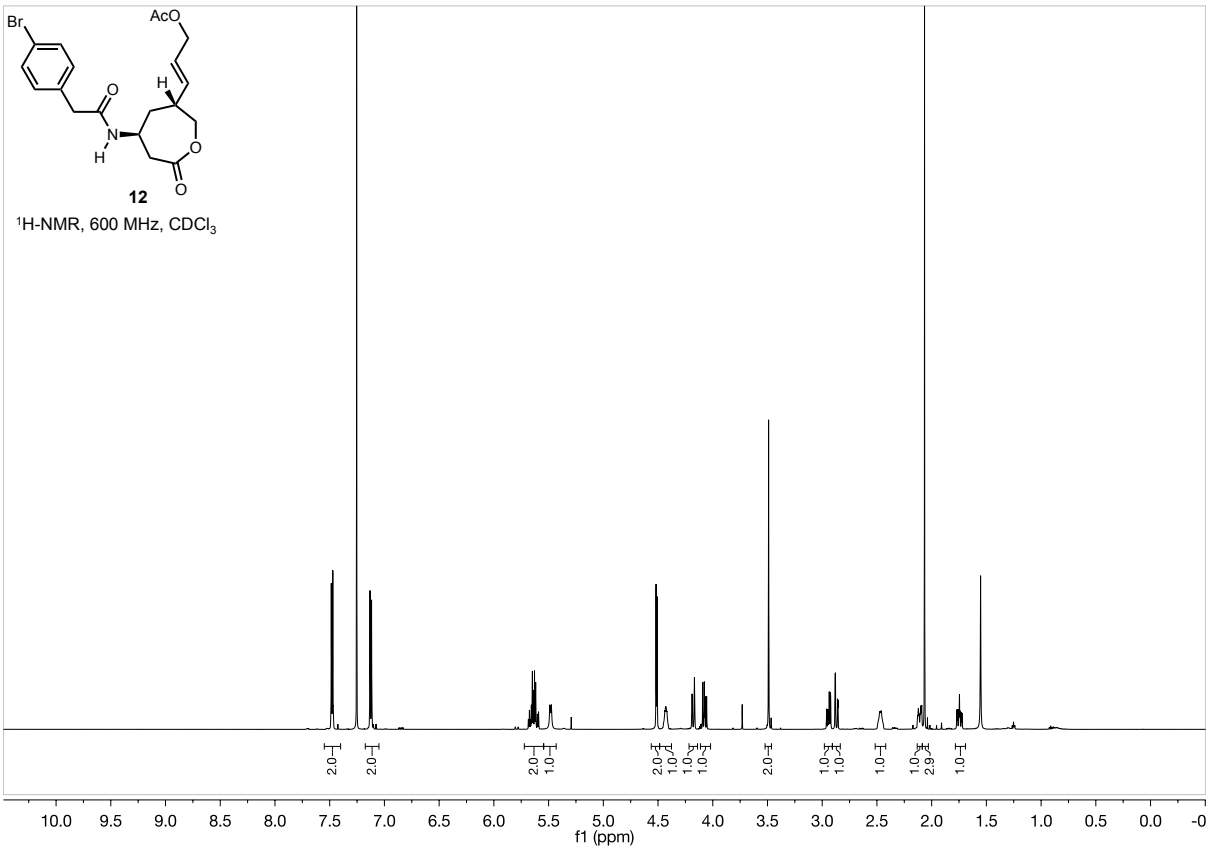

Br
AcO
O
H
N
H
O
9-trans
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

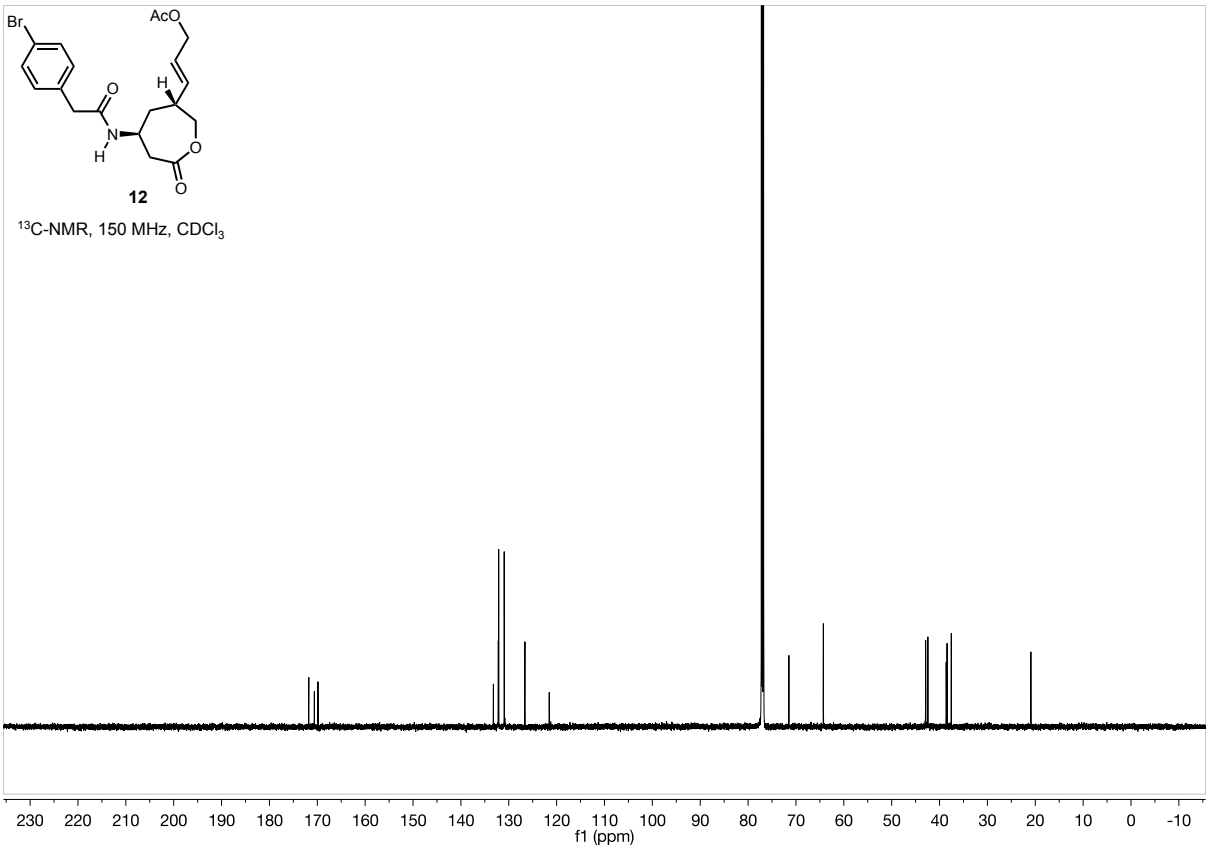

Br
AcO
H
O
N
H
O
O
10
1H-NMR, 600 MHz, CDCl3
2.0
2.0
2.0
0.9
2.0
1.0
2.0
2.0
0.9
1.0
1.0
0.9
3.0
1.1
f1 (ppm)

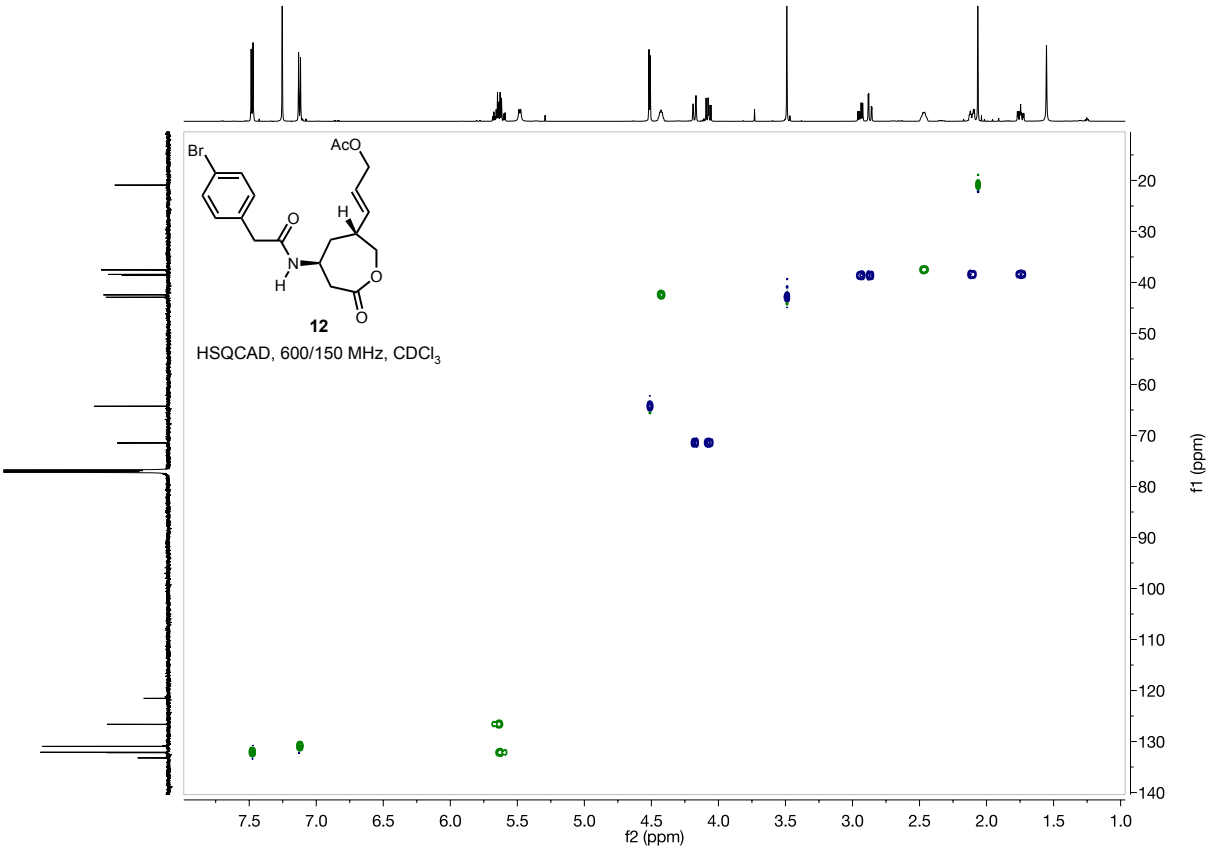

Br
AcO
H
O
N
H
O
O
10
13C-NMR, 150 MHz, CDCl3
f1 (ppm)

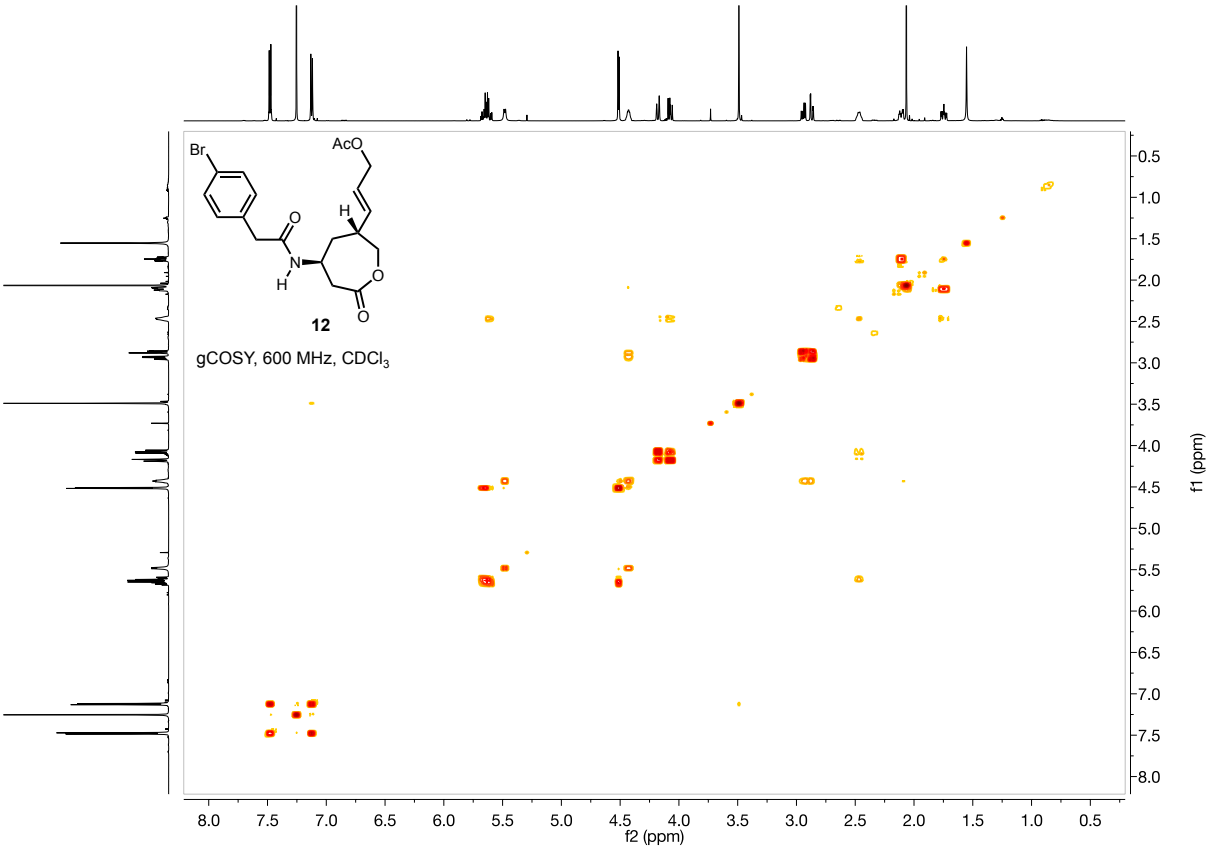

Br
AcO
H
O
N
H
O
O
10
HSQCAD 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

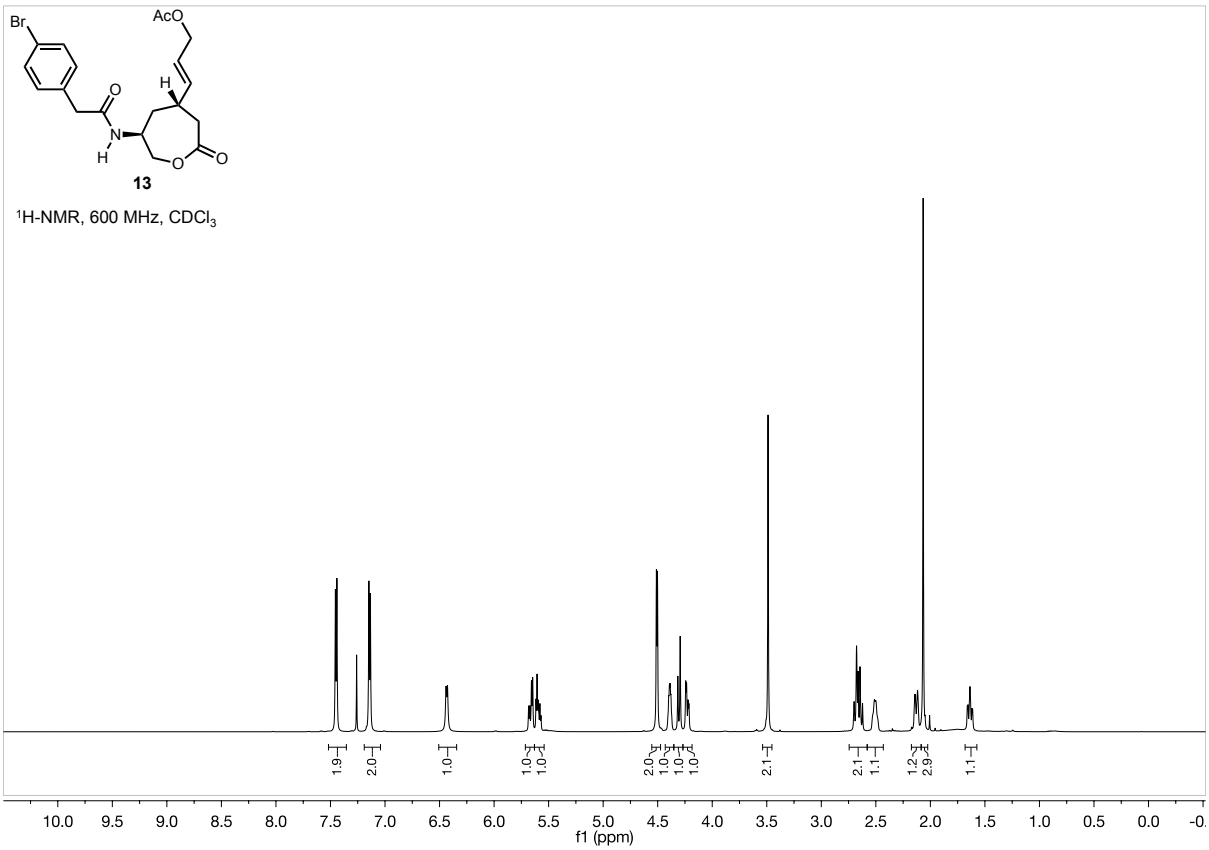

Br
AcO
H
O
N
H
O
O
10
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

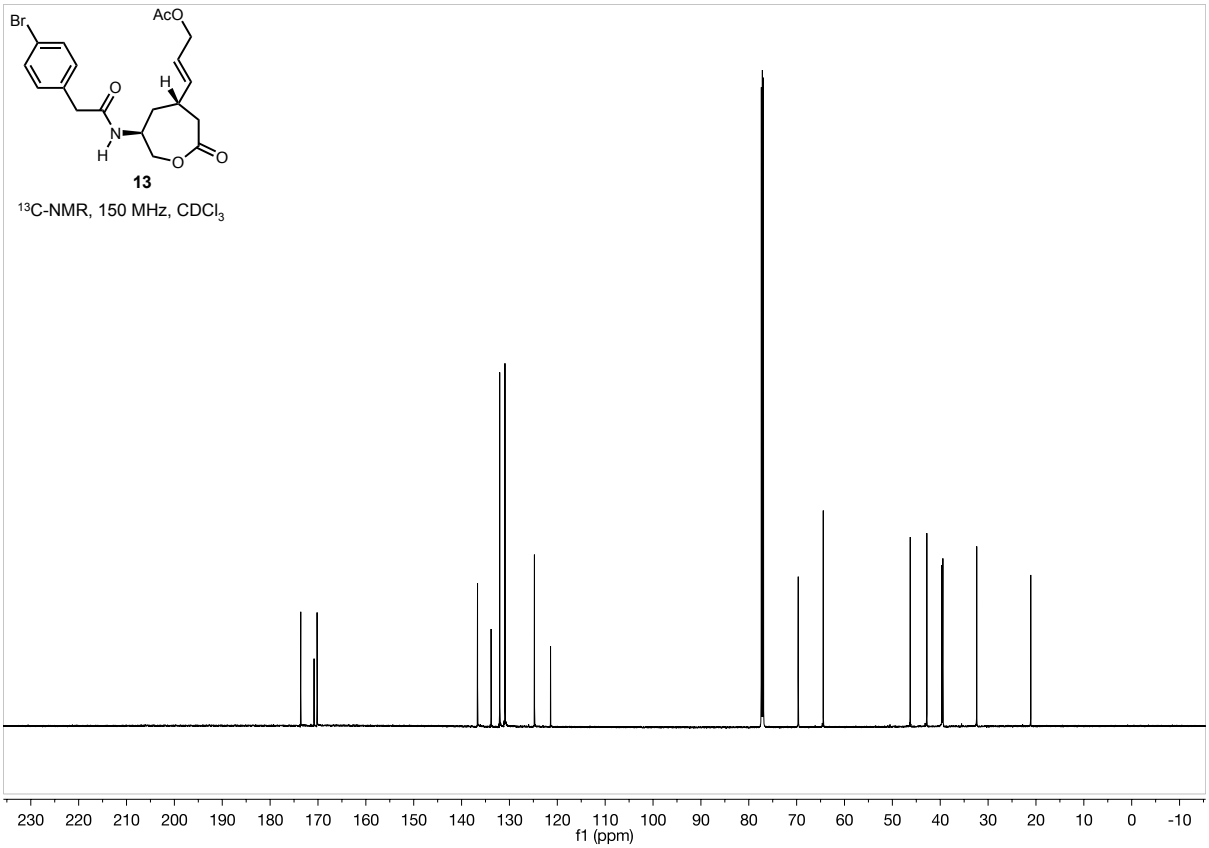

Br
AcO
H
O
N
H
O
O
12
^{1}H-NMR, 600 MHz, $CDCl_3$
2.0
2.0
2.0
1.0
2.0
1.0
1.0
1.0
2.0
1.0
1.0
1.0
2.9
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

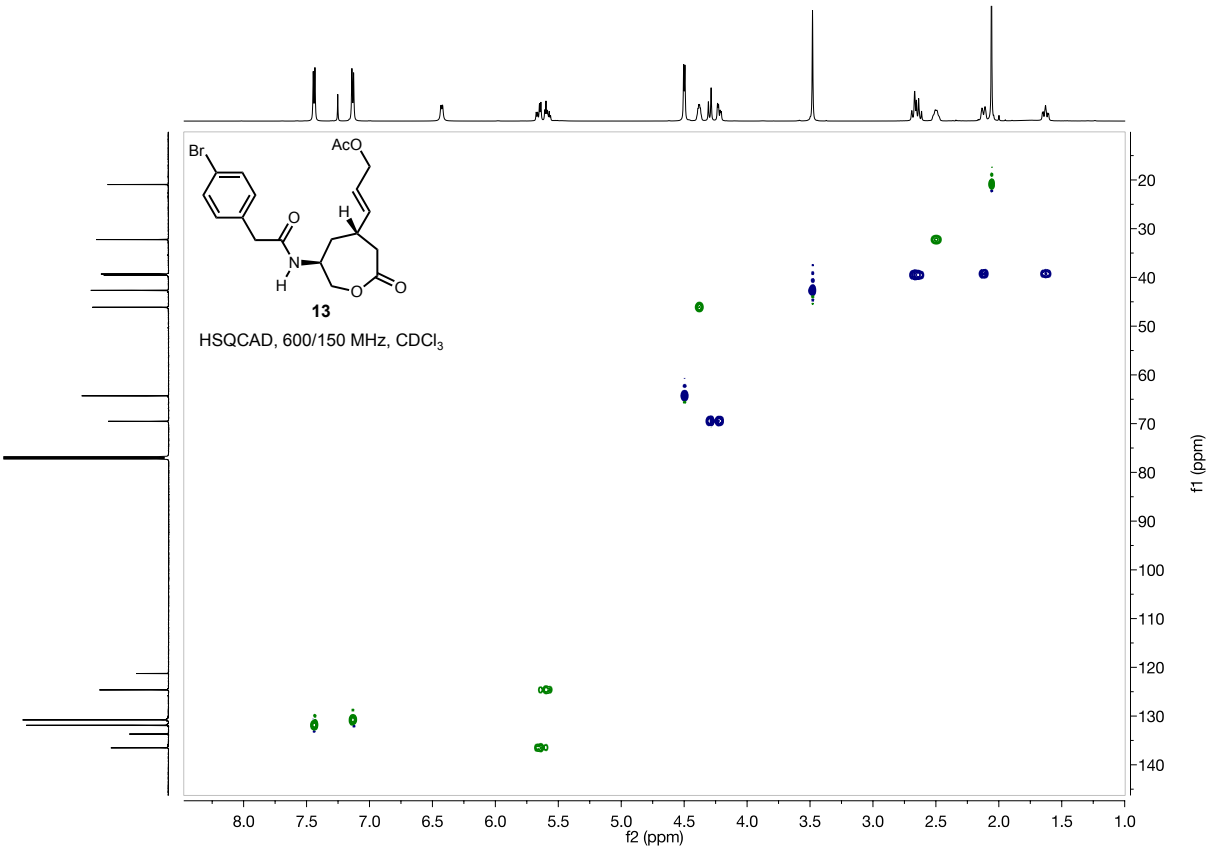

Br
AcO
H
O
N
H
O
O
12
^{13}C-NMR, 150 MHz, $CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

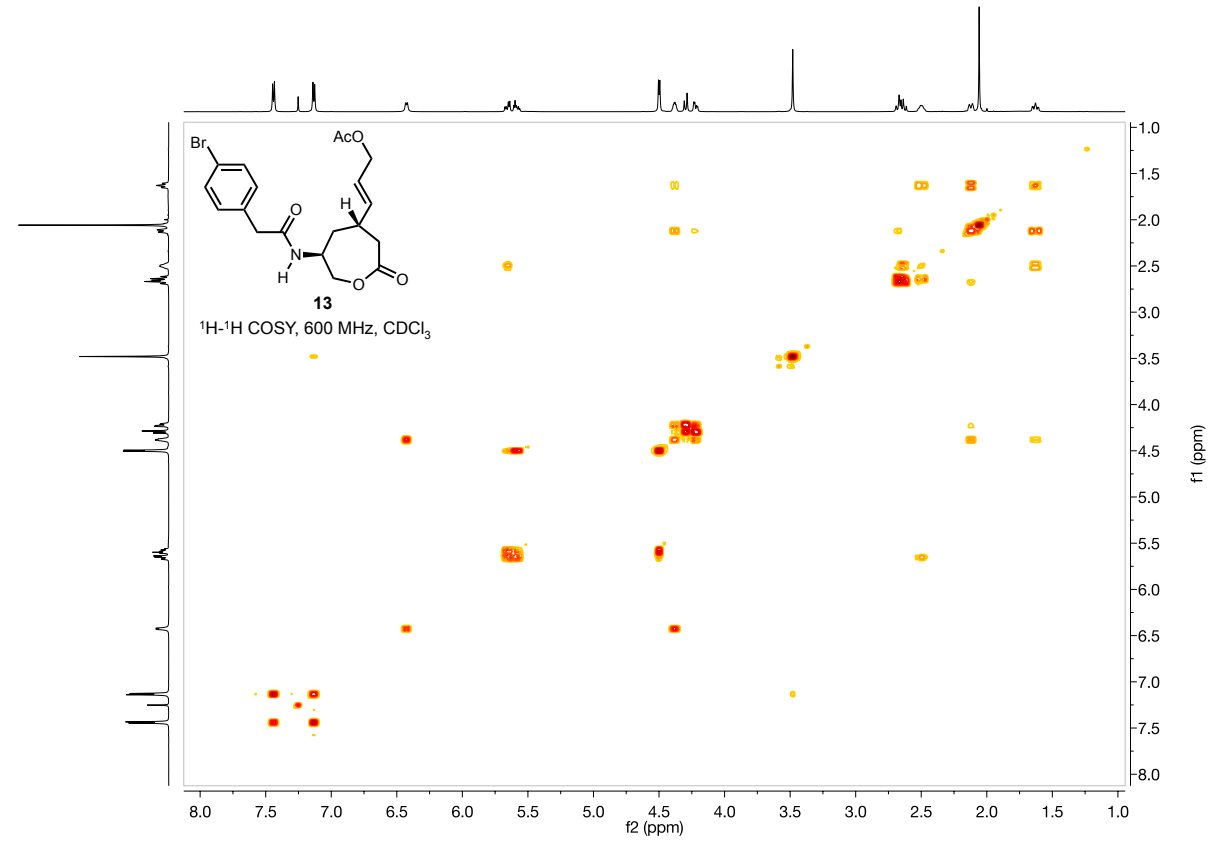

Br
AcO
H
O
N
H
O
O
12
HSQCAD, 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

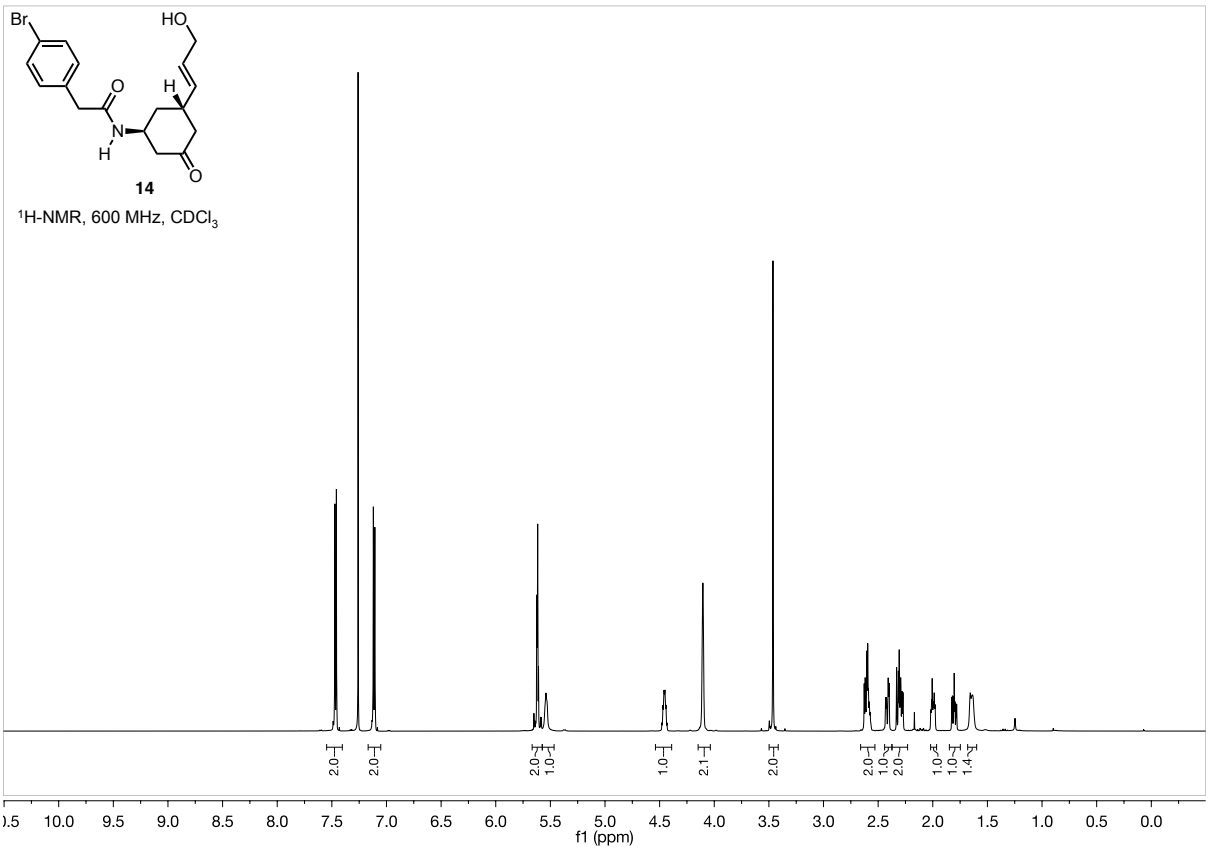

Br
AcO
H
O
N
H
O
O
12
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

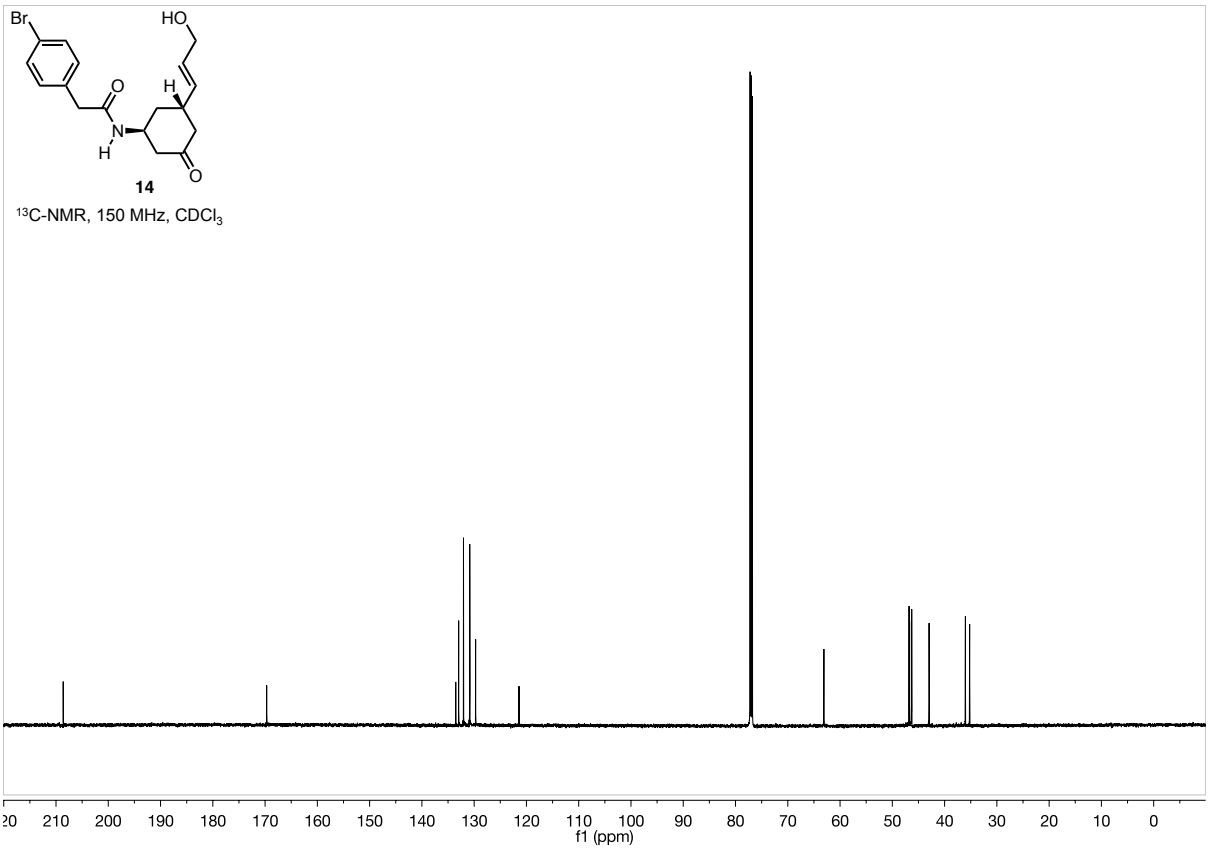

Br
AcO
O
H
N
H
O
O
13
1H-NMR, 600 MHz, CDCl3
1.9
2.0
1.0
1.0
1.0
2.0
1.0
1.0
1.0
2.1
2.1
1.1
1.2
2.9
1.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

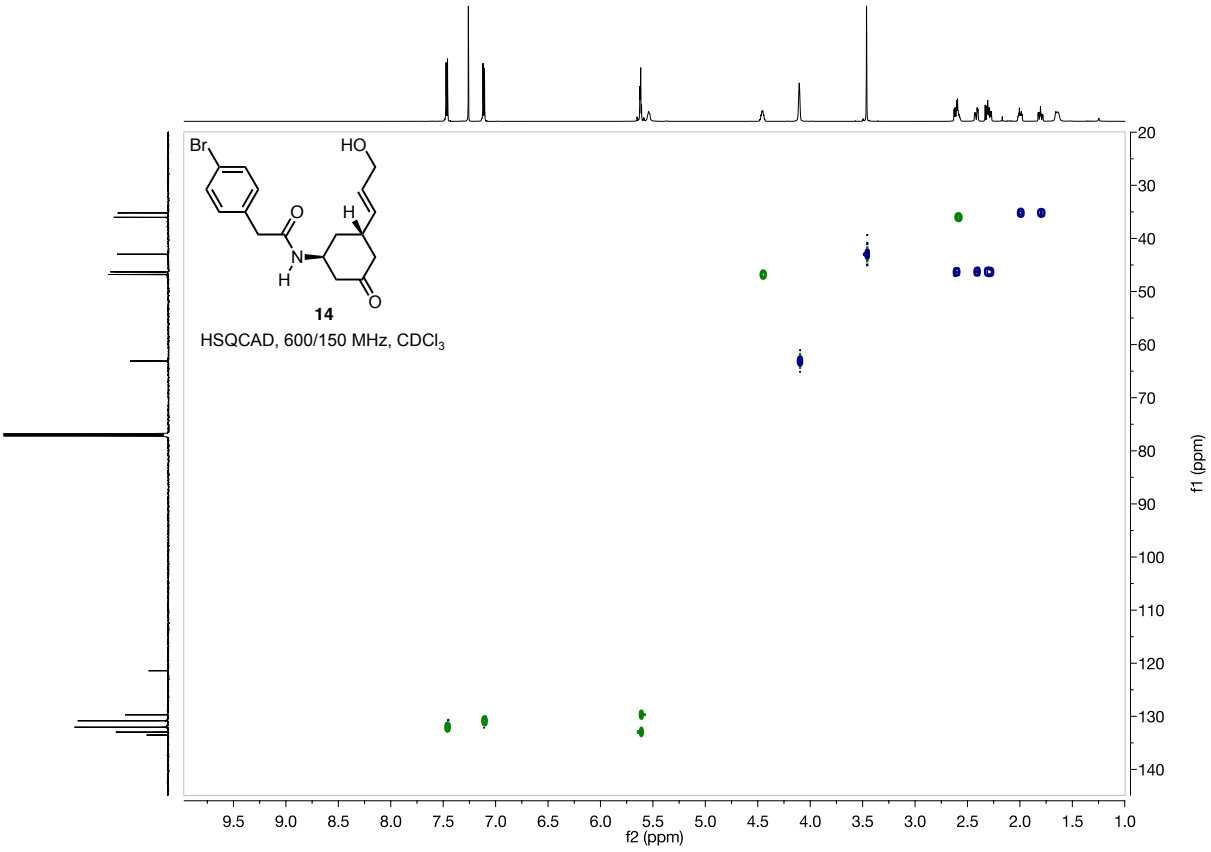

Br
AcO
O
H
N
H
O
O
13
13C-NMR, 150 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

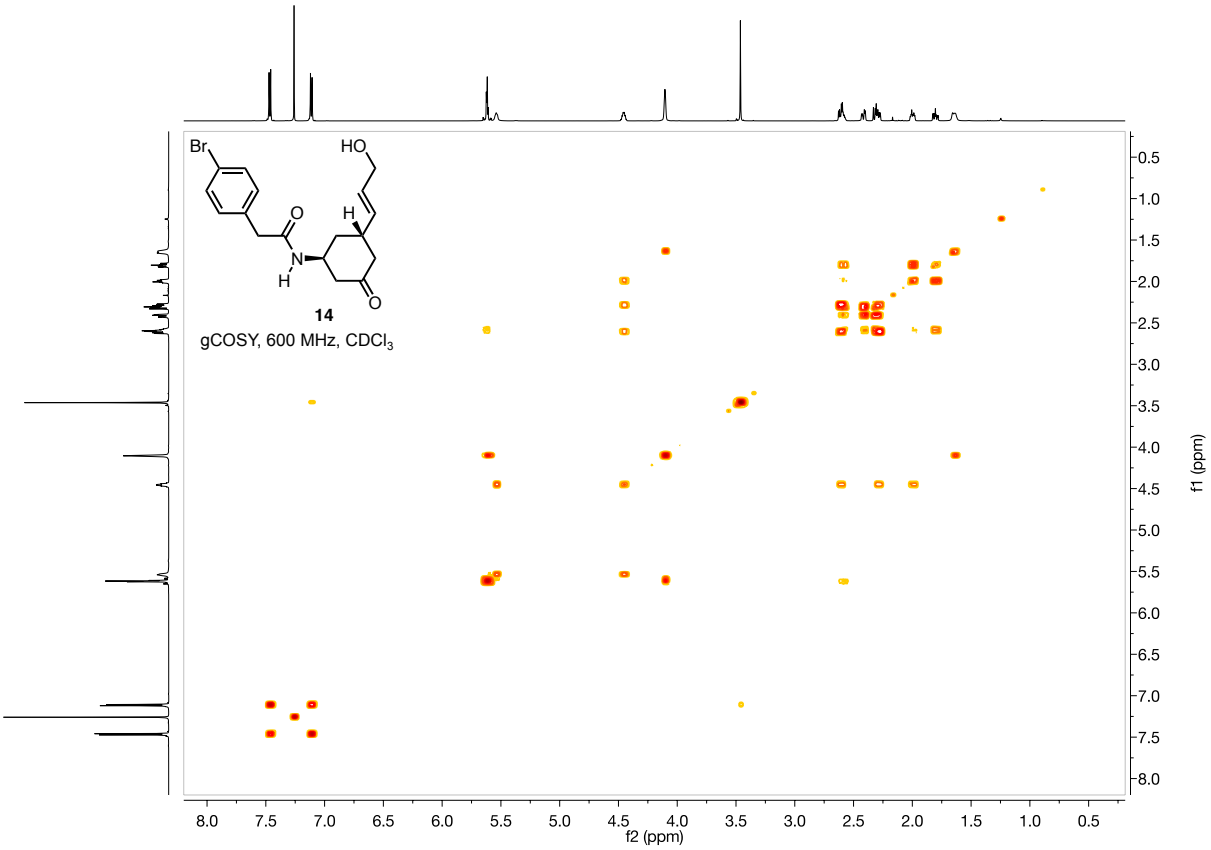

Br
AcO
H
O
N
H
O
O
13
HSQCAD, 600/150 MHz, CDCl3
f1 (ppm)
f2 (ppm)

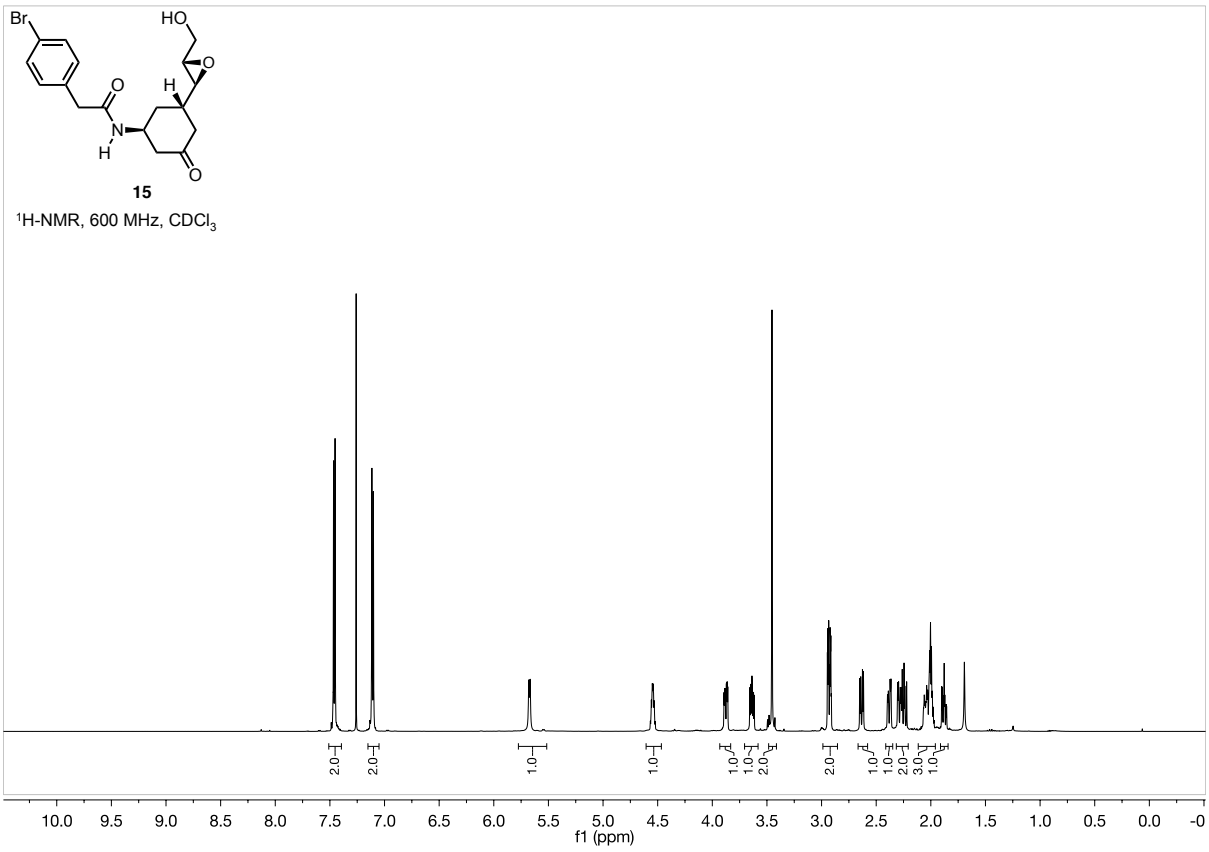

Br
AcO
H
O
N
H
O
O
13
1H-1H COSY, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)

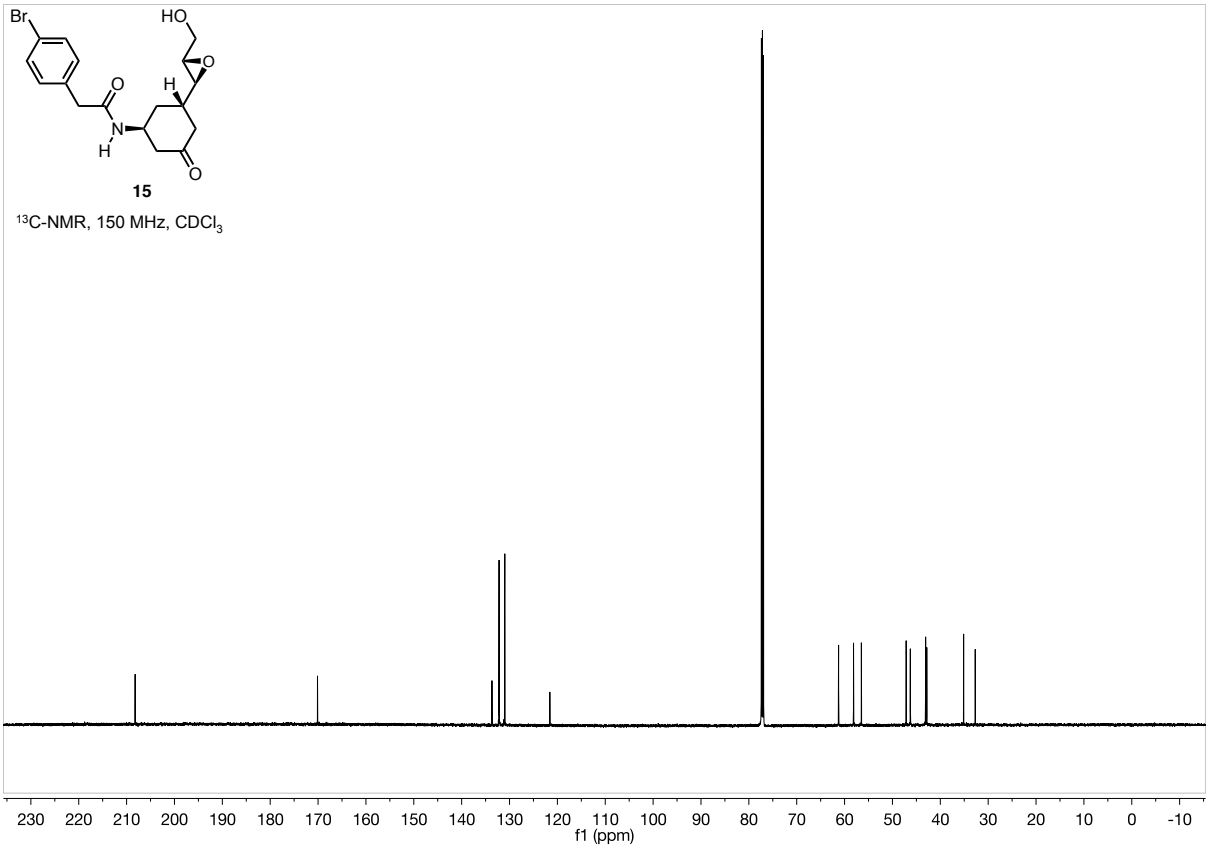

Br
HO
O
H
N
H
O
14
^{1}H-NMR, 600 MHz, $CDCl_3$
2.0
2.0
2.0
1.0
1.0
2.1
2.0
2.0
1.0
2.0
1.0
1.0
1.4
f1 (ppm)

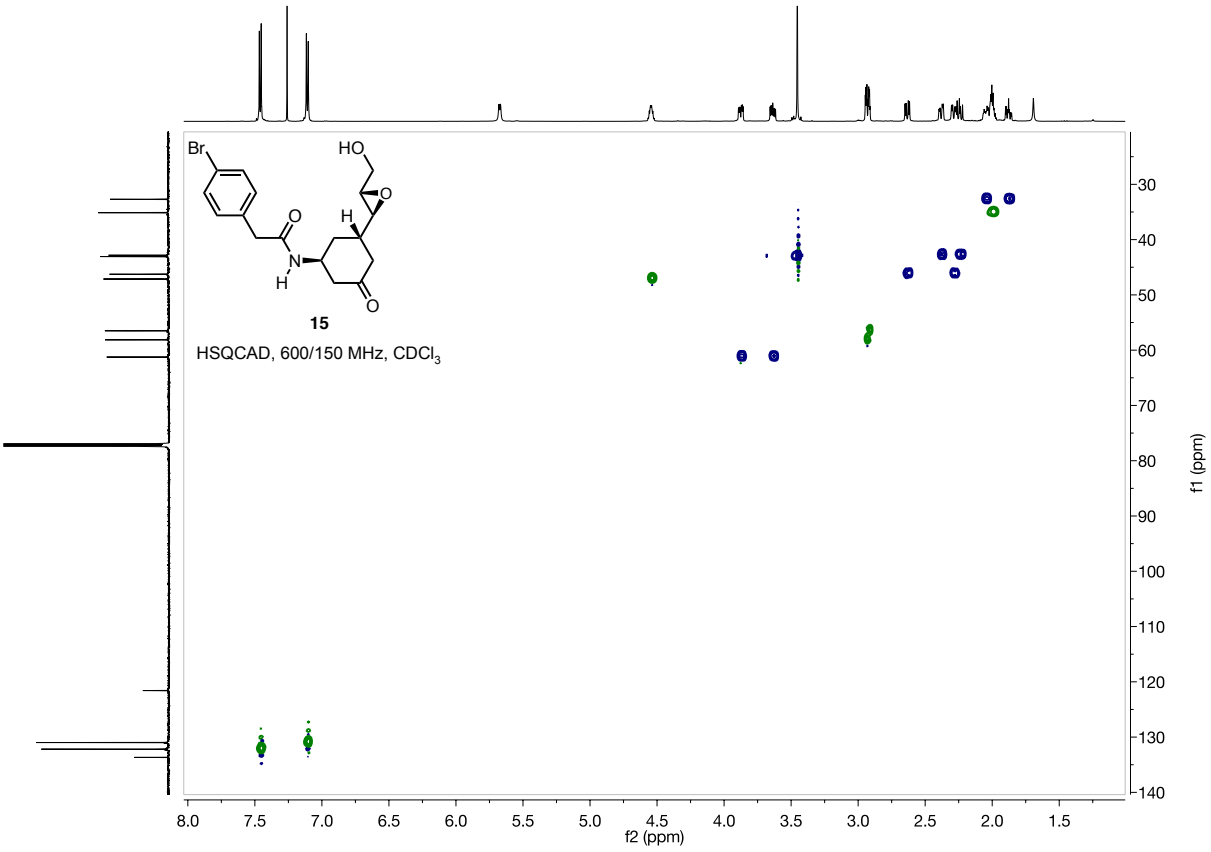

Br
HO
O
H
N
H
O
14
^{13}C-NMR, 150 MHz, $CDCl_3$
f1 (ppm)

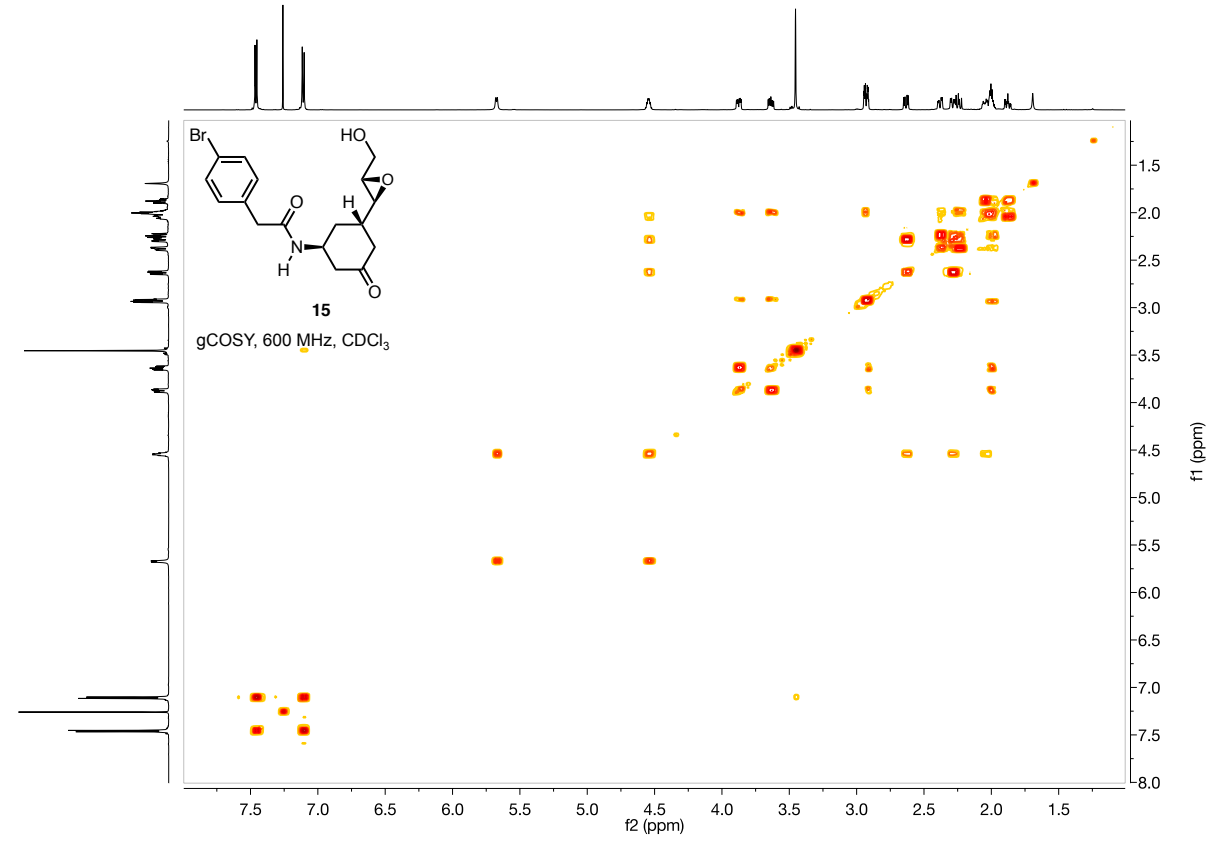

Br
HO
O
H
N
H
O
14
HSQCAD, 600/150 MHz, CDCl3
f2 (ppm)
f1 (ppm)

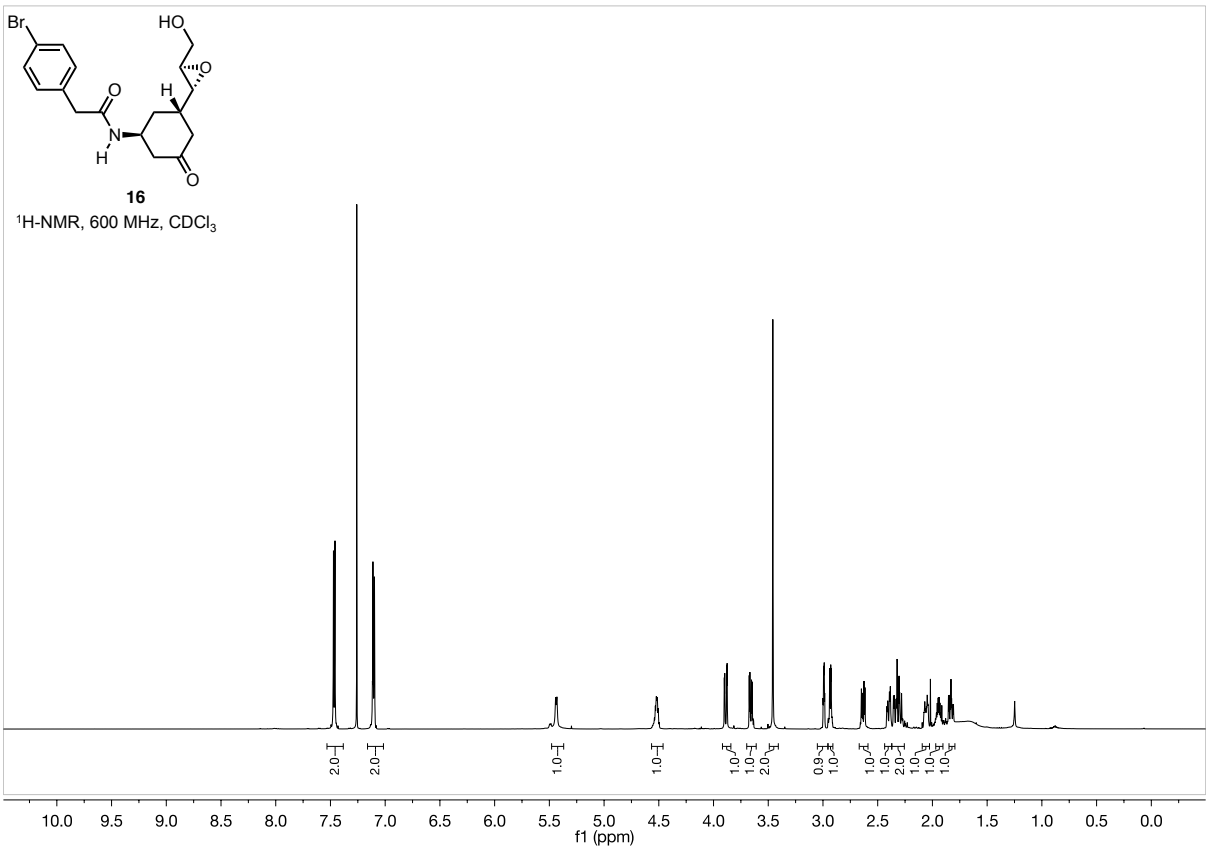

Br
HO
O
H
N
H
O
14
gCOSY, 600 MHz, CDCl3
f2 (ppm)
f1 (ppm)

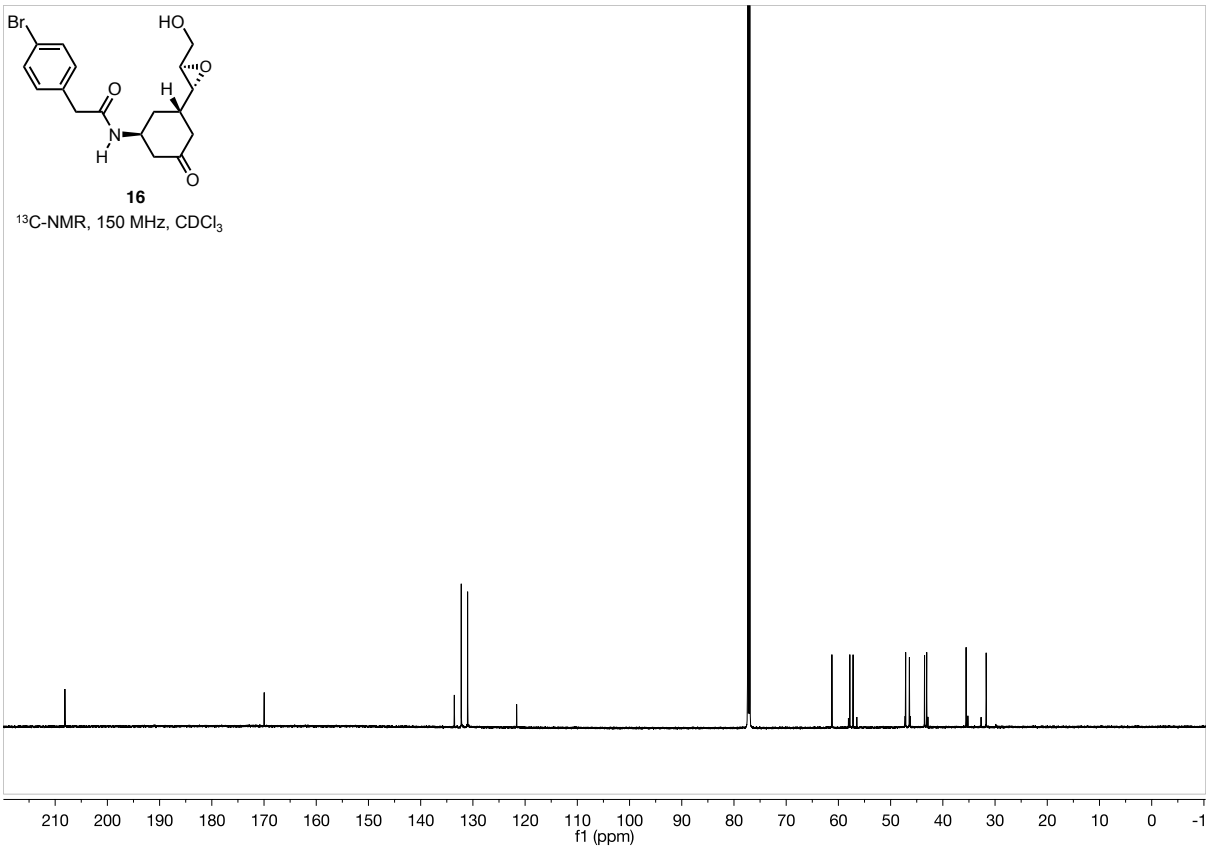

Br
HO
O
H
O
N
H
O
15
1H-NMR, 600 MHz, CDCl3
2.0
2.0
1.0
1.0
1.0
1.0
2.0
2.0
1.0
1.0
2.0
3.0
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

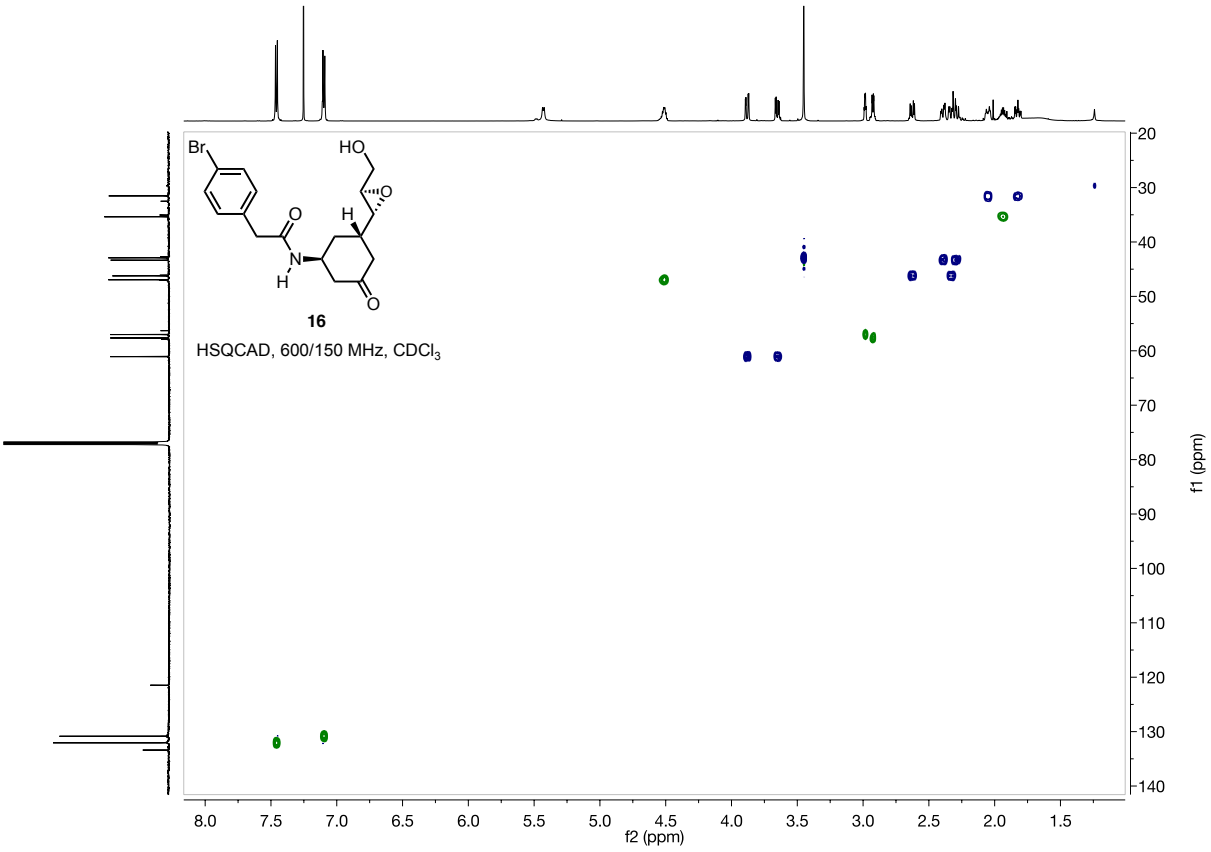

Br
HO
O
H
O
N
H
O
15
13C-NMR, 150 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

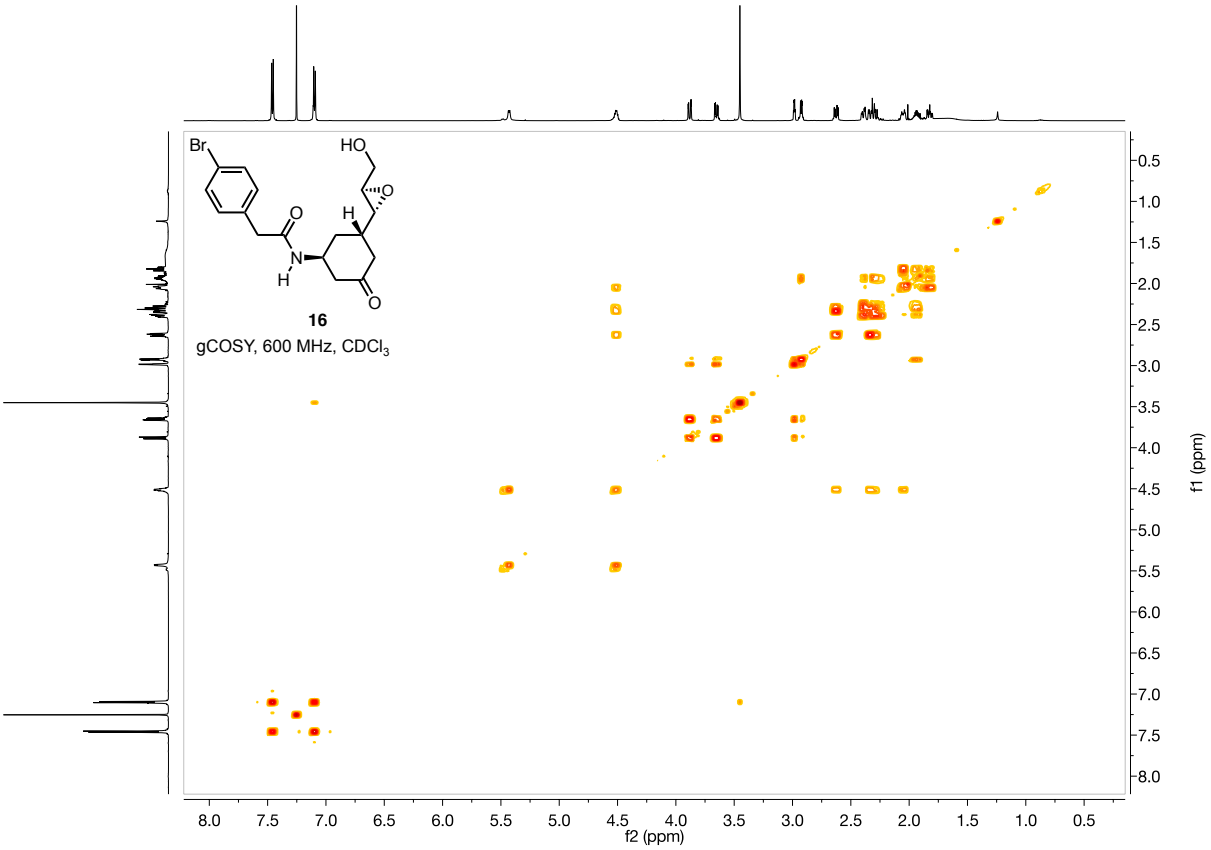

Br
HO
O
H
N
H
O
15
HSQCAD, 600/150 MHz, CDCl3
f1 (ppm)
f2 (ppm)

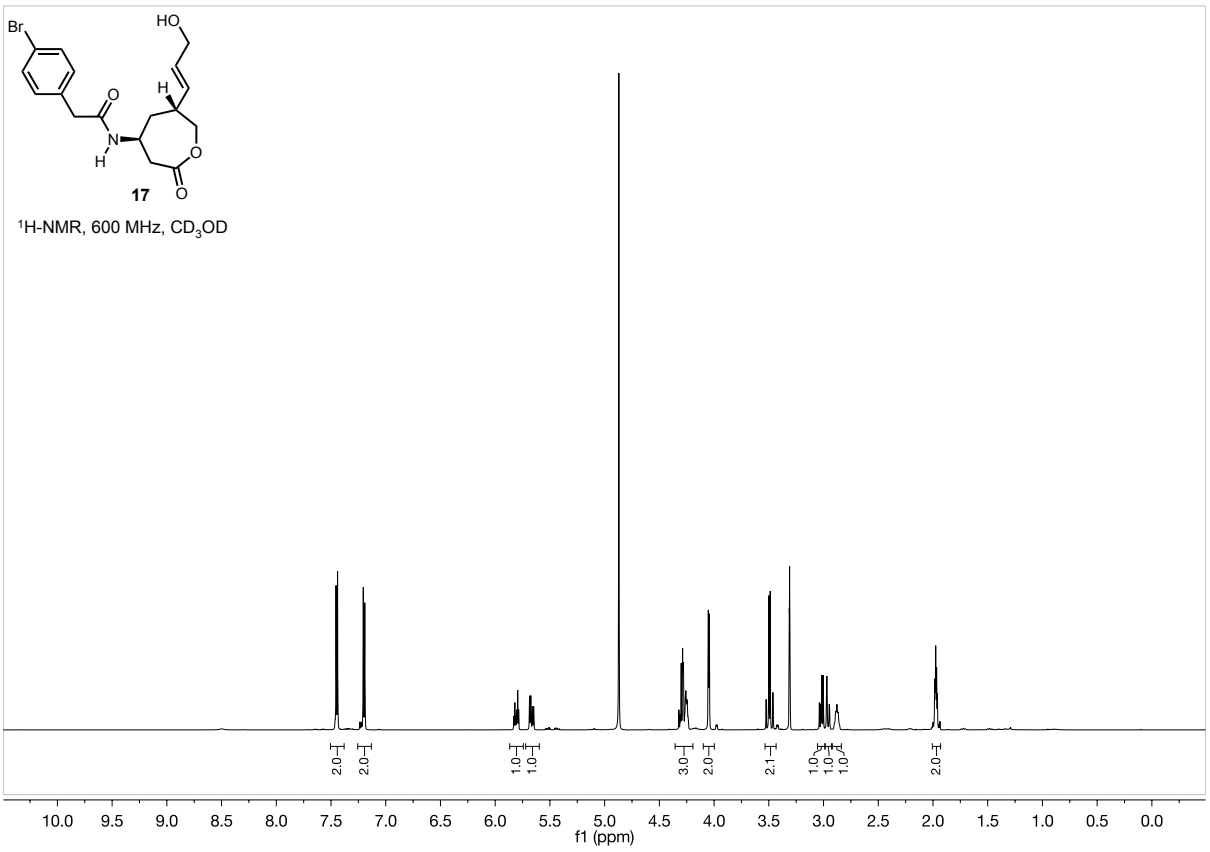

Br
HO
O
H
N
H
O
15
gCOSY, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)

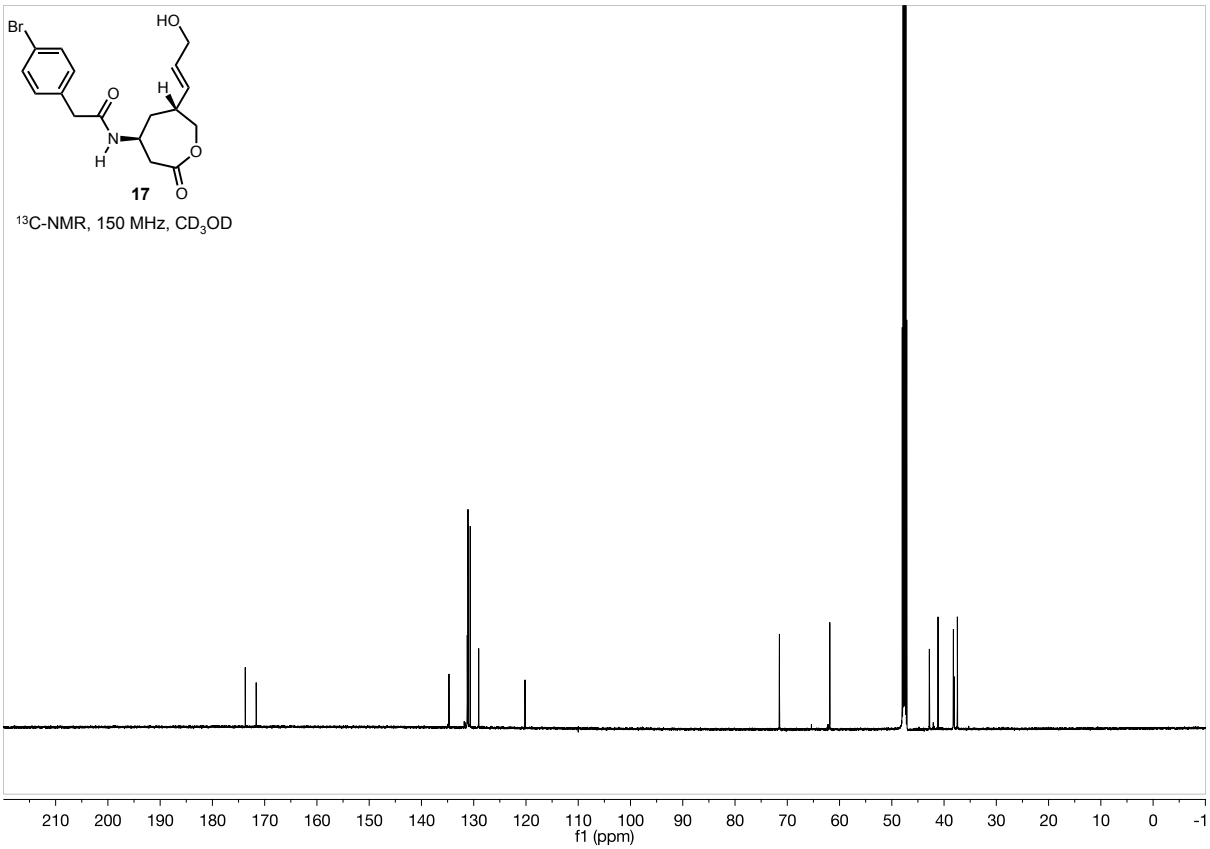

Br
HO
O
H
O
N
H
O
16
1H-NMR, 600 MHz, CDCl3
2.0
2.0
1.0
1.0
1.0
1.0
2.0
0.9
1.0
1.0
1.0
2.0
1.0
1.0
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

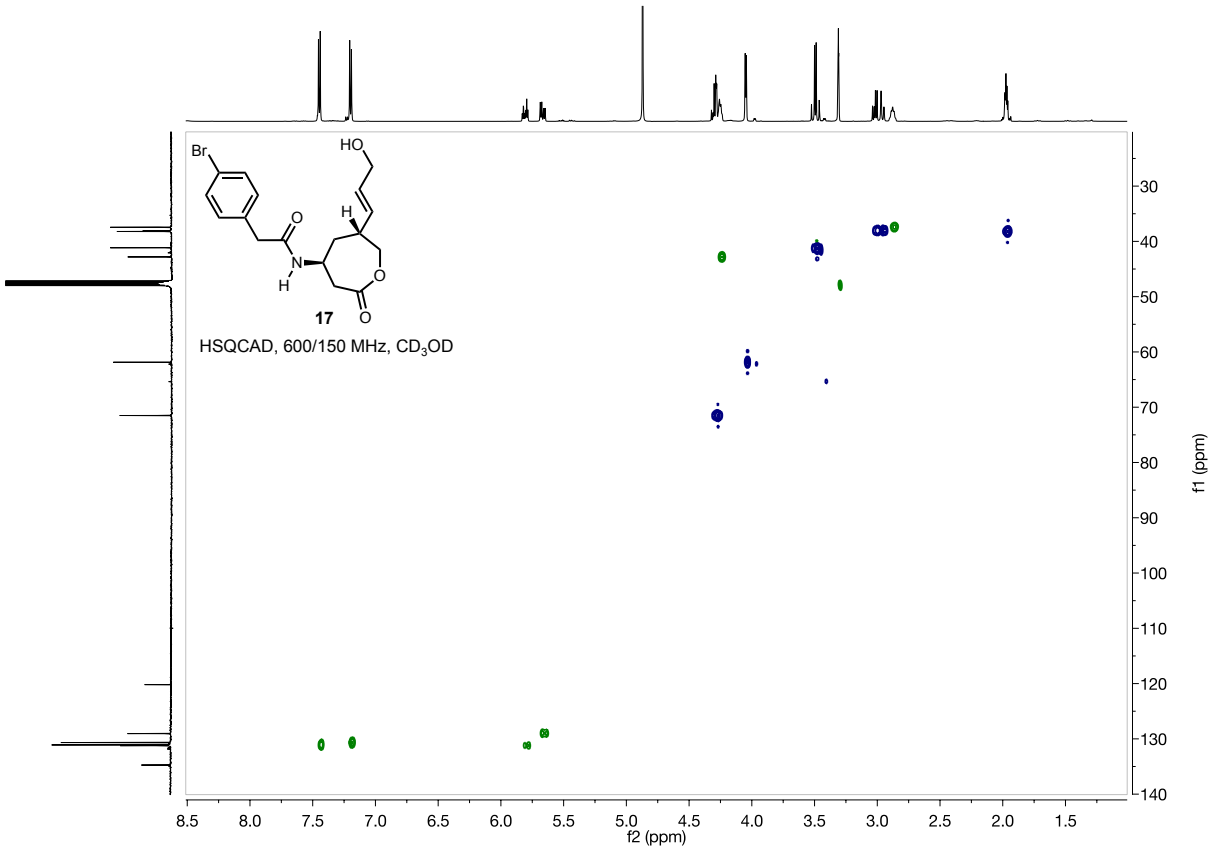

Br
HO
O
H
O
N
H
O
16
13C-NMR, 150 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

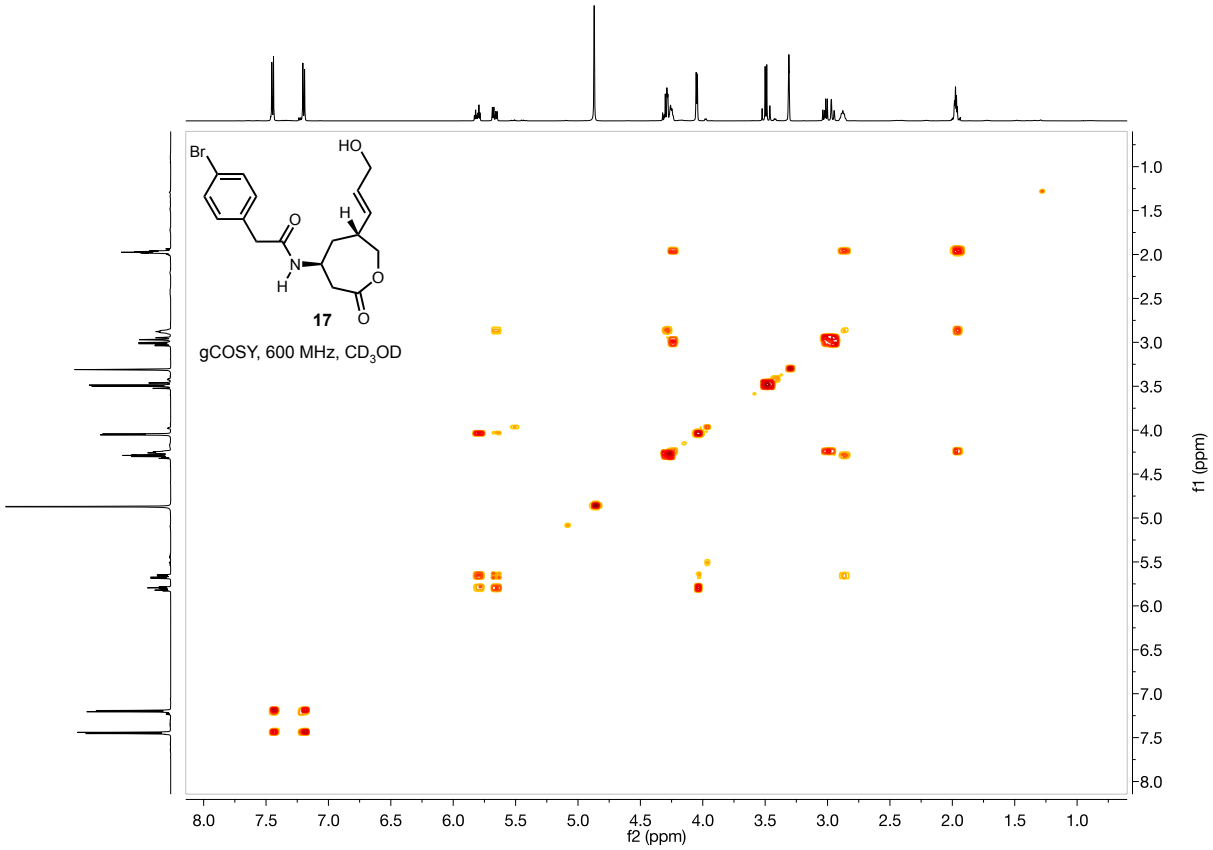

Br
HO
O
H
N
H
O
O
16
HSQCAD, 600/150 MHz, CDCl3
f1 (ppm)
f2 (ppm)

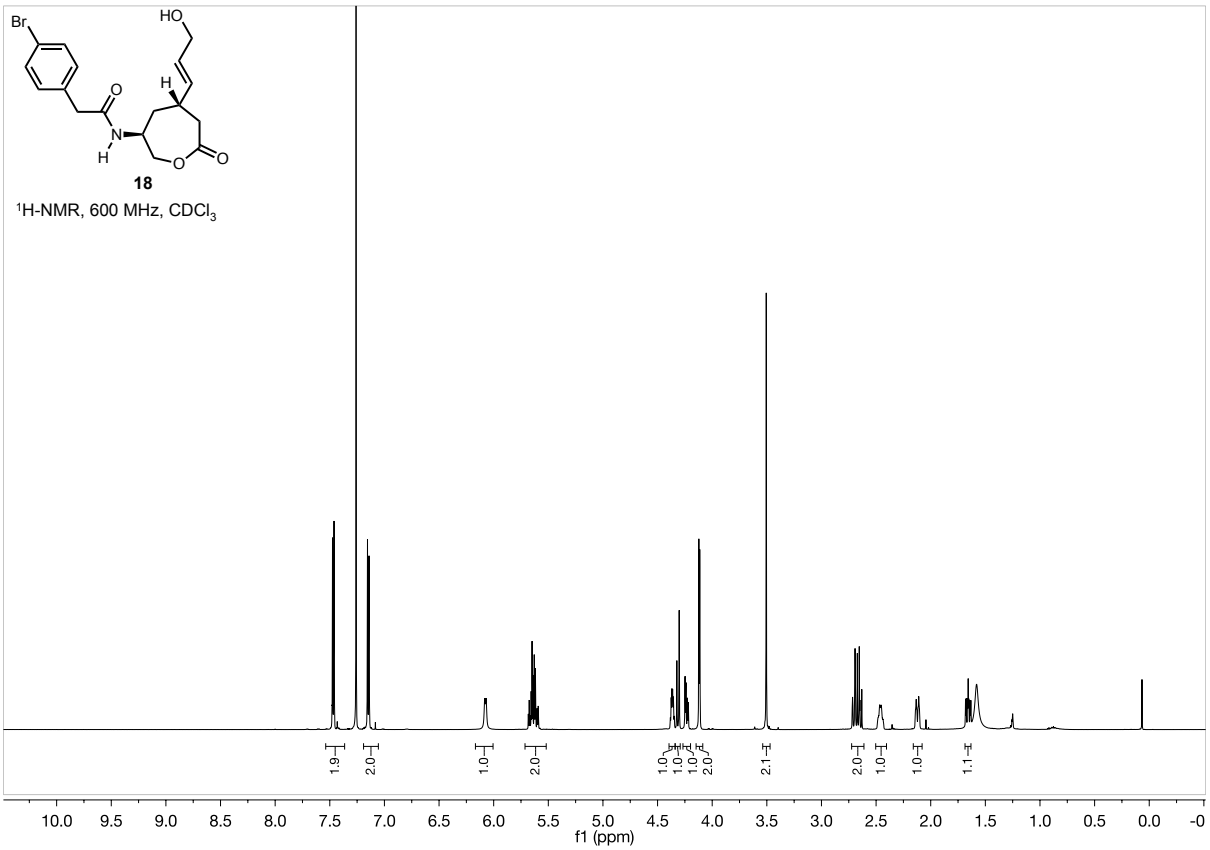

Br
HO
O
H
N
H
O
O
16
gCOSY, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)

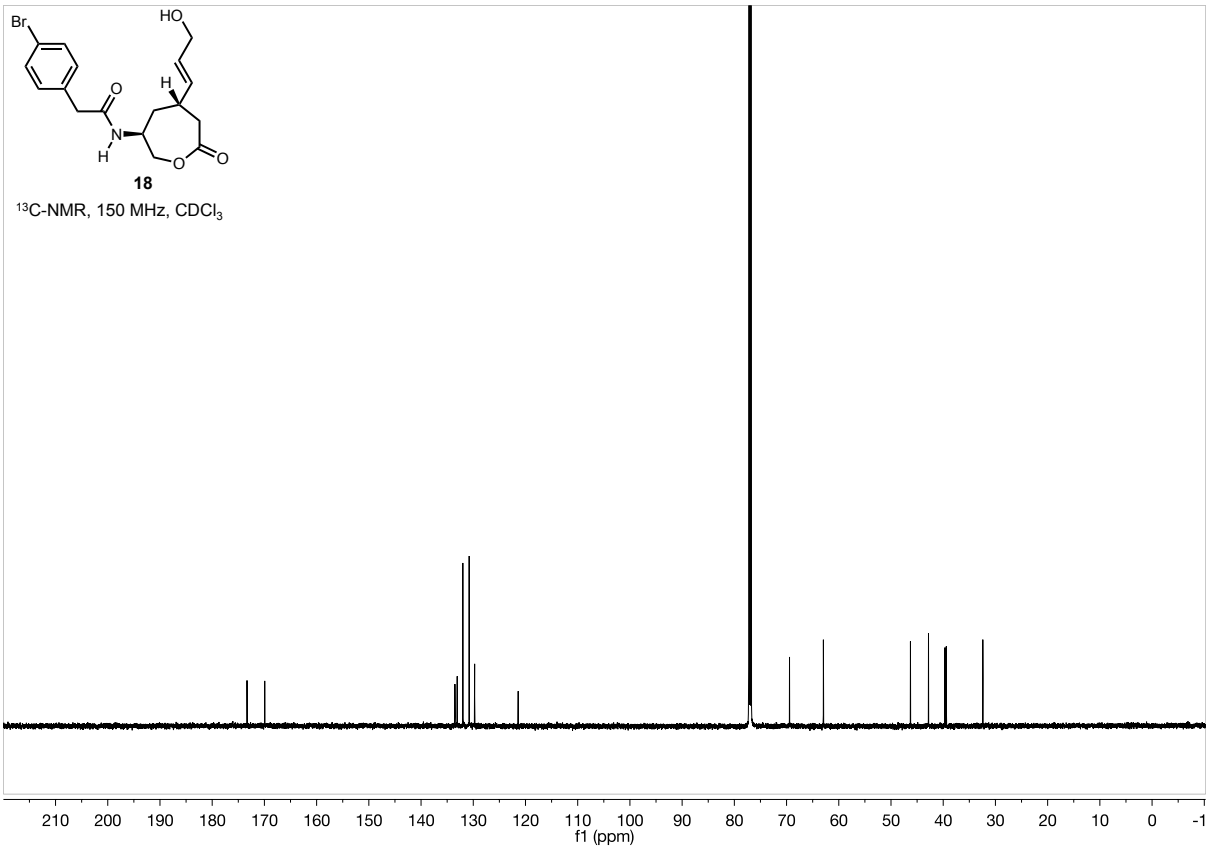

Br
HO
H
O
N
H
O
O
17
^{1}H-NMR, 600 MHz, CD_3OD
2.0
2.0
1.0
1.0
3.0
2.0
2.1
1.0
1.0
1.0
2.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

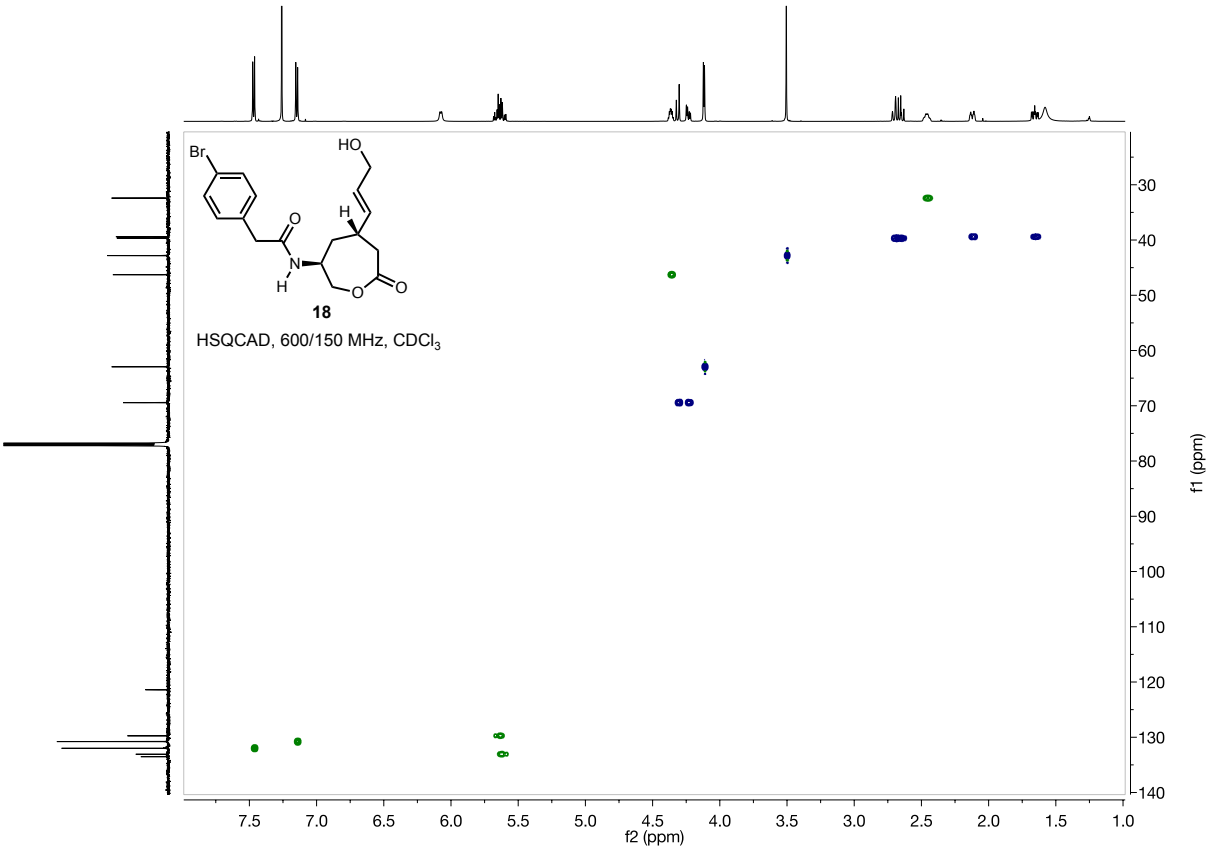

Br
HO
H
O
N
H
O
O
17
^{13}C-NMR, 150 MHz, CD_3OD
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

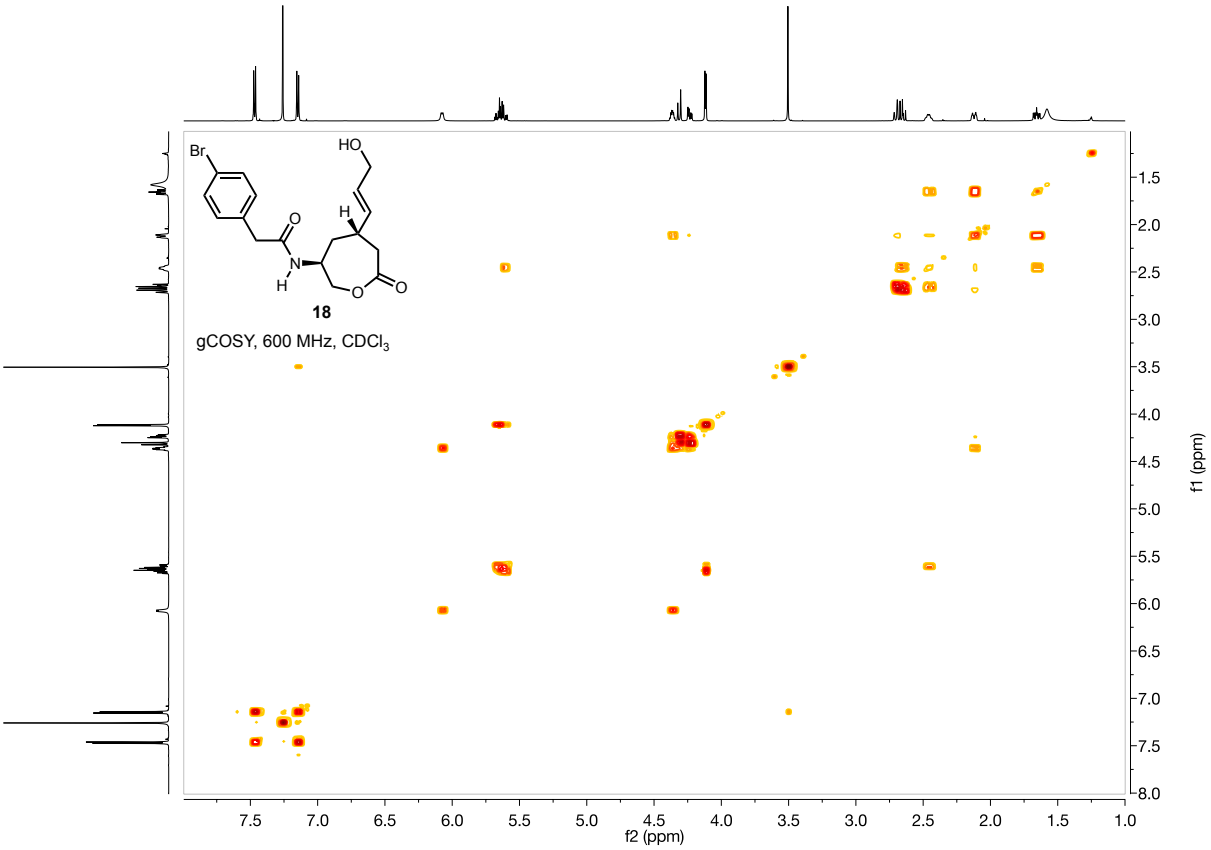

Br
HO
H
O
N
H
O
O
17
HSQCAD, 600/150 MHz, CD3OD
f1 (ppm)
f2 (ppm)

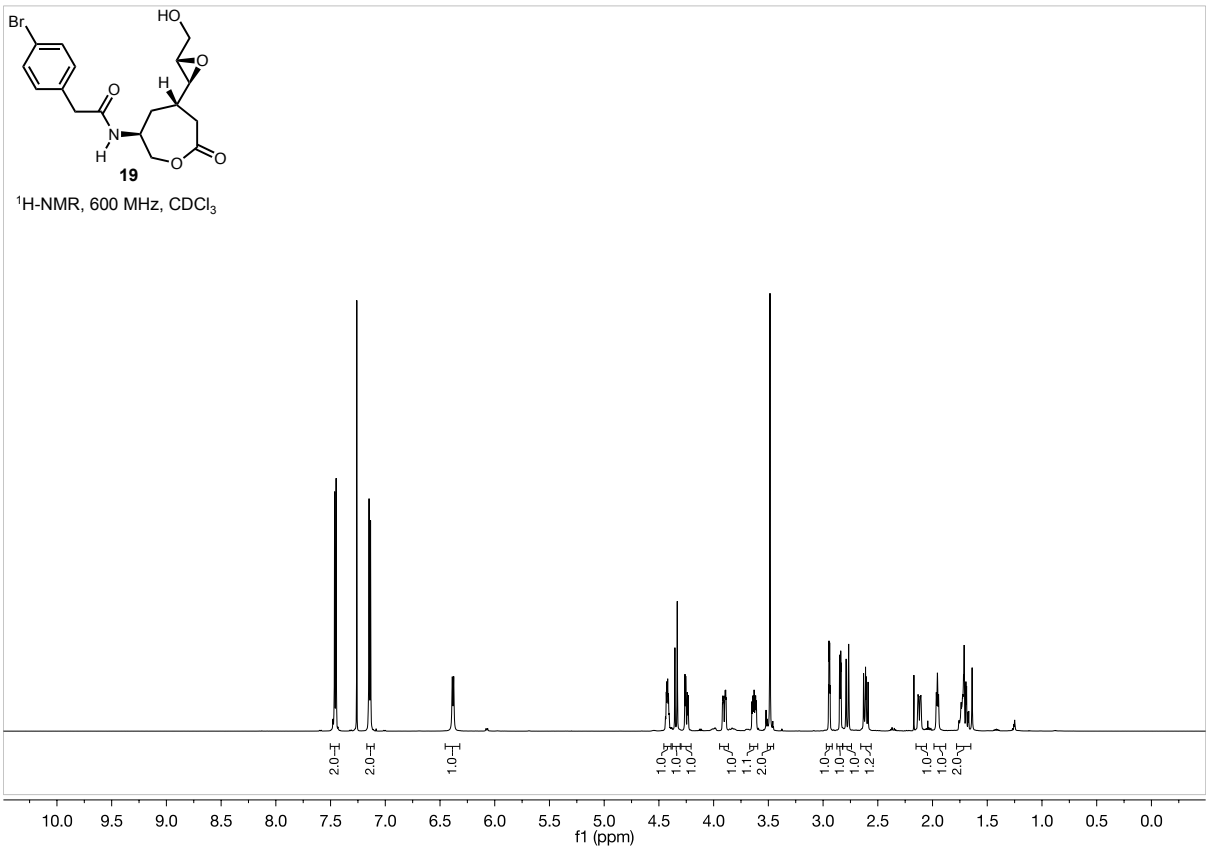

Br
HO
H
O
N
H
O
O
17
gCOSY, 600 MHz, CD3OD
f1 (ppm)
f2 (ppm)

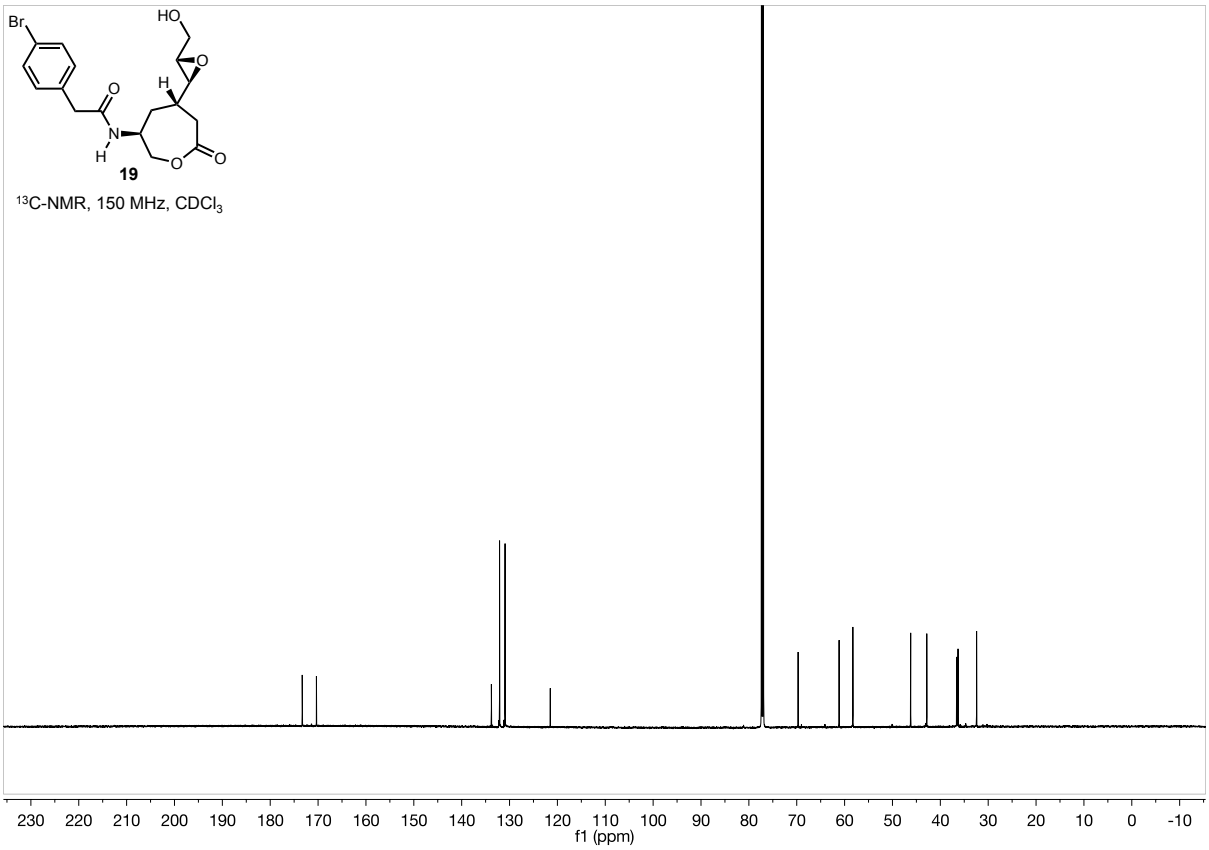

Br
HO
O
H
N
H
O
O
18
1H-NMR, 600 MHz, CDCl3
1.9
2.0
1.0
2.0
1.0
1.0
1.0
2.0
2.1
2.0
1.0
1.0
1.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

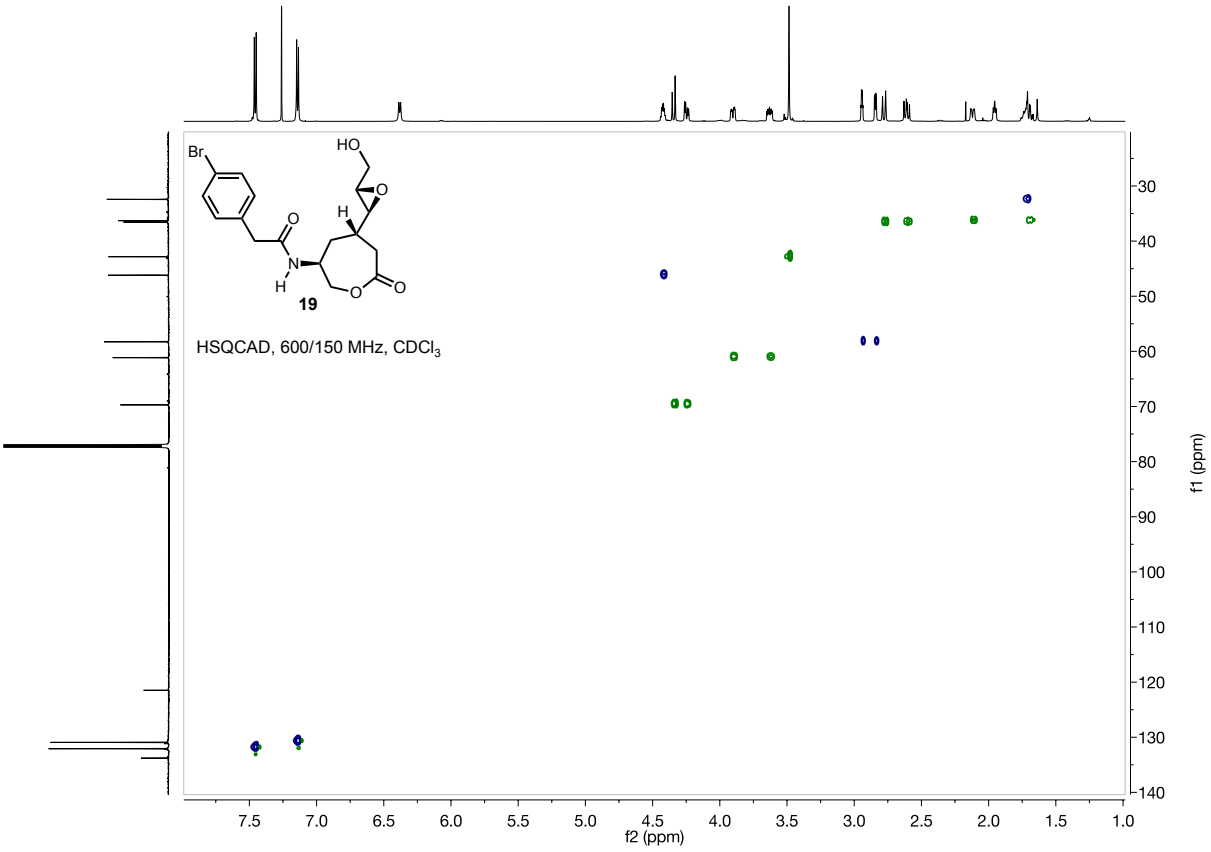

Br
HO
O
H
N
H
O
O
18
13C-NMR, 150 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

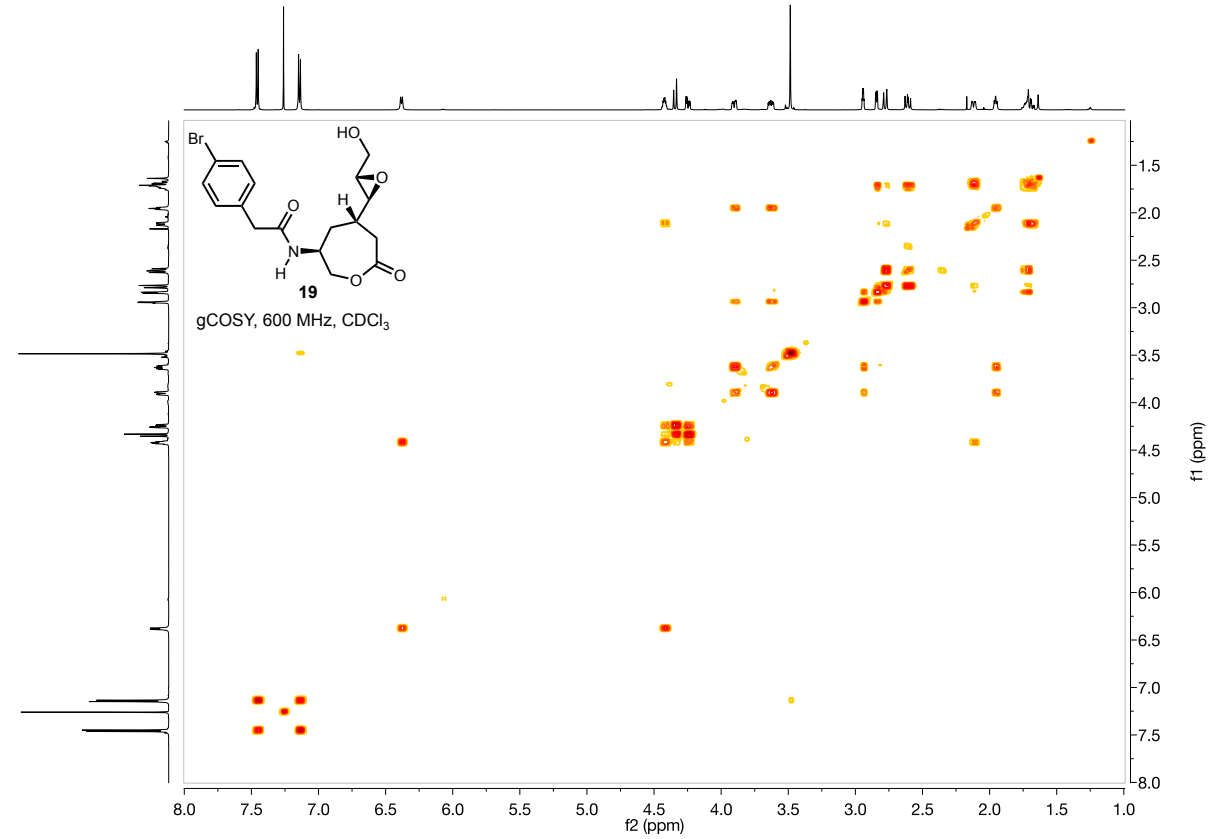

Br
HO
H
O
N
H
O
O
18
HSQCAD, 600/150 MHz, CDCl3
f1 (ppm)
f2 (ppm)

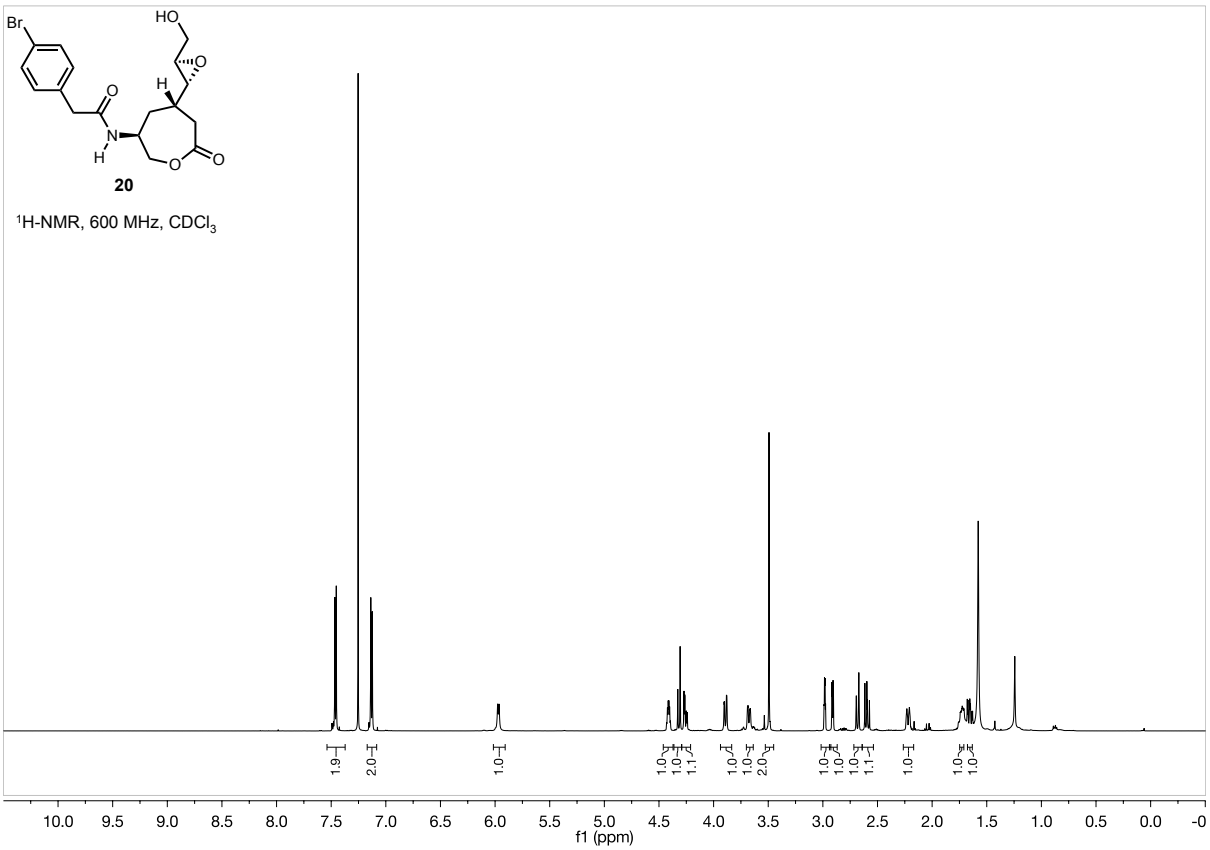

Br
HO
H
O
N
H
O
O
18
gCOSY, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)

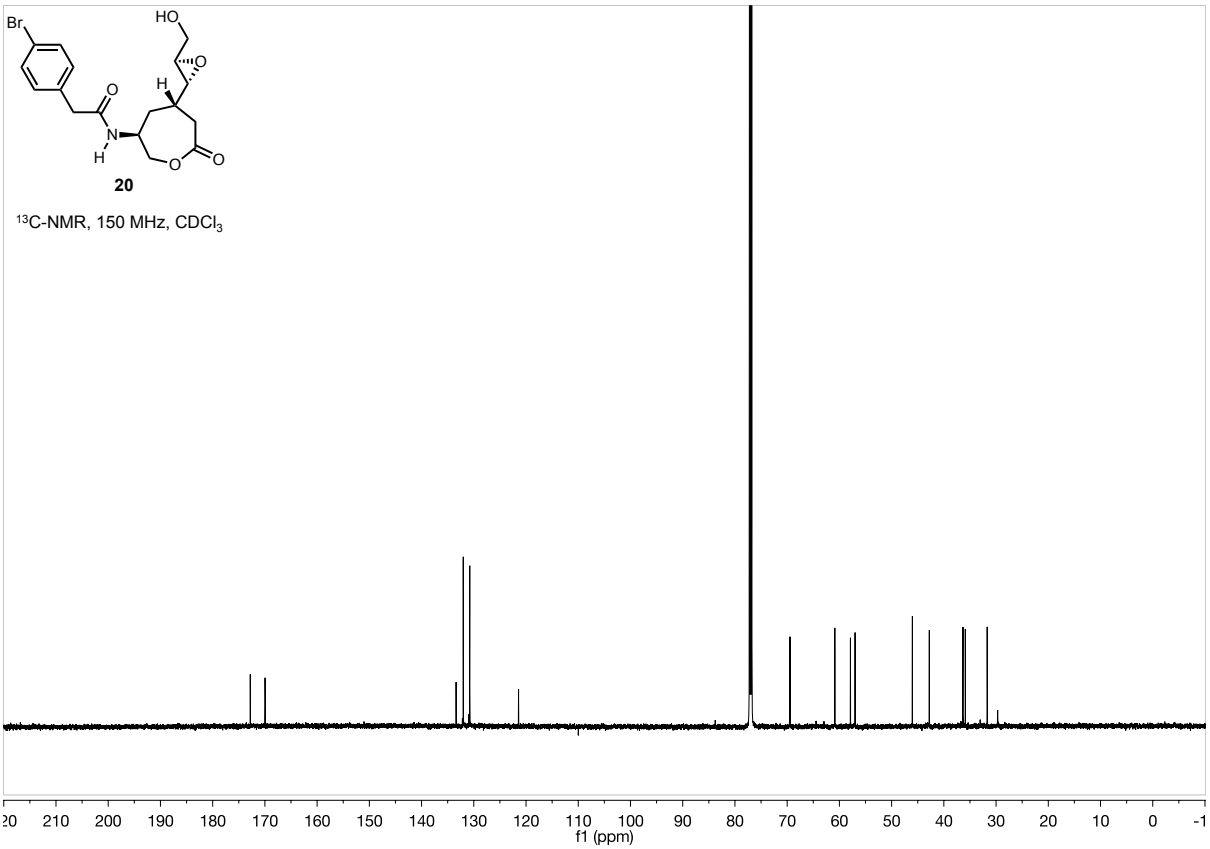

Br
HO
O
H
O
N
H
O
O
19
1H-NMR, 600 MHz, CDCl3
2.0
2.0
1.0
1.0
1.0
1.0
1.0
1.1
2.0
1.0
1.0
1.0
1.2
1.0
1.0
2.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

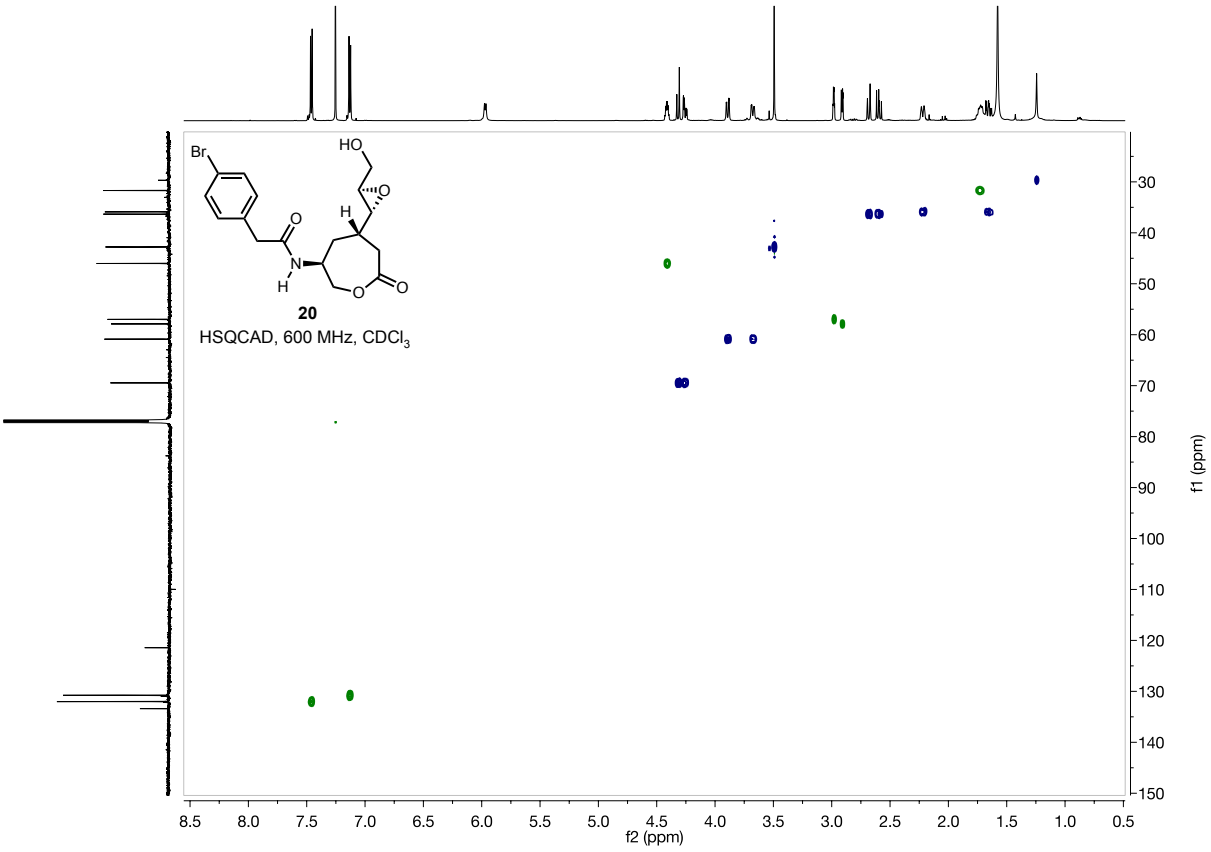

Br
HO
O
H
O
N
H
O
O
19
13C-NMR, 150 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

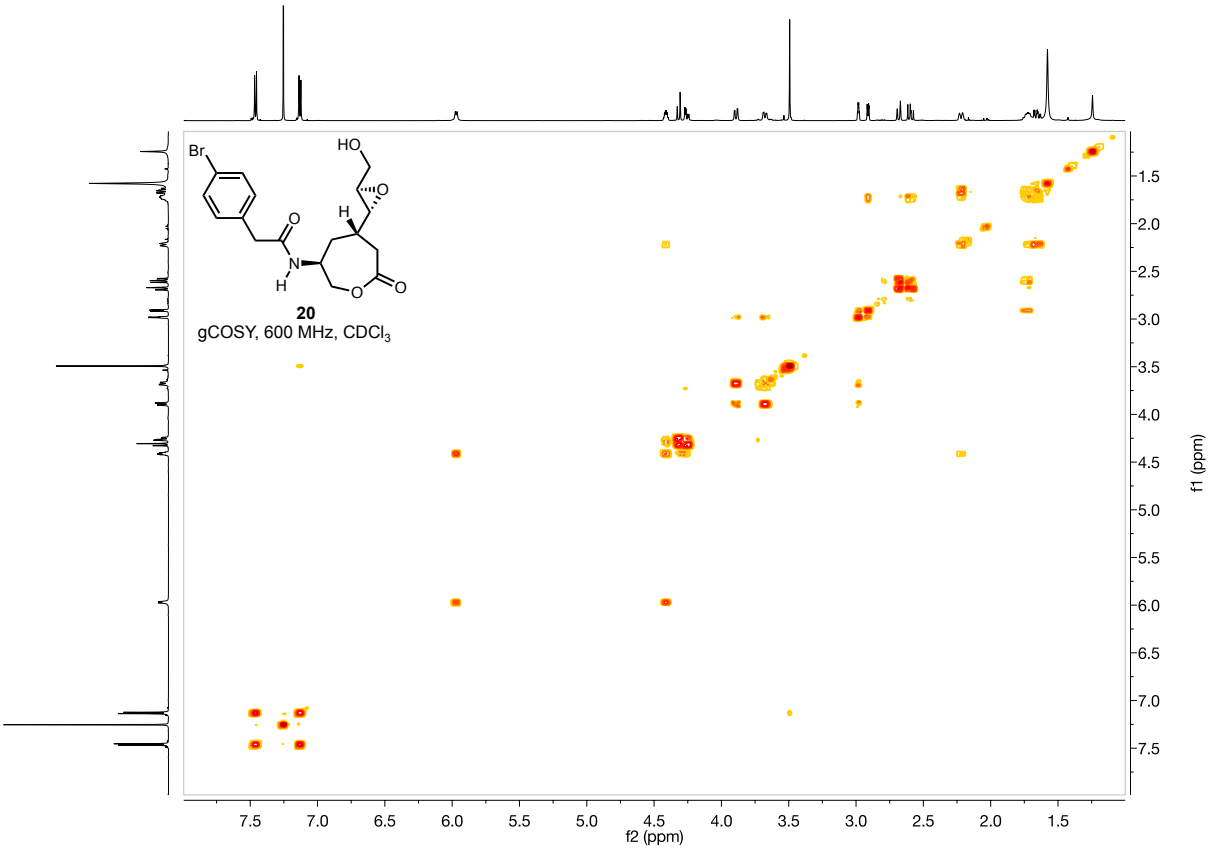

Br
HO
O
H
N
H
O
O
19
HSQCAD, 600/150 MHz, CDCl3
f1 (ppm)
f2 (ppm)

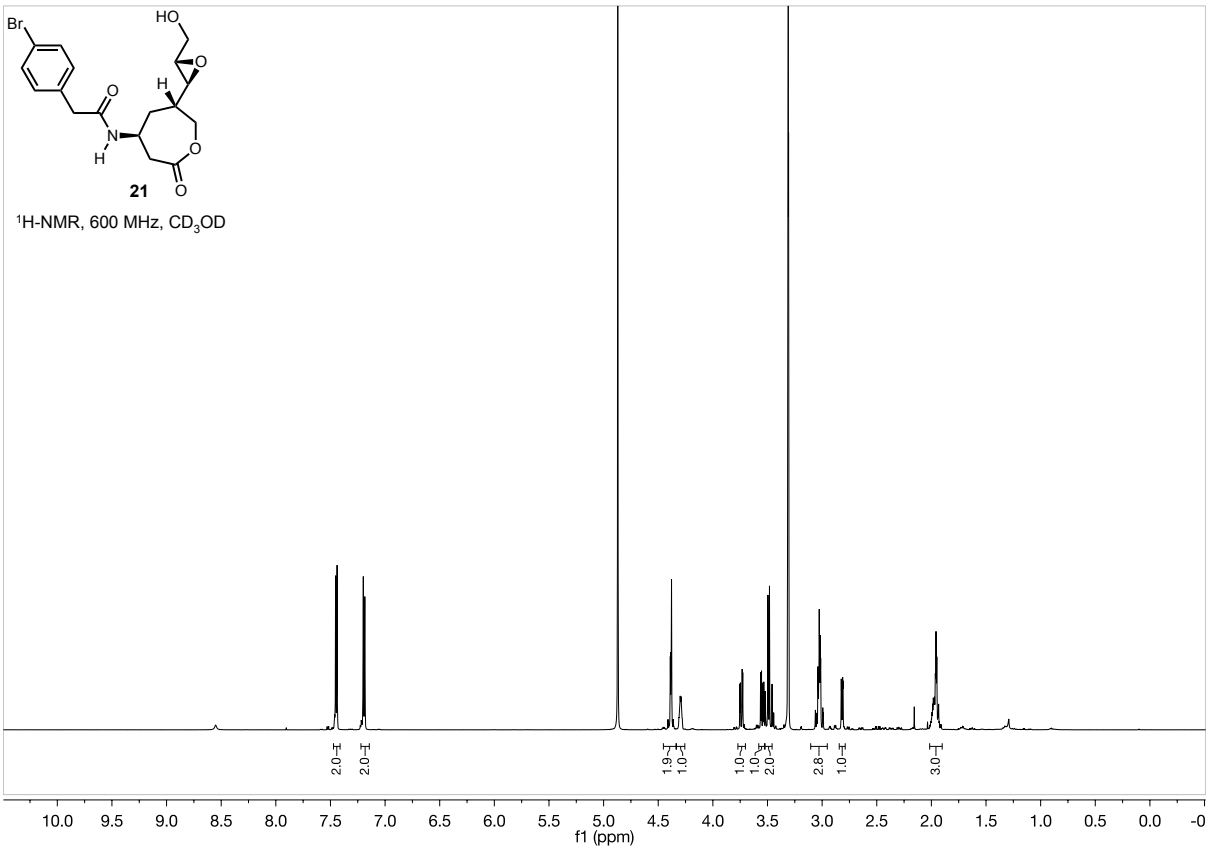

Br
HO
O
H
N
H
O
O
19
gCOSY, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)

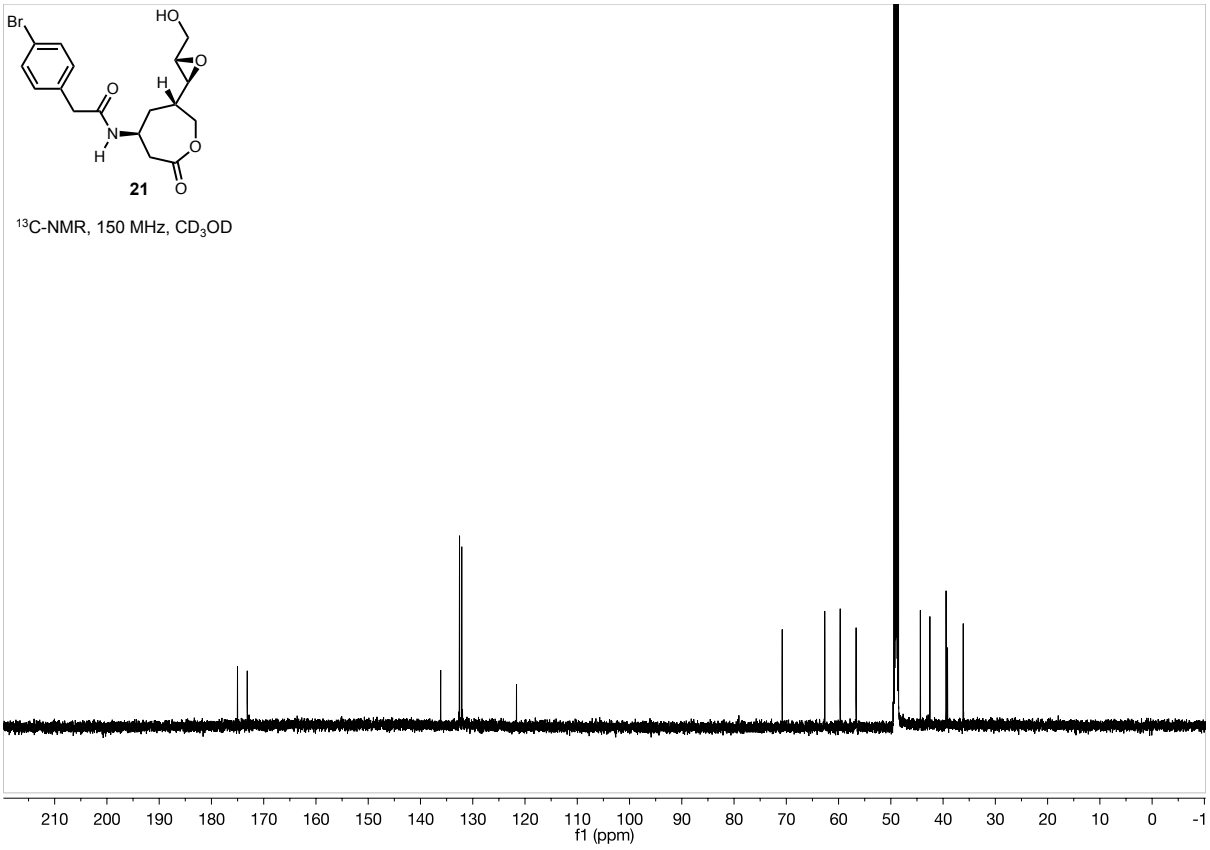

Br
HO
O
H
O
N
H
O
O
20
1H-NMR, 600 MHz, CDCl3
1.9
2.0
1.0
1.0
1.0
1.1
1.0
1.0
2.0
1.0
1.0
1.0
1.1
1.0
1.0
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

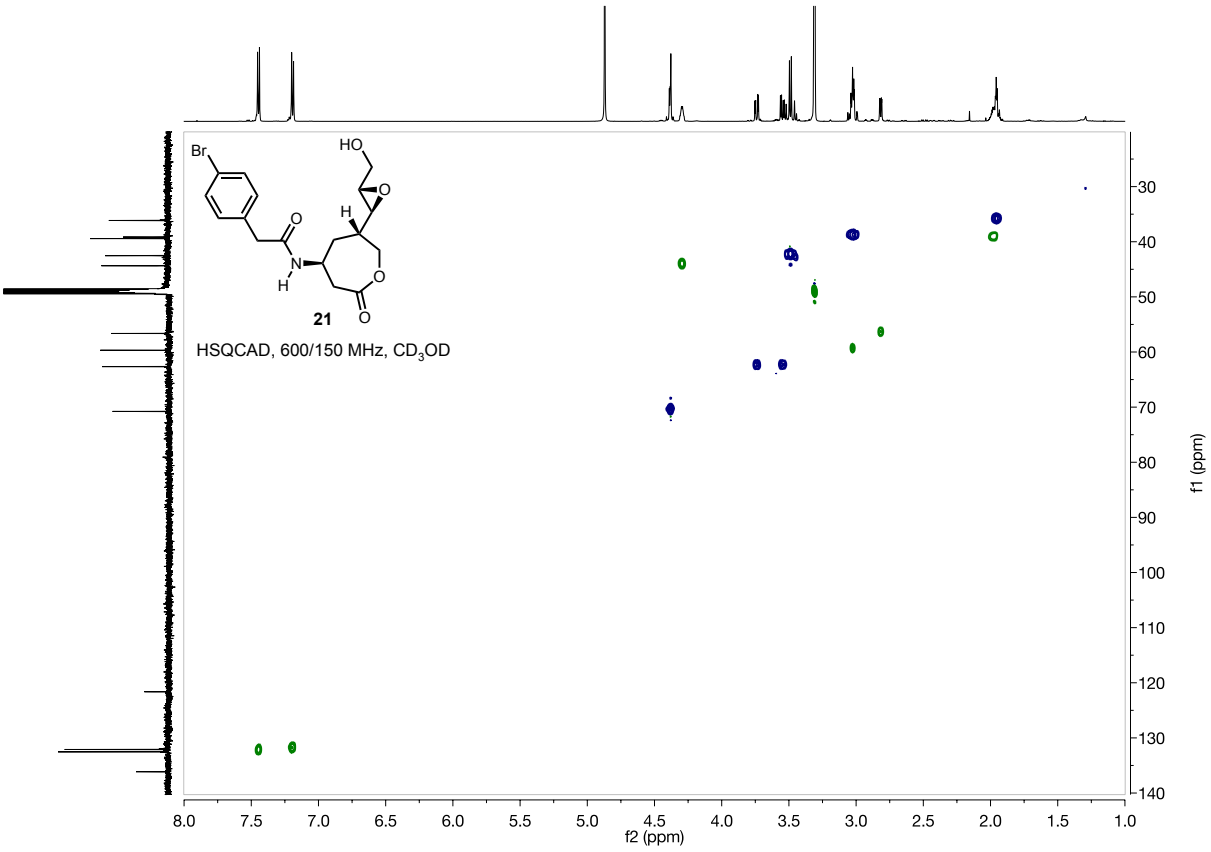

Br
HO
O
H
O
N
H
O
O
20
13C-NMR, 150 MHz, CDCl3
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

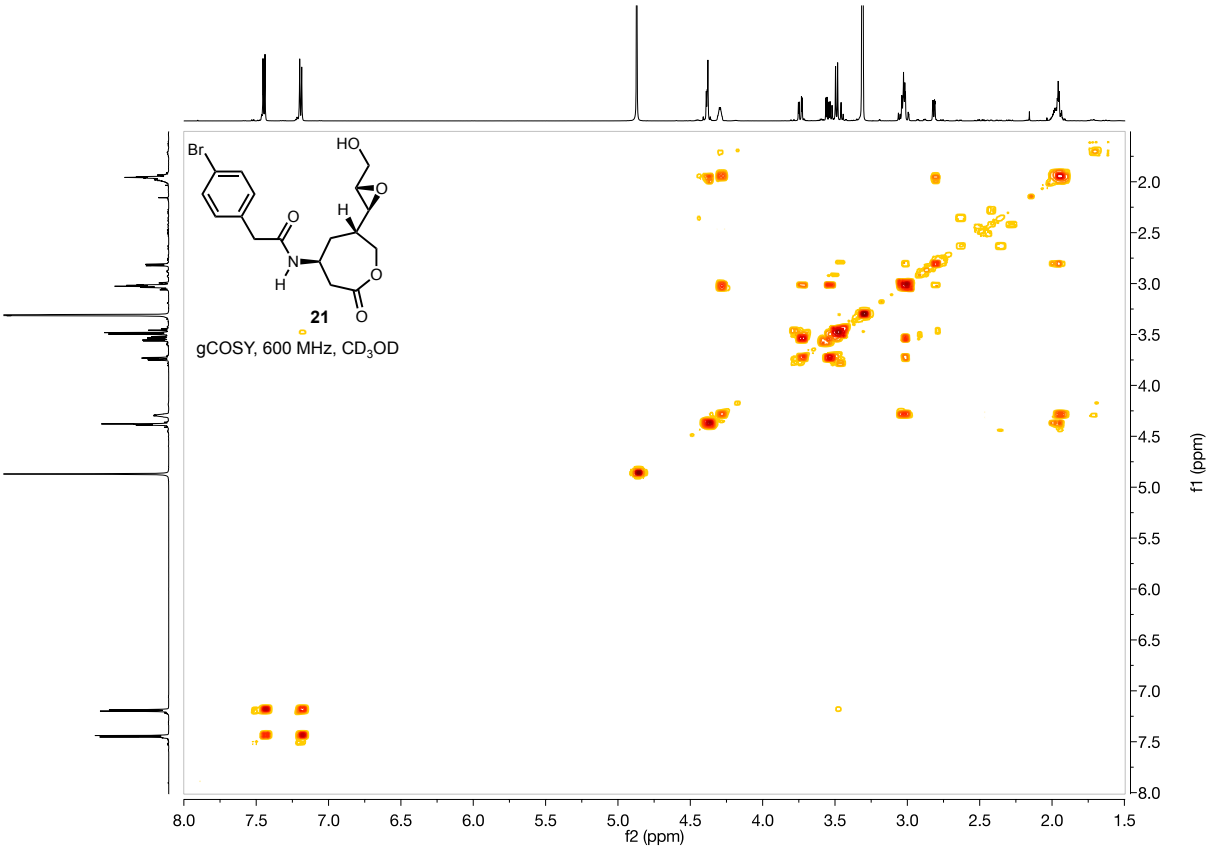

Br
HO
O
H
N
H
O
O
20
HSQCAD, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)

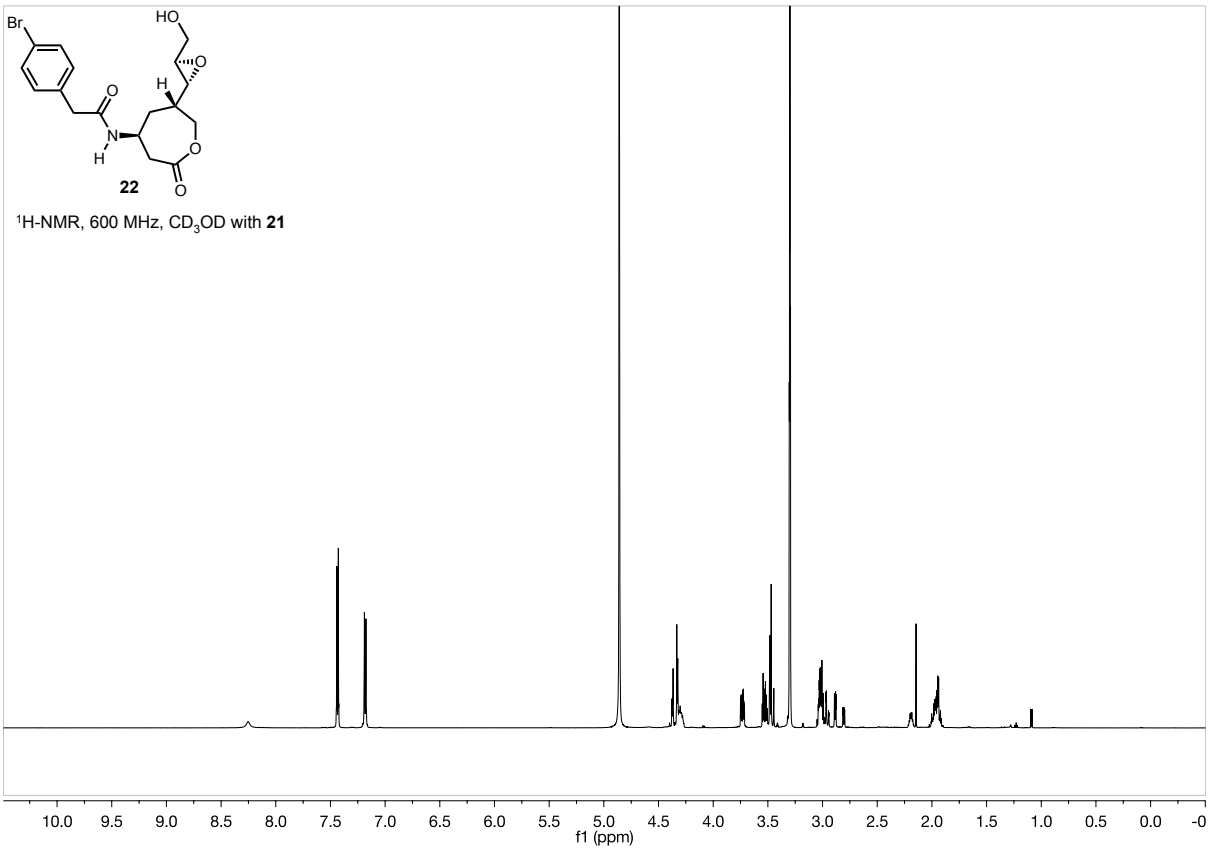

Br
HO
O
H
N
H
O
O
20
gCOSY, 600 MHz, CDCl3
f1 (ppm)
f2 (ppm)


Br
HO
O
H
O
N
H
O
O
21
^{1}H-NMR, 600 MHz, CD_3OD
2.0
2.0
1.9
1.0
1.0
1.0
2.0
2.8
1.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

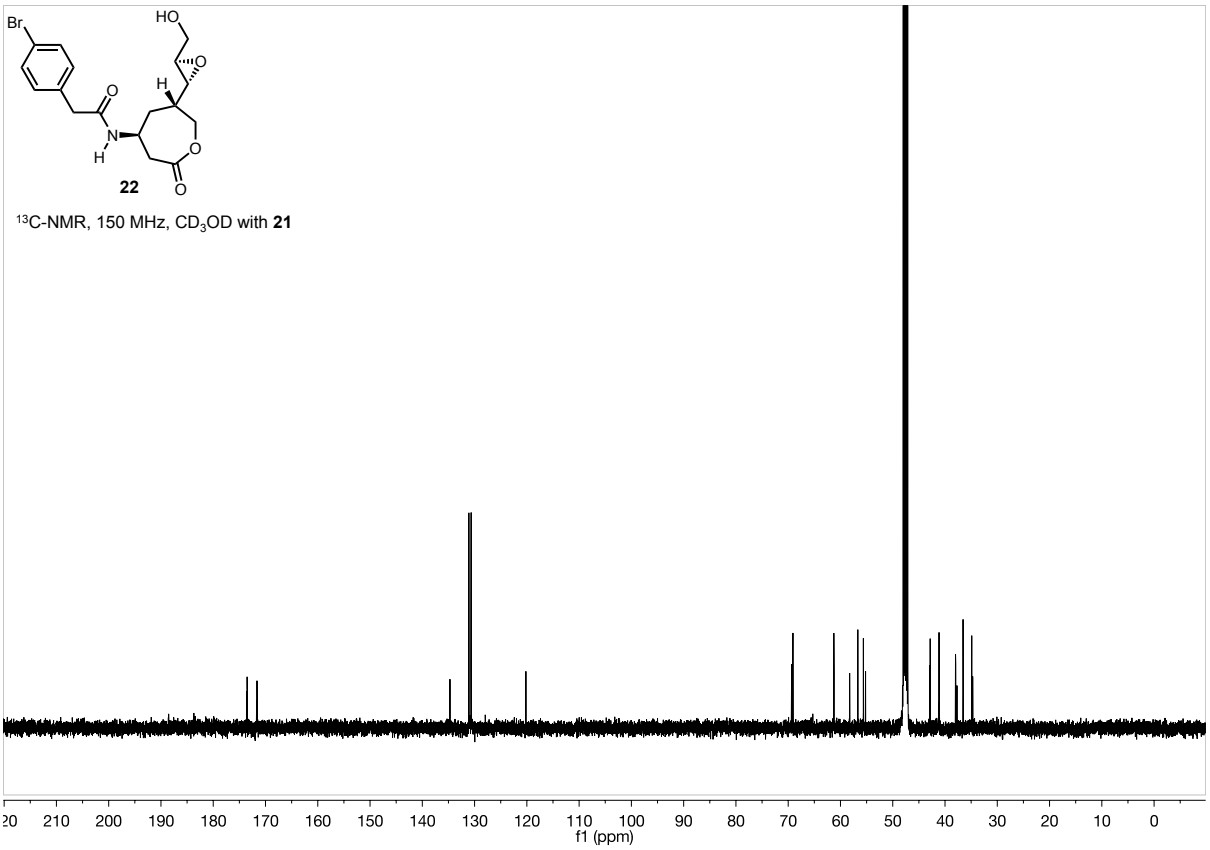

Br
HO
O
H
O
N
H
O
O
21
^{13}C-NMR, 150 MHz, CD_3OD
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


Br
HO
O
H
O
N
H
O
O
21
HSQCAD, 600/150 MHz, CD3OD
f1 (ppm)
f2 (ppm)


Br
HO
O
H
O
N
H
O
O
21
gCOSY, 600 MHz, CD3OD
f1 (ppm)
f2 (ppm)



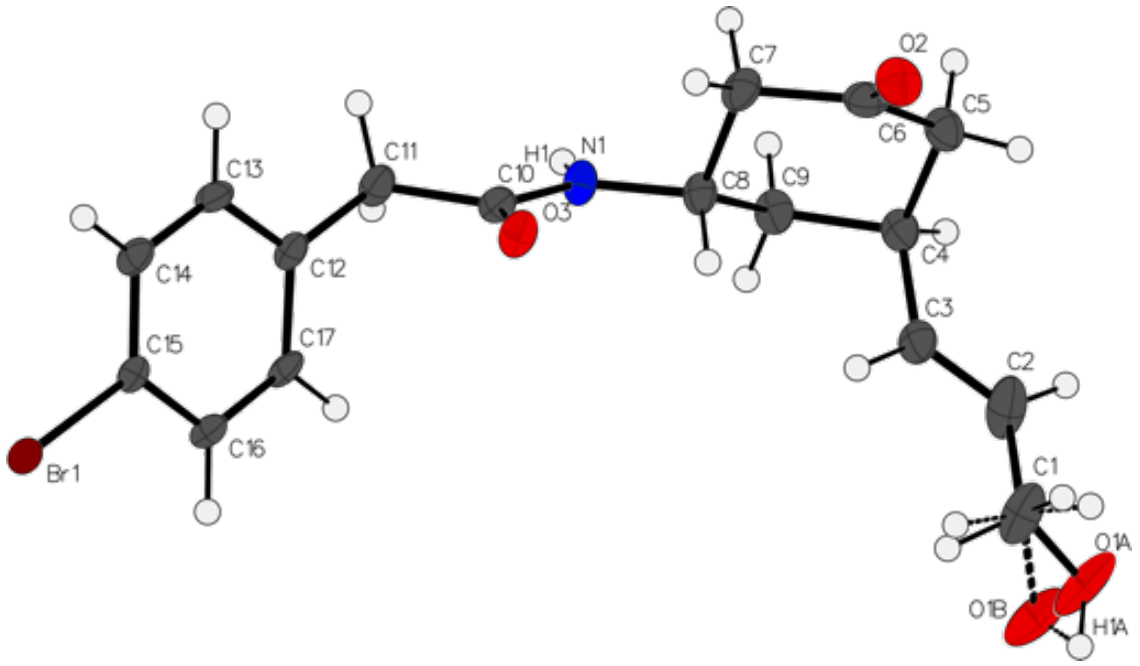
^{1}H-NMR, 600 MHz, CD_3OD with **21**



^{13}C-NMR, 150 MHz, CD_3OD with **21**

1.6 Crystallographic Data for the Substrate 14 and Epoxide 15

Substrate 14: Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007-16080. The diffraction images were processed and scaled using the Rigaku CrystalClear software (CrystalClear and CrystalStructure; Rigaku/MSC: The Woodlands, TX, 2005). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl and alcohol groups). The alcohol oxygen O1 is disordered equally over two positions, but each position shares only one hydrogen atom. The O-H distances and thermal parameters of O-C were restrained to be similar. The full numbering scheme of compound 007-16080 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1480519 (007-16080) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.



Supplementary Figure S49: The complete numbering scheme of 007-16080 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Supplementary Table S7: Crystal data and structure refinement for 007-16080.

Identification code	007-16080	
Empirical formula	C17 H20 Br N O3	
Formula weight	366.25	
Temperature	93(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.9054(4) Å	α= 90°.
	b = 4.8839(3) Å	β= 92.5890(19)°.
	c = 27.8255(19) Å	γ = 90°.
Volume	801.70(9) $Å^3$	
Z	2	
Density (calculated)	1.517 Mg/m^3	
Absorption coefficient	3.599 mm^{-1}	
F(000)	376	
Crystal size	0.200 x 0.200 x 0.010 mm^3	
Theta range for data collection	4.772 to 68.036°.	
Index ranges	-7<=h<=7, -5<=k<=5, -33<=l<=33	
Reflections collected	28613	
Independent reflections	2877 [R(int) = 0.1073]	
Completeness to theta = 67.679°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.685	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2877 / 9 / 212	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0321, wR2 = 0.0782	
R indices (all data)	R1 = 0.0327, wR2 = 0.0784	
Absolute structure parameter	-0.014(11)	
Largest diff. peak and hole	0.661 and -0.489 $e.Å^{-3}$	

Supplementary Table S8: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 007-16080. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	1064(1)	7334(1)	419(1)	20(1)
O(1A)	6316(16)	2060(30)	4930(3)	46(2)
O(1B)	5267(16)	2060(30)	4797(3)	46(2)
O(2)	14471(4)	2767(7)	3295(1)	31(1)
O(3)	8286(4)	2608(7)	2084(1)	26(1)
N(1)	8680(5)	-1718(7)	2358(1)	21(1)
C(1)	7356(9)	2971(8)	4534(1)	37(1)
C(2)	8641(8)	631(9)	4351(2)	39(1)
C(3)	9014(6)	204(9)	3901(1)	26(1)
C(4)	10418(6)	-2042(8)	3699(1)	23(1)
C(5)	12938(6)	-1178(9)	3668(1)	25(1)
C(6)	13318(6)	703(9)	3255(1)	25(1)
C(7)	12237(6)	-124(9)	2777(1)	25(1)
C(8)	9720(6)	-825(8)	2820(1)	20(1)
C(9)	9448(6)	-3004(9)	3202(1)	23(1)
C(10)	8032(6)	134(8)	2020(1)	20(1)
C(11)	7065(7)	-1052(9)	1550(1)	23(1)
C(12)	5602(6)	962(7)	1274(1)	18(1)
C(13)	6279(5)	2115(10)	847(1)	21(1)
C(14)	4948(6)	4002(8)	591(1)	20(1)
C(15)	2884(5)	4759(8)	770(1)	18(1)
C(16)	2162(6)	3668(9)	1195(1)	22(1)
C(17)	3509(6)	1760(8)	1438(1)	20(1)

Supplementary Table S9: Bond lengths [Å] and angles [°] for 007-16080.

Br(1)-C(15)	1.896(3)
O(1A)-C(1)	1.360(9)
O(1A)-H(1A)	0.85(6)
O(1B)-C(1)	1.529(10)
O(1B)-H(1A)	0.83(6)
O(2)-C(6)	1.219(5)
O(3)-C(10)	1.230(6)
N(1)-C(10)	1.346(4)
N(1)-C(8)	1.465(4)
N(1)-H(1)	0.8800
C(1)-C(2)	1.475(6)
C(1)-H(1BC)	0.9900
C(1)-H(1BD)	0.9900
C(1)-H(1AA)	0.9900
C(1)-H(1AB)	0.9900
C(2)-C(3)	1.299(6)
C(2)-H(2)	0.9500
C(3)-C(4)	1.499(6)
C(3)-H(3)	0.9500
C(4)-C(9)	1.545(5)
C(4)-C(5)	1.553(5)
C(4)-H(4)	1.0000
C(5)-C(6)	1.496(5)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.506(5)
C(7)-C(8)	1.535(5)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.519(5)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.519(5)
C(11)-C(12)	1.497(5)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.391(5)
C(12)-C(17)	1.393(5)
C(13)-C(14)	1.387(5)
C(13)-H(13)	0.9500
C(14)-C(15)	1.388(5)
C(14)-H(14)	0.9500
C(15)-C(16)	1.381(5)
C(16)-C(17)	1.383(5)
C(16)-H(16)	0.9500

C(17)-H(17)	0.9500
C(1)-O(1A)-H(1A)	102(5)
C(1)-O(1B)-H(1A)	90(4)
C(10)-N(1)-C(8)	120.4(3)
C(10)-N(1)-H(1)	119.8
C(8)-N(1)-H(1)	119.8
O(1A)-C(1)-C(2)	106.4(7)
C(2)-C(1)-O(1B)	112.2(7)
C(2)-C(1)-H(1BC)	109.2
O(1B)-C(1)-H(1BC)	109.2
C(2)-C(1)-H(1BD)	109.2
O(1B)-C(1)-H(1BD)	109.2
H(1BC)-C(1)-H(1BD)	107.9
O(1A)-C(1)-H(1AA)	110.4
C(2)-C(1)-H(1AA)	110.4
O(1A)-C(1)-H(1AB)	110.4
C(2)-C(1)-H(1AB)	110.4
H(1AA)-C(1)-H(1AB)	108.6
C(3)-C(2)-C(1)	124.7(4)
C(3)-C(2)-H(2)	117.7
C(1)-C(2)-H(2)	117.7
C(2)-C(3)-C(4)	126.8(4)
C(2)-C(3)-H(3)	116.6
C(4)-C(3)-H(3)	116.6
C(3)-C(4)-C(9)	111.7(3)
C(3)-C(4)-C(5)	111.7(3)
C(9)-C(4)-C(5)	110.5(3)
C(3)-C(4)-H(4)	107.6
C(9)-C(4)-H(4)	107.6
C(5)-C(4)-H(4)	107.6
C(6)-C(5)-C(4)	112.8(3)
C(6)-C(5)-H(5A)	109.0
C(4)-C(5)-H(5A)	109.0
C(6)-C(5)-H(5B)	109.0
C(4)-C(5)-H(5B)	109.0
H(5A)-C(5)-H(5B)	107.8
O(2)-C(6)-C(5)	122.8(3)
O(2)-C(6)-C(7)	121.0(4)
C(5)-C(6)-C(7)	116.2(3)
C(6)-C(7)-C(8)	111.4(3)
C(6)-C(7)-H(7A)	109.4
C(8)-C(7)-H(7A)	109.4
C(6)-C(7)-H(7B)	109.4
C(8)-C(7)-H(7B)	109.4
H(7A)-C(7)-H(7B)	108.0
N(1)-C(8)-C(9)	110.7(3)
N(1)-C(8)-C(7)	111.5(3)
C(9)-C(8)-C(7)	110.1(3)

N(1)-C(8)-H(8)	108.1
C(9)-C(8)-H(8)	108.1
C(7)-C(8)-H(8)	108.1
C(8)-C(9)-C(4)	111.6(3)
C(8)-C(9)-H(9A)	109.3
C(4)-C(9)-H(9A)	109.3
C(8)-C(9)-H(9B)	109.3
C(4)-C(9)-H(9B)	109.3
H(9A)-C(9)-H(9B)	108.0
O(3)-C(10)-N(1)	122.1(3)
O(3)-C(10)-C(11)	122.5(3)
N(1)-C(10)-C(11)	115.4(3)
C(12)-C(11)-C(10)	112.1(3)
C(12)-C(11)-H(11A)	109.2
C(10)-C(11)-H(11A)	109.2
C(12)-C(11)-H(11B)	109.2
C(10)-C(11)-H(11B)	109.2
H(11A)-C(11)-H(11B)	107.9
C(13)-C(12)-C(17)	117.5(3)
C(13)-C(12)-C(11)	121.5(3)
C(17)-C(12)-C(11)	121.1(3)
C(14)-C(13)-C(12)	122.0(3)
C(14)-C(13)-H(13)	119.0
C(12)-C(13)-H(13)	119.0
C(13)-C(14)-C(15)	118.6(3)
C(13)-C(14)-H(14)	120.7
C(15)-C(14)-H(14)	120.7
C(16)-C(15)-C(14)	121.0(3)
C(16)-C(15)-Br(1)	120.4(3)
C(14)-C(15)-Br(1)	118.6(2)
C(15)-C(16)-C(17)	119.1(3)
C(15)-C(16)-H(16)	120.4
C(17)-C(16)-H(16)	120.4
C(16)-C(17)-C(12)	121.8(3)
C(16)-C(17)-H(17)	119.1
C(12)-C(17)-H(17)	119.1

Symmetry transformations used to generate equivalent atoms:

Supplementary Table S10. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 007-16080. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	24(1)	21(1)	15(1)	0(1)	2(1)	4(1)
O(1A)	94(7)	23(4)	24(4)	-2(4)	27(4)	-3(7)
O(1B)	77(6)	32(5)	31(4)	0(5)	29(4)	-4(6)
O(2)	27(1)	31(2)	34(1)	3(1)	0(1)	-8(1)
O(3)	39(1)	19(2)	20(1)	0(1)	0(1)	2(1)
N(1)	31(2)	15(2)	16(2)	3(1)	-2(1)	-2(1)
C(1)	64(3)	26(3)	22(2)	-2(2)	4(2)	-5(2)
C(2)	65(3)	27(2)	24(2)	0(2)	-8(2)	5(2)
C(3)	25(2)	33(2)	19(2)	8(2)	3(1)	-5(2)
C(4)	23(2)	25(3)	20(2)	9(2)	1(1)	-3(1)
C(5)	24(2)	28(2)	24(2)	6(2)	-1(2)	-2(2)
C(6)	19(2)	29(2)	27(2)	2(2)	5(1)	1(2)
C(7)	28(2)	30(2)	18(2)	3(2)	6(1)	-6(2)
C(8)	24(2)	21(2)	16(2)	5(2)	0(1)	-3(2)
C(9)	25(2)	23(2)	22(2)	8(2)	1(1)	-6(2)
C(10)	23(2)	19(2)	18(2)	0(2)	3(1)	2(2)
C(11)	33(2)	20(2)	16(2)	-1(2)	1(2)	5(2)
C(12)	26(2)	16(2)	13(2)	-2(1)	2(1)	1(2)
C(13)	23(2)	24(2)	16(1)	2(2)	7(1)	6(2)
C(14)	26(2)	20(2)	15(2)	3(2)	6(1)	1(2)
C(15)	22(2)	19(2)	12(2)	0(2)	2(1)	-1(2)
C(16)	22(2)	29(2)	15(2)	-2(2)	6(1)	1(2)
C(17)	27(2)	21(2)	11(2)	2(1)	8(1)	1(2)

Supplementary Table S11: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 007-16080.

	x	y	z	U(eq)
H(1A)	5420(80)	3380(130)	4980(20)	60(20)
H(1)	8478	-3475	2301	25
H(1BC)	6873	4169	4261	45
H(1BD)	8357	4056	4756	45
H(1AA)	8391	4508	4620	45
H(1AB)	6219	3613	4287	45
H(2)	9238	-657	4579	47
H(3)	8326	1446	3676	31
H(4)	10366	-3636	3924	27
H(5A)	13439	-257	3972	30
H(5B)	13879	-2839	3634	30
H(7A)	13041	-1736	2652	30
H(7B)	12384	1392	2544	30
H(8)	8918	865	2922	24
H(9A)	10242	-4693	3108	28
H(9B)	7820	-3445	3225	28
H(11A)	8327	-1622	1350	28
H(11B)	6158	-2700	1619	28
H(13)	7696	1594	726	25
H(14)	5440	4760	299	24
H(16)	758	4221	1318	26
H(17)	2992	972	1726	23

Supplementary Table S12: Torsion angles [°] for 007-16080.

O(1A)-C(1)-C(2)-C(3)	148.2(6)
O(1B)-C(1)-C(2)-C(3)	119.6(6)
C(1)-C(2)-C(3)-C(4)	176.2(4)
C(2)-C(3)-C(4)-C(9)	146.2(4)
C(2)-C(3)-C(4)-C(5)	-89.5(5)
C(3)-C(4)-C(5)-C(6)	-76.5(4)
C(9)-C(4)-C(5)-C(6)	48.4(4)
C(4)-C(5)-C(6)-O(2)	134.5(4)
C(4)-C(5)-C(6)-C(7)	-47.0(5)
O(2)-C(6)-C(7)-C(8)	-131.5(4)
C(5)-C(6)-C(7)-C(8)	50.0(5)
C(10)-N(1)-C(8)-C(9)	157.4(3)
C(10)-N(1)-C(8)-C(7)	-79.7(4)
C(6)-C(7)-C(8)-N(1)	-178.1(3)
C(6)-C(7)-C(8)-C(9)	-54.9(5)
N(1)-C(8)-C(9)-C(4)	-176.9(3)
C(7)-C(8)-C(9)-C(4)	59.3(4)
C(3)-C(4)-C(9)-C(8)	69.1(4)
C(5)-C(4)-C(9)-C(8)	-55.8(4)
C(8)-N(1)-C(10)-O(3)	0.2(5)
C(8)-N(1)-C(10)-C(11)	177.6(3)
O(3)-C(10)-C(11)-C(12)	-24.6(5)
N(1)-C(10)-C(11)-C(12)	158.0(3)
C(10)-C(11)-C(12)-C(13)	110.3(4)
C(10)-C(11)-C(12)-C(17)	-69.4(5)
C(17)-C(12)-C(13)-C(14)	0.4(6)
C(11)-C(12)-C(13)-C(14)	-179.4(4)
C(12)-C(13)-C(14)-C(15)	0.2(6)
C(13)-C(14)-C(15)-C(16)	0.1(6)
C(13)-C(14)-C(15)-Br(1)	-179.9(3)
C(14)-C(15)-C(16)-C(17)	-1.1(6)
Br(1)-C(15)-C(16)-C(17)	179.0(3)
C(15)-C(16)-C(17)-C(12)	1.7(6)
C(13)-C(12)-C(17)-C(16)	-1.4(6)
C(11)-C(12)-C(17)-C(16)	178.4(4)

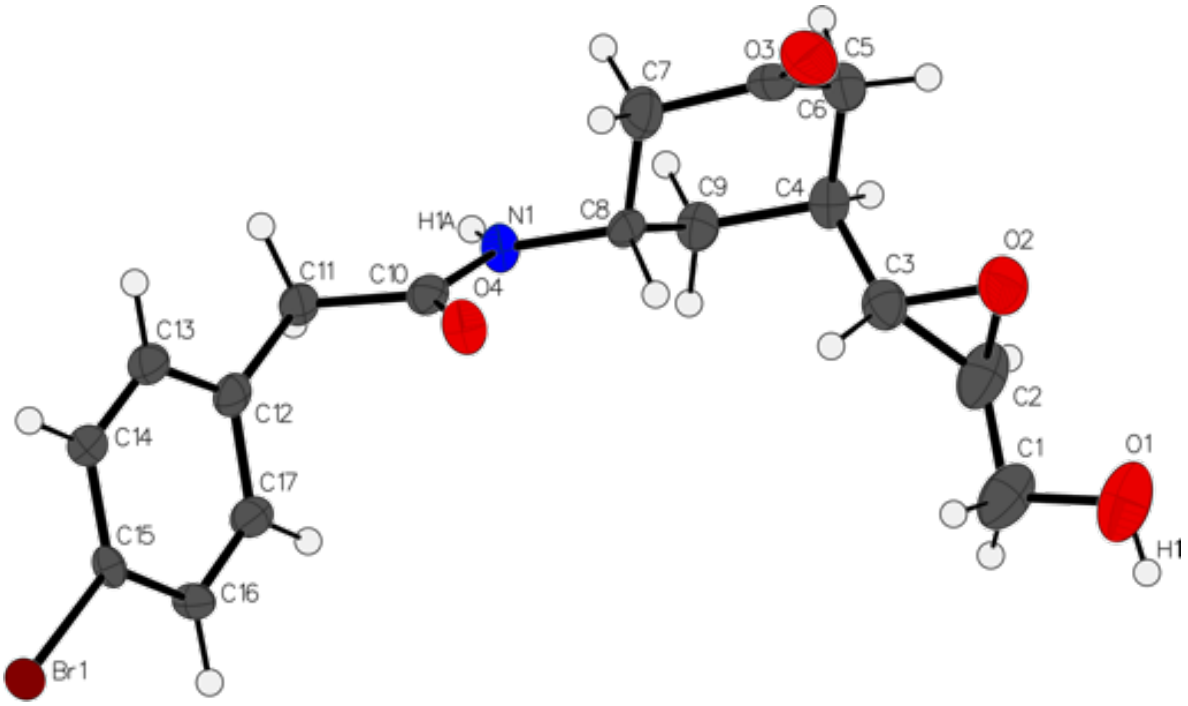
Symmetry transformations used to generate equivalent atoms:

Supplementary Table S13: Hydrogen bonds for 007-16080 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1A)-H(1A)...O(1A)#1	0.85(6)	2.09(6)	2.930(10)	170(6)
O(1B)-H(1A)...O(1B)#1	0.83(6)	1.95(7)	2.716(7)	154(5)
N(1)-H(1)...O(3)#2	0.88	2.01	2.881(5)	171.5

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y+1/2,-z+1 #2 x,y-1,z

Epoxide 15: Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007-16082. The diffraction images were processed and scaled using the Rigaku CrystalClear software (CrystalClear and CrystalStructure; Rigaku/MSC: The Woodlands, TX, 2005). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl and alcohol groups). The thermal parameters of the aryl group with carbon atoms C12, C13, C14, C15, C16, and C17 were refined with rigid bond restraints, as their freely refined anisotropic parameters presented opposing directions. Several reflections were improperly recorded and subsequently omitted. The full numbering scheme of compound 007-16082 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1480521 (007-16082) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.



Supplementary Figure S50: The complete numbering scheme of 007-16082 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Supplementary Table S14: Crystal data and structure refinement for 007-16082.

Identification code	007-16082
Empirical formula	C17 H20 Br N O4
Formula weight	382.25
Temperature	93(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 4.96560(10) Å a= 90°.
	b = 5.9207(2) Å b= 90°.
	c = 54.632(4) Å g = 90°.
Volume	1606.17(13) $Å^3$
Z	4
Density (calculated)	1.581 Mg/m^3
Absorption coefficient	3.668 mm^{-1}
F(000)	784
Crystal size	0.200 x 0.200 x 0.010 mm^3
Theta range for data collection	7.525 to 66.524°.
Index ranges	-5<=h<=5, -7<=k<=6, -64<=l<=64
Reflections collected	16072
Independent reflections	2638 [R(int) = 0.0972]
Completeness to theta = 66.524°	96.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.827
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2638 / 36 / 209
Goodness-of-fit on F2	1.110
Final R indices [I>2sigma(I)]	R1 = 0.0721, wR2 = 0.1839
R indices (all data)	R1 = 0.0759, wR2 = 0.1877
Absolute structure parameter	0.04(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.972 and -1.474 $e.Å^{-3}$

Supplementary Table S15: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å2x 10^3) for 007-16082. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	1985(3)	-1546(2)	5211(1)	24(1)
O(1)	5970(20)	4030(20)	7499(2)	60(4)
O(2)	8270(20)	7302(16)	7189(2)	43(2)
O(3)	7610(20)	11609(16)	6654(2)	46(3)
O(4)	6920(20)	5293(14)	6059(1)	29(2)
N(1)	11241(18)	5524(17)	6192(1)	22(2)
C(1)	7160(30)	3370(30)	7276(2)	49(4)
C(2)	9290(30)	5040(30)	7215(2)	46(4)
C(3)	9330(30)	6180(20)	6976(2)	31(3)
C(4)	11900(30)	7230(20)	6868(2)	33(3)
C(5)	11480(30)	9790(20)	6831(2)	35(3)
C(6)	9520(30)	10340(20)	6634(2)	33(3)
C(7)	10100(30)	9120(20)	6391(2)	37(3)
C(8)	10500(20)	6570(20)	6427(2)	25(3)
C(9)	12560(30)	6110(20)	6622(2)	31(3)
C(10)	9390(30)	4990(20)	6023(2)	25(3)
C(11)	10440(20)	4050(20)	5783(2)	25(3)
C(12)	8400(30)	2694(19)	5644(2)	24(2)
C(13)	7190(30)	3486(19)	5427(2)	27(2)
C(14)	5370(30)	2262(19)	5300(2)	26(3)
C(15)	4500(20)	145(18)	5387(2)	18(2)
C(16)	5650(20)	-706(19)	5606(2)	21(2)
C(17)	7510(30)	554(19)	5726(2)	26(3)

Supplementary Table S16: Bond lengths [Å] and angles [°] for 007-16082.

Br(1)-C(15)	1.865(11)
O(1)-C(1)	1.411(15)
O(1)-H(1)	0.8400
O(2)-C(2)	1.437(17)
O(2)-C(3)	1.437(14)
O(3)-C(6)	1.216(17)
O(4)-C(10)	1.254(16)
N(1)-C(10)	1.342(14)
N(1)-C(8)	1.474(12)
N(1)-H(1A)	0.8800
C(1)-C(2)	1.49(2)
C(1)-H(1B)	0.9900
C(1)-H(1C)	0.9900
C(2)-C(3)	1.470(16)
C(2)-H(2)	1.0000
C(3)-C(4)	1.53(2)
C(3)-H(3)	1.0000
C(4)-C(9)	1.534(14)
C(4)-C(5)	1.544(17)
C(4)-H(4)	1.0000
C(5)-C(6)	1.485(18)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.537(16)
C(7)-C(8)	1.534(18)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.502(16)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.514(14)
C(11)-C(12)	1.500(17)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.407(15)
C(12)-C(17)	1.414(16)
C(13)-C(14)	1.352(17)
C(13)-H(13)	0.9500
C(14)-C(15)	1.409(16)
C(14)-H(14)	0.9500
C(15)-C(16)	1.419(13)
C(16)-C(17)	1.360(16)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500

C(1)-O(1)-H(1) 109.5
C(2)-O(2)-C(3) 61.5(8)
C(10)-N(1)-C(8) 121.9(10)
C(10)-N(1)-H(1A) 119.1
C(8)-N(1)-H(1A) 119.1
O(1)-C(1)-C(2) 108.0(13)
O(1)-C(1)-H(1B) 110.1
C(2)-C(1)-H(1B) 110.1
O(1)-C(1)-H(1C) 110.1
C(2)-C(1)-H(1C) 110.1
H(1B)-C(1)-H(1C) 108.4
O(2)-C(2)-C(3) 59.2(8)
O(2)-C(2)-C(1) 113.1(13)
C(3)-C(2)-C(1) 121.0(14)
O(2)-C(2)-H(2) 116.8
C(3)-C(2)-H(2) 116.8
C(1)-C(2)-H(2) 116.8
O(2)-C(3)-C(2) 59.2(8)
O(2)-C(3)-C(4) 115.5(11)
C(2)-C(3)-C(4) 122.6(13)
O(2)-C(3)-H(3) 115.7
C(2)-C(3)-H(3) 115.7
C(4)-C(3)-H(3) 115.7
C(3)-C(4)-C(9) 110.2(11)
C(3)-C(4)-C(5) 109.5(13)
C(9)-C(4)-C(5) 109.6(10)
C(3)-C(4)-H(4) 109.2
C(9)-C(4)-H(4) 109.2
C(5)-C(4)-H(4) 109.2
C(6)-C(5)-C(4) 113.6(11)
C(6)-C(5)-H(5A) 108.8
C(4)-C(5)-H(5A) 108.8
C(6)-C(5)-H(5B) 108.8
C(4)-C(5)-H(5B) 108.8
H(5A)-C(5)-H(5B) 107.7
O(3)-C(6)-C(5) 125.3(11)
O(3)-C(6)-C(7) 121.2(12)
C(5)-C(6)-C(7) 113.5(12)
C(8)-C(7)-C(6) 112.1(9)
C(8)-C(7)-H(7A) 109.2
C(6)-C(7)-H(7A) 109.2
C(8)-C(7)-H(7B) 109.2
C(6)-C(7)-H(7B) 109.2
H(7A)-C(7)-H(7B) 107.9
N(1)-C(8)-C(9) 111.7(10)
N(1)-C(8)-C(7) 109.5(9)
C(9)-C(8)-C(7) 110.9(10)
N(1)-C(8)-H(8) 108.2
C(9)-C(8)-H(8) 108.2

C(7)-C(8)-H(8)	108.2
C(8)-C(9)-C(4)	113.3(11)
C(8)-C(9)-H(9A)	108.9
C(4)-C(9)-H(9A)	108.9
C(8)-C(9)-H(9B)	108.9
C(4)-C(9)-H(9B)	108.9
H(9A)-C(9)-H(9B)	107.7
O(4)-C(10)-N(1)	121.9(10)
O(4)-C(10)-C(11)	121.6(10)
N(1)-C(10)-C(11)	116.5(11)
C(12)-C(11)-C(10)	113.8(10)
C(12)-C(11)-H(11A)	108.8
C(10)-C(11)-H(11A)	108.8
C(12)-C(11)-H(11B)	108.8
C(10)-C(11)-H(11B)	108.8
H(11A)-C(11)-H(11B)	107.7
C(13)-C(12)-C(17)	115.8(11)
C(13)-C(12)-C(11)	122.5(11)
C(17)-C(12)-C(11)	121.7(10)
C(14)-C(13)-C(12)	122.6(11)
C(14)-C(13)-H(13)	118.7
C(12)-C(13)-H(13)	118.7
C(13)-C(14)-C(15)	120.6(10)
C(13)-C(14)-H(14)	119.7
C(15)-C(14)-H(14)	119.7
C(14)-C(15)-C(16)	118.5(11)
C(14)-C(15)-Br(1)	120.6(8)
C(16)-C(15)-Br(1)	120.9(8)
C(17)-C(16)-C(15)	119.2(10)
C(17)-C(16)-H(16)	120.4
C(15)-C(16)-H(16)	120.4
C(16)-C(17)-C(12)	123.3(10)
C(16)-C(17)-H(17)	118.4
C(12)-C(17)-H(17)	118.4

Symmetry transformations used to generate equivalent atoms:

Supplementary Table S17: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 007-16082. The anisotropic displacement factor exponent takes the form: -2p2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br(1)	26(1)	25(1)	22(1)	-2(1)	0(1)	-3(1)
O(1)	54(8)	84(9)	41(5)	7(5)	12(5)	16(7)
O(2)	41(6)	47(6)	42(4)	-9(4)	12(5)	-1(5)
O(3)	54(8)	33(5)	50(5)	-6(4)	7(4)	4(6)
O(4)	17(5)	41(5)	28(3)	-6(3)	-4(4)	4(5)
N(1)	5(5)	37(6)	23(4)	-7(4)	1(3)	1(4)
C(1)	50(10)	50(8)	47(7)	15(7)	19(7)	21(10)
C(2)	49(10)	55(10)	33(6)	11(6)	6(6)	15(9)
C(3)	34(8)	31(7)	26(5)	0(5)	-4(5)	4(7)
C(4)	40(8)	36(7)	23(5)	-4(4)	4(6)	-1(7)
C(5)	40(10)	36(7)	29(5)	-6(5)	5(5)	-7(7)
C(6)	39(9)	24(7)	36(6)	-2(5)	10(6)	-11(7)
C(7)	56(10)	33(7)	23(5)	1(5)	0(6)	5(7)
C(8)	22(7)	31(6)	22(4)	-3(5)	8(4)	-11(7)
C(9)	33(9)	34(7)	26(5)	-2(4)	5(5)	-1(6)
C(10)	30(8)	26(7)	20(5)	4(4)	-4(5)	-5(6)
C(11)	16(7)	33(7)	24(5)	-4(4)	4(4)	-7(5)
C(12)	24(6)	25(5)	23(4)	0(3)	9(4)	3(4)
C(13)	37(6)	21(5)	24(4)	2(3)	5(4)	1(5)
C(14)	33(7)	23(5)	22(4)	1(3)	3(4)	-2(4)
C(15)	15(6)	22(5)	16(4)	-4(3)	-5(3)	2(4)
C(16)	21(6)	20(5)	22(4)	3(4)	-9(4)	-4(4)
C(17)	29(7)	26(5)	23(4)	3(3)	0(4)	-4(5)

Supplementary Table S18: Hydrogen coordinates (x 104) and isotropic displacement parameters ($Å^2$x 10^3) for 007-16082.

	x	y	z	U(eq)
H(1)	5194	2918	7563	90
H(1A)	12948	5239	6162	26
H(1B)	5791	3328	7145	58
H(1C)	7959	1846	7293	58
H(2)	11059	4870	7301	55
H(3)	7964	5649	6855	37
H(4)	13427	6981	6984	40
H(5A)	10833	10456	6986	42
H(5B)	13230	10491	6791	42
H(7A)	8582	9374	6277	45
H(7B)	11742	9767	6316	45
H(8)	8744	5908	6482	30
H(9A)	14334	6669	6565	37
H(9B)	12710	4460	6646	37
H(11A)	11055	5313	5679	29
H(11B)	12015	3076	5818	29
H(13)	7679	4939	5368	33
H(14)	4673	2834	5150	31
H(16)	5117	-2138	5668	25
H(17)	8266	-33	5873	31

Supplementary Table S19: Torsion angles [°] for 007-16082.

C(3)-O(2)-C(2)-C(1)	-113.4(14)
O(1)-C(1)-C(2)-O(2)	-59.7(15)
O(1)-C(1)-C(2)-C(3)	-126.6(14)
C(2)-O(2)-C(3)-C(4)	-114.3(14)
C(1)-C(2)-C(3)-O(2)	100.1(15)
O(2)-C(2)-C(3)-C(4)	102.3(13)
C(1)-C(2)-C(3)-C(4)	-157.6(12)
O(2)-C(3)-C(4)-C(9)	-171.4(10)
C(2)-C(3)-C(4)-C(9)	120.2(14)
O(2)-C(3)-C(4)-C(5)	-50.7(14)
C(2)-C(3)-C(4)-C(5)	-119.1(13)
C(3)-C(4)-C(5)-C(6)	-69.2(13)
C(9)-C(4)-C(5)-C(6)	51.8(18)
C(4)-C(5)-C(6)-O(3)	128.7(14)
C(4)-C(5)-C(6)-C(7)	-50.6(16)
O(3)-C(6)-C(7)-C(8)	-129.2(13)
C(5)-C(6)-C(7)-C(8)	50.2(16)
C(10)-N(1)-C(8)-C(9)	155.5(11)
C(10)-N(1)-C(8)-C(7)	-81.2(14)
C(6)-C(7)-C(8)-N(1)	-175.8(11)
C(6)-C(7)-C(8)-C(9)	-52.1(15)
N(1)-C(8)-C(9)-C(4)	178.5(10)
C(7)-C(8)-C(9)-C(4)	56.0(14)
C(3)-C(4)-C(9)-C(8)	65.5(13)
C(5)-C(4)-C(9)-C(8)	-55.0(17)
C(8)-N(1)-C(10)-O(4)	-2.3(18)
C(8)-N(1)-C(10)-C(11)	176.7(10)
O(4)-C(10)-C(11)-C(12)	-23.1(17)
N(1)-C(10)-C(11)-C(12)	157.9(10)
C(10)-C(11)-C(12)-C(13)	108.2(13)
C(10)-C(11)-C(12)-C(17)	-70.3(15)
C(17)-C(12)-C(13)-C(14)	-2.1(17)
C(11)-C(12)-C(13)-C(14)	179.4(11)
C(12)-C(13)-C(14)-C(15)	3.0(18)
C(13)-C(14)-C(15)-C(16)	-2.3(17)
C(13)-C(14)-C(15)-Br(1)	-179.9(9)
C(14)-C(15)-C(16)-C(17)	1.0(17)
Br(1)-C(15)-C(16)-C(17)	178.5(9)
C(15)-C(16)-C(17)-C(12)	-0.2(18)
C(13)-C(12)-C(17)-C(16)	0.6(17)
C(11)-C(12)-C(17)-C(16)	179.2(11)

Symmetry transformations used to generate equivalent atoms:

Supplementary Table S20: Hydrogen bonds for 007-16082 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(1)#1	0.84	2.40	3.112(8)	143.6
O(1)-H(1)...O(2)#1	0.84	2.22	2.895(15)	137.5
N(1)-H(1A)...O(4)#2	0.88	2.05	2.916(13)	167.1

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+3/2 #2 x+1,y,z

2. Computational Data

General computational information: All calculations were carried out on the supercomputer clusters provided by the Yale University Faculty of Arts and Science High Performance Computing Center.[10] These calculations were performed using Gaussian 09 revision *C*.01,[11] and the all input and output files were created and visualized using GaussView 5.0. All calculations were carried out at 25 °C and 1 atm of pressure in either the gas phase or solvated in chloroform using the IEF-PCM solvation model.[12-15]

In order to determine the Gibbs free energy difference ($\Delta G°$) between the two chair conformers of each compound, the optimized geometries of both the axial and equatorial conformations were found. First, potential energy scans were performed on the axial and equatorial phenyl-acetamide and alkene substituents using B3LYP/6-31+G(d,p) in order to determine the preferred dihedral angles of the compounds. The relevant dihedral angles were defined as constrained coordinates and a relaxed torsional potential energy scan from 0° to 360° at 10° increments was performed for each. On the dihedral scans shown below, the positive direction represents clockwise rotation of the functional group and the negative direction represents counterclockwise rotation. Red numbers on the y-axis of these scans represent the global maximum. Red numbers on the x-axis represent the dihedral angle that provide the lowest energy structure. Using these minimized dihedral angles, the compounds were then submitted for unconstrained geometry optimization and vibrational frequency calculation using B3LYP/6-311+G(d,p) in both the gas phase and chloroform. As a control, the dihedral angles of each compound were varied outside their absolute minimum and submitted for the same optimization and frequency calculation to ensure the previously calculated structures were the true energy minimum. Finally, single-point energies for the optimized geometries were calculated using M06-2X/6-311++G(2d,3p).[16-20]

The energies derived from these calculations are expressed as total energy ($E°$) in Hartree atomic units (a.u.). Each calculation performing a frequency calculation also contained a thermal correction of the total energy value to a Gibbs free energy value (G°).[21] These values can be used to calculate the change in Gibbs free energy (ΔG°) between the chair conformers in kilocalories per mole using the following equation:

$$\Delta G° = \left(G°_{axial} - G°_{equatorial}\right)\left(\frac{627.51\ kcal}{mol{\cdot}a.u.}\right) \quad (1)$$

Using 0.001987 kcal·mol^{-1}·K^{-1} as the gas constant (R) and 298 K as temperature (T), the equilibrium constant (K) can then be derived from this value by:

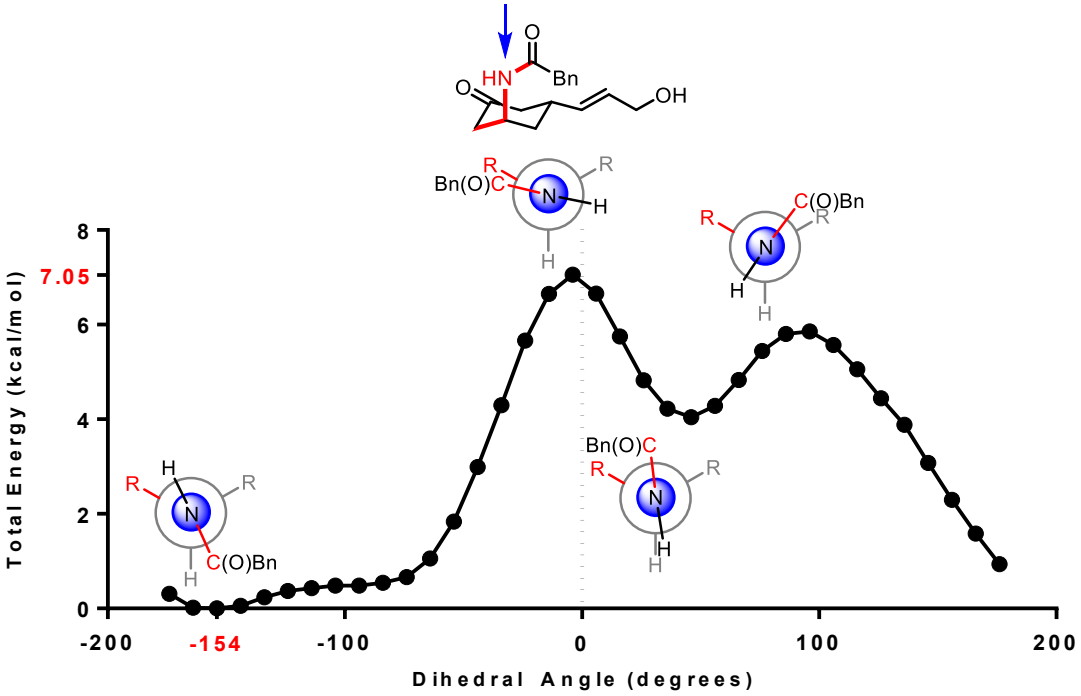
$$\Delta G° = -RTlnK \quad (2)$$

The equilibrium ratio of the two conformers can be obtained by the following equation [major:minor]:

$$\left[\left(100 - \frac{100}{1+K}\right) : \left(\frac{100}{1+K}\right)\right] \quad (3)$$

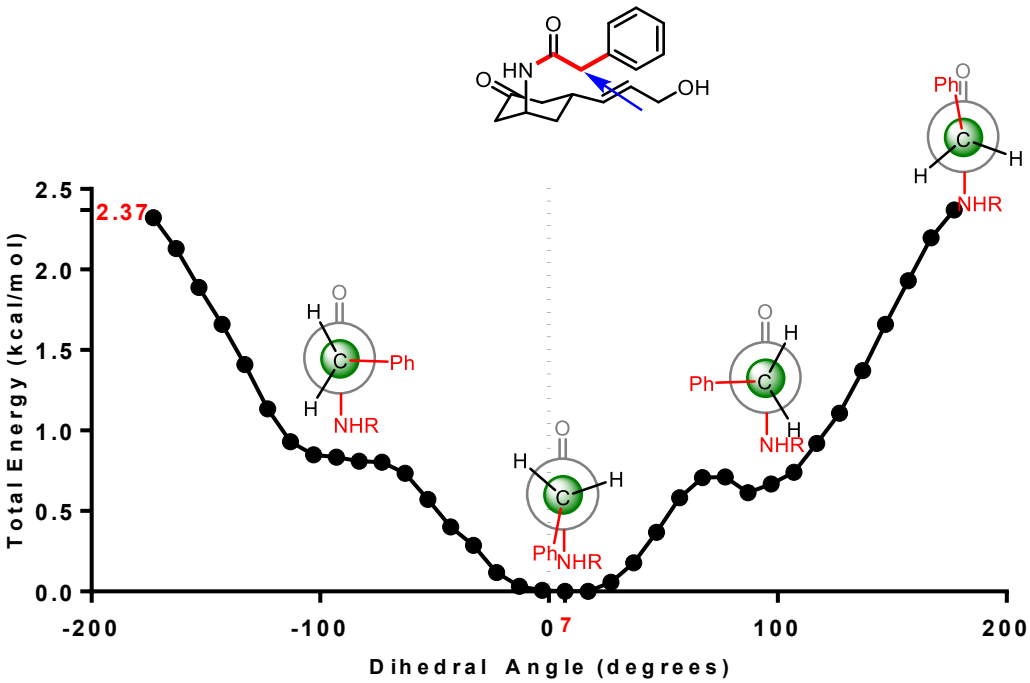
Geometry optimization and energy calculation of 7a (Section 1):

A. Relaxed potential energy scan of phenyl-acetamide HN-C dihedral with B3LYP/6-31+G(d,p)



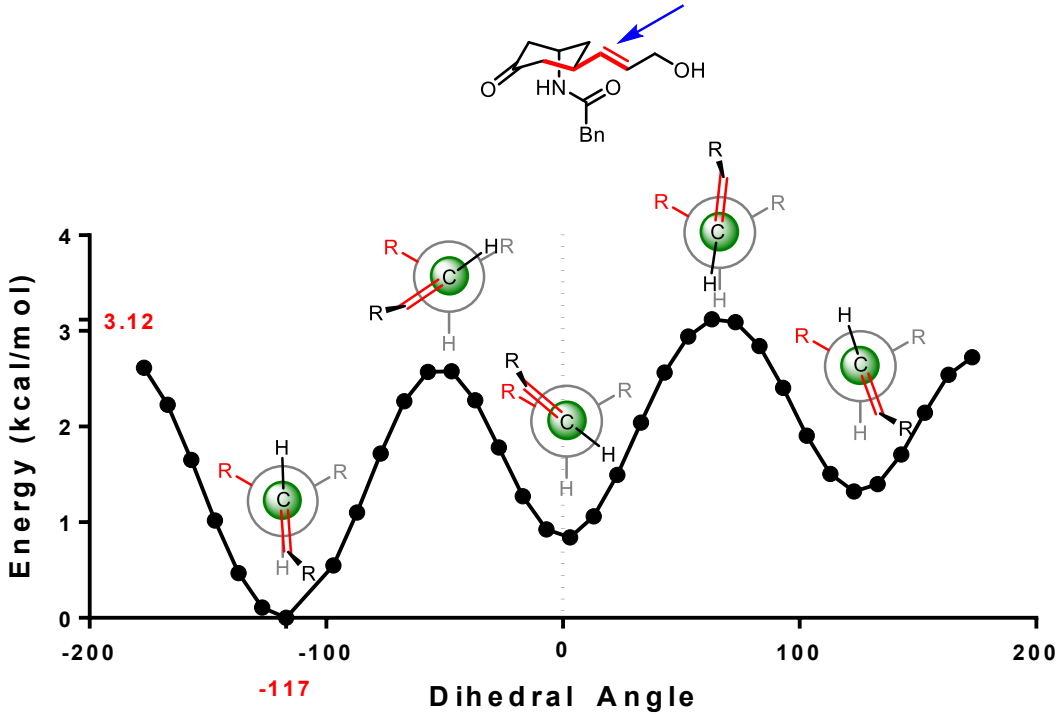
H*N*–C Dihedral (°)	Total Energy (kcal/mol)	H*N*–C Dihedral (°)	Total Energy (kcal/mol)
176	0.937	-4	7.054
166	1.582	-14	6.649
156	2.299	-24	5.662
146	3.079	-34	4.299
136	3.886	-44	2.993
126	4.444	-54	1.839
116	5.054	-64	1.057
106	5.573	-74	0.663
96	5.858	-84	0.543
86	5.801	-94	0.485
76	5.445	-104	0.48
66	4.829	-114	0.433
56	4.285	-124	0.372
46	4.044	-134	0.234
36	4.221	-144	0.059
26	4.826	-154	0
16	5.749	-164	0.014
6	6.657	-174	0.307

B. Relaxed potential energy scan of benzamide benzyl C-NH dihedral with B3LYP/6-31+G(d,p)



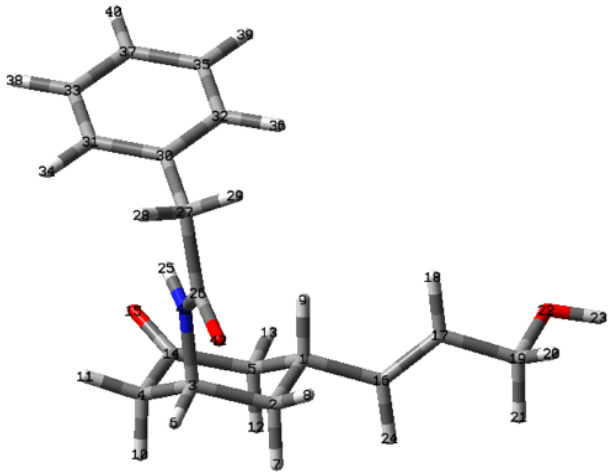
C–*N*H Dihedral (°)	Total Energy (kcal/mol)	C–*N*H Dihedral (°)	Total Energy (kcal/mol)
-173	2.322	7	0
-163	2.13	17	0.001
-153	1.888	27	0.058
-143	1.659	37	0.177
-133	1.409	47	0.369
-123	1.134	57	0.583
-113	0.93	67	0.708
-103	0.848	77	0.712
-93	0.835	87	0.613
-83	0.81	97	0.668
-73	0.802	107	0.741
-63	0.735	117	0.919
-53	0.572	127	1.107
-43	0.402	137	1.372
-33	0.287	147	1.659
-23	0.118	157	1.93
-13	0.033	167	2.196
-3	0.007	177	2.369

C. Relaxed potential energy scan of alkene C-C dihedral with B3LYP/6-31+G(d,p)



C–C Dihedral (°)	Total Energy (kcal/mol)	C–C Dihedral (°)	Total Energy (kcal/mol)
173	2.726	-7	0.924
163	2.543	-17	1.273
153	2.147	-27	1.781
143	1.709	-37	2.277
133	1.399	-47	2.578
123	1.321	-57	2.573
113	1.507	-67	2.267
103	1.906	-77	1.719
93	2.404	-87	1.103
83	2.842	-97	0.548
73	3.093	-117	0
63	3.12	-127	0.11
53	2.94	-137	0.468
43	2.564	-147	1.018
33	2.042	-157	1.652
23	1.494	-167	2.229
13	1.062	-177	2.616
3	0.84		

D. Geometry optimization of 7a in the gas phase using B3LYP/6-311+G(d,p)



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	-1.940864	-0.55683	0.27474	22	O	-5.420587	2.671814	0.015719
2	C	-1.487923	-1.690921	-0.665513	23	H	-6.232856	3.057202	-0.327054
3	C	-0.069865	-2.203067	-0.347503	24	H	-4.11962	-0.863292	0.080414
4	C	0.039302	-2.644318	1.124253	25	H	1.357845	-0.658188	0.118279
5	C	-1.830117	-1.003922	1.757494	26	C	1.446905	-1.014311	-1.893088
6	H	0.140511	-3.053276	-0.999698	27	C	2.566085	0.027218	-2.061336
7	H	-2.185059	-2.534837	-0.584682	28	H	3.427497	-0.530664	-2.440067
8	H	-1.516246	-1.354736	-1.703821	29	H	2.241373	0.672635	-2.881581
9	H	-1.269649	0.297247	0.129916	30	C	2.953379	0.84937	-0.855122
10	H	-0.59609	-3.527663	1.258743	31	C	3.959164	0.416848	0.01822
11	H	1.061494	-2.919617	1.389642	32	C	2.302853	2.057639	-0.573849
12	H	-2.569129	-1.79599	1.942786	33	C	4.300368	1.164873	1.143847
13	H	-2.043777	-0.179564	2.439119	34	H	4.482127	-0.511911	-0.187723
14	C	-0.458407	-1.568924	2.079364	35	C	2.641947	2.808378	0.549863
15	O	0.20361	-1.18538	3.020171	36	H	1.528015	2.414931	-1.245027
16	C	-3.341829	-0.107304	-0.038398	37	C	3.641085	2.362466	1.413673
17	C	-3.685099	1.114066	-0.443453	38	H	5.081631	0.812885	1.808039
18	H	-2.927294	1.887684	-0.55133	39	H	2.128096	3.742083	0.749424
19	C	-5.081079	1.530977	-0.783466	40	H	3.90462	2.944641	2.289174
20	H	-5.136039	1.793185	-1.849942	41	N	0.957131	-1.197849	-0.635892
21	H	-5.778473	0.703119	-0.601954	42	O	1.040188	-1.644479	-2.858363

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311++G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.14355901 a.u.
RMS Gradient Norm= 0.00000278 a.u.

Imaginary Freq= 0
Dipole Moment= 1.7306 Debye
Point Group= C1
Job cpu time= 1 day 0 hours 54 minutes 15.7 seconds

Zero-point correction= 0.351965 (Hartree/Particle)
Thermal correction to Energy= 0.372542
Thermal correction to Enthalpy= 0.373486
Thermal correction to Gibbs Free Energy= 0.298679
Sum of electronic and zero-point Energies= -940.791594
Sum of electronic and thermal Energies= -940.771017
Sum of electronic and thermal Enthalpies= -940.770073
Sum of electronic and thermal Free Energies= -940.844880

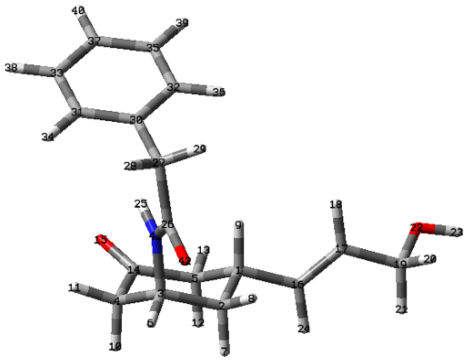
E. Single-Point Energy Calculation of 7a in the Gas Phase using M06-2X/6-311++G(2d,3p)

Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -940.78328393 a.u.
Dipole Moment= 1.6465 Debye
Point Group= C1
Job cpu time= 3 hours 23 minutes 27.7 seconds

From Section 1.D.:
Thermal correction to Gibbs Free Energy= 0.298679

Sum of electronic and thermal Free Energies= -940.78328393 + 0.298679 = -940.48460493 a.u.

F. Geometry optimization of 7a in chloroform using B3LYP/6-311+G(d,p) and the IEF-PCM Solvation Model



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	-1.965203	-0.533899	0.269519	22	O	-5.499778	2.631609	-0.023791
2	C	-1.499814	-1.679702	-0.650087	23	H	-6.314449	3.000951	-0.381285
3	C	-0.076849	-2.169186	-0.322375	24	H	-4.139739	-0.868178	0.069017
4	C	0.042202	-2.577786	1.158347	25	H	1.293676	-0.558156	0.085342
5	C	-1.859858	-0.959848	1.758391	26	C	1.487818	-1.04635	-1.877836
6	H	0.142834	-3.034782	-0.949026	27	C	2.575281	0.02178	-2.064161
7	H	-2.186418	-2.52963	-0.553945	28	H	3.43909	-0.510331	-2.471985
8	H	-1.53367	-1.359045	-1.693443	29	H	2.213544	0.67257	-2.865158
9	H	-1.303565	0.32559	0.113861	30	C	2.977044	0.839669	-0.858896
10	H	-0.566278	-3.477907	1.305751	31	C	3.989093	0.396297	0.002664
11	H	1.071227	-2.821491	1.427283	32	C	2.340566	2.054085	-0.571737
12	H	-2.594624	-1.753862	1.950035	33	C	4.351052	1.142164	1.123445
13	H	-2.08513	-0.128113	2.427325	34	H	4.499703	-0.537949	-0.208473
14	C	-0.49566	-1.519952	2.106556	35	C	2.700361	2.802472	0.548386
15	O	0.127582	-1.156564	3.086366	36	H	1.561438	2.418736	-1.233631
16	C	-3.370395	-0.104915	-0.055176	37	C	3.70617	2.347318	1.400245
17	C	-3.723761	1.108166	-0.478863	38	H	5.137783	0.783705	1.777712
18	H	-2.970479	1.885178	-0.596643	39	H	2.198206	3.741404	0.75297
19	C	-5.12314	1.502329	-0.831888	40	H	3.987462	2.928481	2.271013
20	H	-5.173392	1.779127	-1.893371	41	N	0.94221	-1.163833	-0.642974
21	H	-5.808956	0.663134	-0.665971	42	O	1.148049	-1.7511	-2.825796

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.15912249 a.u.
RMS Gradient Norm= 0.00000436 a.u.
Imaginary Freq= 0
Dipole Moment= 2.2874 Debye
Point Group= C1
Job cpu time= 1 day 0 hours 23 minutes 12.3 seconds

Zero-point correction= 0.351844 (Hartree/Particle)
Thermal correction to Energy= 0.372432
Thermal correction to Enthalpy= 0.373376
Thermal correction to Gibbs Free Energy= 0.298605
Sum of electronic and zero-point Energies= -940.807279
Sum of electronic and thermal Energies= -940.786690
Sum of electronic and thermal Enthalpies= -940.785746
Sum of electronic and thermal Free Energies= -940.860518

G. Single-point energy calculation of 7a in chloroform using M06-2X/6-311++G(2d,3p)

Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)

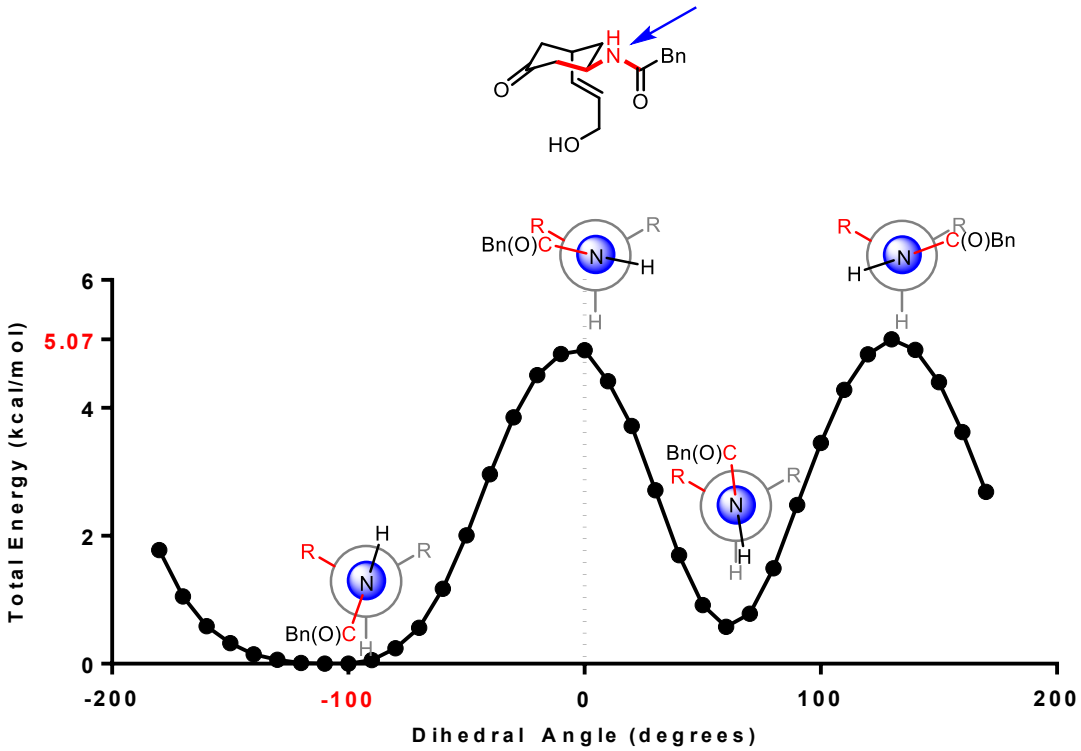
Charge= 0
Spin= Singlet
E(RB3LYP)= -940.79749473 a.u.
Dipole Moment= 2.1942 Debye
Point Group= C1
Job cpu time= 3 hours 30 minutes 45.5 seconds

From Section 1.F.:
Thermal correction to Gibbs Free Energy= 0.298605

Sum of electronic and thermal Free Energies= -940.79749473 + 0.298605 = -940.4988897 a.u.

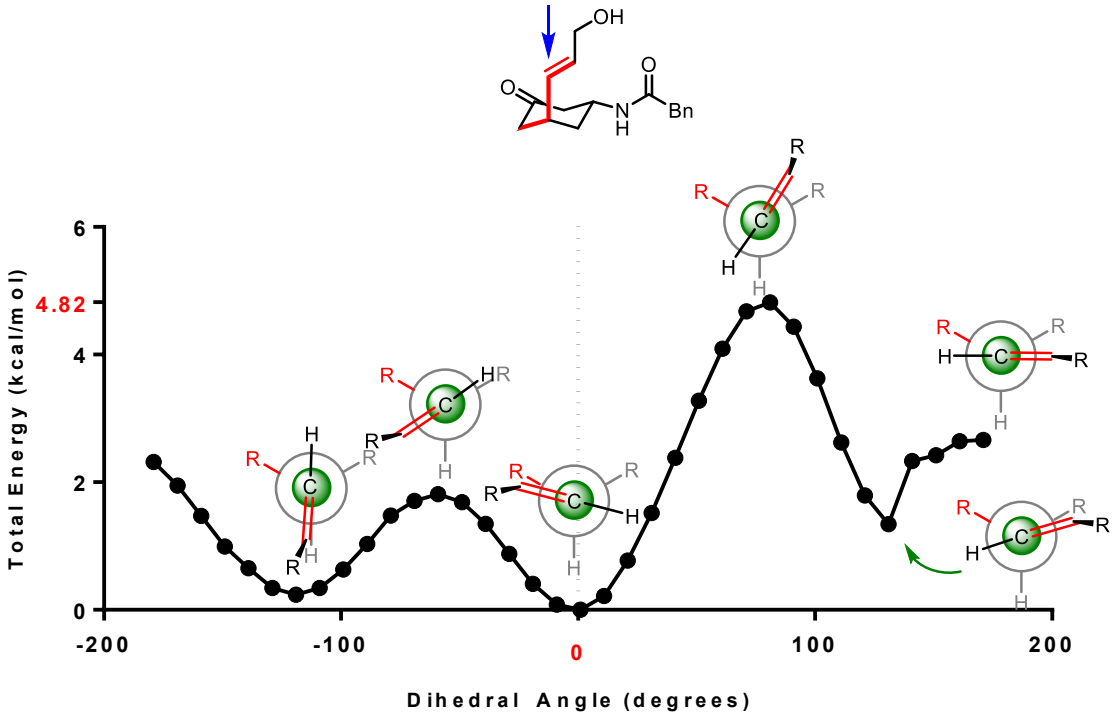
Geometry optimization and energy calculation of 7b (Section 2):

A. Relaxed potential energy scan of phenyl-acetamide HN-C dihedral with B3LYP/6-31+G(d,p)



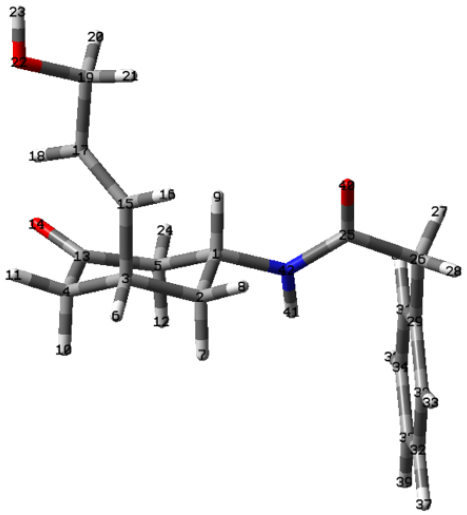
HN–C Dihedral (°)	Total Energy (kcal/mol)	HN–C Dihedral (°)	Total Energy (kcal/mol)
170	2.689	-10	4.842
160	3.622	-20	4.514
150	4.404	-30	3.853
140	4.905	-40	2.962
130	5.072	-50	2.005
120	4.837	-60	1.173
110	4.282	-70	0.565
100	3.452	-80	0.244
90	2.482	-90	0.058
80	1.494	-100	0
70	0.785	-110	0.002
60	0.575	-120	0.012
50	0.92	-130	0.062
40	1.697	-140	0.148
30	2.712	-150	0.324
20	3.716	-160	0.586
10	4.418	-170	1.053
0	4.902	-180	1.779

B. Relaxed potential energy scan of alkene C-C Dihedral with B3LYP/6-31+G(d,p)



C–C Dihedral (°)	Total Energy (kcal/mol)	C–C Dihedral (°)	Total Energy (kcal/mol)
171	2.66	-9	0.08
161	2.642	-19	0.41
151	2.423	-29	0.875
141	2.332	-39	1.349
131	1.343	-49	1.689
121	1.792	-59	1.811
111	2.622	-69	1.706
101	3.627	-79	1.478
91	4.435	-89	1.033
81	4.818	-99	0.633
71	4.675	-109	0.344
61	4.095	-119	0.239
51	3.276	-129	0.341
41	2.383	-139	0.653
31	1.52	-149	0.992
21	0.771	-159	1.47
11	0.218	-169	1.949
1	0	-179	2.319

C. Geometry optimization of 7b in the gas phase using B3LYP/6-311+G(d,p)



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	0.419379	0.096145	-0.024497	22	O	6.498932	-1.002296	-0.374053
2	C	0.936905	0.094552	1.42294	23	H	7.052243	-1.584823	-0.903288
3	C	2.406329	0.570739	1.506616	24	H	0.292669	1.477432	-1.719329
4	C	2.541504	1.981516	0.897116	25	C	-1.286424	-1.681482	-0.268003
5	C	0.54237	1.492998	-0.657317	26	C	-2.786802	-2.022479	-0.321986
6	H	2.655926	0.646302	2.5728	27	H	-2.934295	-2.5312	-1.278595
7	H	0.305537	0.752193	2.033551	28	H	-2.940537	-2.781332	0.450038
8	H	0.844557	-0.914921	1.831859	29	C	-3.774504	-0.891328	-0.162061
9	H	1.014394	-0.61373	-0.603189	30	C	-4.226101	-0.506508	1.107052
10	H	1.993785	2.684845	1.538578	31	C	-4.248379	-0.188099	-1.276975
11	H	3.577176	2.320486	0.857306	32	C	-5.119633	0.552439	1.258985
12	H	-0.160552	2.176271	-0.157282	33	H	-3.879138	-1.046228	1.982706
13	C	1.930005	2.101048	-0.489966	34	C	-5.142061	0.871127	-1.129123
14	O	2.483112	2.679497	-1.399102	35	H	-3.917532	-0.477184	-2.269497
15	C	3.342948	-0.458701	0.916739	36	C	-5.579153	1.24604	0.140428
16	H	3.231096	-1.456201	1.342006	37	H	-5.461747	0.83087	2.249548
17	C	4.258169	-0.279688	-0.034992	38	H	-5.500699	1.399365	-2.005472
18	H	4.420214	0.6932	-0.490206	39	H	-6.276869	2.067524	0.256463
19	C	5.127474	-1.378344	-0.562537	40	O	-0.451296	-2.567149	-0.371996
20	H	4.924095	-1.522056	-1.633051	41	H	-1.710777	0.297652	0.011225
21	H	4.905879	-2.320383	-0.045401	42	N	-0.961937	-0.368335	-0.113437

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.14203504 a.u.

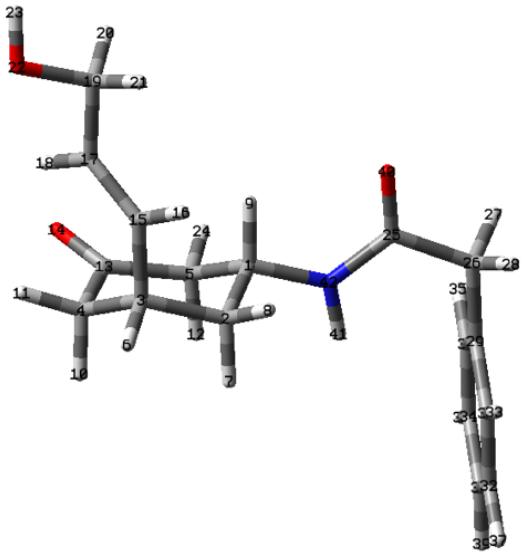
RMS Gradient Norm= 0.00002253 a.u.
Imaginary Freq= 0
Dipole Moment= 4.4360 Debye
Point Group= C1
Job cpu time= 21 hours 14 minutes 3.2 seconds

Zero-point correction= 0.352116 (Hartree/Particle)
Thermal correction to Energy= 0.372650
Thermal correction to Enthalpy= 0.373595
Thermal correction to Gibbs Free Energy= 0.298598
Sum of electronic and zero-point Energies= -940.789919
Sum of electronic and thermal Energies= -940.769385
Sum of electronic and thermal Enthalpies= -940.768441
Sum of electronic and thermal Free Energies= -940.843437

D. Single-point energy calculation of 7b in the gas phase using M06-2X/6-311++G(2d,3p)

Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -940.78282114 a.u.
Dipole Moment= 4.3704 Debye
Point Group= C1
Job cpu time= 3 hours 13 minutes 18.9 seconds
From Section 2.C:
Thermal correction to Gibbs Free Energy= 0.298598
Sum of electronic and thermal Free Energies= -940.78282114 + 0.298598 = -940.48422314 a.u.

E. Geometry optimization of 7b in chloroform using B3LYP/6-311+G(d,p) and the IEF-PCM Solvation Model



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	0.424447	0.088638	-0.105899	22	O	6.509875	-1.083331	0.003084
2	C	0.868631	0.245367	1.355777	23	H	7.078991	-1.731037	-0.426301
3	C	2.335587	0.723355	1.45958	24	H	0.401034	1.27164	-1.948652
4	C	2.512722	2.060246	0.711003	25	C	-1.30104	-1.648191	-0.523386
5	C	0.59394	1.408779	-0.883679	26	C	-2.802728	-1.974592	-0.543783
6	H	2.531748	0.912912	2.522064	27	H	-3.007016	-2.346849	-1.551474
7	H	0.216238	0.968845	1.85894	28	H	-2.92458	-2.829505	0.126978
8	H	0.749582	-0.710564	1.872873	29	C	-3.771769	-0.874018	-0.179667
9	H	1.031781	-0.684368	-0.579059	30	C	-4.145695	-0.66056	1.153737
10	H	1.940754	2.828594	1.247641	31	C	-4.310083	-0.036787	-1.165337
11	H	3.551993	2.390284	0.688333	32	C	-5.028318	0.363823	1.493758
12	H	-0.132979	2.14121	-0.504213	33	H	-3.747166	-1.305909	1.930143
13	C	1.965947	2.039679	-0.70466	34	C	-5.193899	0.98796	-0.828996
14	O	2.559588	2.543361	-1.638763	35	H	-4.039086	-0.192887	-2.20458
15	C	3.290124	-0.367826	1.032997	36	C	-5.55455	1.192226	0.50265
16	H	3.142496	-1.314369	1.553312	37	H	-5.309838	0.510163	2.530607
17	C	4.260651	-0.298151	0.121462	38	H	-5.604077	1.622072	-1.606979
18	H	4.461153	0.62117	-0.422002	39	H	-6.244362	1.986203	0.765231
19	C	5.140237	-1.454482	-0.239431	40	O	-0.481752	-2.522276	-0.796361
20	H	5.010379	-1.69937	-1.301599	41	H	-1.697034	0.265056	0.040822
21	H	4.871054	-2.338692	0.350002	42	N	-0.955425	-0.377062	-0.203215

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.15783184 a.u.
RMS Gradient Norm= 0.00000568 a.u.
Imaginary Freq= 0
Dipole Moment= 6.1107 Debye
Point Group= C1
Job cpu time= 17 hours 56 minutes 52.8 seconds

Zero-point correction= 0.352197 (Hartree/Particle)
Thermal correction to Energy= 0.372689
Thermal correction to Enthalpy= 0.373633
Thermal correction to Gibbs Free Energy= 0.298299
Sum of electronic and zero-point Energies= -940.805635
Sum of electronic and thermal Energies= -940.785143
Sum of electronic and thermal Enthalpies= -940.784199
Sum of electronic and thermal Free Energies= -940.859533

F. Single-point energy calculation of 7b in chloroform using M06-2X/6-311++G(2d,3p)
Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)
Charge= 0

Spin= Singlet
E(RB3LYP)= -940.79692801 a.u.
Dipole Moment= 6.0131 Debye
Point Group= C1
Job cpu time= 3 hours 13 minutes 26.5 seconds

From Section 2.E.:
Thermal correction to Gibbs Free Energy= 0.298299

Sum of electronic and thermal Free Energies= -940.79692801 + 0.298299 = -940.49862901 a.u.

Calculation of ΔG°, K, and Equilibrium ratio between 7a and 7b using M06-2X/6-311++G(2d,3p) Single-point Energies in (Section 4):

Gas Phase

7a: From Section 1.E.: $G°_{axial} = -940.48460493$
7b: From Section 2.D.: $G°_{equatorial} = -940.48422314$

Using Equation 1: $\Delta G° = (-940.48460493 + 940.48422314)\left(\frac{627.51\ kcal}{mol{\cdot}a.u.}\right) = -0.240\ kcal/mol$
Using Equation 2: $K = 0.667$
Using Equation 3: $\boldsymbol{7a}:\boldsymbol{7b} \rightarrow \mathbf{60}:\mathbf{40}$

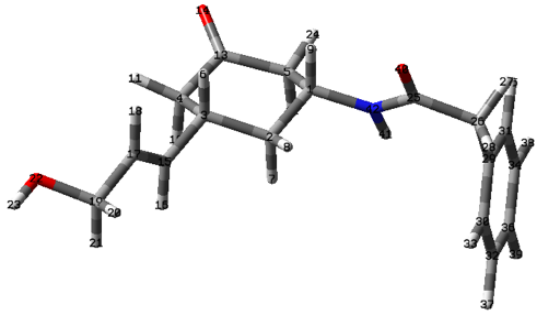
Chloroform

7a: From Section 2.G.: $G°_{axial} = -940.4988897$
7b: From Section 3.F.: $G°_{equatorial} = -940.49862901$

Using Equation 1: $\Delta G° = (-940.4988897 + 940.49862901)\left(\frac{627.51\ kcal}{mol{\cdot}a.u.}\right) = -0.164\ kcal/mol$
Using Equation 2: $K = 0.759$
Using Equation 3: $\boldsymbol{7a}:\boldsymbol{7b} \rightarrow \mathbf{57}:\mathbf{43}$

Geometry Optimization and Energy Calculation of 6a (Section 5):

A. Geometry optimization of 6a in the gas phase using B3LYP/6-311+G(d,p)



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	-0.165639	0.759779	0.661721	22	O	-6.928158	-1.513583	-0.482779
2	C	-1.179046	-0.223459	0.054189	23	H	-7.565497	-2.208974	-0.672514
3	C	-2.60078	0.372043	0.020551	24	H	0.483096	2.832966	0.390814
4	C	-2.609302	1.708941	-0.763479	25	C	1.653338	-0.488861	1.786854
5	C	-0.148443	2.094211	-0.10466	26	C	3.09547	-1.018431	1.689817
6	H	-2.905184	0.583145	1.052856	27	H	3.63099	-0.554256	2.52292
7	H	-0.864197	-0.488435	-0.964296	28	H	3.03143	-2.083292	1.928041
8	H	-1.177504	-1.143472	0.643423	29	C	3.840193	-0.805034	0.393392
9	H	-0.449656	0.944938	1.701199	30	C	3.788355	-1.761174	-0.628977
10	H	-2.401914	1.499264	-1.822605	31	C	4.585821	0.360873	0.175752
11	H	-3.582188	2.198802	-0.70748	32	C	4.456507	-1.557247	-1.835025
12	H	0.255792	1.923338	-1.11333	33	H	3.224466	-2.675811	-0.474821
13	C	-1.54535	2.677091	-0.275706	34	C	5.254456	0.568857	-1.029437
14	O	-1.782852	3.842065	-0.045061	35	H	4.646413	1.108747	0.960078
15	C	-3.590294	-0.594092	-0.571107	36	C	5.190631	-0.389864	-2.039513
16	H	-3.398422	-0.896538	-1.601738	37	H	4.409077	-2.312424	-2.611706
17	C	-4.653205	-1.088851	0.060639	38	H	5.830708	1.475525	-1.176258
18	H	-4.873111	-0.78415	1.081914	39	H	5.714294	-0.231638	-2.975402
19	C	-5.609018	-2.072237	-0.537384	40	O	0.993917	-0.682083	2.796564
20	H	-5.576756	-3.009342	0.036808	41	H	1.774668	0.28543	-0.101408
21	H	-5.321934	-2.29882	-1.572387	42	N	1.181429	0.20122	0.711478

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.14432838 a.u.
RMS Gradient Norm= 0.00000528 a.u.
Imaginary Freq= 0
Dipole Moment= 6.1291 Debye
Point Group= C1
Job cpu time= 19 hours 4 minutes 56.7 seconds

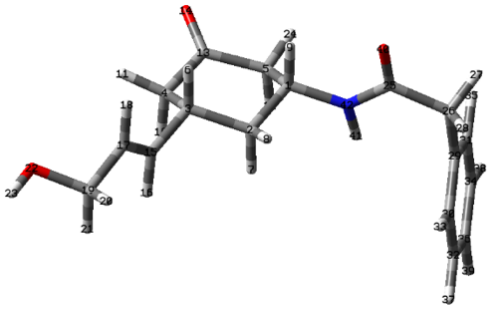
Zero-point correction= 0.351708 (Hartree/Particle)
Thermal correction to Energy= 0.372443
Thermal correction to Enthalpy= 0.373387
Thermal correction to Gibbs Free Energy= 0.296751
Sum of electronic and zero-point Energies= -940.792621
Sum of electronic and thermal Energies= -940.771886
Sum of electronic and thermal Enthalpies= -940.770942
Sum of electronic and thermal Free Energies= -940.847578

B. Single-point energy calculation of 6a in the gas phase using M06-2X/6-311++G(2d,3p)

Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -940.78203372 a.u.
Dipole Moment= 5.9946 Debye
Point Group= C1
Job cpu time= 3 hours 4 minutes 54.1 seconds
From Section 4.A.:
Thermal correction to Gibbs Free Energy= 0.296751

Sum of electronic and thermal Free Energies= -940.78203372 + 0.296751= -940.48528272 a.u.

C. Geometry optimization of 6a in chloroform using B3LYP/6-311+G(d,p) and the IEF-PCM Solvation Model



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	-0.175247	0.899046	0.546155	22	O	-6.861585	-1.734606	-0.199533
2	C	-1.164841	-0.194779	0.116293	23	H	-7.466732	-2.480029	-0.277294
3	C	-2.596988	0.359039	-0.027851	24	H	0.434925	2.90615	-0.075809
4	C	-2.622229	1.536607	-1.0357	25	C	1.777557	0.149475	1.885108
5	C	-0.181073	2.083356	-0.440841	26	C	3.211964	-0.400273	1.849325
6	H	-2.91592	0.740103	0.949451	27	H	3.810742	0.313435	2.421993
7	H	-0.839515	-0.627812	-0.83858	28	H	3.188252	-1.32024	2.439652
8	H	-1.153541	-0.998548	0.856607	29	C	3.839137	-0.653862	0.498356
9	H	-0.458854	1.259602	1.53717	30	C	3.718209	-1.902516	-0.125551
10	H	-2.394074	1.148436	-2.038079	31	C	4.546343	0.357627	-0.164898
11	H	-3.606528	2.004918	-1.075572	32	C	4.282218	-2.13256	-1.379923
12	H	0.233891	1.748984	-1.401773	33	H	3.183528	-2.701927	0.37758
13	C	-1.584028	2.59419	-0.719708	34	C	5.111048	0.131057	-1.419374
14	O	-1.848608	3.780877	-0.703514	35	H	4.659631	1.328136	0.307531
15	C	-3.559617	-0.716324	-0.452456	36	C	4.978998	-1.115225	-2.031435
16	H	-3.364677	-1.167842	-1.426179	37	H	4.182466	-3.107068	-1.844781
17	C	-4.598123	-1.144725	0.264395	38	H	5.658765	0.924932	-1.914733
18	H	-4.81544	-0.695408	1.231769	39	H	5.42092	-1.294117	-3.005059
19	C	-5.517198	-2.245512	-0.162308	40	O	1.231687	0.36599	2.964203
20	H	-5.460137	-3.073651	0.556527	41	H	1.69646	0.148233	-0.148341
21	H	-5.222842	-2.628225	-1.146797	42	N	1.179991	0.378017	0.689708

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.16071753 a.u.
RMS Gradient Norm= 0.00000202 a.u.
Imaginary Freq= 0
Dipole Moment= 8.1663 Debye
Point Group= C1
Job cpu time= 22 hours 4 minutes 41.5 seconds

Zero-point correction= 0.351829 (Hartree/Particle)
Thermal correction to Energy= 0.372503
Thermal correction to Enthalpy= 0.373448
Thermal correction to Gibbs Free Energy= 0.297965
Sum of electronic and zero-point Energies= -940.808888
Sum of electronic and thermal Energies= -940.788214
Sum of electronic and thermal Enthalpies= -940.787270
Sum of electronic and thermal Free Energies= -940.862752

D. Single-point energy calculation of 6a in chloroform using M06-2X/6-311++G(2d,3p)

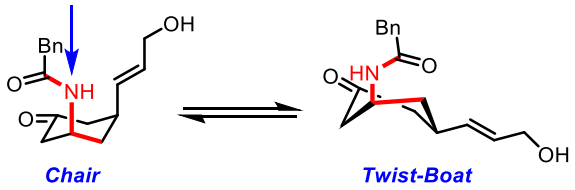
Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)

Charge= 0
Spin= Singlet
E(RB3LYP)= -940.79719299 a.u.
Dipole Moment= 7.9926 Debye
Point Group= C1
Job cpu time= 3 hours 12 minutes 36.5 seconds

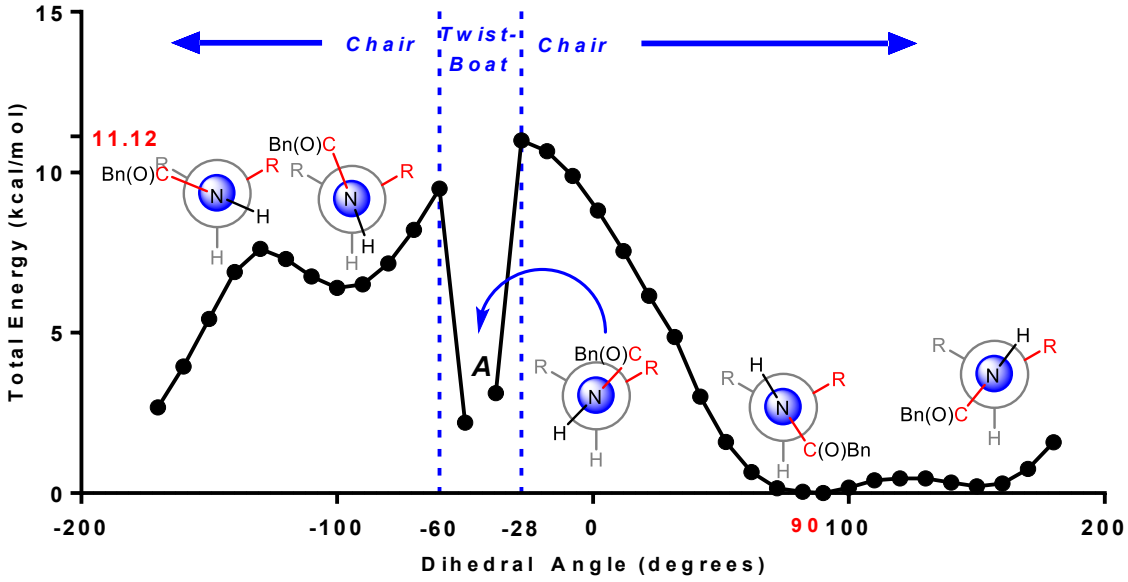
From Section 4.C.:
Thermal correction to Gibbs Free Energy= 0.297965

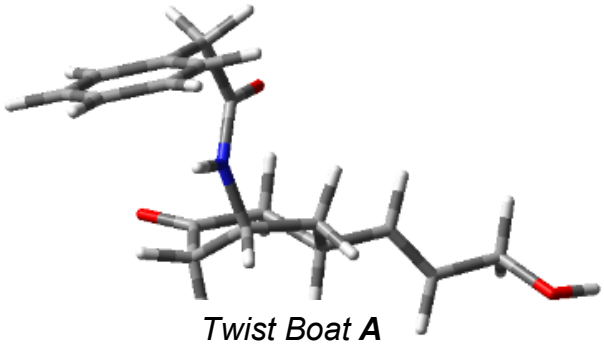
Sum of electronic and thermal Free Energies= -940.79719299 + 0.297965= -940.49922799 a.u.

Geometry Optimization and Energy Calculation of 6b (Section 5):
A. Relaxed potential energy scan of phenyl-Acetamide HN-C Dihedral with B3LYP/6-31+G(d,p)a



Due to the highly strained nature of this conformation, it was difficult to obtain a consistent dihedral scan of the diaxial chair conformations. The primary problem came from the propensity for the higher energy intermediates to convert to the twist-boat conformations (see above). This was especially problematic when the phenylacetamide carbonyl was pointed directly into the ring at the alkene. We took the dihedral angle around 100° and heavily optimized this structure by subtly altering various dihedral angles and submitting these new structures for geometry optimization and frequency calculations to find the true minimum. We also compared this minimized structure with the most optimized twist-boat conformation, and it was found that the chair was slightly more stable.

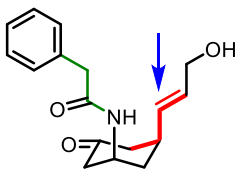




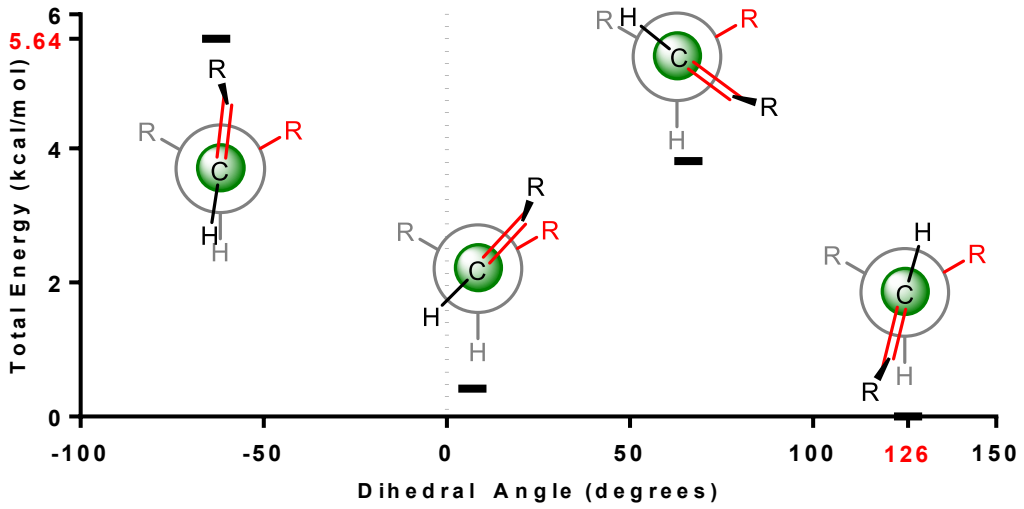
*Twist Boat **A***

C-C Dihedral (°)	Total Energy (kcal/mol)	C-C Dihedral (°)	Total Energy (kcal/mol)
180	1.582564	2	8.812004
170	0.758272	-8	9.888914
160	0.298072	-18	10.65241
150	0.212192	-28	10.99411
140	0.330335	-38	3.117854
130	0.458112	-50	2.198934
120	0.454677	-60	9.487434
110	0.401444	-70	8.203364
100	0.169513	-80	7.161004
90	0	-90	6.502904
82	0.045471	-100	6.394564
72	0.156064	-110	6.754044
62	0.660517	-120	7.299534
52	1.593284	-130	7.611084
42	3.010974	-140	6.896374
32	4.865164	-150	5.426494
22	6.155234	-160	3.944354
12	7.547074	-170	2.676484

B. Relaxed potential energy scan of alkene C-C Dihedral with B3LYP/6-31+G(d,p)

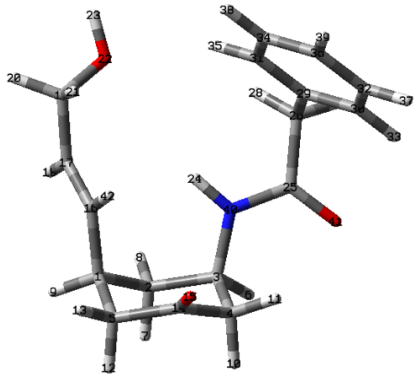


Due to the highly strained nature of this conformation, it was difficult to obtain a consistent dihedral scan, with each intermediate rigorously optimized. The primary problem came from the dihedral angle shown in green above, which changed dramatically during scans, and heavily affected the energies. The points shown below represent general trends in the dihedral angle scans. We took the dihedral angle around 126° and heavily optimized this structure by subtly altering various dihedral angles and submitting these new structures for geometry optimization and frequency calculations to find the true minimum.



C-C Dihedral (°)	Total Energy (kcal/mol)
-63	5.636
7	0.417
66	3.812
126	0

C. Geometry optimization of 6b in the gas phase using B3LYP/6-311+G(d,p)



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	-3.219537	0.195906	0.322611	22	O	-0.234452	3.581027	-0.898333
2	C	-2.96937	-0.555533	-1.010778	23	H	0.228919	4.424635	-0.882944
3	C	-1.696895	-1.416141	-1.034333	24	H	-0.556906	0.397581	-0.937225
4	C	-1.61581	-2.34621	0.204197	25	C	0.651414	-1.063427	-1.721144
5	C	-3.229823	-0.816824	1.49096	26	C	1.786518	-0.044243	-1.848562
6	H	-1.72064	-2.060377	-1.9164	27	H	2.385419	-0.362439	-2.704385
7	H	-3.823668	-1.219125	-1.184475	28	H	1.383404	0.948081	-2.065723
8	H	-2.946854	0.151979	-1.844006	29	C	2.646378	0.017562	-0.599147
9	H	-4.215464	0.646069	0.252395	30	C	3.43603	-1.075519	-0.222962
10	H	-2.351542	-3.150561	0.067145	31	C	2.660661	1.165378	0.199018
11	H	-0.632024	-2.808453	0.274928	32	C	4.221756	-1.019029	0.925111
12	H	-4.078919	-1.499647	1.362336	33	H	3.425517	-1.97364	-0.830856
13	H	-3.341466	-0.320986	2.456937	34	C	3.449571	1.22321	1.348016
14	C	-1.960405	-1.658938	1.513532	35	H	2.051712	2.018376	-0.084774
15	O	-1.288844	-1.782557	2.514678	36	C	4.232162	0.131033	1.714535
16	C	-2.225384	1.312708	0.593958	37	H	4.827397	-1.874121	1.204408
17	C	-2.163387	2.469174	-0.066767	38	H	3.452678	2.121755	1.955677
18	H	-2.851067	2.677603	-0.88471	39	H	4.845374	0.173948	2.607647
19	C	-1.144249	3.528363	0.216492	40	N	-0.504446	-0.58003	-1.181907
20	H	-1.636316	4.501105	0.34254	41	O	0.778173	-2.230029	-2.066524
21	H	-0.602308	3.294646	1.140696	42	H	-1.508919	1.14143	1.397147

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.13760667 a.u.
RMS Gradient Norm= 0.00000204 a.u.
Imaginary Freq= 0
Dipole Moment= 6.1529 Debye
Point Group= C1
Job cpu time= 1 day 0 hour 27 minutes 53.9 seconds

Zero-point correction= 0.352389 (Hartree/Particle)
Thermal correction to Energy= 0.372873
Thermal correction to Enthalpy= 0.373818
Thermal correction to Gibbs Free Energy= 0.298639
Sum of electronic and zero-point Energies= -940.785217
Sum of electronic and thermal Energies= -940.764733
Sum of electronic and thermal Enthalpies= -940.763789
Sum of electronic and thermal Free Energies= -940.838967

D. Single-point energy calculation of 6b in the gas phase using M06-2X/6-311++G(2d,3p)

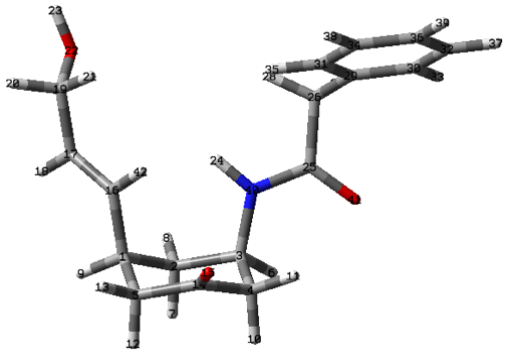
Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)

Charge= 0
Spin= Singlet
E(RB3LYP)= -940.77974371 a.u.
Dipole Moment= 6.0079 Debye
Point Group= C1
Job cpu time= 3 hours 31 minutes 51.6 seconds

From Section 5.C.:
Thermal correction to Gibbs Free Energy= 0.298639

Sum of electronic and thermal Free Energies= -940.77974371 + 0.298639= -940.48110471 a.u.

E. Geometry optimization of 6b in chloroform using B3LYP/6-311+G(d,p) and the IEF-PCM Solvation Model



Tag	Element	X	Y	Z	Tag	Element	X	Y	Z
1	C	-3.332512	-0.577599	-0.008629	22	O	-2.412245	4.030646	-0.62232
2	C	-2.679123	-1.15882	-1.289359	23	H	-2.271877	4.944698	-0.35208
3	C	-1.232736	-1.646386	-1.122653	24	H	-0.658208	0.399835	-0.844777
4	C	-1.0878	-2.584608	0.102517	25	C	1.001852	-0.626929	-1.442434
5	C	-3.215379	-1.603538	1.147385	26	C	1.814228	0.671559	-1.405987
6	H	-0.95113	-2.223173	-2.005782	27	H	2.193842	0.824449	-2.41963
7	H	-3.277906	-2.019701	-1.603962	28	H	1.172224	1.521869	-1.164532
8	H	-2.729235	-0.426614	-2.09933	29	C	2.968912	0.598921	-0.42741
9	H	-4.394349	-0.442251	-0.233031	30	C	4.22518	0.135131	-0.831243
10	H	-1.561449	-3.541107	-0.153776	31	C	2.791244	0.979212	0.907712
11	H	-0.038543	-2.782202	0.32007	32	C	5.278617	0.049993	0.078438
12	H	-3.814512	-2.486365	0.892371	33	H	4.379173	-0.161615	-1.862763
13	H	-3.59539	-1.197813	2.086252	34	C	3.842351	0.895224	1.819689
14	C	-1.787244	-2.07571	1.347714	35	H	1.824263	1.345747	1.237325
15	O	-1.247711	-2.06887	2.438782	36	C	5.090433	0.428908	1.40728
16	C	-2.780927	0.767441	0.412493	37	H	6.246486	-0.310654	-0.251929
17	C	-3.31814	1.944852	0.091395	38	H	3.68677	1.195488	2.849961
18	H	-4.2113	1.986062	-0.529893	39	H	5.90974	0.364575	2.114425
19	C	-2.776608	3.265543	0.540952	40	N	-0.297656	-0.516707	-1.062321
20	H	-3.544713	3.80496	1.109701	41	O	1.498306	-1.691828	-1.798861
21	H	-1.90825	3.120595	1.194243	42	H	-1.892936	0.761409	1.045408

Calculation Type= FREQ
Calculation Method= RB3LYP
Basis Set= 6-311+G(d,p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -941.15386152 a.u.
RMS Gradient Norm= 0.00000435 a.u.
Imaginary Freq= 0
Dipole Moment= 6.7455 Debye
Point Group= C1
Job cpu time= 20 hours 36 minutes 45.6 seconds

Zero-point correction= 0.352227 (Hartree/Particle)
Thermal correction to Energy= 0.372712
Thermal correction to Enthalpy= 0.373656
Thermal correction to Gibbs Free Energy= 0.298375
Sum of electronic and zero-point Energies= -940.801635
Sum of electronic and thermal Energies= -940.781150
Sum of electronic and thermal Enthalpies= -940.780206
Sum of electronic and thermal Free Energies= -940.855486

F. Single-point energy calculation of 6b in chloroform using M06-2X/6-311++G(2d,3p)

Calculation Type= SP
Calculation Method= RM062X
Basis Set= 6-311++G(2d,3p)
Charge= 0
Spin= Singlet
E(RB3LYP)= -940.79176960 a.u.
Dipole Moment= 6.5256 Debye
Point Group= C1
Job cpu time= 3 hours 24 minutes 2.4 seconds

From Section 5.E.:
Thermal correction to Gibbs Free Energy= 0.298375

Sum of electronic and thermal Free Energies= -940.79176960 + 0.298375= -940.49339460 a.u.

Calculation of ΔG°, K, and equilibrium ratio between 6a and 6b using M06-2X/6-311++G(2d,3p) Single-point Energies (Section 6):

A. Gas Phase
6b: From Section 5.D.: $G°_{axial} = -940.48110471$
6a: From Section 4.B.: $G°_{equatorial} = -940.48528272$

Using Equation 1: $\Delta G° = (-940.48110471 + 940.48528272\ )\left(\frac{627.51\ kcal}{mol{\cdot}a.u.}\right) = 2.622\ kcal/mol$
Using Equation 2: $K = 83.7$
Using Equation 3: $\boldsymbol{6a{:}6b \rightarrow 99{:}1}$

B. Chloroform
6b: From Section 5.F.: $G°_{axial} = -940.49339460$
6a: From Section 4.D.: $G°_{equatorial} = -940.49922799$

Using Equation 1: $\Delta G° = (-940.49339460\ + 940.49922799\ )\left(\frac{627.51\ kcal}{mol{\cdot}a.u.}\right) = 3.661\ kcal/mol$

Using Equation 2: $K = 483.9$
Using Equation 3: $\boldsymbol{6a}:\boldsymbol{6b} \rightarrow \mathbf{99.8}:\mathbf{0.2}$

3. References and Notes

[1] Trost, B. M.; Verhoeven, T. R.Allylic alkylation. Palladium-catalyzed substitutions of allylic carboxylates. Stereo- and regiochemistry. *J. Am. Chem. Soc.* **1980**, *102*, 4730-4743.
[2] Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. Highly (*E*)-Selective Wadsworth-Emmons Reactions Promoted by Methylmagnesium Bromide. *Org. Lett.* **2008**, *10*, 5437-5440.
[3] Guerin, D. J.; Horstmann, T. E.; Miller, S. J. Amine-Catalyzed Addition of Azide Ion to α,β-Unsaturated Carbonyl Compounds. *Org. Lett.* **1999**, *1*, 1107-1109.
[4] Ariza, X.; Urpi, F.; Viladomat, C.; Vilarrasa, J. One-pot conversion of azides to Boc-protected amines with trimethylphosphine and Boc-ON. *Tetrahedron Lett.* **1998**, *39*, 9101-9102.
[5] Raghavan, S.; Babu, V. S. Enantioselective synthesis of oseltamivir phosphate. *Tetrahedron* **2011**, *67*, 2044-2050.
[6] Marshall, J. A.; Xie, S. Synthesis of a C22-34 Subunit of the Immunosuppressant FK-506. *J. Org. Chem.* **1995**, *60*, 7230-7237.
[7] Srivastava, N.; Banik, B. K. Bismuth Nitrate-Catalyzed Versatile Michael Reactions. *J. Org. Chem.* **2003**, *68*, 2109-2114.
[8] Lichtor, P. A.; Miller, S. J. Combinatorial evolution of site- and enantioselective catalyst for polyene epoxidation. *Nature Chem.* **2012**, *4*, 990-995.
[9] Romney, D. K.; Colvin, S. M.; Miller, S. J. Catalyst Control over Regio- and Enantioselectivity in Baeyer-Villiger Oxidations of Functionalized Ketones. *J. Am. Chem. Soc.* **2014**, *136*, 14019-14022.
[10] The work was partially supported by the facilities and staff of the Yale University Faculty of Arts and Science High Performance Computing Center, and by the National Science Foundation under the grant that partially funded acquisition of the facilities (#CNS 08-21132).
[11] Gaussian 09, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.
[12] For a review on solvation models, see: Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanism Continuum Solvation Models. *Chem. Rev*. **2005**, *105*, 2999–3093.
[13] For recent combinations of the M06-2x functional with the IEF-PCM solvation model, see: a. Simon, A.; Lam, Y.-h.; Houk, K. N. Transition States of Vicinal Diamine-Catalyzed Aldol Reactions. *J. Am. Chem. Soc*. **2016**, *138*, 503–506.
[14] Sowlati-Hashjin, S.; Wetmore, S. D. Quantum mechanical study of the beta- and delta-lyase reactions during the base excision repair process: application to FPG. *Phys. Chem. Chem. Phys*. **2015**, *17*, 24696–24706.
[15] Lopez, S. A.; Munk, M. E.; Houk ,K. N. Mechanisms and Transitions States of 1,3-Dipolar Cycloadditions on Phenyl Azide with Enamines: A Computational Analysis. *J. Org. Chem*. **2013**, *78*, 1576–1582.
[16] Zhao, Y. & Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
[17] For recent energy difference calculations performed on chair conformations using M06-2X functional, see: Jahn, M. K.; Dewald, D.; Vallejo-Lopez, M.; Cocinero, E. J.; Lesarri, A.; Grabow, J.-U. Rotational Spectra of Bicyclic Decanes: The Trans Conformation of (–)-Lupine. *J. Phys. Chem. A* **2013**, *117*, 13673–13679.
[18] Cocinero, E. J.; Lesarri, A.; Ecija, P.; Basterretxea, F. J.; Grabow, J.-U.; Fernandez, J. A.; Castano, F. Ribose Found in the Gas Phase. *Angew. Chem. Int. Ed.* **2012**, *51*, 3119–3124.
[19] Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. Mechanistic Insights into the BINOL-Derived Phosphoric Acid-Catalyzed Asymmetric Allylboration of Aldehydes. *J. Am. Chem. Soc.* **2012**, *134*, 2716–2722.
[20] Wallevik, S. O.; Bjornsson, R.; Kvaran, A.; Jonsdottir, S.; Girichev, G. V.; Giricheva, N. I.; Hassler, K.; Arnason, I. Conformational properties of 1-fluoro-1-methyl-silacyclohexane and 1-methyl-1-trifluoromethyl-1-

silacyclohexane: Gas electron diffraction, low-temperature NMR, temperature-dependent Raman spectroscopy, and quantum chemical calculations. *J. Mol. Struc*. **2010**, *978*, 209–219.

[21] The single point energy calculations do not contain vibrational frequency calculations and hence do not contain thermal corrections to G°. Yet, the thermal correction provided by the original geometry optimization of each compound may be used to convert the single-point values to values of G°.