Chemodivergent Synthesis of *cis*-4-Hydroxyprolines from Diastereomerically Enriched Epoxides

Clement DaSilva,[a] Grace Mauk,[a] Lucas Forshee,[a] Oliver Pope,[a] Mathilde Doherty,[a] Max Ongbongan,[a] Nicholas Lutz,[a] Zemirah Kamanya,[a] Kara Chris Bhatt,[a] Andrew Braham,[a] Miranda Kubek,[a] Summer Hawthorne,[a] Gonzalo Campillo-Alvarado,[a] Avik Bhattacharjee,[b] Miriam A. Bowring,[a] and Robert V. O'Brien.*[a]

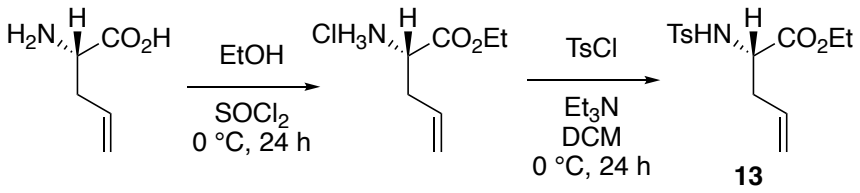
[a] *Reed College, 3203 SE Woodstock Blvd., Portland, OR, USA, 97202.*
[b] *York University, 4700 Keele St., Toronto, ON, Canada, M3J 1P3.*
* Email: obrienb@reed.edu

Table of Contents

I. General information

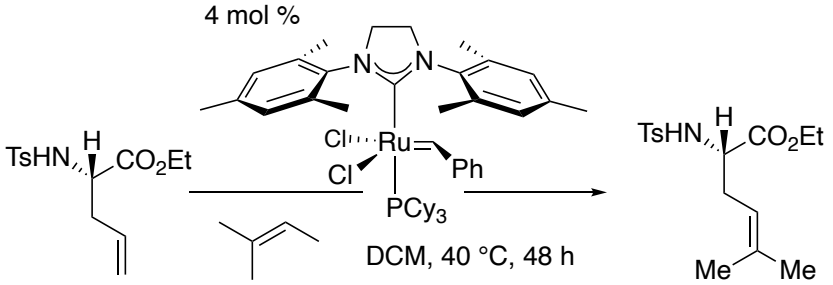
All compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, high resolution mass spectrometry (HRMS), and for enantiomerically pure products optical rotations were measured. IR spectra were collected on a Nicolet FT-IR with a diamond ATR plate. Optical rotations were measured on a Rudolph Research Analytical Autopol III polarimeter, with a 100 mm cell. Diastereomeric ratios were determined by ^{1}H NMR, and confirmed by HPLC, using an Agilent HP-1100 chromatography system equipped with a Regis Technologies, column (Reflect C-Cellulose B). X-ray quality crystals were grown for compounds **5**, **8**, and **9** by slow evaporation from acetone. Single crystal X-ray diffraction (SCXRD) data was collected on a Rigaku XtaLAB Mini II diffractometer with a CCD area detector (λMoKα = 0.71073 Å, monochromator: graphite). The collected data was refined with CrysAlisPro through standard data reduction and background corrections. Crystals were mounted in Paratone oil on a Mitegen magnetic mount. Structure solution and refinement were performed using SHELXT and SHELXL, respectively within the Olex2 graphical user interface. The NMR spectra were recorded on a Brüker ASCEND EVO 400 (400 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz, with deuterated $CDCl_3$ as solvent. All chemicals and solvents were used as received without further purification unless otherwise stated. Solvent was purchased from Sigma and Spectrum Chemical. (±)-Allylglycine, L-allylglycine, D-allylglycine, the *D*-Shi catalyst (1,2,4,5-Di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose) were purchased from Ambeed. Oxone® was purchased from Oakwood. 2-Ethylbutene, 2-methyl-2-butene were purchased from TCI, America. Methylenecyclohexane, tosyl chloride, Second generation Grubbs catalyst, second generation Hoveyda-Grubbs catalyst, 1,2,3-trimethoxybenzene, tetrabutylammonium hydrogensulfate, dimethoxymethane, sodium hydroxide, thionyl chloride, triethylamine, and *m*-chloroperbenzoic acid (*m*-CPBA) were purchased from Sigma. Chloroform-d was purchased from Cambridge Isotopes. Column chromatography was performed on silica gel (200- 300 mesh). The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). The following abbreviations were used to describe multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All splitting patterns were assigned based on the appearance of the multiplet, and clearly defined coupling constants. Splitting patterns that were difficult to interpret were designated as multiplet (m) or broad (br). IR spectral signals are designated strong (s), medium (m), weak (w). High resolution mass spectrometry analysis (HRMS) was performed on a Waters Synapt G2Si mass spectrometer. Analytical thin layer chromatography (TLC) was carried out on precoated silica gel plates (0.2 mm thickness). TLC plates were visualized with aqueous potassium permanganate stain.

II. Alkene synthesis by Ru-catalyzed alkene metathesis



***N*-tosylallylglycine ethyl ester** (Scheme S1, compound **13**), was prepared according to a modified literature procedure.[1] 10.0 g (86.9 mmol, 1.00 equiv) Allylglycine was dissolved in 50 mL 200 proof ethanol in a 500 mL round bottom flask equipped with a stir bar, and cooled on an ice-bath. 13.0 mL thionyl chloride (21.3g, 179 mmol, 2.05 equiv) was added dropwise, and the resulting mixture stirred overnight as it slowly warmed to room temperature. Ethanol was distilled off under reduced pressure, and the resulting white solids were redissolved in 200 mL dichloromethane in a 500 mL round bottom flask equipped with a stir bar, which was cooled on an ice-bath and treated with 33.0 g tosyl chloride (174 mmol, 2.00 equiv) and 50 mL triethylamine (36.3 g, 358 mmol, 4.12 equiv). Mixture stirred as it slowly warmed to room temperature overnight. Reaction was quenched by addition of 1M $HCl_{(aq)}$, aqueous layer was extracted with dichloromethane (5 x 50 mL), organics were pooled, washed in saturated aqueous sodium bicarbonate, then water, then brine, then dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Crude product was purified by silica gel chromatography (gradient of 20% → 40% ethyl acetate/hexanes eluent), delivering 20.2 g product **13** as a yellow oil (78% isolated yield). Spectral data matched the values reported in the literature.[1]

Trisubstituted alkenes were prepared by Ru-catalyzed cross-metathesis following a modified literature procedure:[2]

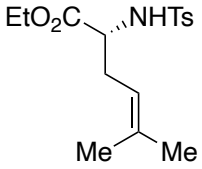


13 **6**

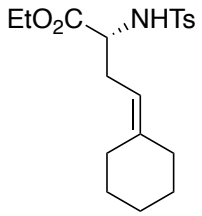
General procedure: 1.0 g Alkene **13** (3.71 mmol) was transferred to a 100 mL round bottom flask equipped with a stir bar. 15 mL of 2:1 anhydrous dichloromethane:2-methylbutene was added, followed by 64 mg (2 mol %) second generation Grubbs catalyst. Flask was sealed with a glass stopper, wrapped with Teflon tape, and heated at 40 °C for 24 h. An additional 64 mg catalyst was added (4 mol % total), and the reaction proceeded for an additional 24 h, at which point the mixture was concentrated *in vacuo*, yielding a brown oil. Crude product was purified

[1] Kotha, S.; Sreenivasachary, N. *Eur. J. Org. Chem.* **2001**, 3375-3383.
[2] Elaridi, J. Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 2025-2029

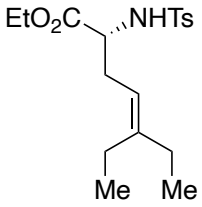
by silica gel chromatography (gradient of 15% → 20% ethyl acetate/hexanes eluent), delivering 1.15 g alkene **6** as a light brown oil (95% isolated yield).



(±)-*N*-tosyl-5,5-dimethylallylglycine ethyl ester (**6).** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 4 Hz, 2H), 5.16 (d, *J* = 8 Hz, 1H), 3.97 (dd, *J* = 4, 8 Hz, 1H), 3.99-3.94 (3H, m), 2.48-2.39 (5H, m), 1.68 (s, 3H), 1.58 (s, 3H), 1.14 (t, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 143.7, 137.1, 136.8, 129.7, 117.0, 61.7, 55.7, 31.2, 26.0, 21.6, 18.1, 14.1; IR (neat): 3273 (w), 2978 (w), 2917 (w), 1732 (s), 1598 (w), 1495 (w), 1444 (w), 1370 (w), 1339 (m), 1305 (w), 1201 (w), 1157 (s), 1090 (m), 1020 (w), 951 (w), 854 (w), 814 (m), 744 (w), 707 (w), 661 (m) cm^{-1} ; HRMS: calcd for $C_{16}H_{24}NO_4S$: 326.1426, found: 326.1429 (M+H); (*R*)-enantiomer: $[\alpha]_D$ -0.81° (c = 1.31, $CHCl_3$); (*S*)-enantiomer: $[\alpha]_D$ +0.17° (*c* = 1.19, $CHCl_3$).

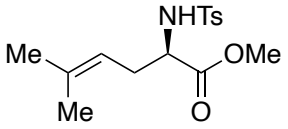


(2*R*)-*N*-tosyl-2-amino-4-cyclohexylidenebutanoic acid ethyl ester (6b). Following the general procedure (substituting methylenecyclohexane for 2-methy-2-butene), following purification by silica gel chromatography, alkene **6b** was obtained in 70% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 4 Hz, 2H), 5.08 (d, *J* = 12 Hz, 1H), 4.90 (t, *J* = 8 Hz, 1H), 3.98-3.91 (3H, m), 2.47-2.40 (5H, m), 2.06-2.01 (m, 4H), 1.55-1.45 (m, 6H, overlapping with H_2O), 1.12 (t, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 145.0, 143.5, 137.0, 130.0, 127.3, 113.3, 61.6, 55.7, 37.2, 31.1, 28.9, 28.5, 27.8, 26.7, 21.5, 14.0; IR (neat): 2988 (w), 2927 (m), 2853 (w) 2185 (w), 2160 (w) 1753 (s), 1598 (w), 1446 (w), 1369 (w), 1341 (m), 1305 (w) 1201 (w) 1162 (s), 1093 (w), 1020 (w), 952 (w), 853 (w), 815 (w), 707 (w), 664 (w); HRMS: calcd for $C_{19}H_{28}NO_4S$: 366.1739, found: 366.1738 (M+H); (*R*)-enantiomer: $[\alpha]_D$ -0.12° (*c* = 1.69, $CHCl_3$).

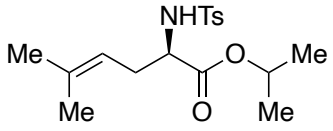


(2*R*)-*N*-tosyl-5,5-diethylallylglycine ethyl ester (**6c).** Following the general procedure, with the following modifications: substituting 2-ethyl-1-butene for 2-methy-2-butene; substituting second generation Grubbs catalyst for second generation Hoveyda-Grubbs catalyst; substituting

toluene for dichloromethane; carrying out reaction at 80 °C instead of 40 °C. Following purification by silica gel chromatography, alkene **6c** was obtained in 39% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 4 Hz, 2H), 5.12 (d, *J* = 12 Hz, 1H), 4.90 (t, *J* = 8 Hz, 1H), 3.97-3.91 (3H, m), 2.50-2.39 (5H, m), 1.98 (q, *J* = 8 Hz, 4H), 1.12 (t, *J* = 8 Hz, 3H), 0.92 (q, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 147.8, 143.6, 137.0, 129.6, 127.3, 114.8, 61.6, 56.7, 31.6, 29.1, 23.3, 21.5, 14.0, 13.1, 12.7; IR (neat): 3275 (br), 2965 (w), 2934 (w), 1732 (s), 1598 (w), 1444 (w), 1369 (w), 1340 (m), 1189 (w), 1157 (s), 1090 (m), 1019 (w), 919 (w), 853 (w), 813 (w), 707 (w), 661 (w), 552 (w), 429 (w) cm^{-1}; HRMS: calcd for $C_{18}H_{28}NO_4S$: 354.1739, found: 354.1734 (M+H); (*R*)-enantiomer: $[\alpha]_D$ -0.21° (*c* = 1.22, $CHCl_3$).



(2*R*)-*N*-tosyl-5,5-dimethylallylglycine methyl ester (**6d**)**.** Ethyl ester **6** (1.06 g, 3.26 mmol, 1 equiv) was dissolved in 100 mL 10:1 THF:30% aqueous sodium hydroxide and stirred overnight at room temperature. 2.0 M HCl was added until pH reached 4, then the mixture was extracted with five volumes of 50 mL ethyl acetate. Organic layers were pooled, washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oily residue was redissolved in 50 mL methanol and cooled on an ice bath. 1.0 mL thionyl chloride (1.64 g, 13.8 mmol, 4.2 equiv) was added dropwise, and mixture stirred overnight as it slowly warmed to room temperature. Quenched by addition of saturated aqueous sodium bicarbonate, extracted with five volumes of 50 mL ethyl acetate. Organic layers were pooled, washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Following purification by silica gel chromatography, 582 mg alkene **6d** was obtained (57% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, , *J* = 8 Hz, 2H) 7.28 (d, *J* = 8 Hz, 2H), 5.13 (d, *J* = 8 Hz, 1H), 4.93 (t, *J* = 8 Hz, 1H), 3.99-3.94 (m, 1H), 3.51 (s, 3H), 2.45-2.37 (m, 5H), 1.65 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 143.7, 137.0, 129.7, 127.4, 116.9, 55.6, 52.5, 32.0, 26.0, 21.6, 18.0; IR (neat): 3267 (br), 3073 (w), 3035 (w), 2971 (w), 2952 (w), 2918 (w) 1736 (s), 1701 (w), 1671 (w), 1598 (w), 1497 (w) 1449 (m), 1442 (m), 1377 (w), 1358 (w), 1339 (s), 1321 (w), 1309 (w), 1279 (w), 1224 (w), 1199 (w), 1161 (s) 1111 (w), 1081 (s), 1018 (w), 988 (m), 950 (m), 907 (w), 863 (m), 817 (m), 801 (w), 783 (w), 726 (w), 699 (s) cm^{-1}; HRMS: calcd for $C_{15}H_{22}NO_4S$: 312.1270, found: 312.1273 (M+H); (*R*)-enantiomer: $[\alpha]_D$ -0.23° (*c* = 14.1, $CHCl_3$).



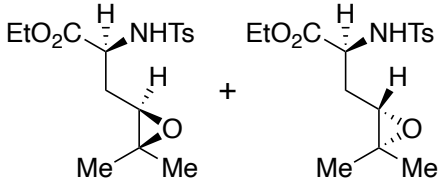
(2*R*)-*N*-tosyl-5,5-dimethylallylglycine isopropyl ester (**6e**)**.** Ethyl ester **6** (1.06 g, 3.26 mmol, 1 equiv) was dissolved in 100 mL 10:1 THF:30% aqueous sodium hydroxide and stirred overnight at room temperature. 2.0 M HCl was added until pH reached 4, then the mixture was extracted with five volumes of 50 mL ethyl acetate. Organic layers were pooled, washed with brine, dried

with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oily residue was redissolved in 50 mL isopropanol and cooled on an ice bath. 1.0 mL thionyl chloride (1.64 g, 13.8 mmol, 4.2 equiv) was added dropwise, and mixture stirred overnight as it slowly warmed to room temperature. Quenched by addition of saturated aqueous sodium bicarbonate, extracted with five volumes of 50 mL ethyl acetate. Organic layers were pooled, washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Following purification by silica gel chromatography, 447 mg alkene **6e** was obtained (40% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 5.13 (d, *J* = 12 Hz, 1H), 4.96 (t, *J* = 8 Hz, 1H), 4.81-4.72 (m, 1H), 3.93-3.88 (m, 1H), 2.45-2.36 (m, 5H), 1.66 (s, 3H), 1.57 (s, 3H), 1.11 (d, *J* = 8 Hz, 3H), 1.05 (d, *J* = 4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 143.7, 137.1, 136.6, 129.7, 127.4, 117.1, 69.5, 55.7, 33.3, 26.0, 21.62, 21.59, 18.1; IR (neat): 3329 (br), 2973 (w), 2919 (w), 1736 (s), 1597 (w), 1496 (w), 1450 (w), 1423 (w), 1375 (w), 1352 (w), 1331 (s), 1307 (w), 1291 (w), 1276 (w), 1234 (w), 1203 (m), 1188 (w), 1156 (s), 1108 (w), 1087 (s), 1017 (w), 939 (m), 911 (w), 864 (w), 853 (w), 816 (s), 743 (m), 704 (w), 669 (s) cm^{-1}; HRMS: calcd for $C_{17}H_{26}NO_4S$: 340.1583, found: 340.1580 (M+H); (*R*)-enantiomer: $[\alpha]_D$ -0.72° (*c* = 7.7, $CHCl_3$).

III. Epoxide synthesis

(A) ***m*-CPBA oxidation:** 3.42 g (10.5 mmol, 1 equiv) alkene (±)-**6** was combined with 150 mL dichloromethane in a 500 mL round bottom flask equipped with a stir bar, and the resulting mixture was cooled on an ice-bath. 2.6 g (15.1 mmol, 1.43 equiv) *m*-CPBA was dissolved in 50 mL dichloromethane, and the resulting solution was added dropwise to the reaction mixture. Mixture stirred as it slowly warmed to room temperature overnight. The reaction was quenched in saturated aqueous sodium thiosulfate, and the organic layer was separated in a separatory funnel. The aqueous layer was extracted 5 x 25 mL dichloromethane, and organic layers were pooled, washed in saturated aqueous sodium bicarbonate, then deionized water, then brine. The organic layer was then dried with $MgSO_4$, filtered, and concentrated *in vacuo.* Crude product was purified by silica gel chromatography (gradient of 30% → 40% ethyl acetate/hexanes eluent), affording 9.43 g epoxide (±)-**7** as a yellow oil (70% yield), as a 49:51 mixture of *cis*:*trans* diastereomers (as determined by HPLC and ^{1}H NMR).

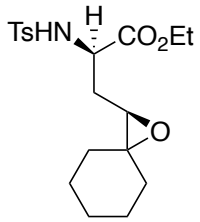
(B) Shi epoxidation: 512 mg (1.57 mmol, 1 equiv) alkene (*R*)-**6** was combined with 204 mg *D*-Shi catalyst (0.790 mmol, 50 mol %), 266 mg tetra-*n*-butylammonium hydrogensulfate (0.783 mmol, 50 mol %) in a 250 mL round bottom flask equipped with a stir bar. The mixture of solids was dissolved in 42 mL 2:1 dimethoxymethane:acetonitrile, and 28 mL borate buffer (0.05 M $Na_2B_4O_7$, 0.0004 M Na_2EDTA_2) was added while stirring vigorously. Resulting mixture was cooled on an ice-bath, and 20 mL 0.68 M aqueous Oxone® and 20 mL 1.27 M aqueous K_2CO_3 were added via syringe pump, at a flow rate of 20 mL/hour, over 1 hour. When the syringe pump additions were complete, the reaction was quenched in saturated aqueous sodium thiosulfate, and the organic layer was separated in a separatory funnel. The aqueous layer was extracted 5 x 25 mL ethyl acetate, and organic layers were pooled, washed in saturated aqueous sodium bicarbonate, then deionized water, then brine. The organic layer was then dried with $MgSO_4$, filtered, and concentrated *in vacuo.* Crude product was purified by chromatography using basified silica gel[3] (gradient of 30% → 40% ethyl acetate/hexanes eluent), delivering 499 mg epoxide (2*R*,4*R*)-**7** as a yellow oil (93% yield), as a 89:11 mixture of *cis*:*trans* diastereomers (as determined by ^{1}H NMR).



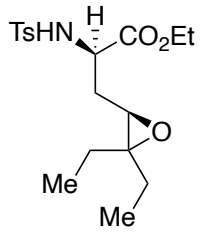
(±)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (7). ^{1}H NMR (400 MHz, $CDCl_3$): (49:51 *cis*:*trans*) δ 7.68-7.65 (m, 4H, overlapping *cis*/*trans*), 7.24-7.21 (m, 4H, overlapping *cis*/*trans*), 5.37 (d, *J* = 8

[3] Silica gel was basified by flushing with 1% triethylamine/hexanes prior to equilibrating the column. All the epoxides we synthesized proved sensitive to degradation on normal silica gel, causing generation of unknown byproducts and reduction of yield. Even with basified silica some degradation still occurs, making purification more difficult than the alkene or proline compounds.

Hz, 1H, *trans,* N*H*), 5.23 (d, *J* = 8 Hz, 1H, *cis*, N*H*), 4.06-3.87 (m, 6H, overlapping *cis*/*trans*), 2.78-2.70 (m, 2H, overlapping *cis*/*trans*), 2.35 (apparent d, *J* = 4 Hz, 6H, overlapping *cis*/*trans*), 2.04 (dt, *J* = 12, 4 Hz, 1H, *cis*), 1.90-1.80 (m, 3H, overlapping *cis*/*trans*), 1.24 (s, 3H, *trans*); 1.21 (3H, s, *cis*), 1.17 (s, 6H, overlapping *cis*/*trans*), 1.08 (t, *J* = 8 Hz, 3H, *trans*), 1.04 (t, *J* = 6 Hz, 3H, *cis*); ^{13}C NMR (100 MHz, $CDCl_3$): (49:51 *cis*:*trans*)δ171.3, 171.0, 143.94 143.87, 136.9, 136.7, 129.9, 129.3, 127.5, 127.4, 62.3, 62.1, 60.6, 60.0, 54.2, 54.0, 33.2, 32.7, 24.71, 24.68, 21.66, 19.1, 19.0, 14.0; ; IR (neat): 3271 (w), 2980 (w), 2927 (w), 1735 (s), 1598 (w), 1495 (w), 1447 (w), 1370 (w), 1338 (m), 1305 (w), 1217 (w), 1185 (w), 1159 (s), 1119 (w), 1091 (w), 1020 (w), 895 (w), 855 (w), 814 (m), 736, 706, 661 (s) cm^{-1}; HRMS: calcd for $C_{16}H_{24}NO_5S$: 342.137, found: 342.1368 (M+H).

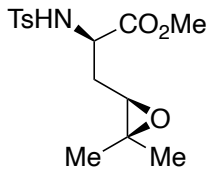


(2*R*,4*R*)-*N*-tosyl-2-amino-4,5-epoxy-4-cyclohexylidenebutanoic acid ethyl ester (7b). ^{1}H NMR (400 MHz, $CDCl_3$): (91:9 *cis*:*trans*) δ7.75-7.71 (m, 2H, overlapping *cis*/*trans*), 7.30-7.26 (m, 2H, overlapping *cis*/*trans*), 5.46 (d, *J* = 8 Hz, 1H, *trans,* N*H*), 5.33 (d, *J* = 12 Hz, 1H, *cis*, N*H*), 4.17-4.10 (m, 1H, overlapping *cis*/*trans*), 4.09-3.94 (m, 2H, overlapping *cis*/*trans*), 2.87-2.84 (m, 1H, overlapping *cis*/*trans*), 2.43 (s, 3H, overlapping *cis*/*trans*), 1.98-1.87 (m, 2H, overlapping *cis*/*trans*), 1.73-1.65 (m, 2H, overlapping *cis*/*trans*), 1.59-1.44 (m, 8H, overlapping *cis*/*trans*); 1.17 (t, *J* = 6 Hz, 3H, *trans*), 1.12 (t, *J* = 8 Hz, 3H, *cis*); ^{13}C NMR (100 MHz, $CDCl_3$): (91:9 *cis*:*trans*) δ171.3, 171.1, 143.9 143.8, 136.9, 136.6, 129.9, 129.8, 127.5, 127.4, 63.0, 62.8, 60.6, 60.0, 54.2, 54.0, 33.2, 32.7, 24.71, 24.68, 21.66, 19.1, 19.0, 14.0; ; IR (neat): 3270 (w), 2857 (w), 2931 (w), 1734 (s), 1598 (w), 1494 (w), 1447 (m), 1369 (w), 1339 (w), 1289 (w), 1184 (w), 1160 (s), 1118 (w), 1091 (m), 1020 (w), 905 (w), 854 (w), 814 (m), 735 (w), 706 (w), 662 (s); HRMS: calcd for $C_{19}H_{28}NO_5S$: 382.1688, found: 382.1685 (M+H).

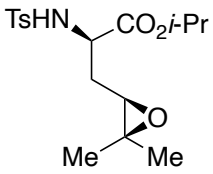


(2*R*,4*R*)-*N*-tosyl-2-amino-4,5-epoxy-5-ethylheptanoic acid ethyl ester (7c). ^{1}H NMR (400 MHz, $CDCl_3$): (88:12 *cis*:*trans*) δ7.73 (d, J = 12 Hz, 2H, overlapping *cis*/*trans*), 7.30 (d, J = 12 Hz, 2H, overlapping *cis*/*trans*), 5.44 (d, *J* = 8 Hz, 1H, *cis*), 5.31 (d, *J* = 8 Hz, 1H, *trans*), 4.10-3.94 (m, 3H, overlapping *cis*/*trans*), 2.85-2.82 (m, 1H, overlapping *cis*/*trans*), 2.41 (s, 3H, overlapping *cis*/*trans*), 2.18-2.12 (m, 1H, overlapping *cis*/*trans*), 1.94-1.87 (m, 1H, overlapping *cis*/*trans*), 1.54-1.40 (m, 4H, overlapping *cis*/*trans*), 1.15 (t, *J* = 8 Hz, 3H, overlapping *cis*/*trans*), 0.95 (t, *J* =

8 Hz, 3H, overlapping *cis*/*trans*), 0.88 (t, *J* = 8 Hz, 3H, overlapping *cis*/*trans*); ^{13}C NMR (100 MHz, $CDCl_3$): (88:12 *cis*:*trans*) δ 175.4, 143.4, 138.1, 129.3, 128.0, 79.3, 77.7, 62.1, 60.9, 36.4, 30.0, 29.3, 21.5, 13.8, 10.5, 9.9; IR (neat): 3261 (w), 2965 (w), 2939 (w), 2879 (w), 1738 (s), 1728 (w), 1597 (w), 1497 (w), 1450 (w), 1420 (w), 1370 (w), 1339 (s), 1309 (w), 1276 (w), 1215 (w), 1185 (w), 1160 (s), 1121 (w), 1086 (m), 1017 (w), 967 (w), 927 (w), 896 (w), 865 (w), 852 (w), 818 (w), 735 (w), 705 (w), 666 (s), 608 (w), 569 (w), 554 (m), 504 (w), 490 (w), 443 (w), 425 (w) cm^{-1}; HRMS: calcd for $C_{18}H_{28}NO_5S$: 370.1688, found: 370.1685 (M+H).



(2*R*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine methyl ester (7d). ^{1}H NMR (400 MHz, $CDCl_3$): (89:11 *cis*:*trans*) δ 7.73 (d, J = 8 Hz, 2H, overlapping *cis*/*trans*), 7.29 (d, , J = 8 Hz, 2H, overlapping *cis*/*trans*), 5.40 (d, *J* = 8 Hz, 1H, *trans*), 5.28 (d, *J* = 8 Hz, 1H, *cis*), 4.16-4.11 (m, 1H, overlapping *cis*/*trans*), 4.05-4.00 (m, 1H, *trans*), 3.59 (s, 3H, *trans*), 3.53 (s, 3H, *cis*), 2.83-2.80 (m, 1H, overlapping *cis*/*trans*), 2.42 (s, 3H, overlapping *cis*/*trans*), 1.96-1.85 (2H, m, overlapping *cis*/*trans*), 1.29 (s, 3H, *cis*), 1.28 (s, 3H, *trans*), 1.23 (s, 3H, overlapping *cis*/*trans*; ^{13}C NMR (100 MHz, $CDCl_3$): (89:11 *cis*:*trans*) δ 171.8, 143.9, 136.9, 129.9, 129.8, 127.4, 60.5, 58.7, 54.2, 52.8, 33.0, 24.7, 21.7, 19.0; IR (neat): 3276 (br), 2923 (w), 2853 (w), 1741 (s), 1598 (w), 1436 (m), 1379 (w), 1337 (s), 1275 (w), 1220 (w), 1159 (s), 1120 (w), 1091 (m), 1019 (w), 952 (w), 845 (w), 841 (m), 776 (w), 706 (w), 662 (s), 575 (w), 555 (s) cm^{-1}; HRMS: calcd for $C_{15}H_{22}NO_5S$: 328.1219, found: 328.1219 (M+H).



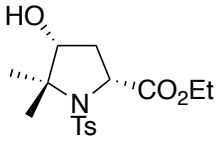
(2*R*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine isopropyl ester (7e). ^{1}H NMR (400 MHz, $CDCl_3$): (89:11 *cis*:*trans*) δ 7.72 (d, *J* = 8 Hz, 2H, overlapping *cis*/*trans*), 7.27 (d, *J* = 8 Hz, 2H, overlapping *cis*/*trans*), 5.46 (d, *J* = 8 Hz, 1H, *trans*), 5.33 (d, *J* = 12 Hz, 1H, *cis*), 4.81-4.74 (m, 1H, overlapping *cis*/*trans*), 4.06-4.00 (m, 1H, *cis*), 3.97-3.90 (m, 1H, *trans*), 2.86-2.83 (m, 1H, overlapping *cis*/*trans*), 2.40 (s, 3H, overlapping *cis*/*trans*), 1.93-1.79 (m, 2H, overlapping *cis*/*trans*), 1.33 (s, 3H, *trans*), 1.30 (s, 3H, *cis*), 1.28 (s, 3H, *trans*), 1.24 (s, 3H, *cis*), 1.14 (d, *J* = 8 Hz, 3H, *trans*), 1.11 (d, *J* = 4 Hz, 3H, *cis*), 1.07 (d, *J* = 4 Hz, 3H, *trans*), 1.01 (d, *J* = 8 Hz, 3H, *cis*); ^{13}C NMR (100 MHz, $CDCl_3$): (89:11 *cis*:*trans*) δ 170.8, 143.8, 136.9, 129.8, 127.5, 70.0, 60.7, 58.8, 54.3, 33.3, 24.71, 24.69, 21.6, 21.51, 19.1; IR (neat): 3289 (br), 2981 (w), 2928 (w), 2878 (w), 1735 (s), 1597 (w), 1496 (w), 1442 (w), 1422 (w), 1402 (w), 1374 (w), 1357 (w), 1331 (s), 1307 (w), 1283 (w), 1214 (m), 1185 (w), 1192 (w), 1160 (s), 1139 (w), 1111 (s) 1088 (s), 1045 (w), 1016 (m), 943 (m), 915 (w), 893 (w), 858 (m) 816 (s), 800 (w), 784 (m), 736 (m), 683 (w), 668 (s) 633 (w) cm^{-1}; HRMS: calcd for $C_{17}H_{26}NO_5S$: 356.1532, found: 356.1530 (M+H).

IV. Epoxide opening

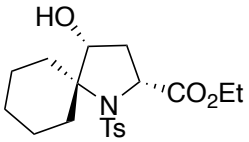
A. A 20 mL scintillation vial was charged with 48.6 mg (0.142 mmol, 1 equiv) epoxide *cis*-**7** and equipped with a stir bar. Anhydrous dichloromethane (5 mL) was added and mixture was cooled on an ice-bath. 10 μL (17 mg, 0.11 mmol, 75 mol %) trifluoromethanesulfonic acid was added via syringe and the mixture stirred for 1 hour. Mixture was filtered through a plug of anhydrous K_2CO_3, plug was washed in 5 x 2 mL dichloromethane, and solution was concentrated *in vacuo*. Percent conversion was assayed by ^{1}H NMR using 1,2,3-trimethoxybenzene as an internal standard in $CDCl_3$. Crude product was purified by silica gel chromatography (gradient of 20% → 30% ethyl acetate/hexanes eluent), and 26.1 mg proline **5** was obtained as a white solid residue (54% yield).

B. A 20 mL scintillation vial was charged with 50.3 mg (0.147 mmol, 1 equiv) epoxide *cis*-**7** inside a glovebox. Anhydrous dichloromethane (5 mL) was added and mixture was transferred via syringe to a second 20 mL scintillation vial containing 5.0 mg (0.014 mmol, 10 mol %) $InBr_3$ and 500 mg 4 Å molecular sieves (which were dried in the oven at 150 °C for 24 hours and cooled under vacuum prior to use). Vial was equipped with a stir bar, and mixture stirred for 3 hours at room temperature, and was then removed from the glovebox and filtered through a plug of Celite. Plug was washed in 5 x 2 mL dichloromethane, and solution was concentrated *in vacuo*. Percent conversion was assayed by ^{1}H NMR using 1,2,3-trimethoxybenzene as an internal standard in $CDCl_3$. Crude product was purified by silica gel chromatography (gradient of 20% → 30% ethyl acetate/hexanes eluent), and 20.3 mg proline **5** was obtained as a white solid residue (40% yield).

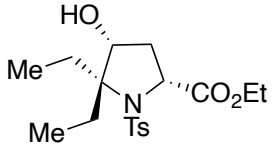
C. A 20 mL scintillation vial was charged with 22.4 mg (0.0656 mmol, 1 equiv) epoxide *trans*-**7**, and vial was equipped with a stir bar. Anhydrous dichloromethane (5 mL) was added and mixture was transferred via syringe to a second 20 mL scintillation vial containing 3.6 mg (0.0064 mmol, 10 mol %) $In(OTf)_3$. Mixture stirred for 24 hours at room temperature, and was then filtered through a plug of Celite. Plug was washed in 5 x 2 mL dichloromethane, and solution was concentrated *in vacuo*. Percent conversion was assayed by ^{1}H NMR using 1,2,3-trimethoxybenzene as an internal standard in $CDCl_3$. Crude product was purified by silica gel chromatography (gradient of 20% → 30% → 40% ethyl acetate/hexanes eluent), and 20.3 mg proline **5** was obtained as a white solid residue (38% yield).



(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline ethyl ester (5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 4.46 (dd, *J* = 8 Hz, 2 Hz, 1H), 4.14-4.03 (m, 2H), 3.74-3.67 (m, 2H), 2.57-2.50 (m, 1H), 2.41 (s, 3H), 1.88 (d, , *J* = 12 Hz, 1H), 1.51 (s, 3H), 1.33 (s, 3H), 1.24 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$: δ 175.3, 143.7, 138.3, 129.51, 129.47, 128.1, 127.8, 80.6, 71.0, 62.3, 60.3, 34.9, 26.4, 23.1, 21.7, 14.0; IR (neat): 3529 (m), 2987 (w), 2924 (w), 1757 (s), 1596 (w), 1497 (w), 1449 (w), 1326 (s), 1308 (w), 1245 (w), 1231 (w), 1210 (w), 1147 (w), 1132 (s), 1098 (w), 1075 (w), 1040 (w), 1026 (w), 1013 (w), 983 (w), 931 (w), 867 (w), 855 (w), 817 (m), 714 (m), 676 (m), 652 (m) cm^{-1}; HRMS: calcd for $C_{16}H_{24}NO_5S$: 342.1375, found: 342.1378 (M+H); (2*R*,4*R*)-enantiomer: $[\alpha]_D$ -0.96° (*c* = 1.45, $CHCl_3$).

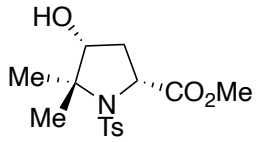


Ethyl (2*R*,4*R*)-*N*-tosyl-4-hydroxy-1-azaspiro[4.5]decane-2-carboxylate (10).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H), 4.49 (dd, *J* = 4, 12 Hz, 1H); 4.30 (d, *J* = 4 Hz, 1H), 4.11-3.96 (2H, m), 2.53-2.44 (m, 1H), 2.41 (s, 3H), 2.34-2.26 (m, 1H), 2.22-2.14 (m, 1H), 2.11-2.06 (m, 1H), 1.89 (d, *J* = 16 Hz, 1H), 1.73-1.62 (m, 3H), 1.47-1.25 (m, 4H), 1.22 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 143.4, 138.7, 129.3, 127.9, 76.0, 74.2, 62.2, 60.1, 35.0, 34.5, 31.7, 25.0, 24.8, 24.4, 21.5, 13.9; IR (neat): 3445 (br), 2935 (w), 2866 (w), 1721 (s), 1598 (w), 1449 (w), 1379 (w), 1329 (w), 1265 (m), 1208 (w), 1155 (s), 1113 (w), 1093 (w) 1065 (w), 1002 (w), 950 (w), 094 (w), 816 (w), 732 (s), 702 (w), 670 (w), 642 (w) cm^{-1}; HRMS: calcd for $C_{19}H_{28}NO_5S$: 382.1688, found: 382.1690 (M+H); (2*R*,4*R*)-enantiomer: $[\alpha]_D$ -0.22° (*c* = 1.31, $CHCl_3$).

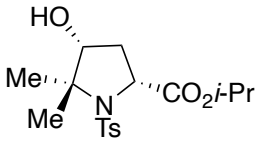


(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-diethylproline ethyl ester (11). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 4.43 (dd, *J* = 2, 8 Hz, 1H); 4.08-3.92 (2H, m), 3.83 (d, *J* = 12 Hz, 1H), 2.61-2.43 (m, 1H), 2.41 (s, 3H), 2.33-2.24 (m, 1H), 2.06-1.99 (m, 1H), 1.96-1.83 (m, 3H), 1.22 (t, , *J* = 8 Hz, 3H), 1.07 (t, *J* = 8 Hz, 3H), 0.86 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 143.4, 138.1, 129.3, 127.9, 79.3, 77.7, 62.1, 60.9, 36.4, 30.0, 29.3, 21.5, 13.8, 10.5, 9.9; IR (neat): 3463 (br), 2975 (w), 1720 (s), 1598 (w), 1495 (w), 1446 (w), 1378 (w), 1331 (w), 1304 (w), 1266 (w), 1210 (w), 1154 (s), 1092 (m), 1052 (w), 1021 (w), 1004 (w), 925 (w), 816 (w), 733

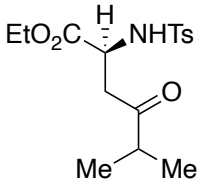
(s), 703 (w), 668 (m), 599 (w), 580 (m), 546 (m) cm^{-1}; HRMS: calcd for $C_{18}H_{28}NO_5S$: 370.1688, found: 370.1687 (M+H); (2*R,4R*)-enantiomer: $[\alpha]_D$ -0.12° (*c* = 1.99, $CHCl_3$).



(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline methyl ester (12). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8 Hz, 2H), 7.28 (d, , *J* = 8 Hz, 2H), 4.49 (d, , *J* = 8 Hz, 1H), 3.76-3.72 (m, 1H), 3.66 (s, 3H), 3.58 (d, *J* = 12 Hz, 1H), 2.57-2.50 (m, 1H), 2.42 (s, 3H), 1.89 (d, *J* = 16 Hz, 1H), 1.51 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 143.7, 138.2, 129.5, 128.1, 80.6, 71.0, 60.1, 53.1, 34.9, 26.4, 23.1, 21.6; IR (neat): 3527 (br), 2993 (w), 2950 (w), 2928 (w), 1766 (s), 1727 (w), 1596 (m), 1497 (w), 1439 (m), 1410 (w), 1387 (w), 1369 (w), 1327 (s), 1308 (w), 1289 (w), 1265 (w), 1246 (w), 1197 (m), 1135 (s), 1095 (m), 1073 (m), 1043 (w), 1025 (w), 1012 (w), 985 (w), 942 (w), 902 (m), 865 (w), 820 (s), 806 (w), 735 (w), 718 (m), 672 (m), 654 (m), 636 (w) cm^{-1}; HRMS: calcd for $C_{15}H_{22}NO_5S$: 328.1219, found: 328.1216 (M+H); (2*R,4R*)-enantiomer: $[\alpha]_D$ +0.20° (*c* = 0.99, $CHCl_3$).

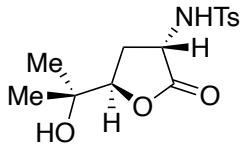


(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline isopropyl ester (13). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 4.95-4.89 (m, 1H), 4.43 (d, *J* = 12 Hz, 1H), 3.75-3.72 (m, 1H), 3.71-3.65 (m, 1H), 2.56-2.49 (m, 1H), 2.41 (s, 3H), 1.86 (d, *J* = 16 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.25 (d, *J* = 8 Hz, 3H), 1.22 (d, , *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 143.7, 138.4, 129.6, 128.1, 80.7, 71.0, 70.3, 60.5, 35.0, 26.4, 23.2, 21.7, 21.6; IR (neat): 3469 (br), 2983 (w), 2937 (w), 1719 (s), 1599 (w), 1496 (w), 1456 (w), 1375 (w), 1331 (m), 1265 (m), 1219 (m), 1175 (w), 1152 (s), 1104 (w), 1092 (m), 1073 (w), 1050 (w), 1021 (w), 1009 (w), 990 (w), 935 (w), 903 (w), 864 (w), 835 (w), 815 (w), 802 (w), 733 (s), 703 (w), 673 (m), 659 (w) cm^{-1}; HRMS: calcd for $C_{17}H_{26}NO_5S$: 356.1532, found: 356.1530 (M+H); (2*R,4R*)-enantiomer: $[\alpha]_D$ +0.11° (*c* = 1.24, $CHCl_3$).



(2*S*)-*N*-tosyl-4-oxo-homoleucine (9).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 5.61 (d, *J* = 8 Hz, 1H), 4.07-3.97 (m, 3H), 3.10 (ddd, *J* = 28 Hz, 18 Hz, 4 Hz, 2H), 2.57-

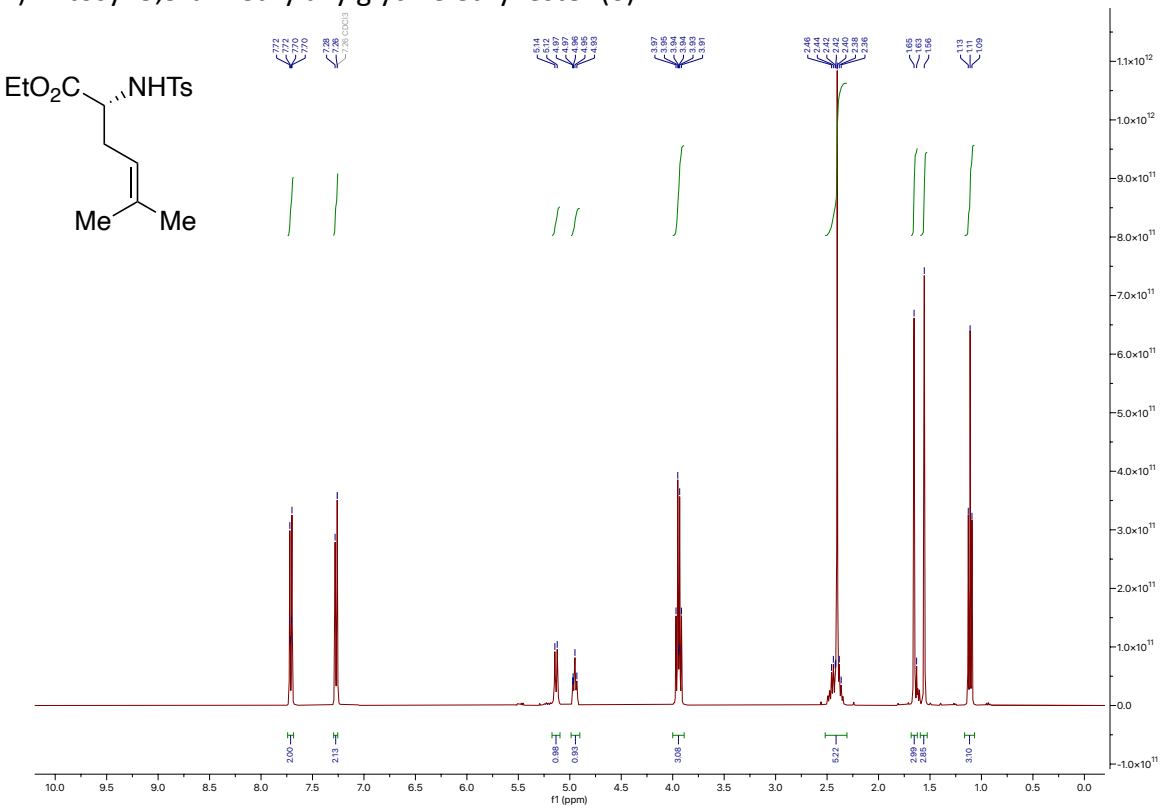
2.50 (m, 1H), 2.41 (s, 3H), 1.25-1.06 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.9, 170.4, 143.7, 137.0, 129.8, 127.4, 62.1, 51.9, 43.6, 40.8, 21.7, 18.1, 14.0; IR (neat): 3282 (m), 2973 (w), 2933 (w), 1732 (s), 1709 (m), 1598 (w), 1496 (w), 1445 (w), 1427 (w), 1383 (w), 1340 (w), 1306 (w), 1272 (w), 1225 (w), 1209 (w), 1187 (w), 1165 (w), 1122 (w), 1089 (w), 1060 (w), 1027 (w), 1004 (w), 939 (w), 818 (w), 748 (w), 706 (w), 681 (w), 661 (w) cm^{-1}; HRMS**:** calcd for $C_{16}H_{24}NO_5S$: 342.1375, found: 342.1375 (M+H); (*R*)-enantiomer: $[\alpha]_D$ -0.29**°** (*c* = 0.77, $CHCl_3$).

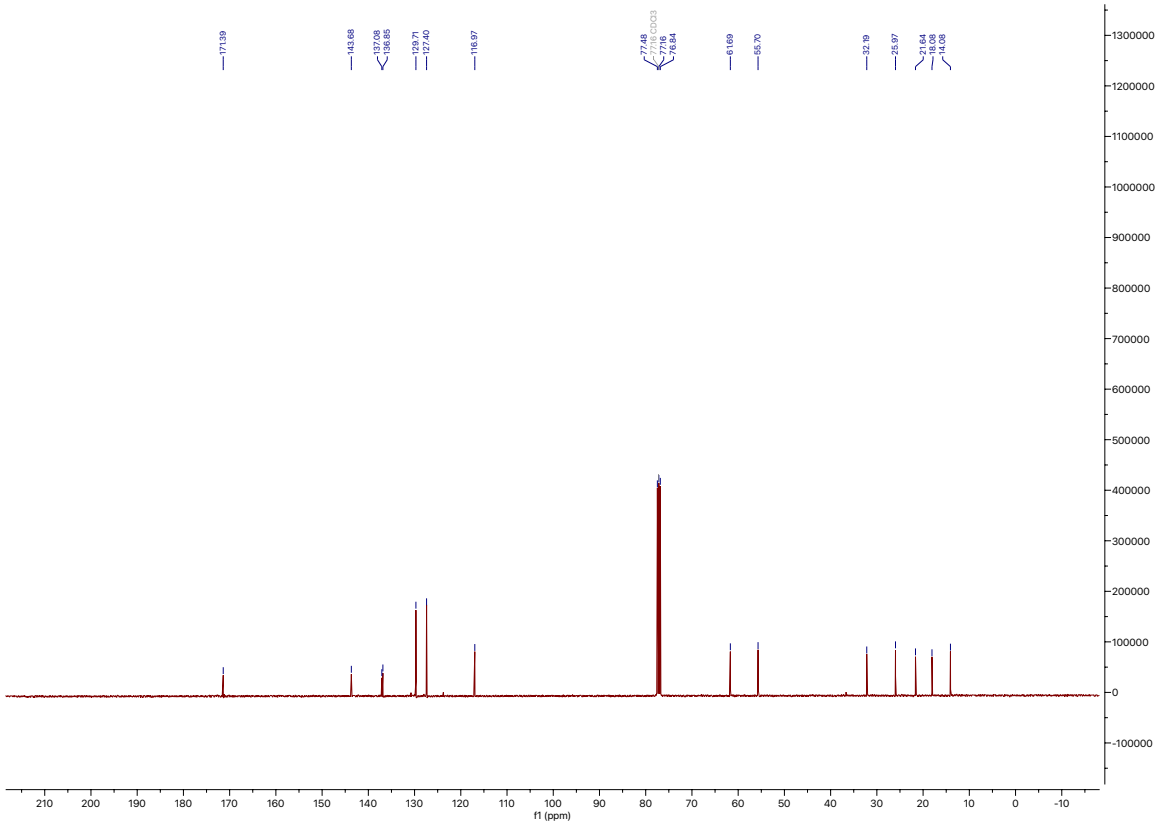


(2*S*,4*R*)-*N*-tosyl-2-amino-5-hydroxy-5-methyl-4-hexanolide (8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, , *J* = 8 Hz, 2H), 7.34 (d, , *J* = 8 Hz, 2H), 4.98 (d, *J* = 4 Hz, 1H), 4.32 (dd, *J* = 2, 8 Hz, 1H), 4.16 (td, *J* = 2, 8 Hz, 1H), 2.83-2.77 (m, 1H), 2.44 (s, 3H), 2.38-2.30 (m, 1H), 1.31 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 144.4, 135.8, 130.1, 127.5, 127.4, 84.5, 72.1, 51.7, 31.5, 26.7, 25.9, 21.7; IR (neat): 3523 (br), 3241 (m), 2965 (w), 2920 (w), 1753 (s), 1599 (w), 1458 (w), 1371 (w) 1351 (w), 1327 (m), 1307 (w), 1260 (w), 1213 (w), 1184 (w), 1150 (m), 1124 (m), 1092 (w), 1057 (w), 1022 (w), 1006 (w), 985 (w), 954 (w), 909 (w), 864 (w), 846 (w), 821 (w), 803 (w), 780 (w), 740 (w), 698 (w), 664 (w), 617 (w), 562 (w), 541 (w), 433 (w), 426 (w), 419 (w) cm^{-1} ; HRMS: calcd for $C_{14}H_{20}NO_5S$: 314.062, found: 314.1059 (M+H); (2*R*,4*S*)-enantiomer: $[\alpha]_D$ +0.09° (*c* = 0.46, $CHCl_3$).

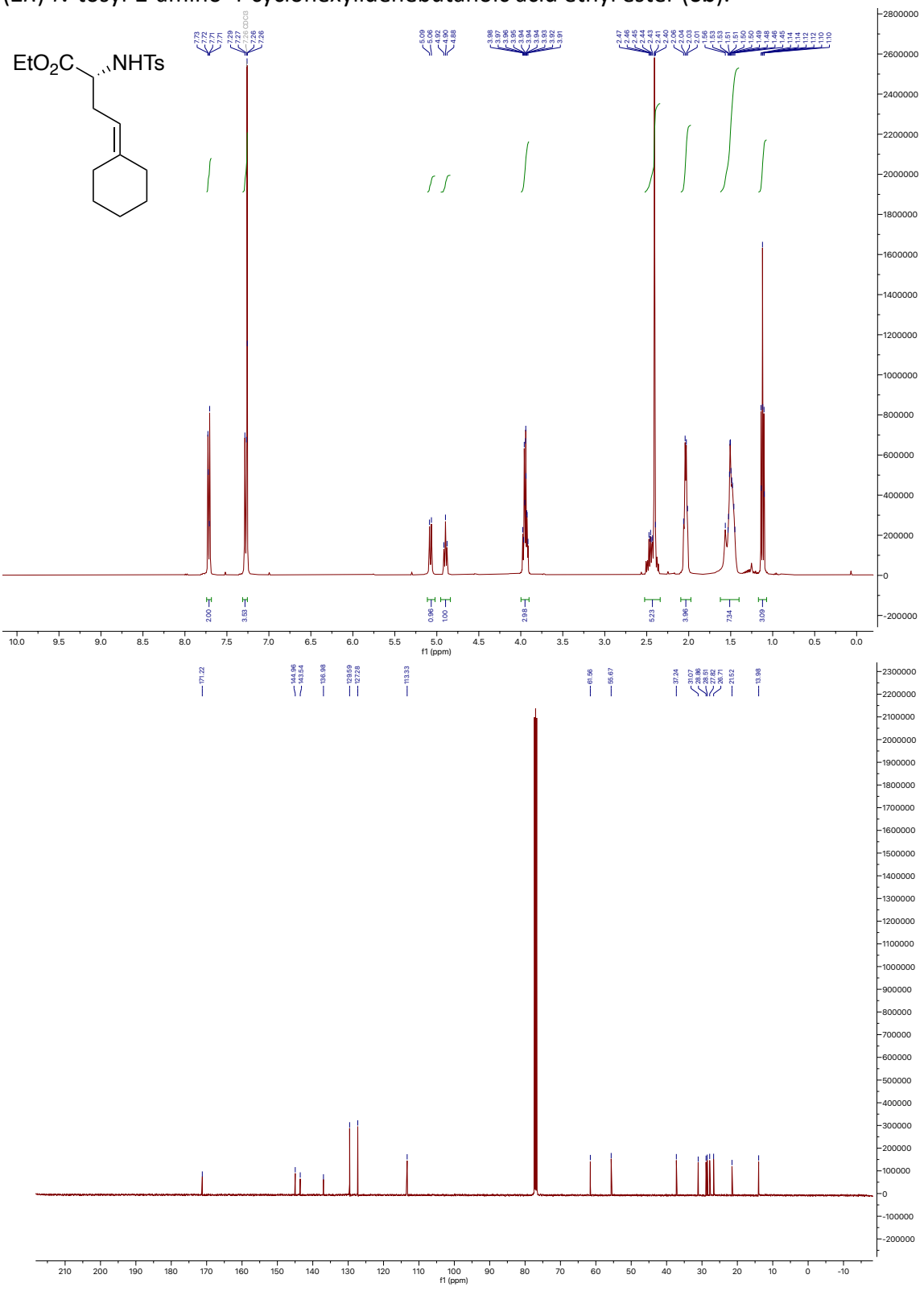
V. ^{1}H and ^{13}C NMR data

(±)-*N*-tosyl-5,5-dimethylallylglycine ethyl ester (**6**).

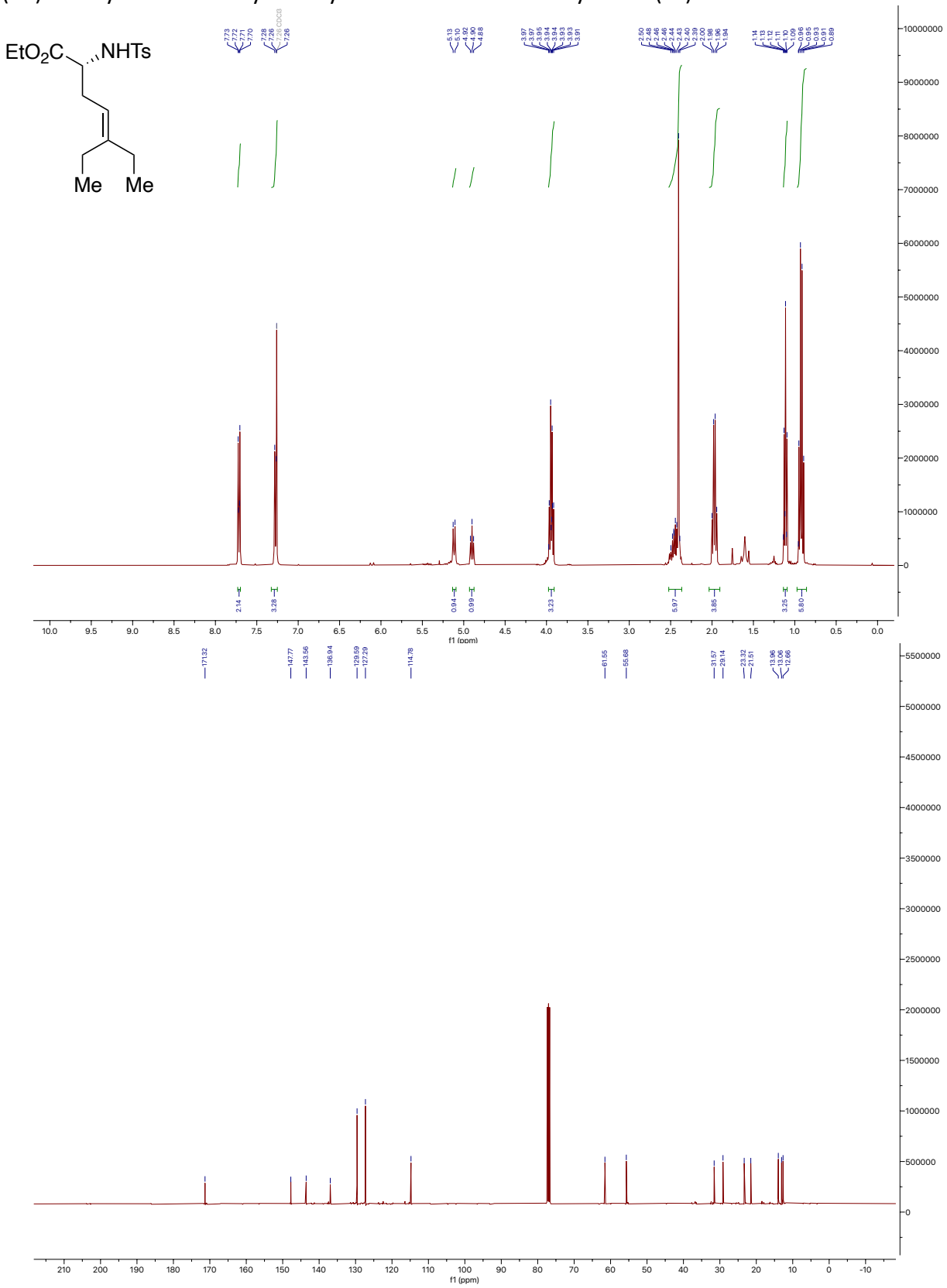




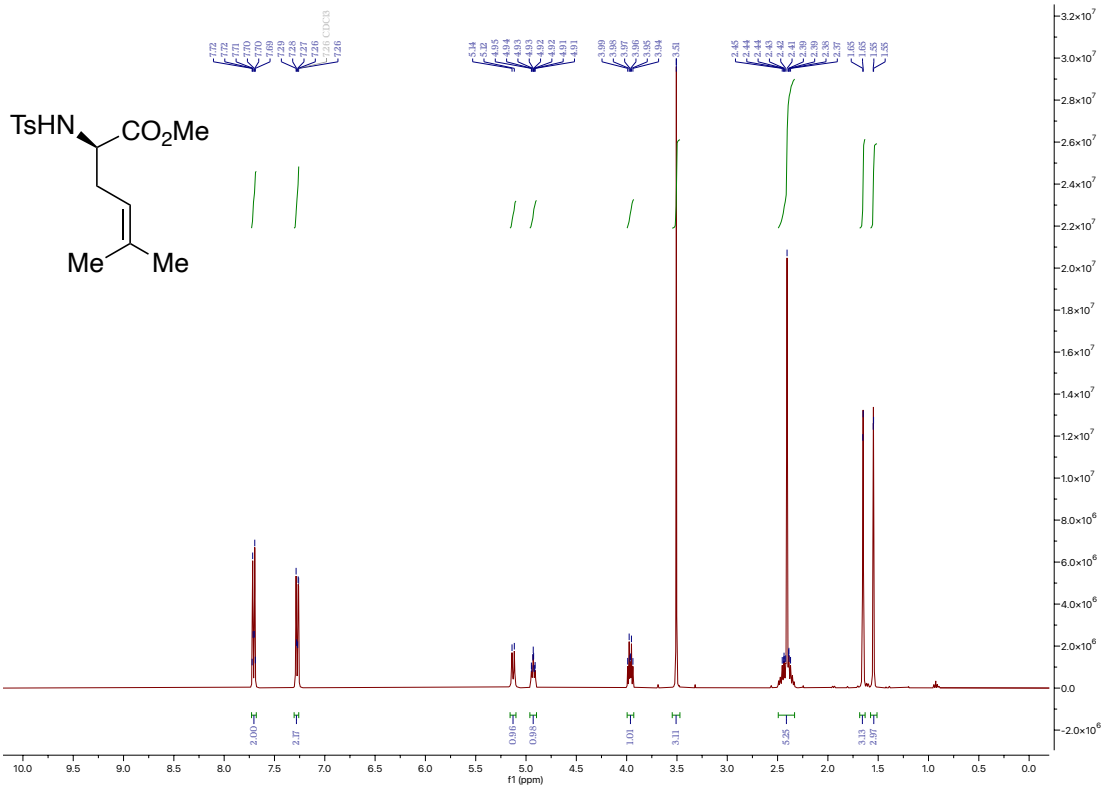
(2*R*)-*N*-tosyl-2-amino-4-cyclohexylidenebutanoic acid ethyl ester (**6b**).

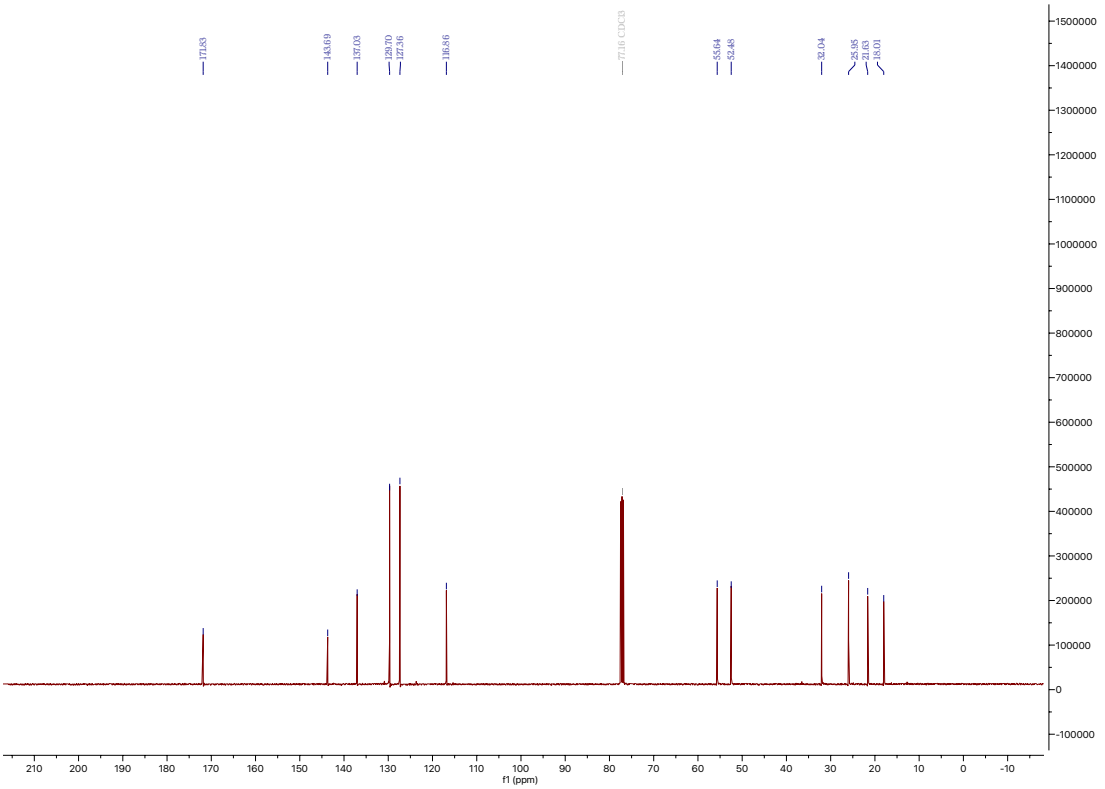


(2*R*)-*N*-tosyl-2-amino-4-cyclohexylidenebutanoic acid ethyl ester (**6c**).

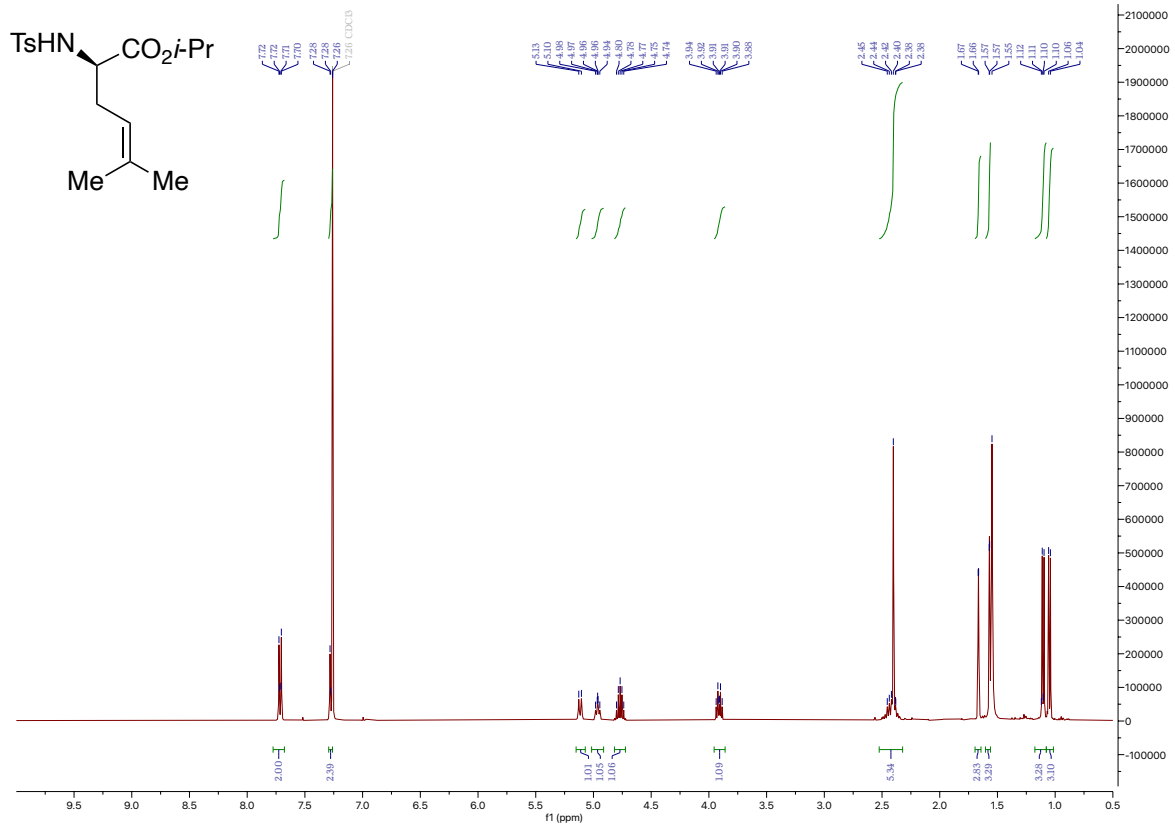


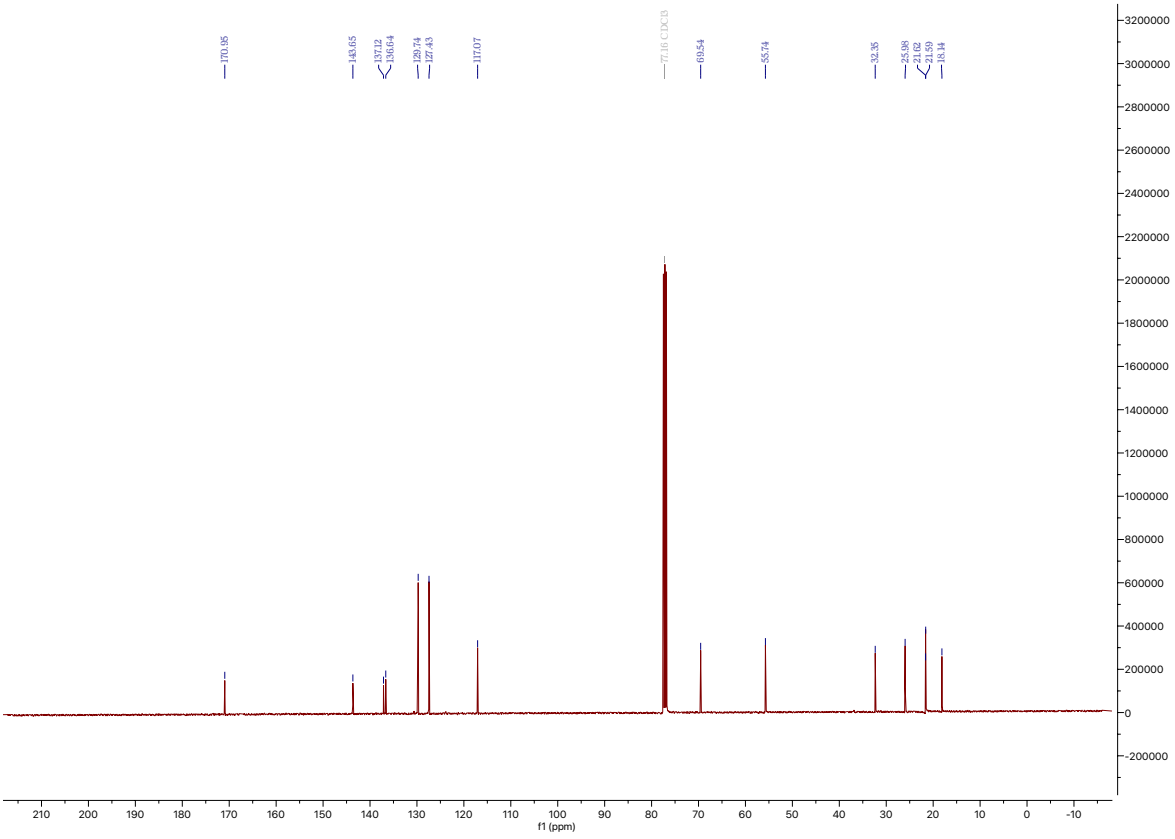
(2*R*)-*N*-tosyl-5,5-dimethylallylglycine methyl ester (**6d**).



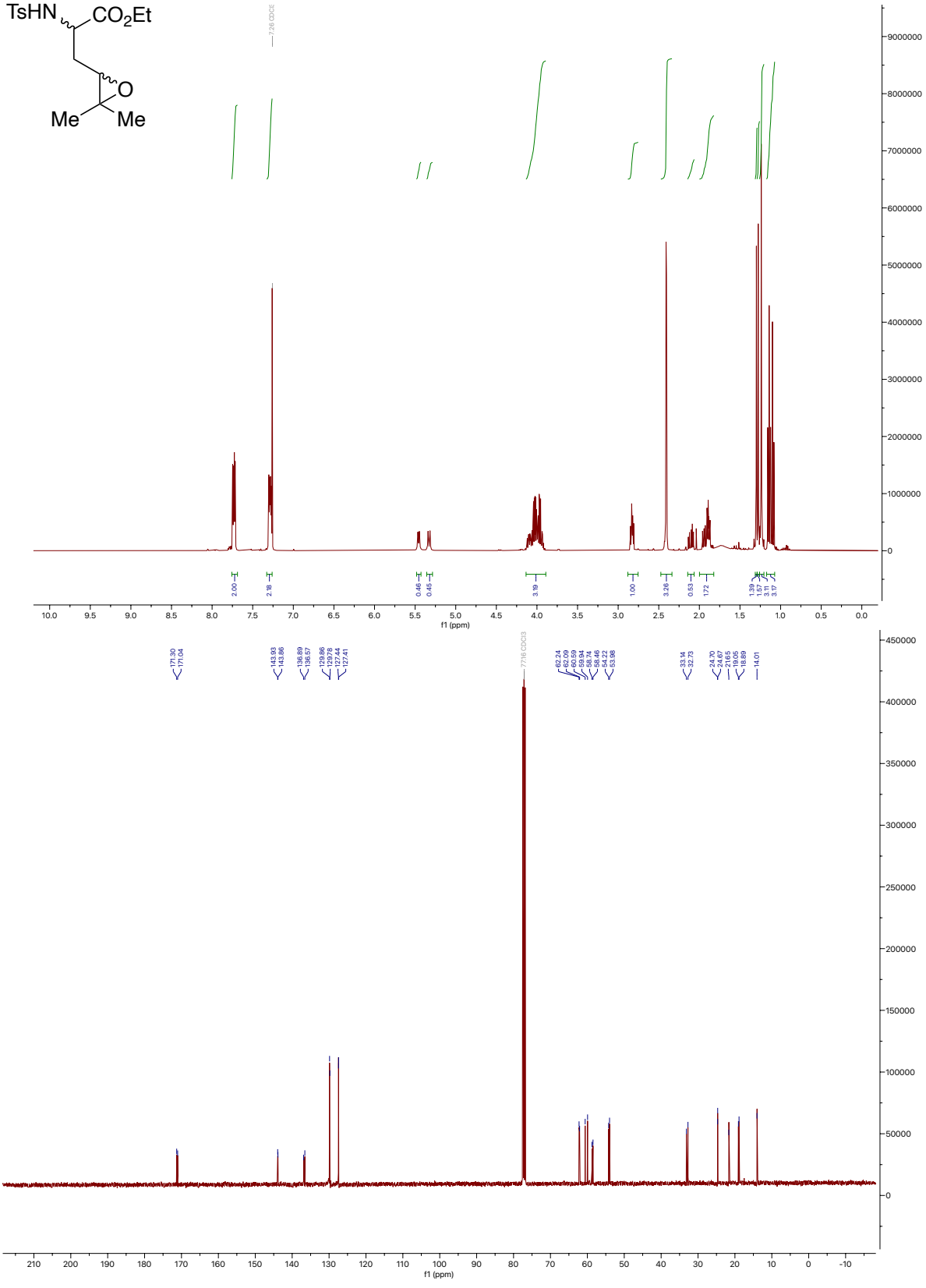


(2*R*)-*N*-tosyl-5,5-dimethylallylglycine isopropyl ester (**6e**).



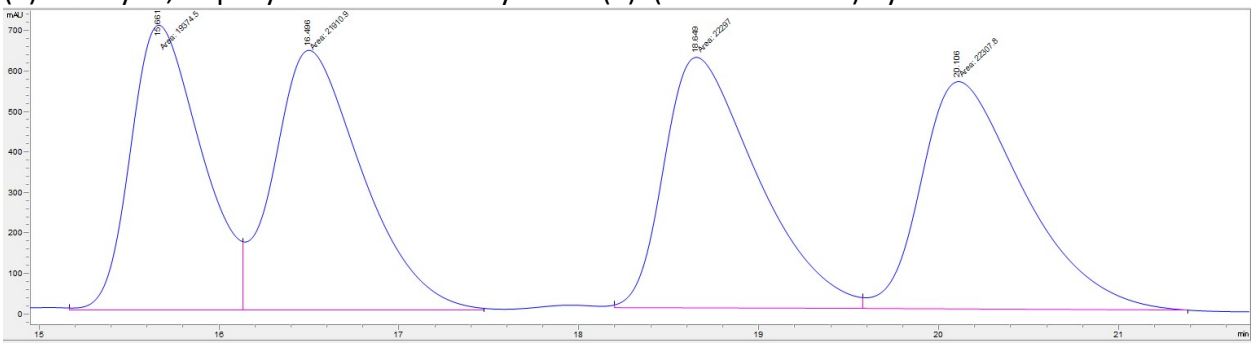


(±)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (**7**). (49:51 *cis*:*trans*)



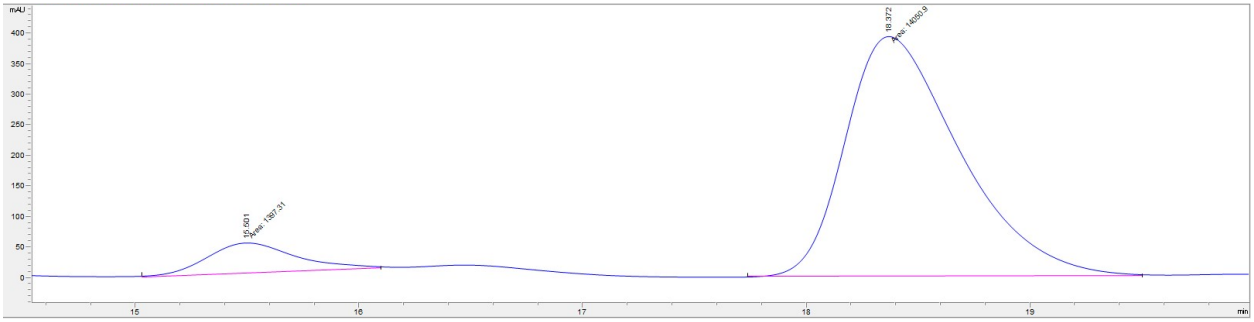
HPLC DATA: Reflect C-Cellulose B column, 98:2 hexanes:ethanol, 230 nm, 0.25 mL/min

(±)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (**7**). (48:52 *cis*:*trans*) by HPLC:



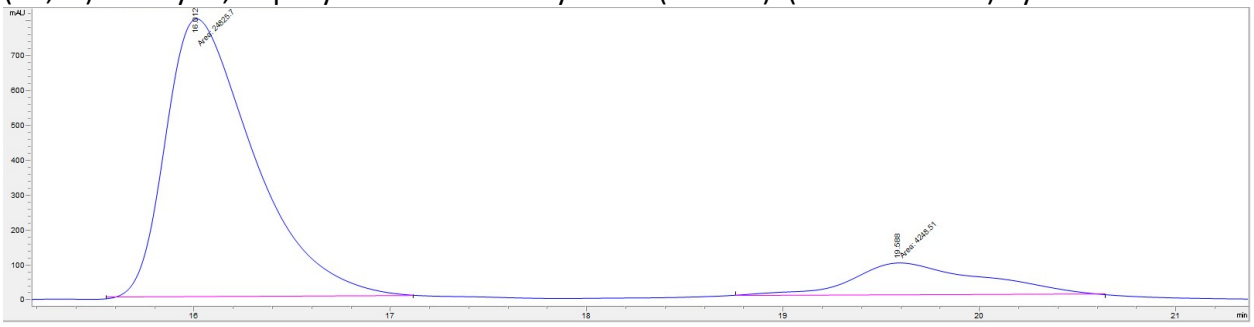
Peak (min)	retention time	integration
(2S,4R)-*trans* epoxide	15.681	19374.5
(2R,4S)-*trans* epoxide	16.496	21910.9
(2R,4R)-*cis* epoxide	18.849	19374.5
(2S,4S)-*cis* epoxide	20.106	22307.8

(2*R*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (***cis*-7**). (91:9 *cis*:*trans*) by HPLC:



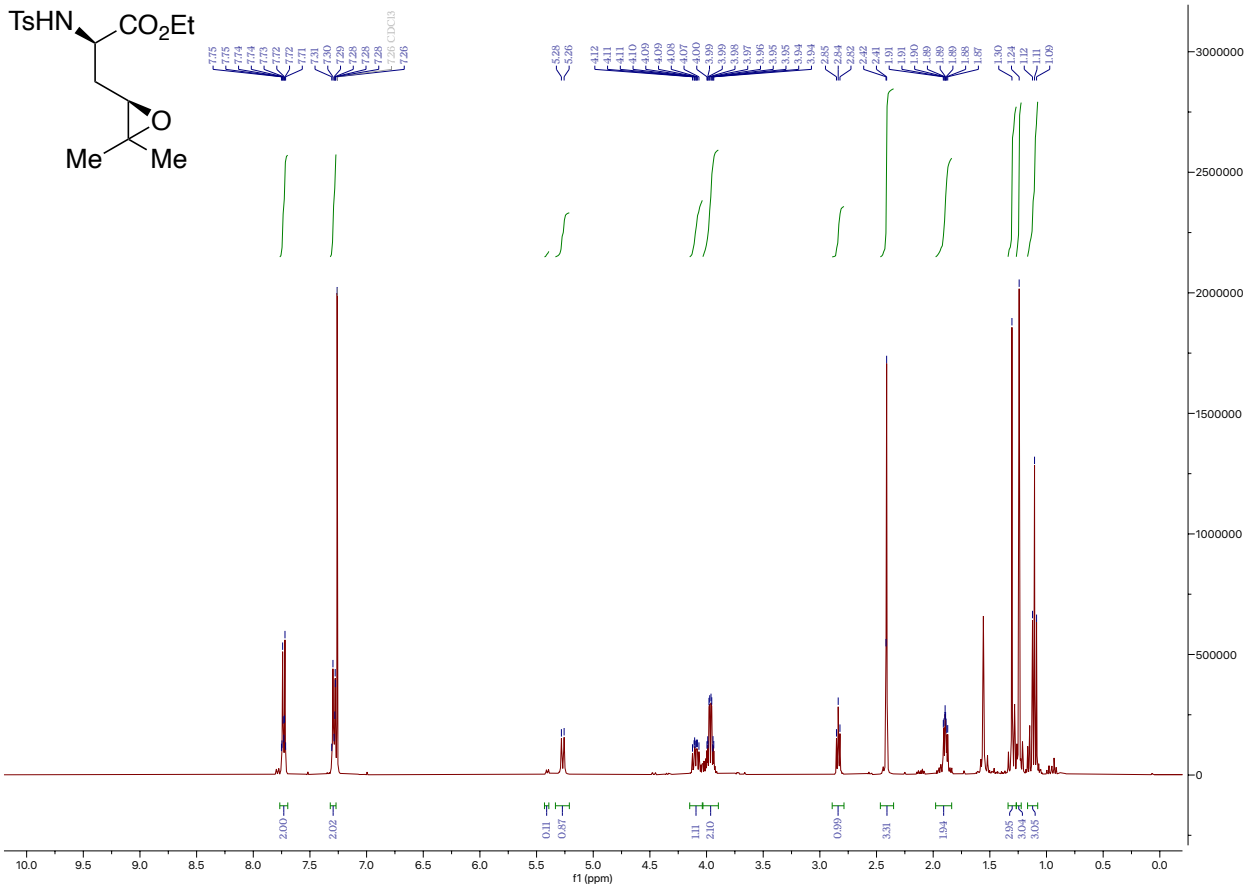
Peak (min)	retention time	integration
(2S,4R)-*cis* epoxide	15.501	1397.31
(2S,4S)-*cis* epoxide	18.372	14050.9

(2*R*,4*S*)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (***trans*-7**). (15:85 *cis*:*trans*) by HPLC:

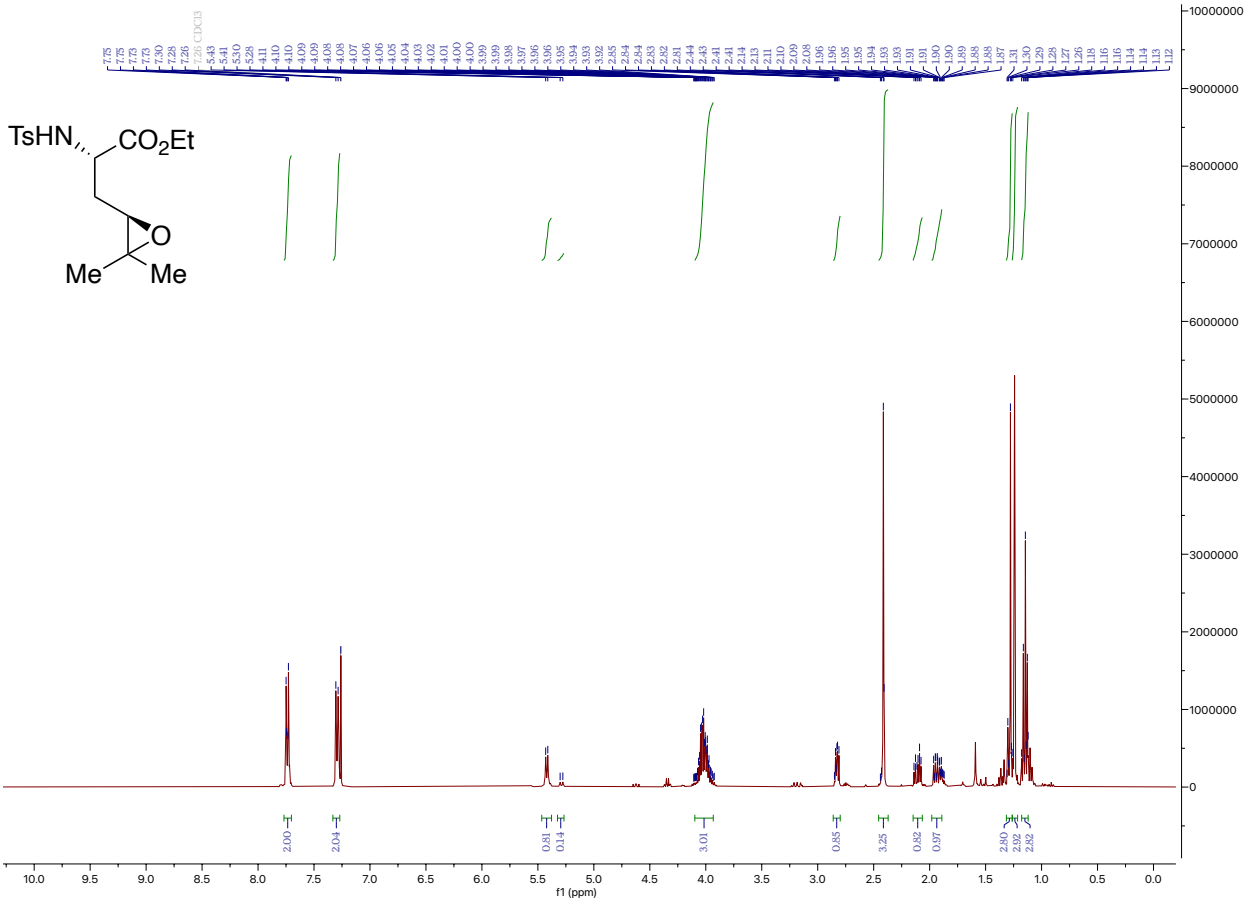


Peak (min)	retention time	integration
(2S,4R)-*trans* epoxide	16.612	24825.7
(2S,4S)-*cis* epoxide	19.558	4248.51

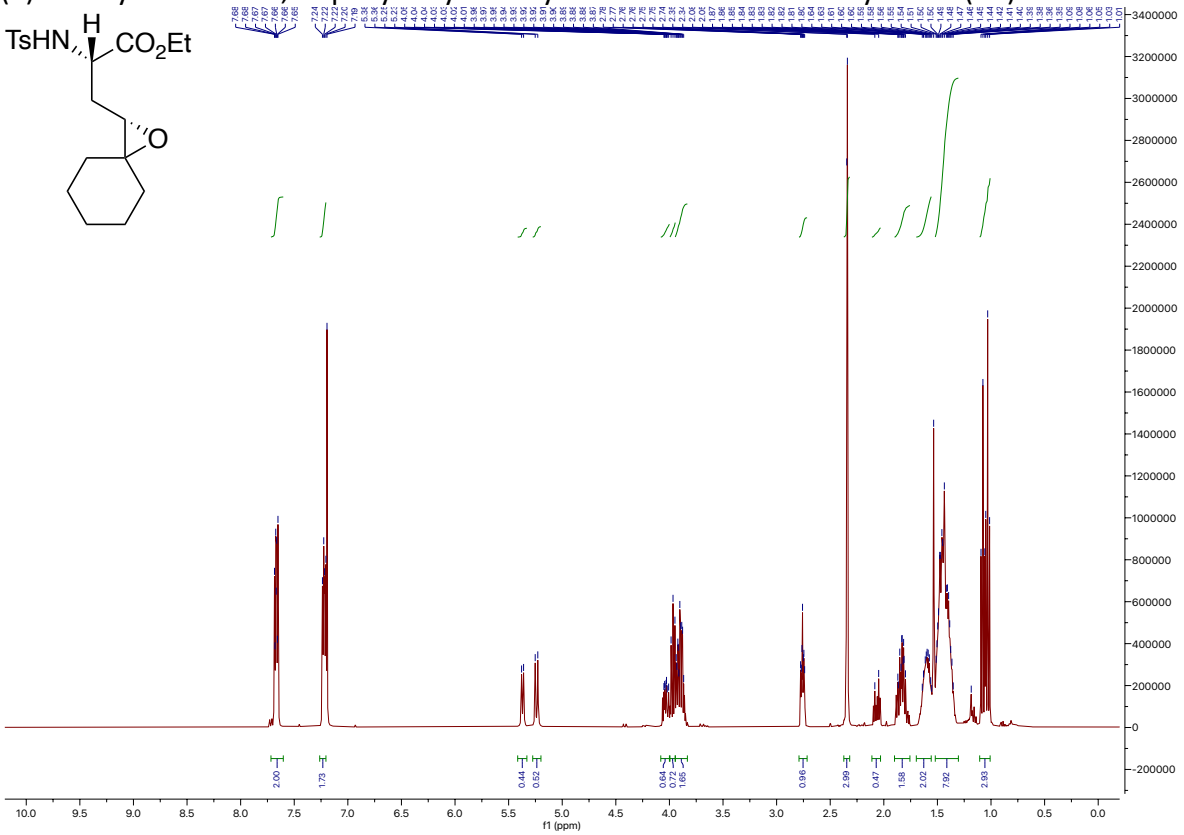
(2*R*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (***cis*-7**). (89:11 *cis*:*trans*)

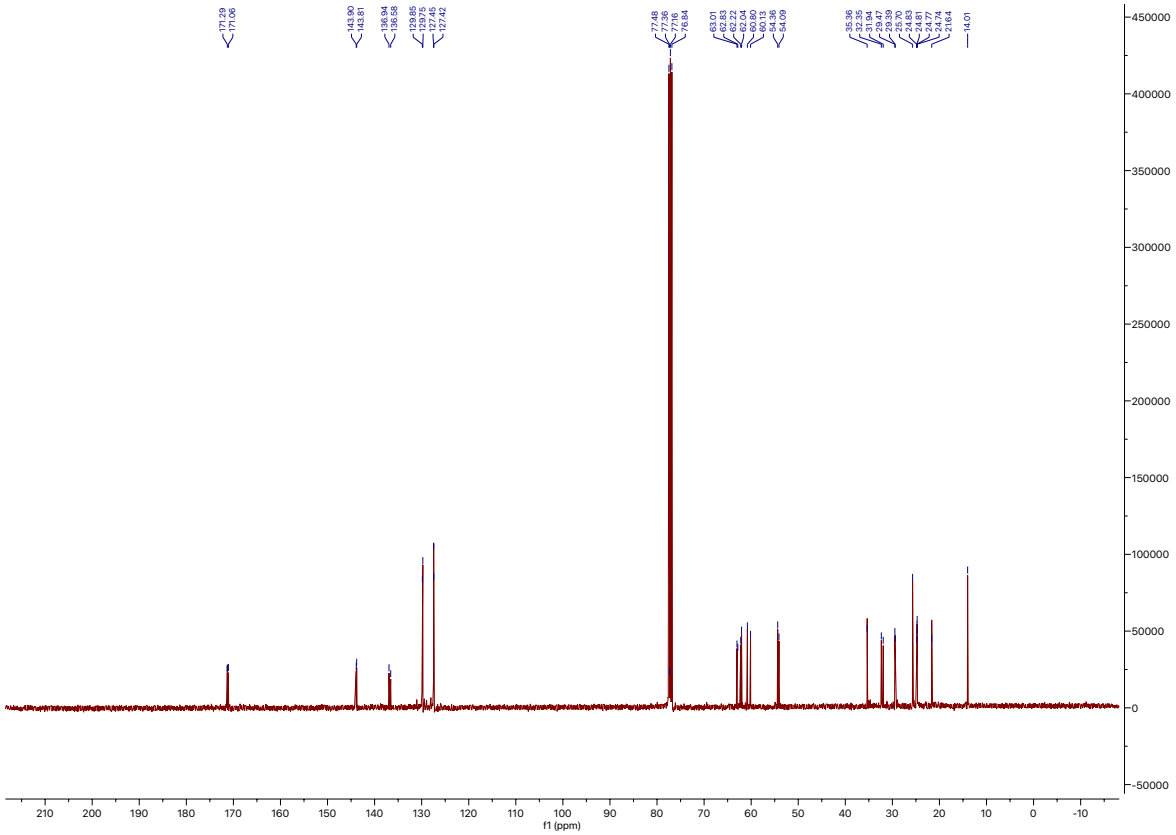


(2*S*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine ethyl ester (***trans*-7**). (15:85 *cis*:*trans*)

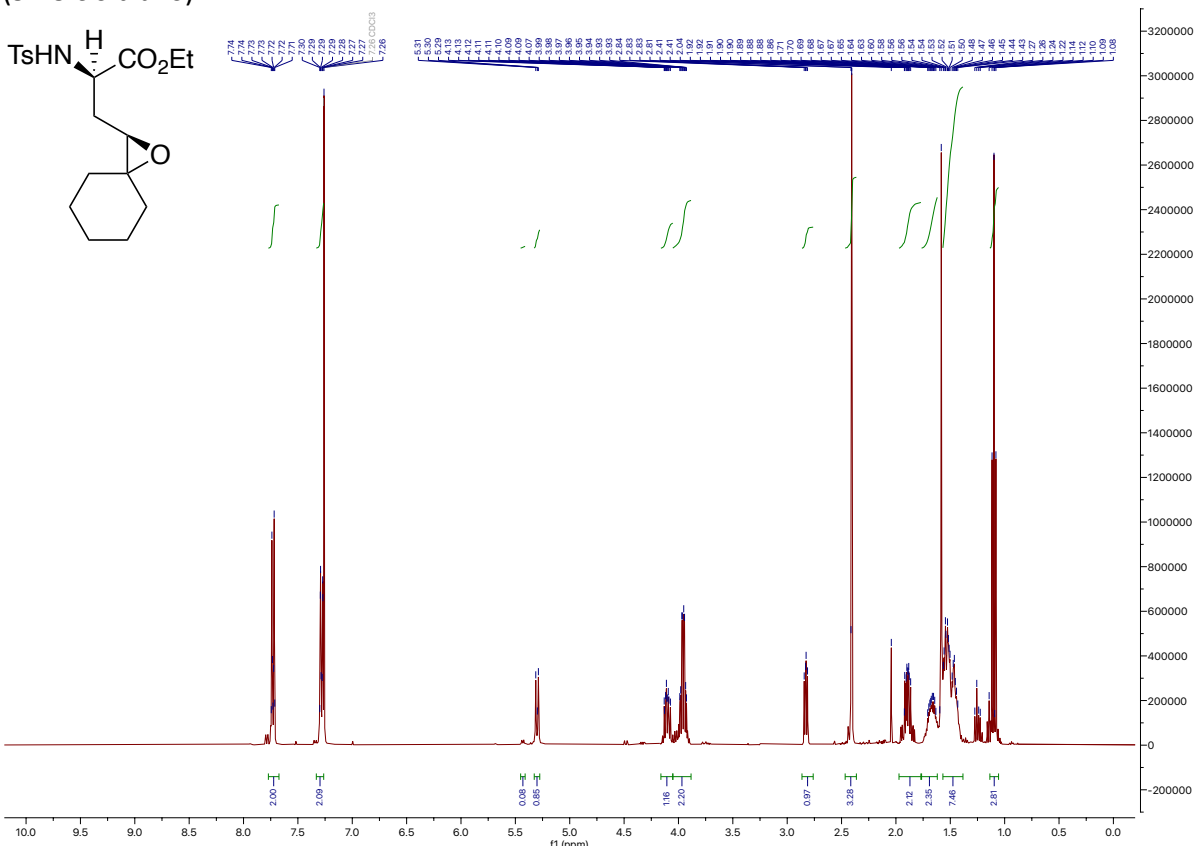


(±)-*N*-tosyl-2-amino-4,5-epoxy-4-cyclohexylidenebutanoic acid ethyl ester (**7b**).

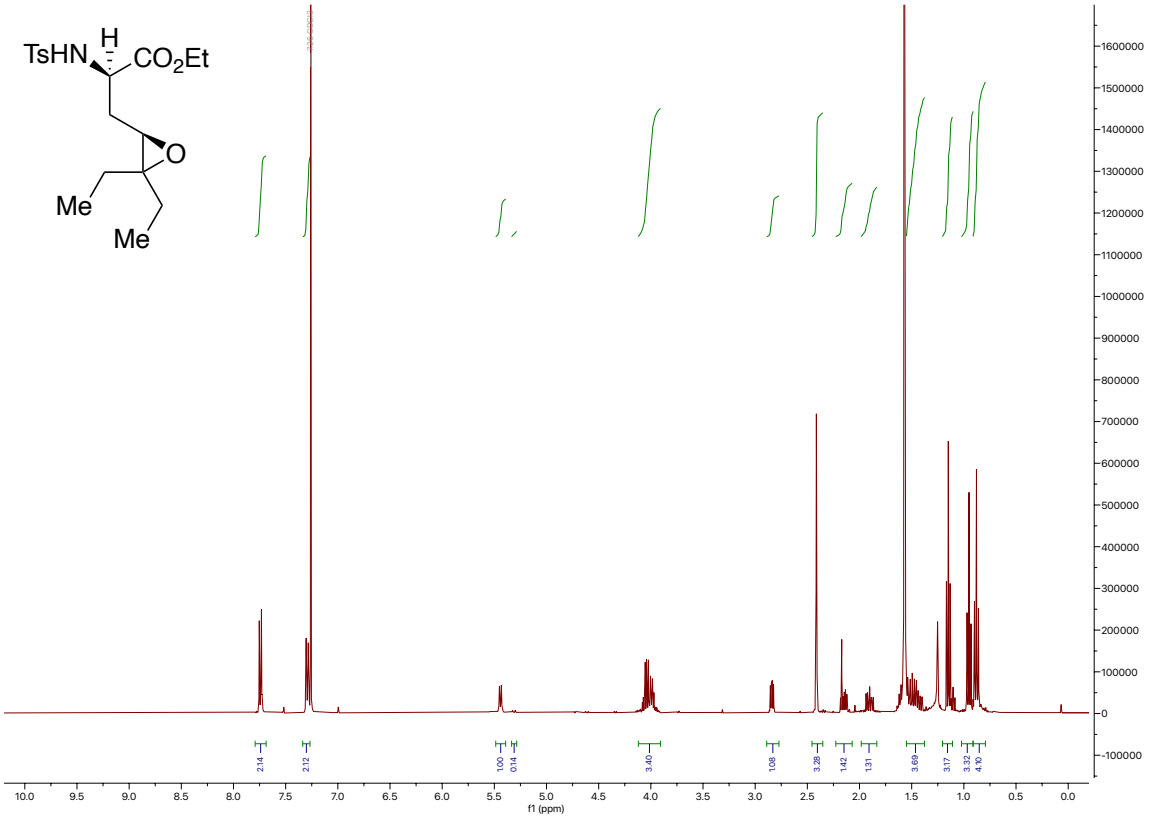


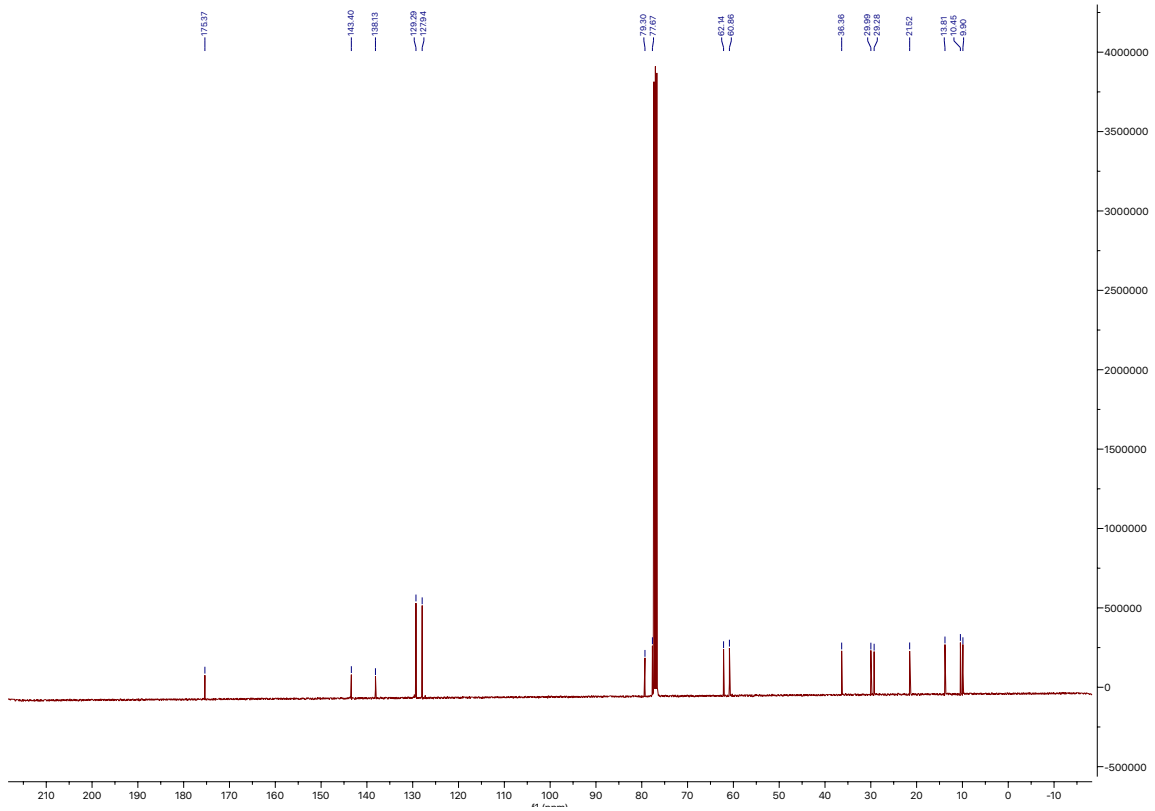


(2*R*,4*R*)-*N*-tosyl-2-amino-4,5-epoxy-4-cyclohexylidenebutanoic acid ethyl ester (***cis*-7b**). (91:9 *cis*:*trans*)

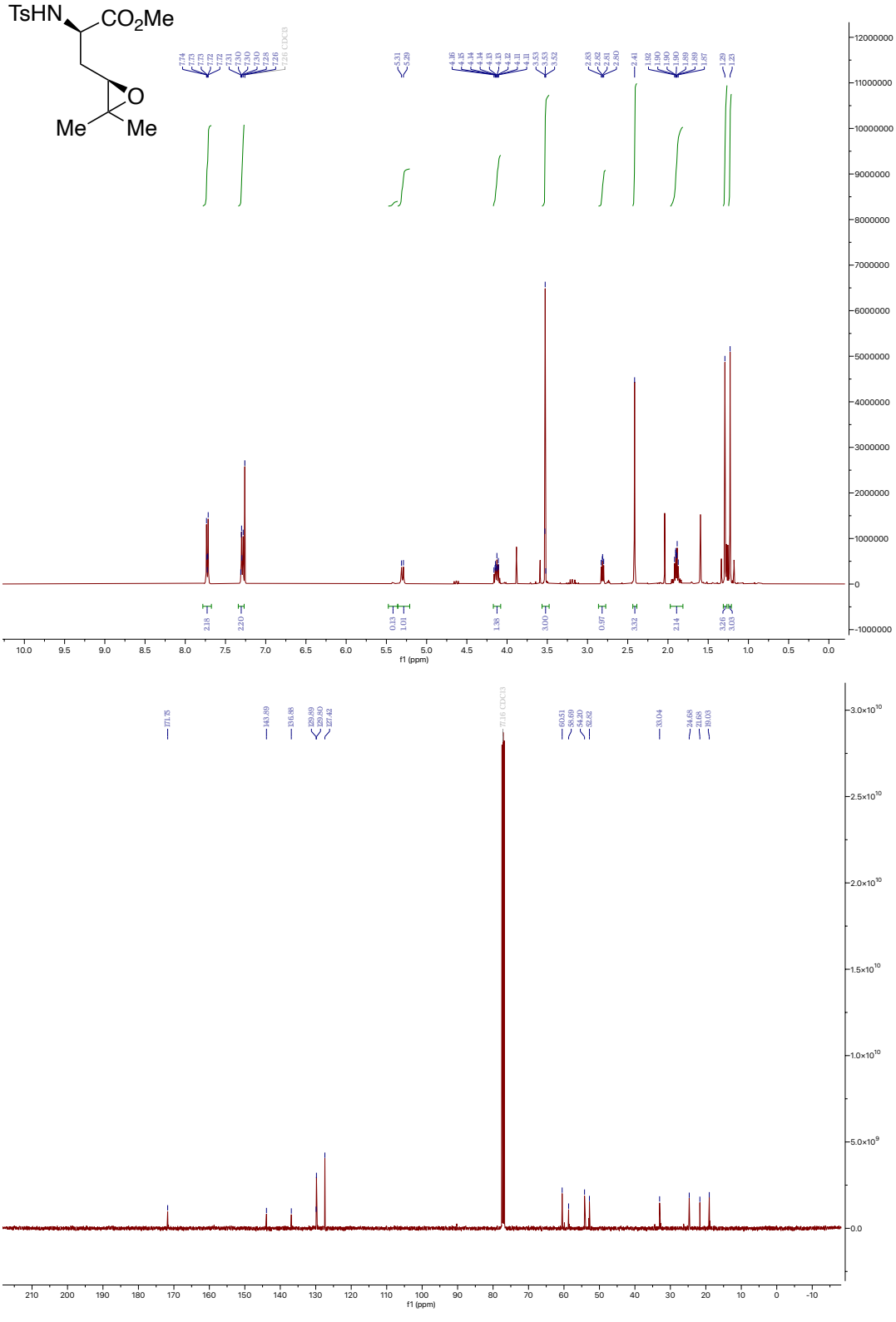


(2*R*,4*R*)-*N*-tosyl-2-amino-4,5-epoxy-5-ethylheptanoic acid ethyl ester (*cis*-**7c**). (88:12 *cis*:*trans*)

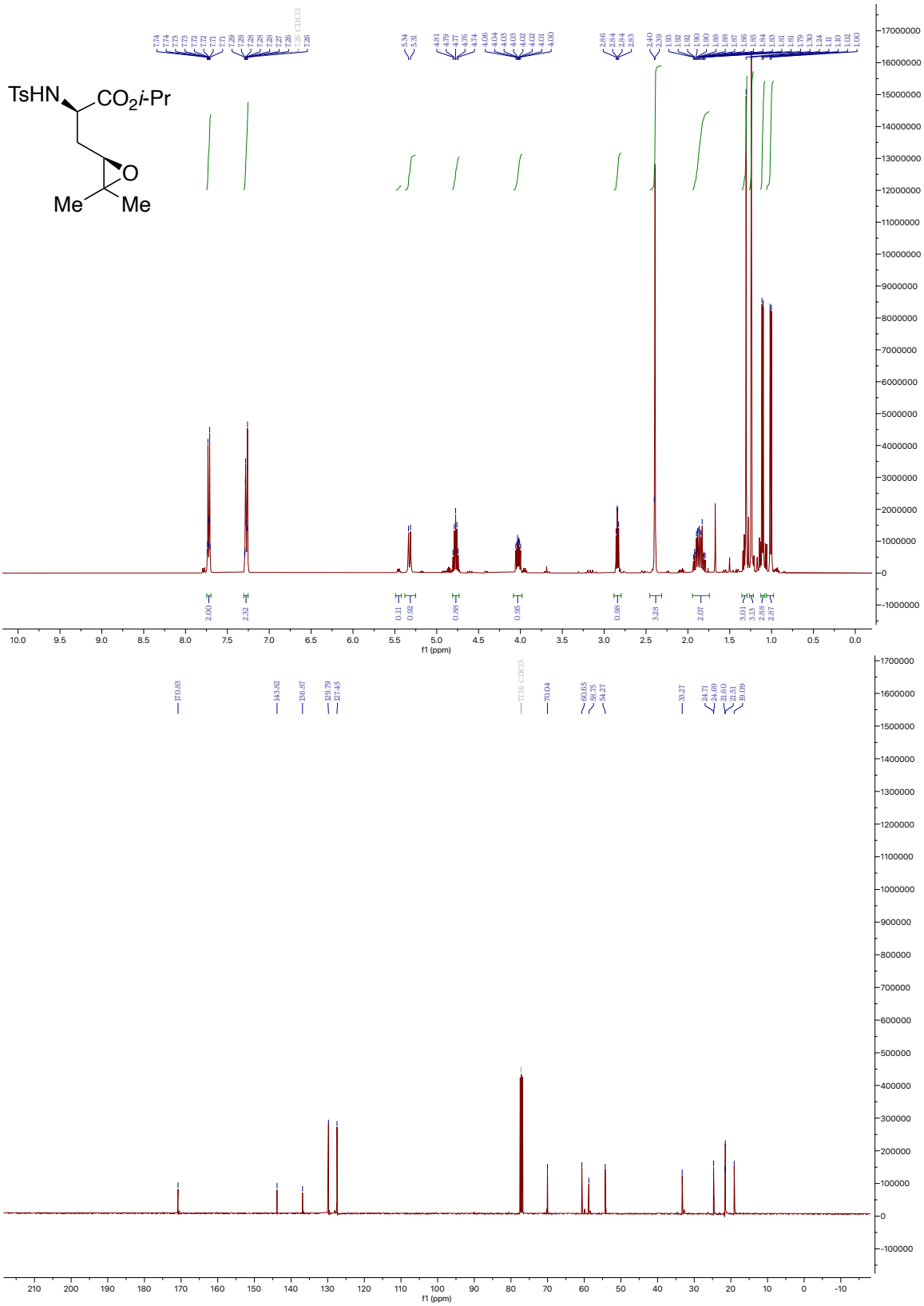




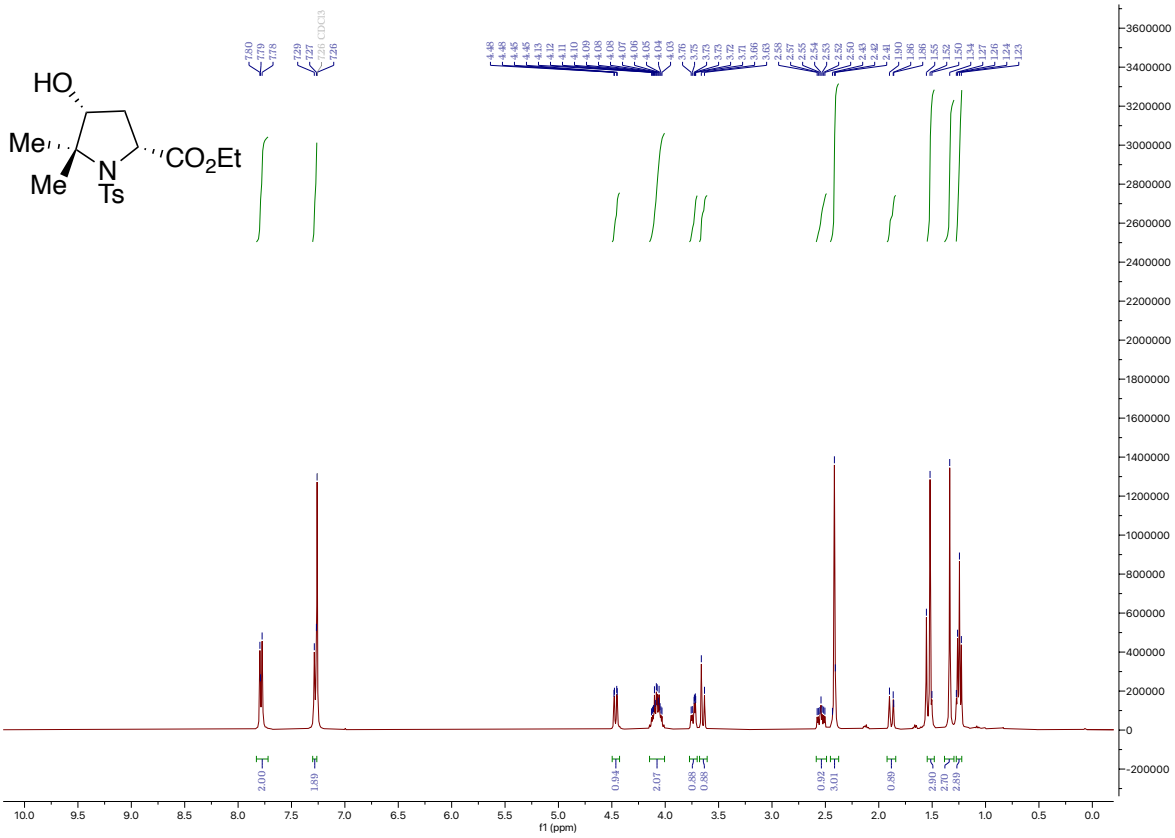
(2*R*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine methyl ester (*cis*-**7d**). (89:11 *cis*:*trans*)

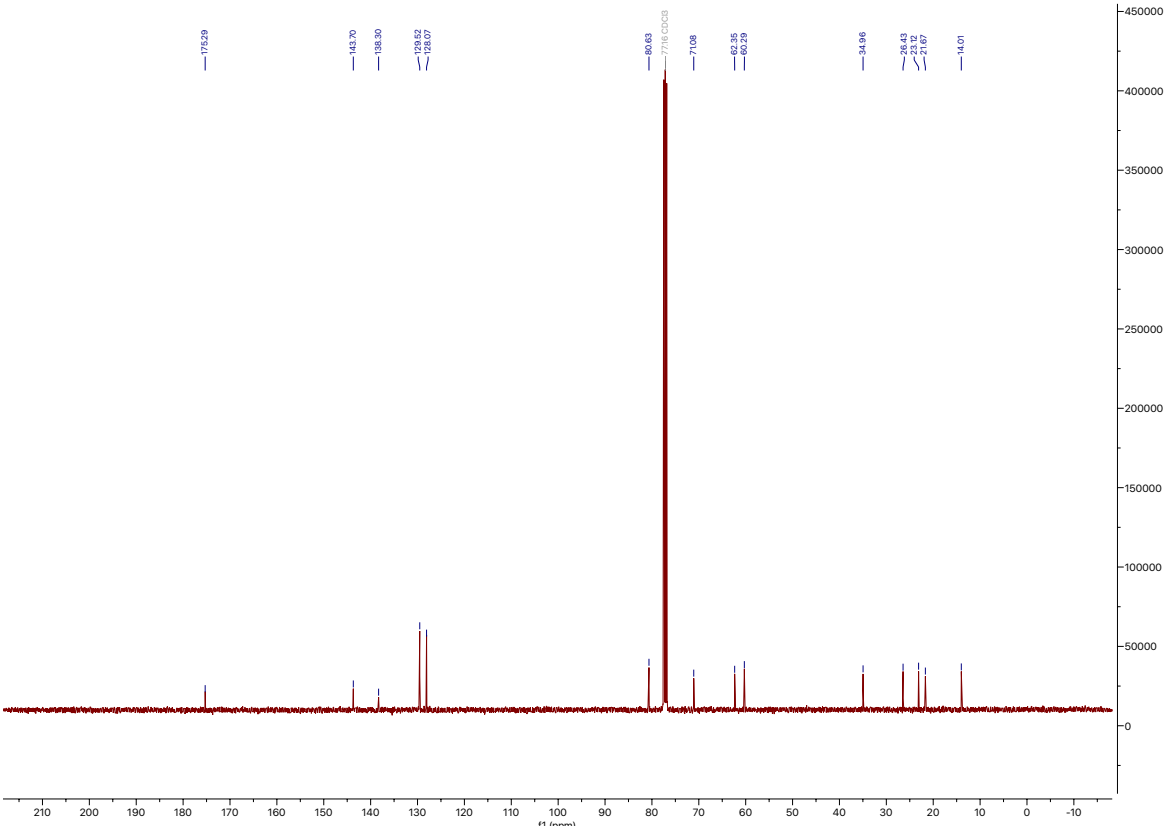


(2*R*,4*R*)-*N*-tosyl-4,5-epoxyhomoleucine isopropyl ester (*cis*-**7e**). (89:11 *cis*:*trans*)

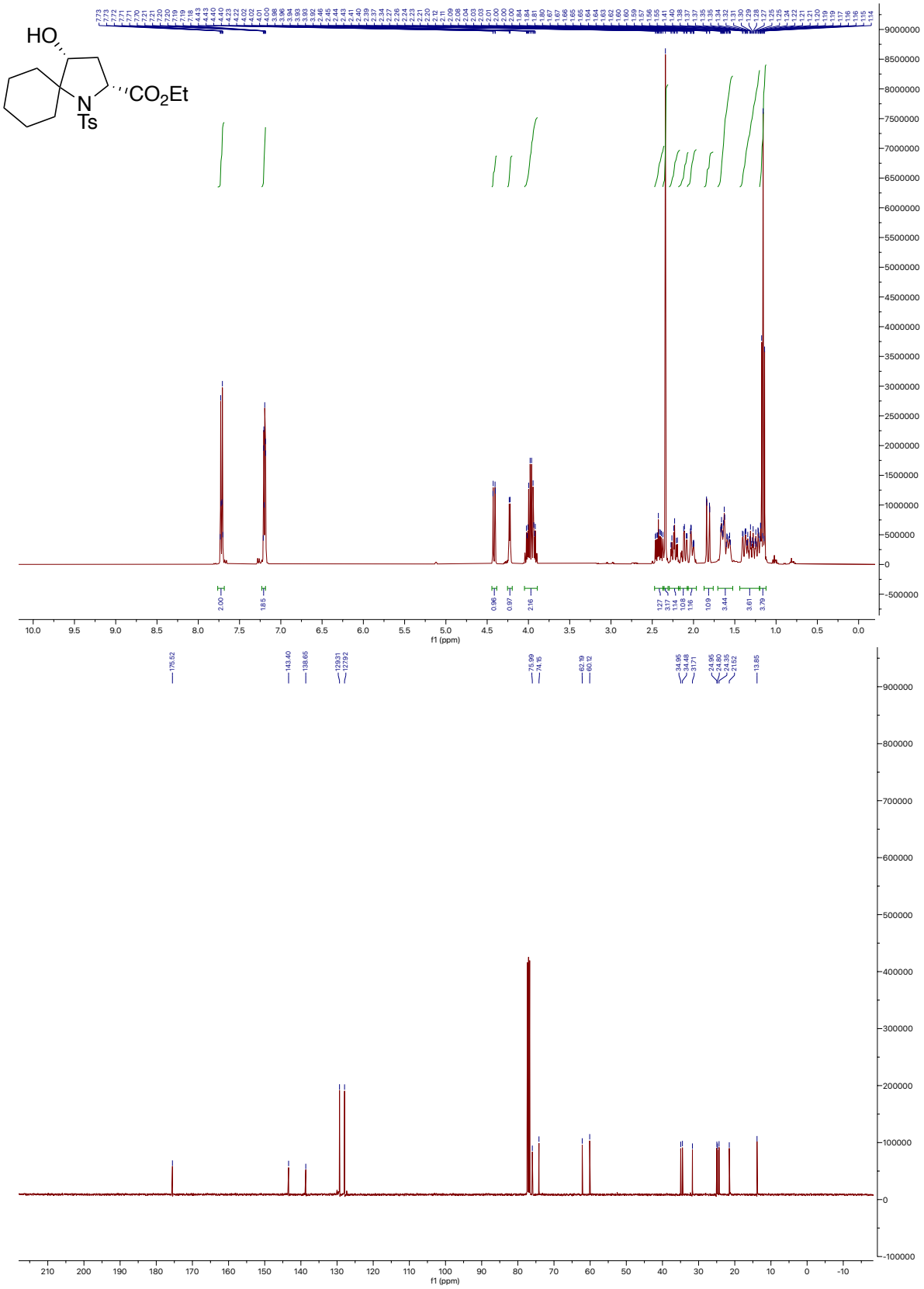


(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline (**5**).

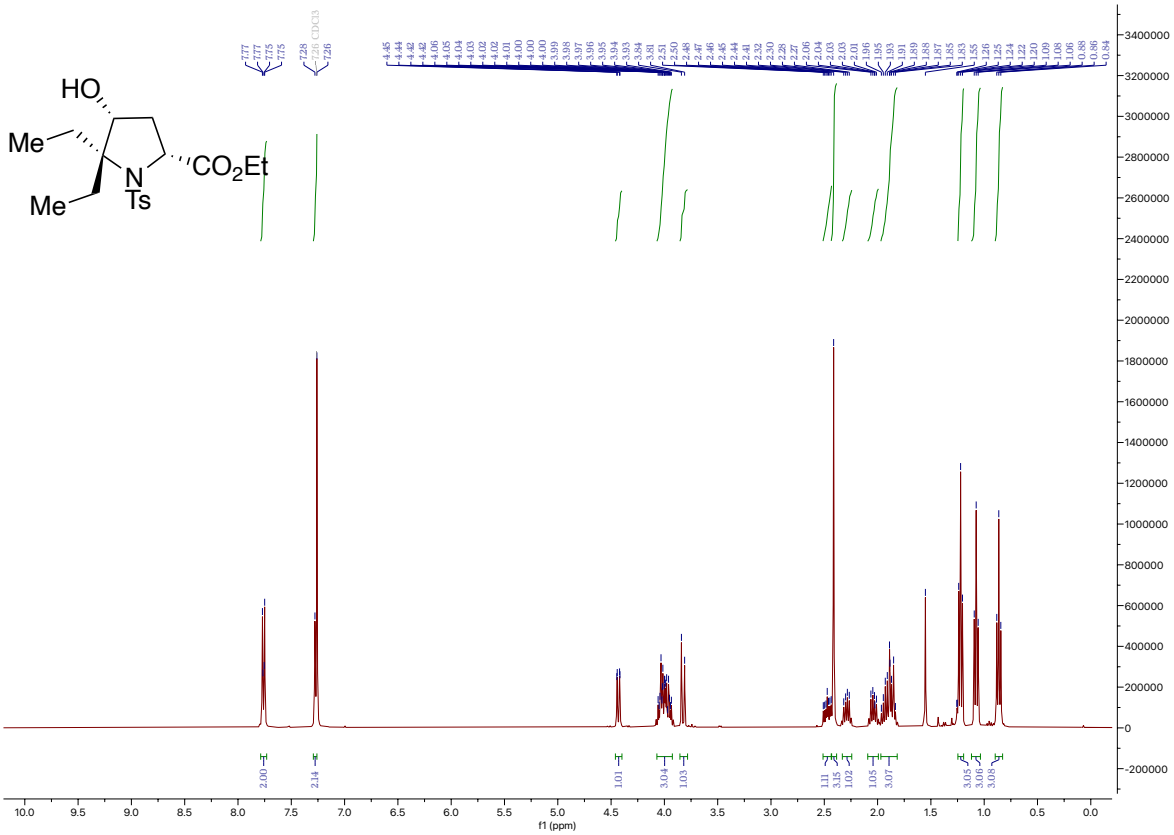


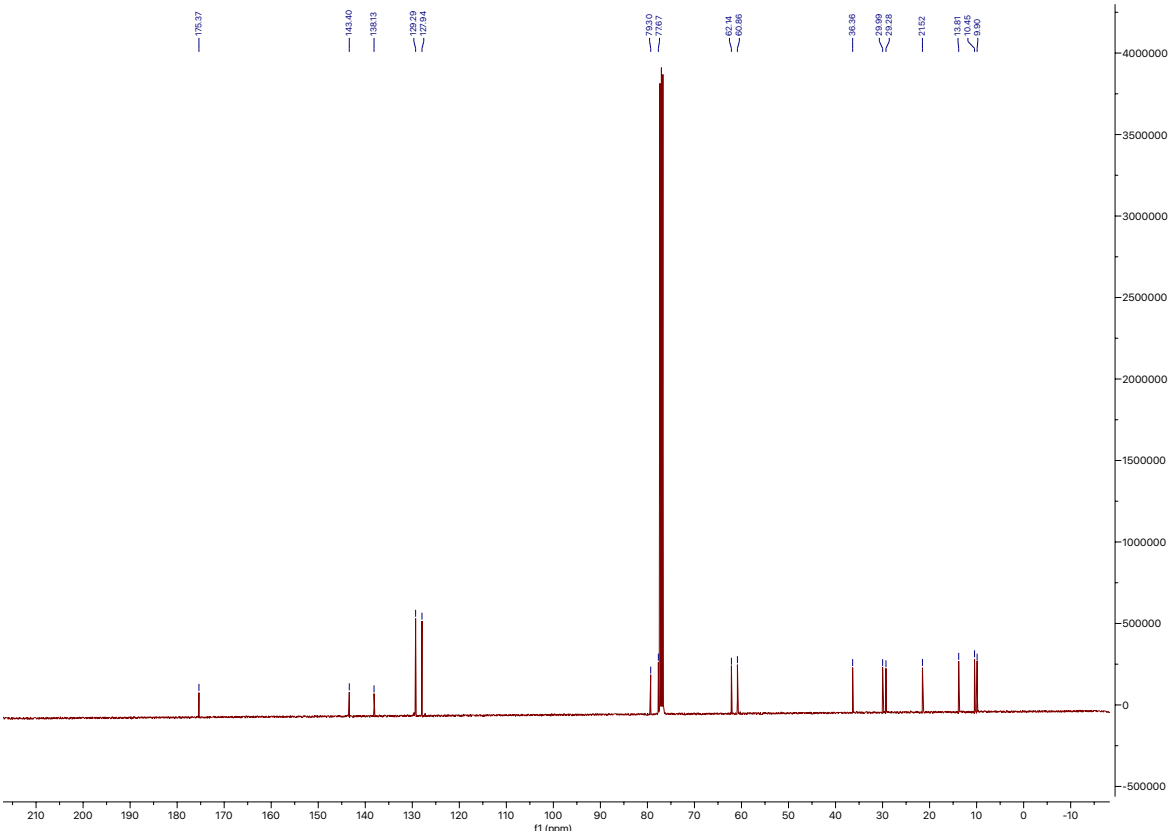


Ethyl (2*R*,4*R*)-*N*-tosyl-4-hydroxy-1-azaspiro[4.5]decane-2-carboxylate (**10**).

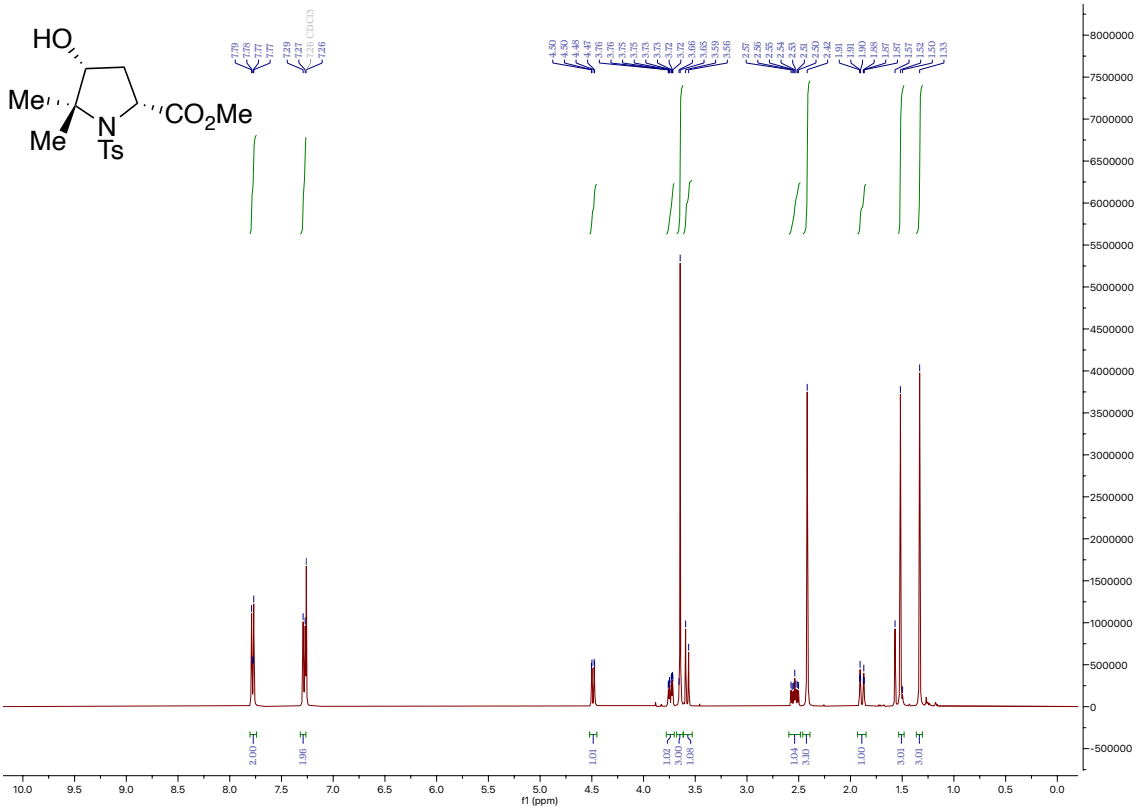


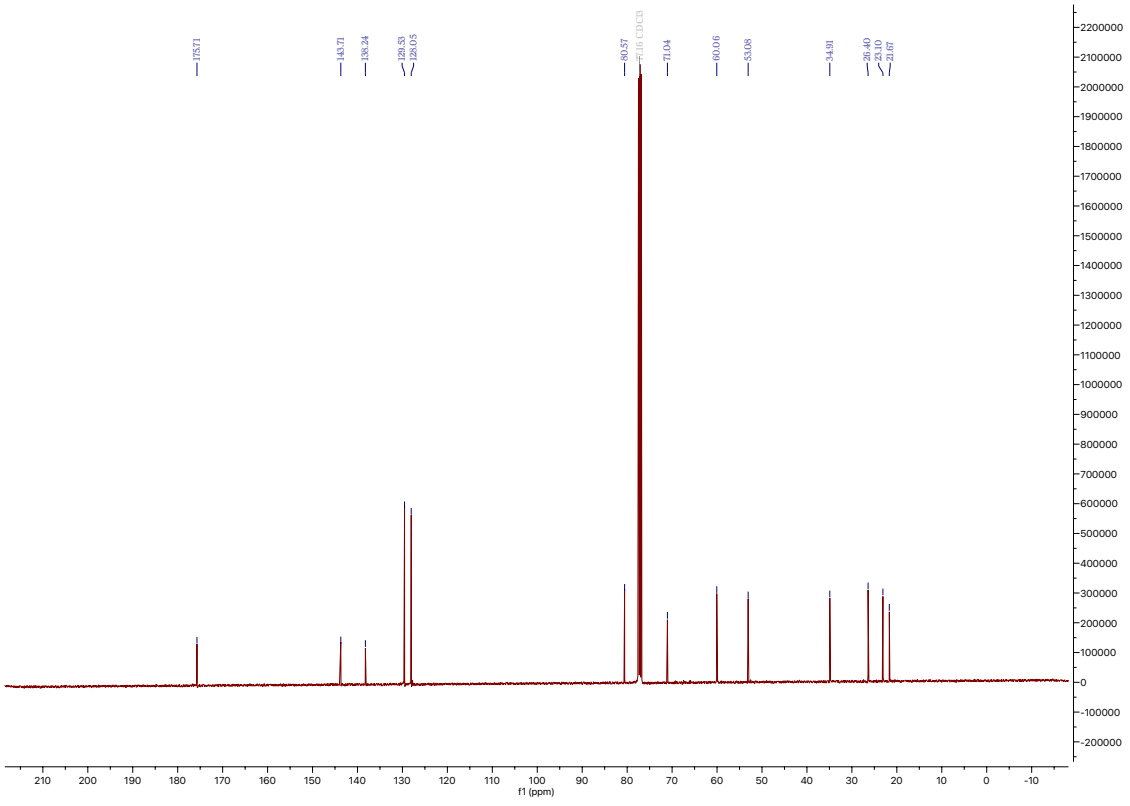
(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-diethylproline ethyl ester (**11**).



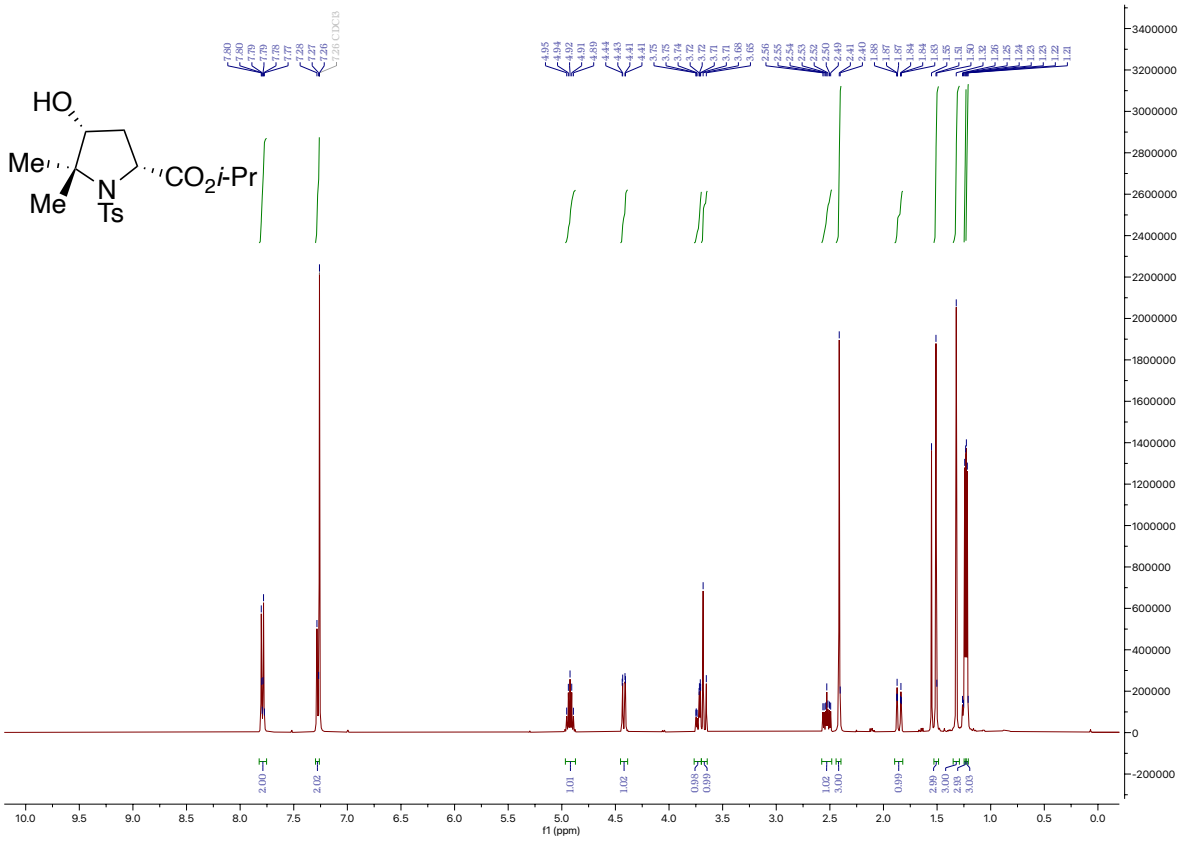


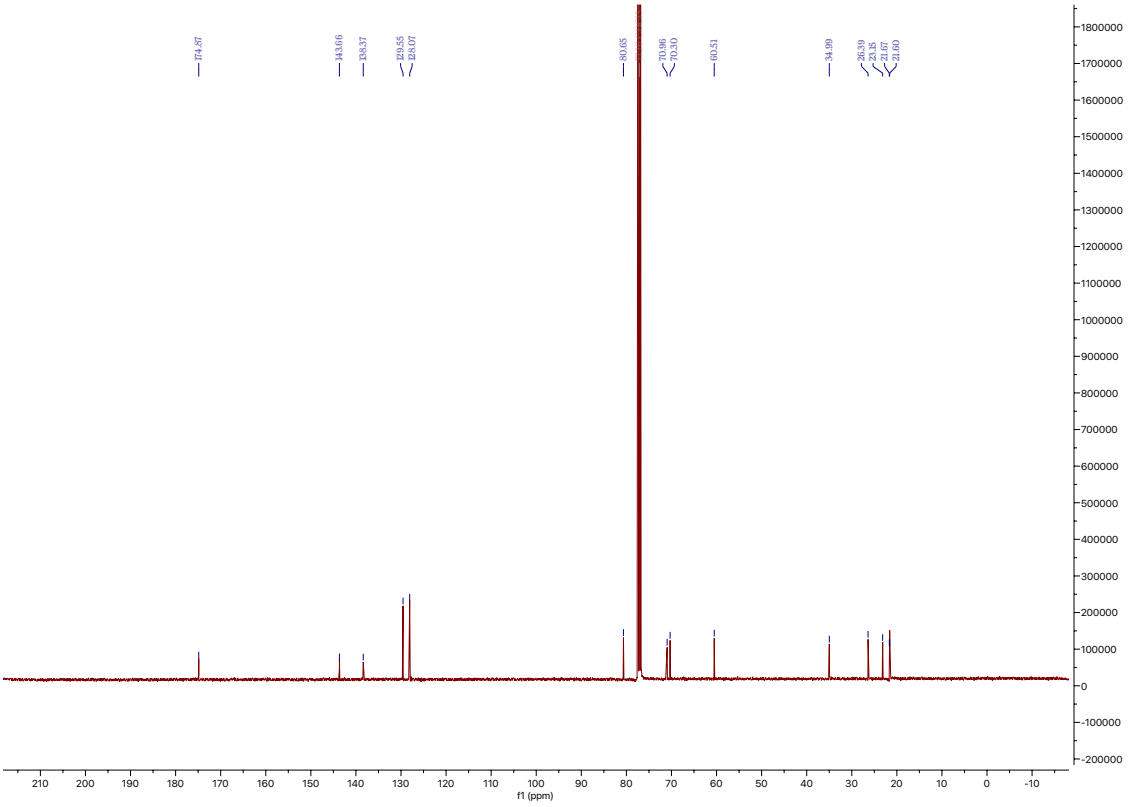
(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline methyl ester (**12**).



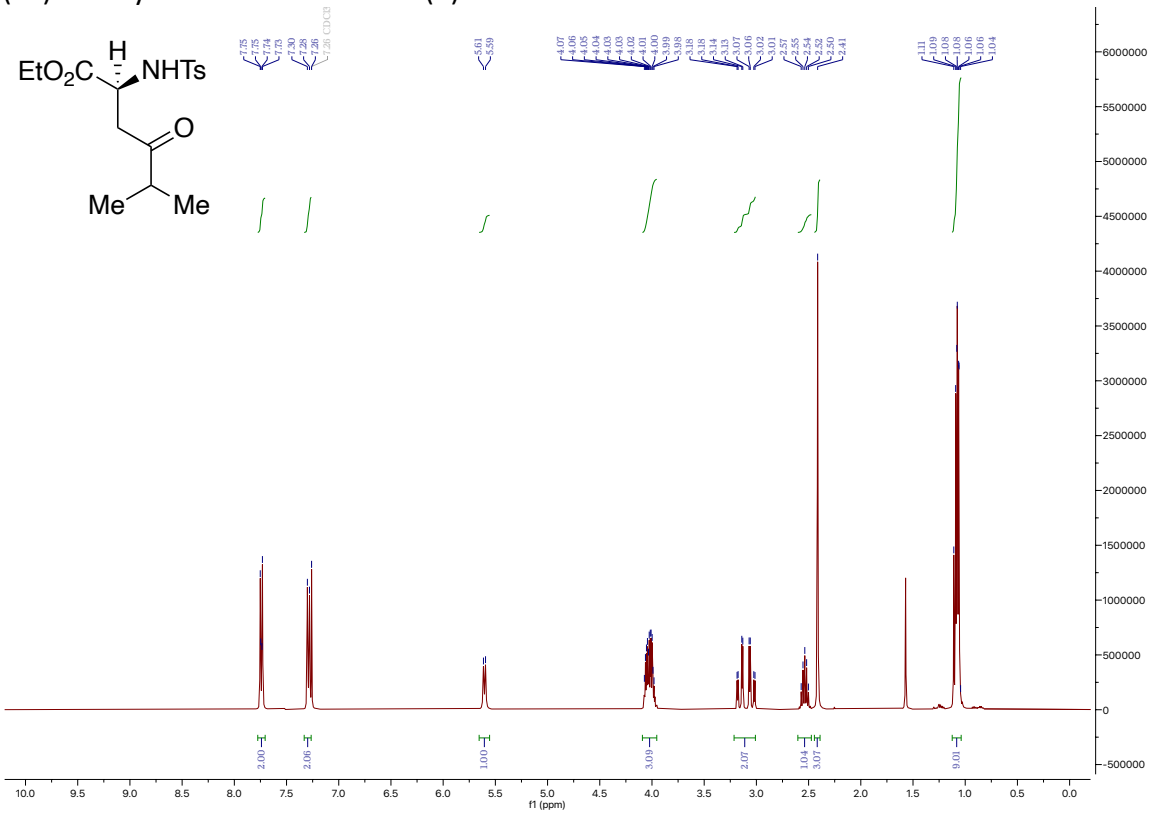


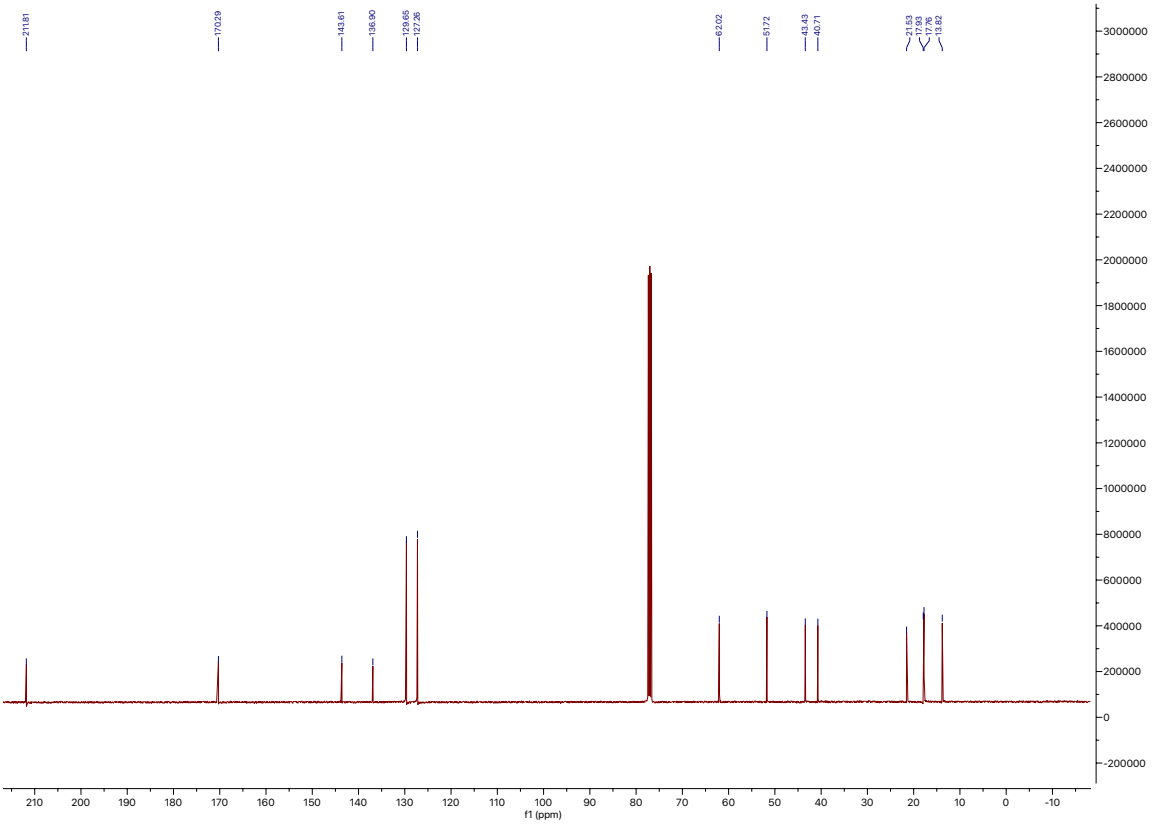
(2*R*,4*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline isopropyl ester (**13**).



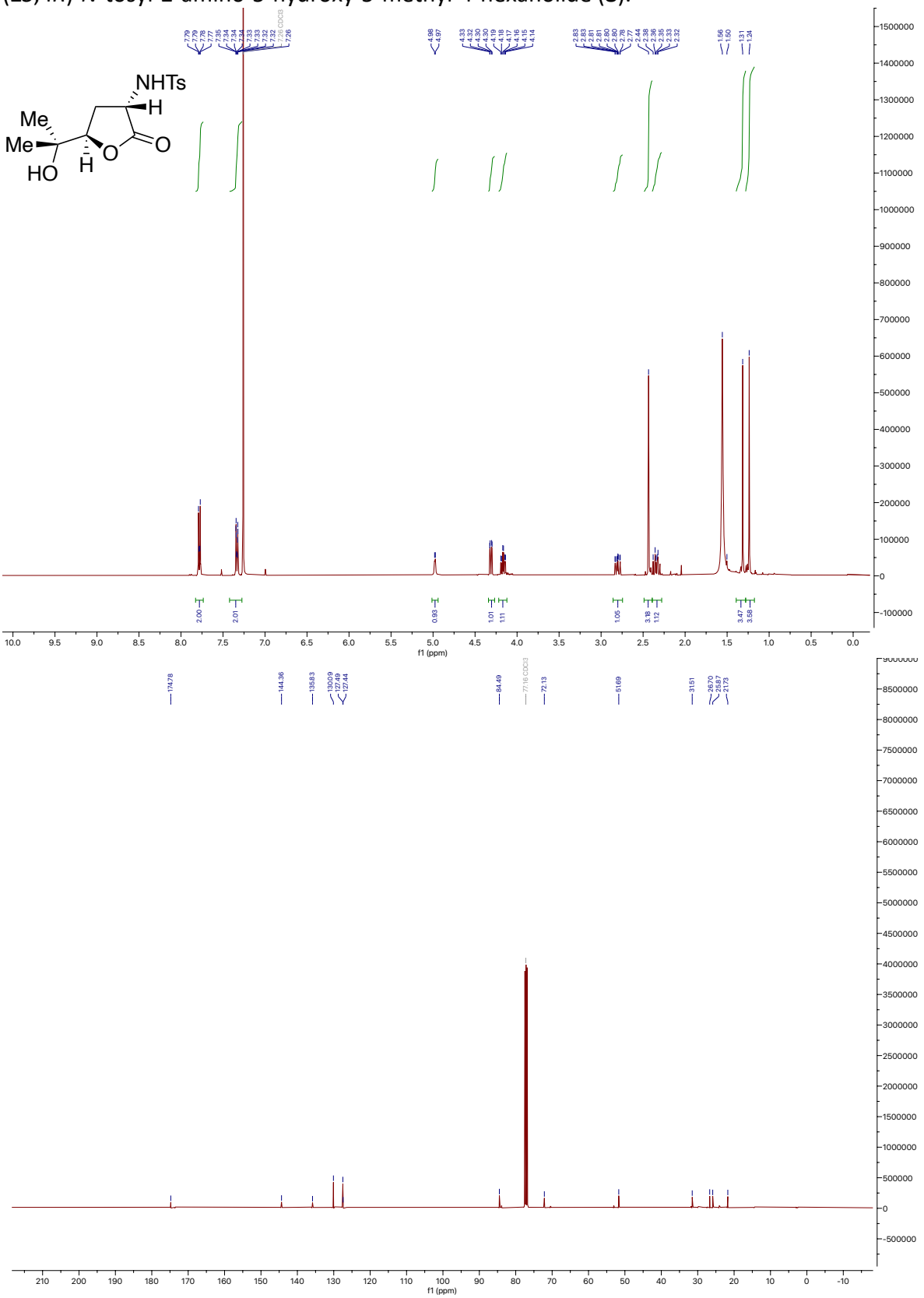


(2*S*)-*N*-tosyl-4-oxo-homoleucine (**9**).



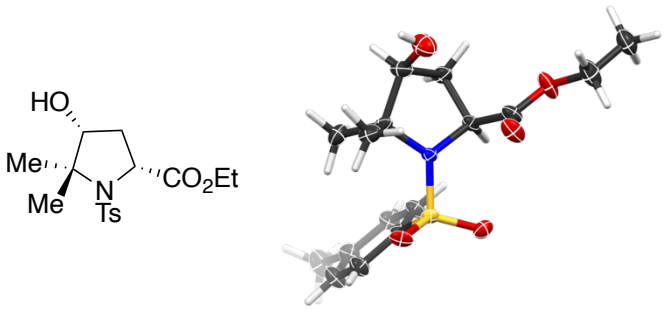


(2*S*,4*R*)-*N*-tosyl-2-amino-5-hydroxy-5-methyl-4-hexanolide (**8**).



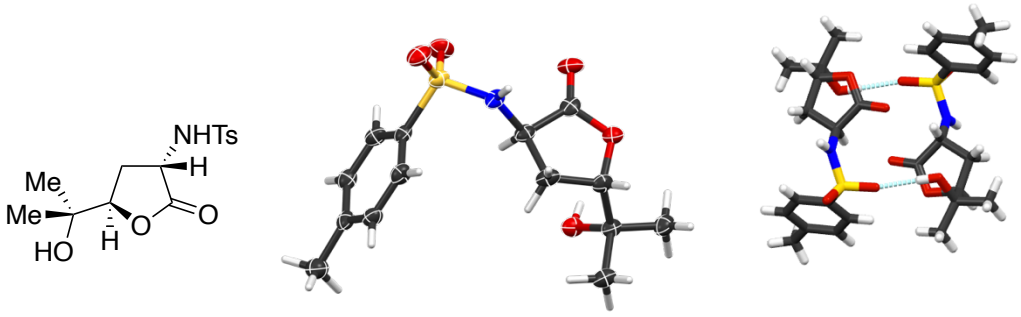
VI. X-ray crystallographic data

Crystallographic information for (2*R*)-*N*-tosyl-4-hydroxy-5,5-dimethylproline (**5**).



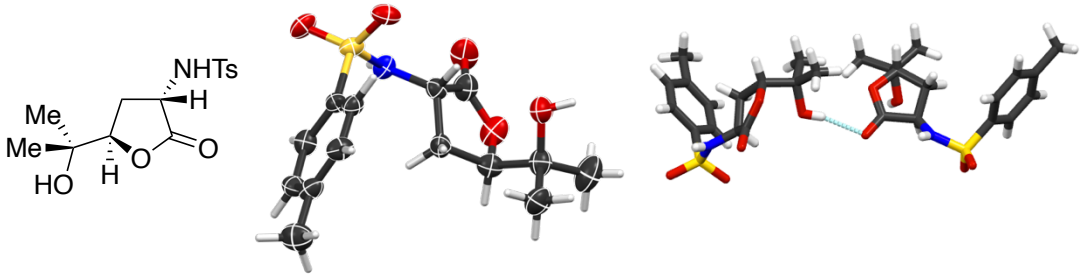
Empirical formula	$C_{16}H_{23}NO_5S$
Formula weight	341.41
Temperature/K	100.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.4892(3)
b/Å	12.0747(5)
c/Å	18.9252(10)
α/°	90
β/°	98.818(5)
γ/°	90
Volume/Å^3	1691.17(13)
Z	4
ρ_{calc}g/cm^3	1.341
μ/mm^{-1}	0.216
F(000)	728.0
Crystal size/mm^3	0.595 × 0.128 × 0.055
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.356 to 49.992
Index ranges	-8 ≤ h ≤ 8, -14 ≤ k ≤ 14, -22 ≤ l ≤ 22
Reflections collected	9970
Independent reflections	2963 [R_{int} = 0.0559, R_{sigma} = 0.0635]
Data/restraints/parameters	2963/0/213
Goodness-of-fit on F^2	1.102
Final R indexes [I>=2σ (I)]	R_1 = 0.0597, wR_2 = 0.1715
Final R indexes [all data]	R_1 = 0.0779, wR_2 = 0.1807
Largest diff. peak/hole / e Å^{-3}	1.43/-0.39
CCDC number	2385171

Crystallographic information for (2*R*,4*S*)-*N*-tosyl2-amino-5-hydroxy-5-methyl-4-hexanolide ($P2_1/c$ polymorph, **8a**).



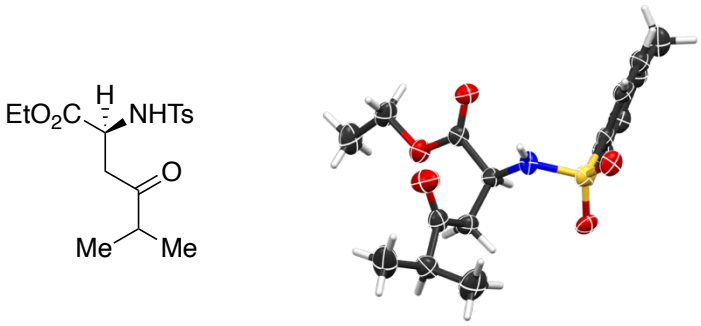
Empirical formula	$C_{14}H_{19}NO_5S$
Formula weight	313.36
Temperature/K	99.97(17)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.5944(8)
b/Å	11.4209(7)
c/Å	11.4442(6)
α/°	90
β/°	102.045(5)
γ/°	90
Volume/Å^3	1482.06(16)
Z	4
ρ_{calc}g/cm^3	1.404
μ/mm^{-1}	0.239
F(000)	664.0
Crystal size/mm^3	0.28 × 0.14 × 0.07
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.062 to 50
Index ranges	-13 ≤ h ≤ 13, -12 ≤ k ≤ 13, -13 ≤ l ≤ 13
Reflections collected	12516
Independent reflections	2607 [R_{int} = 0.0786, R_{sigma} = 0.0819]
Data/restraints/parameters	2607/0/194
Goodness-of-fit on F^2	0.985
Final R indexes [I>=2σ (I)]	R_1 = 0.0481, wR_2 = 0.1018
Final R indexes [all data]	R_1 = 0.0919, wR_2 = 0.1114
Largest diff. peak/hole / e Å^{-3}	0.22/-0.40
CCDC number	2385172

(2*R*,4*S*)-*N*-tosyl2-amino-5-hydroxy-5-methyl-4-hexanolide (*Pna*2_1polymorph, **8b**).



Empirical formula	$C_{14}H_{19}NO_5S$
Formula weight	313.36
Temperature/K	99.97(16)
Crystal system	orthorhombic
Space group	*Pna*2_1
a/Å	11.4970(17)
b/Å	20.881(3)
c/Å	6.4271(12)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1543.0(4)
Z	4
ρ_{calc}g/cm^3	1.349
μ/mm^{-1}	0.230
F(000)	664.0
Crystal size/mm^3	0.988 × 0.053 × 0.033
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.27 to 49.98
Index ranges	-13 ≤ h ≤ 13, -24 ≤ k ≤ 24, -7 ≤ l ≤ 7
Reflections collected	10443
Independent reflections	2707 [R_{int} = 0.0928, R_{sigma} = 0.1095]
Data/restraints/parameters	2707/1/194
Goodness-of-fit on F^2	0.983
Final R indexes [I>=2σ (I)]	R_1 = 0.0577, wR_2 = 0.1030
Final R indexes [all data]	R_1 = 0.1056, wR_2 = 0.1127
Largest diff. peak/hole / e Å^{-3}	0.25/-0.32
Flack parameter	0.06(13)
CCDC number	2385173

Crystallographic information for (2*R*)-*N*-tosyl-4-oxo-homoleucine (**9**).



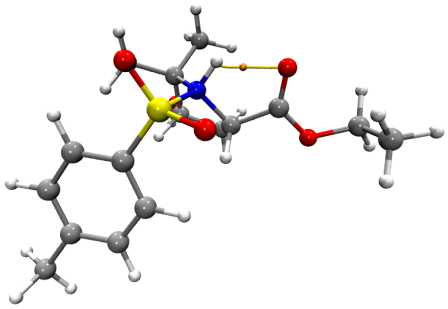
Empirical formula	$C_{16}H_{23}NO_5S$
Formula weight	341.41
Temperature/K	100.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	20.066(2)
b/Å	5.1482(5)
c/Å	18.0857(18)
α/°	90
β/°	110.174(12)
γ/°	90
Volume/Å^3	1753.7(3)
Z	4
ρ_{calc}g/cm^3	1.293
μ/mm^{-1}	0.208
F(000)	728.0
Crystal size/mm^3	0.614 × 0.05 × 0.033
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.532 to 49.99
Index ranges	-21 ≤ h ≤ 23, -6 ≤ k ≤ 6, -21 ≤ l ≤ 21
Reflections collected	11944
Independent reflections	3064 [R_{int} = 0.1116, R_{sigma} = 0.1082]
Data/restraints/parameters	3064/0/212
Goodness-of-fit on F^2	0.965
Final R indexes [I>=2σ (I)]	R_1 = 0.0654, wR_2 = 0.1521
Final R indexes [all data]	R_1 = 0.1125, wR_2 = 0.1691
Largest diff. peak/hole / e Å^{-3}	0.49/-0.54
CCDC number	2386128

VII. Computational data

All Density Functional Theory (DFT) calculations were performed at B3LYP/6-311+g(d,p) using Grimme's D3 dispersion correction with Becke-Johnson damping (DFT-D3(BJ)) employing an implicit solvation model (iefpcm) for benzene using the Gaussian 16 suite of quantum chemistry program. Quantum Theory of Atoms in Molecules (QTAIM) analyses to get an insight about the intramolecular H-bonding interactions were performed using Multiwfn3.7 programs.[4,5]

	Free Energy (in Hartrees)	
intermediate	***cis***	***trans***
protonated proline **12**	-1453.056482	-1453.046334
proline **5**	-1452.673372	-1452.67546

***cis*-18**



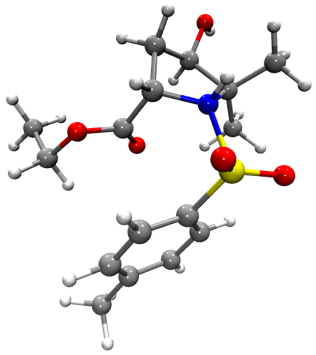
Atom	x	y	z
S1	-0.43260800	-0.43348000	1.64813500
O2	3.26747100	-1.10260300	-1.17180600
O3	0.41624800	-1.60922100	1.68504500
O4	-0.73091800	0.37288600	2.81135800
O5	3.24974200	0.05273000	0.77445300
C6	-1.86088800	-0.72830600	0.66613000

[4] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.;. Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16, Revision C.01, Gaussian, Inc., Wallingford CT, 2016.

[5] (a) Lu, T.; Chen, F.; *J. Comput. Chem.* **2012**, *33*, 580-592, DOI: 10.1002/jcc.22885; (b) Emamian, S.; Lu, T.; Kruse, H.; Emamian, H. *J. Comput. Chem.* **2019**, *40*, 2868-2881, DOI: 10.1002/jcc.26068

Atom	x	y	z
C7	2.72283400	-0.35561300	-0.23685400
C8	-0.01286100	1.86701400	-1.35887000
H9	-0.98281100	1.35874400	-1.43526500
C10	1.10466100	0.91514300	-1.79937700
H11	2.01155700	1.48461500	-2.00363800
H12	0.85171000	0.34328800	-2.69038300
C13	1.28006000	-0.01190800	-0.58697500
H14	0.73364800	-0.93986100	-0.72729700
C15	0.27266800	2.13977400	0.13413600
C16	-1.80827600	-1.70613000	-0.33218900
H17	-0.91489700	-2.29519500	-0.48834500
C18	-4.13702700	-1.23949100	-0.84372000
C19	-2.94765400	-1.94127700	-1.08648800
H20	-2.92189900	-2.69667800	-1.86230600
C21	-3.03578000	-0.02805300	0.95208200
H22	-3.06820400	0.68339200	1.76541700
C23	-0.92850900	2.71200900	0.86728000
H24	-1.09489800	3.71237900	0.46586700
H25	-0.75342000	2.79376300	1.93869900
H26	-1.83277800	2.13620900	0.68937900
C27	4.66609400	-1.52524900	-0.98079800
H28	5.21334600	-0.68522200	-0.55550400
H29	5.01078000	-1.71479900	-1.99481400
C30	-5.37538600	-1.53255700	-1.64045500
H31	-5.13146300	-1.93682200	-2.62348800
H32	-5.98737400	-0.63813400	-1.76708500
H33	-5.98613200	-2.27629700	-1.11812600
H34	-4.16306800	-0.29268000	0.19099900
H35	-5.08251800	0.23689700	0.40928500
C36	4.73404100	-2.75976100	-0.10757100
H37	5.77412100	-3.08655100	-0.03487900
H38	4.14984400	-3.57493800	-0.53870900
H39	4.37211700	-2.55108200	0.90004900
C40	1.49265200	3.04380200	0.34189700
H41	2.40144300	2.64592600	-0.10834800
H42	1.66995300	3.18801500	1.40966000
H43	1.28796600	4.01278200	-0.11078900
O44	-0.04167200	3.09901200	-2.04136800
H45	-0.47579300	2.98965200	-2.89364300
H46	1.48774900	0.82318700	1.26442800
N47	0.69733600	0.72566800	0.60040800

***trans*-18**

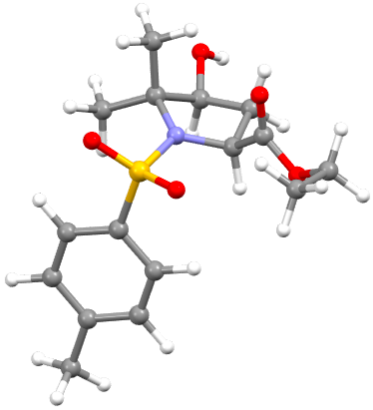


Atom	x	y	z
S1	-0.40134600	-1.92783300	-0.90789800
O2	0.82217300	2.14700800	-1.11835600
O3	-1.01503200	-2.99488200	-0.14698800
O4	-0.41192800	-1.87723600	-2.35863900
O5	0.28673000	1.27504300	0.89465000
C6	1.15838600	-1.46247300	-0.27254200
C7	0.07567500	1.43723200	-0.28260100
C8	-2.81071400	1.21990800	0.73564800
H9	-2.19711400	1.65160200	1.52791900
C10	-2.37996300	1.77982600	-0.62227100
H11	-2.15049900	2.84388000	-0.58397800
H12	-3.18394200	1.63321500	-1.34738600
C13	-1.16432800	0.93307800	-1.01734400
H14	-0.97450800	0.91029800	-2.08713500
C15	-2.51801600	-0.33000300	0.69299100
C16	1.47287000	-1.76298000	1.05443200
H17	0.76405600	-2.27431700	1.68939500
C18	3.64842500	-0.74242600	0.70453100
C19	2.71978300	-1.39490300	1.52967600
H20	2.98113800	-1.61771500	2.55685600
C21	2.05931000	-0.82491300	-1.13053800
H22	1.79668200	-0.62377500	-2.16014900
C23	-3.76360900	-1.16552800	0.41827800
H24	-4.43360900	-1.10425500	1.27472100
H25	-3.48624300	-2.21126400	0.27590500
H26	-4.31852300	-0.80747500	-0.45198400
C27	1.96938700	2.86346900	-0.55079300
H28	2.65578900	2.95191600	-1.39058300
H29	2.40989200	2.23453700	0.22097100
C30	5.00544500	-0.37121100	1.22813500
H31	4.98094300	-0.18893700	2.30326500
H32	5.39741400	0.51494200	0.72657500
H33	5.71070000	-1.18938400	1.04796800
C34	3.30039800	-0.47124700	-0.62643900
H35	4.01294100	0.02169900	-1.27647500
C36	1.54264700	4.21368100	-0.01376700
H37	2.42248100	4.74724500	0.35377500

H38	0.84357300	4.10298600	0.81713100

Atom	x	y	z
H39	1.07981700	4.81799000	-0.79608400
C40	-1.81103200	-0.80132200	1.95704000
H41	-0.86067200	-0.29287500	2.09868000
H42	-1.67309800	-1.88145100	1.96085400
H43	-2.45943300	-0.55177400	2.80040700
O44	-4.17231500	1.52642900	0.93889900
H45	-4.35199600	1.61273600	1.88068500
H46	-2.28088000	-0.71066700	-1.32347200
N47	-1.62405300	-0.43940600	-0.58494700

***cis*-5**

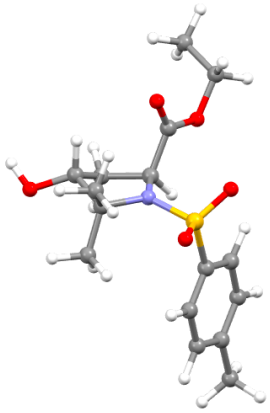


Atom	x	y	z
S1	-0.22567900	-0.25517900	1.25805700
O2	2.55045200	-1.90243900	-1.09341400
O3	0.46780600	-1.54513900	1.22453300
O4	-0.42510700	0.47122600	2.51031700
O5	3.33419900	-0.40850600	0.41075000
N6	0.61364900	0.72509500	0.22438200
C7	-1.83983400	-0.53023000	0.52811800
C8	2.52186900	-0.74861100	-0.41302500
C9	0.90733300	2.45731000	-1.29200400
H10	-0.02003800	2.32003100	-1.86197300
C11	1.89807800	1.35271500	-1.65299000
H12	2.88716300	1.62639100	-1.28334600
H13	1.96074400	1.16307300	-2.72474400
C14	1.36413600	0.12670800	-0.89078300
H15	0.70807100	-0.47247900	-1.52550000
C16	0.57543500	2.22095200	0.20097700
C17	-1.95878900	-1.43731200	-0.52430300
H18	-1.09947700	-2.00790600	-0.85163600
C19	-4.32883400	-0.92167700	-0.67670000
C20	-3.20000200	-1.62006300	-1.12262700
H21	-3.29622800	-2.32474500	-1.94128700
C22	-2.94618300	0.16976000	0.99808600

H23	-2.83819800	0.85264800	1.82966800
C24	-0.79213300	2.81914800	0.52508400

Atom	x	y	z
H25	-0.74859300	3.88917200	0.31165600
H26	-1.04778400	2.68750100	1.57521600
H27	-1.57612000	2.37732200	-0.09246200
C28	3.58547500	-2.85623100	-0.72450400
H29	4.50885300	-2.30908100	-0.53340900
H30	3.70597900	-3.47390800	-1.61385200
C31	-5.67661800	-1.15734000	-1.30653900
H32	-5.58493800	-1.36879000	-2.37391000
H33	-6.33104600	-0.29299300	-1.18029900
H34	-6.17168800	-2.01705800	-0.84307700
C35	-4.18240000	-0.03173600	0.39260800
H36	-5.04744900	0.50905600	0.76007800
C37	3.15819400	-3.67381700	0.48000500
H38	3.93143500	-4.41204100	0.71006200
H39	2.22356200	-4.20088900	0.27854900
H40	3.01434500	-3.03484400	1.35147900
C41	1.64776400	2.77658200	1.14214000
H42	2.62674000	2.35277700	0.91751900
H43	1.39047400	2.50519700	2.16687700
H44	1.70166900	3.86288400	1.05852900
O45	1.40073900	3.77472200	-1.47694200
H46	1.39218900	3.98000000	-2.41692400

***trans*-5**



Atom	x	y	z
S1	-0.52095200	0.22867600	1.51188000
O2	2.28758300	-2.22384100	-0.23667500
O3	0.09392500	-0.96918900	2.08777400
O4	-0.89588800	1.36866500	2.34590300
O5	3.20253300	-0.34307300	0.61867900
N6	0.53913400	0.77710400	0.36105600
C7	-1.98813500	-0.33183000	0.64465500
C8	2.31341600	-0.91084600	0.03203800

C9	1.77996100	1.99091300	-1.19018500
H10	2.75352000	1.96175600	-0.69507800
C11	1.47607700	0.62113200	-1.79376200
Atom	**x**	**y**	**z**
H12	2.31858700	0.20016400	-2.34379700
H13	0.62406900	0.70039400	-2.47143600
C14	1.09040900	-0.21908500	-0.56658200
H15	0.35406000	-0.97898300	-0.82724800
C16	0.70096700	2.19551600	-0.09021100
C17	-2.04030000	-1.64031300	0.16771300
H18	-1.22960100	-2.32570800	0.37670900
C19	-4.23119400	-1.19063800	-0.78271700
C20	-3.15848800	-2.05671700	-0.54841500
H21	-3.20068800	-3.07390900	-0.92163500
C22	-3.04812500	0.54735600	0.43655100
H23	-3.00760400	1.54968200	0.83995900
C24	-0.59271700	2.77448600	-0.66884900
H25	-0.38786600	3.74415700	-1.12240100
H26	-1.32223100	2.91436700	0.12861100
H27	-1.02563000	2.12171300	-1.42903400
C28	3.41530700	-3.01717600	0.22740400
H29	3.00713500	-4.02193200	0.32761600
H30	3.71433600	-2.64774300	1.20794600
C31	-5.45444100	-1.65879600	-1.52632200
H32	-5.89335700	-0.85165900	-2.11647300
H33	-6.22018300	-2.00604100	-0.82486900
H34	-5.21966700	-2.48840000	-2.19555800
C35	-4.15988400	0.11224100	-0.27405400
H36	-4.98859000	0.79357600	-0.43200500
C37	4.56196700	-2.97258600	-0.76520700
H38	5.36685200	-3.62825900	-0.42239900
H39	4.96188200	-1.96122500	-0.85419700
H40	4.23707100	-3.31637700	-1.74998900
C41	1.25212400	3.08707600	1.02166800
H42	2.12127400	2.61673500	1.48489900
H43	0.50289100	3.26821300	1.79015700
H44	1.55355600	4.04433600	0.58780600
O45	1.73860300	3.05544400	-2.13125200
H46	2.62577700	3.19814100	-2.47282400