Supporting Information

Organocatalytic Asymmetric Epoxidation and Tandem Epoxidation/Passerini Reaction under Eco-friendly Reaction Conditions

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Contents

1. Materials and Methods.

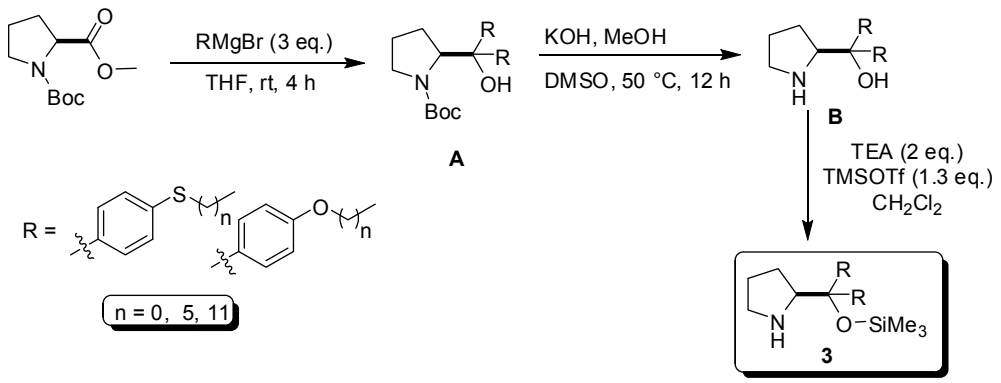
^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 (400 and 100 MHz respectively). All NMR spectra were obtained with $CDCl_3$. HPLC chromatograms were obtained on a Shimadzu apparatus, LC-10AT Pump, SPD-10A UV-Vis Detector, SCL-10A System Controller, using a Chiralpak AD-H (4,6 mmØ x 250 mmL, particle size 5 μm) or a Chiralcel OD-H or OD (4,6 mmØ x 250 mmL, particle size 5 μm). Optical rotations were measured with a Perkin-Elmer Polarimeter, Mod. 241, at 589 nm, 30 °C. Melting point was obtained on a MQAPF-301 apparatus. High-resolution mass spectra were recorded on a Bruker - AutoFlex Speed, MALDI-TOF/TOF MS (λ = 355 nm, f = 500 Hz, matrix HCCA, calibration standard TPP, PEG 600). Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. The following solvents were dried and purified by distillation from the reagents indicated: tetrahydrofuran from sodium with a benzophenone as indicator; dichloromethane from calcium hydride. All other solvents were ACS grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques. Non-commercial aldehydes were prepared from literature procedures.[1]

2. Synthesis of the organocatalysts

Bromides derivatives from 4-bromophenol and 4-bromothiophenol were prepared from described procedures.[2] The proline-ester derivative was also synthesized based on literature procedures.[3]

[1] (a) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.* 2009, **11**, 1627. (b) J. Kang, G. J. Lim, S. K. Yoon and M. Y. Kim, *J. Org. Chem.* 1996, **60**, 564. (c) M. Avi, R. Gaisberger, S. Feichtenhofer and H. Griengl, *Tetrahedron* 2009, **65**, 5418.
[2] (a) S. N. Crane, *et al. J. Med. Chem.* 2006, **49**, 1066. (b) U. B. Vasconcelos, A. Schrader, G. D. Vilela, A. C. A. Borges and A. A. Merlo, *Tetrahedron*. 2008, **64**, 4619.
[3] X. Ding, M. D. Vera, B. Liang, Y. Zhao, M. S. Leonard and M. M. Joullie, *Bioorg. Med. Chem. Lett.* 2001, **11**, 231.

2.1 General procedure to synthesis of organocatalysts 3a-d.

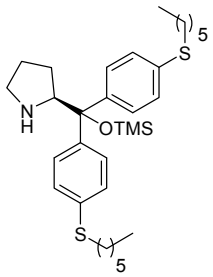


To a round bottom flask under a nitrogen atmosphere were added magnesium strips (20 mmol, 0.48 g), a small crystal of iodine, and dry THF (30 mL). The reaction mixture was heated to reflux. A solution of the corresponding bromide (20 mmol) in dry THF (6 mL) was added dropwise over 30 min. After addition, the reaction mixture was continued to stirring at reflux for aditional 2 h and cooled to rt. Then a solution of (*S*)-1-tert-butyl 2-methyl pyrrolidine-1,2-dicarboxylate (6,7 mmol; 1,52 g) in dry THF (6 mL) was added dropwise to the Grignard reagent at rt over 30 min. The resulting mixture was further stirred for 4 h and then quenched with saturated aqueous solution of NH_4Cl (30 mL). The product was extracted with ethyl acetate (3 x 20 mL) and the combined organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (hexane: ethyl acetate = 4: 1) to give the product **A**.

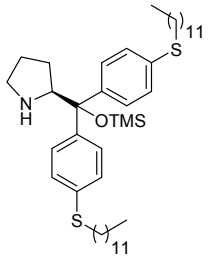
Compound **A** (4.35 mmol) and KOH (53 mmol, 2.98 g) were dissolved in methanol (6 mL) and DMSO (27 mL). The reaction mixture was stirred at 50 °C for 12 h and was then quenched with water (50 mL). The product was extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (ethyl acetate: methanol = 9: 1) to give the product **B**.

To a round bottom flask under a nitrogen atmosphere was added the pure aminoalcohol **B** (2.6 mmol) in dry CH_2Cl_2 (18 mL) and triethylamine (3.4 mmol, 0.47 mL), the reaction mixture was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate, TMSOTf, (3.4 mmol, 0.61 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with water

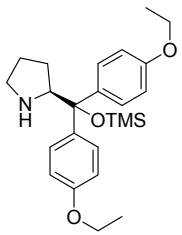
(20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (0.1% triethylamine in hexane: ethyl acetate = 4:1) to give the organocatalysts.



(*S*)-α,α-Bis(4-hexylphenylsulfide)-2-pyrrolidinemethanol trimethylsilylether (3a): Global yield: 80%, light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 (d, *J* = 8 Hz, 2H), 7.26-7.19 (m, 6H), 3.99-3.96 (m, 1H), 3.72 (q, *J* = 7 Hz, 1H), 2.92-2.88 (m, 4H), 2.85-2.80 (m, 1H), 2.77-2.72 (m, 1H), 1.67-1.59 (m, 5H), 1.58-1.54 (m, 2H), 1.45-1.37 (m, 5H), 1.30-1.24 (m, 8H), 0.89-0.86 (m, 6H), -0.10 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 143.89, 142.82, 135.70, 128.92, 128.20, 127.86, 127.61, 125.99, 65.31, 64.36, 47.10, 33.43, 31.32, 29.05, 28.48, 27.47, 25.07, 22.49, 13.99, 2.16. $[\alpha]_D$ = -0.025 (c = 0.005 g/mL, CH_2Cl_2). HRMS: calculated to $C_{32}H_{51}NOS_2Si$ $[M + H]^+$ 558.3181, found 558.3254.

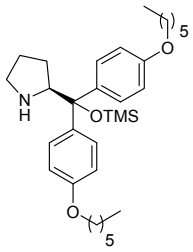


(*S*)-α,α-Bis(4-dodecylphenylsulfide)-2-pyrrolidinemethanol trimethylsilylether (3b): Global yield: 75%, light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 (d, *J* = 8 Hz, 2H), 7.27-7.19 (m, 6H), 3.98-3.95 (m, 1H), 3.70 (q, *J* = 7 Hz, 1H), 2.92-2.87 (m, 4H), 2.84-2.79 (m, 1H), 2.77-2.71 (m, 1H), 1.82 (bs, 1H), 1.67-1.56 (m, 6H), 1.43-1.37 (m, 5H), 1.30-1.22 (m, 32H), 0.88 (t, *J* = 7 Hz, 6H), -0.10 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 143.89, 142.82, 135.70, 135.54, 128.90, 128.18, 127.82, 127.57, 82.66, 65.28, 58.31, 47.07, 33.33, 31.87, 29.59, 29.46, 29.31, 29.14, 29.07, 28.81, 27.47, 25.05, 22.65, 18.38, 14.08, 2.14. $[\alpha]_D$ = -29,245 (c = 0.006 g/mL, ethyl acetate). HRMS: calculated to $C_{44}H_{75}NOS_2Si$ $[M + H]^+$ 726.5059, found 726.5132.



(*S*)-α,α-Bis(4-ethylphenylether)-2-pyrrolidinemethanol trimethylsilylether (3c): Global yield: 80%, brown oil. RMN ^{1}H ($CDCl_3$, 400 MHz) δ = 7.18 (d, *J* = 9 Hz, 4 H), 6.68 (d, *J* = 9 Hz, 4H),

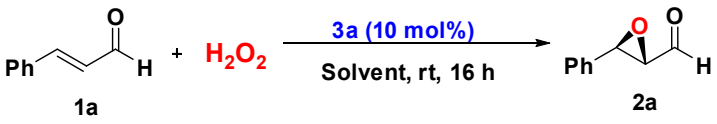
3.88 (q, *J* = 7 Hz, 4 H), 3.84 – 3.79 (m, 2 H), 2.46 – 2.41 (m, 2 H), 1,91 (s, 1H), 1.71 – 1.63 (m, 2 H), 1.33-1.25 (m, 7 H), - 0.26 (s, 9 H). RMN ^{13}C ($CDCl_3$, 100 MHz) δ = 132.15, 129.78, 113.80, 113.35, 82.69, 63.63, 63.27, 35.23, 22.17, 14.78, 14.65, 1.62. $[\alpha]_D$ = -72.14 (c = 0.007 g/mL, ethyl acetate). HRMS: calculated to $C_{24}H_{35}NO_3Si$ $[M + H]^+$ 414.2386, found 414.2461.



(*S*)-α,α-Bis(4-hexylphenylether)-2-pyrrolidinemethanol trimethylsilylether (3d): Global yield: 78%, light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.33 (d, *J* = 9 Hz, 2H), 7.24 (d, *J* = 9 Hz, 2H), 6.80-6.77 (m, 4H), 3.95-3.91 (m, 5H), 2.83-2.77 (m, 1H), 2.75-2.69 (m, 1H), 1.80-1.73 (m, 5H), 1.62-1.55 (m, 3H), 1.49-1.41 (m, 4H), 1.35-1.31 (m, 8H), 0.92-0.88 (m, 6H), -0.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 157.97, 157.90, 138,69, 137.65, 129.67, 129.01, 113.32, 113.17, 82.61, 67.87, 65.71, 47.17, 31.60, 29.28, 27.64, 25.73, 25.21, 22.58, 14.02, 2.10. $[\alpha]_D$ = -0,029 (c = 0.005 g/mL, CH_2Cl_2). HRMS: calculated to $C_{32}H_{51}NO_3Si$ $[M + H]^+$ 526.3638, found 526.3710.

3. Asymmetric epoxidation of the *α,β*-unsaturated aldehydes.

3.1 Optimization on reaction conditions to asymmetric epoxidation.



Entry	Solvent	Yield (%)[a]	*ee* (%)[b]
1	EtOH	90	92
2	EtOH/ H_2O (1:1)	30	nd[c]
3	H_2O	26	nd[c]

4	Brine	32	nd[c]
5	EtOH/ H_2O (3:1)	95	88[d]
6	EtOH/ H_2O (3:1)	32	99[e]
7	EtOH/ H_2O (3:1)	88	94[f]

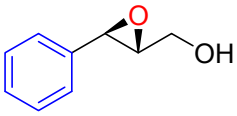
[a] Isolated yields. [b]Determinated to *trans* isomer. [c]Not determinated. [d]Twice reagents concentration. [e]5 mol% of catalyst. [f]*t*-BuOOH was used as oxidant.

3.2 General procedure to asymmetric epoxidation of the *α,β*-unsaturated aldehydes.

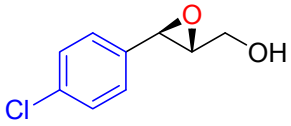
In a vial, the catalyst (10 mol%, 0.03 mmol) was dissolved in ethanol and distilled water (0.45 mL, 0.15 mL), followed by addition of the α,β-unsaturated aldehyde (0.3 mmol) and H_2O_2 (0.9 mmol, 0.075 mL, 35% aqueous solution). The resulting homogeneous mixture was stirred for 16 h. Water (1 mL) was added and extracted with diethylether (3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in methanol (2 mL), cooled to 0 ºC and followed by addition of $NaBH_4$ (0.030 g). After 20 min, the reaction was quenched by water (5 mL), extracted with diethylether (3 x 20 mL), dried over $MgSO_4$ and concentrated. The products were obtained after flash chromatography using hexane and ethyl acetate.

The NMR data of the epoxyalcohols are described to diastereoisomeric mixtures (*anti* and *syn*). Accordingly, the signs of each estereoisomer are discriminated. NMR data are in agreement with the literature (**2a**,[4] **2b-2d** and **2h**,[5] **2e**,[6] **2f** and **2h**,[7] **2g** and **2e**[8]).

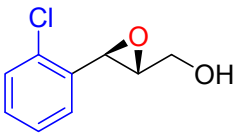
[4] S. K. Cherian and P. Kumar, *Tetrahedron:Asymmetry,* 2007, **18**, 982.
[5] G.-L. Zhao, I. Ibrahem, H. Sundén and A. Córdova, *Adv. Synth. Catal.* 2007, **349**, 1210.
[6] K. Mori, S. Sano, Y. Yokoyama, M. Bando and M. Kido, *Eur. J. Org. Chem.* 1998, 1135.
[7] J. M. Schomaker, S. Bhattacharjee, J. Yan and B. Borhan, *J. Am. Chem. Soc.* 2007, **129**, 1996.
[8] C. Bonini, G. Righi and G. Sotgiu, *J. Org. Chem.* 1991, **56**, 6206.



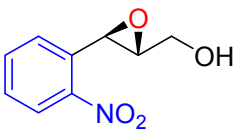
3-Phenyloxiranemethanol (2a). Yield: 85%, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30-7.19 (m, 10H, *syn* and *anti*), 4.12 (d, *J*= 4 Hz, 1H, *syn*), 3.97 (dd, ^{1}J= 13 Hz, ^{2}J= 2 Hz, 1H, *anti*), 3.85 (d, *J*= 2 Hz, 1H, *anti*), 3.72 (dd, ^{1}J= 13 Hz, ^{2}J= 4 Hz, 1H, *anti*), 3.51-3.46 (m, 1H, *syn*), 3.41-3.35 (m, 2H, *syn*), 3.17-3.15 (m, 1H, *anti*), 2.02 (bs, 1H, *syn*), 1.69 (bs, 1H, *anti*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 136.65, 134.66, 128.87, 128.55, 128.36, 128.31, 127.92, 126.19, 125.73, 62.43, 61.23, 60.53, 58.58, 57.08, 55.59. $[\alpha]_D$ = +33.39 (c = 0.010 g/mL, ethyl acetate).



3-(4-Chloro-phenyl)oxiranemethanol (2b). Yield: 79%, yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34-7.31 (m, 4H, *syn* and *anti*), 7.27-7.20 (m, 4H, *syn* and *anti*), 4.16 (d, *J*= 4 Hz, 1H, *syn*), 4.04 (dd, ^{1}J= 13 Hz, ^{2}J= 2 Hz, 1H, *anti*), 3.91 (d, *J*= 2 Hz, 1H, *anti*), 3.81 (dd, ^{1}J= 13 Hz, ^{2}J= 3 Hz, 1H, *anti*), 3.56-3.51 (m, 1H, *syn*), 3.46-3.41 (m, 2H, *syn*), 3.19-3.17 (m, 1H, *anti*), 2.01 (bs, 1H, *syn*), 1.72 (bs, 1H, *anti*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 135.26, 134.13, 133.81, 133.22, 128.75, 128.55, 127.60, 127.06, 62.49, 61.01, 60.36, 58.58, 56.52, 54.91. $[\alpha]_D$ = +34.12 (c = 0.011 g/mL, ethyl acetate).

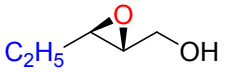


3-(2-Chloro-phenyl)oxiranemethanol (2c). Yield: 88%, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.38-7.34 (m, 2H, *syn* and *anti*), 7.27-7.22 (m, 6H, *syn* and *anti*), 4.26-4.25 (m, 2H, *syn* and *anti*), 4.08 (dd, ^{1}J= 13 Hz, ^{2}J= 2 Hz, 1H, *anti*), 3.84 (dd, ^{1}J= 13 Hz, ^{2}J= 4 Hz, 1H, *anti*), 3.59-3.52 (m, 2H, *syn*), 3.36-3.31 (m, 1H, *syn*), 3.11-3.09 (m, 1H, *anti*), 1.98 (bs, 1H, *anti*), 1.70 (bs, 1H, *syn*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 134.78, 133.02, 129.12, 129.04, 128.15, 127.06, 126.71, 126.00, 61.95, 61.44, 60.78, 58.33, 55.76, 53.31. $[\alpha]_D$ = -10.66 (c = 0.005 g/mL, ethyl acetate).



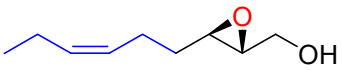
3-(2-Nitrophenyl)oxiranemethanol (2d). Yield: 92%, white solid. M.p. 83-84 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 – 8.17 (m, 2H, *syn* and *anti*), 7.71 – 7.63 (m, 4H, *syn* and *anti*), 7.54 – 7.48 (m, 2H, *syn* and *anti*), 4.57 (d, *J*= 4 Hz, 1H, *syn*), 4.47 (d, *J*= 2 Hz, 1H, *anti*), 4.11 –

4.08 (m, 1H, *anti*), 3.95 – 3.90 (m, 1H, *anti*), 3.71 – 3.67 (m, 1H, *syn*), 3.53 – 3.49 (m, 1H, *syn*), 3.36 – 3.31 (m, 1H, *syn*), 3.12 – 3.09 (m, 1H, *anti*), 1.95 (bs, 1H), 1.68 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 134.42, 133.97, 129.41, 128.93, 128.66, 127.26, 124.82, 124.74, 61.77, 61.64, 60.84, 58.97, 56.41, 54.35. $[\alpha]_D$ = +122.64 (c = 0.010 g/mL, ethyl acetate).



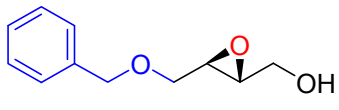
3-Ethyloxiranemethanol (2e): Yield: 86%, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.06 (dd, ^{1}J= 12 Hz, ^{2}J= 3 Hz, 1H, *syn*), 3.91 (d, *J*= 13 Hz, 1H, *anti*), 3.78 (dd, ^{1}J= 12 Hz, ^{2}J= 5 Hz, 1H, *syn*), 3.62 (d, *J*= 13 Hz, 1H, *anti*), 3.19-3.14 (m, 1H, *syn*), 2.97 – 2.93 (m, 2H, *anti*), 2.85 – 2.81 (m, 1H, *syn*), 1.96 (bs, 2H, *anti* and *syn*), 1.66 – 1.58 (m, 2H, *anti*), 1.29 – 1.25 (m, 2H, *syn*), 1.07 – 0.98 (m, 3H, *anti*), 0.89 – 0.84 (m, 3H, *syn*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 61.77, 58.17, 57.05, 24.59, 9.80. $[\alpha]_D$ = +21.00 (c = 0.0003 g/mL, ethyl acetate).

3-Heptyloxiranemethanol (2f). Yield: 90%, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.91 (dd, ^{1}J= 12 Hz, ^{2}J= 2 Hz, 1H, *anti*), 3.84 – 3.83 (m, 1H, *syn*), 3.69 – 3.67 (m, 1H, *syn*), 3.62 (dd, ^{1}J= 12 Hz, ^{2}J= 3 Hz, 1H, *anti*), 3.17 – 3.14 (m, 1H, *syn*), 3.05 – 3.02 (m, 1H, *syn*), 2.97 – 2.91 (m, 2H, *anti*), 2.00 (bs, 1H, *anti*), 1.80 (bs, 1H, *syn*), 1.60 – 1.55 (m, 4H, *anti* and *syn*), 1.50 – 1.39 (m, 4H, *anti* and *syn*), 1.36 – 1.28 (m, 16H, *anti* and *syn*), 0.90-0.87 (m, 6H, *anti* and *syn*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 61.71, 60.90, 58.46, 57.32, 56.66, 56.00, 31.71, 31.52, 29.32, 29.15, 27.93, 26.61, 25.91, 22.59, 21.32, 14.04, 12.14. $[\alpha]_D$ = +7.03 (c = 0.002 g/mL, ethyl acetate).



(3*Z*)-Hexenyloxiran-3-methanol (2g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.46 – 5.40 (m, 2H, *anti* and *syn*), 5.37 – 5.32 (m, 2H, *anti* and *syn*), 3.91 (dd, ^{1}J= 12 Hz, ^{2}J= 2 Hz, 1H, *anti*), 3.86 – 3.82 (m, 1H, *syn*), 3.71 – 3.67 (m, 1H, *syn*), 3.62 (dd, ^{1}J= 12 Hz, ^{2}J= 4 Hz, 1H, *anti*), 3.18 – 3.14 (m, 1H, *syn*), 3.07 – 3.03 (m, 1H, *syn*), 2.99 – 2.93 (m, 2H, *anti*), 2.23 – 2.17 (m, 4H, *anti* and *syn*), 2.09 – 2.02 (m, 4H, *anti* and *syn*), 1.71 – 1.57 (m, 4H, *anti* and *syn*), 0.97 (t, *J*= 7 Hz, 6H, *anti* and *syn*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 133.06, 132.77,

127.48, 127.40, 61.69, 60.86, 58.53, 56.89, 56.84, 55.56, 31.66, 28.04, 24.11, 23.57, 20.49, 14.25. Yield: 90%, colorless oil. $[\alpha]_D$ = -10.869 (c = 0.002 g/mL, ethyl acetate).



3-Benzyloximethyloxiranemethanol (2h). Yield: 40%, yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.73 – 7.69 (m, 1H, *syn*), 7.54 – 7.52 (m, 1H, *syn*), 7.38 – 7.26 (m, 6H, *anti* and *syn*), 7.20 – 7.18 (m, 2H, *syn*), 5.11 – 5.05 (m, 2H, *syn*), 4.62 – 4.54 (m, 2H, *anti*), 4.33 – 4.27 (m, 2H, *syn*), 3.95 (dd, ^1J= 12 Hz, ^2J= 2 Hz, 1H, *anti*), 3.77 (dd, ^1J= 12 Hz, ^2J= 3 Hz, 1H, *anti*), 3.73 – 3.71 (m, 1H, syn), 3.66 (dd, ^1J= 12 Hz, ^2J= 4 Hz, 1H, *anti*), 3.54 (dd, ^1J= 12 Hz, ^2J= 5 Hz, 1H, *anti*), 3.41 – 3.38 (m, 2H, *syn*), 3.31 – 3.29 (m, 1H, *syn*), 3.26 – 3.23 (m, 1H, *anti*), 3.12 – 3.10 (m, 1H, *anti*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 128.58, 128.46, 127.84, 127.78, 73.39, 69.61, 61.10, 55.68, 54.24. $[\alpha]_D$ = +10.00 (c = 0.003 g/mL, athyl acetate).

4. HPLC analysis of epoxyalcohols 2a-h.

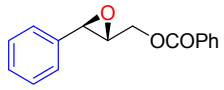
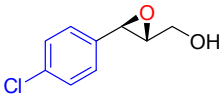
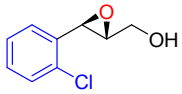
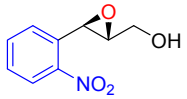
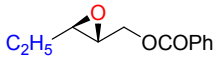
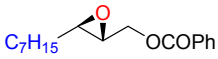
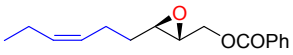
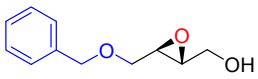
4.1 General procedure to esterification of epoxyalcohols.

In order to obtain a good separation in the HLPC analysis, some epoxyalcohols were converted to their corresponding esters.

The epoxide (0.25 mmol) was dissolved in DCM (4 mL), followed by the addition of triethylamine (0.37 mmol, 0.050 mL) and distilled benzoyl chloride (0.29 mmol, 0.034 mL). The solution was stirred for 2h at rt, then was diluted with DCM (10 mL), washed with water (10 mL) and sodium bicarbonate (2 x 10 mL), dried over $MgSO_4$ and concentrated. The product was purified by chromatography column using hexane and ethyl acetate (90:10).[9]

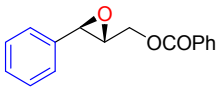
[9] D. L. J. Clive and E. J. L. Stoffman, *Chem. Commun.* 2007, 2151.

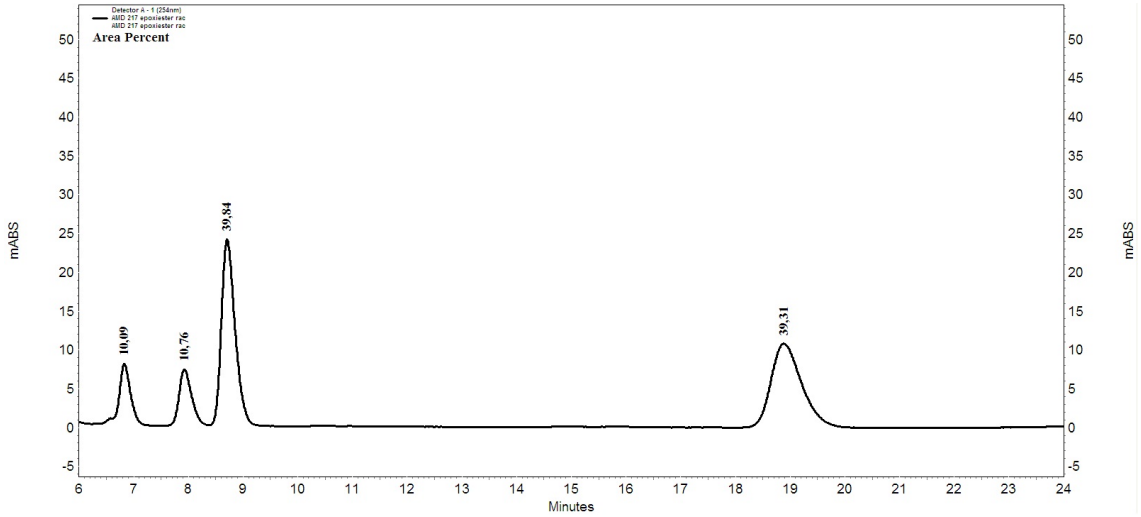
4.2 Conditions and data of the HPLC analysis using chiral columns.

Epoxide analised	Chiral column	Hexane: Isopropanol	Conditions Used[a]	Retention Time[b]
	OD	85:15	0.8 mL/min	8.98, 19.15
	OD-H	85:15	0.8 mL/min	7.88, 9.46
	OD-H	95:05	1.0 mL/min	13.26, 14.74
	OD-H	95:05	1.0 mL/min	30.14, 35.00
	OD-H	98:02[c]	1.0 mL/min	11.35, 12.44
	OD-H	98:02	0.2 mL/min	30.57, 33.20
	OD-H	98:02	0.5 mL/min	13.66, 15.84
	OD-H	85:15	0.8 mL/min	20.38, 21.59

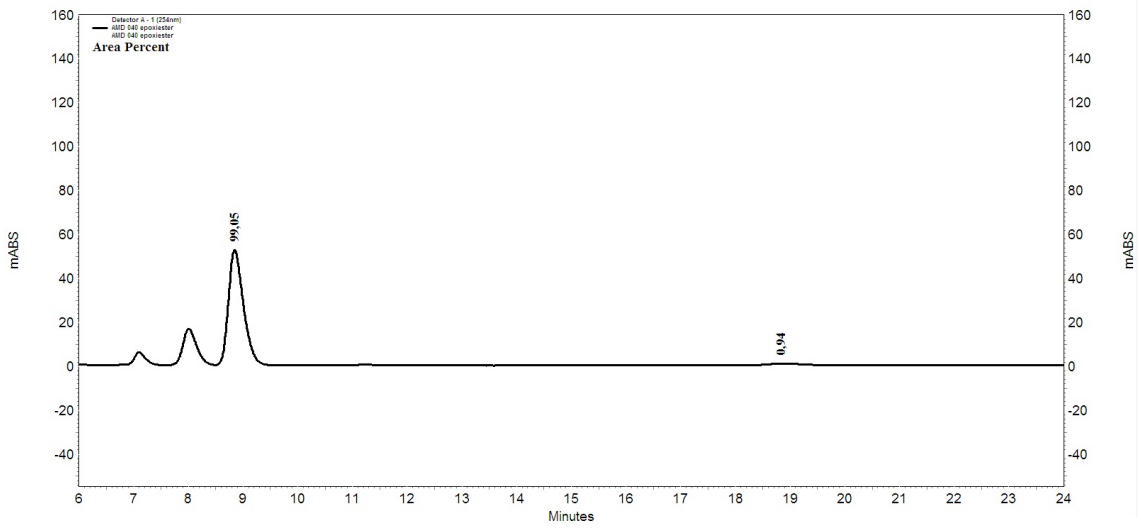
[a] 254 nm. [b] To the major diastereoisomer. [c] Hexane:ethanol was used.

4.3 Chromatograms of racemic mixtures and epoxides obtained by organocatalysis.

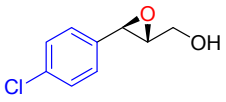


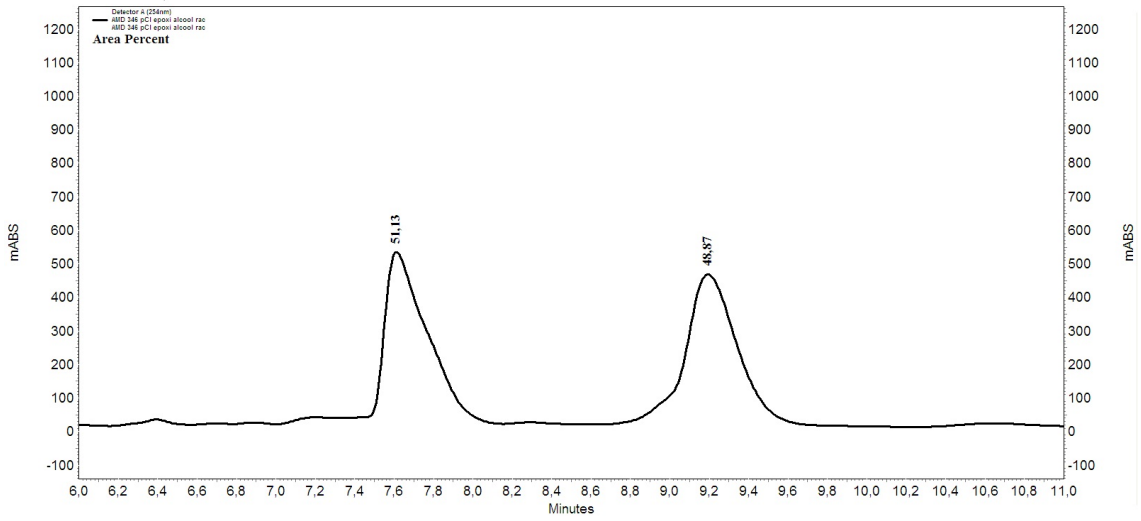


Racemic sample

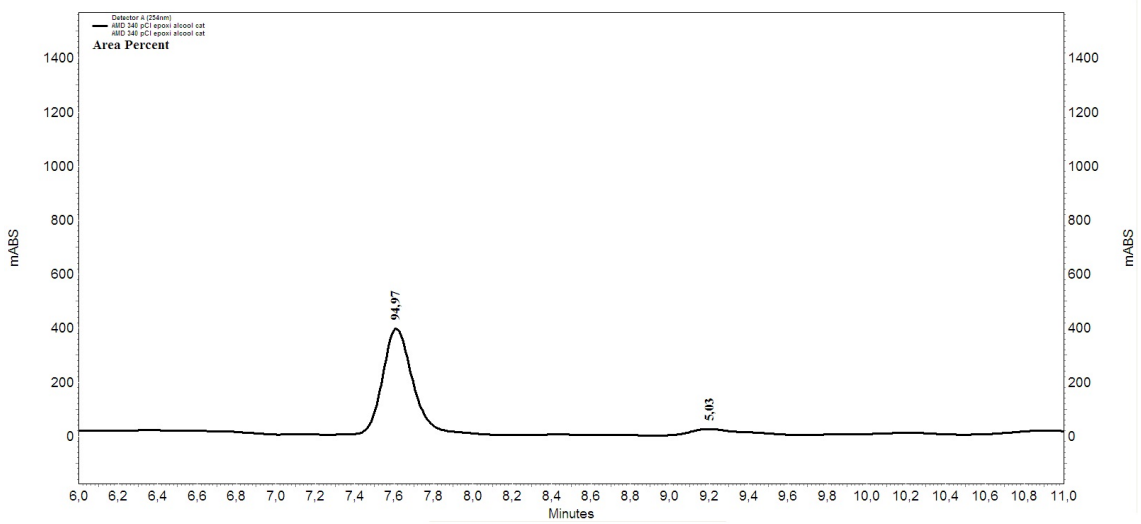


Via asymmetric epoxidation (major diastereomer: 98% *ee*)

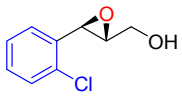


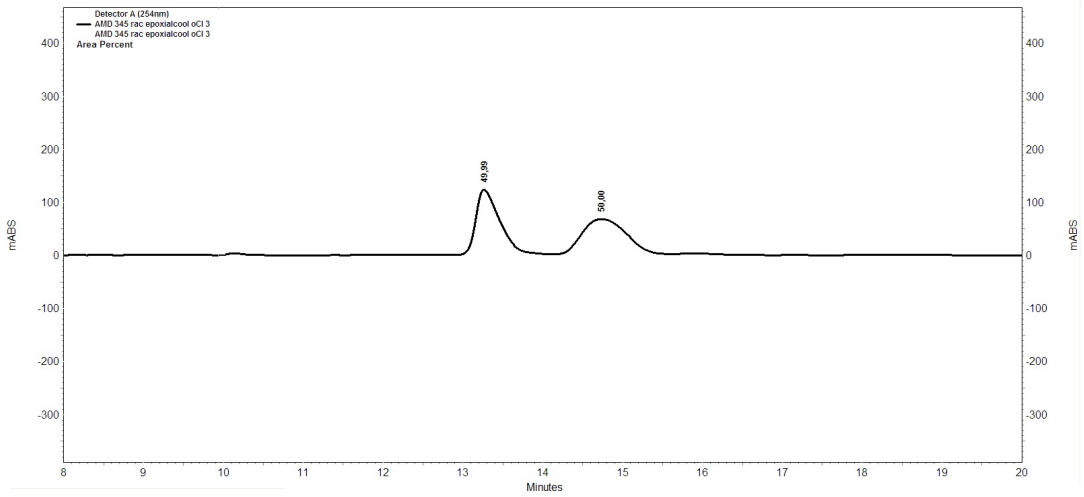


Racemic sample

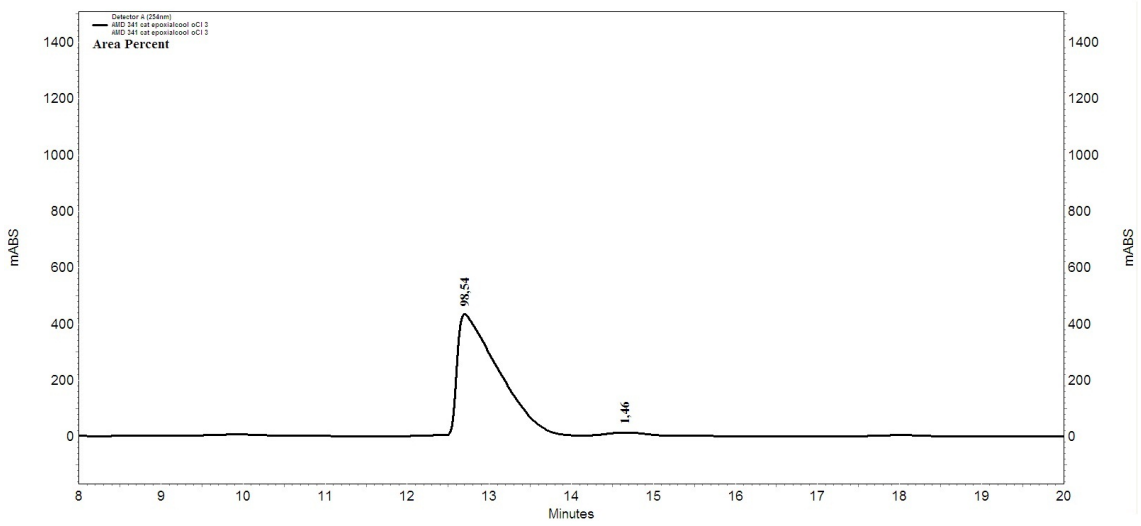


Via asymmetric epoxidation (major diastereomer: 90% *ee*)

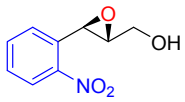


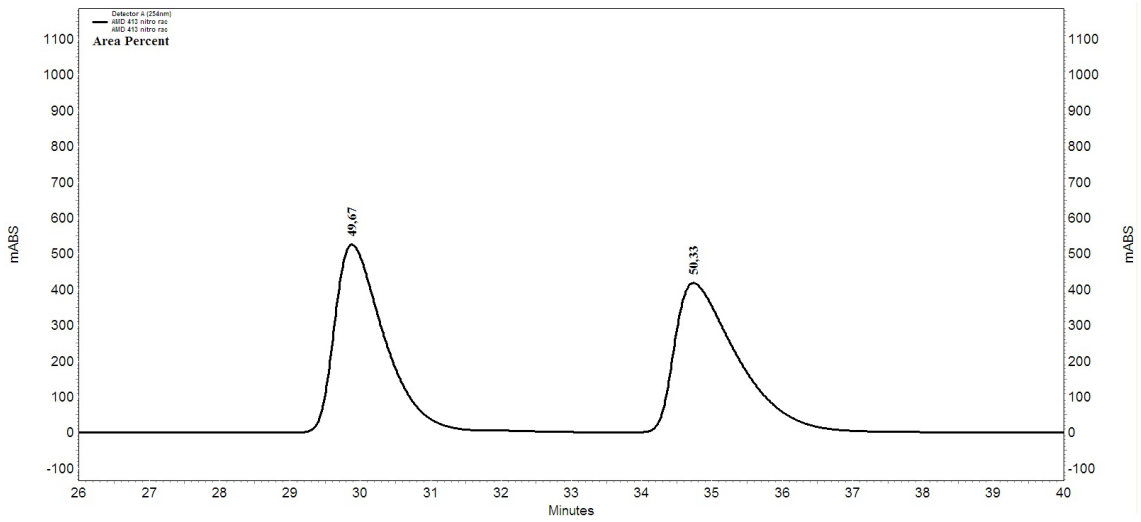


Racemic sample

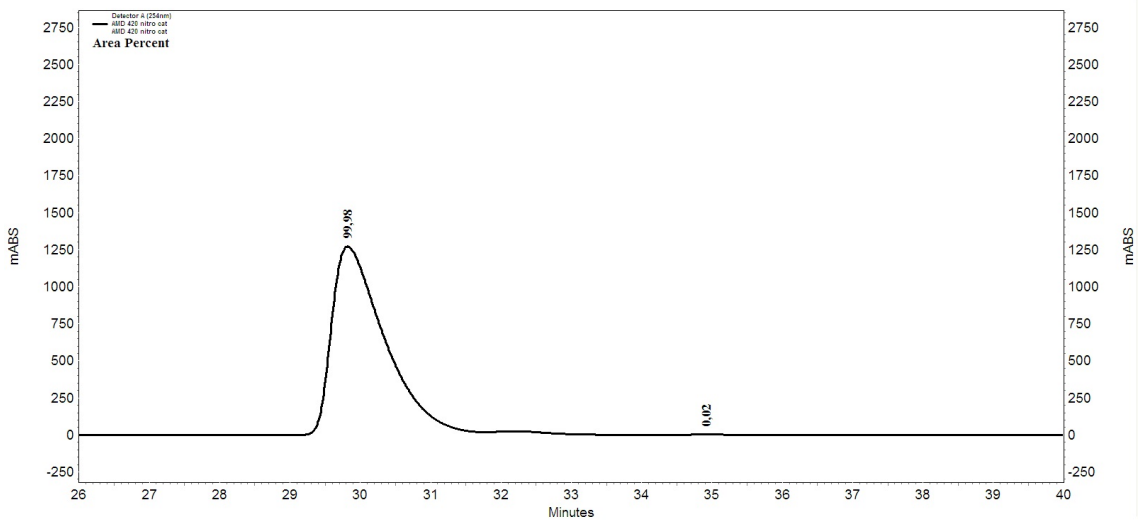


Via asymmetric epoxidation (major diastereomer: 97% *ee*)

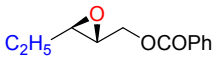


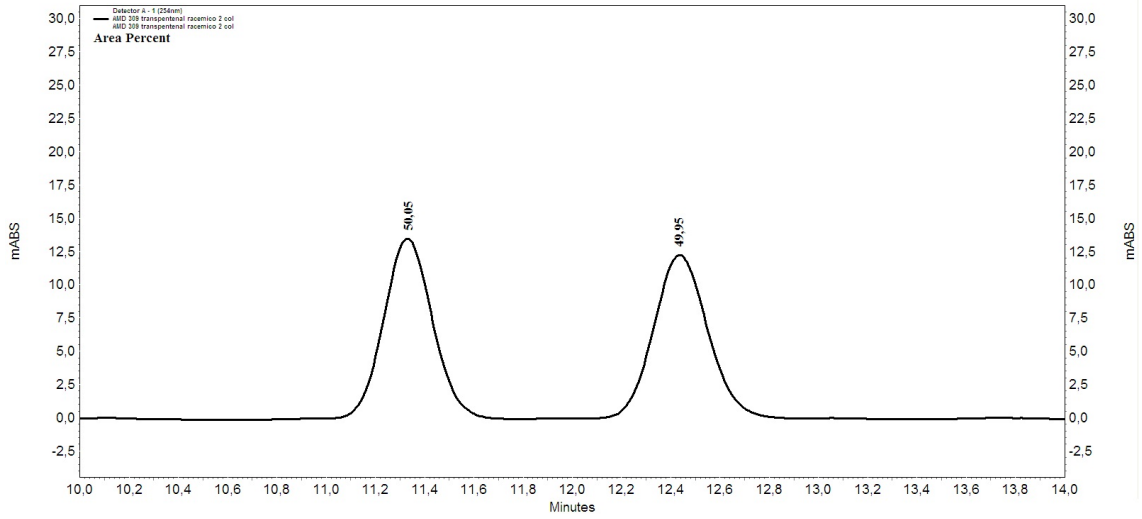


Racemic sample

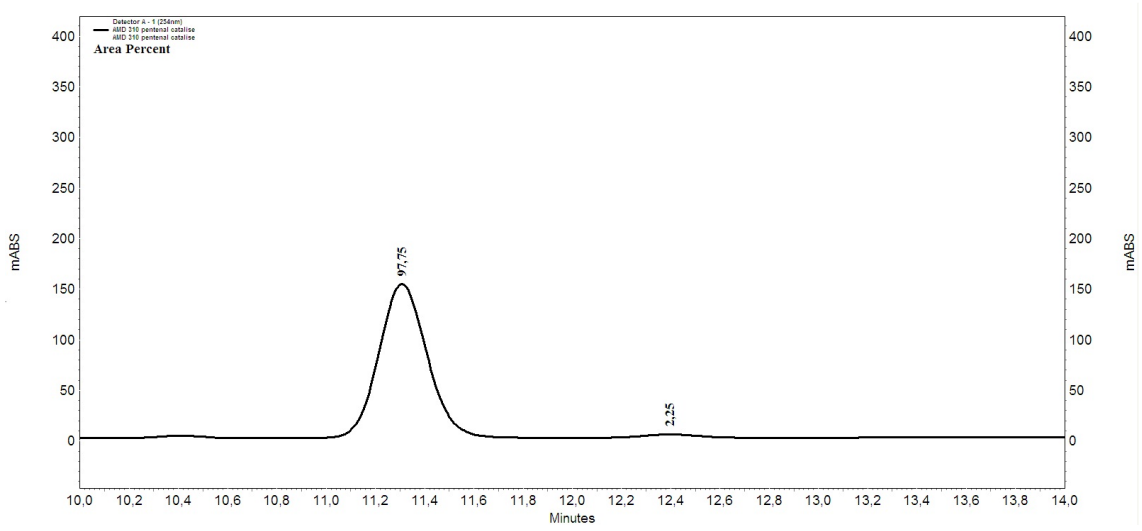


Via asymmetric epoxidation (major diastereomer: 99% *ee*)

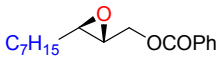


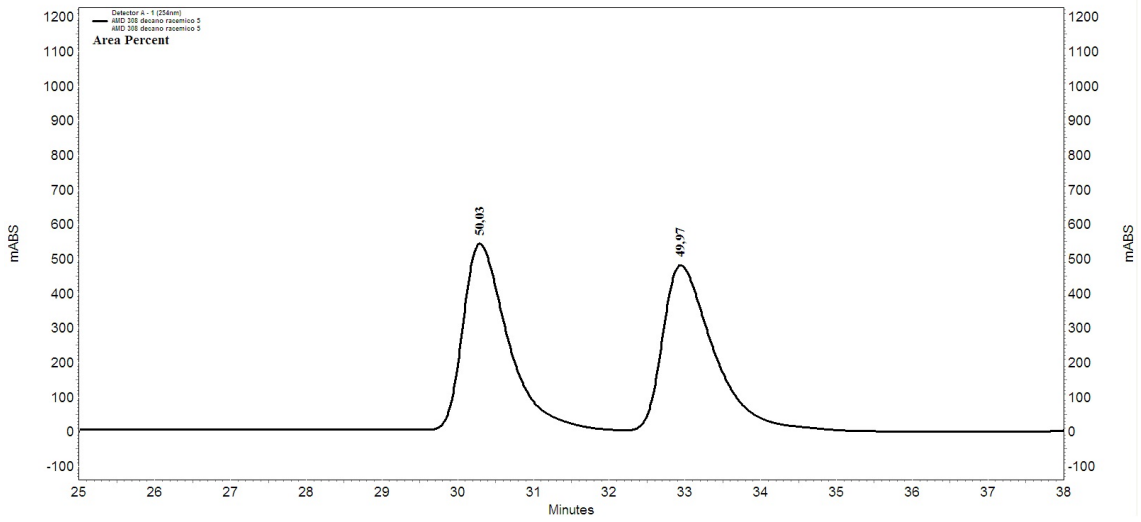


Racemic sample

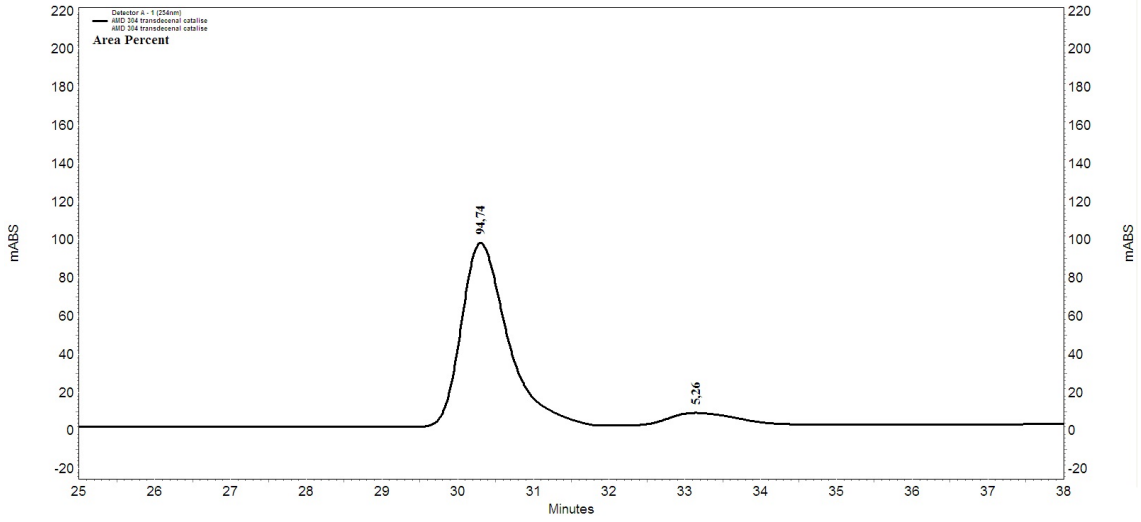


Via asymmetric epoxidation (major diastereomer: 95% *ee*)

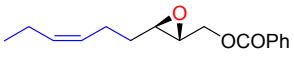


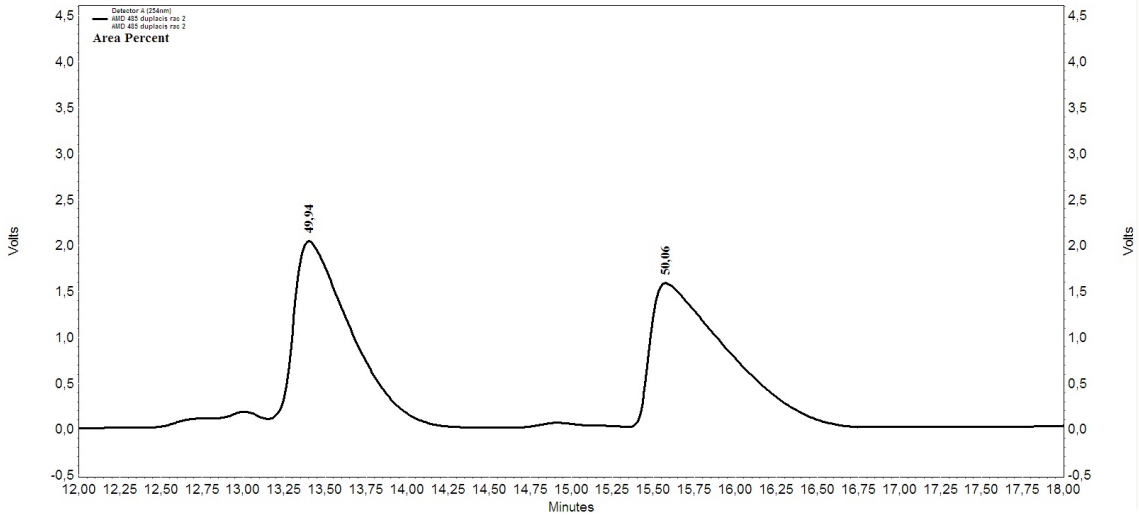


Racemic sample

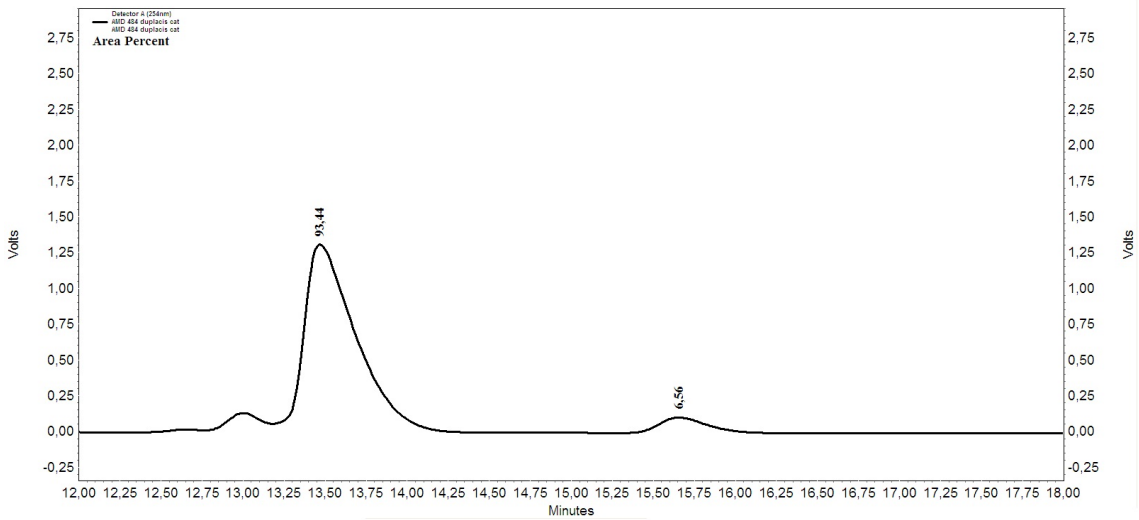


Via asymmetric epoxidation (major diastereomer: 90% *ee*)

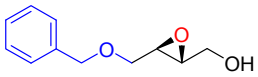


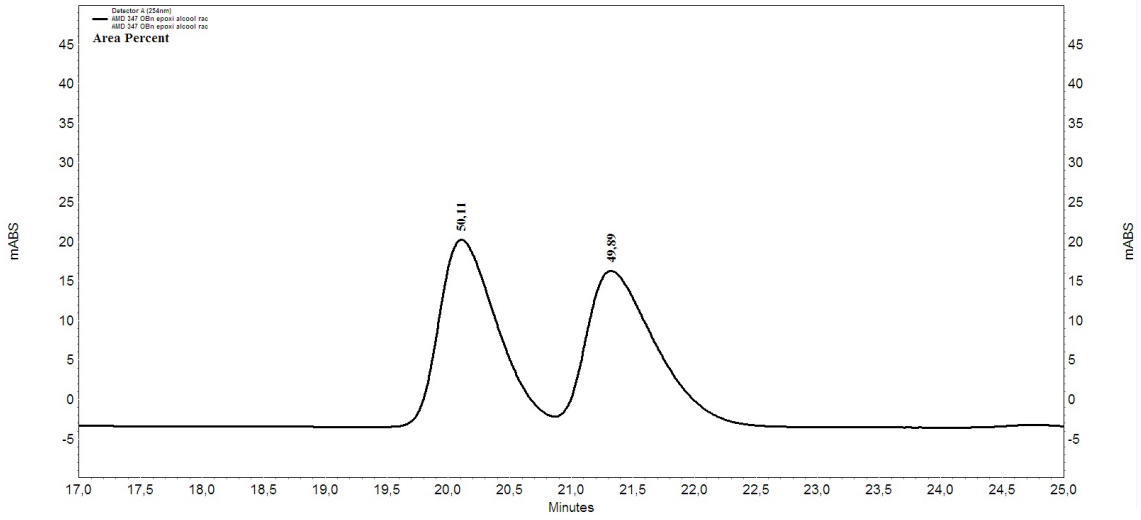


Racemic sample

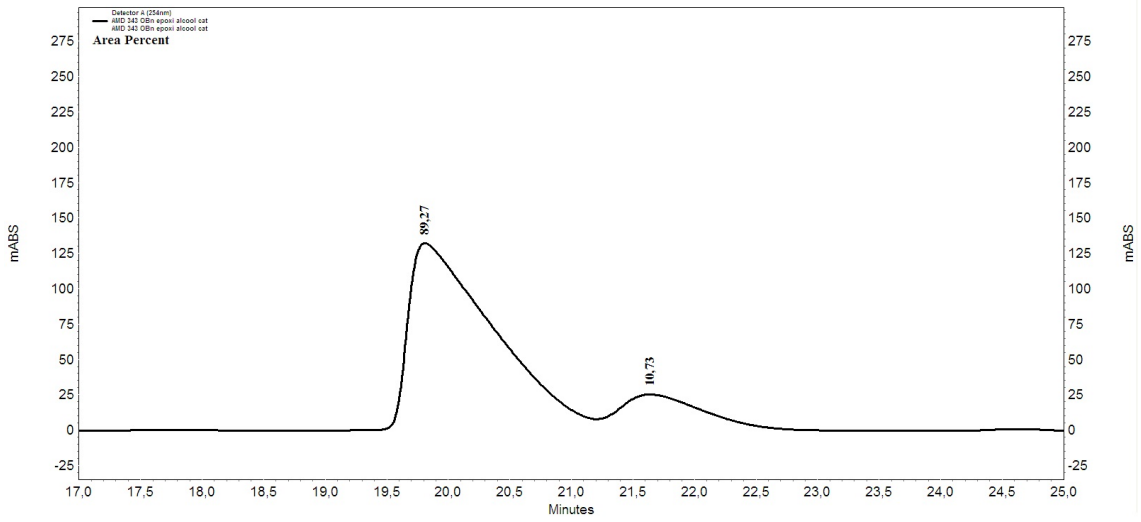


Via asymmetric epoxidation (major diastereomer: 87% *ee*)





Racemic sample



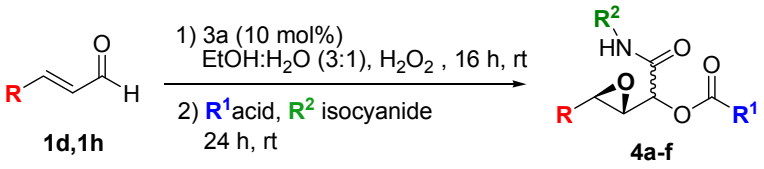
Via asymmetric epoxidation (major diastereomer: 78% *ee*)

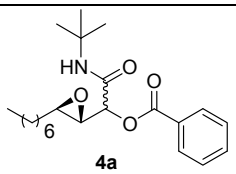
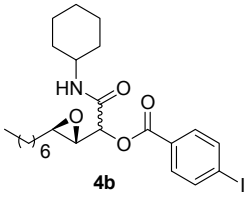
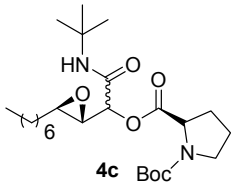
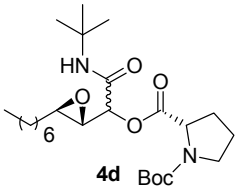
5. One pot Passerine reaction

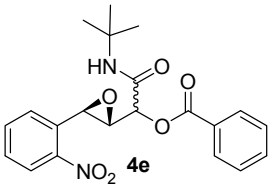
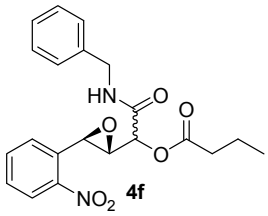
5.1 General procedure to one pot Passerine Reaction

In a vial, the catalyst (10 mol%, 0.03 mmol) was dissolved in ethanol (0.45 mL) and distilled water (0.15 mL). Followed by addition of the α,β-unsaturated aldehyde (0.3 mmol) and H_2O_2 (0.9 mmol, 0.075 mL, 35% aqueous solution). The resulting mixture was stirred for 16 h, then the corresponding acid (0.3 mmol) and the isocyanide (0.5 mmol) were added. The resulting solution was stirred for additional 24 h at rt and then directed submitted to flash chromatography.

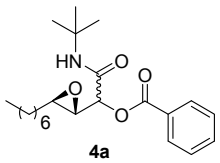
Scope of the asymmetric organocatalytic tandem epoxidation/MCPR under eco-friendly solvent system



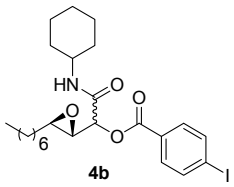
Entry	Product	Yield (%)[a]	*d.r.*[b] (*ee*)[c]
1	 **4a**	72	5:32:63 (96)
2	 **4b**	61	4:66:30
3	 **4c** Boc	53	3:50:19:26:2
4	 **4d** Boc	57	49:4:14:2:6:3:22

5	 **4e**	75	40:60
6	 **4f**	58	48:52 (98)

[a]Yield after isolation by flash chromatography. [b]Determined by crude ^{1}H-NMR spectroscopy and chiral-phase HPLC. [c]Determined on the major diastereomer by HPLC analysis on a chiral stationary phase.

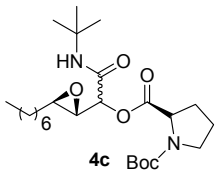

4a

Yield: 72%. White solid. M.p. 92-93 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.09 – 8.07 (m, 6H), 7.64-7.59 (m, 3H), 7.51 – 7.46 (m, 6H), 5.96 (s, 1H), 5.29 – 5.27 (m, 2H), 4.96 (d, *J*= 9 Hz, 1H), 3.43 (dd, ^1J= 9 Hz, ^2J= 4 Hz, 1H), 3.29 (dd, ^1J= 5 Hz, ^2J= 2 Hz, 1H), 3.21 (dd, ^1J= 5 Hz, ^2J= 2 Hz, 1H), 3.08 (td, ^1J= 6 Hz, ^2J= 2 Hz, 2H), 3.02 (td, ^1J= 6 Hz, ^2J= 2 Hz, 1H), 1.62 – 1.53 (m, 3H), 1.48 – 1.41 (m, 3H), 1.39 – 1.37 (m, 27H), 1.32 – 1.25 (m, 15H), 0.89 – 0.85 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.21, 165.95, 165.66, 164.91, 133.77, 133.62, 133.47, 129.99, 129.83, 129.60, 129.07, 128.86, 128.67, 128.57, 128.43, 73.54, 73.02, 70.43, 57.83, 57.34, 57.28, 56.61, 56.45, 55.01, 51.75, 51.62, 31.67, 31.59, 31.40, 31.35, 29.20, 29.13, 29.10, 28.76, 28.66, 27.57, 26.34, 25.73, 22.59, 14.03. $[\alpha]_D$ = +21.14 (c = 0.007 g/mL, ethyl acetate). HRMS: calculated to $C_{22}H_{33}NO_4$ $[M + H]^+$ 376.2487, found 376.2481.


4b

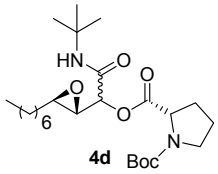
Yield: 56%. White solid. M.p. 122-123 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.86 – 7.83 (m, 6H), 7.79 – 7.75 (m, 6H), 5.98 – 5.96 (m, 2H), 5.31 (d, *J*= 5 Hz, 2H), 5.28 (d, *J*= 5 Hz, 1H), 3.84 – 3.75 (m, 3H), 3.27 (dd, ^1J= 5 Hz, ^2J= 2 Hz, 1H), 3.21 (dd, ^1J= 5 Hz, ^2J= 2 Hz, 2H), 3.14 – 3.11 (m, 1H), 3.06 (td, ^1J= 6 Hz, ^2J= 2 Hz, 1H), 3.02 (td, ^1J= 6 Hz, ^2J= 2 Hz, 1H), 1.94 – 1.88 (m, 6H), 1.71 – 1.64 (m, 6H), 1.61 – 1.55 (m,

9H), 1.47 – 1.11 (m, 46H), 0.89 – 0.85 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.60, 165.32, 164.64, 164.57, 138.06, 137.98, 131.18, 128.49, 128.27, 101.85, 101.67, 73.89, 73.19, 57.35, 57.11, 56.70, 56.23, 48.32, 32.86, 32.81, 31.69, 31.35, 31.32, 29.21, 29.14, 25.73, 25.68, 25.41, 24.65, 22.60, 14.06. $[\alpha]_D$ = +17.561 (c = 0.008 g/mL, ethyl acetate). HRMS: calculated to $C_{24}H_{34}INO_4$ $[M + H]^+$ 528.1610, found 528.1597.



4c

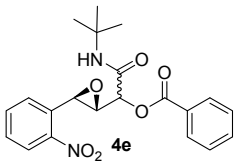
Yield: 43%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.81 (s, 1H), 6.70 (s, 1H), 5.86 (s, 1H), 5.32 (d, *J*= 3 Hz, 1H), 5.17 (d, *J*= 3 Hz, 1H), 5.00 (d, *J*= 5 Hz, 1H), 4.96 (d, *J*= 6 Hz, 1H), 4.78 (d, *J*= 6 Hz, 1H), 4.39 (dd, ^1J= 8 Hz, ^2J= 4 Hz, 2H), 4.32 (dd, ^1J= 8 Hz, ^2J= 4 Hz, 1H), 4.26 (dd, ^1J= 8 Hz, ^2J= 5 Hz, 2H), 3.59 – 3.38 (m, 10H), 3.19 – 3.18 (m, 1H), 3.14 – 3.12 (m, 3H), 3.09 – 3.08 (m, 1H), 3.05 – 3.02 (m, 3H), 2.96 – 2.93 (m, 2H), 2.34 – 1.97 (m, 15H), 1.93 – 1.87 (m, 10H), 1.49 (s, 25H), 1.44 – 1.35 (m, 80H), 1.31 – 1.26 (m, 40H), 0.89 – 0.86 (m, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 172.43, 172.10, 171.32, 170.93, 166.04, 165.97, 155.00, 154.44, 80.19, 80.14, 80.11, 74.32, 72.64, 71.87, 59.03, 58.97, 57.44, 57.22, 56.51, 56.12, 55.28, 51.74, 51.63, 50.15, 46.87, 46.72, 46.43, 31.71, 31.67, 31.48, 31.43, 31.34, 30.82, 30.10, 29.96, 29.60, 29.26, 29.20, 29.14, 29.11, 28.62, 28.54, 28.48, 28.33, 25.85, 25.74, 25.70, 24.83, 24.31, 23.65, 22.60, 14.06. $[\alpha]_D$ = -8.636 (c = 0.004 g/mL, ethyl acetate). HRMS: calculated to $C_{25}H_{44}N_2O_6$ $[M + H]^+$ 469.3277, found 469.3192.



4d

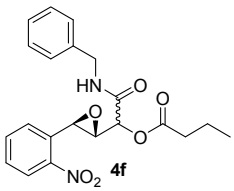
Yield: 52%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.98 (s, 1H), 6.52 (s, 1H), 5.87 (s, 1H), 5.82 (s, 1H), 5.33 (d, *J*= 3 Hz, 1H), 5.18 (d, *J*= 3 Hz, 1H), 5.16 (d, *J*= 4 Hz, 1H), 5.04 (d, *J*= 7 Hz, 1H), 5.00 (d, *J*= 5 Hz, 1H), 4.96 (d, *J*= 6 Hz, 1H), 4.78 (d, *J*= 6 Hz, 1H), 4.38 (dd, ^1J= 8 Hz, ^2J= 4 Hz, 4H), 4.35 – 4.30 (m, 1H), 4.24 (dd, ^1J= 8 Hz, ^2J= 5 Hz, 2H), 3.58 – 3.49 (m, 7H), 3.46 – 3.37 (m, 7H), 3.24 – 3.23 (m, 4H), 3.20 – 3.18 (m, 1H), 3.16 – 3.13 (m, 1H), 3.10 – 3.06 (m, 4H), 3.03 – 3.00 (m, 5H), 2.97 – 2.93 (m, 2H), 2.33 – 3.15 (m, 7H), 2.12 – 1.97 (m, 14H), 1.95 – 1.66 (m, 10H), 1.61 – 1.53 (m, 8H), 1.50 (s, 14), 1.45 – 1.42 (m, 56H), 1.40 – 1.36 (m, 70H), 1.31 – 1.22 (m, 56H), 0.89 – 0.86 (m, 21H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 172.09, 171.38, 171.13, 166.01,

165.94, 155.10, 154.46, 153.59, 80.22, 80.11, 75.64, 72.09, 70.95, 60.36, 59.07, 59.03, 59.00, 58.97, 58.83, 57.36, 56.93, 56.54, 56.33, 56.18, 55.18, 53.41, 51.77, 51.65, 46.84, 46.69, 46.38, 31.69, 31.48, 31.42, 30.98, 30.25, 29.92, 29.60, 29.23, 29.20, 29.14, 29.11, 28.60, 28.53, 28.44, 28.33, 25.76, 24.73, 24.41, 23.56, 22.60, 21.01, 14.18, 14.04. $[\alpha]_D$ = +11.905 (c = 0.004 g/mL, Ethyl Acetate). HRMS: calculated to $C_{25}H_{44}N_2O_6$ $[M + H]^+$ 469.3277, found 469.3192.



4e

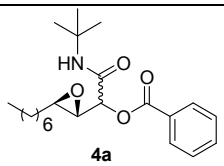
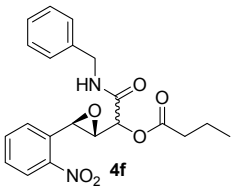
Yield: 75%. Yellowish solid. M.p. 131-132 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.19 – 8.09 (m, 6H), 7.70 – 7.59 (m, 6H), 7.53 – 7.47 (m, 6H), 6.17 (s, 1H), 6.05 (s, 1H), 5.83 (d, *J*= 2 Hz, 1H), 5.59 (d, *J*= 4 Hz, 1H), 4.66 (d, *J*= 2 Hz, 1H), 4.62 (d, *J*= 2 Hz, 1H), 3.57 – 3.56 (m, 2H), 1.41 – 1.40 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.44, 165.40, 164.87, 164.44, 147.57, 147.48, 134.52, 134.48, 133.93, 133.87, 133.24, 132.91, 129.99, 129.81, 129.74, 129.03, 128.85, 128.81, 128.73, 128.48, 127.15, 127.01, 124.87, 124.84, 72.09, 70.53, 60.48, 56.63, 54.36, 53.28, 51.95, 51.84, 28.68, 28.65. $[\alpha]_D$ = +94.44 (c = 0.004 g/mL, ethyl acetate). HRMS: calculated to $C_{21}H_{22}N_2O_6$ $[M + Na]^+$ 421.13759, found 421.1374.



4f

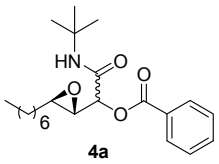
Yield: 53%. Light yellow solid. M.p. 124-125 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.17 (d, *J*= 8 Hz, 2H), 7.69 – 7.65 (m, 2H), 7.61 – 7.58 (m, 2H), 7.53 – 7.48 (m, 2H), 7.38 – 7.29 (m, 10H), 6.55 (t, *J*= 5 Hz, 1H), 6.45 (t, *J*= 5 Hz, 1H), 5.72 (d, *J*= 3 Hz, 1H), 5.54 (d, *J*= 4 Hz, 1H), 4.63 – 4.45 (m, 6H), 3.50 – 3.47 (m, 2H), 2.48 – 2.40 (m, 4H), 1.74 – 1.66 (m, 4H), 0.99 – 0.94 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 171.82, 171.51, 166.48, 147.55, 147.43, 137.77, 134.48, 134.24, 134.06, 133.02, 132.75, 129.04, 128.89, 128.78, 127.88, 127.71, 127.66, 127.01, 125.05, 124.88, 124.80, 71.79, 71.18, 69.91, 69.55, 60.48, 59.90, 58.43, 57.00, 56.68, 56.54, 54.18, 53.19, 43.48, 35.83, 35.78, 35.31, 31.59, 22.65, 22.47, 18.32, 18.03, 14.12, 13.58, 13.53. $[\alpha]_D$ = +68.831 (c = 0.008 g/mL, ethyl acetate). HRMS: calculated to $C_{21}H_{22}N_2O_6$ $[M + Na]^+$ 421.1376, found 421.1385.

5.2 Conditions and datas of HPLC analysis to Passerine products.

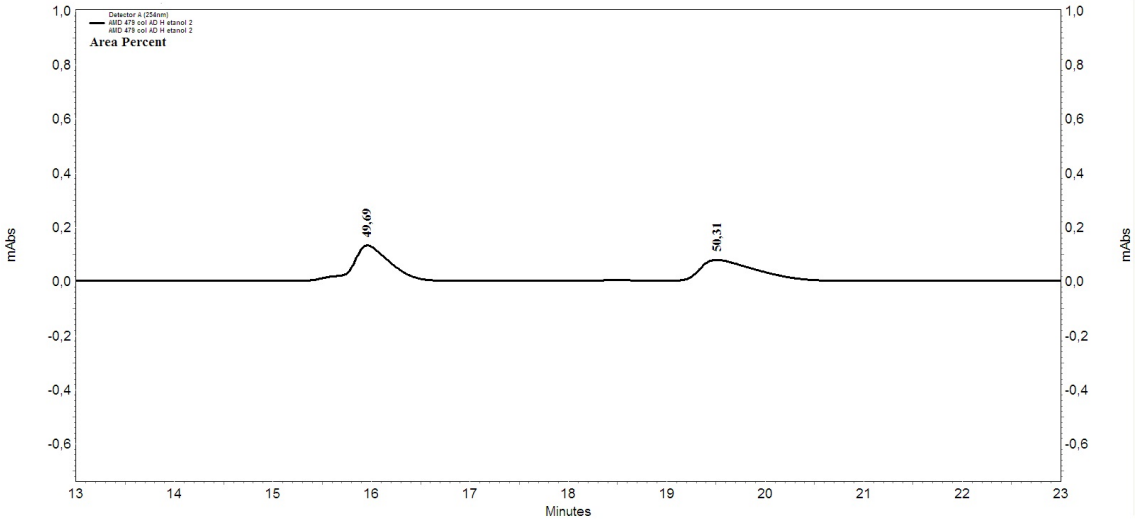
Analyzed Compounds[a]	Chiral column	Hexane: Etanol	Conditions used	Retention Time[b]
 4a	AD-H	98:2	0.8 mL/min 254 nm	16.23, 19.79
 4f	OD-H	95:5	0.5 mL/min 254 nm	69.79, 100.24, 109.42, 128.52

[a] It was unable to separare the compounds 4b-e using the chiral columns available. [b]To the major diastereoisomer.

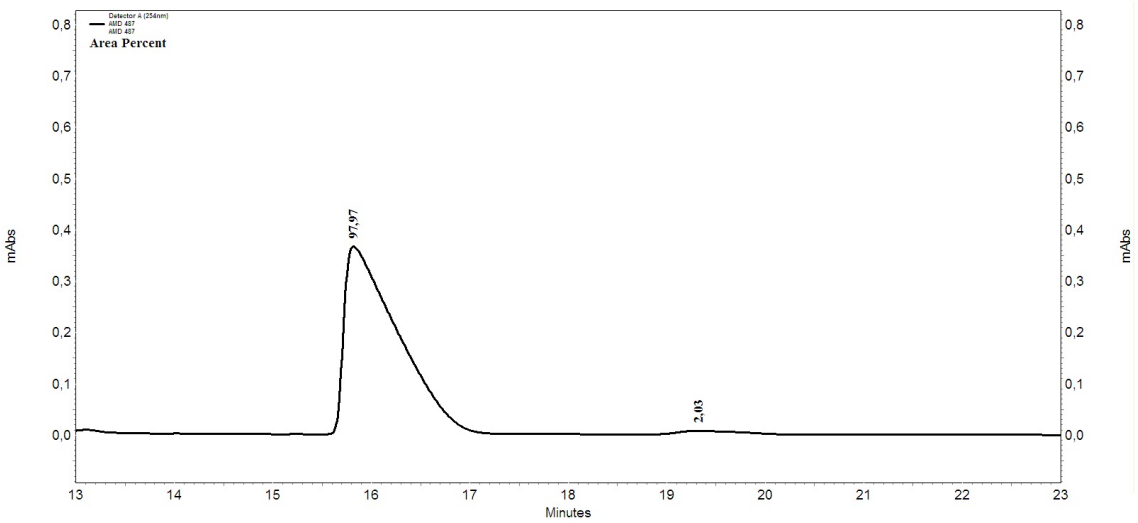
5.3 HPLC chromatograms to Passerine products.



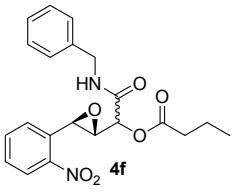
4a



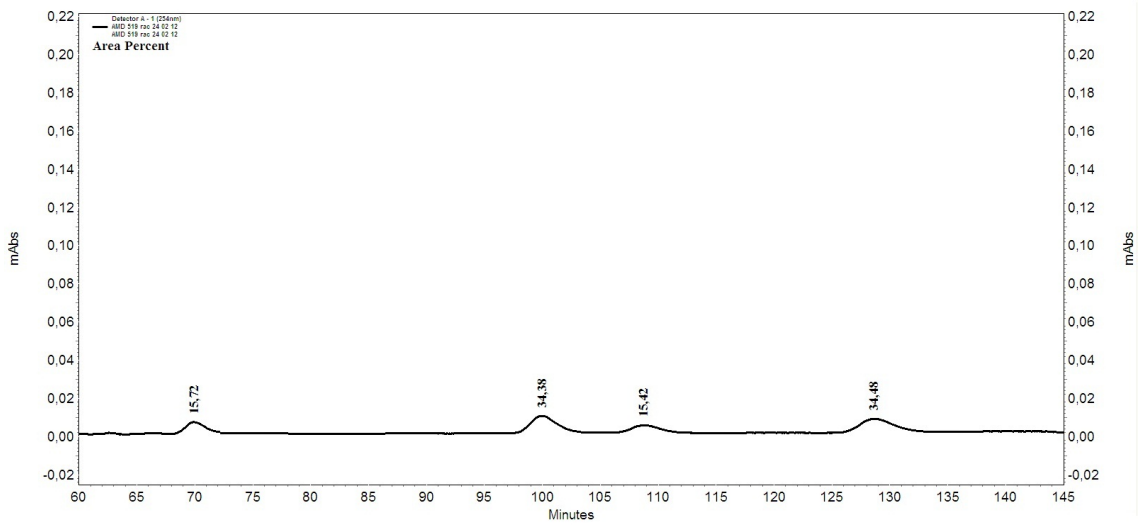
Racemic sample



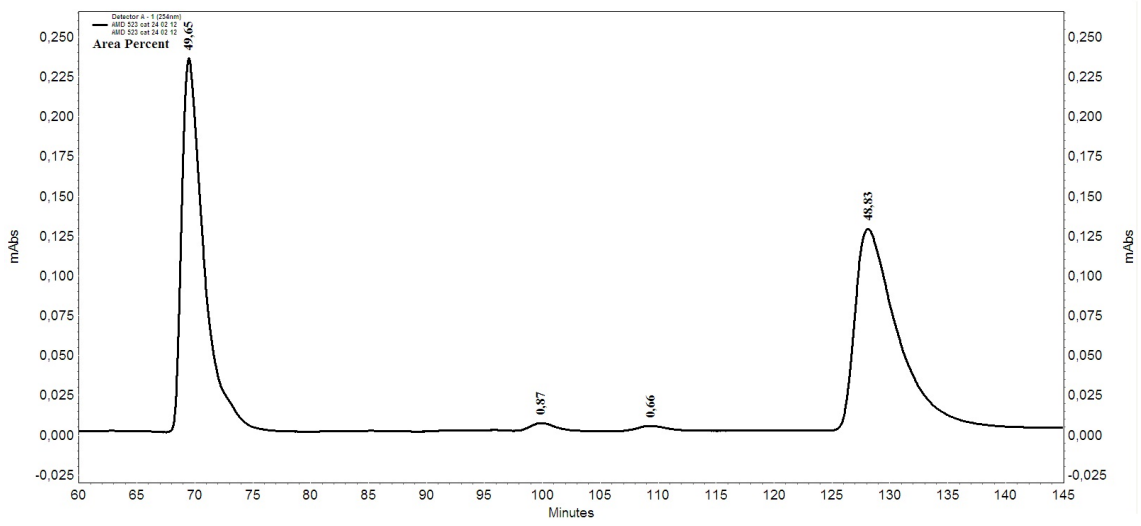
Via asymmetric epoxidation (major diastereomer: 96% *ee*)



4f

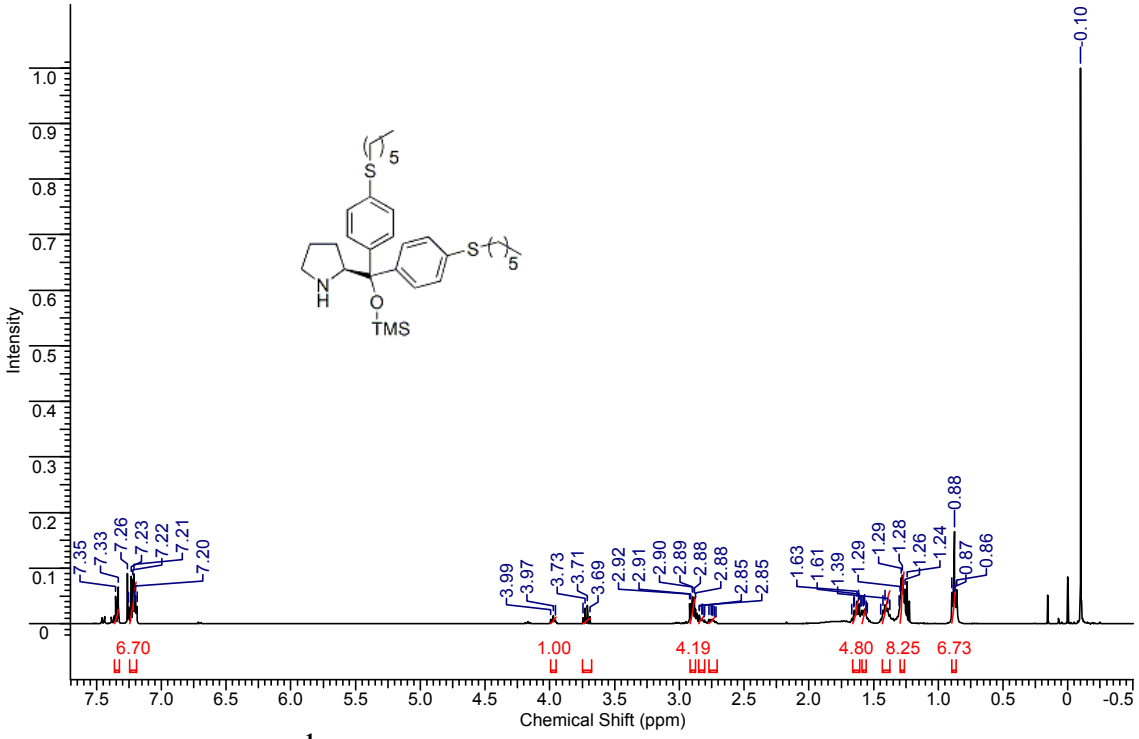


Racemic sample

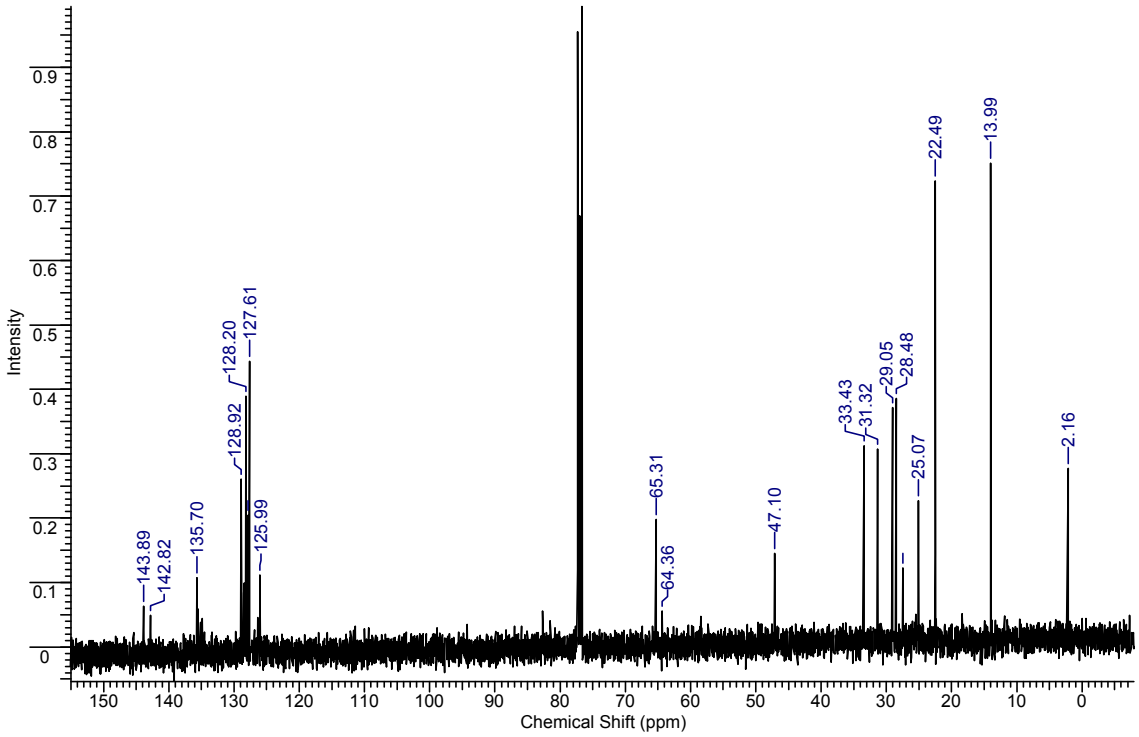


Via asymmetric epoxidation (major diastereomer: 98% *ee*)

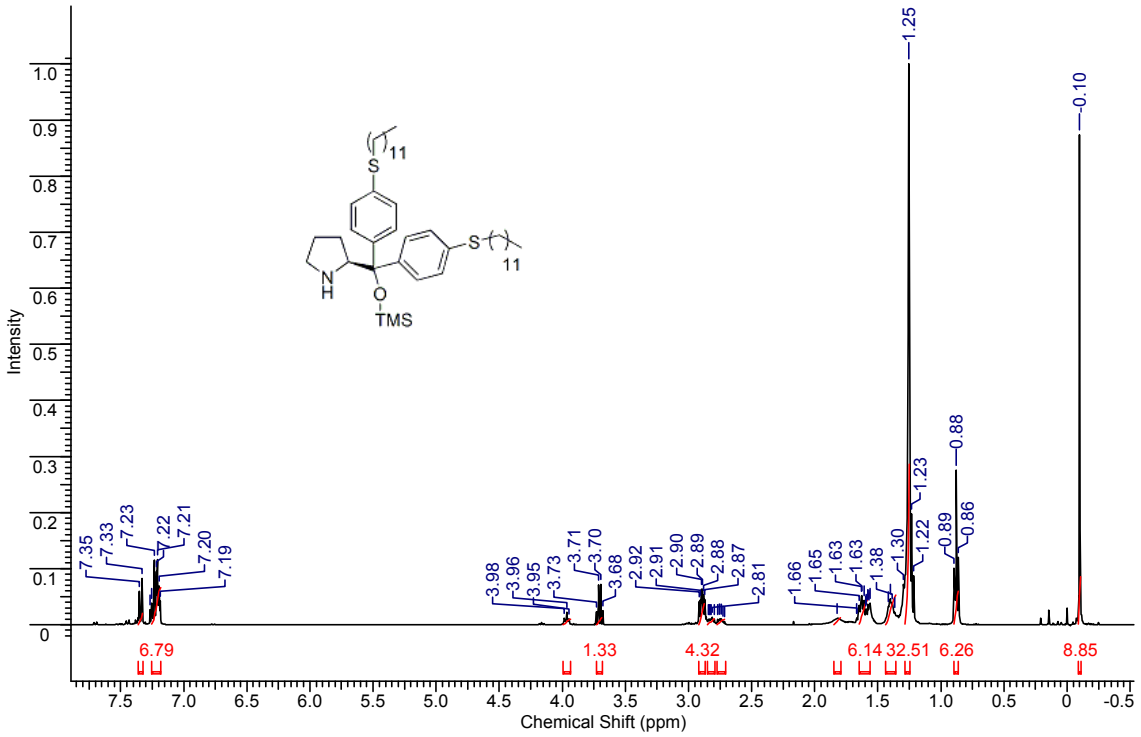
6. ^{1}H and ^{13}C NMR spectra of organocatalysts 3a-d.



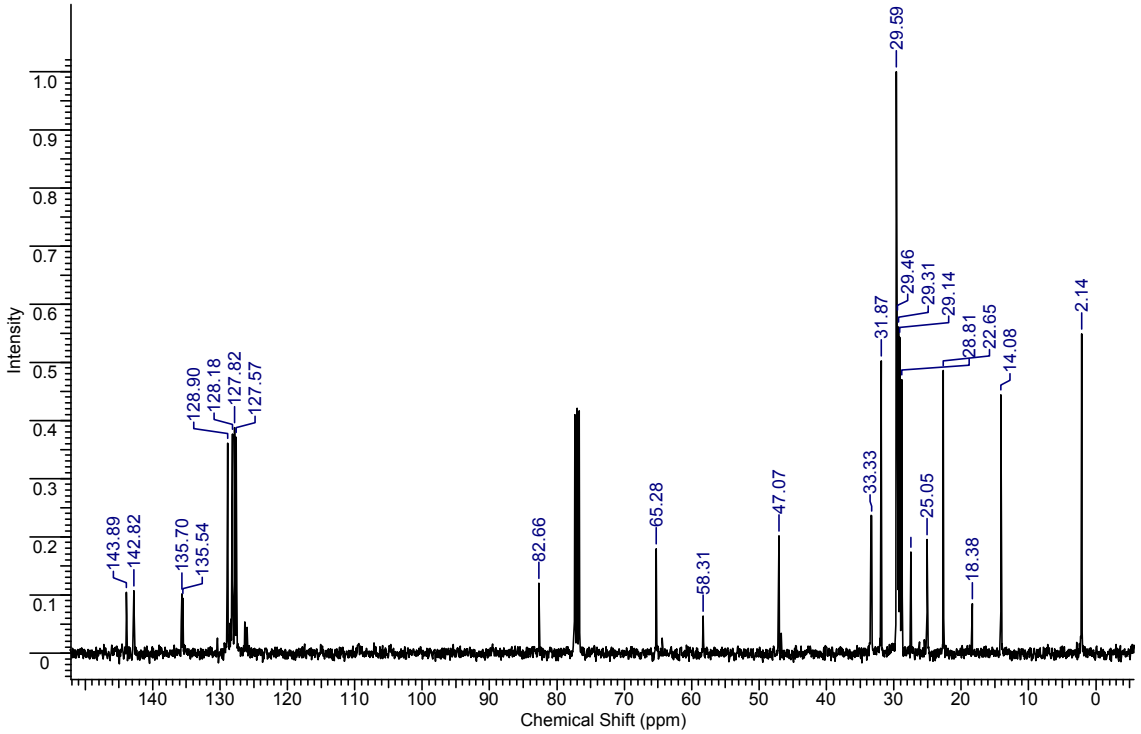
^{1}H NMR spectrum of 3a.



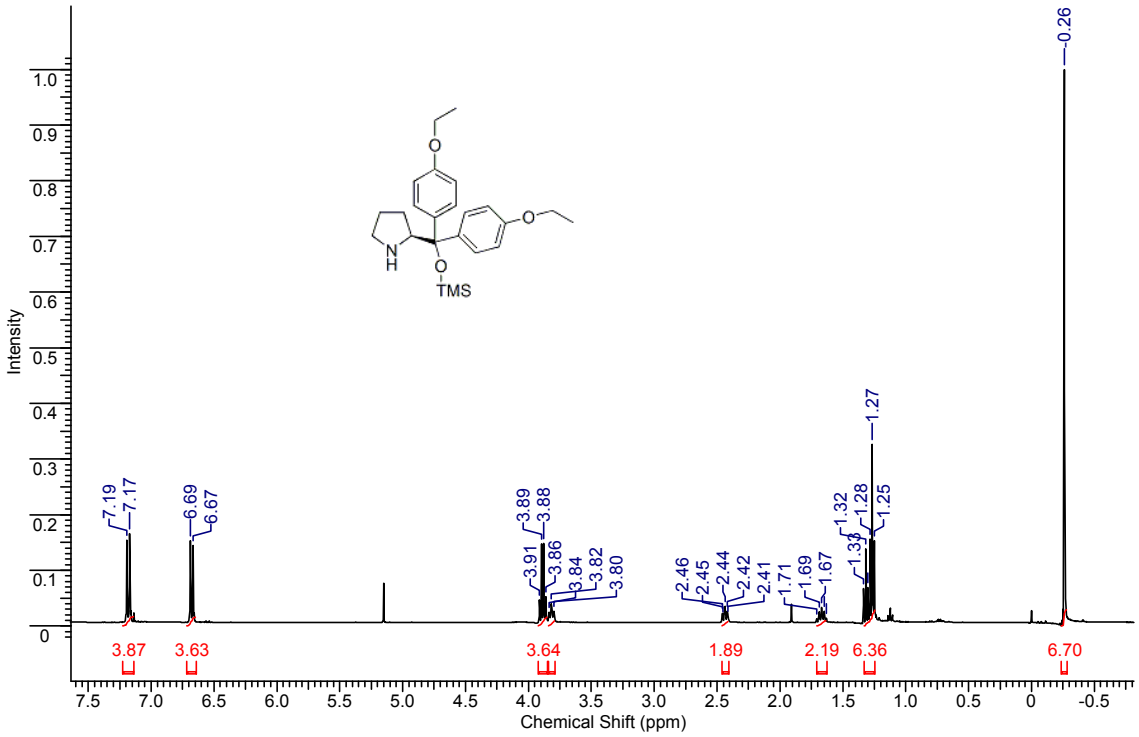
^{13}C NMR spectrum of 3a.



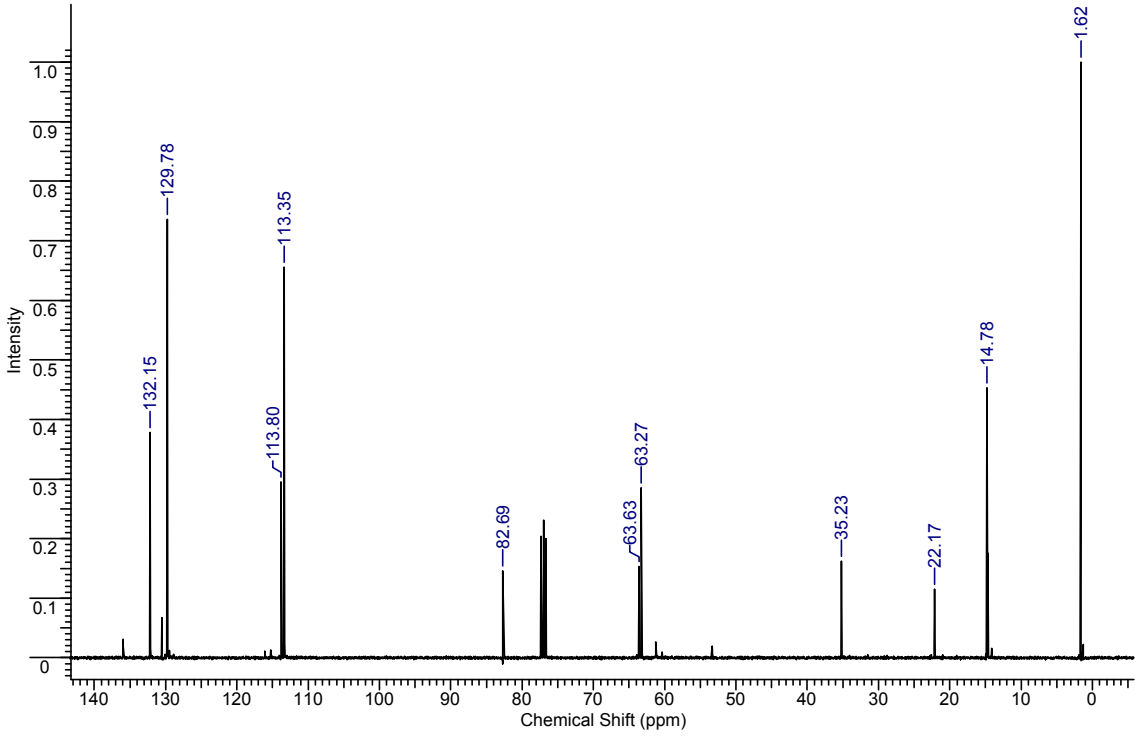
^{1}H NMR spectrum of 3b.



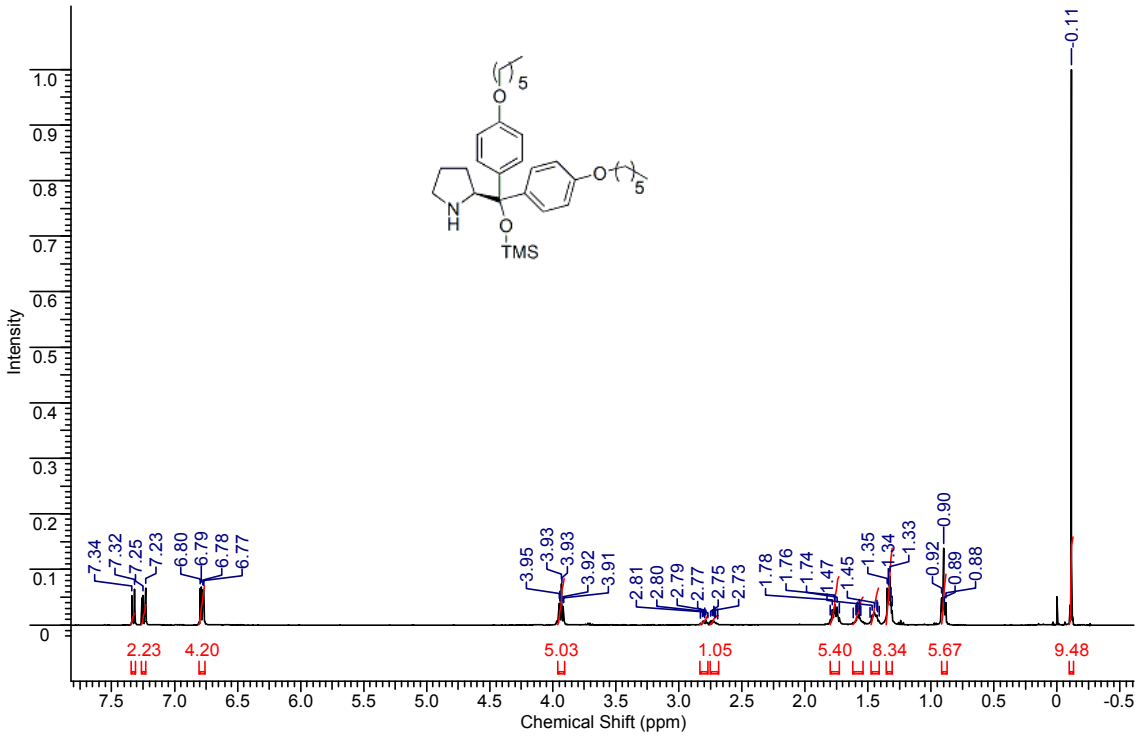
^{13}C NMR spectrum of 3b.



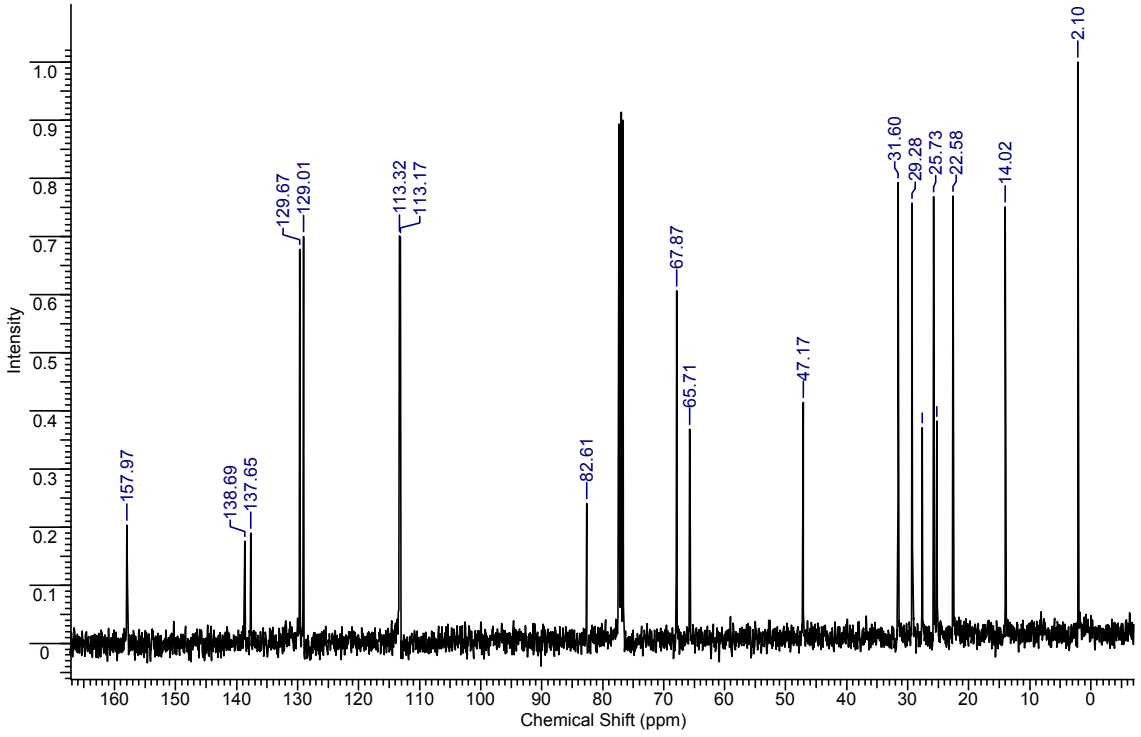
^{1}H NMR spectrum of 3c.



^{13}C NMR spectrum of 3c.

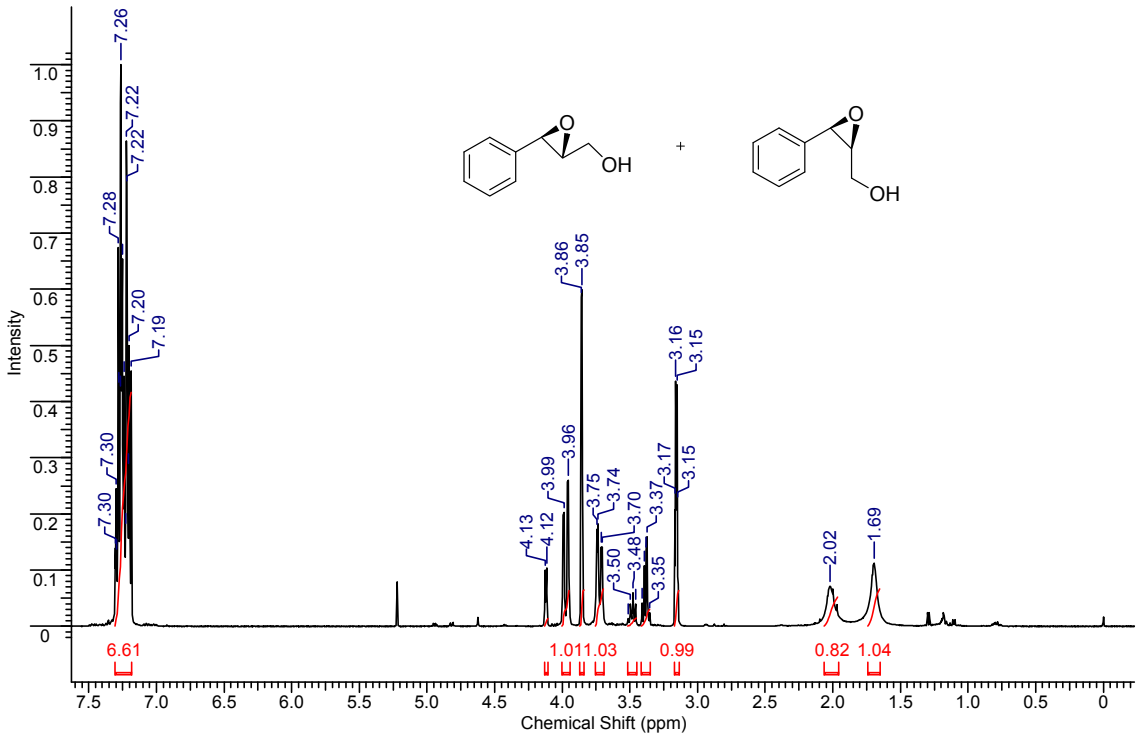


^{1}H NMR spectrum of 3d.

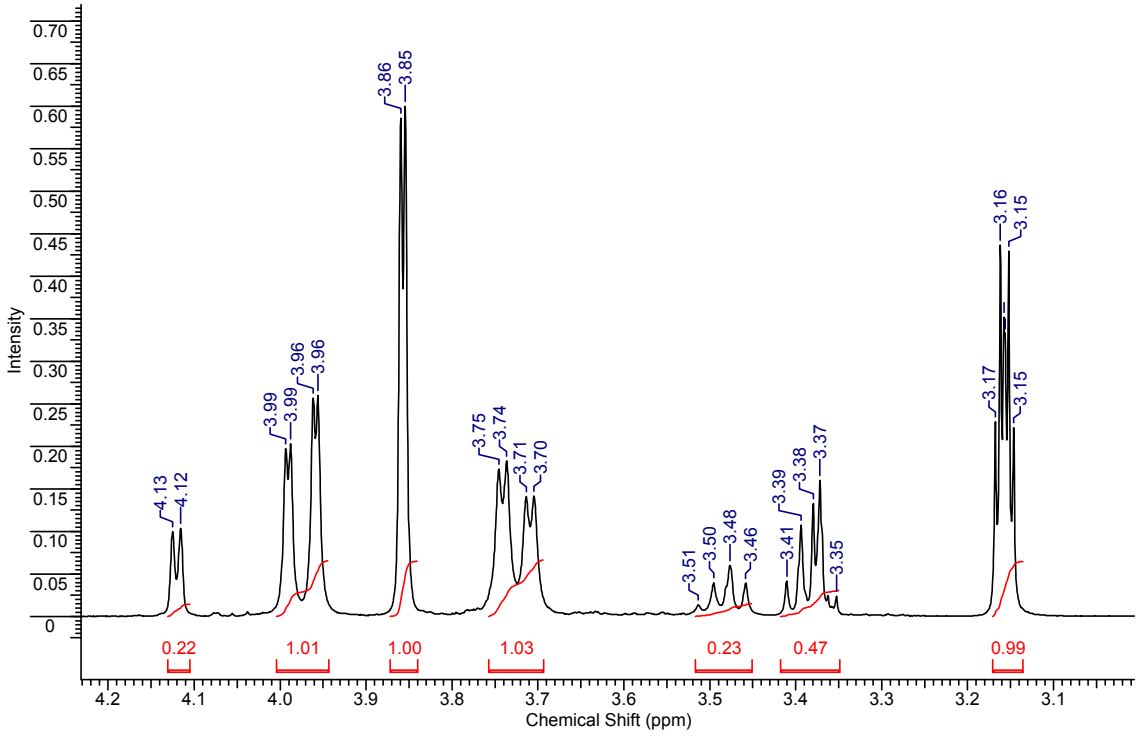


^{13}C NMR spectrum of 3d.

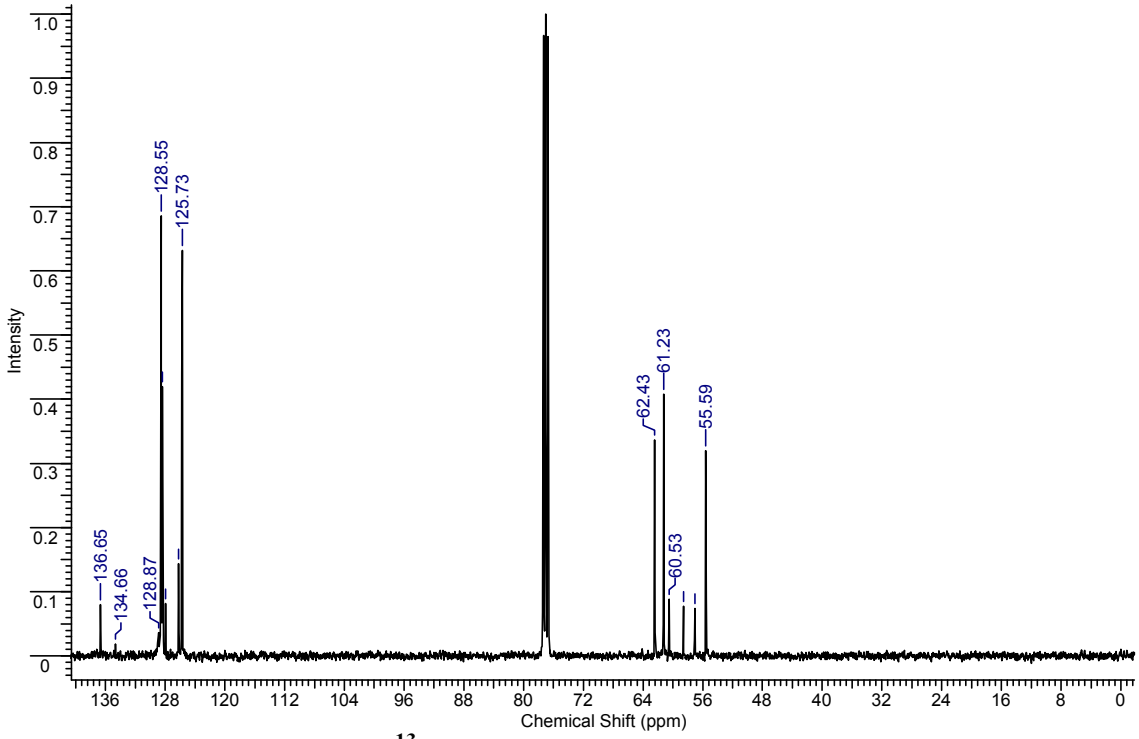
7. ^{1}H, ^{13}C, ^{1}H–^{1}H Cosy and ^{1}H–^{13}C HSQC NMR spectra of epoxyalcohols 2a-h.



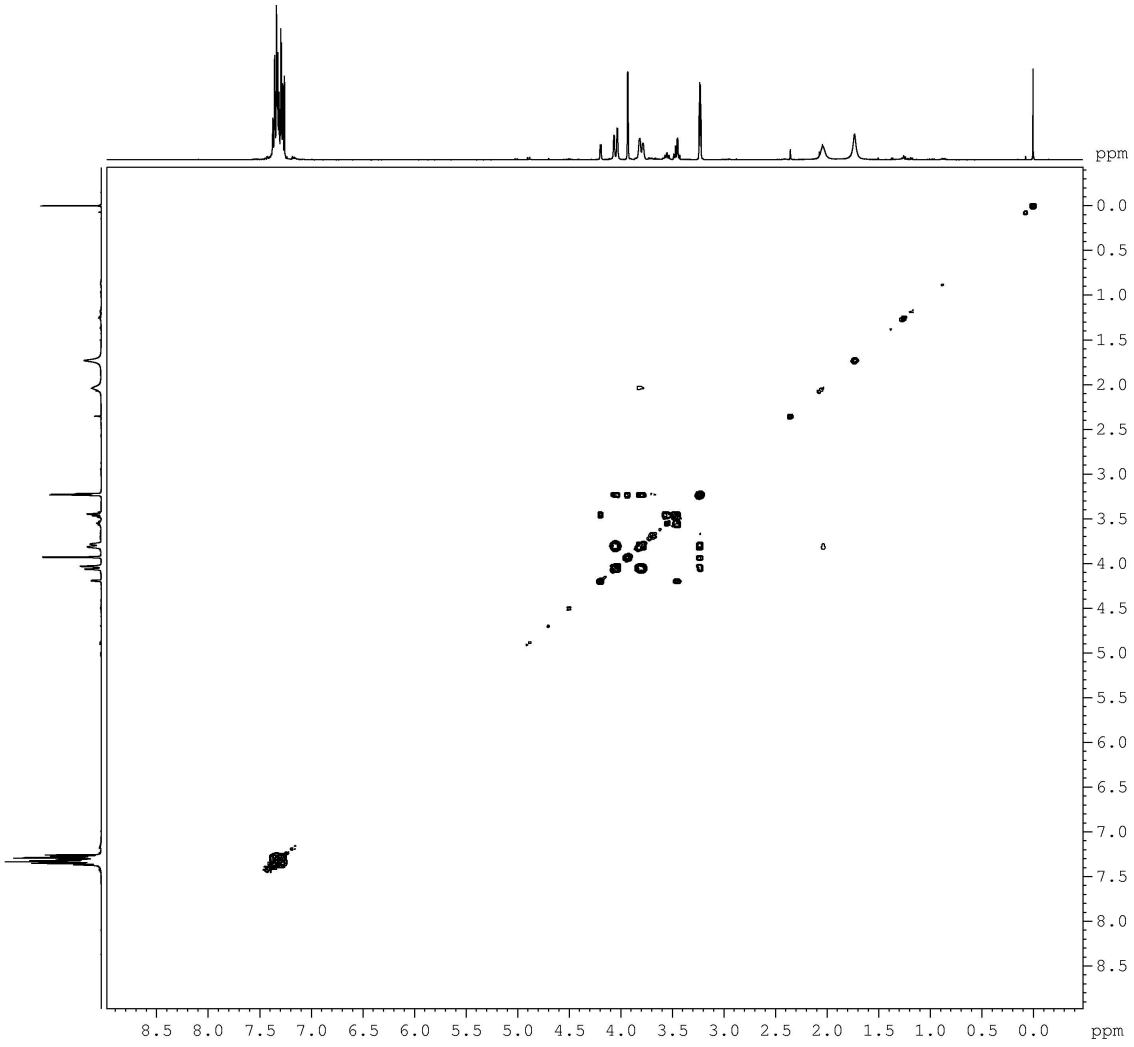
^{1}H NMR spectrum of 2a.



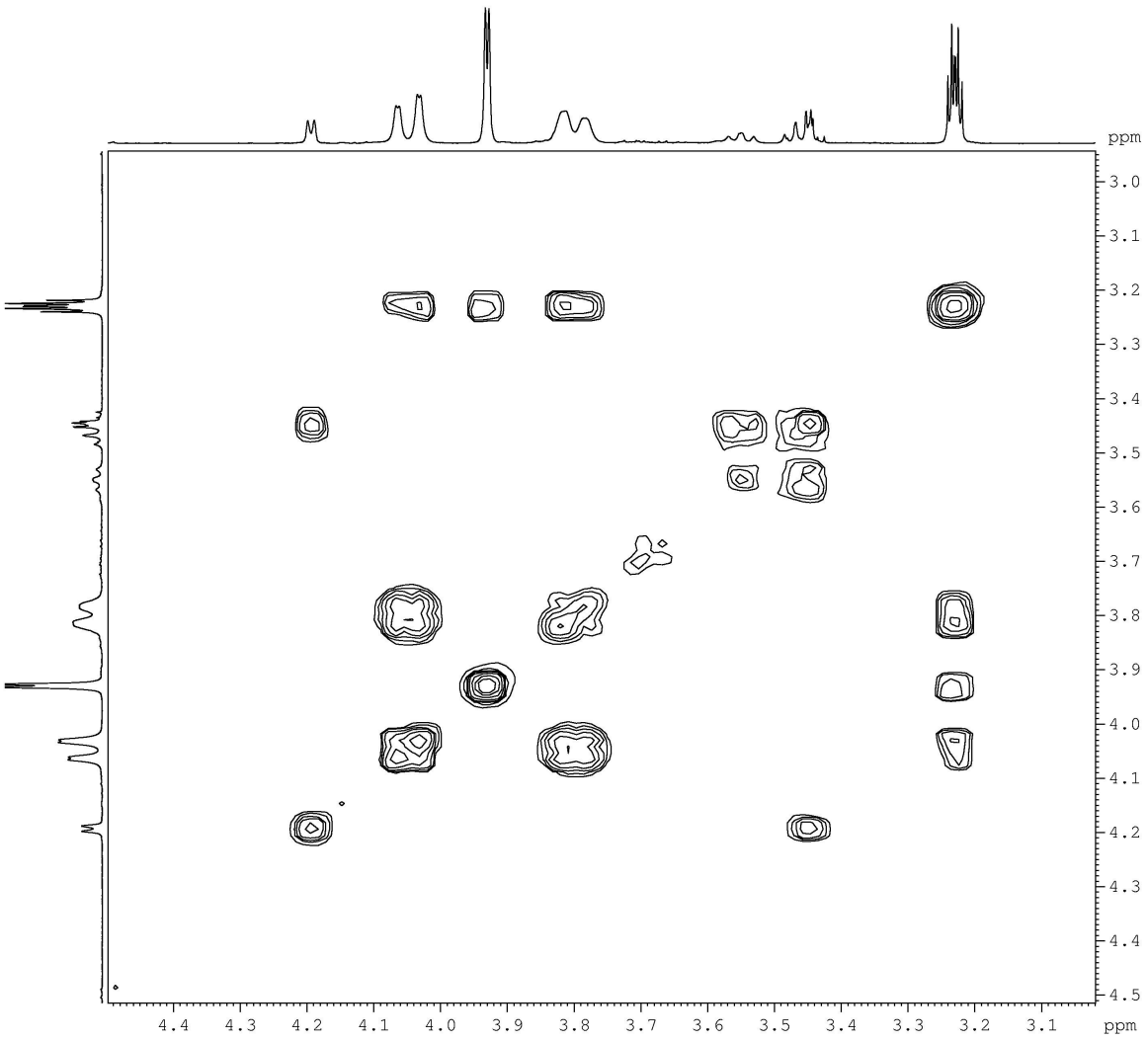
Expanded region of ^{1}H NMR spectrum of 2a.



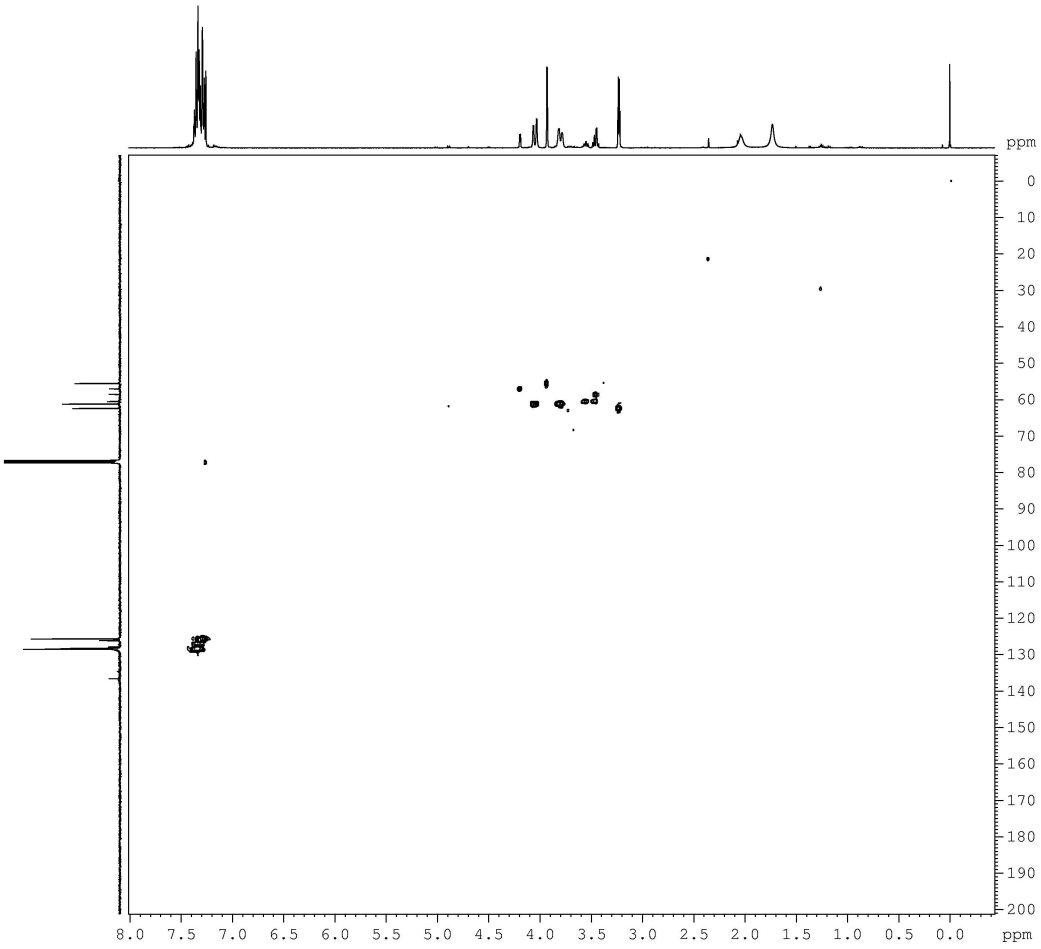
^{13}C NMR spectrum of 2a.



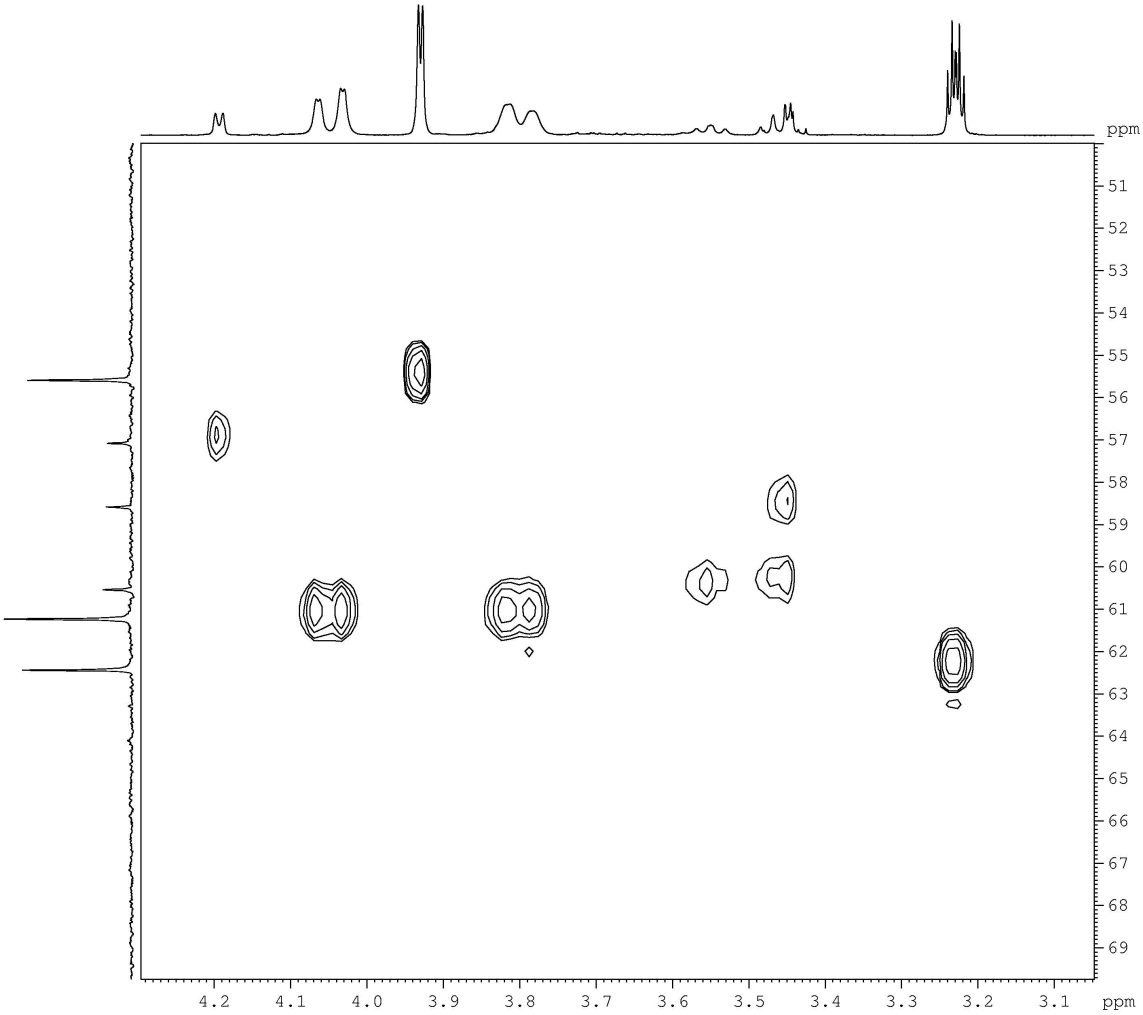
^{1}H–^{1}H Cosy NMR spectrum of 2a.



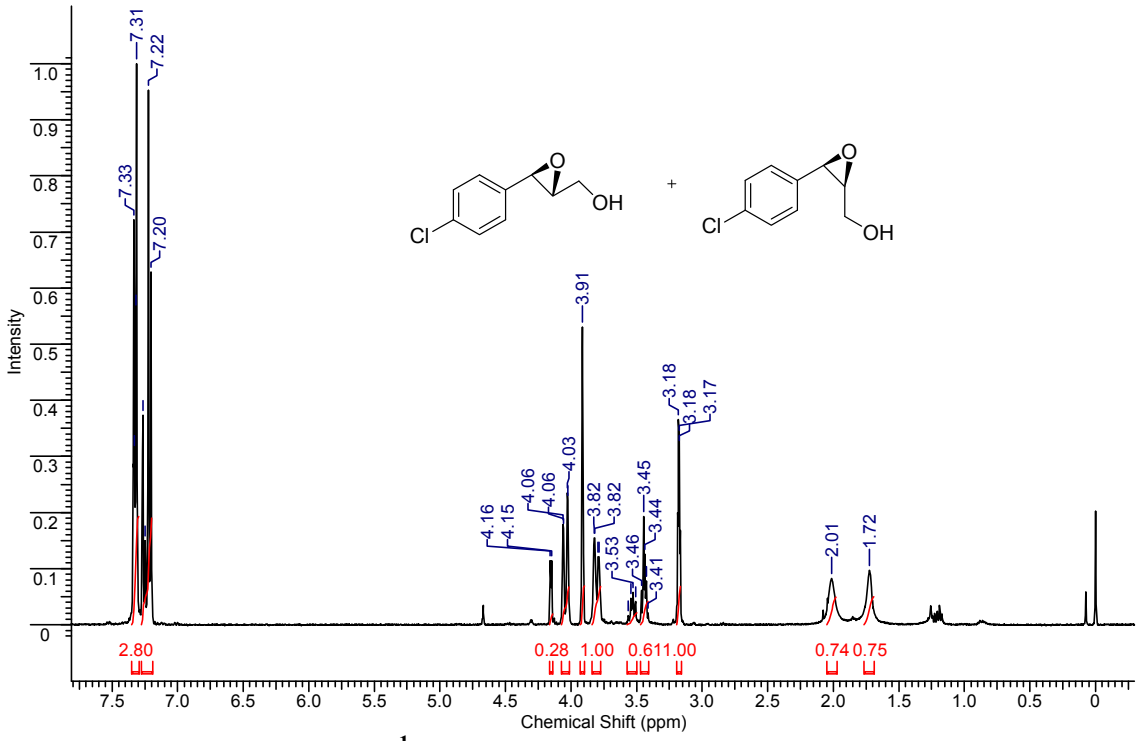
Expanded region of ^{1}H–^{1}H Cosy NMR spectrum of 2a.



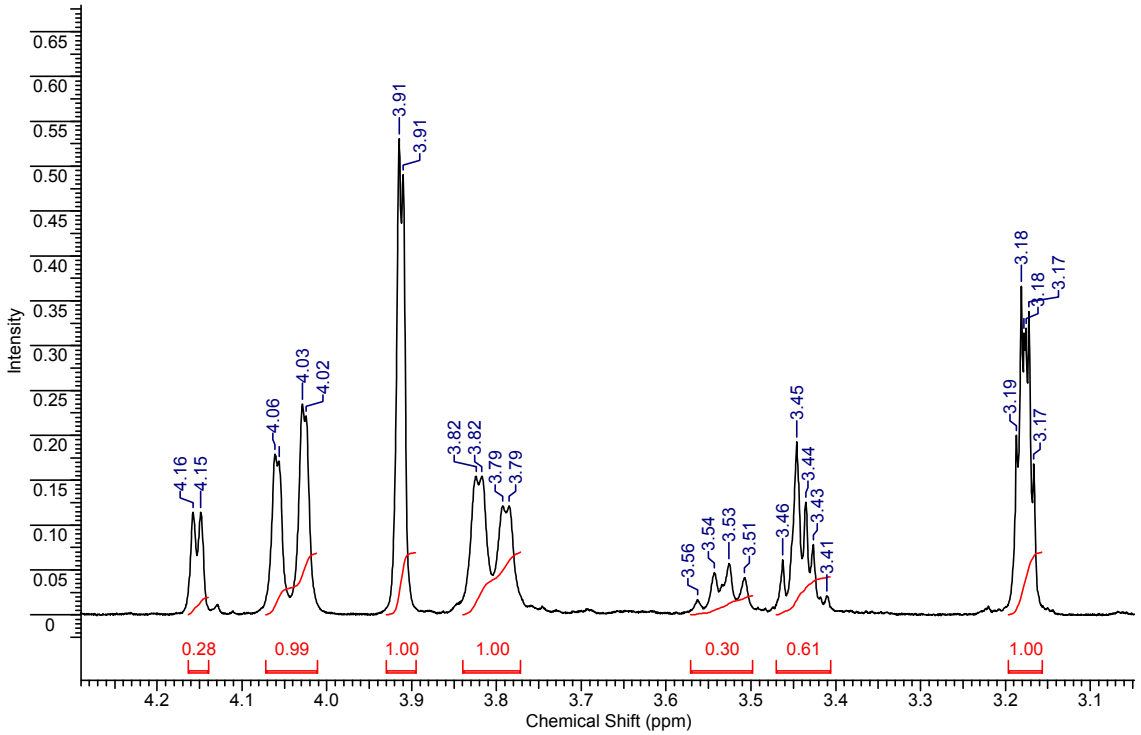
^{1}H–^{13}C HSQC NMR spectrum of 2a.



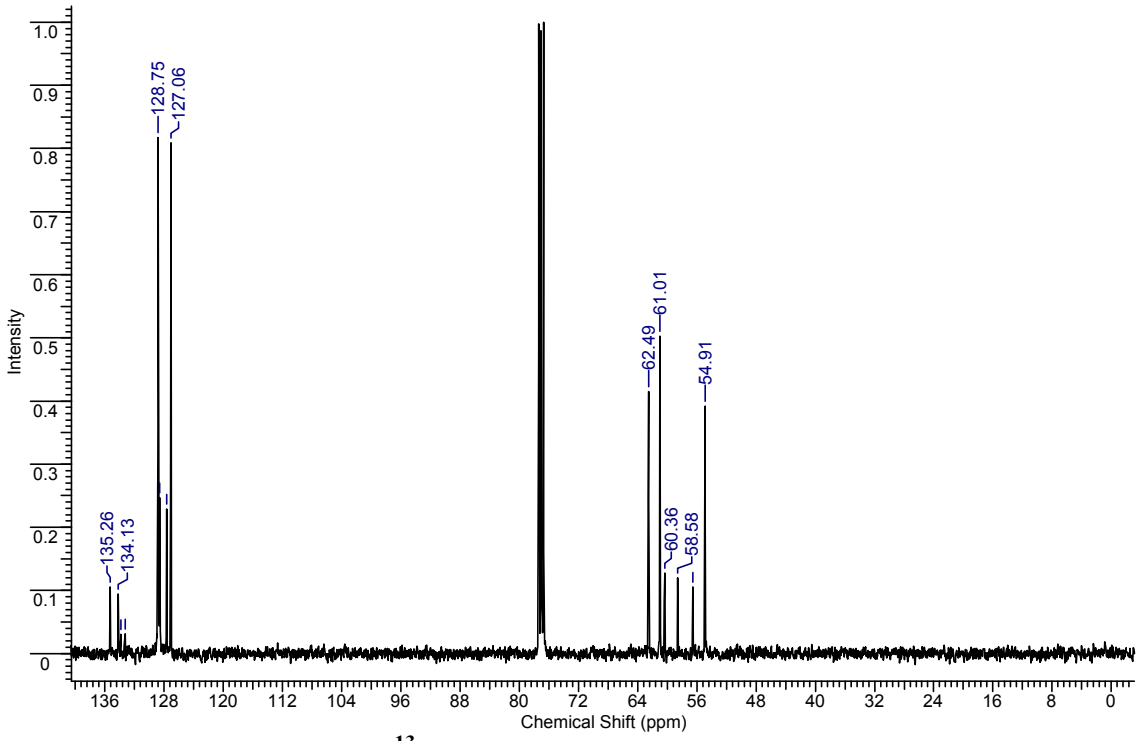
Expanded region of ^{1}H–^{13}C HSQC NMR spectrum of 2a.



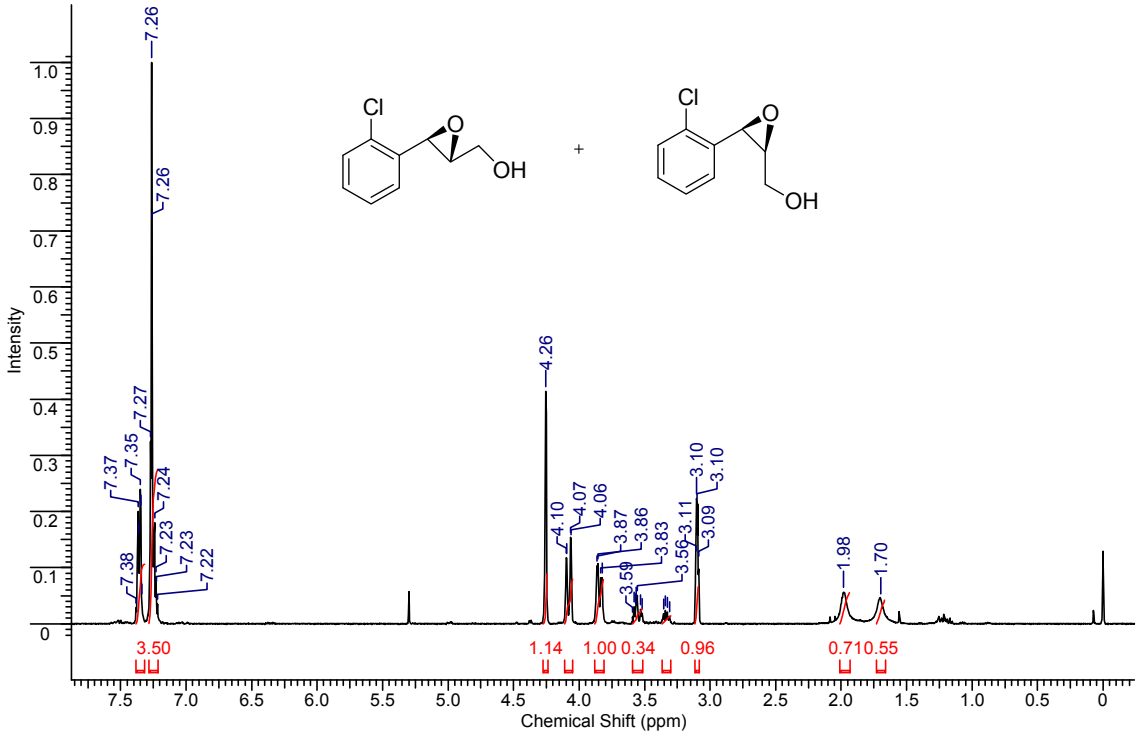
^{1}H NMR spectrum of 2b.



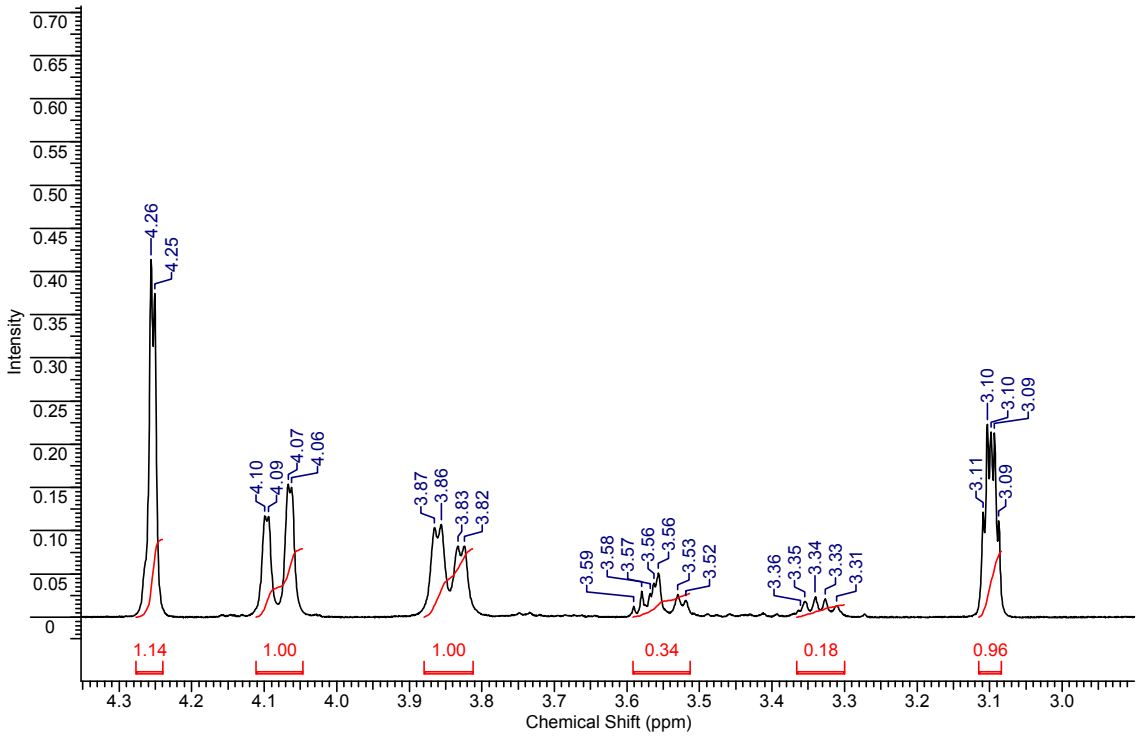
Expanded region of ^{1}H NMR spectrum of 2b.



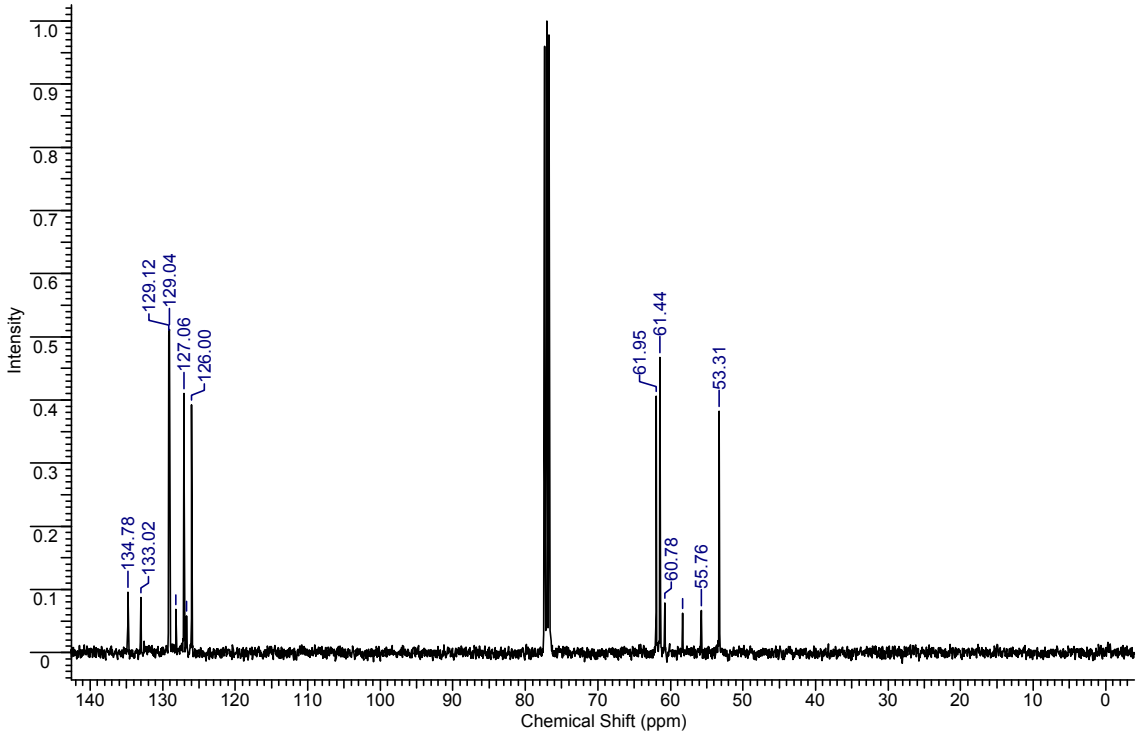
^{13}C NMR spectrum of 2b.



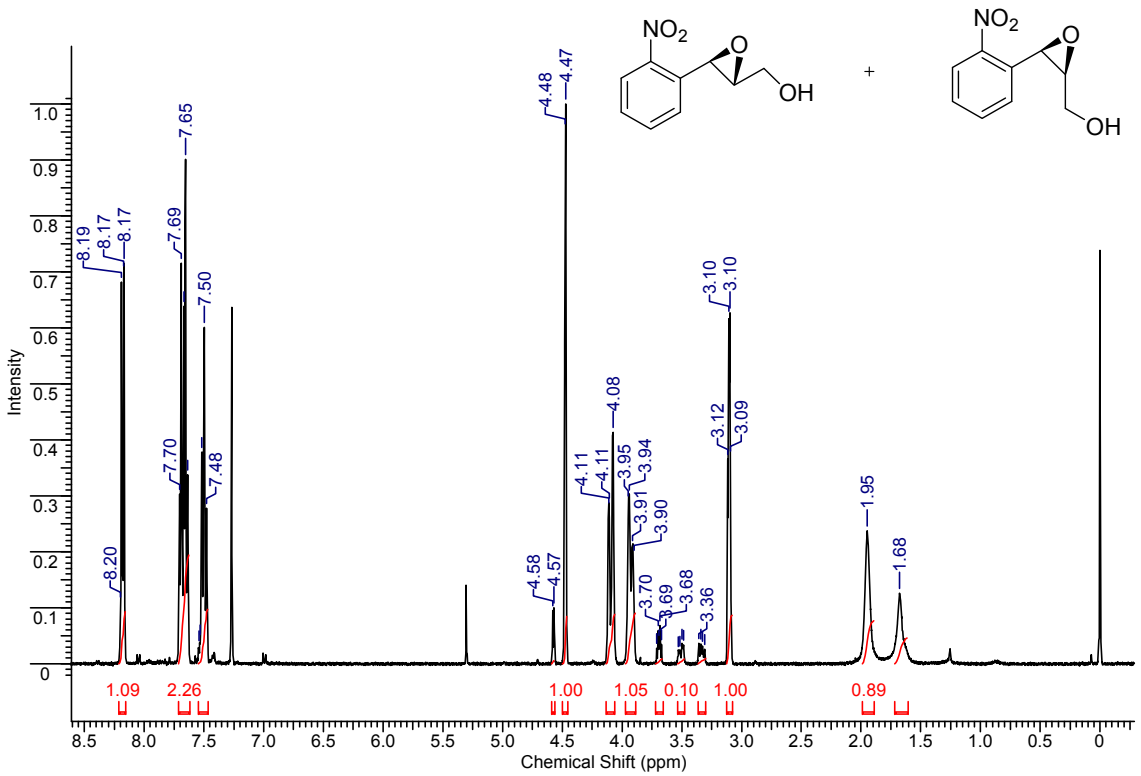
^{1}H NMR spectrum of 2c.



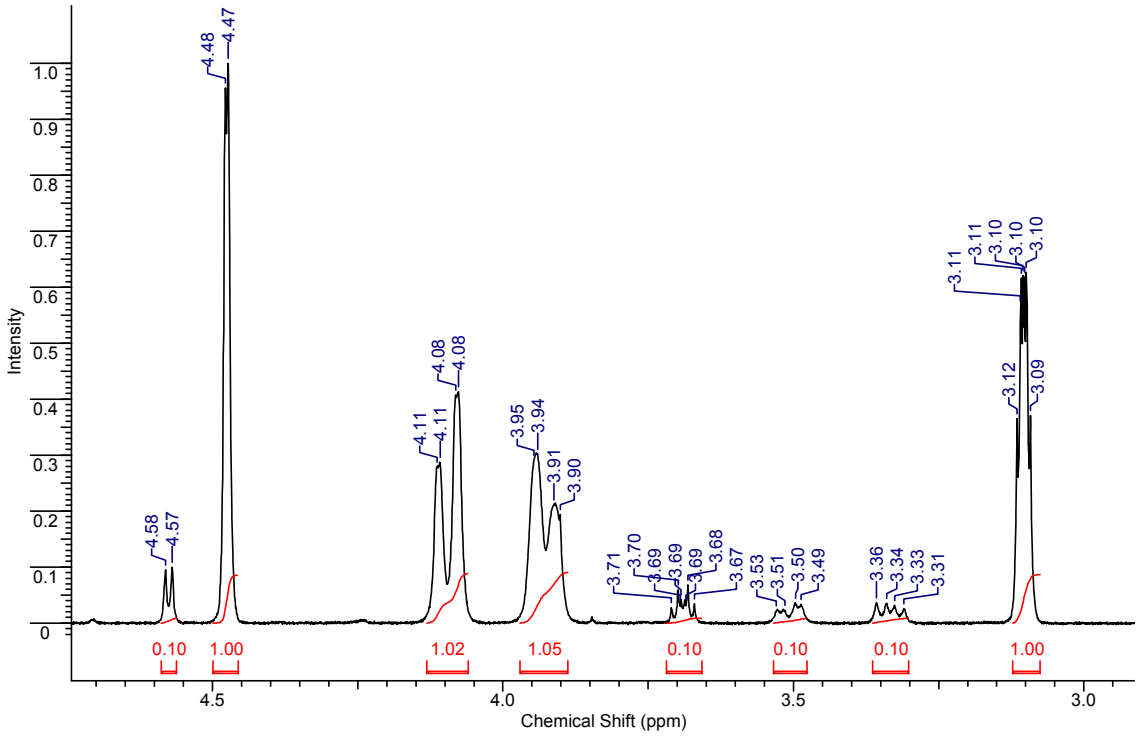
Expanded region of ^{1}H NMR spectrum of 2c.



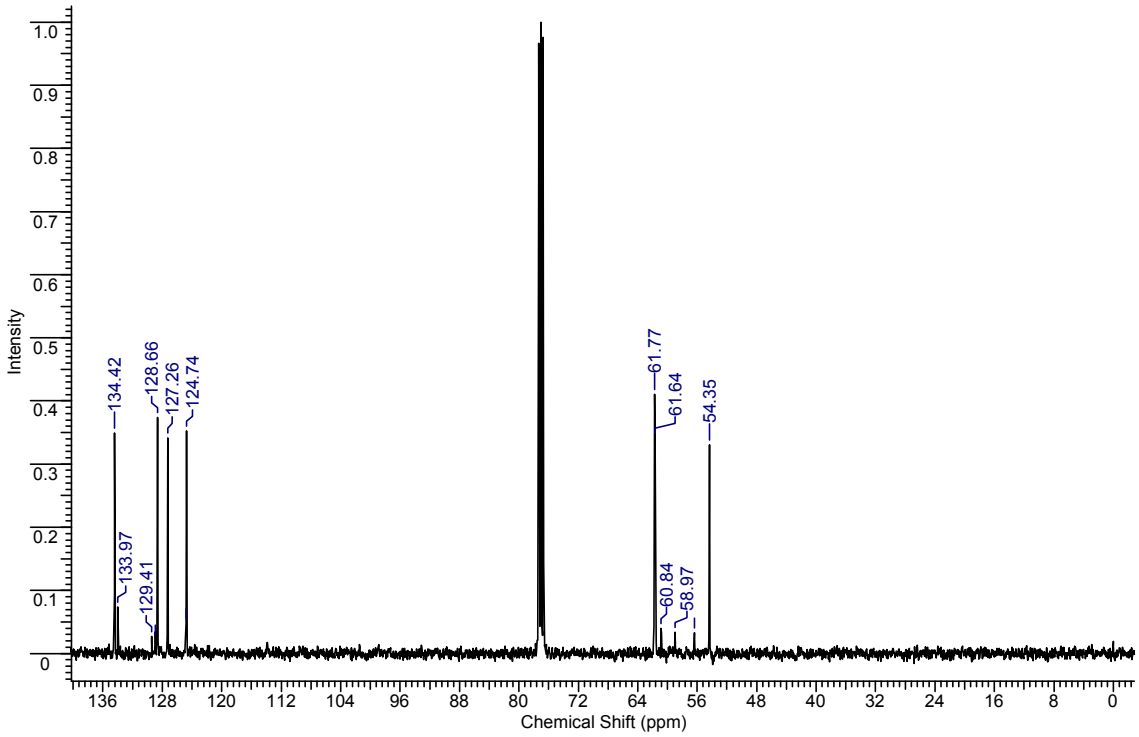
^{13}C NMR spectrum of 2c.



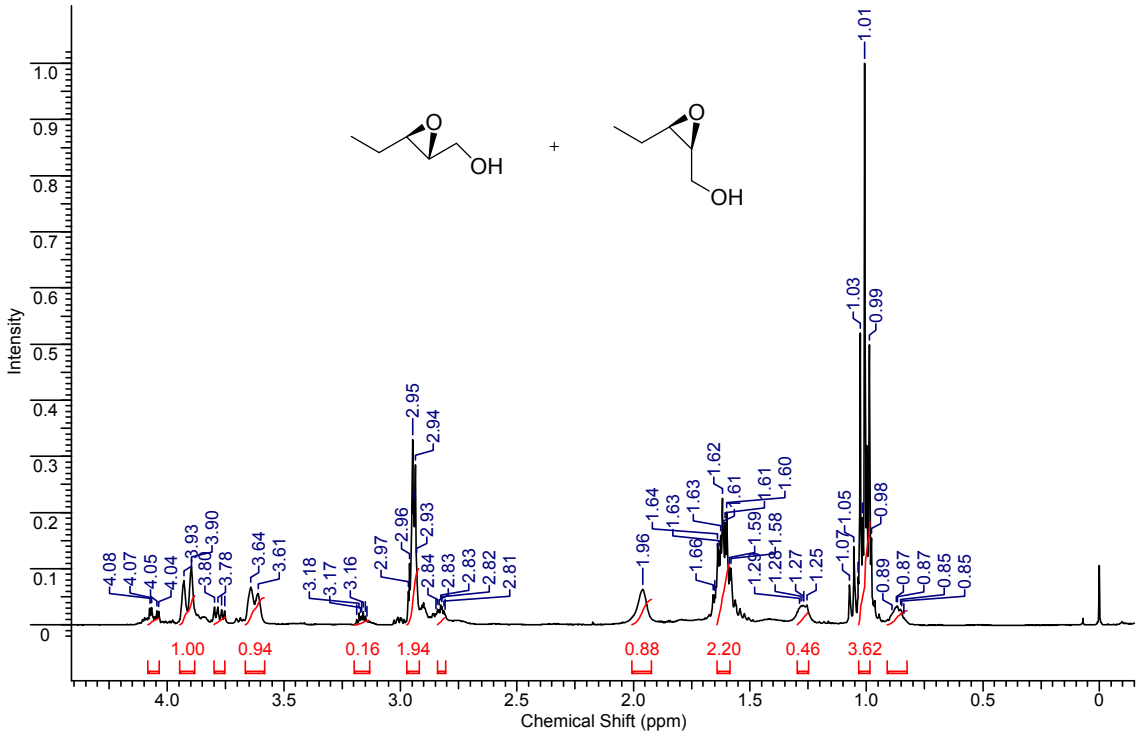
^{1}H NMR spectrum of 2d.



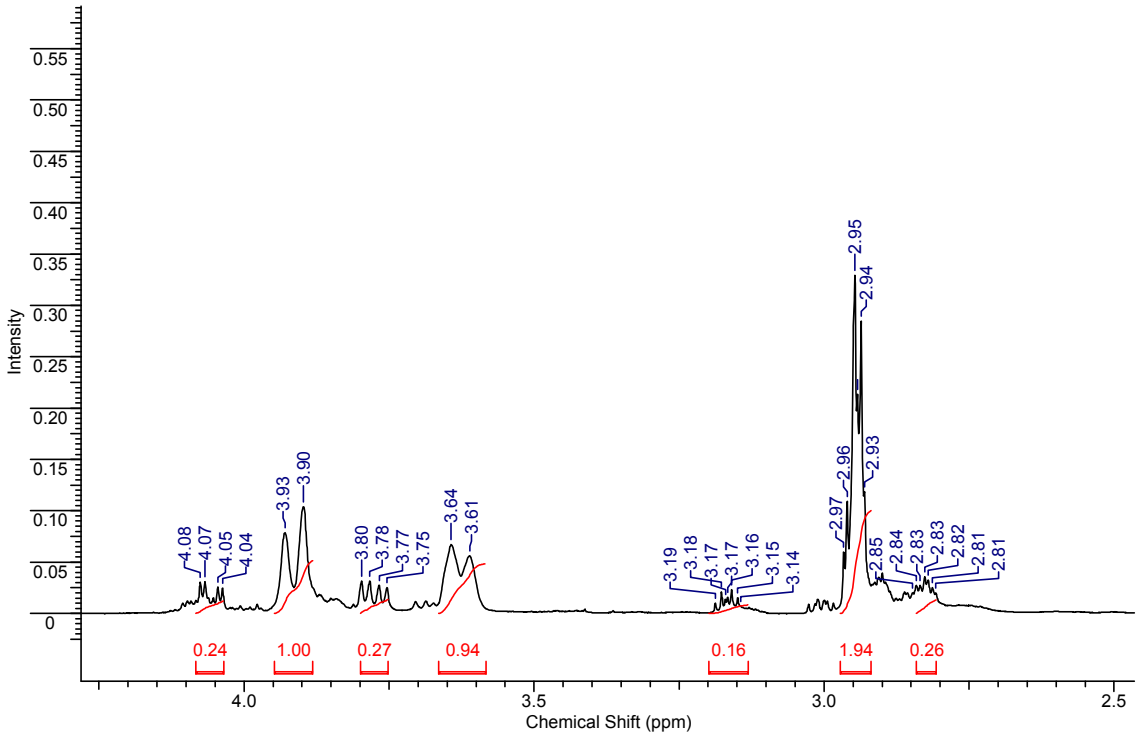
Expanded region of ^{1}H NMR spectrum of 2d.



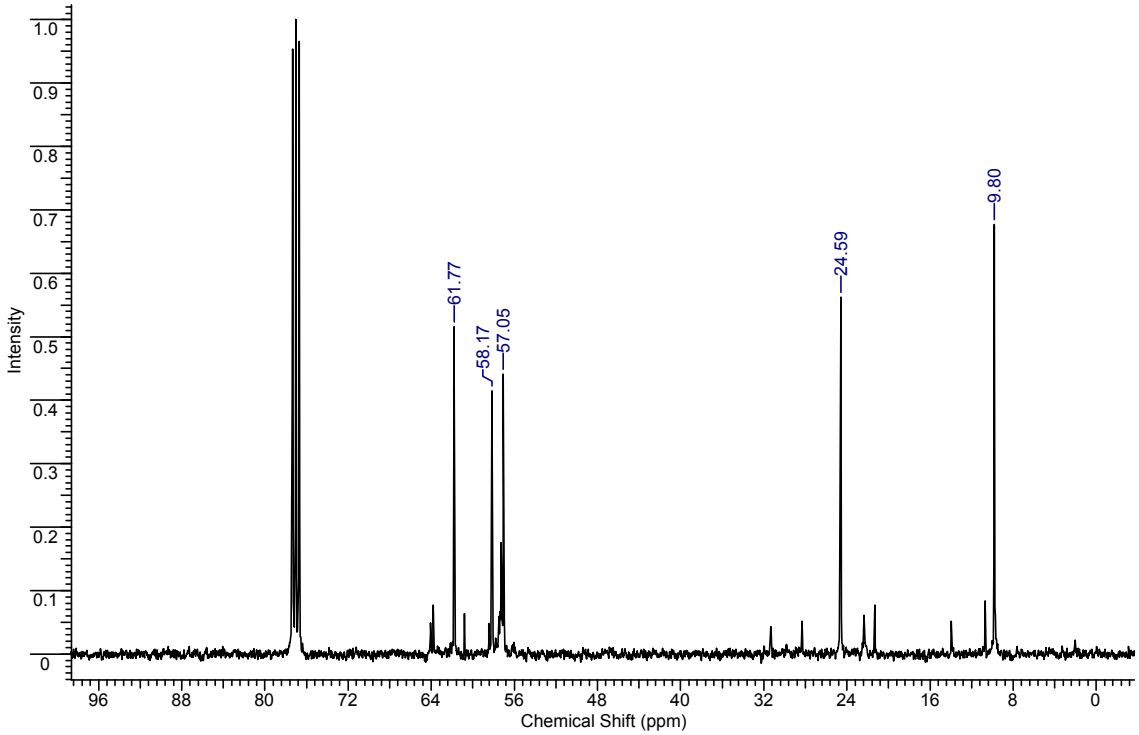
^{13}C NMR spectrum of 2d.



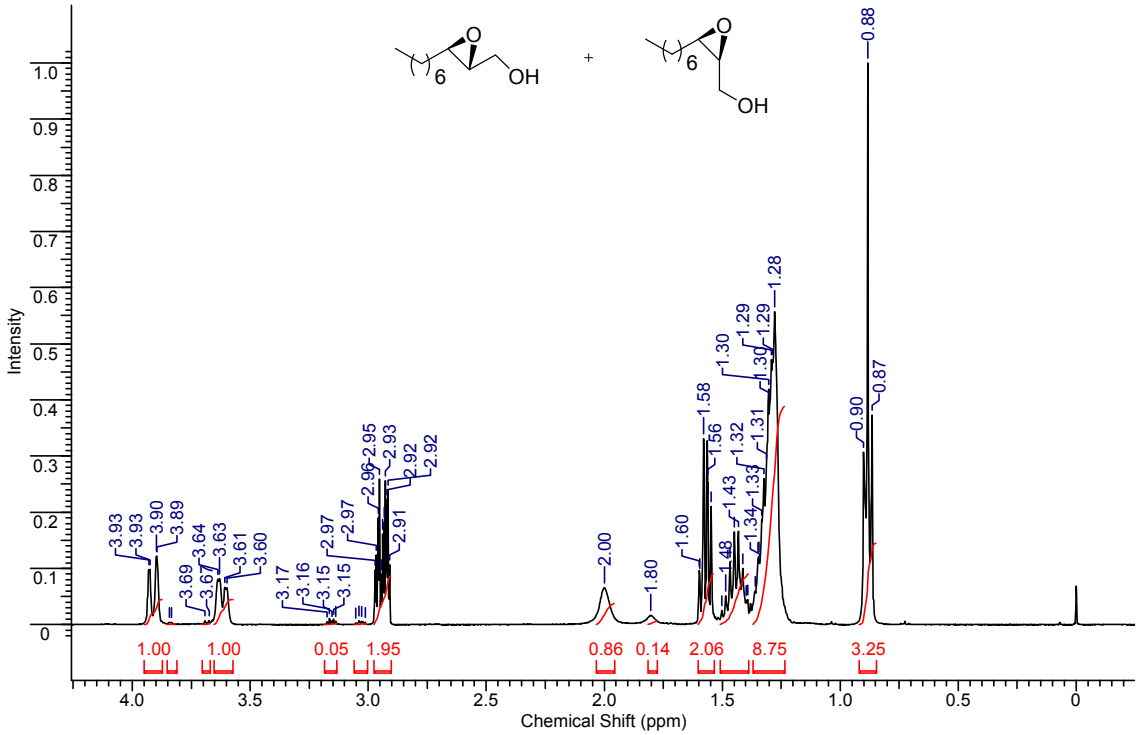
^{1}H NMR spectrum of 2e.



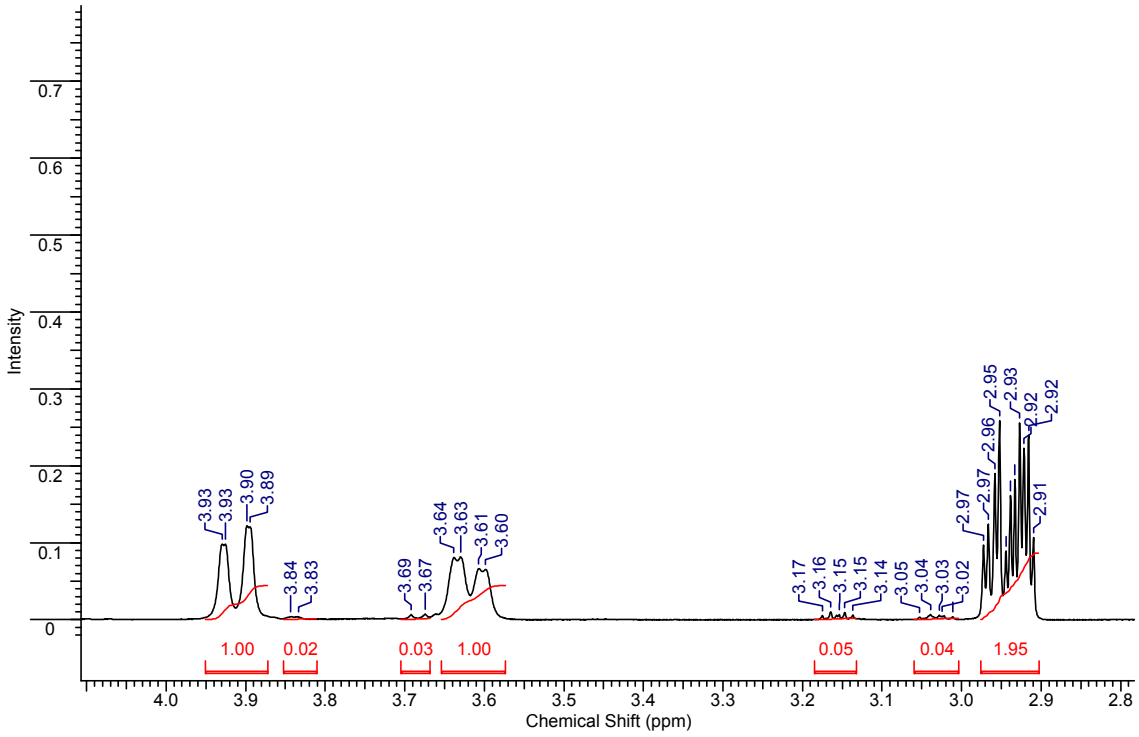
Expanded region of ^{1}H NMR spectrum of 2e.



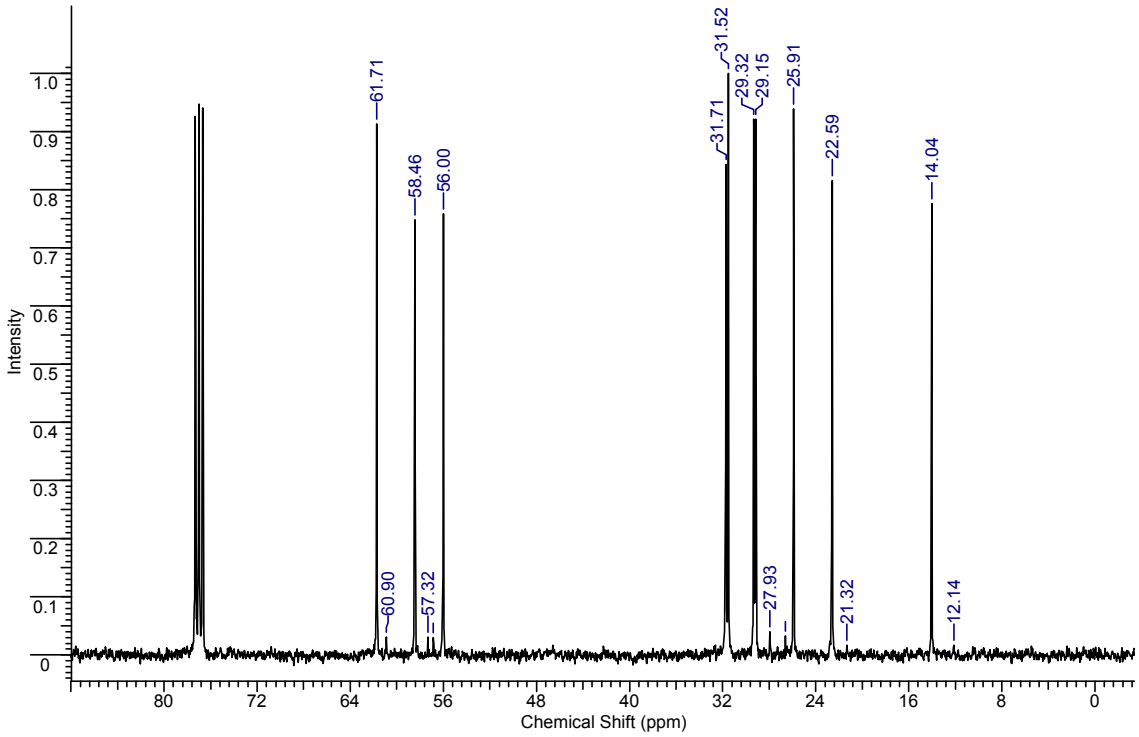
^{13}C NMR spectrum of 2e.



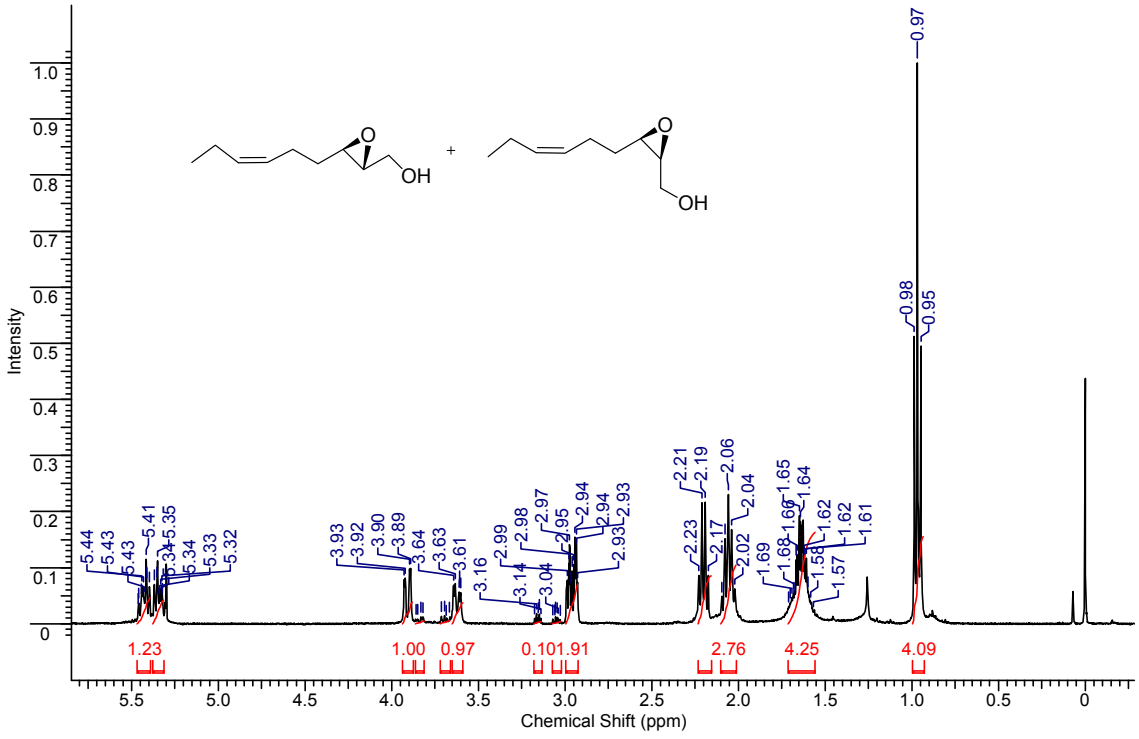
^{1}H NMR spectrum of 2f.



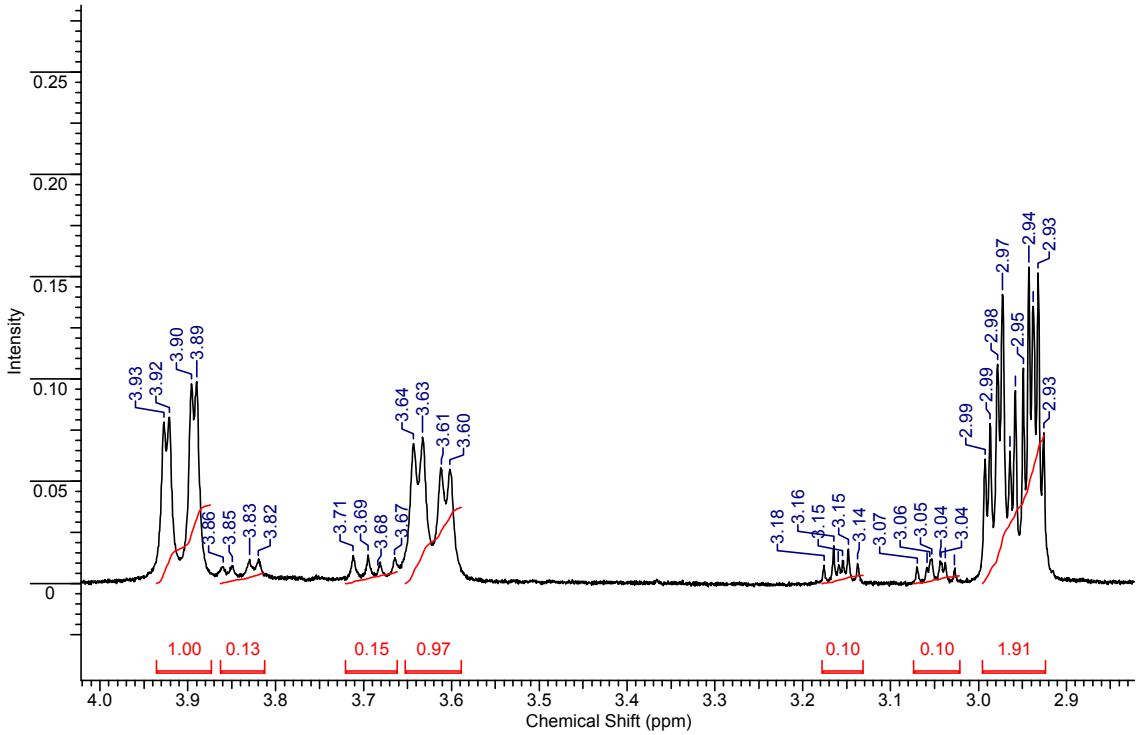
Expanded region of ^{1}H NMR spectrum of 2f.



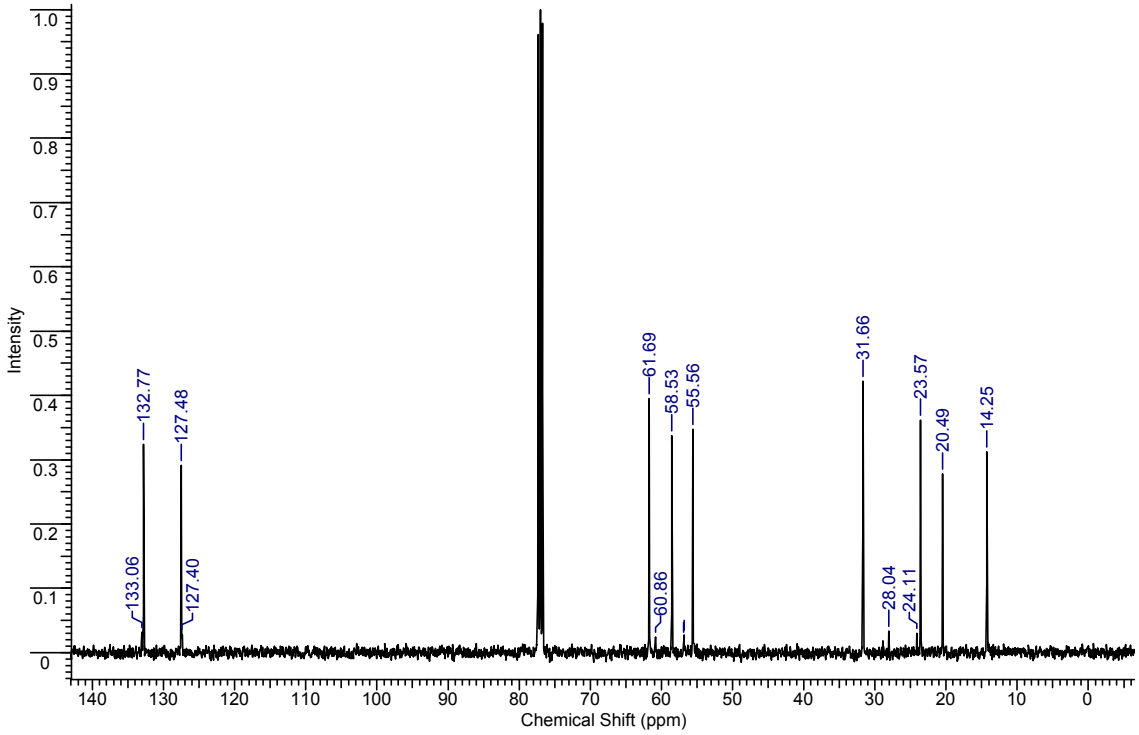
^{13}C NMR spectrum of 2f.



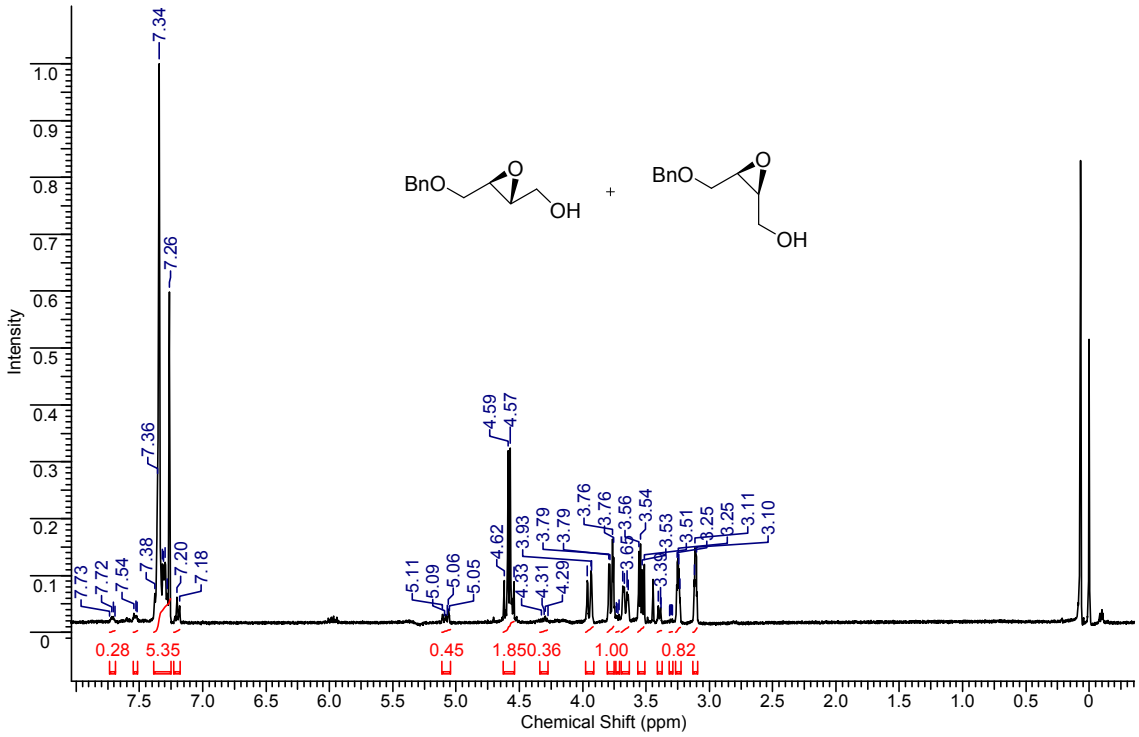
^{1}H NMR spectrum of 2g.



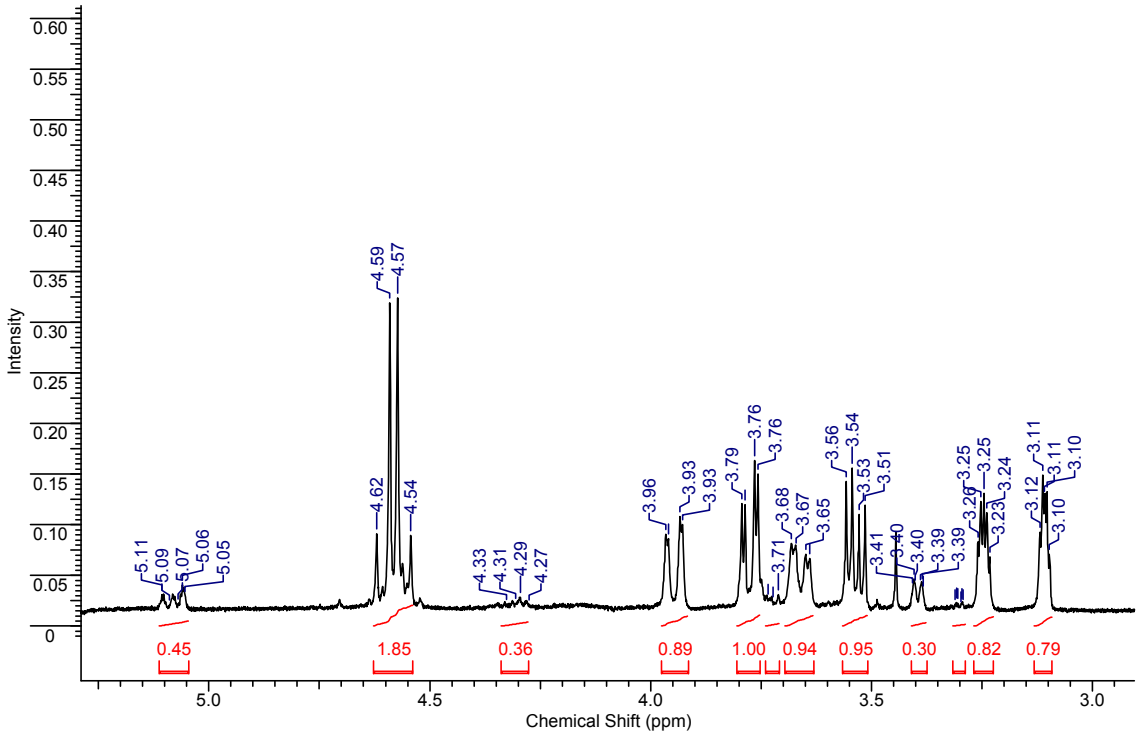
Expanded region of ^{1}H NMR spectrum of 2g.



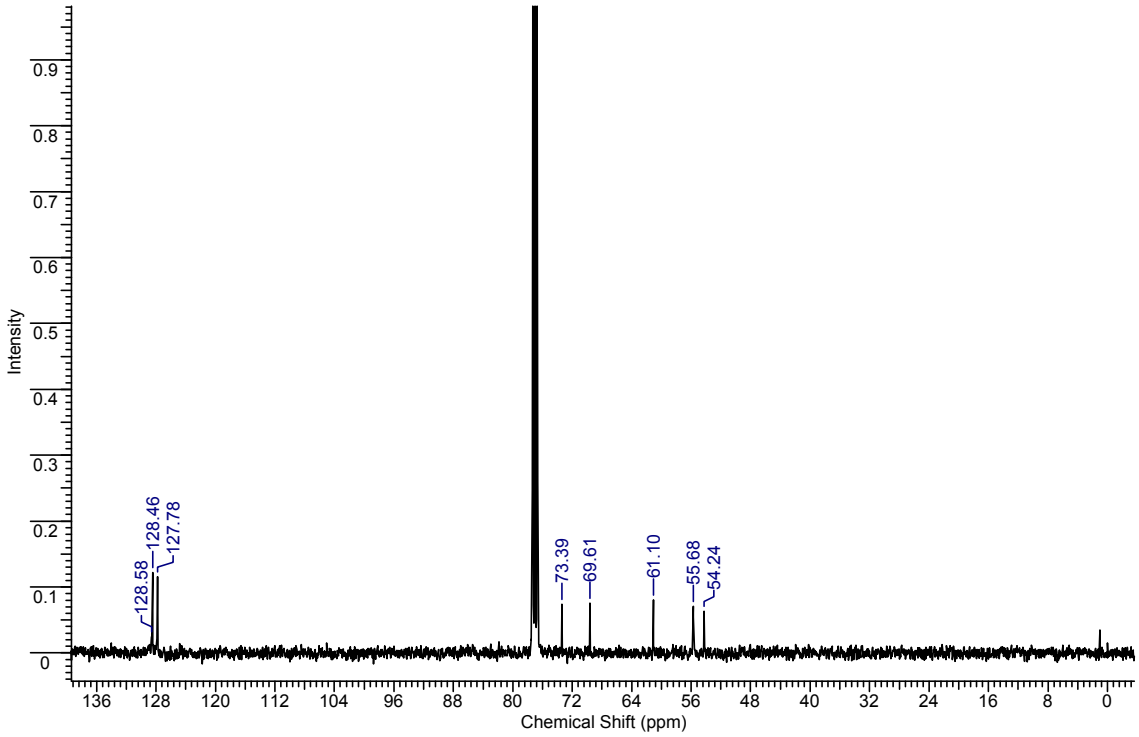
^{13}C NMR spectrum of 2g.



^{1}H NMR spectrum of 2h.

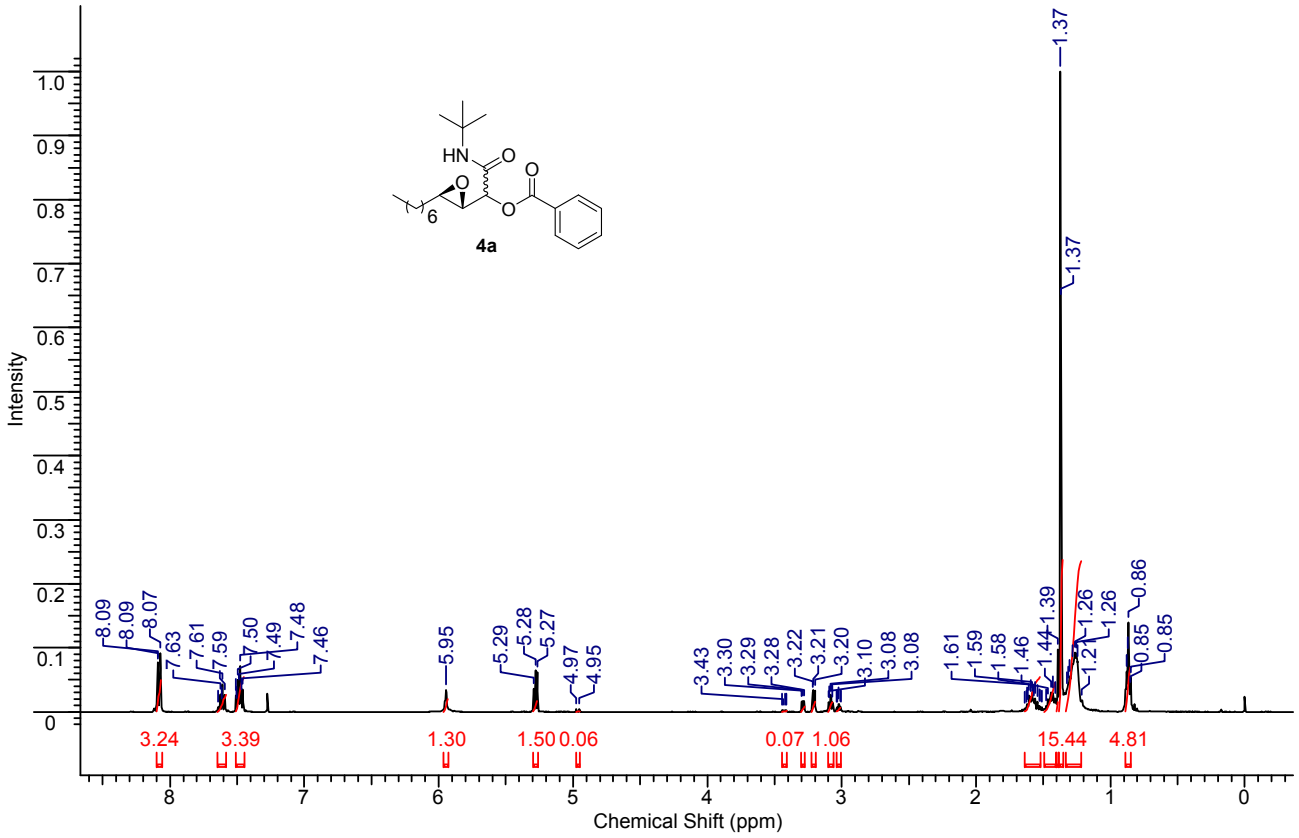


Expanded region of ^{1}H NMR spectrum of 2h.

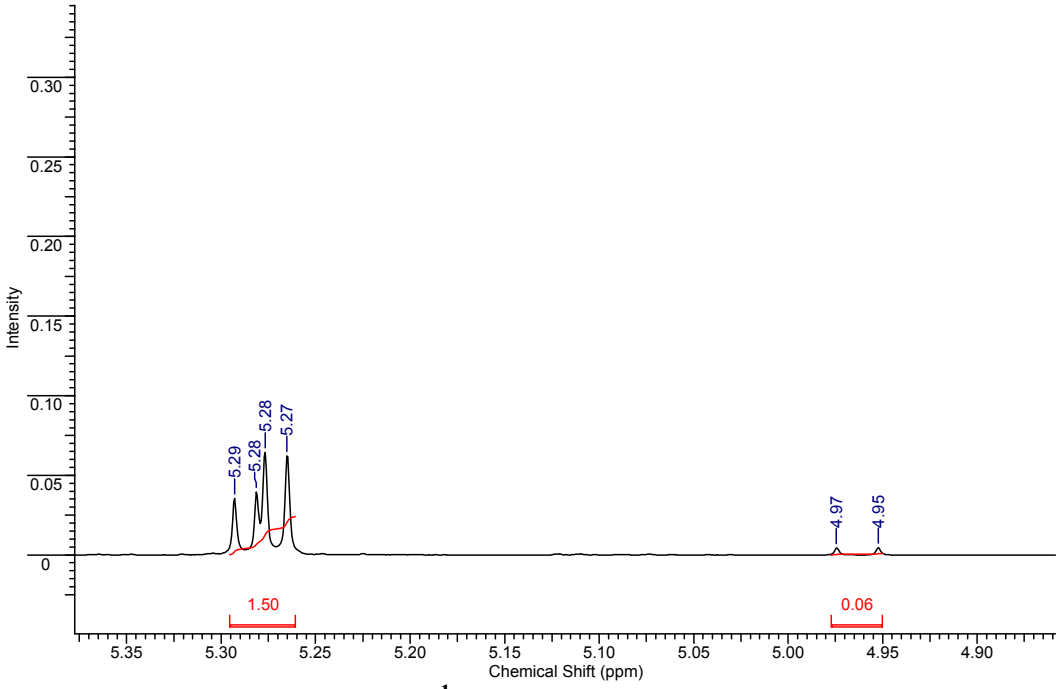


^{13}C NMR spectrum of 2h.

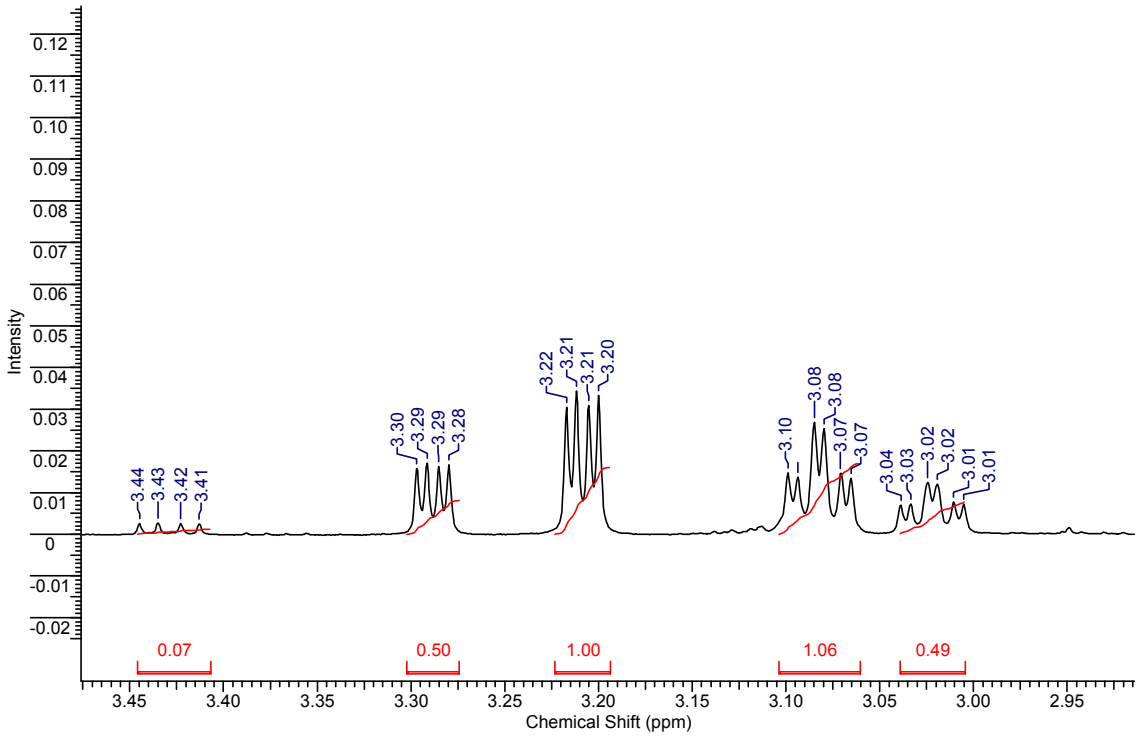
8. ^{1}H, ^{13}C, $^{1}H–^{1}H$ Cosy and $^{1}H–^{13}C$ HSQC NMR spectra of Passerini products 4a-f.



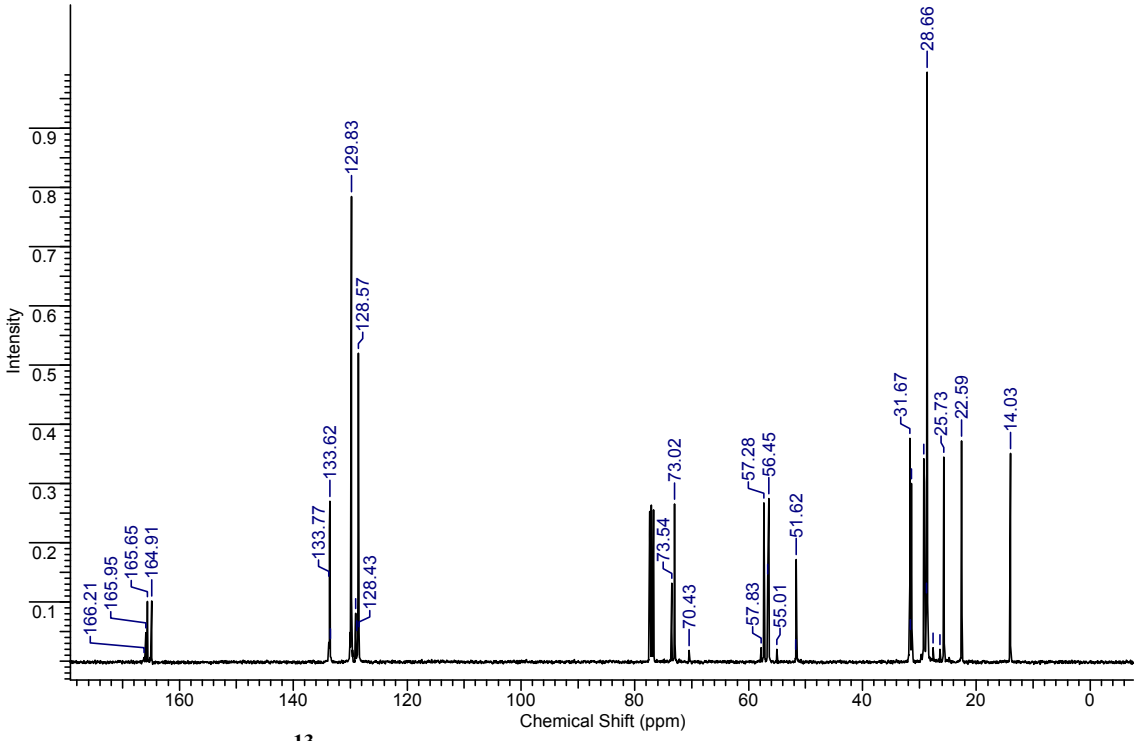
^{1}H NMR espectrum of 4a.



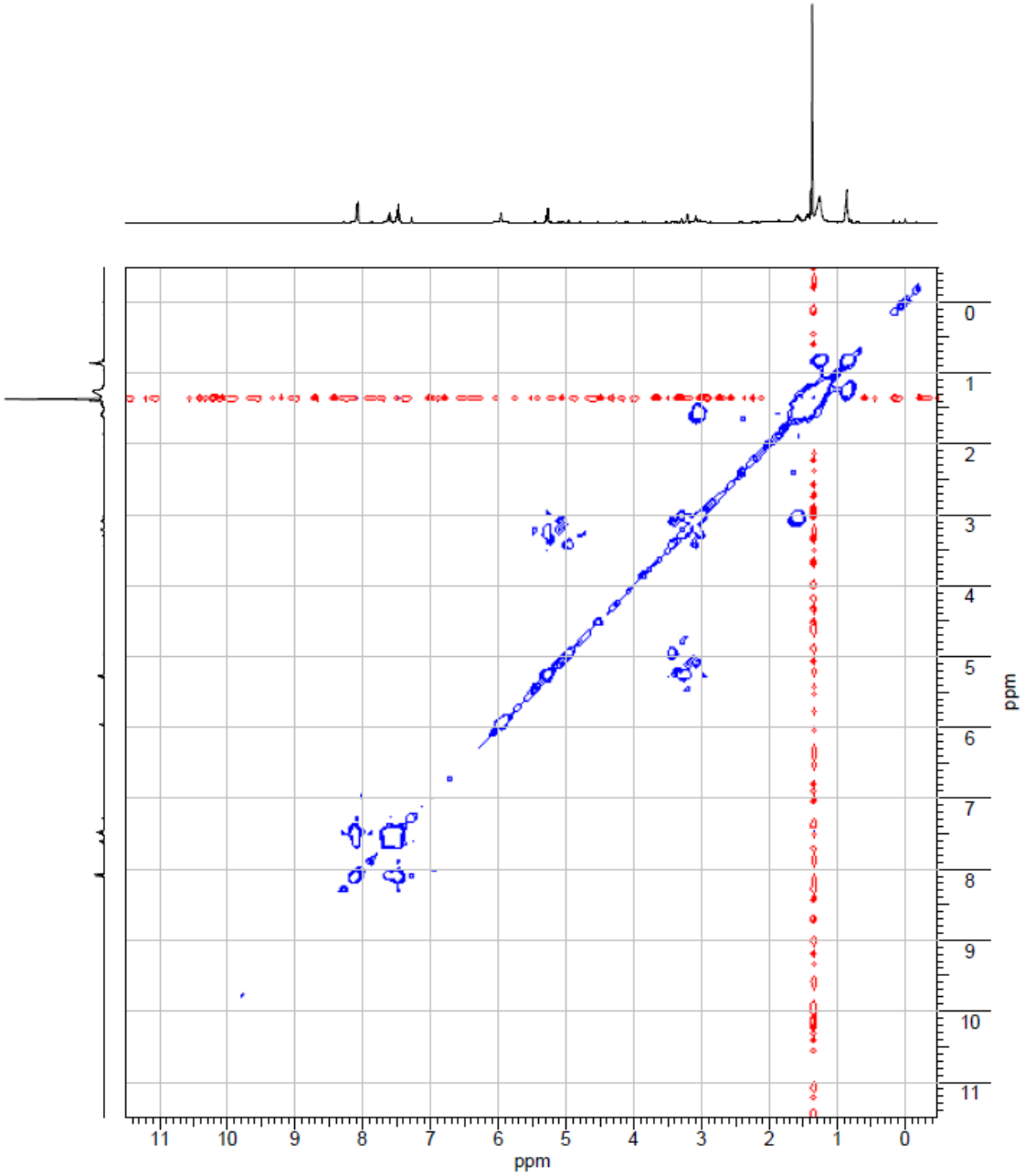
Expanded region of ^{1}H NMR espectrum of 4a.



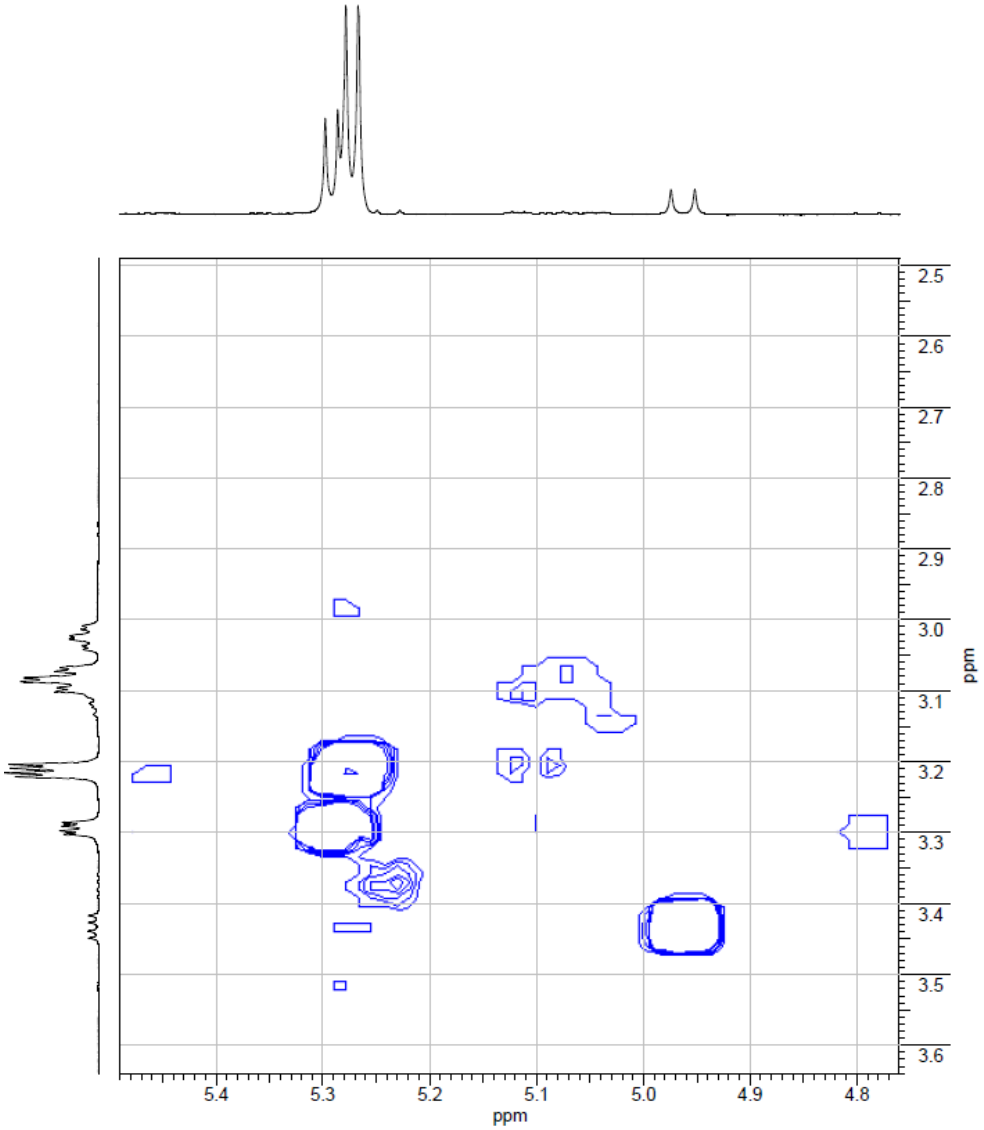
Expanded region of ^{1}H NMR espectrum of 4a.



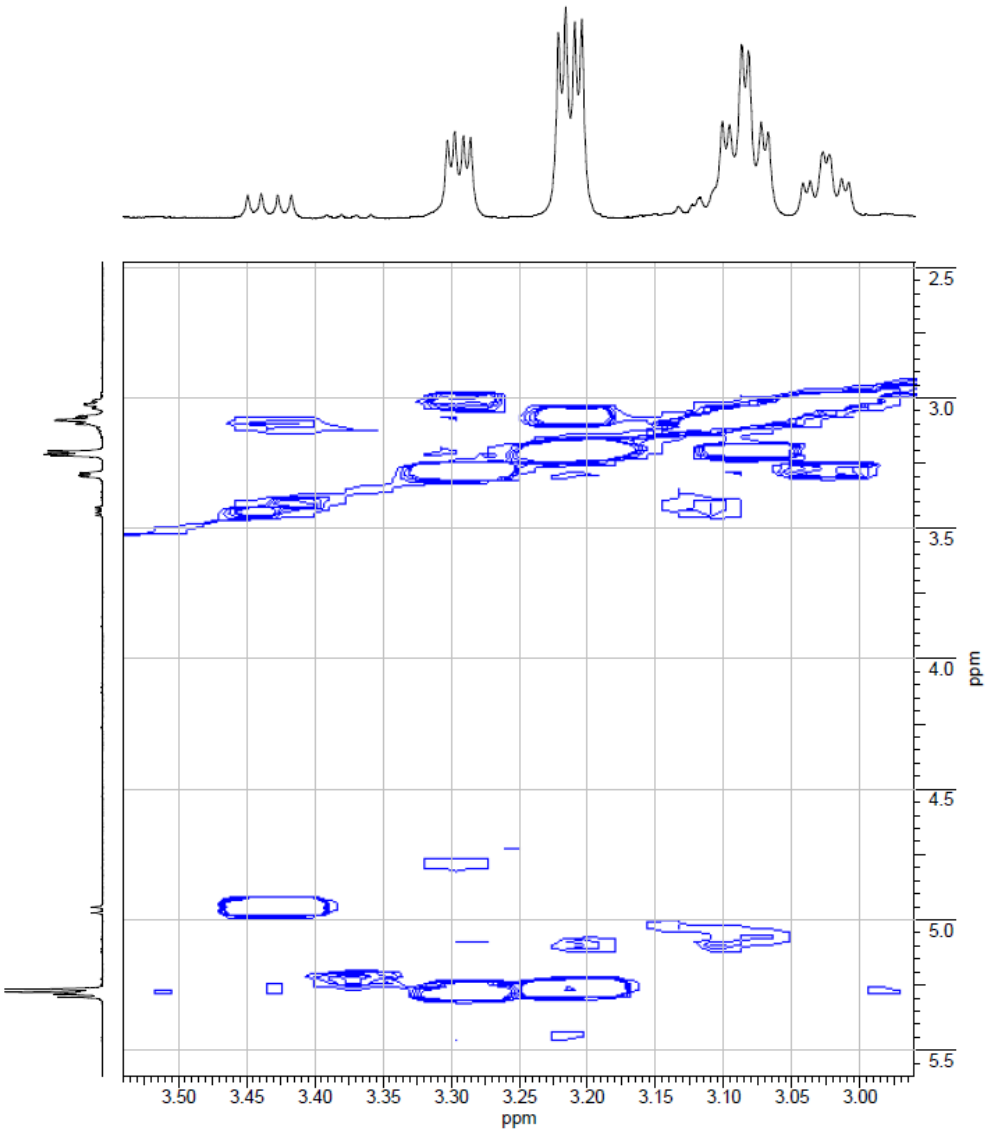
^{13}C NMR espectrum of 4a.



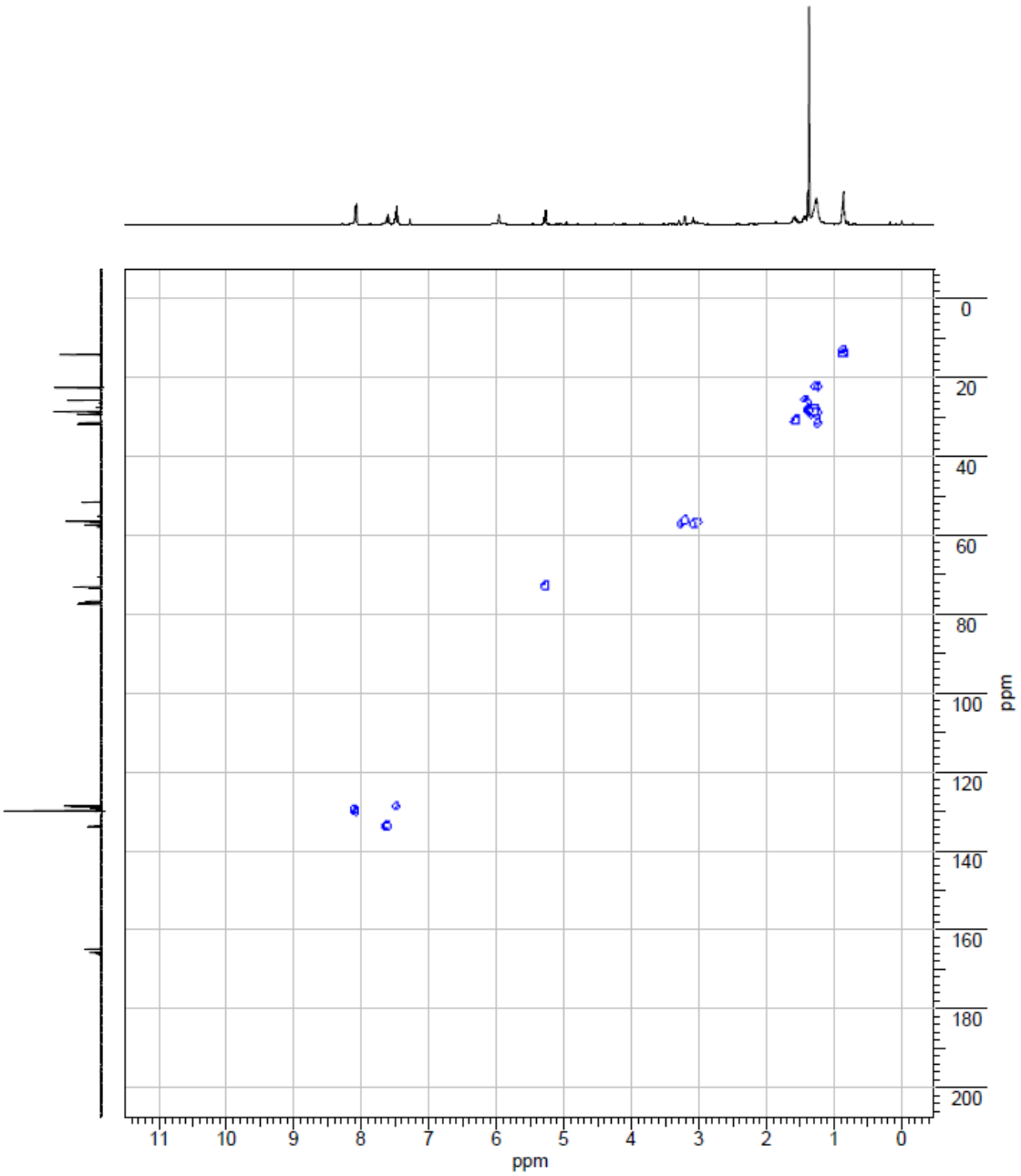
^{1}H–^{1}H Cosy NMR spectrum of 4a.



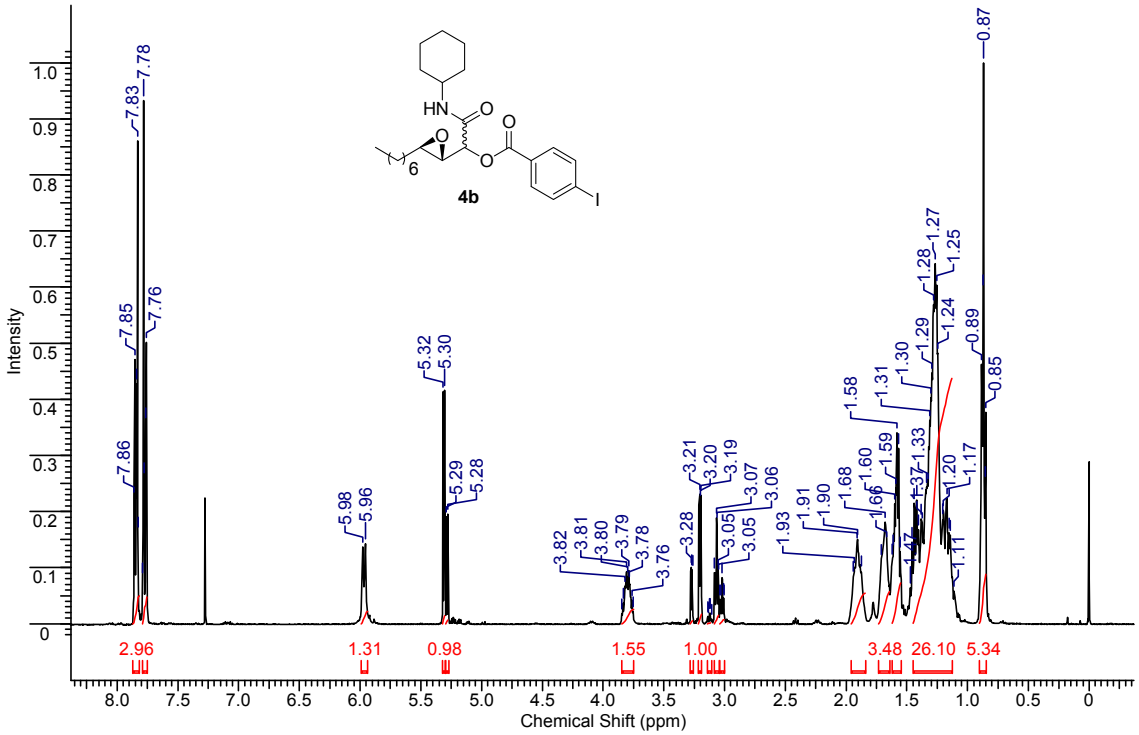
Expanded region of $^{1}H–^{1}H$ Cosy NMR spectrum of 4a.



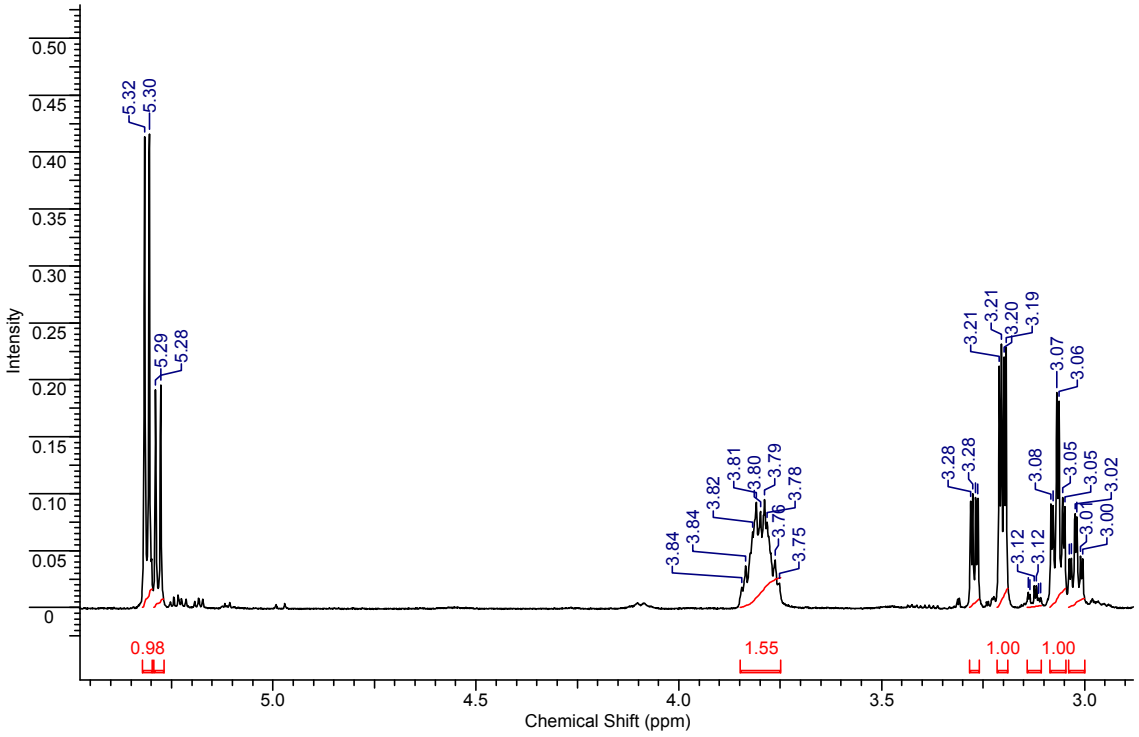
Expanded region of ^{1}H–^{1}H Cosy NMR spectrum of 4a.



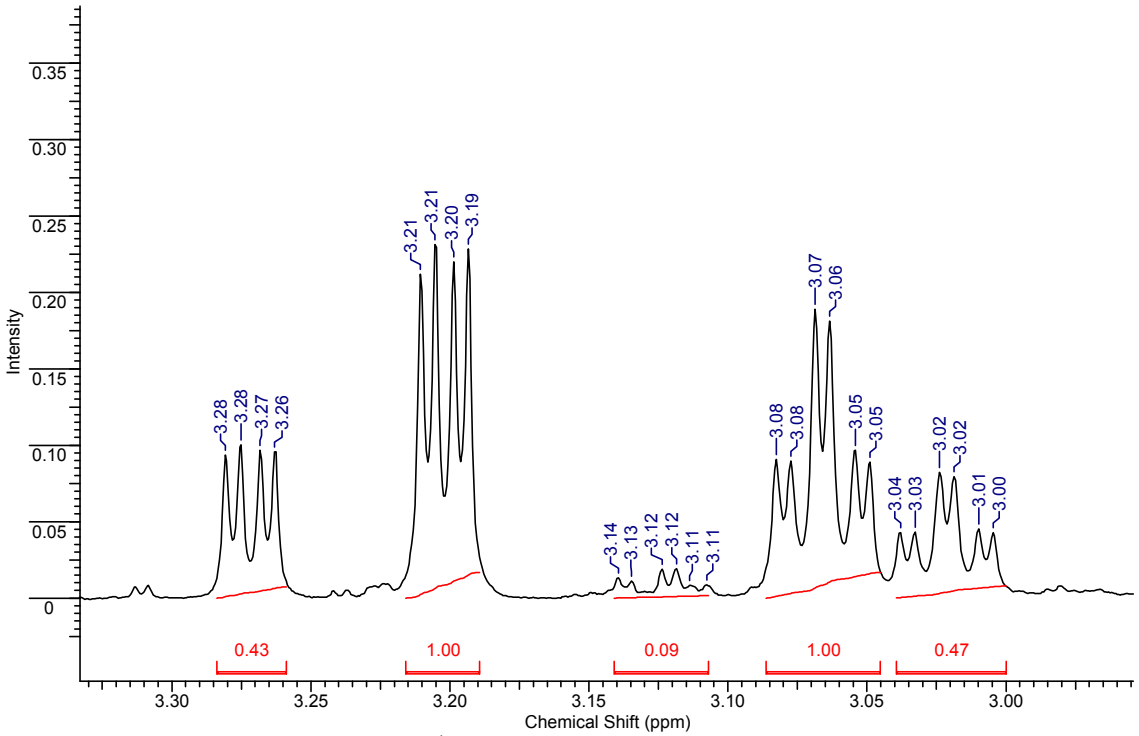
^{1}H–^{13}C HSQC NMR spectrum of 4a.



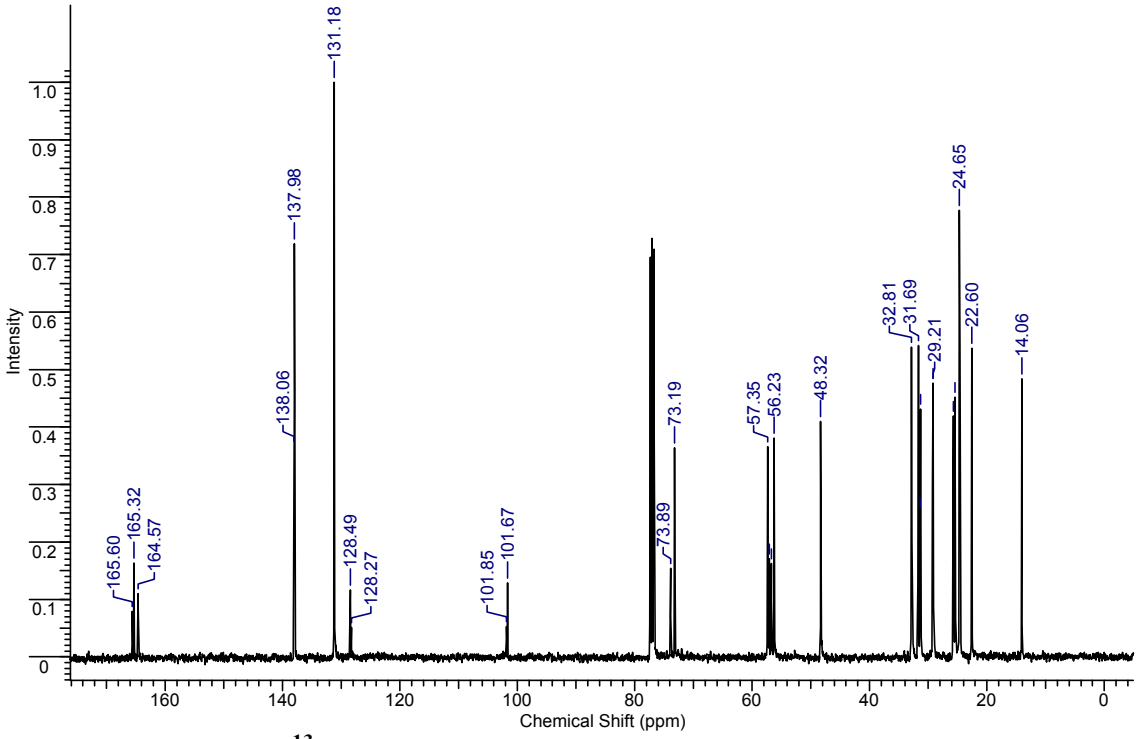
^{1}H NMR espectrum of 4b.



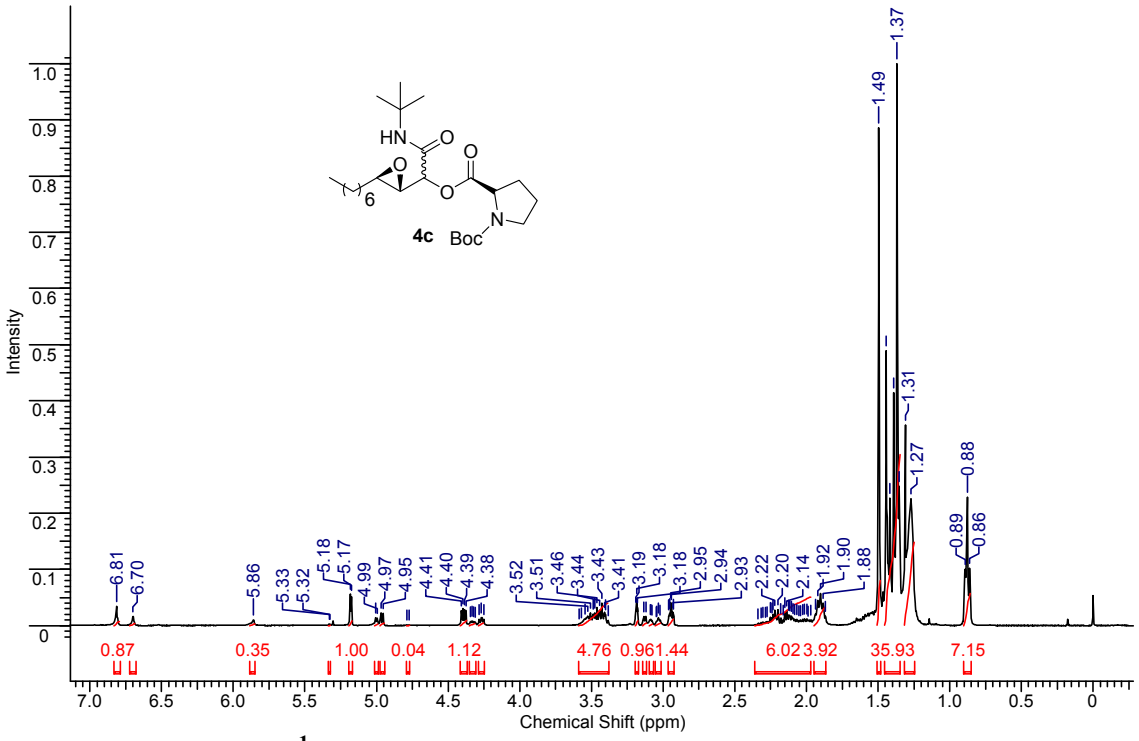
Expanded region of ^{1}H NMR espectrum of 4b.



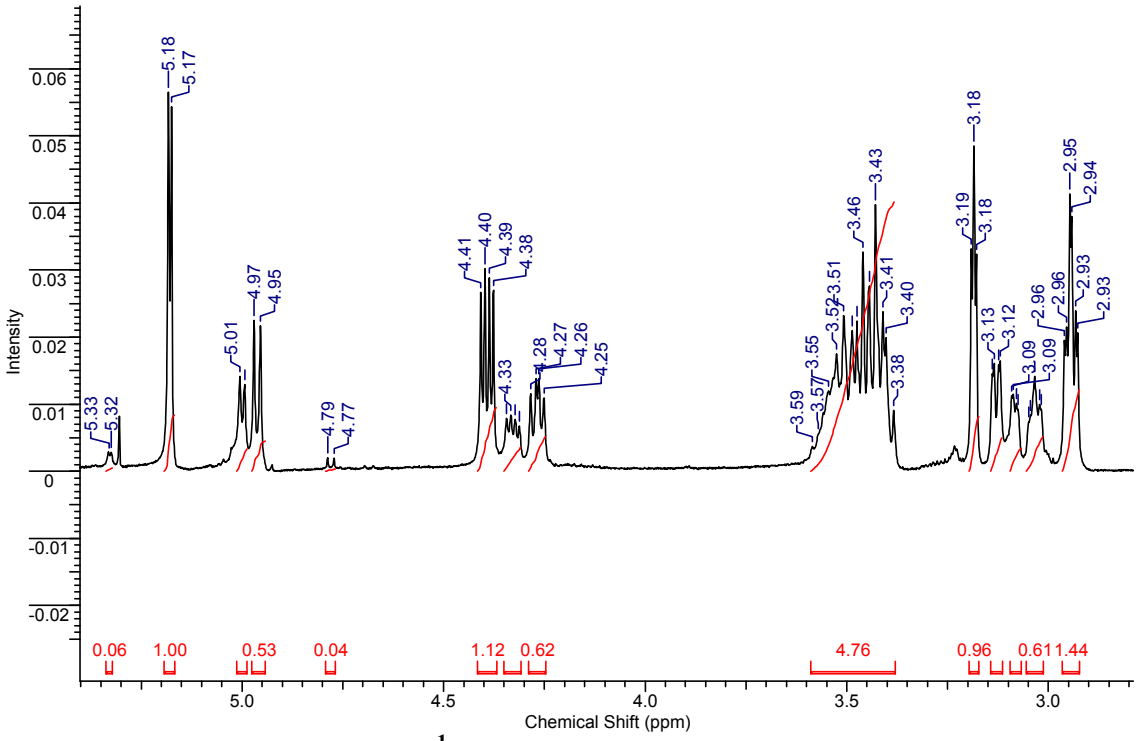
Expanded region of ^{1}H NMR espectrum of 4b.



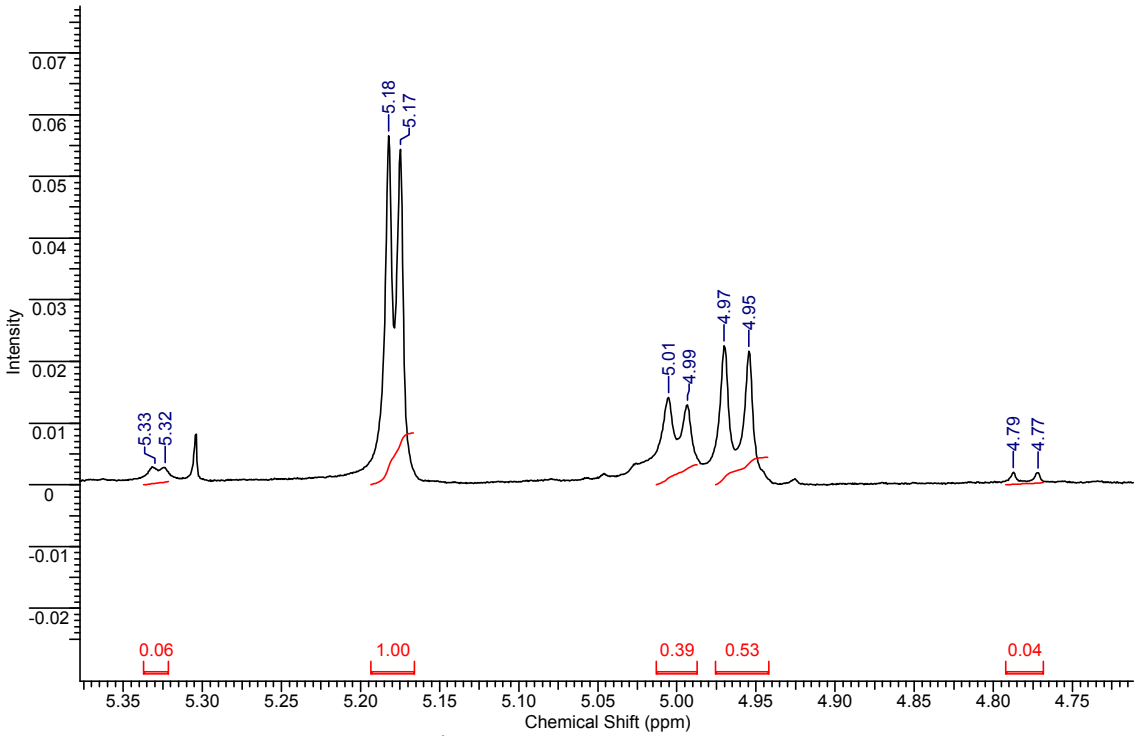
^{13}C NMR espectrum of 4b.



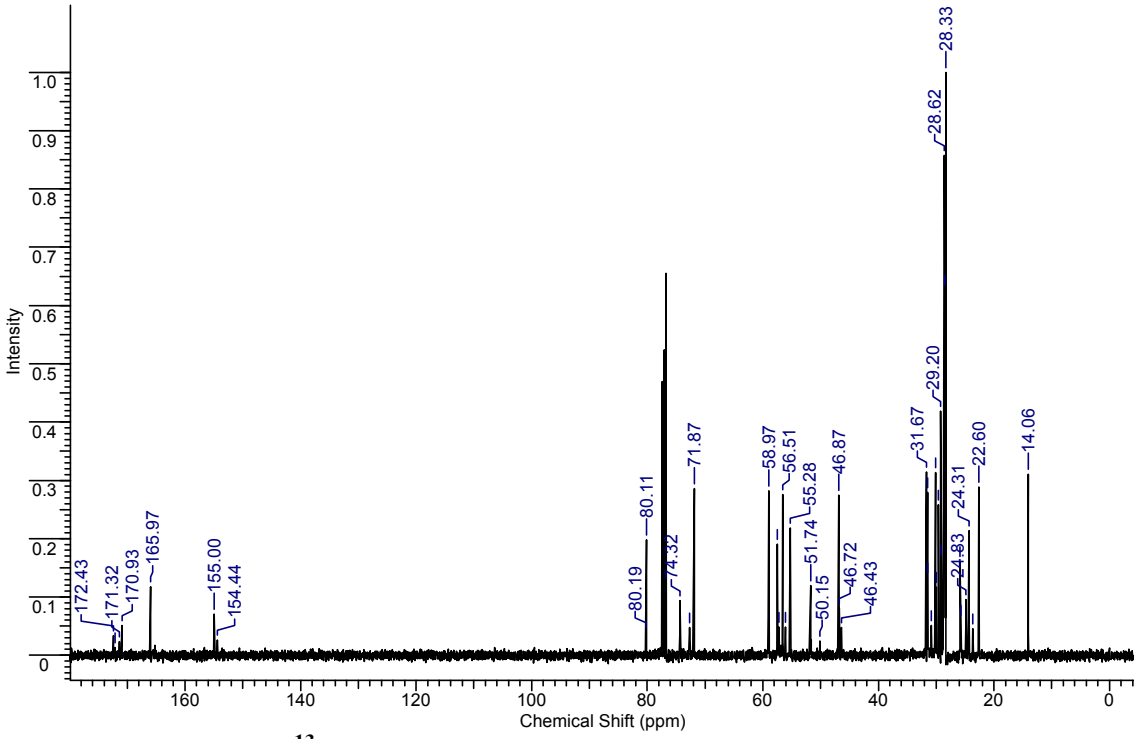
^{1}H NMR espectrum of 4c.



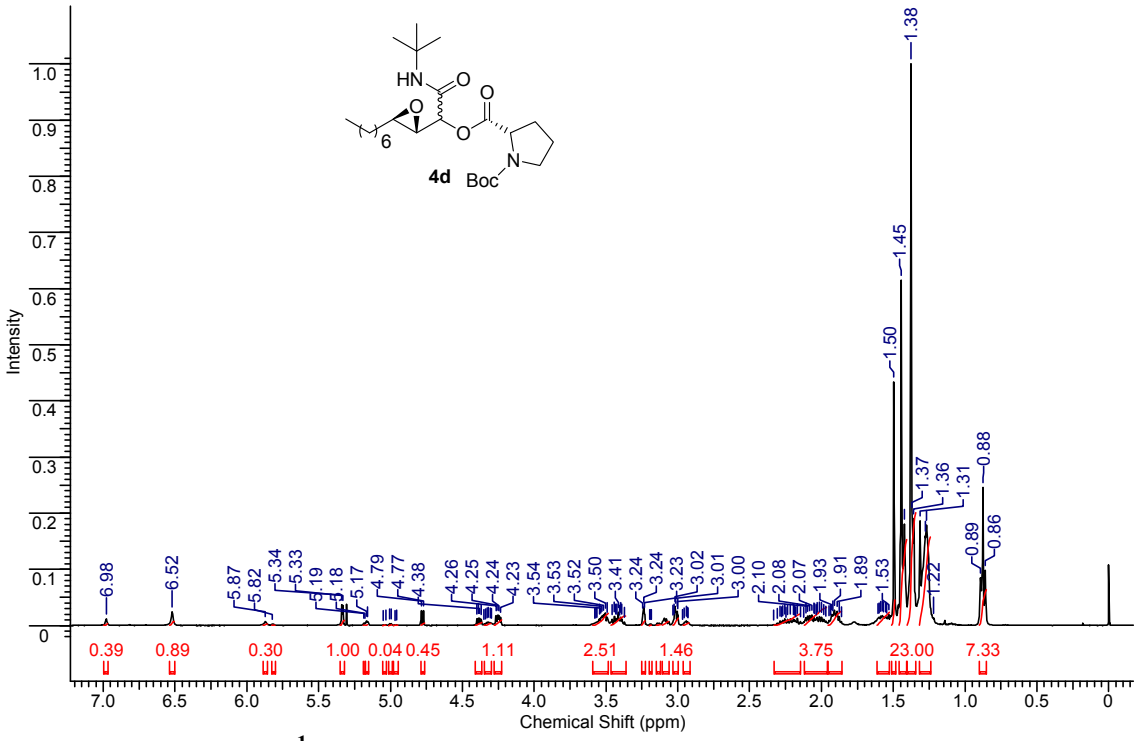
Expanded region of ^{1}H NMR espectrum of 4c.



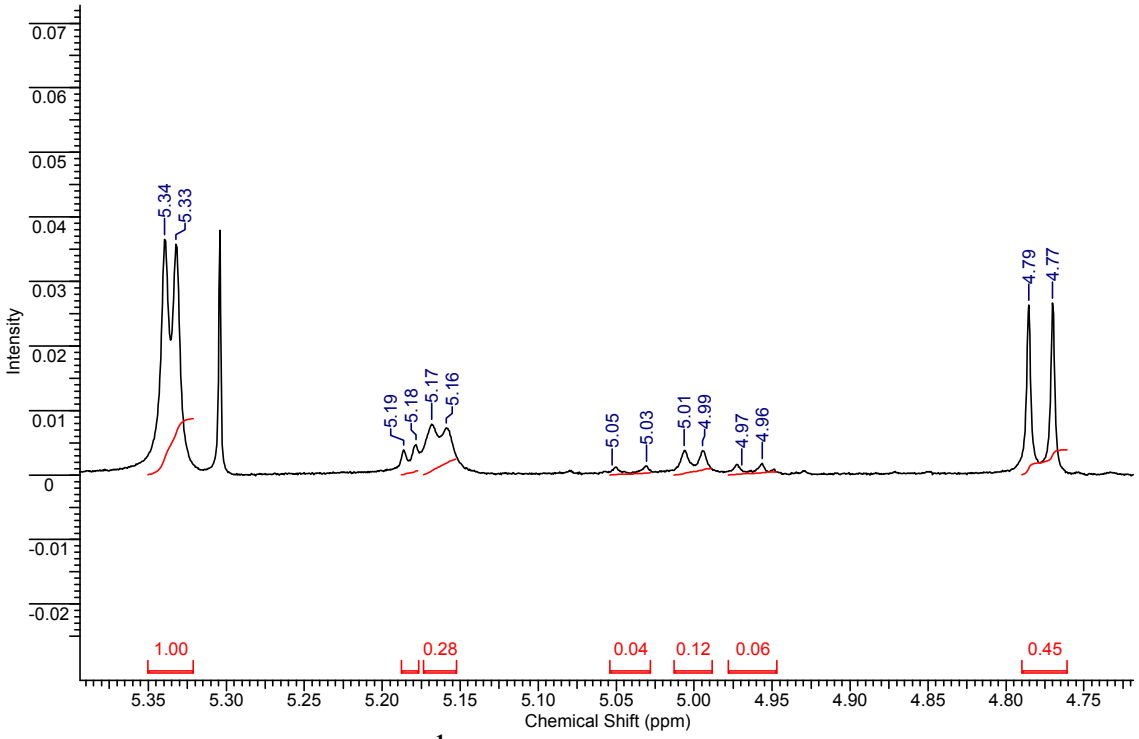
Expanded region of ^{1}H NMR espectrum of 4c.



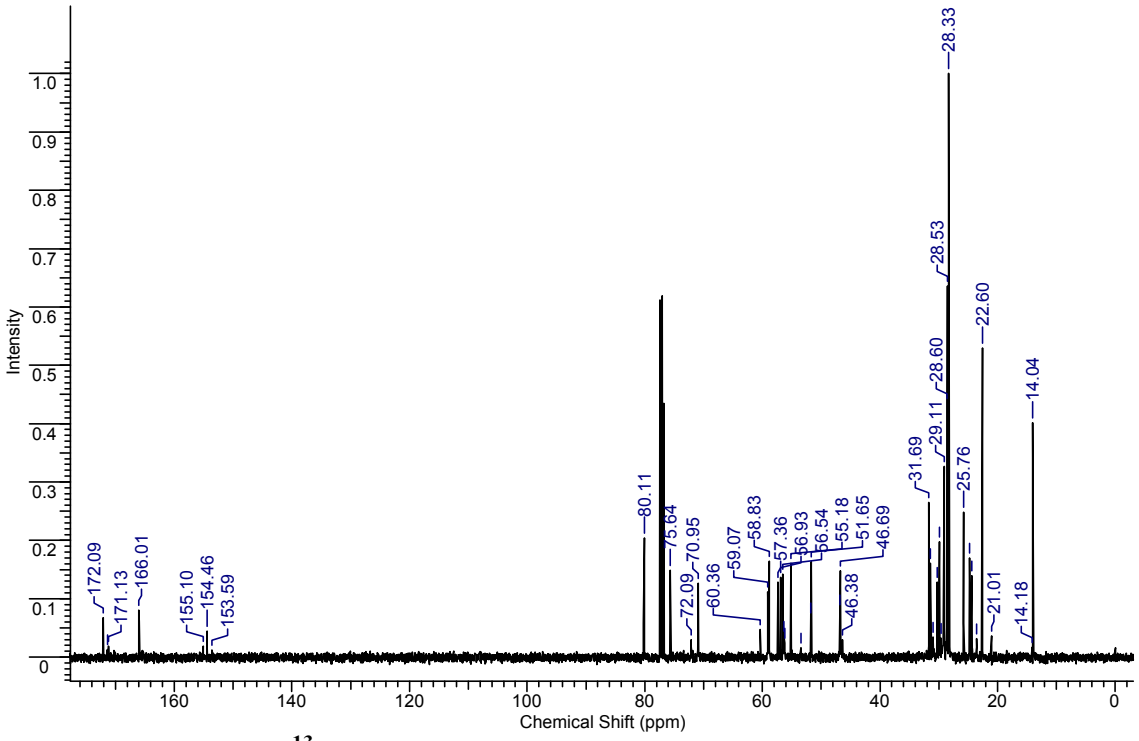
^{13}C NMR espectrum of 4c.



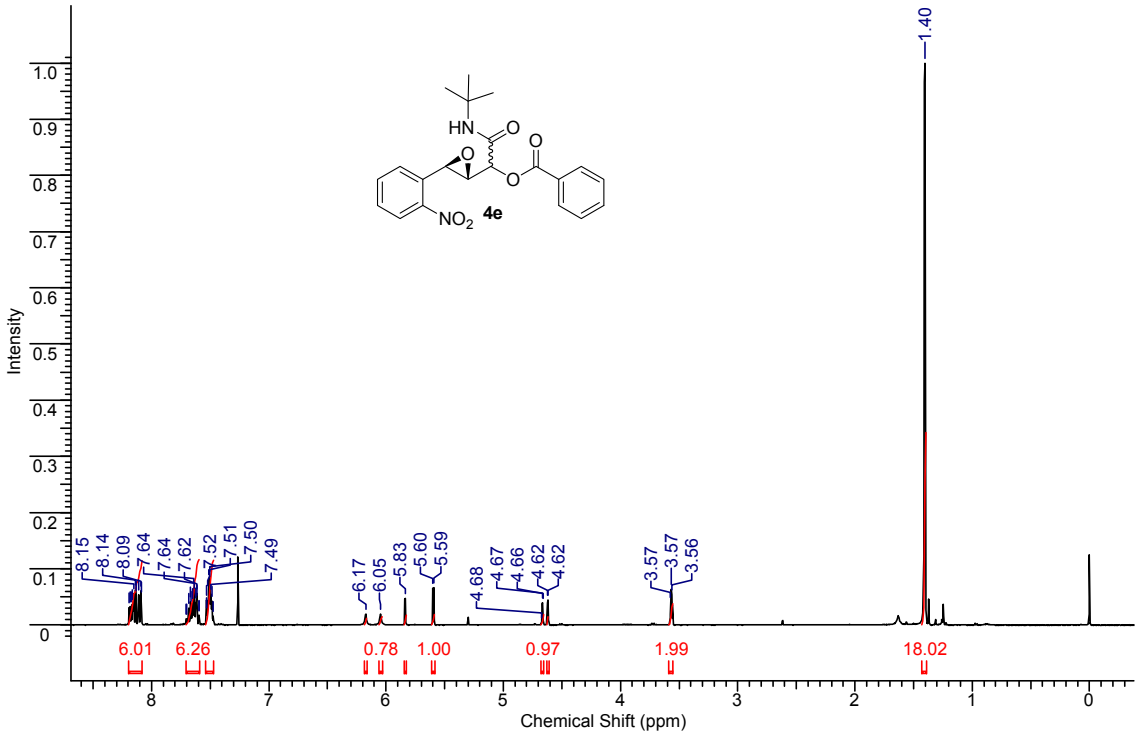
^{1}H NMR espectrum of 4d.



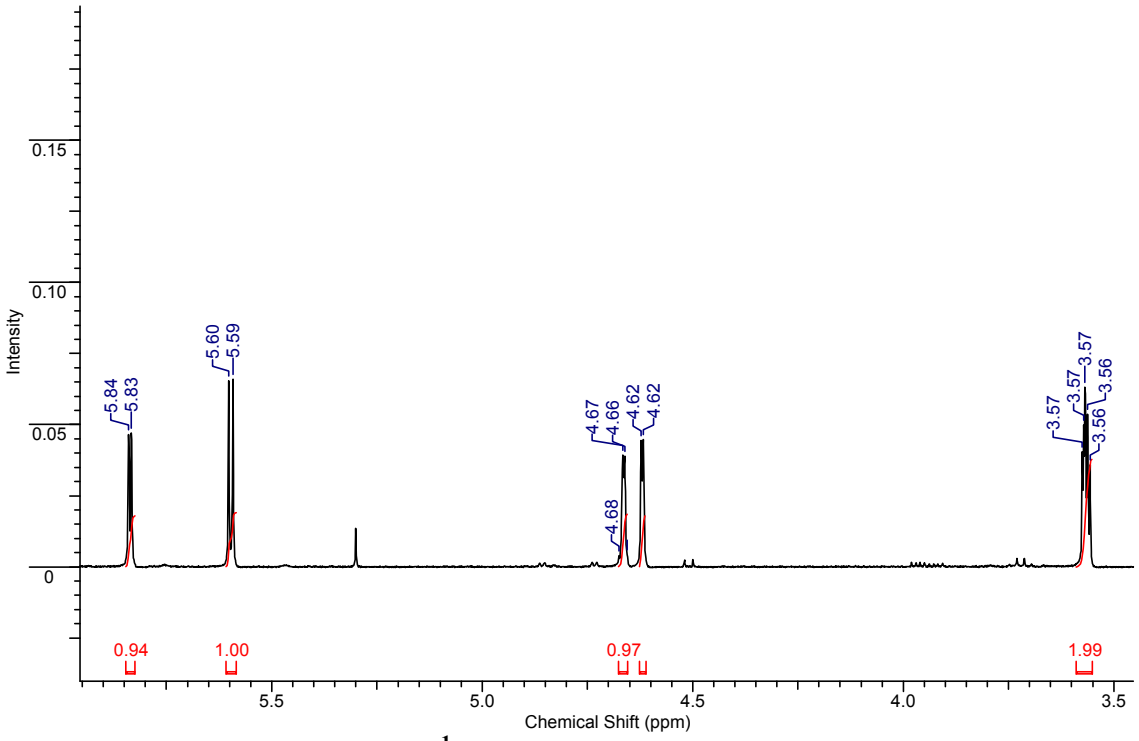
Expanded region of ^{1}H NMR espectrum of 4d.



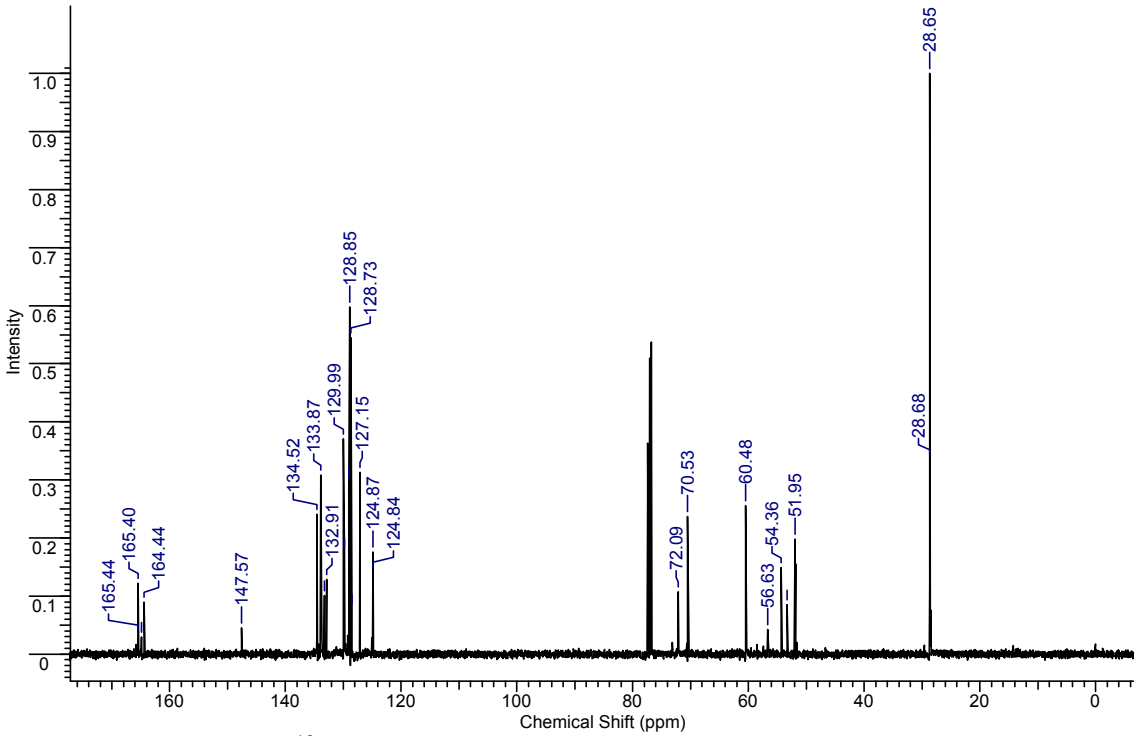
^{13}C NMR espectrum of 4d.



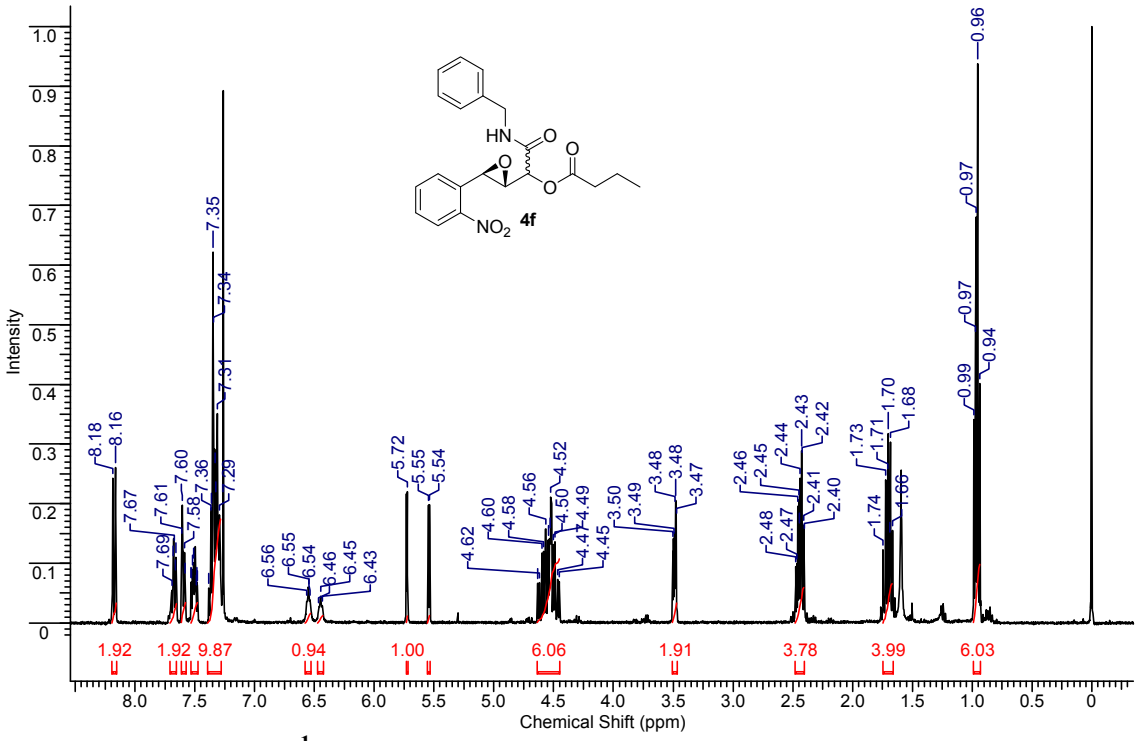
^{1}H NMR espectrum of 4e.



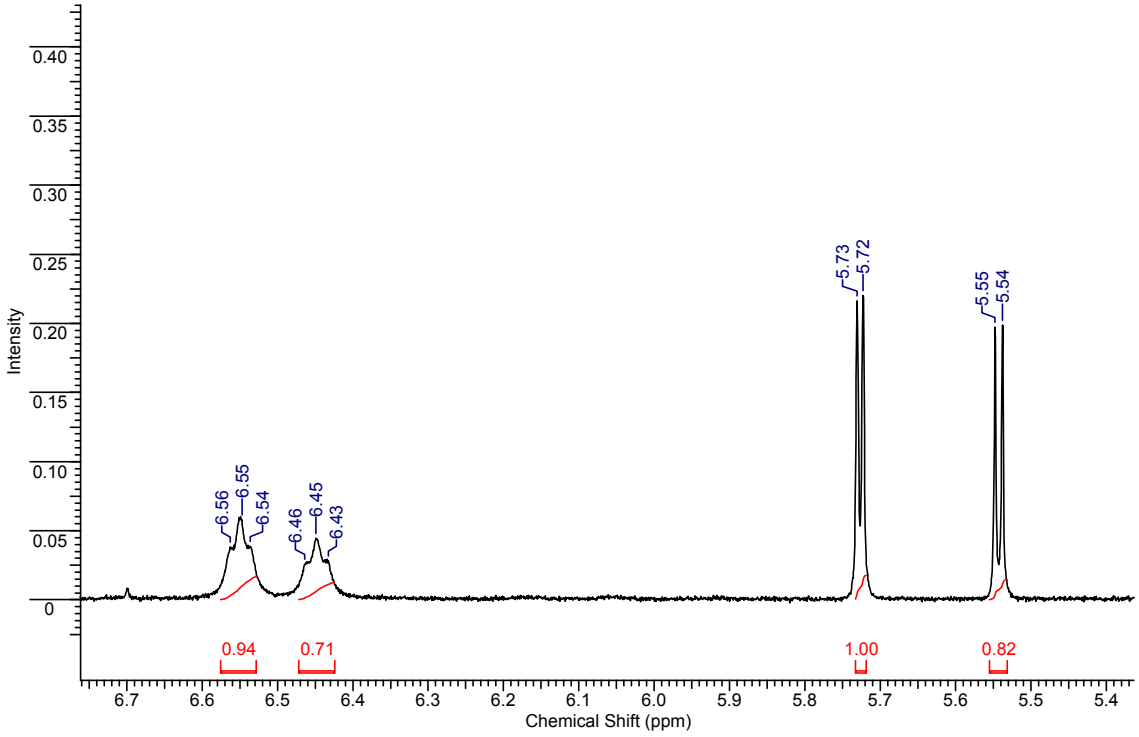
Expanded region of ^{1}H NMR espectrum of 4e.



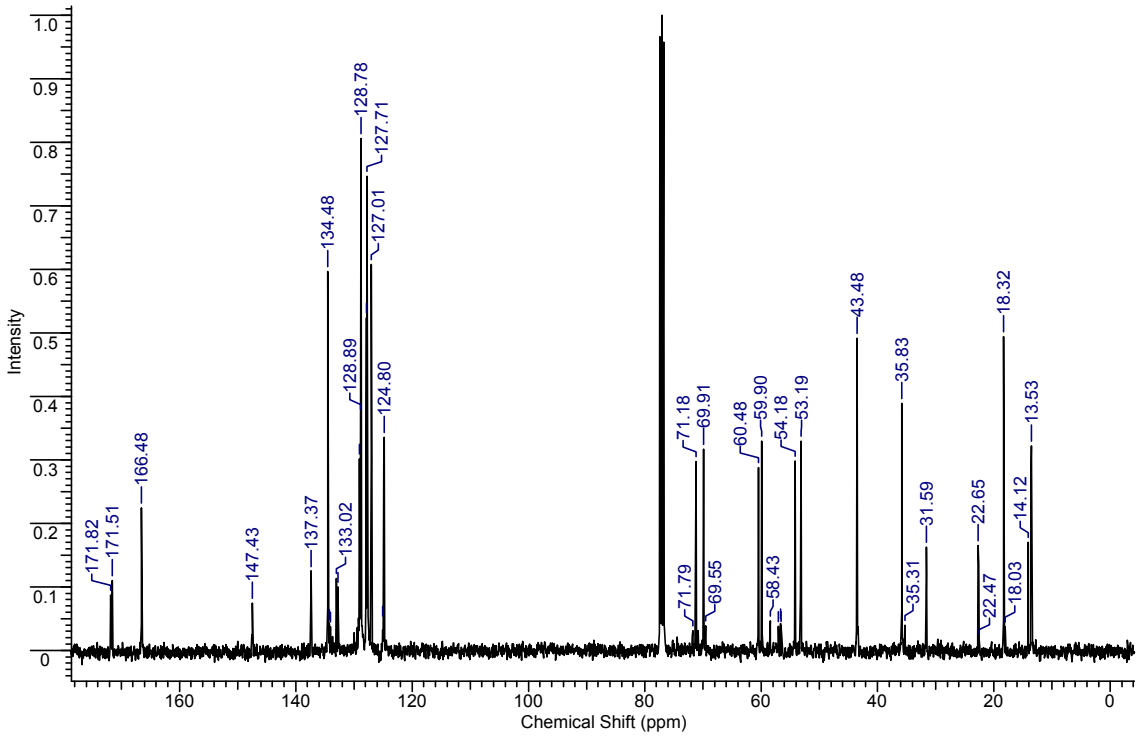
^{13}C NMR espectrum of 4e.



^{1}H NMR espectrum of 4f.



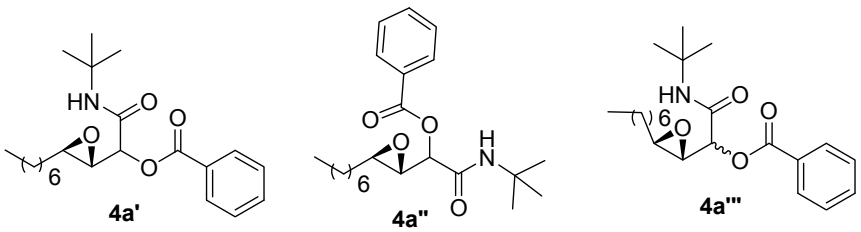
Expanded region of ^{1}H NMR espectrum of 4f.

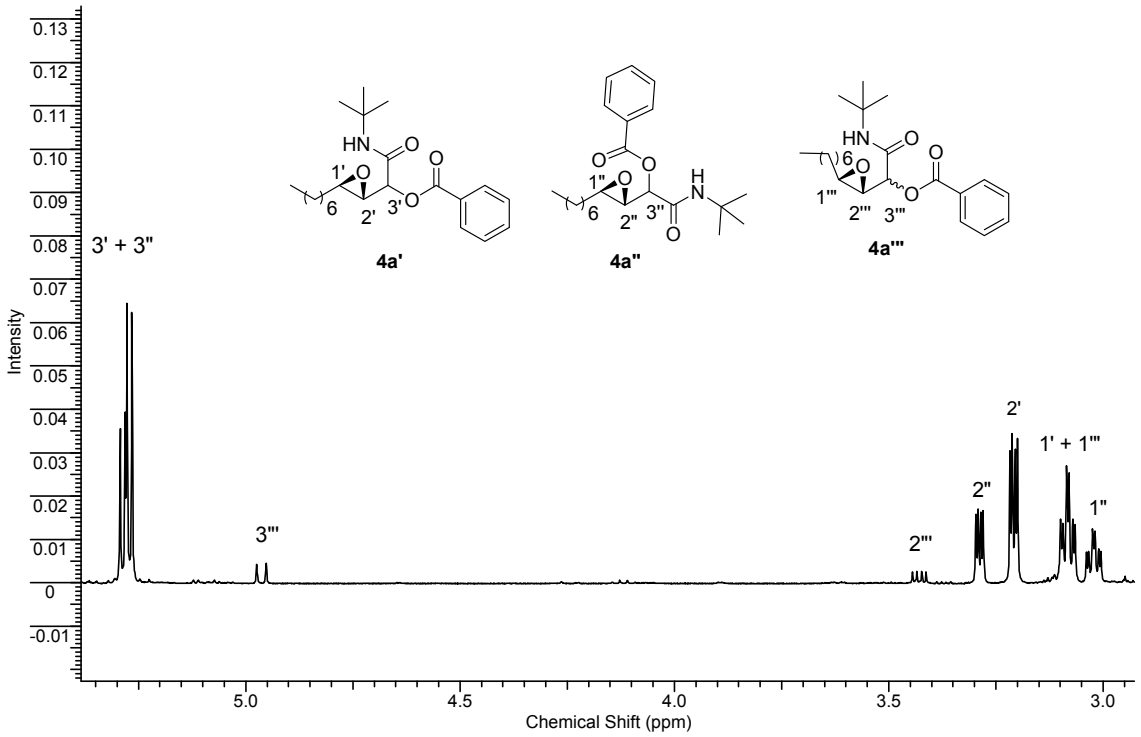


^{13}C NMR espectrum of 4f.

9.0 NOE spectra and theoretical calculation of products 4a.

Probable diastereoisomers observed in the ^{1}H NMR spectrum of **4a:**

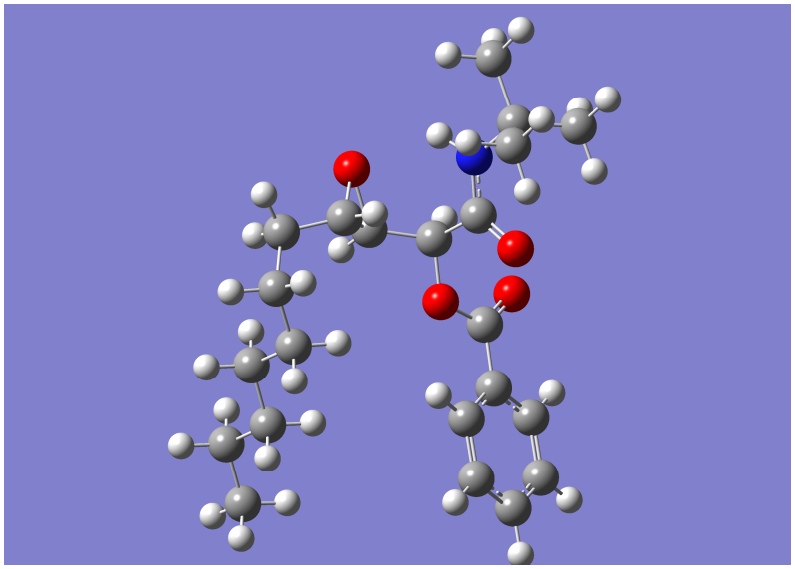




Expanded region of ^{1}H NMR espectrum of 4a.

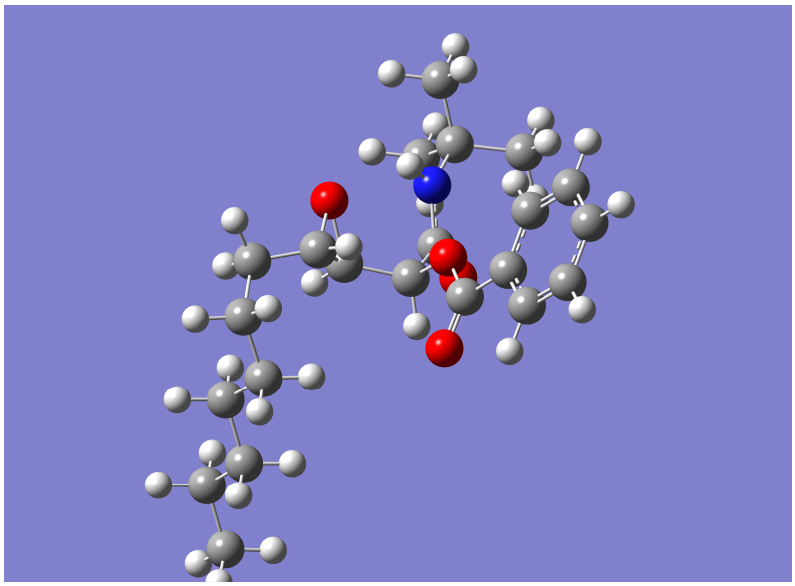
Optimized structures by theoretical calculation using Gaussian, B3LYP.[10]

To 4a' (761422.19205 Kcal/mol)

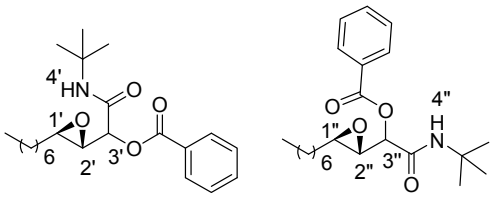


[10] Gaussian 03: x86-Win32-G03RevB.01 3-Mar-2003, Gaussian, J. A. P. et. Al. Inc., Pittsburgh PA, 2003.

To 4a" (761422.268605 Kcal/mol)



Spatial distances observed between the hydrogens in **4a'** and **4a"**:



4a' **4a"**

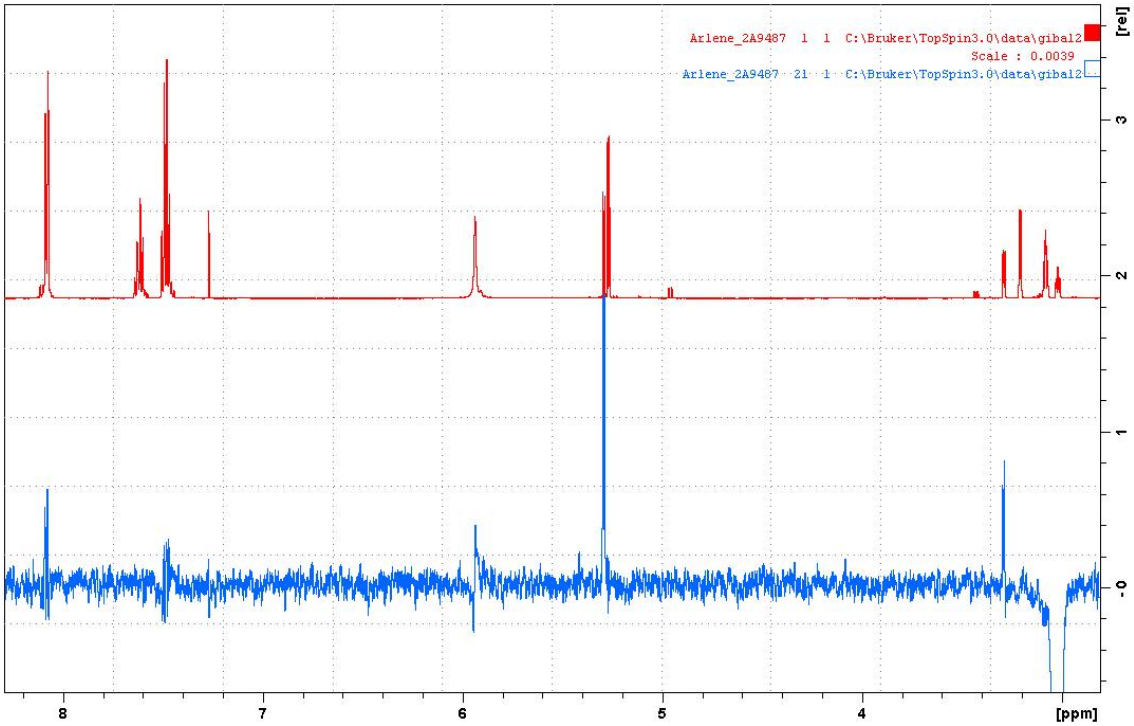
Hydrogens	Distance measured (Å)	Hydrogens	Distance measured (Å)
1' – 2'	3.08	1" – 2"	3.08
1' – 3'	3.74	1" – 3"	3.40
1' – 4'	2.74	1" – 4"	3.62
2' – 3'	2.49	2" – 3"	2.45
2' – 4'	3.66	2" – 4"	3.30
3' – 4'	2.65	3" – 4"	3.53

NOE data of stereoisomeric mixture of **4a**.

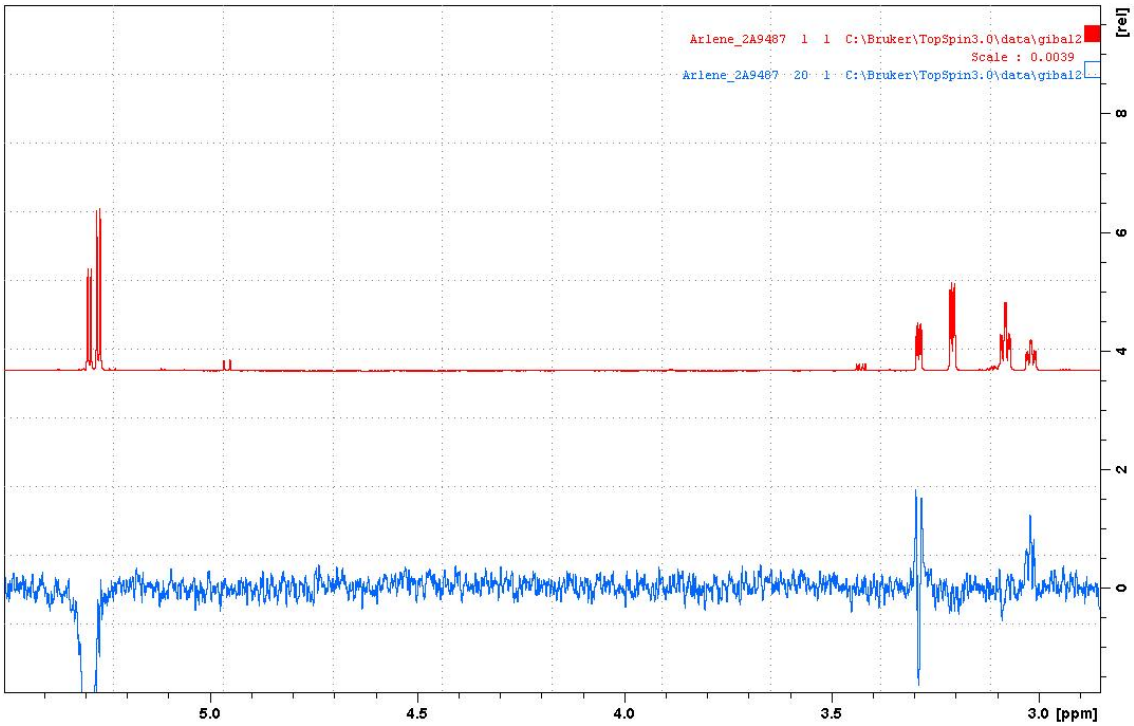
Diastereoisomer analysed	irradiated signal	Observed NOE
Epoxide *anti* majority (**4a'**)	3.08	8.09 – 8.07, 5.95, 5.27, 3.21
Epoxide *anti* majority (**4a'**)	3.21	5.95, 5.27, 3.08
Epoxide *anti* majority (**4a'**)	5.27	5.95, 3.21, 3.08
Epoxide *anti* minority (**4a**")	3.02	8.09 – 8.07, 5.29, 3.29
Epoxide *anti* minority (**4a"**)	5.29	3.29, 3.02

#

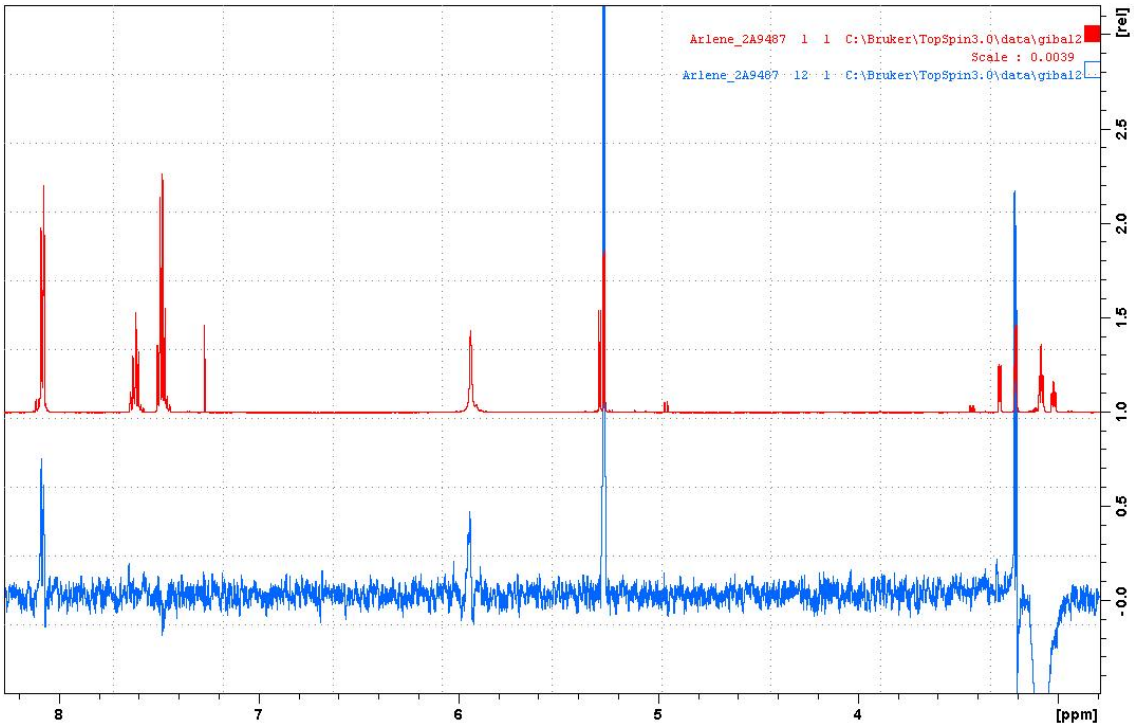
^{1}H and NOE spectra.



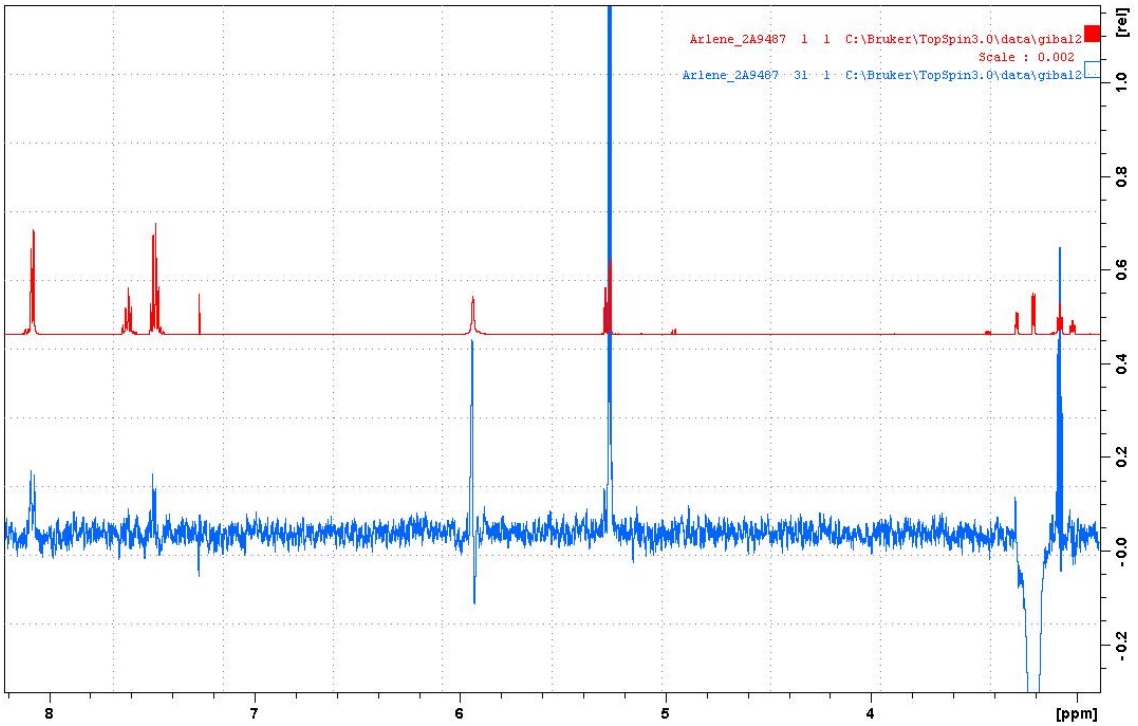
Irradiated signal 3.02 ppm.



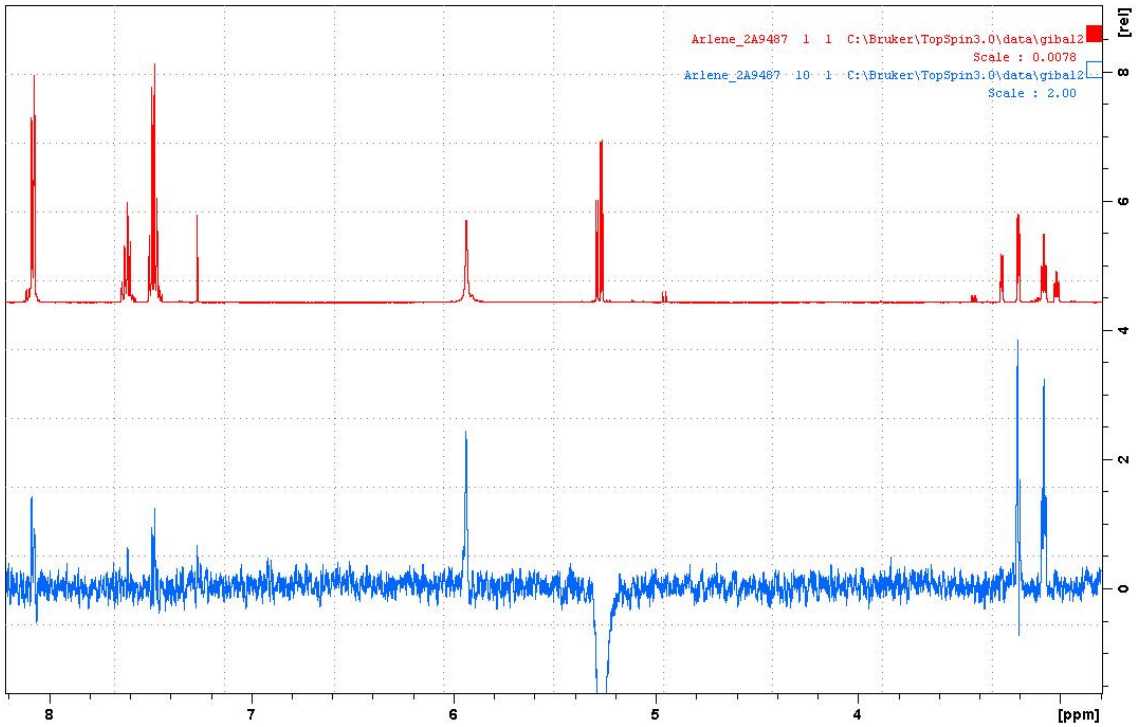
Irradiated signal 5.29 ppm.



Irradiated signal 3.08 ppm.



Irradiated signal 3.21 ppm.



Irradiated signal 5.27 ppm.