Synthesis

Reviews and Full Papers in Chemical Synthesis

Supporting Information
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Supporting Information

Racemization-Free Synthesis of Morpholinone Derivatives from α-Amino Acids

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1. General Information

Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} pre−coated plates. Visualization was accomplished with UV lamp or I_2 stain. Silica gel 230−400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as eluent. Unless noted, all reactions were carried out in oven−dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz/500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz/125 MHz. Mass spectra (MS) were obtained using ESI mass spectrometers. IR spectra were recorded as neat for liquid and in KBr for solids. Melting points were determined using a hot stage apparatus and were uncorrected. Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]^{25}_{D}$ (*c* in g per 100 mL, solvent) at 25 °C. Enantiomeric excess (*ee*) was determined by HPLC using chiralcel AD-H, OD-H or AS-H analytical column (detection at 254 nm).

2. Selected NMR Spectra

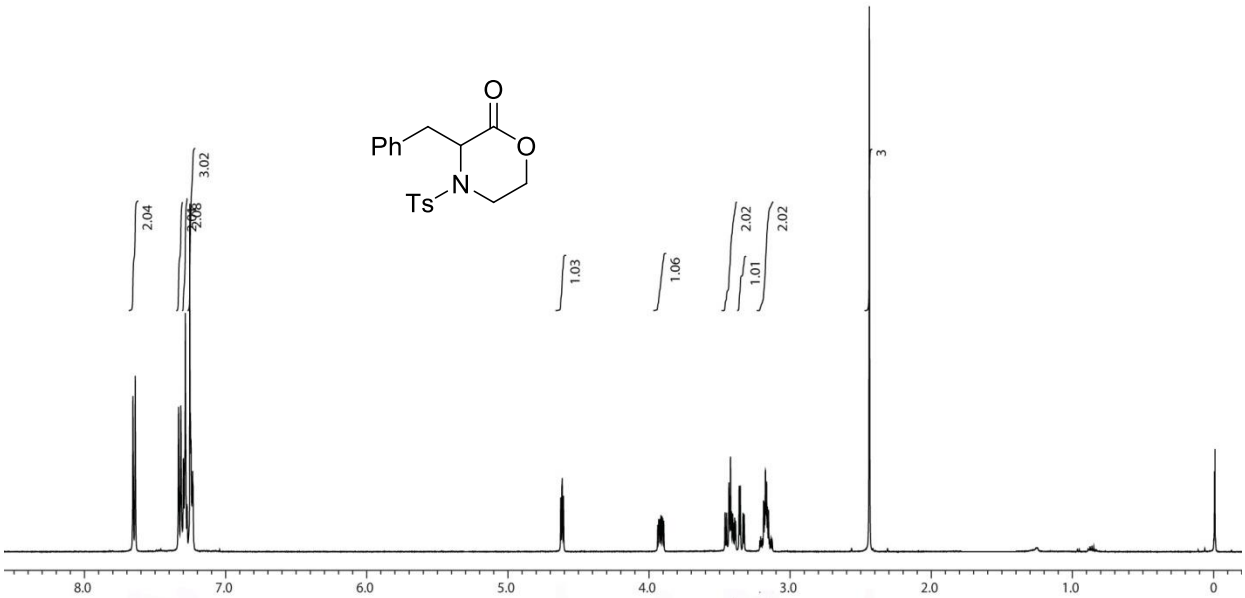

Figure 1. ^{1}H NMR spectrum of **2a** ($CDCl_3$, 500 MHz)

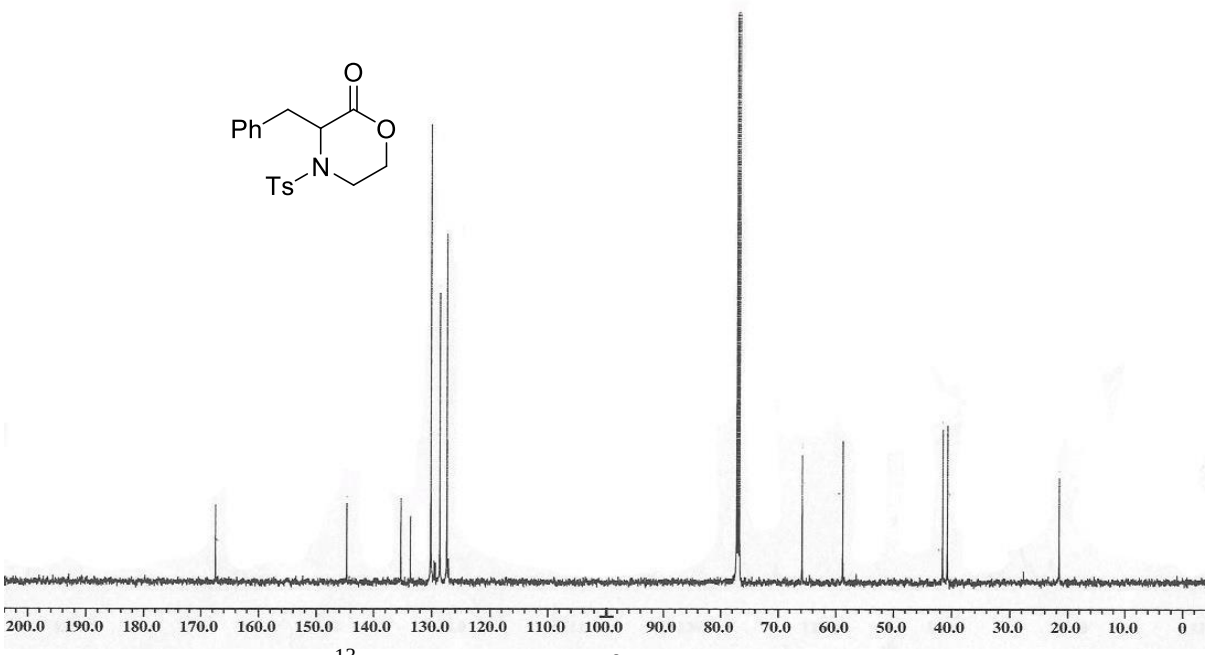

Figure 2. ^{13}C NMR spectrum of **2a** ($CDCl_3$, 125 MHz)

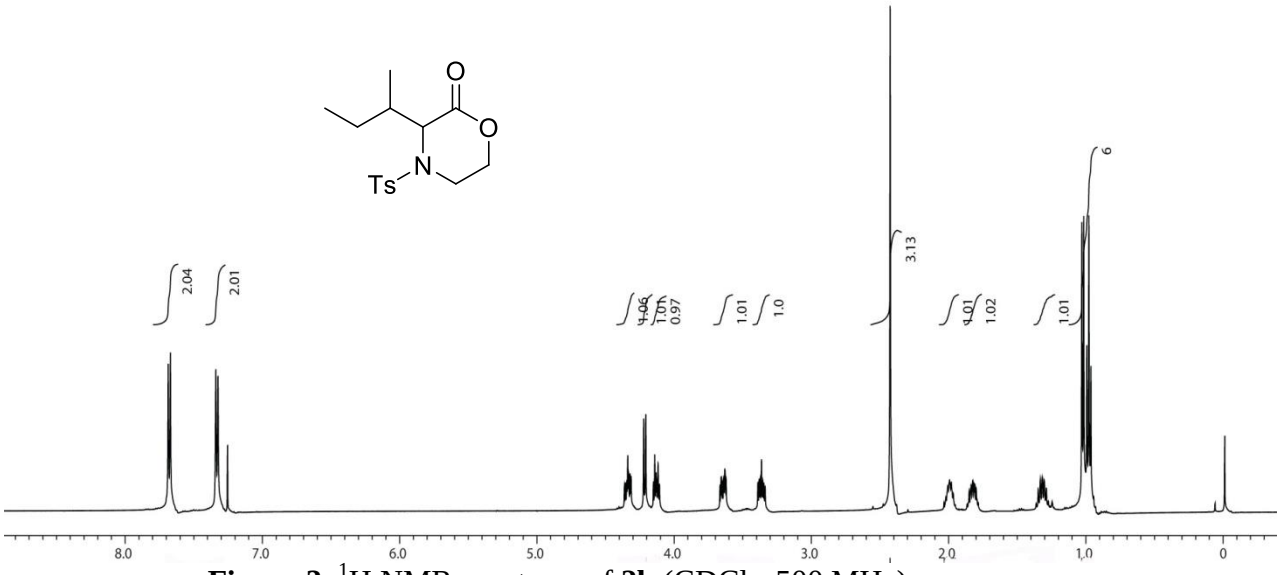

Figure 3. ^{1}H NMR spectrum of **2b** ($CDCl_3$, 500 MHz)

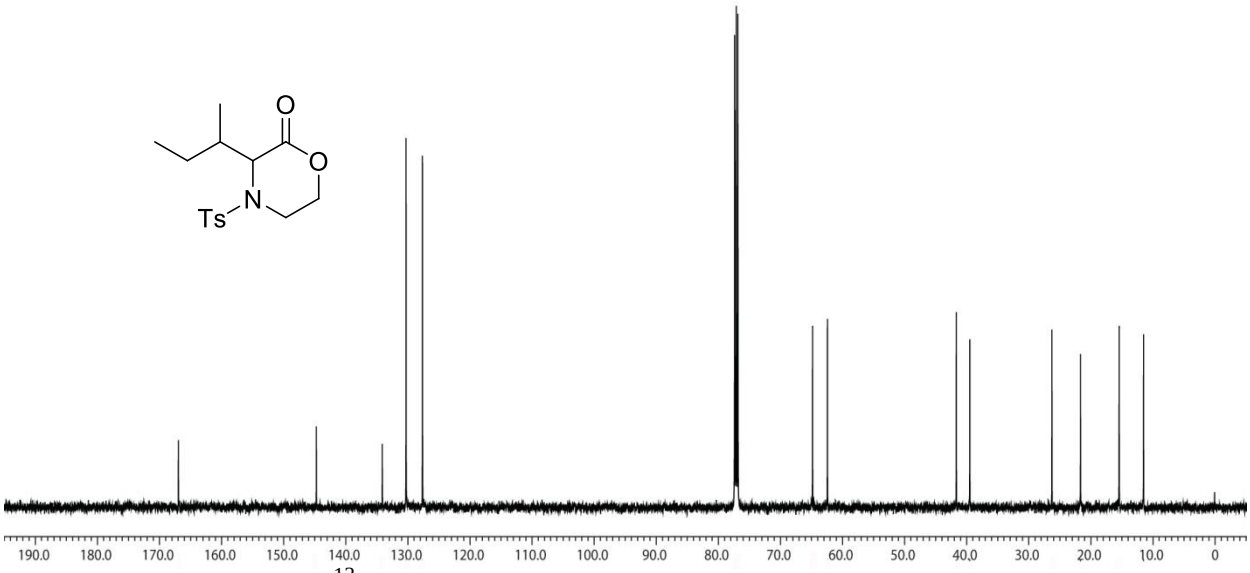

Figure 4. ^{13}C NMR spectrum of **2b** ($CDCl_3$, 125 MHz)

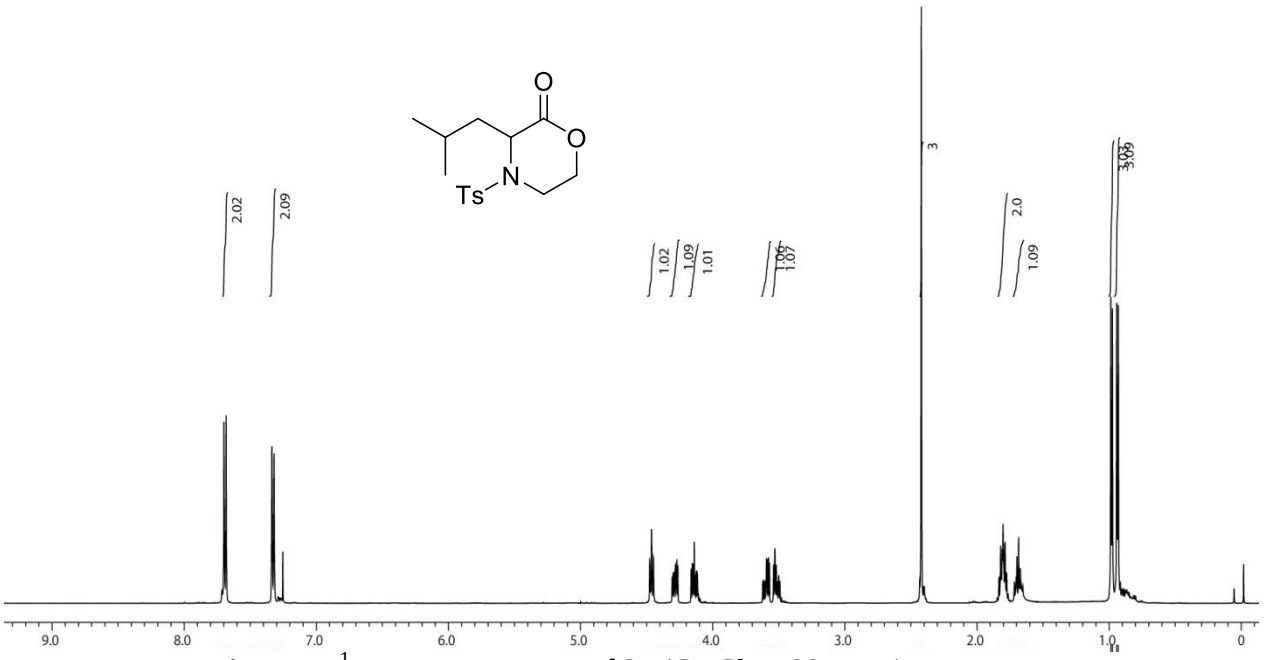

Figure 5. ^{1}H NMR spectrum of **2c** ($CDCl_3$, 500 MHz)

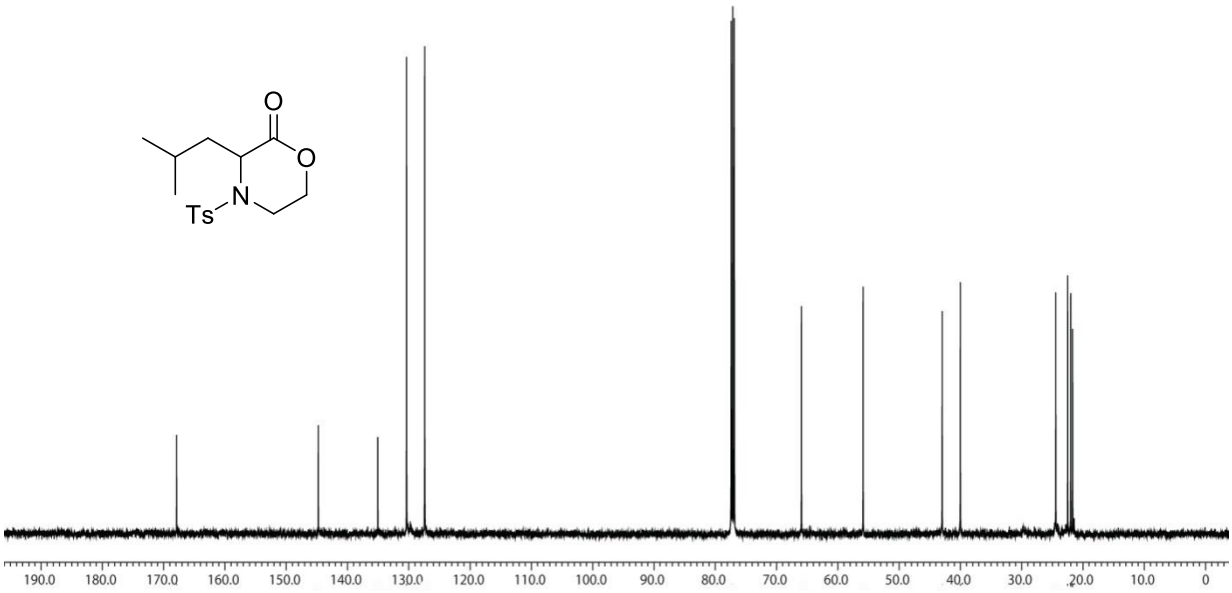

Figure 6. ^{13}C NMR spectrum of **2c** ($CDCl_3$, 125 MHz)

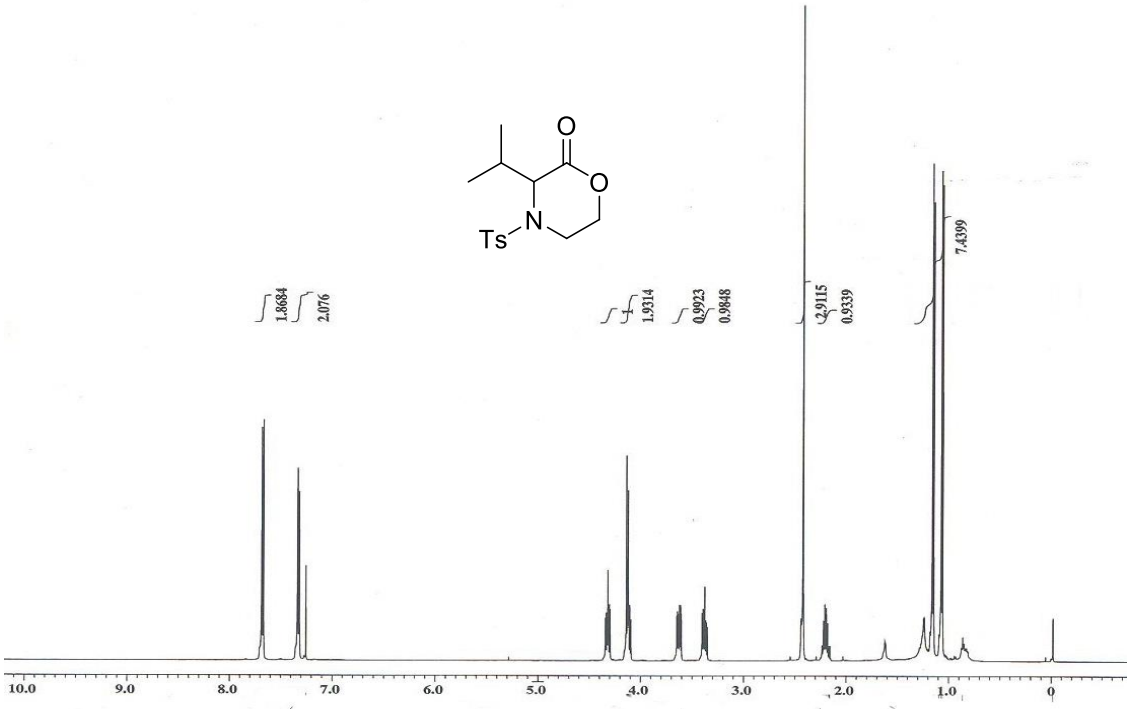

Figure 7. ^{1}H NMR spectrum of **2d** ($CDCl_3$, 500 MHz)

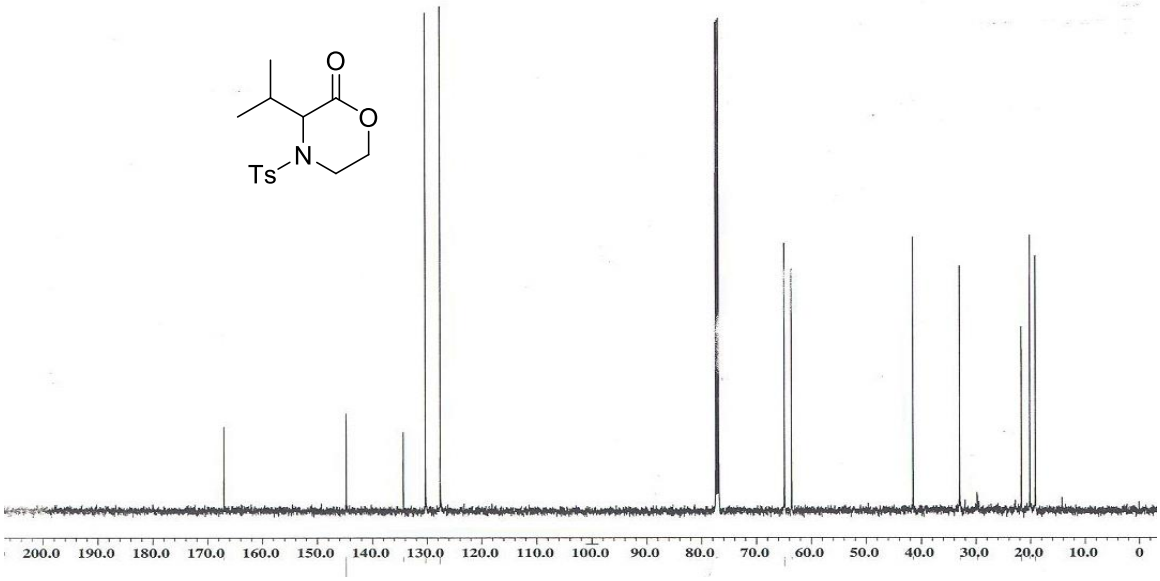

Figure 8. ^{13}C NMR spectrum of **2d** ($CDCl_3$, 125 MHz)

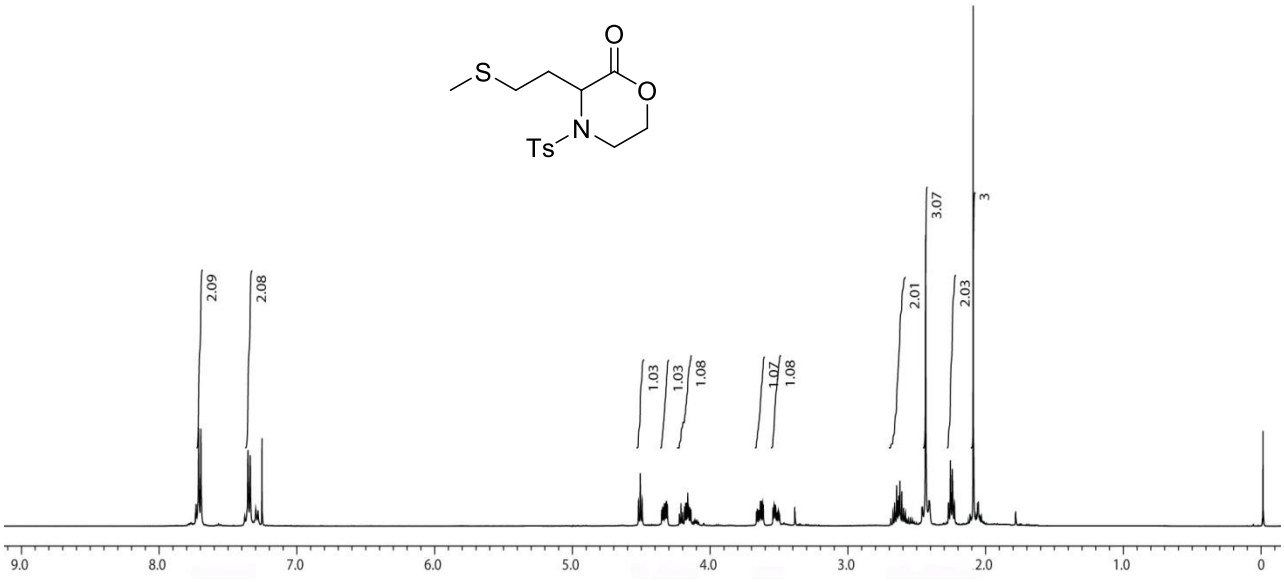

Figure 9. ^{1}H NMR spectrum of **2e** ($CDCl_3$, 500 MHz)

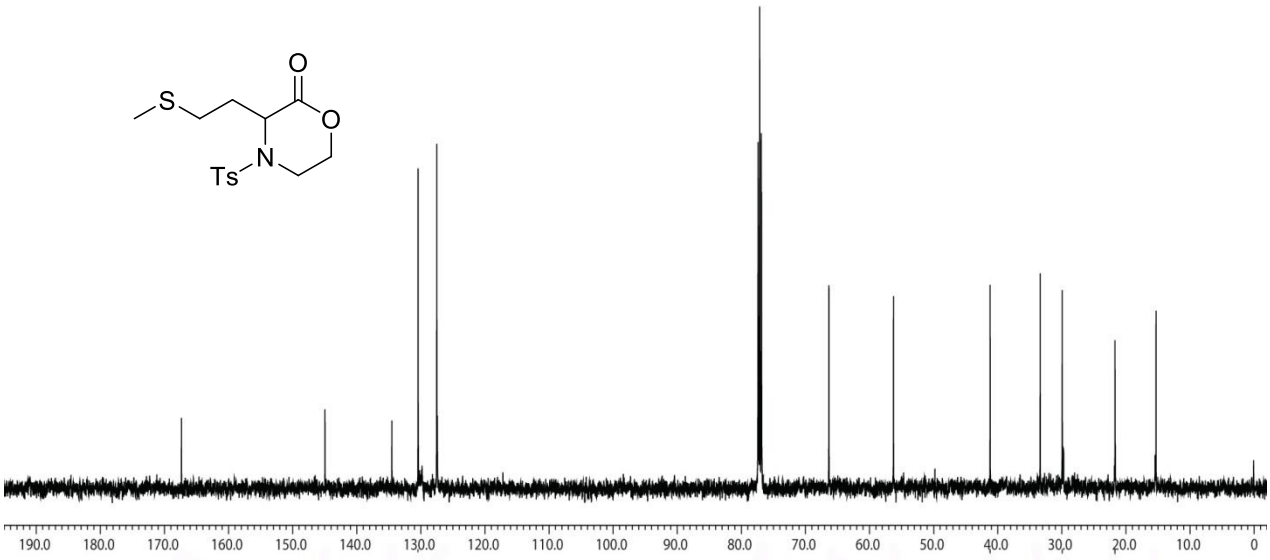

Figure 10. ^{13}C NMR spectrum of **2e** ($CDCl_3$, 125 MHz)

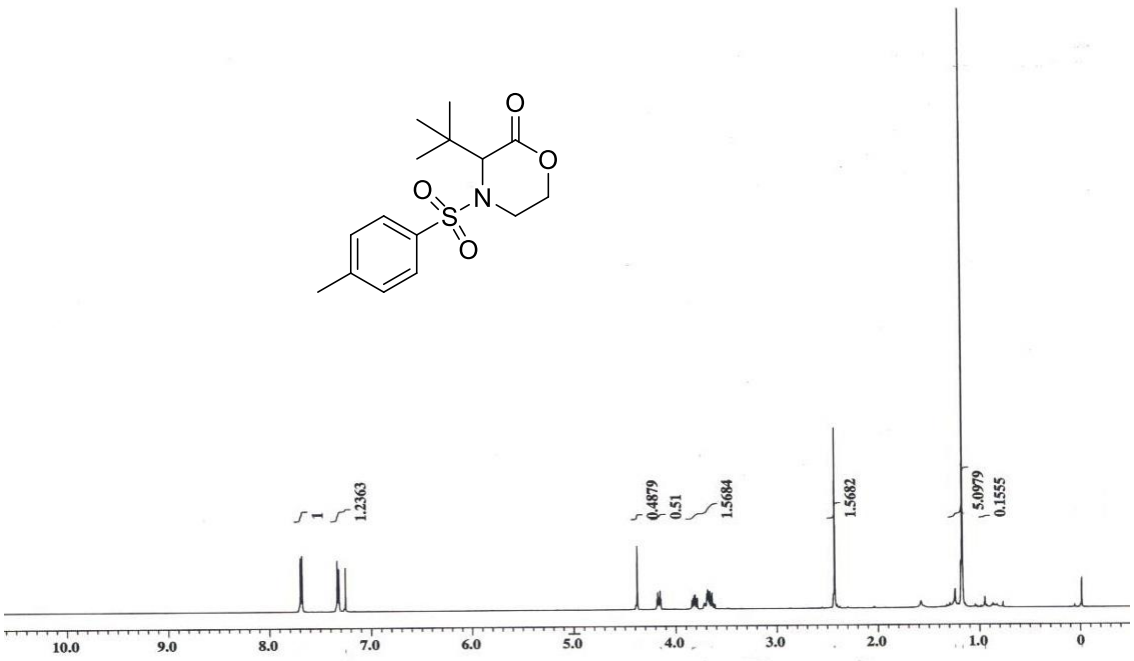

Figure 11. ^{1}H NMR spectrum of **2f** ($CDCl_3$, 500 MHz)

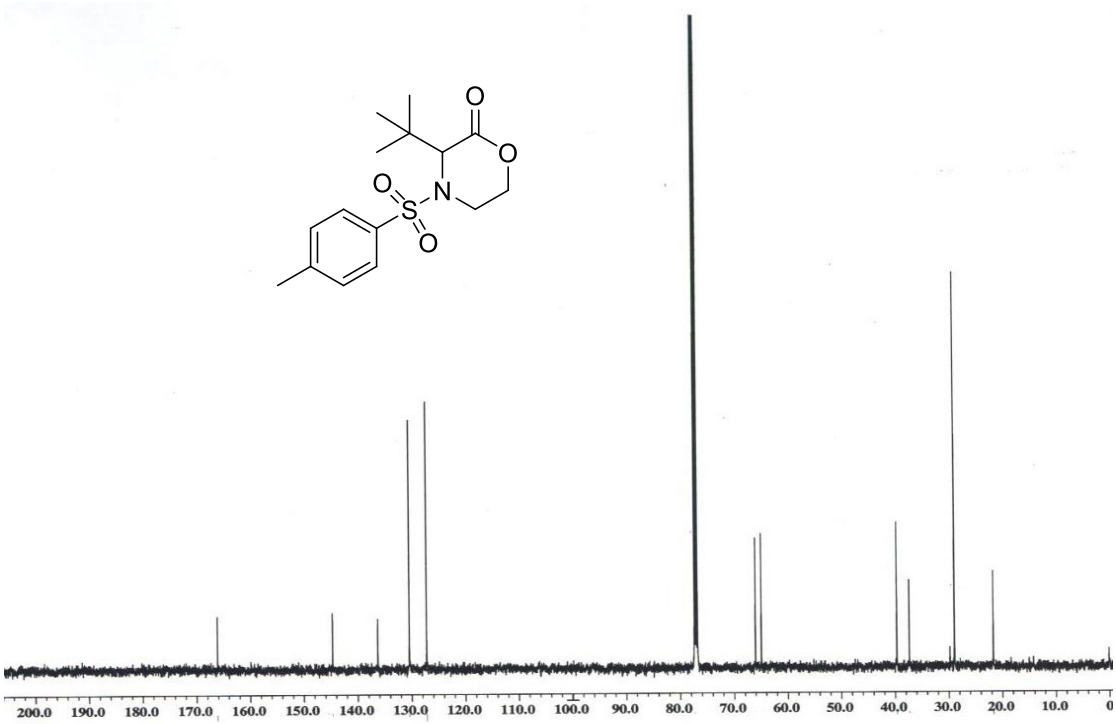

Figure 12. ^{13}C NMR spectrum of **2f** ($CDCl_3$, 125 MHz)

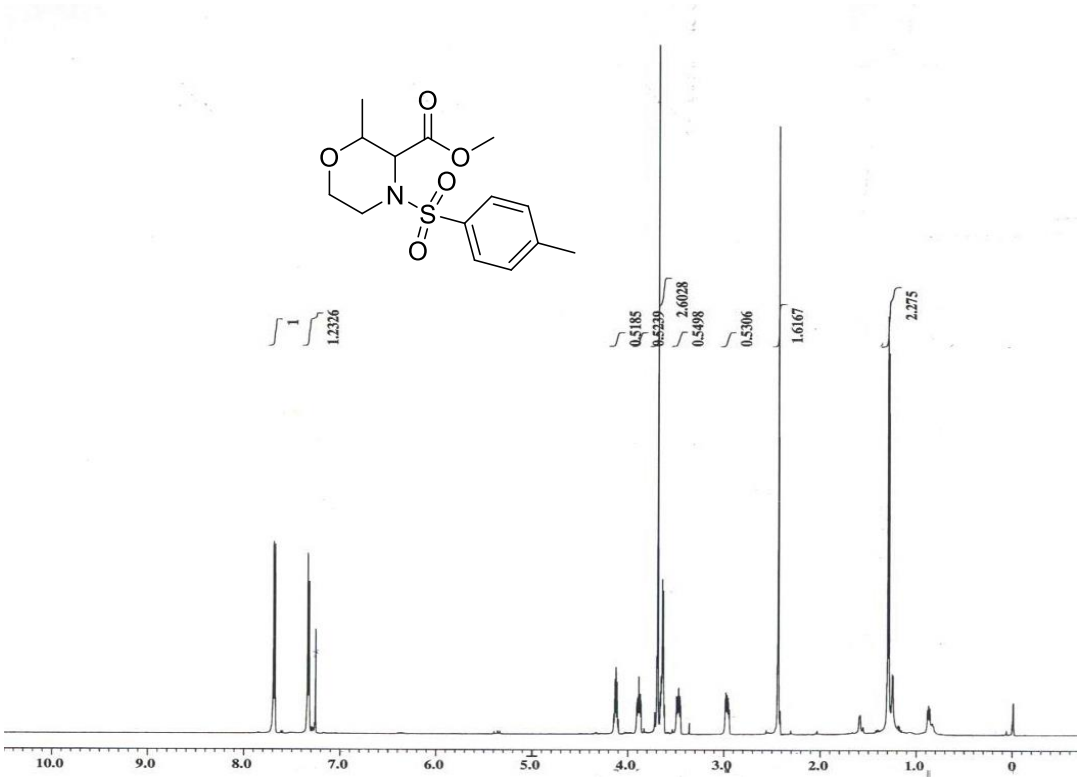

Figure 13. ^{1}H NMR spectrum **7** ($CDCl_3$, 500 MHz)

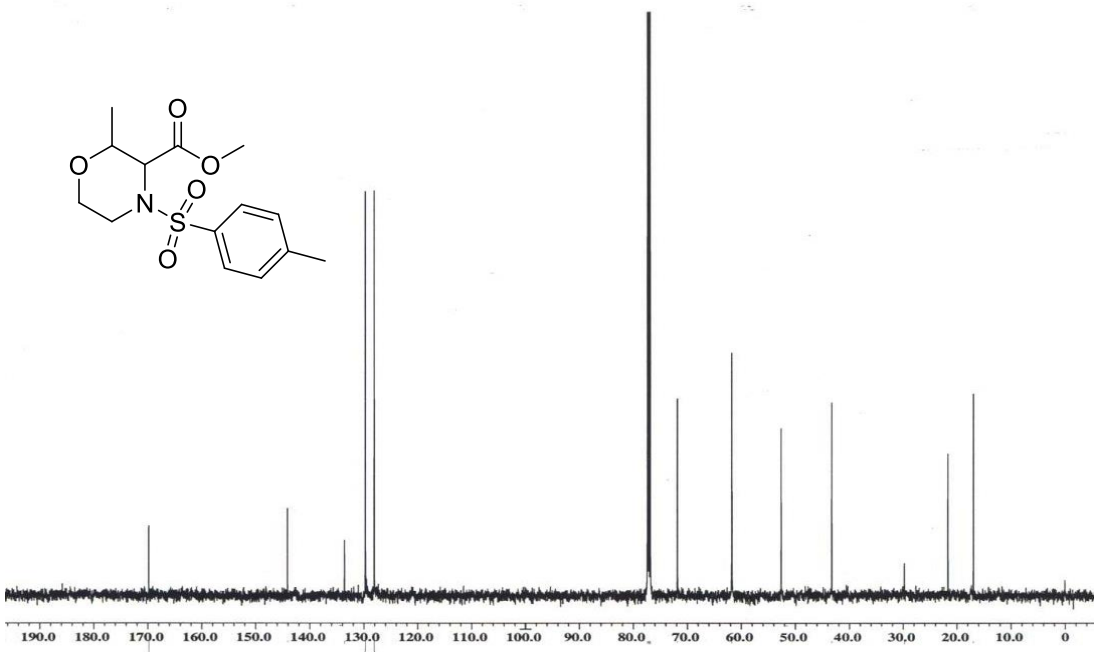

Figure 14. ^{13}C NMR spectrum **7** ($CDCl_3$, 125 MHz)

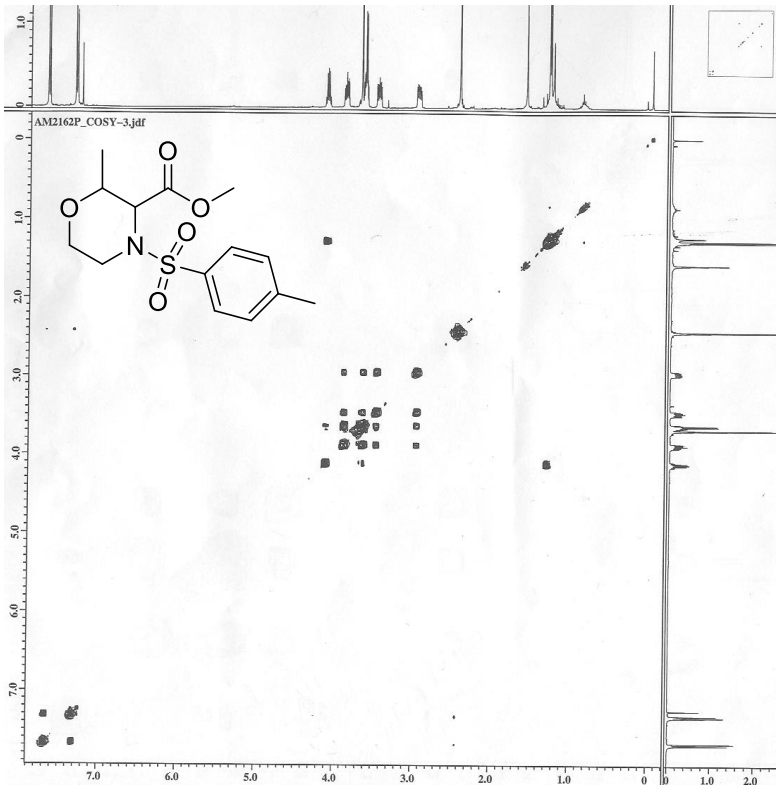

Figure 15. ^{1}H-^{1}H COSY spectrum of **7** ($CDCl_3$, 400 MHz)

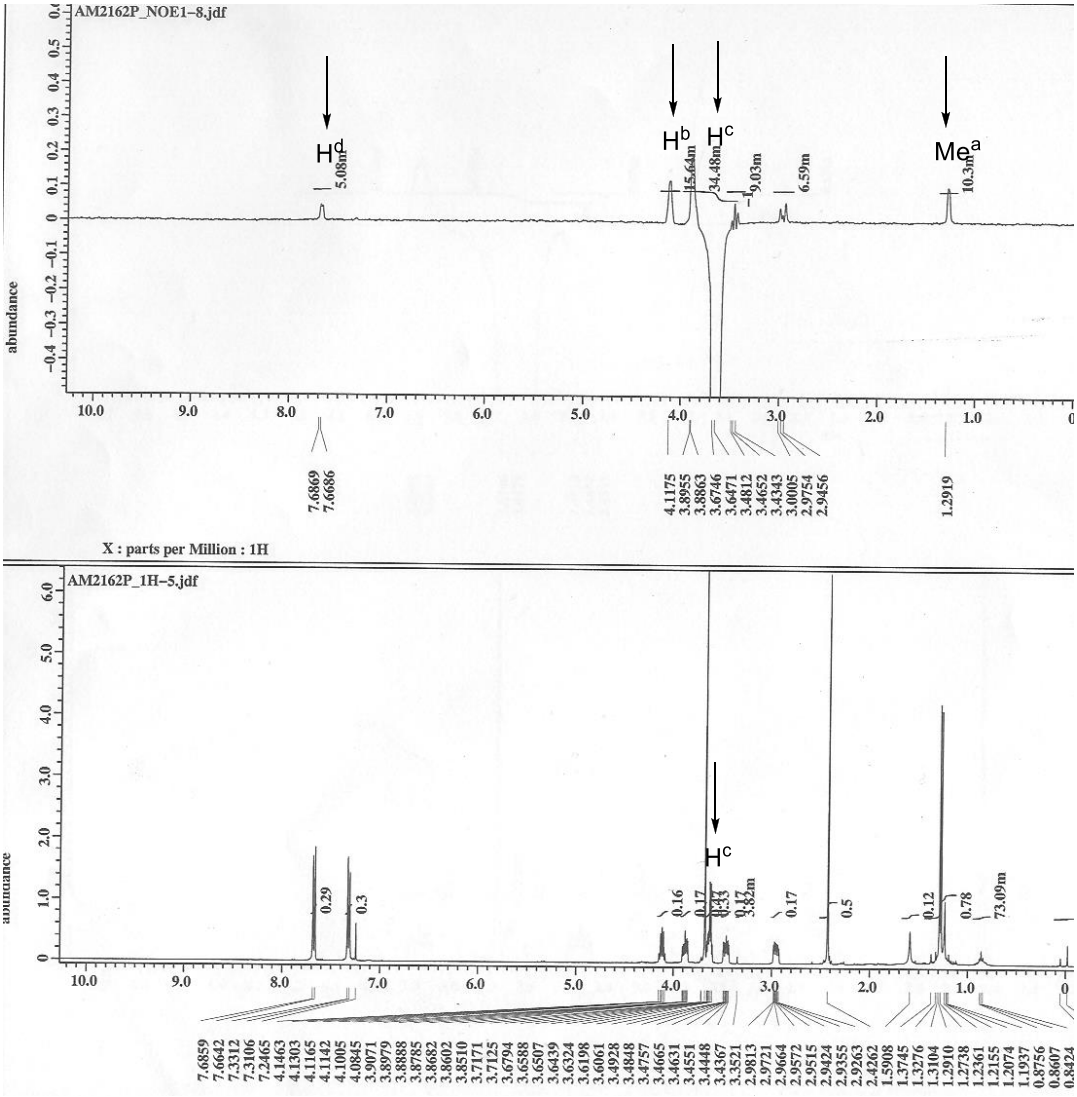

Figure 16. ^{1}H nOe spectrum of **7** showing correlation between H^{c}-Me^{a}, H^{c}-H^{b} and H^{c}-H^{d} (when H^{c} is irradiated, intensities of Me^{a}, H^{b} and H^{d} are enhanced)

($CDCl_3$, 400 MHz)

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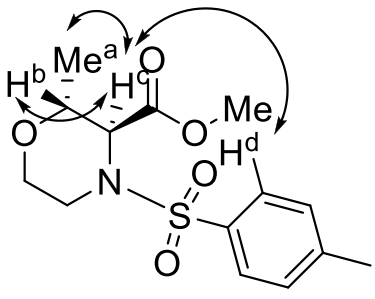


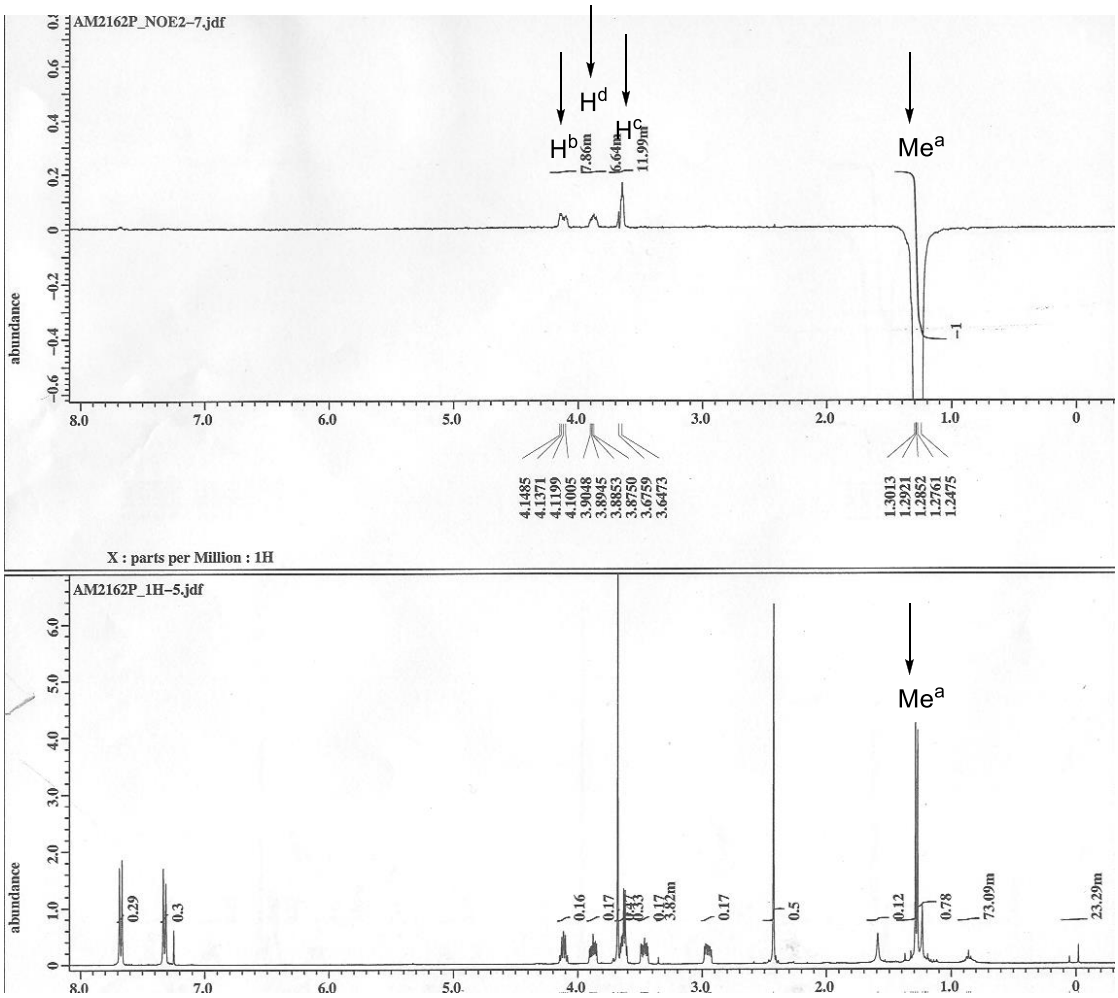
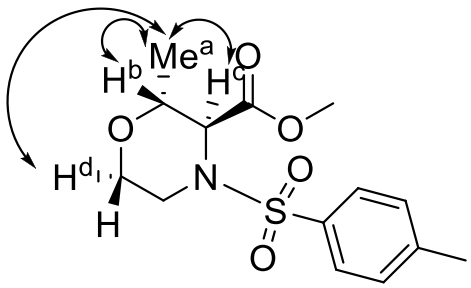


Figure 17. ^{1}H nOe spectrum of **7** showing correlation between Me^{a}-H^{b}, Me^{a}-H^{c} and Me^{a}-H^{d} (when Me^{a} is irradiated, intensities of H^{b}, H^{c} and H^{d} are enhanced) ($CDCl_3$, 400 MHz)



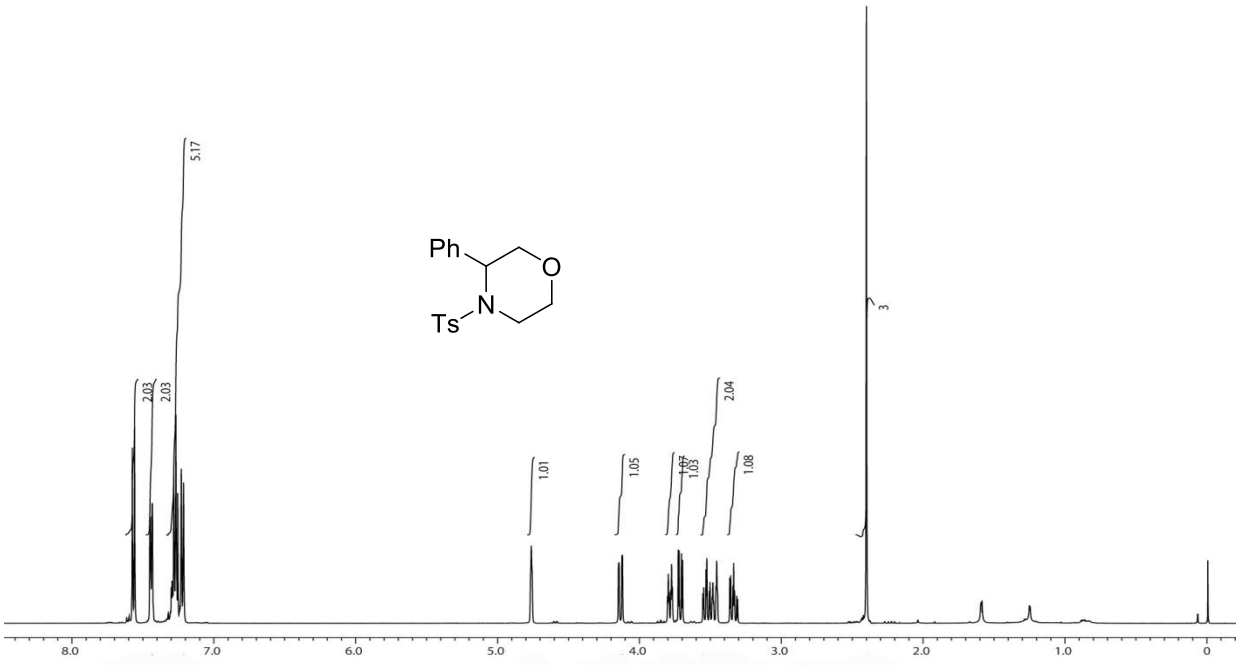


Figure 18. ^{1}H NMR spectrum of **9a** ($CDCl_3$, 500 MHz)

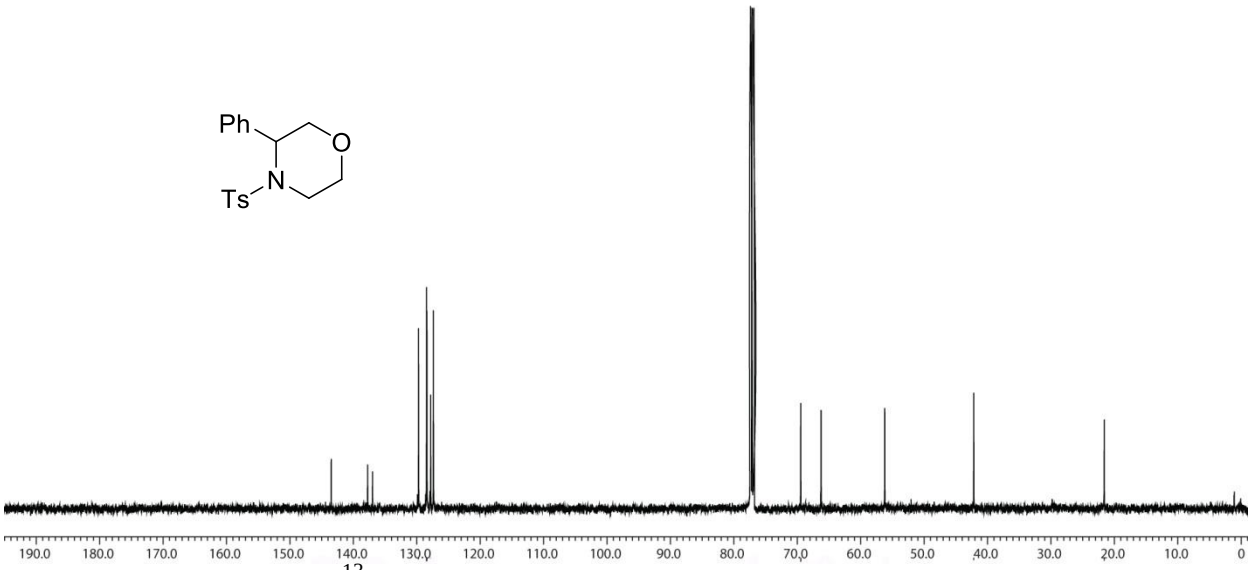


Figure 19. ^{13}C NMR spectrum of **9a** ($CDCl_3$, 125 MHz)

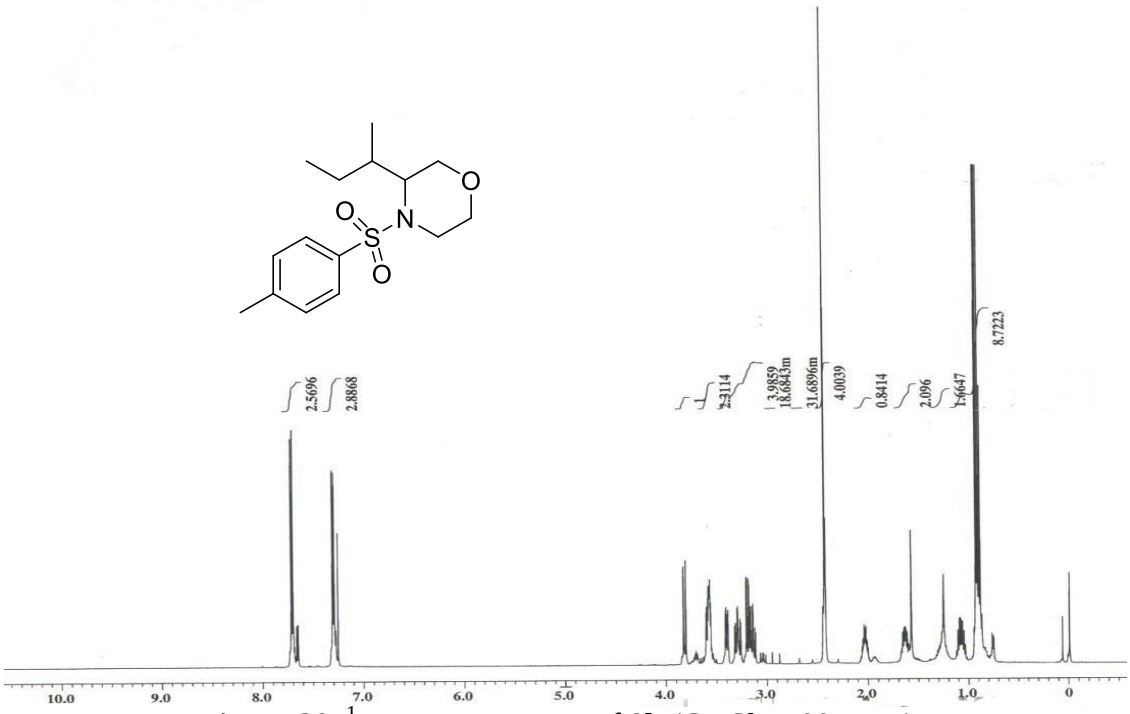


Figure 20. ^{1}H NMR spectrum of **9b** ($CDCl_3$, 500 MHz)

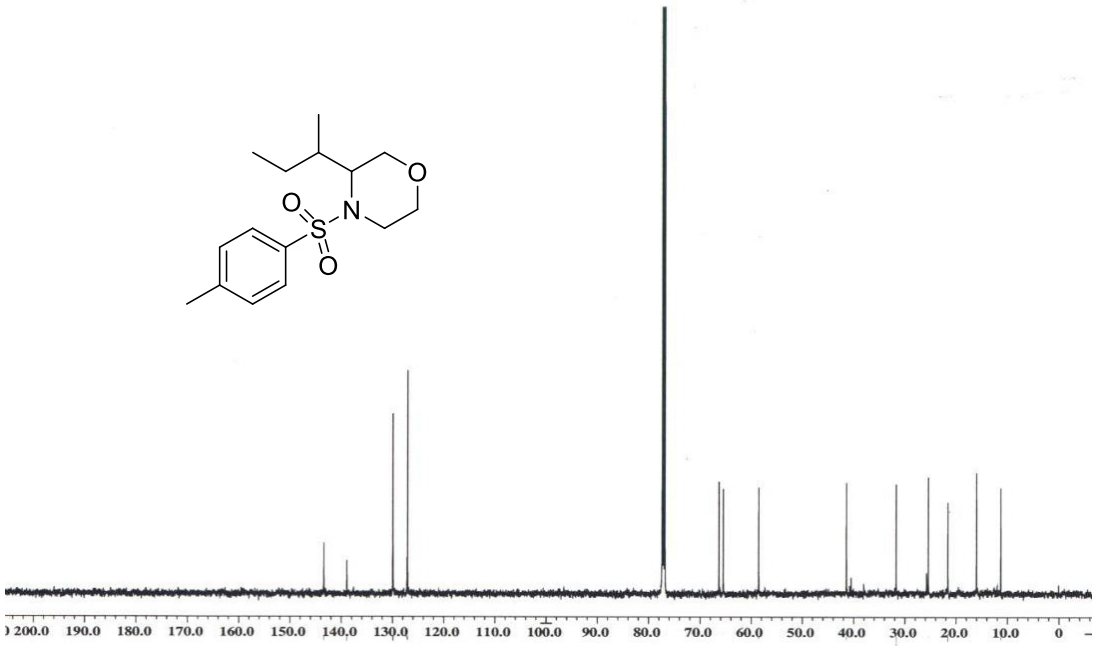


Figure 21. ^{13}C NMR spectrum of **9b** ($CDCl_3$, 125 MHz)

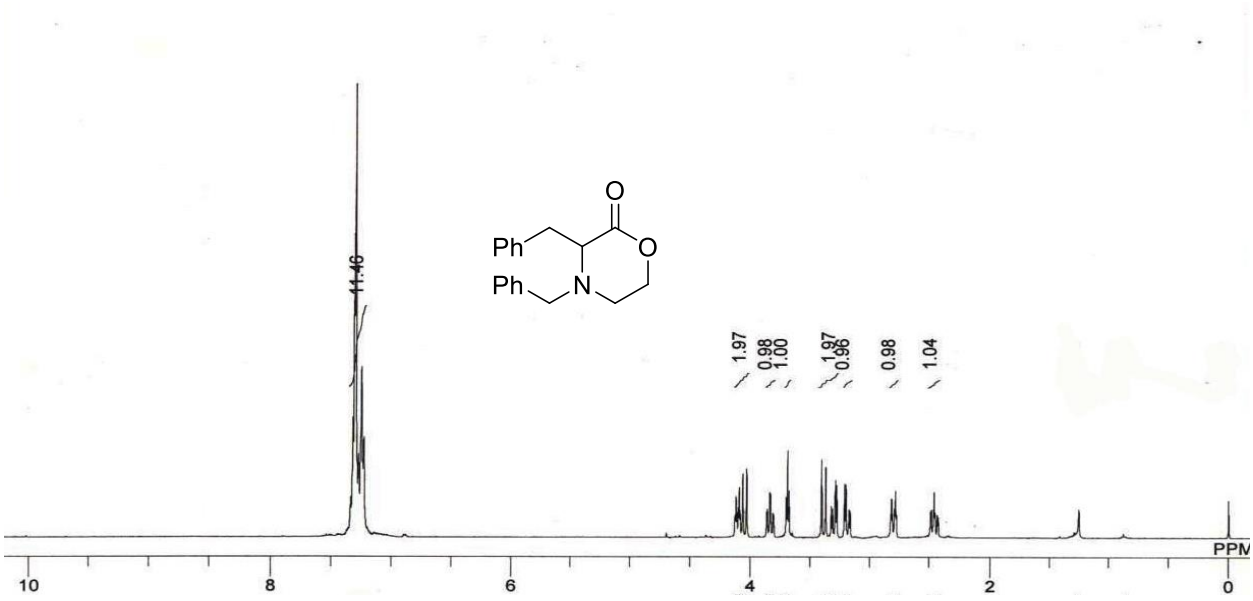


Figure 22. ^{1}H NMR spectrum of **11a** ($CDCl_3$, 400 MHz)

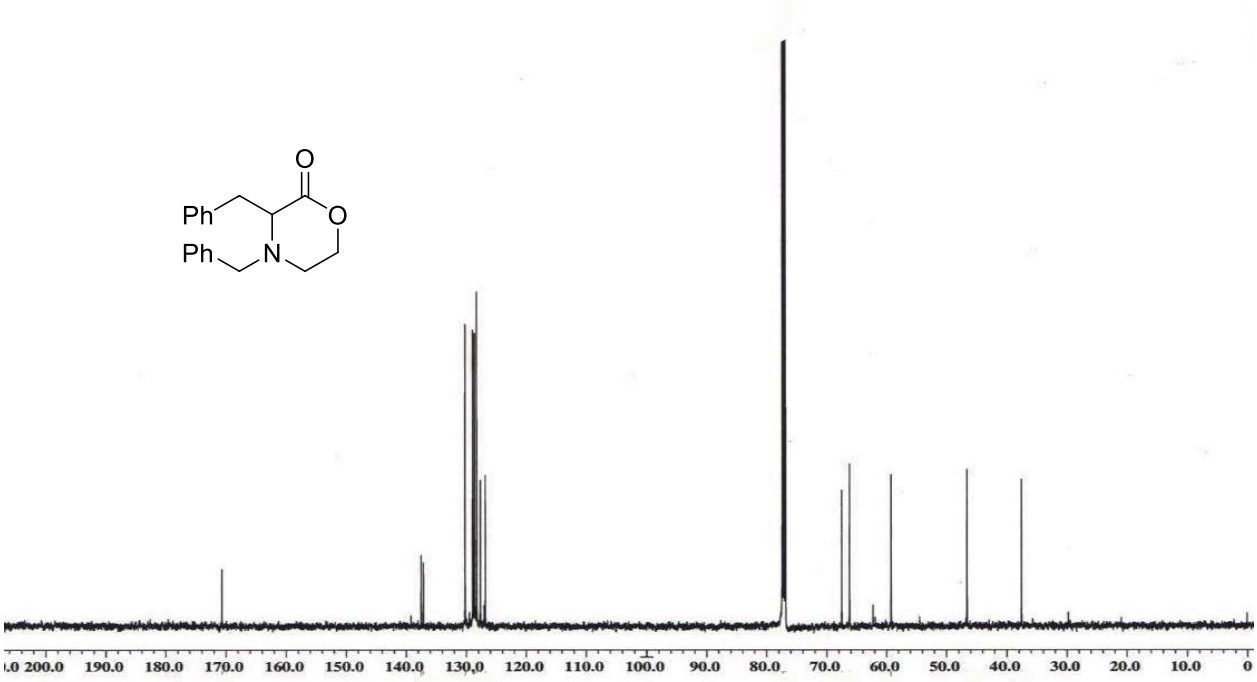


Figure 23. ^{13}C NMR spectrum of **11a** ($CDCl_3$, 100 MHz)

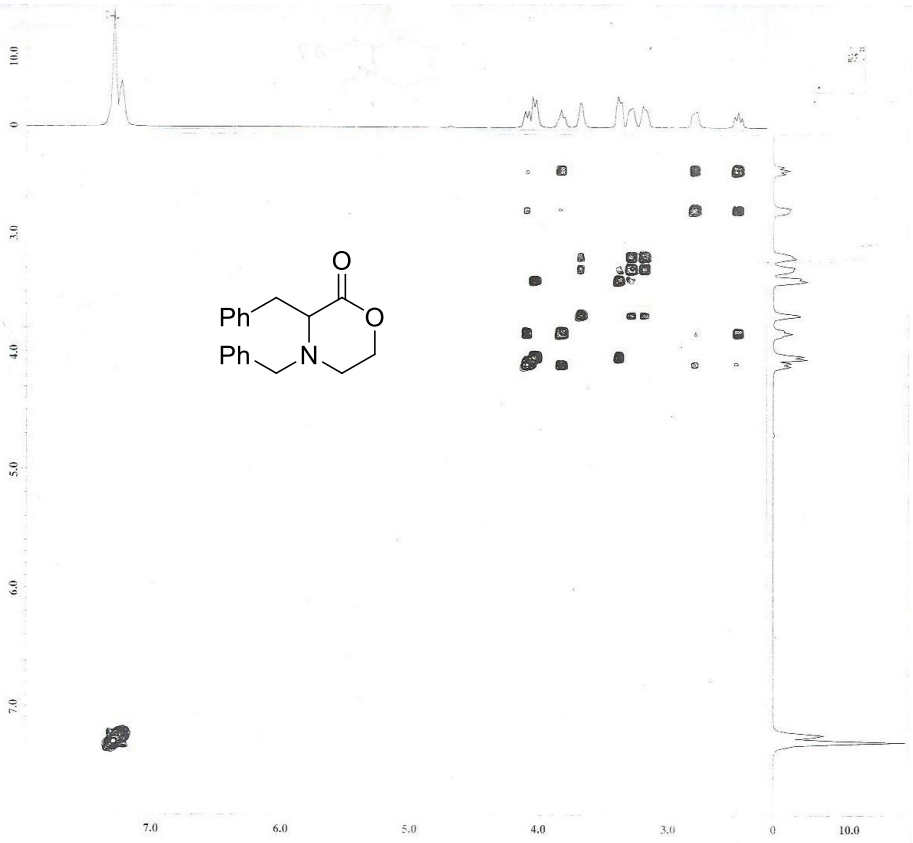


Figure 24. ^{1}H-^{1}H COSY spectrum of **11a** ($CDCl_3$, 500 MHz)

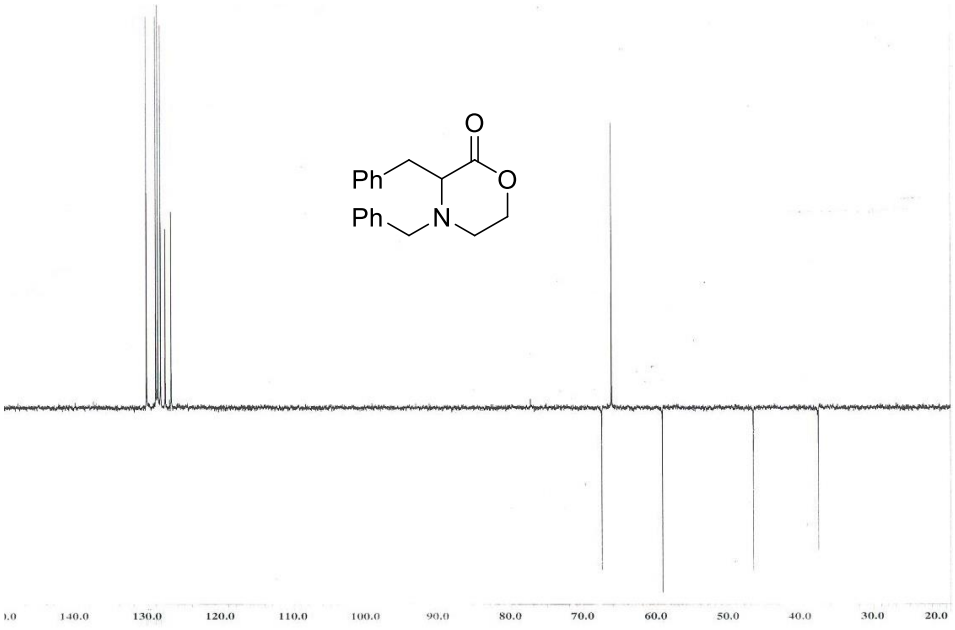


Figure 25. DEPT 135 spectrum of **11a** ($CDCl_3$, 125 MHz)

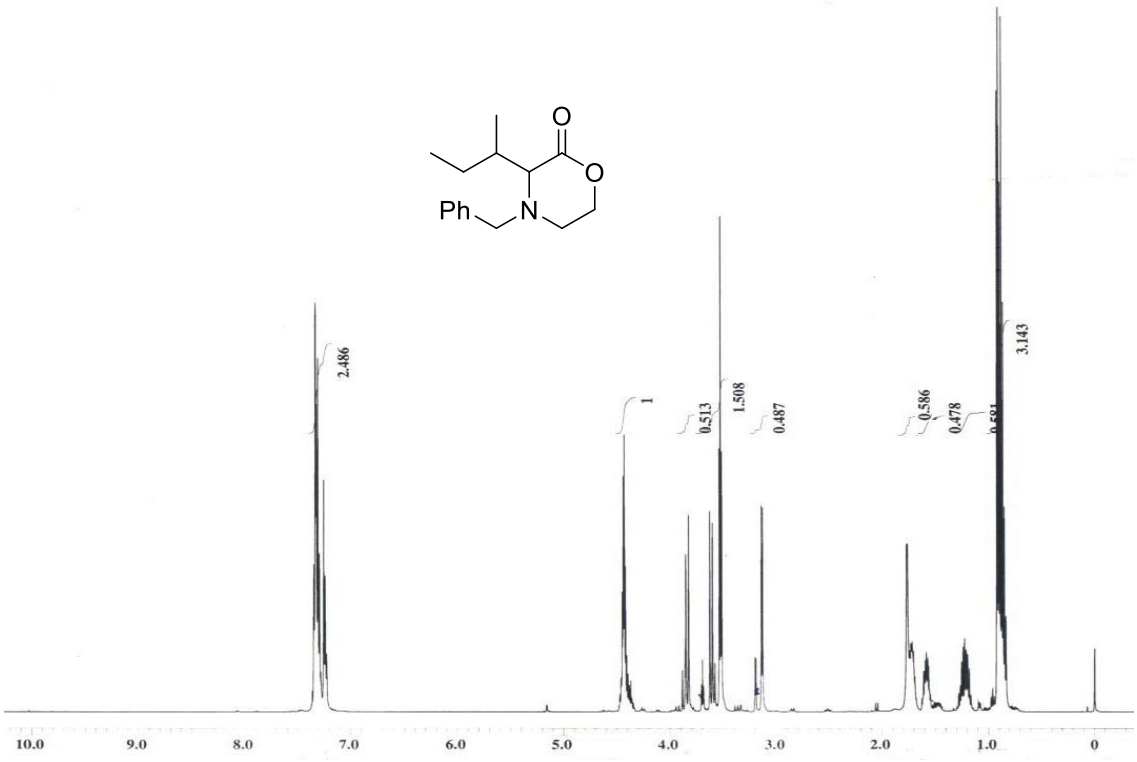


Figure 26. ^{1}H NMR spectrum of **11b** ($CDCl_3$, 500 MHz)

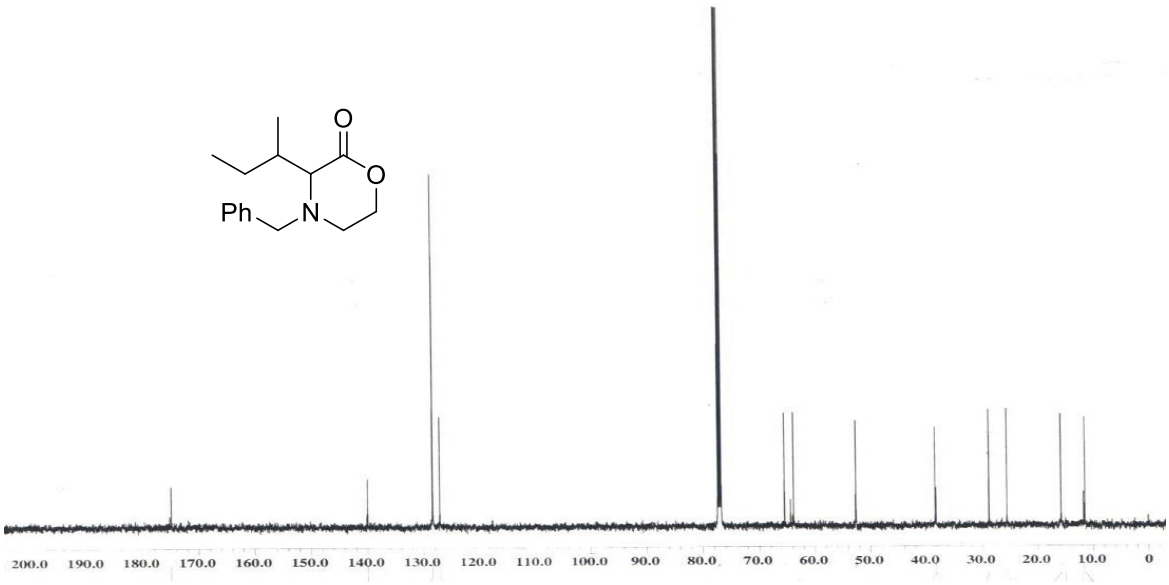


Figure 27. ^{13}C NMR spectrum of **11b** ($CDCl_3$, 125 MHz)

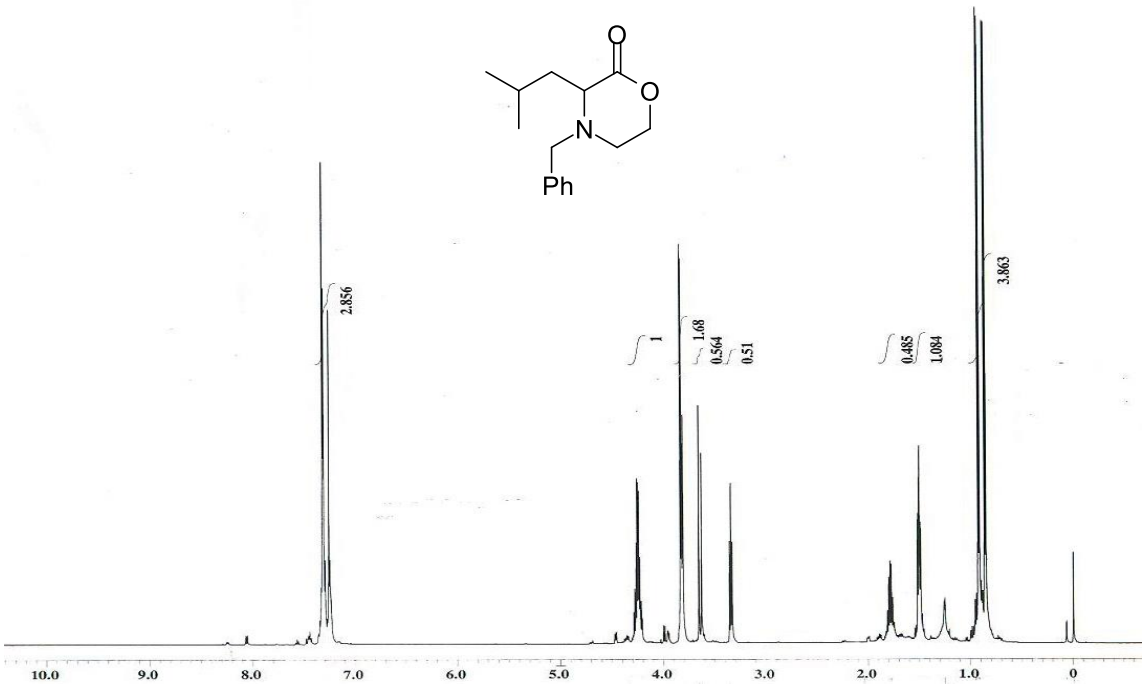


Figure 28. ^{1}H NMR spectrum of **11c** ($CDCl_3$, 500 MHz)

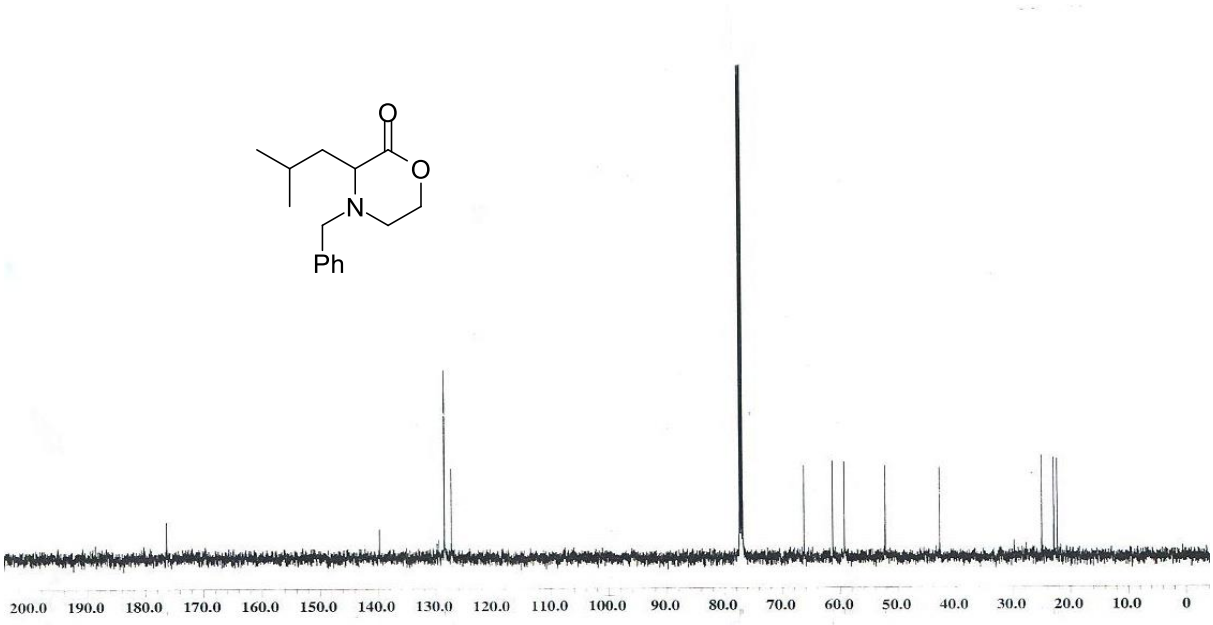


Figure 29. ^{13}C NMR spectrum of **11c** ($CDCl_3$, 125 MHz)

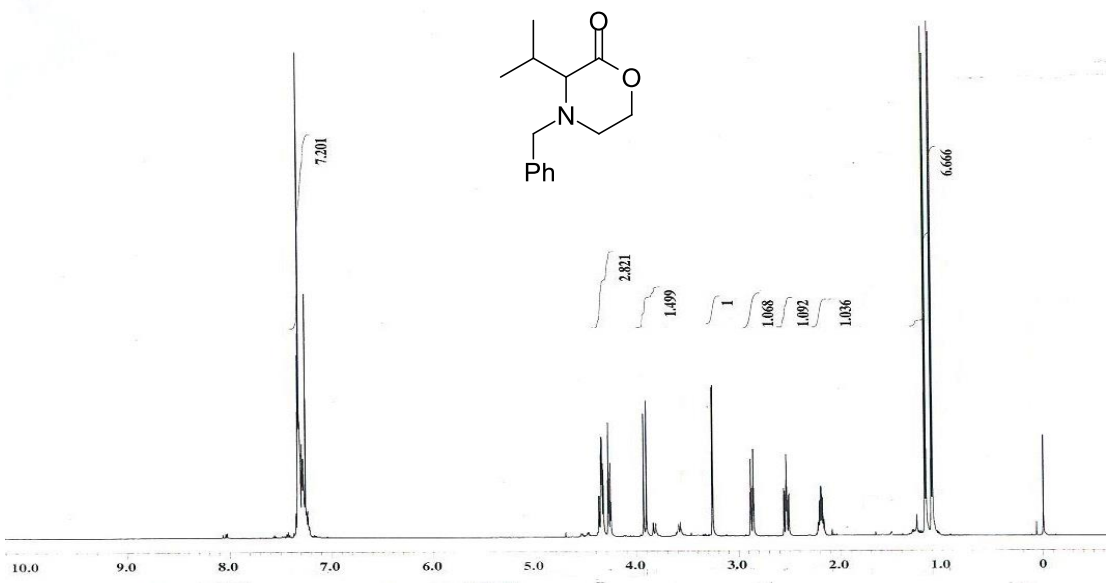


Figure 30. ^{1}H NMR spectrum of **11d** ($CDCl_3$, 500 MHz)

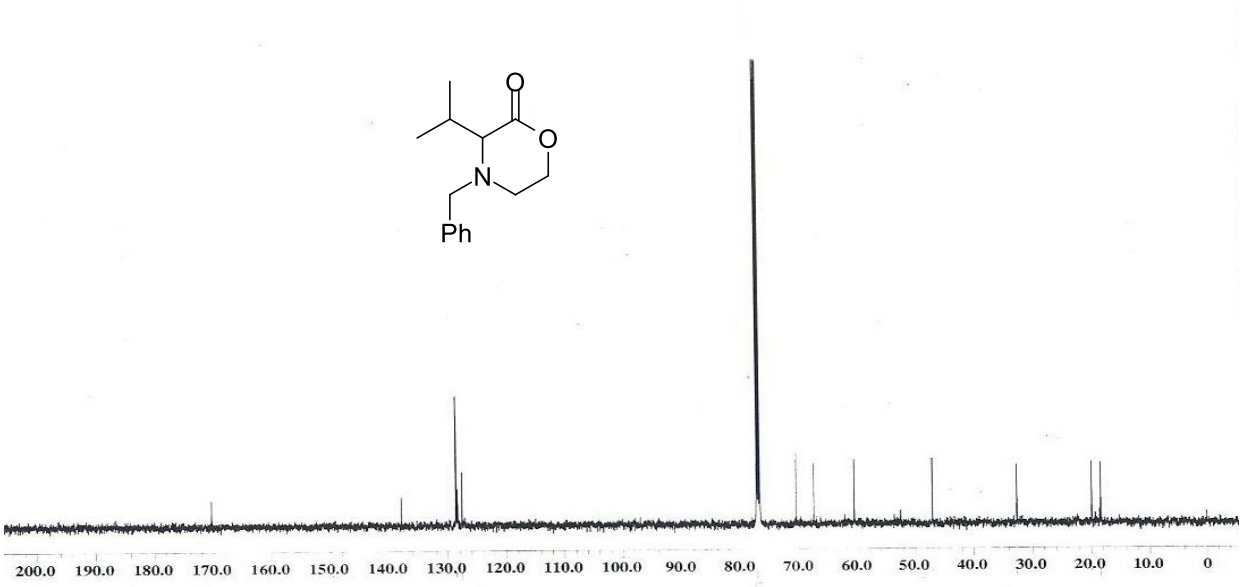


Figure 31. ^{13}C NMR spectrum of **11d** ($CDCl_3$, 125 MHz)

3. Selected HPLC chromatograms for *ee* determination:

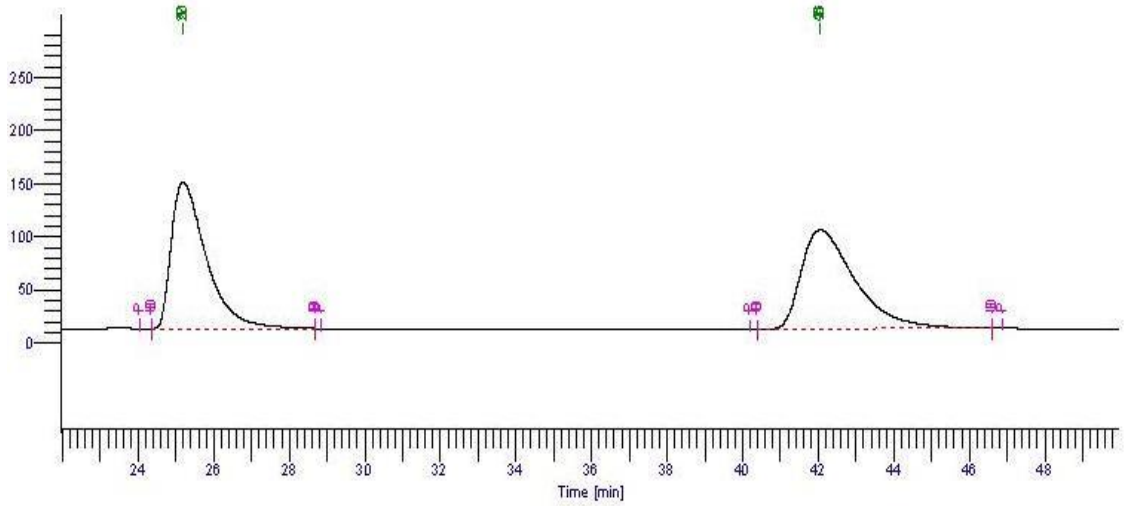


Figure 32. HPLC chromatogram of racemic compound **2b** (Cellulose 2 column; 90:10 Hexane−Isopropanol; 1.0 mL min^{-1})

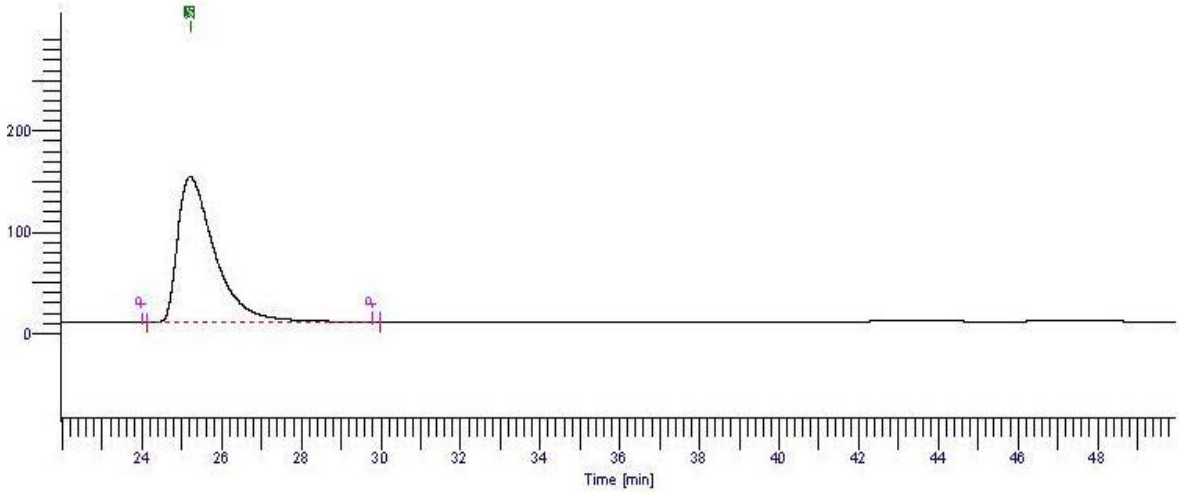


Figure 33. HPLC chromatogram of chiral compound **2b** (>99% *ee*; Cellulose 2 column; 90:10 Hexane−Isopropanol; 1.0 mL min^{-1})

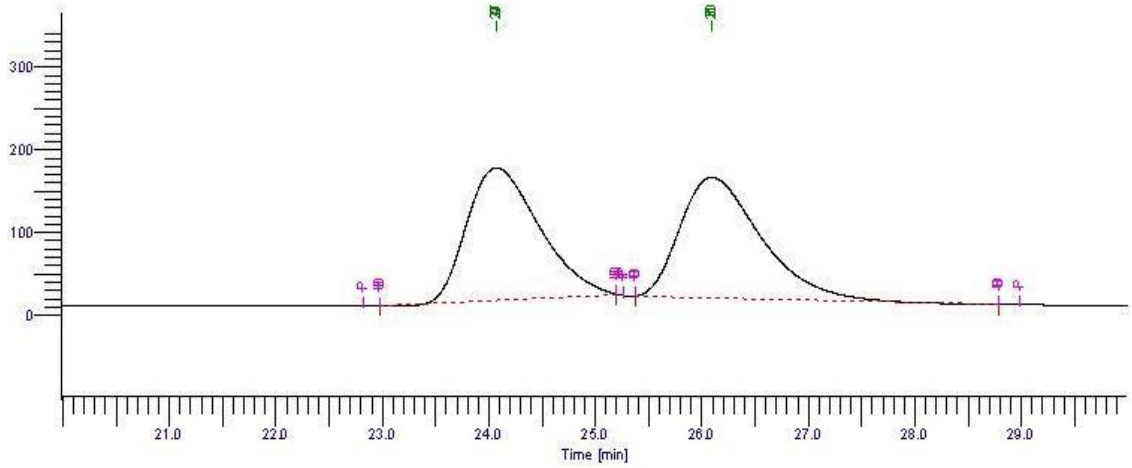


Figure 34. HPLC chromatogram of racemic compound **9a** (Cellulose 2 column; 90:10 Hexane−Isopropanol; 1.0 mL min^{-1})

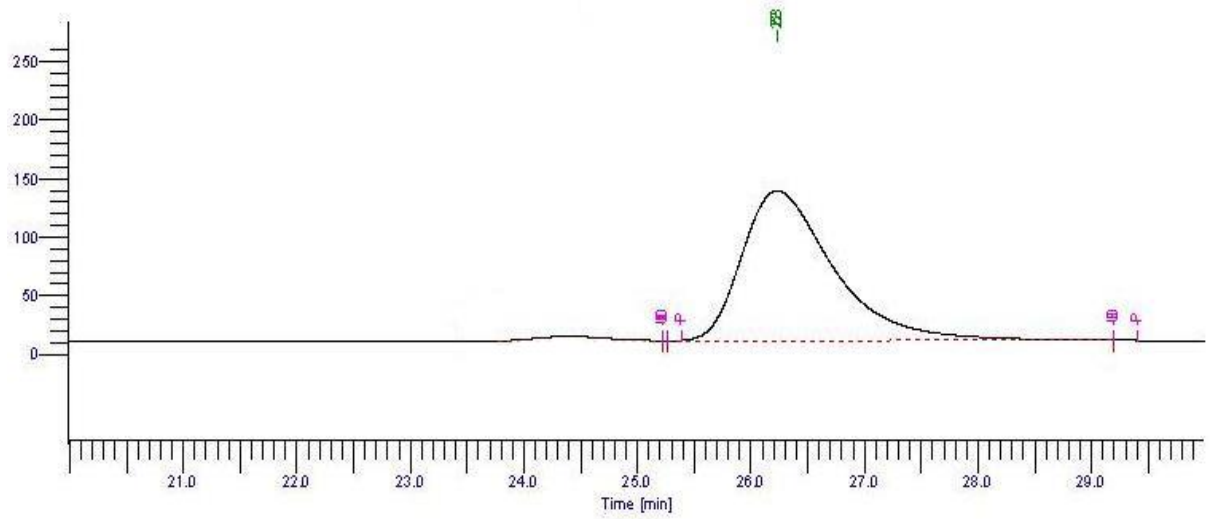


Figure 35. HPLC chromatogram of chiral compound **9a** (>99% *ee*; Cellulose 2 column; 90:10 Hexane−Isopropanol; 1.0 mL min^{-1})

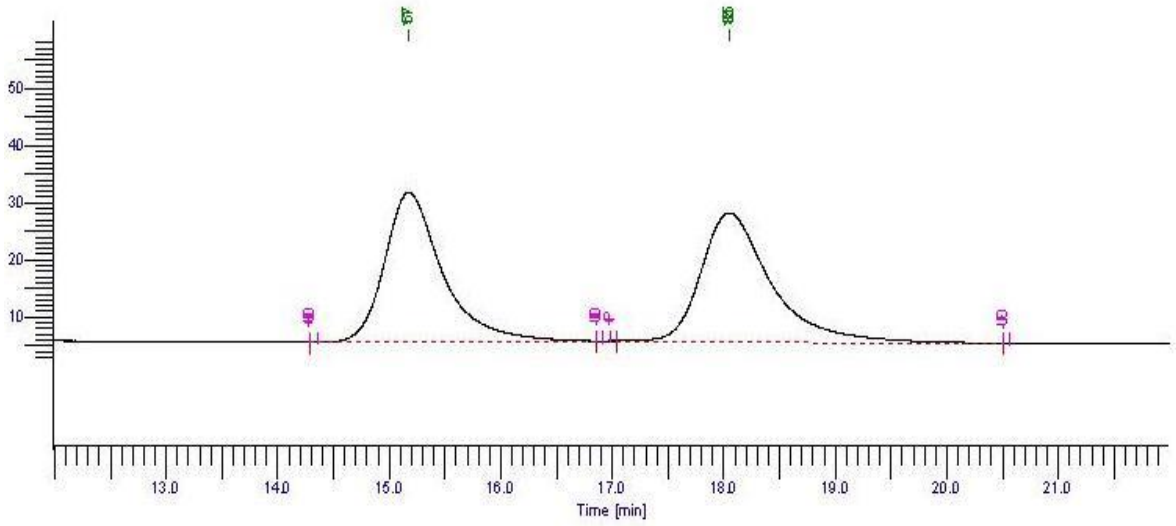


Figure 36. HPLC chromatogram of racemic compound **11a** (Cellulose 2 column; 90:10 Hexane−Isopropanol; 1.0 mL min^{-1})

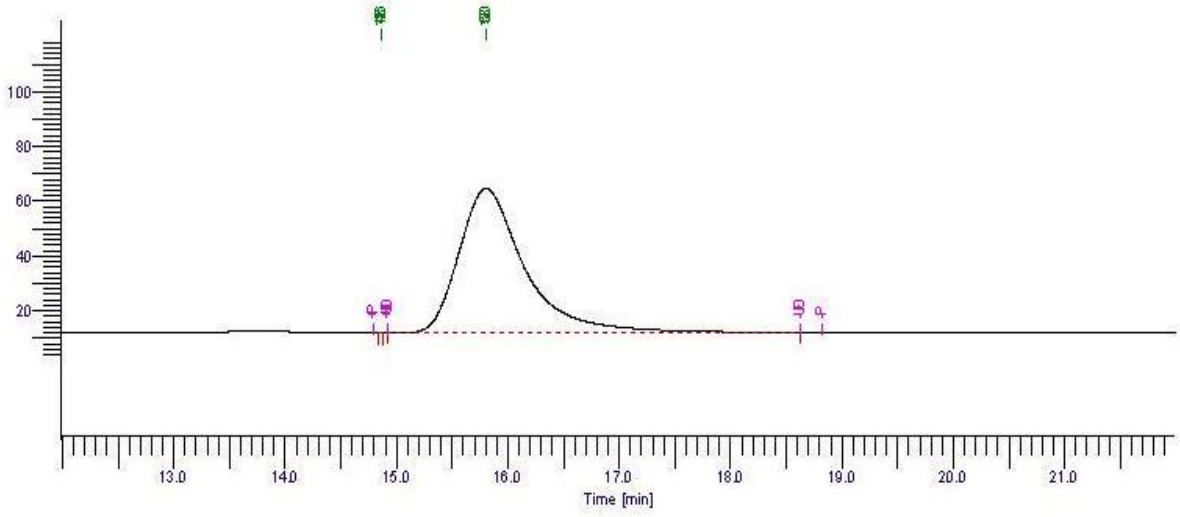
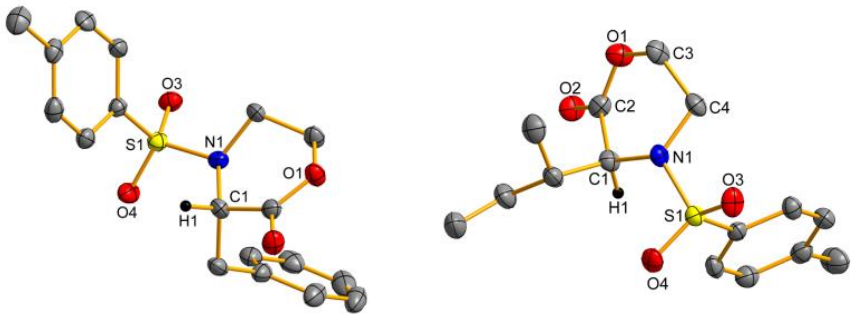


Figure 37. HPLC chromatogram of chiral compound **11a** (>99% *ee*; Cellulose 2 column; 90:10 Hexane−Isopropanol; 1.0 mL min^{-1})

4. X-ray crystal structures:



2a
CCDC No. 1033183

2b
CCDC No. 1033184

Figure 38. X-ray crystal structure of **2a** and **2b**

5. X-ray crystallographic analysis of 2a and 2b:

The crystals used in the analyses were glued to a glass fiber and mounted on SMART APEX diffractometer. The instrument was equipped with CCD area detector and data were collected using graphite-monochromated Mo Kα radiation (λ= 0.71069 Å) at low temperature (100K). Cell constants were obtained from the least-squares refinement of three-dimensional centroids through the use of CCD recording of narrow ω rotation frames, completing almost all-reciprocal space in the stated θ range. All data were collected with SMART 5.628 and were integrated with the SAINT[2] program. An empirical absorption correction was applied to collect reflections with SADABS[3] using XPREP[4]. The structure was solved using SIR-97[5] and refined using SHELXL-97[6]. The space group of the compounds was determined based on the lack of systematic absence and intensity statistics. Full matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All the hydrogen atoms are fixed by using geometrical constrains using idealized geometries and have been defined isotropically.

Table 1. X-ray crystallographic data and structure refinement

Compounds	**2a**	**2b**
Formula	$C_{18}H_{19}NO_4S$	$C_{15}H_{21}NO_4S$
Formula Weight	345.40	311.39
Crystal System	monoclinic	monoclinic
Space Group	$P2_1$	$P2_1$
Z	2	2
a, Å	6.2717(16)	8.0088(16)
b, Å	17.050(4)	6.2986(13)
c, Å	8.096(2)	15.589(3)
α, deg	90.00	90.00
β, deg	103.844(4)	90.284(4)
γ, deg	90.00	90.00
V, Å^3	840.6(4)	786.4(3)
d_{calcd}, g/cm^3	1.365	1.315
μ, mm^{-1}	0.214	0.221
F(000)	364	332
Refl. collected	5341	3983
Independent refl.	3094	2581
Refl. Observed [I >2σ (I)]	2527	2453
GOOF (F^2)	1.085	1.106
R_{int}	0.0494	0.0270
Final R indices	0.0484	0.0546
***[I > 2σ(I)]*[a]**	0.0963	0.1391
R indices (all data) [a]	0.0688	0.0575
	0.1180	0.1417

[a]Mo Kα radiation, [b]$R_1 = \sum \| F_0 \| - \| F_c \| / \sum | F_0 |$, [c]$wR_2 = \{\sum[w(F_0^2 - F_c^2)^2]/\sum[w(F_0^2)^2]\}^{1/2}$

6. References

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