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Minor Research Project

"Asymmetric Synthesis of (*R*)-Baclofen Using Nitrene Addition Via Aziridination Reaction."

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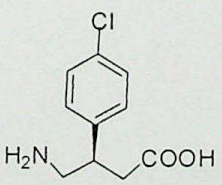
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"Asymmetric Synthesis of (*R*)-Baclofen Using Nitrene Addition Via Aziridination Reaction."

Introduction

(R)-Baclofen is the strongly lipophilic β-substituted analogue. Baclofen (γ-amino-β-(p-chlorophenyl)butyric acid is a derivative of γ-aminobutyric acid (GABA), plays an important role as an inhibitory neurotransmitter in central nervous system (CNS) of mammalians. The simple amino acid has two major receptor subtypes, GABAA and GABAB. These receptors play a distinct role in central and peripheral nervous system through ion-channel regulation. The overall physiological effects are transmission inhibitions, mediated, pre and post-synaptically by GABAA sites and presynaptically by GABAB sites. However, baclofen is the only potent and selective GABAB agonist known so far against bicuculline receptor. In contrast to that of simple GABA, baclofen is the most lipophilic and can penetrate to blood/brain barrier. Consequently, baclofen helps to reduce the excitatory effect of active compounds such as benzodiazepine, barbiturates, etc. The deficiency of GABA is associated with diseases that exhibit neuromuscular dysfunctions such as epilepsy, Huntington, Parkinson's' disease, etc. Baclofen is one of the promising drugs in treatment of the paroxysmal pain of trigeminal neuralgia as well as spasticity of spinal without influencing the sedation. Research has shown that for baclofen, the pharmacological activity resides in the (R)-enantiomer only.



(*R*)-(-)-Baclofen

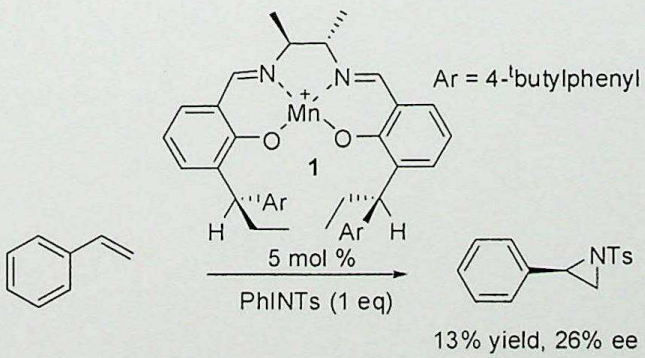
Figure 1.

There are many methods available in the literature on the synthesis of (*R*)-baclofen.[3-5] They are concerned mostly with resolution, chemoenzymatic or enantioselective synthesis.[6] In this context, a more practical approach for the synthesis of (*R*)-baclofen is highly desirable. The present synthetic strategy for the synthesis of (*R*)-baclofen is depicted in **Scheme 11**. The key precursor, asymmetric aziridination via nitrene insertion reaction of 4-chlorostyrene with bromamine-T as a nitrene source and selectively aziridine ring opening, decarboxylation, and hydrolysis.

Chiral aziridines are used widely in organic synthesis.[7-18] The readily available methods for stereo- and regioselective ring opening or expansion of the strained aziridine rings allow quick access to a variety of chiral amines, which would be useful building blocks for natural product synthesis. Due to the versatile utilities of chiral aziridines in organic synthesis, the development of efficient enantioselective synthetic methods for chiral aziridines has received considerable interest.

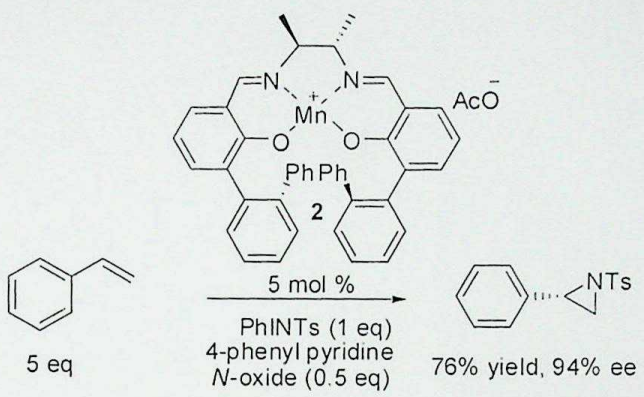
Review of Literature: Asymmetric aziridination of alkenes

Katsuki *et al.*[7] reported for the first time asymmetric aziridination of alkene catalysed by chiral salen-manganese(III) complexes **1**. Optically active salen complex was found to show moderate level of asymmetric induction in the aziridination of styrene, though chemical yield was poor (**Scheme 1**).



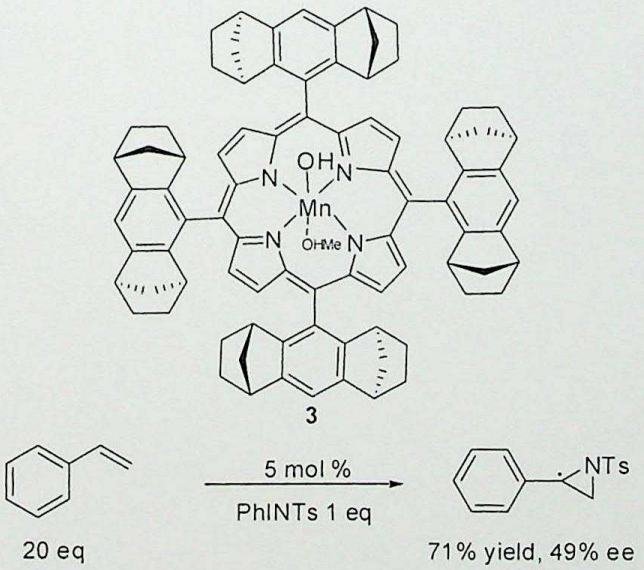
Scheme 1: First asymmetric Mn^{III} catalytic aziridination

High enantioselectivity was obtained with newly designed salen-manganese(III) complex **2** as a catalyst in combination with 4-phenylpyridine *N*-oxide (**Scheme 2**). Thus styrene is converted to its *N*-tosyl aziridine compound in 76% yield and in 94% ee.



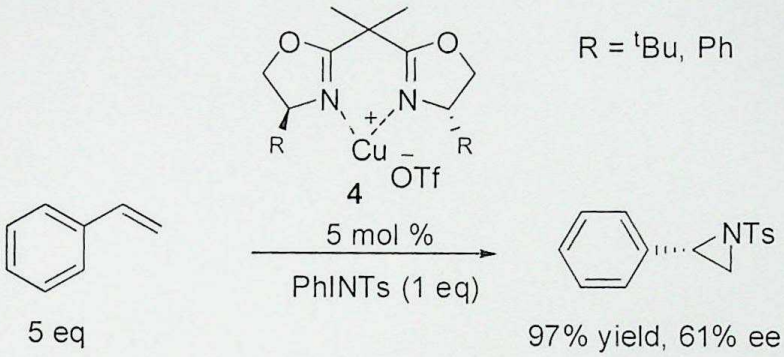
Scheme 2: Asymmetric Mn^{III} catalytic aziridination

Che *et al.*[8] reported that D_4-manganese(III) porphyrin complex **3** catalyzed aziridination of alkenes in which the complex **3** enables asymmetric aziridination of styrene derivatives with moderate enantioselectivities (**Scheme 3**).



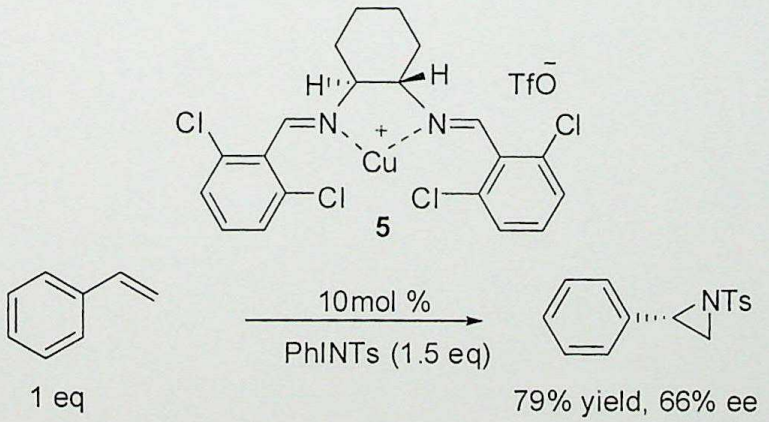
Scheme 3: D_4-Mn^{III} Porphyrin catalyst for asymmetric aziridination

Among all the reported methods, transition metal-catalyzed asymmetric alkene aziridination has drawn a lot of attention. Evans *et al.*[9] introduced a series of bis(oxazoline)-Cu-complexes **4** as chiral catalysts for the enantioselective aziridination of olefins. Upto 67% ee was achieved with aryl substituted olefins with PhINTs as the nitrene source and CuOTf as the metal salt (**Scheme 4**).



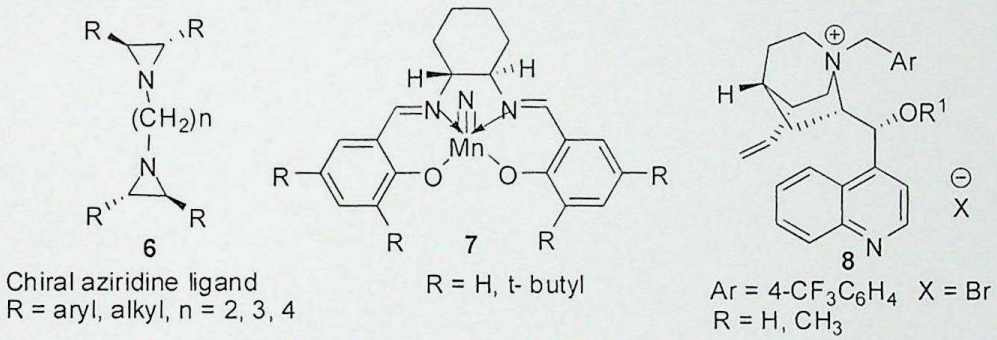
Scheme 4: Evans bis(oxazoline)-Cu catalyzed asymmetric aziridination

In the same year, Jacobsen *et al.*[10] published a paper on asymmetric aziridination of styrene with readily available chiral diamine-based catalyst **5**. Three such ligands/catalysts are reported and upto 98% ee was achieved with some of the substrates (**Scheme 5**).



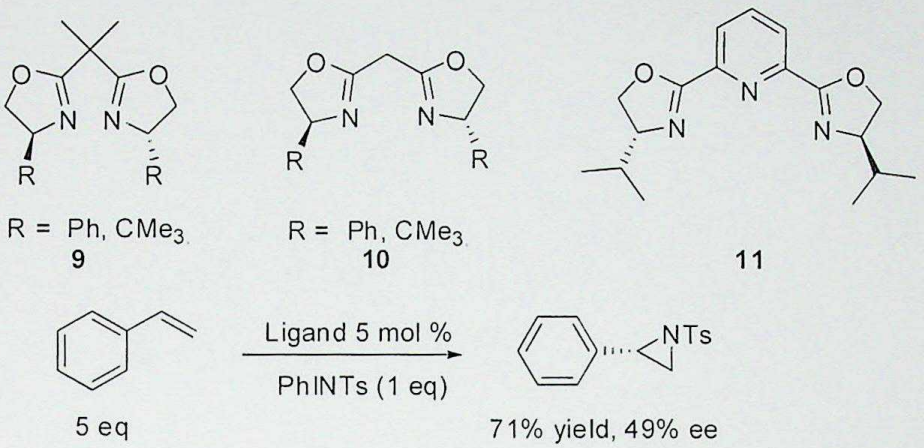
Scheme 5: Jacobsen's Cu-catalyzed asymmetric aziridination

C_2-Symmetric bis(aziridines) **6** as a new class of chiral ligands for transition metal-mediated asymmetric synthesis was developed by Tanner *et al.*[11] who reported upto 33% ee with styrene in the aziridination reaction. Komatsu[12] reported a novel asymmetric and stereospecific aziridination of alkenes with a chiral nitridomanganese complex **7** where use of additives like pyridine N-oxide to enhance performance and selectivity was also mentioned. Moderate to good enantioselectivity of aziridination could be achieved[13] with chiral quaternary salts based on cinchona alkaloid **8**, especially with that of cinchonine (**Scheme 6**).



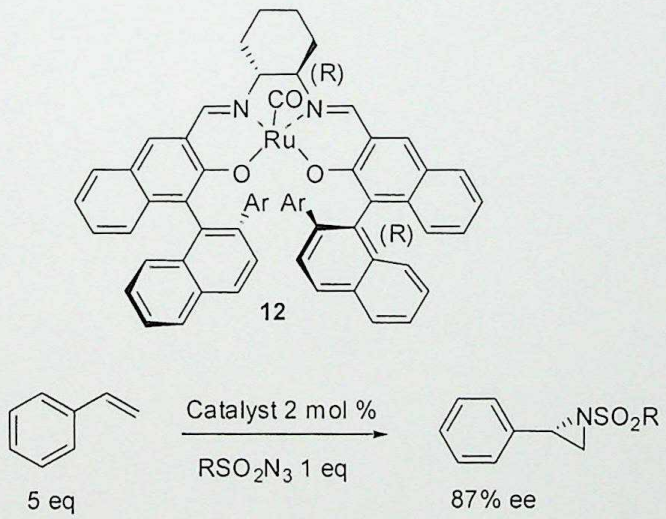
Scheme 6: Jacobsen's Cu-catalyzed asymmetric aziridination

The first catalytic asymmetric heterogeneous aziridination of styrene with CuHY (copper exchanged zeolite H-Y) and modified by chiral bisoxazolines (**9, 10, 11**) with moderate ees was reported by Hutchings *et al.*[14] who used PhINTs as the source of nitrene (**Scheme 7**).



Scheme 7: Bis-oxazolines Cu-catalyzed asymmetric aziridination

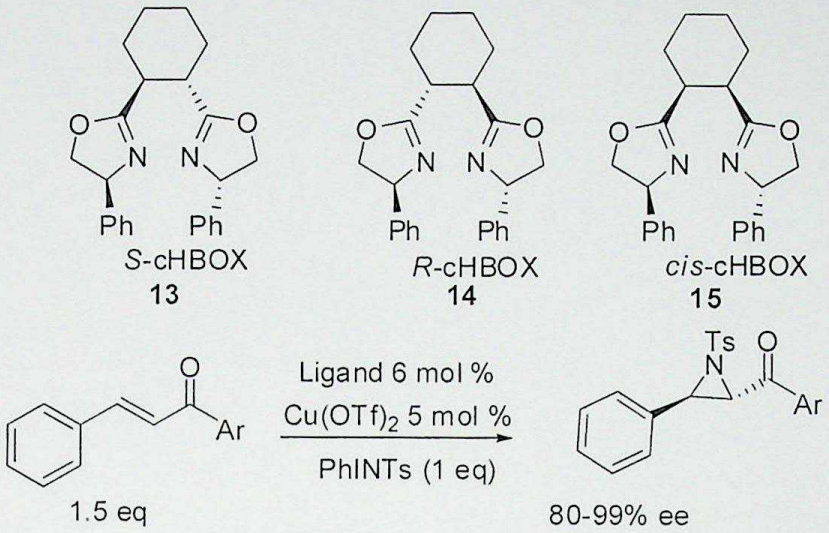
Recently Katsuki *et al.*[15] reported design of a robust Ru(salen) complex **12** in aziridination of alkenes with an improved turnover number (TON). Enantioselectivities up to 87% have been reported with styrene and other alkenes (**Scheme 8**).



Scheme 8: Ru(salen)(CO)-catalyzed asymmetric aziridination using azide compound

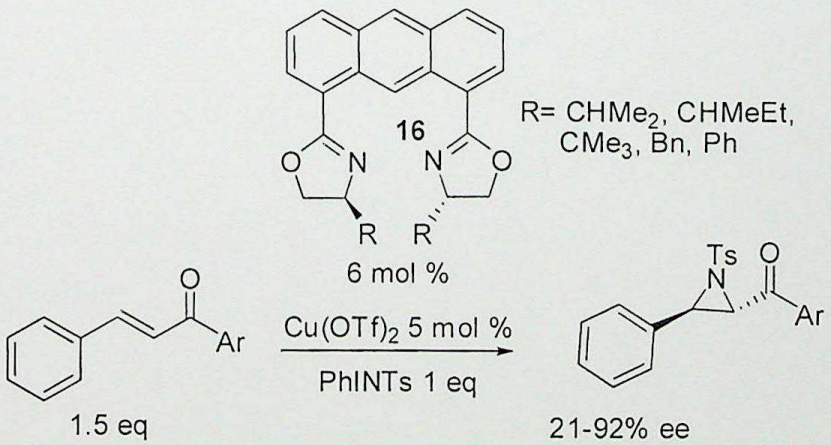
Other ligands used are S-Vapol and S-Vanol[16] in the catalytic asymmetric aziridination from benzhydryl imines and ethyldiazoacetate.

Jiaxi *et al.*[17] developed a new class of cyclohexane-linked bis-oxazolines (**13**, **14**, **15**). They found that highly enantioselective aziridination of chalcones with >99% ee could be achieved using these ligands (**Scheme 9**).



Scheme 9: cHBOX- Cu-catalyzed asymmetric aziridination of chalcones

In the same year Jiaxi *et al.*[18] reported a rigid backbone 1,8-anthracene-linked bis-oxazolines (AnBOXs) **16** and evaluated them for the catalytic asymmetric aziridination with PhINTs as a nitrene source. The results indicated that highly enantioselective aziridination of chalcones catalyzed by AnBOX and CuOTf complex could be achieved with excellent ees and the opposite enantioselectivity, compared with the Evans bis(oxazoline) ligands (**Scheme 10**).



Scheme 10: Cu-catalyzed asymmetric aziridination of chalcones

Present Work:

The development of $CuCl_2$ and chiral catalytic system for enantioselective aziridination reaction using bromamine-T[19] as a source of nitrene donor, utilizing substrates which can be valuable intermediates for further transformation. Different chiral ligand utilized for this reaction Therefore, we are the first to show the use of combination of bromamine-T and chiral ligand (**Figure 2**) is useful method for chiral aziridination reaction of alkene.

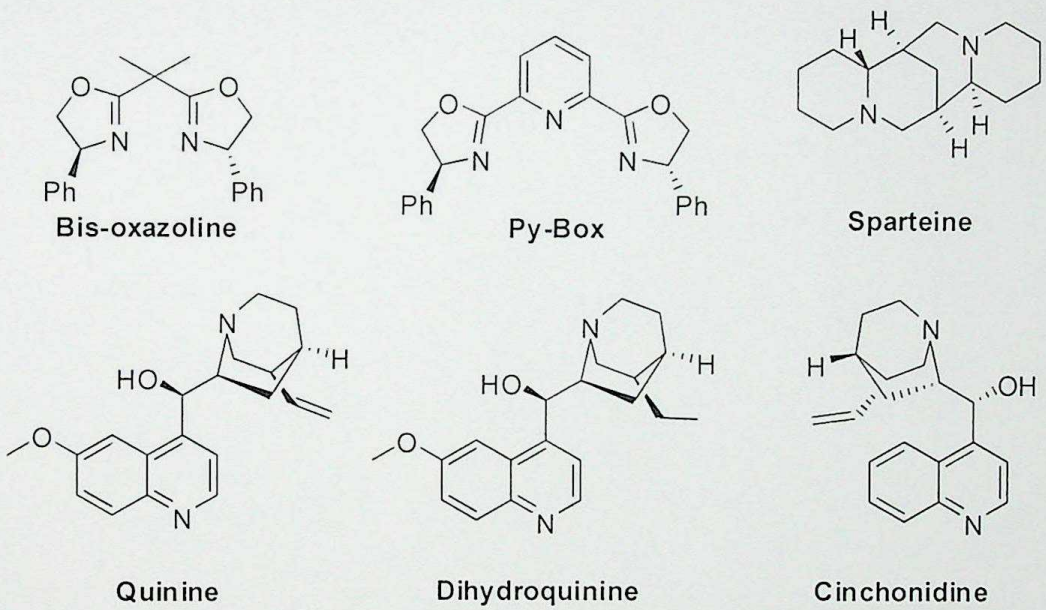
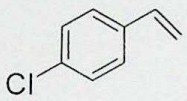
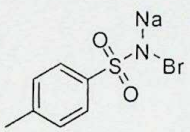


Figure 2

Result and discussion:

Strategy for asymmetric synthesis of (*R*)-(-)-Baclofen is as represented in the **Scheme 11**. Herein, we made use of asymmetric aziridination of 4-Chlorostyrene **17** to bromamine-T and $CuCl_2$ and different chiral ligands as a catalyst in dry acetonitrile solvent for 6 h to provide aziridine **18** in 87% yield with highest 68% ee (**Table 1**)

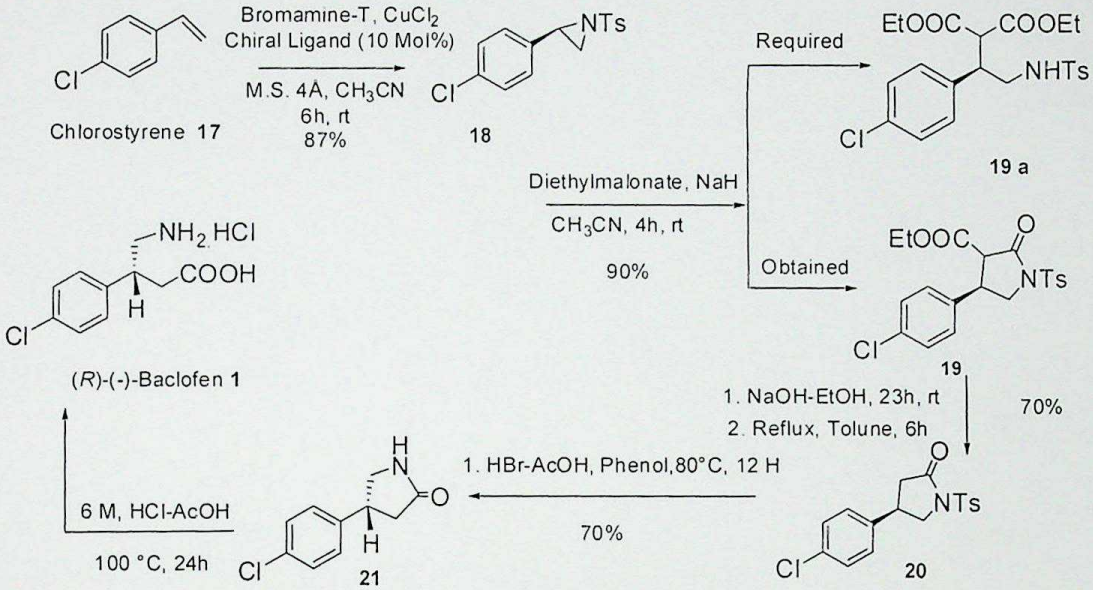
Table 1. Asymmetric aziridination of 4-chlorostyrene using chiral ligands with Bromoamine-T

Substrate		Ligand	Cu(II)	Yield (%)	ee (%)
 4-chlorostyrene	 Bromoamine-T	Quinine	$CuCl_2$	69	10
		Dihydroquinine	$CuCl_2$	46	25
		Cinchonidine	$CuCl_2$	52	13
		Bis-oxazoline	$CuCl_2$	87	68
		Py-Box	$CuCl_2$	65	-
		Sparteine	$CuCl_2$	47	-
		Quinine	$Cu(OTf)_2$	59	14
		Dihydroquinine	$Cu(OTf)_2$	62	20
		Cinchonidine	$Cu(OTf)_2$	74	-
		Bis-oxazoline	$Cu(OTf)_2$	60	55
		Py-Box	$Cu(OTf)_2$	55	-
		Sparteine	$Cu(OTf)_2$	44	-

The aziridine **18** ring open with diethylmalonate anion in base like sodium hydride formation of required addition product **19a** but after product analysis using FT-IR and NMR we could not find out required compound, instead of formation of cyclised monoester derivative **19** .

Cyclised Monoester **19** was characterized by the spectroscopic method by ^{1}H NMR spectrum **shows** only one **–COOCH$_2$CH$_3$** resonate triplet at δ 1.21 (–COOCH$_2$**CH$_3$**) and δ 4.13 - 4.19 as quartet (–COO**CH$_2$**CH$_3$), benzylic **CH** as multiplet at δ 4.23. In cyclic methylinic group neighboring to Nitrogen resonate at δ 3.59-3.64 as a doublet and active

acidic proton in between carbonyl and ester group is resonating as doublet at δ 3.78-3.82 remaining signals belong to aromatic proton.



Scheme 11: Synthesis of (*R*)-(-)-Baclofen:

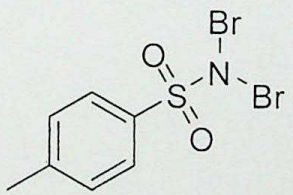
Its ^{13}C-NMR and DEPT spectrum showed carbon signal at δ 51.55, 62.18 and 166, 167 corresponding to methylinic group (ethyl ester **CH_2** and cyclic -N-**CH_2**- respectively and relative peak observed in conform in DEPT spectra another ester carbonyl group and cyclic ketone **–C=O**, resonate at δ 166 and δ 167 respectively

Decarboxylation of **19** with 20 % sodium hydroxide solution in ethanol (15 ml) resulted in the formation of salt which subsequently reflux in toluene. The formed compound **20** was characterized by the ^{1}H NMR in which ethyl group signal absent and additional proton involved in spectra confirming the formation of compound **20.** In next step, detosylution carried out in acidic mediumin using phenol with HBr in acetic acid to obtained lactum **21** which confirm my spectroscopic data like PMR and CMR, related tosyl group signal absent in spectra. Finally, it was hydrolyzed with 6N HCl afford enantiomerically pure (R)-(-)-Baclofen as its hydrochloric Salt. The IR, ^{1}H-NMR and ^{13}C-NMR spectral data of R)-(-)-Baclofen matched very well with reported data.

Experimental Section:

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC at 300 MHz and 50 MHz respectively. IR spectra were recorded on Perkin-Elmer FT IR instrument. Optical rotations were measured as $CHCl_3$ solution using Jasco P-1020 digital polarimeter. Microanalyses were performed on a Flash EA-1112 Thermo Finnigan Elemental Analyser. Chiral HPLC was performed on a SHIMADZU Class-VP using a Chiracel OD column. Melting points were determined by using a Yanco Micro Melting point apparatus and were uncorrected. Purification and separations by column chromatography were performed on silica gel, using flash chromatography. Acetonitrile and DCM were dried and distilled under nitrogen. TLC visualization was achieved by spraying with 2% ethanolic phosphonomolybdic acid and anisaldehyde charring solution. 4-Chlorostyrene, quinine, cinchonidine, dihydrocinchonidine, spartine was purchased from adrich, and loba, Bis-oxazoline and Py-Box synthesize using reported method.

Preparation of Dibromamine-T



Recrytsallized chloramine-T (1.0 g, 4 mmol) was dissolved in water (20 mL) and liquid bromine (2 ml, 12 mmol) was added dropwise from addition funnel with constant stirring of the solution. The golden yellow precipitate of the dibromamine-T was thoroughly washed with water, filtered under suction and dried in a vacuum dessicator for 24 h.

Mol. Formula : $C_7H_7O_2Br_2NS$

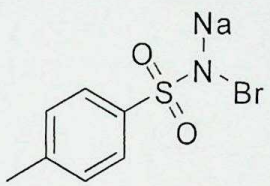
Mol. Weight : 329

M.P. : 92 °C (lit M.P. 92-93 °C)

Analysis : Calcd: N, 4.20; S, 9.70; Br, 48.6 %

: Found: N, 4.26; S, 9.73; Br, 48.56 %

Preparation of Bromamine –T



Dibromamine-T (3.3 g, 11 mmol) was dissolved in small lots at a time with stirring, in aqueous solutions of sodium hydroxide (0.8 g, 20 mmol) in 50 mL of water, and the solution was cooled in ice. Pale yellow crystals of bromamine-T separated out. The solid was filtered under suction, washed quickly with minimum quantity of water and dried over P_2O_5 in a desiccator, yield 2.8 g (86%), mp. 112 °C.

Mol. Formula : $C_7H_7BrNNaO_2S$

Mol. Weight : 272

FT IR ($CHCl_3$) : 3020,1741, 1331, 1215, 1163, 882, 759 cm^{-1}

^{1}H NMR (300 MHz, D_2O) : δ 2.41 (s, 3H), 7.43 (d , *J* = 1.9 Hz, 2H), 7.71 (d, *J* = 1.9 Hz, 2H)

^{13}C NMR (75 MHz, D_2O) : δ 143.38, 134.30, 131.26, 129.31

ESI-MS *m/z* : 273.09 $[M+H]^+$

Elemental Analysis : Calcd: C, 30.90; H, 2.59; Br, 29.37; N, 5.15; S, 11.78 %

Found: C, 30.87; H, 2.63; Br, 29.05; N, 5.28; S, 11.61 %

N-p-Toluenesulfonyl-2-(p-chlorophenyl)-aziridine 18.

To a stirred suspension of Bromamine-T (2 g, 7.35 mmol) and $CuCl_2$ (98 mg, 0.735: 10 mol %), Molecular sieves 4Å and chiral ligand 10 mol% in dry acetonitrile (20 mL) was added dropwise p-chlorostyrene **17** (5.09 g, 36.75 mmol) at 0°C. The mixture was stirred for 6 h at room temperature. In this reaction were added ice cold water and extracted with ethylacetate, the extract was washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by column chromatography over silica gel with hexane-ethylacetate (9 : 1) gave a crystalline residue. Recrystallization from hexane-AcOEt gave the compound **28** as colorless crystals (1.98 g, 87 %), m.p. 113-114 °C.

Mol. Formula : $C_{15}H_{14}ClNO_2S$

Mol. Weight : 307

FT IR ($CHCl_3$) : 3017, 1600, 1327, 1217, 1161, 867 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : 2.41 (s, 3 H), 3.35 (dd, J = 7.0 & 4.3 Hz, 1 H), 3,43 (dd, J = 7.0 & 4.3 Hz, 1 H), 4.84 (t, J = 7.0, 1H), 7.17-7.30 (m, 6 H), 7.66-7.70 (d, 2 H);

^{13}C NMR (75 MHz, $CDCl_3$) : 21.5, 35.9; 40.2; 122.9; 128.7; 129.7; 133.6; 134.6; 134.1; 134.8; 144.7.

Ethyl 4-(4-chlorophenyl)-2-oxo-1-tosylpyrrolidine-3-carboxylate **19.**

To a stirred suspension of Sodium hydride (2 g, 7.35 mmol) in dry acetonitrile (25 ml), was added solution of aziridine **18** (1.46 g, 4.74 mmol) and Diethylmalonate (0.911 g, 5.69 mmol) in dry acetonitrile at 0°C. The mixture was stirred for 4 h at room temperature. In this reaction were added ice cold solution of ammonium chloride and extracted with ethyl acetate, the extract was washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by column chromatography over silica gel gave a colorless crystals of **19** (1.82 g, 90 %), m.p. **82** °C.

Mol. Formula : $C_{20}H_{20}ClNO_5S$

Mol. Weight : 421

FT IR ($CHCl_3$) : 1765, 1715,, 1635, 1450 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.21 (t, *J* = 7.6 Hz, 3H), 2.46 (s, 3H), 3.59 (d, 1H), 3.72-4.12 (dd, 2H), 4.13-4.19(m, 3H), 4.31-4.40(q, *J* = 7.6 Hz, *2H*), 7.15-7.38 (dd, *J* = 2.5 Hz, 6H), 7.92-7.96 (d, *J* = 2.5 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 13.95, 21.70, 40.95, 51.56, 56.37, 62.19, 126.80, 128.19, 129.15, 129.81, 134.53, 137.73, 145.62, 166.98, 167.30

N-Tosyl-4-(p-chlorophenyl)-pyrrolidin-2-one 20.

Compound **19** (500mg, 1.19 mmol) hydrolyze with 20 % sodium hydroxide solution in ethanol (15 ml) with stirring at room temperature for 23h. The sodium salt of

compound 19 then refluxed in toluene for 6 h. The mixture was extracted with CH_2Cl_2 and the extracts were washed with water, dried over $Na2SO_4$. The organic phase was removed *in vacuo* and the residue obtained was purified using silica gel chromatography to yield the lactam **20** as colorless needles (70%), m.p. 105°C.

Mol. Formula : $C_{17}H_{16}ClNO_3S$

Mol. Weight : 349

FT IR ($CHCl_3$) : 1665, 1545, 1452, 890 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : 2.46 (s, 3 H), 2.56 (dd, J = 17.2 and 8.9 Hz, 1 H), 2.85 (dd, J = 17.2 and 8.3 Hz, 1H), 3.42 (m, 1 H), 3.76 (dd, J = 9.8 and 7.6 Hz, 1 H), 4.32 (dd, J = 9.8 and 8.0 Hz, 1 H), 7.04-7.11 (m, 2 H), 7.25-7.38 (m, 2 H), 7.90-7.96 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.5; 36.4, 39.2, 53.3, 127.7, 127.9, 129.5, 129.9

(*R*)-4-(4-chlorophenyl) pyrrolidin-2-one (21)

Lactum **20** (400 mg, 1.14 mmol), phenol (107 mg, 1.14 mmol), and 10 ml of 32% hydrogen bromide in acetic acid was heated in a round bottom flask for 12 hours at 80 °C. The reaction mixture was allowed to cool to room temperature and then extracted with CH_2Cl_2 solution and concentrated under vacuum at room temperature and purified with column chromatography on silica gel (MeOH/$CHCl_3$ = 10/90 as an eluent) to afford desired product **21** (149 mg, 66 %) as a white solid, m.p.115°C .

Molecular Formula $C_{10}H_{10}ClNO$

Mol. Wt 195

M.P. : 109-111 °C

$[\alpha]_D^{25}$: 34.0°, c = 1, EtOH, litt.[7] -35.8° (c = 1 EtOH).

^{1}H-NMR (300MHz, $CDCl_3$) : δ. 7.33 (d, 2H, *J* = 8.8), 7.19 (d, 2H, *J* = 8.8), 3.80 (apt, t, 1H, *J* = 8.8 Hz), 3.74-3.63 (m, 1H) , 3.37-3.42 (dd, 1H, *J* = 7.1, 8.8 Hz) 2.81-2.72 (dd, 1H, *J* = 8.8, 17.0 Hz), 2.52-2.71 (dd, 1H, *J* = 8.2, 17.0 Hz). ppm

^{13}C-NMR (75 MHz, $CDCl_3$) : δ 37.85, 39.65, 49.49, 128.06, 128.97, 132.87, 140.61, 178.50.

(*R*)-4-amino-3-(4-chlorophenyl)butanoicacid hydrochloride, *Baclofen, hydrochloryde*

The solution of **21** (100 mg, 0.51 mmol) in 6N HCl (2.7 mL) was refluxed at 100 °C. After 24 h, the reaction mixture was concentrated in *vacuo* to afford (*R*)-(–)-Baclofen as colorless solid 93 mg, in 73% yield.

Molecular Formula : $C_{10}H_{13}ClNO_2$

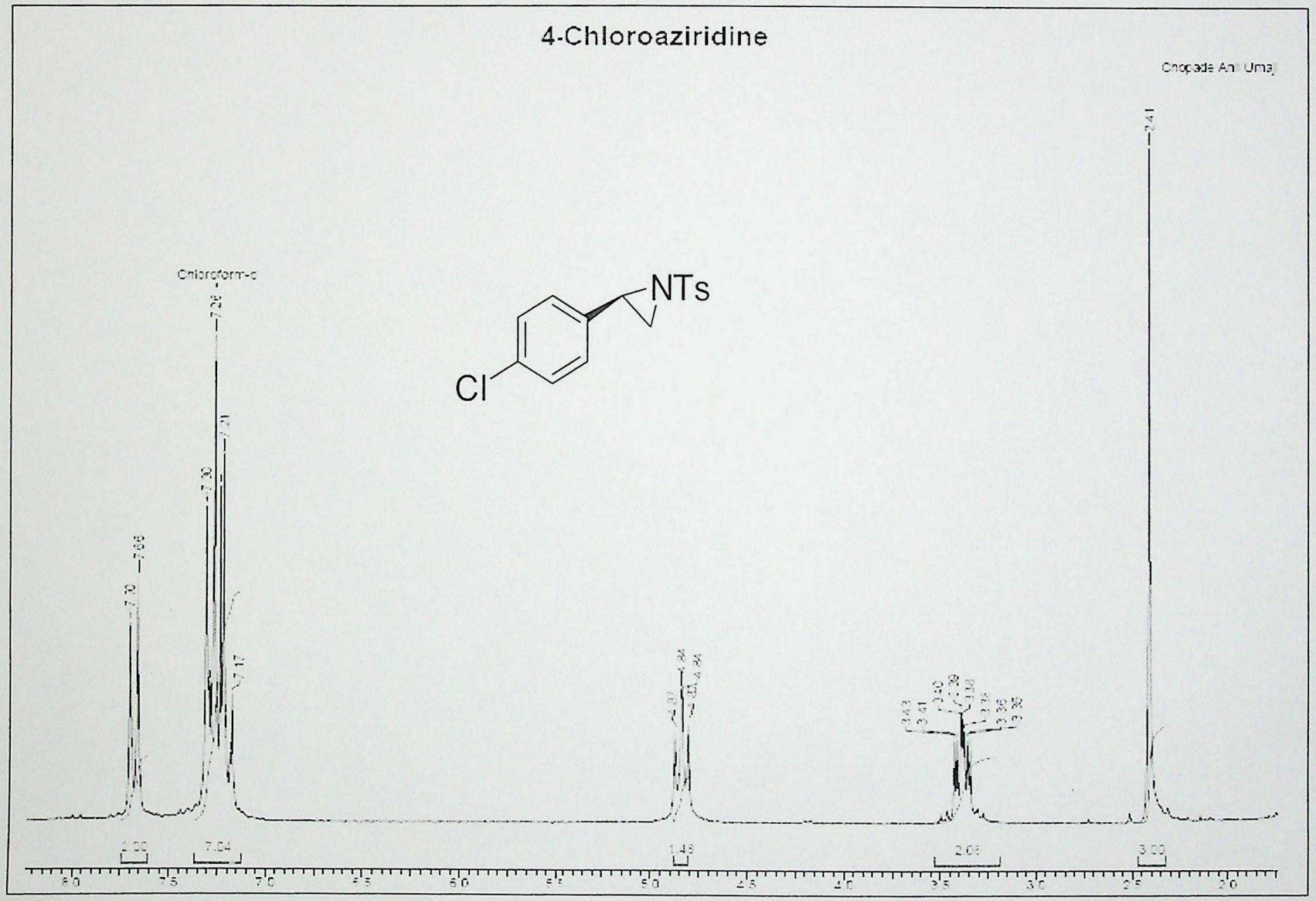
M.P. : 188-189 °C

$[\alpha]_D^{25}$: –3.4° (c = 0.65, H_2O), lit.[7] –3.79° (c = 0.65, H_2O, 99 % ee)

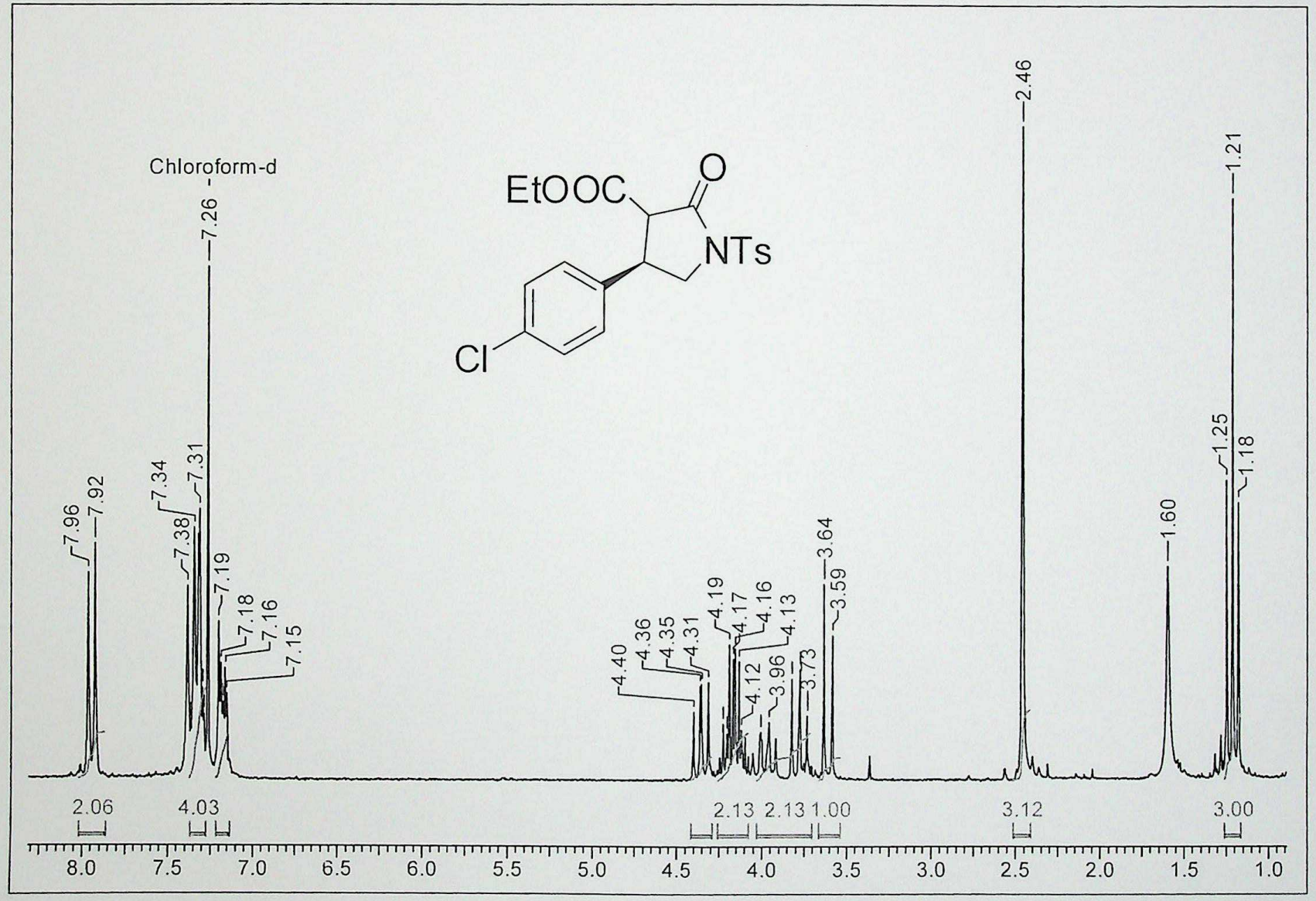
^{1}H-NMR (300MHz, D_2O) : δ. 7.36-7.49 (m, 4H) 3.50-3.37 (m, 2H), 2.30-3.22 (m, 1H), 2.71-2.92 (dd, 2H,) *J* = 9.5, 16.5 Hz).ppm

^{13}C-NMR (75MHz, D_2O) : δ. 175.46, 138.28, 136.95, 133.32, 129.32, 128.25, 127.81, 43.75, 39.91, 38.18.

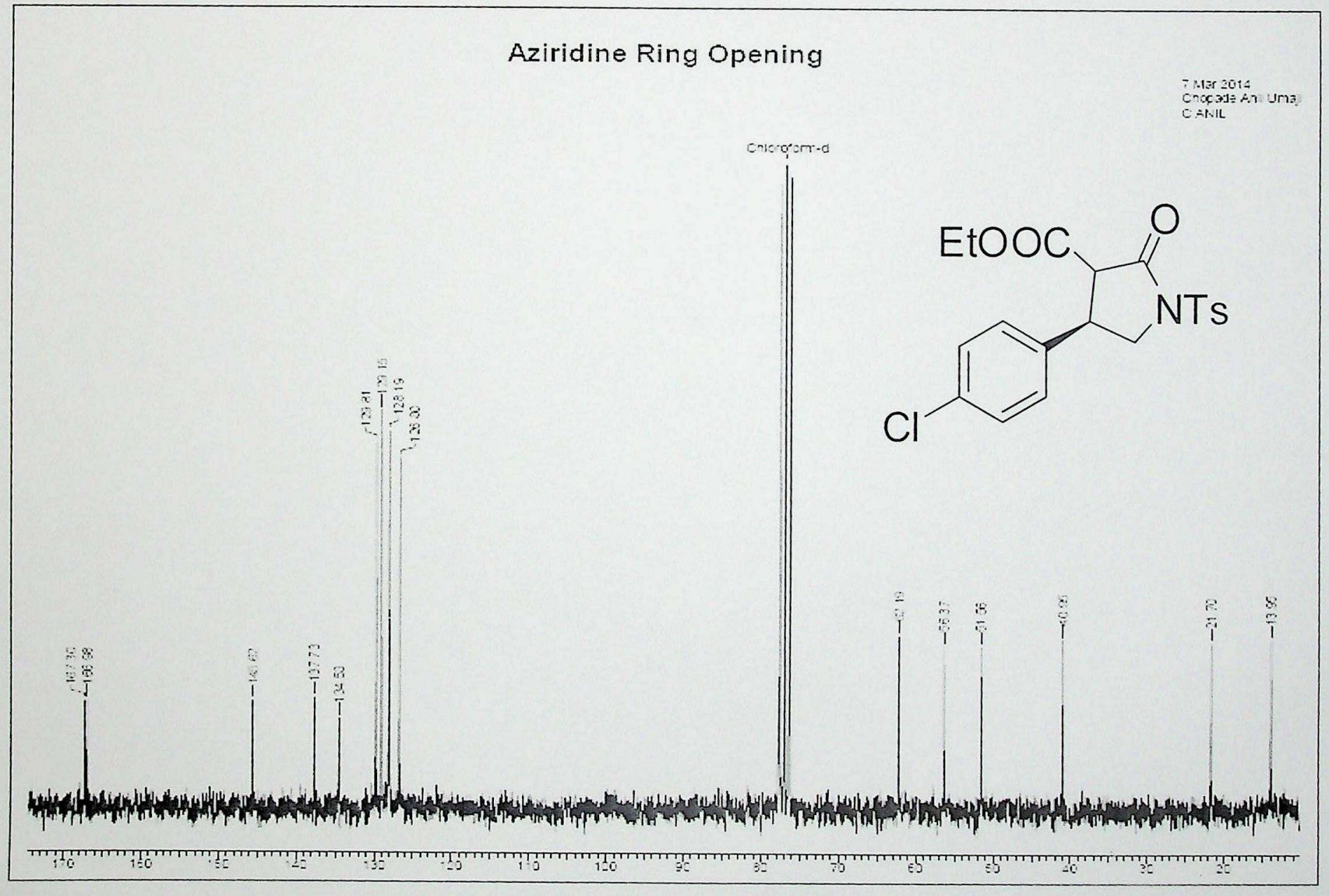
4-Chlorostyrene Aziridine 18 (^{1}H-NMR)



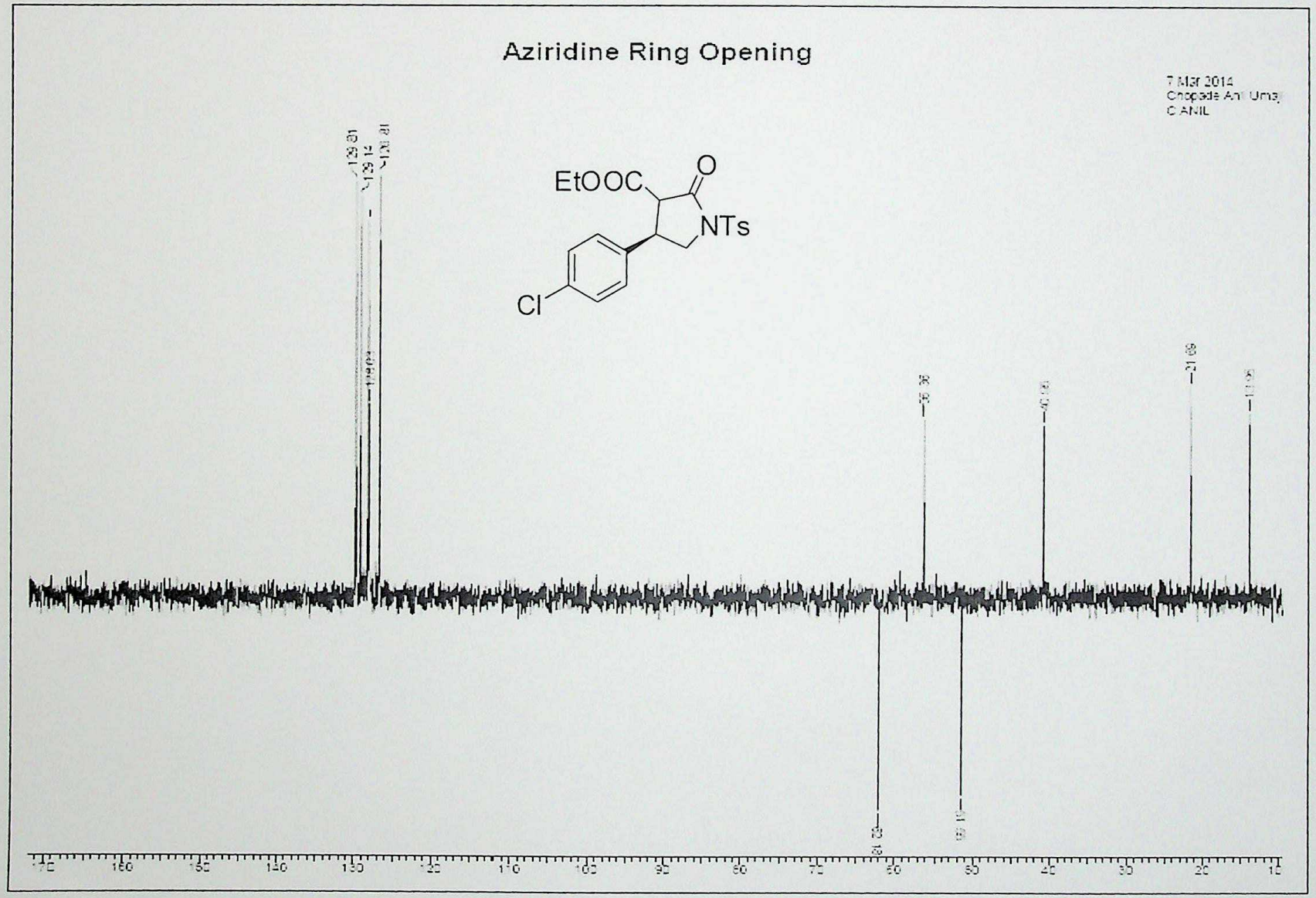
Ethyl 4-(4-chlorophenyl)-2-oxo-1-tosylpyrrolidine-3-carboxylate 19 (^{1}H-NMR)



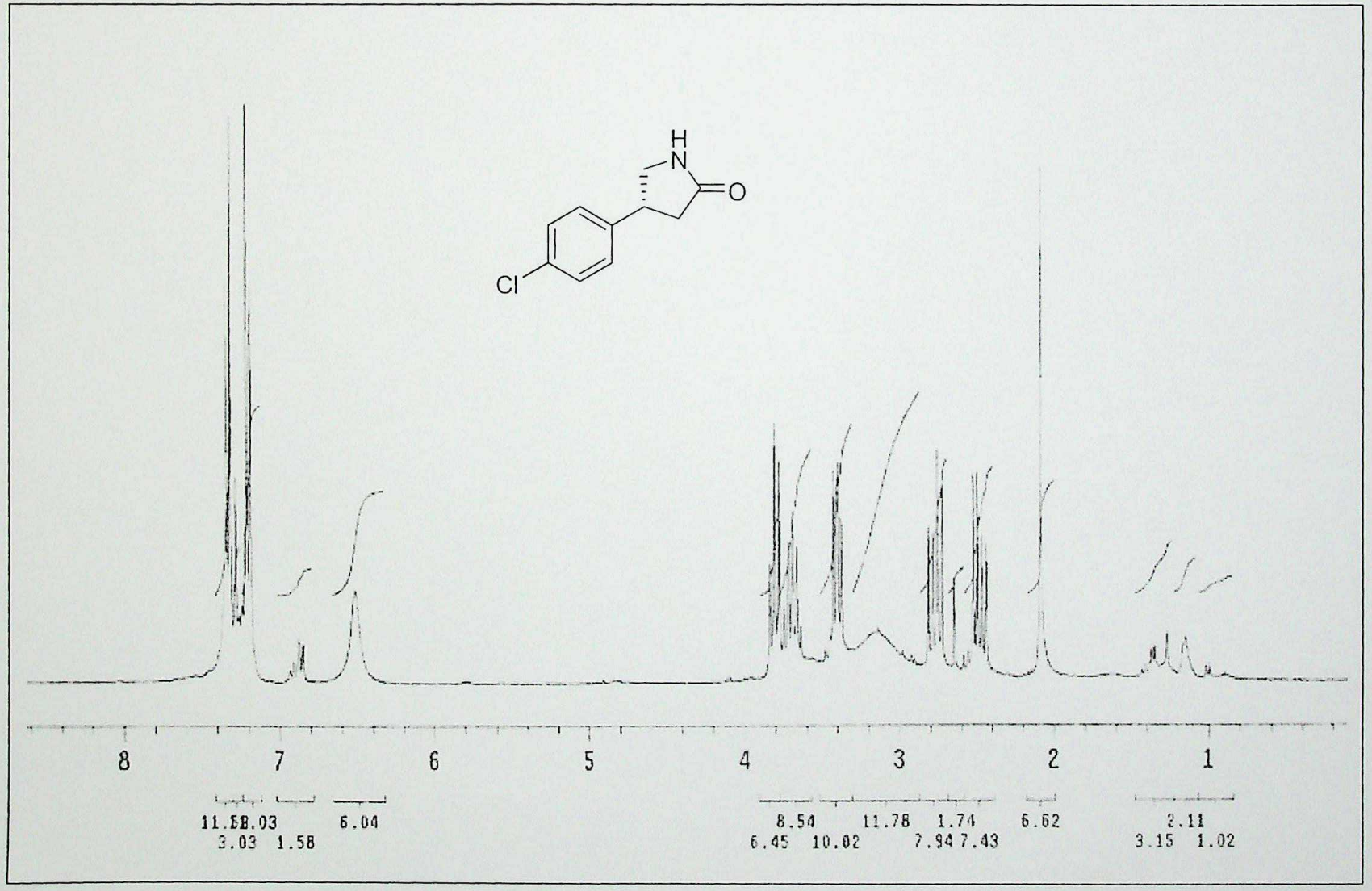
Ethyl 4-(4-chlorophenyl)-2-oxo-1-tosylpyrrolidine-3-carboxylate 19 (^{13}C-NMR)



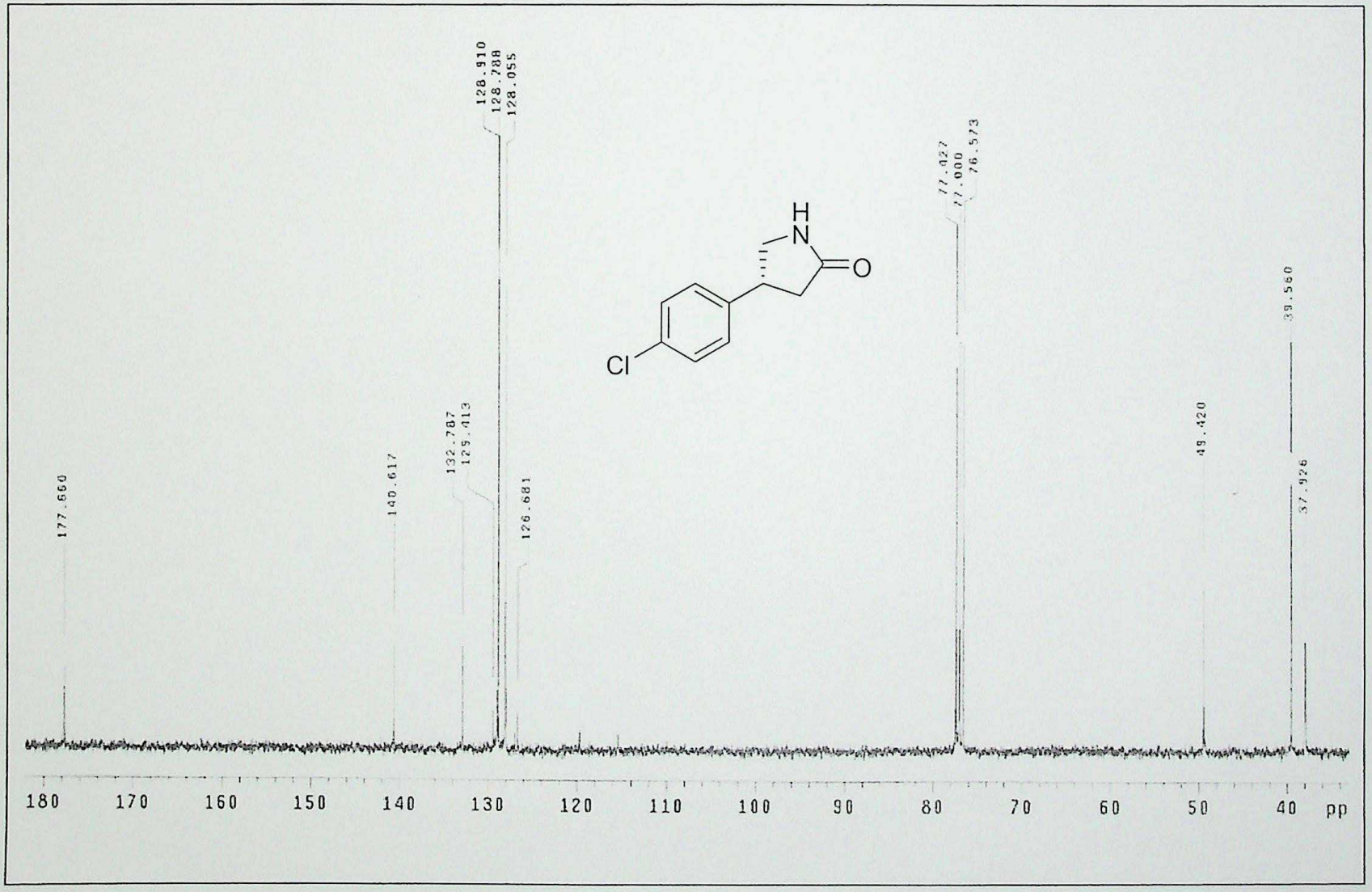
Ethyl 4-(4-chlorophenyl)-2-oxo-1-tosylpyrrolidine-3-carboxylate 19 (DEPT-NMR)



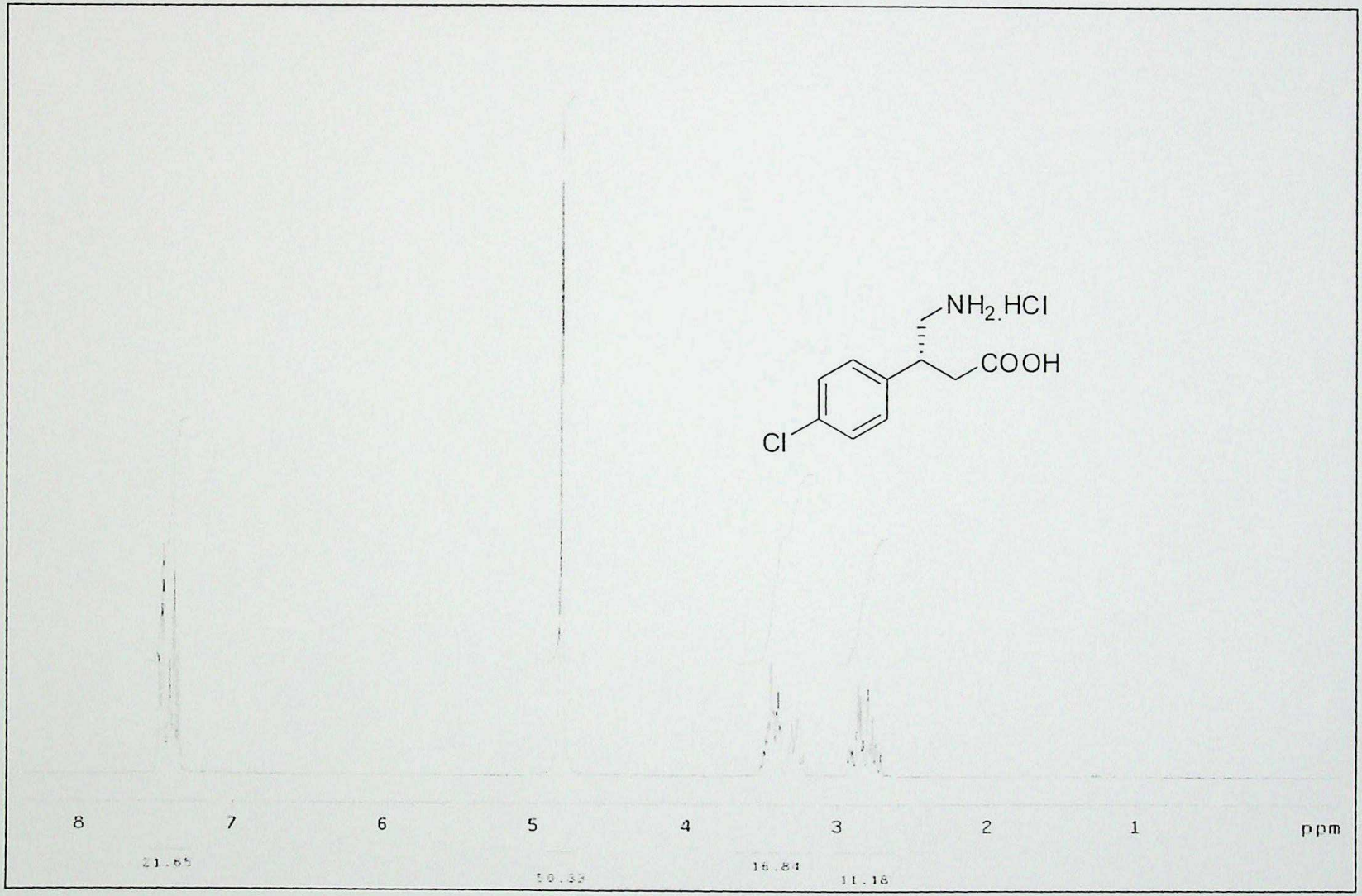
(*R*)-4-(4-chlorophenyl) pyrrolidin-2-one 21 (^{1}H NMR)



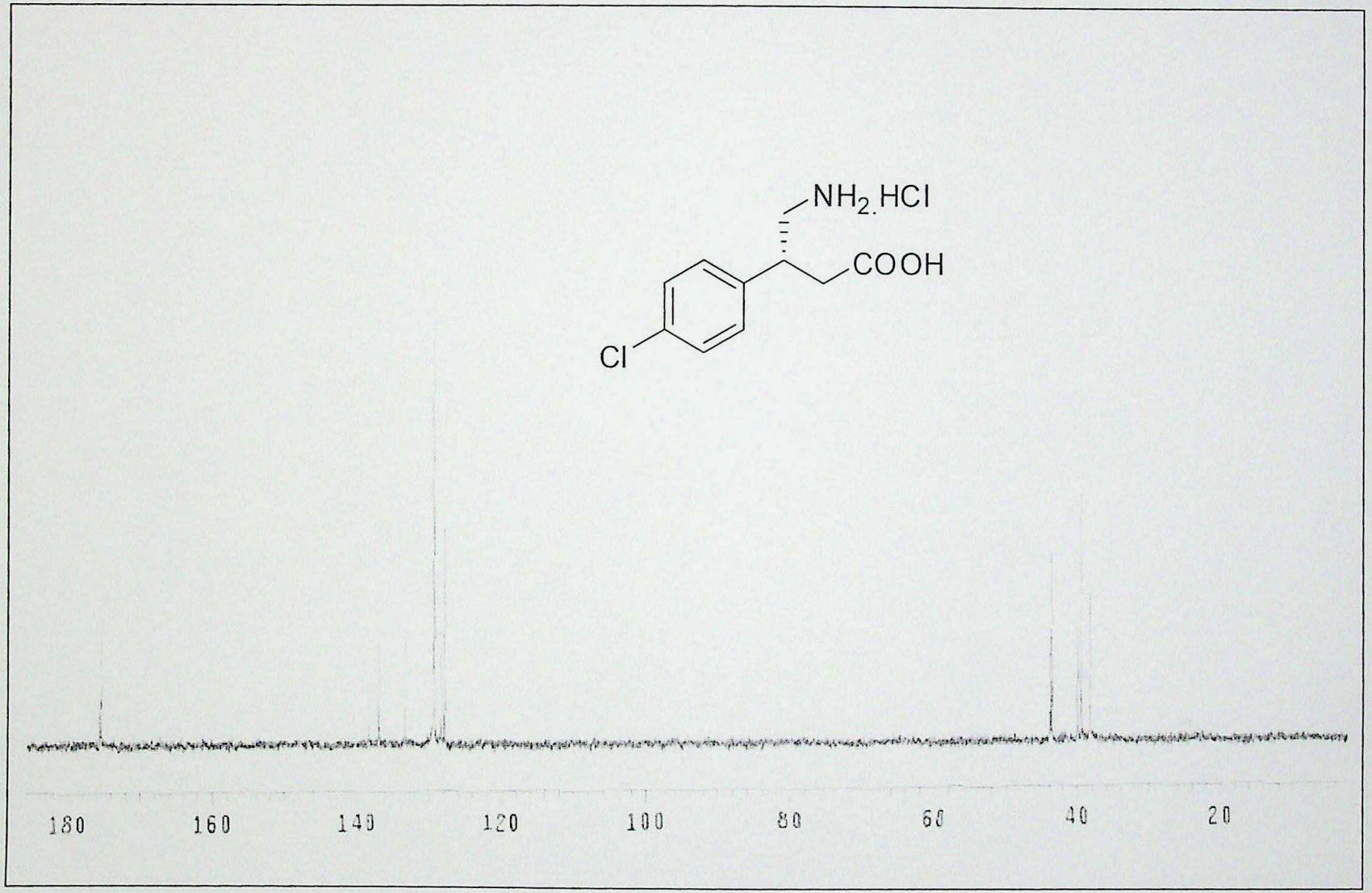
(*R*)-4-(4-chlorophenyl) pyrrolidin-2-one 21 (^{13}C-NMR)



(*R*)-4-amino-3-(4-chlorophenyl)butanoic acid hydrochloride {Baclofen, Hydrochloride}(^{1}H-NMR)



(*R*)-4-amino-3-(4-chlorophenyl)butanoic acid hydrochloride {Baclofen, Hydrochloride} ^{13}C-NMR



References:

1. (a)Y. Yamada, T. Yamamoto, M. Okawara, *Chem. Lett.* **1975**, 361; (b) D.A. Evans, M.M. Faul, M.T. Bilodeau, B.A. Anderson, D.M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328; (c) D.B. Ilewellyn, D.M. Adamson, B.A. Amdtsen, *Org. Lett.* **2000**, *2*, 4165; (d) T. Ando, S. Minakata, I. Ryu, M. Komatsu, Tetrahedron Lett. **1998**, *39*, 309; (e) T. Ando, D. Kano, S. Minakata, I. Ryu, M.Komatsu, *Tetrahedron* **1998**, *54*, 13485; (f) D. Kano, S. Minakata, M. Komatsu, *J. Chem. Soc. Perkin Trans.* **2001**, 3186; (g) V.V. Thakur, A. Sudalai, *Tetrahedron Lett.* **2003**, *44*, 989; (h) S.L. Jain, V.B. Sharma, B. Sain, *Tetrahedron Lett.* **2004**, *45*, 8731.; i. H. Wu, C.-G. Xu, J. Ge, L. Yang, *Synth. Commun.* **2005**, *35*, 1413.

2. (a) Jacobsen, E. N. In Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Springer: Berlin*, **1999**; Vol. 2, pp 607-618; (b) Gao, G. Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2005**, *7*, 3191-3193; (c) Minakata, S.; Komatsu, M. In Modern Amination Methods; Ricci, A., Ed.; Wiley-VCH: *Weinheim*, 2000; pp 169-194; (d) Mohr, F.; Binfield, S. A.; Vedernikoy, A. N. *J. Org. Chem.* **2005**, *70*, 4833; (e) Catino, A. J.; Nichols, J. M.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787-2790; (f) Keaney, G. F.; Wood, J. L. *Tetrahedron Lett.* **2005**, *46*, 4031; (g) Vyas, R.; Gao, G. Y.; Zhang, X. P. Org. Lett. **2004**, *6*, 1907-1910

3. (a) Chenevert, R.; Desjardins, M. *Tetrahedron Lett.* **1991**, *32*, 4249; (b) Brenna, E.; Carraccia, N.; Fuganti, C.; Fuganti, D.; Graselli, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3801; (c) Levadoux, W.; Groleau, D.; Trani, M.; Lortie, R. US Pat. 5,843,765, 1998, 12 pp.; *Chem. Abstr.* **1998**, *130*, 24139.

4. Mazzini, C.; Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.* **1997**, *38*, 1195.

5 (a) Herdeis, C.; Hubmann, H. P. Tetrahedron: Asymmetry 1992, 3, 1213; (b) Langlois, N.; Dahuron, N.; Wang, H.-S. *Tetrahedron* **1996**, *52*, 15117; (c) Resende, P.; Almeida, W. P.; Coelho, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2113; (d) Licandro, E.; Maiorana, S.; Baldoli, C.; Capella, L.; Perdichia, D. *Tetrahedron: Asymmetry* **2000**, *11*, 975; (e) Baldoli, C.; Maiorana, S.; Licandro, E.; Perdicchia, D.; Vandoni, B. *Tetrahedron: Asymmetry* **2000**, *11*, 2007; (f) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257.

6. (a) Watanabe, M.; Ikagawa, A.;Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148; (b) Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K.W. *Org. Lett.* **2003**, *5*, 2259;(c) Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 870.

7. (a) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469. (b) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245.

8. Lai, T-S.; Knog, H-L.; Che, C-M.; Peng, S-M. *Chem. Commun.* **1997**, 2373.

9. (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

10. (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (b) Kim, S. K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3952.

11. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

12. Minakata, S.; Ando, T.; Nishimura, M.; Ryu, I.; Komatsu, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 3392.

13. Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. *Tetrahedron : Asymm.* **2001**, *12*, 3349.

14. Taylor, S.; Gullick, J.; McMorn, P.; Bethell, D.; Bulman Page, P. C.; Hancock, F. E.; King, F.; Hutchings, G. J. *J. Chem. Soc. Perkin Trans 2*, **2001**, 1714.

15. Omura, K.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Commun.* **2004**, 2060.

16. Patwardhan, A. P.; Lu, Z.; Reddy, V.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 2201.

17. Ma, L.; Jiao, P.; Zhang, Q.; Xu, J. *J. Org. Chem.* **2005**, *70*, 10155.

18. a) Chanda, B. M.; Vyas R.; Landge, S. S. *J. Mol. Cat. A: Chemical,* **2004**, *223,* 57. (b) Chanda, B. M.; Vyas, R.; Belhekar, A. A.; Patel, D. R.; Ram, R. N.; Bedekar A.V. *J. Mol. Cat. A: Chemical,* **2000,** *160,* 237.

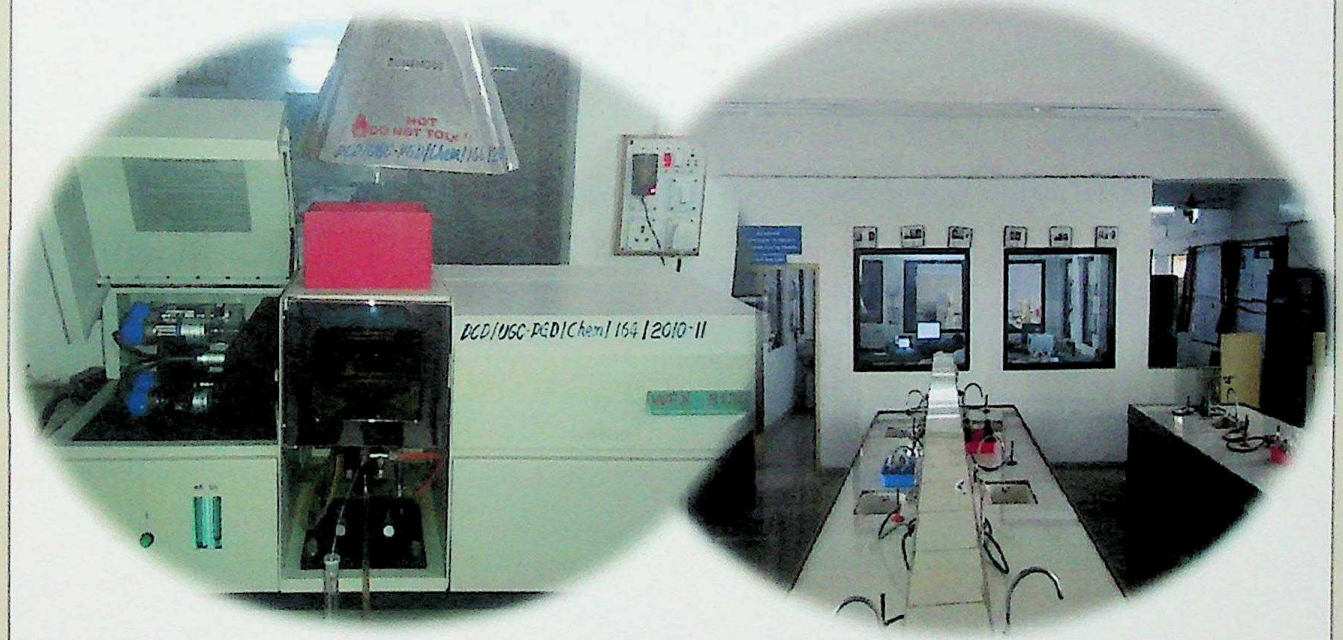
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