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Toward the Synthesis of [4.2.1]di-azabicyclic Systems

Carlos Abel Gomez

MONTCLAIR STATE UNIVERSITY

TOWARD THE SYNTHESIS OF [4.2.1]DI-AZABICYCLIC SYSTEMS

By

CARLOS ABEL GOMEZ

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Dean: Robert S. Prezant

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Date

Thesis Committee:

[redacted]

Thesis Sponsor: David P. Rotella

[redacted]

Committee Member: David W. Konas

[redacted]

Committee Member: Saliya A. de Silva

[redacted]

Graduate Program Coordinator:

Marc L. Kasner

TOWARD THE SYNTHESIS OF [4.2.1]DI-AZABICYCLIC SYSTEMS

Abstract

Conformationally restricted bicyclic amines have been found to be very useful scaffolds in medicinal chemistry. Examples can be found in the chemical literature for the application of conformationally restricted diamines. These molecules can be used as enzyme inhibitors or GPCR ligands. Conformational restriction can improve affinity and selectivity toward receptors. The stereochemical diversity-oriented approach is a method that explores stereochemical effects in small molecule ligands for proteins. It is an effective strategy when the bioactive conformation of a ligand and the pharmacophore of the binding site are unknown. These concepts are applied in the design the target [4.2.1]di-azabicyclic compounds. The nitrogen atoms can be functionalized differently if they are protected appropriately to provide increased structural diversity. The shift of the nitrogen atom along the four-atom bridge provides the opportunity to scan a broad region of space. The modified approach of the synthesis toward these targets utilizes selective oxidation/reduction and stereochemically well-defined reactions to modify the functional groups and stereochemistry in the compound. This paper describes the research done so far to obtain these conformationally restricted diamine targets and the characterization of the novel intermediates.

Toward the Synthesis of [4.2.1]di-azabicyclic Systems

A Thesis

Submitted in partial fulfillment of the requirements

For the degree of Master of Science in Chemistry

By

Carlos Gomez

Montclair State University

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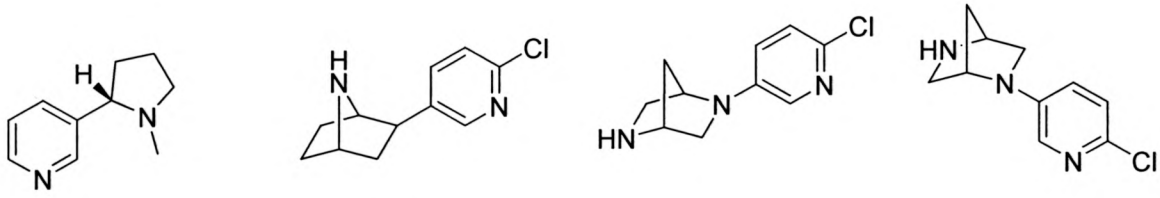
Introduction

There are several techniques that a medicinal chemist can apply when optimizing a lead compound. The flexibility of a compound may affect its affinity toward a target protein. Conformational restriction can be utilized to promote the rigidity of a molecule which may result in improved receptor selectivity, increased potency, and increased metabolic stability. Approaches to conformational restriction include incorporation of steric bulk, unsaturation, or cyclization.[1] Designing a small molecule to act as an enzyme inhibitor or G-protein coupled receptor ligand requires a methodical approach. The stereochemical diversity-oriented approach explores altering stereochemistry and positions of atoms within compounds that may alter biological activity, target selectivity and pharmaceutical properties. The target molecules presented in this paper are conformationally restricted diamines.

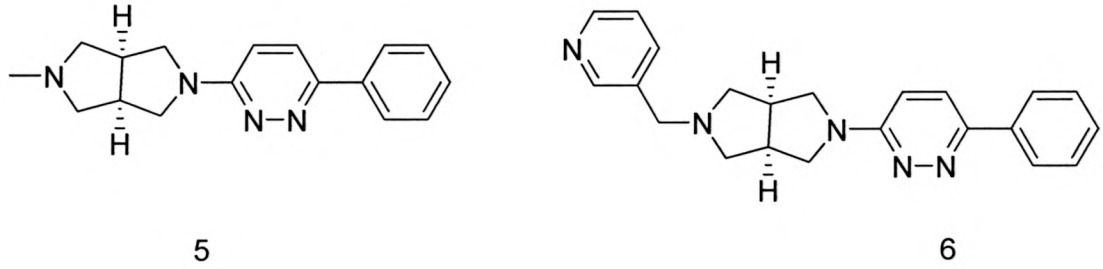
Conformationally restricted diamines have been reported as very useful molecules in medicinal chemistry. Epibatidine, (**2**), is a potent bicyclic ligand for the acetylcholine receptor that binds to α4β2 receptors in rat brain in the picomolar range. Its high toxicity prevents it from being used clinically which led to the synthesis of [2.2.1] diamine scaffold analogues, **3** and **4**, by Bunnelle and coworkers.[2] The compounds were tested to displace [^{3}H]-cysteine from rat brain membranes. When compared to a flexible compound like nicotine (**1**) the conformationally restricted bicyclic diamine structures showed higher affinity and selectivity. These bicyclic diamine scaffolds proved to be useful in making potent nAChR ligands that rival the affinity of epibatidine.

Figure 1: Nicotine (**1**, K_i = 0.94 nM), epibatidine (**2**, K_i = 0.047 nM), and conformationally restricted bicyclic diamine analogues **3** (K_i = 0.018 nM) and **4** (K_i = 0.10 nM).[2]



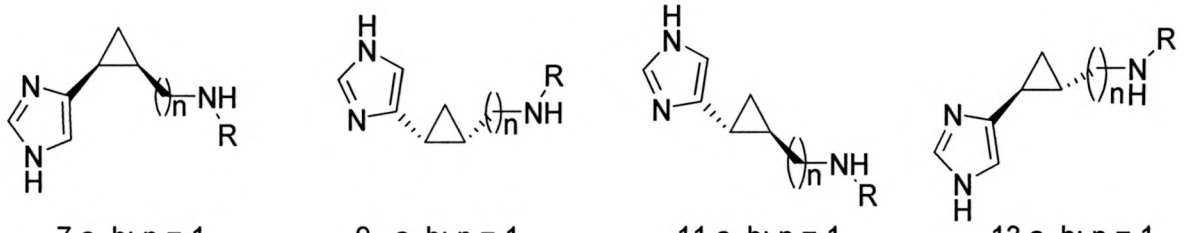
Epibatidine is a non-selective nAChR ligand that has influenced research toward other nAChR subtypes. Mortell and coworkers utilize [3.3.0] bicyclic diamines as nAChR ligands. These rigid structures provide an opportunity to explore the changing of functional groups in a specific position and its effect on activity. Compound **5** was a lead nAChR ligand with selectivity toward rat α7 receptors over other subtypes. Compound **6** was developed by combining elements from epibatidine and **5**. It was found to be more effective as an agonist than its parent compound **5**.[3] This study shows how different functionalization in a specific orientation in space can be useful in improving the activity of a compound.

Figure 2: Parent compound **5** (K_i = 11 nM) and its analogue **6** (K_i = 3.6 nM).[3]



A method to improve understanding of the effects of stereochemistry is the stereochemical diversity-oriented approach. This involves the synthesis of templates that are stereoisomers. It is an effective strategy in developing protein ligands, when neither the bioactive conformation nor the pharmacophore are known.[4] Watanabe and coworkers developed conformationally restricted analogues of histamine which introduced chiral *cis*- and *trans*-cyclopropane. Through stereoselective synthesis, sixteen unique compounds (Figure 3) were made and tested for H_3 and H_4 receptor antagonism. It was discovered that **12a** had good antagonist activity to both H_3 (K_i = 8.4 nM) and H_4 (K_i = 7.6 nM) receptors. Compound **14a** showed high selectivity for H_3 receptors (K_i = 3.6 nM) while **11a** was selective toward H_4 receptors (K_i = 118 nM). Compound **11a** was the first H_4 subtype selective antagonist designed using this style of approach.[4] This study illustrates the importance of conformational restriction, exploration of functionality on nitrogen atoms, and the exploration of stereochemistry through a wide array of compounds to obtain active and selective molecules.

Figure 3: H_3/H_4 receptor ligands developed from stereochemical diversity-oriented approach.[4]



7 a, b: n = 1
8 a, b: n = 2

9 a, b: n = 1
10 a, b: n = 2

11 a, b: n = 1
12 a, b: n = 2

13 a, b: n = 1
14 a, b: n = 2

a series: R = 4-chlorobenzyl
b series: R = cyclohexylmethyl

A useful description of conformationally restricted diamines was outlined by Grygorenko and co-workers and is shown in Figure 4. The nitrogen atoms can be either primary or secondary amines and ideally will permit differential functionalization to provide structural diversity. The target compounds presented in this research (Figure 5) have amino groups which are part of the ring system, or endocyclic.[5] Conformational restriction presents molecules with the nitrogen atoms in well-defined orientations with specific torsional angles and N-N distance. This can be helpful when these molecules are used to map a binding site on a protein. Functional groups attached via the nitrogen atoms can then be arrayed to explore defined regions of space.

Figure 4: Exocyclic (exo) amines are not part of the bicyclic scaffold. Endocyclic (endo) are involved in the bicyclic scaffold.[5]

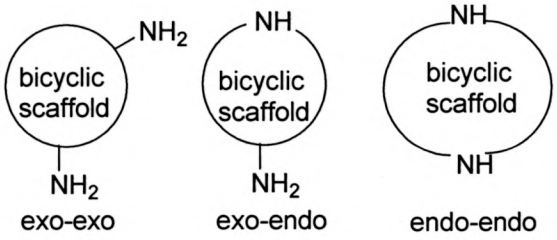
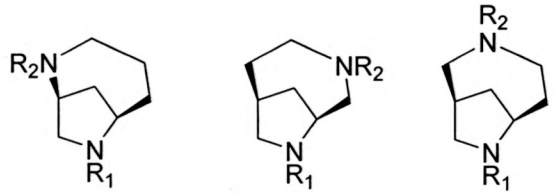


Figure 5: [4.2.1]di-azabicyclic targets.

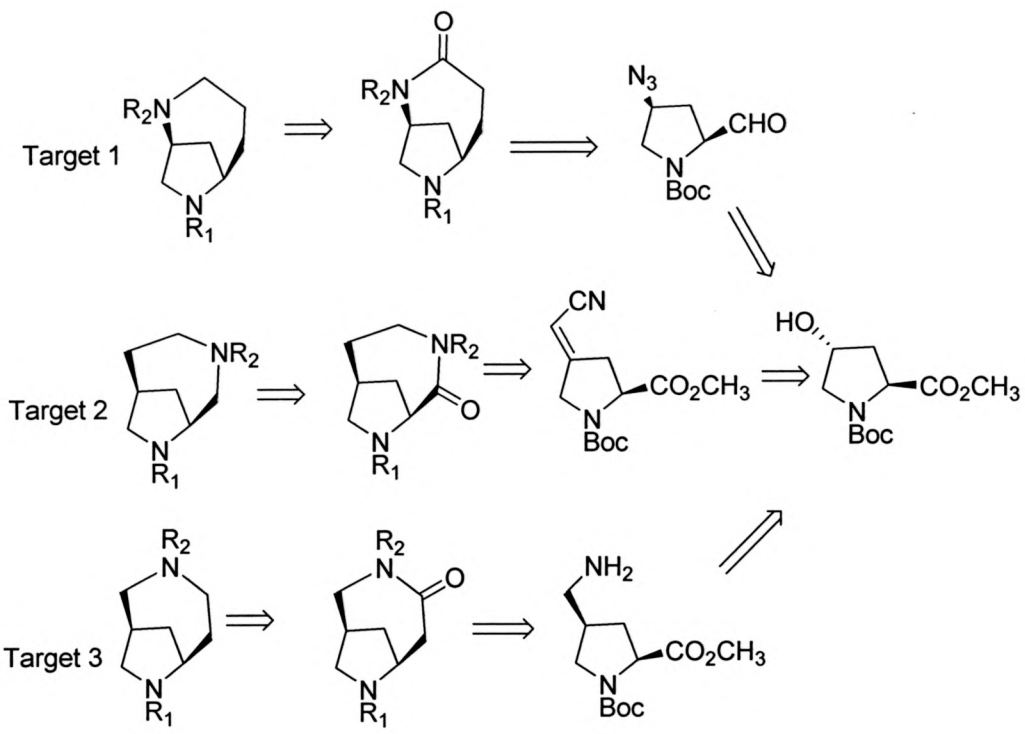


These structurally rigid, azabicyclic diamines have nitrogen atoms arrayed in a [4.2.1] framework which is rare and under-explored in the chemical literature.[5] The

target molecules presented are novel compounds that have not been previously reported in the chemical literature. The three target compounds are regioisomers that differ in the position of the nitrogen on the four atom bridge. The approach toward the scaffolds in this research is similar to the stereochemical diversity-oriented approach. Moving the nitrogen along the four atom bridge provides the opportunity to scan a broader region of space with structurally related ligands. This can provide useful structure-activity data for targets of choice. The reaction schemes for the three targets all originate from the same starting material. As outlined below, the synthesis begins with amino acid derivatives with defined absolute stereochemistry and will provide specific stereoisomers. Because the enantiomeric amino acid starting material is available and because the same synthetic pathways can be applied to furnish products, it will be possible to evaluate potential stereochemical effects on activity, selectivity and other properties. This paper describes the work done so far toward the synthesis of two (**15**, **16**) of the [4.2.1]di-azabicyclic systems as well as characterization of novel intermediates.

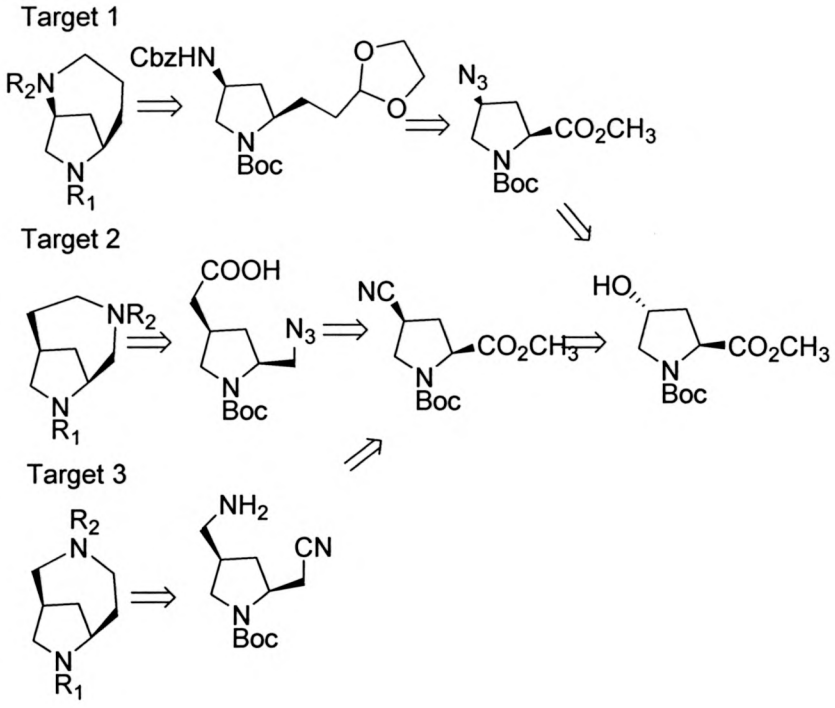
The original retrosynthetic approach toward the target bicyclic diamines is outlined below (Scheme 1). These compounds can all be synthesized from an N-protected hydroxy proline (**18**) starting material. This route toward **15** and **16** was unsatisfactory due to of low yields and lack of stereospecificity in key reactions. As a result, our approach was modified as shown in Scheme 2.

Scheme 1: Initial retrosynthetic approach toward [4.2.1] bicyclic scaffolds.



Our primary interest is in the synthesis of targets **15** and **16**. Scheme 2 is a more promising approach as it utilizes selective reduction/oxidation and stereochemically well-defined reactions at key steps toward the final product. The three targets can all be synthesized from the same hydroxy proline derivative (**18**) mentioned above.

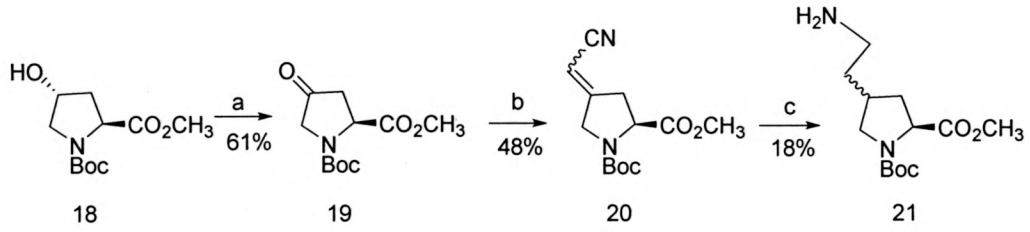
Scheme 2: Modified retrosynthetic approach toward [4.2.1] bicyclic scaffolds.



Results and Discussion

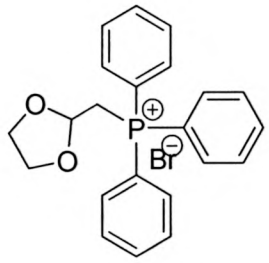
Scheme 3 outlines our initial approach toward **16**. N-Boc-protected 2S, 4R hydroxy proline ester (**18**) was oxidized to the corresponding ketone (**19**) using potassium chlorochromate in DCM. This ketone underwent a Horner-Wadsworth-Emmons reaction with diethyl cyanomethylphosphonate and sodium hydride in THF to afford an E/Z mixture of the known α, β unsaturated nitrile, **20**.[6] The nitrile (**20**) was then hydrogenated with a platinum catalyst in ethanol to get the amine (**21**) in 18% yield.[7] It was possible to isolate a single amine isomer, however it was not possible to determine the stereochemistry of the product because of our inability to identify diagnostic protons at 300 MHz. This sequence proved to be unsatisfactory for this reason as well as because of variability in the net yield for the oxidation-Horner-Wadsworth-Emmons-reduction sequence.

Scheme 3: Initial synthetic scheme toward **16**. (a) PCC, DCM (b) NaH, diethyl cyanomethylphosphonate, THF (c) H_2, Pt(IV) oxide, EtOH.



Scheme 4 describes the forward reaction scheme toward **15**. The synthesis begins with conversion of (**18**) to known mesylate, **23**,[8] followed by S_N2 displacement using sodium azide in DMF to obtain known azide, **24**.[9] The methyl ester was reduced chemoselectively using lithium borohydride in ether and methanol to get the known corresponding alcohol **25**.[8] We observed that this solvent system provided a better yield and more rapid reaction compared to tetrahydrofuran as the sole solvent.[10] The alcohol in **25** was oxidized using pyridinium chlorochromate in DCM to furnish aldehyde **26** in 58% yield. Wittig olefination using the protected acetaldehyde derivative (**22**) and potassium t-butoxide in THF afforded **27** in 84% yield as a mixture of geometric isomers that were not separated. **27** was reduced by catalytic hydrogenation in ethanol at room temperature to afford **28** in 87% yield. The amine was protected with CbzCl in THF to **29** in 69% yield. Amine protection was carried out to facilitate isolation and characterization.

Figure 6: (1,3-Dioxolan-2-ylmethyl)(triphenyl)phosphonium bromide



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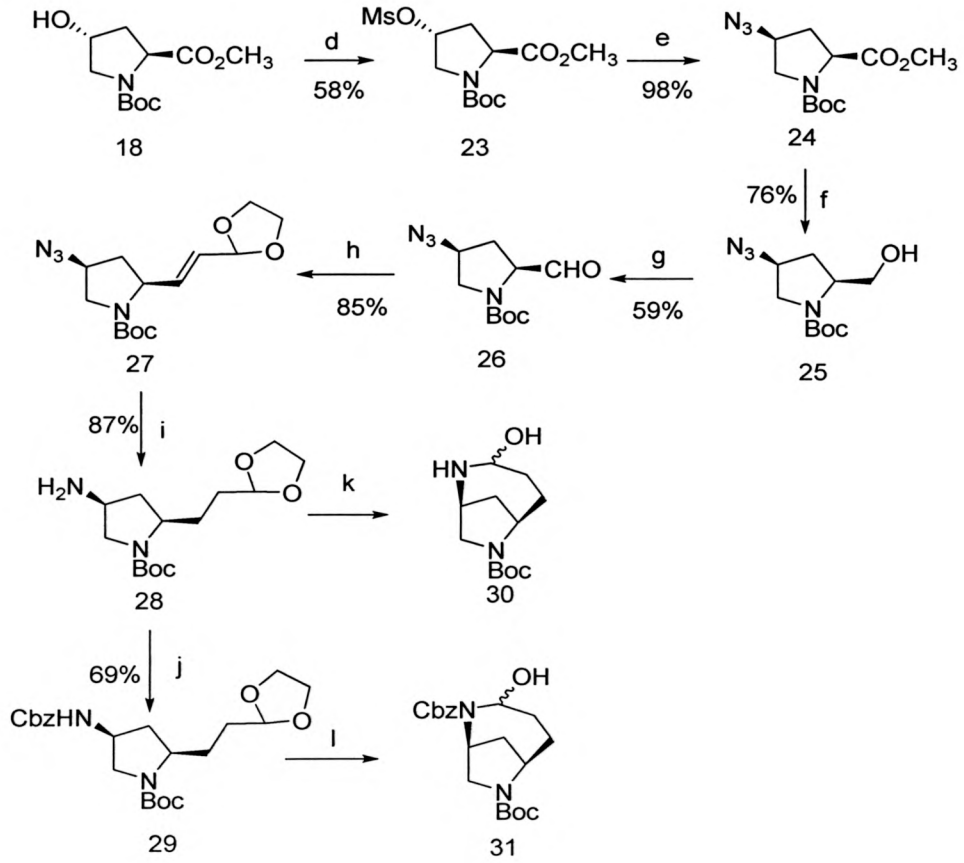
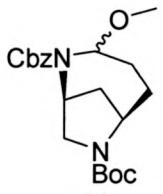
Scheme 4: Reaction scheme used toward the synthesis of **15**. (d) MsCl, Et_3N, DCM (e) NaN_3, DMF, 90°C (f) $LiBH_4$, Et_2O, MeOH, 0°C (g) PCC, DCM (h) t-BuOK, **22**, THF (i) H_2, Pd-C, EtOH (j) $NaHCO_3$, CbzCl, THF, H_2O (k) 1N HCl, THF (l) Toluenesulfonic acid, acetone, H_2O.



Acetal cleavage was explored on a small scale to attempt to synthesize the hemiaminal **30** by stirring **28** in 1N HCl and THF. Unfortunately, the reaction was not successful and will require further investigation in the future. A similar reaction was carried out on the carboxybenzyl protected **29** with toluenesulfonic acid in acetone and water. Although there is no recorded yield, a product was isolated and analyzed by ^{1}H and ^{13}C NMR which can be found in the Spectral Analysis section (Figure 15 and Figure 16). Based on this data, we propose the Cbz protected hemiaminal **31** structure. This assignment is supported by data in the literature.[11] MS analysis of this product gave an m/z = 391. This mass is consistent with formation of a methoxy aminal (**32**) that forms on the HPLC column in acidic methanol. Additional analysis is required before we can confidently determine the structure of the molecule.

Figure 7: Proposed structure of methoxy aminal formed in HPLC column.



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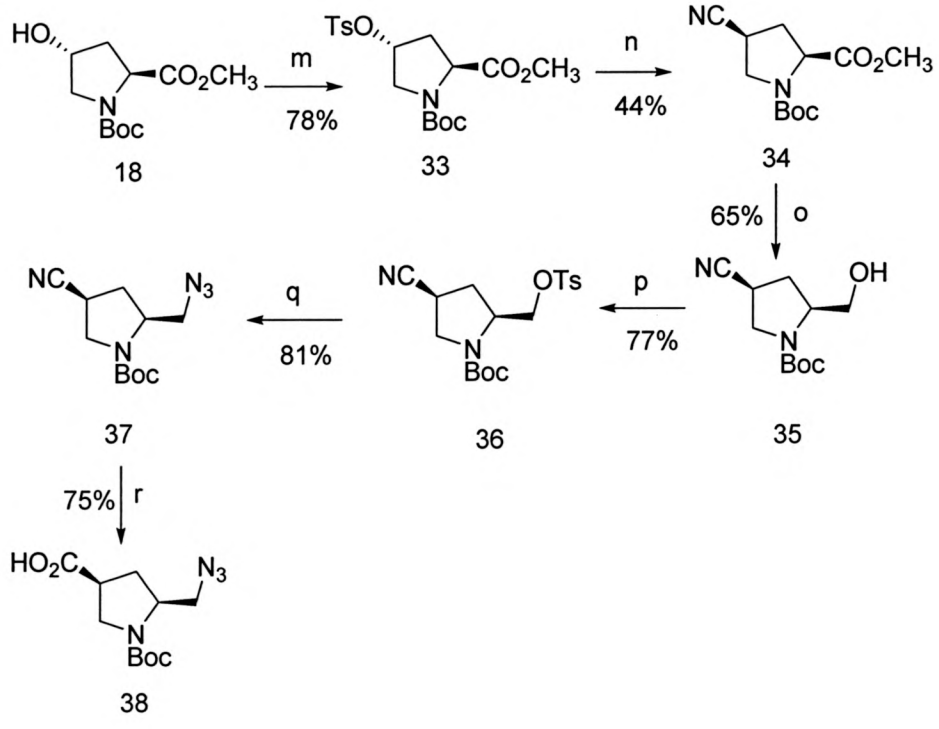
The modified reaction scheme toward the target **16** is shown in Scheme 5. The synthesis begins with conversion of **18** to known tosylate (**33**)[12] followed by a S_N2 displacement using sodium cyanide and DMSO to make known **34**.[12] The methyl ester was chemoselectively reduced to the corresponding alcohol (**35**) using lithium borohydride in ether and methanol in a 65% yield. The alcohol was tosylated (**36**) in a 77% yield and underwent S_N2 substitution in DMF to afford **37** in 81% yield. **37** was

hydrolyzed with sodium hydroxide in water and ethanol to the carboxylic acid (**38**) in a 75% yield.

Scheme 5: Reaction scheme used toward the synthesis of **16**. (m) TsCl, DMAP, Et_3N, DCM (n) NaCN, DMSO, 90°C (o) $LiBH_4$, MeOH, Et_2O, 0°C (p) TsCl, DMAP, Et_3N, DCM (q) NaN_3, DMF, 90°C (r) NaOH, H_2O, EtOH, reflux.



Experimental Section

Nuclear magnetic resonance spectra were recorded on Bruker Avance 300 FT-NMR Spectrometer. All samples were prepared in $CDCl_3$ unless stated otherwise and chemical shifts are reported in δ values (ppm) relative to TMS. Mass spectrometry was obtained from a Shimadzu LCMS-2020.

(**19**) – **18** (5.0 g, 20.4 mmol) and PCC (5.75 g, 26.7 mmol) were dissolved in DCM (200 mL) and stirred overnight at room temperature. The reaction was filtered through celite then washed with 1N HCl (3 x 50 mL) and brine (35 mL). The organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. The crude material was purified on an 80 g ISCO column (25% EtOAc – hexanes) obtaining the **19** (3.0 g, 61%).[6]

(**20**) – In anhydrous THF (6 mL) and NaH (40 mg of 60% oil dispersion, 1.7 mmol) was cooled to 0° C. Diethyl cyanomethylphosphonate (0.26 mL, 1.66 mmol) was added dropwise by syringe and stirred for 30 minutes at 0°C. A solution of **19** (500 mg, 2.1 mmol) in THF (1 mL) was added then the reaction solution was warmed to room temperature and stirred overnight. Reaction was poured into EtOAc (50 mL) then washed with 1N HCl (2 x 10 mL) and brine (10 mL). Organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. Crude material was purified on 12 g ISCO column (30% EtOAc – hexanes) obtaining **20** (265 mg, 48.4%).[6]

(**21**) – Solution of **20** (300 mg, 1.1 mmol) in ethanol (25 mL) was added to wet Pt(IV) Oxide (60 mg, 20% by weight) in Parr bottle. Reaction was hydrogenated at 35 psi overnight then filtered through celite and concentrated down. The crude compound was purified on 24 g ISCO column (10% MeOH – DCM) obtaining the ethyl **21** (54 mg, 18%)[7]

(**23**) – **18** (5.1 g, 21.1 mmol) was dissolved in DCM (100 mL) and Et_3N (3.8 mL, 27.4 mmol) and cooled to 0° C. Mesyl chloride (2.1g, 27.4 mmol) was added dropwise then warmed to room temperature and stirred overnight. Reaction was washed with 1N HCl (3 x 25 mL) and washed with brine (1 x 25 mL), then dried with Na_2SO_4 and

concentrated on rotary evaporator. The crude product was purified on a 120 g ISCO column (50% ethyl acetate - hexanes) obtaining **23** (3.95 g, 58.0%).[8]

(**24**) – **23** (1.78 g, 5,5 mmol) and NaN_3(0.93 g, 14.3 mmol) were dissolved in DMF (25 mL), heated to 90° C and stirred overnight. Cooled to room temperature and poured into water (200 mL). Extracted with ethyl acetate (4 x 40 mL) and washed with brine (30 mL). Organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. Crude product was purified on 40 g ISCO column (30% ethyl acetate - hexanes) obtaining **24** (1.45 g, 97.7%).[9]

(**25**) – Dry ether (25.0 mL) and methanol (0.84 mL) were added to $LiBH_4$ (0.45 g, 20.7 mmol) under N_2 atmosphere. Mixture was cooled to 0° C and solution of **24** (4.0 g, 14.8 mmol) in ether (25.0 mL) was added to dropwise and stirred for 2.5 h. Reaction was warmed to room temperature and poured into 150 mL diethyl ether. Washed with 1N HCl (3 x 35 mL) and brine (25 mL). Dried organic layer with Na_2SO_4 and concentrated down on rotary evaporator. The crude material was purified on 40 g ISCO column (30% ethyl acetate – hexanes) obtaining **25** (2.71 g, 75.7%).[8]

(**26**) – Dissolved **25** (2.7 g, 11.2 mmol) and pyridinium chlorochromate (3.1 g, 14.5 mmol) in dichloromethane (80 mL) and stirred at room temperature overnight. Reaction was filtered through celite and washed with 1N HCl (3 x 25 mL) and brine (25 mL). Organic layer was dried with Na_2SO_4 and concentrated down on rotary evaporator. Crude material was purified on 40 g ISCO column (35% ethyl acetate – hexanes) obtaining **26** (1.57 g, 58.5%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 9.649 – 9.526 (1H, m), 4.284 – 4.152 (1H, m), 4.15 – 4.019 (1H, m), 3.64 – 3.45 (2H, m), 2.398 – 2.152

(2H, m), 1.45 (9H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 201.83, 153.78, 81.32, 81.04, 63.35, 63.22, 59.90, 59.03, 51.93, 51.65, 35.39, 33.93, 28.31. **MS**: m/z calcd for $C_{10}H_{16}N_4O_3$: 241.13 ($M + H^+$), found 241.10.

(**27**) – Dry THF (60 mL) was added to t-BuOK (0.93 g, 8.3 mmol) and **22** (3.7 g, 8.6 mmol) and stirred at room temperature for 30 minutes. **26** (1.0 g, 4.2 mmol) was added and stirred for 1.5 h. Reaction was poured into water (200 mL) and extracted with ethyl acetate (3 x 50mL). Washed organic layer with brine, then dried with Na_2SO_4 and concentrated on rotary evaporator. The crude material was purified on a 40 g ISCO column (25% ethyl acetate – hexanes) obtaining the **27** (1.1 g, 84.5%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 6.048 – 5.868, 5.867 – 5.758 (1H, t), 5.709 – 5.419 (2H, m), 5.363 – 5.232, 4.823 – 4.595 (1H, m), 4.235 – 4.09 (1H, m), 4.08 – 3.965 (2H, m), 3.964 – 3.799 (2H, m), 3.758 – 3.599 (1H, m), 3.488 – 3.336 (1H, m), 2.512 – 2.325 (1H, m), 1.958 – 1.848 (1H, m), 1.68 (1H, s), 1.44 (9H, s).

(**28**) – Solution of **27** (160 mg, 0.5 mmol) in ethanol (10 mL) was added to wet 10% Pd-C (32 mg, 20% by weight) catalyst in Parr bottle. Reaction was hydrogenated at 35 PSI overnight then filtered through celite and concentrated on rotary evaporator. The crude material was purified on a 12 g ISCO column (5% methanol – methylene chloride) obtaining the **28** (124 mg, 86.9%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 4.909 – 4.843 (1H, m), 4.015 – 3.927 (2H, m), 3.898 – 3.737 (4H, m), 3.488 – 3.348 (1H, m), 2.931 – 2.828 (1H, m), 2.418 – 2.301 (1H, quint), 2.176 – 1.854 (4H, m), 1.682 – 1.59 (3H, m), 1.45 (9H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 154.45, 104.38, 79.24, 64.86, 64.80, 56.61, 54.64, 49.99, 40.90, 30.04, 29.65, 28.45

(**29**) – Dissolved **28** (487 mg, 1.7 mmol) and $NaHCO_3$ (285 mg, 3.4 mmol) in solution of THF (9 mL) and water (1 mL). Solution of CbzCl (0.3 mL, 2.0 mmol) in THF (2 mL) was added dropwise and stirred at room temperature 1 h. Reaction was poured into water (35 mL), then extracted with EtOAc (4 x 10 mL) and washed with brine (10 mL). Organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. Crude material was purified on 12 g ISCO column (50% EtOAc – hexanes) obtaining the protected **29** (496 mg, 69.4%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 7.434 – 7.309 (5H, m), 5.171 – 4.965 (2H, m), 4.885 – 4.826 (1H, m), 4.231 – 4.04 (1H, m), 4.018 – 3.746 (6H, m), 3.07 – 2.96 (1H, m), 2.468 – 2.336 (1H, m), 2.138 – 1.939 (1H, m), 1.711 – 1.528 (4H, m), 1.45 (9H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 155.82, 154.39, 136.30, 128.59, 128.25, 128.19, 104.22, 79.59, 66.86, 64.94, 64.85, 56.09, 29.96, 28.47

(**31**) – Added **29** (100 mg, 0.23 mmol) and tosylic acid (13 mg, 0.07 mmol) to acetone (3 mL) and water (1 mL) solution and stirred at room temperature overnight. Poured into saturated $NaHCO_3$ (10 mL), extracted with EtOAc (4 x 10 mL), and washed with brine (10 mL). Organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. Crude material was purified on 12 g ISCO column (50% EtOAc – hexanes). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 7.37 (5H, s), 6.831 – 6.611 (1H, m), 5.377 – 5.083 (3H, m), 4.745 – 4.554 (1H, m), 4.348 – 4.113 (1H, m), 3.768 – 3.54 (1H, m), 3.335 – 3.173 (1H, t), 2.901 – 2.644 (1H, m), 2.439 – 2.233 (1H, m), 2.16 – 1.991 (1H, d), 1.917 – 1.741 (1H, d), 1.587 – 1.396 (12H, m), 0.242 – 0.007 (s, silicon grease). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 135.99, 128.63. 128.35, 128.16, 106.35, 79.44, 68.22, 28.53, 1.04 (silicon grease). **MS**: m/z calcd for $C_{21}H_{31}N_2O_5$: 391.22 ($M + H^+$), found 391.

(**33**) – **18** (6.95 g 28.3 mmol), Et_3N (5.1 mL, 36.8 mmol) and DMAP (0.86 g, 7.1 mmol) were dissolved in DCM (50 mL). Solution of tosyl chloride (7.0 g, 36.8 mmol) in DCM (50 mL) was added dropwise and stirred at room temperature overnight. Washed reaction with 1N HCl (3 x 20 mL) and brine (20 mL). Dried organic layer with Na_2SO_4 and concentrated down on rotary evaporator. The crude material was purified one 220 g ISCO column (30% ethyl acetate – hexanes) obtaining **33** (8.4 g, 77.5%).[12]

(**34**) - **33** (1.93 g, 5.0 mmol) and NaCN (1.5 g, 30 mmol) were dissolved in DMSO (15 mL) and stirred at 90° C for 1.5 h. Reaction was cooled to room temperature and poured into solution of saturated $NaHCO_3$ (25 mL) and water (25 mL). The mixture was extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were washed with brine. Organic layer was dried with Na_2SO_4 and concentrated down on rotary evaporator. The crude material was purified on a 40 g ISCO column (30% ethyl acetate – hexanes) obtaining the **34** (559 mg, 44.0%).[12]

(**35**) – Dry Et_2O (15 mL) was added to $LiBH_4$ (220 mg, 10.0 mmol) under argon atmosphere and cooled to 0°C. Solution of **34** (1.41 g, 5.6 mmol) dissolved in dry Et_2O (10 mL) and dry MeOH (0.4 mL, 10 mmol) was added dropwise and stirred at 0° C for 3h. Reaction was warmed to room temperature and poured into Et_2O (30 mL). Washed organic layer with saturated NH_4Cl (3 x 20mL), then dried with Na_2SO_4 and concentrated on rotary evaporator. Crude material was purified on a 40 g ISCO column (40% ethyl acetate – hexanes) obtaining **35** (0.82 g, 65.0%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 4.548 – 4.399, 4.091 – 3.881 (2H, m), 3.81 – 3.71 (2H, m), 3.543 – 3.445 (1H, m), 3.086 – 2.939 (1H, quint), 2.552 – 2.418 (1H, quint), 2.018 – 1.877 (1H, m), 1.47 (9H, s). **^{13}C**

NMR (300 MHz, $CDCl_3$): δ (ppm) = 119.39, 81.61, 66.29, 59.89, 50.02, 32.68, 29.73, 28.36, 26.59.

(**36**) – **35** (0.82 g, 3.6 mmol), Et_3N (0.7 mL, 5.0 mmol) and DMAP (0.1 g, 0.8 mmol) were dissolved in DCM (10 mL). Solution of tosyl chloride (1.3 g, 7.2 mmol) in DCM (10 mL) was added dropwise and stirred at room temperature overnight. Reaction was washed with 1N HCl (3 x 10 mL). Organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. Crude product was purified on a 24 g ISCO column (40% ethyl acetate – hexanes) obtaining **36** (1.05 g, 76.8%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 7.847 – 7.762 (2H, d), 7.421 – 7.318 (2H, d), 4.38 – 3.778 (5H, m), 3.469 – 3.35 (1H, m), 3.065 – 2.923 (1H, quint), 2.511 – 2.416 (3H, m), 2.297 – 2.162 (1H, m), 1.42 (9H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 145.61, 132.52, 130.73, 128.08, 121.08, 80.23, 80.21, 55.35, 28.30, 21.62, 21.57, 21.55.

(**37**) – **36** (1.85 g, 4.9 mmol) and NaN_3 (1.6 g, 25.5 mmol) were dissolved in DMF (10 mL) and stirred at 90° C for 2.5 h. Cooled reaction to room temperature and poured into water (40 mL). Solution was extracted with ethyl acetate (3 x 10 mL). Organic layer was dried with Na_2SO_4 and concentrated on rotary evaporator. The crude material was purified on a 24 g ISCO column (30% ethyl acetate – hexanes) obtaining **37** (992 mg, 80.7%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 4.123 – 3.75 (2H, m), 3.722 – 3.538 (1H, m), 3.503 – 3.348 (2H, m), 3.066 – 2.925 (1H, quint), 2.495 – 2.34 (1H, m), 2.298 – 2.129 (1H, m), 1.44 (9H, s). m), 1.44 (9H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 153.52, 119.77, 119.56, 81.01, 56.20, 55.60, 53.20, 51.87, 49.82, 33.42, 32.35, 28.34, 26.96, 26.65, 26.16. **MS**: m/z calcd for $C_{11}H_{17}N_5O_2$: 252.14 ($M + H^+$), found 252.21.

(**38**) – Solution of NaOH (140 mg, 3.5 mmol) and water (2 mL) were added to solution of **37** (180 mg, 0.71 mmol) in ethanol (3 mL) and refluxed overnight. Reaction was cooled to room temperature and concentrated down on rotary evaporator. Added ice while adding 1N HCl to get solution to pH = 2.0, then saturated the solution with NaCl. The solution was extracted with ethyl acetate (3 x 10 mL). The organic layer was dried with Na_2SO_4 and concentrated down on rotary evaporator. The crude material was purified on a 24 g ISCO column (5% methanol – DCM) obtaining the **38** (143 mg, 74.7%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 11.19 (1H, m), 4.22 – 3.89 (1H, m), 3.87 – 3.60 (2H, m), 3.57 – 3.42(1H, m), 3.41 – 3.15 (2H, m), 2.48 – 2.06 (2H, m), 1.46 (9H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ (ppm) = 178.31, 154.37, 80.55, 56.60, 56.28, 53.81, 52.88, 49.03, 41.68, 32.53, 31.70, 28.42. **MS**: m/z calcd for $C_{11}H_{13}N_4O_4$ 269.13($M - H^+$), found 269.00.

Spectral Analysis

Figure 8: ^{1}H NMR of **26**

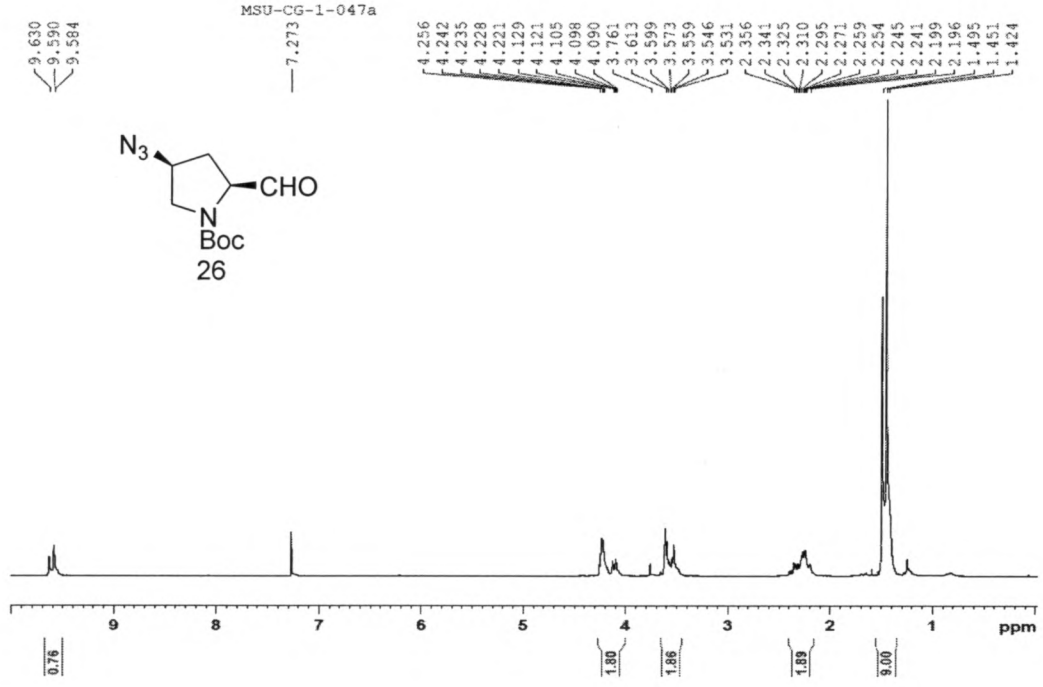


Figure 9: ^{13}C NMR of **26**

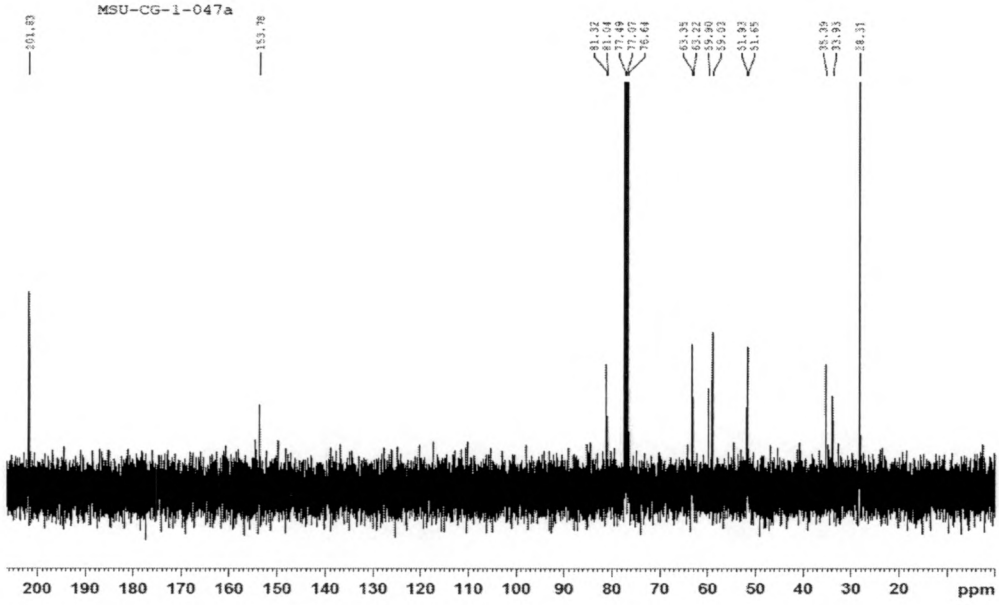


Figure 10: ^{1}H NMR of **27**

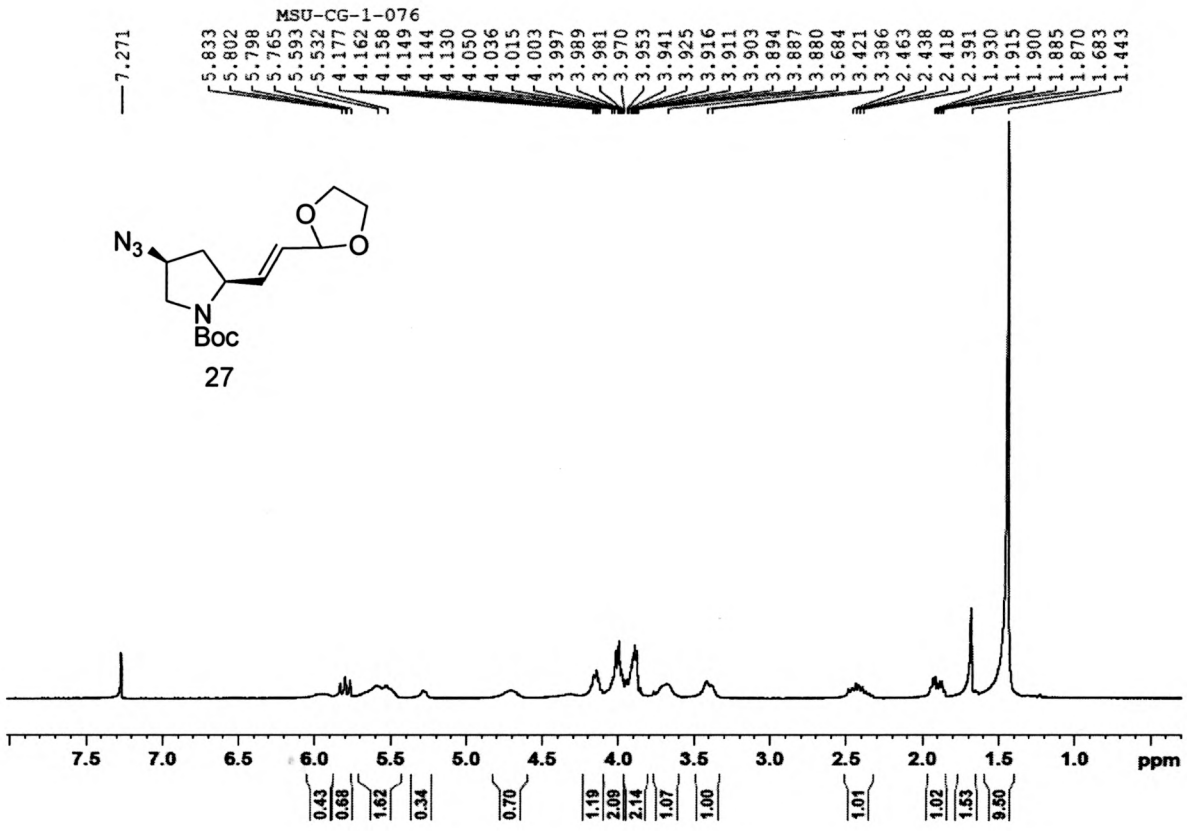


Figure 11: ^{1}H NMR of **28**

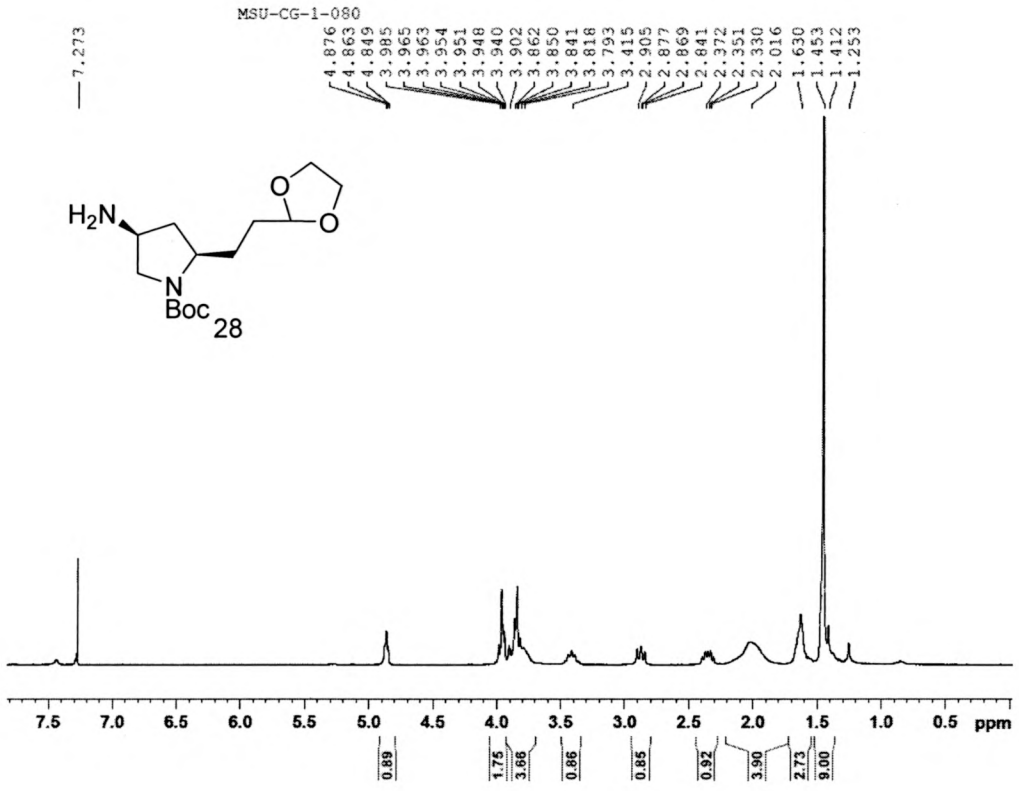


Figure 12: ^{13}C NMR of **28**

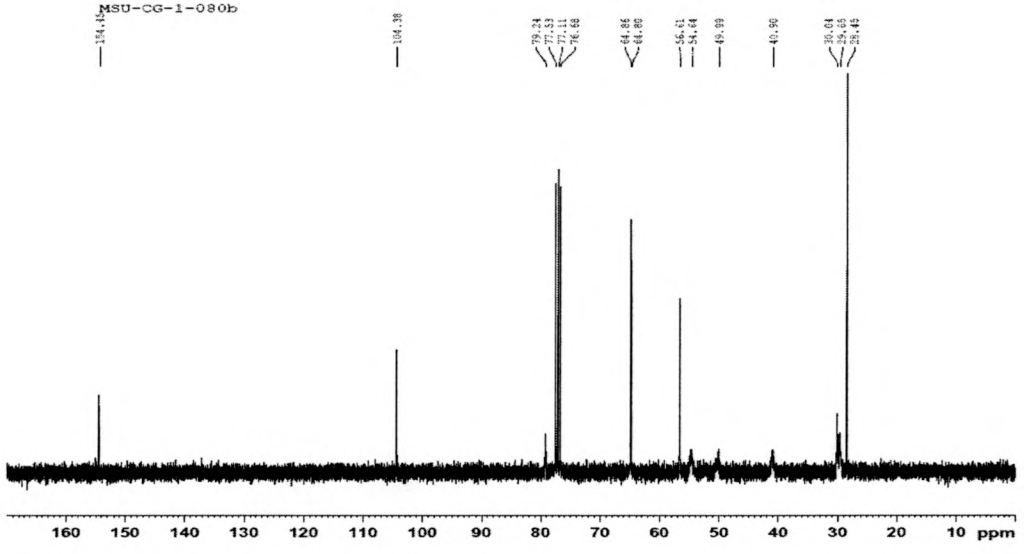


Figure 13: ^{1}H NMR of **29**

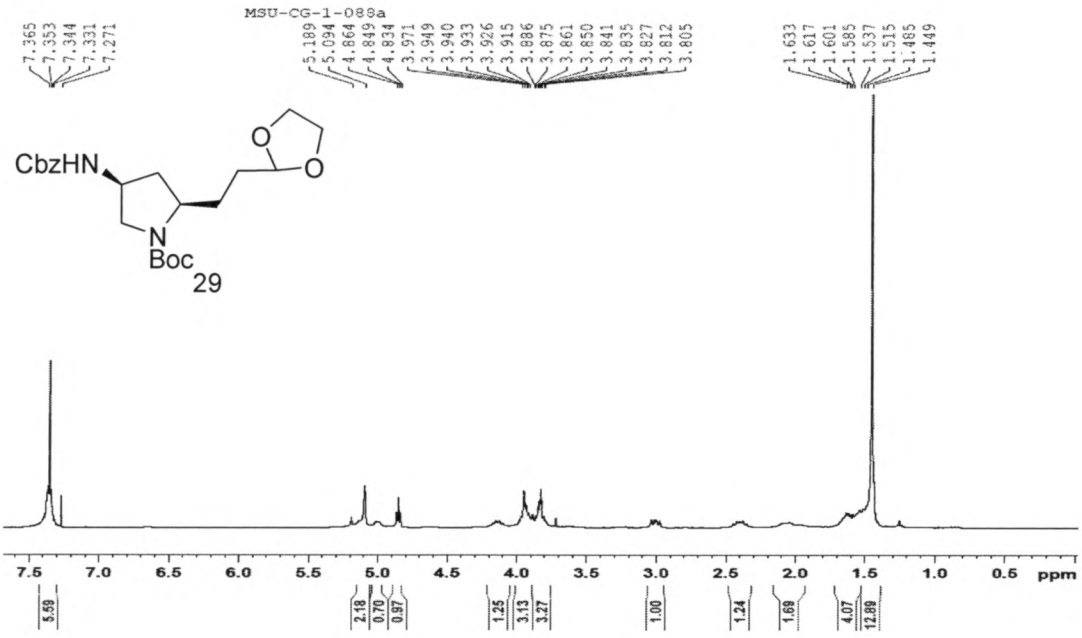


Figure 14: ^{13}C NMR of **29**

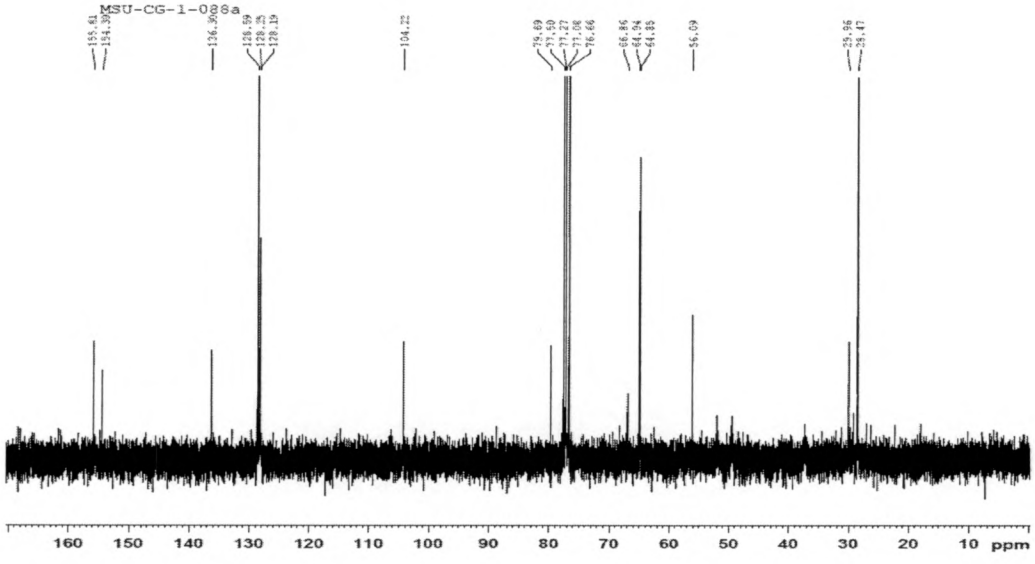


Figure 15: ^{1}H NMR of **31**

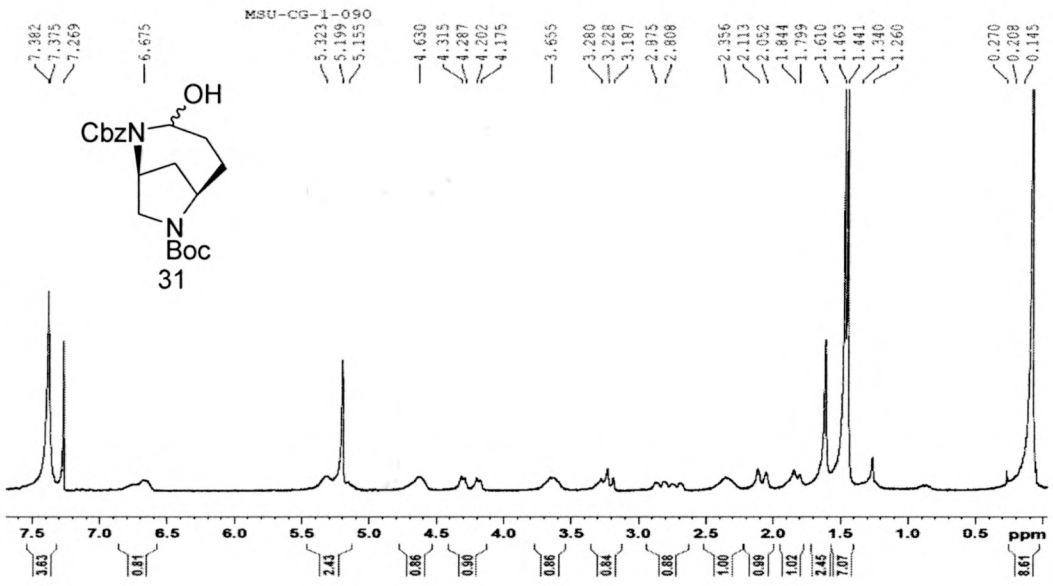


Figure 16: ^{13}C NMR of **31**

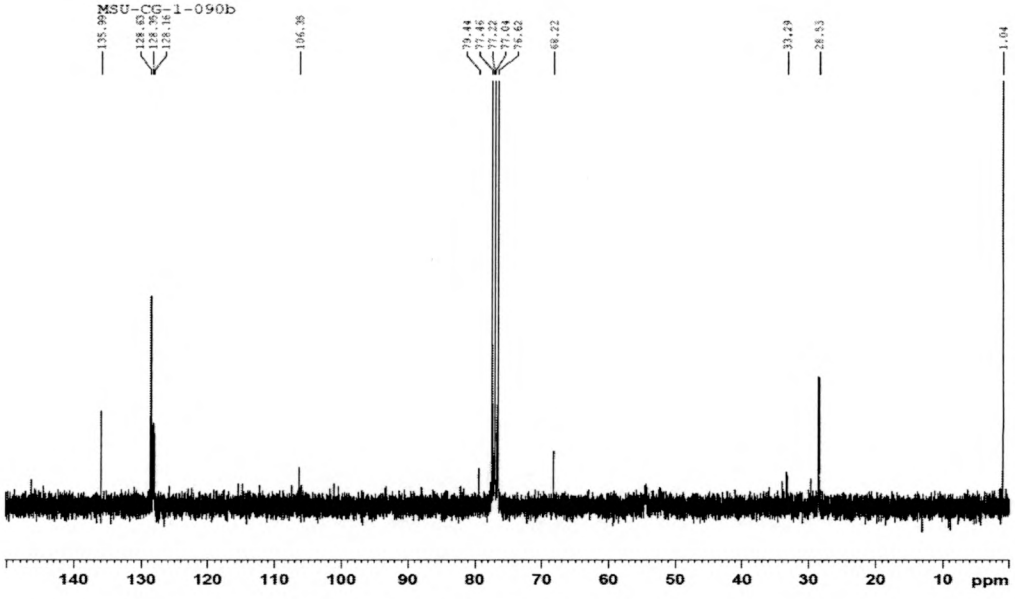


Figure 17: ^{1}**H NMR** of **35**

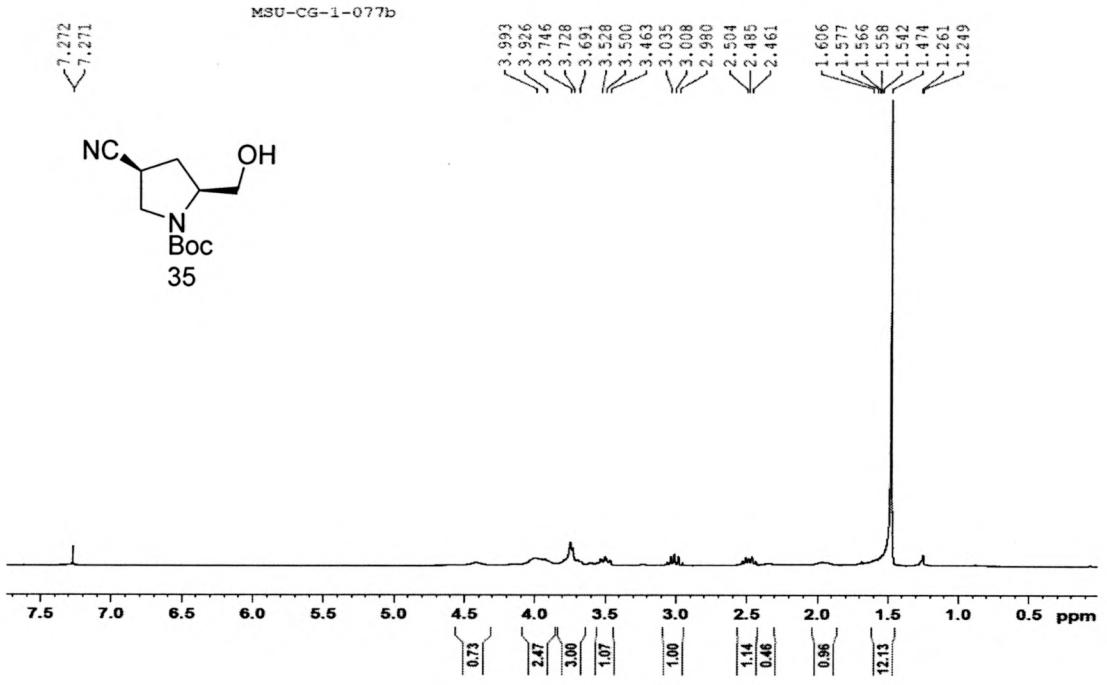


Figure 18: ^{13}C NMR of **35**

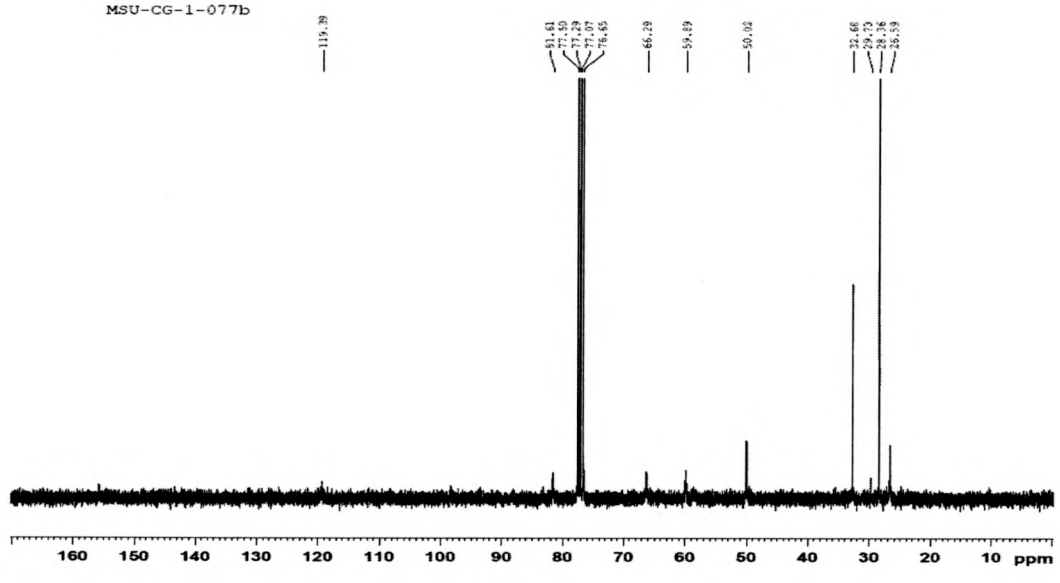


Figure 19: ^{1}H NMR of **36**

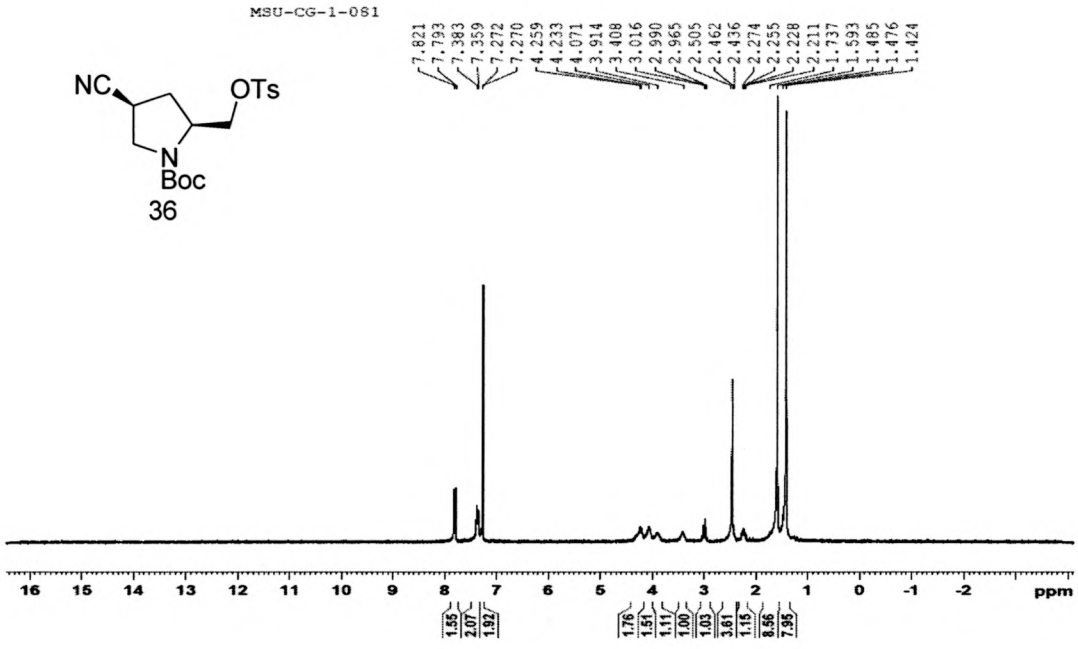


Figure 20: ^{13}C NMR of **36**

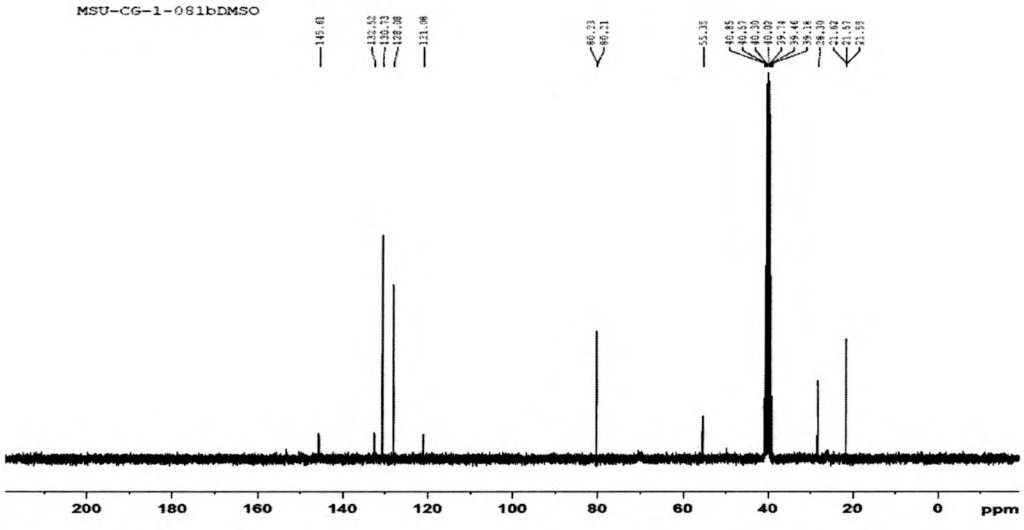


Figure 21: ^{1}H NMR of **37**

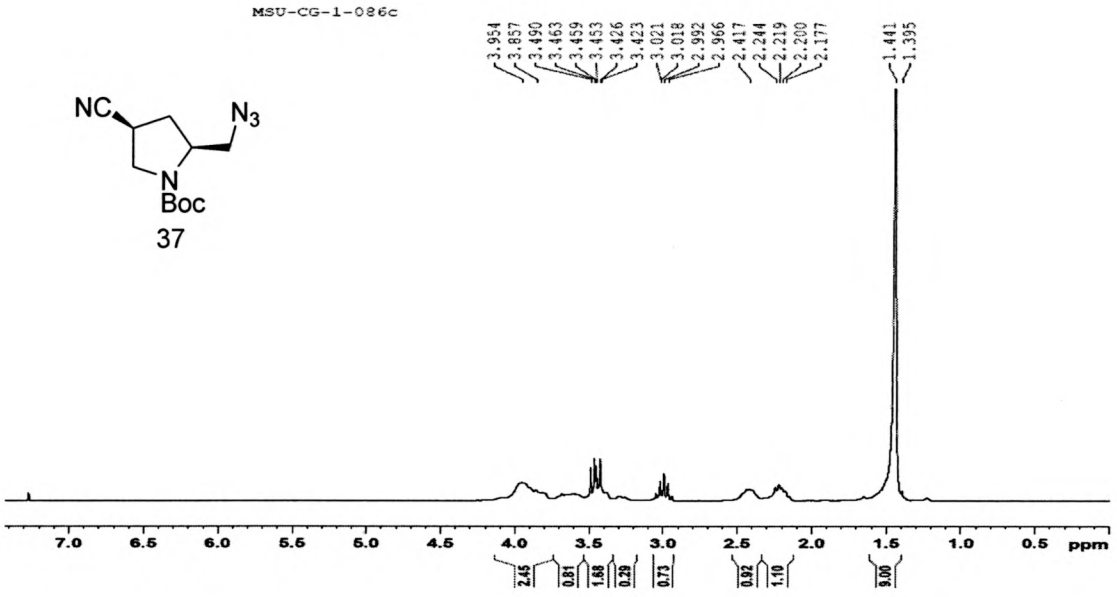


Figure 22: ^{13}C NMR of **37**

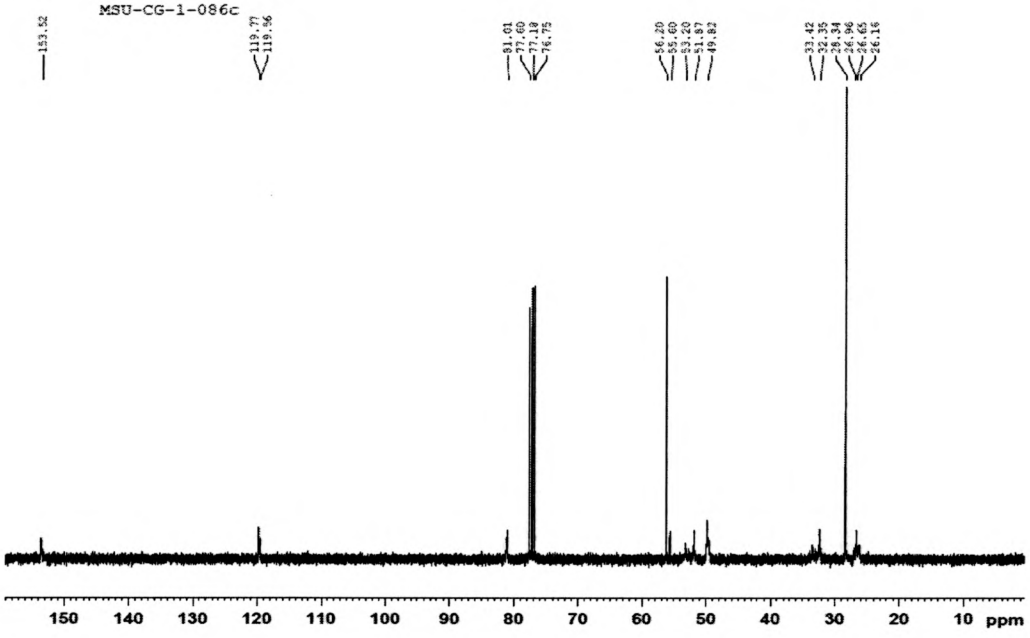


Figure 23: ^{1}H NMR of **38**

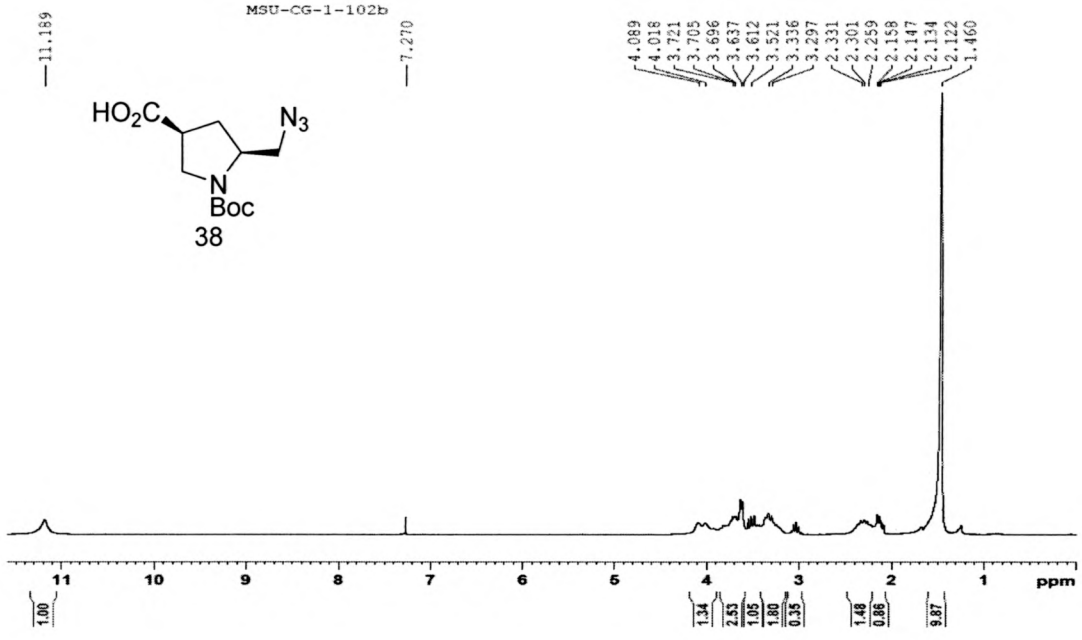
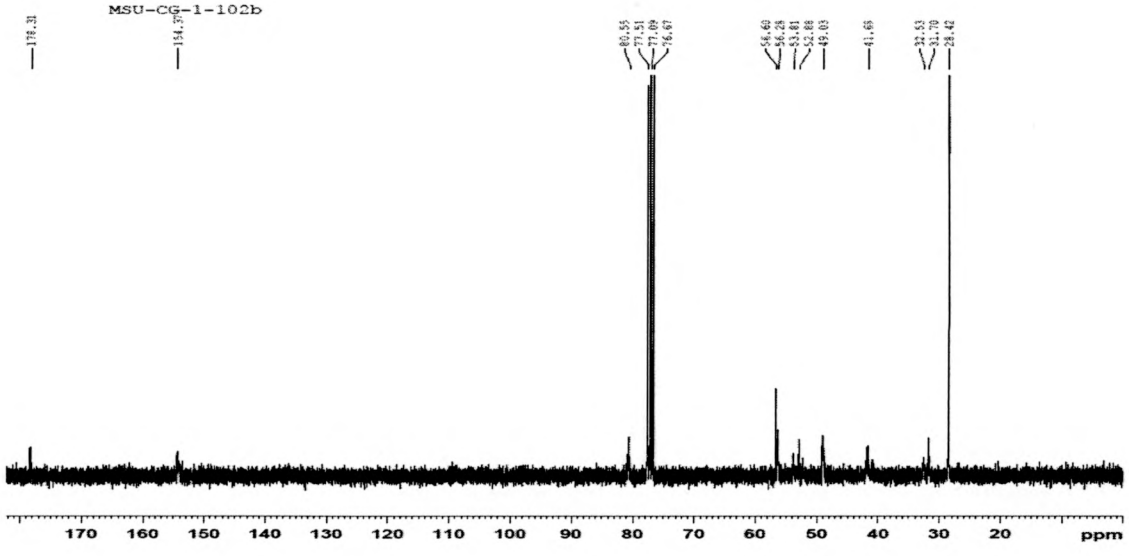


Figure 24: ^{13}C NMR of **38**



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