TOWARD NEUROACTIVE PYRROLIDINES AND SYNTHETIC EFFICIENCY: DEVELOPMENT OF AN ASYMMETRIC AZA-MICHAEL ALDOL-LACTONIZATION ORGANOCASCADE PROCESS

An Undergraduate Research Scholars Thesis

by

BIANCA LIZETTE RAMIREZ

Submitted to Honors and Undergraduate Research
Texas A&M University
in partial fulfillment of the requirements for the designation as

UNDERGRADUATE RESEARCH SCHOLAR

Approved by
Research Advisor: Dr. Daniel Romo

May 2013

Major: Chemistry

TABLE OF CONTENTS

Page

ABSTRACT

Toward Neuroactive Pyrrolidines and Synthetic Efficiency: Development of an Asymmetric Aza-Michael Aldol-Lactonization Organocascade Process. (May 2013)

Bianca Lizette Ramirez
Department of Chemistry
Texas A&M University

Research Advisor: Dr. Daniel Romo
Department of Chemistry

Described is the development an asymmetric aza-Michael aldol-lactonization organocascade process. This process enables the synthesis of highly-substituted pyrrolidines from α-amino ketones through an organocascade process. Boc-*N*-*(L)*-phenylalanine and Ts-*N*-*(L)*-alanine α-amino ketone substrates were synthesized by carrying out Weinreb ketone syntheses on their parent α-amino acid. The α-amino ketone substrates and acryloyl chloride were subjected to different aza-Michael aldol-lactonization conditions in order to test for the efficiency at which they react to form pyrrolidine products. The Ts-*N*-*(L)*-alanine α-amino ketone substrate, when reacted with homobenzootetramisole (± HBTM) as a nucleophile promoter and EtN(*i*-Pr)$_2$ as stoichiometric base, showed the most promise in favoring the formation of pyrrolidine products.

DEDICATION

To my parents, Paulino and Blanca Ramirez Jr.

ACKNOWLEDGMENTS

I would like to thank Dr. Daniel Romo for his support throughout the course of this research and for giving me the opportunity to become a part of his research group. Thanks also goes to Jeremy Chris P. Reyes, Mikail Abbasov, Dr. Omar Robles and all the members of the Romo research group who I have been lucky enough to work with this past year. Their constant guidance has greatly increased my confidence in my research ability and their lessons will stay with me as I continue on with my academic career.

Thanks also goes to my family and friends whose love and support has helped me strive to do my best every day.

NOMENCLATURE

Bn	benzyl
Boc	tert-butyloxycarbonyl
$CDCl_3$	chloroform-d
CH_2Cl_2	dichloromethane
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
EtN(*i*-Pr)$_2$	*N*,*N*-diisopropylethylamine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
h	hour
IR	infrared spectroscopy
HOBt	hydroxybenzotriazole
HBTM	homobenzotetramisol
LiHMDS	lithium bis(trimethylsilylamide)
Me	methyl
CD_3OD	methanol-d_4
NMM	*N*-methylmorpholine
PMB	*para*-methoxybenzyl

PMP	*para*-methoxyphenyl
R	alkyl group
THF	tetrahydrofuran
Ts	tosyl

CHAPTER I

AN INTRODUCTION TO PYRROLIDINES AND THE PRECEDENT BEHIND THE DEVELOPMENT OF THE ASYMMETRIC AZA-MICHAEL ALDOL-LACTONIZATION ORGANOCASCADE PROCESS

Introduction

Pyrrolidines are the subject of coninued studies in organic synthesis, with a primary focus the simplification of their construction.[1] Pyrrolidines are targeted by synthetic methodology studies and are commonly found in natural product synthesis.[2] Pyrrolidines are an important structural component in many chiral catalysts for imine and enamine based organocatalytic reactions.[3] Pyrrolidines also plays a pertinent role in biological chemistry due to their recurrence in numerous bioactive natural products such as spirotryprostatin B, which has shown to inhibit progression in the cell cycle from the G_2 phase to the M phase, and brouaonetinines, which are strong inhibitors of α- and β-glucosidase and other enzymes which are involved in the breakdown of carbohydrates.[4,5] The pyrrolidine ring structure is also present in an important class of naturally occurring organic compounds called alkaloids. Alkaloids, which contain at least one nitrogen atom in a heterocyclic ring, have been discovered to possess many neuroactive properties and are known to interact with receptors at nerve endings.[6] Because of the potent neuroactive properties of nitrogen containing heterocycles, the pyrrolidine moiety is an important structural motif that appears in the structures of anticonvulsant active molecules which are currently being used in pharmaceutical drugs such as Keppra to treat epilepsy.[7,8] In addition, pyrrolidine-based compounds, such as saxagliptin, are currently being sold as a hypoglycemic

drugs used in the treatment of diabetes due to their inhibitory properties toward dipeptidyl peptidase-4 (DPP-4).[9]

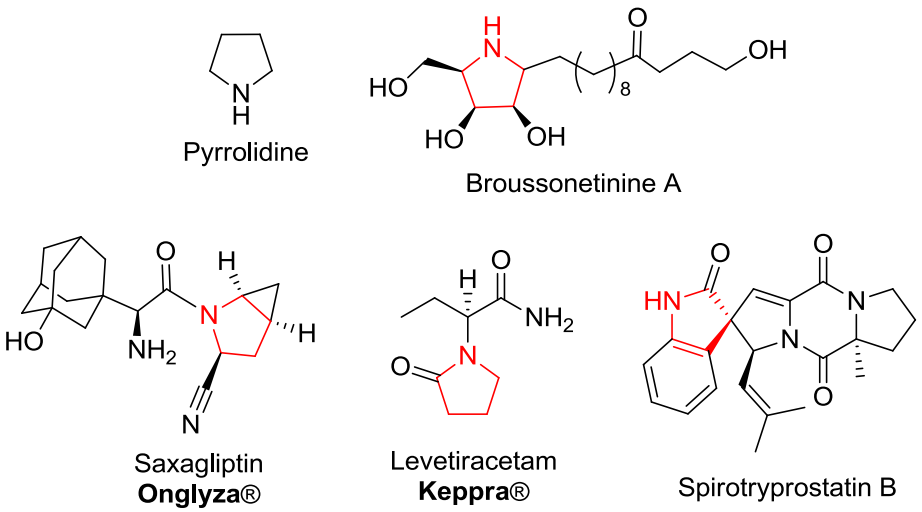
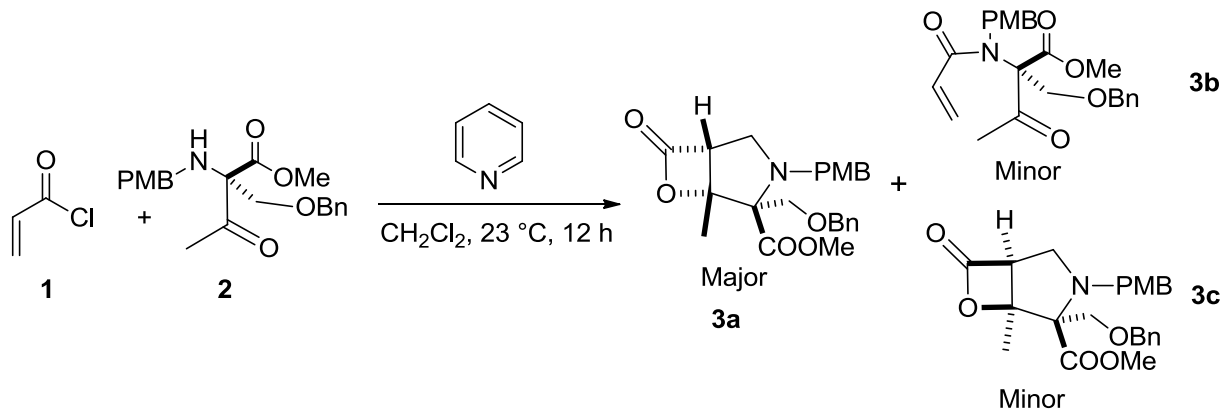


Figure 1. The structure of pyrrolidine along with the structure of several pyrrolidine based alkaloids and pharmaceutical agents.

Literature precedent

The recently developed Nucleophile-Catalyzed Michael Aldol- Lactonization (NCMAL) enables construction of cis-fused β-lactones with a 4, 5 ring system through an organocascade process.[10] In the NCMAL, a Lewis base or nucleophile is used to activate an acid chloride in order to produce an α, β-unsaturated acyl ammonium species. A base, LiHMDS, is used to form an enolate by α-deprotection. The nucleophilic enolate attacks the acyl ammonium species by 1, 4 Michael addition to produce an ammonium enolate. This enolate in turn undergoes an intermolecular aldol-lactonization to yield a cis 4, 5 ring β-lactone.

Further precedent for this project comes from the Corey involving a failed acylation attempt of acryloyl chloride **1** with amino ketone **2** shown in Scheme 1.[11] Surprisingly, the



Scheme 1. Precedent for aza-Michael aldol-lactonization.

reaction favored a 1,4 Michael addition of **2** to **1** followed by an internal cyclization which yielded **3a**, a highly substituted pyrrolidine with an attached β-lactone, as the major product**. 3b**, the product of N-acylation, and **3c**, the diastereomer of **3a** were isolated as minor products. This unexpected formation of **3a** and **3b** could also be controlled by varying the conditions under which the reaction was carried out. The ratio of acylation addition to pyrrolidine formation varied with the use of different catalytic amines. Corey's group found that hindered bases such as 2,6-di-tert-butylpyridine and triisobutylamine did not lead to pyrrolidine formation, but instead favored *N*-acylation. Likewise, unhindered bases, such as the pyridine in Scheme 1, favored the organocascade process. The mechanistic pathway for the formation of pyrrolidine with pyridine as a base believed by the Corey group to have taken place is shown in Figure 2. In the proposed mechanism, because pyridine is unhindered, the acryloyl chloride can form an activated *N*-acrylylammonium complex similar to **4**. This activated electrophile then undergoes a

nucleophilic attack by **2** to afford intermediate **5** which then cyclizes by internal cycloaddition to give **3a** and **3b**.

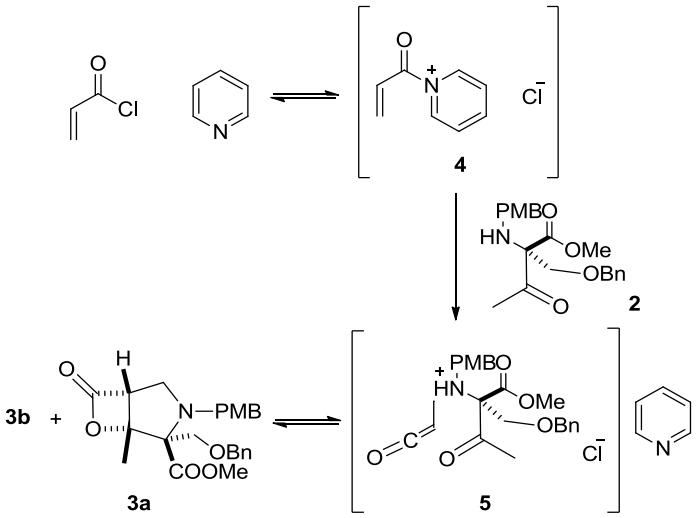


Figure 2. Corey precedent proposed mechanism.

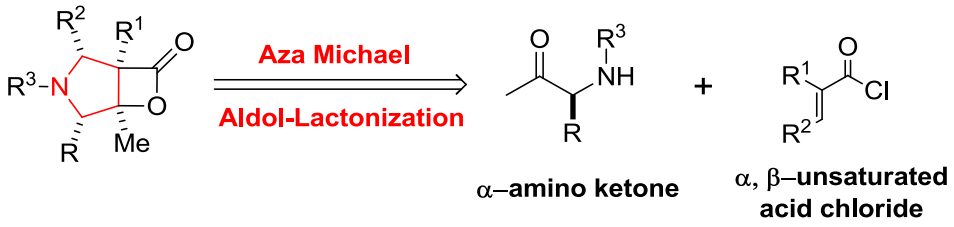
This mechanism also explains why highly hindered bases do not lead to pyrrolidine formation because they are sterically unable to form an activated *N*-acrylylammonium complex. Thus the acryloyl chloride undergoes direct *N*-acylation with **2,** while the base serves as a simple Bronsted base.

Based upon the precedent of the NCMAL methodology and the work of Corey, the proposed project sought to develop a more general, asymmetric aza-Michael aldol-lactonization organocascade process which would allow for an efficient synthesis of highly substituted pyrrolidines. This organocascade process involves an aza-Michael reaction followed by an intermolecular aldol-lactonization to form pyrrolidines bearing fused β-lactones.

CHAPTER II

METHODS

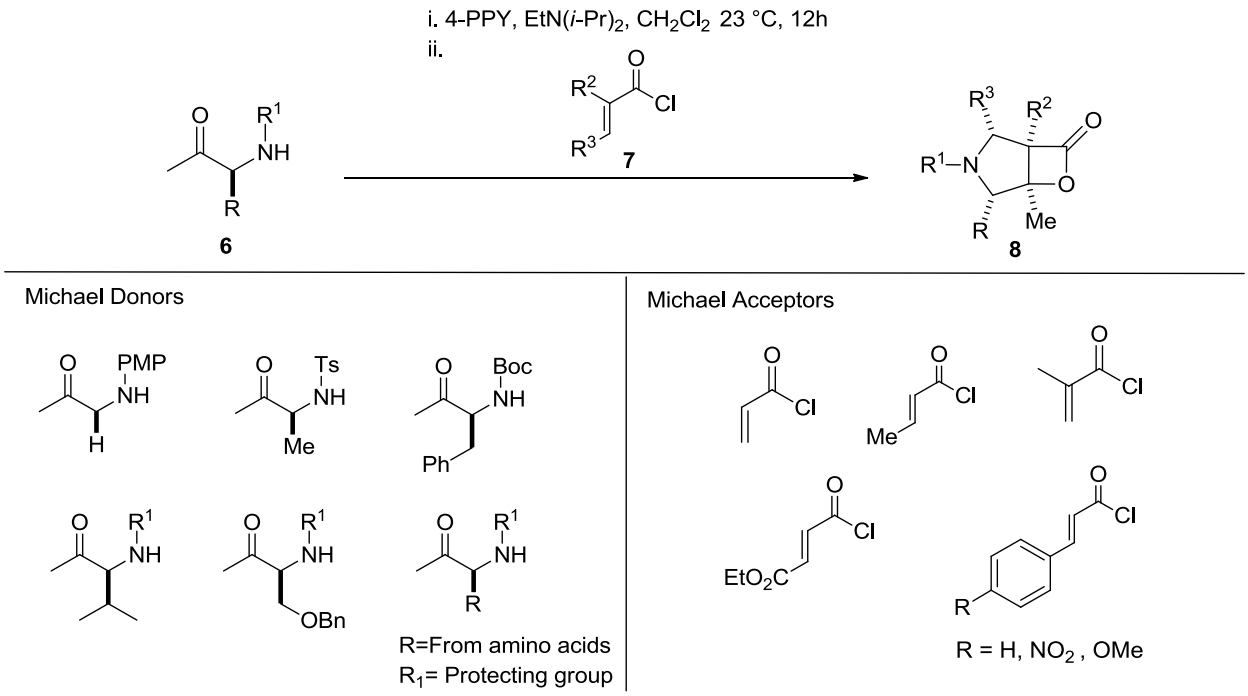
A retro-synthesis was developed for the asymmetric aza-Michael aldol-lactonization organocascade process, Scheme 2. The synthesis of highly substituted asymmetric pyrrolidines bearing fused β-lactones was envisioned to involve the reaction of an α amino ketone as a Michael donor with an unsaturated acid chloride as a Michael acceptor. The Michael acceptors consist of different commercially available α, β-unsaturated acid chlorides, such as acryloyl chloride. On the other hand, the Michael donors are α-amino ketones substrates derived from their parent amino acids which are commercially available and enantomerically pure.



Scheme 2. Tandem aza-Michael aldol-lactonization to be studied.

In performing the aza-Michael aldol-lactonization, conditions similar to those performed by the Romo group would be tested first. 4-pyrrolidinopyridine (4-PPY) would be used as an activator of the Michael acceptor and diisopropyl ethyl amine (EtN(*i*-Pr)$_2$) would be used as a stoichiometric Bronsted base. The reaction would be carried out in dichloromethane solvent (CH_2Cl_2) at 23 °C would initially follow the Corey precedent. A tandem aza-Michael aldol-

lactonization reaction is shown in Scheme 3, along with various Michael donors and Michael acceptors to be studied.

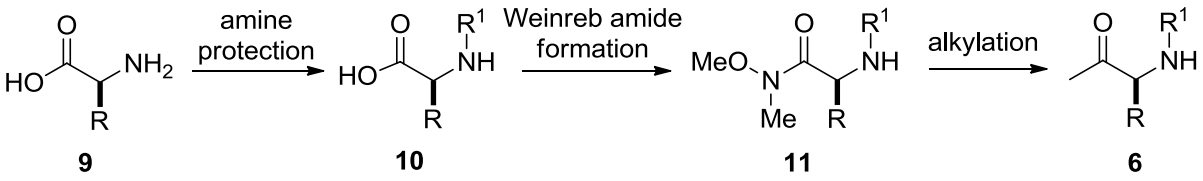


Scheme 3. Tandem aza-Michael aldol-lactonization and various Michael donors and acceptors to be studied.

The variations of the Michael donors and acceptors to be studied will test the effects of steric hindrance, electron withdrawing groups, and electron donating groups on the performance of the aza-Michael aldol-lactonization. Based on results of the first attempt of the aza-Michael aldol-lactonization, subsequent changes will also be made to the reaction condition in order to test their effects on the yield of pyrrolidine. Such changes include varying the hindrance of the

nucleophile, varying the type and amount of base added, and varying the reaction temperature. The main aim is to start off simple and increase the complexity of the reactions gradually.

Because α-amino ketones are not sold commercially, the route shown in Scheme 4 was developed for the synthesis of the required α-amino ketone substrates. The *N*-terminus of the amino acid will be protected to yield **10**. This resulting compound is then subjected to a Weinreb ketone synthesis in order to yield the α-amino ketone **6**. The Weinreb ketone synthesis consists of the formation of Weinreb amide **11** by reacting **10** with *N*, *O*-dimethylhydroxylamine. The final methyl alkylation to form the desired Michael donor **6** is then be performed by subjecting **11** to an organolithium reagent MeLi.[12]



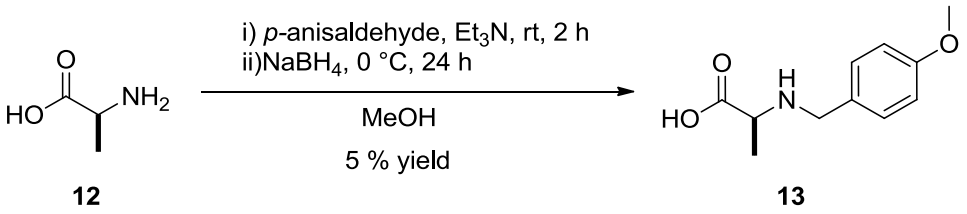
Scheme 4. General Michael donor synthesis route.

CHAPTER III

RESULTS

Synthesis of α-amino ketone substrates

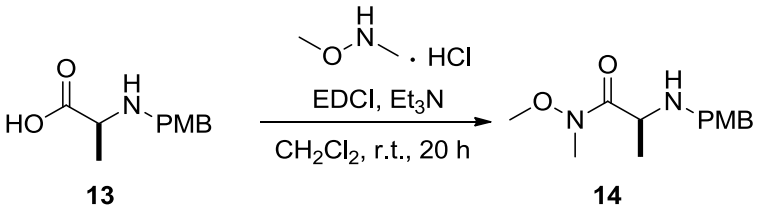
The first Michael donor α-amino ketone targeted was PMB-*N*-*(L)*-alanine amino ketone. The *N*-PMB group is one of several groups which could varied to probe electronic effects of this group on the aza-Michael aldol lactonizaiton. In the Corey precedent, a *N*-PMB group was utilized. Alanine was studied initially because it only bears a simple methyl group but yet has greater steric hindrance than that of glycine, R group = H. Experiments performed previously by a graduate student, J.C. Reyes, have confirmed the need for the Michael donor to have a more sterically hindered α carbon and the Corey precedent also suggests that steric hindrance can improve the desired reaction over simple acylation. Protection of the *L*-alanine **12** with the PMB group was performed by reductive amination as shown in Scheme 5.[13]



Scheme 5. PMB protection of *L*-alanine *N*-terminus.

Reductive amination involves the conversion of a carbonyl group to an amine via in situ formation of an imine. Amine **12** was condensed *p*-anisaldehyde to generate an imine intermediate. Any water produced over the course of the reaction was removed by the addition of anhydrous $MgSO_4$. The $MgSO_4$ was then removed by filtration and the imine was reduced to an

amine by the addition of $NaBH_4$. The reaction proved to be very problematic and the overall yield of the reaction was low with a 5 % yield. The small amount of pure product was carried onto the Weinreb ketone synthesis. In the formation of the Weinreb ketone, the reactions involve two subsequent nucleophilic acyl substitutions, the conversion of the acid into an N, O-dimethylhydroxylamide, also known as a Weinreb amide, followed by treatment with a Grignard reagent or an organolithium reagent. Scheme 6 shows the first step of this ketone synthesis as applied to the formation of PMB-*N*-(*L)*-alanine amino ketone.

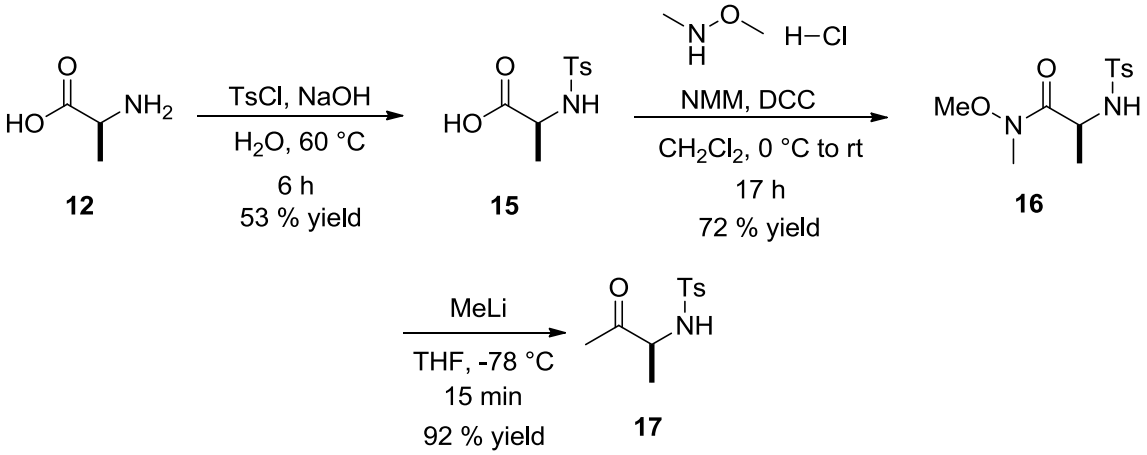


Scheme 6. Weinreb amide formation of **13**.

The *N*-protected amino acid was reacted with *N, O*-dimethylhydroxylamine hydrochloride in order to form the Weinreb amide. EDCI was used as a catalyst and Et_3N was used as a base.[14] Formation of amide **14** was successful however the initial scale of the reaction was ~ 25 mg and the overall reaction yield was low. The many problems associated with the synthesis of the PMB-*N-(L)*-alanine amino ketone made progress slow, thus because of time limitations the synthesis of this amino ketone was halted.

In order to make up for lost time, two different amino ketones, Boc-*N-(L)*-phenylalanine amino ketone and Ts-*N*-(*L)*-alanine amino ketone, were synthesized simultaneously. The synthesis route of Ts-*N-(L)*-alanine amino ketone **17** will be described first. Use of the *N*-Ts group would enable

us to determine the electronic effect of this group on reaction outcome given it is a strong electron withdrawing group. As shown in Scheme 7, addition of the *N*-Ts group to **12** was accomplished with *p*-toluenesulfonyl chloride to deliver sulfonylamide **15**. NaOH was used as base and the reaction was carried out in aqueous solvent at 60 °C for 6 hours.[15] The yield of this reaction was 53 % delivering 5.4 g of amide **15** as a white solid. This overall reaction was simple and because the product could be collected by crystallization without the need for further purification.

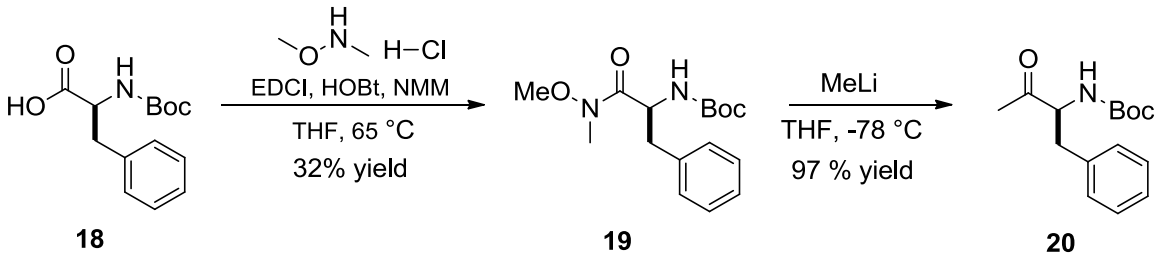


Scheme 7. Synthesis route taken in the formation of Ts-*N*-*(L)*-alanine amino ketone **17** which includes a tosyl protection of the N-terminus followed by a Weinreb ketone

The Weinreb ketone synthesis was then performed. The formation of the Weinreb amide **16** was carried out by a procedure similar to the one used by Aggarwai.[16] The *N*-protected amino acid was coupled to *N, O*-dimethylhydroxylamine hydrochloride using dicyclohexylcarbodiimide (DCCas carboxylic acid activator and 4-methylmorpholine as base. The reaction was carried out in dichloromethane at 0 °C for 3 h and then at 23 °C for an additional 14 h. The reaction gave a 72 % yield of amide **16** (1.71 g) as an off white solid. Due to the acidic NH group, 2 equivalents

of methyl lithium were used to ensure that it reacted with the *N, O*-dimethylhydroxylamine of **16**. The reaction was successful and a total of 1.22 g (92 %) of **17** was collected as an off white solid.

In addition, Boc-*N*-(*L)*-phenylalanine amino ketone **20** was synthesized in through the reaction sequence shown in Scheme 8.



Scheme 8. Synthesis route taken in the formation of Boc-*N*-*(L)*-phenylalanine **18** via a Weinreb ketone synthesis.

This ketone was synthesized since the phenylalanine R provided greater sterics which we expected would aid β-lactone formation while minimizing *N*-acylation. Because *N*-Boc-phenylalanine **18** is commercially available, it was also decided to test the effects of the Boc group on β-lactone formation. Protected amino acid **18** was reacted with *N, O*-dimethylhydroxylamine hydrochloride as before but using EDCI as activator and *N*-methylmorpholine as base. However when *N, O*-dimethylhydroxylamine hydrochloride and *N*-methylmorpholine were added to the reaction the solution was kept at 0 °C for 15 minutes.[17] The reaction gave a 32 % yield, 1.84 g, of **19** as a yellow oil which directly to the final methyl lithium addition while making sure to add 2 equivalents of methyl lithium to ensure full

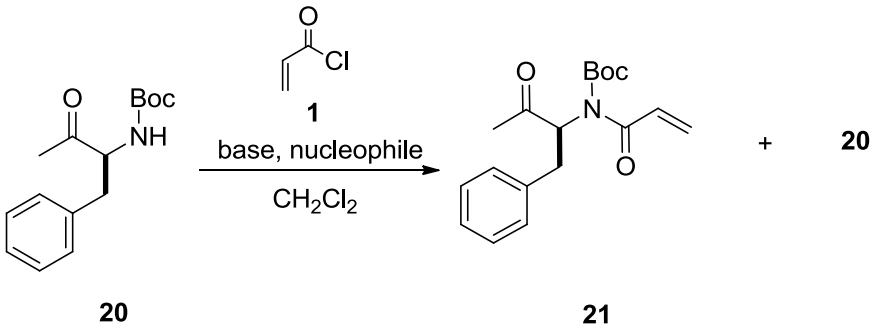
conversion. The reaction was successful and a total of 1.33 g of **20** (97%) was collected as an off white solid.

Studies on the asymmetric aza-Michael aldol-lactonization organocascade process

With the Boc-*N-(L)*-phenylalanine amino ketone and Ts-*N-(L)*-alanine amino ketone substrates in hand, these were submitted to the aza-Michael aldol-lactonization. There are many variables which could be tested in developing the ideal reaction conditions to favor the aza-Michael aldol-lactonization organocascade process. The first variable to be tested in these studies was the nucleophile used in order to generate the desired α, β- unsaturated acylammonium intermediare. The nucleophiles commonly employed in the Romo group for related reactions include dimethylaminopyridine, 4-pyrrolidinopyridine (4-PPY) and homobenzotetramisol ((±) HBTM and optically pure). All other aspects of the reaction were kept constant.

The results of the aza-Michael aldol-lactonization reaction conditions performed thus far on the Boc-*N-(L)*-phenylalanine amino ketone substrate **20** are illustrated in Table 1. The initial aza-Michael aldol-lactonization performed using 4-PPY as a nucleophile resulted in no reaction (Entry 1). It was realized after initiating reaction that the 4-PPY used in Entry 1 was impure and thus the substrate was resubmitted to the same reaction conditions using a new batch of 4-PPY (Entry 2).

Table 1. Studies performed on Boc-*N*-*(L)*-phenylalanine amino ketone substrate **20.**



Entry	Base (equiv.)	Nucleophile (equiv.)	Temp	Results
1[a]	EtN(*i*-Pr)$_2$ (1.1)	4-PPY (1.1)	0 °C to 23 °C	no reaction
2	EtN(*i*-Pr)$_2$ (1.1)	4-PPY (1.1)	0 °C to 23 °C	Recovered **20**, trace amounts **21**
3	EtN(*i*-Pr)$_2$ (1.1)	(±) HBTM (1.1)	0 °C to 23 °C	Recovered **20**, trace amounts **21**

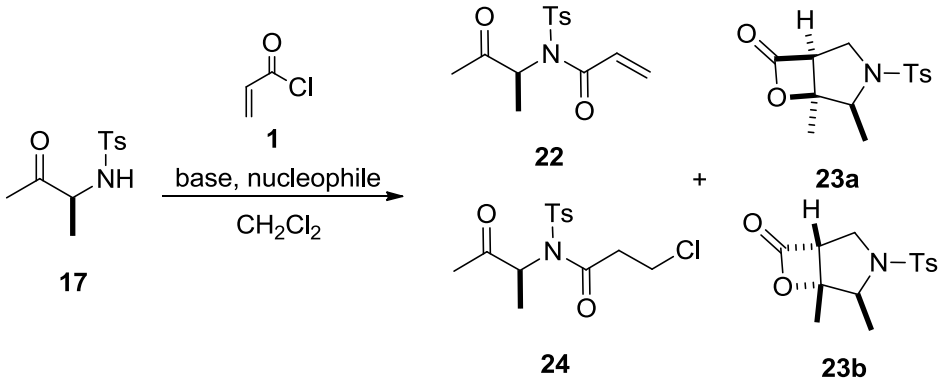
[a]**1** not added dropwise.

Using fresh 4-PPY yielded only a slight difference with a trace amount of **22** being produced over the course of the reaction. (±) HBTM also gave results similar to that of 4-PPY where only trace amounts of *N*-acylation product **21** was produced over the course of the reaction (Entry 3). To date, none of the reactions carried out thus far with ketone **20** have yielded the desired pyrrolidine product.

Similar reactions were also carried out on the Ts-*N*-(*L)*-alanine amino ketone substrate **17** (Table 2). The first reaction was performed with **17** using 4-PPY as nucleophile (Entry 1) which resulted in incomplete conversion and the isolation of an unexpected product. The product did not show either the ^{1}H NMR peaks in the 5-7 ppm region of its spectra which are characteristic

of alkene protons which would be present in **22**, nor the characteristic β-lactone carbonyl peak around 1820 cm^{-1} which would be present in **23**. After further characterization, it was concluded that the product of Entry 1 was likely **22** where chloride ion had reacted to form acylated product **24**.

Table 2. Studies performed on Ts-*N*-*(L)*-alanine amino ketone substrate **17.**



Entry	Base (equiv.)	Nucleophile (equiv.)	Temp	Results
1[a]	EtN(*i*-Pr)$_2$ (1.1)	4-PPY (1.1)	0 °C to 23 °C	recovered **17** 60%, **24** N-acylation product 29 %
2	EtN(*i*-Pr)$_2$ (1.1)	4-PPY (1.1)	0 °C to 23 °C	**22** 23 %
3	EtN(*i*-Pr)$_2$ (1.1)	(±) HBTM (1.1)	0 °C to 23 °C	**23a** and **23b**[b]

[a]**1** not added dropwise. [b]Further purification needed in order to determine yields of each individual diastereomers.

It is possible that use of an older bottle of 4-PPY led to inferior results, yet it is important to point out that the product which was isolated from this reaction shows *N*-acylation did take place. The reaction was repeated with fresh 4-PPY (Entry 2) and this second attempt confirmed that *N*-acylation was favored by 4-PPY with respect to the Ts protected alanine substrate. IR showed the absence of β-lactone peak around 1820 cm^{-1} and ^{1}H NMR confirmed that **22** was the

major product isolated with the presence of alkene proton peaks at 5.82, 6.41, and 7.01 ppm. On the other hand, (±) HBTM (Entry 3) gave more promising results with the characteristic β-lactone IR carbonyl peak at 1828 cm^{-1}. A first attempt at purification allowed only for the isolation of **22**. The diastereomers **23a** and **23b** however, were isolated together. ^{1}H NMR confirmed the formation of pyrrolidine product by the presence of methyl proton peaks which had been shifted up field before 2.00 ppm. The ^{1}H and ^{13} C NMR also confirmed the presence of both diastereomers in the second isolated product. Further purification and characterization will be necessary in order separate the diastereomers and obtain an accurate yield of **23a** and **23b**.

CHAPTER IV

CONCLUSIONS

Conclusion

The development of the asymmetric aza-Michael aldol-lactonization organocascade process is still in its infancy as there are many substrates, acid chlorides, and reaction conditions which have yet to be studied. However, the results obtained in studies performed thus far have provided useful information for future work. The successful production of **23a** and **23b** involving Michael donor Ts-*N*-*(L)*-alanine amino ketone substrate **17** when HBTM is used as a nucleophile (Table 2, Entry 3) has confirmed that highly substituted pyrrolidines can indeed be formed between an α-amino ketone and acryloyl chloride via an aza-Michael aldol-lactonization organocascade process. However the contrasting results obtained from the changing the nucleophile in the reaction to 4-PPY, in which *N*-acylation was the major product and pyrrolidine was not formed, raises questions as to what exactly is the effect the nucleophile on the reaction. Does the steric hindrance introduced by the (±) HBTM nucleophile help drive the reaction to undergo the organocascade process rather than *N*-acylation? If so, then why was there no production of pyrrolidine product with the Boc-*N*-*(L)*-phenylalanine amino ketone substrate? Thus, the protecting group of the amino ketone substrate may also play an important role in driving the reaction toward the aza-Michael aldol-lactonization organocascade process. Further research will be necessary in order to determine which nucleophiles and protecting groups possess the ideal chemical properties for the desired organocascade process.

Future work

Currently, further purification is being carried out in order to separate the pyrrolidine diastereomers produced in the HBTM study and determine a yield for the reaction. Because of the positive results obtained with the Ts-*N*-*(L)*-alanine amino ketone substrate and HBTM nucleophile, further screening will be conducted on this substrate in order to optimize the reaction and increase the overall yield of the reaction. Further screening will be conducted on amino ketone substrates **17** and **20** using various bases, nucleophiles, and reaction conditions in order to test which other conditions can produce the desired pyrrolidine. In addition, acid chlorides will also begin to be varied in order to try and increase the substitution of the final pyrrolidine products.

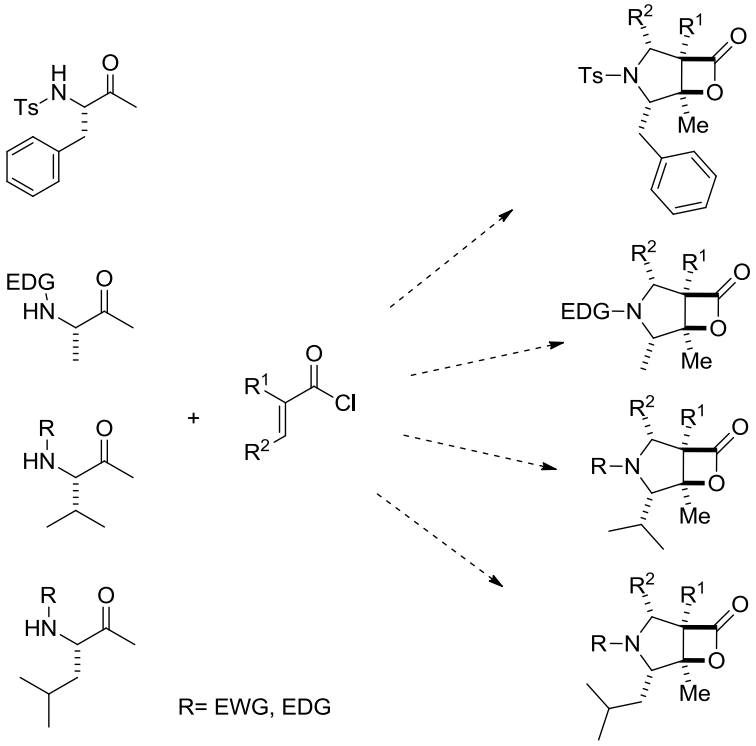


Figure 3. Planned substrates for future studies of aza-Michael aldol-lactonization**.**

Alanine and phenylalanine amino ketone substrates will also be remade with different protecting groups in order to test how changing the chemical properties of the protecting groups affect the outcome of the aza-Michael aldol-lactonization. Finally, additional α-amino ketone substrates, Figure 3, will continue to be synthesized in order to test their efficiency in undergoing the aza-Michael aldol-lactonization organocascade process.

REFERENCES

1. a) Enders, D.; Thiebes, C. *Pure. Appl. Chem.* **2001**, *73*, 573; b) O'hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435; c) A. Pinder, R. *Nat. Prod. Rep.***1992** 9, 17; d) Massiot, G.; Ddelaude in, C. *Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1996**, *27*, 269.

2. Ma, S.; Jiao, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 4737-4740.

3. Notz, W.; Tanaka, F.; Barnas, C. *Acc. Chem. Res*. **2004**, *37*, 580-591.

4. Sebahar, P.; Williams, R. *J. Am. Chem. Soc.* **2000**, *122*, 5666-5667.

5. Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435-446.

6. Hanson, J. *Natural Products: The Secondary Metabolites*; The Royal Society of Chemistry: Cambridge, 2003.

7. Abou-Khalil, B. *Neuropsychiatr Dis Treat.* **2008**, *3*, 507.

8. Kolodzeij, S.; Nikiforovich, G.; Skeean, R, Lignon, M.; Martinez, J.; Marshall G. *J. Med. Chem.* **1995**, *38*, 137-149.

9. Augeri, D.; Robi, J.; Betebenner, D.; Magnin, D.; Khanna III, A.; Roberston, J.; et al. *J. Med. Chem.* **2005**, *48*, 5025-5037.

10. Liu, G.; Shirley, M.; McFarlin, R.L.; Romo, D. *Unpublished results.*

11. Corey, E. J.; Reddy, L. R. *Org. Lett.* **2006**, *8*, 1717-1719.

12. Panda, G.; Rao N. V. *Synlett*. **2004**, *4*, 714-716.

13. Nquyen, H.; Gil, Ma.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2.

14. Dunlap, N.; Lankford, K.; Pathiranage, A.; Taylor, J.; Reddy, N.; Gouger, D.; Singer, P.; Griffin, K., Reibenspies, R. *Org. Lett.* **2011**, *13*, 4879.

15. Sdira, S.; Felix, C.; Giudicelli, M.; Seigle-Ferrand, P.; Perrin, M.; Lamartine, R. *J. Org. Chem.* **2003**, *68*, 6632.

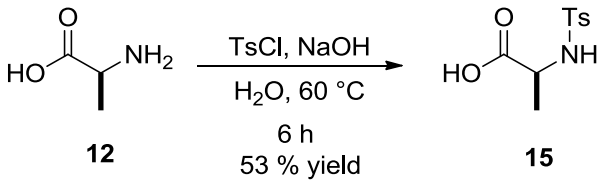
16. Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501-1504.

17. Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133*, 462-477.

APPENDIX

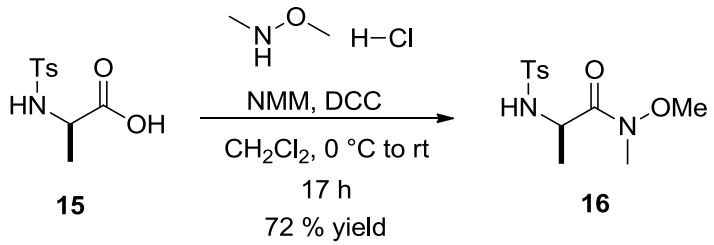
Experimental procedures and characterization data

All chemicals were purchased from EMD, BioSciences, and Aldrich. Reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F_{254}. TLCs were carried out in a EtOAc:Hexane solvent system. Purification of products was carried out *via* column chromatography and extraction techniques. ^{1}H NMR and ^{13}C NMR characterization was performed on an Inova 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm and are referenced to deutero-chloroform (δ 7.23 ppm) unless otherwise noted. Multiplicities are represented as follows: s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplets), m (multiplet), bs (broad singlet)**.**

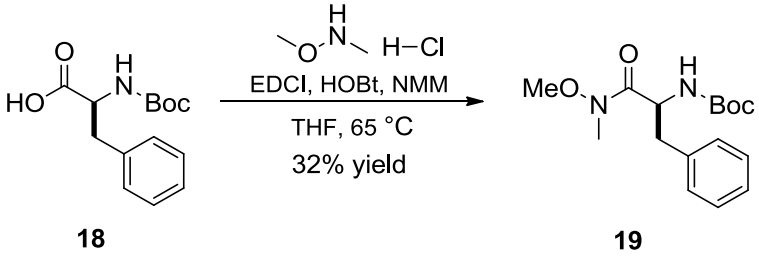


12 **15**

Tosyl-N-L-alanine (15). To a stirred suspension of L-alanine **12** (5.00 g, 56 mmol) in 125 mL of water at room temperature was added 6.4 g (168 mmol) of NaOH and 12.81 g (67.2 mmol) of *p*-toluene sulfonyl chloride. The mixture was stirred at 60 °C for 6 hours. The solution was then cooled to 0 °C and acidified to a pH 1 by addition of concentrated HCl. The solution was put in freezer to aid in solidification. The precipitate was collected by filtration and washed with cold H_2O. The collected solid was air dried to yield **5** as a white solid (1.71 g, 53 %). **^{1}H NMR** (300 MHz, CD_3OD) δ 7.22 (d, J=7.8 Hz, 2H), 6.84 (d, J=7.8 Hz, 2H), 3.28 (t, 1H), 1.89 (s, 3H), 0.78 (d, J=7.2 Hz, 3H).



(R)-N-methoxy-N-methyl-2-(4-methylphenylsulfonamido)propanamide (8). To a solution of **5** (2.00g mg, 8.22 mmol), *N*-methylmorpholine (0.99 mL, 9.04 mmol), N,O-dimethylhydroxylamine.HCl (0.88 g, 9.04 mmol) in anhydrous CH_2Cl_2 (37.7 mL) was cooled to 0 °C under nitrogen and treated with N,N-dicyclohexylcarbodiimide (1.86 g, 9.04 mmol) portion-wise over 10 minutes. The reaction mixture was stirred at 0 °C for 3 hours followed by a further 15 hours at room temperature, then filtered through Celite and concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous sodium bicarbonate solution (2 × 50 mL), 1 M aqueous HCl solution (2 × 50 mL), brine (1 × 50 mL) and dried ($MgSO_4$). The resulting crude oil was then purified by flash chromatography, eluting with 50 % EtOAc/Hexane, to give the desired Weinreb amide as an opaque oil after concentration under reduced pressure (1.71 g, 72%). R_f (EtOAc/hexanes 3:5) = 0.35; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71-7.68 (m, 2 H), 7.27-7.24 (m, 2H), 5.60 (d, J= 9.5 Hz, 1H), 4.34 (m, 1H) 3.54 (s, 3H), 2.97 (s, 3H), 2.40 (s, 3H), 1.30 (d, J= 7.0 Hz, 3H).

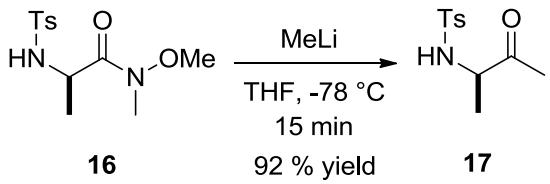


Tert-butyl (1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (19). To a solution of Boc-N-L-phenylalanine (1.0 equiv) in dichloromethane (0.24 M) were added HOBt

(1.1 equiv) and EDC (1.2 equiv) at 0 °C. The solution was stirred at 0 °C for 15 min and then *N,O*-dimethylhydroxylamine hydrochloride salt (1.15 equiv) and *N*-methyl morpholine (1.2 equiv) were added. The reaction mixture was stirred at 25 °C for 14 h. After the solvent was removed under vacuum, the resulting residue was partitioned between 1N HCl (aq.) and EtOAc. The phases were separated and the organic layer was washed with 1 M HCl (aq.), followed by saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$. After completely removing the solvent, the Weinreb amide was purified by flash chromatography. R_f (EtOAc/hexanes 1:5) = 0.25; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 3H), 5.23 (d, 1H, J = 7.0 Hz), 4.90 (br, 1H), 3.69 (s, 3H), 3.20 (s, 3H), 3.02 (dd, 1H, J = 4.5, 13.5 Hz), 2.81 (dd, 1H, J = 7.0, 13.0 Hz), 1.40 (s, 9H).

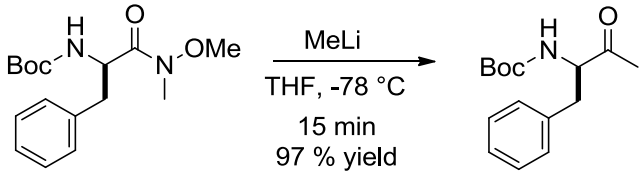
*General procedure for amino ketones **17** and **19***

The Weinreb amide (1.00 equiv) was placed in an oven dried round bottom flask equipped with a magnetic stir bar and placed under N_2 atmosphere. The Weinreb amide was then dissolved in anhydrous THF (15 mL) and cooled to -78 °C. While stirring vigorously, MeLi (2 equiv) was added dropwise via syringe over 10 minutes. After the addition, the reaction was allowed to stir while gradually increasing the temperature to 0 °C. After 20 minutes, the reaction was quenched with saturated NH_4Cl solution and the mixture was then extracted with EtOAc. The organic layer was combined, dried with $MgSO_4$, and concentrated by rotary evaporation. The crude was then purified by flash column chromatography (gradient SiO_2, EtOAc/hexanes solvent system) to afford the α-amino ketone.



16 **17**

(R)-4-methyl-N-(3-oxobutan-2-yl)benzenesulfonamide (**17)** was prepared from **16** (1.30 g, 4.54 mmol). Flash chromatography (50% EtOAc/Hexanes) afforded 1.01 g of **17** as an off-white solid. R_f (EtOAc/hexanes 3:5) = 0.60; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 (d, J= 6.0 Hz, 2 H), 7.30 (d, J= 12.0 Hz, 2H), 5.51 (d, J= 6.0 Hz, 1H), 3.93 (m, 1H), 2.42 (s, 3H), 2.1 (s, 3H), 1.38 (d, J=9.0 Hz, 3H). **^{13}C NMR** (300 MHz; $CDCl_3$) δ 164.8, 143.6, 136.7, 129.67, 126.9, 57.5, 26.1, 21.4, 18.7.

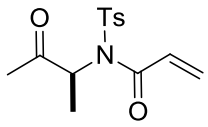


19 **20**

(R)-tert-butyl (3-oxo-1-phenylbutan-2-yl)carbamate (20) was prepared from **19** (1.41 g, 5.59 mmol). Flash chromatography (30% EtOAc/Hexanes) afforded 1.18 g of **20** as an off-white solid. . R_f (EtOAc/hexanes 1:5) = 0.47; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.625 (m, 3 H), 7.17 (d, J=9.0 Hz, 2H), 5.13 (d, J= 6.0 Hz, 1H), 4.54 (q, 1H), 2.42 (dd, 2H), 2.14 (s, 3H), 1.42 (s, 9H). **^{13}C NMR** (300 MHz, $CDCl_3$) δ 27.8, 28.2, 37.4, 48.0, 60.6, 126.9, 128.5, 128.5, 129.1, 136.0 206.8.

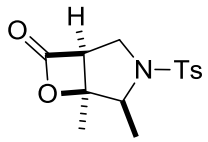
General procedure for asymmetric aza-Michael aldol-lactonization

To an oven-dried vial equipped with a stir bar was added the α-amino ketone substrate (50 mg, 1 .0 equiv). The nucleophile (1.1 equiv) was added to the vial. The vial was capped, sealed with Parafilm, put under N_2 atmosphere for 2 minutes. The solids were then dissolved in CH_2Cl_2 solvent (0.7 mL), followed by the addition of base (1.1 equiv). The solution was then cooled to 0 °C in an ice bath. **1** (2.0 mL of 0.1 M solution in CH_2Cl_2, 1.5 equiv) was then added dropwise via syringe pump over 2 hours. The reaction was then quenched with water (2.0 mL) and extracted with EtOAc (3 × 2.0 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated via rotary evaporation. The crude was then purified by flash column chromatography (gradient SiO_2, 20 → 60 % EtOAc/hexanes solvent system).



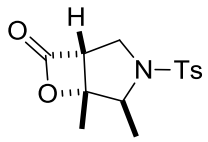
22

(S)-N-(3-oxobutan-2-yl)-N-tosylacrylamide (22). Prepared from **17** (50 mg, 0.12 mmol) and 4-PPY nucleophile (32 mg, 0.22 mmol). Flash chromatography afforded **22** as a solid (20 mg, 23 %). R_f (EtOAc/hexanes 3:5) = 0.76; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 (d, J= 9.0 Hz, 2 H), 7.39 (d, J= 6.0 Hz, 2H), 7.01 (q, J= 6.0 Hz, 1H), 6.39 (dd, 1H), 5.80 (dd, 1H), 4.71 (q, J= 6.0 Hz, 1H), 2.47(s, 3H), 2.16 (s, 3H), 1.52 (d, J= 6.0 Hz, 3H). **^{13}C NMR** (300 MHz; $CDCl_3$) δ 203.1, 164.9, 145.3, 136.3, 131.8, 130.0, 127.4, 62.4, 25.9, 21.6, 15.03.



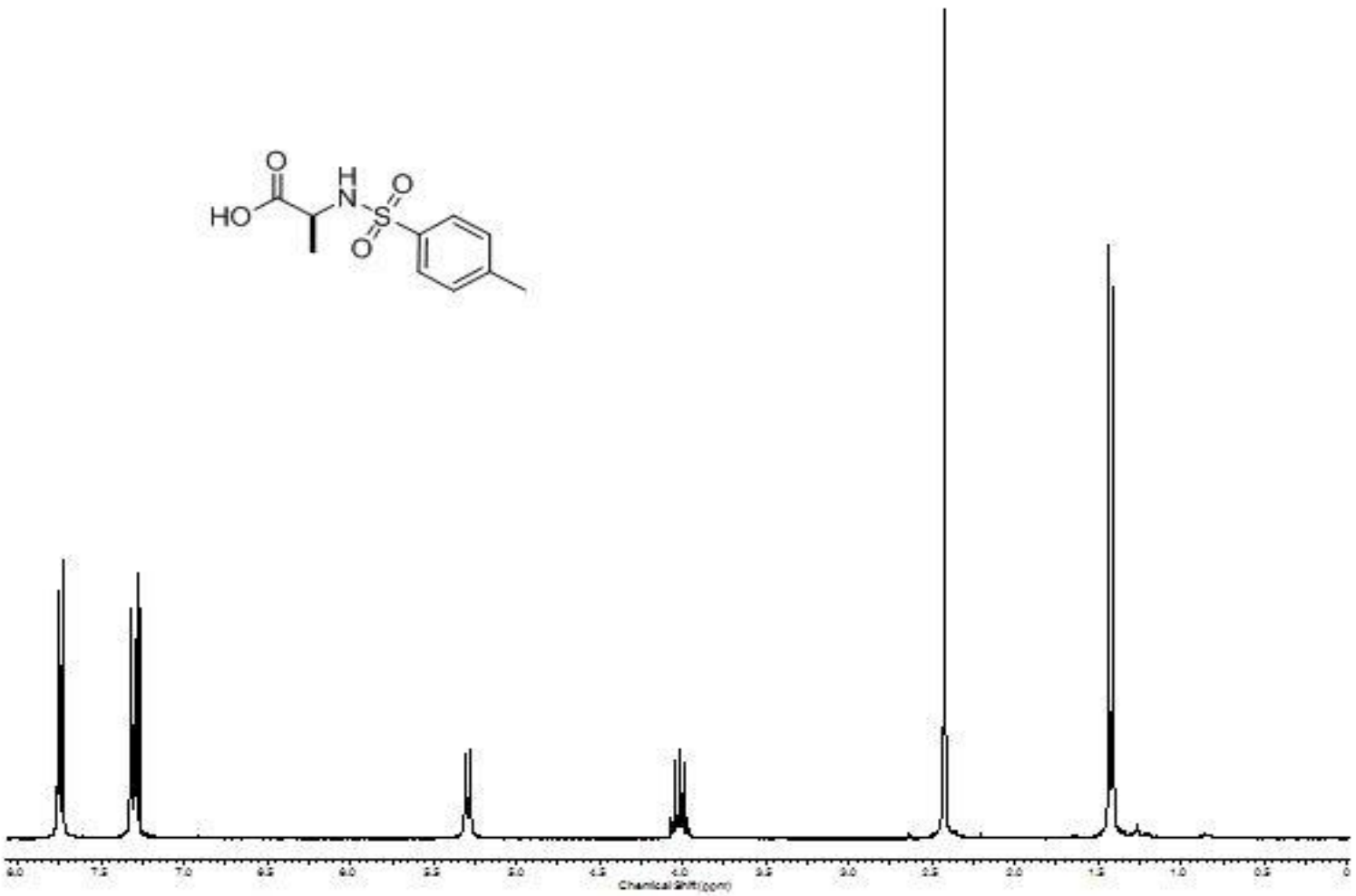
23a

(1S,4S,5S)-4,5-dimethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (23a). Prepared from **17** (50 mg, 0.12 mmol) and (±) HBTM nucleophile (58 mg, 0.22 mmol). **IR:** 1828 cm $^{-1}$ (C=O). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (d, J= 6.0 Hz, 2 H), 7.36 (d, J= 9.0 Hz, 2H), 4.29 (q, J= 6.0 Hz, 1H), 3.98 (d, J= 9.0 Hz, 1H), 3.60 (q, J= 6.0 Hz, 3H), 4.71 (q, J= 6.0 Hz, 1H), 2.11 (s, 3H), 1.63 (s, 3H), 1.47 (d, J= 6.0 Hz, 3H). **^{13}C NMR** (300 MHz; $CDCl_3$) δ 167.3, 144.3, 129.8, 127.7, 86.9, 61.3, 59.0, 48.1, 21.5, 18.48, 12.9.

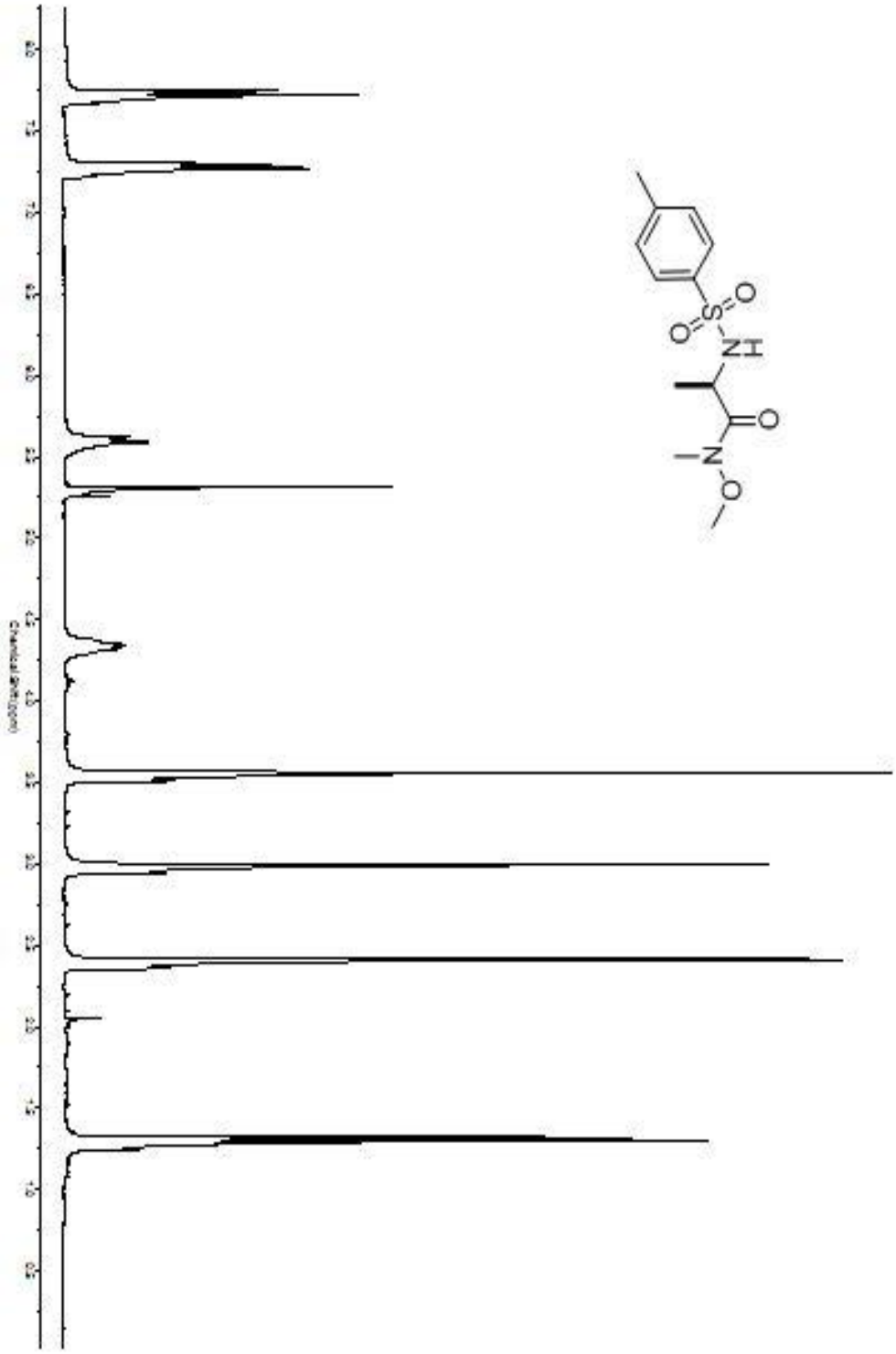


23b

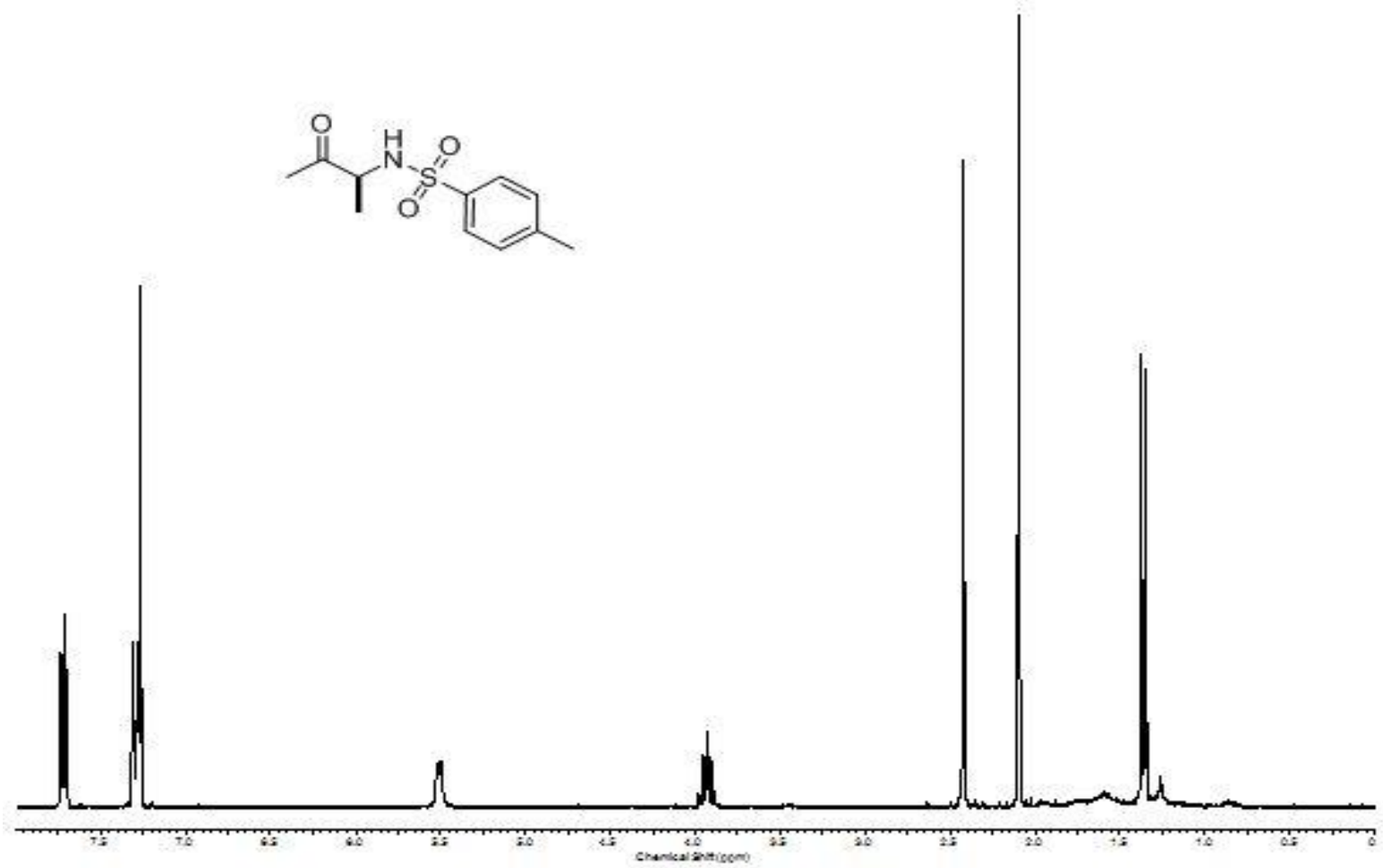
(1R,4S,5R)-4,5-dimethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (23b). Prepared from **17** (50 mg, 0.12 mmol) and (±) HBTM nucleophile (58 mg, 0.22 mmol). **IR:** 1828 cm $^{-1}$ (C=O). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (d, J= 6.0 Hz, 2 H), 7.31 (d, J= 9.0 Hz, 2H), 4.13 (q, J= 6.0 Hz, 1H), 3.87 (q, J= 9.0 Hz, 1H), 2.99 (d, J= 6.0 Hz, 3H), 4.71 (q, J= 6.0 Hz, 1H), 2.06 (s, 3H), 1.58 (s, 3H), 1.1.32 (d, J= 6.0 Hz, 3H). **^{13}C NMR** (300 MHz; $CDCl_3$) δ 167.1, 143.8, 129.6, 127.0, 85.8, 80.8, 55.2, 45.2, 17.7, 16.01, 12.9.



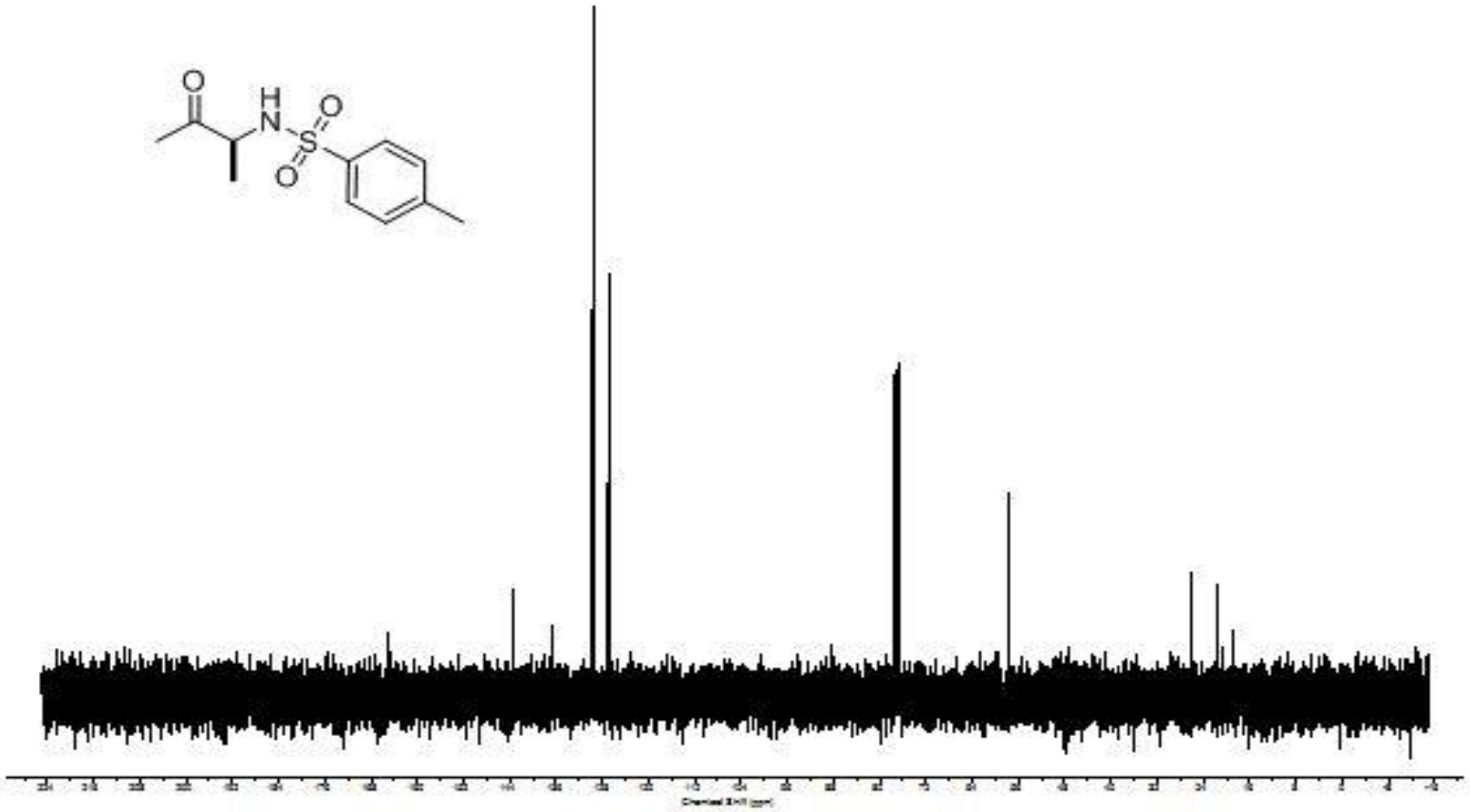
^{1}H NMR spectrum of Ts-N-alanine **15**. (in CD_3OD)



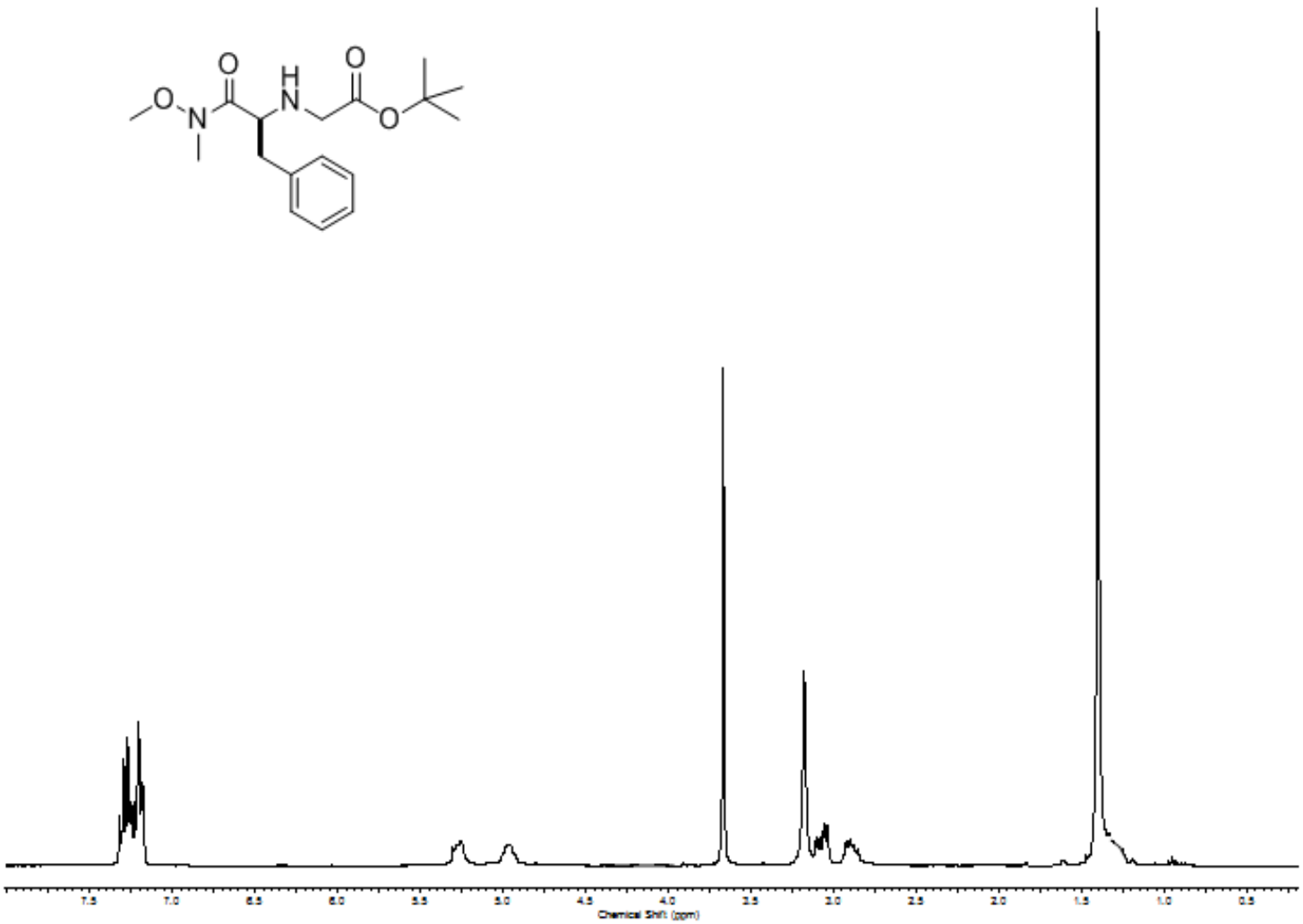
^{1}H NMR spectrum of Ts-N-alanine Weinreb amide **16**. (in $CDCl_3$)



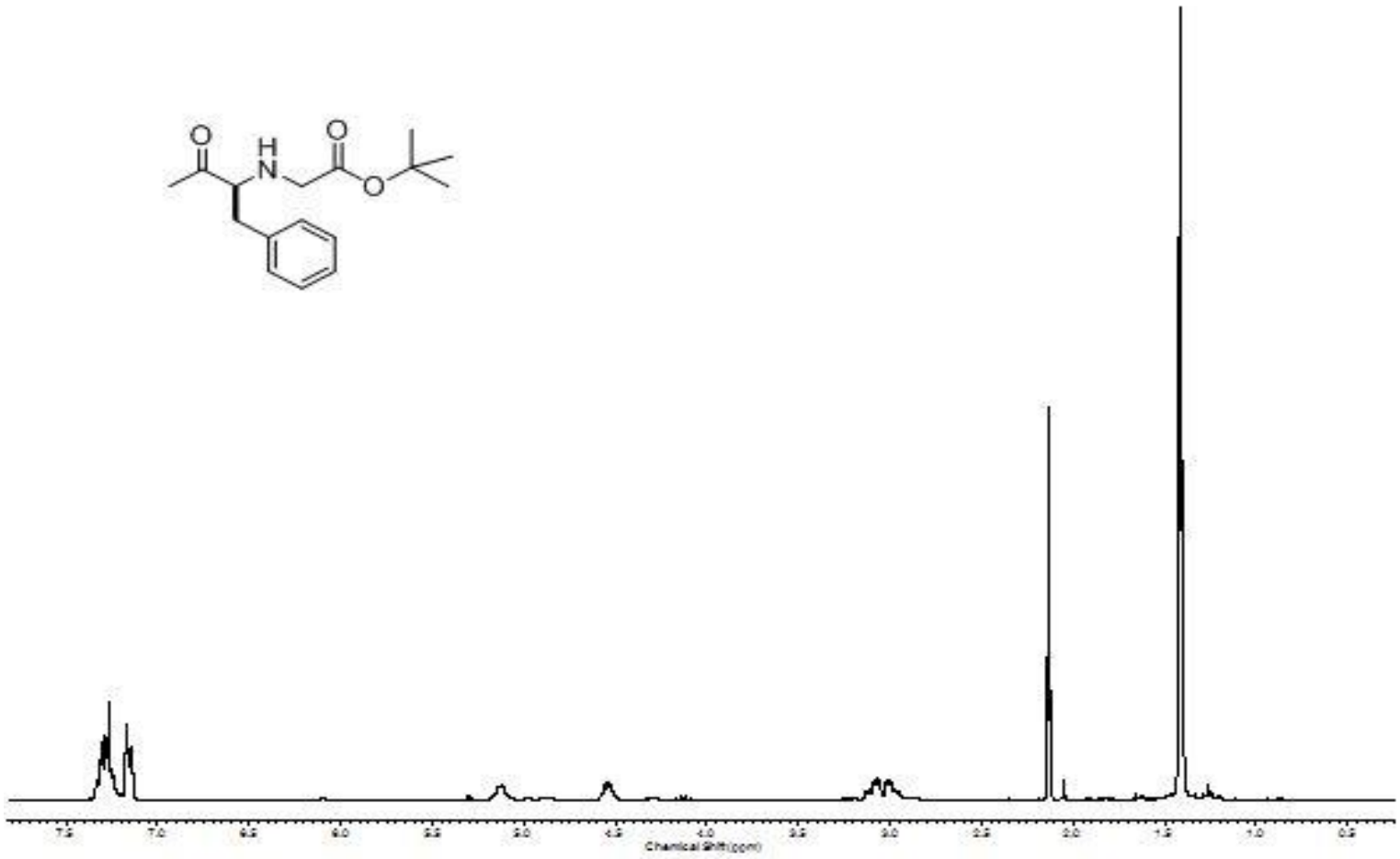
^{1}H NMR spectrum of Ts-N-alanine amino ketone **17**. (in $CDCl_3$)



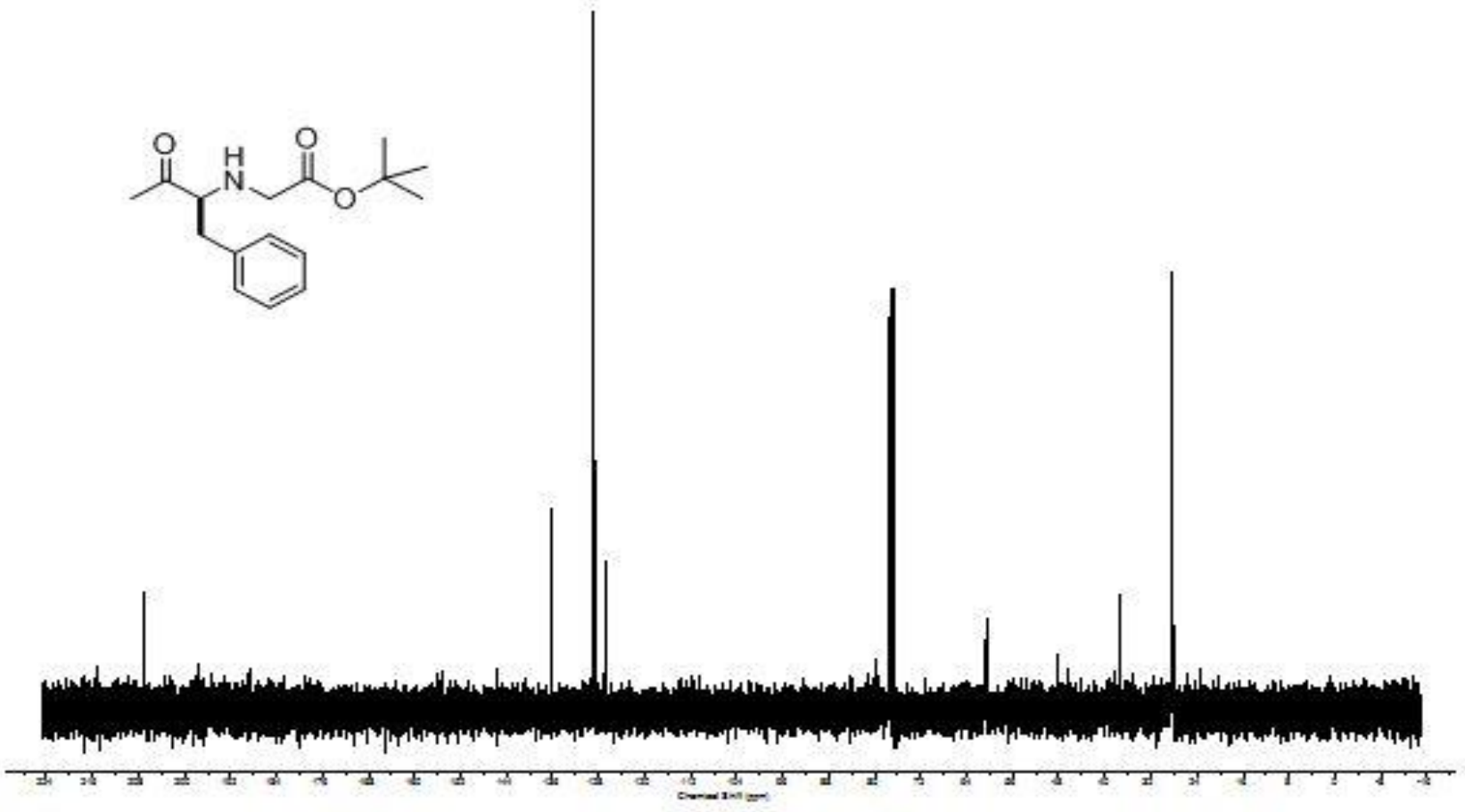
^{13}C NMR spectrum of Ts-N-alanine amino ketone **17**. (in $CDCl_3$)



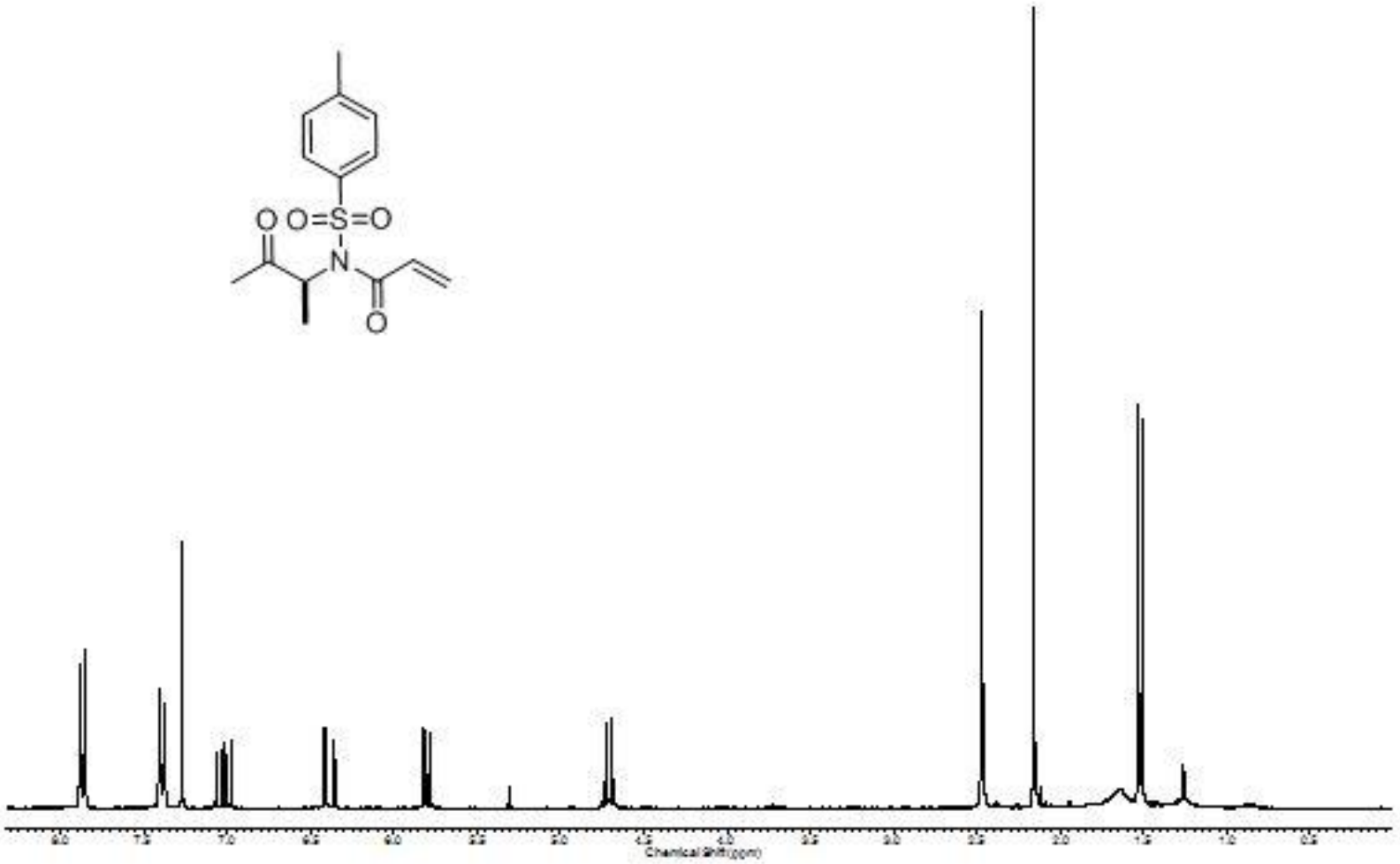
^{1}H NMR spectrum of Boc-N-L-phenylalanine Weinreb amide **19**. (in $CDCl_3$)



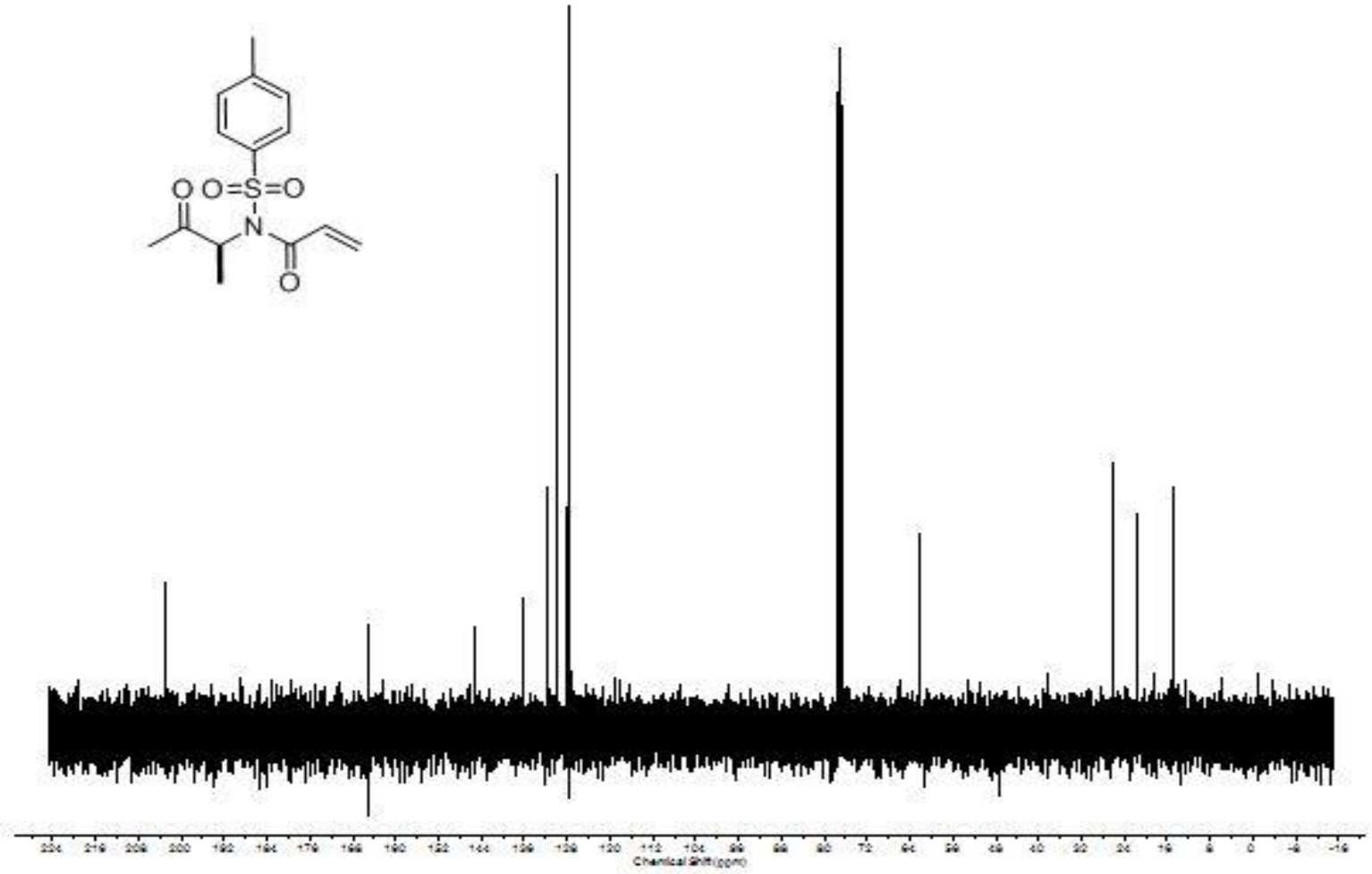
^{1}H NMR spectrum of Boc-N-L-pheynylalanine amino ketone **20**. (in $CDCl_3$)



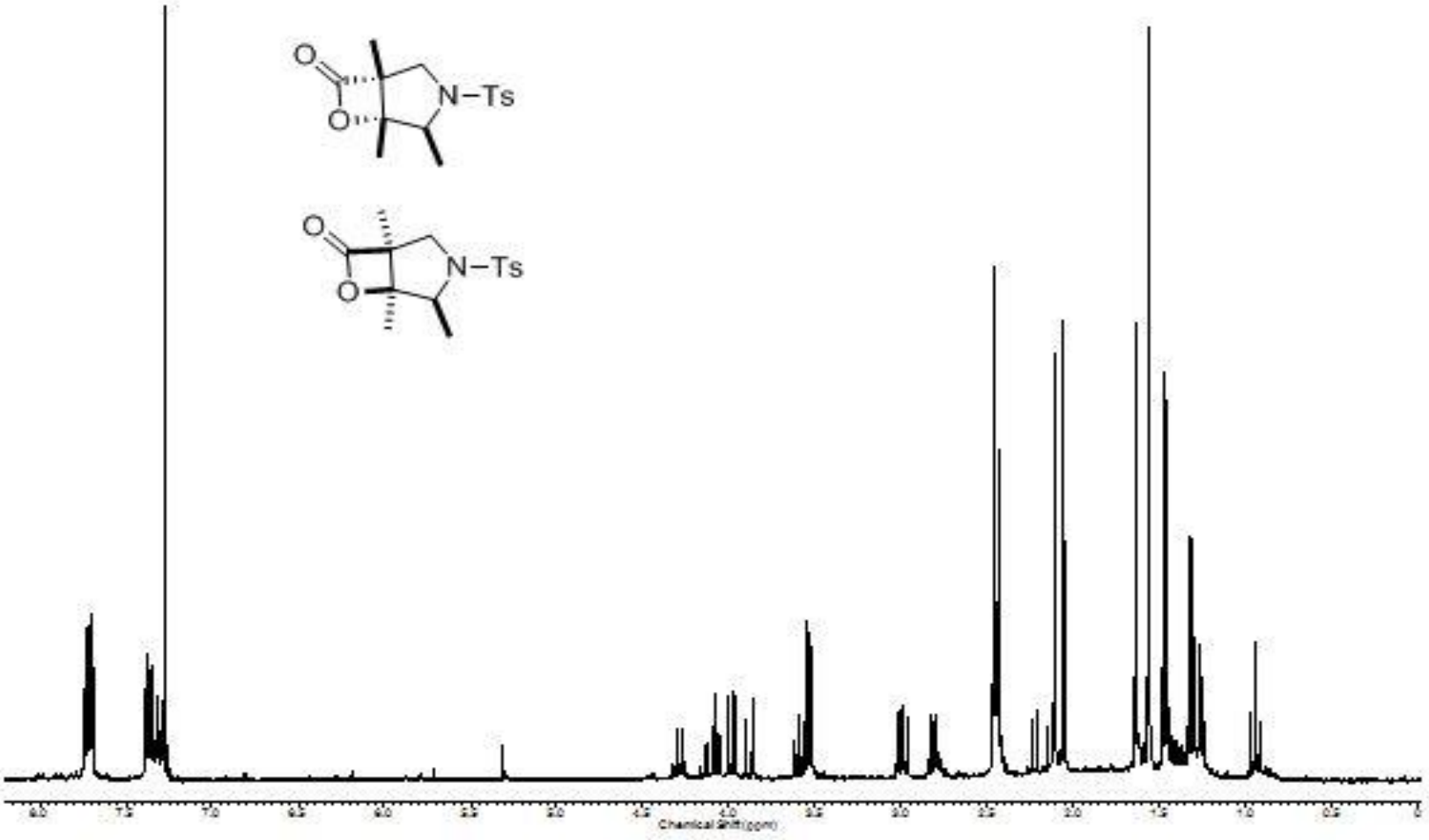
^{13}C NMR spectrum of Boc-N-L-pheynylalanine amino ketone **20**. (in $CDCl_3$)



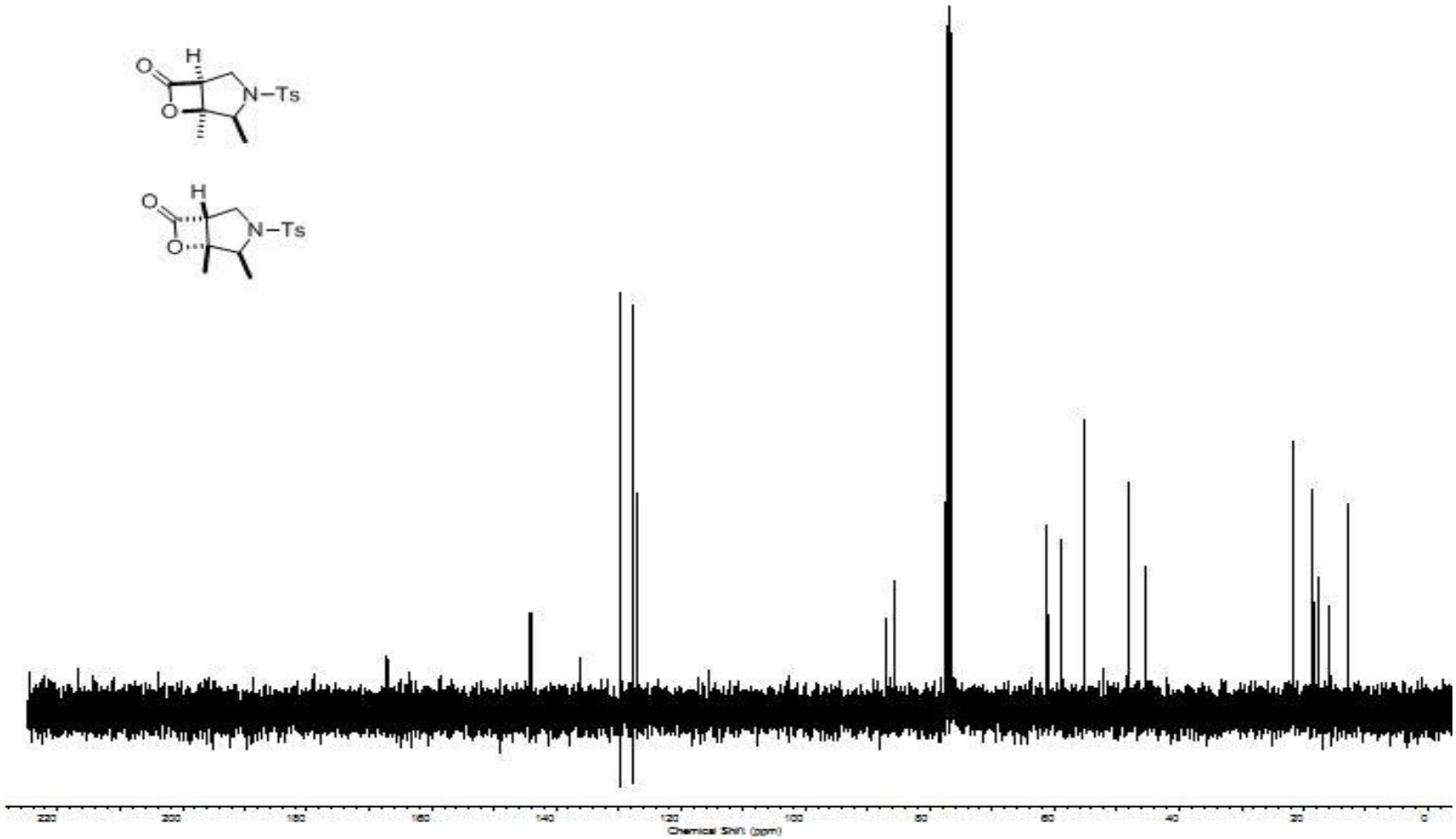
^{1}H NMR spectrum of Ts-N-L-alanine N-acylation product **22**. (in $CDCl_3$)



^{13}C NMR spectrum of Ts-N-L-alanine N-acylation product **22.** (in $CDCl_3$)



^{1}H NMR spectrum of Ts-N-L-alanine pyrrolidine products **23a** and **23b**.
(in $CDCl_3$)



^{13}C NMR spectrum of Ts-N-L-alanine pyrrolidine products **23a** and **23b**.
(in $CDCl_3$)