TOWARDS THE SYNTHESIS OF DUAL-INHIBITORS OF FATTY ACID SYNTHASE AND THE HUMAN 20S PROTEASOME AS ANTICANCER AGENTS

An Undergraduate Research Scholars Thesis

by

JAMES THOMAS MOORE

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ABSTRACT

Towards the Synthesis of Possible Dual Inhibitors of Fatty Acid Synthase and the Human 20S Proteasome as Anticancer Agents. (May 2013)

James Thomas Moore
Department of
Chemistry
Texas A&M University

Research Advisor: Dr. Daniel Romo
Department of
Chemistry

Human fatty acid synthase (FAS) and the human 20S proteasome are useful targets for anticancer chemotherapy, and the latter target has been validated as a target for treatment of various forms of cancer. Belactosin C, cinnabaramide A, and orlistat are three β-lactone containing compounds that have been shown to inhibit either FAS or the human 20S proteasome, leading to tumor cell death via apoptosis. This project describes the design and synthesis of novel dual inhibitors of these two enzyme targets premised on these three β-lactone containing compounds with the goal of finding a more potent and "druggable" inhibitor. The key step in this synthesis of the described synthetic strategy toward these dual inhibitors is a nucleophile catalyzed aldol lactonization (NCAL) process to form the γ-lactam fused β-lactone core.

DEDICATION

To my parents, sister, and grandparents: James L. Moore, Rose A. Moore, Jennifer A. Moore, Thomas Carlo, Jane Carlo.

ACKNOWLEDGMENTS

I would like to thank my research advisor, Dr. Daniel Romo for his guidance throughout the course of this project. I would also like to thank Jeremy Chris Reyes, Dr. Sreekumar Vellalath, Dr. Omar Robles, Dr. Mingzhao Zhu, and Bianca Ramirez for their helpful advice and continuous support throughout the course of this research.

NOMENCLATURE

NCAL	Nucleophile-Catalyzed Aldol Lactonization
R	alkyl group
Bn	benzyl
i-Pr	iso-propyl
Me	methyl
Et	ethyl
Ph	phenyl
TFA	triflouroacetic acid
PPY	4-pyrrolidinopyridine
THF	tetrahydrofuran
DEAD	diethyl azodicarboxylate
PPh_3	triphenyl phosphine
DMF	dimethyl formamide
PCC	pyridinium chlorochromate
pTSA	*p*-toluenesulfonic acid
Tos	*p*-toluenesulfonate
FAS	fatty acid synthase

CHAPTER I

INTRODUCTION

In many types of cancers, fatty acid synthase (FAS) is an overexpressed protein that regulates the synthesis of the fatty acids necessary for the growth of the tumor cell.[1] Another protein, the human 26S proteasome, is responsible for the timely degradation of numerous regulatory proteins in the eukaryotic cell.[2] Incidentally, studies have shown that the inhibition of either FAS or the 20S proteolytic core of the human 26S proteasome lead to tumor cell death via apoptosis for various forms of cancer, including multiple myeloma and mantle cell lymphoma. Generally, normal cells can survive therapeutic doses of proteasome and FAS inhibitors, making these drugs even more attractive candidates for the treatment of various forms of cancer.[1,2]

One common characteristic of a group of inhibitors is the presence of a β-lactone, as seen in Figure 1. Proteasome inhibitors have been used in the treatment of advanced multiple myeloma since 2003, with approximately one third of patients with relapsed and refractory multiple myeloma showing significant clinical benefit. [3] One compound shown in Figure 1, salinosporamide A, has already entered phase I human clinical trials for the treatment of multiple myeloma.[4]

Remarkably, the mechanism of proteasome and FAS inhibition with β-lactone inhibitors occur through very similar mechanisms that involve the acylation of hydroxyl moieties in the active site of both proteins with the β-lactone, as seen in Figure 2.[5] The result is a trans-esterification within the active sites, yielding a non-functioning protein.

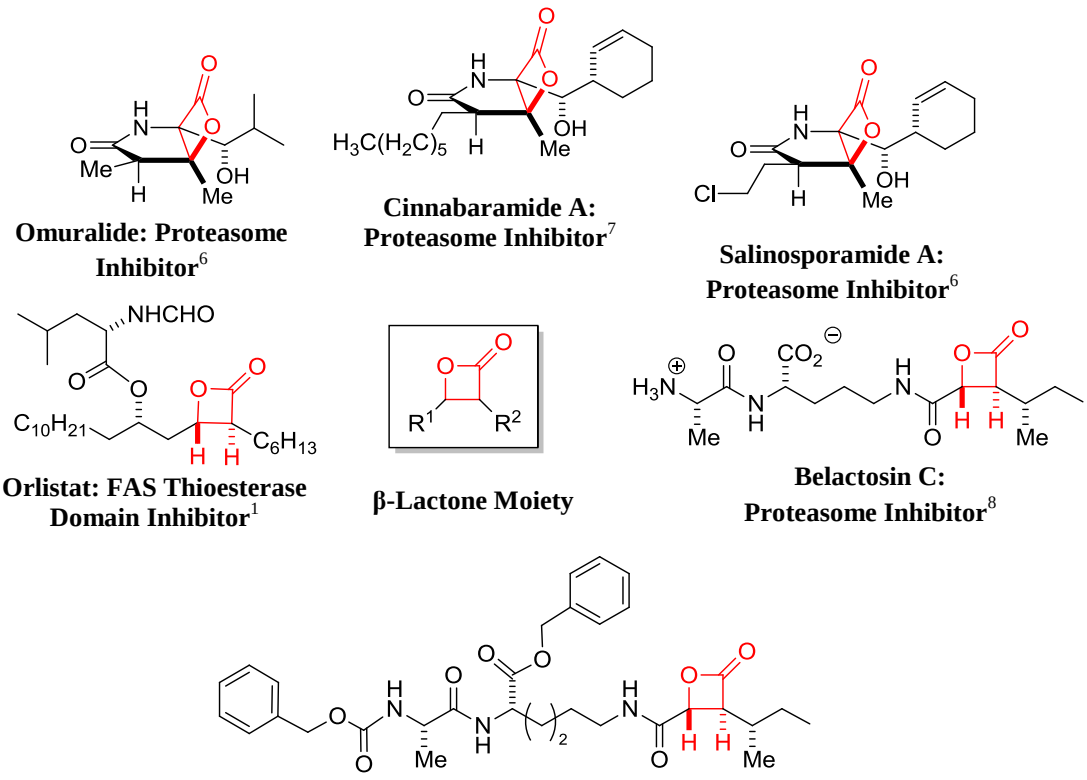


Figure 1. Structures of various inhibitors containing the β-lactone moiety.

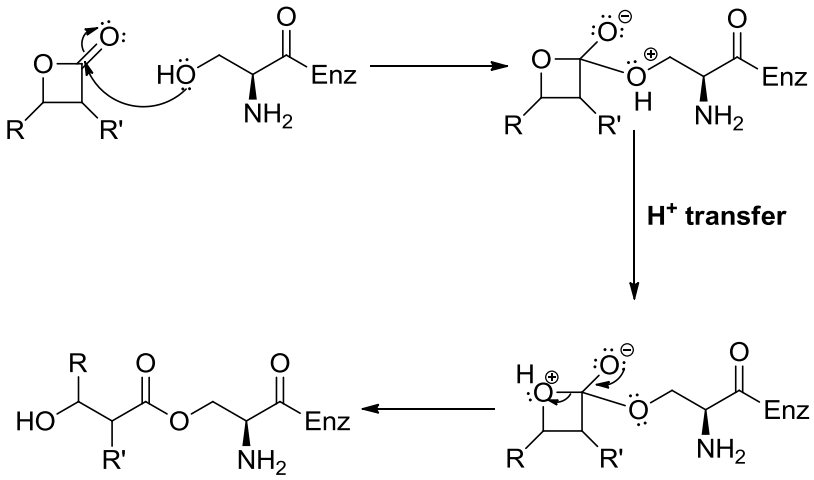


Figure 2. Reaction mechanism that depicts the inhibition of either FAS or the 20S proteasome.[1,2,9]

In 2007, a derivative of orlistat and N-Cbz, O-Bn-(-)-homobelactosin C (shown in Figure 1) was synthesized and was shown to inhibit both FAS and the proteasome. As can be seen in Figure 3, YE-X02 is composed of a dipeptide chain consisting of L-alanine and L-ornithine coupled to a β-lactone.[10] This compound affects malignant cells thorough the targeting and inhibition of two different protein complexes, each of which induces preferential tumor cell apoptosis. Because of YE-X02's ability to inhibit both FAS and the human 20S proteasome, numerous analogs of YE-X02 consisting of various dipeptides were synthesized, each with a varying percentage of inhibition of both FAS and the human 20S proteasome.[11]

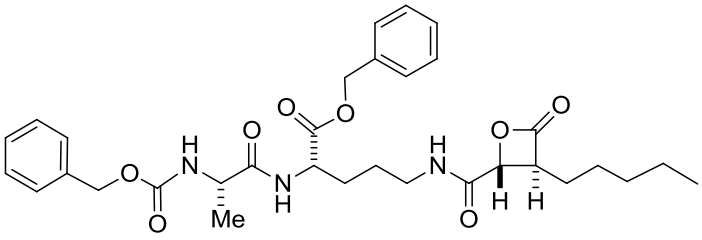
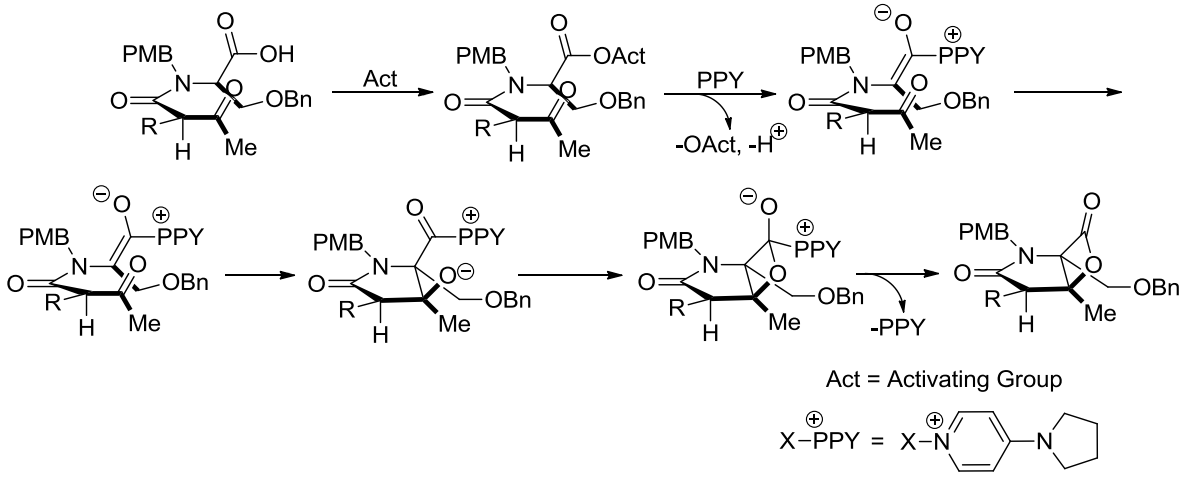


Figure 3. Structure of dual proteasome and FAS inhibitor, YE-X02.

It was also in 2007 that Ma, G. et. al. succeeded in synthesizing salinosporamide A and cinnabaramide A.[6,7,8] The key step in their synthesis is the use of a nucleophile catalyzed aldol lactonization (NCAL) process in which the γ-lactam fused β-lactone is created in a single reaction.

A likely reaction mechanism for the NCAL process is shown in Scheme 1. First, the carboxylic acid moiety is activated, followed by transacylation with 4-pyrrolidino pyridine. Subsequent deprotonation leads to an ammonium enolate, which leads to an aldol lactonization that produces

a γ-lactam fused β-lactone.[6] However, a [2 + 2] cycloaddition mechanism via an intermediate ketene has not been excluded.[7]



Scheme 1. Likely reaction mechanism for the formation of the γ-lactam fused β-lactone.[6]

With such a versatile reaction, numerous analogs of the γ-lactam fused β-lactone inhibitors can be synthesized. It is through this NCAL process that an inhibitor that builds on the structures of YE-X02 and the γ-lactam fused β-lactone, such as cinnabaramide A, can be synthesized. It should be noted that the proposed γ-lactam fused β-lactone core possesses the opposite stereochemistry as salinosporamide A and cinnabaramide A. (Figure 4)

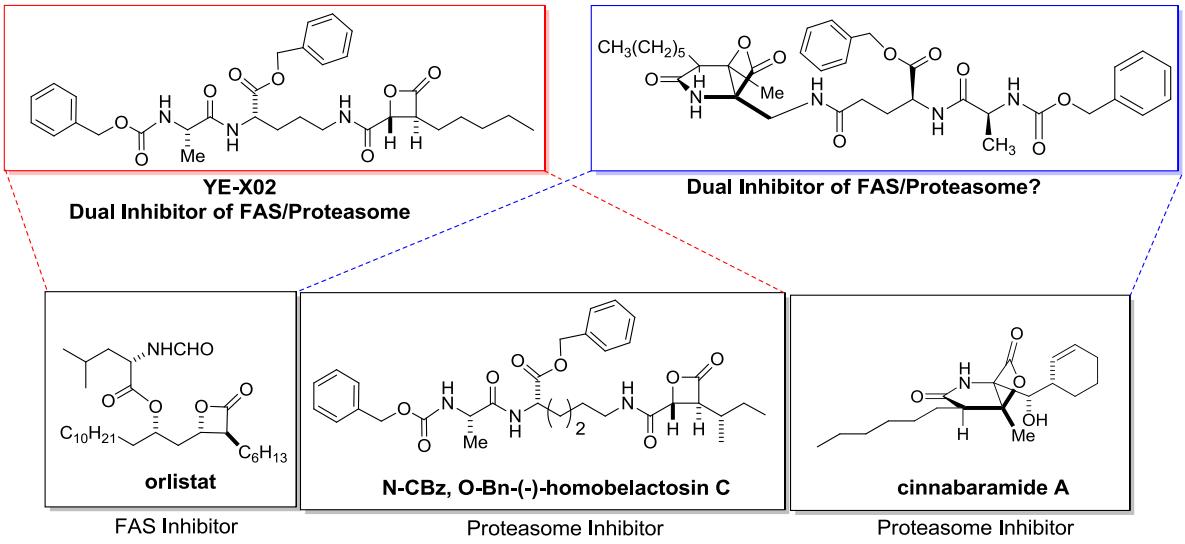


Figure 4. Depiction of the various inhibitors used to devise a dual inhibitor such as the one shown above.

CHAPTER II

METHODS

The retrosynthesis of a possible inhibitor derived from both YE-X02 and cinnabaramide A, **1**, is shown in Figure 5.

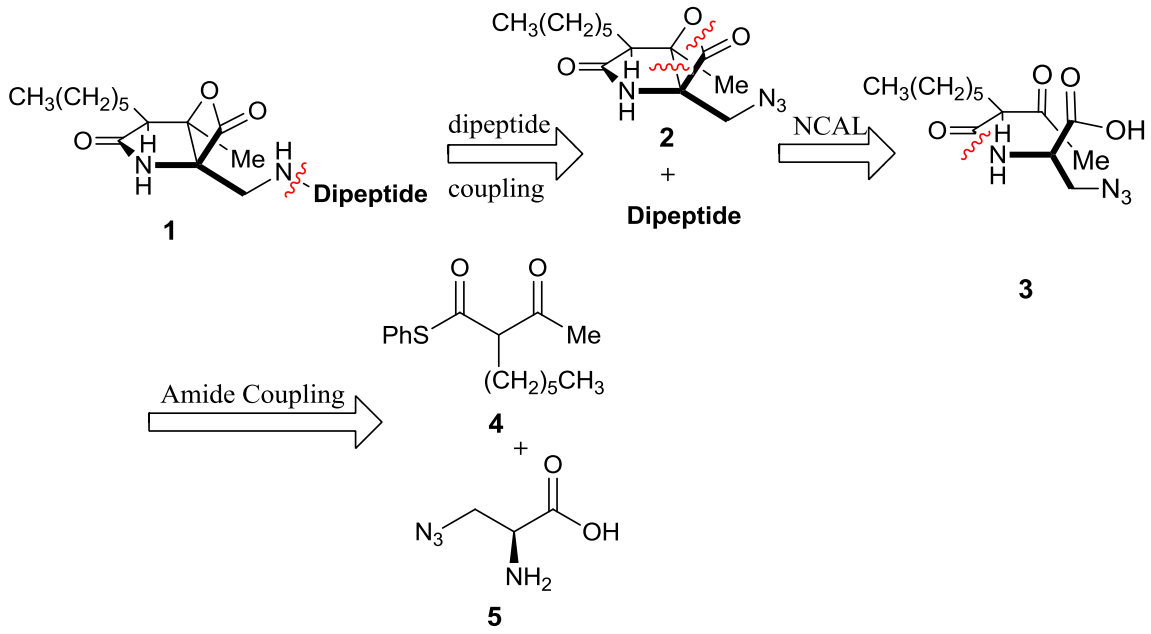
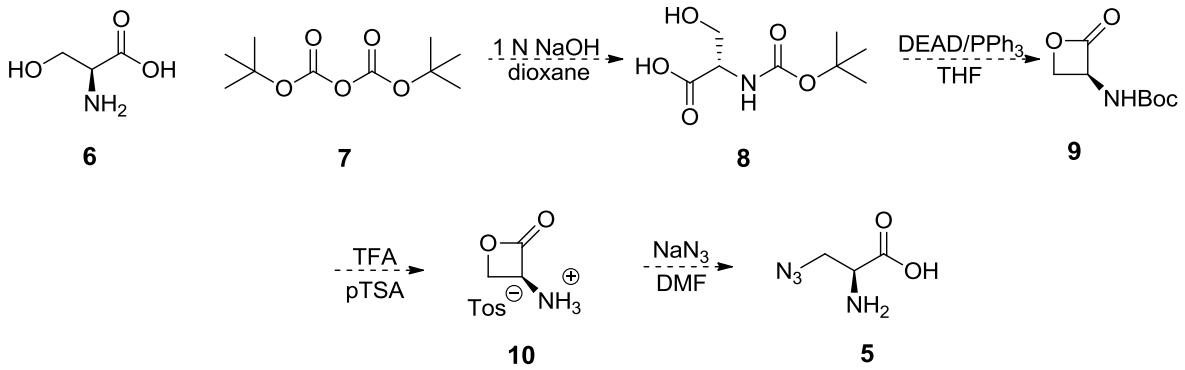


Figure 5. Retrosynthetic strategy for derivatives of YE-X02 and cinnabaramide A.

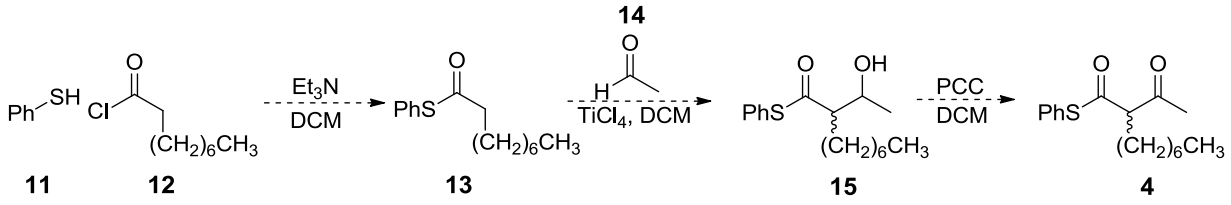
In order to couple a dipeptide to the cinnabaramide A derivative, it must possess a non-nucleophilic nitrogen containing functional group such as the azide in **2**. The bis-cyclization of the compound can be achieved via an NCAL process, in which various carbocycle-fused β-lactones have been synthesized.[6] The carboxylic acid-azide intermediate **3** can be created via an amide coupling between the β-keto-thioester, **4**, and β-azidoalanine, **5**. This synthetic pathway can lead to various derivatives of cinnabaramide A and YE-X02.

The synthesis of this possible dual-inhibitor begins with the synthesis of β-azidoalanine, **5** (Scheme 2). This will begin with treatment of L-serine, **6**, with boc-anhydride, **7**. The product, Boc-serine, **8**, is subjected to Mitsunobu Esterification to yield Vederas's β-lactone, **9.**[12] The amine is deprotected, then treated with sodium azide to afford β-azidoalanine.[13]



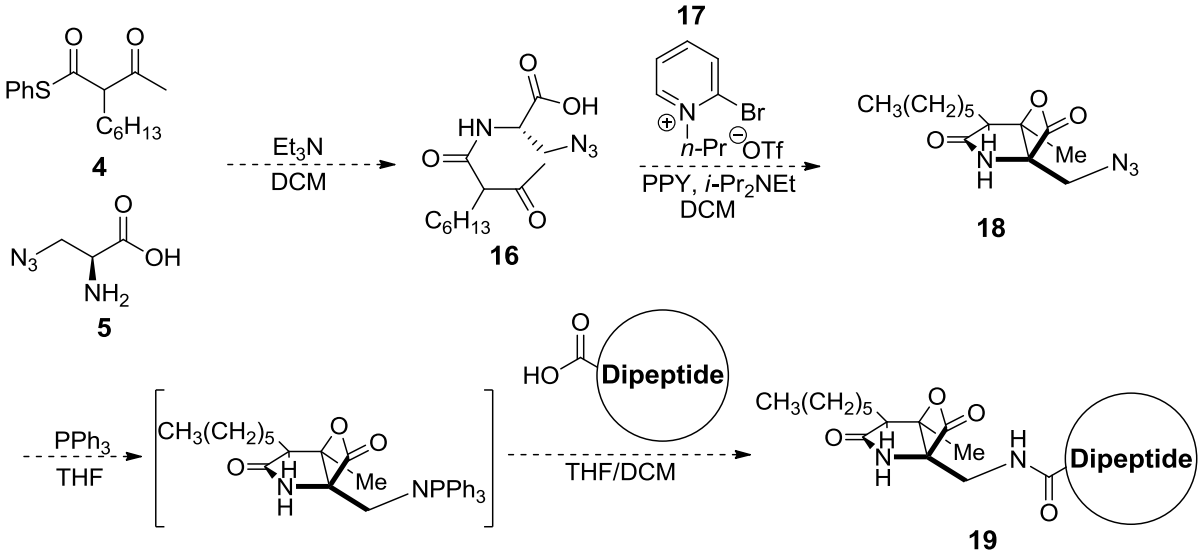
Scheme 2. Synthetic route to β-azidoalanine.

The synthesis of the β-keto thioester, **4**, will begin with the reaction between thiophenol, **11**, and octanoyl chloride, **12**, to form thioester **13**. This is then subjected to aldol reaction with acetaldehyde, **14**, to yield the β-hydroxy thioester, **15**.[14] The alcohol is then oxidized to form the β-keto thioester (Scheme 3).



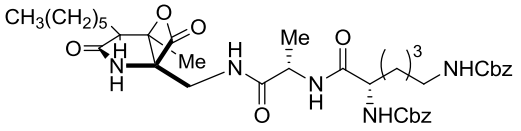
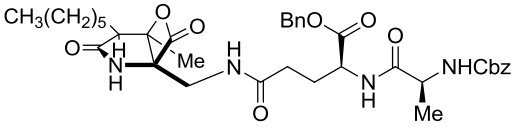
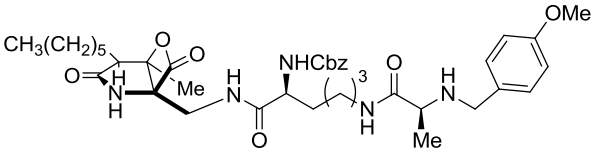
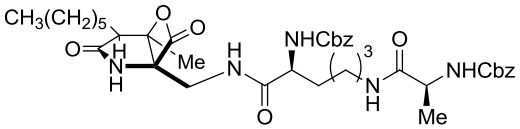
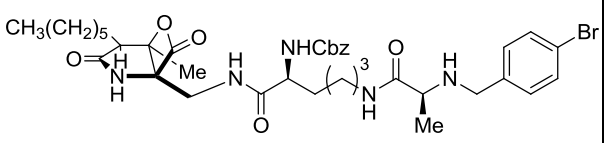
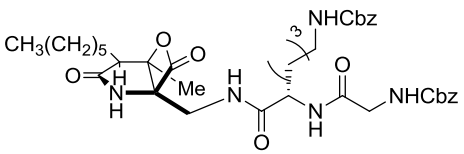
Scheme 3. Synthetic route to β-keto thioester.

Next, **4** and **5** is coupled via amide linkage, followed by a NCAL of keto acid **16** using modified Mukaiyama's reagent, **17**, and 4-pyrrolidino-pyridine to form bi-cyclic β-lactone core, **18**.



Scheme 4. Coupling of azido-alanine and keto-thioester, NCAL, then dipeptide coupling to form the proposed dual-inhibitors.

Table 1. A list of proposed dual inhibitors.

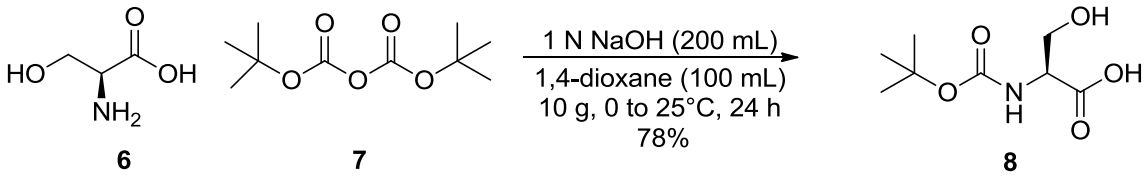
 **-Ala-Lys(Cbz)$_2$**	 **-Glu(Bn)-Ala(Cbz)**
 **-Lys(Cbz)-Ala(PMB)**	 **-Lys(Cbz)-Ala(Cbz)**
 **-Lys(Cbz)-Ala(*p*-BrBn)**	 **-Lys(Cbz)-Gly(Cbz)**

The azide is then treated with triphenylphosphine followed by treatment of the resulting intermediate with various protected dipeptides (Scheme 4) to yield the dual inhibitors shown in Table 1.

CHAPTER III

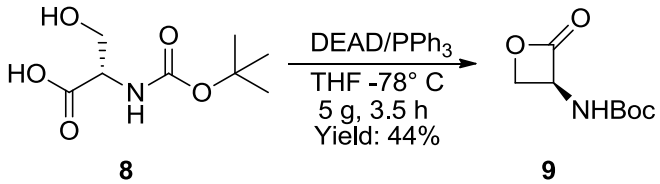
RESULTS

The first step in the synthesis of the β-azidoalanine, **5**, was the protection of L-serine, as seen in Scheme 5.



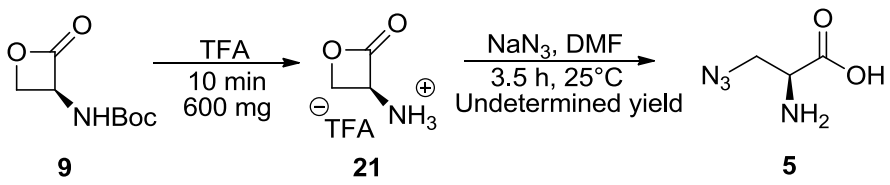
Scheme 5. Boc-protection of L-serine.

Boc-serine, **8**, was isolated in this reaction as a clear oil. However, pure Boc-serine is actually a white solid, which suggests that the oil that was isolated is impure. So purification via trituration was attempted to try to isolate the Boc-serine. However, Boc-serine could not be isolated as a solid, presumably because of trace amounts of di-*tert* butyl carbonate that did not react in solution. However, the ^{1}H NMR showed that there were only traces of this impurity. Therefore it was decided that the next reaction be attempted using this oil, which is shown in Scheme 6.



Scheme 6. Synthesis of Vederas's β-lactone.[12]

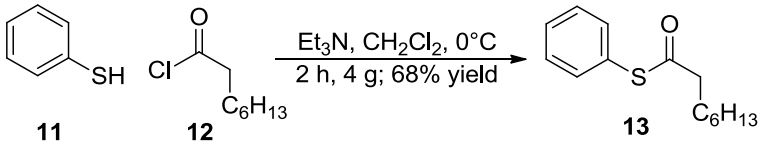
Despite the fact that the Boc-serine was not pure, the reaction was able to form the β-lactone, however the yield was lower than that reported by Arnold, et. al. (44% compared to 72%). The following reaction is the deprotection of the amine in **9** (Scheme 7).



Scheme 7. Boc-deprotection followed by addition of azide functional group.

In the publication by Arnold et. al.[12], after **9** is treated with trifluoroacetic acid, the trifluoroacetate salt is then treated with *p*-toluenesulfonic acid and recrystallized to replace the trifluoroacetate anion with the tosylate anion. This is done to prevent the decomposition of the β-lactone. However, the following reaction was attempted using the trifluoroacetate salt instead, in which we were pleased to find that it proceeded efficiently to provide β-azidoalanine, **5**.

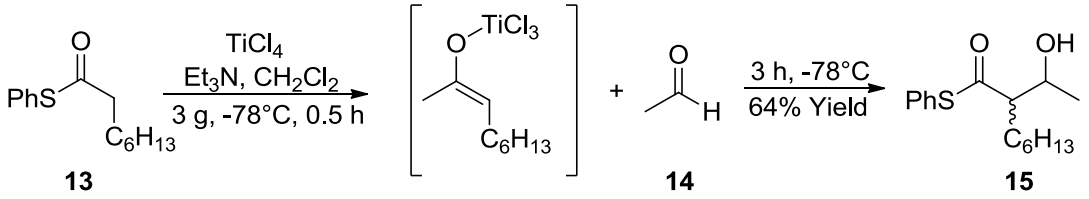
The synthesis of the β-keto thioester, **16**, begins with the reaction between thiophenol and octanoyl chloride, shown in Scheme 8.



Scheme 8. Formation of thioester.

In this reaction, thiophenol is a nucleophile and attacks the electrophilic carbonyl carbon. Hydrogen chloride is also formed in this reaction which makes the use of a base such as triethylamine necessary to neutralize this acid. After purification, the thioester was isolated with a 68% yield.

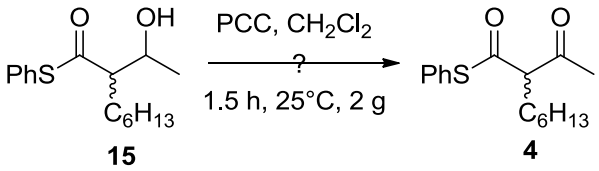
The next reaction is the aldol reaction between **13** and acetaldehyde, shown in Scheme 10. In this reaction, $TiCl_4$ is used to make the α protons in **13** more acidic, making the formation of an enolate favorable. (Scheme 9)



Scheme 9. Aldol reaction for the formation of the β-hydroxy-thioester.[12]

Once acetaldehyde is added to the solution, the nucleophilic enolate attacks the electrophilic carbonyl in acetaldehyde. After aqueous work-up, the β-hydroxy thioester, **15**, was isolated with a 68% yield.

The final reaction for the synthesis of the β-keto thioester is the oxidation of the hydroxyl group of **15**, shown in Scheme 10.



Scheme 10. Oxidation of the β-hydroxyl group to form the β-keto thioester.

Pyridinium chlorochromate (PCC), a mild oxidizing agent, is used in this reaction in order to ensure that the thioester is not cleaved. A brown oil is isolated from the column, however there were numerous compounds eluted from the column at the same time. Examination of the ^1H NMR spectrum of this crude reaction mixture provided the identities of a few of the compounds found in the oil. A chemical shift found at 11.63 ppm possibly illustrates the characteristic enol

tautomer peak prevalent in β-dicarbonyl groups. However, the large number of impurities in this ^{1}H NMR spectrum makes it difficult to determine whether this reaction produced the desired product. Future studies will be conducted to determine whether this reaction really produced the β-keto thioester.

CHAPTER IV

CONCLUSIONS AND FUTURE WORK

As of this time, the synthesis route is proving to be promising in allowing for the production of these dual inhibitors. Once the proposed dual inhibitors are successfully synthesized, they will be assayed to determine strength of inhibition of both FAS and the human 20S proteasome. These results will then be evaluated to determine which dipeptide structure optimizes the inhibitory properties towards these two proteins. This process includes varying one structural moiety at a time followed by submitting these inhibitors to biological assays in order to determine if these new variables increase the compound's inhibition properties. Molecular modeling will be used in order to determine what types of structural moiety variations will be considered. Experiments involving computer simulations are currently being carried out in order to approximate association and dissociation constants the inhibitors will have with the targeted protein active sites. This, in turn, aids in ruling out proposed inhibitors which will ultimately not be compatible and produce poor inhibition results before any time is spent synthesizing and assaying them. These results can potentially lead to a more effective treatment for various forms of cancer, which in turn can save millions of lives in the future.

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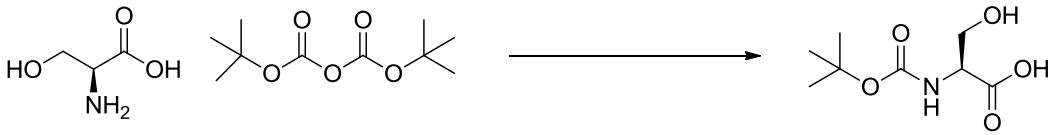
APPENDIX

EXPERIMENTAL PROCEDURES

General Methods

All chemicals were purchased from Aldrich and used without purification. Reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F_{254}. TLCs were stained using potassium permanganate and annisaldehyde stain. Purification of products was carried out *via* flash column chromatography using silica (60 Å, 230-400 mesh). ^{1}H and ^{13}C NMR characterization was performed on an Inova 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm and are referenced to deuterated chloroform (δ 7.27 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).

N-tert-butoxy-L-serine (8)

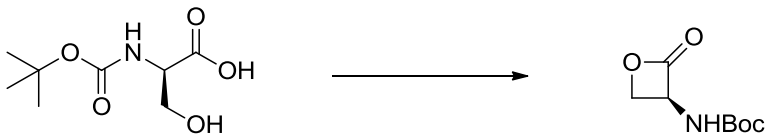


6 **7** **8**

To a solution of L-serine (**6**) (10.01 g, 95.15 mmol) in 1 N NaOH (200 mL, 8.02 g, 200.5 mmol) at 0°C, was added a solution of di-*tert*-butyl dicarbonate (20.97 g, 96.11 mmol) in 1,4-dioxane (100 mL). The resulting two phase solution was stirred at 0°C for 30 min, then at room temperature for an additional 4 h. The mixture was concentrated, then acidified to pH 2-3 by careful addition of 1 N HCl (~225 mL). The product was extracted with EtOAc (4 x 100 mL) and then the combined extracts were dried over anhydrous $MgSO_4$, filtered, and then evaporated

in vacuo to afford boc-serine (**8**) (15.23 g, 78% yield) as a colorless oil and data matched that reported previously.[15] Boc-serine was used in the following reactions without further purification. ^{1}H NMR (300 MHz, CD_3OD): δ 6.37 (d, *J* = 9 Hz, 1H), 4.22 (t, *J* = 6.6 Hz, 1H), 4.09 (q, *J* = 6 Hz, 1H), 3.90 (dd, *J* = 3.6 Hz, 1H), 3.81 (dd, *J* = 3.6 Hz, 1H), 1.44 (s, 9H).

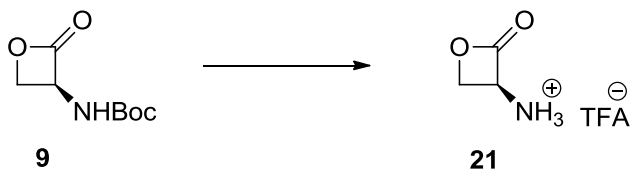
***N*-(*tert*-butoxycarbonyl)-L-serine-β-lactone (8).**



8 **9**

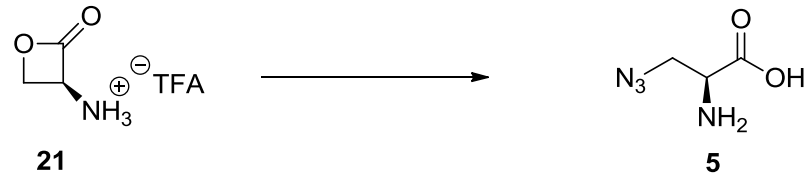
To a stirred solution of PPh_3 (6.39 g, 24.4 mmol) in anhydrous THF (100 mL) at -78°C was added 40% diethyl azodicarboxylate in toluene (11.10 mL, 24.4 mmol) dropwise over 20 min. After 10 min of additional stirring, a solution of Boc-L-serine (5.00 g, 24.4 mmol) in anhydrous THF (100 mL) was added dropwise over 20 min to the stirred solution at -78°C, then 3 h at 20°C. Solvent was removed in vacuo, and the residue was chromatographed on silica gel (EtOAc/hexane 4.5:5.5) to afford **8** (2.05 g, 45% yield) as a white crystalline solid and data matched that previously reported.[12] IR ($CHCl_3$ cast): 3354 (s), 1832 (s), 1674 (vs), 1528 (s), 1287 (m), 1100 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.53 (d, *J* = 10 Hz, 1H), 5.05 (dd, *J* = 5 Hz, 1H), 4.47 (d, *J* = 6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.0, 155.1, 81.5, 66.6, 59.9, 28.2.

L-serine-β-lactone trifluoroacetate (21)



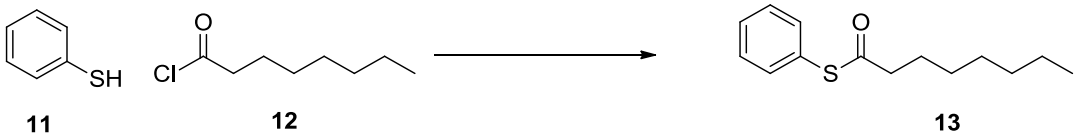
Boc-L-serine-β-lactone (305 mg, 1.61 mmol) is treated with CF_3COOH (5 mL) at 0°C for 10 min. The excess CF_3COOH is then removed in vacuo. The resulting oil is immediately taken to the next reaction.

β-azidoalanine (5)



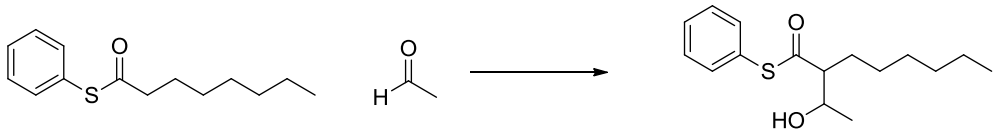
To a stirred solution of trifluoroacetate salt **21** (3.21 mmol) in DMF (3 mL) is added a solution of NaN_3 (115 mg, 1.77 mmol) in DMF (6 mL) at room temperature. The solution is allowed to stir for 3.5 h. The solvent is then evaporated in vacuo to afford **5** as a brown oil. Data obtained matched that previously reported.[13] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.57 (d, J = 6 Hz, 1H), 4.34 (dd, J = 3.6 Hz, 1H), 3.79 (dd, J = 3 Hz, 1H), 3.76 (dd, J = 6 Hz, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162.4, 60.2, 55.8.

S-Phenyl Octanethioate (13)



To a 100-mL round-bottomed flask was added CH_2Cl_2 (30 mL), triethylamine (5.06 mL, 36.3 mmol) and thiophenol (3.73 mL, 36.3 mmol). A solution of octanoyl chloride (6.20 mL, 36.3 mmol) in 35 mL dichloromethane was added over 30 min while stirring the solution with a magnetic stirrer. Precipitating triethylammonium chloride made the reaction mixture turn to a turbid suspension. After 45 min of additional stirring the reaction was completed as monitored by TLC (hexanes, $R_f = 0.43$). The organic mixture was washed twice with 50 mL saturated sodium hydrogen carbonate solution and once with 50 mL brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated in vacuo to yield 3.68 g of S-phenyl-octanethioate, **6**, as a clear oil (48%). Data obtained matched that reported previously.[16] ^1H NMR (300 MHz, $CDCl_3$): δ 7.29-7.25 (m, 5H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.8 Hz, 2H), 1.63-1.56 (m, 4H), 1.25-1.21 (m, 4H), 0.77 (t, *J* = 1.8 Hz, 3H).

_S_-phenyl 2-(1-hydroxyethyl)octanethioate (15)

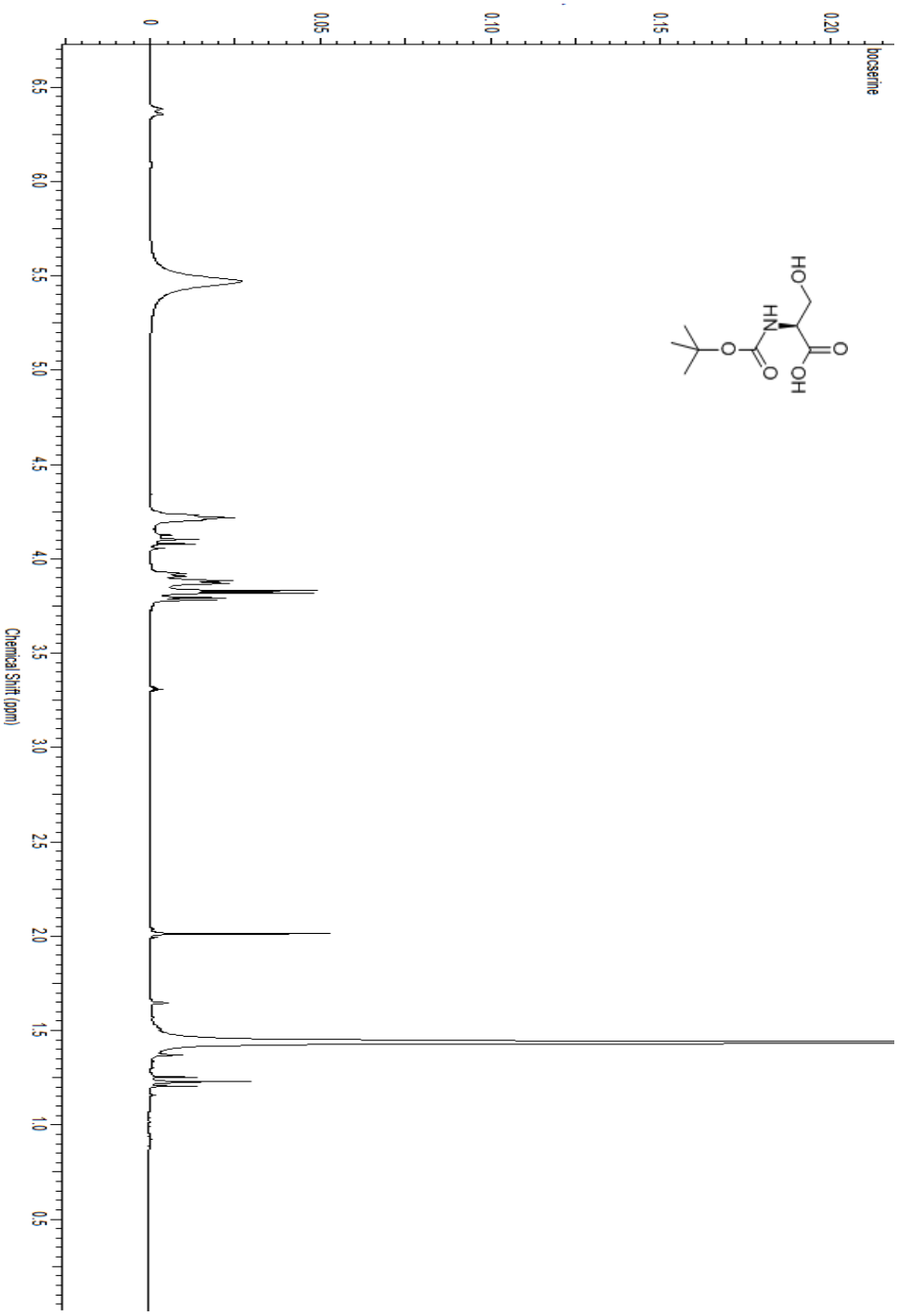


13 **14** **15**

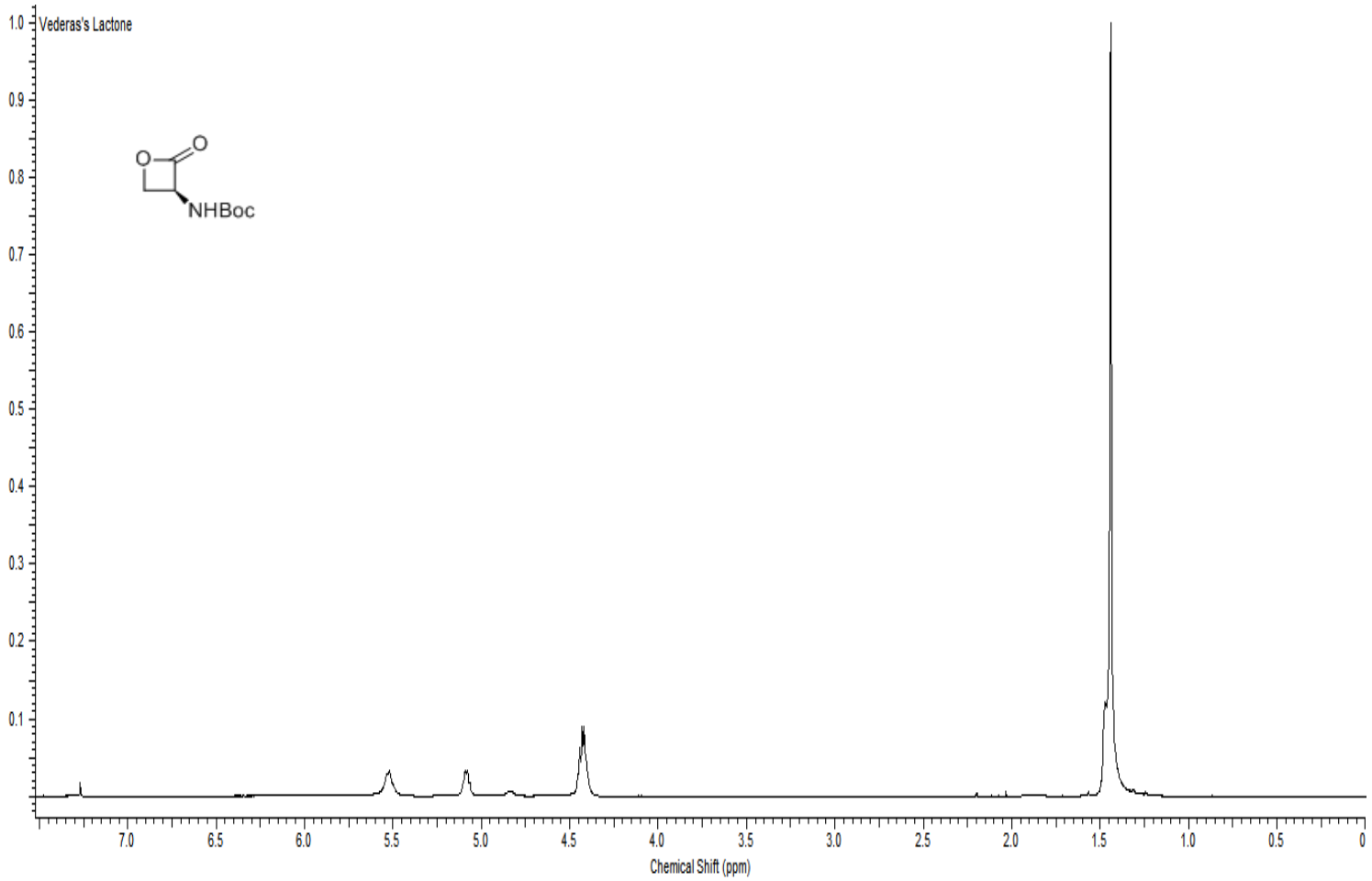
1 M $TiCl_4$ in CH_2Cl_2 (9.51 mL, 25.38 mmol) and Et_3N (4.13 mL, 29.61 mmol) were successively added to a stirred solution of phenyl-thioester **13** (5.00 g, 21.15 mmol) in CH_2Cl_2 (50 mL) at -78°C under an atmosphere of N_2. After stirring for 30 min, acetaldehyde (3.5 mL, 25.38 mmol) was added to the mixture. After 2.5 h of additional stirring at the same temperature, the reaction was completed as monitored by TLC (EtOAc/hexanes 3:7, $R_f = 0.42$). The mixture was poured into ice water, which was extracted with Et_2O (2 x 100 mL). The organic phase was then washed with water, brine, and then dried ($MgSO_4$) and concentrated. The resulting oil was

chromatographed on silica using EtOAc/hexanes (3:7) as eluent to afford the β-hydroxy thioester, **15** as a clear oil (2.28 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.40 (m, 5H), 4.07 (quint, *J* = 6 Hz, 1H), 4.00 (quart, *J* = 6 Hz, 1H), 2.71 (quint, *J* = 6 Hz, 1H), 1.89-1.60 (m, 2 H), 1.54-1.28 (m, 8 H), 0.91 (t, *J* = 3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 201.4, 134.5, 129.7, 129.4, 127.7, 68.7, 31.8, 29.6, 27.8, 27.4, 22.8, 20.9, 14.3.

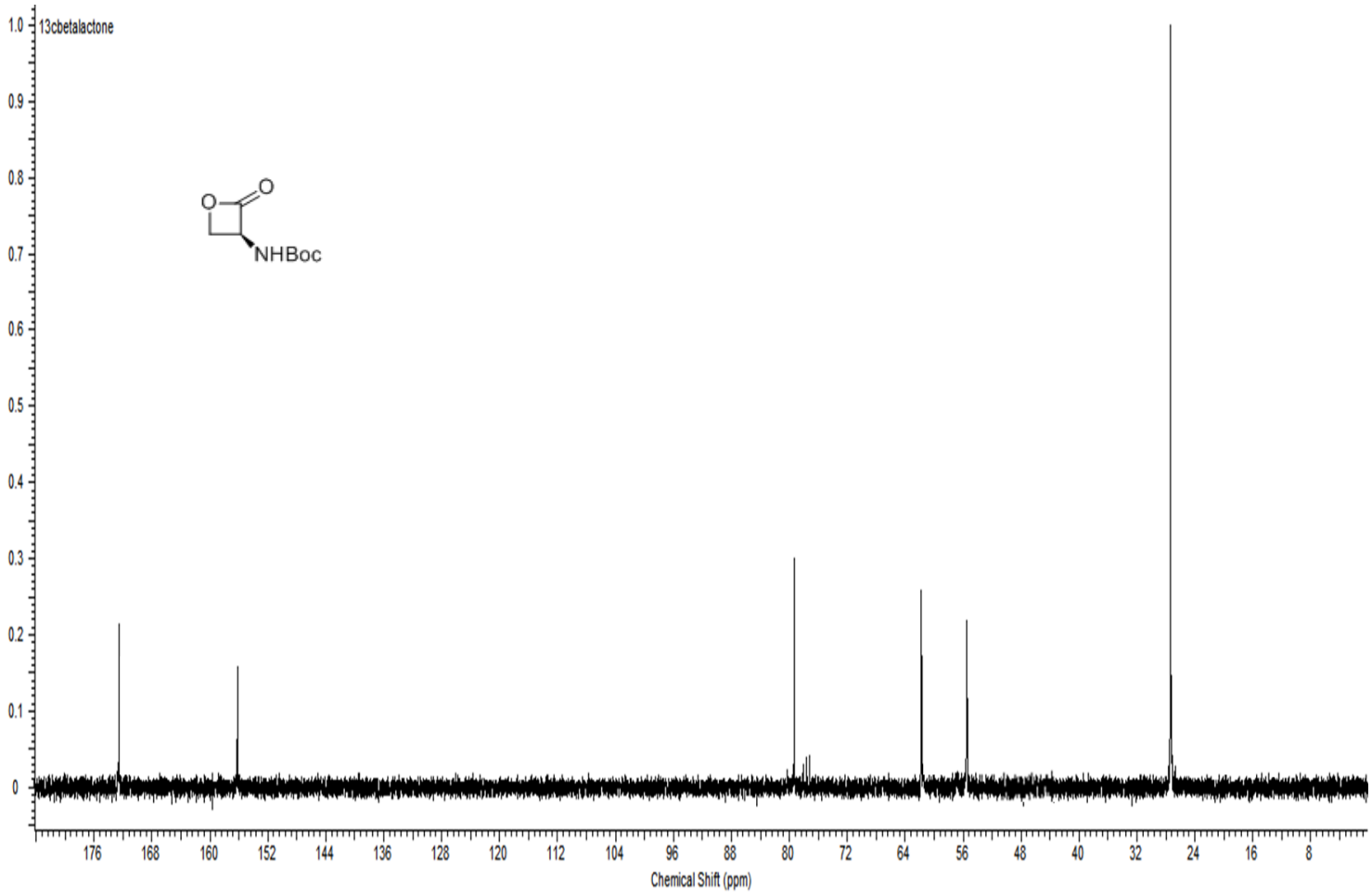
NMR SPECTRA



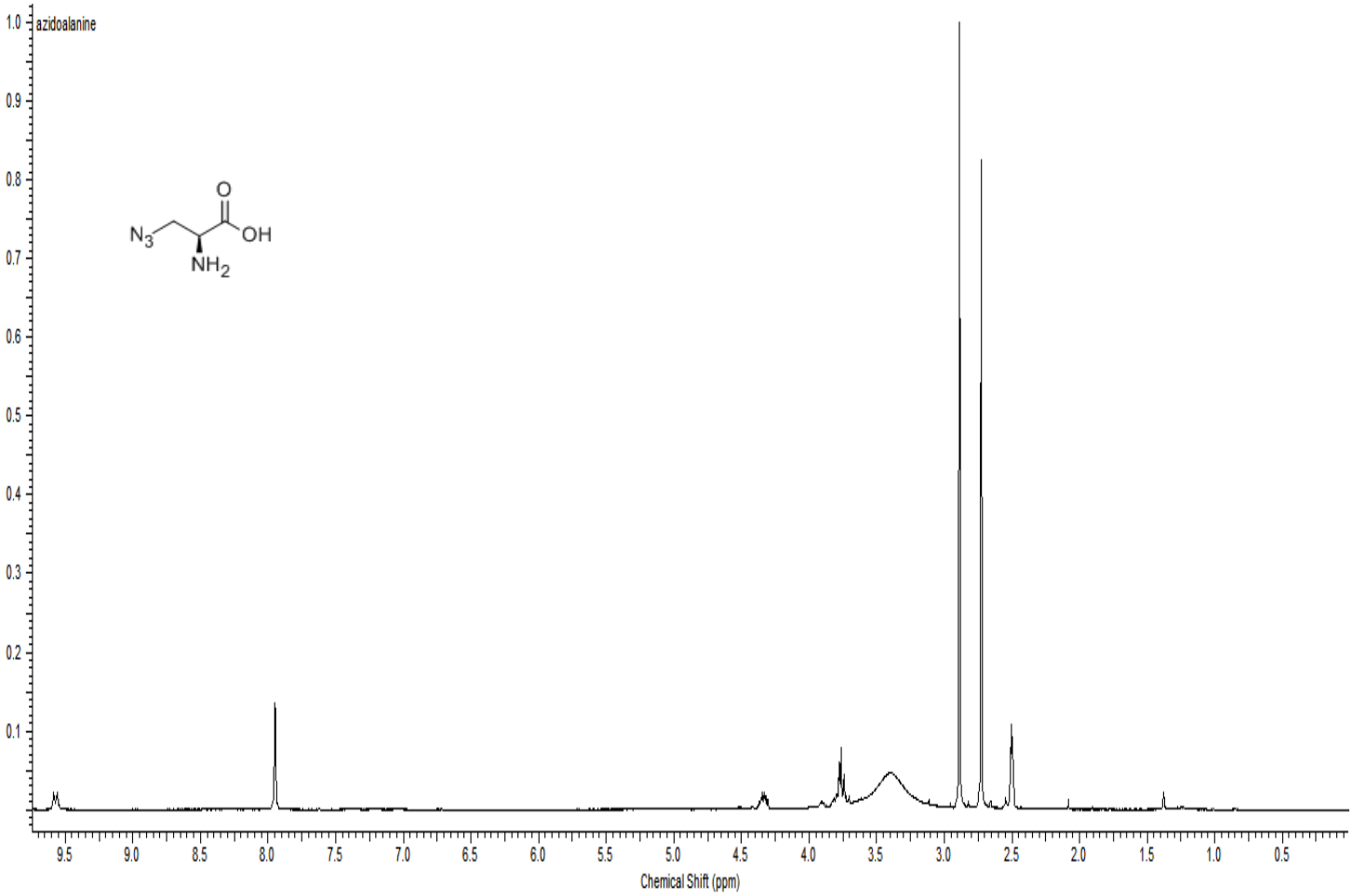
^{1}H NMR of N-(tert-butoxycarbonyl)-L-serine, **8**. (in CD_3OD).



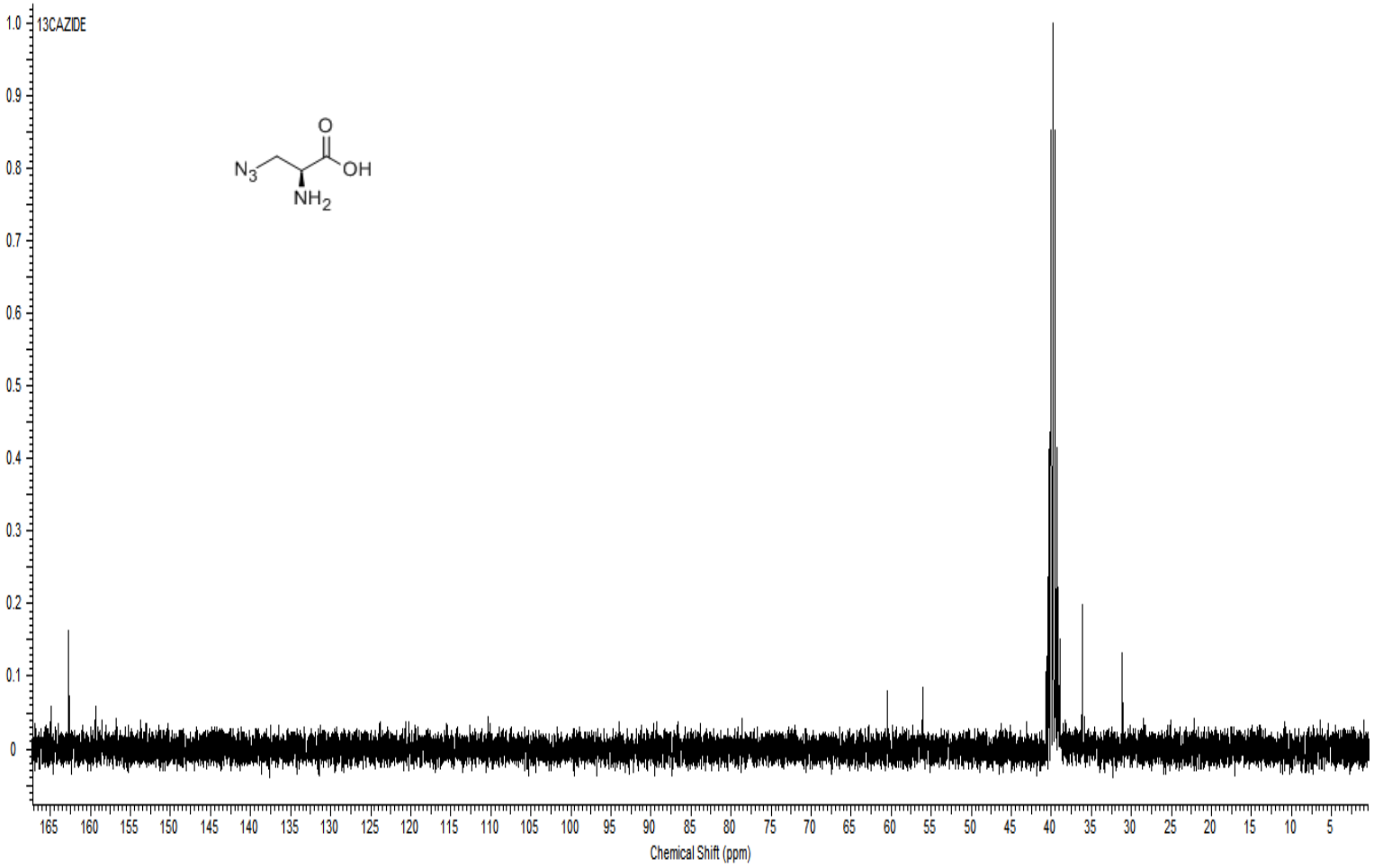
^{1}H NMR of N-(tert-butoxycarbonyl)-L-serine-β-lactone, **9.** (in $CDCl_3$).



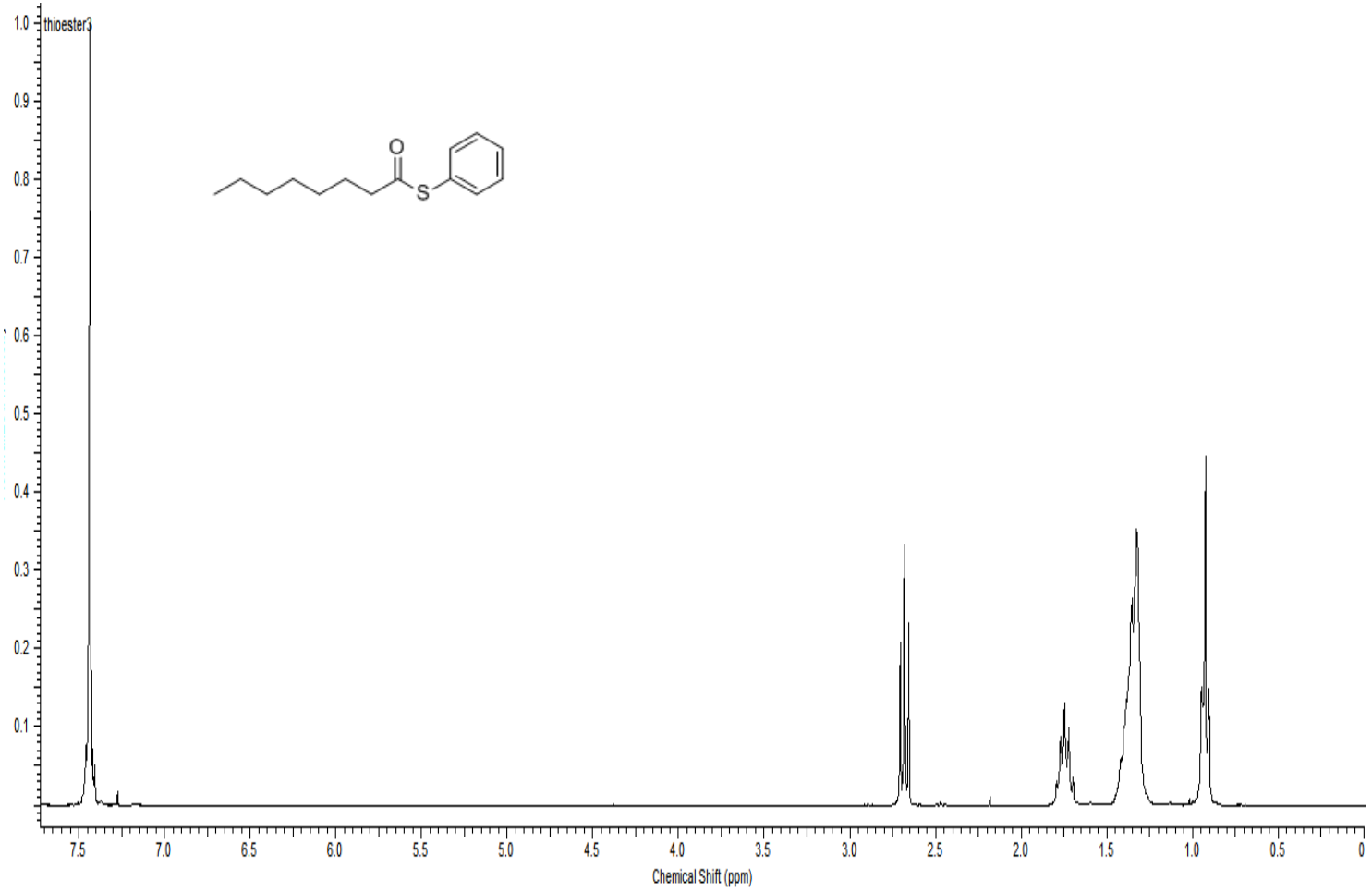
^{13}C NMR of N-(tert-butoxycarbonyl)-L-serine-β-lactone, **9.** (in $CDCl_3$).



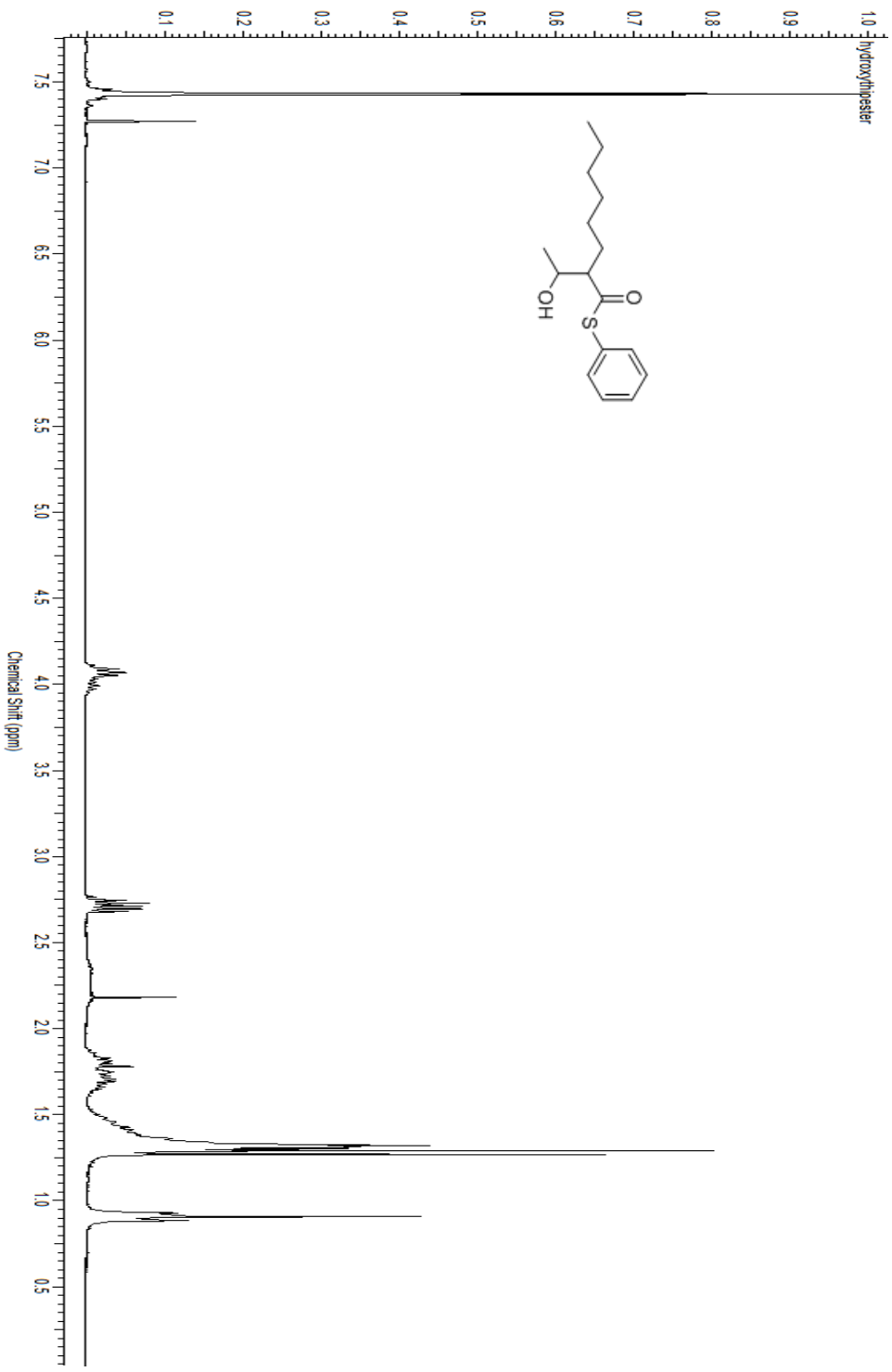
^{1}H NMR of 3-azidoalanine, **5** (in dimethyl sulfoxide-d_6).



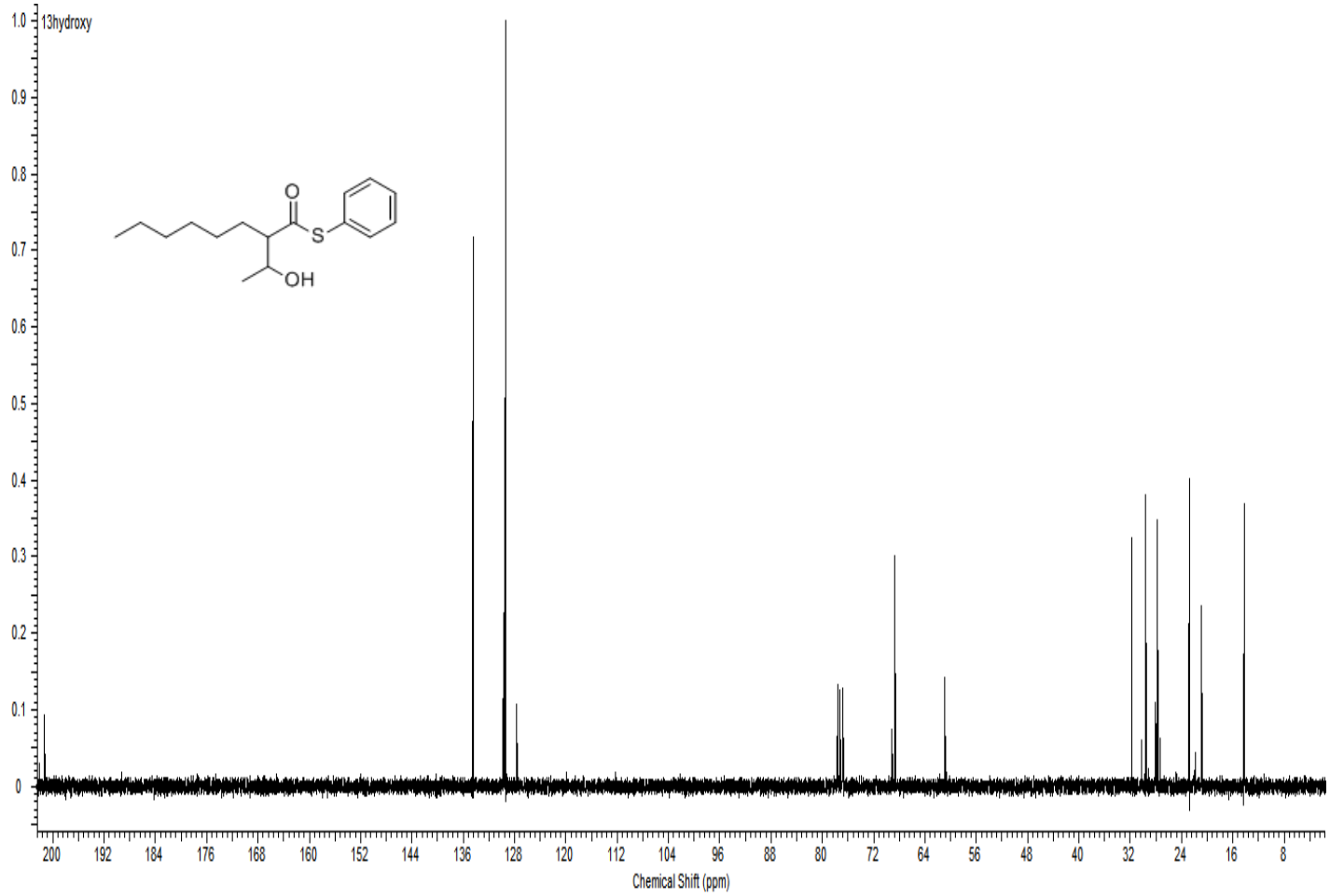
^{13}C NMR of 3-azidoalanine, **5** (in dimethyl sulfoxide-d_6).



^{1}H NMR of *S*-phenyl octanethioate, **13**. (in $CDCl_3$).



^{1}H NMR of *S*-phenyl 2-(1-hydroxyethyl)octanethioate, **14**. (in $CDCl_3$).



^{13}C NMR of *S*-phenyl 2-(1-hydroxyethyl)octanethioate, **14**. (in $CDCl_3$).