Catalytic Asymmetric Construction of β-Amino Acid Precursors and Their Use in an Iterative Method Towards β-Peptide Synthesis

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Iterative Method Towards β-Peptide Synthesis

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Towards the goal of novel β-peptide synthesis, a method to access a variety of enantioenriched β-amino acid precursors was developed. These β-amino acid precursors were then utilized in the synthesis of numerous β-peptides in solution and on solid support. The β-amino acid precursors allowing this unique technology are thiazinone and β-lactam heterocycles which were accessed via asymmetric cycloadditions of *N*-acyl imines and ketenes utilizing cinchona alkaloid catalysts. The methodology developed herein provides access to unique and previously unavailable β-amino acids and β-peptides.

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PREFACE

ACKNOWLEDGMENTS

I am incredibly grateful for the support and guidance by my advisor Professor Scott Nelson and my committee members Seth Horne, Craig Wilcox and Lin Zhang. I'd also like to thank my friends, family and my fellow graduate students who were always there to lend intellectual and emotional support. I've learned an incredible amount on this journey and I truly appreciate everyone's support along the way. Thank You!

ABBREVIATIONS

BOC…………………………………………………………………*tert*-Butyloxycarbonyl

CBZ…………………………………………………………………….Carbobenzyloxy

DMAP…………………………………………………………..4-Dimethylaminopyridine

DMF…………………………………………………………..Dimethylformamide

 FMOC………………………………………………………….Fluorenylmethyloxycarbonyl

HATU…………………1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium

3-oxidhexafluorophosphate

LYS……………………………………………………………………….Lysine

NOVAPEG…………………………………………………………NOVA Polyethylene glycol

PHE……………………………………………………………….Phenylalanine

SRIF………………………………………………..Somatotropin release-inhibiting factor

THF…. …………………………………………………………………Tetrahydrofuran

THR………………………………………………………………...Threonine

TLC………………………………………………………Thin Layer Chromatograpy

TMS……………………………………………………………..Trimethylsilane

TRP……………………………………………………………..Tryptophan

TS………………………………………………………………………..Tosyl

1.0   INTRODUCTION

Due to the increased interest in β-amino acids and β-peptides for use in peptidomimetics and the limited number of naturally occurring β-amino acids, we worked to develop methodology to synthesize these compounds efficiently and with variability. Inspired by asymmetric cycloaddition chemistry already developed within the group, we saw an opportunity to prepare heterocycles that could be used as β- amino acid precursors. We envisioned an asymmetric cycloaddition that would provide access to heterocycles that are masked β-amino acids that would also mimic natural amino acids. From the heterocycles, ring-opening and deprotection reactions would allow for synthesis of peptides in solution and on solid support. We also wanted to ensure that the β- amino acids synthesized from this methodology could also participate in traditional peptide coupling reactions and help to add versatility in the synthesis of peptidomimetics.

1.1 BETA-AMINO ACIDS IN PEPTIDOMIMETICS

In the development of drug candidates, peptides are known to have high selectivity toward their targeted proteins and can be synthesized efficiently with natural amino acids. Unfortunately, what they have in selectivity does not compensate for their poor solubility and poor bioavailability. Peptides are recognized and degraded very quickly in the body, often

making them inferior drug candidates. One strategy to access the selectivity of peptides in the body but also improve the bioavailability of peptides is to synthesize unnatural peptides that mimic the structure and activity of natural peptides such as peptidomimetics and specifically, β-peptides. Due to these unique characteristics, β-peptide research has grown considerably in the past decade with much of the research devoted to the conformation, biological activity and synthesis of β-peptides and their monomers, β-amino acids.

β^2-amino acid, R^3=H
β^3-amino acid, R^2=H
cyclic β-amino acid, R^2-R^3=$(CH_2)_n$
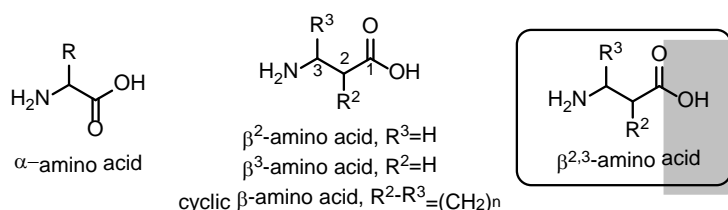
Figure 1. Seebach convention for naming substituted β-amino acids

Observing the structure of β-amino acids compared to α-amino acids (Figure 1), the similarity of their structures and increased structural diversity of β-amino acids makes β-amino acids very useful in peptidomimetics. Unfortunately, there are not many β-amino acids produced naturally and the synthesis of these compounds can be difficult. Production of β-amino acids is especially rare in mammals, where most of the natural β-amino acids produced are β-alanine, β-aminoisobutrate or derivatives thereof. It was observed, however, that bacteria are able to produce a variety of β-amino acids[1]. There have been several isolated natural products with high biological activity that contain β-amino acids such as Dolastatin 11 and Kulokekahilide 1 (Figure 2).
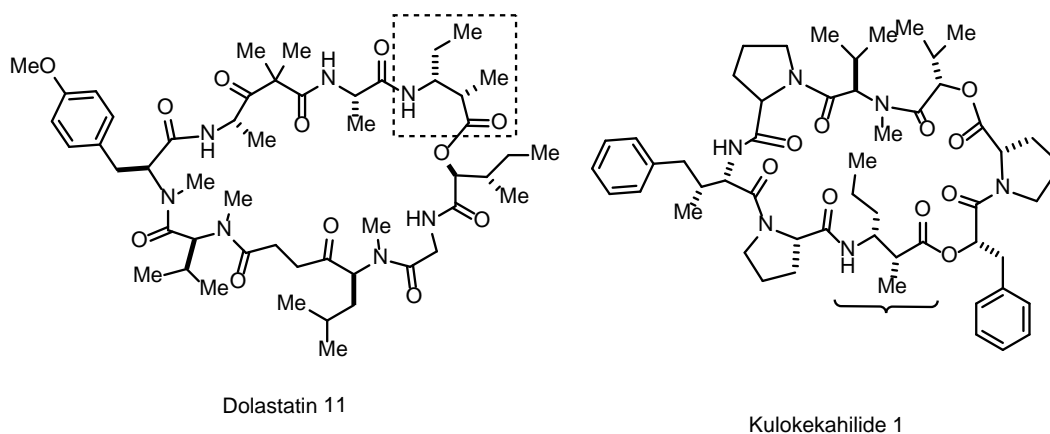
Figure 2. Natural products, Dolastatin 11 and Kulokekahilide 1 that contain $\beta^{2,3}$-amino acids

The unique characteristics of the β-amino acid functionality have been recognized and utilized in many well-known drugs, including Taxol, penicillin G, cephalosporin C and betastatin (Figure 3). The β-amino acid in Taxol is essential for its microtubule-stabilizing activity[2] and betastatin's β-amino acid is critical for active site binding[3]. In penicillin G and cephalosporin, the β-amino acid motif is present as a β-lactam and is the source of their antibacterial activity.[4] The β-amino acid motif present in these molecules is critical for their high activity which showcases the utility of β-amino acids in drug development.
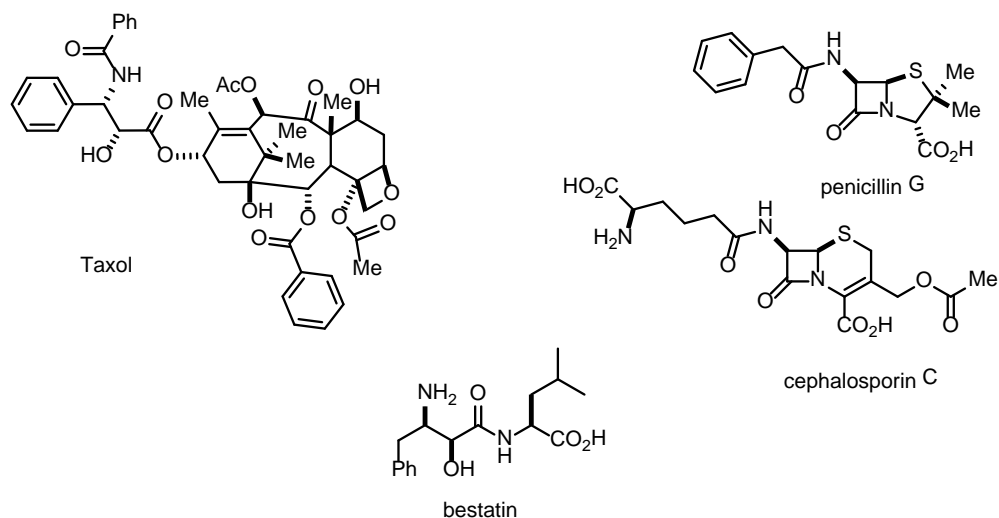
Figure 3. Clinical drugs that have a β-amino acid moiety

The conformation of peptidomimetics and β-peptides has become a very large area of research due to the importance of secondary structure on the selectivity and activity towards targeted proteins. Also of importance is their biological activity where β-peptides are more resistant to degradation within the body and therefore can provide a longer half-life than their analogous α-peptides. Subsequently, one of the major strategies of peptidomimetics is utilizing β-amino acids in the place of natural α-amino acids. This modification is specifically useful when the cleavage site of a peptide is recognized by peptidases within the body and replacement of that amino acid with a β-amino acid can effectively prevent the degradation while also incorporating the correct substitution on the molecule. The success of this modification was showcased by Gademann et al in the synthesis and biological evaluation of a cyclo β-tetrapeptide as a somatostatin analogue[5,6]. The natural α-peptide hormone, somatostatin, is important in the regulation and release of growth hormone and insulin. Additionally, sandostatin, **1**, a cyclic α-octapeptide derived from somatostatin is in clinical use but has a very short half-life (90 min)[5].

Their goal was to synthesize an analogue of this compound that would mimic the activity of the original sandostatin as well as provide a longer half-life in the body. Structure-activity relationship studies were done revealing the importance of the (Phe-Trp-Lys-Thr) sequence for activity. To mimic the (Phe-Trp-Lys-Thr) sequence, they synthesized the cyclic β-tetrapeptide, **2** (Figure 4). Due to the cyclic structure of the compound, the β-turn site where the major binding occurred was enforced in the molecule. They found that the affinity of **2** was in the micromolar range, at least one order of magnitude lower than those of the sandostatin **1**. Although the affinity for the target protein was not as large as that of sandostatin, it did show potential for use of β-peptide compounds in peptidomimetics.
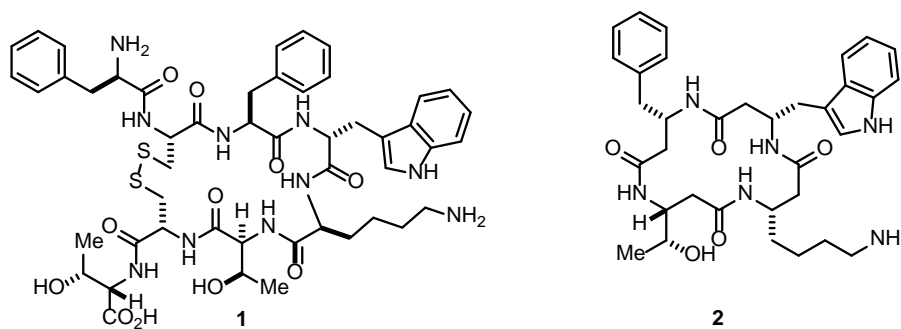
Figure 4. Synthesis of **2** which was designed to mimic **1**

Gademann et al. then proposed the synthesis of linear peptides to mimic **2**. They believed the linear peptide would adopt the active conformation based on the folding preference of β-amino acids themselves and the intramolecular hydrogen bonding that can stabilize these structures. Using the same sequence of β-amino acids as their cyclic tetrapeptide **2**, they synthesized **3**, which they believed would adopt a 10-membered turn stabilized by intramolecular hydrogen bonding (Scheme 1). The synthesized linear peptide **3** showed significant and

selective affinity for one of the human SRIF receptors, in which it was 20 times more selective than **1**, but 20 times lower than **2**. From this case study, it was evident that replacing an α-amino acid with a β-amino acid was a very effective method of modifying both the metabolism as well as the conformation and selectivity of the peptide. Due to the success and enormous potential success of β-amino acids and β-peptides in peptidomimetics, it is important to have the capability to synthesize a large variety of these compounds.

Scheme 1. Synthesis of linear peptide to mimic cyclic peptide
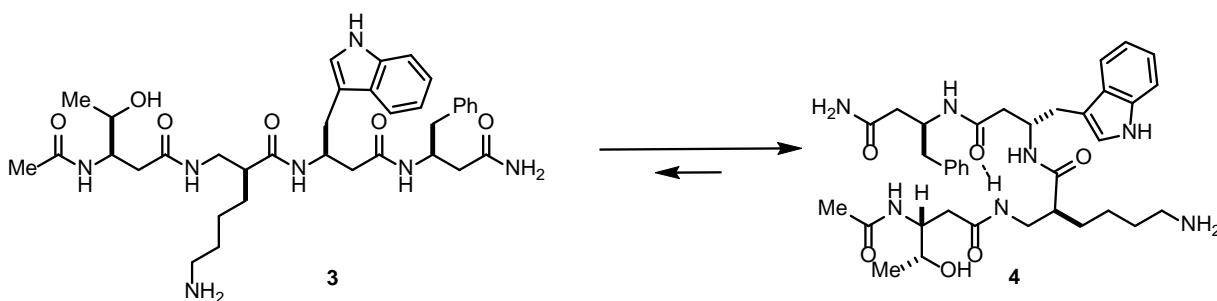
1.2 PREVIOUS CATALYTIC ASYMMETRIC SYNTHESES OF BETA[2,3]-AMINO ACIDS

Critical to the development of β-peptides and peptidomimetics is the synthesis of the individual monomers, β-amino acids. β-amino acids provide incredible potential in peptidomimetics due to their similarities to natural amino acids with the advantage of having increased diversity from the extra substitution and conformational differences. With the same

functionality as α-amino acids, β-amino acids can also be incorporated into a peptide chain using similar peptide coupling reaction conditions.

Although there have been a variety of methods developed to synthesize β-amino acids[1,7] and there are a number of commercially available β-amino acids, most of the methods require stoichiometric chiral auxiliaries or homologation of α-amino acids. The majority of the easily accessible β-amino acids are either β^2 or β^3-amino acids, while the synthesis and availability of disubstituted $\beta^{2,3}$-amino acids is more rare. Mannich-type reactions provide the correct connectivity for β-amino acids while also allowing for a diverse substrate scope and enantioenriched products, whereby one can control the substitution and stereochemistry about the newly formed bond depending on imine and enol substitution as well as the chiral environment. These compounds have been successfully synthesized with a variety of metal catalysts and organocatalysts for the formation of the metal enolate and activation of the aldehyde, respectively.

A recent example of a catalyzed Mannich- type reaction resulting in enantioenriched *syn*-substituted $\beta^{2,3}$-amino acids is the lanthanum aryloxide/ pybox catalyzed Mannich reaction developed by Morimoto et al., (Scheme 2).[8] In these reactions, a trichloromethyl ketone (**5**) is utilized as the pronucleophile. These reactions were found to provide good yields, diastereoselectivity and enantioselectivity. In terms of substrate scope, it was found that aryl substitution on the imine was superior and only a methyl substitution was attempted on the trichloromethyl ketone unit. The resulting Mannich adduct could also be modified to be useful in β-amino acid synthesis. With solvolysis, the trichloromethyl ketone can be quantitatively transformed into a methyl ester, **6**.

Scheme 2. Lanthanum aryloxide/pybox catalyzed Mannich reaction by Marimoto et al

X=2-thienyl
X=2-pyridyl

12 examples
72-99%
(*syn/anti*) 8:1-30:1
92-99% *ee*

Ar=4-MeO-C$_6$H$_4$$^-$
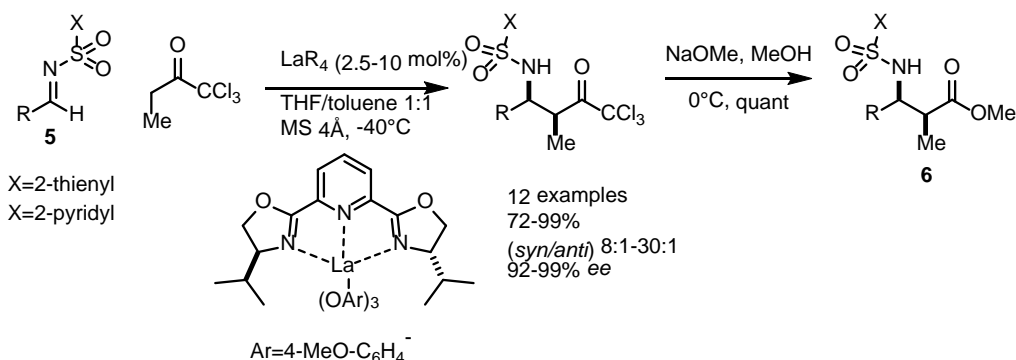
Copper catalyzed reactions resulting in *anti*-substituted β-amino acids were developed by Suzuki et al.[9] They utilized catalytic amounts of a soft Lewis acid [Cu(MeCN)$_4$]PF$_4$ and a hard Bronsted base Li(OC$_6$H$_4$-*o*-OMe) in a Mannich-type reaction with *N*-Dpp imine (**7**) (Scheme 3). The reactions were found to proceed with good yield and enantioselectivity. In this reaction, R^1 is limited to H, Me, Et, or Prop and the substitution on the imine is limited primarily to aryl groups. The thioamide functional group of the Mannich reaction product can also be further modified.

Scheme 3. Copper catalyzed Mannich-type reaction by Suzuki et al.

17 examples
54-99%
dr 89:11 - 90:10
53-97% *ee*

8
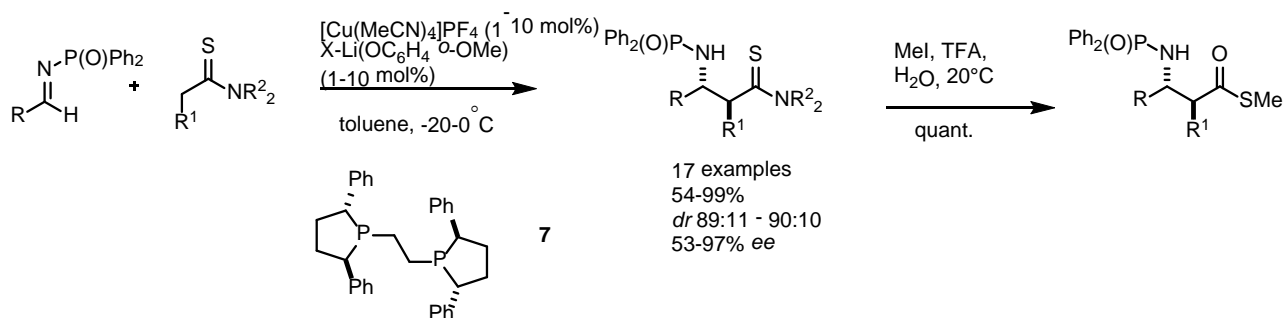
Organocatalytic Mannich-type reactions have also been developed, where proline was used as the organocatalyst and aldehydes as the pronucleophiles. Notz et al., utilizing a one pot, 3-step procedure with in-situ imine formation, synthesized 23 different amino alcohols in moderate to good yields and enantioselectivity[10] (Scheme 4).

Scheme 4. Synthesis of amino alcohols with proline in a 3 step procedure by Notz et al.
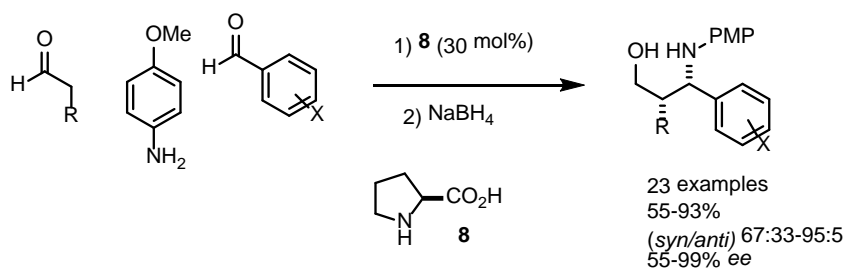
With the success of the 3 component Mannich reaction, it was clear that the imine can be generated in-situ with proline, successfully catalyzing the reaction as well as providing excellent enantioselectivity. The products associated with the proline catalyzed reactions were all *syn*-disubstituted $\beta^{2,3}$-amino acid precursors. Yang et al. and Vesely et al. also developed proline catalyzed Mannich-type reactions, but instead of generating the imine in-situ, they utilized boc protected imines and added them directly to the reaction. Their products had limited substrate scope, where there were only aryl groups on the imine and a limited number of aliphatic groups, such as *n*-Bu, Me, and ^{i}Pr on the aldehyde[11,12] (Scheme 5). The products of this reaction had excellent diastereoselectivity and enantioselectivity.

Scheme 5. β-amino acid synthesis with proline as organocatalysts
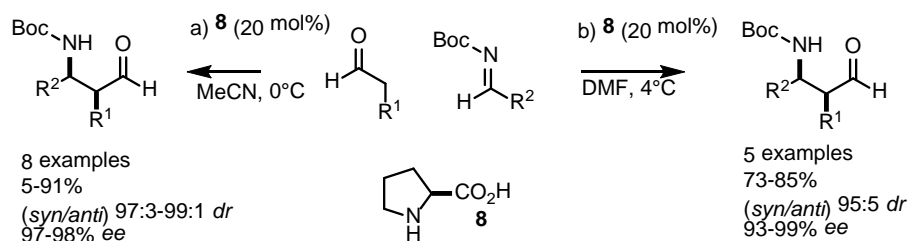
The Mannich type reactions above (Schemes 2- 5) provide precedent in the synthesis of compounds with similar backbone and functionality as β-amino acids. The products of the reactions also have diversity and good diastereoselectivity and enantioselectivity. Based upon these reactions, it is evident that Mannich type reactions can be utilized in the synthesis of diverse and enantiomerically enriched β-amino acids required for peptidomimetics.

1.3 SYNTHESIS OF B-LACTAMS IN EFFORTS TOWARDS B-AMINO ACIDS AND APPLICABILITY IN PEPTIDE SYNTHESIS

Another strategy in the synthesis of β-amino acids is to use a β-lactam as a β-amino acid precursor because they have the same structural motifs. With the same connectivity as β-amino acids, and being biologically active, themselves, the synthesis of β-lactams is an important area of β-amino acid synthesis and research. One method of synthesizing β-lactams is through the synthesis of β-amino acids and their subsequent ring-closure. Alternatively, β-lactams have been

previously ring-opened to access β-amino acids (Scheme 6).   The known interconversion between β-lactams and β-amino acids provides even more options for synthesizing β-amino acids as well as their use in peptidomimetics.

Scheme 6. Interconversion between β-lactams and β-amino acids
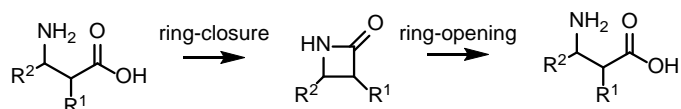
Although it is possible to synthesize β-lactams via ring closure of β-amino acids, there are a limited number of reactions that provide a diverse substrate scope of β-amino acids in good yields, diastereoselectivity and enantioselectivity. The asymmetric synthesis of a number of β-lactams has been accomplished by Hart et. al in 1986[13] and Lectka in 2002 (Scheme 7).[14,15] Hart's example utilized a chiral auxiliary to obtain good enantioselectivity with a limited substrate scope including phenyl and cinnamyl groups on the imine portion and ethyl and isopropyl on the ketene portion.   Lectka's example, albeit catalytic and providing excellent enantioselectivity, had limited substrate scope with only ester functionality present on the imine.

Scheme 7. Previous syntheses of enantioenriched β-lactams
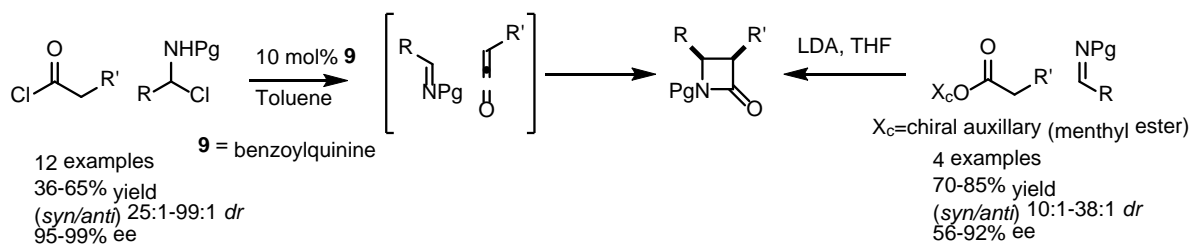
With the ability to synthesize β-lactams shown by Hart and Lectka and the known interconversion between β-lactams and β-amino acids, ring-opening of β-lactams can be extended to β-peptide synthesis. As seen in Scheme 8, the free amine of an amino acid acts as a nucleophile to ring-open the β-lactam, providing an alternative to the typical peptide coupling reactions. In the use of β-lactams in the elongation of a peptide chain, typically an additive such as NaN$_3$ or KCN is used (Scheme 8).[16]

Scheme 8. Ring-opening of β-lactam with an amino acid
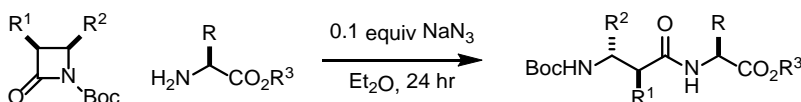
Although there have been a number of methods to directly synthesize β-amino acids as well as β-lactams that can lead to β-amino acids, current methods do not provide much diversity in functionality and stereochemistry. There is still a great need for enantioselective synthesis of a large variety of β-amino acids with a diverse substrate scope.

1.3.1   PREVIOUS METHODS OF β-PEPTIDE SYNTHESIS

The majority of peptide synthesis is based on the formation of an amide bond via coupling of amines and carboxylic acids. The coupling of amines and carboxylic acids typically consists of activation, deprotection and coupling (Scheme 9). Due to the same terminal functionality, the same strategy used for α-amino acids can be also extended to β-amino acids. Other than the most common method of coupling carboxylic acids with amines, ring-opening of β-lactams as well as Wolff rearrangements have also been utilized. Choosing the appropriate

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coupling method depends on the availability of the β-amino acid, sensitivity of the substitution and protecting scheme.

Scheme 9. Traditional Strategy for peptide coupling
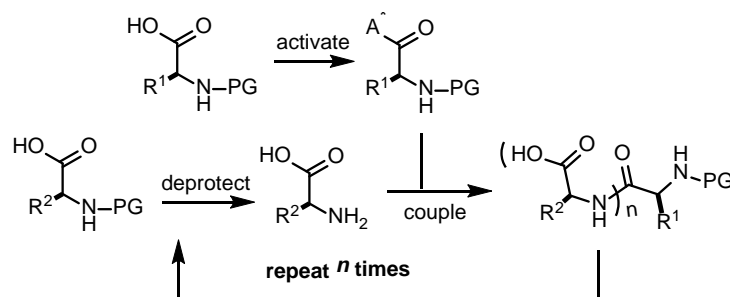
β-Peptide synthesis has been accomplished both in solution and with solid phase. Chung et al. have synthesized a series of β-peptides in solution including a homochiral β-peptide (S) Boc-(β^{3}HPro)$_n$-OBn where n = 18 and heterochiral Boc-[(S)-β^{3}HPro-(R)β^{3}HPro]$_n$-OBn where n = 3. These β-peptides were synthesized via standard coupling reaction conditions with Boc as the nitrogen protecting group and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) as the coupling reagents.[17] β-Peptide synthesis has also been extended to solid phase where there are obvious advantages including ease of reagent removal and no isolation or purification of intermediates. The typical method for solid phase peptide coupling involves the main-chain Fmoc/ side-chain t-butyl protecting scheme which is common in peptide synthesis.[18] Other than the typical strategies for β-peptide synthesis, the Seebach group has also used the Wolff rearrangement conditions to perform peptide coupling (Scheme 10).[19]

Scheme 10. Synthesis of trimer **10** via Wolff rearrangement and typical peptide coupling

14
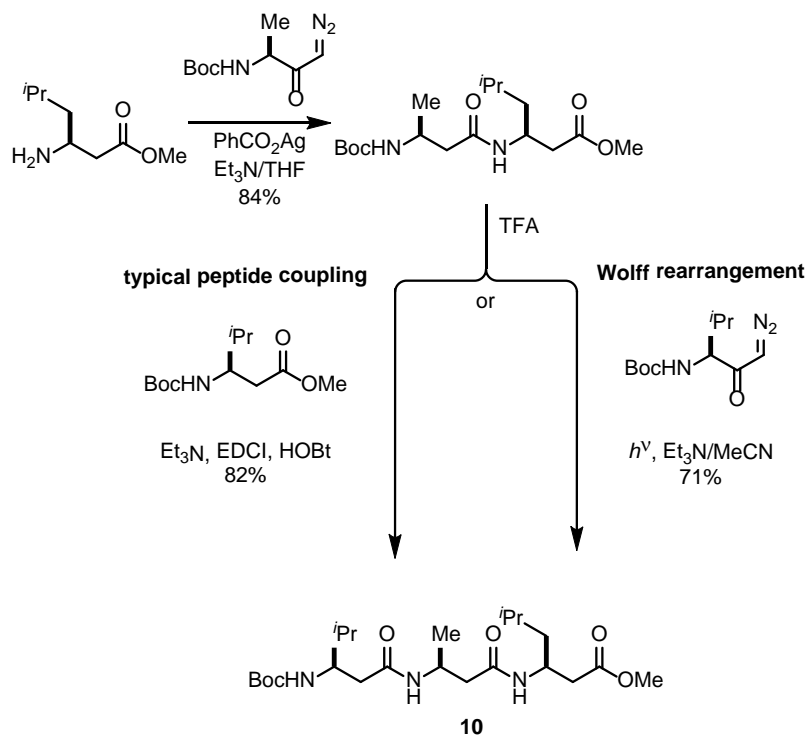
Accessing new β-amino acids and providing a new strategy of β-peptide assembly would allow the synthesis of novel β-peptides. One strategy for improving peptide synthesis is having preactivated amino acids, which would eliminate the activation step present in most standard peptide coupling sequences (Scheme 11).

Scheme 11. Strategy for peptide synthesis with preactivated amino acid
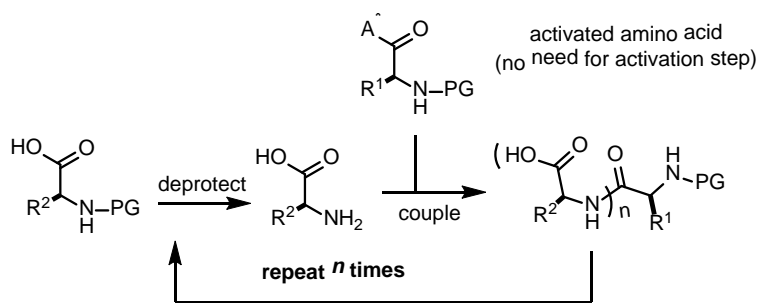
1.3.2 PAST RELATED RESEARCH WITHIN THE GROUP

Acknowledging the need and utility of β-amino acids, research in the Nelson group has provided advances in the asymmetric synthesis of β-amino acid precursors with a variety of functionalization. All of the developed methodologies were based upon Mannich reactions via catalytic asymmetric acyl halide-aldehyde cyclocondensation[20] to form β-lactones (**11**) or acyl halide- imine cyclocondensation to form thiazinones (**12**) (Scheme 11).[21] With the same strategy used for β-lactams, these heterocycles also have the same connectivity as β-amino acids and have proven to be useful building blocks for β-peptide synthesis upon ring-opening.

Scheme 12. Strategy for use of heterocycles synthesized within the group using the acyl halide

aldehyde or acyl halide imine cyclocondensation for β-amino acid synthesis
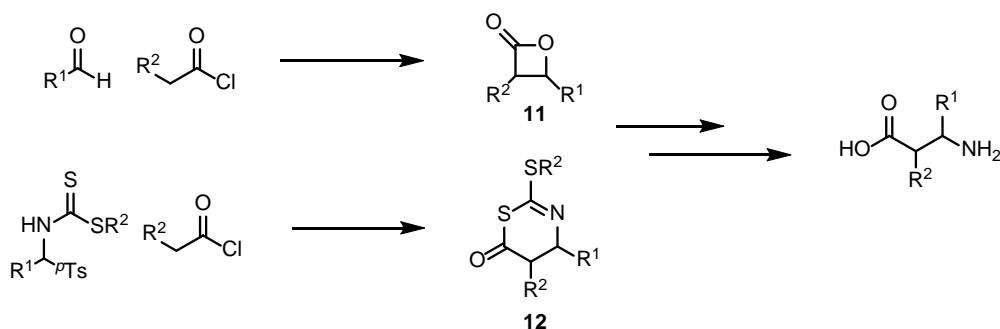
Peptide synthesis utilizing β-lactones has been accomplished with azide ring-opening of

the lactone, reduction to the amine (**13**), followed by standard coupling of amine (**13**) and acid

chloride (**14**), also generated from a ring opened lactone (Scheme 13).

Scheme 13. Coupling of β-amino acids with β-lactones as starting material
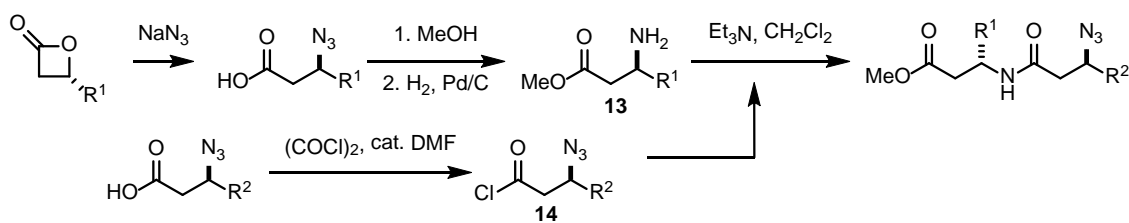
The thiazinone heterocycle, with *syn*-4,5 stereochemistry (**15**, Scheme 14) can also

provide structurally diverse $\beta^{2,3}$-amino acids, which can be utilized as building blocks in β-

peptide synthesis.   Ring-opening of these heterocycles has been previously shown to be

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successful with both an amino acid, (S)-MeO-Val and with a hydride in good yields (Scheme 13). With the successful ring-opening of the thiazinone heterocycles and access to compounds that were very similar to β-amino acids, it was clear that there was great potential for their use in β-peptide synthesis.

Scheme 14. Strategy for synthesis and ring-opening of thiazinone heterocycles
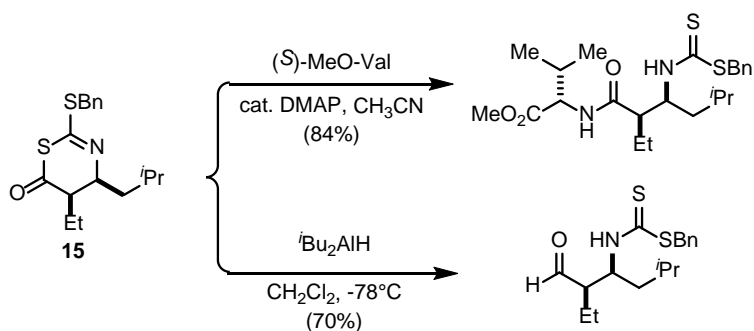
The utility of these thiazinone compounds in β-peptide synthesis can be appreciated when realizing the advantages in this method. These compounds can be synthesized asymmetrically with cinchona alkaloid organocatalysts in good yield and exceptional diastereoselectivity and enantioselectivity. They can also provide a new method of peptide construction where the typical coupling can be avoided and peptide elongation is obtained via ring opening. These enantioenriched highly substituted compounds are superb precursors of β-amino acids.

1.3.3 β-AMINO ACID SYNTHESIS VIA ASYMMETRIC KETENE, IMINE CYCLOADDITIONS

Successful ring-opening and deprotection of the thiazinone heterocycles is critical for their utility in peptide synthesis. Previous work in the group demonstrated that the thiazinones could be successfully ring-opened with an amino acid or hydride as the nucleophile (Scheme 13). With the ultimate goal of these compounds to be used in peptide synthesis, it was also necessary to have a deprotection strategy that supplies the primary amine for future peptide elongation and does not affect the peptide backbone. A protecting group that allows selective, mild and fast deprotection was critical for success of this methodology. We needed to avoid the most common amine protecting groups such as BOC, CBZ, FMOC and Ts, which require strong acids or hydrogenolysis for deprotection. Although there are many alternatives for amine protecting groups, we are also limited by the origin of the protecting group in our substrate, which participates in the cycloaddition reaction. With these limitations in mind and the success of dithiocarbamates in the cycloaddition reaction, we began to investigate strategies for the deprotection of different thiocarbamates. There are multiple thiocarbamates to consider as potential protecting groups on the amine (Figure 5). Assessing the use of thiocarbamates as an activating group in the cycloaddition and as a protection group for the amine was very important for the success in our peptide synthesis methodology.
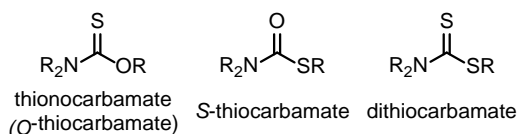
Figure 5. Nomenclature for thiocarbamate groups

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There is no precedent for using a thiocarbamate group as an amine protecting groups in synthesis but these functional groups are observed in biological systems as protecting groups which are metabolized via oxidative processes. In the oxidative metabolism of sulfides in nature, sulfides are oxidized to their corresponding sulfone, **17** (Scheme 15). Dithiocarbamates, **18** are also known to be oxidized to sulfine compounds, **19** which can then be converted to stable disulfide compounds (**20**). The metabolism of thionocarbamate groups where X =O also produced disulfide compounds upon oxidation.[22] Oxidation of these compounds to their corresponding disulfide provides a more electrophilic center allowing for potential hydrolysis and access to the free amine. Taking advantage of the known susceptibility of the thiocarbamate functional groups to oxidation, oxidative deprotection became our strategy.

Scheme 15. Proposed oxidation pathway of dithiocarbamates based on isolated intermediates[22]
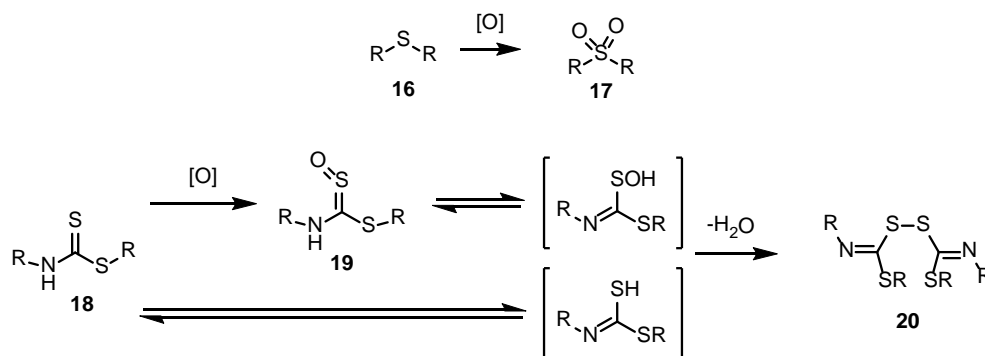
With the known susceptibility of the thiocarbamate functionality towards oxidation, we anticipated that a mild oxidation agent would selectively oxidize the thiocarbamate over other functionality present on the substrate. Upon selective oxidation of the thiocarbamate followed by hydrolysis, we could achieve orthogonal amine deprotection without affecting the peptide backbone. For this purpose, we focused on a mild oxidation agent, Oxone®. No analogous

reactions with Oxone® in deprotection of a dithiocarbamate group were seen in literature; however, there are many examples of Oxone® related oxidations of sulfur.[23-26]

Our initial efforts toward deprotection were focused on the ring-opened products resulting from thiazinones with an inherent dithiocarbamate group. At that time, we had only synthesized the thiazinones with the dithiocarbamate group. All of our attempts to fully deprotect the dithiocarbamate group utilizing Oxone® were unsuccessful; however we did observe the conversion of the dithiocarbamate group to thiocarbamic acid (Scheme 16).

Scheme 16. Unsuccessful deprotection of dithiocarbamate
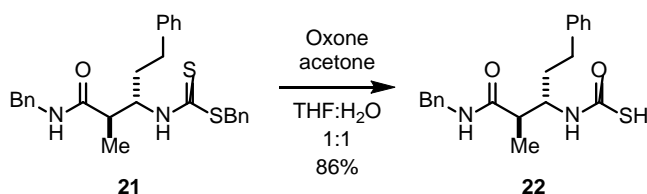
The conversion of the dithiocarbamate present in **21** to **22** with thiocarbamic acid functionality was unexpected and inconsistent with our initial proposed oxidation scheme. We concluded that the thioether was being oxidized instead of the thiocarbonyl on the dithiocarbamate (Scheme 17).

Scheme 17. Proposed oxidation scheme for dithiocarbamate functionality
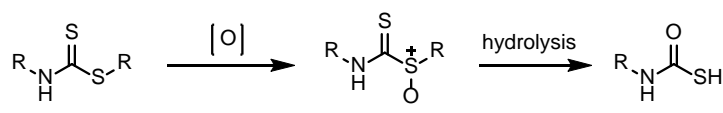
It was necessary to identify a protecting group that would both participate similarly to activate the cycloaddition reaction and be susceptible to the desired oxidative deprotection. Due to the proposed cycloaddition mechanism where the sulfur of the thiocarbonyl functionality participated as a nucleophile in the cycloaddition, we investigated the thionocarbamate group,

(Figure 5). The thionocarbamate group, similar to the dithiocarbamate, is electron withdrawing, activating the nitrogen towards deprotection and imine formation. The nitrogen is also nucleophilic enough to participate in the Lewis acid coordination and nucleophilic addition. As seen in Figure 6, the carbamate group on the amine has a significant role in the cycloaddition reaction. The carbamate group contributes to the acidity of the amine, **23** coordinates with lithium in the transition state, **24** and nucleophilically adds into the activated acid, **25** resulting in the thiazinone cycloaddition products. Although the characteristics of the thionocarbamate group makes it a good candidate for use in the cycloaddition, we also needed to consider its reactivity in the oxidative deprotection reaction.
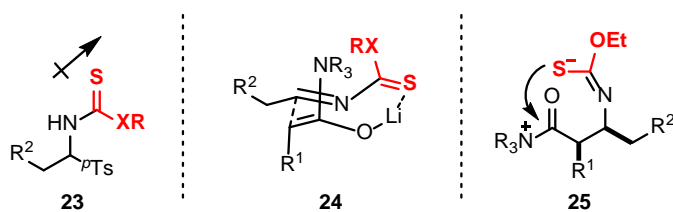
Figure 6. Participation of thiocarbamate functionality on the cycloaddition reaction

Our proposed route of oxidative deprotection (Scheme 17) was still plausible if we could alter the protecting group to favor oxidation at the thiocarbonyl instead of the thioether. Based upon the analysis in Figure 6, the thionocarbamate has the correct functionality to participate in the cycloaddition, and lacked the thioether which was observed to oxidize instead of the desired thiocarbonyl when oxidative deprotection was attempted on the dithiocarbamate (Scheme 18). By changing the dithiocarbamate group on the α-amido sulfones to a thionocarbamate (**23**), we could accomplish this preference for thiocarbonyl oxidation and achieve the fully deprotected product. A model substrate **26** was synthesized to test the success of deprotection of the S-carbonyl thiocarbamate group (Scheme 18).

Scheme 18. Model substrate deprotection
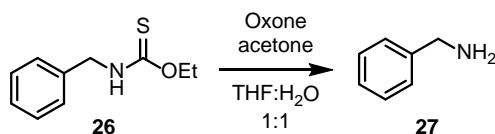
Conversion to the free amine was observed on this model substrate (Scheme 18). This is consistent with our proposed oxidation scheme where the substrate with the thiocarbonyl **26** was oxidized and subsequent hydrolysis resulted in the free amine **27**.

The only difference between the dithiocarbamate and the thionocarbamate functional groups was the presence of oxygen in the place of sulfur (Figure 5). As mentioned previously (Scheme 15), oxidative metabolism of both of these compounds has been shown to result in stable disulfide compounds. Upon hydrolysis of these compounds, the desired primary amines would be obtained. The electronics of the thionocarbamate compared to the dithiocarbamate group would allow the imine **23**, where X=O to successfully undergo the cycloaddition and provide the necessary functionality for oxidative deprotection, making it a superior protecting group for our peptide synthesis methodology.

Scheme 19. β- Amino acid synthesis via thiazinone precursor
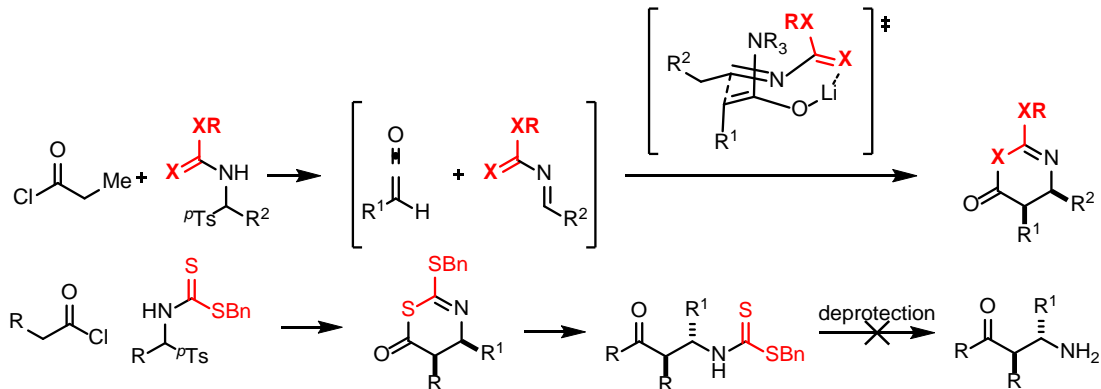
1.4 SYNTHESIS OF THIOCARBAMATE PROTECTED SULFONES AND THEIR USE IN THE CYCLOADDITION

Acknowledging that the thionocarbamate is a good candidate for both the cycloaddition and oxidative deprotection, we began the synthesis of a variety of thiazinones containing the thionocarbamate group on the amine. A series of thionocarbamate-derived α-amido sulfones were prepared and their performance in the cycloaddition was examined. Synthesis of the sulfones was easily accomplished where each of the desired aldehydes was either commercially available or could be synthesized in a short number of steps in high yields. With the ultimate goal to utilize these compounds in peptide synthesis, we designed our substrate scope to mimic naturally occurring amino acid side chains (Figure 7).
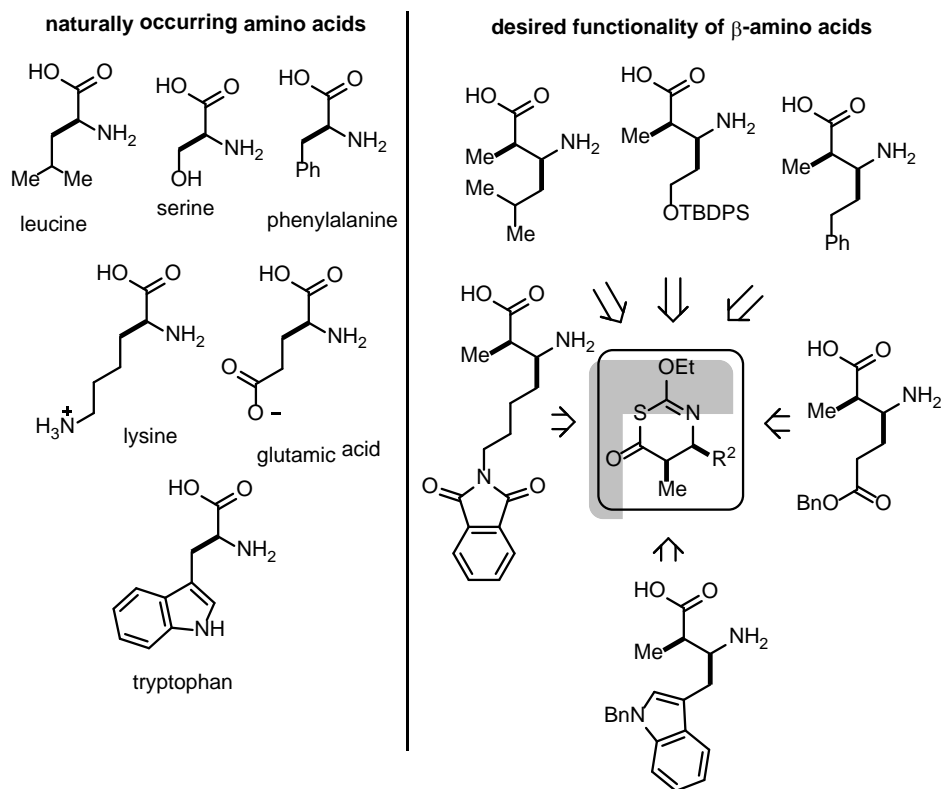
Figure 7. Synthesis of β-amino acid based on side chains of α-amino acids

From a mechanistic perspective, the thionocarbamate group can participate in the cycloaddition reaction similar to the dithiocarbamate group (Figure 8). In practice, however, when running the cycloaddition reaction with the thionocarbamate group on the sulfone, a much less productive cycloaddition was observed with minimal product formation. Further optimization for this reaction with the thionocarbamate was necessary. The difference in reactivity between the thionocarbamate and the dithiocarbamate was attributed to the difference in electronics of these functional groups and their coordination with the Lewis acid which is believed to coordinate with the dithiocarbamate. With a few modifications of the cycloaddition reaction, which included changing the Lewis acid from $LiClO_4$ to LiI (Figure 9) and adding the

acyl chloride portion-wise, we were able to obtain the desired heterocycles in good yield with the

thionocarbamate functionality.
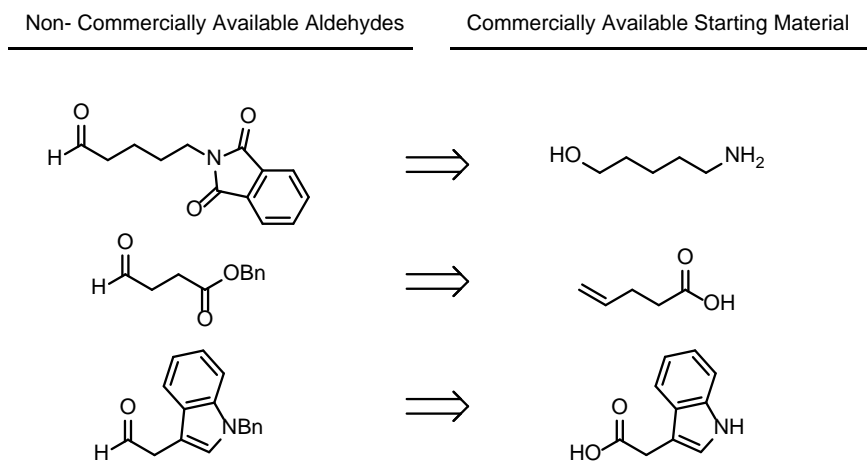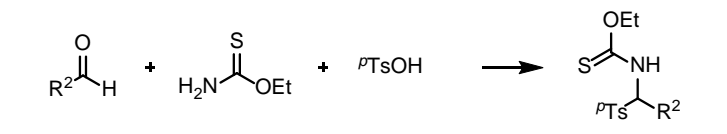
Figure 8. Synthesis of sulfone starting material
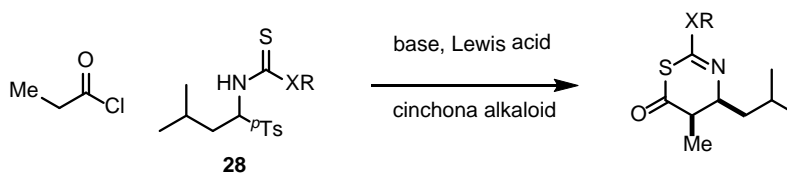
28 (X=)	base	Lewis Acid	yield
S	^{i}Pr$_2$NEt (3.3 equiv)	LiClO$_4$ (3.1 equiv)	74
O	^{i}Pr$_2$NEt (3.3 equiv)	LiI (3 equiv)	79

Figure 9. Optimal Lewis Acid for cycloaddition reactions

Catalysts

TMS-quinine   TMS-quinidine

Yield (%ee)

R²	30	31	combined
A	79(>99)	10 (98)	89
B	46 (94)	38(94)	84
C	54(97)	32(>99)	86
D	56	-	56
E	48(>99)	24(>99)	72
F*	12(>99)	27(>99)	39

* 100% catalyst loading and portionwise addition of 29
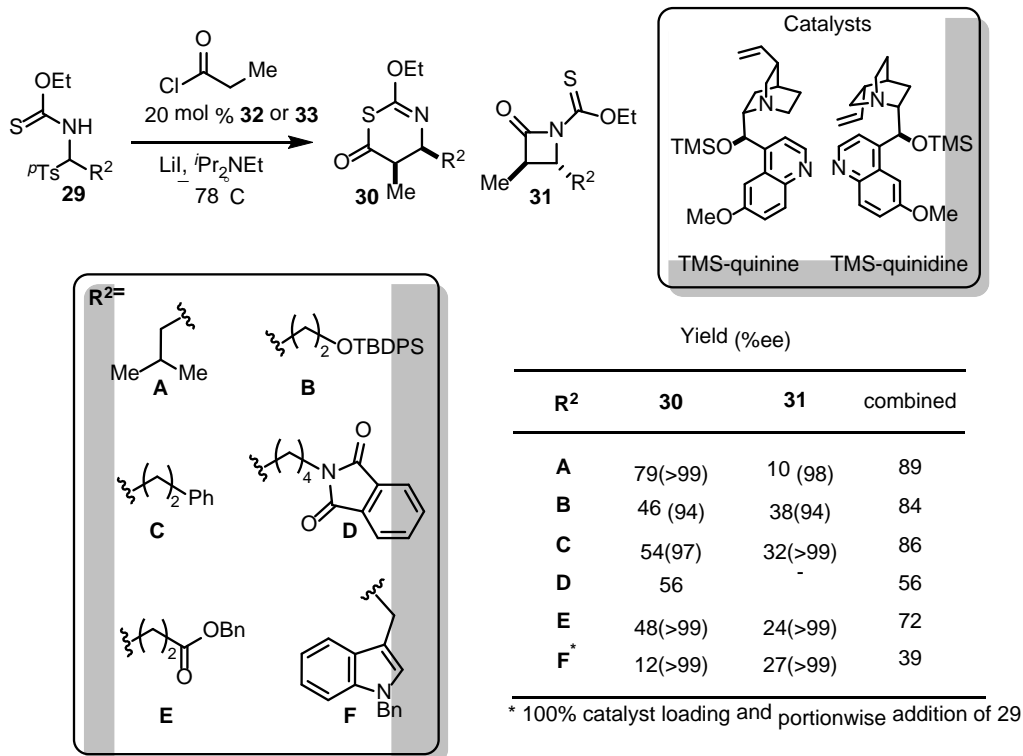
Figure 10. Cycloaddition Results with Thionocarbamate Protection and Amino Acid based

Substitution

With the optimized reaction conditions, different substituents designed to mimic amino acids were subjected to the cycloaddition reaction involving the thionocarbamate. From these series of cycloaddition reactions, it was clear that there were several differences between the thionocarbamate cycloaddition reaction and the dithiocarbamate cycloaddition reaction. The most significant difference between the cycloadditions was the formation of both the thiazinone and β-lactam (Figure 10). Previously, in the dithiocarbamate reaction, only the thiazinone was observed (Figure 11). In the thionocarbamate cycloadditions, thiazinone (**30**) and β-lactam (**31**) were both observed and in different ratios depending on the sulfone substrate (Figure 10). In all cases, with the exception of the indole substituent (Figure 10, Entry F), the thiazinone (**30F**) was

the major product formed. The greatest selectivity in terms of preference for thiazinone formation was with the isovaleryl functionality on the sulfone (Figure 10, Entry A), where the ratio of isolated thiazinone (**30A**) to β-lactam (**31A**) was 8:1. The two different cycloaddition products from the reaction involving the thiocarbamate group also had different relative stereochemistry, where the side groups on the thiazinone were syn and on the β-lactam, they were anti. The product formation and the stereochemistry of these products gave us insight into how the mechanism of the cycloaddition reaction with the thionocarbamate functionality was different from the reaction with the dithiocarbamate functionality.
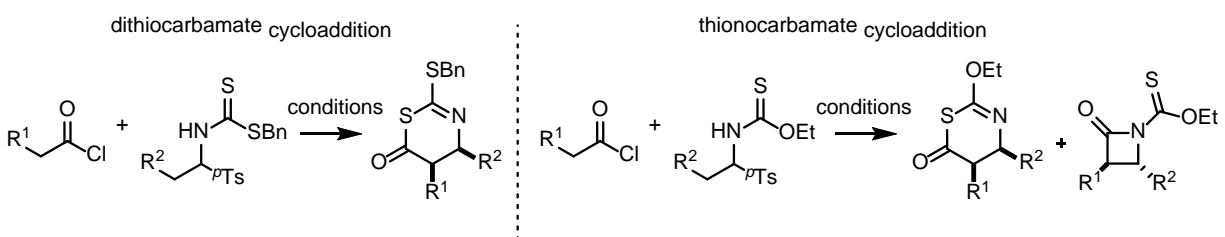
Figure 11. Difference in product formation between the dithiocarbamate and thionocarbamate substrates in the cycloaddition

The difference in product formation upon modification of the carbamate can be rationalized by looking at the proposed mechanism of the cycloaddition in Scheme 19. Both the sulfur and the nitrogen of the thionocarbamate can act as nucleophiles in the cycloaddition. The thiazinone is formed when sulfur acts as the nucleophile and the β-lactam results from addition of the nitrogen into the activated acid. Additionally, it was observed that the thiazinones and β-lactams exhibit different relative stereochemistry about the newly formed bond, whereas the enantioselectivity was consistent in both the thiazinone and β-lactam and R^1 was always *R*. The difference in relative stereochemistry for these two products indicated that the mechanism differed not only by which nucleophile added into the activated acid, but also by the transition

27

state during addition of the enol into the imine. The *anti-* relative stereochemistry of the β-lactam suggested that the ketene added into the opposite face of the imine component **TS2**. Following the enol addition, either the sulfur or the nitrogen of the carbamate can add into the activated acid and produce the thiazinone or β-lactam, respectively (Scheme 19). Based on the observation that the *syn-* products were only seen as the thiazinone and the *anti-* products were only seen as β-lactams, it was evident that the *syn-* organization enforced the conformation for the sulfur addition and the *anti-* organization enforced the conformation for nitrogen addition.

Scheme 20. Proposed mechanism for rationalizing synthesis of thiazinone and β-lactam
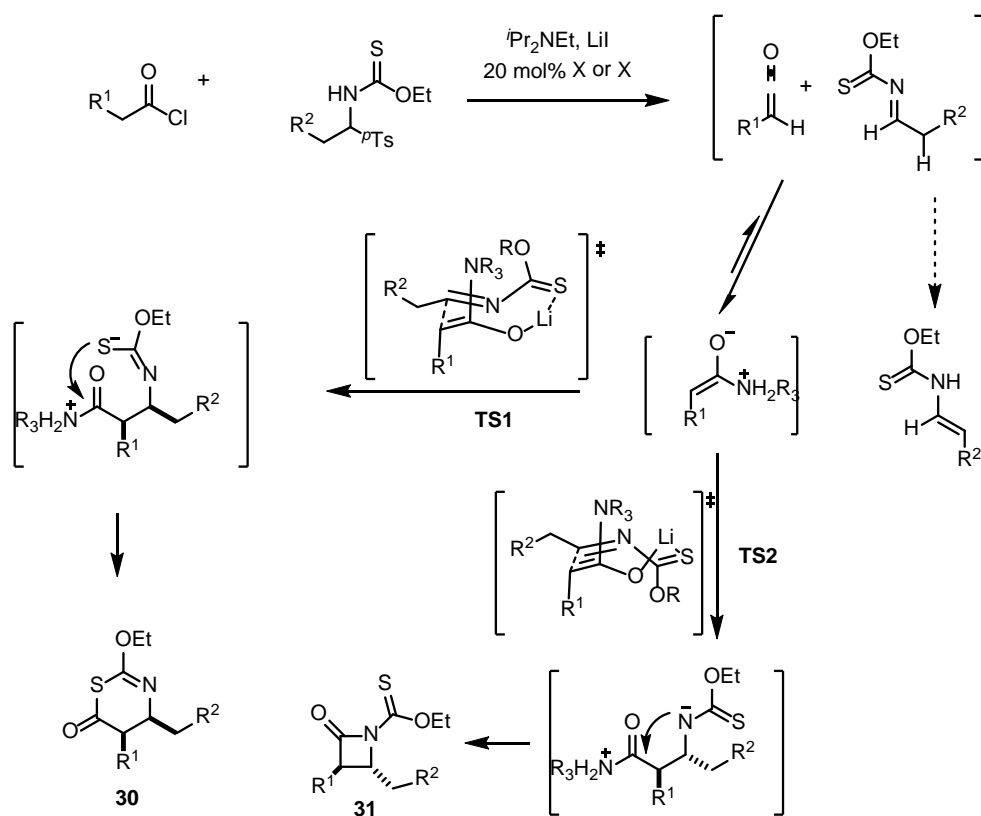
As mentioned previously, the ratio of thiazinone and β-lactam differed for each substrate. The ratio was strongly influenced by the R^2 group on the substrate. An analysis of the proposed cyclocondensation transition states reveals one possible explanation for the substrate-dependent chemoselectivity. The strength of coordination to the Lewis acid in the transition state would differ between the dithiocarbamate and the thionocarbamate. The participation of the Lewis acid in the cycloaddition was demonstrated to be necessary when in order to achieve the cycloaddition reaction with the thionocarbamate sulfone instead of the dithiocarbamate, we needed to change the Lewis acid from $LiClO_4$ to LiI. Due to the electronic difference between the dithiocarbamate and the thionocarbamate, LiI, a stronger Lewis acid than $LiClO_4$ was needed to aid in coordination with the carbamate in the transition state. There would be a tighter coordination with the dithiocarbamate than the thionocarbamate and therefore greater energy difference between the two proposed transition states, **TS1** and **TS2**, providing a definite preference for *syn* stereochemistry leading to the thiazinone. This preference was reflected in the isolated thiazinones having exclusively *syn-* stereochemistry.

The proposed transition state, leading to the *syn*-stereochemistry of the thiazinone is a chair-like, closed transition state **TS1** where the lithium Lewis acid can coordinate to the oxygen of the enol and the sulfur of the thionocarbamate. The formation of the thiazinone, **30** containing the dithiocarbamate group participates in the same transition in the formation of the thiazinone with *syn*-stereochemistry. The transition state leading to the anti-stereochemistry **TS2** found on the β-lactam, **31** suggests that the enol would add to the other face of the imine. When the substituents on the imine were more remote, such as in entries B-E (Figure 10) where there were at least 2 methylenes between the reactive center and the bulky functionality, it was observed that approximately 50% of thiazinone and 30% of β-lactam was isolated. In the case of entry A

containing an isovaleryl group, 79% isolated yield of thiazinone with *syn*-stereochemistry and 10% isolated yield of β-lactam with *anti*-stereochemistry was obtained. There was a clear preference for transition state **TS1**, leading to the *syn*-diastereomer and thiazinone formation.
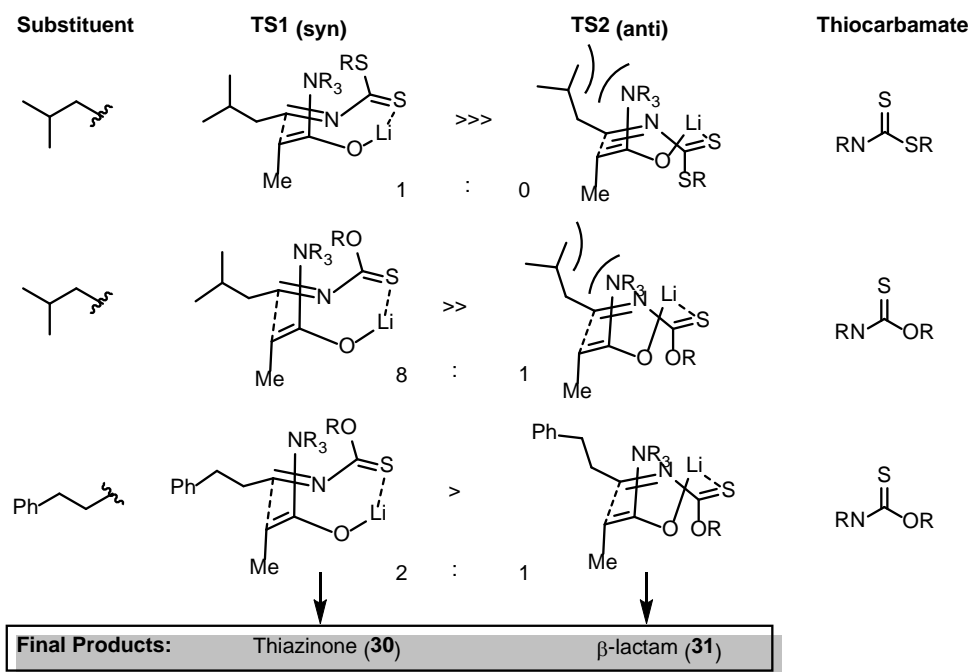
Figure 12. Syn- vs Anti- orientation in transition state for different side chains and thiocarbamates

Out of the substituents utilized in the cycloaddition reaction, the indole substituent (Table 1, Entry F), was the only example where there was more isolated β-lactam than thiazinone. Unfortunately, the combined yield of both of the cycloaddition with the indole substrate was only 39%, indicating the sensitivity of the substrate which complicated the analysis of the preferred transition state based on isolated product distribution. The combined yield of 39% was obtained after further modification of the cycloaddition reaction for this sensitive indole substrate. Under the initial cycloaddition reaction conditions that were used for the other substrates, the combined isolated yield when using the indole sulfone, **29F**, was only 30% which

consisted of a 3:1 ratio of enamine to thiazinone (Figure 10, Entry F). The formation of a large

amount of enamine was attributed to the high acidity of the α-proton on the imine. The indole, in

conjugation with the anion, stabilizes the intermediate leading to the enamine (Scheme 21). The

indole substrate is very reactive to the basic conditions which led to unproductive side products

such as enamine formation and decomposition. The production of a large amount of enamine

when the sulfone contained the indole functionality was unique in the cycloaddition reactions,

where most of the sulfones contained alkyl groups or other remote functionalities did not lead to

a significant amount of enamine formation. Because the enamine formation prevented

productive cycloaddition, this sensitive functionality required a modified procedure.

Scheme 21. Enamine formation of indole substituent
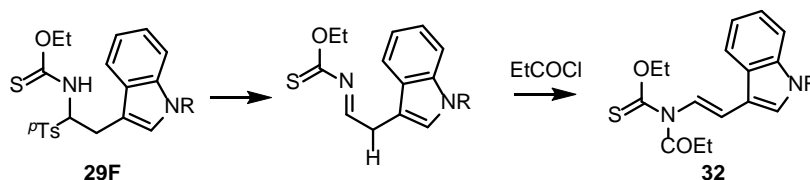
1.5 MODIFICATION OF THE CYCLOADDITION REACTION DUE TO

SENSITIVITY OF INDOLE CONTAINING SUBSTITUENT

In efforts to improve the cycloaddition reaction with the indole substrate and to avoid

enamine formation, it was necessary to facilitate the reaction with the imine intermediate and

prevent unproductive tautomerization leading to enamine. Any additional time that the

unreacted imine is present in the reaction mixture is a potential opportunity for tautomerization

or other unwanted side reactions leading to decomposition to occur. From the proposed

mechanism (Scheme 22), the cinchona alkaloid catalyst plays a critical role in the desired reaction of the imine. It is believed that the cinchona alkaloid adds into the ketene to form an enolate, **34** which can then add into the imine, **37**. The increase of the cinchona alkaloid catalyst would result in more of the reactive intermediate **34**, facilitating the desired reaction with the imine and interrupting the tautomerization process. When the amount of cinchona alkaloid catalyst was increased to 100%, as seen in Table 2, the isolated yield of cycloaddition products increased from 8% to 18% and the amount of isolated enamine decreased from 22% to 18%. Although a slight improvement in yield was observed with the increase of cinchona alkaloid catalyst, further optimization was still required to improve the 34% combined isolated yield.

Scheme 22. Mechanism of Indole substrate in the cycloaddition reaction
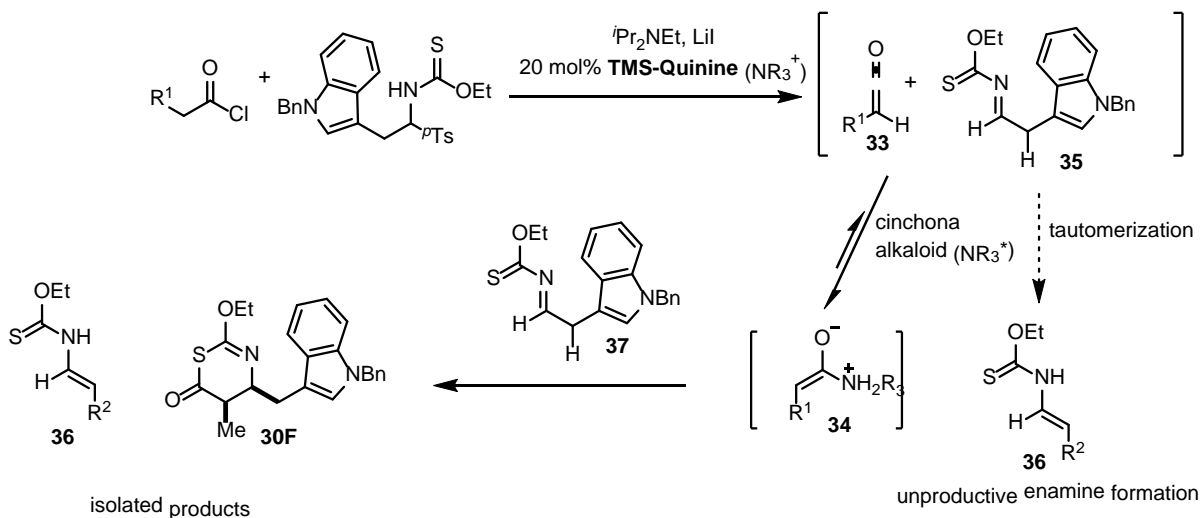
The cycloaddition reaction involving the indole sulfone required more optimization when considering that the total amount of isolated compounds including the enamine and both cycloaddition products never exceeded 34%. Based on the isolated products from the reaction, approximately 60% of the sulfone starting material resulted in unidentified decomposition

products. To decrease the amount of time that the sensitive unreacted imine was present in the reaction, the sulfone, **29F** was added portion-wise to the solution. Combined isolated yield of enamine and cycloaddition products rose from 34% to 81%. Although a large amount (18%) of enamine was still isolated, there was a marked improvement in the reaction where 20% of thiazinone and 43% of β-lactam was obtained as productive cycloaddition products. The portion-wise addition of the sulfone dramatically increased the amount of desired products, **30F** and **31F**. There was not a large amount of unidentified sulfone decomposition products as seen in the previous reactions. The optimized addition procedure for the cycloaddition reaction with the indole substrates (Figure 13), can be extended to the use of other sensitive substrates that are found to quickly tautomerize in the cycloaddition reaction conditions. Although the optimized method was procedurally intensive, the portion-wise addition of the sensitive sulfone starting material dramatically increased the success of the reaction.
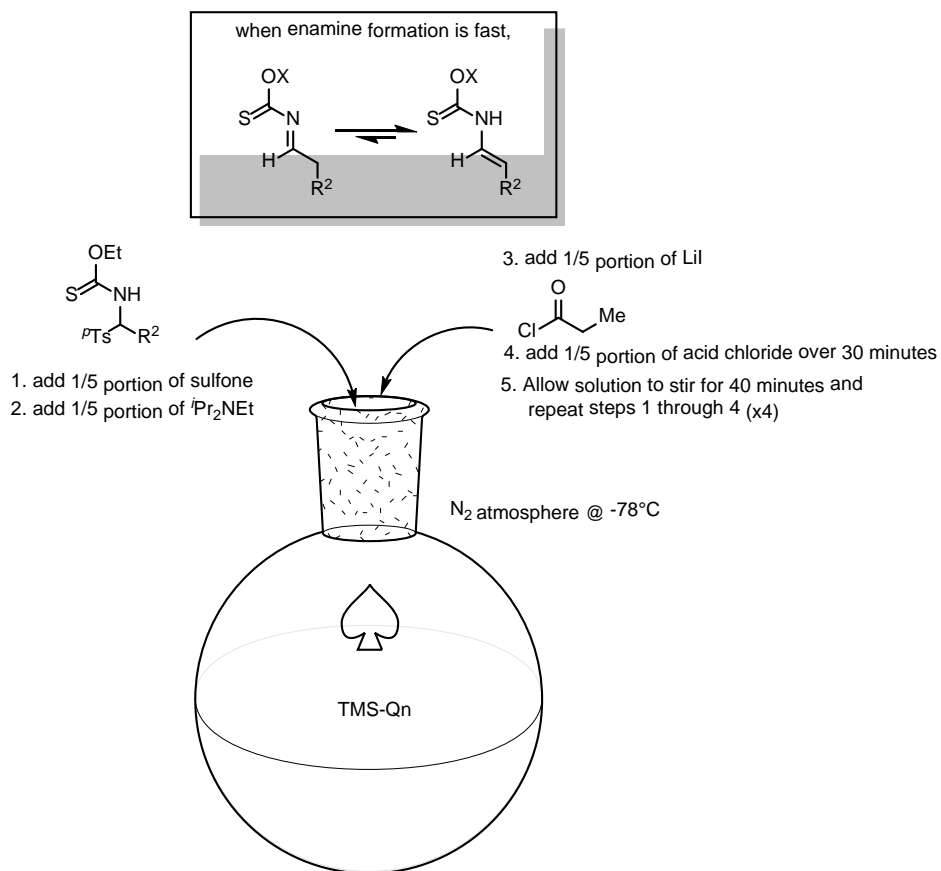
Figure 13. Optimized procedure for compounds with fast tautomerization

For the cycloaddition reactions involving a sulfone that quickly tautomerizes to an unproductive enamine compound, an optimized procedure was developed where the amount of cinchona alkaloid catalyst was increased and the sensitive sulfone was added portion-wise. This new procedure was developed with the indole substrate and the most dramatic increase in yield occurred when the sulfone was added in multiple small portions. With the significant amount of isolated enamine (18%) persisting throughout these improvements, another method of modifying the indole substrate to decrease enamine formation was examined. Modification of the protecting group on the indole provides an opportunity to attenuate the acidity of the α-proton. Modification of the protecting group on the nitrogen affects the electron density of the nitrogen

therefore also affecting the contribution of the nitrogen to the conjugated system. A small screen was run with different protecting groups on the indole nitrogen. Electron rich protecting groups such as benzyl and allyl performed better in the reaction and the isolated yield of the thiazinone and β-lactam was 50% or greater. With electron withdrawing groups on the indole nitrogen, such as tosyl, only enamine was isolated in 22% yield and no cycloaddition products were observed. The CBZ protecting group on the nitrogen only resulted in β-lactam in 22% yield (Table 1).

Table 1. Cycloaddition results with the indole substituent with different protecting groups and reaction conditions
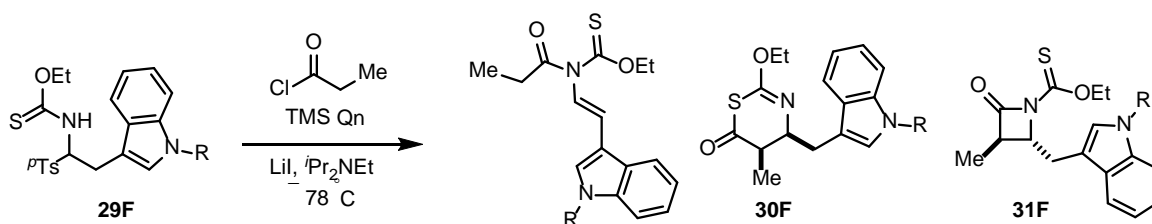
Reaction conditions[a]	R=	enamine	thiazinone (**30F**)	β-lactam (**31F**)	combined isolated yield
A	Bn	22%	8%	-	30%
B	Bn	16%	6%	12%	34%
C	Bn	18%	20%	43%	81%
C	CBZ	21%	-	22%	43%
C	Ts	24%	-	-	24%
C	allyl	16%	17%	29%	62%

[a.] Reaction conditions: A = standard reaction conditions; B = 100% TMS Qn;
C = 5 portions of 1, 5 portions of ^{i}Pr$_2$NEt, 100% TMS Qn

Overall, electron- donating groups on the indole nitrogen were found to give more amounts of cycloaddition products than electron- withdrawing counterparts. The difference in reactivity we observed with the different protecting groups on the amine correlated well with the predicted sensitivity of the compound due the acidity of the α-proton. The electron withdrawing groups on the nitrogen of the indole would make the α-proton more acidic and facilitate deprotonation and tautomerization to the enamine. Electron donating groups would provide more electron density to the α-proton and destabilize the anion leading to enamine formation. The electron rich benzyl protecting group on the nitrogen of the indole was found to be superior in the cycloaddition reaction with the greatest combined isolated yield of 81%. In this cycloaddition reaction, tautomerization to enamine only contributed 18% of sulfone conversion. The electron rich benzyl protection group succeeded in decreasing the sensitivity of the indole sulfone. The final optimized conditions for the indole sulfone involved 100% cinchona alkaloid, portion- wise addition of sulfone and a benzyl protecting group on the nitrogen of the indole.

2.0 PEPTIDE SYNTHESIS UTILIZING THIAZINONE AND BETA-LACTAMS

Diversity is a key component of peptide synthesis. The diversity found in peptides originates from the structure and stereochemistry found in the amino acids that construct the peptides. With increased structural and stereochemical diversity of amino acids, it is possible to synthesize peptides with desired characteristics. Similar to most organic compounds, desirable characteristics for peptides include solubility, stability and diversity of functionalization. Although α-peptides have the same backbones as β-peptides, their conformational preference and the secondary structure they adopt is significantly different. This conformational difference has major implications on solubility and biological activity of peptides. The ability to control not only the substitution pattern, but also the relative and absolute stereochemistry of the β-peptide building blocks would provide the diversity that is critical for the synthesis of unnatural peptides with the desired characteristics.

Scheme 23. Ring-opening of heterocycles in the formation of β-amino acids
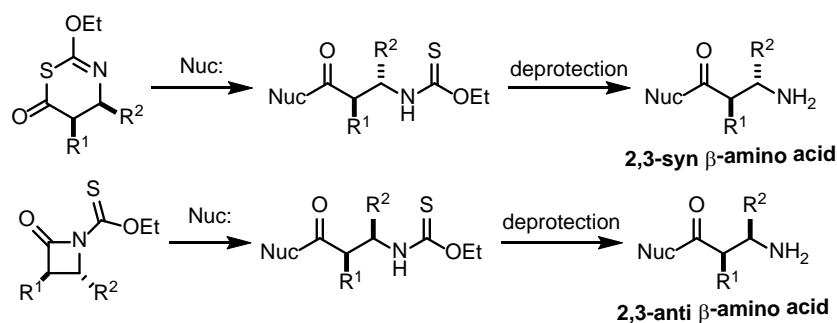
In our synthesis of β-amino acid precursors, two different heterocycles, the thiazinone and β-lactam, were obtained from the cyclocondensation reaction. These compounds have different relative stereochemistry and are also easily separable via routine column chromatography. Upon ring opening and deprotection, the thiazinones provide 2,3-*syn* β-amino acid while the β-lactam affords 2,3-*anti* β-amino acids (Scheme 23) which can both be incorporated into peptides. The ability to synthesize and ring open a variety of thiazinones and β-lactams and achieve their respective β-amino acids would significantly add to the diversity available in synthetic peptides and peptidomimetics.

2.1 METHOD DEVELOPMENT OF RING-OPENING REACTIONS

Dithiocarbamate thiazinones have been successfully ring opened via addition into the thioester carbonyl functionality on the heterocycle by both amino acid and hydride nucleophiles (Scheme 14).[27] The addition into the thiazinone heterocycle is very favorable due to the increased electrophilic nature of the thioester compared to standard esters or ketones. The increased electrophilic nature of the thioester can be attributed to the relatively poor orbital overlap of the large sulfur to carbon compared to the better matched overlap between oxygen and carbon of the analogous ester[28]. Accordingly, the thiazinones emerge from the cyclocondensation reactions preactivated for ring-opening with a variety of nucleophiles. Although β-lactams do not contain the electrophilic thioester functionality, they are also inherently activated towards nucleophilic ring opening at their amide bond linkage due to the ring strain that is released upon ring opening. With both of our synthesized amino acid building blocks preactivated towards ring opening and the importance of ring opening in our ultimate goal

of peptide synthesis, we anticipated that both of the products of our cycloaddition reaction would be exceptional precursors for β-amino acid synthesis.

To further investigate the electrophilic properties of the thiazinone and β-lactam compounds towards nucleophilic ring opening, we examined the success of the ring opening reaction with a variety of nucleophiles. Secondary and primary amines were found to effect ring opening of the thiazinones in exceptional yields of 88-98%. Additionally, methanol was also found to be an effective nucleophile and provided the ring opened products in 90-96% yield. From these investigations, it was clear that we were not limited in our use of nucleophile and both the thiazinone and β-lactam would perform well in a variety of ring opening reactions which are necessary in the initial ring opening and elongation of the peptide.

Another important quality of our compounds and their use in peptide synthesis is their ability to be deprotected. As discussed previously, the dithiocarbamate group from the ring opened dithiocarbamate thiazinones was not successfully oxidatively deprotected. With the modification of the dithiocarbamate group to a thionocarbamate group, the oxidative deprotection was successful using oxone as a mild oxidant. When the thionocarbamate was treated with Oxone, the primary amine, **27**, was obtained in near quantitative yields, regardless of the functionalization of the thionocarbamate. With both the ring opening and deprotection reactions developed, these reactions could be utilized in an iterative fashion towards the synthesis of $\beta^{2,3}$-peptides. (Scheme 24).

Scheme 24. Proposed iterative β-peptide synthesis with thiazinones as β-amino acid precursors
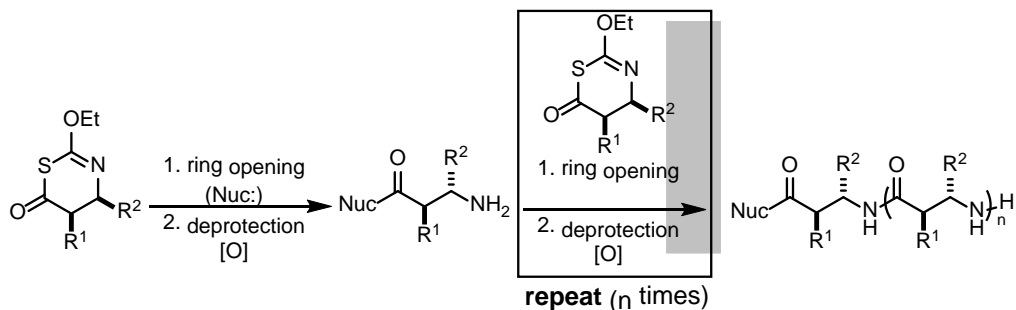
Like most organic reactions, it was found that the solubility of the substrate had a major effect on the success of both the ring opening and deprotection reactions. To optimize the solubility of the substrate without affecting the stereochemistry or substitution on the amino acid backbone, the functionality on the *C*-terminus was modified. The functionality of the *C*-terminus originates from the nucleophile which is used to ring open the first thiazionone as seen above in Scheme 23. Methanol was used as the first nucleophile and was maintained throughout the synthesis on the *C*-terminus as a methylester. In changing the initial nucleophile, we could modify the solubility of the peptide while not affecting the stereochemistry or substitution on the amino acid backbone. The dimers in Scheme 25 were synthesized via the methodology seen in Scheme 24 to investigate the effect of the C-termini functionality on the solubility of the substrate. Due to the observation that insolubility problems arose at the dimer level, the success of deprotection of the dimers was compared (Scheme 25). As seen in the results of the deprotection reaction of each of the synthesized dimers, there was a major difference in reaction success depending on the *C*-termini and solubility of the substrate (Scheme 25).

Scheme 25. Solubility effects on deprotection reaction success
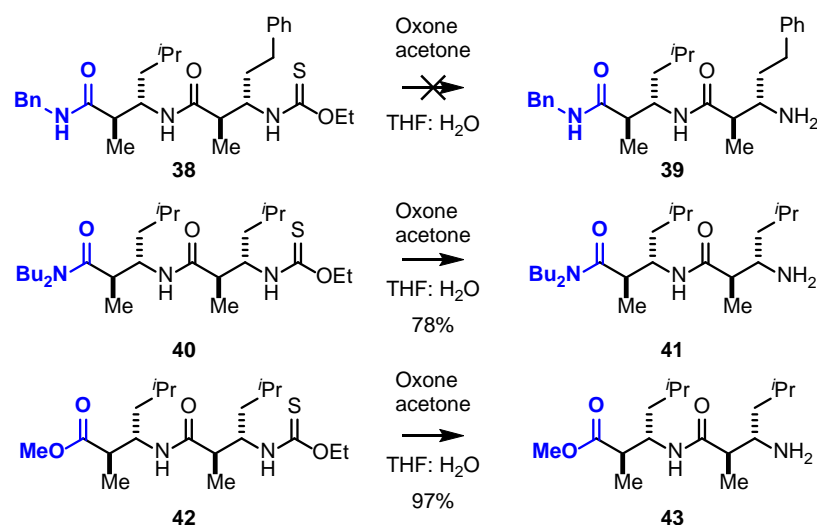
It was observed that the success of the reaction was directly related to the solubility of the substrate. When a benzylamide was present on the *C*-terminus of the dimer, the starting material, **38** was insoluble in the aqueous THF solution. The insolubility resulted in a lack of reactivity. When the starting material **38** was subjected to the deprotection conditions, no reaction was observed. Due to previously successful deprotection reactions on compounds with very similar functionality, the lack of reactivity was assigned to the insolubility of the starting material. Insolubility of the benzyl amide, **38** was not surprising due to the tendency of benzylamides to aggregate and form highly organized crystalline structures.[29] Anticipating that an N,N-dialkyl amide would exhibit enhanced solubility in common organic solvents compared to the benzyl amide, a dibutyl amine was used as the initial ring opening nucleophile in the synthesis of dimer **40**. Dimer **40**, with the dibutyl amide on the *C*-terminus was then tested in the deprotection reaction. As expected, the more soluble dimer **40** performed much better in the deprotection reaction, where 78% yield of desired deprotected dimer **41** was obtained compared

to 0% of deprotected dimer **39**. Increased solubility of **40** was not only observed through the much improved yield of the deprotection reaction but also could be seen visually in the reaction solution, where most of the starting material was soluble in the aqueous THF solution. Due to the heterogeneity of the reaction solution which contained the insoluble reagent, Oxone, it was difficult to visually determine the solubility of the starting material. Although the dimer with the dibutyl amide *C*-terminus performed much better in the reaction than the dimer with the benzyl amide on the *C*-terminus, we had previously found the deprotection reaction to be near quantitative in reactions where the starting material was completely soluble.

Fixing the solubility issue and obtaining better yields in the ring opening and deprotection reactions was critical for the success of synthesizing peptides past the dimer stage. In the previously discussed dimers **38** and **40**, the solubility issues originated from the nature of the rigid polyamide backbones and potential hydrogen bonding between molecules. Although these characteristics are present in all peptides, we synthesized dimer **42** where the methyl ester functionality on the *C*-terminus would avoid the potential hydrogen bonding of an amide bond. When subjected to the same deprotection condition on the dimer with the methyl ester on the C-terminus, the deprotected product was obtained in 97% yield. Dimer **42** was much more soluble that the previous dimers and an overall better candidate for peptide synthesis. Changing the nucleophile to modify the functionality of the terminus greatly affected the solubility of the peptides and their subsequent success in future reactions. Peptides possessing methyl ester termini were found to exhibit superior solubility in the reaction conditions and performed better in the reactions. The methyl ester at the *C*-terminus is also easily saponified to the carboxylic acid which is the functionality typically used in traditional peptide synthesis. With the conversion of the *C*-terminal methyl ester to a carboxylic acid, our peptides can be incorporated

into traditional peptide synthesis schemes, particularly into peptidomimetics when it is desired to install a β-amino acid into an α-peptide. For these reasons it was determined that the methyl ester was superior to the amide for use in our reactions and for application into traditional peptide synthesis.

With the methyl ester determined as the preferred functionality on the *C*-terminus, our methodology based upon reiterative ring opening and deprotection reactions (Scheme 26) was utilized to accomplish highly complex and functionalized β-peptides. To show the capability of this methodology towards the synthesis of diverse β-peptides, we synthesized a variety of β-peptides consisting of either 3 or 4 β-amino acids with varying backbone substitution and stereochemistry. Using our optimized ring opening and deprotection procedures (Schemes 26 & 27), the peptides, (**49, 51 & 53**) were efficiently synthesized. In the synthesis of **49**, yields of the deprotection reaction using Oxone in an aqueous THF solution were good and within the range of 73-97%, with the exception of the deprotection of the tetramer which was a low 57%. The ring opening reactions in the synthesis of **51**, using the same methodology as the synthesis of **49,** were consistently high yielding where the yields ranged from 90-93% except one low yield of 53% yield in the ring opening to synthesize the trimer. The low yield of this ring opening is attributed to the insolubility of the protected trimer of this series and the difficulty in its isolation and purification.

Although both of our synthesized thiazinones and β-lactams can be used as β-amino acid precursors, only thiazinones were utilized in the synthesis of peptides (**49,51&53**). The substitution on the peptide backbone is not affected by the choice β-amino acid precursor as they both have the same substitution, but the stereochemistry between them does differ. The thiazinone has *syn*-stereochemistry, resulting in the *syn*-β-amino acid stereochemistry seen on the

peptides (**49,51&53**). If β-lactams, with *anti*-stereochemistry were used, they would result in *anti* β-amino acid stereochemistry upon ring opening.

Scheme 26. Peptides synthesized in solution (yields in parentheses are after ring-opening and deprotection steps)

$$\begin{Bmatrix} \textbf{45}(66\%); \ \textbf{46}(91\%); \\ \textbf{50}(56\%); \ \textbf{51}(69\%) \end{Bmatrix}$$
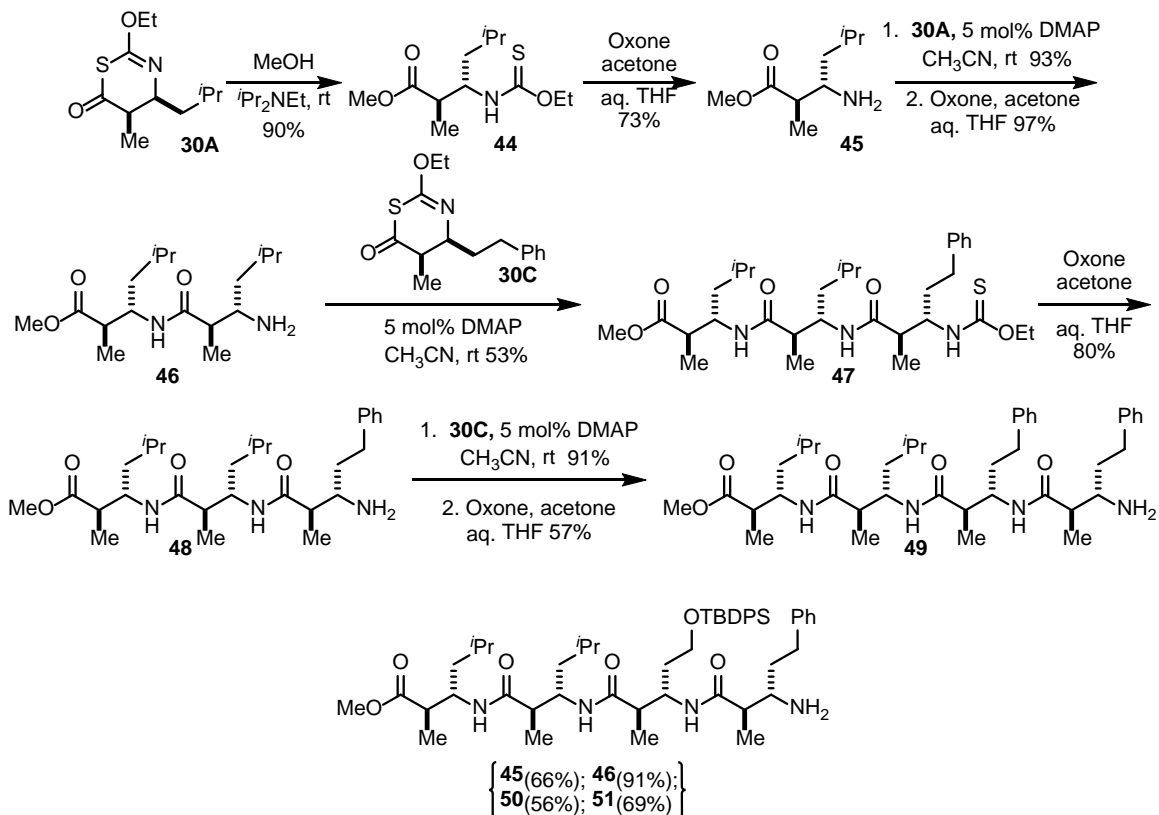
Peptide **53** was only extended to 3 β-amino acids due to the sensitivity of the indole substituent when subjected to the oxidative deprotection conditions (Scheme 27). Upon exposure of the indole containing peptide to the oxidative deprotection reaction conditions, many undesired side products were observed in the crude reaction mixture including many of which were debenzylated. It is suspected that the electron-rich nitrogen of the indole was susceptible to undesired oxidation. Other substrates which did not contain the indole did not exhibit this

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sensitivity. The inability to utilize the oxidative deprotection on peptide **53**, which contained the indole substituent prevented any further ring openings with this peptide and thus was not extended past the trimer.

Scheme 27. Synthesis of peptide with indole functionality
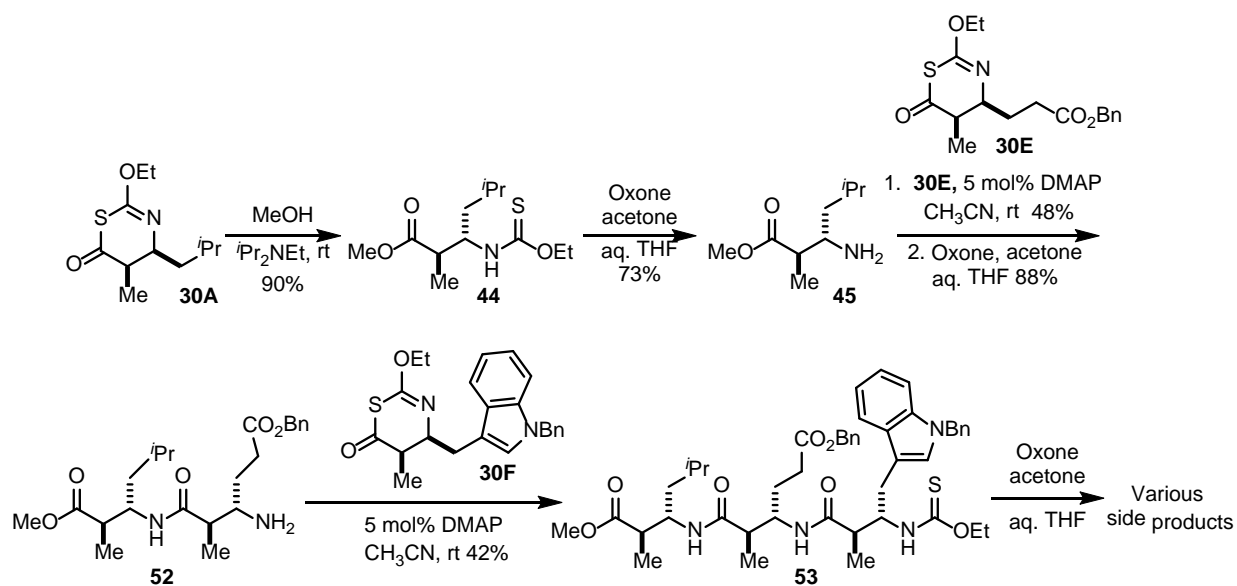
The presence of the methyl ester instead of the amide bond at the *C*-terminus of the peptide was advantageous not only for solubility reasons as discussed previously, but also for purposes of incorporating our amino acids and peptides into traditional peptides. The methyl ester can be easily converted into a carboxylic acid via saponification. Traditional peptide coupling reactions involve the reaction of an amine and a carboxylic acid and with the conversion of the methyl ester to a carboxylic acid, our peptides can also be utilized in this traditional peptide coupling manner. Compatibility with traditional peptide synthesis provides an easier way to incorporate these compounds seamlessly in a traditional peptide synthesis scheme as well as allowing for convergent synthesis of peptides instead of growing the peptide chain

sequentially. The convergent synthesis of a tetramer was performed where two dimers were synthesized via our ring-opening and deprotection scheme followed by saponification of one of the methyl ester **54** to obtain acid **55** in 96% yield, and traditional coupling with deprotected dimer, **46** to obtain tetramer **56** in 65% yield.

Scheme 28. Utility of synthesis of methyl ester β-peptides in standard peptide coupling reactions
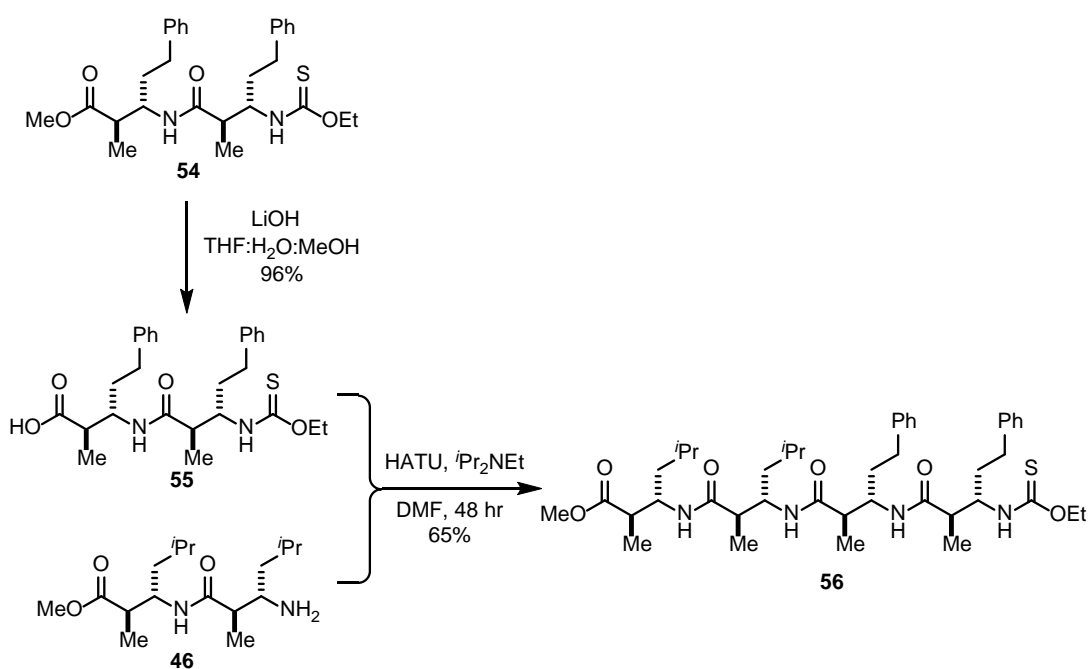
As demonstrated by the various peptides synthesized, the developed ring opening and deprotection reactions were very amenable to peptide synthesis in solution. We accomplished what we had initially intended which was to develop an efficient method for the de novo synthesis of highly functionalized β-peptides with high enantiopurity. As previously discussed, the methyl ester termini can be converted to a carboxylic acid which can then be used in

traditional peptide coupling between amino acids as demonstrated in Scheme 28. This methodology is potentially most useful in the context of peptidomimetics where incorporation of a β-amino acid with a peptide is desired. In our synthesis of peptides (**49,51&53**), the only problems we encountered were due to insolubility and substrate sensitivity which arose when the β-peptide was extended to four amino acids and contained other highly oxidizable functionalities. The design of our methodology to utilize our building blocks to be easily ring-opened and deprotected has proven to be very successful and allowed for the synthesis of multiple β-peptides that can also be easily utilized in the context of typical peptide synthesis and peptidomimetics.

2.2 SOLID SUPPORT SYNTHESIS OF PEPTIDES

Due to the iterative design of peptide synthesis which is conducive to automation, as well as the difficulty in purifying peptides, it is not surprising that most peptide synthesis is done on solid support. There are many advantages to solid support synthesis such as ease of operation and purification. Solid support synthesis provides the ability to remove all reagents and by-products in solution by rinsing of the solid support beads. Furthermore, there is no isolation and purification of intermediate compounds needed. Although our β-amino acid precursors are unique and require different coupling and deprotection reaction conditions relative to traditional peptide coupling between amino acids with carboxylic acid and primary amine termini, the similar iterative design makes our method very amenable to solid support peptide synthesis. Performing our ring-opening based β-peptide synthesis on solid support was an obvious

extension for our methodology where it would make our reactions significantly more efficient and convenient.

Scheme 29. β-Peptide synthesis on solid support
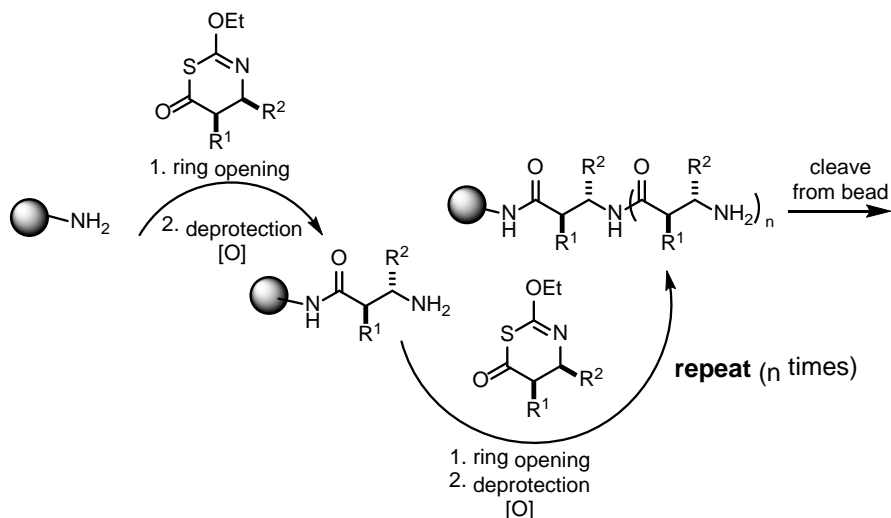
The general scheme for peptide synthesis on solid support is identical to the scheme for solution phase peptide synthesis. In the general scheme, amide peptide bonds are formed via the coupling of amines with activated acids. Although the scheme is identical, modifying certain reaction conditions for the solid support peptide synthesis is necessary. For example, the solvent of the reaction must be changed to accommodate for the solvation and swelling of the solid support bead, allowing proper mixing and reacting. The solid support that was used in our solid support synthesis was the NovaPEG rink resin (Figure 14) which has relatively uniform swelling properties across a range of solvents including very polar solvents such as water, DMF, DMSO and acetonitrile with swelling of 11, 9, 8 and 6 (mL/g) respectively[30].
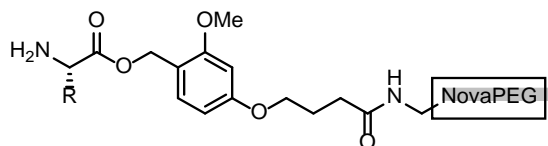
Figure 14. NovaPEG rink resin used in solid support

Acetonitrile, which is the solvent utilized in the solution phase ring opening reactions has a much smaller swelling capability than DMF, where acetonitrile is 6 mL/g and DMF is 9 mL/g. For this reason, DMF was used as the solvent in the solid support ring opening reactions. Our deprotection reactions in solution were run in a solution of aqueous THF. In the analogous solid support reaction, we utilized dioxane instead due to the higher boiling point of dioxane considering the possibility that heating of the reaction may be desired. Matching the desired polarity for the success of the reaction as well as the necessary swelling of the solid support bead, we determined the appropriate solvents to be DMF for the ring opening reaction and aqueous dioxane in the deprotection reaction.

Different from typical peptide coupling reactions found in most solid support peptide synthesis, we needed to develop reaction conditions to accommodate our methodology of ring opening and deprotection reactions on solid support. Solid support reaction conditions that were conducive to loading the first residue on the bead required the use of a resin with a free amine. Utilizing the NovaPEG rink resin, we began to investigate conditions in which this solid support could add into our thiazinone or β-lactam precursors. It is also critical in solid support reactions that there is 100% reaction completion before the next step. Inefficient solid support coupling reactions lead to a variety of peptide fragments which would be difficult to separate from the desired peptide where all of the amino acids had added successfully. Accordingly, it was essential to identify optimal reaction conditions that provided complete reaction.

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We began our solid support synthesis with similar reaction conditions used in solution, where the reaction was run at room temperature for 17 hours in a DMF solution. After cleavage of the monomer off of the bead, only 56% of the cleaved monomer was isolated (Table 2, Entry A). In order to improve the yield and reaction efficiency, microwave irradiation, which has been previously utilized in solid support β-peptide synthesis[1], was also explored. Based upon typical peptide coupling between primary amines and activated carboxylic acids, we utilized standard microwave conditions that were previously successful for solid-phase peptide synthesis on β-peptides with our thiazinones.[31] Accordingly, the reaction conditions involved the addition of the solid support, thiazinone, DMAP and DMF, irradiating the solution up to 40ºC and holding at that temperature for 4 minutes (Table 2, Entry A). Unfortunately, we obtained only a 37% isolated yield of desired product from this method after cleaving the monomer from the bead. In order to cleave the product off the solid support, a 95% TFA solution was added. After appropriate mixing, the solution was filtered off and concentrated to afford the final product. Purity of the isolated product off of the resin was verified by NMR Even with higher temperatures and longer times, the maximum yield of cleaved product was only 46% (Table 2, entries C & D). The yields obtained from these experiments, where the highest yield of isolated product was found to be 56%, are unacceptable for solid support peptide synthesis, especially when considering the need for complete reaction of the free amine. It was necessary to determine whether the low yield was due to the coupling reaction or the process of cleaving the product from the bead.

Table 2. Solid Support Coupling using Microwave Conditions
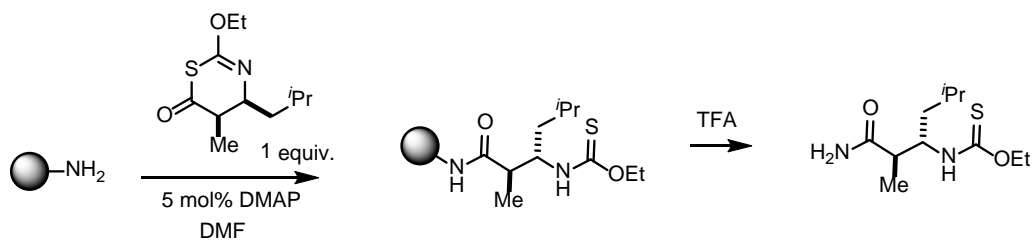
Entry	Reaction Conditions	TLC After Coupling	% yield of X
A	Room temperature 17 hrs	No starting material observed	56%
B	microwave ramp to 40°C hold 4 min	starting material present	37%
C	microwave ramp to 70°C hold 10 min	starting material present	46%
D	microwave ramp to 70°C hold 20 min	starting material present	46%

In order to study the success of both the ring opening and cleavage reactions in the solid support peptide synthesis, we needed to develop a new method to analyze these reactions. Although yields are frequently useful for determining conversion and success of reactions, in solid support reactions isolated yields represent multiple steps including cleaving the final product from the solid support. It was necessary to determine the success of the ring opening independent of the cleavage reaction. For more evidence of the success of the ring opening reaction, TLC's were taken after each reaction. The β-amino acid precursors, the thiazinone and β-lactam are both UV active and the loss of these compounds upon reaction with the amine could be monitored via TLC. The product, which would consist of the protected amino acid on the bead would not be soluble and would not be observed on the TLC. This difference in UV activity of the starting material and product would provide a method to monitor and analyze the success of the ring opening reaction. Upon complete reaction there would be no remaining UV active starting material. Interestingly, in the reaction that was run at room temperature where 56% of the cleaved product was obtained, reaction completion was confirmed when no UV

active starting material was observed by TLC. If this reaction was complete as the TLC suggested, the cleavage reaction should provide near quantitative yield. It was evident that the cleavage reaction needed to be optimized, where a reaction that was observed to be complete by TLC only provided a 56% yield of cleaved isolated product.

A: Starting Material
B: Reaction Solution
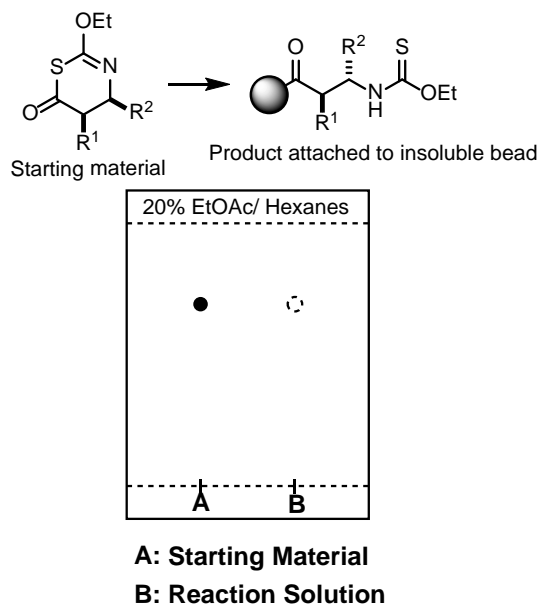
Figure 15. Analysis of Reaction Through Monitoring loss of Starting Material on TLC

Other than the qualitative method of monitoring the reaction progress via TLC, it was necessary to also quantitatively analyze the success of the reaction. We selected gas chromatography for this purpose since it was determined to be the most appropriate method to observe the progress of this reaction via loss of starting material. To the acetonitrile solution with solid support was added naphthalene, DMAP and thiazinone (Scheme 30). At specified time points, a very small aliquot of the solution was removed from the sample and analyzed via GC using naphthalene as an internal standard. To determine the consumption of thiazinone, the ratio of naphthalene to thiazinone was calculated. It was determined through these experiments that 80% of the reaction was completed in the first 5 hours followed by a slower reaction where

by 15 hours, the reaction had completed. It was evident that the reaction was occurring immediately upon addition of the substrate and initially proceeded at a fast rate, but the extended time was necessary to ensure complete reaction. After optimization of the ring-opening reaction in the solid support peptide synthesis which involved lengthier reaction time at room temperature and excess thiazinone (5 equiv.), we achieved the monomer in 81% yield after cleaving (Scheme 31).

Scheme 30. General Scheme for GC Experiment
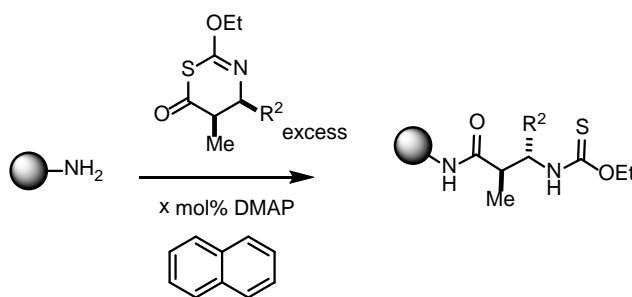
Scheme 31. Cleavage of product off of solid support with TFA
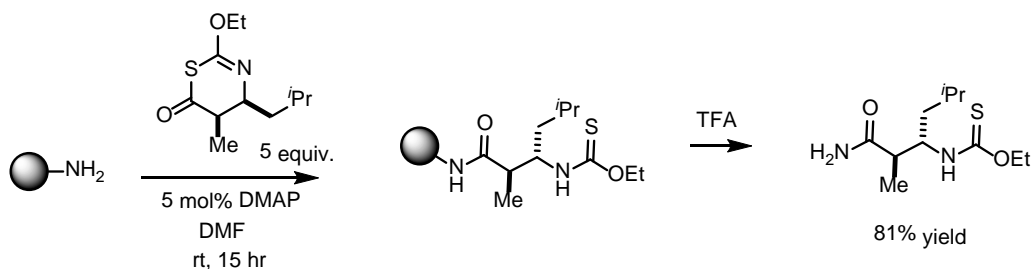
At this point, we have achieved successful ring opening and cleavage on the solid support. However, to elongate the chain, it was necessary to also accomplish deprotection on the solid support in order to allow for subsequent coupling reactions. We needed to verify that our thionocarbamate deprotection conditions were compatible with solid phase synthesis. Investigating the deprotection reaction was more difficult than the ring opening. As it was

difficult to monitor the deprotection reaction using conventional methods (TLC, GC, etc.) we adopted a protocol where the deprotected material was used directly without quantification. We chose to run the deprotection reactions and instead of cleaving to see the amount of deprotection, continue with the coupling reaction. Due the high efficiency we observed in the solution phase, we believed the deprotection would work similarly well in the solid support reactions. Indeed, our original reaction conditions did prove effective requiring only a change of solvent to achieve maximum yields. Thus, a mixture of dioxane and water was used. The preceding investigations led to the following optimized procedure that was used to make **57**, **58** & **59** (Figure 16). Although we were unable to isolate the deprotected monomer after cleavage, it was clear from the high yields obtained from the solid support synthesis of the trimers (96% and 87%) and tetramer (53%), the deprotection reactions were successful (Figure 16). The yields of trimers were much greater than the tetramers. This is believed to be caused by the increased insolubility observed as the length of the peptide increased. Consistent with the efficiency provided in the use of solid support instead of solution phase, we observed much higher yield (53%) in the solid support synthesis of peptide **59**, whereas only 23% of very similar peptide **56** was obtained from synthesis in solution (Figure 17).
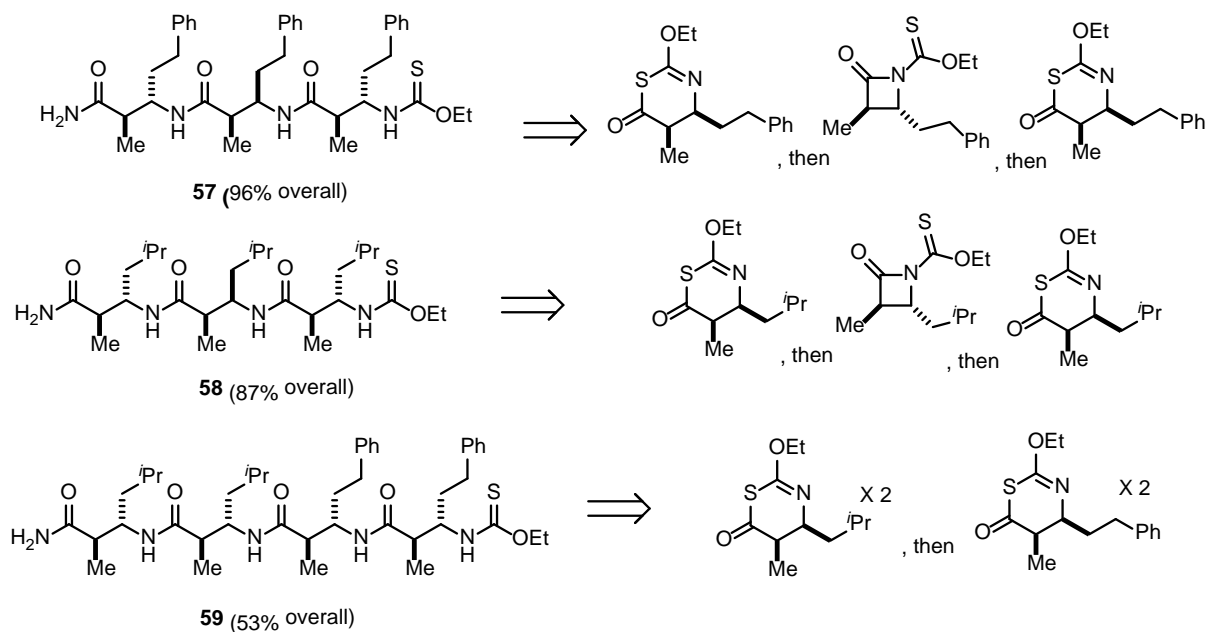
Figure 16. Peptides synthesized on Solid Support

Figure 17. Comparison of yields for solution vs. solid support

With the increased yield observed and operational efficiency of our methodology on solid support, it was important for us to be able to incorporate our synthesized peptides into traditional peptide synthesis to allow for use in peptidomimetics. As seen in Figure 16, the products from the solid support which result from the cleavage of the compounds from the rink amide resin resulted in primary amide functionality. Unable to use these primary amides directly in peptide

synthesis, a method was desired to convert a primary amide into a carboxylic acid, but would not affect the thionocarbamate on the amino terminus of the molecule. Sodium nitrate was found to do just that, where 62% of the desired carboxylic acid **60** was obtained (Scheme 32). The successful conversion of the primary amide to the carboxylic acid allows for the solid support products to be utilized in future peptide coupling and peptidomimetics.

Scheme 32. Hydrolysis of primary amide
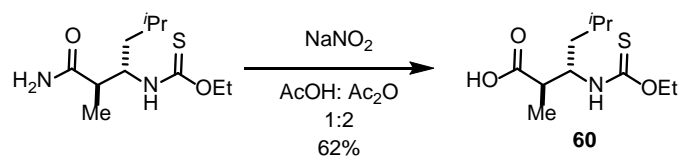
2.3 SYNTHESIS OF GAMMA AMINO ACIDS VIA WOLFF REARRANGEMENT

With successful synthesis of a variety of $\beta^{2,3}$-amino acids, we decided to extend our methodology to the synthesis of disubstituted γ-amino acids. The Wolff rearrangement has been used with great success to synthesize β-amino acids from α-amino acids via rearrangement of a diazoketone.[19] This homologation could also be applied to easily ring-opened heterocycles, such as the thiazinone and β-lactams. β-lactams have been shown to undergo ring expansions to γ-amino acids with reaction of β-lactams with trimethylsilyldiazomethane[4]. Ring-opening of our heterocycles with trimethylsilyldiazomethane provided the diazoketone in modest yields, which was then subject to the silver catalyzed Wolff rearrangement. The protected γ-amino acid was isolated in 41% yield and with the stereochemistry maintained (Scheme 33). This process gives us access to even greater diversity of unnatural highly substituted amino acids.

Scheme 33. Synthesis of γ-amino acids via the Wolff rearrangement
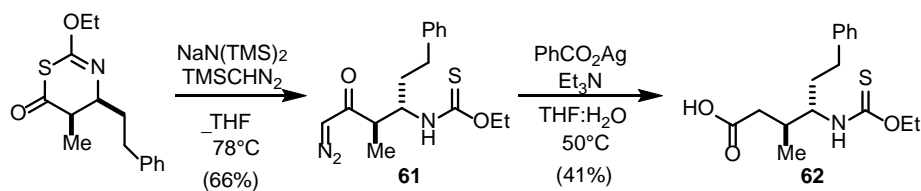
3.0   CONCLUSION

Due to the increased interest in β-amino acids and β-peptides for use in peptidomimetics and the limited number of naturally occurring β-amino acids, it is necessary to develop methodology to synthesize these compounds efficiently and with much variability. Many of the methods of β-amino acid synthesis are based on the Mannich reaction, whereby an enolate adds into an imine to form the correct connectivity and substitution while also allowing for diversity of stereochemistry and side chains. Many of the reactions developed to do just that have a limited substrate scope. We successfully developed an asymmetric cycloaddition reaction to synthesize heterocycles as masked β-amino acids. These compounds were synthesized with amino acids in mind where the substituents on these β-amino acid precursors mimicked the substitution patterns on natural amino acids. Ring-opening and deprotection reactions were developed and allowed for synthesis of multiple peptides in solution and on solid support. The products of these reactions in solution and on solid support can also participate in traditional peptide coupling reactions and will add much more versatility in the synthesis of peptidometics.

4.0   EXPERIMENTAL

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D$ (c [g/100 mL], solvent). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 or -500 as indicated, with chemical shifts reported relative to residual C**H**Cl$_3$ (7.26 ppm), C**H**$_3$OD (3.30 ppm), or pyridine-*d5* (8.74) for ^{1}H and **C**DCl$_3$ (77.0 ppm), **C**D$_3$OD (49.2), or pyridine-*d5* (150.4) for ^{13}C NMR spectra. Most compounds bearing an *O*-ethyl carbamothioyl group exist as a mixture of atropisomers in solution; where possible, ^{1}H NMR integration values were attributed to either the major (R^1) or minor (R^2) atropisomer, or a mixture of both, based on the atropisomer ratio. Analytical chiral gas-liquid chromatography was performed using a flame ionization detector and split mode capillary injection system with a Chirasil - Dex CB column (25 m x 0.25 mm) (Advanced Separation Technologies Inc.). Helium was used as the carrier gas. Analytical high-performance liquid chromatography (HPLC) was performed using a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Chiracel OD-H column and HPLC-grade isopropanol and hexanes as the eluting solvents. Melting points are uncorrected.

All reactions run using General Procedure B were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents.   All reactions run using General Procedure F were carried out in disposable

polypropylene reaction vessels (syringe with a frit) fitted with a leur slip cap. NovaPEG Rink

Amide Resin was purchased from Novabiochem. Washes and filtrations were done via vacuum

after removal of the leur slip cap. Anhydrous solvents (CH_2Cl_2, THF, DMF, diethyl ether,

pentane, and toluene) were obtained by passage through successive alumina and Q5 reactant-

packed columns on a solvent purification system. DIPEA was distilled under a nitrogen

atmosphere from CaH_2. *O*-Trimethylsilylquinine and *O*-trimethylsilylquinidine,[32] and 3-(*tert*-

butyldiphenylsilyloxy (propionaldehyde)[33] were prepared according to literature procedures.

Propionyl chloride was distilled before use. Column chromatography was performed on EM

silica gel 60 (230-240 mesh).[34]
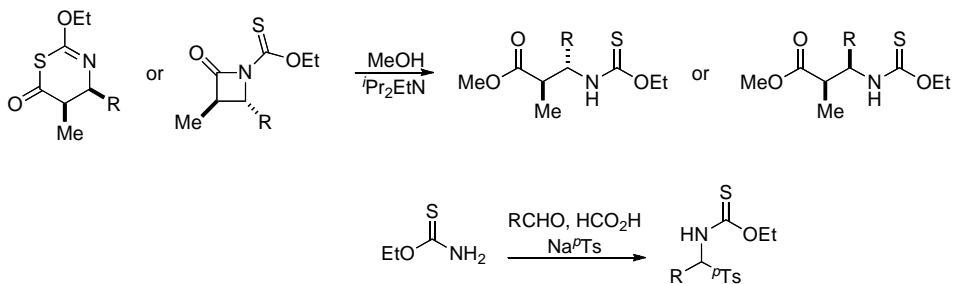

General Procedure A: Preparation of α-Amido Sulfones (29a-f): *O*-Ethyl

carbamothioate (1 equiv) and sodium *p*-toluenesulfinate 1.2 equiv) were suspended, with stirring,

in water (110 mL). The aldehyde and ~98% formic acid (6.9 equiv) were added, and the reaction

was stirred vigorously at room temperature. After 48 h, the reaction was processed in the

indicated manner.
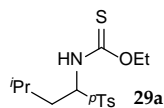
O-Ethyl 3-methyl-1-(p-tosyl)butylcarbamothioate (29a): General Procedure A was followed using 10 g of *O*-ethyl carbamothioate (95 mmol, 1 equiv) and 11.5 mL of isovaleraldehyde (110 mmol, 1.2 equiv). The reaction was filtered, and the resulting solid was washed with water and pentanes, yielding 25 g (80%) of the title compound as a white powder. mp 100-113 °C; IR (thin film): 3298, 2959, 2871, 1597, 1521, 1468, 1444, 1372, 1303, 1258, 1201, 1142, 1085 cm^{-1}; 1H NMR (400 MHz, CDCl$_3$) Atropisomer ratio: 2:3 (R^2:R^1) δ 7.81 (d, *J* = 8.0 Hz, 1.4H (R^2)), 7.77 (d, *J* = 8.4 Hz, 2H (R^1)), 7.36 (d, *J* = 8.4 Hz, 1.4H (R^2)), 7.30 (d, *J* = 8.0 Hz, 2H (R^1)), 6.85 (br d, *J* = 9.6 Hz, 0.6H (R^2)), 6.54 (d, *J* = 10.4 Hz, 1H (R^1)), 5.74 (dt, *J* = 11.6, 3.2 Hz, 1H (R^1)), 5.05 (dt, *J* = 11.6, 3.2 Hz, 0.7H (R^2)) 4.35-4.18 (m, 2.75H (R^1 + R^2)), 3.88-3.80 (m, 0.7H (R^2)), 2.43-2.42 (m, 5.3H (R^1 + R^2)), 2.09-1.96 (m, 1.8H (R^1 + R^2)), 1.86-1.70 (m, 3.5H (R^1 + R^2)), 1.20 (t, *J* = 6.8Hz, 3H (R^1)), 1.00-0.96 (m, 10.5H (R^1 + R^2)), 0.89 (d, *J* = 6.4 Hz, 2.2H, (R^2)); ^{13}C NMR (100 MHz) δ 190.9, 189.3, 145.3, 145.1, 133.7, 133.6, 129.8, 129.6, 129.5, 129.5, 72.7, 70.9, 68.1, 67.0, 35.0, 34.5, 24.7, 24.6, 23.3, 23.1, 21.7, 21.7, 21.6, 20.9, 14.0, 13.5; HRMS (ES) *m/z* calcd for C$_{15}$H$_{23}$NO$_3$NaS$_2$ (M+Na)$^+$: 352.1017; found: 352.1048.
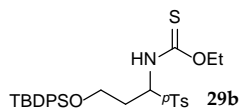
O-Ethyl 3-(t-butyldiphenylsilyloxy)-1-(p-tosyl)propylcarbamo-thioate (29b): General Procedure A was followed using 8.45 g of *O*-ethyl carbamothioate (25.7 mmol, 3.3 equiv) and 2.42 g of 3-(*tert*-butyldiphenylsilyloxy) propionaldehyde (7.8 mmol, 1 equiv). After 48 h, 50 mL of methylene chloride was added, the layers were separated, and the organic portion was dried and concentrated. The residue was triturated with diethyl ether and pentane, yielding 3.66 g (84%) of the title compound as a white solid. mp 121-124 °C; IR (thin film): 3301, 2957, 2931, 2858, 1711, 1596, 1521, 1472, 1428,

1375, 1316, 1203, 1145, 1109 cm^{-1}; 1H NMR (400 MHz, CDCl$_3$) Atropisomer ratio: 0.9:1 (R^2:R^1) δ 7.83 (d, J = 8.4 Hz, 2.0H, (R^1)), 7.78 (d, J = 8.0 Hz, 1.9H (R^2)), 7.68-7.62 (M, 6H (R^1 + R^2)), 7.59-7.56 (m, 2.1H (R^1 + R^2)), 7.45-7.35 (m, 14.3H (R^1 + R^2)), 7.31 (d, J = 8 Hz, 2H (R^1)), 6.92 (d, J = 10.8 Hz, 0.9H (R^2)), 6.86 (d, J = 10.8 Hz, 1H (R^1)), 6.00 (ddd, J = 14.0 9.2, 3.6 Hz, 0.9H (R^2)), 5.49 (dt, J = 10.4, 3.2 Hz, 1H (R^1)), 4.32 (m, 1.8H (R^1 + R^2)), 4.14 (dq, J = 10.4, 6.8 Hz, 1H (R^1)), 3.98-3.83 (m, 2.3H (R^1 + R^2)), 3.81-3.76 (m, 3H (R^1 + R^2)), 2.59-2.46 (m, 1.7H (R^1 + R^2)), 2.45-2.44 (m, 6H (R^1 + R^2)), 2.09 (app ddd, J = 18.4, 8.8, 4.4, 1H (R^1)), 1.82 (dddd, J = 13.6, 6.4, 3.6, 3.6 Hz, 1H (R^1)), 1.23 (t, J = 7.2 Hz, 3H), 1.03-1.03 (m, 17H (R^1 + R^2)), 0.92 (t, J = 7.2 Hz, 3H) ^{13}C NMR (100 MHz) δ 190.9, 189.7, 145.3, 145.2, 135.6, 135.5, 135.5, 135.3, 134.0, 134.0, 133.0, 132.9, 132.7, 129.9, 129.9, 129.8, 129.8, 129.8, 129.7, 127.8, 127.7, 127.7, 72.1, 69.4, 68.3, 67.0, 59.8, 58.7, 30.0, 29.5, 26.7, 26.7, 21.7, 21.6, 19.1, 19.0, 14.0, 13.3; HRMS (ES) m/z calcd for C$_{29}$H$_{37}$NO$_4$NaSiS$_2$ (M+Na)$^+$: 578.1831; found: 578.1835.

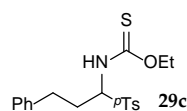**O-Ethyl 3-phenyl-1-(p-tosyl)propylcarbamothioate (29c)**: General Procedure A was followed using 10.0 g of O-ethyl carbamothioate (95 mmol, 1 equiv) and 14 mL of hydrocinnamaldehyde (106 mmol, 1.1 equiv). The reaction was filtered, and the resulting solid was washed with water and pentanes, yielding 31.6 g (88%) of the title compound as a wet white solid. IR (thin film): 3303, 3026, 2982, 2930, 2865, 1598, 1519, 1453, 1374, 1304, 1204, 1144, 1084, 1059 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) Atropisomer ratio 0.9:1 (R^2:R^1) δ 7.75-7.72 (m, 3.9H (R^1 + R^2)), 7.34-7.28 (m, 7.8H (R^1 + R^2)), 7.24-7.12 (m, 8.3H (R^1 + R^2)), 6.68 (d, J = 10.8 Hz, 0.9H (R^2)), 6.43 (d, J = 10.8 Hz, 1H, R^1), 5.74 (dt, J = 3.6 Hz, 1H, R^1), 4.88 (dt, J = 3.6 Hz, 0.9H, R^2), 4.36-4.24 (m, 2H, R^1), 4.18-4.09 (m, 1H, R^2), 3.80 (dq, J =

10.8, 7.2 Hz, 0.9H, R^2), 2.96-2.88 (m, 1H), 2.84-2.56 (m, 6.8, (R^1 + R^2)), 2.43 (app s, 6H (R^1 +

R^2)), 2.20-2.01 (m, 3H (R^1 + R^2)), 1.22 (t, J = 7.2 Hz, 3H (R^1)), 0.90 (t, J = 7.2 Hz, 2.8H (R^2));

^{13}C NMR (100 MHz, CDCl$_3$) δ 191.2, 189.5, 145.2, 145.2, 139.9, 139.0, 129.7, 129.6, 128.5,

128.5, 128.4, 128.4, 128.2, 126.5, 126.3, 73.6, 71.2, 68.0, 67.0, 31.3, 31.1, 28.5, 27.5, 21.6, 21.5,

14.0, 13.3; HRMS (ES) m/z calcd for C$_{19}$H$_{23}$NONaS$_2$ (M+Na)$^+$: 400.1017; found: 400.1052.
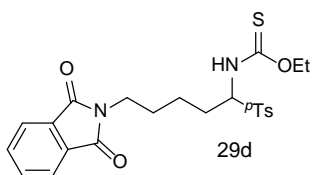
O-Ethyl(5-(1,3-dioxoisoindolin-2-yl)-1-tosylpentyl)carbamothioate

(29d): General Procedure A was followed using 0.317 g of *O*-ethyl

carbamothioate (3.02 mmol, 1 equiv) and 0.700 g of 5-(1,3-dioxo-

isoindolin-2-yl)pentanal (3.02 mmol, 1 equiv). The reaction mixture was extracted with DCM,

dried and concentrated to afford 1.31 g of yellow oil was obtained. After flash chromatography

(10% EtOAc: Hex), 0.99 g (69%) of desired compound was isolated as a white solid. IR (thin

film): 3292, 2933, 1770, 1709, 1519, 1398, 1372, 1201, 1143 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$)

Atropisomer ratio 0.6:1 (R^2:R^1) δ 7.86–7.69 (m, 10H (R^1+R^2)), 7-34-7.29 (m, 3.3H (R^1+R^2)),

6.72 (d, J = 10.8 Hz, 0.6H (R^2)), 6.48 (d, J = 3.6 Hz, 1H (R^1)), 5.68 (dt, J = 3.2, 11.2 Hz, 1H

(R^1)), 4.96 (dt, J = 3.2, 11.2 Hz, 0.6H (R^2)), 4.30-4.25 (m, 2.5H (R^1+R^2)), 3.86-3.80 (m, 0.6H

(R^2)), 3.73-3.67 (m 3.6H (R^1+R^2)), 2.44 (s, 1.7H (R^2)), 2.43 (s, 3H (R^1)), 2.32 (m, 1.8H

(R^1+R^2)), 1.99-1.60 (m, 5.6H (R^1+R^2)), 1.55-1.40 (m, 3.8H, (R^1+R^2)), 1.19 (t, J = 7.2 Hz, 3H

(R^1)), 0.96 (t, J = 7.2 Hz, 2H (R^2)); ^{13}C NMR (100 MHz, CDCl$_3$) δ 191.2, 189.5, 171.1, 168.4,

168.3, 145.3, 145.1, 133.9, 133.9, 133.7, 133.7, 132.0, 131.9, 129.8, 129.7, 129.4, 129.4, 123.3,

123.2, 73.5, 71.8, 68.1, 67.0, 60.3, 53.4, 37.0, 36.9, 27.9, 27.6, 25.9, 25.6, 22.4, 22.1, 21.7, 21.6,

21.0, 14.1, 13.9, 13.4; HRMS (ES) *m/z* calcd for $C_{23}H_{27}N_2O_5S_2$ (M+H)$^+$: 475.1361; found: 475.1366.
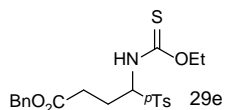
Benzyl 4-((ethoxycarbonothioyl)amino)-4-tosylbutanoate (29e): General Procedure A was followed using 0.547 g of *O*-ethyl carbamothioate (5.2 mmol, 1 equiv) and 1.0 g of benzyl 4-oxobutanoate (5.2 mmol, 1 equiv). The reaction mixture was extracted with DCM, dried and concentrated to afford 2.09 g of clear oil. After flash chromatography (10% EtOAc: hexanes), 1.60 g (71%) of desired compound was isolated as a white solid. IR (thin film): 3289, 2981, 1734, 1596, 1520, 1451, 1304, 1202, 1146, 1083 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) Atropisomer ratio 0.5:1 (R^2:R^1) δ 7.78 (d, *J* = 8.4 Hz, 1H (R^2)), 7.74 (d, *J* = 8 Hz, 2H (R^1)) 7.38-7.29 (m, 9.5H (R^1 + R^2)), 6.67 (d, *J* = 10.4 Hz, 0.5H (R^2)), 6.49 (d, *J* = 11.2 Hz, 1H), 5.80 (dt, *J* = 10.8, 3.2 Hz, 1H (R^1)), 5.17-5.11 (m, 4H (R^1 + R^2)), 4.34-4.24 (m, 2H (R^1 + R^2)), 3.90-3.85 (m, 0.5H (R^2)), 2.70-2.54 (m, 5H (R^1 + R^2)), 2.44-2.43 (m, 4.5H (R^1 + R^2)), 2.22-2.17 (m, 1H (R^1)), 2.09-2.04 (m, 0.5H (R^2)), 1.20 (t, *J* = 7.2 Hz, 3H (R^1)), 0.93 (t, *J* = 7.2 Hz, 1.5H (R^2); ^{13}C NMR (100 MHz, CDCl$_3$) δ 191.3, 189.3, 171.7, 171.5, 145.2, 125.1, 135.4, 135.3, 133.3, 129.6, 129.5, 129.3, 129.2, 128.3, 128.3, 128.1, 128.0, 128.0, 72.9, 10.9, 67.8, 67.0, 66.4, 60.2, 29.5, 22.1, 21.8, 21.5, 21.4, 20.8, 13.9, 13.7, 13.2; HRMS (ES) *m/z* calcd for $C_{21}H_{26}NO_5S_2$ (M+H)$^+$: 436.1252; found: 436.1253.
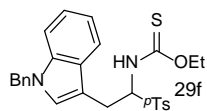
**O-Ethyl (2-(1-benzyl-1H-indol-3-yl)-1-tosylethyl)carbamothioate (29f)**: General Procedure A was followed using 3.80 g of *O*-ethyl carbamothioate (36.1 mmol, 1 equiv) and 9.00 g of 2-(1-benzyl-1H-indol-3-yl)acetaldehyde (36.1 mmol, 1

equiv). The reaction was extracted with DCM, dried, and concentrated. Flash chromatography was performed (10% EtOAc: hexanes) and 3.30 g (19%) of desired compound was obtained as a pale red solid was obtained. IR (thin film): 3295, 3028, 1521, 1468, 1442, 1373, 1356, 1301, 1202, 1144, 1083, 742 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) Atropisomer ratio 0.7:1 (R^2:R^1) δ 7.84 (d, J = 8 Hz, 1.4H (R^2)), 7.79 (d, J = 8.4 Hz, 2H (R^1)), 7.60 (d, J = 7.6 Hz, 0.7H (R^2)), 7.57 (d, J = 7.6 Hz, 1H), 7.37-7.00 (m, 22.7H (R^1 + R^2)), 6.79 (d, J = 10.8 Hz, 0.7H (R^2)), 6.52 (d, J = 10.8 Hz, 1H (R^1)), 6.06 (dt, J = 10.4, 4 Hz, 1H (R^1)), 5.33 (dt, J = 10.4, 2.8 Hz, 0.7H (R^2)), 5.25 (s, 3.4H (R^1 + R^2)), 4.26-4.10 (m, 2H (R^1)), 3.92-3.68 (m, 3.4H (R^1 + R^2)), 3.43 (dd, J = 15.6, 9.6 Hz, 1H (R^1)), 3.16 (dd, J = 14.8, 10.8 Hz, 0.7H (R^1 + R^2)), 2.44 (s, 2.1H (R^2)), 2.43 (s, 3H (R^1)), 1.11 (t, J = 7.2 Hz, 3H (R^1)), 0.67 (t, J = 7.2 Hz, 2.1H (R^2)); ^{13}C NMR (125 MHz, CDCl$_3$) δ 191.0, 189.4, 145.3, 145.2, 137.3, 137.2, 136.5, 136.4, 133.9, 133.7, 129.9, 129.7, 129.4, 128.7, 128.6, 128.2, 127.6, 127.5, 127.5, 127.4, 127.1, 126.7, 122.1, 121.9, 119.6, 119.4, 118.6, 118.4, 110.0, 109.8, 107.4, 107.3, 73.5, 71.8, 67.9, 66.9, 50.0, 23.2, 22.9, 21.7, 21.6, 13.9, 13.1HRMS (ES) m/z calcd for C$_{27}$H$_{29}$N$_2$O$_3$S$_2$ (M+H)$^+$: 493.1620; found: 493.1649.
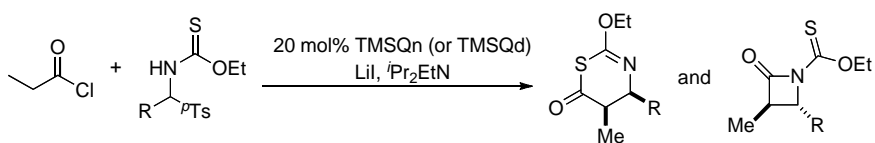
General Procedure B: Preparation of Thiazinones and β-Lactams: The α-amido sulfone (1 equiv) and *O*-trimethylsilylquinine or *O*-trimethylsilylquinidine (0.20 equiv) were dissolved in methylene chloride (0.03 M) and cooled to –78 °C with stirring.   *N*, *N*-diisopropylethylamine (3.6 equiv) was added. A solution of lithium iodide (0.7 equiv) in diethyl ether (0.5 M) was added in one portion, followed by propionyl chloride (0.51 equiv) in methylene chloride (4 M) over 20 min. One hour after addition, an identical portion of lithium

iodide in diethyl ether was added at once, followed by an identical portion of propionyl chloride in dichloromethane over 20 min. This process was repeated 3 times. After 16 h, acetic acid (1.5 equiv) in diethyl ether (1.9 M) was added, and the reaction was immediately extracted with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The aqueous portion was extracted with diethyl ether (50 mL), the combined organic portion was washed with brine (3 x 30 mL), and passed through a silica gel plug, eluting with diethyl ether. The eluent was then concentrated and purified by column chromatography.
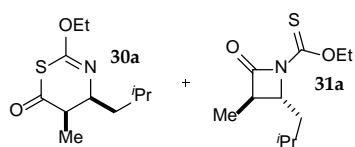
(4S,5R)-2-Ethoxy-4-isobutyl-5-methyl-4H-1,3-thiazin-6(5H)-one (30a) and **(2R,3R)-O-ethyl 2-isobutyl-3-methyl-4-oxoazetidine-1-carbothioate (31a)**: General Procedure B was followed using 2.03g of **29a** (6.18 mmol) and 2.30 g of propionyl chloride (24.7 mmol). Flash column chromatography (2% to 3% ethyl acetate in hexanes) afforded 1.12 g (79%) of **30a** as a colorless oil and 0.139 g of **31a** (9.7%) as a colorless oil.

30a: Separating the enantiomers by chiral GLC [Chirasil - Dex CB column (25 m x 0.25 mm), flow rate 0.6 mL/min, method: 105 °C for 10 min, ramp @ 0.7 °C/min to 160 °C, hold for 5 min; T_r 51.6 min (4R,5S) and 53.8 min(4S,5R)] provided the enantiomer ratio: 4S,5R:4R,5S > 100:1 (>99% ee); $[\alpha]_D^{23}$ –37.3 (c 1.1, CHCl₃); IR (Thin Film) 2956, 2870, 1707, 1657, 1463, 1385, 1193, 1136 cm^{-1}; ^{1}H NMR (300 MHz, CDCl₃) δ 4.29 (q, J = 7.2 Hz, 2H), 3.73 (dt, J = 7.8, 3.9 Hz, 1H), 2.59 (dq, J = 7.2, 3.6 Hz, 1H), 1.90-1.77 (m, 1H), 1.64-1.54 (m, 1H), 1.32 (t, J = 6.9 Hz, 3H), 1.17 (ddd, J = 13.2, 9.0, 4.2 Hz, 1H), 1.08 (d, J = 7.2 Hz, 3H), 0.93 (app dd, J = 6.6, 2.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl₃) δ 200.2, 153.4, 64.2, 64.1, 58.2, 56.6, 45.6, 45.3, 45.1,

42.5, 39.5, 24.7, 24.6, 23.4, 23.2, 21.6, 14.2, 14.1, 10.0; HRMS (ES) *m/z* calcd for $C_{11}H_{20}NO_2S$ (M+H)$^+$: 230.1215; found: 230.1215.

31a: Separating the enantiomers by chiral GLC [Chirasil - Dex CB column (25 m x 0.25 mm), flow rate 0.6 mL/min, method: 105 °C for 10 min, ramp @ 0.7 °C/min to 160 °C, hold for 5 min; T_r 63.0 min (2*R*,3*R*) and 74.1 min (2*S*,3*S*)] provided the enantiomer ratio: 2*R*,3*R*:2*S*,3*S* = 96.1:1 (98–103.5 (% ee); $[\alpha]_D^{23}$ *c* 1.7, CHCl$_3$); IR (Thin Film) 2959, 2872, 1798, 1465, 1349, 1310, 1275, 1251, 1222 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.58 (q, *J* = 7.2 Hz, 2H), 3.30 (dt, *J* = 6.3, 3.3 Hz, 1H), 2.84 (dq, *J* = 7.5, 3.3 Hz, 1H) 2.38 (ddd, *J* = 12.6, 9, 3.3 Hz, 1H), 1.75-1.63 (m, 1H), 1.44-1.36 (m, 6H), 0.98 (app dd, *J* = 6.6, 3.6 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 185.2, 166.2, 67.6, 61.5, 50.1, 40.4, 25.5, 23.4, 22.0, 13.7, 13.2; HRMS (ES) *m/z* calcd for $C_{11}H_{19}NO_2NaS$ (M+Na)$^+$: 252.1034; found: 252.1051.
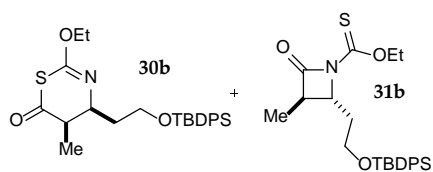
(4*S*,5*R*)-4-[2-(*t*-Butyldiphenylsilyloxy)ethyl]-2-ethoxy-5-methyl-4*H*-1,3-thiazin-6(5*H*)-one (30b) and **(2*R*,3*R*)-*O*-ethyl 2-[2-(*t*-butyldiphenyl-silyloxy)ethyl]-3-methyl-4-oxoazetidine-1-carbothioate (31b)**: General Procedure B was followed using 1.30 g of **29b** (2.34 mmol) and 0.87 g of propionyl chloride (9.4 mmol). Flash column chromatography (2% ethyl acetate in hexanes) afforded 0.480 g (46%) of **30b** as a colorless oil and 0.400 g of **31b** (38%) as a colorless oil.

30b: Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 0.8 ml/min, 0% *i*PrOH, 100% hexanes, hold for 5 min, 0.5% *i*PrOH, 99.5% hexanes hold for 20 min, 1% *i*PrOH, 99% hexanes hold for 10 min, T_r 20.9 min (4*R*,5*S*) and 30.7 min (4*S*,5*R*)]

provided the enantiomer ratio: (4S,5R):(4R,5S) 97:3 (94% ee); $[\alpha]_D^{23}$ –22.7 (*c* 1.1, CHCl$_3$); IR (Thin Film) 3070, 2928, 2854, 1707, 1656, 1470, 1427, 1388, 1189 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69-7.66 (m, 4H), 7.45-7.36 (m, 6H) 4.16 (q, *J* = 7.2 Hz); 3.94-3.80 (m, 3H), 2.63 (dq, *J* = 7.2, 3.6 Hz), 1.82-1.70 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.3, 153.9, 135.6, 135.5, 133.7, 133.7, 129.6, 129.6, 127.6, 127.6, 64.3, 60.6, 55.0, 45.1, 34.0, 26.8, 19.2, 14.1, 10.0; HRMS (ES) *m/z* calcd for C$_{25}$H$_3$NO$_3$NaSiS (M+Na)$^+$: 478.1848; found: 478.1829.

31b: Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 0.8 ml/min, 1% *i*PrOH, 99% hexanes, T$_r$ 8.2 min (2*R*,3*R*) and 8.9 min (2*S*,3*S*)] provided the enantiomer ratio: (2R,3R):(2S,3S) 97:3 (94% ee); $[\alpha]_D^{23}$ –38 (*c* 1.3, CHCl$_3$); IR (Thin Film) 2958, 2932, 2858, 1798, 1472, 1428, 1372, 1346, 1298, 1278 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70-7.63 (m, 4H), 7.47-7.37 (m, 6H), 4.57 (q, *J* = 7.2 Hz, 2H), 3.92 (dt, *J* = 6.3, 3.3 Hz, 1H) 3.79 (t, *J* = 5.7 Hz, 2H), 3.09 (dq, *J* = 7.5, 3.3 Hz, 1H), 2.69 (m, 1H), 1.75 (dddd, *J* = 14.1, 9.9, 5.7, 5.7 Hz, 1H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 7.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 185.3, 166.4, 135.4, 133.2, 133.1, 29.8, 127.7, 67.7, 61.2, 60.8, 49.9, 33.8, 26.7, 19.0, 23.7, 13.1; HRMS (ES) *m/z* calcd for C$_{25}$H$_3$NO$_3$NaSiS (M+Na)$^+$: 478.1848; found: 478.1830.
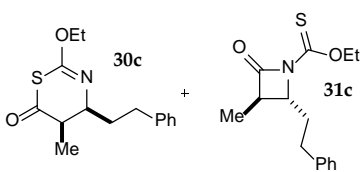
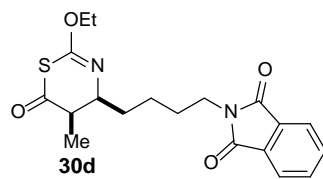**(4*S*,5*R*)-2-Ethoxy-5-methyl-4-phenethyl-4*H*-1,3-thiazin-6(5*H*)-one (30c)** and **(3*R*,4*R*)-*O*-ethyl 3-methyl-2-oxo-4-phenethyl-azetidine-1-carbothioate (31c)**: General Procedure B was followed using 2.12 g of **29c** (5.62 mmol) and 1.06 g of propionyl chloride (11.4 mmol). Flash

column chromatography (2% to 3% ethyl acetate in hexanes) afforded 0.824 g (54%) of **30c** as a colorless oil and 0.487 g of **31c** (32%) as a colorless oil.

30c: Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 1.0 ml/min, 2% *i*PrOH, 98% hexanes, T_r 7.0 min (4*R*,5*S*) and 11.0 min (4*S*,5*R*) min] provided the enantiomer ratio: (4*S*,5*R*):(4*R*,5*S*) = 68.6:1 (97% ee); $[\alpha]_D^{23}$ –88.3 (*c* 1.3, CHCl$_3$); IR (Thin Film) 2981, 2940, 1705, 1657, 1496, 1454, 1384, 1202 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37-7.34 (m, 2H), 7.28-7.26 (m, 3H), 4.41 (q, *J* = 7.2H, 2H), 3.69 (dt, *J* = 7.2, 3.6 Hz, 1H), 2.98 (ddd, *J* = 14, 9.2, 4.8 Hz, 1H) 2.82-2.75 (m, 1H), 2.65 (dddd, *J* = 10.8, 7.2, 7.2, 3.6 Hz, 1H), 2.05-1.98 (m, 1H), 1.84-1.76 (m, 1H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 199.9, 153.8, 141.5, 128.3, 128.3, 125.8, 64.3, 57.6, 32.7, 32.4, 14.1, 9.9; HRMS (ES) *m/z* calcd for C$_{15}$H$_{20}$NO$_2$S (M+H)$^+$: 278.1215; found: 278.1195.

31c: Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 1.0 ml/min, 2% *i*PrOH, 98% hexanes, T_r 14.8 min (2*S*,3*S*) and 23.2 min (2*R*,3*R*)] provided the enantiomer ratio: (2R,3*R*):(2S,3S) >100:1 (>98% ee); $[\alpha]_D^{23}$ –60 (*c* 1.4, CHCl$_3$); IR (Thin Film) 2931, 1796, 1724, 1453, 1372, 1311, 1277 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35-7.30 (m, 2H), 7.26-7.23 (m, 2H), 4.60 (q, *J* = 7.2 Hz, 2H), 3.80 (dt, *J* = 5.6, 2.8 Hz, 1H), 2.91-2.78 (m, 2H), 2.73 (t, *J* = 8.4 Hz, 2 H) 1.99-1.90 (m, 1H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 185.2, 165.7, 140.2, 128.4, 128.1, 126.1, 67.6, 61.9, 49.4, 32.3, 31.0, 13.6, 12.9; HRMS (ES) *m/z* calcd for C$_{15}$H$_{19}$NO$_2$NaS (M+Na)$^+$: 300.1034; found: 300.1039.

2-(4-((4S,5R)-2-Ethoxy-5-methyl-6-oxo-5,6-dihydro-4H-1,3-thiazin 4-yl)butyl)isoindoline-1,3-dione (30d): General Procedure B was followed using 0.500 g of **29d** (1.05 mmol) and 0.198 g of propionyl chloride (2.10 mmol). Flash chromatography (5% EtOAc in Hexanes) afforded 0.131 g (55%) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85-7.82 (m, 2H), 7.73-7.71 (m, 2H), 4.25 (q, J = 6.8 Hz, 2H), 3.70 (t, J = 7.2 Hz, 2H), 3.61-3.60 (m, 1H), 2.63-2.57 (m, 1H), 1.77-1.70 (m, 2H), 1.69-1.57 (m, 2H), 1.55-1.45 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.3, 168.4, 153.9, 133.9, 132.1, 123.2, 64.4, 58.6, 45.2, 37.8, 30.5, 28.3, 23.8, 14.1, 10.0; HRMS (ES) m/z calcd for C$_{19}$H$_{23}$N$_2$O$_4$S (M+H)$^+$: 375.1379; found: 375.1364.
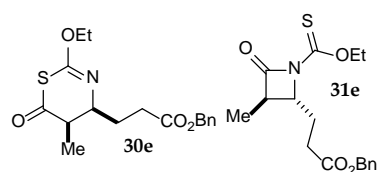
3-((4S,5R)-2-Ethoxy-5-methyl-6-oxo-5,6-dihydro-4H-1,3-thiazin-4-yl)propanoate (**30e**): and **Benzyl 3-((2R,3R)-1-(ethoxy-carbonothioyl)-3-methyl-4-oxoazetidin-2-yl) propanoate** (**31e**) General Procedure B was followed using 0.500 g of **29e** (1.15 mmol) and 0.205 g of propionyl chloride (2.30 mmol). Flash column chromatography (2% to 3% ethyl acetate in hexanes) afforded 0.187 g (48%) of **30e** as a colorless oil and 0.093 g of **31e** (24%) as a colorless oil.

30e: Separating the enantiomers by chiral GLC [Chirasil - Dex CB column (25 m x 0.25 mm), flow rate 3.0 mL/min, method: 105 °C for 10 min, ramp @ 3.0 °C/min to 225 °C, hold for 30 min; T$_r$ 48.76 min (4S,5R) and 48.56 min (4R,5S)] provided > 99% ee (4R,5S enantiomer was not detected) ; [α]$_D^{23}$ −12.8 (c 3.2, CHCl$_3$); IR (Thin Film) 2980, 1735, 1706, 1656, 1499, 1454, 1384, 1350, 1194, 1164, 1141, 1020 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36-7.33 (m, 5H),

5.13 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.63 (dt, J = 7.2, 3.6 Hz, 1H), 2.66-2.51 (m, 3H), 1.98-1.88 (m, 1H), 1.87-1.75 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 199.8, 173.0, 154.5, 135.8, 128.5, 128.5, 128.2, 128.2, 128.1, 66.18, 64.4, 57.6, 45.1, 31.0, 26.4, 14.0, 9.7; HRMS (ES) m/z calcd for C$_{17}$H$_{22}$NO$_4$S (M+H)$^+$: 336.1270; found: 336.1310.

31e Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 1.0 ml/min, 1% iPrOH, 99% hexane, T$_r$ 24.7 min (3R,4*R*) and 28.1 min (3S,4*S*) min] provided >99% ee (enantiomer 3S,4S was not detected); $[\alpha]_D^{23}$ −64 (*c* 0.7, CHCl$_3$); IR (Thin Film) 2976, 1797, 1735, 1454, 1347, 1293, 1165, 1100, 1073, 1010 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38- 7.31 (m, 5H), 5.13 (s, 2H), 4.57 (q, J = 7.2 Hz, 2H), 3.77 (dt, J = 9.2, 3.2 Hz, 1H), 2.87 (dq, J = 7.6, 3.6 Hz, 1H), 2.73-2.66 (m, 1H), 2.45 (t, J = 7.2 Hz, 2H), 2.01-1.92 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 185.4, 172.4, 165.6, 135.5, 128.5, 128.5, 128.4, 128.3, 128.2, 67.9, 66.6, 61.4, 49.3, 30.0, 26.6, 13.7, 12.9; HRMS (ES) m/z calcd for C$_{17}$H$_{22}$NO$_4$S (M+H)$^+$: 336.1270; found: 336.1304.
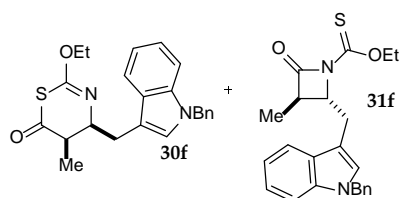
(4S,5R)-4-((1-Benzyl-1H-indol-3-yl)methyl)-2-ethoxy-5-methyl-4,5-dihydro-6H-1,3-thiazin-6-one (**30f**) and **O-Ethyl (2R,3R)-2-((1-benzyl-1H-indol-3-yl)methyl)-3-methyl-4-oxo-aze tidine-1--carbothioate** (**31f**): General Procedure B was followed using 0.500 g of **29f** (1.02 mmol) and 0.193 g of propionyl chloride (2.04 mmol). Flash column chromatography (2% to 3% ethyl acetate in hexanes) afforded 0.048 g (12%) of **30f** as a colorless oil and 0.108 g of **31f** (27%) as a colorless oil.

30f: Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 1.0 ml/min, 2% *i*PrOH, 98% hexanes, T_r 8.1 min (4*S*,5*R*) and 17.2 min (4*R*,5*S*) min] provided >99% ee (enantiomer 4R,5S was not detected); $[\alpha]_D^{23}$ +10.0 (*c* 0.2 CHCl$_3$); IR (thin film) 2927, 1702, 1656, 1466, 1358, 1185, 1115, 1017 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.35-7.10 (m, 10H), 7.02 (s, 1H), 5.31 (s, 2H), 4.25 (dq, *J* = 7.2, 1.5 Hz, 2H), 4.01 (dt, *J* = 8.1, 3.3 Hz, 1H), 3.20 (dd, *J* = 14.7, 8.4 Hz, 1H), 3.04 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.70 (ddd, *J* = 7.2, 6.9, 3.3 Hz, 1H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.6, 154.3, 137.5, 136.6, 128.9, 128.8, 128.7, 128.2, 127.6, 126.8, 126.6, 121.8, 119.1, 119.0, 111.6, 109.7, 64.4, 59.4, 49.9, 44.3, 14.1, 9.7; HRMS (ES) *m/z* calcd for C$_{23}$H$_{25}$N$_2$O$_2$S (M+H)$^+$: 393.1637; found: 393.1669.

31f: Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 1.0 ml/min, 1% *i*PrOH, 99% hexanes, T_r 49.8 min (3*R*,4*R*) and 54.5 min (3*S*,4*S*) min] provided >99% ee (enantiomer 3S,4S was not detected); $[\alpha]_D^{23}$ –1.0 (*c* 2.0, CHCl$_3$); IR (thin film) 2978, 1794, 1495, 1466, 1345, 1315, 1285, 1243, 1138, 1095, 1014 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (d, *J* = 8 Hz, 1H), 7.32-7.10 (m, 9H), 6.93 (s, 1H), 5.29 (s, 2H), 4.71-4.59 (m, 3H), 4.02 (dd, *J* = 14.5, 2 Hz, 1H), 3.39 (app p, *J* = 7 Hz, 1H), 2.96 (dd, *J* = 15, 11.5 Hz, 1H), 1.45 (t, *J* = 7 Hz, 3H), 1.28 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.4, 166.4, 137.4, 136.6, 128.8, 127.9, 127.7, 126.7, 126.1, 122.2, 119.4, 119.4, 110.4, 109.8, 67.9, 57.2, 49.9, 46.8, 23.0, 13.8; HRMS (ES) *m/z* calcd for C$_{23}$H$_{25}$N$_2$O$_2$S (M+H)$^+$: 393.1637; found: 393.1672
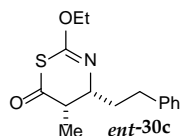
(4*R*,5*S*)-2-Ethoxy-5-methyl-4-phenethyl-4*H*-1,3-thiazin-6(5*H*)-one (***ent*-30c**): Separating the enantiomers by chiral HPLC [Daicel Chiralpak OD-H column, flow rate 1.0 ml/min, 2% *i*PrOH, 98% hexane, T_r 7.0 min (4*R*,5*S*) and 11.0 min (4*S*,5*R*) min] provided the enantiomer ratio: (4*R*,5*S*):(4*S*,5*R*) > 100:1 (>98% ee). $[\alpha]_D^{23}$ 36 (*c* 1.5, CHCl$_3$).
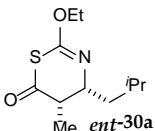
(4*R*,5*S*)-2-Ethoxy-4-isobutyl-5-methyl-4*H*-1,3-thiazin-6(5*H*)-one (***ent*-30a**): Separating the enantiomers by chiral GLC [Chirasil - Dex CB column (25 m x 0.25 mm), flow rate 0.6 mL/min, method: 105 °C for 10 min, ramp @ 0.7 °C/min to 160 °C, hold for 5 min; T_r 51.6 min (4*R*,5*S*) and 53.8 min (4*S*,5*R*)] provided the enantiomer ratio: 4*S*,5*R*:4*R*,5*S* > 100:1 (>99% ee). $[\alpha]_D^{23}$ 42 (*c* 1.6, CHCl$_3$).
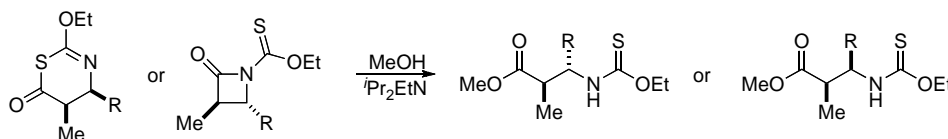
General Procedure C: Ring-opening of Thiazinones and β-Lactams with Methanol: The thiazinone or β-lactam (1 equiv) was dissolved in methanol at ambient temperature. *N*, *N*-diisopropylethylamine (1.5 equiv) was added. After 20 min, the reaction was concentrated *in vacuo* to afford the product, which could be purified by column chromatography, or used without further purification.
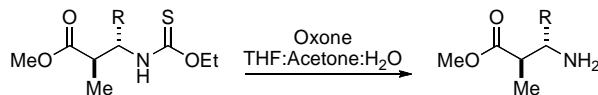
General Procedure D: Deprotection of β-Amino Acid Derivatives: To the protected substrate (1 equiv) was added THF, acetone, and H$_2$O (2:1:1 v:v, 0.2 M) with vigorous stirring. The mixture was cooled to 0 °C, and Oxone (1.5 equiv) was added all at once. After 5 min, the

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reaction was warmed to ambient temperature, and allowed to stir for 20 min. The reaction was then cooled to 0 °C, and saturated $K_2CO_{3(aq)}$ was added slowly to pH 11. The heterogeneous mixture was then concentrated *in vacuo*, and enough water was added to the residue to create a homogeneous solution. The aqueous portion was then extracted with 5:1 chloroform:isopropanol or ethyl acetate. The combined organics were then dried (Na_2SO_4) and concentrated to afford the crude product, which can be used without further purification.
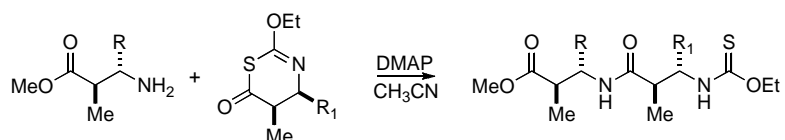
**General Procedure E: Ring-Opening of Thiazinones or β-Lactams with a β-Amino Acid Derivative**: To a stirring mixture of the β-amino acid derivative (1 equiv) and thiazinone or β-lactam in acetonitrile was added a trace amount of 4-(dimethylamino)pyridine. The reaction was then stirred overnight at ambient temperature, concentrated *in vacuo*, and purified in the indicated manner.
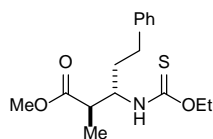
(2*R*,3*S*)-Methyl 3-(ethoxycarbonothioylamino)-2-methyl-5-phenyl-pentan-oate (MeO-(30c)-NHC(S)OEt): General Procedure C was followed using 252 mg of **30c** (0.91 mmol) and 0.34 mL of ^{i}Pr₂NEt (1.4 mmol). The solvent was removed in vacuo to yield 272 mg (97%) of the title compound as a clear, colorless oil that was used without further purification. $[\alpha]_D^{23}$ –9.0 (*c* 3.0, CHCl₃). IR (thin film): 3320, 3027, 2980, 2985, 1735, 1518, 1435, 1400, 1382, 1334, 1257, 1177 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) Atropisomer ratio: 2:3 (R²:R¹) δ 7.28-7.16 (m, 6.6 H (R¹ + R²)), 6.71 (br d, *J* = 9.6 Hz, 0.6 H (R¹)), 4.59-4.47 (m, 3 H (R¹ + R²)), 4.13-4.10 (m, 0.5H), 3.68 (s, 3H (R¹ + R²)), 2.90-2.88 (m, 0.7 H (R¹)), 2.77-2.60

(m, 3.1 H (R^1 + R^2)), 1.82-1.75 (m, 3.8H (R^1 + R^2)), 1.33 (dt, J = 6.8, 6.4 Hz, 3.3 H (R^1 + R^2)),

1.21-1.6 (m, 3.4H (R^1 + R^2)); ^{13}C NMR (100 MHz, CDCl$_3$) δ 190.2, 189.9, 174.5, 174.2, 141.3,

140.6, 128.3, 128.3, 128.2, 126.0, 125.9, 67.7, 66.2, 56.9, 54.5, 51.8, 51.7, 44.1, 42.7, 33.7, 32.5,

32.4, 32.2, 14.1, 14.1, 13.8, 13.6; HRMS (ES) *m/z* calcd for $C_{16}H_{23}NO_3NaS$ (M+Na)$^+$: 332.1296;

found: 332.1281.
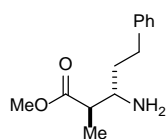
(2R,3S)-Methyl 3-amino-2-methyl-5-phenylpentanoate (MeO-(30c)-NH$_2$):
General Procedure D was followed using 0.242 g of **7** (0.78 mmol) and 0.721 g of

Oxone$^®$ (1.2 mmol). The title compound was obtained as a clear oil in 100% yield (0.181 g).

$[α]_D^{23}$ –21 (*c* 1.7, CHCl$_3$); IR (thin film): 3359, 3026, 2981, 2949, 1725, 1506, 1454, 1401, 1302,

1208, 1177, 1101 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31-7.25 (m, 2H), 7.20-7.15 (m, 3H),

3.68 (s, 3H), 3.07 (dt, J = 9.0, 4.5 Hz, 1H), 2.81 (ddd, J = 15.6, 10.2, 5.7 Hz, 1H), 2.67-2.49 (m,

2H), 1.83-1.53 (m, 2H), 1.14 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.9, 141.8,

128.4, 128.3, 125.8, 52.6, 51.6, 45.2, 37.0, 32.9, 11.0; HRMS (ES) *m/z* calcd for $C_{13}H_{20}NO_2$

(M+H)$^+$: 222.1494; found: 222.1481.
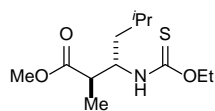
(2R,3S)-Methyl 3-(ethoxycarbonothioylamino)-2,5-dimethyl-hexanoate
(44): General Procedure C was followed using 0.724 g of **30a** (3.16 mmol)

and 0.82 mL of ^{i}Pr$_2$NEt (4.74 mmol). The crude oil was purified by flash chromatography (5%

EtOAc/hexanes on silica gel) to afford 0.746 g (90%) of the title compound as a clear colorless

oil. $[α]_D^{23}$ –54 (*c* 3.3, CHCl$_3$). IR (thin film): 3317, 2955, 2871, 1737, 1523, 1194 cm^{-1}; ^{1}H NMR

(400 MHz, CDCl$_3$) Atropisomer ratio: 2:3 (R^2:R^1) δ 6.67 (br d, J = 9.6 Hz, 0.6H (R^2)), 6.50 (br d,

J = 9.6Hz, 1H (R^1)), 4.63 – 4.50 (m, 2.3H (R^1+R^2)), 4.44 (dq, J = 1.6, 4.8Hz, 2H (R^1)), 4.21 –

4.13 (m, 0.6H, R^2), 3.70 (s, 2H (R^2)), 3.69 (s, 3H (R^1)), 2.86 (dq, J = 4.0, 7.2Hz, 1H (R^1)), 2.55 (app quint, J = 6.8Hz, 0.6H (R^2), 1.68 – 1.57 (m, 2H (R^2)), 1.45 – 1.24 (m, 8H (R^1+R^2)), 1.19 (d, J = 7.2Hz, 3H (R^1)), 1.16 (d, J = 7.2Hz, 2H (R^1)), 0.95 – 0.87 (m, 10H (R^1+R^2)); ^{13}C NMR (75 MHz, CDCl$_3$) δ 189.8, 189.4, 174.4, 174.3, 67.6, 66.1, 55.2, 52.2, 51.7, 51.6, 44.4, 42.6, 41.4, 39.4, 24.8, 24.5, 23.3, 23.3, 21.8, 21.0, 14.1, 13.7, 13.5; HRMS (ES) m/z calcd for C$_{12}$H$_{23}$NO$_3$S (M+Na)$^+$: 284.1296; found: 284.1271.
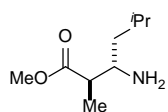
(2R,3S)-Methyl 3-amino-2,5-dimethylhexanoate (45): General Procedure D was followed using 0.265 g of 44 (1.01 mmol) and 0.934g of Oxone® (1.52 mmol). An acid/ base extraction was done and 0.128 g (73%) of the title compound was obtained as a clear colorless oil. $[α]_D^{23}$ –31 (c 1.8, CHCl$_3$) IR (thin film): 3363, 2955, 2871, 1735, 1199 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.65 (s, 3H), 3.08 (app. quintet, J = 4.4 Hz, 1H), 2.40 (dq, J = 4.4, 7.2 Hz, 1H), 1.72–1.61 (m, 1H), 1.23 – 1.16 (m, 2H), 1.14-1.10 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.1, 51.5, 50.5, 45.2, 44.4, 24.8, 23.4, 21.7, 10.8; HRMS (ES) m/z calcd for C$_9$H$_{19}$NO$_2$ (M+Na)$^+$: 196.1313; found: 196.1328.
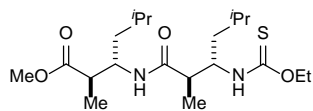
(2R,3S)-Methyl-3-[(2R,3S)-3-(ethoxycarbonothioylamino)-2,5 di-methyl-hexanamido]-2,5-dimethylhexanoate (MeO-(30a-30a) NHC(S)OEt): General Procedure E was followed using 0.252g of 45 (1.45 mmol, 1 equiv) and 0.296g of 30a (1.31 mmol, 0.9 equiv). The residue was dissolved in methylene chloride and washed with 1 M HCl. The organic portion was then dried (Na$_2$SO$_4$) and concentrated in $vacuo$ to obtain 0.493 g (93%) of the title compound as a white solid. mp: 170 °C (dec); $[α]_D^{23}$ –65 (c

1.0, CHCl$_3$) IR (thin film): 3364, 3254, 2956, 2871, 1714, 1657, 1535, 1186, 1137 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) Atropisomer ratio: 3:2 (R^1:R^2) δ 6.71–6.66 (m, 0.9H (R^1+R^2)), 5.89 (br d, J = 9.3 Hz, 0.6H (R^1)), 5.78 (br d, J = 9.6 Hz, 0.4H (R^2)), 4.65-4.48 (m, 0.8H (R^1+R^2)), 4.47-4.38 (m, 1.8H (R^1+R^2)), 4.27-4.10 (m, 1.3H (R^1+R^2)), 3.69-3.6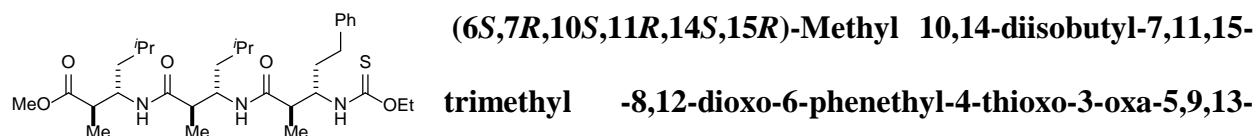8 (m, 3H (R^1+R^2)), 2.77 (dq, J = 5.1, 7.2Hz, 0.6H (R^2)), 2.63 (dq, J= 4.5, 7.2Hz (R^1)), 2.18 (app quintet, J = 7.2Hz, 0.4H), 1.66-1.50 (m, 3H (R^1+R^2)), 1.38-1.13 (m, 13H (R^1+R^2)), 0.97-0.84 (m, 13H (R^1+R^2)); ^{13}C NMR (75 MHz, CDCl$_3$) δ 189.8, 174.9, 174.8, 173.3, 173.1, 67.7, 66.2, 55.7, 54.0, 51.8, 49.0, 48.9, 47.2, 43.8, 43.8, 43.6, 42.2, 40.1, 40.0, 39.3, 25.0, 25.0, 24.8, 24.7, 23.6, 23.5, 23.5, 23.4, 21.9, 21.4, 21.3, 21.0, 15.4, 14.5, 14.4, 14.2, 13.0; HRMS (ES) m/z calcd for C$_{23}$H$_{34}$N$_2$O$_4$ (M+Na)$^+$: 425.2416; found: 425.2431.
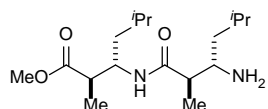
(2R,3S)-Methyl 3-[(2R,3S)-3-amino-2,5-dimethylhexan-amido]-2,5-dimethyl-hexanoate (46): General Procedure D was followed using 0.100g of **MeO-(30a-30a)-NHC(S)OEt** (0.244 mmol) and 0.225g of Oxone$^®$ (0.366 mmol). 0.074 g (97%) of the title compound was obtained as a clear oil. $[\alpha]_D^{23}$ –58 (c 0.41 CHCl$_3$) IR (thin film): 3295, 2956, 1737, 1644, 1545 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50 (br d, J = 9.3 Hz, 1H), 4.28–4.19 (m, 1H), 3.66 (s, 3H), 3.06–2.98 (m, 1H), 2.62 (dq, J = 5.1, 7.2 Hz, 1H), 2.20 (dq, J = 3.6, 7.2 Hz, 1H), 1.72–1.53 (m, 2H), 1.40–1.16 (m, 4H), 1.12 (d, J = 7.2 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H), 0.92 – 0.86 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) 175.4, 175.1, 51.6, 50.4, 48.6, 45.7, 44.6, 43.7, 40.8, 25.1, 24.8, 23.5, 23.4, 21.7, 21.7, 12.6, 11.7; HRMS (ES) m/z calcd for C$_{17}$H$_{34}$N$_2$O$_3$ (M+Na)$^+$: 337.2467; found: 337.2483.

(6S,7R,10S,11R,14S,15R)-Methyl 10,14-diisobutyl-7,11,15-trimethyl -8,12-dioxo-6-phenethyl-4-thioxo-3-oxa-5,9,13-triazahexadecan-16-oate (MeO-(30a-30a-30c)-NHC(S)OEt): General Procedure E was followed using 0.213g of **46** (0.677 mmol, 1 equiv) and 0.169g of **30c** (0.609 mmol, 0.9 equiv). The residue was dissolved in methylene chloride and washed with 1 M HCl. The organic portion was then dried (Na$_2$SO$_4$) and concentrated *in vacuo* to obtain 0.204 g (57%) of the title compound as a yellow solid. mp: 170 °C (dec); $[\alpha]_D^{23}$ –39 (*c* 1.3, CHCl$_3$) IR (thin film): 3286, 2955, 1716, 1649, 1540, 1452, cm^{-1}, ^{1}H NMR (300 MHz, MeOD) 7.85–7.70 (m, 2H), 7.28–7.08 (m, 3H), 4.70–4.40 (m, 3H), 4.30–4.05 (m, 2H), 3.64 (s, 3H), 2.75–2.15 (m, 5H), 1.85–1.38 (m, 4H), 1.35–1.22 (m, 4H), 1.20–1.00 (m, 12H), 0.95–0.70 (m, 12H); ^{13}C NMR (100 MHz, pyridine-*d5*) δ 192.0, 191.1, 177.8, 177.6, 175.6, 143.0, 142.4, 129.3, 129.3, 126.7, 67.5, 66.5, 63.7, 60.8, 58.8, 58.1, 56.0, 55.4, 52.8, 52.1, 49.6, 48.3, 48.0, 47.7, 46.3, 45.5, 45.2, 43.9, 43.8, 43.6, 42.3, 35.7, 34.8, 34.5, 33.6, 33.5, 30.5, 26.5, 25.8, 24.6, 24.2, 22.0, 16.7, 15.5, 15.2, 14.9, 14.6, 13.8, 13.6, 8.5; HRMS (ES) *m/z* calcd for C$_{32}$H$_{53}$N$_3$O$_5$S (M+Na)$^+$: 614.3604; found: 614.3604.
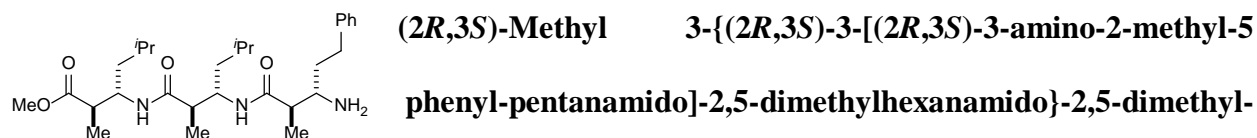
(2R,3S)-Methyl 3-{(2R,3S)-3-[(2R,3S)-3-amino-2-methyl-5 phenyl-pentanamido]-2,5-dimethylhexanamido}-2,5-dimethyl-hexanoate (48) General Procedure D was followed using 0.046 g of **MeO-(30a-30a-30c)-NHC(S)OEt** (0.078 mmol) and 0.072 g of Oxone$^®$ (0.117 mmol). 0.031 g (80%) of the title compound was obtained as a white solid. mp: 180 °C (dec); $[\alpha]_D^{23}$ –45 (*c* 1.0, CHCl$_3$) IR (thin film): 3208, 2955, 1733, 1641, 1544, 1143 cm^{-1}, ^{1}H NMR (400 MHz, CDCl$_3$) 7.48 (br d, *J* = 9.2 Hz, 1H), 7.30-7.16 (m, 5H), 6.33 (br d, *J* = 8.8 Hz, 1H), 4.25-4.18 (m, 1H), 4.12-4.01 (m, 1H),

3.68 (s, 3H), 3.01 (app quintet, J = 4 Hz, 1H), 2.75 (m, 1H), 2.65-2.58 (m, 2H), 2.49 (m, 1H), 2.29 (dq, J = 6.8, 3.2 Hz, 1H) 1.80-1.72 (m, 1H), 1.67-1.20 (m, 7H), 1.15-1.11 (m, 9H), 0.88 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.6, 175.1, 174.0, 141.7, 128.4, 128.2, 125.9, 52.9, 52.8, 51.7 49.0, 46.0, 45.5, 44.0, 40.9, 40.3, 37.6, 33.1, 29.7, 25.1, 23.6, 21.5, 21.4, 14.2, 13.2, 11.9; HRMS (ES) m/z calcd for C$_{29}$H$_{49}$N$_3$O$_4$ (M+Na)$^+$: 526.3621; found: 526.3663.
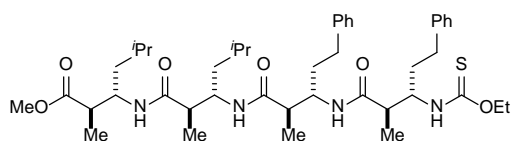
(6S,7R,10S,11R,14S,15R,18S,19R)-Methyl 14,18-di-isobutyl-7,11,15,19-tetramethyl-8,12,16-trioxo-6,10-diphenethyl-4-thioxo-3-oxa-5,9,13,17-tetraazaicosan-20-oate (**MeO-(30a-30a-30c-30c)-NHC(S)OEt**): General Procedure E was followed using 0.122g of **48** (0.242 mmol, 1 equiv) and 0.067g of **30c** (0.242 mmol, 1 equiv). The residue was dissolved in methylene chloride and washed with 1 M HCl. The organic portion was then dried (Na$_2$SO$_4$) and concentrated *in vacuo* to obtain 0.171 g (91%) of the title compound as a yellow solid. mp: 185 °C (dec); $[\alpha]_D^{23}$ –25 (*c* 0.44, CHCl$_3$) IR (thin film): 3281, 2955, 2930, 1717, 1645, 1538, 1454, 1197 cm^{-1}, ^1H NMR (300 MHz, CDCl$_3$) 7.34-7.05 (m, 10H), 4.57-4.42 (m, 3H), 4.40-4.00 (m, 4H), 3.68 (s, 3H), 3.61-3.47 (m, 1H), 3.00-2.40 (m, 8H), 2.00-1.45 (m, 6H), 1.39-1.01 (m, 15H), 0.98-0.78 (m, 12H); ^{13}C NMR (100 MHz, CDCl$_3$) 191.1, 190.3, 190.0, 179.1, 178.3, 178.2, 174.9, 141.3, 140.7, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 126.2, 126.0, 126.0, 68.0, 67.8, 66.5, 66.4, 56.9, 56.6, 54.3, 54.3, 51.8, 49.1, 43.6, 42.6, 42.5, 42.2, 40.0, 35.5, 34.9, 33.2, 32.7, 32.6, 32.4, 32.0, 29.7, 25.0, 24.8, 23.6, 23.5, 21.5, 21.3, 14.8, 14.6, 14.2, 14.1, 13.9, 13.5, 13.0, 7.5; HRMS (ES) m/z calcd for C$_{44}$H$_{68}$N$_4$O$_6$S (M+Na)$^+$: 803.4757; found: 803.4744.

(2*R*,3*S*)- Methyl 3-((2*R*,3*S*)-3-{(2*R*,3*S*)-3-[(2*R*,3*S*)–3 amino -2-methyl-5-phenyl- pentanamido] -2-methyl-5-phenyl-pentan-amido}-2,5-dimethylhexana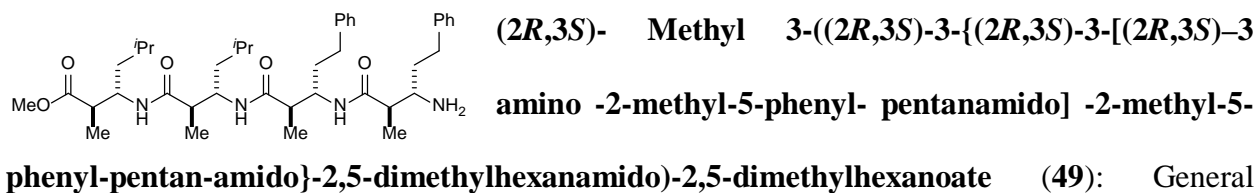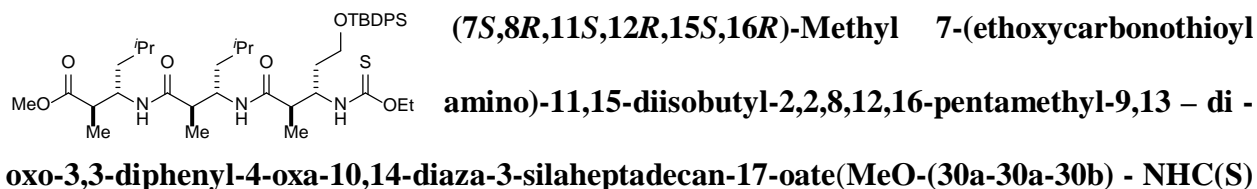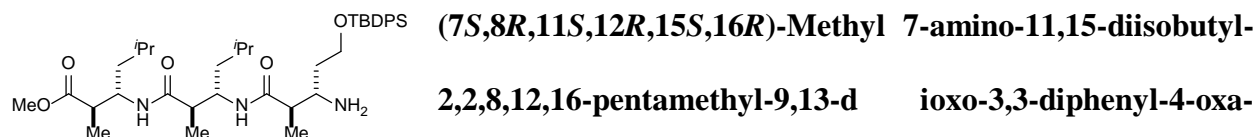mido)-2,5-dimethylhexanoate (**49**): General Procedure D was followed using 0.063g of **MeO-(30a-30a-30c-30c)-NHC(S)OEt** (0.090 mmol) and 0.083g of Oxone® (0.135 mmol). 0.035 g (57%) of the title compound was obtained as a yellow solid. mp: 140 °C (dec); $[\alpha]_D^{23}$ –37 (*c* 0.61, CHCl$_3$) IR (thin film): 3285, 2955, 2871, 1732, 1644, 1543, 1454, 1173, cm^{-1}, ^{1}H NMR (300 MHz, MeOD) δ 7.90–7.85 (m, 2H), 7.30–7.09 (m, 7H), 4.30–4.05 (m, 3H), 3.64 (s, 3H), 2.85–2.20 (m, 9H), 2.05–1.40 (m, 8H), 2.30–1.00 (m, 14H), 0.93-0.71 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.1, 51.5, 50.5, 45.2, 44.4, 24.8, 23.4, 21.7, 10.8; HRMS (ES) *m/z* calcd for C$_{41}$H$_{64}$N$_4$O$_5$ (M+Na)$^+$: 715.4774; found: 715.4763.

(7*S*,8*R*,11*S*,12*R*,15*S*,16*R*)-Methyl 7-(ethoxycarbonothioyl amino)-11,15-diisobutyl-2,2,8,12,16-pentamethyl-9,13 – di - oxo-3,3-diphenyl-4-oxa-10,14-diaza-3-silaheptadecan-17-oate(MeO-(30a-30a-30b) - NHC(S)OEt): General Procedure E was followed using 0.040g of **46** (0.127 mmol, 1 equiv) and 0.052g of **30b** (0.114 mmol, 0.9 equiv). The residue was dissolved in methylene chloride and washed with 1 M HCl. The organic portion was then dried (Na$_2$SO$_4$) and concentrated *in vacuo* to obtain 0.056 g (64%) of the title compound as a yellow solid. mp: 175 °C (dec); $[\alpha]_D^{23}$ –23 (*c* 0.32, CHCl$_3$) IR (thin film): 3290, 2954, 1710, 1640, 1529, 1374, 1183, 1109cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.7 (br s, 5H), 7.40 (br s, 5H), 4.70-4.30 (m, 3H), 4.29-4.00 (m, 2H), 3.68 (s, 3H), 3.03-2.95 (m, 1H), 2.68-2.30 (m, 4H), 2.00-1.45 (m, 8H), 1.40-1.00 (m, 21H), 0.95-0.85 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 191.22, 191.15, 190.65, 190.58, 175.39, 175.20, 174.76, 174.60, 134.34, 134.18, 130.13, 130.08, 128.36, 128.30, 128.22, 128.09, 66.88, 65.91, 65.73,

61.68. 61.38, 55.70, 55.58, 53.22, 51.68, 49.67, 48.98, 47.74, 47.23, 45.19, 45.07, 44.02, 43.22, 41.77, 36.48, 35.23, 30.03, 27.03, 26.96, 25.63, 25.48, 25.34, 24.34, 23.71, 21.67, 21.56, 19.37, 16.31, 14.48, 13.13; HRMS (ES) m/z calcd for $C_{42}H_{67}N_3O_6SiS$ (M+Na)$^+$: 792.4418; found: 792.4352.

(7S,8R,11S,12R,15S,16R)-Methyl 7-amino-11,15-diisobutyl-2,2,8,12,16-pentamethyl-9,13-dioxo-3,3-diphenyl-4-oxa-10,14-diaza-3-silaheptadecan-17-oate (50): General Procedure D was followed using 0.074g of **MeO-(30a-30a-30b)-NHC(S)OEt** (0.096 mmol) and 0.089g of Oxone$^®$ (0.144 mmol). 0.057 g (87%) of the title compound was obtained as a yellow solid. $[\alpha]_D^{23}$ −11 (*c* 1.0, CHCl$_3$) IR (thin film): 3285, 2956, 2931, 1734, 1643, 1544, 1460, 1110 cm^{-1}, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87 (br d, J = 8.8 Hz, 1H), 7.72-7.63 (m, 5H), 7.45-7.36 (m, 5H), 6.40 (br d, J = 9.6 Hz, 1H), 4.25-4.18 (m, 1H), 4.15-4.07 (m, 1H), 3.76 (t, J = 6 Hz, 1H), 3.71-3.66 (m, 4H), 3.22 (dt, J = 9.6, 3.2 Hz, 1H), 2.65-2.56 (m, 1H), 2.50-2.43(m, 1H), 2.26 (dq, J = 7.2, 3.2 Hz, 1H), 1.67-1.04 (m, 26H), 0.90-0.87 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.5, 175.1, 173.9, 135.5, 135.4, 134.8, 133.4, 133.3, 129.7, 129.5, 128.0, 127.7, 127.6, 62.2, 51.7, 51.5, 49.0, 48.9, 45.7, 45.5, 43.9, 41.1, 41.3, 36.7, 29.7, 29.4, 26.8, 26.5, 25.0, 23.5, 23.1, 21.5, 21.4, 21.2, 19.1, 14.1, 13.1 HRMS (ES) m/z calcd for $C_{39}H_{63}N_3O_5Si$ (M+Na)$^+$: 704.4435; found: 704.4423.

(6S,7R,10S,11R,14S,15R,18S,19R)-Methyl 10-[2-(t-butyl-diphenylsilyloxy)ethyl]-14,18-diisobutyl-7,11, 15,19-tetra-methyl-8,12,16-trioxo-6-phenethyl-4-thioxo-3-oxa-5,9,13,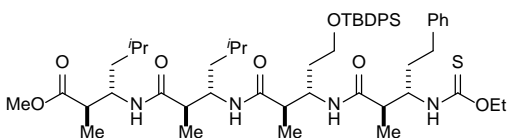17-tetraazaicosan-20 – oate (MeO-(30a-30a-30b-30c)-NHC(S)OEt): General Procedure E was followed using 0.045 g of **50** (0.066 mmol, 1 equiv) and 0.016g of **30c** (0.059 mmol, 0.9 equiv). The residue was dissolved in methylene chloride and washed with 1 M HCl. The organic portion was then dried (Na$_2$SO$_4$) and concentrated *in vacuo* to obtain 0.045 g (80%) of the title compound as a yellow solid. mp: 125 °C (dec); $[\alpha]_D^{23}$ –53.9 (*c* 3.30, CHCl$_3$) IR (thin film): 3281, 2955, 1719, 1640, 1542, 1455, 1110 cm^{-1}, ^{1}H NMR (400 MHz, MeOD) δ 7.87-7.78 (m, 2H), 7.75-7.63 (m, 3H), 7.42-7.37 (m, 5H), 7.23-7.13 (m, 5H), 4.45-4.42 (m, 2H), 4.25-4.02 (m, 3H), 3.64 (s, 3H), 2.77-2.22 (m, 8H), 1.98-1.40 (m, 8H), 1.34-0.85 (m, 36H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.1, 51.5, 50.5, 45.2, 44.4, 24.8, 23.4, 21.7, 10.8; HRMS (ES) *m/z* calcd for C$_{54}$H$_{82}$N$_4$O$_7$SiS (M+Na)$^+$: 981.5571; found: 981.5506.
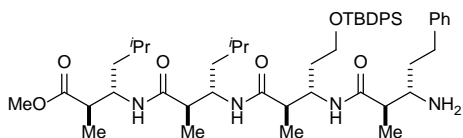
(7S,8R,11S,12R,15S,16R)-Methyl 7-((2R,3S)-3-amino - 2-methyl-5-phenylpentanamido)-11,15-diisobutyl-2,2,8, 12,16-pentamethyl-9,13-dioxo-3,3-diphenyl-4-oxa-10,14-diaza-3-silahepta-decan-17-oate (51): General Procedure D was followed using 0.155g of **MeO-(30a-30a-30b-30c)-NHC(S)OEt** (0.161 mmol) and 0.149g of Oxone$^®$ (0.242 mmol). 0.121 g (86%) of the title compound was obtained as a yellow solid. mp: 115°C (dec); $[\alpha]_D^{23}$ –28 (*c* 0.35, CHCl$_3$) IR (thin film): 3284, 2956, 1735, 1644, 1542, 1455, 1110 cm^{-1}, ^{1}H NMR (400 MHz, MeOD) δ 7.72-7.50 (m, 5H), 7.42-7.32 (m, 5H), 7.22-7.05 (m, 5H), 4.25-4.02 (m, 3H), 3.64 (s, 3H), 2.80-2.20 (m, 9H), 2.00-1.30 (m, 10H), 1.28-0.85 (m, 33H); ^{13}C NMR (100 MHz, MeOD) δ 177.3, 176.9, 137,4, 136.8,

136.1, 135.0, 131.0, 130.6, 129.7, 129.5, 129.1, 129.0, 128.7, 127.3, 52.4, 45.9, 44.0, 42.7, 27.5, 27.3, 26.3, 24.6, 24.1, 21.9, 21.7, 20.1, 16.3, 16.1, 13.5, 13.3, 13.1; HRMS (ES) *m/z* calcd for C$_{51}$H$_{78}$N$_4$O$_6$Si (M+Na)$^+$: 893.5588; found: 893.5513.
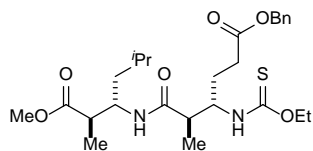
(4S,5R)-Benzyl-4-((ethoxycarbonothioyl)amino)-6-(((2R,3S)- 1-methoxy-2,5-dimethyl-1-oxohexan-3-yl)amino) -5-methyl-6-oxo-hexanoate (MeO-(30a-30e)-NHC(S)OEt): General Procedure E was followed using 0.090 g of **45** (0.521 mmol, 1 equiv) and 0.175 g of **30e** (0.521 mmol, 1 equiv). The residue was dissolved in methylene chloride and washed with 1 M HCl. The organic portion was then dried (Na$_2$SO$_4$) and concentrated *in vacuo* to obtain 0.109 g (42%) of the title compound as pale yellow solid. mp 114-118 ºC; [α]$_D^{23}$ –50 (*c* 1.4, CHCl$_3$); IR (thin film): 3305, 2956, 1736, 1648, 1529, 1453, 1381, 1263, 1176, 1142 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33 (s, 5H), 7.10 (dd, *J* = 9.6, 3.6 Hz, 0.8H), 6.00 (d, *J* = 9.3 Hz, 0.8H), 5.09 (s, 2H), 4.50 (q, *J* = 6.9 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 1.4H), 4.27-4.13 (m, 1.2H) 3.67 (s, 3H), 2.78-2.69 (m, 0.6H), 2.67-2.56 (m, 1.1H), 2.52-2.30 (m, 2.5H), 2.07-1.92 (m, 0.8H), 1.91-1.74 (m 1H), 1.60-1.47 (m, 1H), 1.32-1.15 (m, 8.5H), 1.13 (d, *J* = 7.2 Hz, 3H), 0.88 (dd, *J* = 2.4, 6.6 Hz, 6H); ^{13}C NMR (125 MHz,CDCl$_3$) δ 190.4, 190.1, 174.8, 174.8, 173.1, 172.9, 172.8, 135.8, 135.7, 128.5, 128.3, 128.2, 128.2, 67.8, 66.5, 66.3, 66.3, 60.3, 57.1, 55.2, 51.8, 51.8, 49.1, 49.1, 46.1, 43.6, 43.6, 40.1, 40.0, 30.9, 27.4, 25.3, 25.0, 23.4, 21.4, 21.4, 21.0, 15.4, 14.5, 14.4, 14.1, 12.9, 12.9, 12.8; HRMS (ES) *m/z* calcd for C$_{26}$H$_{40}$N$_2$O$_6$NaS (M+Na)$^+$: 531.2505; found: 531.2487.
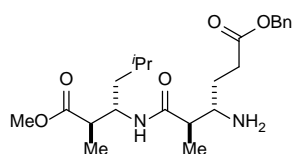
**(4S,5R)-Benzyl 4-amino-6-(((2R,3S)-1-methoxy-2,5-dimethyl-1-oxo-hexan-3-yl)amino)-5-methyl-6-oxohexanoate (52)**: General Procedure D was followed using 0.052 g of **MeO-(30a-30e)-NHC(S)OEt** (0.102 mmol) and 0.094 g of Oxone® (1.5 mmol). The crude product was extracted with 1M HCl$_{(aq)}$, and the aqueous layer was basified to pH 10 with NaOH, then extracted with ethyl acetate (3 x 10mL). The organic layer was then dried (Na$_2$SO$_4$) and concentrated. 0.037 g (88%) of the title compound was obtained as a clear oil. ^{1}H NMR (500 MHz, CDCl$_3$) 7.37-7.30 (m, 5H), 7.10 (d, *J* = 9.5 Hz, 1H), 5.11 (s, 2H), 4.25-4.18 (m, 1H), 3.66 (s, *3H*), 2.95 (app p, *J* = 4.0 Hz, 1H), 2.613 (dq, *J* = 7, 4.5 Hz, 1H) 2.52- 2.38 (m, 3H), 2.22 (dq, *J* = 7.5, 4 Hz, 1H), 1.80-1.74 (m, 1H), 1.66-1.52 (m, 5H), 1.36-1.27 (m, 2H), 1.24-1.56 (m, 4H), 1.10 (dd, *J* = 7.5, 5 Hz, 6H), 0.89 (dd, *J* = 6.5, 4 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.0, 175.0, 173.2, 135.82, 128.5, 128.5, 128.2, 128.2, 66.3, 52.4, 51.7, 48.7, 45.9, 43.6, 40.6, 31.6, 30.7, 25.1, 23.4, 21.6, 12.6, 11.6; HRMS (ES) *m/z* calcd for C$_{23}$H$_{37}$N$_2$O$_5$ (M+)[+]: 421.2702; found: 421.2684.
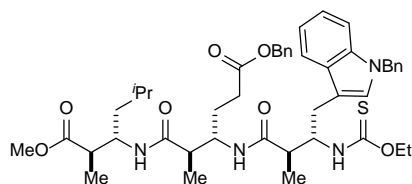
(6S,7R,10S,11R,14S,15R)-Methyl 6-((1-benzyl-1H-indol-3-yl)methyl)-10-(3-(benzyloxy)-3-oxopropyl)-14-isobutyl 7,11,15-trimethyl-8,12-dioxo-4-thioxo- 3-oxa-5,9,13- triazahexadecan-16-oate (53): General Procedure E was followed using 0.037 g of **52** (0.088 mmol, 1 equiv) and 0.035 g of **19f** (0.088 mmol, 1 equiv). The reaction mixture was concentrated and triturated with hot hexanes and filtered. The title compound was obtained in 42% yield (0.030 g) as a white solid. mp 182-188 ºC; $[\alpha]_D^{23}$ -37 (*c* 1.5, CHCl$_3$); IR (thin film): 3286, 2959, 1736, 1646, 1538, 1453, 1377, 1264, 1172 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-*d5* w/ TMS) δ 10.21 (d,

J = 9.5 Hz, 0.3H), 10.15 (d, *J* = 9.5 Hz, 0.5H), 9.19 (d, *J* = 9 Hz, 0.3H), 9.00 (d, *J* = 9 Hz, 0.4H),

8.64 (t, *J* = 8 Hz, 0.8H), 8.24-8.23 (m, 0.3H), 8.02-8.00 (m, 0.4H), 7.39-7.10 (m, 16H), 5.61 (dq,

J = 8.5, 4 Hz, 0.5H), 5.24-5.10 (m, 6H), 4.94-4.86 (m, 1H), 4.84-4.77 (m, 1H), 4.55-4.48 (m,

1H), 4.36-4.33 (m, 0.4H), 4.25-2.22 (m, 0.4H), 3.77 (dd, *J* = 4, 15 Hz, 0.5H), 3.70 (s, 1.5H),

3.69 (s, 1.5H), 3.60 (dd, *J* = 14.5, 8 Hz, 0.5H), 3.35 (t, *J* = 7.5 Hz, 0.4H), 3.19 (dd, *J* = 14, 10 Hz,

0.4H), 3.08-2.89 (m, 2H), 2.84-2.77 (m, 1.5H), 2.72 (m, 0.6H), 2.50-2.45 (m, 0.8H), 2.36-2.28

(m, 0.9H), 1.95-1.90 (m, 0.9H), 1.64-1.58 (m, 5.7H), 1.30 (dd, *J* = 3, 7 Hz, 3.5H), 1.1 (t, *J* =

7.5Hz, 1.3H), 1.0 (t, *J* = 6 Hz, 2.5H), 0.87 (dd, 6.5, 2 Hz, 2.5H), 0.71 (t, *J* = 7 Hz, 1H); ^{13}C NMR

(125 MHz, pyridine-*d5* w/ TMS) δ 191.7, 191.0, 176.1, 175.9, 175.8, 175.5, 175.4, 173.8, 173.7,

139.2, 139.1, 137.6, 137.5, 137.4, 137.4, 130.2, 129.8, 129.6, 129.4, 129.3, 129.3, 128.9, 128.8,

128.8, 128.8, 128.3, 128.2, 128.1, 128.1, 127.8, 127.7, 122.5, 122.4, 120.5, 120.4, 120.1, 119.9,

112.7, 112.6, 110.7, 67.0, 66.7, 66.1, 59.0, 57.4, 52.3, 52.1, 50.3, 49.7, 47.3, 47.0, 45.6, 45.4,

42.2, 32.5, 30.9, 29.6, 29.5, 28.1, 25.9, 24.2, 22.0, 17.7, 16.9, 16.9, 16.7, 14.9, 14.2, 13.6, 13.5;

HRMS (ES) *m/z* calcd for C$_{46}$H$_{60}$N$_4$O$_7$NaS (M+Na)$^+$: 835.4080; found: 835.4110.
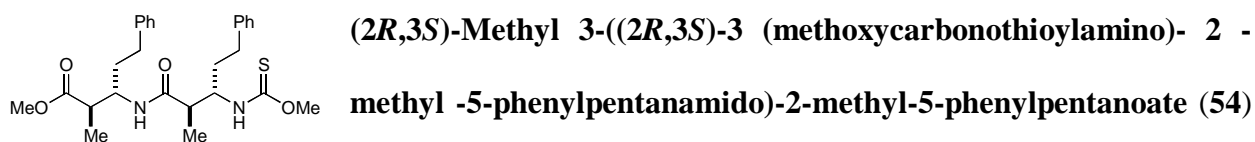
(2*R*,3*S*)-Methyl 3-((2*R*,3*S*)-3 (methoxycarbonothioylamino)- 2 - methyl -5-phenylpentanamido)-2-methyl-5-phenylpentanoate (54)
General procedure E was followed using 61 mg of compound **30c** (0.277 mmol, 1 equiv) and 77

mg of compound **(MeO-(30c)-NH$_2$)** (0.277 mmol, 1 equiv) The solvent was removed in vacuo

and the crude material was purified by flash chromatography (50% EtOAc/ hexanes on silica gel)

to afford 47 mg (34%) of the title compound as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ

7.82-7.09 (m, 15H), 4.59-4.40 (m, 5H), 4.24-4.15 (m, 2.5H), 3.67 (s, 1.5H), 3.63 (s, 3H), 2.81-

2.52 (m, 11.6), 2.0-1.6 (m, 9H), 1.37-1.33 (m, 3H), 1.26 (app. t, J = 3.3 Hz, 5 H) 1.19-1.13 (m, 11H)
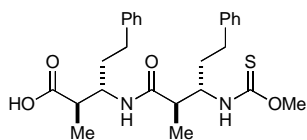
(2R,3S)-3-((2R,3S)-3-(Methoxycarbonothioylamino)-2-methyl- 5 - phenylpentanamido)-2-methyl-5-phenylpentanoic acid (55) 50 mg (0.10 mmol) of **54** was stirred in MeOH:THF:H$_2$O (2:6:1) (0.07M). 42 mg (1.0 mmol, 10 equiv) of LiOH was added to the solution and was stirred for 12 hrs at rt. Saturated ammonium chloride was added to the solution until a pH of 6 was obtained. The aqueous solution was extracted with 5: 1 chloroform: isopropanol (3 x 5 mL). The organics were dried with anhydrous Na$_2$SO$_4$ and concentrated to afford 46 mg (96%) of the title compound as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25-7.04 (m, 10H), 4.54-4.43 (m, 2H), 4.25-4.05 (m, 2H), 2.72-2.55 (m, 7H), 1.94-1.70 (m, 5H), 1.34-1.11 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 190.3, 189.9, 178.9, 174.1, 173.5, 141.3, 141.1, 141.0, 140.8, 128.4, 128,4, 128.3, 126.1, 126.0, 125.9, 68.0, 66.5, 57.2, 55.2, 50.9, 50.8, 46.5, 43.6, 43.4, 43.3, 34.7, 32.8, 32.6, 32.4, 32.3, 29.7, 15.2, 15.0, 14.2, 14.1, 13.3, 13.1, 12.9
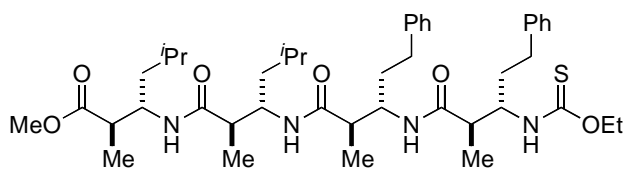

**(6S,7R,10S,11R,14S,15R,18S,19R)- Methyl 14,18-diisobutyl-7,11,15,19- tetra-methyl-8,12,16 -trioxo-6,10-diphenethyl-4-thioxo-3-oxa-5,9,13,17-tetraazaicosan-20-oate (56):** In 0.30 mL of DMF was solvated 21 mg (0.043 mmol) of **55** (0.14M). To the solution was added 16 mg (0.043 mmol, 1 equiv.) HATU and 0.015 mL (0.086 mmol, 2 equiv.) of ^{i}Pr$_2$NEt. After stirring at rt for 30 min, a solution of 16 mg (0.043 mmol, 1 equiv) of **46** in 0.20 mL (0.22M) DMF was added dropwise over 10 min. The

solution was stirred at rt for 48 hrs. To the solution was added saturated ammonium chloride and extracted with 5:1 chloroform: isopropanol (3 x 2 mL). The organics were combined and dried with anhydrous Na_2SO_4. The mixture was filtered and concentrated in vacuo to afford 0.022g (65%) of title compound as a yellow solid.

General Procedures F: Solid Support Synthesis of β-Amino Acid Oligomers:
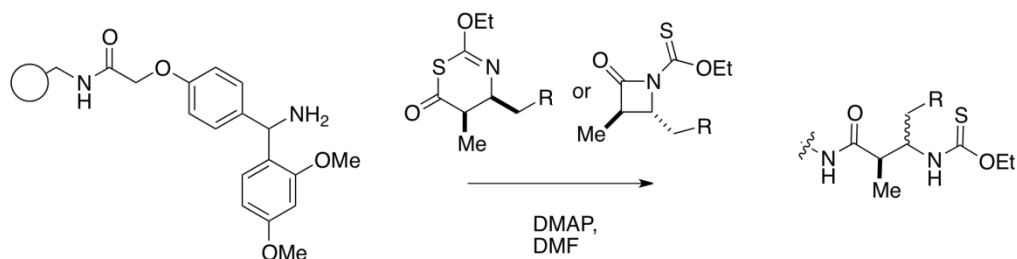
Coupling of β-Amino Acids: To a heterogeneous solution of resin in DMF was added thiazinone or β-lactam solvated in DMF. The heterogeneous solution was stirred at room temperature for 24 hours. When the reaction was complete, the solvent was removed via vacuum filtration followed by 3 rinses with DMF.
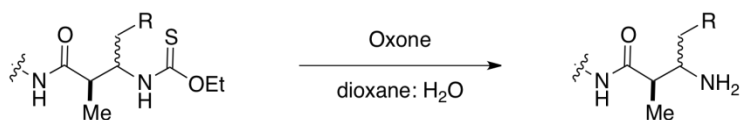
Removal of thiocarbamate group: To a heterogeneous solution of resin in 1:1 dioxane and H_2O was added Oxone (1.5 equiv). The heterogeneous solution was stirred at room temperature for 2 to 4 hours. Upon complete reaction, the solvent was removed via vacuum filtration, 3 rinses with H_2O and 3 rinses with DMF.
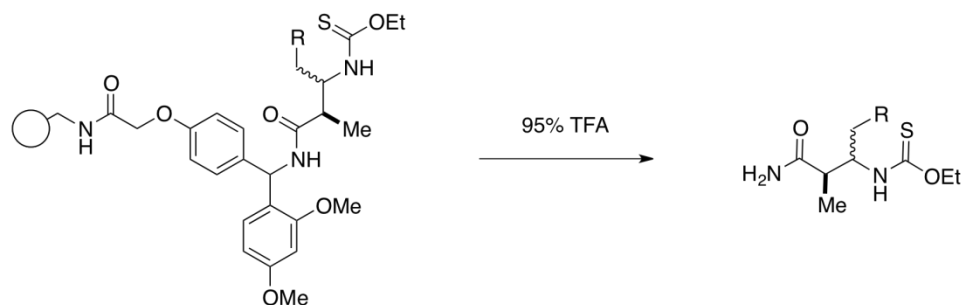
Cleavage of compound from resin: Prior to cleavage, the resin was rinsed multiple times with acetonitrile. To dry resin after acetonitrile washes, was added a 95% TFA solution (95% TFA, 2.5% Et$_3$SiH, 2.5% H$_2$O) at room temperature. When cleavage was complete the TFA solution was collected via vacuum filtration, followed by 3 rinses with ACN. The collected TFA and ACN filtrates were combined and concentrated to afford pure compound. To ensure complete recovery of material, the resin was resubjected to cleavage conditions.
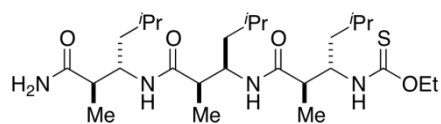
O-Ethyl ((2*R*,3*S*)-1-(((2*R*,3*R*)-1-(((2*R*,3*S*)-1-amino- 2,5- dimethyl-1-oxohexan-3-yl)amino) -2,5- dimethyl-1- oxo hexan-3-yl)amino)-2,5-dimethyl-1-oxohexan-3-yl)carbamothioate (**58**): General procedures A and B were followed for each β-amino acid addition starting with 0.119g of resin (0.044mmol). After 3 iterations of procedures A and B, without the final deprotection of the trimer, general procedure C was followed, providing **58** in 87.0% yield (0.020g, 0.039mmol) of pale yellow solid.
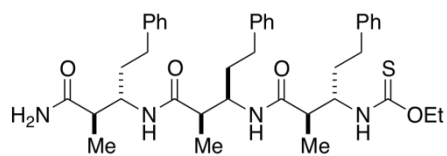
***O*-Ethyl ((2*R*,3*S*)-1-(((2*R*,3*R*)-1-(((2*R*,3*S*)-1- amino-2 - methyl -1-oxo-5-phenylpentan-3-yl)amino) -2-methyl-1-oxo-5-phenylpentan-3-yl)amino) -2-methyl-1-oxo- 5- phenylpentan-3-yl)carbamothioate (57)**: General procedures A and B were followed for each β-amino acid addition starting with 0.235g (0.087mmol) of resin. After 3 iterations of procedures A and B, without the final deprotection of the trimer, general procedure C was followed, providing **57** in 95.7% yield (0.056g, 0.083mmol) as a white solid.
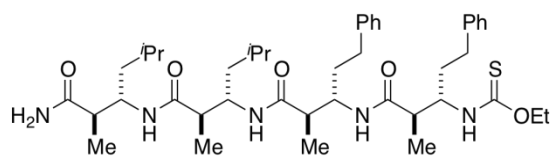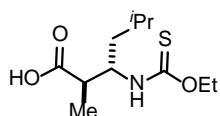

***O*-Ethyl ((2*R*,3*S*)-1- (((2*R*,3*S*)-1-(((2*R*,3*S*)-1 - (((2*R*,3*S*)-1-amino-2,5- dimethyl-1-oxohexan- 3- yl)amino)-2,5-dimethyl-1-oxohexan-3-yl)amino)- 2-methyl-1-oxo-5-phenylpentan-3-yl)amino)-2-methyl-1-oxo-5-phenylpentan-3-yl)carbamo- thioate (59)**: General procedures A and B were followed for each β-amino acid addition starting with 0.235g of resin (0.087mmol). After 3 iterations of procedures A and B, without the final deprotection of the trimer, general procedure C was followed, providing **59** in 52.6% yield (0.035g, 0.0457mmol) as a yellow solid.

(2*R*,3*S*)-3-((Ethoxycarbonothioyl)amino)-2,5-dimethylhexanoic acid (60): To a solution of O-ethyl ((2R,3S)-1-amino-2,5-dimethyl-1-oxohexan-3-yl)carbamothioate (0.050g, 0.203mmol) in AcOH and Ac$_2$O (1:2) at 0°C was added 1 portion of NaNO$_2$ (0.175g, 2.03mmol) stirred for 30 minutes at 0°C and another portion of NaNO$_2$ (0.175g, 2.03mmol) was added. The solution was warmed to room temperature over 10 hours. To the solution was added aqueous NaHCO$_3$ to a pH of 8 and extracted with 5:1 chloroform:

Isopropyl alcohol. The organics were dried and **60** was isolated in a 62% yield (0.031g, 0.126mmol) as a white solid. IR (thin film): 3400, 2960, 2874, 1742, 1710, 1528, 1466, 1374, 1314, 1278, 1178 cm^{-1} ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.55-4.51 (q, J=7 Hz, 2H), 4.30-4.26 (m, 0.5H), 4.13-4.06 (m, 0.5H), 3.14-3.07 (m, 1H), 2.04-1.98 (m, 4H), 1.46-1.43 (m, 3.5H), 1.38-1.31 (m, 1H), 1.27-1.24 (m, 3H), 0.96 (d, *J*=6.5Hz, 1H), 0.92 (d, *J*=7Hz, 3H), 0.80 (d, J=6.5Hz, 3H), 0.76 (d, *J*=6.5Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.9, 166.4, 165.9, 64.5, 53.7, 47.0, 43.0, 43.0, 39.0, 25.5, 25.3, 25.2, 23.3, 22.5, 22.2, 22.2, 21.2, 15.0, 14.4, 14.3, 14.2, 8.6
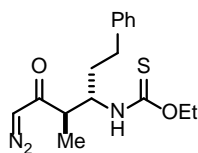

O-Ethyl ((3*S*,4*R*)-6-diazo-4- methyl-5-oxo-1-phenylhexan-3-yl) carbamo-thioate (61): To a 2M solution of TMSCHN$_2$ in Ether (0.216 mL, 0.432 mmol) was added **30c** (0.100 g, 0.360 mmol) in THF (3.6 mL, 0.1M) at - 78ºC. To that solution was added NaN(TMS)$_2$ (0.432 mL, 0.432 mmol in 1 M in THF). This solution was allowed to stir at - 78ºC for 1 hour. To the solution was added 2 mL Et$_2$O followed by 2 mL of H$_2$O. The solution was extracted with three portions of Et$_2$O. Flash Column Chromatography was run with 20% EtOAc/ hexanes and 0.076 g (66% yield) of title compound was isolated as a yellow oil. IR (thin film): 3258, 2977, 2928, 2106, 1628, 1528, 1453, 1378, 1203, 1178 cm^{-1} ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31-7.15 (m, 10H), 6.92 (s, 0.8H), 6.65 (s, 1H), 5.32 (s, 1H), 5.25 (s, 0.8H), 4.57 (dq, J=1.5, 7 Hz, 2H), 4.54-4.45 (m, 4H), 4.16-4.12 (m, 1.5H), 2.88 (br s, 1H), 2.78-2.72 (m, 2.5H), 3.69-2.63 (m, 1.5H), 2.61-2.55 (m, 1H), 2.48 (br s, 0.8H), 1.96-1.88 (m, 3.7H), 1.72-1.67 (m, 1.5H), 1.34 (t, J=7 Hz, 6H), 1.18 (d, *J*=7.5 Hz, 3H), 1.15 (d, *J*=7 Hz, 2.4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.6, 195.6, 190.3, 190.2, 141.3, 140.7, 128.5, 128.4, 128.4, 128.3, 126.1, 126.0, 68.0, 66.4, 60.4, 57.6, 55.1, 55.0, 49.3, 47.3, 34.2, 32.7, 32.4, 14.3, 14.2, 14.1, 13.9
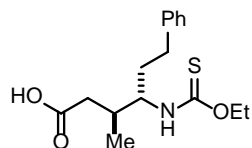
(3S,4S)-4-((Ethoxycarbonothioyl)amino)-3-methyl-6-phenyl hexanoic acid (62): To a solution of **61** in THF:H$_2$O (10:1, 0.252mL) wrapped in foil at -25 °C. PhCO$_2$Ag (0.002g, 0.0069mmol) in Et$_3$N (0.026mL, 0.186 mmol) was added to the solution and allowed to slowly come to room temperature in bath over 3 hours. The solution was concentrated and flash column chromatography was done with 20% ETOAc/ hexanes to obtain 0.008 g (41% yield) of the title compound was obtained as a clear oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30-7.18 (m, 5H), 4.71 (dt, *J*=4, 7 Hz, 1H) 4.58 (dq, J= 4, 7 Hz, 2H) 2.74-2.66 (m, 2H), 2.64-2.56 (m, 2H), 2.44-2.38 (m, 1H), 2.08-2.03 (m, 1H), 2.01-1.94 (m, 1H), 1.42 (t, *J*=7 Hz, 3H), 1.20 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 188.2, 171.4, 141.4, 128.5, 128.2, 126.1, 68.3, 64.7, 40.2, 33.3, 31.0, 30.8, 14.4, 13.7

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