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**An Alternative Synthetic Pathway to  $\gamma$ -Lactam  
Compounds Through the Application of Novel  
Reformatsky-Type Chemistry**

By

Dylan Dupont

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Submitted in partial fulfillment of the requirements for Honors in the  
Department of Chemistry

UNION COLLEGE

June 2020

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## Abstract

DUPONT, DYLAN. An Alternative Synthetic Pathway to  $\gamma$ -Lactam Compounds Through the Application of Novel Reformatsky-Type Chemistry. Department of Chemistry, June 2020

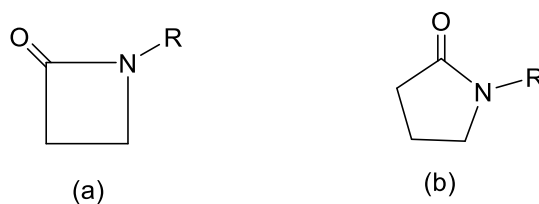
ADVISOR: James C. Adrian Jr. Ph.D.

It is the intent of the present report to relate the results of our attempt to elucidate and optimize a novel preparation of  $\gamma$ -lactam compounds. To achieve this end, it is proposed that the use of novel Reformatsky-type chemistry may provide a viable means. Generally, it has herein been validated that employment of  $\alpha$ -amino ketones in traditional Reformatsky chemistry will form the traditional Reformatsky ester-adduct, and that this adduct is capable of spontaneously undergoing an intramolecular cyclization event that yields the desired  $\gamma$ -lactam moiety. The main hurdle in this chemical pathway is an energetic one, as the cyclization event has showed itself to be slightly less spontaneous than predicted. However, this obstacle can be overcome by altering the solvent identity as to increase the heating capacity of the system.

The present study was hindered by inefficiencies in the preparations of ketone starting materials, all of which performed with markedly less fidelity than was purported by the literature. Therefore, improvements to the curation of starting materials will be necessary. Barring necessary amendments to the preparation of starting materials, the presently proposed Reformatsky-type chemistry appears to have great potential as a cogent and useful addition to the repertoire of synthetic strategies.

## 1. Introduction

Since their introduction in the mid-20th century, penicillin derivatives have comprised the majority of our library of antibacterial pharmaceuticals.<sup>1,2</sup> The aspect of their structure responsible for their antibacterial activity is a four membered cyclic amide known as the  $\beta$ -lactam ring (Fig. 1.a). The mechanism by which the  $\beta$ -lactam interacts with bacteria involves opening of the ring to inhibit transpeptidase and carboxypeptidase, enzymes crucial in the formation of peptidoglycan cell walls.<sup>3</sup> Therefore, the bacterial lethality of penicillins is attributed to the inhibition of peptidoglycan synthesis, which compromises bacteria cell wall integrity. Given the high fidelity of this interaction,  $\beta$ -lactam antibiotics have been heavily relied upon since their initial application. Due to the constant exploitation of this biochemical vulnerability, microbial resistance to these medications has developed.<sup>4</sup> In response, researchers have begun to explore possible analogues to combat bacterial resistance. One such category of analogues that would logically be of interest are compounds containing the  $\gamma$ -lactam moiety (Fig. 1.b).

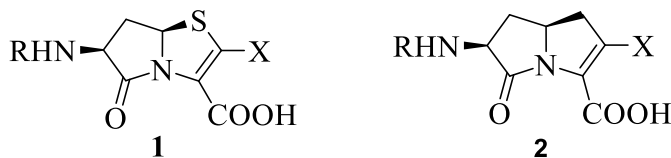


**Figure 1.** (a) General structure of the  $\beta$ -lactam moiety. (b) General structure of the  $\gamma$ -lactam moiety.

In 1986 the first two biologically active  $\gamma$ -lactam analogues were reported by independent research groups, one being Baldwin and co-workers (**1**) and another at Eli Lilly and Company (**2**).<sup>5</sup> Both reported synthesizing penem analogues containing  $\gamma$ -lactam cores,



while the Eli Lilly group also reported slight biological activity of a carbapenem  $\gamma$ -lactam analogue which also incorporated the presence of an electron withdrawing group (**2**).<sup>6-8</sup>

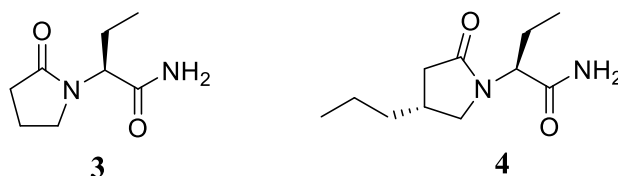


**Figure 2.** The first biologically active  $\gamma$ -lactam compounds.<sup>3</sup>

Multiple reports had previously concluded an absence of biological activity in synthesized  $\gamma$ -lactams, and so it was assumed that the strict presence of the  $\beta$ -lactam moiety endowed antibiotics with their activity. However, the findings of these two research groups disqualified the notion that only the  $\beta$ -lactam core itself could grant drugs antibiotic properties. It was agreed upon that the delocalization of the lactam nitrogen lone pair by the  $\pi$ -character of the thiophene-type ring or cyclopentene of the bicyclic system must be responsible for the reactivity of the analogues. This conclusion agreed with the findings of the Lilly group regarding **1** (Figure 2).<sup>9</sup> This implies that the five-membered  $\gamma$ -lactam ring is less inclined to mimic the ring opening mechanism by which the more strained four-membered  $\beta$ -lactam ring derives its activity. For the  $\gamma$ -lactam core to be a reactive antibiotic, and thereby be capable of replacing its predecessor, a more electrophilic aspect must be present for these compounds to participate in a suicide inhibition mechanism similar to that of  $\beta$ -lactam antibiotics.

Compounds containing  $\gamma$ -lactam cores have since been shown to display a broad array of other biological activities, including antibiotic, cytotoxic, anti-inflammatory and anticancer effects through various mechanisms.<sup>5</sup> In fact, several non-antibacterial  $\gamma$ -lactam based

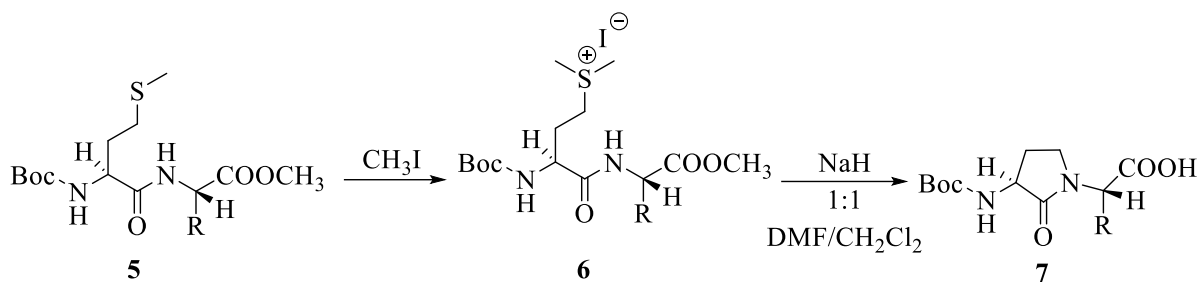
pharmaceuticals have already been brought to market. One such successful drug is an anticonvulsant with the trade name of Keppra™ (**3**).<sup>5, 10</sup> Another example is Briviact™ (**4**), a levetiracetam analogue- commonly referred to as brivaracetam- involving a cis-n-propyl substituent at the  $\beta$  position of the lactam, which was found to be ten-fold more effective in the treatment of epilepsy than its precursor **3** (Fig. 3).<sup>5, 11</sup> In a similar fashion, it has been shown that potency, metabolic stability and bioavailability can be enhanced by altering substituents on the lactam ring of  $\gamma$ -lactam based antitumor drugs that act as histone deacetylase inhibitors.<sup>12</sup> While the reactivities of these compounds are greatly influenced by the substituents of the lactam ring, the lactam moiety itself is also responsible for some properties demonstrated by these species. Pharmacokinetic studies found that compounds containing  $\delta$ -lactams exhibited weaker histone deacetylase inhibition than those containing  $\gamma$ -lactams. Docking studies concluded that  $\delta$ -lactams were less effective due to the poor fit of the expanded lactam ring within the enzyme's active site.<sup>13, 14</sup>



**Figure 3.** Anticonvulsant drugs Briviact™ (**4**) and its precursor Keppra™ (**3**).

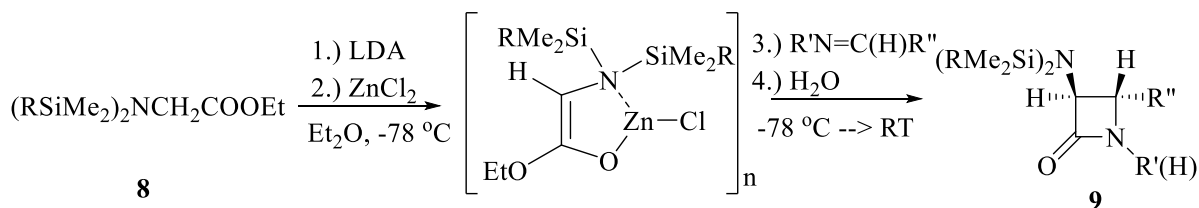
Given the wide range of biological capabilities of  $\gamma$ -lactam containing compounds, and the contribution of all structural aspects to their degree of reactivity, it seems that the utilization of biologically active starting reagents would best orient any proposed synthetic pathway towards biologically active end products. The literature supports this notion as there

exists a history of lactam syntheses involving amino acid and peptide starting materials. One such example is the formulation of renin inhibitory peptides containing the  $\gamma$ -lactam moiety. Renin, the enzyme responsible for a cascade pathway which physiologically leads to retention of sodium and water, plays a critical role in the maintenance of blood pressure. Artificial peptide mimics of renin pathway substrates- known as angiotensins- have been found to be successful inhibitors of the renin-angiotensin system. However, the longevity of the hypotensive effect these inhibitors produce has been essentially limited to the duration of the drug infusion. Therefore, improvement in the lifetime of the inhibitor-enzyme complex was desirable. This was accomplished by introducing a  $\gamma$ -lactam moiety to the peptide backbone of an angiotensin-type isostere. Formation of this ring structure along the backbone increased conformational rigidity, allowing the inhibitor to resist metabolic re-conformation upon encountering its target (Fig. 4). The success of this strategy is notable in that the presence of the lactam group did not interfere with substrate activity, thus reinforcing the notion that the lactam moiety will not be rejected by proteo-metabolic enzymes. This study employed two synthetic routes to achieve their desired  $\gamma$ -lactam bridged dipeptide isostere, with the most relevant preparation involving the formation of a  $\gamma$ -lactam structure via an intramolecular displacement reaction induced by basification of a methylated methionine sidechain.<sup>15-17</sup>



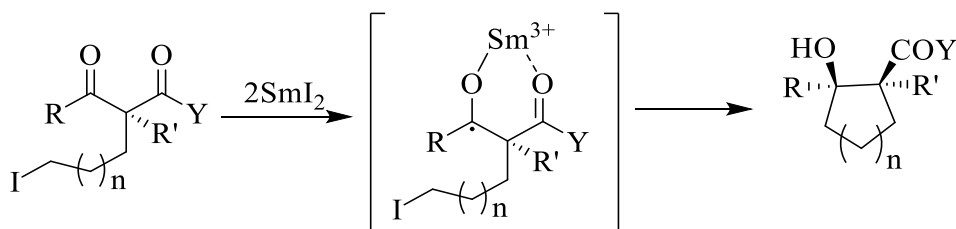
**Figure 4.** The pathway used to induce the intramolecular displacement and subsequent cyclization of a methionine residue side chain to its peptide backbone.<sup>17</sup>

Generally, there is a history of employing Reformatsky-type chemistry, involving the formation of zinc enolates which are reactive towards polar reagents with  $\pi$ -character, to induce cyclization in  $\alpha$ -amino acid type reagents to yield lactams. Many such preparations have been reported regarding the synthesis of  $\beta$ -lactams. One such technique employs imines to react with cyclized zinc-enolate adducts derived from  $\alpha$ -amino esters prepared via LDA. This reaction produces  $\beta$ -lactam structures that have maintained the N-protecting groups and the various possible substituents of the imine (Figure 5). These reactions offered good yield as well as remarkable stereoselectivity, favoring the trans conformation.<sup>18</sup> Other similar pathways to  $\beta$ -lactams, which exercise slightly alternative chemistry, have also been reported as generally stereoselective for the cis conformation.<sup>19</sup>



**Figure 5.** Reported Reformatsky-type chemistry involving  $\alpha$ -amino esters and imines to form  $\beta$ -lactams.<sup>18</sup>

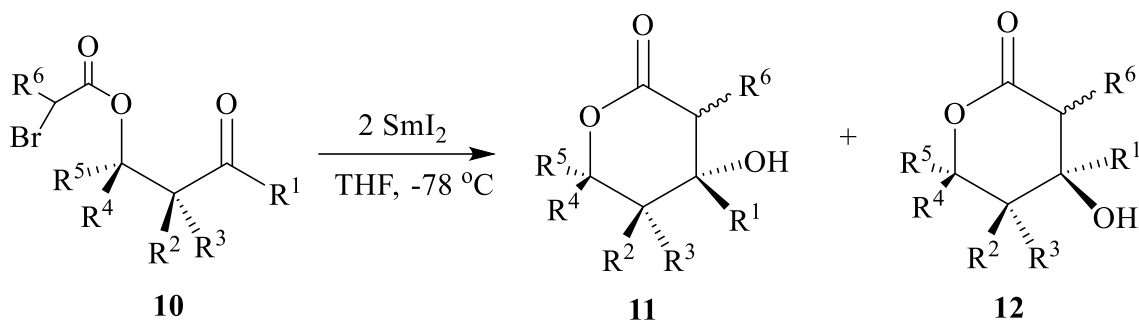
Intramolecular cyclizations have also been achieved at the carbonyl position of certain species using Barbier-type chemistry. These reactions, in much the same manner as Grignard reactions, reduce carbonyl positions to alcohols through the exploitation of alkyl halides. Much work has been reported concerning the employment of samarium diiodide ( $\text{SmI}_2$ ) as the reducing agent in Barbier-type chemistry (Fig. 6).  $\text{SmI}_2$  is widely reactive and the conditions required for the formation of carbocycles via this catalyst are mild. Given that the mechanism proceeds through a radical intermediate, introduction of a Lewis basic substituent can direct the cyclization such that stereospecific carbocycles are formed in a predictable fashion.<sup>20</sup>



**Figure 6.** The formation of carbocycles via intramolecular cyclization induced by Barbier-type chemistry catalyzed by samarium diiodide.<sup>20</sup>

This notion was applied to Reformatsky-type chemistry, where identical substrates with *a priori*  $\alpha$ -haloester substituents were subjected to react with  $\text{SmI}_2$  in place of alkyl zinc (Fig. 7). This chemistry successfully yielded lactone rings of various sizes with various degrees of stereospecificity. Reactions wherein the identity of the ester substrate was some  $\beta$ -haloacetoxy ketone proceeded with great stereochemical fidelity regarding 1,2 and 1,3-asymmetric inductions, producing  $\delta$ -valerolactone compounds. Such lactones synthesized by way of this chemistry are structurally similar to the pharmaceutically important compound

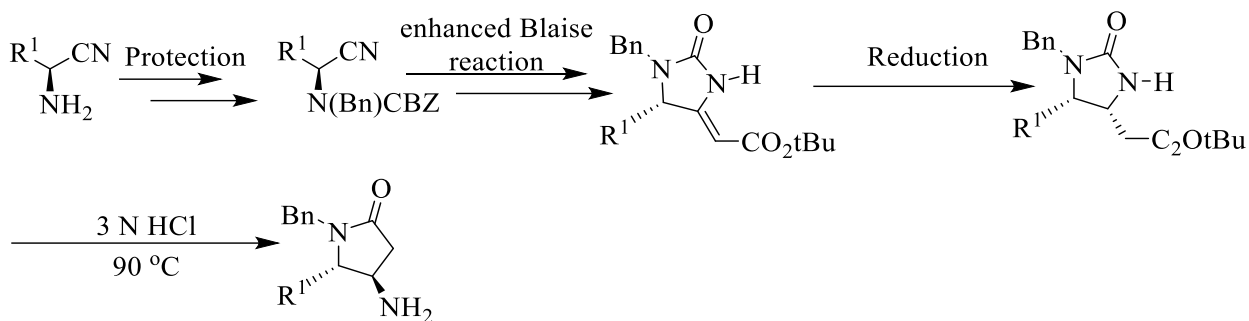
known as compactin.<sup>21</sup> This compound, isolated from *Penicillium citrium* in the search for additional antibacterial species, was found to act as an HMG-CoA Reductase inhibitor and was the first statin to be tested in clinical trials. It has served as the template for a majority of subsequent statin drugs.<sup>22</sup> However, it was observed by Molander, *et al.* that the obligate stereospecificity required for pharmacological import was only achieved when the directing stereocenter was within the Sm (III) chelate intermediate. It was also noted that Reformatsky-type reactions catalyzed by SmI<sub>2</sub> never appear to yield unsaturated lactones, whereas traditional Reformatsky chemistry catalyzed by alkyl zincs may tend towards dehydration of the newly formed alcohol position. However, this approach is not applicable to bulky ketones. Such groups sterically hinder the formation of the lactone forming C-C bond in the intermediate configuration. Therefore, the breadth of viable ring substituents is limited by the mechanistic pathway of this chemistry.<sup>21</sup>



**Figure 7.** The application of samarium diiodide catalyzed intramolecular cyclizations to Reformatsky-type chemistry.<sup>21</sup>

Similar chemistry has also been proven viable in the formation of  $\gamma$ -lactams. It has long been known that Blaise-type chemistry using THF as solvent is capable of synthesizing  $\beta$ -enamino

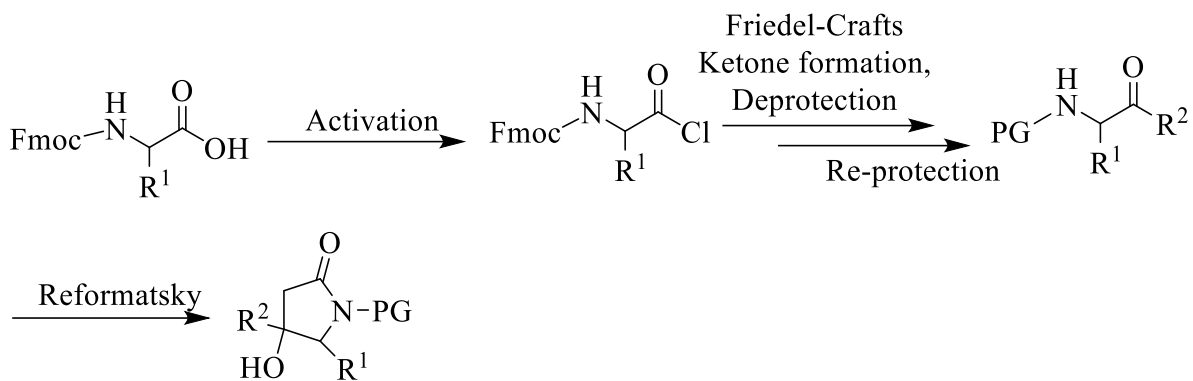
esters with great fidelity.<sup>23</sup> The Blaise reaction is in itself a deviation of Reformatsky chemistry. Its accepted mechanistic pathway involves an  $\alpha$ -imine zincate ester intermediate which results from the complexation of  $\alpha$ -bromozinc esters with nitriles. This is opposed to traditional Reformatsky reactions, which mechanistically include the formation of  $\alpha$ -bromozinc ester dimers that interact with carbonyl moieties. It has been reported that  $\beta$ -enamino esters produced by enhanced Blaise chemistry involving  $\alpha$ -amino nitrile derivatives of  $\alpha$ -amino acids can yield 4-aminopyrrolidinone, a  $\gamma$ -lactam compound. The initial general approach used to induce the intramolecular cyclization involved reduction and deprotection of the resulting  $\beta$ -enamino ester. However, this approach resulted in a complex mix of poor yield. Yields and stereospecificity were improved through further protection of the  $\alpha$ -amino nitrile. The major products obtained by the subsequent Blaise reaction were 2-imidazolidinone analogues, while the minor products, acyclic enamino esters, could be converted to the major product by introduction of NaH. These compounds were then reduced and subjected to hydrogenolysis to give the desired  $\gamma$ -lactams (Figure 8).<sup>24</sup> Particular reduction conditions imparted particular diastereotopic outcomes in good yields. However, possible substituents are limited to the  $\gamma$  and nitrogen positions of the lactam. Furthermore, the only substituent types confirmed using this approach are alkyl groups and benzyl.



**Figure 8.** General approach to the preparation of  $\gamma$ -lactams by way of Blaise-type chemistry. Only major products are included. It should also be noted that the most stereoselective approach involved iso-propyl at the  $R^1$  position, resulting in a 99-fold preference for the cis conformation following reduction with sodium cyanoborohydride.<sup>21</sup>

It is the intention of the current report to introduce a new approach to the preparation of  $\gamma$ -lactam compounds. The proposed pathway should produce more substituted  $\gamma$ -lactams with a wider variety of substituents, which will in turn grant entry to the modification of chemical species with  $\gamma$ -lactam cores. To enhance the probability of biologically active end products, we wish to use L-amino acid starting materials in order to exploit the chiral pool. These Fmoc-protected amino acids are activated to allow for the formation of  $\alpha$ -amino ketones, invoking conditions under which the amine is deprotected. Subsequent reprotection of the  $\alpha$ -amino ketone, and subjection of this compound to Reformatsky-type conditions, produces an adduct which independently cyclizes to give the desired  $\gamma$ -lactam (Figure 9).





**Figure 9.** Generalization of the synthetic pathway currently proposed.

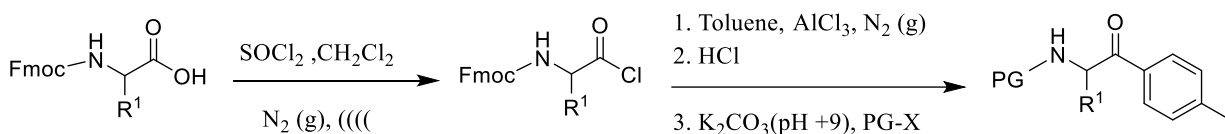
Variability in substituent identity may be introduced by this general pathway at three of the five ring positions: identity of the amino acid controls the substituent at the  $\gamma$  position as its side chain remains present, the ketone forming substituent at what would be the C-terminus of the amino acid is present at the  $\beta$  position and removal of the N-protecting group would allow for alterations at the N-position. Outcomes using the described pathway to synthesize various  $\gamma$ -lactam compounds are described herein.

## 2. Results & Discussion

The presently proposed pathway can be conceived of in two sequential processes: the preparation of N-protected cathinone-type reagents and their subsequent employment in the Reformatsky-type chemistry of interest. Each aspect of the preparation has been compartmentalized and addressed in an individualistic manner.

### 2.1. Preparation of the N-protected cathinone-type materials

Initiation of this procedure requires the preparation of  $\alpha$ -amino acid chlorides. This was easily accomplished by sonicating commercially obtained Fmoc-amino acids with thionyl chloride, as dictated by the literature.<sup>25</sup> This activated acid was then taken up in a “one-pot” fashion and subjected to Friedel-Crafts chemistry. It is worthy of note that catalyzing this reaction with a small excess of aluminum chloride resulted in cleavage of the Fmoc protecting group, as reported by DiGioia and co-workers.<sup>26</sup> The resulting free amine was subsequently isolated and re-protected by some easily removable substituent (Scheme 1).



**Scheme 1.** Pathway traversed to acquire the N-protected cathinone-type starting materials.

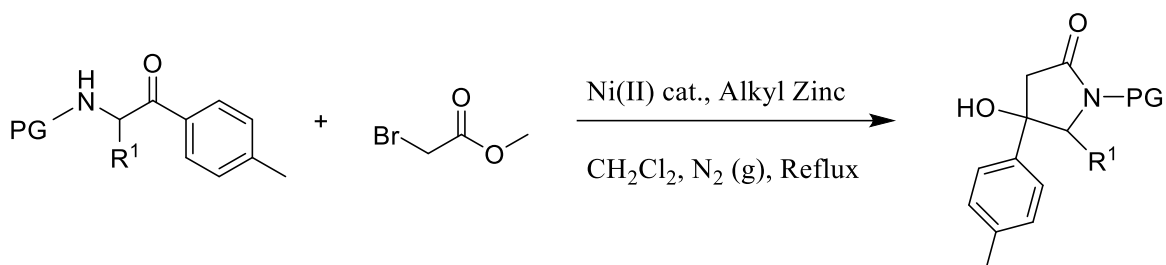
Several limitations presented themselves upon execution of this process, the first of which being the breadth of allowable aromatic moieties installed via the Friedel-Crafts acylation. It is known that Friedel-Crafts chemistry is incapable of substituting both mildly and strongly deactivated aromatics. Accordingly, this chemistry was found to be successful

in substituting the activated acid when the aromatic moiety employed was either benzene or toluene. However, more activated species, such as anisole, gave poor yields. This is in alignment with the literature, which reports that such nucleophilic species tend to complex with aluminum chloride.<sup>27,28</sup> Such complexing renders the electrophilic-aromatic substitution of moderately to strongly activated species a non-viable preliminary step for sequential synthetic pathways. Further constraining our scope of possible aromatic ketones was the apparent inability of species bearing multiple mildly activating substituents to participate in the desired chemistry. Attempts to convert the activated acid halides to *o*-xylene ketones resulted in poor yields. This particular result could not be reconciled with expectations. Meanwhile, the range of possible protecting groups added to the free amine was limited by its resilience towards Reformatsky conditions and the desire for a  $\gamma$ -lactam end-product easily suited to further manipulation. The protecting group only complicated this phase of the pathway when the identity of the group was trifluoro acetyl. Recovery of the ketone was less efficient when the protecting group was incorporated following the formation of the free amine and was markedly decreased when the amino acid identity was L-alanine.

## 2.2. Formation of $\gamma$ -lactam compounds

The resulting collection of N-protected cathinone-type compounds were subsequently employed in Reformatsky-type chemistry to attain  $\gamma$ -lactam species as described by scheme 2. The conditions were altered such that the identities of the solvent and nickel catalyst were varied in concert to enhance the efficacy of the present chemistry. The first nickel catalyst used was [1,3-Bis(diphenylphosphino)propane]dichloronickel (II) (Ni(dppp)Cl<sub>2</sub>). Modest yields were obtained following a separation made challenging both by a persistent emulsion that presented itself upon quenching and residual nickel material that was not consumed

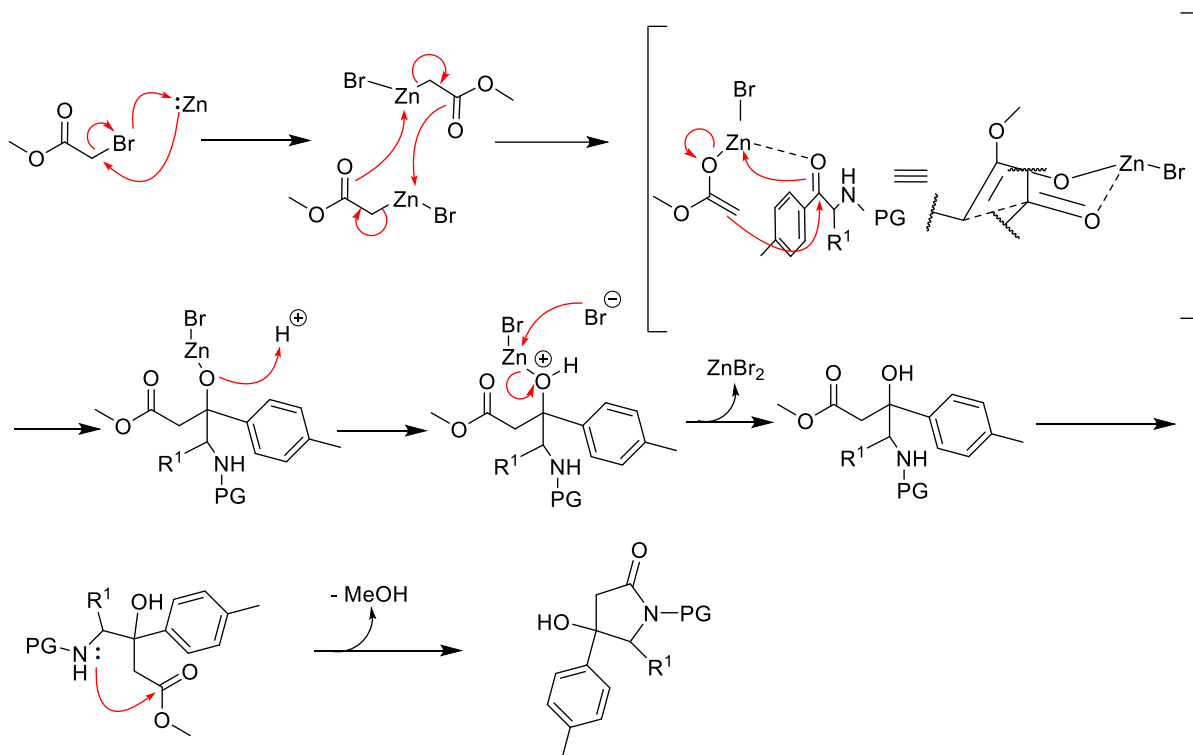
within the emulsion. The second nickel catalyst utilized was Bis(triphenylphosphine)nickel (II) chloride ( $\text{Ni}(\text{tppp})\text{Cl}_2$ ), which presented with similarly modest yields but a less persistent emulsion that did not result in residual nickel material in the aqueous phase during separation. While the identity of the nickel (II) catalyst did not have a notable effect on the yield, the identity of the solvent appeared to be of greater import to the efficiency and efficacy of the reaction. A sequence of solvents was exploited to manipulate the heating capacity of the system to address the inefficacy of the anticipated spontaneous cyclization of the Reformatsky adduct.



**Scheme 2.** Formation of the desired  $\gamma$ -lactam via novel Reformatsky-type chemistry

Generally, most attempts led to the formation of a mixture of adduct and cyclized lactam. The traditional Reformatsky aspect of the chemistry occurred with expected fidelity, and so our efforts came to be focused on ushering the consistently formed adduct towards spontaneous cyclization. The mechanistic pathway of this phase is illustrated in figure 10. Initially, the system composition included dry dichloromethane. The collection of N-protected cathinone-type compounds previously prepared were employed under such conditions, and all appeared to yield some mix. It appears that L-glycine material may have produced greater total yields as well as possibly having resulted in more favorable adduct-

lactam ratios comparatively to the L-alanine population. Given that excess time was allotted to all preparations according to TLC, it was determined that raising the reflux point of the system might provide conditions sufficient to increase the probability of achieving the proper intermediate orientation for the intramolecular interaction that is the quintessence of the cyclization event.



**Figure 10.** Mechanistic pathway underlying the second phase of the second phase of the general synthetic pathway, describing both the formation of the traditional Reformatsky adduct and the subsequent crucial cyclization event.

It followed that the same chemistry was attempted in tetrahydrofuran. The trend of lower total yields for the L-alanine compounds continued in the new solvent. However, it was confirmed that under these conditions all ester adduct species formed from the Ac-

alanine-toluene ketone performed the desired intramolecular cyclization. In the case of the Ac-glycine-toluene ketone, it seems that the adduct only partially cyclized. It could be the case that the less sterically incumbered glycine aspect of the adduct has somewhat greater probability of existing in a wider range of three-dimensional orientations relative to the rest of the adduct. This increase in possible locants could explain the apparent decreased probability of the glycine adduct orienting itself in a manner conducive to spontaneous cyclization. However, further trials are necessary to substantiate this claim. The results for the Ac-alanine-toluene trial supported the notion that increased thermal input could improve  $\gamma$ -lactam formation, thus cyclization of the glycine species was reattempted within a system utilizing dichloroethane as solvent to increase its heating capacity. Strangely, these conditions unexpectedly led to a null reaction. It is suspected that impurities or some other procedural error compromised this trial, therefore further work is necessary to assess the viability of this solvent for use in the present chemistry.

### 3. Conclusions

The potential utilization of Reformatsky-type chemistry in the preparation of  $\gamma$ -lactam compounds from  $\alpha$ -amino acid starting materials has shown promise. Once the allowed aromatic ketone starting materials were identified, the Reformatsky-type chemistry efficaciously formed the traditional Reformatsky adduct. The proposed novel application of this Reformatsky chemistry was complicated by the intramolecular cyclization of this adduct, which proved less spontaneous than predicted. However, this issue was seemingly resolved by increasing the heating capacity of the system. Under the proper conditions, ketone formation and subsequent employment of the Reformatsky-type chemistry produce the desired lactams in good yields. Further experimentation will be required to optimize both phases of this pathway. Firstly, it will be necessary to enhance the efficacy of the *in situ* cyclization of the adduct. Secondly, it will also be necessary to continue attempting to incorporate a spectrum of possible substituents on the lactam core as to grow the library of compounds accomplished by this chemistry.

#### 4. Future Works

Improving the efficacy of the intramolecular cyclization event will be key to optimizing the Reformatsky phase of the pathway. It was observed that the use of THF as solvent during this phase of the preparation lead to greater yields of cyclized adduct when compared to prior attempts made with DCM as solvent. It is believed that the greater refluxing point of the THF system granted the adduct sufficient energy to perform the desired cyclization, thus it would seem that the use of solvents with even higher boiling points would further enhance the efficacy of the cyclization event. In particular, future trials should implement dichloroethane as the choice solvent. The use of this solvent inexplicably resulted in a null reaction during the present study. This bizarre finding will require reaffirmation if it is to disprove the notion that greater system heating capacity is the solution to the apparent energetic hurdle challenging the cyclization event.

The most obvious avenue by which the  $\alpha$ -amino acid modification phase could be enhanced, granting a wider variety of  $\alpha$ -amino ketones, would be to abandon the Friedel-Crafts electrophilic aromatic substitution approach to forming the ketones. With knowledge that the overall pathway is viable with aromatic ketones prepared by this method when using singly substituted, weakly activated aromatic moieties, it might be necessary to move towards testing the feasibility of ketones with normal alkyl chains, bulky alkyl groups or other possible substituents. No steric implications should be introduced to the process according to the accepted mechanisms for the Reformatsky reaction and the presently proposed cyclization event. Another possible avenue could be the use of different amino acid starting materials, as only glycine and alanine were explored in the present report. Both modifications would contribute to expanding the library of compounds produced through this



novel synthetic pathway and lend the current proposal greater validity regarding its applicability as a general approach to produce  $\gamma$ -lactam compounds.

## 5. Experimental Section

### 5.1. General methods

NMR spectra were acquired using a 400 MHz Bruker Avance III. The resulting spectroscopic data was presented across a delta scale in units of parts per million (ppm) relative to a tetramethylsilane (TMS) signal lock introduced to the sample upon collection of the isolated product in deuterated chloroform.

### 5.2. General procedure for *N*-protected $\alpha$ -amino ketone materials

Thionyl chloride (15.0 mmol, 1.10 mL) was introduced to a solution of Fmoc-protected L-amino acid (1.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15.0 mL). The system was placed under an inert atmosphere and then sonicated for approximately 1 h. The system was then placed *in vacuo* to afford the isolated acid chloride in the form of a white solid.<sup>25</sup> This material was taken up in toluene (approximately 10 mL) and the resulting solution received a portion of pulverized AlCl<sub>3</sub> (4.14 mmol, 0.55 g). The reaction was stirred under argon for approximately 3.5 h before being quenched with 1M HCl<sub>(aq.)</sub> (approximately 8 mL). The biphasic system was then separated, and the organic phase was washed 3x with 1M HCl<sub>(aq.)</sub>. The aqueous portions were collected and basified by K<sub>2</sub>CO<sub>3</sub> to a pH of 9. CH<sub>2</sub>Cl<sub>2</sub> (approximately 10 mL) was then introduced to induce a biphasic system which was subsequently subjected to some protecting-group reagent (1.8 mmol).<sup>26</sup> The organic phase was then separated, the aqueous layers washed 3x with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic portions were then washed sequentially with deionized H<sub>2</sub>O, saturated NaHCO<sub>3</sub> and brine. The washed organic bulk was then dried over MgSO<sub>4</sub>, filtered and placed *in vacuo* to afford the isolated *N*-protected cathinone type material in the form of a white solid.

#### 5.2.1. 2-(*N*-CBZ-amino)-1-(methylphenyl)-1-propanone (**13**)

The title compound was obtained by masking the free alanine-amine with benzyl chloroformate. Yield: 78%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.83 (d, 2H, J = 0.02), 7.30 (m, 9H), 7.18 (d, 2H, J = 0.02), 5.88 (d, 1H, J = 0.01), 5.38 (m, 1H), 5.12 (s, 2H), 2.42 (s, 3H), 1.43 (d, 3H, J = 0.01).

#### 5.2.2. 2-(*N*-Ac-amino)-1-(methylphenyl)-1-propanone (**14**)

The title compound was obtained by masking the free alanine-amine with acetic anhydride. Yield: 78%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.89 (d, 2H, J = 0.02), 7.29 (d, 2H, J = 0.02), 6.63 (d, 1H, J = 0.01), 5.46 (m, 1H), 2.43 (s, 3H), 2.06 (s, 3H), 1.42 (d, 3H, J = 0.01).

#### 5.2.3. 2-(*N*-TFA-amino)-1-(methylphenyl)-1-propanone (**15**)

The title compound was obtained by masking the free alanine-amine with trifluoroacetic anhydride. Yield: 26%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.84 (d, 2H, J = 0.02), 7.23 (d, 2H, J = 0.02), 5.22 (m, 1H), 4.47 (d, 1H, J = 0.01), 2.35 (s, 3H), 1.42 (d, 3H, J = 0.02).

#### 5.2.4. 2-(*N*-CBZ-amino)-1-(methylphenyl)-1-ethanone (**16**)

The title compound was obtained by masking the free glycine-amine with benzyl chloroformate. Yield: 66%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.86 (d, 2H, J = 0.02), 7.38 (m, 6H), 7.29 (d, 2H, J = 0.02), 5.82 (d, 1H, J = 0.01), 5.15 (s, 2H), 4.70 (d, 2H, J = 0.01), 2.42 (s, 3H).

#### 5.2.5. 2-(*N*-Ac-amino)-1-(methylphenyl)-1-ethanone (**17**)

The title compound was obtained by masking the free glycine-amine with Acetic anhydride. Yield: 62%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.87 (d, 2H, J = 0.02), 7.29 (d, 2H, J = 0.02), 6.58 (s, 1H), 4.73 (d, 2H, J = 0.01), 2.43 (s, 3H), 2.10 (s, 3H).

### 5.2.6. 2-(*N*-TFA-amino)-1-(methylphenyl)-1-ethanone (**18**)

The title compound was obtained by masking the free glycine-amine with trifluoroacetic anhydride. Yield: 51%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.87 (d, 2H,  $J = 0.02$ ), 7.24 (d, 2H,  $J = 0.02$ ), 4.71 (d, 2H,  $J = 0.01$ ), 2.36 (s, 3H).

### 5.3. General procedure for $\gamma$ -lactam materials

Bis(triphenylphosphine)nickel (II) chloride ( $\text{Ni}(\text{tppp})\text{Cl}_2$ ) (0.02 mmol, 0.0133 g) and methyl bromoacetate (0.663 mmol, 0.0634 mL) were added to a solution of the cathinone-type material (0.51 mmol) in dry organic solvent (approximately 5 mL). The system was set stirring and refluxing under an inert atmosphere prior to the dropwise addition of 1M diethyl zinc in hexanes (5.1 mmol, 5.1 mL). The reaction proceeded in this manner for approximately 3 h before being quenched with 1M  $\text{HCl}_{(\text{aq.})}$  (approximately 8 mL) and then being subsequently set to stir for an additional 30 min. The organic phase was then separated, the aqueous phase was washed 3x with aliquots of the organic solvent which were combined with the primary organic portion and then washed sequentially with deionized  $\text{H}_2\text{O}$ , saturated  $\text{NaHCO}_3$  and brine. The washed organic bulk was then dried over  $\text{MgSO}_4$ , filtered and placed *in vacuo* to afford the desired  $\gamma$ -lactam compound in the form of a brownish-yellow oil.

#### 5.3.1. 3,3-hydroxyl,methylphenyl-4-methyl-5-(*N*-CBZ)-azolidone (**19**)

The title compound was obtained through the employment of **13** in the Reformatsky-type chemistry presently proposed in dry  $\text{CH}_2\text{Cl}_2$ . Total cyclization was not afforded. Yield: 39%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.89 (d, 2H,  $J = 0.02$ ), 7.31 (m, 14H), 6.23 (s, 1H), 3.76 (s, 1.5H), 3.15 (m, 3H), 2.30 (s, 3H), 1.45 (d, 1H,  $J = 0.02$ ), 1.37 (d, 2H,  $J = 0.02$ ).

### 5.3.2. 3,3-hydroxyl,methylphenyl-4-methyl-5-(N-Ac)-azolidone (**20**)

The title compound was obtained through the employment of **14** in the Reformatsky-type chemistry presently proposed in both dry CH<sub>2</sub>Cl<sub>2</sub> and THF. Complete adduct cyclization was afforded using THF as solvent. Yield: 30% (CH<sub>2</sub>Cl<sub>2</sub>), 21% (THF); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.28 (d, 2H, J = 0.02), 7.14 (d, 2H, J = 0.02), 5.99 (d, 1H, J = 0.02), 3.49 (s, 3H, only observed in CH<sub>2</sub>Cl<sub>2</sub>), 2.99 (q, 2H, J = 0.04, shift for product of THF system), 2.93 (q, 2H, J = 0.04, shift for product of CH<sub>2</sub>Cl<sub>2</sub> system), 2.32 (s, 3H), 2.04 (s, 4H), 0.81 (d, 3H, J = 0.02).

### 5.3.3. 3,3-hydroxyl,methylphenyl-5-(N-CBZ)-azolidone (**21**)

The title compound was obtained through the employment of **16** in the Reformatsky-type chemistry presently proposed in dry CH<sub>2</sub>Cl<sub>2</sub>. A slight amount of ester-adduct is suspected to have gone uncyclized. However, cyclization in this instance was notably improved relative to the preparation of **19**. Yield: 43%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.84 (d, 2H, J = 0.02), 7.31 (m, 9H), 4.64 (s, 1H), 3.73 (m, 3H), 2.93 (q, 2H, J = 0.04, 0.22).

### 5.3.4. 3,3-hydroxyl,methylphenyl-5-(N-Ac)-azolidone (**22**)

The title compound was obtained through the employment of **17** in the Reformatsky-type chemistry presently proposed in THF and dry CH<sub>2</sub>Cl<sub>2</sub>. In this instance as well, it seems cyclization was better achieved in THF as opposed to CH<sub>2</sub>Cl<sub>2</sub>. Yield: 72% (in CH<sub>2</sub>Cl<sub>2</sub>), 73% (in THF); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.79 (d, 2H, J = 0.02), 5.95 (s, 1H), 3.49 (s, 3H), 2.81 (q, 2H, J = 0.04, 0.14), 2.25 (s, 3H), 1.87 (s, 3H).

### 5.3.5. 3,3-hydroxyl,methylphenyl-5-(N-TFA)-azolidone (**23**)

The title compound was obtained through the employment of **18** in the Reformatsky-type chemistry presently proposed in dry CH<sub>2</sub>Cl<sub>2</sub>. Yield: 49%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.19 (m, 4H), 3.73 (s, 0.6H), 2.77 (m, 2H), 2.27 (d, 2H, J = 0.02), 1.18 (s, 3H).

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