
Two important facets that are found in many biologically active compounds and complex natural products are chirality and heterocyclic motifs, in particular lactones and lactams. Biologically active compounds found in nature often need to be synthesized due to the fact that only a minute amount of the active molecule is produced.

In the research described herein, an asymmetric methodology known as desymmetrization is utilized to produce enantioenriched compounds that can be used as building blocks in the synthesis of biologically active natural products. We have developed an efficient synthesis of enantioenriched γ- and δ-lactones via an enantioselective desymmetrization. In this process, racemic diesters in the presence of a chiral Brønsted acid selectively undergo cyclization to yield enantioenriched γ- and δ-lactones. The methodology is also expanded to include the synthesis of spirocyclic molecules. The desymmetrization is highly selective and the products formed contain an all-carbon quaternary stereocenter that would be difficult to install using other methodologies.
ENANTIOSELECTIVE CYCLIZATION OF SYMMETRIC DIESTERS

by

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the Faculty of The Graduate School at
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Doctor of Philosophy

Greensboro
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Approved by

Committee Chair
To my family and friends, thank you for your endless belief in me throughout my academic journey.

To Chris, thank you for your extraordinary support and encouragement.
This dissertation written by Jennifer E. Wilent has been approved by
the following committee of the Faculty of The Graduate School at The University
of North Carolina at Greensboro.

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Committee Members ________________________________

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Date of Acceptance by Committee

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Date of Final Oral Examination
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CHAPTER I
INTRODUCTION

1.1 Chirality and Heterocyclic Compounds

Two important components that are commonly found in various biologically active compounds are chirality and heterocyclic structures. Many biologically important compounds contain a chiral center whose absolute configuration is vital to its physiological activity. The specific geometry of a bioactive molecule can dictate its interaction with a chiral protein or enzyme. Thus, chirality plays a critical role in the activity of biologically important compounds such as drug candidates and complex natural products. A classic example of the importance of chirality is the infamous drug, thalidomide (Figure 1).

![Figure 1. (R)- and (S)-Thalidomide](image)

Racemic thalidomide was first introduced to the market in the early 1950s and was prescribed to treat nausea in pregnant women.² It was withdrawn from the
market in 1961 due to the fact that it caused birth malfunctions such as as phocomelia. It is proposed that the $R$ enantiomer (1) is the effective anti-nausea agent whereas the $S$ enantiomer (2) is the cause of the negative side effects. Thalidomide is currently banned in many countries because of its ability to racemize in vivo thus the enantiomers can interconvert in the body. The thalidomide crisis brought to light that the absolute configuration of drug compounds is important and the different stereoisomers of the molecules may have different biological activities. This has caused the FDA and the pharmaceutical industry to focus on the production of single enantiomer drugs rather than racemic mixtures.

Compounds found in nature that are identified as medicinally beneficial to human health frequently exist as a complex mixture and are sometimes produced in such small quantities that they cannot be fully evaluated for their potential health advantages. A well-known example is the anticancer drug Taxol (3), a natural product isolated from the extracts of the bark of the Pacific Yew, *Taxus brevifolia* (Figure 2). Taxol was first discovered in the early 1960s and exhibited significant cytotoxic and antileukemic activity for several cancers however its production in nature was limited. The availability of the bark is sparse with a reported isolation yield of 0.014% and isolating a sufficient amount of taxol would lead to the depletion in the yew tree population. Hence, the total synthesis of taxol became a prime synthetic target for organic chemists and has been of interest since the 1980s with several advancements being made.
The exploration and future use of these significant materials often is parallel to the ability of a synthetic chemist to prepare them in an efficient and selective manner. Thus, it is essential for synthetic chemists to develop facile high yielding syntheses for enantioenriched molecules such as drug candidates and biologically active natural products. In particular, syntheses need to focus on chiral highly functionalized small molecules that can be building blocks for the synthesis of complex molecules.

1.2 Asymmetric Methodologies

The field of asymmetric methodology development has been of much interest due to the need for the synthesis of non-symmetric molecules. Types of methodologies that have been developed include kinetic resolutions and desymmetrizations.

Figure 2. The Anti-Cancer Drug, Taxol
1.2.1 Kinetic Resolution

Kinetic resolution is a synthetic technique which allows chemists to achieve separation of enantiomers in a racemic mixture by utilizing a chiral catalyst or reagent (Figure 3). In kinetic resolution, both enantiomers of a racemic starting material (SM) react with the chiral catalyst at different rates \( k_S \) and \( k_R \) to form an enantioenriched product (P). The relative rate of the reaction is determined by the difference in the activation energies of each enantiomer in the rate limiting step \( \Delta \Delta G^\ddagger \). The difference of rates will result in the enantioenriched product \( P_S \) as well as enantioenriched recovered starting material \( SM_R \). The faster rate has the lower activation energy which leads to the enantiomeric product being formed selectively. Both \( P_S \) and \( SM_R \) have the potential of achieving up to 50% yield and 100% enantiomeric excess (ee). The maximum possible yield of a single enantiomer compound is 50% due to the fact that you begin with a racemate. However the theoretical total mass recovery of enantioenriched material is 100%.
An example of a kinetic resolution can be seen in a recent publication from the Petersen lab which reported an efficient synthesis of α-substituted hydroxy esters via a kinetic resolution. Bulky racemic esters (4) in the presence of a chiral Brønsted acid selectively lactonize to yield a recoverable enantioenriched hydroxy esters (3) and produced enantioenriched lactones (5) (Figure 4).
1.2.2. Desymmetrization

Desymmetrization of prochiral molecules to yield enantioenriched products is a powerful synthetic technique and is a variant of kinetic resolution.\textsuperscript{8} Desymmetrization begins with a symmetrical prochiral molecule that possesses a plane of symmetry and two enantiotopic groups (Figure 5). A chiral reagent is introduced which allows for the differentiation of the two enantiotopic groups to yield an enantioenriched product. In contrast to the kinetic resolution of a racemic mixture, in a desymmetrization the product has the potential result of 100\% yield and 100\% ee.

Figure 5. General Schematic of Desymmetrization

An example of a desymmetrization can be seen in a recent publication which involves asymmetric bromolactonization of alkynes.\textsuperscript{9} The stereoselective synthesis of bromoenol lactones (7) via enantioselective halolactonization of nonconjugated alkynoic acids (6) was reported (Figure 6). The produced bromoenol lactones contained a tetrasubstituted alkene and a quaternary stereocenter and were formed with high yield and excellent selectivity.
1.3 Chiral Brønsted Acid Catalysts

The desymmetrization of prochiral molecules to obtain chiral enantioenriched products with an enzyme or organocatalyst is a powerful synthetic technique. In particular, the desymmetrization of prochiral diester malonates via enzyme-mediated partial hydrolysis has generated much synthetic interest.\textsuperscript{10} However, this technique is limited by enzyme instability and the difficulty in catalyst recovery and reuse.

The use of chiral Brønsted acid catalysts is a rapid growing area in organocatalysis.\textsuperscript{11} Typical catalysts are based on TADDOL (8), thiourea (9), camphoric sulfonic acid (10), or BINOL phosphoric acids (11-14) (Figure 7).\textsuperscript{12} The benefits of these catalysts are the low catalyst loadings, mild reaction conditions, and the application to a wide range of substrates
The BINOL-based phosphoric acid catalyst 14 contains a triisopropyl phenyl group at the 3 and 3’ position and will be the catalyst of choice for the enantioselective cyclization processes discussed in later chapters. The chiral acid serves to activate carbonyl compounds through either a hydrogen bonding event or full Brønsted acid catalysis (Figure 8). The catalyst selectively promotes cyclization of one enantiomer of a prochiral diester by initializing a nucleophilic attack of the carbonyl which is then followed by the release of the product and turnover of the catalyst.
It is proposed that because of steric clashing, one enantiotopic group of the diester substrate will bind preferentially to the chiral catalyst (complex 15 favored and complex 16 disfavored) (Figure 9). The enantiotopic group that binds more favorably will then progress to the enantioenriched product.

Figure 8. BINOL Phosphoric Acid Catalyst 14 and Carbonyl Activation

Figure 9. Proposed Binding of Chiral Catalyst 14
1.4 Conclusion

In the research presented in this dissertation, the asymmetric methodology known as desymmetrization will be utilized to produce enantioenriched compounds that have the potential to be used as building blocks in the synthesis of biologically active natural products. We describe an efficient synthesis of enantioenriched γ- and δ-lactones that contain an all-carbon quaternary stereocenter via an enantioselective desymmetrization. Racemic diesters in the presence of a chiral Brønsted acid selectively undergo cyclization to yield enantioenriched γ- and δ-lactones. The methodology is also expanded to include the synthesis of spirocyclic molecules.
CHAPTER II
ASYMMETRIC SYNTHESSES OF ENANTIOENRICHED LACTONES

2.1 Introduction

The stereoselective formation of all-carbon quaternary centers is typically achieved by the asymmetric construction of a new carbon-carbon bond. The challenge encountered with this approach is the steric repulsion between the carbon substituents. A different method involves the desymmetrization of prochiral molecules which entails the formation of a quaternary center as separate from the enantiodetermining step (Figure 10). The prochiral molecule 17 contains a pre-existing all-carbon quaternary center and upon the introduction of a chiral catalyst, a new compound 18 is produced with an all-carbon quaternary stereocenter.

Figure 10. Desymmetrization of a Prochiral Molecule
The lactone motif is seen in many biologically active molecules, and in particular enantiopure lactones with a fully substituted carbon α to the carbonyl are common. (+)-Hopeahainol A (19)\(^{14}\) which has proven to be an acetylcholinesterase inhibitor that is associated with Alzheimer’s disease and (S)-camptothecin (20)\(^{15}\) which exhibits anti-cancer activity through topoisomerase I inhibition are two examples (Figure 11).

Figure 11. Lactone Natural Products with an α-Chiral Center

As recently published by the Petersen lab, the desymetrization of hydroxy diester 21a in the presence of chiral Brønsted acid 14 produced lactone 22a in high yield and excellent enantioselectivity (Figure 12).\(^ {16}\) It is hypothesized that the reaction proceeds through selective activation of one of the esters with the chiral phosphoric acid followed by an intramolecular lactonization. Based on this
encouraging initial result, we also explored the full scope of the desymmetrization process and the utilization of the lactone product.

![Figure 12. Initial Desymmetrization of Hydroxy Diester](image)

Construction of enantioenriched α-carboxy-γ-lactones such as 22a containing a quaternary center has been previously explored due to the high utility of such compounds. Acylation of silyl ketene acetals has been accomplished with chiral DMAP derivatives,\textsuperscript{17} isothiourea,\textsuperscript{18} or thiourea catalysts,\textsuperscript{19} however results are limited to aryl R groups and/or a need for dissubstitution of the γ-carbon. Diastereoselective conjugate addition of an enolate equivalent is another strategy that has yielded some promising results, yet the scope of acceptable Michael acceptors is limited.\textsuperscript{20} Most recently, a method for the enantioselective α-alkylation of α-\textit{tert}-butoxycarbonyllactones through phase-transfer catalysis was revealed, however substitution was limited to benzylic or allylic groups.\textsuperscript{21} The methodology described here, whereby a chiral Brønsted acid 14 catalyzes the
cyclization of a symmetric substrate to deliver an enantioenriched lactone, takes advantage of the differentiation of the two enantiotopic ester groups. The lactone products obtained through variation of the methyl group to other substitution patterns are valuable compounds carrying a challenging all-carbon quaternary center (when R \neq H).

2.2 Results and Discussion

The synthesis of diester substrates such as 21a begins with the mono alkylation of di-tert-butyl malonate (23) with sodium hydride and methyl iodide. A second alkylation with 2-bromoethyl acetate and subsequent hydrolysis yields hydroxy diester 21a in 3 short steps and 52% overall yield (Figure 13).

![Figure 13. Preparation of Prochiral Substrates](image)

Various substrates (Table 1, 21b–g) were studied, ranging in length and branching. Each substrate was prepared as substrate 21a, but using the appropriate alkyl halide in the first alkylation step. Gratifyingly, modification of the original methyl group in 21a with larger groups such as ethyl 21c, isopropyl
21d, allyl 21e and benzyl 21f all yielded enantioenriched lactones containing an all-carbon quaternary stereocenter that would be difficult to install using other methodologies in good to excellent yields (67–97%) and enantiopurity greater than 90%. Replacement of the methyl group with a proton 21b, generated lactone 22b in excellent yield and good enantiopurity (93% yield and ee = 91%).

Based on the successful generation of enantioenriched γ-lactones, the desymmetrization was expanded to include preparation of a δ-lactone. Lactonization of the one carbon homologated hydroxyl diester 21g, which was prepared through hydroboration and oxidation of methyl, allyl di-tert-butyl malonate, occurred with the Brønsted acid chiral catalyst 14 in dichloromethane at room temperature to yield lactone 22g in good yield (84%) and selectivity (86%).

Table 1. Lactone Substrate Scope.

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<td>allyl</td>
<td>1</td>
<td>35</td>
<td>168</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>21f</td>
<td>S-14</td>
<td>benzyl</td>
<td>1</td>
<td>35</td>
<td>155</td>
<td>67</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>21g</td>
<td>S-14</td>
<td>CH₃</td>
<td>2</td>
<td>rt</td>
<td>144</td>
<td>84</td>
<td>86</td>
</tr>
</tbody>
</table>
In order to fully exploit the desymmetrization process, lactone 22a was prepared on a 1.3 gram scale from 1.9 grams 21a and 20 milligrams catalyst 14, yielding lactone 22a in 95% yield and 98% ee. To further explore the scalability and flexibility of the desymmetrization process, lactone 22a was prepared on a 5.9 gram scale from 8.9 grams of 21a and 0.23 grams catalyst 14, yielding lactone 22a in 96% yield and 98% ee (submitted for publication in *Organic Syntheses*). The reaction conditions such as solvent, temperature and catalyst load were varied and pleasingly no selectivity loss was observed as seen in Figure 14. One of the conditions for the submission to *Organic Syntheses* was that the cost of reagents and starting materials could not exceed $500. To achieve this, the catalyst load was lowered from 5 mol% to 1 mol%. We also were able to decrease the reaction time from 4 days to 2 days by using toluene at 80 °C.

![Figure 14. Scale-Up Reaction of Lactone 22a](image)

Figure 14. Scale-Up Reaction of Lactone 22a

Lactones with enantioenriched all-carbon containing stereocenters such as 22a prepared from prochiral diesters in good yield and enantioselectivity are
prime candidates for incorporation into more complex molecules. The utility of these highly enantioenriched lactone substrates was shown through the transformation of lactone (−)-22a into a variety of highly functionalized building blocks (Figure 15). Successful reduction of lactone 22a with lithium tri-tert-butoxyaluminum hydride yielded diol (−)-24 in 92% yield and without loss of enantiopurity (ee = 98%). Amide ester (−)-25 was formed upon treatment of lactone 22a with the benzyl amine in 76% yield and retention of 98% ee. Cleavage of the tert-butyl ester of lactone 22a with TFA followed by conversion of the resulting carboxylic acid to the acyl azide and subsequent Curtius rearrangement yielded amido lactone (+)-26 in 56% overall yield and 98% ee. Treatment of lactone 22a with aqueous ammonium hydroxide followed by acetylation of the resulting alcohol yielded an amide ester that then underwent a Hofmann rearrangement with lead (IV) acetate and hydrolysis with potassium carbonate to give α-amino ester (+)-27 in 65% overall yield and 96% ee.
The absolute configuration of lactone products \textbf{22a–22g} was assigned as \textit{R} through comparison of a known optical rotation value. Diol \textbf{(+)-28} is readily prepared from lactone \textbf{(+)\textendash22f} and the sign of rotation matches literature values for \textbf{\textit{R\textendash28}} (Figure 16).\textsuperscript{26}
2.3 Conclusion

In summary, we have developed a highly generalized and scalable desymmetrization of hydroxy di-tert-butyl esters to produce enantoienriched lactones in high yields and selectivities, many of which contain a challenging all-carbon quaternary center that are difficult to prepare using other methods. The lactone products readily undergo transformations to generate highly functionalized small molecules that are potentially valuable intermediates in the synthesis of bioactive molecule.
CHAPTER III
ASYMMETRIC SYNTHESSES OF ENANTIOENRICHED SPIROCYCLIC COMPOUNDS

3.1 Introduction

Construction of enantioenriched spirocyclic molecules containing a quaternary center has become of substantial synthetic interest due to the high utility of such compounds and the commonality of the motif in complex natural products. Azaspirene (29) which is an angiogenesis inhibitor associated with cancer therapy and horsfiline (30) which exhibits analgesic effects are two examples (Figure 17).

Figure 17. Natural Products Containing a Spirocyclic Motif

The construction of spirocyclic compounds is a synthetic challenge due to their conformational rigidity. One approach for the formation of a spirocenter is a catalytic asymmetric process. A recent publication describes a catalytic
asymmetric three component 1,3-dipolar cycloaddition synthetic method for the construction of the center.\textsuperscript{30} The enantioselective catalytic method involves reacting methyleneindolinones 31 with amino esters 32 and aldehydes 33 by using phosphoric acid catalyst 35 to yield enantioenriched spirocyclic compounds 34 in excellent yields and selectivities (Figure 18).

Figure 18. Three Component 1,3-Dipolar Cycloaddition

Thus, our aim was to expand the desymmetrization of diesters to incorporate spirocyclic bislactone and lactone-lactam targets. The approach will include a double cyclization process which will begin with a selective lactonization via chiral catalyst 14 to set the absolute configuration of the quaternary carbon center followed by spirocyclization via an achiral acid catalyst (Figure 19).
Therefore, the methodology described here, whereby chiral Brønsted acid 14 catalyzes the cyclization of a symmetric substrate to deliver an enantioenriched lactone, takes advantage of our previously established ester activation by a chiral acid.

3.2 Results and Discussion

3.2.1 Preparation of Spirocyclic Bislactones

The synthesis of bislactones diester substrates begins with the mono alkylation of di-tert-butyl malonate (23) utilizing sodium hydride and 2-bromoethylacetate. This is followed by a second alkylation with the appropriate benzyl ether and sodium hydride yielding masked diol substrates 36a-b in up to 60% yield (Figure 20).
Next, deprotection of one of the alcohols is accomplished via potassium carbonate and is followed by asymmetric lactonization with chiral catalyst 14 to yield enantioenriched $\gamma$-lactone 37a-b with yields up to 96% (Figure 21). Removal of the benzyl group is carried out by hydrogenolysis followed by achiral lactonization with $p$-toluenesulfonylic acid ($p$-TSA) to yield enantioenriched spirocyclic bislactones 38a-b (see Table 2).
3.2.2. Preparation of Spirocyclic Lactone-Lactam

Preparation of the spirocyclic lactone-lactam was carried out in a similar fashion to our previous substrates. The synthesis begins with the mono alkylation of di-tert-butyl malonate (23) utilizing sodium hydride and the appropriate benzyl ether. Next, second alkylation is performed using N-tosylaziridine with sodium hydride to yield compounds 39 (65% yield) (Figure 22).

![Reaction Scheme](image)

Figure 22. Preparation of Prochiral Substrates

The removal of the benzyl group is carried out by hydrogenolysis followed by asymmetric lactonization with chiral catalyst 14 to yield enantioenriched γ-lactone 40 in quantitative yields (Figure 23). Next, an achiral lactamization is carried out with trifluoroacetic acid (TFA) to yield enantioenriched spirocyclic lactone-lactam 41 (see Table 2).
3.2.3. Results of Spirocyclizations

As hypothesized, the proposed desymmetrization syntheses yielded enantioenriched spirocyclic compounds containing an all-carbon quaternary stereocenter that would be difficult to install using other methodologies. Each spirocyclic compound 43b-c exhibited good to excellent yields and enantiopurity greater than 80% ee (Table 2).

Table 2. Spirocyclic Compounds

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Structure</th>
<th>catalyst</th>
<th>solvent</th>
<th>HA</th>
<th>temp (°C)</th>
<th>time (h)*</th>
<th>% yield</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42a</td>
<td><img src="image" alt="Structure of 42a" /></td>
<td>R-14</td>
<td>CH₂Cl₂</td>
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<td>rt</td>
<td>144</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
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<td><img src="image" alt="Structure of 42b" /></td>
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<td>pTSA</td>
<td>rt</td>
<td>144</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>42c</td>
<td><img src="image" alt="Structure of 42c" /></td>
<td>R-14</td>
<td>DCE</td>
<td>TFA</td>
<td>35</td>
<td>216</td>
<td>54</td>
<td>81</td>
</tr>
</tbody>
</table>
3.3 Future Work

Future work for the enantioenriched spirocycle 43c will include x-ray crystallography analysis for absolute configuration assignment. In addition, the preparation of spiro-pyrrolidine/tetrahydrofuran 45 will be performed utilizing compound 43c. The spirocyclic lactone-lactam 43c will be treated with Lawesson’s reagent followed by reduction through hydrogenation over Raney nickel to give spirocyclic pyrrolidine-lactone 44. Next, reduction of the lactone will give the diol followed by cyclization under Mitsunobu conditions to yield spiro-pyrrolidine/tetrahydrofuran 45 (Figure 24).

![Figure 24. Reduction of Spirocycle 43c](image)

Future work will also include expanding the synthesis to include spirocyclic bislactams. Preparation of bislactams will be carried in a similar fashion as described for the spirocyclic blislactones and lactone-lactams. The synthesis will began with the mono alkylation of di-tert-butyl malonate (23) with sodium hydride and N-tosylaziridine then the second alkylation is performed using an aziridine with a different protecting group (PG) such as nosyl or benzyl with sodium
hydride to yield compound 46 (Figure 25). Selective cyclization will be carried out using catalyst 14 followed by achiral cyclization with p-TSA to yield enantioenriched bislactam 47.

Figure 25. Proposed Synthesis for Enantioenriched Spirocyclic Bislactams

3.4 Conclusion

In summary, we have developed a desymmetrization of hydroxy and amino diesters to produce enantioenriched spirocyclic bislactones and lactone-lactams in high yields and selectivities all of which contain a challenging all-carbon quaternary center that are difficult to prepare using other methods.
CHAPTER IV
ASYMMETRIC SYNTHESSES OF ENANTIOENRICHED LACTAMS

4.1 Introduction

The development of an asymmetric Brønsted acid catalyzed cyclization was expanded to include enantioenriched lactams containing a quaternary center at the alpha position. Nitrogen containing molecules are commonly seen in biologically important compounds and new methods to generate carbon-nitrogen bonds selectively are continuously needed. In particular, functionalized γ-lactams are prevalent among the structures of a large number of biologically active natural products and pharmaceutical targets.\textsuperscript{33} Salinosporamide A (48)\textsuperscript{34} which is a bioactive metabolite that exhibits anticancer activity and (−)-pramanicin (49)\textsuperscript{35} which exhibits antifungal activity are two examples (Figure 26).
Asymmetric methodologies have been previously explored for the construction of enantioenriched lactams containing a quaternary chiral center because of their usefulness. A recent publication reports the application of the desymmetrization of prochiral diesters in the total synthesis of (−)-leuconoxine (51) (Figure 27). The selective formation of δ-lactam 50 was a key step in the overall synthesis of compound 51 and set the absolute configuration of the quaternary center in the molecule.
Our objective is to expand the desymmetrization of diesters to include the synthesis of enantioenriched γ-lactams containing an all-carbon quaternary center. The approach will involve prochiral amino diester 52 undergoing a selective lactamization via chiral catalyst 14 to obtain enantiopure lactam 53 (Figure 28). Because amines are more nucleophilic and basic than alcohols, modification of the amino group to make it less reactive will be taken into consideration.

Figure 28. Synthetic Approach for Lactams

4.2 Results and Discussion

The initial synthesis of diester substrates such as 54 begins with the mono alkylation of di-tert-butyl malonate (23) with sodium hydride and methyl iodide (Figure 26). A second alkylation with N-tosylaziridine yields compound 54 in 2 short steps with an overall yield of 78%. Enantioselective cyclization of
compound 54 in the presence of chiral Brønsted acid 14 resulted in lactam 55 in high yield and excellent enantioselectivity.

Figure 29. Initial Desymmetrization of Amino Diester 54a

With the initial result using sulfonamide 54a, a protecting group screen was performed to ensure the tosyl protecting group was the best option for the selective lactamization (Table 3). Various nitrogen protecting groups were screened such as benzoyl and nosyl and the asymmetric cyclization of each resulting amino diester 56b-d was performed. Even though N-nosylaziridine produced promising results, it was decided that N-tosylaziridine was the protecting group of choice.
Table 3. Protecting Group Screen

In order to explore the scope of the reaction, various substrates (Table 4, 54a–e) were synthesized, ranging in chain length, branching, and size. Each substrate was prepared as substrate 54a, but using the appropriate alkyl halide in the first alkylation step. Modification of the original methyl group in 54a with larger groups such as allyl 54c and alkynyl 54e all yielded enantioenriched lactams containing an all-carbon quaternary stereocenter in good yields and enantiopurity.
Table 4. Lactam Substrate Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R</th>
<th>catalyst</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>% yield</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54a</td>
<td>CH₃</td>
<td>R·14</td>
<td>DCE</td>
<td>rt</td>
<td>144</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>54b</td>
<td>CH₂CH₃</td>
<td>R·14</td>
<td>DCE</td>
<td>rt</td>
<td>144</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>54c</td>
<td>allyl</td>
<td>R·14</td>
<td>DCE</td>
<td>rt</td>
<td>192</td>
<td>74</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>54d</td>
<td>CH₂CH₂CH(CH₃)₂</td>
<td>R·14</td>
<td>toluene</td>
<td>80</td>
<td>204</td>
<td>41</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>54e</td>
<td>CH₃C=CH₃</td>
<td>R·14</td>
<td>toluene</td>
<td>80</td>
<td>192</td>
<td>96</td>
<td>93</td>
</tr>
</tbody>
</table>

Replacement of the methyl group with a proton generated lactam 59 and its activity was evaluated against *Staphylococcus aureus* (Figure 30). The preliminary assay can be seen in Figure 30 and was conducted by the Cech laboratory of UNC-Greensboro Department of Chemistry and Biochemistry. The test compound demonstrates dose-dependent inhibition of the growth of *Staphylococcus aureus* (strain NCTC-8325-4) and exhibited moderate potency with an IC₅₀ of 55 μM.
4.3 Current Status

Compared to the desymmetrization of hydroxy diesters, the preparation of γ-lactams has been much more challenging. As seen in Table 4, a consistent set of optimized reaction conditions was not established and variation of solvent and temperature was often required to obtain the needed reactivity. Unfortunately, after generating the above table, a reproducibility issue was encountered. It was first brought to attention in the scale up reaction of the enantioselective cyclization of compound 54a in the presence of chiral Brønsted acid 14 to yield
lactam 55a. The primary result of the stated reaction was the isolation of recovered starting material 54a. At the same time, reproduction of other entries in Table 4 was attempted with similar unsuccessful outcomes. Several reaction conditions were analyzed in hopes of resolving the issue. Catalyst load, solvent, concentration and temperature screenings were performed (Table 5 and 6). However, the issue has not been corrected and still remains a goal.

Table 5. Reaction Conditions for Achiral Lactamization

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
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<th>solvent</th>
<th>catalyst</th>
<th>equiv</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>35</td>
<td>CH₂Cl₂</td>
<td>pTSA</td>
<td>2</td>
<td>RSM</td>
</tr>
<tr>
<td>2</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>35</td>
<td>CH₂Cl₂</td>
<td>pTSA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>pTSA</td>
<td>1</td>
<td>14% yield</td>
</tr>
<tr>
<td>4</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>110</td>
<td>toluene</td>
<td>pTSA</td>
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<td>RSM</td>
</tr>
<tr>
<td>5</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>110</td>
<td>toluene</td>
<td>pTSA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>THF</td>
<td>Cu(OTf)₂</td>
<td>0.2</td>
<td>RSM</td>
</tr>
<tr>
<td>7</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>CH₂Cl₂</td>
<td>Cu(OTf)₂</td>
<td>0.2</td>
<td>RSM</td>
</tr>
<tr>
<td>8</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>90</td>
<td>THF/toluene</td>
<td>LiHMDS</td>
<td>2</td>
<td>10% yield</td>
</tr>
<tr>
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<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
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<td>FeCl₃</td>
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<td>Ts</td>
<td>23</td>
<td>CH₂Cl₂</td>
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<td>0.05</td>
<td>RSM</td>
</tr>
<tr>
<td>12</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>FeCl₃</td>
<td>0.05</td>
<td>RSM</td>
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</table>
**Table 6. Reaction Conditions for Chiral Lactamization**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R₁</th>
<th>temp (°C)</th>
<th>solvent</th>
<th>catalyst</th>
<th>equiv</th>
<th>additives</th>
<th>results</th>
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<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>14</td>
<td>0.05 short-path distillation of DCE</td>
<td>RSM</td>
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<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
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<td>0.05 10 μL H₂O</td>
<td>RSM</td>
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<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>14</td>
<td>0.05 4 Å molecular sieves</td>
<td>RSM</td>
</tr>
<tr>
<td>4</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>14</td>
<td>0.2 10 μL H₂O</td>
<td>RSM</td>
</tr>
<tr>
<td>5</td>
<td>tBu</td>
<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>14</td>
<td>0.2 16 μL tBuOH</td>
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</tr>
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<td>tBu</td>
<td>Me</td>
<td>Ts</td>
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<td>14</td>
<td>0.2 5M HCl</td>
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<td>0.05 ----</td>
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<td>0.05 14 washed with 4M HCl</td>
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<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>14</td>
<td>----</td>
<td>RSM</td>
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<td>Me</td>
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Table 6 cont.

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<th>catalyst</th>
<th>equiv</th>
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<td>Me</td>
<td>Ts</td>
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<td>glovebox</td>
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<td>Me</td>
<td>Ts</td>
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<td>NDP</td>
</tr>
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<td>Me</td>
<td>Ts</td>
<td>23</td>
<td>DCE</td>
<td>14</td>
<td>0.25</td>
<td>Meldrum’s Acid (1 eq.)</td>
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<td>14</td>
<td>0.05</td>
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<td>0.15</td>
<td>----</td>
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4.4 Conclusion

The initial results seen in Table 4 are promising and it is an ongoing process to overcome the reproducibility issue. New avenues are currently being explored such as catalyst type for both achiral and chiral lactamization. For example, consistent results have been obtained in the achiral lactamization of amino diester 54 with trifluoroacetic acid (TFA) which resulted in lactam 60 in good yield (90%) (Figure 31).

Figure 31. Achiral Lactamization using TFA
CHAPTER V
EXPERIMENTAL

5.1 General Information

Unless noted, all solvents and reagents were obtained from commercial sources and used without further purification; anhydrous solvents were dried following standard procedures. The \(^1\)H and \(^{13}\)C nuclear magnetic resonance (NMR) spectra were plotted on 400 and 500 MHz spectrometer using CDCl\(_3\) as a solvent at rt. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for \(^1\)H NMR: s = singlet, d = doublet, m = multiplet, b = broad, t = triplet, q = quartet, p = pentet. The reactions were monitored by TLC using silica G F\(_{254}\) precoated plates. Flash chromatography was performed using flash grade silica gel (particle size: 40-63 \(\mu\)m, 230 \(\times\) 400 mesh). Enantiomeric excess was determined by GC analysis and HPLC analysis. IR data was obtained with a FTIR spectrometer one with frequencies reported in cm\(^{-1}\). High Resolution Mass Spectra were acquired on an Orbitrap XL MS system. The specific rotations were acquired on an analytical polarimeter.
5.2 Synthesis of Compound 22a

5.2.1 Di-t-butyl 2-methylmalonate intermediate

To a solution of sodium hydride (60% in mineral oil, 0.89 g, 22.3 mmol) in THF (15 mL) was added di-t-butyl malonate dropwise (4.83 g, 22.3 mmol) and the solution was stirred for 10 minutes at rt. To the reaction mixture, iodomethane (1.39 mL, 22.3 mmol) was added dropwise and the solution was stirred for 24 h at rt. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→15% EtOAc in hexanes) to afford the di-t-butyl 2-methylmalonate intermediate as a colorless oil (3.61 g, 70% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.24 (q, J = 7.2 Hz, 1H), 1.41 (s, 18H), 1.33 (d, J = 7.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.7, 81.3, 48.2, 28.0, 13.5; IR (neat) cm⁻¹ 2979, 1725, 1456, 1367, 1136, 848; HRMS (C₁₂H₂₂O₄, ESI): calculated 253.1415 [M+Na]⁺¹, found 253.1403.
5.2.2 Acetyl methylmalonate intermediate

![Chemical structure of acetyl methylmalonate intermediate]

Figure 33. Acetyl methylmalonate Intermediate

To a solution of sodium hydride (60% in mineral oil, 0.82 g, 20.6 mmol) in THF (15 mL) was added di-\textit{t}-butyl 2-methylmalonate intermediate (2.37 g, 10.3 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, 2-bromoethyl acetate (2.84 mL, 25.8 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 4 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→20% EtOAc in hexanes) to afford the acetyl methylmalonate intermediate as a colorless oil (2.43 g, 75% yield). $^1$H NMR (300 MHz, CDCl₃) δ 4.09 (t, $J = 7.2$ Hz, 2H), 2.08 (t, $J = 7.2$ Hz, 2H), 2.00 (s, 3H), 1.46 (s, 18H), 1.32 (s, 3H); $^{13}$C NMR (126 MHz, CDCl₃) δ 171.1, 171.0, 81.4, 60.9, 53.1, 33.9, 27.8, 20.9, 19.9; IR (neat) cm$^{-1}$ 3004, 1723, 1641, 1456, 1392, 1367, 1237, 1119, 846; HRMS (C₁₆H₂₈O₆, ESI): calculated 339.1783 [M+Na]$^{+1}$, found 339.1786.
5.2.3 Compound **21a**

![Chemical Structure](image)

**Figure 34.** Compound **21a**

To a solution of the acetyl methylmalonate intermediate (0.45 g, 1.42 mmol) in MeOH (7.0 mL) was added K$_2$CO$_3$ (0.90 g) and the solution was stirred for 1 h at rt. The reaction mixture was diluted with CH$_2$Cl$_2$ and was extracted with CH$_2$Cl$_2$ (2 x 15 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to afford compound **21a** as a colorless oil (0.26 g, 78% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 3.69 (t, $J = 6.3$ Hz, 2H), 2.73 (bs, 1H), 2.07 (t, $J = 6.3$ Hz, 2H), 1.47 (s, 18 H), 1.39 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.9, 81.4, 58.8, 53.6, 38.1, 27.8, 20.1; IR (neat) cm$^{-1}$ 3440, 2974, 2934, 1723, 1456, 1367, 1156, 1113, 847; HRMS (C$_{14}$H$_{26}$O$_5$, ESI): calculated 297.1677 [M+Na]$^+$, found 297.1667.
5.2.4 Compound **22a**

![Chemical structure](image)

Figure 35. Compound **22a**

To a solution of acid (S)-**14** (35 mg, 0.05 mmol) in CH$_2$Cl$_2$ (5 mL) was added compound **21b** (258 mg, 0.94 mmol) and the solution was stirred for 5 d at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford compound **22a** as a white crystal (184 mg, 97% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 4.35 (m, 2H), 2.64 (m, 1H), 2.13 (m, 1H), 1.46 (s, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 176.4, 169.5, 83.0, 65.9, 50.6, 35.2, 27.8, 20.1; IR (neat) cm$^{-1}$ 2980, 1735, 1448, 1372, 1235, 1043; HRMS (C$_{10}$H$_{16}$O$_4$, ESI): calculated 223.0946 [M+Na]$^+$, found 223.0934, [α]$_D^{23}$ = -3.6° (c =0.5, CHCl$_3$).
5.3 Synthesis of Compound 22b

5.3.1 Allyl malonate intermediate

![Chemical Structure](image)

Figure 36. Allyl malonate Intermediate

To a solution of sodium hydride (60% in mineral oil, 0.13 g, 3.13 mmol) in THF (7 mL) was added di-\textit{t}-butyl malonate (0.68 g, 3.13 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, allyl bromide (0.27 mL, 3.13 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and stir for 21 h. The reaction was quenched with saturated NH₄Cl (5 mL) at 0 °C, phases were separated, and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→10% EtOAc in hexanes) to afford the allyl malonate intermediate as a colorless oil (0.66 g, 82% yield). $^1$H NMR (500 MHz, CDCl₃) δ 5.76 (m, 1H), 5.08 (m, 2H), 3.20 (t, $J$ = 7.6 Hz, 1H), 2.54 (m, 2H), 1.46 (s, 18H); $^{13}$C NMR (126 MHz, CDCl₃) δ 168.4, 134.6, 117.1, 81.5, 53.5, 32.9, 28.0; IR (neat) cm$^{-1}$ 2979, 1726,
1643, 1456, 1367, 1135, 917, 846; HRMS (C_{14}H_{24}O_{4}, ESI): calculated 279.1572 [M+Na]^+, found 279.1556.

5.3.2 Compound 21b

![Chemical Reaction Diagram]

**Figure 37. Compound 21b**

To a solution of the allyl malonate intermediate (0.66 g, 2.57 mmol) in 3:1 dioxane/H_{2}O (7 mL) was added 2,6-lutidine (0.60 mL, 5.14 mmol), OsO_{4} (2.5% wt. % in tert-butanol, 0.51 mL, 0.05 mmol) and NaIO_{4} (2.2 g, 10.3 mmol) and the solution was stirred for 2 h at rt. The reaction mixture was vacuum filtered through a pad of Celite and the filtrate was extracted with CH_{2}Cl_{2} (1 x 10 mL) and H_{2}O (1 x 10 mL). The organic layer was washed with brine (5 mL) and dried over MgSO_{4}. The solution was concentrated to yield the crude aldehyde diester intermediate as a clear yellow oil (0.51 g).

The crude aldehyde diester intermediate (0.51 g, 2.00 mmol) was dissolved in MeOH (4 mL) and to it was added NaBH_{4} (0.29 g, 8.00 mmol) in MeOH (4 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with 1 M HCl at 0 °C and partially concentrated. The reaction mixture was
extracted with CH₂Cl₂ (2 x 10 mL) and H₂O (1 x 10 mL). The organic layer was
dried over MgSO₄ and concentrated. The residue was purified by flash
chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to
afford compound 21b as a colorless oil (0.28 g, 54% yield). ¹H NMR (500 MHz,
CDCl₃) δ 3.71 (m, 2H), 3.34 (t, J = 15.6 Hz, 1H), 2.07 (m, 2 H), 1.96 (bs, 1H),
1.45 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 169.1, 81.8, 60.7, 51.3, 31.5, 28.0;
IR (neat) cm⁻¹ 3441, 2977, 2933, 1723, 1456, 1367, 1137, 843; HRMS (C₁₃H₂₄O₅,
ESI): calculated 283.152 [M+Na]⁺, found 283.1523.

5.3.3 Compound 22b

Figure 38. Compound 22b

To a solution of acid (S)-14 (41 mg, 0.05 mmol) in CH₂Cl₂ (6 mL) was
added compound 21b (282 mg, 1.08 mmol) and the solution was stirred for 72 h
at 5 °C. The reaction was extracted using EtOAc (2 x 10 mL) and H₂O (1 x 10
mL). The organic phase was dried over MgSO₄ and concentrated. The residue
was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes)
to afford compound 22b as a colorless oil (188 mg, 93% yield). ¹H NMR (500
MHz, CDCl$_3$) δ 4.43 (m, 1H) 4.30 (m, 1H), 3.42 (m, 1H), 2.59 (m, 1H), 2.46 (m, 1H), 1.48 (s, 9 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.9, 166.9, 83.1, 67.3, 47.0, 27.9, 26.5; IR (neat) cm$^{-1}$ 2980, 1772, 1725, 1369, 1138, 1016; HRMS (C$_9$H$_{14}$O$_4$, ESI): calculated 185.0813, [M-H]$^{-1}$, found 185.0807; [$\alpha$]$_D^{23}$ = +3.6° (c = 2.8, CHCl$_3$).

5.4 Synthesis of Compound 22c

5.4.1 Di-t-butyl 2-ethylmalonate intermediate

![Figure 39. Di-t-butyl 2-ethylmalonate Intermediate](image)

To a solution of sodium hydride (60% in mineral oil, 93 mg, 2.32 mmol) in THF (7 mL) was added di-t-butyl malonate dropwise (0.5 g, 2.32 mmol) and the solution was stirred for 10 minutes at rt. To the reaction mixture, iodoethane (0.18 mL, 2.32 mmol) was added dropwise and the solution was stirred for 22 h at rt. The reaction was quenched with saturated NH$_4$Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (5→15% EtOAc in hexanes) to afford the di-t-butyl 2-ethylmalonate intermediate as a white crystal.
(0.44 g, 78% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.02 (t, $J = 7.3$ Hz, 1H), 1.79 (m, 2H), 1.41 (s, 18H), (s, 18 H), 0.91 (t, $J = 7.3$, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.9, 81.0, 55.4, 27.8, 21.9, 11.7; IR (neat) cm$^{-1}$ 2973, 1724, 1458, 1365, 1134, 850; HRMS (C$_{13}$H$_{24}$O$_4$, ESI) calculated 267.1572 [M+Na]$^{+1}$, found 267.1560.

5.4.2 Acetyl ethylmalonate intermediate

![Acetyl Ethylmalonate Intermediate](image)

Figure 40. Acetyl Ethylmalonate Intermediate

To a solution of sodium hydride (60% in mineral oil, 0.14 g, 3.6 mmol) in THF (7 mL) was added di-$t$-butyl 2-ethylmalonate intermediate (0.44 g, 1.8 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, 2-bromoethyl acetate (0.5 mL, 4.5 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 23 h. The reaction was quenched with saturated NH$_4$Cl (5 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (5→10% EtOAc in hexanes) to afford the acetyl ethylmalonate intermediate as a white crystal (0.45 g, 76% yield). $^1$H NMR
(500 MHz, CDCl$_3$) $\delta$ 4.11 (t, $J$ = 7.2 Hz, 2H), 2.13 (t, $J$ = 7.2 Hz, 2H), 2.00 (s, 3H), 1.81 (q, $J$ = 7.4 Hz, 2H), 1.44 (s, 18H), 0.82 (t, $J$ = 7.4, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.0, 170.5, 81.3, 60.8, 57.3, 30.0, 28.0, 25.1, 21.0, 8.2; IR (neat) cm$^{-1}$ 2942, 1740, 1723, 1641, 1457, 1366, 1140, 1118, 848; HRMS (C$_{17}$H$_{30}$O$_6$, ESI): calculated 353.1940 [M+Na]$^+$, found 353.1942.

5.4.3 Compound 21c

![Chemical structure of compound 21c]

Figure 41. Compound 21c

To a solution of the acetyl ethylmalonate intermediate (0.41 g, 1.23 mmol) in methanol (6 mL) was added K$_2$CO$_3$ (0.82 g) and the solution was stirred for 1 h at rt. The reaction mixture was diluted with CH$_2$Cl$_2$ and was extracted with CH$_2$Cl$_2$ (2 x 15 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated to afford compound 21c as a white crystal (0.31 g, 87% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.65 (m, 2H), 2.07 (t, $J$ = 6.6 Hz, 2H), 1.88 (m, q, $J$ = 7.5 Hz, 2H), 1.44 (s, 18 H), 0.83 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.4, 81.3, 59.1, 57.7, 34.7, 27.9, 25.9, 8.6; IR (neat) cm$^{-1}$ 3434, 2975, 2934, 1745, 1474, 1365, 1154, 1117, 851; HRMS (C$_{15}$H$_{28}$O$_5$, ESI): calculated 311.1834 [M+Na]$^+$, found 311.1835.
5.4.4 Compound 22c

Figure 42. Compound 22c

To a solution of acid (S)-14 (18 mg, 0.02 mmol) in CH$_2$Cl$_2$ (5 mL) was added compound 21c (136 mg, 0.47 mmol) and the solution was stirred for 6 d at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford compound 22c as a white crystal (94 mg, 93% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.32 (m, 2H), 2.63 (m, 1H), 2.21 (m, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 1.46 (s, 9 H), 0.95 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.3, 168.7, 82.9, 66.1, 55.4, 31.3, 27.9, 27.1, 9.1; IR (neat) cm$^{-1}$ 2979, 1741, 1466, 1370, 1236, 1043; HRMS (C$_{11}$H$_{18}$O$_4$, ESI): calculated 237.1102 [M+Na]$^+$, found 237.1105; $[\alpha]_D^{23}$ = +1.6° (c= 2.2, CHCl$_3$).
5.5 Synthesis of Compound 22d

5.5.1 Di-t-butyl 2-isopropylmalonate intermediate

![Diagram](attachment:image.png)

Figure 43. Di-t-butyl 2-isopropylmalonate Intermediate

To a solution of sodium hydride (60% in mineral oil, 0.09 g, 2.32 mmol) in THF (7 mL) was added di-t-butyl malonate dropwise (0.5 g, 2.32 mmol) and the solution was stirred for 10 minutes at rt. To the reaction mixture, 2-iodopropane (0.23 mL, 2.32 mmol) was added dropwise and the solution was stirred for 22 h at rt. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→10% EtOAc in hexanes) to afford the di-t-butyl 2-isopropylmalonate intermediate as a colorless oil (0.4 g, 67% yield). ¹H NMR (500 MHz, CDCl₃) δ 2.87 (d, J = 8.9 Hz, 1H), 2.27 (m, 1H), 1.44 (s, 18H), 0.97 (d, J = 6.7, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 168.3, 81.2, 61.1, 28.4, 28.0, 20.4; IR (neat) cm⁻¹ 2967, 1721, 1473, 1365, 1118, 981; HRMS (C₁₄H₂₆O₄, ESI): calculated 281.1728 [M+Na]⁺, found 281.1717.
5.5.2 Compound 21d

![Chemical Structure](image)

To a solution of sodium hydride (60% in mineral oil, 0.11 g, 2.76 mmol) in THF (8 mL) was added di-t-butyl 2-ethylmalonate intermediate (0.36 g, 1.38 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, allyl bromide (0.6 mL, 6.9 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 26 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→20% EtOAc in hexanes) to afford the allyl isopropylmalonate intermediate as a colorless oil (0.372 g, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.70 (m, 1H), 5.00 (m, 2H), 2.50 (d, J = 7.3 Hz, 2H), 2.20 (m, 1H), 1.42 (s, 18H), 0.95 (d, J = 6.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 168.9, 133.7, 117.7, 80.9, 61.6, 37.8, 31.1, 27.9, 18.5.
To a solution of the allyl isopropylmalonate intermediate (0.27 g, 0.9 mmol) in 3:1 dioxane/H$_2$O (6 mL) was added 2,6-lutidine (0.21 mL, 1.8 mmol), OsO$_4$ (2.5% wt. % in tert-butanol, 18 mL, 0.018 mmol) and NaIO$_4$ (0.77 g, 77 mmol) and the solution was stirred for 3 h at rt. The reaction mixture was filtered through a pad of Celite and was extracted with CH$_2$Cl$_2$ (2 x 15 mL) and H$_2$O (1 x 10 mL). The organic layer was washed with brine (5 mL) and dried over MgSO$_4$. The solution was concentrated to yield the crude aldehyde diester intermediate as a clear yellow oil (0.19 g).

The crude aldehyde diester intermediate (0.19 g, 0.65 mmol) was dissolved in MeOH (4 mL) and to it was added NaBH$_4$ (0.01 g, 2.6 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with 1 M HCl at 0 °C and reaction mixture was partially concentrated. The reaction mixture was extracted with CH$_2$Cl$_2$ (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to afford compound 21d as a colorless oil (0.09 g, 46% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 3.74 (m, 2H), 2.23 (m, 1H), 2.01 (t, $J = 6.5$ Hz, 2H), 1.46 (s, 18 H), 0.96 (d, $J = 6.9$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.6, 82.1, 61.5, 59.5, 36.3, 33.3, 28.3, 18.2; IR (neat) cm$^{-1}$ 3004, 2936, 2356, 1712, 1475, 1365, 1147, 1066, 852; HRMS (C$_{16}$H$_{30}$O$_{5}$, ESI): calculated 325.1990 [M+Na]$^+$, found 325.2001.
5.5.3 Compound 22d

![Chemical structure diagram]

Figure 45. Compound 22d

To a solution of acid (R)-14 (7.2 mg, 0.01 mmol) in CH$_2$Cl$_2$ (2.5 mL) was added compound 21d (58.1 mg, 0.19 mmol) and the solution was stirred for 9 d at 32 °C. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford compound 22d as a white crystal (39.2 mg, 89% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.32 (m, 2H), 2.61 (m, 2H), 2.17 (m, 1H), 1.47 (s, 9 H), 0.89 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.5, 167.9, 82.8, 66.2, 59.8, 31.4, 27.7, 26.3, 17.9, 17.7; IR (neat) cm$^{-1}$ 2970, 1734, 1414, 1383, 1201, 1044; HRMS (C$_{12}$H$_{20}$O$_4$, ESI): calculated 251.1259 [M+Na]$^+$, found 251.1259. [α]$_D^{23}$ = -5.6° (c = 1.1, CHCl$_3$).
5.6 Synthesis of Compound 22e

5.6.1 Di-t-butyl 2-(2-acetoxyethyl)-2-allylmalonate intermediate

To a solution of sodium hydride (60% in mineral oil, 54 mg, 1.36 mmol) in THF (7 mL) was added di-t-butyl 2-allylmalonate dropwise (0.29 g, 1.13 mmol) and the solution was stirred for 10 minutes at rt. To the reaction mixture, 2-bromoethyl acetate (0.14 mL, 1.24 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 47 h. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (10→15% EtOAc in hexanes) to afford the di-t-butyl 2-(2-acetoxyethyl)-2-allylmalonate intermediate as a colorless oil (0.14 g, 35% yield). ¹H NMR (500 MHz, CDCl₃) δ 5.61 (m, 1H), 5.11 (m, 2H), 4.12 (t, J = 7.2 Hz, 2H), 2.62 (d, J = 7.6 Hz, 2H), 2.14 (t, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.45 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 171.0, 169.9, 132.4, 119.3, 81.7, 60.7,
56.4, 37.1, 30.7, 27.9, 21.1; IR (neat) cm\(^{-1}\) 2937, 1739, 1723, 1477, 1366, 1221, 1139, 844; HRMS (C\(_{18}\)H\(_{30}\)O\(_6\), ESI): calculated 365.1940 [M+Na]\(^{+}\), 365.1945.

5.6.2 Compound 21e

Figure 47. Compound 21e

To a solution of the di-t-butyl 2-(2-acetoxyethyl)-2-allylmalonate intermediate (59 mg, 0.17 mmol) in MeOH (2 mL) was added K\(_2\)CO\(_3\) (117 mg) and the solution was stirred for 1 h at rt. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (15 mL) and extracted with H\(_2\)O (1 x 10 mL). The organic layer was washed with brine (5 mL) and dried over MgSO\(_4\). The solution was concentrated to yield compound 21e as a colorless oil (38 mg, 74% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.63 (m, 1H), 5.08 (m, 2H), 3.67 (t, \(J = 6.6\) Hz, 2H), 2.58 (d, \(J = 7.4\) Hz, 2H), 2.05 (t, \(J = 6.6\) Hz, 2H), 1.43 (s, 18 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.1, 132.4, 118.8, 81.6, 59.0, 56.9, 37.8, 35.3, 27.3; IR (neat) cm\(^{-1}\) 3010, 2943, 1736, 1477, 1364, 1260, 1142, 1074; HRMS (C\(_{16}\)H\(_{29}\)O\(_5\), ESI): calculated 323.1834 [M+Na]\(^{+}\), found 323.1826.
5.6.3 Compound 22e

![Chemical Structure](image)

Figure 48. Compound 22e

To a solution of acid (R)-14 (3.2 mg, 0.004 mmol) in CH$_2$Cl$_2$ (2 mL) was added compound 21e (26 mg, 0.08 mmol) and the solution was stirred for 8 d at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford compound 22e as a white crystal (18 mg, 95% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.72 (m, 1H), 5.22 (m, 2H), 4.31 (m, 2H), 2.73 (m, 1H), 2.51 (m, 2H), 2.33 (m, 1H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.9, 168.4, 132.2, 120.2, 83.2, 66.7, 54.4, 37.9, 31.1, 27.9; IR (neat) cm$^{-1}$ 2949, 1772, 1349, 1286, 1141, 1066; HRMS (C$_{12}$H$_{18}$O$_4$, ESI): calculated 249.1102 [M+Na]$^+$, found 249.1093, [$\alpha$]$_D^{23}$ = -4.7° (c= 0.5, CHCl$_3$).
5.7 Synthesis of Compound 22f

5.7.1 Allyl benzylmalonate intermediate

To a solution of sodium hydride (60% in mineral oil, 0.13 g, 3.13 mmol) in THF (8 mL) was added di-t-butyl malonate dropwise (0.68 g, 3.13 mmol) and the solution was stirred for 10 minutes at rt. To the reaction mixture, benzylbromide (0.37 mL, 3.13 mmol) was added dropwise and the solution was stirred for 24 h under reflux. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated to yield di-t-butyl 2-benzylmalonate intermediate.

To a solution of sodium hydride (60% in mineral oil, 0.20 g, 5.0 mmol) in THF (8 mL) was added di-t-butyl 2-benzylmalonate intermediate (0.77 g, 2.5 mmol) dropwise and the solution was stirred for 15 minutes at rt. To the reaction mixture, allyl bromide (0.54 mL, 6.25 mmol) was added dropwise at 0°C. The
solution was allowed to warm to rt and react for 47 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→15% EtOAc in hexanes) to afford the allyl benzylmalonate intermediate as a colorless oil (0.77 g, 89% yield). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.23 (m, 5H), 5.77 (m, 1H), 5.14 (m, 2H), 3.15 (s, 2H), 2.49 (d, \(J = 7.4\) Hz, 2H), 1.45 (s, 18 H); \(^13\)C NMR (126 MHz, CDCl₃) δ 170.1, 136.6, 133.1, 130.4, 128.2, 126.9, 119.1, 81.6, 59.2, 37.6, 36.5, 28.1; IR (neat) cm\(^{-1}\) 3324, 2978, 2963, 1758, 1471, 1350, 1332, 1140, 1045, 879; HRMS (C\(_{21}\)H\(_{30}\)O\(_5\), ESI): calculated 385.1990 [M+Na]\(^+\), found 385.1988.

5.7.2 Compound 21f

![Chemical structure diagram](image.png)

To a solution of the allyl benzylmalonate intermediate (0.93 g, 2.75 mmol) in 3:1 dioxane/H\(_2\)O (7 mL) was added 2,6-lutidine (0.64 mL, 5.5 mmol), OsO\(_4\)
(2.5% wt. in t-butanol, 0.44 mL, 0.06 mmol) and NaIO$_4$ (2.35 g, 11.0 mmol) and the solution was stirred for 2 h at rt. The reaction mixture was filtered through a pad of Celite and was extracted with CH$_2$Cl$_2$ (2 x 15 mL) and H$_2$O (1 x 10 mL). The organic layer was washed with brine (5 mL) and dried over MgSO$_4$. The solution was concentrated to yield the crude aldehyde diester intermediate as a clear yellow oil (0.57 g).

The crude aldehyde diester intermediate (0.57 g, 1.63 mmol) was dissolved in MeOH (10 mL) and to it was added NaBH$_4$ (0.25 g, 6.52 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with 1 M HCl at 0 °C and reaction mixture was partially concentrated. The reaction mixture was extracted with CH$_2$Cl$_2$ (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to afford compound 21f as a colorless oil (0.24 g, 42% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.26 (m, 5H), 3.75 (t, $J = 6.6$ Hz, 2H), 3.21 (s, 2H), 2.00 (t, $J = 6.6$ Hz, 2H), 1.47 (s, 18 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.8, 136.4 130.3, 128.2, 126.9, 82.1, 59.2, 58.2, 39.1, 35.5, 28.0; IR (neat) cm$^{-1}$ 3321, 2971, 2963, 1758, 1471, 1330, 1116, 1045, 879; HRMS (C$_{20}$H$_{30}$O$_5$, ESI): calculated 373.1990 [M+Na]$^{+1}$, found 373.1987.
5.7.3 Compound 22f

![Chemical structure of compounds 21f and 22f](image)

**Figure 51. Compound 22f**

To a solution of acid (S)-14 (15.6 mg, 0.021 mmol) in CH$_2$Cl$_2$ (5 mL) was added compound 21f (146 mg, 0.42 mmol) and the solution was stirred for 7 d at 32 °C. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford compound 22f as a colorless oil (77 mg, 67% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.25 (m, 5H), 4.25 (m, 1H), 3.85 (m, 1H), 3.25 (m, 2H), 2.54 (m, 1H), 2.25 (m, 1H), 1.47 (s, 9 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.3, 169.6, 135.7, 130.2, 128.7, 127.3, 83.3, 66.2, 56.1, 38.9, 30.6, 27.9; IR (neat) cm$^{-1}$: 2979, 2360, 1771, 1721, 1454, 1368, 1145, 1029; HRMS (C$_{16}$H$_{20}$O$_4$, ESI): calculated 299.1259 [M+Na]$^+$, found 299.1261; [$\alpha$]$_D^{23}$ = +25.1° (c= 1.1, CHCl$_3$).
5.8 Synthesis of Compound 22g

5.8.1 Compound 21g

![Chemical Structure]

Figure 52. Compound 21g

To a solution of sodium hydride (60% in mineral oil, 1.5 g, 38.2 mmol) in THF (10 mL) was added di-t-butyl 2-methylmalonate intermediate dropwise (4.4 g, 19.1 mmol) and the solution was stirred for 10 minutes at rt. To the reaction mixture, allyl bromide (4.2 mL, 47.8 mmol) was added dropwise and the solution was stirred for 24 h at rt. The reaction was quenched with saturated NH₄Cl (7 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated to afford the di-t-butyl 2-allyl-2-methylmalonate intermediate.

The BH₃-THF (1M in THF, 0.74 mmol) was diluted with THF (0.11 mL). To the solution was added di-t-butyl 2-allyl-2-methylmalonate intermediate (0.4 g) at 0 °C and allowed to warm up to rt. After 2.5 h, a NaOH solution (3 M, 0.89 mL) was added followed by hydrogen peroxide (30 wt % in water, 0.3 mL, 2.87 mmol) at 0 °C. The reaction mixture stirred at 50 °C for overnight. The reaction mixture...
was extracted with Et₂O (2 x 10 mL) and H₂O (1 x 10 mL). The organic layer was
dried over MgSO₄ and concentrated. The residue was purified by flash
chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to
afford compound 21g as a colorless oil (0.13 g, 31% yield). ¹H NMR (500 MHz,
CDCl₃) δ 3.62 (m, 2H), 1.79 (m, 2H), 1.51 (m, 2H), 1.42 (s, 18H), 1.29 (s, 3H);
¹³C NMR (126 MHz, CDCl₃) δ 171.8, 81.1, 62.9, 54.3, 31.6, 27.9, 19.9; IR (neat)
cm⁻¹ 3442, 2970, 2929, 1720, 1457, 1366, 1150, 1112, 851; HRMS (C₁₅H₂₈O₅,

5.8.2 Compound 22g

![Chemical structure of 21g and reaction scheme](image)

Figure 53. Compound 22g

To a solution of acid 14 (3.0 mg, 0.004 mmol) in CH₂Cl₂ (2 mL) was added
compound 21g (46.2 mg, 0.16 mmol) and the solution was stirred for 5 d at rt.
The reaction was extracted with EtOAc (2 x 10 mL) and H₂O (1 x 10 mL). The
organic phase was dried over MgSO₄ and concentrated. The residue was
purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to
afford compound 22g as a colorless oil (29.1 mg, 85% yield). ¹H NMR (500 MHz,
CDCl$_3$) $\delta$ 4.32 (m, 1H), 2.42 (m, 1H), 1.91 (m, 2H), 1.63 (m, 1H), 1.46 (s, 12H);  
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.5, 171.1, 82.7, 68.7, 51.1, 30.8, 27.8, 23.1, 20.5; IR (neat) cm$^{-1}$; 2983, 1730, 1446, 1370, 1229, 1042; HRMS (C$_{11}$H$_{18}$O$_4$, ESI): calculated 237.1102 [M+Na]$^+_{\dagger}$, found 237.1095; $[\alpha]_D^{23}$: +14.1° (c= 1.0, CHCl$_3$).

5.9 Scale Up Synthesis #1 of Compound 22a

![Image of chemical structures](image)

Figure 54. Scale Up Synthesis #1 of Compound 22a

To a solution of acid (S)-14 (0.2 g, 0.35 mmol) in CH$_2$Cl$_2$ (10 mL) was added compound 21b (1.9 g, 6.9 mmol) and the solution was stirred for 5 d at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford compound 22a as a white crystal (1.3 g, 95% yield).
5.10 Scale Up Synthesis #2 of Compound 22a

5.10.1 Methylmalonate intermediate

To a solution of methyl malonic acid (12.0 g, 101.6 mmol) in diethyl ether (50 mL), was added 4-(Dimethylamino)pyridine (1.2 g, 9.0 mmol, 0.1 equiv), tert-butyl alcohol (150 mL), and solid di-tert-butyl dicarbonate (48.0 g, 220 mmol, 2.2 equiv). The heterogeneous slurry was stirred at room temperature for 48 h, after which time the reaction mixture became a clear pale yellow mixture. The reaction mixture was then diluted by addition of diethyl ether (150 mL), and was extracted with water (2 x 50 mL) and HCl (1.0 M, 2 x 50 mL). The organic layer was dried over MgSO4, gravity filtered using coarse filter paper, rinsed with diethyl ether (20 mL), and concentrated to give an oil, which was dissolved in 200 mL of hexanes and ethyl acetate (10:1) and passed through a plug of silica gel using a 60-mL medium fritted filter funnel. The colorless filtrate was concentrated to afford the di-t-butyl 2-methylmalonate intermediate as a colorless oil (23.1 g, 98% yield).
5.10.2 Compound 21a

![Chemical Reaction](attachment:image.png)

Figure 56. Scale Up of Compound 21a

Tetrahydrofuran (100mL) was added via a syringe and the reaction flask was cooled with an ice-water bath. After stirring 15 min, NaH (3.13 g, 78.2 mmol, 1.2 equiv) was added and the slurry was stirred for an additional 15 min. Di-tert-butyl-2-methylmalonate (15.0 g, 65.2 mmol) was dissolved in tetrahydrofuran (30 mL) and this solution was cannulated into the sodium hydride slurry over 15 min. After 30 min 2-bromoethyl acetate (8.6 mL, 78.2 mmol, 1.2 equiv) was added drop wise via a syringe over a period of 5 min. The reaction mixture was allowed to slowly warm to room temperature. TLC analysis indicated consumption of the di-tert-butyl-2-methylmalonate after 16 h. The reaction flask was cooled in an ice-water bath for 15 min, and a solution of saturated NH₄Cl solution (10 mL) was added dropwise via syringe. The mixture was diluted with diethyl ether (300 mL) and extracted with water (2 x 50 mL) and saturated NaCl solution (50 mL), dried over MgSO₄, gravity filtered using coarse filter paper, rinsed with diethyl ether (20 mL), and concentrated to give a pale yellow oil which was dissolved in methanol (50 mL). The solution was transferred to an oven
dried 500-mL two-necked round-bottom flask and was cooled to –10 °C using a saturated NaCl solution/ice bath and K$_2$CO$_3$ (9.0 g, 65.2 mmol) was added in portions. After 2 h, the reaction mixture was diluted with diethyl ether (200 mL) and deionized water (50 mL) was added drop wise. The reaction was extracted with hexanes (100 mL) and water (3 x 50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried over MgSO$_4$, gravity filtered using coarse filter paper, rinsed with diethyl ether (20 mL), and concentrated to give a light yellow oil. The oil was dissolved into hexanes (100 mL) and the flask was cooled with an ice-water bath for one h to yield a layer of white solids. The solids were broken via a spatula and collected via vacuum filtration into a 100 mL ceramic Buchner funnel equipped with filter paper of moderate porosity and washed with ice-cold hexanes (25 mL). A second crop of solids were obtained after the filtrate was concentrated under vacuum and the residue was dissolved in hexanes (20 mL), cooled with an ice water bath for 2 h and filtered as before to yield compound 21a as a white solid (13.5 g, 76% yield).
5.10.3 Compound 22a

![Chemical Structure](attachment:image.png)

**Figure 57. Scale Up of Compound 22a**

To a solution of di-tert-butyl 2-(2-hydroxyethyl)-2-methylmalonate (8.5 g, 31 mmol) in toluene (310 mL) was added acid \((\mathcal{R})-14\) (0.23 g, 0.31 mmol, 0.01 equiv). The reaction mixture was heated to 80 °C and progress of the reaction was monitored by TLC analysis. TLC analysis indicated consumption of the di-tert-butyl 2-(2-hydroxyethyl)-2-methylmalonate after 48 h. The round bottomed flask was allowed to cool slowly in the oil bath to 23 °C and diluted using EtOAc (50 mL). After stirring for 5 min, the reaction mixture was extracted using EtOAc (250 mL) and deionized water (250 mL). The combined EtOAc layers are dried over MgSO\(_4\) and gravity filtered. The crude reaction mixture was purified via flash chromatography (20:1 EthOAc/hexane) to afford compound 22a as a white crystalline solid (5.96 g, 96% yield).
5.11 Compound 24

![Chemical structure of compounds 22a and 24](image)

Figure 58. Compound 24

To a solution of compound 22a (110 mg, 0.5 mmol) in THF (5.0 mL) was added a solution of LiAl(OtBu)\(_3\)H (1.0 M in THF, 2 mL, 2.0 mmol) at -78 °C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated potassium sodium tartrate, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes) to afford compound 24 as a colorless oil (94 mg, 92% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 4.23 (m, 2H), 3.48 (d, \(J = 8.6\) Hz, 1H), 3.23 (d, \(J = 8.0\) Hz, 1H), 2.43 (m, 1H), 1.99 (m, 1H), 1.17 (s, 3H) 1.12 (s, 9 H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) δ 181.5, 73.6, 67.3, 65.9, 43.8, 32.8, 27.0, 20.3; IR (neat) cm\(^{-1}\) 3436, 2976, 2930, 1722, 1456, 1367, 1146, 846; HRMS (C\(_{10}\)H\(_{20}\)O\(_4\), ESI): calculated 227.1259 [M+Na]\(^+\), found 227.1250; \([\alpha]_D^{23} = -0.6^\circ\) (c = 1.0, CHCl\(_3\)).
5.12 Compound 25

![Chemical Structure](image)

Figure 59. Compound 25

To a solution of compound 22a (100 mg, 0.5 mmol) in THF (5.0 mL) was added benzyl amine (0.27 mL, 2.5 mmol) at rt. The solution was allowed to react under reflux for 4 d. The reaction was acidified with 1 M HCl at 0 °C and extracted with Et₂O (2 x 10 mL) and H₂O (1 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→30% EtOAc in hexanes) to afford compound 25 as a colorless oil (90 mg, 77% yield) ³¹H NMR (500 MHz, CDCl₃) δ 7.27 (m, 5H), 4.44 (d, J = 5.7 Hz, 2H), 3.70 (m, 2H), 2.15 (m, 2H), 1.46 (m, 3H) 1.44 (s, 9 H); ¹³C NMR (126 MHz, CDCl₃) δ 174.0, 172.2, 138.1, 128.7, 127.7, 127.5, 82.3, 59.4, 52.9, 43.6, 39.2, 27.7, 22.1; IR (neat) cm⁻¹ 3358, 2980, 2359, 1726, 1369, 1242, 1045; HRMS (C₁₇H₂₅NO₄, ESI): calculated 308.1861 [M+H]⁺, found 308.1866; [α]D²³ = -3.3° (c = 1.5, CHCl₃).
5.13 Compound 26

To a solution of compound 22a (45 mg, 0.22 mmol) was added trifluoroacetic acid (9 mL) at rt. The solution was allowed to react at rt overnight. The reaction mixture was then concentrated. To the reaction residue was added NaN₃ (18 mg, 0.27 mmol) and PPh₃ (0.12 g, 0.44 mmol) at rt. MeCN (10 mL) was then added to reaction mixture at 0 °C and stirred until homologous. Cl₃CCN (0.08 mL, 0.44 mmol) was added at 0 °C and the solution was allowed to warm to rt and react for 30 hr. The reaction mixture was partially concentrated and the residue with dissolved in CH₂Cl₂ (5 mL) and extracted with CH₂Cl₂ (2 x 10 mL) and H₂O (1 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated to yield a yellow clear oil (43 mg).

The crude acyl azide intermediate (43 mg, 0.26 mmol) was dissolved in THF (1.5 mL) and heated to 100 °C for 20 min in a microwave reactor. The observance of an isocyanate peak (2283 cm⁻¹) by IR spectroscopy confirmed the
rearrangement had occurred. A mixture of K$_2$CO$_3$ (0.14 g, 1.02 mmol) in H$_2$O (0.3 mL) was added to the reaction mixture and allowed to stir for 20 min. and to it was added benzoyl chloride (0.027 mL, 0.24 mmol). The solution was allowed to react overnight at rt. The reaction was acidified with 1 M HCl and reaction mixture was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (30→60% Acetone in hexanes) to afford compound 26 as a white crystal (31 mg, 56% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78-7.42 (m, 5H), 6.61 (bs, 1H), 4.56 (m, 1H), 4.33 (m, 1H), 2.83 (m, 1H), 2.57 (m, 1H), 1.63 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.8, 166.8, 133.5, 132.3, 130.2, 128.8, 65.9, 56.2, 35.0, 22.3; IR (neat) cm$^{-1}$ 3296, 2982, 2361, 1763, 1632, 1527, 1319, 1107, 1023, 936; HRMS (C$_{16}$H$_{30}$O$_5$, ESI): calculated 325.1990 [M+Na]$^{+}$, found 325.2001. [α]$^\text{D}_{23} = +2.0 ^\circ$ (c = 1.0, CHCl$_3$).
5.14 Compound 27

5.14.1 Amide ester intermediate

![Chemical structure]

(-)-22a

Figure 61. Amide Ester Intermediate

To a solution of compound 22a (88.1 mg, 0.44 mmol) in dioxane (1.5 mL) was added concentrated NH$_4$OH (5 mL) at rt. The solution was allowed to react at rt overnight. The reaction mixture was then concentrated. The reaction mixture was dissolved in TEA (0.10 mL, 0.66 mmol) in CH$_2$Cl$_2$ (2 mL). DMAP (11 mg, 0.09 mmol) was added followed by Ac$_2$O (0.06 mL, 0.66 mmol) at rt and the solution was allowed to react for 40 hr. The reaction mixture was concentrated and the residue with dissolved in EtOAc (5 mL) and extracted with EtOAc (2 x 10 mL) and H$_2$O (10 mL). The combined organic phases were dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (15→30% acetone in hexanes) to afford amide ester intermediate as a colorless oil (47 mg, 41% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.1 (m, 2H), 2.20 (m, 2H), 2.00 (s, 3H), 1.47 (m, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.5, 173.1, 171.1, 82.7, 61.1, 52.2, 35.5, 27.8, 21.9, 20.9; IR (neat) cm$^{-1}$ 3348, 2979, 2358,
1745, 1669, 1364, 1227, 1121, 1037; HRMS (C_{12}H_{21}NO_{5}, ESI): calculated 282.1317 [M+Na]^{+1}, found 282.1326.

5.14.2 Amide intermediate

![Amide Intermediate Diagram]

Figure 62. Amide Intermediate

To a solution of the amide ester intermediate (28 mg, 0.108 mmol) in tBuOH (0.55 mL) was added Pb(OAc)$_4$ (95.9 mg, 0.216 mmol) at 70 °C. The solution was allowed to react overnight. To the reaction mixture was added Et$_2$O (4 mL) and NaHCO$_3$ (0.11 g) and was allowed to stir for 10 min. The reaction mixture was filtered through SiO$_2$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% acetone in hexanes) to afford the amide intermediate as a colorless oil (20 mg, 57% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.05 (t, $J$ = 6.6 Hz, 2H), 2.41 (m, 1H), 2.23 (m, 1H), 1.99 (s, 3H) 1.50 (s, 3H), 1.46 (s, 9H), 1.41 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.4, 171.0, 154.2, 82.1, 79.4, 60.9, 58.1, 34.5, 28.4, 27.9, 24.2, 21.0; IR (neat) cm$^{-1}$ 3358, 2980, 2359, 1726, 1369, 1242, 1045; HRMS (C$_{16}$H$_{29}$NO$_6$, ESI): calculated 354.1892 [M+Na]$^{+1}$, found 354.1882.
5.14.3 Compound 27

Figure 63. Compound 27

To a solution of the amide intermediate (20 mg, 0.061 mmol) in MeOH (1.5 mL) was added K$_2$CO$_3$ (41 mg) at rt. The solution was allowed to react for 20 min. The reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL) and extracted with H$_2$O (1 x 5 mL). The organic layer was washed with brine (5 mL) and dried over MgSO$_4$. The solution was concentrated to yield compound 27 as a colorless oil (14 mg, 80% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.7 (m, 2H), 2.2 (m, 1H), 2.15 (m, 1H), 1.52 (s, 3H), 1.46 (s, 9 H), 1.41 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.4, 154.7, 81.8, 79.4, 59.2, 58.5, 39.1, 28.4, 28.0, 23.8; HRMS (C$_{14}$H$_{27}$NO$_5$, ESI): calculated 312.1786 [M+Na]$^+$, found 312.1776; [α]$_D^{23}$ = +10.0° (c = 0.9, CHCl$_3$).
To a solution of compound 22f (47 mg, 0.2 mmol) in THF (3.0 mL) was added a solution of LiAl(OtBu)$_3$H (1.0 M in THF, 0.7 mL, 0.7 mmol) at -78 °C. The solution was allowed to warm to rt and react for 21 h. The reaction was quenched with saturated potassium sodium tartrate, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→60% EtOAc in hexanes) to afford compound 28 as a colorless oil (13 mg, 28% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.25 (m, 5H), 3.84 (d, $J = 12.0$ Hz, 1H), 3.69 (m, 2H), 3.54 (d, $J = 12.0$ Hz, 1H), 3.17 (b, 2H), 2.95 (d, $J = 13.7$ Hz, 1H), 2.78 (d, $J = 13.7$ Hz, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 1.44 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.0, 136.5, 130.5, 127.9, 126.8, 82.0, 65.4, 59.2, 51.7, 41.9, 38.9, 27.9; IR (neat) cm$^{-1}$ 3433, 2974, 2932, 1773, 1725, 1453, 1369, 1145, 1104, 844; $[\alpha]_D^{23} = +4.1^\circ$ (c= 1.3, CHCl$_3$)
5.16 Synthesis of Compound 43a

5.16.1 Acetyl intermediate

![Chemical reaction diagram](image)

Figure 65. Acetyl Intermediate

To a solution of sodium hydride (60% in mineral oil, 0.13 g, 3.16 mmol) in THF (7.5 mL) was added di-tert-butyl malonate dropwise (0.68 g, 3.16 mmol) and the solution was stirred until gas evolution was complete. To the reaction mixture was added benzyl 2-bromoethyl ether (0.5 mL, 3.16 mmol) and the solution was stirred under reflux until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→20% EtOAc in hexanes) to afford the di-t-butyl 2-(2-(benzyloxy)ethyl)malonate intermediate as a colorless oil (0.75 g, 68% yield).

To a solution of sodium hydride (60% mineral oil, 72 mg, 1.8 mmol) in THF (7 mL) was added the di-t-butyl 2-(2-(benzyloxy)ethyl)malonate intermediate (315 mg, 0.9 mmol) and the solution was stirred until gas evolution was complete. To
the reaction mixture was added 2-bromoethyl acetate (0.15 mL, 1.35 mmol) and the solution was stirred until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (10→40% EtOAc in hexanes) to afford the acetyl intermediate as a colorless oil (358 mg, 91% yield).

H NMR (500 MHz, CDCl₃) δ 7.29 (m, 5H), 4.43 (s, 2H), 4.06 (t, \( J = 7.2 \) Hz, 2H), 3.43 (t, \( J = 6.9 \) Hz, 2H), 2.17 (m, 4H), 1.97 (s, 3H), 1.40 (s, 18H); C NMR (126 MHz, CDCl₃) δ 170.9, 170.1, 138.2, 128.4, 127.8, 127.6, 81.6, 73.1, 66.0, 60.9, 55.5, 32.0, 30.9, 27.9, 21.0.
5.16.2 Compound 42a

![Chemical Structure](image)

Figure 66. Compound 42a

To a solution of the acetyl intermediate (0.11g, 0.27 mmol) in MeOH (3 mL) was added K$_2$CO$_3$ (0.15 g, 1.1 mmol) and the solution was stirred at rt until reaction completion was determined by TLC analysis. The reaction mixture was diluted with CH$_2$Cl$_2$ and was extracted with CH$_2$Cl$_2$ (2 x 15 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated to afford compound 42a as a colorless oil (94.7 mg, 90% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.30 (m, 5H), 4.45 (s, 2H), 3.64 (t, $J$ = 6.3 Hz, 2H), 3.45 (t, $J$ = 6.9 Hz, 2H), 2.28 (bs, 1H), 2.22 (t, $J$ = 6.6 Hz, 2H), 2.12 (t, $J$ = 6.6 Hz, 2H), 1.40 (s, 18 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.9, 138.1, 128.5, 127.9, 127.5, 81.6, 73.1, 66.2, 59.0, 56.3, 35.3, 32.7, 27.9; HRMS (C$_{22}$H$_{34}$O$_6$, ESI): calculated 417.2253 [M+Na]$^{+1}$, found 417.2245.
5.16.3 Hydroxy Lactone intermediate

To a solution of acid 14 (0.05 mmol) in CH₂Cl₂ (3 mL) was added compound 42a (95 mg, 0.24 mmol) and the solution was stirred for 144 h at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H₂O (1 x 10 mL). The organic phase was dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (10→40% EtOAc in hexanes) to afford benzyl lactone intermediate (60 mg, 78% yield).¹H NMR (500 MHz, CDCl₃) δ 7.30 (m, 5H), 4.45 (q, J = 10.2 Hz, 2H), 4.29 (m, 2H), 3.59 (t, J = 6.2 Hz, 2H), 2.65 (m, 1H), 2.37 (m, 2H), 2.13 (m, 1H), 1.43 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 175.4, 168.6, 138.1, 128.5, 127.8, 83.1, 73.1, 66.5, 53.6, 33.4, 32.0, 27.9.
To a solution of the benzyl lactone intermediate (44.3 mg, 0.14 mmol) in EtOAc (3 mL) was added Pd(OH)$_2$ (20% on carbon, 9.7 mg, 0.07 mmol) and the solution was stirred under hydrogen pressure using a balloon filled with hydrogen gas at rt until reaction completion was determined by TLC analysis. The reaction mixture was filtered through a plug of Celite® and concentrated to afford hydroxy lactone intermediate (28.7 mg, 90% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.34 (m, 2H), 3.79 (m, 2H), 2.63 (m, 1H), 2.38 (m, 1H), 2.31 (bs, 1H), 2.22 (m, 1H), 2.10 (m, 1H), 1.46 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 176.2, 169.1, 83.6, 66.6, 59.1, 53.9, 36.2, 32.7, 27.9.

5.16.4 Compound 43a

![Figure 68. Compound 43a](image)

To a solution of hydroxy lactone intermediate (28.7 mg, 0.12 mmol) in CH$_2$Cl$_2$ (2 mL) was added $p$-toluenesulfonic acid (11.5 mg, 0.6 mmol) and the solution was stirred at rt for 48 h. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and
concentrated to afford compound 43a as a white solid (18 mg, 92% yield). $^1$H
NMR (500 MHz, CDCl$_3$) δ 4.63 (m, 2H), 4.43 (m, 2H), 2.78 (m, 2H), 2.36 (m, 2H);
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.1, 66.8, 50.0, 32.6; HRMS (C$_7$H$_8$O$_4$, ESI):

5.17 Synthesis of Compound 43b

5.17.1 Benzyl intermediate

Figure 69. Benzyl Intermediate

To a solution of sodium hydride (60% in mineral oil, 65 mg, 1.62 mmol) in THF (7.0 mL) was added di-tert-butyl malonate dropwise (0.35 g, 1.62 mmol) and
the solution was stirred until gas evolution was complete. To the reaction mixture
was added 2-bromoethyl acetate (0.18 mL, 1.62 mmol) and the solution was
stirred until reaction completion was determined by TLC analysis. The reaction
was quenched with saturated NH$_4$Cl (6 mL) at 0 °C, phases were separated, and
aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic
phases were dried over MgSO$_4$ and concentrated. The residue was purified by
flash chromatography on silica gel (5→15% EtOAc in hexanes) to afford the di-tert-
butyl 2-(2-acetoxyethyl)malonate intermediate as a colorless oil (0.29 g, 60% yield).

To a solution of sodium hydride (60% mineral oil, 78 mg, 1.94 mmol) in THF (7 mL) was added the di-t-butyl 2-(2-acetoxyethyl)malonate intermediate (291 mg, 0.84 mmol) and the solution was stirred until gas evolution was complete. To the reaction mixture was added benzyl 3-bromopropyl ether (0.17 mL, 0.97 mmol) and the solution was stirred until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (10→40% EtOAc in hexanes) to afford the benzyl intermediate as a colorless oil (212 mg, 49% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.31 (m, 5H), 4.48 (s, 2H), 4.06 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 6.6 Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H), 1.99 (s, 3H), 1.88 (m, 2H), 1.49 (m, 2H), 1.44 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 171.0, 170.4, 138.6, 128.4, 127.7, 81.6, 72.9, 70.3, 60.8, 56.6, 30.6, 29.1, 27.9, 24.5, 21.
5.17.2 Compound 42b

![Chemical Structure]

Figure 70. Compound 42b

To a solution of the benzyl intermediate (146 mg, 0.32 mmol) in MeOH (3 mL) was added K$_2$CO$_3$ (177 mg, 1.28 mmol) and the solution was stirred at rt until reaction completion was determined by TLC analysis. The reaction mixture was diluted with CH$_2$Cl$_2$ and was extracted with CH$_2$Cl$_2$ (2 x 15 mL) and H$_2$O (1 x 10 mL). The organic layer was dried over MgSO$_4$ and concentrated to afford compound 42b as a colorless oil (117 mg, 88% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.32 (m, 5H), 4.48 (s, 2H), 3.66 (m, 2H), 3.44 (t, $J$ = 6.4 Hz, 2H), 2.09 (t, $J$ = 6.5 Hz, 2H), 2.01 (bs, 1H), 1.92 (m, 2H), 1.52 (m, 2H), 1.44 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.3, 138.6, 128.5, 127.7, 127.6, 81.6, 72.9, 70.3, 59.1, 57.1, 35.3, 29.9, 28.0, 24.6; HRMS (C$_{24}$H$_{38}$O$_5$, ESI): calculated 431.2404 [M+Na]$^+$, found 431.2418.
5.17.3 Lactone intermediate

![Diagram of lactone intermediate](image)

**Figure 71. Lactone Intermediate**

To a solution of acid 14 (8.2 mg, 0.011 mmol) in CH₂Cl₂ (3 mL) was added compound 42b (90 mg, 0.22 mmol) and the solution was stirred for 144 h at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H₂O (1 x 10 mL). The organic phase was dried over MgSO₄ and concentrated to afford lactone intermediate (73 mg, 99% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.32 (m, 5H), 4.48 (s, 2H), 4.30 (m, 2H), 3.49 (m, 2H), 2.66 (m, 1H), 2.22 (m, 1H), 2.11 (m, 2H), 1.82 (m, 1H), 1.74 (m, 1H), 1.56 (m, 1H), 1.45 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 175.3, 168.6, 138.4, 128.5, 127.8, 83.1, 73.0, 69.9, 66.2, 54.6, 31.9, 30.8, 27.9, 25.2.

To a solution of the lactone intermediate (73 mg, 0.22 mmol) in EtOAc (3 mL) was added Pd(OH)₂ (20% on carbon, 15.4 mg, 0.11 mmol) and the solution was stirred under hydrogen pressure using a balloon filled with hydrogen gas at rt until reaction completion was determined by TLC analysis. The reaction mixture was filtered through a plug of Celite® and concentrated to afford lactone.
intermediate (50.1 mg, 94% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.31 (m, 2H), 3.64 (m, 2H), 2.61 (m, 1H), 2.23 (m, 1H), 2.03 (m, 1H), 1.80 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.45 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.5, 168.8, 83.3, 66.3, 62.4, 54.5, 32.1, 30.2, 27.9.

5.17.4 Compound 43b

![Diagram of compound 43b]

Figure 72. Compound 43b

To a solution of lactone intermediate (50.1 mg, 0.21 mmol) in CH$_2$Cl$_2$ (2 mL) was added $p$-toluenesulfonic acid (39.1 mg, 0.21 mmol) and the solution was stirred at rt for 24 h. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated to afford compound 43b as white solid (27.2 mg, 78% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.56 (m, 2H), 4.39 (m, 1H), 4.37 (m, 1H), 2.86 (m, 1H), 2.41 (m, 1H), 2.19 (m, 2H), 1.90 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.2, 168.6, 70.9, 66.7, 50.3, 36.4, 30.3, 20.4; HRMS (C$_8$H$_{10}$O$_4$, ESI): calculated 171.0651 [M+H]$^+$, found 171.0654, [α]$^D_{23}$ = -2.5° (c =0.5, CHCl$_3$)
5.18 Synthesis of Compound 43c

5.18.1 Dialkylated intermediate

![Figure 73. Dialkylated Intermediate](image)

To a solution of sodium hydride (60% in mineral oil, 0.13 g, 3.16 mmol) in THF (7.5 mL) was added di-tert-butyl malonate dropwise (0.68 g, 3.16 mmol) and the solution was stirred until gas evolution was complete. To the reaction mixture was added benzyl 2-bromoethyl ether (0.5 mL, 3.16 mmol) and the solution was stirred until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→20% EtOAc in hexanes) to afford the di-t-butyl 2-(2-(benzyloxy)ethyl)malonate intermediate as colorless oil (0.75 g, 68% yield).

To a solution of sodium hydride (60% mineral oil, 0.28 g, 0.8 mmol) in THF (7 mL) was added di-t-butyl 2-(2-(benzyloxy)ethyl)malonate intermediate and the solution was stirred until gas evolution was complete. To the reaction mixture
was added *N*-tosyl aziridine (1M in THF, 0.16 g, 0.08 mmol) at 0 °C and the solution was allowed to slowly warm up to rt and was stirred until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford dialkylated intermediate (211 mg, 48% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.28 (m, 7H), 4.80 (bs, 1H), 4.40 (s, 2H), 3.38 (t, *J* = 6.2, 2H), 2.89 (q, *J* = 6.9 Hz, 2H), 2.38 (s, 3H), 2.09 (t, *J* = 6.2 Hz, 2H), 2.01 (t, *J* = 7.3 Hz, 2H), 1.36 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 170.2, 143.3, 137.9, 136.8, 129.7, 128.5, 127.9, 127.1, 81.9, 73.2, 66.1, 56.4, 39.3, 32.3, 27.8, 21.5.
5.18.2 Compound 42c

![Diagram of compound 42c]

Figure 74. Compound 42c

To a solution of the dialkylated intermediate (58.1 mg, 0.11 mmol) in EtOAc (4 mL) was added Pd(OH)$_2$ (20 % on carbon, 7.7 mg, 0.06 mmol) and the solution was stirred under hydrogen pressure using a balloon filled with hydrogen gas at rt until reaction completion was determined by TLC analysis. The reaction mixture was filtered through a plug of Celite, the filtrate was concentrated under vacuum, to afford compound 42c as colorless oil (46.6 mg, 96% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.70 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 5.13 (bs, 1H), 3.61 (t, $J = 6.3$ Hz, 2H), 2.90 (m, 2H), 2.40 (s, 3H), 2.03 (m, 4H), 1.39 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.6, 143.5, 136.8, 129.8, 127.2, 82.3, 58.7, 56.4, 39.3, 35.3, 32.9, 27.9, 21.6; HRMS (C$_{22}$H$_{35}$NO$_7$S, ESI): calculated 480.2027 [M+Na]$^+$, found 480.2044.
5.18.3 Compound 43c

Figure 75. Compound 43c

To a solution of acid 14 (3.0 mg, 0.004 mmol) in CH$_2$Cl$_2$ (2 mL) was added compound 42c (36.5 mg, 0.08 mmol) and the solution was stirred for the 216 h at rt. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated to afford lactone intermediate (28 mg, 92% yield).

To a solution of lactone intermediate (26.4 mg, 0.07 mmol) in CH$_2$Cl$_2$ (1 mL) was added excess trifluoroacetic acid (1 mL) and the solution was stirred until reaction completion was determined by TLC analysis. The reaction was extracted with EtOAc (2 x 10 mL) and H$_2$O (1 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated to afford compound 43c as white solid (18.5 mg, 87% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 4.48 (m, 1H), 4.32 (m, 1H), 4.07 (m, 2H), 2.73 (m, 1H), 2.52 (m, 1H), 2.43 (s, 3H), 2.16 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.1, 170.1, 145.6, 133.8, 129.7, 128.1, 66.9, 52.9, 43.0, 32.1, 28.5, 21.6; HRMS (C$_{14}$H$_{15}$NO$_5$S, ESI): calculated 310.0744 [M+Na]$^+$, found 310.0745, $[^{[\alpha]}]_D^{23} = -6.4^\circ$ (c =0.5, CHCl$_3$).
5.19 Synthesis of Compound 55a

5.19.1 Compound 54a

![Chemical structure of 54a]

To a solution of sodium hydride (60% in mineral oil, 0.14 g, 3.48 mmol) in THF (10 mL) was added di-t-butyl 2-methylmalonate intermediate (0.4 g, 1.74 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, N-tosylaziridine (1M in THF, 0.5 g, 2.61 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0°C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford the compound 54a as white solid (0.59 g, 80% yield). ^1H NMR (500 MHz, CDCl₃) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.8 (bs, 1H), 2.95 (q, J = 8.1 Hz, 2H), 2.40 (s, 3H), 1.91 (t, J = 7.3 Hz, 2H), 1.39 (s, 18H), 1.24 (s, 3H);
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.3, 143.5, 136.8, 129.8, 127.2, 81.8, 53.6, 39.1, 35.1, 27.9, 21.6, 20.1. HRMS (C$_{21}$H$_{33}$NO$_6$S, ESI): calculated 450.1918 [M+Na]$^{+1}$, found 450.1927.

5.19.2 Compound 55a

![Chemical Structure](image)

Figure 77. Compound 55a

To a solution of acid (R)-14 (4.4 mg, 0.006 mmol) in CH$_2$Cl$_2$ (2 mL) was added compound 54a (50 mg, 0.12 mmol) and the solution was stirred for 96 h at rt. The reaction was extracted with EtOAc (2 x 5 mL) and H$_2$O (1 x 5 mL). The organic phase was dried over MgSO$_4$ and concentrated to afford compound 55a as white crystalline solid (40.8 mg, 99% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, $J$ = 8.2 Hz, 2H), 7.34 (d, $J$ = 8.2 Hz, 2H), 3.93 (m, 1H), 3.79 (m, 1H), 2.42 (m, 4H), 1.96 (m, 1H), 1.32 (s, 3H), 1.21 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.1, 169.5, 145.3, 134.8, 129.7, 128.3, 82.6, 53.5, 44.8, 31.3, 27.6, 21.7, 19.9; HRMS (C$_{17}$H$_{23}$NO$_{5}$S, ESI): calculated 376.1195 [M+Na]$^{+1}$, found 376.1184.
5.20 Synthesis of Compound 55b

5.20.1 Compound 54b

$$\text{NaH, } \text{NTs}$$

\[\text{THF, } 0 \degree \text{C} \rightarrow \text{rt} \]

$54b$ NHTs

Figure 78. Compound 54b

To a solution of sodium hydride (60% in mineral oil, 33 mg, 0.82 mmol) in THF (5 mL) was added di-t-butyl 2-ethylmalonate intermediate (100 mg, 0.41 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, N-tosylaziridine (1M in THF, 81 mg, 0.41 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated NH$_4$Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to
afford the compound 54b as white solid (135 mg, 75% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.88 (t, J = 4.8 Hz, 1H), 2.88 (q, J = 8.5 Hz, 2H), 2.39 (s, 3H), 1.92 (t, J = 6.1 Hz, 2H), 1.75 (q, J = 9.1 Hz, 2H), 1.38 (s, 18H), 0.73 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.6, 143.4, 136.8, 129.8, 127.2, 81.2, 57.6, 39.3, 31.7, 27.9, 25.9, 21.5, 8.3; HRMS (C₂₂H₃₅NO₆S, ESI): calculated 464.2082 [M+Na]^⁺, found 464.2077.

5.20.2 Compound 55b

![Diagram](54b to 55b conversion)

Figure 79. Compound 55b

To a solution of acid (R)-14 (3.0 mg, 0.004 mmol) in DCE (1 mL) was added compound 54b (35 mg, 0.08 mmol) and the solution was stirred for 144 h at rt. The reaction was extracted with EtOAc (2 x 5 mL) and H₂O (1 x 5 mL). The organic phase was dried over MgSO₄, concentrated, and filtered through a silica plug to afford compound 55a as white crystalline solid (16.0 mg, 55% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (m, 2H), 7.28 (m, 2H), 2.98 (m, 2H), 2.92 (m, 1H), 2.62, (m, 1H), 2.43 (m, 3H), 1.76 (m, 1H), 1.65 (m, 1H), 1.38 (m, 1H), 1.38 (s, 9H), 1.05 (m, 3H) ; ¹³C NMR (126 MHz, CDCl₃) δ 175.3, 174.3, 143.6, 132.1,
129.8, 127.1, 80.8, 56.7, 45.3, 41.7, 31.7, 28.1, 21.6, 11.5. HRMS (C_{18}H_{25}NO_{5}S, ESI): calculated 390.1351 [M+Na]^+, found 390.1343.

5.21 Synthesis of Compound 55c

5.21.1 Compound 54c

![Chemical Reaction](image)

Figure 80. Compound 54c

To a solution of sodium hydride (60% in mineral oil, 35 mg, 0.88 mmol) in THF (5 mL) was added allyl malonate intermediate (113.4 mg, 0.44 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, N-tosylaziridine (1M in THF, 130 mg, 0.66 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford the compound 54c as white solid (86 mg, 43% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 5.50 (m, 1H), 5.03 (m,
2H), 4.74 (t, J = 4.7 Hz, 1H), 2.92 (q, J = 8.6 Hz, 2H), 2.47 (t, J = 7.3 Hz, 2H),
2.39 (s, 3H), 1.91 (t, J = 6.2 Hz, 2H), 1.38 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ
170.1, 143.5, 136.8, 132.1, 129.8, 127.2, 119.3, 82.1, 56.9, 39.1, 37.7, 32.3,
27.9, 21.6; HRMS (C$_{23}$H$_{35}$NO$_6$S, ESI): calculated 476.2082 [M+Na]$^{+1}$, found
476.2073.

5.21.2 Compound 55c

![Chemical Structure](image)

Figure 81. Compound 55c

To a solution of acid (R)-14 (3.0 mg, 0.004 mmol) in CH$_2$Cl$_2$ (1 mL) was added compound 54c (35 mg, 0.08 mmol) and the solution was stirred for 192 h at rt. The reaction was extracted with EtOAc (2 x 5 mL) and H$_2$O (1 x 5 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford compound 55c as white crystalline solid (21.0 mg, 74% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.54 (m, 1H), 5.04 (m, 2H), 3.87 (m, 1H), 3.79 (m, 1H), 2.55 (m, 1H), 2.41 (m, 4H), 2.31 (m, 1H), 2.03 (m, 1H) 1.22 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.8, 168.4,
145.3, 134.7, 132.0, 129.7, 128.3, 120.0, 82.7, 57.2, 44.9, 37.9, 32.0, 27.6, 21.7;
HRMS (C_{19}H_{25}NO_{5}S, ESI): calculated 402.1351 [M+Na]^+, found 402.1347.

5.22 Synthesis of Compound 55d

5.22.1 Compound 54d

![Reaction Scheme for 54d](image)

Figure 82. Compound 54d

To a solution of sodium hydride (60% in mineral oil, 37 mg, 0.92 mmol) in THF (7 mL) was added di-t-butyl malonate dropwise (200 mg, 0.92 mmol) and the solution was stirred until gas evolution was complete. To the reaction mixture was added 1-bromo-2-methylpropane (0.11 mL, 0.92 mmol) and the solution was stirred under reflux until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH_{4}Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO_{4} and concentrated. The residue was purified by flash chromatography on silica gel (5→20% EtOAc in hexanes) to afford the di-t-butyl 2-isopentylmalonate intermediate as a colorless oil (205 mg, 86% yield.)
To a solution of sodium hydride (60% in mineral oil, 47.5 mg, 1.19 mmol) in THF (6 mL) was added di-\(t\)-butyl 2-isopentylmalonate intermediate (205 mg, 0.79 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, \(N\)-tosylaziridine (1M in THF, 155.8 mg, 0.79 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated \(\text{NH}_4\text{Cl}\) (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford the compound 54d as white solid (181.9 mg, 48% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, \(J = 8.2\) Hz, 2H), 7.28 (d, \(J = 8.2\) Hz, 2H), 4.77 (t, \(J = 4.7\) Hz, 1H), 2.88 (q, \(J = 8.6\) Hz, 2H), 2.39 (s, 3H), 1.91 (t, \(J = 6.2\) Hz, 2H), 1.70 (m, 3H), 1.45 (m, 2H), 1.23 (s, 18H), 0.80 (d, \(J = 2.5\) Hz, 6H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.7, 143.4, 136.8, 129.7, 127.2, 81.7, 57.2, 39.3, 32.7, 32.0, 30.6, 28.3, 27.9, 22.5, 21.5; HRMS (C\(_{25}\)H\(_{41}\)NO\(_6\)S, ESI): calculated 506.2552 [M+Na]\(^+\), found 506.2545.
5.22.2 Compound 55d

![Reaction Scheme](image)

Figure 83. Compound 55d

To a solution of acid (R)-14 (3.5 mg, 0.004 mmol) in toluene (2 mL) was added compound 54d (45 mg, 0.09 mmol) and the solution was stirred for 204 h at 80 °C. The reaction was extracted with EtOAc (2 x 5 mL) and H₂O (1 x 5 mL). The organic phase was dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford compound 55d as white crystalline solid (15.7 mg, 41% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.7 (d, J = 8.2 Hz, d), 7.25 (d, J = 8.2 Hz, 2H), 2.88 (m, 2H), 2.40 (s, 3H), 2.11 (t, J = 7.1 Hz, 2H), 1.86 (m, 1H), 1.77 (m, 1H), 1.47 (s, 9H), 0.84 (d, J = 6.9 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 174.6, 173.9, 143.7, 136.5, 129.8, 127.2, 84.4, 55.6, 39.6, 35.1, 33.4, 28.1, 27.8, 22.5, 22.3, 21.6; HRMS (C₂₁H₃₁NO₅S, ESI): calculated 432.1820 [M+Na]⁺¹, found 432.1819.
5.23 Synthesis of Compound 55e

5.23.1 Di-t-butyl 2-(but-2-yn-1-yl)malonate intermediate

![Chemical Structure](image)

Figure 84. Di-t-butyl 2-(but-2-yn-1-yl)malonate Intermediate

To a solution of sodium hydride (60% in mineral oil, 29 mg, 0.69 mmol) in THF (5 mL) was added di-t-butyl malonate dropwise (150 mg, 0.69 mmol) and the solution was stirred until gas evolution was complete. To the reaction mixture was added 1-bromo-2-butyne (0.06 mL, 0.69 mmol) dropwise at 0 °C. The reaction was allowed to warm to rt and react until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH₄Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (5→10% EtOAc in hexanes) to afford the di-t-butyl 2-(but-2-yn-1-yl)malonate intermediate as a colorless oil (180 mg, 97% yield). ^1H NMR (500 MHz, CDCl₃) δ 3.29 (t, J = 7.7 Hz, 1H), 2.60 (m, 2H), 1.73 (t, J = 2.6 Hz, 2H), 1.45 (s, 18H); ^13C NMR (126 MHz, CDCl₃) δ 167.0, 81.7, 77.5, 75.2, 53.5, 27.9, 18.7, 3.5.
5.23.2 Compound 54e

![Chemical Structure](image)

Figure 85. Compound 54e

To a solution of sodium hydride (60% in mineral oil, 23 mg, 0.56 mmol) in THF (4 mL) was added di-\textit{t}-butyl 2-(but-2-yn-1-yl)malonate intermediate (74.1 mg, 0.28 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, \textit{N}-tosylaziridine (1M in THF, 140 mg, 0.7 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated NH\textsubscript{4}Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO\textsubscript{4} and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford the compound 54e as white solid (63.5 mg, 49% yield). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.78 (d, \textit{J} = 8.6 Hz, 2H), 7.28 (d, \textit{J} = 8.0 Hz, 2H), 5.18 (bs, 1H), 3.04 (m, 2H), 2.54 (s, 2H), 2.41 (s, 3H), 2.03 (m, 2H), 1.71 (s, 3H), 1.43 (s, 18H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 169.1, 143.6, 135.8, 129.9, 127.2, 82.2, 79.2, 73.3

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56.3, 45.2, 42.3, 30.91, 27.8, 21.7, 3.5; HRMS (C_{24}H_{35}NO_{6}S, ESI): calculated 488.2082 [M+Na]^+^1, found 488.2077

5.23.3 Compound 55e

![Chemical structure of compound 55e](image)

Figure 86. Compound 55e

To a solution of acid (R)-14 (2.0 mg, 0.002 mmol) in toluene (1 mL) was added compound 54e (25 mg, 0.05 mmol) and the solution was stirred for 192 h at 80 °C. The reaction was extracted with EtOAc (2 x 5 mL) and H_{2}O (1 x 5 mL). The organic phase was dried over MgSO_{4} and concentrated to afford compound 55e as white crystalline solid (17.9 mg, 85% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.87 (m 2H), 7.32 (m, 2H), 3.87 (m, 2H), 2.47 (m, 1H), 2.41 (m, 3H), 2.09 (m, 1H), 1.90 (m, 1H), 1.71 (m, 1H), 1.39 (s, 3H), 1.20 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 173.9, 171.5, 143.8, 136.3, 129.9, 127.2, 80.1, 60.6, 55.6, 48.3, 45.5, 42.1, 27.7, 21.6, 14.2, 3.6; HRMS (C_{20}H_{25}NO_{5}S, ESI): calculated 414.1351 [M+Na]^+^1, found 414.1343.
5.24 Synthesis of Compound 57d

5.24.1 Compound 56d

\[
\begin{align*}
&\text{THF, } 0^\circ \text{C} \rightarrow \text{rt} \\
\text{NaH, } &\text{NNS} \\
\text{di-t-butyl 2-methylmalonate intermediate} &\rightarrow \text{N-nosylaziridine} \\
&\text{Compound 56d}
\end{align*}
\]

Figure 87. Compound 56d

To a solution of sodium hydride (60% in mineral oil, 45 mg, 1.12 mmol) in THF (5 mL) was added di-t-butyl 2-methylmalonate intermediate (127.9 mg, 0.56 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, N-nosylaziridine (1M in THF, 147 mg, 0.56 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 23 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0 °C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford the compound 56d as pale yellow oil (154 mg, 60% yield). \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 8.32 (d, \(J = 3.7\) Hz, 2H), 8.04 (d, \(J = 3.7\) Hz, 2H), 5.42 (bs, 1H), 3.04 (q, \(J = 8.1\) Hz, 2H), 1.93 (t, \(J = 5.7\) Hz, 2H), 1.40 (s, 18H), 1.25 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta\) 174.3, 150.1, 145.9, 128.42, 124.5, 82.1, 53.7, 39.6,
35.2, 27.9, 20.3. HRMS (C_{20}H_{30}N_{2}O_{8}S, ESI): calculated 481.1620 [M+Na]^{+1}, found 481.1622

5.24.2 Compound 57d

![Figure 88. Compound 57d](image)

To a solution of acid (R)-14 (9.4 mg, 0.05 mmol) in CH$_2$Cl$_2$ (2 mL) was added compound 56d (45.4 mg, 0.1 mmol) and the solution was stirred for 96 h at rt. The reaction was extracted with EtOAc (2 x 5 mL) and H$_2$O (1 x 5 mL). The organic phase was dried over MgSO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford compound 57d as white crystalline solid (32.4 mg, 85% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.33 (d, $J = 3.6$ Hz, 2H), 8.04 (d, $J = 3.6$ Hz, 2H), 3.09 (m, 2H), 2.12 (m, 1H), 2.06 (m, 1H), 1.45 (s, 9H), 1.41 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 176.3, 171.6, 150.1, 145.6, 128.5, 124.5, 83.5, 52.7, 39.6, 35.5, 28.8, 20.9. HRMS (C$_{16}$H$_{20}$N$_2$O$_7$S, ESI): calculated 407.0888 [M+Na]$^{+1}$, found 407.0880.
5.25 Synthesis of Compound 59

5.25.1 Compound 58

Figure 89. Compound 58

To a solution of sodium hydride (60% in mineral oil, 20mg, 0.46 mmol) in THF (4 mL) was added di-t-butyl 2-methylmalonate intermediate (100 mg, 0.46 mmol) dropwise and the solution was stirred for 10 minutes at rt. To the reaction mixture, N-tosylaziridine (1M in THF, 85 mg, 0.46 mmol) was added dropwise at 0°C. The solution was allowed to warm to rt and react for 23 h. The reaction was quenched with saturated NH₄Cl (10 mL) at 0°C, phases were separated, and aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel (15→60% EtOAc in hexanes) to afford the compound 58 as white solid (130 mg, 68% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.71 (t, J = 6.3 Hz, 1H), 3.21 (t, J = 7.1 Hz, 1H), 2.99 (q, J = 10.0 Hz, 2H), 2.41 (s, 3H), 1.97 (q, J =
5.25.2 Compound 59

To a solution of acid (R)-14 (5.2 mg, 0.007 mmol) in CH$_2$Cl$_2$ (2 mL) was added compound 54a (56.4 mg, 0.14 mmol) and the solution was stirred for 48 h at rt. The reaction was extracted with EtOAc (2 x 5 mL) and H$_2$O (1 x 5 mL). The organic phase was dried over MgSO$_4$ and concentrated to afford compound 59 as white crystalline solid (39.9 mg, 86% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.90 (m, 2H), 7.32 (m, 2H), 3.88 (m, 2H), 2.43 (m, 5H), 2.06 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.7, 169.1, 145.9, 134.3, 129.9, 128.3, 48.7, 32.2, 27.8, 21.8.
5.26 Synthesis of Compound 60

To a solution of compound 54a (61.7 mg, 0.14 mmol) in CH$_2$Cl$_2$ (2 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred for 24 h at rt. The reaction was extracted with EtOAc (2 x 5 mL) and H$_2$O (1 x 5 mL). The organic phase was dried over MgSO$_4$ and concentrated to afford compound 60 as white crystalline solid (38.6 mg, 90% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 8.0$ Hz, 2H), 7.74 (d, $J = 8.0$ Hz, 2H), 3.87 (m, 2H), 2.52 (m, 1H), 2.42 (s, 3H), 2.05 (m, 1H), 1.36 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 176.3, 171.9, 145.9, 135.1, 129.8, 126.9, 62.2, 44.7, 30.7, 21.8, 19.4 HRMS (C$_{13}$H$_{15}$NO$_5$S, ESI): calculated 320.0569 [M+Na]$^+$, found 320.0531.
REFERENCES


28. (a) Thomson, J. E.; Kyle, A. F.; Ling, K. B.; Smith, S. R. Applications of NHC-mediated O- to C-carboxyl transfer: synthesis of (±)-N-benzyl-


34. Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. Salinosporamide A: A Highly Cytotoxic Proteasome


APPENDIX A

NMR SPECTRA

The $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were plotted on JEOL 400 and 500 MHz spectrometer using CDCl$_3$ as a solvent at rt. The NMR chemical shifts ($\delta$) are reported in ppm.
APPENDIX B

CHROMATOGRAMS

GC chromatograms were obtained using an Agilent 7890A. The chiral column used was a Supelco Betadex 110 Fused Silica Capillary Column (30m x 0.25mm x 0.25 μm). HPLC chromatograms were obtained using an Agilent 1260 Infinity. The chiral column used was a CHIRALCEL OJ-H (4.6 mm x 250 mm x 5 μm). Analysis details can be found with each chromatogram.
Table 1. Substrate 22a

![Chemical Structure](image1)

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Racemic

![Chromatogram](image2)

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Totals: 34.07781 1.67365

Enantiomeric
Table 1. Substrate 22b

![Chemical Structure]

**GC Conditions:** Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 80 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

**Racemic**

![Racemic Chromatogram]

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**Totals:** 21.90498 3.50933

**Enantiomeric**

![Enantiomeric Chromatogram]

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**Totals:** 358.84277 121.70097
Table 1. Substrate 22c

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/ min; Temperature Ramp: 90 °C for 60 min, ramp 5 °C/min → 170 °C, 170 °C for 60 min

Racemic

Enantiomeric
Table 1. Substrate 22d

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 6% IPA/hexane; Monitoring wave: 254 nm

Racemic

Enantiomeric
Table 1. Substrate 22e

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 50 °C for 30 min, ramp 2 °C/min→170 °C, 170 °C for 10 min

Racemic

Enantiomeric
Table 1. Compound 22f

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 120 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

Racemic

Enantiomeric
Table 1. Compound 22g

![Chemical Structure Image]

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/ min; Temperature Ramp: 120 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

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Totals: 9.18084e-1 1.54816e-1

Racemic

![GC Trace Image]

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Totals: 285.49648 38.04903

Enantiomeric
Figure 15. Compound 24

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 90 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

Racemic

Enantiomeric
Figure 15. Compound 25

\[
\begin{align*}
\text{GC Conditions: Column: } & \text{ 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: } 3 \text{ mL/min; Temperature Ramp: } 120 \degree C \text{ for 60 min, ramp } 5 \degree C/\text{min}\rightarrow 170 \degree C, \text{ 170 } \degree C \text{ for 60 min.}
\end{align*}
\]
Figure 15. Compound 26

![Chemical Structure](image)

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 120 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

Racemic

![GC Chromatogram](image)

Enantiomeric

![GC Chromatogram](image)
Figure 15. Compound 27

GC Conditions: Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 90 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

Racemic

Enantiomeric
Table 2. Compound 43a

![Compound 43a](image)

**GC Conditions:** Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 120 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

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<td>5.02782</td>
<td>8.45136e-1</td>
<td>48.79975</td>
</tr>
<tr>
<td>2</td>
<td>69.521</td>
<td>VR</td>
<td>5.27514</td>
<td>9.02342e-1</td>
<td>51.20025</td>
</tr>
</tbody>
</table>

**Totals:** 10.30296 1.74738

**Racemic**

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time (min)</th>
<th>Sig Type</th>
<th>Area (μV)</th>
<th>Height (μV)</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69.262</td>
<td>BV</td>
<td>56.64048</td>
<td>8.63708 49.39219</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>69.543</td>
<td>VR</td>
<td>50.02444</td>
<td>9.7411e 60.60781</td>
<td></td>
</tr>
</tbody>
</table>

**Totals:** 114.67496 18.37826

**Enantiomeric**
Table 2. Compound 43b

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1 mL/min; Eluent: 5% IPA/hexane; Monitoring wave: 210 nm

Racemic

<table>
<thead>
<tr>
<th>Peak RetTime Sig Type</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[mAU*sec]</td>
<td>[mAU]</td>
<td>%</td>
</tr>
<tr>
<td>1 6.731</td>
<td>2368.97998</td>
<td>183.90520</td>
<td>46.8720</td>
</tr>
<tr>
<td>2 7.336</td>
<td>2687.16870</td>
<td>257.58347</td>
<td>53.1676</td>
</tr>
<tr>
<td>Totals</td>
<td>5054.14866</td>
<td>439.48866</td>
<td></td>
</tr>
</tbody>
</table>

Enantiomeric

<table>
<thead>
<tr>
<th>Peak RetTime Sig Type</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[mAU*sec]</td>
<td>[mAU]</td>
<td>%</td>
</tr>
<tr>
<td>1 6.835</td>
<td>154.56346</td>
<td>4.32209</td>
<td>2.6734</td>
</tr>
<tr>
<td>2 7.705</td>
<td>5628.99219</td>
<td>367.30270</td>
<td>97.3612</td>
</tr>
<tr>
<td>Totals</td>
<td>5761.55566</td>
<td>369.62479</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Compound 43c

![Chemical Structure of 43c]

**GC Conditions:** Column: 190916-13213, 30 m x 0.25 mm x 0.25 μm; Eluent Rate: 3 mL/ min; Temperature Ramp: 140 °C for 60 min, ramp 5 °C/min→170 °C, 170 °C for 60 min

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Sig Type</th>
<th>Area [pA*s]</th>
<th>Height [pA]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 11.193</td>
<td>MM</td>
<td>2.59200</td>
<td>3.32335e-1</td>
<td>47.72555</td>
</tr>
<tr>
<td>2 13.314</td>
<td>MM</td>
<td>2.83906</td>
<td>3.26438e-1</td>
<td>52.27445</td>
</tr>
</tbody>
</table>

Totals: 5.43106 6.58773e-1

**Racemic**

![Chromatogram of Racemic]

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Sig Type</th>
<th>Area [pA*s]</th>
<th>Height [pA]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 11.174</td>
<td>BB</td>
<td>1.66701e-1</td>
<td>3.48522e-2</td>
<td>9.62398</td>
</tr>
<tr>
<td>2 13.316</td>
<td>BB</td>
<td>1.56544</td>
<td>1.45886e-1</td>
<td>90.37602</td>
</tr>
</tbody>
</table>

Totals: 1.73215 1.86738e-1

**Enantiomeric**
Table 3. Compound 57d

![Chemical Structure](image)

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 5% IPA/hexane; Monitoring wave: 254 nm

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Sig Type</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.254</td>
<td>2</td>
<td>1359.16138</td>
<td>76.39809</td>
<td>49.2033</td>
</tr>
<tr>
<td>14.211</td>
<td>2</td>
<td>1405.17725</td>
<td>66.62695</td>
<td>50.8691</td>
</tr>
</tbody>
</table>

Totals: 2762.33862 141.02503

Racemic

![Graph](image)

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Sig Type</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.013</td>
<td>1</td>
<td>34.26452</td>
<td>1.51687</td>
<td>4.5875</td>
</tr>
<tr>
<td>13.879</td>
<td>1</td>
<td>714.64087</td>
<td>32.84026</td>
<td>95.6802</td>
</tr>
</tbody>
</table>

Totals: 746.90539 32.35713

Enantiomeric
Table 4. Compound 54a

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 3% IPA/hexane; Monitoring wave: 254 nm

Racemic

Enantiomeric
Table 4. Compound 54b

![Structural formula](image)

**HPLC Conditions:** Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 1% IPA/hexane; Monitoring wave: 210 nm

<table>
<thead>
<tr>
<th>Peak RetTime Sig Type</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[mAU*μs]</td>
<td>[mAU]</td>
<td>%</td>
</tr>
<tr>
<td>1 14.474 1 HB</td>
<td>210.64626</td>
<td>8.22701</td>
<td>50.5155</td>
</tr>
<tr>
<td>2 19.266 1 MMA</td>
<td>209.44696</td>
<td>6.77400</td>
<td>49.9544</td>
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</tbody>
</table>

**Totals:** 416.99321 11.99101

Racemic

![Graph](image)

<table>
<thead>
<tr>
<th>Peak RetTime Sig Type</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[mAU*μs]</td>
<td>[mAU]</td>
<td>%</td>
</tr>
<tr>
<td>1 14.644 1 BB</td>
<td>199.56953</td>
<td>7.72843</td>
<td>97.9206</td>
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<tr>
<td>2 19.693 1 MM</td>
<td>6.23793 3.82077e-1</td>
<td>3.0607</td>
<td></td>
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</tbody>
</table>

**Totals:** 203.80747 6.11050

Enantiomeric
Table 4. Compound 54c

\[
\begin{align*}
\text{TsN} & \quad \text{O} \\
\text{O} & \quad \text{CH}_2 \\
\end{align*}
\]

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 9% IPA/hexane; Monitoring wave: 210 nm

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time [min]</th>
<th>Sig Type</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.583</td>
<td>VB</td>
<td>8697.66797</td>
<td>697.58417</td>
<td>49.7438</td>
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<tr>
<td>2</td>
<td>12.171</td>
<td>VB</td>
<td>8779.15820</td>
<td>401.58334</td>
<td>50.2677</td>
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</tbody>
</table>

Totals: 1.74648e4 1097.16751

Racemic

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time [min]</th>
<th>Sig Type</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.858</td>
<td>BB</td>
<td>3.88913e4</td>
<td>1408.96399</td>
<td>97.0482</td>
</tr>
<tr>
<td>2</td>
<td>12.462</td>
<td>BB</td>
<td>1184.92590</td>
<td>66.98778</td>
<td>2.9568</td>
</tr>
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</table>

Totals: 4.00742e4 1473.95177

Enantiomeric
Table 4. Compound 54d

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 9% IPA/hexane; Monitoring wave: 210 nm

Racemic

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Sig Type</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.017</td>
<td>HR</td>
<td>1.42707e4</td>
<td>328</td>
<td>11.90192</td>
</tr>
<tr>
<td>2</td>
<td>12.217</td>
<td>VB</td>
<td>1.35038e4</td>
<td>702</td>
<td>48.6228</td>
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Totals : 2.77725e4 1029.04413

Enantiomeric

<table>
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<th>Sig Type</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.083</td>
<td>BB</td>
<td>479.70433</td>
<td>30.02638</td>
<td>3.803</td>
</tr>
<tr>
<td>2</td>
<td>12.422</td>
<td>BB</td>
<td>1.19540e4</td>
<td>595.45496</td>
<td>96.1568</td>
</tr>
</tbody>
</table>

Totals : 1.24318e4 523.48026
Table 4. Compound 54e

HPLC Conditions: Column: HPLC OD-H 4.6 mm x 250 mm x 5 μm; Eluent Rate: 1mL/min; Eluent: 9% IPA/hexane; Monitoring wave: 210 nm

Racemic

Enantiomeric