12-15-2007

Synthesis of Novel Chiral Heterocyclic Compounds for Antibacterial Agents and Peptidomimetics

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Synthesis of Novel Chiral Heterocyclic Compounds for Antibacterial Agents and Peptidomimetics

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
In
The Department of Chemistry

By

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M.S. Université Louis Pasteur (France) 2002
Pharm. D. Université Louis Pasteur (France) 2002

December 2007

Dedicated to:

My mother, Bernadette

My Father, Paul

My other mother and father, Georges and Rita

Ackowledgements:

I would like to give a very special thank to my advisor, Dr. Guijun Wang for her guidance and support throughout the 5 years I spent working with her at the University of New Orleans. I also wish to thank my Ph.D. committee members, Dr. Mark L. Trudell, Dr. Branko Jursic, Dr. Richard B. Cole and Dr. Steven P. Nolan. Thank you to my current and former group members, Dr. Xiaoping Nie, Dr. Vibha Sharma, Sherwin Cheuk, Kris Williams, Michael St. Martin and Navneet Goyal. I am grateful to the American Heart Association and the University of New Orleans for the financial support. Thank you to the *Laboratory for Advanced Applications in GlycoChemistry* for the biological testing and thank you to Professor R. I. Hollingsworth from Michigan State University for providing the lactone starting material. Thank you to the Louisiana State University Department of Chemistry for lending us lab space for a year during the Katrina evacuation. Finally, I wish to offer my deepest gratitude to Dr. Clementine Féau, for her love and constant support.

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Abstract

Small chiral molecules are very important building blocks in the synthesis of biologically active compounds. These building blocks include nitrogen and oxygen-containing heterocycles such as 2-oxazolidinones, 1,3-oxazinan-2-ones, 2-oxazolines, oxazines, morpholine and morpholinones. Because of their interesting properties, chiral heterocycles have stirred great interest in the synthetic chemist community to develop useful and efficient strategies to these molecules. In this dissertation, the design and syntheses of various heterocyclic building blocks are presented, as well as the testing of their biological activities as antibacterial. Another very interesting family of heterocycle-containing molecules are the Aeruginosins. They are a family of marine natural products isolated from a blue-green algae, which display inhibitory activity against serine proteases such as thrombin, trypsin, and factor VIIa. Most aeruginosins contain an heterocyclic moiety called the 2-carboxy-6-hydroxyoctahydroindole (Choi) ring; this Choi moiety is a rigid bicyclic unnatural amino acid and is the core structure in the aeruginosins, indispensable to their biological activity. A synthesis of a ring-oxygenated variant of the Choi from D-mannose is reported in this dissertation. The ring-oxygenated variant of 2-carboxy-6-hydroxyoctahydroindole can potentially be used as a surrogate of Choi in the design and synthesis of aeruginosin-based thrombin inhibitors.

Keywords: Chiral heterocycles; 2-oxazolidinones; 1,3-oxazinan-2-ones; aeruginosins; 2-carboxy-6-hydroxyoctahydroindole; serine protease inhibitors.

Chapter I. Introduction

I. Chiral nitrogen and oxygen-containing molecules as building blocks for the synthesis of biologically active molecules.

Small chiral molecules are very important building blocks in the synthesis of biologically active compounds. These building blocks include nitrogen and oxygen-containing heterocycles such as oxazolidinones, oxazinanones, oxazolines, oxazines, morpholine and morpholinones. For example, the (*S*)-5-aminomethyl-2-oxazolidinone **1** is the core structure in antibacterial agent linezolid **3**[1-2] which is the first member of the synthetic oxazolidinone antibiotics[3–7] effective against resistant Gram-positive bacterial infection. The six-membered ring 1,3-oxazinan-2-one **2** derivatives also exhibit biological activities, such as anti-inflammatory,[8] anti-thrombotic,[9] and antibacterial activities.[10] The oxazolines heterocycles also display a wide variety of biological properties. For instance molecule **4** has antibiotic activity;[11] other 2-oxazolines have shown neuroprotective[12] and cytotoxic activities[13]. The homologous oxazines have equally useful properties, they are important synthetic intermediates,[14] but also 1,4-oxazine **5** is a human 5-HT_6 receptor inhibitor[15] and can be developed as an anti-depressant. Other oxazines have shown good potential as drugs against hereditary obesity by inhibiting cholesteryl ester transfer proteins;[16] additionally, anti-cardiovascular disease activity by inhibition of the thromboxane A2 (TXA2) receptor[17] has been reported, as well as potential as antibacterial agents[18-19]. Morpholine and morpholinone-containing molecules have also shown very interesting biological activities. The antibiotic Linezolid **3** contains a morpholine cycle that is important for its biological properties. Other molecules such as **6** have displayed an anti-schizophrenic activity[20] via interaction with the

N-methyl-D-aspartate (NMDA) receptor in the brain. Reboxetine **7** is a commercially available anti-depressant that contains a morpholine cycle essential to its activity[21]. Morpholinone cycles are found in many biologically active molecules and the reported properties include thrombin inhibitors[22], selective T-type calcium channel blockers[23], HIV-protease inhibitors[24] and important intermediate in vitamin B_5 synthesis[25] as well as antibacterial compounds' synthesis.[26] Besides being used as synthetic intermediates and displaying interesting biological properties, many small heterocyclic molecules, notably 2-oxazolidinones, 1,3-oxazinan-2-ones and 2-oxazolines are very useful as chiral auxiliaries in asymmetric synthesis[27-29] or as a form of protecting groups[30] for amino alcohols.

Because of their importance as synthetic intermediates and their good potential as medicinally active molecules, many efforts have been made and are ongoing to synthesize these small chiral heterocycles efficiently. Many methods have been described for the synthesis of chiral cyclic carbamates, such as the Hoffmann rearrangement reaction on a chiral hydroxyl-amide,[31] or the carbonylation of 1,3-amino alcohols.[32] Most of these methods occur with a retention of stereochemistry.[33-46] Only a few other synthetic routes to cyclic carbamates afford a product with opposite stereochemistry from that of the starting material.[36, 47-51] An example of the synthesis of an *N*-substituted chiral 1,3-oxazinan-2-one from a 1,3-amino alcohol in scheme 1.1; the synthesis occurs with retention of stereochemistry.[32, 52]

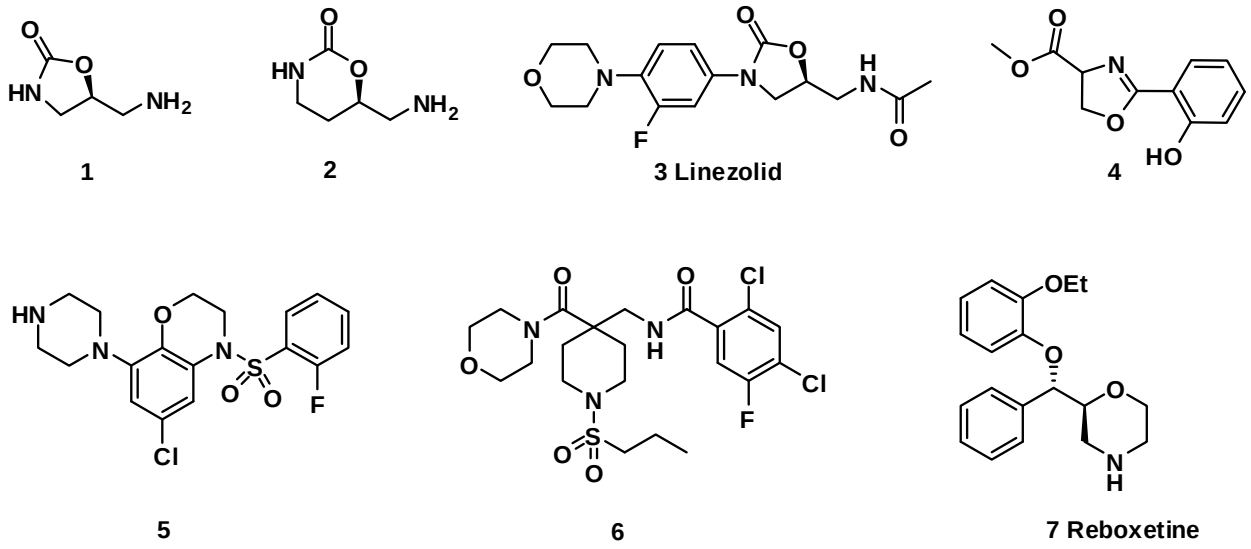
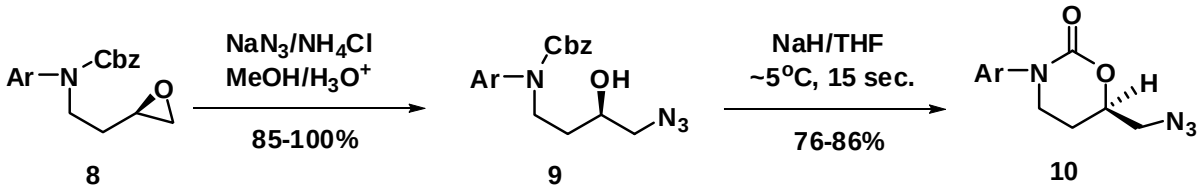


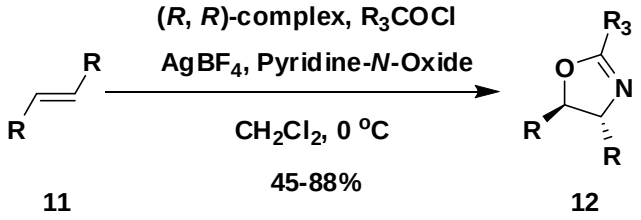
Figure 1.1 Representative nitrogen and oxygen-containing heterocycles.



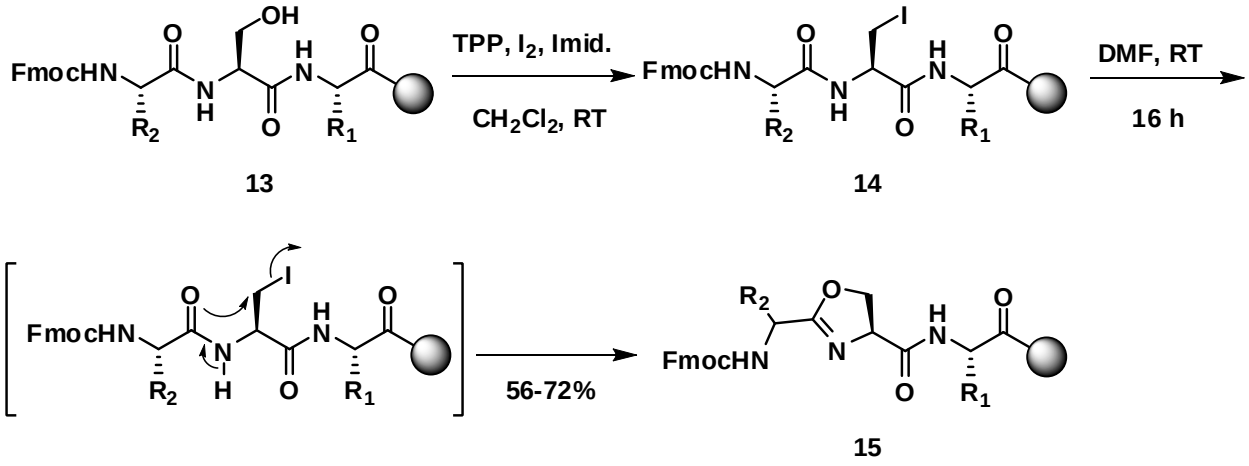
Scheme 1.1. Synthesis of *N*-aryl-1,3-oxazinan-2-one from Aspartic acid.

In scheme 1.1 an epoxide-containing Cbz-protected arylamine **8** was obtained as an intermediate from aspartic acid; the epoxide ring was then opened by sodium azide to yield **9** and cyclization of the hydroxyl group with the Cbz group gave the desired 1,3-oxazinan-2-one **10**. Several methods have been reported for the synthesis of chiral oxazoline and oxazine cycles. Some of the representative methods are the asymmetric cyclization of olefins using a chiral nitridomanganese complex[53] (Scheme 1.2), the solid phase cyclization of a β-halogeno-amide in basic conditions[54]

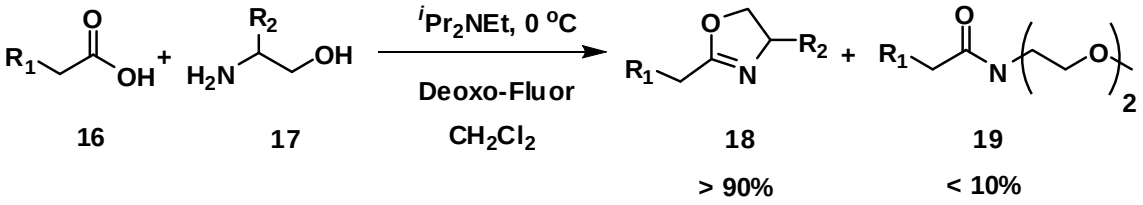
(Scheme 1.3) or the cyclization of a β-halogeno-amide by electrochemical reduction.[55] The cyclization of a β-hydroxy-amide in which the hydroxyl group has been transformed into a good leaving group has also been reported.[47] Another recent strategy uses a one-pot synthesis by mixing a carboxylic acid and a 1,3-amino alcohol in presence of the fluorinating agent bis-(2-methoxyethyl) amino-sulfurtrifluoride (Deoxo-fluor) (Scheme 1.4).[56-57] This one-pot reaction is similar to the technique using the combination of a carboxylic ester with a 1,3-amino alcohol in the presence of lanthanide chloride as a catalyst.[58] More specific to the synthesis of 1,2-oxazines, a tandem "oxime formation-epoxide ring opening" reaction has also been described[18] and is shown in scheme 1.5.



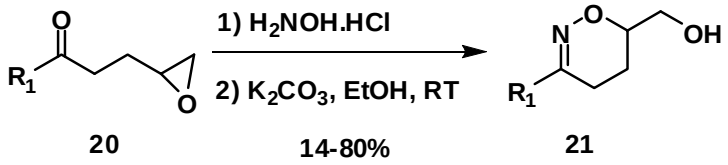
Scheme 1.2. Synthesis of 2-oxazoline by cyclization under nitridomanganese complex catalysis.



Scheme 1.3. Solid phase synthesis of 2-oxazolines using a NH-Rink-PEGA$_{800}$ resin.

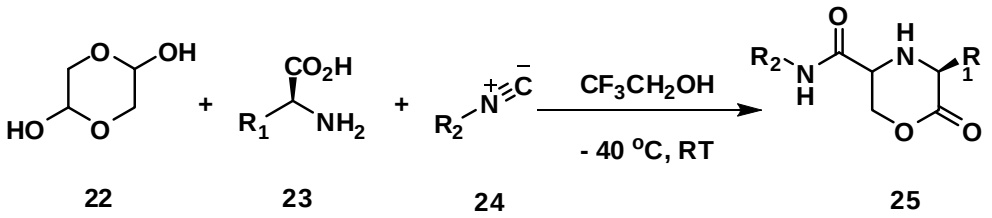


Scheme 1.4. Synthesis of 2-oxazoline in a one-pot reaction using Deoxo-Fluor reagent.



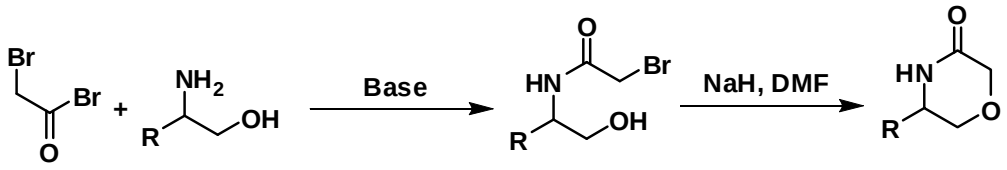
Scheme 1.5. Synthesis of 1,2-oxazine via tandem "oxime formation-epoxide ring opening".

Similarly to the cyclic carbamates, oxazoline and oxazine heterocycles, several synthetic strategies to the morpholinone and morpholine cycles have been reported in the literature. One method uses the Ugi five-center-three component reaction,[59,60] reacting the glycolaldehyde dimer **22** with an aminoacid **23** and an isocyanide **24** to afford a 3-substituted morpholin-2-one-5-carboxamide[23] **25** (Scheme 1.6). A more common method is the intramolecular cyclization of a β-hydroxy-amide by elimination of a leaving group such as a mesylate of a halogen[22, 24] (Scheme 1.7). Other reactions involve the cyclization of an amino alcohol with an oxalyl chloride derivative to afford a morpholin-1,3-dione followed successively by a Wittig reaction and a reduction on the 1-carbonyl to give a 1-substituted morpholin-2-one[25,61] (Scheme 1.8). Morpholine cycles, which are found in many medicinally active molecules, are generally derived from morpholinones by controlled reduction of the ring's carbonyl group[21] (Scheme 1.9). A less common method is the cyclization of diol **38** by dehydration in refluxing acidic conditions to yield morpholine **39** (Scheme 1.10).[62]



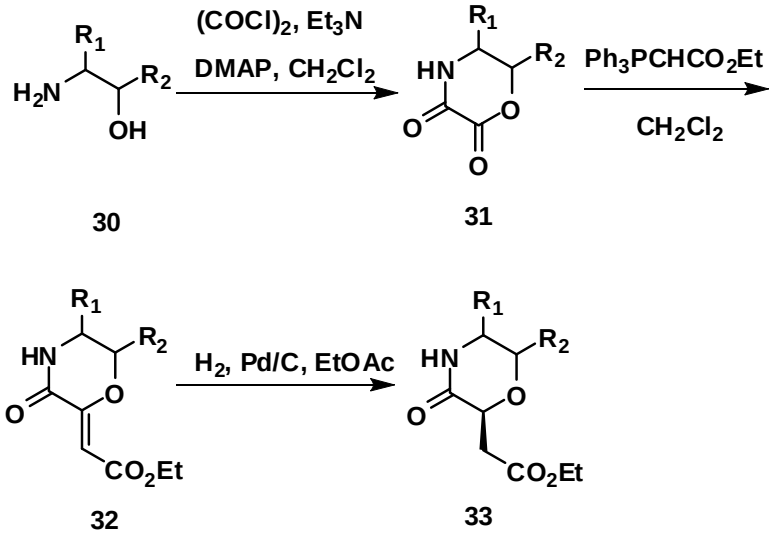
22 23 24 25

Scheme 1.6. Synthesis of 3-morpholin-2-one-5-carboxamide via Ugi's reaction.



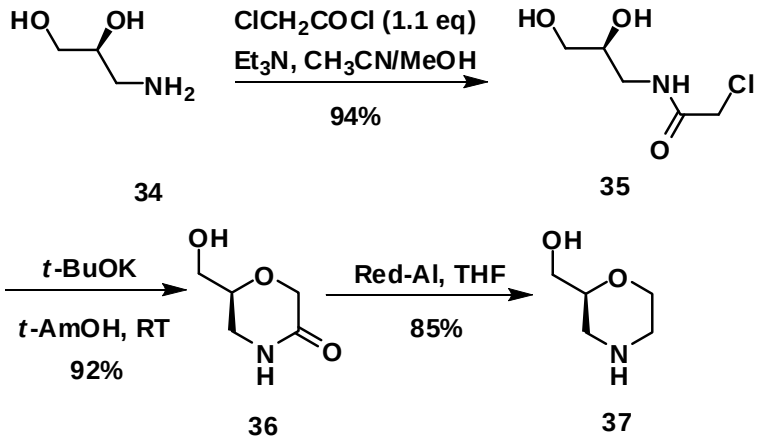
26 27 28 29

Scheme 1.7. Synthesis of morpholin-2-one intramolecular cyclization.

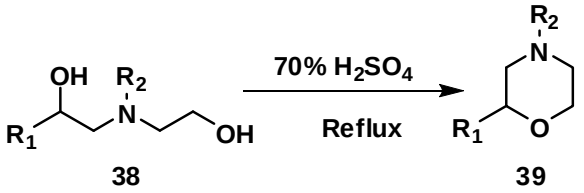


30 31 32 33

Scheme 1.8. Synthesis of morpholin-2-one via oxalyl chloride condensation.



Scheme 1.9. Synthesis of a morpholine cycle by reduction of a morpholin-2-one.



Scheme 1.10. Synthesis of a morpholine cycle by acidic dehydration.

Because of their ubiquitous presence in biologically active molecules many of which are commercially available drugs, and because of their importance as building blocks in organic synthesis, nitrogen and oxygen-containing heterocycles have drawn great interest from the organic synthetic chemists' community. As well as others, we have developed several synthetic strategies to these molecules in our laboratory. The subject of our syntheses of small chiral heterocycles as building blocks for the synthesis of bioactive molecules will be the focus of the second chapter of this dissertation.

II. Synthesis of rigid bicyclic aminoacids as building blocks for peptidomimetics.

Despite being naturally biologically active, peptides show many disadvantages when used as drugs.[63-65] The most noticeable drawbacks are a very limited stability towards proteolysis by peptidases, in the gastrointestinal tract as well as in the serum. The high molecular weight decreases the bioavailability and subsequently the excretion through the liver is rapid and the clearance is very high. Finally, the molecules flexibility reduces the selectivity to one biological target and would potentially result in a lot of unwanted side effects. The potent activity of peptides coupled to their inconveniences as drugs have led to the development of the field of peptidomimetics. Peptidomimetics are molecules that bear identifiable structural resemblance to a natural peptide, leading to them mimicking or inhibiting the effect of that natural peptide.[66-67] The advantages of the peptidomimetics as drugs are based mostly on the circumvolution of peptides shortcomings; firstly and most importantly, the constrained structure will minimize the ability to bind to multiple biological receptors and increase the interaction with the desired biological target, therefore increasing the desired therapeutic effect, while reducing the potential unwanted side effects. Finally, the structural modifications of peptidomimetics compared to its corresponding peptide decrease the susceptibility to be degraded by peptidases *in vivo*, enabling the drug to stay in the serum longer and therefore increasing the chances of interaction with the biological target. As a result of their properties cited above, peptidomimetics are of high interest as bioactive agents and as drugs. Some of the main biological properties observed in peptidomimetics include Angiotensine Converting Enzyme (ACE) inhibitors,[68] protease inhibitors,[69-81] somatostatin inhibitors,[82] antimicrobial agents,[83-96] anti-cancerous,[97-106] analgesics,[107-112] thrombin and trypsin inhibitors,[113-132] psychotropic;[133-134] some peptidomimetics

have been used as chemical probes,[135] catalysts for asymmetric synthesis,[136-139] and even as organogelators.[140] Within the peptidomimetics compounds, a prominent class of molecules is the rigid bicyclic amino acids.

Among the most notable molecules containing a bicyclic amino acid moiety are the aeruginosins, a family of natural compounds isolated from a blue-green algae *Microcystis aeruginosa.*[114-115] Aeruginosins are generally linear oligopeptides, that contain a core structure, the constrained bicyclic amino acid 2-carboxy-6-hydroxyloctahydroindole (Choi) moiety **57**. Some of the representative aeruginosins and related molecules are shown in Figure 1.2. These molecules typically display serine protease inhibition activities, some of them are inhibitors of the blood coagulation cascade factors, such as thrombin and factor VIIa. These properties give these compounds a strong potential to be developed into antithrombotic drugs and have stirred the interest of the organic chemists community into designing efficient strategies towards the synthesis of the Choi moiety and its variants, this moiety being a key structure of aeruginosins and their analogs. Aeruginosins belong to the class of *direct thrombin inhibitors*, as indicated by the X-ray crystal structures of the complex formed between aeruginosins and thrombin during the inhibition process.[119,121,143] The interaction mode of aeruginosin 298-A with the protein is similar to that of other direct thrombin inhibitors as it binds to the active site of thrombin in a noncovalent way forming an antiparallel strand with thrombin.[119] The five-membered ring of the Choi residue occupies the hydrophobic binding site, while its six-membered ring projects out and loosely interacts with thrombin. The crystal structures of oscillarin and dysinosin-A complexes with thrombin revealed similar binding patterns. The amide *NH* from the octahydroindole carboxamide interacts with thrombin, however no interactions were observed with the 6-

hydroxyl group of the Choi moiety. The terminal phenyl group has no interaction with the enzyme.[143] On the basis of the crystal structures and the binding sites interactions, organic chemists can design novel inhibitors with similar core structure motifs but with different substituents and functionalization to enhance binding, activity, and pharmacokinetic properties. Thrombin generally can tolerate imprecise binding from different molecules, however the rigid bicyclic amino acid structure is very important in defining the conformation of the molecule and it is essential to their antithrombin activity. Modifications on the core structure in the area of the 6-hydroxyl group should not impact negatively on binding to the protein while some changes will increase contact and enhance binding. Such changes include introducing an oxygen atom at the C-4 position and/or adding an additional hydroxyl group to the C-5 or C-7 position.[149] Because pharmacokinetics are very unpredictable, these changes will result in new biological properties and might broaden the scope for improving the pharmacokinetic profile of this compound class if required. The availability of different stereoisomers is also important in elucidating structure-activity relationships. Studies to rationalize electronic and steric influence of different inhibitors have not given good correlations so far. Modification from the natural analogues can allow us to understand the stereo-electronic factors that determine the activity of these inhibitors, as well as provide us with molecules with a good potential as new and better antithrombotics.

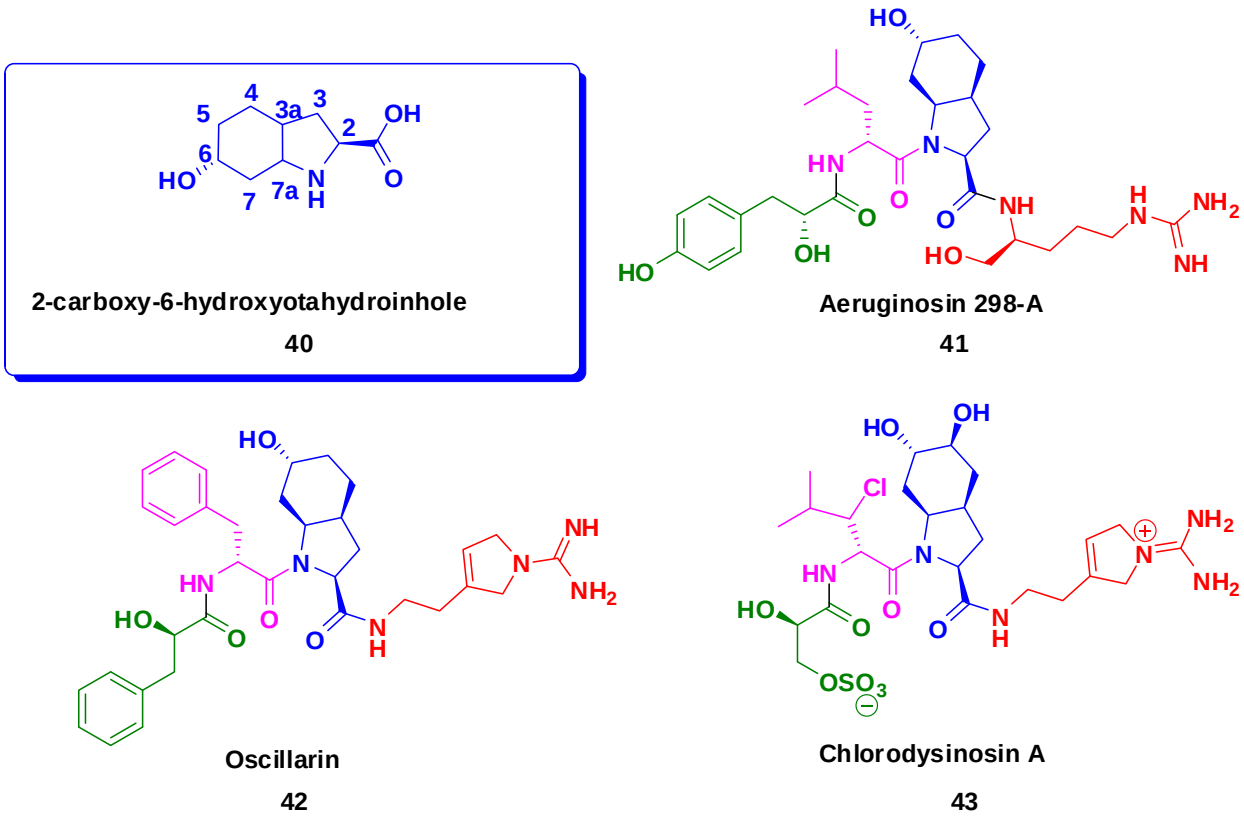
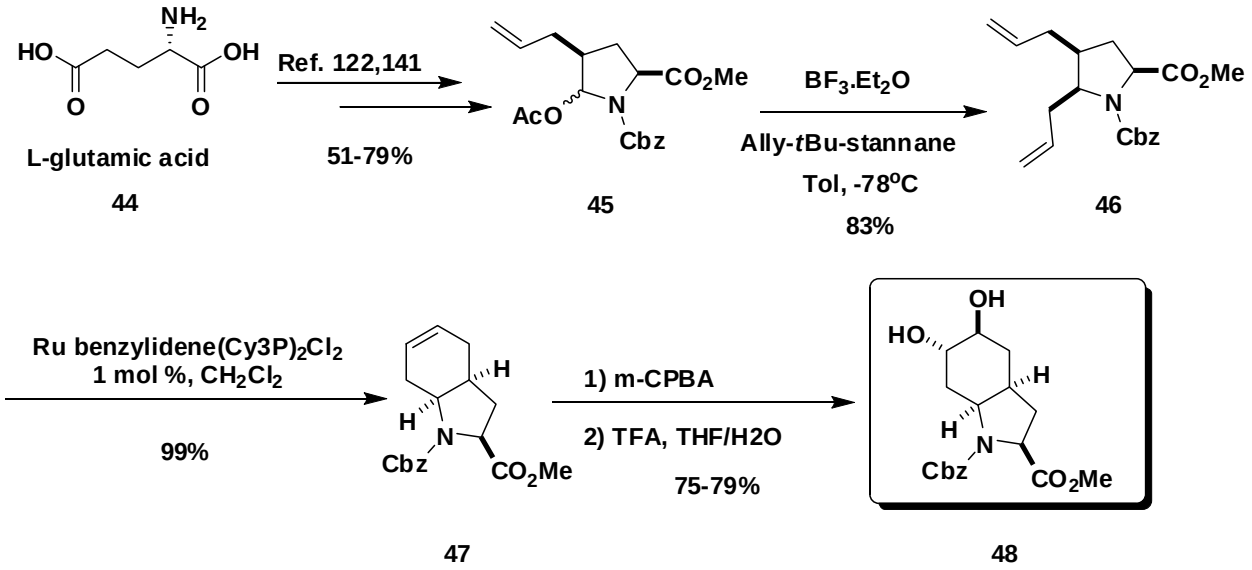


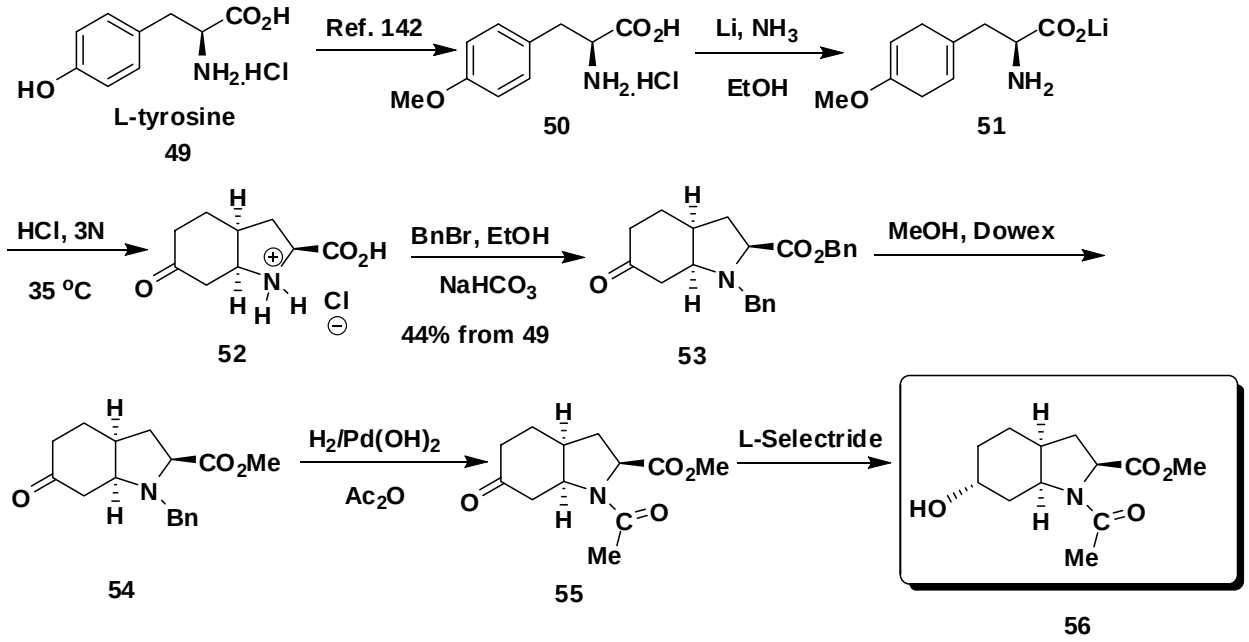
Figure 1.2. Structures of aeruginosins and related compounds.

A few syntheses to the octahydroindole structure have been reported in the literature and some of the most representative methods are described here. One strategy uses a chiral synthon derived from L-glutamic acid, which can yield the desired bicycle after a ring-closing metathesis, followed by a stereoselective epoxidation and eventually an epoxide ring-opening[122, 141] to give the *N*-protected 2-carboxy-5,6-hydroxyloctahydroindole ester **48** (Scheme 1.11), which corresponds to the Choi subunit found in Chlorodysinosin A **43**.



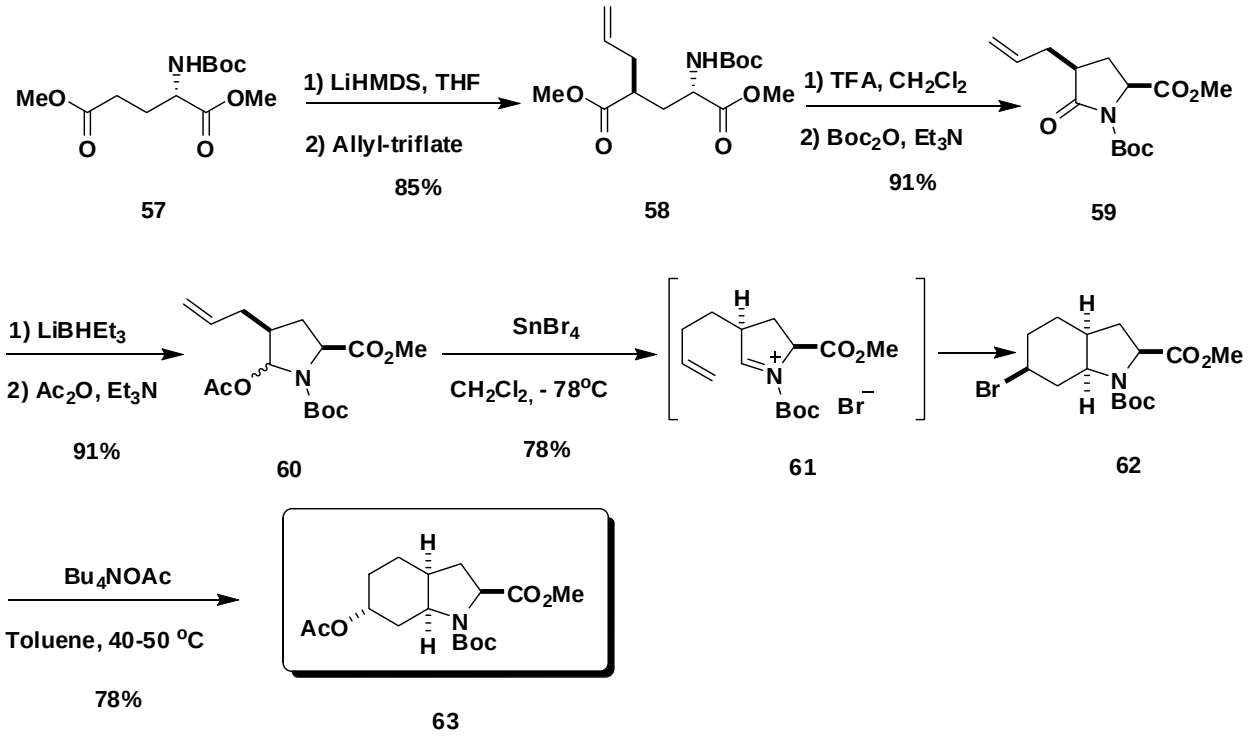
Scheme 1.11. Synthesis of a protected 2-carboxy-5,6-dihydroxyl-octahydroindole ester from L-glutamic acid.

Another approach to the synthesis of the octahydroindole cycle starts with L-tyrosine which is methylated to afford *O*-methyl-L-tyrosine **50**.[142] Birch reduction of **50**, followed by a treatment in 3N HCl of the resulting dihydroanisole **51** leads to a mixture of diastereomeric amino acids with a *cis*-fusion of the bicyclic nucleus (only diastereomer **52** is showed here in scheme 1.12). Compound **52** was then reacted with benzyl bromide in basic conditions to give benzyl ester **53**. Transesterification of **53** leads to methyl ester **54**; benzyl deprotection and amidation give **55** which after reduction of its ketone group yields the Choi moiety **56**.[116a,116b]



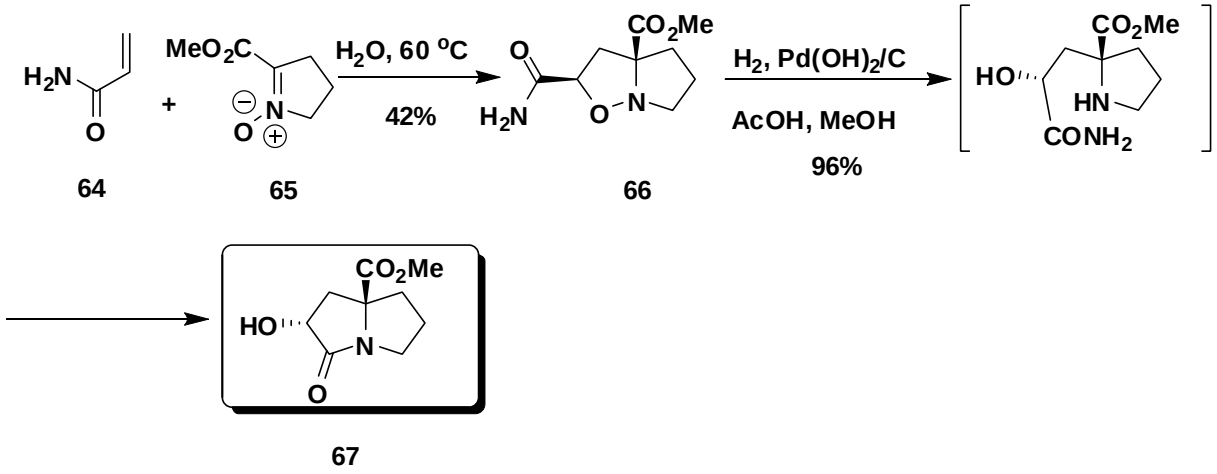
Scheme 1.12. Synthesis of a protected 2-carboxy-6-hydroxyloctahydroindole ester from L-tyrosine.

Another method that has been used to synthesize aza-heterocycles and more importantly octahydroindole bicycles is the *N*-acyliminium ion cyclization.[128,143-146] The synthesis of 2-carboxy-6-octahydroindole via the *N* -acyliminium ion aza-Prins cyclization is detailed in scheme 1.13. The sequence starts with *N*-Boc-L-glutamate **57** which undergoes enolate alkylation[141] to afford **58**. *N*-deprotection, cyclization and *N*-Boc protection lead to the corresponding pyroglutamate **59**. Partial reduction and protection of the lactam carbonyle group give the hemiaminal **60**. The [4,3,0] bicyclic structure **62** is obtained via the *N*-acyliminium intermediate **61** by treatment with tin tetrabromide at low temperature. Displacement of the bromide with tetra-*n*-butyl ammonium acetate affords the L-Choi subunit **63**.



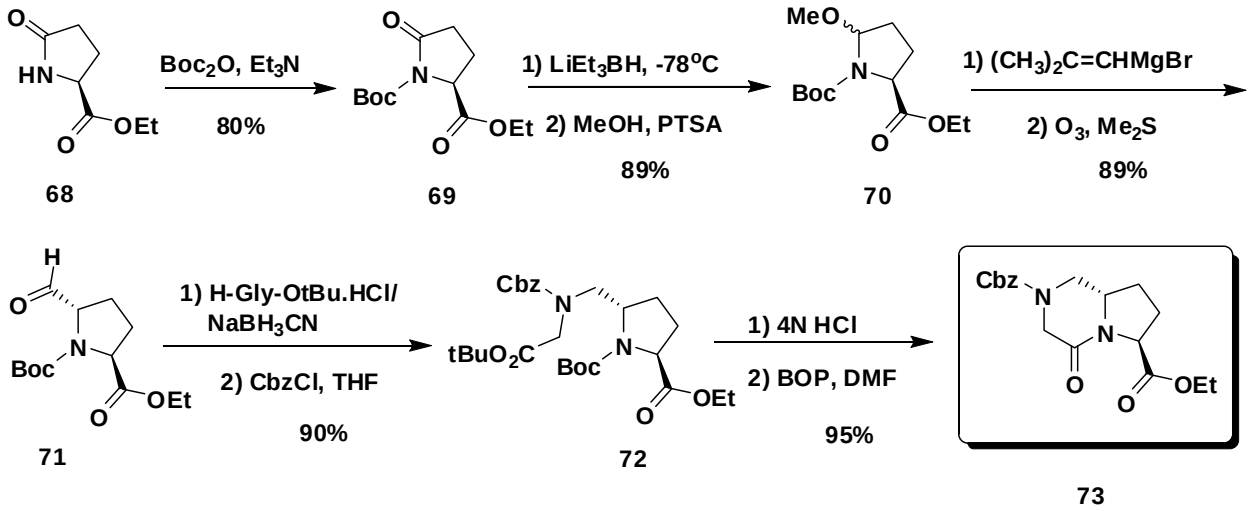
Scheme 1.13. Synthesis of a protected 2-carboxy-6-hydroxyloctahydroindole ester Via *N*-Acyliminium aza-Prins Cyclization.

Besides the Choi bicyclic structures in the aeruginosins, many other constrained bicyclic moieties have been synthesized as peptidomimetics and have displayed interesting biological activities. Some representative molecules are the bicyclic lactams, which are found in many biologically relevant peptidomimetics.[86,89,101] One method uses a 1,3-dipolar cycloaddition between a cyclic nitrone **65** and acrylamide **64** to afford the [1,2-*b*]isoxazolidine **66** (only major diastereomer is shown in scheme 1.14). Compound **70** is then reduced in acidic conditions to give peptidomimetic bicyclic lactam **67**.[89]



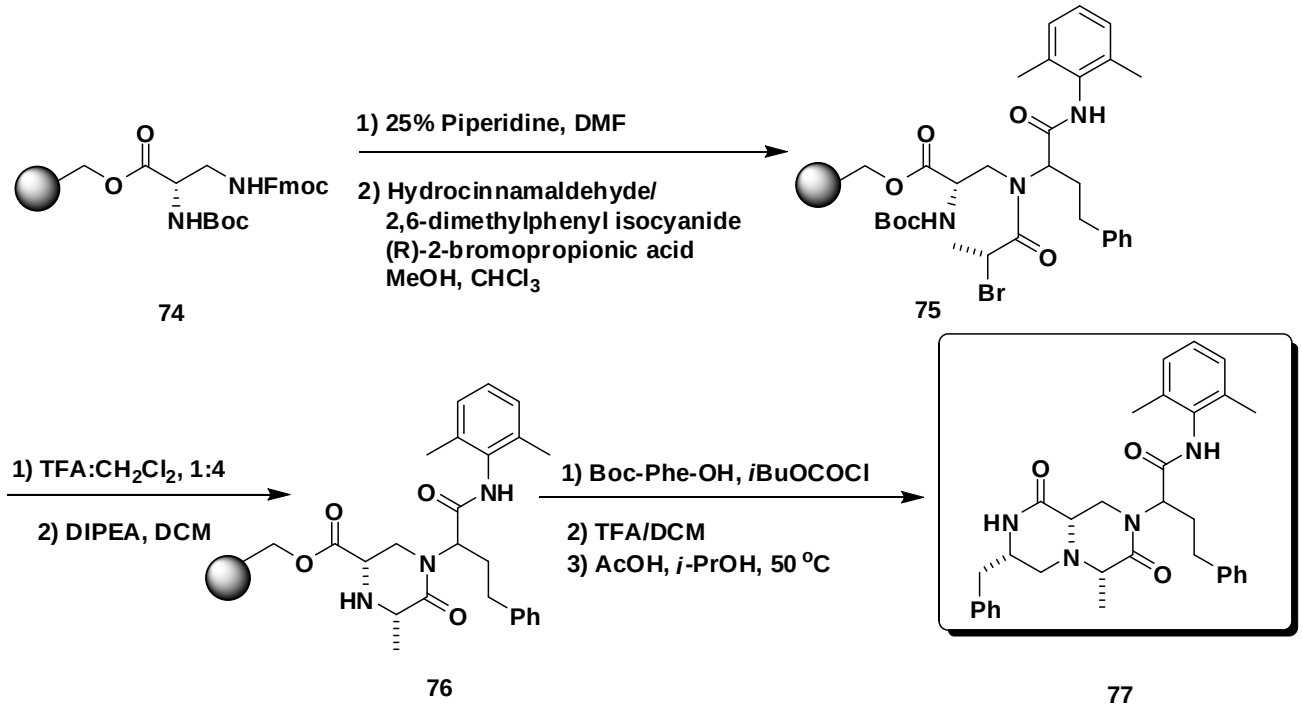
Scheme 1.14. Synthesis of a bicyclic lactam peptidomimetic via 1,3-dipolar addition.

Another method to prepare bicyclic lactams uses a pyroglutamate **68** as starting material. After the *N*-Boc protection gives compound **69**, selective reduction of the lactam and reaction of the resulting hemiaminal intermediate with methanol in acidic conditions gives the aminal **70**. After Grignard reaction and oxidative cleavage, the *trans* aldehyde major isomer **71** is obtained. Reductive amination with tert-butyl glycinate and $NaBH_3CN$, followed by Cbz protection affords intermediate **72**. After simultaneous removal of the Boc group and hydrolysis of the *t*-butyl ester in acidic conditions, cyclization is achieve using a BOP coupling reagent to give the desired bicyclic lactam **73**.[147]



Scheme 1.15. Synthesis of a bicyclic lactam peptidomimetic by BOP coupling.

Besides bicyclic lactams and octahydroindole cycles there are a multitude of bicyclic amino acid structures widely explored as peptidomimetics. Among these molecules are the "β-turn peptide mimetics". A β-turn is an important secondary structure that involves four consecutive residues. It folds the polypeptide chain back onto itself by nearly 180° and makes the protein a compact globular structure. It is also an internal component of antiparallel beta-strand so that it plays an important role in protein folding and molecular recognition.[148] Diketopiperazines are bicyclic structures that are synthesized as potential β-turn-peptidomimetics.[92] One method to these bicycles uses a solid-phase synthesis starting with *α*-*N*-Boc-*β*-*N*-Fmoc-L-diaminopropionic acid **74** attached to a Merrifield resin. Fmoc group of **74** is deprotected using 25% piperidine in DMF, then Ugi three-component reaction yields intermediate **75**. Deprotection of the Boc group followed by displacement of the bromide by the free amine in basic conditions gives compound **76**. The second ring system is created via Boc-amino acid coupling, Boc amino deprotection, and cyclitive cleavage induced by heating in acidic conditions to give diketopiperazine **77**.



Scheme 1.16. Solid-phase synthesis of a β-turn petidomimetic diketopiperazine.

Peptidomimetics are a very good alternative to peptides as drugs. Their constrained conformation enables them to interact with biological targets selectively, a property that peptides, with their inherent flexibility, do not possess. Also, the chemical and physical properties of peptidomimetics as synthetic drugs can be optimized to increase their therapeutic effects. Notable peptidomimetics are the rigid bicyclic amino acids, which are widely explored for their multiple biological properties. Among these bicyclic amino acids are the aeruginosins, a family of marine natural products isolated from a blue-green algae; these molecules have serine protease inhibitory activities and present a strong potential as anti-thrombotic drugs. A moiety that has been found to be the core structure in the compounds of this family is the 2-carboy-6-hydroxyloctahydroindole (Choi) cycle. Because of its importance, the Choi subunit and its variants has been subject to many total syntheses. In our laboratory, we have developed an

efficient method to the Choi bicyclic structure and its analogs; these works will be reported with details in the fifth chapter of this dissertation.

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Chapter II. Design and Synthesis of New Chiral 1,3-Oxazinan-2-ones from Carbohydrate Derivatives.

Abstract

Small chiral molecules are very important building blocks in the synthesis of biologically active compounds. These building blocks include nitrogen and oxygen-containing heterocycles such as oxazolidinones, oxazinanones, oxazolines, oxazines, morpholine and morpholinones. Because of their interesting properties, chiral heterocycles have stirred great interest in the synthetic chemist community to develop useful and efficient strategies to these molecules. Chiral oxazinanones in general are useful intermediates in the synthesis of pharmaceutical compounds and amino alcohols. The works presented in this chapter introduce a new synthetic method to chiral 6-hydroxymethyl-1,3-oxazinan-2-ones and their analogs from carbohydrate derivatives. The synthesis was accomplished by the reaction of optically pure (*S*)-3-hydroxy-γ-butyrolactone with different primary amines, thus opening the lactone cycle to form butyramides with different *N*-substitutions. The amides where reduced to the corresponding amines, which were carbonylated and cyclized to give the desired chiral 6-hydroxymethyl-1,3-oxazinan-2-ones.

Introduction

Small chiral molecules are very important building blocks in the synthesis of compounds presenting a pharmaceutical interest. Chiral 5-substituted-2-oxazolidinones **1** and **2** and the homologous 6-substituted 1,3-oxazinan-2-ones **3** and **4** shown in figure 2.1 are important core structures in many drug molecules and useful intermediates in the synthesis of chiral aminoalcohols. 5-Hydroxymethyl or 5-aminomethyl-2-oxazolidinones (**1**, **2**) are important in the preparation of oxazolidinone antibacterial agents.[1-10] Representative 2-oxazolidinones antibiotics include Linezolid (Zyvox®).[1-2] **5** and dihydrothiazine analog **6**.[5] 2-Oxazolidinones are also important as synthetic intermediates and have been used in the synthesis of chiral aminoalcohols such as beta-blocker carvedilol (Eucardic®).[11-20] Because of their usefulness as both synthetic tools and biologically relevant molecules, there have been great interests in developing efficient synthesis towards 2-oxazolidinones. We and others have developed several efficient synthetic methods towards the synthesis of chiral 5-substituted-2-oxazolidinones.[21-29] Like their 5-membered ring counterpart, the homologous 6-membered cyclic carbamate 1,3-oxazinan-2-ones are found in many biologically active compounds.[30-36] Some 6-phenyl-1,3-oxazinan-2-ones like compound **7** (Figure 2.2), possess phosphodiesterase IV inhibitory effects and have shown to be potential remedies for inflammatory diseases and asthma.[30] These six-membered ring carbamates are found in the cytotoxic alkaloid maytansine **8** and its analogs, which are explored as potential anti-cancerous drugs (Figure 2.2).[37-40] They are also being explored as anti-inflammatory agents, for the treatment of ulcers, allergies, asthma, arthritis and diabetes.[41] 1,3-Oxazinan-2-ones have been extensively used as synthetic tools;[17, 41-47] they are key intermediates in Woodward's total synthesis of erythromycin A,[48] in the synthesis of thrombolytics such as **9**[31] (Figure 2.2) and in the synthesis of liquid crystal devices.[49] The six-membered 1,3-oxazinan-2-one ring systems

have also been used as chiral auxiliaries or other chiral control elements[50-51] although in that role, they are not used as extensively as the corresponding 2-oxazolidinones; The major reason for this is probably the difficulties in synthesizing chiral 1,3-oxazinan-2-ones.

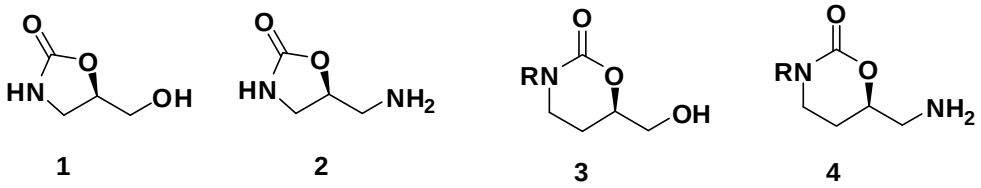


Figure 2.1. 2-oxazolidinones and 1,3-oxazinan-2-ones building blocks

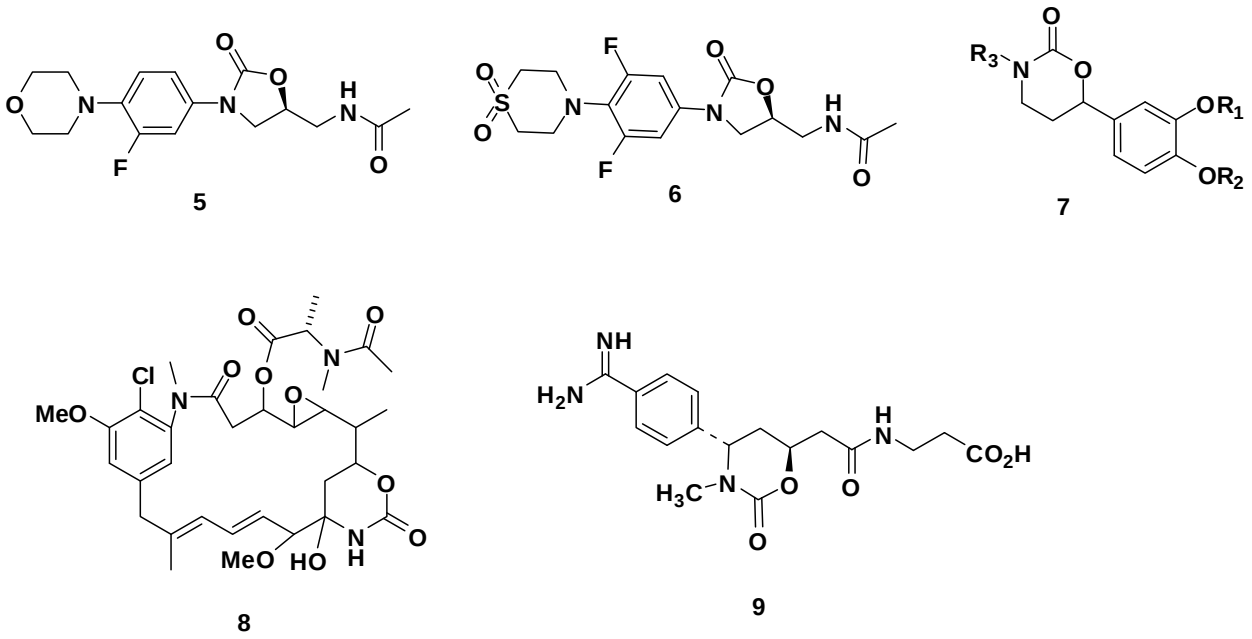
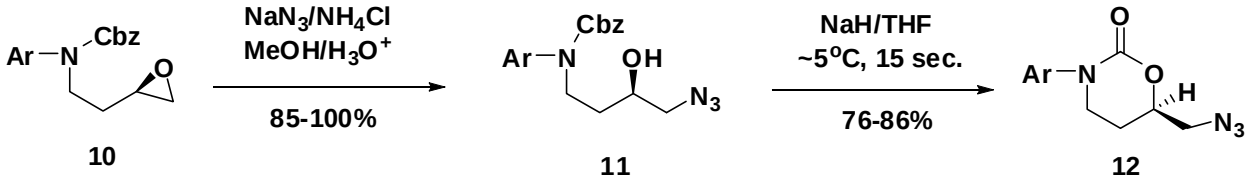


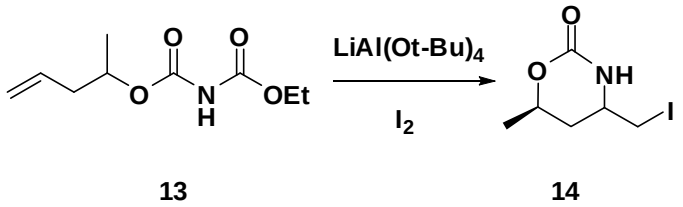
Figure 2.2. Representative compounds containing a 1,3-oxazinan-2-one ring.

There are not many available syntheses for chiral 1,3-oxazinan-2-ones in the literature.[34, 52-56] One chiral pool approach method utilizes aspartic acid as the starting material (Scheme 2.1), an epoxide containing Cbz protected arylamine was obtained as an intermediate **10**, then the epoxide ring was opened by sodium azide and cyclization of hydroxyl group with the Cbz group gave the desired 1,3-oxazinan-2-one **12**.[57] A short synthesis for 1,3-oxazinan-2-one **14** was

accomplished by reductive amination of 2-deoxy-D-ribose followed by cyclization of the arylchloroformate derivatized amine.[58] Other methods to synthesize 1,3-oxazinan-2-ones include halogen mediated cyclization reactions,[59-61] a trans-sulfamoylation through sulfamides intermediates,[62] selenium mediated cyclization of aminoalcohol with carbon monoxide,[63] rearrangement from cyclic sulfates,[64] intramolecular Michael additions,[65] asymmetric dihydroxylation of homoallylic amines,[66] and a Hoffmann rearrangement of a primary amide to form the carbamate.[67] The iodoaminocyclization reaction is highly stereoselective when using a homoallyl carbamate with a chiral center at the homoallylic position (Scheme 2.2).[59]



Scheme 2.1. Synthesis of *N*-aryl-1,3-oxazinan-2-ones from aspartic acid.

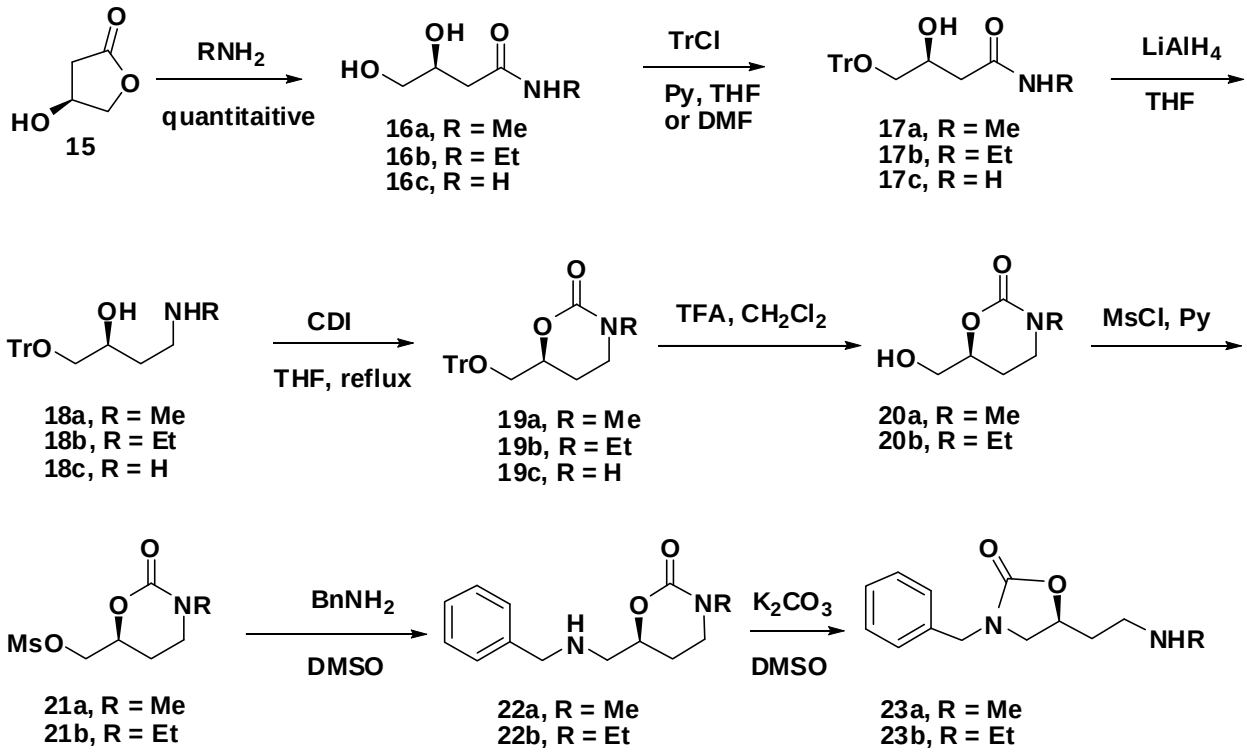


Scheme 2.2. Synthesis of 1,3-oxazinan-2-one by iodoaminocyclization.

Because of their great potential as biologically active molecules and as part of our interests in synthesizing new chiral heterocylic derivatives as therapeutic agents, we developed a novel method to synthesize these chiral 6-membered ring carbamates from carbohydrate derivative (S)-γ-butyrolactone.

Results and Discussions

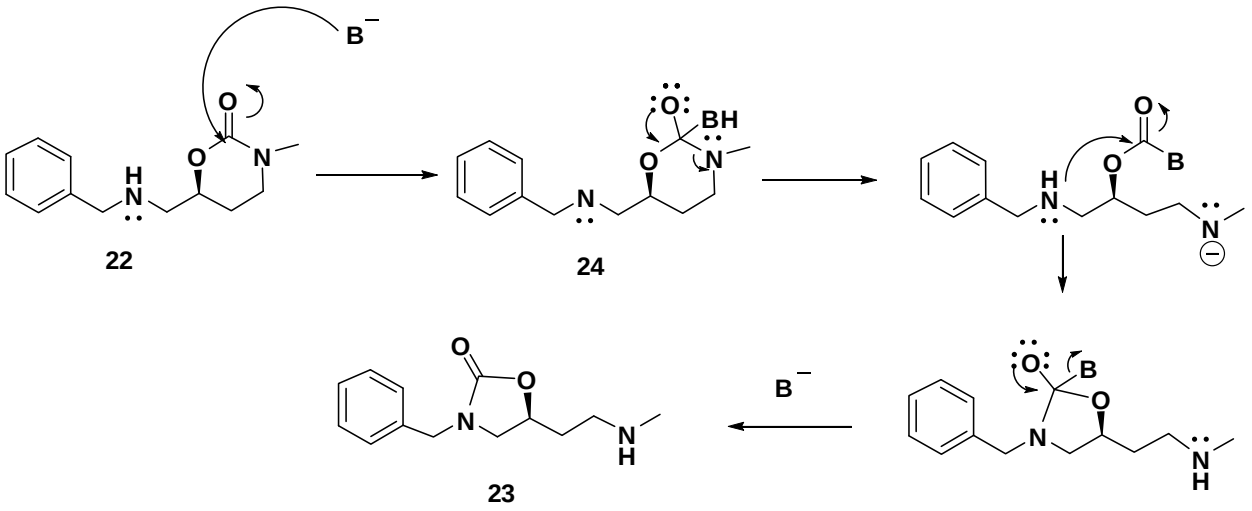
We designed and carried out the syntheses of these important chiral compounds from carbohydrate derivative, (*S)*-3-hydroxy-γ-butyrolactone **15** as shown in Scheme 2.3. Starting from optically pure lactone **15**,[68] ring opening with amines led to the dihydroxy butyramide **16** quantitatively.[69] The diol was selectively protected with a trityl group to increase the hydrophobicity of the compound. This is necessary for the reduction step when the R group is a small alkyl group. Without a protecting group, the reduction product is too polar and it is hard to recover it from the reaction mixture. Trityl group showed excellent selectivity to primary hydroxyl group although some small amount of di-protected byproduct can be obtained under prolonged period of stirring. Reduction of the protected amide **17** using $LiAlH_4$ in THF gave the corresponding intermediate aminoalcohol **18** in excellent yield. Cyclization of the intermediate **18** using carbonyl diimidazole gave the protected 1,3-oxazinan-2-ones **19** in 70-93% yield. Attempt of using Cbz protected amine and using the carbonyl group of the Cbz group to form the carbamate ring resulted in a lower yield. The trityl protecting group was removed using TFA in dichloromethane quantitatively. The primary hydroxyl group in **20** can then be converted to an amino group by converting it to the mesylate **21** and displacement of the mesylate by benzylamine in DMSO at 60-80°C. The benzyl protecting group in **22** can be removed by catalytic hydrogenation to give the corresponding 6-aminomethyl-1,3-oxazinan-2-ones. The displacement product is mainly the direct S_N2 displacement product **22** when using DMSO as solvent and 2 to 2.5 equivalent of benzylamine at 60-80°C. However, we found that when the temperature is higher than 85°C and in the presence of potassium carbonate, a significant quantity of compound **23** was obtained. This is presumably obtained from rearrangement of the 1,3-oxazinan-2-one **22**.



Scheme 2.3. Synthesis of chiral 1,3-oxazinan-2-ones from lactone **15**.

In order to understand the requirement for the rearrangement, we monitored the compound **22b** (R = CH_2CH_3) in D6-DMSO at >85 °C by ^1H NMR spectroscopy. The 1,3-oxazinan-2-ones are stable under neutral conditions. Heating at over 85 °C for 48 hours resulted in almost no decomposition of pure compound **22b** in DMSO. Addition of benzylamine to the sample did not cause rearrangement of compound **22b** either. However, addition of potassium carbonate promoted the rearrangement in the presence of benzylamine. In the absence of benzylamine, K_2CO_3 promoted the rearrangement to completion after 18 hours of heating at >85 °C. This indicated that participation of a non-bulky base is important to the reaction. We also carried out the rearrangement reaction for compound **22a** cleanly in DMSO using 2 equivalents of potassium carbonate at 100 °C for 24 hours. A possible mechanism of the formation of **23** is

shown in Scheme 2.4. A base B^- (such as hydroxide) molecule attacks the carbamate and opens up the 6-member ring forming a tetrahedral intermediate **24**, cyclization with the neighbor 6-benzylamino group leads to the formation of the 5-member ring carbamate, the oxazolidinone **23**.



Scheme 2.4. A possible mechanism of the rearrangement from 6-membered to 5-membered-ring carbamates promoted by base.

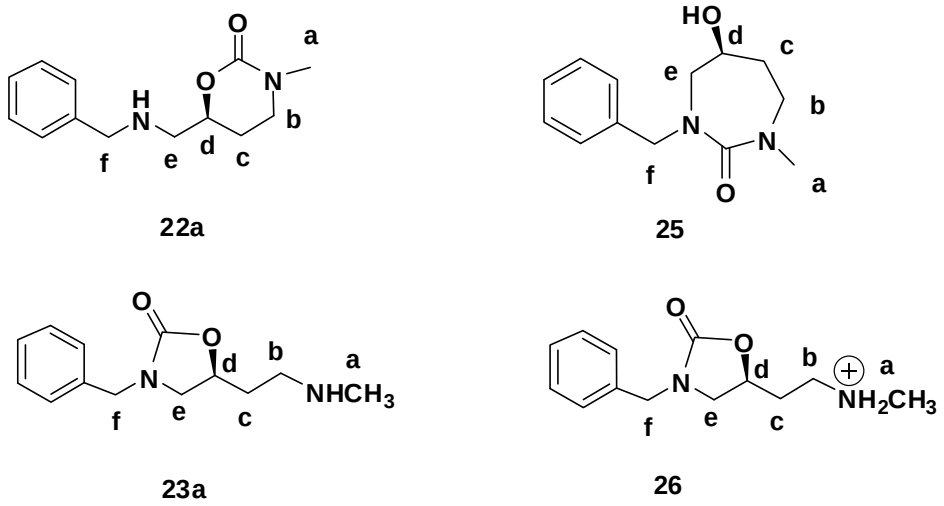


Figure 2.3. Starting material and different potential products of the rearrangement reaction

Besides the 5-membered ring oxazolidinone, another possible rearrangement product could be the 7-membered urea **25** by cleaving C-O bond instead of C-N bond. However, this possibility is ruled out for the above rearrangement reaction based on both ^{1}H and ^{13}C NMR spectra data. The five-membered ring is also, according to Baldwin rules of cyclization, more stable than the seven-membered ring. The amine **23a** has certain solubility (~10mg/mL) in water, and it is easily protonated. The protonated form **26** would exhibit changes of chemical shifts for the methyl *a* and methylenes *b*, *c*. The ^{1}H NMR spectra of the three compounds are shown in Figure 2.4. If the 7-member ring urea **25** is the rearrangement product, the ^{1}H NMR chemical shifts for the methyl *a* and methylene *b* should not change significantly since the chemical environment for *a* and *b* are essentially the same in **22a** and **25**. However, if the rearrangement product is the amine **23a**, then the ^{1}H NMR absorptions of *a* and *b* should change significantly. This is what we have observed as shown in Figure 2.4. The chemical shift for methyl *a* moved upfield from 2.94 ppm in **22a** to 2.38 ppm, the methylene group *b* also shifted upfield from 2.78 in **22a** to 2.68 ppm. The methine proton *d* moved upfield from 4.34ppm in **22a** to 4.68 ppm in the rearrangement product. This is a strong evidence that the structure **25** is not the rearrangement product, in which the methine proton *d* is expected to have a chemical shift around 4.00 ppm. Furthermore, the absorption for *a* and *b* in the ammonium salt **26** should move down field comparing to the neutral form **23a**. For the urea, addition of acid will not affect the chemical shifts of *a* and *b* significantly. As shown in Figure 1, the chemical shifts of the groups close to the nitrogen have significantly moved downfield after addition of acid: methyl *a* shifted from 2.38 ppm to 2.60 ppm and methylene *b* shifted from 2.68 ppm to 3.01 ppm. We have also compared the ^{1}H and ^{13}C spectra data to existing 2-oxazolidinones[6] and the similarities of the 5-member ring absorption data confirmed that the structure **23a** is the correct product. The above results confirm

our hypothesis that the rearrangement product is the 5-member ring 2-oxazolidinone **23** instead of the 7-member ring urea **25**.

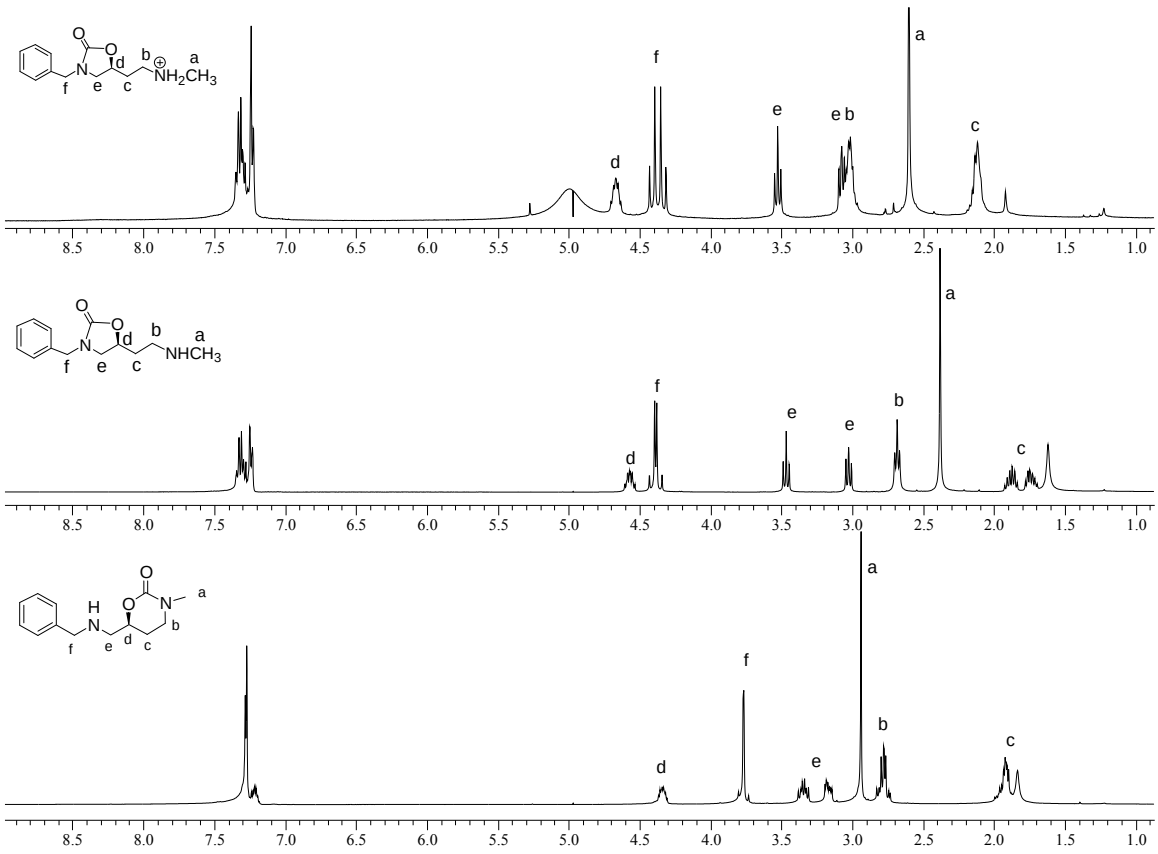
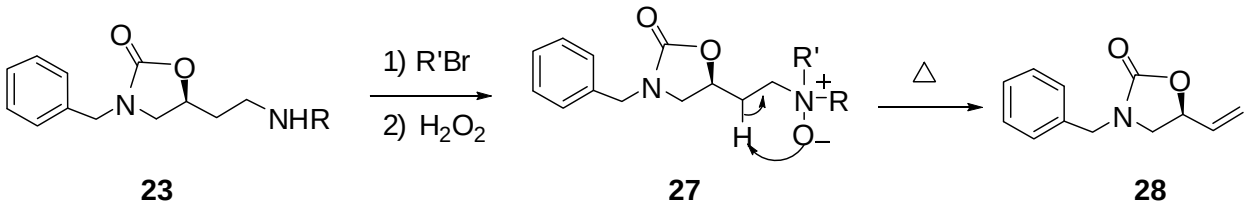


Figure 2.4. The ^{1}H NMR spectra of compounds **22a** (bottom), neutral amine **23a** (middle), and the protonated amine **26** (top), all spectra obtained in $CDCl_3$.

The formation of **23** is another method of synthesizing chiral oxazolidinones that have opposite stereochemistry as the Hoffmann rearrangement method from **16c**.[22] The rearrangement product **23** can be used to synthesize 2-oxazolidinones with an alkene functional group by oxidation of the amine (after converting to a tertiary amine and treatment with hydrogen peroxide) and followed by Cope elimination (Scheme 2.5). The 2-oxazolidinone **28** after Cope elimination can

be used as a general building block in the synthesis of 2-oxazolidinone derivatives. Substituted 2-oxazolidinones can be obtained by electrophilic addition to the double bonds.



23 **27** **28**

Scheme 2.5. A proposed synthesis of a new oxazolidinone building block **28**.

Conclusions

Small chiral molecules, featuring 5-membered ring and six-membered ring carbamates are important building blocks in the synthesis of biologically active molecules and are found in many drugs that are currently available commercially. They are also useful synthetic tools and can be used as chiral auxiliaries and catalysts in asymmetric synthesis. Because of their interesting chemical properties, these heterocycles have been the subject of many strategies with the common goal of finding simple and efficient ways to synthesize them. We have developed a new efficient method to synthesize chiral 6-substituted 1,3-oxazinan-2-ones from (*S)*-3-hydroxy-γ-butyrolactone. The reaction scheme is straightforward, efficient and with complete retention of stereochemistry. We also discovered that under basic conditions, heat can promote the rearrangement of the 6-membered ring 1,3-oxazinan-2-ones to the more stable 5-membered ring 2-oxazolidinones. The product 2-oxazolidinone has opposite stereochemistry comparing to the 2-oxazolidinone synthesized by Hoffman rearrangement. This method allows us to synthesize chiral core structures with complementary stereocenter since the priority order is switched. The efficient syntheses of these chiral carbamates are important in the preparation of biologically active pharmaceutical compounds. The synthesis also provides intermediates for synthesizing chiral aminoalcohol derivatives.

Experimental Section:

General procedure for the synthesis when R = Me is used as an illustration for the procedure. The compounds with R = Et and H are synthesized by a similar method. The characterization data for the N-Et analogues and when R = H are given. Melting point was measured using Fisher-Jones melting point apparatus.

***(S)*-3,4-Dihydroxy-*N*-methylbutyramide 16a.** Compounds **16a-c** were obtained by similar methods in the literature.[21] The lactone (20.2 g, 198 mmol) and methyl amine (77.7 g, 1.00 mol, 40%wt in water) were mixed at room temperature for 6 to 8 h. The excess methyl amine was removed by washing with hexane and the last trace of solvent and methyl amine were removed on a vacuum pump. The crude product was obtained as a brown viscous liquid (26.3 g, 198 mmol) and was used directly in the second step without further purification. Yield: 100% $[\alpha]_D^{25}$ –25.9 (*c* 1.08, EtOH). ^{1}H NMR (D_2O, 400 MHz) δ ppm 3.94 (m, 1H), 3.48 (dd, 1H, *J* = 11.7, 3.9 Hz), 3.38 (dd, 1H, *J* = 11.7, 6.8 Hz), 2.61 (s, 3H), 2.32 (dd, *J* = 14.7, 3.9 Hz), 2.22 (dd, *J* = 14.7, 8.8 Hz). ^{13}C NMR (CD_3OD, D_2O, 100 MHz) δ ppm, 175.1, 70.1, 69.2, 40.8, 26.9.

***(S)*-*N*-Ethyl-3,4-dihydroxybutyramide 16b** Yield: 99%, yellow crystals. m.p. 59.0-61.0°C. $[\alpha]_D^{25}$ –26.7 (*c* 1.07, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm. 5.69 (bs, 1H), 4.07 (m, 1H), 2.41 (dd, 1H, *J* = 15.6, 8.8 Hz), 2.31 (dd, 1H, *J* = 15.6, 3.9 Hz), 3.67 (m, 1H), 3.51 (m, 1H), 3.29 (m, 2H), 1.14 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (D_2O, 5%CD_3OD, 100 MHz) δ ppm. 174.2, 70.1, 66.2, 40.9, 35.6, 14.6.

***(S)*-3-Hydroxy-*N*-methyl-4-trityloxybutyramide 17a.** 3,4-Dihydroxy-*N*-methylbutyramide **16a** (19.4 g, 146 mmol) was dissolved in 52 mL of anhydrous DMF under N_2. Trityl chloride (49.0 g, 176 mmol) and pyridine (35.0 mL, 438 mmol) were added to the solution, which was then stirred at room temperature for 24 to 36 h. The reaction was quenched by addition of ice water (100 mL) to the solution. The water was decanted and the solid precipitate was dissolved in EtOAc (150 mL). The organic phase was washed 3 to 4 times with 30 mL of water and finally with 30 mL of brine. After drying with Na_2SO_4, the ethyl acetate was removed on a rotavap and the product was obtained as an off white solid (55.0 g, 146 mmol) without further purification. The crude product however can be purified by flash chromatography on silica gel using a gradient of solvent system of hexane: ethyl acetate 3:1 to 1:1. Yield: 100%. m.p. 107.0-108.0 °C. $[\alpha]_D^{25}$ –18.3. (*c* 1.12, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm δ 7.40 (d, 6H, *J* = 7.8 Hz), 7.19-7.34 (m, 9H), 5.98 (bs, 1H), 4.14 (m, 1H), 3.55 (s, 1H), 3.15 (dd, 1H, *J* = 9.8, 5.9 Hz), 3.10 (m, 1H), 2.72 (d, 3H, *J* = 4.9 Hz), 2.40 (dd, 1H, *J* = 15.6, 2.9 Hz), 2.31 (dd, 1H, *J* = 15.6, 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 172.3, 143.5, 128.4, 127.6, 126.9, 86.4, 67.8, 66.6, 39.4, 25.9. HRMS calcd for $C_{24}H_{25}NO_3Na^+$ $[M+Na]^+$ 398.1732, found 398.1746. IR ($CHCl_3$): 3347, 3015, 1653, 1550, 1491, 1448, 1217, 1074, 758 cm^{-1}.

***(S)*-*N*-Ethyl-3-hydroxy-4-trityloxybutyramide 17b** Yield: 95% after purification using hexane: ethyl acetate 1:1, R_F = 0.3. (0.05 mmol scale). Product is obtained as a white solid. m.p. 119.0 °C. $[\alpha]_D^{25}$ –19.1 (*c* 1.11, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 7.50-7.16 (m, 15H), 5.90 (bs, 1H), 4.16 (m, 1H), 3.52 (sb, 1H), 3.23 (m, 2H), 3.13 (m, 2H), 2.38 (dd, 1H, *J* = 15.6, 2.9 Hz), 2.31 (dd, 1H, *J* = 15.6, 7.8 Hz,), 1.08 (t, 3H, *J* = 6.8Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 171.5, 143.7, 128.6, 127.8, 127.1, 86.7, 68.0, 66.6, 39.6, 34.2, 14.7. HRMS calcd for

$C_{25}H_{27}NO_3Na^+$ $[M+Na]^+$ 412.1889, found 412.1909. IR ($CHCl_3$): 3444, 3372, 3062, 3017, 2934, 2878, 1651, 1533, 1448, 1217, 1074, 758 cm^{-1}.

***(S)*-3-Hydroxy-4-trityloxybutyramide 17c.** Yield after purification: 90%. m.p. 107.5-108.5º C. $[\alpha]_D^{25}$ –18.4 (*c* 1.00, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 7.41 (d, 6H, *J* = 7.8 Hz), 7.34-7.19 (m, 9H), 6.06 (bs, 1H), 5.64 (bs, 1H), 4.15 (m, 1H), 3.45 (bs, 1H), 3.16 (d, 2H, *J* = 5.9 Hz), 2.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 174.1, 143.6, 128.5, 127.8, 127.1, 86.8, 67.7, 66.7, 39.2. IR ($CHCl_3$): 3494, 3408, 3019, 2929, 2878, 1675, 1594, 1492, 1448, 1217, 1075, 742 cm^{-1}.

***(S)*-4-Methylamino-1-trityloxybutan-2-ol 18a.** 3-Hydroxy-*N*-methyl-4-trityloxy-butyramide **17a** (55.0 g, 146 mmol) was dissolved in anhydrous THF (240 mL) and the reaction flask was cooled to 0 °C in an ice-salt bath. $LiAlH_4$ (16.5 g, 434 mmol) was added to the flask at 0 °C under dry N_2. The ice bath was removed after the generation of hydrogen settled down. The mixture was left stirring at room temperature for 12 to 18 h after which time the reaction is essentially completed based on NMR spectroscopy. The reaction mixture was then cooled in an ice-bath and the reducing agent was quenched by adding 50 mL of a 1:1 mixture of MeOH and H_2O. The white precipitate formed after addition of water and MeOH was removed by vacuum filtration and the filtrate was extracted several times with $CHCl_3$. The combined organic phase was dried using Na_2SO_4 overnight. The solvent was removed on a rotovap and the residue was dried on a vacuum pump. The product was obtained as an off white solid (51.4 g, 142 mmol) without further purification. Yield: 97% m.p. 120.0°C. $[\alpha]_D^{25}$ –19.0 (*c* 1.02, EtOH). ^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 7.45 (d, 6H, *J* = 6.8 Hz), 7.28 (t, 6H, *J* =7.8 Hz), 7.21 (t, 3H, *J* = 6.8

Hz), 4.00 (m, 1H), 3.47 (bs, 2H), 3.17 (dd, 1H, J = 9.8, 5.9 Hz), 3.00 (dd, 1H, J = 9.8, 5.9 Hz), 2.83 (m, 1H), 2.73 (m, 1H), 2.36 (s, 3H), 1.75 (m, 1H), 1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm 144.0, 128.6, 127.6, 126.8, 86.2, 71.6, 67.4, 49.8, 85.9, 31.8. HRMS ES+ calcd for $C_{24}H_{27}NO_2$ $[M+1]^+$ 362.2120, found 362.2127. IR ($CHCl_3$): 3318, 3061, 3011, 2929, 2872, 1598, 1491, 1448, 1217, 1075, 766 cm^{-1}.

***(S)*-4-Ethylamino-1-trityloxybutan-2-ol 18b.** Yield: 73% (unoptimized yield). Product is obtained as white crystals, m.p. 109.0-110.0° C. $[\alpha]_D^{25}$ –17.7 (*c* 1.07, EtOH). ^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 7.50-7.16 (m, 15H), 4.00 (m, 1H), 3.16 (dd, 1H, J = 8.8, 5.9 Hz), 2.98 (dd, 1H, J = 8.8, 5.9 Hz), 2.90 (m, 1H), 2.76 (m, 1H), 2.62 (m, 2H), 1.80-1.70 (m, 1H), 1.58 (m, 1H), 1.07 (t, 2H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 144.1, 128.7, 127.7, 126.9, 86.4, 72.0, 67.5, 47.7, 43.8, 31.9, 14.8. HRMS calcd for $C_{25}H_{30}NO_2$ $[M+1]^+$ 376.2277, found 376.2281. IR ($CHCl_3$): 3062, 3019, 2972, 1491, 1448, 1216, 1075, 757 cm^{-1}.

***(S)*-4-Amino-1-trityloxy-butan-2-ol 18c.** Yield: 93% m.p. 104.0-106.0º C. $[\alpha]_D^{25}$ –16.0 (*c* 1.01, EtOH,). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 7.62-7.18 (m, 15H), 3.98 (m, 1H), 3.14 (dd, 1H, J = 8.8, 5.9 Hz), 3.04 (dd, 1H, J = 8.8, 4.9 Hz), 2.95 (m, 1H), 2.82 (m, 1H), 1.65 (m, 1H), 1.53 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 143.8, 128.4, 127.5, 126.7, 86.2, 70.3, 67.6, 39.3, 35.1. IR ($CHCl_3$): 3377, 3061, 3015, 2929, 2873, 1596, 1491, 1448, 1217, 1073, 767 cm^{-1}.

***(S)*-3-Methyl-6-trityloxymethyl-1,3-oxazinan-2-one 19a.** 4-Methylamino-1-trityloxy-butan-2-ol **18a** (10.9 g, 30.0 mmol) was dissolved in anhydrous THF or dioxane (50.0 mL). After the compound **18a** was completely dissolved, carbonyldiimidazole (9.98 g, 60.0 mmol) was added to the flask and the solution was stirred under refluxing for 24 h. The solvent was evaporated on the

rotovap and the remaining solid was extracted in EtOAc. The organic phase was washed with about 10.0 mL of H_2O several times and with 30.0 mL of brine. The EtOAc phase was concentrated on the rotovap to afford a brown solid that was purified on SiO_2 gel with a gradient of solvent of hexane: ethyl acetate 5:1 to 1:1. The purified product was obtained as a white crystalline solid (10.9 g, 28.0 mmol). Yield: 93%. m.p. 161.0-162.0° C. $[\alpha]_D^{25}$ +36.2 (*c* 1.08, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, 6H, *J* = 6.8 Hz), 7.32-7.20 (m, 9H), 4.32 (m, 1H), 3.32 (m, 1H), 3.21 (m, 1H), 2.96 (s, 3H), 2.07 (m, 1H), 1.96 (m. 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 143.3, 128.3, 127.56, 126.9, 86.5, 75.4, 64.5, 45.8, 36.2, 24.3. HRMS ES+ calcd for $C_{25}H_{26}NO_3$ $[M+1]^+$ 388.1913, ES found: 388.1928. IR ($CHCl_3$): 3061, 3018, 2938, 2880, 1690, 1494, 1448, 1217, 1083, 760 cm^{-1}.

***(S)*-3-Ethyl-6-trityloxymethyl-1,3-oxazinan-2-one 19b** Yield: 79%. Product was obtained as white crystals, m.p. 141.0-142.0° C. $[\alpha]_D^{25}$ +26.7 (*c* 1.07, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.52-7.16 (m, 15H), 4.32 (m, 1H), 3.42-3.26 (m, 4H), 3.24-3.14 (m, 2H), 2.10 (m, 1H), 1.93 (m, 1H), 1.12 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 153.0, 143.5, 128.6, 127.8, 127.1, 86.7, 75.5, 64.7, 44.0, 43.4, 24.7, 12.1. HRMS calcd for $C_{26}H_{28}NO_3$ $[M+1]^+$ 402.2069, found 402.2079. IR ($CHCl_3$): 3062, 3019, 2982, 2938, 1685, 1491, 1450, 1280, 1217, 1094, 763 cm^{-1}.

***(S)*-6-Trityloxymethyl-1,3-oxazinan-2-one 19c** Yield: 70% m.p. 182.5-183.5º C. $[\alpha]_D^{25}$ +20.8 (*c* 1.01, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 7.60-7.18 (m, 15H), 7.42 (d, 6H, *J* = 7.8 Hz), 7.29 (t, 6H, *J* = 7.8 Hz), 7.21 (d, 3H, *J* = 7.8 Hz), 5.25 (bs, 1H), 4.38 (m, 1H), 3.34 (m, 3H), 3.23 (dd, 1H, *J* = 9.8, 5.9 Hz), 2.03 (dd, 1H, *J* = 12.7, 2.9 Hz), 1.92 (m, 1H), 1.55 (bs, 1H). ^{13}C

NMR ($CDCl_3$, 100 MHz) δ ppm 154.5, 143.5, 128.5, 127.9, 127.1, 86.8, 76.1, 64.7, 38.7, 23.6. IR ($CHCl_3$): 3448, 3261, 3062, 3018, 2939, 2882, 1707, 1490, 1450, 1292, 1217, 1110, 1079, 750 cm^{-1}.

***(S)*-6-Hydroxymethyl-3-methyl-1,3-oxazinan-2-one 20a.** The solution of 3-methyl-6-trityloxymethyl-1,3-oxazinan-2-one **19a** (5.00 g, 13.0 mmol) in a mixture of TFA and CH_2Cl_2 (20 mL, 1:1) was stirred for 12 h at room temperature. The TFA and the solvent were evaporated to dryness on a rotovap. Ice water was then added to the viscous liquid residue and a solid precipitate formed. The solid was removed by vacuum filtration and the water phase was extracted with hexane to remove trace amount of trityl compound. The water phase was then evaporated on an oil pump and MeOH was added to the product and then evaporated several times. The product was obtained as a light brown viscous liquid (1.90 g, 13.0 mmol) and was used directly in the next step. Yield: 100% $[\alpha]_D^{25}$ +75.6 (*c* 1.09, EtOH). ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (m, 1H), 3.74 (dd, 1H, *J* = 11.7, 3.9 Hz), 3.65 (dd, 1 H, *J* = 11.7, 4.9 Hz), 3.38 (m, 1H), 3.22 (m, 1H), 2.95 (s, 3H), 2.77 (bs, 1H), 1.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 77.5, 63.7, 46.0, 36.3, 23.3. HRMS ES+ calcd for $C_6H_{12}NO_3$ $[M+1]^+$ 146.0817, found 146.0820. IR ($CHCl_3$): 3381, 3009, 2939, 1677, 1499, 1450, 1256, 1079, 756 cm^{-1}.

***(S)*-3-Ethyl-6-hydroxymethyl-1,3-oxazinan-2-one 20b** Yield: quantitative, $[\alpha]_D^{25}$ +64.1 (*c* 0.91, EtOH). ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 4.28 (m, 1H), 3.79 (m, 1H), 3.66 (m, 1H), 3.38 (m, 3H), 3.26 (dd, 1H, *J* = 5.9, 2.9 Hz), 1.95 (m, 2H), 1.16 (t, 3H, *J* =6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 153.5, 77.5, 63.6, 43.8, 43.4, 23.3, 12.0. HRMS ES+ calcd for $C_7H_{14}NO_{23}$ $[M+1]^+$ 160.0974, found 160.0972. IR ($CHCl_3$): 3393, 3013, 2927, 1664, 755 cm^{-1}.

***(S)*-Methanesulfonic acid 3-methyl-2-oxo-1,3-oxazinan-6-ylmethyl ester 21a.** 6-Hydroxymethyl-3-methyl-1,3-oxazinan-2-one **20a** (1.87 g, 13.0 mmol) was dissolved in dry dichloromethane (20.0 mL). Pyridine (12.0 mL, 156 mmol) and methanesulfonyl chloride (5.00 mL, 65.0 mmol) were added and the solution was stirred at room temperature for 12 h. $NaHCO_3$ (5.00 g, 59.0 mmol) was then added to the flask and the mixture was stirred for 30 min after which the solvent was removed on a rotavap. The residue was cooled in an ice bath and water (30.0 to 40.0 mL) was added to quench the unreacted sulfonyl chloride. The water phase was extracted 5 times using 30.0 mL of EtOAc each time. The combined organic extracts were dried using Na_2SO_4 and the solvent was evaporated to give the product as dark brown solid without further purification (2.38 g, 11.0 mmol). Yield: 85%. m.p. 81.5-82.0° C. $[\alpha]_D^{25}$ +59.1 (*c* 1.14, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.49 (m, 1H), 4.34 (dd, 1H, *J* = 11.7, 3.9 Hz), 4.30 (dd, 1H, *J* = 11.7, 3.9 Hz), 3.42 (m, 1H), 3.27 (m, 1H), 3.08 (s, 3H), 2.98 (s, 3H), 2.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 152.5, 73.9, 69.6, 45.6, 37.5, 36.3, 23.2. HRMS calcd for $C_7H_{13}NO_5S$ $[M+1]^+$ 224.0593, found 224.0583. IR ($CHCl_3$): 3019, 2942, 1693, 1496, 1448, 1356, 1177, 756 cm^{-1}.

***(S)*-Methanesulfonic acid 3-ethyl-2-oxo-1,3-oxazinan-6-ylmethyl ester 21b** After purification by chromatography, product was obtained as a white crystal, Yield: 92% m.p. 68.0-70.0° C. $[\alpha]_D^{25}$ +52.2 (*c* 1.14, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 4.47 (m, 1H), 4.34 (dd, 1H, *J* = 11.7, 3.9 Hz), 4.30 (dd, 1H, *J* = 11.7, 4.9 Hz), 3.38 (m, 3H), 2.29 (m, 1H), 3.08 (s, 3H), 2.10-1.92 (m, 2H), 1.15 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 152.1, 73.9, 69.5,

44.2, 43.2, 37.8, 23.6, 12.1. HRMS ES+ calcd for $C_8H_{16}NO_5S$ $[M+1]^+$ 238.0749, found 238.0745. IR ($CHCl_3$): 3436, 3020, 1694, 1491, 1456, 1217, 758 cm^{-1}.

***(S)*-6-(Benzylaminomethyl)-3-methyl-1,3-oxazinan-2-one 22a.** Methanesulfonic acid 3-methyl-2-oxo-[1,3]oxazinan-6-ylmethyl ester **21a** (0.810 g, 3.67 mmol) and benzylamine (0.800 mL, 8.00 mmol) were dissolved in anhydrous DMSO (10.0 mL). The mixture was stirred at 75 to 80 °C for 48 h under anhydrous atmosphere. The reaction mixture was cooled to room temperature and ice water (10 – 20 mL) was added to the flask. The water phase was extracted several times with dichloromethane. The combined organic phase was dried using Na_2SO_4 and concentrated on a rotavap to remove the solvent to give the crude product as a yellow viscous liquid. The crude compound was purified by silica gel chromatography using a gradient of solvent system of hexane:THF/9:1 to hexane:CH_2Cl_2:THF/6:3:1 to CH_2Cl_2:MeOH/9.9:0.1. The product was obtained as a light brown viscous liquid (0.770 g, 3.30 mmol). Yield: 91% $[\alpha]_D^{25}$ +68.2 (*c* 1.07, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.13 (m, 5H), 4.34 (m, 1H), 3.77 (m, 2H), 3.34 (m, 1H), 3.17 (m, 1H), 2.94 (s, 3H), 2.80 (dd, 1H, J = 12.7, 6.8 Hz), 2.75 (dd, 1H, J = 12.7, 3.9 Hz), 1.92 (m, 2H), 1.83 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 139.4, 128.3, 128.0, 127.0, 76.3, 53.5, 52.3, 46.2, 36.3, 25.0. HRMS calcd for $C_{13}H_{19}N_2O_2$ $[M+1]^+$ 235.1447, found 235.1447. IR ($CHCl_3$): 3330, 3009, 2938, 1690, 1496, 1449, 1409, 1354, 754 cm^{-1}.

***(S)*-6-(Benzylaminomethyl)-3-ethyl-1,3-oxazinan-2-one 22b** The reaction temperature was 65 °C and time was 36 h. Crude yield 96%, ^{1}H NMR spectroscopy indicated quantitative conversion). After purification on SiO_2 gel with a gradient of hexane: CH_2Cl_2 6:1 to hexane: CH_2Cl_2:THF 6:3:1. Yield: 78%. $[\alpha]_D^{25}$ +55.3 (*c* 0.64, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 7.40-7.18 (m, 5H), 4.34 (m, 1H), 3.80 (d, 1H, J = 12.7 Hz), 3.76 (d, 1H, J = 12.7 Hz), 3.34

(m, 2H), 3.20 (m, 1H), 2.81(dd, 1H, *J* = 12.7, 6.8 Hz), 2.76 (dd, 1H, *J* = 12.7, 4.9 Hz), 1.94 (m, 2H), 1.85 (s, 1H), 1.13 (t, 3H, *J* =6.8 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 153.2, 139.8, 128.4, 128.1, 127.0, 76.4, 53.7, 52.6, 44.0, 43.6, 25.3, 12.1. HRMS ES+ calcd for $C_{14}H_{21}N_2O_2$ $[M+1]^+$ 249.1603, found 249.1597. IR ($CHCl_3$): 3472, 2974, 2934, 1682, 1492, 1455, 1282, 1221, 1095, 755 cm^{-1}.

***(S)*-3-Benzyl-5-(2-methylaminoethyl)-oxazolidin-2-one 23a.** 6-(Benzylaminomethyl)-3-methyl-1,3-oxazinan-2-one **22a** (0.160 g, 0.070 mmol), anhydrous DMSO (5.00 mL) and K_2CO_3 (0.200 g, 1.40 mmol) were mixed and stirred at 95-100°C for 24 h. ^{1}H NMR spectrum indicated complete conversion to the 5-membered ring product. The flask was cooled to room temperature and ice water (5 mL) was added to the solution. The water phase was then extracted with CH_2Cl_2 several times. The combined organic phase was concentrated on a rotovap and the yellow liquid obtained was purified by SiO_2 chromatography using a gradient of hexane:THF 9:1 to hexane:CH_2Cl_2:THF 6:3:1 to CH_2Cl_2:MeOH 9.9:0.1. The pure product was obtained as a light brown viscous liquid (0.130 g, 0.057 mmol). Yield: 81%. $[\alpha]_D^{25}$ +68.5 (*c* 1.00, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.21 (m, 5H), 4.57 (m, 1H), 4.41 (d, 1H, *J* = 14.7 Hz), 4.36 (d, 1H, *J* = 14.7 Hz), 3.47 (t, 1H, *J* = 8.8 Hz), 3.03 (t, 1H, *J* = 7.8 Hz), 2.69 (t, 2H, *J* = 6.8 Hz), 2.38 (s, 3H), 1.88 (m, 1H), 1.74 (m, 1H),1.62 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 135.7, 128.8, 128.1, 127.9, 72.3, 49.4, 48.3, 47.5, 36.4, 35.1. HRMS calcd for $C_{13}H_{19}N_2O_2$ $[M+1]^+$ 235.1447, found 235.1449. IR ($CHCl_3$): 3018, 2936, 1742, 1493, 1442, 1217, 756 cm^{-1}.

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Chapter III. Synthesis of Chiral 2-Oxazolidinones, 2-Oxazolines and Their Analogs.

Abstract

Small chiral molecules are very important building blocks in the synthesis of biologically active compounds. These building blocks include nitrogen and oxygen-containing heterocycles such as oxazolidinones, oxazinanones, oxazolines, oxazines, morpholine and morpholinones. Because of their interesting properties, chiral heterocycles have stirred great interest in the synthetic chemist community to develop useful and efficient strategies to these molecules. In this chapter, chiral 5-membered ring 2-oxazolidinones and 6-membered ring 1,3-oxazinan-2-ones are synthesized from the corresponding amino alcohols with either complete inversion or retention of stereochemistry. Chiral 5-substituted 2-oxazolines and 6-substituted 2-oxazines are also synthesized from the same starting materials with inversion of stereochemistry through an intramolecular S_N2 reaction. These compounds are useful intermediates in organic synthesis and crucial building blocks for many pharmaceutical compounds.

Introduction

Small chiral molecules are very important building blocks in the synthesis of biologically relevant compounds. Chiral 5-substituted-2-oxazolidinones **1** and **2** shown in figure 3.1 are important core structures in many drug molecules and useful intermediates in the synthesis of chiral aminoalcohols. 5-Hydroxymethyl or 5-aminomethyl-2-oxazolidinones (**1** and **2**) are important in the preparation of oxazolidinone antibacterial agents.[1-10] Representative 2-oxazolidinones antibiotics include Linezolid (Zyvox®) **5**[1-2] and dihydrothiazine analog **6**[5]. 2-Oxazolidinones have been used in the synthesis of chiral aminoalcohols such as beta-blocker carvedilol (Eucardic®).[11-20] The 6-membered ring 1,3-oxazinan-2-ones **3** and **4** derivatives also exhibit biological activities, such as anti-inflammatory,[21] anti-thrombotic,[22] and antibacterial activities.[23] These heterocycles can be synthesized from amino alcohols or related starting materials. Another class of heterocyclic compounds that can be interconverted from amino alcohols is the oxazolines.[24-25] They are also important pharmacophores in many drug molecules; for instance natural product **7** has antibiotic activity,[26] compound **8** is a tubulin polymerization inhibitor and is a potential anticancer agent, while Deflazacort (Calcort®) **9** is a commercially available anti-inflammatory drug (Figure 3.2).[27] The homologous oxazine rings are also found in many compounds with interesting chemical and biological properties.[28-32] Besides being important building blocks for the preparation of biologically active compounds, 2-oxazolidinones, 1,3-oxazinan-2-ones and 2-oxazolines are also used as chiral auxiliaries or as protected forms of amino alcohols in the synthesis of complex molecules.[33-38] Because of the importance of these heterocycles as pharmaceutical core structures and in asymmetric synthesis, there have been great interests in developing their effective syntheses. The preparations of optically pure cyclic carbamates include the conversion of a chiral hydroxyl amide by Hofmann

rearrangement[39] and the carbonylation reaction of chiral 1,3-amino alcohols.[40] Many examples are available for the synthesis of cyclic carbamates from chiral amino alcohols with retention of stereochemistry.[41-55] There are fewer methods for the preparation of cyclic carbamates with opposite stereochemistry to the starting amino alcohol derivatives.[44, 56-59]

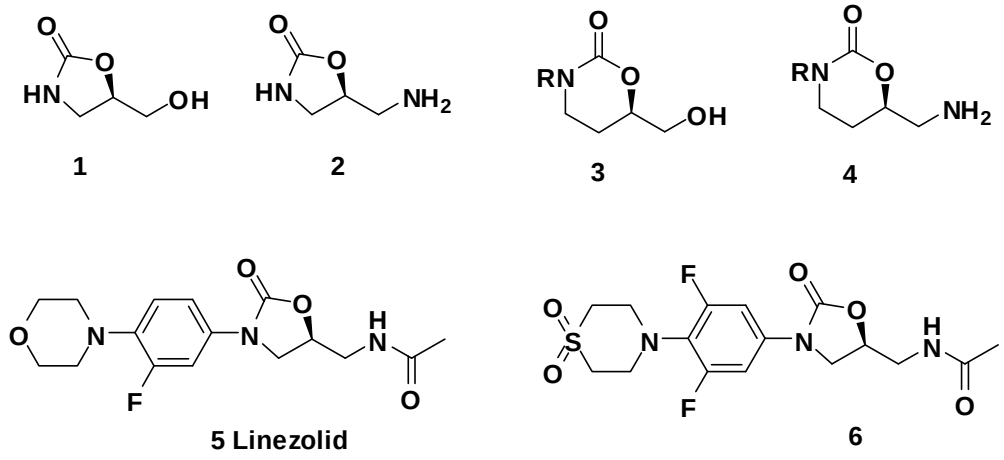


Figure 3.1. 2-oxazolidinones and 1,3-oxazinan-2-ones compounds.

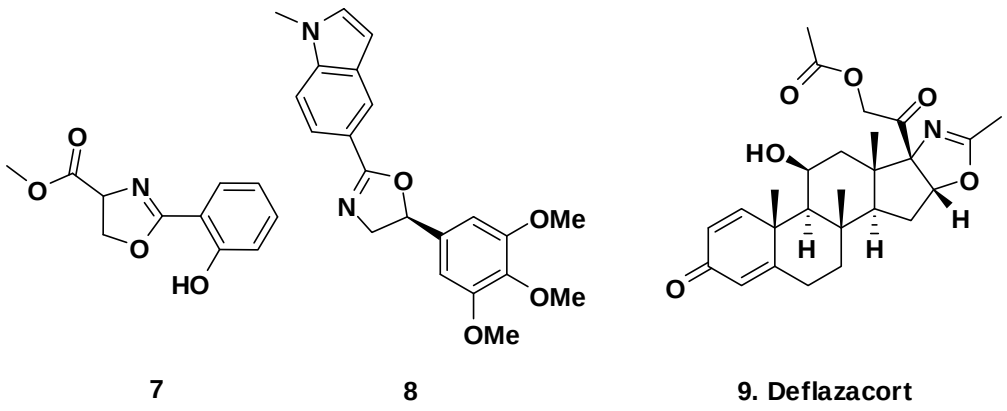


Figure 3.2. Biologically active molecules containing the 2-oxazoline moiety.

For the preparation of the opposite stereoisomers, the hydroxyl group is usually converted to a better leaving group through mesylation or Mitsunobu reaction, and the nitrogen is derivatized with Boc_2O or CbzCl. The S_N2 cyclization from the displacement of the activated hydroxyl group affords the cyclic carbamate with opposite stereochemistry.

A general precursor for oxazoline synthesis is a β-hydroxy amide. The hydroxyl group is usually converted to a better leaving group such as a sulfonate or halide, then an intramolecular S_N2 cyclization reaction gives the corresponding oxazoline. Many chiral 1,2-amino alcohols can be prepared from naturally occurring α-amino acids, and the oxazolines formed from these amino alcohols are 2,4-disubstituted oxazolines. Relatively fewer 5-substituted 2-oxazolines have been synthesized because of the lack of accessibility of the corresponding amino alcohols. There are also fewer 6-membered ring 2-oxazines comparing to 5-membered ring oxazolines, for the same reason as above, 1,3-amino alcohols are less accessible than the amino acid derived 1,2-amino alcohols which are used often in the synthesis of 2-oxazolines.

(*S*)-3-hydroxy-γ-butyrolactone is a commercially available compound that can be synthesized readily from starch or lactose.[60] The lactone has been converted to chiral (*S*)-1,2-amino alcohols, (*S*)-1,3-amino alcohols and their derivatives via efficient methods.[39,61] These chiral amino alcohols have structures that are complementary to those of natural amino acids derived amino alcohols. As part of our effort in synthesizing chiral building blocks that are useful in drug discovery, we devised new routes for several chiral heterocycles from intermediates generated from (*S*)-3-hydroxy-γ-butyrolactone. These chiral heterocycles include 5-substituted 2-

oxazolines, 6-substituted 2-oxazines, and both enantiomers of 5-trityloxymethy-2-oxazolidinones and 6-trityloxymethyl-1,3-oxazinan-2-ones.

Results and discussion

For the preparation of the 5-membered ring compounds, we started from the trityloxymethyl oxazolidinones **10a** and **10b** (Scheme 3.1). These can be prepared from *(S)*-3-hydroxyl-γ-butyrolactone according to literature procedures.[22,39] Compound **10** was decarbonylated by refluxing with NaOH in a mixture of THF, ethanol and water to give the trityl protected amino alcohol **11** with excellent yield. The amino alcohol **11** was then treated with trifluoroacetic anhydride at low temperature to give the corresponding amide **7**, followed by mesylation of the free hydroxyl group in **7** to give the intermediate **13**. The mesylate **13b** (R = Me) was cyclized to *N*-methyl-oxazolidinone **14** ($[\alpha]_D^{25}$ = -41.0, EtOAc, c = 1.00) under basic condition using potassium carbonate in DMF. Compound **14** has a stereochemistry opposite to that of the starting material **10b** ($[\alpha]_D^{25}$ = +40.9, EtOAc, c = 1.00). The cyclization to the oxazolidinone occurred through intramolecular S_N2 displacement of the mesylate and subsequent rearrangement. The yield for the transformation is excellent with complete inversion of stereochemistry.[62]

A small amount of compounds **10b** and **14** were deprotected using TFA to remove the trityl group and the free alcohol treated with Mosher's acid chloride to form the corresponding esters **10b'** and **14'** (Figure 3.3). Integration of the signals on the ^{1}H NMR spectrum of the crude reaction products allowed us to confirm the optical purity with the optical rotation data. The crude 500MHz ^{1}H NMR spectrum of compound **10b'** indicated no presence of diastereomer, the chemical shifts of protons a and b are: δ (ppm), 4.76 (sb, H*a*), 4.58 (d, 1H, H$_b$, *J* = 0,11.7Hz), 4.41 (dd, H$_b$′, *J* = 3.9, 11.7Hz), compound **25:** 4.78 (sb, H*a*), 4.58 (dd, 1H, H$_b$, *J* = 2.9, 12.2),

4.37 (dd, H_b', J = 3.9, 12.2Hz), a small doublet impurity signal at 4.41 estimated less than 1% of the H_b' integration indicates that the purity of the enantiomer is 99%.

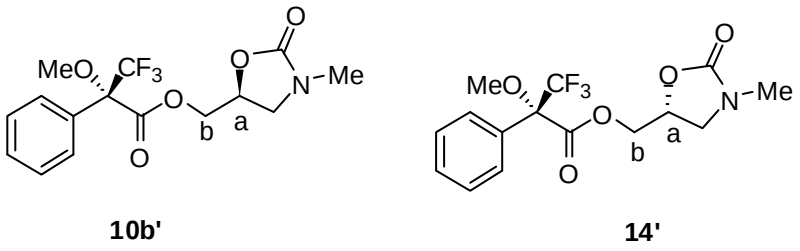
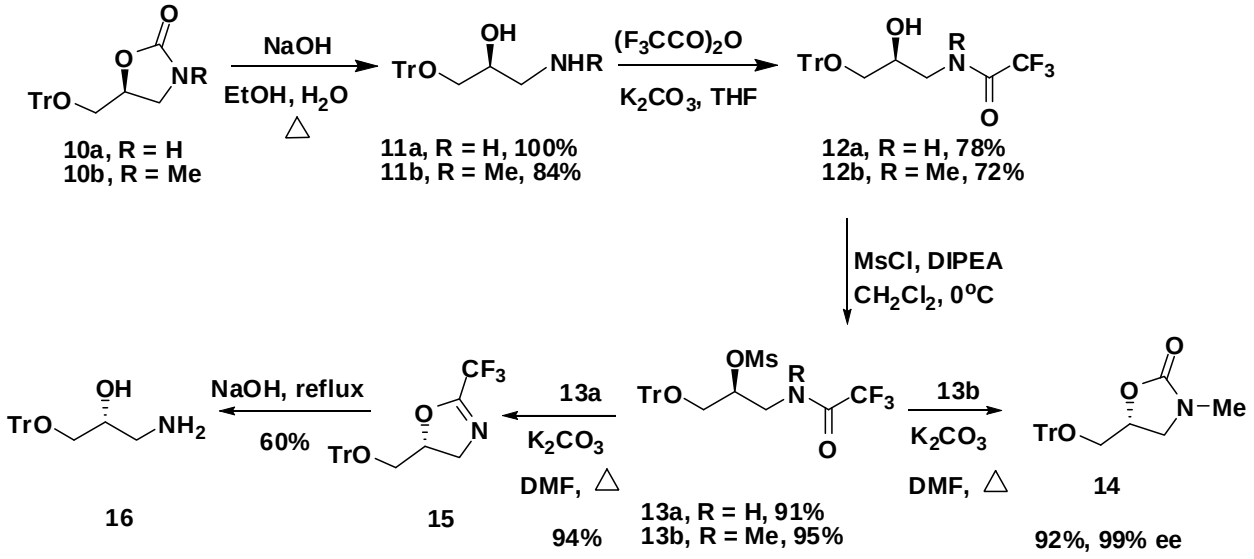


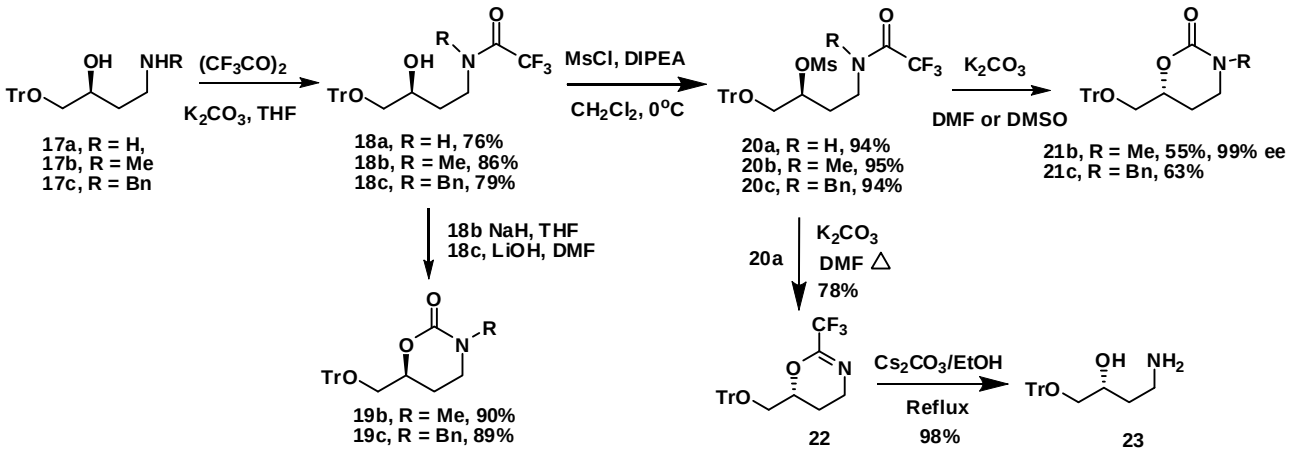
Figure 3.3. Mosher's esters **10b'** and **14'**.

When the amide contains a hydrogen atom such as in compounds **13a** (R = H), under the same mild basic conditions, the 2,5-disubstituted oxazoline **15** with inverted stereochemistry was obtained. The oxazoline was then hydrolyzed to give the amino alcohol **16** ($[\alpha]_D^{25}$ = +15.3, EtOH, c = 1.10), which has inverted stereochemistry compared to compound **11a** ($[\alpha]_D^{25}$ = -15.9, EtOH, c = 1.00). Because the oxazoline **15** is formed through an intramolecular reaction, it is expected to have high integrity of stereochemistry. Therefore, the stereochemistry of the amino alcohol **11a** can be inverted through a 4-step sequence as shown in Scheme 3.1.



Scheme 3.1. Synthesis of 2-oxazolidinone **14** and trityl protected 2-oxazoline **15**.

In the preparation of the 6-membered ring analogs, the trityl protected amino alcohols **17b-c** were used as starting materials. These compounds are synthesized by reacting (*S*)-3-hydroxy-γ-butyrolactone with amines to produce the corresponding dihydroxyl butyramides followed by the reduction of the trityl protected amides with lithium aluminum hydride.[60] As shown in Scheme 4. 2, by a similar method as for the 5-membered ring oxazolidinone synthesis, the amino alcohols **17** were converted to the trifluoroacetamide **18**. From compounds **18b-c**, direct acyl transfer cyclization under anhydrous basic conditions led to the formation of (*S*)-1,3-oxazinan-2-ones **19b** ($[\alpha]_D^{25}$ = +32.5, EtOAc, c = 1.03), and **19c** ($[\alpha]_D^{25}$ = +29.0, EtOAc, c = 1.01) in excellent yields. This demonstrated the feasibility of converting the amino alcohols into cyclic carbamates using trifluoroacetamide intermediate through elimination of the trifluoromethyl group. To prepare the carbamates with opposite stereochemistry, the mesylates **20b-c** were treated with potassium carbonate to afford the cyclization products **21b** ($[\alpha]_D^{25}$ = -31.9, EtOAc, c = 1.03) and **21c** ($[\alpha]_D^{25}$ = -28.6, EtOAc, c = 1.00) in moderate yields. Although the reaction suffered from lower yields, the optical purities of the oxazinanones with inverted stereochemistry are over 99% ee.[63]



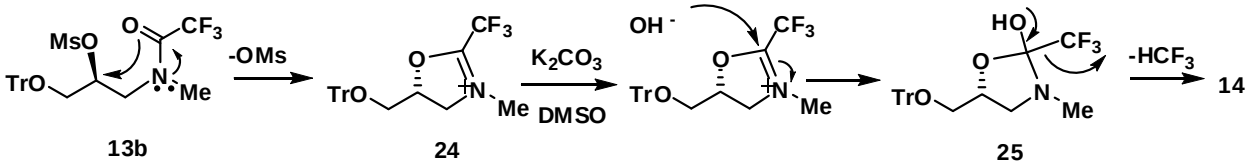
Scheme 3.2. Synthesis of both enantiomers of trityl protectected 1,3-oxazinan-2-ones (**19**, **21**) and oxazine **22**.

The 6-membered ring 2-oxazine homolog **22** can be synthesized by a similar method as the synthesis of 2-oxazoline **15**. The mesylate **20a** was converted to the 2-oxazine **22** and the hydrolysis of **22** using cesium carbonate gave the amino alcohol **23** with excellent yield. The isolated product amino alcohol **23** ($[\alpha]_D^{25}$ = +15.0, EtOH, c = 1.00) has reasonably good optical purity as compared to the optical rotation data of compound **17a** ($[\alpha]_D^{25}$ = -15.7, EtOH, c = 1.01).

The intramolecular S_N2 cyclizations in the 6-membered ring formation suffered lower yields than the 5-membered ring system. Several attempts using different bases, solvents and lengths of reaction time failed to improve the yield of the 1,3-oxazinan-2-ones. The *N*-benzyl derivative **21c** was obtained in 63% yield from the corresponding mesylate **20c**; we then synthesized the *N*-methyl derivatives considering the substituents on the nitrogen might affect the reaction outcome. The reaction of *N*-methyl derivative afforded poorer yield than the *N*-benzyl derivative. Compound **20b** in DMF treated with potassium carbonate and other bases only gave a small amount (20%) of the desired product **21b** with a large percentage of decomposition. When the reaction was done in DMSO with K_2CO_3 as the base, the desired product was obtained with a 55% yield. Therefore, this rearrangement reaction proved to be more effective for the formation of 5-membered ring system, which follows the established Baldwin's rules on the intramolecular cyclization reactions.

In the direct acyl transfer reaction leading to the cyclic carbamate with the same stereochemistry as the starting material, the cyclization occurred presumably by nucleophilic addition to the carbonyl group followed by elimination. Similar reactions are commonly used in the formation

of cyclic carbamates, these include using a *t*-Boc or Cbz derivative of the amines. For the S_N2 cyclization reaction leading to heterocycles with opposite stereochemistry, a possible mechanism is shown in Scheme 3.3 using the oxazolidinone as an example. The first step here is the displacement of the mesylate and maybe through the formation of an unstable intermediate **24**. The second step involves the attack of a base to the intermediate **24**, a hydroxide ion or other base present in the reaction attacks the carbon-2 and gives the tetrahedral intermediate **25** which then undergoes elimination to afford the 2-oxazolidinone **14**.

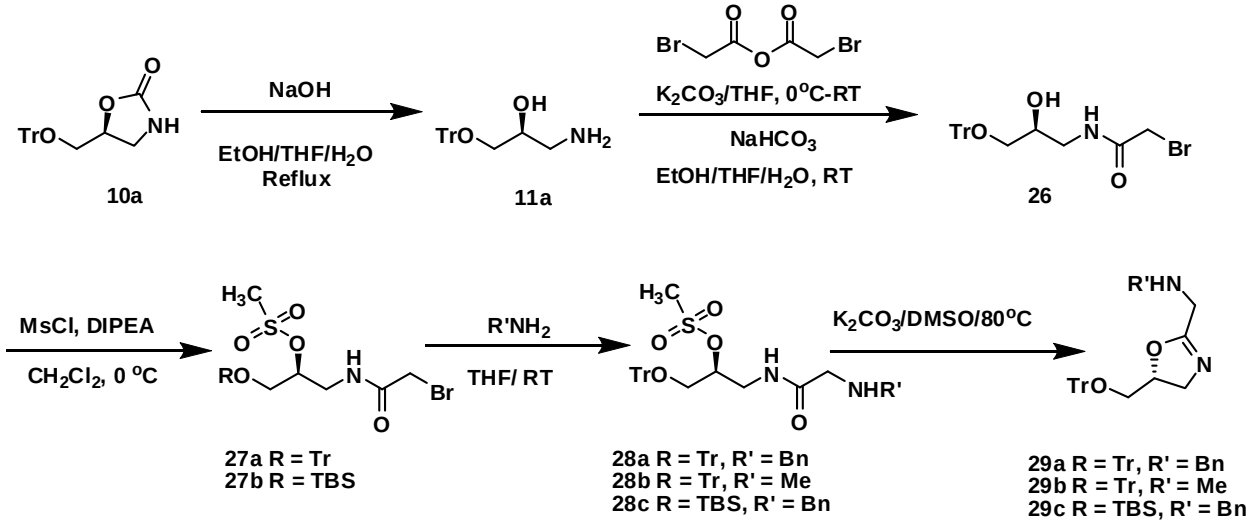


Scheme 3.3. A possible mechanism for the formation of 2-oxazolidinone **14**.

In our effort to go further in our exploration and development of synthetic methods to 2-oxazoline and 2-oxazine rings, we used 2-oxazolidinone **10a** and 1,3-amino alcohol **17a** as starting materials to carry out the synthesis of respectively 2-aminomethyl-1,3-oxazolines and 2-aminomethyl-1,3-oxazines, with complete inversion of the stereochemistry. Compared to their 2-trifluoromethyl analogs **15** and **22**, they possess a secondary amine site which could undergo further substitutions. These molecules could therefore be useful intermediates in the synthesis of more complex molecules such as hetereocyclic tertiary amines with a pharmacological potential.

The synthesis of 2-oxazolines **29a-c** was started with (*S*)-5-trityloxymethyl-oxazolidin-2-one **10a** (Scheme 3.4), which was decarbonylated by refluxing with NaOH in a mixture of THF, ethanol and water to give aminoalcohol **11a**. Compound **11** was reacted with bromoacetic anhydride,

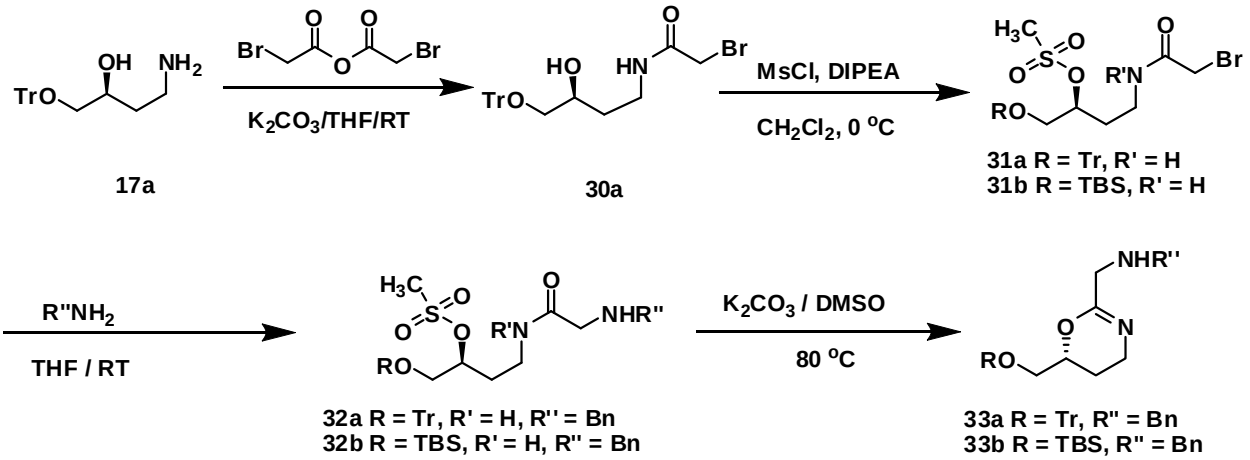
which affords mono and di-acetylated compounds. The ester was selectively hydrolyzed using sodium bicarbonate at room temperature to give β-hydroxyamide **26** quantitatively. The secondary alcohol of **26** was transformed into a good leaving group by mesylation with a very good yield to afford **27**. At this stage, cyclization into a 2-oxazoline was already possible, but the presence of the bromine atom proved to interfere and lower the yield. Substitution of the bromine of **27** with a primary amine to obtain **28** solved the problem, while it also increased the versatility of the molecule by adding another site of functionalization. Intermediate **28** was then cyclized into 2-oxazoline **29** with a good yield using potassium carbonate in DMSO at 80 °C. The reaction proceeds with complete inversion of stereochemistry from the starting (*S*)-2-oxazolidinone to the product (*R*)-2-oxazoline.



Scheme 3.4. Synthesis of 2-aminomethyl-oxazolines from 2-oxazolidinone **10a**.

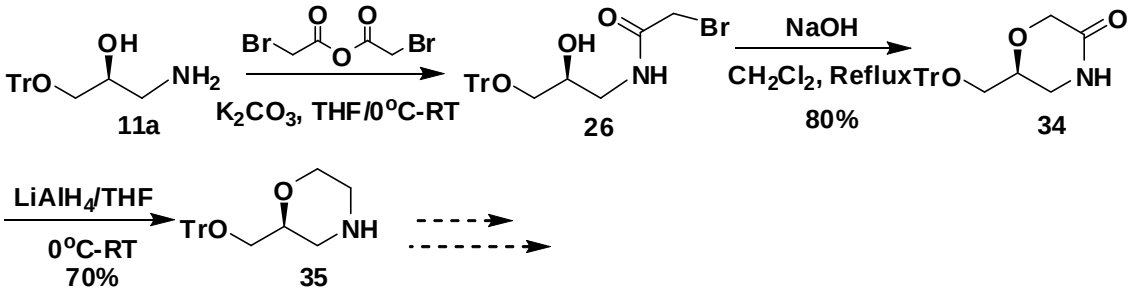
The synthesis of 2-oxazines **33a-c** started with the (*S*)-3-hydroxy-4-trityloxy-butyramine **17a**. The **17a** was selectively acylated using stoichiometric amount of bromoacetic acid to afford **30**. The secondary alcohol function was then mesylated to give **31** in a very good yield and the bromine atom was displaced by a primary amine to give intermediate **32**. The cyclization to the

2-oxazine **33** was achieved with a good yield and with complete inversion of the stereochemistry from the starting oxazinan-2-one.



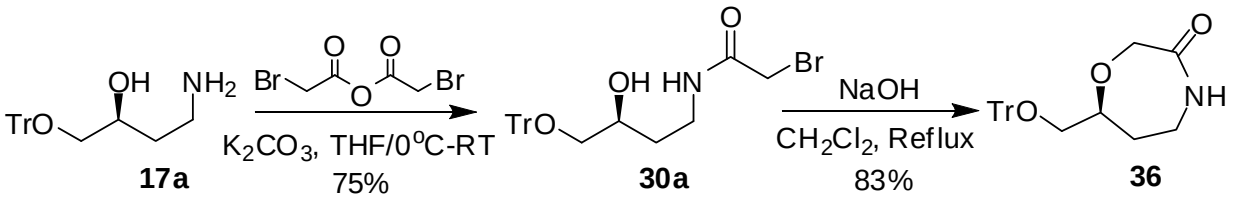
Scheme 3.5. Synthesis of 2-aminomethyl-oxazines from (*S*)-3-hydroxy-4-trityloxy-butyramide.

From bromoacetamide intermediates **26** and **30a**, the morpholin-3-one and the oxazepan-3-one respectively can also be synthesized. These heterocycles, like the previous ones synthesized in this project, can be found in pharmaceutically active compounds and present a good potential as synthetic intermediates. The synthesis of morpholin-3-one **34** was achieved by intramolecular cyclization of **26** using sodium hydroxide in refluxing dichloromethane (scheme 3.6). Compound **34** was subsequently reduced into morpholine **35**, which in turn could undergo further transformations towards the synthesis of biologically active molecules.



Scheme 3.6. Synthesis of morpholin-3-one **34** and morpholine **35**.

Following a similar procedure as the one used with intermediate **26**, the cyclization of the homologous bromoacetamide **30a** into oxazepan-3-one **36** was achieved by refluxing in dichloromethane in the presence of sodium hydroxide (Scheme 3.7).



Scheme 3.7. Synthesis of oxazepan-3-one **36** from intermediate **30a**.

Conclusions

We have developed an efficient method to convert chiral trityl protected 3-amino-1,2-propane diol and 4-amino-1,2-butane diol to the corresponding optically pure cyclic carbamate derivatives. Direct acyl transfer reactions under basic conditions led to cyclic carbamates with retention of stereochemistry; while intramolecular S_N2 cyclization yielded 2-oxazolidinones or 1,3-oxazinan-2-ones with inversion of stereochemistry. The direct acyl transfer cyclization using trifluoroacetamide intermediate can be used as a complementary method to cyclizations using *t*-Boc or Cbz carbamates as intermediates to synthesize cyclic carbamates. From bromoacetamide derivatives, direct acyl transfer lead to morpholin-3-ones and oxazepan-3-ones cycles. The intramolecular S_N2 cyclization methods can be used to synthesize oxazolidinones with inverted stereochemistry. Chiral 2,5-disubstituted oxazolines, 2,6-disubstituted oxazines, were also synthesized from the corresponding amino alcohols; hydrolysis of these heterocycles yielded amino alcohols with opposite configuration to that of the starting materials. The effective synthesis of these chiral heterocycles allows feasible access to a variety of biologically active compounds including antibacterial agents.

Experimental Section

(*S*)-3-Methyl-5-(trityloxymethyl)oxazolidin-2-one 10b. (*S*)-5-(Trityloxymethyl)oxazolidin-2-one **10a** (118 mg, 0.328 mmol) was dissolved in anhydrous THF (5 mL). The reaction flask was cooled to 0 °C and potassium tert-butoxide (74.0 mg, 0.660 mmol) was added to the solution which was stirred for 1 h. Iodomethane (0.051 mL, 0.819 mmol) was added to the mixture and the reaction was stirred at room temperature for 2 h after which NMR of the crude mixture showed all starting material had been transformed. The reaction flask was cooled to 0 °C and the reaction was quenched with cold methanol. The solvents were evaporated and the crude residue was taken up in dichloromethane. The solid residue was filtered out and the solvent was evaporated to afford a crude residue that was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 8:1:1. The pure product was isolated as a white solid (108 mg, 0.290 mmol). Yield: 88%. m.p. 157-158 °C $[\alpha]_D^{25}$ = +40.9 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.49-7.22 (m, 15H), 4.56 (m, 1H), 3.49 (t, 1H, J = 8.7 Hz), 3.34 (m, 2H), 3.22 (dd, 1H, J = 10.2, 4.5 Hz), 2.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 158.1, 143.4, 128.5, 127.9, 127.2, 86.8, 71.7, 64.3, 48.8. 30.9. HRMS calcd for $C_{24}H_{23}NO_3$. $[M+H]^+$ 374.1756, found 374.1748.

***(S)*-1-Amino-3-trityloxy-2-propanol 11a.** (*S*)-5-Trityloxymethyl-2-oxazolidinone **10a** (2.00 g, 5.56 mmol) was dissolved in a (1:1) mixture of ethanol and THF (40 mL). Sodium hydroxide (1.35 g, 33.8 mmol) in distilled water (10 mL) was added dropwise to the solution. The mixture was refluxed overnight. The solvents were evaporated and the residue taken-up in THF. A precipitate was formed and filtered out. The solution was concentrated to dryness under vacuum

and the crude was dried on the vacuum pump without further purification to afford a white semi-solid (1.85 g, 5.55 mmol). Yield: 100%. $[\alpha]_D^{25}$ = -15.9 (EtOH, c = 1.00). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.47-7.21 (m, 15H), 3.75 (m, 1H), 3.15 (d, 2H, J = 5.0 Hz), 2.77 (m, 2H), 2.09 (bs, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 143.8, 128.6, 127.8, 127.1, 86.6, 71.3, 65.6, 44.4. HRMS Calcd for $C_{22}H_{23}NO_2$ $[M+Na]^+$ 356.1651, found 356.1626.

(*S*)-1-(Methylamino)-3-(trityloxy)propan-2-ol 11b. (*S*)-3-Methyl-5-(trityloxymethyl)oxazolidin-2-one **10b** (154 mg, 0.412 mmol) was dissolved in a mixture of THF and ethanol (2 mL each). Lithium hydroxide (100 mg, 4.18 mmol) and sodium hydroxide (85.0 mg, 2.12 mmol) were dissolved in water (4 mL) and added to the solution. The mixture was refluxed for 48 h and the solvents were evaporated. The crude residue was taken-up in THF and the insoluble salts were filtered out; the THF was evaporated and the crude product was purified on silica gel with a gradient of hexane:CH_2Cl_2 1:9 to CH_2Cl_2:methanol 9:1. The product was obtained as a light brown semi-solid (120 mg, 0.345 mmol). Yield: 84%. $[\alpha]_D^{25}$ = -14.2 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.47-7.19 (m, 15H), 3.90 (m, 1H), 3.17 (m, 2H), 2.67 (m, 2H), 2.42 (s, 3H), 2.34 (bs, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 143.8, 128.6, 127.7, 126.9, 86.6, 68.6, 66.2, 54.3, 35.9. HRMS calcd for $C_{23}H_{25}NO_2$. $[M+H]^+$ 348.1964, found 348.1961.

(*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)acetamide 12a. (*S*)-1-Amino-3-(trityloxy)propan-2-ol **11a** (1.00 g, 3.00 mmol) was dissolved in anhydrous THF (25 mL). The solution was stirred at 0 °C for about 5 min then potassium carbonate (2.50 g, 18.1 mmol) was added to the solution. After another 5 min, trifluoroacetic anhydride (0.500 mL, 3.54 mmol) was

added and the mixture was stirred for 30 min at 0 °C. The solution was diluted with CH_2Cl_2 and the K_2CO_3 was filtered out. The organic solvents were evaporated on the rotovap, the crude mixture taken up in CH_2Cl_2 and washed with water twice. The dichloromethane was then evaporated and the crude mixture purified on SiO_2 gel using a gradient of solvent of pure hexane to hexane:CH_2Cl_2:THF 6:3:1. The pure product was obtained as an off-white solid (1.01 g, 2.33 mmol). Yield: 78%. m.p. 98-100 °C $[\alpha]_D^{25}$ = -19.2 (EtOH, c = 1.03). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.41-7.12 (m, 15H), 7.04 (bs, 1H), 3.82 (m, 1H), 3.49 (m, 1H), 3.23 (dd, 1H, *J* = 12.8, 5.9 Hz), 3.17 (dd, 1H, *J* = 9.1, 4.1 Hz), 3.08 (dd, 1H, *J* = 9.1, 5.4 Hz), 3.00 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 157.5 (q, C=O, ^2J = 36.5 Hz), 143.2, 128.4, 127.9, 127.2, 115.7 (q, CF_3, ^1J = 287.9), 87.0, 68.8, 64.9, 42.7. HRMS calcd for $C_{24}H_{22}F_3NO_3$ $[M+Na]^+$ 452.1449, found 452.1440.

(*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)-*N*-methylacetamide 12b. (*S*)-1-(Methylamino)-3-(trityloxy)propan-2-ol **11b** (172 mg, 0.495 mmol) was dissolved in anhydrous THF (4 mL) and the reaction was cooled to -20 °C. DIPEA (0.431 mL, 2.47 mmol) was added and the reaction was stirred for 5 min. Trifluoroacetic anhydride (0.077 mL, 0.545 mmol) was then added and the reaction was stirred for about 40 min at -20 °C. The solvent was evaporated to dryness and the crude residue was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 20:1:1. The clean product was isolated as a brown oil (158 mg, 0.356 mmol). Yield: 72% $[\alpha]_D^{25}$ = -17.7 (EtOAc, c = 1.01). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.49-7.23 (m, 15H), 4.08 (m, 1H), 3.61 (dd, 1H, *J* = 13.9, 3.6 Hz), 3.51 (dd, 1H, *J* = 13.6, 7.9 Hz), 3.30 (dd, 1H, *J* = 9.5, 4.8 Hz), 3.17 (m, 1H), 3.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major rotomer) 157.9 (q, C=O, ^2J = 35.9 Hz), 143.4, 128.5, 127.9, 127.2, 116.4 (q, CF_3, ^1J = 287.6 Hz),

87.0, 69.3, 65.2, 53.1, 36.7 (q, CH_3, ^4J = 3.7 Hz). (minor rotomer) 157.8 (q, C=O, ^2J = 35.9 Hz), 143.3, 128.5, 127.9, 127.3, 116.5 (q, CF_3, ^1J = 287.9 Hz), 87.1, 69.7, 65.4, 53.2 (q, CH_2N, ^4J = 2.1 Hz), 35.9. HRMS calcd for $C_{25}H_{24}F_3NO_3$. $[M+Na]^+$ 466.1606, found 466.1614.

(*S*)-1-(2,2,2-Trifluoroacetamido)-3-(trityloxy)propan-2-yl methanesulfonate 13a. (*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)acetamide **12a** (880 mg, 2.05 mmol) was dissolved in anhydrous dichloromethane (20 mL). The solution was cooled to 0 °C and methanesulfonate chloride (0.240 mL, 3.09 mmol) was added. After 1 min, diisopropylethylamine (1.00 mL, 5.74 mmol) was added and the mixture was stirred for 40 min. Ice water (2-3 mL) was added to quench the reaction and the organic phase was separated. Dichloromethane was evaporated and the crude mixture purified on SiO_2 gel using a gradient of pure hexane to hexane:CH_2Cl_2:THF 8:1:1. The pure product was obtained as a white solid (948 mg, 1.87 mmol). Yield: 91%. m.p. 118-119 °C $[\alpha]_D^{25}$ = -10.1 (EtOAc, c = 1.04). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.37-7.18 (m, 15H), 6.83 (bs, 1H), 4.75 (m, 1H), 3.71 (m, 1H), 3.47 (m, 1H), 3.39 (dd, 1H, *J* = 11.3, 4.4 Hz), 3.27 (dd, 1H, *J* = 10.9, 5.5 Hz), 2.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 157.6 (q, C=O, ^2J = 38.4 Hz), 142.9, 128.4, 128.1, 127.5, 115.6 (q, CF_3, ^1J = 287.9 Hz), 87.5, 78.2, 63.3, 40.9, 38.4. HRMS calcd for $C_{25}H_{24}F_3NO_5S$ $[M+Na]^+$ 530.1225, found 530.1219.

(*S*)-1-(2,2,2-Trifluoro-*N*-methylacetamido)-3-(trityloxy)propan-2-yl-methanesulfonate 13b. (*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-3-(trityloxy)propyl)-*N*-methylacetamide **12b** (336 mg, 0.758 mmol) was dissolved in anhydrous dichloromethane (10.0 mL). The solution was stirred at 0 °C for 5 min and methanesulfonyl chloride (0.100 mL, 1.29 mmol) followed by DIPEA (0.400 mL, 2.29 mmol) were added to the mixture and the reaction was stirred at 0 °C for 30 min. The

solvent was evaporated to dryness and the crude residue purified on silica gel with a solvent system of hexane:dichloromethane:THF 10:1:1 to afford a white solid (375 mg, 0.720 mmol). Yield: 95%. m.p. 47-48 °C $[\alpha]_D^{25}$ = -8.4 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.97-7.26 (m, 15H), 7.25 (bs ,1H), 5.00 (m, 1H), 3.75 (dd, 1H, J = 14.2, 4.0 Hz), 3.63 (dd, 1H, J = 14.2, 8.2 Hz), 3.47 (dd, 1H, J =11.1, 3.5 Hz), 3.31 (dd, 1H, J =11.1, 5.6 Hz), 3.20 (s, 3H), 3.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 157.7 (q, C = O, ^2J = 36.5 Hz), 143.0, 128,5, 128.0, 127.9, 116.1 (q, CF_3, ^1J = 287.7 Hz), 87.5, 78.0, 63.4, 51.2, 38.4, 36.9 (q, CH_3, ^4J = 3.8 Hz). (minor tautomer) 157.8 (q, C=O, ^2J = 38.4 Hz), 142.9, 128.4, 128.1, 127.5, 116.2 (q, CF_3, ^1J = 288.7 Hz), 87.6, 77.9, 63.3, 50.2, 38.7, 35.6. HRMS calcd for $C_{26}H_{26}F_3NO_5S$ $[M+Na]^+$ 544.1381, found 544.1392.

(*R*)-3-Methyl-5-(trityloxymethyl)oxazolidin-2-one 14. (*S*)-1-(2,2,2-Trifluoro-*N*-methylacetamido)-3-(trityloxy)propan-2-yl-methanesulfonate **13b** (87.0 mg, 0.167 mmol) was dissolved in DMF (4.00 mL). Potassium carbonate (92.0 mg, 0.667 mmol) was added and the solution was stirred at 120 °C for 45 min. The K_2CO_3 was filtered out and the solvent was evaporated to dryness under nitrogen and then under vacuum. The pure product was obtained as a white solid (57.0 mg, 0.153 mmol). Yield: 92%. m.p. 154-155 °C $[\alpha]_D^{25}$ = -41.0 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.46-7.22 (m, 15H), 4.60 (m, 1H), 3.55 (t, 1H, J = 8.7 Hz), 3.35 (m, 2H), 3.22 (dd, 1H, J = 10.2, 4.6 Hz), 2.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 158.1, 143.4, 128.5, 127.9, 127.2, 86.7, 71.7, 48.8, 30.9. HRMS calcd for $C_{24}H_{23}NO_3$ $[M+H]^+$ 374.1756, found 374.1764.

(*R*)-2-(Trifluoromethyl)-5-(trityloxymethyl)-oxazoline 15. (*S*)-1-(2,2,2-Trifluoroacetamido)-3-(trityloxy) propan-2-yl methanesulfonate **13a** (106 mg, 0.210 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (10.0 mL). Potassium carbonate (60.0 mg, 0.434 mmol) was added and the solution was stirred at 85 °C for 1 h. The K_2CO_3 was then filtered out and the DMF evaporated. The crude mixture was clean enough after drying under vaccum and did not require purification. The product was obtained as a white solid (81.6 mg, 0.198 mmol). Yield: 94%. m.p. 180-182 °C $[\alpha]_D^{25}$ = -43.5 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.50-7.26 (m, 15H), 4.99 (m, 1H), 4.07 (m, 1H), 3.93 (dd, 1H, J = 14.3, 6.6 Hz), 3.21 (dd, 1H, J = 10.7, 4.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 155.2 (q, C=N, ^2J = 39.9 Hz), 143.3, 128.5, 127.9, 127.2, 116.4 (q, CF_3, ^1J = 274.4 Hz), 86.7, 81.3, 64.3, 56.4. HRMS calcd for $C_{24}H_{20}F_3NO_2$ $[M+Na]^+$ 412.1524, found 412.1542.

(*R*)-1-Amino-3-(trityloxy)propan-2-ol 16. (*R*)-2-(Trifluoromethyl)-5-(trityloxymethyl)-oxazoline **15** (88.9 mg, 0.216 mmol) was dissolved in a mixture of THF and EtOH (5.00 mL each). Sodium hydroxide (94.0 mg, 2.35 mmol) was dissolved in 2 mL of H_2O and added to the solution. The reaction was refluxed for 14 h then the solvents were evaporated. The crude residue was taken up in CH_2Cl_2 and the solid salts were filtered out. The solvent was evaporated and the crude product was purified on SiO_2 gel using solvent system of CH_2Cl_2:MeOH 95:5. After drying under vacuum a colorless semi-solid was obtained (43.0 mg, 0.129 mmol). Yield: 60%. $[\alpha]_D^{25}$ = +15.3 (EtOH, c = 1.10). ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.48-7.19 (m, 15H), 3.79 (m, 1H), 3.17 (m, 5H), 2.84 (m, 1H), 2.72 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 143.7, 128.6, 127.8, 126.9, 86.6, 70.6, 65.6, 44.2.

(*S*)-4-(Benzylamino)butane-1,2-diol 17c. (*S*)-*N*-Benzyl-3-hydroxy-4-(trityloxy)butanamide (160 mg, 0.354 mmol) was dissolved in anhydrous THF (4 mL). Lithium aluminum hydride (41.0 mg, 1.08 mmol) was added at 0 °C and the mixture was stirred for 48 h. The mixture was cooled to 0 °C and the reaction was quenched by addition of cold methanol and water. The aluminum salts formed were filtered out, and after concentration, the crude product was purified on silica gel with a gradient of CH_2Cl_2:hexane 9:1 to CH_2Cl_2:MeOH 20:1. The pure product was dried on vacuum pump and obtained as a white solid (109 mg, 0.249 mmol). Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.49-7.22 (m, 20H), 4.05 (m, 1H), 3.77 (dd, 2H, J = 19.4, 13.1 Hz), 3.22 (dd, 1H, J = 9.0, 5.7 Hz), 3.06 (dd, 1H, J = 9.0, 5.8 Hz), 2.94 (m, 1H), 2.81 (m, 1H), 1.81 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 144.0, 139.3, 128.6, 128.4, 128.1, 127.7, 127.1, 126.9, 86.3, 71.9, 67.4, 53.7, 47.4, 32.2. HRMS calcd for $C_{30}H_{31}NO_2$ $[M+H]^+$ 438.2433, found 438.2418.

(*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl) acetamide 18a. (*S*)-4-Amino-1-(trityloxy)butan-2-ol **17a** (583 mg, 1.68 mmol) was dissolved in anhydrous THF (10.0 mL). Pyridine (0.405 mL, 5.03 mmol) was added to the solution which was stirred for 30 min. Trifluoroacetic anhydride (0.475 mL, 3.36 mmol) was added to the mixture and after stirring for another 30 min, the reaction was quenched with ice-water (2 mL). The solvent was then evaporated and the crude residue was dissolved in CH_2Cl_2 and washed twice with water and once with brine. The organic phase was then evaporated and the crude residue was purified on SiO_2 gel using a gradient of pure hexane to hexane:CH_2Cl_2:THF 9:1:1. The pure product was obtained as a white solid (565 mg, 1.27 mmol). Yield: 76%. m.p. 80-82 °C $[\alpha]_D^{25}$ = +16.3 (CH_2Cl_2, c = 1.04). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.60 (bs, 1H), 7.48-7.24 (m, 15H), 3.93 (m, 1H), 3.65 (m,

1H), 3.32 (m, 1H), 3.21 (dd, 1H, J = 9.5, 3.8 Hz), 3.13 (m, 1H), 2.93 (bs, 1H), 1.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 157.1 (q, C=O, ^2J = 36.5 Hz), 143.5, 128.5, 127.9, 127.2, 115.9 (q, CF_3, ^1J = 287.9 Hz), 86.9, 70.7, 67.3, 37.9, 30.9. HRMS calcd for $C_{25}H_{24}F_3NO_3$ $[M+Na]^+$ 466.1606, found 466.1598.

(*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-*N*-methylacetamide 18b. This compound was prepared via a similar method as the one used for the synthesis of **18a**. Compound **17b** (300 mg, 0.830 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 15:1:1. The pure product was obtained as a white solid (318 mg, 0.700 mmol). Yield: 86%. m.p. 106-107 °C $[\alpha]_D^{25}$ = -14.0 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.52-7.23 (m, 15H), 3.73 (m, 2H), 3.43 (m, 1H), 3.20 (m, 2H), 3.10 (s, 2H), 2.98 (s, 1H), 2.84 (bs, 1H), 1.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 156.9 (q, C=O, ^2J = 35.7 Hz), 143.6, 128.5, 127.7, 126.9, 116.3 (q, CF_3, ^1J = 287.7 Hz), 86.6, 67.9, 67.4, 46.5, 35.0 (q, CH_3, ^4J = 3.8 Hz), 30.2. (minor tautomer) 156.7 (q, C=O, ^2J = 35.7 Hz), 143.5, 128.4, 127.8, 127.0, 116.4 (q, CF_3, ^1J = 287.6 Hz), 86.7, 68.2, 67.3, 46.4, 34.5, 32.0. HRMS calcd for $C_{26}H_{26}F_3NO_3$ $[M+Na]^+$ 480.1762, found 480.1764.

(*S*)-*N*-Benzyl-2,2,2-trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-acetamide 18c. This compound was prepared via a similar method as the one used for the synthesis of **18a**. Compound **17c** (88.6 mg, 0.202 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 15:1:1. The pure product was obtained as a white solid (85.0 mg, 0.159 mmol). Yield: 79%. m.p. 139-140 °C $[\alpha]_D^{25}$ = -16.8 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.47-7.21 (m, 20H), 4.67 (m, 2H), 3.74 (m,

1H), 3.56 (m, 1H), 3.40 (m, 1H), 3.17 (m, 1H), 3.10 (m, 1H), 1.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major rotomer) 157.3 (q, C=O, ^2J = 35.7 Hz), 143.5, 134.8, 128.7, 128.5, 127.9, 127.8, 127.2, 127.1, 116.5 (q, CF_3, ^1J = 287.9 Hz), 86.7, 68.1, 67.2, 49.4, 43.4, 30.3. (minor rotomer) 157.3 (q, C=O, ^2J = 35.7 Hz), 143.7, 135.4, 128.9, 128.7, 128.1, 127.9, 127.2, 127.1, 116.6 (q, CF_3, ^1J = 287.9 Hz), 86.8, 68.4, 67.3, 50.9 (q, CH_2Ph, ^4J = 3.1 Hz), 43.7 (q, CH_2N, ^4J = 2.9 Hz), 32.2. HRMS calcd for $C_{32}H_{30}F_3NO_3$ $[M+Na]^+$ 556.2075, found 556.2090.

(*S*)-3-Methyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 19b. (*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-*N*-methylacetamide **18b** (54.0 mg, 0.118 mmol) was dissolved in anhydrous DMF (5.00 mL). Lithium hydroxide (31.0 mg, 1.30 mmol) was added and the solution was stirred at 65 °C for 12 h. The organic solvent was evaporated and the crude mixture taken-up in CH_2Cl_2. The solid LiOH was filtered out and the solvent evaporated under nitrogen. The crude residue was purified on silica gel with a solvent system of hexane:THF:CH_2Cl_2 15:1:1. The pure product was isolated as white crystals (41.2 mg, 0.106 mmol). Yield: 90%. m.p. 160.5-161 °C. $[\alpha]_D^{25}$ = + 32.5 (EtOAc, c = 1.03). ($CDCl_3$, 400 MHz); δ 7.45-7.19 (m, 15H), 4.34 (m, 1H), 3.35 (dd, 1H, *J* = 9.8, 4.7 Hz), 3.31 (dd, 1H, *J* = 11.5, 5.7 Hz), 3.21 (m, 2H), 2.97 (s, 3H), 2.08 (m, 1H), 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 153.6, 143.5, 128.6, 127.8, 127.1, 86.8, 75.7, 64.7, 46.1, 36.5, 24.6. HRMS calcd for $C_{25}H_{25}NO_3$ $[M+Na]^+$ 410.1732, found 410.1737.

(*S*)-3-Benzyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 19c. (*S*)-*N*-Benzyl-2,2,2-trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)-acetamide **18c** (156 mg, 0.292 mmol) was dissolved in anhydrous THF (4.00 mL). The mixture was cooled to 0 °C and sodium hydride (14.0 mg, 0.583 mmol) was added. The solution was stirred for 20 min and quenched by addition of methanol. The solvent

was evaporated and the crude mixture was taken up in CH_2Cl_2. The organic solvent was washed with H_2O three times, separated from the aqueous solvent and dried on Na_2SO_4. After filtration, the solvent was evaporated and the residue was dried under vacuum. The pure product (120 mg, 0.260 mmol) was obtained without further purification. Yield: 89%. m.p. 167-168 °C $[\alpha]_D^{25}$ = +29.0 (EtOAc, c = 1.01). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.52-7.25 (m, 20H), 4.60 (dd, 2H, J = 21.1, 14.9 Hz), 4.43 (m, 1H), 3.43 (dd, 1H, J = 9.7, 4.7 Hz), 3.23 (m, 3H), 2.10 (m, 1H), 1.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 153.5, 143.4, 136.5, 128.5, 128.4, 127.9, 127.7, 127.5, 127.0, 86.6, 75.7, 64.6, 52.4, 43.2, 24.5. HRMS calcd for $C_{31}H_{29}NO_3$ $[M+H]^+$ 464.2226, found 464.2222.

(*S*)-4-(2,2,2-Trifluoroacetamido)-1-(trityloxy)butan-2-yl methanesulfonate 20a. (*S*)-2,2,2-Trifluoro-*N*-(3-hydroxy-4-(trityloxy)butyl)acetamide **18a** (486 mg, 1.10 mmol) was dissolved in anhydrous CH_2Cl_2 (10.0 mL). The solution was cooled to 0 °C. Methanesulfonyl chloride (0.130 mL, 1.67 mmol) was added, followed by diisopropylethylamine (0.570 mL, 3.30 mmol). The mixture was stirred at 0 °C for 30 min and some ice-water was added to quench the reaction. The solution was diluted with dichloromethane and washed twice with water. The organic solvent was evaporated and the crude residue purified on SiO_2 gel using a gradient of pure hexane to hexane:CH_2Cl_2:THF 8:1:1. The pure product was obtained as a colorless semi-solid (536 mg, 1.03 mmol). Yield: 94%. $[\alpha]_D^{25}$ = - 17.7 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.45-7.22 (m, 15H), 7.18 (bs, 1H), 4.61 (m, 1H), 3.59 (m, 1H), 3.38 (m, 2H), 3.27 (m, 1H), 3.02 (s, 3H), 1.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 157.3 (q, C=O, ^2J = 36.5 Hz), 143.0, 128.4, 128.0, 127.4, 115.7 (q, CF_3, ^1J = 287.9 Hz), 87.6, 79.7, 65.4, 38.6, 35.4, 30.6. HRMS calcd for $C_{26}H_{26}F_3NO_5S$ $[M+Na]^+$ 544.1381, found 544.1368.

(*S*)-4-(2,2,2-Trifluoro-*N*-methylacetamido)-1-(trityloxy)butan-2-ylmethanesulfonate 20b. This compound was prepared via a similar method as the one used for the synthesis of **20a**. Compound **18b** (194 mg, 0.424 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 15:1:1. The pure product was obtained as a brown oil (215 mg, 0.401 mmol). Yield: 95%. $[\alpha]_D^{25}$ = +5.8 (EtOAc, c = 1.05). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.47-7.24 (m, 15H), 4.77 (m, 1H), 3.42 (m, 4H), 3.10 (s, 2H), 3.04 (s, 2H), 3.03 (s, 1H), 2.99 (s, 1H), 1.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 156.9 (q, C=O, ^2J = 35.7 Hz), 143.1, 128.5, 127.9, 127.3, 116.3 (q, CF_3, ^1J = 287.7 Hz), 87.4, 79.6, 64.9, 46.0, 38.7, 35.2 (q, CH_3, ^4J = 3.9 Hz), 28.7. (minor tautomer) 156.9 (q, C=O, ^2J = 35.7 Hz), 143.0, 128.4, 128.0, 127.4, 116.4 (q, CF_3, ^1J = 287.3 Hz), 87.5, 78.7, 64.5, 45.7 (q, CH_2N, ^4J = 2.9 Hz), 38.6, 34.6, 30.7. HRMS calcd for $C_{27}H_{28}F_3NO_5S$ $[M+Na]^+$ 558.1538, found 558.1532.

(*S*)-4-(*N*-Benzyl-2,2,2-trifluoroacetamido)-1-(trityloxy)butan-2-yl methanesulfonate 20c. This compound was prepared via a similar method as the one used for the synthesis of **20a**. Compound **18c** (1.03 g, 1.93 mmol) was used as the starting material. The crude product was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 15:1:1. The pure product was obtained as a colorless semi-solid (1.11 g, 1.81 mmol). Yield: 94%. $[\alpha]_D^{25}$ = +3.50 (EtOAc, c = 1.03). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.43-7.14 (m, 20H), 4.67 (m, 1H), 4.60 (m, 2H), 3.33 (m, 2H), 3.26 (m, 2H), 2.98 (s, 3H), 1.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ (major tautomer) 157.1 (q, C=O, ^2J = 35.1 Hz), 143.1, 134.4, 129.0, 128.9, 128.4, 127.9, 127.4, 127.3, 116.4 (q, CF_3, ^1J = 287.9 Hz), 87.2, 78.5, 64.5, 49.6, 42.9, 38.7, 28.7. (minor tautomer) 157.7 (q, C=O, ^2J = 35.1 Hz), 143.1, 135.1, 129.0, 128.9, 128.3, 128.1, 127.4, 127.3, 116.5 (q, CF_3, ^1J = 288 Hz),

87.4, 78.5, 64.6, 51.2, 42.8, 38.6, 30.8. HRMS calcd for $C_{33}H_{32}F_3NO_5S$ $[M+Na]^+$ 634.1851, found 634.1853.

(*R*)-3-Methyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 21b. (*S*)-4-(2,2,2-Trifluoro-*N*-methylacetamido)-1-(trityloxy)butan-2-ylmethanesulfonate **20b** (147 mg, 0.247 mmol) was dissolved in anhydrous DMSO (4.00 mL). Potassium carbonate (114 mg, 0.825 mmol) was added and the solution was stirred at 120 °C for 3 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with cold water 3 to 4 times. The dichloromethane was evaporated and the crude mixture was purified on silica gel with a solvent system of hexane:CH_2Cl_2:THF 12:1:1. The pure product was isolated as a white solid (58.0 mg, 0.150 mmol). Yield: 55%. m.p. 163-164 °C $[\alpha]_D^{25}$ = -31.9 (EtOAc, c = 1.03). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.45-7.20 (m, 15H), 4.33 (m, 1H), 3.35 (dd, 1H, J = 9.7, 4.7 Hz), 3.30 (dd, 1H, J = 10.9, 5.5 Hz), 3.21 (m, 2H), 2.96 (s, 3H), 2.07 (m, 1H), 1.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 153.6, 143.5, 128.6, 127.8, 127.1, 86.7, 75.7, 64.7, 46.0, 36.5, 24.6. HRMS calcd for $C_{25}H_{25}NO_3$ $[M+H]^+$ 388.1913, found 388.1897.

(*R*)-3-Benzyl-6-(trityloxymethyl)-1,3-oxazinan-2-one 21c. (*S*)-4-(*N*-Benzyl-2,2,2-trifluoroacetamido)-1-(trityloxy)butan-2-yl methanesulfonate **20c** (600 mg, 0.980 mmol) was dissolved in anhydrous DMF (5.00 mL) and potassium carbonate (0.542 g, 3.92 mmol) was added to the solution. The mixture was stirred at 120 °C for 20 h. The organic was evaporated under nitrogen overnight and the residue taken up in CH_2Cl_2. The solid K_2CO_3 was filtered out and the solution concentrated to dryness. The crude product was purified on silica gel with a gradient of hexane:THF 19:1 to hexane:CH_2Cl_2:THF 8:1:1. The pure product was dried under

vacuum and obtained as a white solid (281 mg, 0.606 mmol). Yield: 63%. m.p. 166-167 °C $[\alpha]_D^{25}$ = -28.6 (EtOAc, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.52-7.23 (m, 20H), 4.58 (dd, 2H, J = 21.9, 14.9 Hz), 4.39 (m, 1H), 3.42 (dd, 1H, J = 9.7, 4.8 Hz), 3.23 (m, 1H), 3.15 (m, 2H), 1.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 153.5, 143.4, 136.5, 128.5, 128.4, 127.8, 127.7, 127.4, 127.0, 86.6, 75.7, 64.6, 52.3, 43.2, 24.4. HRMS calcd for $C_{31}H_{29}NO_3$ $[M+H]^+$ 464.2226, found 464.2232.

(*R*)-2-(Trifluoromethyl)-6-(trityloxymethyl)-5,6-dihydro-4H-1,3-oxazine 22. (*S*)-4-(2,2,2-Trifluoroacetamido)-1-(trityloxy)butan-2-yl methanesulfonate **20a** (91.5 mg, 0.175 mmol) was dissolved in anhydrous dimethylformamide (5.00 mL). Potassium carbonate (97.0 mg, 0.702 mmol) was added and the solution stirred at 85 °C for 45 min. The solvent was then evaporated under nitrogen and the crude mixture purified on SiO_2 gel using a solvent system of hexane:CH_2Cl_2:THF 8:1:1. The pure product was obtained as an off-white solid (58.4 mg, 0.137 mmol). Yield: 78%. m.p. 106-108 °C $[\alpha]_D^{25}$ = - 46.1 (CH_2Cl_2, c = 1.03). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.49-7.21 (m, 15H), 4.42 (m, 1H), 3.54 (m, 2H), 3.27 (m, 2H), 1.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 148.4 (q, C=N, ^2J = 38.4 Hz), 143.9, 129.0, 128.4, 127.6, 117.2 (q, CF_3, ^1J = 276.4 Hz), 87.2, 75.9, 65.6, 42.2, 23.8. HRMS calcd for $C_{25}H_{22}F_3NO_2$ $[M+H]^+$ 426.1681, found 426.1672.

(*R*)-4-Amino-1-(trityloxy)butan-2-ol 23. (*R*)-2-(Trifluoromethyl)-6-(trityloxymethyl)-5,6-dihydro-4H-1,3-oxazine **22** (65.6 mg, 0.154 mmol) was dissolved in absolute ethanol (6 mL). Cesium carbonate (0.500 g, 1.53 mmol) dissolved in 2.00 mL of water was added to the solution which was refluxed for 36 h. The solvents were evaporated and the crude mixture was taken up

in CH_2Cl_2. The insoluble salts were filtered out and the organic phase was washed one with water. After drying on Na_2SO_4, the solvent was evaporated and after drying under vacuum, the product was obtained as a colorless semi-solid (52.6 mg, 0.151 mmol). Yield: 98%. $[\alpha]_D^{25}$ = +15.0 (EtOH, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ 7.53-7.19 (m, 16H), 4.02 (m, 1H), 3.18 (dd, 1H, *J* = 9.1, 6.1 Hz), 3.08 (dd, 1H, *J* = 9.1, 5.4 Hz), 2.95 (m, 1H), 2.85 (m, 1H), 1.67 (m, 1H), 1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.5 MHz); δ 143.9, 128.6, 127.8, 126.9, 86.4, 71.2, 67.6, 38.9, 35.1.

(*S*)-2-Bromo-*N*-(2-hydroxy-3-trityloxypropyl)-acetamide 26. *(S)*-1-Amino-3-trityloxy-propan-2-ol **11a** (0.990 g, 2.97 mmol) was dissolved in anhydrous THF (10.0 mL). The reaction was put at 0 °C and bromoacetic anhydride (0.926 g, 3.56 mmol) and potassium carbonate (0.820 g, 5.94 mmol) were added to the solution. After stirring at 0 °C for 30 min and at room temperature for 2 to 3 h, the K_2CO_3 was filtered out and the THF evaporated on the rotovap. Ice-water (2-3 mL) was then added and the di-acetylated product was extracted with EtOAc. After evaporating the ethyl acetate, the product was directly stirred with $NaHCO_3$ in a (1:1:1) mixture of ethanol, THF and H_2O at room temperature for 12 h. The EtOH and THF were removed by concentration on the rotovap and the mono-acetylated product was extracted with CH_2Cl_2. After removing the dichloromethane on the rotovap a white-brown semi-solid product was obtained (1.34 g, 2.94 mmol). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.54-7.15 (m, 15H), 6.77 (bs, 1H), 3.91 (m, 1H), 3.78 (s, 2H), 3.54 (m, 1H), 3.27 (m, 1H), 3.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.3, 143.5, 128.5, 127.9, 127.2, 86.9, 69.7, 64.9, 43.1, 28.9. HRMS ES+ calcd for $C_{24}H_{24}BrNO_3$ $[M+Na]^+$ 476.0837, found 476.0839.

(*S*)-Methanesulfonic acid 2-(2-Bromo-acetylamino)-1-trityloxymethyl-ethyl ester 27a. (*S*)-2-Bromo-*N*-(2-hydroxy-3-trityloxypropyl)-acetamide **26** (310 mg, 0.682 mmol), was dissolved in anhydrous CH_2Cl_2 (5 mL) and the reaction was put in an ice-bath, at 0 °C. Methanesulfonyl chloride (0.080 mL, 1.02 mmol) was added to the solution, then Diisopropylethylamine (0.350 mL, 2.05 mmol) and the reaction was stirred for 5 min. The solution was then washed with ice-cold H_2O (2 X 2 mL) and with brine (2 mL). The organic phase was evaporated under nitrogen. The crude mixture was purified on SiO_2 gel with a gradient of pure hexane to hexane:CH_2Cl_2:THF 7:2:1 to afford a white solid (357 mg, 0.670 mmol). Yield: 98%. $[\alpha]_D^{25}$ = + 11.1 (*c* 1.04, EtOAc).^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.45-7.24 (m, 15H), 6.78 (bs, 1H), 4.84 (m, 1H), 3.78 (q, 2H, J = 13.7 Hz), 3.67 (m, 1H), 3.50-3.40 (m, 2H), 3.30 (m, 1H), 3.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.2, 143.0, 128.5, 127.9, 127.4, 87.3, 79.4, 63.3, 41.2, 38.5, 28.6. HRMS ES+ calcd for $C_{25}H_{26}BrNO_5S$ $[M+Na]^+$ 554.0613, found 554.0612.

(*S*)-Methanesulfonic acid 3-(2-bromo-acetylamino)-1-(t-butyl-dimethyl-silyloxymethyl)-propyl ester 27b. Yield: 61% ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.23 (bs, 1H), 4.66 (m, 1H), 3.99 (s, 2H), 3.70 (m, 2H), 3.59 (m, 1H), 3.25 (m, 1H), 3.07 (s, 2H), 1.89 (m, 1H), 1.76 (m, 1H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.7, 81.4, 65.0, 42.4, 38.4, 35.4, 30.5, 25.7, -5.6.

(*S*)-Methanesulfonic acid 2-(2-benzylamino-acetylamino)-1-trityloxymethyl-ethyl ester 28a. (*S*)-Methanesulfonic acid 2-(2-Bromo-acetylamino)-1-trityloxymethyl-ethyl ester **27a** (200 mg, 0.376 mmol) was dissolved in anhydrous THF (5.00 mL). Benzylamine (0.120 mL, 1.10 mmol) was added and the reaction was stirred at 35 ºC for 1 h. The THF was evaporated and the solid

residue was taken up in dichloromethane and washed with water and brine. The CH_2Cl_2 was then evaporated and the crude mixture purified on SiO_2 gel with a gradient of pure hexane to hexane:CH_2Cl_2:THF 6:3:1 to afford the pure product as a light yellow oil (187 mg, 0.334 mmol). Yield: 89%. $[\alpha]_D^{25}$ = +7.6 (*c* 1.05, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.43-7.23 (m, 15H), 6.73 (bs, 1H), 4.83 (s, 1H), 3.80 (q, 2H, *J* = 17.6, 13.7 Hz), 3.69 (m, 1H), 3.47 (m, 1H), 3.42 (m, 1H), 3.30 (dd, 1H, *J* = 10.7, 4.9 Hz), 3.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 172.14, 143.07, 128.49, 127.96, 127.31, 87.19, 80.26, 63.38, 53.70, 51.61, 39.95, 38.50. HRMS ES+ calcd for $C_{32}H_{34}N_2O_5S$ $[M+Na]^+$ 581.6900, found 579.9791.

(*S*)-Methanesulfonic acid 2-(2-benzylamino-acetylamino)-1-(tert-butyl-dimethyl-silanyloxymethyl)-ethyl ester 28c. Yield: 72%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.41-7.17 (m, 5H), 4.72 (m, 1H), 4.11 (m, 2H), 3.70 (m, 2H), 3.52 (m, 1H), 3.30 (m, 2H), 3.01 (s, 3H), 0.81 (s, 9H), 0.01 (d, 6H, *J* = 2.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 165.6, 130.4, 129.0, 129.5, 80.8, 63.3, 51.4, 47.7, 40.4, 38.7, 25.7, 18.1, -5.5.

(*R*)-2-(Benzylaminomethyl)-5-trityloxymethyl-oxazoline 29a. (*S*)-Methanesulfonic acid 2-(2-benzylamino-acetylamino)-1-trityloxymethyl-ethyl ester **28a** (22.6 mg, 0.040 mmol) was dissolved in anhydrous DMSO (3.00 mL). Potassium carbonate (12.0 mg, 0.087 mmol) was added to the medium and the solution was stirred at 80 ºC for 2 h. The solvent was then evaporated off and CH_2Cl_2 added to the residue. K_2CO_3 was filtered out, the solvent was removed and after drying on the vaccum pump without further purification, the product was obtained as a brown oil (15.0 mg, 0.032 mmol). Yield: 80%. $[\alpha]_D^{25}$ = - 8.0 (*c* 0.71, EtOAc).^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.48-7.20 (m, 20H), 4.71 (m, 1H), 3.86 (m, 3H), 3.65 (dd,

1H, J = 13.8, 7.5 Hz), 3.48 (s, 2H), 3.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.2, 143.6, 139.5, 128.6, 127.8, 127.1, 86.5, 78.6, 65.2, 56.5, 53.3, 45.5. HRMS ES+ calcd for $C_{31}H_{30}N_2O_2$ $[M+1]^+$ 463.5800, found 463.4865.

(*R*)-2-(Methylaminomethyl)-5-trityloxymethyl-oxazoline 29b. Yield: 86%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.47-7.18 (m, 15H), 4.70 (m, 1H), 3.85 (m, 1H), 3.63 (dd, 1H, J = 13.8, 7.5 Hz), 3.43 (s, 2H), 3.20 (m, 2H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.2, 143.6, 128.6, 127.8, 127.1, 86.5, 78.6, 65.2, 56.4, 48.1, 36.1.

(*R*)-2-(Benzylaminomethyl)-5-(tert-butyl-dimethylsilyloxymethyl)-oxazoline 29c. Yield: 46%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.32-7.18 (M, 5H), 4.60 (m, 1H), 3.83 (m, 1H), 3.80 (s, 2H), 3.74 (m, 1H), 3.66 (m, 2H), 3.40 (s, 2H), 0.86 (s, 9H), 0.04 (d, 6H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.5, 138.9, 128.5, 128.3, 128.2, 80.5, 64.1, 55.4, 55.1, 53.3, 52.9, 45.1, 25.6, 18.1, -5.5.

(*S*)-2-Bromo-*N*-(3-hydroxy-4-trityloxy-butyl)-acetamide 30a. (*S*)-4-Amino-1-trityloxy-2-butanol **17a** (3.85 g, 11.1 mmol) was dissolved in anhydrous THF (60.0 mL). Potassium carbonate (3.06 g, 22.1 mmol) then bromoacetic anhydride (3.80 g, 14.6 mmol) were added and the solution was stirred at room temperature for 5 to 6 h. The K_2CO_3 was filtered out and the THF was evaporated on the rotovap. The solid residue was purified on SiO_2 gel with a gradient of pure hexane to hexane/CH_2Cl_2/THF 6:3:1 and the pure product was isolated as a white solid (3.89 g, 8.31 mmol). Yield: 75%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.46-7.23 (m, 15H), 7.18 (s, 1H), 3.87 (m, 1H), 3.84 (s, 2H), 3.58 (m, 1H), 3.26 (m, 1H), 3.14 (m, 2H), 2.93 (bs, 1H),

1.65 (m, 1H), 1.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 165.7, 143.6, 128.5, 127.8, 127.1, 86.8, 69.8, 67.4, 37.8, 32.0, 29.2.

(*S*)-Methanesulfonic acid 3-(2-bromo-acetylamino)-1-trityloxymethyl-propyl ester 31a. (*S*)-2-Bromo-*N*-(3-hydroxy-4-trityloxy-butyl)-acetamide **30a** (570 mg, 1.21 mmol) was dissolved in anhydrous CH_2Cl_2 (10.0 mL) at 0 ºC. Methanesulfonyl chloride (0.122 mL, 1.57 mmol) was added and the solution was stirred for one minute then DIPEA (0.560 mL, 3.22 mmol) was added and the solution was stirred for 30 min. Ice H_2O was added to the mixture, more CH_2Cl_2 was added and the product was extracted. The organic phase was washed with H_2O then brine and the organic solvent was evaporated. The crude mixture was purified on SiO_2 gel with a gradient of pure hexane to hexane/CH_2Cl_2/THF 6:3:1. The pure product was obtained as a light yellow oil (610 mg, 1.12 mmol). Yield: 92%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.44-7.23 (M, 15H), 6.96 (bs, 1H), 4.75 (m, 1H), 3.82 (s, 2H), 3.57 (m, 1H), 3.36 (m, 2H), 3.21 (m, 1H), 3.05 (s, 3H), 1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 165.9, 143.1, 128.5, 127.9, 127.4, 87.4, 79.9, 65.5, 38.7, 35.8, 31.0, 28.9.

(*S*)-Methanesulfonic acid 3-(2-bromo-acetylamino)-1-(t-butyl-dimethyl-silyloxymethyl)-propyl ester 31b. Yield: 61%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.23 (bs, 1H), 4.66 (m, 1H), 3.99 (s, 2H), 3.70 (m, 2H), 3.59 (m, 1H), 3.25 (m, 1H), 3.07 (s, 2H), 1.89 (m, 1H), 1.76 (m, 1H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 166.7, 81.4, 65.0, 42.4, 38.4, 35.4, 30.5, 25.7, -5.6.

(*S*)-Methanesulfonic acid 3-(2-benzylamino-acetylamino)-1-trityloxymethyl-propyl ester 32a. (*S*)-Methanesulfonic acid 3-(2-bromo-acetylamino)-1-trityloxymethyl-propyl ester **31a** (688 mg, 1.26 mmol) was dissolved in anhydrous THF (10.0 mL). Benzylamine (0.700 mL, 6.41 mmol) was added and the solution was stirred at room temperature for 2 h. The solvent was then evaporated off and the crude mixture was taken up in dichloromethane. Insoluble residue was filtered out and the solvent removed on the rotovap. The residue was purified on SiO_2 gel with a gradient of pure hexane to hexane/CH_2Cl_2/THF 6:3:1. The pure product was obtained as a light yellow oil (714 mg, 1.25 mmol). Yield: 99%. $[\alpha]_D^{25}$ = +4.3 (*c* 1.10, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.50-7.23 (m, 20H), 4.80 (m, 1H), 3.77 (s, 2H), 3.50 (m, 1H), 3.34 (m, 2H), 3.27 (s, 2H), 3.23 (m, 1H), 3.03 (s, 3H), 1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 171.7, 143.1, 139.2, 128.5, 127.9, 127.3, 87.2, 80.1, 65.3, 53.8, 51.8, 38.6, 34.6, 31.5.

(*S*)-Methanesulfonic acid 2-(2-benzylamino-acetylamino)-1-(tert-butyl-dimethyl-silanyloxymethyl)-ethyl ester 32b. Yield: 72%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.41-7.17 (m, 5H), 4.72 (m, 1H), 4.11 (m, 2H), 3.70 (m, 2H), 3.52 (m, 1H), 3.30 (m, 2H), 3.01 (s, 3H), 0.81 (s, 9H), 0.01 (d, 6H, *J* = 2.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 165.6, 130.4, 129.0, 129.5, 80.8, 63.3, 51.4, 47.7, 40.4, 38.7, 25.7, 18.1, -5.5.

(*R*)-2-Benzylaminomethyl-6-trityoxymethyl-oxazine 33a. (*S*)-Methanesulfonic acid 3-(2-benzylamino-acetylamino)-1-trityloxymethyl-propyl ester **32a** (450 mg, 0.786 mmol) was dissolved in anhydrous DMSO (10.0 mL). Potassium carbonate (217 mg, 1.57 mmol) was added to the solution and the mixture was stirred at 80 ºC for 1 h. CH_2Cl_2 was then added and the solution was washed 4 times with about 3 mL of H_2O and with brine. The organic solvent was

evaporated on the rotovap and the crude mixture purified on SiO_2 gel with a gradient of pure hexane to hexane/CH_2Cl_2/THF 6:3:1 and finally CH_2Cl_2/THF 7:1 to obtain a yellow oil (263 mg, 0.552 mmol). Yield: 70%. $[\alpha]_D^{25}$ = +7.2 (*c* 1.08, EtOAc).^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.51-7.21 (m, 20H), 4.26 (m, 1H), 3.83 (s, 2H), 3.40 (m, 3H), 3.31 (s, 2H), 3.17 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 158.1, 143.6, 139.9, 128.5, 127.7, 126.9, 86.5, 73.6, 65.7, 53.3 51.1, 41.6, 24.1. HRMS ES+ calcd for $C_{32}H_{32}N_2O_2$ $[M+1]^+$ 477.6100, found 477.3175.

(*S*)-6-(Trityloxymethyl)-morpholin-3-one 34. (*S*)-2-bromo-*N*-(2-hydroxy-3-(trityloxy)propyl)-acetamide **26** (211 mg, 0.464 mmol) was dissolved in anhydrous dichloromethane (8.00 mL). Sodium hydroxide (93.0 mg, 2.33 mmol) was added to the solution, which was refluxed for 1.5 h. The solid residue was filtered out and the organic solution was washed twice with saturated ammonium chloride, twice with water and once with brine. The aqueous phase was separated and the organic phase dried on Na_2SO_4. The sodium sulfate was filtered out, the solvent was evaporated and the pure product (139 mg, 0.372 mmol) was obtained as a white crystalline solid after drying under vacuum without further purification. Yield: 80%. m.p. 187-187.5 °C $[\alpha]_D^{25}$ = -47.4 (CH_2Cl_2, c = 1.04). ^{1}H NMR ($CDCl_3$, 300 MHz); δ (ppm): 7.52-7.22 (m, 16H), 4.24 (dd, 2H, *J* = 31.1, 16.9 Hz), 3.87 (m, 1H), 3.37 (m, 3H), 3.15 (dd, 1H, *J* = 9.6, 5.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz); δ (ppm): 169.4, 143.4, 128.5, 127.8, 127.1, 86.8, 72.0, 67.4, 63.8, 43.9. HRMS calcd for $C_{24}H_{23}NO_3$ $[M+Na]^+$ 374.1756, found 374.1773.

(*S*)-6-(trityloxymethyl)-morpholine 35. (*S*)-6-(trityloxymethyl)-morpholin-3-one **34** (55.0 mg, 0.147 mmol) was dissolved in anhydrous THF (5.00 mL). The solution was put at 0 °C and

stirred for 10 min. $LiAlH_4$ (17.0 mg, 0.448 mmol) was added to the solution under nitrogen and the reaction was stirred for 2 h. Ice-water was added to quench the reaction, and the precipitated aluminum salts were filtered out. The THF was evaporated and the product was extracted with CH_2Cl_2. The organic solvent was washed with water and brine, then evaporated and the product was dried under nitrogen and under vacuum to afford a colorless semi-solid without further purification. (37.0 mg, 0.103 mmol). Yield: 70%. $[\alpha]_D^{25}$ = +13.0 (EtOH, c = 1.00). ^{1}H NMR ($CDCl_3$, 250 MHz); δ (ppm): 7.49-7.19 (m, 16H), 3.86 (m, 1H), 3.69 (m, 1H), 3.59 (dd, 1H, *J* = 11.2, 3.4 Hz), 3.22 (dd, 1H, *J* = 9.3, 5.1 Hz), 3.04 (m, 2H), 2.81 (m, 2H), 2.62 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ (ppm): 143.9, 128.6, 127.8, 127.0, 86.5, 75.9, 67.9, 65.1, 49.0, 45.9.

(*S*)-7-(trityloxymethyl)-1,4-oxazepan-3-one 36. (*S*)-2-Bromo-*N*-(3-hydroxy-4-(trityloxy)butyl) acetamide **30a** (156 mg, 0.333 mmol) was dissolved in anhydrous dichloromethane (10.0 mL). Sodium hydroxide (66.6 mg, 1.67 mmol) was added to the solution and the mixture was stirred for 6 h. The solid residue was filtered out and the organic solvent washed with saturated NH_4Cl twice, then H_2O and brine. After drying on Na_2SO_4 and filtration, the solvent was evaporated and the residue dried under vacuum to afford a fluffy white solid (107 mg, 0.276 mmol). Yield: 83%. m.p. 88-90 °C $[\alpha]_D^{25}$ = -36.2 (CH_2Cl_2, c = 1.02). ^{1}H NMR ($CDCl_3$, 250 MHz); δ (ppm): 7.41-7.11 (m, 15H), 6.42 (bs, 1H), 4.32 (d, 1H, *J* = 15.9 Hz), 4.05 (d, 1H, *J* = 15.9 Hz), 3.70 (m, 1H), 3.34 (m, 1H), 3.20 (dd, 1H, *J* = 9.6, 5.9 Hz), 2.94 (dd, 1H, *J* = 9.6, 5.0 Hz), 1.92 (m, 1H), 1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ (ppm): 175.4, 143.8, 128.6, 127.8, 86.6, 79.9, 71.5, 65.8, 39.2, 32.5. HRMS calcd for $C_{25}H_{25}NO_3$ $[M+Na]^+$ 410.1732, found 410.1734.

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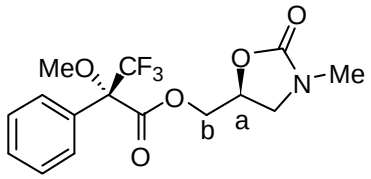
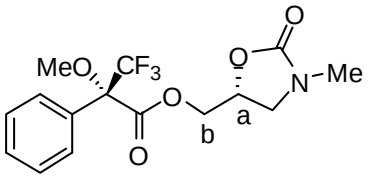
62. A small amount of compounds **10b** and **14** were deprotected using TFA to remove the trityl group and the free alcohol treated with Mosher's acid chloride to form the corresponding esters **10b'** and **14'**, integration of the signals on the ^{1}H NMR spectrum of the crude reaction products allowed us to confirm the optical purity with the optical rotation data. The crude 500MHz ^{1}H NMR spectrum of compound **10b'** indicated no presence of diastereomer, the chemical shifts of protons a and b are: δ (ppm), 4.76 (sb, H*a*), 4.58 (d, 1H, H_b, J = 0,11.7Hz), 4.41 (dd, H_b', J = 3.9, 11.7Hz), compound **25:** 4.78 (sb, H*a*), 4.58 (dd, 1H, H_b, J = 2.9, 12.2), 4.37 (dd, H_b', J = 3.9, 12.2Hz), a small doublet impurity signal at 4.41 estimated less than 1% of the H_b' integration indicates that the purity of the enantiomer is 99%.



10b'



14'

63. A small amount of compound **14b**, **16b**, and their 1:1 mixture are converted to the corresponding hydroxyl trifluoromethyl ester derivatives by treating with TFA and trifluoroacetic anhydride. GC analysis of the derivatives using cyclodextrin column indicates that the optical purities of compound **14** and **21b** are both over 99% ee, there is no detectable presence of the opposite isomer.

Chapter IV. Synthesis and Antibacterial Activities of 1,3-Oxazinan-2-ones Derivatives.

Abstract

1,3-Oxazinan-2-ones and 2-oxazolidinones are very important heterocycles in synthetic organic chemistry because they are useful intermediates in the synthesis of biologically relevant molecules; they are also found in many pharmaceutical compounds, including drugs that are commercially available today such as antibiotic Linezolid (Zyvox®)[1-2] or the HIV reverse-transcriptase inhibitor Efavirenz (Sustiva®).[3] Knowing these properties the efficient syntheses of these heterocycles become of prime importance as well as their insertion in molecules with a potential as drugs. In this chapter, the design, synthesis, and antibacterial activities of novel classes of compounds containing chiral 1,3-oxazinan-2-ones and 2-oxazolidinones as the basic core structures are reported. These compounds are tertiary amines containing the core structures and two aryl substituents. Several of these molecules exhibit potent antibacterial activities against the tested Gram-positive bacteria, including *Staphylococcus aureus*, *Enterococcus faecalis*, and *Bacillus subtilis*. These compounds represent new structure scaffolds and can be further optimized to give new antibacterial agents with structures significantly different from those of existing classes of antibiotics.

Introduction

Antibiotic resistance is a growing problem that threatens human health globally. The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE)[4-5] is very dangerous and can be life threatening especially for patients whose immune system has been compromised due to HIV, surgery or other illnesses. During the recent decades, the effort to discover novel antibacterial agents has slowed down; in fact, 2-oxazolidinones are the only new class of synthetic antibacterial agents over the past 30 years that possesses totally new structures compared to existing antibacterial agents.[6-9] The first compound of this class, Linezolid **1** (Figure 4.1), was approved by the FDA in 2000 for the treatment of multi-drug resistant bacterial infections including diseases caused by MRSA, VRE and *Streptoccus pneumoniae*. 2-Oxazolidinones bind to the 50S subunit of the bacterial ribosome and inhibit protein synthesis at a very early stage by preventing the initiation of mRNA translation. Because they target the bacterial protein synthesis at an early stage, drug resistance was expected to be rare; however resistance to Zyvox® (Linezolid) has already been reported.[1, 10] Typical examples of the existing synthetic antibacterial agents are shown in Figure 4.1; these include Linezolid **1**, Ciprofloxacin **2**, Sulfonamide **3** and Chloramphenicol **4**. The very general features of these agents are that they all contain aromatic and/or heterocyclic structures and they have heteroatom substituents such as halo, amino and hydroxyl groups. Linezolid **1** has the oxazolidinone as the core structure, which is important for its activity. Ciprofloxacin **2** is one example of the fluoroquinolone class of antibiotics.[11-15] They kill bacteria by inhibiting DNA gyrase enzyme which is essential for DNA replication. The structure of **2** contains an aromatic ring with a fluorine and a polar piperazine unit. Sulfonamide **3** contains phenyl sulfonyl phenyl amines.

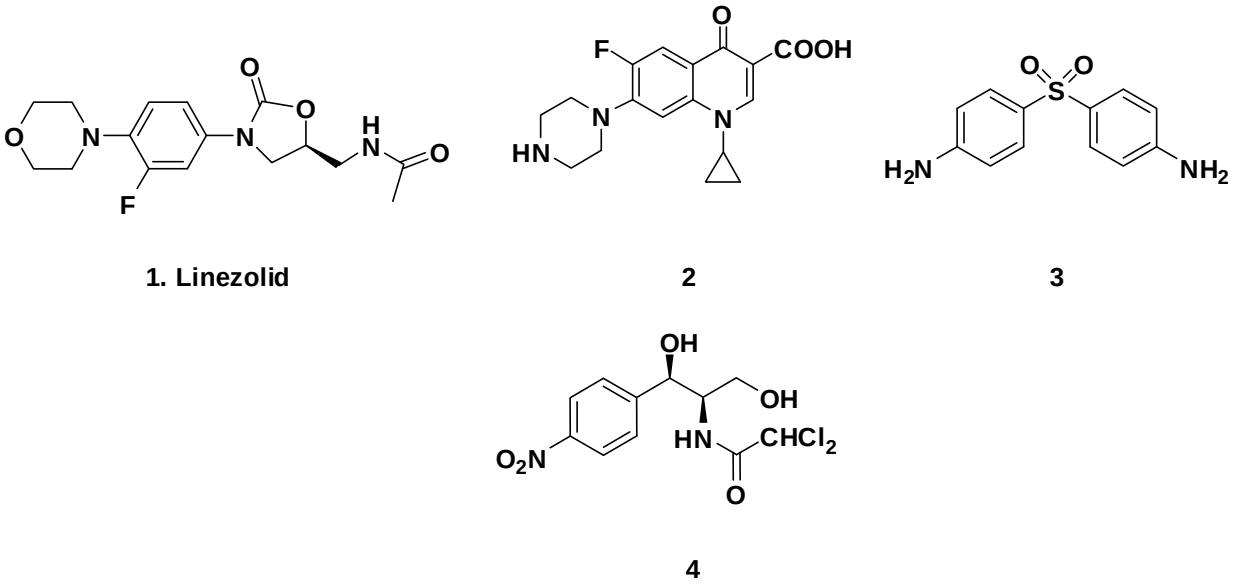
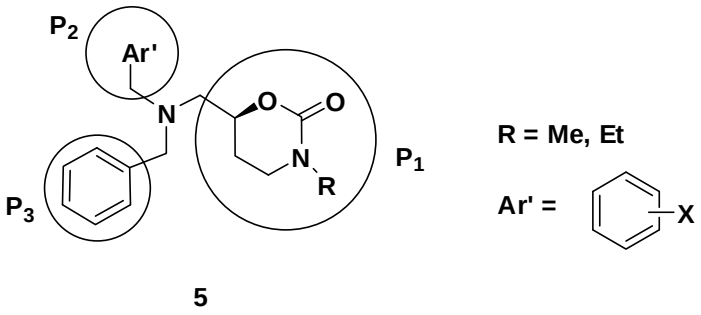


Figure 4.1. Structures of some common synthetic antibacterial agents.

The sulfonamides are inhibitors of the bacterial enzymes required for the synthesis of tetrahydrofolate,[16] an essential nutrient for bacterial growth. Chloramphenicol **4** contains substituted nitrophenol with dichloromethyl acetamido functional groups. It also inhibits bacterial protein synthesis and is a broad spectrum antibiotic for both Gram positive and Gram negative bacteria; unfortunately compound **4** has shown some serious side effects.[17] The general features of these compounds can be used to design new structures that can be potentially useful antibacterial agents.

Many new antibacterial agents are designed based on modification of the existing structural classes; since the antibiotic assay is easy to carry out, the modes of action of the agents are often discovered after finding them active. With the advancement of synthetic organic chemistry, it is now quite common to identify drug-like structures and incorporate them into a *de novo* design of a new agent; this method can be efficiently used to discover new drugs and is somewhat related

to the concept of chemical structure evolution. Through the combination of drug-like properties in existing drug classes, it is possible to create new drugs with significantly different structure motifs. In our efforts to discover new classes of antibacterial agents, we designed and synthesized a small library of compounds containing very general structural features of existing synthetic antibacterial agents, using chiral cyclic carbamates as the core structures. The general structure **5** of the library compounds is shown in Figure 4.2.



5

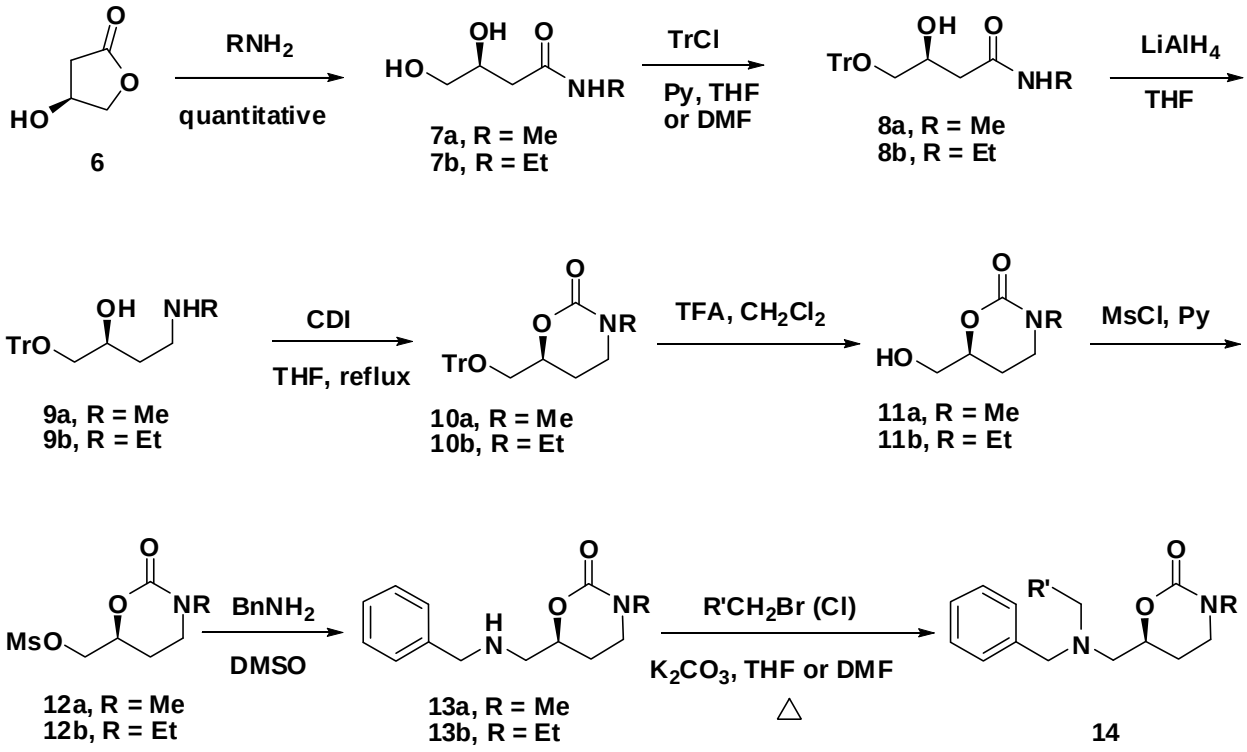
Figure 4.2. The general structures of the preliminary compound library.

The basic platform is a tertiary amine composed of a 1,3-oxazinan-2-one and two aromatic groups. The core structure is a homolog of the 2-oxazolidinone in Linezolid but with the opposite stereochemistry. Three sites $\mathbf{P_1}$, $\mathbf{P_2}$, $\mathbf{P_3}$ can be optimized to obtain better potencies. One main reason for this design is the easy access to the compounds synthetically; the second most important reason is that tertiary amines and heteroatom substituted aryl groups are found often in different classes of drugs, therefore, it is foreseeable that this design could give rise to good biological activities. The 1,3-oxazinan-2-one chiral core structure has been found in many natural product and drug classes as well.[18-24] Another advantage of this platform is that we can easily modify the structures of the three sites by *N*-alkylation or *N*-arylation reactions. Site $\mathbf{P_1}$ contains the chiral core structure 1,3-oxazinan-2-one or other chiral heterocycles, groups $\mathbf{P_2}$ and

P_3 can be substituted aromatic groups or heterocycles. The synthesis of 1,3-oxazin-2-one ring derivatives is shown in Scheme 4.1.

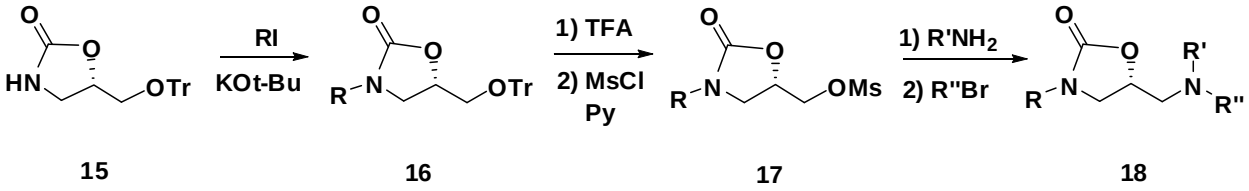
Results and discussions

The starting material compound **13** was synthesized according to literature procedures using a carbohydrate derivative (*S)*-3-hydroxyl-γ-butyrolactone **6** as the starting material.[25-26] Alkylation with alkyl halides using potassium carbonate in THF or DMF at 70-90 °C gave the desired product **14**. These compounds were synthesized by solution phase synthesis and purified by flash chromatography.



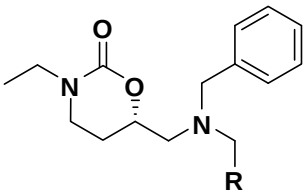
Scheme 4.1. The synthetic route to the target compound library.

For structure comparison purposes, we also synthesized a few compounds containing the 2-oxazolidinone core structure (Scheme 4.2). From the optically pure trityl protected 2-oxazolidinone **15**,[27] alkylation by treating with a base and alkyl halides gave intermediate **16**. Deprotection of trityl group followed by mesylation afforded **17**. After displacement of the mesylate with an amine and subsequent alkylation, we obtained compounds with the general structure **18**.

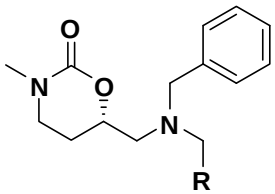


Scheme 4.2. Synthesis of oxazolidinone derivatives.

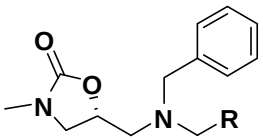
The library compounds synthesized present general structures **A**, **B** and **C** as shown in Figure 3.3. The structures **A** and **B** are close analogs with the substituents on ring nitrogen differing from ethyl to methyl group. Structure **C** contains the smaller 2-oxazolidinone ring instead of the 1,3-oxazinan-2-one. The antibacterial activities of these compounds were evaluated by standard methods. These include the assay against several strains of Gram positive bacteria, *Staphylococcus aureus* 29213, *Staphylococcus aureus* 43300, *Enterococcus faecalis* 29212, and *Bacillus subtilis* PY79. The inhibition of bacterial growth was monitored using a standard colorimeter at 600 nm using a serial dilution at concentrations 238, 119, 59.5, 29.8, 14.9, 7.44, 3.72, 1.86, 0.93, 0.46 μg/ml. Their minimum inhibition concentration (MIC) results at 50% growth inhibition are shown in Table 4.1. We also tested chloramphenicol as a control, it inhibits bacteria growth (MIC_{90}) at 7.44, 7.44, 4.0, 2.0 μg/mL respectively to the four bacteria listed in Table 4.1.



Structure A



Structure B



Structure C

Figure 4.3. The structures of the small compound library synthesized.

Compound	Structure of R	ClogP	*S. aureus* 29213	*S. aureus* 43300	*E. faecalis* 29212	*B. subtilis* PY79
A1	4-nitrophenyl	4.68	N	N	45.0	N
A2	3-nitrophenyl	4.68	90.0	22.0	47.0	108
A3	2-nitrophenyl	4.60	72.0	100	43.0	100
A4	4-cyanophenyl	4.37	180	59.5	12.0	10.0
A5	3-cyanophenyl	4.37	238	N	45.0	238
A6	2-cyanophenyl	4.51	130	180	33.0	160
A7	4-fluorophenyl	5.08	64.0	47.0	35.0	42.5
A8	2,4-difluorophenyl	5.23	45.0	50.5	59.5	38.0
A9	2,6-difluorophenyl	5.23	47.0	70.0	59.5	77.0
A10	3,5-diflurophenyl	5.16	40.0	45.0	37.0	43.0
A11	3,4-dichlorophenyl	6.25	5.60	6.56	N	5.00
A12	2-naphthalenyl	6.11	15.0	N	13.0	29.0
A13	1-naphthalenyl	6.11	10.0	35.0	7.40	7.60
A14	3-pyridinyl	3.44	N	N	238	N
A15	2-pyridinyl	3.44	N	N	N	N
A16	3-methoxyphenyl	4.86	90.0	90.0	80.5	95.0
A17	2-methylphenyl	5.39	22.0	22.5	8.10	26.0
B1	4-nitrophenyl	4.15	81.0	N	119	98.0
B2	3-nitrophenyl	4.15	138	N	119	238
B3	2-nitrophenyl	4.07	179	N	238	238
B4	4-cyanophenyl	3.84	200	N	238	238
B5	3-cyanophenyl	3.84	180	238	7.40	180
B6	2-cyanophenyl	3.98	166	180	59.5	180
B7	4-fluorophenyl	4.55	87.1	119	120	95.0
B8	2,4-difluorophenyl	4.69	50.0	72.0	59.5	55.0
B9	2-naphthalenyl	5.58	11.5	13.0	14.9	12.0
C1	4-fluorophenyl	3.99	N	N	N	N
C2	2,4-difluorophenyl	4.14	85.0	119	N	90.0

C3	3,4-difluorophenyl	4.07	119	N	N	80.0
C4	4-bromophenyl	4.71	20.0	59.5	N	22.0
C5	2-bromophenyl	4.71	18.0	21.0	7.40	22.0

Table 4.1. The minimum inhibition concentration (MIC, μg/mL) of the compound library against four bacterial strains. The MICs are reported as the concentrations at 50% inhibition of bacteria growth, N stands for no inhibition.

The biological assay data have shown that several compounds have moderate to potent activity against all four strains of bacteria. Some active compounds also exhibited certain strain-specificity. It is common for some bacteria strains to be resistant and others susceptible to a particular antibiotic.[28,29] For instance, the tested strain *S. aureus* 29213 is methicillin susceptible, while *S. aureus* 43300 is methicillin resistant. The *E. faecalis* 29212 is vancomycin susceptible, another strain *E. faecalis* 51299 is vancomycin resistant. Compound **A12** showed promising activity against *S. aureus* 29213 but no activity against *S. aureus* 43300. Meanwhile, **A11** showed excellent activity against both strains of *S. aureus* and *B. subtilis* PY79 but no activity against *E. faecalis* 29212. These indicate that the potent compounds can be developed into narrow spectrum antibiotics. This may have some advantages in controlling the spread of resistance. In Table 4.1, the most potent compounds are **A11**, **A13**, **A17**, and **B9**. Their concentrations of inhibition of *S. aureus* 29213 and *B. Subtilis* 79 at 90% are shown in Figure 4.4.

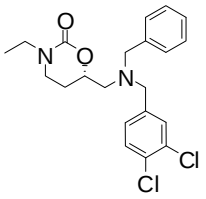
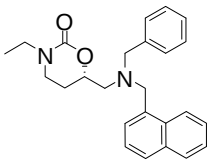
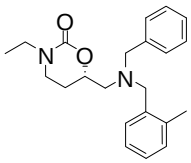
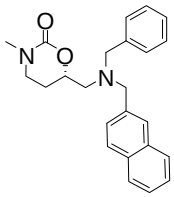
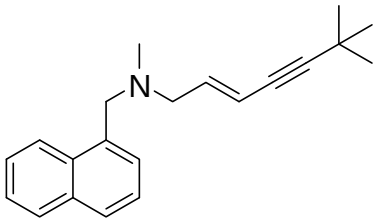
		 **A11**	 **A13**	 **A17**	 **B9**
MIC_{90} μg/mL	S. aureus 29213	9.85	14.9	29.8	14.9
	B. subtilis PY79	7.44	30.0	59.5	30.0

Figure 4.4. The compound structures and their concentrations of 90% inhibition of bacterial growth.

Compounds **A17** and the oxazolidinone derivative **C5** also inhibit over 90% growth of *E. facecalis* 29212 at concentrations of 14.9 and 29.8 μg/mL, respectively. The most potent compound **A11** has MIC90 below 10 μg/mL, it is in the same range as chloramphenicol. These are reasonable good activities considering the simplicity of the structure and the differences with Linezolid or other existing antibacterial agents. The structure–activity relationship (SAR) of site **P2** can be analyzed when **P1** contains an 1,3-oxazinan-2-one ring. The nature of substituents and their positions on the benzyl group affected the activity significantly. A general trend is that non-polar groups are more favorable than polar groups on the benzyl ring. It seems that *ortho* position substituents on the **P2** site favor the activity as well. *Ortho*-methyl and halogen groups are generally good substituents. Fluoro substituents frequently appear in many antibacterial drug structures, however, for our tertiary amine systems, chloro and bromo substituted compounds seem to be more potent than fluoro-containing compounds. The polar nitro substituent is not very active. Naphthalenyl groups showed better activity than benzene ring only. When replacing one of the phenyl rings with a pyridinyl ring (**A14** and **A15**), the activity is completely lost. This also indicates that it is favorable to have a non-polar group at the site **P2**. For site **P1**, substituents on

the 3-nitrogen of the 1,3-oxazinan-2-one ring also influence the activity. The similar structures with methyl instead of ethyl groups showed somewhat diminished activity. This trend can be proved by testing the propyl, butyl, and pentyl substituents in the future. For the oxazolidinone series, molecules with the same **P2** and **P3** groups indicated that the 6-membered ring 1,3-oxazinan-2-one is slightly more potent than the 5-membered ring oxazolidinones. But with bromo substituents on the benzene ring (**P2**), oxazolidinone compounds still showed good activity especially when the bromine is at *ortho* position.



Terbinafine

It is worth noting that compounds **A13** and **B9** have some structure similarities with an antifungal drug, the tertiary amine Terbinafine (Lamisil®).[30] They all contain a naphthalenyl substituted tertiary amine as the general structure. Terbinafine inhibits the synthesis of ergosterol, an essential component for the fungi cell wall. It has a different mode of action compared to 'azole' antifungal agents. The structure resemblance to Terbinafine may indicate that our tertiary amine systems also can have antifungal activities in addition to the observed antibacterial activities. These are currently under evaluation. From the above discussions, we can draw several preliminary conclusions of SAR. For site **P2** aromatic systems, naphthalene is more active than benzene; bromo, methyl are good candidates for the substituent on benzene ring. The 6-membered ring 1,3-oxazinan-2-one seems to have a slightly better activity than the 2-oxazolidinone for the compounds tested so far. It is necessary to have one or two substituted aryl systems for antibacterial activities. The minimum inhibition concentrations of several

compounds are around 10 μg/mL, which should be a good starting point for us to optimize the structure and obtain more potent antibacterial agents with this novel scaffold.

Conclusions

1,3-oxazinan-2-ones and 2-oxazolidinones rings are important heterocycles in organic synthesis, both as useful synthetic intermediates of as intricate part of biologically active molecules. We have designed, synthesized, and evaluated the antibacterial activities of a small, focused compound library of tertiary amines containing novel chiral 1,3-oxazinan-2-one core structures, 2-oxazolidinone rings and aryl substituents. Several compounds with the general scaffold have shown promising antibacterial activities. They exhibit promising activity against several types of Gram-positive bacteria including *S. aureus*, *E. faecalis*, and *B. subtilis*. The structure–activity relationship of one aryl substitution site **P2** was evaluated thoroughly. We found that bromo, chloro, and methyl groups generally give rise to good antibacterial activity. The structures of these compounds and the structure–activity relationship observed from this library can be used to further optimize the structures to obtain potent novel antimicrobial drugs.

Experimental Section

I. General procedure for the alkylation reaction:

(*S*)-6-(Benzylamino-methyl)-3-methyl-1,3-oxazinan-2-one **13** (60.8 mg, 0.260 mmol) was dissolved in 5 to 10 mL of anhydrous THF. 4-nitrobenzylbromide (56.0 mg, 0.260 mmol) and potassium carbonate (72.0 mg, 0.520 mmol) were added. The solution was stirred at 60 to 70ºC for 48 h. The reaction was then cooled to room temperature and filtered on paper to remove inorganic materials. The solvent was evaporated and the residue was purified by SiO_2 gel chromatography using a gradient of solvent systems of Hexane/THF 9:1 to Hexane/CH_2Cl_2/THF 6:3:1. The product was obtained as a brown oil (49.0 mg, 0.133 mmol). In the case of substituted benzyl chlorides, DMF is generally used as the solvent instead of THF. The general yield range: 51%-90%.

Compound A1 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.15 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.8 Hz), 7.31-7.21 (m, 5H), 4.28 (m, 1H), 3.81 (d, 1H, *J* = 14.6 Hz), 3.71 (d, 1H, *J* = 14.6 Hz), 3.68 (d, 1H, *J* = 12.7 Hz), 3.57 (d, 1H, *J* = 12.7 Hz), 3.30 (q, 2H, *J* = 14.6, 6.8 Hz), 3.22 (dt, 1H, *J* = 11.2, 4.9 Hz), 3.08 (m, 1H), 2.75 (dd, 1H, *J* = 13.7, 5.9 Hz), 2.64 (dd, 1H, *J* = 13.7, 5.9 Hz), 1.95 (m, 1H), 1.69 (m, 1H), 1.08 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 147.3, 138.4, 129.4, 128.8, 128.4, 127.4, 123.5, 75.3, 59.4, 58.7, 56.7, 43.9, 43.3, 25.5, 12.1.

Compound A2 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.24 (s, 1H), 8.09 (d, 1H, *J* = 7.8 Hz), 7.67 (d, 1H, *J* = 7.8 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 7.33-7.23 (m, 5H), 4.28 (m, 1H), 3.82 (d, 1H, *J* = 13.7 Hz), 3.71 (d, 2H, *J* = 3.9 Hz), 3.68 (d, 1H, *J* = 3.9 Hz), 3.57 (d, 1H, *J* = 13.7 Hz), 3.31(q,

2H, *J* = 14.6, 6.8 Hz), 3.22 (dt, 1H, *J* = 11.7, 4.9 Hz), 3.08 (m, 1H), 2.76 (dd, 1H, *J* = 13.7, 5.9 Hz), 2.66 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.99 (m, 1H), 1.69 (m, 1H), 1.09 (t, 3H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 148.3, 141.6, 138.3, 134.8, 129.2, 128.8, 128.4, 127.4, 123.3, 122.2, 75.3, 59.3, 58.6, 56.5, 43.9, 43.3, 25.5, 12.0. HRMS (*m*/*z*): calcd for $C_{21}H_{26}N_3O_4$ $[M + H]^+$, 384.1923; found, 384.1904. IR (CH_2Cl_2; cm^{-1}): 3046, 2977, 1685, 1415, 1262, 735, 694 cm^{-1}.

Compound A3 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.76 (d, 1H, *J* = 8.8 Hz), 7.53 (m, 2H), 7.40 (t, 1H, *J* = 6.8 Hz), 7.32-7.14 (m, 5H), 4.23 (d, 1H, *J* = 13.7 Hz), 4.13 (m, 1H), 3.75 (d, 1H, *J* = 14.6 Hz), 3.56 (d, 1H, *J* = 13.7 Hz), 3.38 (d, 1H, *J* = 12.7 Hz), 3.28 (m, 2H), 3.15 (dt, 1H, *J* = 11.7, 4.9 Hz), 2.96 (m, 1H), 2.64 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.53 (dd, 1H, *J* = 12.7, 7.8 Hz), 1.90 (m, 1H), 1.36 (m, 1H), 1.06 (t, 3H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.1, 150.1, 138.0, 133.8, 132.3, 131.8, 129.2, 128.3, 127.3, 124.4, 74.3, 59.6, 57.6, 56.8, 43.9, 43.3, 25.5, 12.1.

Compound A4 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.59 (d, 2H, *J* = 7.8 Hz), 7.46 (d, 2H, *J* = 7.8 Hz), 7.33-7.23 (m, 5H), 4.25 (m, 1H), 3.77 (d, 1H, *J* = 14.6 Hz), 3.68 (d, 1H, *J* = 5.9 Hz), 3.64 (d, 1H, *J* = 5.9 Hz), 3.55 (d, 1H, *J* = 13.7 Hz), 3.30 (q, 2H, *J* = 13.7, 6.8 Hz), 3.20 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.06 (m, 1H), 2.73 (dd, 1H, *J* = 13.7, 5.9 Hz), 2.62 (dd, 1H, *J* = 13.7, 5.9 Hz), 1.94 (m, 1H), 1.66 (m, 1H), 1.08 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 145.1, 138.4, 132.1, 129.4, 128.8, 128.4, 127.4, 118.8, 110.9, 75.2, 59.4, 59.1, 56.6, 43.9, 43.2, 25.5, 12.1.

Compound A5 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.64 (bs, 1H), 7.57 (d, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 6.8 Hz), 7.40 (t, 1H, *J* = 7.8 Hz), 7.33-7.23 (m, 5H), 4.25 (m, 1H), 3.74 (d, 1H, *J* = 14.6 Hz), 3.67 (d, 1H, *J* = 13.7 Hz), 3.61 (d, 1H, *J* = 13.7 Hz), 3.53 (d, 1H, *J* = 13.7 Hz), 3.30 (q, 2H, *J* = 14.6, 7.8 Hz), 3.21 (dt, 1H, *J* = 11.7, 59 Hz), 3.07 (m, 1H), 2.73 (dd, 1H, *J* = 13.7, 5.9 Hz), 2.62 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.95 (m, 1H), 1.68 (m, 1H), 1.08 (t, 3H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 141.0, 138.4, 133.3, 132.1, 130.8, 129.1, 128.8, 128.4, 127.4, 118.9, 112.4, 75.2, 59.4, 58.7, 56.5, 43.9, 43.3, 25.5, 12.01.

Compound A6 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.64 (D, 1H, *J* = 7.8 Hz), 7.53 (m, 2H, *J* = 4.9 Hz), 7.34 (m, 1H), 7.30-7.19 (m, 5H), 4.27 (m, 1H), 3.99 (d, 1H, *J* = 13.7 Hz), 3.73 (d, 1H, *J* = 13.7 Hz), 3.67 (d, 1H, *J* = 13.7 Hz), 3.51 (d, 1H, *J* = 13.7 Hz), 3.28 (q, 2H, *J* = 14.6, 6.8 Hz), 3.17 (dt, 1H, *J* = 11.7, 5.9 Hz), 2.99 (m, 1H), 2.75 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.63 (dd, 1H, *J* = 13.7, 6.8 Hz), 2.05 (m, 1H), 1.51 (m, 1H), 1.06 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 142.9, 138.3, 133.3, 132.6, 130.6, 129.1, 128.3, 127.8, 127.3, 118.0, 112.8, 74.7, 59.3, 58.4, 56.8, 43.8, 43.2, 25.6, 12.0. HRMS (*m*/*z*): calcd for $C_{22}H_{26}N_3O_2$ $[M + H]^+$, 364.2025; found, 364.2013. IR (CH_2Cl_2; cm^{-1}): 3054, 2986, 1689, 1454, 740, 705 cm^{-1}.

Compound A7 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.33-7.21 (m, 6H), 6.98 (t, 2H, *J* = 8.8 Hz), 4.20 (m, 1H), 3.69 (d, 1H, *J* = 13.7), 3.66 (d, 1H, *J* = 6.8 Hz), 3.52 (d, 1H, *J* = 13.7 Hz), 3.49 (d, 1H, *J* = 6.8 Hz), 3.28 (q, 2H, *J* = 14.6, 6.8 Hz), 3.14 (dt, 1H, *J* = 10.7, 4.9 Hz), 3.00 (m, 1H), 2.70 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.60 (dd, 1H, *J* = 13.7, 7.8 Hz), 1.97 (m, 1H), 1.62 (m, 1H), 1.06 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.2 (d, C_4-F, ^{1}J = 244.1 Hz), 152.9, 138.9, 134.8, 130.6 (d, C_2-F, C_6-F, ^{3}J = 9.2 Hz), , 128.8, 128.3, 127.1, 115.3 (d, C_3-F, C_5-

F, ^{2}J = 21.4 Hz), 75.1, 59.4, 58.7, 56.1, 43.8, 43.1, 25.3, 12.0. HRMS (*m*/*z*): calcd for $C_{21}H_{26}N_2O_2F$ $[M + H]^+$, 357.1978; found, 357.1982. IR (CH_2Cl_2; cm^{-1}): 3054, 2983, 1690, 1446, 1266, 739, 700 cm^{-1}.

Compound A8 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.37-7.19 (m, 6H), 6.83 (t, 1H, *J* = 7.8 Hz), 6.76 (t, 1H, *J* = 8.8 Hz), 4.22 (m, 1H), 3.72(d, 1H, *J* = 13.7 Hz), 3.68 (d, 1H, *J* = 13.7 Hz), 3.59 (d, 1H, *J* = 13.7 Hz), 3.51 (d, 1H, *J* = 13.7 Hz), 3.29 (q, 2H, *J* = 14.6, 7.8 Hz), 3.16 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.01 (m, 1H), 2.72 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.59 (dd, 1H, *J* = 13.7, 7.8 Hz), 1.97 (m, 1H), 1.60 (m, 1H), 1.07 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.4 (dd, C_4-F, ^{1}J = 250.2 Hz, ^{3}J = 12.2 Hz), 161.6 (dd, C_2-F, ^{1}J = 247.2 Hz, ^{3}J = 12.2 Hz), 152.9, 138.8, 132.4 (t, C_6-F, ^{3}J = 9.2 Hz), 128.8, 128.2, 127.2, 121.9 (d, C_1-F, ^{2}J = 15.3 Hz), 111.3 (d, C_5-F, ^{2}J = 21.4 Hz), 103.9 (t, C_3-F, ^{2}J = 24.4 Hz), 75.1, 59.3, 56.2, 51.9, 43.9, 43.2, 25.3, 12.0.

Compound A9 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.28-7.18 (m, 6H), 6.86 (t, 2H, *J* = 7.8 Hz), 4.23 (m, 1H), 3.80 (d, 1H, *J* = 13.7 Hz), 3.73 (d, 1H, *J* = 6.8 Hz), 3.70 (d, 1H, *J* = 6.8 Hz), 3.50 (d, 1H, *J* = 13.7 Hz), 3.28 (m, 2H), 3.12 (dt, 1H, *J* = 11.7, 5.9 Hz), 2.96 (m, 1H), 2.72 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.56 (dd, 1H, *J* = 13.7, 8.8 Hz), 2.02 (m, 1H), 1.54 (m, 1H), 1.06 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.3 (dd, C_2-F, C_6-F, ^{1}J = 250.2 Hz, ^{3}J = 9.2 Hz), 153.1, 139.0, 129.6 (t, C_4-F, ^{3}J = 12.2 Hz), 129.2, 128.1, 127.1, 114.5 (t, C_1-F, ^{2}J = 18.3 Hz), 111.5 (dd, C_3-F, C_5-F, ^{2}J = 18.3 Hz, ^{4}J = 6.1 Hz), 74.9, 59.5, 55.8, 46.4, 43.9, 43.2, 25.1, 12.0. HRMS (*m*/*z*): calcd for $C_{21}H_{25}N_2O_2F_2$ $[M + H]^+$, 375.1884; found, 375.1883. IR (CH_2Cl_2; cm^{-1}): 3054, 2987, 1687, 1471, 740, 705 cm^{-1}.

Compound A10 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.33-7.21 (m, 5H), 6.88 (d, 2H, *J* = 6.8 Hz), 6.67 (t, 1H, *J* = 8.8 Hz), 4.24 (m, 1H), 3.71 (d, 1H, *J* = 3.9 Hz), 3.68 (d, 1H, *J* = 3.9 Hz), 3.56 (d, 1H, *J* = 6.8 Hz), 3.53 (d, 1H, *J* = 6.8 Hz), 3.31 (q, 2H, *J* = 13.7, 6.8 Hz), 3.21 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.07 (m, 1H), 2.73 (dd, 1H, *J* = 13.7, 4.8 Hz), 2.63 (dd, 1H, *J* = 13.7, 7.8 Hz), 1.99 (m, 1H), 1.70 (m, 1H), 1.09 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 163.3 (dd, C_3-F, C_5-F, ^{1}J = 250.2 Hz, ^{3}J = 12.2 Hz), 152.9, 143.9 (t, C_1-F, ^{3}J = 9.2 Hz), 138.5, 128.8, 128.4, 127.3, 111.4 (dd, C_2-F, C_6-F, ^{2}J = 18.3 Hz, ^{4}J = 6.1 Hz), 102.7 (t, C_4-F, ^{2}J = 24.4 Hz), 75.3, 59.4, 58.8, 56.4, 43.9, 43.3, 25.5, 12.1.

Compound A11 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.42 (bs, 1H), 7.36 (d, 1H, *J* = 7.8 Hz), 7.33-7.23 (m, 5H), 7.17 (d, 1H, *J* = 7.8 Hz), 4.23 (m, 1H), 3.68 (d, 1H, *J* = 1.9 Hz), 3.65 (d, 1H, *J* = 1.9 Hz), 3.54 (d, 1H, *J* = 2.9 Hz), 3.50 (d, 1H, *J* = 2.9 Hz), 3.30 (q, 2H, *J* = 14.6, 6.8 Hz), 3.19 (dt, 1H, *J* = 11.7, 4.9 Hz), 3.05 (m, 1H), 2.71 (dd, 1H, *J* = 13.7, 5.9 Hz), 2.60 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.96 (m, 1H), 1.67 (m, 1H), 1.08 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 139.7, 138.5, 132.3, 130.9, 130.5, 130.2, 128.8, 128.4, 128.1, 127.3, 75.2, 59.3, 58.3, 56.3, 43.9, 43.2, 25.5, 12.1. HRMS (*m*/*z*): calcd for $C_{21}H_{25}N_2O_2Cl_2$ $[M + H]^+$, 407.1293; found, 407.1292. IR (CH_2Cl_2; cm^{-1}): 3048, 2969, 1690, 1462, 1266, 740, 703 cm^{-1}.

Compound A12 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.79 (d, 3H, *J* = 7.7 Hz), 7.72 (s, 1H), 7.50-7.42 (m, 3H), 7.37-7.22 (m, 5H), 4.23 (m, 1H), 3.87 (d, 1H, *J* = 13.7 Hz), 3.76 (d, 1H, *J* = 13.7 Hz), 3.67 (d, 1H, *J* = 13.7 Hz), 3.57 (d, 1H, *J* = 13.7 Hz), 3.25 (q, 2H, *J* = 14.3, 7.1 Hz), 3.09 (dt, 1H, *J* = 10.9, 4.9 Hz), 2.94 (m, 1H), 2.77 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.67 (dd, 1H, *J* = 13.7, 7.7 Hz), 1.99 (m, 1H), 1.63 (m, 1H), 1.02 (t, 3H, *J* = 7.1 Hz). HRMS (*m*/*z*): calcd for

$C_{25}H_{29}N_2O_2$ $[M + H]^+$, 389.2229; found, 3891.2236. IR (CH_2Cl_2; cm^{-1}): 3054, 2987, 1688, 1438, 1266, 740, 705 cm^{-1}.

Compound A13 ^1H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.07 (m, 1H), 7.78 (m, 2H), 7.48-7.24 (m, 9H), 4.15 (d, 1H, *J* = 12.7 Hz), 4.03 (m, 1H), 3.92 (d, 1H, *J* = 12.7 Hz), 3.82 (d, 1H, *J* = 13.7 Hz), 3.62 (d, 1H, *J* = 13.7 Hz), 3.20 (m, 2H), 2.86-2.61 (m, 4H), 1.69 (m, 1H), 1.32 (m, 1H), 0.99 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.8, 138.7, 134.5, 133.7, 132.1, 129.3, 128.3, 128.1, 128.0, 127.7, 127.2, 125.5, 125.4, 125.1, 124.6, 74.9, 60.6, 58.3, 56.0, 43.7, 42.7, 24.9, 11.9. HRMS (*m*/*z*): calcd for $C_{25}H_{29}N_2O_2$ $[M + H]^+$, 389.2229; found, 389.2236. IR (CH_2Cl_2; cm^{-1}): 3046, 2977, 1692, 1465, 1292, 766, 706 cm^{-1}.

Compound A14 ^1H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.57 (bs, 1H), 7.73 (d, 1H, *J* = 7.8 Hz), 7.34-7.21 (m, 6H), 4.27 (m, 1H), 3.77 (d, 1H, *J* = 14.6 Hz), 3.72 (d, 1H, *J* = 14.6 Hz), 3.63 (d, 1H, *J* = 14.6 Hz), 3.58 (d, 1H, *J* = 14.6 Hz), 3.30 (q, 2H, *J* = 13.7, 6.8 Hz), 3.20 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.04 (m, 1H), 2.75 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.65 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.96 (m, 1H), 1.66 (m, 1H), 1.08 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.0, 139.1, 136.7, 133.2, 132.7, 128.9, 128.3, 127.9, 127.7, 127.6, 127.1, 126.0, 125.6, 75.2, 59.8, 56.2, 43.9, 43.1, 25.3, 12.0. HRMS (*m*/*z*): calcd for $C_{20}H_{26}N_3O_2$ $[M + H]^+$, 340.2025; found, 340.2025. IR (CH_2Cl_2; cm^{-1}): 3054, 2987, 1692, 1422, 1266, 740, 705 cm^{-1}.

Compound A15 ^1H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.51 (d, 1H, *J* = 4.9 Hz), 7.65 (t, 1H, *J* = 6.8 Hz), 7.47 (d, 1H, *J* = 6.8 Hz), 7.35-7.21 (m, 5H), 7.15 (t, 1H, *J* = 5.9 Hz), 4.27 (m, 1H), 3.86 (d, 1H, *J* = 14.6 Hz), 3.77 (d, 1H, *J* = 5.9 Hz), 3.74 (d, 1H, *J* = 5.9 Hz), 3.64 (d, 1H, *J* = 14.6 Hz),

3.30 (q, 2H, *J* = 13.7, 6.8 Hz), 3.18 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.04 (m, 1H), 2.82 (dd, 1H, *J* = 13.7, 5.9 Hz), 2.67 (dd, 1H, *J* = 13.7, 6.8 Hz), 2.00 (m, 1H), 1.67 (m, 1H), 1.07 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 159.4, 153.1, 149.0, 138.9, 136.4, 128.9, 128.3, 127.2, 123.2, 122.1, 75.2, 61.1, 59.8, 56.7, 43.9, 43.3, 25.5, 12.1.

Compound A16 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.33-7.18 (m, 6H), 6.90 (d, 2H, *J* = 6.8 Hz), 6.76 (d, 1H, *J* = 7.8 Hz), 4.20 (m, 1H), 3.78 (s, 3H), 3.69 (d, 1H, *J* = 13.7 Hz), 3.67 (d, 1H, *J* = 8.8 Hz), 3.52 (d, 1H, *J* = 13.7 Hz), 3.49 (d, 1H, *J* = 7.8 Hz), 3.27 (q, 2H, *J* = 9.8, 6.8 Hz), 3.12 (dt, 1H, *J* = 10.7, 4.9 Hz), 2.98 (m, 1H), 2.71 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.61 (dd, 1H, *J* = 12.7, 7.8 Hz), 2.01 (m, 1H), 1.64 (m, 1H), 1.05 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 159.5, 152.9, 140.8, 139.0, 129.2, 128.8, 128.2, 127.0, 121.1, 114.5, 112.2, 75.1, 59.5, 56.2, 55.1, 43.8, 43.1, 25.3, 12.0. HRMS (*m*/*z*): calcd for $C_{22}H_{29}N_2O_3$ $[M + H]^+$, 369.2178; found, 369.2160. IR (CH_2Cl_2; cm^{-1}): 3054, 2985, 1686, 1469, 1285, 738, 692 cm^{-1}.

Compound A17 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.33-7.21 (m, 6H), 7.14 (m, 3H), 4.11 (m, 1H), 3.73 (d, 1H, *J* = 6.8 Hz), 3.69 (d, 1H, *J* = 5,9 Hz), 3.51 (m, 2H), 3.52 (d, 1H, *J* = 1.9 Hz), 3.49 (d, 1H, *J* = 1.9 Hz), 3.26 (m, 2H), 3.04 (dt, 1H, *J* = 11.7, 5.9 Hz), 2.88 (m, 1H), 2.69 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.62 (dd, 1H, *J* = 12.7, 7.8 Hz), 2.29 (s, 3H), 1.91 (m, 1H), 1.52 (m, 1H), 1.05 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 152.9, 138.9, 137.2, 136.9, 130.3, 129.9, 129.2, 128.2, 127.2, 125.6, 127.1, 74.9, 60.2, 58.0, 56.3, 43.8, 42.9, 25.2, 19.2, 12.0. HRMS (*m*/*z*): calcd for $C_{22}H_{29}N_2O_2$ $[M + H]^+$, 353.2229; found, 353.2221. IR (CH_2Cl_2; cm^{-1}): 3054, 2987, 1688, 1431, 1266, 747, 705 cm^{-1}.

Compound B1 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.16 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.8 Hz), 7.42-7.22 (m, 5H), 4.28 (m, 1H), 3.81 (d, 1H, *J* = 14.3 Hz), 3.73 (d, 1H, *J* = 8.8 Hz), 3.67 (d, 1H, *J* = 14.8 Hz), 3.58 (d, 1H, *J* = 13.2 Hz), 3.24 (dt, 1H, *J* = 11.5, 5.5 Hz), 3.07 (m, 1H), 2.91 (s, 3H), 2.76 (dd, 1H, *J* = 13.7, 5.5 Hz), 2.65 (dd, 1H, *J* = 13.7, 6.0 Hz), 1.92 (m, 1H), 1.72 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.5, 147.2, 147.2, 138.4, 129.3, 128.8, 128.4, 127.4, 123.6, 75.5, 59.4, 58.8, 56.7, 46.0, 36.4, 25.5.

Compound B2 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 8.24 (bs, 1H), 8.09 (d, 1H, *J* = 7.8 Hz), 7.67 (d, 1H, *J* = 7.8 Hz), 7.47 (t, 2H, *J* = 7.8 Hz), 7.36-7.21 (m, 4H), 4.28 (m, 1H), 3.82 (d, 1H, *J* = 14.6 Hz), 3.72 (d, 1H, *J* = 14.6 Hz), 3.69 (d, 1H, *J* = 13.7 Hz), 3.59 (d, 1H, *J* = 13.7 Hz), 3.24 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.07 (m, 1H), 2.91 (s, 3H), 2.76 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.66 (dd, 1H, *J* = 13.7, 5.9 Hz), 1.96 (m, 1H), 1.73 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.5, 148.3, 141.7, 138.3, 134.8, 128.3, 128.9, 128.5, 127.4, 123.3, 122.2, 75.5, 59.4, 58.7, 56.6, 46.1, 36.4, 25.5.

Compound B3 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.76 (d, 2H, *J* = 7.8 Hz), 7.57-7.13 (m, 7H), 4.22 (d, 1H, *J* = 13.7 Hz), 4.13 (m, 1H), 3.76 (d, 1H, *J* = 13.7 Hz), 3.55 (d, 1H, *J* = 12.7 Hz), 3.39 (d, 1H, *J* = 13.7 Hz), 3.18 (dt, 1H, *J* = 10.7, 4.9 Hz), 2.93 (m, 1H), 2.87 (s, 3H), 2.64 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.53 (dd, 1H, *J* = 13.7, 7.8 Hz), 1.88 (m, 1H), 1.36 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.7, 150.1, 137.9, 133.8, 132.3, 131.7, 129.2, 128.4, 128.2, 127.3, 124.3, 74.5, 59.7, 57.6, 56.8, 46.1, 36.4, 25.5. HRMS (*m*/*z*): calcd for $C_{20}H_{24}N_3O_4$ $[M + H]^+$, 370.1767; found, 370.1753. IR (CH_2Cl_2; cm^{-1}): 3055, 2971, 1694, 1531, 1431, 1266, 740, 700 cm^{-1}.

Compound B4 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.59 (d, 2H, *J* = 7.8 Hz), 7.47 (d, 2H, *J* = 7.8 Hz), 7.33-7.21 (m, 5H), 4.26 (m, 1H), 3.76(d, 1H, *J* = 13.7 Hz), 3.68 (d, 1H, *J* = 5.9 Hz), 3.65 (d, 1H, *J* = 4.9 Hz), 3.57 (d, 1H, *J* = 12.7 Hz), 3.23 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.05 (m, 1H), 2.90 (s, 3H), 2.74 (dd, 1H, *J* = 13.7, 5.0 Hz), 2.63 (dd, 1H, *J* = 13.7, 5.9 Hz), 1.91 (m, 1H), 1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.5, 145.1, 138.4, 132.1, 129.3, 128.8, 128.4, 127.4, 118.8, 110.9, 75.4, 59.4, 59.1, 56.6, 46.0, 36.4, 25.4. HRMS (*m*/*z*): calcd for $C_{21}H_{24}N_3O_2$ $[M + H]^+$, 350.1869; found, 350.1873. IR (CH_2Cl_2; cm^{-1}): 3055, 2987, 1695, 1495, 1462, 1266, 744, 705 cm^{-1}

Compound B5 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.64 (bs, 1H), 7.54 (m. 1H), 7.40 (t, 1H, *J* = 7.8 Hz), 4.25 (m, 1H), 3.73 (d, 1H, *J* = 14.6 Hz), 3.66 (d, 1H, *J* = 8.8 Hz), 3.62 (d, 1H, *J* = 9.7 Hz), 3.55 (d, 1H, *J* = 12.7 Hz), 3.23 (dt, 1H, *J* = 10.7, 4.9 Hz), 3.05 (m, 1H), 2.90 (s, 3H), 2.67 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.63 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.92 (m, 1H), 1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.5, 140.9, 138.4, 133.2, 132.1, 130.1, 129.1, 128.8, 128.4, 127.4, 118.9, 112.3, 75.4, 59.3, 58.7, 56.4, 45.9, 36.4, 25.5.

Compound B6 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.59 (d, 1H, *J* = 7.8 Hz), 7.50 (m, 2H), 7.33-7.14 (m, 6H), 4.24 (m, 1H), 3.94 (d, 1H, *J* = 13.7 Hz), 3.71(d, 1H, *J* = 13.7 Hz), 3.62 (d, 1H, *J* = 12.7 Hz), 3.49 (d, 1H, *J* = 13.7 Hz), 3.17 (dt, 1H, *J* = 11.7, 5.9 Hz), 2.95 (m, 1H), 2.71 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.60 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.98 (m, 1H), 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.4, 142.7, 138.1, 132.9, 132.4, 130.3, 128.8, 128.1, 127.7, 127.1, 117.8, 112.5, 74.7, 59.0, 58.1, 56.6, 45.8, 36.1, 25.4. HRMS (*m*/*z*): calcd for $C_{21}H_{24}N_3O_2$

$[M + H]^+$, 350.1869; found, 350.1872. IR (CH_2Cl_2; cm^{-1}): 3056, 2937, 1694, 1496, 1450, 1266, 1133, 1077, 738, 701 cm^{-1}.

Compound B7 ^1H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.42-7.18 (m, 7H), 6.98 (t, 2H, *J* = 7.8 Hz), 4.20 (m, 1H), 3.68 (d, 1H, *J* = 5.9 Hz), 3.65 (d, 1H, *J* = 5.9 Hz), 3.54 (d, 1H, *J* = 5.9 Hz), 3.51 (d, 1H, *J* = 5.9 Hz), 3.17 (dt, 1H, *J* = 11.7, 5.9 Hz), 2.99 (m, 1H), 2.71 (dd, 1H, *J* = 12.7, 4.9 Hz), 2.61 (dd, 1H, *J* = 13.7, 6.8 Hz), 1.95 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.0 (d, C_4-F, ^1J = 247.2 Hz), 153.6, 138.9, 134.8, 130.4 (d, C_2-F, C_6-F, ^3J = 9.2 Hz), 128.8, 128.3, 127.2, 115.2 (d, C_3-F, C_5-F, ^2J = 21.2 Hz), 75.3, 59.4, 58.7, 56.2, 45.9, 36.4, 25.4.

Compound B8 ^1H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.40-7.20 (m, 6H), 6.80 (m, 2H), 4.22 (m, 1H), 3.72 (d, 1H, *J* = 13.7 Hz), 3.64 (d, 1H, *J* = 16.6 Hz), 3.60 (d, 1H, *J* = 13.7 Hz), 3.54 (d, 1H, *J* = 13.7 Hz), 3.19 (dt, 1H, *J* = 11.7, 5.9 Hz), 3.00 (m, 1H), 2.89 (s, 3H), 2.73 (dd, 1H, *J* = 13.7, 4.9 Hz), 2.60 (dd, 1H, *J* = 13.7, 7.8 Hz), 1.95 (m, 1H), 1.62 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.2 (dd, C_4-F, ^1J = 247.2 Hz, ^3J = 12.2 Hz), 161.5 (dd, C_2-F, ^1J = 247.2 Hz, ^3J = 9.2 Hz), 153.5, 138.7, 132.3 (t, C_6-F, ^3J = 9.2 Hz), 128.7, 128.1, 127.1, 121.7 (d, C_1-F, ^2J = 15.3 Hz), 111.1 (d, C_5-F, ^2J = 21.4 Hz), 103.7 (t, C_3-F, ^2J = 24.4 Hz), 75.3, 59.2, 56.2, 51.9, 45.9, 36.3, 25.2. HRMS (*m*/*z*): calcd for $C_{20}H_{23}N_2O_2F_2$ $[M + H]^+$, 361.1728; found, 361.1736. IR (CH_2Cl_2; cm^{-1}): 3055, 2985, 1694, 1504, 1438, 1266, 1137, 740, 705 cm^{-1}.

Compound B9 ^1H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.91-7.21 (m, 12H), 4.23 (m, 1H), 3.85 (d, 1H, *J* = 13.7 Hz), 3.85 (d, 1H, *J* = 12.7 Hz), 3.75 (d, 1H, *J* = 14.6 Hz), 3.70 (d, 1H, *J* = 13.7 Hz), 3.60 (d, 1H, *J* = 13.7 Hz), 3.13 (dt, 1H, 11.7, 5.9 Hz), 2.94 (m, 1H), 2.85 (s, 3H), 2.78 (dd,

1H, J = 13.7, 4.9 Hz), 2.68 (dd, 1H, J = 13.7, 7.8 Hz), 1.98 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 153.6, 139.1, 136.6, 133.1, 132.7, 128.9, 128.3, 127.9, 127.0, 125.9, 125.6, 75.4, 59.8, 59.6, 56.3, 45.9, 36.4, 25.4. HRMS (*m*/*z*): calcd for $C_{24}H_{27}N_2O_2$ [M + H]$^+$, 375.2073; found, 375.2077. IR (CH_2Cl_2; cm^{-1}): 3055, 2992, 2930, 1694, 1496, 1446, 1266, 1132, 1076, 740, 705 cm^{-1}.

Compound C1 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.21-7.35 (m, 7H), 7.00 (t, 2H, J = 8.8Hz), 4.46 (m, 1H), 3.69 (d, 2H, J =13.7Hz), 3.55 (d, 2H, J =13.7Hz), 3.38 (t, 1H, J = 8.8Hz), 3.00 (dd, 1H, J= 6.8, 8.8Hz), 2.74 (s, 3H), 2.73 (dd, 1H, J = 5.9, 13.7Hz), 2.65 (dd, 1H, J = 6.8, 13.7Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.0 (d, C-F, J = 244Hz), 159.1, 138.8, 134.6, 130.4 (d, meta to F, ^3J = 6.1Hz), 128.9, 128.4, 127.3, 115.2 (d, ortho to F, ^2J = 21.4Hz), 71.4, 59.3, 58.7, 56.3, 50.3, 30.8.

Compound C2 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.17-7.32 (m, 6H), 6.88 (m, 2H), 4.49 (m, 1H), 3.83 (d, 1H of AB system, J = 12.7Hz), 3.77 (d, 1H of AB system, J = 12.7Hz), 3.69 (d, 1H, J = 13.7 Hz), 3.55 (d, 1H, J = 13.7Hz), 3.37 (m, 1H), 3.03 (dd, 1H, J = 6.8, 8.8Hz), 2.76 (dd, 1H, J = 4.8, 13.7 Hz), 2.72 (s, 3H), 2.62 (dd, 1H, J = 7.8, 13.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 162.2 (dd, C_2-F, ^1J = 250.2, ^3J = 12.2Hz), 161.4 (dd, C_4-F, ^1J = 250.2, ^3J = 12.2Hz), 158.0, 138.6, 132.1 (m, C_1), 128.8, 128.3, 127.3, 127.4 (m, C_6), 111.1 (d, C_5, ^2J = 21.4 Hz), 103.7 (dd≈t, C_3, ^2J = 24.4 Hz), 71.3, 59.2, 56.2, 51.9, 50.2, 30.8.

Compound C3 ^{1}H NMR ($CDCl_3$, 500 MHz); δ (ppm): 7.25-7.38 (m, 5H), 7.19 (m, 1H), 7.11 (m, 1H), 7.02-7.08 (m, 1H), 4.53 (m, 1H), 3.71 (d, 2H, J = 13.7 Hz), 3.58 (d, 2H, J =13.7Hz),

3.44 (dd, 1H, J = 7.8, 8.8 Hz), 3.05 (dd, 1H, J = 6.8, 8.8 Hz), 2.79 (s, 3H), 2.77 (dd, 1H, J = 5.9, 13.7Hz), 2.69 (dd, 1H, J = 5.9, 13.7 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz); δ (ppm): 157.9, 150.4 (dd, C_3-F, ^1J = 247.8 Hz, ^2J = 12.8Hz), 149.5 (dd, C_4-F, ^1J = 247.8Hz, ^2J = 12.8Hz), 138.4, 136.1 (m, C_1), 128.9, 128.5, 127.4, 124.5 (dd, C_6, ^3J = 6.0, ^4J = 3.4Hz), 117.3 (d, ^2J = 17.1Hz), 117.0 (d, ^2J = 17.1Hz), 71.5, 59.2, 58.5, 56.4, 50.3, 30.9.

Compound C4 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.42 (d, 2H, J = 8.8Hz), 7.19 (d, 2H, J = 8.8Hz), 7.22-7.33 (m, 5H), 3.68 (d, 1H, J = 13.7Hz), 3.67(d, 1H, J = 13.7Hz), 3.55(d, 1H, J = 13.7Hz), 3.54 (d, 1H, J = 13.7Hz), 3.38 (t, 1H, J = 8.8Hz), 3.00 (m, 1H), 2.74 (s, 3H), 2.73 (dd, 1H, J = 5.9, 13.7Hz), 2.65 (dd, 1H, J = 5.9, 13.7Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 157.9, 138.6, 138.0, 131.4, 130.5, 128.8, 128.3, 127.3, 120.9, 71.4, 59.3, 58.7, 56.3, 50.2, 30.8.

Compound C5 ^{1}H NMR ($CDCl_3$, 400 MHz); δ (ppm): 7.52 (d, 1H, J = 7.8Hz), 7.47 (d, 1H, J = 7.8Hz), 7.19-7.32 (m, 6H), 7.10 (dd, 1H, J = 1.95, 7.8Hz), 4.43 (m, 1H), 3.83 (d, 1H, J = 13.7Hz), 3.72 (d, 1H, J = 13.7Hz), 3.71 (d, 1H, J = 13.7Hz), 3.60 (d, 1H, J = 13.7Hz), 3.34 (t, 1H, J = 8.8Hz), 2.96 (dd, 1H, J = 5.9, 8.8 Hz), 2.78 (dd, 1H, J = 5.9, 13.7Hz), 2.69(s, 3H), 2.66(dd, 1H, J = 6.8, 13.7Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (ppm): 157.9, 138.5, 137.9, 132.8, 131.1, 129.0, 128.7, 128.2, 127.3, 127.2, 124.5, 71.1, 59.4, 59.1, 56.4, 50.3, 30.7.

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Chapter V. Synthesis of a Ring-Oxygenated Variant of the 2-Carboxy-6-hydroxyoctahydroindole Core of Aeruginosin 298-A from D-Mannose

Abstract

Cardiovascular diseases are the leading cause of death in the United States as they are responsible for more than 35% of all the deaths per year.[1-2] Among the most prominent cardiovascular diseases are thromboembolic disorders which are caused by the formation of clots in the blood vessels. Thromboembolism occurrence is usually due to many factors, a major one being abnormally high blood coagulation. Thrombin (factor IIa) is an enzyme from the trypsin family, which plays a key role in the blood coagulation cascade by converting the fibrinogen into fibrin monomers, thus regulating hemostasis. Because of its influence on the coagulation process, inhibiting thrombin's action allows for a better blood flow and potentially solves the problems encountered with blood clots. Aeruginosins are a family of marine natural products isolated from a blue-green algae, which display inhibitory activity against serine proteases such as thrombin, trypsin, and factor VIIa. Most aeruginosins contain a 2-carboxy-6-hydroxyoctahydroindole (Choi) ring; this Choi moiety is a rigid bicyclic unnatural amino acid and is the core structure in the aeruginosins, indispensable to their biological activity. A synthesis of a ring-oxygenated variant of the Choi from D-mannose is reported in this chapter. The ring-oxygenated variant of 2-carboxy-6-hydroxyoctahydroindole can potentially be used as a surrogate of Choi in the design and synthesis of aeruginosin-based thrombin inhibitors.

Introduction

The process of the blood coagulation is initiated when a vascular injury occurs; the plasma protein Factor VIIa then comes in contact with its cofactor, the Tissue Factor (TF), which is a membrane protein normally not in contact with blood. These two proteins (TF/VIIa) will form a complex, which will activate Factors IX and X and trigger a cascade of reactions, ultimately resulting in the generation of thrombin and of a blood clot.[3-5] Thrombin, also known as Factor IIa, is the key enzyme in the last step of this coagulation cascade, in which it cleaves the fibrinogen into fibrin monomers and also activates several other coagulation factors; therefore, thrombin has been seen as a very attractive target for the synthesis of inhibitors in the treatment of thrombotic disorders.[6-13] Many antithrombotics drugs are currently commercially available; the first class of molecules are the *indirect thrombin inhibitors*, molecules that limit and decrease the endogenous production of thrombin by inhibiting blood coagulation factors such as Factor VIIa or Factor Xa, or by activating internal anticoagulation mechianisms.[14,15] This class is made essentially of heparins and coumarins: heparin, a highly sulfated glycosaminoglycan, is one of the oldest anticoagulant isolated[16] and is still widely used clinically. However, added to the risk of hemorrhage, one of its main side effect is the heparin induced thrombocytopenia (HIT) which severely limits its effectiveness on long-term treatments. Many low molecular weight heparins (LMWH) such as fondaparinux, or enoxaparin have been synthesized and present improved safety profiles.[17-21] Warfarin is a synthetic derivative of naturally occurring coumarin; it was isolated in the 1940s and unlike heparin is available orally; its main side effect is excessive bleeding or hemorrhage.[22] A more recent class of antithrombotics are the *direct thrombin inhibitors* (DTIs). They consist of the bivalent DTIs, led by hirudin, which bind both to the active site and exosite of thrombin, and the univalent DTIs, which bind only to the active site of

thrombin; notable compounds are Argatroban, Ximelagatran and Dabigatran.[23] Hirudin is a naturally occurring peptide isolated from the salivary glands of medicinal leeches; it is made of 65 amino acids and is the most potent natural inhibitor of thrombin.[24-25] However, hirudin is very difficult to extract from it natural sources in large amounts; therefore, several analogs such as bivalirudin (Angiomax™) or lepirudin (Refludan®) have been synthesized and are commercially available as anticoagulants.[26-27] They are administered parenterally and their main setback is a short duration and the risk of hemorrhage. Argatroban is a small molecule that is administered intravenously and binds directly to the active site of thrombin. It is mainly indicated in patients with HIT.[28] Ximelagatran (Exanta®), which had been extensively investigated as a replacement for warfarin, has been discontinued in 2006 after reports of hepatotoxicity during trials.[29-33] Dabigatran is currently in phase III of clinical trials and is administered orally. Figure 5.1 shows some representative indirect and direct thrombin inhibitors currently in clinical trials.[34]

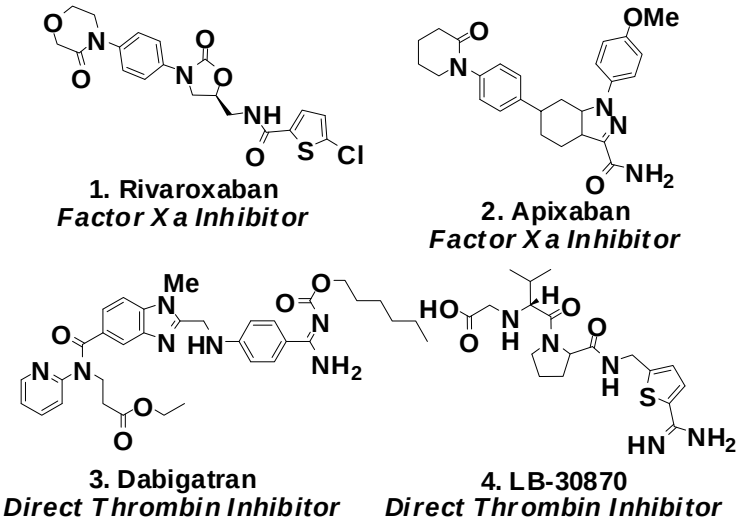


Figure 5.1. Anticoagulant compounds currently in clinical trials

Recently, marine natural products isolated from a blue-green algae *Microcystis aeruginosa*[34-35] have displayed serine protease inhibitory activities. These molecules belong to the family of the aeruginosins, most of which contain a peptidomimetic bicyclic unit, the constrained bicyclic amino acid 2-carboxy-6-hydroxyloctahydroindole (Choi) moiety; the Choi **5** (Figure 5.2)[36] is the core structure in the aeruginosins, and is indispensable to their biological activity. Some of the representative aeruginosins and related molecules are also shown in Figure 5.2. These compounds have a strong potential to be developed into antithrombotic drugs and have stirred the interest of the organic chemists community into designing efficient strategies towards the synthesis of the Choi and its variants, this moiety being a key structure in the aeruginosins and their analogs.

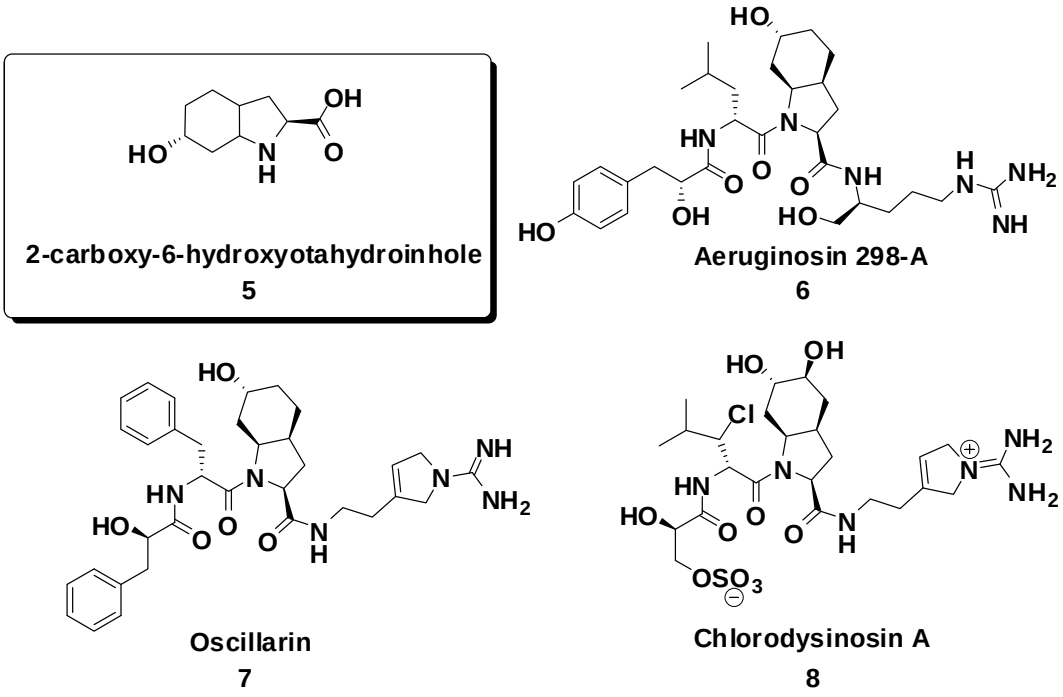
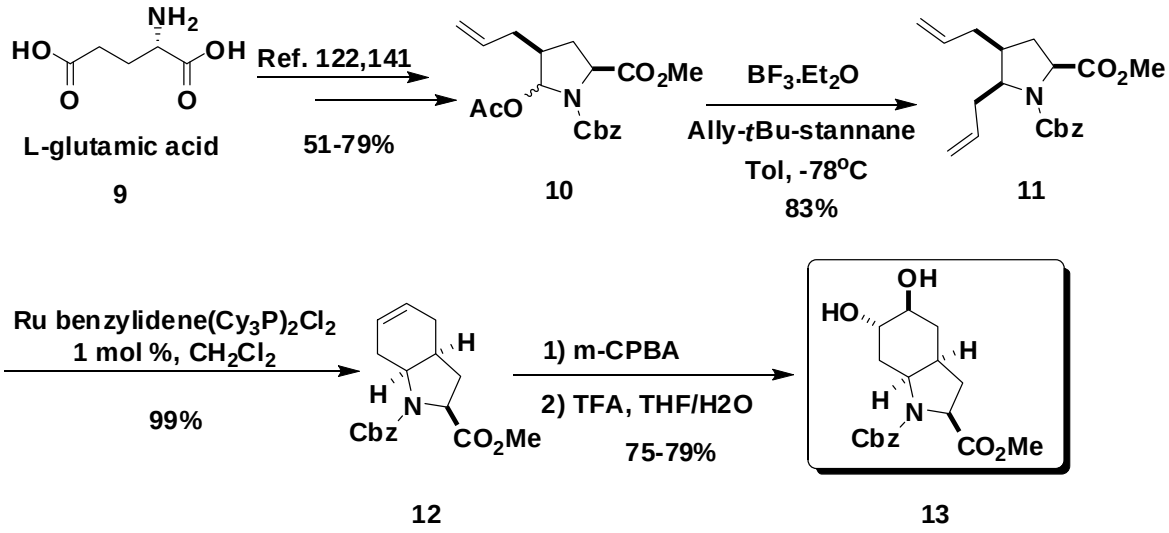


Figure 5.2. Structures of aeruginosins and related compounds.

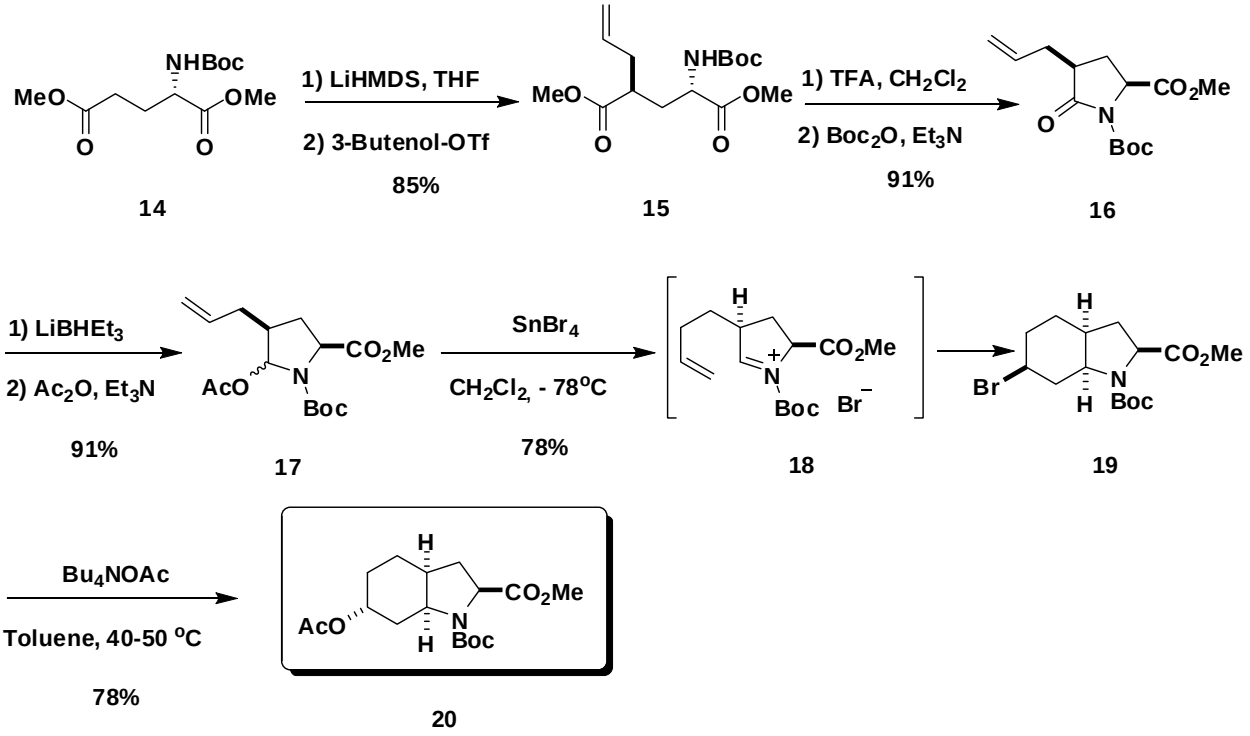
Because of the interesting structure and biological activities of these compounds, several total synthesis and preparation for octahydroindole structures have been reported in the literature and some of the most representative methods are briefly described here. One strategy uses a chiral synthon derived from L-glutamic acid, which can yield the desired bicycle after a ring-closing metathesis, followed by a stereoselective epoxidation and eventually an epoxide ring-opening[40-41] to give the *N*-protected 2-carboxy-5,6-hydroxyloctahydroindole ester **13** (Scheme 5.1), which corresponds to the Choi subunit found in compound **8** Chlorodysinosin A.



Scheme 5.1. Synthesis of a protected 5,6-dihydroxyl-Choi ester from L-glutamic acid.

Another method uses the *N*-acyliminium ion cyclization.[42-45] The synthesis of 2-carboxy-6-octahydroindole via the *N* -acyliminium ion aza-Prins cyclization is detailed in Scheme 5.2. The sequence starts with *N*-Boc-L-glutamate **14** which undergoes enolate alkylation[38] to afford **15**. *N*-deprotection, cyclization and *N*-Boc protection lead to the corresponding pyroglutamate **16**. Partial reduction and protection of the lactam carbonyl group give the hemiaminal **17**. The [4,3,0] bicyclic structure **19** is obtained via the *N*-acyliminium intermediate **18** by treatment with

tin tetrabromide at low temperature. Displacement of the bromide with tetra-*n*-butyl ammonium acetate affords the L-Choi subunit **20**.



Scheme 5.2. Synthesis of a protected Choi ester Via *N*-Acyliminium aza-Prins Cyclization.

Aeruginosins are serine protease inhibitors and they also can inhibit thrombin and factor VIIa. The X-ray crystal structures of the complex formed between aeruginosins and thrombin complexes have been determined.[37-39] The interaction mode of aeruginosin 298-A with the protein is similar to that of other direct thrombin inhibitors as it binds to the active site of thrombin in a noncovalent way forming an antiparallel strand with thrombin.[37] The five-membered ring of the Choi residue occupies the hydrophobic binding site, while its six-membered ring projects out and loosely interacts with thrombin. The crystal structures of oscillarin and dysinosin-A complexes with thrombin revealed similar binding patterns. The amide *NH* from the octahydroindole carboxamide interacts with thrombin, however no

interactions were observed with the 6-hydroxyl group of the Choi moiety. The terminal phenyl group has no interaction with the enzyme.[39] On the basis of the crystal structures and the binding sites interactions, organic chemists can design novel inhibitors with similar core structure motifs but with different substituents and functionalization to enhance binding, activity, and pharmacokinetic properties. Thrombin generally can tolerate imprecise binding from different molecules, however the rigid bicyclic amino acid structure is very important in defining the conformation of the molecule and it is essential to their antithrombin activity. Modifications on the core structure in the area of the 6-hydroxyl group should not impact negatively on binding to the protein while some changes will increase contact and enhance binding. Such changes include introducing an oxygen at the C-4 position and/or adding an additional hydroxyl group to the C-5 or C-7 position; these would lead to structures such as **21** to **24** as surrogates for **5** (Figure 5.3). Because pharmacokinetics are very unpredictable, these changes will result in new biological properties and might broaden the scope for improving the pharmacokinetic profile of this compound class if required. The availability of different stereoisomers is also important in elucidating structure-activity relationships. Studies to rationalize electronic and steric influence of different inhibitors have not given good correlations so far. Modification from the natural analogues can allow us to understand the stereoelectronic factors that determine the activity of these inhibitors. The proposed Choi analogues shown in Figure 5.3, compounds **21** and **22** can be prepared from D-glucose,[36] **23** and **24** can be prepared from D-mannose; they present a great potential for the discovery of better antithrombotics agents.

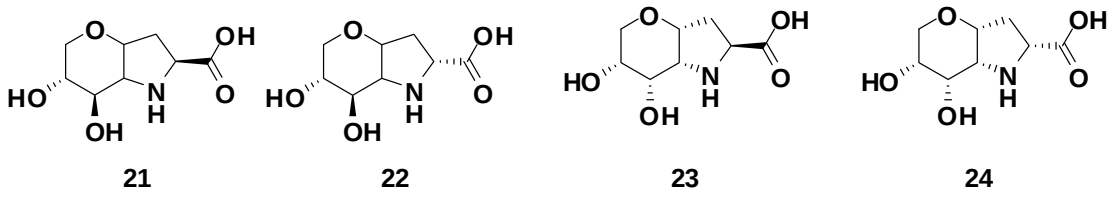
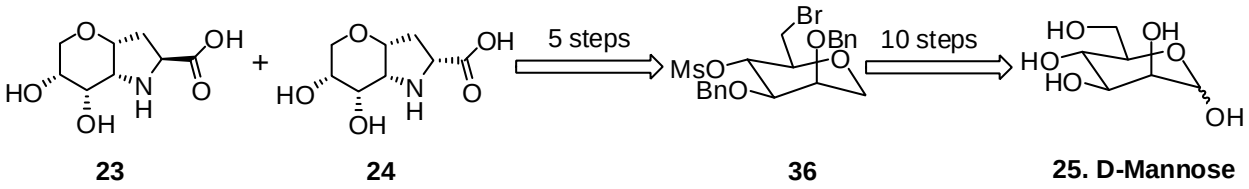


Figure 5.3. O-Choi variants from D-glucose or D-mannose.

The synthesis of a ring-oxygenated variant of Choi from D-glucose has previously been achieved in our laboratory.[36] Using a similar strategy, we have designed and carried out the synthesis of a ring oxygenated variant of the Choi moiety from D-mannose. The retrosynthetic analysis of our strategy shows that Choi analogs **23** and **24** are obtained in 5 steps from a 2,3-*O*-dibenzyl-mesylate bromide **36**, which itself is obtained from commercially available D-mannose in 10 steps.

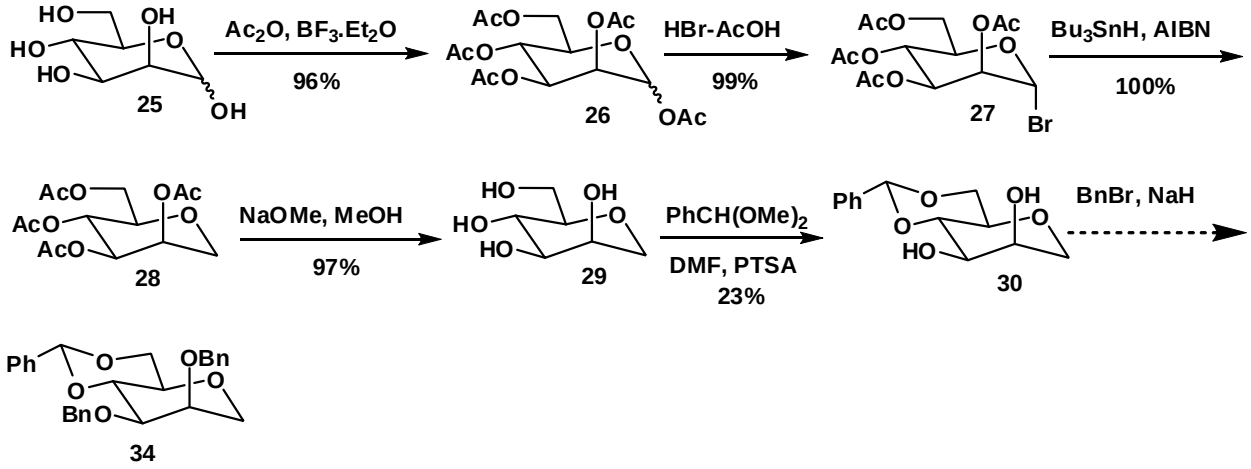


Scheme 5.3. Retrosynthetic strategy to **23** and **24** from D-mannose.

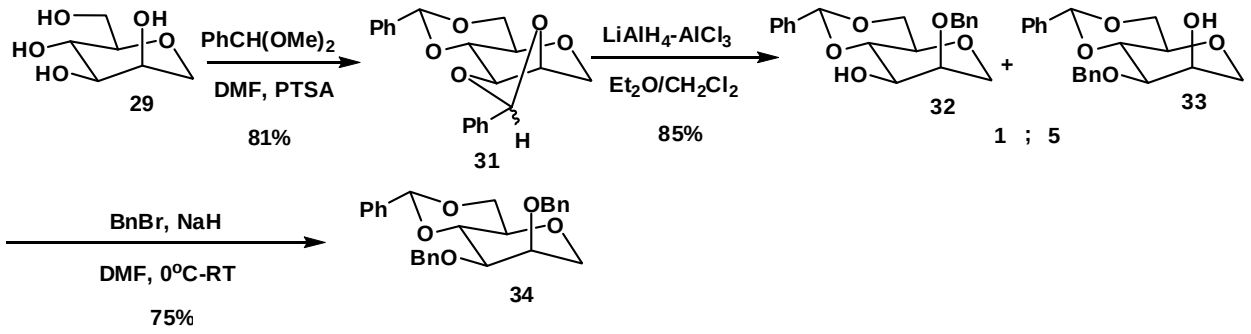
Results and discussion

We designed and carried out the synthesis of the ring-oxygenated Choi analog D-mannose; our first goal was the synthesis of intermediate 2,3-*O*-dibenzyl-4,6-*O*-benzylidene-1-deoxy-mannose **34** (Scheme 5.4). D-mannose **25** was peracetylated using acetic anhydride in the presence of boron trifluoride diethyl etherate to form pentaacetate **26**. Reaction with hydrobromic acid in acetic acid afforded the α-bromo-mannose tetraacetate **27**. Reduction of the bromide was achieved by refluxing in benzene using tert-butyltin hydride catalyzed by AIBN to obtain 1-deoxy-mannose tetraacetate **28**. Removal of the four acetate groups was done by trans-esterification with sodium methoxide in methanol to give 1-deoxy-mannose tetra-alcohol **29** in excellent yield. From intermediate **29**, our initial approach was to synthesize 4,6-benzylidene acetal **30** using a strategy similar to the one we had successfully used in the Choi analog synthesis from D-glucose.[36] Unfortunately, forming the 4,6-monoacetal proved to be very difficult with mannose; the *cis* configuration between the C-2 and C-3 positions makes it easier to form the 2,3-*O*-benzylidene acetal as well, leading the reaction to yield a mixture of products. Given the poor yield of the reaction to **30**, we had to use a different route to obtain 2,3-*O*-dibenzyl-monoacetal **34**, as shown in scheme 5.5. The difference in stability between the 6-membered dioxane type acetal and the 5-membered dioxolane acetal has been previously reported in the literature.[46] The dioxolane type acetal is less stable in controlled reductive conditions; using this knowledge, we synthesized the 2,3,4-6-di-O-benzylidene acetal **31** by reacting tetra alcohol **29** with an excess of benzaldehyde dimethyl acetal in slightly acidic conditions. From compound **31**, partial reduction of the dioxolane 2,3-benzylidene acetal was achieved by using a complex of $LiAlH_4$ and $AlCl_3$; in 30 minutes, the reaction yields a mixture

of the 2-benzyl-3-hydroxy-monoacetal **32** and 3-benzyl-3-hydroxy-monoacetal **33** in good yield.



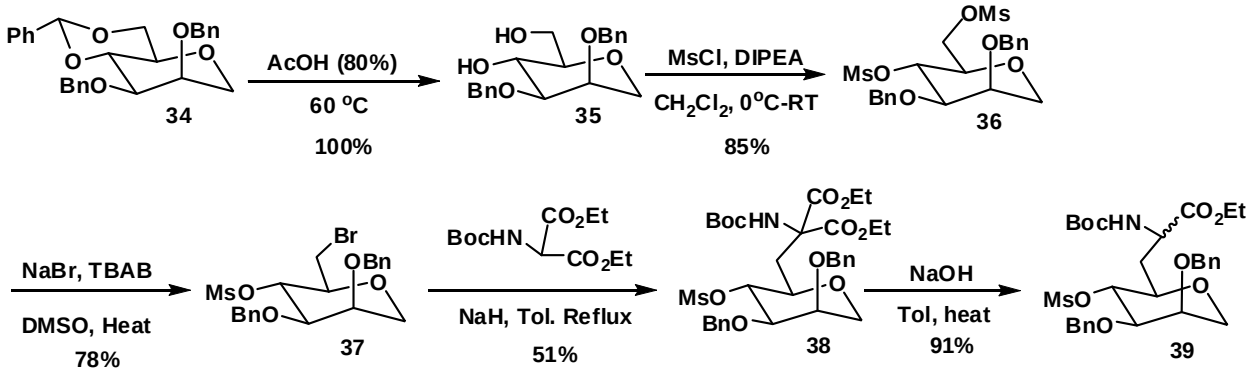
Scheme 5.4. Attempt of synthesis of 4,6-*O*-benzylidene monoacetal intermediate **30**.



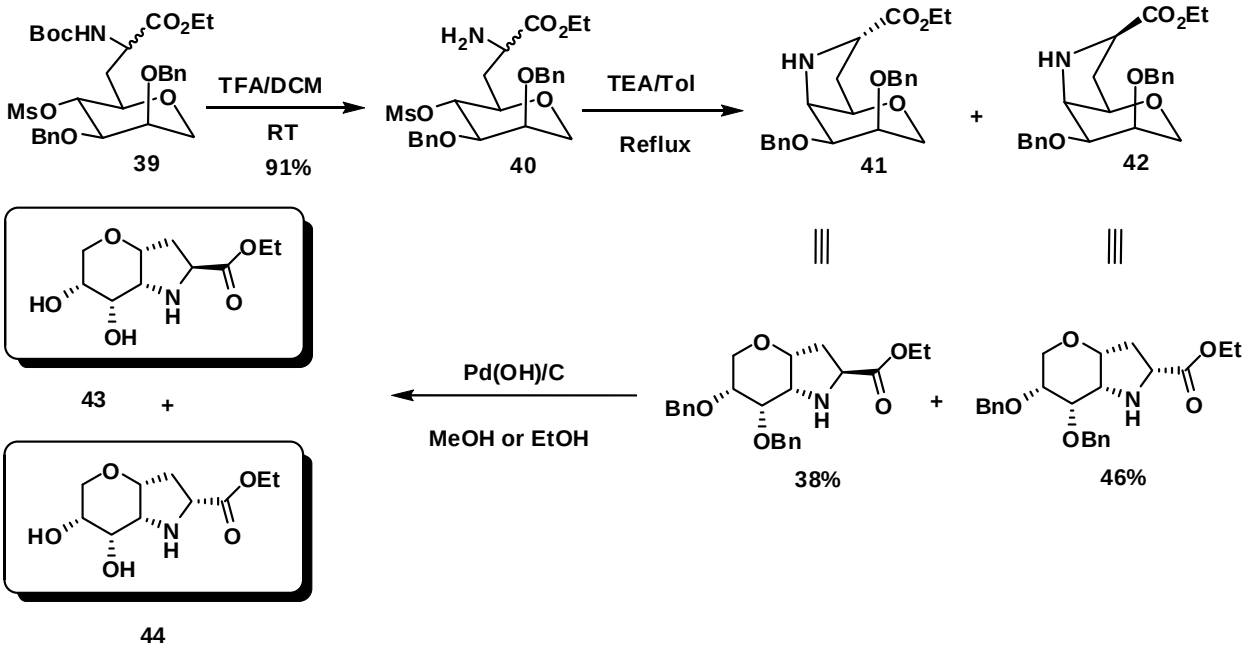
Scheme 5.5. Synthesis of 2,3-*O*-dibenzyl-4,6-benzylidene acetal intermediate **34**.

The mixture of **32** and **33** was immediately submitted to benzylation conditions using benzyl bromide and sodium hydride in DMF to yield a unique product 2,3-*O*-dibenzyl-4,6-*O*-dibenzylidene acetal **34** in reasonable yield. The 4,6-*O*-benzylidene acetal of **34** was hydrolyzed by heating in concentrated acetic acid to yield 4, 6-dihydroxy compound **35** in quantitative fashion. Exhaustive mesylation gave the 4,6-dimesylate **36** with a good yield. The 6-mesylate group of **36** was selectively turned into a bromine by reaction with sodium bromide in the presence of tetrabutyl ammonium bromide to give important intermediate **37**. In the next step, we

used *N*-Boc-dimethylamino malonate that we had previously synthesized according to a literature procedure.[36,47] Reaction of the *N*-protected malonate with **37** in the presence of sodium hydride afforded intermediate **38** in which the 6-bromine has been displaced by the malonate. Decarboxylation in basic conditions gave compound **39** in good yield. Deprotection of the *Boc* group using TFA in dichloromethane yielded free amine **40**. Cyclization was achieved using triethylamine and refluxing in toluene to give diastereomers **41** and **42** in 84% overall yield. From these bicycles, deprotection of the benzyl groups can be done in good yield using palladium hydroxide in either methanol or ethanol to afford the esterified Choi analog **43** (Scheme 5.7).



Scheme 5.6. Synthesis of intermediate **39**.



Scheme 5.7. Synthesis of ring-oxygenated Choi esters **43** and **44**.

Conclusions

Aeruginosins are a family of marine natural products isolated from a blue-green algae; they display a serine protease inhibitory activity, especially towards several enzymes involved in the blood coagulation cascade, such as thrombin or factor VIIa. Most of these compoundsy contain a 2-carboxy-6-hydroxy-octahydroindole (Choi) rigid bicyclic structure, which is essential to their biological activity. The synthesis of variants of the Choi structure, their insertion in aeruginosins analogs and the testing of these compounds can provide a better understanding of the interaction of aeruginosins with serine proteases and lead to the synthesis of potential antithrombotics. Presented in this chapter are the design and synthesis of ring-oxygenated analogs of 2-carboxy-6-hydroxy-octahydroindole (Choi) from D-mannose. The synthesis proceeds with good yields and affords diastereomers of the Choi analog, which can be used to synthesize different aeruginosin

analogs. Studies of the activities of the resulting compounds can give more information on the influence of the Choi moiety on the serine-protease inhibitory properties of the aeruginosins. Also, the different stereochemistry of the diastereomers will help in the structure-activity-relationship (SAR) studies and give better insight on the interactions between the inhibitor and the thrombin active site, leading to the optimization of the inhibitory effect of future synthetic analogs. Given the current extent of thrombotic disorders and the side effects associated with most of the antithrombotic drugs currently available, the synthesis and study of molecules presenting a potential as future antithrombotics such as aeruginosin analogs containing various Choi moieties gives us the hope of finding less toxic and more efficient antithrombotic drugs.

Experimental Section

Mannose pentaacetate 26. D-mannose **25** (19.0 g, 106 mmol) was dissolved in acetic anhydride (55.0 mL, 582 mmol) and the mixture was cooled to 0 °C. Boron trifluoride diethyl etherate (8.00 mL, 64.0 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature for 1.5 h. The mixture was poured into a beaker containing 200 mL of ice and stirred for 1 h. The product was extracted using CH_2Cl_2, the organic phase was washed with saturated $NaHCO_3$ and water and dried on Na_2SO_4. After filtration and concentration, drying under vacuum afforded the pure product as a brown oil (39.9 g, 102 mmol). Yield: 96%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 5.86 (d, 1H, J = 1.0 Hz), 5.49 (dd, 1H, J = 3.2, 0.9 Hz), 5.29 (t, 1H, J = 9.9 Hz), 5.13 (dd, 1H, J = 9.9, 3.3 Hz), 4.31 (dd, 1H, J = 12.4, 5.4 Hz), 4.14 (dd, 1H, J = 12.4, 2.3 Hz), 3.80 (m, 1H), 2.22 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 170.2, 169.8, 169.4, 169.3, 168.0, 90.1, 72.8, 70.3, 67.9, 65.2, 61.8, 20.4. HRMS calcd for $C_{16}H_{22}O_{11}$ $[M+Na]^+$ 413.1060, found 413.1055.

α-Bromo-mannose tetraacetate 27. Mannose pentaacetate **26** (19.8 g, 51.0 mmol) was mixed with acetic anhydride (14.4 mL, 152 mmol) and the mixture was cooled to 0 °C. HBr (33% in acetic acid, 45.0 mL, 2.57 mmol) was added to the solution, which was stirred at room temperature for 4.5 h. The mixture was poured in an beaker containing about 200 mL of ice, stirred for 10 min and extracted with dichloromethane. The organic phase was washed with saturated $NaHCO_3$ and water then dried on Na_2SO_4. After filtration and concentration, the crude mixture was dried under high vacuum and the product is obtained as light yellow oil (20.9 g, 50.8 mmol). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 6.29 (bs, 1H), 5.71 (dd, 1H, J = 10.2,

3.4 Hz), 5.44 (dd, 1H, J = 3.4, 1.6 Hz), 5.36 (t, 1H, J = 10.2 Hz), 4.32 (dd, 1H, J = 12.5, 4.9 Hz), 4.21 (m, 1H), 4.13 (dd, 1H, J = 12.4, 2.1 Hz), 2.17 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 170.5, 169.7, 169.6, 169.7, 83.0, 72.8, 72.1, 67.9, 65.3, 61.4, 20.8, 20.7, 20.6, 20.5. HRMS calcd for $C_{14}H_{19}BrO_9$ $[M+Na]^+$

1-Deoxy-mannose tetraacetate 28. α-Bromo-mannose tetraacetate **27** (16.8 g, 40.9 mmol) was dissolved anhydrous benzene (20.0 mL). Tributyltin hydride (11.0 mL, 41.5 mmol) and AIBN (a few mg) were added to the solution and the mixture was refluxed for 1.5 h. The mixture was cooled to room temperature and diluted with anhydrous ether (100 mL). Potassium fluoride (7.20 g, 124 mmol in 30 mL of water) was added to the mixture and stirred for 2 h. The precipitated Bu_3SnF formed was filtered out and the water phase separated from the ether. The organic phase was washed with water and dried on Na_2SO_4. After filtration and concentration, drying under high vacuum afforded the product as a light yellow oil (13.6 g, 40.9 mmol). Yield: 100%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 5.27 (bs, 1H), 5.24 (t, 1H, J = 10.2 Hz), 5.01 (dd, 1H, J = 10.0, 3.5 Hz), 4.19 (dd, 1H, J = 12.3, 5.6 Hz), 4.08 (dd, 1H, J = 12.2, 2.0 Hz), 4.01 (dd, 1H, J = 13.2, 1.8 Hz), 3.64 (d, 1H, J = 13.2 Hz), 3.55 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 170.6, 170.3, 170.0, 169.5, 76.6, 71.5, 68.5, 68.0, 66.0, 62.6, 20.8, 20.7, 20.6, 20.5. HRMS calcd for $C_{14}H_{20}O_9$ $[M+Na]^+$ 355.1005, found 355.1015.

1-Deoxy-mannose tetraalcohol 29. 1-Deoxy-mannose tetraacetate **28** (15.5 g, 46.7 mmol) was dissolved in anhydrous methanol (20.0 mL). Sodium methoxide (0.252 g, 4.67 mmol) was added to the solution and the mixture was stirred for 16 h at room temperature. The methanol was evaporated under vacuum and the crude mixture was co-distilled with anhydrous toluene. After

drying under high vacuum, the crude product was obtained as a viscous yellow oil (7.40 g, 45.1 mmol). Yield: 97%. ^{1}H NMR (D_2O, 400 MHz); δ 3.78 (m, 3H), 3.50 (m, 4H), 3.15 (m, 1H). ^{13}C NMR (D_2O, 100 MHz); δ 81.9, 74.9, 71.2, 70.5, 68.7, 62.7. HRMS calcd for $C_6H_{12}O_5$ $[M+Na]^+$ 187.0582, found 187.0584.

1-Deoxy-mannose-4,6-benzylidene acetal 30. 1-Deoxy-mannose-tetraalcohol **29** (3.99 g, 24.3 mmol) was dissolved in anhydrous DMF (10.0 mL) and the solution was cooled to 0 °C. Benzaldehyde dimethylacetal (3.65 mL, 24.3 mmol) and HBF_4 (50% in Et_2O, 1.28 mL, 7.29 mmol) were added and the mixture was stirred at room temperature for 12 h. The mixture was cooled to 0 °C, triethylamine (3.39 mL, 24.3 mmol) was added dropwise and the solution was stirred at room temperature for 15 min. DMF was evaporated under nitrogen and the crude mixture was purified on SiO_2 gel using a gradient of solvent of pure hexane to hexane:acetone 4:1. The pure product was obtained as a white solid (1.40 g, 5.55 mmol). Yield: 23%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.48 (m, 2H), 7.37 (m, 3H), 5.53 (s, 1H), 4.27 (dd, 1H, J = 10.0, 5.0 Hz), 4.00 (d, 1H, J = 12.7 Hz), 3.86 (m, 2H), 3.75 (m, 2H), 3.52 (d, 1H, J = 12.7 Hz), 3.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.2, 129.3, 128.3, 126.3, 102.1, 79.0, 71.3, 71.0, 70.4, 69.3, 68.4.

2,3,4,6-di-*O*-benzylidene mannose acetal 31. 1-Deoxy-mannose tetraalcohol **29** (0.157 g, 0.958 mmol) was dissolved in anhydrous DMF (2.00 mL). *p*-Toluenesulfonic acid (0.055 g, 0.289 mmol) and benzaldehyde dimethyl acetal (0.580 mL, 3.86 mmol) were added to the solution and the mixture was stirred at 60 °C for 24 h. The solution was cooled to room temperature, diluted with dichloromethane and then cooled to 0 °C. The reaction was quenched by addition of

saturated $NaHCO_3$. The organic phase was separated from the water layer and washed 3 times with 60 mL of H_2O. After drying on sodium sulfate, the CH_2Cl_2 was evaporated and the product was dried under high vacuum without further purification to afford a light yellow solid containing both endo and exo isomers (0.264 g, 0.776 mmol). Yield: 81%. Mp: 142-143 °C ^1H NMR ($CDCl_3$, 400 MHz); **endo isomer**: δ 7.58-7.33 (m, 10H), 6.35 (s, 1H), 5.65 (s, 1H), 4.51 (m, 1H), 4.37 (m, 2H), 4.20 (dd, 1H, J = 5.3, 2.2 Hz), 3.93 (m, 1H), 3.78 (m, 2H), 3.32 (dt, 1H, J = 15.0, 9.9, 5.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.9, 137.2, 129.3, 129.0, 128.3, 128.2, 126.2, 125.9, 103.0, 101.8, 78.2, 76.0, 73.5, 69.2, 68.6, 67.1. HRMS calcd for $C_{20}H_{20}O_5$ $[M+H]^+$ 341.1389, found 341.1378. **exo isomer**: δ 7.58-7.33 (m, 10H), 6.00 (s, 1H), 5.54 (s, 1H), 4.51 (m, 1H), 4.37 (m, 2H), 4.20 (dd, 1H, J = 5.3, 2.2 Hz), 3.93 (m, 1H), 3.78 (m, 2H), 3.32 (dt, 1H, J = 15.0, 9.9, 5.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.9, 137.1, 129.3, 128.9, 128.4, 128.1, 126.5, 126.1, 104.2, 101.6, 81.3, 76.4, 74.7, 69.1, 68.6, 66.8. HRMS calcd for $C_{20}H_{20}O_5$ $[M+H]^+$ 341.1389, found 341.1378.

2-*O*-Benzyl- and 3-*O*-Benzyl-1-deoxy-mannose-4,6-*O*-benzylidene acetal 32 and 33. 2,3,4,6-di-*O*-benzylidene mannose acetal **31** (0.207 g, 0.608 mmol) was dissolved in a 1:1 mixture of anhydrous CH_2Cl_2 and ether (2.00 mL). The solution was cooled to 0 °C and aluminum chloride (0.081 mg, 0.607 mmol) and lithium aluminum hydride (0.023 g, 0.606 mmol) were added to the mixture. After stirring at room temperature for 30 min, the solution was cooled to 0 °C and the reaction was quenched by addition of ice. The solution was diluted with CH_2Cl_2 and the phases were separated. The organic phase was washed with a solution of saturated $NaHCO_3$ and with H_2O. After drying on Na_2SO_4, the organic phase was evaporated and the product was obtained as a colorless oil, mixture of the 2-OBn and 3-OBn isomers (0.176 g, 0.514 mmol). Yield: 85%. A

portion of the mixture was purified on SiO_2 gel with a gradient of solvent of pure hexane to hexane:EtOAc 3:1 to give the following NMR data: **2-OBn isomer 32**: ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.52-7.29 (m, 10H), 5.58 (s, 1H), 4.79 (d, 1H, J = 1.8 Hz), 4.62 (d, 1H, J = 1.8 Hz), 4.29 (dd, 1H, J = 10.4, 4.9 Hz), 4.16 (dd, 1H, J = 12.9, 1.6 Hz), 3.85 (m, 4H), 3.51 (dd, 1H, J = 12.9, 0.7 Hz), 3.35 (td, 1H, J = 13.4, 10.4, 4.9 Hz), 2.29 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.6, 137.3, 129.1, 128.6, 128.2, 128.0, 127.9, 126.3, 102.0, 79.7, 76.7, 72.1, 71.8, 71.4, 68.5, 67.8. HRMS calcd for $C_{20}H_{22}O_5$ $[M+Na]^+$ 365.1365, found 365.1365. **3-OBn isomer 33**: ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.56-7.32 (m, 10H), 5.64 (s, 1H), 4.89 (d, 1H, J = 12.0 Hz), 4.77 (d, 1H, J = 12.0 Hz), 4.33 (dd, 1H, J = 10.4, 4.9 Hz), 4.13 (t, 1H, J = 9.4 Hz), 4.10 (dd, 1H, J = 12.7, 1.6 Hz), 4.00 (t, 1H, J = 1.7 Hz), 3.84 (t, 1H, J = 10.3 Hz), 3.69 (dd, 1H, J = 9.4, 3.5 Hz), 3.56 (dd, 1H, J = 12.7, 1.2 Hz), 3.35 (dt, 1H, J = 14.7, 9.8, 4.9 Hz), 2.79 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.8, 137.5, 128.8, 128.3, 128.1, 127.8, 127.7, 125.9, 101.3, 78.9, 77.4, 72.5, 71.6, 70.1, 68.4, 68.2. HRMS calcd for $C_{20}H_{22}O_5$ $[M+Na]^+$ 365.1365, found 365.1365.

2,3-Dibenzyl-1-deoxy-mannose-4,6-*O*-benzylidene acetal 34. A mixture of 2-*O*-Benzyl- and 3-*O*-Benzyl-1-deoxy-mannose-4,6-*O*-benzylidene acetal (155 mg, 0.453 mmol) was dissolved in anhydrous DMF (2.50 mL). The solution was cooled to 0 °C and sodium hydride (54.4 mg, 2.27 mmol) was added. The mixture was stirred at room temperature for 30 to 35 min. Benzyl bromide (0.220 mL, 1.85 mmol) was added to the mixture and the reaction stirred for 12 h. The solution was cooled to 0 °C and diluted with CH_2Cl_2. The reaction was quenched by addition of ice. After stirring for another 15 min. the organic phase was separated from the water layer and washed with saturated NH_4Cl and with H_2O three times. After drying on Na_2SO_4, the CH_2Cl_2 was evaporated and the crude mixture was purified on SiO_2 gel with a gradient of solvent of pure

hexane to hexane:CH_2Cl_2:THF 15:1:1. The pure product was obtained as a white solid (146 mg, 0.338 mmol). Yield: 75%. Mp: 84-85 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.55-7.24 (m, 15H), 5.67 (s, 1H), 4.81 (q, 2H, *J* = 20.0, 12.4 Hz), 4.77 (q, 2H, *J* = 50.7, 12.4 Hz), 4.29 (m, 2H), 4.08 (dd, 1H, *J* = 12.6, 1.9 Hz), 3.87 (t, 1H, *J* = 10.3 Hz), 3.81 (m, 1H), 3.69 (dd, 1H, J = 9.8, 3.3 Hz), 3.45 (d, 1H, *J* = 12.6 Hz), 3.36 (dt, 2H, *J* = 14.8, 9.9, 4.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.5, 138.2, 137.7, 128.8, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 125.9, 101.3, 79.2, 78.5, 74.3, 72.6, 72.4, 72.2, 68.9, 68,6. HRMS calcd for $C_{27}H_{28}O_5$ $[M+Na]^+$ 455.1834, found 455.1827.

2,3-Dibenzyl-4,6-dihydroxy-1-Deoxy-mannose 35. 2,3-Dibenzyl-1-Deoxy-mannose-4,6-benzylidene acetal **34** (1.71 g, 3.95 mmol) was dissolved in acetic acid (80% in H_2O, 20.0 mL). The solution was stirred at 45-50 °C for 12 h and cooled to 0 °C. Neutralization was achieved using a saturated solution of sodium bicarbonate and the water was evaporated under vacuum. The crude mixture was taken up in EtOAc and the organic phase was washed with H_2O and dried on Na_2SO_4. After filtration and drying under high vacuum, the product was obtained as a white solid (1.36 g, 3.95 mmol). Yield: 100%. Mp: 82-83 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.41-7.25 (m, 10H), 4.73 (d, 1H, *J* = 12.4 Hz), 4.61 (t, 2H, *J* = 11.8 Hz), 4.46 (d, 1H, *J* = 11.8 Hz), 4.11 (dd, 1H, *J* = 12.8, 2.0 Hz), 4.00 (t, 1H, *J* = 9.5 Hz), 3.89 (dd, 1H, *J* = 11.8, 3.3 Hz), 3.79 (d, 1H, *J* = 5.6 Hz), 3.76 (m, 1H), 3.39 (dd, 1H, *J* = 9.4, 3.2 Hz), 3.35 (d, 1H, J = 12.7 Hz), 3.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.0, 137.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 82.2, 80.1, 71.9, 71.3, 71.1, 67.5, 67.1, 62.9. HRMS calcd for $C_{20}H_{24}O_5$ $[M+Na]^+$ 367.1521, found 367.1517.

2,3-Dibenzyl-4,6-dimethanesulfonyl-1-Deoxy-mannose 36. 2,3-Dibenzyl-4,6-dihydroxy-1-Deoxy-mannose **35** (1.08 g, 3.14 mmol) was dissolved in dichloromethane (15.0 mL). Methanesulfonyl chloride (0.980 mL, 12.6 mmol) and triethylamine (3.00 mL, 21.5 mmol) were added at 0 °C. The solution was stirred at 0 °C for 30 min and then at room temperature 14 h. the solution was diluted with CH_2Cl_2 and the reaction was quenched with ice. After separating the phases, the organic phase was washed with water and dried on Na_2SO_4. The solvent was evaporated and the crude mixture was purified on SiO_2 gel using a gradient of pure hexane to hexane:EtOAc 2:1. The pure product was obtained as a light brown semi solid (1.34 g, 2.68 mmol). Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.38-7.24 (m, 10H), 4.84 (t, 1H, J = 9.6 Hz), 4.69 (d, 1H, J = 12.2 Hz), 4.59 (m, 2H), 4.44 (d, 1H, J = 11.3 Hz), 4.36 (dd, 1H, J = 11.5, 5.7 Hz), 4.14 (d, 1H, J = 12.9 Hz), 3.88 (bs, 1H), 3.68 (dd, 1H, J = 9.4, 2.8 Hz), 3.62 (m, 1H), 3.37 (d, 1H, J = 12.9 Hz), 3.01 (s, 3H), 2.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.5, 136.7, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 79.1, 76.2, 71.7, 71.0, 70.9, 68.4, 66.3, 38.4, 37.3. HRMS calcd for $C_{22}H_{28}O_9S_2$ $[M+Na]^+$ 523.1072, found 523.1087.

2,3-Dibenzyl-6-bromo-4-methanesulfonyl-1-Deoxy-mannose 37. 2,3-Dibenzyl-4,6-dimethanesulfonyl-1-Deoxy-mannose **36** (0.920 g, 1.84 mmol) was dissolved in anhydrous DMSO (10.0 mL). Sodium bromide (1.14 g, 11.1 mmol) and tetrabutylammonium bromide (0.178 g, 0.552 mmol) were added to the solution and the mixture was stirred at 60 °C for 36 h. DMSO was evaporated under nitrogen and the crude residue was taken up in CH_2Cl_2. The organic phase was washed with H_2O, dried on Na_2SO_4, filtered and evaporated under vacuum. The crude mixture was purified on SiO_2 gel using a gradient of pure hexane to hexane:EtOAc 6:1. The pure product was obtained as a light yellow solid (0.691 g, 1.42 mmol). Yield: 78%.

Mp: 74-75 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.39-7.27 (m, 10H), 4.77 (m, 1H), 4.74 (m, 2H), 4.59 (t, 1H, J = 12.5 Hz), 4.39 (d, 1H, J = 11.3 Hz), 4.22 (dd, 1H, J = 12.9, 2.3 Hz), 3.86 (m, 1H), 3.81 (dd, 1H, J = 10.9, 1.8 Hz), 3.63 (dd, 1H, J = 9.4, 3.2 Hz), 3.52 (m, 2H), 3.36 (d, 1H, J = 12.9 Hz), 2.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.5, 136.8, 128.6, 128.5, 128.3, 127.9, 79.3, 79.0, 78.5, 71.7, 71.1, 71.0, 66.4, 38.6, 31.7. HRMS calcd for $C_{21}H_{25}BrO_6S$ $[M+Na]^+$ 507.0453, found 507.0471.

2,3-Dibenzyl-6-(*N*-boc-diethylaminomalonyl)-4-methanesulfonyl-1-Deoxy-mannose 38. *N*-Boc-diethylaminomalonate (0.426 g, 1.55 mmol) was dissolved in anhydrous toluene (1.00 mL). After cooling to 0 °C, sodium hydride (57-63% in mineral oil, 65.3 mg, 1.55 mmol) was added and the solution was stirred for 45 min. 2,3-Dibenzyl-6-bromo-4-methanesulfonyl-1-Deoxy-mannose **37** (0.146 g, 0.301 mmol) in 1.00 mL of anhydrous toluene and TBAI (34.4 mg, 0.093 mmol) were added to the mixture and the solution was stirred under reflux for 14 h. The solution was cooled to room temperature, diluted with CH_2Cl_2 and quenched with ice. After separating the phases, the organic phase was washed twice with water and dried on Na_2SO_4. After filtration and concentration, the crude mixture was purified on SiO_2 gel using a gradient of solvent of pure hexane to hexane:EtOAc 6:1. The pure product was obtained as a white solid (104 mg, 0.153 mmol). Yield: 51%. Mp: 41-42 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.37-7.25 (m, 1H), 6.03 (bs, 1H), 4.73 (m, 1H), 4.59 (m, 3H), 4.17 (q, 4H, J = 13.6, 6.6 Hz), 3.80 (m, 2H), 3.55 (d, 1H, J = 8.3 Hz), 3.39 (t, 1H, J = 9.9 Hz), 3.15 (d, 1H, J = 12.8 Hz), 2.93 (m, 3H), 2.54 (dd, 1H, J = 14.9, 10.8 Hz), 1.42 (s, 9H), 1.22 (t, 3H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (major rotomer) 168.4, 153.9, 137.8, 128.4, 128.3, 127.9, 127.6, 81.6, 79.5, 74.7, 72.5, 71.2, 71.1, 66.3, 64.2, 62.5, 38.9, 35.0, 28.1, 13.7. (minor rotomer) 167.8, 153.5, 137.3, 128.4, 128.3, 127.9, 127.6,

81.6, 79.3, 74.7, 72.4, 71.4, 70.9, 66.1, 64.2, 62.0, 38.6, 35.1, 27.8, 13.8. HRMS calcd for $C_{33}H_{45}NO_{12}S$ $[M+Na]^+$ 702.2560, found 702.2571.

2,3-Dibenzyl-6-(*N*-boc-2-amino-ethylacetate)-4-methanesulfonyl-1-Deoxy-mannose 39. ^1H NMR ($CDCl_3$, 400 MHz); δ 7.39-7.25 (m, 10H), 4.64 (m, 5H), 4.38 (m, 2H), 4.16 (m, 3H), 3.83 (d, 1H, J = 15.8 Hz), 3.58 (dt, 1H, J = 9.5, 5.5, 2.8 Hz), 3.43 (t, 1H, J = 9.0 Hz), 3.27 (m, 2H), 2.91-2.85 (m, 3H), 2.11 (m, 1H), 1.44 (s, 9H), 1.28-1.23 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (major isomer): 172.3, 155.6, 137.5, 136.7, 128.4, 128.3, 127.8, 79.8, 79.5, 75.7, 72.1, 71.9, 71.1, 70.8, 66.6, 61.1, 50.6, 38.5, 33.9, 28.1, 13.9. (minor isomer): 172.1, 155.0, 137.6, 136.8, 128.4, 128.2, 127.8, 79.8, 79.3, 75.6, 72.1, 71.9, 71.1, 70.9, 66.3, 61.1, 50.9, 38.5, 33.9, 28.1, 13.8. Yield: 91%. HRMS calcd for $C_{30}H_{41}NO_{10}S$ $[M+Na]^+$ 630.2349, found 630.2346.

2,3-Dibenzyl-6-(2-amino-ethylacetate)-4-methanesulfonyl-1-Deoxy-mannose 40. ^1H NMR ($CDCl_3$, 400 MHz); δ 7.43-7.22 (m, 10H), 4.70 (m, 2H), 4.57 (m, 2H), 4.39 (d, 1H, J = 11.1 Hz), 4.19 (m, 4H), 3.86 (s, 1H), 3.65 (m, 1H), 3.41 (m, 1H), 2.89 (s, 3H), 2.38 (m, 2H), 1.26 (m, 3H). Yield: 96%.

(2*S*,3a*R*,6*R*,7*S*,7a*S*)- 2-ethyl-carboxylate-6,7-bis(benzyloxy)octahydroindole 41. ^1H NMR ($CDCl_3$, 400 MHz); δ 7.41-7.27 (m, 10H), 4.77 (d, 1H, J = 12.5 Hz), 4.76 (q, 2H, J = 23.6, 12.2 Hz), 4.65 (d, 1H, J = 12.2 Hz), 4.17 (q, 2H, J = 14.2, 7.0 Hz), 4.14 (t, 1H, J = 7.9 Hz), 4.03 (d, 1H, J = 12.6 Hz), 3.94 (bs, 1H), 3.69 (m, 2H), 3.52 (bs, 1H), 3.27 (d, 1H, J = 12.7 Hz), 2.26 (dd, 1H, J = 13.9, 8.7 Hz), 2.09 (m, 1H), 1.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 175.3, 138.2,

138.1, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 79.6, 73.6, 72.7, 72.3, 69.1, 67.1, 60.7, 60.6, 58.5, 37.4, 14.1. Yield: 38%. HRMS calcd for $C_{24}H_{29}NO_5$ $[M+H]^+$ 412.2124, found 412.2133.

(2*R*,3a*R*,6*R*,7*S*,7a*S*)- 2-ethyl-carboxylate-6,7-bis(benzyloxy)octahydroindole 42. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.49-7.26 (m, 10H), 4.79 (q, 2H, J = 29.9, 12.4 Hz), 4.68 (q, 2H, J = 33.3, 12.4 Hz), 4.14 (m, 2H), 4.07 (dd, 2H, J = 12.9, 1.9 Hz), 3.82 (m, 2H), 3.72 (m, 2H), 3.23 (d, 2H, J = 12.7 Hz), 2.27 (m, 1H), 2.08 (dd, 1H, J = 14.3, 4.5 Hz), 1.19 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 173.3, 138.3, 138.1, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 78.8, 73.8, 72.2, 71.9, 69.3, 66.9, 61.7, 60.9, 59.3, 38.1, 14.0. Yield: 46%. HRMS calcd for $C_{24}H_{29}NO_5$ $[M+H]^+$ 412.2124, found 412.2112.

Ethyl-6,7-dihydroxyl-octahydropyrano[3,2-b]pyrrole-2-carboxylate (43 + 44). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 4.79 (m, 2H), 4.27 (m, 5H), 3.52 (m, 2H), 2.58 (m, 1H), 2.29 (m, 1H), 1.29 (t, 3H, J = 7.1 Hz).). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 171.1, 83.2, 75.2, 68.8, 66.9, 63.2, 58.0, 52.4, 36.0, 13.7. HRMS calcd for $C_{10}H_{17}NO_5$ $[M+H]^+$ 232.1185, found 232.1181.

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