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PREPARATION OF THIOALKYL SUBSTITUTED SMALL RING NITROGEN HETEROCYCLES AND 5-DISUBSTITUTED-ETHYL-2-OXAZOLIDINONES FOR ANTIBACTERIAL AND ANTIVIRAL CANDIDACY

presented by

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of the requirements for the

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Date

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ABSTRACT

PREPARATION OF THIOALKYL SUBSTITUTED SMALL RING NITROGEN HETEROCYCLES AND 5-DISUBSTITUTED-ETHYL-2-OXAZOLIDINONES FOR ANTIBACTERIAL AND ANTIVIRAL CANDIDACY

By

Zhen Xu

Oxazolidinones are a new type of synthetic antibacterial drugs with unique mechanism of action. General and concise syntheses towards novel antibacterial oxazolidinone intermediates from naturally occurring carbohydrates were developed. An efficient four-step sequence was achieved in the synthesis of homochiral 5-D-erythro-2-oxazolidinones using 2-deoxy-D-ribose as chiral synthon. Furthermore, a methodology of *in situ* deprotection and rearrangement of N-*p*-methoxybenzyl-β-hydroxyamide to form 5-substituted-2-oxazolidinones was succeeded. An application of this methodology in the solid-state synthesis was suggested.

A template family of novel homochiral thioalkyl substituted small ring nitrogen heterocycles was established from carbohydrate precursors. The target molecules were designed as the transition-state analogs of glycosidase inhibitors. Preliminary bio-test showed promising inhibitory activities against a gram-positive bacterial strain.

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CHAPTER 1 ANTIBACTERIAL OXAZOLIDINONES

1.1. BACKGROUND

The development of bacterial resistance to almost all currently available antibacterial agents is a growing global health problem. In particular, the most cited gram-positive bacteria, including methicillin resistant *Staphylococcus aureus* (MRSA), penicillin resistant *Streptococcus pneumoniae*, and vancomycin resistant *Enterococci* (VRE), are of major concern because they have acquired multidrug resistance and formidable treatment problems with these pathogens, which could easily result in mortality. The molecular mechanisms by which bacteria become resistant usually involve drug efflux, drug inactivation, or alterations in the antibiotic target site.[1] A number of solutions to the problem of bacterial resistance are possible. The most common approach is to modify the existing classes of antibacterial agents to provide new analogs with improved attributes. More importantly, another approach is to explore novel classes of antibacterial agents with new mechanisms of action because such agents would have the advantage of lack of cross-resistance with existing drugs. However, over the past forty years, very few new classes of antibacterial agents have been developed. **(Table 1.1)** The large number of antibiotics available on the market were developed through extensive effort in structure activity relationships (SAR), which led to a very large array of antibiotics within existing classes when improvements in activity, or safety were realized relative to pre-existing members of the classes. For example, the "new" macrolides and fluoroquinolones, are modified variants of agents known since the 1950s and 1960s, respectively.[2]

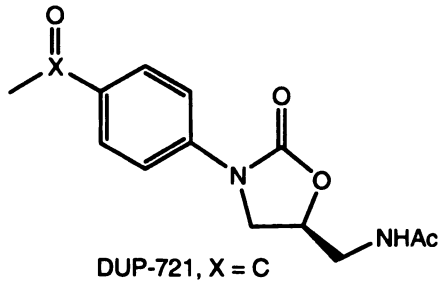
Table 1.1. Introduction of new drug classes by the pharmaceutical industry

Year of launch	Antibiotic	Targets
1936	Sulphonamides (SMZ)	Folic acid antagonists
1940	Penicillins (β-lactams)	Cell-wall synthesis
1949	Tetracyclines	Protein synthesis
1949	Chloramphenicol	Protein synthesis
1950	Aminoglycosides	Protein synthesis
1952	Macrolides (Erythromycin)	Protein synthesis
1958	Glycopeptides (Vancomycin)	Cell-wall synthesis
1962	Streptogramins	Protein synthesis
1962	Quinolones (fluoroquinolone)	DNA replication
2000	Oxazolidinones [3] (Linezolid)	Initiation of protein synthesis

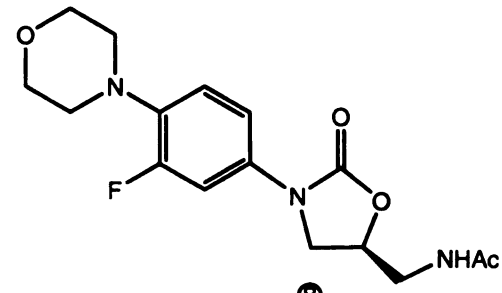
A novel class of antibacterial agents, oxazolidinones,[3] are being developed to fill the gap caused by the increasing instances of resistance to the last-line defense drugs such as β-lactams, vancomycin and a host of other agents. The oxazolidinones were originally developed as monoamine oxidase (MAO-A) inhibitors for treatment of depression.[4,5] The first oxazolidinones to show any appreciable activity against bacteria were described by a South African group in a 1968 patent.[6] In the late 1970s, the oxazolidinones were developed by E. I. DuPont de Nemours Company for control of bacterial and fungal foliage diseases of tomatoes and other plants.[5] By the late 1980s, after chemical modification of the early agents, the same company released two main candidates of (S)-

5-acetamidomethyl-3-aryloxazolidin-2-ones: DUP-721 and DUP-105 **(Figure 1.1)**, which showed a broad in vitro spectrum against most gram-positive bacteria, as well as several anaerobes.[2] Toxic effects (myelosuppression caused by inhibition of protein synthesis) in animal models prevented their clinical development. However, they served as the key structural templates on which the first successful oxazolidinone candidates were based. Scientists at Pharmacia continued to work with the oxazolidinones, exploring a series of chemical modifications. Their efforts led to the discovery of two agents, Linezolid and Eperezolid in 1994, with improved antibacterial activity and markedly diminished toxicity compared with DUP-721. In April 2000, Linezolid (Zyvox®) was approved by the Food and Drug Administration (FDA) as the first of this new class of antibacterial agent for treatment of infections associated with vancomycin-resistant *Enterococcus faecium, E. faecium* related bacteremia, complicated and uncomplicated skin and soft-tissue infections, and nosocomial (hospital-acquired) pneumonia.[7, 8]

Figure 1.1: Template examples of antibacterial oxazolidinones



DUP-721, X = C
DUP-105, X = S



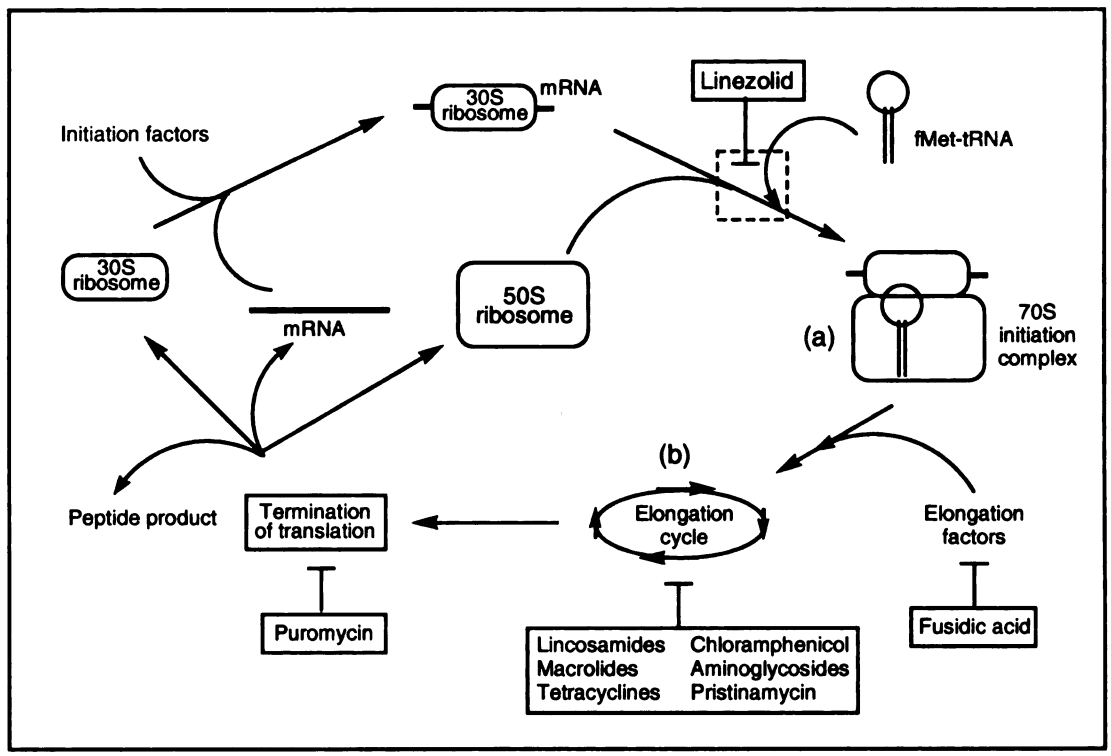
Linezolid (Zyvox®)

1.2. MECHANISM OF ACTION (Figure 1.2)

The oxazolidinones have excellent in vitro activity against most of the major gram-positive bacteria that are pathogenic in humans. The oxazolidinones such as linezolid are orally active and bear excellent pharmacokinetic behavior (100 % bioavailability). Also, the drug is a totally synthetic compound, which lessens the likelihood of naturally occurring resistance mechanism. And more importantly, the oxazolidinones have a unique mechanism of action so that cross-resistance with existing resistance mechanisms in bacteria is believed to be unlikely. Based on the studies of oxazolidinone binding sites, and the solution of the crystal structure of the entire ribosome[9] including high-resolution structure of the 50S subunit[10] and a structure for the 30S subunit,[11] it became mainly accepted that oxazolidinones inhibit bacteria protein synthesis by interacting with the ribosome at the initiation step. Initiation of protein synthesis occurs when the 30S ribosomal subunit, mRNA, fMet-tRNA, and the 50S ribosomal subunit combine. Collective data suggest that the ribosomal interaction of oxazolidinones is between these two subunits. For example, linezolid binding to the 23S rRNA component of the 50S subunit distorts the binding site for fMet-tRNA, preventing the formation of fMet-tRNA-mRNA-70S (70S initiation complex), thus inhibiting initiation of protein synthesis.[12] It is worth mentioning that most marketed antibiotics that inhibit protein synthesis by binding to the 23 rRNA at the peptidyl transferase cavity[13] such as chloramphenicol, clindamycin, erythromycin, clarithromycin and roxithromycin, inhibit later steps in the pathway involving elongation of the growing peptide chain rather than the initiation step. To date a crystal structure of an oxazolidinone bound to a

ribosomal subunit has not been described. But the availability of the ribosome structures[14] will, no doubt, facilitate rational drug design.

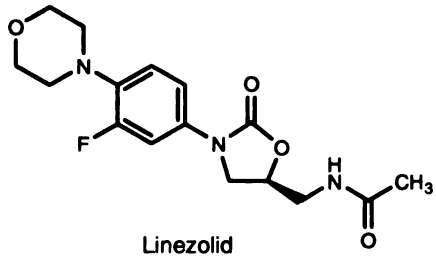
Figure 1.2: Mechanism of action[15]



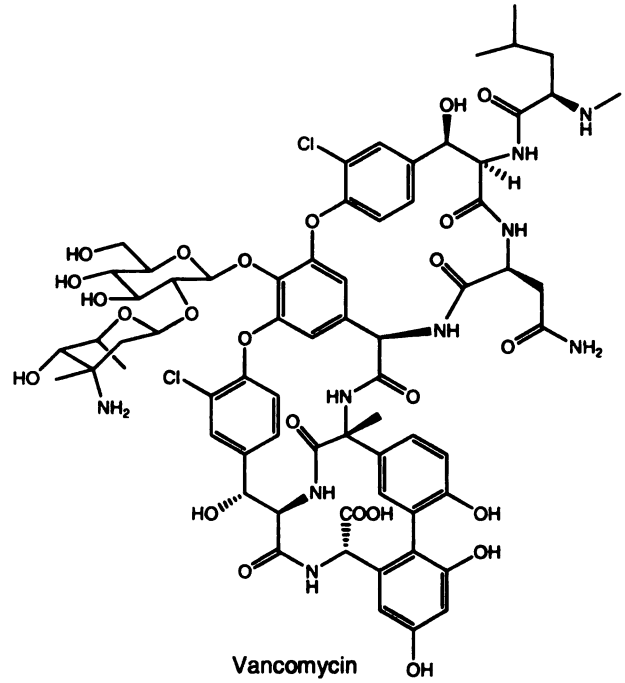
Schematic representation of oxazolidinone mechanism of action in bacterial cell (fMet-tRNA: N-formylmethionyl transfer RNA)

1.3. STRUCTURE-ACTIVITY RELATIONSHIP (SAR) STUDY

Figure 1.3: Comparison between Linezolid and Vancomycin



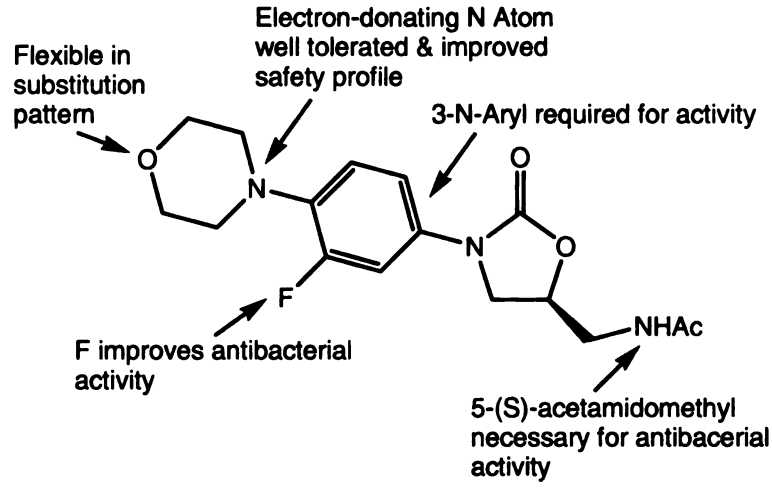
Linezolid



Vancomycin

One of the striking features of the antibacterial oxazolidinones is their structural simplicity compared to vancomycin, the previous last-resort drug. **(Figure 1.3)** The oxazolidinone drugs are totally synthetic. The structural simplicity of oxazolidinones could lead to a good understanding of structure-activity relationships (SAR) and it is possible to see how new oxazolidinone drugs have evolved based on the structures of earlier drugs.

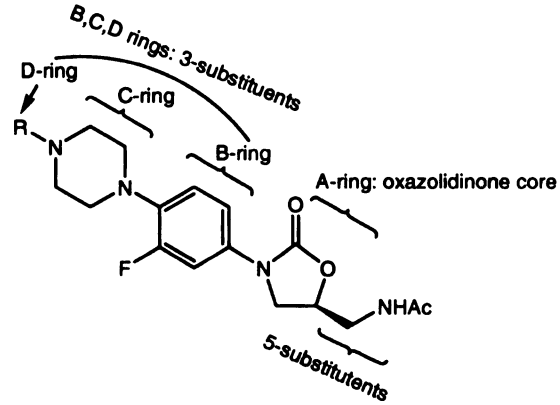
Figure 1.4: Structure-activity relationships of antibacterial oxazolidinones (Linezolid)

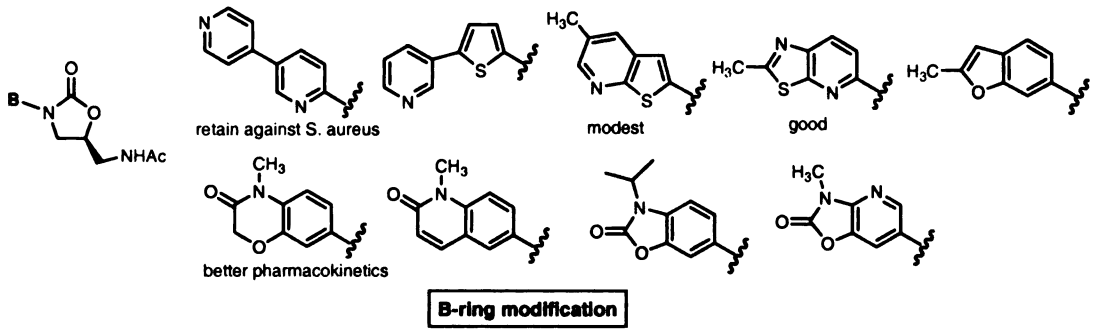


During the development of oxazolidinones as antimicrobial drugs, some structure-activity trends began to emerge. Activity was determined to be a function of the size and nature of the 5-substituent, the nature of the 3-substituent and the configuration at the 5-position.[16,17] The 5-substituent was mostly small, non-basic and the (S)-acetamido methyl group was thought to be optimum.[18] This dogma was mainly limited to carbonyl functionalities. The 3-substituent was invariably an aryl group with different substitution pattern.[15] Among those variations, the 3-substituent was most extensively investigated from different perspectives including antibacterial activity,[19-21] safety profile,[22] pharmacokinetic issue,[19] and antibacterial spectra.[23,15b] For example, the linezolid and eperezolid candidates were selected after rigorous SAR study of the 3-substituent, the modification of structural template DUP-721 with the finding that para electron-donating nitrogen heterocycle improves safety profile by marked diminution of bone marrow toxicity, meta- fluorination of phenyl ring not only increased antibacterial potency but

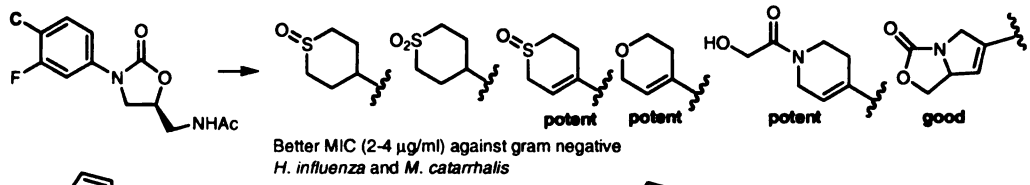
also enhanced pharmocokinetic performance.[16] **(Figure 1.4)** Recent years there are some distinct departures in structure from the earlier candidates. But most of these departures still occurred in the 3-substituent on the oxazolidinone ring which was believed to tolerate more functional modification. There are fewer variations in the 5-substituent **(Figure 1.5)**. However, recent studies have reported the introduction of substituents such as the 5-thiourea and 5-thiocarbamate, 5-dithiocarbamate and N- or O-substituted heterocyclic aryl moieties as potential replacements for the acetamidomethyl side chain at the C-5 position.[24-26] Three noteworthy publications were launched in a row discussing comprehensively the 5-substituents on oxazolidinones beyond the conventional acetamidomethyl function on the basis of structure-activity relationship (SAR).[27-29] The study revealed that replacing sulfur function 5-substituents may increase the antibacterial activity. And the balance of lipophilicity between the 5-hydrophilic substituents and hydrophobic substituents on the aromatic ring is very important for the antibacterial activity. These attempts led to more active compounds with increased range of therapeutic spectrum.

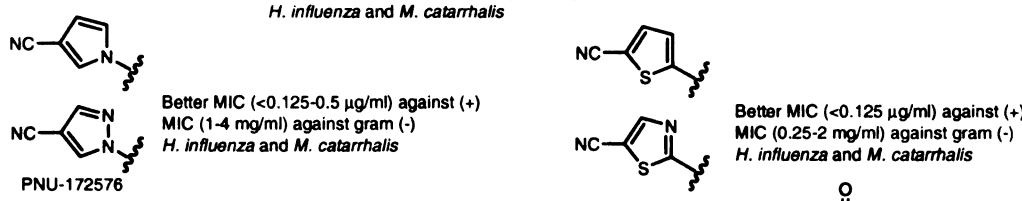
Figure 1.5: Oxazolidinone modification trends in recent years

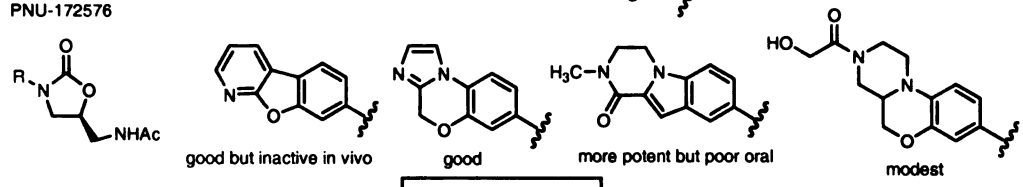




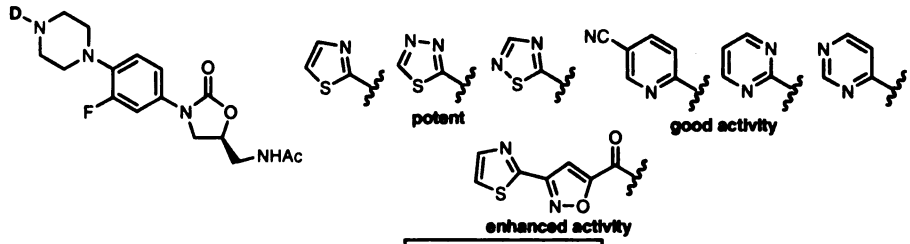
B-ring modification



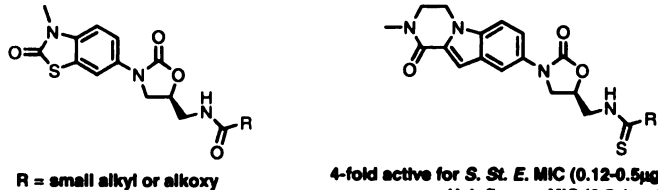


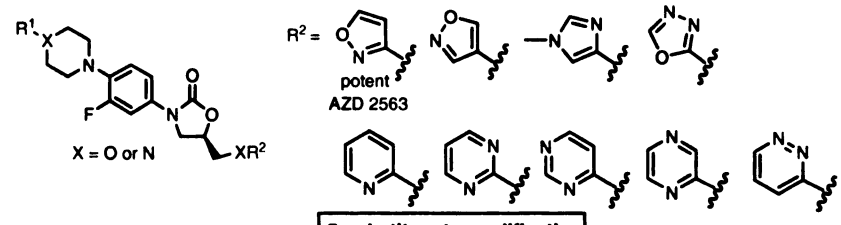


C-ring modification



D-ring modification





5-substituents modification

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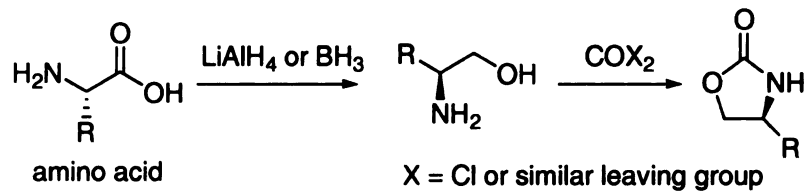
CHAPTER 2 SYNTHESIS OF OXAZOLIDINONE MOIETIES

2.1. INTRODUCTION

The oxazolidinone nucleus is a simple heterocyclic system that is not frequently found in drug structure. The 4-substituted systems are better known because they are readily obtained from amino acids by reduction and carbonylation.[35-36] (**Scheme 2.1**) The 5-substituted oxazolidinones are more difficult to prepare but are of special relevance to the area of antibacterials.

Scheme 2.1:



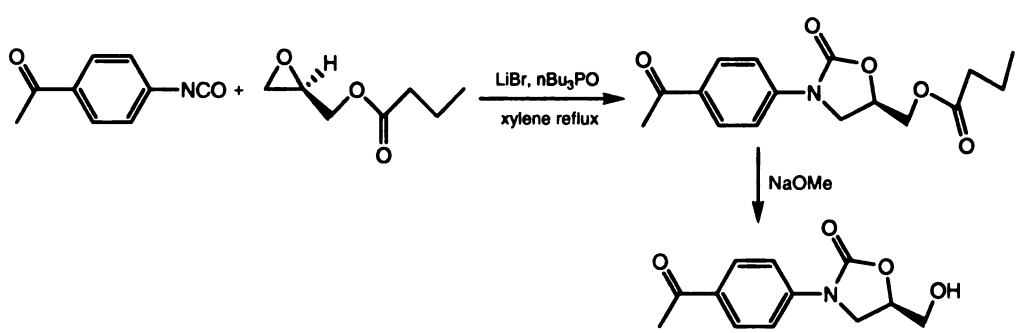
A growing effort focused on the synthesis of 5-substituted oxazolidinones started around 1987, when Dupont Company formally reported the structure and anti-bacterial activity profiles of two agents, DuP-105 and DuP-721. Subsequently, a great variety of methodologies including asymmetric catalysis (transition metal and enzymatic), bio-transformations, and chiral pool approaches such as chiral 3-carbon fragment or synthon were developed to meet the needs of structure diversity of the oxazolidinone candidates for drug discovery. Later on, SAR-guided oxazolidinone liberaries based on solid phase synthesis were generated to accelerate the quality leads synthesis. More recently, with the success of the first marketed antibacterial oxazolidinone drug Linezolid, the development of more efficient, cost-effective, and large-scale synthesis

approaches is becoming imperative.

2.2. CHIRAL 3-CARBON SYNTHON

Among the numerous methodologies, the chiral 3-carbon fragment or synthon condensed with an activated nitrogen compound dominates the literature on antibacterial oxazolidinone synthesis. In the preparation of DUP-721, an aryl isocyanate was reacted with commercially available (R)-glycidyl butyrate in the presence of tri-n-butylphosphine oxide to yield the N-arylated oxazolidinones. (**Scheme 2.2**) The hydroxymethyl group was then transformed to an acetamido group by mesylation, displacement by azide, reduction to amino group and acylation to form the 5-acetamidomethyl group.[1,2] This methodology was effective but not general because of the unavailability of a large variety of isocyanates starting material.

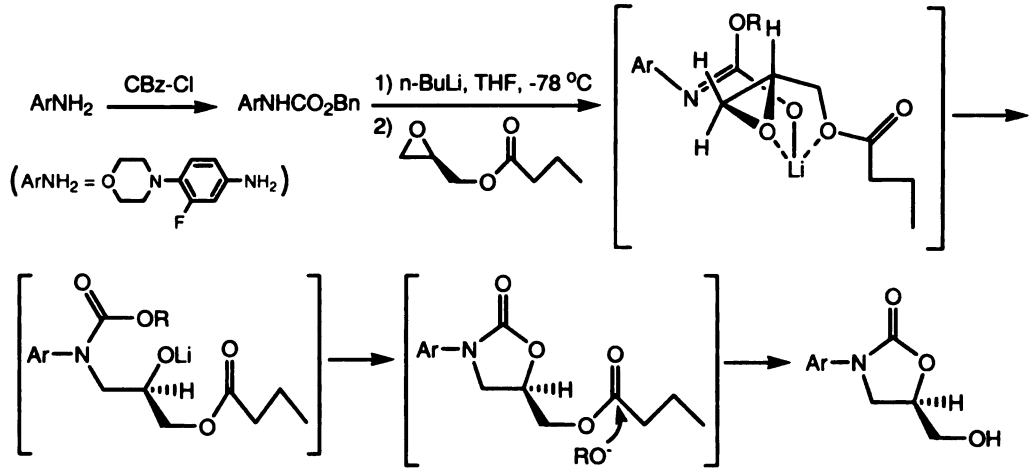
Scheme 2.2:



A more effective approach was developed by Manninen and co-workers at Pharmacia and used in the preparation of Linezolid in 1996.[3,4] In this approach, an aniline was transformed to a carbamate by reaction with benzyloxycarbonyl chloride. The carbamate was then lithiated and reacted with (R)-glycidyl butyrate to directly generate (R)-3-aryl-5-(hydroxymethyl) oxazolidinones. (**Scheme 2.3**) The

hydroxymethyl substituents were then elaborated in a linear manner to the 5-acetamidomethyl group with the same process.

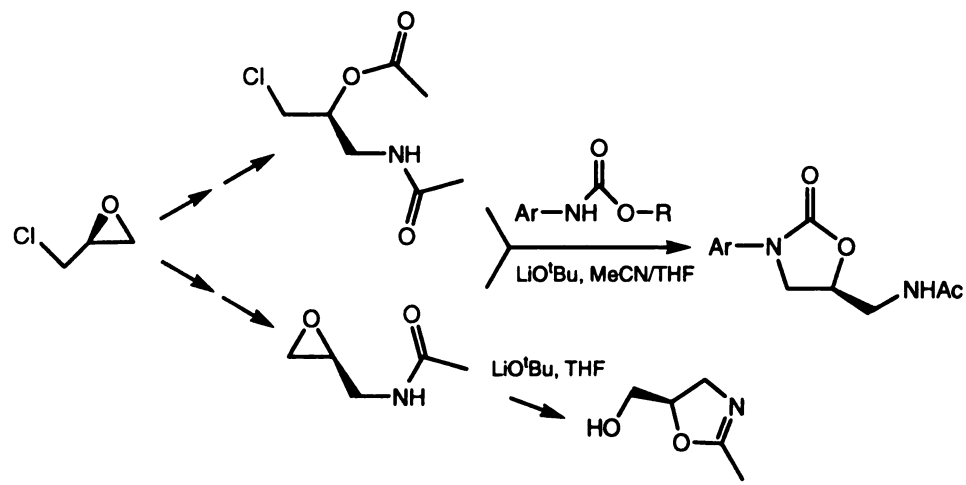
Scheme 2.3:



It was subsequently found in an effort to develop the synthesis on a process scale that (S)-3-chloro-1,2-propanediol could be used as a substitute for (R)-glycidyl butyrate with lithium tert-butoxide as base and DMF and DMAc as solvent.[5] From the commercial standpoint, the resulting hydroxymethyl intermediates were activated by nosylation and a large excess of ammonia (100 equiv) was used for the subsequent displacement reaction.[4] The excess of aqueous ammonia suppressed competing dimer formation and accelerated the displacement reaction. To reduce the number of steps from the aryl carbamate to the desired 5(S)-acetamido oxazolidinones, convergent early amination approaches using chiral oxiranylmethylacetamide were explored.[6,9] The chiral oxiranylmethylacetamide was obtained by dynamic kinetic resolution of cheap racemic epichlorohydrin using Jacobsen's chiral transition metal complex with azide as the nucleophile.[6] However, the 3-carbon fragment oxiranylmethylacetamide in

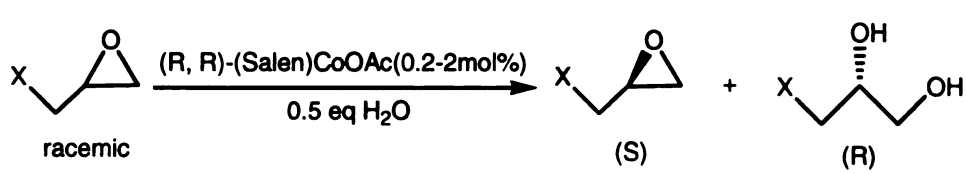
the Manninen conditions resulted in only a moderate yield (70%) due to its competitive formation of the oxazoline byproduct. (**Scheme 2.4**) Also, the oxiranylmethylacetamide was relatively unstable and could not be isolated on large scale.

Scheme 2.4:



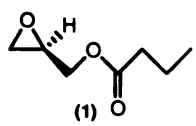
In 1998, Jacobsen developed a highly effective hydrolytic kinetic resolution of racemic epichlorohydrin[7] using chiral Mn-salen complexes (**Scheme 2.5**) and directed towards the large-scale synthesis.[8] The cost of (S)-epichlorohydrin became less prohibitive. In 1999, Chirex began making tonne quantities of (S)-epichlorohydrin from cheap racemic epichlorohydrin using Jacobsen's methodology. A large portion of the chiral epichlorohydrin starting material used in the manufacture of antibacterial oxazolidinones relies on this methodology.

Scheme 2.5:



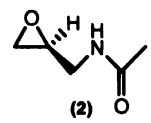
Jacobsen Hydrolytic Kinetic Resolution

Scheme 2.6: Chiral 3-Carbon Synthon



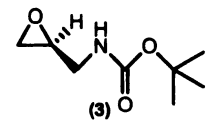
(1)

J. Med. Chem. **1992**, *35*, 1156
J. Med. Chem. **1996**, *3*, 673



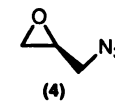
(2)

Tetrahedron Lett. **1998**, *37*, 7937



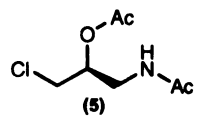
(3)

WO 9940094, Aug. 12, **1999**
WO 9937641, Jul. 29, **1999**



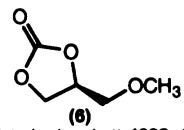
(4)

Tetrahedron Lett. **1996**, *37*, 7937



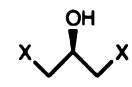
(5)

Org. Pro. R. & D. **2003**, *7*, 533



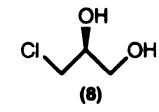
(6)

Tetrahedron Lett. **1998**, *39*, 4453



X = Cl or Br,NH_2 (7)

Tetrahedron Lett. **2000**, *41*, 4301
Heterocycles **2001**, *55*, 353



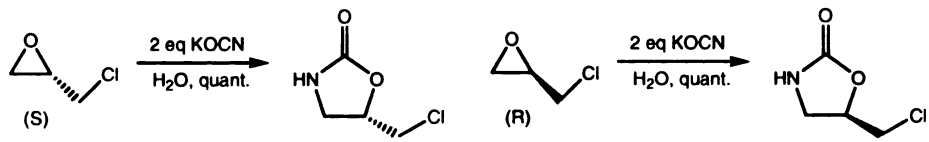
(8)

Tetrahedron Lett. **2000**, *41*,4301

It was found that the chiral 3-carbon intermediate (**5**) could afford oxiranylmethylacetamide *in situ* by deacetylation in the Manninen condition and (**5**) was crystalline in enantiopure form making it an attractive synthetic target for large-scale synthesis. (**Scheme 2.6**) Thus a shortened route of one-pot synthesis of 5(S)-acetamidomethyl-2-oxazolidinone was developed with N-aryl carbamate and (**5**).[9]

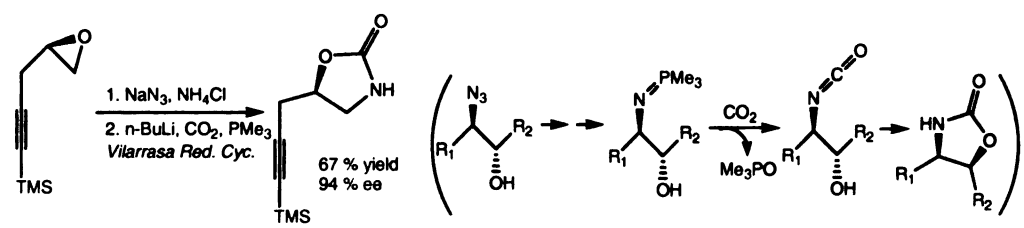
In 2001, E. Steckhan et al[10] reported an even more direct and concise route for preparing 5-substituted oxazolidinones by starting with the same chiral synthon epichlorohydrin, which is now commercially available in both enantiomerically pure forms. Either enantiomer can be transformed in one step into the respective chiral 5-chloromethyl-2-oxazolidinone in nearly quantitative yield by using potassium cyanate as nucleophile for the opening of the epoxide. This synthesis has been described previously for racemic 5-chloromethyl-2-oxazolidinone from racemic epichlorohydrin.[11] (**Scheme 2.7**) It is noteworthy that the reaction was carried out in aqueous solution and the potassium cyanate is considerably cheap.

Scheme 2.7:

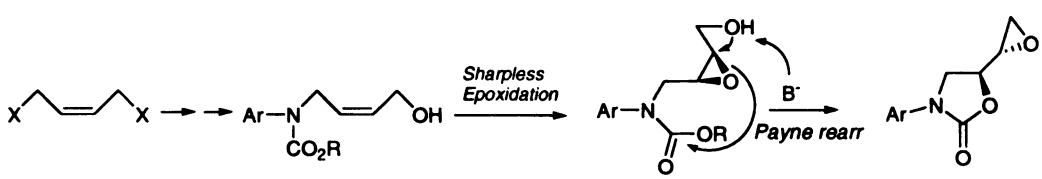


Some other interesting 3-carbon chiral synthon manipulations to afford 5-substituted oxazolidinones have been reported such as the reaction of cyclic carbonate with carbamate ester,[12] Vilarrasa reductive cyclization of hydroxyl azide,[13] **(Scheme 2.8)** iodolactonization of allylic olefin,[14] Sharpless epoxidation followed by tandem Payne rearrangement and cyclization of carbamate,[15] **(Scheme 2.9)** etc. These methodologies demonstrate the versatility of synthesis of antibacterial oxazolidinone moieties from various perspectives.

Scheme 2.8:



Scheme 2.9:

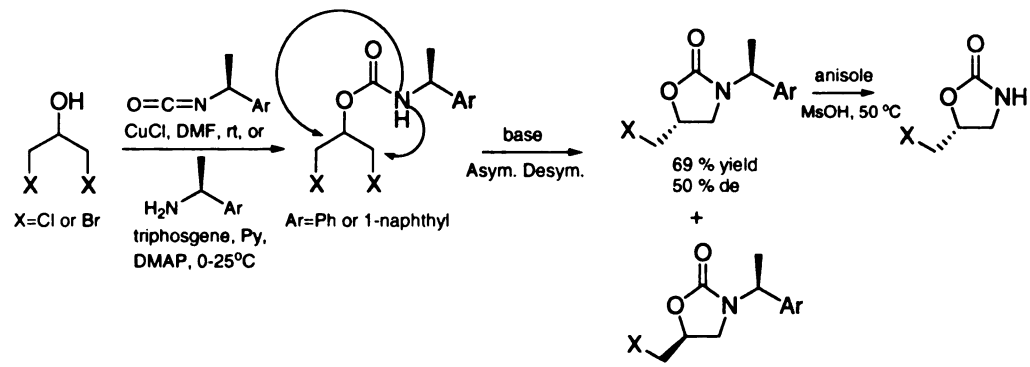


2.3. CHIRAL AUXILIARIES

The use of chiral auxiliaries to form optically enriched oxazolidinones from achiral 3-synthons represents another approach to the synthesis of oxazolidinones. In one

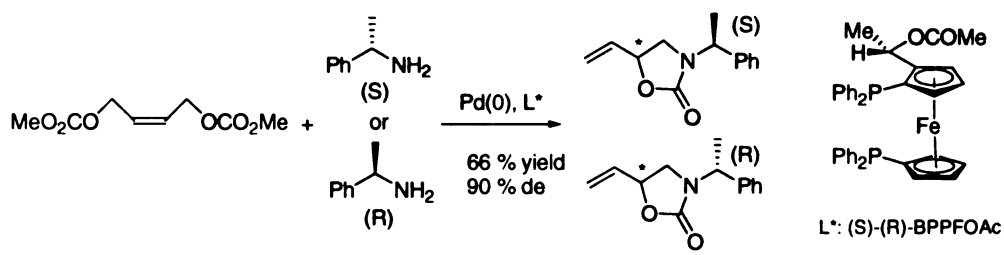
example, prochiral 1,3-dibromo-2-propanol was converted into carbamate with optically pure 1-phenylethylisocyanate or 1-phenylethylamine. Intramolecular asymmetric desymmetrization with base afforded the protected oxazolidinone moieties with moderate yield and diastereoselectivity. The diastereomers were separated by chromatography and the 5-bromomethyl oxazolidinones were obtained after debenzylation with anisole-methanesulfonic acid.[16] **(Scheme 2.10)**

Scheme 2.10:



However, the presence of chiral auxiliary may not necessarily generate enantiomerically enriched oxazolidinones. In another example, the palladium catalyst-mediated reaction of cis-2-butenylene dicarbonate and chiral amine failed to give enantio-discriminated oxazolidinones, thus chiral ligand was added to promote the enantio-differentiation and afford the 5-vinyl oxazolidinone moieties in moderate yield and fair to good diastereoselectivity.[17] **(Scheme 2.11)**

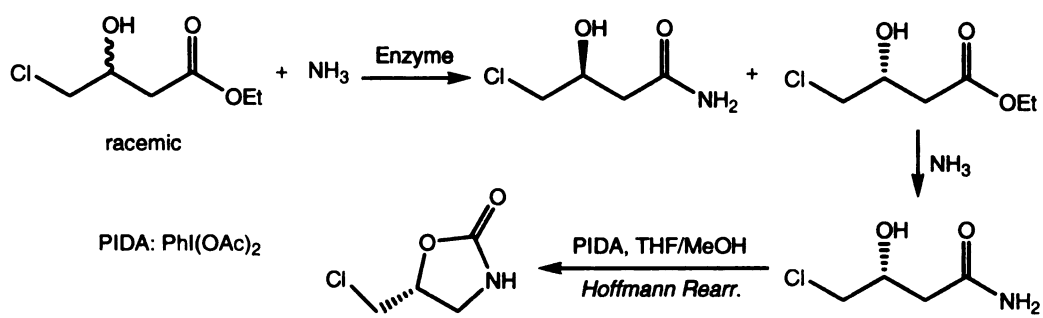
Scheme 2.11:



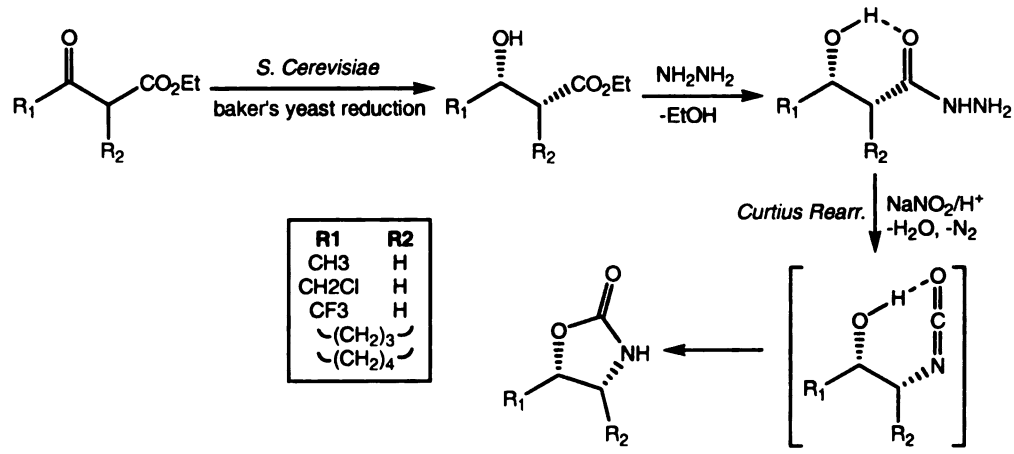
2.4. ENZYMATIC AND BIOCATALYSIS

Enzymatic resolution and biotransformation have been manipulated to generate chiral synthon intermediate that can be used to form 5-substituted oxazolidinones. Lipase B from *Candida antarctica* catalyzed the kinetic resolution of racemic ethyl-4-chloro-3-hydroxybutanoate through an ammonolysis reaction, selectively forming the (R)-β-hydroxyamide intermediate which could be processed to yield chiral 5-chloromethyl-2-oxazolidinone via a Hoffmann rearrangement.[18] **(Scheme 2.12)** Just like the normal kinetic resolution, the maximum yield of the product was 50 %. Another method employed bioreduction with *S. cerevisiae* (Baker's yeast) to produce homochiral β-hydroxy esters. The β-hydroxy esters were transformed into their hydrazides and furnished optically pure 5-substituted oxazolidinones via a Curtius rearrangement.[19] **(Scheme 2.13)** It is worth mentioning that both of these concise routes have the potential of process-scale synthesis due to the highly effective catalytic ability of enzymatic transformation.

Scheme 2.12:



Scheme 2.13:

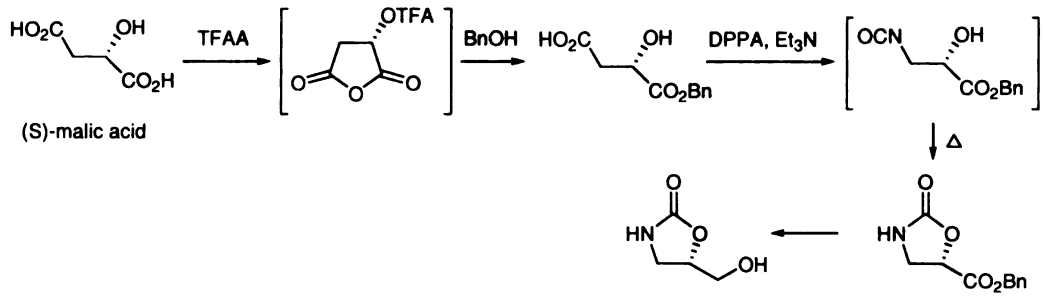


2.5. CHIRAL POOL

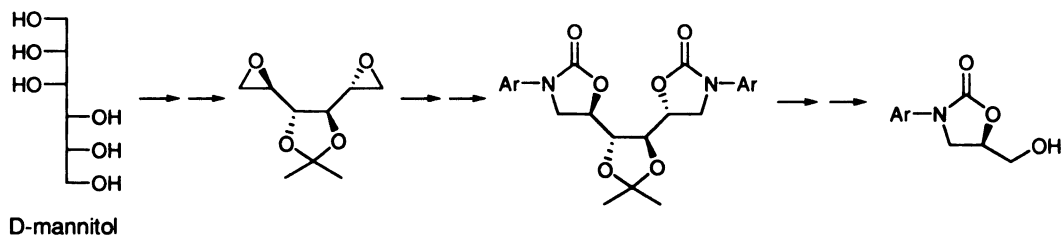
The chiral pool represents another important access to optically pure oxazolidinones. Carbohydrates and their derivatives are known for their ready availability and chiral richness in the syntheses of antibacterial oxazolidinones. In 1995, Danielmeier and Steckhan reported synthesis of optically pure 5-hydroxymethyl-2-oxazolidinones starting from D-mannitol (6 steps with overall yield 19%), L-ascorbic acid (9 steps, 7%), and (R)- or (S)-malic acid (5 steps, 42%) respectively.[20,21] **(Scheme 2.14)** The syntheses involved multiple steps and complicated conversions of functional groups from chiral natural precursors. However, this was the first example of exploiting stereochemistry from the chiral natural resources for the preparation of 5-substituted oxazolidinones. A related synthesis was reported in which the C_2-symmetry character of the D-mannitol was manipulated in the reactions.[22] Two directional syntheses starting from 1,2,5,6-dianhydro-3,4-O-isopropylidine-D-mannitol with aniline and then with carbonyldiimidazole formed a C_2-symmetric bis-oxazolidinone. Removal of

acetal group followed by periodate oxidation of the diol formed two molecules of identical 5-formyloxazolidinone. Reduction of the aldehyde group yielded the enantiomerically pure (S)-5-hydroxymethyl-2-oxazolidinone.[22-24] **(Scheme 2.15)**

Scheme 2.14:

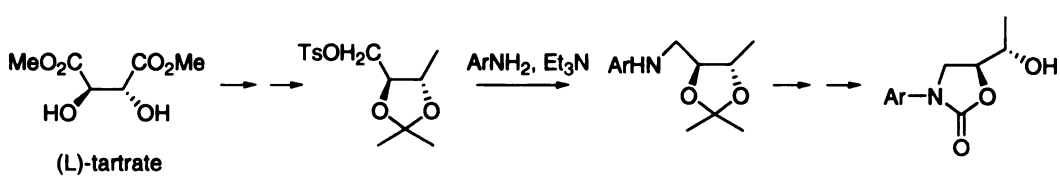


Scheme 2.15:



Another report exploiting C_2-symmetry in the natural precusor is from dimethyl L-tartrate. The starting L-tartrate underwent mono-functionalization according to Font's methodology to afford a tosylate derivative.[25] Aryl amination followed by deprotection of acetal, and carbonylation reached the 3-N-aryl-5-(1'-hydroxyethyl) oxazolidinones.[15] **(Scheme 2.16)**

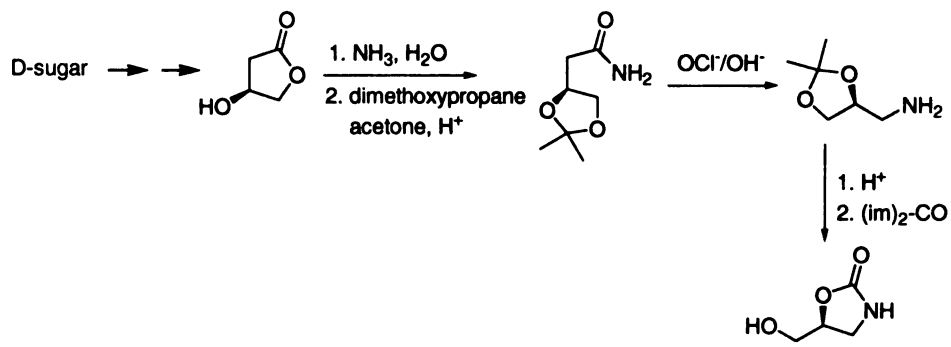
Scheme 2.16:



Though abundantly available from nature as the chiral precursor in the oxazolidinone synthesis, regio- and stereocontrolled functionalization of carbohydrate derivatives in a nimble and efficient way is still an extremely important issue to commercialize the synthesis. On the other hand, the complexity and chiral richness of carbohydrates allow for a high degree of flexibility in the functional group transformation.

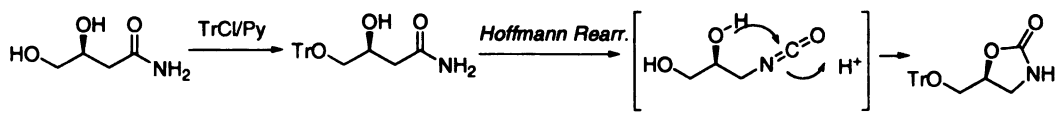
The introduction of commercially important methods for preparing optically pure 3,4-dihydroxybutyric acid and various 3- and 4-carbon derivatives has opened up ways to the preparation of optically pure oxazolidinones.[26-31] The ready availability of enantiopure 3,4-dihydroxybutyramides by treatment of 3-hydroxybutyrolactone by ammonia has facilitated several routes. In one method the isopropylidene acetal of 3,4-dihydroxybutyramide was subjected to Curtius rearrangement to afford the protected 3-amino-1,2-dihydroxypropane. This latter intermediate can be deprotected and converted to 5-hydroxymethyl-2-oxazolidinone by treatment with carbonylimidazole.[32] **(Scheme 2.17)** The 3-amino-1,2-dihydroxypropane can also be converted to 1-halo-2,3-dihydroxypropanes which can be used in alternative synthesis of oxazolidinones.

Scheme 2.17:

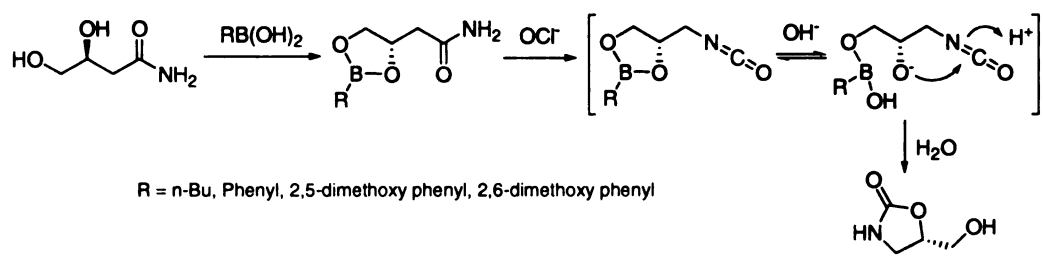


Enantiopure 3,4-dihydroxybutyramide can also be converted to its 4-trityloxy derivative that readily yields 5-trityloxymethyl-2-oxazolidinone when subjected to Hoffmann rearrangement.[33] **(Scheme 2.18)** The resultant can be used for the quick and efficient synthesis of oxazolidinone template familes as antibacterial drug candidates. One-pot synthesis by means of dynamic protection of enantiopure 3,4-dihydroxybutyramide with alkyl or arylboronic acids followed by Hoffmann rearrangement yields the free 5-hydroxymethyloxazolidinones directly in high yield.[34] **(Scheme 2.19)** This is an important new development since enantiopure 3,4-dihydroxybutyramides are available in only 2 steps from starch, lactose, maltose and hemicelluloses. The boronic acid derivatives can be generated *in situ* and transformed directly.

Scheme 2.18:



Scheme 2.19:

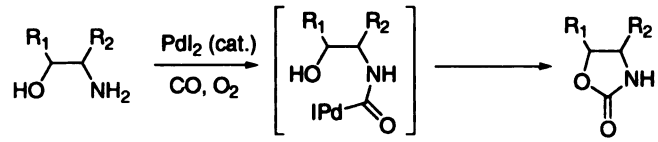


2.6. CARBONYLATION OF β-AMINOALCOHOLS

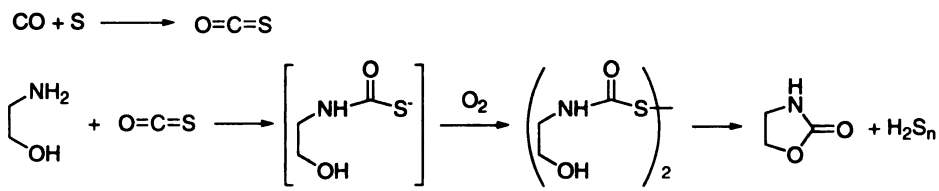
One of the conventional approaches to make oxazolidinones is the carbonylation of β-amino alcohols with toxic phosgene-based reagents[35-36] or cyanates[37]. Recently,

several groups have reported on the use of carbon monoxide and carbon dioxide with β-amino alcohols including palladium-catalyzed oxidative carbonylation with carbon monoxide,[38-39] (**Scheme 2.20**) sulfur-assisted thiocarboxylation with carbon monoxide followed by oxidative cyclization with oxygen,[40] (**Scheme 2.21**) and dehydrative condensation with carbon dioxide catalyzed by dibutyltin oxide[41] (Bu_2SnO) or 1,3-Dicyclohexylcarbodiimide (DCC) (**Scheme 2.22**).[42] Due to the prohibitive cost of chiral β-amino alcohols that could be used in the synthesis of enantiomerically pure 5-substituted oxazolidinones, these methods were complementary to the preparation of antibacterial oxazolidinones.

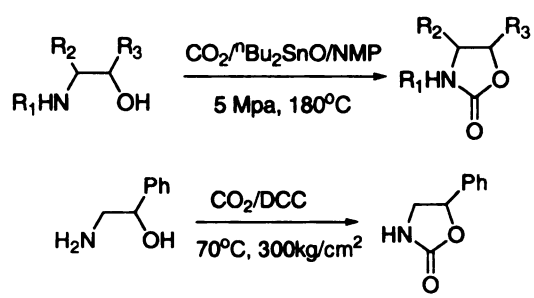
Scheme 2.20:



Scheme 2.21:



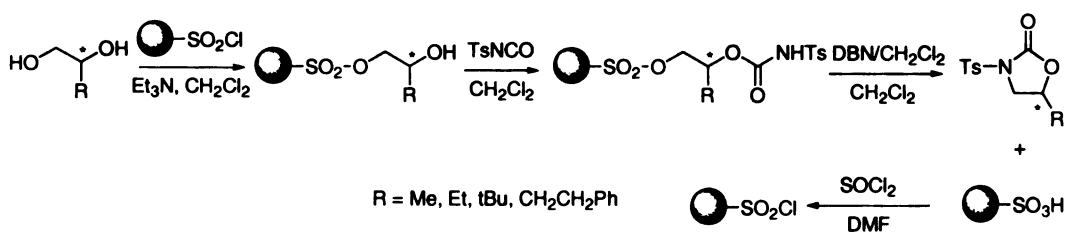
Scheme 2.22:



2.7. SOLID-PHASE SYNTHESIS

SAR studies have revealed that substitution features surrounding the oxazolidinone nucleus, especially the 3 and 5 attachments are responsible for the biological acitivity of the entire molecule. The character of oxazolidinones inspired the preparation of combinatorial libraries of oxazolidinones to discover the next generation leads with enhanced potency and improved activity ranges compared to Linezolid. In one example, a set of commercially available chiral 1,2-diols was immobilized by reaction with polymer-bound sulfonyl chloride which also activated the primary alcohol sites. The subsequent reaction of the secondary alcohol with p-toluenesulfonyl isocyanate gave carbamates that were then susceptible to base-promoted cycloelimination and afford the enantiopure oxazolidinones with concurrent detachment from the resin. The detached sulfonate could be readily regenerated using thionyl chloride.[43-44] **(Scheme 2.23)** This methodology could provide the preparation of optically pure libraries because it started from chiral diol.

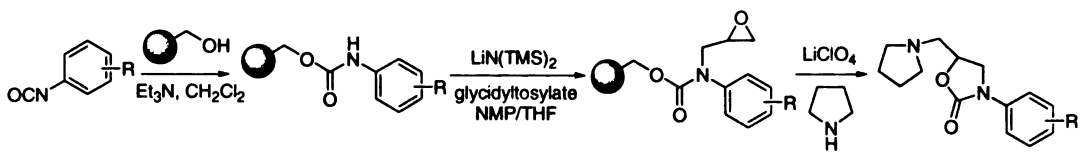
Scheme 2.23:



Another solid-phase synthesis of oxazolidinones involving a cyclization/cleavage reaction is reported earlier. Resin-bound carbamates were alkylated with glycidyltosylate to the corresponding epoxides. Nucleophilic opening of the epoxides

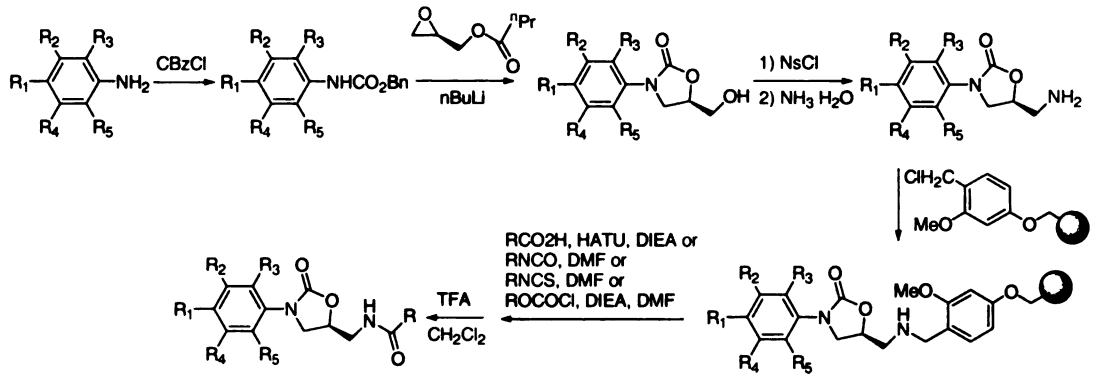
with pyrrolidine and subsequent cyclization with concurrent detachment of the resin yielded functionalized oxazolidinones.[45] **(Scheme 2.24)**

Scheme 2.24:



Gordeev from Versicor Inc. reported one of the most practical approaches for the solid-phase syntheses of oxazolidinone libraries. A library of 3-aryl-5-aminomethyl-oxazolidinone templates with various functionalities in the aryl group was first prepared via conventional solution-phase reaction described in **Scheme 2.3**. Then the oxazolidinones were immobilized with a resin via their amino groups and modification of the 5-position was made by solid-phase synthesis followed by detachment from the resin.[46-47] **(Scheme 2.25)** This methodology also allows the preparation of enantiopure libraries because the oxazolidinone skeleton is prepared from optically pure glycidylbutyrate. This approach has been used to prepare quite a few oxazolidinone libraries and led to the discovery of some new antibacterial oxazolininones with improved potency and broadened spectrum compared with Linezolid.[48-49]

Scheme 2.25:


CBzCl
nBuLi
1) NsCl
2) NH3 H2O
RCO2H, HATU, DIEA or
RNCO, DMF or
RNCS, DMF or
ROCOCl, DIEA, DMF
TFA
CH2Cl2

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CHAPTER 3 AN EFFICIENT ROUTE TOWARDS HOMOCHIRAL 5-D-ERYTHRO-2-OXAZOLIDINONES, IMPORTANT CHIRAL PRECURSORS OF DIVERSE PHARMACEUTICALS ESPECIALLY ANTIBIOTICS

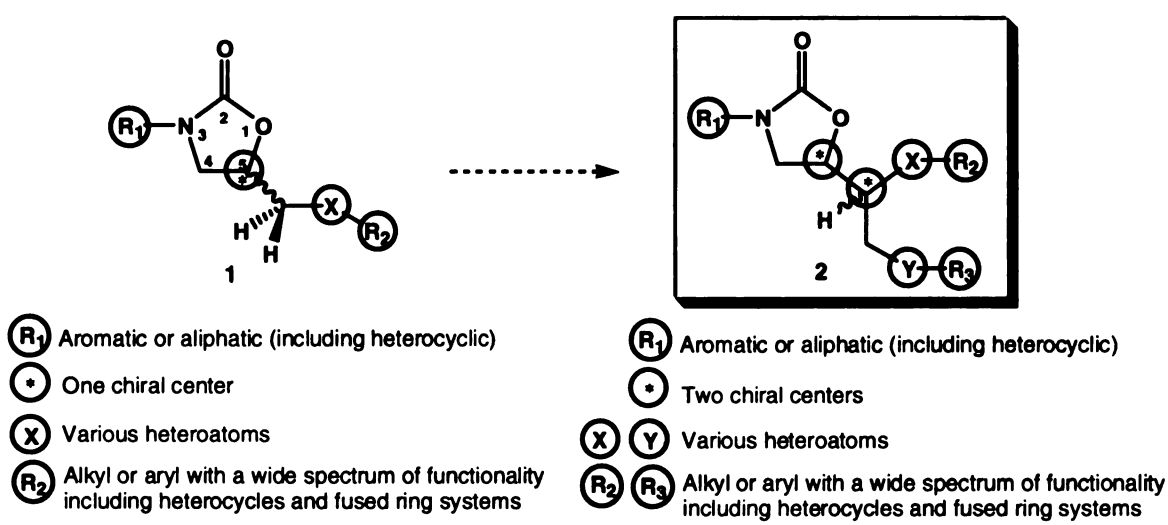
3.1. INTRODUCTION

The synthesis of biologically active oxazolidinones has been of keen interest in the last two decades because they have been shown to be multitherapeutic candidates including antibiotics,[1] antifungal,[2] and antidepressants.[3] For example, Linezolid (Zyvox®), has been approved in 2000 as a new antibiotic drug with a completely different mechanism of action since 1950s. Numerous methods and approaches have been developed thus far including asymmetric catalysis, biotransformations, chiral pool approaches, etc.

The 3-carbon chiral synthon has been extensively used in the synthesis of 5-substituted oxazolidinones and results in one carbon unit in the 5-sidechain. Based on the former structure-activity relationship (SAR) studies, limited to the carbonyl functionalities, most of the functional group transformation on the 5-substituents was 1-carbon unit such as the acetamido-methyl group. **(Figure 3.1: 1)** Although recent studies have reported variation of the 5-substituents such as 5-thiourea, 5-thiocarbamate, 5-dithiocarbamates and N- or O-substituted heterocyclic rings as potential replacements for the acetamidomethyl side chain and found quite a few antibacterial candidates with increased potency and broadened therapeutic spectrum, but a concise and efficient synthetic route of novel oxazolidinones with more than one carbon unit in the 5-substituents was still not available. **(Figure 3.1: 2)** In comparison with the extensively studied antibacterial

oxazolidinone series **1**, the new molecules **2** are a series of 5-substituted-2-oxazolidinones in which one of the hydrogen atoms is replaced by a carbon unit, a heteroatom and consequently an additional chiral center compared to the earlier candidates. This novel substitution pattern has never been explored before. According to the generally accepted mechanism of antibacterial action, oxazolidinones bind to the 23S ribosomal subunit and prevent the formation of the functional initiation complex (fMet-tRNA-mRNA-70S), thus inhibiting protein synthesis at the initiation step. It is expected that the extended substitutions in the 5-side chain of oxazolidinones could have the chance to contribute extra substrate-acceptor binding to the ribosomal binding site, and change the subtle conformation required for increased antibacterial activities. Also, this modification could associate with the 3-substituent and optimize to obtain the desired lipophilicity. More importantly, this structural modification could trigger a new round of SAR study of various R1, R2, R3, X, Y functional groups and establish oxazolidinone libraries that would lead to new drug discovery based on functional group diversity.

Figure 3.1: 5-Substituent modification

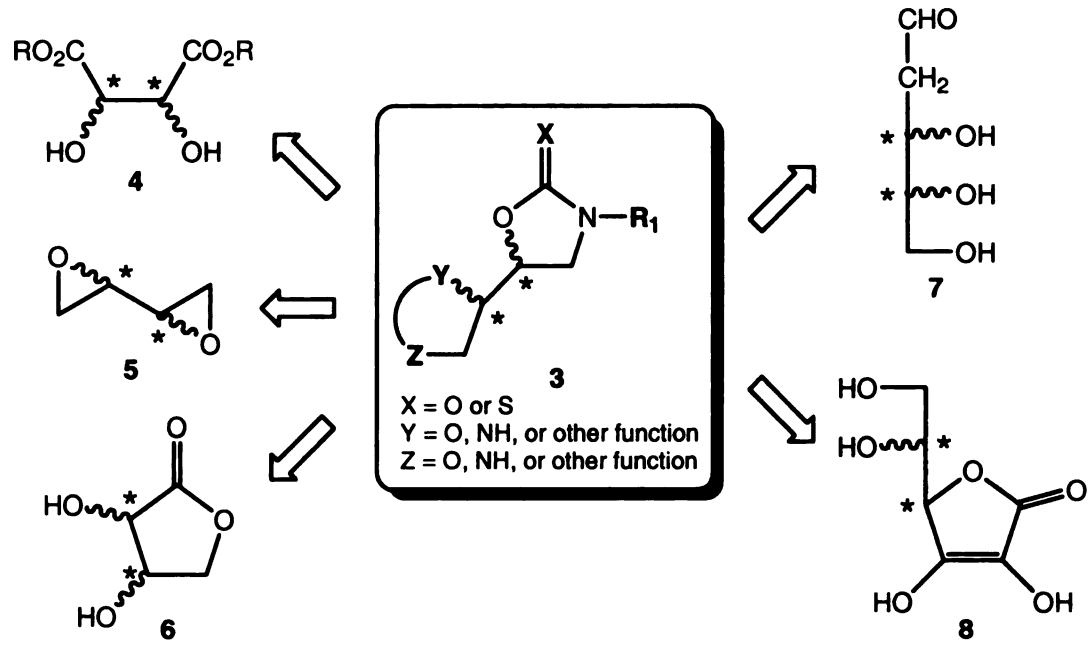


3.2. DESIGN AND SYNTHESIS

The efficient synthesis of the target oxazolidinones **2** is challenging because the small molecules incorporate highly condensed functionalities and two stereogenic centers. Carbohydrate based chiral synthons have the advantage in the preparation of the oxazolidinone **2** series molecules because a number of chiralities and functionalities have already integrated into the molecular target. Moreover, carbohydrate abundance could lead to the substantial large-scale synthesis in industry.[4]

Chiral 4-carbon building blocks such as tartaric acid, butadiene diepoxide, 3,4-O-isopropylidine-L-erythronate, D-erythronate, L-threose, D-erythrose, L-threonolactone, D-erythronolactone, etc, could play an important role in the synthesis of oxazolidinones. **3**. **(Figure 3.2)** While the former compounds tartaric acids **4** and their derivative diepoxides **5** are available in abundance as C_2 symmetric D, L, or *meso* forms, the latter compounds **6-7** and their isopropylidene derivatives are the most versatile four-carbon entities being prepared by degradative processes starting with L-rhamnose, D-ribose, D-ribonolactone, potassium glucuronate, ascorbic acid, arabinose, etc.[5,6]

Figure 3.2: Chiral 4-carbon building blocks



For the C_2 symmetric four-carbon units, the synthesis involves monofunctionalization of the precursor termini; Threo- series oxazolidinones could then be prepared after carbonylation of the corresponding chiral amino alcohol. For example, commercially available L-tartrate could afford 5-L-threo-2-oxazolidinones in this fashion. **(Figure 3.3)** However, the erythro- series oxazolidinones require the introduction of chiral factors to enantioselectively differentiate between the termini of the *meso* precursors thus complicating the process. An alternative route that circumvents the desymmetrization process could start from the L-threonolactone and D-erythronolactone. This process involves aminolysis of the starting lactones, correct protection with isopropylidenes, reduction, and carbonylation. A related synthesis could begin from cheaper 5, 6-O-isopropylidene L- and D-ascorbic acids.[7] Oxidative degradation with hydrogen peroxide in basic condition affords 3,4-O-isopropylidine-L-threonate and D-erythronate

respectively.**(Figure 3.4)** Similar process involving aminolysis, reduction and carbonylation could lead to the desired oxazolidinones.[8] The latter route could effectively circumvent the need for regioselectivity in the acetal protection step by protection of ascorbic acid at an early stage.[9] However, this approach has several limitations and drawbacks. The chirality at the α-hydroxyl function adjacent to the carbonyl could be scrambled during the reaction and lose the diastereoselectivity. Only two diastereomers, D-erythro- and L-threo-2-oxazolidinones would be afforded due to the availability of the starting ascorbic acids. The other two configurations would need to be prepared by other approaches. Furthermore, the prohibitive cost of the starting L-threono- and D-erythronolactone and the requirement of the toxic phosgene or phosgene related derivatives in the carbonylation step hamper these methodologies to be applied in large-scale synthesis.

Figure 3.3: Strategies for preparing oxazolidinones

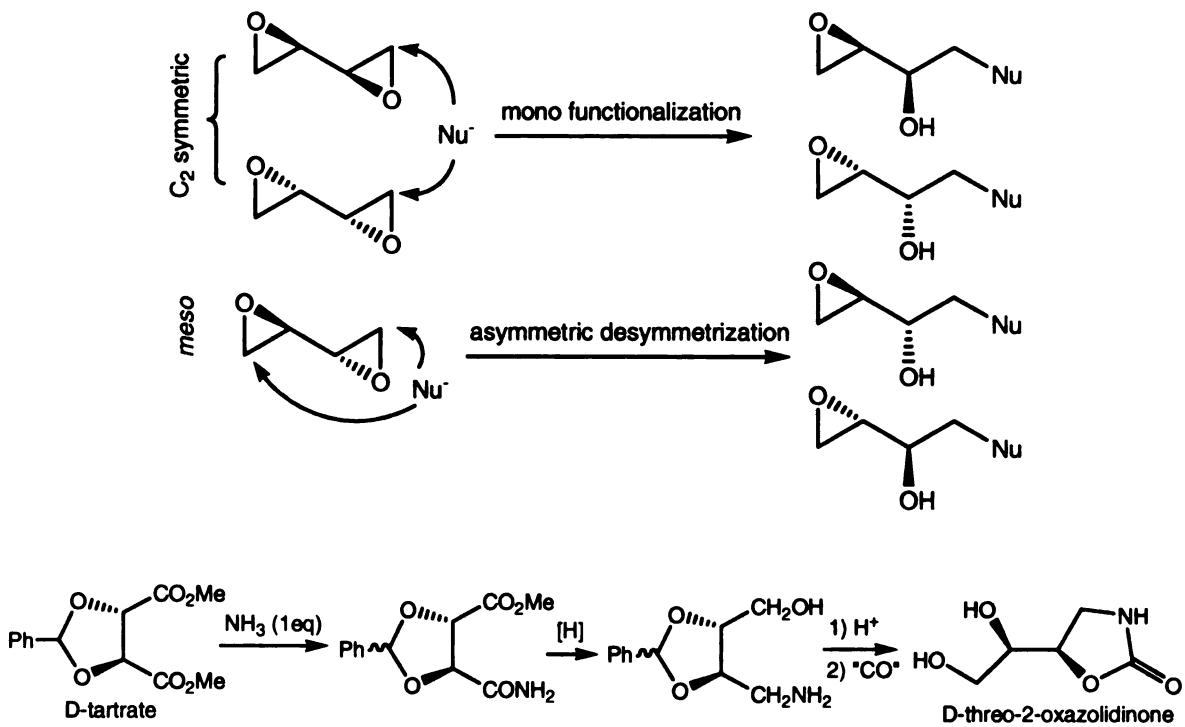
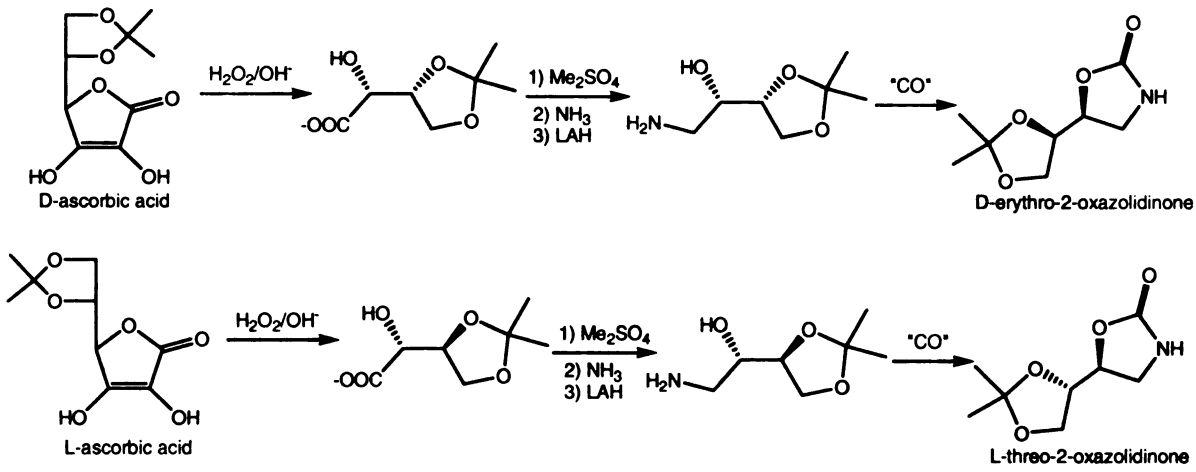


Figure 3.4: Strategies for preparing oxazolidinones (continued)



On the other hand, the exploitation of the natural 5-carbon pentoses as synthons would probably be the optimum choice as chiral raw materials. For instance, 2-deoxy-D-ribose could afford D-erythro-2-oxazolidinones in only four steps with high yield including oxidation, aminolysis, isopropylidene protection and Hoffmann rearrangement. The advantage of this approach includes, firstly, the reagents used are all conventional and generally inexpensive. Secondly, during the reaction, the correct C_3 and C_4 stereochemistry would remain intact throughout the reaction sequence and therefore ensure both chiralities being inherited by the final product, which guarantees high enantiomeric purity. Thirdly, the resulting isocyanate intermediate formed during the Hoffmann rearrangement could trap a vicinal hydroxyl group as a nucleophile in cyclization to form an oxazolidinone system so that a separate carbonylation reaction using phosgene, ethyl-chloroformate or some similar reagent would be avoided. Thus, an atom economical "green" synthetic methodology could be developed from 2-deoxypentoses and used in the large-scale synthesis. Fourthly, the availability of all the

four 2-deoxypentose sugar from a variety of cheaper precursors allow the transformation to all the four configurations of the desired products with the same methodology. **(Figure 3.5)** The novel oxazolidinone products would be greatly amenable to functional modification. The hydroxyl function could be transformed into a wide variety of substituents. And N-arylation of the corresponding function by means of Buchwald and Hartwig protocol could give the novel bioactive oxazolidinone candidates.[10]

From a broader perspective, this methodology is not only important to the target oxazolidinones themselves, but even more to optically pure 4-carbon β-amino alcohols such as **9**, which can easily be obtained from the corresponding 2-oxazolidinones by basic hydrolysis. For instance, the four-carbon chiral synthon 1-amino-erythronotriol converted from asymmetric desymmetrization of the corresponding tetraol **10** could be complex.[11-14] However, Hoffmann rearrangement from the corresponding 5-carbon amide **11** followed by base hydrolysis (acyl carbon is lost) could easily reach the target. **(Figure 3.6)** The 4-carbon β-amino alcohol subunits are important structural element in a number of different enzyme inhibitors, β-blockers, and chiral synthon used in the natural product synthesis. The amino and hydroxy functional groups are very amenable to transformations to other functionalities.

Figure 3.5: Synthesis of novel oxazolidinones from 2-deoxypentoses

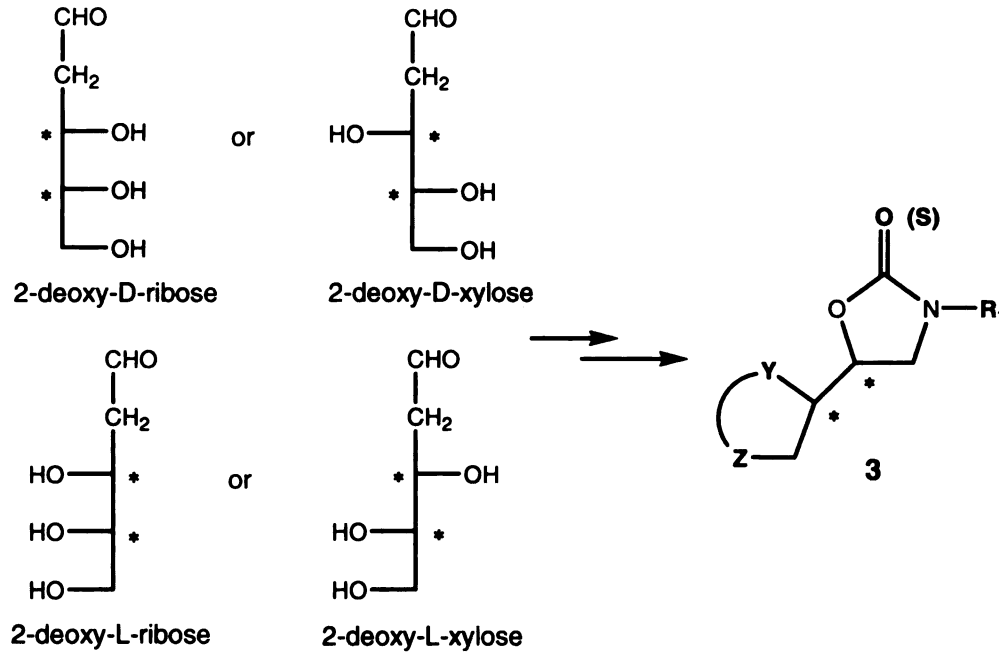
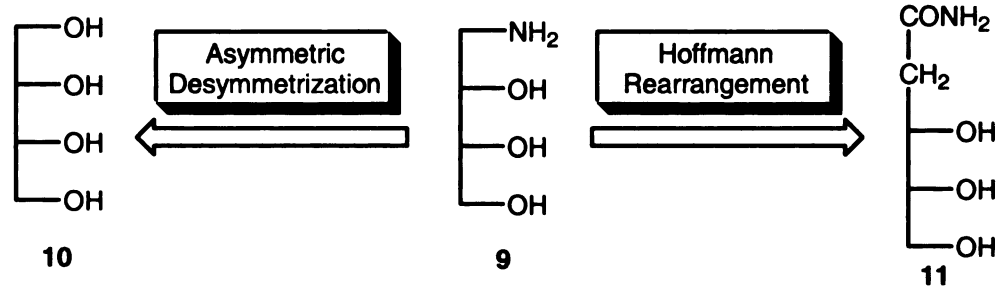


Figure 3.6: Retrosynthetic analysis

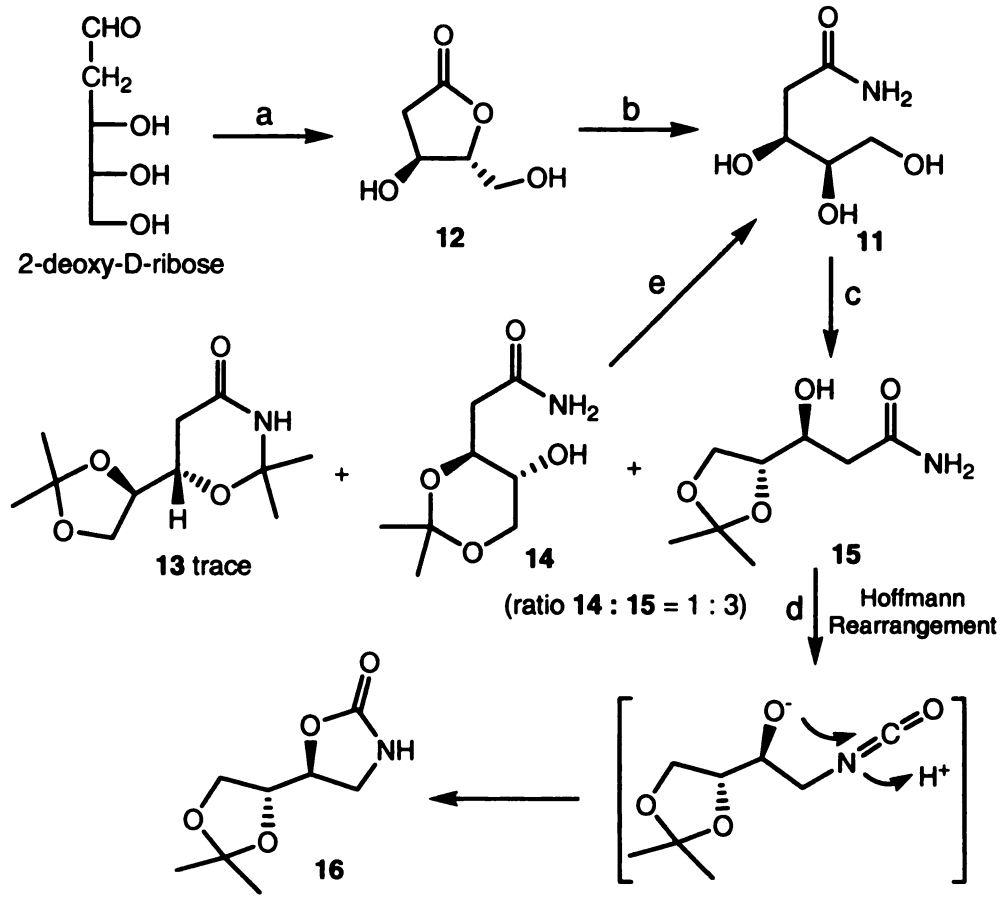


3.3. RESULTS AND DISCUSSION

The reactions are summarized in **Scheme 3.1**. Commercially available 2-deoxyribose was first oxidized to 5-membered lactone **12** by bromination in darkness at 0 °C for 36 h using standard procedure.[15] Aminolysis of lactone **12** with 28-30 % ammonium hydroxide at room temperature opened the lactone ring quantitatively to give 2-deoxy-erythro-pentyramide **11**, which upon treatment with 2,2-dimethoxypropane in dry DMF and catalytic amount of p-toluenesulfonic acid afforded the desired 4,5-isopropylidene acetal **15** and 3,5-O-isopropylidene **14** in about 3:1 ratio (separated by recrystallization), together with trace amount (5-6 mol%) of bisacetal **13**. The problem with this step is the lower regioselectivity in the reaction. A pure starting material **11** is required because any moisture or inorganic salt from the earlier steps could make the reaction inoperative. And a slight excess of acid and the 2,2-dimethoxypropane could result in appreciable byproduct **13**, which is thermodynamically more stable. Selective hydrolysis of bisacetal **13** gave undesired aminal product. The acetal **15** was then subjected to Hoffmann rearrangement condition to result in D-erythro-2-oxazolidinones **16** in high yield. And 3,5-O-isopropylidene **14** could be hydrolyzed to amide **11** with 70 % acetic acid and went back to the reaction route. Decarbonylation of the resulting oxazolidinones **16** with potassium hydroxide can give corresponding chiral β-amino alcohol **9**. This reaction sequence involved efficient four-step synthesis of enantiomerically pure D-erythro-2-oxazolidinones as antibacterial oxazolidinone precursors using very mild reaction condition and inexpensive, environmentally tolerated reagents. The overall yield was 51 %. Using the same methodology, the other three configurations of the desired

oxazolidinones should be obtained from 2-deoxy-D-xylose and their L-pentose counterparts.

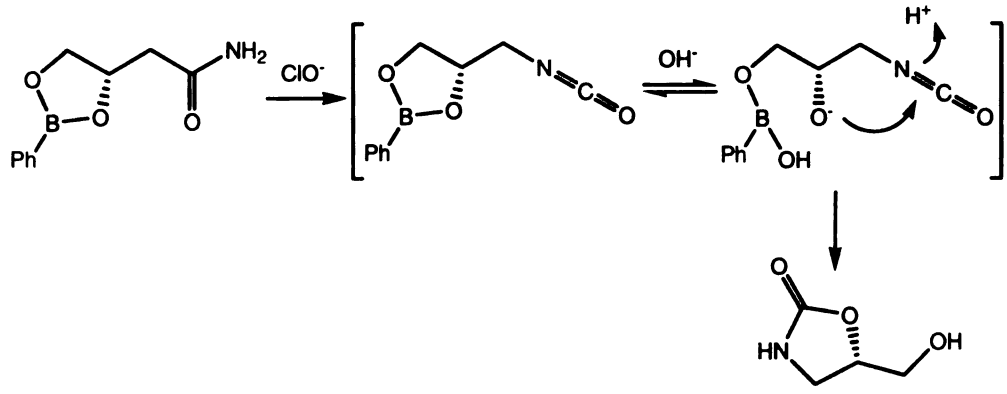
Scheme 3.1:



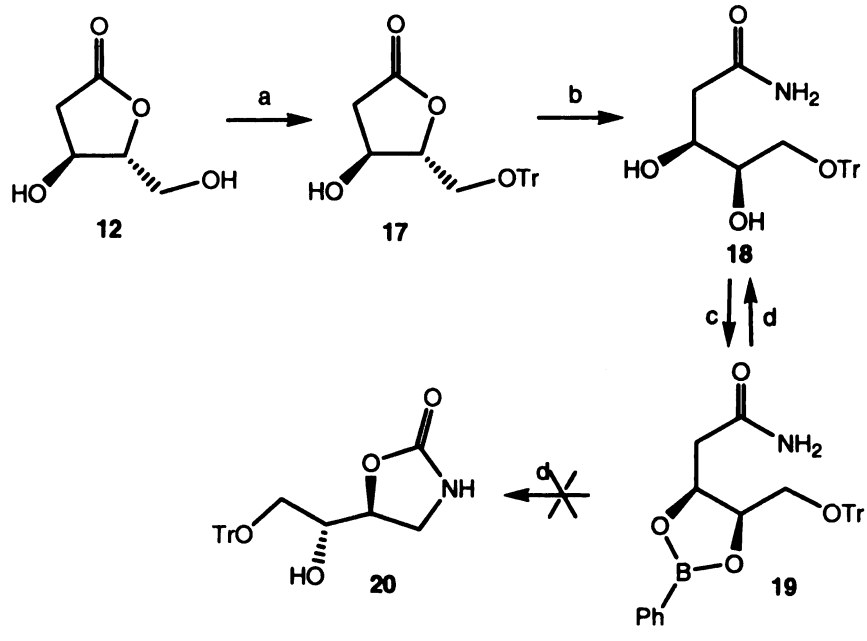
Scheme 3.1. Synthesis of D-erythro-2-oxazolidinones **16**. *Reagents, conditions and yields:* (a) Br_2 / H_2O, 0 °C, 36 h, 92.4 %; (b) 28-30 % ammonium hydroxide, methanol, 0 °C to r.t., overnight, quantitative; (c) 2,2-dimethoxypropane, DMF (anhydrous), p-toluene-sulfonic acid (cat.), r.t., overnight, **14+15:** 86%, ratio: **14:15** = 1:3, trace bisacetal **13**; (d) NaOCl, THF / H_2O, 35 °C, 12 h, 85 %; (e) AcOH (70 %), r.t., 12 h., 95 %

A one-pot synthesis of 5-hydroxymethyl-2-oxazolidinone using arylboronic acid protection and *in situ* Hoffmann rearrangement process was developed and patented in 2001.[16] In this invention, an unfavorably positioned free hydroxyl group was dynamically masked from participating in the Hoffmann reaction and yielded the preferred oxazolidinone. **(Scheme 3.2)** An attempt was made in order to see whether the same methodology could be used to mask one of the two secondary hydroxyl groups and gave desired oxazolidinones. The synthesis was summarized in **Scheme 3.3**. The primary hydroxyl group in 2-deoxy-D-ribonolactone **12** was protected with trityl group followed by aminolysis to open the lactone and the resulting secondary hydroxyl groups was protected with phenylboronic acid. However, the following Hoffmann conditions did not produce any detectable amount of desired oxazolidinone **20**, but went back to amide **18**. This result showed that the similarity of the two secondary hydroxyl groups of compound **18** caused the masking and unmasking to take place simultaneously, thus would not allow a dynamic differentiation in the standard Hoffmann rearrangement conditions to form desired oxazolidinone product.

Scheme 3.2: Process for the preparation of 5-hydroxymethyl 2-oxazolidinone via aryl-boronic acid protection[16]



Scheme 3.3:



Scheme 3.3. Attempted synthesis of oxazolidinone **20** via phenylboronic acid protection. *Reagents, conditions and yields:* (a) Trityl chloride, DMF / pyridine, r.t., overnight; (b) 28-30 % ammonium hydroxide, methanol, 0 °C to r.t., 12 h, 81 % for two steps; (c) phenylboronic acid, toluene, azeotrope, quantitative; (d) sodium hypochlorite, sodium hydroxide, THF / H_2O

3.4. CONCLUSION

In conclusion, a concise and efficient synthese towards the novel enantiomerially pure oxazolidinones as pharmacologically active precursors from naturally occurring carbohydrates has been developed. The route developed with Hoffmann rearrangement of deoxypentoses as key step could be used to generate oxazolidinones with novel, more complex 5-substitution. It is expected that the additional molecular interaction offered by such modification would enhance the protein-substrate binding. These structure modifications could trigger a new round of SAR study at the various sites around the core oxazolidinone periphery and possible new drug discovery. Also, the short reaction sequence, mild reaction condition, cheap and environmentally friendly reagents employed great potential for large-scale synthesis of 5-oxazolidinones and chiral amino alcohol analogs as chiral synthon.

3.5. EXPERIMENTAL

General Techniques

All reagents used were reagent grade. Reaction temperatures were measured externally. Column chromatography was performed on Aldrich silica gel (60 Å 200-400 mesh). Yields refer to chromatographically (isolated yields) and spectroscopically (^{1}H NMR) homogeneous materials.

NMR spectra were recorded on a Varian 300 MHz or 500 MHz VXR spectrometer at ambient temperature. Chemical shifts were reported relative to the residue solvent peak. Melting points were measured on a Fischer-Johns melting point meter and uncorrected. IR spectra were recorded on a Nicolet 710 FT-IR spectrometer. MS spectra were performed on an AX-505H mass spectrometer operating in positive ion mode.

Synthesis

2-Deoxy-D-ribonolactone (12).

13.5 g (0.1 mol) of 2-deoxy-D-ribose was stirred with 19.2 g (0.12 mol) of bromine in 1.8 L of water at 0 ^{0}C in darkness for 36 hours. The product was concentrated in vacuo with careful heating (< 40 ^{0}C). The residue was dissolved in 50 mL of methanol and undissolved substance was filtered. The filtrate was concentrated again to give crude product. Small amounts of impurities were removed with short flash column to result in a

colorless syrup product **12**. Isolated yield: (12.2 g, 92.4 %). ^{1}H NMR (500MHz, D_2O): δ 4.52-4.56 (1H, m), 4.49-4.51 (1H, m), 3.82 (1H, dd, J = 12.5, 3 Hz), 3.73 (1H, dd, J = 12.5, 5 Hz), 3.01 (1H, dd, J = 18.5, 7 Hz), 2.54 (1H, dd, J = 18.5, 3.5 Hz); ^{13}C NMR (125 MHz, D_2O): δ 179.67, 89.09, 68.45, 61.28, 38.00.

2-Deoxy-erythro-pentyramide (11).

10 g (75.8 mmol) of 2-deoxy-D-ribonolactone **12** was dissolved in 100 mL of methanol and cooled with ice-bath. 19 g (152 mmol) of ammonium hydroxide (28-30 %) was added dropwise with vigorous stirring. The reaction mixture was stirred at room temperature for 12 hours. The liquid was concentrated under vacuum to remove most of the solvent and the residue was rinsed with a small portion of acetone. The acetone was decanted and the residue was dissolved in 50 mL DMF and concentrated to dryness to give a light yellow syrup product **11** in quantitative yield. Yield: (11.2 g). ^{1}H NMR (300MHz, D_2O): δ 3.95-4.08 (1H, m), 3.72-3.80 (1H, m), 3.56-3.72 (2H, m), 2.50-2.65 (1H, m), 2.26-2.48 (1H, m); ^{13}C NMR (75 MHz, D_2O): δ 177.15, 74.41, 69.02, 62.52, 38.86. FT IR cm^{-1} 3331, 1660, 1419, 1069, 1036, 738.

2-Deoxy-4, 5-O-isopropylidene-erythro-pentyramide (15).

11 g (73.8 mmol) of amide **11** and 1 g (cat.) of p-TsOH were dissolved in 200 mL of anhydrous DMF. 10 g (96.0 mmol) of 2, 2-dimethoxypropane was added dropwise to the solution while stirring at room temperature. The mixture was kept stirring overnight. 5 g of sodium bicarbonate was added to quench the reaction. The mixture was concentrated to dryness and the residue was taken up twice with 40 mL of acetone and

filtered. The filtrate was concentrated to give light yellow syrup, which was subject to column chromatography with ethyl acetate to remove small amount of bis-acetal by-product. NMR indicated a mixture of **14:15** in about 1:3 ratio (86 % total yield). Careful recrystallization over EtOAc / hexanes gave pure colorless needles **15**. Isolated yield: (8.8 g, 63.3 %). ^{1}H NMR (300MHz, CD_3OD): δ 4.05-4.09 (1H, m), 3.85-3.97 (3H, m), 2.48-2.56 (1H, m), 2.24-2.32 (1H, m), 1.36 (6H, d, J = 12.0 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 176.77, 110.59, 79.70, 70.66, 67.64, 40.56, 26.90, 25.47. Mp: 78-79 °C

5-D-erythro-2-oxazolidinones (16).

0.25 g (1.32 mmol) of 2-deoxy-4, 5-O-isopropylidene-erythro-pentyramide **15** was dissolved in 5 mL of THF. 5 mL (10-13 %) of NaOCl was added dropwise into the solution with vigorous stirring to get a fine mixture of two phases. The stirring was kept at 30-35 °C for about 12 h until TLC indicated that the conversion was complete. The THF phase was partitioned and the water phase was extracted with 5 mL of THF twice. The THF was combined and evaporated to dryness. 10 mL of chloroform was applied to remove the inorganic salt and the organic phase was concentrated to afford the crude product **6**. Yield: (0.21 g, 85 %). The crude product could be recrystallized in ether to give colorless needles. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56 (1H, s), 4.34-4.42 (1H, m), 4.06-4.12 (1H, m), 4.03 (1H, dd, J = 9.0, 6 Hz), 3.81 (1H, dd, J = 9.0, 5 Hz), 3.60 (1H, t, J = 9.0 Hz), 3.43 (1H, dd, J = 9.0, 6 Hz); 1.31 (3H, s), 1.24 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.65, 109.75, 75.92, 75.44, 66.29, 42.76, 26.43, 24.68. Mp: 106-107 °C. MS (EI+, $CHCl_3$) *m/z* 57, 69, 83, 101, 129, 172; MS (FAB+, $CHCl_3$) MH+, *m/z* 188.19; Theoreticals: $C_8H_{13}NO_4$, mass: 187.0845

Trityl lactone (17).

In a 250 mL flask, 5.0 g (38 mmol) of 2-deoxy-D-ribonolactone **12** was dissolved in 30 mL of pyridine and 30 mL of DMF mixed solvents and stirred at room temperature. 10.5 g (38 mmol) of trityl chloride was added. The reaction was kept stirring overnight at r.t. until TLC indicated that most of the starting lactone was converted. Rotary evaporation removed most of the solvents and the residue was partitioned with 50 mL of chloroform and 25 mL of 0.5 N HCl. The organic phase was collected and washed with 25 mL water, brine respectively and dried over sodium sulfate. Then the organic phase was concentrated. The residue was triturated with hexanes and ether to remove most of the impurities and filtration to yield crude white product **17**. The crude product was used directly without further purification. ^{1}H NMR (300 MHz, CD_3Cl): δ 7.22-7.46 (15H, m, broad), 4.40-4.50 (1H, m), 3.55 (1H, dd, J = 10.8, 4 Hz), 3.22 (1H, dd, J = 10.8, 3 Hz), 3.03-3.13 (1H, m), 2.52 (1H, dd, J = 29.5, 3 Hz), 2.14 (1H, d, J = 3 Hz); ^{13}C NMR (75MHz, CD_3Cl): δ 175.87, 143.39, 128.76, 128.33, 127.61, 86.57, 70.23, 63.45, 38.76. Mp: 126-127 °C.

Trityl amide (18).

The crude product **17** was used directly without further purification. 30 mL of MeOH was added and stirred to form a clear solution. The solution was cooled to 0 °C with ice bath. 9.5 g (76 mmol, 28-30 %) of ammonium hydroxide was added dropwise to the solution. The reaction mixture was allowed to stir at room temperature for 12 h for the complete conversion. The solvent was removed and the residue was washed with 30 mL of ether twice. Recrystallization over EtOAc / ether result in white crystal **18**. Overall

yield, two steps: (12.0 g, 81.0 %). ^{1}H NMR (500 MHz, CD_3Cl): δ 7.43 (6H, d, J = 7.0 Hz), 7.20-7.34 (9H, m), 5.95 (1H, s), 5.80 (1H, s), 3.97-4.01 (1H, m), 3.73 (1H, q), 3.28-3.33 (2H, m), 2.31-2.42 (2H, m); ^{13}C NMR (75MHz, CD_3Cl): δ 175.34, 143.83, 128.84, 128.19, 127.46, 87.35, 72.82, 69.92, 64.83, 37.79.

Phenyl Boronic ester (19).

2.0 g (5.1 mmol) of trityl amide **18,** 0.62 g (5.1 mmol) of phenyl boronic acid and 100 mL of toluene were placed in a 250 mL of flask and stirred at room temperature for 6 h to form a clear solution. The water formed was vacuum distilled azeotropically with toluene to give phenyl boronic ester **19** in quantitative yield (2.5 g). ^{1}H NMR (500 MHz, CD_3Cl): δ 7.37-7.58 (11H, m), 7.19-7.35 (9H, m), 5.62 (1H, s), 5.43 (1H, s), 4.98-5.06 (1H, m), 4.73-4.79 (1H, m), 3.57 (1H, dd, J = 17.5, 6 Hz), 3.07 (1H, dd, J = 17.5, 2 Hz); 2.79 (1H, dd, J = 25.0, 13 Hz), 2.52 (1H, dd, J = 25.0, 7.5 Hz); ^{13}C NMR (75MHz, CD_3Cl): δ 175.34, 143.83, 128.84, 128.19, 127.46, 87.35, 72.82, 69.92, 64.83, 37.79.

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CHAPTER 4 *IN SITU* DEPROTECTION AND REARRANGEMENT OF N-*p*-METHOXYBENZYL-β-HYDROXYAMIDES TO FORM 5-SUBSTITUTED-2-OXAZOLIDINONES

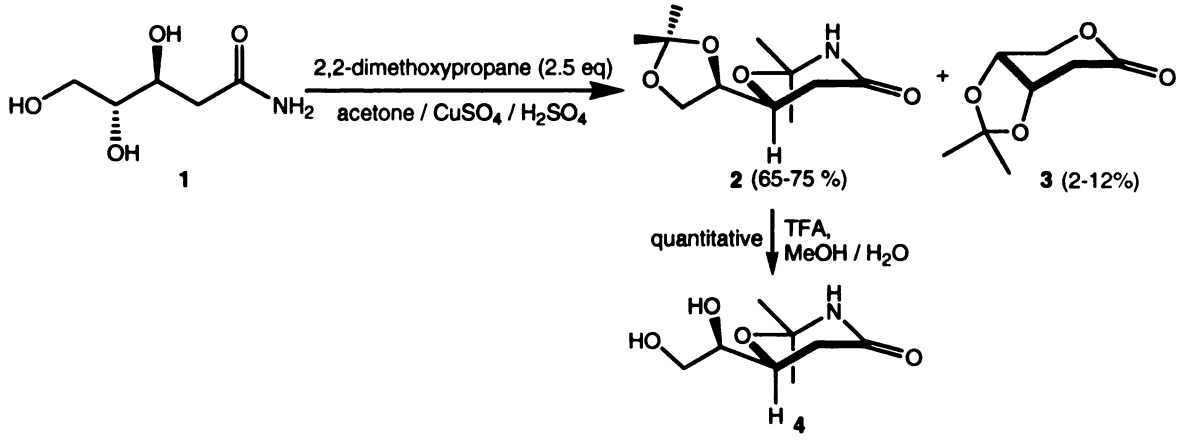
4.1. INTRODUCTION

During the synthesis of 5-D-erythro-2-oxazolidinones, the major obstacle was the isopropylidene protection step due to the interfering protons of the amide. Very subtle differences in reactivity of the hydroxyl and amide groups need to be exploited in case the bisacetal-protected product prevails. Regioisomers may predominate if a small excess of acid catalyst or isopropylidene reagent was presented. 2-deoxy-erythro-pentyramide **1**, together with inorganic salt carried from the previous steps, was a syrup soluble in water and other polar solvents. However a small amount of moisture could make the acetal protection inoperative. The crude product was sticky syrup, and separation by recrystallization was not very efficient. All these difficulties could be solved by introduction of N-benzyl or N-4-methoxybenzyl protection groups. The benzyl protection could effectively suppress formation of the unwanted regioisomers and greatly simplify the after-treatment process and increase the reaction yield because of the fine crystalline products obtained in each step. The question remained was: how to deprotect the protection groups for further transformation? Numerous debenzylation reagents were screened and an *in situ* deprotection and rearrangement method was achieved to give 5-substituted-2-oxazolidinones in fair yield.

4.2. RESULT AND DISCUSSION

Using a general protection strategy described in **Scheme 4.1** [1] resulted in the formation of thermodynamically more stable bisacetal **2** as major product and minor lactone acetal **3**. The desired 4,5-O-isopropylidene product was not afforded in appreciable amout. Selective hydrolysis of bisacetal **2** gave lactam **4** in quantitative yield. **(Scheme 4.1)** Besides, trace impurities or moisture would make the starting amide **1** as a sticky syrup with limited solubility in less polar and aprotic solvent, which would not be favored in the large-scale synthesis.

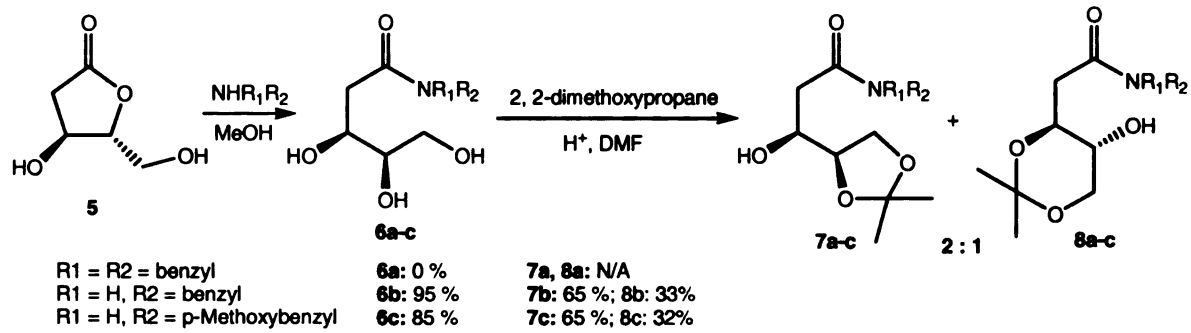
Scheme 4.1:



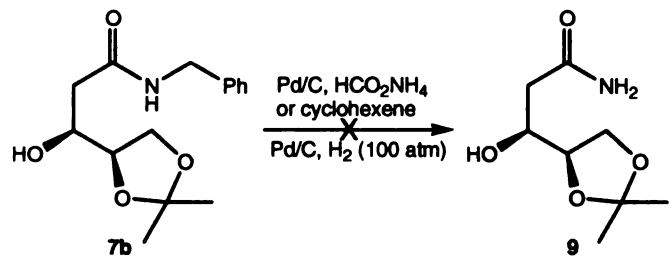
To block the interfering amide hydrogen from participating in acetal formation, and to simplify the workup due to the high water solubility of starting material and the desired product, a benzyl-protecting group was introduced. While introduction of dibenzylamine by aminolysis approach was not successful, the benzyl or p-methoxybenzyl protected compounds **6b** and **6c** were prepared with surprising ease and excellent yield. **(Scheme 4.2)** Both compounds were crystalline and after-treatment was simply filtration. In the subsequent isopropylidene protection step, no bisacetal product was formed. Isomers **7** (solid) and **8** (liquid) were obtained in about 2:1 ratio and easily separated by

recrystallization. Compound **8** could be recycled to **6** with 70% acetic acid and returned to the reaction route.

Scheme 4.2:



Scheme 4.3:

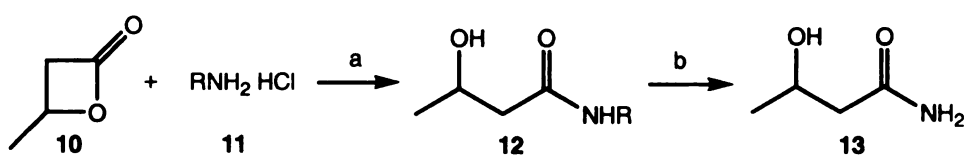


The debenzylation was then attempted at first by hydrogenolysis with catalytic 10 % Pd/C, but the starting material **7b** was recovered unchanged. **(Scheme 4.3)** Among reported N-debenzylation of amide or carbamate, the most commonly employed methods besides hydrogenolysis are acid hydrolysis in refluxing TFA;[2,3] methanesulfonic acid or p-toluenesulfonic acid in the presence of benzyl cation scavengers such as anisole or toluene;[4-6] formic acid;[7] Birch reduction in Na or Li / NH_3 condition;[8-10] oxidative N-debenzylation using CAN,[11,12] DDQ;[13,14] and radical oxidation using Br_2[15, 16] or NBS.[17] Among these methodologies, the TsOH-toluene or MsOH-anisole conditions are

considered effective and mild for the debenzylation of compounds in the presence of oxidation sensitive groups such as alcohols, and base sensitive or surprisingly, even acid sensitive functionalities such as t-BOC, N-trityl, N-Fmoc and carbamate.[4,5] p-Methoxybenzyl, 2,4-methoxylbenzyl and 2,4,6-trimethoxylbenzyl groups with increased acid sensitivity were often incorporated for N-debenzylation of amide rather than benzyl group.

Thus, a model reaction with simpler starting material, β-butyrolactone, was used for the debenzylation. The N-benzyl and N-*p*-methoxybenzyl protected β-hydroxylamides **12** were prepared by aminolysis of β-butyrolactone **10** with the corresponding aryl amine hydrochloric acid salt **11** in good yield.[18] Debenzylation in TsOH/toluene was achieved for the p-methoxybenzyl derivatives, but not benzyl ones. **(Scheme 4.4)**

Scheme 4.4



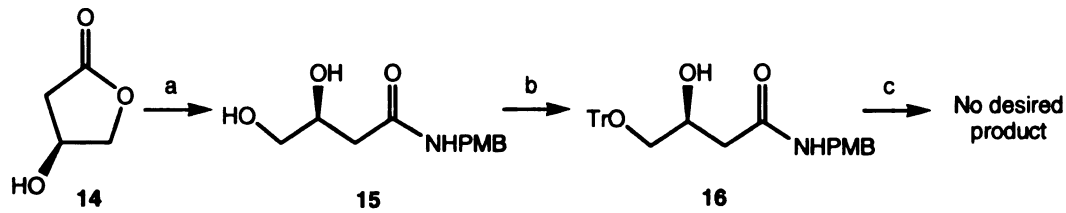
11a: R = benzyl
11b: R = *p*-Methoxybenzyl

Scheme 4.4: Synthesis of 3-hydroxybutyramide **13**. *Reagents, conditions and yields:* (a) THF, Sodium 2-ethyl-hexanoate, 12 h, r.t. 1) R = benzyl, 90 %; 2) R = *p*-Methoxybenzyl, 81 %. (b) TsOH, toluene, reflux, 2 h, 1) R = benzyl, unaffected; 2) R = *p*-Methoxybenzyl.

The N-*p*-methoxybenzyl protected amide **16** was then prepared from 3-hydroxy-γ-butyrolactone **14**. However, the O-trityl group could not survive the debenzylation with TsOH/toluene and was readily cleaved before the *p*-methoxybenzyl

group. **(Scheme 4.5)**

Scheme 4.5



Scheme 4.5: Attempted synthesis. *Reagents, conditions and yields:* (a) 4-methoxybenzylamine, CH_2Cl_2, r.t., overnight, quantitative; (b) TrCl, pyridine/DMF, r.t. 15 h, 92 %; (c) TsOH, toluene, reflux, 2 h.

It was found that free radical oxidation by bromine could be used for the debenzylation of N-benzylacetamides in a two-phase system.[19], or NBS debenzylation, which was formerly used for oxidation of O-benzyl group, [17] shared a similar radical mechanism and could be used for removal of *p*-methoxybenzyl protected amide.

According to the debenzylation mechanism, $Br^{\cdot}$ is initiated by incandescent or ambient light and reacts with benzylic hydrogen to form benzylic radical, then oxidative radical addition of another $Br^{\cdot}$ forms benzyl bromide. After that, base such as saturated sodium carbonate, calcium hydroxide, or barium carbonate is generally used to displace the Br group with hydroxyl group, and subsequent hydrolysis of the resulting unstable hemiacetal forms benzaldehyde derivative and the free amide. The base also functions as hydrogen bromide scavengers. **(Figure 4.1)**

On the other hand, the Hoffmann rearrangement mechanism shows that the reaction of primary amide with equal molar quantities of Br_2 and alkali yields N-bromoacetamide that

reacts with another equivalent of alkali to give an unstable salt. The salt readily decomposes to give isocyanate that is converted to urethane immediately in alcoholic solution.[20] **(Figure 4.2)**

Figure 4.1 Proposed mechanism of debenzylation of n-benzyl protection

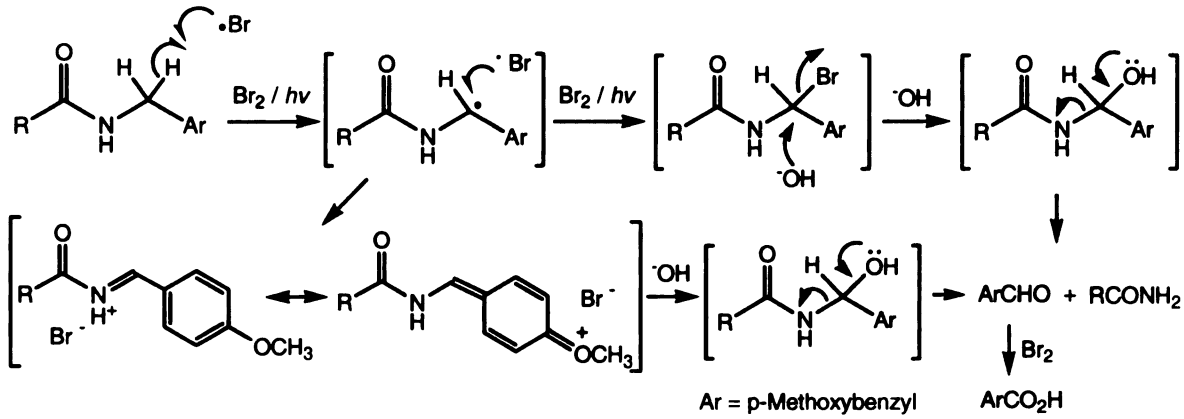
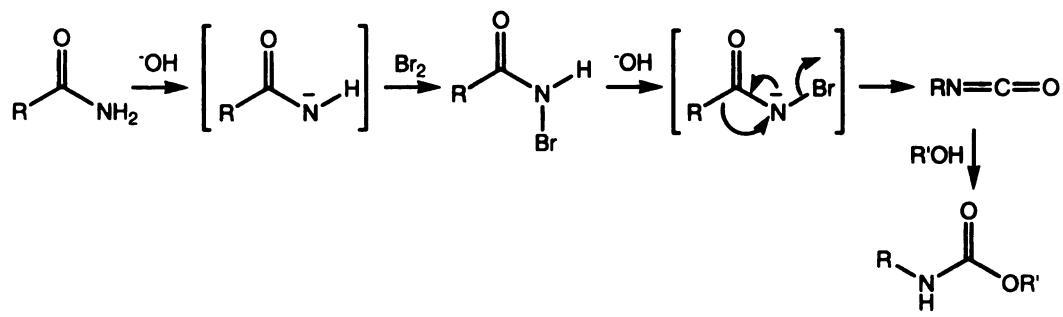
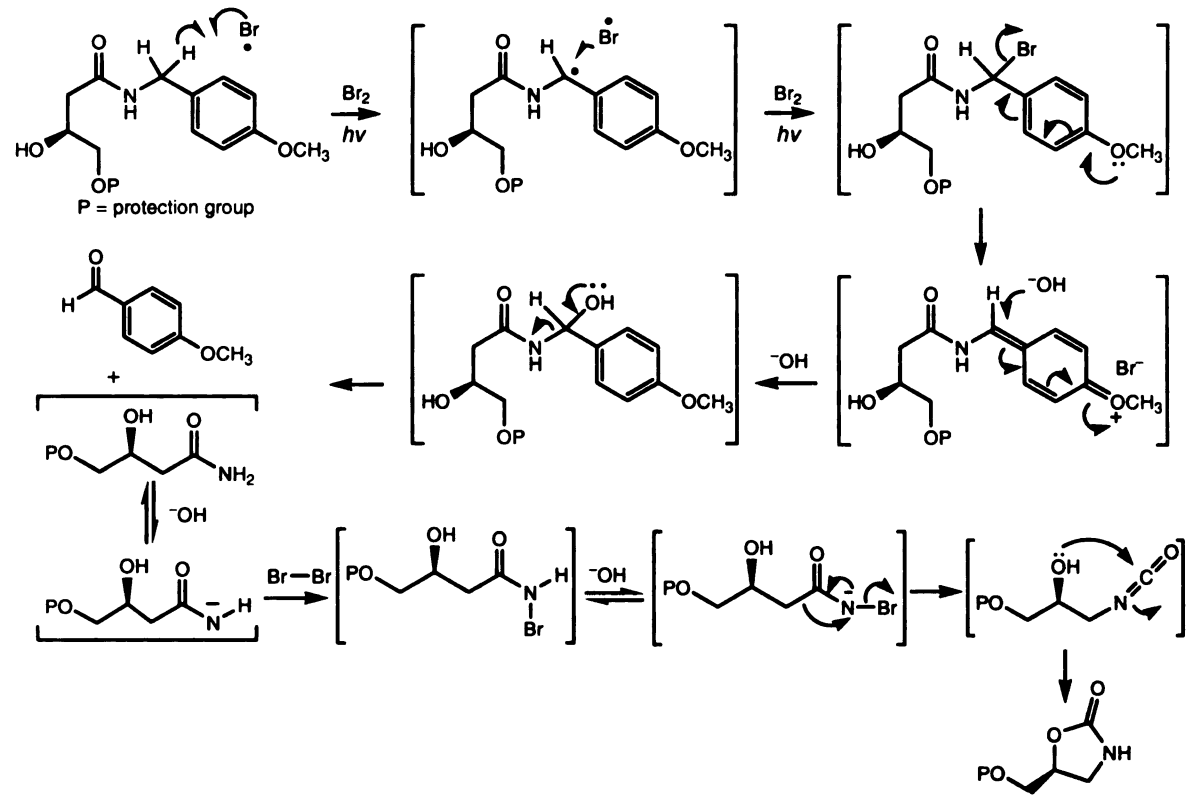


Figure 4.2 Mechanism of Hoffmann rearrangement



Scheme 4.6 Proposed mechanism of *in situ* deprotection and Hoffmann rearrangement of N-*p*-methoxybenzyl-β-hydroxyamides to form 5-substituted-2-oxazolidinones

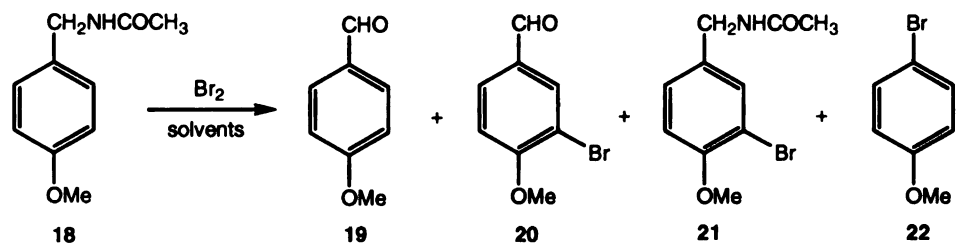


Based on the understanding of debenzylation and Hoffmann rearrangement mechanism, we found it is possible to establish an *in situ* reaction towards antibacterial oxazolidinone moieties by Hoffmann rearrangement immediately following debenzylation because of the compatibility of the reaction conditions. **(Scheme 4.6)** This methodology has the advantage that the deprotection and product formation could be accomplished in one step. Thus, in conjunction with the benzyl protection, which greatly simplifies the after treatment, a novel route to obtain antibacterial oxazolidinone moieties without increasing

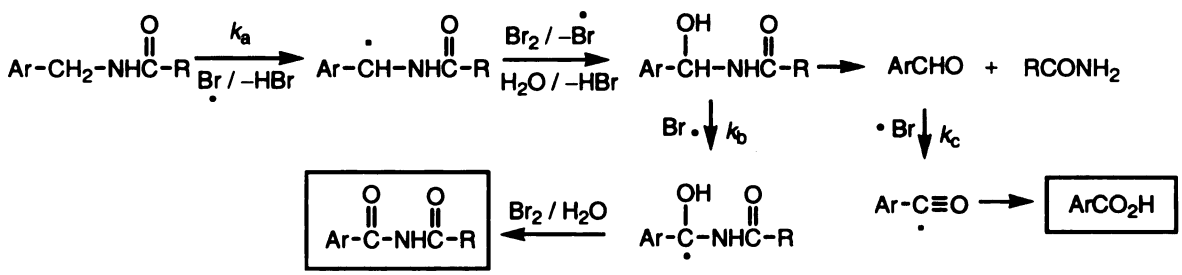
a single step could be established. However, there were several problems that need to be tackled. Firstly, the oxidative cleavage of the *p*-methoxybenzyl group initiated from a radical mechanism, while the subsequent Hoffmann rearrangement followed an ionic mechanism. Moreover, it is well known that by raising the pH above 5, Br_2 is converted to OBr^-.[21] Whether enough $Br^\cdot$ could be generated in the basic medium was not yet known. And how many equivalents of base would be enough need to be figured out. Secondly, it was previously reported that the reaction of N-(*p*-methoxybenzyl)acetamide **18** with Br_2 led to four compounds.[19] Three competitive processes were involved including free radical oxidation **(19+20)**, electrophilic ring bromination **(20+21)** and *ipso* substitution **(22)**.[22] **(Scheme 4.7)** The desired radical oxidation process could be increased by appropriate solvent selection and irradiation with incandescent light source. The percentage of hydrogen abstraction product by $Br^\cdot$ versus electrophilic ring bromination product was determined by the relative reaction rates. A higher concentration of $Br^\cdot$ was necessary for the former product to prevail. In this case, appropriate solvent systems should be found to cater to the radical oxidation. Thirdly, in principle, **20** could be formed either by electrophilic bromination of anisaldehyde **19** or by free radical oxidation of **21**. Fourthly, in excess bromine, the free-radical chain reaction could further oxidize the resulting anisaldehyde to the benzoic acid and α-hydroxyamide to the imide. **(Scheme 4.8)** If the formation of imide prevailed before cleavage, it would greatly lower the reaction yield. It was indicated that the different electronic configurations of the alkyl (π-type) and acyl (σ-type) radicals determine the different reactivity (For R = aryl, $k_a << k_c$; and for R = alkyl, $k_a >> k_c$).[23, 24] However, what mole percentage of bromine would be optimum still requires further exploration. Moreover, the starting material contains β-hydroxyl function.

Whether it would be labile or not in the oxidizing and basic condition also needs to be concerned. Finally, the Hoffmann rearrangement product in the strong base may cause decarbonylation to yield β-aminoalcohol instead of oxazolidinones. With all those questions in concern, the reaction was tried in different conditions and it was found that it worked in two-solvent system.

Scheme 4.7



Scheme 4.8



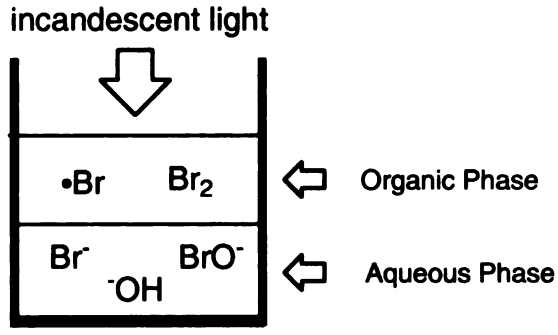
For reasons of solubility in organic solvent and facile detection, the starting material was chosen as compound **22** which could be easily prepared from 3-hydroxy-γ-butyrolactone by aminolysis. The trityl group was used to selectively protect the primary hydroxyl group because of the Hoffmann rearrangement reaction in the excess of base.

The attempted solvent systems included CCl_4, MeOH, DME, and two-solvent systems THF/H_2O, DME/H_2O, ether/H_2O, CH_2Cl_2/H_2O, hexanes/H_2O, EtOAc/H_2O, CCl_4/H_2O. The attempted bases were NaOH, K_2CO_3, CaO, and $NaHCO_3$. The ratio of bromine and

base was initially chosen as 1: 2 according to the *in situ* reaction mechanism. **(Figure 4.3)** It was found that less than 15 mol% of trityl group was cleaved in Br_2/NaOH (1:3) while the trityl group was quite labile in Br_2/NaOH (1: 2). Also, the weaker bases such as K_2CO_3, CaO, and $NaHCO_3$ could allow more $Br^{\cdot}$ to be generated, but the resulting HBr could not be scavenged quick enough to avoid trityl group cleavage. A two-solvent system was better applied than homogeneous solvent for the same reason. The concentration of HBr was very low in the organic phase because of its much higher solubility in the aqueous phase. **(Figure 4.3)** On the other hand, the $Br^{\cdot}$ could be generated transiently in the organic phase. Thus, the debenzylation happened in two stages: First, radical oxidation in the organic phase; then, cleavage of benzyl group in the basic aqueous solution. The subsequent Hoffmann rearrangement was carried out in the aqueous phase as well, but the desired product would stay in the organic phase to prevent further decarbonylation in the basic condition. Furthermore, the reaction rate was directly related to the concentration of Br_2, $Br^{\cdot}$ and NaOH, and a faster reaction was shown to increase the conversion and lessen the by-product formation. However, increasing the reaction temperature would also accelerate the reaction rate, but higher temperature would give more byproduct. The optimized condition was SM/Br_2/NaOH (1:15: 40) in equalmolar solvents THF/H_2O. The reaction was carried out under a 160 W Tungsten light at 35-40 °C with vigorous stirring for 3 h. The result was shown in **Scheme 4.9**. The desired product **17** was obtained in around 25-35 % yield. There was 25-35 % of unreacted starting material **16** retrieved. Cleavage of the trityl group still happened and resulted in about 15 % of TrOH. The cleaved *p*-methoxybenzaldehyde showed that no electrophilic bromination happened. The result showed that in NaOH solution, Br_2 was largely in the form of BrO^-, and $Br^{\cdot}$ was not

generated in sufficient amount to completely oxidize the benzylic hydrogen. It could be possible that the solvent THF also consumed a small amount of Br_2 by radical oxidation to form γ-butyrolactone,[21] But, the Hoffmann rearrangement for the preparation of

Figure 4.3 *in situ* Debenzylation and Hoffmann rearrangement



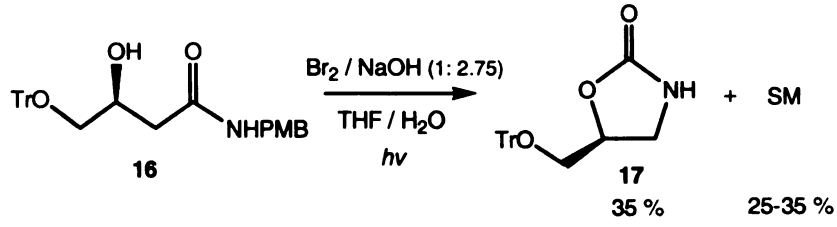
N-Debenzylation:

$$SM\ (1eq) + Br_2\ (1eq) + OH^-\ (1eq) \rightarrow TM + Br^-\ (2eq) + H_2O$$

Hoffmann rearrangement:

$$SM\ (1eq) + Br_2\ (1eq) + OH^-\ (2eq) + R'OH\ (1eq) \rightarrow TM + Br^-\ (2eq) + H_2O$$

Scheme 4.9

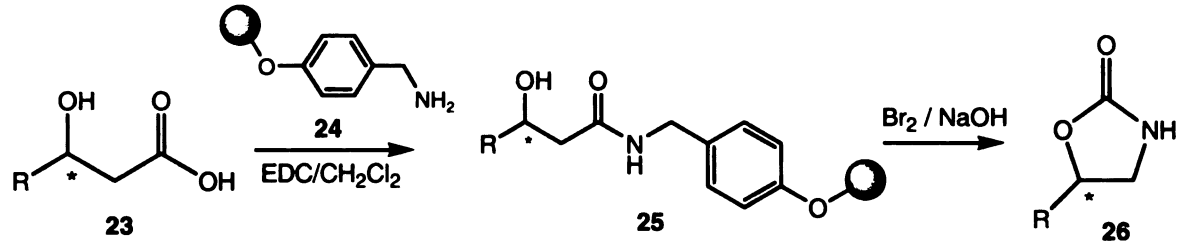


oxazolidinones was carried out best in the THF/H_2O,[26,27] which explained that the best yield was obtained in this solvent system. On the other hand, an experiment using N-benzyl protection instead of N-*p*-methoxybenzyl group at the same condition did not afford any appreciable N-debenzylation products, though there were reports of effective O-benzyl group deprotection.[17,25]

4.3. CONCLUSION

An *in situ* deprotection and rearrangement of N-*p*-methoxybenzyl-β-hydroxyamides to form 5-substituted-2-oxazolidinones was established. The yield was moderate and was influenced by multi-factors including concentration of Br_2, $Br^{\cdot}$ and OH^-, solvents, and temperature. A practical application could involve the solid-phase synthesis and fast establishment of the 5-substituted-2-oxazolidinone family **26** from β-hydroxycarboxylic acid **23**. **(Scheme 4.10)** In the *in situ* experiment, the major impurities were attributed to the *p*-methoxybenzyl deprotection. When this moiety was immobilized in a solid state, the 3-hydroxyamide moieties could be converted by Hoffmann rearrangement without much difficulty. The purification process is expected to be simple filtration. The exploration of this solid-phase synthesis approach is underway.

Scheme 4.10



EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

4.4. EXPERIMENTAL

General Techniques

All reagents used were reagent grade. Reaction temperatures were measured externally. Column chromatography was performed on Aldrich silica gel (60 Å 200-400 mesh). Yields refer to chromatographically (isolated yields) and spectroscopically (^{1}H NMR) homogeneous materials.

NMR spectra were recorded on a Varian 300 MHz or 500 MHz VXR spectrometer at ambient temperature. Chemical shifts were reported relative to the residue solvent peak. Melting points were measured on a Fischer-Johns melting point meter and uncorrected. IR spectra were recorded on a Nicolet 710 FT-IR spectrometer. MS spectra were performed on an AX-505H mass spectrometer operating in positive ion mode.

Bisacetal (2) and lactone (3)

In a 250 mL of flask with 15 g (0.1 mol) of 2-deoxy-D-erythro-pentyramide **1** was

added 8 g (0.05 mol) of $CuSO_4$, 100 mL of anhydrous acetone and 5 drops of sulfuric acid. The suspension was stirred and 25 g (0.25 mol) of 2, 2-dimethoxypropane was added dropwise at room temperature. The amide **1** was gradually dissolved in acetone (several hours) and the stirring was continued overnight. Then 5 g of sodium bicarbonate was added and the stirring was kept for 30 min. The solids were filtered and the filtrate was concentrated. The residue was partitioned with 150 mL of $CHCl_3$ and 75 mL H_2O. The organic layer was extracted and brine, and dried over Na_2SO_4. $CHCl_3$ was evaporated and the residue was recrystallized over acetone / hexanes to yield light yellow needles **2** (isolated yield: 16.8 g, 73 %) and light brown solid **3** (isolated yield: 2 g, 12 %). ^{1}H NMR for **2** (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, s), 4.15-4.19 (1H, m), 3.96-4.01 (1H, m), 3.80-3.86 (2H, m), 2.44 (1H, dd, J = 11.5, 2 Hz), 2.29 (1H, dd, J = 11.5, 7.5 Hz), 1.45 (6H, d, J = 2 Hz), 1.35 (6H, d, J = 22.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.79, 109.83, 84.89, 77.45, 69.40, 66.89, 33.80, 30.55, 26.91, 26.66, 25.04. FTIR cm^{-1} 2968, 2935, 2896, 1670, 1400, 1377, 1206, 1195, 1077. Mp: 154-155 °C. ^{1}H NMR for **3** (300MHz, $CDCl_3$) δ 4.69-4.77 (1H, m), 4.45-4.51 (1H, m), 4.41 (1H, dd, J = 13.8, 2 Hz), 4.22 (1H, dd, J = 13.8, 3 Hz), 2.87 (1H, dd, J = 16.2, 3 Hz), 2.54 (1H, dd, J = 16.2, 4 Hz), 1.40 (6H, d, J = 33.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.90, 109.67, 71.73, 71.45, 68.67, 34.95, 26.18, 24.29. FTIR cm^{-1} 2991, 1741, 1261, 1222, 1097, 736, 489. Mp: 119 °C.

Lactam (4)

The bisacetal **2** was stirred in methanol containing trifluoroacetic acid at room temperature for 5 h. The solvent was removed and the pure product **4** was obtained as white solid in

quantitative yield. ^{1}H NMR (300 MHz, D_2O) δ 4.01-4.10 (1H, m), 3.56-3.68 (1H, m), 3.50-3.56 (1H, m), 3.40-3.48 (1H, m), 2.15-2.37 (2H, m); ^{13}C NMR (75 MHz, D_2O) δ 171.50, 85.31, 72.96, 67.88, 61.96, 31.19, 29.00, 25.53.

N-Benzyl-2-deoxy-erythro-pentyramide and N-*p*-methoxybenzyl-2-deoxy-erythro-pentyramide (6b and 6c)

In a 50 mL round-bottom flask, 1.0 g (8 mmol) of 2-deoxy-D-ribonolactone **5** was dissolved in 10 mL of methanol. At room temperature, 1.7 g (16 mmol) of benzylamine was added dropwise. White precipitate was formed gradually. The reaction was stirred overnight to completion. The reaction mixture was filtered and the filter cake was triturated with acetone and filtered to dryness. A white solid **6b** was obtained in pure form. Isolated yield: (1.72 g, 95 %). ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.20 (1H, s), 7.16-7.30 (5H, m), 4.68 (2H, dd, J = 32.5, 5 Hz), 4.27-4.50 (1H, m), 3.75-3.85 (1H, m), 3.36-3.56 (1H, m), 3.15-3.35 (1H, m), 2.43 (1H, d, J = 15.0 Hz), 2.19 (1H, dd, J = 15.0, 6 Hz); ^{13}C NMR (75MHz, d_6-DMSO): δ 172.31, 140.29, 128.88, 127.81, 127.30, 75.42, 69.64, 63.84, 42.64, 39.32. Mp: 174-175 °C. Amide **6c** followed the same procedure. Isolated yield: (1.54 g, 85 %) 1H NMR (300 MHz, d_6-DMSO): δ 8.21 (1H, t, broad), 7.18 (2H, d, J = 8.7 Hz), 6.82 (2H, d, J = 8.7 Hz), 4.71 (1H, d, J = 5 Hz), 4.60 (1H, d, J = 5 Hz), 4.38 (1H, t, J = 4 Hz), 4.18 (2H, d, J = 5 Hz), 3.66 (3H, s), 3.41-3.49 (1H, m), 3.18-3.26 (1H, m), 2.41 (1H, dd, J = 15.5, 2Hz), 2.15 (1H, dd, J = 15.5, 10 Hz). ^{13}C NMR (75MHz, d_6-DMSO): δ 172.17, 158.76, 132.19, 129.15, 114.26, 75.40, 69.63, 63.82, 55.70, 42.10, 39.07.

Dioxolane (7c)

1.0 g (3.7 mmol) of **6c**, 4 mL of dry DMF and 0.04 g (cat.) of *p*-toluenesulfonic acid was placed in a 25 mL vial and stirred at room temperature. 0.8 g (7.7 mmol) of 2, 2-dimethoxypropane was added dropwise to the solution. The stirring was continued at the same temperature for 1 h. 1.0 g of sodium bicarbonate was added and stirred for 15 min. Then the reaction mixture was concentrated. The residue was dissolved and partitioned with 15 mL of $CHCl_3$ and 10 mL of H_2O. Water phase was extracted twice with 10 mL of $CHCl_3$. The $CHCl_3$ was combined, washed with brine, dried and concentrated to give a mixture of **7c** and **8c** in 2:1 ratio. Recrystallization from EtOAc / hexanes afforded **7c**. Isolated yield: (0.75 g, 65 %) as colorless needles. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (2H, d, J = 9.0 Hz), 6.82 (2H, d, J = 9.0 Hz), 6.20 (1H, s, broad), 4.36 (1H, d, J = 5.5 Hz), 4.01-4.13 (1H, m), 3.84-4.00 (2H, m), 3.78 (3H, s), 2.55 (1H, dd, J = 17.0, 2 Hz), 2.34 (1H, dd, J = 17.0, 11 Hz), 1.34 (6H, d, J = 18.5 Hz); ^{13}C NMR (75MHz, CD_3Cl): δ 172.13, 159.20, 130.06, 129.35, 114.36, 109.65, 76.86, 70.23, 67.04, 55.54, 43.20, 38.69, 26.89, 25.37.

N-Benzyl-3-hydroxybutyramide and N-*p*-Methoxybenzyl-3-hydroxybutyramide (12a and 12b)

To the mixture of 2.0 g (23.2 mmol) of β-butyrolactone (from Aldrich Co.), 6.0 g (34.8 mmol) of benzylamine, and 9.6 g (58.0 mmol) of sodium 2-ethylhexanoate (NaEH) was added 120 mL of THF, then the reaction mixture was stirred at room temperature for 12 h. After the lactone was consumed, 50 mL of saturated sodium chloride solution and 100 mL of ethyl acetate were added. The two layers were separated, and the aqueous layer was back-extracted four times with 100 mL ethyl acetate. The organic phase was

combined and dried over Na_2SO_4. After concentration, the product **12a** was obtained by recrystalization over ether. Yield (2.0 g, 90 %). ^1H NMR (300 MHz, CD_3OD): δ 7.27 (5H, s), 4.96 (1H, s), 4.38 (2H, s), 4.15-4.23 (1H, m), 2.29-2.43 (2H, m), 1.20 (3H, d, J = 7.5 Hz); The same procedure was applied for the preparation of **12b**. Yield (2.1 g, 81 %). ^1H NMR (300 MHz, CD_3OD): δ 7.20 (2H, d, J = 12.0 Hz), 6.84 (2H, d, J = 12.0 Hz), 4.83 (1H, s), 4.29 (2H, s), 4.14-4.20 (1H, m), 3.76 (3H, s), 2.26-2.42 (2H, m), 1.18 (3H, d, J = 7.5 Hz).

N-*p*-Methoxybenzyl-3,4-dihydroxybutyramide (15)

In a 500 mL flask, 5.0 g (4.9 mmol) of 3(S)-hydroxybutyrolactone **14** was dissolved in 150 mL of CH_2Cl_2. 7.5 g of *p*-methoxybenzylamine dissolved in 50 mL of CH_2Cl_2 was added dropwise into the solution with stirring at room temperature. The precipitate was formed gradually. The reaction was allowed to continue overnight to ensure completion. Then dichloromethane was filtered to dryness and the white filter cake was collected to give the pure product **15** in quantitative yield (12.3 g). ^1H NMR (300 MHz, CD_3OD): δ 7.21 (2H, d, J = 8.5 Hz), 6.84 (2H, d, J = 8.5 Hz), 4.30 (2H, s), 3.98-4.10 (1H, m), 3.75 (3H, s), 3.48 (2H, d, 3 Hz), 2.28-2.46 (2H, m); ^{13}C NMR (75MHz, CD_3Cl): δ 172.57, 159.10, 130.67, 128.77, 113.74, 69.36, 65.77, 54.58, 42.47, 39.99. Mp: 119-120 °C.

Trityl protected N-*p*-Methoxybenzyl-3,4-dihydroxybutyramide (16)

In a 250 mL flask, 12.3 g (0.05 mol) of amide **15** was dissolved in 50 mL of pyridine and 50 mL DMF mixed solvents. The solution was stirred while 15.3 g (0.055 mol) of trityl chloride was added portionwise to it. The reaction was continued for 15 h while TLC

indicated a complete conversion. Rotary evaporation removed most of the solvents and the residue was dissolved in 100 mL of $CHCl_3$. The chloroform solution was washed with 30 mL of 0.5 N HCl, 30 mL of sodium bicarbonate solution, brine, and dried over Na_2SO_4. Then the chloroform was concentrated and the residue was recrystallized over ether to afford compound **16** in good yield (22.0 g, 92 %). ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (6H, d, J = 6.8 Hz), 7.22-7.32 (9H, m), 7.16 (2H, d, J = 8.0 Hz), 6.84 (2H, d, J = 8.0 Hz), 6.37 (1H, t, J = 5.0 Hz), 4.32 (2H, d, J = 5.0 Hz), 4.18-4.22 (1H, m), 3.78 (3H, s), 3.59 (1H, d, J = 3.5 Hz), 3.16-3.23 (2H, m), 2.42 (1H, dd, J = 15.0, 3.5 Hz), 2.35 (1H, dd, J = 15.0, 8.5 Hz); ^{13}C NMR (125MHz, CD_3Cl): δ 171.68, 159.27, 143.98, 130.43, 129.32, 128.87, 128.13, 127.39, 114.35, 87.05, 68.31, 67.12, 55.53, 43.17, 40.01.

5-Trityloxymethyl-2-oxazolidinone (17)

NaOH (1.6 g, 40 mmol) was dissolved in 8 mL of H_2O and put in an Erlenmeyer flask, in which was added dropwise 2.4 g (15 mmol) of Br_2 when the solution was chilled in ice bath. 0.5 g (1 mmol) of trityl protected amide **16** was dissolved in 10 mL of THF and poured all at once into the Br_2/NaOH solution while it was stirred vigorously. 160 W incandescent light was applied and the temperature was quickly raised to 35-40 °C with heating. After about 1 h, the yellow color was retreated and the heating was kept at 40 °C for 2 h more. After standing still for a couple of minutes, the organic layer was separated, and the water layer was extracted twice with 10 mL of THF. The combined organic layer was concentrated and taken up by dichloromethane (20 mL), and the solution was dried over Na_2SO_4. It was concentrated again and the residue was purified by column chromatography. Yield: (0.12 g, 35 %). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.52 (5H, m),

7.39-7.18 (10H, m), 5.96 (1H, s), 4.71-4.79 (1H, m), 3.56-3.62 (1H, m), 3.39-3.45 (1H, m), 3.28 (1H, dd, J = 9.6, 4.2 Hz), 3.23 (1H, dd, J = 9.6, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.74, 143.45, 128.60, 127.94, 127.21, 86.90, 75.40, 64.25, 42.63. The NMR agreed with the reported Data.[26]

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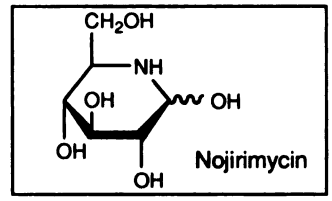
CHAPTER 5 PREPARATION OF THIOALKYL SUBSTITUTED SMALL RING NITROGEN HETEROCYCLES FOR GLYCOSIDASE INHIBITORS

5.1. INTRODUCTION

Interest in glycosidase inhibitors was stimulated by the finding that plants and microorganisms produce a variety of monosaccharide-like alkaloids such as nojirimycin (discovered from the cultured broth of the *Streptomyces* species) that are involved in a number of physiologically important processes including intestinal digestion, catabolism and post-translational process of glycoproteins.[1] During the past decade the interest has grown due to the chemotherapeutic potential of the glycosidase inhibitors in the prevention and treatment of a variety of diseases, including lowering blood glucose levels by affecting carbohydrate metabolism;[2,3] inhibition of tumor metastasis by interruption of the glycosylated expression product;[4,5] inhibition of viral replication by interfere the co- and post-translational process of glycoproteins;[6,7] and treatment of genetic disorder by quality control of the endoplasmic reticulum of the N-linked glycoprotein.[8] Mreover, some inhibitors could be useful tools in preparing affinity ligands for the purification of specific glycosidases or glycosyltransferases.[9]

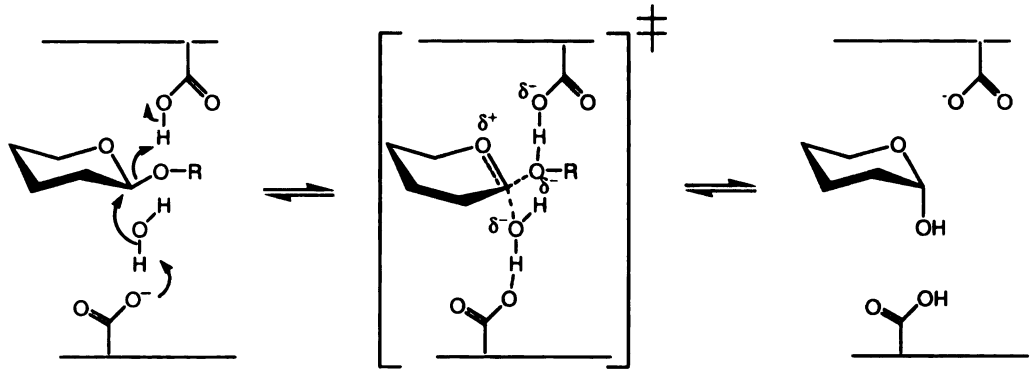
Figure 5.1.



Most of the naturally occurring and synthetic glycosidase inhibitors are carbohydrate derivatives or their structural analogs. According to their way of action, they can be classified into reversible and irreversible inhibitors by the dissociation abilities of the inhibitor from the enzyme-inhibitor complex. According to the mechanism, there are inverting glycosidase and retaining glycosidase.[10] Retaining glycosidases convert the substrate to product with retention of anomeric configuration. This mechanism has two separate steps and therefore, involving two oxacarbenium-ion-like transition states. The inverting glycosidase involves only one transition state and the product is obtained with inversion of configuration at anomeric center. The generally accepted enzymatic glycoside hydrolysis mechanism shows that most α- and β-glycosidases have an active site proton donating group (usually a carboxylic acid) in the proximity of glycosidic oxygen atom and another carboxylate group that can stabilize the partial positive charge developing on the anomeric carbon. And then a covalent glycosyl-enzyme intermediate with cation/oxocarbenium ion may form which is subsequently hydrolyzed by cleavage of the glycosyl bond.[11,12] **(Figure 5.2)** The relationship between structure and inhibitory activity in glycosidase inhibitors based on X-ray crystallography studies on complexes with substrate analogs and inhibitors show that good glycosidase inhibitors should have a flattened half-chair conformation with a positive charge character around the trigonal anomeric carbon center and ring heteroatom, and proper hydroxyl group configurations. The structures, shapes and charge of these inhibitors closely resemble the glycosyl cation transition state involved in glycosidase mechanism. **(Figure 5.3)**

Figure 5.2. General enzymatic glycoside hydrolysis mechanism

(A) Inverting glycosidase



(B) Retaining glycosidase

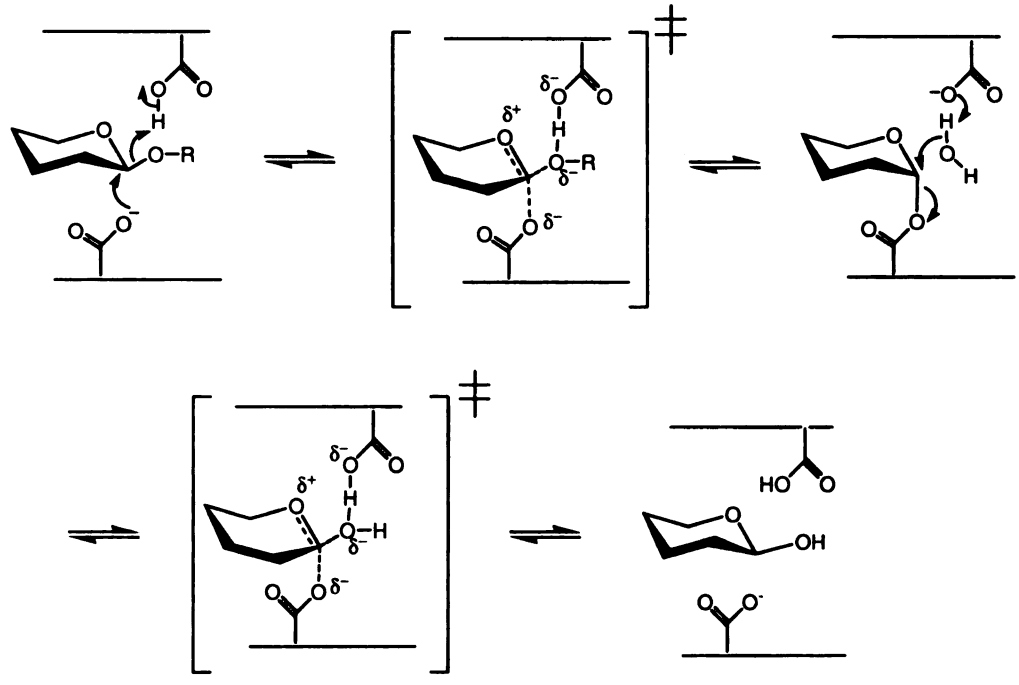


Figure 5.3. Mimic of pyranosyl oxacarbenium ion trigonal planar configuration

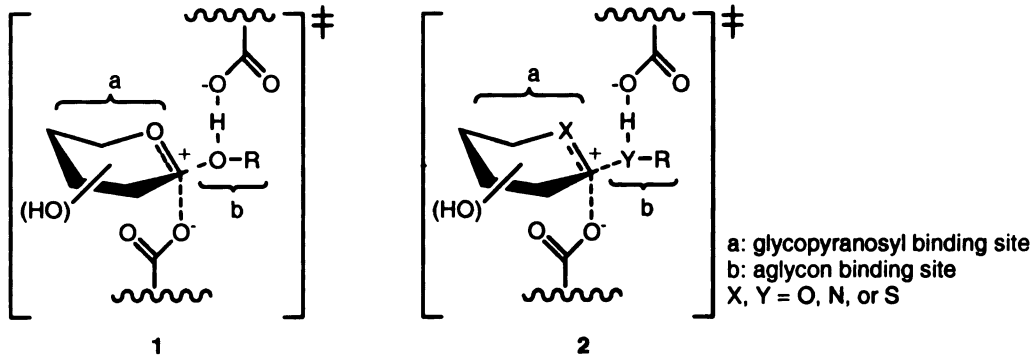


Figure 5.3: Analogy between **(1)** the transition state in the glycosidase mechanism and **(2)** the possible binding mode of a glycosidase inhibitor with the active catalytic site of a glycosidase

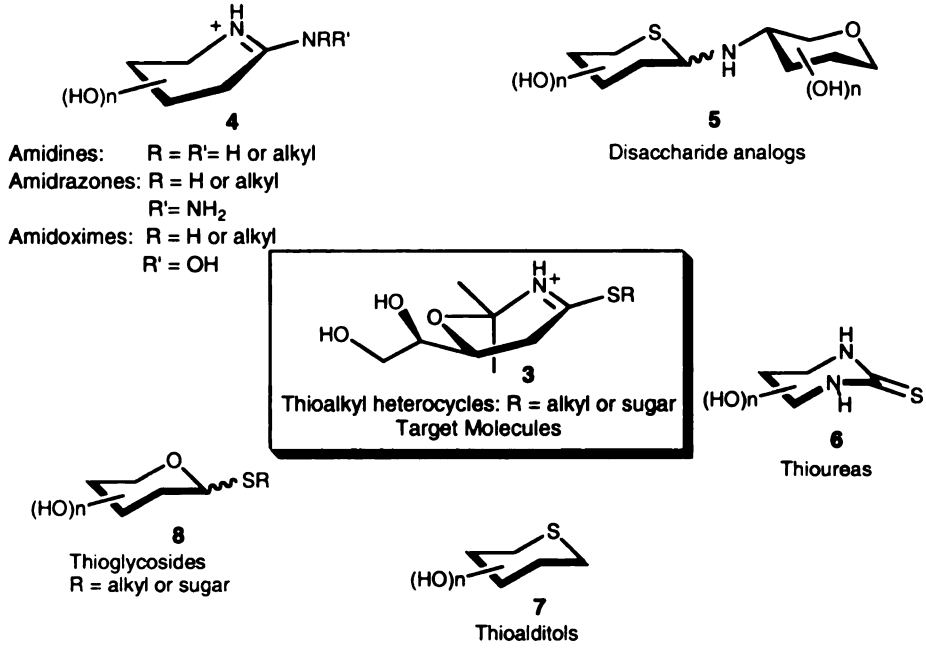
5.2. DESIGN AND SYNTHESIS

A large fraction of glycosidase inhibitors have general structural similarity with natural glycosides and are designed based on the glycoside transition state of the reaction catalyzed by glycosidase. In the past decade, several new types of synthetic inhibitors have emerged that are very potent.[13] Development of novel structures as glycosidase inhibitors is of considerable interest that could lead to new insight in the glycoside cleavage process and therapeutically active leads for drug discovery.

Earlier studies have indicated various degrees of sp^2 character at the anomeric carbon with the formation of an oxacarbenium-ion-like transition state. A good transition-state analogue must necessarily be a strong inhibitor. The design of the desired transition-state analogue focused on forming the generally accepted flattened

half-chair conformation, the sp^2-hybridized anomeric carbon, and mimicking partial charge build-up on the endo- and exocyclic heteroatoms. In 1990, the Ganem group synthesized the first amidine **(4)** analogue of D-glucose, which was shown to be a strong competitive inhibitor of β-glucosidase.[14] Later on, amidrazones and amidoximes **(Figure 5.3)** have also been prepared to show broad-spectrum inhibition of glycosidases.[15,16] Those glycosidase inhibition families were considered as transition-state analogues that mimic both partial positive charges on the endo- and exocyclic oxygens, the sp^2-hybridized anomeric carbon and the flattened chair conformation. Various substituents at the exocyclic nitrogen were also synthesized as mimic of aglycon moieties to enhance the selectivity and inhibitory properties of the compounds. On the other hand, several classes of thio-containing carbohydrates, including thiodisaccharides **(5)**,[17-19] thioglycosides **(8)**,[20] thioureas **(6)**,[21] and thioalditols **(7)**[22] were synthesized as the transition-state analogs of glycosidase inhibitors. Since the report of the synthesis of 5-thio-D-xylopyranose, the first example of thiosugars ever described, there have been a large number of thiosaccharides and their analogs of biological interest being synthesized and characterized. However, the thioalkyl heterocycles or their pseudo-disaccharides with endocyclic nitrogen atom and sulfur in the pseudo-interglycosidic linkage as glycosidase inhibition candidates have never been explored so far. **(Figure 5.4)**

Figure 5.4. A comparison of novel thioalkyl heterocycles with the existing glycosidase inhibitors



The target molecule thioalkyl heterocycles **(3)** could be prepared from carbohydrate precursor 2-deoxy-D-ribose as the transition-state analogs of such candidates. The reason to introduce sulfur linkage includes: Firstly, the sulfur moieties were believed to participate more readily than the corresponding oxygen moieties in heterolytic processes so that the chemistry of these thiosugar analogs is more subtle and delicate than that of the corresponding sugar analogs.[17,23] Secondly, the thiolactam functionality was a weak nucleophile, which could be alkylated with a variety of proper alkylating agents (mimicking the aglycon part), including sugar moieties such as glucose, galactose, fructose, ribose, etc., to quickly establish a template family for biological screening. By introduction of various structural features of the alkyl or sugar groups that mimic the aglycon moieties, it is possible to modify the transition state to more efficient and specific inhibition. Thirdly, the amidines and their derivatives have

controversial endo- or exocyclic double bond, upon which has cast doubt as the transition-state analogs.[24,25] Unlike amidines, the alkylated thiolactams have well-defined endocyclic double bond location. This is important because the location of the double bond has a large effect on the conformation of the compound and thereby on the interpretation of the inhibitory properties. Also, unlike amidine and their derivatives, alkylated thiolactams are more stable in the neutral and relatively basic condition, which allow the compounds to adopt a half-chair-like conformation without the protonation step.

5.3. RESULTS AND DISCUSSION.

The reactions are summarized in **Scheme 5.1.** (see pp 85) Starting from the same commercially available 2-deoxyribose as described in the antibacterial oxazolidinones synthesis. **(Chapter 3)** The same oxidation followed by aminolysis gave 2-deoxy-D-erythro-pentyramide **(9)** in high yield. The crude product **(9)** could be used after being lyophilized to dryness. Treatment with 2,2-dimethoxypropane, 1 eq of cupric sulfate and catalytic amount of sulfuric acid (1 %) in acetone gave thermodynamic bisacetal **(10)** as major product and trace lactonoacetal by-product **(11)**. The other possible acetal regioisomers were not detected. The lactam function of bisacetal **(10)** was then converted to thiolactam **(12)** with Lawessons' reagent. And the resulting thiolactam **(12)**, a mimic of glycopyranoside, was alkylated with a variety of

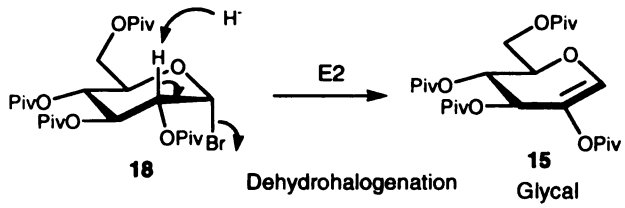
alkylating agents (mimic of aglycon) to give a variety of compounds **(28-45)**, which after hydrolysis, served as glycosidase inhibitor candidates. The representative alkyl groups were aliphatic acyclic and cyclic alkanes, aromatic benzyls, and sugars.

Upon treatment with NaH in DMF at room temperature, the alkylation reaction was successful for most of the iodoalkanes and substituted benzyl halides, except p-nitrobenzyl and cyclohexyl because of the electronic or steric effect, and ethylamide because of the protic amide hydrogen.

Alkylation with sugars was successful for β-methyl-2,3-O-isopropylidene-5-tosylated riboside in NaH/DMF at 80 °C. The corresponding iodo-riboside was unaffected in the same condition. The tosylated riboside could be synthesized according to the reported procedure.[26,27] However, alkylation with acetobromo-α-D-glucose under the optimized condition (NaH/DMF) gave a series of inseparable acyl hydrolysis products due to the labile acyl protection group in basic condition. A synthesis of pivaloylbromo-α-D-glucose **(18)** was achieved from D-glucose in three steps: **(Scheme 5.2**, see page 88) Glycobenzylation followed by pivaloyl protection of all the free hydroxyl groups, then a one-pot radical oxidation of the benzylic proton with NBS and rearrangement to give desired glucosyl bromide **(18)**.[28] The replacement of the acyl groups with pivaloyl groups could solve the protection group problem but gave predominantly a glycal product **(15)**, presumably following an E2 mechanism.[29] **(Figure 5.5)** The desired product was not detected. Blank reaction with pivaloylbromo-α-D-glucose **(18)** in the same condition afforded the same E2 glycal product **(15)**, which indicated that the elimination of the β-bromo group at the

anomeric carbon of glucosyl bromide happened much faster than the Sn2 displacement.[30-31]

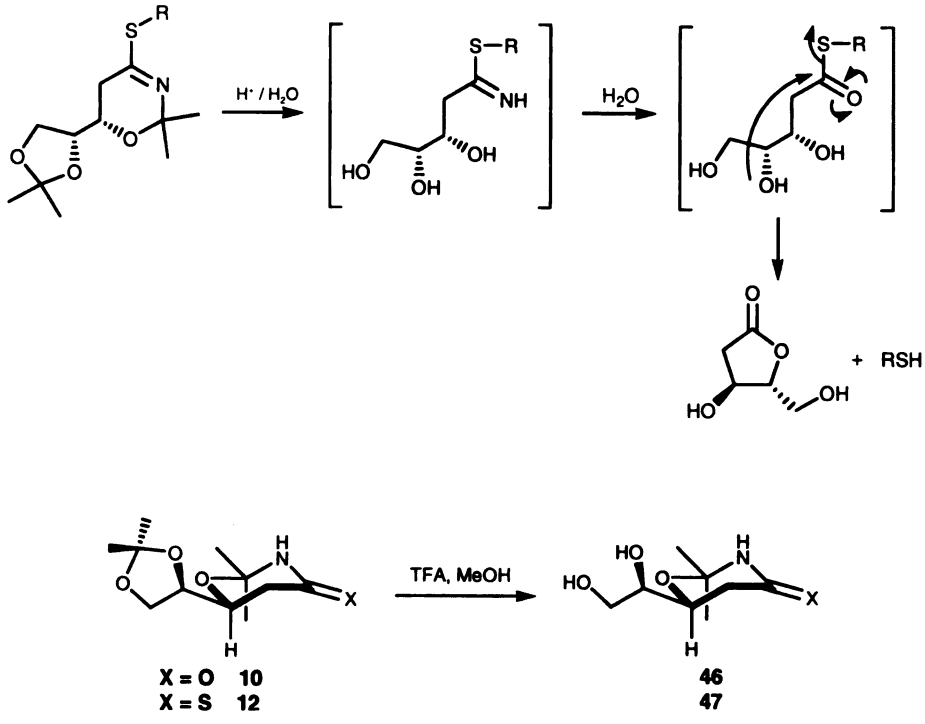
Figure 5.5. Dehydrohalogenation



Alkylation with 2,3:4,5-di-O-isopropylidene-β-D-bromofructopyranose **(23) (Scheme 5.2**, see page 88) at room temperature gave full recovery of the starting materials. Raising the temperature to reflux (in DMF) resulted in the decomposition of both starting materials and no desired product was detected. This could be explained as an overwhelming steric bulk of both isopropylidenes in the vicinity of the methylene bromide.

The selective hydrolysis with TFA was first carried out in methanol. It was found that the ring aminal function was labile in acidic methanol condition and complete decomposition of the desired product was observed within 8-12 h at room temperature. The decomposition product was detected as mainly 2-deoxy-D-ribonolactone. **(Figure 5.6)** Dichloromethane was replaced and the hydrolysis was done smoothly with protonation of the aminal to stabilized the ring structure followed by selective hydrolysis of the acetal function with TFA to give desired product in quantitative yield. **(Scheme 5.1**, see page 86)

Figure 5.6. Selective hydrolysis

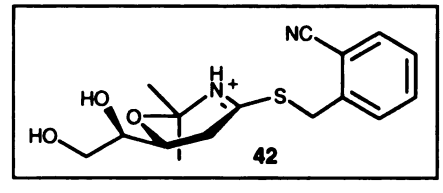


5.4. BIOLOGICAL TEST

Among the eighteen compounds prepared, sixteen of them were tested against three bacterial strains *Enterococcus faecalis 29212*, *Staphylococcus aureus 29213*, *Staphylococcus aureus 43300*, respectively. The concentrations used 250 μg/ml down to 0.49 μg/ml. The absorbance to monitor bacterial growth was 600 nm. All of the compounds were taken up in 5 % DMSO, except **(32)**, which was taken up in 10 % DMSO. Two DMSO controls were done. (5 % and 10 %) The known antibiotic chloramphenicol was used as a positive control for inhibition.

In general, the compounds did not inhibit the bacterial growth except **(42)** **(Figure 5.7)**, which appears to inhibit *E. faecalis 29212*. The greatest inhibition was at a concentration of 62.5 μg/ml. The percent inhibition at this concentration is 77 %.

Figure 5.7. Thioalkyl heterocycle candidate



5.5. CONCLUSION

In summery, a facile and effective synthesis of thioalkyl substituted small ring nitrogen heterocycles has been developed as potential glycosidase inhibitors starting from carbohydrate precursor 2-deoxy-D-ribose. Eighteen compounds have been made thus far and a preliminary biological test has been done. A large number of transition-state analogues are being evaluated for inhibition of glycosidases and many potent inhibitors with nanomolar affinity have been found for the last forty years. Nevertheless, the transition state catalyzed by glycosidase must be bound much more strongly by a glycosidase than any known inhibitor. Even the best glycosidase inhibitors are "imperfect" transition-state analogues. However, while a small number of glycosidase inhibitors owe their activities to coincidental bindings to the enzyme, the transition-state mimicking is still the major guidance for discovery of the glycosidase inhibitors.

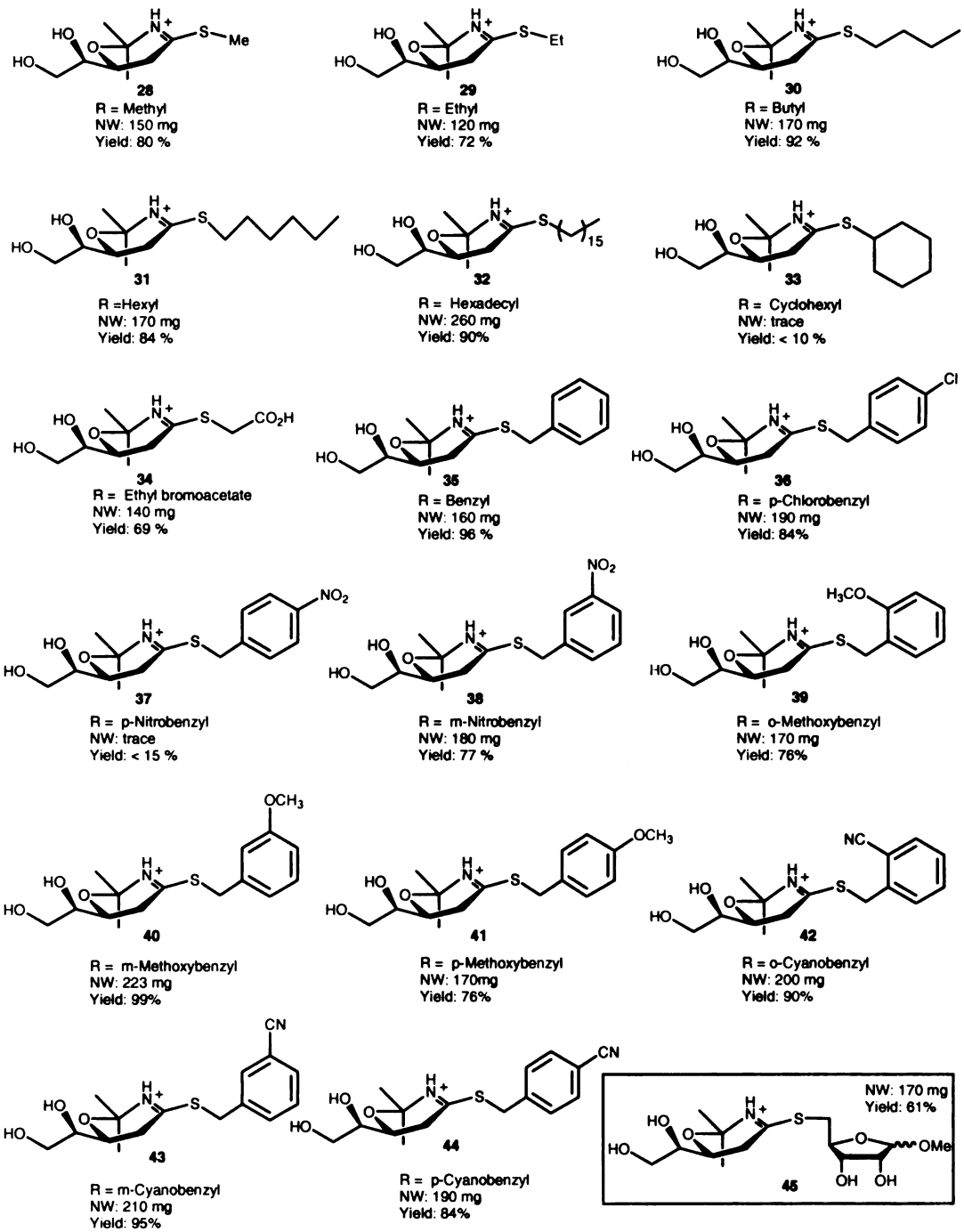
5.6. EXPERIMENTAL

General Techniques

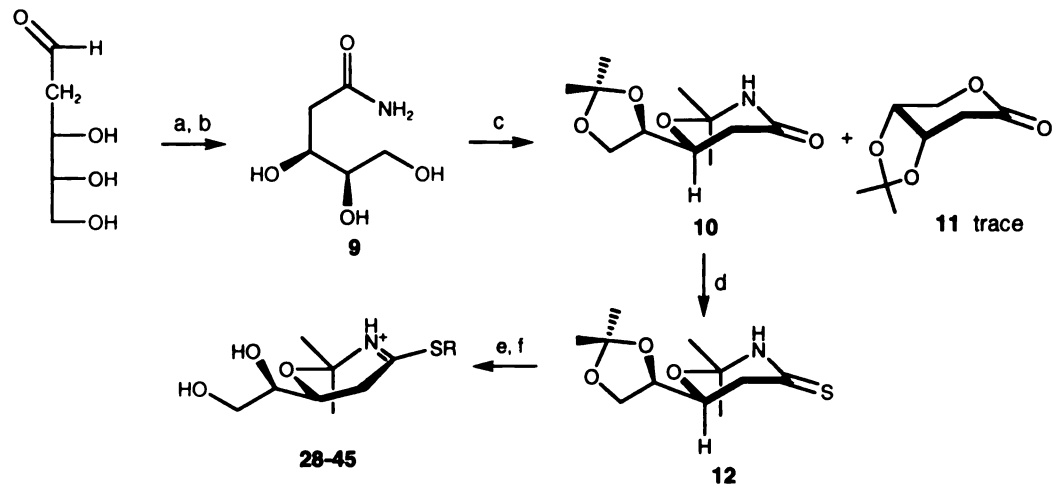
All reagents used were reagent grade. Reaction temperatures were measured externally. Column Chromatography was performed on Aldrich silica gel (60 Å 200-400 mesh). Yields refer to chromatographically (isolated yields) and spectroscopically (^{1}H NMR) homogeneous materials.

NMR spectra were recorded on a Varian 300 MHz or 500 MHz VXR spectrometer at ambient temperature. Chemical shifts were reported relative to the residue solvent peak. Melting points were measured on a Fischer-Johns melting point meter. IR spectra were recorded on a Nicolet 710 FT-IR spectrometer operating in positive ion mode.

Figure 5.8. Thioalkyl substituted heterocycles for glycosidase inhibitor



Scheme 5.1.



Scheme 5.1 Synthesis of thioalkyl substituted heterocycles as glycosidase inhibitor candidates. *Reagents, conditions and yields:* (a) Br_2 / H_2O, 0 °C, 36 h, 92.4 %; (b) 28-30 % ammonium hydroxide, methanol, 0 °C to r.t., overnight, quantitative; (c) 2,2-dimethoxypropane (2.5 ~ 3 eq), $CuSO_4$, H_2SO_4 (cat.), acetone, r.t., overnight, 73 %; (d) Lawessons' reagent, toluene/pyridine, 65-70 °C, 1.5 h, 80 %; (e) NaH, DMF, RX, 0 °C ~ r.t. (80 °C for compound **45**), 2-12 h; (f) TFA, CH_2Cl_2, r.t., 5 min.

Synthesis

Bisacetal 10

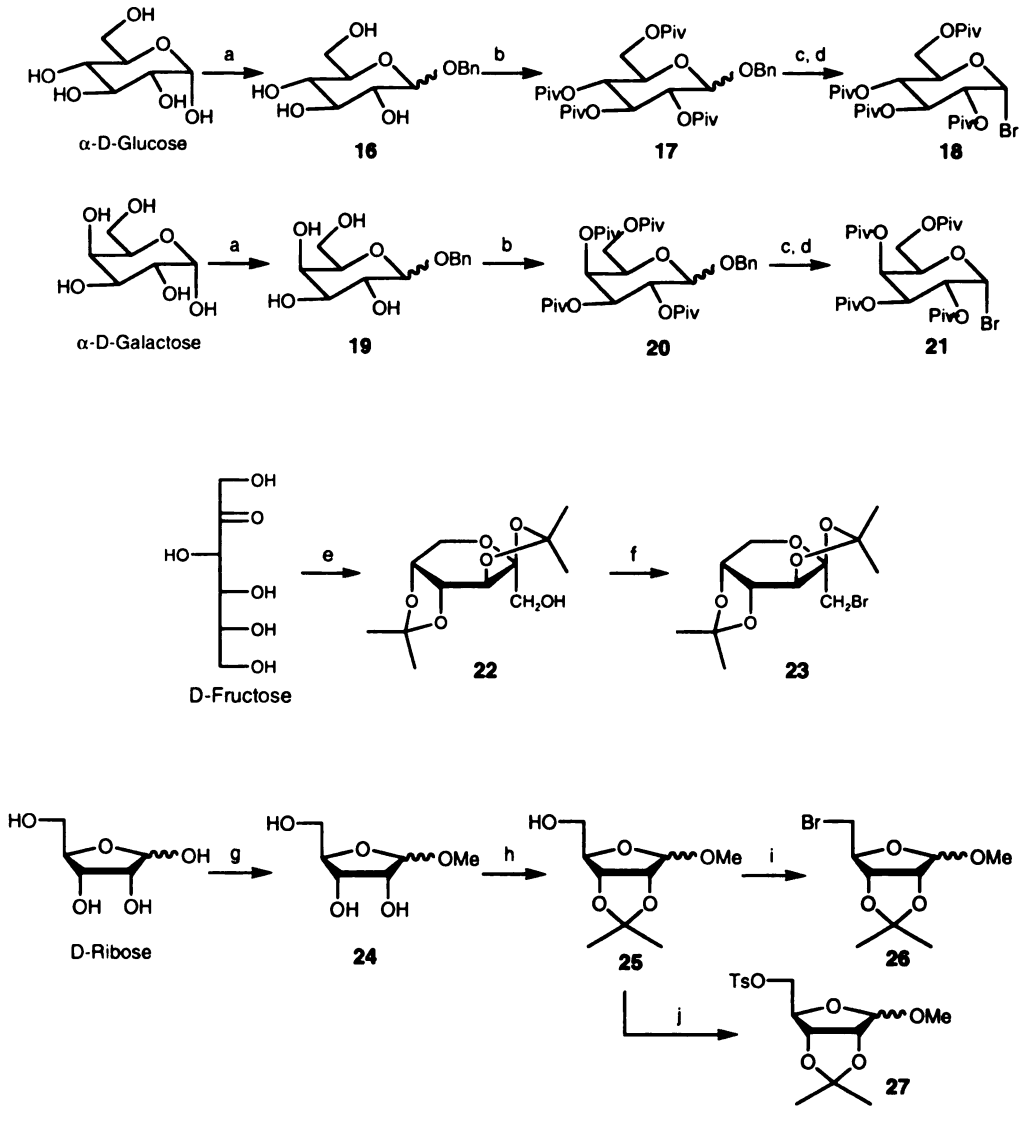
In a 250 ml of flask with 15 g (0.1 mol) of 2-deoxy-erythro-pentyramide **(9)** was added 8 g (0.05 mol) of $CuSO_4$, 100 ml of anhydrous acetone and 0.5 ml of sulfuric acid. The suspension was stirred and 25 g (0.25 mol) of 2, 2-dimethoxypropane was added dropwise into it at room temperature. The amide **(9)** was gradually dissolved in acetone (several hours) and the stirring was continued overnight. Then 5 g of sodium bicarbonate was added and the stirring was continued for 30 min. The solids were filtered and the filtrate was concentrated. The residue was partitioned with 150 ml of $CHCl_3$ and 75 ml H_2O. The organic layer was extracted with brine, and dried over Na_2SO_4. $CHCl_3$ was evaporated and the residue was recrystallized over acetone / hexanes to yield light yellow needles **(10)** (isolated yield: 16.8 g, 73 %) ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (1H, m), 3.98 (1H, m), 3.83 (2H, m), 2.44 (1H, dd, J = 11.5, 2 Hz), 2.29 (1H, dd, J = 11.5, 7.5 Hz), 1.45 (6H, d, J = 2 Hz), 1.35 (6H, d, J = 22.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.79, 109.83, 84.89, 77.45, 69.40, 66.89, 33.80, 30.55, 26.91, 26.66, 25.04. FT IR cm^{-1} 2968, 2935, 2896, 1670, 1400, 1377, 1206, 1195, 1077. Mp: 154-155 °C.

Thionolactam 12

11.4 g (0.05 mol) of bisacetal **10** was dissolved and stirred in 80 ml of anhydrous toluene and 5 ml (1 eq) of pyridine mixed solvent. 10 g (0.25 mol) of Lawessons'

regent was added all at once into the solution. The mixture was quickly heated to 65 °C while stirring and all the suspension was dissolved. The homogeneous mixture was kept heating at 65-70 °C for 1.5 h until TLC indicated reaction complete. Solvent was distilled azeotropically and the residue was purified by column chromatography (EtOAc: Hexanes = 1:2) to afford **12** as light yellow needles. (Isolated yield: 10 g, 80 %) 1H NMR (300 MHz, $CDCl_3$) δ 9.64 (1H, br), 4.06 (1H, m), 3.98 (1H, m), 3.81 (1H, m), 3.79 (1H, m), 3.09 (1H, dd, J = 18.3, 3 Hz), 2.67 (1H, dd, J = 18.3, 10.8 Hz), 1.48 (6H, d, J = 2 Hz), 1.36 (6H, d, J = 21.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.22, 109.93, 87.10, 77.30, 68.78, 66.63, 40.49, 29.26, 26.65, 26.01, 24.93. Mp: 121-122 °C

Scheme 5.2.



Scheme 5.2 Synthesis of Sugar halides (RX). *Reagents, conditions and yields:* (a) $PhCH_2OH$, Acetyl chloride, r.t., overnight, 75 %; (b) t-Bu(C=O)Cl (5 eq), pyridine, r.t. 3 d, 69 %; (c) NBS, CCl_4, $BaCO_3$, *hv*, reflux, 8 h; (d) HMPA; 75-80 °C, 24 h, 74 % in two steps; (e) acetone, sulfuric acid (≥ 5 %), r.t., 1.5 h; (f) PPh_3 (2 eq), CBr_4 (3 eq), pyridine, reflux, 36 h, 84 %; (g) Methanol, H_2SO_4, 0 °C, 15 h, 97 %, (α : β = 1 : 3); (h) 2,2-Dimethoxypropane, acetone, r.t., overnight, quantitative; (i) PPh_3, CBr_4, pyridine, 60-65 °C, 5 h, 70 %; (j) TsCl, pyridine, CH_2Cl_2, r.t. 15 h, quantitative.

Benzyl-glucopyranoside (16)

To a suspension of glucose (10.0 g, 0.056 mol) in 80 ml of benzyl alcohol was added 4 ml of acetyl chloride. The mixture was stirred vigorously and a homogeneous solution was formed. The solution was stirred overnight until TLC indicated the complete conversion. The reaction mixture was diluted with 400 ml of hexane/ether (1: 2) mixed solvent and placed in fridge for 3 h. The top layer was decanted and the lower layer was washed with another 200 ml of hexane to give a sticky liquid. Column chromatograph with dichloromethane/methanol (6:1) afforded 11.3 g of white crystals. **(16)** (α, β mixture, Yield: 75 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.31 (5H, m), 5.54-5.62 (1H, m), 5.30 (1H, m), 5.07 (1H, s), 4.86 (1H, s), 4.58 (2H, m), 4.24 (2H, s), 3.75 (2H, s), 3.52 (3H, m), 3.26 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.54, 128.68, 128.57, 128.29, 102.20, 98.11, 74.00, 73.89, 72.10, 69.71, 61.05, 50.28.

Benzyl-2,3:4,5-pivaloyl-glucopyranoside (17)

11.0 g (42.0 mmol) of benzyl-glucopyranoside **16** was dissolved in 100 ml of pyridine and stirred at room temperature. To the solution was added 25.5 g (210 mmol) of pivaloyl chloride and the reaction mixture was kept stirring at room temperature for 3 days until TLC indicated that most of the starting material was converted. Solvent was removed together with excess pivaloyl chloride by vacuum distillation. The residue was partitioned by 200 ml of chloroform and 100 ml of sodium bicarbonate solution. The organic layer was then washed twice with 50 ml of water, brine and evaporated. The residue was crystallized in EtOAc / hexanes and used without further purification.

(Yield: 17.5 g, 69 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (5H, m), 5.58 (1H, t), 5.09 (2H, m), 4.83 (1H, m), 4.70 (1H, d), 4.57 (1H, t), 4.48 (1H, d), 4.10 (4H, m).

Pivaloylbromo-α-D-glucose (18)

The starting pivaloyl protected glucopyranoside **17** (14.5 g, 24 mmol) was dissolved in 300 ml of CCl_4. In the solution was added 8.5 g (48 mmol) of NBS and 10.0 g (50 mmol) of barium carbonate. The suspension was heated to reflux and irradiated with a 375-W Tungsten lamp while stirring vigorously for 8 h. Then 3.2 g (24 mmol) of HMPA was added and the reaction mixture was kept at the same condition for 24 h more. The suspension was filtered. The filtrate was concentrated in vacuo and the residue was chromatographed to give 10.2 g (Yield: 74 %) of white crystals **18**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (1H, d, J = 4.2 Hz), 5.61 (1H, t, J = 9.6 Hz), 5.20 (1H, t, J = 9.6 Hz), 4.79 (1H, dd, J = 10.2, 4.2 Hz), 4.29 (1H, d, J = 10.2 Hz), 4.15 (2H, s), 1.07-1.28 (36H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.91, 177.29, 176.75, 176.56, 86.85, 72.50, 70.83, 69.52, 66.48, 60.84, 38.72, 38.38.63, 27.12, 27.05, 27.01, 26.97.

2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (22)

The preparation followed the procedure described by Brady.[32] In this approach, acetone and over 5 % of sulfuric acid was added to obtain the thermodynamically favored bisacetal fructopyranose product **22**.

2,3:4,5-di-O-isopropylidene-β-D-bromofructopyranose (23)

Bisacetal fructopyranose **22** (8.0 g, 32 mmol), triphenylphosphine (16.8 g, 64 mmol),

and carbon tetrabromide (31.2 g, 96 mmol) were placed in a 250 ml flask equipped with a magnetic stirrer and ice bath. Anhydrous pyridine (120 ml) was poured slowly into the flask with stirring while the mixture was cooled over ice bath. A reflux condenser was then added and the homogeneous resultant was then heated over oil bath to mild reflux. The reaction mixture turned into a dark brown solution and the heating was continued for 36 h. TLC indicated the disappearance of starting material. Methanol (300 ml) was added to quench the reaction. The reaction mixture was stirred at room temperature for 30 min more. Then the solvent was removed by vacuum distillation. The residue was taken up by 100 ml of dichloromethane and the solid substance was filtered. The filtrate was concentrated and column chromatographed with Ethyl acetate/hexanes (1: 5) to afford a golden liquid **23**. (Yield: 8.3 g, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (1H, dd, J = 8.4, 3 Hz), 4.26 (1H, d, J = 3 Hz), 4.14 (1H, d, J = 8.4 Hz), 3.84 (1H, dd, J = 13.2, 1.5 Hz), 3.69 (1H, d, J = 13.2 Hz), 3.54 (1H, d, J = 11.4 Hz), 3.40 (1H, d, J = 11.4 Hz), 1.45 (3H, s), 1.37 (6H, d, J = 6.6 Hz), 1.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.23, 109.06, 101.17, 71.63, 70.83, 70.36, 62.11, 35.82, 26.84, 26.05, 25.73, 24.21.

Methyl D-ribofuranoside (24)

1 ml of sulfuric acid was added to a solution of 5.0 g (33 mmol) of D-ribose in 100 ml of methanol. The solution was stirred in the cold room (5 °C) for 15 h and then quenched by stirring with Amberlyst resin. After filtration, the solution was concentrated in vacuo to yield a thick golden syrup **24**.(Yield: 5.1 g, 95 %, α:β = 1 : 3)

Methyl-2, 3-O-isopropylidene-D-ribofuranoside (25)

In a solution of 5.4 g (33 mmol) of methyl ribofuranoside **24** in 100 ml of anhydrous acetone was added 8.0 g (76 mmol) of 2, 2-dimethoxypropane and 0.5 ml of sulfuric acid. The solution was stirred overnight and 5 g of sodium bicarbonate was added to quench the reaction. The stirring was kept for 30 min more and the suspension was filtered. The filtrate was concentrated in vacuo to form a light yellow liquid near quantitative yield. The α- and β- isomers could be further separated by column chromatography to give β-isomer in 4.5 g isolated yield. (67 %), and α-isomer 1.6 g (24 %). ^{1}H NMR for α-isomer (300 MHz, $CDCl_3$) δ 4.80 (1H, d, J = 2.4 Hz), 4.55 (2H, d, J = 2.4 Hz), 4.05 (1H, t, J = 3.0 Hz), 3.68 (1H, dd, J = 12.0, 3 Hz), 3.58 (1H, dd, J = 12.0, 4 Hz), 3.56 (3H, s), 2.85 (1H, s, br), 1.45 (3H, s), 1.25 (3H, s); ^{13}C NMR for α-isomer (75 MHz, $CDCl_3$) δ 115.16, 102.59, 81.39, 80.58, 80.14, 62.35, 55.52, 25.63, 25.46; ^{1}H NMR for β-isomer (300 MHz, $CDCl_3$) δ 4.84 (1H, s), 4.68 (1H, d, J = 6 Hz), 4.46 (1H, d, J = 6 Hz), 4.26 (1H, t, J = 3.6 Hz), 3.53 (1H, dd, J = 8.7, 3.6 Hz), 3.49 (1H, dd, J = 8.7, 3.9 Hz), 3.29 (3H, s), 3.23 (1H, q, J = 4.8 Hz), 1.35 (3H, s), 1.18 (3H, s); ^{13}C NMR for β-isomer (75 MHz, $CDCl_3$) δ 110.83, 109.60, 87.95, 85.46, 81.27, 63.63, 55.08, 26.10, 24.46.

Methyl-2, 3-O-isopropylidene-5-tosyl-β-D-ribofuranoside (27)

2.0 g (10 mmol) of Methyl-2,3-O-isopropylidene-β-D-ribofuranoside and 2.2 g (12 mmol) of tosyl chloride were dissolved in 20 ml of CH_2Cl_2 at room temperature while stirring. 6 ml of pyridine was added and the reaction mixture was kept stirring for 15 h.

The solvent CH_2Cl_2 was evaporated in vacuo and the residue was poured in ice-water mixture. Suction filtration followed by rinsing the filter cake twice with cold water gave white solid **27** in quantitative yield. (3.6 g)

2,3:4,6-O-pivaloylglucose glycal (15)

Sodium hydride (0.09 g, 2.2 mmol) was suspended in 4 ml of anhydrous DMF. The suspension was cooled to 0 °C and the pivaloyl-bromoglucose **18** (0.5 g, 0.87 mmol) dissolved in 1 ml DMF was added dropwise to the suspension while stirring vigorously. Temperature was raised slowly to r.t. in 1 h. The suspension was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column directly and 0.3 g of colorless needles **15** were obtained. (Yield: 69 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (1H, s), 5.50 (1H, d, J = 2.5 Hz), 5.26 (1H, t, J = 2.5 Hz), 4.35 (1H, dd, J = 6.0, 3 Hz), 4.27 (1H, m), 4.21 (1H, dd, J = 6.0, 1 Hz), 1.08-1.28 (36H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.82, 177.04, 176.89, 176.45, 138.96, 127.84, 74.14, 67.35, 66.33, 60.80, 38.73, 38.70, 38.67, 27.00, 26.98, 26.97, 26.85. Mp: 86 °C.

Selective hydrolyzed lactam bisacetal (46)

The bisacetal **10** was stirred in methanol containing trifluoroacetic acid at room temperature for 5 h. The solvent was removed and the pure product was obtained as white solid **46** in quantitative yield. ^{1}H NMR (300 MHz, D_2O) δ 4.05 (1H, m), 3.62 (1H, m), 3.54 (1H, m), 3.44 (1H, m), 2.23 (2H, m); ^{13}C NMR (75 MHz, D_2O) δ 171.50, 85.31, 72.96, 67.88, 61.96, 31.19, 29.00, 25.53.

Selective hydrolyzed thiolactam bisacetal (47)

The thiolactam **12** was stirred in methanol containing trifluoroacetic acid at room temerature for 5 h. The solvent was removed and the product was crystallized from methanol as colorless crystals **47**. The yield was near quantitative. ^{1}H NMR (500 MHz, CD_3OD) δ 4.07 (1H, m), 3.74 (1H, dd, J = 10.0, 3 Hz), 3.67 (2H, m), 3.01 (1H, dd, J = 18.0, 3 Hz), 2.79 (1H, dd, J = 18.0, 11 Hz), 1.56 (6H, d, J = 2.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 199.06, 87.95, 74.67, 68.83, 63.63, 40.89, 29.32, 25.67.

General Procedure for the Preparation of Thioalkyl Substituted Heterocycles (28-44)

A suspension of 80 mg (60 %, 2 mmol) NaH in 8 ml of anhydrous DMF was cooled to 0 °C with sodium chloride ice-bath. 0.25 g (1 mmol) of thiolactam **12** dissolved in 5 ml of DMF was added dropwise into the suspension while stirring. The stirring was kept for 1 h at room temperature and cooled back to 0 °C. Alkyl halide (1.5-2.0 mmol) dissolved in 3 ml DMF was added dropwise to the reaction mixture and the stirring was kept at 0 °C to room temperature for 2-12 h as indicated by TLC. The desired bisacetal product could be purified by column chromatography. (Ethyl acetate: Hexanes = 1: 20). Treatment with TFA in CH_2Cl_2 gave first the protonated and then selective hydrolyzed products in quantitative yield. Due to the labile character of the hydrolyzed products (they were readily decomposed to 2-deoxy-D-ribonolactone in methanol/TFA within 8-12 h), the products were stored in their bisacetal form.

Thioalkyl substituted heterocycles (45)

The treatment of NaH and thiolactam **12** followed the general procedure above. methyl-2,3-O-isopropylidene-5-tosyl-β-D-ribofuranoside **27** (0.43 g, 1.2 mmol) was dissolved in 3 ml DMF was added to the reaction mixture. The reaction was stirred at 80 °C for 36 h. Then the suspension was filtered and the filtrate was concentrated in vacuo. The residue was place onto column chromatography directly (Ethyl acetate: hexanes = 1:5) to give colorless needles **45**. (Yield: 0.17 g, 61 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (1H, s), 4.61 (1H, d, J = 6.0 Hz), 4.54 (1H, d, J = 6.0 Hz), 4.22 (1H, dd, J = 9.0, 7 Hz), 4.03 (1H, dd, J = 8.0, 6 Hz), 3.85-3.90 (1H, m), 3.81 (1H, dd, J = 9.0, 5 Hz), 3.56-3.62 (1H, m), 3.30 (3H, s), 3.09 (1H, dd, J = 13.0, 9 Hz), 3.02 (1H, dd, J = 13.0, 6 Hz), 2.26 (1H, dd, J = 17.0, 4 Hz), 2.20 (1H, dd, J = 17.0, 10 Hz), 1.40 (3H, s), 1.35 (6H, s), 1.32 (3H, s), 1.28 (3H, s), 1.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.36, 112.16, 109.59, 109.49, 89.72, 85.59, 85.30, 83.14, 77.70, 67.81, 67.01, 54.77, 33.28, 31.14, 29.96, 26.65, 26.30, 25.66, 24.94, 24.89. Mp: 76.5-77.5 °C.

Thioalkyl substituted heterocycles (28-44)

R = Methyl (28) (Yield: 150 mg, 80 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01-4.06 (1H, m), 3.87-3.91 (1H, m), 3.81-3.85 (1H, m), 3.56-3.64 (1H, m), 2.14-2.31 (2H, m), 2.22 (3H, s), 1.35 (6H, d, J = 1 Hz), 1.30 (6H, d, J = 12.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.75, 109.43, 89.67, 77.77, 67.82, 67.04, 33.25, 30.12, 26.66, 25.84, 24.96, 11.61.

R = Ethyl (29) (Yield: 120 mg, 72 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (1H, dd, J = 9.0, 8 Hz), 3.82-3.94 (2H, m), 3.62-3.66 (1H, m), 2.83-2.91 (2H, m), 2.21-2.27 (2H, m), 1.38 (6H, d, J = 2.1 Hz), 1.36 (3H, s), 1.31 (3H, s), 1.21 (3H, t, J = 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.04, 109.48, 89.58, 77.88, 67.94, 67.13, 33.42, 30.10, 26.74, 25.81, 25.06, 22.81, 14.29.

R = n-Butyl (30) (Yield: 170 mg, 92 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (1H, dd, J = 8.5, 6Hz), 3.89 (1H, m), 3.83 (1H, dd, J = 8.5, 5 Hz), 3.62 (1H, m), 2.92 (1H, q), 2.85 (1H, q), 2.26 (1H, dd, J = 17.0, 3.5 Hz), 2.19 (1H, dd, J = 17.0, 10.5 Hz), 1.54 (2H, q), 1.30-1.37 (14H, br, m), 0.88 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.22, 109.45, 89.55, 78.04, 68.11, 67.14, 33.60, 31.28, 30.12, 27.97, 26.72, 25.82, 25.10, 21.91, 13.53.

R = n-Hexyl (31) (Yield: 170 mg, 84 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (1H, dd, J = 8.5, 8 Hz), 3.84-3.88 (1H, m), 3.80 (1H, dd, J = 8.5, 5 Hz), 3.60 (1H, m), 2.88 (1H, q), 2.80 (1H, q), 2.24 (1H, dd, J = 17.0, 3.5 Hz), 2.16 (1H, dd, J = 17.0, 10 Hz), 1.54 (2H, q), 1.22-1.38 (18H, br, m), 0.84 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.17, 109.34, 89.45, 77.91, 68.01, 67.09, 33.47, 31.25, 30.03, 29.05, 28.42, 28.23, 26.62, 25.72, 25.01, 22.34, 13.82.

R = n-Hexadodecyl (32) (Yield: 260 mg, 90 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (1H, dd, J = 8.5, 6 Hz), 3.89 (1H, m), 3.84 (1H, dd,

J = 8.5, 5.5 Hz), 3.60-3.66 (1H, m), 2.91 (1H, q), 2.85 (1H, q), 2.27 (1H, dd, J = 17.0, 4 Hz), 2.19 (1H, dd, J = 17.0, 10 Hz), 1.56 (2H, q), 1.24-1.73 (38H, br, m), 0.86 (3H, t, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.24, 109.42, 89.52, 77.98, 68.07, 67.16, 33.54, 31.86, 30.10, 29.61, 29.59, 29.55, 29.43, 29.27, 29.15, 29.14, 28.86, 28.32, 26.68, 25.79, 25.06, 22.60, 13.98

R = Cyclohexyl (33) (Yield: 16 mg, 8 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (1H, dd, J = 8.5, 6 Hz), 3.85-3.91 (1H, m), 3.84 (1H, dd, J = 8.5, 5 Hz), 3.60-3.66 (2H, m), 2.22 (1H, dd, J = 13.5, 4 Hz), 2.17 (1H, dd, J = 13.5, 10 Hz), 1.86-1.98 (4H, br, m), 1.62-1.74 (4H, br, m), 1.54 (2H, m), 1.37 (3H, s), 1.36 (3H, s), 1.34 (3H, s), 1.31 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.86, 109.53, 89.53, 77.94, 67.99, 67.13, 48.69, 41.10, 33.51, 32.76, 30.10, 26.73, 25.93, 25.85, 25.78, 25.08.

R = Ethyl bromoacetate (34) (Yield: 140 mg, 69 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (1H, d, J = 9.0 Hz), 4.05 (1H, d, J = 9.0 Hz), 3.99 (1H, dd, J = 7.5, 6 Hz), 3.82-3.86 (1H, m), 3.77 (1H, dd, J = 7.5, 4 Hz), 3.57-3.59 (2H, m), 3.55-3.57 (1H, m), 2.23 (1H, dd, J = 18.0, 15 Hz), 2.18 (1H, dd, J = 18.0, 6 Hz), 1.31 (3H, s), 1.26 (9H, d, J = 6.0 Hz), 1.18 (3H, t, J = 6.0 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.19, 157.70, 109.38, 89.55, 77.61, 67.72, 66.92, 61.14, 32.77, 31.07, 29.77, 26.56, 25.54, 24.86, 14.02.

R = Benzyl (35) (Yield: 195 mg, 95 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.34 (5H, m), 4.18 (2H, dd, J = 30.0, 13.5 Hz), 4.08-4.12 (1H, m), 3.93-3.96 (1H, m), 3.87-3.91 (1H, m), 3.66-3.70 (1H, m), 2.33 (1H, dd, J = 16.5, 4 Hz), 2.26 (1H, dd, J = 16.5, 10 Hz), 1.43 (6H, J = 18.0 Hz), 1.39 (6H, d, J = 37.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.11, 138.87, 129.29, 128.56, 127.10, 109.80, 90.02, 78.15, 68.27, 67.40, 33.51, 32.74, 30.40, 26.99, 26.15, 25.33.

R = p-Chlorobenzyl (36) (Yield: 190 mg, 84 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (4H, q), 4.10 (2H, dd, J = 26.5, 16 Hz), 4.04-4.08 (1H, m), 3.90-3.94 (1H, m), 3.84-3.88 (1H, m), 3.63-3.71 (1H, m), 2.30 (1H, dd, J = 17.0, 3.5 Hz), 2.23 (1H, dd, J = 17.0, 10 Hz), 1.40 (9H, d, J = 11.5 Hz), 1.36 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.55, 137.26, 132.53, 130.29, 128.28, 109.44, 89.66, 77.82, 67.97, 67.08, 33.21, 31.67, 30.05, 26.65, 25.79, 25.01.

R = m-Nitrobenzyl (38) (Yield: 180 mg, 77 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (1H, d, J = 2 Hz), 8.01 (1H, d, J = 8.0 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.38 (1H, t, J = 8.0 Hz), 4.18 (1H, d, J = 14.5 Hz), 4.12 (1H, d, J = 14.5 Hz), 4.03 (1H, dd, J = 8.5, 6.5 Hz), 3.86-3.90 (1H, m), 3.81 (1H, dd, J = 8.5, 5 Hz), 3.60-3.66 (1H, m), 2.26 (1H, dd, J = 17.0, 4 Hz), 2.20 (1H, dd, J = 17.0, 10 Hz), 1.29-1.39 (9H, m), 1.28 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.05, 147.96, 141.33, 135.02, 128.90, 124.16, 121.70, 109.44, 89.74, 77.71, 67.80, 66.99, 33.03, 31.34, 29.97, 26.59, 25.71, 24.90.

R = o-Methoxybenzyl (39) (Yield: 170 mg, 76 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (1H, d, J = 7.5 Hz), 7.21 (1H, t, J = 8 Hz), 6.87 (2H, q), 4.24 (1H, d, J = 13.0 Hz), 4.19 (1H, d, J = 13.0 Hz), 4.09 (1H, dd, J = 8.0, 2 Hz), 3.91-3.94 (1H, m), 3.88 (1H, dd, J = 8.0, 5 Hz), 3.85 (3H, s), 3.66-3.70 (1H, m), 2.31 (1H, dd, J = 17.0, 4 Hz), 2.24 (1H, dd, J = 17.0, 10 Hz), 1.48 (3H, s), 1.44 (3H, s), 1.41 (3H, s), 1.34 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.06, 157.30, 130.62, 128.13, 126.71, 120.08, 110.24, 109.34, 89.57, 77.75, 67.86, 66.95, 55.22, 33.09, 30.10, 26.78, 26.59, 25.84, 24.94.

R = m-Methoxybenzyl (40) (Yield: 223 mg, 100 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (1H, t, J = 8.0 Hz), 6.89 (1H, d, J = 8.0 Hz), 6.88 (1H, s), 6.75 (1H, dd, J = 8.0, 1 Hz), 4.16 (1H, d, J = 13.0 Hz), 4.11 (1H, d, J = 13.0 Hz), 4.07 (1H, dd, J = 8.5, 6.5 Hz), 3.89-3.93 (1H, m), 3.86 (1H, dd, J = 8.5, 5 Hz), 3.76 (3H, s), 3.65-3.69 (1H, m), 2.31 (1H, dd, J = 17.0, 4 Hz), 2.24 (1H, dd, J = 17.0, 10 Hz), 1.43 (3H, s), 1.40 (3H, s), 1.39 (3H, s), 1.32 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.62, 158.90, 140.11, 129.18, 121.29, 114.55, 112.51, 109.45, 89.66, 77.86, 68.00, 67.09, 55.02, 33.22, 32.41, 30.10, 26.65, 25.84, 25.02.

R = p-Methoxybenzyl (41) (Yield: 170 mg, 76 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (2H, d, J = 8.5 Hz), 6.78 (2H, d, J = 8.5 Hz), 4.10 (1H, d, J = 13.5 Hz), 4.05 (1H, d, J = 13.5 Hz), 4.03 (1H, dd, J = 8.5, 2.5 Hz), 3.87-3.91 (1H, m), 3.83 (1H, dd, J = 8.5, 5 Hz), 3.73 (3H, s), 3.61-3.66 (1H, m), 2.26 (1H, dd, J =

16.5, 3.5 Hz), 2.20 (1H, dd, J = 16.5, 10 Hz), 1.40 (3H, s), 1.38 (3H, s), 1.36 (3H, s), 1.30 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.96, 158.51, 130.50, 130.05, 113.70, 109.46, 89.67, 77.82, 67.92, 67.07, 55.09, 33.18, 31.90, 30.11, 26.66, 25.85, 24.98.

R = o-Cyanobenzyl (42) (Yield: 200 mg, 90 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.59 (2H, m), 7.47 (1H, t, J = 7.5 Hz), 7.28 (1H, t, J = 7.5 Hz), 4.35 (1H, d, J = 14.0 Hz), 4.25 (1H, d, J = 14.0 Hz), 4.05 (1H, dd, J = 8.0, 6 Hz), 3.87-3.91 (1H, m), 3.83 (1H, dd, J = 8.0, 5 Hz), 3.60-3.64 (1H, m), 2.28 (1H, dd, J = 11.0, 3.5 Hz), 2.21 (1H, dd, J = 11.0, 10 Hz), 1.36 (9H, d, J = 9.5 Hz), 1.30 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.86, 142.75, 132.43, 132.36, 130.24, 127.16, 117.50, 112.81, 109.46, 89.76, 77.69, 67.82, 67.00, 32.94, 30.45, 29.83, 26.62, 25.66, 24.94.

R = m-Cyanobenzyl (43) (Yield: 210 mg, 95 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (1H, s), 7.52 (1H, d, J = 6.5 Hz), 7.45 (1H, d, J = 6.5 Hz), 7.34 (1H, t, J = 6.5 Hz), 4.15 (1H, d, J = 13.5 Hz), 4.07 (1H, d, J= 13.5 Hz), 4.03-4.08 (1H, m), 3.87-3.91 (1H, m), 3.80-3.84 (1H, m), 3.61-3.64 (1H, m), 2.26 (1H, dd, J = 15.0, 13.5 Hz), 2.10 (1H, dd, J = 15.0, 10 Hz), 1.36 (9H, d, J = 4.0 Hz), 1.29 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.09, 140.56, 133.32, 132.67, 130.23, 128.82, 118.50, 112.09, 109.40, 89.65, 77.63, 67.78, 66.96, 33.01, 31.41, 29.93, 26.57, 25.68, 24.89.

R = p-Cyanobenzyl (44) (Yield: 190 mg, 84 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (2H, d, J = 8.0 Hz), 7.39 (2H, d, J = 8.0 Hz), 4.16 (1H, d, J = 14.0 Hz), 4.06 (1H, d, J = 14.0 Hz), 4.04 (1H, dd, J = 8.5, 6 Hz), 3.87-3.91 (1H, m), 3.82 (1H, dd, J = 8.5, 4.5 Hz), 3.58-3.62 (1H, m), 2.25 (1H, dd, J = 17.0, 4 Hz), 2.19 (1H, dd, J = 17.0, 10 Hz), 1.35 (6H, d, J = 2 Hz), 1.33 (3H, s), 1.28 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.99, 144.55, 131.95,131.80, 129.77, 129.61, 118.74, 110.37, 109.46, 89.68, 77.63, 67.71, 66.85, 32.95, 31.78, 29.93, 26.59, 25.68, 24.84.

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