ABSTRACT

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The thesis entitled "***Developing a novel synthetic methodologies and their application to the total synthesis of Ternatusine A, Nojirimycin analogues, Boronolide, Anamarine, 8-epispicegerolide*** " has been divided into five chapters. Each chapter is complete in itself.

Chapter I: This chapter describes the development of new synthetic methodologies based on dipolar cycloaddition of azomethine ylides to C-2 formyl glycols and it application to the synthesis of pyrrole alkaloid Ternatusine A, which is further divided into two sections.

Section A: This section describes the general introduction of dipolarcycloaddition of azomethine ylides, synthesis of substituted pyrrole derivatives and biological activity based on pyrrole as a core structure contained natural products.

Section B: This section deals 1,3-DC reaction of azomethine ylide with C-2 formyl glycol derived from D-glucose/D-galactose reacted with secondary amino acids (sarcosine/proline/piperidine-2-carboxylic acid) to give the corresponding pyrrole derivatives, it application to the total synthesis of pyrrole alkaloid Ternatusine A.

Chapter II: This chapter describes the development of new synthetic methodology for the synthetic studies related to azasugars. The best known biological activity of azasugars is that of inhibition of glycosidases and carbohydrate-processing enzymes, which is further divided into two sections.

Section A: This section describes brief overview of the isolation, structure and bioactivity of the azasugars family of natural products and stereoselective synthesis of azasugar C-glycosides, previous approaches of the synthesis of nojirimycin anlogues

Section B: This section deals with silvertriflate-catalyzed synthetic methodology developed to produce azasugar scaffolds. Taken as a whole, the applicability of the variety of alkylamines and terminal alkynes, an understanding of the factors controlling the diastereoselectivity of the reaction should make this methodology towards to the synthesis of nojirimycin analogues.

<u>Chapter III</u>: This chapter describes the development of novel synthetic methodologies from Sugar derived enynones undergo a sequential glycosylation/endo-dig cyclization with alcohols to afford a novel class of sugar annulated furan scaffolds, which is further divided into two sections.

Section A: This section deals with general introduction of metal catalyzed synthesis of substituted furans, biological activity of furan contained natural products.

Section B: This section deals introduction of *endo-dig* cyclizations, $AgSbF_6$ catalyzed synthesis of sugar annulated furans from sugar derived enynones derived from D-glucose/D-galactose reacted with alcohols.

<u>Chapter IV</u>: This chapter describes the total synthesis of Boronolide, Anamarine, 8-epispicegerolide, which is further divided into two sections.

Section A: This section deals with general introduction of six-membered lactones and previous approaches, biological activity of Boronolide, Anamarine, Spicegerolide.

Section B: This section deals with the total synthesis of Boronolide, Anamarine, 8-epispicegerolide form common intermediate, which is derived from D-xylose.

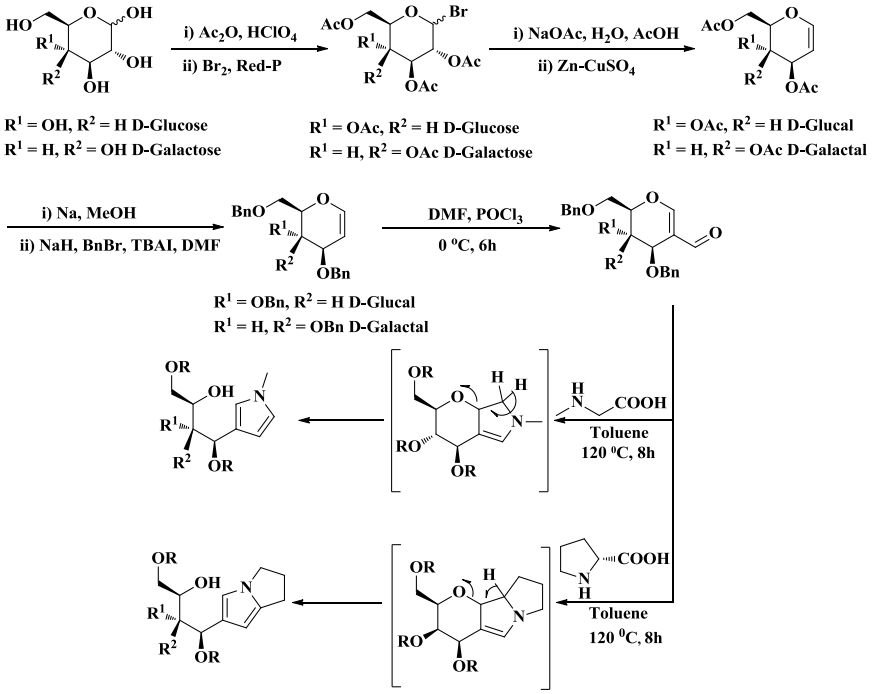
Chapterwise brief outline of Thesis

<u>CHAPTER I</u>: This chapter decribes "1,3-DC reaction of azomethine ylide with C-2 formyl glycol derived from D-glucose/D-galactose reacted with secondary amino acids (sarcosine/proline/piperidine-2-carboxylic acid) to give the corresponding pyrrole derivatives, it application to the total synthesis of pyrrole alkaloid Ternatusine A".

The formation of new C-C bonds is a central challenge in organic chemistry. Among the best known and most efficient methods for achieving by cycloaddition reactions. Two major types of cycloaddition reactions are the Diels-Alder reaction, for the formation of 6-membered rings and the 1,3-dipolar cycloaddition, affording 5-membered rings. In a single synthetic operation, the 1,3-dipolar cycloaddition reaction of an azomethine ylide

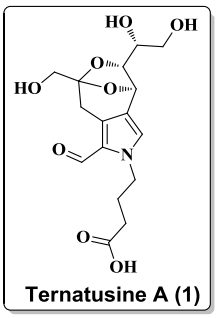
Intramolecular cycloadditions with azomethine ylides have significant interest for the formation of substituted cyclic amine products, many of which form the basis of a variety of alkaloid natural products. However, that it is necessary to construct a substrate containing both a dipole and a dipolarophile within the same molecule.

A unique dipole and a dipolarophile (α,β–unsaturated aldehyde) derived from D-glucose/D-galactose reacted with secondary amino acids (sarcosine/proline/piperidine-2-carboxylic acid) to give the corresponding pyrrole.

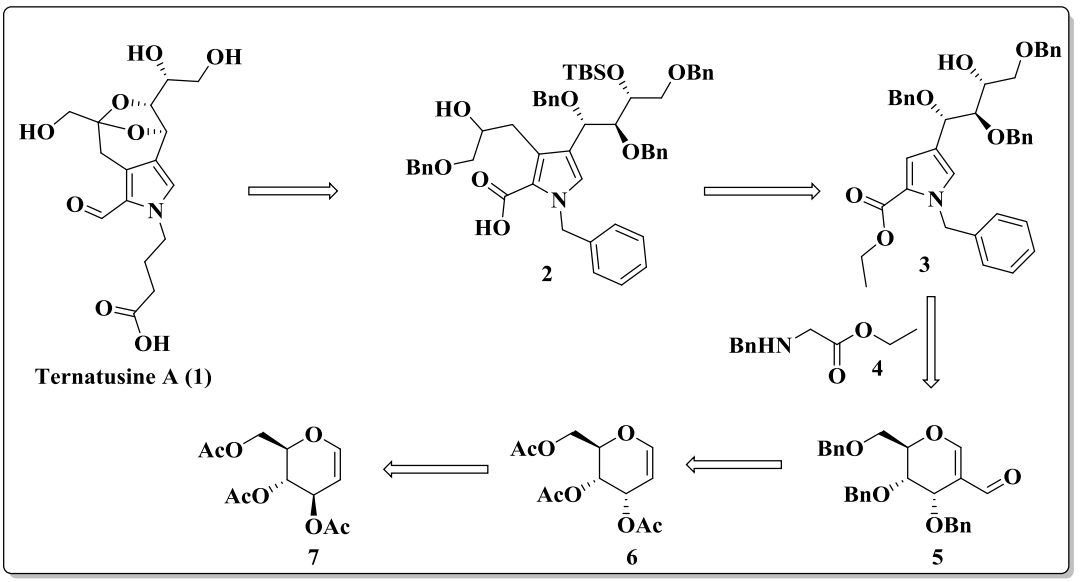


This approach seems ideally suited to access the pyrrole alkaloid Ternatusine A, as an intramolecular cycloaddition reaction would allow, in a single step, the simultaneous formation together with all three chiral centres. Suggested that the azomethine ylide cycloaddition reaction would proceed to give the desired stereochemical arrangement found within the Ternatusine A. Herein we report a successful model study using this strategy.

Ternatusine A, a novel pyrrole alkaloid with a rare epoxyoxepino[4,5-c]pyrrole ring was isolated from the roots of **Ranunculus ternatus thunb** by yanan and co-workers. It shows exhibited potent hepatoprotective activity against d-galactosamine-induces diffuse injury of liver tissue. 4-[2-formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]butanoic acid was isolated and showed potent inhibitory activity against Mycobacterium tuberculosis H37Rv in vitro.



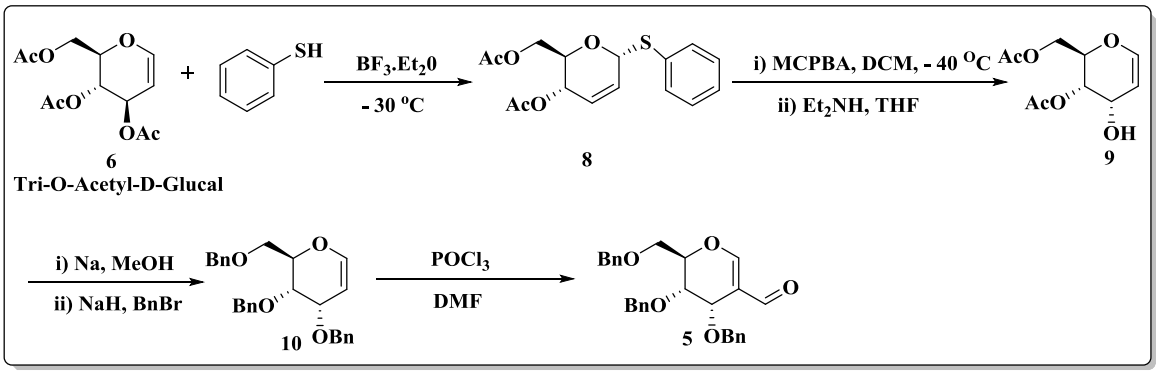
Retrosynthetic strategy for the synthesis of Ternatusine A:



Scheme 1: Retrosynthetic analysis of **1**

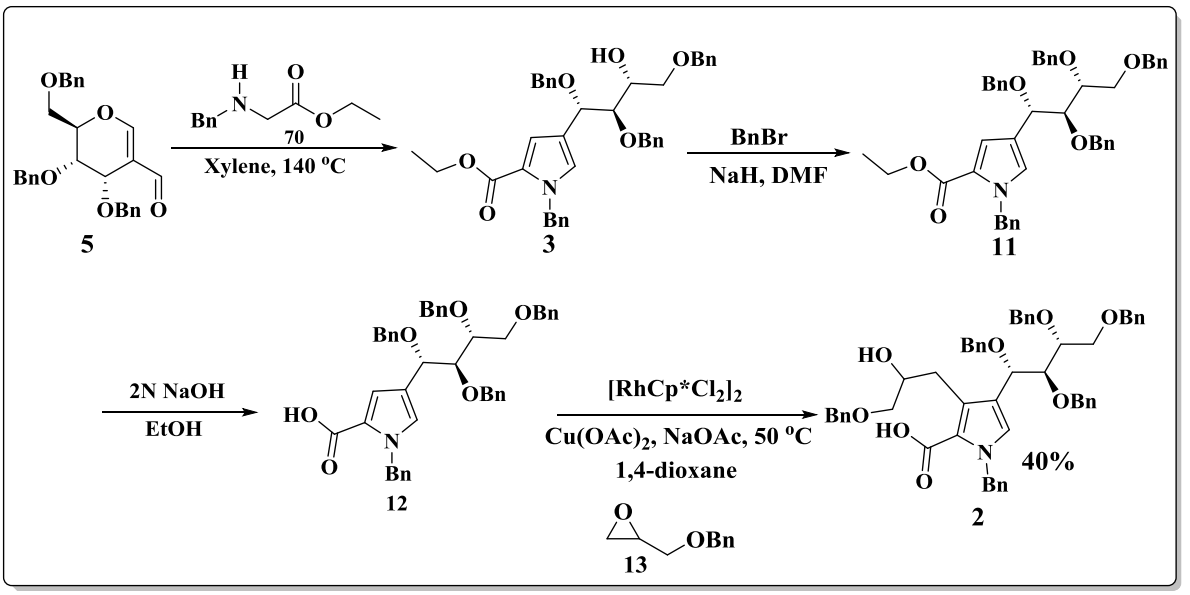
The retro synthetic analysis (**Scheme 1**) revealed that the Ternatusine A can be synthesized from the acid fragment **2** which in turn, can be synthesized from the pyrrole fragment **3.** For the synthesis of **3**, we identified 2-*C*-formyl allal **5** as a key intermediate in the s-*cis* enal system that can be transformed to the desired pyrrole **3** (**Scheme 1**). The compound **4** synthesis from commercially available D-glucose.

Our route started with triacetylglucal **6**, which was converted by Ferrier rearrangement with Thiophenol in the presence of $BF_3.Et_2O$. Oxidation of sulfide **8** in the usual manner with 3,3-dimethyldioxirane cleanly afforded the desired sulfoxide and Et_2NH-mediated [2,3]-sigmatropic rearrangement with simultaneous acyl migration to provide **9** in 96% yield. Deacetylation followed by perbenzylation afforded **10** in 92% yield over two steps. A Vilsmeier–Haack reaction was carried out smoothly to give the 2-C-formyl-D-allal **5** (scheme 2).



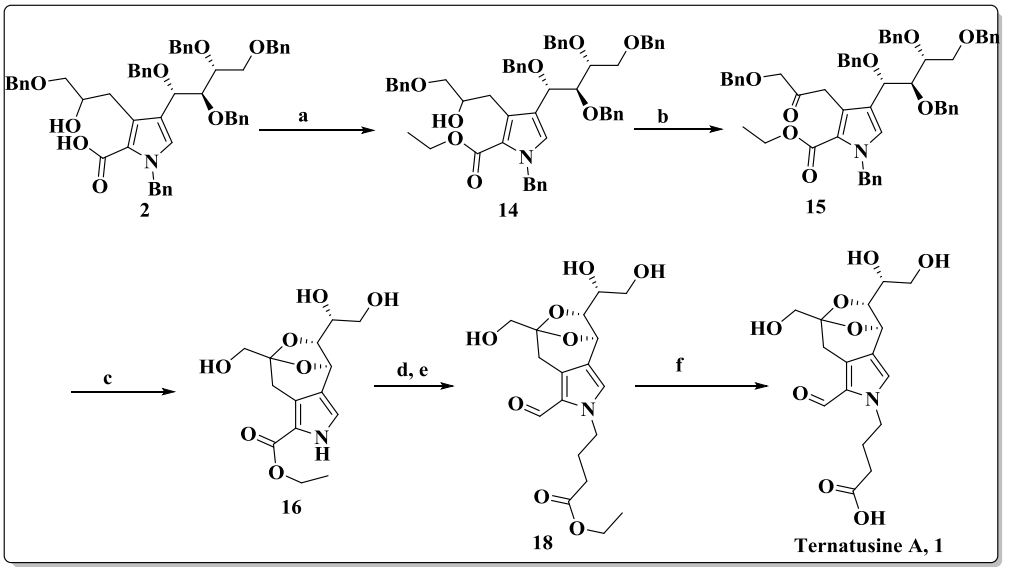
Scheme 2: Synthesis of C-2 formyl Tri-O-Benzyl-D-allal

Treatment of **4** with N-benzylglycine ethyl ester **5** in refluxing xylene formed an azomethine ylide, which underwent cycloaddition to afford the product as core structure of pyrrole **3** with desired stereochemistry of Ternatusine A. Selctive protection of **3** secondary alcohol with benzyl ether **11**, then followed by ester hydrolysis with 2N NaOH in ethanol to gave the acid **12.** Here we attemted acid directed ortho alkylation, reaction of acid (**12**) with 2-((benzyloxy)methyl)oxirane **13** was carried out in the presence of $[RhCp^*Cl_2]_2$ (2 mol %), $Cu(OAc)_2$ (0.2 equiv.,), and NaOAc (3 equiv.,) as catalyst, oxidant, and additive, respectively, in dioxane at 50 °C for 6 h under Argon for 12 h, which only generated the alkylation product **2** in 58% yield.



Scheme 3: Synthesis of **2**

Eserification of acid with bromoethane and K_2CO_3 gave the **14**, Dess-Martin periodinane oxidation of the alcohol **14** gave the ketone **15** in quantitative yield. The epoxyoxepino[4,5-c]pyrrole, were then formed by debenzylation and subsequent ketal formation. Thus, debenzylation of **15** under hydrogenation conditions (H_2, $Pd(OH)_2$ and AcOH) afforded the corresponding pyrroles **16** in good yields (70%). Partial reduction of the ester **16** using DIBAL-H in dry DCM at -78 °C afforded the corresponding aldehyde **17** which was subsequently subjected to alkylation with Ethyl 4-bromobutanoate and anhydrous K_2CO_3 afforded **18**, Which was then subjected to hydrolysis with aq.NaOH furnished the Ternatusine A (**1**) in 42% overall yield over three steps.

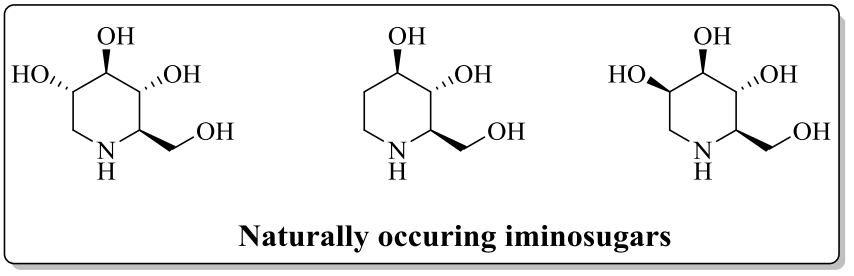


Scheme 4: Synthesis of Ternatusine A.

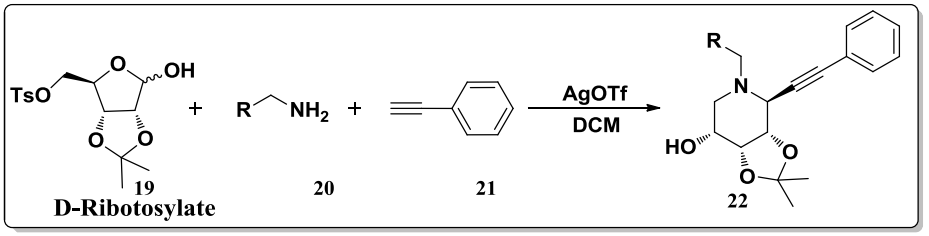
***Reagents and conditions*:** a) Ethyl bromide, K2CO3, DMF, 0 °C to rt, 2h, 91%; b) Dess-Martin periodinane, CH2Cl2, 0 °C to rt, 2h, 80%; c) Pd(OH)2, H2, AcOH, IPA:H2O, 16h, 65%; d) DIBAL-H, CH2Cl2, -78 °C to rt, 0.5 h, 60%; e) **17**, Ethyl 4-bromobutanoate, n-Bu4NBr, K2CO3, CH3CN, 50 °C, 4 h, 62%; f) Aq. NaOH

Chapter II: This chapter describes the development of new synthetic methodology for the synthetic studies related to azasugars. The best known biological activity of azasugars is that of inhibition of glycosidases and carbohydrate-processing enzymes., which is further divided into two sections.

Azasugars, or iminosugars, are structural analogues of native carbohydrates in which the ring oxygen has been replaced by a nitrogen. These sugar mimics are a valuable class of compounds that play an important role in drug development, primarily due to their ability to mimic the charge density in the transition state of glycosidic hydrolase enzymes. Other biological activities of azasugars have also been noted, such as their ability to act as molecular chaperones, as immunomodulators, or as inhibitors of other enzymes and proteins.



Given the potential of azasugars as glycosidase inhibitors, we were interested in developing an efficient methodology for their synthesis. Herein, we wish to report our preliminary results on a silver(I) triflate-catalyzed one-pot three component reaction for the direct synthesis of nojirimycin analogues through adition of terminal alkynes to iminosugars.



Scheme 5: Silvertriflate catalyzed synthesis of nojirimycins

Our synthetic route involves **19** as the starting compound, which was prepared in high yield from d-ribose. Thus, treatment of D-ribose tosylate **19** at room temperature with alkyl amine (**20**) and subsequent stereoselective alkynylation of the in situ generated iminium ions with terminal alkynes (**21**) in the presence of silvertriflate, resulted in the isolation of a functionalized iminosugar β-C-glycoside **22** as the only product in 88% yield (Scheme 4). The structure and stereochemistry of the iminosugar β-C-glycoside **22** was unambiguously confirmed by ^{1}H and ^{13}C-NMR. Encouraged by the efficacy of this transformation, the generality of this reaction was tested using a wide variety of amines and terminal alkynes.

Entry	Catalyst	yield(%)	Time (h)
1	$Sc(OTf)_3$	10	6.0
2	$In(OTf)_3$	<15	8.0
3	$Zn(OTf)_2$	0	6.0
4	$CuBr_2$, $AgNO_3$	35	5.5
5	$AuCl_3$, AgOTf	78	4.5
6	AgOTf	80	2.0
7	CuCl	70	4.0
8	PPh_3AuCl, $AgSbF_6$	75	4.0

Table 1. Screening of catalysts in the formation of **22**

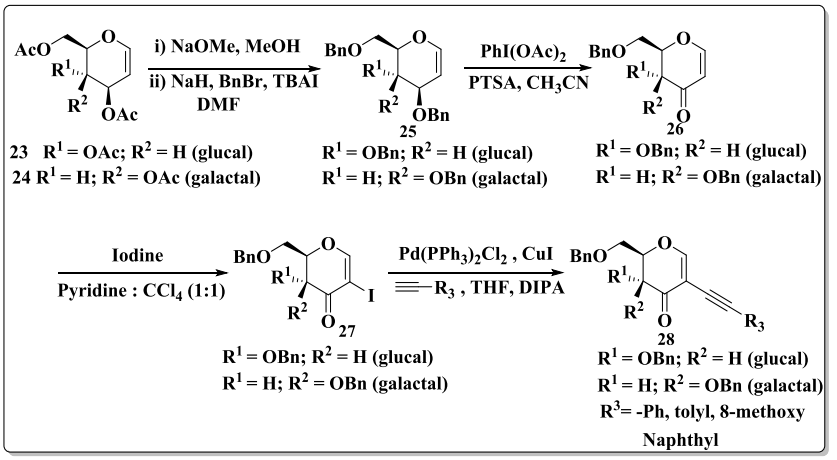
To test the feasibility of this idea, the tosylate 65a, 65b was prepared and treated with triflate salts (**Table 1**). To our delight, when **19** was subjected to reaction conditions employing 2 mol % of AgOTf at 0 °C in the presence of molecular sieves, the nojirimycin was obtained in 80% yield (Table 1, entry 6). Using $AuCl_3$ and CuCl in place of, the product was also easily produced; however, a slightly longer reaction time was required. No reaction was observed with catalyst 3, and control experiments (entries 1, 3) indicated that AgOTf was the catalytically active species. In order to improve the yield, we next began a systematic screening of various catalysts such as $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, and $CuBr\text{-}AgNO_3$ (entries 1-4, Table 1), which are known to promote similar type of transformations.

The synthetic utility of this methodology was further explored in the domino synthesis of skeletally challenging to deoxynojirimycinn analogues. Using our new methodology, a domino reaction based strategy has been developed for the stereoselective synthesis of novel polyhydroxy deoxynojirimycin(DNJ) derivatives.

<u>Chapter III</u>: This chapter describes the development of novel synthetic methodologies from Sugar derived enynones undergo a sequential glycosylation/*endo-dig* cyclization with alcohols to afford a novel class of sugar annulated furan scaffolds, which is further divided into two sections.

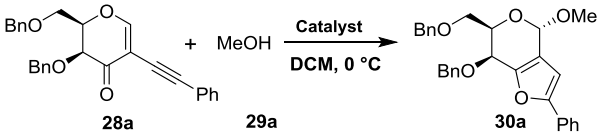
The furan skeleton is one of the most important five-membered-ring heterocycles, and is frequently found in many natural products arising from various sources like plants and marine organisms. A large number of natural products such as pallescensin A, tubipofurane, echinofuran, (+)-furodysin, pinguisone, norpinguisone, and furodysinin possess furan ring as a core structure. It is a key component of various flavors, fragrances, pesticides, and insecticides. Thus, the development of efficient synthetic methods for substituted furan derivatives is of prime importance. As a result, several approaches have been developed for the synthesis of furan scaffolds.

Following our interest on transition metal catalyzed cascade cyclizations, we report a novel strategy for the synthesis of sugar annulated furan derivatives from the corresponding sugar enynones and alcohols through a sequential glycosidation/*endo-dig* cyclization.(**scheme 6**)



Scheme 6: Synthesis of Sugar enynone **28**

A detailed strategy towards pyrano[3,2-*c*]furan (**28**) from suitably substituted 2-iodoglycals as starting material is depicted in **Scheme 6**. 2-Iodoglycals (**27**) can easily be synthesized from the corresponding appropriately functionalized monosaccharides or commercially available glycals in a few steps by following a well-documented literature procedure. To obtain the carbohydrate congeners, we used hexoses such as D-glucose (**23**), D-galactose (**24**). 2-Alkynylated sugars (**28a-c**) were synthesized by the [$Pd(PPh_3)_2Cl_2$]/CuI-catalyzed standard Sonogashira coupling reaction (Scheme 6). We used a variety of different commercially available terminal aromatic alkynes as coupling partners.

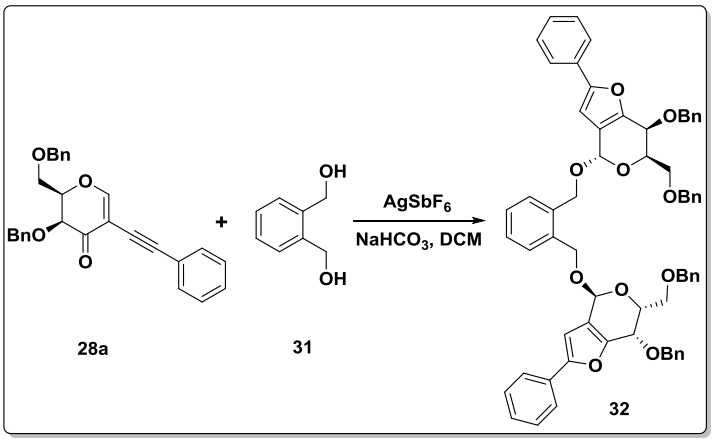


Entry	Catalyst	Mol%	Time (h)	Yield (%)
a	$AuCl_3$	5	0.5	68
b	$AuCl_3/AgSbF_6$	5/10	3.0	72
c	$AgSbF_6$	10	1.5	65
d	AuCl	5	0.5	65
e	Au(TPP)Cl	5	0.5	60
f	$AgBF_4$	10	2.0	60
g	AgOTf	10	3.0	50
h	$Cu(OTf)_2$	10	3.5	45
i	$AuCl_3/NaHCO_3$	5/1 equiv	0.5	79
j	$AgSbF_6/NaHCO_3$	10/1 equiv	0.5	82
k	$AgOTf/NaHCO_3$	10/1 equiv	3.0	65
l	$AgBF_4/NaHCO_3$	10/1 equiv	1.5	75
m	$Cu(OTf)_2/NaHCO_3$	10/1 equiv	3.5	55

Table 2. Screening of catalysts in the formation of **30a**

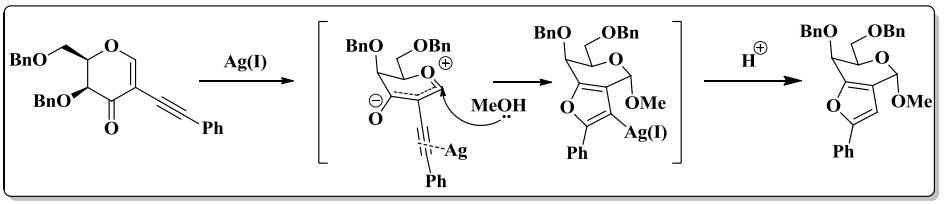
$AuCl_3/NaHCO_3$ and $AgSbF_6/NaHCO_3$ systems were found be superior for this conversion (entries i-j, Table 1). Both $AuCl_3/NaHCO_3$ and $AgSbF_6/NaHCO_3$ reagent systems gave the desired glycoside **30a** in almost similar yields. Since $AuCl_3$ is expensive, further reactions were performed using $AgSbF_6/NaHCO_3$ system. In this catalytic system, $NaHCO_3$ can quench the acid, which is formed during the reaction.

The scope of the reaction is further exemplified with *bis*-alcohol. Interestingly, C2 symmetric dimer **32** was formed in 60% yield.(**Scheme 7**)



Scheme 7. Synthesis of C2 symmetric dimer **32**

Mechanistically, the reaction was expected to proceed through the activation of alkyne by Ag(I) with a concomitant glycosydation by alcohol. A subsequent cycloisomerization of ynone followed by protodemetation would give the desired product. We assume that $AgSbF_6$ acts as a bifunctional catalyst, it activates the alkyne as well as sugar moiety to facilitate both glycosidation and cycloisomerization.(**Scheme 8**)



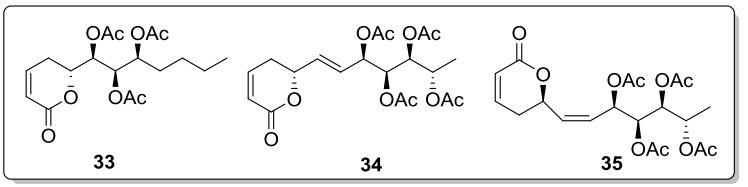
Scheme 8. A possible reaction pathway

In all cases, α-anomer is formed predominantly due to anomeric effect of the ring oxygen and the conformation of the pyranose ring, which favor α-attack of the incoming alcohol to produce the pseudoaxial glycoside. The α-predominance of *O*-glycoside is due to thermodynamic control.

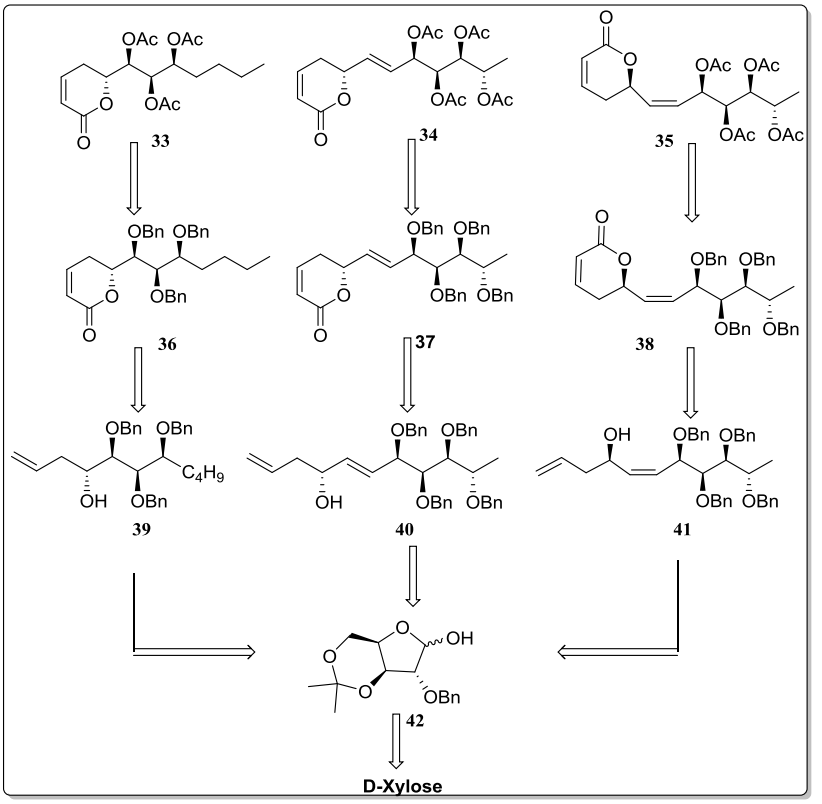
Chapter V: This chapter describes the total synthesis of Boronolide, Anamarine, 8-epispicegerolide, which is further divided into two sections.

Polyhydroxylated *δ*-lactones are common structural motifs found ubiquitously in natural products displaying a variety of biological profiles. In that *α,β*-unsaturated lactones moiety are frequently found in several natural products which display a broad spectrum of biological activities such as cytotoxicity against human tumour cells,

antibacterial and/or antifungal activity. Examples of such molecules include (+)-Boronolide (**33**), (+)-Anamrine (**34**) and 8-epi-spicigerolide (**35**).



As a part of our current interest in naturally occurring, pharmacologically active *δ*-lactones, we became interested in the synthesis of bioactive natural products from a chiral source. The construction of four contiguous oxygenated stereocenters of lactones **33**, **34** and **35** was achieved from D-xylose as the configuration of hydroxyl groups of side chain coincides with D-xylose.

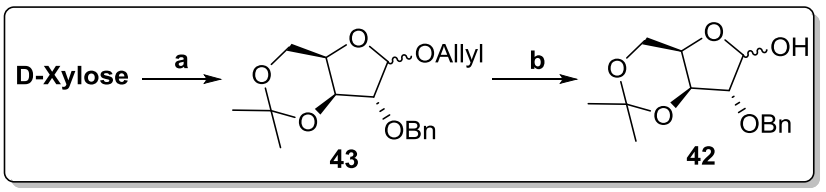


Scheme 9. Retrosynthetic analysis of (+)-Boronolide (**33**), (+)-Anamarine (**34**) and 8-*epi*-spicigerolide (**35**)

As shown in retrosynthetic analysis, the total syntheses of **33, 34** and **35** could be accomplished from the corresponding lactones **36, 37** and **38** which in turn could be prepared by ring-closing metathesis of the acryloyl esters derived from compounds **39,**

40 and **41** respectively. Compounds **39**, **40** and **41** could be prepared by diastereoselective allylation of the aldehydes which are derived from a common intermediate **42** which in turn could be prepared from D-xylose (**Scheme 9**).

According to our approach, the synthesis of **33**, **34** and **35** began from D-xylose which was converted into D-xylofuranoside **42** in three steps. Thus treatment of D-xylose with allyl alcohol in the presence of pyridinium-*p*-toluenesulfonate gave the *O*-allyl-D-xylofuranoside. Protection of C-3 and C-5 hydroxyl groups as isopropylidene acetal followed by C-2 hydroxy group as benzyl ether afforded the fully protected *o*-allylglycoside **43**. Removal of the allyl group from **43** gave the hemi-acetal **42** in 40% yield using Gigg and Warren conditions.(**Scheme 10**)

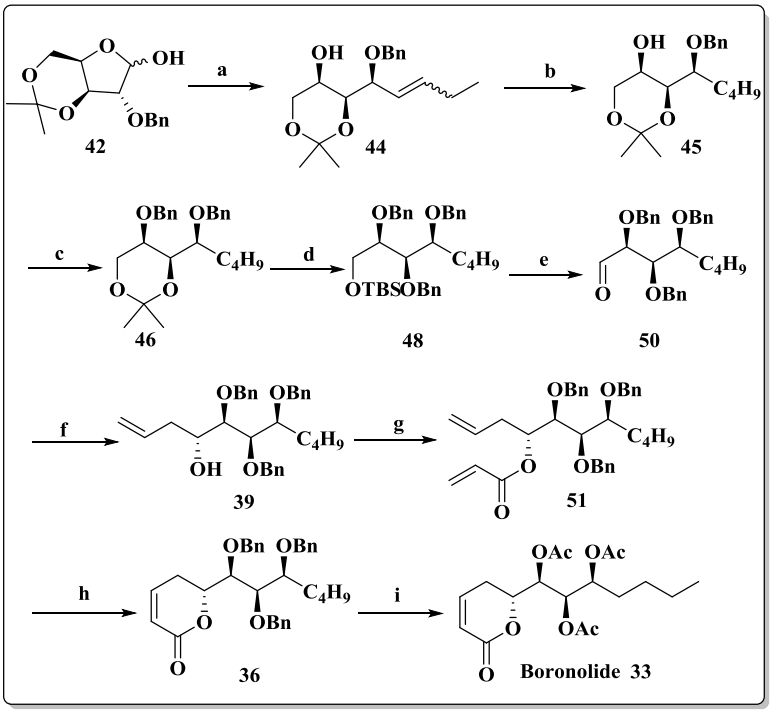


Scheme 10: Synthesis of common intermediate **42**

During the synthesis of (+)-boronolide (**33**), the hemi-acetal **42** was treated with propyltriphenylphosphonium bromide (prepared from *n*-propyl bromide and triphenylphosphine) in the presence of NaHMDS in dry THF at -20 ^{o}C to afford the olefin **44** as a 9:1 mixture of *Z*- and *E*-isomers. Reduction of the olefinic mixture **44** in the presence of 10% Pd/C gave the saturated compound **45.** Protection of the hydroxyl group of **45** with benzyl bromide in the presence of NaH in DMF afforded the benzyl ether **46** in 85% yield. Removal of the isopropylidene group with *p*-TsOH in MeOH at 0 ^{o}C gave the diol **47** in which the primary hydroxyl group was protected as its TBDMS ether and the secondary alcohol was protected as its benzyl ether to give the **48** in 85% yield. Deprotection of the silyl ether **48** with TBAF in THF at 0 ^{o}C gave the primary alcohol **49** in 78% yield. Dess-Martin periodinane oxidation of the alcohol **49** gave the aldehyde **50** in quantitative yield without any epimerization at α-stereogenic center.

Asymmetric allylation of the aldehyde **50** under the Brown's protocol for asymmetric allylation. The Brown's allylating reagent (allylBIpc$_2$), was prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride), which

was then treated with **50** in anhydrous ether at -80 °C to furnish the desired homoallylic alcohol **39** in 82% yield with high diastereoselectivity (9:1). Esterification of **39** with acryloyl chloride afforded the acryloyl ester **51**, which was easily separated from its diastereomer by simple silica gel column chromatography. Ring-closing metathesis (RCM) of the acrylate **51** with Grubbs first generation catalyst in DCM at room temperature afforded the *α,β*-unsaturated lactone **36** in 85% yield. Removal of the benzyl groups using 1M solution of $TiCl_4$ in DCM at 0 °C for 4 h gave the trihydroxy lactone which was then per acetylated with acetic anhydride and pyridine to furnish the target (+)-Boronolide (**33**) in 53% yield.(**Scheme 11**)

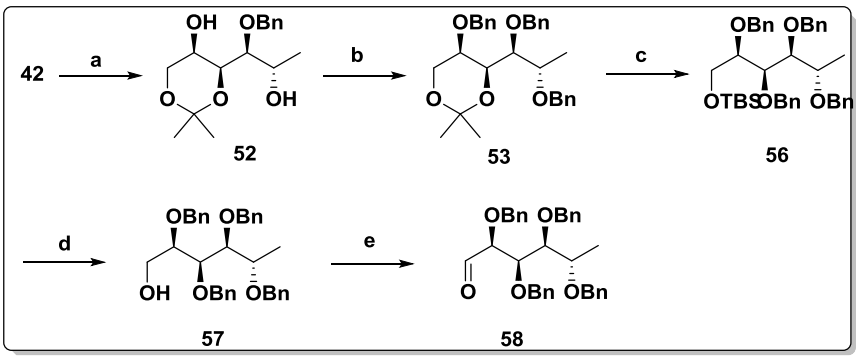


Scheme 11: Synthesis of Boronolide (**33)**

Reagents and conditions: **a**) *n*-$PrPPh_3Br$, NaHMDS, THF, -20 °C to rt, 5h, 75%; **b**) H_2, Pd/C, $NaHCO_3$, MeOH, rt, 2h, 86%; **c**) NaH, BnBr, DMF, 0 °C, 6h, 85%; **d**) (1)*p*-TSA, MeOH, 0 °C, 3h, 80%; (2)TBSCl, imidazole, DCM, 0 °C to rt, 1h, 90%; (3) NaH, BnBr, DMF, 0 °C to rt, 3h, 85%; **e**) (1)TBAF, THF, 0 °C to rt, 2h, 78%; (2) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 2h, 80%; **f**) $AllylBIpc_2$ [prepared from allylmagnesium bromide and (+)-DIPCl], Et_2O, −80 °C (82%, 9:1 diastereomeric mixture); **g**) Acryloyl chloride, Et_3N, DMAP, DCM, 0 °C to rt, 3h, 85%; **h**) Grubb's

first generation catalyst, DCM, rt, 6h, 85%; **i**) (1) $TiCl_4$ (1M in DCM), DCM, 0 °C to rt, 4h; (2) Ac_2O, Pyridine, DMAP, 0 °C to rt (overall 2 steps 53%).

After successful synthesis of (+)-boronolide (**33**), we attempted the synthesis of **34** and **35** from intermediate **42**. Thus treatment of hemi-acetal **42** with MeLi (1.6 M in ether) in anhydrous ether at -20 ^oC afforded the diol as a separable diastereomeric mixture (9:1) favoring **52** as the major product in 82% yield via a chelation controlled mode. Protection of hydroxy groups of **52** using benzyl bromide in the presence of NaH furnished the benzyl ether **53** in 90% yield. Removal of the isopropyledine group of **53** using *p*-TSA in methanol gave the diol **54** in 80% yield. Protection of the primary alcohol of **54** using TBSCl gave the TBDMS ether **55** in 90% yield. The secondary OH of **55** was then protected as its benzyl ether using benzyl bromide in the presence of NaH in DMF gave the **56** in 85% yield. Desilylation of **56** using TBAF in THF gave the alcohol **57** in 78% yield. which was used as a key intermediate for the synthesis of **34** and **35** (**Scheme 11**).

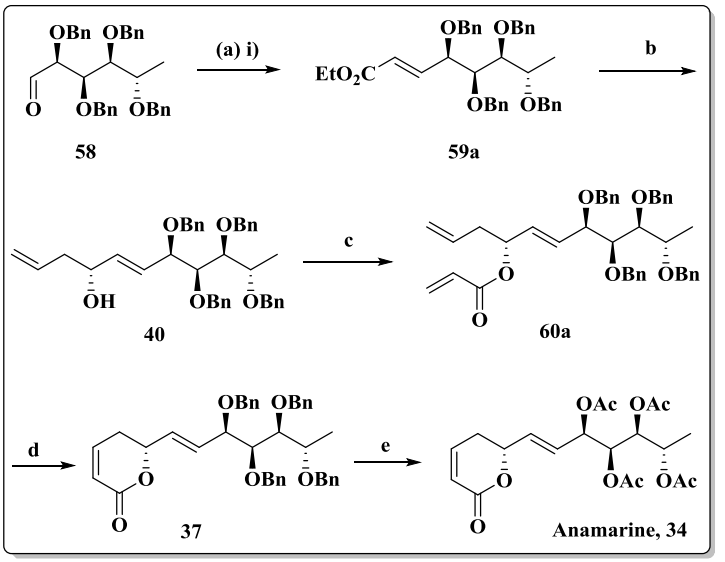


Scheme 12. Synthesis of common intermediate **58**

Reagents and conditions: **a**) MeLi (1.6 M), Et_2O, -20 °C, 4h, 82%; **b**) NaH, BnBr, DMF, 0 °C, 6h, 90%; **c**) (i) *p*-TSA, MeOH, 0 °C, 3h, 80%; (ii) TBSCl, imidazole, DCM, 0 °C to rt, 1h, 90%; (iii) NaH, BnBr, DMF, 0 °C to rt, 3h, 85%; **d**) TBAF, THF, 0 °C to rt , 2h, 78%; **e**) DMSO, $(COCl)_2$, DCM, - 78 °C, Et_3N, 3h, 80%.

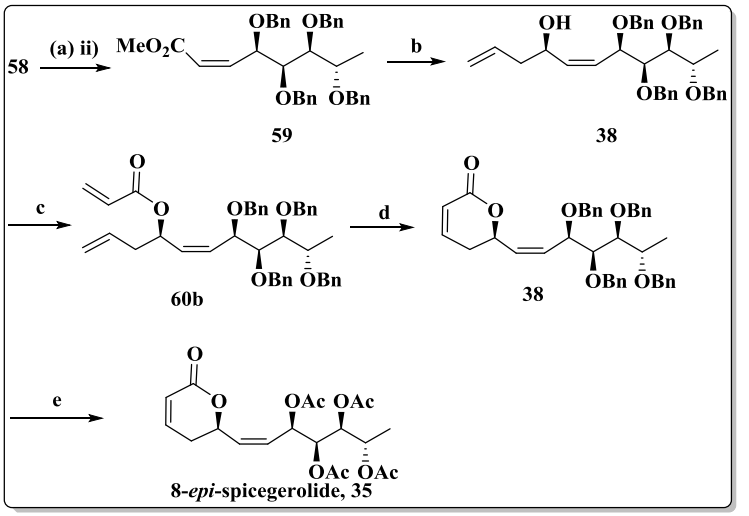
Swern oxidation of the alcohol **57** followed by Wittig olefination with triethylphosphonoacetate gave the (*E*)-α,β-unsaturated ester **59a** as a sole product in 93% yield. Reduction of the ester **59a** using DIBAL-H in dry DCM at -78 ^oC afforded the corresponding aldehyde which was subsequently subjected to enantioselective

allylation using allylBIpc2, prepared *insitu* from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride), in anhydrous ether at -80 ^{o}C to furnish the desired homoallylic alcohol **40** (92% de) in 82% overall yield over two steps. Esterification of **40** with acryloyl chloride afforded the acryloyl ester **60a** which was then subjected to RCM reaction using Grubbs first generation catalyst to afford the perbenzylated lactone **37** in 85% yield. Eventually, the debenzylation of **37** with $TiCl_4$ followed by peracetylation with Ac_2O furnished the anamarine (**34**) in 62% overall yield over two steps (**Scheme 12**).



Scheme 13. Synthesis of Anamarine (**34**)

Similarly, Swern oxidation of **58** followed by Still-Gennari olefination with bis(2,2,2-trifluoromethyl)(methoxycarbonylmethyl)phosphonate gave the *cis*-olefinic ester **59b** in 84% yield. Reduction of the ester **59b** with DIBAL-H (1M in toluene) in dry DCM at -78 ^{o}C afforded the aldehyde which was then subjected to allylation with allylBIpc$_2$, prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride), in anhydrous ether at -80 ^{o}C to furnish the homoallylic alcohol **41** (92% de) in 82% overall yield over two steps. Esterification of the alcohol **41** with acryloyl chloride gave the acryloyl ester **60b** which was subsequently subjected to RCM reaction using Grubb's first generation catalyst to afford the perbenzylated lactone **38** in 85% yield. Finally the debenzylation of **38** with $TiCl_4$ followed by peracetylation with Ac_2O afforded the 8-epi-spicegerolide **35** in 62% overall yield over two steps.



Scheme 14: Synthesis of 8-epispicegerolide (**35**)

Reagents and conditions for 34 & 35 : a) (i) PPh_3CHCO_2Et, benzene, rt, 2h, 93%; (ii) NaH/THF, 0 °C, $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, 30 min, then, - 78 °C, THF, 30–45 min, 84%; b) (i) DIBAL-H, CH_2Cl_2, -78 °C to rt, 0.5 h, 80%; ii) $AllylBIpc_2$ [prepared from allylmagnesium bromide and (+)-DIP-Cl], Et_2O, −80 °C (82%, 92:8 diastereomeric mixture); c) Acryloyl chloride, Et_3N, DMAP, DCM, 0 °C to rt, 3h, 85%; d) Grubbs first generation catalyst, DCM, rt, 6h, 85% ; e) i) $TiCl_4$ (1M in dichloromethane), DCM, 0 °C to rt, 6h; ii) Ac_2O, Et_3N, DMAP, DCM, 0 °C to rt (overall 2 steps 62%).