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**NANYANG
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UNIVERSITY**

**SYNTHETIC METHODOLOGY OF CARBOHYDRATES:
ACCESS TO CARBOHYDRATE-LINKED HETEROCYCLES
AND DIMYCOLYL DIARABINOGLYCEROL**

CAI SHUTING

SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

2014

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**Synthetic Methodology Development of Carbohydrates: Quick
Access to Carbohydrate-Integrated Heterocycles and
Arabinosylated Glycerol Dimycolate**

CAI SHUTING

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
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ABSTRACT

Carbohydrates have always attracted large interests in their synthesis and applications. Due to their diversified roles, they have been employed in many synthetic methodologies as well as building blocks of numerous natural products. This thesis would explore the different roles of carbohydrates and successful examples of their applications would be demonstrated.

Part 1:

In the first part of the thesis, pyrrolidine derivatives were constructed in high diastereoselectivities and good yields through a [3 + 2] cycloaddition of a *tert*-butyldimethylsilyl protected carbohydrate allene with a range of imines. Following which, the carbohydrate auxiliary was removed and pyrrolidines were afforded with excellent enantioselectivities of up to 99% *ee*. The potential of this strategy was further demonstrated by the selective reduction of the pyrrolidines.

Part 2:

In the second part, carbohydrate-integrated isoxazolines were synthesized from 2-nitroglycals and sulfur ylides in the presence of 1-phenylthiourea catalyst. The reactions underwent [4 + 1] annulations and rearrangement to afford the

corresponding carbohydrate-integrated isoxazolines in high yields with excellent diastereoselectivities of up to 95% *de*.

Part 3:

In the final chapter of this thesis, protected dimycolyl-diarabino-glycerol (purified from *Mycobacterium marinum*) was successfully synthesized by using Mitsunobu reaction and selective arabinofuranosylation. This glycolipid was found to stimulate a pro-inflammatory response in macrophages and investigation of this cell wall glycoconjugate in driving host-pathogen interactions and contributing to the immunopathogenesis of mycobacterial infections is currently underway.

INDEX OF ABBREVIATIONS

δ	chemical shift	ddd	doublets of doublets of
$^{\circ}\text{C}$	degree celsius		doublet
Ac	acetyl	<i>de</i>	diastereomeric excess
AcCl	acetyl chloride	DEAD	diethyl azodicarboxylate
AcOH	acetic acid	DDQ	2,3-dichloro-5,6-
Ac ₂ O	acetic anhydride		dicyano-1,4-
aq.	aqueous		benzoquinone
Bn	benzyl	DHP	2,3-dihydropyran
Boc	<i>tert</i> -butoxycarbonyl	DIAD	diisopropyl
Brs	broad singlet		azodicarboxylate
BuLi	butyllithium	DIBAL-H	diisobutylaluminium
Bz	benzoyl		hydride
BSA	bis(trimethylsilyl)- acetamide	DMAP	4-(<i>N,N</i> -dimethylamino)- pyridine
calcd.	calculated	DME	dimethoxyethane
cat.	catalytic	DMF	dimethylformamide
Cbz	benzyloxycarbonyl	DMSO	dimethyl sulfoxide
Cl ₃ CCOCl	trichloroacetyl chloride	dt	doublets of triplet
CDCl ₃	deuterated chloroform	<i>ee</i>	enantiomeric excess
CH ₂ Cl ₂	dichloromethane	EI	electron ionization
CHCl ₃	chloroform	EDC	1-ethyl-3-(3-
cm ⁻¹	inverse centimeter		dimethylaminopropyl)ca
Cy	cyclohexanyl		rbodiimide
d	doublet	equiv.	equivalent
dba	dibenzylideneacetone	ESI	electron spray ionization
DBU	1,8-diazabicyclo[5.4.0]- undec-7-ene	Et	ethyl
DCM	dichloromethane	Et ₃ N	triethylamine
DCE	dichloroethane	EtOAc	ethyl acetate
dd	doublets of doublet	EtOH	ethanol

FTIR	fourier transform infrared spectroscopy	OTf	trifluoromethane- sulfonate
g	gram	<i>p</i>	para
h	hour	Pd/C	palladium on carbon
HRMS	high resolution mass spectroscopy	Ph	phenyl
HMDS	bis(trimethylsilyl)amine	Piv	pivaloyl; 2,2- dimethylpropanoyl
Hz	hertz	PMB	<i>p</i> -methoxybenzyl
IR	infrared	PMP	<i>p</i> -methoxyphenyl
<i>i</i> Pr	isopropyl	ppm	parts per million
<i>J</i>	coupling constants	PPTS	pyridinium <i>p</i> - toluenesulfonate
M	concentration (mol/L)	Pyr	pyridine
M ⁺	parent ion peak (mass spectrum)	q	quartet
m	multiplet	rt	room temperature
Me	methyl	s	singlet
MeCN	acetonitrile	t	triplet
MeOH	methanol	TBAF	tetrabutylammonium fluoride
mg	milligram	TBDPS	<i>tert</i> -butyldiphenylsilyl
MHz	megahertz	TBAD	di-(<i>t</i> -butyl)azodi- carboxylate
min	minute	TBS	<i>tert</i> -butyl dimethylsilyl
mL	milliliter	<i>t</i> Bu	<i>tert</i> -butyl
μm	micrometer	TFA	trifluoroacetic acid
mm	millimeter	TfOH	triflic acid
mmol	millimoles	Tf ₂ O	triflic anhydride
mol	moles	THF	tetrahydrofuran
μmol	micromoles	TLC	thin layer chromatography
MS	mass spectrum	TMS	trimethylsilyl
M.S.	molecular sieves	Tr	triphenylmethyl
<i>n</i> Bu	<i>n</i> -butyl	Ts	<i>p</i> -toluenesulfonyl
NMR	nuclear magnetic resonance		
NMP	<i>N</i> -methyl-2-pyrrolidone		
V	volume		

CHAPTER 1

[3 + 2] Cycloaddition on Carbohydrate Templates: Stereoselective Synthesis of Pyrrolidines

Chapter 1

[3 + 2] Cycloaddition on Carbohydrate Templates: Stereoselective Synthesis of Pyrrolidines

1. Introduction

Medicinal chemistry, as well as synthetic chemistry such as natural product synthesis, often requires the preparation of enantiomerically pure compounds.^[1] Consequently, this led to the evolution of many chiral auxiliaries, based mainly on α -amino acids, terpenoids and alkaloids.^[2] In comparison, chiral auxiliaries based on carbohydrates have been largely overlooked. However, with the recent reviews and reports of successful carbohydrate auxiliaries, an intriguing area of research has been spurred and interests in carbohydrate auxiliaries have augmented.^[3]

Carbohydrates, being low cost and readily available, are essential chiral building blocks in synthetic organic chemistry. In addition, there are many previous reports of oligosaccharides' and glycoproteins' involvement with the alteration of certain biological functions. This suggests that the chiral environment established by the carbohydrates provides utmost potential for molecular recognition.^[3]

The initial deterrence of using carbohydrates as an auxiliary was due to the presence of many functional groups that are highly polar. This problem was solved by the modification of the functional groups to introduce coordinative sites into the carbohydrate.^[4] The variety of template geometries created by the different configurations of the carbohydrates provides wide environmental choices whereby a reacting group can be coordinated (Figure 1).^[3] Moreover, affixing bulky groups onto these functional groups can selectively block specific faces of the substrates. Aromatic

groups coordinated on the carbohydrate auxiliary can also affect the reaction's stereochemistry through *pi*-stacking.^[5]

Figure 1. Examples of commonly used monosaccharides

Another problem that could arise from the use of carbohydrate as an auxiliary is the availability of the L-enantiomers. Most naturally occurring carbohydrates exist in the D-enantiomer form and L-enantiomers can be relatively expensive and not easily available. To rectify this problem, *pseudo*-enantiomers were prepared. These *pseudo*-enantiomers are mirror images only at parts that are important for stereo-differentiation. Notably, D-mannose is a *pseudo*-enantiomer of L-rhamnose, while D-arabinose is a *pseudo*-enantiomer of D-galactose (Figure 2).^[6]

Figure 2. Examples of monosaccharides which are *pseudo*-enantiomers

Exploiting the different concepts, many crucial carbohydrate auxiliaries have been generated. Hence, the development of carbohydrate auxiliaries over the recent years has been substantial.^[7] Among the many successful applications of carbohydrate auxiliaries, cycloaddition has been one of the key reactions. Cycloaddition occurs when unsaturated molecules (two or more) combine to form a cyclic adduct, resulting in the reduction of bond multiplicity. The possibility of creating two new bonds and stereogenic centers renders cycloaddition a powerful strategy in organic synthesis.^[8] Producing pure cycloadducts with stereochemistry is extensively aided with the usage of carbohydrate auxiliaries.^[9]

In this chapter, an overview of applications of carbohydrate auxiliaries in cycloaddition reactions would be demonstrated. Herein, prominent examples, both past and recent, will be given to portray development of the applications.

2. Asymmetric Cycloaddition Reactions with Carbohydrate Auxiliaries

2.1 [2 + 1] Cycloadditions

The smallest ring construction through cycloaddition is derived from the [2 + 1] cycloaddition, or otherwise known as cyclopropanation reactions. Over the years,

there have been numerous reports of carbohydrate auxiliaries assisted cycloadditions and [2 + 1] cycloaddition is a prominent reaction in these reports.^[10]

One of the earliest and efficient syntheses of cyclopropanes is examined by Charette and group.^[11] Charette revealed that allylic glycosides attached to 3,4,6-*tri-O*-benzyl- β -D-glucopyranose go through highly diastereoselective Simmons-Smith cyclopropanations, generally with selectivities of more than 50:1. They conducted the reaction by using allyl β -D-glucopyranosides **1** in the presence of diethyl zinc/diodomethane. The chiral cyclopropyl-methylglucosides **2** were afforded in excellent yields and exceptional diastereoselectivities. Moreover, the reaction was shown to tolerate a wide range of substrates, as illustrated in Scheme 1. In this cyclopropanation, the unprotected 2-hydroxyl group in **1** plays an important role for the diastereofacial differentiation. This 2-hydroxyl group reacts with diethyl zinc to form a coordinative anchor for the iodomethyl zinc unit with the Simmons-Smith intermediate.

[a] Values in brackets are ratios obtained from ¹³C NMR

Scheme 1. Simmons–Smith cyclopropanations using carbohydrate auxiliary

Another example involving asymmetric Simmons–Smith cyclopropanation was demonstrated by Kang *et al.* in 1995 (Scheme 2).^[12] Firstly, β -D-fructopyranoside **3** produced *endo* acetal derivative **4** when treated with α,β -unsaturated aldehydes. Then, cyclopropanation of **4** to **5** occurred mainly on the "rear" face of the alkene, as the R¹ group on O-3 was adequately bulky to restrict access through the "front" face. Acid hydrolysis of **5** and subsequent reduction afforded the hydroxymethyl cyclopropanes **6**. The *endo* acetals were obtained in good to excellent selectivities, generating (2*R*,3*R*)-**6** with 65-85% *e.e.*.

Scheme 2. Simmons–Smith cyclopropanations using carbohydrate auxiliary by Kang

2.2 [2 + 2] Cycloadditions

[2 + 2] cycloaddition reactions using carbohydrate auxiliaries are relatively less reported and developed than other cycloaddition reactions.^[13] The reason behind this is due to the lower success rates of carbohydrate auxiliaries in controlling the stereoselectivity and facial selectivity of such reactions. One of the prominent examples of [2 + 2] cycloaddition reaction is the work reported by Gan and coworkers.^[14]

Employing vinyl D-glucofuranosides and D-galactopyranosides as the starting material, chiral cyclobutanes were synthesized by Kunz and Ganz. Trichloroacetyl chloride (Cl_3CCOCl) with zinc/copper (Zn/Cu) couple produces the ketene which reacts with glycosyl enol ether **7**, under room temperature, to form the chiral cyclobutanol **8** in a diastereomeric ratio of 4:1 (Scheme 3).

Scheme 3. [2 + 2] cycloaddition reported by Gan to form chiral cyclobutanol **8**

Cyclobutanol derivatives, with up to four chiral centers, can then be produced in pure diastereomeric form by reduction. Importantly, the carbohydrate auxiliary can be removed without any modification to the chiral centers on the cyclobutanol derivatives. In this cycloaddition reaction, the interaction between the metal salts and the carbohydrate auxiliary did not have significant effect on the stereoselectivity. Instead, Lewis acids were needed to activate the ketenes. This activation will allow the ketenes to add to the less nucleophilic glycosyl enol ethers.

Kaluza *et al.* further examined the effects of the carbohydrate moiety on the stereochemistry of [2 + 2] cycloadditions.^[15] 3-*O*-Vinyl furanose ether **9**, underwent [2 + 2] cycloaddition reaction with chlorosulfonyl isocyanate to produce furanose enol ether **10** (Scheme 4).

Scheme 4. [2 + 2] cycloaddition of furanose ether **9** to produce furanose enol ether **10**

The C-4 of the furanose ring was attached to a relatively large substituent, causing the blockage of the entry of the isocyanate from the *Re* face (Figure 2). In this way, the stereoselectivity of the cycloaddition reactions can be controlled.^[16]

Figure 2. Addition of isocyanate from the *Re* face, aided by the furanose ring

2.3 [3 + 2] Cycloadditions

Totani and co-workers employed [3 + 2] cycloaddition (1,3-dipolar cycloaddition) of nitrile oxide and acyloxy ester on a carbohydrate template.^[17] This is particularly useful and beneficial for the synthesis of heterocycles such as α -hydroxy- γ -carbonyl esters.^[18] Benzonitrile oxide and pivalonitrile oxide were synthesized by dehydrogenation of their respective aldehyde oximes with chloramine-T.^[19] At room temperature, the cycloaddition reactions with 4-*O*-acyloxy ester **11** proceeded smoothly for both nitrile oxides. **12a** from benzonitrile oxide and **12b** from pivalonitrile oxide were produced with excellent yields and good diastereoselectivities (Scheme 5). These demonstrated the effectiveness of **11** as an asymmetric tool aided by carbohydrates.

Scheme 5. [3 + 2] cycloaddition of nitrile oxide and acryloyl ester **11**

A transition-state model could be used to explain the excellent diastereoselectivity obtained. 4-*O*-Acryloyl ester **11** adopts an *s-cis,syn*-conformation under thermal conditions. The nitrile oxides then attack from the rear, where it is less hindered. The front side of the acryloyl ester was efficiently shielded from the nitrile oxides by the *tert*-butyldimethylsilyl (TBS) protecting group.

In another example, Goti and coworkers investigated on cycloaddition reactions of nitrones.^[20] Oxidation of *N*-benzyl-*N*-glycosylhydroxylamine **12** with manganese dioxide (MnO₂) afforded the *N*-glycosylnitrones **13** (Scheme 6). The glycosyl group in **12** acts as the chiral auxiliary to moderate selectivity in the subsequent step. Reaction with dimethyl maleate **19** proceeded smoothly at 80 °C for 4 days. The [3 + 2] cycloaddition (1,3-dipolar cycloaddition) between **13** and **14** gave the corresponding enantio-enriched isoxazolidine **15** in 77% yield. Isoxazolidine **15** was obtained as the major isomer, with diastereoselectivity of more than 94%.

Scheme 6. [3 + 2] cycloaddition of glycosylnitrones **13** to afford isoxazolidine **15**

2.4 [4 + 2] Cycloadditions

The most prominent and well known cycloaddition reaction is the Diels–Alder (DA) reaction between a substituted alkene (dienophile) and a conjugated diene. In terms of carbohydrate auxiliaries, this form of cycloaddition is basically split into two categories. The carbohydrate template can be attached to the dienes as well as the dienophiles. As such, the discussion of [4 + 2] cycloadditions herein would focus on these two areas and various reports over the past years of carbohydrate-linked dienes and carbohydrate-linked dienophiles would be provided.

2.4.1 Carbohydrate-Linked Dienes

In 1993, Aspinall and coworkers reported an efficient route to the synthesis of dehydropiperazic acid **17**, employing butadienyl- β -D-glucoside **16** as the starting material.^[21] A [4 + 2] cycloaddition of **16** with di-(*t*-butyl) azodicarboxylate (TBAD) at 85°C , gave **17**. Upon hydrogenation and subjecting it under trifluoroacetic acid

(TFA), amino acid **18** was obtained, releasing the glucose auxiliary. Enantiomerically pure **18** was obtained in this reaction (Scheme 7).

Scheme 7. Diels–Alder reaction of butadienyl-β-D-glucoside **16** with TBAD to afford dehydropiperazic acid **17**

The production of sole cycloadducts when **16** was reacted with a library of cyclic azo compounds was explained with the *exo*-anomeric model proposed by Stoodley *et al.*^[22] The reason behind the azodienophiles having a higher selectivity was attributed to the relatively short C–N bond length. The short bond length causes steric hindrance in the transition state and hence, led to greater diastereoselectivity. The extensive functionality present in cycloadduct **17** and its derivatives provides abundant opportunities for many comprehensive and complex synthetic manipulations. The high diastereoselectivities obtained will greatly aid these synthetic manipulations.

In 2008, Hung *et al.* synthesized a variety of carbohydrate-linked masked dienes (**19–22**) to investigate the selectivity of these dienes in an intramolecular Diels–Alder reaction.^[23] The usage of different carbohydrates (glucose and mannose), the employment of different protecting groups (benzyl and acetyl) and the choice of both α and β anomer provided a range of dienes for investigation (Figure 3).

Figure 3. Carbohydrate-linked dienes for intramolecular Diels Alder reaction

These carbohydrate-linked masked dienes (**19-22**) were reacted with allyl alcohols. A subsequent one-pot intramolecular Diels–Alder reaction produced the products **19a-22a** and **19b-22b** (Scheme 8). There are two general stages to the reactions - they were initially subjected to low temperatures, and the temperatures were raised progressively. Among the oxidants that were investigated for generating the diene from masked benzene derivatives, iodobenzene diacetate ($\text{PhI}(\text{OAc})_2$)-oxidized intramolecular $[4 + 2]$ cycloaddition produced the best results. For most cases, two isomers were produced, with high selectivity of one over the other. In some exclusive examples, only a single product was formed, demonstrating the high selectivity of these reactions.

Scheme 8. Diels–Alder reactions of carbohydrate-linked dienes (**19-22**) with allyl alcohols

2.4.2 Carbohydrate-Linked Dienophiles

In a most recent example, Alejandra *et al.* synthesized carbohydrate auxiliaries **23-26**.^[24] These acrylate auxiliaries were investigated in asymmetric [4 + 2] cycloadditions. Four diastereomers, two *exo* and two *endo* adducts, were produced when the [4 + 2] cycloaddition reactions were performed under thermal conditions (Scheme 9). From the observations, the π -facial selectivity results in the preference for *endo-S*-adduct as the major diastereomer. This is due to the steric hindrance caused by the substituents on the dienes.

Scheme 9. Acrylate auxiliaries in asymmetric [4 + 2] cycloadditions

Improvement to the selectivity was obtained when the reactions were performed under Lewis acids. Diethylaluminium chloride (Et₂AlCl) and ethylaluminium dichloride (EtAlCl₂) were found to be very efficient, and the reactions produced high yields, excellent *endo/exo* adduct ratios and π -facial selectivities. The

coordination of the metal in the Lewis acid to the enolate moiety is the crucial factor as it determines the conformation of the moiety towards the dienes' attack. The reaction proceeds through a chelated complex and the diene then attacks from the less hindered face of the transition state, producing *R* isomers as the major products (Figure 4).^[25]

Figure 4. Preference for *R* isomers as the major products

The [4 + 2] cycloaddition between 5-glucopyranosyloxy-1,4-naphthoquinone **27** and Danishefsky's diene **28** produced compound **29**. This reaction achieved full regioselectivity and stereoselectivity and compound **29** was obtained as a single isomer in a very high yield of 92%. An explanation was provided by Stoodley and coworkers with regards to the selectivity.^[26] The *syn*-face of the double bond was efficiently shielded by the boat-like geometry adopted by the quinone ring. Hence, the *anti*-face of the double bond would undergo an *endo*-attack from the diene.

Scheme 10. [4 + 2] cycloaddition of Danishefsky's diene **28** to produce compound **29**

Coordination of the oxygen atom on the carbohydrate ring to metal ions can help to promote the stereoselectivity *via* a transition state. This coordination was extensively studied by Kun and coworkers in 1988 (Scheme 11).^[27] As shown in Scheme 11, the oxygen atom coordinates to the titanium atom and functions as the titanium atom's sixth ligand. The formation of an *endo* transition state **31** led to the product, (1'*R*, 2'*R*)-diastereomer **32**.

Scheme 11. Promoting stereoselectivity through coordination of the oxygen atom on the carbohydrate ring to metal ions

2.5 Aim of the Project

Owing to the successful applications of carbohydrates as auxiliaries in cycloaddition reactions, we envisioned the versatility of carbohydrates in inducing good to excellent selectivities. As such, in the chapter herein, we report the stereoselective synthesis of pyrrolidines by using carbohydrates as auxiliaries to induce excellent selectivities. By employing [3 + 2] cycloaddition on carbohydrate templates, we aim to synthesize pyrrolidines with exceptional selectivities through cycloaddition and subsequent cleavage of the auxiliary.

3. [3 + 2] Cycloaddition on Carbohydrate Templates: Stereoselective Synthesis of Pyrrolidines

3.1 Introduction

Pyrrolidines and their derivatives are imperative building blocks of many biologically active natural products (Figure 5)^[28] and essential components in various bioactive molecules.^[29] Pyrrolidines' ability to exhibit a wide variety of biological activities,^[30] to produce antibacterial, antibiotic and cytotoxic effects^[31] and their efficacious use as neuroexcitatory agents,^[32] fungicides^[33] and glycosidase inhibitors^[34] have rendered their utilization in the pharmaceutical and the biochemical sectors.^[35] Consequently, the therapeutic effects of pyrrolidines have garnered substantial interests in their expedient synthesis.^[36] During the past few years, numerous attempts to synthesize stereoselective pyrrolidines and their derivatives have been demonstrated. Some of the key methods include employing *aza* heterocycles,^[37] cyclizing *bis*-allylic amines^[38] and utilizing 1, 3 dipolar cycloaddition of azomethine ylides in the presence of chiral auxiliaries.^[39] Among the abundant strategies, cycloaddition-based reactions are particularly attractive due to their ability to induce stereoselectivity, engender remarkable efficiency and most importantly, achieve atom economy by constructing multiple bonds in a single step.^[40] The initial development of the chiral auxiliaries deployed in the cycloaddition reactions predominantly employed α -amino acids, terpenoids and alkaloids.^[2] Subsequent introduction of carbohydrates as chiral templates in a 1, 3-dipolar cycloaddition reaction of chiral *N*-(alkoxyalkyl)nitrones by Vasella^[41] and in a diels-alder reaction with acrylates by Kunz^[42] prompted a widespread employment of carbohydrate matrices to construct diversified and highly stereoselective molecular skeletons.^[43]

Undeniably, carbohydrates are considered as enantiomerically pure candidates which exert chirality into prochiral faces to synthesize many chiral drugs as well as natural products.^[44] They are readily available at a low cost^[45] and the differing configurations of the carbohydrate moiety aids in installing diverse template geometries, thus enabling the introduction of a wide variety of coordinative sites.^[46] The efficient application of carbohydrate derivatives as stereodifferentiating auxiliaries in chiral synthesis, particularly in cycloaddition reactions, has been ubiquitous.^[47] Notably, an allene ether version of the Nazarov cyclization recently reported by Tius *et al.* employed carbohydrate chiral auxiliaries consisting of lithiated allenes.^[48] Interestingly, lithiated allenes have been widely used as building blocks in the synthesis of pyrrolidinones and pyrrole derivatives.^[49] Utilizing a [3 + 2] cycloaddition reaction, Ressig reported the synthesis of a variety of pyrrolidines and pyrrole derivatives from lithiated allenes.^[50]

Figure 5. Biologically active natural products

Inspired by the research conducted in this area, we herein report a proficient synthesis of pyrrolidinones with the aid of a [3 + 2] cycloaddition between a TBS protected carbohydrate-based lithiated allenes and a diversified imine scope.

3.2 Results and Discussion

The initial plan started off with the synthesis of carbohydrate auxiliaries with different protecting groups such as methyl, benzyl, acetyl and pivaloyl groups.

Scheme 12. Synthesis of various carbohydrate auxiliaries

The reaction was then carried out with methyl- and benzyl-protected galactose allene **35**. However, the reaction using benzyl-protected galactose allene did not work. We postulate that the benzyl substituents (especially the benzyl coordinated to C-2 OH) are relatively bulky and might block the attack of the nucleophile. Hence, reaction was unable to proceed and starting material remained.

Scheme 13. Initial attempt using methyl-protected carbohydrate auxiliary

Gratifyingly, the reaction proceeded with the methyl-protected galactose allene **35a** to provide the two diastereomers **38** in a 1:2 ratio (*R:S*).

In order to improve the diastereoselectivity, the methyl protecting group was replaced with the TBS protecting group. As emphasized in a recent report by Tius and group, the auxiliary consisting of TBS ether-protected carbohydrate produces decent selectivity as well as prevents aggregation when butyllithium is added, consequently presenting a better nucleophile during the reaction with different imines.^[51] In the report, 2-deoxy-D-galactose derived lithioallene proved to be an excellent reagent. Cyclic products were formed with *ee* up to 95% (Scheme 13a).

Scheme 13a. Tius's allene ether Nazarov cyclization using TBS ether-protected 2-deoxy-galactose

This discovery supported our choice of TBS protected carbohydrate auxiliary in this cycloaddition reaction. However, when fully protected TBS galactose was used as the auxiliary, the reaction did not proceed. We postulated that the TBS group at the C-2 position is too bulky and might hinder the reaction. Therefore, attention was directed to the use of TBS ether-protected 2-deoxygalactose. Starting from D-galactose, the TBS-protected carbohydrate auxiliary **45** was achieved through a series of reactions: glycosylation of the propargyl alcohol, deprotecting the acetyl groups, protecting with TBS groups and converting the alkyne into allene. (The α -isomer **41**

was columned and separated from an α/β mixture of 4:1, subsequent reactions leading to the sole auxiliary **45** all provided α -isomer due to anomeric effect.)^[51]

Scheme 14. Changing the protecting group of the carbohydrate auxiliary

Gratifyingly, when TBS-protected carbohydrate auxiliary **45** was subjected to the same set of conditions, the anticipated product was obtained. Hence, to study the effectiveness of the carbohydrate auxiliary on the stereoselectivity, we first established a set of ideal conditions by examining the reaction of TBS-protected carbohydrate allene **45** with an imine bearing a phenyl substituent **36a**. A range of gold and silver catalysts was selected for the preliminary screening. Notably, silver and gold catalysts have been proven to be highly efficient in many synthetic reactions.^[52] Of which, their role in cycloaddition reactions has been significant and has attracted a considerable amount of interests.^[53] To begin with, the reaction between **45** and **36a** was subjected to AgBF_4 and AgClO_4 catalysts in acetone (Table 1, entries 1 and 2). However, the reaction for both catalysts afforded the desired cyclization product **3a** in low yields

(20% and 11% respectively), although the diastereoselectivities were promising. Interestingly, amidst the variety of silver catalysts tested, AgNO₃ significantly

Table 1. Optimization studies.^[a]

45 36a 46a					
Entry	Catalyst	Solvent	Time (h)	Yield ^[b] (%)	De ^[c] (%)
1	AgBF ₄	Acetone	3	20	79
2	AgClO ₄	Acetone	3	11	77
3	AgNO ₃	Acetone	1	71	86
4	AgOTf	Acetone	2	54	81
5	AuCl	Acetone	1	62	83
6	AuCl ₃	Acetone	1	64	84
7	AgNO ₃	DCM	1	48	87
8	AgNO₃	Toluene	0.5	75	92
9	AgNO ₃	THF	0.5	71	90

^a After step (i), the mixture was filtered and concentrated and subjected to step (ii) immediately. ^b Isolated yield of main diastereomer. ^c Resolved by the crude ¹H NMR spectroscopy.

enhanced the reaction yield to 71% as well as the diastereoselectivity to 86% *de*.

Subsequently, gold catalysts were investigated as we anticipated that they would produce equal or better yields and diastereoselectivities. Noteworthy, the results obtained coincided with our predictions *i.e.* AuCl and AuCl₃ (Table 1, entries 5 and 6) displayed reasonably good yields of 62 to 64% and diastereoselectivities of 83 to 84%. Although the results were comparable for AuCl, AuCl₃ and AgNO₃, AgNO₃ was selected as the catalyst because it is able to achieve reasonable yields and diastereoselectivities at a lower cost. With the catalyst chosen, we proceeded to examine the solvent effects. Unexpectedly, all of the solvents that were screened

produced relatively high diastereoselectivities, with small deviation in the reaction timings (Table 1, entries 3 and 7-9). Upon a thorough analysis of the results, toluene was recognised as the best solvent, affording **46a** in a good yield of 75% and an excellent *de* of 92% over 30 min (Table 1, entry 8). From the optimization studies conducted, we established that 0.2 equivalents of AgNO₃ catalyst in toluene is the set of conditions most suitable for this reaction.

After resolving the optimal conditions, we went on to examine the scope and flexibility of this cyclization reaction by testing it on a diverse range of imines. The results are displayed in Table 2. It was found that this method is suitable for a wide variety of non-aromatic as well as aromatic imines. Utilizing 0.2 equivalents of AgNO₃ in toluene, diastereomers **46a-46n** were afforded in good yields between 62 to 80% and excellent diastereoselectivities between 90 to 95%. A careful analysis of the results exposed numerous characteristics of this reaction. The existence of electron-donating (**46b-46c**) as well as electron-withdrawing substituents (**46d-46h**) on the phenyl group of the imines delivered consistent yields, suggesting that the substituents on the phenyl group of the imines have insignificant effect on the reaction yields. Based on this result, we can deduce that the aryl rings do not cause steric hindrance to the reaction and the ring is likely to be positioned away from the allene moiety. Hence, changing the phenyl substituent did not affect the reaction yield. In addition, the electron-donating and withdrawing substituents on the aryl rings mentioned above did not produce significant electronic effect on the nucleophilicity of the neighboring nitrogen. Therefore, the reaction yields are generally similar. However, when the phenyl group of the imine bears an NO₂ group (**46g**) or when the imine bears a furan moiety (**46j**), lower yields of the cyclized products were obtained. In contrast to the yields, the substituents on the phenyl group of the imines were rather important factors

in determining the diastereoselectivities. As demonstrated, electron-withdrawing substituents on the phenyl group of the imines generally afforded the cyclized products **46e-46h** with high *de* of about 95%, whereas electron-donating substituents on the phenyl group of the imines, heterocyclic imines, aliphatic imines and naphthyl imines provided the product in marginally lower *de* (90-92%). In addition to the aromatic imines, reactions involving aliphatic imines (**46k-46m**) also showed relatively good yields (72-80%) and excellent *de* (90-93%). This further strengthened and supported our strategy by demonstrating the tolerance and flexibility this cycloaddition reaction to a wide variety of imine substrates.

Table 2. Exploration of the substrate scope of pyrrolidine derivatives' formation.

Entry ^[a]	46	R	Yield ^[b] (%)	<i>De</i> ^[c] (%)
1	a		75	92
2	b		80	91
3	c		75	92
4	d		75	94
5	e		74	95

6	f	75	95
7	g	65	94
8	h	70	95
9	i	75	92
10	j	62	90
11	k	80	93
12	l	72	90
13	m	80	91

^b Isolated yield of major diastereomer. ^c Determined by crude ¹H NMR spectroscopy.

The diastereomer structures were confirmed by the X-ray crystallography of product **46c** (Figure 6).

Figure 6. X-Ray of pyrrolidine derivative **46c**

Gaussian calculations were carried out to understand the selective diastereoselectivity (Scheme 14a, DFT, B3LYP/6-31G* level). As depicted in the diagrams, Figure A (producing (-)-diastereomer) possesses large steric hindrance and is therefore higher in energy. In contrast, Figure B (producing (+)-diastereomer) is less hindered with lower energy and therefore more preferential.

Figure A - (-)-diastereomer

Figure B - (+)-diastereomer

Scheme 14a. Gaussian diagrams of the two possible diastereomers

After achieving the cyclized product, the next step was to cleave off the carbohydrate auxiliary. However, when the pyrrolidine derivative **46a** was subjected to hydrochloric acid, the desired auxiliary and pyrrolidine were not obtained; TBS protecting groups were deprotected too, resulting in a complex mixture that is highly polar.

Scheme 15. Unsuccessful cleavage of carbohydrate auxiliary with hydrochloric acid

Hence, another cleaving method was employed. Using a method developed by Danishefsky, after purification, the desired product was produced when the carbohydrate auxiliary was cleaved off.^[54] By using 5 equivalents of benzenethiol with 0.1 equivalents of boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{OEt}_2$), pyrrolidines were effectively synthesized. Worthy of note, since the carbohydrate auxiliary that was cleaved can be recovered and recycled; the atom economy of this kind of reaction is largely improved. The thioglycoside could be easily converted back to the respective hydroxyl-glycoside starting material by using a conventional protocol of subjecting the thioglycoside with NIS, TFA and water.^[54i] The cleaving reaction was conducted in dichloromethane from a temperature range of $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, acquiring the desired pyrrolidinones in excellent yields between 90 to 96% and outstanding enantiomeric ratios (89-99%). Initial assessment was carried out on pyrrolidine derivatives with aromatic substituents. These derivatives displayed excellent enantiomeric selectivities, with methoxy (**48b**), bromine (**48d**) and trifluoro (**48e**) substituted phenyls displaying an almost exclusive enantiomeric ratio of 99% or more. This reaction was then extended to furan substituted pyrrolindine (**48f**) in which good enantioselectivity of 89% and an excellent 92% yield were also achieved.

Table 3. Evaluation of the enantioselectivities of pyrrolidine derivatives.

Entry	48	Product	Yield ^[a] (%)	<i>Ee</i> ^[b] (%)
1 ^[c]	a		92	98
2	b		96	>99
3	c		94	97
4	d		94	99
5	e		94	99
6	f		92	89

^a Isolated yield. ^b Determined by chiral HPLC. ^c Stereochemistry resolved by optical rotation and X-ray crystallography (see experimental section).

Correspondingly, the major isomer structures were established by X-ray crystallography of product **48a** (Figure 7)

Figure 7. X-Ray structure of pyrrolidine **48a**

Inspired by these results, we went on to reduce the pyrrolidine derivative **48b** which is substituted with an aromatic ring bearing a methoxy group. By using sodium borohydride (NaBH_4) in methanol and cerium trichloride heptahydrate ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) as the catalyst, **48b** was reduced, affording **50** as the main diastereomer.^[54iii] By comparing the coupling constant with previous known literature report,^[54iii] analysis of the crude ^1H NMR spectroscopy showed a diastereomeric ratio of 96%, with preference for the *cis* isomer.

This could be attributed to the fact that the aryl ring next to the nitrogen will block the attack of the nucleophile from the top face. Attack of the nucleophile from the bottom face will therefore give the final compound, with the OH group *cis* to the aryl ring. This strategy is effective for retaining the stereoselectivity of natural products like (+)-preussin,^[55] which plays crucial roles in peptidomimetics.^[56]

Scheme 16. Selective reduction of pyrrolidine derivative **48b**

3.3 Conclusion

In conclusion, we have demonstrated a successful application of TBS-protected carbohydrate auxiliary in controlling the stereochemistry of a [3 + 2] cycloaddition reaction between lithiated allenes and a variety of imine scope. Using AgNO₃ as the promoter, high yields and excellent diastereoselectivities were obtained. The resulting good enantioselectivity after the removal of the carbohydrate auxiliary allows the synthesis of a large variety of pyrrolidine derivatives which are important components in many chiral natural products and drugs that have a plethora of applications in the research arena. Furthermore, the selective reduction of pyrrolidines strengthened the potentials of this strategy in synthetic applications, signifying the importance to organic chemistry. This novel protocol establishes one of the best examples in using chiral carbohydrate auxiliaries to synthesize bioactive and optically pure pyrrolidines, thus paving a route for future investigation in employing carbohydrate templates for stereoselective synthesis.

4. Experimental Section

All reactions were conducted under a nitrogen atmosphere, unless otherwise specified. Anhydrous solvents were transferred *via* oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. All solvents and reagents were attained from commercial suppliers (Sigma-Aldrich, Fluka and Alfa Aesar) and used without additional purification unless otherwise stated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Purification of product by flash column chromatography was achieved using silica gel 60 (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Optical rotations were measured in CHCl₃ on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu) and reported in cm⁻¹. Optical purity was obtained using Shimadzu HPLC (SPD-20A UV-vis detector) with Diacel Chem. Ind., Ltd. Chiralcel OD-H column (0.46 cm x 25 cm) and AD-H column (0.46 cm x 25 cm). High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ mass spectrometer (quadrupole ion trap), attached with the Crystal 310 CE system and the TSP4000 HPLC system. Precise masses are accounted for the molecular ion [M+H]⁺ or an appropriate fragment ion. NMR spectra were documented at room temperature on a 400 MHz Bruker ACF 400 NMR spectrometer. Residual solvent signals were used as the reference (7.26 ppm for ¹H NMR spectroscopy and 77.0 ppm for ¹³C NMR spectroscopy). Chemical shifts are stated in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is denoted in terms of ppm, coupling constants (*J*) are specified in Hz. The following abbreviations categorize the multiplicity: s = singlet, d

= doublet, t = triplet, q = quartet, m = multiplet or unresolved. X-ray crystallographic data was collected by employing a Bruker X8Apex diffractometer with Mo K/ α radiation (graphite monochromator).

4.1 Procedure for preparation of the starting material – allenyl 3,4,6-tri-*O*-*t*-butyldimethylsilyl-2-deoxy- α -D-galactopyranoside (45)^[51]

4.1.1 Characterization of Allenyl 3,4,6-tri-*O*-*t*-butyldimethylsilyl-2-deoxy- α -D-galactopyranoside (45):

The title compound was prepared according to the procedures reported.^[51] The product was obtained as a colourless oil; $[\alpha]_D^{24} +144.8$ (c 1.0, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 6.60 (t, J = 6.0 Hz, 1H), 5.38-5.29 (m, 1H), 5.13-5.12 (m, 1H), 4.06 (ddd, J = 11.9, 4.6, 2.3 Hz, 1H), 3.87 (s, 1H), 3.71-3.62 (m, 3H), 2.14 (dt, J = 12.6, 3.6 Hz, 1H), 1.72 (dd, J = 12.6, 4.4 Hz, 1H), 0.91(s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 201.7, 117.5, 97.6, 88.7, 73.3, 69.9, 68.1, 62.1, 33.0, 26.2, 26.2, 25.8, 25.7, 18.6, 18.5, 18.2, -3.9, -4.4, -4.7, -4.9, -5.3, -5.3; **IR (neat)** 3021, 2955, 2930, 2857, 1632, 1256, 1215, 837, 758 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₇H₅₆O₅Si₃ [M+H]⁺, 545.3514, found 545.3522.

4.2. General procedure for preparation of sugar incorporated pyrrolidinones (46)

To a round bottomed flask of flame dried LiCl (20 mg, 0.55 mmol, 3.0 equiv) was added **45** (100 mg, 0.18 mmol, 1.0 equiv) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to stir for 5 min, then $n\text{-BuLi}$ (0.24 mL, 0.37 mmol, 2.0 equiv) was added dropwise into the mixture, forming a dark brown suspension. The suspension was stirred for 45 min at $-78\text{ }^{\circ}\text{C}$ and then **36a** (95 mg, 0.37 mmol, 2.0 equiv) in THF (10 mL) was added dropwise over a period of 15 min. The reaction mixture was stirred for another 3 h (TLC monitored). The mixture was then brought to rt and extracted with ether (50 mL) and washed with brine (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield a brown oil. To a solution of the brown oil in toluene (10 mL) was added AgNO_3 (6 mg, 0.04 mmol, 0.2 equiv). The mixture was allowed to stir at $60\text{ }^{\circ}\text{C}$ for 30 min (TLC monitored). Upon completion of the reaction, the mixture was brought to rt, filtered through celite and concentrated under reduced pressure to yield a yellow oil. Purification of the crude residue by flash column chromatography on silica gel (10% EtOAc in hexanes) afforded compound **46a**.

4.2.1 Characterisation of the sugar incorporated pyrrolidinones (46a-46m):

46a

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (46a)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (74% yield); $[\alpha]_D^{24} +146.7$ (c 0.5, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 7.55 (d, J = 8.2 Hz, 2H), 7.34-7.21 (m, 4H), 7.23-7.21 (d, J = 8.2 Hz, 2H), 5.25-5.24 (m, 1H), 5.09-5.08 (m, 1H), 4.95 (s, 1H), 4.33-4.23 (m, 2H), 3.91-3.88 (m, 1H), 3.80 (s, 1H), 3.63-3.57 (m, 3H), 2.41 (s, 3H), 1.97 (dt, J = 12.4, 3.2 Hz, 1H), 1.33 (dd, J = 12.4, 3.8 Hz, 1H), 0.88 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), -0.02 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 152.9, 143.1, 139.8, 135.6, 129.5, 128.1, 127.7, 127.4, 127.2, 99.1, 93.2, 74.1, 70.0, 67.7, 67.5, 62.7, 52.6, 32.8, 26.1, 26.1, 25.8, 21.5, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 3036, 2955, 2930, 2857, 1636, 1254, 835, 777 cm⁻¹; **HRMS (ESI):** m/z calcd for C₄₂H₇₂NO₈SSi₃ [M+H]⁺, 804.4181, found 804.4149.

46b

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butylidimethylsilyl)oxy)-6-(((tert-butylidimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(o-tolyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46b)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (80% yield); $[\alpha]_D^{24} +191.6$ (c 0.2, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.47 (d, $J = 8.2$ Hz, 2H), δ 7.16 (d, $J = 8.2$ Hz, 2H), 7.08 (d, $J = 7.0$ Hz, 2H), 7.03 (t, $J = 7.0$ Hz, 2H), 5.57-5.56 (m, 1H), 5.04-5.03 (m, 1H), 4.95-4.96 (m, 1H), 4.35-4.32 (m, 1H), 4.23-4.19 (m, 1H), 3.84-3.82 (m, 1H), 3.76 (s, 1H), 3.62-3.56 (m, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 1.93 (dt, $J = 12.5, 3.3$ Hz, 1H), 1.26 (dd, $J = 12.5, 4.1$ Hz, 1H), 0.87 (s, 9H), 0.85 (s, 9H), 0.81 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.06 (s, 3H), -0.07 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 153.5, 142.9, 137.9, 135.7, 130.1, 129.4, 127.4, 127.3, 127.2, 126.1, 99.0, 93.3, 74.0, 70.0, 67.8, 63.8, 62.9, 52.5, 32.8, 26.1, 26.1, 25.8, 21.5, 19.4, 18.5, 18.4, 18.2, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 2957, 2930, 2857, 1628, 1254, 835, 775 cm^{-1} ; **HRMS (ESI)**: m/z calcd for $\text{C}_{42}\text{H}_{71}\text{NO}_7\text{Si}_3$ $[\text{M}+\text{H}]^+$, 818.4337, found 818.4302.

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyltrimethylsilyl)oxy)-6-(((tert-butyltrimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46c)

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (75% yield); **m.p.** 137-138 °C; $[\alpha]_D^{24} +82.8$ (c 0.2, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 7.51 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 5.18-5.16 (m, 1H), 5.08-5.06 (m, 1H), 4.92-4.90 (m, 1H), 4.25 (dt, J = 12.3, 2.2 Hz, 1H), 4.19 (ddd, J = 12.3, 5.3, 1.6 Hz, 1H), 3.86 (ddd, J = 11.6, 3.9, 2.4 Hz, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.61-3.54 (m, 3H), 2.38 (s, 3H), 1.95 (dt, J = 12.5, 3.2 Hz, 1H), 1.32 (dd, J = 12.5, 4.1 Hz, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H), -0.04 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 159.2, 151.3, 143.1, 135.2, 132.2, 129.5, 128.4, 127.5, 113.6, 96.8, 92.2, 73.7, 70.0, 67.6, 67.1, 62.5, 55.2, 52.8, 32.8, 26.2, 26.1, 25.8, 21.5, 18.5, 18.5, 18.2, 0.0, -4.0, -4.6, -5.0, -5.4, -5.4; **IR (neat)** 3018, 2957, 2930, 2857, 1639, 1215, 837, 756 cm⁻¹; **HRMS (ESI):** m/z calcd for C₄₂H₇₂NO₈SSi₃ [M+H]⁺, 834.4286, found 834.4207.

46d

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(4-fluorophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46d)

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (75% yield); **m.p.** 102-103 °C; $[\alpha]_D^{24} +102.5$ (c 0.4, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 7.53 (d, J = 8.2 Hz, 2H), 7.22-7.18 (m, 4H), 6.93 (t, J = 8.7 Hz, 2H), 5.20-5.19 (m, 1H), 5.08-5.07 (m, 1H), 4.94-4.93 (m, 1H), 4.27 (dt, J = 12.4, 2.3 Hz, 1H), 4.21 (ddd, J = 12.4, 5.2, 1.6 Hz, 1H), 3.85 (ddd, J = 11.7, 4.0, 2.3 Hz, 1H), 3.77 (s, 1H), 3.61-3.55 (m, 3H), 2.39 (s, 3H), 1.97 (dt, J = 12.5, 3.4 Hz, 1H), 1.33-1.29 (m, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H), -0.04 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 152.6, 143.3, 135.7, 135.7, 135.4, 129.5, 128.9, 128.8, 127.3, 115.1, 114.9, 99.1, 93.3, 74.2, 70.0, 67.7, 66.8, 62.8, 52.5, 32.8, 26.1, 26.1, 25.8, 21.5, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 3021, 2957, 2930, 2857, 1605, 1215, 1018, 839, 756 cm⁻¹; **HRMS (ESI):** m/z calcd for C₄₁H₆₉FNO₇SSi₃ [M+H]⁺, 822.4087, found 822.4032.

46e

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(4-chlorophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46e)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (74% yield); $[\alpha]_D^{24} +125.8$ (c 0.6, CHCl_3); **^1H NMR (400 MHz, CDCl_3):** δ 7.53 (d, $J = 8.2$ Hz, 2H), 7.22-7.20 (m, 4H), 7.16 (d, $J = 8.5$ Hz, 2H), 5.19-5.17 (m, 1H), 5.08-5.07 (m, 1H), 4.94-4.93 (m, 1H), 4.26 (dt, $J = 12.3, 2.3$ Hz, 1H), 4.21 (ddd, $J = 12.3, 5.0, 1.8$ Hz, 1H), 3.85 (ddd, $J = 11.8, 4.1, 2.3$ Hz, 1H), 3.77 (s, 1H), 3.61-3.53 (m, 3H), 2.40 (s, 3H), 1.97 (dt, $J = 12.5, 3.3$ Hz, 1H), 1.32 (dd, $J = 12.5, 4.1$ Hz, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 152.5, 138.5, 135.5, 133.6, 129.5, 128.6, 128.3, 127.4, 99.1, 93.5, 74.3, 70.1, 67.8, 66.8, 62.8, 52.6, 32.8, 30.9, 26.1, 26.1, 25.8, 21.5, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 2955, 2930, 2857, 1645, 1254, 835, 775 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{41}\text{H}_{69}\text{ClNO}_7\text{SSi}_3$ $[\text{M}+\text{H}]^+$, 838.3791, found 838.3706.

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(4-bromophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46f)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (75% yield); $[\alpha]_D^{24} +92.8$ (c 0.4, CHCl_3); **^1H NMR (400 MHz, CDCl_3):** δ 7.53 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 5.16-5.15 (m, 1H), 5.08-5.07 (m, 1H), 4.93-4.92 (m, 1H), 4.26 (dt, $J = 12.5, 2.3$ Hz, 1H), 4.21 (ddd, $J = 12.5, 5.2, 1.7$ Hz, 1H), 3.85 (ddd, $J = 11.9, 4.1, 2.1$ Hz, 1H), 3.77 (s, 1H), 3.60-3.53 (m, 3H), 2.40 (s, 3H), 1.97 (dt, $J = 12.5, 3.5$ Hz, 1H), 1.32 (dd, $J = 12.5, 4.0$ Hz, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 152.3, 143.3, 139.0, 135.3, 131.3, 129.6, 128.9, 128.6, 128.5, 127.4, 121.7, 99.1, 93.4, 74.2, 70.0, 67.7, 66.9, 62.8, 52.6, 32.8, 26.1, 26.1, 25.8, 21.5, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 3111, 2953, 2930, 2857, 1667, 1258, 837, 775 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{41}\text{H}_{69}\text{BrNO}_7\text{SSi}_3$ $[\text{M}+\text{H}]^+$, 884.3286, found 884.3295.

46g

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(4-nitrophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46g)

The title compound was prepared according to the general procedure. The product was obtained as a yellow oil; (65% yield); $[\alpha]_D^{24} +91.0$ (c 0.9, CHCl_3); **^1H NMR (400 MHz, CDCl_3):** δ 8.14 (d, $J = 8.7$ Hz, 2H), 7.60 (d, $J = 8.1$ Hz, 2H), 7.46 (d, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 5.29-5.28 (m, 1H), 5.08-5.07 (m, 1H), 4.98-4.97 (m, 1H), 4.31-4.22 (m, 2H), 3.85 (ddd, $J = 11.6, 3.8, 2.3$ Hz, 1H), 3.76 (s, 1H), 3.61-3.52 (m, 3H), 2.41 (s, 3H), 1.97 (dt, $J = 12.7, 3.4$ Hz, 1H), 1.32 (dd, $J = 12.7, 4.3$ Hz, 1H), 0.85 (s, 9H), 0.84 (s, 18H), 0.05 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 151.5, 147.6, 147.5, 143.8, 134.8, 129.8, 128.0, 127.4, 123.5, 99.2, 94.0, 74.4, 70.0, 67.7, 66.8, 62.9, 52.8, 32.8, 26.1, 26.0, 25.8, 21.6, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 3021, 2955, 2930, 2857, 1667, 1524, 1256, 837, 758 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{41}\text{H}_{69}\text{N}_2\text{O}_9\text{SSi}_3$ $[\text{M}+\text{H}]^+$, 849.4035, found 849.3995.

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole (46h)

The title compound was prepared according to the general procedure. The product was obtained as a pale yellow oil; (70% yield); $[\alpha]_D^{24} +100.7$ (c 2.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.64-7.59 (m, 2H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 5.55-5.54 (m, 1H), 5.05-5.04 (m, 1H), 4.91-4.90 (m, 1H), 4.37 (ddd, $J = 12.2, 5.2, 1.5$ Hz, 1H), 4.18 (dt, $J = 12.2, 2.3$ Hz, 1H), 3.80 (ddd, $J = 11.6, 3.8, 2.1$ Hz, 1H), 3.72 (s, 1H), 3.57-3.48 (m, 3H), 2.41 (s, 3H), 1.90 (dt, $J = 12.5, 3.5$ Hz, 1H), 1.18 (dd, $J = 12.5, 4.4$ Hz, 1H), 0.85 (s, 9H), 0.81 (s, 9H), 0.79 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), -0.05 (s, 3H), -0.07 (s, 3H), -0.08 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 152.8, 143.5, 134.2, 132.2, 129.8, 128.8, 127.7, 127.5, 98.4, 92.9, 73.9, 70.0, 67.4, 62.9, 62.4, 52.9, 32.8, 26.1, 25.7, 21.5, 18.5, 18.4, 18.1, -3.9, -4.8, -5.0, -5.1, -5.4, -5.4; IR (neat) 3134, 2955, 2930, 2857, 1668, 1254, 1165, 1123, 1105, 837, 775 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{42}\text{H}_{69}\text{F}_3\text{NO}_7\text{Si}_3$ $[\text{M}+\text{H}]^+$, 872.4055, found 872.4029.

46i

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyl dimethylsilyl)oxy)-6-(((tert-butyl dimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(naphthalen-1-yl)-1-tosyl-2,5-dihydro-1H-pyrrole (46i)

The title compound was prepared according to the general procedure. The product was obtained as a pale yellow oil; (75% yield); $[\alpha]_D^{24} +98.2$ (c 0.1, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.04-8.01 (m, 1H), 7.80-7.78 (m, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.45-7.32 (m, 5H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.01-5.97 (m, 1H), 5.02-5.00 (m, 2H), 4.48 (dt, $J = 12.5, 2.1$ Hz, 1H), 4.38 (ddd, $J = 12.5, 5.5, 1.7$ Hz, 1H), 3.70 (s, 1H), 3.63-3.56 (m, 3H), 2.30 (s, 3H), 1.78 (dt, $J = 12.8, 3.2$ Hz, 1H), 0.97 (dd, $J = 12.8, 4.6$ Hz, 1H), 0.89 (s, 9H), 0.82 (s, 9H), 0.67 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.31 (s, 3H), -0.34 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 152.4, 143.0, 135.4, 135.1, 133.6, 131.5, 129.2, 128.6, 128.3, 127.5, 126.4, 126.2, 125.3, 125.2, 122.7, 97.1, 92.3, 73.6, 69.8, 67.2, 52.9, 32.7, 29.7, 26.0, 26.0, 25.8, 21.4, 18.5, 18.2, 18.1, -4.0, -5.0, -5.1, -5.2, -5.3, -5.4; IR (neat) 2957, 2926, 2855, 1639, 1260, 833, 775 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{44}\text{H}_{69}\text{NO}_7\text{SSi}_3$ $[\text{M}+\text{H}]^+$, 854.4337, found 854.4293.

46j

(*S*)-3-(((2*R*,4*R*,5*S*,6*R*)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-2-yl)oxy)-2-(furan-2-yl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (46j)

The title compound was prepared according to the general procedure. The product was obtained as a brown oil; (75% yield); $[\alpha]_D^{24} +89.9$ (c 0.3, CHCl₃); **¹H NMR (400 MHz, CDCl₃)**: δ 7.48 (d, J = 8.2 Hz, 2H), 7.20-7.18 (m, 3H), 6.31 (d, J = 3.2 Hz, 1H), 6.26 (dd, J = 3.2, 1.8 Hz, 1H), 5.37-5.36 (m, 1H), 5.21-5.20 (m, 1H), 5.02-5.01 (m, 1H), 4.27 (dt, J = 12.1, 2.1 Hz, 1H), 4.11 (ddd, J = 12.1, 5.5, 1.7 Hz, 1H), 3.90 (ddd, J = 11.6, 3.8, 2.1 Hz, 1H), 3.79 (s, 1H), 3.62-3.58 (m, 3H), 2.38 (s, 3H), 2.03 (dt, J = 12.3, 3.4 Hz, 1H), 1.40 (dd, J = 12.3, 4.3 Hz, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)**: δ 151.5, 150.3, 142.9, 142.2, 135.9, 129.4, 127.1, 110.2, 109.5, 99.1, 94.6, 74.1, 70.1, 67.7, 62.7, 60.7, 51.9, 33.0, 26.1, 26.1, 25.8, 21.5, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 2955, 2930, 2857, 1630, 1254, 835, 775 cm⁻¹; **HRMS (ESI)**: m/z calcd for C₃₉H₆₈NO₈SSi₃ [M+H]⁺, 794.3973, found 794.3953.

46k

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-(tert-butyl)-1-tosyl-2,5-dihydro-1H-pyrrole (46k)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (80% yield); $[\alpha]_D^{24} +66.2$ (c 0.05, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.68 (d, $J = 8.2$ Hz, 2H), 7.26-7.24 (m, 2H), 4.82-4.81 (m, 1H), 4.69 (s, 1H), 4.06-4.05 (m, 1H), 3.96 (ddd, $J = 11.6, 3.6, 2.3$ Hz, 1H), 3.93-3.87 (m, 2H), 3.82 (s, 1H), 3.61-3.52 (m, 3H), 2.41 (s, 3H), 2.09 (dt, $J = 12.4, 3.4$ Hz, 1H), 1.56-1.53 (m, 1H), 1.04 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 153.9, 143.4, 134.5, 129.3, 127.8, 98.1, 95.3, 74.3, 73.0, 70.1, 68.1, 62.8, 53.4, 36.5, 33.2, 26.8, 26.2, 26.1, 25.7, 21.5, 18.5, 18.1, -3.9, -4.4, -4.8, -5.0, -5.4, -5.5; IR (neat) 2955, 2930, 2857, 1659, 1256, 835, 775 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{39}\text{H}_{74}\text{NO}_7\text{Si}_3$ $[\text{M}+\text{H}]^+$, 784.4494, found 784.4448.

46l

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyl dimethylsilyl)oxy)-6-(((tert-butyl dimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-((E)-but-2-en-2-yl)-1-tosyl-2,5-dihydro-1H-pyrrole (46l)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (72% yield); $[\alpha]_D^{24} +80.3$ (c 0.7, CHCl_3); **^1H NMR (400 MHz, CDCl_3):** δ 7.66 (d, $J = 8.3$ Hz, 2H), 7.28-7.26 (m, 2H), 5.48 (q, $J = 6.6$, 1H), 5.22-5.21 (m, 1H), 4.90-4.89 (m, 1H), 4.59-4.58 (m, 1H), 4.19 (dt, $J = 12.3$, 2.3 Hz, 1H), 4.06 (ddd, $J = 12.3$, 5.4, 1.8 Hz, 1H), 3.97 (ddd, $J = 11.6$, 4.0, 2.3 Hz, 1H), 3.79 (s, 1H), 3.62-3.52 (m, 3H), 2.41 (s, 3H), 2.11 (dt, $J = 12.3$, 3.3 Hz, 1H), 1.58 (d, $J = 6.6$, 3H), 1.55-1.54 (m, 1H), 1.29 (s, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 150.0, 143.1, 135.6, 133.5, 129.5, 127.5, 124.1, 97.0, 93.1, 74.0, 71.5, 70.1, 67.9, 62.5, 52.9, 32.9, 26.2, 26.1, 25.8, 21.5, 18.6, 18.1, 13.4, 10.5, -4.0, -4.5, -4.9, -5.0, -5.4, -5.4; **IR (neat)** 2953, 2928, 2857, 1667, 1254, 835, 777 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{38}\text{H}_{70}\text{NO}_7\text{Si}_3$ $[\text{M}+\text{H}]^+$, 782.4337, found 782.4280.

46m

(S)-3-(((2R,4R,5S,6R)-4,5-bis((tert-butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-((E)-styryl)-1-tosyl-2,5-dihydro-1H-pyrrole (46m)

The title compound was prepared according to the general procedure. The product was obtained as a orange solid; (80% yield); **m.p.** 111-113 °C; $[\alpha]_D^{24} +61.9$ (c 0.3, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 7.71 (d, J = 8.2 Hz, 2H), 7.28-7.25 (m, 2H), 6.59 (d, J = 15.8 Hz, 1H), 5.93 (dd, J = 15.8, 8.2 Hz, 1H), 5.33-5.31 (m, 1H), 4.86-4.81 (m, 2H), 4.20-4.10 (m, 2H), 3.90-3.84 (m, 1H), 3.67 (s, 1H), 3.41 (t, J = 6.2 Hz, 1H), 2.39 (s, 3H), 2.10 (dt, J = 12.7, 3.4 Hz, 1H), 1.61 (dd, J = 12.7, 4.0 Hz, 1H), 0.86 (s, 9H), 0.83 (s, 9H), 0.78 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.05 (s, 3H), -0.08 (s, 3H), -0.10 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 151.5, 143.2, 136.4, 136.1, 132.7, 129.6, 128.4, 128.4, 127.9, 127.6, 127.6, 126.7, 98.7, 93.3, 70.1, 67.8, 66.0, 62.7, 52.2, 32.9, 29.7, 26.1, 26.1, 25.8, 25.7, 21.5, 18.5, 18.5, 18.1, -3.9, -4.6, -4.9, -5.0, -5.3, -5.4; **IR (neat)** 2957, 2928, 2857, 1599, 1256, 837, 779 cm⁻¹; **HRMS (ESI):** m/z calcd for C₄₂H₆₉NO₇SSi₃ [M+H]⁺, 830.4337, found 830.4296.

4.3 General procedure for preparation of the pyrrolidinones (**48**)⁵⁴

To a solution of **46a** (30 mg, 0.04 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) was added benzenethiol (0.02 mL, 0.20 mmol, 5.0 equiv) and BF₃·OEt₂ (2 μL, 0.02 mmol, 0.5 equiv). The reaction mixture was stirred at -78 °C for 1 h, the cooling bath was removed and the mixture was allowed to warm to 0 °C and stirred for 15 to 30 min (TLC monitored). The resulting mixture was extracted with CH₂Cl₂ (20 mL), washed with 10% NaHCO₃ (2 x 20 mL) and brine (2 x 20 mL). The combined organic layers were dried using Na₂SO₄, then filtered and concentrated under reduced pressure to obtain a pale yellow oil. Purification of the crude residue by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **49** and (30% EtOAc in hexanes) compound **48a**.

4.3.1 Characterization of pyrrolidinones (48a-f) and carbohydrate template (49):

48a

(S)-2-phenyl-1-tosylpyrrolidin-3-one (48a)

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (92% yield); **m.p.** 122-123 °C; **¹H NMR (400 MHz, CDCl₃):** δ 7.62 (d, J = 8.2 Hz, 2H), 7.32-7.26 (m, 6H), 4.57 (s, 1H), 3.97-3.90 (m, 1H), 3.74-3.67 (m, 1H), 2.63-2.454 (m, 1H), 2.48-2.40 (m, 1H), 2.42 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 208.2, 144.3, 135.5, 133.7, 129.9, 128.7, 128.3, 127.7, 126.9, 67.2, 44.1, 35.8, 21.6; **IR (neat)** 3021, 2926, 2857, 1634, 756 cm⁻¹; **[α]_D²¹** +180.3 (c 0.2, CHCl₃); **chiral HPLC** (Chiralcel AD-H, (hexane/isopropanol, 95/5), 1 mL/min.); t_R (–)-**48a** 29.67 min (1.1%), t_R (+)-**48a** 33.13 min (98.9%), 97.8% *ee*; **HRMS (ESI):** m/z calcd for C₁₇H₁₈NO₃S [M+H]⁺, 316.1007, found 316.0993.

48b

(S)-2-(4-methoxyphenyl)-1-tosylpyrrolidin-3-one (48b)

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (96% yield); **m.p.** 107-109 °C; **¹H NMR (400 MHz, CDCl₃):** δ 7.61 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H),

6.84 (d, $J = 8.8$ Hz, 2H), 4.49 (s, 1H), 3.97-3.90 (m, 1H), 3.79 (s, 3H), 3.70-3.63 (m, 1H), 2.64-2.55 (m, 1H), 2.49-2.43 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 208.6, 159.7, 144.2, 133.7, 129.8, 128.2, 127.7, 127.6, 114.2, 66.8, 55.3, 44.0, 35.7, 21.6; IR (neat) 1639, 754 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +181.0$ (c 0.05, CHCl_3); chiral HPLC (Chiralcel AD-H, (hexane/isopropanol, 90/10), 1 mL/min.); t_{R} (+)-**48b** 39.00 min (>99%), >99% *ee*; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$, 346.1113, found 346.1117.

(S)-2-(4-chlorophenyl)-1-tosylpyrrolidin-3-one (48c)

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (94% yield); m.p. 151-152 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.61 (d, $J = 8.2$ Hz, 2H), 7.30-7.25 (m, 6H), 4.48 (s, 1H), 3.97-3.91 (m, 1H), 3.68-3.62 (m, 1H), 2.61-2.54 (m, 1H), 2.49-2.46 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 207.7, 144.6, 134.3, 134.1, 133.3, 130.0, 128.9, 128.3, 127.8, 66.6, 44.1, 35.7, 21.6; IR (neat) 2916, 2849, 1639, 816, 754 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +103.0$ (c 0.1, CHCl_3); chiral HPLC (Chiralcel OD-H, (hexane/isopropanol, 95/5), 1 mL/min.); t_{R} (–)-**48c** 19.43 min (1.6%), t_{R} (+)-**48c** 20.43 min (98.4%), 96.8% *ee*; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{17}\text{ClNO}_3\text{S}$ $[\text{M}+\text{H}]^+$, 350.0618, found 350.0610.

48d**(S)-2-(4-bromophenyl)-1-tosylpyrrolidin-3-one (48d)**

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (94% yield); **m.p.** 152-154 °C; **¹H NMR (400 MHz, CDCl₃):** δ 7.62 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 4.48 (s, 1H), 3.98-3.91 (m, 1H), 3.70-3.64 (m, 1H), 2.64-2.55 (m, 1H), 2.51-2.44 (m, 1H), 2.43 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 207.5, 144.6, 134.5, 133.4, 131.8, 130.0, 128.6, 127.8, 122.5, 66.7, 44.1, 35.7, 21.6; **IR (neat)** 2965, 2926, 1630, 772 cm⁻¹; **[α]_D²⁴** +104.2 (c 0.1, CHCl₃); **chiral HPLC** (Chiralcel OD-H, (hexane/isopropanol, 95/5), 1 mL/min.); t_R (–)-**48d** 30.77 min (0.2%), t_R (+)-**48d** 32.39 min (99.8%), 99.6% *ee*; **HRMS (ESI):** m/z calcd for C₁₇H₁₇BrNO₃S [M+H]⁺, 396.0092, found 396.0092.

48e**(S)-1-tosyl-2-(4-(trifluoromethyl)phenyl)pyrrolidin-3-one (48e)**

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (94% yield); **m.p.** 106-108 °C; **¹H NMR (400 MHz, CDCl₃):** δ 7.70 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H),

7.50 (t, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.32 (d, $J = 8.3$ Hz, 2H), 4.80 (s, 1H), 4.15-4.09 (m, 1H), 3.49-3.42 (m, 1H), 2.80-2.71 (m, 1H), 2.61-2.54 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 205.5, 144.6, 132.1, 131.9, 129.9, 128.9, 128.2, 128.2, 126.6, 63.7, 44.3, 35.7, 21.6; IR (neat) 2926, 1767, 1611, 1163, 1123, 1092, 814, 756 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +236.6$ (c 0.5, CHCl_3); chiral HPLC (Chiralcel AD-H, (hexane/isopropanol, 90/10), 1 mL/min.); t_{R} (–)-**48e** 11.20 min (0.6%), t_{R} (+)-**48e** 16.28 min (99.4%), 98.8% *ee*; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{17}\text{F}_3\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$, 384.0881, found 384.0884.

(S)-2-(furan-2-yl)-1-tosylpyrrolidin-3-one (48f)

The title compound was prepared according to the general procedure. The product was obtained as a brown oil; (92% yield); ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, $J = 8.2$ Hz, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 7.12 (d, $J = 1.6$ Hz, 1H), 6.40 (d, $J = 3.2$ Hz, 1H), 6.27 (dd, $J = 3.2, 1.6$ Hz, 1H), 4.81 (s, 1H), 3.89-3.83 (m, 1H), 3.80-3.74 (m, 1H), 2.70-2.64 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.3, 148.3, 143.7, 143.2, 134.3, 129.6, 127.3, 111.0, 110.4, 60.7, 43.8, 36.4, 21.5; IR (neat) 2916, 2849, 1633, 756 cm^{-1} ; $[\alpha]_{\text{D}}^{24} +37.9$ (c 0.1, CHCl_3); chiral HPLC (Chiralcel AD-H, (hexane/isopropanol, 95/15), 1 mL/min.); t_{R} (+)-**48f** 29.36 min (5.7%), t_{R} (–)-**48f** 35.17 min (94.3%), 88.6% *ee*; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$, 306.0800, found 306.0794.

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(((2*R*,3*S*,4*R*,6*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(phenylthio)tetrahydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (49)

The title compound was prepared according to the general procedure. The product was obtained as a colourless oil; (90% yield); $[\alpha]_D^{24} +136.2$ (c 0.2, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 7.50 (d, J = 8.3 Hz, 2H), 7.28-7.21 (m, 3H), 5.63 (d, J = 5.3 Hz, 1H), 4.14 (t, J = 6.4 Hz, 1H), 4.06-4.03 (m, 1H), 3.89 (s, 1H), 3.73-3.63 (m, 2H), 2.50 (dt, J = 12.7, 5.3 Hz, 1H), 1.82 (dd, J = 12.7, 4.1 Hz, 1H), 1.55 (s, 1H), 0.94 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 135.3, 131.7, 128.8, 127.0, 77.2, 70.3, 69.4, 62.5, 34.5, 26.2, 26.1, 25.9, 18.6, 18.5, 18.3, -3.89, -4.35, -4.66, -4.89, -5.29, -5.39; **IR (neat)** 3017, 2955, 2930, 2857, 1634, 1258, 1217, 837, 758 cm⁻¹; **HRMS (ESI):** m/z calcd for C₃₀H₅₈O₄SSi₃ [M+H]⁺, 599.3442, found 599.3434.

4.4 Procedure for preparation of the pyrrolidine (50)^[54ii]

To a solution of **48b** (30 mg, 0.09 mmol, 1.0 equiv) in methanol (3 mL) was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (36 mg, 0.10 mmol, 1.1 equiv), followed by NaBH_4 (4 mg, 0.10 mmol, 1.1 equiv) at 0 °C. The reaction mixture was stirred for 30 min (TLC monitored) and then quenched with water. The resulting mixture was extracted with ether (20 mL) and washed with brine (2 x 20 mL). The combined organic layers were dried using Na_2SO_4 , then filtered and concentrated under reduced pressure to obtain a colourless oil. Purification of the crude residue by flash column chromatography on silica gel (40% EtOAc in hexanes) afforded compound **50** with a diastereomeric ratio of 96% (*cis* isomer was obtained in excess by comparing the coupling constant with previous literature report).^[54ii]

4.4.1 Characterization of the pyrrolidine (50):

(2*S*,3*S*)-2-(4-methoxyphenyl)-1-tosylpyrrolidin-3-ol (50)

The title compound was prepared according to the general procedure. The product was obtained as a white solid; (97% yield, 96% *de*); **m.p.** 137-139 °C; $[\alpha]_D^{24} +164.8$ (c 0.1, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.66 (d, *J* = 5.6 Hz, 1H), 4.18-4.12 (m, 1H), 3.80 (s, 3H), 3.77-3.70 (m, 1H), 3.62-3.57 (m, 1H), 2.43 (s, 3H), 1.89-1.82 (m, 1H), 1.76-1.71 (m, 1H), 1.17 (d, *J* = 4.7 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 159.5, 143.5, 134.8, 129.6, 129.0, 128.2, 127.5, 114.1, 73.5, 67.1, 55.3, 47.0, 32.2, 21.5; **IR (neat)** 3439, 3021, 1634, 752 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₁₈H₂₂NO₄S [M+H]⁺, 348.1270, found 348.1267.

4.5 X-Ray Structure of Pyrrolidine (48a)

Table 1. Crystal data and structure refinement for liu33.

Identification code	liu33	
Empirical formula	C ₁₇ H ₁₇ N O ₃ S	
Formula weight	315.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.1324(2) Å	$\alpha = 90^\circ$.
	b = 7.2369(3) Å	$\beta = 90^\circ$.

	$c = 33.9295(13) \text{ \AA}$	$\gamma = 90^\circ$.
Volume	$1505.78(10) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	0.227 mm^{-1}	
F(000)	664	
Crystal size	$0.40 \times 0.20 \times 0.10 \text{ mm}^3$	
Theta range for data collection	2.88 to 30.51° .	
Index ranges	$-7 \leq h \leq 8$, $-10 \leq k \leq 10$, $-48 \leq l \leq 48$	
Reflections collected	26347	
Independent reflections	4596 [$R(\text{int}) = 0.0421$]	
Completeness to $\theta = 30.51^\circ$	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9776 and 0.9146	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4596 / 0 / 200	
Goodness-of-fit on F^2	1.041	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0384$, $wR2 = 0.0858$	
R indices (all data)	$R1 = 0.0485$, $wR2 = 0.0904$	
Absolute structure parameter	-0.05(6)	
Largest diff. peak and hole	0.280 and $-0.357 \text{ e.\AA}^{-3}$	

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CHAPTER 2

**Synthesis of Carbohydrate-Integrated Heterocycles
through [4 + 1] Cycloaddition and Rearrangement**

Chapter 2

Synthesis of Carbohydrate-Integrated Heterocycles through [4 + 1]

Cycloaddition and Rearrangement

1. Introduction

In the previous chapter, we touched on the role of carbohydrates in inducing the stereoselectivities of organic compounds by acting as an auxiliary. In all cases, the carbohydrates were ultimately cleaved off from the compound to afford the final product. However, it is also worthy of note that in some ring structure systems, the carbohydrates are part of the building blocks and are not cleaved off. They adopt roles by being essential components of the structure as well as influencing the stereochemistry of neighbouring groups.

Carbohydrate-fused heterocycles have been found to be inhibitors of glycosidases, which are enzymes responsible for the biosynthesis of oligosaccharides. These heterocycles exhibit a wide range of biological activities and have been extensively employed in both the pharmaceutical and agricultural industries.^[1] Due to their benefits, increased efforts have been made to synthesize these potent inhibitors.^[2] Examples of inhibitors possessing O- and N-containing heterocycles are illustrated in Figure 1. Trehazolin^[3] and allosamidin^[4] have been shown to possess biological activities against fungi and insects. Castanospermine and Nagstatin on the other hand, have potential against cancers and viral infections.^[5] In addition to their importance as potent inhibitors, carbohydrate-fused heterocycles have also been shown to be relatively effective as ligands in several organic reactions involving asymmetric synthesis.

Figure 1. Examples of inhibitors with O- and N-containing heterocycles

Encouraged by the versatility of such carbohydrate-fused systems, in this chapter, various reports on their synthesis would be demonstrated. Herein, prominent examples, both past and recent, will be given to portray the development and application of these carbohydrate-fused heterocyclic systems.

2. Applications and Synthesis of Carbohydrate-fused Heterocycles

2.1 Carbohydrate- and Pseudocarbohydrate-fused Heterocycles as Glycosidase Inhibitors

Both natural as well as synthetic glycosidase inhibitors can provide extensive insights into the enzymatic studies. Their inhibitory properties are connected to their ability to imitate the transition state for the hydrolysis of glycosides. In addition, the

heterocyclic system in their structures play a crucial role in attaching to the binding pocket through hydrogen bonding to the phenolic or carboxylic residues present.^[6]

In 1996, Knapp and group reported the synthesis of an *N*-acetyl- α -hexosaminidase inhibitor (NAG-thiazoline **3**) (Scheme 1).^[7] Reaction of 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose **1** with Lawesson's reagent led to the production of thioamide **1a** selectively. Subsequently, cyclization occurs by displacement of the acetate to afford the thiazoline triacetate **2**. Deprotection of the acetate groups then furnished the desired NAG-thiazoline **3** in a 68% yield over two steps.

Scheme 1. Synthesis of NAG-thiazoline **3**

In the same year, Uchida and coworkers synthesized glycosylamino-oxazolines, derivatives of the trehalase inhibitor trehazolin.^[8] The glycosylamino-oxazolines were synthesized with five different sugars i.e. α -, β -galactose, α -, β -glucose and α -mannose (Scheme 2). After which, all the compounds were tested for inhibitory activities against six different sugar-enzyme hydrolases and α -manno-oxazoline **8** was shown to have a modest inhibitory effect against α -mannosidase.

Scheme 2. Synthesis of glycosylamino-oxazolines

Many synthetic strategies have been developed in the past decades to synthesize potent inhibitors with carbohydrate-fused heterocyclic structures. The development of novel synthetic approaches to these potent inhibitors would ensure the synthesis of new analogues for biological testings. In a more recent example, Cronin and coworkers reported an elegant synthesis of Castanospermine **12** from methyl α -D-glucopyranoside **9**. The synthetic route comprises of an aldol reaction, producing ester **10** from aldehyde **9**. Subsequently, a novel and interesting reductive amination cascade (catalytic) was developed to produce the indolizidine ring from ester **10**, eventually generating the desired product Castanospermine **12** (Scheme 3).^[9]

Scheme 3. Synthesis of Castanospermine **12**

The synthesis of imidazole-pentoses in 2001 by Tschamber^[10] prompted their evaluation as glycosidase inhibitors. Examination into their inhibitory potentials revealed that none of the sugars showed inhibition to the replication of HIV-1. Although some sugars were found to be rather selective, they were only moderate inhibitors of α -glycosidases (affirmed by Michaelis-Menten kinetics). Nevertheless, it was worthy of note that these *azasugars* inhibit α -glycosidases much better than β -glycosidases.

Figure 2. The eight imidazole-pentoses that were synthesized by Tschamber

2.2 Carbohydrate-fused Heterocycles as Ligands for Asymmetric Synthesis

To obtain the best reactivities and selectivities in enantioselective reactions, there are several factors to consider and optimize. One of the most important variables is the design and choice of the chiral ligand. A simple way to acquire chiral ligands is to essentially transform or develop ligands from natural chiral substrates, omitting the need for cumbersome optical-resolution steps. Carbohydrates are not only useful as building blocks for the synthesis of natural and biologically active compounds; they are also frequently employed in asymmetric synthesis as chiral auxiliaries and ligands. Over the past years, remarkable results have been achieved in using carbohydrate-fused ligands in a variety of catalytic asymmetric reactions.^[11] The benefits of carbohydrates, such as being highly functionalized, have numerous stereogenic centers and are readily available allows an extensive library of chiral ligands to be produced and tested in various asymmetric reactions. However, few examples of successful applications utilizing carbohydrates as ligands for catalysis have been reported.

2.2.1 Carbohydrate-fused Heterocycles as Phosphine Ligands

In a recent example, Nakano and group successfully developed phosphinooxathiane and phosphinooxazinane ligands from D-(+)-xylose.^[12] The ligands were tested on palladium-catalyzed allylic substitution reactions, in which dimethyl malonate was reacted with 1,3-diphenylprop-2-enyl acetate **17**. Enantioselectivities of up to 91% was obtained. From the results acquired, xylose-oxathiane ligand **19** produced the best results, providing high yields and good enantiomeric excess in the palladium-catalyzed aminations. Both ligands **19** and **20** are expected to achieve similar good results in other asymmetric reactions.

Scheme 4. Efficient phosphinooxathiane and phosphinooxazinane ligands (from D-(+)-xylose) in palladium-catalyzed aminations

An innovative and enantiomerically pure phosphine-oxazoline ligand **24** was synthesized from glucosamine **25**, by Glaser and Kunz in 1998.^[13] The ligand was employed in palladium-catalyzed allylic reactions of allyl acetates. The corresponding products were obtained in high yields and excellent enantioselectivities of up to 98% ee as shown in Scheme 5.

Scheme 5. Enantioselective allylation of catalyzed by palladium complex **24**

The synthesis of the complex **24** is shown in Scheme 6. From the starting material glucosamine **25**, it was first *N*-acylated with 2-fluoro-benzoylchloride. Then, the hydroxyl groups were protected with pivaloyl and subsequently converted into glucopyranosyl bromide. Following which, treatment with tetraethylammonium bromide afforded the oxazoline **29** through an *in-situ* anomerization pathway. Finally, nucleophilic aromatic substitution produced the palladium complex **24**.

Scheme 6. Synthesis of the carbohydrate-fused phosphinoaryloxazoline ligand

In terms of synthesizing carbohydrate-fused ligands, Uemura and group have contributed and examined carbohydrate-phosphino ligands substantially.^[14] Similar to Glaser's synthesis, they made use of the starting material D-glucosamine to synthesize a variety of novel phosphinite ligands (Scheme 7). Employing them in palladium-catalyzed allylic alkylation produced excellent enantioselectivities of up to 96%.^[15]

The ligands were prepared as illustrated in Scheme 8. Beginning from D-glucosamine hydrochloride **25**, *N*-acylation of **25**, protection of the hydroxyl groups

by benzylidene and acetyl afforded D-glucopyranoside **38** in good yield. Compound **38** was then converted into oxazoline **39** in the presence of SnCl_4 . Finally, deacetylation and subsequent reaction with Ph_2PCl afforded the phosphinite-nitrogen ligand **32**.

Scheme 7. Uemura's application of novel phosphinite ligands **32-37** on palladium-catalyzed allylic alkylation

Scheme 8 . Uemura's synthesis of novel phosphinite ligand **32**

2.2.2 Carbohydrate-based bis(oxazolines) in Copper-Catalyzed Reactions

Over the last two decades bis(oxazolines) have emerged as a flexible class of ligands for metal-catalyzed asymmetric reactions. They can be readily prepared from chiral dicarboxylic acid derivatives and β -amino alcohols and are very useful in many important enantioselective reactions. Boysen and group has explored widely on the incorporation of bis(oxazolines) into carbohydrates to create a chiral ligand for copper-catalyzed reactions.^[16] In 2008, Irmak successfully demonstrated the use of *glucoPybox* **42** in asymmetric reactions.^[17] Synthesis of the *glucoPybox* **42** began from amide **41** (produced from D-glucosamine hydrochloride **25**). Amide **41** was treated with acetyl chloride and NaHCO_3 in a one pot reaction to afford the desired ligand in an overall 27% yield (Scheme 9).

Scheme 9. Synthesis of *glucoPybox* **42**

The desired *glucoPybox* **42** was then utilized in a copper(I)-catalyzed asymmetric reaction. By reacting a range of imines **43** and alkynes **44**, propargylamine **45** was obtained with an enantiomeric excess of up to 99% in the presence of *glucoPybox* **42** as ligand and copper triflate (CuOTf) as the catalyst.

Scheme 10. Employing *glucoPybox* **42** in copper(I)-catalyzed addition of imines to alkynes

2.2.3 Cyclization strategies to Carbohydrate-fused Heterocyclic Systems

The emerging potentials of carbohydrate-fused systems as inhibitors as well as ligands for asymmetric catalysis prompted various groups to develop methodologies and strategies to their expedient synthesis. Cyclization using various glycosides is one of the most prominent and common strategies employed.

In 1994, Samet reported a carbohydrate-pyrimidine fused system by the reaction between levoglucosenone **46** with thiourea and guanidine derivatives.^[18] Interaction of levoglucosenone **46** with thiourea, *N*-cyanoguanidine and *N*-nitroguanidine (in the presence of base) causes ring closure, generating the pyrimidine ring and forming the desired carbohydrate-pyrimidine compounds **48a-48d** (Scheme 11). Noteworthy, there is no elimination of water from the final compounds **48a-48d** due to the Bredt rule, in which double bond formation in a bridgehead system is not allowed or favoured.

Scheme 11. Synthesis of carbohydrate-pyrimidine ring system

Avalos and group created a stereoselective synthesis of carbohydrate-fused imidazoline in 1999.^[19] The reaction of 2-amino-2-deoxy-D-glucopyranose **49** with isocyanates afforded 2-deoxy-2-ureido-D-glucopyranoses **50** (X=O) under neutral conditions (Scheme 12). Subsequent cyclization produced *S*-hydroxyimidazolidine-2-ones **52** when pH > 7. On the other hand, imidazolidine-2-ones **53** were obtained when pH < 7. The intermediate thioureido derivative **51** could not be isolated as it cyclized immediately to afford **52** (X=S). Compounds such as **52** and **53** have potentials to be useful as chiral auxiliaries and ligands for asymmetric catalysis when the C=X groups are good donors for the metal.

Scheme 12. Synthesis of carbohydrate-imidazoline ring system

In a recent study, Zou's group developed a strategy to synthesize carbohydrate-fused triazoles through the treatment of nitroalkene *C*-glycosides with sodium azide.^[20] At elevated temperatures, β -elimination first occurred. Following which, a 1,3-dipolar cycloaddition of the nitroalkene to the azide group produced an open chain intermediate which comprised of a conjugated ketone with a triazole moiety. This intermediate then proceeded through an intramolecular Michael addition to afford the 1,5-disubstituted carbohydrate-fused triazoles **55**, **58**, **59** (Scheme 13). The thermodynamic stability of the transition state influences the stereochemistry of this reaction,^[21] leading to the synthesis of carbohydrate-fused triazole **55** from nitroalkene *C*-glycoside **54** and a mixture of **58** and **59** from nitroalkene *C*-glycoside **57**. However, the yield of the reaction is relatively low, possibly due to the result of side reactions such as intermolecular couplings.

Scheme 13. Synthesis of carbohydrate-fused triazole ring system

2.3 Aim of the Project

The potentials of carbohydrate-fused heterocyclic ring system and the successful examples of synthesis through cycloaddition encouraged our interests. Noteworthy, the use of these systems as glycosidase inhibitors as well as catalysts are highly intriguing. Therefore, in the chapter herein, we will demonstrate the investigation of such compounds and report an expedient synthesis to carbohydrate-fused isoxazolines through tandem [4 + 1] cycloaddition and rearrangement of 2-nitroglycals. These carbohydrate-fused structures could play important and essential roles and their hidden potentials cannot be ignored.

3. Facile Synthesis of Carbohydrate-Integrated Isoxazolines through tandem [4 + 1] Cycloaddition and Rearrangement of 2-nitroglycals

3.1 Introduction

The development of new methodologies that would provide easy access to optically active isoxazoline and its derivatives has always been of considerable interest due to the abundant benefits associated to these compounds.^[22] Not only can isoxazolines be readily converted to β -amino acids which are constituents of many pharmaceutical agents and biologically natural products,^[23] they have been reported to possess diverse pharmacological activities such as antibacterial,^[24] antifungal,^[25] antiviral and anti-inflammatory^[26] activity. In addition, they have been reported to have great potentials as catalysts in organic synthesis.^[27] The significance of optically active isoxazoline and its derivatives renders the intense efforts to develop innovative strategies but despite the upsurge of methods over the recent years,^[28] the challenges posed by the asymmetric synthesis of these compounds still remain.

Among the various methods generated such as 1,3-dipolar cycloaddition,^[29] Pd-assisted cycloalkylation^[30] and recently reported oxidative N–O coupling,^[31] the [4 + 1] cycloaddition utilizing nitroolefins to produce isoxazoline derivatives is particularly attractive due to the acquirement of excellent stereoselectivity with remarkable efficiency.^[32] Compared to other cycloaddition reactions, [4+1] cycloaddition has drawn substantial interests over the recent years as it is relatively less explored and therefore presents an intriguing area of expansion. Intrigued by the potentials of such strategy, Yu *et al.* successfully implemented the racemic synthesis of sugar-fused isoxazoline *N*-oxides from 2-nitroglycals.^[33]

2-nitroglycals are versatile glycosyl donors which are useful in the synthesis of

many biologically active compounds and natural products,^[34] underlying the rationale behind their periodical employment in organic reactions.^[35] By virtue of the advantages associated with 2-nitroglycols^[36] and in line with our ongoing efforts to develop new methodologies employing carbohydrates,^[37] we hereby report a successful [4 + 1] cycloaddition between 2-nitroglycols and a range of sulphur ylides to produce highly selective carbohydrate-incorporated isoxazoline derivatives. Isoxazolines that are tethered to carbohydrates are very useful in organic synthesis, especially for the stereoselective synthesis of heterocycles and carbocycles that are bulky and complex.^[38] The presence of numerous hydroxyl groups not only provides opportunities for attachment of an array of ligands,^[39] they increase the functionalities, drawing attention to their applications in both the biological and chemical fields.^[40]

3.2 Results and Discussion

Preliminary studies were carried out with the intention to investigate and find a suitable catalyst for the cyclization reaction between 2-nitroalactal **60a** and sulphur ylide **61a**.^[41] Remarkably, the two compounds possess excellent reactivities, allowing the reaction to proceed without the need of a catalyst. However, the reaction time was long and only modest yield was acquired (Table 1, entry 1). Subsequently, Lewis acid catalyst (SnCl₄) was screened but the reaction did not proceed well and only little amount of product was afforded (Table 1, entry 2). Due to a recent report by Xiao and coworkers, we started to investigate the reaction with thiourea catalysts.^[41] Gratifyingly, when thiourea **A** was added to the reaction, good yields and diastereoselectivities (*de*) were provided (Table 1, entry 3). Worthy of note, the use of thiourea catalysts in organic synthesis is relatively well known since there has been extensive usage of these catalysts in asymmetric catalysis.³³ Motivated by this result; we proceeded to study the reaction by using an array of thiourea derivatives (Table 1, entries 4-6). In comparison to other catalysts, thiourea **A** and 1-phenylthiourea **B** produced good results when considering both the yields and the *de* (reactions were conducted in dichloromethane with 0.4 equivalents of the catalytic loading). To recognize the better catalyst out of the two, the catalyst loading was reduced to 0.2 equivalents and interestingly, there was a strong distinction between the two catalysts with regards to the yield (Table 1, entry 7-8). Thiourea **A** produced a 45% yield with a 86% *de* while 1-phenylthiourea **B** produced a 82% yield and a 90% *de*.

Having identified the optimal catalyst, we further reduced the catalyst loading to 0.1 equivalents (Table 1, entry 9). The yield and the *de* were not affected greatly therefore, we deduced that 0.1 equivalents of 1-phenylthiourea **B** is also suitable for

the reaction. An assessment of the solvents showed that great levels of efficiency (85% yield) as well as diastereoselectivity (91% *de*) could be obtained when using dichloromethane as the solvent (in contrast to other solvents such as THF, toluene, chloroform and DMF) (Table 1, entry 10-13). Judging from the optimization results, we concluded that 0.1 equivalents loading of 1-phenylthiourea **B** in dichloromethane at rt is the optimal set of condition for this reaction.

Table 1. Optimization studies.

Entry ^a	Catalyst (eq.)	Solvent	Time (h)	Yield ^b (%)	De ^c (%)
1	none	CH ₂ Cl ₂	24	56	70
2	SnCl ₄ (0.4)	CH ₂ Cl ₂	24	trace	n.d. ^d
3	A (0.4)	CH ₂ Cl ₂	24	74	92
4	B (0.4)	CH ₂ Cl ₂	4	80	92
5	C (0.4)	CH ₂ Cl ₂	24	44	91
6	D (0.4)	CH ₂ Cl ₂	24	36	79
7	A (0.2)	CH ₂ Cl ₂	7	40	86

8	B (0.2)	CH ₂ Cl ₂	5	77	90
9	B (0.1)	CH₂Cl₂	5.5	80	91
10	B (0.1)	CHCl ₃	7	77	84
11	B (0.1)	Toluene	2	80	82
12	B (0.1)	THF	3	75	81
13	B (0.1)	DMF	24	trace	n.d. ^d

^a Unless otherwise specified, all reactions were conducted with 1 equivalent of **60a**, 1.5 equivalents of **61a** and solvent (2 mL) at rt. ^b Isolated yield of diastereomeric mixture. ^c Resolved by crude ¹H NMR spectroscopy. ^d not determined.

With the protocol defined, examination of the reaction's versatility was carried out by using a diverse substrate scope on 2-nitrogalactal and 2-nitroglucal derivatives (Table 2). When subjected to the optimized conditions, reactions between 2-nitroglycals and an array of electron-withdrawing and electron-donating aryl substituents progressed smoothly *via* a [4+1] annulation to provide carbohydrate-integrated isoxazolines with excellent yields (83 to 88%) and exceptional diastereoselectivities (90-95%). This outcome demonstrates tolerance of the reaction to the steric and electronic effects of the aryl substituents on the side chain of the ketone. Notably, expansion of the reaction to aliphatic substituents (*tert*-butyl) on the sulphur ylides^[41] proved to be effective as well, signifying that this strategy is suitable for a wide range of substituents (Table 2, entries 7 and 12). Although aliphatic *tert*-butyl substituents provided excellent diastereoselectivities, a closer inspection of the results points to the trend that such substituents provided less yields in contrast to the aryl substituents. There are no substantial differences in the yields and *de* when the reaction was carried out with different carbohydrate scaffolds (2-nitrogalactal **60a** and

2-nitroglucal **60b**). This further exemplifies the flexibility of this method in the synthesis of carbohydrate-incorporated isoxazolines. From the X-ray crystallography, it was shown that: A) at the anomeric carbon of the carbohydrates, the isoxazolines adopted β -substitution and B) the chiral center of the isoxazolines has an *R* configuration (Figure 3).

Table 2. Exploration of the substrate scope.

Entry ^a	60	62	R	Yield ^b (%)	De ^c (%)
1	60a	62a		80	91
2	60a	62b		78	92
3	60a	62c		81	90
4	60a	62d		78	90
5	60a	62e		80	94
6	60a	62f		83	90

7	60a	62g		68	95
8	60b	62h		83	90
9	60b	62i		81	93
10	60b	62j		81	93
11	60b	62k		79	92
12	60b	62l		70	92

^aUnless otherwise specified, all reactions were conducted with 0.1 equivalents of phenylthiourea catalyst in CH₂Cl₂ at rt. ^b Isolated yield of diastereomeric mixture. ^c Resolved by crude ¹H NMR spectroscopy.

Figure 3. X-ray crystallography of carbohydrate-integrated isoxazoline **62b**.

Theoretical calculations were carried out on the half-chair conformations of 2-nitrogallactal **60a** to comprehend the exclusive anomeric β -selectivity of the carbohydrate motif. It was detected that half-chair conformation **II** is energetically favored over half-chair conformation **I**, by a difference of -3.1 kcal/mol (Scheme 1 (a), DFT, B3LYP/6-31G* level). The conformational inclination towards **II** enables the entry of incoming nucleophiles at β -position. Hence, theoretical findings validated our results, producing β -selective galactosides **3**. The rationale behind such selectivity is possibly due to the 1,3 allylic strain. 1,3 allylic strain would result when the substituents on C-1 and C-2 are in *cis* relation therefore, a β -isomer on the C-1 (*trans* to C-2 substituent) would be preferable. In addition, calculations were also carried out to determine the exact attachment of 1-phenylthiourea to 2-nitrogallactal **60a** *i.e.* the phenyl group's position on 1-phenylthiourea **B** relative to the more stable conformation **II**. 1-phenylthiourea and the benzyl protecting groups were also shown to be important in reducing the energy when coordinated to conformation **II** (See Experimental Section).

Scheme 14. Determining the energetically favored conformations of 2-nitrogalactal **60a** and 1-phenylthiourea through theoretical calculations.

Further studies on the reaction encouraged the development of a plausible mechanism, as illustrated in Scheme 15. Based on our conjecture, the reaction would undergo tandem [4 + 1] cycloaddition and rearrangement. At first, 1-phenylthiourea **B** interacts with the nitro group of 2-nitroglycal **60** through the formation of two hydrogen bonds. Insertion of sulphur ylide **61** then proceeds at the anomeric carbon, resulting in a β -configured hydrogen bond stabilized nitronate **64**. Upon oxygen alkylation, the [4 + 1] cycloaddition could be accomplished, forming carbohydrate-integrated isoxazoline *N*-oxides **65**, 1-phenylthiourea **B** and dimethyl sulfide. At the outset, we envisioned that isoxazoline *N*-oxides **65** would be our final compound. Surprisingly, it was not the case in this reaction. A subsequent rearrangement occurred in which a keto-enol tautomerization of the carbonyl group resulted in the ring opening of isoxazoline *N*-oxide **66**. *E/Z* isomerization of oximes is a known process and such isomerism has been a classical problem in stereochemistry.^[41i] For oxime *O*-anion **67**, bond rotation of the C–N bond will achieve *E/Z* isomerization of the oxime easily. We proposed that the isomer closer to the carbonyl is more favorable since the closer proximity to the carbonyl group would lead to the subsequent attack. Thereafter,

an attack of the oxygen anion on the carbonyl group then afforded *R*-isomer isoxazoline **62**. In comparison, the *S*-isomer is less stable as the carbonyl group may increase steric interactions with the pyran ring. Furthermore, preference for the *R*-isomer might also be due to the hydrogen bond formation with the pyran oxygen. This demonstrates the importance of carbohydrates in inducing diastereoselectivities in these isoxazolines and concurs with reports on carbohydrates in stereoselective reactions.³⁵

Scheme 15 Proposed mechanism for the generation of carbohydrate-integrated isoxazolines **62**.

3.3 Conclusion

In conclusion, an expedient synthesis of carbohydrate-integrated isoxazolines was developed through a [4 + 1] cycloaddition, followed by a subsequent rearrangement. The reaction between 2-nitroglycals and a variety of sulphur ylides afforded the isoxazolines in good yields and excellent diastereoselectivities. The synthesis of such compounds represents great potentials. In addition to their pharmaceutical and biological uses, reduction of the N–O bond of the isoxazoline derivatives permits the acquirement of *C*-glycosides which are important constituents and building blocks of many natural products and synthetic pharmaceuticals. This protocol establishes an important example to synthesize highly selective carbohydrate isoxazolines and *C*-glycosides, paving a way for further investigation in utilizing such strategy for organic synthesis.

4. Experimental section

All reactions were conducted under a nitrogen atmosphere, unless otherwise specified. Anhydrous solvents were transferred *via* oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. All solvents and reagents were acquired from commercial suppliers (Sigma-Aldrich, Fluka and Alfa Aesar) and utilized without additional purification unless otherwise indicated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Purification of the product by flash column chromatography was achieved using silica gel 60 (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Optical rotations were measured in CHCl₃ on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu) and reported in cm⁻¹. High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ mass spectrometer (quadrupole ion trap), coupled with the Crystal 310 CE system and the TSP4000 HPLC system. Accurate masses are reported for the molecular ion [M+H]⁺ or a suitable fragment ion. NMR spectra were documented at room temperature on a 400 MHz Bruker ACF 400 NMR spectrometer. The residual solvent indicators were used as the reference (7.26 ppm for ¹H NMR spectroscopy and 77.0 ppm for ¹³C NMR spectroscopy). Chemical shifts are stated in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is denoted in terms of ppm, coupling constants (*J*) are specified in Hz. The following abbreviations categorize the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or

unresolved. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/ α radiation (graphite monochromator).

4.1 Preparation of starting material 3,4,6-tri-*O*-benzyl-2-nitroglycals (**60**)

The starting 3,4,6-tri-*O*-benzyl-2-nitroglycals (**60**) were prepared according to the known procedure.^[42] Experimental results obtained were in accordance with the reported reference.

(2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-nitro-3,4-dihydro-2*H*-pyran (**60a**)

The product was obtained as a pale yellow solid; (1.12 g, 56 % yield); **m.p.** 53-56 °C; **¹H NMR (400 MHz, CDCl₃):** δ 8.21 (s, 1H), 7.35-7.22 (m, 15H), 4.68-4.44 (m, 8H), 3.87 (dd, $J_1 = 3.2$ Hz, $J_2 = 2.4$ Hz, 1H), 3.72 (dd, $J_1 = 10.1$ Hz, $J_2 = 14.2$ Hz, 1H), 3.60 (dd, $J_1 = 7.1$ Hz, $J_2 = 14.2$ Hz, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 154.7, 137.6, 137.0, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 78.6, 73.6, 73.2, 72.0, 71.4, 68.0, 67.7; **IR (KBr):** 3007, 2918, 2870, 1719, 1599, 1557, 1362, 1096 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₇H₂₈NO₆ [M+H]⁺, 462.1917, found: 462.1916.

60b

(2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-nitro-3,4-dihydro-2*H*-pyran (60b)

The product was obtained as a yellow solid; (1.10 g, 57 % yield); **¹H NMR (400 MHz, CDCl₃):** δ 8.10 (s, 1H), 7.41-7.26 (m, 15H), 4.91-4.46 (m, 8H), 3.97-3.91 (m, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 154.6, 138.1, 137.7, 136.9, 131.6, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 78.1, 77.4, 77.1, 76.8, 75.0, 73.5, 73.1, 72.2, 67.6; **IR (KBr):** 3013, 2922, 2870, 1748, 1636, 1558, 1504, 1344, 1323, 1202, 1094 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₇H₂₈NO₆ [M+H]⁺, 462.1920, found: 462.1917.

4.2 General synthetic procedure for carbohydrate-integrated isoxazolines (62)

To a solution of 3,4,6-tri-*O*-benzyl-2-nitrogalactal **60a** (50 mg, 0.11 mmol) and 1-phenylthiourea (2 mg, 0.01 mmol) in CH₂Cl₂ (2 mL) was added sulphur ylide **61a** (29 mg, 0.17 mmol). The reaction mixture was stirred at rt for 5.5 h. The resulting mixture was extracted with ether (2 × 50 mL), washed with 10% NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the crude residue as a dark yellow oil. Purification of the crude residue by flash column chromatography on silica gel (20% EtOAc in hexanes) afforded compound **62a** (54 mg, 0.09 mmol, 85% yield of diastereomer mixture) as a colourless oil.

4.2.1. Characterization of the carbohydrate-integrated isoxazolines (62)

62a

((3*R*,3*aR*,5*R*,6*R*,7*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)(phenyl)methanone (62a)

The title compound was prepared according to the general procedure and the compound was obtained as a colourless oil (50 mg, 80% yield of diastereomer mixture, 91% *de*); $[\alpha]_D^{24}$ -174.0 (*c* 0.02, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 8.28 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.41-7.28 (m, 15H), 5.59 (s, 1H), 5.47 (s, 1H), 5.06 (dd, *J* = 11.9, 3.9 Hz, 2H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.56-4.55 (m, 1H), 4.42 (dd, *J* = 19.5, 11.9 Hz, 2H), 4.19-4.18 (m, 1H), 3.97 (t, *J* = 6.5 Hz, 1H), 3.59 (d, *J* = 6.5 Hz, 2H); **¹³C NMR (100 MHz, CDCl₃):** δ 189.6, 156.1, 137.8, 137.5, 137.2, 133.8, 132.8, 131.0, 128.6, 128.6, 128.5, 128.4(2), 128.3, 128.1, 128.0, 127.9(2), 127.7, 105.9, 81.1, 77.8, 76.6, 75.1, 75.0, 73.6, 72.4, 67.8; **IR (neat)** 3424, 3030, 2922, 2872, 1688, 1645, 1597 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₃₅H₃₃NO₇ [M+H]⁺, 580.2257, found 580.2335.

((3R,3aR,5R,6R)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3a,5,6,7-tetrahydro-3H-pyrano[3,2-c]isoxazol-3-yl)(p-tolyl)methanone (62b)

The title compound was prepared according to the general procedure and the compound was obtained as a white solid (50 mg, 78% yield of diastereomer mixture, 92% *de*); **m.p.** 144-145 °C; $[\alpha]^{24}_{\text{D}} -164.7$ (*c* 0.2, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 8.18 (d, *J* = 8.2 Hz, 2H), 7.41-7.25 (m, 17H), 5.59 (s, 1H), 5.38 (s, 1H), 5.06 (dd, *J* = 11.9, 4.6 Hz, 2H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.56-4.55 (m, 1H), 4.41 (dd, *J* = 19.4, 11.9 Hz, 2H), 4.18-4.17 (m, 1H), 3.96 (t, *J* = 6.5 Hz, 1H), 3.59 (d, *J* = 6.5 Hz, 2H), 2.42 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 189.2, 156.2, 144.8, 137.8, 137.5, 137.2, 131.2, 130.2, 129.1, 128.6, 128.5(2), 128.4, 128.1, 128.0(2), 127.9(2), 127.7, 106.0, 81.2, 77.8, 76.6, 75.1, 75.0, 73.6, 72.4, 67.8, 21.8; **IR (neat)** 3584, 3030, 2920, 2870, 1690, 1607 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₃₆H₃₅NO₇ [M+H]⁺, 594.2414, found 594.2492.

((3R,3aR,5R,6R)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3a,5,6,7-tetrahydro-3H-pyrano[3,2-c]isoxazol-3-yl)(4-methoxyphenyl)methanone (62c)

The title compound was prepared according to the general procedure and the compound was obtained as a colourless oil (54 mg, 81% yield of diastereomer mixture,

90% *de*); $[\alpha]^{24}_{\text{D}}$ -201.8 (*c* 0.1, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.27 (d, J = 9.0 Hz, 2H), 7.41-7.25 (m, 15H), 7.14 (d, J = 9.0 Hz, 2H), 5.59 (s, 1H), 5.35 (s, 1H), 5.08-5.04 (m, 2H), 4.69 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H), 4.55-4.54 (m, 1H), 4.41 (dd, J = 19.5, 11.9 Hz, 2H), 4.19-4.18 (m, 1H), 3.96 (t, J = 6.5 Hz, 1H), 3.88 (s, 3H), 3.59 (d, J = 6.5 Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 188.1, 156.1, 137.8, 137.4, 137.2, 133.5, 128.7, 128.6, 128.5(2), 128.4, 128.1, 128.0, 127.8(2), 127.7(2), 81.1, 77.7, 76.5, 75.1, 75.0, 73.6, 72.4, 67.7, 55.5; **IR** (neat) 3418, 3030, 2926, 2874, 1682, 1599, 1090 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{36}\text{H}_{33}\text{NO}_8$ $[\text{M}+\text{H}]^+$, 610.2363, found 610.2441.

((3*R*,3*aR*,5*R*,6*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)(4-fluorophenyl)methanone (62d)

The title compound was prepared according to the general procedure and the compound was obtained as a pale yellow oil (50 mg, 78% yield of diastereomer mixture, 90% *de*); $[\alpha]^{24}_{\text{D}}$ -202.3 (*c* 0.6, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.34-8.30 (m, 2H), 7.41-7.25 (m, 15H), 7.14 (t, J = 8.6 Hz, 2H), 5.59 (s, 1H), 5.48 (s, 1H), 5.08-5.05 (m, 2H), 4.69 (d, J = 11.8 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.56-4.55 (m, 1H), 4.42 (dd, J = 19.5, 11.8 Hz, 2H), 4.19-4.18 (m, 1H), 3.97 (t, J = 6.5 Hz, 1H), 3.59 (d, J = 6.5 Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 188.0, 156.3, 137.9, 137.5, 137.2, 134.0, 133.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 115.6, 115.4, 105.8, 81.1, 77.9, 77.2, 75.1, 75.0, 73.6, 72.5, 67.8; **IR** (neat) 3582, 3030, 2924, 2855,

1688, 1599, 1364 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{35}\text{H}_{32}\text{FNO}_7$ $[\text{M}+\text{H}]^+$, 598.2163, found 598.2241.

((3*R*,3*aR*,5*R*,6*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)(4-chlorophenyl)methanone (62e)

The title compound was prepared according to the general procedure and the compound was obtained as a yellow oil (53 mg, 80% yield of diastereomer mixture, 94% *de*); $[\alpha]_D^{24}$ -165.6 (*c* 0.1, CHCl_3); **^1H NMR (400 MHz, CDCl_3):** δ 8.22 (d, J = 8.7 Hz, 2H), 7.45-7.27 (m, 17H), 5.71 (s, 1H), 5.57 (s, 1H), 5.06 (dd, J = 11.9, 4.2 Hz, 2H), 4.69 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.56-4.55 (m, 1H), 4.42 (dd, J = 20.1, 11.9 Hz, 2H), 4.20-4.19 (m, 1H), 3.97 (t, J = 6.5 Hz, 1H), 3.59 (d, J = 6.5 Hz, 2H); **^{13}C NMR (100 MHz, CDCl_3):** δ 188.4, 156.2, 140.4, 137.7, 137.4, 137.1, 132.8, 132.4, 131.1, 129.0, 128.6(2), 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 105.8, 81.0, 77.8, 76.5, 75.1, 73.5, 72.4, 67.7; **IR (neat)** 3422, 3030, 2924, 2868, 1597, 735 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{35}\text{H}_{32}\text{ClNO}_7$ $[\text{M}+\text{H}]^+$, 614.1867, found 614.1946.

[1,1'-biphenyl]-4-yl((3*R*,3*aR*,5*R*,6*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)methanone (62f)

The title compound was prepared according to the general procedure and the compound was obtained as a white solid (59 mg, 83% yield of diastereomer mixture, 90% de); **m.p.** 156-157 °C; $[\alpha]_D^{24}$ -233.7 (*c* 0.1, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 8.35 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.47 (t, *J* = 7.1 Hz, 2H), 7.42-7.25 (m, 16H), 5.62 (s, 1H), 5.28 (s, 1H), 5.07 (dd, *J* = 11.9, 2.9 Hz, 2H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.57-4.56 (m, 1H), 4.41 (dd, *J* = 19.2, 11.9 Hz, 2H), 4.19-4.18 (m, 1H), 3.98 (t, *J* = 6.4 Hz, 1H), 3.59 (d, *J* = 6.4 Hz, 2H); **¹³C NMR (100 MHz, CDCl₃):** δ 189.2, 156.1, 146.4, 140.0, 137.7, 137.4, 137.2, 132.1, 131.6, 131.5, 131.3, 128.9, 128.8, 128.5(2), 128.4, 128.2, 128.1, 128.0, 127.9, 127.8(2), 127.7(2), 127.3, 127.0, 106.0, 81.0, 77.8, 76.5, 75.1(2), 73.6, 72.4, 67.7; **IR (neat)** 3387, 3030, 2924, 2870, 1682, 1603 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₄₁H₃₇NO₇ [M+H]⁺, 656.2570, found 656.2648.

1-((3*R*,3*aR*,5*R*,6*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)-2,2-dimethylpropan-1-one (62g)

The title compound was prepared according to the general procedure and the compound was obtained as a colourless oil (41 mg, 68% yield of diastereomer mixture, 95% *de*); $[\alpha]_D^{24}$ -224.1 (*c* 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.24 (m, 19H), 5.33 (s, 1H), 5.22 (s, 1H), 5.06 (d, *J* = 11.8, 1H), 5.02 (d, *J* = 11.2, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.52-4.51 (m, 1H), 4.41 (dd, *J* = 16.2, 11.8 Hz, 2H), 4.14-4.13 (m, 1H), 3.90 (t, *J* = 6.5 Hz, 1H), 3.56 (d, *J* = 6.5 Hz, 2H), 1.33 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 205.5, 155.5, 137.9, 137.5, 137.3, 128.5(2), 128.4, 128.3, 128.0(3), 127.9(2), 127.8, 127.3, 127.2, 106.1, 81.8, 77.7, 77.2, 75.1, 73.6, 72.4, 67.8, 53.4, 43.8, 29.7, 27.7, 27.1; IR (neat) 3406, 3030, 2959, 2930, 2872, 1713, 1557, 1250 cm⁻¹; HRMS (ESI): *m/z* calcd for C₃₃H₃₇NO₇ [M+H]⁺, 560.2570, found 560.2648.

((3*R*,3*aR*,5*R*,6*S*,7*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)(phenyl)methanone (62h)

The title compound was prepared according to the general procedure and the compound was obtained as a colourless oil (52 mg, 83% yield of diastereomer mixture, 90% *de*); $[\alpha]_D^{24}$ -234.2 (*c* 0.2, CHCl₃); **¹H NMR (400 MHz, CDCl₃):** δ 8.26 (d, *J* = 7.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.41-7.19 (m, 15H), 5.60 (s, 1H), 5.57 (s, 1H), 5.05 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.62-4.59 (m, 2H), 4.49 (dd, *J* = 19.7, 11.9 Hz, 2H), 3.88-3.68 (m, 4H); **¹³C NMR (100 MHz, CDCl₃):** δ 189.5, 156.3, 137.6, 137.4, 137.4, 137.2, 133.9, 132.5, 131.0, 128.6, 128.5(2), 128.4, 128.3, 128.1(2), 128.0(2), 127.8, 127.7, 106.1, 80.8, 78.6, 78.3, 75.5, 73.5, 73.1, 68.2; **IR (neat)** 3443, 3030, 2918, 2872, 1694, 1682, 1599 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₃₅H₃₃NO₇ [M+H]⁺, 580.2257, found 580.2335.

((3R,3aR,5R,6S,7R)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3a,5,6,7-tetrahydro-3H-pyrano[3,2-c]isoxazol-3-yl)(4-methoxyphenyl)methanone (62i)

The title compound was prepared according to the general procedure and the compound was obtained as a colourless oil (54 mg, 81% yield of diastereomer mixture, 93% *de*); $[\alpha]^{24}_{\text{D}} -243.4$ (*c* 0.5, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.25 (d, *J* = 9.0 Hz, 2H), 7.41-7.19 (m, 15H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.61 (s, 1H), 5.50 (s, 1H), 5.05 (d, *J* = 11.4 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.61-4.57 (m, 2H), 4.51 (dd, *J* = 21.0, 12.0 Hz, 2H), 4.03-3.66 (m, 4H), 3.87 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 188.1, 164.2, 156.3, 137.7, 137.4, 137.3, 133.5, 128.5(3), 128.3, 128.1(2), 128.0, 127.9, 125.4, 113.7, 106.4, 80.9, 78.6, 78.5, 78.3, 76.7, 75.5, 73.5, 73.1, 68.2, 55.5; **IR** (neat) 3418, 3030, 2934, 2872, 1682, 1599, 1098 cm^{-1} ; **HRMS** (ESI): *m/z* calcd for $\text{C}_{36}\text{H}_{33}\text{NO}_8$ $[\text{M}+\text{H}]^+$, 610.2363, found 610.2441.

((3R,3aR,5R,6S,7R)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3a,5,6,7-tetrahydro-3H-pyrano[3,2-c]isoxazol-3-yl)(4-fluorophenyl)methanone (62j)

The title compound was prepared according to the general procedure and the compound was obtained as a pale yellow oil (52 mg, 81% yield of diastereomer

mixture, 93% *de*); $[\alpha]^{24}_{\text{D}}$ -155.4 (*c* 0.5, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.33-8.29 (m, 2H), 7.40-7.13 (m, 17H), 5.60 (s, 1H), 5.51 (s, 1H), 5.04 (d, $J = 11.4$ Hz, 1H), 4.94 (d, $J = 10.8$ Hz, 1H), 4.68 (d, $J = 11.4$ Hz, 1H), 4.61-4.58 (m, 2H), 4.48 (dd, $J = 19.5, 11.90$ Hz, 2H), 3.95-3.72 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 188.0, 165.0, 156.4, 137.6, 137.3, 137.2, 134.0, 133.9, 129.0, 128.6, 128.5(2), 128.3, 128.1(2), 128.0, 127.9, 115.7, 115.5, 106.3, 80.6, 78.6, 78.5, 78.2, 75.6, 73.5, 73.1, 68.2; **IR** (*neat*) 3383, 3030, 2957, 2922, 2870, 1599, 1099 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{35}\text{H}_{32}\text{FNO}_7$ $[\text{M}+\text{H}]^+$, 598.2163, found 598.2241.

[1,1'-biphenyl]-4-yl((3*R*,3*aR*,5*R*,6*S*,7*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)methanone (62k)

The title compound was prepared according to the general procedure and the compound was obtained as a colourless oil (56 mg, 79% yield of diastereomer mixture, 92% *de*); $[\alpha]^{24}_{\text{D}}$ -173.0 (*c* 0.1, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.34 (d, $J = 8.4$ Hz, 2H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 7.3$ Hz, 2H), 7.46 (t, $J = 7.3$ Hz, 2H), 7.41-7.19 (m, 16H), 5.63 (s, 1H), 5.52 (s, 1H), 5.05 (d, $J = 11.4$ Hz, 1H), 4.94 (d, $J = 10.8$ Hz, 1H), 4.68 (d, $J = 11.4$ Hz, 1H), 4.63-4.57 (m, 2H), 4.48 (dd, $J = 20.6, 11.9$ Hz, 2H), 3.95-3.75 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 189.2, 156.4, 146.5, 139.9, 137.7, 137.5, 137.3, 131.8, 131.6, 131.3, 129.0, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1(2), 128.0, 127.9, 127.4, 127.2, 127.1, 126.7, 106.3, 80.9, 78.7,

78.6, 78.3, 75.6, 73.5, 73.1, 68.2; **IR (neat)** 3420, 3030, 2922, 2870, 1684, 1603 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{41}\text{H}_{37}\text{NO}_7$ $[\text{M}+\text{H}]^+$, 656.2570, found 656.2648.

1-((3*R*,3*aR*,5*R*,6*R*)-6,7-bis(benzyloxy)-5-((benzyloxy)methyl)-3-hydroxy-3*a*,5,6,7-tetrahydro-3*H*-pyrano[3,2-*c*]isoxazol-3-yl)-2,2-dimethylpropan-1-one (62l)

The title compound was prepared according to the general procedure and the compound was obtained as a pale yellow oil (42 mg, 70% yield of diastereomer mixture, 92% *de*); $[\alpha]_D^{24}$ -176.3 (*c* 0.1, CHCl_3); **^1H NMR (400 MHz, CDCl_3):** δ 7.38-7.25 (m, 19H), 5.31 (s, 1H), 5.06-5.03 (m, 1H), 4.92 (d, $J = 10.8$ Hz, 1H), 4.67-4.47 (m, 7H), 3.84-3.73 (m, 3H), 1.34 (s, 6H), 1.20 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 205.3, 155.6, 137.6, 137.4, 137.2, 128.5, 128.4(2), 128.2(2), 128.1, 128.0, 127.9, 127.8(2), 127.7(2), 106.3, 81.3, 78.6, 78.5, 78.4, 75.5, 73.4, 73.3, 72.9, 72.2, 72.1, 68.2, 43.7, 27.7, 27.1, 25.9, 25.6; **IR (neat)** 3391, 3030, 2959, 2930, 2872, 1713, 1557, 1059 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{33}\text{H}_{37}\text{NO}_7$ $[\text{M}+\text{H}]^+$, 560.2570, found 560.2648.

4.3 X-ray spectra of carbohydrate-integrated isoxazolines (62b)

Table 1. Crystal data and structure refinement.

Identification code	Compound 3b	
Empirical formula	C ₃₆ H ₃₅ N O ₇	
Formula weight	593.65	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	$a = 10.4039(4) \text{ Å}$ $b = 11.4624(4) \text{ Å}$ $c = 12.6741(4) \text{ Å}$	$\alpha = 90^\circ$. $\beta = 91.861(2)^\circ$. $\gamma = 90^\circ$.
Volume	$1510.64(9) \text{ Å}^3$	
Z	2	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	628	
Crystal size	$0.40 \times 0.38 \times 0.26 \text{ mm}^3$	
Theta range for data collection	1.61 to 33.16° .	
Index ranges	$-15 \leq h \leq 15$, $-16 \leq k \leq 17$, $-19 \leq l \leq 19$	
Reflections collected	37285	
Independent reflections	5923 [R(int) = 0.0371]	
Completeness to theta = 33.16°	98.6 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9769 and 0.9647
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5923 / 264 / 472
Goodness-of-fit on F ²	1.080
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.1015
R indices (all data)	R1 = 0.0507, wR2 = 0.1139
Largest diff. peak and hole	0.535 and -0.412 e.Å ⁻³

4.4 Gaussian Calculations^[43]

0 1			
C	-1.04307900	-2.79705000	-0.93814800
C	0.18429600	-3.12224700	-1.40884300
H	0.44501700	-4.12765800	-1.70959100
O	1.19881100	-2.23878300	-1.58880100
C	-1.41655300	-1.40669000	-0.51830100
H	-2.44857000	-1.18000100	-0.80296500
C	-0.45595800	-0.44164000	-1.23978700
H	-0.69645700	-0.48665800	-2.31363100
N	-2.01917700	-3.84774100	-0.81477900
O	-3.20154000	-3.52068900	-0.49218900
O	-1.66302000	-5.04628700	-1.04905200
O	-1.28936900	-1.35873300	0.93595200
O	-0.67107000	0.90741600	-0.75004900
C	1.02167900	-0.84859000	-1.06575900
H	1.65517100	-0.26362500	-1.73639300
C	-2.02427100	-0.29130500	1.65782300
H	-1.80052300	-0.53640300	2.70011400
H	-1.58491400	0.67671600	1.41050100
C	-0.44428700	1.97753700	-1.74190300
H	0.60214000	1.95548100	-2.07297100
H	-1.08763300	1.79070200	-2.61167600
C	-3.51351800	-0.27667600	1.41107600
C	-4.29713000	-1.41700900	1.66008400
C	-4.13937500	0.89386700	0.95149500
C	-5.67957300	-1.38238000	1.46095800
H	-3.81722800	-2.33375400	1.98411800
C	-5.52603300	0.93243600	0.76180000
H	-3.53644100	1.77382000	0.74507600
C	-6.29829800	-0.20604200	1.01679700
H	-6.27295900	-2.27142200	1.64829500
H	-5.99981500	1.84503600	0.41276200
H	-7.37323200	-0.18026700	0.86680700
C	-0.77309900	3.29214600	-1.09248500
C	-2.07387000	3.81660700	-1.16607700
C	0.20536700	3.99453400	-0.37125600
C	-2.38976800	5.02362200	-0.53347900
H	-2.83698700	3.27820300	-1.72086200
C	-0.10748400	5.20098700	0.26281000

H	1.21335800	3.59419200	-0.30712400
C	-1.40643700	5.71744700	0.18217200
H	-3.39684600	5.42236300	-0.60048500
H	0.65758800	5.73646200	0.81562600
H	-1.65007200	6.65502300	0.67139600
C	1.56286700	-0.76844600	0.36294900
H	1.15603900	-1.57298200	0.97388600
H	1.25583100	0.18955000	0.80229000
O	3.00609500	-0.91552300	0.39540600
C	3.76008800	0.30273200	0.14470800
H	3.37790800	1.09875100	0.80748400
H	3.62175700	0.64698400	-0.89222400
C	5.22522500	0.04651500	0.40837100
C	6.19949000	0.80530600	-0.25878700
C	5.63013600	-0.91599900	1.34530000
C	7.55844100	0.61541200	0.01352100
H	5.89621000	1.54338700	-0.99748400
C	6.98954100	-1.11158700	1.61098600
H	4.87590000	-1.51490600	1.84105100
C	7.95714800	-0.34502400	0.95041300
H	8.30217500	1.20788300	-0.51036300
H	7.29296800	-1.86405000	2.33234700
H	9.01134100	-0.49862400	1.15871200

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C	0.07360600	0.07684600	-0.68136200
C	-0.91937100	-0.30167200	-1.53061800
H	-0.75073200	-0.46808100	-2.58613700
O	-2.18205300	-0.56040300	-1.14929000
C	-0.17391300	0.38447100	0.77292200
H	0.12769500	-0.45419800	1.41639400
C	-1.69571900	0.64684200	0.95177800

H	-1.92539200	0.68809800	2.02716900
C	-2.51261100	-0.47352800	0.31045600
H	-2.25150300	-1.44955100	0.73468300
O	0.59921100	1.55925300	1.12878400
C	0.90022200	1.74288900	2.56674700
H	1.54090400	2.62754200	2.55049500
H	-0.02282600	1.99781400	3.10446400
C	1.58560600	0.57767500	3.23716900
C	2.86082000	0.15800300	2.81755800
C	0.96827800	-0.08510300	4.31129400
C	3.50489500	-0.89968600	3.46517400
H	3.33744500	0.65310700	1.97905500
C	1.61374400	-1.14249900	4.96338300
H	-0.01417400	0.23760200	4.64791400
C	2.88316400	-1.55026800	4.54012800
H	4.48790100	-1.21319200	3.13029700
H	1.12906000	-1.64228400	5.79609600
H	3.38755200	-2.36803300	5.04504900
O	-2.14864200	1.84937700	0.28867500
C	-1.92770300	3.14756700	0.95983500
H	-0.88709100	3.44261700	0.81813700
C	-4.01230700	-0.27258100	0.38674700
H	-4.28783700	0.06810000	1.39728100
H	-4.31369000	0.49748100	-0.33181200
O	-4.61964300	-1.55075100	0.09515400
C	-6.05368100	-1.48981000	-0.16486600
H	-6.59136100	-1.18655900	0.74595500
H	-6.23842900	-0.72003400	-0.93219400
C	-6.52299900	-2.84363600	-0.63489900
C	-5.74156400	-3.59598300	-1.52669100
C	-7.76254700	-3.34899300	-0.21596000
C	-6.19772200	-4.83266700	-1.99217700
H	-4.77492000	-3.21200900	-1.83266000
C	-8.22356800	-4.58286200	-0.68942300
H	-8.36763100	-2.77895400	0.48421500
C	-7.44128700	-5.32781200	-1.57844100
H	-5.58464500	-5.40992300	-2.67731000
H	-9.18472100	-4.96347200	-0.35829800
H	-7.79451200	-6.28738600	-1.94264500
H	-2.12058400	3.02267000	2.03531400
C	-2.87922600	4.14125300	0.35393300
C	-4.18610600	4.27712700	0.84998800
C	-2.48279700	4.92381600	-0.74210100
C	-5.07918800	5.18069300	0.26639000
H	-4.50116100	3.67673000	1.69946000
C	-3.37412200	5.82744000	-1.32991600
H	-1.47504100	4.82163700	-1.13400300
C	-4.67375800	5.95746000	-0.82620800
H	-6.08470100	5.28206000	0.66246500
H	-3.05585500	6.42833500	-2.17572100

H	-5.36483600	6.66119500	-1.27919000
N	1.38994500	0.13561600	-1.21601400
O	2.37790100	0.03066100	-0.42076300
O	1.54542200	0.25745700	-2.48135500
C	5.50479800	0.47538100	-2.70595600
N	4.39719100	1.01993700	-3.28303200
H	3.44775300	0.78712100	-3.00594000
S	7.06395000	0.77664000	-3.41830800
N	5.22284000	-0.26579600	-1.58661900
H	4.25158100	-0.22676900	-1.28029400
C	6.02323700	-1.09733800	-0.76373400
C	5.32143700	-1.89788900	0.16371800
C	7.42662300	-1.16969900	-0.80248400
C	6.00636300	-2.75411600	1.02649100
H	4.23675100	-1.84924900	0.19679300
C	8.09846200	-2.03516300	0.06833600
H	7.97319100	-0.56022800	-1.50645900
C	7.40425400	-2.83101000	0.98454600
H	5.44455600	-3.37004400	1.72272100
H	9.18233000	-2.08034300	0.02400700
H	7.93904100	-3.49985300	1.65112900
H	4.54335200	1.59790700	-4.09401100

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C	-0.22724000	-1.47029900	-0.67944100
C	0.64286600	-2.38048800	-1.19654800
H	0.34385400	-3.38318500	-1.47154700
O	1.94020600	-2.13018800	-1.45555200
C	0.18573300	-0.08192500	-0.28479600
H	-0.60220700	0.64291700	-0.51240900
C	1.44839800	0.26518800	-1.09804200
H	1.14397600	0.34373300	-2.15378000
N	-1.56983300	-1.88396900	-0.46293600
O	0.42054700	-0.12211200	1.15305400
O	1.96902200	1.53892300	-0.64499100
C	2.53151600	-0.82765800	-0.99426500
H	3.31606300	-0.65839700	-1.73467300
C	0.38314200	1.16528700	1.89894500
H	0.53025300	0.82448400	2.92713800
H	1.23217700	1.77806100	1.59180100

C	2.63781900	2.35178800	-1.68571800
H	3.51789000	1.81256100	-2.05868400
H	1.93761100	2.49500300	-2.51872200
C	-0.90921400	1.92857700	1.75511600
C	-2.12559300	1.36905400	2.18516600
C	-0.90890600	3.22153000	1.20593900
C	-3.31592200	2.09317100	2.07752100
H	-2.13573200	0.36296300	2.59159100
C	-2.09976500	3.95107300	1.10412800
H	0.02712100	3.65435100	0.86451600
C	-3.30415300	3.38821600	1.54006300
H	-4.25050100	1.65168200	2.40666800
H	-2.08687100	4.95304500	0.68618800
H	-4.22951100	3.95015700	1.46282700
C	3.03206700	3.66414400	-1.07114000
C	2.16776900	4.76933200	-1.13626200
C	4.25496100	3.79307800	-0.39322700
C	2.52084800	5.98291900	-0.53677000
H	1.22067400	4.67848200	-1.66069700
C	4.60993800	5.00459200	0.20769700
H	4.92920700	2.94294600	-0.33753000
C	3.74265200	6.10162800	0.13655700
H	1.84828400	6.83227700	-0.59744900
H	5.55869000	5.09406000	0.72667600
H	4.01859500	7.04338300	0.59965900
O	-1.88808500	-3.10812500	-0.65493100
O	-2.42195200	-1.01085900	-0.09625800
N	-5.45972700	-1.74386400	-0.17093800
N	-4.70721300	-3.86018100	0.24576400
H	-4.88297100	-4.81274700	0.51920900
H	-3.76771000	-3.58999300	-0.03021200
H	-4.46147100	-1.54044800	-0.17638100
C	-5.78690200	-3.03363700	0.16257100
S	-7.36997200	-3.67166800	0.50338600
C	-6.25347500	-0.60411500	-0.45695000
C	-5.55887200	0.62061200	-0.55027700
C	-7.64090000	-0.62159000	-0.68253600
C	-6.23661200	1.80088500	-0.85555500
H	-4.48707700	0.64276900	-0.37772600
C	-8.30625300	0.57134000	-0.98592800
H	-8.18449400	-1.55139600	-0.60921000
C	-7.61946800	1.78636000	-1.07465900
H	-5.67981400	2.73106600	-0.91939100
H	-9.37831500	0.54139700	-1.15526300
H	-8.14976300	2.70356400	-1.31008100
C	3.15300200	-1.02335300	0.39006900
H	2.44294300	-1.49677900	1.06700000
H	3.41390800	-0.03774100	0.79741700
O	4.31327500	-1.88913700	0.33059300
C	5.56716300	-1.22431100	-0.00212500

H	5.69618600	-0.36114100	0.67326400
H	5.54539400	-0.83498200	-1.03183600
C	6.70601100	-2.20287800	0.15329300
C	7.84546600	-2.08720500	-0.65760600
C	6.66077700	-3.20697900	1.13260300
C	8.93104300	-2.95290700	-0.48586900
H	7.88319700	-1.32154400	-1.42859700
C	7.74233400	-4.07811700	1.29775900
H	5.77051600	-3.30834900	1.74171900
C	8.88162100	-3.95145300	0.49338300
H	9.80644300	-2.85387300	-1.12007000
H	7.69523000	-4.85643000	2.05303700
H	9.71999500	-4.62829700	0.62425500

O 1			
C	0.58973800	0.24243600	-0.90457900
C	0.20609200	1.46704200	-1.35675100
H	0.91369500	2.23036600	-1.65205800
O	-1.07528600	1.84701300	-1.52162000
C	-0.38938700	-0.81341200	-0.48308000
H	-0.03492200	-1.80944900	-0.76584300
C	-1.71958800	-0.51889600	-1.20233300
H	-1.55675400	-0.69259300	-2.27836400
N	1.98027000	-0.02319700	-0.78373900
O	-0.49637300	-0.72099700	0.96834000
O	-2.72379500	-1.43718500	-0.70939400
C	-2.16965000	0.94580300	-1.02021200
H	-2.98852300	1.18293700	-1.70243500
C	-0.94087900	-1.93979500	1.69872200
H	-0.93225200	-1.58995500	2.73417500
H	-1.96357700	-2.17748100	1.40162500
C	-3.82384800	-1.74491200	-1.64949200
H	-4.45649500	-0.85777500	-1.77670100
H	-3.38517700	-2.00427100	-2.62235800
C	-0.03161600	-3.12766800	1.51253900
C	1.30485900	-3.08066300	1.94720800
C	-0.51136700	-4.30147500	0.90839000
C	2.14118100	-4.18825900	1.78900000
H	1.68667900	-2.17098900	2.39949900
C	0.32437000	-5.41444200	0.75393100
H	-1.54192600	-4.34109200	0.56582600

C	1.65106600	-5.35925400	1.19435800
H	3.17072500	-4.14054900	2.12911800
H	-0.05831400	-6.31917900	0.29173800
H	2.30028200	-6.22112700	1.07626900
C	-4.61309100	-2.89066000	-1.08307400
C	-4.20218000	-4.21489000	-1.31081600
C	-5.74790000	-2.65469100	-0.29168400
C	-4.91480400	-5.28373500	-0.75890600
H	-3.32591200	-4.40561800	-1.92404500
C	-6.46289500	-3.72219700	0.26143000
H	-6.07178000	-1.63372000	-0.10972800
C	-6.04690000	-5.03819600	0.02852500
H	-4.59242000	-6.30301600	-0.94499500
H	-7.34044200	-3.52849800	0.86957400
H	-6.60230000	-5.86727500	0.45478600
O	2.82388400	0.91704700	-0.98867200
O	2.34130900	-1.20694200	-0.48613900
N	5.34034200	-1.71040400	-0.33643000
N	5.83580300	0.52038400	-0.29021400
H	4.84402800	0.59879500	-0.51073500
H	4.34962800	-1.50397300	-0.41946100
C	6.31015300	-0.76189500	-0.20044500
S	7.95557700	-1.27756000	0.04662500
H	5.63808200	-2.67114300	-0.30371500
C	6.46186500	1.78729100	-0.16163300
C	5.62680400	2.90494300	-0.37699500
C	7.81235900	1.99710700	0.16651500
C	6.13053200	4.20051500	-0.26961400
H	4.58149500	2.74939300	-0.62757700
C	8.30216500	3.30398200	0.27021200
H	8.46120100	1.15020200	0.33105500
C	7.47629100	4.41126100	0.05511700
H	5.46986100	5.04525100	-0.44009100
H	9.34797100	3.44923600	0.52351500
H	7.87111200	5.41868800	0.13851100
C	-2.54027700	1.35590900	0.40600500
H	-1.64983800	1.42041400	1.03014100
H	-3.20075700	0.58802400	0.82976100
O	-3.16660200	2.66186200	0.43396200
C	-4.60706800	2.66550000	0.21285900
H	-5.07139200	1.94951000	0.91250900
H	-4.84947900	2.33049600	-0.80784100
C	-5.14193100	4.05938700	0.43731200
C	-6.28689600	4.48901300	-0.25117200
C	-4.53292000	4.92289800	1.36050500
C	-6.82501300	5.75821800	-0.01314200
H	-6.75715600	3.83228200	-0.97903500
C	-5.06588700	6.19531400	1.59124700
H	-3.63626600	4.59651800	1.87343800
C	-6.21465100	6.61532000	0.90966000

H	-7.71058200	6.07924800	-0.55266500
H	-4.58346700	6.85911800	2.30192300
H	-6.62663400	7.60292000	1.09140000

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C	-1.81590200	0.15950300	0.13130000
S	-3.42908900	-0.37027000	-0.21971400
N	-1.57188400	1.30267600	0.82027000
H	-2.36672500	1.83908700	1.12633500
H	-0.64650800	1.57659800	1.11637700
N	-0.73758600	-0.58990300	-0.26713600
H	-0.99685000	-1.47832400	-0.67404800
C	0.65340900	-0.29684400	-0.15297500
C	1.52556400	-1.31977500	0.25691000
C	1.17432500	0.96556000	-0.49030700
C	2.89948100	-1.08037200	0.33635400
H	1.12009500	-2.29185900	0.51959300
C	2.54931700	1.20161800	-0.38619400
H	0.51474000	1.74033500	-0.86517000
C	3.41660200	0.18353900	0.02535000
H	3.56419400	-1.87809200	0.65139300
H	2.94311000	2.17804000	-0.64944700
H	4.48287000	0.36975400	0.09582700

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C	1.53751500	-0.76372900	-0.47114200
C	2.38368300	-1.70448700	-0.97175100
H	2.05399600	-2.69055200	-1.27154800
O	3.69952200	-1.50316300	-1.17375100

C	1.99021900	0.60317000	-0.05670100
H	1.24462300	1.35412500	-0.33846900
C	3.31154200	0.90608100	-0.78488600
H	3.08243600	1.02681700	-1.85558700
N	0.17195200	-1.10517000	-0.28445100
O	2.15720400	0.59261700	1.38802500
O	3.84895900	2.13936700	-0.25553400
C	4.32818000	-0.24399600	-0.63876700
H	5.16794600	-0.10207400	-1.32165200
O	-0.22633600	-2.28916700	-0.55040800
O	-0.61917300	-0.19759500	0.13783600
N	-3.68134600	-0.58798400	0.03625500
N	-3.19431100	-2.82006700	0.09358800
H	-3.49016100	-3.77712100	0.19135700
H	-2.21481800	-2.62222200	-0.08611800
H	-2.66660800	-0.50643200	0.07064900
C	-4.16697700	-1.86670800	0.13488400
S	-5.82553300	-2.35607600	0.32873500
C	-4.33141200	0.67020500	-0.03773000
C	-3.51455300	1.80081000	0.17379900
C	-5.69058500	0.85630900	-0.34318300
C	-4.04557500	3.08773100	0.08828100
H	-2.46309000	1.66120200	0.40795700
C	-6.20949400	2.15319400	-0.42107900
H	-6.32597900	-0.00173300	-0.50299900
C	-5.40126200	3.27440000	-0.20763900
H	-3.39985200	3.94433200	0.25762400
H	-7.26207800	2.28080000	-0.65467300
H	-5.81820600	4.27439500	-0.27024100
C	4.84189800	-0.50164600	0.77944900
H	4.06106900	-0.93912700	1.40050200
H	5.13067100	0.45956600	1.22385800
O	5.94541800	-1.43982700	0.77831200
C	7.24932200	-0.85243300	0.53221700
H	7.32965000	-0.41509700	-0.47379400
H	7.48331100	-0.07873500	1.27679300
H	7.96586700	-1.66966600	0.61836500
C	1.76258900	1.82303600	2.07452800
H	2.38877300	2.66134200	1.76007400
H	0.70480400	2.04055000	1.88528000
H	1.90824100	1.61762300	3.13538900
C	4.65909500	2.91857400	-1.18602000
H	4.08813300	3.16643000	-2.08971400
H	4.91773900	3.83339100	-0.65335200
H	5.57814600	2.39103400	-1.46862300

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C	1.64003800	-0.59332900	-0.05263600
C	2.57390000	-1.57078300	-0.21496000
H	2.32464500	-2.62359500	-0.20013300
O	3.87335000	-1.33677700	-0.45412300
C	1.99483200	0.87219100	0.02100400
H	1.76779500	1.37873600	-0.92848800
C	3.51678400	0.98947500	0.30560900
H	3.81730000	2.03588000	0.14812800
C	4.31596500	0.08639700	-0.63154500
H	4.11912500	0.32910100	-1.68195800
O	1.28878500	1.53072000	1.10229600
O	3.87502300	0.55380100	1.63335300
C	5.81027700	0.09450700	-0.38612500
H	6.14834500	1.12475000	-0.19095800
H	6.03830300	-0.51589300	0.49488400
O	6.43350400	-0.42875600	-1.58019300
N	0.28210000	-0.99385500	0.01763800
O	-0.61431100	-0.10472900	-0.16681200
O	-0.01070400	-2.21961300	0.22981300
C	-4.03541700	-1.95707600	0.24567400
N	-3.02354400	-2.84102600	0.46887400
H	-2.03798900	-2.60427200	0.40404600
S	-5.68375000	-2.50909900	0.32852900
N	-3.60130200	-0.69105700	-0.04986900
H	-2.59076300	-0.57350200	-0.10620500
C	-4.31442300	0.49848900	-0.34910800
C	-3.61229100	1.47949800	-1.07905100
C	-5.62740500	0.76731000	0.07290500
C	-4.21110100	2.70274900	-1.38340000
H	-2.60195000	1.26746500	-1.41702000
C	-6.21812700	1.99448000	-0.24690900
H	-6.17410800	0.01998800	0.62854000
C	-5.52248800	2.96811900	-0.97148500
H	-3.65629000	3.44329900	-1.95190800
H	-7.23472700	2.18699800	0.08186800
H	-5.99338200	3.91553700	-1.21309800
H	-3.28525700	-3.78866100	0.68419000

C	0.40797700	2.63258400	0.71806700
H	-0.40833300	2.27383700	0.08791200
H	0.00755600	3.01790200	1.65584300
H	0.96883500	3.42561600	0.20657000
C	3.70647000	1.49831300	2.73583300
H	2.65775500	1.58468900	3.01677300
H	4.29729900	1.08595800	3.55501900
H	4.09857100	2.48729800	2.46103600
C	7.85354300	-0.68505100	-1.43602200
H	8.18590900	-1.08550300	-2.39391800
H	8.40789600	0.23769000	-1.21267800
H	8.04632300	-1.42056800	-0.64319100

Calculation 1:

Calculation 2:

Calculation 3:

Calculation 4:

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CHAPTER 3

Synthesis of Arabinosylated Glycerol Dimycolate From Mycobacteria

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Synthesis of Arabinosylated Glycerol Dimycolate From Mycobacteria

1. Introduction

1.1 *Mycobacterium tuberculosis* and *Mycobacterium marinum*

Despite the accessibility to cheap and efficient treatment, tuberculosis (TB) remains a serious problem as it accounts for millions of deaths throughout the world.^[1] TB is a highly contagious and infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), an aerobic pathogenic bacterium that primarily attacks the lungs, and was first identified by Dr Koch in 1882.^[2] The increase in drug resistance and drug sensitivity issues result in a need to better understand the immunopathogenesis in order to identify new and more effective drugs.

There are two main reasons that could explain and justify the difficulties of eradicating this disease. Firstly, the cell wall of the *M. tuberculosis* is highly hydrophobic, resulting in low permeability of the membrane which acts as a barrier to drug treatment.^[3] Secondly, the presence of drug-modifying and hydrolytic enzymes, such as amino-glycoside acetyl-transferases and periplasmic β -lactamases, in *M. tuberculosis* makes them resistant to numerous chemotherapeutic agents and antibiotics.^[4] Different drugs have been developed to treat TB and they are classified into first-line drugs such as rifampicin, isoniazid, streptomycin (high efficacy, relative toxicity) and second-line drugs such as ethionamide and cycloserine (lower efficacy and more toxic) (Figures 1 and 2). Among these drugs, isoniazid (first-line) possesses the best anti-bactericidal activity. However, a major shortcoming of this drug is the high degree of toxicity and hence, causes fever as a side effect.^[5]

Figure 1. First-line drugs for TB treatment

Figure 2. Second-line drugs for TB treatment

Mycobacterium marinum (*M. marinum*) was first isolated in 1926 from a diseased fish by Joseph D. Aronson. Following which, several studies were conducted and *M. marinum* was revealed to be very closely linked to *Mycobacterium ulcerans* (nucleotide identity of >97%) and *M. tuberculosis* (nucleotide identity of >85%).^[6] The infection of *M. marinum* in humans is termed aquarium or fish tank granuloma.

When scratches and cuts on the skin get into contact with a diseased fish or polluted aquatic environments, *M. marinum* is introduced into the body.^[7] This phenomenon of granulomatous infection is typically limited to soft tissues and is pathologically indistinguishable from *M. tuberculosis*.

M. marinum disease can be efficiently treated with anti-tuberculosis agents, such as rifampicin and ethambutol (Figure 1) in addition to other agents, which include clarithromycin and doxycycline (Figure 3).

Figure 3. Examples of agents for the treatment of *M. marinum* disease

M. marinum is highly adaptable and is able to survive in intracellular environments (vertebrate hosts and amoeba) as well as fluctuating extracellular conditions. In addition, it was discovered that *M. marinum* induced diseases in fish and frogs share important similarities with *M. tuberculosis* in humans. Firstly, when infected with the disease, both mycobacteria cause granuloma formation. Secondly, they can also exist as latent infection - existing in dormant form in the organism without causing diseases.^[8] Lastly, both mycobacteria are facultative anaerobes and display a wide range of *in-vitro* metabolism. Therefore, infection of *M. marinum* in a natural host could be used as an effective model to examine human tuberculosis.

Indeed, recent reports of using *M. marinum* infected zebrafish as a model has been relatively successful.^[9]

1.2 Mycobacterial cell wall

Mycobacteria are usually classified as gram-positive. However, in contrast to gram-positive and gram-negative bacteria, they possess an uncommon and unique lipid-rich cell wall (Figure 4).^[10] The role of the cell wall of mycobacteria^[11] is to act as a barrier for many molecules and antibiotics. In addition, it also offers protection by aiding the bacteria to survive in infected macrophages with harsh environment. This uncommon cell wall provides the bacteria with a distinctive acid fast-staining property hence, cells are resistant to decolourization of acid-alcohol when stained with a dye. As the cell wall is the outermost component of mycobacteria, it allows efficient interaction with the host cell and is largely responsible for immune virulence and modulation.

Figure 4. Illustration of the mycobacteria cell wall^[12]

Over the years, various drugs have been developed with the aim of interfering with the biosynthetic pathways of the mycobacterial cell wall. For example, ethambutol acts on the enzyme arabinosyltransferase, which is involved in the arabinan biosynthesis of the cell wall while isoniazid acts on the enoyl-ACP reductase which is essential for the biosynthesis of mycolic acids.^[13] Taking into consideration all of the above, a thorough and deep understanding of the biosynthesis and structure of the cell wall will be extremely beneficial to the development of new anti-mycobacterial drugs, as well as increase our knowledge of mycobacterium and host cell interactions to aid future development in this area.

One of the major components of the mycobacterial cell wall is mycolic acids which compose of a class of long alpha-alkyl and beta-hydroxy chains of fatty acids (C₇₀-C₉₀). Mycolic acids provide the organisms with better resistance to chemical dehydration and damage, as well as prevent the activity of hydrophobic antibiotics. Moreover, they permit the bacterium to readily cultivate inside macrophages, successfully concealing it from the immune system of the host. Mycolic acids in the mycobacterial cell wall can be classified into three main categories, namely, the α -mycolates (most abundant), the keto-mycolates and the methoxy-mycolates.^[14] They are generally linked to glycolipids which are extractable or connected to the insoluble backbone of arabinogalactan-peptidoglycan to generate mycolyl-arabinogalactan-peptidoglycan (mAGP).

1.3 Glycolipids containing mycolic acids

A diverse range of glycolipids that adopts crucial roles in the regulation of the immune system uses mAGP as the anchoring matrix. Among these glycolipids, the immunological properties and structures of the glucose-monomycolate (GMM),

trehalose-dimycolates (TDM) and glycerol-monomycolate (GroMM) have been extensively examined. For example, TDM is considered one of the glycolipids with the highest granulomatogenic activity and bioactivity, which acts as an immunologic adjuvant and adopts an important role in mycobacterial virulence.^[15] In addition, through other earlier studies, glycolipids have also been shown to play crucial roles in biofilm formation and sliding motility. A report by Rombouts and group in 2009 indicates that lipooligosaccharides (LOSs) from *M. marinum* might be essential cell wall glycolipids to inhibit tumor necrosis in human macrophages.^[16]

In the 1990s, another amphipathic and hydrophobic glycolipid that comprises of mycolic acids was uncovered. This glycolipid is characterized as dimycolyl-diarabino-glycerol (DMAG), and is located in both *M. kansasii* and *M. avium-intracellulare* complex (Figure 5). Most recently, DMAG has also been discovered to be present in mycobacterial cell walls of *M. bovis* (BCG), *M. scrofulaceum*, *M. tuberculosis* and *M. marinum*. The exploration of DMAG led to interesting discoveries that suggest exciting potentials of this glycolipid. When anti-tuberculosis agents that hinder mycolate and mAGP biosynthesis were introduced, DMAG production was altered in *M. marinum*, leading to the speculation that DMAG and mAGP might be connected *via* a metabolic relationship. Furthermore, patients infected with *M. avium* were found to possess anti-DMAG antibodies, suggesting that DMAG is released or produced during infection as an immunogenic compound.

Through structural analysis, DMAG extracted from *M. bovis* BCG is detected to have similar structures with the end-terminal of mycolyl-arabinogalactan-peptidoglycan, signifying the possibility of using this glycan as a target for DMAG. In addition, the immunostimulatory activities of glycerol monomycolate (GroMM) and

arabino-mycolates from *M. bovis* BCG have been suggested to improve the activity of novel vaccine formulations.

Figure 5. Structure of DMAG from *M. marinum*

1.4 DMAG from *M. marinum*

Although there are great potentials of DMAG (as mentioned above), investigation on the immunomodulatory aspects of DMAG and the interaction of DMAG with immune receptors of hosts have been scarce. It is therefore of utmost interests among researchers to identify the role of DMAG in mycobacterial pathogenesis. Subsequently, a very recent study by Ellass-Rochard and coworkers unveiled some of the biological properties of DMAG through examining its ability to regulate immune response of macrophages.^[17] They also analyzed the recognition of macrophages to DMAG by investigating this phenomenon at the molecular level. The results showed that DMAG from *M. marinum* has wide inflammatory activity, thus indicating the possibility of DMAG as an active glycoconjugate that drives pathogen-host interactions, regulates immune response of hosts and contributes to the immunopathogenesis of infections.

Subsequent investigation of the *M. marinum* infection is substantially aided by the use of zebrafish embryos. The DMAG from *M. marinum* is first conjugated with

fluorescent beads, then through injection into zebrafish, gathering of phagocytes and formation of granuloma could be freely visualized by fluorescence microscopy and plate fluorimetry.^[18] Zebrafish larvae are relatively small in size and optically transparent, which permits fast analysis of bacteria-host response to manipulations. As such, zebrafish infected with *M. Marinum* are very useful for studying tuberculosis pathogenesis and identifying novel antituberculosis drugs.^[19]

1.5 Aim of the project

Inspired by the numerous potentials and benefits of DMAG from *M. marinum*, the aim of this project is to synthesize this glycolipid to study its role in the host immune response. We envisioned that this cell wall glycoconjugate would drive host-pathogen interactions and contribute to the immunopathogenesis of mycobacterial infections. The structure of DMAG consists of two arabino sugars, coinciding with our previous reports of extensive research done on carbohydrates. As such, by employing Mitsunobu conditions for the synthesis of 2,3-anhydrosugars, followed by epoxide-ring opening through sodium benzyolate, as well as our recent work on selective arabinofuranosylation, we would be able to develop a general and efficient route to the synthesis of arabinosides. Subsequent attachment of the mycolic acids to the arabinosides will result in arabinosylated glycolipids, which can then be examined for their biological activities and roles in mycobacterial infections.

2. Introduction to key methodology for the synthesis of DMAG

Our group has been actively researching on new methodologies and synthetic strategies of carbohydrates.^[20] Over the years, we have reported a number of synthetic methods generating excellent results. The development of glycosylation methods has always been of great interests and many groups have attempted to produce strategies that bring about high selectivities. To date, several different methods have been reported on various carbohydrates and many furnished good to excellent selectivities. However, upon closer examination of such reports, it is noticeable that a large number of them focus on pyranose glycosides. Therefore, there is a need to direct the attention towards furanosylation. As mentioned in the previous sections, glycoconjugates play critical roles in mycobacterial infections. The mycobacterial cell walls contain many arabinofuranoside residues hence, the progress of arabinofuranosylation^[21] would be extremely beneficial for the investigation of the pathogenesis of mycobacterial infections.

In 2010, Imamura reported a β -selective glycosylation of arabinofuranosides (Scheme 1).^[22] Using 2,3-*O*-xylylene-protected D-arabinofuranose donor as the starting material, a range of arabinofuranosides were afforded in good to excellent selectivities of 12.6-4.8:1 (β : α). It was discovered that for this reaction, the selectivity of the desired products is highly dependent on the reaction conditions. Noteworthy, among all the glycosyl donors tested, the 5-*O*-PMB donor produced the best result. This novel methodology was further applied to synthesize an arabinan fragment from mycobacterial, showcasing the synthetic applicability of this methodology.

Scheme 1. β -Selective arabinofuranosylation

3. Synthesis of DMAG

3.1 Retrosynthesis of DMAG

The retrosynthetic scheme is illustrated in Scheme 2. As shown in Scheme 2, the target molecule can be constructed from **18** by esterification with two equivalents of mycolic acid derivative. Disaccharide **18** could be achieved through the β -selective glycosylation between glycosyl acceptor **13** and glycosyl donor **7**. Both the glycosyl acceptor **13** and glycosyl donor **7** could be generated from protected thioarabinosides **11** and **5** respectively. Glycosyl acceptor **13** could be formed by the glycosylation between thioarabinosides **11** and isopropylidene glycerol. On the other hand, glycosyl donor **7** could be constructed from thioarabinosides **5** through a series of protection and deprotection. Both thioarabinosides **11** and **5** could be readily synthesized from benzyl-protected arabinose **4**. To obtain thioarabinose **11**, benzyl-protected arabinose **4** first undergoes deprotection, followed by Mitsunobu reaction, ring opening of the epoxide and finally thioglycosylation. Thioarabinose **5** in contrast, has a more straightforward synthesis from benzyl-protected arabinose **4** which only involves a thioglycosylation step.

Scheme 2. Retrosynthetic scheme for DMAG

3.2 Synthesis of Donor

The synthetic approach commenced with the synthesis of the glycosyl donor by employing D-arabinose as the starting material (Scheme 3). Employing a conventional method of using methanolic hydrochloric acid, methoxyarabinose was synthesized in a 1:1 mixture of the α - and β -isomer.^[23] Subsequently, the hydroxyl groups were protected with benzoyl chloride. Based on previous reports, the crude compound was then allowed to recrystallize from ethanol. The α -isomer formed white crystals while the β -isomer remained as liquid in solution. This allows for the easy separation of both isomers and upon collection of the solids, benzoyl-protected methoxyarabinose **4** was afforded in a 41% yield over two steps.

A-Methoxyarabinose **4** was then converted to benzoyl-protected α -thioarabinose **5**. Due to anomeric effect, the more stable α -thioarabinose was obtained selectively in this case. Thioglycosides have always been one of the top choices for glycosyl donors.^[24] Although glycosyl halides are frequently used as donors, they often produced low yields during the transformation of an oligosaccharide into the donor halide.^[25] Hence, to circumvent this problem and ensure reasonable yields, thioglycosides became the natural solution. Thioglycosides are relatively stable during manipulations in carbohydrate synthesis. They can be converted into glycosyl halides or used directly as glycosyl donors.^[26] As such, thioglycoside was chosen as the donor for the synthesis of DMAG in this project.

Subsequently, the benzoyl-protected thioarabinose **5** was deprotected using sodium methoxide (NaOCH₃) in methanol. The crude product was then subjected to *tert*-butyldiphenylchlorosilane (TBDPSCI) protection of the primary alcohol, producing an overall yield of 86% over two steps.

Scheme 3. Synthetic strategy for glycosyl donor

Finally, the 2-OH and 3-OH were protected using α, α' -dibromo-*o*-xylene in the presence of sodium hydride (NaH) and dimethylformamide (DMF) to afford the thioglycoside donor **7** in a 65% yield. With the donor in hand, the attention was then devoted to synthesizing the acceptor.

3.3 Synthesis of Acceptor

The synthesis of the acceptor also began with D-arabinose as the starting material (Scheme 4). Similar to the donor, D-arabinose was converted to benzoyl-protected methoxyarabinose **4** over two steps. Then, the benzoyl groups were deprotected using NaOCH₃ in methanol. The deprotected methoxyarabinose was converted to 2,3 anhydrosugar through a Mitsunobu reaction. Employing diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in tetrahydrofuran (THF), the arabinose oxirane **8** was obtained in 78% yield over two steps. There can be two reasons for this selective ring closure to form the epoxide. One, the primary alcohol will first attack the PPh₃, making the upper face sterically hindered and the C-3 OH cannot attack the PPh₃. Secondly, the C-2 OH might be a more reactive alcohol in contrast to the C-3 OH. Hence, the C-2 OH will preferentially attack the PPh₃.

Subsequently, ring opening of the oxirane was attempted. Many reports have studied the ring opening of oxiranes in carbohydrates and various efficient methods have been uncovered.^[27] In this synthesis, we utilized benzylate as the nucleophile, which was derived from sodium benzylate solution (made by adding sodium into benzyl alcohol) in benzyl alcohol. The epoxide ring was successfully opened with a good yield of 75%. This selective epoxide ring opening with the nucleophile attacking at the C-3 position can be attributed to the fact that groups which are trans-related obstruct substitution at the neighboring carbon. As such, the methoxy group at the C-1 position, which is in a trans-position with respect to the C-2 epoxide ring, hinders the substitution of the nucleophile at the C-2 position. Following which, the two hydroxyl groups were protected with benzoyl groups to form the benzoyl-protected methoxyarabinose **10**, and this compound was consequently converted to arabinose

thioglycoside **11** using 4-methylbenzenethiol and boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$).

In order to construct the glycerol moiety in DMAG, arabinose thioglycoside **11** was glycosylated with (*S*)-(+)-1,2-isopropylidene glycerol. The glycosylation was carried out using the method developed our group, which involves employing *N*-iodosuccinimide (NIS), silver triflate (AgOTf) in dichloromethane at 0 °C. This glycosylation is highly efficient and stereoselective (due to neighboring group participation) thus, an excellent yield of 90% was obtained for the glycerol-arabinose **12**. This glycosylation is highly selective and only the α -isomer was obtained due to the anomeric effect as well as neighbouring group (in this case benzoyl) participation.

Scheme 4. Synthetic strategy for glycosyl acceptor

Although a diastereomeric mixture of 1:1 (at the glycerol moiety) was obtained, we decided to proceed with the reaction to test the viability of the route, as well as test the possibility of separating the isomers at a later stage of the synthetic pathway.

Hence, the benzoyl groups on glycerol-arabinose **12** were deprotected with NaOMe and methanol. The primary hydroxyl group of the crude product was then selectively protected with TBDPSCl in pyridine to afford the desired acceptor **13** in a 92% overall yield over two steps.

3.4 Synthesis of disaccharide – Part 1

Having acquired the donor and the acceptor, the next step would be to test out the glycosylation reaction to form the desired disaccharide (Scheme 5). Donor **7** was reacted with acceptor **13** in the presence of NIS, AgOTf in dichloromethane. However, the desired glycosylated product **14** was not observed and there was no reaction even after increasing the temperature to from -45 °C to rt or increasing the stoichiometric amount of NIS and AgOTf added.

Scheme 5. Glycosylation to form disaccharide **14**

A closer examination into the problem was conducted. Interestingly, in 2006, Ishiwata and group reported that when there is a TBDPS protecting group on the O-5 position, it will hinder the formation of the glycoside. The bulkiness of the TBDPS group might prevent the nucleophilic attack; thus, the reaction could not proceed smoothly.

3.5 Modification of the donor

Following the report by Imamura in 2010, the PMB protecting group became the obvious choice to replace the TBDPS group of the primary hydroxyl in the glycosyl donor. In this report, Imamura tested a few protecting groups such as benzyl, benzoyl as well as PMB. It was found that the PMB protecting group gave the best selectivity for this type of glycosylation.

Therefore, with the original TBDPS-protected donor **7** in hand, the TBDPS group was deprotected using tetrabutylammonium fluoride (TBAF) in THF to afford the free hydroxyl sugar **15** in 90% yield. Subsequently, the 5-OH was subjected to PMBCl in dichloromethane to afford the PMB-protected glycosyl donor **1** in a 88% yield (Scheme 6).

Scheme 6. Changing the protecting group of the primary hydroxyl to PMB

3.6 Synthesis of disaccharide – Part 2

The glycosylation reaction to form the disaccharide was carried out again with the new donor having a PMB group on the 5-OH position (Scheme 7). Employing NIS, AgOTf reaction conditions, the disaccharide was successfully obtained with an exclusive β -selectivity at the anomeric carbon (this selectivity will be explained in the later part). However, as the acceptor **13** employed contain a diastereomeric mixture of 1:1 at the glycerol moiety, a diastereomeric mixture of 1:1 (at the glycerol moiety) was obtained (β/α ratio 12:1). Subsequent deprotections of the primary alcohol using TBAF (for deprotection of TBDPS group) as well as DDQ in dichloromethane and water (for deprotection of PMB group) were conducted, but it was impossible to separate the isomers (1:1 mixture). Hence, it was concluded that a different glycerol protected alcohol should be employed to ensure a single isomer of the glycerol.

Scheme 7. Glycosylation and subsequent deprotections in an attempt to separate the diastereomeric glycerol moiety

3.7 Modification of the acceptor

A proposed mechanism was deduced for the epimerization of the (*S*)-(+)-1,2-isopropylidene glycerol during acidic glycosylation (Scheme 8). The Lewis acid (Ag^+) promoted the formation of an oxocarbenium ion. Thereafter, attack of the oxocarbenium ion by the oxygen would result in the formation of (*R*)-(-)-1,2-isopropylidene glycerol. Therefore, during the glycosylation, both diastereomers were formed, resulting in an inseparable mixture. To prevent epimerization during the glycosylation, the glycerol has to be modified, and a dibenzyl glycerol was selected. The selection of the dibenzyl protecting group on the glycerol was based on the fact that all the protecting groups on the donors and acceptors of the final disaccharide (that is linked to the mycolic acid) can be removed by hydrogenation. Hence, the protecting group should be chosen such that all the protecting groups on the disaccharide, as well as on the glycerol, can be removed in a one-step hydrogenation reaction.

Scheme 8. Plausible mechanism for the epimerization

The synthesis of the dibenzyl glycerol **23** began with (*S*)-(+)-1,2-isopropylidene glycerol.^[27i] The glycerol was first protected with benzyl chloride in the presence of sodium hydride (NaH) in DMF. The isopropylidene ring was then cleaved by using acetic acid at 70 °C to afford the dihydroxyl-benzyl glycerol **20**. Subsequently, the primary alcohol was selectively protected with trityl chloride (TrCl)

in pyridine to give glycerol **21**, which was further subjected to benzyl chloride, NaH in DMF. Following which, the trityl group from the dibenzyl-trityl glycerol was removed by acetic acid under heat, affording the desired dibenzyl glycerol **23** (Scheme 9).

Scheme 9. Synthesis of benzyl-protected glycerol **23**

With the dibenzyl-glycerol **23**, glycosylation was again carried out to obtain the glycosyl acceptor. Using the same reaction condition as previously mentioned, 91% of the α -glycoside **24** was obtained. Similarly, anomeric effect and neighboring group participation ensues the acquirement of only the α -isomer. Deprotection of the benzoyl groups with NaOCH_3 in methanol gave 96% dihydroxyl glycoside **25**, which upon protection of the primary alcohol by TBDSPCl in pyridine afforded the final glycosyl acceptor **26** in a 90% yield.

Scheme 10. Synthesis of the acceptor, dibenzyl-glycerol monosaccharide **26**.

3.8 Synthesis of disaccharide – Part 3

Dibenzyl-protected glycerol monosaccharide **26** was reacted with glycosyl donor **1** under NIS, AgOTf in dichloromethane at -45 °C (Scheme 11b). Gratifyingly, the desired disaccharide **27** was finally obtained in an 80% yield with β/α ratio 12:1. Such selectivity is not surprising as β -arabinofuranosylation has been reported in 2010 by Lowary and coworkers.^[22] Furanosides are flexible and can adopt various conformations as well as glycosylate through different transition states, thereby compromising on their anomeric selectivities. As the oxocarbenium ions have substantial double-bond character between the endocyclic oxygen and C-1, these two atoms, C-2 and C-4 are positioned in one plane. By introducing the xylene protecting group on the C-2 and C-3 position, it causes the glycosyl donor **1** to adopt an E_3 conformer. Hence, a 1, 2-*cis* attack leading to β -isomer would be preferred to avoid unfavorable interactions (Scheme 11a).

Scheme 11a. Explanation of β -arabinofuranosylation

Scheme 11b. Formation of disaccharide **27**

Subsequently, in order to attach the mycolic acid derivatives onto the disaccharide, deprotection of the primary alcohols was carried out. The compound was first subjected to TBAF in THF to remove the TBDPS protecting group. Disaccharide **28** was obtained in a 86% yield after the first deprotection. Following which, under the reaction conditions of DDQ in dichloromethane and water, disaccharide **29** with free primary hydroxyls was afforded in a 81% yield. This disaccharide is the key intermediate for this synthetic strategy (Scheme 11c).

Scheme 11c. Formation of disaccharide **29**

3.9 Synthesis of mycolic acid derivative

The synthesis of the mycolic acid derivative started off with alcohol-ester **30**. The alcohol-ester **30** was first protected with acetylmandelic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 4-dimethylaminopyridine (DMAP) in dichloromethane. This coupling reaction was conducted with the aim of identifying the enantiomeric ratio of **30** through determining the diastereomeric ratio of the acetylmandelic-protected ester **31**. From the ^1H NMR, it was observed that the diastereomeric excess of acetylmandelic-protected **31** was 95%, indicating that alcohol-ester **30** has an enantiomeric excess of 95%. This excellent enantiomeric ratio permitted the use of alcohol ester **30** as the starting material for the synthesis of the mycolic acid derivative (Scheme 12).^[28]

Scheme 12. Investigating the enantiomeric excess of alcohol-ester **30** by acetylmandelic protection

At the outset, the alcohol-ester **30** was alkylated by the use of 1-iodotetracane (obtained from the reaction between 1-bromotetracane and sodium iodide in acetone) in the presence of lithium diisopropylamine (LDA) and hexamethylphosphoramide (HMPA) in THF. The alkylation proceeded at low temperatures and the alkylated alcohol-ester **32** was produced in a 42% yield.^[29] This Frater-Seebach alkylation proceeds through a 6-membered transition state with chelating metal ions and the 1-iodotetracane will attack from the opposite face to avoid steric hindrance, affording

exclusive trans-product. Subsequently, the hydroxyl group of the alkylated alcohol-ester **32** was protected with benzyl group by using benzyl 2,2,2-trichloroacetimidate and triflic acid in dichloromethane/cyclohexane. The resulting ester **33** was obtained in a 65% yield after 16 hours. In order to couple the mycolic acid derivative with the disaccharide, it was necessary to remove the ester group to produce an acid. This reaction was efficiently carried out by using 1 M sodium hydroxide in ethanol at 70 °C, affording the desired mycolic acid derivative **34** in a 80% yield (Scheme 13).

Scheme 13. Synthesis of the mycolic acid derivative **34**

3.10 Esterification of mycolic acid with disaccharide

With the synthesis of mycolic acid derivative **34**, the esterification reaction was carried out using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and DMAP in dichloromethane. 2 Equivalents of the mycolic acid derivative **34** were reacted with dihydroxyl disaccharide **29**. Under the esterification conditions mentioned previously, the desired arabinosylated glycerol dimycolate product **35** was afforded in a 75% yield (Scheme 14).

Scheme 14. Synthesis of the arabinosylated glycerol dimycolate **35**

The synthesis of the final arabinosylated glycerol dimycolate will involve the final deprotection of the benzyl protecting groups of arabinosylated glycerol dimycolate product **35**. This work, together with the biological testings, is currently underway.

4. Conclusion

In summary, a successful synthesis of the disaccharide was carried by employing Mitsunobu conditions for the synthesis of 2,3-anhydrosugars, followed by epoxide-ring opening through sodium benzyolate, as well as our recent work on selective arabinofuranosylation. Subsequent attachment of the mycolic acids to the arabinosides afforded the desired arabinosylated glycolipids which would be deprotected and examined for their biological activities and their role in mycobacterial infections.

Inspired by the numerous potentials and benefits of DMAG from *M. marinum*, we envisioned that this cell wall glycoconjugate would drive host-pathogen interactions and contribute in the immunopathogenesis of mycobacterial infections. Therefore, future biological testings would be carried out to investigate the biological activity of this glycolipid.

5. Experimental section

All reactions were conducted under a nitrogen atmosphere, unless otherwise specified. Anhydrous solvents were transferred *via* oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. All reagents and solvents were acquired from commercial suppliers (Sigma-Aldrich, Fluka and Alfa Aesar) and used without further purification unless otherwise indicated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Optical rotations were measured in CHCl₃ on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu) and reported in cm⁻¹. High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. Accurate masses are reported for the molecular ion [M+H]⁺ or a suitable fragment ion. NMR spectra were documented at room temperature on a 400 MHz Bruker ACF 400 NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ¹H NMR spectroscopy and 77.0 ppm for ¹³C NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (*J*) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet,

m = multiplet or unresolved. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/ α radiation (graphite monochromator).

5.1 Preparation of Acceptor

((2*R*,3*R*,4*S*,5*S*)-4-(benzoyloxy)-3-(benzyloxy)-5-((*S*)-2,3-bis(benzyloxy)propoxy)tetra-hydrofuran-2-yl)methyl benzoate (24)

To a mixture of glycosyl donor **11**^[27i] (100 mg, 0.2 mmol) and glycerol acceptor **23**^[22] (40 mg, 0.2 mmol) in CH₂Cl₂ (5 mL) was added 4 Å molecular sieves (100 mg) at rt. After stirring for 1 h, the mixture was cooled to 0 °C and NIS (80 mg, 0.3 mmol) and AgOTf (9 mg, 36 μmol) were added to the mixture. The reaction was stirred at 0 °C for 30 min (TLC monitored). The resulting mixture was quenched with triethylamine, diluted with CH₂Cl₂ and filtered through Celite. The filtrate was then washed with saturated aqueous Na₂S₂O₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (3:1 hexanes–EtOAc) to afford **24** (α only) as a colourless oil (148 mg, 91%). *R*_f 0.53 (3:1 hexanes–EtOAc); [α]_D +26.0 (*c* 0.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ_H) 8.03 (dd, 2H, *J* = 8.5, 1.5 Hz, ArH), 7.97 (dd, 2H, *J* = 8.5, 1.0 Hz, ArH), 7.59 (t, 1H, *J* = 9.5 Hz, ArH), 7.50 (t, 1H, *J* = 9.5 Hz, ArH), 7.44 (t, 2H, *J* = 8.0 Hz, ArH), 7.42–7.19 (m, 17H, ArH), 5.43 (d, 1H, *J* = 1.0 Hz, H-4), 5.25 (s, 1H, H-1), 4.90 (d, 1H, *J* = 12.0 Hz, PhCH₂O), 4.73 (dd, 2H, *J* = 20.0, 12.0 Hz, PhCH₂O), 4.64 (d, 1H, *J* = 12.0 Hz, PhCH₂O), 4.59–4.56 (m, 1H, H-1'), 4.56 (d, 2H, *J* = 4.5 Hz, PhCH₂O), 4.47 (dd, 1H, *J* = 9.0, 5.0 Hz, H-3), 4.41 (dd, 1H, *J* = 11.5, 4.5 Hz, H-1'), 4.12 (dt, 1H,

$J = 5.5, 1.0$ Hz, H-2), 3.95 (dd, 1H, $J = 10.5, 6.0$ Hz, H-5a), 3.88 (quin, 1H, $J = 5.0$ Hz, H-2'), 3.72 (dd, 1H, $J = 10.5, 4.5$ Hz, H-5b), 3.68 (dd, 1H, $J = 25.5, 5.0$ Hz, H-3'), 3.67 (t, 1H, $J = 5.0$ Hz, H-3'); ^{13}C NMR (125 MHz, CDCl_3 , δ_{C}) 166.2 (C=O), 165.4 (C=O), 138.6 (Ar), 138.2 (Ar), 137.4 (Ar), 133.4 (Ar), 133.0 (Ar), 129.7 (Ar $\times$ 2), 129.6(7) (Ar), 129.6(3) (Ar $\times$ 2), 129.3 (Ar), 128.5 (Ar $\times$ 2), 128.3 (Ar $\times$ 2), 128.2(8) (Ar $\times$ 2), 128.2(3) (Ar $\times$ 4), 127.9 (Ar $\times$ 2), 127.8 (Ar), 127.7(7) (Ar $\times$ 2), 127.6 (Ar $\times$ 2), 127.5 (Ar), 127.4(5) (Ar), 106.1 (C-1), 83.6 (C-2), 81.7 (C-4), 80.9 (C-3), 76.7 (C-2'), 73.3 (PhCH₂O), 72.5 (PhCH₂O), 72.3 (PhCH₂O), 70.0 (C-3'), 67.2 (C-5), 63.5 (C-1').
HRMS (ESI) calcd for (M+Na) C₄₃H₄₂NaO₉: 725.2721. Found: 725.2711.

(2*S*,3*S*,4*S*,5*R*)-4-(benzyloxy)-2-((*S*)-2,3-bis(benzyloxy)propoxy)-5-(hydroxymethyl)tetra-hydrofuran-3-ol (25)

To a solution of glycosyl glycerol **24** (100 mg, 0.1 mmol) in methanol (5 mL) was added sodium methylate (4 mg, 71 μmol). The mixture was allowed to stir for 2 h (TLC monitored) at rt. The resulting mixture was then quenched using Amberlite resin and filtered. The filtrate was concentrated and purified by flash column chromatography on silica gel (1:3 hexanes–EtOAc) to afford **25** as a colourless oil (68 mg, 96%).

R_f 0.48 (1:3 hexanes–EtOAc); $[\alpha]_{\text{D}} +60.2$ (c 1.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3 , δ_{H}) 7.35–7.25 (m, 15H, ArH), 4.96 (s, 1H, H-1), 4.69 (s, 1H, PhCH₂O) 4.67 (d, 2H, J

= 16.5 Hz, PhCH₂O), 4.54 (d, 2H, *J* = 12.0 Hz, PhCH₂O), 4.51 (d, 1H, *J* = 2.5 Hz, PhCH₂O), 4.20 (dd, 1H, *J* = 0.5, 2.0 Hz, H-2), 4.16 (ddd, 1H, *J* = 7.0, 5.0, 2.5 Hz, H-4), 3.88-3.78 (m, 4H, H-3, H-1'), 3.81 (dd, 1H, *J* = 9.0, 2.5 Hz, H-5a), 3.65-3.63 (m, 1H, H-2'), 3.62 (dd, 1H, *J* = 5.5, 2.0 Hz, H-3'), 3.59 (dd, 1H, *J* = 9.0, 2.5 Hz, H-5b), 2.38 (br s, 2H, OH × 2); ¹³C NMR (125 MHz, CDCl₃, δ_C) 138.6 (Ar), 138.3 (Ar), 137.8 (Ar), 128.4 (Ar × 2), 128.3 (Ar × 2), 128.2(7) (Ar × 2), 127.8 (Ar), 127.7(9) (Ar × 2), 127.7 (Ar × 2), 127.6 (Ar × 2), 127.5(4) (Ar), 127.5 (Ar), 109.0 (C-1), 85.1 (C-3), 83.5 (C-4), 78.9 (C-2), 76.7 (C-2'), 73.3 (PhCH₂O), 72.2 (PhCH₂O), 72.1(8) (PhCH₂O), 70.1 (C-3'), 67.4 (C-1'), 62.1 (C-5). HRMS (ESI) calcd for (M+Na) C₂₉H₃₄NaO₇: 517.2197. Found: 517.2186.

(2S,3S,4S,5R)-4-(benzyloxy)-2-((S)-2,3-bis(benzyloxy)propoxy)-5-(((tert-butyl)dimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol (26)

To a solution of dihydroxyl-glycoside **25** (50 mg, 0.1 mmol) in pyridine (3 mL) was added TBDPSCl (29 μL, 0.1 mmol). The reaction mixture was allowed to stir for 16 h at rt (TLC monitored). The mixture was then quenched with methanol, diluted with CH₂Cl₂ and washed with 2M HCl (2 × 50 mL), NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (3:1 hexanes–EtOAc) to afford **26** (68 mg, 90%) as a colourless oil.

R_f 0.37 (3:1 hexanes-EtOAc); $[\alpha]_D +35.4$ (c 1.2, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ_{H}) 7.71 (dd, 2H, $J = 8.0, 1.5$ Hz, ArH), 7.65 (dd, 2H, $J = 7.5, 1.5$ Hz, ArH), 7.47 (dd, 1H, $J = 8.0, 1.0$ Hz, ArH), 7.42 (dd, 2H, $J = 9.5, 1.0$ Hz, ArH), 7.49-7.27 (m, 18H, ArH), 5.10 (s, 1H, H-1), 4.73 (dd, 2H, $J = 26.0, 12.0$ Hz, PhCH_2O), 4.70 (d, 1H, $J = 11.5$ Hz, PhCH_2O), 4.54 (d, 1H, $J = 11.5$ Hz, PhCH_2O), 4.53 (d, 2H, $J = 1.0$ Hz, PhCH_2O), 4.25 (d, 1H, $J = 9.0$ Hz, H-2), 4.19 (dd, 1H, $J = 5.5, 2.5$ Hz, H-4), 4.02 (d, 1H, $J = 3.0$ Hz, H-3), 3.92 (dd, 1H, $J = 10.0, 5.0$ Hz, H-1'), 3.84 (dd, 1H, $J = 11.5, 2.5$ Hz, H-5a), 3.83 (d, 1H, $J = 5.0$ Hz, H-2'), 3.69 (dd, 1H, $J = 10.5, 4.5$ Hz, H-1'), 3.65 (dd, 2H, $J = 12.0, 4.5$ Hz, H-3'), 3.63 (dd, 1H, $J = 13.5, 2.0$ Hz, H-5b), 3.32 (d, 1H, $J = 10.0$ Hz, OH), 1.09 (s, 9H, t -butyl $\text{CH}_3 \times 3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , δ_{C}) 138.7 (Ar), 138.4 (Ar), 137.9 (Ar), 135.6 (Ar $\times 2$), 135.5(7) (Ar $\times 2$), 132.5 (Ar), 132.3 (Ar), 130.0 (Ar), 129.9(1) (Ar), 128.4 (Ar $\times 2$), 128.3 (Ar $\times 2$), 128.2(9) (Ar $\times 2$), 128.2 (Ar $\times 2$), 127.8(4) (Ar $\times 2$), 127.8(1) (Ar $\times 2$), 127.7 (Ar $\times 2$), 127.7(6) (Ar), 127.5(4) (Ar $\times 2$), 127.5 (Ar), 127.4(7) (Ar), 109.0 (C-1), 84.8 (C-3), 84.3 (C-4), 77.7 (C-2), 76.7 (C-2'), 73.3 (PhCH_2O), 72.2 (PhCH_2O), 71.9 (PhCH_2O), 70.4 (C-3'), 67.3 (C-1'), 64.0 (C-5), 26.7 (t -butyl $\text{CH}_3 \times 3$), 19.1 (t -butyl C). HRMS (ESI) calcd for (M+Na) $\text{C}_{45}\text{H}_{52}\text{NaO}_7\text{Si}$: 755.3375. Found: 755.3363.

5.2 Disaccharide synthesis

(((2*R*,3*R*,4*S*,5*S*)-3-(benzyloxy)-5-((*R*)-2,3-bis(benzyloxy)propoxy)-4-(((1*S*,3*R*,3*aR*,11*aS*)-3-(((4-methoxybenzyl)oxy)methyl)-1,3,3*a*,5,10,11*a*-hexahydrobenzo[*f*]furo[3,4-*b*][1,4]-dioxocin-1-yl)oxy)tetrahydrofuran-2-yl)methoxy)(*tert*-butyl)diphenylsilane (27)

To a mixture of glycosyl donor **1** (100 mg, 0.2 mmol) and glycerol acceptor **26** (66 mg, 0.1 mmol) in CH₂Cl₂ (5 mL) was added 4 Å molecular sieves (50 mg) at rt. After stirring for 1 h, the mixture was cooled to -45 °C and NIS (57 mg, 0.3 mmol) and AgOTf (7 mg, 28 μmol) were added to the mixture. The reaction was stirred at -45 °C for 1 h (TLC monitored). The resulting mixture was quenched with triethylamine, diluted with CH₂Cl₂ and filtered through Celite. The filtrate was then washed with saturated aqueous Na₂S₂O₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (3:1 hexanes–EtOAc) to afford **27** as a colourless oil (97 mg, 80%, β/α ratio 12:1).

R_f 0.25 (3:1 hexanes–EtOAc); [*α*]_D +7.2 (*c* 1.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃, *δ*_H) 7.70 (dt, 2H, *J* = 14.5, 7.5, 1.5 Hz, ArH), 7.41–7.21 (m, 25H), 7.11 (d, 2H, *J* = 8.5 Hz, ArH), 6.77 (d, 2H, *J* = 8.5 Hz, ArH), 5.05 (d, 1H, *J* = 0.5 Hz, H-1B), 5.02 (d, 1H,

$J = 5.0$ Hz, H-1A), 4.92 (d, 1H, $J = 13.0$ Hz, PhCH₂O), 4.79 (dd, 2H, $J = 28.5, 13.0$ Hz, PhCH₂O), 4.71 (d, 1H, $J = 12.5$ Hz, PhCH₂O), 4.67 (dd, 2H, $J = 17.0, 12.0$ Hz, PhCH₂O), 4.61 (d, 1H, $J = 11.5$ Hz, PhCH₂O), 4.52 (s, 2H, PhCH₂O), 4.43 (d, 1H, $J = 11.5$ Hz, PhCH₂O), 4.37 (d, 1H, $J = 11.5$ Hz, PhCH₂O), 4.30 (d, 1H, $J = 11.5$ Hz, PhCH₂O), 4.29-4.28 (m, 1H, H-2B), 4.14 (dd, 1H, $J = 11.5, 5.5$ Hz, H-3A), 4.09 (dd, 2H, $J = 6.5, 3.0$ Hz, H-4A, H-4B), 4.03 (dd, 1H, $J = 6.0, 3.0$ Hz, H-3B), 3.95 (m, 1H, H-2A), 3.85 (dd, 1H, $J = 10.0, 5.0$ Hz, H-1'), 3.82-3.77 (m, 3H, H-5aA, H-5aB, H-2'), 3.75 (s, 3H, OCH₃), 3.64-3.61 (m, 3H, H-1', H-3', H-5bB), 3.57-3.49 (m, 2H, H-5, H-5bA), 1.04 (s, 9H, *t*-butyl CH₃ × 3); ¹³C NMR (125 MHz, CDCl₃, δ_C) 159.1, 138.7 (Ar), 138.4 (Ar), 138.2 (Ar), 136.9 (Ar), 135.9 (Ar), 135.7 (Ar × 2), 135.6(7) (Ar × 2), 133.6 (Ar × 2), 131.5 (Ar), 131.2 (Ar), 130.2 (Ar), 129.6 (Ar × 2), 129.3(3) (Ar), 129.3 (Ar), 129.1 (Ar × 2), 128.3 (Ar × 2), 128.2(3) (Ar × 2), 128.2(1) (Ar × 2), 127.7 (Ar × 2), 127.6(4) (Ar × 2), 127.6(3) (Ar × 2), 127.6 (Ar × 3), 127.5 (Ar), 127.4(6) (Ar), 127.4(5) (Ar), 127.3(9) (Ar), 113.7 (Ar × 2), 106.6 (C-1B), 102.6 (C-1A), 86.3 (C-2B), 83.9 (C-3B), 82.8 (C-3A), 82.0 (C-4B), 82.6 (C-4A), 81.9 (C-2A), 76.8 (C-2'), 73.4 (PhCH₂O), 72.6 (PhCH₂O), 72.3 (PhCH₂O), 72.2 (PhCH₂O), 72.1(6) (PhCH₂O), 70.5 (PhCH₂O), 69.6 (C-5A), 69.1 (C-3'), 67.2 (C-1'), 64.1 (C-5B), 55.2 (OCH₃), 26.9 (*t*-butyl CH₃ × 3), 19.4 (*t*-butyl C). HRMS (ESI) calcd for (M+Na) C₆₆H₇₄NaO₁₂Si: 1109.4842. Found: 1109.4832.

**((2*R*,3*R*,4*S*,5*S*)-3-(benzyloxy)-5-((*R*)-2,3-bis(benzyloxy)propoxy)-4-
(((1*S*,3*R*,3*aR*,11*aS*)-3-(((4-methoxybenzyl)oxy)methyl)-1,3,3*a*,5,10,11*a*-
hexahydrobenzo[*f*]furo[3,4-*b*][1,4]-dioxocin-1-yl)oxy)tetrahydrofuran-2-
yl)methanol (28)**

To a solution of glycoside **27** in THF (5 mL) was added TBAF (1M in THF, 0.1 mL, 0.1 mmol). The reaction mixture was allowed to stir for 3 h at rt (TLC monitored). The mixture was diluted with CH₂Cl₂, washed with 2M HCl (2 × 50 mL), NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (3:1 hexanes–EtOAc) to afford **28** as a colourless oil (67 mg, 86%).

R_f 0.58 (1:3 hexanes–EtOAc); [*α*]_D +21.8 (*c* 0.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃, *δ*_H) 7.39 (dd, 1H, *J* = 5.5, 3.5 Hz, ArH), 7.38 (dd, 1H, *J* = 7.5, 3.5 Hz, ArH), 7.34–7.23 (m, 18H, ArH), 7.18 (d, 2H, *J* = 9.0 Hz, ArH), 6.81 (d, 2H, *J* = 8.5 Hz, ArH), 5.07 (s, 1H, H-1B), 5.01 (d, 1H, *J* = 5.0 Hz, PhCH₂O), 4.97 (s, 1H, H-1A), 4.79 (dd, 2H, *J* = 23.5, 13.0 Hz, PhCH₂O), 4.76 (d, 1H, *J* = 9.0 Hz, PhCH₂O), 4.67 (dd, 2H, *J* = 17.5, 11.5 Hz, PhCH₂O), 4.63 (d, 1H, *J* = 11.5 Hz, PhCH₂O), 4.49 (s, 2H, PhCH₂O), 4.45 (dd, 2H, *J* = 20.0, 11.5 Hz, PhCH₂O), 4.40 (d, 1H, *J* = 11.5 Hz, PhCH₂O), 4.31 (d, 1H, *J* = 1.5 Hz, H-2B), 4.16–4.11 (m, 3H, H-3A, H-4A, H-4B), 4.03 (dd, 1H, *J* = 5.0, 2.0 Hz, H-3B), 3.97 (t, 1H, *J* = 5.0 Hz, H-2A), 3.85 (ddd, 1H, *J* = 15.5, 10.0, 5.0 Hz, H-1'),

3.80-3.77 (m, 2H, H-5aB, H-2'), 3.77 (s, 3H, ArOCH₃), 3.63-3.57 (m, 5H, H-5aA, H-5bB, H-1', H-3'), 3.52 (dd, 1H, *J* = 10.0, 5.0 Hz, H-5bA), 1.71 (br s, 1H, OH); ¹³C NMR (125 MHz, CDCl₃, δ_C) 159.2 (Ar), 138.7 (Ar), 138.3 (Ar), 138.0 (Ar), 136.9 (Ar), 135.5 (Ar), 131.6 (Ar), 131.3 (Ar), 130.1 (Ar), 129.6 (Ar), 129.5 (Ar), 129.3 (Ar × 2), 128.3 (Ar × 3), 128.2(9) (Ar × 2), 127.8 (Ar × 2), 127.7 (Ar), 127.6(8) (Ar), 127.6(5) (Ar × 2), 127.5(9) (Ar × 2), 127.5 (Ar), 127.4(8) (Ar), 113.8 (Ar × 2), 106.0 (C-1B), 102.2 (C-1A), 83.9 (C-2B), 83.7 (C-3B), 83.5 (C-3A), 82.7 (C-4B), 82.2 (C-4A), 81.8 (C-2A), 76.8 (C-2'), 73.4 (PhCH₂O), 72.7 (PhCH₂O), 72.3 (PhCH₂O), 72.2 (PhCH₂O), 72.0 (PhCH₂O), 70.3 (PhCH₂O), 69.7 (C-3'), 68.9 (C-1'), 67.4 (C-5B), 62.4 (C-5A), 55.3 (OCH₃). HRMS (ESI) calcd for (M+Na) C₅₀H₅₆NaO₁₂: 871.3664. Found: 871.3649.

((1*R*,3*S*,3*aS*,11*aR*)-3-(((2*S*,3*S*,4*R*,5*R*)-4-(benzyloxy)-2-((*S*)-2,3-bis(benzyloxy)propoxy)-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)-1,3,3*a*,5,10,11*a*-hexahydrobenzo[*f*]furo[3,4-*b*][1,4]dioxocin-1-yl)methanol (29)

To a solution of glycoside **28** (50 mg, 59 μmol) in CH₂Cl₂ (2 mL) and water (2 mL) was added DDQ (15 mg, 66 μmol). The reaction mixture was allowed to stir for 6 h at rt (TLC monitored). The mixture was then diluted CH₂Cl₂ and with washed with saturated aqueous NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was

dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (1:3 hexanes–EtOAc) to afford **29** as a colourless oil (35 mg, 81%).

R_f 0.29 (1:3 hexanes–EtOAc); [*α*]_D +19.7 (*c* 0.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃, *δ*_H) 7.40–7.38 (m, 2H), 7.34–7.23 (m, 17H, ArH), 5.09 (d, 1H, *J* = 0.5 Hz, H-1B), 5.03 (s, 1H, H-1A), 5.01 (d, 1H, *J* = 8.0 Hz, PhCH₂O), 4.79 (s, 2H, PhCH₂O), 4.75 (d, 1H, *J* = 13.0 Hz, PhCH₂O), 4.69 (d, 1H, *J* = 11.5 Hz, PhCH₂O), 4.68 (d, 2H, *J* = 2.5 Hz, PhCH₂O), 4.54 (d, 1H, *J* = 11.5 Hz, PhCH₂O), 4.52 (s, 2H, PhCH₂O), 4.34 (t, 1H, *J* = 6.0 Hz, H-3A), 4.29 (s, 1H, H-2B), 4.12 (d, 2H, *J* = 1.5 Hz, H-4A, H-4B), 4.01 (dt, 1H, *J* = 8.0, 3.0 Hz, H-3B), 3.99 (t, 1H, *J* = 6.0 Hz, H-2A), 3.86 (dd, 1H, *J* = 10.5, 5.5 Hz, H-1'), 3.82 (dd, 1H, *J* = 8.5, 2.0 Hz, H-5aB), 3.79 (d, 1H, *J* = 5.5 Hz, H-2'), 3.70 (dd, 1H, *J* = 12.5, 3.0 Hz, H-1'), 3.63 (dd, 2H, *J* = 10.5, 4.5 Hz, H-3'), 3.62–3.58 (m, 3H, H-5aA, H-5bA, H-5bB), 1.94 (br s, 2H, OH); ¹³C NMR (125 MHz, CDCl₃, *δ*_C) 138.6 (Ar), 138.3 (Ar), 137.8 (Ar), 137.1 (Ar), 135.2 (Ar), 131.7 (Ar), 131.3 (Ar), 129.6 (Ar), 129.5 (Ar), 128.4 (Ar × 2), 128.3(8) (Ar × 2), 128.3 (Ar × 2), 127.9 (Ar), 127.8 (Ar × 2), 127.7 (Ar × 2), 127.6 (Ar × 2), 127.5(9) (Ar), 127.5(5) (Ar), 106.4 (C-1B), 102.5 (C-1A), 85.9 (C-2B), 84.6 (C-3B), 83.1 (C-2A), 82.9 (C-4B), 82.0 (C-4A), 80.5 (C-3A), 76.8 (C-2'), 73.4 (PhCH₂O), 72.4 (PhCH₂O), 72.3(PhCH₂O), 70.2 (PhCH₂O), 69.9 (PhCH₂O), 68.8 (C-3'), 67.4 (C-1'), 63.2 (C-5B), 62.2 (C-5A). HRMS (ESI) calcd for (M+Na) C₄₂H₄₈NaO₁₁: 751.3089. Found: 751.3074.

5.3 Preparation of Mycolic acid derivative 34

(2R,3R)-methyl 3-((S)-2-acetoxy-2-phenylacetoxymethyl)-2-tetradecyloctadecanoate (31)

To a solution of ester **30** (100 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added (*S*)-(+)-*O*-acetylmandelic acid (64 mg, 0.3 mmol), EDC (32 mg, 0.2 mmol) and DMAP (cat. amt.). The reaction mixture was allowed to stir overnight at rt (TLC monitored). The mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous NaHCO_3 (2×50 mL) and brine (2×50 mL). The organic layer was dried over Na_2SO_4 , concentrated and purified by flash column chromatography on silica gel (5:1 hexanes–EtOAc) to afford **31** as a yellow oil (98 mg, 60%).

R_f 0.82 (3:1 hexanes–EtOAc); $[\alpha]_D^{25} +45.13$ (c 0.4, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ_H) 7.49–7.46 (m, 2H, ArH), 7.42–7.36 (m, 3H, ArH), 5.89 (s, 1H, H-c), 5.29–5.23 (m, 1H, H-a), 3.66 (s, 3H, OCH_3), 2.66 (dd, 1H, $J = 15.0, 7.0$ Hz, H-b), 2.55 (dd, 1H, $J = 15.0, 7.0$ Hz, H-b), 2.21 (s, 3H, COCH_3), 1.52–1.47 (m, 2H, CH_2), 1.34–0.97 (m, 26H, $\text{CH}_2 \times 13$), 0.90 (t, 3H, $J = 7.0$ Hz, CH_3); $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , δ_C) 170.5 (COOCH_3), 170.2 (COOR), 168.2 (COCH_3), 133.9 (Ar), 129.2 (Ar $\times 2$), 128.7 (Ar $\times 2$), 127.6 (Ar), 74.6 (C-c), 71.9 (C-a), 51.8 (C-b), 39.1 (CH_2), 33.8 (CH_2), 31.9 (CH_2), 29.7 ($\text{CH}_2 \times 2$), 29.6(4) (CH_2), 29.6(3) (CH_2), 29.6(0) (CH_2), 29.4 (CH_2), 29.3(4) (CH_2), 29.3(2) (CH_2), 29.1 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 20.7 (CH_3), 14.1 (CH_3). **HRMS (ESI)** calcd for $(\text{M}+\text{Na}) \text{C}_{29}\text{H}_{46}\text{NaO}_6$: 513.3187. Found: 513.3177.,

(2*R*,3*R*)-methyl 3-(benzyloxy)-2-tetradecyloctadecanoate (33)

To a solution of ester **32**^[29] (10 mg, 19 μ mol) in CH₂Cl₂ (1 mL) and cyclohexane (1 mL) was added 4Å molecular sieves (spat.), triflic acid (0.2 μ L, 2 μ mol) and benzyl 2,2,2-tri-chloroacetimide (5 μ L, 29 μ mol). The reaction mixture was allowed to stir overnight at rt (TLC monitored). The mixture was then acidified with 1M HCl, concentrated and diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ (2 $\times$ 50 mL) and brine (2 $\times$ 50 mL). The organic layer was dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (5:1 hexanes–EtOAc) to afford **33** as a yellow oil (7 mg, 65%).

R_f 0.56 (10:1 hexanes-EtOAc); [α]_D -3.75 (*c* 0.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ _H) 7.37-7.24 (m, 5H, ArH), 4.49 (dd, 2H, *J* = 27.5, 11.0 Hz, PhCH₂O), 3.66 (s, 3H, OCH₃), 3.64 (dd, 1H, *J* = 7.0, 3.5 Hz, H-a), 2.66 (dt, 1H, *J* = 15.0, 4.0 Hz, H-b), 1.60-1.26 (m, 54H, CH₂ $\times$ 27), 0.88 (t, 6H, *J* = 7.0 Hz, CH₃ $\times$ 2); ¹³C NMR (125 MHz, CDCl₃, δ _C) 175.2 (COOCH₃), 138.6 (Ar), 128.2 (Ar), 127.7 (Ar $\times$ 2), 127.4 (Ar $\times$ 2), 80.5 (C-a), 72.1 (PhCH₂O), 51.4 (OCH₃), 49.9 (C-b), 31.9 (CH₂ $\times$ 2), 31.0 (CH₂), 29.8(1) (CH₂ $\times$ 2), 29.8(0) (CH₂ $\times$ 2), 29.7(7) (CH₂ $\times$ 2), 29.7 (CH₂), 29.6(6) (CH₂ $\times$ 2), 29.6(3) (CH₂), 29.6 (CH₂), 29.5(8) (CH₂), 29.5(6) (CH₂), 29.5(3) (CH₂), 29.5 (CH₂ $\times$ 2), 29.4(3) (CH₂), 29.3(6) (CH₂ $\times$ 2), 27.9 (CH₂), 27.7 (CH₂), 24.5

(CH₂), 22.7 (CH₂ × 2), 14.1 (CH₃ × 2). **HRMS (ESI)** calcd for (M+Na) C₄₀H₇₂NaO₃: 623.5374. Found: 623.5382.

(2R,3R)-3-(benzyloxy)-2-tetradecyloctadecanoic acid (34)

To a solution of ester **33** (20 mg, 33 μmol) in ethanol (2 mL) was added 1M NaOH (0.4 mL). The reaction mixture was allowed to stir overnight at 70° C (TLC monitored). The mixture was then acidified with 1M HCl, concentrated and diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na₂SO₄, concentrated and purified by flash column chromatography on silica gel (4:1 hexanes–EtOAc) to afford **34** as a colourless oil (16 mg, 80%).

R_f 0.23 (10:1 hexanes–EtOAc); [*α*]_D +22.7 (*c* 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ_H) 7.35–7.26 (m, 5H, ArH), 4.57 (dd, 2H, *J* = 29.6, 11.6 Hz, PhCH₂O), 4.57 (dt, 1H, *J* = 13.2, 1.6 Hz, H-a), 2.66 (dt, 1H, *J* = 11.2, 4.4 Hz, H-b), 1.65–1.27 (m, 54H, CH₂ × 27), 0.87 (t, 6H, *J* = 13.6 Hz, CH₃ × 2); ¹³C NMR (125 MHz, CDCl₃, δ_C) 179.2 (COOH), 138.0 (Ar), 128.3 (Ar × 2), 127.9 (Ar × 2), 127.7 (Ar), 79.9 (C-a), 72.2 (PhCH₂O), 49.7 (C-b), 31.9 (CH₂ × 2), 31.3 (CH₂), 29.7(1) (CH₂ × 2), 29.6(7) (CH₂), 29.6(2) (CH₂ × 2), 29.6 (CH₂ × 2), 29.5(5) (CH₂ × 2), 29.5 (CH₂ × 2), 29.4(8) (CH₂ × 2), 29.4(6) (CH₂ × 2), 29.4(2) (CH₂ × 2), 29.3(7) (CH₂ × 2), 28.0 (CH₂), 27.6 (CH₂), 24.8 (CH₂), 22.7 (CH₂ × 2), 14.1 (CH₃ × 2). **HRMS (ESI)** calcd for (M-H)- C₃₉H₆₉O₃: 585.5252. Found: 585.5257.

5.4 Synthesis of diarabinosylated glycerol dimycolate

(2*R*,3*R*)-((2*R*,3*R*,4*S*,5*S*)-3-(benzyloxy)-4-(((1*S*,3*R*,3*aR*,11*aS*)-3-(((2*R*,3*R*)-3-(benzyloxy)-2-tetradecyloctadecanoyl)oxy)methyl)-1,3,3*a*,5,10,11*a*-hexahydrobenzo[*f*]furo[3,4-*b*][1,4]dioxocin-1-yl)oxy)-5-((*S*)-2,3-bis(benzyloxy)propoxy)tetrahydrofuran-2-yl)methyl-3-(benzyloxy)-2-tetradecyloctadecanoate (35)

To a mixture of glycoside **29** (12 mg, 16 μ mol), mycolic acid **34** (20 mg, 35 μ mol) and in CH_2Cl_2 (3 mL) were added 4Å molecular sieves (spat.), EDC (13 mg, 66 μ mol) and DMAP (2 mg, 16 μ mol). The reaction mixture was allowed to stir for 12 h at rt (TLC monitored). The mixture was then diluted CH_2Cl_2 and with washed with saturated aqueous NaHCO_3 (2×50 mL) and brine (2×50 mL). The organic layer was dried over Na_2SO_4 , concentrated and purified by flash column chromatography on silica gel (5:1 hexanes–EtOAc) to afford **35** as a colourless oil (20 mg, 65%).

R_f 0.23 (5:1 hexanes–Et₂O); $[\alpha]_D +3.4$ (c 0.05, CHCl_3); ^1H NMR (500 MHz, CDCl_3 , δ_H) 7.34–7.20 (m, 28H, ArH), 5.02 (s, 1H, H-1B), 4.96 (d, 1H, J = 5.0 Hz, H-1A), 4.90 (d, 1H, J = 12.5 Hz, PhCH_2O), 4.74 (dd, 2H, J = 26.5, 13.0 Hz, PhCH_2O), 4.69 (d, 1H, J = 13.0 Hz, PhCH_2O), 4.67–4.64 (m, 1H, PhCH_2O), 4.64 (d, 2H, J = 3.0 Hz, PhCH_2O), 4.51 (t, 4H, J = 2.5 Hz, PhCH_2O), 4.46 (s, 2H, PhCH_2O), 4.45 (d, 1H, J =

11.5 Hz, PhCH₂O), 4.31-4.27 (m, 2H, H-4B, H-5aB), 4.24-4.16 (m, 4H, H-4A, H-5aA, H-5bA, , H-5bB), 4.12-4.08 (m, 2H, H-3A, H-3B), 3.89 (t, 1H, $J = 5.0$ Hz, H-2A), 3.87-3.83 (m, 1H, H- H-2B), 3.82 (dd, 1H, $J = 11.0, 5.5$ Hz, H-1') 3.76 (t, 1H, $J = 5.0$ Hz, H-3'), 3.66-3.57 (m, 3H, H-1', H-2', H-3'), 3.58 (d, 2H, $J = 5.5$ Hz, H-a $\times 2$), 3.10 (ddd, 4H, $J = 15.0, 7.5, 5.0$ Hz, CH₂ $\times 2$), 2.67 (ddd, 2H, $J = 20.8, 8.0, 3.5$ Hz, H-b $\times 2$), 1.42 (t, 8H, $J = 7.0$ Hz, CH₂ $\times 4$), 1.25 (m, 96H, CH₂), 0.88 (t, 12H, $J = 6.5$ Hz, CH₃ $\times 4$); ¹³C NMR (125 MHz, CDCl₃, δ_C) 174.3 (C=O), 174.1 (C=O), 138.7 (Ar), 138.6(6) (Ar $\times 2$), 138.3 (Ar), 137.8 (Ar), 136.9 (Ar), 135.5 (Ar), 131.6 (Ar), 131.2 (Ar), 129.5 (Ar), 129.4(8) (Ar $\times 2$), 129.4(4) (Ar), 128.3 (Ar $\times 4$), 128.2(7) (Ar $\times 5$), 127.7(4) (Ar $\times 3$), 127.7 (2) (Ar $\times 4$), 127.6(6) (Ar $\times 2$), 127.6 (Ar $\times 2$), 127.5(2) (Ar), 127.4(6) (Ar), 127.4(2) (Ar), 106.6 (C-1B), 102.8 (C-1A), 86.0 (C-4B), 84.2 (C-2B), 82.8 (C-3B), 81.7 (C-2A), 80.9 (C-3A), 80.4 (C-4A, C-2', C-a), 79.6 (C-a), 73.4 (PhCH₂O, C-3'), 72.5 (PhCH₂O), 72.2 (PhCH₂O), 72.0 (PhCH₂O), 70.4 (PhCH₂O), 69.6 (PhCH₂O), 69.0 (PhCH₂O), 67.4 (C-1'), 66.3 (C-5B), 64.2 (C-5A), 49.7 (C-b), 49.5 (C-b), 45.8 (CH₂ $\times 2$), 32.0 (CH₂ $\times 5$), 31.1 (CH₂), 29.9, 29.8(6) (CH₂ $\times 2$), 29.8 (CH₂ $\times 2$), 29.7(4) (CH₂ $\times 18$), 29.6(9) (CH₂ $\times 8$), 29.5 (CH₂), 29.4(6) (CH₂), 29.4 (CH₂ $\times 5$), 27.7 (CH₂), 27.5 (CH₂), 24.9 (CH₂), 24.8 (CH₂), 22.7 (CH₂ $\times 5$), 14.1 (CH₃ $\times 4$). HRMS (ESI) calcd for (M+Na) C₁₂₀H₁₈₄NaO₁₅: 1888.3527. Found: 1888.3517.

6. References

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APPENDICES – PART I

**Access to Quinolines through Gold-catalyzed
Intermolecular Cycloaddition of 2-Aminoaryl Carbonyls
and Internal Alkynes**

Appendix – Part I

Access to Quinolines through Gold-catalyzed Intermolecular Cycloaddition of 2-Aminoaryl Carbonyls and Internal Alkynes

1. Introduction

Looking at the widespread reports surrounding quinolines,¹ the introduction of an effective platform for their convenient synthesis has, undeniably, been of interests for many years. Besides their extensive presence in many natural products (Figure 1) and pharmaceutical compounds,² derivatives of quinoline have been described to possess important biological properties such as antibacterial,^{3a} anti-inflammatory^{3b} and antimicrobial activities.^{3c} Hence, the benefits accompanying them justify the constant search for methods to develop their synthesis.

Figure 1. Examples of natural products containing quinoline moiety.

The construction of quinolines was first presented by Koenigs⁴ in 1879, drawing huge attention. This initiated a search as the initial method requires harsh conditions.⁵ Amid the methods reported, conventional and prominent examples are the Skarup reactions, the Friedländer synthesis as well as the Doebner-Miller reactions.⁶ However, recent increase of reports on constructing quinolines have established that novel cycloadditions of appropriate precursors through acid catalysis⁷ and new metal-

catalysed coupling-cyclization reactions⁸ could contest and exceed conventional methods in terms of celerity and efficiency. One example is the work done by Li and group recently, whereby they reported the use of terminal ynones and aminoaryls to produce 3-carbonyl quinolines *via* Fe-catalyzed Michael addition-cycloaddition approach.⁹

Alkyne moieties have been universally employed in numerous organic syntheses. Mainly, metal-catalyzed intermolecular alkyne reactions have been very popular in cycloadditions due to the fact that they offer a convenient approach to attain cyclic compounds.¹⁰ Our group has been developing novel synthetic routes to heterocycles through efficient methodologies.¹¹ One example is the microwave-assisted three component synthesis of pyrimidinones, using copper catalyst.¹² Inspired by the opportunities surrounding alkyne moieties and our interests in the construction of heterocycles, we envisioned the employment of alkyne in the synthesis of a variety of quinoline derivatives.

Although there have been many reports on quinoline synthesis using alkynes,^{9,13} the present methods often uses terminal alkynes and have a relatively limited substrate applicability. Internal alkynes, in comparison to terminal alkynes, allow incorporation of more functional groups, increasing their employability. Due to the lack of reports on using internal alkynes to synthesize quinolines, herein, we report successful applications of an array of 2-aminoaryl carbonyls and internal alkynes in the construction of quinoline derivatives.

2. Results and Discussion

Table 1. Optimization of Quinoline **3a**.

entry ^a	catalyst	ligand/	solvent	temp (°C)	time (h)	yield (%)
1	Ni(cod) ₂	PPh ₃	DMF	100	24	-
2	Sc(OTf) ₃	-	DMF	100	24	n.r.
3	AuCl ₃	-	DMF	100	4	30
4	(Ph ₃ P)AuCl	AgOTf	DMF	100	2	88
5 ^b	RAuCl	AgOTf	DMF	100	3	72
6 ^c	(Ph ₃ P)AuCl	AgNO ₃	DMF	100	24	<10
7	(Ph ₃ P)AuCl	Ag ₂ CO ₃	DMF	100	24	n.r.
8	(Ph ₃ P)AuCl	AgOTf	ACN	reflux	12	58
9	(Ph ₃ P)AuCl	AgOTf	THF	60	12	47
10 ^c	(Ph ₃ P)AuCl	AgOTf	CH ₂ Cl ₂	reflux	24	<10
11	(Ph ₃ P)AuCl	AgOTf	DMF	50	5	66
12 ^d	(Ph ₃ P)AuCl	AgOTf	DMF	100	8	82
13 ^e	(Ph ₃ P)AuCl	AgOTf	DMF	100	1	80

^a Unless specified, reactions were carried out by treating **1a** (1 equiv) and **2a** (1.5 equiv) with catalyst (10 mol%) and ligand/ additive (10 mol%) in solvent (2 mL). ^b R = [P(*t*-Bu)₂(*o*-biphenyl)]. ^c more than 80% of the starting materials were recovered. ^d

Initial studies were carried out with the aim to find a suitable catalyst to induce the reaction between 2-aminobenzaldehyde **1a** and ethyl 3-phenylpropiolate **2a**. Ni(cod)₂ was selected as the preliminary experimental catalyst because there have been many reports reporting nickel's applications in this type of addition reactions.¹⁴ However, the catalyst was unable to produce the desired product. In addition, for Sc(OTf)₃, no reaction was observed even after heating at 100 °C for 24 h (Table 1, entries 1-2). Subsequently, attention was then directed to gold catalysts. Gold catalysts provide enormous possibilities in synthetic reactions and many reports have acknowledged

Table 2. Substrate scope: An insight to the flexibility of the reaction through various 2-aminoaryl carbonyls **1**

entry ^a	1	3	yield (%)
1			88
2			91
3			91
4			90
5			83
6			38
7			88
8			82
9			83
10			80
11			91

^a Reactions were treated **1** (1 equiv) and **2** (1.5 equiv) with (Ph₃P)AuCl (10 mol%) and AgOTf (10 mol%) in DMF (2 mL) at 100 °C.

their potentials, particularly in cycloadditions of alkyne as they preferentially coordinates to the alkyne bonds.¹⁵ Moreover, gold catalysts have also been confirmed to aid substantially in the synthesis of quinolines¹⁶ and isoquinolines¹⁷. Gratifyingly, successful acquirement of the product when catalytic amount of AuCl₃ was used validated our hypothesis, although only 30% of the yield was obtained (Table 1 entry 3). Silver additives, on the other hand, have been known to complement gold catalysts. Through halide abstraction, they can increase the electrophilicity of the gold center.¹⁸ Therefore, the reaction was subsequently examined with silver additives. Interestingly, the yield was increased to 88% and the time was reduced to 2 h when AuCl₃ was replaced by (Ph₃P)AuCl, with AgOTf additive. Additional attempt to change the catalyst to [P(*t*-Bu)₂(*o*-biphenyl)]AuCl gave a less satisfactory result (72% yield, Table 1 entry 5). These results show that (Ph₃P)AuCl catalyst is suitable for this reaction and the attention was then turned towards searching for an additive most compatible with (Ph₃P)AuCl. After screening different additives including Ag₂CO₃ and AgNO₃, it was obvious that the combination of (Ph₃P)AuCl with AgOTf additive afforded the best yield (Table 1, entries 4, 6-7). Following which, investigation of the solvent effect reveals DMF to be the best solvent in contrast to THF, ACN, and CH₂Cl₂ (Table 1, entries 8-10). When the temperature was reduced to 50 °C, longer reaction times and lower yields were obtained (Table 1, entry 11) hence, the reaction temperature was fixed at 100 °C. In the last part of the studies, the additive and catalyst loadings were examined. Though there were no substantial effects of the loadings on the yields, observable variations in the reaction times were documented (Table 1, entries 12-13). When the loadings were reduced to 5 mol%, the reaction time was increased to 8 h. Increase of the loadings to 20 mol% did not reduce the reaction time significantly thus, 10 mol% of catalyst and additive loadings were selected as the

most favourable loading amounts. Through the optimization studies, the set of optimal conditions was defined as 10 mol% (Ph₃P)AuCl, 10 mol% AgOTf in DMF at 100 °C. These conditions provided the product in a high yield of 88% within 2 h.

Elucidation of the conditions allowed investigation of the reaction scope and flexibility. To investigate the adaptability of this reaction, an array of 2-aminoaryl carbonyls **1** were used. From Table 2, it was noteworthy that most of the 2-aminoaryl carbonyls **1** afforded the desired products in good to excellent yields (80-91%). A closer analysis of the results revealed that in comparison to the 5-Cl, 5-NO₂, 4'-Cl and 4'-Br substituted 2-aminobenzophenones, the 4-Me and 4'-Me substituted benzophenones provided observable higher yields (Table 2, entries 4-9, **3d-3i**). This led to the conjecture that electron-donating substituents perform slightly better than electron-withdrawing substituents. In particular, when strong electron-withdrawing 5-NO₂ substituted 2-aminobenzophenone was subjected to the optimal conditions, the reaction could not go to completion even after 48 h and the final yield of 38% (**3f**) was rather inferior to other products (Table 2, entry 6). In addition, when 2-aminobenzophenone was replaced with 5-Cl and 2'-F, the yield was marginally lower (80%), probably due to the presence of two electron-withdrawing substituents (Table 2, entry 10). Motivated by the success of these aryl substituents, the focus was turned to the possibility of introducing alkyl substituents in the system. Noteworthy, the reaction proceeded efficiently in the presence of 2-aminoacetophenone, producing an excellent yield of 91% (Table 2, entry 2, **3b**). Extending the alkyl chain did not have any effect on the yield and compound **3k** was also afforded with an exceptional yield (Table 2, entry 11).

Table 3. Substrate scope: An insight to the flexibility of the reaction through various internal alkyne substituents **2**

entry ^a	1	2	3	yield (%)
1	1a	2b	R ¹ =4-CH ₃ Ph, R ² =OEt 3l	90
2	1a	2c	R ¹ =4-OCH ₃ Ph, R ² =OEt 3m	93
3	1a	2d	R ¹ =4-BrPh, R ² =OEt 3n	85
4	1a	2e	R ¹ =4-NO ₂ Ph, R ² =OEt 3o	80
5	1a	2f	R ¹ =naphthalene, R ² =OEt 3p	88
6 ^b	1c	2g	R ¹ =CH ₃ , R ² =OEt 3q	90
7 ^b	1c	2h	R ¹ =CH ₂ CH ₂ CH ₃ , R ² =OEt 3r	91
8 ^b	1c	2i	R ¹ =(CH ₂) ₅ CH ₃ , R ² =OEt 3s	88
9	1a	2j	R ¹ =Ph, R ² =piperidine 3t	75
10	1a	2k	R ¹ =Ph, R ² =CH ₃ 3u	65

^a Reactions carried out by treating **1a** (1 equiv) and **2** (1.5 equiv) with (Ph₃P)AuCl (10 mol%) and AgOTf (10 mol%) in DMF (2 mL) at 100 °C. ^b Reactions with **1c** (1 equiv).

Extension of the initial studies on the substrate scope (Table 3) is important and therefore, the reaction was explored using different alkyne substituents **2**. Gratifyingly, good to excellent yields (80-90%) were produced in the presence of electron-donating or electron-withdrawing substituents on the aryl ring of the alkyne (Table 3, entries 1-4, **3l-3o**). Although there was a slight reduction in the yields for electron-withdrawing substituents in contrast to electron-donating substituents, the difference is less obvious and good yields were obtained even for NO₂ substituted aryl alkynes. In addition, bulky substituent (naphthalene) on the aryl alkyne did not impede the reaction and **3p** was obtained in a high yield of 88% (Table 3, entry 5). For alkyl alkyne, smooth development of the reaction also occurred and excellent yields between 88% to 91% were provided (Table 3, entries 6-8, **3q-3s**). Consequently, the ethoxy group in the alkyne was replaced with a piperidine group, and a relatively good

yield of 75% was afforded for **3t** (Table 3, entry 9). Finally, a ketone-substituted alkyne was used and the reaction gave a reasonable yield of 65% (Table 3, entry 10, **3u**). This further demonstrates the diversity of the reaction and delivers a favourable conclusion to our investigations.

3. Conclusion

In summary, a convenient methodology for the efficient synthesis of quinolines was established with the aid of $(\text{PPh}_3)\text{AuCl}$ catalyst and AgOTf additive. This intermolecular cyclisation of internal alkynes permitted the effective integration of additional functional groups into quinolines. Moreover, the adaptability of this strategy was exhibited by the good to excellent yields obtained for a wide variety of substrates. The importance of quinolines extends beyond being components of natural products; they have also been recognised for their widespread applications in biological and pharmaceutical fields.¹⁻³ Hence, the success of this strategy offers immediate access to a broad library of quinolines, contributing significantly in the field of research.

4. Experimental Section

All reactions were conducted under an atmosphere of nitrogen, unless otherwise indicated. All reagents and solvents were obtained from commercial suppliers and used without further purification. Product purification by flash column chromatography was accomplished using silica gel (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. IR spectra were recorded and reported in cm^{-1} . High-resolution mass spectra (HRMS) were obtained on an ion trap mass spectrometer, coupled with the HPLC system and the CE system. Accurate masses are reported for the molecular ion $[\text{M}+\text{H}]^+$ or a suitable fragment ion. NMR spectra were recorded at room temperature on a 400 MHz NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ^1H NMR spectroscopy and 77.0 ppm for ^{13}C NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved.

2-Aminoaryl carbonyls **1b-1j** and internal alkynes **2a**, **2g-2i** were obtained from commercial suppliers and used without further purification. Other 2-aminoaryl carbonyls **1a**^{19a} and **1k**^{19b} and internal alkynes **2b-2f**,^{20a} **2j**,^{20b} **2k**^{20c} were prepared from the standard literature procedures.

4.1 General procedure for the Synthesis of Quinolines:

To a solution of 2-aminobenzaldehyde **1a** (10.0 mg, 0.08 mmol, 1.0 equiv), (PPh₃)AuCl (0.4 mg, 0.008 mmol, 0.1 equiv) and AgOTf (0.2 mg, 0.008 mmol, 0.1 equiv) in DMF (2 mL) was added ethyl 3-phenylpropiolate **2a** (15.0 μ L, 0.09 mmol, 1.1 equiv). The reaction mixture was stirred at 100 °C for 2 h (TLC monitored). The resulting mixture was then diluted with EtOAc and filtered through celite. The filtrate was washed with water (2 $\times$ 20 mL) and brine (2 $\times$ 20 mL) and the organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the crude residue as a dark yellow oil. The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3a** (20.1 mg, 0.07 mmol, 88% yield) as a yellow oil.

Ethyl 2-phenylquinoline-3-carboxylate (**3a**)

R_f = 0.34 (EtOAc/Hex: 20/80); **¹H NMR (400 MHz, CDCl₃)**: δ 8.65 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.83-7.79 (m, 1H), 7.65-7.59 (m, 3H), 7.50-7.44 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)**: δ 168.0, 158.1, 148.4, 140.8, 139.0, 131.5, 129.5, 128.6, 128.5, 128.2(2), 127.2, 125.8, 125.5, 61.5, 13.7; **FT-IR (neat)** $\nu_{\max}$ 3063, 2986, 2901, 1721, 1620, 1597, 1451, 1234, 1096, 833 cm⁻¹; **HRMS (ESI)**: m/z calcd for C₁₈H₁₅NO₂ [M+H]⁺, 278.1103, found 278.1181.

Ethyl 4-methyl-2-phenylquinoline-3-carboxylate (**3b**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3b** (19.6 mg, 0.07 mmol, 91% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex: 20/80); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.70-7.68 (m, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.48-7.43 (m, 3H), 4.15 (q, J = 7.2 Hz, 2H), 2.76 (s, 3H), 1.01 (t, J = 7.2 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 169.1, 156.2, 147.2, 142.7, 140.6, 130.3, 128.6, 128.3, 127.4, 126.9, 126.0, 124.1, 61.5, 15.6, 13.6; **FT-IR** (neat) ν_{max} 3063, 2986, 1721, 1644, 1582, 1497, 1450, 1296, 1234 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 292.1259, found 292.1338.

Ethyl 2,4-diphenylquinoline-3-carboxylate (**3c**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3c** (16.3 mg, 0.05 mmol, 91% yield) as a yellow solid. R_f = 0.34 (EtOAc/Hex: 20/80); **m.p.** 89-91 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.23 (d, J = 8.3 Hz, 1H), 7.79-7.75 (m, 3H), 7.62 (d, J = 8.3 Hz, 1H), 7.52-7.41 (m, 9H), 3.87 (q, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.2, 156.0, 147.8, 147.1, 140.2, 135.5, 130.4, 129.8, 129.4, 129.1, 128.8, 128.6, 128.5, 128.4, 128.2, 127.2, 127.0, 126.5, 125.5, 61.2, 13.4; **FT-IR** (neat) ν_{max}

3063, 2978, 2893, 1728, 1612, 1551, 1481, 1443, 1296, 1227, 1103 cm^{-1} ; **HRMS** (**ESI**): m/z calcd for $\text{C}_{24}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 354.1416, found 354.1494.

Ethyl 7-methyl-2,4-diphenylquinoline-3-carboxylate (**3d**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3d** (15.7 mg, 0.04 mmol, 90% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex: 20/80); **^1H NMR (400 MHz, CDCl_3)**: δ 8.00 (s, 1H), 7.75-7.73 (m, 2H), 7.51-7.40 (m, 9H), 7.31 (d, J = 8.7 Hz, 1H), 3.86 (q, J = 7.2 Hz, 2H), 2.57 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 168.3, 156.0, 148.1, 146.9, 141.0, 140.4, 135.8, 129.4, 129.3, 128.8, 128.7, 128.5, 128.4(2), 128.2, 126.4, 126.2, 123.5, 61.2, 21.8, 13.4; **FT-IR (neat)** ν_{max} 3063, 2978, 2932, 2870, 1728, 1620, 1551, 1489, 1450, 1412, 1288, 1227, 1173 cm^{-1} ; **HRMS (ESI)**: m/z calcd for $\text{C}_{25}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 368.1572, found 368.1650.

Ethyl 6-chloro-2,4-diphenylquinoline-3-carboxylate (**3e**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3e** (13.8 mg, 0.04 mmol, 83% yield) as a yellow oil. R_f = 0.35 (EtOAc/Hex: 20/80); **^1H NMR (400 MHz, CDCl_3)**: δ 8.16 (d, J = 9.0 Hz, 1H), 7.76-7.73 (m, 2H), 7.70 (dd, J = 2.2, 9.0 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.52-7.46 (m, 6H), 7.46-7.39 (m, 2H), 3.88 (q, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2

Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.8, 156.2, 146.3, 146.2, 139.8, 134.8, 133.0, 131.4, 129.3, 129.1, 128.8, 128.5(2), 128.4, 127.9, 126.3, 125.3, 61.4, 13.4; **FT-IR** (neat) ν_{max} 3063, 2986, 2932, 1728, 1643, 1551, 1474, 1443, 1296, 1219, 1111, 756, 702 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{24}\text{H}_{18}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$, 388.1026, found 388.1104.

Ethyl 6-nitro-2,4-diphenylquinoline-3-carboxylate (3f)

The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **3f** (6.2 mg, 0.02 mmol, 38% yield) as a yellow solid. R_f = 0.31 (EtOAc/Hex: 20/80); **m.p.** 126-128 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 8.56 (d, J = 2.4 Hz, 1H), 8.53 (dd, J = 2.4, 9.2 Hz, 1H), 8.34 (d, J = 9.2 Hz, 1H), 7.79-7.77 (m, 2H), 7.57-7.56 (m, 3H), 7.51-7.49 (m, 3H), 7.43-7.41 (m, 2H), 3.91 (q, J = 7.1 Hz, 2H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.3, 159.4, 149.8, 149.1, 145.9, 138.3, 134.0, 131.7, 129.7, 129.4, 129.3, 128.9, 128.7, 128.6(2), 124.9, 123.9, 123.6, 61.7, 13.3; **FT-IR** (neat) ν_{max} 1728, 1643, 1558, 1528, 1481, 1443, 1342, 1288, 1219, 1111, 1088 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$, 399.1267, found 399.1345.

Ethyl 2-phenyl-4-*p*-tolylquinoline-3-carboxylate (3g)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3g** (15.3 mg, 0.04 mmol, 88% yield) as a

yellow oil. $R_f = 0.34$ (EtOAc/Hex: 20/80); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.22 (d, $J = 8.4$ Hz, 1H), 7.78-7.74 (m, 3H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.50-7.45 (m, 4H), 7.31 (s, 4H), 3.88 (q, $J = 7.1$ Hz, 2H), 2.46 (s, 3H), 0.83 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.3, 156.0, 147.8, 147.3, 140.3, 138.3, 132.5, 130.4, 129.8, 129.3, 128.9, 128.8, 128.6, 128.4, 126.9, 126.6, 125.7, 61.2, 21.4, 13.4; **FT-IR** (neat) ν_{max} 2978, 2924, 1728, 1636, 1551, 1489, 1458, 1296, 1227, 1103 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{25}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 368.1572, found 368.1650.

Ethyl 4-(4-chlorophenyl)-2-phenylquinoline-3-carboxylate (**3h**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3h** (13.7 mg, 0.04 mmol, 82% yield) as a yellow solid. $R_f = 0.35$ (EtOAc/Hex: 20/80); **m.p.** 107-109 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.23 (d, $J = 8.4$ Hz, 1H), 7.80-7.73 (m, 3H), 7.57-7.56 (m, 1H), 7.52-7.45 (m, 6H), 7.37 (d, $J = 8.4$ Hz, 2H), 3.90 (q, $J = 7.1$ Hz, 2H), 0.85 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.0, 156.0, 147.8, 156.8, 140.1, 134.8, 133.9, 130.8, 130.6, 129.9, 128.9, 128.5(2), 128.4, 127.3, 127.2, 126.2, 125.3, 61.4, 13.4; **FT-IR** (neat) ν_{max} 3017, 2986, 1721, 1636, 1574, 1551, 1481, 1404, 1219, 1103, 756, 664 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{24}\text{H}_{18}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$, 388.1026, found 388.1104.

Ethyl 4-(4-bromophenyl)-2-phenylquinoline-3-carboxylate (3i)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3i** (13.0 mg, 0.03 mmol, 83% yield) as a yellow solid. $R_f = 0.35$ (EtOAc/Hex: 20/80); **m.p.** 138-140 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.23 (d, $J = 8.4$ Hz, 1H), 7.80-7.73 (m, 3H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.58-7.45 (m, 5H), 7.30 (d, $J = 8.4$ Hz, 2H), 3.90 (q, $J = 7.1$ Hz, 2H), 0.85 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.0, 156.0, 147.8, 145.8, 140.1, 134.4, 131.5, 131.1, 130.6, 129.9, 128.9, 128.5, 128.4, 127.3, 127.1, 126.2, 125.2, 123.0, 61.4, 13.4; **FT-IR** (neat) ν_{max} 3071, 2986, 2932, 1728, 1636, 1551, 1481, 1443, 1296, 1227, 1103, 694, 664 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{24}\text{H}_{18}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$, 432.0521, found 432.0599.

Ethyl 6-chloro-4-(2-fluorophenyl)-2-phenylquinoline-3-carboxylate (3j)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3j** (13.0 mg, 0.03 mmol, 80% yield) as a yellow oil. $R_f = 0.35$ (EtOAc/Hex: 20/80); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.17 (d, $J = 9.0$ Hz, 1H), 7.76-7.70 (m, 3H), 7.54-7.46 (m, 5H), 7.34-7.25 (m, 3H), 3.90 (q, $J = 7.1$ Hz, 2H), 0.85 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 167.5, 160.9, 158.5, 156.5, 146.1, 140.9, 139.8, 133.4, 131.7, 131.5, 131.3, 131.2, 129.1, 128.5(2),

126.2, 124.8, 124.3(2), 122.6, 116.0, 115.8, 61.5, 13.4; **FT-IR (neat)** $\nu_{\max}$ 3017, 2986, 2940, 1728, 1636, 1574, 1551, 1474, 1450, 1296, 1219, 1111, 756, 664 cm^{-1} ; **HRMS (ESI)**: m/z calcd for $\text{C}_{24}\text{H}_{17}\text{FCINO}_2$ $[\text{M}+\text{H}]^+$, 406.0932, found 406.1010.

Ethyl 4-butyl-2-phenylquinoline-3-carboxylate (**3k**):

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3k** (17.1 mg, 0.05 mmol, 91% yield) as a yellow oil. R_f = 0.42 (EtOAc/Hex: 20/80); **^1H NMR (400 MHz, CDCl_3)**: δ 8.17 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.69-7.67 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.48-7.42 (m, 3H), 4.13 (q, J = 7.1 Hz, 2H), 3.15-3.11 (m, 2H), 1.80-1.73 (m, 2H), 1.52 (sext, J = 7.4 Hz, 2H), 1.03-0.97 (m, 6H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 169.1, 156.4, 147.7, 147.4, 140.7, 130.5, 130.2, 128.6, 128.4, 128.3, 126.9(2), 125.3, 124.1, 61.4, 33.2, 29.7, 23.3, 13.8, 13.6; **FT-IR (neat)** $\nu_{\max}$ 3063, 2955, 2924, 2870, 1721, 1620, 1574, 1497, 1458, 1404, 1288, 1234, 1165, 1103 cm^{-1} ; **HRMS (ESI)**: m/z calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 334.1729, found 334.1807.

Ethyl 2-p-tolylquinoline-3-carboxylate (**3l**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3l** (21.6 mg, 0.07 mmol, 90% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex: 20/80); **^1H NMR (400 MHz, CDCl_3)**: δ 8.62 (s,

1H), 8.17 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.80 (t, $J = 7.6$ Hz, 1H), 7.59 (t, $J = 7.6$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 2H), 7.28-7.26 (m, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.42 (s, 3H), 1.13 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.1, 158.1, 148.5, 138.9, 138.5, 137.8, 131.4, 129.5, 128.9, 128.5, 128.2, 127.0, 125.8, 125.5, 61.5, 21.3, 13.8; **FT-IR (neat)** ν_{max} 3017, 2932, 1721, 1620, 1458, 1427, 1219, 1096 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 292.1259, found 292.1338.

Ethyl 2-(4-methoxyphenyl)quinoline-3-carboxylate (3m)

The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **3m** (23.6 mg, 0.08 mmol, 93% yield) as a yellow oil. $R_f = 0.21$ (EtOAc/Hex: 20/80); ^1H NMR (400 MHz, CDCl_3): δ 8.60 (s, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.80 (t, $J = 7.7$ Hz, 1H), 7.61 (d, $J = 8.6$ Hz, 2H), 7.60-7.56 (m, 1H), 7.00 (d, $J = 8.6$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 3.87 (s, 3H), 1.16 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.3, 160.2, 157.7, 148.4, 138.9, 133.2, 131.4, 130.1, 129.4, 128.2, 127.0, 125.7, 125.5, 113.7, 61.6, 55.4, 13.9; **FT-IR (neat)** ν_{max} 3017, 2978, 2940, 2839, 1721, 1612, 1558, 1512, 1458, 1420, 1250, 1219, 1096, 1034 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$, 308.1208, found 308.1287.

Ethyl 2-(4-bromophenyl)quinoline-3-carboxylate (3n)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3n** (24.9 mg, 0.07 mmol, 85% yield) as a pale yellow solid. $R_f = 0.35$ (EtOAc/Hex: 20/80); **m.p.** 86-88 °C; **^1H NMR (400 MHz, CDCl_3):** δ 8.68 (s, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.83 (t, $J = 8.3$ Hz, 1H), 7.64-7.60 (m, 3H), 7.52 (d, $J = 8.3$ Hz, 2H), 4.23 (q, $J = 7.2$ Hz, 2H), 1.16 (t, $J = 7.2$ Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 167.5, 157.0, 148.4, 139.7, 139.4, 131.8, 131.3, 130.3, 129.5, 128.3, 127.5, 125.9, 125.0, 123.0, 61.7, 13.8; **FT-IR (neat)** ν_{max} 3017, 2986, 1721, 1620, 1597, 1558, 1481, 1450, 1420, 1265, 1227, 1096 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{18}\text{H}_{14}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$, 356.0208, found 356.0286.

Ethyl 2-(4-nitrophenyl)quinoline-3-carboxylate (3o)

The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **3o** (21.3 mg, 0.07 mmol, 80% yield) as a yellow solid. $R_f = 0.23$ (EtOAc/Hex: 20/80); **m.p.** 146-148 °C; **^1H NMR (400 MHz, CDCl_3):** δ 8.80 (s, 1H), 8.34 (d, $J = 8.5$ Hz, 2H), 8.18 (d, $J = 8.5$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.88 (t, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 2H), 7.68 (t, $J = 8.0$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 166.7, 156.2, 148.4, 147.8, 147.3, 140.0, 132.2, 129.7, 129.6, 128.4, 128.1, 126.2, 124.4, 123.3, 61.8, 13.9; **FT-IR (neat)** ν_{max} 3017, 2986, 1721, 1620, 1597, 1558, 1481,

1450, 1420, 1373, 1265, 1227, 1096 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$, 323.0954, found 323.1032.

Ethyl 2-(naphthalen-2-yl)quinoline-3-carboxylate (3p)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3p** (23.8 mg, 0.07 mmol, 88% yield) as a pale yellow oil. R_f = 0.34 (EtOAc/Hex: 20/80); **^1H NMR (400 MHz, CDCl_3):** δ 8.87 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.94-7.84 (m, 3H), 7.67 (t, J = 7.6 Hz, 1H), 7.60-7.52 (m, 3H), 7.46 (t, J = 7.0 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 3.85 (q, J = 7.1 Hz, 2H), 0.60 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 166.8, 158.1, 148.7, 139.5, 139.1, 133.4, 131.9, 131.8, 129.6, 128.5(2), 128.3, 127.5, 126.4, 126.3(2), 125.7, 125.2, 125.1, 61.1, 13.1; **FT-IR (neat)** ν_{max} 3055, 2978, 2932, 1721, 1620, 1597, 1558, 1489, 1458, 1427, 1250, 1234, 1204, 1072 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{22}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 328.1259, found 328.1338.

Ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3q):

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3q** (13.3 mg, 0.05 mmol, 90% yield) as a yellow solid. R_f = 0.42 (EtOAc/Hex: 20/80); **m.p.** 85-87 $^{\circ}\text{C}$; **^1H NMR (400 MHz, CDCl_3):** δ 8.07 (d, J = 8.4 Hz, 1H), 7.74-7.70 (m, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.50-

7.47 (m, 3H), 7.45-7.41 (m, 1H), 7.38-7.35 (m, 2H), 4.06 (q, $J = 7.1$ Hz, 2H), 2.79 (s, 3H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.5, 154.6, 147.7, 146.2, 135.7, 130.2, 129.4, 128.9, 128.4, 128.2, 127.4, 126.5, 126.4, 125.2, 31.3, 23.8, 13.6; **FT-IR (neat)** ν_{max} 2978, 2932, 1728, 1566, 1489, 1443, 1404, 1296, 1227, 1180, 1065 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 292.1259, found 292.1338.

Ethyl 4-phenyl-2-propylquinoline-3-carboxylate (3r)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3r** (14.7 mg, 0.05 mmol, 91% yield) as a pale yellow solid. $R_f = 0.42$ (EtOAc/Hex: 20/80); **m.p.** 85-87 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 8.10 (d, $J = 8.4$ Hz, 1H), 7.73-7.69 (m, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.50-7.35 (m, 6H), 4.04 (q, $J = 7.2$ Hz, 2H), 3.02-2.98 (m, 2H), 1.88 (sext, $J = 7.4$ Hz, 3H), 1.05 (t, $J = 7.4$ Hz, 3H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.5, 158.3, 147.8, 146.3, 135.8, 130.1, 129.4, 129.0, 128.4, 128.2, 127.4, 126.4, 126.3, 125.1, 61.2, 39.2, 23.1, 14.2, 13.6; **FT-IR (neat)** ν_{max} 3017, 2963, 2870, 1721, 1566, 1481, 1458, 1404, 1219, 1065 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 320.1572, found 320.1650.

Ethyl 2-hexyl-4-phenylquinoline-3-carboxylate (3s)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3s** (16.1 mg, 0.04 mmol, 88% yield) as a pale yellow oil. $R_f = 0.42$ (EtOAc/Hex: 20/80); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.10 (d, $J = 8.4$ Hz, 1H), 7.73-7.69 (m, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.49-7.35 (m, 6H), 4.04 (q, $J = 7.2$ Hz, 2H), 3.04-3.00 (m, 2H), 1.89-1.81 (m, 2H), 1.45 (t, $J = 7.2$ Hz, 2H), 1.34-1.30 (m, 4H), 0.95 (t, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.0$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.5, 158.5, 147.8, 146.3, 135.9, 130.1, 129.4, 129.0, 128.4, 128.2, 127.3, 126.4, 126.3, 125.1, 61.2, 37.3, 31.7, 29.8, 29.4, 22.5, 14.0, 13.6; **FT-IR** (neat) ν_{max} 3024, 2955, 2932, 2862, 1721, 1643, 1556, 1489, 1458, 1404, 1219, 1173, 1065 cm^{-1} ; **HRMS** (ESI): m/z calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 362.2042, found 362.2120.

(2-Phenylquinolin-3-yl)(piperidin-1-yl)methanone (3t)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3t** (19.6 mg, 0.06 mmol, 75% yield) as a yellow oil. $R_f = 0.03$ (EtOAc/Hex: 20/80); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.24 (s, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.90-7.85 (m, 3H), 7.77 (t, $J = 7.2$ Hz, 1H), 7.58 (t, $J = 7.2$ Hz, 1H), 7.51-7.45 (m, 3H), 3.72-3.66 (m, 1H), 3.53-3.47 (m, 1H), 2.93-2.86 (m,

1H), 2.73-2.67 (m, 1H), 1.58-1.50 (m, 1H), 1.44-1.30 (m, 3H), 1.18-1.09 (m, 1H), 0.62-0.53 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.4, 155.2, 148.0, 139.4, 136.0, 130.5, 130.1, 129.6, 129.2(2), 128.5, 127.7, 127.1, 126.5, 47.7, 42.5, 25.2, 24.9, 24.1; **FT-IR (neat)** $\nu_{\max}$ 3017, 2947, 2862, 1620, 1474, 1443, 1219, 1026 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₂₁H₂₀N₂O [M+H]⁺, 317.1576, found 317.1654.

1-(2-phenylquinolin-3-yl)ethanone (**3u**)

The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3u** (15.2 mg, 0.06 mmol, 65% yield) as a yellow oil. *R_f* = 0.17 (EtOAc/Hex: 20/80); ¹H NMR (400 MHz, CDCl₃): δ 8.11 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 7.3 Hz, 2H), 7.79-7.75 (m, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.56-7.47 (m, 3H), 2.74 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 196.7, 156.6, 148.0, 137.2, 136.7, 133.7, 132.2, 131.0, 130.1, 128.7, 128.6, 128.1, 126.6, 125.2, 24.2; **FT-IR (neat)** $\nu_{\max}$ 3061, 3019, 2958, 1663, 1568 cm⁻¹; **HRMS (ESI):** *m/z* calcd for C₁₇H₁₃NO [M+H]⁺, 248.0997, found 248.1075.

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APPENDICES – PART II

Polysubstituted Pyrrole Derivatives *via* 1,2-Alkenyl

**Migration of Novel γ -Amino- α,β -Unsaturated Aldehydes
and α -Diazocarbonyls**

Appendix – Part II

Polysubstituted Pyrrole Derivatives *via* 1,2-Alkenyl Migration of Novel γ -Amino- α,β -Unsaturated Aldehydes and α -Diazocarbonyls

1. Introduction

In the field of pyrrole synthesis, the continuous efforts to develop competent strategies emphasize the inadequacy of current available methods. A probe into the existing methods provided an insight to the inefficacy as well as substantiated the need to refine and surpass current approaches. The use of non-environmental catalysts,^[1] harsh reaction conditions and deprived yields^[2] contributed to the general consensus that there is still a huge underlying potential in pyrrole synthesis. Not only are pyrroles omnipresent in natural products^[3] and drugs^[4] (Figure 1), they also exhibit a wide range of biological activities (anti-inflammatory,^[5] antibiotic^[6] and anti-tumour^[7] activities), provide an excellent choice in catalytic systems^[8] and adopt a leading spot

Figure 1. Pyrrole-containing natural products/ drugs

over other aromatic heterocycles in drug discovery.^[9] With such compelling benefits, it is not surprising that their synthesis has engaged the chemical society over the past century.

Classical approaches to the synthesis of substituted pyrroles often revolve around the concept of Paal-Knorr synthesis in 1884.^[10] This work, involving the reaction between an amine and a 1,4-dicarbonyl compound, has brought great expansion to the otherwise limited synthesis of pyrroles. Noteworthy, other conventional methods such as Huisgen^[11] and Hantzsch^[12] pyrrole synthesis have also contributed significantly to the development of pyrrole derivatives. Over the past decades, various strategies which attempted to improve on these traditional approaches have emerged and produced remarkable results, such as multi-component one-pot reactions^[13] and palladium catalyzed C-H activation.^[14] They served as alternatives to synthesize poly-functionalized pyrrole derivatives and have created excellent opportunities for researchers. Inspired by the abundant benefits and possibilities, our group has decided to develop new methodologies in the synthesis of pyrrole derivatives,^[15] continuing our constant efforts in the construction of heterocyclic compounds.^[16]

Successful representations of transition metal-catalyzed 1,2-migration in the assembly of heterocycles^[17] sparked off our interests in adopting this method for the synthesis of pyrroles. A widely used and highly efficient strategy in organic synthesis, 1,2-migration can be generally classified into 1,2-hydride,^[18] alkyl^[19], aryl and alkenyl migration^[20]. Although the reactions involving 1,2 migrations generally produce promising results, 1,2-alkenyl migration seems to be less prevalent in contrast to the other categories.

Therefore, due to the increasing popularity of diazo compounds at the same time, we envisioned the possibility of using diazo compounds to participate in a 1,2-alkenyl migration, forming pyrrole derivatives simultaneously.^[21] The generation of metal carbene species through the diazo compounds provides diverse reactivities, which in turn helps to induce 1,2-shift formations, cyclopropanations and bond insertions.^[22] With the integration of both aspects, herein, we report an efficient synthesis of polysubstituted pyrrole derivatives through the addition of diazocarbonyl compounds to various γ -amino- α,β -unsaturated aldehydes. We envisioned that the successful execution of such a system will provide an interesting insight through the implementation of 1,2-alkenyl shift from novel γ -amino- α,β -unsaturated aldehydes.

2. Results and Discussion

Table 1. Optimisation of the synthesis of polysubstituted pyrrole derivatives from *N*-Boc- γ -amino- α,β -unsaturated aldehyde **1a** and α -diazocarbonyl **2a** ^[a]

Reaction scheme showing the synthesis of polysubstituted pyrrole derivative **3a** from *N*-Boc- γ -amino- α,β -unsaturated aldehyde **1a** and α -diazocarbonyl **2a**. The reaction conditions are catalyst, solvent, and temperature.

Entry	Catalyst	Solvent	Temp (°C)	Yield ^[b] (%)
1	BF ₃ ·Et ₂ O	CH ₂ Cl ₂	r.t	-
2	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	r.t	n.r
3	SnCl ₄	CH ₂ Cl ₂	r.t	35
4	ZnBr ₂	CH ₂ Cl ₂	r.t	n.r
5	ZnCl ₂	CH ₂ Cl ₂	r.t	n.r
6	AlCl ₃	CH ₂ Cl ₂	r.t	n.r
7	TiCl ₄	CH ₂ Cl ₂	r.t	63
8	TiCl ₄	CH ₂ Cl ₂	reflux	78
9	TiCl ₄	Toluene	60	55
10	TiCl ₄	THF	reflux	28
11	TiCl ₄	MeCN	r.t	20
12	TiCl ₄	DMF	reflux	-
13 ^[c]	TiCl ₄	CH ₂ Cl ₂	reflux	64
14 ^[d]	TiCl ₄	CH ₂ Cl ₂	reflux	79

[a] All reactions were conducted in CH₂Cl₂ with 2.0 equiv of aldehyde **1a** and 1.0 equiv of α -diazocarbonyl **2a** in the presence of 10 mol% TiCl₄. [b] Isolated yield. [c] Reaction was conducted with 5 mol% TiCl₄. [d] Reaction was conducted with 20 mol% TiCl₄.

Preliminary studies focus on the optimisation of a suitable and efficient set of conditions for the reaction between ethyl diazoacetate **2a** and *N*-Boc- γ -amino- α,β -unsaturated aldehyde **1a**. The search began with the identification of an appropriate catalyst to encourage this reaction. Based on earlier reports, it could be observed that successful 1,2-migration often involves the incorporation of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the Lewis acid catalyst.^[20a, 23] With this noticeable trend, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ naturally became the first choice of catalyst for the initial optimization. Although $\text{BF}_3 \cdot \text{Et}_2\text{O}$ appears to be a promising catalyst at the outset, no desired product was obtained when it was employed in this reaction. Therefore, the change in focus towards other possible catalyst was essential and further review of past literatures revealed $\text{Rh}_2(\text{OAc})_4$ ^[24] and SnCl_4 ^[25] as highly efficient catalysts for 1,2-shifts. While $\text{Rh}_2(\text{OAc})_4$ did not manage to induce the reaction, SnCl_4 successfully produced the desired product, albeit a relatively low yield (35%) was obtained with long reaction time. Despite the success of SnCl_4 in obtaining the desired product, the search for an optimal catalyst continued as attempts to raise the yields through changing the solvent, reaction times and temperature were unproductive. After several unsuccessful tries involving ZnBr_2 , ZnCl_2 and AlCl_3 , TiCl_4 was finally located as an efficient catalyst which could catalyse the reaction with a reasonably good yield of 63%.^[26]

Having identified the suitable catalyst, other factors such as solvent and temperature were then taken into consideration and varied. When the reaction was subjected to reflux condition instead of normal room temperature, the yield was exponentially increased to 78%. In addition, after some analysis, it was found that CH_2Cl_2 remains the most appropriate solvent in contrast to other common solvents such as toluene, DMF, MeCN and THF. Finally, the catalyst loading was modified and 20 mol% of the catalyst proves to be the best loading (similar results were

$\text{R}^1 = \text{Boc} \quad 78\%$
 $\text{Bn} \quad 55\%$
 $\text{Cbz} \quad -$
 $\text{Ts} \quad -$

[a] All reactions were conducted in CH₂Cl₂ with 2.0 equiv of *N*-protected- γ -amino- α,β -unsaturated aldehyde **1** and 1.0 equiv of α -diazocarbonyl **2a** in the presence of 10 mol% TiCl₄. [b] Isolated yield after column chromatography.

Scheme 2. Pyrrole derivatives from 1,2-migration of *N*-protected- γ -amino- α,β -unsaturated aldehyde **1** and α -diazocarbonyl **2**^{[a],[b]}

[a] Reactions were conducted in CH₂Cl₂ with 1.0 equiv of *N*-protected- γ -amino- α,β -unsaturated aldehyde **1** and 2.0 equiv of α -diazocarbonyl **2** in the presence of 10 mol% TiCl₄. [b] Isolated yield.

Acquirement of the ideal condition permitted investigation of the reaction's versatility through modification of the protecting group on γ -amino- α,β -unsaturated aldehyde **1** (Scheme 1). Although several protecting groups were screened, only the *tert*-butoxycarbonyl (Boc) and the benzyl protecting groups were suitable for the reaction, obtaining yields of 78% and 55% respectively. Since the Boc protecting group proved superior over others, we carried out the screening of the substrates using *N*-Boc- γ -amino- α,β -unsaturated aldehyde **1a**.

As the initial results amplified the suitability of diphenyl aldehydes, a range of electron donating and electron withdrawing substituents on the phenyl group was introduced (Scheme 2). Beginning from symmetrical diarylaminoaldehydes, the electron donating methyl-substituted **1b** was able to produce the pyrrole derivative **3b** in outstanding yield of 85%. Subjecting the reaction to electron withdrawing fluoro-substituted **3c** proved to be successful as well, obtaining a yield comparable to electron donating substituents (83%). To ensure that the reaction works on non-symmetrical diarylaminoaldehydes, single substituted methyl- and methoxy- **1d** and **1e** were synthesized and excellent yields were obtained for both compounds **3d** (83%) and **3e** (85%). However, when attempts to increase the scope were made by employing aliphatic aminoaldehyde, the reaction did not proceed as desired and no product was obtained.

Having investigated the aminoaldehydes component, the investigation was then drawn towards modifying the α -diazocarbonyls. Fixing on diazocarbonyl ester, branched ester substituents such as isopropyl ester **3g** and 2-methyl 2-butanol **3h** were examined and the reactions were able to give good to moderate yields of 76% and 58% respectively. Further extension of the chain length to 4 carbons **3i** did not deter the reaction and satisfactory result was also obtained. Finally, the successful application

of butyl- diazocarbonyl on both γ -amino- α,β -unsaturated aldehyde **3j** and difluoro- **3k** further indicated the tolerance of the reaction to an array of α -diazocarbonyls. To round up on our investigation of the substrate scope, the protecting group of the γ -amino- α,β -unsaturated aldehyde was changed to benzyl group. Although the reaction was generally less satisfactory and slower as compared to using Boc protecting group, the pyrrole derivative **3l** was still obtained in a moderate yield of 55%.

Figure 1. X-ray crystal structure of compound **3c**

The crystal structure of the γ -amino- α,β -unsaturated aldehyde confirms with our theory that during the synthesis of this aldehyde, the ring opening of the non-symmetrical cyclopropanone occurs in a manner whereby the amine will attack the more electron deficient carbon site. This preference is largely influenced by the substituents on the phenyl ring (electron donating or withdrawing). Although the crystal structure shows a *trans*-form of the γ -amino- α,β -unsaturated aldehyde (**1f** without protecting group), it can be expected that such compounds are present in an equilibrium mixture of *trans*- and *cis*-isomers.^[27] However, it is worthy of note that the *cis*-isomer might predominate after protection due to stabilization through intramolecular hydrogen bonding and steric hindrance.^[28] Subsequently, confirmation

of the structure of the polysubstituted pyrrole product was further done by obtaining the X-ray crystallography data of **3c** (Figure 1). With this product confirmation, a plausible mechanism can be deduced. Through a Lewis acid-catalyzed addition of diazoacetates with *N*-protected- γ -amino- α,β -unsaturated aldehyde **1**, an alkoxide intermediate **Int-1** could be formed. A 1,2-alkenyl shift would then produce **Int-2**. Following which, cyclization would then result in the desired pyrroles **3** (Scheme 3).

3. Conclusion

In conclusion, successful reactions between γ -amino- α,β -unsaturated aldehydes and α -diazocarbonyls were established. Polysubstituted pyrrole derivatives were obtained, using TiCl_4 as the catalyst, in moderate to excellent yields. The flexibility of the reaction was demonstrated by the range of substrates, as well as protecting group. The successful implementation of this methodology provides profound potentials as pyrrole derivatives are essential components of many natural products and biological drugs. In addition, the similarity in structure to the natural product amphorstatin indicates the possibility of using this straightforward strategy to the synthesis of this highly effective and largely in demand drug. Not only does this elegant methodology originates from the use of novel γ -amino- α,β -unsaturated aldehydes, the 1,2-alkenyl migration to produce polysubstituted pyrroles contributes an interesting discovery. Further studies for the application as well as extending the derivatives are underway.

4. Experimental Section

All reactions were conducted under an atmosphere of nitrogen, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Fluka and Alfa Aesar) and used without further purification unless otherwise stated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010 - 0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. IR spectra were recorded using FTIR Restige-21 (Shimadzu) and reported in cm^{-1} . High-resolution mass spectra (HRMS) were obtained on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. Accurate masses are reported for the molecular ion $[\text{M}+\text{H}]^+$ or a suitable fragment ion. NMR spectra were recorded at room temperature on a 400 MHz Bruker ACF 400 NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ^1H NMR spectroscopy and 77.0 ppm for ^{13}C NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet or unresolved. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/ α radiation (graphite monochromator).

4.1 General Synthetic procedure for the preparation of starting material, γ -amino- α,β -unsaturated aldehyde (S3)

Procedure (i):

To a suspension of tetrachlorocyclopropene (0.07 mL, 0.64 mmol, 1.0 equiv) and anhydrous AlCl_3 (180 mg, 1.35 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added dropwise, a solution of benzene (0.11 mL, 1.28 mmol, 2.0 equiv) in CH_2Cl_2 (1 mL) at -78°C . The mixture was stirred for 2 h then warm up to r.t and stirred for another 2 h (TLC monitored). The resulting mixture was quenched with water, diluted with CH_2Cl_2 , washed with water (2×50 mL) and brine (2×50 mL). The organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the crude residue as a orange oil. The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford diarylcyclopropenone **S2a** (224 mg, 1.09 mmol, 85% yield) as a yellow solid.¹

Procedure (ii):

To a suspension of diarylcyclopropenone **S2a** (100 mg, 0.49 mmol) in Et_2O at -78°C was added liquid ammonia. The suspension was then allowed to stir for 3 h at -40°C . After completion of the reaction, the cooling bath was removed and the mixture was concentrated under reduced pressure to yield the crude residue as a brown oil. The

crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford γ -amino- α,β -unsaturated aldehyde **S3a** (100 mg, 0.45 mmol, 92% yield) as a yellow solid.

(Z)-3-amino-2,3-diphenylacrylaldehyde (S3a)

m.p. 125-127 °C; **¹H NMR (400 MHz, CDCl₃):** δ 10.71 (s, 1H), 9.46 (s, 1H), 7.35-6.96 (m, 10H), 5.37 (s, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 191.2, 161.5, 137.9, 137.0, 130.7(2), 129.7, 129.4, 129.1, 128.6, 128.4, 128.0, 127.5, 125.5, 110.7; **FT-IR (neat)** $\nu_{\max}$ 3439, 3316, 3306, 3080, 3061, 3028, 1600 cm⁻¹; **HRMS (ESI):** m/z calcd for C₁₅H₁₃NO [M+H]⁺, 224.1075, found 224.1071.

(Z)-3-amino-2,3-di-*p*-tolylacrylaldehyde (S3b)

Orange solid, decomposes upon heating; **¹H NMR (400 MHz, CDCl₃):** δ 10.70 (s, 1H), 9.43 (s, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 5.30 (s, 1H), 2.31 (s, 3H), 2.27 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 191.3, 161.4, 139.9, 135.0, 130.6, 130.2, 130.0, 129.9, 129.7, 129.3, 129.1, 128.8, 128.4, 128.2, 29.7, 21.3; **FT-IR (neat)** 3445, 3308, 3022, 2920,

2860, 1715, 1626 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{17}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$, 252.1388, found 252.1388.

(Z)-3-amino-2,3-bis(4-fluorophenyl)acrylaldehyde (S3c)

Yellow solid; **m.p.** 134-136 $^{\circ}\text{C}$; ^1H **NMR (400 MHz, CDCl_3):** δ 10.66 (s, 1H), 9.42 (s, 1H), 7.20-7.17 (m, 2H), 6.97-6.83 (m, 6H), 5.32 (s, 1H); ^{13}C **NMR (100 MHz, CDCl_3):** δ 191.0, 164.5, 162.5, 160.3, 133.7, 130.6, 130.5, 128.6, 128.4, 128.2, 115.9, 115.8, 115.5, 115.2, 109.9; **FT-IR (neat)** ν_{max} 3443, 3383, 1614, 1603, 1217 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{15}\text{H}_{11}\text{F}_2\text{NO}$ $[\text{M}+\text{H}]^+$, 260.0887, found 260.0885.

(Z)-3-amino-3-phenyl-2-(p-tolyl)acrylaldehyde (S3d)

Pale yellow oil; ^1H **NMR (400 MHz, CDCl_3):** δ 10.73 (s, 1H), 9.45 (s, 1H), 7.33-7.20 (m, 3H), 7.17-7.08 (m, 2H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.99-6.94 (m, 2H), 6.85 (d, $J = 8.0$ Hz, 1H), 5.19 (s, 1H), 2.30-2.26 (m, 3H); ^{13}C **NMR (100 MHz, CDCl_3):** δ 191.4, 161.2, 137.2, 134.8, 134.1, 130.7, 129.9, 129.6, 129.3, 129.1, 128.7, 128.4, 128.0, 125.4, 110.6, 21.3; **FT-IR (neat)** ν_{max} 3445, 3329, 3312, 3057, 3030, 1607 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{16}\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$, 238.1232, found 238.1232.

(Z)-3-amino-2-(4-methoxyphenyl)-3-phenylacrylaldehyde (S3e)

Orange oil; ^1H NMR (400 MHz, CDCl_3): δ 10.72 (br s, 1H), 9.41-9.40 (m, 1H), 7.29-7.10 (m, 5H), 7.01-6.97 (m, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.68 (d, $J = 8.8$ Hz, 1H), 3.76-3.73 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.3, 161.5, 157.6, 138.3, 131.8, 130.7, 130.0, 129.5, 129.1, 128.6, 128.4, 128.0, 125.3, 113.7, 110.1, 55.2; FT-IR (neat) ν_{max} 3445, 3312, 3167, 3156, 3078, 3061, 3005, 1749, 1607 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 254.1181, found 254.1179.

(Z)-3-amino-3-(4-fluorophenyl)-2-phenylacrylaldehyde (S3f)

Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 10.68 (br s, 1H), 9.46 (s, 1H), 7.58-6.83 (m, 9H), 5.37 (br s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.3, 161.4, 137.9, 137.1, 130.7(2), 130.6, 129.8, 129.7, 129.3, 129.1, 128.6, 128.5, 128.4, 128.1, 128.0(2), 125.5, 114.8; FT-IR (neat) ν_{max} 3445, 3389, 3055, 1732, 1661, 1148 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{13}\text{FNO}$ $[\text{M}+\text{H}]^+$, 242.0981, found 242.0978.

4.2 General Synthetic procedure for the preparation of starting material, *N*-Boc- γ -amino- α,β -unsaturated aldehyde (**1**)

Procedure (iii):

To a solution of γ -amino- α,β -unsaturated aldehyde **S3a** (100 mg, 0.45 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) were added DMAP (11 mg, 0.09 mmol, 0.2 equiv) and triethylamine (0.19 mL, 1.35 mmol, 3.0 equiv). The solution was stirred for 15 mins at r.t, Boc_2O (147 mg, 0.67 mmol, 1.5 equiv) was added and then continued to stirred overnight (TLC monitored). The resulting solution was diluted with CH_2Cl_2 , washed with water (2×50 mL) and brine (2×50 mL). The organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the crude residue as a orange oil. The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford *N*-Boc- γ -amino- α,β -unsaturated aldehyde **1a** (64 mg, 0.20 mmol, 44% yield) as a yellow solid.

(Z)-tert-butyl (3-oxo-1,2-diphenylprop-1-en-1-yl)carbamate (1a)

m.p. 116-118 °C; **¹H NMR (400 MHz, CDCl₃):** δ 11.58 (s, 1H), 9.60 (s, 1H), 7.49-7.47 (m, 1H), 7.28-7.09 (m, 7H), 6.95-6.93 (m, 2H), 1.36 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 193.8, 153.6, 151.5, 136.2, 134.3, 130.8, 130.4, 130.1, 129.2, 129.0, 128.9, 128.4, 128.2, 128.1, 127.6, 126.5, 118.9, 81.8, 27.9; **FT-IR (neat)** $\nu_{\max}$ 3443, 3404, 2978, 2920, 2851, 1732 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₀H₂₁NO₃ [M+H]⁺, 324.1600, found 324.1602.

(Z)-tert-butyl (3-oxo-1,2-di-p-tolylprop-1-en-1-yl)carbamate (1b)

Orange oil; **¹H NMR (400 MHz, CDCl₃):** δ 11.5 (s, 1H), 9.57 (s, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.21-7.14 (m, 1H), 6.98 (s, 3H), 6.96 (d, J = 7.8 Hz, 2H), 6.82 (d, J = 7.8 Hz, 2H), 2.27 (d, J = 8.4 Hz, 6H), 1.37 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 194.0, 155.1, 151.6, 140.4, 138.8, 138.2, 136.0, 133.3, 130.6, 130.2, 130.0, 129.9, 128.9, 128.4, 125.6, 118.8, 82.1, 27.9, 27.8, 21.5, 21.1; **FT-IR (neat)** $\nu_{\max}$ 3443, 3387, 3021,

2982, 2851, 1732, 1584 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]^+$, 352.1913, found 352.1913.

(Z)-tert-butyl (1,2-bis(4-fluorophenyl)-3-oxoprop-1-en-1-yl)carbamate (1c)

Pale yellow solid; **m.p.** 120-122 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 9.34 (s, 1H), 7.49-7.46 (m, 2H), 7.26-7.16 (m, 6H), 6.56 (s, 1H), 1.28 (s, 6H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.0, 154.1, 150.8, 132.3, 132.0, 131.9, 130.0, 128.2, 125.0, 116.5, 116.3, 115.7, 115.5, 82.6, 27.9, 27.8, 27.7; **FT-IR (neat)** ν_{max} 3393, 3331, 3171, 3017, 2978, 1730, 1634, 1601, 1215, 1148 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{25}\text{H}_{25}\text{F}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$, 360.1411, found 360.1411.

(Z)-tert-butyl (3-oxo-1-phenyl-2-(p-tolyl)prop-1-en-1-yl)carbamate (1d)

Pale yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 11.54 (s, 1H), 9.59 (s, 1H), 7.50-7.35 (m, 2H), 7.20-7.09 (m, 4H), 6.98 (s, 1H), 6.95 (d, $J = 8.0$ Hz, 2H), 6.82 (d, $J = 8.0$ Hz, 1H), 2.27-2.24 (m, 3H), 1.40-1.36 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.0, 153.2, 138.9, 134.4, 130.8, 130.6, 130.2, 129.7, 129.2, 129.0, 128.7, 128.4, 127.6, 127.2, 126.4, 125.8, 118.8, 81.7, 27.9, 21.3; **FT-IR (neat)** ν_{max} 3393, 3017, 2980,

2930, 2855, 1807, 1717, 1653, 1585 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_3$ $[\text{M}+\text{H}]^+$, 338.1756, found 338.1756.

(Z)-tert-butyl (2-(4-methoxyphenyl)-3-oxo-1-phenylprop-1-en-1-yl)carbamate (1e)

Yellow solid; **m.p.** 79-81 $^{\circ}\text{C}$; **^1H NMR (400 MHz, CDCl_3):** δ 11.47 (s, 1H), 9.59-9.58 (m, 1H), 7.47 (s, 1H), 7.21-7.09 (m, 3H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.95 (d, $J = 7.3$ Hz, 1H), 6.85 (d, $J = 8.5$ Hz, 1H), 6.70-6.67 (m, 2H), 3.73 (d, $J = 6.2$ Hz, 3H), 1.40 (s, 3H), 1.35 (s, 6H); **^{13}C NMR (100 MHz, CDCl_3):** δ 194.0, 158.2, 153.1, 151.6, 131.9, 130.8, 130.1, 128.9, 128.7, 128.2, 127.6, 113.6, 113.1, 81.7, 55.1, 27.9; **FT-IR (neat)** ν_{max} 3406, 3389, 3015, 2976, 2959, 2938, 1728, 1634, 1585 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$ $[\text{M}+\text{H}]^+$, 354.1705, found 354.1705.

(Z)-tert-butyl (1-(4-fluorophenyl)-3-oxo-2-phenylprop-1-en-1-yl)carbamate (1f)

Pale yellow oil; **^1H NMR (400 MHz, CDCl_3):** δ 9.36 (s, 1H), 7.51-7.40 (m, 6H), 7.28-7.18 (m, 3H), 6.63 (s, 1H), 1.27-1.23 (m, 9H); **^{13}C NMR (100 MHz, CDCl_3):** δ 191.5, 155.0, 132.0, 131.9, 130.4, 130.3, 130.1, 129.3, 129.2, 129.0, 128.9, 128.5, 128.4, 128.2, 115.6, 82.5, 27.7; **FT-IR (neat)** ν_{max} 3428, 3387, 2976, 2920, 2849,

1749, 1722, 1684 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{20}\text{H}_{21}\text{FNO}_3$ $[\text{M}+\text{H}]^+$, 342.1505, found 342.1505.

4.3 General Synthetic procedure for the preparation of starting material, N-Benzyl- γ -amino- α,β -unsaturated aldehyde (**1l**)

Procedure (iii):

To a solution of γ -amino- α,β -unsaturated aldehyde **S3a** (100 mg, 0.45 mmol, 1.0 equiv) in DMF (10 mL) was added NaH (16 mg, 0.67 mmol, 1.5 equiv). The solution was stirred for 15 mins at r.t, benzyl bromide (116 mg, 0.67 mmol, 1.5 equiv) was added and then continued to stirred overnight (TLC monitored). The resulting solution was diluted with ether, washed with water (2×50 mL) and brine (2×50 mL). The organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the crude residue as a orange oil. The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford N-Benzyl- γ -amino- α,β -unsaturated aldehyde **1n** (47 mg, 0.15 mmol, 33% yield) as a yellow oil.

(Z)-3-(benzylamino)-2,3-diphenylacrylaldehyde (11)

¹H NMR (400 MHz, CDCl₃): δ 12.13 (s, 1H), 9.37 (s, 1H), 7.37-7.21 (m, 5H), 7.12-7.03 (m, 3H), 6.95-6.93 (m, 2H), 4.36 (d, J = 6.4 Hz, 2H); **¹³C NMR (100 MHz, CDCl₃):** δ 193.8, 153.6, 151.5, 136.2, 134.3, 130.8, 130.4, 130.1, 129.2, 129.0, 128.9, 128.4, 128.2, 128.1, 127.6, 126.5, 118.9, 81.8, 27.9; **FT-IR (neat)** ν_{max} 3421, 3400, 2975, 2935, 2851, 1732 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₀H₂₁NO₃ [M+H]⁺, 324.1600, found 324.1602.

4.4 General Synthetic procedure for the synthesis of polysubstituted pyrrole derivatives (3)

To a solution of N-Boc- γ -amino- α,β -unsaturated aldehyde **1a** (20 mg, 0.06 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) were added ethyl diazoacetate **2a** (0.02 mL, 0.19 mmol, 3.0 equiv) and TiCl_4 (1 M in CH_2Cl_2 , 0.01 mL, 0.01 mmol, 0.2 equiv) at r.t. The suspension was then stirred at reflux for 6 h (TLC monitored). The resulting mixture was diluted with CH_2Cl_2 , washed with water (2×20 mL) and brine (2×20 mL). The organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the crude residue as a brown oil. The crude residue was then purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to afford polysubstituted pyrrole derivative **3a** (18 mg, 0.05 mmol, 78% yield) as a yellow oil.

1-tert-butyl 3-ethyl 4,5-diphenyl-1H-pyrrole-1,3-dicarboxylate (**3a**)

^1H NMR (400 MHz, CDCl_3): δ 8.04 (s, 1H), 7.22-7.21 (m, 3H), 7.17-7.09 (m, 7H), 4.16 (q, $J = 7.1$ Hz, 2H), 1.30 (s, 9H), 1.17 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.9, 148.6, 133.5, 132.5, 132.4, 130.8, 130.7, 127.5, 127.2, 127.0, 126.5,

117.0, 84.8, 59.9, 27.4, 14.1; **FT-IR (neat)** $\nu_{\max}$ 3055, 1749, 1647, 1558, 1362, 1219 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{H}]^+$, 392.1862, found 392.1854.

1-tert-butyl 3-ethyl 4,5-di-*p*-tolyl-1*H*-pyrrole-1,3-dicarboxylate (3b)

Yellow solid, decomposes upon heating; **^1H NMR (400 MHz, CDCl_3):** δ 8.00 (s, 1H), 7.00 (d, $J = 12.5$ Hz, 8H), 4.17 (q, $J = 7.1$ Hz, 2H), 2.29 (s, 3H), 2.27 (s, 3H), 1.33 (s, 9H), 1.19 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 163.9, 148.7, 137.0, 135.9, 132.4, 130.5(2), 129.5, 128.2, 127.9, 127.2, 126.8, 116.9, 84.6, 59.9, 27.5, 21.3, 21.2, 14.2; **FT-IR (neat)** $\nu_{\max}$ 3584, 3289, 2957, 2922, 2851, 1609 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{26}\text{H}_{29}\text{NO}_4$ $[\text{M}+\text{H}]^+$, 420.2175, found 420.2179.

1-tert-butyl 3-ethyl 4,5-bis(4-fluorophenyl)-1*H*-pyrrole-1,3-dicarboxylate (3c)

Yellow oil; **^1H NMR (400 MHz, CDCl_3):** δ 8.03 (s, 1H), 7.10-7.03 (m, 4H), 6.96-6.85 (m, 4H), 4.17 (q, $J = 7.1$ Hz, 2H), 1.35 (s, 9H), 1.19 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 163.8, 148.4, 133.3, 132.4, 132.2, 131.4, 130.7, 130.6, 129.2,

128.3, 127.6, 127.1, 126.8, 126.7, 116.9, 114.7, 114.6, 114.4, 114.3, 114.2, 85.1, 60.0, 27.4, 14.1; **FT-IR (neat)** $\nu_{\max}$ 3584, 3406, 3387, 2957, 2934, 2918, 2851, 2806, 1749, 1607, 1595, 1153 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{24}\text{H}_{23}\text{F}_2\text{NO}_4$ $[\text{M}+\text{H}]^+$, 428.1673, found 428.1673.

1-tert-butyl 3-ethyl 5-phenyl-4-(p-tolyl)-1H-pyrrole-1,3-dicarboxylate (3d)

Yellow solid; **m.p.** 96-98 °C; **^1H NMR (400 MHz, CDCl_3):** δ 8.03-8.02 (m, 1H), 7.23-7.21 (m, 2H), 7.18-7.09 (m, 3H), 7.01-6.98 (m, 4H), 4.17 (d, $J = 7.2$ Hz, 2H), 2.29-2.26 (m, 3H), 1.34 (s, 3H), 1.29 (s, 6H), 1.22-1.14 (m, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 164.0, 148.7, 137.1, 136.0, 132.7, 132.5, 132.2, 130.7, 130.5, 130.4, 129.3, 128.6, 128.2, 127.9, 127.5, 127.1, 126.9, 126.5, 116.9, 84.7, 59.9, 27.4, 21.3, 14.1; **FT-IR (neat)** $\nu_{\max}$ 3019, 2932, 2870, 1748, 1703, 1371, 1360, 1256, 1215 cm^{-1} ; **HRMS (ESI):** m/z calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$, 406.2018, found 406.2005.

1-tert-butyl 3-ethyl 4-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-1,3-dicarboxylate (3e)

Yellow oil; **¹H NMR (400 MHz, CDCl₃):** δ 8.03-8.02 (m, 1H), 7.23-7.21 (m, 2H), 7.18-7.16 (m, 1H), 7.13-7.09 (m, 2H), 7.05-7.00 (m, 2H), 6.76-6.70 (m, 2H), 4.21-4.13 (m, 2H), 3.76-3.74 (m, 3H), 1.36 (s, 3H), 1.30 (s, 6H), 1.22-1.16 (m, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 164.0, 158.7, 148.5, 131.9, 131.7, 130.8, 130.7, 127.5, 127.4, 127.2, 127.0, 113.0, 112.7, 84.7, 59.9, 55.1, 27.5; **FT-IR (neat)** $\nu_{\max}$ 3019, 2978, 2959, 2934, 1742, 1719, 1686 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₅H₂₇NO₅ [M+H]⁺, 422.1967, found 422.1964.

1-tert-butyl 3-ethyl 5-(4-fluorophenyl)-4-phenyl-1H-pyrrole-1,3-dicarboxylate (3f)

Yellow oil; **¹H NMR (400 MHz, CDCl₃):** δ 8.04 (s, 1H), 7.22-7.11 (m, 9H), 4.16 (q, J = 6.8 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 6H), 1.17 (t, J = 6.8 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 163.9, 132.5, 132.4, 130.8, 130.7, 130.6, 127.5, 127.3, 127.2, 127.0, 126.5, 114.5, 84.8, 59.9, 27.5, 14.1; **FT-IR (neat)** $\nu_{\max}$ 3017, 2957, 2918, 2851, 1755, 1722, 1682, 1651, 1213, 1153 cm⁻¹; **HRMS (ESI):** m/z calcd for C₂₄H₂₄FO₄ [M+H]⁺, 409.1595, found 409.1861.

1-tert-butyl 3-isopropyl 4,5-bis(4-fluorophenyl)-1H-pyrrole-1,3-dicarboxylate (3g)

Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 8.03 (s, 1H), 7.23-7.20 (m, 3H), 7.19-7.08 (m, 7H), 5.05 (qt, $J = 6.2$ Hz, 1H), 1.30 (s, 9H), 1.14 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.5, 148.7, 133.6, 132.6, 132.3, 130.7(2), 127.5, 127.4, 127.1, 126.9, 126.5, 117.5, 84.7, 67.2, 27.4, 21.7; FT-IR (neat) ν_{max} 3019, 2976, 2920, 2851, 1749, 1717, 1373, 1215 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$, 406.2018, found 406.2017.

1-tert-butyl 3-(2-methylbutyl) 4,5-diphenyl-1H-pyrrole-1,3-dicarboxylate (3h)

Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 8.06 (s, 1H), 7.21-7.20 (m, 3H), 7.16-7.08 (s, 7H), 4.01-3.89 (m, 2H), 1.56 (m 1H), 1.29 (s, 9H), 1.27 (s. 2H), 0.82 (t, $J = 7.4$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.2, 148.7, 133.6, 132.5, 132.4, 130.7, 130.6, 127.4, 127.3, 127.2, 127.1, 126.5, 117.1, 84.8, 68.8, 34.0, 27.4, 25.9, 16.3, 11.2; FT-IR (neat) ν_{max} 3057, 3032, 2963, 2934, 2876, 1748, 1703, 1558, 1522, 1287, 1258, 1213 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{31}\text{NO}_4$ $[\text{M}+\text{H}]^+$, 434.2331, found 434.2332.

1-tert-butyl 3-butyl 4,5-diphenyl-1H-pyrrole-1,3-dicarboxylate (3i)

Yellow oil; **¹H NMR (400 MHz, CDCl₃)**: δ 8.05 (s, 1H), 7.22-7.20 (m, 3H), 7.16-7.09 (m, 7H), 4.10 (t, J = 6.5 Hz, 2H), 1.53-1.46 (m, 2H), 1.30 (s, 9H), 1.26-1.19 (m, 2H), 0.85 (t, J = 7.4 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)**: δ 164.1, 148.6, 133.6, 132.5, 132.4, 130.7, 130.6, 127.5, 127.4, 127.2, 127.0, 126.5, 117.0, 84.8, 63.9, 30.6, 27.4, 23.0, 19.1, 13.7; **FT-IR (neat)** $\nu_{\max}$ 2959, 2932, 2872, 1748, 1724, 1705, 1362 cm⁻¹; **HRMS (ESI)**: m/z calcd for C₂₆H₂₉NO₄ [M+H]⁺, 420.2175, found 420.2191.

tert-butyl 4-butyl-2,3-diphenyl-1H-pyrrole-1-carboxylate (3j)

Yellow oil; **¹H NMR (400 MHz, CDCl₃)**: δ 8.00 (s, 1H), 7.22-7.20 (m, 3H), 7.17-7.16 (m, 3H), 7.12-7.07 (m, 4H), 2.58 (t, J = 7.4 Hz, 2H), 1.68-1.60 (m, 2H), 1.28 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)**: δ 196.7, 148.8, 133.8, 132.5, 130.7, 130.58, 127.5(2), 127.4, 126.9, 126.7, 126.2, 125.4, 84.9, 42.6, 35.8, 27.4, 17.8, 13.8; **FT-IR (neat)** $\nu_{\max}$ 3021, 2970, 2920, 2878, 1755, 1668, 1647, 1215, 1152 cm⁻¹; **HRMS (ESI)**: m/z calcd for C₂₅H₂₇NO₃ [M+H]⁺, 390.2069, found 390.2069.

***tert*-butyl 4-butryl-2,3-bis(4-fluorophenyl)-1*H*-pyrrole-1-carboxylate (3k)**

Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.38-7.30 (m, 2H), 7.15-7.03 (m, 4H), 6.91 (t, $J = 8.6$ Hz, 2H), 2.80 (t, $J = 7.4$ Hz, 2H), 1.80 (q, $J = 7.4$ Hz, 2H), 1.38 (s, 9H), 1.02 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 190.0, 149.7, 134.7, 132.7, 131.8, 130.6, 130.0, 129.6, 128.9, 128.3, 128.0, 126.5, 123.6, 117.1, 115.6, 115.4, 115.3, 115.2, 115.1, 85.5, 40.5, 27.2, 18.6, 14.0; FT-IR (neat) ν_{max} 3019, 2968, 2934, 2878, 2857, 1767, 1761, 1732, 1215 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{25}\text{F}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$, 426.1881, found 426.1881.

ethyl 1-benzyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (3l)

Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.34 (s, 1H), 7.33-7.13 (m, 13H), 6.84 (d, $J = 7.0$ Hz, 2H), 5.50 (s, 2H), 4.24 (q, $J = 7.1$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.1, 139.1, 138.0, 135.1, 131.6, 131.0, 128.6, 128.3, 128.1, 127.7, 126.8, 125.8, 125.7, 123.5, 122.5, 117.7, 60.0, 49.0, 29.7, 14.4; FT-IR (neat) ν_{max} 3019, 2976, 2920, 2899, 1749, 1722, 1215 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 382.1807, found 382.1809

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Publications

- 1) Polysubstituted Pyrrole Derivatives *via* 1,2-Alkenyl Migration of Novel γ -Amino- α,β -Unsaturated Aldehydes and α -Diazocarbonyls, Shuting Cai, Jing Zeng, Yongxin Li and Xue-Wei Liu, *Manuscript Submitted*.
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- 3) Direct and Stereoselective Synthesis of 1,3-*cis*-3-Arylsulphonaminodeoxydisaccharides and Oligosaccharides. Feiqing Ding, William Ronny, Shuting Cai, Jimei Ma, Xue-Wei Liu, *J. Org. Chem.* **2012**, 77, 5245.
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2. “Facile synthesis of carbohydrate-integrated isoxazolines through tandem [4 + 1] cycloaddition and rearrangement of 2-nitroglycals” Shuting Cai and Xue-Wei Liu, 3rd Asia-Oceania Conference on Green & Sustainable Chemistry, Melbourne, Australia, December 2011.
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